MICROWAVE AS AN ENERGY SOURCE IN THE SYNTHESIS OF 2-ARYL-4-QUINOLONE ALKALOIDS AND NAPHTHYRIDINES

Thesis submitted in fulfilment of the requirements for the degree of

Masters of Technology

Organic Chemistry

By

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Thesis submitted in fulfilment of the requirements for the degree of Master of Technology, Organic Chemistry, in the Faculty of Applied Sciences at Durban University of Technology

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BTech (Chemistry)

December 2011

PROMOTER: Dr. R.M Gengan

Declaration

I, Hlengiwe Glenrose Ndaba, hereby declare that this dissertation entitled “Microwave an as energy source in the synthesis of 2-aryl-4-quinoline alkaloids and naphthyrindine’’, 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 Sciences, is the result of my own work and that all sources used or quoted have been indicated and acknowledged by means of complete references.

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December 2011

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I thank GOD for watching over me and giving me strength, health and courage during difficult times.

Abstract

One of the greatest medical challenges facing mankind is the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) which has now become a major epidemic with more than 40 million people infected worldwide. Of equal concern is its implication in high mortality and the onset of a number of opportunist mycobacterial infections, principally tuberculosis. In spite of the discovery of some relatively effective anti-retroviral (ARV) drugs such as Azido Thymidine (AZT), Nevirapine (NVP) and Efavirenz (EFV), its' application as either a single or combinational form causes side effects by harming the bone marrow. Drug resistance is a key cause of failure for treatment of HIV infection. Hence greater interdisciplinary efforts, involving both natural and social sciences, are needed urgently to combat this HIV/AIDS pandemic.

Heterocyclic nitrogen based compounds, obtained from either natural sources or synthesis are adequately documented to have increased biological activity against several diseases. Recently a study of drugs containing the naphthyridine scaffold has acquired increasing attention because of its potential against HIV/AIDS. Generally, naphthyridines demonstrate good potency in both the enzyme and cellular systems and this prompted our interest in the synthesis of naphthyridine derivatives from simple and readily available starting compounds. Furthermore we wanted to form an intermediate quinolone moiety since it has good biological potential.

In this study we report the synthesis of three naphthyridine derivatives, i.e. 6-phenyl-dibenzo [b, h] [1, 6] naphthyridine, 4-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine and 2-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine from easily available chemicals such as aniline, *ortho*-toludine, *para*-toluidine and ethyl benzoylacetate via a five step reaction scheme using either conventional reflux, microwave irradiation or both methodologies. It was found that microwave irradiation was several folds faster than conventional reflux methodology and the yield of the product was higher.

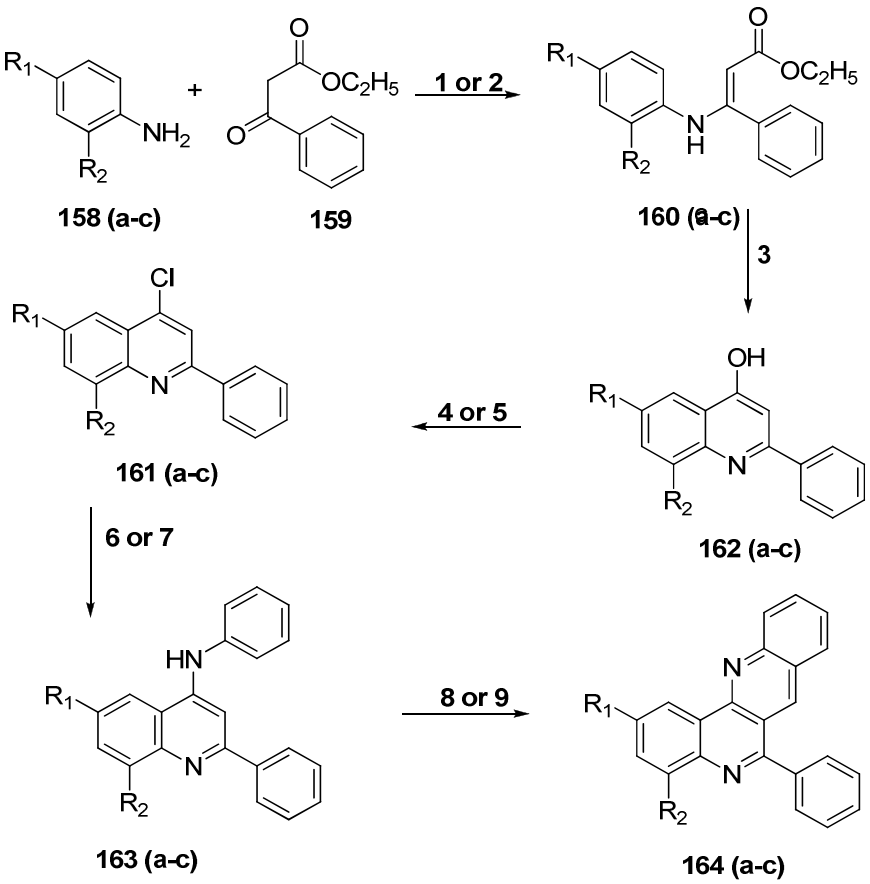
The first step of the reaction scheme is a simple condensation reaction: three acrylate derivatives, viz. ethyl-3-aniline-3-phenyl acrylate, ethyl-3-phenyl-3-(*ortho*-tolylamino) acrylate and ethyl-3-phenyl-3-(*para*-tolylamino) acrylate were synthesized by refluxing ethyl benzoylacetate in an acidified ethanolic solution with aniline, *ortho*-toluidine and *para*-toluidine respectively for three hours; the yields were 95, 87.5 and 80 % respectively.

In the second step, thermal cyclisation was achieved for the synthesis of three quinoline derivatives, viz. 2-phenylquinoline-4(1H)-one, 8-methyl-2-phenylquinoline-4(1H)-one and 6-methyl-2-phenylquinoline-4(1H)-one from their respective acrylates under microwave irradiation for 5 minutes at 180 °C and 250 watts; the yields were 92, 84 and 80 % respectively.

In the third step of the reaction, synthesis of 4-chloro-2-phenylquinoline, 4- chloro-8-methyl-2-phenylquinoline and 4- chloro-6-methyl-2-phenylquinoline was achieved from a mixture of $POCl_3$ and their respective quinolines via microwave irradiation for 3 minutes at 75 °C and 150 watts and via conventional reflux for 5 hours. It was found that under microwave irradiation, the reaction occurred nearly 100 fold faster but the % yield of the product was marginally higher.

The fourth step of the reaction resulted in the formation of three schiff's base, viz. 4-(N-phenyl)-2-phenyl-4-aminoquinoline, 8-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline and 6-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline from their respective quinolines via microwave irradiation for 20 minutes at 180 °C and 180 watts and via conventional reflux for 2 hours. It was found that under microwave irradiation, the reaction occurred nearly 6 fold faster and the % yield of the product was over 10 % higher.

The final step of the reaction was achieved by a Vilsmeir Haack reaction and *in situ* base catalyzed thermal cyclisation: 6-phenyl-dibenzo [b, h] [1, 6] naphthyridine, 4-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine and 2-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine were synthesized from their respective schiffs base via microwave irradiation for 20 minutes at 75 °C at 120 watts and via conventional reflux for 21 hours. It was found that under microwave irradiation, the reaction occurred over 60 fold faster and the % yield of the product was over 20 % higher.The outline for the five step synthesis of the three naphthyridines is presented graphically below:



Key:

(a) R_1= H; R_2=H

(b) R_1 = H; R_2 = CH_3

(c) R_1 = CH_3; R_2 =H

Reaction Conditions:

1) conc.HCl, EtOH, 3hrs, 50 °C; **2**) conc. HCl, hand stirring 10 min;

3) 180 °C, MWI, 250 watts, 5 min; **4**) $POCl_3$, MWI, 75 °C, 150 watts, 2 min;

5) $POCl_3$, 100 ^oC, 5 hrs; **6**) aniline, t-BuOH, MWI, 180 °C, 180 watts, 20 min;

7) aniline, t-BuOH, 80 °C, 3 hrs; **8**) DMF, $POCl_3$, MWI, 75 °C,120 watts 20 minute; **9**) DMF, $POCl_3$, 100 ^oC, 21 hrs.

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Abbreviations

Aids	Acquired immunodeficiency syndrome
AZT	Azidothymidine
br.s	Broad singlet
$CDCl_3$	Deuterated Chloroform
Conc.	Concentrated
D	Doublet
dd	Doublet of doublet
DMF	Dimethyl formamide
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonuclei acid
dt	Doublet of triplet
EtOAc	Ethyl acetate
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
Hz	Hertz
IN	Intergrase
IR	Infra red Spectroscopy
MeOD	Methanol
MIW	Microwave irradiation
NH	Amine
NMR	Nuclear Magnetic Resonance
PE	Petroleum ether
$POCl_3$	Phosphoryl Oxychloride
q	Quatert
S	Singlet
t	Triplet
t- BuOH	Tertial butanol
td	Triplet of doublet
TLC	Thin layer chromatography
V/V	Volume per volume

Chapter One: Introduction

Mankind is blessed with an abundance of plants which are used to provide food, shelter, medicines and other resources. Since plants are living entities, they have their own mechanistic route of assembling simple molecules into complex structures, some of which are cleverly utilized by man for medicinal purposes. Since time immemorial, traditional healers have been using different parts of plants to alleviate several illnesses. However, due to improved methodologies, important compounds have been extracted from these plants, purified and applied as medicinal drugs. For example, salicylic acid, morphine and codeine and quinine were isolated from willow bark, poppy and cinchona respectively. However, it was not until the recognition that many infectious diseases were caused by micro-organisms that the real impetus in the development of therapeutic agents, both natural and non-natural, began to occur. Concurrent with discoveries in medical microbiology were major advances in synthetic organic chemistry and biochemistry that provided further momentum in the area of therapeutic agents. Synthetic sulfa drugs, the natural antibiotic penicillin, the semi-synthetic antibiotic tetracycline and the anti-tubercular aminoglycoside streptomycin were some of the landmark discoveries of the 1900's. Unfortunately, in parallel to technological developments, new diseases have become rampant thereby posing a huge threat to human life. The Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS), Malaria, Tuberculosis (TB) and cancer are now household words; families are being destroyed due to premature death, chronic ailments and a detrimental social impact.

At present, the number of organic compounds that have been synthesized in research laboratories is far greater than that isolated from nature. However, not all organic compounds display properties suitable for application beneficial to mankind. Hence, an important requirement for the new generation synthetic organic chemists is to interrogate his research plan by addressing important issues such as:

- Cost of the starting material
- Time duration of the synthesis
- Overall yield of the desired product
- Feasibility of scale-up of the reaction
- Environmental impact
- Feasibility of application

Arising from these questions, an ideal synthesis can be described as one that uses cheap and readily available starting materials, produces high yields in each step of the reaction scheme proceeds very rapidly, requires little time on the part of the chemist and/ is environmentally benign. The reasons for synthesizing natural products in the laboratory are to make substances more widely available at a lower cost than it would be if the compound had to be extracted from its natural source and to create new substances that may have new and useful properties.

Among the nitrogen heterocyclic compounds, quinoline alkaloids, fused quinoline heterocycles and naphthyridines represent some important classes of organic molecules that display good biological activity against a host of organisms that are responsible for various diseases. Naphthyridines have recently been used as pharmaceuticals, fungicides, bactericides, herbicides and insecticides as well as providing an important scaffold for the preparation of several important alkaloids.[4, 9] Furthermore, literature shows naphthyridines as good DNA intercalators thereby showing potential against HIV/AIDS, malaria and tuberculosis.

The first naphthyridine ring system was prepared[1] in 1893 which opened the doors to the synthesis of the 1, 5-naphthyridine[3], 1, 8-naphthyridine[5], 1, 6- naphthyridine[6] 1, 7-naphthyridine[7] and 2, 7- naphthyridine[8]. Also, an efficient three-component one-pot synthesis of several benzo[b] [1, 8] naphthyridines derivatives was prepared by using acidic bismuth salts. Although many other reaction schemes are available for the synthesis of naphthyridines, the development of new synthetic approaches remains an active research area and warrants greater interest especially in light of the biological potency of naphthyridines in the fight against HIV/AIDS. Hence the objectives of this study are to:

- Synthesize quinoline derivatives from simple, readily available and cost effective starting compounds
- Synthesise naphthyridines from the quinoline scaffolds
- Purify and characterise all synthesised compounds by relevant spectroscopic techniques
- Compare the conventional and microwave energy sources

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Chapter Two: Literature Review

2.1 History of Organic Chemistry

Organic chemistry is undoubtedly one of the most important branches of chemistry since both living and non-living matter is invariably built up from organic compounds. In this field of chemistry, the physical and/or chemical properties of carbon-containing compounds, which are either known or novel, are studied. In the quest for knowledge and biological research, organic chemists, biochemists and other academics are developing new strategies to reach their goals.

Prior to 1828 it was postulated that organic compounds could be produced only by living organisms thereby giving rise to the “vital force” theory which existed for several centuries. However, in 1828 Friedrich Wöhler, by a serendipitous reaction, synthesized an organic compound from an inorganic compound in a test tube; urea, a constituent of urine, was synthesised from ammonium cyanate. This synthesis is a landmark achievement in the history of science since it disproved and undermined the “vital force”theory.

Another great discovery was made in 1856 by William Henry Perkin: Whilst he was trying to manufacture quinine, by serendipity, he manufactured the organic dye called Perkin's mauve. The industrial application of this product generated a huge amount of money thereby stimulating greater interest in organic chemistry.[1]

Prior to World War I, organic chemistry research in universities and industries was limited to a few schools and very few companies. Hence the industrial production of organic chemicals was inadequate. However, during World War I, there arose a huge demand for large quantities of foods, meat, oils, coke, iron, steel, nonferrous metals, ships, trucks, guns, tanks, airplanes, gasoline, kerosene, lubricating oils, war gases, phenol, toluene, glycerol and nitric acid, protective agents, dyes and drugs. This demand resulted in universities becoming more active in research. From about 1922, organic chemical industries became more serious about production of commodities and real research laboratories with better facilities and resources for high powered research were established.

Due to the great demand by society for new medicinal drugs, cosmetics, foods, dyes and other allied commodities, research in synthetic organic chemistry has grown rapidly resulting in the formation of several sub-disciplines such as photo chemical, sono-chemical and microwave organic synthesis.

2.2 Heterocyclic Chemistry

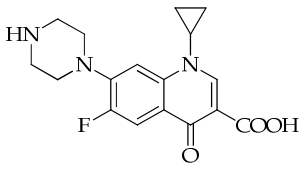
Heterocyclic compounds are those which have a cyclic structure with two or more different kinds of atoms embedded in the ring. The number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds are known and this number is increasing very rapidly. Literature on the subject is correspondingly plenty; nearly six million compounds have been recorded in *Chemical Abstracts* and approximately half of those are heterocyclic.

Heterocyclic compounds are very widely distributed in nature and are essential to life as they play a vital role in the metabolism of all living cells. There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example, antibiotics such as penicillin and cephalosporin, alkaloids such as vinblastine, ellipticine, morphine and reserpine, and cardiac glycosides such as those of digitalis. However, the large majority are synthetic heterocycles which have found widespread use, for example, as anti-cancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers, and as pesticides, insecticides and weed-killers.

There are also a large number of synthetic heterocyclic compounds with other important practical applications such as dyes, copolymers, solvents, photographic sensitizers and developers, anti-oxidants and vulcanization accelerators, and many are valuable intermediates in synthesis.

Ciprofloxacin **1** and norfloxacin **2** are examples of currently available fluoroquinolone antibacterials that are used extensively in both community clinics and hospitals.

Since the discovery[2] that Nalidixic acid [1-ethyl-3-carboxy-7-methyl [1,8] naphthyridin-4-one] **3** is a powerful antibacterial agent, numerous publications describing its derivatives,[3] detection[4], physiological and chemical properties have been documented. This new drug has high efficacy against gram negative bacteria[5, 6] found in chronic urinary tract infections.



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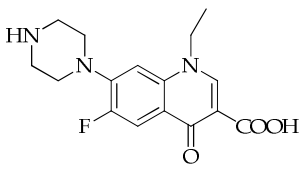

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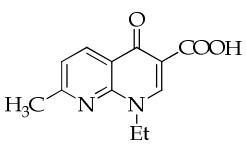

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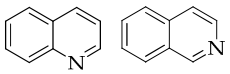
2.2.1 Quinolines as Anti- Malaria Drugs



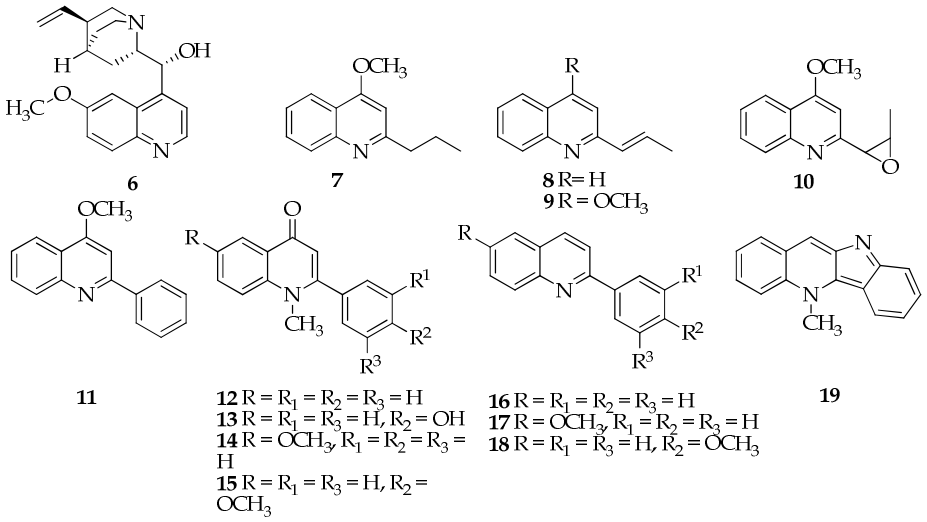
4 **5**

Quinoline derivatives represent a major class of heterocycles and numerous methods of synthesis have been known since the late 1800s. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties.

Malaria is endemic throughout much of the tropics and sub-tropics placing at risk approximately 40 % of the world's population. More than 100 million clinical cases of the disease are thought to occur annually and ½ -2 million die from the disease; it is one of the most lethal human parasitic infections. The most important reason for this alarming situation is the rapid spread of malaria parasites that are resistant to anti-malarial drugs, especially chloroquine, which is by far the most frequently used.
Hence there is a renewed research thrust to develop a new generation of anti-malarial drugs of improved efficacy.

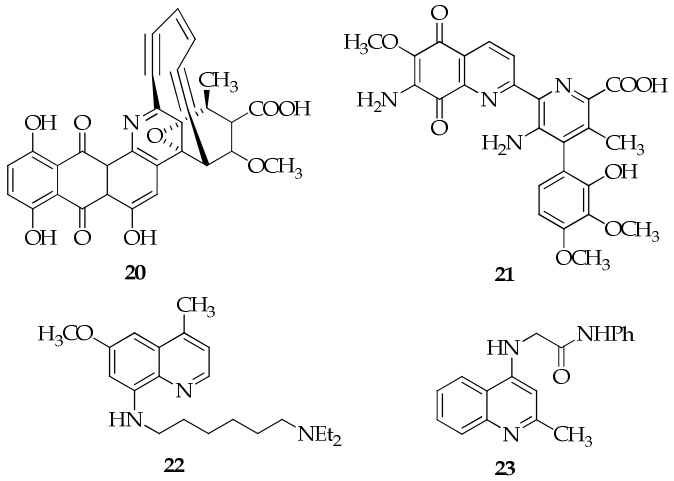
The quinolines are historically among the most important anti-malarial drugs ever used. Prior to 1820, a crude bark concoction of the Cinchona tree was used for the treatment of malaria. In 1820 quinine **6** was isolated as the active ingredient and provided new hope for the eradication of malaria. However its relatively low efficacy and tolerability became evident. Quinine still plays an important role in the treatment of multi-resistant malaria.[7] This molecule has also played a historical role in organic chemistry as a target for structural determination and total synthesis,[8] and recently both stereoselective[9] and enantioseletcive[10] total synthesis.

Chimanine alkaloids, simple quinoline **7-18**, isolated from the bark of *Galipia longiflora* trees of the Rutaceae family[11-13] are effective against the parasites *Leishmania*, which are the agents of leishmaniasis, a protozoan disease of the tropical areas in South America, particularly in the Amazonium forest.

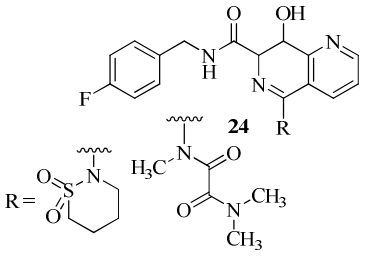


Cryptolepine **19** is an indoloquinoline alkaloid found in the West African climbing shrub *Cryptolepis sanguinolenta*. A crude concoction of the roots of this species is used in traditional medicine for the treatment of malaria as well as for a number of other diseases.[14]

Dynemicin A **20** and Streptonigrin **21**, anti-tumor antibiotics, are synthesised via quinoline derivatives.[15,16] The 8-(diethylaminohexylamino)-6-methoxy-4-methylquinoline **22**, is highly effective against the protozoan parasite *Trypnosoma cruzy*, which is the agent of Chagas' disease[17] and the 2-(2-methylquinolin-4-ylamino)-*N*-phenylacetanilide **23** is more active than the standard anti-leishmanial drug sodium antimony gluconate.[18]



2.2.2 Quinolines and Naphthyridines as HIV Integrase Inhibitors



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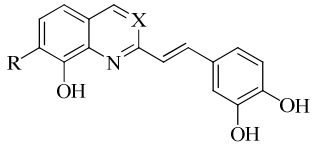


25a) X = CH, R = COOH
25b) X = N, R = H

Acquired immunodeficiency syndrome (AIDS) is one of the greatest challenges to humankind. AIDS and HIV infection represent global health hazards, complex scientific puzzles, obvious targets for drug discovery and vaccination, and both have enormous social, economic and ethical ramifications. First reported in 1981 in a small number of patients, AIDS has now become a major epidemic with more than 38 million people infected worldwide, including approximately 1 million in the United States, 580,000 in Western Europe and more than 25 million in Sub-Saharan Africa (www.unaids.org). Since AIDS was first clinically identified, scientific and therapeutic progress has been extraordinary. It took less than 6 years to identify the pathogenic virus, HIV, that caused AIDS and develop sensitive tests to detect infected people during the latency period and to introduce the first rationally designed effective therapy azidothymidine (AZT). However, AIDS still remains out of control, especially in developing countries where societal factors are a major hurdle to combating the epidemic.[19]

HIV-1 integrase (IN) catalyzes two distinct reactions: the terminal cleavage at each 3' end of the proviral DNA removing a pair of bases and the strand transfer which results in the joining of each 3' end to 5'-phosphates in the target DNA. Such integration is essential for the production of progeny viruses, and therefore therapeutic agents that can inhibit this process should be effective anti-HIV agents. HIV IN has also been recognized as a safe target against HIV because there are no similar enzymes involved in human cellular function. Recently, several aryl 1,3-diketo acids that can inhibit strand transfer reaction of HIV-1 IN have been identified as potent anti-HIV agent. The 1,3-diketo acid moiety is postulated to be essential for the inhibitory activity of HIV-1 IN strand transfer since these groups are believed to interact with catalytically important Mg^{2+} in the active site of HIV-1 integration step. Accordingly, variations of structural features of aryl-1,3-diketo acids have been made leading to 8-hydroxy-1,6-naphthyridine carboxamides, which mimic the metal cation interaction of the 1,3-diketo acid pharmacophore. French scientists from CNRS identified styrylquinoline carboxylic acid as a potent HIV-1 IN inhibitor that can block 3'-processing as well as strand

transfer step of HIV-1 IN. For styrylquinoline compounds, the hydroxyl group at C-8 as well as carboxyl group at C-7 of quinoline ring were important for inhibitory activity against HIV-1 integrase. On the other hand, the free catechol moiety was required in styrylquinazoline compound for the inhibitory activity against 3'-processing step of HIV-1 IN.[20]

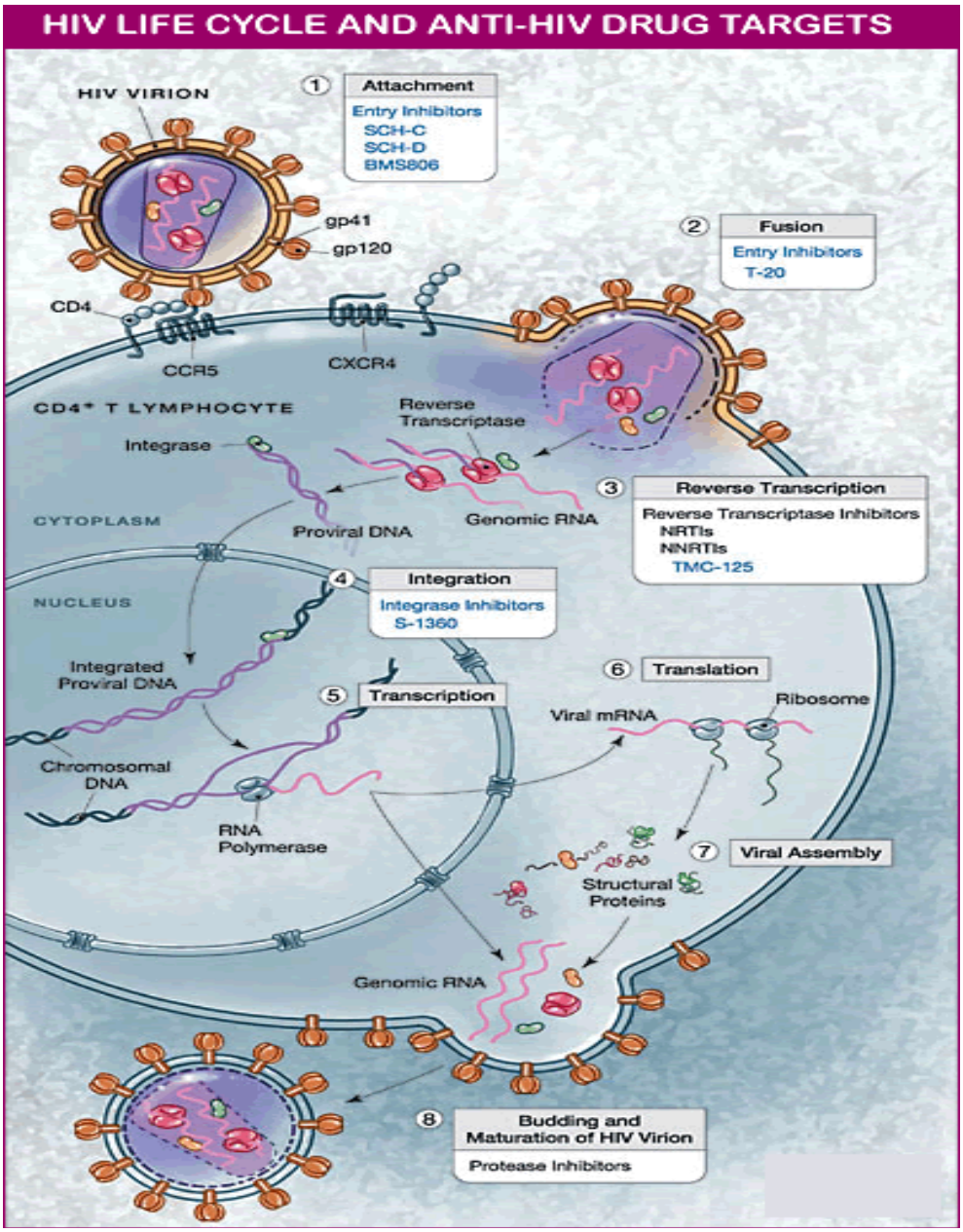
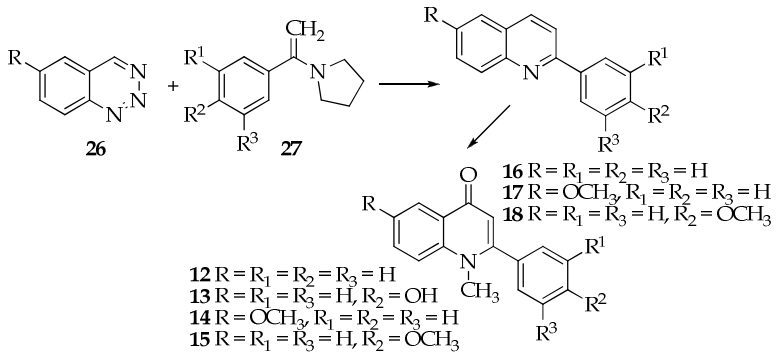


Figure 1: A Schematic Diagram Showing the HIV Life Cycle and Anti- HIV Aids Drug Targets

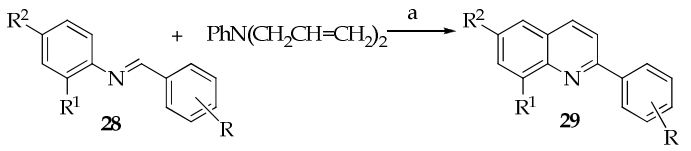
The hybridization of biologically active compounds has been proposed as a promising strategy in the development of new leads for medicinal application. The biological activities of several new hybrids have been found to exceed those of the parent compounds. In this regard, we designed a new structure of compounds by combining structures of 8-hydroxy-1,6-naphthyridine carboxamide and styrylquinoline carboxylic acid to form a styrylquinoline carboxamides.[20]

2.2.3 Synthesis of 2-arylquinoline and 2-aryl-4-quinolone alkaloids

Junko Koyama *et al.*[21]synthesized 2-arylquinoline and 2-aryl-4-quinolone alkaloids *via* Diels–Alder Reaction of 1, 2, 3-benzotriazine **26** with enamines **27**. This is one of the known synthetic methods in the limited publications for these types of alkaloids.



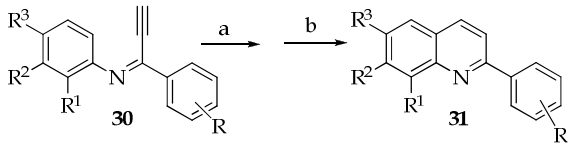
Recently Jones *et al.*[22] discovered a cobalt-catalyzed conversion of *N*-aryaldimines **28** to afford different 2-hetarylquinolines **29**.



R = 4-CH_3, 2-CH_3, 2-OCH_3, H; R^1 = H, Bu, CH_3; R^2 = H, Me_2N, PhNH, Cy, *t*-Bu, H.

a) 10 mol% $Co_2(CO)_8$, 100-105°C.

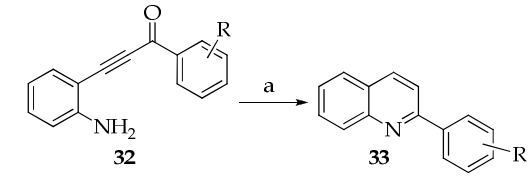
Akiyama and Co-workers[23] described a novel quinoline synthesis that proceeds via catalytically tungsten vinylidene complexes $W(CO)_5$(THF). Alkynyl imines **30** underwent [4+2] electrocyclization in the presence of 20 mol% catalyst to give 2-arylquinolines **31** in good yields.



R = H, 4-CH_3, 3-CH_3, 4-Cl; R^1 = H, CH_3; R^2 = H, CH_3; R^3 = H, CH_3, OCH_3.

a) 20 mol% $W(CO)_5$/ THF; b) 3equiv. NMO, CH_2Cl_2.

The palladium-catalyzed transfer hydrogenation/heterocyclization (3 equiv. of $HCOONH_4$, 10 mol% Pd/C in MeOH) of β-(ortho-aminophenyl)-α, β-ynones **32** yielded the corresponding arylquinolines.[24]



32 **33**

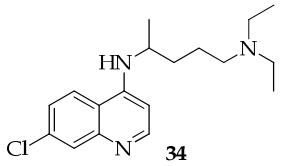
R = 4-OCH_3, 4-$CH_3(O)C$, 4-Cl, 4-CH_3OOC, 4-F, 3-CH_3

a) $HCOONH_4$/Pd/C, MeOH/70°C

2.2.4 Naphthyridines as Anti-Malaria Drugs

Quinine, chloroquine and some of other chinchona alkaloids, discussed earlier, are currently used as anti-malarial drugs. These and other drugs presently available for the treatment of malaria suffer from two serious deficiencies. First, no single agent is suitable for all purposes. Secondly, drug resistant strains of the parasite have evolved hence encouraging further developments in drug design which must lead toagents which possess pharmacologic and chemotherapeutic properties which aresuperior to those presently available.

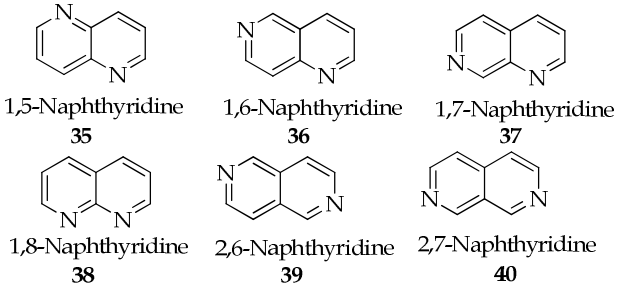
The phenanthrene alkaloids[25], which are called naphthyridines, and indoloquinoline alkaloid[26] drugs are now prescribed since they show high potency, minimal side effects and long duration of activity.



34

2.2.4.1 Synthesis of Naphthyridine Alkaloids

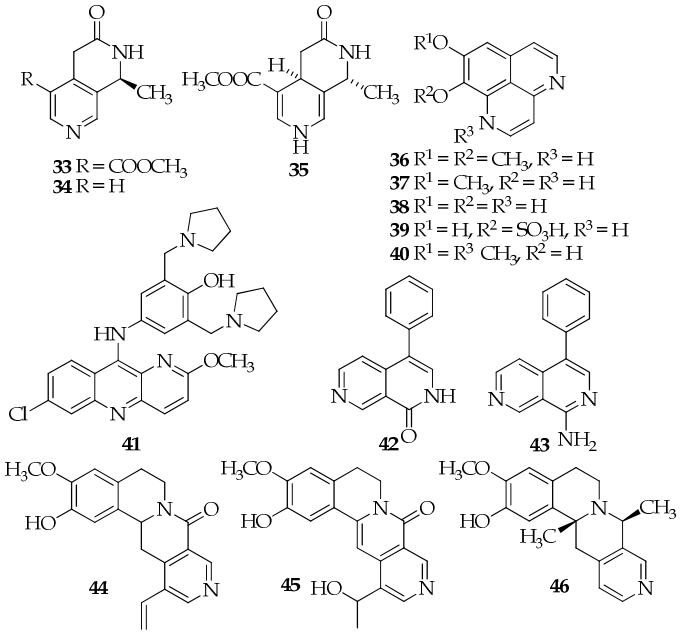
Most quinoline alkaloids are isolated from the plants of the *Rutaceae* family but naphthyridine alkaloids are isolated from different types of species like jasminine from *Jasminum gracile* (*Oleaceae* family),[27] lophocladines A and B from *Lophocladia* (*Rhodomelaceae* family)[28] perloline and perlolidine from tall fescue (*Festuca arundinacea* Schreb.) and ryegrass (*Lolium perenne* L.)[29] and aaptamines from *Aaptos aaptos*.[30]



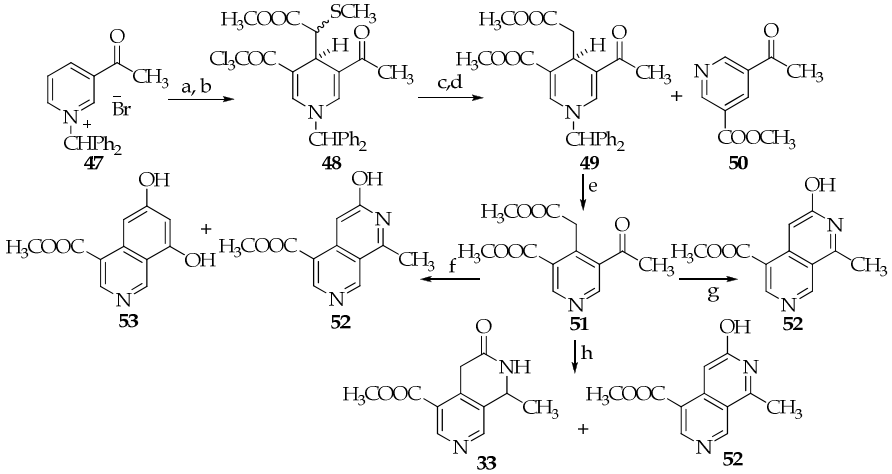
1,5-Naphthyridine **35** 1,6-Naphthyridine **36** 1,7-Naphthyridine **37**

1,8-Naphthyridine **38** 2,6-Naphthyridine **39** 2,7-Naphthyridine **40**

Among the nitrogen heterocycles, naphthyridines and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. Funtionalized naphthyridines have found applications as pharmaceuticals, fungicides, bactericides, herbicides and insecticides as well as useful synthetic blocks in the preparation of several alkaloids.[31,32] Many syntheses of naphthyridines are known, but due to their importance, the development of new synthetic approaches remains an active research area.

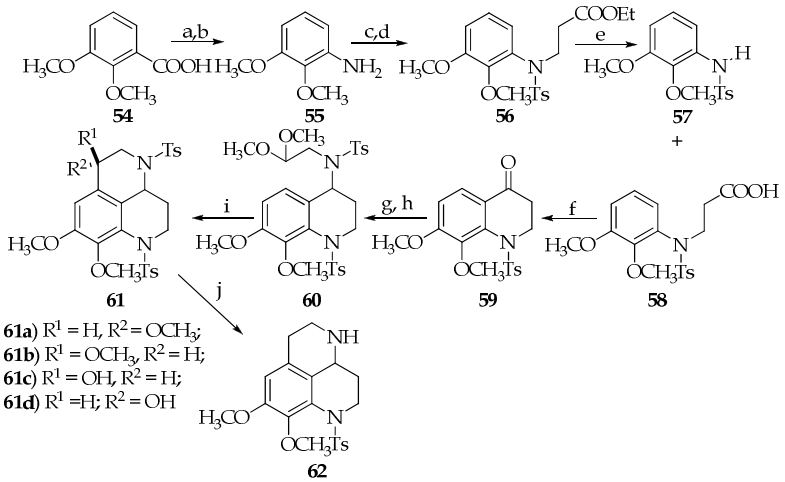


The total synthesis of (±)-jasminine **33**, a member of a small group of naphthyridine alkaloids, has been achieved by M. L. Bennasar *et al.*[33] The synthetic route takes advantage of the reactivity of dihydropyridine intermediates **49** for the preparation of trisubstituted pyridine **51**, which gives access to the alkaloid by a reductive amination-lactamization tandem reaction.



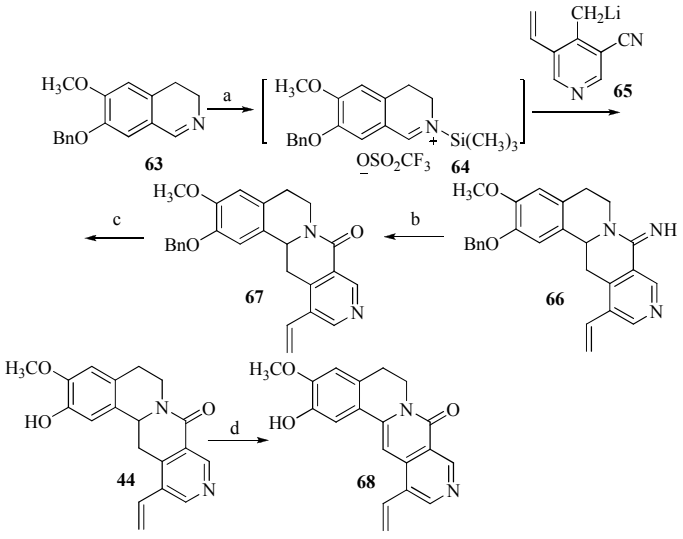
a) $MeSCH_2CO_2Me$, LDA, THF, -78°C, 30 min, then -40°C, 2 h; b) $(Cl_3CCO)_2O$, triethylamine, rt, 12 h; c) MeONa, MeOH, rt, 1min.; d) Ph_3SnH, AIBN, benzene, reflux, 2 h; e) $Mn(OAc)_3 \cdot 2H_2O$, 1:1TFA–AcOH, 45°C, 1h, then phenol, 45°C, 2 h; f) $MeAl(Cl)NH_2$, C_6H_6, rt, 5 h; (g) ammonium formate, 150°C, 10 min.; h) NH_4Cl, Et_3N, $Ti(i\text{-}PrO)_4$, rt, overnight, then $NaBH_4$, rt, 2 h

A new strategy for the synthesis of benzo[d,e][1,6]naphthyridine derivative 2,3,3a,4,5,6-hexahydroaaptamine **62** was given by T. S. Kaufman and his Co-workers,[34] which involves the construction of the isoquinoline ring after elaboration of the quinoline moiety.



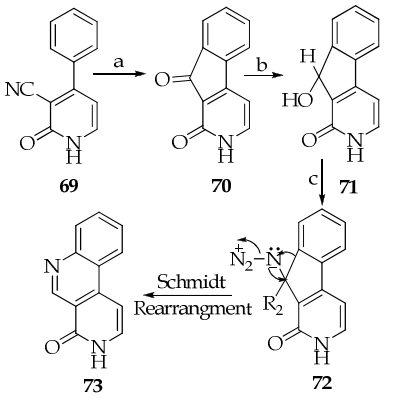
a) $(PhO)_2P(O)N_3$, EtOH, Et_3N, THF, 65°C, 2 h; b) KOH, EtOH, reflux, overnight; c) $H_2C{=}CHCO_2Et$, AcOH (cat.), reflux, 24 h; d) TsCl, iPr_2NEt, $CHCl_3$, reflux,14 h; e) (1) 10% LiOH, EtOH–H_2O, reflux 24 h; (2) HCl,pH¼; f) PPA, 90°C, overnight, PPE, PhMe, 55°C, 2 h; g) (1) $H_2NCH_2CH(OMe)_2$, AcOH, $MgSO_4$, 4 Å MS, EtOH, overnight; (2) $NaCNBH_3$, reflux, 24 h; h) TsCl, iPr_2NEt, $CHCl_3$, reflux, 14 h; i) $SnCl_4$, CH_2Cl_2, 78°C, 1.5 h, 60°C, overnight; j) (1) Na, NH_3, 33°C; (2) NH_4Cl

D. B. Maclean *et al.*[35] reported the total synthesis of alangium alkaloids, alangimaridine **45** and anagimarine **68** in 1987. They activated 3,4-dihydroisoquinolines toward nucleophilic attack by reaction with trimethylsilyltrifluoromethanesulfonate.



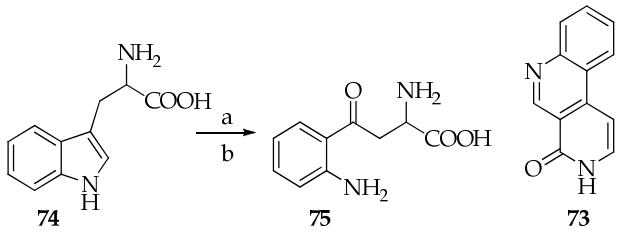
a) TMSOTf; b) 20% KOH, dioxane; c) HCl, MeOH; d) I_2

A total synthesis of the diazaphenanthrene alkaloid perlolidine **73** is reported[36] by J.C.Powers *et al*, using 3-cyano-4-phenylpyridone **69** as an intermediate. The intermediate was then converted to 2-aza-1-keto-fluorenone by a polyphosporic acid cyclization. Perlolidine **73** was prepared from **72** by a Schmidt rearrangement.



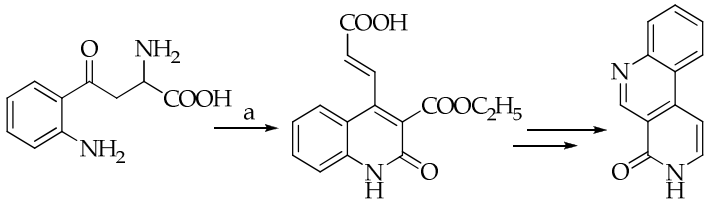
a) PPA; b) $NaBH_4$; c) HN_3, $H_2SO_4/CHCl_3$;

The biosynthesis of perlolidine **73** was achieved from tryptophan **74** which was oxidized to *N*-formylkynurenine, by the action of an enzyme tryptophan pyralase. The further *N*-deformylation was done with formylkynurenineformylase, the intermediate kynurenine **75** was formed. Introduction of a three-carbon fragment, probably as malonyl CoA as in the fatty acid biosynthesis would yield perlolidine **73**.[36]



a) Tryptophan pyralose; b) Formylkynurenineformidase; c) Malonyl CoA

The base catalysed condensation of diethylmalonate with kynurenine **75** was investigated. Under the influence of sodium ethoxide the reaction produced the 2-quinolone acid **76**[36] which contains most of the structural features of the perlolidine **73** skeleton.

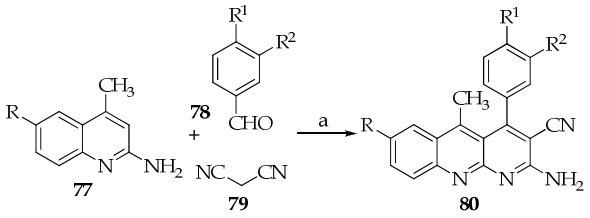


a) diethylmalonate, EtONa

The first derivative of a naphthyridine ring system was prepared in 1893 by Reissert[37]. No unsubstituted naphthyridine was known until 1926, when 1, 5-naphthyridine[38] and 1, 8-naphthyridine[39] was prepared. The 1, 6- naphthyridine [40] 1, 7- naphthyridine [41] and the 2, 7-

naphthyridine [42] were prepared in 1958 by Ikekawa. Albert[43] reported the synthesis of 1, 6- and 1, 7-naphthyridine in 1960, unaware of Ikekawa's earlier work. Two papers[44, 45] have reported independent syntheses of the isomer 2, 6-naphthyridine.

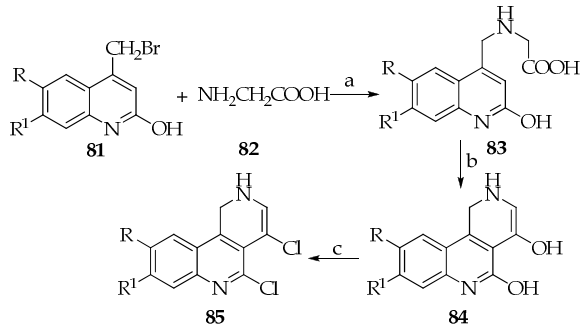
A novel and efficient three-component one-pot synthesis of benzo[b][1,8]naphthyridines **80** by 2-amino-4-methylquinoline **77**, aromatic aldehydes **78**, and malononitrile **79** was done by T. R. R. Naik *et al.*[46] The reaction was catalyzed by an acidic bismuth (III) chloride, functionalized bismuth (III) chloride, at room temperature to give various benzo[b][1,8]naphthyridines **80** in high yields.



R = H, CH_3, OCH_3, Cl; R^1 = H, CH_3; R^2 = H, Ch_3, OCH_3, Cl

a) $BiCl3$, 4-5 h

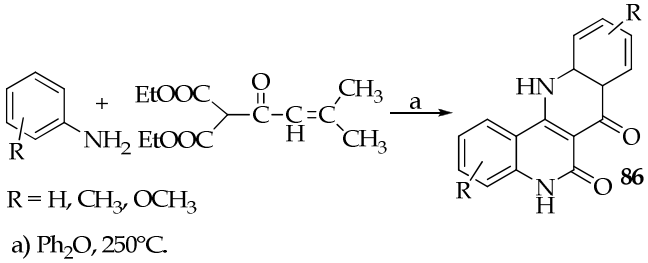
Reaction of 4-bromomethylquinoline derivatives **81** with glycine **82** gave corresponding quinolylmethylglycine derivatives **83**. Cyclization was carried by using either polyphosphoric acid or concentrated sulphuric acid to obtain the compound **84**.[47]



R = H, OCH_3, CH_3; R^1 = H, Cl.

a) 5N NaOH; b) PPA or conc. H_2SO_4; c) $POCl_3$

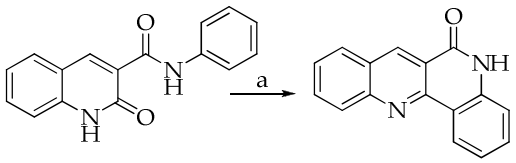
Rajendra Prasad *et al.*[48] prepared dibenzo[*b*,*h*][1,6]naphthyridine-5,6-dione **86** from diethyl-2-(3'-methyl-1-oxo-but-2'-enyl)malonate and aniline, which resulted by dimerization.



R = H, CH_3, OCH_3

a) Ph_2O, 250°C.

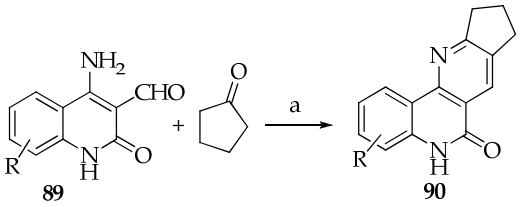
Rajendran *et al.*[49] synthesized dibenzo [*b, h*] [1, 6] naphthyridin-6-(5*H*)-ones **88** by treating various 2-oxoquinoline-3-carboxanilides **87** with polyphosphoric acid.



87 **88**

a) PPA

Rajendran *et al.*[50] have reported the benzo[*h*]cyclopenta[*b*] [1, 6] naphthyridines **90** from 4-amino-3-formylquinolin-2-one **89**.

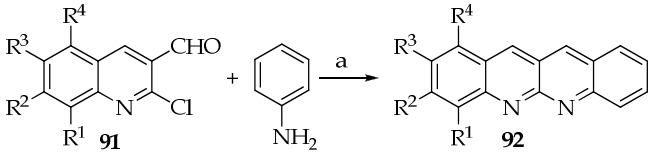


89 **90**

R = H, Me, OMe

a) AcOH / H_2SO_4

Recently Rajendran *et al.*[51] prepared the dibenzo [*b, g*] [1, 8] naphthyridines **92** by a one step procedure.

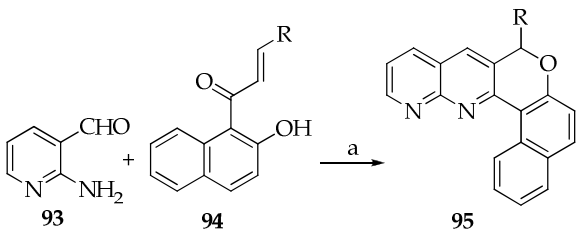


91 **92**

R^1 = H, CH_3, OCH_3; R^2 = H, CH_3, OCH_3; R^3 = H, CH_3, OCH_3; R^4 = H, CH_3, OCH_3

a) DMF 75°C

An extensive amount of work has been carried out by Sreenivasalu *et al,*[52] on the naphthyridine system. The fused naphthyridine of the type **95** was synthesized as shown below.



93 **94** **95**

a) AcOH / Con. H_2SO_4

2.3 Microwave Assisted Synthesis

Microwave dielectric heating uses the ability of some liquids and solids to transform electromagnetic energy into heat and thereby drive chemical reactions. This *in situ* mode of energy conversion has many attractions for chemists, [53, 54] because its magnitude depends on the properties of the molecules. This allows some control of the material's properties and may lead to reaction selectivity. There are a variety of methods for carrying out microwave-assisted organic reactions using domestic or commercial ovens; this is basically known as microwave-induced organic reaction enhancement (MORE) chemistry.[55] Microwave heating has not been restricted to organic chemistry as various aspects of inorganic chemistry and polymer chemistry have also been investigated. However, usually the same chemistry (conventional heating) has been observed when the organic reactions involved were carried out. The difference lies in the choice of reaction conditions. Reactions can be conducted in either an open reaction vessel, equipped with a condenser, or sealed test tube. Bose[55] reported that the microwave irradiation method is more cost effective since only simple glassware is needed and environmentally friendly because minimum solvent is needed for a reaction.

Solid state reactions are generally of three types.56

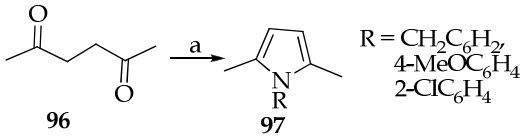
- Reactions between neat reactants
- Reactions between supported reagents on solid mineral supports in "dry media" by impregnation of compounds on silica, alumina or clays
- Phase transfer catalysis (PTC) conditions in the absence of organic solvents.

Microwave irradiation is a clean, efficient, and economical technology; safety is largely increased, work up is considerably simplified, cost is reduced, increased amounts of reactants can be used in some equipment and the reactivities and sometimes selectivities are enhanced without dilution. Due to these advantages there is an increasing interest in the use of environmentally-benign reagents and procedures. The absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive for synthesis.

2.3.1 Five-Membered Heterocyclic Rings

2.3.1.1 Pyrroles

The classical Paal-Knorr cyclization of 1, 4-diketones to give pyrroles is dramatically speeded up by microwave irradiation and high yields of products are obtained.[57]

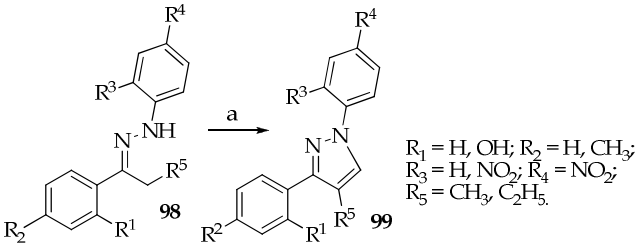


a) RNH_2, MW, 100-200 W, 0.5-2.0 min., solvent-free

Microwave: 2 min,
Conventional: Lewis acid activation, 12 h

2.3.1.2 Pyrazoles

Another recent application of microwaves in cyclization is the preparation of pyrazoles from hydrazones using the Vilsmeier cyclization method by treatment with $POCl_3$ and DMF.[58]

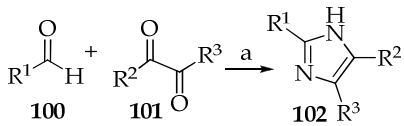


Microwave: 35-50 sec., 45-78%
Conventional: 4-5 h, 41-76%

a) $POCl_3$, MWI, 210 W. 30-50 sec., DMF

2.3.1.3 Imidazoles

An important classical preparation of imidazoles is from an α-diketone, an aldehyde and ammonia. Here again, excellent yields can be obtained in reaction times of a few minutes.[59]



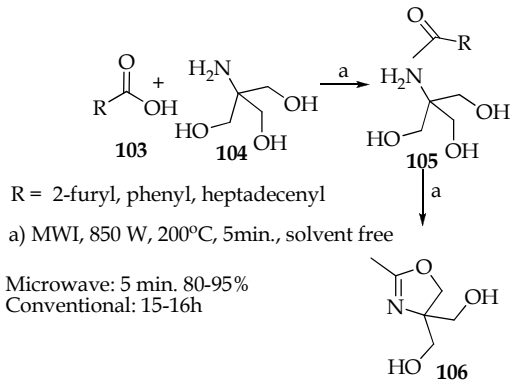
$R_1 = C_6H_5$, 4-ClC_6H_4, 2-thiophenyl, etc;
$R_2 = R_3 = C_6H_5$, 4-MeC_6H_4

a) Al_2O_3, NH_4OAc, MWI, 130 W, 10min., solvent free

Microwave: 10 min. 75-85%
Conventional: 4h, AcOH reflux

2.3.1.4 Oxazolines

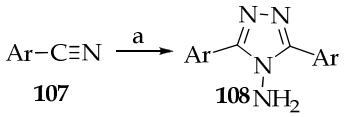
The preparation of an oxazoline **106** shows that partially saturated five membered rings can also be prepared advantageously using microwaves.[60]



103 **104** **105** **106**

2.3.1.5 Triazoles and Tetrazoles

The 1, 2, 4-triazoles were synthesized by treatment of aryl cyanides with either hydrazinehydrochloride or hydrazinehydrate under microwave condition.[61]



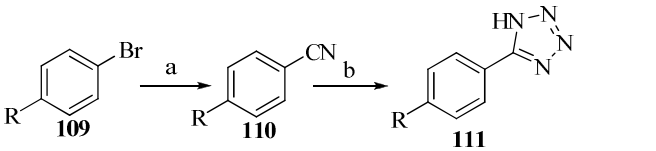
107 **108**

Ar = C_6H_5, 4-CH_3-C_6H_4, 4-$NH_2C_6H_4$, 4-OHC_6H_4, 4-$CH_3OC_6H_4$I

a) NH_2NH_2.2HCl, $NH_2NH_2.H_2O$. MWI, 60 W, 130°C, 4-10min., ethylene glycol

Microwave:10 min.130°C 63-96%
Conventional:60 min., 130°C 45-60%

The tetrazole was also obtained by reaction of an arylbromide in the presence of a small quantity of palladium as catalyst under microwave conditions.[62]



109 **110** **111**

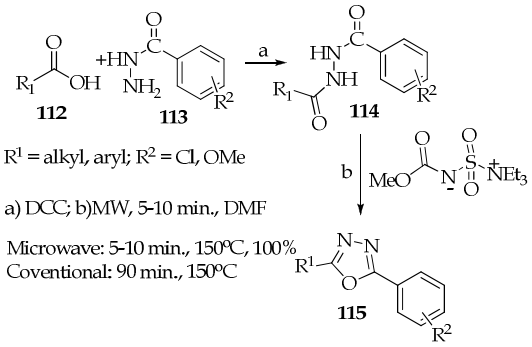
Microwave: 10-25 min. 36-96%
Conventional: 3-96 h, 35-97%

Microwave: 2 min. 78-93%
Conventional: 2-16 h, 71-97%

a) $Zn(CN)_2$, $Pd(PPh_3)_4$, MWI, 60 W, 175°C, 2min., DMF;
b)NaN_3, NH_4Cl, MWI, 20 W, 220°C, 10-25min., DMF

2.3.1.6 Oxadiazoles

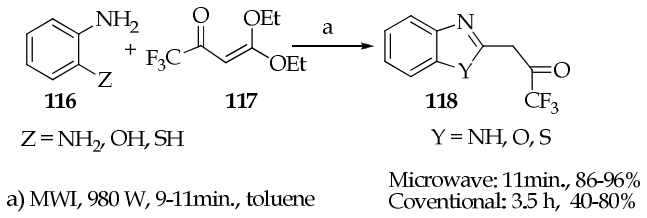
The dehydration of unsymmetrical diacylhydrazines (themselves prepared by a conventional Mitsunobu reaction) using Burgess's reagent to give 1, 3, 4-oxadiazoles rapidly under microwave irradiation is also reported.[63]



2.3.2 Benzo-Derivatives of Five-Membered Rings

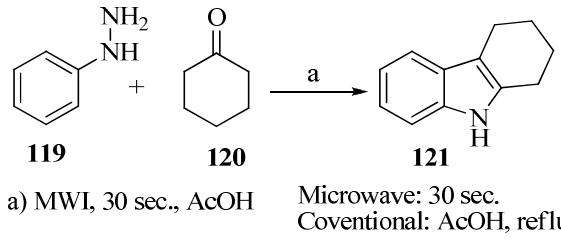
2.3.2.1 Benz-imidazoles, -Oxazoles, and -Thiazoles

Ring closure reactions of appropriate *o*-substituted anilines to give benzimidazoles, benzoxazoles, and benzthiazoles takes place much faster and in significantly high yield under microwave conditions than conventional heating.[64]



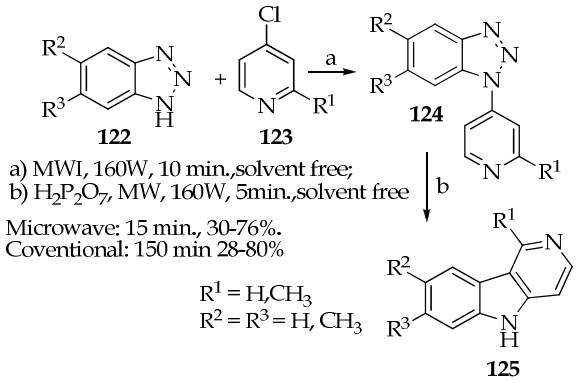
2.3.2.2 Indoles

The classical Fisher-indole synthesis using an arylhydrazine and a ketone, presented below, is speeded up by several 100-fold as documented.[65]



2.3.2.3 γ-Carbolines

The Graebe-Ullmann synthesis which converts 1-arylbenzotriazoles into carbazoles or their heterocyclic analogues is also accelerated under microwave conditions; 1-(4-pyridyl) benzotriazole is converted into a γ-Carboline.[66]

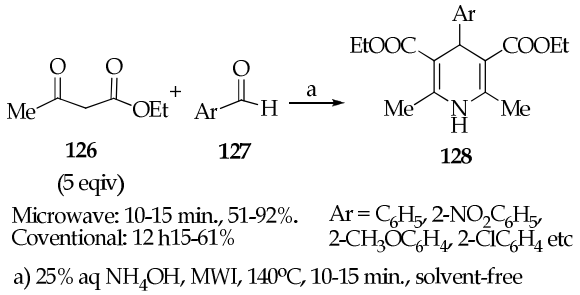


122 123 124 125

2.3.3 Six Membered Rings

2.3.3.1 Dihydropyridines

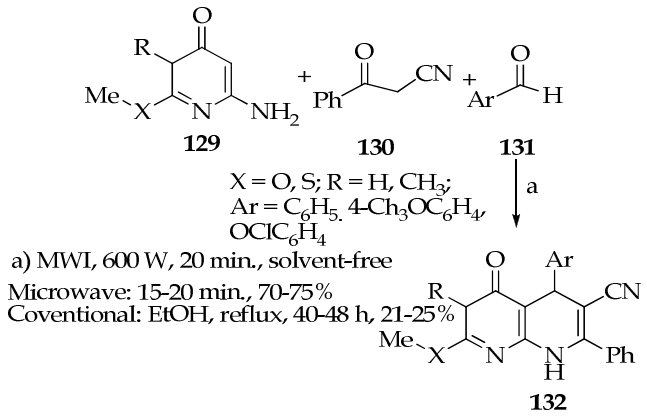
The Hantzsch dihydropyridine synthesis remains one of the most important routes to pyridine ring systems. Under conventional conditions long periods of heating are required and yields are poor to moderate whereas microwave irradiation dramatically reduces the reaction time and also significantly increases the yield.[67]



126 (5 eqiv) 127 128

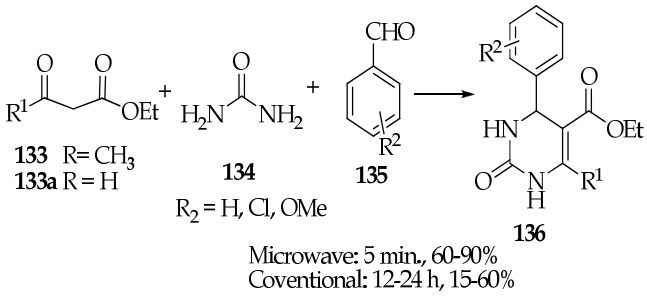
2.3.3.2 Dihydropyridopyrimidinones

Dihydropyridopyrimidinones have been produced by ring annulations of aminopyrimidinones. Once again the reaction time is dramatically reduced and yields are much better with the solvent free microwave conditions.[68]



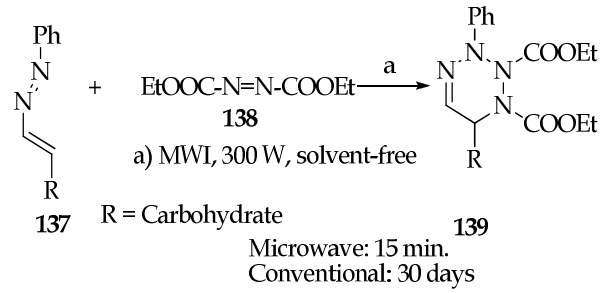
2.3.3.3 Dihydropyrimidines

The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out under optimum microwave reaction conditions.[63]



2.3.3.4 Tetrazines

The Diels-Alder reaction between aza-olefins and aza-dicarboxylic ester to give tetrazines is speeded-up by a factor of 1000 by microwave irradiation.[69]

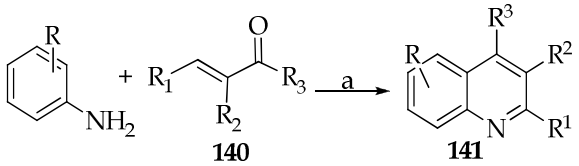


2.3.4 Polycyclic Six-Membered Rings

2.3.4.1 Quinolines

The synthesis of quinolines by the Skraup method has several disadvantages such as low yields of products when carried out by conventional heating methods. Recently, it has been

reported that microwave irradiation reduces the reaction time to a few minutes and allows yields to be isolated.[70]



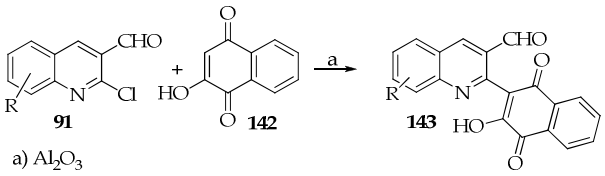
a) $InCl_3/SiO_2$, MWI, 600 W, 5-12 min., solvent-free

R = H, *o*-CH_3, *p*-CH_3, *o*-OMe, *p*-OMe, *m*-OH, *m*-Cl etc.

R^1 = H, CH_3, *n*-C_3H_7; R^2 = H, C_2H_5; R^3 = CH_3, *p*-MeC_6H_4

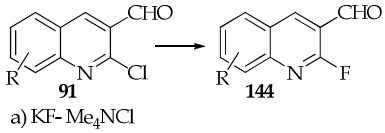
Until now we have concentrated on reactions in which heterocyclic rings are formed. However, microwave irradiation can also be extremely valuable in many other types of reactions such as heterocyclic *C*-alkylations and heterocyclic *N*-alkylations. Some typical reactions are presented below.

_C_-arylation- nucleophilic substitution[71]



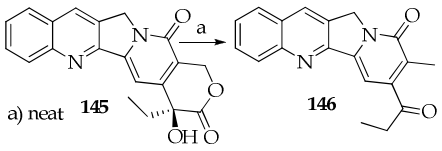
a) Al_2O_3

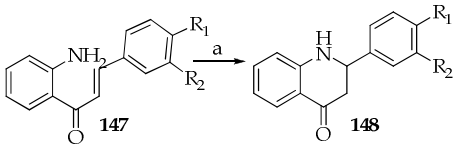
Nucleophilic substitution[72]



a) KF- Me_4NCl

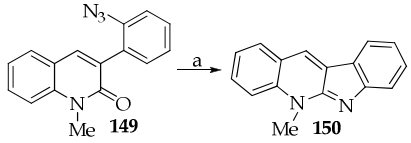
Ring fission through decarboxylation[73] & dehydrogenation[74]





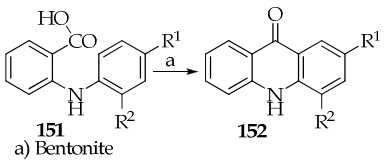
a) K10 clay

Aza Wittg Reaction[75]



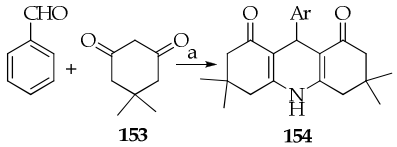
a) $P(CH_3)_3$, $PhNO_2$

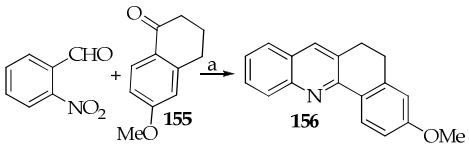
Ring fusion through dehydration[76]



a) Bentonite

Crossed Cannizaro reaction[77, 78]





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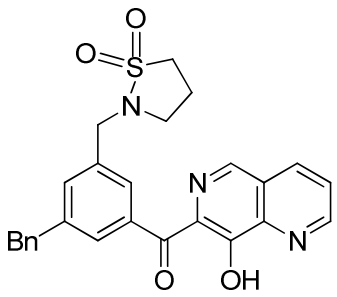
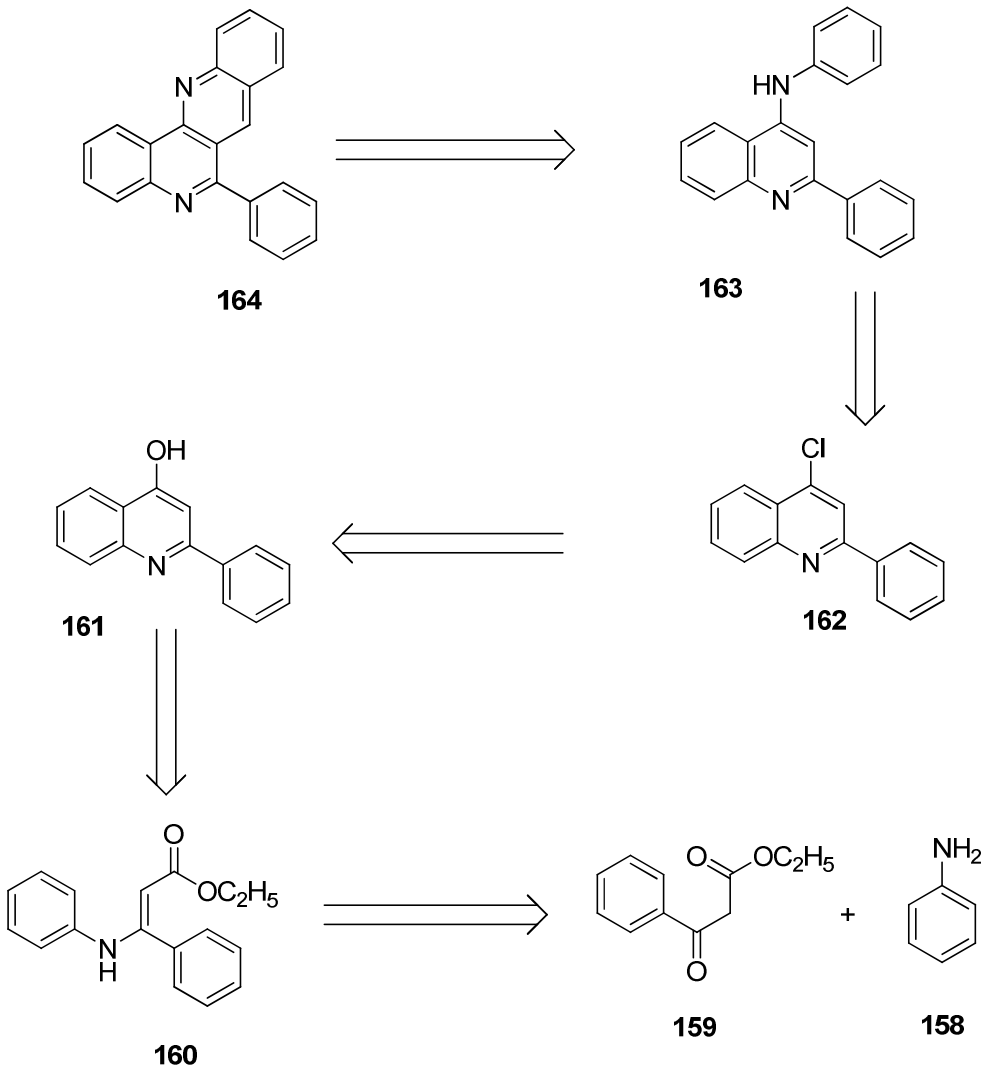
Chapter Three: Results and discussions

Fused heterocycles containing the naphthyridine nucleus are reported to enhance the biological activity of organic compounds. Hence the synthesis of drugs containing the naphthyridine scaffold is increasing rapidly. One typical example is the naphthyridine**157**, presented below, which inhibits the strand transfer of the integration process catalyzed by integrase. This compound inhibits 95 % of the spread of HIV-1 infection in cell-culture at 0.39 μM.



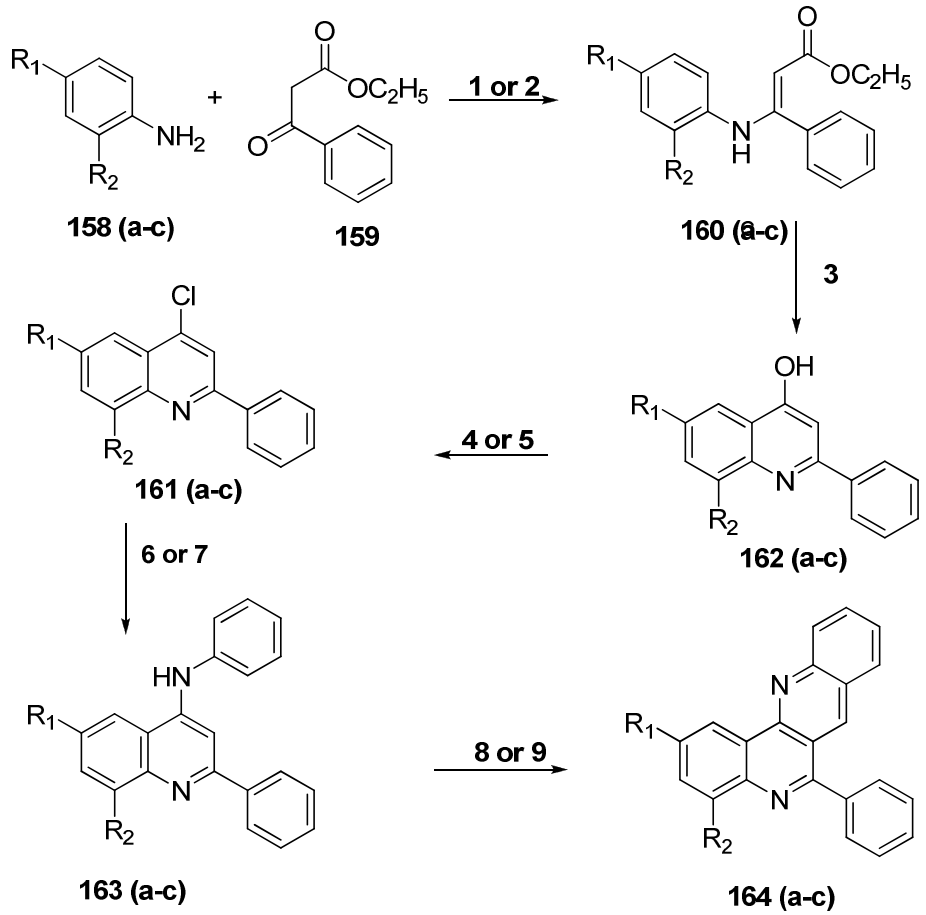
157

Quinoline and its derivatives have been employed as convenient starting materials for the synthesis of various fused pyranoquinolines,[2] pyrimidoquinolines[3] and acridines.[4] Currently, studies in the synthesis of quinolines are being undertaken in our laboratory. We have utilised simple and inexpensive starting compounds to synthesise selected target molecules. Furthermore, the Vilsmeier-Haack reaction has become a standard protocol in our laboratory and we planned to use this expertise to provide a facile and general route to some new simple derivatives of naphthyridines. Our target compound **164** and the retro-synthesis pathway is presented in scheme 1:



Scheme 1: Retro-synthesis of 6-phenyldibenzo [b, h] [1, 6] naphthyridine

Our plan was to use aniline **158** and ethyl benzoylacetate **159** to prepare a quinoline scaffold; our preference of this system arises from the fact that quinoline constitutes the parent ring feature of 1, 6-naphthyridines, which are cited in various applications of medicine[1] and also available as natural source. Once this objective is met, we wanted to complete the reaction by preparing a 1, 6-naphtharidine derivative via a cyclization step. The successful completion of this reaction scheme would then provide us with a new template to prepare other simple 1, 6-naphthyridine derivatives. Our plan was to prepare **164a,** a phenyl substituted 1, 6-naphthyridine, followed by some simple derivatives **164b** and **164c**. The route we used to prepare the novel naphthyrine **164 (a-c)** is presented below in **scheme 2.**



Scheme 2: Summarises outline of the synthesis of three Naphthyridines derivatives 164 (a-c)

Key:

(a) R_1= H ; R_2=H

(b) R_1 = H ; R_2 = CH_3

(c) R_1 = CH_3 ; R_2 =H

Reaction Conditions:

1) conc. HCl, EtOH, 3hrs, 50°C; **2**) conc. HCl, hand stirring 10 minute;

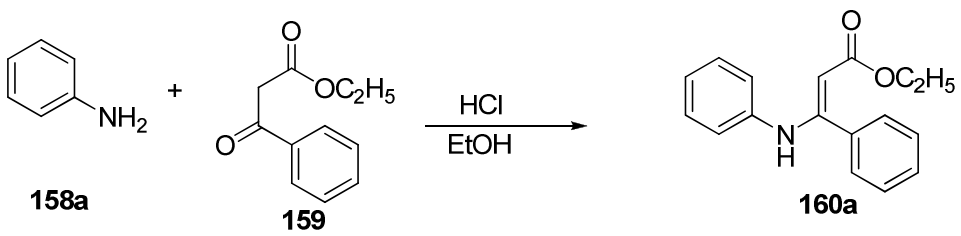
3) 180°C, MWI, 250 watts, 5 minute; **4**) $POCl_3$, MWI, 75 °C, 150 watts, 2 minute;

5) $POCl_3$, 100 ^oC, 5 hours; **6**) aniline, t-BuOH, MWI, 180 °C, 180 watts, 20 minute;

7) aniline, t-BuOH, 80 °C, 3 hours; **8)** DMF, $POCl_3$, MWI, 75 °C, 120 watts, 20 minute;

9) DMF, $POCl_3$, 100 ^oC, 21 hours.

3.1 Synthesis and characterisation of ethyl-3-aniline-3-phenyl acrylate 160a.



Scheme 3: Synthesis of ethyl-3-aniline-3-phenyl acrylate

We commenced our synthesis by using aniline **158a** and ethyl benzoylacetate **159** in ethanol. According to literature the first step of the reaction to produce **160a** can be conducted by using acetic acid as a catalyst for a reaction of 24 hours. It was also reported that N-acylation also occurred when the amount of acetic acid was increased. Therefore, we decided not to use acetic acid and opted for a strong acid, viz. concentrated hydrochloric acid. Aniline was distilled before use to remove any trace impurities. We monitored the progress of the reaction by thin layer chromatograph (TLC) and found that only 3 hours were needed for the complete conversion of the starting material to the product **160a** in high yield (95 %).The mechanism for the condensation reaction is presented below:

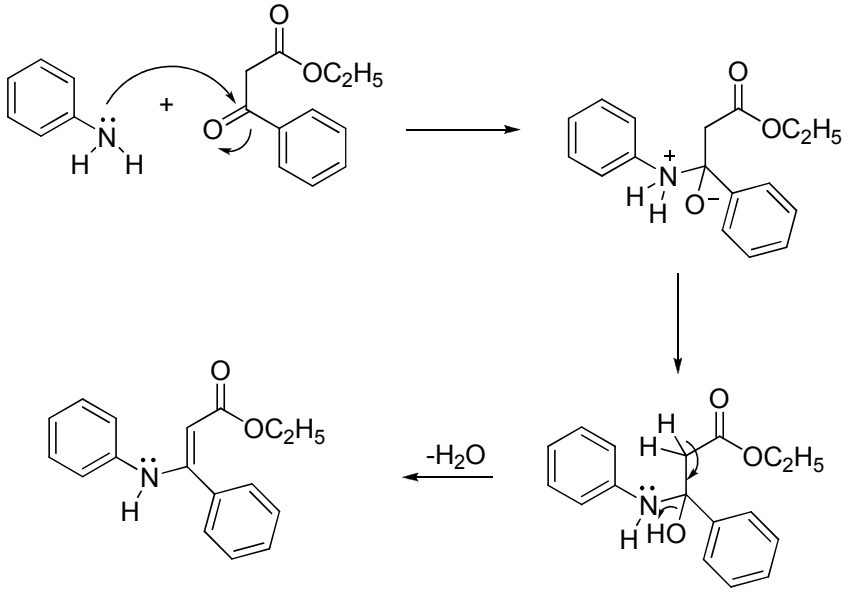
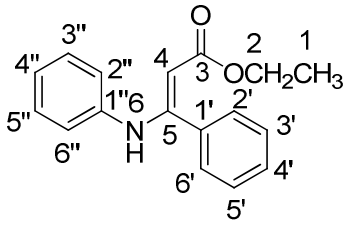
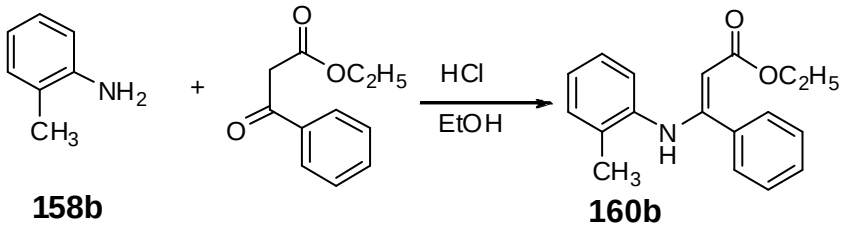


Figure 2: Proposed mechanism for the formation of 160a



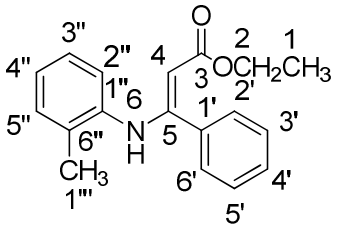
The ^{1}H NMR spectrum (400 MHz; $CDCl_3$) of the pure crystals indicates a proton singlet at δ 4.99 ppm for the –CH-CO proton; a singlet at δ 10.29 ppm for the N-H, the presence of the triplet at δ 1.33 ppm corresponding to methyl in an ester group; this multiplicity is due to the coupling of these protons with the neighbouring methylene protons. On the other hand, the deshielded -CH_2- attached to oxygen appeared as a quartet at δ 4.21 ppm. The other ^{1}H NMR signals are presented in **Figure 4** (**Appendix 1**, **page 64**). The ^{13}C NMR spectrum of compound **160a,** presented in **Figure 5** (**Appendix 2**, **page 65**), is characterised by the presence of a group of resonance in the aromatic region and ester carbonyl at δ 170.1 ppm, therefore confirming **160a**. Furthermore, the IR spectra indicates the C=O, C-O and NH at 1645, 1175 and 3250 cm^{-1} respectively. The IR spectrum of compound **160a** is presented in **Figure 6 (Appendix 3, page 66**). The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 1 (page 34)** and**Table 2 (page 35)** respectively.

3.2 Synthesis and characterisation of ethyl-3-phenyl-3-(0-tolylamino) acrylate 160b



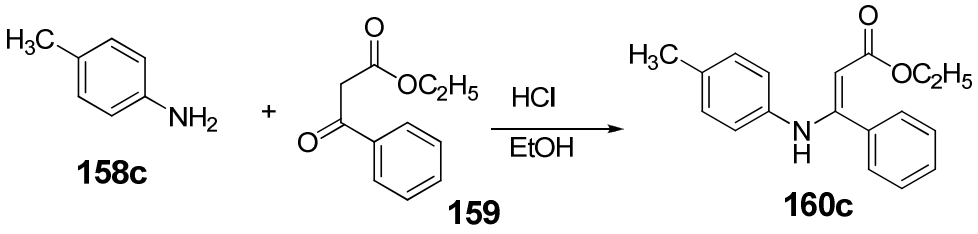
Scheme 4: Synthesis of ethyl-3-phenyl-3-(0-tolylamino) acrylate 160b

Ethyl-3-phenyl-3-(o-tolylamino) acrylate **160b** was synthesized by condensing ortho-toluidine **158b** with ethyl benzoylacetate in ethanol.



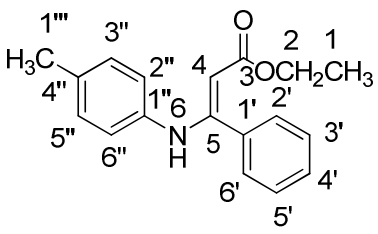
The ^{1}H NMR spectrum of **160b,** presented in **Figure 7** (**Appendix 4**, **page 67),** shows two sets of methyl signals, i.e. a triplet at δ 1.33 ppm (OCH_2CH_3) and a singlet at δ 2.41 ppm (Ar-CH_3) for the methyl group attached to position C-6″ of the molecule. The presence of a methylene proton signal at δ 4.20 ppm, a proton singlet at δ 5.02 ppm for the -CH-CO and the disappearance of H-6″ proton, present in **160a** at δ 6.89ppm confirmed the structure. The ^{13}C NMR spectrum of **160b**, presented in **Figure 8 (Appendix 5, page 68)** shows two sets of methyl signal at δ 14.5 ppm (OCH_2CH_3), δ 18.2 ppm (Ar-CH_3) and the carbonyl occurs at δ170.3 ppm (-C=O) . The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in T**able 1 (page 34)** and **Table 2 (page 35)** respectively.

3.3 Synthesis and characterisation of ethyl-3-phenyl-3-(p-tolylamino) acrylate 160c



Scheme 4: Synthesis of ethyl-3-phenyl-3-(p-tolylamino) acrylate

Ethyl-3-phenyl-3-(p-tolylamino) acrylate **160c** was synthesised by a condensation reaction of p-toluidine and ethyl benzoylacetate in ethanol.



The ^{1}H NMR spectrum of **160c,** presented in **Figure 9 (Appendix 6, page 69)** shows a three proton singlet at δ 2.19 ppm corresponding to the Ar-CH_3 which is upfieled compared to the Ar-CH_3 group of **160b**. The ^{13}C NMR spectrum, **Figure 10 (Appendix 7, page 70)** is characterised by the (Ar-CH_3) signal at δ 20.6 ppm, the presence of methylated carbon atom (C-4″) at δ 132.6 ppm and the carbonyl signal occurs at δ 170.2 (-C=O) . The triplet at δ 1.33 ppm is assigned to the (OCH_2CH_3) methyl group. The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in T**able 1 (page 34)** and **Table 2 (page 35)** respectively.

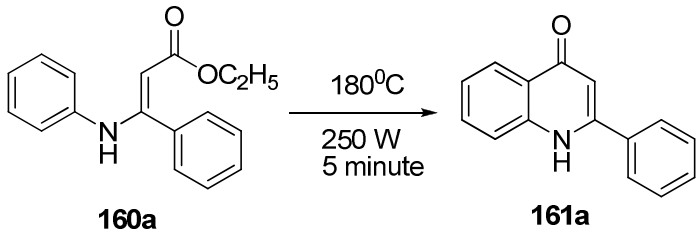
Table 1: ^{1}H NMR chemical shifts of 160a, 160b and 160c

Protons	**160a**	**160b**	**160c**
CH_3	-	2.41, s	2.19, s
NH	10.29, s	10.1, s	10.2, s
H-1	1.29, t, J=7.06	1.33, t, J=7.08	1.33, t, J=7.08
H-2	4.23, q, J=7.08	4.20, q, J=7.12	4.20, q, J=7.12
H-4	4.99, s	5.02, s	4.94, s
H-2′& H-6′	7.29, m	7.31, m	7.33, m
H-3′& H-5′	7.35, m	7.30, m	7.31, m
H-4′	7.27, m	7.29, m	7.30, m
H-2″	6.89, m	6.31, m	7.24, m
H-3″	7.25, m	7.11, m	6.87, m
H-4″	6.87, m	6.75, m	-
H-5″	7.25, m	7.22, m	6.87, m
H-6″	6.89, m	-	7.24, m

Table 2: ^{13}C NMR chemical shift of 160a, 160b and 160c

Carbon	160a	160b	160c
NH	-	-	-
CH_3	-	18.2	20.6
C1	14.5	14.5	14.5
C2	76.7	61.5	59.2
C3	170.1	170.3	170.2
C4	91.2	90.7	90.3
C5	159.0	159.8	159.4
C1′	140.4	136.2	136.1
C2′& 6′	128.4	128.3	128.3
C3′&5′	128.6	128.7	128.5
C4′	128.2	128.0	128.2
C1″	136.0	138.9	136.1
C2″	122.2	123.4	115.2
C3″	129.4	127.0	129.7
C4″	123.0	123.8	132.6
C5″	129.4	130.6	129.7
C6″	122.2	125.8	115.2

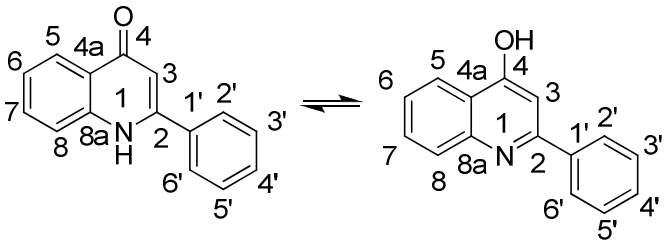
3.4 Synthesis and characterisation of 2-phenylquinoline-4(1H)-one 161a



160a **161a**

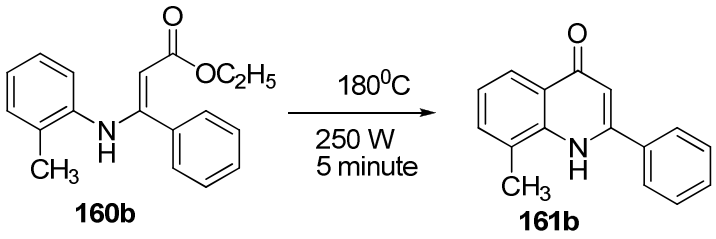
Scheme 5: Synthesis of 2-phenylquinoline-4(1H)-one

When **160a** was subjected to super heating temperatures for 3 minutes under microwave conditions, a yellow solid was formed. It was purified by washing with chloroform and petroleum ether and identified as **161a**. The tautomeric forms are presented below:



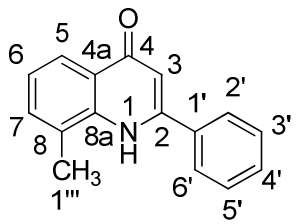
The ^{1}H NMR spectrum of **161a,** presented in **Figure 11** (**Appendix 8**, **page 71**), shows the disappearance of the ester group, present in compound **160a**. The N-H proton appears at δ 11.7 ppm. A broad singlet at δ 6.34 ppm is assigned to the olefinic proton (H-3). Aromatic proton signals in the region δ 7.32-7.78 ppm are present. The signal corresponding to H-5 proton is shifted downfield to δ 7.78 ppm due to the deshielding effect of the carbonyl group in the peri-position. The presence of group of resonances in the aromatic region and the carbonyl group signal at δ 176.9 ppm (C = O) in the ^{13}C NMR spectrum, presented in **Figure 12** (**Appendix 9**, **page 72**) further confirmed the structure of **161a**. The ^{1}H NMR and ^{13}C NMR chemical shifts of **161a** are presented in **Table 3 (page 38)** and **Table 4 (page 38)** respectively.

3.5 Synthesis and characterisation of 8-methyl-2-phenylquinoline-4(1H)-one 161b



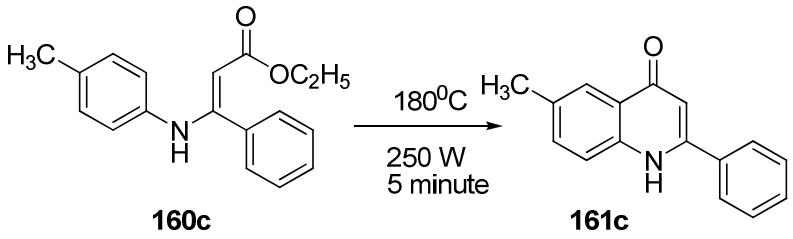
Scheme 6: Synthesis of 8-methyl-2-phenylquinoline-4(1H)-one

Compound **161b** was prepared by thermal cyclisation of compound **160b** under microwave conditions. The crude yellow solid formed was then purified by washing with a solvent mixture of chloroform and petroleum ether.



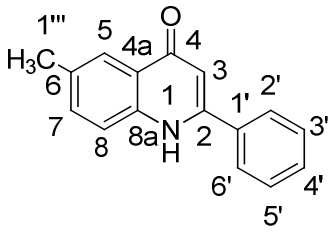
The ^{1}H NMR spectrum of **161b,** presented in **Figure 14** (**Appendix 11**, **page 74**), shows the disappearance of the ester group which was present in **160b.** The N-H proton appears at δ 10.5 ppm. The signal corresponding to H-5 the proton is shifted down fieled to δ 7.58 ppm due to the deshielding effect of a carbonyl group in the peri-position. The three proton singlet at δ 2.08 ppm indicates the methyl group bonded to C-8. The ^{13}C NMR spectrum of **161b**, presented in **Figure 15** (**Appendix 12**, **page 75**), is characterised by the methyl signal at δ 18.0 ppm, carbonyl carbon signal at δ 206.4 ppm and a group of resonances in the aromatic region. The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 3 (page 38)** and **Table 4 (page 38)** respectively.

3.6 Synthesis and characterasation of 6-methyl-2-phenylquinoline-4(1H)-one 161c



Scheme 7: Synthesis of 6-methyl-2-phenylquinoline-4(1H)-one

Compound **161c** was prepared by thermal cyclization of **160c** under microwave conditions. The crude yellow solid formed was then purified by washing with a solvent mixture of chloroform and petroleum ether.



The ^{1}H NMR spectrum of **161c,** presented in **Figure 16** (**Appendix 13**, **page 76**), shows the disappearance of an ester group which was present in **160c**. The N-H proton appears at δ 9.29 ppm. The presence of a three proton singlet at δ 3.30 ppm (Ar-CH_3) indicates the methyl group bonded to C-6. The ^{13}C NMR spectrum of **161c,** presented in **Figure 17 (Appendix 14, page 77),** is characterised by the methyl signal at δ 41.5 ppm (Ar-CH_3) and the ketone group

at 158.5 ppm (C=O). The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 3 (page 38)** and **Table 4 (page 38)** respectively.

Table 3: ^{1}H MNR chemical shift of 161a, 161b and 161c

Protons	**161a**	**161b**	**161c**
CH_3	-	2.08, s	3.30, s
NH	11.7, br.s	10.5, br.s	9.29, br.s
H-3	6.34, s	7.28, s	7.64, s
H-5	7.78, d, J=8.3	7.58, d, J=8	8.05, s
H-6	7.32, m	7.30, dt, J=1.4 &7.6	-
H-7	7.56, dt, J=3.8 & 7.2	7.54, m	7.67, dt, J= 3.0 & 8.9
H-8	7.34, m	-	7.21, d, J= 9
H-2′& H-6′	7.69, m	7.91, m	8.15, m
H-3′& H-5′	7.67, m	7.57, m	8.14, m
H-4′	7.35, m	7.56, m	8.13, m

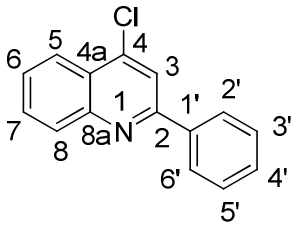
Table 4: ^{13}C NMR chemical shift of 161a, 161b and 161c

Carbons	**161a**	**161b**	**161c**
NH	-	-	-
CH_3	-	18.0	41.5
C-2	149.9	130.0	135.7
C-3	107.3	79.1	106.4
C-4	176.9	206.4	158.5
C-4a	124.6	121.4	122.5
C-5	127.4	126.0	122.5
C-6	123.3	123.6	131.7
C-7	134.2	135.2	132.0
C-8	118.7	122.3	108.7
C-8a	140.5	130.0	133.1
C-1′	134.2	132.4	130.1
C-2′& 6′	128.9	127.7	129.8
C-3′& 5′	130.4	128.7	125.1
C-4′	127.4	126.0	122.5

3.7 Synthesis and characterisation of 4-chloro-2-phenylquinoline162a

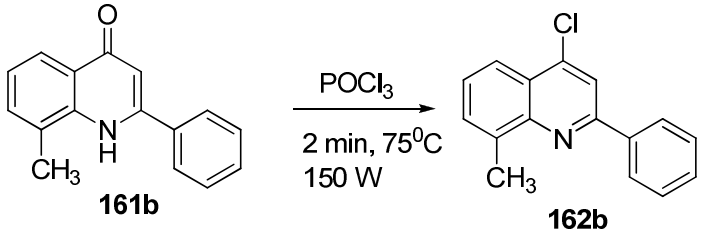
Scheme 8: Chlorination of 2-phenylquinolin-4(1H)-one

The reaction of 2-phenylquinolin-4(1H)-one **161a** with phosphorus oxychloride ($POCl_3$) under microwave conditions afforded **162a**.



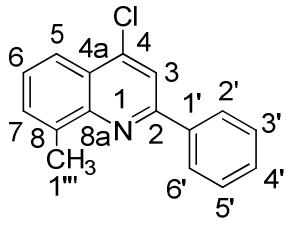
The ^{1}H NMR spectrum of **162a**, presented in **Figure 18** (**Appendix 15, page 78**), is characterised by signals in the aromatic region at δ 7.53 – 8.40 ppm. The N-H signal, which is present in **161a**, is absent. The ^{13}C NMR spectrum of **162a**, presented in **Figure 19** (**Appendix 16**, **page 79**), shows a group of resonance in the aromatic region and also the carbonyl carbon signal present in **161a**, is absent. The chlorinated carbon atom (C-4) at δ 142.4 ppm confirmed the replacement of carbonyl carbon present in **161a**, by chlorine. The Mass spectrum of **162a** presented in **Figure 20 (Appendix 17, page 80),** shows a molecular ion peak at 239 [M^+]. The presence of the Cl group is indicated by the 3:1 ratio of ^{35}Cl: ^{37}Cl at 239 and 241. The loss of Cl shows the fragment at 204. The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 5 (page 41)** and **Table 6 (page 41) respectively**.

3.8 Synthesis and characterisation of 4-chloro-8-methyl-2-phenylquinoline 162b



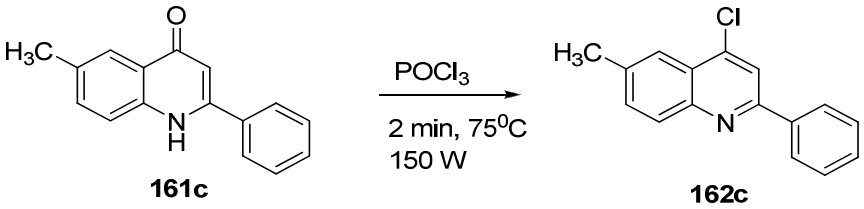
Scheme 9: Synthesis of 4-chloro-8-methyl-2-phenylquinoline

The reaction of compound **161b** with $POCl_3$ under microwave conditions afforded **162b**.



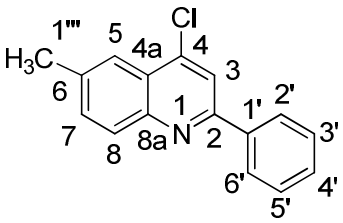
The ^1H NMR spectrum of **162b**, presented in **Figure 22** (**Appendix 19**, **page 82**) is characterised by the three proton singlet at δ 2.88 ppm for the Ar-CH_3 group.The ^{13}C NMR spectrum of **162b**, presented in **Figure 23** (**Appendix 20**, **page 83**), is characterised by methyl signal at δ 18.3 ppm (Ar-CH_3), and the disappearance of carbonyl carbon at δ 206.4 ppm found in **161a.**The ^1H NMR and ^{13}C NMR chemical shifts are presented in **Table 5 (page 41)** and **Table 6 (page 41)** respectively.

3.9 Synthesis and characterisation of 4-chloro-6-methyl-2-phenylquinoline 162c



Scheme 10: Synthesis of 4-chloro-6-methyl-2-phenylquinoline

The reaction of **161c** with $POCl_3$ under microwave conditions afforded **162c**.



The ^1H NMR spectrum of **162c, presented in Figure 24** (**Appendix 21**, **page 84),** is characterised by the three proton singlet at δ 2.57 ppm for the methyl group (Ar-CH_3). The ^{13}C NMR spectrum of **162c**, presented in **Figure25** (**Appendix 22, page 85**), is characterised by the methyl signal at δ 21.8 ppm (Ar-CH_3), and the disappearance of carbonyl carbon which appeared at δ 158.5 ppm in the spectrum of the precursor **161c**. The ^1H NMR and ^{13}C NMR chemical shifts are presented in **Table 5 (page 41)** and **Table 6 (page 41)** respectively.

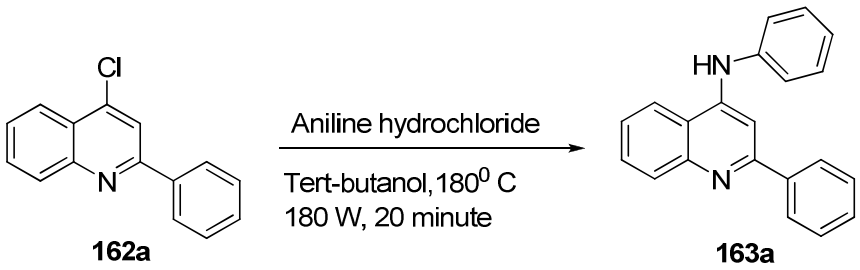
Table 5: ^{1}H NMR chemical shift of 162a, 162b and 162c

Proton	162a	162b	162c
CH_3	-	2.88, s	2.57, s
H-3	7.53, s	7.43, s	7.46, s
H-5	8.30, d, J=6.3	8.22, d, J=5.2	8.11, s
H-6	7.77, t, J=7.6	7.97, t, J=6.9	-
H-7	7.89, t, J=6.0	8.04, d, J=8.2	7.97, d, J=6.9
H-8	8.14, d, J=8.4	-	8.04, d, J=8.6
H-2′&H-6′	8.30, m	8.21, m	8.10, m
H-3′&H-5′	7.55, m	7.54, m	7.60, m
H-4′	7.54, m	7.47, m	7.59, m

Table 6: ^{13}C NMR chemical shift of 162a, 162b and 162c

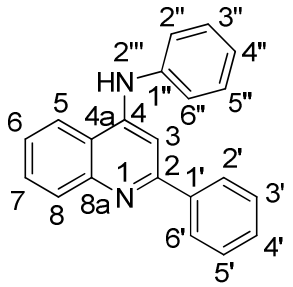
Carbons	162a	162b	162c
-N=	-	-	-
CH_3	-	18.3	21.8
C-2	156.3	148.0	156.4
C-3	123.5	118.4	119.1
C-4	142.4	143.3	142.4
C-4a	123.5	125.2	125.2
C-5	125.3	121.8	122.8
C-6	128.8	126.8	137.4
C-7	131.2	130.6	132.8
C-8	1129.6	138.1	129.8
C-8a	148.2	155.3	147.7
C-1′	137.4	138.8	138.7
C-2′; 6′	127.9	128.8	128.9
C-3′; 5′	129.3	127.4	129.5
C-4′	127.4	129.6	127.4

3.10 Synthesis and characterisationof 4-(N-phenyl)-2-phenyl-4-aminoquinoline 163a



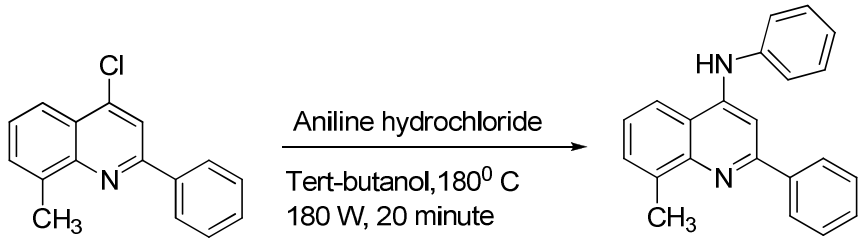
Scheme 11: Synthesis of 4-(N-phenyl)-2-phenyl-4-aminoquinoline

4-chloro-2-phenylquinoline **162a** was aminated with aniline hydrochloride by refluxing in tertiary butanol under microwave conditions. The pale yellow crude solid was recrystalised with a mixture of chloroform and methanol. The pure product was characterised by ^{1}H NMR and ^{13}C NMR to confirm **163a**.



The ^{1}H NMR spectrum of **163a**, presented in **Figure 26** (**Appendix 23, page 86**), is characterised by the presence of a singlet at δ 6.94 ppm (NH), two doublet at δ 7.42 and 7.20 ppm corresponding to H - 2′′ & H - 6′′ and H - 3′′ & H - 5′′ and other signals corresponding to aromatic protons. The ^{13}C NMR spectrum of **163a**, presented in **Figure 27 (Appendix 24, page 87**), is distinguished from **162a** by an increased number of resonances in the aromatic region. The IR spectrum of **163a,** presented in **Figure 28** (**Appendix 25, page 88**), shows the amine absorption at 3035.6cm^{-1}. The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 7 (page 45)** and **Table 8 (page 45)** respectively.

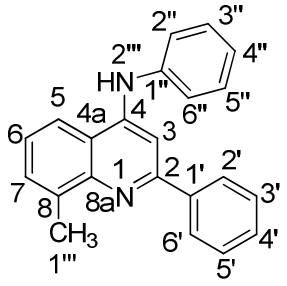
3.11 Synthesis and characterisation of 8-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline 163b



162b **163b**

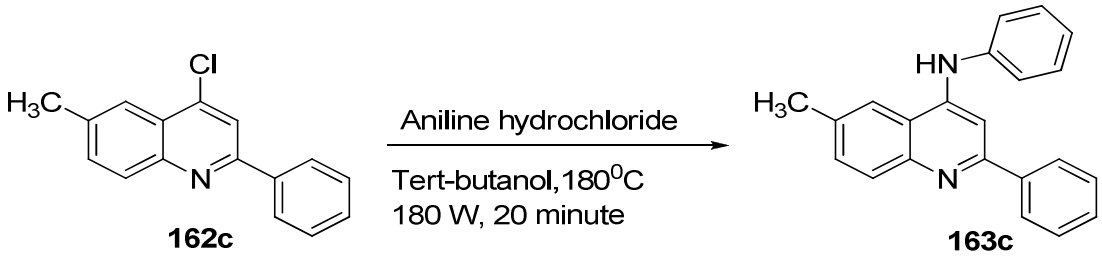
Scheme 12: Synthesis of 8-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline

4-chloro-2-phenylquinoline **162b** was aminated with aniline hydrochloride by refluxing in tertiary butanol under microwave conditions. The pale yellow crude solid was recrystalised with a mixture of chloroform and methanol. The pure product was characterised by ^{1}H NMR and ^{13}C NMR to confirm the compound **163b**.



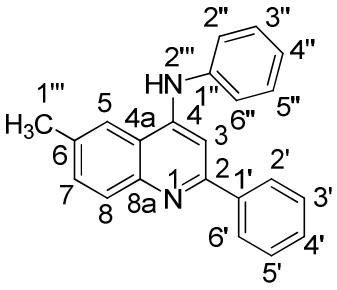
The spectrum of **163b,** presented in **Figure 29** (**Appendix 26, page 89**), is characterized by the presence of singlet at δ 8.22 ppm corresponding to amine group (NH); three proton singlet at δ 2.88 ppm which corresponds to the methyl proton bonded at (C-8) and the aromatic protons appear at δ 7.43-8.21 ppm. The ^{13}C NMR spectrum of **163b,** presented in **Figure 30 (Appendix 27, page 90**), is distinguished from **162b** by an increased number of resonances in the aromatic region and the methyl signal at δ 18.2 ppm (Ar-CH_3). The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 7 (page 45)** and **Table 8 (page 45)** respectively.

3.12 Synthesis and characterisation of 6-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline 163c



Scheme 13: Synthesis of 6-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline

4-chloro-2-phenylquinoline **162c** was aminated with aniline hydrochloride by refluxing in tertiary butanol under microwave conditions. The pale yellow crude solid was recrystalised with a mixture of chloroform and methanol. The pure product was characterised by ^{1}H NMR and ^{13}C NMR to confirm the compound **163c**.



The ^{1}H NMR spectrum of **163c,** presented in **Figure 31** (**Appendix 28, page 91**) is characterised by a three proton singlet at δ 3.20 ppm for a methyl group (Ar-CH_3). The ^{13}C NMR spectrum of **163c,** presented in **Figure 32 (Appendix 29, page 92**), is characterised by a new signal at δ 21.2 ppm for a methyl group (Ar-CH_3). The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 7 (page 45)** and **Table 8 (page 45)** respectively.

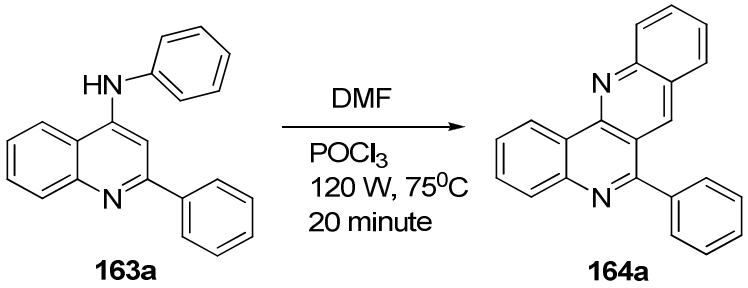
Table 7: ^{1}H NMR chemical shift of 163a, 163b and 163c.

Protons	163a	163b	163c
CH_3	-	2.88, s	3.20, s
NH	11.1, s	8.22, s	8.00, s
H-3	6.94, s	7.24, s	7.02, s
H-5	8.07, d, J=7.6	8.04, d, J=8.3	7.65, s
H-6	7.56, m	7.61, m	-
H-7	7.79, m	7.97, m	7.53, d, J=7.3
H-8	7.89, m	-	7.88, d, J=7.5
H-2′&H-6′	8.33, m	8.21, m	8.39, m
H-3′&H-5′	7.56, m	7.54, m	7.55, m
H-4′	7.45, m	7.47, m	7.45, m
H-2″&H-6″	7.42, m	7.46, m	7.43, m
H-3″&H-5″	7.40, m	7.45, m	7.41, m
H-4″	6.94, m	7.43, m	7.03, m

Table 8: ^{13}C chemical shift of 163a, 163b and 163c

Carbon	163a	163b	163c
-N=	-	-	-
CH_3	-	18.2	121.3
C-2	154.6	155.3	153.9
C-3	98.7	77.3	98.6
C-4	152.9	147.9	152.2
C-4a	166.5	118.4	117.9
C-5	123.5	121.8	120.7
C-6	125.3	125.3	135.5
C-7	131.8	129.7	131.7
C-8	123.4	138.1	137.3
C-8a	138.0	148.0	154.0
C-1′	137.2	138.7	138.0
C-2′& 6′	127.4	127.4	128.3
C-3′& 5′	129.2	128.9	129.2
C-4′	126.9	126.8	127.2
C-1′	139.2	145.9	142.0
C-2″& 6″	117.8	117.8	118.0
C-3″& 5″	129.9	129.6	129.9
C-4″	127.3	121.8	122.3

3.13 Synthesis and characterisation of 6-phenyl-dibenzo [b, h] [1, 6] naphthyridine 164a



Scheme 14: Synthesis of 6-phenyl-dibenzo [b, h] [1, 6] naphthyridine

The Vilsmeier-Haack reaction is a useful reaction to synthesise precursors for medicinally active alkaloids. This reaction employs a basic medium to formulate aromatic and aliphatic compounds and is also used in most of the ring closure reactions to produce considerably high yield procedures. We used this same reaction by conventional (100 ^{o}C; 21hrs) and microwave irradiation (75 ^{o}C; 20min). The mechanism showing the formation of the electrophile, formylation and condensation is represented on the next page:

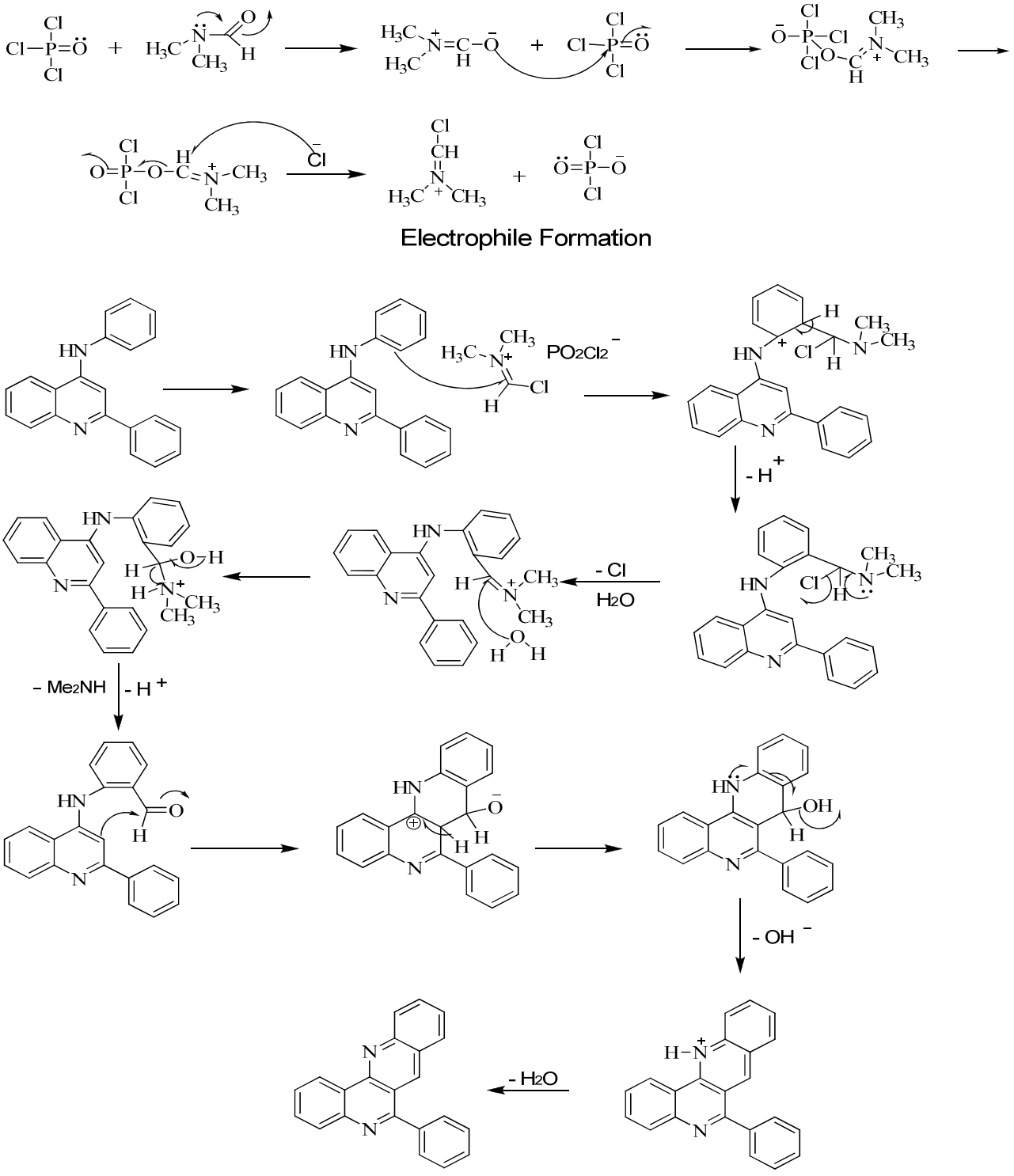
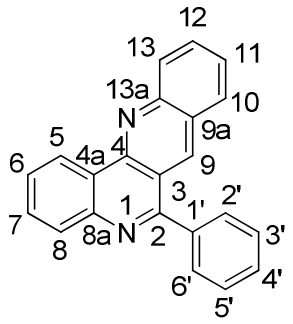
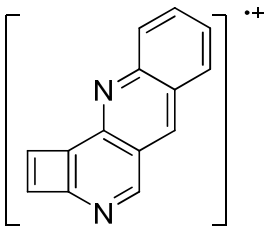


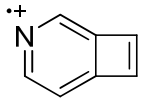
Figure 3: Proposed mechanism for the formation of 164a



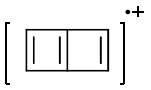
The ^{1}H NMR spectrum of **164a**, presented in **Figure 33** (**Appendix 30, page 93**), shows the disappearance of 3–H signals of **163a** (δ 6.94 ppm) due to ring closure. The aromatic signals at δ 8.20 ppm (H-9), 8.11 ppm (H-10), 7.60 ppm (H-11), 7.77 ppm (H-12) and 7.79 ppm (H-13) are evident. The ^{13}C NMR spectrum, presented in **Figure 34** (**Appendix 31, page 94**), confirms **164a** by an increased number of resonances in the aromatic region and the presence of C-3 signal at δ119.1 ppm which was present at δ 98.7 ppm for **163a**. The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 9 (page 51)** and **Table 10 (page 51)** respectively. The Mass spectrum in **Figure 35 (Appendix 32, page 95)** shows molecular fragmentation ion [$M^{+\cdot}$] as indicated below:



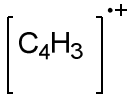
m/z = 204



m/z = 102

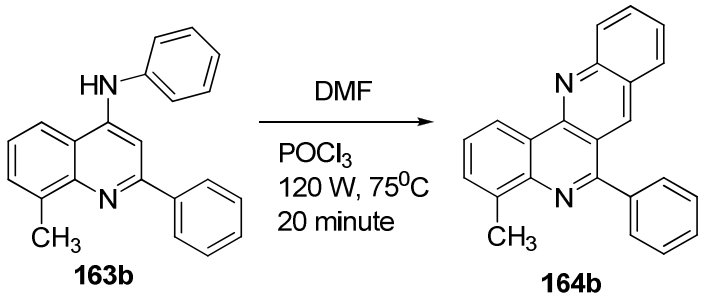


m/z = 75



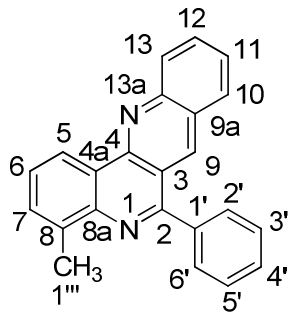
m/z = 51

3.14 Synthesis and characterisation of 4-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine 164b



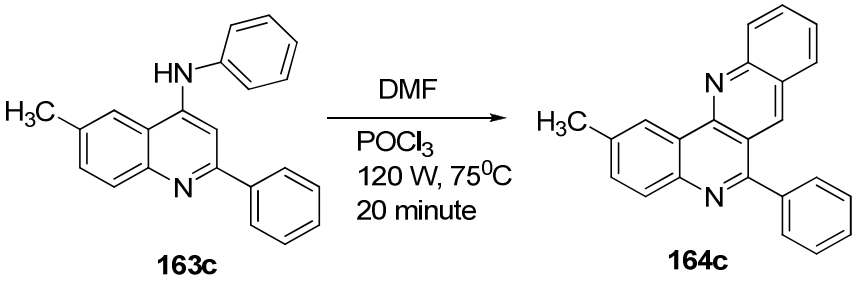
Scheme 15: Synthesis of 4-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine

Since our interest was to synthesize **164b** from **163b** with high yields and less time, dimethyl formamide and $POCl_3$ were used under microwave conditions.



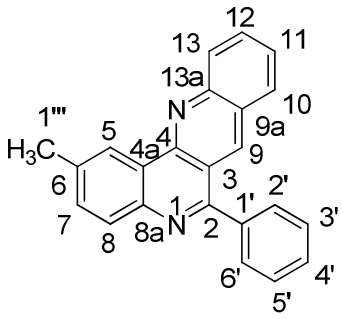
The ^{1}H NMR spectrum of **164b,** presented in **Figure 37** (**Appendix 34, page 97**) reveals a three proton singlet at δ 1.55 ppm (Ar-CH_3) and also the disappearance of H-3 proton signal, present in **163b** at δ 7.24 ppm due to ring closure. The ^{13}C NMR spectrum of **164b**, presented in **Figure 38** (**Appendix 35, page 98**) is characterised by the methyl signal at δ 16.8 ppm (Ar-CH_3). The signal corresponding to C-3 carbon is shifted downfield to δ 118.4 ppm due to the ring closure. The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 9 (page 51)** and **Table 10 (page 51)** respectively. The Mass spectrum in **Figure 39 (Appendix 36, page 99)** shows similar fragmentation pattern as discussed above for **164b** structure elucidation.

3.15 Synthesis and characterisation of 2-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine 164c



Scheme 16: Synthesis of 2-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine

Since our interest was to synthesize **164c** from **163c** with high yields and less time, dimethyl formamide and $POCl_3$ were used under microwave conditions.



The ^{1}H NMR Spectrum of **164c**, presented in **Figure 41** (**Appendix 38, page 101**), reveals a three proton singlet at δ 2.57 ppm (Ar-CH_3) and also the disappearance of H-3 proton signal, present in **163c** at δ 7.02 ppm due to ring closure. The ^{13}C NMR spectrumpresented in **Figure 42** (**Appendix 39, page 102**) is characterised by the methyl signal at δ 21.86 ppm (Ar-CH_3). The signal corresponding to C-3 carbon is shifted downfield to δ 119.1 ppm due to the ring closure.The ^{1}H NMR and ^{13}C NMR chemical shifts are presented in **Table 9 (page 51)** and **Table 10 (page 51)** respectively. The Mass spectrum in **Figure 43 (Appendix 40, page 103)** shows similar fragmentation pattern as discussed above for **164c** structure elucidation.

Table 9: ^{1}H NMR chemical shift of 164a, 164b and 164c.

Proton	164a	164b	164c
CH_3	-	1.55, s	2.57, s
H-5	8.18, d, J=8.5	8.06, d, J=8.4	7.60, s
H-6	7.6, m	7.63, m	-
H-7	7.77, m	7.79, m	7.52, m
H-8	7.79, m	-	7.92, m
H-9	8.20, m	8.22, m	8.11, m
H-10	8.11, m	8.06, m	8.06, m
H-11	7.60, m	7.61, m	7.59, m
H-12	7.77, m	7.79, m	7.60, m
H-13	7.79, m	7.99, m	7.97, m
H2′&H-6′	8.23, m	8.23, m	8.12, m
H-3′&H-5′	7.54, m	7.54, m	7.57, m
H-4′	7.47, m	7.47, m	7.47, m

Table 10: ^{13}C chemical shift 164a, 164b and 164c.

Carbons	164a	164b	164c
-N=	-	-	-
CH_3	-	16.8	21.9
C-2	157.3	155.3	156.4
C-3	119.1	118.4	119.1
C-4	138.6	138.2	137.4
C-4a	123.9	121.8	122.8
C-5	125.3	125.3	125.2
C-6	127.2	126.9	137.5
C-7	130.1	130.6	132.0
C-8	128.9	138.8	128.9
C-8a	149.1	147.9	147.7
C-9	138.6	138.1	138.7
C-9a	130.6	130.6	132.8
C-10	130.0	129.7	132.4
C-11	127.2	127.4	127.1
C-12	130.1	130.6	129.8
C-13	124.0	121.8	122.7
C-13a	143.2	143.3	142.4
C-1′	137.1	138.2	137.0
C-2′& C-6′	127.5	127.4	128.9
C-3′& C-5′	129.8	128.9	129.8
C-4′	127.2	126.8	127.4

3.16 Conclusion

In conclusion, a simple five step reaction scheme has been developed to synthesise three naphthyridine derivatives, i.e. 6-phenyl-dibenzo [b, h] [1, 6] naphthyridine, 4-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine and 2-methyl-6-phenyl-dibenzo [b, h] [1, 6] naphthyridine from easily available chemicals such as aniline, *ortho*-toludine, *para*-toluidine and ethyl benzoylacetate using either conventional reflux, microwave irradiation or both methodologies. It was found that although the yields of products were slightly higher via microwave irradiation, the reaction was many folds faster than conventional reflux methodology. The features of this scheme are mild conditions, high yields, operational simplicity and environmental friendliness and more importantly, may be utilized as a template for the synthesis of complex naphthyridine derivatives.

3.17 References

1. M Sekar and K J R Prasad, *Indian J.Chem*., 38B, 969 (1999).

2. G Timari, T Soos and G.Hajos, *Synlett*, 1067 (1997).

3. D C Sanyi, G Tamari, GHajos, Synth. Commun., 29, 3959 (1999).

4. P M Fresneda, P Molina and S Delgado, *Tetrahedron*, 57, 6197 (2001).

Chapter Four: Experimental

4.1 General

Solvents and commercially available reagents such as aniline, ethyl benzoylacetate, *ortho* and *para* toluidine, phosphoryl oxychloride, hydrochloric acid, aniline hydrochloride, tert-butanol, dimethyl formamide, petroleum ether, ethanol, dichloromethane, ethyl acetate, hexane and methanol were purchased from Lasec S.A, Aldrin, Fluka and Merck. These reagents and solvents were used without further purification.

4.2 Instrumental

Microwave-assisted reactions were conducted using a microwave synthesizer (CEM Discover). Proton and carbon NMR spectra, recorded at 400 MHz were obtained from a Bruker ultra shield spectrometer. Chemical shifts are reported in parts per million (ppm) relative to the peak of tetra methyl silane as internal standard (0.00 ppm). The coupling constants were measured from the spectra and are expressed in Hertz (Hz). The multiplicities are abbreviated as: singlet (s), doublet (d), triplet (t), quartet (q), broad singlet (br.s). Infrared (IR) spectra were recorded on a Perkin Elmer 100 FT-IR spectrometer. Mass spectrometric data was obtained using a Bruker micrOTOF- Q11. Melting points were determined from a Stuart SMP3 melting point apparatus using open-ended capillary tubes. All melting points were uncorrected. Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica gel (thickness 0.25mm) aluminium backed plates with a fluorescent indicator. Column chromatography was performed with silica gel 60 (Merck particle size (0.040 – 0.063) mm.

4.3 Thin layer chromatography and Column chromatography

4.3.1 Thin layer chromatography

A pencil line was drawn 2 cm above and below the rim of a pre-cut TLC plate and approximately 10 µl of a solution of the crude mixture was placed on the bottom line and air dried. The mobile phase consisting of hexane and ethyl acetate (4:1, v/v) was placed in a TLC chamber, closed and allowed to equilibrate until the atmosphere was saturated with the solvent vapor. The TLC plate was placed gently in the chamber and allowed to run until the mobile phase reached the top pencil mark. It was removed, air dried and viewed under the

UV lamp followed by staining in an iodine chamber containing sea sand, iodine crystals and H_2SO_4. The retention factor (Rf) was calculated by using the formula[4]:

$$R_f = \frac{\text{Distance moved from point of application by the analyte}}{\text{Distance moved from point of application by mobile phase}}$$

4.3.2 Column Chromatography

The pre-weighed crude synthesized mixture was dissolved in a minimum amount of chloroform and about 100 mg of silica gel. The beaker with the mixture was placed on a boiling water bath until the solvent evaporated and only a dry powder remained. The dry powder was transferred into a glass column and hexane was added and elution process started. Equal sized fractions were collected sequentially and carefully labelled for further analyses. The polarity of the mobile phase was changed by varying the composition of the solvent mixture. All fractions were analysed by TLC.

4.4. Synthesis of Dibenzonaphthyridines

4.4.1 Synthesis of ethyl-3- aniline-3-phenyl acrylate 160a by a Conventional Heating Method

In a 100 mL round bottom flask, a mixture of ethyl benzoylacetate (19.2 mL) **159** and aniline (12.3 mL) **158a** was dissolved in ethanol (25 mL) and hydrochloric acid (2 mL) as a catalyst was added. The mixture was stirred and heated under reflux for 3 hours at 50 ^oC, cooled to room temperature and was left overnight. The colourless crystals formed were then washed with petroleum ether to remove unreacted starting material. The mass obtained was 28 g, 95 %, m. p. 248 ^oC; ^1H NMR (400 MHz, $CDCl_3$) 1.33 (3H, t, J=7.06, H-1); 4.33 (2H, q, J=70.8, H-2); 4.99 (1H, s, H-4); 10.29 (1H, br.s, H-6); 7.27-7.35 (5H, m, H-2′ and H-6′, H-3′ and H-5′, H-4); 6.87-7.25 (5H, m, H-2″ and H-6″, H-3″ and H-5″, H-4″); ^{13}C NMR (400 MHz, $CDCl_3$) 14.5 (C-1), 76.7 (C-2), 170.1 (C-3), 91.2 (C-4), 159.0 (C-5), 140.4 (C-1′), 128.4 (C-2′ and C-6′), 128.6 (C-3′ and C-5′), 128.2 (C-4′), 136.0 (C-1″), 122.2 (C-2″ and C-6″), 129.4 (C-3″and C-6″), 123.0 (C-4″). IR (neat): Vmax/cm^{-1} 1645 (C=O), 1175 (C-O) and 3250 (NH) cm^{-1}.

4.4.2 Synthesis of 160a derivatives 160b and 160c

4.4.2.1 Synthesis of ethyl-3-phenyl-3-(o-tolylamino) acrylate 160b by a Conventional Heating Method

In a 100 mL round bottom flask, a mixture of ethyl benzoylacetate (19.2 mL, 0.1 mol.) and *ortho*-toluidine (10.70 mL, 0.1 mol) was dissolved in ethanol (15 mL) and hydrochloric acid (2 mL) as a catalyst was added. The mixture was stirred and heated under reflux for 3 hours at 50 ^{o}C, cooled to room temperature and was left overnight. The colourless crystals formed were washed with petroleum ether to produce colourless crystals of mass 27.5 g, 85.7 %; m.p. 101.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.41 (3H, s,H-1‴); 1.33 (3H, t, J=7.08, H-1) 4.20 (2H, q, J=7.12, H-2); 5.02 (1H, s, H-4); 10.11 (1H, br.s, H-6); 7.11-7.31 (7H, m, H-3″, H-5″, H-4′, H3′ and H-4′, H-2′ and H-6′); 6.31-6.75 (2H, m, H-2″, H-4″); ^{13}C NMR (400 MHz, $CDCl_3$) 14.5 (C-1); 18 .2 (C-1‴); 61.5 (C-2); 170.3 (C-3); 90.7 (C-4); 159.8 (C-5); 136.2 (C-1′); 128.3 (C-2′ and C-6′); 128.7 (C-3′ and C-5′); 128.0 (C-4′); 138.9 (C-1″); 123.4 (C-2″); 127.0 (C-3″); 123.8 (C-4″); 130.6 (C-5″); 125.8 (C-6″).

4.4.2.2 Synthesis of ethyl-3-phenyl-3-(p-tolylamino) acrylate 160c by Conventional Heating Method

In a 100 mL round bottom flask a mixture of para-toluidine **158c** (10.70 mL, 0.1 mol); ethyl benzoylacetate **159** (19.20 mL) and 3-4 drops of conc. hydrochloric acid in ethanol (20 mL) was heated under reflux for 3 hours at 50 ^{o}C and was left overnight at room temperature. Pale yellow crystals formed were washed with petroleum ether (20 mL) to remove any un-reacted starting material. The mass obtained for compound **160c** was 23.5 g, 80 %; m.p 79 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.19 (3H, s, H-1‴); 1.33 (3H, t, J=7.08, H-1); 4.20 (2H, q, J=7.12, H-2) 4.94 (1H, s, H-4); 10.2 (1H, s, H-6); 6.87 (2H,m, H-3″ and H-5″); 7.24-7.33 (7H, m, H-2″ and H-6″, H-4′, H-3′ and H-5′, H-2′ and H-6′); ^{13}C NMR (400 MHz, $CDCl_3$) 14.5 (C-1); 20.6 (C-1‴); 59.2 (C-2); 170.2 (C-3); 90.3 (C-4); 159.4 (C-5); 136.1 (C-1′); 128.3 (C-2′ and C-6′); 128.5 (C-3′ and C-5′); 128.2 (C-4′); 136.1 (C-1″); 115.2 (C-2″ and C-6″); 129.7 (C-3″ and C-5″); 132.6 (C-4″).

4.4.3 Synthesis of 2-phenylquinolin-4(1H)-one 161a by Microwave Method

Thermal cyclization of **161a** was afforded by placing 0.5 g of **160a** in a 100 mL round bottom flask and subjected to microwave irradiation at 250 watts and 180 ^{o}C for 5 minutes. A yellow solid was formed. Petroleum ether was added to wash any trace impurities. The yellow solid produced was 0.46 g, 92 %; m.p. 248 ^{o}C; ^{1}H NMR (400 MHz, DMSO-$_6$) 6.34 (1H, s, H-3),

11.7 (1H, s, H-1), 7.32-7.35 (3H, m, H-6, H-8, H-4′), 7.78 (1H, d, J= 8.3 Hz, H-5), 7.56 (1H, dt, J= 3.8 and J= 7.2, H-7), 7.67 – 7.69 (4H, m, H-3′ and H-5′, H-2′ and H-6′), ^{13}C NMR (400 MHz, DMSO-d_6) 149.9 (C-2), 107.3 (C-3), 176.9 (C-4), 124.6 (C-4a), 127.4 (C-5), 123.3 (C-6), 134.2 (C-7 and C-1′), 118.7 (C-8), 140.5 (C-8a), 128.9 (C-2′ and C-6′), 130.4 (C-3′ and C-5′), 127.4 (C-4′).

4.4.4 Synthesis of 161a derivatives 161b and 161c

4.4.4.1 Synthesis of 8-methyl-2-phenylquinolin-4(1H)-one 161b by Microwave Method

Thermal cyclization of **161b** was afforded by placing 0.5g of **160b** in a 100 mL round bottom flask and subjected to microwave irradiation at 250 watts and 180 ^{o}C for 5 minutes. A yellow solid was formed. The mass obtained was 0.4187 g, 84 %; m.p. 215^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) 2.08 (3H, s, H-1‴) 7.28 (1H, s, H-3), 10.5 (1H, s, H-1), 7.58 (1H, d, J=8, H-5), 7.30 (1H, dt, J= 1.4 and J= 7.6, H-6), 7.54 – 7.57 (4H, m, H-7, H-4′, H-3′ and H-5′) 7.91 (2H, m, H-2′ and H-6′) , ^{13}C NMR (400 MHz, DMSO-d_6) 18.0 (C-1‴), 130.0 (C-2 and C-8a), 79.1 (C-3), 206.4 (C-4), 121.4 (C-4a), 126.0 (C-5), 123.6 (C-6), 135.2 (C-7), 122.3 (C-8), 132.4 (C-1′), 127.7 (C-2′ and C-6′), 128.7 (C-3′ and C-5′), 126.0 (C-4′).

4.4.4.2 Synthesis of 6-methyl-2-phenylquinolin-4(1H)-one 161c by Microwave Method

Thermal cyclization of **161c** was afforded by placing 0.5g of **160c** in a 100 mL round bottom flask and subjected to microwave irradiation at 250 watts and 180 ^{o}C for 5 minutes. The mass obtained was 0.4 g, 80 %; m.p. 230 ^{o}C; ^{1}H NMR (400 MHz, MeOD-d_4) 3.30 (3H, m, H-1‴) 7.64 (1H, s, H-3), 9.29 (1H, s, H-1), 8.05 (1H, s, H-5), 7.67(1H, dt, J=3.0 and J= 8.9, H-7) 7.21 (1H, d, J=9.0, H-8), 8.13 – 8.15 (5H, m, H-2′ and H′-6, H-3′ and H-5′, H-4′); ^{13}C NMR (400 MHz, MeOD-d_4) 41.5(C-1‴), 135.7 (C-2), 106.4 (C-3), 158.5 (C-4), 122.5 (C-5 and C-4a) 131.7 (C-6), 132.0 (C-7), 108.7 (C-8), 133.1 (C-8a), 130.1 (C-1′), 129.8 (C-2′ and C-6′), 125.1 (C-3′ and C-5′), 122.5 (C-4′).

4.4.5 Synthesis of 4-chloro-2-phenylquinoline 162a by Microwave Method

5.0377 g of **161a** was dissolved inphosphorus oxychloride ($POCl_3$) (10 mL) in a 100 mL round bottom flask and was subjected to microwave irradiation at 75 ^{o}C and 150 watts for 2 minute. The completion of reaction was monitored by TLC. There was incomplete conversion to the product and hence the reaction was heated for a further minute. The flask was cooled to room temperature and the solution was poured into ice cold water (1000 mL). With stirring, a 25 % sodium hydroxide solution (5 mL) was then added to neutralise the solution. The precipitate was collected under suction filtration and dried to afford **162a**. The

weight of the product was recorded as 4.7754 g. The product was purified by column chromatography using hexane and ethyl acetate (4:1, v/v) as the eluting solvent system. The mass of **162a** obtained was 4.7754 g, 95 %**;** m.p. 144 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) 7.53 (1H, s, H-3), 8.30 (1H, d, J=6.3, H-5), 7.77 (1H, t, J=7.6, H-6), 7.89 (1H, t, J=6.0, H-7), 8.14 (1H, d, J=8.4, H-8), 8.30 (2H, m, H-2′ and H-6′) 7.54-7.55 (3H, m, H-4′, H-3′and H-5′), ^{13}C NMR (400 MHZ, DMSO-d_6) 156 (C-2), 123.5 (C-3), 142.4 (C-4), 123.5 (C-4a), 125.3 (C-5), 128.8 (C-6), 131.2 (C-7), 129.6 (C-8), 148.2 (C-8a), 137.4 (C-1′), 127.9 (C-2′and C-6′), 129.3 (C-3′and C-5′), 127.4 (C-4′); IR (neat) : Vmax/cm^{-1} 700 C-Cl.

4.4.5.1 Synthesis of 4-chloro-2-phenylquinoline 162a by a Conventional Heating Method

4.5370 g of **161a** was dissolved in $POCl_3$ (10 mL) in a 100 mL round bottom flask and heated under reflux at 100 ^{o}C for 5 hours. The flask was cooled to room temperature and the solution was poured into ice cold water (1000 mL). With stirring, a 25 % sodium hydroxide solution (5 mL) was then added to neutralise the solution. The precipitate was collected under suction filtration and dried to afford **162a**. The mass of **162a** obtained was 4.0581 g, 89 %. The m.p was recorded as 144 ^{o}C.

4.4.6. Synthesis of 162a derivatives 162b and 162c

4.4.6.1 Synthesis of 4- chloro-8-methyl-2-phenylquinoline 162b by Microwave Method

A mixture of **161b** (5.0420 g) and $POCl_3$ (10 mL) was subjected to microwave irradiation at 75 ^{o}C, 150 watts, for 2 minutes; cooled to room temperature and poured into ice cold water (1000 mL). With stirring, a 25 % sodium hydroxide solution (5 mL) was then added to neutralise the solution. The resulting precipitate was filtered to dryness, to afford **162b**. The product was purified by column chromatography using hexane and ethyl acetate (4:1, v/v) as the eluting solvent system. The mass obtained was 4.8310 g, 96 %; m.p. 82 ^{o}C; ^{1}HNMR (400 MHZ, $CDCl_3$) 2.88 (3H, s, H-1‴), 7.43 (1H, S, H-3), 8.22 (1H, d, J=5.2, H-5), 7.97 (1H, t, J=6.9, H-6), 8.04 (1H, d, J=8.2, H-7), 8.21 (2H, m, H-2′ and H-6′), 7.47-7.54 (3H, m, H-4′, H-3′ and H-5′); ^{13}CNMR (400 MHz, $CDCl_3$) 18.3 (C-1‴), 148.0 (C-2), 118.4 (C-3), 143.3 (C-4), 125.2 (C-4a), 121.8 (C-5), 126.8 (C-6), 130.6 (C-7), 138.1 (C-8), 155.3 (C-8a), 138.8 (C-1′), 128.8 (C-2′and C-6′), 127.4 (C-3′and C-5′), 129.6 (C-4′).

4.4.6.1.1 Synthesis of 4- chloro-8-methyl-2-phenylquinoline 162b by a Conventional Heating Method

The mixture of **161b** (5.0420 g) and $POCl_3$ (10 mL) was heated under reflux at 100 ^{o}C for 5 hours, cooled to room temperature and poured into ice cold water (1000 mL).With stirring, a

25 % sodium hydroxide solution (5 mL) was then added to neutralise the solution. The resulting precipitate was filtered to dryness, to afford **162b**. The mass obtained for compound **162b** was 3.8750 g, 77 %; m.p. 82 ^{o}C.

4.4.6.2 Synthesis of 4- chloro-6-methyl-2-phenylquinoline 162c by Microwave Method

5.0831 g of **161c** was dissolved in $POCl_3$ (10 mL) in a 100 mL round bottom flask and was subjected to microwave irradiation at 75 ^{o}C and 150 watts for 2 minutes. The completion of reaction was monitored by TLC. There was incomplete conversion to the product and hence the reaction was heated for a further minute. The flask was cooled to room temperature and the solution was poured into ice cold water (1000 mL). With stirring, a 25 % sodium hydroxide solution (5 mL) was then added to neutralise the solution. The precipitate was collected under suction filtration and dried to afford **162c**. The product was purified by column chromatography using hexane and ethyl acetate (4:1, v/v) as the eluting solvent system. The mass of **162c** obtained was 4.2987 g, 85 %; m.p. 82 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.57 (3H, s, H-1‴), 7.46 (1H, s, H-3), 8.11 (1H, s, H-5), 7.97 (1H, d, J=6.9, H-7), 8.04 (1H, d, J=8.6, H-8), 8.10 (2H, m, H-2′and H-6′), 7.59-7.60 (3H, m, H-4′, H-3′and H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) 21.8 (C-1‴), 156.4 (C-2), 119.1 (C-3), 142.4 (C-4), 125.2 (C-4a), 122.8 (C-5), 137.4 (C-6), 132.8 (C-7), 129.8 (C-8),9 147.7 (C-8a),156.4 (C-1′),128 (C-2′ and C-6′), 129.5 (C-3′and C-5′), 127.4 (C-4′).

4.4.6.2.1 Synthesis of 4- chloro-6-methyl-2-phenylquinoline 162c by a Conventional Heating Method

5.0831 g of **161c** was dissolved in $POCl_3$ (10 mL) in a 100 mL round bottom flask and heated under reflux at 100 ^{o}Cfor 5 hours. After heating was completed, the flask was cooled to room temperature and the solution was poured into ice cold water (1000 mL). With stirring, a 25 % sodium hydroxide solution (5 mL) was then added to neutralise the solution. The precipitate was collected under suction filtration and dried to afford **162c**. The mass of **162c** obtained was 3.5151 g, 69 %; m.p. 82 ^{o}C.

4.4.7 Synthesis of 4-(N-phenyl)-2-phenyl-4-Aminoquinoline 163a by Microwave Method

Treatment of **162a** (2.4810 g) with aniline hydrochloride (1.4 mL, 0.01 mol.) in t-butanol (20 mL) at 180 ^{o}C, 180 watts for 20 minutes under microwave irradiation produced **163a**. The reaction completion was monitored by TLC. The reaction mixture was cooled, poured into ice cold water (1000 mL), filtered and dried. The yellow solid was washed with petroleum ether, then recrystalised with a mixture of chloroform and methanol (3:1, v/v). The solid was

air dried and purified by column chromatography using hexane and ethylacetate (4:1, v/v) as eluting solvent system. The mass obtained was 2.2750 g, 92 %; m.p. 257 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) 11.1 (1H, s, H-2‴), 6.94 (1H, s, H-3), 8.07 (1H, d, J=7.6, H-5) 7.40-7.56 (7H, m, H-3″ and H-5″, H-2″ and H-6″, H-4′, H-3′ and H-5′), 7.59-7.89 (3H, m, H-6, H-7, H-8) 8.33 (2H, m, H-2′ and H-6′), ^{13}C NMR (400 MHz, DMSO-d_6) 154.6 (C-2), 98.7 (C-3), 152.9 (C-4), 116.5 (C-4a), 123.5 (C-5), 125.3 (C-6), 131.8 (C-7), 123.4 (C-8), 138.0 (C-8a), 137.2 (C-1′), 127.4 (C-2′and C-6′), 129.2 (C-3′ and C-5′), 126.9 (C-4′), 139.2 (C-1″), 117.8 (C-2″ and C-6″), 129.9 (C-3″ and C-5″), 127.3 (C-4″).

4.4.7.1 Synthesis of 4-(N-phenyl)-2-phenyl-4-Aminoquinoline 163a by a Conventional Heating Method

Treatment of **162a** (2.4810 g) with aniline hydrochloride (1.4mL, 0.01 mol.) in t-butanol (20 mL) was placed in a (100 mL) round bottom flask. The mixture was heated under reflux at 80 ^{o}C. After one hour, the colourless solution yielded a yellow solid. The heating was further continued for 1-2 hours. Excess solvent was evaporated; the mixture was cooled to room temperature and poured into ice cold water (1000 mL). The resulting precipitate was filtered, dried and recrystalized with chloroform and methanol (3:1, v/v)**.** The mass obtained was 1.8720 g, 76 %; m. p was 257 ^{o}C.

4.4.8 Synthesis of 163a derivatives 163b and 163c

4.4.8.1 Synthesis of 8-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline 163b by Microwave Method

Treatment of **162b** (2.74 g) with aniline hydrochloride (1.4mL, 0.01 mol.) in t-butanol (20 mL) at 180 ^{o}C and 180 watts for 20 minutes under microwave irradiation produced **163b**. The reaction completion was monitored by TLC. The reaction mixture was cooled, poured into ice cold water (1000 mL), filtered, dried and purified by column chromatography using hexane and ethylacetate (4:1, v/v) as eluting solvent system. The mass obtained was 2.15 g, 75 %; m. p. 88 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) 8.22 (1H, s, H-2‴), 7.24 (1H, s, H-3), 8.04 (1H, d, J=7.2 H-5), 2.88 (3H, s, H-1‴), 7.61-7.97 (2H, m, H-6, H-7), 7.43-7.54 (8H, m, H-4″,H-3″ and H-5″, H-2″ and H-6″, H-4′, H-3′ and H-5′), 8.21 (2H, m, H-2′ and H-6′); ^{13}C NMR (400 MHz, $CDCl_3$) 18.2 (C-1‴), 77.3 (C-3), 147.9 (C-4), 118.4 (C-4a), 121.8 (C-5), 125.3 (C-6), 129.7 (C-7), 138.1 (C-8), 148.0 (C-8a), 138.7 (C-1′), 127.4 (C-2′ and C-6′), 128.9 (C-3′ and C-5′), 126.8 (C-4′), 145.9 (C-1″), 117.8 (C-2″ and C-6″), 129.6 (C-3″ and C-5″), 121.8 (C-4″).

4.4.8.1.1 Synthesis of 8-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline 163b by a Conventional Heating Method

Treatment of **162b** (2.7791 g) with aniline hydrochloride (1.4 mL, 0.01 mol.) in t-butanol (20 mL) was placed in a (100 mL) round bottom flask. The mixture was heated under reflux at 80 ^{o}C. After one hour, the colourless solution yielded a yellow solid. The heating was further continued for 1-2 hours. Excess solvent evaporated, the mixture was cooled to room temperature and poured into ice cold water (1000 mL). The resulting precipitate was filtered, dried and recrystalized with chloroform and methanol (3:1, v/v)**.** The mass obtained was 1.8542 g, 67 %; m. p. 88 ^{o}C.

4.4.8.2 Synthesis of 6-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline 163c by Microwave Method

Treatment of 3.9744 g of **162c** with aniline hydrochloride (1.40 mL) in tert-butanol (20 mL) was transferred to a round bottom flask (100 mL). The reaction mixture was subjected to microwave irradiation at 180 ^{o}C, 180 watts for 20 minutes. The yellow solution which was formed was then poured into ice cold water (1000 mL), filtered through suction and dried. The yellow solid was washed with petroleum ether, then recrystalized with a mixture of chloroform and methanol (3:1, v/v). The solid was air dried. The mass obtained was 3.8760 g, 97 %; m. p. 181 ^{o}C; ^{1}H NMR (400 MHz, MeOD-d_4) 3.20 (3H, s, H-1‴), 8.01 (1H, s, H-2‴), 7.02 (1H, s, H-3), 7.65 (1H, s, H-5), 7.53 (1H, d, J=7.3, H-7), 7.88 (1H, d, J=7.5, H-8), 8.39 (2H, m, H-2′ and H-6′) 7.03-7.55 (8H, m, H-4″, H-3″ and H-5″, H-2″ and H-6″, H-4′, H-3′ and H-5′); ^{13}C NMR (400 MHz, MeOD-d_4) 21.2 (C-1‴), 153.9 (C-2), 98.6 (C-3), 152.2 (C-4), 117.9 (C-4a), 120.7 (C-5),135.5 (C-6), 131.7 (C-7), 137.3 (C-8), 154.0 (C-8a), 138.0 (C-1′), 128.3 (C-2′ and C-6′), 129.2 (C-3′ and C-5′), 127.2 (C-4′), 142.0 (C-1″), 118.0 (C-2″ and C-6″), 129.9(C-3″ and C-5″), 122.3 (C-4″).

4.4.8.2.1 Synthesis of 6-methyl-4-(N-phenyl)-2-phenyl-4-aminoquinoline 163c by a Conventional Heating Method

Treatment of 3.9744 g of **162c** and aniline hydrochloride (1.40 mL) in tert-butanol (20 mL) was heated under reflux at 80 ^{o}C for 2 hours to afford **163C**. The yellow solution which was formed was then poured into ice cold water (1000 mL), filtered through suction and dried. The yellow solid was washed with petroleum ether, then recrystalized with a mixture of chloroform and methanol (3:1, v/v). The solid was air dried. The mass obtained was 2.9180 g, 73 %; m. p 181 ^{o}C.

4.4.9 Synthesis of 6-phenyl-dibenzo [b, h] [1, 6] Naphthyridine 164a by Microwave Method

Dimethyl formamide (3.85 mL; 0.05 mol.) was cooled to 0 ^{o}C in a flask equipped with a dropping funnel. Phosphoryl chloride (12.97 mL; 0.14 mol.) was added drop-wise from the funnel while stirring. The resultant reagent was stirred for a further 30 minutes at room temperature[3] and then cooled to 5 ^{o}C **163a** (3.9924 g; 0.012 mol.) was added and the stirring was continued for 30 minutes. The reaction mixture was transferred to the microwave synthesizer which was set at 75 ^{o}C and 120 watts for 20 minutes. The initial colour of the reaction mixture was a pale yellow colloidal matter. After 15 minutes the reaction mixture changed to a clear red solution. After cooling to room temperature, the reaction mixture was poured into cold water (1000 mL) and neutralised with a 25 % sodium carbonate solution. The resulting filtrate was dried and purified by column chromatography (elution with 4:1 hexane-EtOAc, v/v).The mass obtained was 3.5775 g, 90 %**;** m. p. 59 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.18 (1H, d, J=8.5, H-5), 7.60-7.79 (6H, m, H-6 and H-11, H-7 and H-12, H-8 and H-13), 7.47-7.54 (3H, m, H-4′, H-3′ and H-5′), 8.11-8.23 (4H, m, H-10, H-9, H-2′ and H-6′); ^{13}C NMR (400 MHz, $CDCl_3$) 157.29 (C-2), 119.1 (C-3), 138.6 (C-4 and C-9), 123.9 (C-4a and C-13), 125.3 (C-5), 127.2 (C-6 and C-11), 130.1 (C-7 and C-12, C-10), 128.9 (C-8 and C-13), 149.1 (C-8a), 130.6 (C-9a), 143.2 (C-13a), 137.1 (C-1′), 127.5 (C-2′ and C-6′), 129.8 (C-3′ and C-5′), 127.2 (C-4′).

4.4.9.1 Preparation of 6-phenyl-dibenzo [b, h] [1, 6] Naphthyridine 164a by a Conventional Heating Method

3.9924g of **163a**was dissolved in dimethyl formamide (3.85 mL; 0.05 mol.) and $POCl_3$ (12.97 mL; 0.14 mol.). The mixture was heated under reflux at 100 ^{o}C for 21 hours. The reaction was monitored by TLC. After cooling to room temperature, the reaction mixture was poured into ice cold water (1000 mL) and subsequently neutralised with sodium carbonate. The precipitate was collected and dried, then purified with column chromatography using hexane-EtOAc (4:1, v/v) as the eluent. The mass obtained was 2.5741 g, 64 %. The m.p. was 59 ^{o}C.

4.4.10 Synthesis of 164a derivatives 164b and 164c

4.4.10.1 Synthesis of 4-methyl-6-phenyldibenzo [b, h] [1, 6] naphthyridine 164b by microwave method

A fresh solution of the DMF and $POCl_3$ mixture was prepared as in 4.4.9. **163b** (2.2840g) was added and stirring was continued for 30 minutes.The reaction mixture was transferred to

the microwave synthesizerset at 75 ^{o}C and 120 watts for 20 minute. The reactions were monitored by TLC. After cooling to room temperature, the reaction mixture was poured into cold water (1000 m L) and neutralised with sodium carbonate (25 %). The resultant precipitate was filtered, dried and purified with column chromatography using hexane and ethylacetate (4:1, v/v) as the eluent. The mass obtained was 1.9854 g; 87 %; m.p. 83 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, s, H-1‴), 8.06 (2H, d, J=8.4,H-5 and H-10), 7.61-7.79 (4H, m, H-6, H-11, H-7 and H-12), 7.99-8.23 (4H, m, H-13, H-9,H-2′and H-6′), 7.47-7.54 (3H, m, H-4′, H-3′and H-5′); ^{13}C NMR (400 MHz, $CDCl_3$) 16.8 (C-1‴), 155.3 (C-2), 118.4 (C-3), 138.2 (C-4), 121.8 (C-4a), 125.25 (C-5), 126.9 (C-6), 130.6 (C-7 and C-12 and C-9a), 138.8 (C-8), 148.0 (C-8a), 138.2 (C-9 and C-1′), 129.7 (C-10), 127.4 (C-11), 121.8 (C-13), 143.3 (C-13a), 127.4 (C-2′and C-6′), 128.9 (C-3′and C-5′), 126.8 (C-4′).

4.4.10.1.1 Synthesis of 4-methyl-6-phenyldibenzo [b, h] [1, 6] naphthyridine 164b by a Conventional Heating Method

2.2840 g of **163b** was dissolved in dimethyl formamide (3.85 mL; 0.05 mol.) and $POCl_3$ (12.97 mL; 0.14 mol.).The reaction mixture was heated under reflux at 100 ^{o}C for 21 hours. The mixture was allowed to cool to room temperature and was poured into ice cold water (1000 mL) and subsequently neutralised with sodium carbonate solution (25 %). The solid was filtered and dried. The mass obtained was 1.3941 g, 61 %; m.p 83 ^{o}C.

4.4.10.2 Synthesis of 2-methyl-6-phenyldibenzo [b, h] [1, 6] naphthyridine 164c by Microwave Method

A fresh solution of the DMF and $POCl_3$ mixture was prepared as in 4.4.9. **163c** (3.7814 g, 0.012 mol) was added and stirring was continued for 30 minutes. The reaction mixture was then transferred to the microwave synthesizer which was set at 75 ^{o}C and 120 watts for 20 minutes. The initial colour of the reaction mixture was a pale yellow colloidal matter. After 15 minutes the reaction mixture changed to a clear red solution. After cooling to room temperature, the reaction mixture was poured into ice cold water (1000 mL) and neutralised with a 25 % sodium carbonate solution. The resulting filtrate was dried and purified by column chromatography (elution with 4:1, hexane-EtOAc, v/v). The mass obtained was 2.9010 g, 77 %; m. p. 89 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 2.57 (3H, s, H-1‴), 7.60 (1H, s, H-5), 7.47-7.59 (5H, m, H-4′, H-7, H-3′and H-5′, H-11); 7.92-8.12 (6H, m, H-8, H-13, H-10, H-9, H-2′and H-6′); ^{13}C NMR (400 MHz, $CdCl_3$) 21.6 (C-1‴), 156.4 (C-2), 119.1 (C-3), 137.4 (C-4), 122.8 (C-4a), 125.2 (C-5),137.5 (C-6), 132.0 (C-7 and C-12), 128.9 (C-8), 147.7

(C-8a), 138.9 (C-9), 132,8 (C-9a), 132.4 (C-10), 127.0 (C-11), 129.8 (C-12), 122.7 (C-13), 142.4 (C-13a), 137.0 (C-1′), 128.9 (C-2′and C-6′), 129.8 (C-3′and C-5′),127.4 (C-4′).

4.4.10.2.1 Synthesis of 2-methyl-6-phenyldibenzo [b, h] [1, 6] naphthyridine 164c by a Conventional Heating Method

3.7814g of **163c** was dissolved in dimethyl formamide (3.85 mL; 0.05 mol.) and $POCl_3$ (12.97 mL; 0.14 mol.). The mixture was heated under reflux at 100 ^{o}C for 21 hours. The reaction was monitored using TLC. After cooling to room temperature, the reaction mixture was poured into cold water (1000 mL) and subsequently neutralised with sodium carbonate. The precipitate was collected and dried, then purified with column chromatography using hexane and ethylacetate (4:1,v/v) as the eluent.The mass obtained was 1.9510 g, 51 %; m. p. 89 ^{o}C.

4.5. References

1. Mphahlele M.J, Mabusela M.R.C, S.Afr. J. Chem.,1999, 52,157-160
2. Kaye P.T, Mphahlele M.J, S. Afr. J. Chem.,1994, 47, 21-25
3. Vilsmeier Anton, Haack, A. B, 1927, 60, 119
4. Wijesekera R.O.B., The Medical plant industry, Boston, London, 1991, 100-102

Spectroscopic Data

Appendix 1

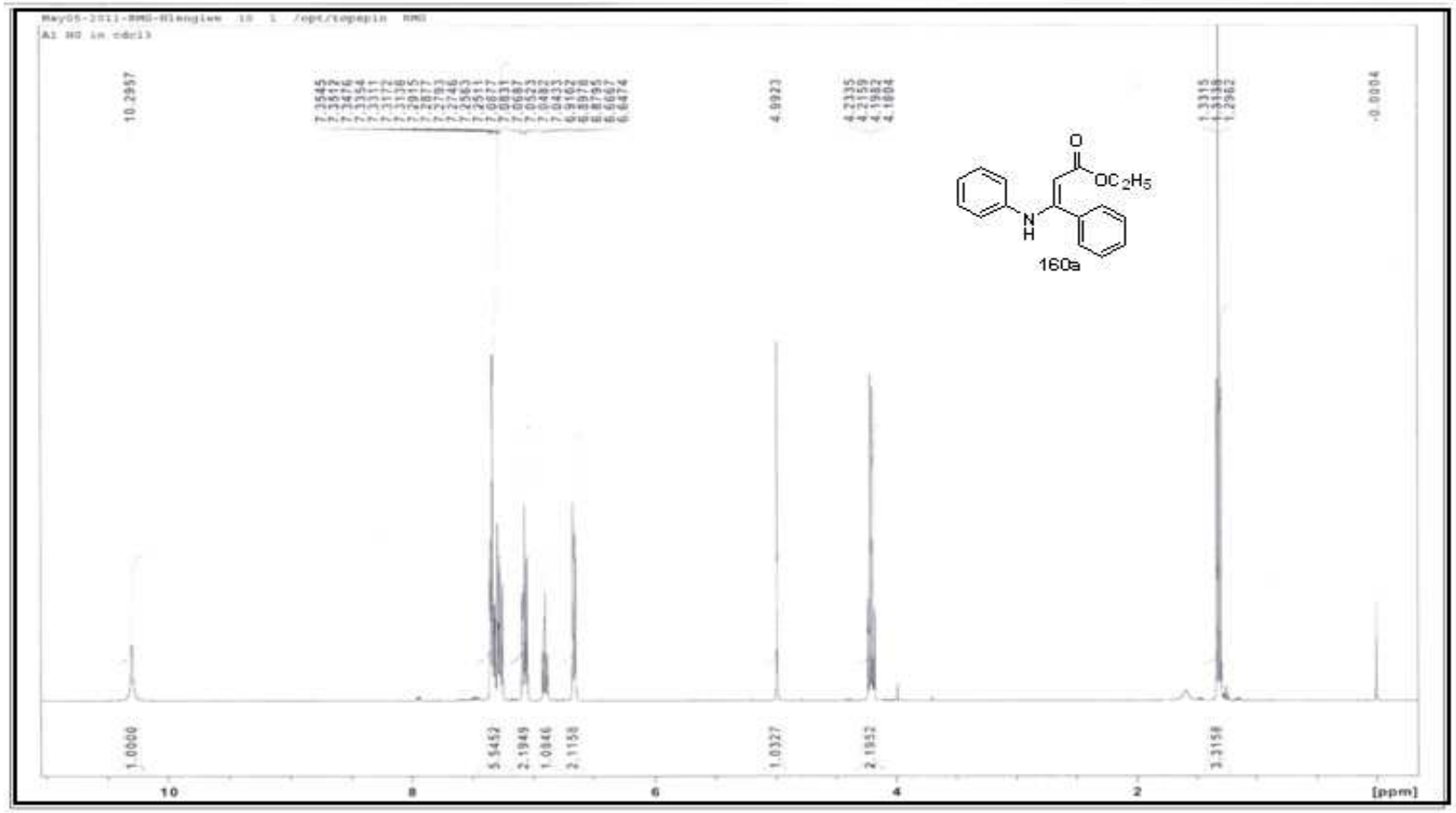


Figure 4: ^{1}H NMR Spectrum of ethyl – 3 – aniline -3 – phenyl acrylate 160a

Appendix 2

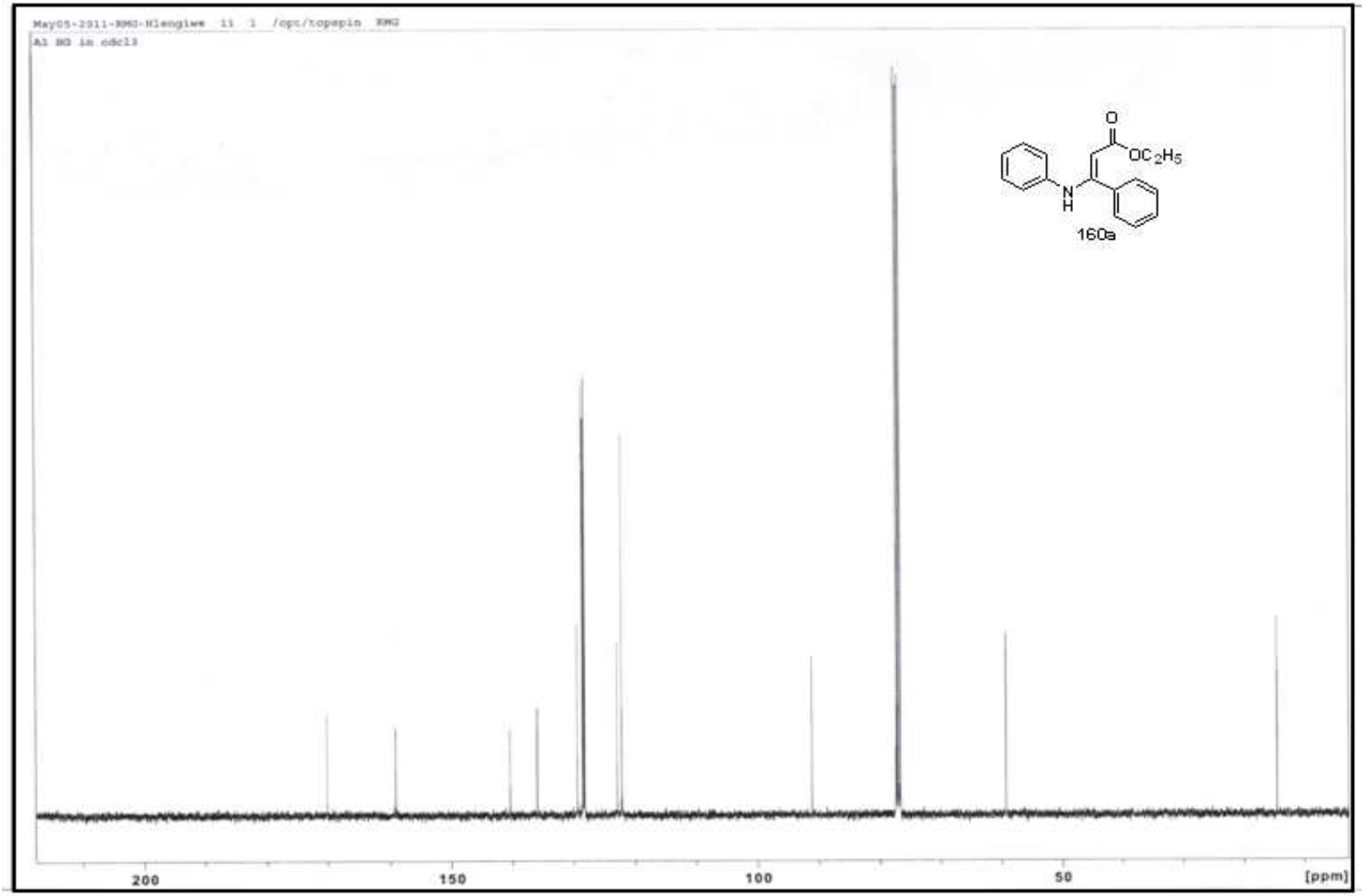


Figure 5: ^{13}C NMR Spectrum of ethyl – 3 – aniline – 3 phenyl acrylate 160a

Appendix 3

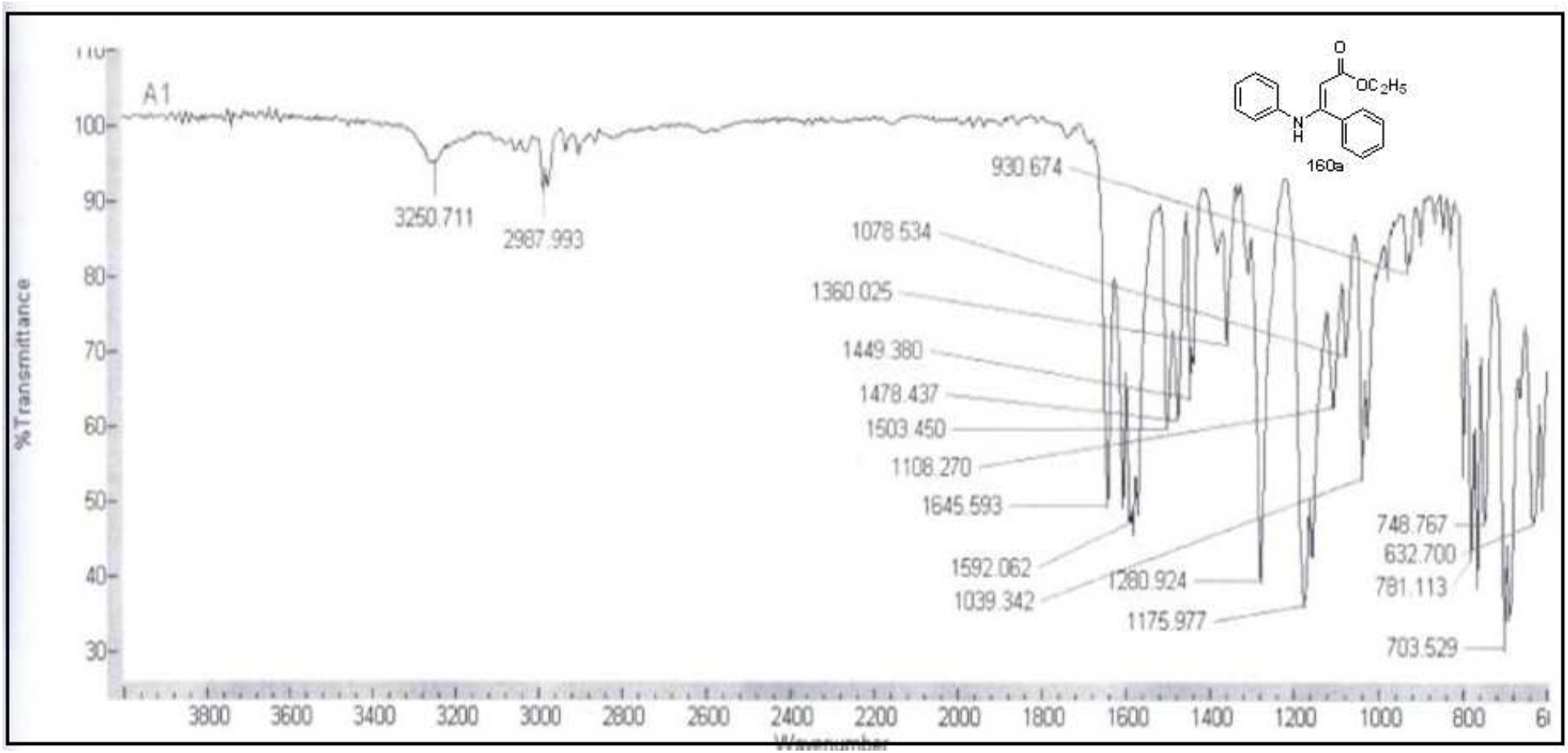


Figure 6: IR Spectrum of ethyl – 3 – aniline – 3 –phenyl acrylate 160a

Appendix 4

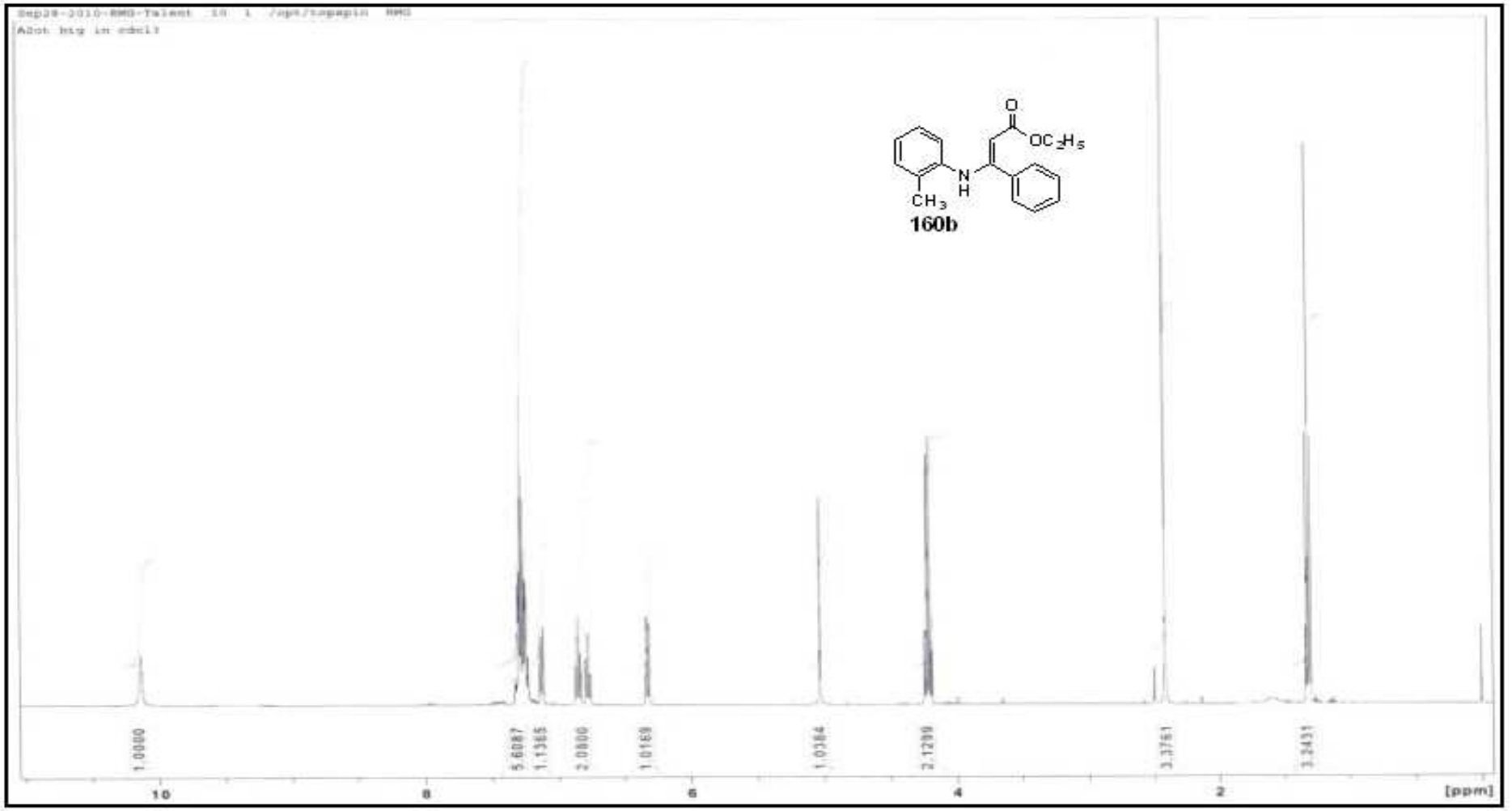


Figure 7: ^{1}H NMR Spectrum of ethyl – 3 – phenyl – 3 – (o - tolylamino) acrylate 160b

Appendix 5

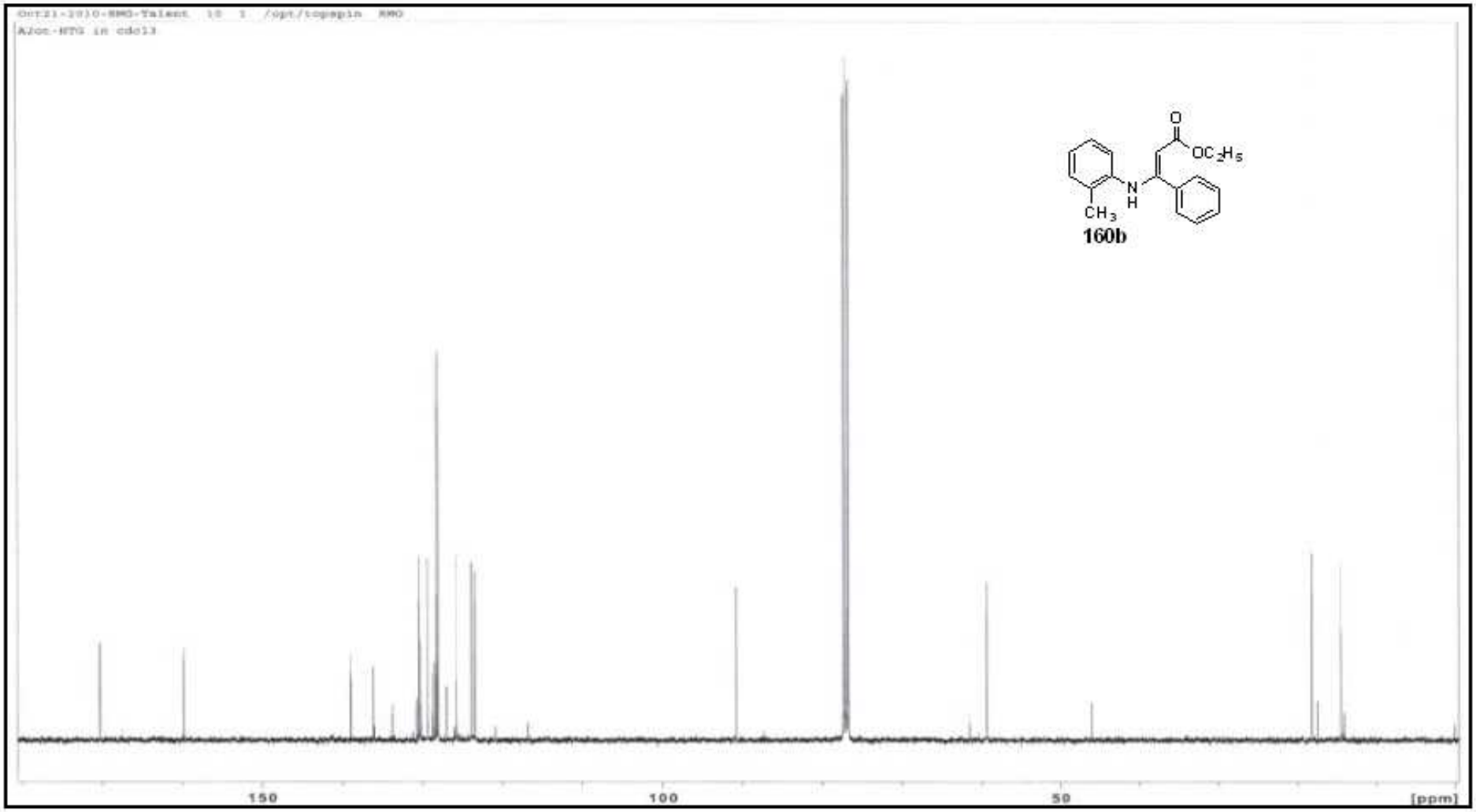


Figure 8: ^{13}C NMR Spectrum of 160b

Appendix 6

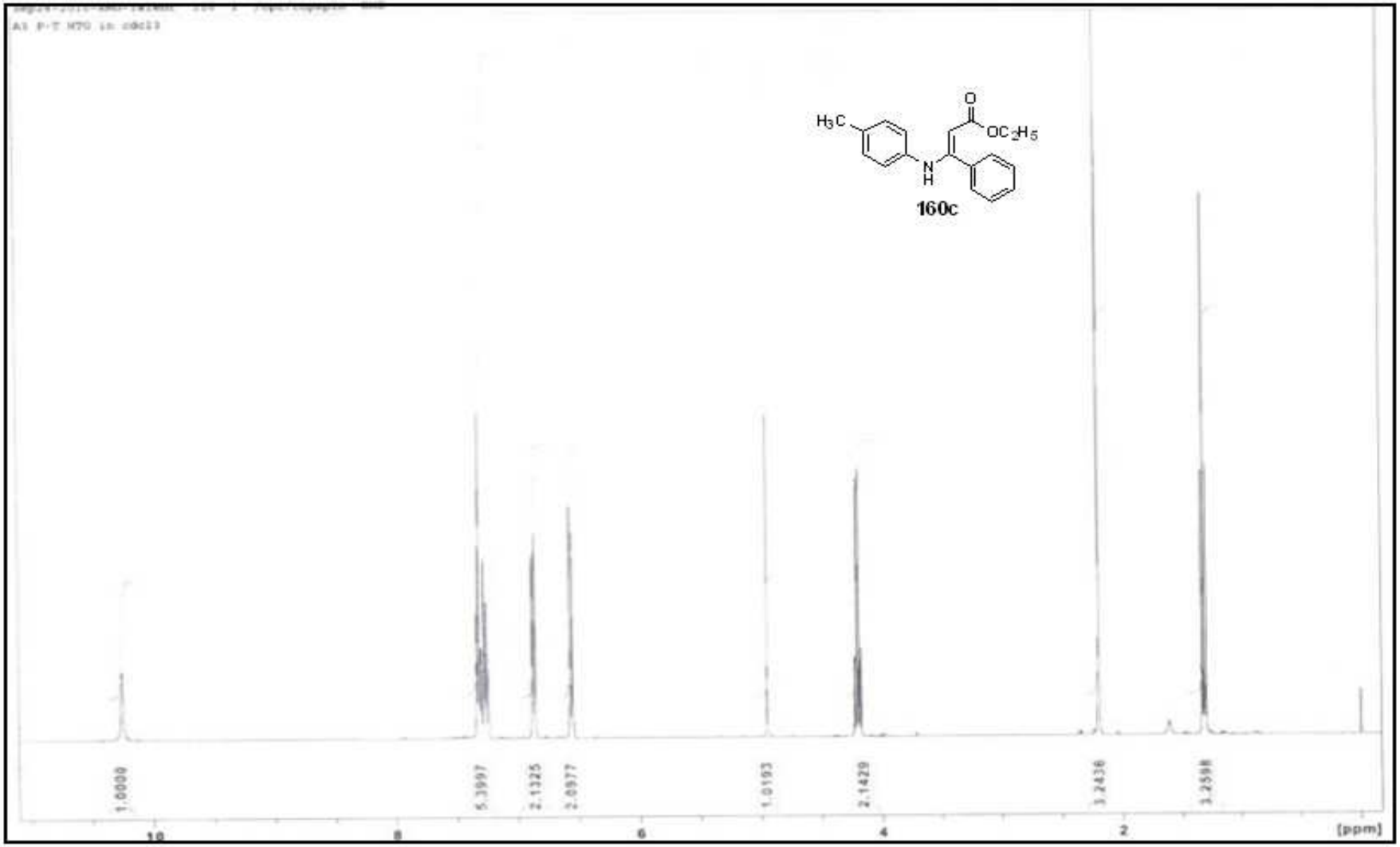


Figure 9: ^{1}H NMR Spectrum of ethyl – 3 – phenyl – 3 – (p - tolylamino) acrylate 160c

Appendix 7

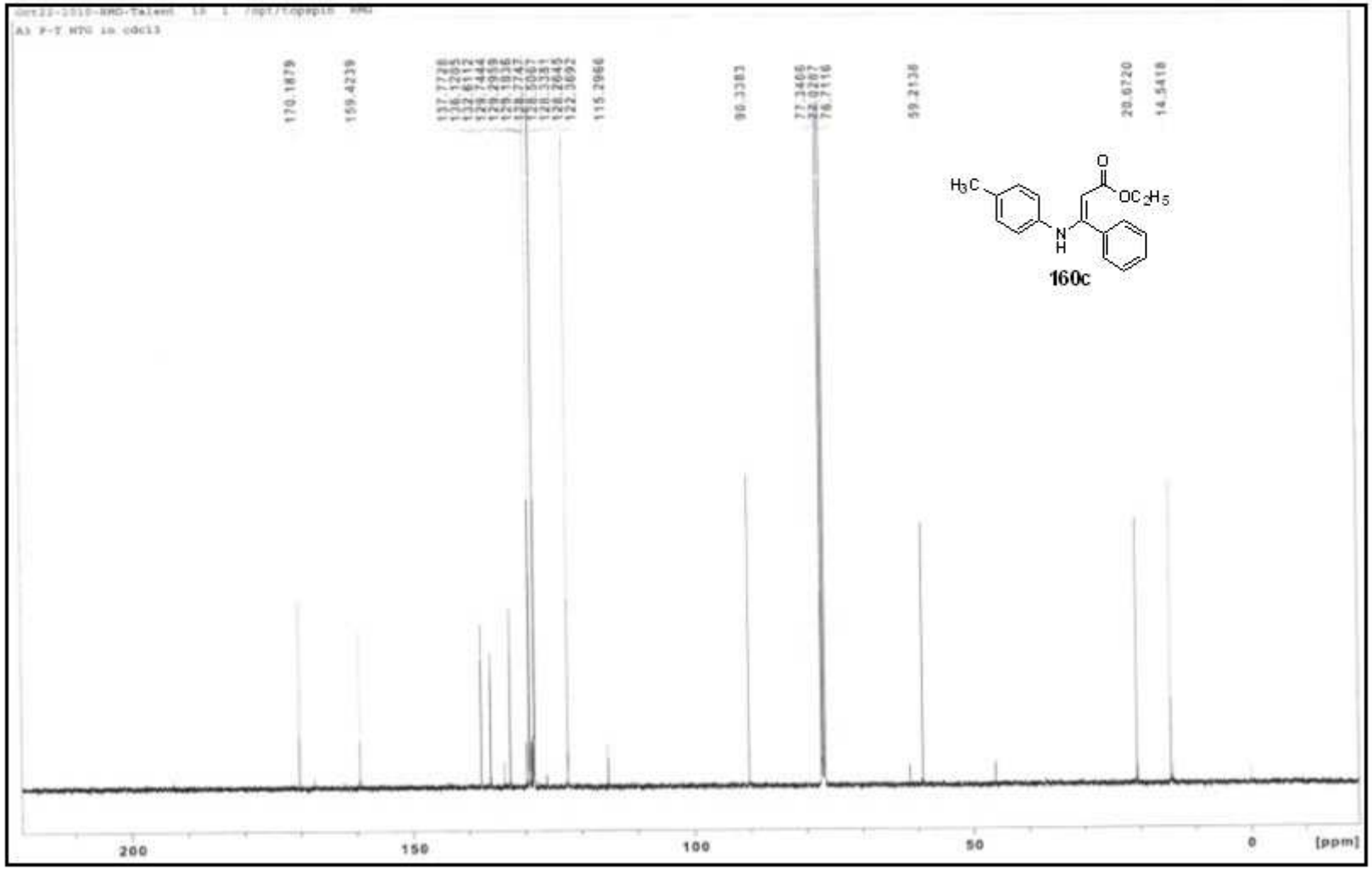


Figure 10: ^{13}C NMR Spectrum of ethyl – 3 – phenyl – 3 – (p - tolylamino) acrylate 160c

Appendix 8

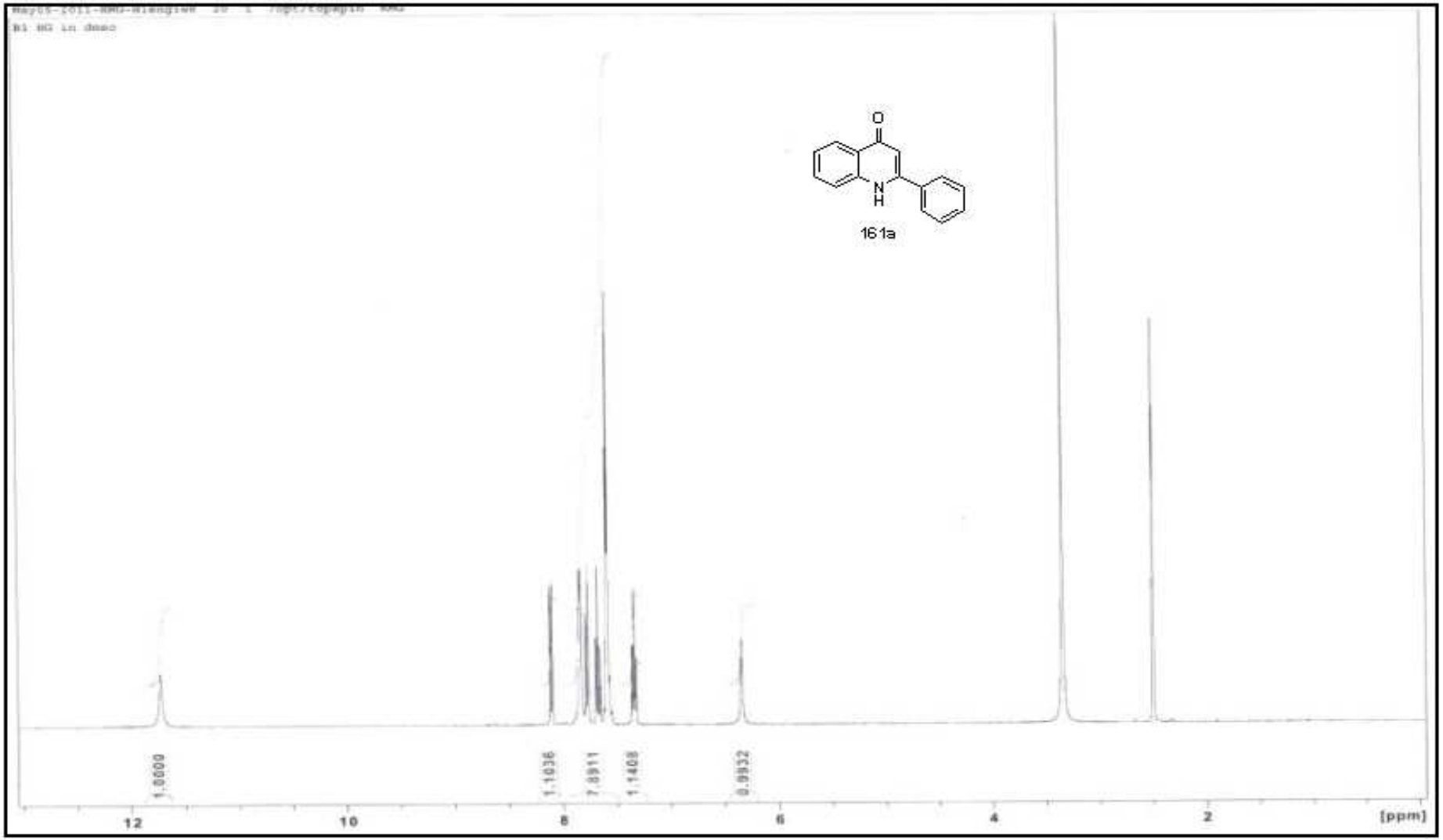


Figure 11: ^{1}H NMR Spectrum of 2 – phenylquinoline – 4 (1H) – one 161a

Appendix 9

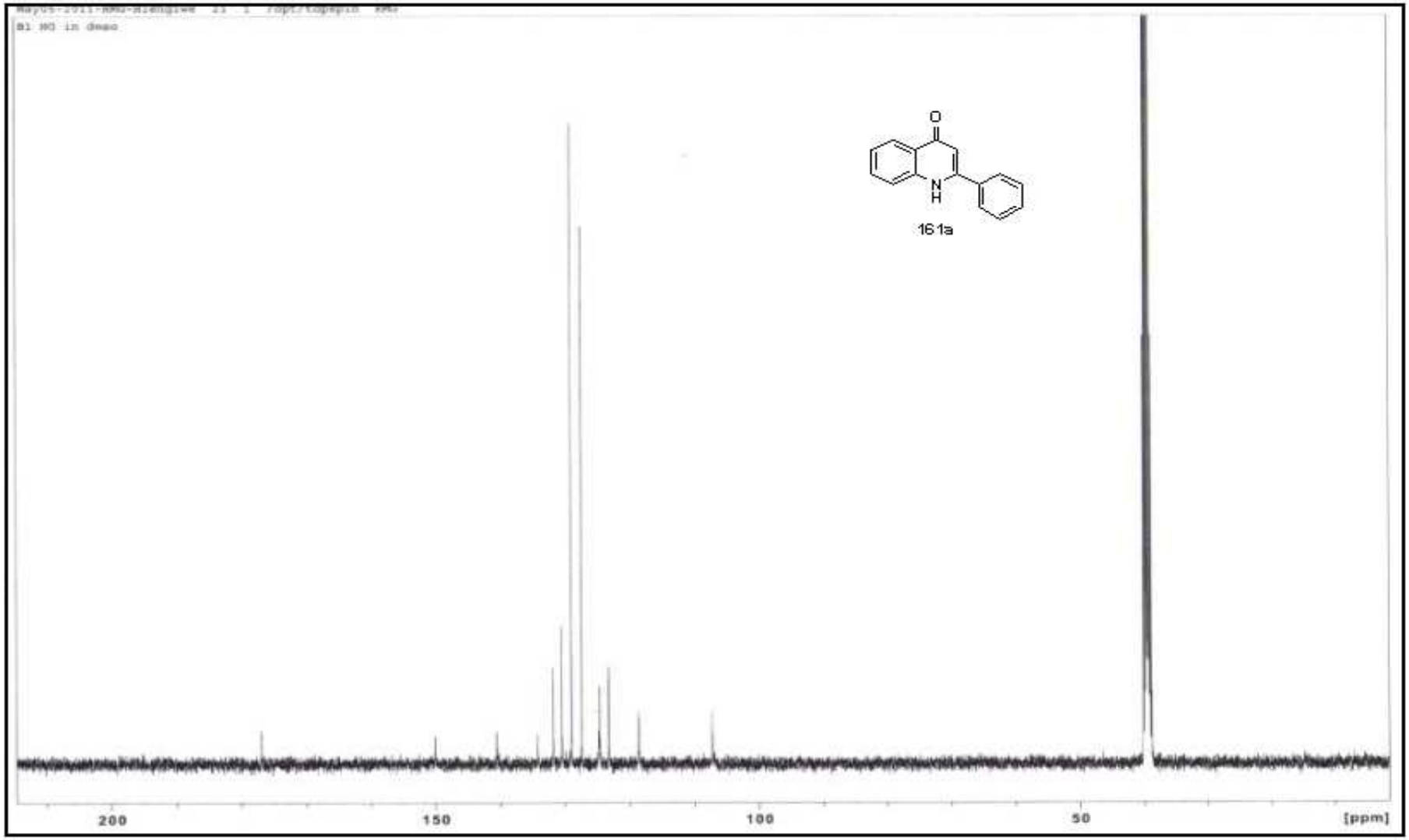


Figure 12: ^{13}C NMR spectrum of 2 – phenylquinoline – 4 (1H) – one 161a

Appendix 10

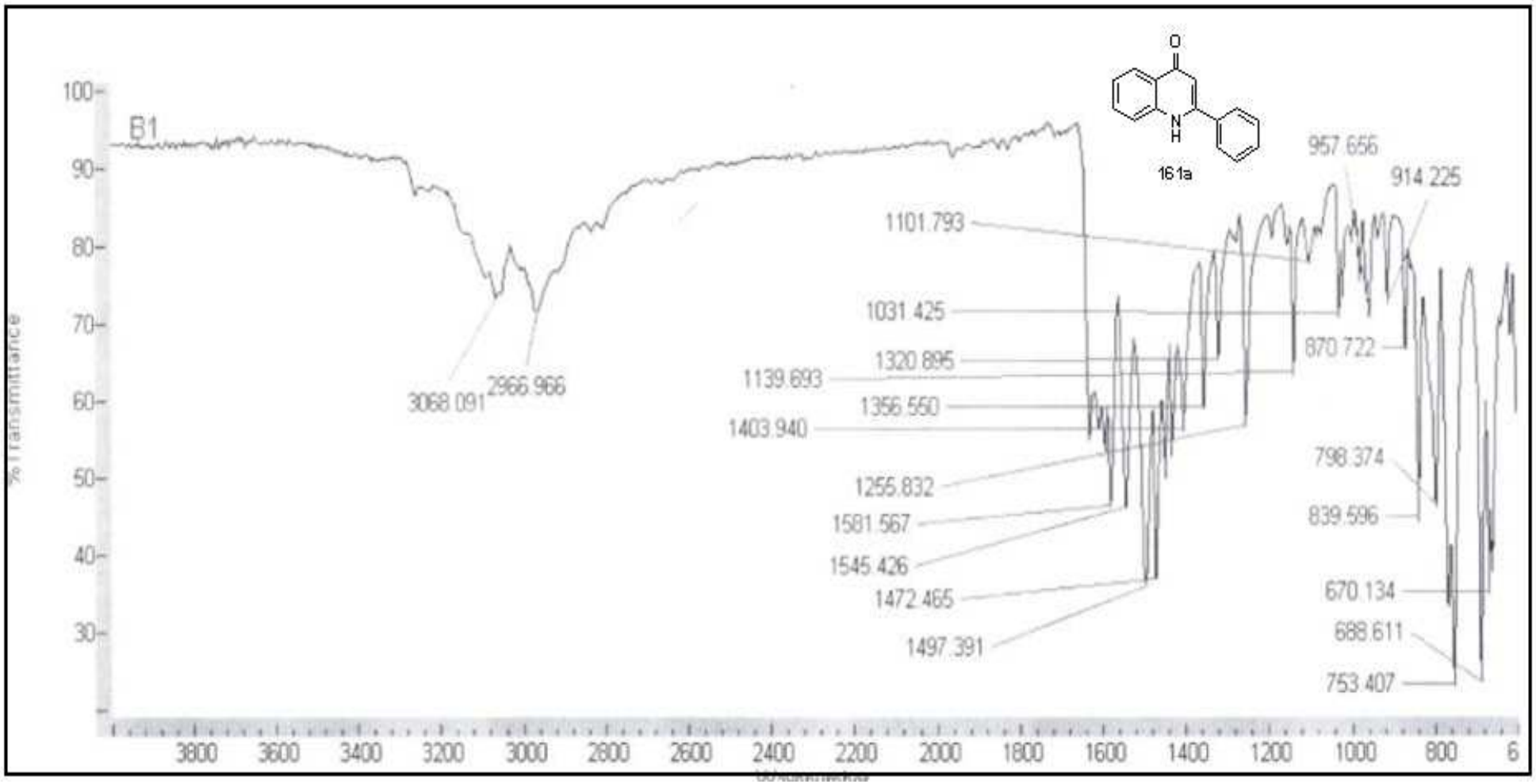


Figure 13: IR Spectrum of 2 – phenylquinoline – 4 (1H) – one 161a

Appendix 11

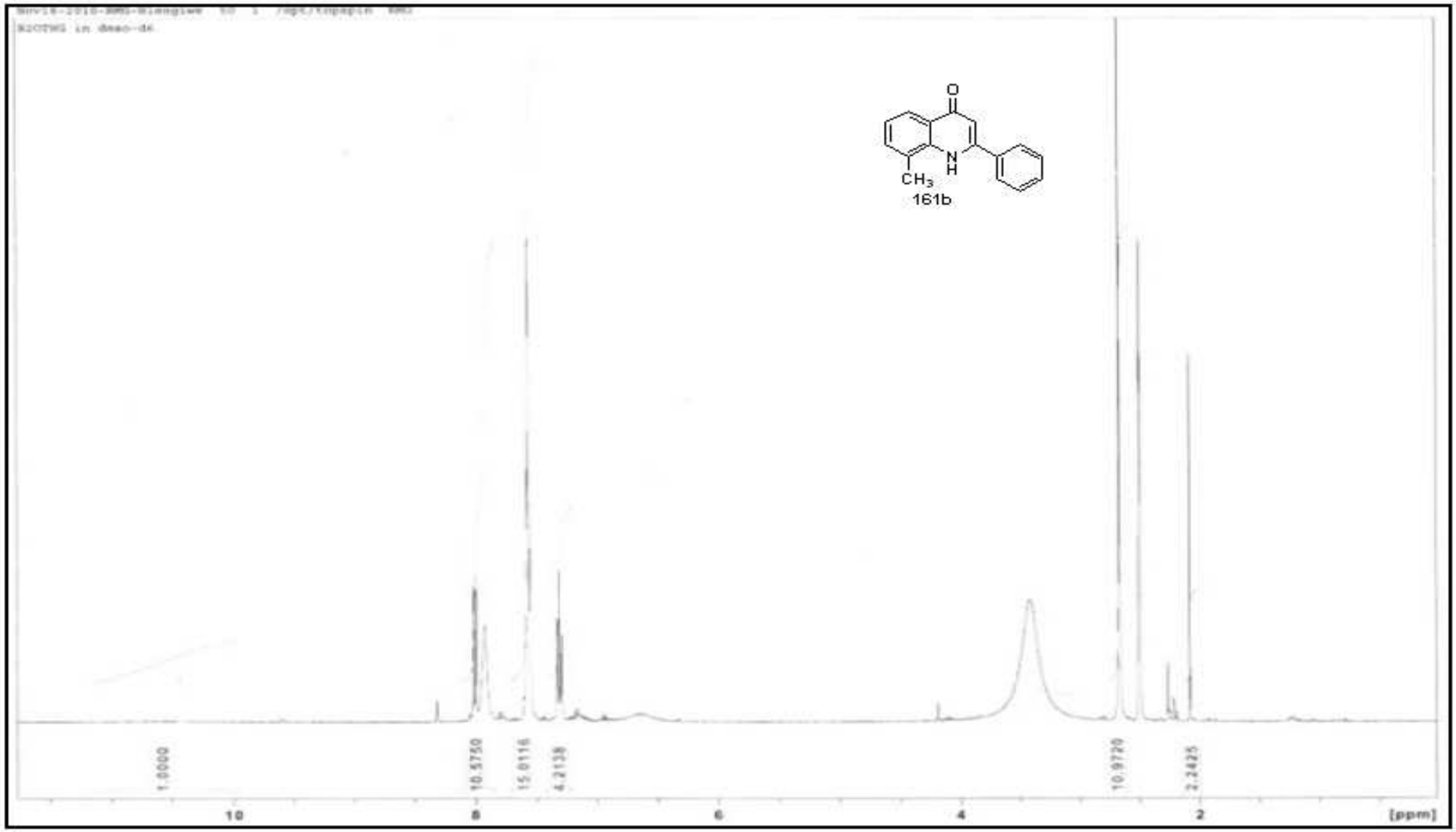


Figure 14: ^{1}H NMR Spectrum of 8 – methyl – 2 – phenylquinoline – 4 (1H) – one 161b

Appendix 12

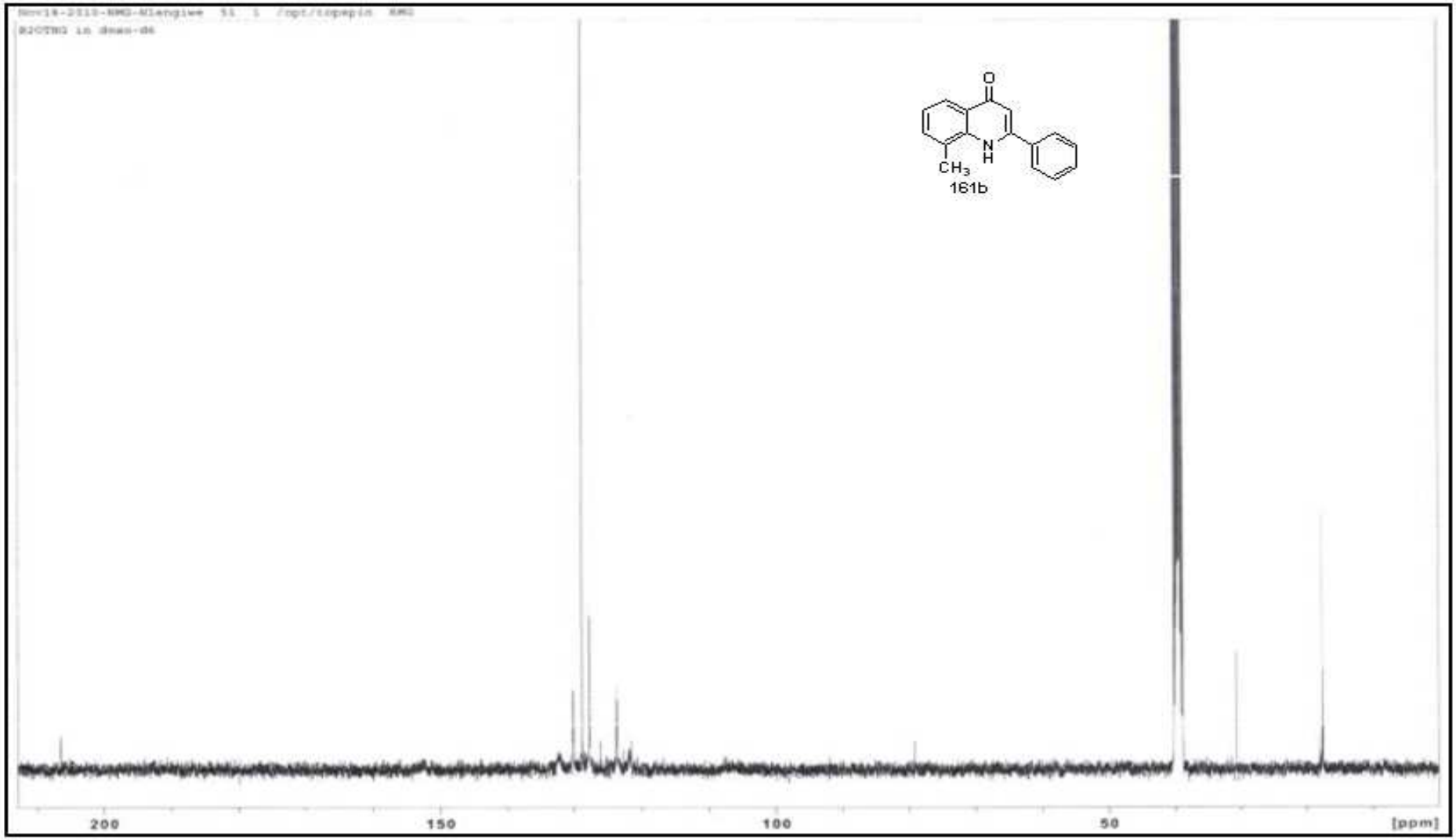


Figure 15: ^{13}C NMR Spectrum of 8 – methyl – 2 – phenylquinoline – 4 (1H) – one 161b

Appendix 13

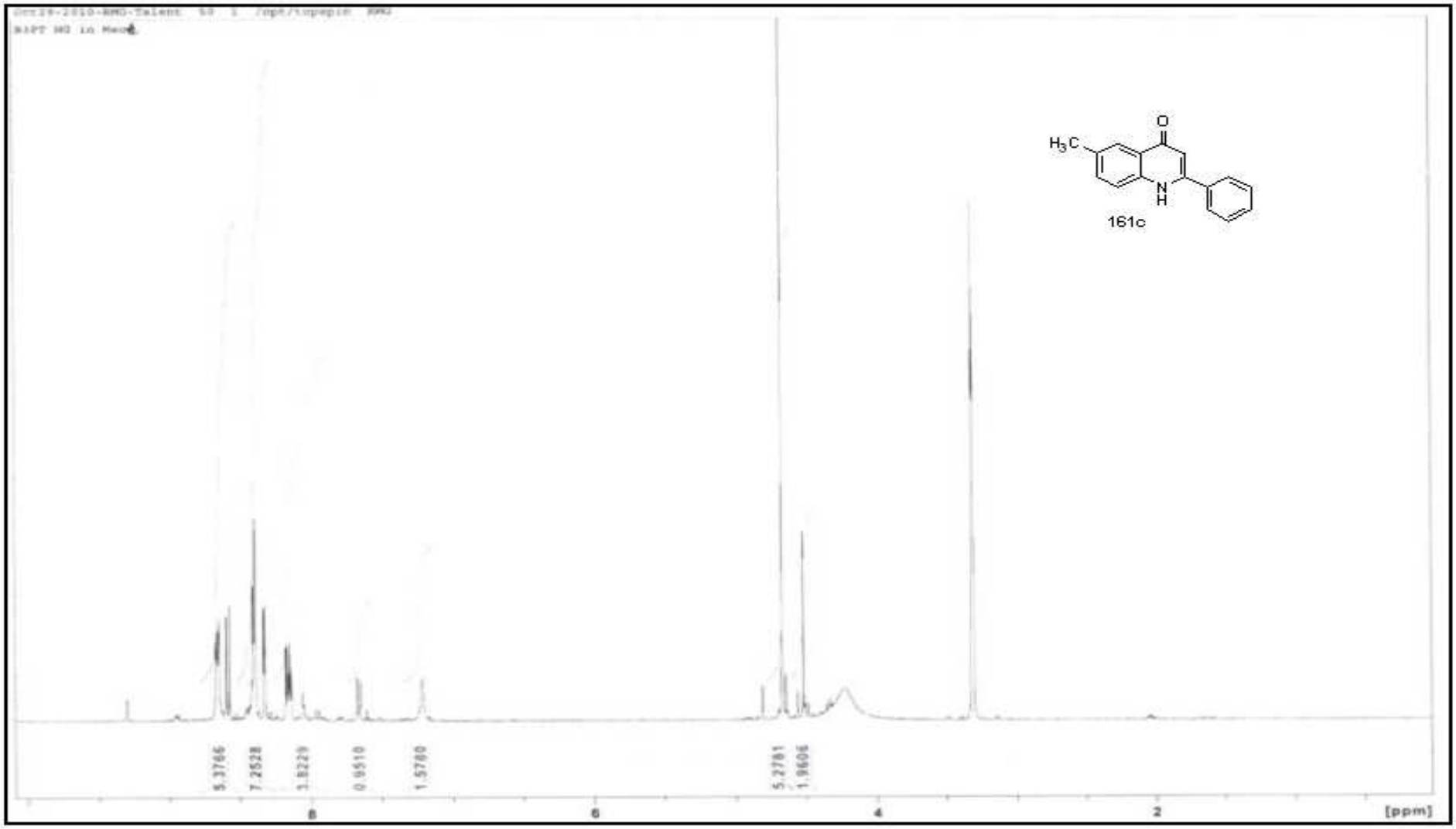


Figure 16: ^{1}H NMR Spectrum of 6 – methyl – 2 – phenylquinoline – 4 (1H) – one 161c

Appendix 14

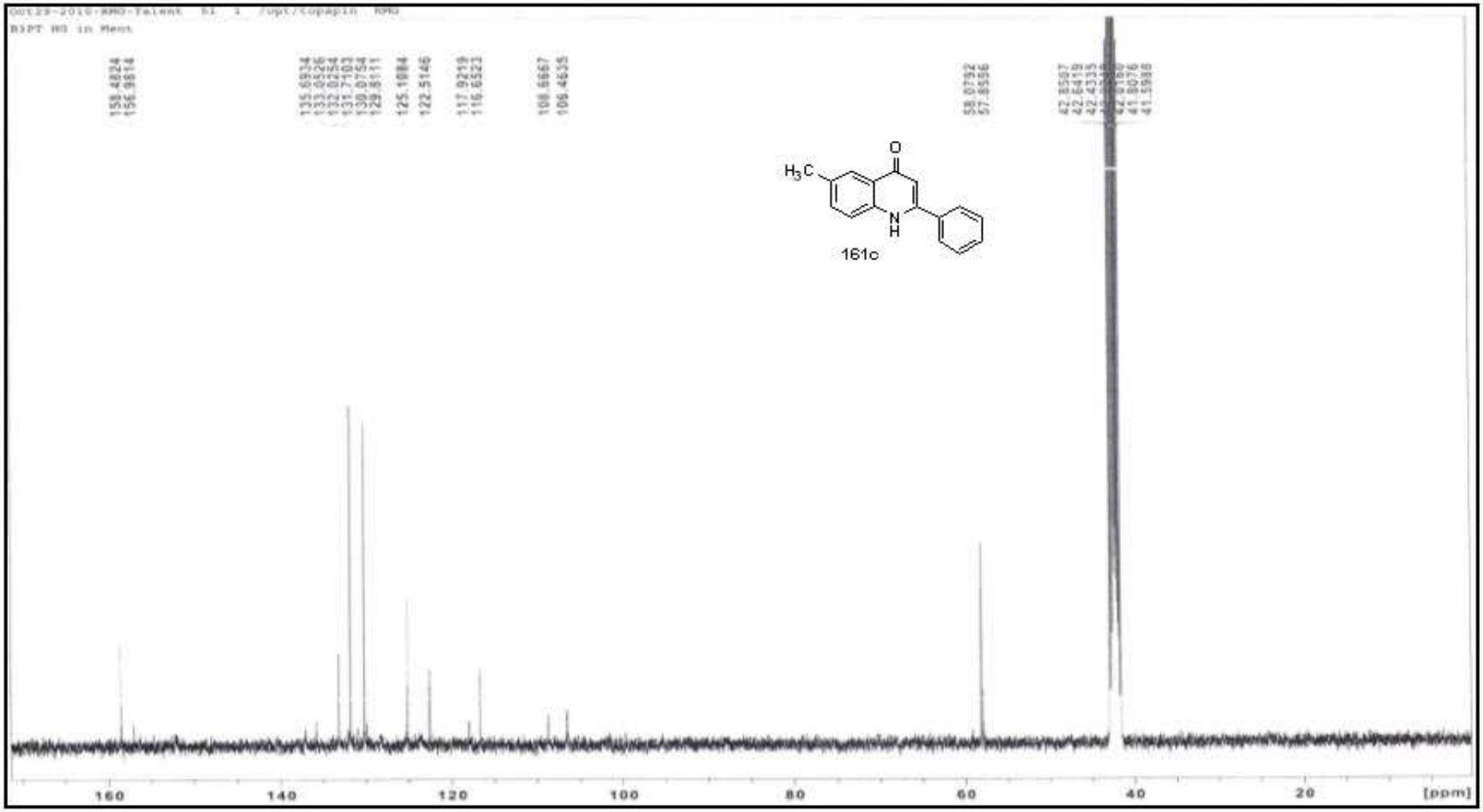


Figure 17: ^{13}C NMR Spectrum of 6 – methyl – 2 – phenylquinoline – 4 (1H) – one 161c

Appendix 15

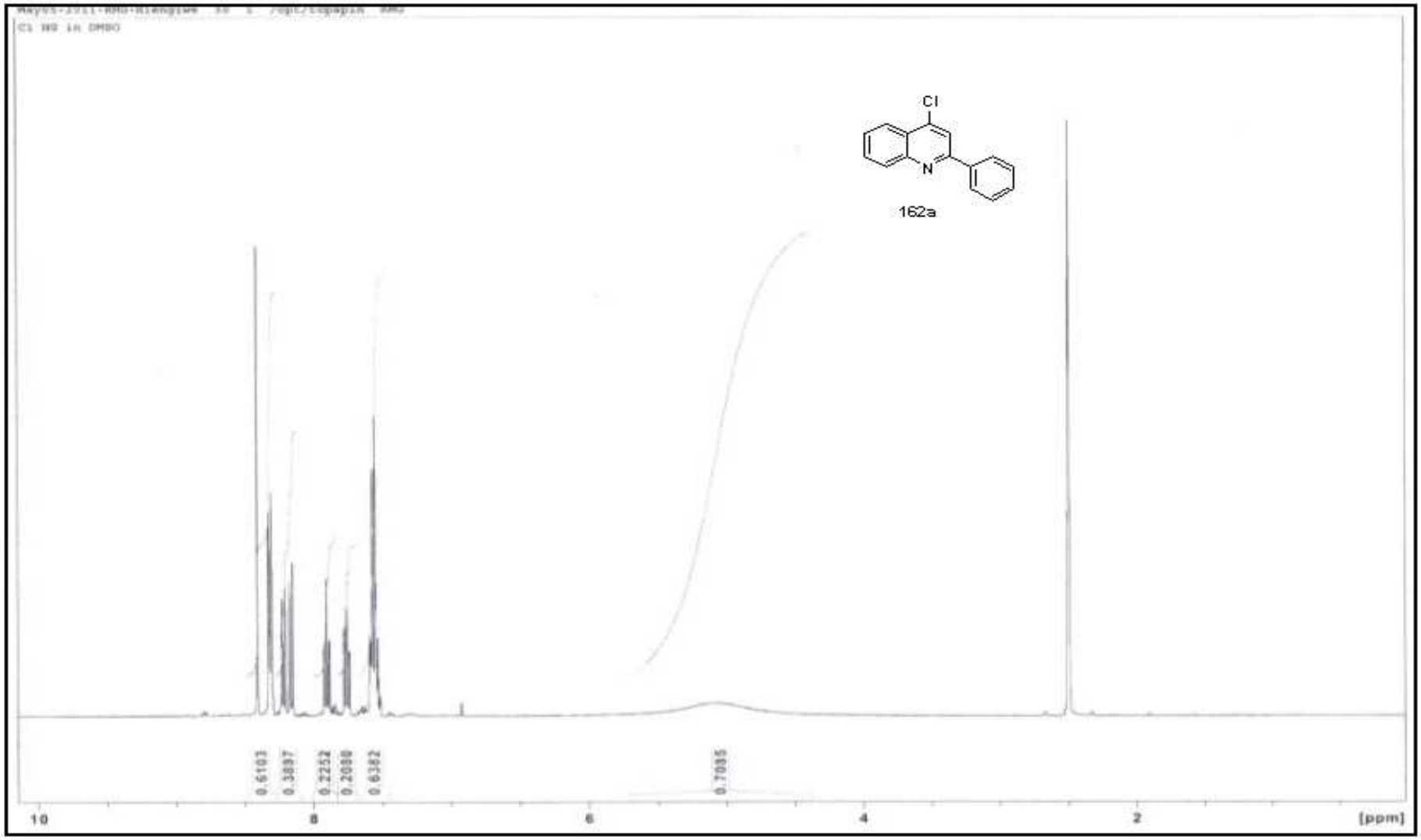


Figure 18: ^{1}H NMR Spectrum of 4 – chloro – 2 phenylquinoline 162a

Appendix 16

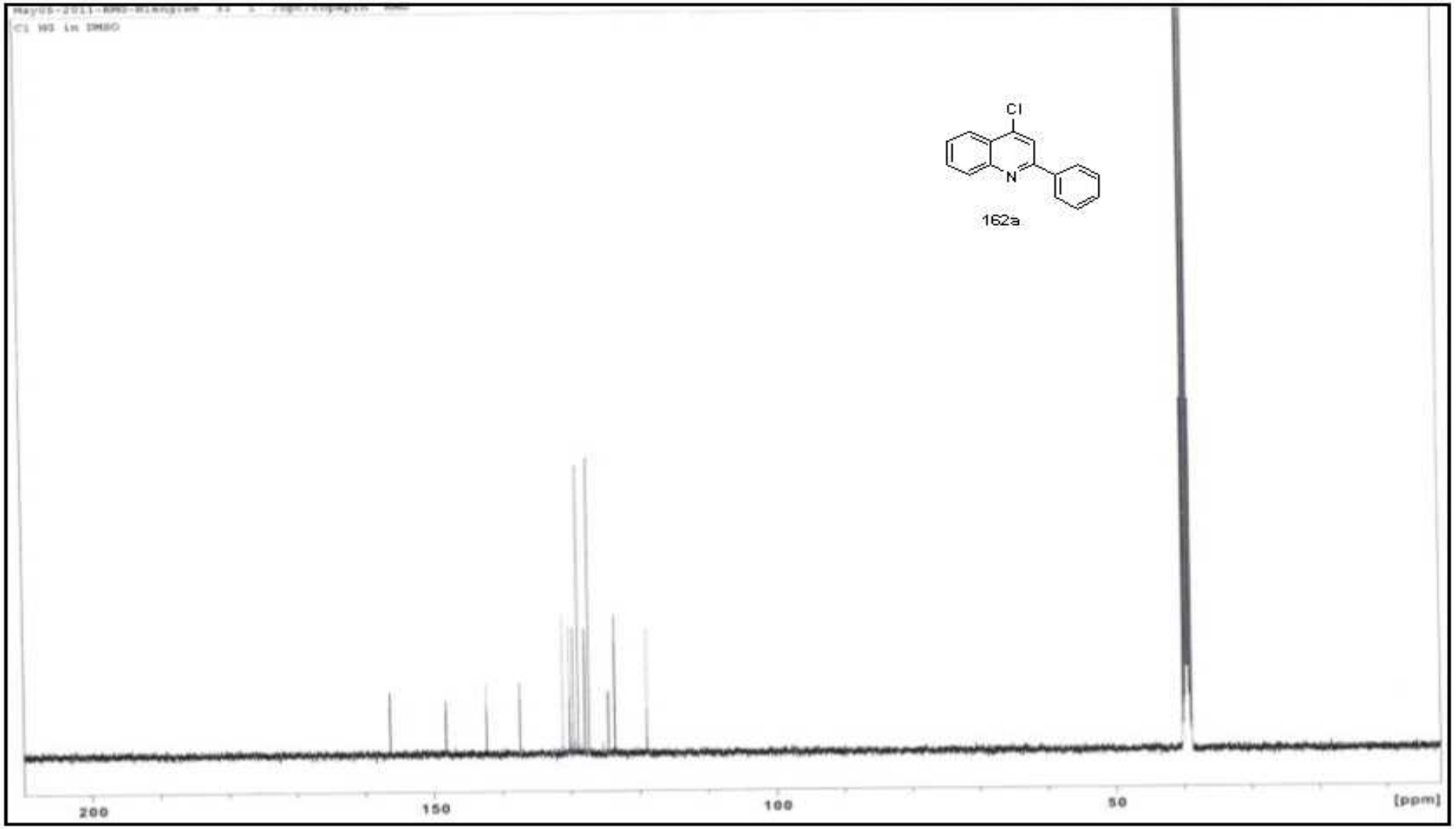


Figure 19: ^{13}C NMR Spectrum of 4 – chloro – 2 phenylquinoline 162a

Appendix 17

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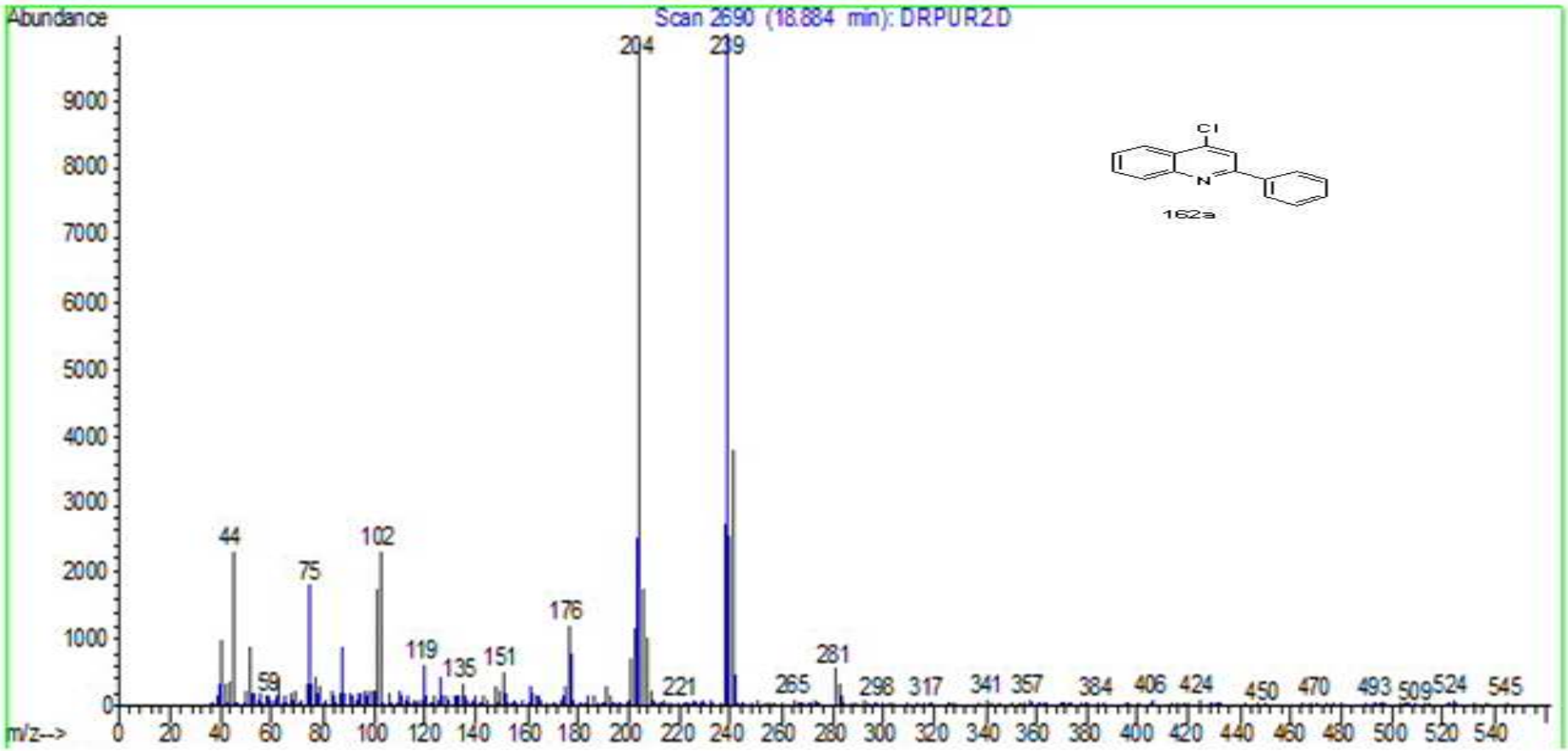

Figure 20: Mass spectrum of 4 – chloro – 2 – phenylquinoline 162a

Appendix 18

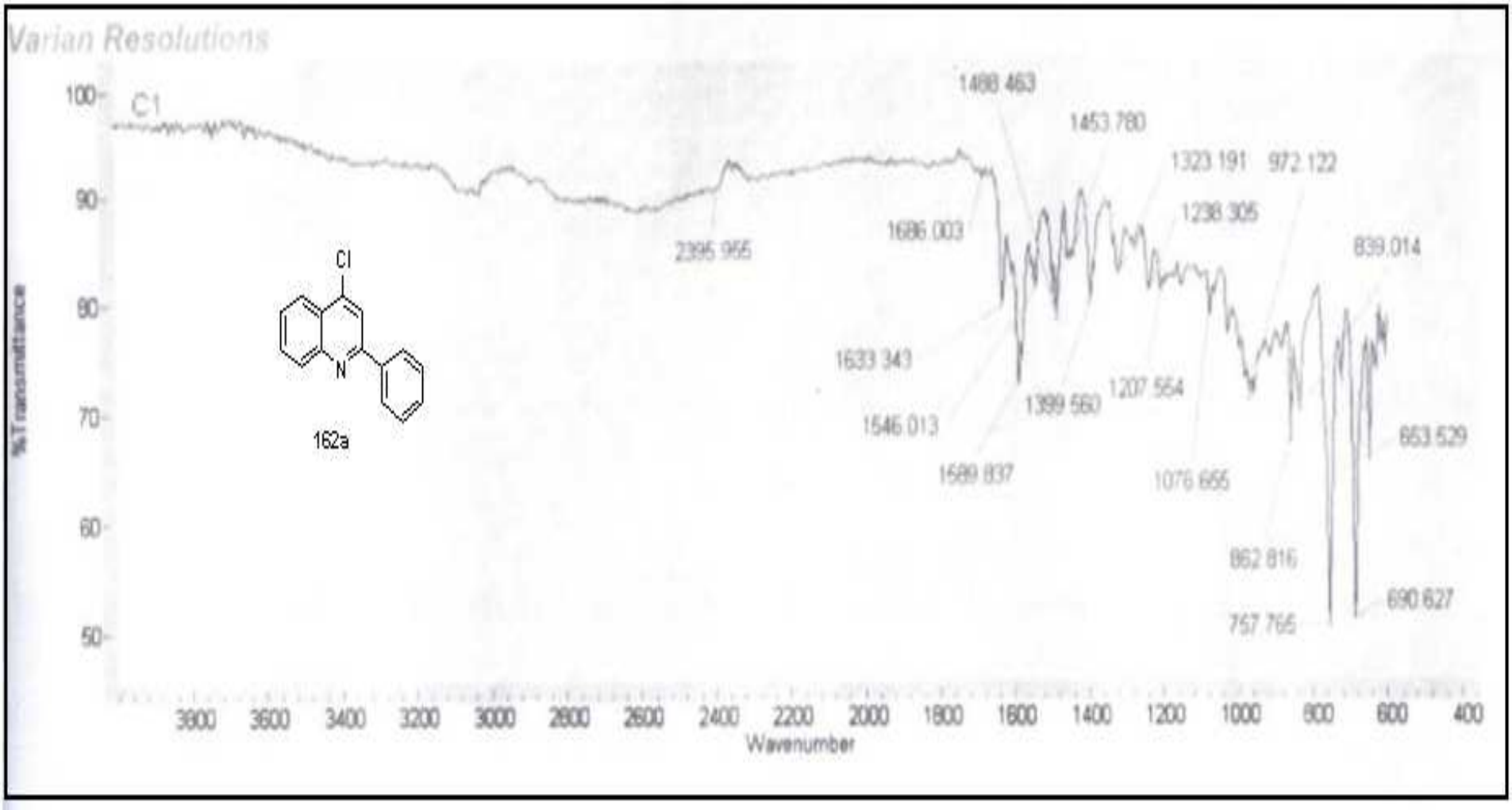

Figure 21: IR Spectrum of 4 – chloro – 2 – phenylquinoline 162a

Appendix 19

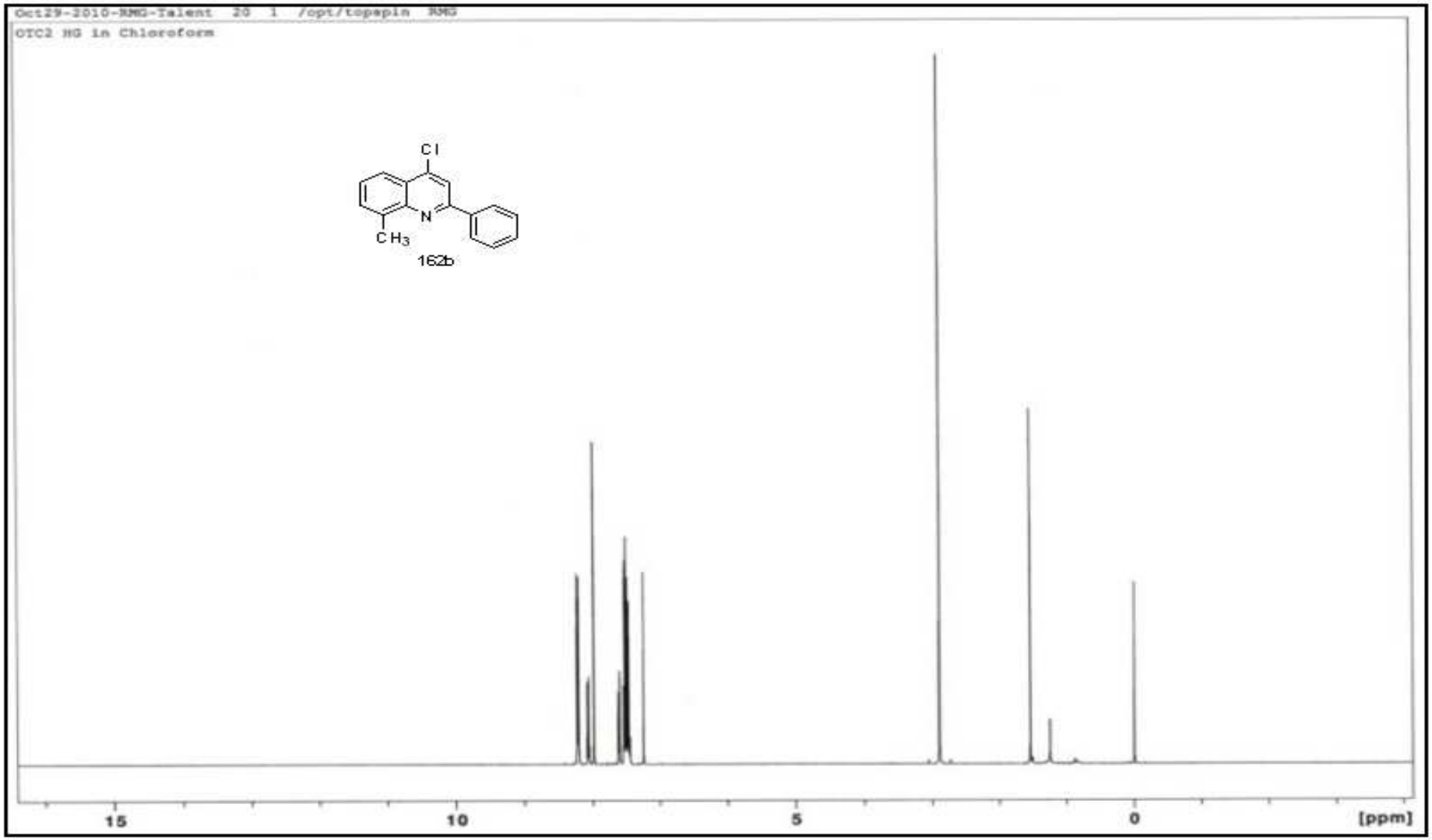

Figure 22: ^{1}H NMR Spectrum of 4 – chloro – 8 – methyl – 2 – phenylquinoline 162b

Appendix 20

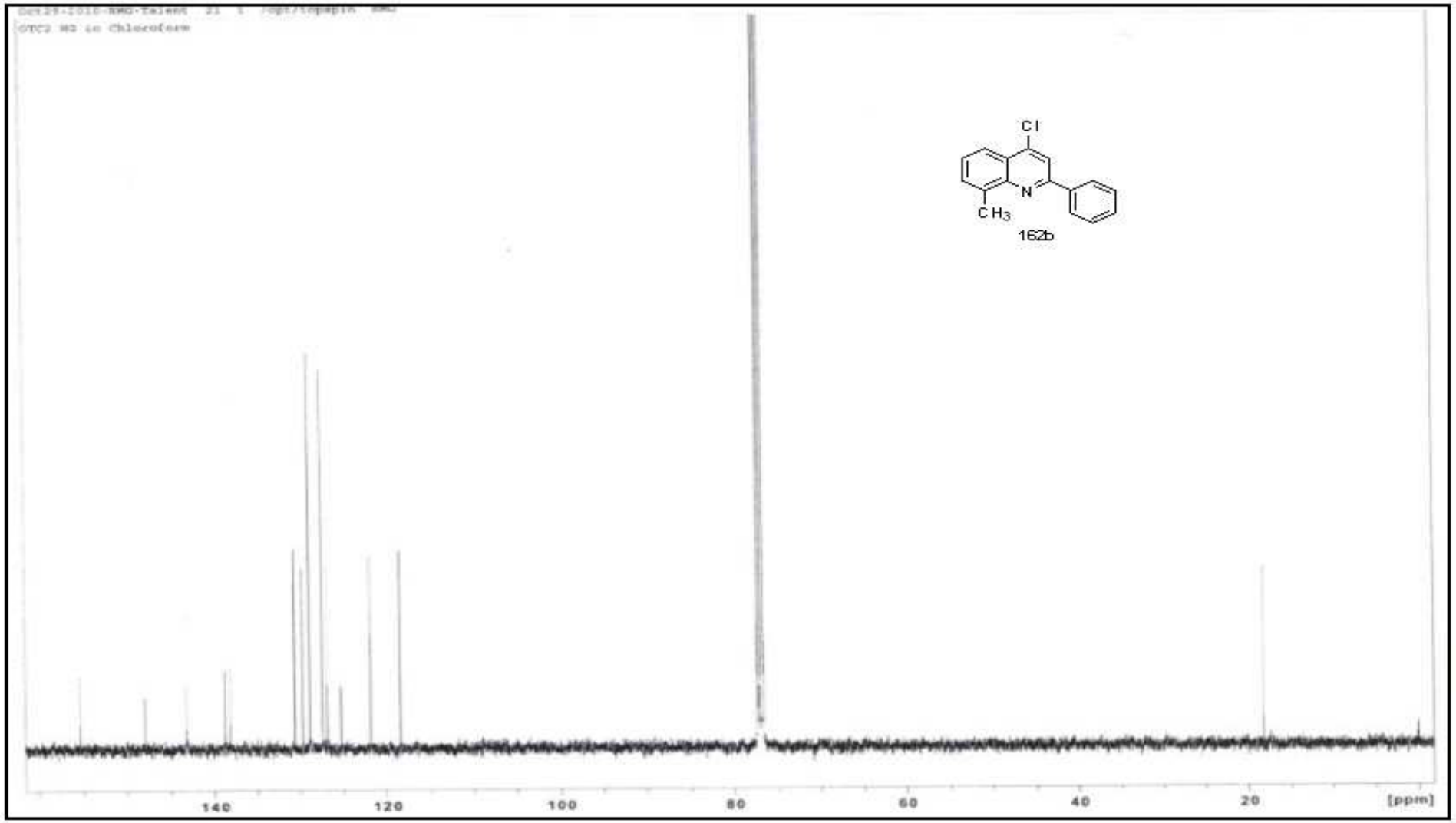

Figure 23: ^{13}C NMR Spectrum of 4 – chloro – 8 – methyl – 2 – phenylquinoline 162b

Appendix 21

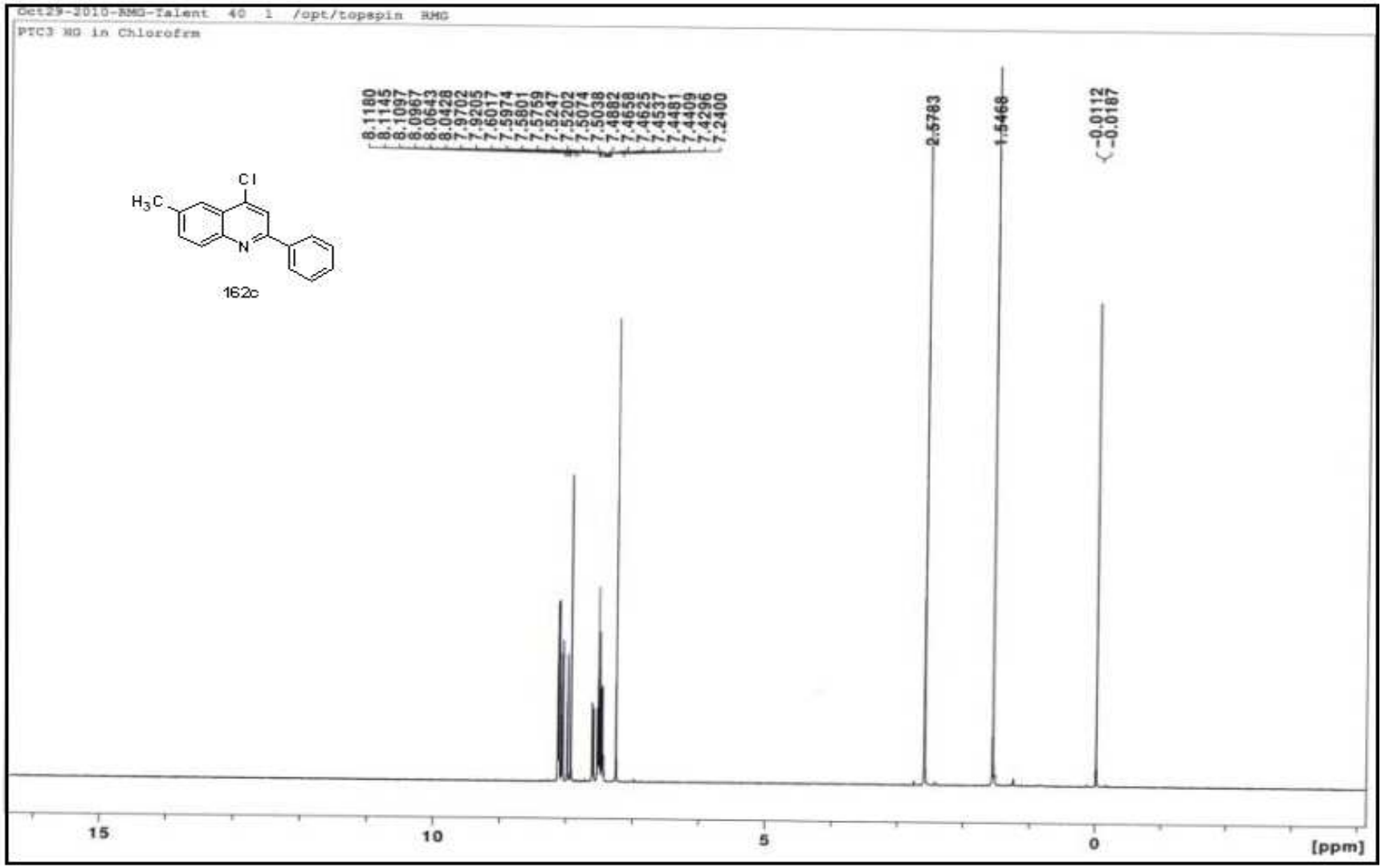

Figure 24: ^{1}H NMR Spectrum of 4 – chloro – 6 – methyl – 2 – phenylquinoline 162c

Appendix 22

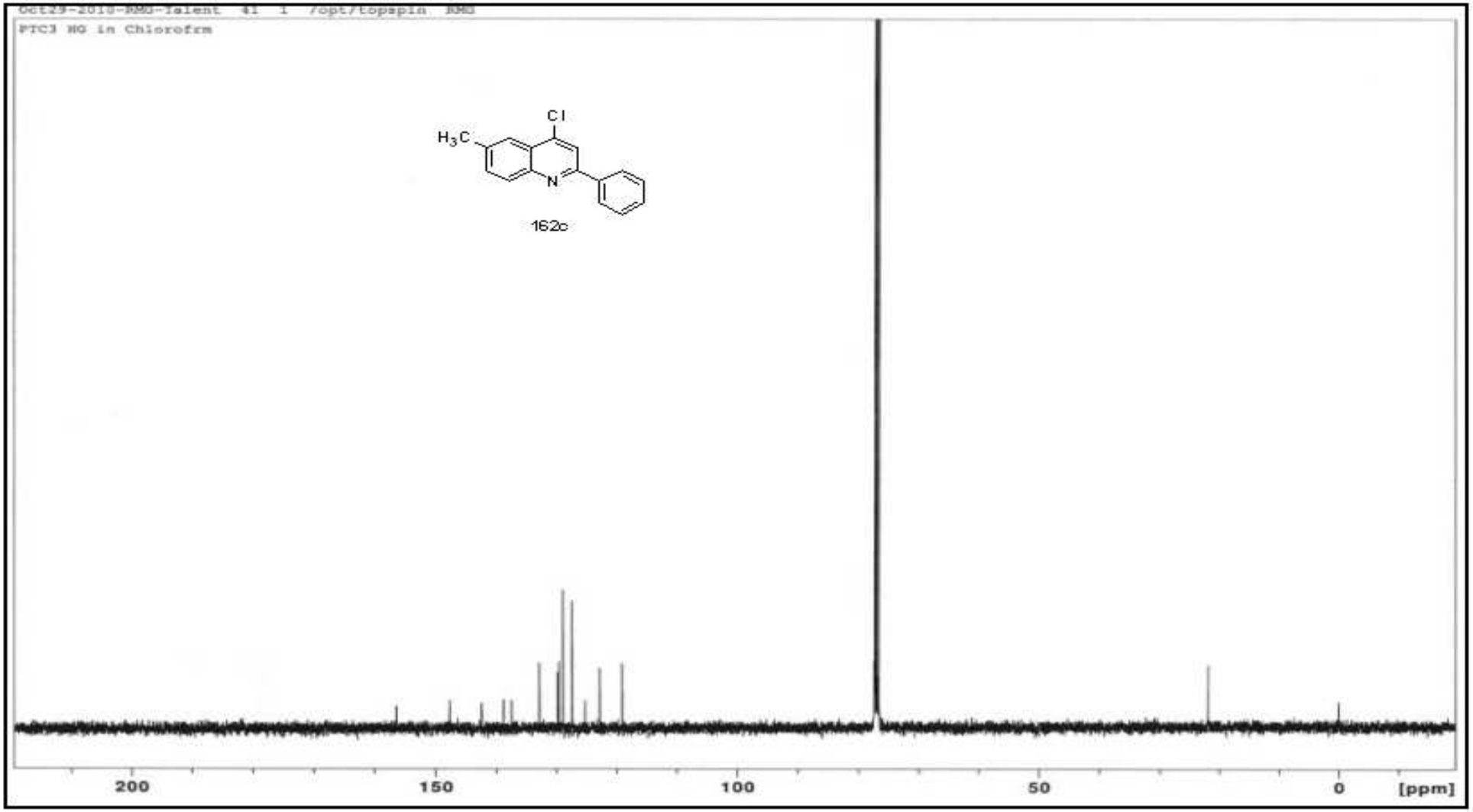

Figure 25:^{13}C NMR Spectrum of 4 – chloro – 6 – methyl – 2 – phenylquinoline 162c

Appendix 23

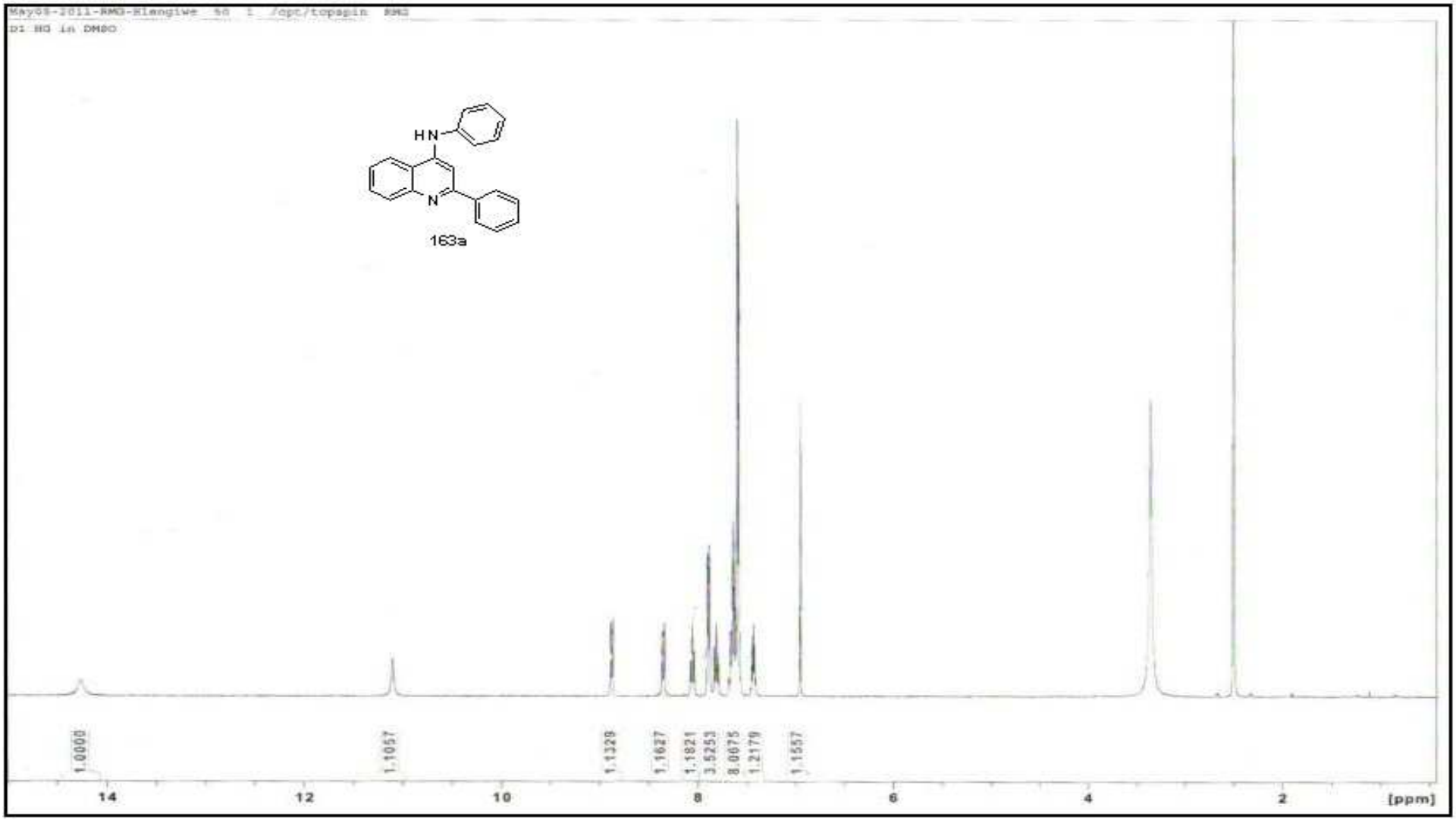

Figure 26: ^{1}**H NMR Spectrum of 4 – (N - phenyl) – 2- phenyl – 4 – aminoquinoline 163a**

Appendix 24

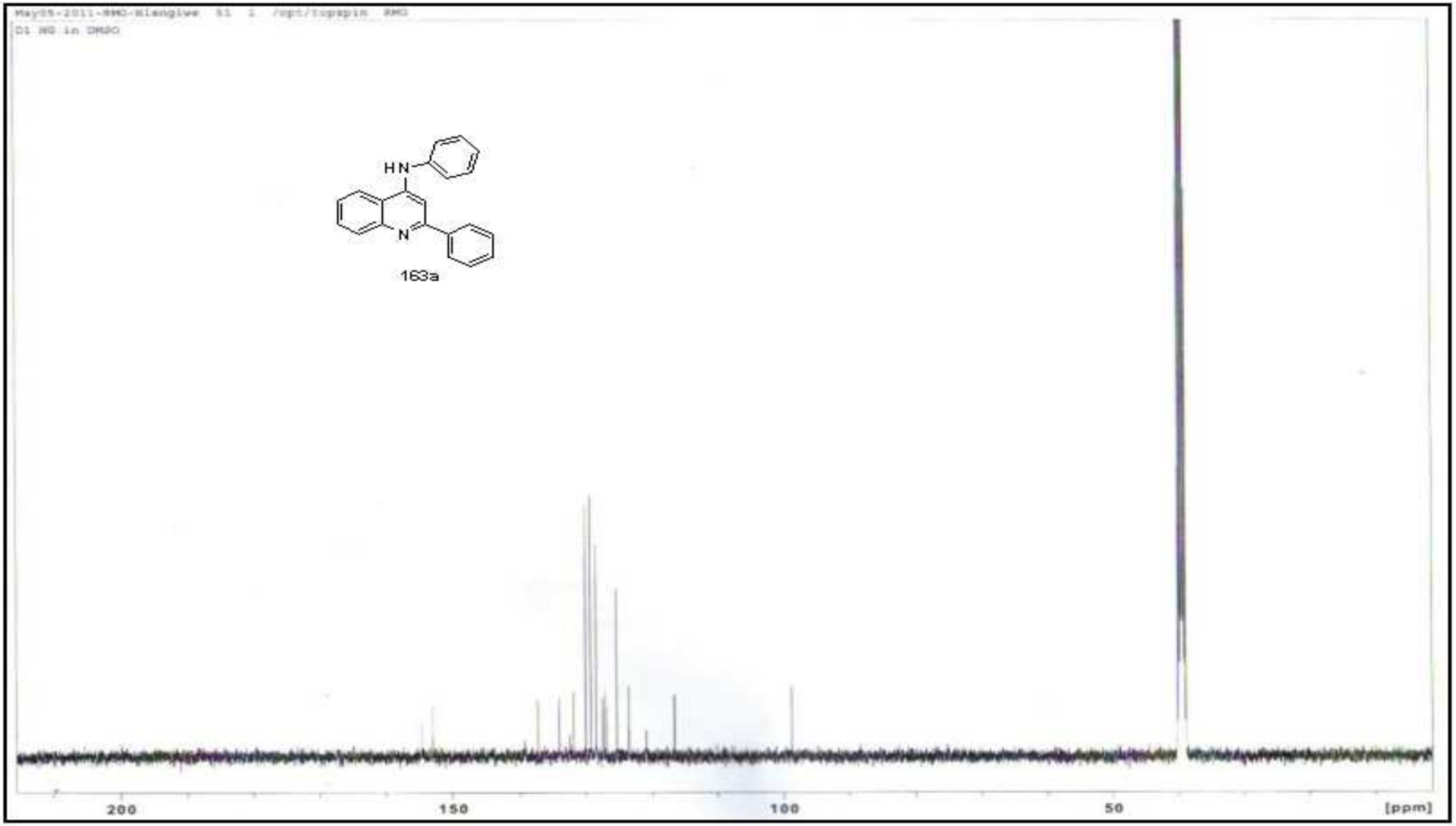

Figure 27: ^{13}C NMR Spectrum of 4 – (N - phenyl) – 2- phenyl – 4 – aminoquinoline 163a

Appendix 25

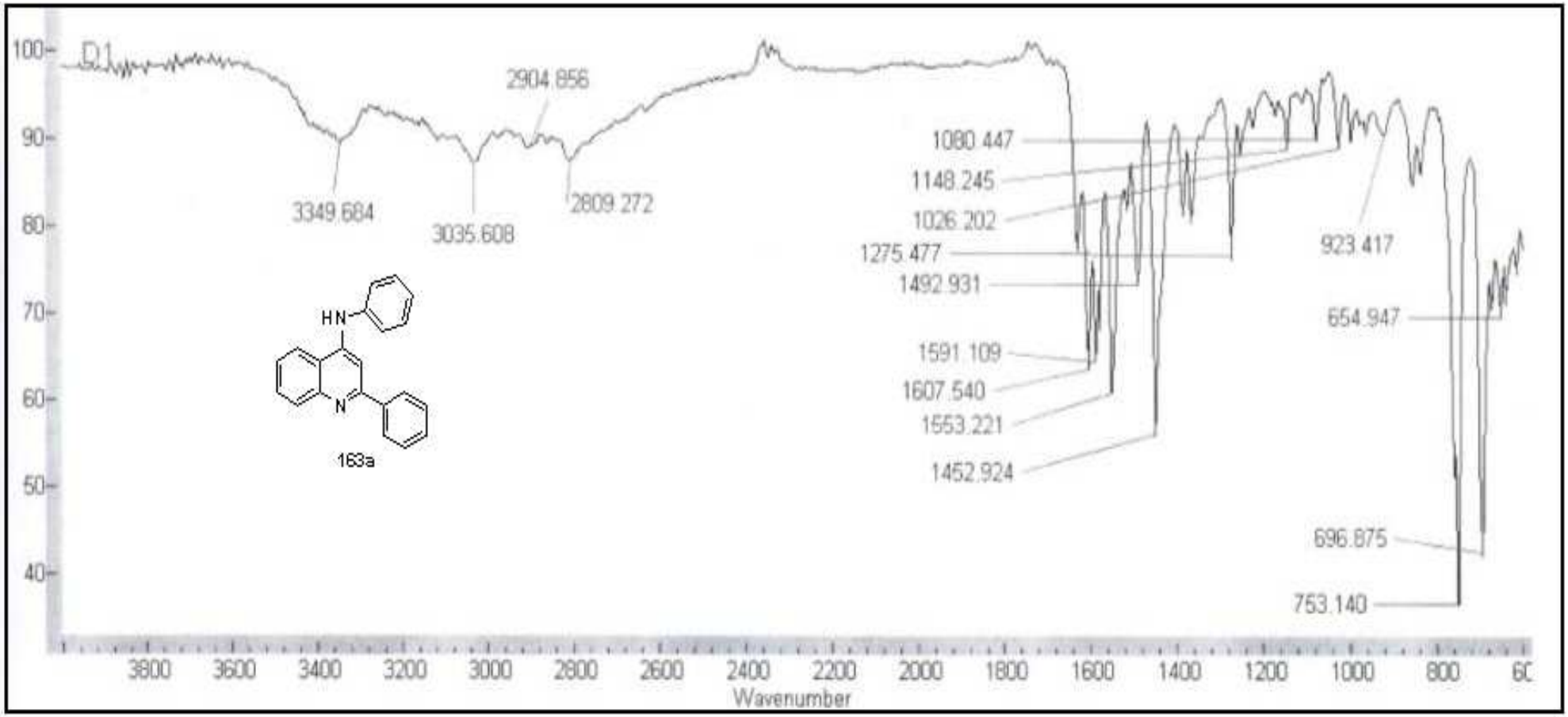

Figure 28: IR Spectrum of 4 – (N - phenyl) – 2- phenyl – 4 – aminoquinoline 163a

Appendix 26

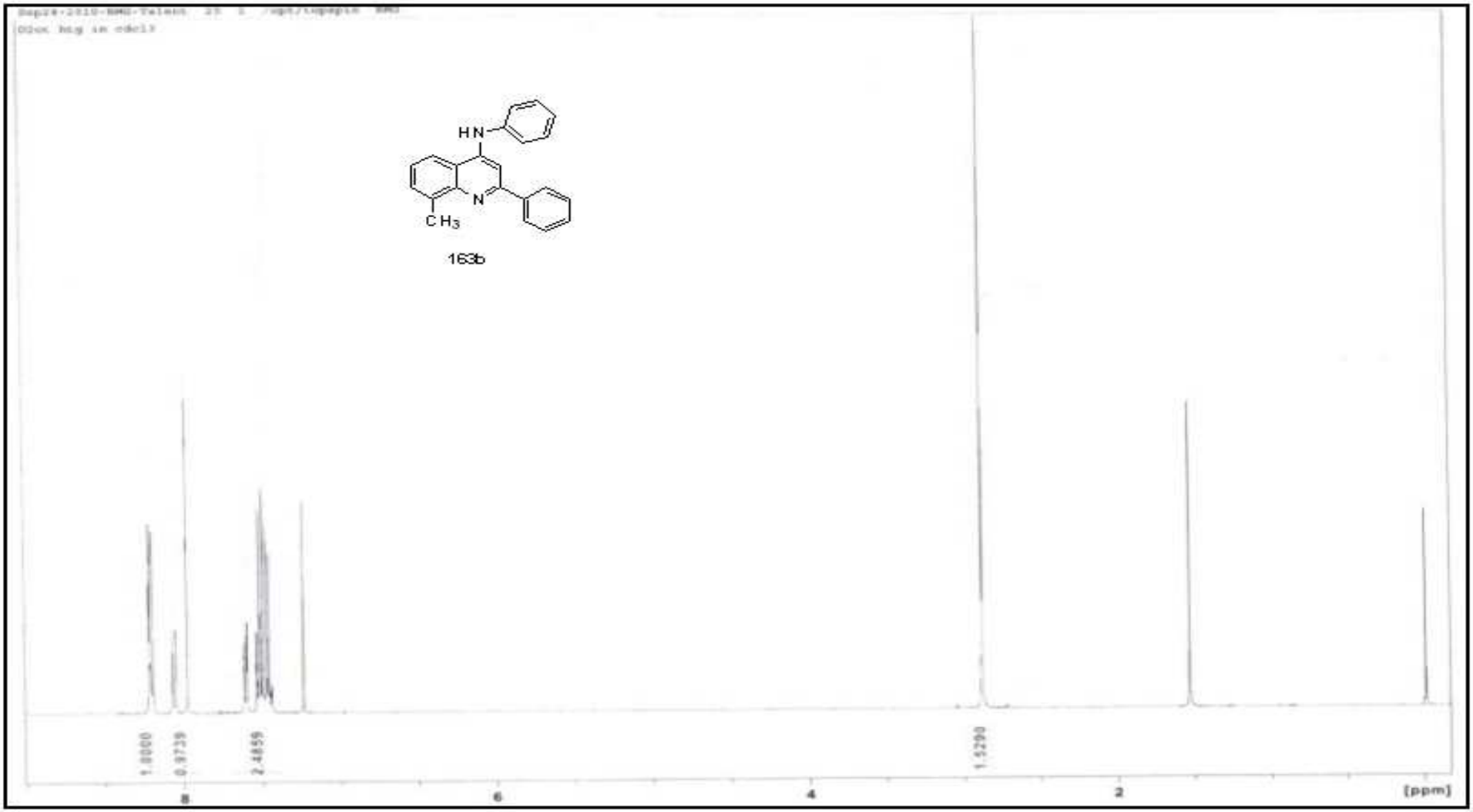

Figure 29: ^{1}H NMR Spectrum of 8 – methyl – 4 (N - phenyl) – 2 – phenyl – 4 – aminoquinoline 163b

Appendix 27

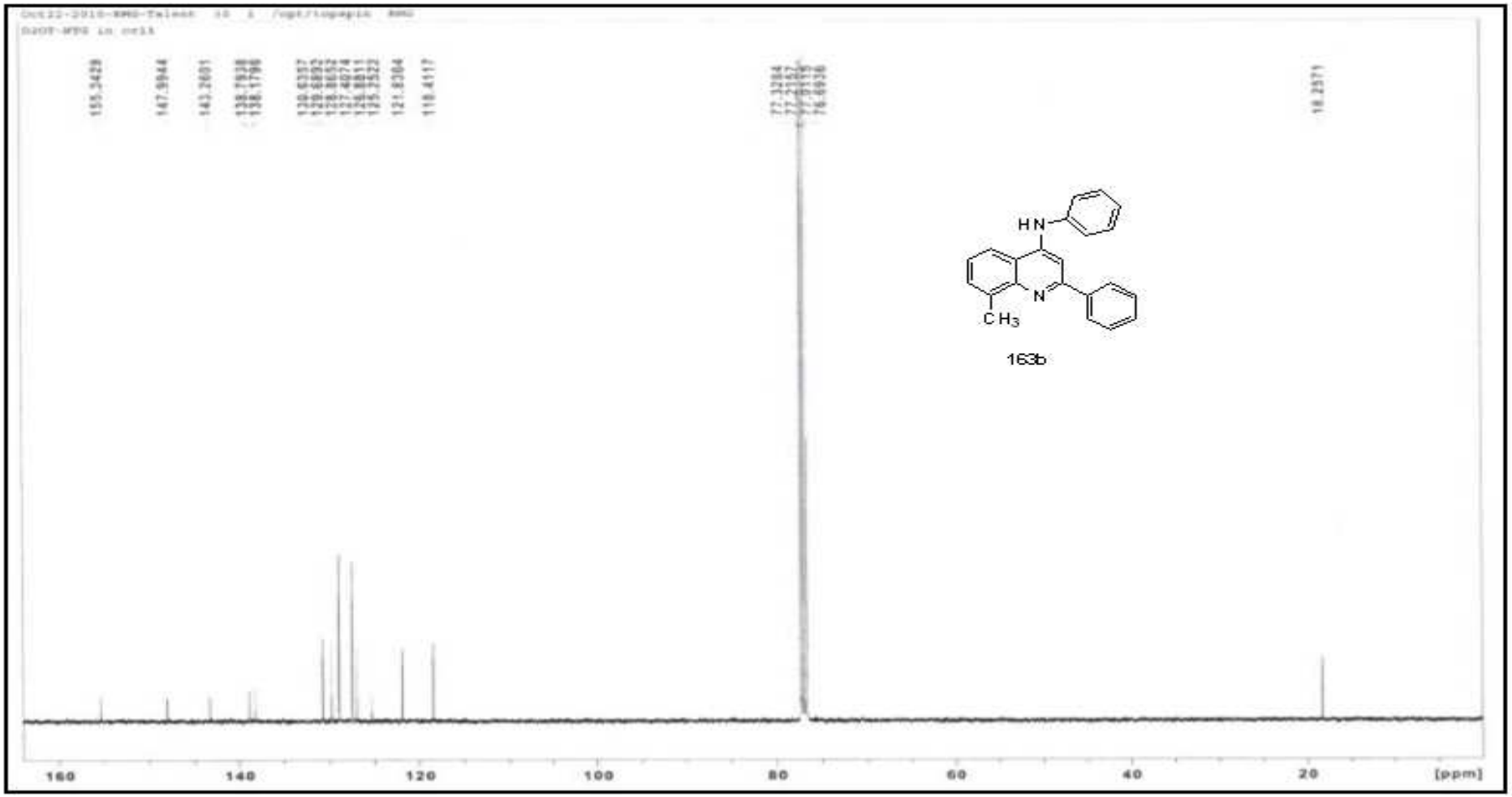

Figure 30: ^{13}C NMR Spectrum of 8 – methyl – 4 (N - phenyl) – 2 – phenyl – 4 – aminoquinoline 163b

Appendix 28

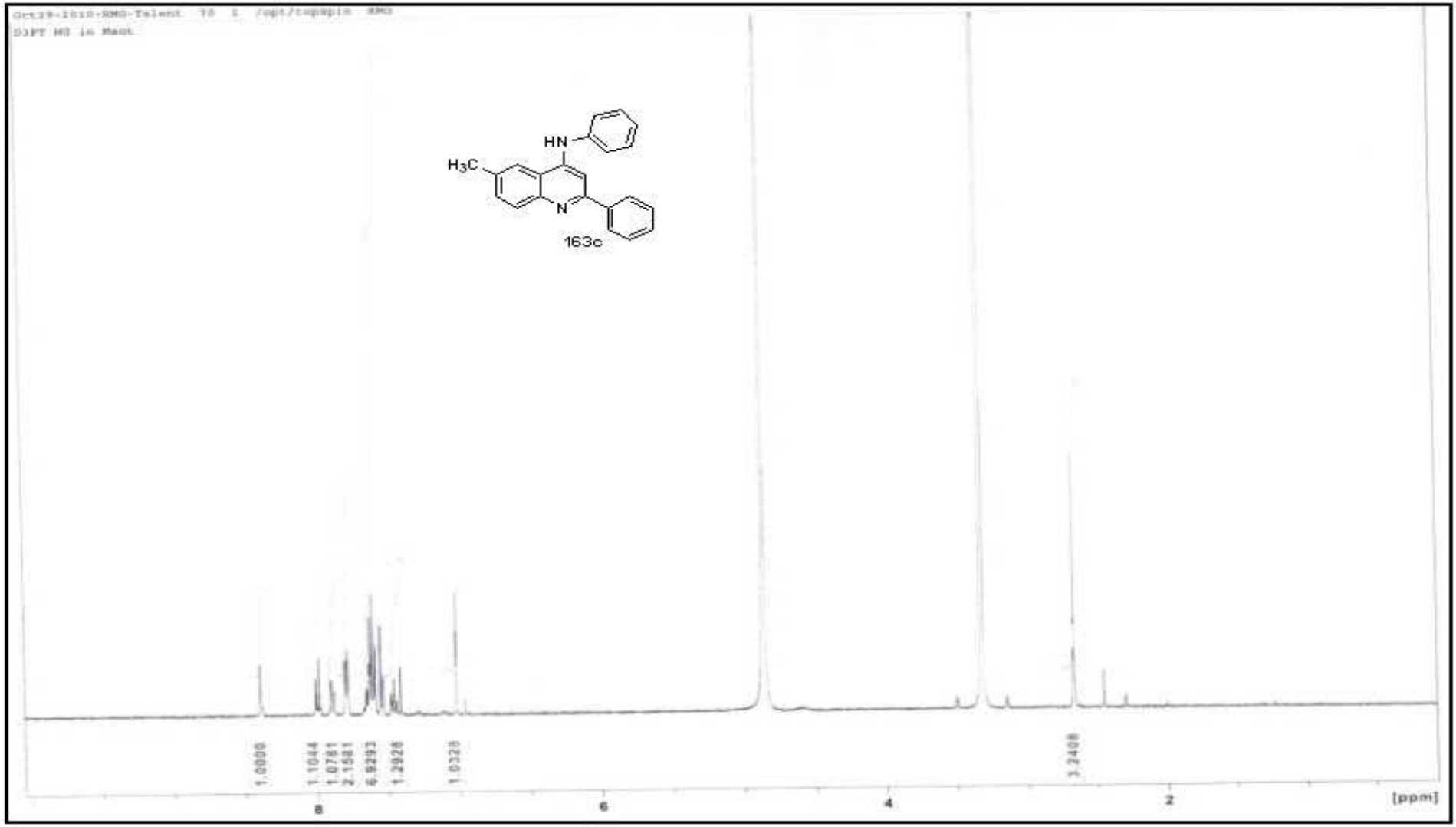

Figure 31: ^{1}H NMR Spectrum of 6 – methyl – 4 – (N - phenyl) – 2 – phenyl – 4 – amonoquinoline 163c

Appendix 29

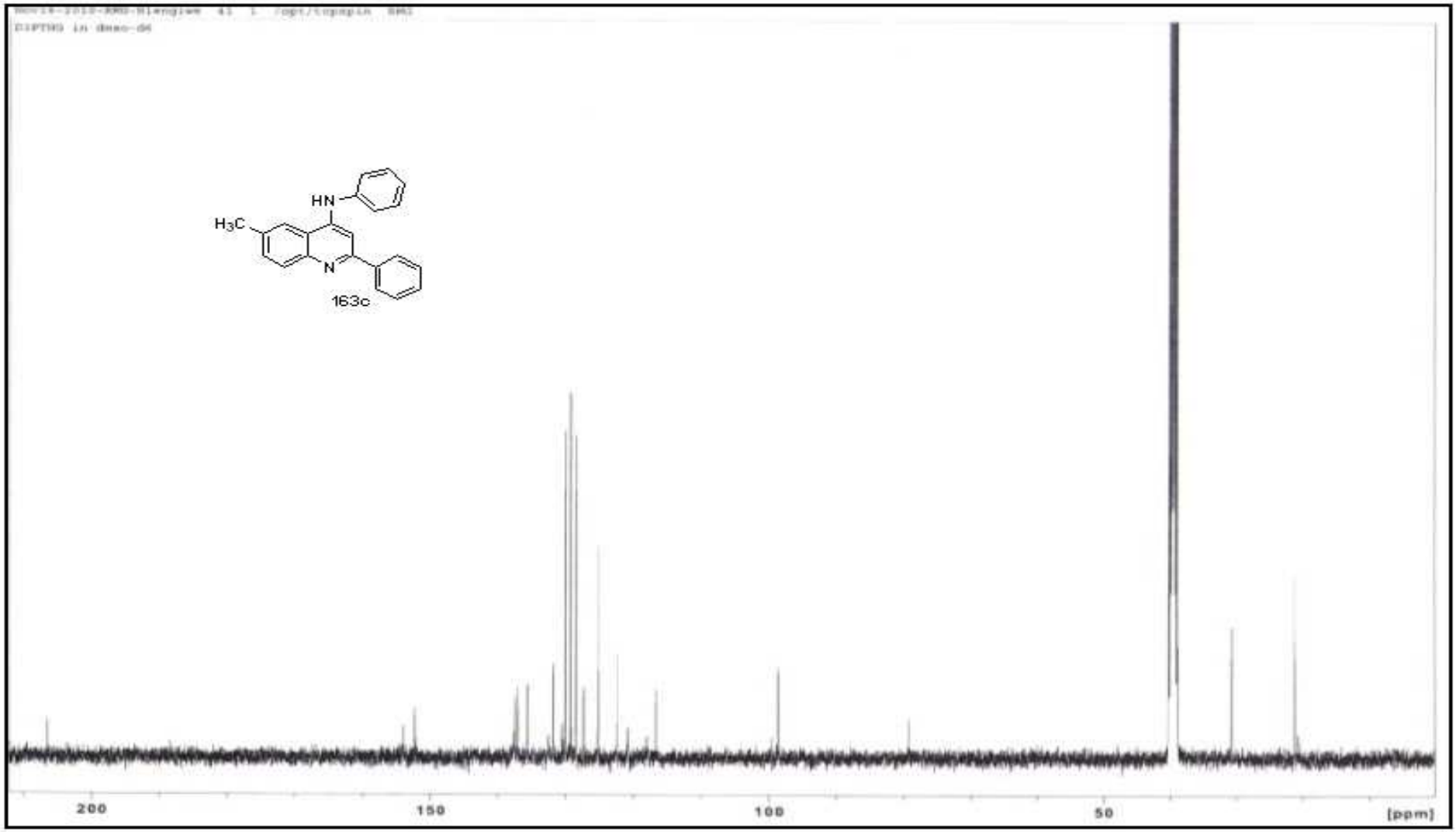

Figure 32: ^{13}C NMR Spectrum of 6 – methyl – 4 – (N - phenyl) – 2 – phenyl – 4 – amonoquinoline 163c

Appendix 30

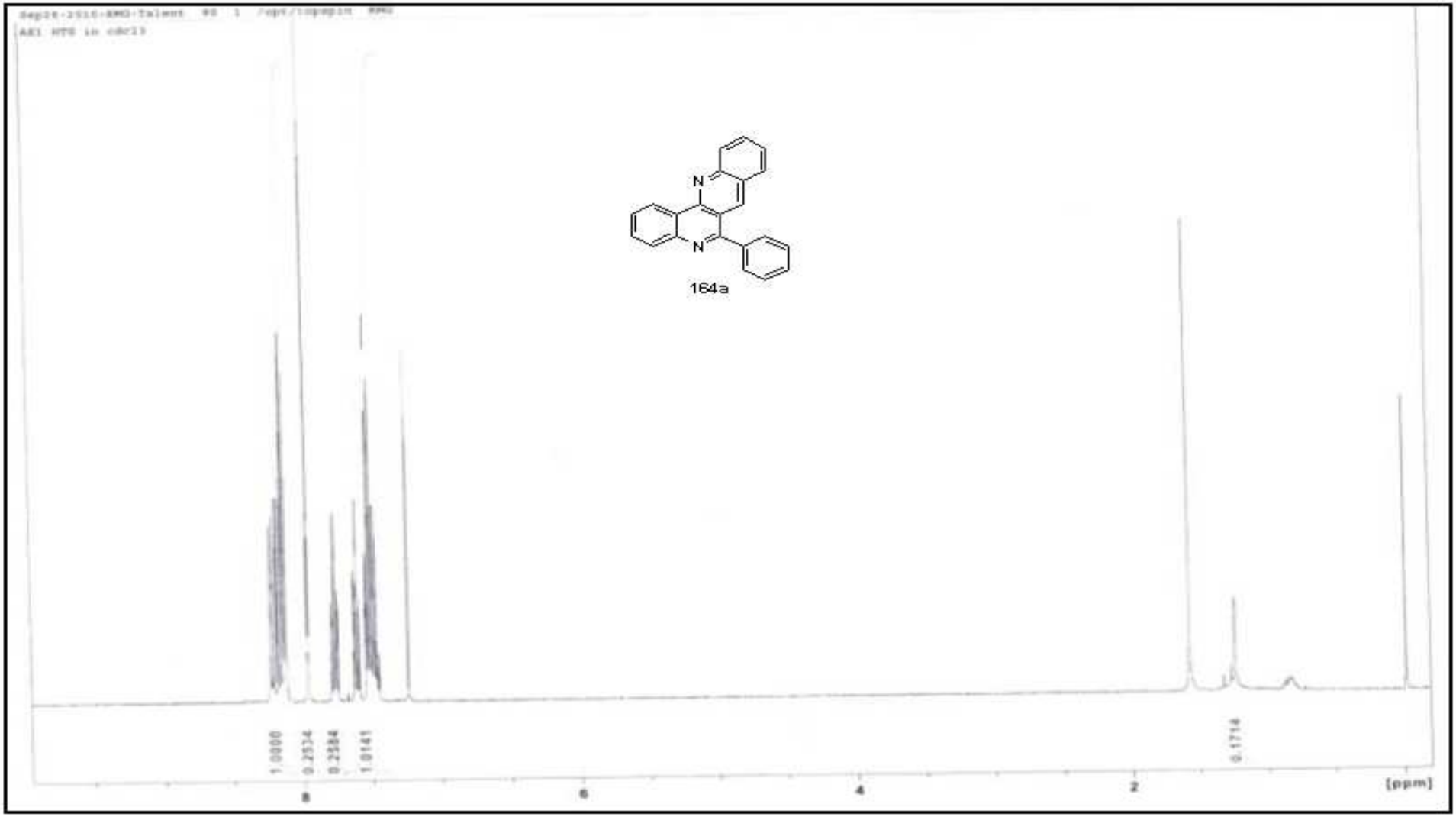

Figure 33: ^{1}H NMR Spectrum of 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164a

Appendix 31

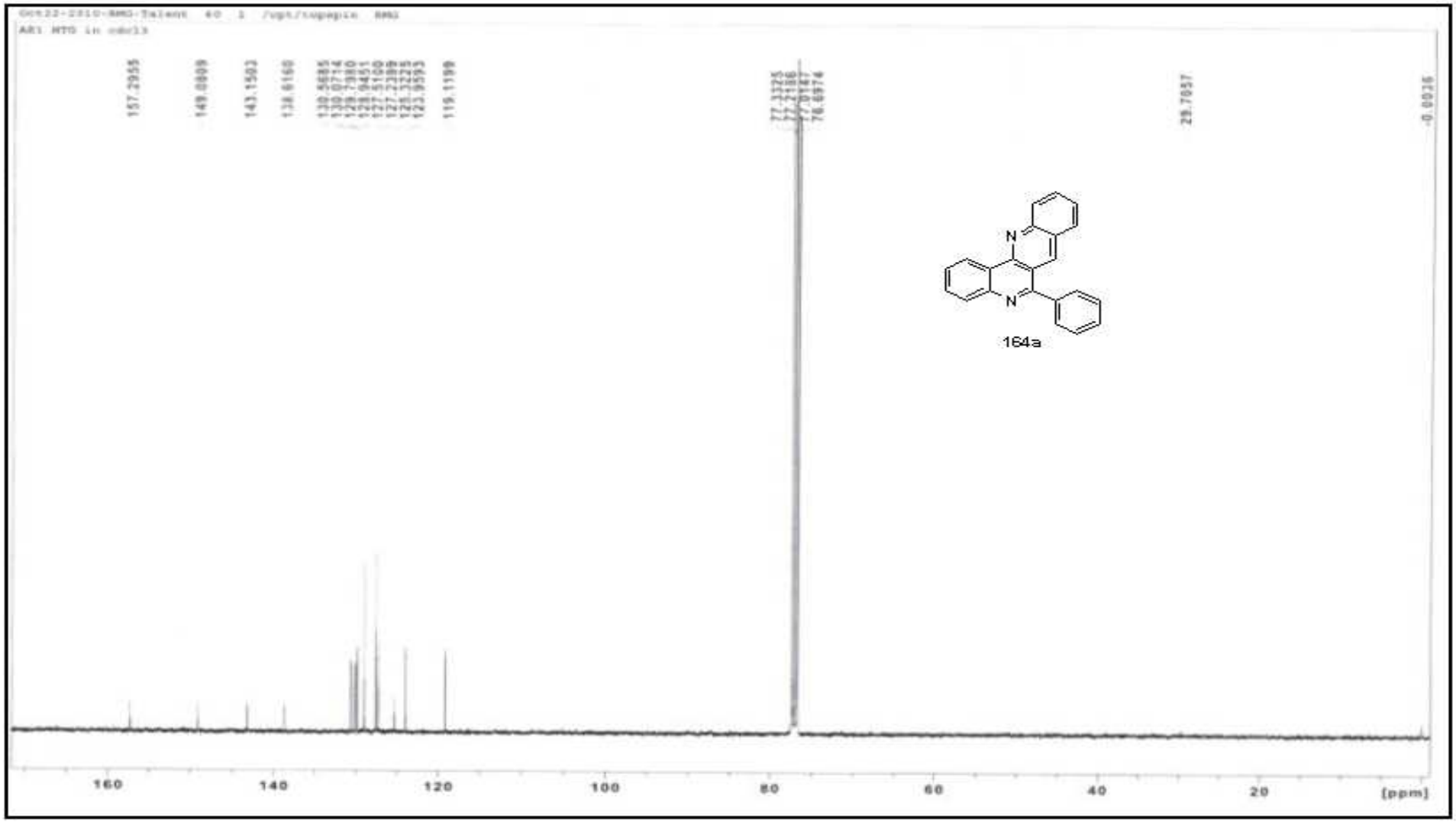

Figure 34: ^{13}C NMR Spectrum of 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164a

Appendix 32

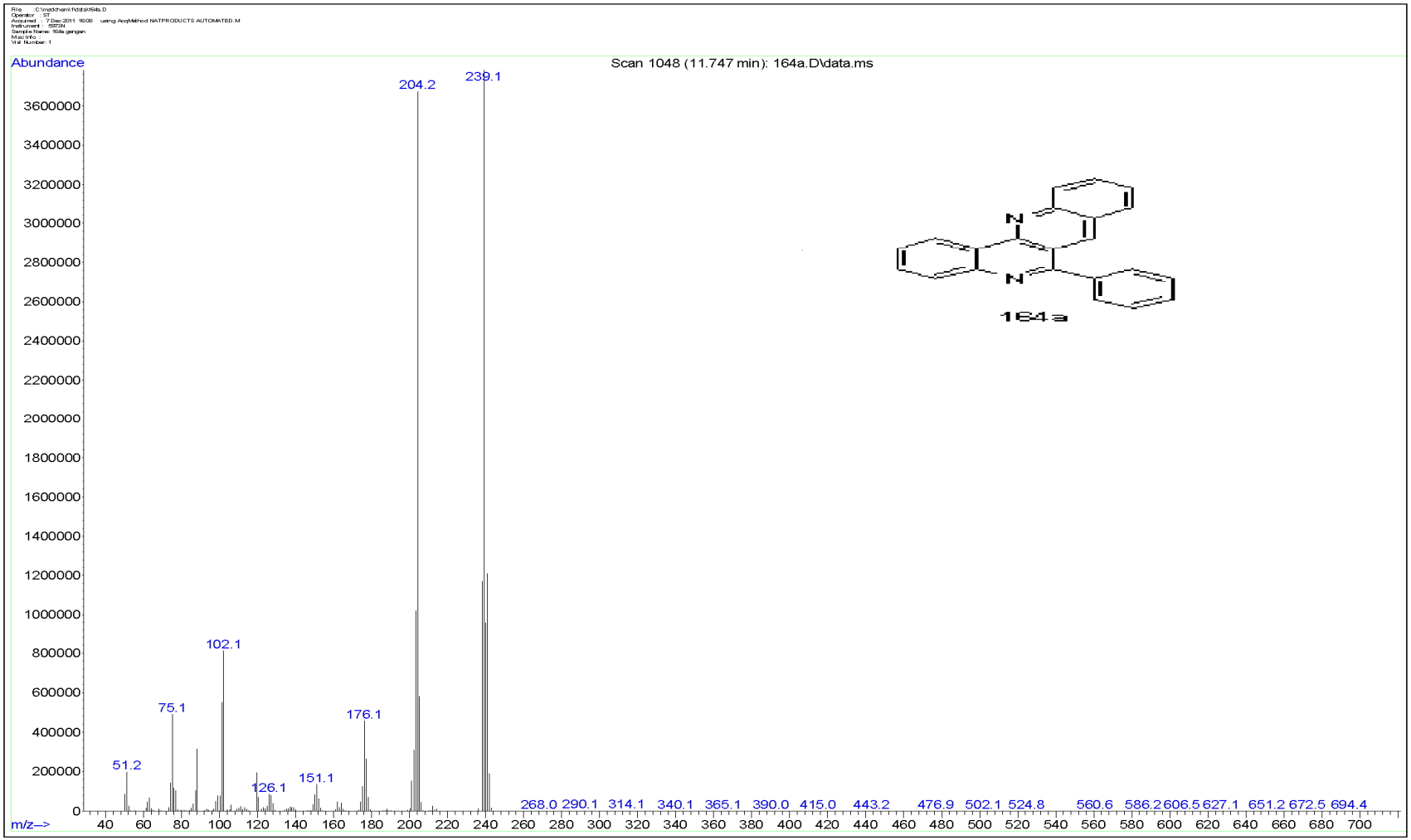

Figure 35: Mass spectrum of 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164a

Appendix 33

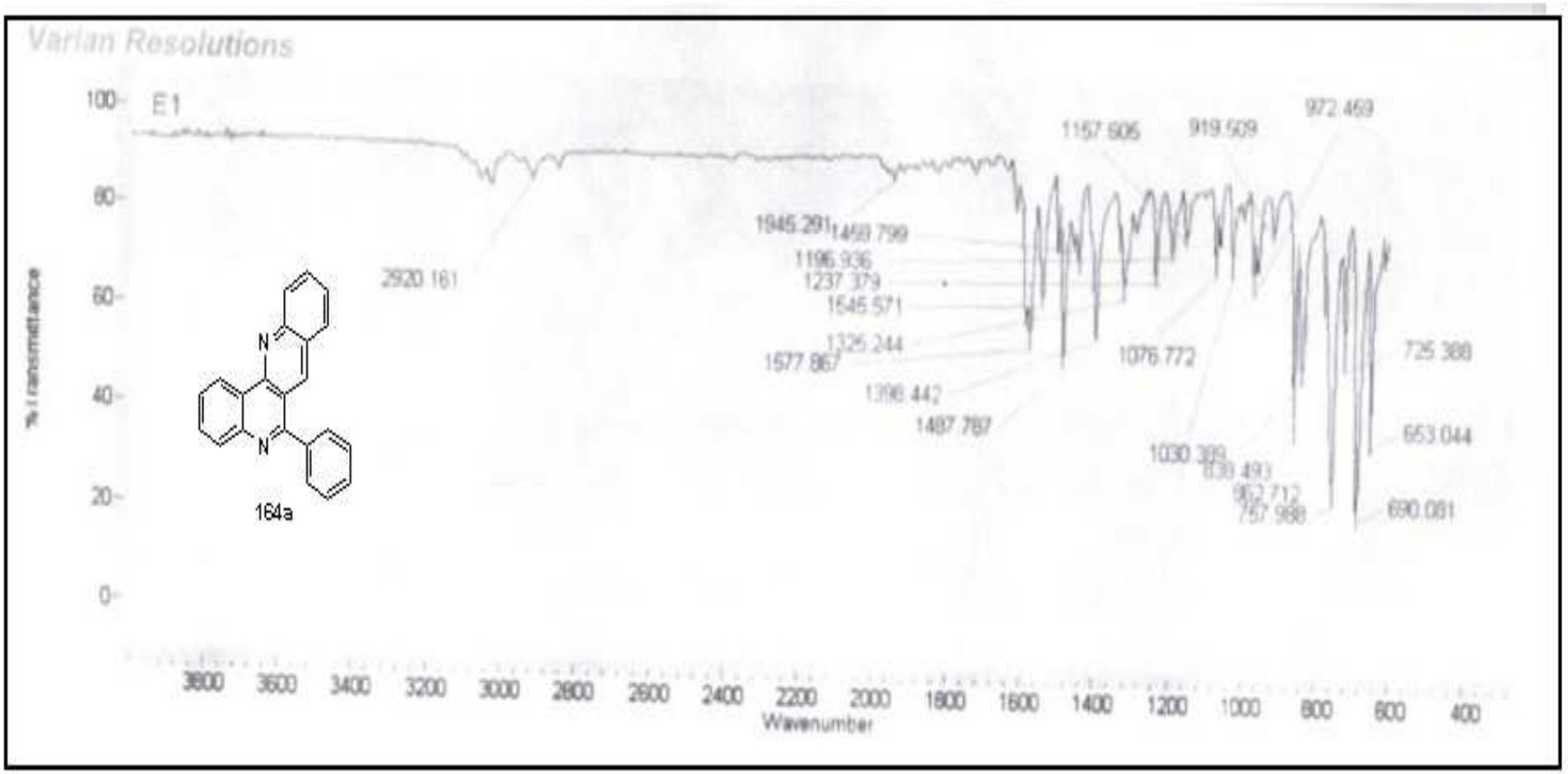

Figure 36: IR Spectrum of 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164a

Appendix 34

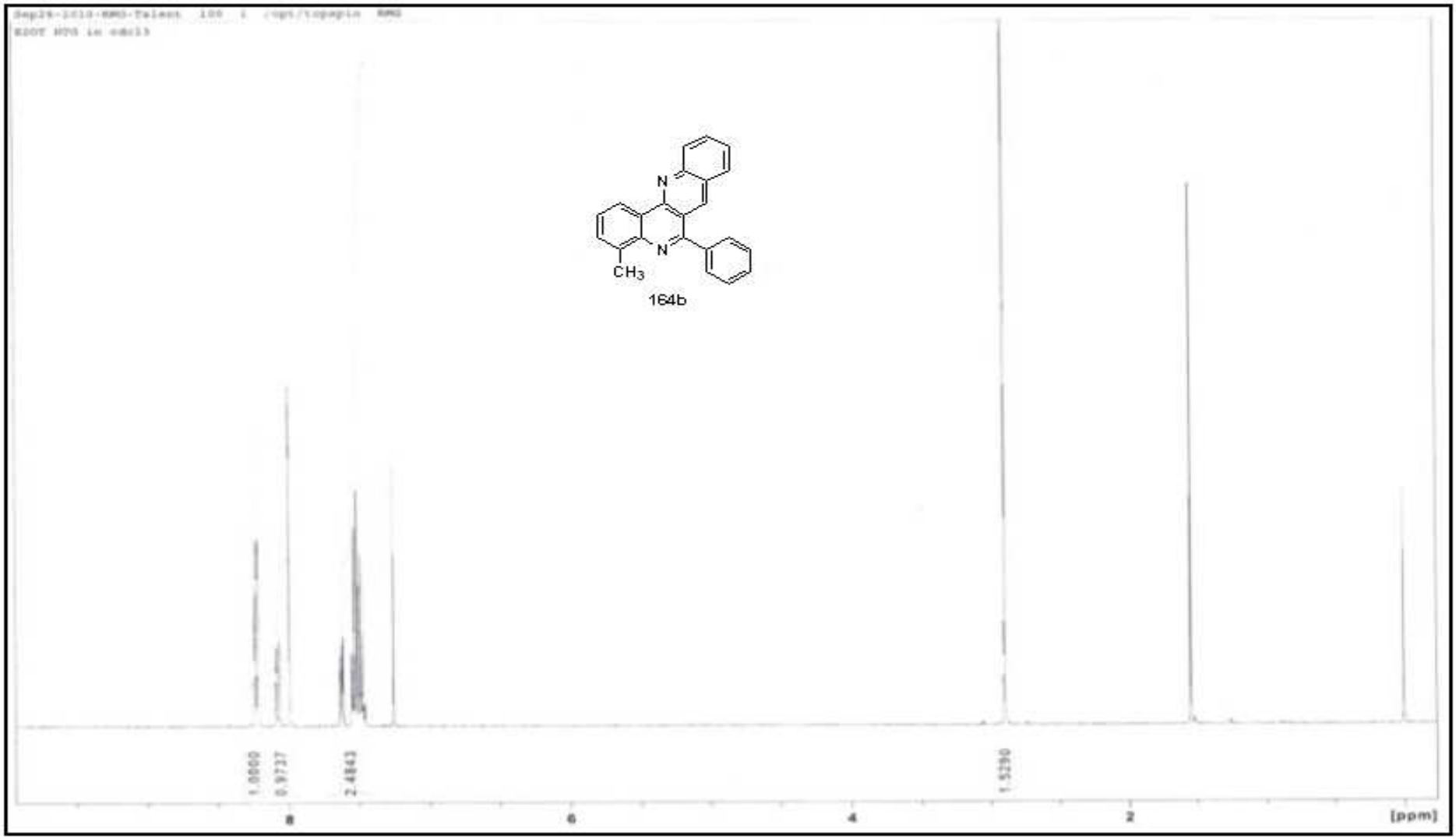

Figure 37: ^{1}H NMR Spectrum of 4 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164b

Appendix 35

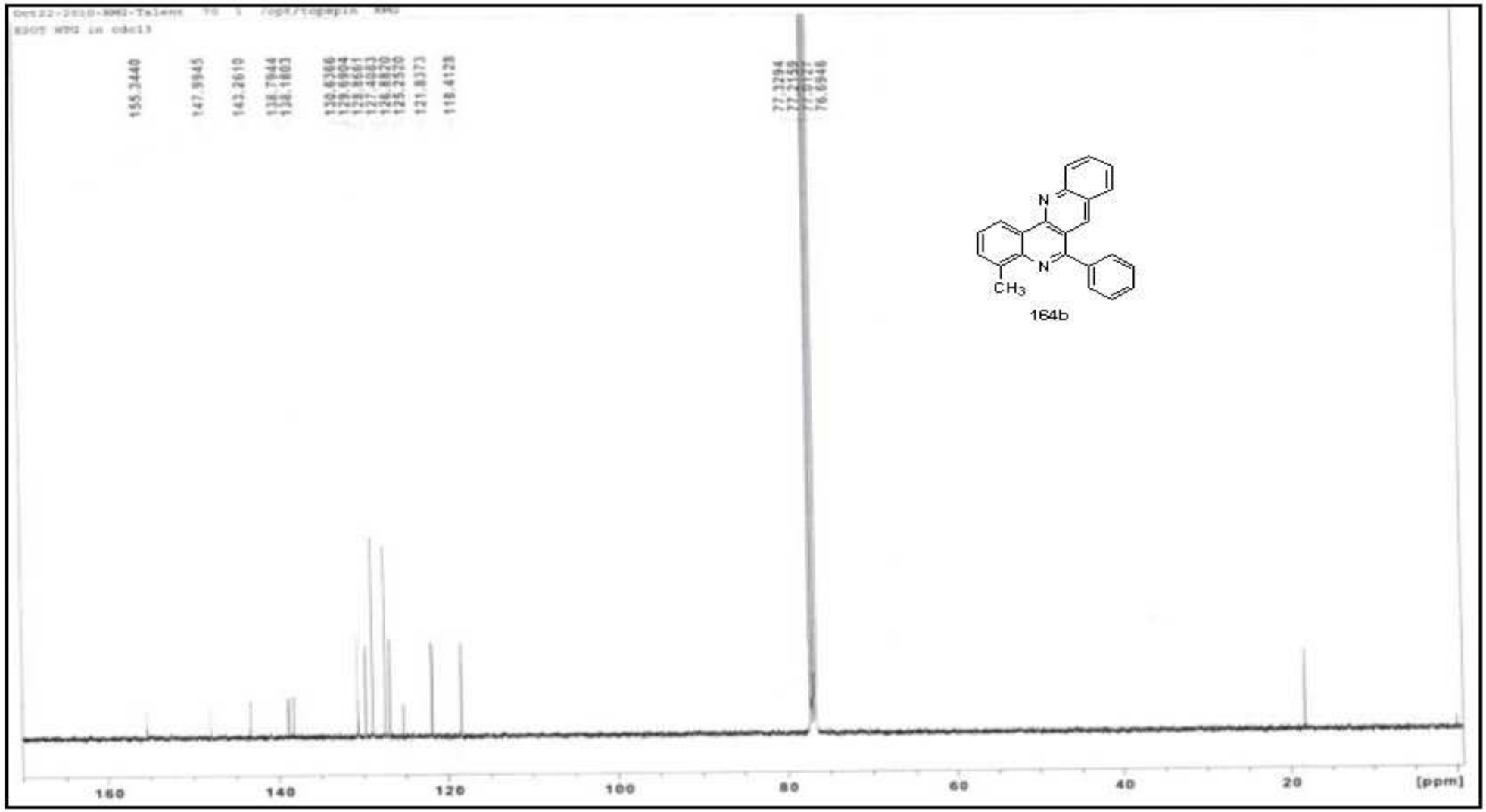

Figure 38: ^{13}C NMR Spectrum of 4 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164b

Appendix 36

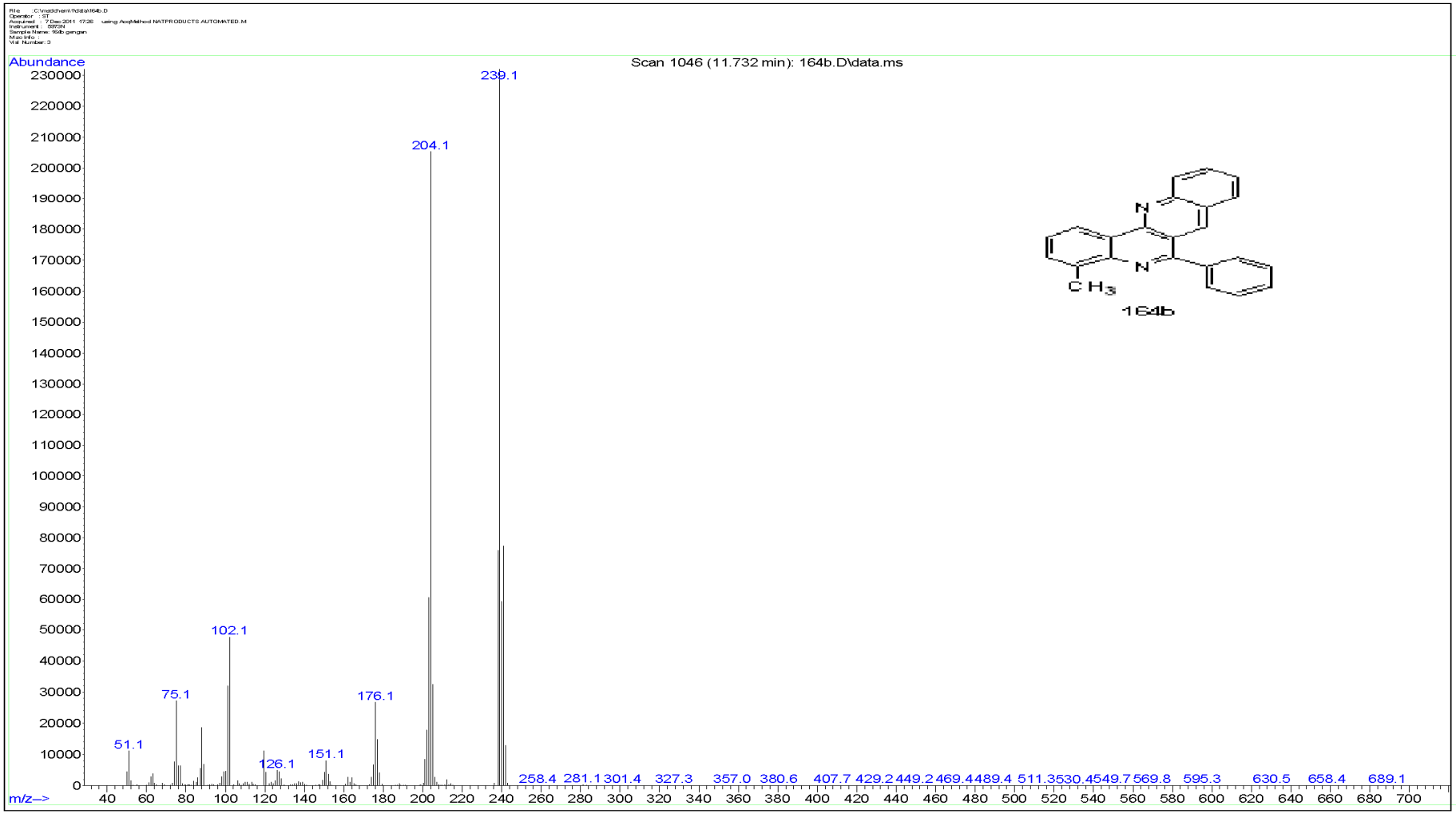

Figure 39: Mass spectrum of 4 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164b

Appendix 37

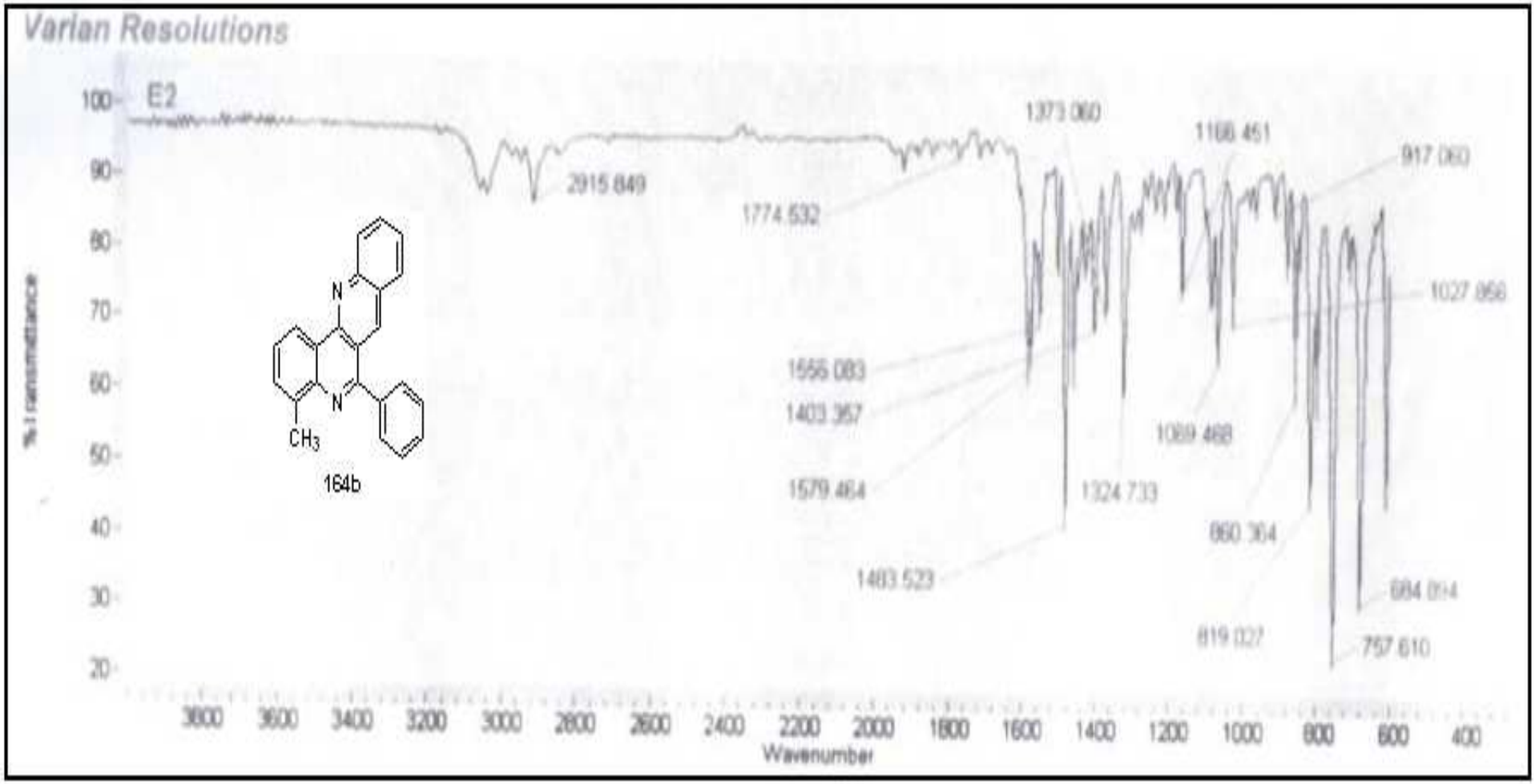

Figure 40: IR Spectrum of 4 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164b

Appendix 38

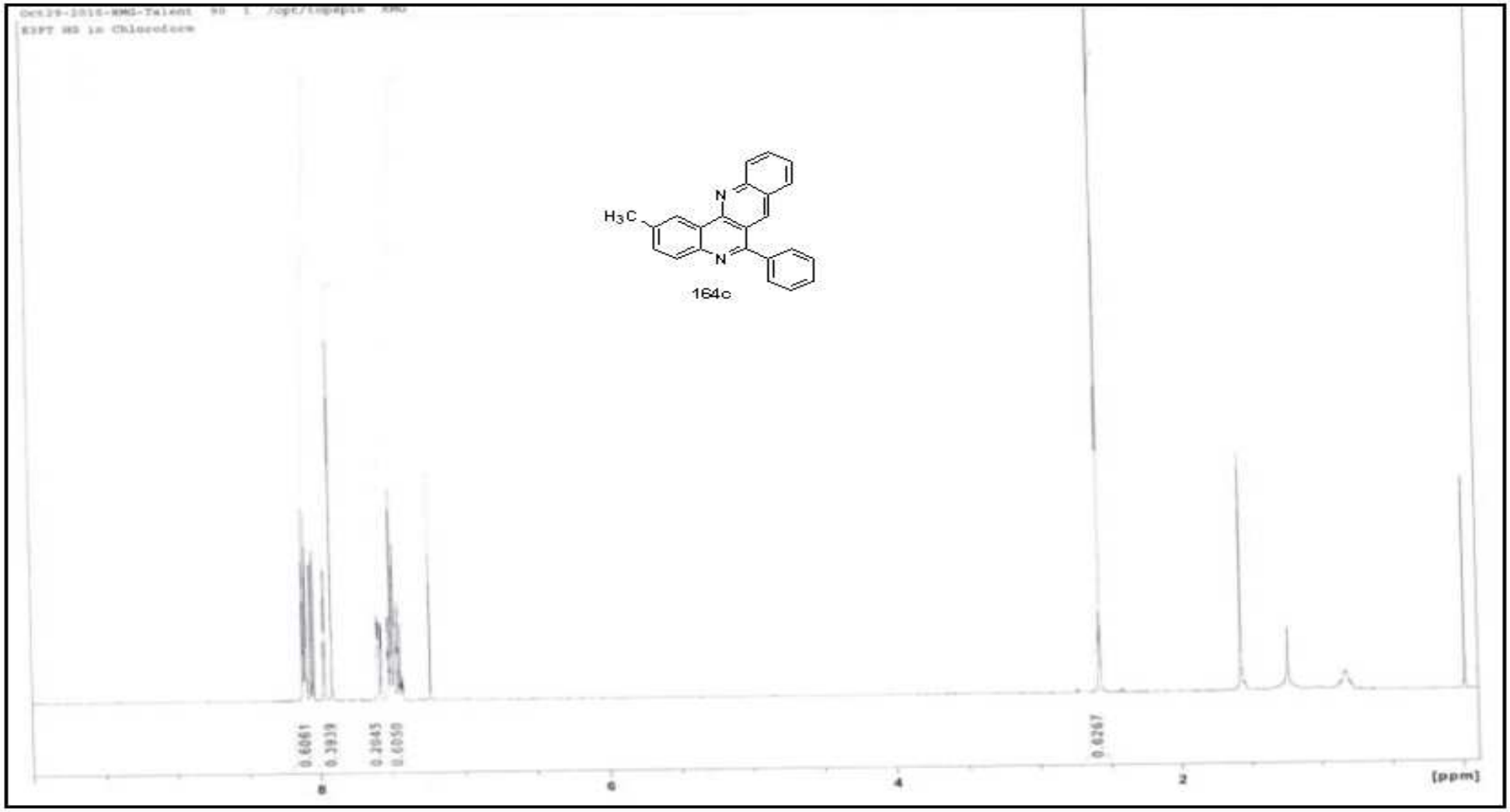

Figure 41: ^{1}H NMR Spectrum of 2 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164c

Appendix 39

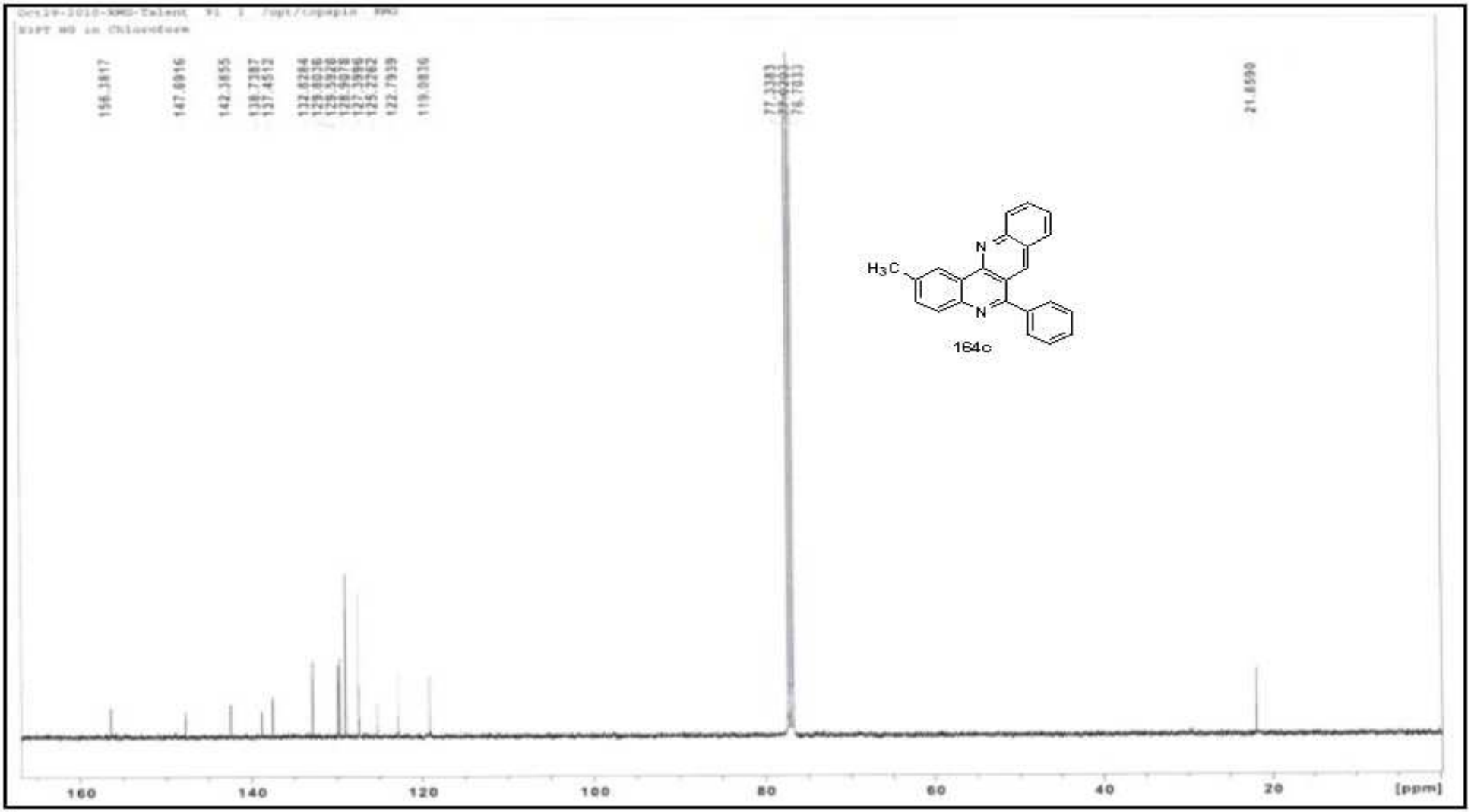

Figure 42: ^{13}C Spectrum of 2 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164c

Appendix 40

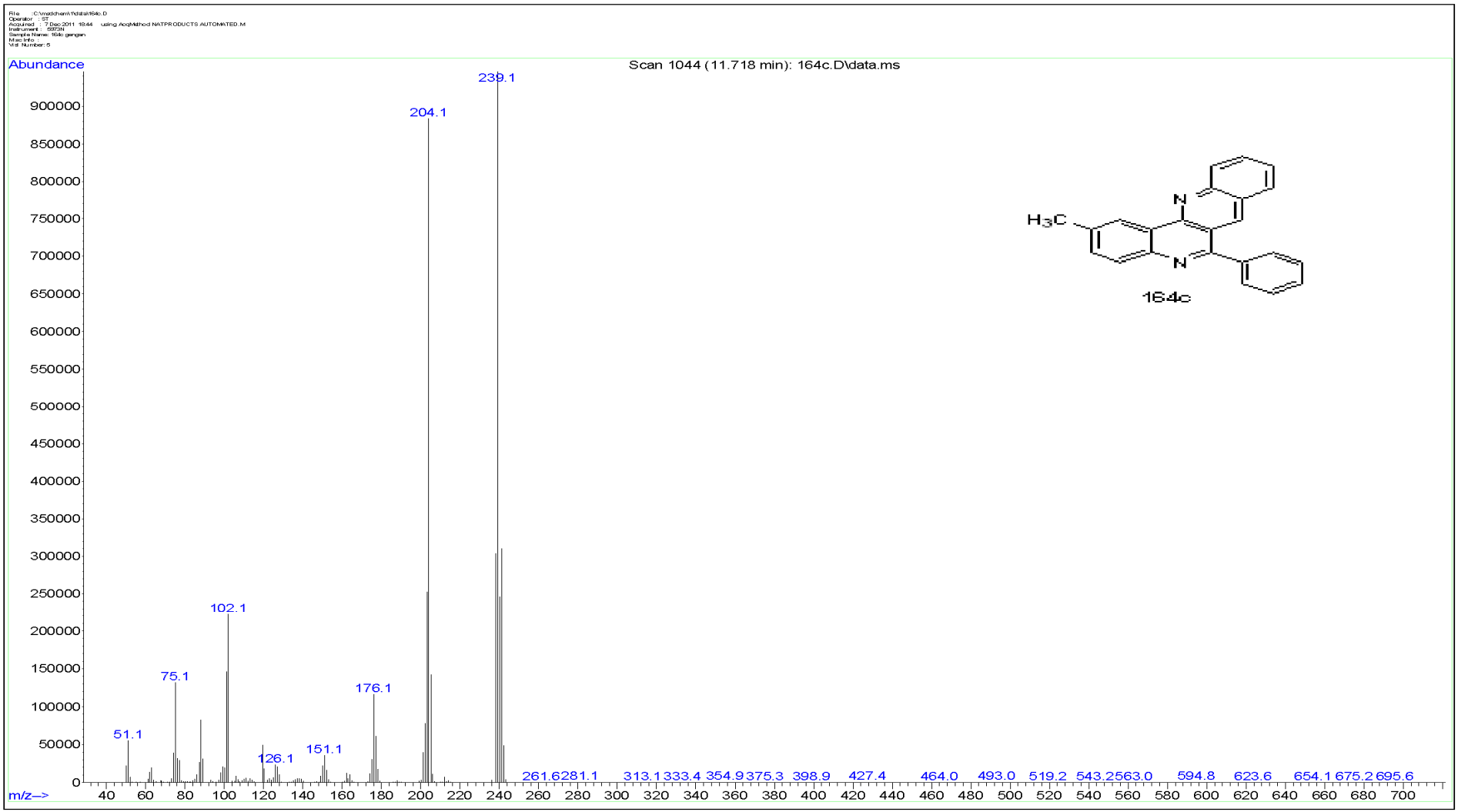

Figure 43: Mass spectrum of 2 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164c

Appendix 41

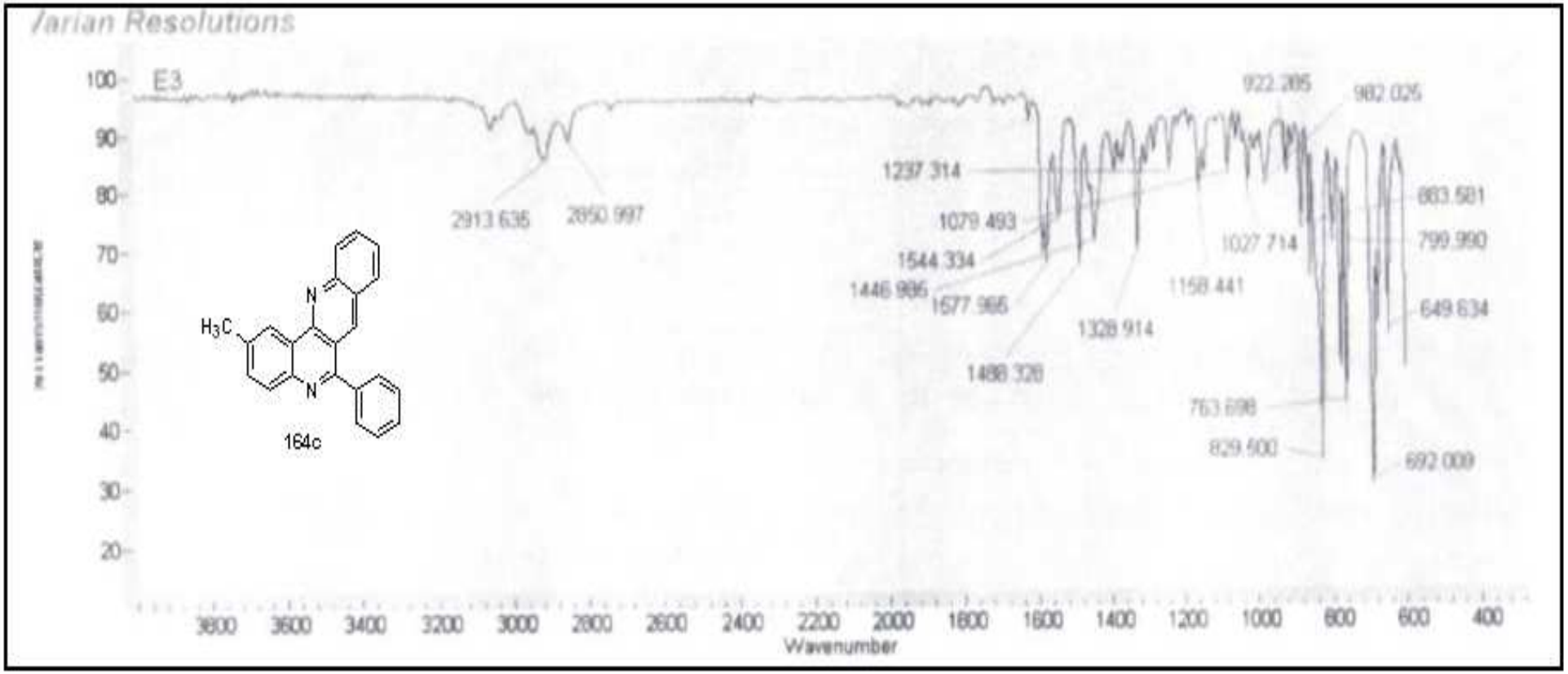

Figure 44: IR Spectrum of 2 – methyl – 6 – phenyl – dibenzo [b, h] [1, 6] naphthyridine 164c