SYNTHESIS AND CHARACTERIZATION OF PRECURSORS FOR QUINOXALINE CYCLIZATION

by

Aylin Aykanat

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APPROVED BY:

Assoc. Prof. A. Ersin Acar (Thesis Supervisor)	…….
Assoc. Prof. Ece Bulak	…….
Prof. Safiye Erdem	…….

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To Can, Asu and Sara…

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ABSTRACT

SYNTHESIS AND CHARACTERIZATION OF PRECURSORS FOR QUINOXALINE CYCLIZATION

Quinoxaline compounds are essential nitrogen containing heterocyclic compounds of various biological properties and have several pharmaceutical applications. In this work, several precursors to be used in quinoxaline cyclization were synthesized from diamine- and tetra-aminobenzene hydrochloride precursors. Our group added several substituents to phenylenediamine or used directly 1,2,4,5-Benzenetetramine tetrahydrochloride before a coupling reaction with 1,2-Acenaphthylenedione. The systematic characterization of the quinoxaline derivatives and final products were done via ^{1}H-NMR and^{13}C-NMR.

ÖZET

KİNOKSALİN SİKLİZASYON ÖNCÜLERİNİN SENTEZİ VE KARAKTERİZASYONU

Kinoksalin bileşikler, nitrojen içeren çeşitli biyolojik özellikleri olan heterosiklik bileşiklerdir ve birçok farmasötik uygulamaları mevcuttur. Bu projede, diamin ve tetra-aminobenzen hidroklorür kullanılarak, kinoksalin siklizasyonunda kullanılacak olan çeşitli öncü bileşikler sentezlenmiştir. 1,2- Asenaftilendion ile yapılan birleştirme reaksiyonları için 1,2-phenylendiamine benzen ve 1,2,3,4-tetraamin tetrahidroklorür bileşiklerinin türevleri sentezlenmiştir. Kinoksalin türevlerinin ve son ürünlerin karakterizasyonu ^{1}H-NMR ve ^{13}C-NMR ile yapılmıştır.

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LIST OF ACRONYMS/ABBREVIATIONS

2D	Two Dimensional
3D	Three Dimensional
ACS	American Cancer Society
CMV	Cytomegalovirus
$CDCl_3$	Deutorated chloroform
DCM	Dichloromethane
COSY	Correlation Spectroscopy
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EtOAc	Ethyl acetate
EtOH	Ethanol
H_2SO_4	Sulphuric acid
HOAc	Acetic acid
HOMO	Highest occupied molecular orbital
ICT	Intramolecular charge transfer
LC-MS	Liquid Chromatography-Mass Spectroscopy
LUMO	Lowest Unoccupied Molecular Orbital
LH-RH	Luteinizing Hormone-Releasing Hormone
MABA	Microplate Alamar Blue Assay
MAO	Methyl-aluminoxane
MeOH	Methanol
$NaBH_4$	Sodium Borohydride
$NaCNBH_3$	Sodium Cyanoborohydride
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
OFETs	Organic filter-effect transistor semiconducters
p-TsCl	4-Toluenesulfonyl chloride
QSAR	Quantitative Structure Activity Relationship
TLC	Thin Layer Chromatography
UV	Ultraviolet

VZV	Varicella-zoster virus
WHO	World Health Organization
Zn	Zinc

1. INTRODUCTION

1.1. Quinoxalines

Organometallic chemistry is a unique branch of science that gives insight into the complicated marriage of organic and inorganic chemistry. Since the discovery of ferrocene in 1951, there has been an ever-increasing interest in the field of organometallic chemistry and the applications it can potentially have in various fields of science, including pharmaceutical chemistry.

Quinoxalines, also called benzopyrazines, are heterocyclic compounds that are the combination of a benzene and pyrazine ring as seen in Figure 1.1 [1]. They contain at least two nitrogen atoms infused into their framework. The incorporation of an imine into the scaffold of this molecule gives the cyclic compound unique and functional properties due to the increase in stabilization. There is a consequential increase in electron affinity seen with the supplement of an extra pi-system. The sp^2 hybridized nitrogen atoms in the molecule help increase the stability of the electrons in the framework, which can render the complex a potential ligand.

Furthermore, adding functional groups onto the scaffolds of these potential ligands can make these complexes excellent chelating agents. Depending on the number and positions of the amines in the arene framework, various stability, molecular packing, solubility and electronic properties can be observed. It is also relevant to note that a fusion of a five-membered ring into the framework of the arene can lower the LUMO energy of the molecule, due to its tendency to accept electrons through 4n + 2 stabilization [2].

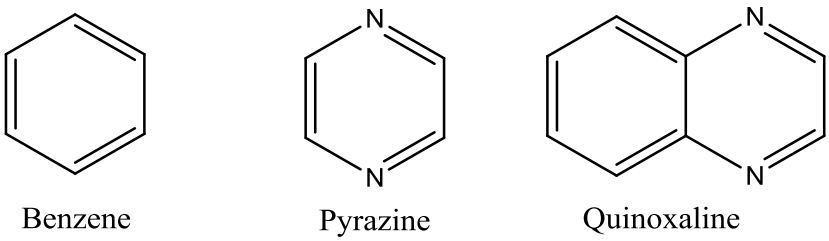


Figure 1.1. Fusion of benzene and pyrazine ring to make quinoxaline.

1.2. Quinoxalines and their use in Medicinal Chemistry

Sandra P. have synthesized Methyl [4-(substituted 2- quinoxalinyloxy) phenyl] acetates and ethyl N-{[4- (substituted 2-quinoxalinyloxy) phenyl] acetyl} glutamate analogs of Methotrexate and evaluated for *in vitro* anti-cancer activity by bioisosteric replacement [3].

Harmenberg J. synthesized the compound 2,3-dimethyl-6(2-dimethylaminoethyl)6H-indolo-(2,3-b) quinoxaline (B-220) which has been shown to exhibit potent antiviral activity against herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV) and cytomegalovirus (CMV). The mechanism of antiviral action of B-220 against HSV-1 was studied and from the results it seems that B-220 binds by intercalation into the DNA helix and then disturbs steps that are vital for viral uncoating [3].

Ganapaty *et.al,* has synthesized some novel condensed bridgehead nitrogen heterocycles of quinoxalines. All the condensed systems were evaluated for antimicrobial activity against the gram- positive bacteria *Staphyllococus aureus* and *Bacillus subtilis*, the gram-negative *Psudomonas aeruginosa* and *proteus vulgaris*, the fungi *Aspergillus niger* and the *Mycobacterium tuberculosis* H37Rv species. The antitubercular screening was performed by Microplate Alamar Blue Assay (MABA) method at 6.25 μg/ml concentration. DMSO was used as solvent. Nalidixic acid (100 μg/disc) and Clotrimazole (50 μg/disc) were used as standard respectively, for antibacterial and antifungal screening [3].

Asuncion B. Synthesized novel ring substituted 3- phenyl -1- (1, 4-di-N-oxide quinoxaline-2-yl) -2- propen-1-one derivatives and of their 4, 5-dihydro- (1H)-pyrazole analogues. Synthesized compounds were evaluated for anti-inflammatory and antioxidant activity. The tested compounds inhibit the carrageenan-induced rat paw edema (4.5-56.1%) [2].

1.2.1. Redox Active Ligands

When functional groups on the quinoxaline complex are made to coordinate with certain transition metal complexes, redox active character can be observed. Redox active ligands or “non-innocent” ligands are organometallic compounds in which the metal

oxidation state is ambiguous. [4] This special brand of coordination chemistry dates back to the 1960's, when compounds known as dithiolenes were synthesized and investigated. [5] Computational methods revealed one-electron changes upon oxidation or reduction were occurring in the ligand instead of the metal. These ligands became the culprits in the case of the ambiguity of the metals oxidations states by storing high-energy electrons in their electronic framework or conjugated backbone [6].

Establishing "correct" oxidation states and the relationship and characterization of differently charged ligands can give insight into structural and other consequences of ligand redox reactions [7]. An important aspect of redox active ligands is that they can behave in both an innocent and a non-innocent fashion, depending on a particular coordination site, which can depend on the structure of the ligand as seen in Figure 1.2., thus the necessity of considering this particular coordination before labeling a ligand as "non-innocent" has been recently emphasized.

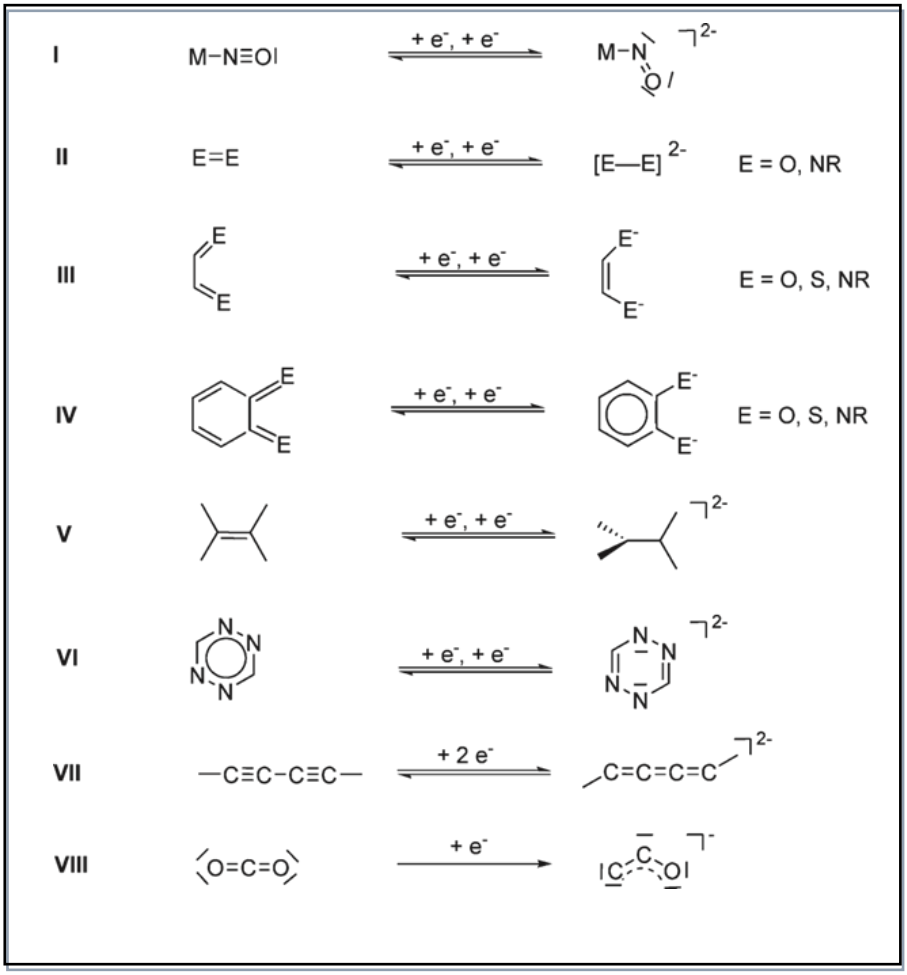


Figure 1.2. Structural changes of certain ligands associated with oxidation state [7].

"Thus, innocence or non-innocence is not the permanent at- tribute of a ligand, but molecules can behave as innocent or non-innocent ligands towards redox-active metals under specific circumstances, in a certain situation". – Wolfgang Kaim [8]

1.3. Quinoxaline Ligands in Transition Metal Catalysis

To avoid high activation barriers, nature typically breaks down challenging catalytic transformations into a sequence of elementary steps. [9] There has been a continuing interest in transition metal complexes and the catalytic transformations in which they aid. Particularly fascinating are systems in which quinoxaline ligands are made to coordinate with redox-active metal centers through rigid-conjugated π-systems, allowing increased electronic communication. [10] Due to the low-lying π*-orbitals, these ligands appear to mix extensively with the valence *d*-orbitals of the metal, giving complexes with covalent frontier orbitals HOMO and LUMO [11].

Much research has been done in an effort to fine tune these quinoxaline ligands that possess redox-active character and their electronic properties when they complex with *d*-block transition metals such as ruthenium, platinum and palladium. In certain quinoline and quinoxaline complexes, the electronic environment at the center of coordination can be modified by changing the substituents on the ligand and/or by varying the *p*- block and *d*-block transition metals at the center [3]. This can allow the electrical fine-tuning of the structure and can also enhance several properties of the ligand, which can make efficient catalysts in various syntheses or other reactions.

The redox active ligands can also be put to use in the synthesis of enantio- and diastereomerically controlled architectures when complexation occurs with ruthenium (II)-diamine centers [7]. Warnmark K. *et al.* have synthesized several ligands designed for multi-ruthenium (II)-2,2'-bipyridyl (bpy),- 1,10-phenanthroline) phen_ and –terpyridine (terpy) complexation for potential inorganic molecular electronic devices.

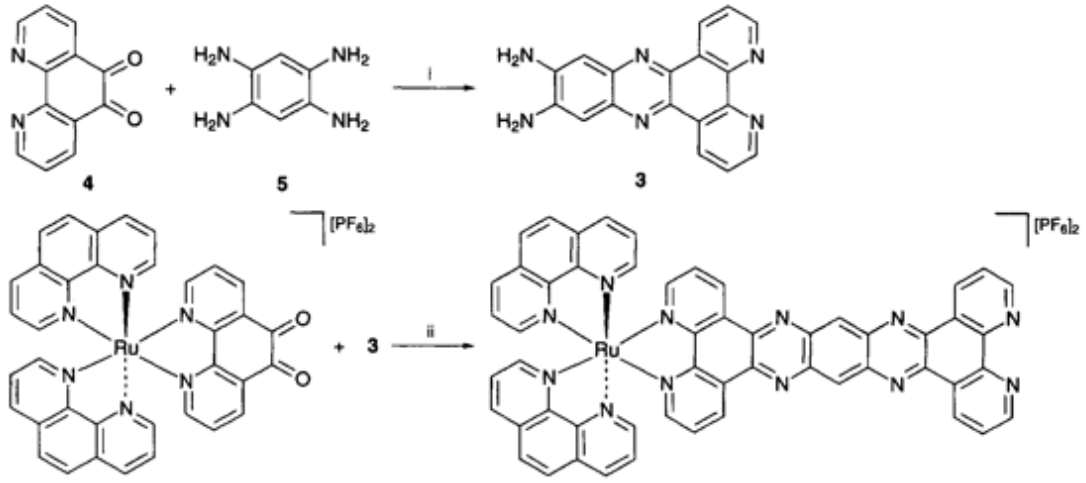


Figure 1.3. Condensation with aromatic 1,2,4,5-Benzenetetramine and diketone to produce redox-active ligand coordinated with Ru metal center [7].

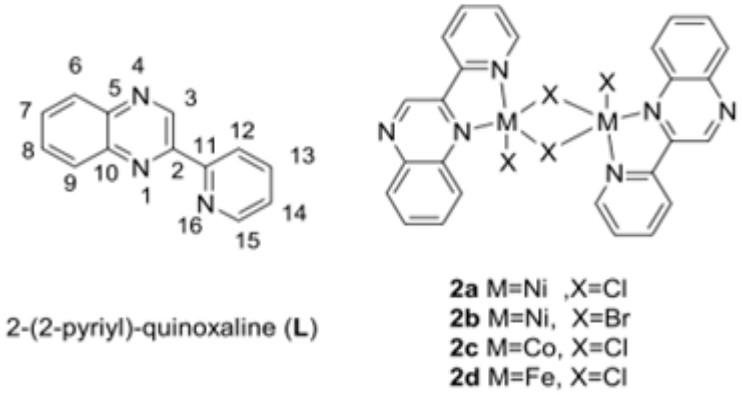
1.3.1. Applications of Quinoxalines in Transition Metal Complexes

Tong. C *et al.* have synthesized several bisacenapthopyrazinoquinoxaline (BAPQ) based derivatives through a condensation reaction between acenapthoquinones and 1,2,4,5-Benzenetetramine tetrahydrochloride. The group investigated their optical, electrochemical and self-assembling properties by varying the substituents on the ligands. Their applications n-channel organic filter-effect transistor semiconductors (OFETs) were investigated [2].

Masui. *et al*. have further synthesized the complex [$(bpy)_2$Ru(1,2,4,5-tetraamino-3,5-diketocyclohexane)Ru$(bpy)_2]^{4+}$] which is a binuclear species that undergoes ligand-based reductions. This bridge could be used to link ruthenium centers in a linear polymeric chain to observe valence and conduction bands, leading to semiconducting or conducting polymers required for molecular electronic devices [12].

Shao. C synthesized complexes of 2-(2-pyridyl) quinoxaline with Ni^{II}, Co^{II} and Fe^{II} seen in Figure 1.4, to be used in ethylene oligomerization with methyl-aluminoxane (MAO) as a co-catalyst. These catalysts were used for the development of late transition metal complexes as catalysts for the polymerization and/ or oligomerization of ethylene. The careful electronic tuning of the quinoxaline ligands was carried out to alter their corresponding catalytic properties and to skew the composition from lower oligomers to

polymer [13].



Scheme 1.

Figure 1.4. Substituted quinoxalines coordinating with various metal centers [13].

1.4. Structure Based Approach for Ligand Design

Numerous methods are available for the synthesis of quinoxaline derivatives that involve a condensation reaction between 1,2-diamines with α-diketones (the Mannich reaction seen in Figure 1.5), 1,4-addition of 1,2-diamines to diazenylbutenes, cyclization–oxidation of phenacyl bromides and oxidative coupling of epoxides with ene-1,2-diamines. [13] However for our target we have chosen the condensation reaction using a specific quinone. There are two potential synthetic routes to attain the desired aromatic ligand that may be used later for coordination with redox active metal centers.

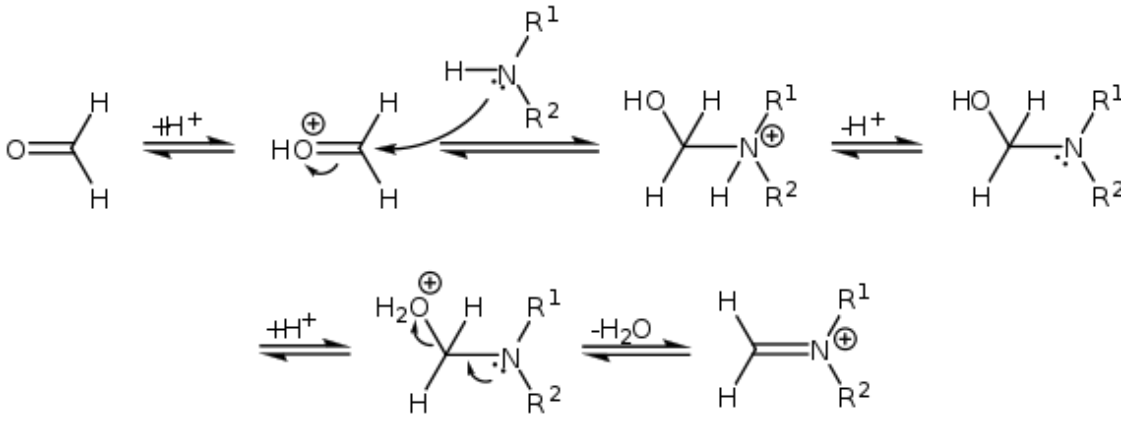


Figure 1.5. Reaction mechanism of Mannich reaction.

It is also important to note that due to the extended π-conjugated system, properties such as photoluminescence and fluorescence are expected to be observed. The presence of electron donating and/or electron withdrawing groups on the scaffold of ligands can often constitute a push-pull system throughout the framework of the molecule. Pyrazine and quinoxaline structures are highly π-deficient aromatic heterocyclic compounds, and can be used with electron withdrawing groups as push-pull structures for intramolecular charge transfer (ICT). Such important intermolecular charge transfer along the backbone of the molecule can induce photo luminescent properties [14].

2. OBJECTIVE

Redox active quinoxaline ligands constitute not only a synthetic challenge but possess an appealing architecture for coordination with various transition metals. Depending on the number and positions of nitrogen's in the framework of the arene, one can observe different electronic properties, solubility, and thermal stabilities. [2] When incorporated with specific functional groups, they have the ability to hold a unique character that can be fine-tuned by varying the molecular framework, and as a result the affinity of the conjugated backbone.

We are interested in the syntheses of two specific functionalized quinoxalines that bear diamine and dimethyl amine functional groups and a five membered ring incorporated into their framework as seen in Figure 2.1. These molecules and potential ligands are expected to have a high electron affinity and a stable 2-dimensional framework made possible by the fusion of the pentane ring. They can be synthesized by the condensation of the diketone, namely acenapthoquinone, and *o*-phenylenediamine or tetraaminobenzene. Once synthesized the electron transfer capacity of the ligand and the metal complex will be investigated by cyclic voltammetry.

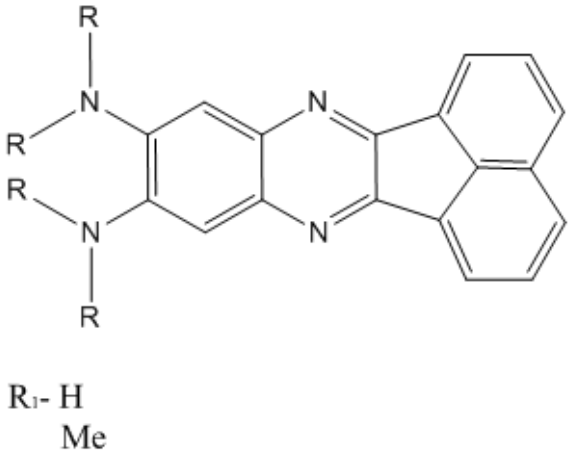


Figure 2.1. Molecular structure of desired quinoxaline ligand.

3. RESULTS AND DISCUSSION

Quinoxaline compounds have been widely used in industrial dyes, biological applications, pharmaceutical chemistry and photochemical materials. There are many proposed synthetic strategies to synthesize substituted quinoxalines, mainly coupling reactions between aromatic 1,2-diamines and 1,2-carbonyl groups. When various electron-donating substituents are added to the framework of these compounds, distinctive photo- and electroluminescent properties can be observed. Several transition metals readily coordinate to such compounds to stimulate high electron affinity and good thermal stability with unique fluorescent characteristics which may act as catalysts in numerous reactions [15].

The purpose of this study was to synthesize two functionalized quinoxaline ligands to be used in coordination with several redox-active metal centers as seen previously in Figure 2.1. There have been two proposed synthetic pathways to synthesize the suggested ligands. The first route involved the synthesis of several quinoxaline derivatives that have been functionalized prior to coupling with a diketone through a condensation reaction. The second method was the direct coupling of a 1,2,4,5-Benzenetetramine tetrahydrochloride to the desired quinone in water and ethanol. This facile 2-steps synthetic route was hypothesized to be more promising due to the diminished probability of side product formation.

Coupling reactions were performed by commercially available phenyl derivatives and purification was ultimately carried out with analytical, thin layer chromatography and various recrystallization methods including vapor diffusion.

In this section we will examine both synthetic pathways and propose mechanisms while assigning peaks to the obtained spectra. To confirm the structure of the products ^{1}H-NMR and ^{13}C-NMR spectroscopies were used.

3.1. Synthetic Approach for Quinoxaline Method 1

The proposed synthetic route followed in synthesizing the desired ligand (Figure 3.1 (6)) with the first method is presented in Figure 3.1. Synthesis of the quinoxaline ligand using the first method was carried out by two potential synthetic schemes (Figure 3.1 and 3.2) whose first three steps were identical. The first phase of the synthesis involved adding two more amine substituents to phenylenediamine (Figure 3.1 (1)) before coupling with acenapthoquinone (Figure 3.1). This would require nitration of the aromatic diamine that would later be reduced into the desired amine substituents after coupling with the diketone. The protection of *o*-phenylenediamine with tosyl chloride protecting groups was mandatory in order to avoid oxidation of the diamine (Figure 3.1 (1)) during the nitration step.

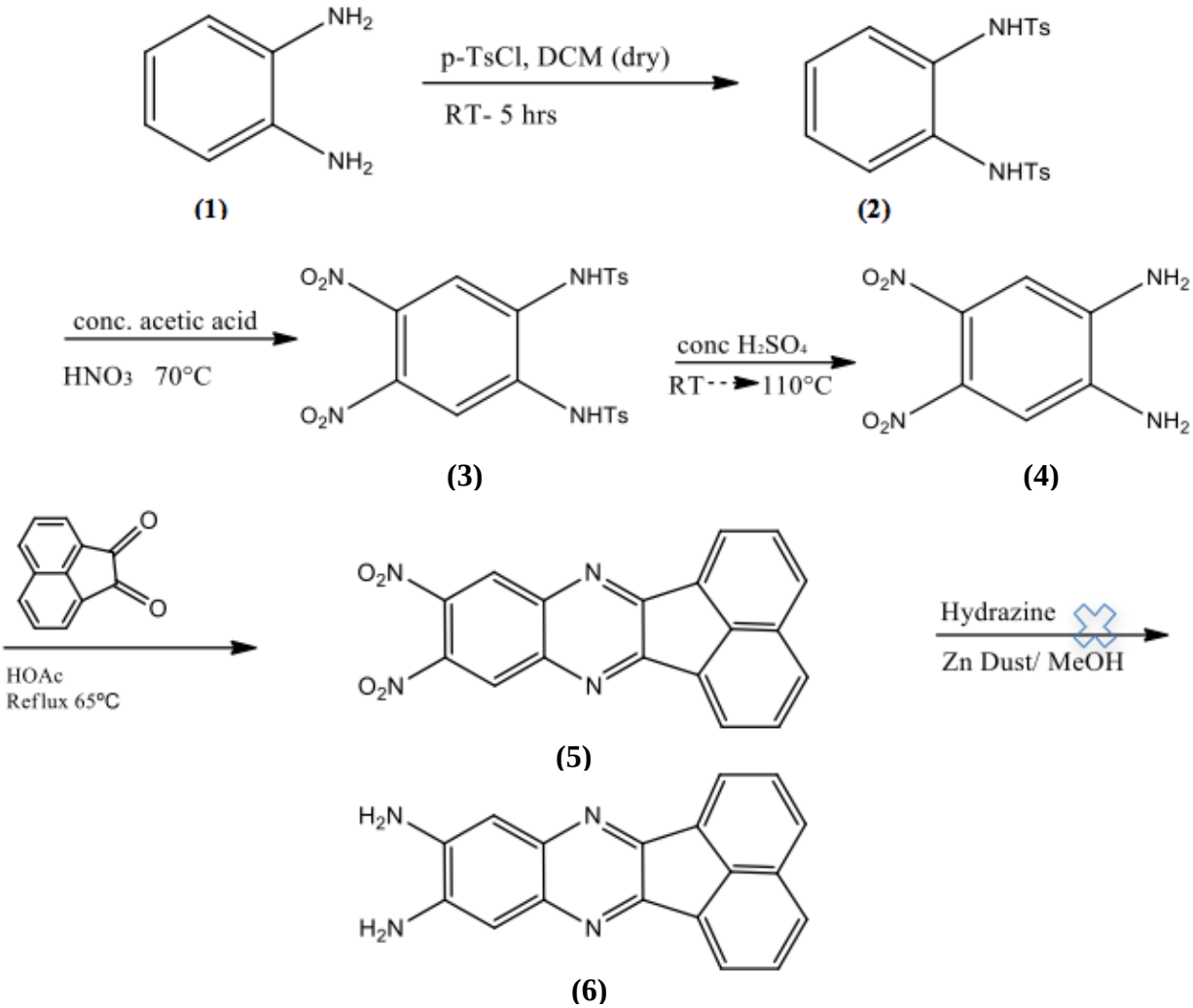


Figure 3.1. Synthesis of acenaphtho[1,2-b]quinoxaline-9,10-diamine (6).

All the necessary transformations were carried out successfully up to compound (Figure 3.1 (5)). The last reduction step using the hydrazine where compound (Figure 3.1 (6)) was targeted proved to be inefficient. Although the reduction, and the following purifications were carried out under inert atmosphere, no product was isolated. It is not clear to us whether the inefficiency is due the poor reaction yield or the difficulties encountered in the purification process. Nonetheless, the reduction of the added nitro groups proved more difficult than expected, thus we proceeded with a different synthetic approach starting with compound (Figure 3.1 (4)).

It was hypothesized that perhaps methylation prior to the reduction of the dinitro substituents could prove to be more efficient, reducing the basicity of the diamine groups before the purification step. Figure 3.2 represents this alternative synthetic route. Tin chloride and sodium borohydride were used in acetic acid with the addition of paraformaldyde as seen below. However the same sensitivity problems were encountered during the extraction of compound (Figure 3.2 (8)). It was hypothesized that compound (Figure 3.2 (8)), 1,2-diamino-4,5-dimethylaminobenzene, may have been oxidized immediately following reduction of the dinitro groups and proved challenging for extraction. Thus an alternative method was investigated to carry out our targeted synthesis.

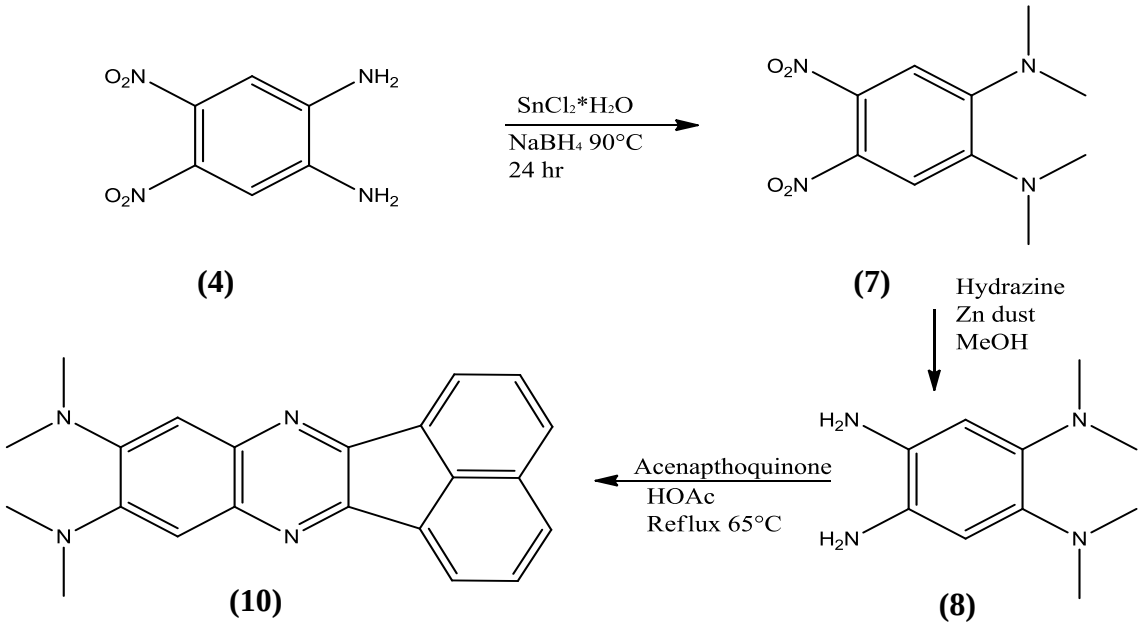


Figure 3.2. Synthesis of Compound (6) through Alternative Method.

3.2. Synthetic Approach for Quinoxaline Method 2

The second synthetic route was developed due to its minimal two-step reaction sequence, easy precipitation of product and diminished probability of side reaction. The leading step of this synthesis was the reaction of 1,2,4,5-Benzenetetramine tetrahydrochloride and the acenapthoquinone in an ethanol and water solvent with stoichiometric amount, with respect to mono addition, of potassium carbonate to avoid bis-addition, as seen in Figure 3.3. However, it has proven to be more difficult to extract the final product from solution due to its high sensitivity. It was feared that a bis-addition of the benzenetetramine to the diketone would take place, however potassium carbonate was added in precisely two equivalents so that no such product was observed. After refluxing at 65^{o}C for 24 hours, a yellow-brown precipitate was observed then filtered and washed with ethyl acetate. The solution was evaporated to 5 mL and water was added dropwise to produce a yellow-brown precipitate, which was filtered, and vacuum dried for a minimum of three days.

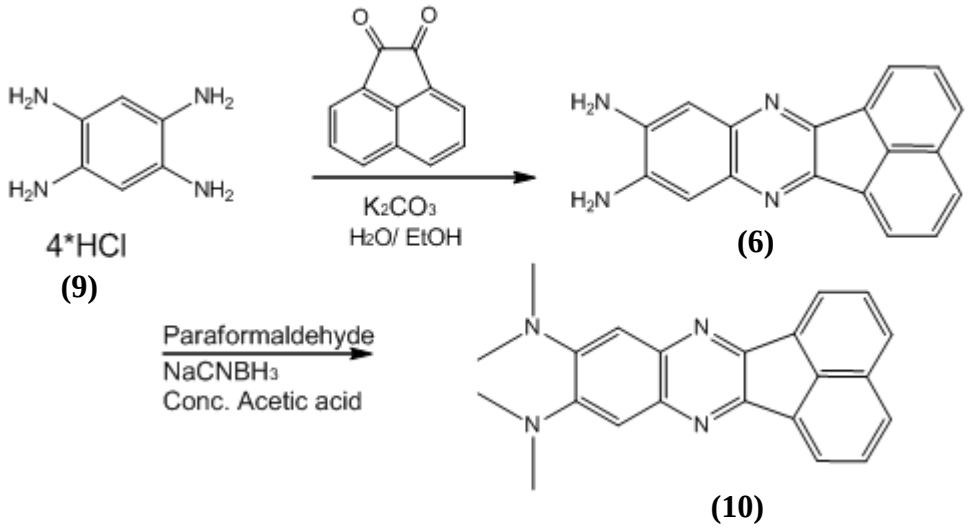


Figure 3.3. Synthesis and methylation of Compound (6).

After obtaining the desired ligand, we continued with the methylation of compound (Figure 3.3 (6)) using sodium cyanoborohydride and paraformaldehyde in a glacial acetic acid solvent. $NaCNBH_3$ is used as a reducing agent while paraformaldehyde is used for methylation in an acidic medium, as seen in Figure 3.4. The product was extracted into the

organic phase using ethyl acetate and analytical thin-layer chromatography was used to obtain a pure sample in 12% yield.

^{1}H-NMR spectroscopy showed a variety impurities for both compounds (Figure 3.3 (6)) and (Figure 3.3 (10)), therefore alternative purification processes were investigated. One method that held promising results was recrystallization from a mixture of toluene and hexane (1:1 v/v). This method produced a dark red precipitate, yet spectroscopy still displayed the presence of water and similar impurities. Column chromatography also proved difficult, which was rationalized with the two basic diamine functional groups interacting with the silica gel. Neutral aluminum oxide chromatography was used instead, yet the product showed difficulty gravitating down the neutral column in any solvent ratio. The impurities remained close and condensed to each other with any applied solvent system.

In the end, analytical thin layer chromatography was used in a 2:1 ethyl acetate and hexane solvent ratio to obtain a pure yet minimal sample of compound (Figure 3.3 (6)) in 42% yield. A sample of compound (Figure 3.3 (8)), N^{9},N^{9},N^{10},N^{10}-tetramethylacenaphtho[1,2-b]quinoxaline-9,10-diamine was also obtained using the same method, yet unfortunately in extremely low yield.

It showed that the final product had high photo luminosity and fluorescence at 550 nm when excited at 365 nm in the UV-Vısible spectrum range. It was hypothesized that the fluorescence was due to the highly aromatic π-conjugated N-heterocyclic backbone.

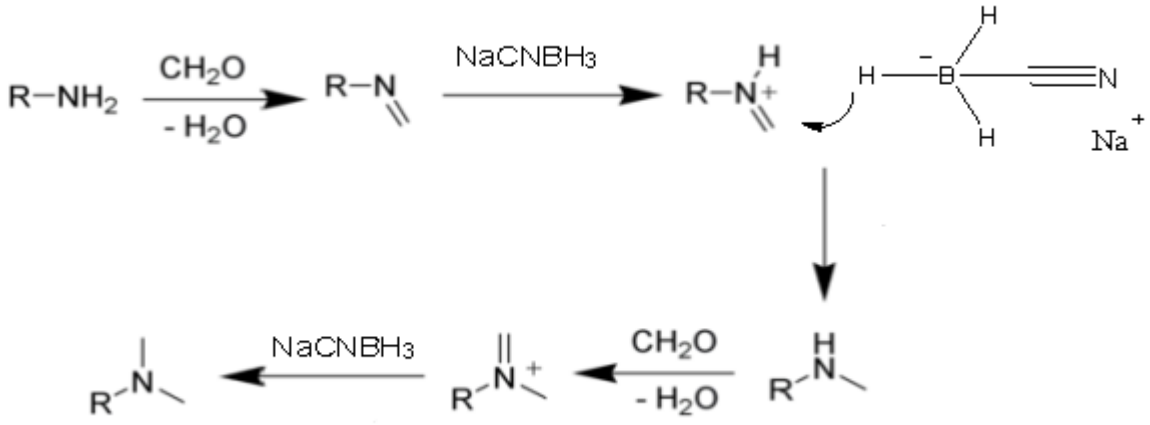


Figure 3.4. Eschweiler–Clarke reaction for Methylation of Compound (8).

4. EXPERIMENTAL

4.1. Methods and Materials

All chemicals were used as received from the manufacturer (Merck, Aldrich, Alfa Aesar, and Riedel de Haen) and included THF, ethyl acetate, dichloromethane, hexane, toluene, diethyl ether, pentane, methanol, ethanol, glacial acetic acid, nitric acid, sulphuric acid, 1,2,4,5 tetraaminobenzene, acenaphthenequinone. etc. Dry solvents (CH_2Cl_2, THF and Toluene) were dried from molecular sieves. 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 and analytical chromatography plates were viewed under 254 nm UV lamp. ^{1}H-NMR and ^{13}C-NMR 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 Boğaziçi University. Fluorescence spectra were recorded in an ethanol solvent and done by Cary Eclipse fluorescence spectrophotometer.

4.3. Synthesis of Lead Compound Precursors and Ligand

In this first synthetic route was a multistep synthesis that included the protection nitration and reduction of phenylenediamine. The second method included only two reactions, which were the coupling and methylation of 1,2,4,5-Benzenetetramine tetrahydrochloride with acenapthoquinone. All reactions are recorded below.

4.3.1. Synthesis of *N,N*- ditoulene-psulfonylo-phenylenediamine

The protection was done according to literature procedure [13]. A mixture of cold, dry DCM (50 mL, 37.0 mmol), *o*-phenylenediamine (2.00 gr, 18.5 mmol) and 3.00 mL of dry pyridine were added to a 100 mL three-neck round bottom flask. In an inert N_2 atmosphere, 7.00 gr (37.0 mmol) of p-TsCl was dissolved in the solution and stirred for 3 hours at room temperature. The reaction was monitored using TLC. After 3 hours the precipitate was seen filtered, and washed with approximately 200 mL of distilled H_2O. The solid was then was extracted twice into the organic phase with approximately 50 mL of DCM. The solvent was evaporated and the product was recrystallized in ethanol. We collected light pink crystals in 83% yield [13]. ^{1}H NMR (400 MHz, DMSO) δ 9.26 (s, 6H), 7.57 (d, J = 7.1 Hz, 1H), 7.31 (d, J = 7.0 Hz, 11H), 6.96 (s, 1H), 3.34 (s, 1H), 2.43 (d, J = 32.4 Hz, 2H), 2.32 (s, 1H), 2.06 (s, 1H), 1.03 (s, 1H).

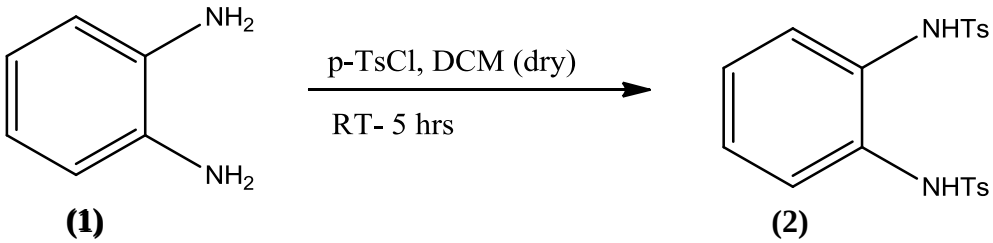


Figure 4.1. Synthesis of *N,N*- ditoulene-psulfonylo-phenylenediamine.

4.3.2. Synthesis of 1,2--dinitro- *N,N*-ditoulene-psulfonylamide

The nitration reaction was done according to literature procedure [16]. Two equivalents of nitric acid (13.92 mmol, 2 mL) were added drop wise to (2) (2.75 g, 6.96 mmol) and glacial acetic acid (25 mL) in a 50 mL 3-neck round bottom flask. The mixture was left to reflux for approximately 24 hours at 70°C. White precipitate was observed after 28 hours which was then filtered and washed with 5 mL of acetic acid. The product was recrystallized from ethanol to produce a 45% yield. ^{1}H NMR (400 MHz, acetone) δ 9.37 – 9.32 (m, 1H), 7.92 – 7.31 (m, 1H), 3.59 – 2.39 (m, 2H), 2.55 – 2.39 (m, 1H), 2.50 – 2.35 (m, 6H), 2.29 – 1.76 (m, 7H), 1.94 (d, J = 11.6 Hz, 1H).

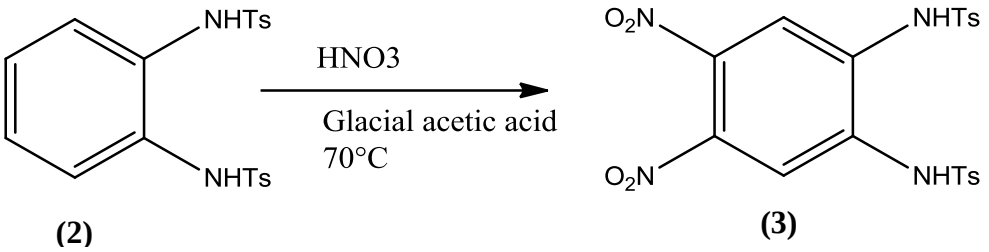


Figure 4.2. Synthesis of 1,2--dinitro- N,N-ditoulene-psulfonylamide.

4.3.3. Synthesis of 1,2--diamine- *N,N*-ditoulene-psulfonylamide

The reduction was done according to literature procedure [28]. A suspension of .05 gr (0.196 mmol) of (3), 0.0244 mL (0.393 mmol) hydrazine and Zinc dust (0.026 gr, 0.393 mmol) were stirred in approximately 3.0 mL of methanol under an inert N_2 atmosphere and left overnight in an ice bath. After TLC showed starting material still present, 0.05 mL of surplus hydrazine was added to mixture and left to stir for another 24 hours. After completion of the reaction, mixture was filtered through celite and evaporated to a minimum. The product was than extracted with chloroform and a 1M HCl solution. The product was then re-extracted with 40% NaOH solution and evaporated to leave dark red oil.

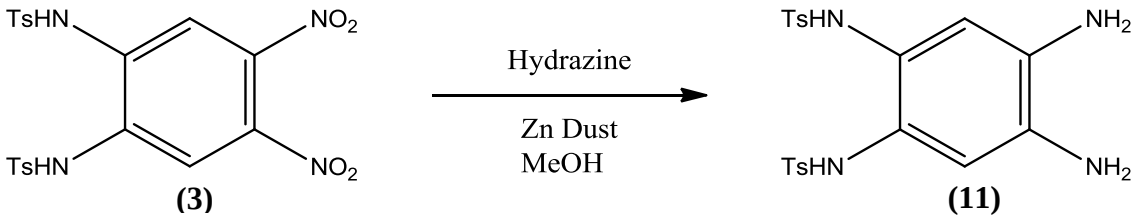
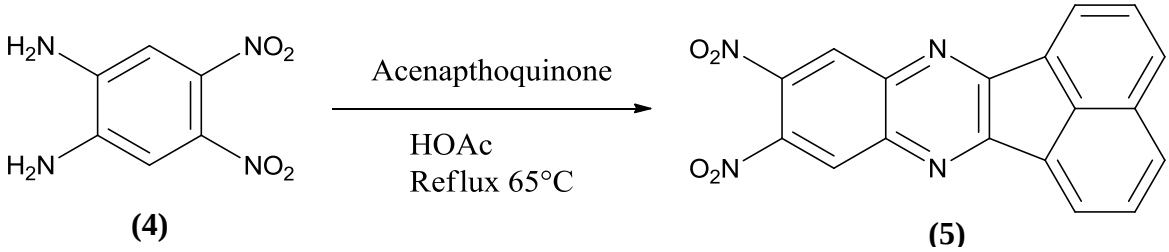


Figure 4.3. Synthesis of 1,2--diamine- *N,N*-ditoulene-psulfonylamide.

4.3.4. Coupling of 4,5- dinitro-1,2-diaminobenzene with acenaphthaquinone

A mixture of one to one equivalents of (4) (0.200 g, 2.02 mmol) with acenapthoquinone (0.184 g, 1.02 mmol) were added to approximately 6 mL of acetic acid and refluxed overnight at 110º C. The mixture turned dark brown and a dark precipitate

was observed in solution. TLC analysis showed formation of a new product **(16)**, which was then extracted in ethyl acetate. After evaporation, recrystallization was done via ethanol to produce a brown precipitate that was filtered with water and vacuumed dried overnight.

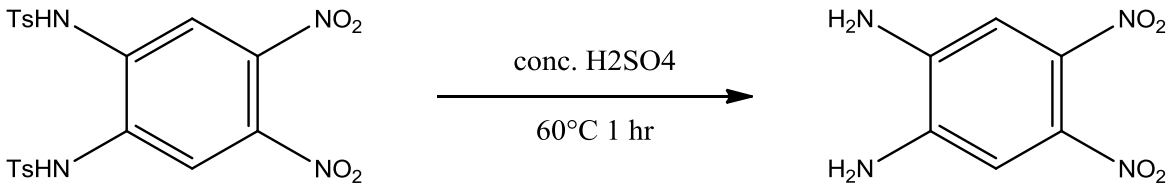


(4) **(5)**

Figure 4.4. Synthesis of 9, 10-dinitroacenaphtho [1,2-b]quinoxaline.

4.3.5. Deprotection of 2,3- ditoulene- 4,5- dinitro-psulfonylo-phenylenediamine

The deprotection reaction was done according to literature procedure [13]. One equivalent of **(3)** (2.0021 g, 3.95 mmol) was added to 25 mL of concentrated sulphuric acid and refluxed for approx. one hour. Solution turned from yellow to black and TLC analysis showed formation of a new product. The solutions were neutralized with 50 mL of cold H_2O and again with a cold 50% NaOH solution added drop wise until precipitate was seen (around PH 6). When no precipitate was observed, the solution was saturated with sodium chloride and extracted with ethyl acetate. Sensitivity of aromatic amines caused difficulty in extraction step from solution and produced very low yield.

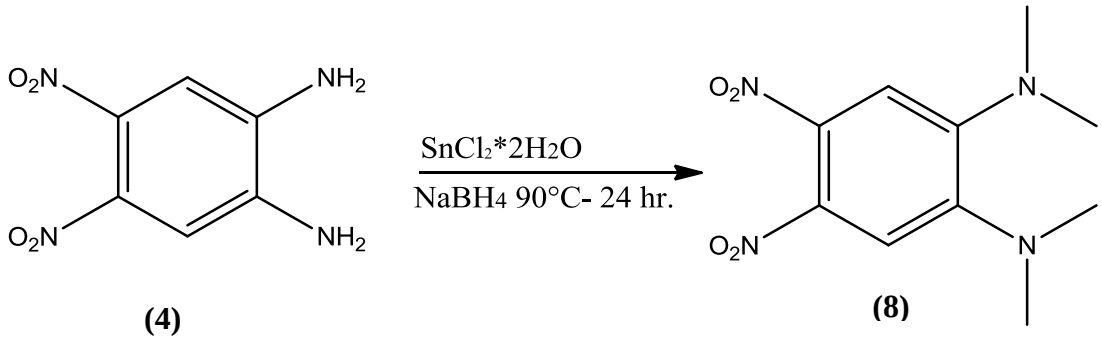


(3) **(4)**

Figure 4.5. Deprotection of 2,3- ditoulene- 4, 5- dinitro psulfonylo phenyenediamine.

4.3.6. Synthesis of 1,2-dinitro-4,5-dimethylaminobenzene

The methylation reaction was done according to literature procedure [17]. To a 25-mL 2-neck round bottom flask was added 0.477 gr (1.88 mmol) of 1,2-dintiro-4,4-diaminobenzene dissolved in 20 mL of absolute ethanol and 2.11 gr (9.38 mmol) of $SnCl_2$.*$2H_2O$. Under an inert N_2 atmosphere, 0.398 gr (3.75 mmol) of $NaBH_4$ is then added to the solution and is refluxed for approximately 6 hours at 90°C. After completion of the reaction monitored by TLC, the reaction is cooled to room temperature and evaporated. The concentrate is dissolved in H_2O and made alkaline with 40% NaOH. The product is then extracted into the organic phase with ethyl acetate three times, dried over Na_2SO_4 and evaporated to a minimum. The product is then recrystallized with ethanol to produce an 86.4% yield. ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (s, 1H), 4.84 (s, 1H), 3.31 (dt, J = 3.2, 1.6 Hz, 36H), 2.89 (s, 6H), 0.86 (s, 2H).



(4) **(8)**

Figure 4.6. Synthesis of 1,2-dinitro-4,5-dimethylaminobenzene.

4.3.7. Synthesis of N^9, N^9,N^{10}, N^{10}-tetramethylacenaphtho[1,2-b]quinoxaline-9,10-diamine

The methylation reaction was done according to literature procedure [6]. Under an inert atmosphere, to a 2-neck round bottom flask was added 20 mg (0.0561 mmol) of (6), 0.017 gr (0.2805 mmol) of paraformaldehyde, and 1 mL (16.7 mmol) glacial acetic acid. The addition of 0.01762 g (0.2805 mmol) of sodium cyanoborohydride was added portion wise and the mixture was stirred overnight to produce a dark red solution. The mixture was filtered and the filtrate was evaporated. After, a 1:1 ethyl acetate and water mixture were

used for extraction. The product was extracted twice and dried with sodium sulfate. After evaporation, a dark red oil was observed. The sample was purified using analytical chromatography to yield 34%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 7.0 Hz, 4H), 7.96 (d, J = 8.3 Hz, 4H), 7.73 (dd, J = 8.2, 7.0 Hz, 4H), 7.46 (s, 4H), 7.22 – 7.16 (m, 8H), 6.93 (s, 1H), 5.28 (s, 1H), 3.09 (s, 1H), 2.93 (s, 22H), 2.23 – 2.06 (m, 3H), 1.97 – 1.92 (m, 2H), 1.71 – 1.63 (m, 2H), 1.71 – 1.32 (m, 25H), 1.71 – 1.09 (m, 58H), 0.80 (d, J = 7.2 Hz, 15H), -0.00 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.53 (s), 138.40 (s), 132.82 (s), 129.89 (s), 129.89 (s), 128.53 (d, *J* = 6.6 Hz), 128.53 (d, *J* = 6.6 Hz), 188.96 – 77.41 (m), 120.85 (s), 115.05 (s), 234.89 – 76.88 (m), 76.66 (s), 41.49 (s), 29.50 (d, *J* = 38.1 Hz).

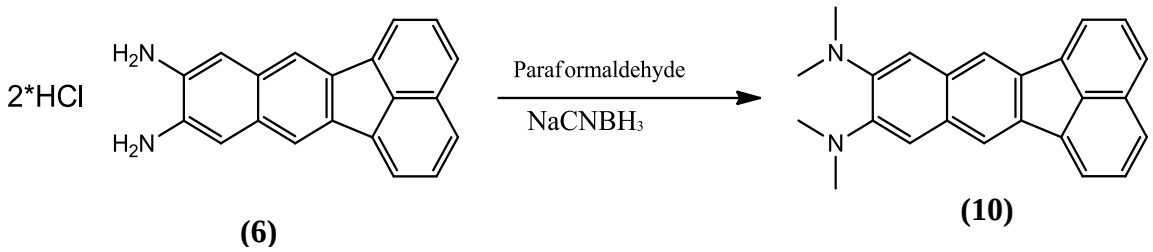
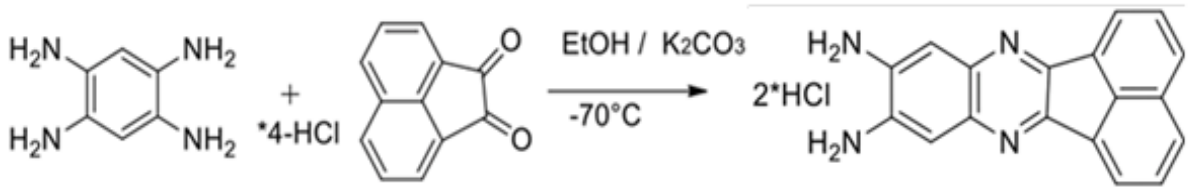


Figure 4.7. Methylation of acenaphtho[1,2-b]quinoxaline-9,10-diamine dihydrochloride.

4.3.8. Synthesis of acenaphtho[1,2-b]quinoxaline-9,10-diamine

The coupling reaction was done according to literature procedure [36]. To a 2-neck 50 ml bottleneck flask was added 1.00 gr (3.52 mmol) 1,2,4,5-benzenetetramine hydrochloride and 0.641 gr (3.52 mmol) acetanapthoquinone under an inert N_2 atmosphere. After the addition of all starting materials, 1.00 gram (7.04 mmol) of K_2CO_3 in a 1:10 ml water to ethanol ratio mixture were added into the mixture by syringe. The solution was left overnight to ensure all of starting material was consumed. A brown-yellow precipitate is seen in solution and is filtered and washed with approximately 30 mL of ethanol. The filtrate is then evaporated to a 5 mL minimum. A brown- red solid is seen to precipitate by drop wise addition of water that is collected by filtration and vacuum dried overnight to produce a yellow film solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.22 (m, 1H), 8.16 – 7.92 (m, 1H), 7.85 – 7.65 (m, 1H), 7.39 (s, 1H), 7.25 (s, 17 H), 2.10 (s, 1H), 1.49 (d, J = 41.5 Hz, 39H), 1.37 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.89 – 134.67 (m), 130.54

(s), 133.49 – 127.27 (m), 143.17 – 113.96 (m), 113.96 – 109.71 (m), 112.86 – 105.46 (m), 90.00 (dd, J = 2598.1, 2586.4 Hz), 76.67 (s), 63.68 (s), 29.68 (s).



(9) **(6)**

Figure 4.8. Synthesis of acenaphtho[1,2-b]quinoxaline-9,10-diamine dihydrochloride.

5. FUTURE WORK

As future work, the coordination of the synthesized ligands with Pt(II) and other redox active metal centers are intended and its photophysical and fluorescent properties investigated. Functionalized quinoxalines have been known to act as DNA cleaving agents and their activity against various transplantable tumors [7] are well acknowledged. Though quinoxalines are also known for their applications in dye. There are many examples in literature concerning their antineoplastic activity. For example, bisquinoxaline derivatives were synthesized by Isikdag and colleagues and screened for their anticancer activity on HT-29 (colon carcinoma) and MCF-7(breast carcinoma) cell lines. Some of the synthesized compounds showed significant cytotoxicity and DNA synthesis inhibition on MCF-7 cell line 2-(4-(7-chloroquinoxalin-2-yl)-phenoxy] propionic acid (XK469) and chloroquinoxalinesulfonamide (CQS), known to have antineoplastic quinoxaline topoisomerase II inhibitors (Scheme 1) [7].

The ligands will be investigated by cyclic voltammetry to better understand the electrochemical properties that it may possess.

6. CONCLUSION

In this study, a specific quinoxaline platform with diamine and dimethyl amine functional groups were synthesized and characterized using ^{1}H-NMR and ^{13}C-NMR spectroscopy. There were two potential synthetic routes to attain the desired aromatic ligand for coordination with redox active metal centers. The first approach involved the use of protected and functionalized aromatic phenylenediamine groups with substituent nitro groups added before condensation with a quinone (Mannich Condensation) to produce the desired substituted quinoxaline. This route, though seemingly secure in its method, required multiple step synthesis, proved difficult to isolate. In fact, we experienced similar difficulties when isolating all phenylenediamine derivatives once they were deprotected. They exhibited severe air sensitivity. The second method involved the reaction of 1,2,4,5- benzenetetramine hydrochloride and the acenapthoquinone diketone directly in an ethanol and water with stoichiometric amount of potassium carbonate. This synthetic route was more favorable due to its minimal 2-step reaction sequence, and diminished appearance of further side products though it proved more difficult to purify. Due to its highly aromatic π-conjugated *N*-heterocyclic backbone and sensitive functional groups on the framework of the ligand, it was proven difficult to purify this material using any method other than thin layer chromatography, which only gave the pure compound in low yield.

In conclusion, we have synthesized a potential ligand that is likely to have redox active character when coordinated with a non-specific *d*-block transition metal. The synthesis of extended π-conjugated systems has been the key to produce a ligand that exhibits this type of electronic behavior. Our compound has the potential to possess redox active character due to its ability to store a transition metals high-energy electron in its highly conjugated cyclic framework.

APPENDIX A: SPECTROSCOPY DATA

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

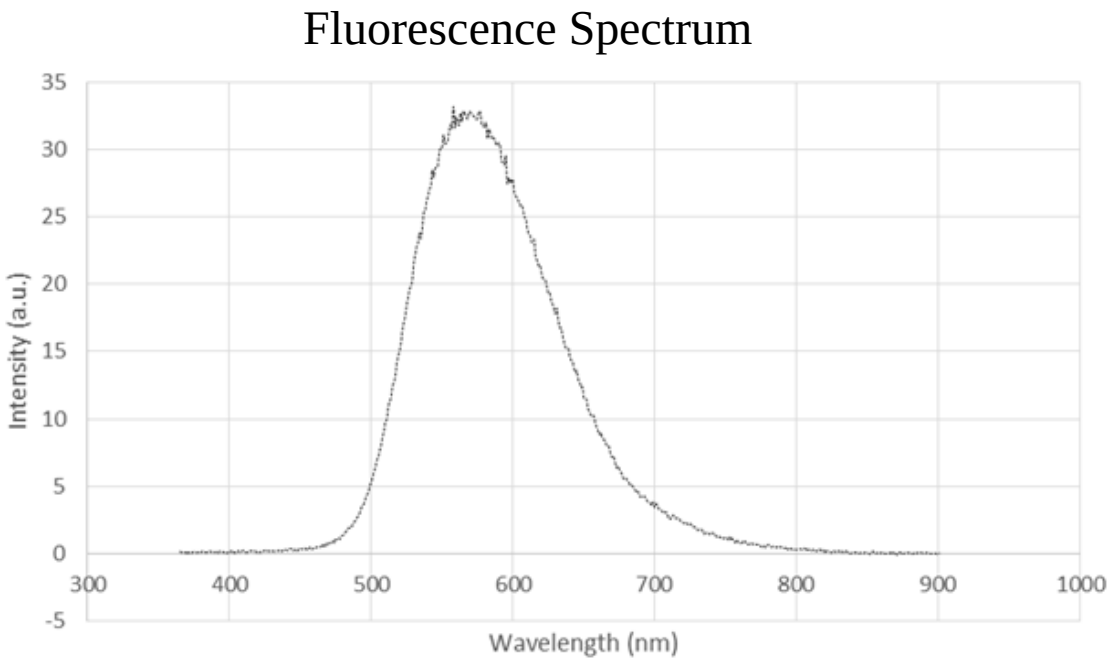


Figure A.1.- Fluorescence spectrum of N^{9},N^{9},N^{10},N^{10}-tetramethylacenaphtho[1,2-b]quinoxaline-9,10-diamine excitation wavelength at 362 nm in EtOH.

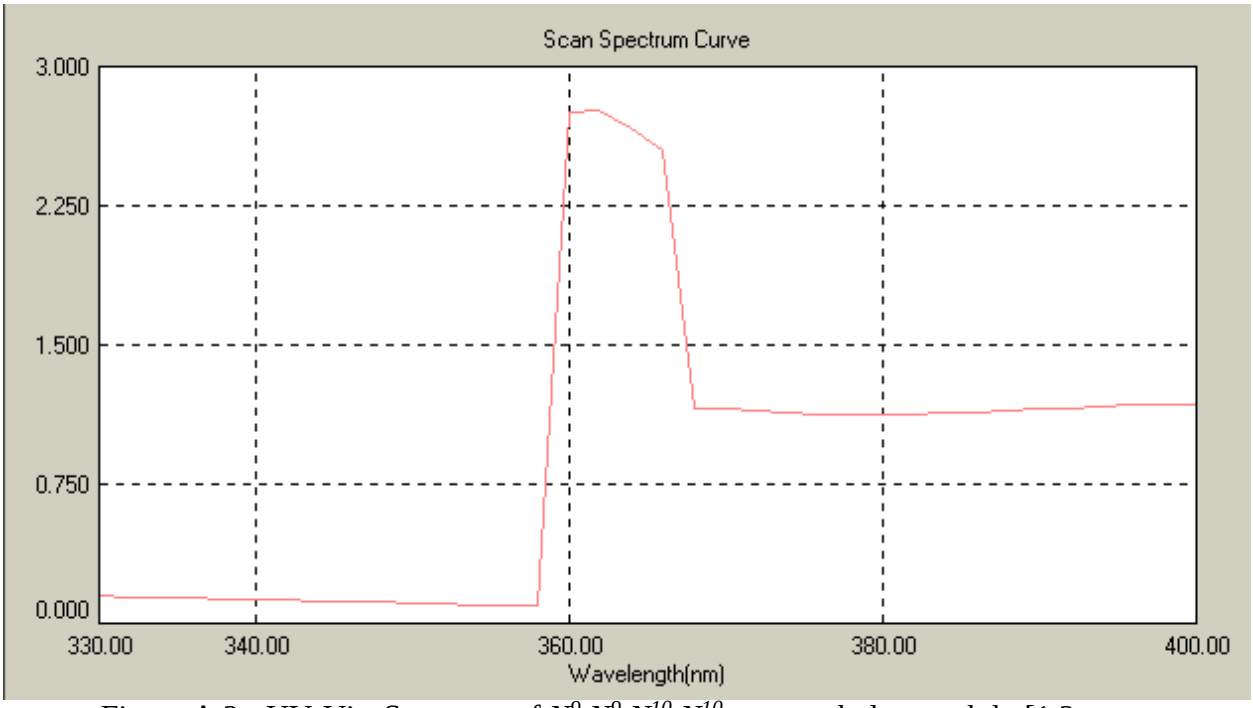


Figure A.2.- UV-Vis. Spectrum of N^9,N^9,N^{10},N^{10}-tetramethylacenaphtho[1,2-b]quinoxaline-9,10-diamine in EtOH.

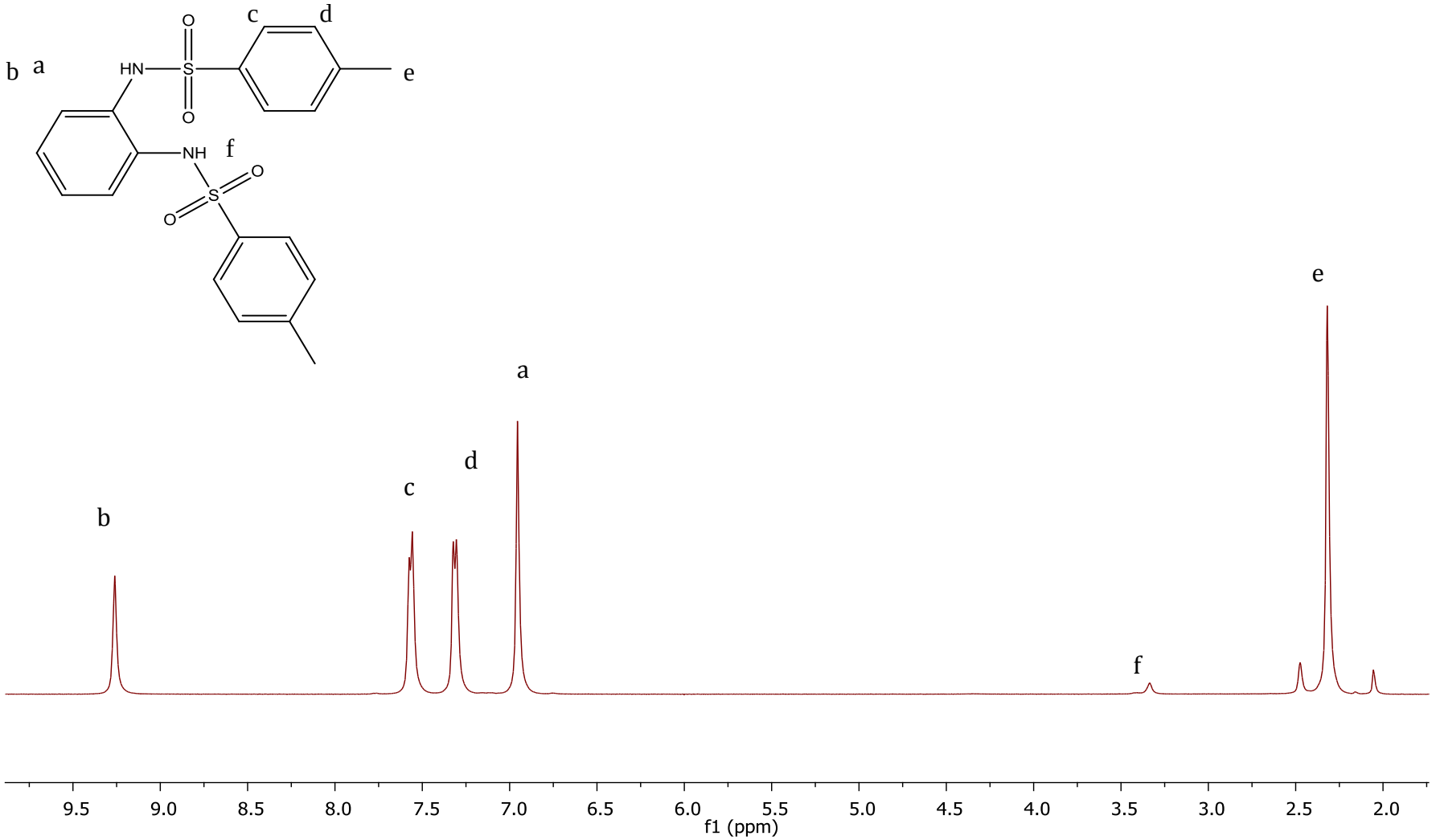


Figure A.3. ^{1}H-NMR spectra of *N,N*- ditoulene-psulfonylo-phenylenediamine in $CDCl_3$.

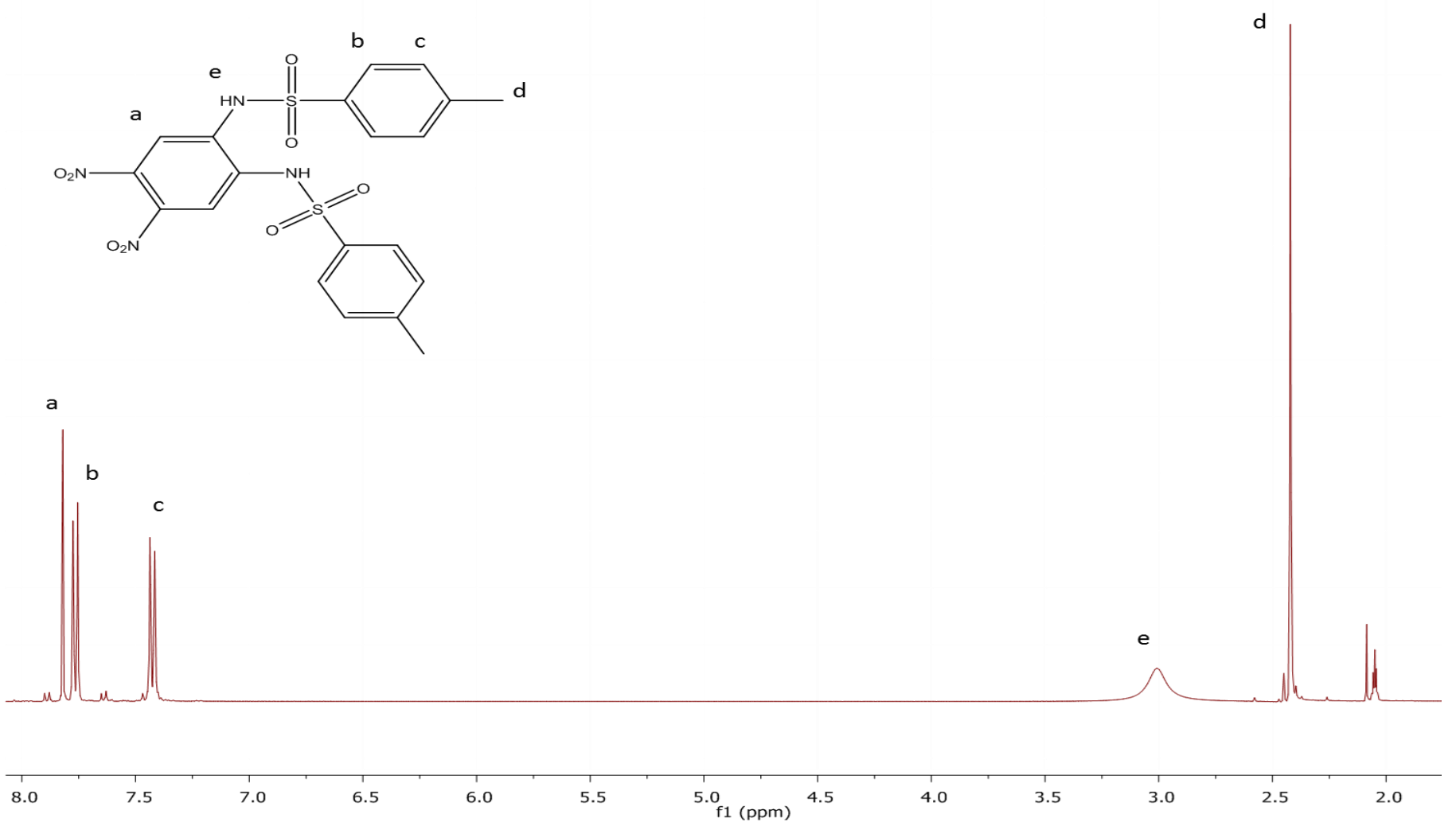


Figure A.4. ^{1}H-NMR spectra of 1,2--dinitro- N,N-ditoulene-psulfonylamide in CD_3OD.

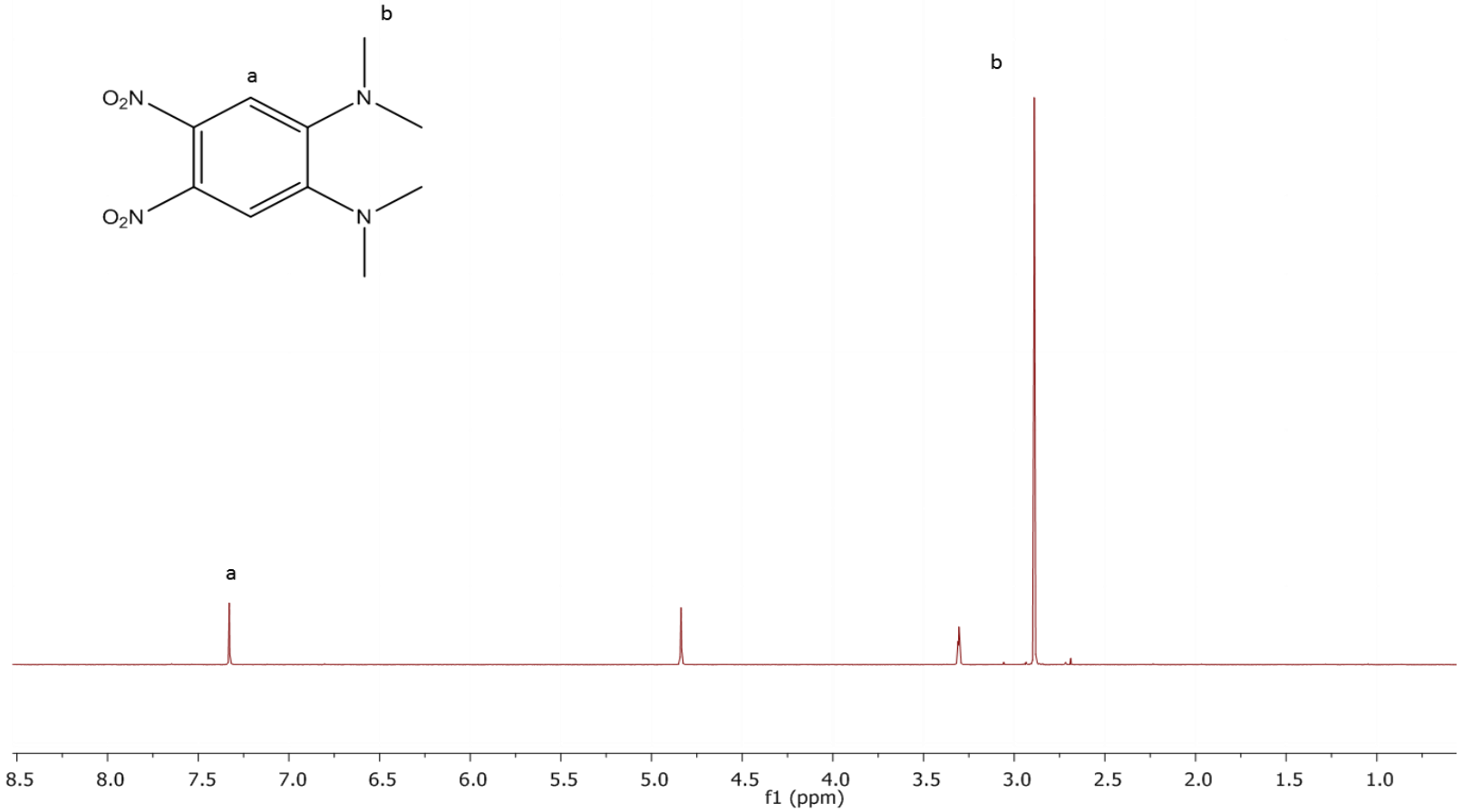


Figure A.5. ^{1}H-NMR spectra of 1,2-dinitro-4,5-dimethylaminobenzene in CD_3OD.

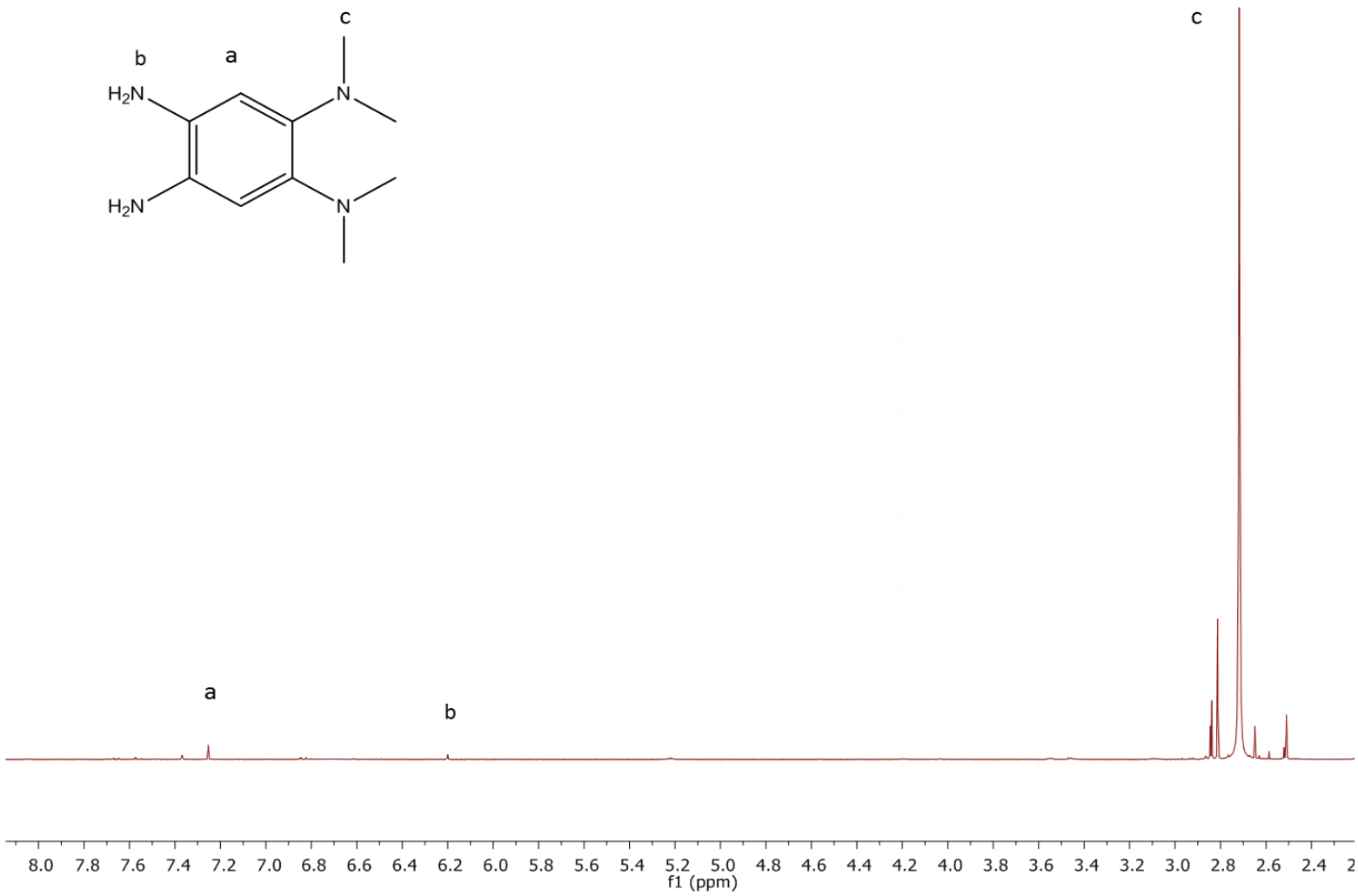


Figure A.6. ^{1}H-NMR spectra of 1,2-diamino-4,5-dimethylaminobenzene in CD_3OD.

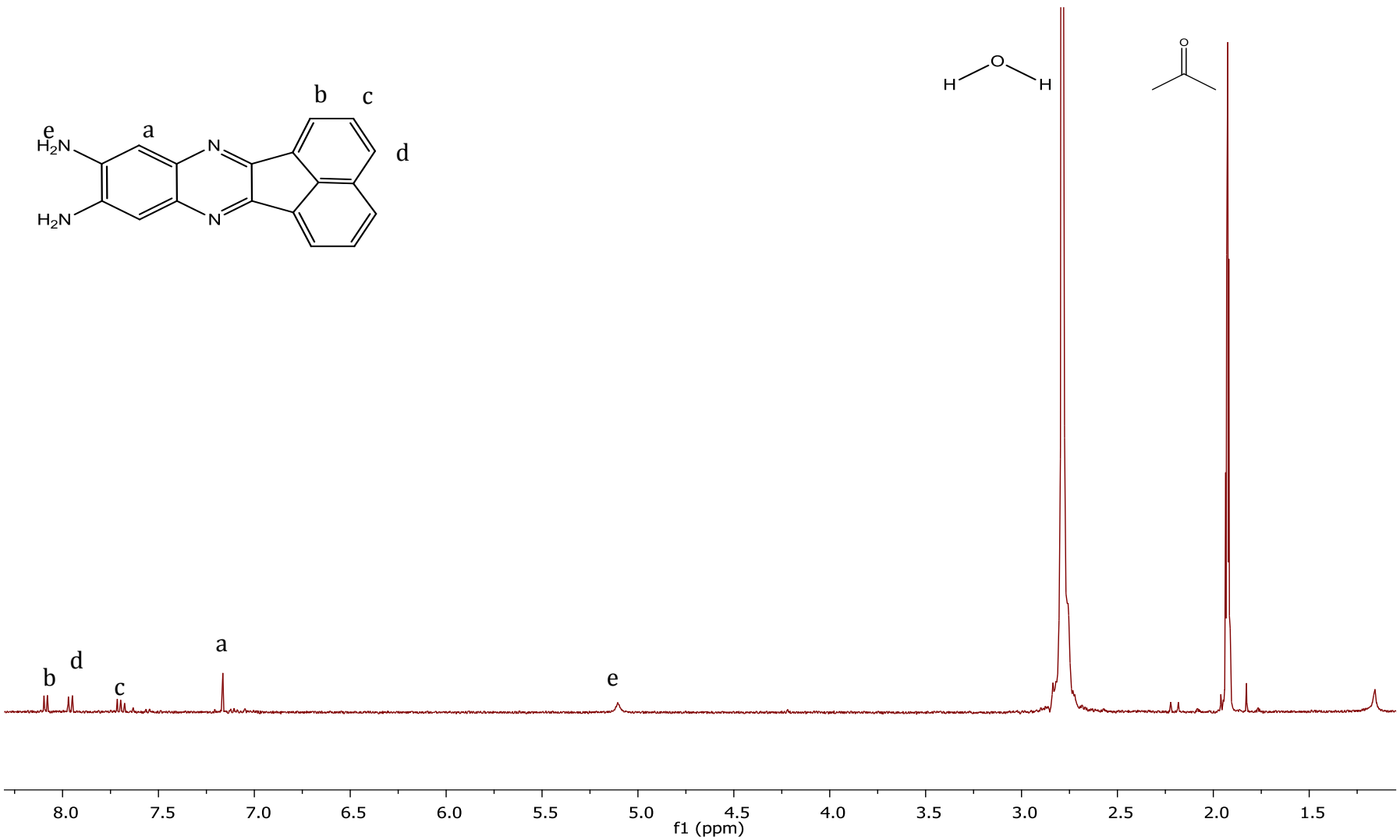


Figure A.7. ^{1}H-NMR spectra of acenaphtho[1,2-b]quinoxaline-9,10-diamine dihydrochloride in $(CD_3)_2CO$.

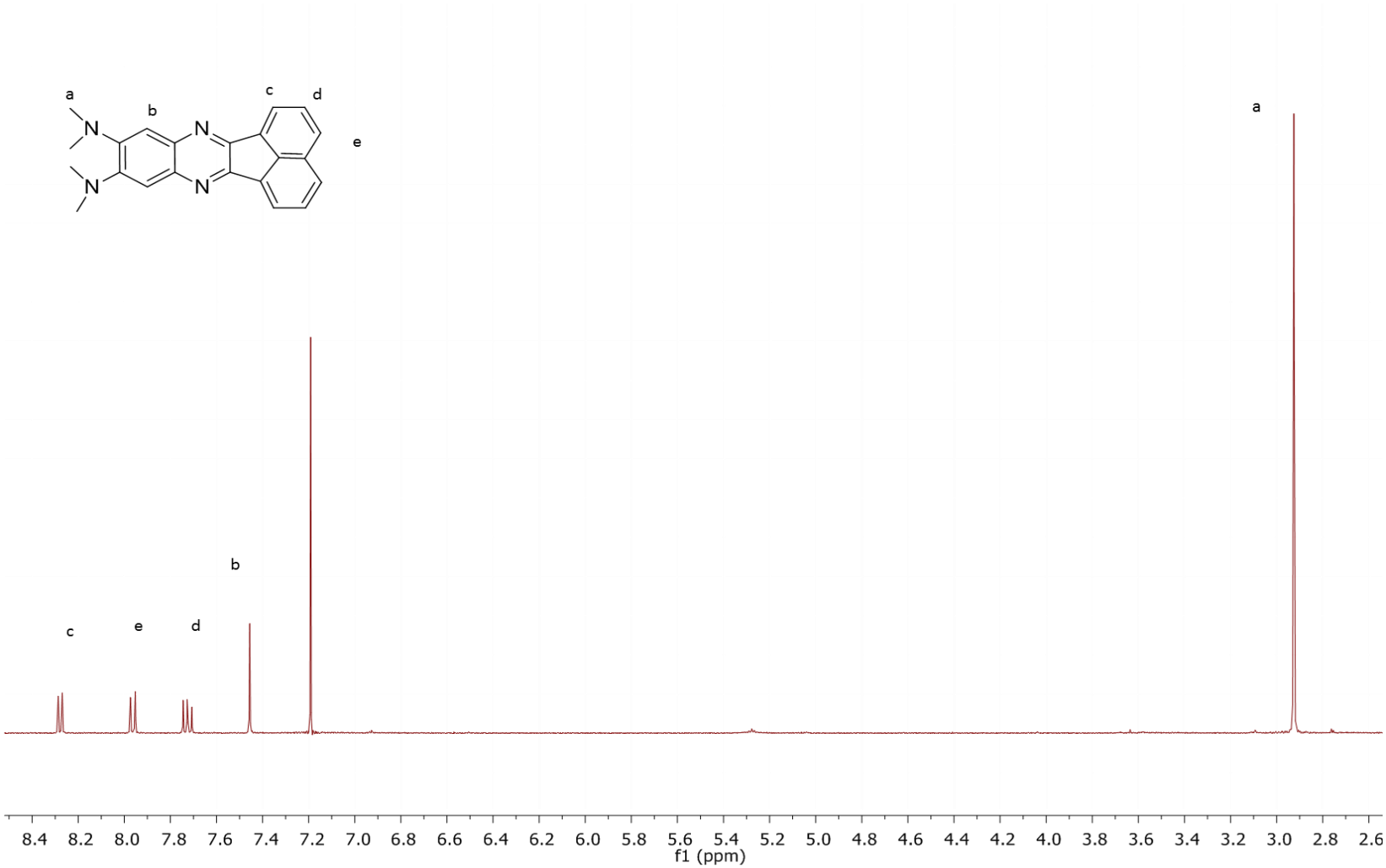


Figure A.8. ^{1}H-NMR spectra of N^{9}, N^{9},N^{10}, N^{10}-tetramethylacenaphtho[1,2-b]quinoxaline-9,10-diamine in $CDCl_3$.

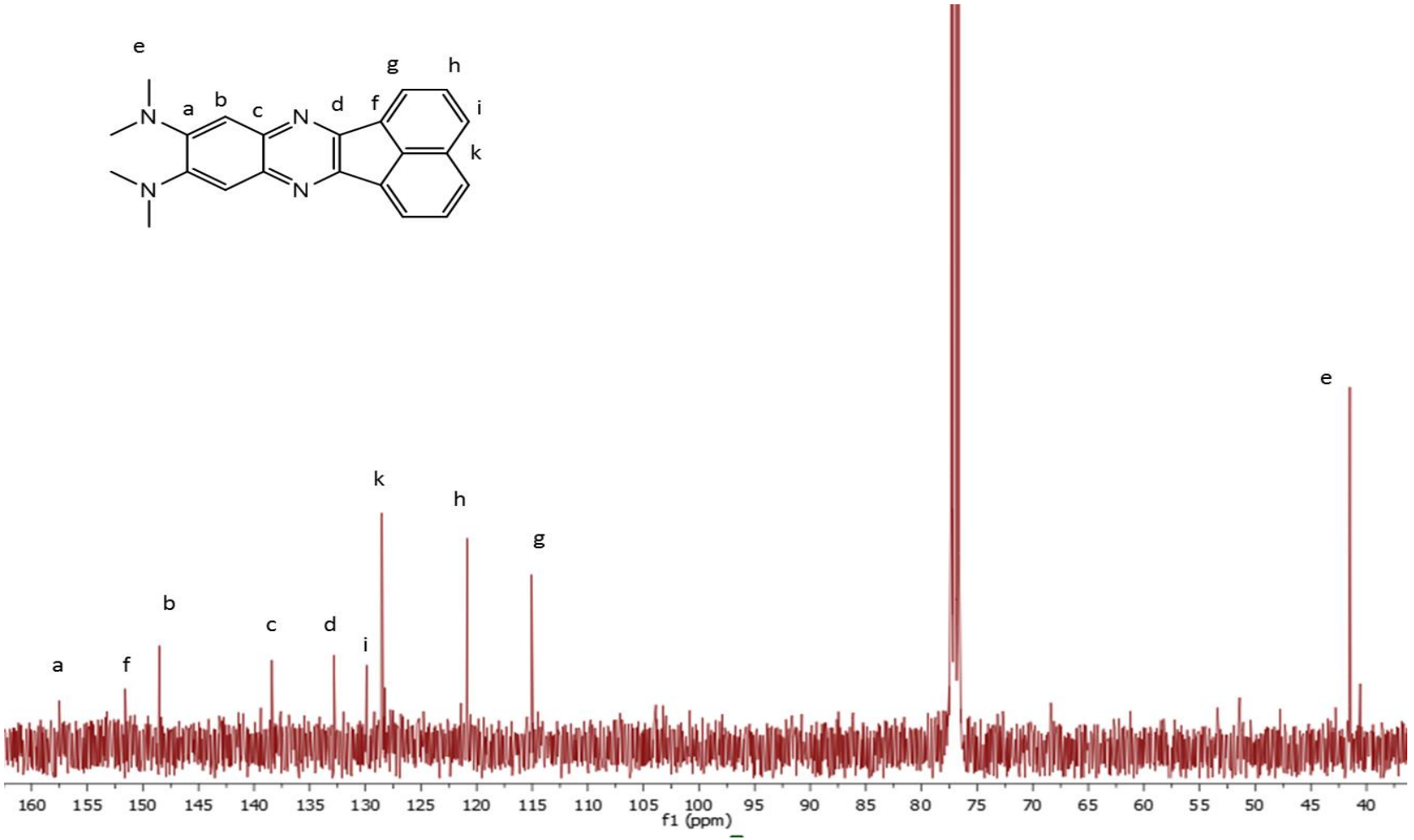


Figure A.9. ^{13}C-NMR spectra of N^9, N^9,N^{10}, N^{10}-tetramethylacenaphtho[1,2-b]quinoxaline-9,10-diamine in $CDCl_3$.

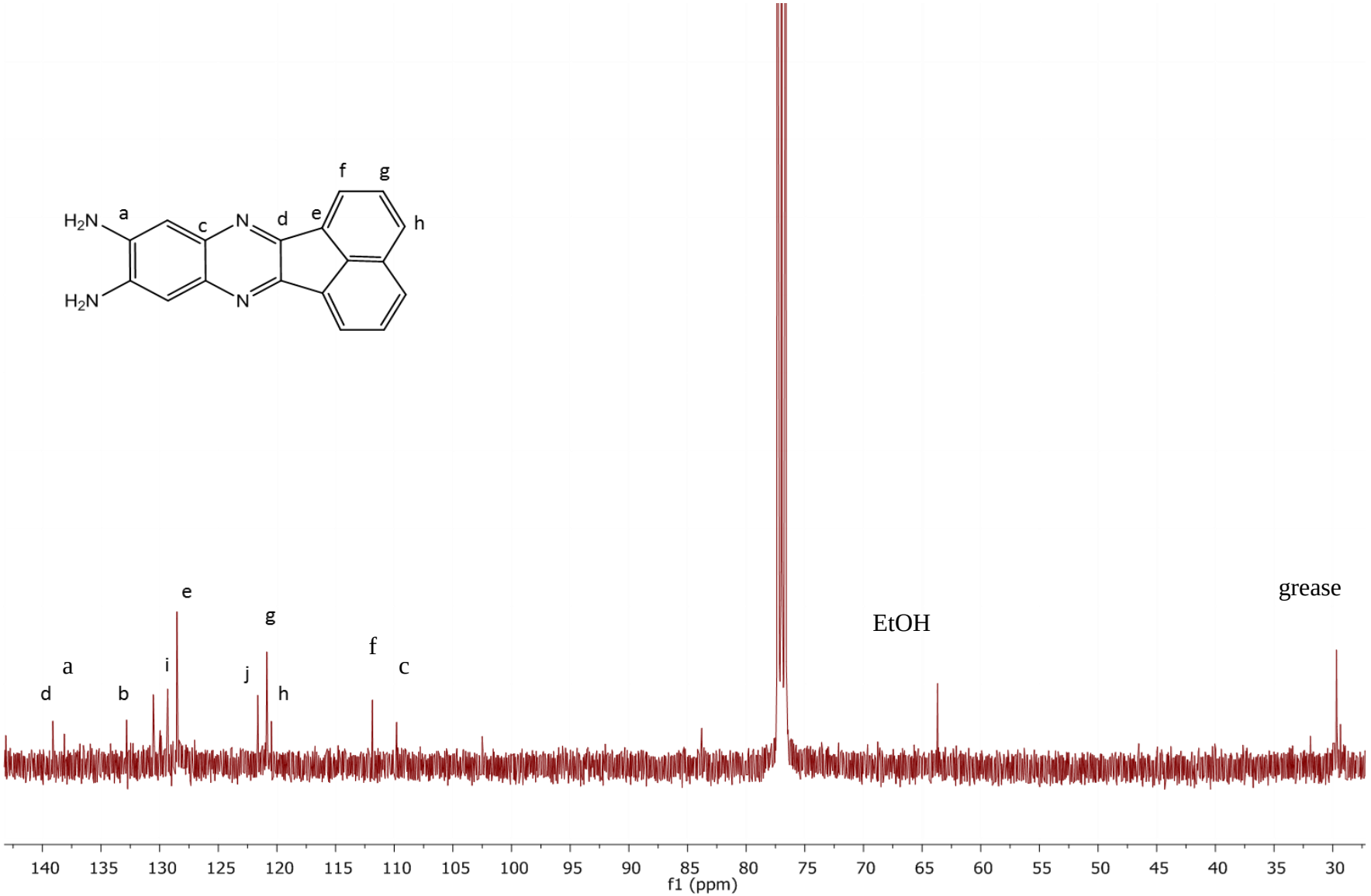


Figure A.10. ^{13}C-NMR spectrum of acenaphtho[1,2-b]quinoxaline-9,10-diamine dihydrochloride in $CDCl_3$.

REFERENCES

1. Al-Hiari, M. Yusuf, R. Abu-Dahab, M. M. El-Abadelah, "Heterocycles [h]-Fused Onto 4-Oxoquinoline-3-Carboxylic Acid, Part VIII [1]. Convenient Synthesis and Antimicrobial Properties of Substituted Hexahydro[1,4]diazepino[2,3-h]quinoline-9-carboxylic Acid and Its Tetrahydroquino[7,8-b]benzodiazepine Analog", *Molecules*, Vol. 13, pp. 2880-893, 2008.

2. Tong, C., J. Chang, J. M. Tan, G. Dai, K. Huang, H. S. O. Chan, C. Chi, "Bisacenaphthopyrazinoquinoxaline Derivatives: Synthesis, Physical Properties and Applications as Semiconductors for N-channel Field Effect Transistors", *Organic & Biomolecular Chemistry*, Vol. 11, pp. 5683, 2013.

3. Patidar, A. K., M. Jeyakandan, A. K. Mobiya, G. Selvam, "ChemInform Abstract: Exploring Potential of Quinoxaline Moiety", *ChemInform*, Vol. 42, pp. 132-134, 2011.

4. Klein, A., T. Scheiring, W. Kaim, "Molecular and Crystal Structure of an Organoplatinum(II) Complex with Dipyrido[3,2-a : 2′,3′-c]phenazine (dppz)", *Zeitschrift für anorganische und allgemeine Chemie*, Vol. 625, pp. 1177-1180, 1999.

5. Eisenberg, R., H. B. Gray, "Noninnocence in Metal Complexes: A Dithiolene Dawn", *Inorganic Chemistry*, Vol. 50, pp. 9741-9751, 2011.

6. Bellefeuille, D. D., M. S. Askari, B. Lassalle-Kaiser, Y. Journaux, A. Aukauloo, M. Orio, F. Thomas, X. Ottenwaelder.,"Reversible Double Oxidation and Protonation of the Non-Innocent Bridge in a Nickel(II) Salophen Complex", *Inorganic Chemistry*, Vol. 51, pp. 12796-2804, 2012.

7. Incesu, Z., I., Y. Ö. Ilhan, G. Akalın, "Anticancer Activity of Some Bisbenzimidazoles", Zeitschrift Für Naturforschung, Vol. 66, pp. 1130-1134, 2014.

8. Kaim, W., "Manifestations of Noninnocent Ligand Behavior", *Inorganic Chemistry*, Vol. 50, pp. 9752-9765, 2011.

9. Refaat, H. M., "ChemInform Abstract: Synthesis and Anticancer Activity of Some Novel 2-Substituted Benzimidazole Derivatives", *ChemInform*, Vol. 41, pp. 6786-6789, 2010.

10. Refaat, H. M., "ChemInform Abstract: Synthesis and Anticancer Activity of Some Novel 2-Substituted Benzimidazole Derivatives", *ChemInform*, Vol. 41, pp. 345-349, 2010.

11. Xie, Y., G. Jiang, J. Yao, G. Lin, H. Huang, X. Wang, Y. Liu, "DNA-binding, Antioxidant Activity, and Bioactivity Studies of Ruthenium (II) Complexes Containing Amino Substituents", *Journal of Coordination Chemistry*, Vol. 66, pp. 2423-2433, 2013.

12. Masui, H., L. F. Assunta, M. C. Zerner, A. B. P. Lever, "Binuclear 1,2,4,5 – Tetraimino - 3,6 - diketocyclohexane Bis[bis(Bipyridine)ruthenium(II)] Redox Series", *Inorganic Chemistry*, Vol. 39, pp. 141-152, 2000.

13. Shao, C., W. Sun, Z. Li, Y. Hu, L. Han, "Ethylene Oligomerization Promoted by Group 8 Metal Complexes Containing 2-(2-pyridyl)quinoxaline Ligands", *Catalysis Communications*, Vol. 3, pp. 405-410, 2002.

14. Barbasiewicz, M., A. Szadkowska, R. Bujok, K. Grela, "Structure and Activity Peculiarities of Ruthenium Quinoline and Quinoxaline Complexes: Novel Metathesis Catalysts", *Organometallics*, Vol. 25, pp. 3599-3604, 2006.

15. Boracic, T., A. Habtemariam, R. J. Deeth, F. P. A. Fabbiani, S. Parsons, P. J. Sadler, "Ruthenium(II) Arene Anticancer Complexes with Redox-Active Diamine Ligands", *Inorganic Chemistry*, Vol. 48, pp. 9444-9453, 2009.

16. Cheeseman, G. W. H. "Quinoxalines and Related Compounds. Part VI. Substitution of 2,3-dihydroxyquinoxaline and Its 1,4-dimethyl Derivative." *J. Chem. Soc. Journal of the Chemical Society, (Resumed)*(1962): 1170

17. Katritzky, A. R., S. Rachwal, and R. Ollmann. "ChemInform Abstract: New Routes to Selectively Methylated Benzimidazoles." *ChemInform*, 26.13 1995.

18. Cantillo, D., M. M. Moghaddam, C. O. Kappe, "ChemInform Abstract: Hydrazine-Mediated Reduction of Nitro and Azide Functionalities Catalyzed by Highly Active and Reusable Magnetic Iron Oxide Nanocrystals", *ChemInform*, Vol. 44, pp. 465-469, 2013.

19. Elshihawy, H., M. Hammad, "Molecular Modeling Studies and Synthesis of Novel Quinoxaline Derivatives with Potential Anti-cancer Activity as Inhibitors of Methionine Synthase", *Medicinal Chemistry Research*, Vol. 22, pp. 3405-3415, 2012.

20. Masui, H., A. L. Freda, M. C. Zerner, A. B. P. Lever, "Binuclear 1,2,4,5-Tetraimino-3,6-diketocyclohexane Bis[bis(Bipyridine)ruthenium(II)] Redox Series", *Inorganic Chemistry*, Vol. 39, pp. 141-152, 2000.

21. Mackeen, L. A., Diperi C., and Schwartz I. "Reductive Methylation of IF-3 and EFTu with [14C]formaldehyde and Sodium Cyanoborohydride." *FEBS Letters*, 101.2 387-90. 1979.

22. Heravi, M. M., "Facile Synthesis of Quinoxaline Derivatives Using O-iodoxybenzoic Acid (IBX) at Room Temperature", *Arkivoc*, Vol. 16, pp.345-349, 2006.

23. Heravi, M. M., M. H. Tehrani, K. Bakhtiari, H. A. Oskooie, "Zn[(l)proline]: A Powerful Catalyst for the Very Fast Synthesis of Quinoxaline Derivatives at Room Temperature", *Catalysis Communications*, Vol. 8, pp. 1341-1344, 2007.

24. Hwang, F., H. Chen, P. Chen, C. Liu, Y. Chi, C. Shu, F. Wu, P. Chou, S. Peng, G. Lee, "Iridium(III) Complexes with Orthometalated Quinoxaline Ligands: Subtle Tuning of Emission to the Saturated Red Color", *Inorganic Chemistry*, Vol. 44, pp. 1344-1353, 2005.

25. Islami, M. R., "One-pot and Efficient Protocol for Synthesis of Quinoxaline Derivatives", Arkivoc, Vol. 15, pp. 280-281, 2008.

26. Jeyakandan, M., A. G. Mobiya, A. Patidar, "ChemInform Abstract: Exploring Potential of Quinoxaline Moiety", *Patidar*, Vol. 45, pp. 123-127, 2015.

27. Kleineweischede, A., J. Mattay, "Synthesis of Amino- and Bis(bromomethyl)-Substitued Bi- and TetradentateN-Heteroaromatic Ligands: Building Blocks for Pyrazino-Functionalized Fullerene Dyads." *European Journal of Organic Chemistry*, Vol. 4, pp. 947-957, 2004.

28. Lauwiner, M., R. Roth, P. Rys, "Reduction of Aromatic Nitro Compounds with Hydrazine Hydrate in the Presence of an Iron Oxide/hydroxide Catalyst. III. The Selective Reduction of Nitro Groups in Aromatic Azo Compounds", *Applied Catalysis A: General*, Vol. 177, pp. 9-14, 1999.

29. Marqués-Gallego, P., M. A. Gamiz-Gonzalez, F. R. Fortea-Pérez, M. Lutz, A. L. Spek, A. Pevec, B. Kozlevčar, J. Reedijk, "Quinoxaline-2-carboxamide as a Carrier Ligand in Two New Platinum(II) Compounds: Synthesis, Crystal Structure, Cytotoxic Activity and DNA Interaction", *Dalton Transactions*, Vol. 39, pp. 5152, 2005.

30. Mokhov, V. M., Y. V. Popov, D. N. Nebykov, "Colloid and Nanosized Catalysts in Organic Synthesis: IX. Hydrogenation of Enamines with Hydrogen at Atmospheric Pressure", *Russian Journal of General Chemistry*, Vol. 84, pp. 2073-2075, 2014.

31. Montana, M., F. Correard, O. Khoumeri, M. Esteve, T. Terme, P. Vanelle, "Synthesis of New Quinoxalines Containing an Oxirane Ring by the TDAE Strategy and in Vitro Evaluation in Neuroblastoma Cell Lines", *Molecules*, Vol. 19, pp. 14987-14998, 2014.

32. Murray, M. J., D. E. Waters, "Ammonium Chloride—Sodium Sulfide Solutions for Organic Nitro Reductions and for Inorganic Qualitative Analysis", *Journal of the American Chemical Society*, Vol. 60, 2818-2819, 1938.

33. Nawn, G., K. M. Waldie, S. R. Oakley, B. D. Peters, D. Mandel, B. O. Patrick, R. Mcdonald, R. G. Hicks, "Redox-Active Bridging Ligands Based on Indigo Diimine ("Nindigo") Derivatives", *Inorganic Chemistry, Journal of Inorganic Chemistry,* Vol. 50, pp. 9826-9837, 2011.

34. Samet, A. V., E. P. Zakharov, V. V. Semenov, A. C. Buchanan, A. A. Gakh, "Synthesis Of 4,6-Dinitroindole From 2,4,6-Trinitrotoluene", *Synthetic Communications*, Vol. 31, pp. 1441-1445, 2001.

35. Warnmark, K., J. A. Thomas, O. Heyke, J. Lehn, "Stereoisomerically Controlled Inorganic Architectures: Synthesis of Enantio- and Diastereo-merically Pure Ruthenium and palladium Molecular Rods from Enantiopure Building Blocks", *Chemical Communications*, Vol. 6, pp. 701, 1996.

36. Xie, Y., G. Jiang, J. Yao, G. Lin, H. Huang, X. Wang, Y. Liu, "DNA-binding, Antioxidant Activity, and Bioactivity Studies of Ruthenium(II) Complexes Containing Amino Substituents", *Journal of Coordination Chemistry*, Vol. 66, pp. 2423-2433, 2013.