SYNTHESIS OF BISQUINOLINES THROUGH CONVENTIONAL AND UNCONVENTIONAL ENERGY SOURCES

Thesis submitted in fulfilment of the requirements for the degree of

Master of Technology

Organic Chemistry

By

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Department of Chemistry

Faculty of Applied Science

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June 2011

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Submitted in fulfilment of the requirements for the degree of Master of Technology, Organic Chemistry, in the Faculty of Applied Science at Durban University of Technology

By

Talent Raymond Makhanya

BTech (Chemistry)

June 2011

PROMOTER: Dr. R.M Gengan

DECLARATION

I, Talent Raymond (Wakhe) Makhanya hereby declare that this dissertation, entitled ''SYNTHESIS OF BISQUINOLINES THROUGH CONVENTIONAL AND UNCONVENTIONAL ENERGY SOURCES'', submitted to the Durban University of Technology, in fulfilment of the requirements for the award of the Degree of Master of Technology, Organic Chemistry, in the Faculty of Applied Science, is the result of my own work and that all sources used or quoted have been indicated and acknowledged by means of complete references.

Signed:_____ _____

Talent Raymond Makhanya DATE

Signed:_____ _____

DR R. M. Gengan (Promoter) DATE

DEDICATION

This dissertation is dedicated to my late father, Fortunatus Mhlabunzima Makhanya, who gave me direction in this world, my late sister, Fikelephi Janis Makhanya, my late grand-parents, my late friend, Liketso Qholoshe, and my mother, Mrs Doreen Thuleleni Makhanya who brought me in this world and made sure that I am well looked after until I was able to fend for myself.

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Abstract

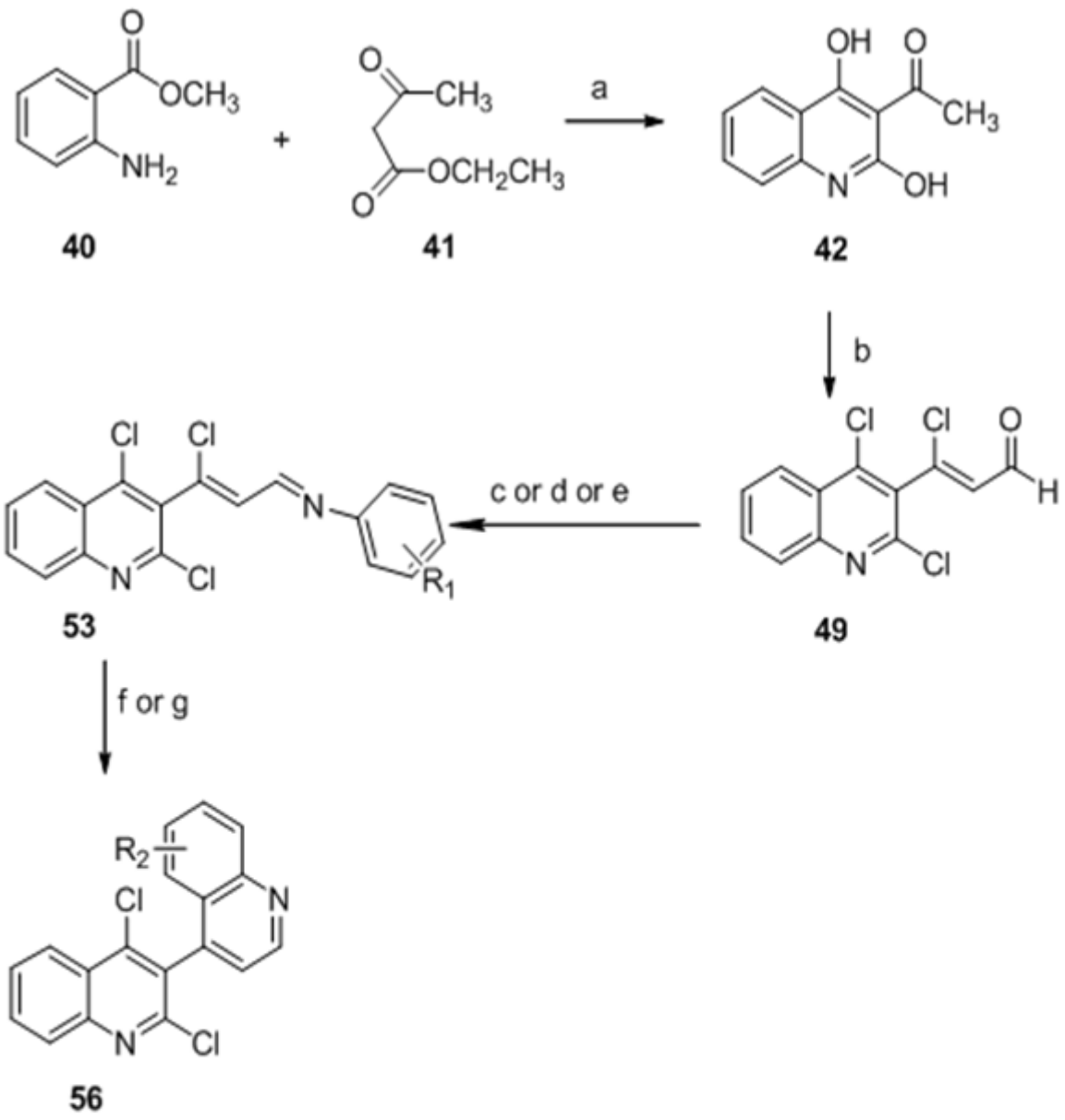
Malaria, the most prevalent parasitic disease, is considered a neglected disease owing to insufficient research and development in synthesis and therapy worldwide. Therapy failures are frequent and are due to a variety of factors such as the intrinsic characteristics of the disease, conditions of transmission, and the difficult control of spreading through tropical areas. Primary factors are the complexity of the parasite life cycle and the development of drug resistance. Another critical factor is the increasing number of immune-compromised patients that suffer from malaria and human immunodeficiency virus (HIV) co-infections.

Most of the drugs currently available to treat malaria are quinoline derivatives modelled on the quinine molecule, found in the bark of *Cinchona* trees. Over the last 50 years the use of quinine has declined owing to the development of synthetic 4-aminoquinolines such as chloroquine. However, the malaria parasite is rapidly becoming resistant to the drugs currently available. Recently bisquinoline compounds were found more potent than chloroquine against both chloroquine-sensitive and resistant strains of malaria; this improved efficacy and prompted an increased interest in the design of these anti-malarial drugs.

Although several synthetic methods are available to synthesise bisquinolines, we report the synthesis of bisquinolines from simple, readily available and cost-effective starting compounds. The synthesis was accomplished in four reaction steps using the Claisen condensation, Vilsmeir-Haack reaction, formation of a Schiff

base and thermal cyclization, sequentially. We used a conventional energy source and microwave irradiation for the synthesis, wherever possible, of 2, 4-dichloro-3, 4'-biquinoline and 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline.

In the first step, 3-acyl-2, 4-dihydroxyquinoline is synthesised from an equimolar mixture of methyl-2-aminobenzoate and ethyl acetoacetate by microwave irradiation for 3 minutes; the yield is 90 % whereas by 6 hours refluxing the yield is 75 %. This is followed by the synthesis of 3-chloro-3-(2,4-dichloroquinolin-3yl) acrylaldehyde, by combining DMF and $POCl_3$ at 0^0C to form the electrophile which reacts with 3-acyl-2,4-dihydroxyquinoline under microwave irradiation for 5 minutes; the yield is 65 % whereas by 6 hours refluxing the yield is 50 %. In the next step, several protocols to prepare a Schiff base 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene aniline are investigated with the best yield of 75% obtained by microwave irradiation for 5 minutes. Subsequently three aniline derivatives viz, 4-methoxyaniline, 4-chloroaniline and 4-methylaniline, are used as substrate to prepare 3-chloro-3-(2,4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline, 3-chloro-3-(2 ,4-dichloroquinolin-3-yl) allylidene-4-methylaniline and 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro aniline at 68, 78 and 64 % yield, respectively. In the final step, 2, 4-dichloro-3, 4'-biquinoline is prepared; several methods were investigated, however, the best yield is 24 % which is obtained under alkaline conditions in the presence of K_2CO_3 and DMF by microwave irradiation for 10 minutes. The 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline derivative is also prepared in 18 % yield under the same alkaline conditions. The outline of the total synthesis of bisquinoline is presented graphically below.



a. NaH, (MWI / Conventional)
b. $POCl_3$, DMF, (MWI / Conventional)
c. DMF, Aniline and Derivative, (MWI / Conventional)
d. Acetic acid, Aniline and Derivatives, (Conventional)
e. Chloroform, HCl, Aniline and Derivatives, (Conventional)
f. K_2CO_3, DMF, (MWI / Conventional)
g. K10 clay, MWI

R_1 = H, OCH_3, CH_3, Cl
R_2 = H, OCH_3

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Abbreviations:

$POCl_3$ – phosphorus trichloride oxide

$POBr_3$ – phosphorus tribromo oxide

CO_2 – carbon dioxide

H_2 – di hydrogen

Pt – platinium

PPA – poly phosphoric acid

KOH – potassium hydroxide

MeI – methyl Iodide

C_6H_5 – phenyl

CH_3OH – methanol

H_2SO_4 – sulphuric acid

Me_2SO_4 – methyl sulphate

CH_3CN – acetonitrile

K_2CO_3 – potassium carbonate

HCl – hydrochloric acid

Cat – catalyst

MWI – microwave irradiation

NaH – sodium hydride

DMF – dimethyl formamide

Na_2CO_3 – sodium carbonate

PTSA – para toluene sulphonic acid

K10 clay – montmorillonite

VHR – Vilsmeir-Haak reaction

$CHCl_3$ – chloroform

TLC – thin layer chromatography

NMR – nuclear magnetic resonance

^{1}H – proton

^{13}C – carbon 13

OH^- – hydroxide

W – watts

^{o}C – degrees celsius

s – second

IR – infra-red

g – grams

% - percentage

mol - mole

ppm – part per million

MS – mass spectrometer

mL – milli Litre

m.p – melting point

min – minute

$FeCl_3$ – iron tri-chloride

General Remarks

All the figures pertinent to a chapter are placed after the relevant discussion in the following sequence, IR, NMR and Mass spectra. All experimental procedures are found in chapter 4.

The solvents and reagents used for the synthesis were of reagent grade (unless otherwise mentioned) and were purified by standard methods. Petroleum ether used was of boiling range 60-80^{0}C. Anhydrous sodium sulphate was used to dry the solutions of organic extracts.

Thin layer chromatography (TLC) was performed using TLC plates. Petroleum ether, hexane, ethyl acetate, chloroform and methanol were used as developing solvents. A chamber containing iodine vapour was used to locate the TLC spots.

Separation or purification of crude products was carried out using chromatographic columns packed with activated neutral alumina or silica gel 60-120 mesh.

Melting points were determined on Mettler FP5 apparatus and were corrected. They were expressed in degree celsius (^{0}C). The Microwave used was a CEM Microwave synthesizer.

The IR spectra were recorded on Perkin Elmer 537 spectrophotometer or Shimadzu-8201 FT instrument, using ATP disc and the absorption frequencies were expressed in reciprocal centimetres (cm^{-1}).

The ^{1}H & ^{13}C NMR spectra were recorded either on Bruker (300 MHz) or Bruker (400 MHz) spectrophotometer in $CDCl_3$ using tetramethylsilane (TMS) as an

internal reference. The chemical shifts were quoted in parts per million (ppm). The following abbreviations were used:

s - singlet

d – doublet

t – triplet

q – quartet

m – multiplet

bs – broad singlet band

J – spin-spin splitting constant in Hertz (Hz)

Mass spectra were recorded on Jeol JMS-D 300 (70 eV) and EI-MS mass spectrometer. For some of the compounds, especially for its ^{1}H NMR values, splitting patterns, integral values and the intensity of peaks were ascertained from its expanded version of the spectrum and the copies of the same were produced in this thesis and *J* values are averaged ones.

Chapter 1: Introduction

Malaria is one of the world's most prevalent infectious diseases and ranks in the top three in human health and developmental challenges facing large parts of the world. Despite the fact that effective anti-malarial drugs exist, drug resistance, particularly to chloroquine, has become an enormous problem. This has necessitated the search for novel and cost-effective drugs with high structural variation. Compounds containing a thiosemicarbazone, indoloquinoline or quinoline moiety have shown a broad spectrum of chemotherapeutic properties, including anti-malarial, anti-tumour, anti-bacterial, anti-trypanosomal and anti-viral activity. [1] These compounds are also members of a class of Schiff bases. In particular, 2-arylquinolines are biologically active and form part of the skeleton of a number of anti-malarial compounds and anti-tumor agents. Interest in this class of compounds is not restricted to the field of medicinal chemistry, since 4-aminoquinolines are also important agrochemicals owing to their fungicidal, insecticidal and pesticidal properties. [2]

Recently the synthesis of bisquinolines such as N, N-bis(7-chloroquinolin4-yl), piperaquine and dequalium, which are used to treat malarial, trichomoniasis and vaginal infections has been reported. [3] Since bisquinoline indicated improved biological activities, IC_{50} values in the range of 1-100 nM against P. Falciparum (in vitro), therefore its study has attracted much attention in organic synthesis. [4] Hence, a potential strategy for the treatment of parasitic diseases is to design bisquinoline compounds with a belief that a rational design of a suitable compound will be active against the blood stages of malaria parasites. We decided to pursue this thought process by targeting bisquinoline derivatives which could be synthesised

from simple starting compounds and hence provide a better synthetic route to other complex bisquinoline structures.

Classical methods for the synthesis of quinolines include Skraup, Doebner-von Miller, Conrad-Limbach, Combes and Pfitzinger quinoline synthesis. [5] A number of general synthetic methods have also been reported; however, some of these methods suffer from several disadvantages such as the use of harsh reaction conditions, multi-steps procedures, large amount of promoters and long time reaction for adequate conversion of starting compound to product. Therefore, the development of new synthetic approaches using mild reaction conditions remains an active research area. [6]

In the past, photochemical reactions were the best ring closing methodology to synthesize quinolines and indoloquinoline alkaloids. [7-9] We decided to investigate microwave irradiation as an alternative method to develop new procedures and alternative chemical synthetic routes for the design of known and novel compounds which may have biological activity against diseases. We also wanted to compare the conventional (simple reflux) and unconventional (microwave irradiation) methods in the synthesis of precursors and the target molecule. We opted for microwave irradiation since a new scientific microwave synthesiser was available in our laboratory and this technique, an eco-friendly methodology, is a valuable technique for the synthesis of heterocycles in short reaction times and in relatively high percentage (%) yield .

The objectives of this study are to:

1. Synthesize bisquinolines from readily available, simple and cost effective starting compounds.
2. Purify the bisquinolines by chromatographic techniques and characterise the compounds by spectroscopy.
3. Compare the conventional and microwave energy sources.

The outcome of our research investigation is outlined in four Chapters as presented below:

In **Chapter 2**, the significance of organic chemistry, brief literature review related to malaria, discovery of anti-malarial drugs and energy sources utilised for the synthesis of anti-malarial drugs, the synthesis of quinoline through the Claisen condensation reaction and thermal cyclization, the use of the Vilsmeir Haack reaction and Schiffs base products are described and discussed.

In **Chapter 3**, we describe and discuss the synthesis of bisquinolines from simple, readily available and cost effective starting compounds. The synthesis was accomplished in four reaction steps using the Claisen condensation, thermal cyclisation, Vilsmeir Haack and thermal cyclization of the Schiffs base product. The discussion in this chapter also includes comparison of conventional versus microwave irradiation as energy sources. Although our original plan to synthesise the bisquionolines was successful, we have also reported some of our unsuccessful attempts which will encourage future investigation.

In **Chapter 4**, we describe the experimental procedures, the purification methods and the spectroscopic data of the pure compound.

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Chapter 2: Literature Review

2.1 Significance of Organic Chemistry

Chemistry occupies a unique place in our understanding of the universe and its composition. It is the science of molecules present in matter and space. But organic chemistry, although a branch of chemistry, is a vibrant and dynamic field of science which literally creates itself as it grows. The study of organic chemistry often involves a study of life by making new molecules that give information either available or unavailable from the molecules actually present in living things. This creation of new molecules has produced new materials such as plastics, dyes, perfumes and drugs.

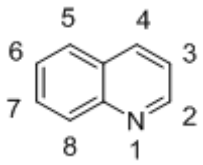
Most organic compounds available to us today are those obtained from living matter and non-living matter formed over millions of years. In earlier times, organic compounds known from nature were those in essential oils, which could be distilled from plants, and alkaloids which were extracted from crushed plants. [1]

The development of new methods for the synthesis of nitrogen-containing heterocycles is of extreme importance in organic chemistry since these types of compounds are used as drugs to alleviate various diseases in man. One such type is quinoline which belongs to the alkaloid class. For more than a century, organic chemists have focused their attention to the synthesis of quinoline and isoquinoline type compounds. Most of the classical synthetic routes are limited to certain substitution patterns and suffer from disadvantages such as harsh reaction conditions and poor yield. Hence, in recent years microwave technology was introduced as an effective energy source thereby enhancing yield and reducing reaction time. [2] Microwave methodology is an important technique and is widely

used in the medical, industrial and related fields for preparing compounds for human benefits.

In 1856 William Henry Perkin attempted the synthesis of quinine but by serendipity he produced the organic dye now called Perkin's mauve. This dye generated a huge amount of money thereby catalysing a huge interest in organic chemistry.

Quinoline compounds represent a major class of heterocycles and a number of preparations have been known since the late 1800s. The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties. [3] The quinoline skeleton structure is presented below:



2.2 Malaria and Its Global Impact on Human Health

Malaria, the most prevalent parasitic disease in the world, is caused by the apicomplex protozoan of the *Plasmodium* genus. Malaria is present all over the tropics, where four species, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* are transmitted to humans by the bites of the female mosquito vector of the *Anopheles* genus. In 2008, 109 countries were endemic for malaria, 45 of which are in Africa. There were an estimated 247 million malaria episodes in 2006. Around 86% of these cases occurred in Africa, causing over 1.25 million deaths.

The reason for such high morbidity and mortality stems from the fact that (i) the majority of the infections in Africa are caused by *P. falciparum*, the most dangerous of the four malarial parasites that infect humans, and (ii) the most effective malaria vector and the most difficult to control (*Anopheles gambiae*) is widespread in that continent. Approximately 80% of malaria cases in Africa were in 13 countries, and over half of them occurred in Nigeria, The Democratic Republic of the Congo, Ethiopia, Tanzania, and Kenya. Among the cases that occurred outside Africa, 80 % occurred in India, Myanmar, Bangladesh, Indonesia, Papua New Guinea and Pakistan. [4]

After Africa, India and Brazil are currently the regions of highest malaria endemicity in the world, being affected also by other *Plasmodium* species. Despite causing less mortality than *P. falciparum*, *P. vivax* is a widely distributed infection that has an enormous socioeconomic impact, being prevalent in South America, Asia and Oceania. There were approximately 881,000 malaria deaths in 2006, of which 91 % were in Africa and 85 % were of children under 5 years of age. The majority of children experienced their first malaria infection during the first few years of life, when they have not yet acquired adequate clinical immunity.

Although efforts of several non-profit partnership initiatives in the world, along with The Tropical Diseases Research Programme of the World Health Organization (TDR/WHO), have been made malaria can still be considered a neglected disease because it suffers from insufficient research and development in therapy and vaccines worldwide. As shown in **Fig. 1**, South-East Asia and the African regions are the most affected areas in the world, with a combined population of more than 700 million.

Currently, eighty countries are in the phase of malaria control; twelve countries are making the transition to an elimination programme, eleven countries are operating a malaria elimination programme, and six countries are actively engaged in preventing the reintroduction of malaria (**Fig. 2**). The latter are located along the edges of the global malaria distribution map (**Fig. 1**).

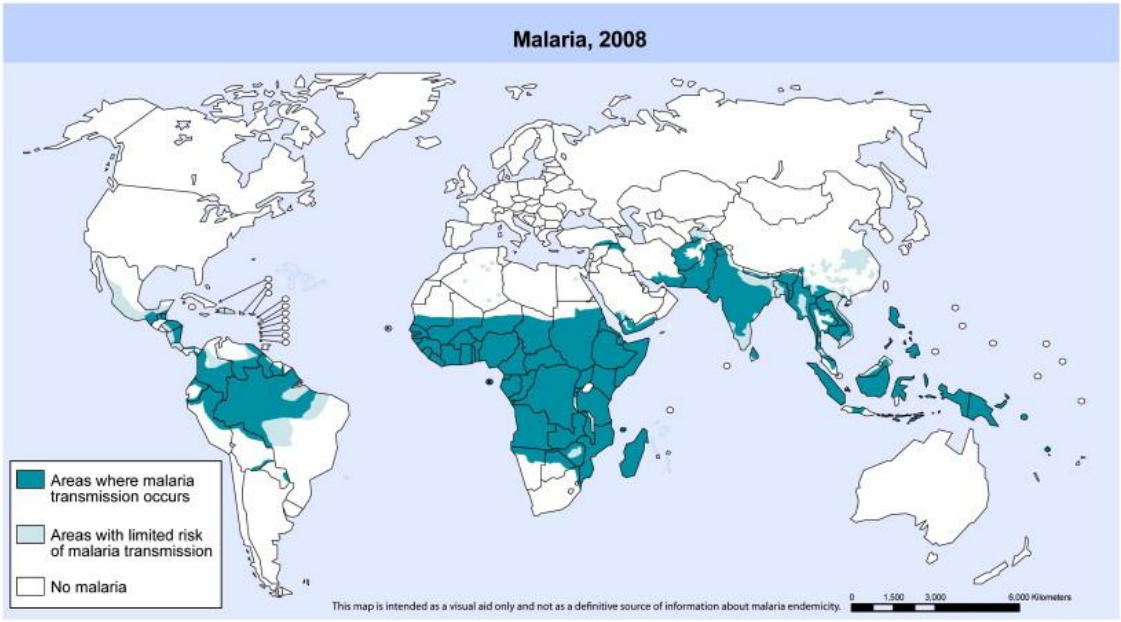


Figure 1: The global malaria distribution map.

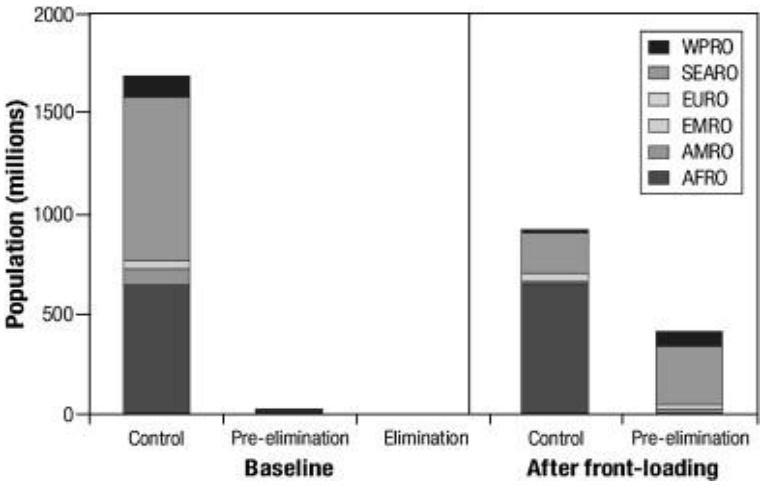


Figure 2: Estimated world population in different phases of malaria.

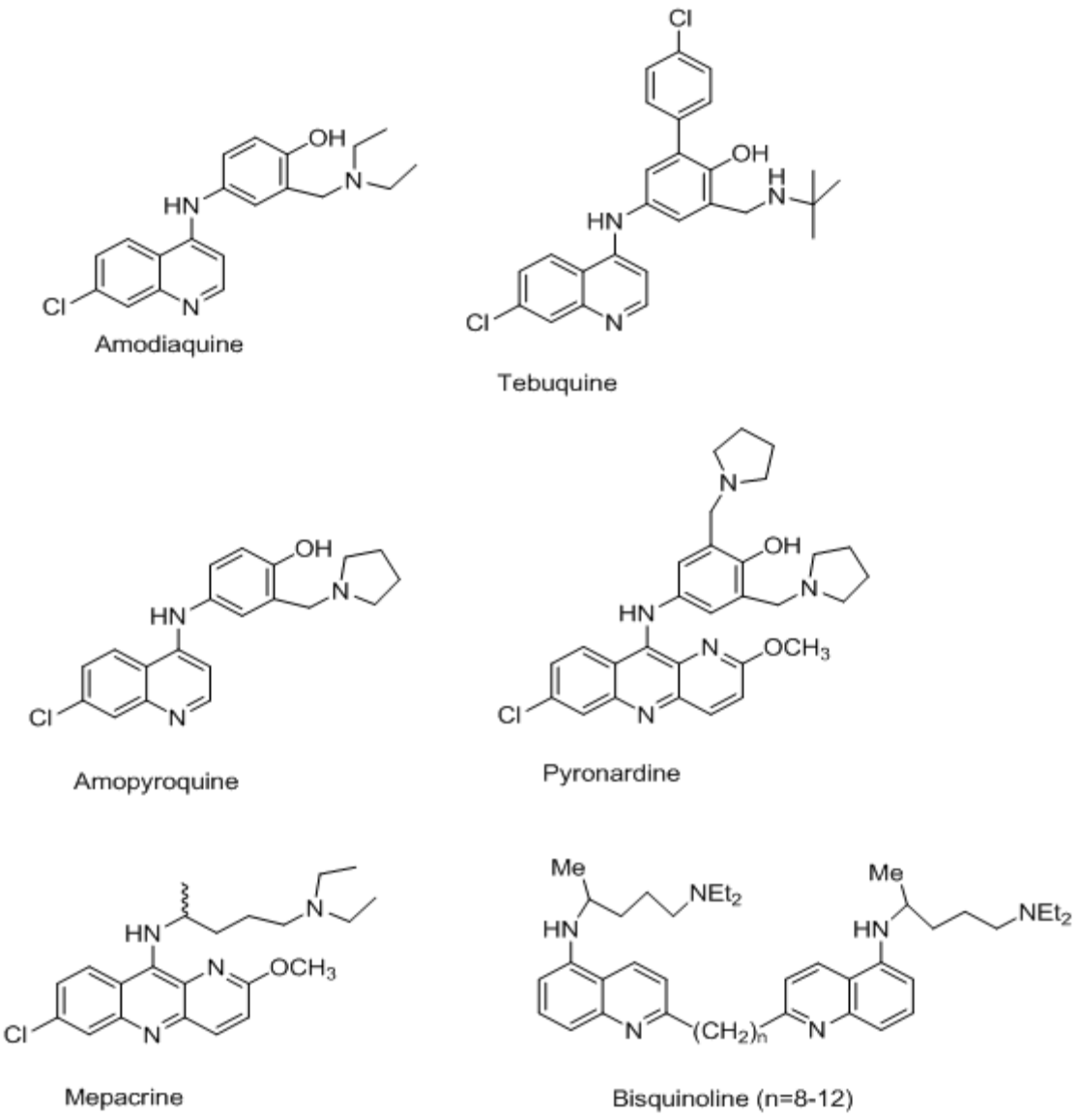
Even though chemotherapy has been successful to some extent, failures are frequent and due to a variety of factors such as the intrinsic characteristics of the disease, related to the conditions of transmission, and the difficult control of spreading through tropical areas. Primary factors are the complexity of the parasite life cycle and the development of drug resistance. Another critical factor is the increasing number of immune-compromised patients that suffer from malaria and human immunodeficiency virus (HIV) co-infections.

Reports suggest that the anti-malaria treatment failure is more common in HIV-infected adults with low CD 4-cell counts than in uninfected HIV- patients. On the other hand, acute malaria episodes causes a temporary increase in the viral replication of HIV and consequently of the plasma viral load. One study showed that HIV-infected children with advanced immune-suppression have more episodes of clinical malaria and higher parasite densities than HIV-infected children without advanced immune-suppression. Another study showed a clear tendency to increased mortality in children with co-infection. Together, these infections cause more than 4 million deaths a year. [4]

2.2.1. The Discovery of Anti-Malarial Drugs

Nature remains an ever evolving source for compounds of medicinal importance. The use of medicinal plants for the treatment of parasitic diseases is well known since ancient times. In the last 10 years anti-malarial drugs have been isolated from all natural sources including plant extracts; marine based bioactive natural products, fungi and bacteria. [5] Anti-malarial drugs were first discovered in the seventeenth century. [6] Despite intensive research attempts have been made, since then, malaria still poses a serious health problem, not only for short-term

travellers but especially for individuals who live permanently in endemic areas and those who are deployed to these areas on humanitarian and military missions. [7] Ethnic medicine has provided two of the most efficacious drugs, i.e. quinine and artemisinin. Various research teams have embarked on the screening of medicinal plants to yield new compounds which could eradicate this high priority disease. [8] Quinolines and its derivatives is an important class of anti-malarial drugs that function by targeting the parasite specific haemoglobin breakdown pathway. Throughout the 20th century, the immense use of chloroquine, the most famous drug of this group, provided well founded hopes for the eradication of malaria. [9] Important members of this class of compounds [9] are presented in **Scheme 1**.

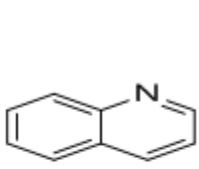


Scheme 1: The Structures of Some Important Quinoline type Compounds.

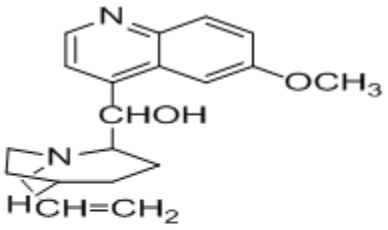
The value of the cinchona bark which is indigenous to certain regions of South America [10] for the treatment of intermittent fever was first known in Peru about 1630. For almost two centuries, a powder prepared from the cinchona bark was used for the treatment of malaria by 1669, the bark was described in early German pharmacopoeias and in 1677 it appeared in the London pharmacopoeia as Cortex peruvianus. In 1820 Pelletier and Caventou isolated the active ingredients of the Cinchona bark; they identified the compounds as quinine and cinchonidine. The

structure elucidation of quinine continued until Rabe was able to arrive at the correct structure; he was also the first researcher to synthesise dihydroquinine in 1931. Quinine was synthesized for the first time in 1944 by Woodward and von Doering and research interest in this field has continued to attract the attention of organic chemists ever since, between 1968 and 1973 several elegant syntheses were developed. [9].

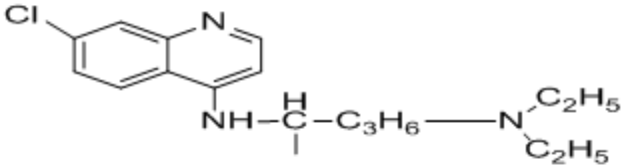
Quinine acts primarily as a blood schizontocide; it has little effect on sporozoites or pre-erythrocytic forms of malarial parasites. Quinine is mainly used intravenously as a rapid acting schizonticial drug to treat severe forms of multidrug resistant falciparum malaria. Over the last 50 years the use of quinine has been declining, due to the development of synthetic 4-aminoquinolines, such as chloroquine. [11] **Figure 2** present the structure of some quinoline-based anti-malarial drugs [8, 10]



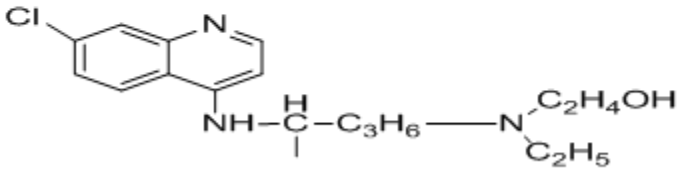
Quinoline



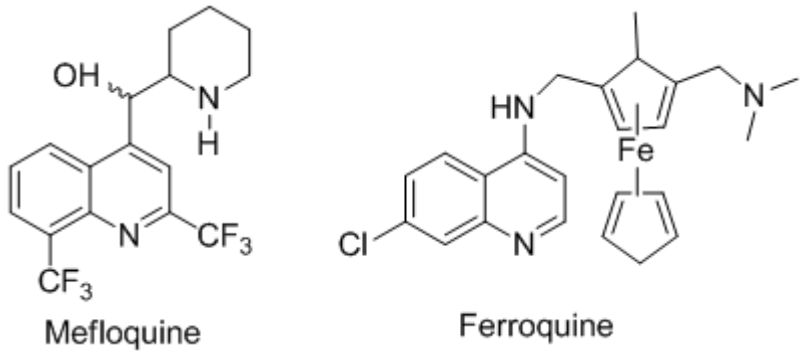
Quinine



Chloroquine

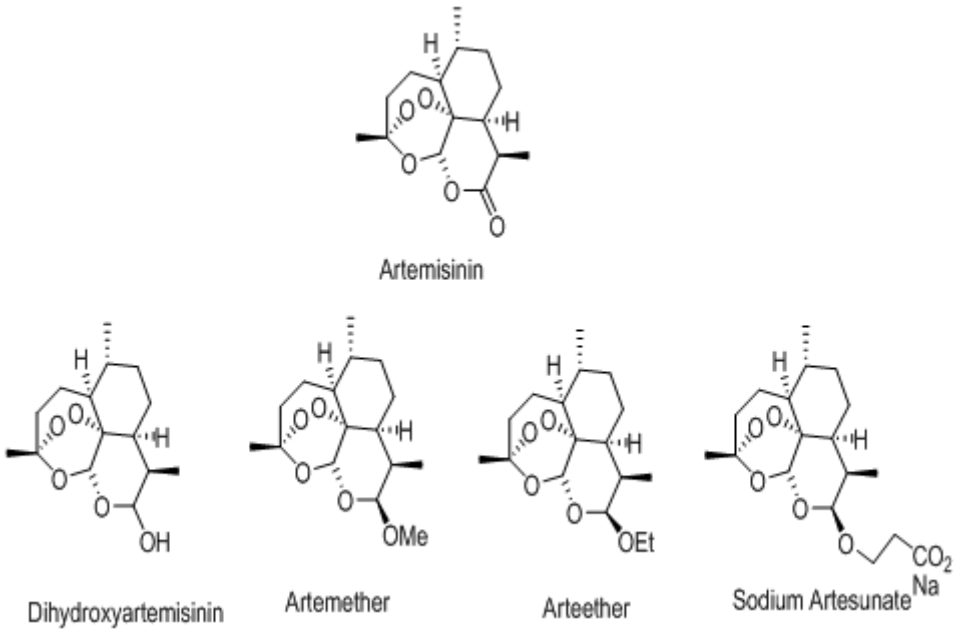


Hydroxychloroquine



Scheme 2: Structures of Some Quinoline-Based Anti-malarial Drugs

Owing to the success of chloroquine in protecting military personnel, in 1946, it rapidly became the most widely used anti-malarial drug. Unfortunately, chloroquine resistant strains of the parasite began to emerge as a consequence of its excessive use. [12] This led to the discovery of Artemisinin which was isolated from the Chinese plant Artemesia annua; this was successfully used against chloroquine-resistant malarial parasites. **Figure 3** indicates the structure of Artemisinin and its derivatives. [13]



Scheme 3: The Structure of Artemisinin and its derivatives

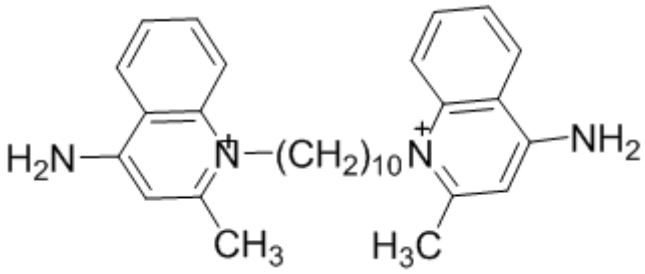
Amodiaquine was also introduced to combat chloroquine resistant malaria and has been used for the prophylaxis of falciparum malaria for over 20 years. Amodiaquine has shown a great efficacy though its use has been restricted due to concerns over its toxicity. This resulted in mefloquine, a quinoline methanol, being administered to patients in 1975. The efficacy of mefloquine unfortunately, was also decreasing owing to the development of mefloquine resistant parasites. Hence, the search for quinoline type compounds which can counteract the resistance mechanism of malaria parasites is still being sought after. [14]

In Africa, Malawi was the first country to switch from chloroquine to sulfadoxine-pyrimethamine for the first line treatment of malaria. [15, 16] In 2001, following high levels of chloroquine resistance in Rwanda, the combination of amodiaquine + sulfadoxine / pyrimethamine was adopted as the first line anti-malarial treatment. [17] A summary of some selected drugs used in malaria treatment caused by different *Plasmodium species* and clinical indications, as well as the main advantages and disadvantages of each is presented in **Table 1**, below. [4]

Table 1: Some Selected Anti-malarial drugs, advantages and disadvantages, clinical indications of *Plasmodium* species

Drug	Advantages	Disadvantages	Clinical indications of *Plasmodium* species
Chloroquine (CQ) phosphate, hydroxychlroquine	Fast action in RBC stages Hydrophilicity, good bioavailability, high volume of distribution	Widespread CQ-resistance, macular retinopathy	Uncomplicated malaria
	Oral dosage forms, low toxicity	Very long terminal elimination half-time (1–2 months)	*P. falciparum* (CQ-sensitive)
Quinine (QN) sulphate	Fast action in RBC stages, hydrophilic drug	Less potent than CQ	Severe malaria (IM/IV)
	Oral route formulation	Drug association is needed	P. vivax and *P. Falciparum*
Artemisinin:	Safe and well-tolerated	Neurotoxicity dose-dependent,	Severe complicated malaria management

Owing to an increased interest in the design of anti-malarial drugs, several bisquinolines were discovered and found to be active against chloroquine resistant strains of malaria. Bisquinoline, as the name suggest are compound that contain two quinoline nuclei combined through an aliphatic or aromatic linker. The design of new methodology for antimalarial drugs, such as, bisquinolines may circumvent the resistance mechanism by gaining access to the food vacuole by various mechanism from that used by chloroquine.[18] Examples of such agents include bis(quinolyl) piperazines, such as piperaquine, hydroxypiperaquine, dichloroquinazine and dequalinium. These bisquinolines compounds were more potent than chloroquine against both chloroquine-sensitive and resistant strains of malaria. [11]



Dequalinium

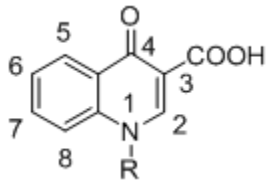
Dequalinium have been used in infectious diseases such as trichomoniasis, superficial mycosis, vaginal infections caused by a range of bacteria, fungi and skin infections. Dequalinium salts have been investigated as a safe and effective approach for the treatment of malaria. The salts are highly effective *in vitro* against strains of *P. Falciparum* at low concentrations. [18] Several compounds containing unique structural variations have been isolated and characterized from natural sources. These natural products have exhibited promising anti-malarial activities *in vitro* and *in vivo*. However, limitations such as toxicity, low bioavailability and poor

solubility have restricted the scope of the use for several natural products in humans. Nevertheless, nature provides novel leads which can be developed into safe drugs by synthetic manner as exemplified by artemether and quinoline class of anti-malarials. [5]

2.3. The Synthesis of Quinolones, Quinolines and Bisquinolines

2.3.1 Quinolones

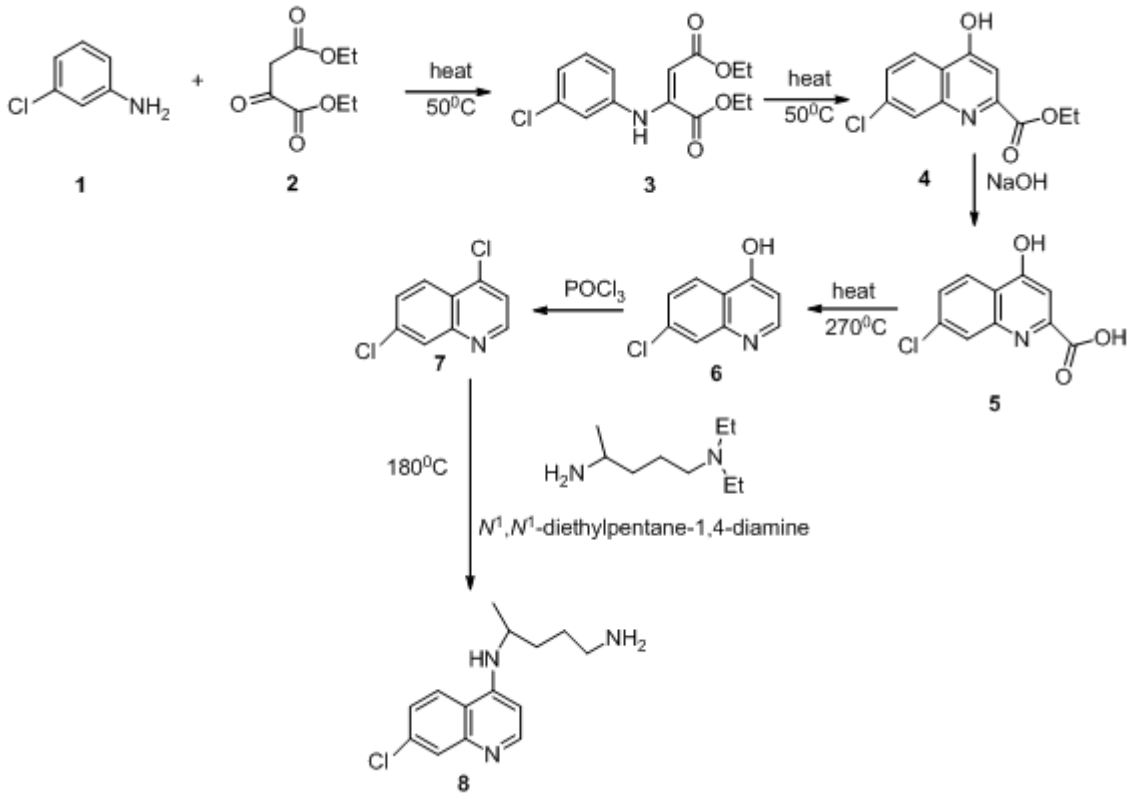
Among the nitrogen heterocycles, quinolones and their derivatives represent an important class of organic molecules attracting the interest of both synthetic and medicinal chemists. The quinolone skeleton structure is presented below:



Functionalized quinolones have found wide applications in the pharmaceutical and agrochemical industries. They are also useful synthetic blocks in the preparation of several alkaloids which are biologically active. Many syntheses of quinolone derivatives are known, but due to their significance, the developments of new synthetic approach remain an active research area. [19] An essential component of the search for new leads in the drug designing program is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features. [20]

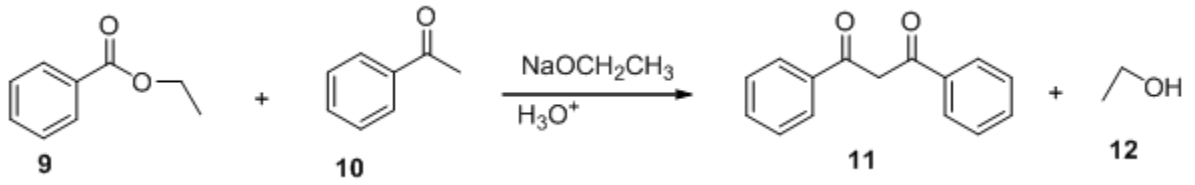
2.3.2 The Synthesise of Quinolines as Anti-Malarial Drugs

For the past six decades, chloroquine and other aminoquinolines have been the frontline anti-marials agents because of their therapeutic efficacy and lower cost. Several of these antimarial drugs, especially the compounds discovered from nature, are synthesised via the Claisen condensation reaction. [21] One such reaction scheme for the synthesis of chloroquine is presented in **Scheme 4**. The first step involves the Claisen condensation of m-chloroaniline with ethyl ethoxylacetate followed by ring closure to generate 4-hydroxyquinolinecarboxylate. The hydrolysis of this compound and subsequent decarboxylation of the resulting acid provided 4-hydroxyquinoline; reaction with $POCl_3$ provided 4, 7-dichloroquinoline which on nucleophilic substitution with N, N-diethylpentane-1, 4-diamine provided chloroquine.



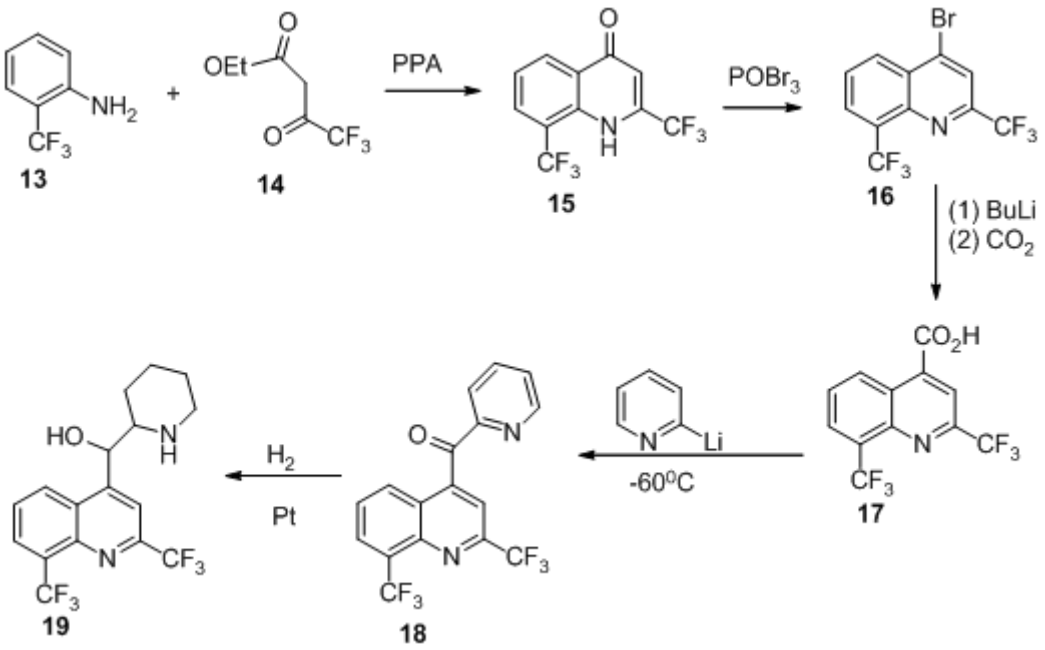
Scheme 4: The Synthesis of Chloroquine Using the Claisen Condensation Reaction.

When carboxylic esters containing a α-hydrogen are treated with a strong base such as sodium ethoxide, condensation occurs to give α-ketoester. This reaction is called the Claisen condensation. When it is carried out with a mixture of two different esters, each of which possesses α-hydrogen, a mixture of all products is obtained and the reaction is seldom useful synthetically. A typical reaction showing the Claisen condensation is presented below:



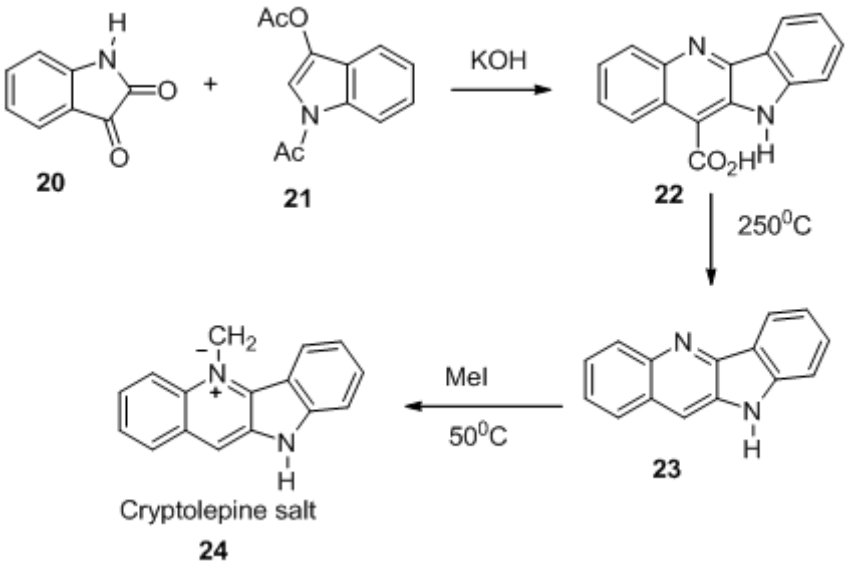
9 **10** **11** **12**

Mefloquine, a quinoline methanol derivative, is a derivative of quinine. A synthetic route was reported by Lutz *et al*. [22] which started with the condensation of p-trifluoromethylaniline with ethyl trifluoroacetoacetate using polyphosphoric acid to provide 4-quinolone. The conversion of the quinolone to 4-bromoquinoline using $POBr_3$, followed by carboxylation produced cinchonic acid and subsequent addition of pyridyllitium to the cinchonic acid provided pyridyl ketone, which on reduction with H_2/Pt gave mefloquine showed in **Scheme 5** below:



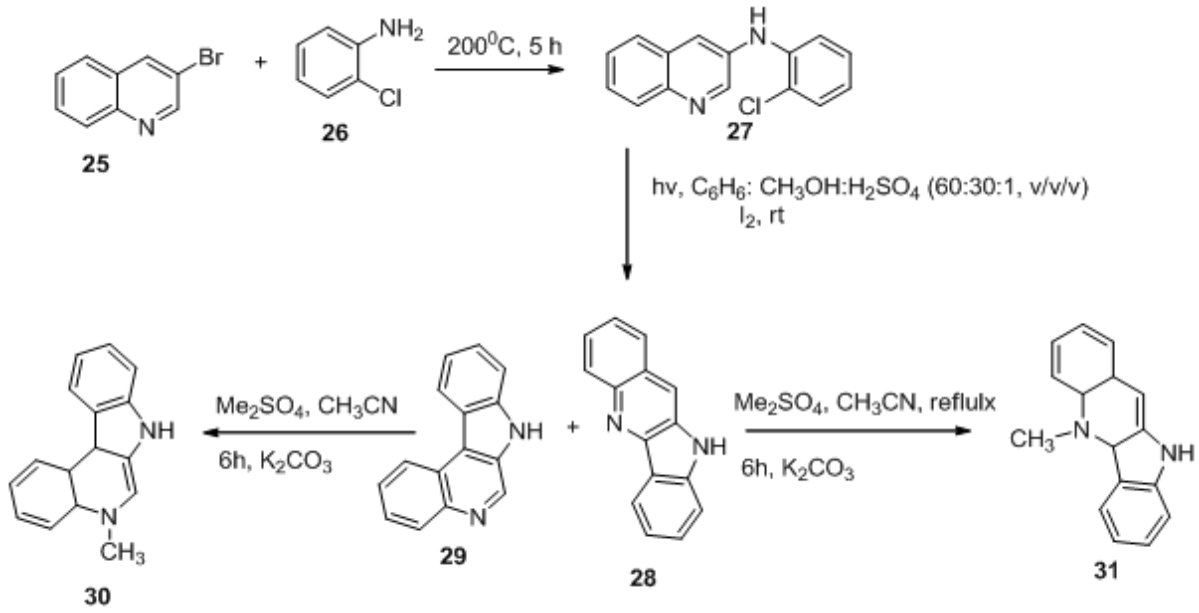
Scheme 5: An Outline for the Synthesis of Mefloquine

Crytolepine salts are indoloquinoline alkaloid present as the major constituent of the roots of the climbing shrub Cryptolepis sanguinolenta, commonly used in West Africa in the clinical therapy of malaria as well as other diseases. The synthesis of cryptolepine was accomplished well before it was even isolated from nature. Several syntheses of the alkaloid are reported in the literature however the most straight forward total synthesis of cryptolepine is based on the synthesis by Holt and Petrow [23], which begins with the condensation of isatin with N, O-diacetylindoxyl, followed by decarboxylation of the resulting quindoline-11-carboxylic acid to provide quindoline. Subsequent methylation of the quindoline with methyl iodide provided the crytolepine salt. This reaction is outlined in **Scheme 6**.



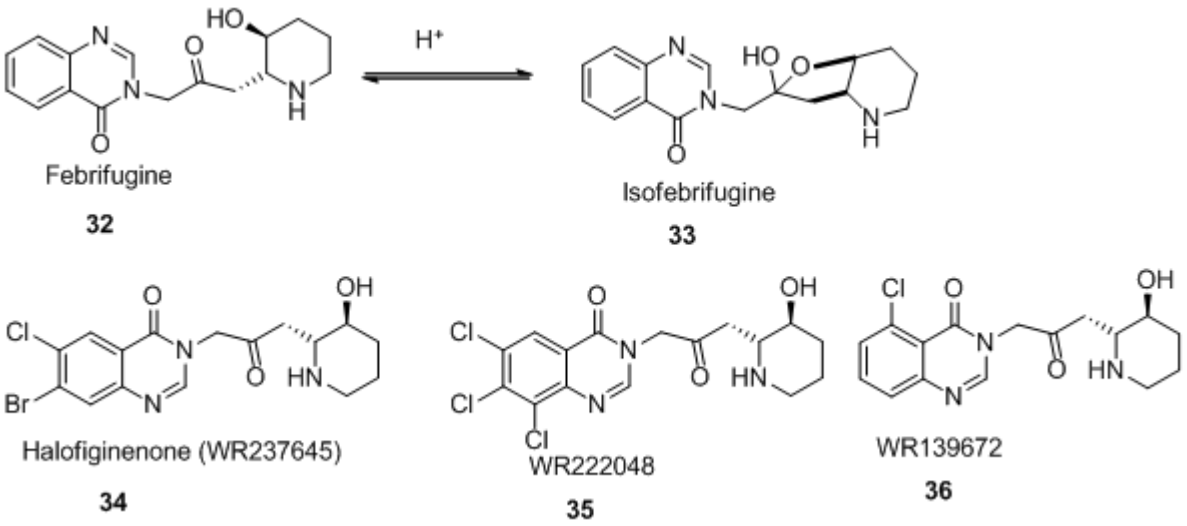
Scheme 6: The Synthesis of Cryptolepine Salt

In 2006 Mohan *et al.* [24] described the synthesis of indoloquinoline alkaloids using the concept of heretoatom-directed photoannulation. This approach involves an efficient three-step synthesis of indoloquinoline alkaloids via amination of appropriate haloquinolines with anilines. The reaction of 3-bromoquinoline with anilines and resulted in intermediates on photochemical irradiation followed by oxidative cyclization afforded the corresponding indoloquinolines. When irradiated, the linear fusion product provided quindoline **23** as a minor product. The quindoline on selective methylation on the quinoline nitrogen afforded the alkaloid cryptolepine. The angularly fused indoloquinoline on methylation afforded isoneocrytolepine, which is a synthetic indoquinoline alkaloid. The reaction is outlined in **Scheme 7**.



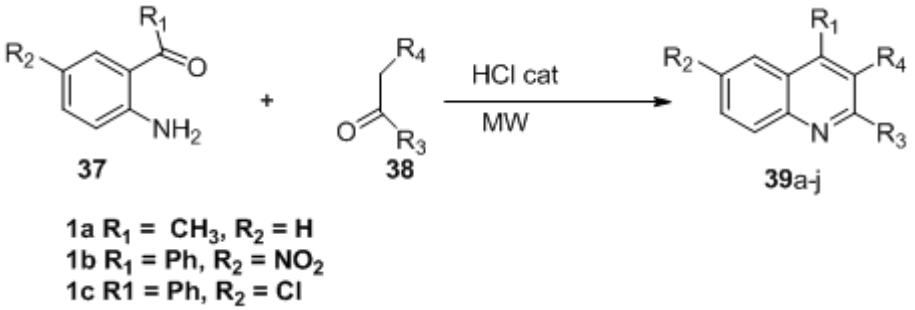
Scheme 7: The Synthesis of Isoneocrytplepine.

The alkaloid mixture febrifugine **28** and isofebrifugine **29** [25] originally isolated from the root of *Dichroa febrifugal* and extracted from the leaves and buds of *Hydrangea macrophylla* var. *Otaksa* has been used in Chinese traditional medicine to treat malaria for over 4000 years. Isofebrifugine **29** is an isomer of febrifugine obtained via the mechanism proposed by Berkelhammer *et al*. Febrifugine is believed to block the proliferation of malarial parasites and acts by impairing haemazoin formation required for maturation of the parasite at the trophozoite stage. The reaction scheme is outlined in **Scheme 8**.



Scheme 8: Febrifugine and Some Selected Derivatives.

In the past decades, synthesis of substituted quinolines via the Friedlander reaction was reported. Although it has been known for more than a century, it is still the most useful method for the preparation of such class of compounds. In many cases acid catalyzed Friedlander condensations have been found to be more effective than those by bases, especially one of the reactants being 2-aminoarylketone. The synthesis of quinoline derivatives carried out in a domestic microwave oven is illustrated in **Scheme 9**:



Scheme 9: Preparation of quinoline derivatives by microwave irradiation

The scheme above indicates the preparation of a series of nine quinoline derivatives (3a-j) in good yields by the reaction of 2-aminoacetophenone or benzophenones (1) with a variety of ketones and keto esters (2) and a catalytic amount of concentrated hydrochloric acid. [26]

2.3.3 The Use of Vilsmeier-Haack Reaction in the Synthesis of Heterocycles

Currently there has been relentless interest towards the use of Vilsmeier-Haack reagent in organic synthesis of several nitrogen and oxygen heterocycles. It is proved to be a mild and efficient method for the formylation of reactive aromatic and hetero aromatic substrates. [27-31] Its versatility has been further extended as an activating agent for acylhalo addition [32] and ring annulation. [33-45] Besides the aromatic formylation, a wide variety of carbonyl compounds [46] activated methyl and methylene groups [47] and oxygen, [48] nitrogen neucleophiles [48] efficiently react with Vilsmeier-Haack reagent to yield the corresponding iminium salts. The intramolecular cyclisation potential of halomethyleniminium salts formed under Vilsmeier condition and microwave induced Vilsmeier conditions were studied and reported [49-50], very recent one being oxazolone [51] and 2-chloro-3-formylquinoline [52] synthesis. The utility of this reagent also explores the intramolecular cyclization of azides by iminium species. [53-54] There has been instances in which chloromethyleniminium salt reacts with active methyl groups followed by intramolecular cyclisation by the neucleophilic attack of adjacent group. [55] Based on the above facts, it is very much evident that the reactive intermediate involved in Vilsmeier-Haack reaction are the halomethyleniminiun salts derived from the respective formamides. [56-57] The classical Vilsmeier-Haack reactions involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium

salt to yield the corresponding iminium species, which facilitates easy entry in to large number of novel heterocyclic systems.

2.3.4 The Importance of Schiff Base in the Synthesis of Imines

Schiff base or azomethine chemistry occurs when a primary amine reacts with a carbonyl compound to give imines. In nature it serves to interconvert amino acids and alpha-ketoacids into one another with the help of vitamin B6 (pyridoxame-pyridoxal) as coenzyme in transamineses. [58] Schiff bases are important chemicals since the imine group is present in a large number of natural and synthetic products. [59] It has also been widely used in organic chemistry for numerous purposes such as in synthesis of metalloprotein models, asymmetric catalysis and corrosion inhibitors since the 1800s. [58] Schiff bases are also an important class of ligands in co-ordination chemistry and find extensive application in different fields.

Ever since Laurent and Gerhard synthesized the first organic imine by condensation of benzylaldehyde with aniline, numerous researchers have been actively investigating this class of compounds. Schiff bases derived from aromatic carbonyl compounds have been widely studied in connection with metalloprotein models and asymmetric catalysis due to the versatility of their steric and electronic properties. Schiff bases and their biologically active complexes have been often used as chelating ligands in the co-ordination chemistry of transition metals as radiopharmaceuticals for cancer targeting, agrochemicals as model systems for biological macromolecules, as catalysts and as dioxygen carriers. [60] The formation of an imine from aldehyde and a primary amine, force the liberation of one molecule of water per molecule of imine. Consequently, for some carbonyl compounds the formation of imines is facilitated when water is removed from the reaction mixture.

Therefore, in many experiments water removing techniques or reagents is employed. [58]

2.3.5 The Cyclization of Imines to Produce Bisquinolines

The presence of a cyclic structure in the basic frame work of many complex and biologically interesting molecules has made their formation a fundamental process in organic synthesis. Therefore, ring forming processes have garnered the attention of synthetic chemists for many years. [61] The most attractive methodology is to apply intramolecular rearrangement, transition metal catalyzed cyclization reaction, simple basic condensation cyclization and solid phase cyclization reaction. Several other cyclization methods have been used to form a heterocycle compound. One such interesting methodology uses a Schiff base product which generally requires a base such as dimethyl formamide and potassium carbonate; this reaction can occur even at room temperature for certain substrates. [62]

2.4 Energy Sources Used For Synthesis

In the early years of synthetic organic chemistry, chemical reactions which required heating was conducted by using traditional heat transfer equipments such as oil, water and sand baths and heating jackets. These heating techniques, although very useful, are rather slow and allows for the development of a temperature gradient within the sample [63] thereby creating a hot surface on the reaction vessel where products, substrates and reagents often decompose over time. [64]

In contrast, microwave energy generated via a dedicated microwave system is introduced into the chemical reactor remotely and direct access by the energy source to the reaction vessel is obtained. The microwave irradiation (MWI) passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel itself. If the apparatus is properly designed, the temperature increase will be uniform throughout the sample which minimises by-products and decomposition products. In a pressurized system, it is possible to rapidly increase the temperature far above the conventional boiling point of the solvent that is used in the reaction.

Microwave oven for the heating of food has existed for more than 50 years. In the 1970s, the construction of the microwave generator, the magnetron, was both improved and simplified. Consequently, the prices of domestic microwave ovens fell considerably, leading to them becoming mass produced. The design of the oven chamber or cavity; however, which is crucial for the heating characteristics, was not significantly improved until end of the 1980s. In inorganic chemistry, microwave technology has been used since the late 1970s, while it has only been implemented in organic chemistry since the mid-1980s. The development of the technology for organic chemistry has been rather sluggish compared, to for example, combinatorial chemistry and computational chemistry. This slow uptake of technology has been principally attributed to its lack of controllability and reproducibility, safety aspects and generally low degree of understanding of the basics of microwave dielectric heating.

Since the mid-1990s, however, the number of publications based on microwave irradiation has increased significantly. The main reasons for this increase include the availability of scientific microwave equipments designed for organic synthesis and

the development of solvent-free technique which has improved the safety aspects but are mostly owing to an increased interest in shorter reaction times. The short reaction times and expanded reaction range that is offered by microwave assisted organic synthesis are suited to the increased demands in industry.[59] This technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes. [64]

For the past five decades, reports on microwave technology for the synthesis of heterocycles and macro molecules have been well documented. [65-66] Different types of mechanisms such as Diels Alder, hetero Diels Alder, 1, 3-dipolar addition and some ring closure reactions have been achieved by microwave technology. In essence it is an eco-friendly, less time consuming, high yield and solvent less methodology.

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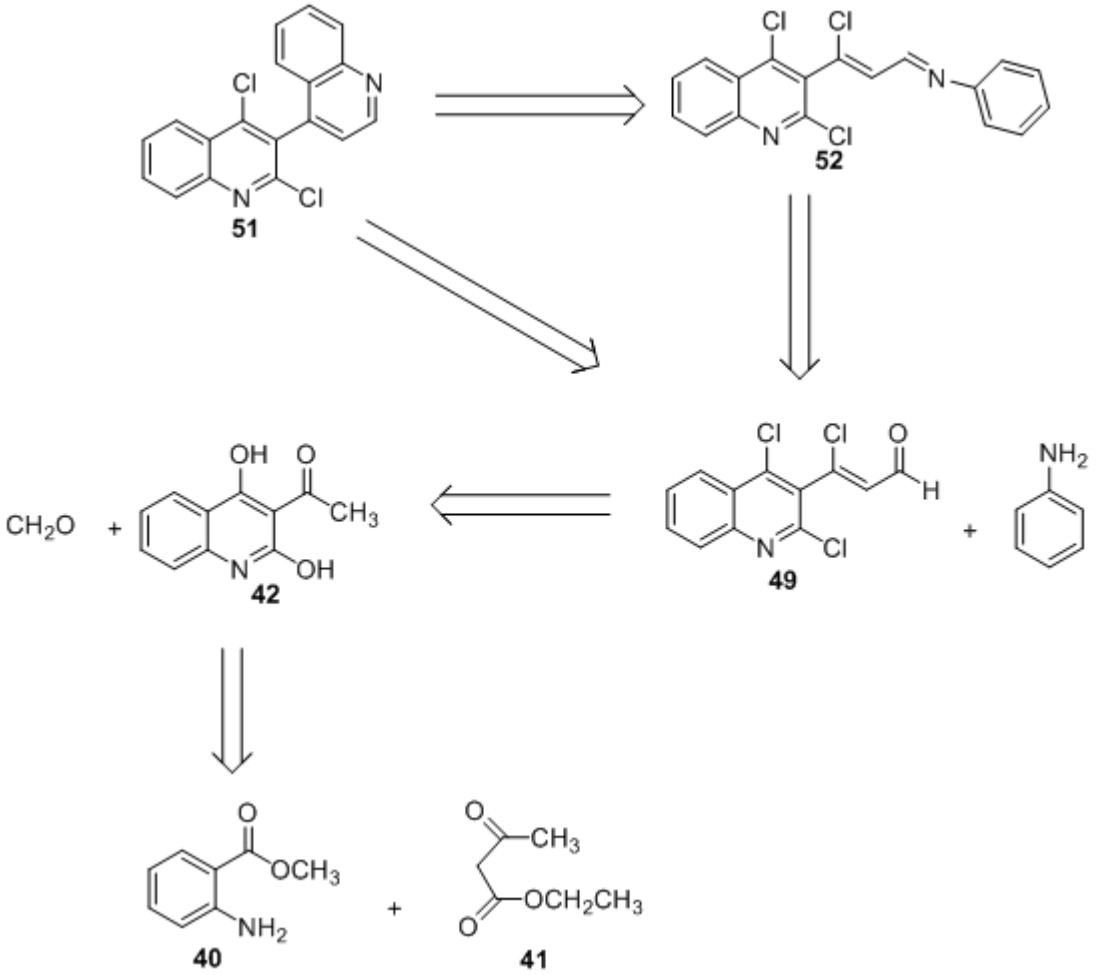
Chapter 3: Results, Discussion and Conclusion

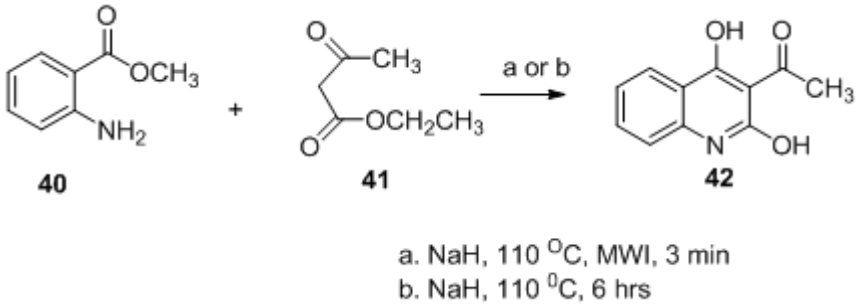
Our research thrust in the synthesis of novel drugs, especially compounds directed towards malaria, arose because of the development of a simple route, by Professor P.S. Mohan from Bharathiar University, who initiated the synthesis of quinolines by photochemical and microwave irradiation techniques. We decided to use this protocol and further develop a strategy to synthesise bisquinolines and some simple derivatives since this class of compounds have been recently reported as active to several life-threatening diseases such as malaria and HIV-AIDS. Furthermore, we decided to use known methods from literature such as the Claisen condensation, Vilsmeir-Haack reaction, Schiff base chemistry and simple thermal cyclization methods to achieve our research goals.

Scheme 10 presents a disconnection approach to the simple precursors. Our approach was to synthesise a quinolone skeleton using methyl 2-aminobenzoate **40** and acetoacetate **41** as these reagents were readily available in our laboratory and our research group reported this synthesis earlier. This product would then be used to prepare the other precursors and eventually to our target molecules.



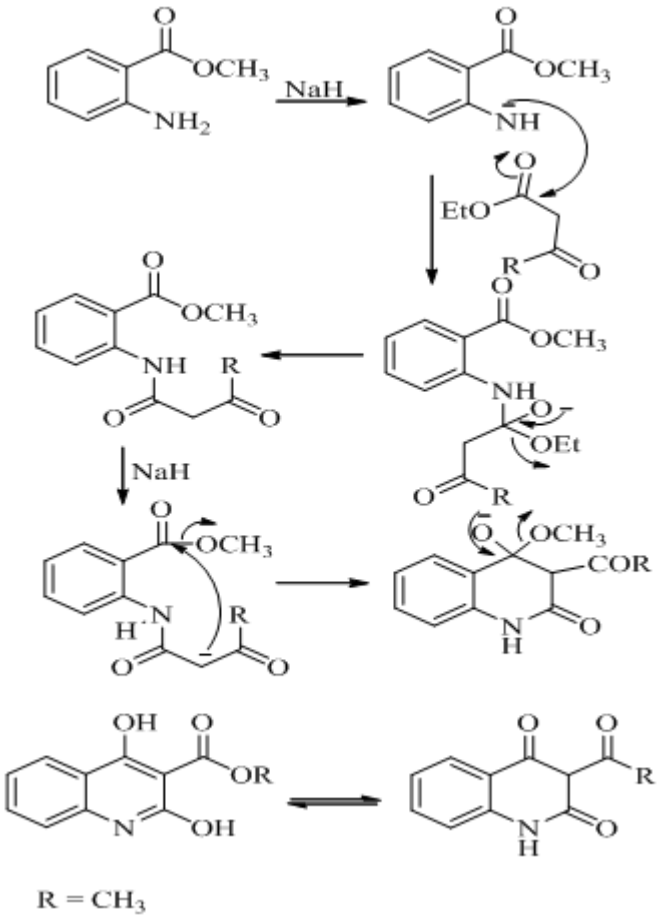
Scheme 10: Retrosynthesis of Bisquinoline (2, 4-dichloro-3, 4'-biquinoline)

The first step in the reaction scheme was to synthesise the 3-acyl-2, 4-dihydroxyquinoline **42**. Here we heated an equimolar mixture of methyl-2-aminobenzoate (methyl anthranilate) and ethyl acetoacetate in the presence of sodium hydride at 110 ^{0}C in a CEM synthetic microwave oven. The time required for complete conversion of substrates to products was only 3 minutes. The yield of 3-acyl-2, 4-dihydroxyquinoline was 90 %**.** The reaction is presented in **Scheme 11**. The reaction was then repeated by refluxing the substrate mixture for 6 hours. The yield of 3-acyl-2, 4-dihydroxyquinoline was 75 %, much lower than by microwave irradiation.

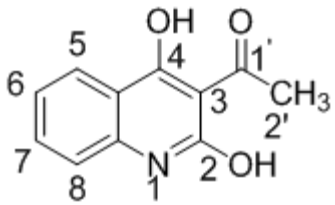


Scheme 11: Preparation of 3-acyl-2, 4 dihydroxyquinoline

In this reaction, two types of Claisen condensation mechanisms were followed during the formation of product as illustrated in **Scheme 12**. In the first step the proton is abstracted from the amino group in methyl anthranilate and this nucleophile attacks the ester carbonyl in the ketoester; this is followed by the removal of an ethoxide ion. The product then undergoes an intramolecular Claisen condensation whereby the proton is abstracted from the active methylene group position in between the two carbonyl groups and the new nucleophile attacks the ester carbonyl group attached to the phenyl ring. This is followed by elimination of an ethoxide ion to produce the required product.



Scheme 12: Reaction mechanism for the synthesis of 3-acyl -2, 4-dihydroxyquinoline



42

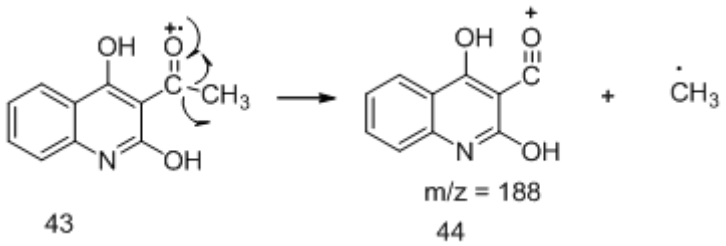
The compound **42** was characterised by IR, ^{1}H, ^{13}C NMR, and Mass spectroscopy; **Figure 3** in Appendix 1 (page 78) shows the IR spectrum. The keto carbonyl stretching is at 1664 cm $^{-1}$ and the phenolic OH stretching is at 3162 cm $^{-1}$. The C=C stretch is at 1487 cm $^{-1}$, the $-CH_3$ of CH_3 CO group occurs at 1410 cm $^{-1}$ and C-CO-C stretching and bend at 1247.

Table 2: ^{1}H NMR and ^{13}C NMR data of 3-acyl -2, 4-dihydroxyquinoline

Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)
C_2	174.74	17.00 (bs, 1H, -OH)
C_3	105.80	-
C_4	161.16	11.31 (bs, 1H, -OH)
C_{4a}	115.45	-
C_5	121.93	8.00 (d, J = 7.1 Hz, 1H)
C_6	124.68	7.65 (t, J = 7.1 Hz, 1H)
$C_7 – C_8$	135 – 128.11	7.10 – 7.32 (m, 1H, H-7 & H-8)
C_{8a}	140.71	-
$C_{1'}$	205.92	-
$C_{2'}$	30.54	2.56 (s, 3H)

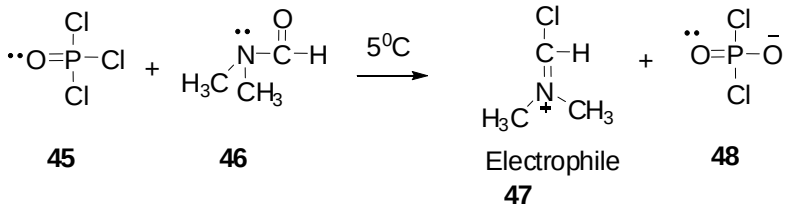
The ^{1}H NMR spectrum is presented in **Figure 4** (Appendix 2, page 79). A singlet at δ 2.56 ppm indicates the methyl hydrogen whereas the two broad singlets at δ 17.00 ppm and δ 11.31 ppm indicates the two OH protons. Four aromatic protons occur at doublet, triplet, doublet, triplet, 8.0, 7.65, 7.25 and 7.20 ppm, respectively. The ^{13} C NMR spectrum in **Figure 5** (Appendix 3, page 80) indicates 11 carbons; the carbonyl group C=O occurs at δ 205 ppm, C_2-OH and C_4-OH at 174 and 161 ppm, respectively. The CH_3 carbon appears at δ 30 ppm.

The Mass spectrum in **Figure 6** (Appendix 4, page 81) shows its molecular ion [$M^{+\cdot}$] signal at m/z 203. The signal at m/z 188 is due to a loss of a CH_3 group as indicated by the mechanism:

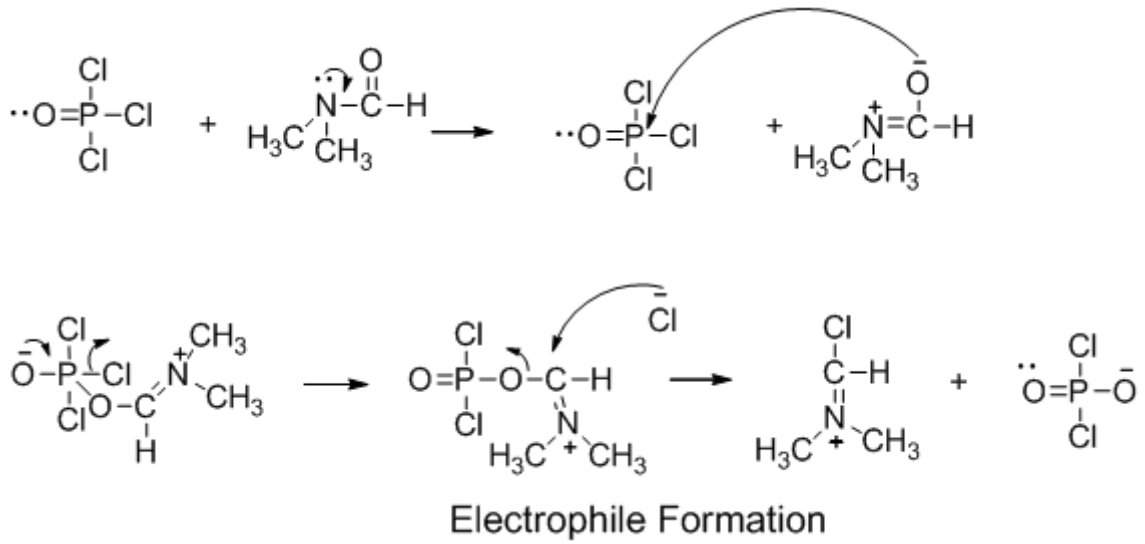


These data were compared to literature values and we confirmed the product of the first step of the reaction as 3-acyl -2, 4-dihydroxyquinoline.

The second step of our reaction outline required the synthesis of 3-chloro-3-(2, 4-dichloroquinolin-3yl) acrylaldehyde. We used the Vilsmeir-Haack reaction by combining DMF and $POCl_3$ at 5 ^{0}C to form an electrophile in the absence of strong acid or Lewis acid. This type of reaction is a substitute for the Friedel-Crafts acylation reaction and works with aromatic compounds at the more reactive end of the molecule. **Scheme 13** shows the reaction for the formation of the electrophile whilst **Scheme 14** shows the mechanism.

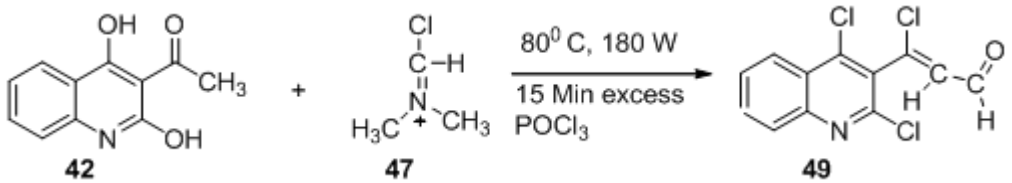


Scheme 13: Preparation of electrophile



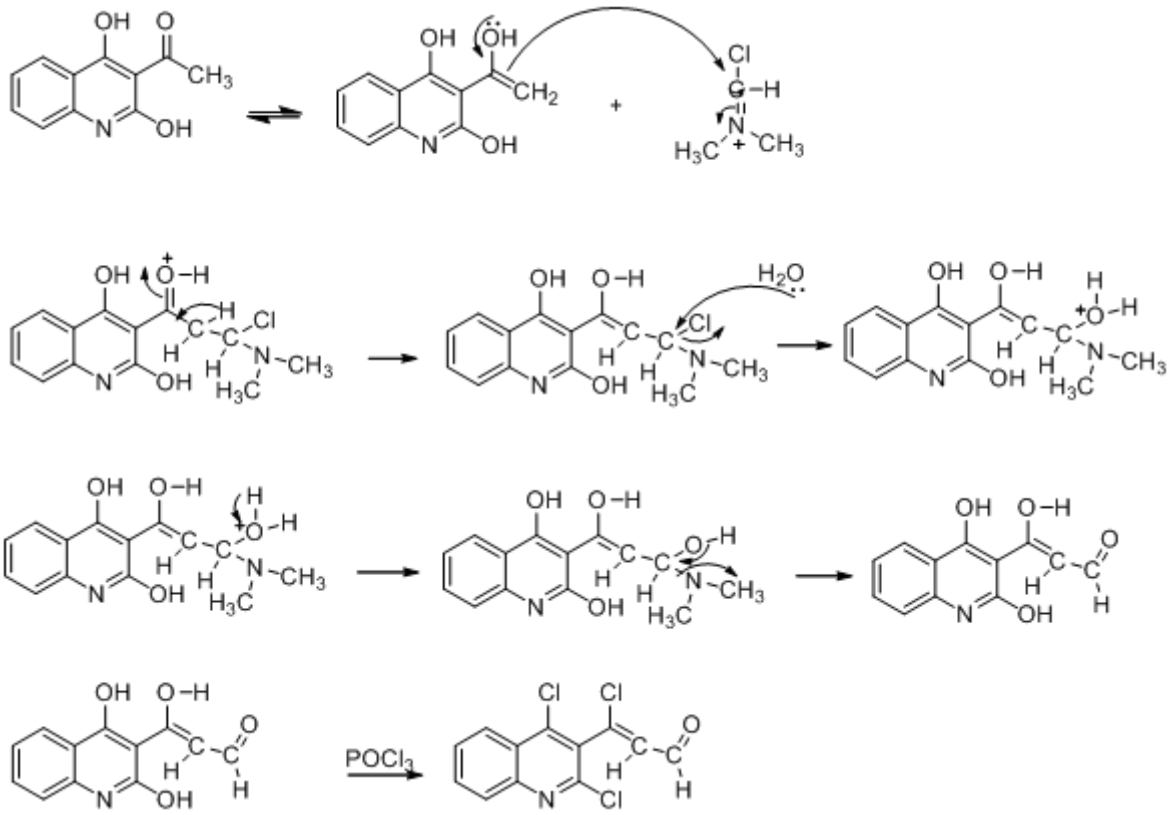
Scheme 14: The Mechanism Showing the Formation of the Electrophile.

This electrophile reacted with 3-acyl-2, 4-dihydroxyquinoline at 80 ^{0}C, 180 Watts for 15 minute under MWI. The work up for the reaction was performed with aqueous sodium carbonate to hydrolyse the imine salt and remove any acid formed. The yield of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline was 72 %. The reaction was then repeated by refluxing the substrate mixture for 17 hours. The yield of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline was 65 %. The reaction is presented in scheme 15. This method of synthesis is very useful because it requires DMF to add a formyl (CHO) group and thereby increases the carbon length. This objective is difficult to achieve via. a conventional Friede-Crafts reaction.



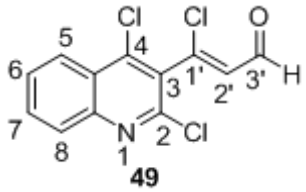
Scheme 15: Preparation of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline

The mechanism for the Vilsmeir-Haack reaction is presented in **Scheme 16**. The *insitu* generated electrophile (**Scheme 14**) reacts with 3-acyl-2, 4-dihydroxyquinoline in its tautomeric form. The movement of lone pairs of electron from the hydroxyl group forces the double bond to break and bond with the electrophile. An unstable intermediate product is formed with the oxygen carrying a positive charge. Therefore, hydrogen is abstracted from the nearest hydrocarbon group to neutralise the positive charge on the hydroxyl group. Water molecules attacks the latter thereby substituting the Cl^-; a positive charge is formed since water uses the lone pairs to create a bond with carbon. An intramolecular rearrangement occurs and results in forcing the *N* $(CH_3)_2$ to leave; hence, it produces a product containing the hydroxyl groups. These hydroxyl groups are substituted by chlorines owing to the excess of $POCl_3$ to form 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline.



Scheme 16: The Mechanism for the Vilsmeir-Haack Reaction

Vilsmeir-Haack reactions are not only used to formylate aromatic and aliphatic compounds but are also employed in most of the ring closure reactions to produce considerably higher yield products. The classical Vilsmeier-Haack reaction, however, involves electrophilic substitution of an activated aromatic ring with a halomethyleniminium salt to yield the corresponding iminium species, which facilitates entry into large number of novel and biologically potential heterocyclic systems.



49

Compound **49** was then characterised; **Figure 7** in Appendix 5 (page 82) shows the IR spectrum. The aldehydic CHO stretching is at 2860 cm $^{-1}$ and the normal aldehyde C=O stretching is at 1677 cm $^{-1}$. The olefinic C=C-C=O stretch is at 1616 cm $^{-1}$, the aldehyde C-H bend occurs at 758 cm $^{-1}$ and C=C stretching occurs at 1556 cm $^{-1}$. The disappearance of OH stretching between 3600 – 3200 cm $^{-1}$ indicates that chlorination was achieved.

The ^{1}H NMR spectrum is presented in **Figure 8** (Appendix 6, page 83); singlet at δ 6.45 ppm indicates the ethylene hydrogen whereas the singlet at δ 10.4 ppm indicates the CHO protons. Four aromatic protons occur as doublet, doublet, triplet, triplet at 8.25, 8.10; 7.9, 7.6 ppm, respectively. The ^{13} C NMR spectrum in **Figure 9** (Appendix 7, page 84) indicates 12 carbons; the carbonyl group C=O occurs at δ 190 ppm and the CH ethylene is at δ 129.5 ppm. The C stretching from δ 130 – 150 ppm is for the quinoline moeity.

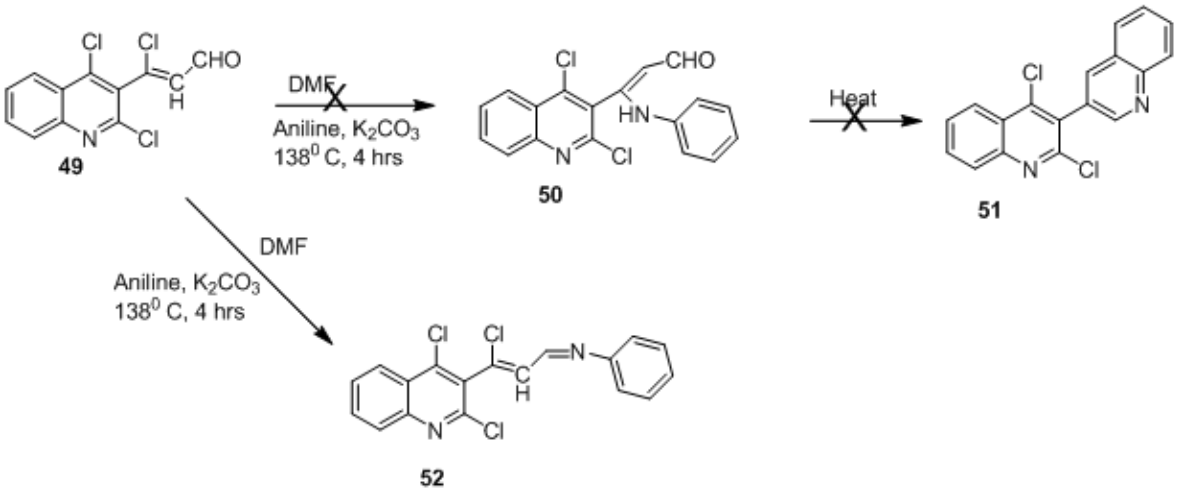
Table 3: ^{1}H NMR and ^{13}C NMR data of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline

Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)
C_2	146.7	-
C_3	131.9	-
C_4	147.7	-
C_{4a}	121.1	-
C_5	124.8	8.26 (d, J = 7.1 Hz, 1H)
C_6	128.9	7.71 (t, J = 7.1 Hz, 1H)
C_7	133.8	7.86 (t, J = 7.1 Hz, 1H)
C_8	131.6	8.00 (d, 1H, J = 7.1 Hz)
C_{8a}	144.7	-
$C_{1'}$	143.1	-
$C_{2'}$	131.9	6.73 (d, J = 8.0 Hz, 1H)
$C_{3'}$	190.0	10.3 (d, J = 8.0 Hz, 1H, -CHO)

The Mass spectrum in **Figure 10** (Appendix 8, page 85) shows its molecular ion [$M^{+\cdot}$] signal at m/z 285. These data were compared to literature values and we confirmed the product of the second step of the reaction as 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline.

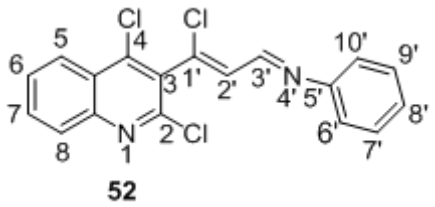
Our next objective was to synthesise bisquinoline from 3-chloro-3-(2, 4-dichloroquinolin-3yl) acrylaldehyde **49** by a one pot reaction in the presence of DMF, weak alkaline salt, and aniline. This reaction was expected to produce a highly reactive imine **50** which would cyclise immediately as reported [64] in the synthesis

of a hydrogenated spiro derivative of quinolines. The reaction is presented in **Scheme 17**.



Scheme 17: The proposed pathway for the formation of Schiff base product

The completion of the reaction of the substrate with aniline, DMF, K_2CO_3 was monitored by TLC. It was observed that the completion of the reaction occurred in 4 hours. A new spot was observed on the TLC plate. Column chromatography was used to purify the crude mixture to produce a yellow compound **52**. The yield of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline **52** was 61 %.



52

The new compound was then characterised by IR, ^1H, ^{13}C and Mass spectra; **Figure 11** (Appendix 9, page 86) shows the IR spectrum. The imine stretching is at

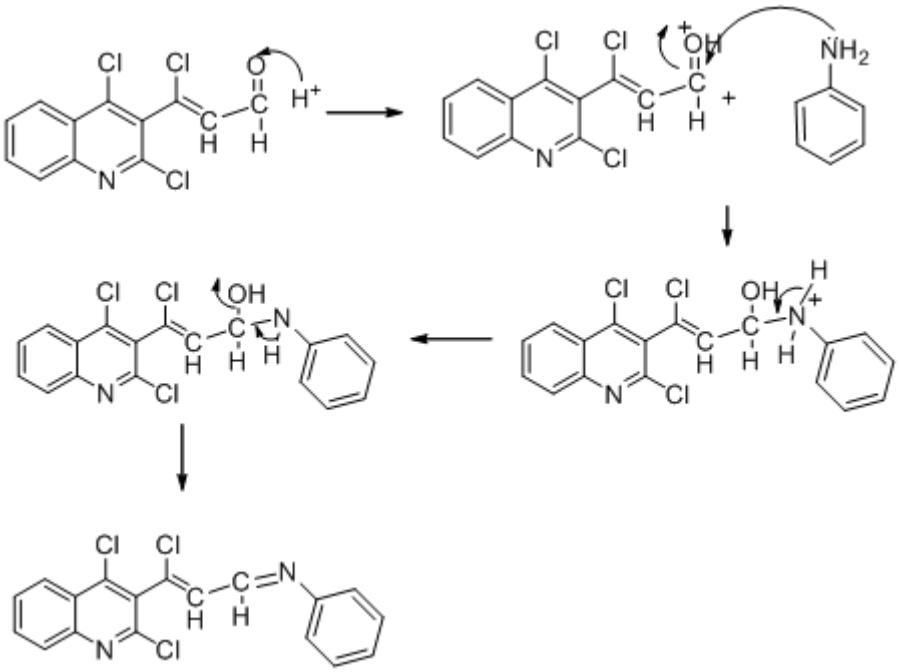
2866 cm $^{-1}$ and the aromatic ring CH stretching is at 3027-3057 cm $^{-1}$. The aromatic C-C (in-ring) stretch is at 1488 cm $^{-1}$and the C=C stretching occurs at 1634 cm $^{-1}$.

The ^{1}H NMR spectrum is presented in **Figure 12** (Appendix 10, page 87); a singlet at δ 6.25 ppm indicates the ethylene hydrogen whereas the multiplet at δ 7.25 ppm indicates the imine and aromatic ring CH protons. Four quinoline and five benzene ring protons occur at doublet, doublet, multiplet, multiplet, δ 8.0, 7.7, 7.2 and 7.0 ppm, respectively. The $C_{6,}$ $C_{7,}$ $C_{3',}$ $C_{7'}$ and $C_{9'}$ protons overlap and therefore appear as multiplets. The expanded ^{1}H NMR Spectrum is presented in **Figure 13** (Appendix 11, page 88). The ^{13} C NMR spectrum in **Figure 14** (Appendix 12, page 89) indicates 17 carbons; the C-Cl quinoline occurs at δ 158 ppm and the C=N imine is at δ 154.5 ppm. The C-Cl ethylene occurs at δ150 ppm, C-H benzene is at δ 114 ppm and C-H ethylene occurs at δ 108 ppm. The Mass spectrum in **Figure 15** (Appendix 13, page 90) shows its molecular ion [$M^{+\cdot}$] signal at m/z 360. The new compound was identified as 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline **52** a Schiff base and not the targeted bisquinoline.

Table 4: ^{1}H NMR and ^{13}C NMR data of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allyllidene-aniline

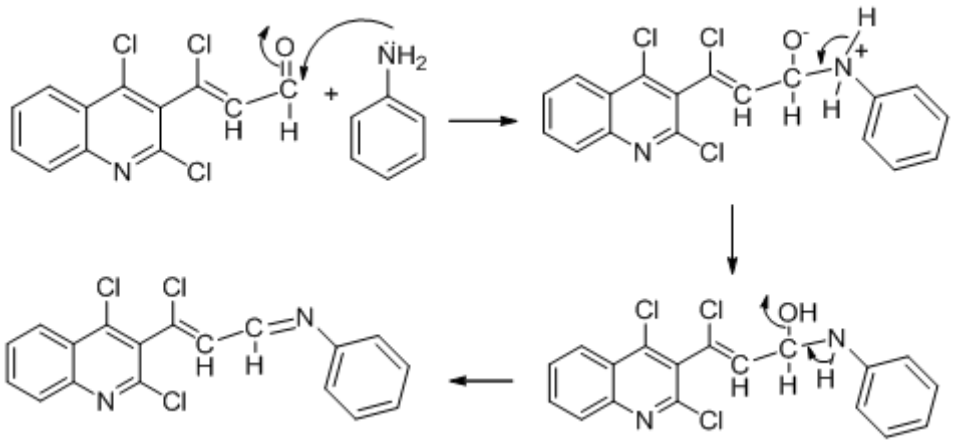
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)
C_2	150	-
C_3	130	-
C_4	158	-
C_{4a}	121	-
C_5	122	8.05 (d, J = 7.7 Hz, 1H)
C_6	128	7.40 (m,1H)
C_7	132	7.50 (m, 1H)
C_8	124	7.6 (d, J = 7.4 Hz, 1H)
C_{8a}	142	-
$C_{1'}$	148	-
$C_{2'}$	108	6.4 (d, J = 7.4 Hz, 1H)
$C_{3'}$	155	7.25 (m,1H)
$C_{5'}$	149	-
$C_{6'}$	110	6.9 (d, J = 7.2 Hz, 1H)
$C_{7'}$	123	7.35 (m, 1H)
$C_{8'}$	120.5	6.8 (t, J = 7.2 Hz, 1H)
$C_{9'}$	123	7.35 (m, 1H)
$C_{10'}$	110	6.9 (d, J = 7.2 Hz, 1H)

During this study we realised that the mechanism for the Schiff base can be performed in both basic and acidic media. The mechanisms for both media are illustrated as follows:



Scheme 18: Mechanism for imine formation in acidic conditions

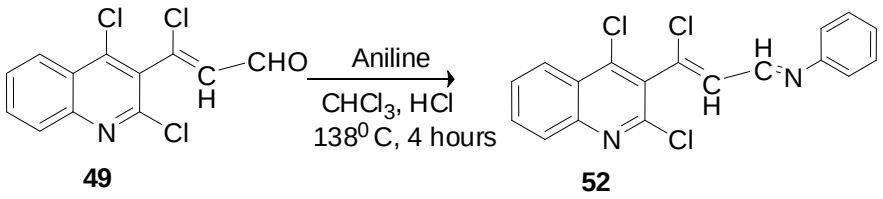
The above mechanism begins by protonation of the aldehyde group to form a positive charge as oxygen uses its electron to bond with hydrogen. This is followed by the nucleophile attacking the electrophile resulting in a positive charge formation on the nitrogen atom owing to electron loss. Intermolecular rearrangement then occurs to form a stable product.



Scheme 19: Mechanism for imine formation in alkaline conditions

In the basic media, the nucleophile attacks the carbonyl group (aldehyde) to form a bond which leaves a positive charge on the nitrogen atom. This is followed intermolecular rearrangement to form a stable product.

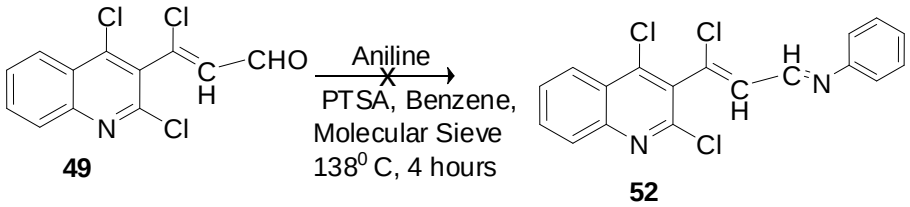
Since we were unable to form the bisquinoline from the aryl aldehyde via a one pot method, we decided to change the approach of the study since the formation of Schiff base product through basic condition was successful but not expected. We decided to perform the same reaction in the presence of HCl, chloroform and aniline since literature [69] indicated higher percentage yield of products in acidic conditions. Initially, the reaction was performed at room temperature but our TLC plate showed that the reaction was unsuccessful even after 3 hours of reaction. We then heated the reaction mixture resulting in product formation as indicated by TLC; the spots exactly matched the Schiff base product **52** we synthesised earlier. Also, the ^{1}H NMR data matched our reference compound **52**. Though the reaction succeeded the yield was very low, 2 %. The reaction outline is given in **Scheme 20**.



49 **52**

Scheme 20: Preparation of the Schiff base product in present of acid

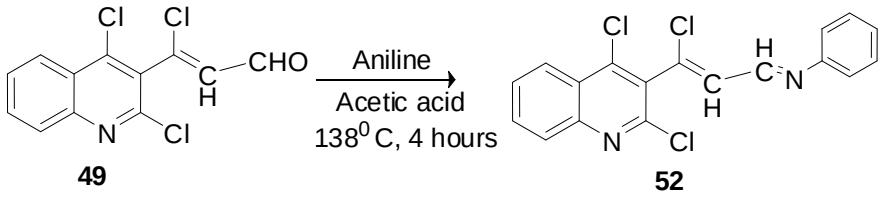
Since we were unsatisfied with the low % yield, we decided to follow the protocol reported [68]; the formation of the Schiff base product in the presence of a Lewis acid , viz. para-toluenesulphonic acid, benzene, molecular sieves and aniline under refluxed conditions using a Dean and Stark apparatus.



49 **52**

Scheme 21: Preparation of Schiff base by Dean Stark reaction

Unfortunately this method was unsuccessful because the starting compound was not converted to products although the reaction was conducted for more than 10 hours. Another research publication on the synthesis of seleno-substituted quinolines [69] showed the formation of a Schiff base product in the presence of acetic acid, aniline and ethanol. This method was applied to our study as illustrated in **Scheme 22**.

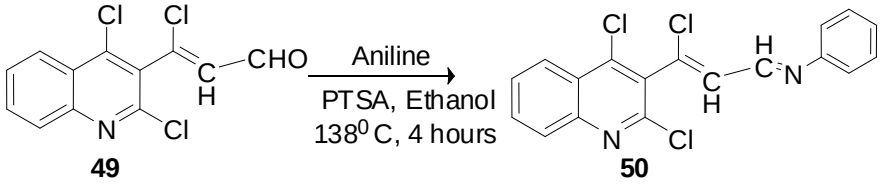


49 **52**

Scheme 22: Synthesis of Schiff base product in polar acidic media

The reaction was initially carried out at room temperature; the colour of the solution was orange and turned to red while stirring overnight, but TLC showed that the product formation was very slow since the starting compound was still present as an intense TLC spot. We then repeated the reaction under reflux; the reaction mixture and the solution turned from red to dark reddish-brown while the reaction was carried out up to 4 hours. The TLC spots matched the Schiff base product and the yield was 48 %. We concluded that either acidic or basic media can be used for synthesis of the Schiff base product therefore we decided to find a better solvent system for the reaction.

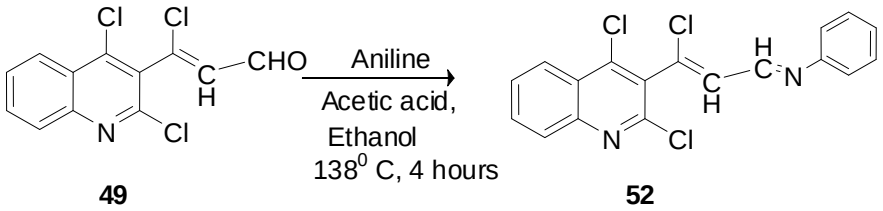
Next, we carried out a reaction using our substrate and PTSA, ethanol and aniline in similar heating conditions as the previous method. The reaction was successful as indicated by our TLC analysis; however, it gave a yield of 42 %.



49 **50**

Scheme 23: Synthesis of Schiff base product in presence of Lewis acid and polar solvent

Another attempt to improve the % yield was the reaction of acetic acid mixed with ethanol, in a 1:1 mixture, aniline and 3-chloro-3-(2,4-dichloroquinolin-3yl) acrylaldehyde under the same heating conditions as previously described.



49 **52**

Scheme 24: Synthesis of Schiff base products in a mixture of acetic acid and ethanol

Analysis of the reaction mixture by TLC indicated the presence of the Schiff base product; after usual work-up we found the percentage yield was a low 44 % but an improvement from our previous investigations.

In conclusion we tried six methods to synthesise the Schiff base product of which five were successful. **Table 5** below summarises the six methods that we conducted to synthesize compound **52** from **49** by conventional method.

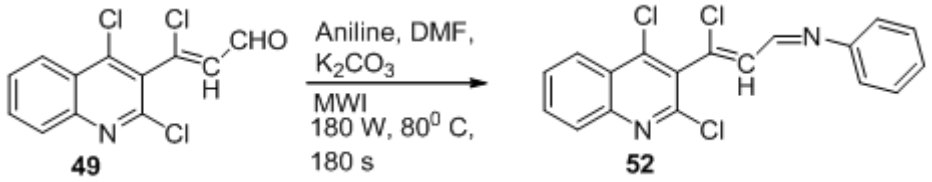
Table 5: Summary of the six methods investigated, by conventional method to synthesize the Schiff base compound 52 from 49.

Method	Reaction mixture	Reaction Conditions	Yield (%)
1	DMF + K_2CO_3+ Aniline	138^0 C, 4 hours	61
2	$CHCl_3$ + HCl + Aniline	138^0 C, 4 hours	2
3	PTSA + Benzene + Aniline	138^0 C, 4 - 10 hours Molecular Sieve	No product
4	Acetic acid+ Aniline	138^0 C, 4 hours	48
5	PTSA + Ethanol + Aniline	138^0 C, 4 hours	42
6	Acetic acid + Ethanol + Aniline	138^0 C, 4 hours	44

All the methods were compared by their percentage yield and it was found that the reaction at 138 ºC, for four hours in the presence of DMF and K_2CO_3 gave the highest percentage yield (61%) of the Schiff base product. We decided to use this optimum protocol to prepare other simple Schiff base derivatives.

Using aniline derivates viz. 4-methoxyaniline, 4-methylaniline and 4-chloroaniline as substrates to prepare 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline **57**, 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline **58** and 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro aniline **59** at 45, 65 and 41 % yield, respectively. The characterisation of these new Schiff base derivatives is discussed in this chapter (page 56 –63).

At this point in our investigation we used only the conventional method, i.e. reflux. We now decided to investigate the effect of the microwave irradiation technique by using the DMF method described earlier (page 54). Our first reaction outline is presented in **Scheme 25**.

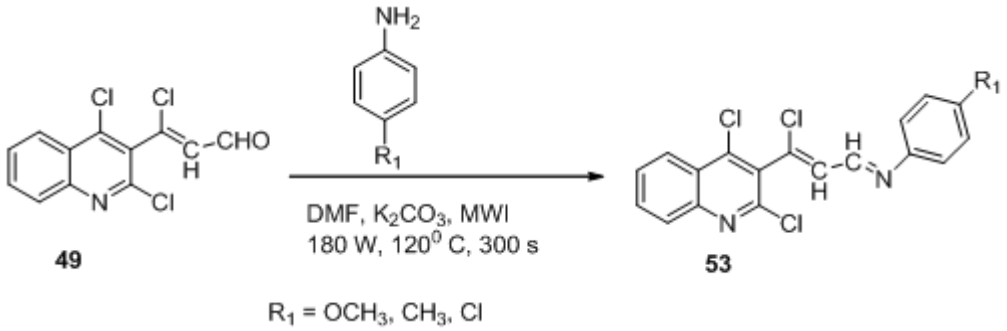


Scheme 25: Preparation of Schiff base by microwave irradiation

For a reaction time of 180 s at 80 ^{0}C, the reaction was incomplete according to TLC analysis since the spot of starting material was observed. We then increased the reaction time to 240 s but the presence of the starting material was still observed. We decided to increase the temperature to 120 ^{0}C; the optimum reaction time

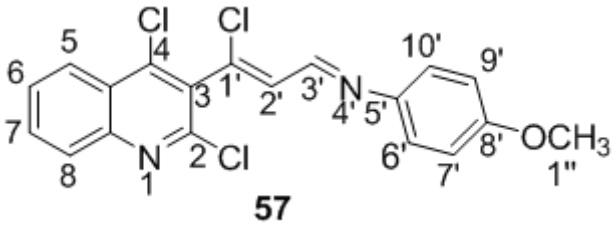
obtained was 300 s and the % yield of the Schiff base product was recorded as 75%. This yield was better than the one obtained via the reflux method (61%); however, the reaction time was significantly reduced from 4 hours to 300 s.

Having developed a quick method to synthesis the aniline derivative of a Schiff base **52**, we decided to use this optimum reaction conditions to prepare other simple Schiff base derivatives by varying our aniline type substrates. Therefore, the data will be available to make a comparative study. We used *p*-methoxyaniline as the first substrate to synthesise a new Schiff base derivative. The reaction outline is presented in **Scheme 26**.



Scheme 26: Preparation of Schiff base derivative using aniline derivatives

The above reaction was monitored by TLC and a new spot was observed below the starting material. The crude mixture was purified by column chromatography. The yield of the product was 68 %. The pure compound was analysed by IR, ^{1}H and ^{13}C NMR spectra to confirm the identity as 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene)-4-methoxyaniline **57**.



57

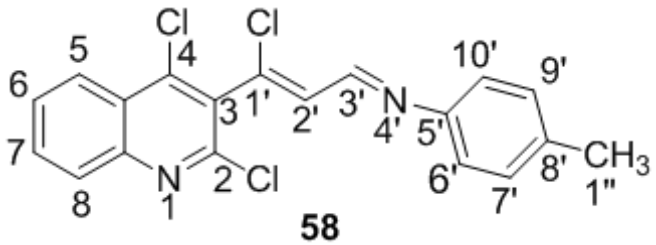
The compound was characterised; **Figure 16** (appendix 14, page 91) shows the IR spectrum. The imine stretching is at 2832 cm $^{-1}$ and the aromatic ring CH stretching is at 2991 cm $^{-1}$. The aromatic ring C=C stretching is at 1633 cm $^{-1}$. The aliphatic C=C stretching occurs at 1584 cm $^{-1}$ and the C-C stretch (in-ring) is at 1498. The C-O-C ether stretching occurs at 1237 cm $^{-1}$.

Table 6: ^{1}H NMR and ^{13}C NMR data of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allyllidene-4-methoxyaniline 57

Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)
C_2	150	-
C_3	130	-
C_4	160	-
C_{4a}	125	-
C_5	123	8.05 (d, J = 8.3 Hz, 1H)
C_6	128	7.45 (m,1H)
C_7	132	7.50 (m, 1H)
C_8	129	7.7 (d, J = 8.9 Hz, 1H)
C_{8a}	147	-
$C_{1'}$	155	-
$C_{2'}$	106	6.2 (d, J = 7.9 Hz, 1H)
$C_{3'}$	158	7.20 (d, J = 7.9 Hz, 1H)
$C_{5'}$	145	-
$C_{6'}$	118	6.85 (m, 1H)
$C_{7'}$	109	7.0 (m, 1H)
$C_{8'}$	157	-
$C_{9'}$	109	7.0 (m, 1H)
$C_{10'}$	118	6.85 (m, 1H)
$C_{1''}$	55	3.98 (s,3H)

The ^{1}H NMR spectrum is presented in **Figure 17** in (Appendix 15, page 92); singlet at δ 6.25 ppm indicates the ethylene hydrogen whereas the multiplet at δ 7.25 ppm indicates the imine and aromatic ring CH protons. The singlet at δ 3.98 ppm indicates the O-CH_3. Four quinoline and five aromatic ring protons occur at doublet, doublet, multiplet, multiplet, 8.0, 7.7, 7.2 and 7.0 ppm, respectively. The C_6, C_7, $C_{6'}$, $C_{7'}$, $C_{9'}$ and $C_{10'}$ protons overlap and therefore appear as multiplets. The expanded ^{1}H NMR Spectrum is presented in **Figure 18** (Appendix 16, page 93). The ^{13}C NMR spectrum in **Figure 19** (Appendix 17, page 94) indicated that the C-Cl quinoline occurs at δ 158 ppm and the C=N imine is at δ 154.5 ppm. The O-CH_3 occurs at δ 54.8 ppm, C-Cl ethylene occurs at δ150 ppm, C-H benzene is at δ 114 ppm and C-H ethylene occurs at δ 108 ppm.

The next substrate we used to synthesise a new Schiff base derivative was *p*-methylaniline. The reaction outline is presented in **Scheme 26**. The reaction was monitored by TLC and a new spot was observed above the starting material. The crude mixture was purified by column chromatography. The yield of the product was 78 %. The pure compound was analysed by IR, ^{1}H NMR and ^{13}C NMR spectra to confirm the identity as 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline **58**.



58

The compound was characterised; **Figure 20** (Appendix 18, page 95) shows the IR spectrum. The imine stretching is at 2832 cm $^{-1}$ and the aromatic ring C-H stretching is at 3030 cm $^{-1}$. The aromatic ring C=C stretching is at 1634 cm $^{-1}$ and the aromatic C-C (in-ring) is at 1501. The aliphatic C=C stretching occurs at 1587 cm $^{-1}$. The C-H methyl bend occurs at 1459 cm $^{-1}$.

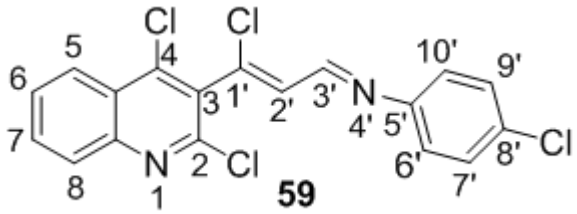
The ^{1}H NMR spectrum is presented in **Figure 21** (Appendix 19, page 96); singlet at δ 6.25 ppm indicates the ethylene hydrogen whereas the multiplet at δ 7.25 ppm indicates the imine and aromatic ring CH protons. The singlet at δ 1.2 ppm indicates the $CH_{3.}$ Four quinoline and five aromatic ring protons occur at doublet, doublet, multiplet, multiplet, 8.0, 7.7, 7.2, 7.0 ppm, respectively. The $C_{6,}$ $C_{7,}$ $C_{6'}$, $C_{7'}$, $C_{9'}$ and $C_{10'}$ protons overlap and therefore appear as multiplets. The expanded ^{1}H NMR Spectrum is presented in **Figure 22** (Appendix 20, page 97). The ^{13} C NMR spectrum in **Figure 23** (Appendix 21, page 98) indicated that the C-Cl quinoline occurs at δ 161 ppm and the C=N imine is at δ 154.5 ppm. The CH_3 occurs at δ 21.1 ppm, C-Cl ethylene occurs at δ150 ppm, C-H benzene is at δ 118 ppm and C-H ethylene occurs at δ 106 ppm.

Table 7: ^{1}H NMR and ^{13}C NMR data of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allyllidene-4-methylaniline 58

Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)
C_2	149	-
C_3	130	-
C_4	160	-
C_{4a}	123	-
C_5	121	8.00 (d, J = 8.6 Hz, 1H)
C_6	129	7.3 (m,1H)
C_7	133	7.45 (m, 1H)
C_8	128	7.7 (d, J = 7.8 Hz, 1H)
C_{8a}	147	-
$C_{1'}$	151	-
$C_{2'}$	106	6.0 (d, J = 7.8 Hz, 1H)
$C_{3'}$	155	7.50 (d, J = 7.9 Hz, 1H)
$C_{5'}$	148.5	-
$C_{6'}$	122	7.24 (m, 1H)
$C_{7'}$	130	7.24 (m, 1H)
$C_{8'}$	138	-
$C_{9'}$	130	7.0 (m, 1H)
$C_{10'}$	122	7.24 (m, 1H)
$C_{1''}$	20	1.3 (s,3H)

The next substrate we used was *p*-chloroaniline to synthesise a new Schiff base derivative. The reaction outline is presented in **Scheme 26**. The reaction was

monitored by TLC and a new spot was observed above the starting material. The crude mixture was purified by column chromatography. The yield of the product was 64 %. The pure compound was analysed by IR, ^{1}H NMR and ^{13}C NMR spectra to confirm the identity of the new compound as 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro-aniline.



59

The compound was characterised by IR, ^{1}H and ^{13}C; **Figure 24** (Appendix 22, page 99) shows the IR spectrum. The imine stretching is at 2832 cm $^{-1}$. The aromatic ring C=C stretching is at 1642 cm $^{-1}$and the aliphatic C=C stretching occurs at 1614 cm $^{-1}$. The ^{1}H NMR spectrum is presented in **Figure 25** (Appendix 23, page 100); a singlet at δ 6.25 ppm indicates the ethylene hydrogen whereas the multiplet at δ 7.25 ppm indicates the imine and aromatic ring CH protons. Four quinoline and five benze ring protons occur at doublet, doublet, multiplet, multiplet, 8.0, 7.7, 7.2, 7.0 ppm, respectively. The $C_{6,}$ $C_{7,}$ $C_{6'}$, $C_{7'}$, $C_{9'}$ and $C_{10'}$ protons overlap and therefore appear as multiplets. The expanded ^{1}H NMR Spectrum is presented in **Figure 26** (Appendix 24, page 101). The ^{13} C NMR spectrum in **Figure 27** (Appendix 25, page 102) indicated that the C-Cl quinoline occurs at δ 158 ppm, C-Cl benzene is at δ 130.5 ppm and the C=N imine is at δ 154.5 ppm. The C-Cl ethylene occurs at δ150 ppm, C-H benzene is at δ 114 ppm and C-H ethylene occurs at δ 108 ppm.

Table 8: ^{1}H NMR and ^{13}C NMR data of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allyllidene-4-chloro-aniline 59

Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)
C_2	150	-
C_3	130	-
C_4	158	-
C_{4a}	123	-
C_5	123	8.00 (d, J = 8.8 Hz, 1H)
C_6	129	7.3 (m,1H)
C_7	134	7.45 (m, 1H)
C_8	128	7.7 (d, J = 8.4 Hz, 1H)
C_{8a}	149	-
$C_{1'}$	150	-
$C_{2'}$	107	6.4 (d, J = 7.8 Hz, 1H)
$C_{3'}$	154	7.50 (d, J = 7.9 Hz, 1H)
$C_{5'}$	151	-
$C_{6'}$	122	7.14 (m, 1H)
$C_{7'}$	130	7.44 (m, 1H)
$C_{8'}$	133	-
$C_{9'}$	130	7.44 (m, 1H)
$C_{10'}$	122	7.14 (m, 1H)

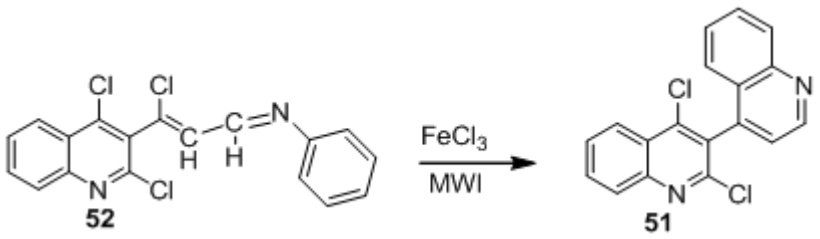
Table 9 indicates the synthesis of the four Schiff base compounds by conventional and microwave.

Table 9: Comparison of the conventional and microwave method in the synthesis of the Schiff base derivatives.

Compound Number	Reaction Time (hrs) by Conventional	Yield (%) obtained in Conventional Method	Reaction Time (s) by Microwave	Yield (%) obtained in Microwave Method
52	4	61	300	75
57	4	45	300	68
58	4	65	300	78
59	4	41	300	64

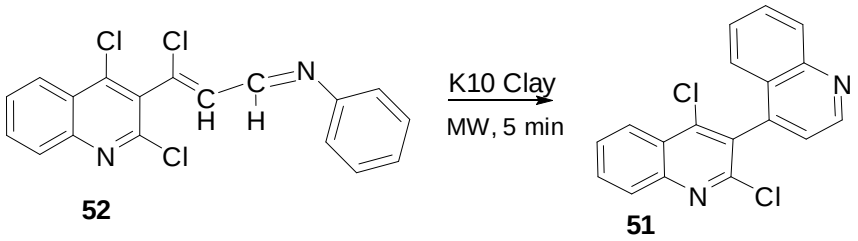
In all cases, the % yield of the product was improved by the microwave method; also the reaction time was drastically reduced.

Our final objective of this study was to cyclise the Schiff base product to obtain our target bisquinoline **51**. Our first reaction was the self coupling reaction using iron (III) chloride as reported, [70] in microwave irradiation, presented in scheme 27. The reaction was monitored by TLC. Unfortunately, we were unable to detect the formation of any new TLC spots even after 20 minute of reaction time. We deduced that the methodology used by Varma *et al.* [70], was inapplicable to our substrate.



Scheme 27: Proposed Outline For The Preparation of 2, 4-dichloro-3,4'-biquinoline

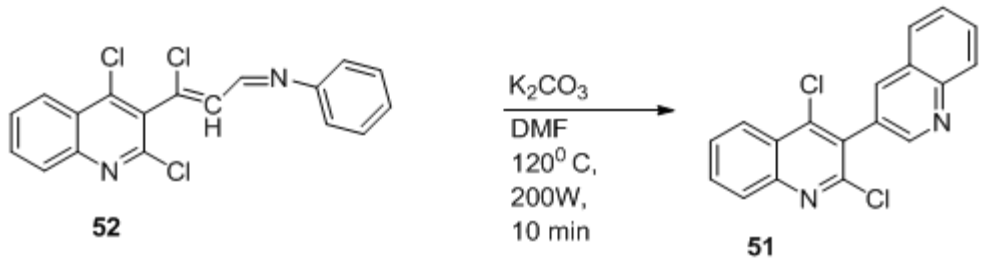
Our next reaction was conducted using a solvent-free system in the presence of montmorillonite K10 clay. [71-73] We decided to use microwave irradiation as reported by other researchers. The reaction outline is presented in **Scheme 28**.



Scheme 28: Preparation Of 2, 4-dichloro-3, 4'-biquinoline By Solvent-Free Method

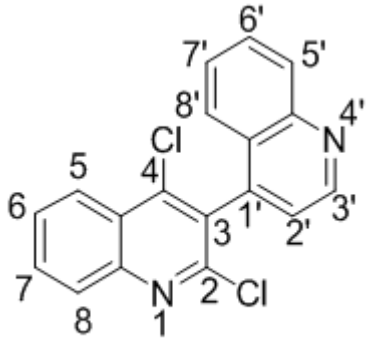
The above reaction was monitored by TLC which indicated the formation of a new spot below the starting material thereby indicating that it was more polar than our starting compound. The product was purified by column chromatography and isolated; the yield was 11 %. This product was analysed by ^{1}H NMR which indicated the presence of the correct proton signals; however, the spectrum showed the presence of impurities as observed by noisy baseline. We were unhappy because of the low yield and the presence of impurities in the sample in spite of using chromatography as a tool for purification. Therefore, we decided to investigate cylisation using the method mentioned early in **Chapter 2** (2.3.5) (page 27), using

dimethyl formamide, potassium carbonate and Schiff base product in a microwave irradiation procedure. The reaction is presented in **Scheme 29**.



Scheme 29: Preparation of 2, 4-dichloro-3, 4'-biquinoline using alkaline condition

The reaction was conducted for 6 minutes and monitored by TLC. Although a new TLC spot was formed, the starting material was observed as an intense spot. Therefore, the reaction was heated for a total time of 10 minutes. After work-up and purification by column chromatography, the yield was recorded as 24 %.



The identity of the bisquinoline was established by ^{1}H NMR and MS. **Figure 28** (Appendix 26, page 103) illustrates the ^{1}H NMR whilst **Figure 29** (Appendix 27, page 104) gives the expanded ^{1}H NMR. The Mass spectrum is presented in **Figure 30** (Appendix 28, page 105).

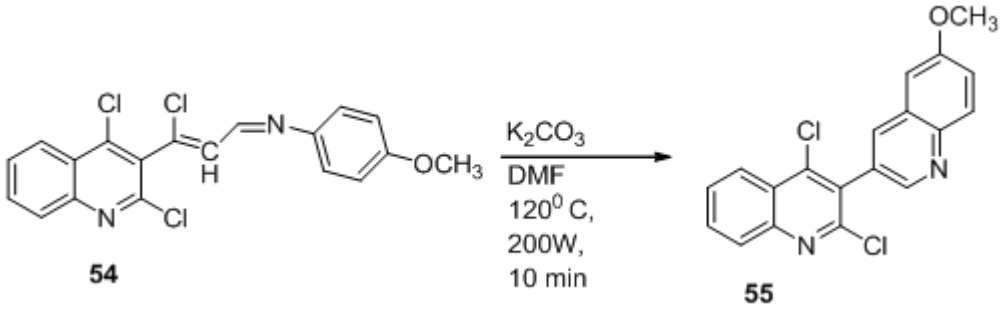
Figure 28 shows a doublet at δ 8.24 ppm indicating the quinoline CH protons. Ten quinoline protons occur at doublet, triplet, doublet, doublet, multiplet, multiplet, multiplet 8.24, 8.1, 8.0, 7.8, 7.7, 7.6 and 7.5 ppm, respectively. The $C_{6,}$ $C_{6'}$, and $C_{7'}$, protons overlap and therefore appear as multiplets. The Mass spectrum in **Figure 30** (Appendix 28, page 105) showed its molecular ion [$M^{+\cdot}$] signal at m/z 320.

Table 10: ^{1}H NMR data of 2, 4-dichloro-3, 4'-biquinoline 51.

Position	δ ^{1}H (ppm)	Position	δ ^{1}H (ppm)
C_2	-	$C_{1'}$	-
C_3	-	$C_{2'}$	6.9 (d, J = 6.8 Hz, 1H)
C_4	-	$C_{3'}$	8.35 (d, J = 8.4 Hz, 1H)
C_{4a}	-	$C_{4a'}$	-
C_5	8.25 (d, J = 8.2 Hz, 1H)	$C_{5'}$	7.98 (d, J = 8.2, 1H)
C_6	7.8 (m,1H)	$C_{6'}$	7.8 (m, 1H)
C_7	8.1 (t, J = 8.5 Hz, 1H)	$C_{7'}$	7.0 (m, 1H)
C_8	8.0 (d, J = 8.4 Hz, 1H)	$C_{8'}$	8.06 (d, J = 7.8 Hz, 1H)
C_{8a}	-	$C_{8a'}$	-

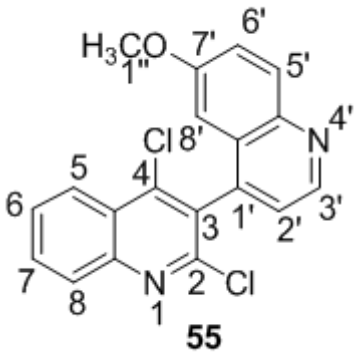
Although the yield was low, we decided to prepare one selected derivative in the hope of obtaining better yields. We used the above mentioned reaction

conditions with our newly synthesised *p*-methoxyaniline Schiff base product **54** as substrate to form bisquinoline derivative **55**, as presented in **Scheme 30**.



Scheme 30: Preparation of 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline by alkaline conditions

After usual work up and purification, the yield was recorded as 18% and the product was analysed by ^{1}H NMR.



The ^{1}H NMR spectrum is presented in **Figure 31** (Appendix 29, page 106); a singlet at δ 3.9 ppm indicates O-CH_3 protons. The nine quinoline protons occurs as doublet, multiplet, doublet, multiplet, multiplet, triplet, doublet at δ 8.34, 8.1, 7.8 , 7.7, 7.6, 7.5, 6.8 ppm , respectively. The $C_{6,}$ $C_{7,}$ $C_{5'}$ and $C_{6'}$ protons overlap and therefore appear as multiplets. These 9 quinoline protons were also assigned to 2, 4-dichloro-

3, 4'-biquinoline. The expanded ^{1}H NMR Spectrum is presented in **Figure 32** (Appendix 30, page 107).

Table 11: ^{1}H NMR data of 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline 55.

Position	δ ^{1}H (ppm)	Position	δ ^{1}H (ppm)
C_2	-	$C_{1'}$	-
C_3	-	$C_{2'}$	7.0 (d, J = 6.8 Hz, 1H)
C_4	-	$C_{3'}$	8.35 (d, J = 8.4 Hz, 1H)
C_{4a}	-	$C_{4a'}$	-
C_5	8.40 (d, J = 8.3 Hz, 1H)	$C_{5'}$	7.0 (m, 1H)
C_6	7.8 (m,1H)	$C_{6'}$	6.9 (m, 1H)
C_7	7.8 (m, 1H)	$C_{7'}$	-
C_8	8.05 (d, J = 7.8 Hz, 1H)	$C_{8'}$	8.06 (d, J = 7.8 Hz, 1H)
C_{8a}	-	$C_{8a'}$	-
-	-	$C_{1''}$	3.83 (s, 3H)

In conclusion, our study resulted in the design of a reaction scheme consisting of four simple steps to produce two bisquinoline which are 2, 4-dichloro-3, 4'-biquinoline **51** and 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline **55**. For those reactions which the conventional and the microwave irradiation were permissible, we found that the microwave method produced higher yield; however, the reaction time was drastically reduced for the Schiff base procedures that we have prepared in this report. Since the final step of the reaction did not provide high yield, we suggest that this step be further investigated to improve the % yield and subsequently synthesise the other two bisquinoline derivatives from the Schiff base derivatives 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline **58** and 4-chloro-3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline **59** that we have prepared in this new protocol.

References:

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Chapter 4: Experimental

General procedure

4.1 Synthesis of 3-acyl 2,4-dihydroxyquinoline 42

Conventional method:

0.1 mol of methylanthranilate **40** and 0.1 mol of **41** were taken and a catalytic amount of sodium hydride was added. Then the reaction mixture was heated for 6 hours at 110 ^{0}C. A white solid was observed; the mixture was cooled to room temperature then poured into 1000 mL cold water, neutralize with dilute HCl, filtered, dried and washed with 200 mL of ethylacetate. The solid was recrystallized with ethanol to yield a pure white powder.

Microwave method

0.1 mol of methylanthranilate **40** and 0.1 mol of **41** were taken and a catalytic amount of sodium hydride was added. Then the reaction mixture was heated for 3 minutes at 110 ^{0}C in 250 watts. A white solid was observed; the mixture was cooled to room temperature then poured into 1000 mL cold water, neutralize with dilute HCl, filtered, dried and washed with 200 mL of ethylacetate. It recrystallized with ethanol; a pure white powder was obtained with good yield. The physical data obtained are exactly matched with the product formed in the conventional method above.

Preparation of 3-acyl-2, 4-dihydroxyquinoline 42

Conventional: methylanthranilate **40** -12.94 mL (0.1 mol), ethylacetoacetate **41** -12.63 mL (0.1 mol) Yield 13.03 g (75 %); **Microwave**: Yield 15.63g (90 %); m.p: 222^{o}C; IR in **Figure 3** (Appendix 1, page 78)(KBr, υ_{max}, cm^{-1}): 3162, 3017, 2886, 1664, 1587; ^{1}H NMR in **Figure 4** (Appendix 2, page 79) (600 MHz, DMSO-D_6, ppm): δ 17.00 (bs, 1H, -OH), δ 11.31 (bs, 1H, -OH), δ 8.00 (d, *J* = 7.1 Hz, 1H, H-5), δ7.65 (t, *J* = 7.1 Hz, 1H, H-7), δ 7.10-7.32 (m, 1H, H-6 & H-8), δ 2.56 (s 3H, -CH_3); ^{13}C NMR in **Figure 5** (Appendix 3, page 80) (400 MHz, DMSO-D_6, ppm) δ 205.92, 174.74, 161.16, 140.71, 135.00, 124.68, 128.11, 121.93, 115.45, 113.41, 105.80, 30.54; MS (EI) in **Figure 6** (Appendix 4, page 81): 203 ($M^{+\cdot}$).

4.2 Synthesis of 3-chloro-3-(2.4-dichloroquinolin-3yl) acrylaldehyde 49

Conventional method

Dimethyl formamide (3.85 mL, 0.05 mol.) was cooled to 0 ^{0}C in a flask equipped with a dropping funnel. Phosphoryl chloride (12.97 ml, 0.14 mol.) was added drop wise from the funnel with stirring. The resultant reagent was stirred for a further 30 min at room temperature and then cooled to 5 ^{0}C then 2.436 g (0.012mol) 3-acetyl-2, 4-dihydroxyquinoline was added and the stirring was further continued for 30 minutes and shifted over water bath and heated for 17 hours cooled and poured into crushed ice and neutralized with sodium carbonate solution. The crude solid was filtered dried and then purified by column chromatography; the yield of 3-(3-chloroprop-2-enal)-2,4-dichloroquinoline **49** was 2.22 g (65 %); m.p: 134 ^{0}C; IR in **Figure 7** (Appendix 5, page 82) (KBr, υ_{max}, cm^{-1}): 3453, 2860, 1677, 1616, 1556,

828, 764, 728; ^{1}H NMR in **Figure 8** (Appendix 6, page 83) (400 MHz, $CDCl_3$): δ in ppm (d, *J* = 8.0 Hz, 1H, -CHO), δ 8.26 (d, *J* = 7.1 Hz, 1H, H-5), δ 8.00 (d, 1H, *J* = 7.1 Hz, H-8), δ (7.86, t, *J* = 7.1 Hz, 1H, H-7), δ 7.71(t, 1H, H-6), δ 6.73 (d, *J* = 8.0 Hz, 1H, H-2'); ^{13}C NMR in **Figure 9** (Appendix 7, page 84) (400 MHz, $CDCl_3$): δ 190.0, 147.7, 146.9, 144.7, 143.1, 133.8, 132.4, 131.9, 131.6, 128.9, 128.7, 128.2, 124.9, 124.8, 121.1; MS (EI) in **Figure 10** (Appendix 8, page 85): 285 ($M^{+\cdot}$).

Microwave method

The reaction mixture after being carried out with stirring at room temperature was transferred to the microwave unit. The colour of the reaction mixture was a pale yellow colloid matter; after 15 minutes the reaction mixture changed to a clear red solution. After cooling to room temperature, the reaction mixture was poured in to 1000 mL cold water and subsequently neutralized with Na_2CO_3. Here the yield was 72 %. The physical data matched the product obtained from the conventional method.

4.3 (a) Synthesis of 3-chloro-3-(2, 4-dichloroquinolin-3-yl)allylidene-aniline 52 by Conventional method

(i) Preparation of Schiff base with aniline

Dimethyl formamide (15 mL, 0.05 mol,) was mixed with 1 mL of aniline and 0.05 mol of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline. The mixture was refluxed for 4 hours and poured into crushed ice. The crude solid was filtered and dried. The product was purified by column chromatography; the yield of 3-chloro-3-(2, 4-

dichloroquinolin-3-yl) allylidene-aniline **52** was 1.751 g (61 %); m.p: 95.7 ^{0}C; IR in **Figure 11** (Appendix 9, page 86) (ATP, υ_{max}, cm^{-1}): 3027-3057, 2866, 1634, 1579, 1488, 1459, ^{1}H NMR in **Figure 12** (Appendix 10, page 87) (400 MHz, $CDCl_3$): δ in ppm (d, J = 7.7 Hz, 5H), δ 7.O (q, J = 7.4 Hz, 7H, H-8), δ 6.60 (m, 10H, J = 1.2 Hz, H-17); ^{13}C NMR in **Figure 14** (Appendix 12, page 89) (400 MHz, $CDCl_3$): δ 156.2, 153.3, 149.6, 149.3, 146.7, 145.4, 141.3, 130.5, 129.9, 128.6, 127.9, 127.4, 125.7, 123.2, 121.9, 120.5, 114.1, 108.1, 105.9; MS (EI) in **Figure 15** (Appendix 13, page 90): 360 ($M^{+\cdot}$).

(ii) Preparation of Schiff base with *p*-methoxyaniline

Dimethyl formamide (15 mL, 0.05 mol,) was mixed with 1 mL of p-methoxyaniline and 0.05 mol of 3-chloro-3-(2, 4-dichloroquinolin-3yl) acrylaldehyde. The mixture was refluxed for 4 hours cooled and poured into crushed ice. The crude solid was filtered and dried. The product was purified by column chromatography; the yield of 3-chloro-3-(2,4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline **57** was 1.0136 g (45 %); m.p: 106 ^{0}C; IR in **Figure 16** (Appendix 14, page 91) (ATP, υ_{max}, cm^{-1}): 2991, 2832, 1633, 1584, 1498, 1457, 1344, 1280, 1238, 1167, 1105, 1030; ^{1}H NMR in **Figure 17** (Appendix 15, page 92) (400 MHz, $CDCl_3$) : δ in ppm (d, J = 8.3 Hz, 5H), δ 7.3 (q, J = 8.9 Hz, 7H, H-8), δ 6.8 (q, 10H, J = 7.9 Hz, H-17); ^{13}C NMR in **Figure 19** (Appendix 17, page 94) (400 MHz, $CDCl_3$): δ 156.2, 153.3, 149.6, 149.3, 146.7, 145.4, 141.3, 130.5, 129.9, 128.6, 127.9, 127.4, 125.7, 123.2, 121.9, 120.5, 114.1, 108.1, 105.9.

(iii) Preparation of Schiff base with *p*-methylaniline

Dimethyl formamide (15 mL, 0.05 mol,) was mixed with 1 mL of *p*-toluidine and 0.05 mol of 3-chloro-3-(2.4-dichloroquinolin-3yl) acrylaldehyde. The mixture was refluxed for 4 hours and poured into crushed ice. The crude solid was filtered and dried. Then the product was purified by column chromatography; the yield of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline **58** was 0.8185 g (65 %); m.p: 75.4 ^{0}C; IR in **Figure 20** (Appendix 18, page 95) (ATP, υ_{max}, cm^{-1}): 3030, 2832, 1634, 1587, 1541, 1501, 1459; ^{1}H NMR in **Figure 21** (Appendix 19, page 96) (400 MHz, $CDCl_3$): δ in ppm (d, J = 8.6 Hz, 5H), δ 7.3 (t, J = 8.3 Hz, 7H, H-8), δ 6.5 (m, 10H, J = 7.8 Hz, H-17); ^{13}C NMR in **Figure 23** (Appendix 21, page 98) (400 MHz, $CDCl_3$): δ 156.2, 153.3, 149.6, 149.3, 146.7, 145.4, 141.3, 130.5, 129.9, 128.6, 127.9, 127.4, 125.7, 123.2, 121.9, 120.5, 114.1, 108.1, 105.9.

(iv) Preparation of Schiff base with *p*-Chloroaniline

Dimethyl formamide (15 mL, 0.05 mol,) was mixed with 1 mL of p-chloroaniline and 0.05 mol of 3-chloro-3-(2, 4-dichloroquinolin-3yl) acrylaldehyde. The mixture was refluxed for 4 hours cooled and poured into crushed ice. The crude solid was filtered and dried. Then the product was purified by column chromatography; the yield of 4-chloro-3-chloro-3-(2,4-dichloroquinolin-3-yl) allylidene-aniline **59** was 0.7952 g (41%); m.p: 87.4 ^{0}C; IR in **Figure 24** (Appendix 22, page 99) (ATP, υ_{max}, cm^{-1}): 2832, 1642, 1614, 1548, 1480, 1436, 1397; ^{1}H NMR in **Figure 25** (Appendix 23, page 100) (400 MHz, $CDCl_3$): δ in ppm (d, J = 8.8 Hz, 5H), δ 7.7 (d, J = 8.4 Hz, 7H, H-8), δ 6.6 (m, 10H, J = 6.6 Hz, H-17); ^{13}C NMR in **Figure 27** (Appendix 25, page

102) (400 MHz, $CDCl_3$): δ 156.2, 153.3, 149.6, 149.3, 146.7, 145.4, 141.3, 130.5, 129.9, 128.6, 127.9, 127.4, 125.7, 123.2, 121.9, 120.5, 114.1, 108.1, 105.9.

4.3(b) Synthesis of 3-chloro-3-(2,4-dichloroquinolin-3-yl) allylidene-aniline 52 by Microwave method

Dimethyl formamide (15 mL, 0.05 mol) was mixed with 1 mL of aniline and 0.05 mol of 3-chloro-3-(2.4-dichloroquinolin-3yl) acrylaldehyde. The mixture was reacted in MWI for 300 s cooled and poured into crushed ice. The crude solid was filtered and dried. Then the product was purified by column chromatography; the yield of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline was 2.013 g (75 %); m.p: 95.7 ^{0}C. Here a higher yield was obtained in a reaction time of 300 s. Using the above protocol, 3-chloro-3-(2,4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline **57**, 3-chloro-3-(2 ,4-dichloroquinolin-3-yl) allylidene-4-methylaniline **58** and 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro aniline **59** were synthesized to produce yield of 68, 64 and 78 % yield, respectively.

4.4 (a) Synthesis of 2, 4-dichloro-3, 4'-biquinoline 51 by Microwave method

Dimethyl formamide (15 mL, 0.05 mol,) was mixed with (1.9g, 0.01 mol) of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline and 0.05 mol of potassium carbonate. The mixture was reacted in MWI for 10 minute, cooled and poured into crushed ice. The crude solid was filtered and dried. Then the product was purified by column chromatography, the yield of 2, 4-dichloro-3, 4'-biquinoline **51** was (24 %). Since the sample was a paste, no melting point was measured. Here a better yield was

obtained in a reaction time of 300 s. ^{1}H NMR in **Figure 28** (Appendix 26, page 103) (400 MHz, $CDCl_3$); δ in ppm (d, J = 8.2 Hz, 10H), δ 8.1 (t, J = 8.5 Hz, 13H, 14H), δ 8.0 (d, J = 8.4 Hz, 2H); δ 7.7 (m, J = 6.1 Hz, 6, 7,15H). MS (EI) in **Figure 30** (Appendix 28, page 105): 320 ($M^{+\cdot}$).

4.4 (b) Synthesis of 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline 55 by Microwave method

Dimethyl formamide (15 mL, 0.05 mol,) was mixed with (2g, 0.01 mol) of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline and 0.05 mol of potassium carbonate. The mixture was reacted in MWI for 10 minute, cooled and poured into crushed ice. The crude solid was filtered and dried. Then the product was purified by column chromatography and the yield of 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline **55** was (18 %). Since the sample was a paste, no melting point was measured. Here better yield was obtained in a reaction time of 300 s. ^{1}H NMR in **Figure 31** (Appendix 29, page 106) (400 MHz, $CDCl_3$); δ in ppm (m, J = 8.3 Hz), δ 8.1 (d, J = 8.6 Hz, 10H), δ 8.0 (d, J = 8.5 Hz, 9H); δ 7.7 (d, J = 1.4 Hz, 2H); δ 6.8 (d, J = 3.7 Hz, 16H).

Appendix 1

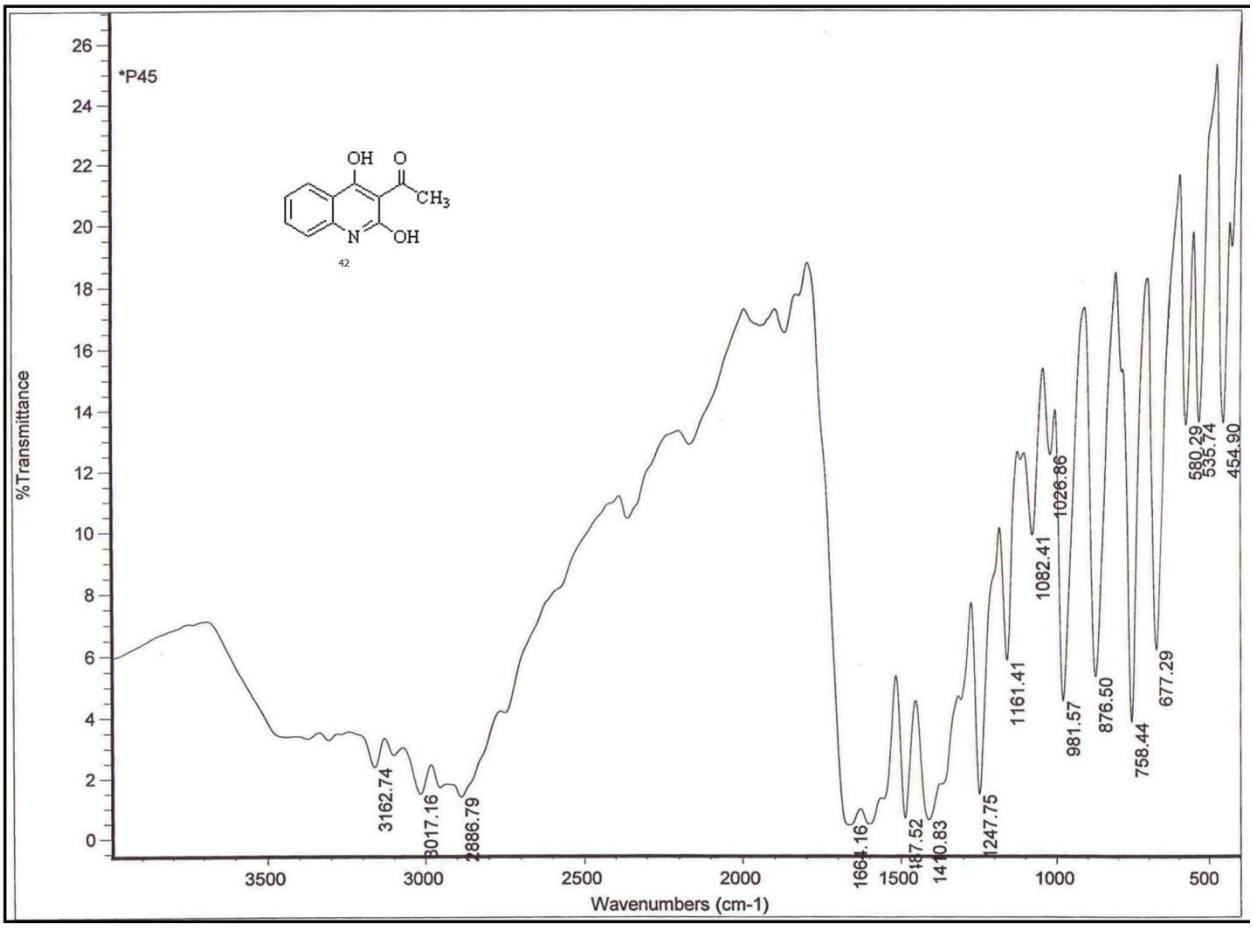

Figure 3: The IR spectrum of 3-acyl-2, 4-dihydroxyquinolin

Appendix 2

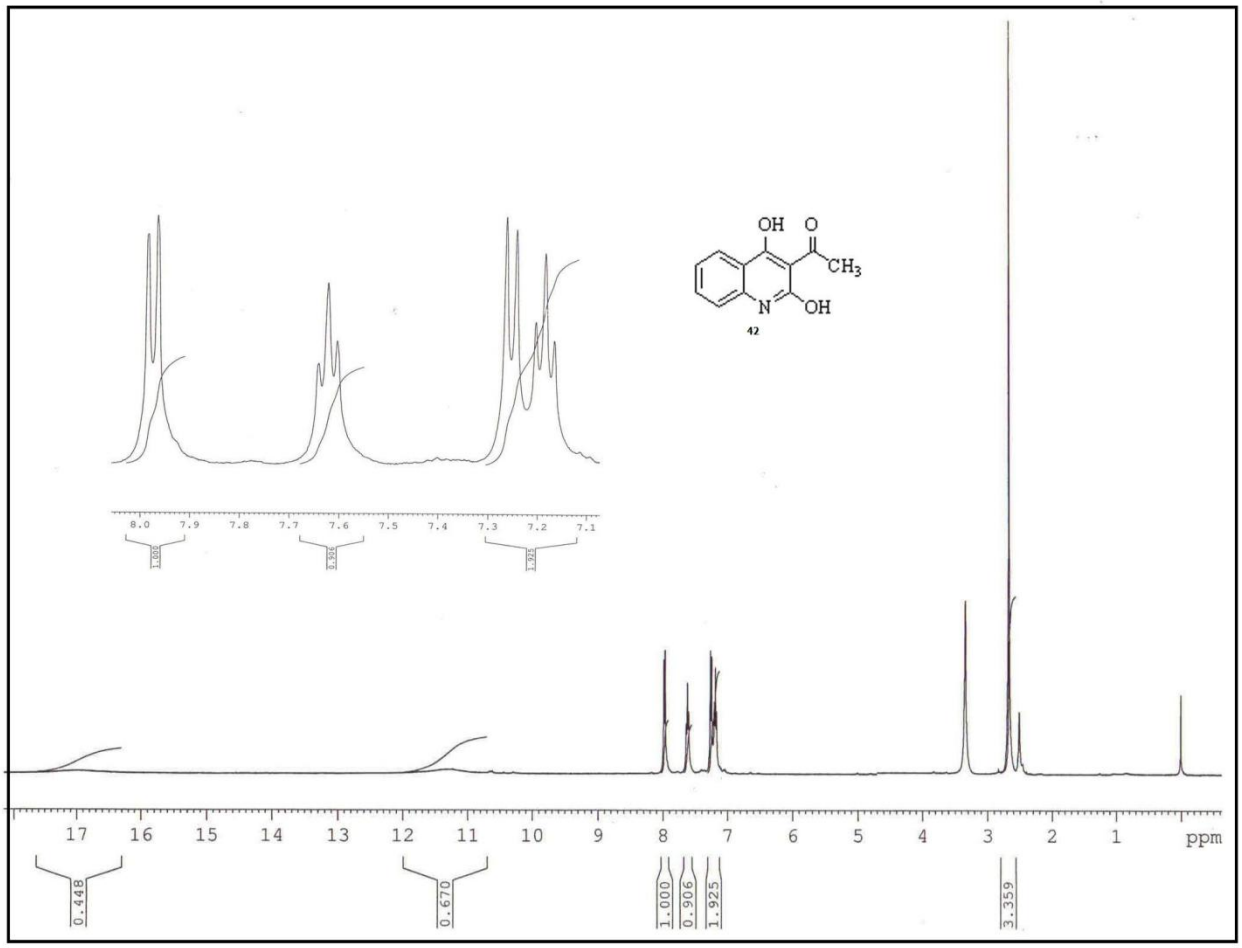

Figure 4: The ^{1}H NMR spectrum of 3.acyl-2, 4-dihydroxyquinoline

Appendix 3

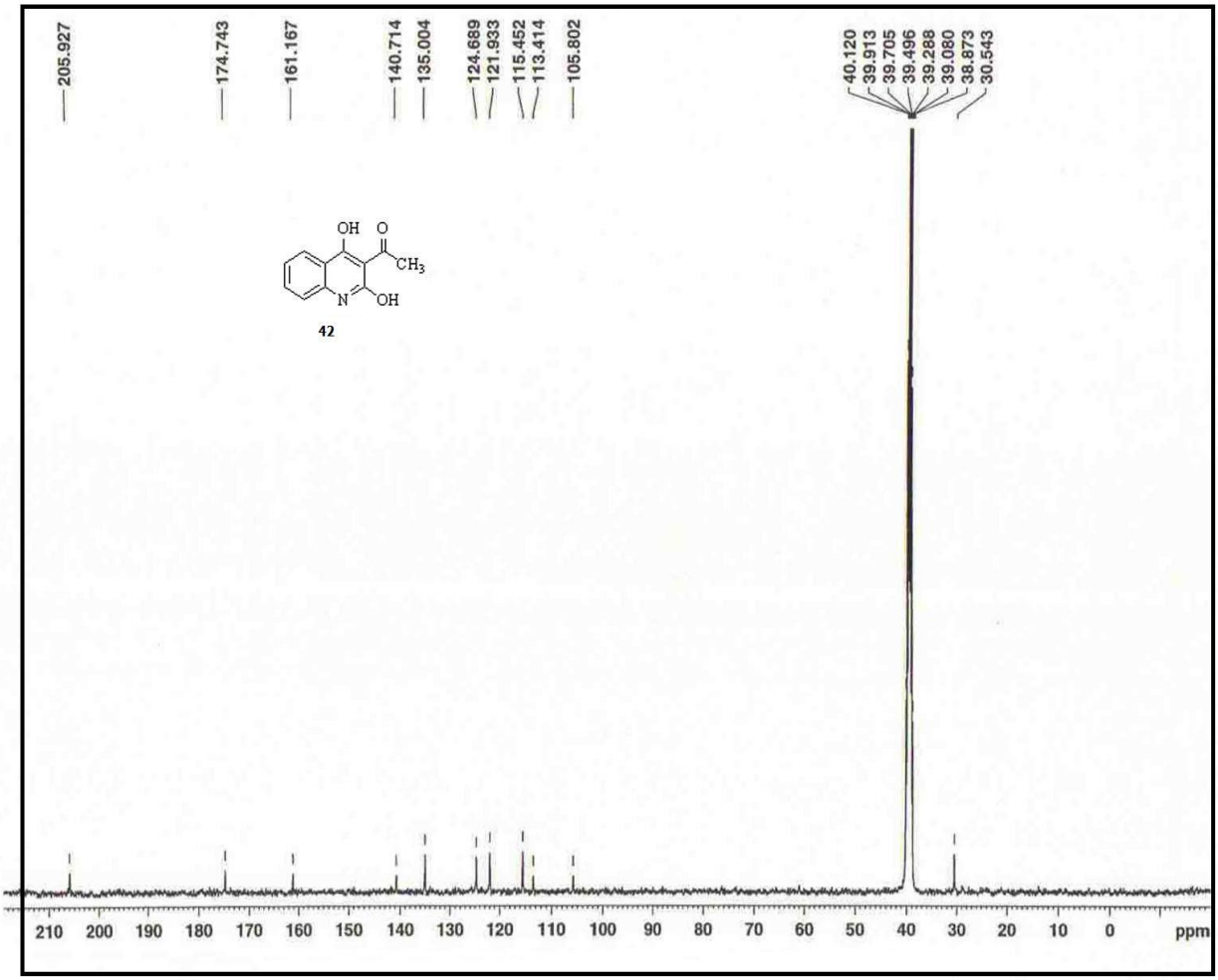

Figure 5: The ^{13}C NMR spectrum of 3, acyl-2, 4-dihydroxyquinoline

Appendix 4

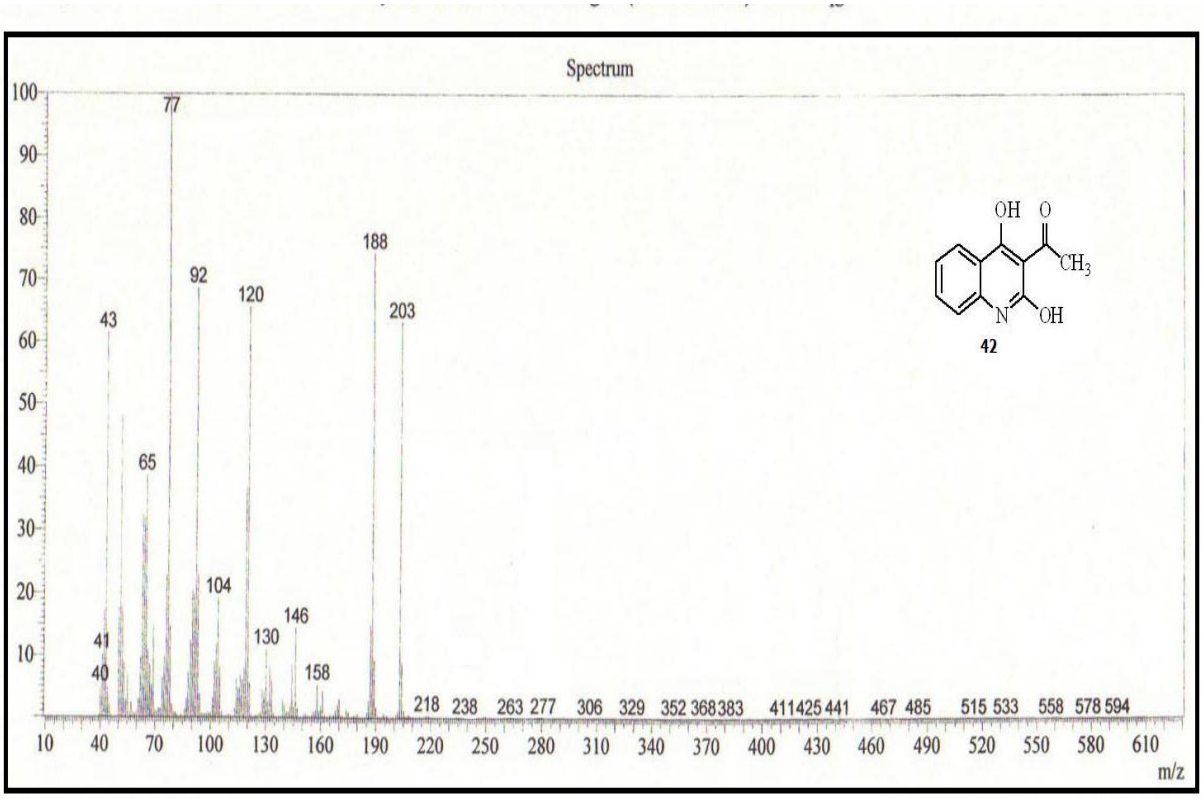

Figure 6: The Mass spectrum of 3, acyl-2, 4-dihydroxyquinoline.

Appendix 5

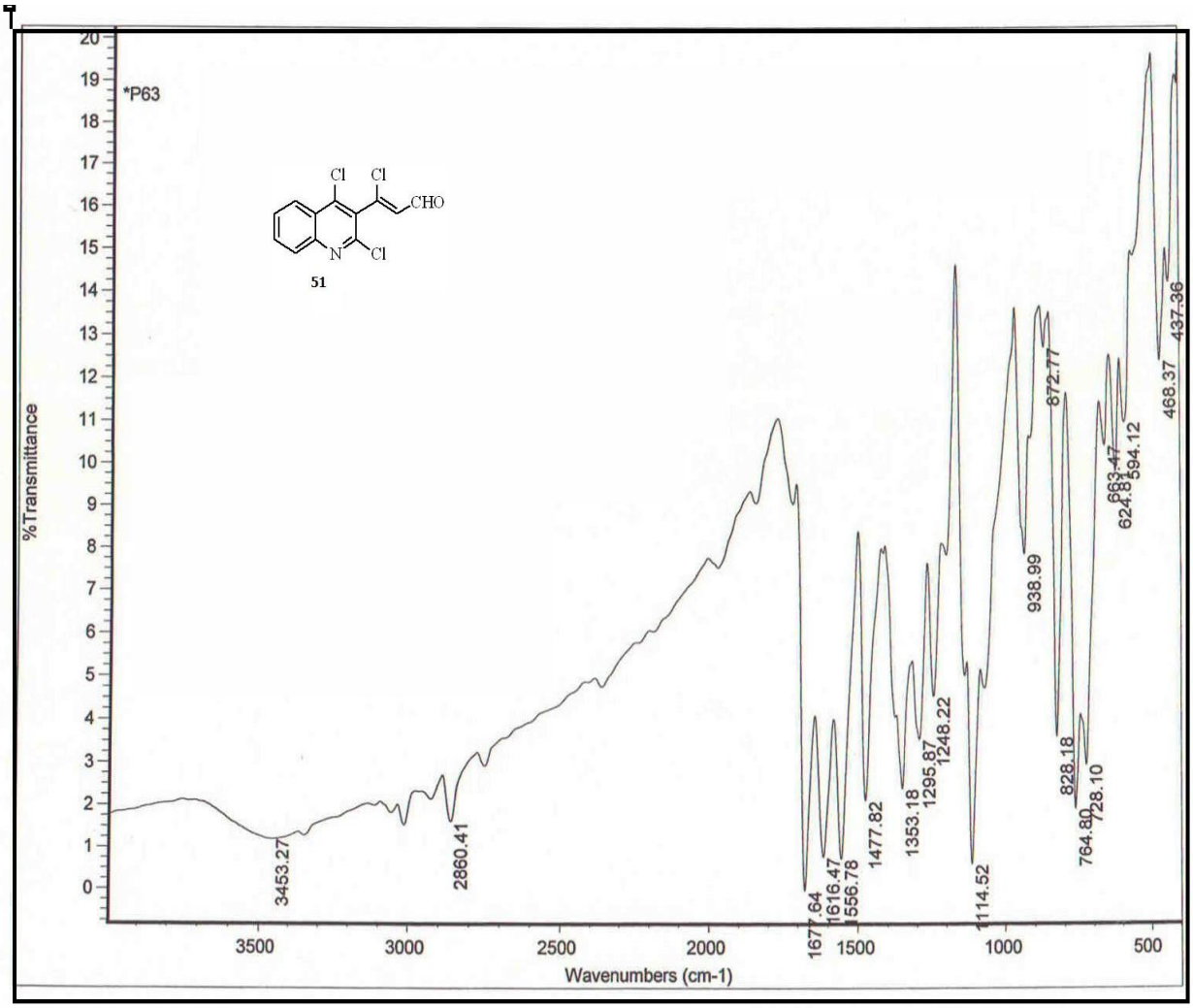

Figure 7: The IR spectrum of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline

Appendix 6

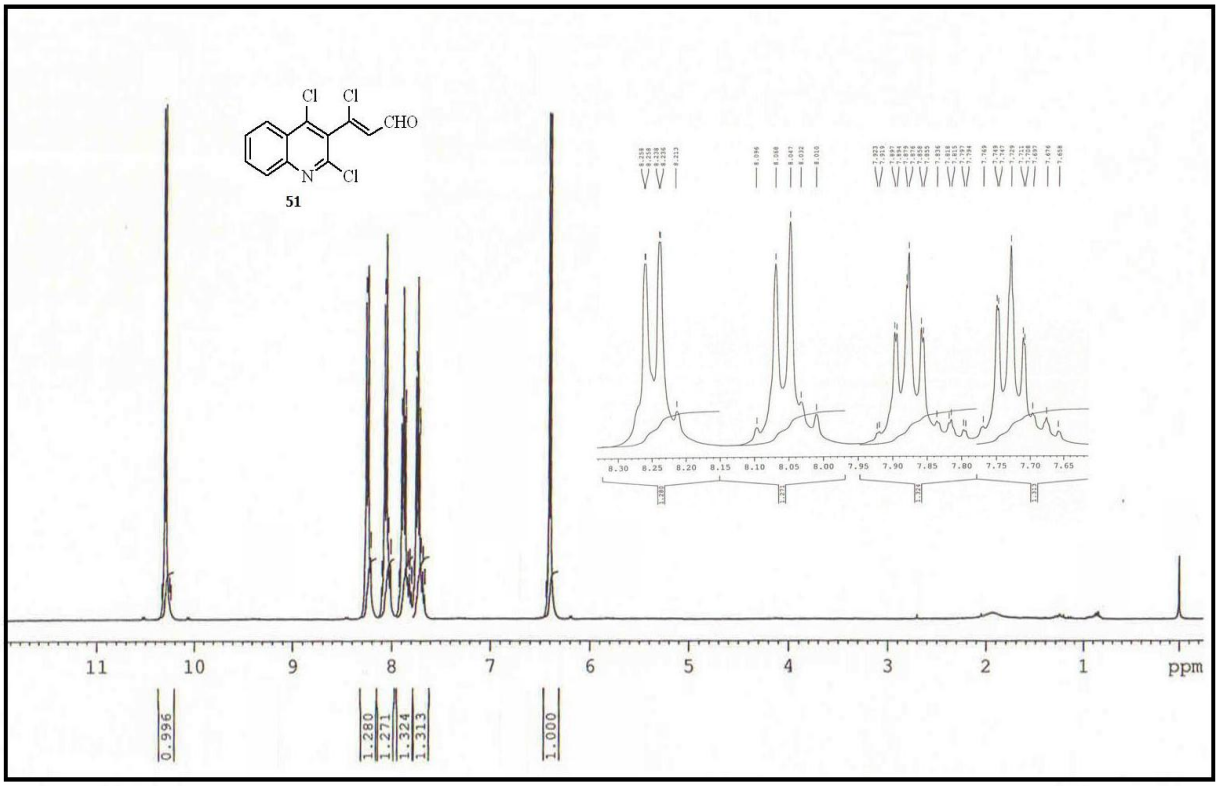

Figure 8: The ^{1}H NMR spectrum of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline

Appendix 7

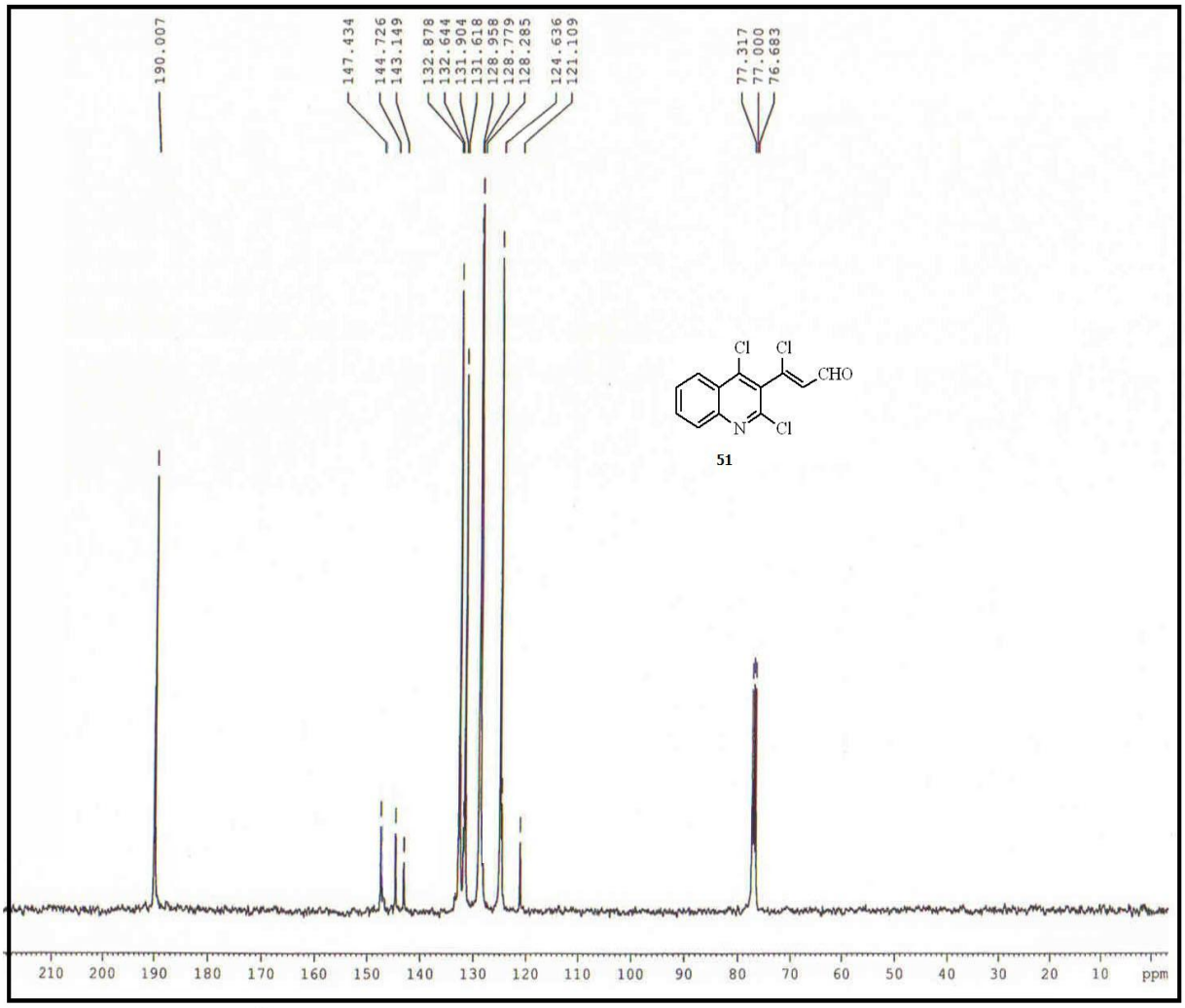

Figure 9: The ^{13}C NMR spectrum of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline

Appendix 8

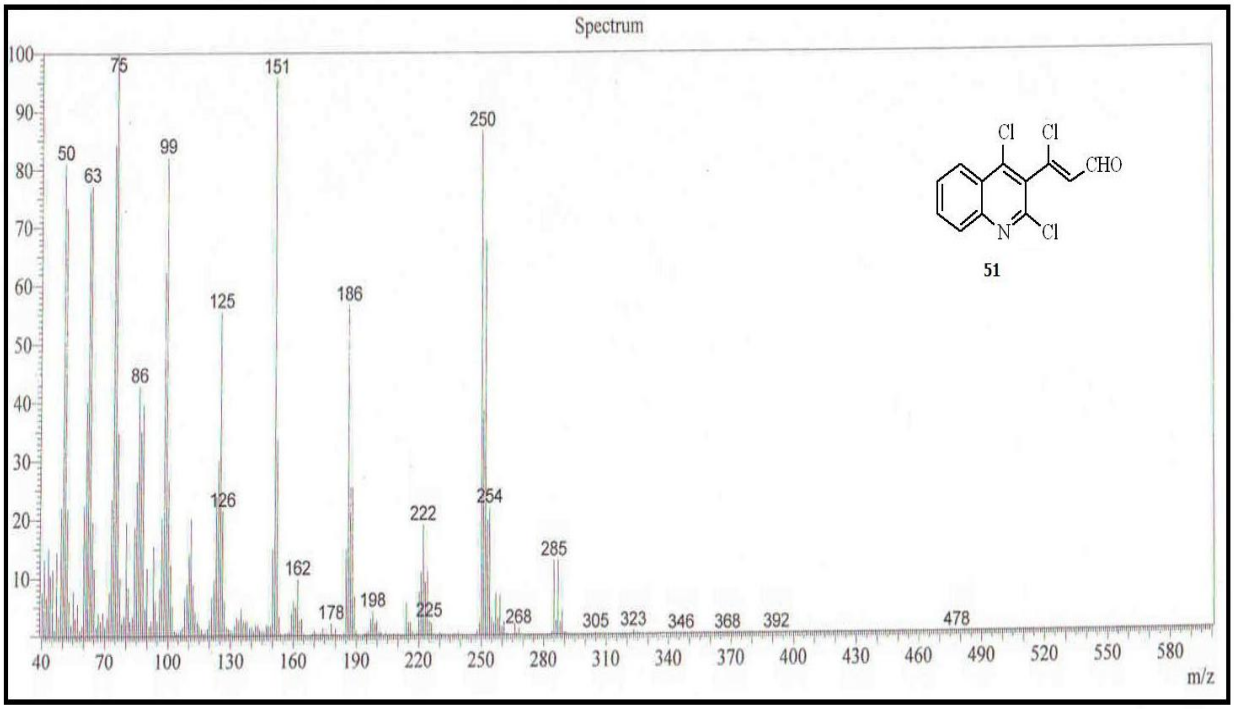

Figure 10: The Mass spectrum of 3-(3-chloroprop-2-enal)-2, 4-dichloroquinoline.

Appendix 9

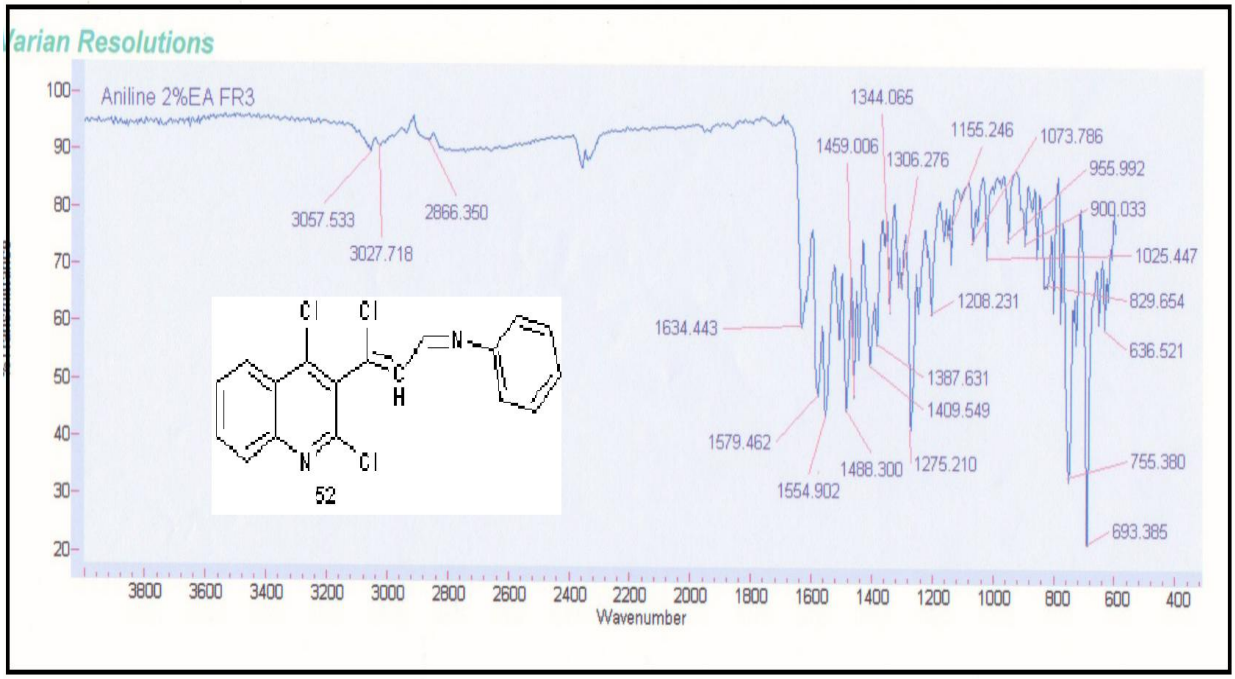

Figure 11: The IR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline.

Appendix 10

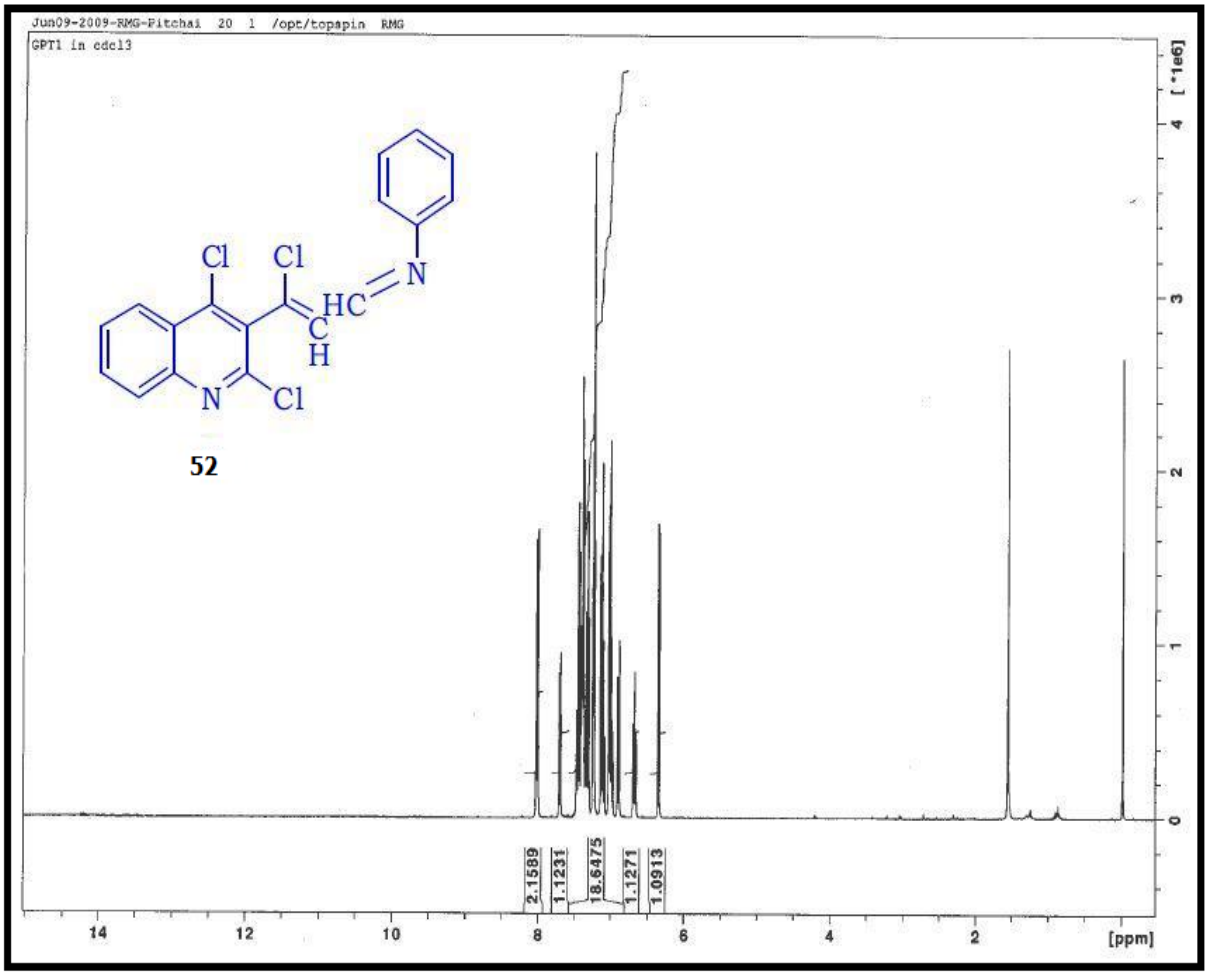

Figure 12: The ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline.

Appendix 11

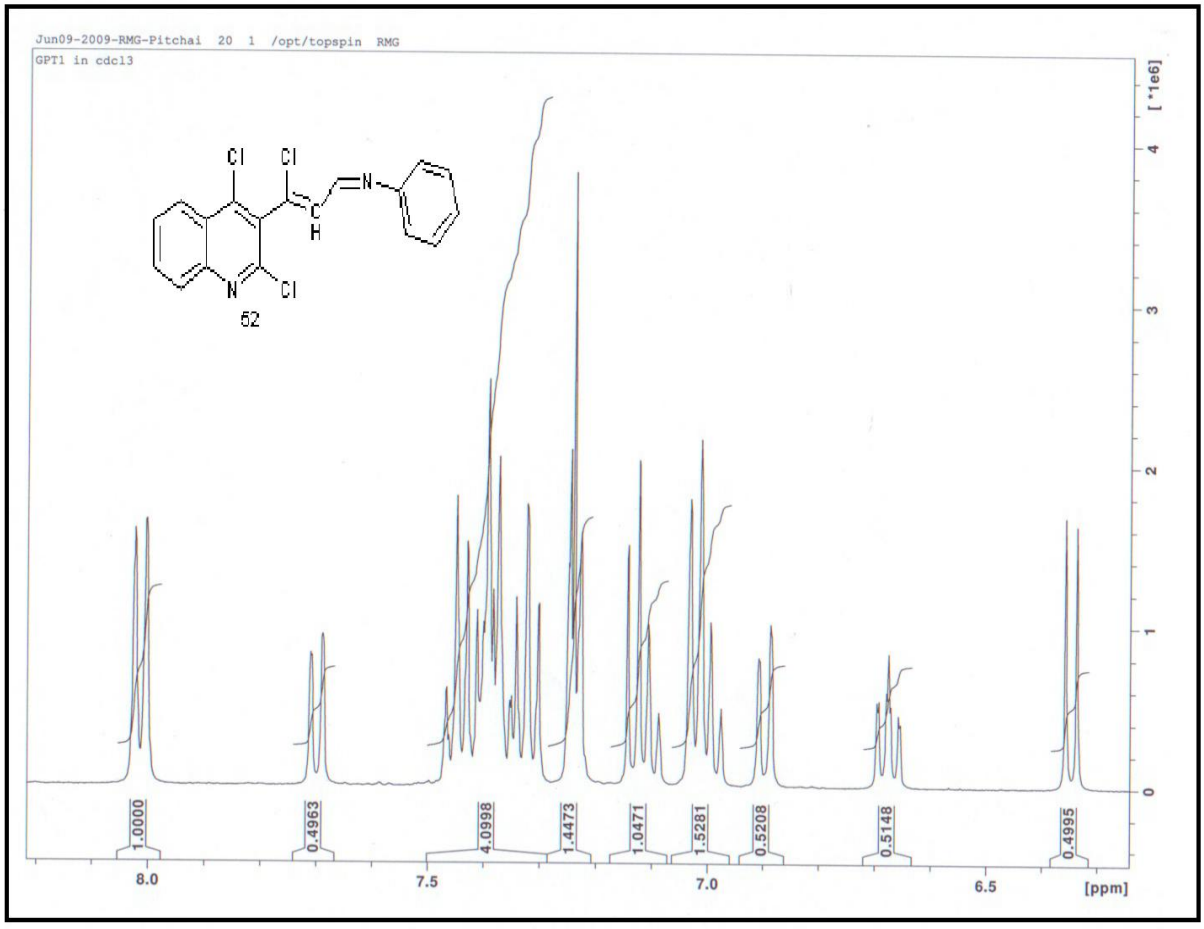

Figure 13: The expanded ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline.

Appendix 12

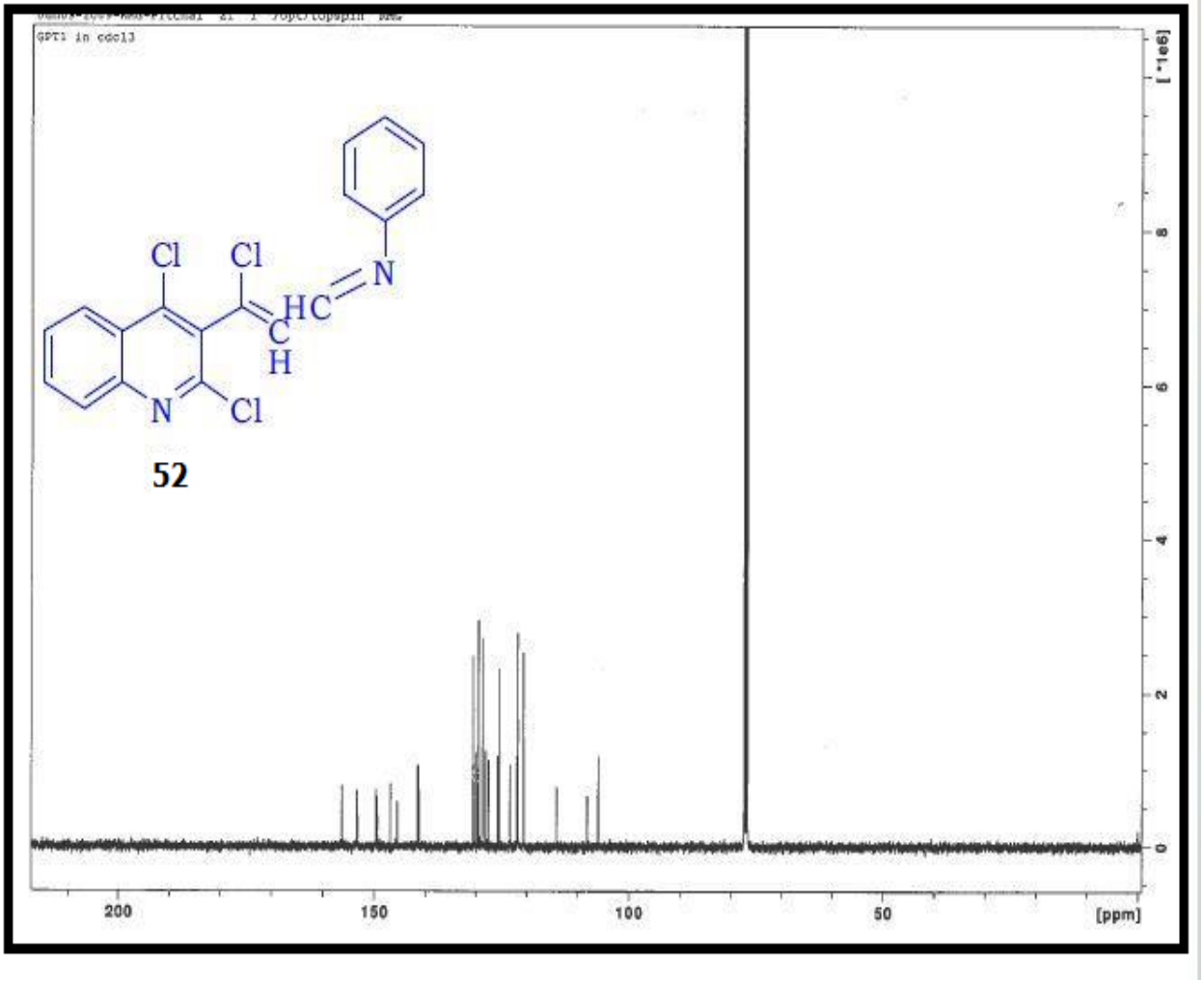

Figure 14: The ^{13}C NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3- yl) allylidene-aniline.

Appendix 13

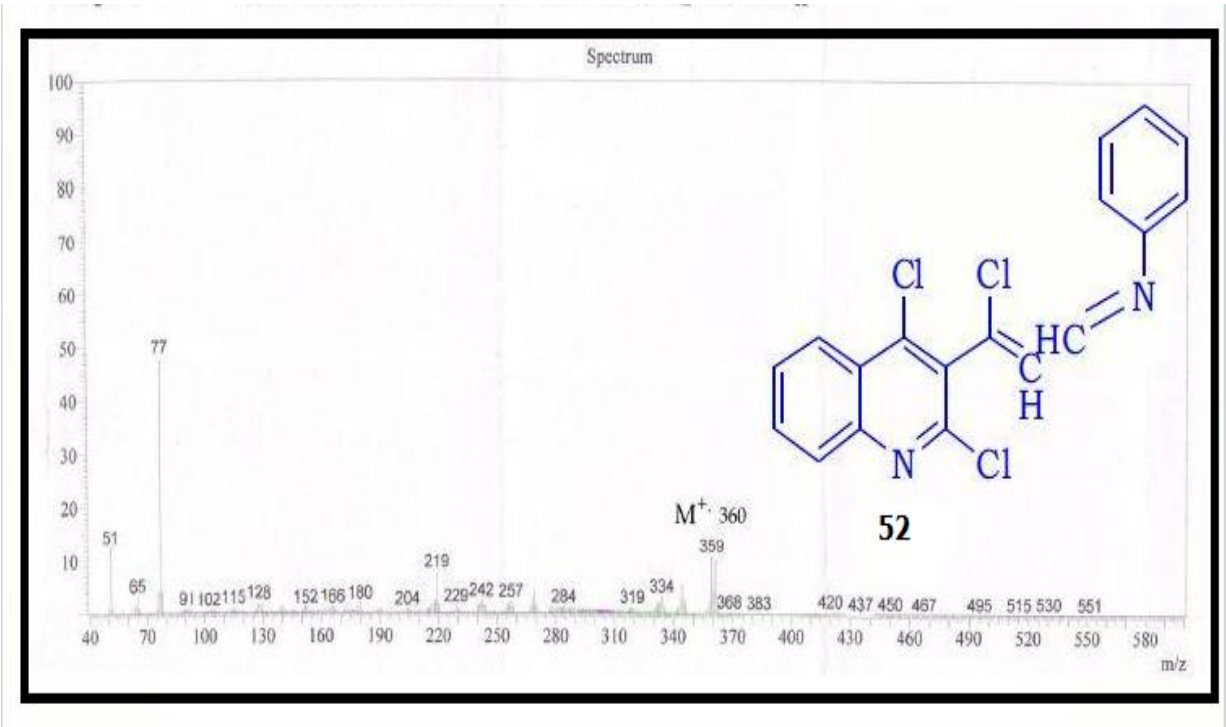

Figure 15: The Mass Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-aniline.

Appendix 14

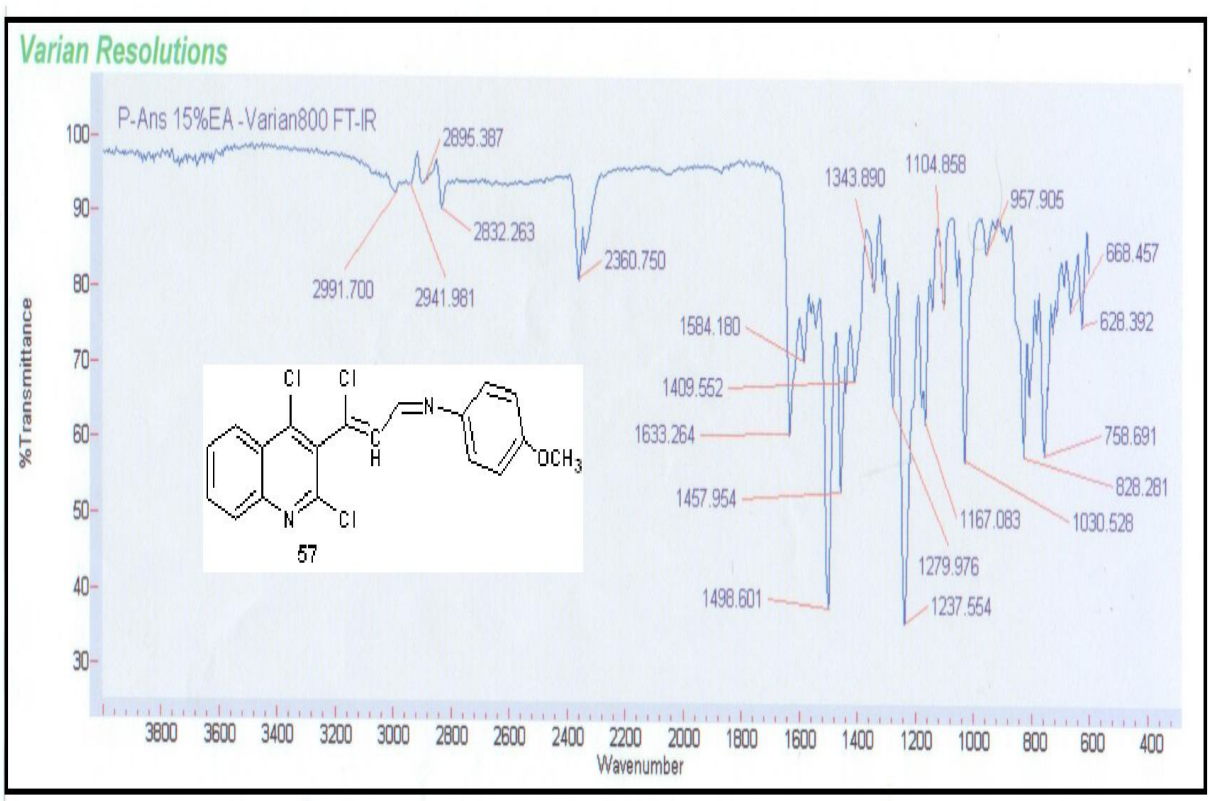

Figure 16: The IR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methoxy-aniline

Appendix 15

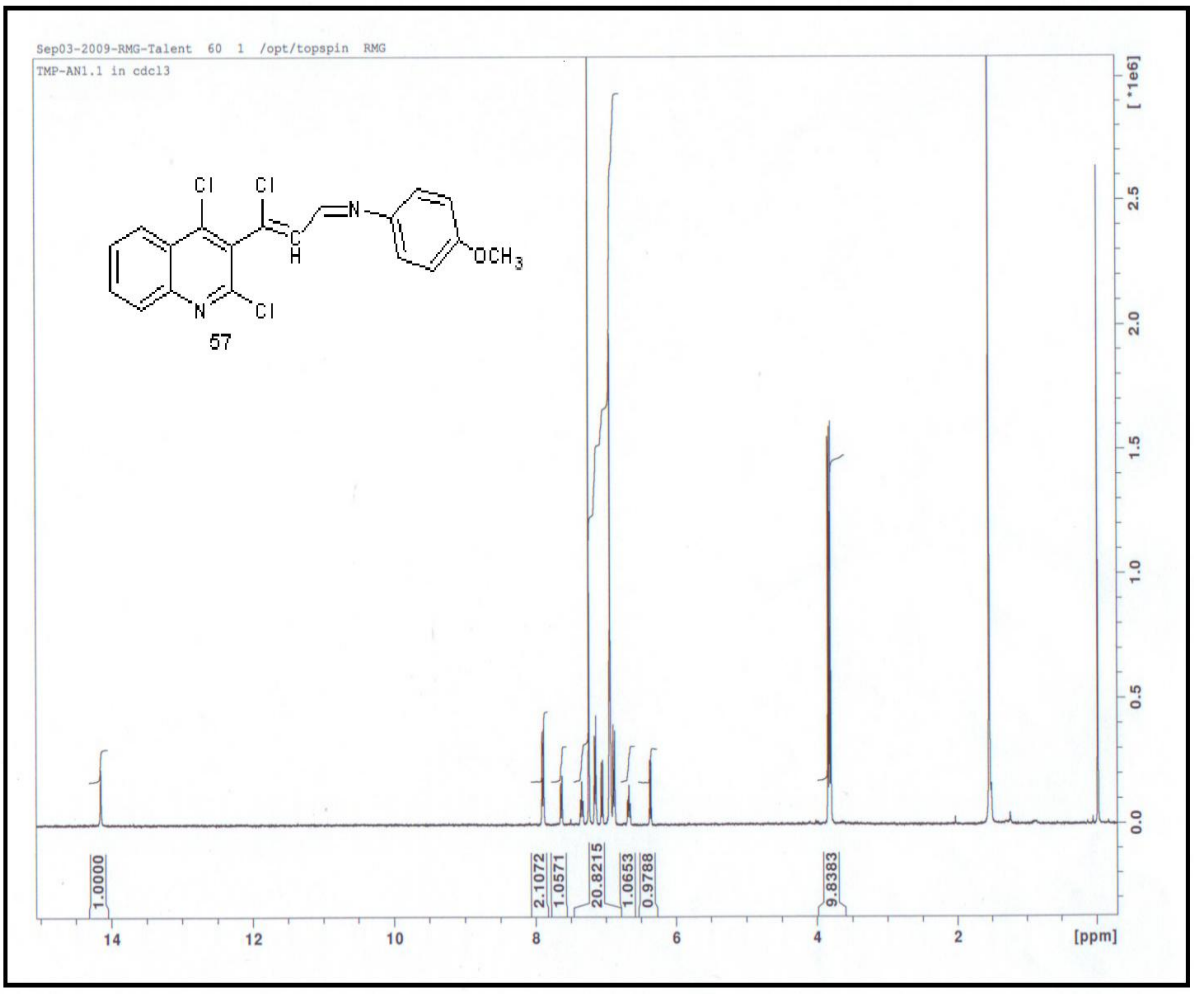

Figure 17: The ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline

Appendix 16

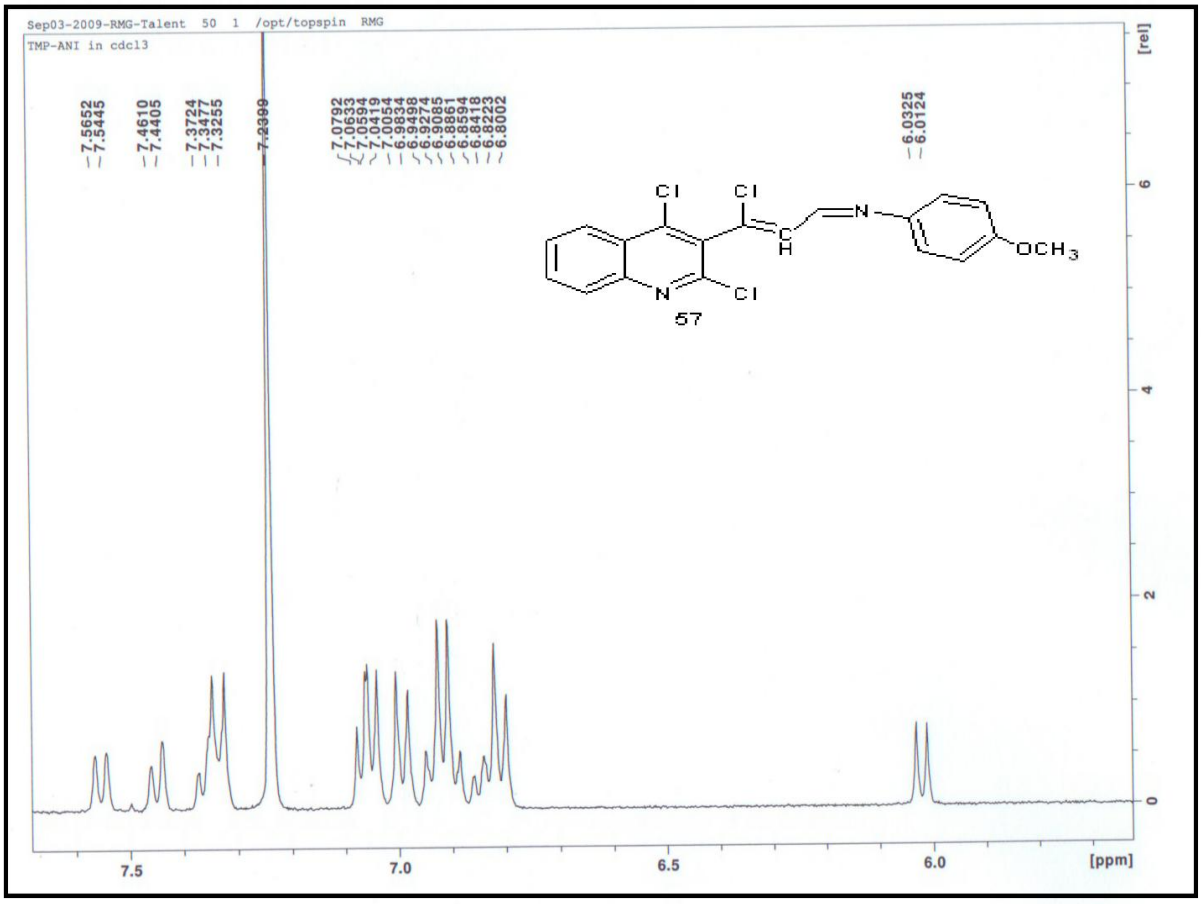

Figure 18: The expanded ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline.

Appendix 17

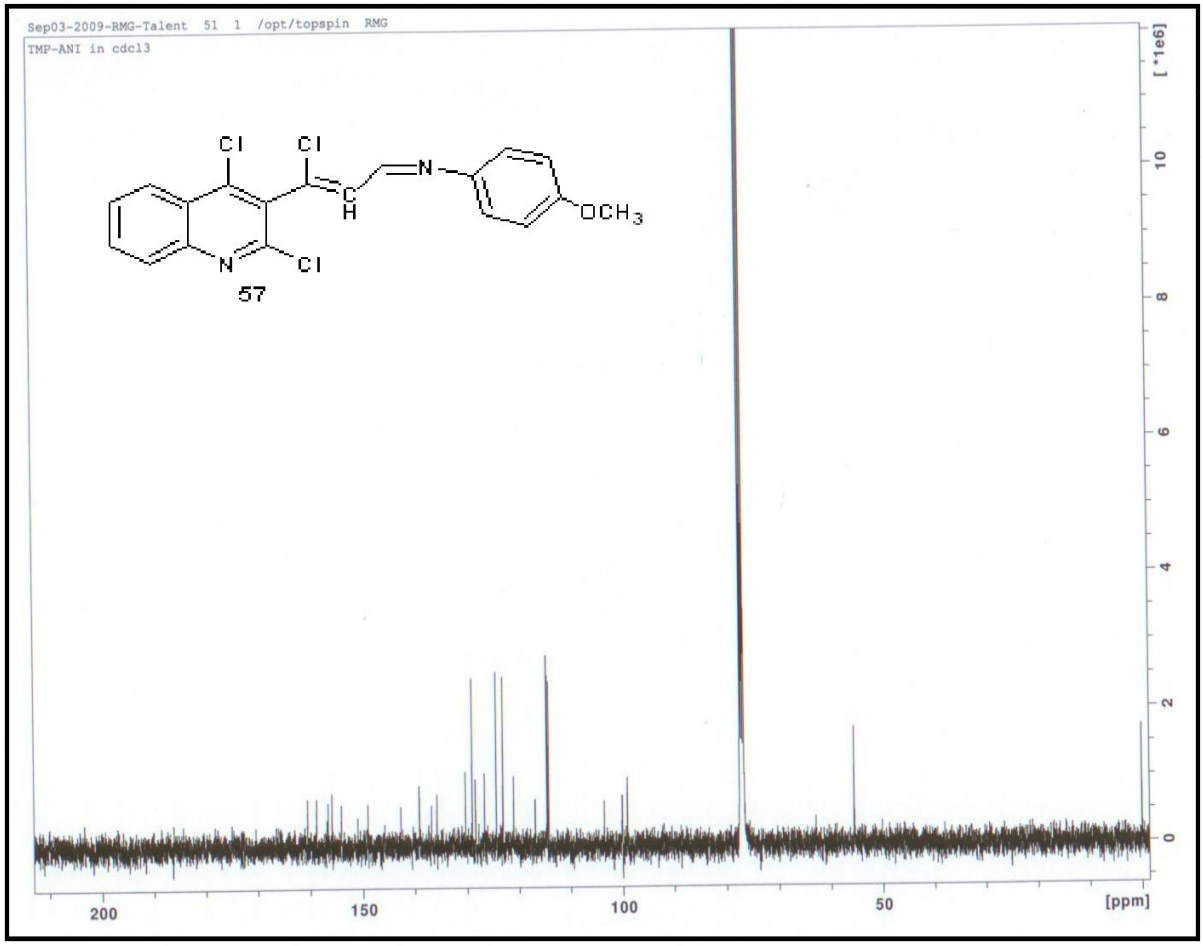

Figure 19: The ^{13}C NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methoxyaniline.

Appendix 18

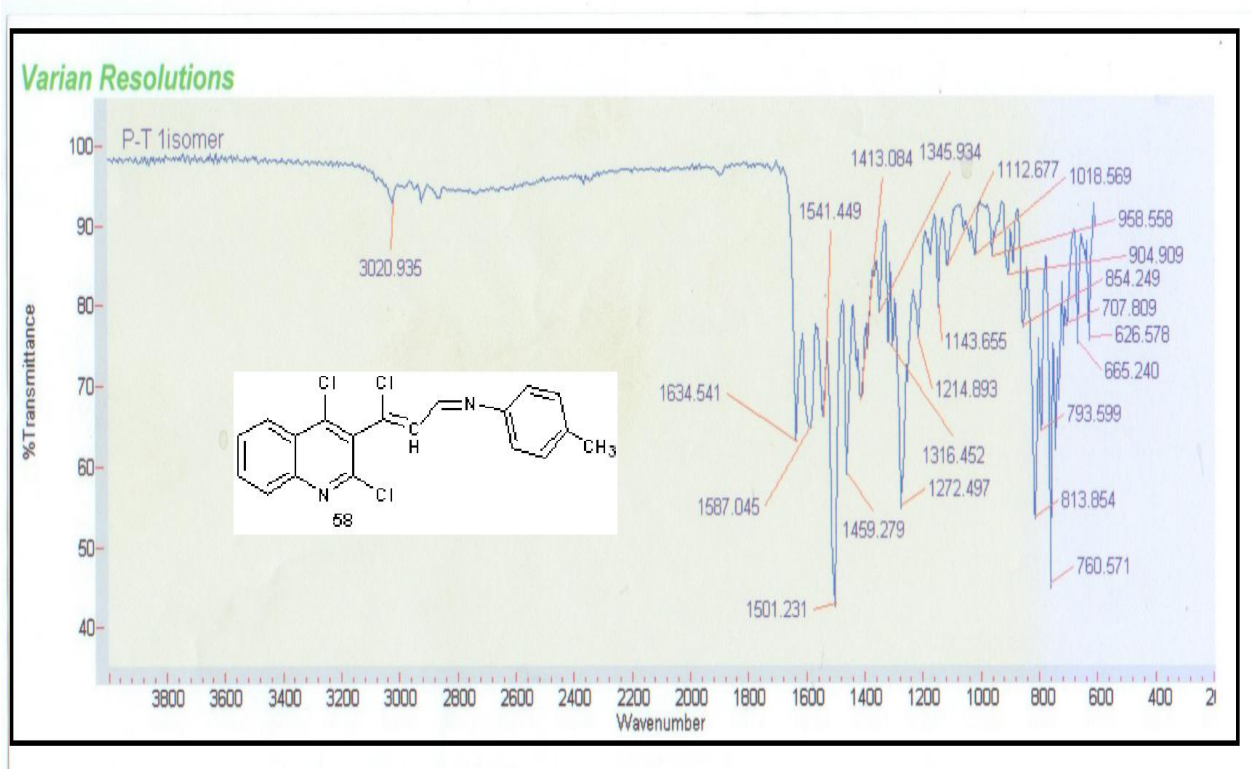

Figure 20: The IR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline.

Appendix 19

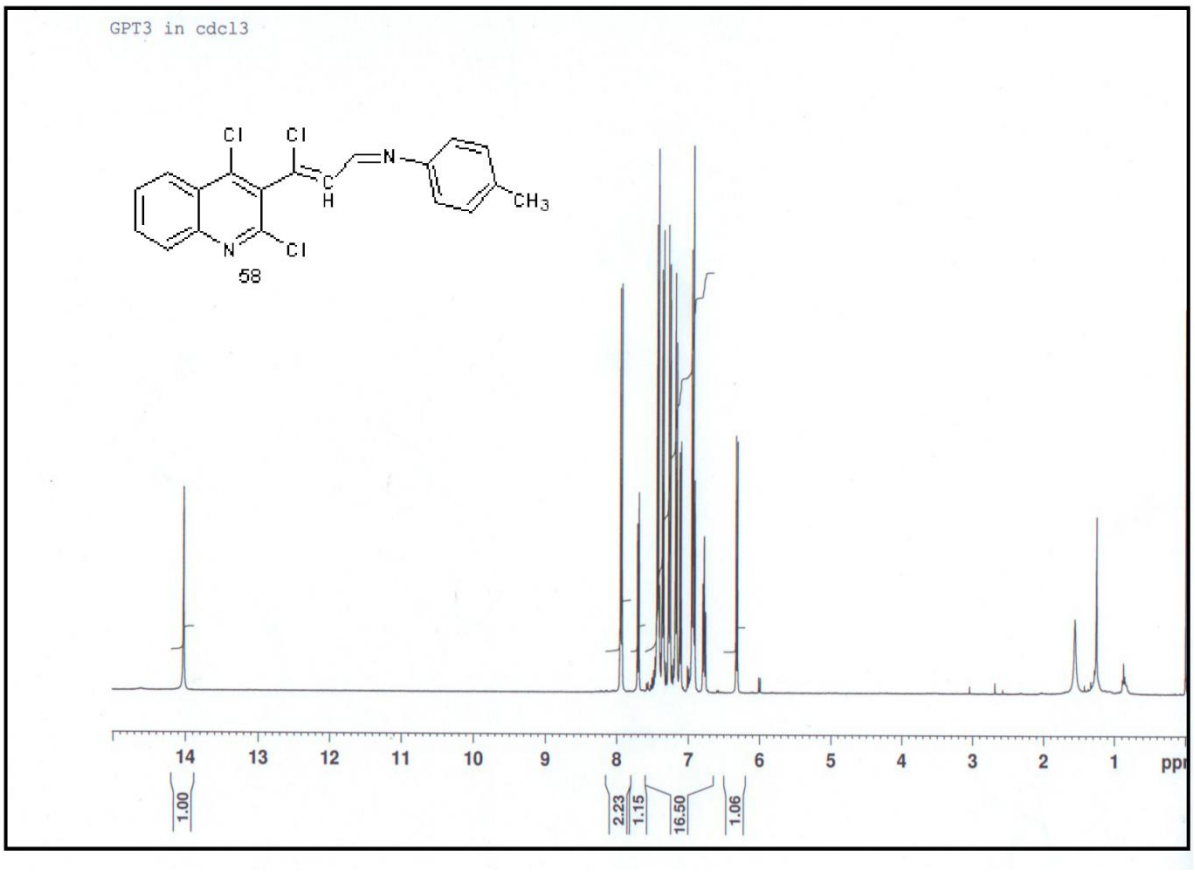

Figure 21: The ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline.

Appendix 20

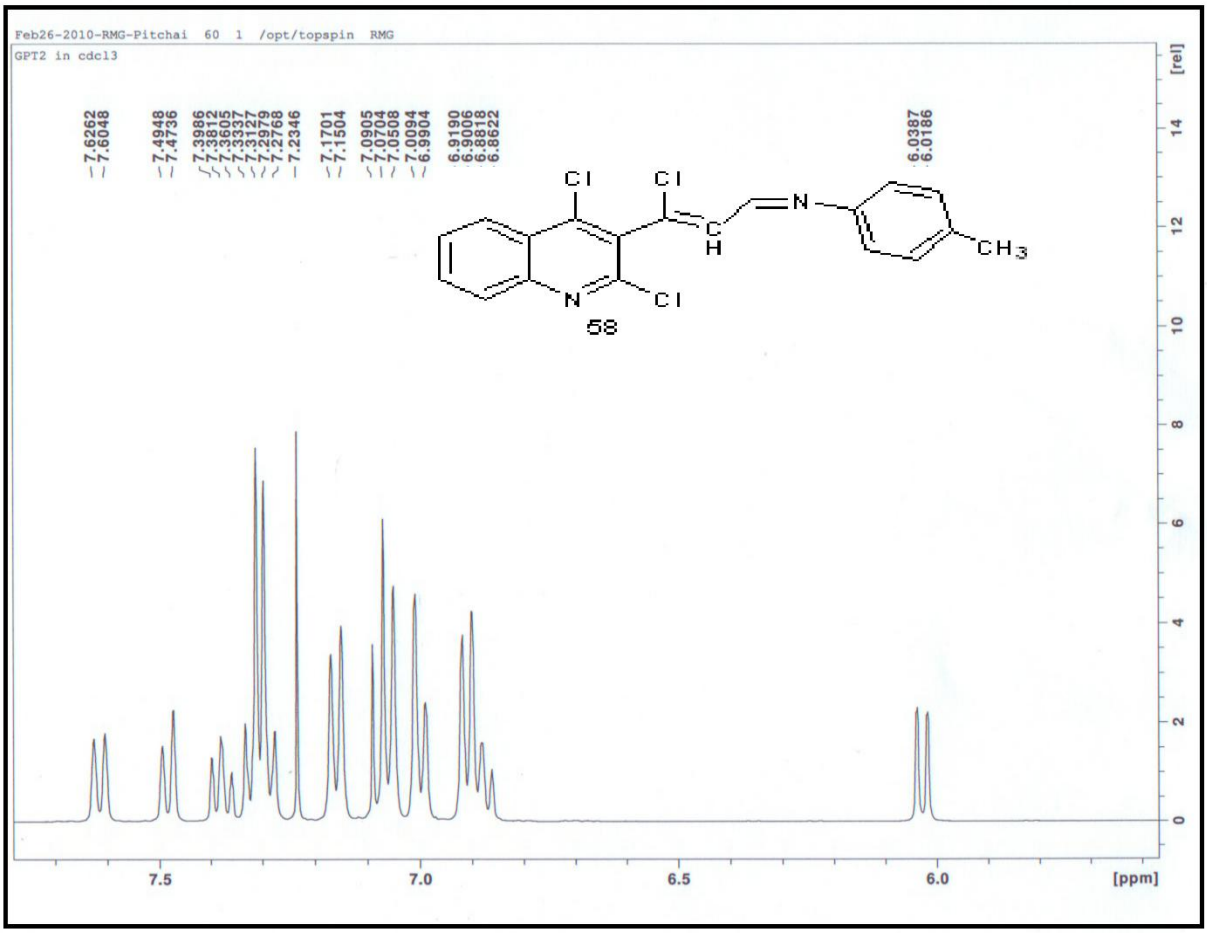

Figure 22: The expanded ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline.

Appendix 21

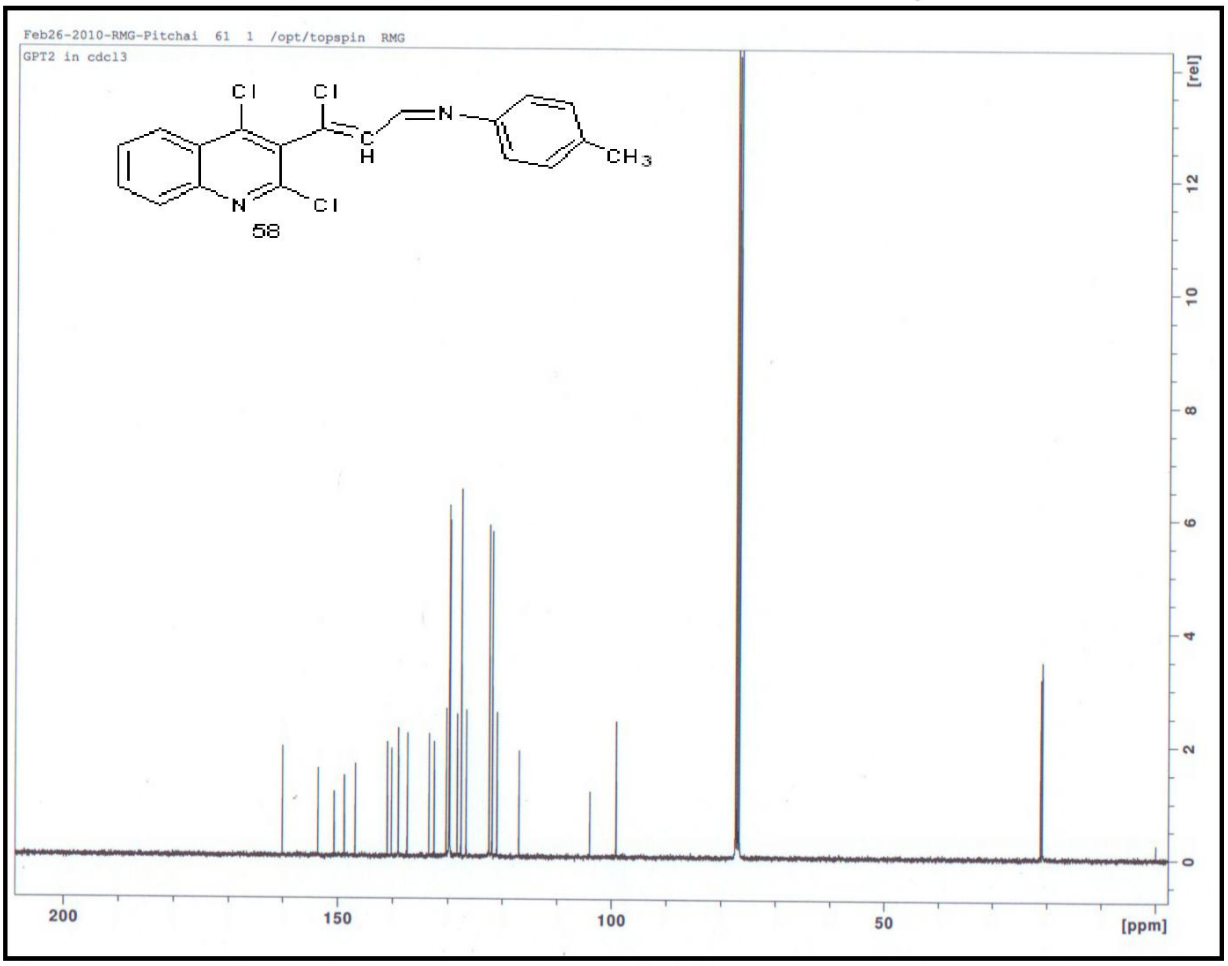

Figure 23: The ^{13}C NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-methylaniline.

Appendix 22

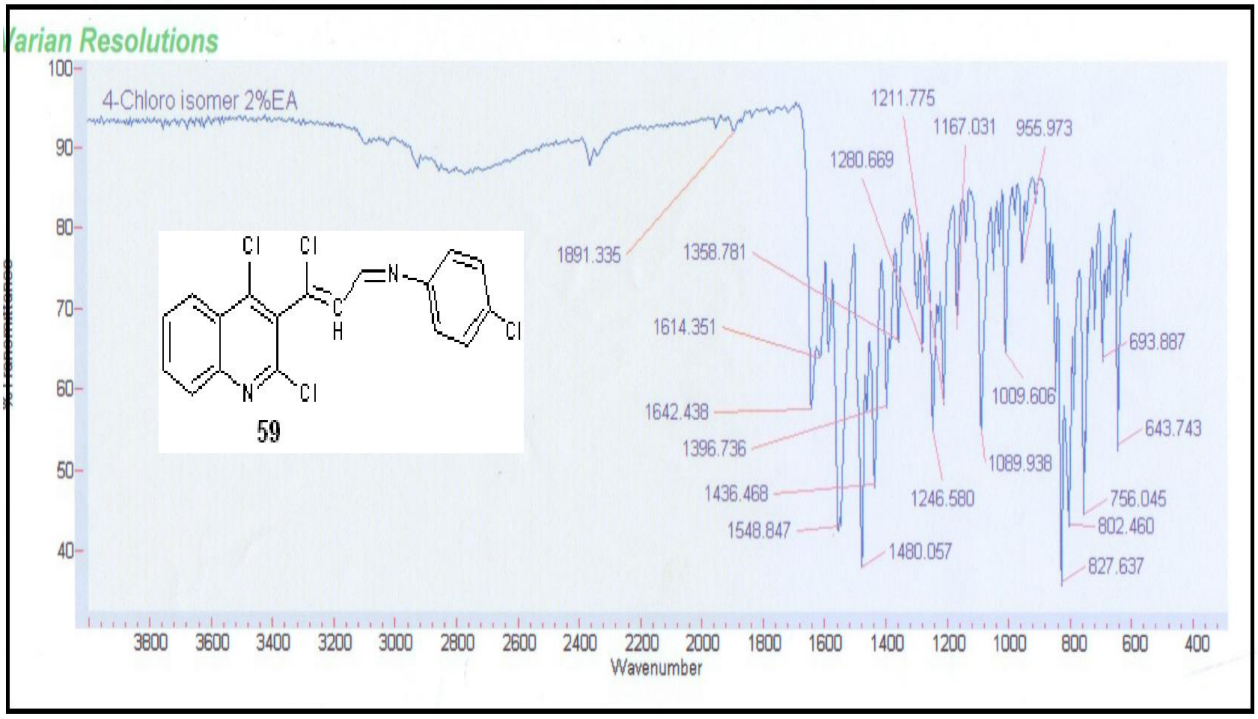

Figure 24: The IR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro-aniline.

Appendix 23

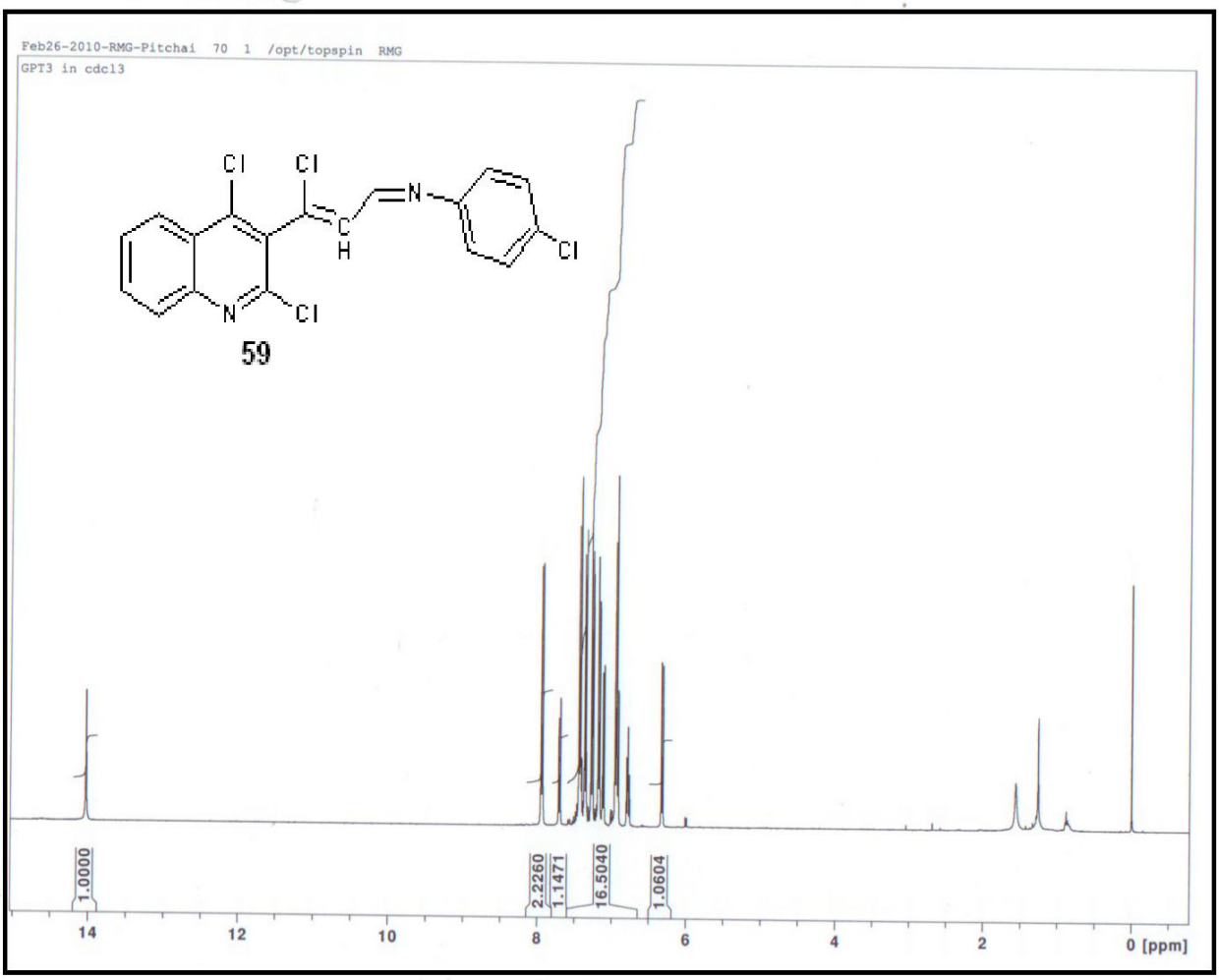

Figure 25: The ^{1}H NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro-aniline.

Appendix 24

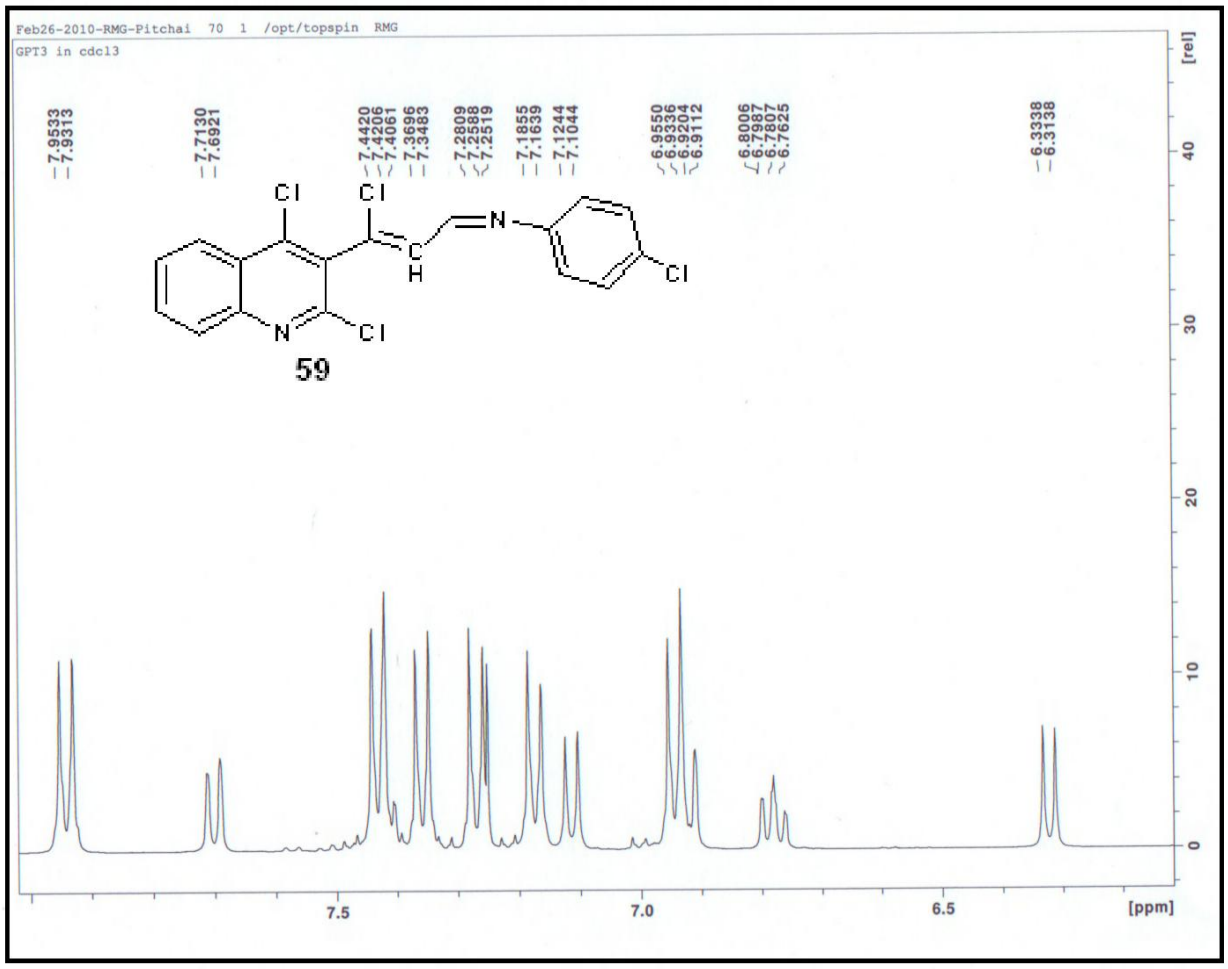

Figure 26: The ^{1}H NMR Spectrum of -3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro aniline.

Appendix 25

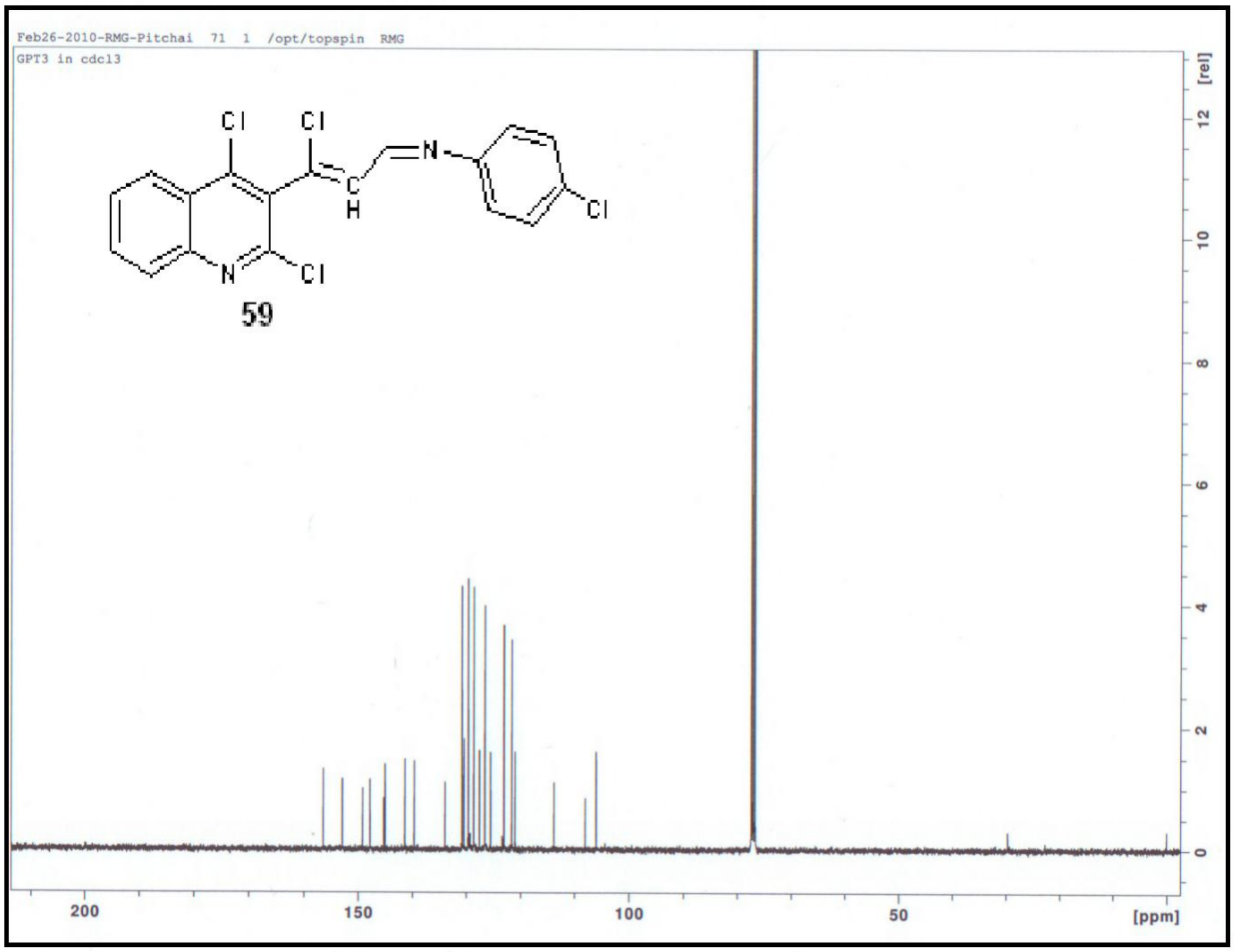

Figure 27: The ^{13}C NMR Spectrum of 3-chloro-3-(2, 4-dichloroquinolin-3-yl) allylidene-4-chloro-aniline.

Appendix 26

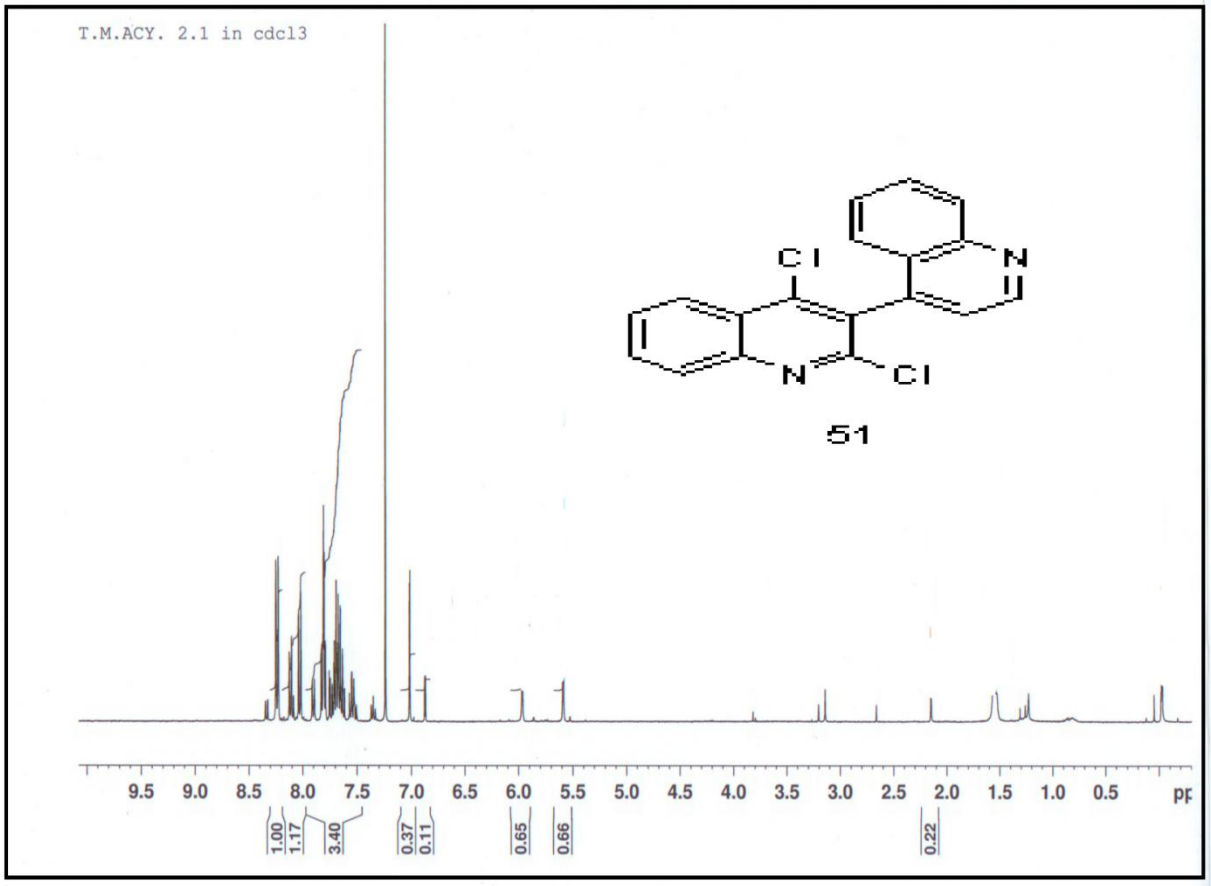

Figure 28: The ^{1}H NMR spectrum of 2, 4-dichloro-3, 4'-biquinoline

Appendix 27

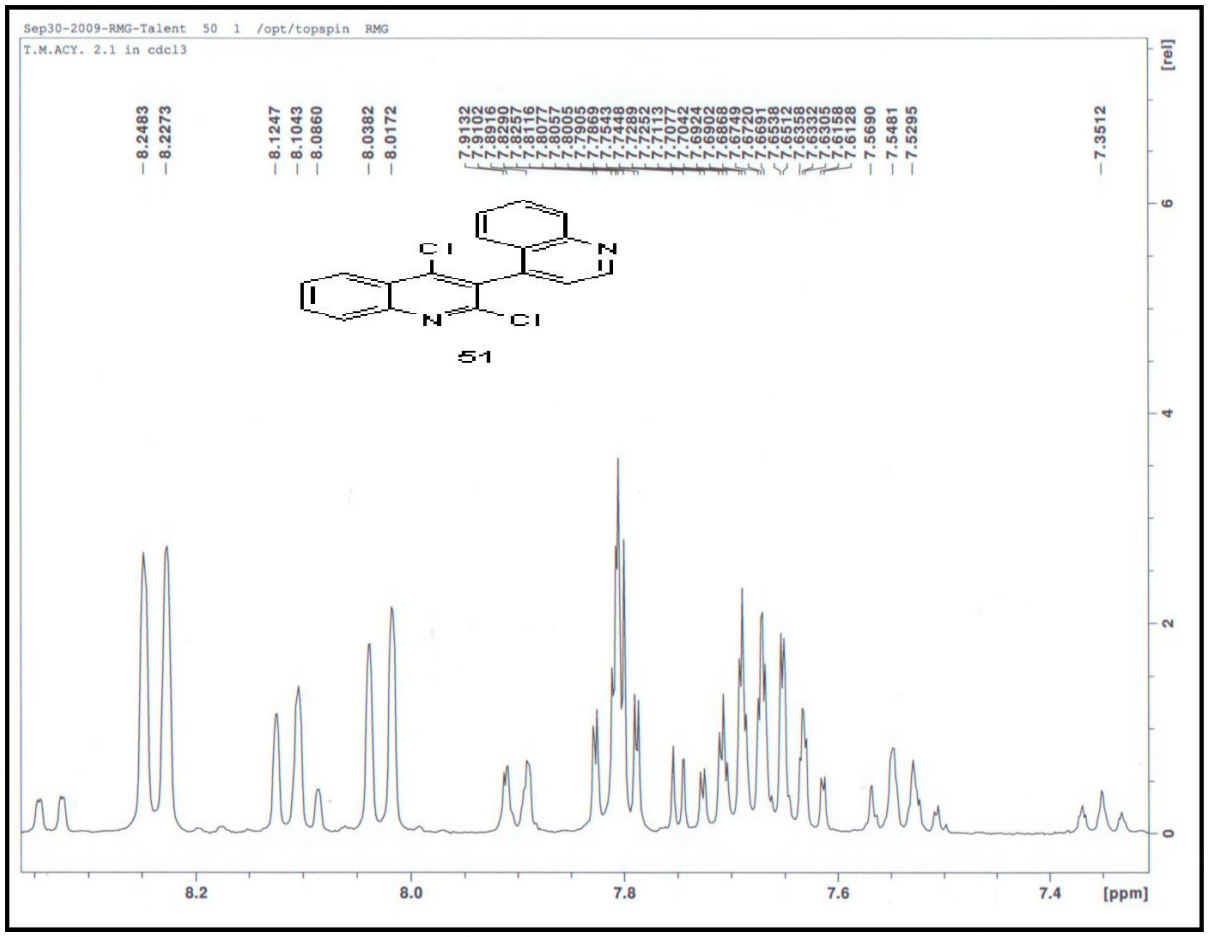

Figure 29: The expanded ^{1}H NMR spectrum of 2, 4-dichloro-3, 4'-biquinoline.

Appendix 28

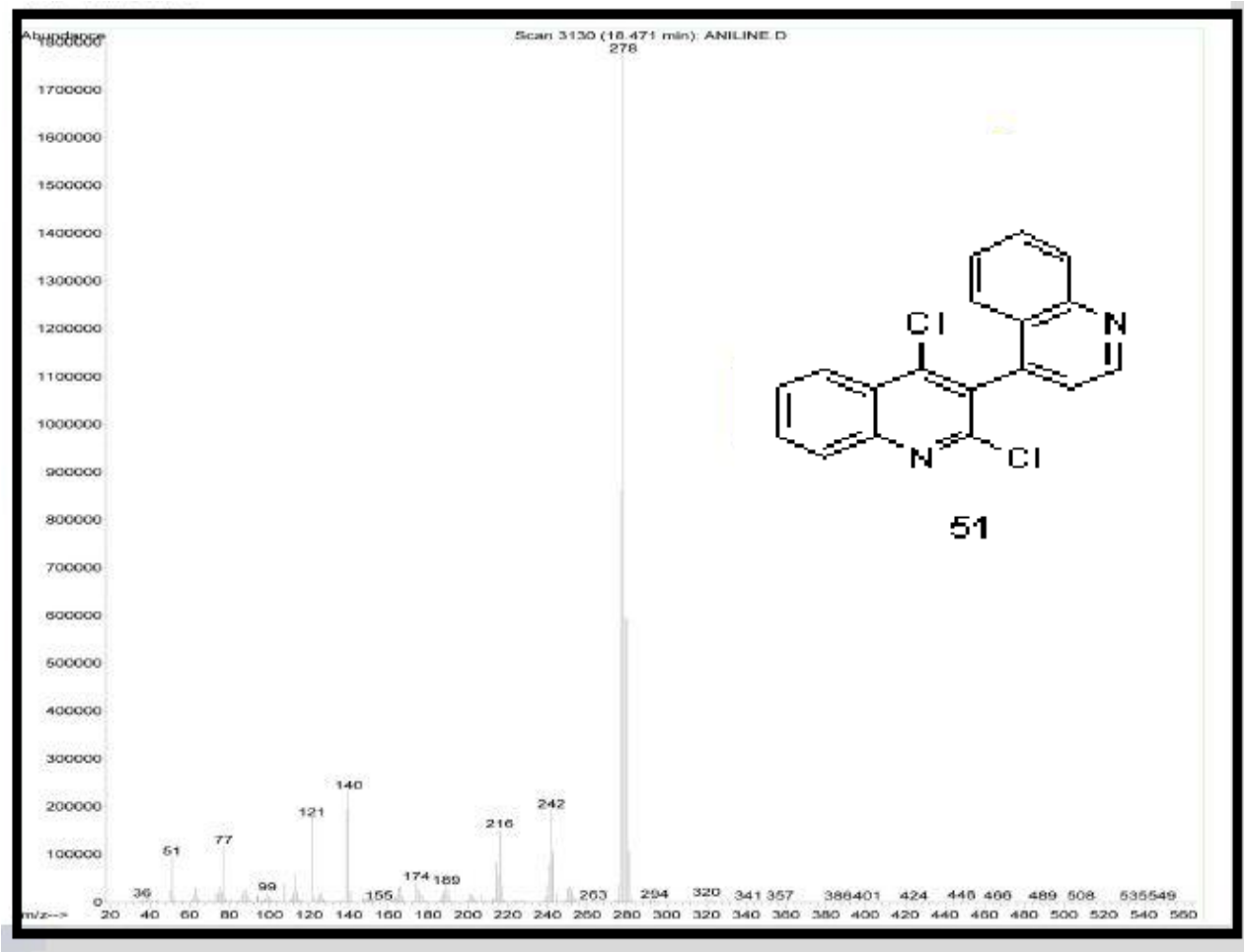

Figure 30: The Mass spectrum of 2, 4-dichloro-3, 4'-biquinoline

Appendix 29

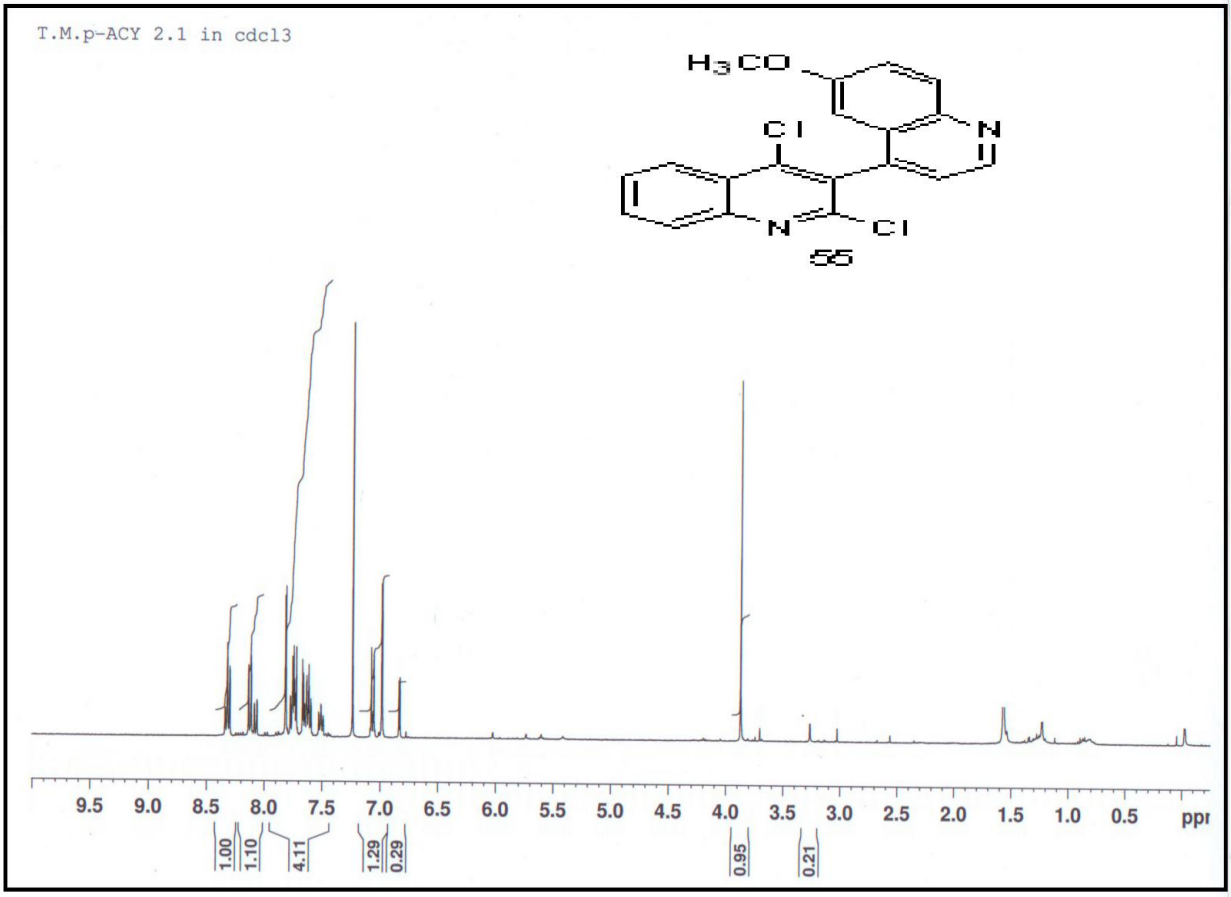

Figure 31: The ^{1}H NMR spectrum of 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline

Appendix 30

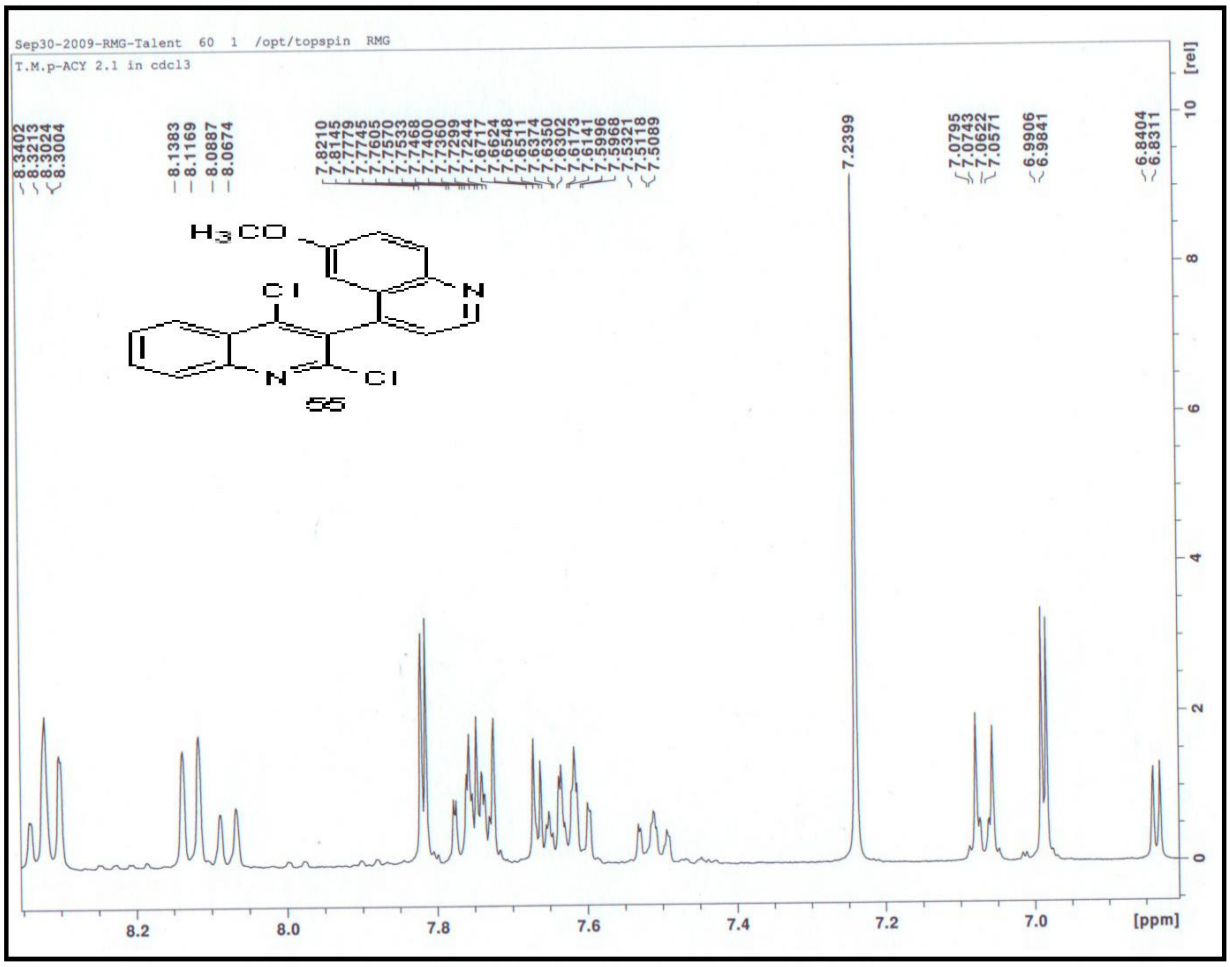

Figure 32: The expanded ^{1}H NMR spectrum of 2, 4-dichloro-7'-methoxy-3, 4'-biquinoline.