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TANDEM AMINATION CATALYSIS IN THE SYNTHESIS OF DIAZAPHENOXAZINE COMPOUNDS OF PHARMACEUTICAL INTEREST

BY

EGBO PEACE IFEYINWA
PG/M.Sc/10/57069

DEPARTMENT OF PURE AND INDUSTRIAL CHEMISTRY
UNIVERSITY OF NIGERIA, NSUKKA

JUNE, 2013
TITLE PAGE

UNIVERSITY OF NIGERIA, NSUKKA
FACULTY OF PHYSICAL SCIENCES
DEPARTMENT OF PURE AND INDUSTRIAL CHEMISTRY

CHM 592, RESEARCH (PROJECT)
TANDEM AMINATION CATALYSIS IN THE SYNTHESIS OF
DIAZAPHENOXAZINE COMPOUNDS OF PHARMACEUTICAL INTEREST

A RESEARCH PROJECT SUBMITTED IN PARTIAL FULFILMENT OF THE
REQUIREMENTS FOR THE AWARD OF MASTER OF SCIENCE (M.Sc) DEGREE IN
ORGANIC CHEMISTRY

BY
EGBO PEACE IFEYINWA
PG/M.Sc/10/57069

PROJECT SUPERVISOR: PROF. U.C. OKORO
This work has been approved by the Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka.

______________________     ____________________
PROF. U.C. OKORO          PROF. P.O. UKOHA
Project Supervisor       Head of Department

Date:__________________     Date:________________

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EXTERNAL EXAMINER

Date:_____________________
CERTIFICATION

This is to certify that the research work titled “Tandem amination catalysis in the synthesis of diazaphenoxazine compounds of pharmaceutical interest” was carried out by EGOBO PEACE IFEYINWA (PG/M.Sc/10/57069) and has been approved by the undersigned of the Department of Pure and Industrial Chemistry University of Nigeria, Nsukka, submitted in partial fulfillment of the requirements for the award of M.Sc in organic chemistry.

_______________________    ____________________
PROF. U.C. OKORO     PROF. P.U. UKOHA
Project Supervisor      Head of Department

Date:________________    Date:________________
DEDICATION

Dedicated to God Almighty.
ACKNOWLEDGEMENT

The adventure into a work of this nature could not have been done in isolation and was by no means an easy one. I shall ever remain grateful to Almighty God for making it possible for me to achieve this educational height in academics. I lack appropriate words to express my profound gratitude to my supervisor Prof. U.C. Okoro for his encouragements, support, patience and fatherly advice.

I shall remain grateful to all the authors and publishers of the various textbooks, journals articles and reports cited in this work. My indebtedness is innumerable for their contributions.

I appreciate in a very special way these colleagues of mine: Ali Florence U, EdokaObianuju, OjarikreEnoo. Thanks for the cooperation and the time we spent together.

I thank all the members of my family, friends and well wishers especially my big cousin, Mr. Nwachukwu Job Osita, for his non-stop encouragement and support both morally, financially and otherwise. To my dear husband KC, I say thanks for understanding me and being there for me.

Egbo Peace Ifeyinwa

June, 2013
ABSTRACT

The synthesis and characterization of five new linear diazaphenoxazine compounds is reported. The key intermediate, 3-chloro-1,9-diazaphenoxazine, was prepared via a base catalyzed reaction of 2-amino-3-hydroxypyridine with 2,3,5-trichloropyridine in aqueous 1, 4-dioxane.

Five 3-amino derivatives of the key intermediate were prepared via Buchwald – Hartwigamination coupling reaction between 3-chloro-1,9-diazaphenoxazine and various heterocyclic amines, under the catalytic influence of palladium acetate.

The assignment of structures to the synthesized compounds was done by the use of combined information from Uv-vis, IR, and NMR spectra.
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CHAPTER ONE

1.0 INTRODUCTION

Phenoxazine(1) is a compound analogous in structure to phenothiazine(2) with oxygen in place of sulphur. Its other systematic names are 10H-phenoxazine and 2,2,5,6-dibenzo-1,4-oxazine\(^1\). They are tricyclic nitrogen-oxygen heterocycles\(^2\).

Owing to the wide range of application of phenoxazine compounds, the synthesis of their derivatives and isolation of the natural phenoxazines have been a subject of great interest over the years\(^3\). Phenoxazine compounds have a wide range of applications, particularly as drugs and dyes.

The naturally occurring phenoxazine derivatives have been classified as Ommochromes, fungal metabolites, Questionycins and Actinomycins\(^4\).

Phenoxazines are generally grouped into linear phenoxazines and angular phenoxazines. The linear phenoxazine, as the name implies, has a linear arrangement of rings like compounds 3 and 4 below.
Angular phenoxazines have their skeleton extended by adding fused benzene rings to a, c, h or j faces such as compounds 5, 6, 7, and 8 below.

There are still other structural arrangements with additional annular nitrogen atom(s). Where additional one, two or three nitrogen atom(s) are added, they are known as monoaza, diaza or triaza analogues respectively. Examples are below;
TANDEM CATALYSIS

Tandem catalysis is the application of transition metal complexes as catalyst. Tandem catalysis has led to the development of simple and efficient methods of carbon-carbon and carbon-heteroatom bond formation\(^5\). Transition metal catalysed reactions have been used extensively in both ring synthesis and functionalisation of heterocycles\(^6\). As well as completely new modes of reactivity, variants of older synthetic methods have been developed using the milder and more selective processes that involve the use of transition metal catalysts\(^7\).

Although there are many processes catalyzed by a range of transition metals, palladium-catalyzed processes vastly outnumber the others such as Ni, Rh, Cu, Fe.\(^8\)

The rate, yield and scope of palladium-catalyzed cross-coupling reactions are influenced by both the reaction parameters and the choice of ligands, allowing for a wide substrate scope through judicious choice of these parameters\(^8\).
1.1 BACKGROUND OF STUDY

The naturally occurring phenoxazine derivatives are numerous\(^9\). The *Ommochromes* such as *xanthommatin*\(^9\) are acidic pigments found in different arthropods and are responsible for the colouration in the wings, cuticle and eyes of insects\(^10\).

\[
\text{HOOC-CHCH}_2\text{C}=\text{O} \quad \text{OH} \quad \text{COOH}
\]

\[
\text{NH}_2 \quad \text{N} \quad \text{O} \quad \text{9} \quad \text{N} \quad \text{O}
\]

Some fungal metabolites derived from phenoxazine ring have been isolated from various wood-rotting fungi and from moulds. The colouration in these organisms has been attributed to these phenoxazine derivatives of type \(\text{10}^{11-13}\).
With the exception of the *actinomycin* antibiotics which have antibacterial and anti-tumor activities, these naturally occurring phenoxazines are not particularly useful compounds.

Interest in the naturally occurring phenoxazines has declined considerably giving way to a systematic synthesis of phenoxazine analogs modeled after the biologically active azaphenothiazines\textsuperscript{14}.

Following reports on the pharmacological activities of phenoxazine, attention was diverted from their dyeing properties to a study of their biological activities.\textsuperscript{15-17}

From tests carried out in laboratory animals and in man, it was found that many phenoxazine derivatives showed pronounced pharmacological activities as CNS depressants\textsuperscript{18}, sedatives\textsuperscript{19}, antiepileptics\textsuperscript{20}, tranquilizers\textsuperscript{21}, antituberculosis\textsuperscript{22}, antitumour\textsuperscript{23}, antibacterial\textsuperscript{24}, spasmolytic\textsuperscript{25}, anthelminthic\textsuperscript{26} and parasiticidal agents\textsuperscript{27}.

### 1.2 STATEMENT OF THE PROBLEM

It was interest to ascertain if tandem catalysis procedures could be extended to C-substituted side chain derivatives of diazaphenoxazine. The extension would validate the generality of optimized tandem molecular amination protocols in terms of substrate scope.

To the best of our knowledge, there is practically no report of the synthesis of side chain amino derivatives of diazaphenoxazine through tandem catalysis. Thus,
a concise application of tandem methodologies would allow access to five hitherto unknown heterocyclic scaffolds of the diazaphenoxazine type shown below.

![Chemical structures](attachment:image.png)

**1.3 OBJECTIVES OF THE STUDY**

The specific objectives of this study were to:

(i) Synthesize the key intermediate, 3-chloro-1,9-diazaphenoxazine.

(ii) Prepare single crystals of this intermediate for X-ray analysis.

(iii) Transform 3-chloro-1,9-diazaphenoxazine to various 3-substituted aminoheterocyclic derivatives via Buchwald–Hartwig tandem amination protocol.

(iv) Characterize the new derivatives using spectroscopic techniques.
1.4 JUSTIFICATION OF THE STUDY

Among the motivations to carry out the research work is the wide range of application of phenoxazine derivatives\textsuperscript{18-27} and the need to synthesize new derivatives which may have better and desirable properties.
2.0 LITERATURE REVIEW

2.1 TANDEM AMINATION AND AMIDATION

Aryl amination was first discovered by Ullman when he reported ipso-substitution of aryl halides mediated by copper in 1901\textsuperscript{28}.

\[
\begin{array}{c}
\text{Ar-X} + \text{HNR}_2 \\
\text{CuX} \\
\text{Ar-NR}_2
\end{array}
\]

Although the scope of Ullman’s reaction has been expanded to include a tremendous variety of nucleophiles, the original reaction was limited by harsh reaction conditions, stoichiometric metal and poorly defined catalytic species.

Several research groups were involved in early studies of Pd(0)-mediated C-N bond formation. Migita and coworkers in 1983 made the major breakthrough when they reported the first example of a palladium-catalyzed reaction between arylbromides and \(N,N\)-diethylamino-tributyltin.\textsuperscript{29}
Only electron neutral aryl bromides gave products in good yields. Vinyl bromides and aryl bromides containing electron donating and electron withdrawing groups gave products in low yield.

In 1984, Boger and Panek reported an example of Pd(0)-mediated C-N bond formation in the context of their work on the synthesis of Lavendamycin using stoichiometric quantities of palladium(0).

Another early example was realized in Kiev in 1985 by Yagupolskii et al. Polysubstituted activated chloroarenes and anilines underwent a C-N coupling reaction catalyzed by [PdPh₂(PPh₃)₂]I (1mol%) in moderate yield.¹⁰⁵

The palladium(0)-catalyzed amination reaction as known today was developed independently by the groups of Stephen L. Buchwald and John F. Hartwig.

Following the precedent of Migita, Hartwig in 1994, for the first time studied the mechanism of Migita’s reaction.³⁰
Their findings indicated that the d^{10} complex Pd[P(o-Tolyl)_{3}] was the active catalyst (with the corresponding chloride entering the catalytic cycle via in situ reduction), and supported a catalytic cycle involving oxidative addition of the aryl bromide.

A palladium dimer was implicated in the catalytic cycle. This dimer does not exchange aryl in cross over experiments.

Still in 1994, three months after Hartwig’s paper was submitted, the Buchwald group published an extension of the Migita paper offering two major
improvements over the original paper. First, transamination of Bu$_3$SnNEt$_2$ followed by argon purge to remove the volatile diethylamine allowed extension of the methodology to a variety of secondary amines (both cyclic and acyclic) and primary anilines. Secondly, the yield for electron rich and electron poor arenes was improved via minor modifications to the reaction procedure (higher catalyst loading, higher temperature, longer reaction time), although no ortho-substituted aryl groups were included in this publication$^{31}$

Buchwald expanded the scope of the reaction by generating tin amines in situ. Although the use of tin reagents were still required, a large variety of amines were made available through transmetallation. The reaction had a lot of restrictions such as use of only aryl bromides, secondary and primary anilines, o-substitution of aryls was not reported and most reactions run for 24hrs.
In 1995, Buchwald and Hartwig showed that the couplings could be conducted with free amines in the presence of a bulky base (NaOtBu in the Buchwald publication, LiHMDS in the Hartwig publication), allowing for organotin-free coupling. Though these improved conditions proceeded at a faster rate, the substrate scope was limited almost entirely to secondary amines due to competitive hydrodehalogenation of the bromoarenes\textsuperscript{32-33}.

In 1996, Buchwald and Hartwig in back-to-back communications, reported vast improvement in scope and yield by use of bidentate phosphine ligands. The catalyst loadings were typically 0.5 – 1.0 mol\% and reactions were typically faster\textsuperscript{34-35}.
Buchwald proposed that monodentate phosphine ligands were ineffective with aryl iodides because they allowed more stable palladium iodide dimers to form\textsuperscript{36}. It was also discovered that triflates are prone to cleavage to phenols by nucleophilic bases at a rate competitive to reductive elimination\textsuperscript{37}

\[
\begin{align*}
\text{OMe} & \quad \text{I} \quad \text{H}_2\text{NPh} \quad \xrightarrow{(\text{DPPF})\text{PdCl}_2/\text{PhCH}_3, 100^\circ\text{C}} \quad \text{OMe} \quad \text{NPh} \\
\text{Me} & \quad \text{OTf} \quad \text{NH}_2 \quad \xrightarrow{\text{Pd}_4(\text{dba})_2/\text{P(o-tolyd)_3}} \quad \text{MeO} \quad \text{Me}
\end{align*}
\]

\text{<5% yield}

Buchwald also gave a general solution to the challenges in the use of aryl iodides and triflates as substrates\textsuperscript{38} such that the previously unusable iodides and triflates are now excellent substrates. Bulky tri- and di-alkyl phosphine ligands like DPPF and BINAP have been shown to be remarkably active catalysts, allowing the coupling of a wide range of amines (primary, secondary, electron withdrawn, hetecyclic, etc.) with aryl chlorides, bromides, iodides, and triflates.
In 1997, Buchwald developed a nickel based catalyst for the amination of aryl chlorides\(^\text{39}\):

\[
\text{Me} \quad \text{Cl} + \text{Me} \quad \text{Me} \quad \text{H}_2\text{N} \quad \text{Ni(COD)}_2/\text{DPPF} \quad \text{NaOtBu, PhCH}_3, 100^\circ\text{C} \rightarrow \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{H} \quad \text{OMe} \quad 96\% \text{ yield}
\]

\[
\text{Me} \quad \text{Me} \quad \text{Cl} + \text{HexNH}_2 \quad \text{Ni(COD)}_2/\text{DPPF} \quad \text{NaOtBu, PhCH}_3, 100^\circ\text{C} \rightarrow \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Hex} \quad \text{H} \quad \text{65\% yield}
\]

In 1998, a palladium system for the amination of aryl chlorides followed, using a new system of ligands\(^\text{40}\):

\[
\text{Me} \quad \text{Cl} + \text{Bu}_2\text{NH} \quad \text{Pd}_2(\text{dba})_3/\text{L} \quad \text{NaOtBu, PhCH}_3, 80^\circ\text{C} \rightarrow \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{NH}_{\text{Bu}} \quad 95\% \text{ yield}
\]

\[
\text{NC} \quad \text{Cl} + \text{H}_2\text{N} \quad \text{Pd}_2(\text{dba})_3/\text{L} \quad \text{NaOtBu, PhCH}_3, \text{RT} \rightarrow \text{NC} \quad \text{Me} \quad \text{Me} \quad \text{N} \quad \text{O} \quad \text{96\% yield}
\]
Buchwald in 1997 reported that ammonia fails in aryl-amine couplings and as such an alternative have been developed to introduce free amines. The use of a benzophenone imine or silylamide can overcome this limitation, with subsequent hydrolysis furnishing the primary aniline.

Hartwig’s P(t-Bu)$_3$ system which involves coupling with LiHMDS, but does not tolerate ortho substituents.

Buchwald’s system gets around this ortho substituents limitation.
Rogeret al.\textsuperscript{44} reported regioselective tandem metal catalyzed aminations on dihaloquinolines with amino (benzo) (di) azines as shown below:

They achieved C-2 intermolecular Pd-catalyzed amination on 2,3-dibromoquinoline by controlling the reaction temperature.

Mouadet al.\textsuperscript{45} reported rapid access to 3–(N-substituted)–aminoquinolin–2(IH)–ones using palladium catalyzed C–N bond coupling reaction. They synthesized in
good to excellent yield a series of 3–(N-substituted)-aminoquinoline by coupling 3-bromoquinolin-2-(IH)-ones with various nucleophiles including amines, amides, sulfonamides, carbamates and ureas.

In 2008, Buchwald et al.\textsuperscript{46} reported a protocol for forming a highly active Pd(o) catalyst from Pd(OAc)\textsubscript{2}, water and biaryldialkyl phosphine ligands.

They reported that the new protocol allowed lower catalyst loadings, shorter reactions times and exclusion of additives, such as Et\textsubscript{3}B, in coupling of amides with aryl chlorides.
Miyaura et al.\textsuperscript{47} reported the $N$-arylation of primary and secondary aliphatic amines, anilines, and imidazole with novel potassium aryl triolborates in the presence of a reoxidant and a catalytic amount of Cu(OAc)$_2$. They reported that aryl triolborates are better reagents than aryl boronic acid or potassium aryl trifluoroborate as the former achieved high yield under mild conditions.

Although C-N and C-O couplings always come as a title, it is important to note at this point that about 80\% of the covered literature is focused on C-N couplings.\textsuperscript{48} Development of Ar-O bond forming reactions developed along similar lines as did aryl-amine couplings. Substrate scope was initially limited but gradually expanded with ligand improvement.

The amidation reactions were traditionally performed with aryl iodides under Goldberg-modified Ullman cross–coupling conditions using stoichiometric Cu and high reaction temperature\textsuperscript{28,49}. Recent advances in this area have allowed for the reactions of amides and aryl iodides or aryl bromides to be performed using catalytic amounts of Cu under milder condition.\textsuperscript{50-52}
Pd-based catalyst system using phosphine ligands have also been developed which allow for the coupling of amides with aryl sulfonates\textsuperscript{53-54}, aryl bromides and most recently, aryl chlorides.\textsuperscript{56}

A catalyst based on a new biarylphosphine ligand for Pd–catalyzed cross coupling reaction of amides and aryl chlorides was reported by Buchwald et al.\textsuperscript{57}

The first intramolecular examples of coupling reaction of amides and aryl chlorides were only applicable to tertiary or certain secondary alcohols.\textsuperscript{58}

Some intermolecular examples involving electron poor aryl halides\textsuperscript{59-61} are given below:
2.2 LINEAR PHENOXAZINES

The first synthesis of phenoxyazine\textsuperscript{1} was reported in 1887 by Bernthsen\textsuperscript{62} soon after his work on phenothiazine\textsuperscript{63}. Phenoxyazine is a colourless compound but several derivatives show intense colouration which makes them useful as dyes and drugs. Bernthsen’s work led to the synthesis of several side chain and $N$-alkyl derivatives which have a wide range of applications, particularly as drugs and dyes. Notable among them are Oxonine,\textsuperscript{64} Brilliant Cresyl Blue,\textsuperscript{65} Alizarine Blue RBN,\textsuperscript{66} MeldolaBlue,\textsuperscript{67} Nile Blue Sulfate,\textsuperscript{68} Resazurin,\textsuperscript{69} Capri Blue,\textsuperscript{70} and the famous Orcein Pigment.\textsuperscript{71}

Other applications of phenoxyazine derivatives include their use as oxidants\textsuperscript{72}, biological stains\textsuperscript{73}, acid-base indicators\textsuperscript{74} and bromometric and stannometric redox indicators.\textsuperscript{75} Phenoxyazine itself has been used as a stabilizer for the
polymerization of vinylpyridines\textsuperscript{76}, polyethylene and polystyrene. Some derivatives were also reported as having radio-protective and anti-oxidative actions.\textsuperscript{77}

A review of the chemistry of phenoxazine has been undertaken by several authors such as Pearson, Ramage, Rodd, Landquist, Mckee, Schaefer, Ionesar and Mantsch.

2.2.1 Non-aza analogues

2.2.1.1 Benzo[b]phenoxazines

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {O};
\node (b) at (1,1) {N};
\node (c) at (2,2) {H};
\node (d) at (3,3) {17};
\node (e) at (4,4) {16};
\node (f) at (5,5) {15};
\node (g) at (6,6) {14};
\node (h) at (7,7) {13};
\node (i) at (8,8) {12};
\node (j) at (9,9) {11};
\node (k) at (10,10) {10};
\node (l) at (11,11) {9};
\node (m) at (12,12) {8};
\node (n) at (13,13) {7};
\node (o) at (14,14) {6};
\node (p) at (15,15) {5};
\node (q) at (16,16) {4};
\node (r) at (17,17) {3};
\node (s) at (18,18) {2};
\node (t) at (19,19) {1};
\node (u) at (20,20) {2};
\node (v) at (21,21) {3};
\node (w) at (22,22) {4};
\node (x) at (23,23) {5};
\node (y) at (24,24) {6};
\node (z) at (25,25) {7};
\node (aa) at (26,26) {8};
\node (ab) at (27,27) {9};
\node (ac) at (28,28) {10};
\node (ad) at (29,29) {11};
\node (ae) at (30,30) {12};
\node (af) at (31,31) {13};
\node (ag) at (32,32) {14};
\node (ah) at (33,33) {15};
\node (ai) at (34,34) {16};
\node (aj) at (35,35) {17};
\draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g) -- (h) -- (i) -- (j) -- (k) -- (l) -- (m) -- (n) -- (o) -- (p) -- (q) -- (r) -- (s) -- (t) -- (u) -- (v) -- (w) -- (x) -- (y) -- (z) -- (aa) -- (ab) -- (ac) -- (ad) -- (ae) -- (af) -- (ag) -- (ah) -- (ai) -- (aj);
\end{tikzpicture}
\end{center}

Benzo[b]phenoxazines\textsuperscript{17} are linear. Substituted derivatives of these are numbered according to the system shown below:

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {O};
\node (b) at (1,1) {N};
\node (c) at (2,2) {H};
\node (d) at (3,3) {1};
\node (e) at (4,4) {2};
\node (f) at (5,5) {3};
\node (g) at (6,6) {4};
\node (h) at (7,7) {5};
\node (i) at (8,8) {6};
\node (j) at (9,9) {7};
\node (k) at (10,10) {8};
\node (l) at (11,11) {9};
\node (m) at (12,12) {10};
\node (n) at (13,13) {11};
\node (o) at (14,14) {12};
\node (p) at (15,15) {13};
\node (q) at (16,16) {14};
\node (r) at (17,17) {15};
\node (s) at (18,18) {16};
\node (t) at (19,19) {17};
\draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g) -- (h) -- (i) -- (j) -- (k) -- (l) -- (m) -- (n) -- (o) -- (p) -- (q) -- (r) -- (s) -- (t);
\end{tikzpicture}
\end{center}

The linear system has been prepared through the high temperature condensation process involving 2-aminophenol and 2,3-dihydroxynaphthalene\textsuperscript{78}.
Compound 17 has absorption and fluorescence emission properties that are characteristic of an extended aromatic heterocycle and does not have substituents that would allow it to be reduced to a phenoxazinone or phenoxazinium form.

Some nitro and amino derivatives of benzo[b]phenoxazines have been reported in the literature according to scheme 2 below.

a

\[
\text{NaNO}_2, \text{CH}_3\text{COOH} \quad \text{DMF, 70°C, 10mins} \quad 34\% \text{ yield}
\]

b

\[
\text{NaNO}_2, \text{CH}_3\text{COOH} \quad 25^\circ\text{C, 3h} \quad 9\% \text{ yield}
\]

30% yield
SCHEME 2: Synthesis of benzo[b]phenoxazine derivatives; (a) 9-nitro; (b) 1,9-dinitro and 9-nitro-1,12-bis(benzo[b]phenoxazine); and (c) 1-amino-9-iminobenzo[b]phenoxazine

2.2.1.2 2-Amino-4,4α-dihydro-4α,7-dimethyl-3H-phenoxazine-3-one

Takahashi et al reported the synthesis of 2-amino-4,4α-dihydro-4α,7-dimethyl-3H-phenoxazine-3-one by reacting 2-amino-5-methylphenol with bovine hemolysate.

SCHEME 3: Synthesis of 2-amino-4,4α-dihydro-4α,7-dimethyl-3H-phenoxazine-3-one.
They reported that the synthesized compound 18 may be used to treat patients affected by different types of leukemia.

Five years later, Kato et al\textsuperscript{81} also reported that compound 18 and 2-aminophenoxazine–3–one 19 exert anticancer effects against human pancreatic cancer cell through distinct action mode.

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

2.2.2 Aza analogues

The synthesis of azaphenoxazine compounds involves the condensation of suitably substituted halonitropyridines 20 and aminophenols 21. The resulting intermediate product. When further treated with strong base, forms the anticipated azaphenoxazine.

\begin{center}
\includegraphics[width=0.5\textwidth]{image2}
\end{center}
3–Bromo–4-chloro–5-aminopyridine 22 was used successfully in place of halonitropyridine20. The use of o-aminohydroxypyridine23 in place of o-aminophenol 21 has also been reported.107

Unlike o-aminomercaptopyridine derivative required for azaphenothiazine synthesis and formed through thiazolopyridine82 or hydroxypyridine83 compound in longer steps, these o-aminohydroxypyridines are more readily accessible. Compound 23 is conveniently obtained by nitration of 2-aminopyridine, followed by separation of isomers, diazotization and hydrolysis of the diazonium salt of the ortho-isomer84. Reduction of the resulting o-hydroxynitropyridine gave a good yield of 23. Picryl chloride 24 and 2,4,6-trinitro anisole 25 have also been used in place of halodinitropyridines, provided that the other reactant is of type 23.
2.2.2.1 1–Azaphenoxazine

Plazek and Rodewald\textsuperscript{85} synthesized 7,9–dinitro-1–azaphenoxazine\textsuperscript{26} by the condensation of 3–hydroxy–2–aminopyridine\textsuperscript{27} with picryl chloride \textsuperscript{24}. When the product was further treated with alcoholic base, it gave the isolated product \textsuperscript{26}. It was proposed that the o–aminopyridylphenyl ether \textsuperscript{28} was formed, followed by smiles rearrangement\textsuperscript{86–87} of the diaryl ether to the corresponding o–hydroxyphridyl aniline \textsuperscript{29}. In excess base, cyclization of this intermediate was achieved leading to the isolated product \textsuperscript{26}. (SCHEME 4)
SCHEME 4: Mechanism for the synthesis of 7,9-dinitro-1-azaphenoxazine

The overall yield was adversely limited by the poor yield of the precursor 27, which was obtained by nitration of 3-hydroxypyridine with mixed concentrated nitric and sulfuric acids, followed by reduction of the nitro group. (SCHEME 5). An improved yield of compound 27 was obtained by Lewicka and Plazek who nitrated 3-hydroxy-1-pyridineoxide with mixed acids followed by reduction and deoxygenation with iron and mercuric chloride.

A number of side chain derivatives were also reported. Moore and Marascia\textsuperscript{89} obtained 7,9-dinitro-4-methyl-3-phenyl-1-azaphenoxazine 30 by reacting 2-amino-3-hydroxy-4-methyl-5-phenylpyridine 31 with picryl chloride 24 in ethanolic sodium ethoxide.

\textbf{SCHEME 6: Synthesis of 7,9-dinitro-4-methyl -3-phenyl-1-azaphenoxazine 30}

While it was hoped that the 10-alkylaminoalkyl derivatives can be obtained by alkylation in the presence of sodamide or sodium hydride in dioxane, DMF, DMAC or DMSO, Takahashi and Yoneda\textsuperscript{90} chose the Scheme 7 outlined below which also established the position that was alkylated.
This reaction led to the formation of intensely coloured compounds which contained chlorine and exploded on warming. When picryl chloride was replaced by 2,4,6-trinitroanisole 25, a product reported as 2,4,6-trinitrophenyl-(4-hydroxy-3-pyridyl) amine 37 was isolated in 70% yield, purified and then treated with alcoholic potassium hydroxide, yielding brilliant red needles of 7,9-dinitro-2-azaphenoxazine 38 in good yield. There was no physical or chemical evidence in support of the assigned intermediate structure 37. Although Petrow claimed that
the isolated intermediate is a diarylamine, 37, it is more likely that 2,4,6-trinitrophenyl-(3-amino-4-pyridyl) ether 39 was first formed followed by Smiles rearrangement in the presence of a base to give 37 which then cyclized to the isolated 2-azaphenoxazine derivative, 38. The following sequence of reactions seems therefore more probable.

**SCHEME 8: Synthesis of 7, 9-dinitro-2-azaphenoxazine 38**

2.2.2.3 3–Azaphenoxazine

Both the parent compound and the side chain derivatives have been reported. 1-Nitro-3-azaphenoxazine 40 was the first known compound in this series. 40 was obtained by treating 3,5-dinitro-4-chloropyridine with o-aminophenol 21 in
the presence of anhydrous sodium acetate in methylated spirit. Petrow and Rewald reported that an isolable diarylamine, 42 was first formed followed by cyclization to the desired product 40. It is proposed that a diaryl ether, 43 was initially formed followed by Smiles rearrangement to 42 when treated with alcoholic base. The latter product readily cyclized to compound 40 in the presence of excess base.

Takahashi also prepared 1-nitro-3-azaphenoxazine by condensing 3-bromo-4-chloro-5-nitropyridine 22 with o-aminophenol 21, followed by cyclization of the diarylamine intermediate with piperidine base.

**SCHEME 9:** Synthesis of 1-Nitro-3-azaphenoxazine.
The parent compound, 3-azaphenoxazine 44 was reported in a U.S. patent\textsuperscript{94}. It was prepared by condensation of benzyl-2-hydroxyaniline 45 with 4-chloro-3-nitropyridine hydrochloride 46, followed by cyclization of the diarylamine 48, in aqueous base to 10-benzyl-3-azaphenoxazine 49. This product was converted to 3-azaphenoxazine 44 by catalytic hydrogenolysis, using palladized charcoal in butanol at 60 – 70\degree C and 40 – 50 psi on a parr-hydrogenator. This compound 44, melting at 246-247\degree C, is the only reported unsubstituted azaphenoxazine

\textbf{SCHEME 10: }Takahashi method of preparation of I-Nitro-3-azaphenoxazine

\textsuperscript{94}
When 3-azaphenoxazine 44 was treated with 3-dimethylaminopropyl chloride in 50% aqueous sodium hydroxide, alkylation took place in the 3-position instead of the usual 10-alkylation. The compound, (3-dimethylaminopropyl)-3-azaphenoxazine 50, thus obtained, reduces high arterial blood pressure and is therefore an effective anti-hypertensive agent.

The orientation in 3-azaphenoxazine was also investigated. Nitration of compound 40 with fuming nitric acid in glacial acetic acid gave a dinitro derivative which was
formulated as 1,7-dinitro-3-azaphenoxazine 51 by analogy with the product obtained by nitration of phenoxazine.\textsuperscript{64}

![Structure of 1,7-dinitro-3-azaphenoxazine](image1)

The assigned structure was confirmed by direct synthesis from 5-nitro-2-aminophenol 52 and 4-chloro-3,5-di-nitropyridine 41. In a similar way the 1,8-dinitro analog, 53, was obtained if compound 52 was replaced by 4-nitro-2-aminophenol 54.

![Structure of 1,8-dinitro-3-azaphenoxazine](image2)

Reduction of 51 and 53 with iron and calcium chloride in 70% alcohol gave the respective diamino derivatives which were isolated as their dihydrochlorides. 1,7-Diamino-3-azaphenoxazine is very susceptible to oxidation and darkens on exposure to air and is therefore preserved as the dihydrochloride salt.
2.2.2.4 4–Azaphenoxazine

Petrow and Rewald\textsuperscript{95} in 1945 reported the synthesis of 7,9-dinitro-4-azaphenoxazine 55 from 3-amino-4-hydroxypyridine by employing the modification of Turpin’s reaction described by Misslin and Bau. When approximately equimolar quantities of the components were heated in methyl alcohol solution, the sparingly soluble 3-picrylamino-4-hydroxypyridine separated. This separated compound passed smoothly on warming with one molecule of potassium hydroxide into 7,9-dinitro-4-azaphenoxazine 55 with simultaneous production of nitrite.

Later in 1958, Takahashi and Yoneda\textsuperscript{96} synthesized 2-chloro-7,9-hydroxy-5-chloropyridine 56 with 2,4,6-trinitroanisole 57 in excess base. The following steps were formulated for the overall reaction, leading to 2-chloro-7,9-dinitro-4-azaphenoxazine.
Scheme 12: Synthesis of 2-Chloro-7,9-dinitro-4-azaphenoxazine

2.2.2.5 3,4-Diazaphenoxazine

The reports of this heterocyclic ring system were made mainly in the patent literature and very few compounds of 3,4-diazaphenoxazine are known. Two derivatives of 10-alkyl and 10-dialkylaminoalkyl-2-oxo-2,3-dihydro-3,4-diazaphenoxazine 58 were reported by Bondar\textsuperscript{97} in a USSR patent without details of the methods of preparation, properties and uses. It was envisaged that their synthetic methods was similar to the methods previously reported by Yoneda\textsuperscript{98} for the synthesis of 1,2-diaza- and 3,4-diazaphenothiazines.
In 1970, Gortinskaya\textsuperscript{99} and his co-workers obtained in good yields some 2,10-disubstituted -3,4-diazaphenoxazines \textbf{59}, which were of biological interest, by condensing 2-methylamino phenol \textbf{60} with 3,4,6-trichloropyridazine \textbf{61} in alcoholic triethylamine.

**SCHEME 13:** Mechanism of reaction for the synthesis of 2,10-disubstituted-3,4-diazaphenoxazine

\textbf{2.2.2.6} 1,4-Diazaphenoxazine
Reports on the interesting pharmacological activities of 3,4-diazaphenoxazines prompted the synthesis of other isomeric diazaphenoxazines. The second azaphenoxazine in this series is the 1,4-diazaphenoxazine system 62 prepared by refluxing a mixture of 2,3,5,6-tetrachloropyrazine 63 with the sodium salt of o-aminophenol 64 in isopropyl alcohol. The resulting diaryl ether 65 was cyclized with or without rearrangement to the desired compound 62 by refluxing with sodium hydroxide in isopropyl alcohol for a period of half an hour.\(^{100}\)

\[
\begin{align*}
\text{Cl}_2\text{N}_2\text{Cl}_2 & \quad + \quad \text{C}_{6}\text{H}_4\text{NH}_2\text{O}^-\text{Na}^+ \\
& \rightarrow \quad \text{C}_{6}\text{H}_4\text{O} \quad \text{N} \quad \text{N} \quad \text{Cl}_2
\end{align*}
\]

**SCHEME 14:** Synthesis of 2,3-dichloro-1,4-diazaphenoxazine.

The same product will be expected if the cyclization proceeded via Smiles rearrangement\(^{101}\) of diaryl ethers and sulfides.

In 1981, Okafor\(^{14}\) reported the synthesis of 1,4-diazaphenoxazine 66 and 1,4-diazabeno[b]phenoxazine 67. 2,3-dichloropyrazine 68 was treated with sodium
salt of o-aminophenol 64 in aqueous N,N-dimethylacetamide to give a creamy white product.

On replacing 2,3-dichloropyrazine 68 with 2,3-dichloro quinoxaline 69, the tetracyclic 1,4-diazabenzo[b]phenoxazine 67 formed.

\[ \text{Scheme 15: Synthesis of 1,4-diazabenzo[b]phenoxazine} \]

2.2.2.7 1,9-Diazaphenoxazine

The synthesis of 1,9-diazaphenoxazine 70 was reported by Okafor in 1974. This is the only known diazaphenoxazine in which the ring nitrogens are located in different rings. The reactions leading to the parent heterocycle involved the base-catalysed condensation of 2-amino-3-hydroxypyridine 27 with 2-chloro-3-nitropyridine 71 in dilute sulfuric acid. The diarylamine obtained in 45% yield, after neutralization with concentrated ammonia, was converted to 1,9-diazaphenoxazine 70 in 31% yield by refluxing with potassium hydroxide in dimethyl sulfoxide for 10 hours.102-103
Okafor reported that 1,9-diazaphenoxazine and its precursor (diarylamine) were tested in mice and rats for their effect on the central nervous system. Both compounds showed both analgesic and CNS-depressant activities. They decreased body temperature by as much as 1.9°C compared to 0.8°C by chlorpromazine.\textsuperscript{104}

2.2.3 Nitro, Amino, $N$-Acetyl and $N$-Alkyl Phenoxazines

Maas\textsuperscript{105} and co-workers reported the synthesis of nitro, amino, $N$-acetyl and $N$-alkyl phenoxazine dyes. They synthesized 3,7-dinitrophenoxazine 72 by nitration of commercially available phenoxazine1 with NaNO$_2$ in the presence of glacial acetic acid at room temperature. When they varied the reaction conditions, they got a mixture of 3,7-dinitrophenoxazine 72 and 3-nitrophenoxazine 73. However,
3,7-dinitrophenoxazine 72 was isolated in good yield (72%) when NaNO₂ (2 equiv) was used and the reaction ran for 70 hours.

Reduction of 3,7-dinitrophenoxazine 72 and 3-nitrophenoxazine 73 catalyzed by iron with hydrochloric acid in ethanol gives after purification corresponding diaminohydrochloride 74 and 75, in 78 and 84% yield, respectively.

Oxidation of 74 in methanolic silver nitrate at room temperature gave the oxonine 76.
Purification by a chromatographic method gave very low yields due to decomposition and difficulties in extracting the dye from the column material. However, the pure product was isolated in 60% yield as a red solid by recrystallization in appropriate solvent. Acylation of 3,7-diaminophenoxazine dihydrochloride with acetyl chloride proceeded under nitrogen in dry dichloromethane with an excess of triethylamine at room temperature to give the \( N \)-acylated compound as a brown solid in 91% yield, after purification by flash chromatography on alumina.

Oxidation of \( 77 \) in ethanolic silver nitrate at room temperature afforded compound \( 78 \) as a dark-green solid in 60% yield.

Reduction of \( 78 \) with LiAlH\(_4\) under nitrogen in dry tetrahydrofuran followed by a similar oxidation procedure as \( 78 \) gave 3,7-bis(ethylamino)phenoxazinium nitrate as \( 79 \) in 53% yield.
The oxidized products 76, 77 and 78 have significantly different spectra from the non-oxidized products due to delocalization of the $\pi$-electrons. The solubility of 78 in methanol was not high due to the nitrate anion$^{47}$

2.2.4 *N*-Substituted Phenoxazines and Related Aza Analogues.

Recently, Isabelle$^{106}$ and his co-workers reported synthesis of *N*-substituted phenoxazines$^{80}$ and related aza-analogues from *N*-acetylated aryloxyanilides$^{81}$ by transition–metal free base-catalyzed cyclization reaction.

In the presence of a mixture of *N*, *N*-dimethyl ethylenediamine (DMEDA) and 2 equivalent of $K_2CO_3$ in toluene at $135^0C$, the products were obtained in good yield. The reaction however required long time (24h).
CHAPTER THREE

3.0 EXPERIMENTAL SECTION

3.1 General Information

All reactions were set up in the air and carried out under an atmosphere of nitrogen. All reagents were of technical grade. 2,3,5-Trichloropyridine and palladium acetate were purchased from SIGMA Chemicals and used as received, without further purification. Most of the amine compounds and solvents were purchased from Aldrich Chemical co. in sure-seal bottles and were used as received. All melting points were determined on a Fischer Johns melting-point apparatus and are uncorrected. The $^1$H-NMR and $^{13}$C-NMR spectrals were obtained in DMSO-$d_6$ on a 400 MHz spectrometer. Ultraviolet and visible spectra were
recorded in ethanol on a Unicon UV-2500 PC spectrometer using matched 1cm quartz cells. The absorptions were measured in nanometers (nm). IR spectra were acquired on a FTIR and are reported in wave numbers (cm$^{-1}$).

### 3.2 3-Chloro-1,9-diazaphenoxazine

To a solution of potassium hydroxide (4.00g, 71mmol) in 50ml of water, 2-amino-3-hydroxypyridine (2.00g, 14.40mmol) was added. The mixture was warmed until the materials dissolved. 2,3,5-Trichloropyridine (3.20g, 17.50mmol) in 50mls of 1,4-dioxane was added in drops during a period of 15mins. The entire mixture was refluxed with stirring for 4h. It was later poured into a 500ml beaker, diluted with water to the 500ml mark, cooled and filtered. The filtrate was further chilled, filtered and the residue crystallized from aqueous ethanol. Creamy white crystals of 3-chloro 1,9-diazaphenoxazine (0.16g, 50%) was obtained; MP 48$^\circ$C, Uv-visible$\lambda_{max}$ 284(log 2.781), IR(KBr): 761, 1053, 1218, 1429, 1532, 1650,
3394cm⁻¹, 1H-NMR (DMSO): δ8.63 (s, IH, NH), δ8.50 (aromatic protons); 13C-NMR (DMSO): δ130, δ131, δ139, δ147.

### 3.3 Preparation of Single Crystal of 3-Chloro-1,9-diazaphenoxazine for X-ray Analysis.

The method used was slow evaporation of a multi-solvent system. The compound was dissolved in a mixture of 50ml of dioxane and 50ml of water and it was left uncovered at room temperature for 2-3 weeks. With time, the solvent composition changes due to the evaporation of the more volatile solvent. The compound was more soluble in the volatile solvent and so the compound became increasingly insoluble in solution and crystallized out.

### 3.4 1,4-Bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazines

A mixture of piperazine (2.20g, 25.54mmol) and 40% aqueous formaldehyde solution (5.3ml, 75.40mmol) was dissolved in methanol (40ml) and heated to reflux for 2h to get a clear solution. 2, 4-Di-tert-butylphenol (10.30g, 50.40mmol) in methanol (60ml) was added to the cooled solution. The resulting solution was refluxed for a further 12h. The reaction mixture was cooled to room temperature
and filtered off to obtain the ligand as a colorless crystalline compound. Yield: 
(8.48g, 65%) Mp: 260°C.

3.5 General Procedure for the Synthesis of 3-Amino Derivatives of 1,9-Diazaphenoxazine.

Palladium acetate (0.002g, 1mmol%) and 1,4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine (0.008g, 2mmol%) were placed in a three-necked 100ml round bottom flask equipped with a magnetic stirring bar. The flask was evacuated and backfilled with nitrogen. This process was repeated a total of three times. One ml of H₂O was added using a syringe and the solution was heated to 80°C for 2mins. Thereafter, 3-chloro-1,9-diazaphenoxazine (0.30g, 1.40mmole), potassium carbonate (0.20g, 1.50mmol), and amine (1.30mmol) were added to the reaction flask. Two ml of DMF was also added. The flask was evacuated and filled with nitrogen three times and the mixture was refluxed with stirring for 2h at a temperature of 110°C. The resulting product was air dried and recrystallized from aqueous ethylacetate.

3.5.1 3-(2-Amino-3-nitropyridino)-1,9-diazaphenoxazine
Yield: (0.19g, 45%); Colour: Golden yellow; Mp: 130-132°C; UV-visible \( \lambda_{\text{max}} \) (ethanol): 388 (log\( \varepsilon \) 2.391), 744 (log\( \varepsilon \) 2.099) nm; IR (KBr): 762, 1074, 1560, 1641, 3121, 3264, 3461 cm\(^{-1}\); \(^1\)H-NMR (DMSO): \( \delta 6.62\) (s, 5H Ar-H), \( \delta 8.20\) (s, IH, NH), \( \delta 8.52\) (s, IH, NH), \( \delta 8.82\) (s, 3H, Ph-H).

### 3.5.2 3-(2-Aminopyrazino)-1,9-diazaphenoxazine

Yield: (0.25g, 70%); Colour: Yellowish brown; Mp: 110-112°C; UV-visible \( \lambda_{\text{max}} \) (ethanol): 231 (log\( \varepsilon \) 3.873), 321 (log\( \varepsilon \) 2.443), 760 (log\( \varepsilon \) 1.756) nm; IR (KBr): 1021, 1382, 1656, 3079, 3175, 3238, 4100 cm\(^{-1}\); \(^1\)H-NMR (DMSO): \( \delta 6.44\) (s, 1H NH), \( \delta 7.62\) (s, 3H, Ph-H), \( \delta 7.80\) (s, 6H, Ar-H); \(^13\)C-NMR (DMSO): \( \delta 142, \delta 157, \delta 133, \delta 132\).

### 3.5.3 3-(2-Aminopyridino)-1,9-diazaphenoxazine

Yield: (0.13g, 35%); Colour: brown; Mp: 116 – 117°C; UV-visible \( \lambda_{\text{max}} \) (ethanol): 747 (log\( \varepsilon \) 2.297) nm; IR (KBr): 669, 1155, 1365, 1455, 1656, 3124, 3214, 3338, 3345 cm\(^{-1}\); \(^1\)H-NMR (DMSO) \( \delta 6.50\) (m, 1H, NH), \( \delta 8.52-7.24\) (m, 9H, Ar-H).
3.5.4  3-(2-Aminophenyl)-1,9-diazaphenoxazine

Yield: (0.32g, 85%); Colour: Dark brown; Mp: 140-142°C; Uv-visible $\lambda_{\text{max}}$ (ethanol): 735(logε 2.112)nm; IR (KBr): 634, 1246, 1377, 1505, 1598, 3345 cm$^{-1}$; $^1$H-NMR (DMSO) δ 8.51 (s, 9H, Ar-H), δ 8.30–8.00 (m, 1H, OH), δ 7.50 – 6.52 (m, 2H, NH).

3.5.5  3-Anilino-1,9-diazaphenoxazine

Yield: (0.18g, 50%); Colour: Black; Mp: 152-153°C, Uv-visible $\lambda_{\text{max}}$ (ethanol): 284(logε 2.768), 320(logε 3.214), 741(logε 2.545), 761(logε 2.562)nm; IR (KBr) : 692, 1017, 1142, 1585, 3121, 3266 cm$^{-1}$; $^1$H-NMR (DMSO) δ 8.20 (s, 2H, NH), δ 7.30-6.84 (m, 10H, Ar-H).

CHAPTER FOUR

4.0  RESULTS AND DISCUSSION
Most of the methods reported for the synthesis of azaphenoxazinering system involve the condensation of suitably substituted halonitropyridine and o-aminophenol or 2-amino-3-hydroxypyridine. In the synthesis of our key intermediate, 3-chloro-1,9-diazaphenoxazine, 2-amino-3-hydroxypyridine and 2,3,5 trichloropyridine were used.

4.1 3-Chloro-1,9-diazaphenoxazine

The base catalyzed reaction of 2-amino-3-hydroxypyridine with 2,3,5-trichloropyridine in aqueous 1,4-dioxane gave 3-chloro-1,9-diazaphenoxazine as creamy–white crystals with melting point of 48°C.

The proposed mechanism for the reaction is as shown below:

**SCHEME 17:** Mechanism of reaction for the synthesis of 3-chloro-1,9-diazaphenoxazine
The first step in the mechanism is the condensation of the two reactants giving away HCl and giving rise to an ether. The chloropyridine undergoes Smiles rearrangement and cyclization of the product takes place in excess base to give the isolated product. The assigned structure is supported by spectral analysis. The Uv-visible absorption at 284nm is consistent with phenoxazines. The IR absorption at 3394cm\(^{-1}\) is due to N-H group of the phenoxazine moiety, 1053cm\(^{-1}\) is due to C-O-C group, 1532cm\(^{-1}\) is due to C=N group and 761cm\(^{-1}\) is due to m-substituted aromatic ring. In \(^1\)H-NMR, the absorption band at δ8.6 is due to N-H proton and that of δ8.5 is assigned to aromatic protons. In the \(^{13}\)C-NMR, the band at δ147-130 is due to aromatic carbons. The colourless crystals of the compound suitable for X-ray diffraction analysis was grown by slow evaporation of two different solvent at room temperature.

4.2 1,4-Bis(2-hydroxyl-3,5-di-tert-butylbenzyl)piperazine

Prior to the amination reaction between the aryl chloride in 4.1 above and different amines, the ligand needed for the tandem catalysis was synthesized. The ligand was obtained as a colorless crystalline compound, melting at 260°C.
4.3 CATALYST PREACTIVATION

Water–mediated catalyst preactivation was employed as reported by Forset et al. A mixture of Pd(OAc)$_2$ (1mmol%), water (4mol%) and piperazine ligand (2mmol%) was heated for 1 min at 80°C in 1,4-dioxane. The activation was monitored by color change; at 0 sec, the colour was yellow, at about 15 sec, it was brick red, at about 30 sec, it turned to wine red and finally at 1 min, it became yellow –black.

\[
Pd(OAc)_2 + 2L \xrightarrow{\text{H}_2\text{O}} \text{Pd}(0) L
\]

Where L = 1, 4-bis (2-hydroxy-3, 5-di-tert-butylbenzyl)piperazine.

4.4 3–(2-Amino-3–nitropyridino)-1,9–diazaphenoxazine

The yield was 45% and colour was golden yellow. Compound melted at 130 – 132°C. The assigned structure is supported by spectral analysis. The Uv-visible absorption band at 388nm is consistent with the phenoxazine moiety and the band at 744nm
is due to the observed colour. The IR absorption band at 3264 cm\(^{-1}\) and 346 cm\(^{-1}\) is due to N-H groups, the band at 1560 cm\(^{-1}\) is due C=N stretch, the band at 1074 cm\(^{-1}\) is due to C-O-C group, the band at 1641 cm\(^{-1}\) is due to C=C and C-N ring stretch (skeletal bands). The \(^1\)H-NMR spectral shows a peak at \(\delta 8.5\) and \(\delta 8.2\) due to N-H group, the band at \(\delta 8.8\) (s, 3H) is due to C\(_{17}\)–C\(_{19}\) hydrogens and the band at \(\delta 6.6\) (s, 5H) is due to C\(_2\)–C\(_8\) hydrogens.

4.5 3-(2-Aminopyrazino)-1,9-diazaphenoxazine

The compound was obtained as a yellowish-brown crystalline compound with yield of 70\% and melting at 110\(^\circ\)C – 112\(^\circ\)C.

The assigned structure is supported by spectral analysis. The UV-visible spectra shows bands at 231 nm and 321 nm which are consistent with the phenoxazine moiety, while another band at 760 nm which is in agreement with the observed colour. The IR spectra shows peaks at 3238 cm\(^{-1}\) and 3175 cm\(^{-1}\) due to N–H groups, at 1656 cm\(^{-1}\) due to C\(\equiv\)C and C\(\equiv\)N ring stretching (skeletal bands), at
1021 cm\(^{-1}\) due to C–O–C group, and at 3079 cm\(^{-1}\) due to aromatic C–H stretch. The \(^1\)H–NMR show peaks at \(\delta 6.4\) for N-H protons, another peak at \(\delta 7.6\) for hydrogens at C\(_{17}\)–C\(_{20}\) and another peak at \(\delta 7.8\) for hydrogens at C\(_2\)–C\(_8\). The \(^{13}\)C–NMR shows peaks at \(\delta 157-132\) due to aromatic carbons.

4.6 3–(2–Aminopyridino)-1,9-diazaphenoxazine

The synthesis gave a yield of 35%, brownish colour and the compound melted at 116\(^0\)C–117\(^0\)C.

The assigned structure is supported by spectra analysis. The Uv-visible spectra show a peak at 747 nm in agreement with the observed colour. The IR spectra shows a peak at 3124 cm\(^{-1}\) due to aromatic C–H stretch, another peak at 1656–1455 cm\(^{-1}\) due to C\(=\)=C and C\(=\)=N ring stretch (skeletal bands), and 3338 cm\(^{-1}\) due to N–H group stretch. The \(^1\)H-NMR shows peaks at \(\delta 6.5\) due to 2H, N-H protons and \(\delta 8.5 – 7.2\) due to aromatic protons.

4.7 3–(2–Aminophenyl)-1,9-diazaphenoxazine
The compound was obtained as a dark-brown powder melting at 140 – 142°C and the yield was 85%.

The assigned structure is in accordance with spectral analysis. The UV-vis spectra shows a peak at 735nm in agreement with the observed colour. The IR spectra shows peaks at 1377 cm⁻¹ due to C=C and C=N ring stretch (skeletal band), 3345 cm⁻¹ due to N–H group stretch, 1585 cm⁻¹ and 1505 cm⁻¹ due to C=N stretch. The ¹H-NMR shows peaks at δ8.5 due to aromatic carbons, at δ8.3-8.0 due to 1H, OH, at δ7.5–6.5 due to N-H protons.

4.8 3-Anilino-1,9-diazaphenoxazine

The compound was obtained as a black powder with a yield of 50% and melting at 152 – 153°C.
The assigned structure is supported by spectral results. The Uv-visible shows a peak at 320nm which is consistent with phenoxazine moiety and another peak at 761nm due to the observed colour. The IR spectral shows peaks at 1451cm\(^{-1}\) due to C\(\equiv\)C and C\(\equiv\)N ring stretch (skeletal band), 1017cm\(^{-1}\) due to C–O–C group, 3266cm\(^{-1}\) due to N–H group and 1585cm\(^{-1}\) due to C=N stretch.

The \(^1\)H-NMR shows peak at \(δ8.2\) due to 2H, N-H protons, and at \(δ7.3–6.8\) due to aromatic hydrogens.
CHAPTER FIVE

5.0 CONCLUSION

We have demonstrated that the catalytic system used allows the general C–N bond forming reaction between 3-chloro-1,9-diazaphenoxazine and various amines. Consequently, various 3-(N-substituted)–amino-1,9-diazaphenoxazines were prepared in good yields.
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