"A SYNTHETIC APPROACH TOWARDS BIOACTIVE MOLECULES & RELATED STUDIES"

A THESIS SUBMITTED TO
THE SAURASHTRA UNIVERSITY

IN THE FACULTY OF SCIENCE

FOR THE DEGREE OF

Doctor of Philosophy

IN
CHEMISTRY

BY

MANISHA N. PARMAR

UNDER THE GUIDANCE OF

PROF. ANAMIK SHAH

DEPARTMENT OF CHEMISTRY
(DST-FIST FUNDED AND UGC-SAP SPONSORED)
SAURASHTRA UNIVERSITY
RAJKOT – 360 005
GUJARAT (INDIA)

JUNE- 2011

Statement under *O. Ph. D. 7* of Saurashtra University

The work included in the thesis is done by me under the supervision of Prof. Anamik K. Shah and the contribution made thereof is my own work.

Date:

Place: Rajkot **Manisha N. Parmar**

CERTIFICATE

This is to certify that the present work submitted for the Ph. D. degree of Saurashtra University by Miss. Manisha N. Parmar has been the result of work carried out under my supervision and is a good contribution in the field of organic, heterocyclic and synthetic medicinal chemistry.

Date:

Place: Prof. Anamik K. Shah

Dedicated To
My Beloved Family

Acknowledgement

I pay my homage to "**The Devine Spirit"**, without whose blessings nothing can possible. I bow my head in utter humility and complete dedication before **Almighty God** for making me capable of doing all that I propose. The work leading to my PhD Thesis submission is one of them.

I express my profound gratitude and thankfulness to my adored guide **Prof. Anamik Shah**, whose expert knowledge, generous guidance and fatherly touch spur me on to the greater efforts. His openhandedness and everlasting supportive nature helped me to build up an optimistic attitude towards my research work. I consider myself fortunate to have the opportunity to work under his inspiring supervision and it is my life time achievement.

I can't adequately express my deep sense of gratitude and heartfelt emotions for my Father and Mother, **Narendrakumar** and **Nirmalaben**, who blessed me with their good wishes, relieving all types of stress and remaining always with me to boost my spirit. I am gratified for their eternal love, trust and support. However I assured them to be worthy of whatever they have done for me. This moment would not possible without great support, love and affection of my beloved family members, **Dr. Rohini** & **Mr. Sandeepkuma**r & my dear niece (**Dhruv**), **Dr. Hetal** & **Dr. Chetan** and my brothers **Dr. Rakshit** & **Milap** (Dr.). They have supported me for each and every moment of my research tenure.

I would like to express my feelings of gratitude to **Prof. P. H. Parsania**, Professor and Head, Department of Chemistry, Saurashtra University, Rajkot for providing adequate infrastructure facilities and full co-operation during my work.

I am also thankful to **Dr. V. H. Shah, Dr. H. S. Joshi, Dr. Shipra Baluja, Dr. M. K. Shah, Dr. Yogesh Naliapara, Dr. U. C. Bhoya** and **Dr. Ranjan Khunt** for their affectionate help. I extend my thankfulness to the teaching and non teaching staff of my department for their kind support.

I am heartily grateful to my colleagues and friends **Dr. Nilay, Sachin, Dr. Shailesh, Dr. Shrey, Hardev, Bhavin, Ravi, Bharat, Abhay, Ashish, Dhairya, Jignesh, Hitesh, Mahesh, Harshad, Mrunal** and **Vaibhav** for their all kind concern, time

being help, best wishes and moral support. I am equally thankful to my juniors **Dipak, Vishwva, Madhavi, Hetal, Ketaki, Sabera, Paresh, Pratik, Dilip, Krunal** and **Wilson** for creating most healthy working atmosphere.

I would also like to thank my seniors **Dr. Priti, Dr. Atul, Dr. Jyoti, Dr. Jalpa, Dr. Jitender, Dr. Kuldip, Dr. Vaibhav, Dr. Naval, Dr. Raju** and **Dr. Dhawal** for their co-operation and valuable support.

I am also thankful to my colleagues whose presence has made this time a memorable time for me and my work in the laboratory was really enjoyable due to them. I thank Dr. Dipti, Vipul, Anil, Pipaliya, Suresh, Pooja, Jignesh, Piyush, Bhavesh, Renish, Ashish, Mehul, Katariya, Meenaxi, Naimish and Rakesh.

Words are inadequate to thanks my most beloved friends **Kashmira, Darshana, Purna** and **Krupali** who always with me and encourage me in all situation. I will never forget whatever they have done for me.

I indebted to **Dr. Ranjanben A. Shah** and **Mr. Aditya A. Shah** for their kind concern and moral support that made my second home in Rajkot.

I am also grateful to Sophisticated Analytical Instrumentation Facility (SAIF), RSIC, Punjab University, Chandigarh for 1H NMR, and 13C NMR, Dept. of Chemistry, Saurashtra University, Rajkot for IR, Mass and Elemental analysis and **"National Facility For drug discovery through new chemical entities development and instrumentation support to small manufacturing pharma enterprises"**, Department of Chemistry, Saurashtra University, Rajkot for instrument support and financial assistance.

Lastly I would like to thank each and every one of them who helped me directly or indirectly during this wonderful and lots of experience gaining journey. I apologize if in any case I am missing out any of the names as I am thankful to one and all.

Manisha N. Parmar

TABLE OF CONTENTS

GENERAL REMARKS

1. Melting points were recorded by open capillary method and are uncorrected.
2. IR spectra were recorded on Shimadzu FT IR-8400 (Diffuse reflectance attachment) using KBr. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}.
3. ^{1}H & ^{13}C NMR spectra were recorded on Bruker Avance II 400 MHz NMR spectrometer. Making a solution of samples in DMSO d_6 and $CDCl_3$ solvents using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned and are given in the δ ppm
4. Mass spectra were recorded on Shimadzu GC MS-QP 2010 spectrometer operating at 70 eV using direct injection probe technique.
5. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel-G F_{254} aluminium plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light.
6. The chemicals used for the synthesis of intermediates and end products were purchased from Spectrochem, Sisco Research Laboratories (SRL), Thomas Baker, Sd fine chemicals, Loba chemie and SU-Lab.
7. Samsung MW83Y Microwave Oven have been used which was locally modified for carrying out chemical reactions.
8. Evaporation of solvents was carried out on Heidolph OROTA-400-efficient under reduced pressure.
9. % Yield reported are isolated yields of material judged homogeneous by TLC and before recrystallization.
10. The structures and names of all compounds given in the experimental section and in physical data table were generated from ChemBio Draw Ultra 10.0.
11. Elemental analysis was carried out on Vario EL Carlo Erba 1108.

ABBREVIATIONS

^{1}H NMR	^{1}H Nuclear Magnetic Resonance spectroscopy
Å	Angstrom
AcOH	Acetic Acid
-Ar	Aryl
Ar	Aromatic
ASA	Acetylsalicylic acid
Asym	Asymmetric
BuLi	Butyllithium
CAN	Ceric ammonium nitrate
CBB	Coomassie Brilliant Blue
CDCl3	Deuterated chloroform
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl Azodicarboxylate
Def	Deformation
DHP	Dihydropyridine
DIBAL	Diisobutylaluminium hydride
DMF	Dimethyl Formamide
DMSO	Dimethyl sulfoxide
DPPP	Diphoronepentaperoxide
Et	Ethyl
FT-IR	Fourier Transform- Infrared spectroscopy
g	Gram
GABA	Gamma Amino Butyric Acid
GC-MS	Gas Chromatograph- Mass Spectrometry
HETE	Hydroxy Eicosa Tetraenoic acid
HHT	Hydroxy-5,8,10-Heptadeca Trienoic Acid
HIV	Human Immunodeficiency Virus
HMO	Huckel Molecular Orbital
hrs / h	Hours/Hour
Hz	Hertz

IR	Infrared
iso-but	isobutyl
iso-pr	isopropyl
m	Meta
MDR	Multi Drug Reverting Agent
Me	Methyl
MeOH	Methanol
mg	Miligram
Mg	Milligram
MHz	Megahertz
mL	Milliliter
MP	Melting Point
MW	Microwave
NAD(P)H	Nicotinamide Adenine Dinucleotide Phosphate
NADH	Nicotinamide Adenine Dinucleotide
NAP	Neutrophil-Activating Peptide
nm	Nano meter
NMR	Nuclear Magnetic Resonance
o	Ortho
oop	Out Of Plane Bending
p	Para
PABA	Paraamino Benzoic acid
PAF	anti platelet activating factor
PCC	Pyridinium Chlorochromate
Pgp	P-glycoprotein
Ph	Phenyl
ppm	Parts per million
ppts	Precipitates
RT	Room Temperature
Str.	Stretching
TB	Tuberculosis
TBAHS	Tetrabutyl Ammonium Hydrogen Sulfate

t-Bu	Tertiary Butyl
TFA	Trifluoroaceitic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
UV	Ultra Violate

PART- I

CHAPTER-1 SYNTHESIS, CHARACTERIZATION AND X-RAY CRYSTALLOGRAPHIC STUDIES OF 2,4-DIMETHYL BENZOPYRYLIUM SALTS

CHAPTER-2 SYNTHESIS OF SOME NEW 4-AMINO COUMARIN DERIVATIVES USING GREEN CHEMISTRY PROTOCOLS

CHAPTER- 1

SYNTHESIS, CHARACTERIZATION AND X-RAY CRYSTALLOGRAPHIC STUDIES OF 2,4-DIMETHYL BENZOPYRYLIUM SALTS

1.1 INTRODUCTION

In the chemistry of heterocycles, compounds having an oxygen as a hetero atom are referred to as oxygen heterocycles, which include several groups of compounds, viz., furans, benzofurans, pyrans, benzopyrans, chromenes, flavenes, chromenones, flavenones, chromenols, flavenols, coumarins, benzopyrylium salts, flavylium salts, xanthylium salts, etc. (Figure 1.1 & 1.2)

Figure 1.1

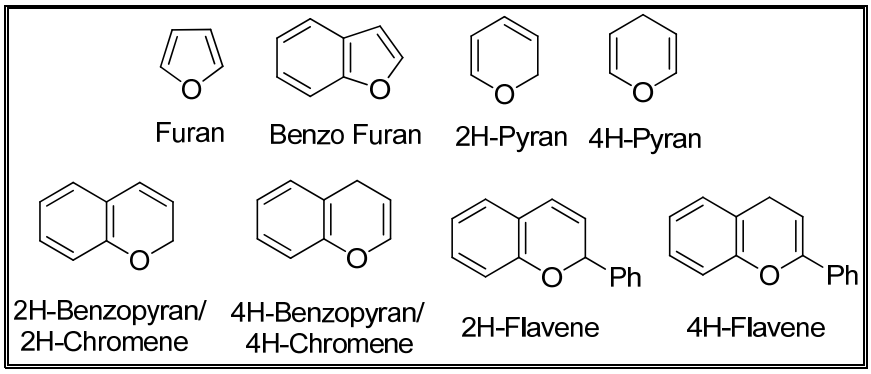
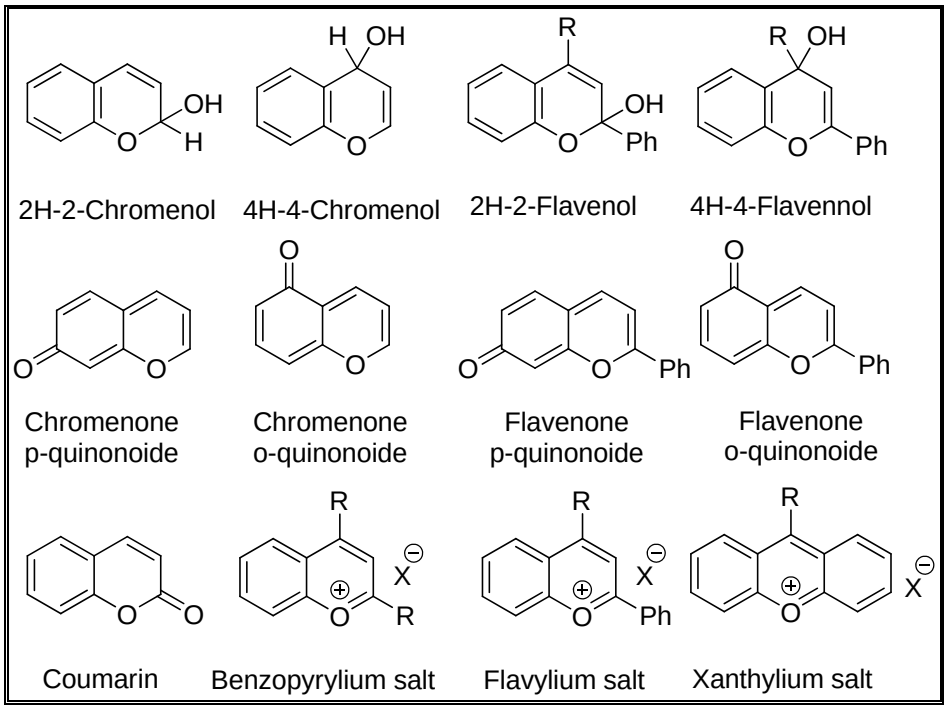


Figure 1.2

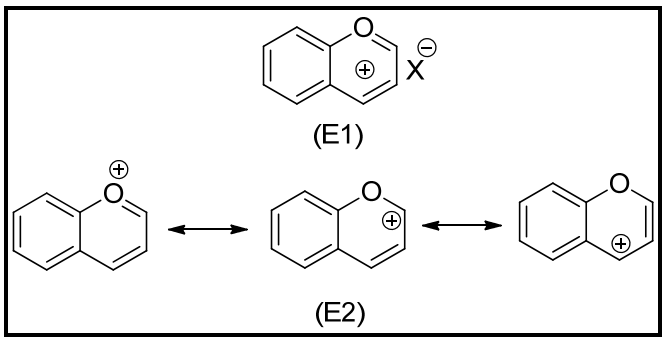


All of these are well known for their occurrence in nature, biological activity and wide applications in various fields. Because of wide occurrences in nature, important applications in many cases and their inter-convertibility, a number of researchers have been attracted to the chemistry of chromenes (flavenes), chromenols (flavenols) and benzopyrylium salts. Several monographs have been devoted to this field. [1-8]

The chromene moiety, known as 2*H*-benzopyran appears as an important structural component in both biologically active and natural compounds such as, alkaloids, flavonoids, vitamin E family (tocopherols and tocotrienes) and anthocyanins. Moreover, functionally substituted chromenes have played increasing roles in synthetic approaches to promising compounds in the field of medicinal chemistry. [9] Chromenes (2*H*-1-benzopyran derivatives) have also serve as the framework of a range of tannins, which are becoming increasingly important because of their health-promoting effects found in teas, vegetables, fruits, fruit juices and red wines. [10]

Benzopyrylium salts often known as chromylium salts (E1), were firstly prepared by Decker and Fellenberg [11] and Perkin and Robinson, [12,13] which differ from other heteocycles due to its aromatic character. The chromylium cation is best represented in terms of the theory of resonance as resonance hybrid (E2), (Figure 1.3). No single atom in the conjugated system carries all the charges; this charge is shared out over the atoms in the ring, but for general practice the charge is shown on oxygen atom. The structure of these salts is stabilized by resonance. The presence of hetero-atom and of a positive charge makes the heterocyclic ring extremely susceptible to attack by nucleophilic reagents, but it is relatively inert to attack by electrophilic reagents.

Figure 1.3

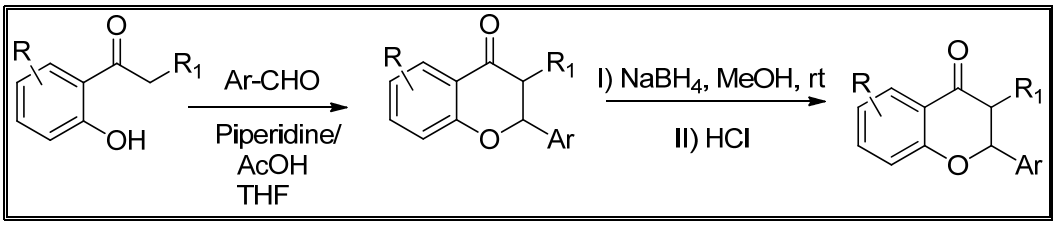


1.2 LITERATURE REVIEW

Various methods have been employed for the synthesis of chromenes (flavenes), chromenols (flavenols) and benzopyrylium salts. Some of them are summarized as under.

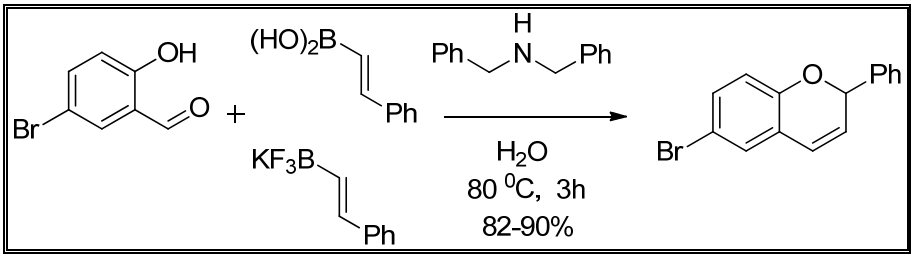
Jie-Fei Cheng *et al.* [14] has shown Knoevenagel condensation of an appropriately substituted 2-hydroxyl acetophenone with aryladehyde in the presence of piperidine and acetic acid provides benzopyrone products in fair to good yields. When R_1=H, the condensation is carried out using lithium hexamethyldisilylamide as a base. Reduction of the benzopyrone with $NaBH_4$ followed by acid-promoted dehydration of the resultant alcohol intermediate give the desired chromene derivatives.

Scheme 1.1



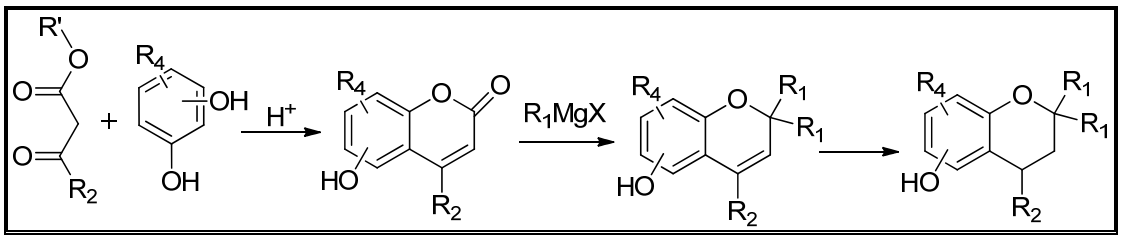
Nicos A. Petasis *et al.* [15] carried out the one-step reaction of salicylaldehydes with amines and alkenyl boronic acids or alkenyl trifluoroborates to form *2H*-chromenes (*2H*-1-benzopyrans) has been investigated in more detail and new suitable conditions have been identified, including the use of tertiary amines and protic solvents including water. This process was applied to a concise synthesis of a tocopherol analog.

Scheme 1.2



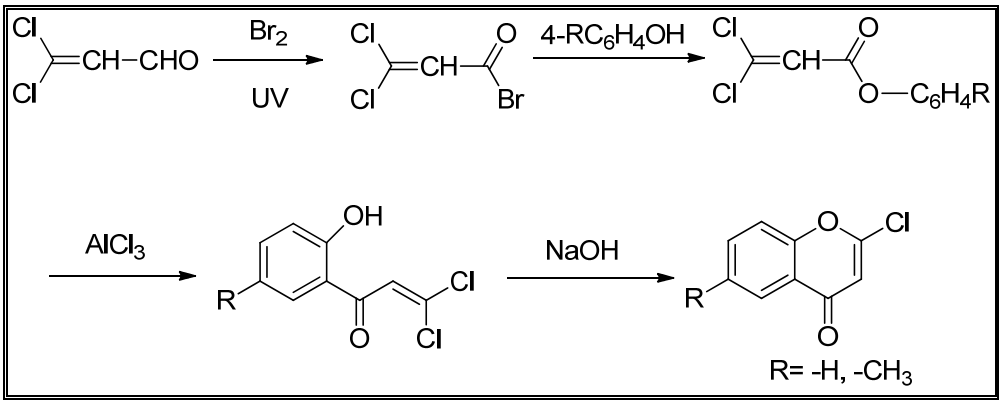
Bender *et al.* [16] prepared some chroman and chromene compounds having pharmacological activity such as central nervous system depressant activity. A preferred compound is 4-cyclohexyl-7(1,2-dimethylheptyl)-5-hydroxy-2,2-dimethyl-*2H*-chromene.

Scheme 1.3



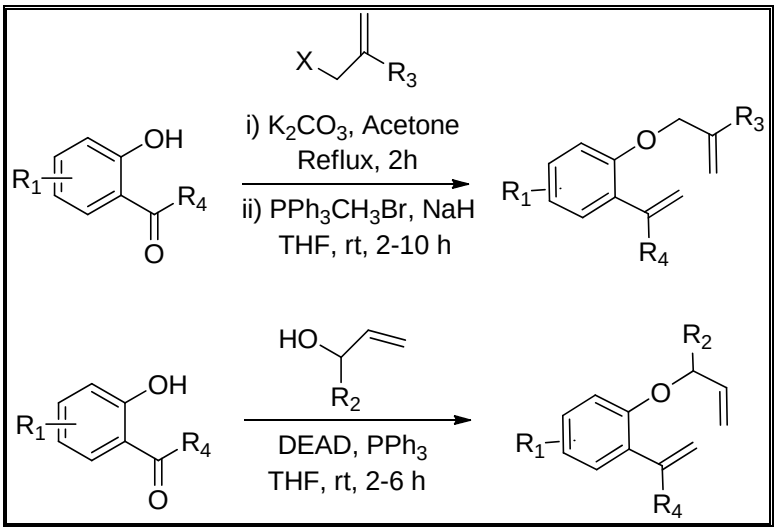
V Ya Sosnovskikh *et al.* [17] reported synthesis and reactions of some halogen-containing chromones.

Scheme 1.4

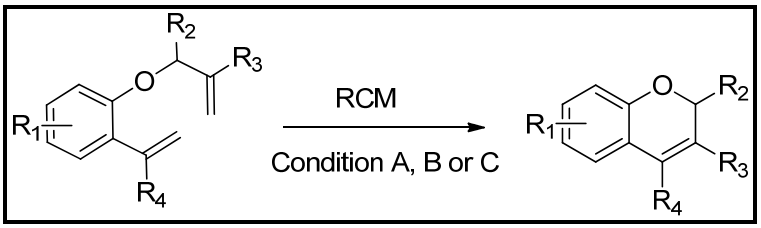


Sukbok Chang *et al.* [10] gave a highly efficient and practical synthesis of chromene derivatives using ring-closing olefin metathesis. (Condition **A**: **1** (2 mol %), CH_2Cl_2 (0.2 M), rt (2 h); condition **B**: **1** (6 mol %), C_6H_6 (0.2 M), 60 °C (2 h); condition **C**: **1** (5 mol %), CH_2Cl_2 (0.2 M), rt (10 h) and R_1, R_2, R_3 and R_4 = different substituent's like methyl, methoxy, nitro etc.)

Scheme 1.5

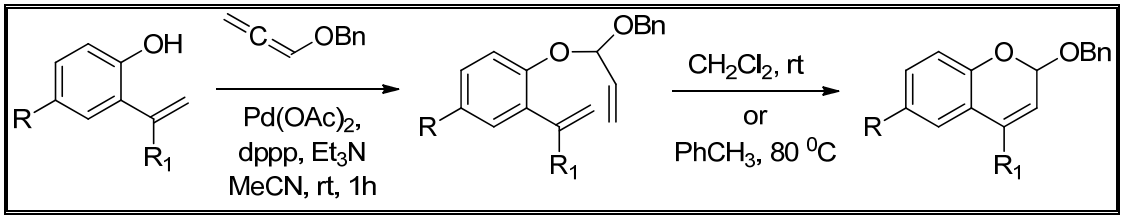


Scheme 1.6



Robin Doodeman *et al.* [18] reported synthesis of 2-substituted chromenes, which were obtained via combination of ring-closing metathesis of allylic acetals to the corresponding cyclic acetals, followed by lewis acid-mediated functionalization of the resulting stable 1-benzopyrylium ion with suitable nucleophiles.

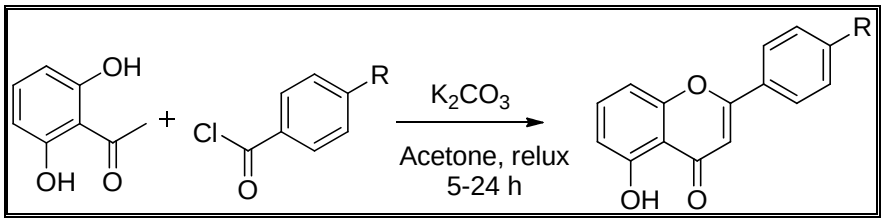
Scheme 1.7



Masato Matsugia *et al.* [19] have synthesized a variety of 5,4-disubstituted flavones, which are anticipated to be androgen receptor antagonists to treat diseases mediated by the androgen receptor, were synthesized. It was found that an intramolecular *ipso*-substitution reaction *via* cesium enolate using 2-fluoro-6-hydroxyacetophenone and

various benzoyl chlorides were effective in the preparation of 5-hydroxy-4-alkylflavones.

Scheme 1.8



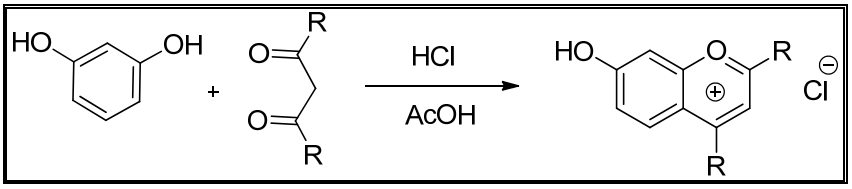
Where R= -Cl, -CF_3, -NO_2, -CN, etc.

Besides these, various chromene derivatives have been reported. [20-33]

The various methods have been reported for the synthesis of benzopyrylium salts which mainly synthesized from phenols, 2-hydroxybenzaldehydes, 2-hydroxyphenyl ketones and from heterocycles. Some of them are discussed here.

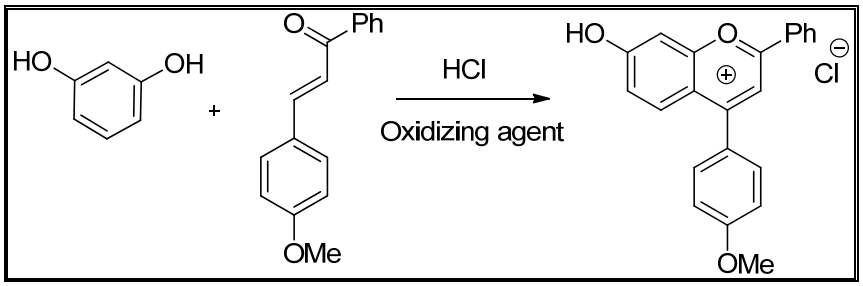
Bulow's *et al.* [34] first reported this method, which consists of condensation of polyhydric phenols with ß-diketones using HCl in acetic acid media. Use of formic acid as a solvent is uncertain as it may enter into the reaction giving the xanthylium salts. Several ß-diketones such as acetyl acetone, methylacetylacetone, [35,36] dibenzoylmethane, [37] benzoyl acetone [38] and benzoylanisoylmethane [39,40] have been used.

Scheme 1.9



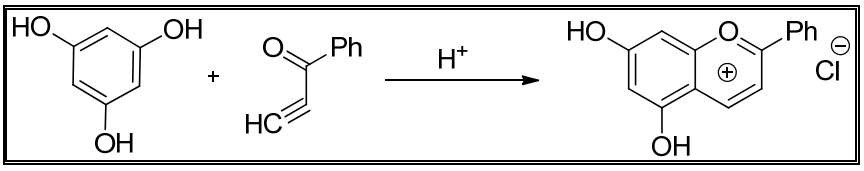
Phenols when treated with α,β-unsaturated ketones (e.g., chalcones) in presence of an oxidizing agent and HCl give benzopyrylium salts. Chloranil, $FeCl_3$, P_2O_5 and I_2 have been found to be the best oxidizing agents. Many ketones such as 2-benzoylcoumarone, dibenzylideneacetone, dibenzylideneacetophenone, tetralone, coumaran-3-one, chromanone and 2-chlorovinylketone have been used. [41-44]

Scheme 1.10



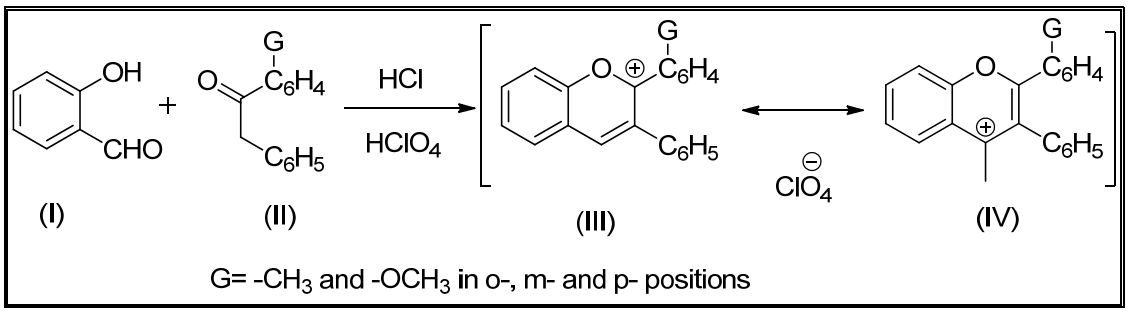
Johnson and Melhuish [45] have reported the condensation of phenols with acetylic ketones in the presence of an acid in acetic acid or ether, which results in the formation of benzopyrylium salts. Unlike in the case of α,β -unsaturated ketones, no oxidizing agent is required here. In this condensation less reactive phenol like phenol itself condense in presence of $HClO_4$ or $FeCl_3$ and HCl while for polyhydric phenols like resorcinol, concentrated sulphuric acid in acetic acid, is the best reagent but HCl in ether also serves well. The main drawback of this synthesis is that it cannot be used for the synthesis of 3-substituted flavylium salts or anthocyanins.

Scheme 1.11



Earlier Richard Otter *et al.* [46] reported condensation of salicaldehyde (I) with α-substituted acetophenones (II) in absolute ether in the presence of hydrogen chloride and perchloric acid produced the substituted flavylium perchlorates. These may be represented by the allylic cationic resonance structures, III to IV as far as their chemical properties indicate.

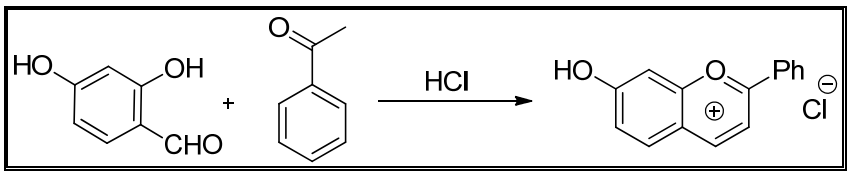
Scheme 1.12



Synthesis of benzopyrylium salts starting from 2-hydroxybenzaldehydes comprises of its condensation with ketones, aldehyde and α-substituted β-ketoeters, it is general method for the synthesis of benzopyrylium salts in which 2-hydroxybenzaldehydes are condensed with α-ketone (containing a $–CH_2$-CO- group) in the presence of an acid. Several ketones and various 2-hydroxybenzaldehydes as well as 2-hydroxynaphthaldehydes have been used in this reaction. Polyhydroxy benzaldehydes do not condense easily but their acetyl derivatives give good results.

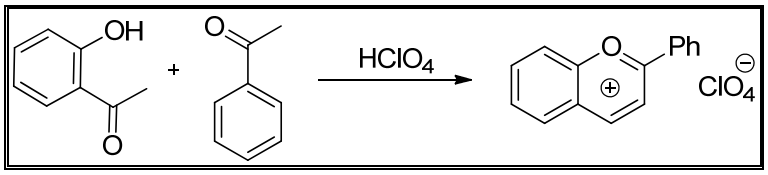
Le Fevre *et al.* [47] described that treatment of a mixture of 2-hydroxybenzaldehyde and acetophenone in ether and 70% $HClO_4$ with HCl at 0 ºC is the best procedure for large scale production of flavylium salts. B-diketones like acetyl acetone may be used in this condensation which gives 2-substituted -3-acylbenzopyrylium salts. [48]

Scheme 1.13



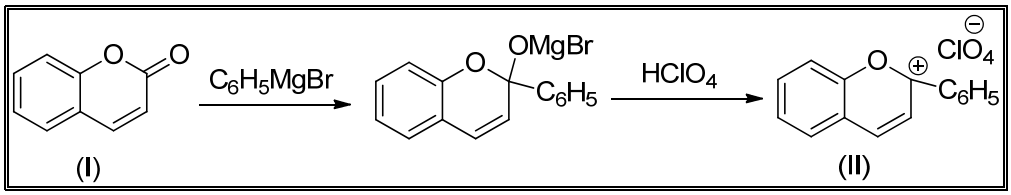
Acetophenones have also been reported to form flavylium salts when treated with $HClO_4$. [49]

Scheme 1.14



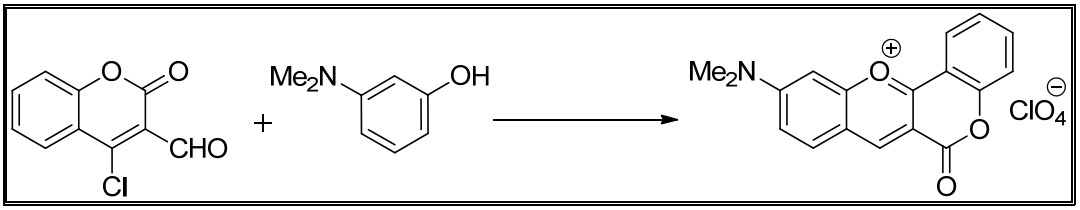
R. L. Shriner *et al.* [50] reported one of the general methods for preparing 1-benzopyrylium salts (II) consists in treating coumarin (I) (or substituted coumarins) with one mole of the Grignard reagent under conditions such that 1,2 addition to the carbonyl group occurs and then reaction of the adduct or the pyranol with a strong acid as shown by the following. 1-Phenyl-2-benzopyrylium perchlorate was produced by the action of phenyl magnesium bromide on isocoumarin followed by treatment with perchloric acid.

Scheme 1.15



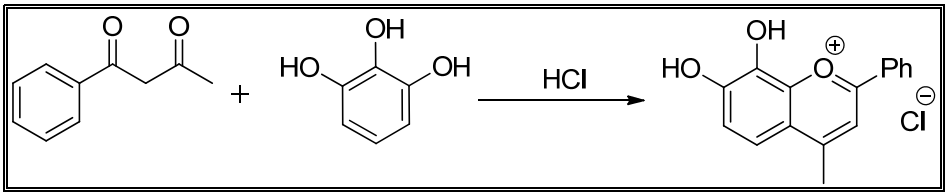
Peter Czerney *et al*. [51] developed preparation of 3,2'-bridged flavylium salts as laser dyes and dye intermediates.

Scheme 1.16



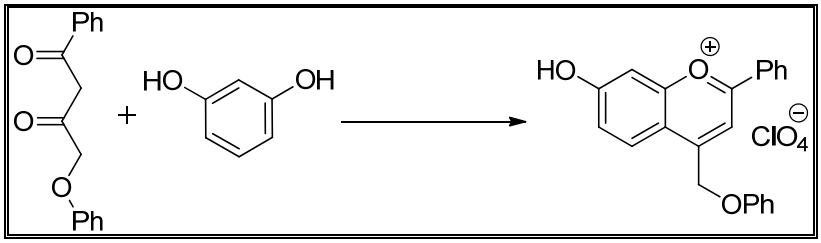
N. L. Olenovich *et al*. [52] reported synthesis and properties of some o-dihydroxychromenols. Condensation of pyrogallol with $PhCOCH_2COR$ in AcOH to obtained desired product which can be used for photometric determination of polyvalentions.

Scheme 1.17



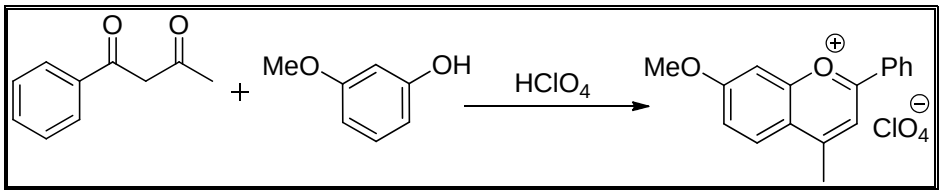
V. I. Dulenko *et al.* [53] described formation of carbene in reactions of salts of 4-aryloxymethyl-7-hydroxyflavylium with triphenylphosphine.

Scheme 1.18



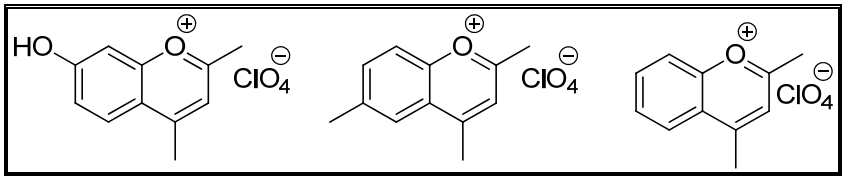
I. M. Gavrilyuk *et al*. [54] synthesized symmetric flavylocyanines from methoxy-substituted 4-methylflavylium salts.

Scheme 1.19



M. M. Evstifeev *et al.* [55] observed the polarographic study of some cations of the pyrylium series. Substituted pyrylium perchlorates were determined by single-sweep polarography. The peak potentials in 2N H_2SO_4 supporting electrolyte were: 2,4,6-trimethylpyrylium, 2,4,7-trimethyl-benzopyrylium and 7-hydroxy-2,4-dimethl-benzopyrylium. The effect of adsorption on the electrochemical processes was also discussed.

Figure 1.4



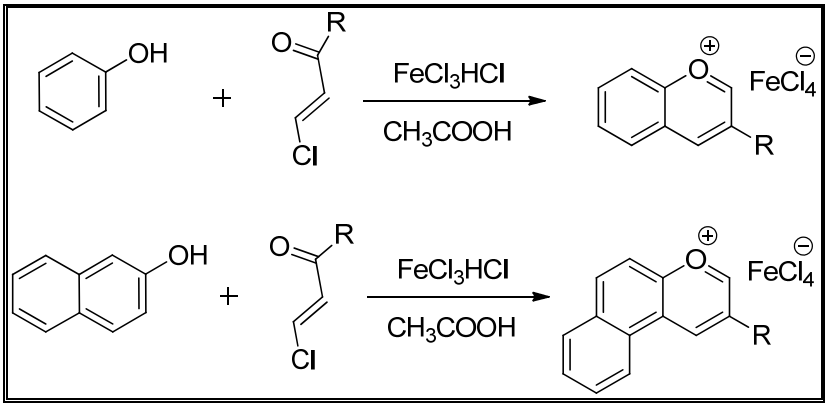
Dorofeenko G. N. *et al.* [56] reported synthesis of pyrylium salts from compounds with a tertiary carbon atom, like in a solution of cumene in acetic acid, 70% $HClO_4$ was added dropwise and heated upto half an hour. After dilution with ether, an oil, which heated with C_6H_6, then taken up in acetone and ppts with ether, gave 6.7% 2,6-dimethyl-4-phenylpyrylium perchlorate, which with NH_4OH gave 2,6-dimethyl-4-phenylpyridine. Similarly, cumic acid gave 5% 2,6-dimethyl-4-p-carboxyphenylpyrylium perchlorate. p-Cymene gave 1.55% 2,6-dimethyl-4-ptolylpyrylium perchlorate also formed from p-$MeC_6H_4CMe_2OH$ and acetic anhydride in the presence of 70% $HClO_4$. p-$MeOC_6H_4CMe_2OH$ gave 2.5% 2,6-dimethyl-4-p-anisylpyrylium perchlorate, p-$Me_2NC_6H_4CMe_2OH$ gave 12% 2,6-dimethyl-4-p-dimethylaminophenylpyrylium diperchlorate. Pulegone gave 58% 2,4,7-trimethyl-5,6,7,8-tetrahydrobenzopyrylium perchlorate. Menthone gave 21% 2,4,7-trimethylbenzopyrylium perchlorate. Me_2BuCOH and acetic anhydride with

70% $HClO_4$ gave an oil which with NH_4OH gave 61.5% mixed 2,6-dimethyl-4-butyl and 2,4,6-trimethyl-3-propylpyridines. $C_6H_{13}CMe_2OH$ gave similarly after treatment with NH_4OH 64% mixed 2,6-dimethyl-4-hexyl- and 2,4,6-trimethyl-3-amylpyridines.

Kojima Akio *et al.* [57(a)] reported some 2-[(Nitro)-9-fluorenylidene-methyl]-benzopyrylium salts. Narkevich A. N. *et al.* [57(b)] studied comparative cytogenetic activity of some pyrylium salts.

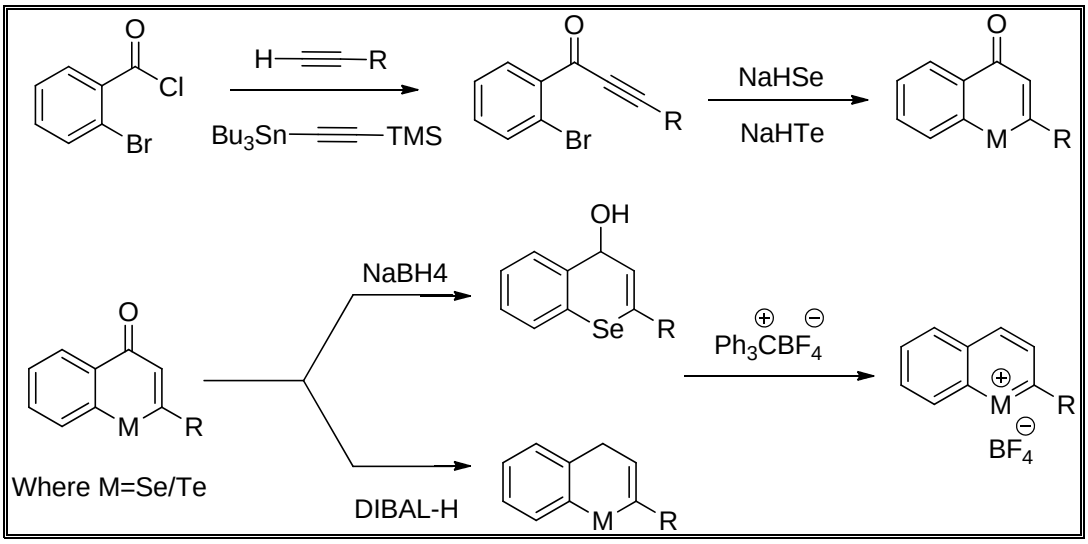
Nesmeyanov, A. N. *et al.* [58] had studied absorption spectra of various pyrylium salts, like 2-methylbenzopyrylium ferrichloride, 2,6-dimethylbenzopyrylium ferrichloride, 6-hydroxy-2-methylbenzopyrylium ferrichloride, 7-hydroxy-2-methylbenzopyrylium ferrichloride, flavylium ferrichloride, 6-methylflavylium ferrichloride, 4',6-dimethylflavylium ferrichloride, 4'-bromo-6-methylflavylium ferrichloride, 6-hydroxyflavylium ferrichloride, 4'-bromo-6-hydroxyflavylium ferrichloride, 7-hydroxyflavylium ferrichloride, 4'-bromo-7-hydroxyflavylium ferrichloride and 7-hydroxy-4-methoxyflavylium ferrichloride.

Scheme 1.20



In recent years, chemistry of thiopyrylium salts, [59] selenopyrylium salts and telluropyrylium salts also have received considerable attention due to their various applications as biologically active substances, medicinal preparations, valuable dyes, indicators and sensitizers. Haruki Sashida studied preparations and reactions of 1-benzoselenopyrylium salts and 1-benzotelluropyrylium salts. [60]

Scheme 1.21



Haruki Sashida also demonstrated X-ray crystallographic study of 1-benzoselenopyrylium and 1-benzotelluropyrylium salt.

Figure 1.5

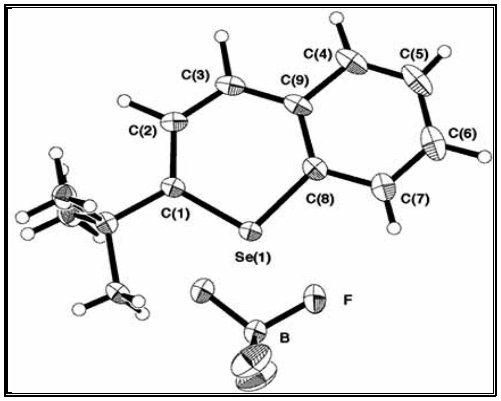
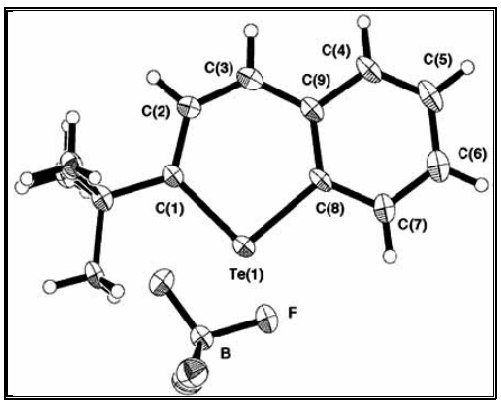
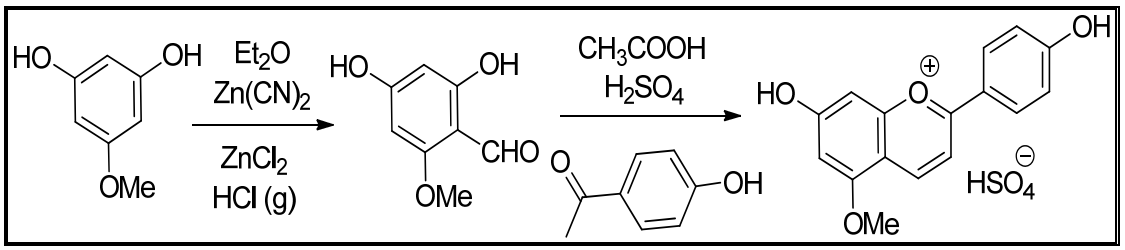


Figure 1.6



Many references are found related to benzopyrylium chloride, perchlorate and some are related to ferrichloride, but less attention has been devoted to benzopyrylium sulphate salts. Maria J. Melo *et al.* [61] demonstrated synthetic approach for 7,4'-dihydroxy-5-methoxyflavylium/dracoflavylium.

Scheme 1.22



Beside these, much work has been carried out in the field of pyrylium, benzopyrylium and isobenzopyrylium salts. [62-95]

1.3 APPLICATIONS

1.3.1 Synthetic Applications

The vigorous development of the chemistry of pyrylium salts observed in recent years is associated not only with the enormous theoretical interest in the reactions of the carboxonium cation but also with the possibility of using such salts for the synthesis of many aliphatic, aromatic and heterocyclic compounds, which sometimes cannot be obtained by other procedures. In this sense, the cyclization reactions of pyrylium salts under the influence of nitrogen-containing nucleophiles are of particular interest. They lead to compounds among which effective biologically active substances, dyes, metal corrosion inhibitors, emulsifying agents, etc. have been found. [96,97]

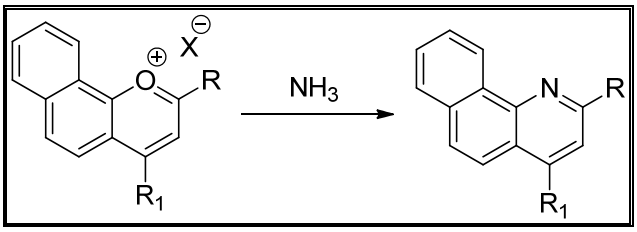
Benzopyrylium salts are true salts in which the presence of the hetero-atom and of a positive charge makes the heterocyclic ring extremely susceptible to attack by nucleophilic reagents, but relatively inert to attack by electrophilic reagents. Recently, the reactivity indexes of flavylium salts have been calculated by HMO, [98] in which they are shown to be most susceptible to electrophilic attack at C_8, C_3 and C_6 and nucleophilic attack at C_4 and C_2.

Various synthetic applications of pyrylium salts are reported, some of them are demonstrated here.

1) Interaction of pyrylium salts with ammonia and the simplest amines

In recent years the interaction of pyrylium salts with ammonia led to the synthesis of new compounds of the pyridine series otherwise difficult to obtain. 2-Benzopyrylium as well as pyrylium salts condensed with -N, -O, -S, and Se-containing heterocycles react with ammonia to give respectively isoquinoline bases of pyridines condensed with heterocycles. [99] 1-Benzopyrylium and xanthylium salts cannot be converted into quinolines and acridines by treatment with ammonia, [100] but naphtha(b) pyrylium salts have been converted into benzoquinoline derivatives in satisfactory yield by reaction with ammonia. [101]

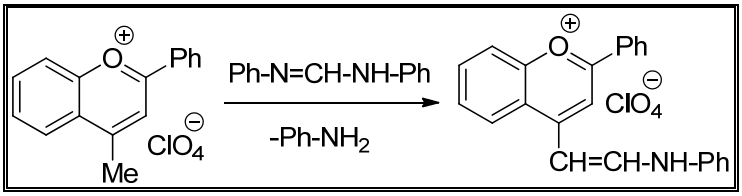
Scheme 1.23



2) Reaction with compounds containing the S=N, C=N and N_3 groups

The reaction of 4-methylflavylium perchlorate with diphenyl formamidine leads to an aminovinylpyrylium salt. [102]

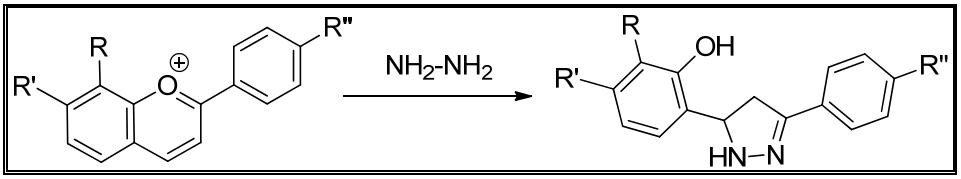
Scheme 1.24



3) Interaction with amines containing other functional groups

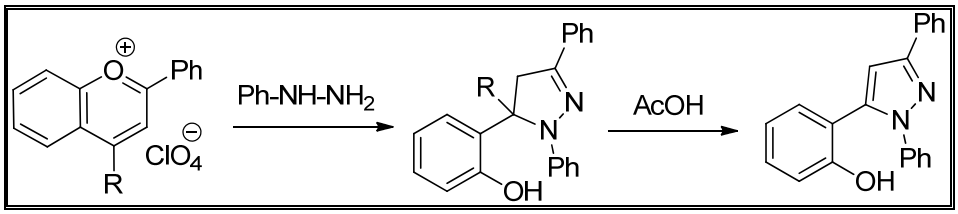
Flavylium salts with the free 4-position are attacked by hydrazine exclusively in the 2-position. The addition product then isomerises with the opening of the pyran ring and cyclises to 4,5-dihydro-*1H*-pyrazole. [103]

Scheme 1.25



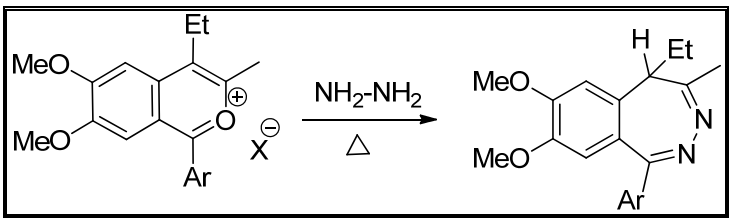
1-Benzopyrylium pyrylia[2,3-c]indole salts react with phenyl hydrazine to form pyrazolines. [104,105]

Scheme 1.26



While in case of l-Aryl-2-benzopyrylium salts react with hydrazine and are converted into *5H*-2,3-benzodiazepines. [106]

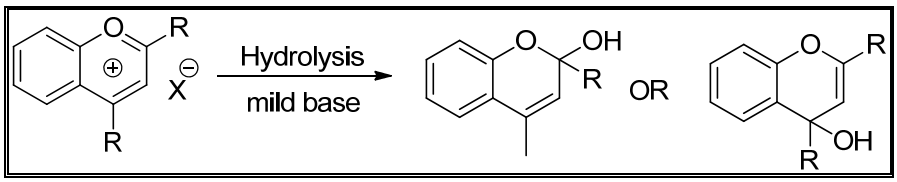
Scheme 1.27



4) Hydrolysis of benzopyrylium salts

The products obtained by the hydrolysis of benzopyrylium salts depend on the substituents present in the molecule, the hydrolyzing agent and the conditions of hydrolysis. Benzopyrylium salts with mild base yield chromenol and flavenols. [107]

Scheme 1.28



5) Grignard reaction of benzopyrylium salts

Grignard reagents attack benzopyrylium salts at C_2 and C_4 and give chromenes or flavenes depending upon the substituents present in the pyran ring. Flavylium chloride and 3-phenyl flavylium ferrichloride with phenyl magnesium bromide give 4-phenyl-2-flavene derivatives, whereas 4-phenyl flavylium ferrichloride gives 2,4-diphenyl-3-flavene. [107]

1.3.2 Pharmacological & Industrial Applications

Chromenes and its derivatives are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. Their basic structural framework for example is a common feature of many types of tannin and polyphenols found in teas, fruits, vegetables and red wines and these compounds have become increasingly important as a result of their health-promoting effects. Many pharmaceutical activities are associated with the derivatives of chromenes. [108]

The 2*H*-benzopyran, daurichromenic acid is known to exhibit anti-HIV properties, [109] while coutareagenin possesses antidiabetic activity. [110] Derivatives of 3,4-diphenylchromans are known to have estrogenic activity. [111] Numerous derivatives of 2*H*-benzopyrans are useful for treatment of proliferative skin disorder and microbial infections [112] and show potent antifungal activity. [113]

Salts of pyrilium, thiopyrilium and selenopyrilium derivatives are studied for their effect on the catalytic activity of acetyl cholinesterase of human blood erythrocytes and butyryl cholinesterase of horse blood serum which is measured by the method of potentiometric titration. All enumerated salts are established to be strong reversible inhibitors of mixed-type cholinesterases. [114] Pyrilium salts like 2,4,6-trimethylpyrilium, 2-methyl-5,6,7,8-tetrahydrochromylium, 1,3-dimethyl-5,6,7,8-tetrahydro-isochromylium and symoctahydro-xanthylium perchlorates are also reported as effective mutagens. [115]

Benzopyrylium salts are widely applicable in industry. They are found to be very useful as surface dyeing of leather, wool, cotton and polyamide textiles. Hydroxybenzopyrylium salts containing methyl radicals in α or γ position of the heterocycles are readily condensed via these methyl groups with aldehydes, ketones, acid anhydrides, nitroso compounds and formic acid and its derivatives. The resulting new compounds have a tanning effect because of their phenolic hydroxy groups and they are valuable dyes for dyeing leather. [116,117] They are also applicable as tanning developers. [118]

Benzopyrylium salts are also applicable for the photometric determination of Germanium in dusts and intermediate products of non-ferrous metallurgy. [119] They

are also found useful for the colorimetric determination of Zirconium and Hafnium. [120]

4-Amino benzopyrylium, 4-amino benzothiopyrylium as well as several pyrylium, benzopyrylium and benzothiopyrylium perchlorates are useful sensitizers for conventional organic photoconductors. [121,122] Pyrylium salts are useful as sensitizing agent for electrophotographic material with panchromatic sensitivity in the visible spectrum region. [123]

7,8-Dihydroxy-2,4-dimethylchromylium chloride can be used as the developing agent, [124,125] while amino substituted 2-(3-coumaryl) chromylium salts are useful in electrography. [126]

Above evidences revealed that these salts can be useful as biologically active substances, medicinal preparations, valuable dyes, indicators, tanning agents and sensitizers. The specific distribution of the electron density of a heteroatom over the aromatic ring system and the specific crystal structure provide transport of both electrons and ions in compounds of this type. [127]

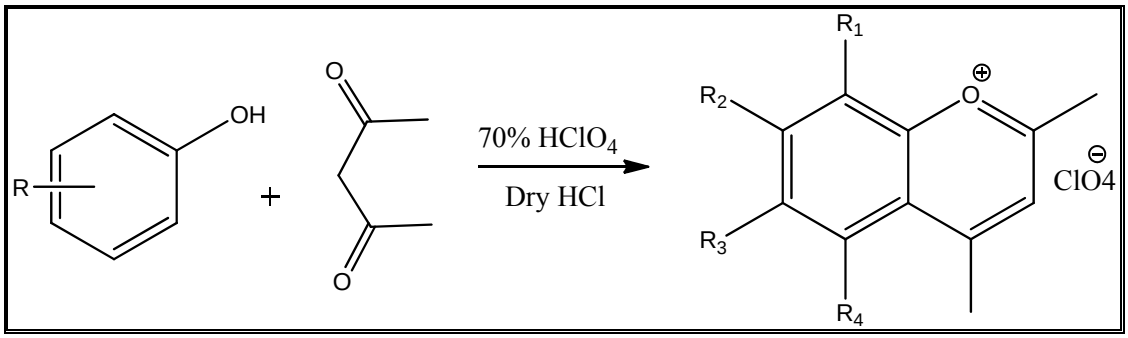
1.4 AIM OF CURRENT WORK

The present work is an off-shoot of the work being carried out on Pechmann condensation. [128,129] The Pechmann condensation [130,131] is between phenols and β-ketonic esters while in this case 1,3-diketone has been condensed with phenols to furnish some benzopyrylium salts.

The aim of current work is to prepare a small series of chromene derivatives, especially benzopyrylium salts by a simple and efficient method in good yield for the biological interest.

1.5 REACTION SCHEME

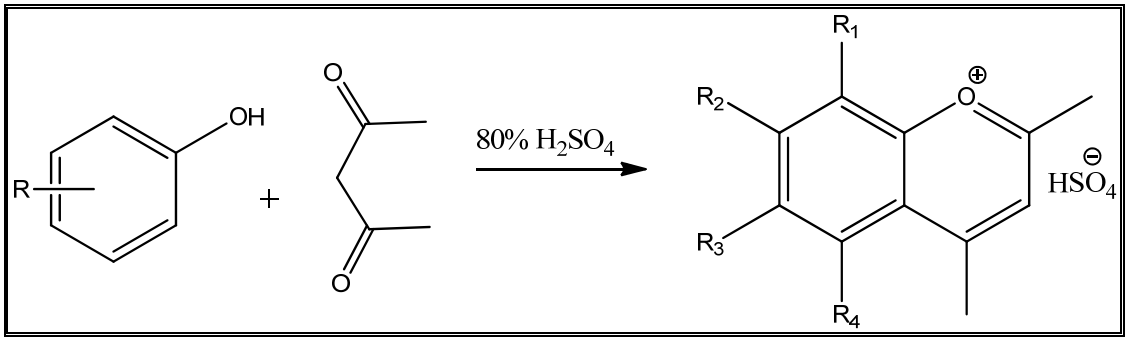
1.5.1 Preparation of 2, 4-Dimethylchromenylium Perchlorate Salts (MNP-001 to 013)



Where R= -OH, $-CH_3$, $-OCH_3$, Allyl etc.

R_1, R_2, R_3 & R_4= -OH, $-CH_3$, $-OCH_3$, Allyl etc.

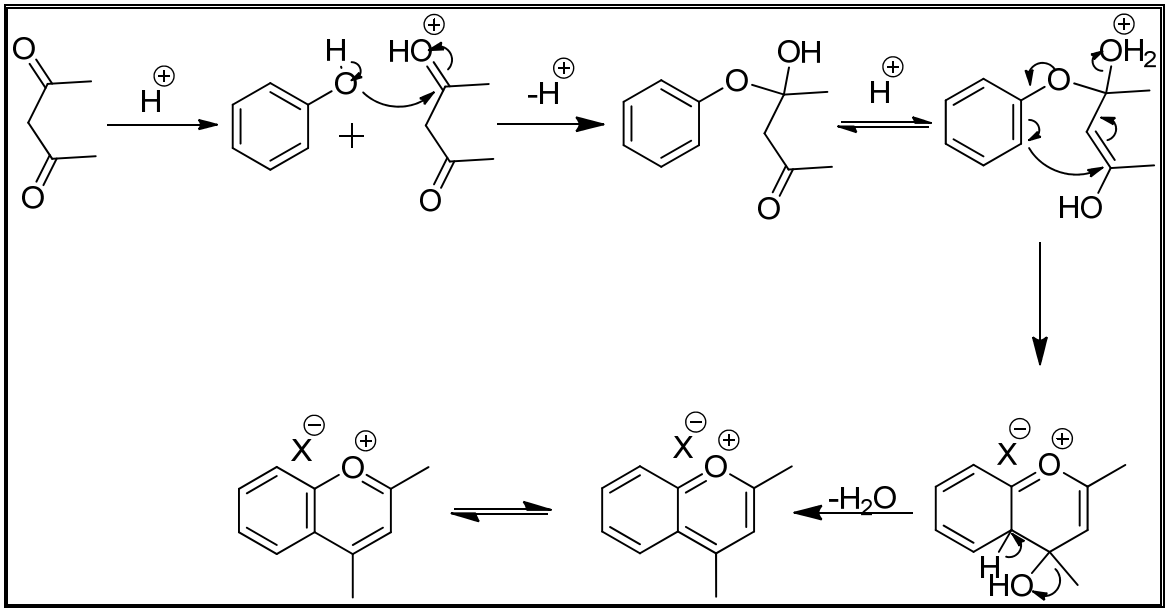
1.5.2 Preparation of 2, 4-Dimethylchromenylium Sulphate Salt (MNP-014 to 017)



Where R= -OH, di OH or 7, 8-benzo

R_1, R_2, R_3 & R_4= -H, -OH or 7, 8-benzo

1.6 PLAUSIBLE REACTION MECHANISM



Where X= ClO_4 or HSO_4

1.7 EXPERIMENTAL

1.7.1 Analysis Protocols

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr Powder method. Mass spectra were recorded on **Shimadzu GC-MS-QP-2010** model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/ DMSO-d_6/MeOD/TFA solution on a **Bruker Avance II 400 MHz NMR spectrometer**. UV analysis was carried out using **Shimadzu UV-Visible** Spectrophotometer Pharmaspec-1700. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model. All the results are in agreements with the structures assigned.

1.7.2 Preparation of substituted-2,4-Dimethylchromenylium Perchlorate Salts (General procedure)

To a mixture of substituted phenol (0.05 mole) and acetyl acetone (0.05 mole), perchloric acid (70%; 7.5 mL) was added drop-wise with external cooling at 5-10 ºC temperature. After addition of perchloric acid, the reaction mixture was further allowed to cool at 5-10 ºC and dry hydrogen chloride gas was bubbled through the reaction mixture for 1 hour. Reaction mixture became reddish in colour and was kept overnight at room temperature. Then reaction mixture diluted with excess of dry ether and coloured precipitates were obtained, which was filtered and thoroughly washed with dry ether. Crude product was recrystallized from glacial acetic acid.

1.7.3 Preparation of substituted-2,4-Dimethylchromenylium Sulphate Salts (General procedure)

To a mixture of substituted phenol (0.05 mole) and acetyl acetone (0.05 mole), sulphuric acid (2.5 mL) was added drop-wise with external cooling at 5-10 ºC

temperature. Reaction mixture was kept overnight at room temperature. Then reaction mixture was diluted with the mixture of dry ether and ethanol (70:30) and coloured precipitates were obtained, which was filtered and thoroughly washed with dry ether. Crude product was recrystallized from ethanol.

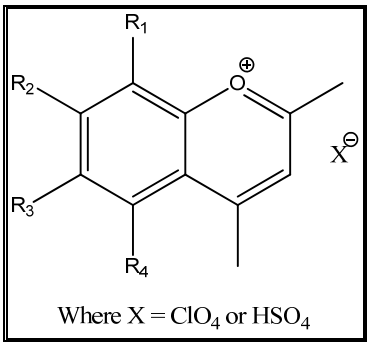
The physical data of newly synthesized compounds are given in Table No. 1.9.1.

1.8 PROPERTIES

All 2,4-dimethylbenzopyrylium salts (Perchlorate & Sulphate) are crystalline solids, soluble in polar solvents like methanol, ethanol, acetic acid and acids; insoluble in non-polar solvents like benzene, diethyl ether and hexane. All the salts are less stable with respect to temperature, moisture and also sometimes light sensitive. 7,8-dihydroxy-2,4-dimethyl benzopyrylium salt, 5,7-dihydroxy benzopyrylium salt and tetra methyl benzopyrylium salts are more stable in comparison with other salts. With base (aqueous sodium bicarbonate, sodium carbonate, sodium hydroxide and sodium acetate) they yield corresponding chromenols or anhydro bases.

1.9 PHYSICAL DATA

1.9.1 Physical Data Table of 2, 4-Dimethylchromenylium Salts



Sr. No.	Sample Code	Substitution				Molecular Formula	M. Wt	MP ° C	Yield %	Colour
		R_1	R_2	R_3	R_4					
1	MNP-001*	H	OH		H	$C_{11}H_{11}O_2\,ClO_4$	274	164	90	Yellow
2	MNP-002*	H	H	CH_3	H	$C_{12}H_{13}O\,ClO_4$	272	160	45	Pale Yellow
3	MNP-003*	H	CH_3		H	$C_{12}H_{13}O\,ClO_4$	272	180	85	Pale Yellow
4	MNP-004	CH_3	H	CH_3	H	$C_{13}H_{15}O\,ClO_4$	286	163	70	Pale Green
5	MNP-005	CH_3	CH_3	H	H	$C_{13}H_{15}O\,ClO_4$	286	219	85	Pale Yellow
6	MNP-006	H	CH_3	H	CH_3	$C_{13}H_{15}O\,ClO_4$	286	251	75	Pale Yellow
7	MNP-007	H	OCH_3	H	H	$C_{12}H_{13}O_2ClO_4$	288	190	80	Reddish
8	MNP-008	H	CH_3	CH_3	H	$C_{13}H_{15}O\,ClO_4$	286	206	70	Pale Yellow
9	MNP-009	Benzo		H	H	$C_{15}H_{13}O\,ClO_4$	308	208	60	Green
10	MNP-010	H	H	Benzo		$C_{15}H_{13}O\,ClO_4$	308	219	58	Brown
11	MNP-011*	OH	OH	H	H	$C_{11}H_{11}O_3\,ClO_4$	290	166	90	Orange
12	MNP-012*	H	OH	H	OH	$C_{11}H_{11}O_3\,ClO_4$	290	240	85	Yellow
13	MNP-013	OCH_3	H	H	Allyl	$C_{15}H_{17}O_2\,ClO_4$	328	172	70	Yellow
14	MNP-014	H	OH	H	H	$C_{11}H_{11}O_2HSO_4$	272	174	78	Yellow
15	MNP-015	OH	OH	H	H	$C_{11}H_{11}O_3\,HSO_4$	288	212	85	Orange
16	MNP-016	H	OH	H	OH	$C_{11}H_{11}O_3\,HSO_4$	288	213	82	Yellow
17	MNP-017	Benzo		H	H	$C_{15}H_{13}O\,HSO_4$	306	335	60	Green

NB: '*' Indicating the compounds are reported. Ref. No. [55, 56, 57(a, b)]

1.10 SPECTRAL DISCUSSION

1.10.1 UV Spectra

UV analysis of the synthesized compounds was recorded on Shimadzu UV-Visible Spectrophotometer Pharmaspec-1700. In the present case ultra-violet absorption spectra of 2,4-dimethylbenzopyrylium perchlorates and 2,4-dimethylbenzopyrylium sulphates have been studied and obtained data are demonstrated here.

Sr. No.	Sample Code	λ_1	λ_2	λ_3	λ_4	λ_5
		log ε_1	log ε_2	log ε_3	log ε_4	log ε_5
1	MNP-001	210	254	308	330	382
		1.008	0.156	0.057	-0.067	0.063
2	MNP-002	218	254	310	-	-
		2.139	0.411	0.230	-	-
3	MNP-003	216	254	310	-	-
		2.474	0.519	0.280	-	-
4	MNP-004	221	254	308	-	-
		2.230	0.648	0.216	-	-
5	MNP-005	216	256	308	-	-
		2.118	0.756	0.222	-	-
6	MNP-006	220	256	310	334	-
		3.286	1.931	0.484	0.550	-
7	MNP-007	212	256	306	↓322	372
		1.658	0.393	0.269	-0.000	0.136
8	MNP-008	222	256	310	340	-
		3.260	1.850	0.480	0.555	-
9	MNP-009	↓208	240	310	346	-
		0.788	2.409	0.216	0.177	-
10	MNP-010	↓208	240	310	346	-
		0.788	2.409	0.216	0.177	-
11	MNP-011	212	276	↓304	344	↓372
		2.741	2.319	0.060	0.632	0.035
12	MNP-012	↓246	268	↓304	346	↓376
		0.654	1.626	0.147	0.747	0.326
13	MNP-013	↓256	284	↓300	326	↓336
		-0.091	0.069	-0.046	-0.019	-0.020
14	MNP-014	212	256	308	↓320	384
		1.299	0.535	0.183	0.083	0.376
15	MNP-015	218	276	-	346	448
		0.455	0.359	-	0.034	0.010
16	MNP-016	↓246	270	348	↓376	422
		0.115	0.518	0.200	0.022	0.106
17	MNP-017	↓240	264	318	348	-
		0.131	0.654	-0.053	-0.041	-

1.10.2 IR Spectra

IR spectra of the synthesized compounds were recorded on Shimadzu FT-IR 8400 model using KBr powder method. Various functional groups present were identified by characteristic frequency obtained for them.

The characteristic bands of OH group showed in the region of 3650-3550 cm^{-1} with the deformation due to in plane bending at 1200-1000 cm^{-1}. Aromatic C-H stretching and bending vibrations showed at 3070-3030 cm^{-1} and 1400-600 cm^{-1} respectively. C-H stretching and bending frequencies for methyl group were obtained near 2950-2850 cm^{-1} and 1450-1375 respectively. Characteristic frequency of C-O stretching and bending vibration showed near 1250 $cm^{-1}$and 1050 cm^{-1} respectively.

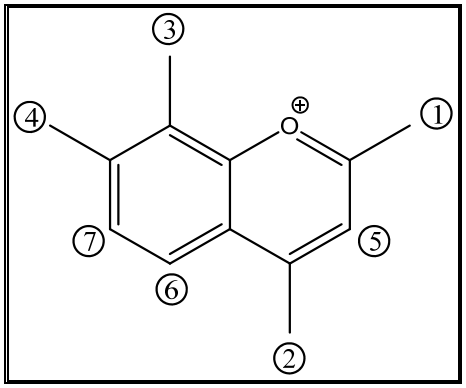
1.10.3 Mass Spectra

Mass spectra of the synthesized compounds were recorded on Shimadzu GC-MS QP-2010 model using direct injection probe technique. The base peak was found in agreement with molecular weight of the respective compound.

1.10.4 ^{1}H NMR Spectra

^{1}H NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR spectrometer by making a solution of samples in $CDCl_3$/ DMSO-d_6/MeOD/TFA solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Number of protons identified from ^{1}H NMR spectra and their chemical shift (δ ppm) were in the agreement of the structure of the molecule. *J* values were calculated to identify o-, m- and p- coupling. In some cases, aromatic protons were obtained as multiplet. Interpretation of representative spectrum is discussed as follows.

1.10.4.1 ^{1}H NMR of 2,4,7,8-Tetramethylchromenylium Perchlorate (MNP-005)



1. Proton no. 3 and 4 of total 6H of $-CH_3$ group gave a singlet at 2.69 δ ppm.
2. Proton no. 1 of total 3H gave a singlet at 3.08 δ ppm.
3. Proton no. 2 of total 3H gave a singlet at 3.13 δ ppm.
4. Proton no. 5 of 1H gave a singlet at 7.80 δ ppm, which was merged with proton no. 6.
5. Proton no. 6 of 1H gave a doublet at 7.83 δ ppm- 7.84 δ ppm and *J* value of this proton is 5.92 Hz which suggest ortho coupling.
6. Proton no. 7 of 1H gave a doublet at 8.11δ ppm- 8.13 δ ppm and *J* value of this proton is 8.52 Hz which suggest ortho coupling.

Thus, by observing and assigning the signals in the NMR spectrum and by the calculation of the *J* values for above proton, we can clearly suggest that the proposed structure for compound MNP-005 has been confirmed. The spectrum is given on page no. 35.

1.10.5 ^{13}C NMR Spectra

^{13}C NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in $CDCl_3$/ DMSO-d_6/MeOD/TFA solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Types of carbons identified from NMR spectrum and their chemical shifts (δ ppm) were in the agreement with the structure of the molecule.

1.10.6 Elemental Analysis

Elemental analysis of the synthesized compounds was carried out on Vario EL Carlo Erba 1108 which showed calculated and found percentage values of Carbon, Hydrogen and Nitrogen in support of the structure of synthesized compounds.

The analytical data for individual compounds synthesized in this chapter is mentioned here.

1.11 ANALYTICAL DATA

1) 7-Hydroxy-2,4-dimethylchromenylium Perchlorate (MNP-001)

Yield: 90 % **IR** (cm^{-1}): 3640-3600 (O-H str.), 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1410-1310 (O-H bend), 1330 (C-OH), 800-750 (C-H oop def); **MS**: m/z: 274.02, 175.08 (BP); **^{1}H NMR** (MeOD) δ ppm: 3.80-3.85 (d, 6H), 8.33-8.34 (d, 1H, *J*=2.8), 8.38-8.41 (m, 2H), 9.11-9.14 (d, 1H, *J*=12); **^{13}C NMR** ($CDCl_3$)δ ppm: 21.9, 23.34, 105.96, 111.67, 115.43, 119.18, 121.39, 122.30, 122.93, 125.06, 131.77, 170.93, 174.78181.25; Anal. Calculated for $C_{11}H_{11}O_2$ ClO_4, C, 48.10; H, 4.04; Cl, 12.91; O, 34.95; Found: C, 48.25; H, 3.93.

2) 2,4,6-Trimethylchromenylium Perchlorate (MNP-002)

Yield: 45 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 272.05, 173.23 (BP); **^{1}H NMR** ($CDCl_3$) δ ppm: 2.66 (s, 3H), 3.09 (s, 3H), 3.14 (s, 3H), 8.055-8.058 (d, 2H, J=1.08,), 8.12-8.14 (s, 2H, *J*=0.48, *J*=5.48); Anal. Calculated for $C_{12}H_{11}O$ ClO_4, C, 52.86; H, 4.81; Cl, 13.00; O, 29.34: Found: C, 52.94; H, 4.73.

3) 2,4,7-Trimethylchromenylium Perchlorate (MNP-003)

Yield: 85 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 272.05, 173.23 (BP); Anal. Calculated for $C_{12}H_{11}O$ ClO_4, C, 52.86; H, 4.81; Cl, 13.00; O, 29.34: Found: C, 52.73; H, 4.78.

4) 2,4,6,8-Tetramethylchromenylium Perchlorate (MNP-004)

Yield: 70 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 286.06, 186.14 (BP); Anal. Calculated for $C_{13}H_{15}O$ ClO_4, C, 54.46; H, 5.27; Cl, 12.37; O, 27.90: Found: C, 54.55; H, 5.14.

5) 2,4,7,8-Tetramethylchromenylium Perchlorate (MNP-005)

Yield: 85 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 286.06, 186.14 (BP); **^{1}H NMR** ($CDCl_3$) δ ppm: 2.69 (s, 6H), 3.08 (s, 3H), 3.13 (s, 3H), 7.80 (s, 1H), 7.83-7.84 (d, 1H, *J*=5.92), 8.11-8.13 (d, 1H, *J*=8.52); **13C NMR** ($CDCl_3$) δ ppm: 23.70, 23.98, 26.83, 29.17, 112.04, 115.80, 119.55, 120.46, 123.31, 125.45, 126.11, 138.57, 143.97, 157.18, 162.10, 178.38, 182.10; Anal. Calculated for $C_{13}H_{15}O\ ClO_4$, C, 54.46; H, 5.27; Cl, 12.37; O, 27.90: Found: C, 54.52; H, 5.36.

6) 2,4,5,7-Tetramethylchromenylium Perchlorate (MNP-006)

Yield: 75 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 286.06, 186.14 (BP); **MS**: m/z: 286.06, 186.14 (BP); **^{1}H NMR** (TFA) δ ppm: 3.46 (s, 3H), 3.78-3.81 (s, 6H), 4.00-4.03 (s, 3H), 8.44 (s, 1H), 8.51 (s, 1H), 8.61 (s, 1H); **^{13}C NMR** ($CDCl_3$) δ ppm: 23.70, 23.98, 26.83, 29.17, 112.04, 115.80, 119.55, 120.46, 123.31, 125.45, 126.11, 138.57, 143.97, 157.18, 162.10, 178.38, 182.10; Anal. Calculated for $C_{13}H_{15}O\ ClO_4$, C, 54.46; H, 5.27; Cl, 12.37; O, 27.90: Found: C, 54.39; H, 5.21.

7) 7-Methoxy-2,4-dimethylchromenylium Perchlorate (MNP-007)

Yield: 80 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1260-1200 (Ar-O-Al str), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 288.68, 189.09 (BP); **^{1}H NMR** (DMSO) δ ppm: 3.07 (s, 6H), 4.14 (s, 3H), 7.53-7.56 (m, 2H), 7.87 (s, 1H), 8.32-8.35 (d, 1H, *J*=6.12); Anal. Calculated for $C_{12}H_{13}O\ ClO_4$, C, 49.93; H, 4.54; Cl, 12.28; O, 33.25: Found: C, 49.88; H, 4.61.

8) 2,4,6,7-Tetramethylchromenylium Perchlorate (MNP-008)

Yield: 70 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 286.06, 186.14 **MS**: m/z: 287.06, 186.14 (BP); **^{1}H NMR** (TFA) δ ppm: 3.35 (s, 3H), 3.42 (s, 3H), 3.81-3.83 (d, 6H),

8.53 (s, 1H), 8.71 (s, 1H), 8.89 (s, 1H); **^{13}C NMR** δ ppm: 21.36, 22.18, 22.82, 23.83, 111.70, 115.45, 119.21, 121.67, 122.96, 123.60, 125.79, 128.07, 145.49, 157.86, 159.12, 175.79, 182.68; Anal. Calculated for $C_{13}H_{15}O\ ClO_4$, C, 54.46; H, 5.27; Cl, 12.37; O, 27.90: Found: C, 54.41; H, 5.30.

9) 2,4-Dimethylbenzo[h]chromen-1-ium Perchlorate (MNP-009)

Yield: 60 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 308.71, 209.26 (BP); Anal. Calculated for $C_{15}H_{13}O\ ClO_4$, C, 58.36; H, 4.24; Cl, 11.48; O, 25.91: Found: C, 58.42; H, 4.19.

10) 1,3-Dimethylbenzo[f]chromen-4-ium Perchlorate (MNP-010)

Yield: 58 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 308.71, 209.26 (BP); **^{1}H NMR** ($CDCl_3$) δ ppm: 3.10 (s, 3H), 3.47 (s, 3H), 7.93-7.97 (t, 1H), 8.01-8.06 (m, 3H), 8.21-8.23 (dd, 1H, *J*=1.28, *J*=6.72), 8.62-8.64 (d, 1H, *J*=9.16), 8.84-8.86 (d, 1H, *J*=8.56); Anal. Calculated for $C_{15}H_{13}O\ ClO_4$, C, 58.36; H, 4.24; Cl, 11.48; O, 25.91: Found: C, 58.30; H, 4.28.

11) 7,8-Dihydroxy-2,4-dimethylchromenylium Perchlorate (MNP-011)

Yield: 90 % **IR** (cm^{-1}): 3600-3640 (O-H str), 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1410-1310 (O-H bend), 1330 (C-OH), 800-750 (C-H oop def); **MS**: m/z: 290.65, 191.20 (BP); **^{1}H NMR** ($CDCl_3$) δ ppm: 2.99-3.028 (d, 6H), 7.52-7.55 (d, 1H, *J*=9.16), 7.66-7.67 (s, 1H), 7.81-7.83 (d, 1H, *J*=9.16); Anal. Calculated for $C_{11}H_{11}O\ ClO_4$, C, 45.46; H, 3.81; Cl, 12.20; O, 38.53: Found: C, 45.53; H, 3.76.

12) 5,7-Dihydroxy-2,4-dimethylchromenylium Perchlorate (MNP-012)

Yield: 85 % **IR** (cm^{-1}): 3600-3640 (O-H str), 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1410-1310 (OH bend), 1330 (C-OH), 800-750 (C-H oop def);

MS: m/z: 290.65, 191.20 (BP); Anal. Calculated for $C_{11}H_{11}O\ ClO_4$, C, 45.46; H, 3.81; Cl, 12.20; O, 38.53: Found: C, 45.39; H, 3.87.

13) 6-Allyl-8-methoxy-2,4-dimethylchromenylium Perchlorate (MNP-013):

Yield: 70 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1260-1200 (Ar-O-Al str), 1120-1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 328.74, 229.29 (BP); ^1H NMR ($CDCl_3$) δ ppm: ;Anal. Calculated for $C_{11}H_{11}O\ ClO_4$, C, 54.80; H, 5.21; Cl, 10.78; O, 29.20: Found: C, 54.74; H, 5.34.

14) 7-Hydroxy-2,4-dimethylchromenylium sulphate (MNP-014)

Yield: 78 % **IR** (cm^{-1}): 3600-3640 (O-H str), 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1410-1310 (O-H bend), 1330 (C-OH), 800-750 (C-H oop def); **MS**: m/z: 272.27, 175.20 (BP); Anal. Calculated for $C_{11}H_{11}O_2\ HSO_4$, C, 48.52; H, 4.44; O, 35.26; S, 11.78: Found: C, 48.46; H, 4.50; S, 11.71.

15) 7,8-Dihydroxy-2,4-dimethylchromenylium Sulphate (MNP-015)

Yield: **85** % **IR** (cm^{-1}): 3600-3640 (O-H str), 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1410-1310 (O-H bend), 1330 (C-OH), 800-750 (C-H oop def); **MS**: m/z: 288.27, 191.20 (BP); Anal. Calculated for $C_{11}H_{11}O_3\ HSO_4$, C, 45.83; H, 4.20; O, 38.85; S, 11.12: Found: C, 45.72; H, 4.31; S, 11.08.

16) 5,7-Dihydroxy-2,4-dimethylchromenylium Sulphate (MNP-016)

Yield: 82 % **IR** (cm^{-1}): 3600-3640 (O-H str), 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1410-1310 (O-H bend), 1330 (C-OH), 800-750 (C-H oop def); **MS:** m/z: 288.27, 191.20 (BP); Anal. Calculated for $C_{11}H_{11}O_3\ HSO_4$, C, 45.83; H, 4.20; O, 38.85; S, 11.12: Found: C, 45.76; H, 4.30; S, 11.19.

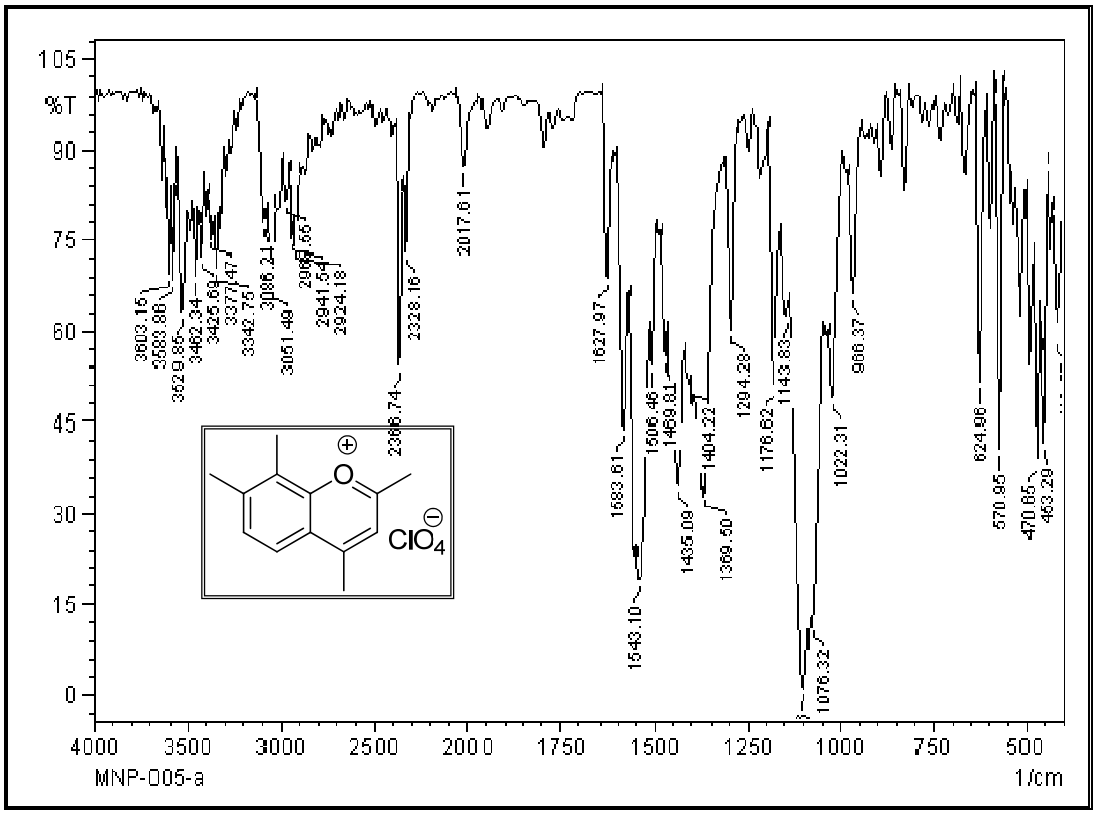
17) 2,4-Dimethylbenzo[h]chromen-1-ium Sulphate (MNP-017)

Yield: 60 % **IR** (cm^{-1}): 3045-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2920 (Sym C-H str. -CH_3), 1545, 1500, 1400 (Ar C=C str.), 1345 (C-H bend –CH_3), 1120-

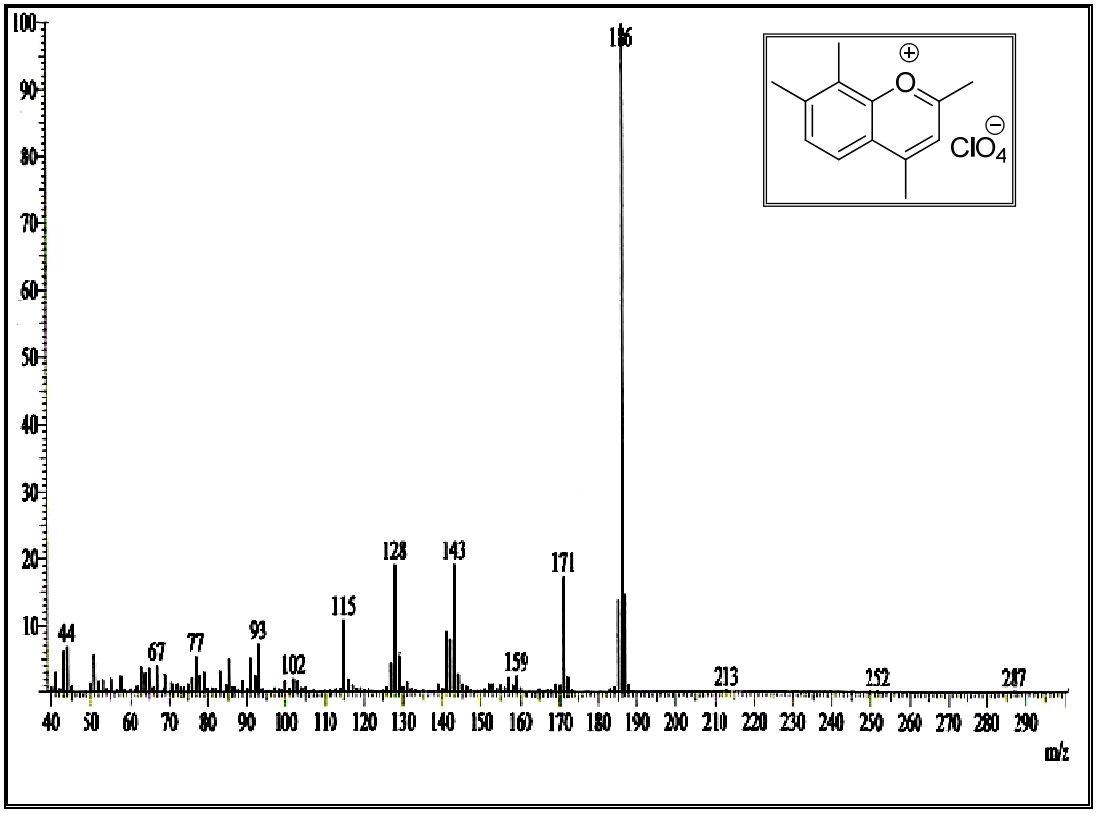
1000 (C-O str), 800-750 (C-H oop def); **MS**: m/z: 306.33, 209.26 (BP); Anal. Calculated for $C_{15}H_{13}O\ HSO_4$, C, 58.81; H, 4.61; O, 26.11; S, 10.47: Found: C, 58.87; H, 4.58; S, 10.39.

1.12 REPRESENTATIVE SPECTRA

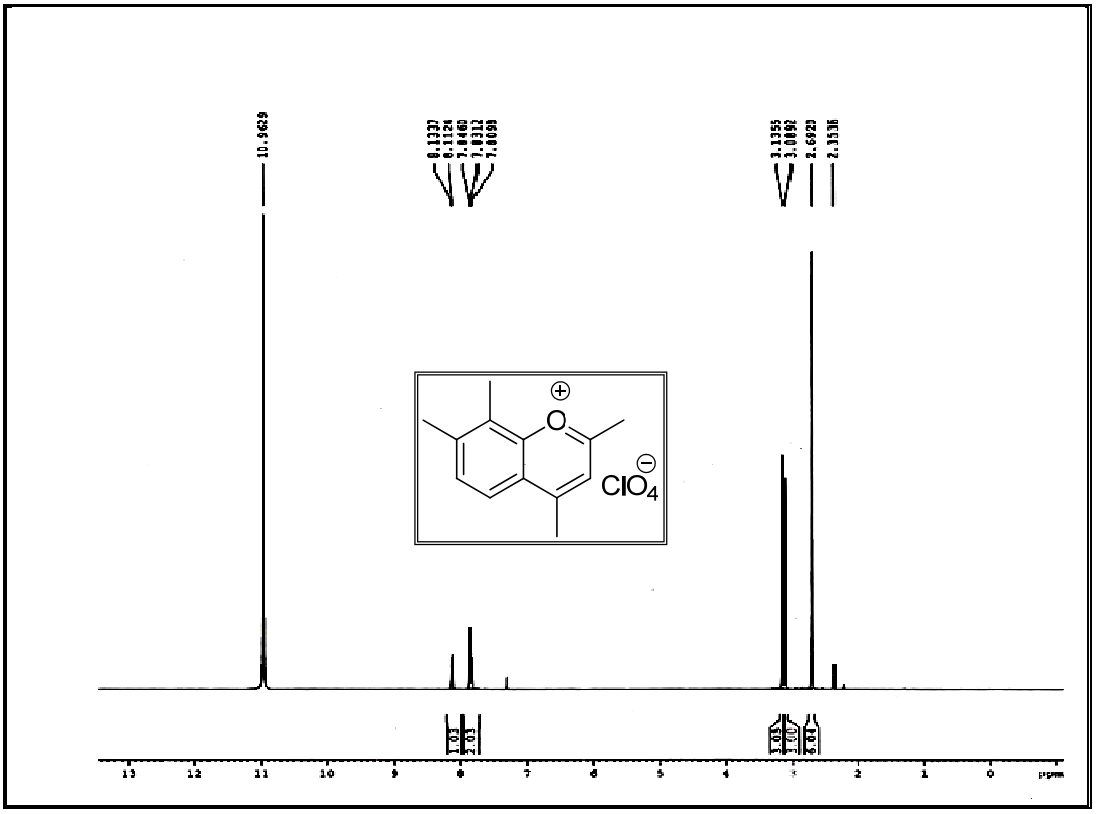
1.12.1 IR Spectrum of MNP-005



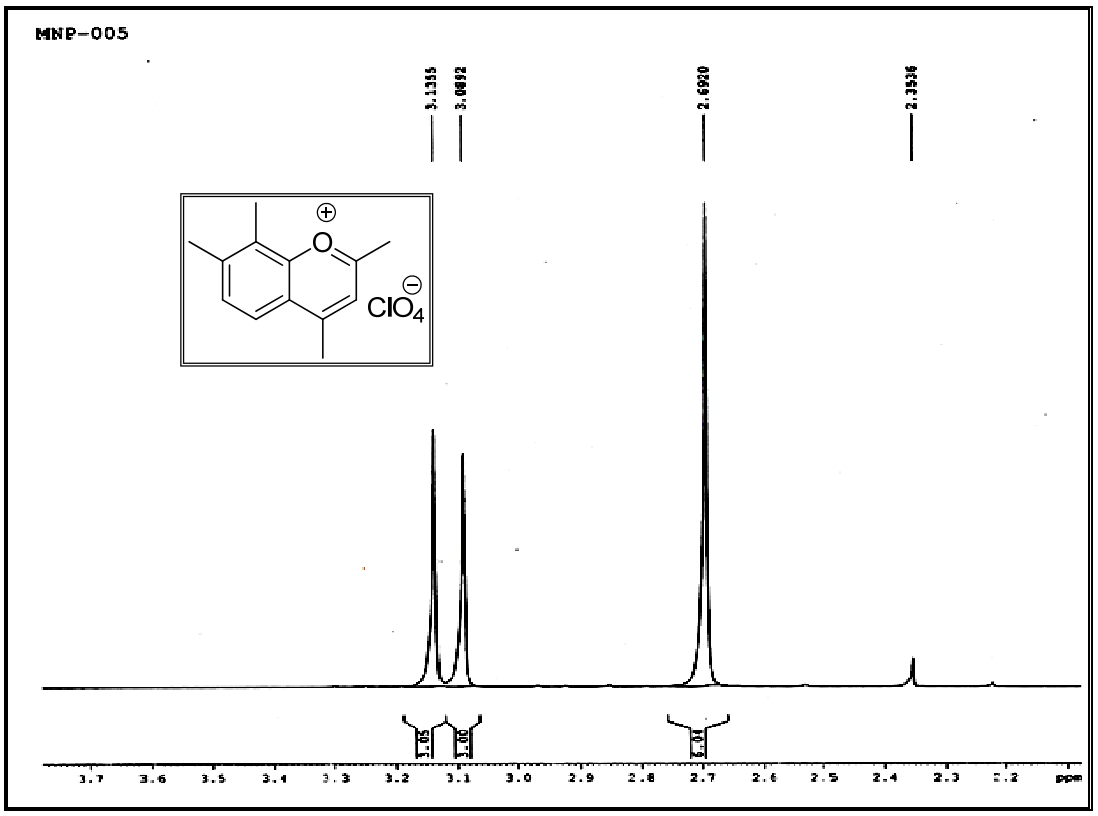
1.12.2 Mass Spectrum of MNP-005



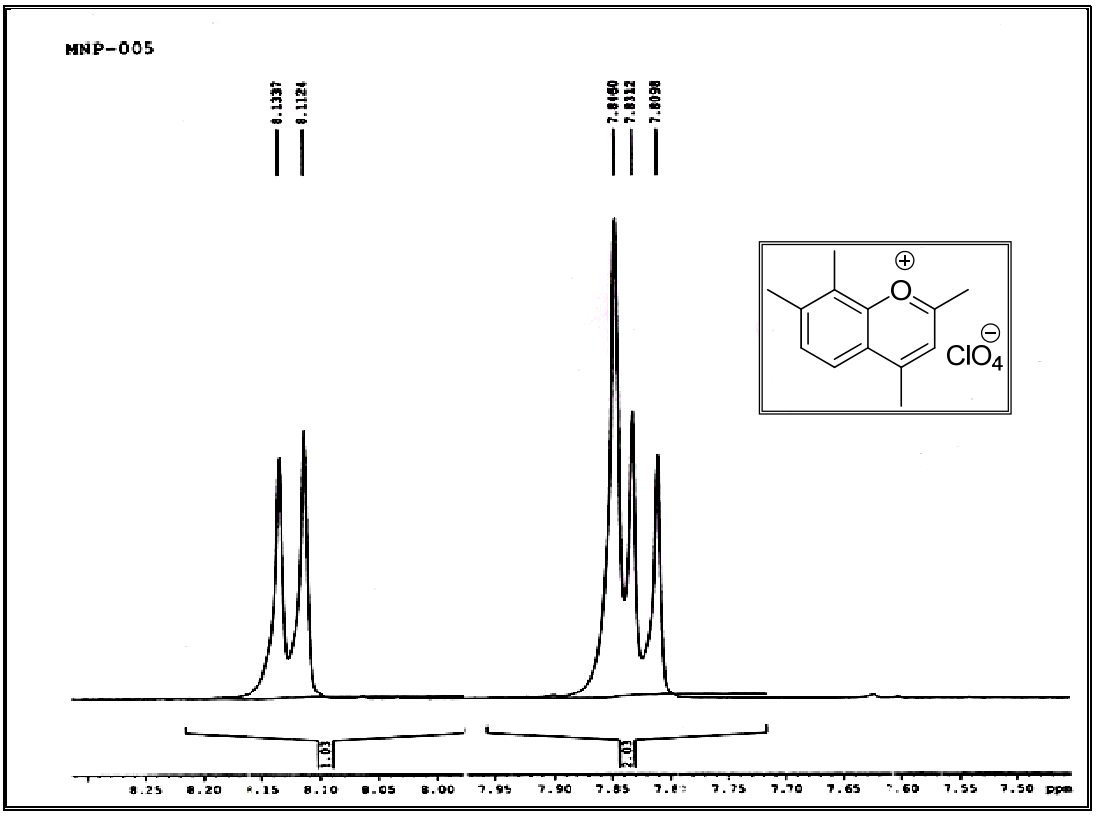
1.12.3 ^{1}H NMR Spectrum of MNP-005



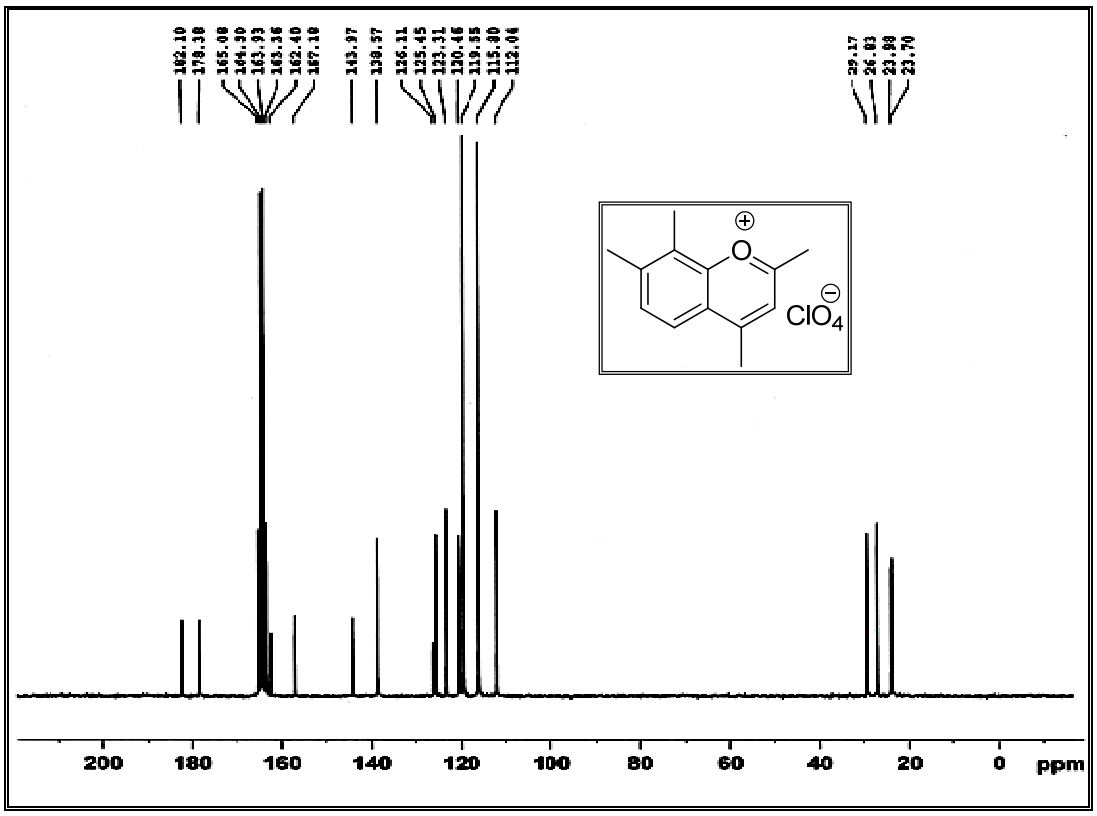
1.12.4 Expanded ^{1}H NMR Spectrum of MNP-005



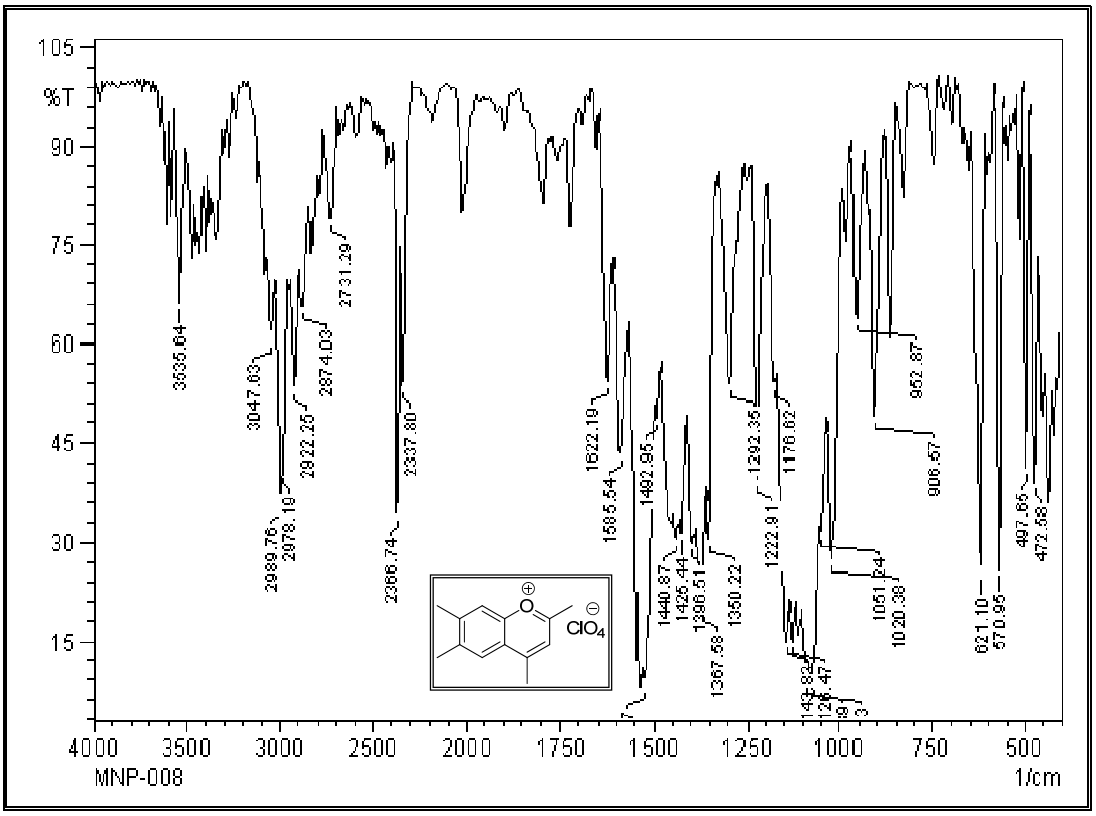
1.12.5 Expanded ^{1}H NMR Spectrum of MNP-005



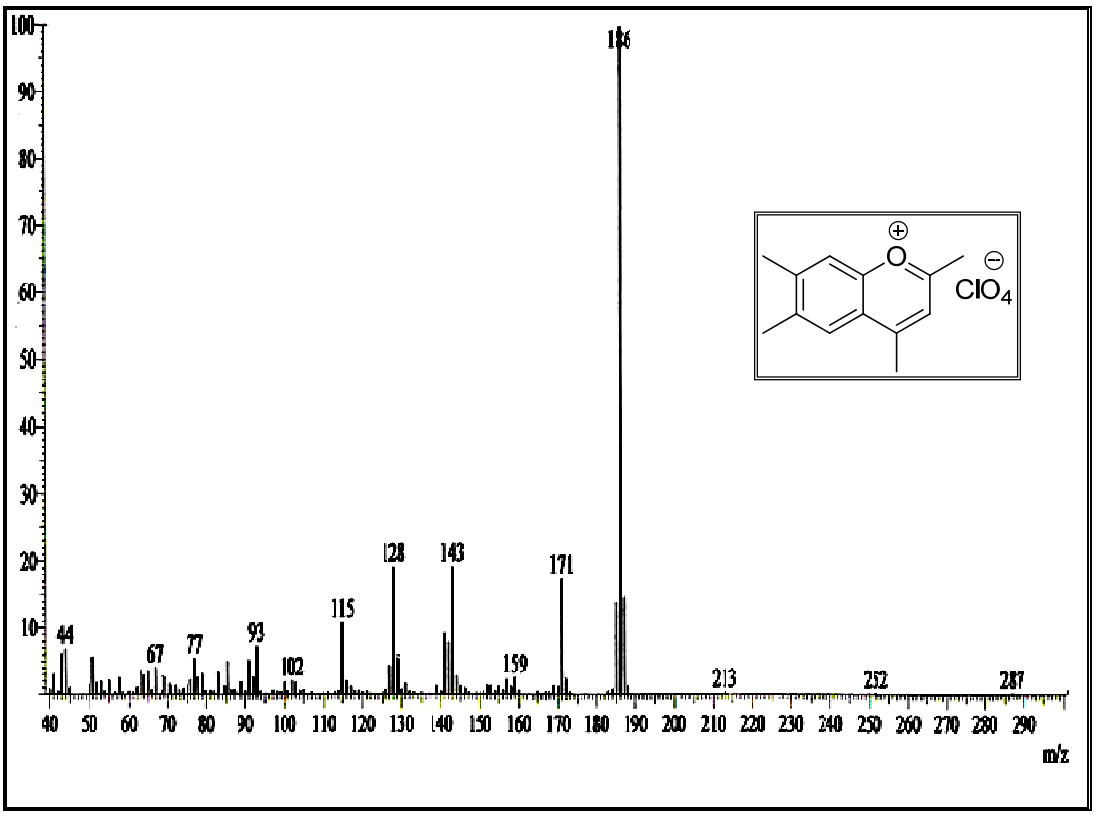
1.12.6 ^{13}C NMR Spectrum of MNP-005



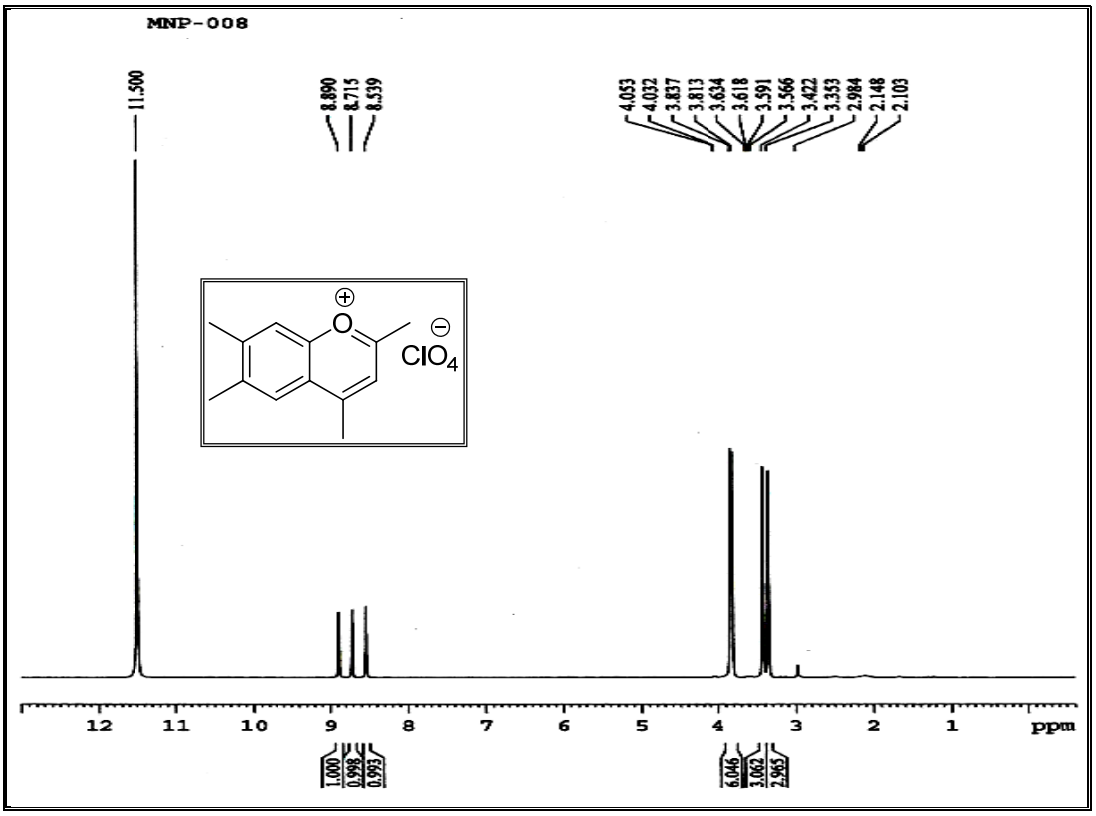
1.12.7 IR Spectrum of MNP-008



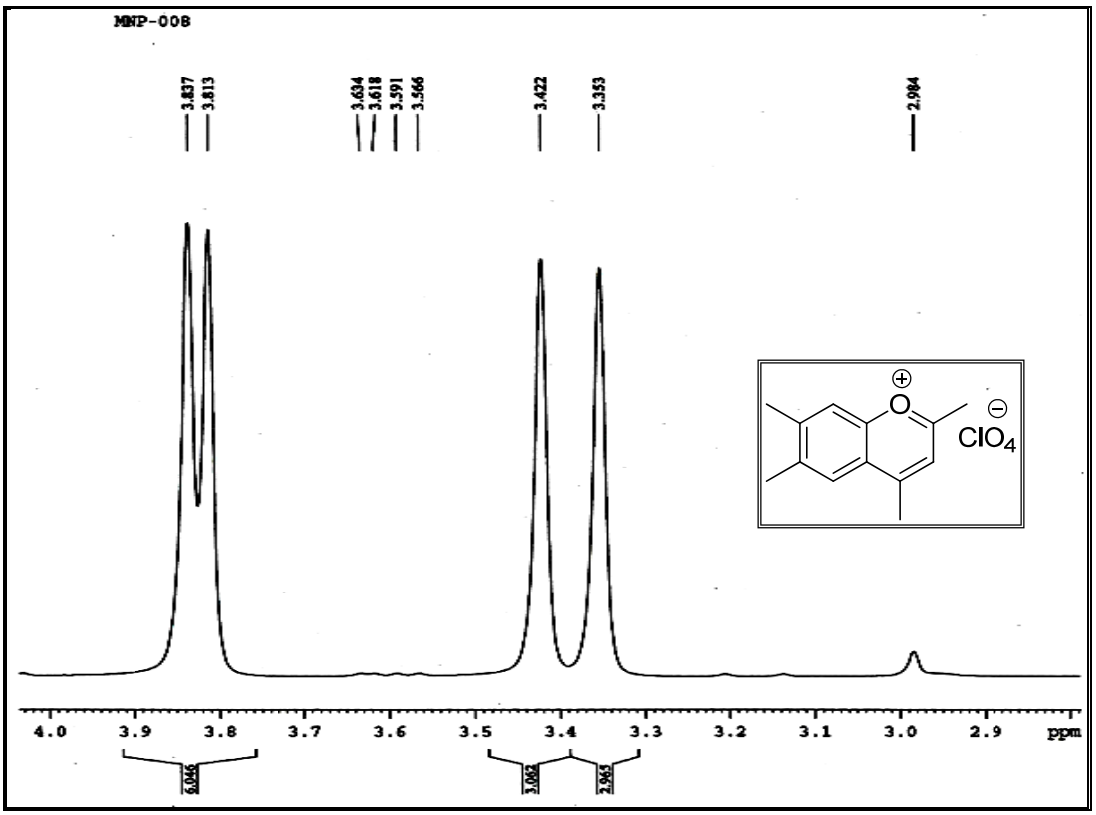
1.12.8 Mass Spectrum of MNP-008



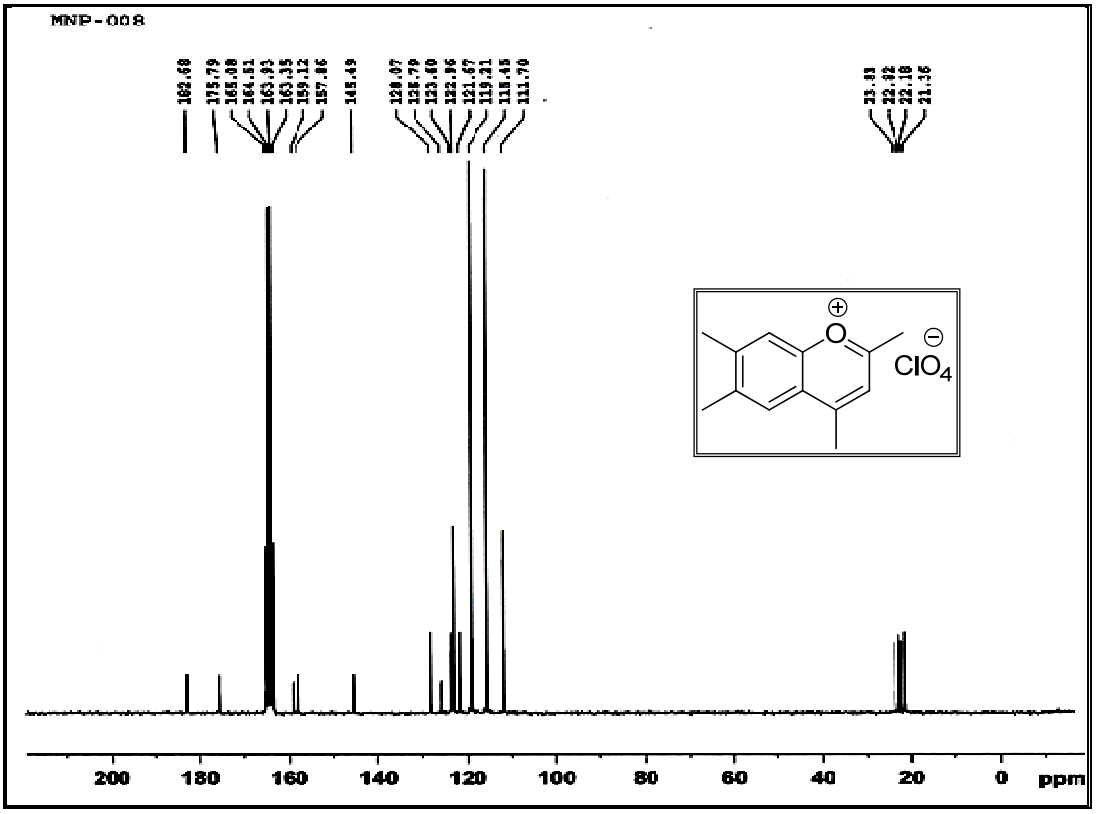
1.12.9 ^{1}H NMR Spectrum of MNP-008



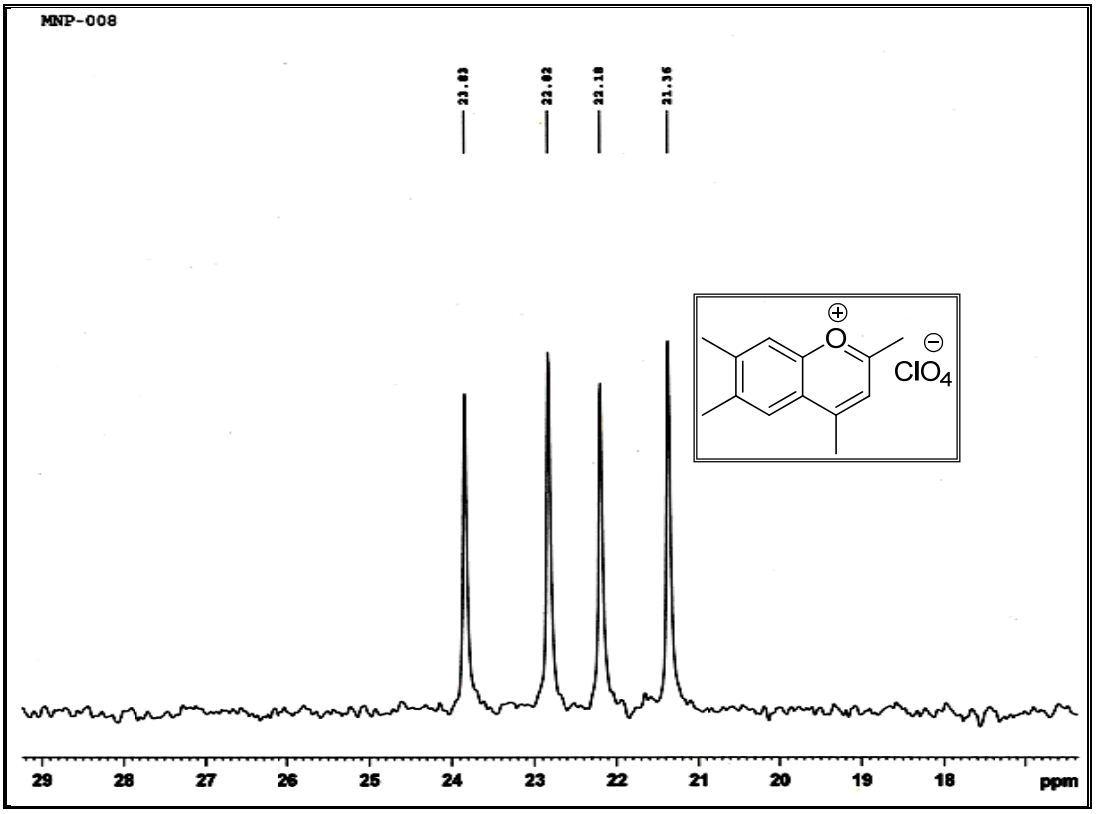
1.12.10 Expanded ^{1}H NMR Spectrum of MNP-008



1.12.11 ^{13}C NMR Spectrum of MNP-008



1.12.12 Expanded ^{13}C NMR Spectrum of MNP-008



1.13 X-RAY CRYSTALLOGRAPHIC STUDY

1.13.1 EXPERIMENTAL

1.13.1.1 Preparation of substituted-2,4-Dimethylchromenylium Perchlorate Salts (General procedure)

To a mixture of substituted phenol (0.05 mole) and acetyl acetone (0.05 mole), perchloric acid (70%; 7.5 mL) was added drop-wise with external cooling at 5-10 ºC temperature. After addition of perchloric acid, the reaction mixture was further allowed to cool at 5-10 ºC and dry hydrogen chloride gas was bubbled through the reaction mixture for 1 hour. Reaction mixture became reddish in colour and was kept overnight at room temperature. Then reaction mixture diluted with excess of dry ether and coloured precipitates were obtained, which was filtered and thoroughly washed with dry ether. Crude product was recrystallized from glacial acetic acid.

1.13.1.2 Preparation of Single Crystals of substituted-2,4-Dimehyl Benzopyrylium Perchlorate Salts

Pure substituted Chromylium Perchlorate Salt (1.0 g) was taken in 25-35 mL glacial acetic acid and heated to 50 ºC for 10-15 minutes till it dissolved. 0.5 g Charcoal was added and further it was heated upto 50 ºC for 5 minutes. The hot solution was filtered through wattmann 41 filter paper. The solution was allowed to cool gradually and kept in a stoppered conical flask slightly opened. The crystals were grown up due to thin layer evaporation.

1.13.2 X-RAY CRYSTALLOGRAPHIC STUDY OF MNP-003

The compound $C_{12}H_{13}ClO_5$, crystallizes in monoclinic crystal class in space group $P2_1/c$ with cell parameters a=8.0400(5) Å, b=11.8590(11) Å, c=13.3490(13) Å, β=102.325(6)°, V=1243.44(18)Å^3 and Z=4. The final residual factor R1=0.0617. The structure exhibits both intra and inter-molecular hydrogen bonding of the type C-H...O.

Tha value of R_{int} and R_{sigma} are 0.0217 and 0.00334 respectively. 2000 phase sets were refined with the best phase set having a CFOM of 0.0703. Using the normalized structure factors with these phases, a total of 1070 phases were generated. The final RE value, equals 21.5%. The non-hydrogen atoms were recognized from the electron density peaks using PLATON and refined using SHELXL-97. All non-hydrogen atoms were refined anisotropically.

The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on the parent atom during successive refinement. 167 parameters were refined with 2057 reflections using SHELXL-97. ORTEP of the molecules is shown in figure.

The title compound shows planar conformation. The dihedral angle between the least squares planes O1-C2-C3-C4-C5-C10 and C5-C6-C7-C8-C9-C10 is 0.76 (13)º. Total puckering amplitude Q for ten membered ring O1-C2-C3-C4-C5-C6-C7-C8-C9-C10 is 0.033(3) Å. The torsion angles about C11-C2-C3-C4 and C13-C8-C9-C10 being -180(3)º and -179(3)º show anti-periplanner conformation respectively.

The molecule exhibits intra and inter-molecular hydrogen bonds of the type C-H...O. The intramoleucular hydrogen bond C6-H6...O18, has a length of 3.419(4) Å with an angle of 171º. The inter-molecular hydrogen bond C11-H11...O17, has a length of 3.493(6) Å and an angle of 172º, with the symmetry codes 2-x, -y, -z.

Figure 1.13.1 Oak Ridge Thermal Ellipsoid Plot (ORTEP) of the MNP-003 molecule at 50% probability

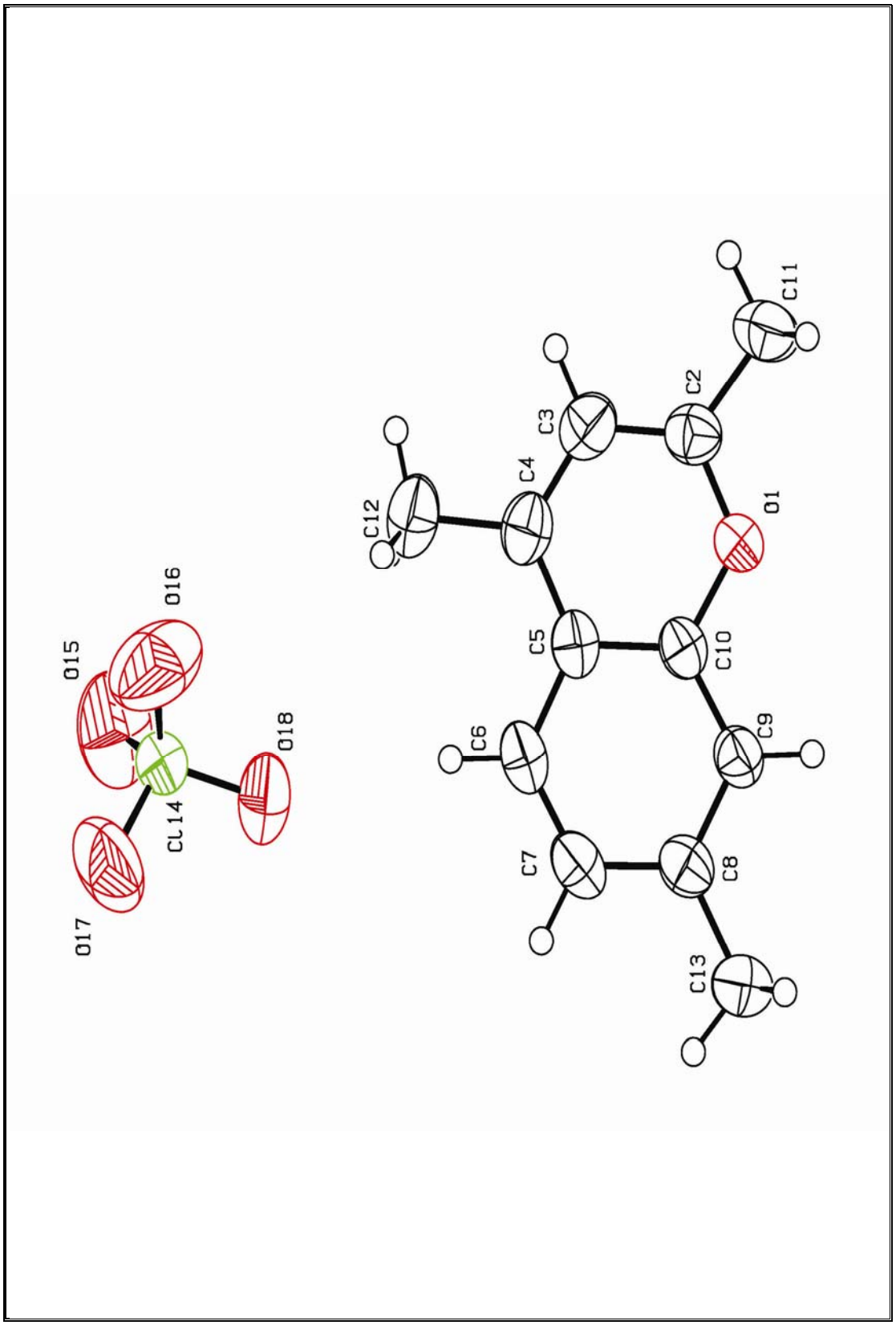


Table 1.13.1 Crystal Data and Structure Refinement for Cell

Empirical formula	$C_{12}H_{13}ClO_5$
Formula weight	272.67
Temperature	293(2)K
Wavelength	0.71
Crystal system	Monoclinic
Space group	$P2_1$ /c
Cell dimensions	*a*=8.0400(5) Å , *b*=11.8590(11) Å, *c*=13.3490(13) Å , β=102.325(6)°
Volume	1243.44(18) $Å^3$
Z	4
Density (calculated)	1.457 Mg/m^3
Absorption coefficent	0.317 mm^{-1}
F_{000}	568
Crystal size	0.3x0.3x0.25 mm
θ range for data collection	2.59 °
Index ranges	-8<= h<=8, -14<=k<=14, -15<=l<=15
Reflections collected	3815
Independent reflections	2057 [R_{int}=0.0219]
Refinement method	Full-matrix least-squares in F^2
Data/restraints/parameters	2057/0/167
Goodness-of-fit on F^2	1.09
Final R indices [I>2\σ(I)]	R1=0.0617, ωR2=0.1730
R indices (all data)	R1=0.0669, ωR2=0.1803
Extinction coefficient	0.105(14)
Largest diff. peak and holes	0.473 and -0.264 e. $Å^{-3}$

Table 1.13.2 Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms

Atom	X	Y	Z	$U_{(eq)}$
O1	1.0369(2)	0.13250(2)	-0.2304(1)	0.0476(5)
C2	0.8937(4)	0.0760(2)	-0.2653(2)	0.0521(7)
C3	0.7840(4)	0.0530(2)	-0.2026(2)	0.0577(7)
C4	0.8161(4)	0.0881(2)	-0.1021(2)	0.0537(7)
C5	0.9712(4)	0.1462(2)	-0.0635(2)	0.0480(6)
C6	1.0264(4)	0.1852(3)	0.0380(2)	0.0562(7)
C7	1.1764(4)	0.2422(3)	0.0666(2)	0.0582(8)
C8	1.2817(4)	0.2646(2)	-0.0029(2)	0.0498(7)
C9	1.2321(3)	0.2261(2)	-0.1019(2)	0.0484(6)
C10	1.0796(3)	0.1683(2)	-0.1308(2)	0.0442(6)
C11	0.8713(5)	0.0423(3)	-0.3744(2)	0.0673(9)
C12	0.6907(4)	0.0660(3)	-0.0370(3)	0.0710(9)
C13	1.4437(4)	0.3292(3)	0.0326(2)	0.0645(8)
Cl14	0.6851(9)	0.1129(6)	0.2787(5)	0.0560(4)
O15	0.6458(5)	0.0030(3)	0.2421(4)	0.1360(2)
O16	0.5348(5)	0.1764(4)	0.2658(3)	0.1230(1)
O17	0.7578(5)	0.1070(4)	0.3838(2)	0.1289(1)
O18	0.8053(4)	0.1612(3)	0.2292(2)	0.1092(1)

$$U_{eq} = (1/3) \sum_i \sum_J U_{ij} (\alpha_i^* \alpha_j^*) (ai \cdot aj)$$

Table 1.13.3 Atomic coordinates and equivalent thermal parameters of the hydrogen atoms

Atom	X	Y	Z	U_{eq}
H3	0.6851	0.0126	-0.2286	0.069
H6	0.9599	0.1719	0.0859	0.067
H7	1.2101	0.2670	0.1340	0.070
H9	1.3002	0.2387	-0.1490	0.058
H11A	0.8642	0.1085	-0.4165	0.101
H11B	0.7685	-0.0009	-0.3944	0.101
H11C	0.9666	-0.0026	-0.3830	0.101
H12A	0.6341	0.1350	-0.0268	0.106
H12B	0.7489	0.0367	0.0282	0.106
H12C	0.6083	0.0120	-0.0703	0.106
H13A	1.4980	0.3405	-0.0241	0.097
H13B	1.5182	0.2875	0.0854	0.097
H13C	1.4186	0.4010	0.0590	0.097

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} (\alpha_i^* \alpha_j^*) (ai \cdot aj)$$

Table 1.13.4 Anisotropic thermal parameters of the non-hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	0.048(1)	0.056(1)	0.034(1)	-0.003(7)	0.009(7)	-0.001(7)
C2	0.053(2)	0.050(1)	0.050(2)	0.001(1)	0.004(1)	0.002(1)
C3	0.050(2)	0.057(2)	0.064(2)	-0.005(1)	0.008(1)	0.006(1)
C4	0.050(2)	0.053(2)	0.061(2)	0.004(1)	0.017(1)	0.012(1)
C5	0.050(2)	0.049(1)	0.047(2)	0.005(1)	0.017(1)	0.006(1)
C6	0.064(2)	0.065(2)	0.045(2)	0.007(1)	0.023(1)	0.007(1)
C7	0.065(2)	0.070(2)	0.040(1)	0.007(1)	0.011(1)	-0.004(1)
C8	0.055(2)	0.050(1)	0.043(1)	0.004(1)	0.007(1)	0.002(1)
C9	0.053(2)	0.052(1)	0.041(1)	-0.001(1)	0.013(1)	0.003(1)
C10	0.049(2)	0.045(1)	0.039(1)	0.004(1)	0.010(1)	0.003(1)
C11	0.071(2)	0.075(2)	0.051(2)	-0.007(2)	0.002(1)	-0.008(1)
C12	0.058(2)	0.084(2)	0.078(2)	-0.002(2)	0.029(2)	0.011(2)
C13	0.066(2)	0.069(2)	0.055(2)	-0.011(1)	0.004(1)	-0.006(1)
Cl14	0.054(6)	0.067(6)	0.048(5)	-0.006(3)	0.014(3)	-0.002(3)
O15	0.111(3)	0.095(2)	0.205(4)	-0.027(2)	0.041(3)	-0.052(2)
O16	0.104(2)	0.142(3)	0.131(3)	0.059(2)	0.045(2)	0.032(2)
O17	0.104(3)	0.224(4)	0.055(2)	0.001(2)	0.009(2)	0.012(2)
O18	0.111(2)	0.138(3)	0.095(2)	-0.042(2)	0.059(2)	-0.007(2)

Table 1.13.5 Bond Lengths (Å)

Atoms	Length	Atoms	Length
O1-C2	1.328(3)	C6-C7	1.364(4)
O1-C10	1.368(3)	C7-C8	1.408(4)
C2-C3	1.366(4)	C8-C9	1.375(4)
C2-C11	1.484(4)	C8-C13	1.498(4)
C3-C4	1.376(4)	C9-C10	1.386(4)
C4-C5	1.421(4)	Cl14-O17	1.402(3)
C4-C12	1.488(4)	Cl14-O15	1.403(3)
C5-C10	1.403(3)	Cl14-O16	1.403(3)
C5-C6	1.411(4)	Cl14-O18	1.405(3)

Table 1.13.6 Bond Angles (º)

Atoms	Angle	Atoms	Angle
C2-O1-C10	121.1(2)	C9-C8-C7	118.6(3)
O1-C2-C3	120.7(2)	C9-C8-C13	121.9(3)
O1-C2-C11	113.3(3)	C7-C8-C13	119.5(3)
C3-C2-C11	126.0(3)	C8-C9-C10	119.3(2)
C2-C3-C4	121.7(3)	O1-C10-C9	116.5(2)
C3-C4-C5	117.9(3)	O1-C10-C5	120.2(2)
C3-C4-C12	120.4(3)	C9-C10-C5	123.2(2)
C5-C4-C12	121.7(3)	O17-Cl14-O15	108.5(3)
C10-C5-C6	116.3(2)	O17-Cl14-O16	108.3(2)
C10-C5-C4	118.4(2)	O15-Cl14-O16	109.4(3)
C6-C5-C4	125.3(2)	O17-Cl14-O18	108.0(2)
C7-C6-C5	120.6(2)	O15-Cl14-O18	110.0(2)
C6-C7-C8	121.9(3)	O16-Cl14-O18	112.6(2)

Table 1.13.7 Torsion Angles (º)

Atoms	Angle	Atoms	Angle
C(2)-O(1)-C(10)-(9)	179.7(2)	C(6)-C(7)-C(8)-C(13)	179.0(3)
C(2)-C(3)-C(4)-(12)	177.4(3)	C(8)-C(9)-C(10)-O(1)	179.8(2)
C(3)-C(4)-C(5)-C(6)	-178.2(3)	C(10)-O(1)-C(2)-C(11)	-178.8(2)
C(4)-C(5)-C(6)-C(7)	-178.7(3)	C(11)-C(2)-C(3)-C(4)	-180.0(3)
C(4)-C(5)-C(10)-C(9)	178.7(2)	C(12)-C(4)-C(5)-C(10)	-177.2(3)
C(6)-C(5)-C(10)-O(1)	179.3(2)	C(13)-C(8)-C(9)-C(10)	-179.0(3)

Figure 1.13.2 Packing of the MNP-003 molecules down a axis

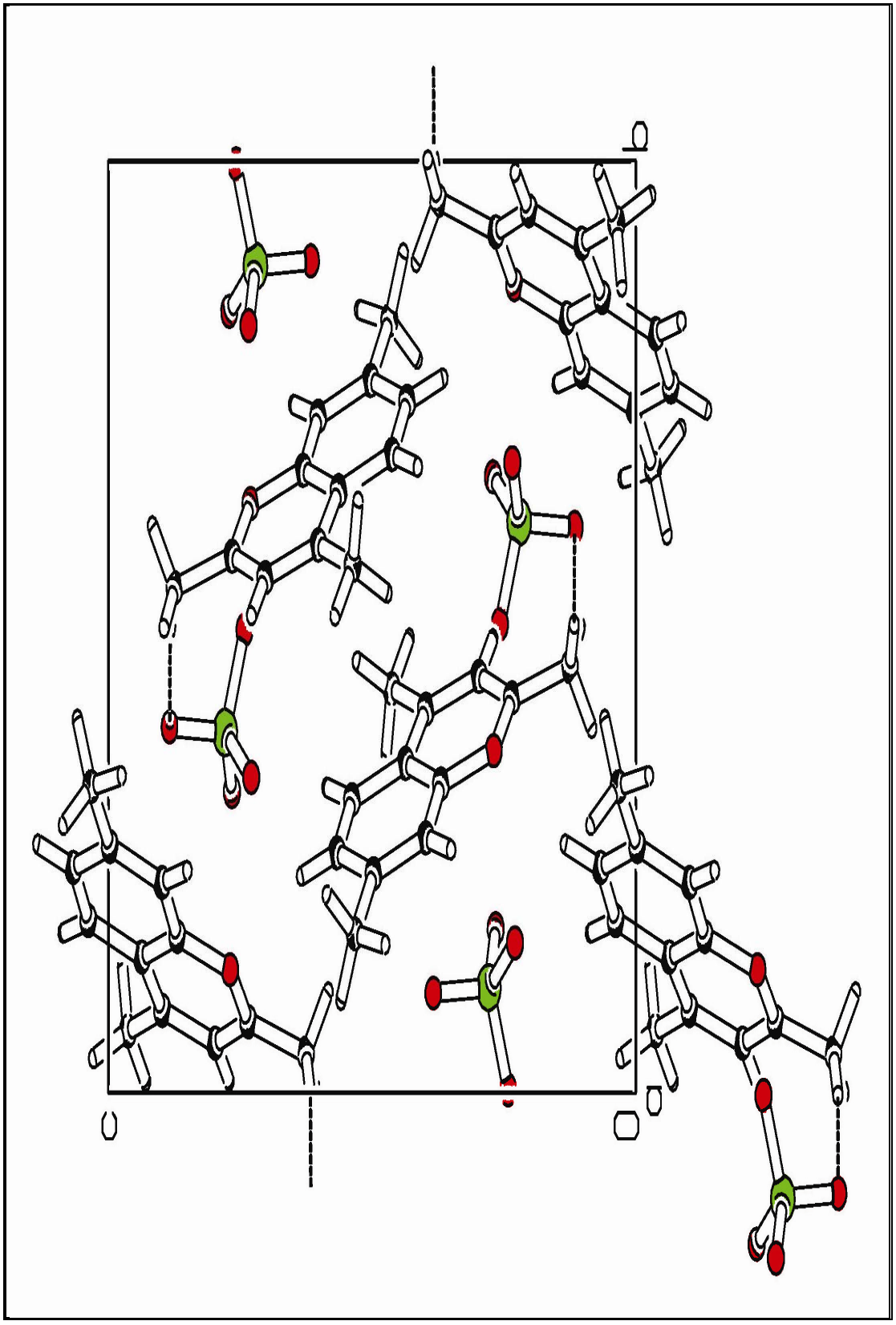


Figure 1.13.3 Packing of the MNP-003 molecules down b axis

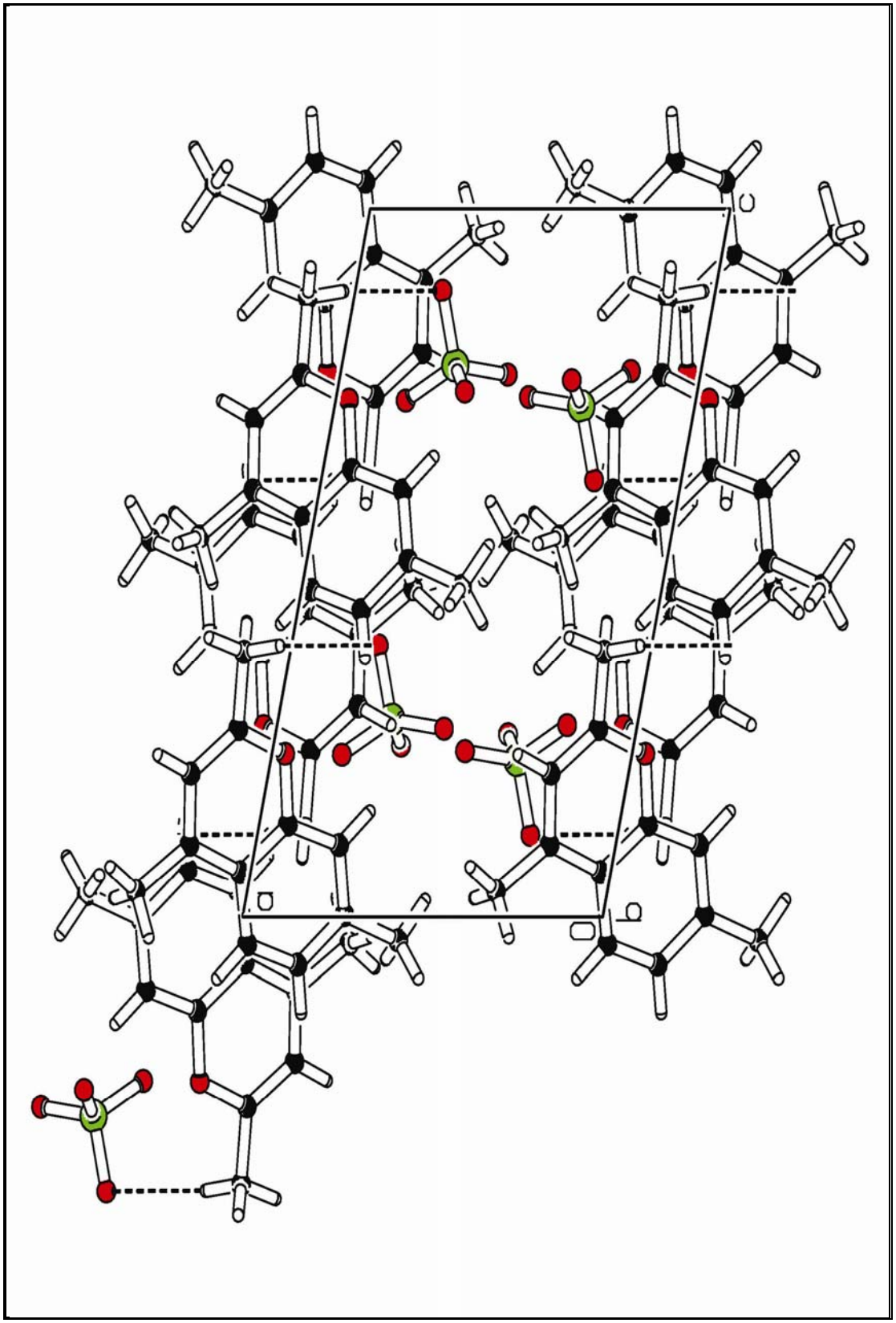
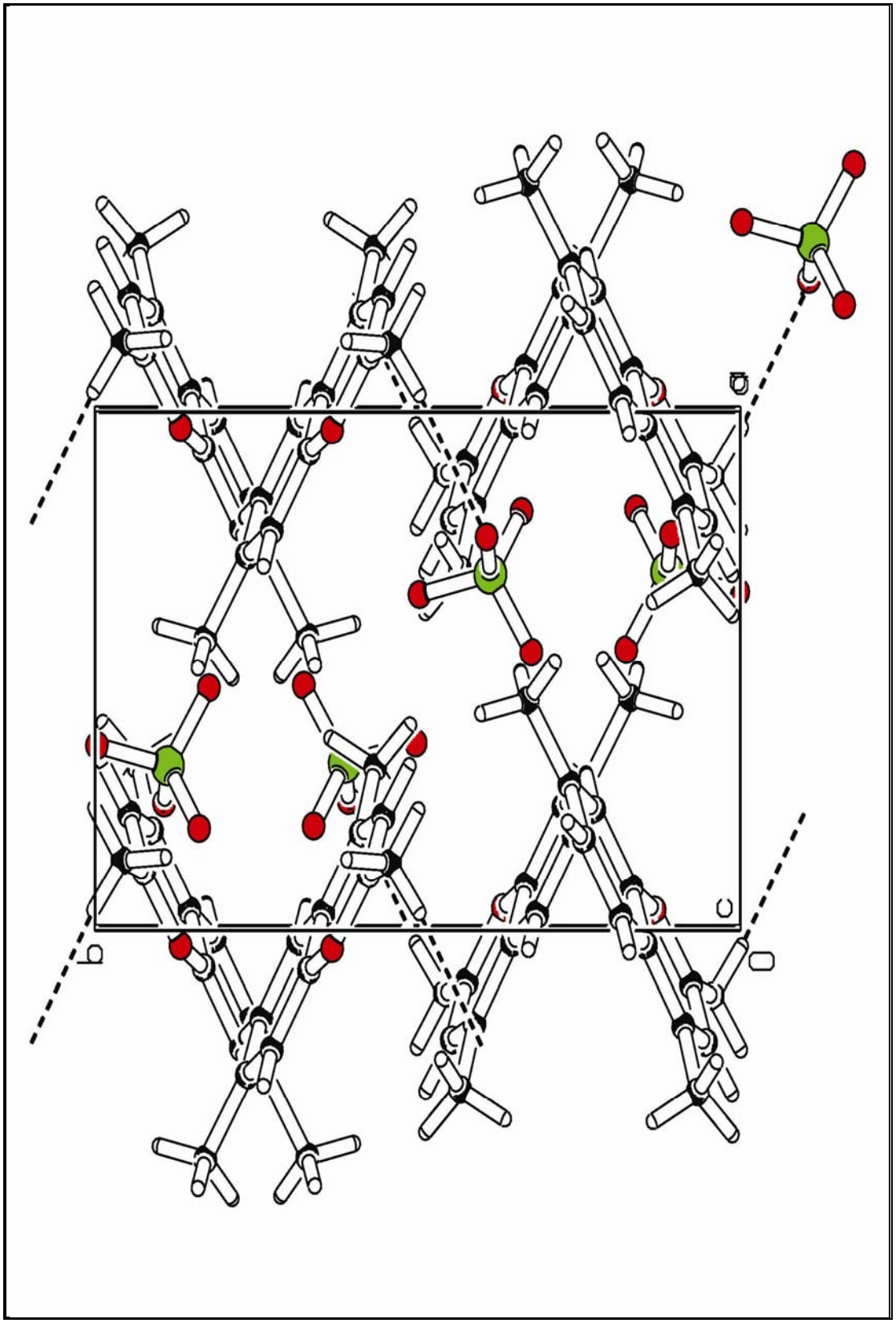


Figure 1.13.4 Packing of the MNP-003 molecules down c axis



1.13.3 X-RAY CRYSTALLOGRAPHIC STUDY OF MNP-011

The compound $C_{11}H_{11}ClO_7$, crystallizes in monoclinic crystal class in space group $P2_1/\eta$ with cell parameters a = 6.8920(4) Å, b = 18.5260(15) Å, c =9.9480(8) Å, β= 106.420(5)º, V = 1218.37(16) $Å^3$ and Z = 4. The final residual factor R1 = 0.0554. The structure exhibits both intra and inter-molecular hydrogen bonding of the type O–H...O and C–H...O.

The values of R_{int} and R_{sigma} are 0.0168 and 0.0306 respectively. 2000 phase sets were refined with the best phase set having a CFOM of 0.0973. Using the normalized structure factors with these phases, a total of 1102 phases were generated. The final RE value, equals 19.8%. The non-hydrogen atoms were recognized from the electron density peaks using PLATON1 and refined using SHELXL-97. All non-hydrogen atoms were refined anisotropically.

The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on the parent atom during successive refinement. 175 parameters were refined with 1895 reflections using SHELXL-97. ORTEP of the molecule is shown in figure.

The title compound shows planar conformation. The dihedral angle between the least squares planes O1-C2-C3-C4-C5-C10 and C5-C6-C7-C8-C9-C10 is 0.29(13)°. Total puckering amplitude Q for ten membered ring O1-C2-C3-C4-C5-C6-C7-C8- C9-C10 is 0.026(3) Å. The torsion angle about C3-C4-C5-C6 being 178.9(3)º show -s anti-periplanar conformation, while that of O13-C8-C9-C10 shows -anti-periplanar conformation being −179.6(2)º, respectively.

The molecule exhibits inter and intra-molecular hydrogen bonds of the type O- H…O and C-H…O. The inter-molecular hydrogen bonds O13– H13…O16, O14–H14…..O16 and C11–H11A…..O16 have lengths of 2.746(4) Å, 3.017(4) Å and 3.194(5) Å and angles of 155º, 168º and 139º, respectively, with the symmetry codes −1+ x, y, z and −1/2+ x, 1/2− y, −1/2+ z. Intra-molecular hydrogen bond O14–H14….O13, has a length of 2.742(3) Å and an angle of 115º. Packing of the molecules viewed down α-axis shows one-dimensional snake shaped chain.

Figure 1.13.5 Oak Ridge Thermal Ellipsoid Plot (ORTEP) of the MNP-011 molecule at 50% Probability

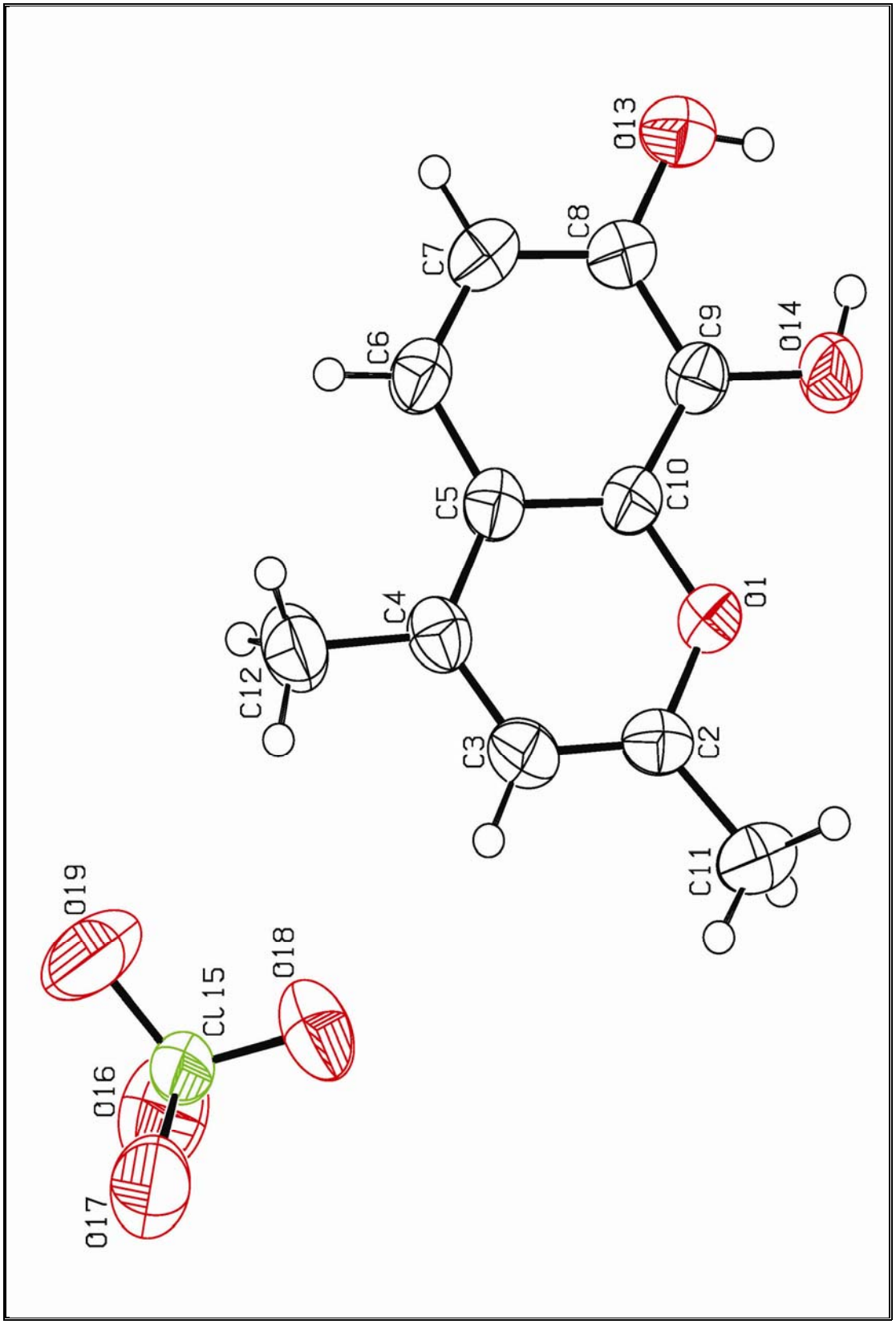


Table 1.13.8 Crystal Data and Structure Refinement for Cell

Empirical formula	C_{11} H_{11} Cl O_7
Formula weight	290.65
Temperature	293(2)K
Wavelength	0.71073Å
Crystal system	Monoclinic
Space group	$P2_1/\eta$
Cell dimensions	a = 6.8920(4) Å b = 18.5260(15) Å c = 9.9480(8) Å α = 90º β= 106.420(5)º γ= 90º
Volume	1218.37(16) $Å^3$
Z	4
Density(calculated)	1.585 Mg/m^3
Absorption coefficient	0.341 mm^{-1}
F_{000}	600
Crystal size	0.3 × 0.25 × 0.25 mm
θ range for data collection	2.40º to 25º
Index ranges	$-7 \leq h \leq 7, -22 \leq k \leq 21, -11 \leq l \leq 11$
Reflections collected	3470
Independent reflections	1895 [R_{int} = 0.0198]
Refinement method	Full-matrix least-squares on F^2
Data/ restraints / parameters	1895 / 0 / 175
Goodness-of-fit on F^2	1.143
Final R indices [I > 2σ(I)]	R1 = 0.0554, ωR2 = 0.1603
R indices (all data)	R1 = 0.0614, ωR2 = 0.1729
Extinction coefficient	0.096(15)
Largest diff. peak and hole	0.460 and −0.599 $e.Å^{-3}$

Table 1.13.9 Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms

Atom	X	Y	Z	U_{eq}
O1	0.2427(3)	0.17700(9)	0.51669(2)	0.0418(5)
C2	0.3647(4)	0.18857(1)	0.4363(3)	0.0437(7)
C3	0.3331(5)	0.15380(2)	0.3102(3)	0.0477(7)
C4	0.1724(5)	0.10591(1)	0.2626(3)	0.0455(7)
C5	0.0392(4)	0.09519(1)	0.3455(3)	0.0406(7)
C6	-0.1319(5)	0.04933(1)	0.3097(3)	0.0471(7)
C7	-0.2497(4)	0.04226(1)	0.3988(3)	0.0480(7)
C8	-0.2037(4)	0.07958(1)	0.5263(3)	0.0435(7)
C9	-0.0375(4)	0.12525(1)	0.5655(3)	0.0425(7)
C10	0.0794(4)	0.13234(1)	0.4736(3)	0.0377(6)
C11	0.5287(5)	0.23995(2)	0.4985(4)	0.0550(8)
C12	0.1448(6)	0.06698(2)	0.1264(3)	0.0630(9)
O13	-0.3263(3)	0.06990(1)	0.6095(2)	0.0563(6)
O14	-0.0007(3)	0.16115(1)	0.6896(2)	0.0559(6)
Cl15	0.5214(1)	0.14498(4)	0.90272(8)	0.0526(4)
O16	0.6950(5)	0.14292(2)	0.8535(3)	0.1011(1)
O17	0.3988(5)	0.08447(2)	0.8549(4)	0.1117(1)
O18	0.4041(5)	0.20626(2)	0.8397(4)	0.1026(1)
O19	0.5809(6)	0.1537(2)	1.0484(3)	0.1035(1)

$$U_{eq} = (1/3) \sum_i \sum_j Uij \, (\alpha_i^* \, \alpha_j^*) \, (ai \cdot aj)$$

Table 1.13.10 Atomic coordinates and equivalent thermal parameters of the hydrogen atoms

Atom	X	Y	Z	U_{eq}
H3	0.4203	0.1623	0.2557	0.057
H6	-0.1642	0.0240	0.2256	0.056
H7	-0.3622	0.0122	0.3743	0.058
H9	0.4740	0.2878	0.4943	0.082
H11A	0.4740	0.2878	0.4943	0.082
H11B	0.6275	0.2384	0.4472	0.082
H11C	0.5915	0.2271	0.5944	0.082
H12A	0.2584	0.0765	0.0912	0.095
H12B	0.0231	0.0835	0.0599	0.095
H12C	0.1353	0.0160	0.1410	0.095
H13	-0.2855	0.0944	0.6805	0.085
H14	-0.0864	0.1501	0.7287	0.084

$$U_{eq} = (1/3) \sum_i \sum_j Uij \, (\alpha_i^* \, \alpha_j^*) \, (ai \cdot aj)$$

Table 1.13.11 Anisotropic thermal parameters of the non-hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1	0.038(1)	0.048(1)	0.045(1)	-0.002(7)	0.011(8)	0.009(7)
C2	0.039(2)	0.042(1)	0.051(2)	0.006(1)	0.014(1)	0.011(1)
C3	0.048(2)	0.050(2)	0.048(2)	0.005(1)	0.018(1)	0.009(1)
C4	0.052(2)	0.043(1)	0.040(2)	0.009(1)	0.012(1)	0.006(1)
C5	0.043(2)	0.036(1)	0.040(2)	0.005(1)	0.007(1)	0.003(1)
C6	0.052(2)	0.041(1)	0.045(2)	-0.002(1)	0.008(1)	-0.005(1)
C7	0.042(2)	0.039(1)	0.060(2)	-0.003(1)	0.010(1)	-0.000(1)
C8	0.039(2)	0.041(1)	0.051(2)	0.040(1)	0.013(1)	0.005(1)
C9	0.040(2)	0.042(1)	0.044(2)	0.004(1)	0.010(1)	-0.002(1)
C10	0.035(1)	0.039(1)	0.042(2)	0.001(9)	0.008(1)	0.001(1)
C11	0.044(2)	0.049(2)	0.069(2)	-0.005(1)	0.013(1)	0.008(1)
C12	0.080(2)	0.066(2)	0.047(2)	0.001(2)	0.024(2)	-0.004(1)
O13	0.051(1)	0.062(1)	0.062(1)	-0.007(9)	0.024(1)	-0.001(1)
O14	0.045(1)	0.078(1)	0.049(1)	-0.007(1)	0.020(1)	-0.017(1)
Cl15	0.047(6)	0.066(6)	0.047(6)	-0.012(3)	0.018(4)	-0.010(3)
O16	0.056(2)	0.165(3)	0.093(2)	-0.029(2)	0.038(2)	-0.053(2)
O17	0.103(3)	0.100(2)	0.135(3)	-0.055(2)	0.039(2)	-0.033(2)
O18	0.100(2)	0.094(2)	0.099(2)	0.011(2)	0.003(2)	-0.011(2)
O19	0.115(3)	0.148(3)	0.047(2)	-0.029(2)	0.022(2)	-0.001(2)

Table 1.13.12 Bond Lengths (Å)

Atoms	Length	Atoms	Length
O1-C2	1.332(3)	C7-C8	1.400(4)
O1-C10	1.364(3)	C8-O13	1.351(3)
C2-C3	1.371(4)	C8-C9	1.388(4)
C2-C11	1.474(4)	C9-O14	1.362(3)
C3-C4	1.394(4)	C9-C10	1.386(4)
C4-C5	1.411(4)	Cl15-O19	1.399(3)
C4-C12	1.498(4)	Cl15-O17	1.403(3)
C5-C10	1.405(4)	Cl15-O16	1.416(3)
C5-C6	1.415(4)	Cl15-O18	1.431(3)
C6-C7	1.367(4)		

Table 1.13.13 Bond Angles (º)

Atoms	Angle	Atoms	Angle
C2-O1-C10	120.9(2)	O13-C8-C7	117.9(2)
O1-C2-C3	120.6(2)	C9-C8-C7	120.9(3)
O1-C2-C11	113.0(3)	O14-C9-C10	123.9(2)
C3-C2-C11	126.3(3)	O14-C9-C8	118.7(3)
C2-C3-C4	121.0(3)	C10-C9-C8	117.4(3)
C3-C4-C5	118.5(3)	O1-C10-C9	115.6(2)
C3-C4-C12	120.0(3)	O1-C10-C5	121.1(2)
C5-C4-C12	121.6(3)	C9-C10-C5	123.3(2)
C10-C5-C4	117.8(3)	O19-Cl15-O17	114.5(2)
C10-C5-C6	117.3(3)	O19-Cl15-O16	109.4(2)
C4-C5-C6	124.8(3)	O17-Cl15-O16	110.4(2)
C7-C6-C5	120.1(3)	O19-Cl15-O18	109.0(2)
C6-C7-C8	121.1(3)	O17-Cl15-O16	105.9(2)
O13-C8-C9	121.2(3)	O16-Cl15-O18	107.3(2)

Table 1.13.14 Torsion Angles (º)

Atoms	Angle	Atoms	Angle
C(2)-O(1)-C(10)-C(9)	-179.3(2)	C(6)-C(7)-C(8)-C(9)	0.4(4)
C(2)-C(3)-C(4)-C(12)	-178.2(3)	C(7)-C(8)-C(9)-O(14)	179.1(2)
C(3)-C(4)-C(5)-C(6)	178.9(3)	C(8)-C(9)-C(10)-O(1)	-179.2(2)
C(4)-C(5)-C(6)-C(7)	179.2(3)	C(10)-O(1)-C(2)-C(11)	178.3(2)
C(4)-C(5)-C(10)-C(9)	-178.7(3)	C(11)-C(2)-C(3)-C(4)	179.7(3)
C(6)-C(5)-C(10)-O(1)	179.3(2)	C(12)-C(4)-C(5)-C(10)	178.3(3)
C(6)-C(7)-C(8)-O(13)	-179.8(3)	O(13)-C(8)-C(9)-C(10)	-179.6(3)
O(14)-C(9)-C(10)-C(5)	-179.7(3)		

Table 1.13.15 Hydrogen Bond Geometry (Å, º)

Atoms	D-H…A	Angle
O13-H13…O16[1]	2.746(4)	155
O14-H14…O16[1]	3.017(4)	168
C6-H6…O17[2]	3.241(5)	130
C11-H11A…O16[3]	3.194(5)	139
Symmetry		
1 x, -1+y, z		
2 -x, -y, 1-z		
3 -1/2+x, ½-y, -1/2+z		

Figure 1.13.6 Packing of the MNP-011 molecules down a axis

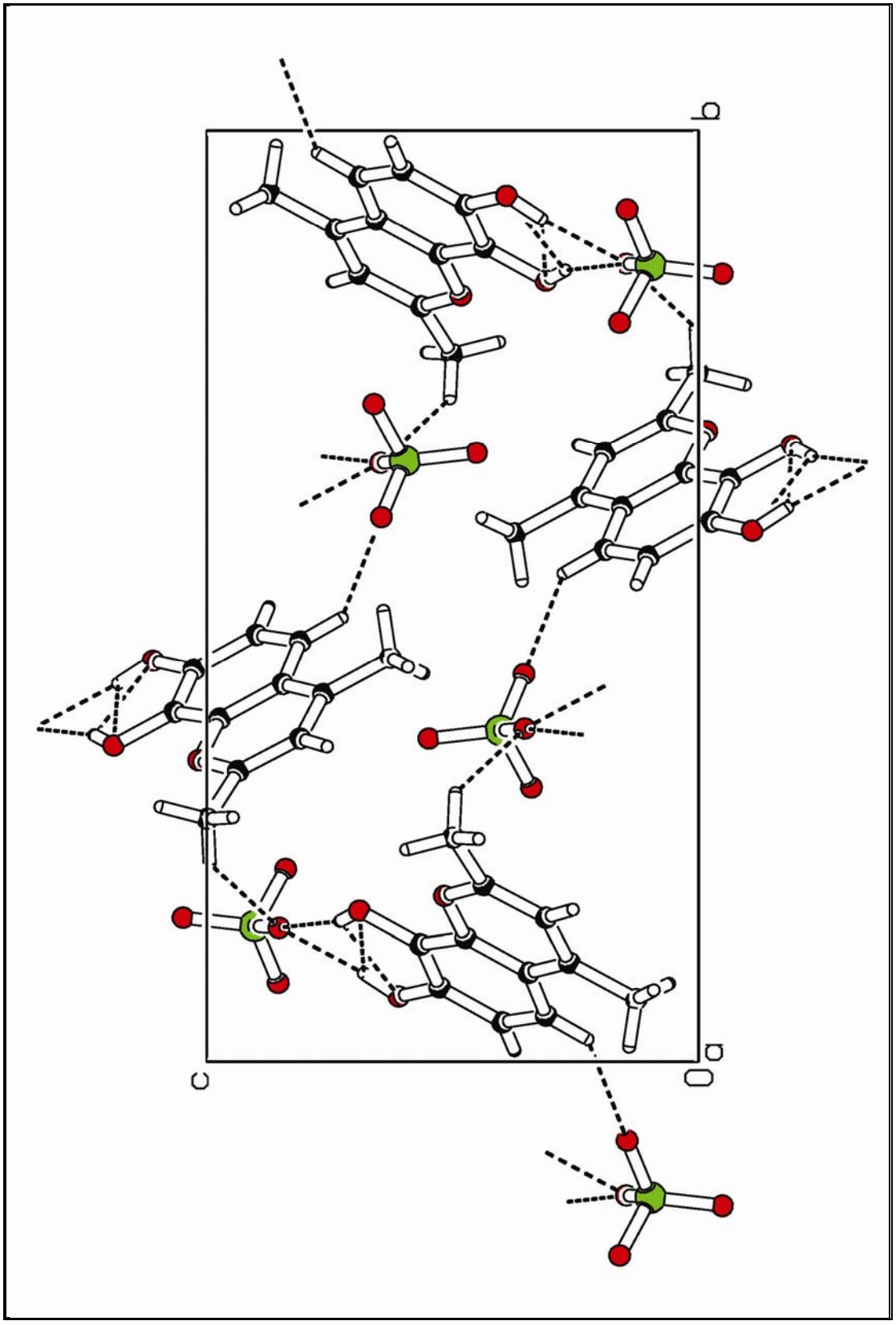


Figure 1.13.7 Packing of the MNP-011 molecules down b axis

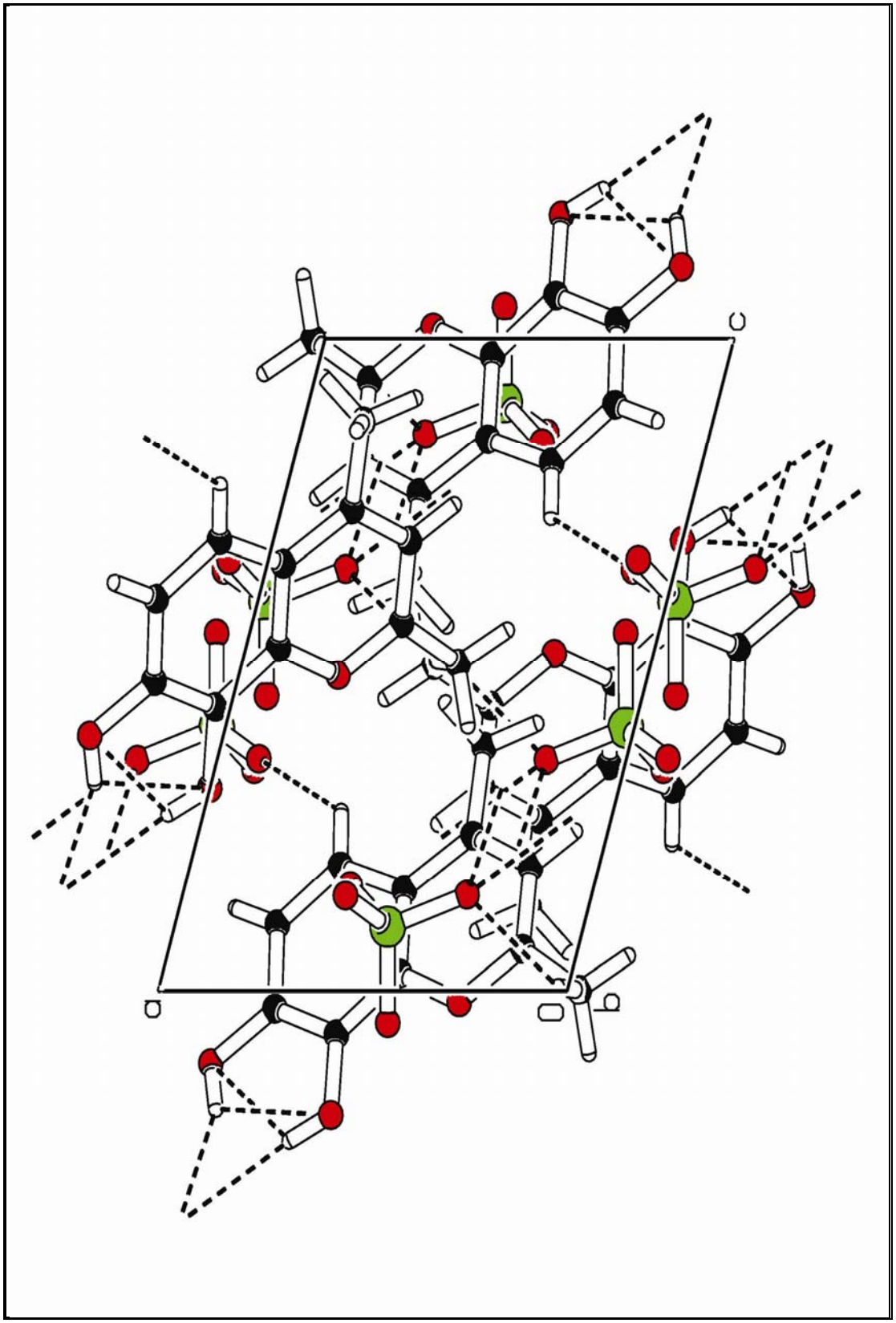


Figure 1.13.8 Packing of the MNP-011 molecules down c axis

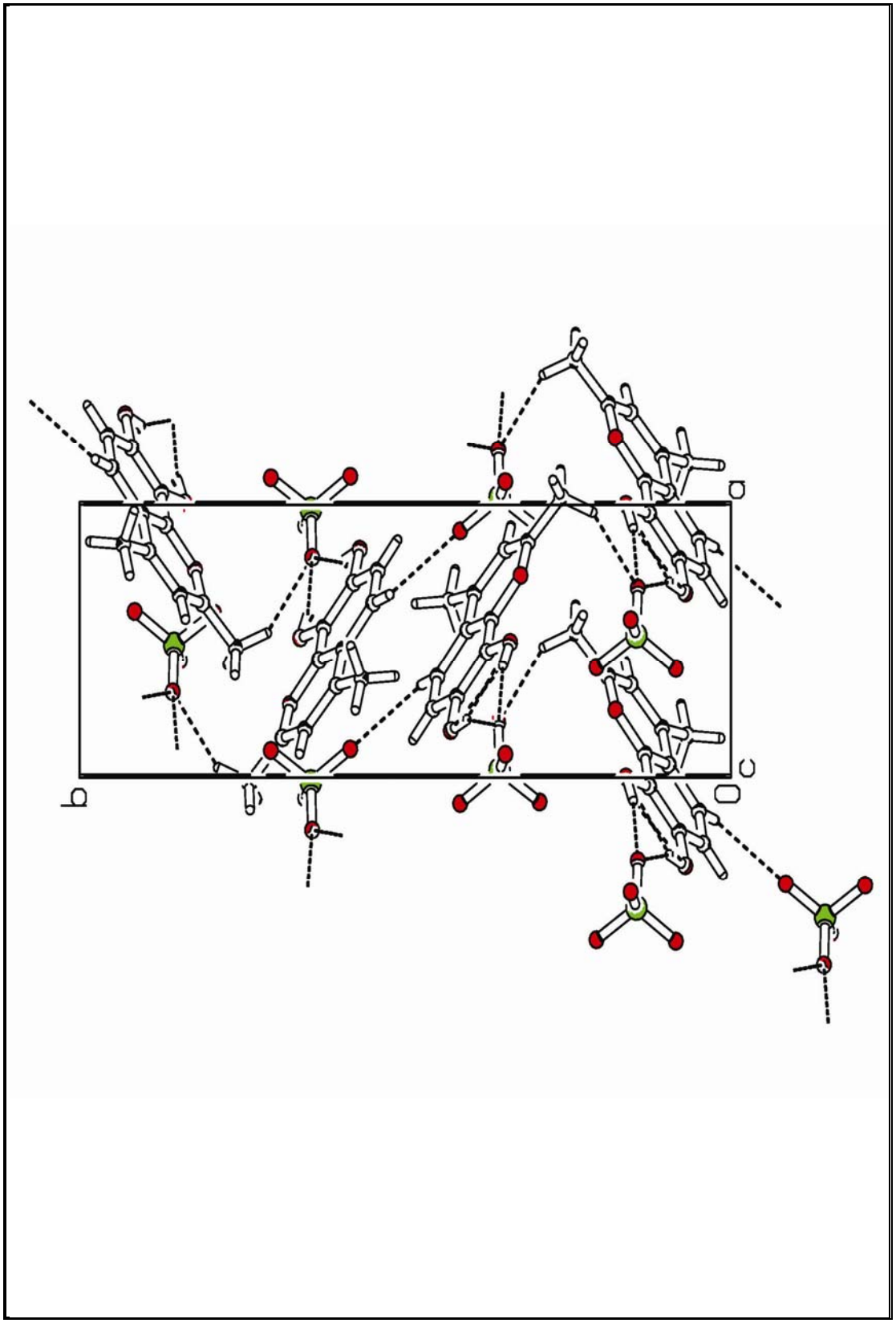
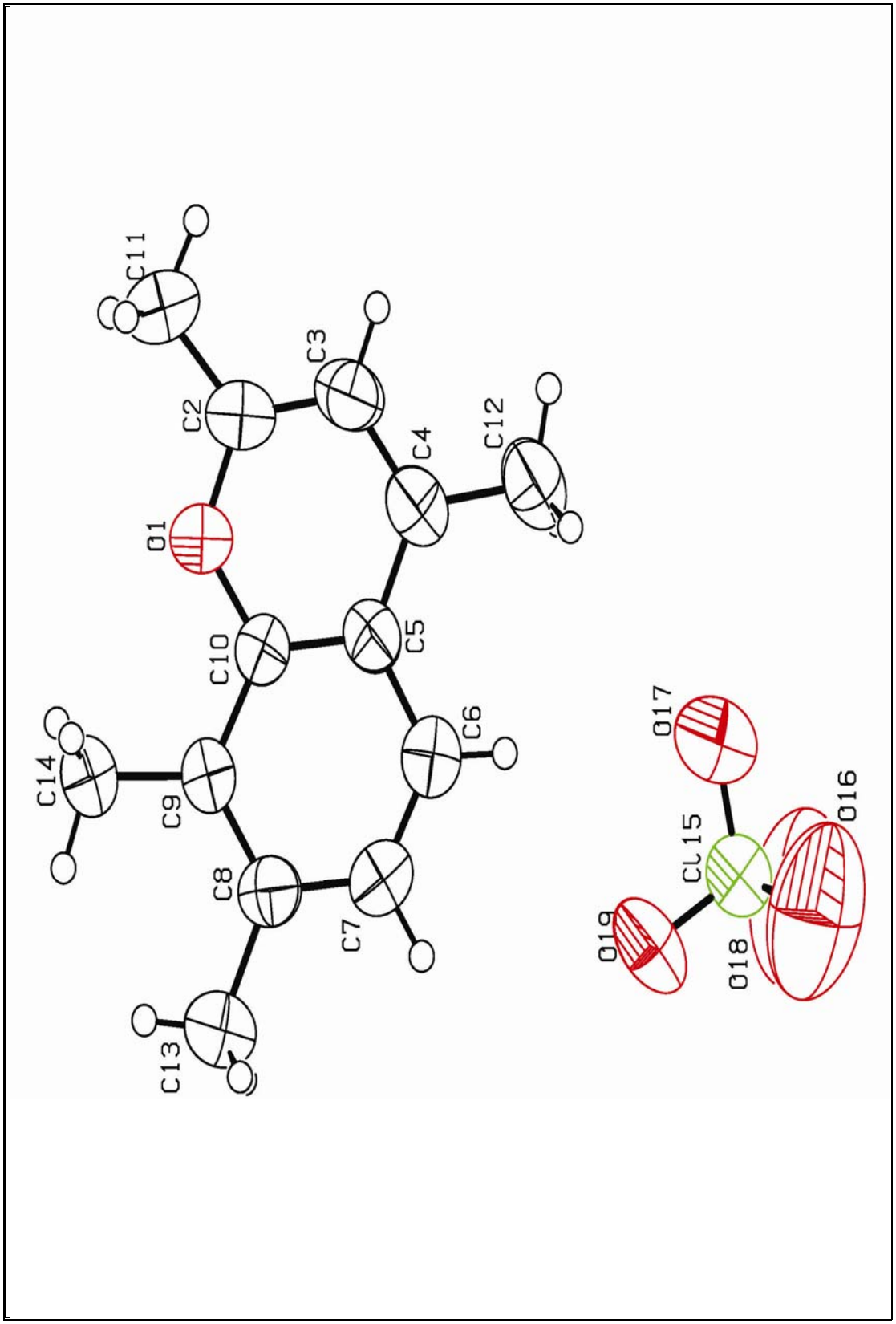


Figure 1.13.9 Oak Ridge Thermal Ellipsoid Plot (ORTEP) of the MNP-005 molecule at 50% Probability



1.14 RESULTS AND DISCUSSION

The chemical entities enlisted in this chapter, the chromylium salts were prepared by a new and very simple synthetic methodology and firstly confirmed by single crystal X-ray crystallographic study. These compounds are also evaluated first time for antimicrobial screening. Primary screening results showed good antimicrobial activity and further investigation is under progress.

Though few compounds are reported but the process employed for the synthesis was totally different and the aim is also different. The previous study about these salts was demonstrated its other applications like dye, lather dye, polarographic study, electro-chemical study and etc.

1.15 CONCLUSION

In this chapter, simple and efficient method was adopted for the synthesis of benzopyrylium salts. Exploration of unreported chemistry and their biological activity were the aim behind the work reported in this chapter.

The crystallographic study of the compounds 2,4,7-trimethylchromenylium perchlorate (MNP-003), 2,4,7,8-tetramethyl chromenylium perchlorate (MNP-005) and 7,8-dihydroxy-2,4-dimethylchromenylium perchlorate (MNP-011) were confirmed the structure of the compounds which are of biological interest.

1.16 REFERENCES

1. D. W. Hill; *Chem. Rev.*; 19, 27, **1936**.
2. F. M. Dean; Naturally occurring oxygen ring compounds, *Butterworths*; London, **1963.**
3. F. Kasprzak and B. Glebko; *Chemik*; 19 (8), 267, **1966;** C.A.; 66, 14004, **1967.**
4. F. M. Dean; The synthesis of natural products; Vol. I, Interscience, **1973.**
5. L. Merlini; Advances in Heterocyclic Chemistry; Vol. 18, N.Y., **1975.**
6. R. Livingstone; Rodd's Chemistry of Carbon Compounds; Vol. IV E, N.Y., **1990.**
7. G. P. Ellis; Chemistry of Heterocyclic Chemistry; Vol. 31, N.Y., **1977.**
8. R. D. H. Murray; Naturally occurring oxygen ring compounds; C.A.; 88, 33221, **1978.**
9. P. Navarrete-Encina, R. Salazar, C. Vega-Retter, K. Perez, J. Squella and L. Nunez-Vergara; *J. Braz. Chem. Soc.*; 21 (3), 413, **2010.**
10. S. Chang and R. H. Grubbs; *J. Org. Chem.*; 63, 864, **1998.**
11. H. Decker and T. V. Fellenberg; Ann. Chem.; 356, 281, **1907**;
12. W. H. Perkin Jr. and R. Robinson; *Proc. Chem. Soc.*; 23, 149, **1907.**
13. W. H. Perkin, R. Robinson and M. R. Turner;*J. Chem. Soc.*; 93, 1085, **1908.**
14. J. Cheng, A. Ishikawa, Y. Ono, T. Arrheniusand A. Nadzan; *Bioorg. & Med. Chem. Lett.*; 13, 3647, **2003.**
15. N. A. Petasis and A. Butkevich; *J. Organomet. Chem*.; 694(11), 1747, **2009.**
16. Bender Paul E., Loev Bernard; US Patent, 3923836, **1975.**
17. V. Y. Sosnovskikh; *Russian Chemical Reviews*; 72 (6), 489, **2003.**
18. R. Doodeman, F. P. J. T. Rutjes and H. Hiemstra; *Tetrahedron Lett.*; 41, 5979, **2000.**
19. Masato Matsugi, Masaki Takeda, Ayano Takahashi, Takahide Tazaki, Hiroto Tamura andTakayuki Shioiri; *Chem. Pharm. Bull.*; 58 (8), 1107, **2010.**
20. A. Lévai, G. Tóth, A. Szollosy, T. Timár; Monatshefte für Chemie Chemical Monthly; 121 (5), 403, **1990.**
21. M. Iyer and G. K. Trivedi; *Synth. Comm.*; 20 (9), 1347, **1990.**

22. E. Tibor, T. Tibor and S. Peter; *Tetrahedron Lett.*; 32 (6), 827, **1991**.
23. P. Champs, M. A. Liuch, M. J. Climent and M. A. Miranda; *Tetrahedron Lett.*; 27 (18), 2041, **1986**.
24. G. Pandey and A. Krishna; *J. Org. Chem.*; 53 (10), 2364, **1988.**
25. L. Albert and T. Tibor; *Synth. Comm.*; 20 (5), 641, **1990.**
26. T. Minami, Y. Matsumato, S. Nakamura, S. Koyanagi and S. Yamaguchi; *J. Het. Chem.*; 29 (4), 755, **1992.**
27. M. Iyer and G. K. Trivedi; *Synthesis-Stuttgart*; 9, 881, **1993.**
28. C. O. Gabutt, D. J. Hartley, J. D. Hapwarth, B. M. Heron, M. Kanjia and M. Rahman; *Tetrahedron*; 50 (8), 2507, **1994.**
29. R. Cruz-Almanza, F. Pérez-Flores, C. Lemini; Heterocycles; 337 (2), 759, **1994.**
30. J. Pozzo, A. Samat, R. Guglielmetti, V. Lokshin, V. Minkin; *Can. J. Chem.*; 74 (9), 1649, **1996.**
31. S. Padmanabhan, R. Peri and D. J. Triggle, *Synth. Comm*.; 26, 827, **1996.**
32. T. Tibor, S. Peter, E. Tibor and Josef; *Hetorocyclic Comm.*; 2 (1), 91, **1996.**
33. N. M. Dodiya, Ph.D. Thesis, Saurashtra University, **2000.**
34. C. Bulow and H. Wagner; *Ber.*; 34, 1189, **1901.**
35. M. Healey and R. Robinson; *J. Chem. Soc.*; 1625, **1934.**
36. F. Kehrmann and M. Rieder; *Helv. Chim. Acta*; 9, 941, **1926.**
37. C. Bulow and W. V. Sicherer; *Ber.*; 34, 2368, 3916, **1901.**
38. C. Bulow and H. Wagner; *Ber*.; 34, 1782, **1901.**
39. R. Robinson and J. Walker; *J. Chem. Soc.*; 1435, **1934.**
40. R. Robinson; *Ber*.; 67A, 85, **1934.**
41. H. Brockmann and H. Junge; *Ber.*; 76, 751, **1944.**
42. R. Robinson and J. Walker; *J. Chem. Soc.*; 941, **1935.**
43. E. Keller and R. Robinson; *J. Chem. Soc.*; 1533, **1934.**
44. A. N. Nesmeyanov, N. K. Kochetkov and M. I. Rybinskaya; *Otdel. Khim. Nauk*; 479, **1953**; C.A.; 48, 10015, **1954.**
45. A. W. Johnson and R. R. Melhuish; J. Chem. Soc.; 346, **1947.**
46. R. R. Otter and R. L. Shriner; *J. Am. Chem. Soc.*; 73 (3), 887, **1951.**
47. C. G. Le Fèvre and R. J. W. Le Fèvre; *J. Chem. Soc.*; 1532, **1933.**
48. R. J. W. Le Fèvre; *J. Chem. Soc.*; 450, **1934.**

49. G. A. Raynolds, J. A. Van Allan and D. Daniel; *J. Het. Chem.*; 7 (6), 1395, **1970.**

50. R. L. Shriner, H. W. Johnstonand C. E. Kaslow; *J. Org. Chem.*; 204, **1948.**

51. P. Czerney, T. Steinfuehrer and M. Weissenfels; Ger. (East), 272852, 25, **1989.**

52. N. L. Olenovich, G. F. Tantsyura, Z. G. Galanets and A. I. *Gavril'chenko; Ukr. Khim. Zh.*; 43 (8), 885, **1977.**

53. V. I. Dulenko and S. V. Tolkunov; *Zhurnal Organicheskoi Khimii*; 18 (9), 2006, **1982.**

54. I. M. Gavrilyuk, A. A. Ishchenko, M. A. Kudinova and A. I. Tolmachev; Khimiya Geterotsiklicheskikh Soedinenii; 3, 304-8, **1983.**

55. M. M. Evstifeev, O. M. Orlova, L. L. Pyshcheva, T. A. Tyagunova, T. M. Rastsvetaeva and Z. Yu Deripasko; *Fiziko-Khimicheskie Metody Analiza i Kontrolya Proizvodstva*; 2, 48, **1976.**

56. G. N. Dorofeenko and G. I. Zhungietu; *Zhurnal Obshchei Khimii*; 35 (6), 963, **1965.**

57. (a)K. Akio, K. Tomio and M. Shoji; *Jpn. Kokai Tokkyo Koho;* 6, JKXXAF JP, 7515815, **1975;** (b) A. N. Narkevich, Yu. D. Beletskii, G. N. Dorofeenko, Yu. A. Zhdanov and E. K. Razoriteleva; *Genetika (Moscow)*; 4 (6), 33, **1968.**

58. A. N.Nesmeyanov, L. A.Kazitsyna, N. K.Kochetkov and M. I.Rybinskaya; *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya*; 784, **1954.**

59. T. G. Dmitrienko and S. S. Popova; *Russian Journal of Applied Chemistry*; 82 (9), 1551, **2009. (**Translated from*Zhurnal Prikladnoi Khimii*); 82 (9), 1453, **2009.**

60. H. Sashida; *Mini-Reviews in Organic Chemistry*; 4, 105, **2007.**

61. M. J. Melo, M. Sousa, A. J. Parola, J. Sergio S. de Melo, F. Catarino, J. Marcalo and F. Pina; *Chem. Eur. J.;* 13, 1417, **2007.**

62. P. P. Parui, N. Manoj, S. Banerjee and M. Chowdhury; *Chemical Physics Letters;* 479(1), 70, **2009.**

63. L. Zhu, Y. Lu, D. D. Miller and R. I. Mahato; *Bioconjugate Chemistry*; 19 (12), 2499, **2008.**

64. M. A. Kostogryz, A. A. Boumber, I. A. Profatilova and M. S. Korobov; *Chemistry of Heterocyclic Compounds;* 43 (10), 1342, **2007.**

65. S. V. Tolkunov, A. I. Khyzhan, S. Yu. Suikov, V. I. Dulenko; *Chemistry of Heterocyclic Compounds;* 41(3), 379, **2005.**

66. A. Rampa, A.Bisi, F. Belluti, S. Gobbi, L. Piazzi, P. Valenti, A. Zampiron; *Farmaco;* 60 (2), 135, **2005.**

67. S. L. Bogza, S. Yu. Suikov, N. M. Bogdan and K. I. Kobrakov; *Chemistry of Heterocyclic Compounds;* 40 (10), 1300, **2004.**

68. J. R. Casey, P. E. Morgan, D. Vullo, A. Scozzafava, A. Mastrolorenzo and C. T. Supuran; *J. Med. Chem;* 47 (9), 2337, **2004.**

69. S. V. Tolkunov, V. S. Tolkunov and V. I. Dulenko; *Chemistry of Heterocyclic Compounds;* 40 (4), 481, **2004.**

70. P. P. Parui, N. Monoj, D. N. Nath and M. Chowdhury; *Journal of Physical Chemistry A;* 108 (2), 275, **2004.**

71. A. O. Manyashin, A. I. Fomenko, V. N. Storozhenko and N. T. Berberova; *Elektrokhimiya;* 39 (11), 1385, **2003.**

72. S. L. Bogza, A. A. Malienko, S. Yu. Sujkov, K. I. Kobrakov and V. I. Dulenko; *Khimiya Geterotsiklicheskikh Soedinenii*; 6, 841, **2002.**

73. S. L. Bogza, O. V. Rozhkov, N. M. Bogdan, K. I. Kobrakov and V. I. Dulenko; *Khimiya Geterotsiklicheskikh Soedinenii*; 6, 840, **2002.**

74. I. K. Spiliopoulos and J. A. Mikroyannidis; *Journal of Polymer Science, Part A: Polymer Chemistry*; 40 (15), 2591, **2002.**

75. S. L. Bogza, O. V. Rozhkov, N. M. Bogdan, K. I. Kobrakov and V. I. Dulenko; *Chemistry of Heterocyclic Compounds*; 38 (6), 741, **2002.**

76. S. L. Bogza, A. A. Malienko, S. Yu. Suikov, K. I. Suikov, K. I. Kobrakov and V. I. Dulenko; *Chemistry of Heterocyclic Compounds*; 38 (6), 743, **2002.**

77. S. P. Denisov, A. I. Moskalenko , V. I. Boev, L. G. Stamova and A. V. Gulin; *Russian Journal of General Chemistry*; 71 (7), 1070, **2001.**

78. R. Pohl, S. Bohm and J. Kuthan; *Collection of Czechoslovak Chemical Communications*; 64 (8), 1274, **1999.**

79. M. Fagnoni, M. Mella and A. Albini; *Journal of Physical Organic Chemistry*; 10 (10), 777, **1997.**

80. A.Nicolae, T. Cristea and C. T. Supuran; *Revue Roumaine de Chimie*; 42 (4), 301, **1997.**

81. S. L. Bogza, Yu. A. Nikolyukin, M. Yu. Zubritskii and V. I. Dulenko; *Chemistry of Heterocyclic Compounds*; 31 (3), 272, **1995.**

82. A. V. Koblik, L. A. Murad'yan, G. V. Gridunova, D. S. Yufit, Yu. T. Struchkov and G. P. Zolotovskova; *Chemistry of Heterocyclic Compounds*; 28 (10), 1116,**1992.**

83. S. L. Bogza, Yu. A. Nikolyukin and V. I. Dulenko; *Chemistry of Heterocyclic Compounds*; 25 (2), 134, **1989.**

84. V. F. Lipnitskii and O. P. Shvaika; *Chemistry of Heterocyclic Compounds*; 24 (12), 1398, **1988.**

85. A. P. Brestkin, E. N. Dmitrieva, I. G. Zhukovskiĭ, A. A. Safonova and V. A. Sedavkina; *Ukrainskii biokhimicheskii zhurnal*; 60 (2), 35, **1988.**

86. A. P. Brestkin, E. N. Dmitrieva, I. G. Zhukovskiĭ, A. A. Safonova and V. A. Sedavkina; *Doklady Akademii nauk SSSR*; 293 (6), 1499,**1987.**

87. M. M. Evstifeev, A. D. Semenov, K. N. Bagdasarov, L. V. Kazarenko, Yu. M. Gavrilko, and E. P. Olekhnovich; *Soviet Journal of Water Chemistry and Technology;* (English Translation of *Khimiya i Tekhnologiya)*; 8 (5), 81, **1986.**

88. T. A. Markina and N. N. Boiko; *Chemistry of Heterocyclic Compounds*; 21 (2), 138, **1985.**

89. A. P. Kriven'ko, O. V. Fedotova, P. V. Reshetov and V. G. Kharchenko; *Chemistry of Heterocyclic Compounds*; 20 (12), 1361, **1984.**

90. V. Gionis, R. Fugnitto, H. Strzelecka and P. Le Barny; *Molecular crystals and liquid crystals*; 95 (3-4), 351, **1983.**

91. A. I. Undzenas and D. D. Rushkis; *Polymer Science U.S.S.R.;* 25(12), 2910, **1983.**

92. V. P. Grigoriev, V. V. Ekilik and V.A. Fevraleva; **1975.**

93. B. M. Savin, L. N. Volovel'skii and G. N. Dorofeenko; *Chemistry of Heterocyclic Compounds*; 6 (2), 133, **1973.**

94. A. N. Nesmeyanov, L. A. Kazitsyna, N. K. Kochetkov and M. N. Rybinskava; *Bulletin of the Academy of Sciences of the USSR Division of Chemical Science*; 3 (5), 675, **1954.**

95. L. R. Row and T.R. Seshadri; *Proceedings of the Indian Academy of Sciences - Section A*; 13 (6), 510, **1941.**

96. V. I. Ivanskii; *Khimiya Geterotsiklicheskikh Soedinenii*; *Chemistry of Heterocyclic Compounds; Izd.Vysshaya Shkola*; 175, 281, **1978**.

97. O. R. Rodig; *Chemistry of Heterocyclic Compounds*; 14 (1), 309, **1974.**

98. H. Ota, H. Watanable and Y.Osajima; *Nippon Nogei Kagaku Kaishi*; 54 (6), 415, **1980;** C.A.; 94, 46500, **1981**.

99. E. A. Zvezdina, M. P. Zhdanova and G. N. Dorofeenko; *Russian Chemical Reviews;* 51 (5), 469, **1982**; Translated from Uspekhi Khimii; 51 817, **1982.**

100. H. M. El-Namaky and M. A. Salama; *Egypt. J. Chem.*; 20, 125, **1977.**

101. K. Dimroth and H. Odenwalder; *Chem. Ber.*; 104, 2984, **1971.**

102. R. Wizinger and W. Haldemann; *Chem.Ber.*; 93, 1533, **1960.**

103. L. Jurd; *Tetrahedron*; 31, 2884, **1975.**

104. G. I. Zhungietu and B. P. Sukhanyuk; *Khim. Geterotsikl.Soed.*; 1032, **1972.**

105. G. I. Zhungietu, I. V. Shantsevoi and S. V. Krivun; *Khim. Geterotsikl. Soedin.*; 45, **1973.**

106. J. Korosi and T. Lang; *Chem. Ber.*; 107, 3883, **1974.**

107. R. V. Raval, Ph.D. Thesis, Saurashtra University, **1984.**

108. R. Doodeman, F. P. J. T. Rutjes and H. Hiemstra; *Tetrahedron Lett.*; 41, 5979, **2000.**

109. (a) J. Zhendong and K. Ying; *PCT Int. Appl.*; WO 2004058738, **2004.** (b) N. Iwata, N. Wang, X. Yao and S. Kitanaka; *J. Nat. Prod.*; 67, 1106, **2004.** (c) H. Hu, T. J. Harrisonand P. D. Wilson; *J. Org. Chem.*; 69, 3782, **2004.**

110. R. Korec, K. H. Sensch and T. Zoukas; *Arzneim. Forsch*; 50, 122, **2000.**

111. (a) R. W. J. Carney, W. L. Bencze, J. Wojtkunski, A. A. Renzi,L. Dorfman and G.De Stevens; *J. Med. Chem.*; 9, 516, **1966**. (b) S. Gauthier, B. Caron, J. Cloutier, Y. L. Dory, A. Favre, D. Larouche,J. Mailhot, C. Ouellet, A. Schwerdtfeger, G. Leblanc, C. Martel, J. Simard, Y. Merand, A. Belanger, C. Labrie and F. Labrie; *J. Med. Chem.*; 40, 21174, **1967.**

112. F. Bonadies, R. Di Fabio and C. Bonini; *J. Org. Chem.*; 49, 1647, **1984**.

113. A. A. Morandim, D. C. B. Bergamo, M. J. Kato, A. J. Cavalheiro, V. S. Bolzani and M.Furlan; *Phytochem. Anal.*; 16, 282, **2005.**

114. A. P. Brestkin, E. N. Dmitrieva, Iu. G. Zhukovskii, A. A. Safonova and V. A. Sedavkina; *Ukrainskii biokhimicheskii zhurnal*; 60 (2), 35, **1988**.

115. Yu. D. Beletskii, A. N. Narkevich, G. N. Dorofeenko and Yu. A. Zhdanov; *Zhurnal Vsesoyuznogo Khimicheskogo Obshchestva im. D. I. Mendeleeva*; 11 (3), 359, **1966.**

116. M. Martin; *Dyes for leather*; *DE* 959668 19570307, **1957.**

117. M. Martin; *Dyeing of leather*; DE 1002286 19570214, **1957.**

118. E. F. Rul, M. S. Khaikin, L. G. Fedorina and Derstuganov; *Journal of Photographic Science*; 15 (4), 174, **1967**.

119. V. F. Vozisova and V. N. Podchainova; *Spektral'n. i Khim. Metody Analiza Materialov, Sb. Metodik;* 82, 179, **1964.**

120. L. I. Kononenko and N. S. Poluektov; *Ukrains'kii Khemichnii Zhurnal*; 26, 246, **1960.**

121. P. P. Chiesa, J. R. Dann and J. W. Gates; *Brit. Pat*.; 903077, 157, **1962.**

122. E. L. Contois and P. D. Specht; *Fr. Demande;* 2, 022, 355, **1970**; C.A.; 74, 133060, **1971.**

123. G. I.Frolova, T. A.Markina, I. I.Boiko and K. K.Koshelev; *U.S.S.R.*; SU, 1381934, A1, 19990210, **1999.**

124. M. S. Khaikin, G. V. Destuganov, V. A. Kukhtin, E. F. Rul and L. G. Fedorina; *USSR;* 148, 722, **1962**; C.A.; 58, 5190, **1963.**

125. E. F. Rul, M. S. Khaikin, L. G. Fedorina and G. V. Destuganov; *Zh. Nauch. Prikl. Fotogr. Kinematogr*; 11 (6), 435, **1966**; C.A.; 66, 50680, **1967.**

126. P. Czerney, H. Hartmann and J. Liebscher; *Fr. Demande*; *FR*, 2, 478, 223; C.A.; 96, 142707, **1982.**

127. T. G. Dmitrienko and S. S. Popova; *Russian Journal of Applied Chemistr*; 82 (9), 1551, **2009.**

128. R. N. Usgaonkar, V. M. Thakor, G. V. Jadhav and R. C. Shah; *J. Ind. Chem. Soc.;* 30, 743, **1953.**

129. V. M. Thakor and A.B.; *J. Indian Chem. Soc*.; 48, 499, **1971.**

130. H.Von Pechmann; *Chem Ber.;* 17, 929, **1884.**

131. H.Von Pechmann and C. Duisberg; *Chem Ber.*; 16, 2119, **1883.**

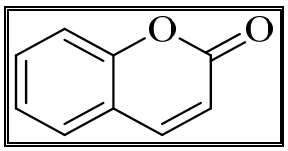
CHAPTER- 2

SYNTHESIS OF SOME NEW 4-AMINO COUMARIN DERIVATIVES USING GREEN CHEMISTRY PROTOCOLS

2.1 INTRODUCTION

The study of coumarins began more than 200 years ago. Coumarin is the best known aromatic lactones. [1] The isolation of coumarin was first reported by Vogel [2] in Munich in 1820. The name coumarin originated [3] from a Caribbean word '*coumarou*' for the tonka tree, which was known botanically at one time as *Coumarouna odorata aubl*. Coumarin is now well accepted trivial name. The IUPAC nomenclature of the coumarin ring system is 2*H*-1-benzopyran-2-one.

Figure 2.1



In 1936, Von Werder [4] referred the coumarins as therapeutic agents and Bose, in 1958 [5] summarized most of the biological properties of the natural coumarins. In 1964, Soine [6] published a revision on the biological and pharmacological effects of coumarins with particular emphasis on the activity associated with the natural products. An excellent account of this naturally occurring coumarin is presented by Murray and co-workers. [7]

Coumarins have attracted intense interest in recent years because of their diverse pharmacological properties. Coumarin derivatives have been shown to possess a remarkably broad spectrum of biological activities including antimicrobial, [8,10] antifungal, [11-13] anticoagulant, [14] anti-inflammatory, [15] antitumor [16,17] and anti-HIV [18] activity. In addition, these compounds are used as additives in food and cosmetics, [19] dispersed fluorescent brightening agents and as dyes for tuning lasers. [20]

Coumarin and its derivatives can be synthesized by various methods, which include Pechmann reaction, Perkin reaction, Reformatsky reaction and Knovenegal reaction. The plant extracts containing coumarin-related heterocycles, which were employed as herbal remedies in early days, have now been extensively studied for their biological

activities. These investigations have revealed their potentials as versatile biodynamic agents. For example, coumarins with phenolic hydroxyl groups have the ability to scavenge reactive oxygen species and thus prevent the formation of 5-HETE and HHT in the arachidonic pathway of inflammation suppression. Recent *in vivo* studies have revealed the role of coumarins in hepatotoxicity and also in depletion of cytochrome P450. Furthermore, several synthetic coumarins with a variety of pharmacophoric groups at C_3, C_4 and C_7 positions have been intensively screened for antimicrobial, anti-HIV, anticancer, lipidlowering, antioxidant and anticoagulation activities. [21]

The coumarins are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence their biological activity. [22] Majority of coumarins are completely innocuous, may be beneficial in a variety of human disorders, in spite of some ongoing controversy. Coumarin turns out to be present in many natural therapeutically utilized products. They hold a place apart in view of their cytotoxic activity. It was suggested that alterations in the chemical structure of coumarin could change their cytotoxic properties. [23] Main representatives of this class are the hydroxyl derivatives, 4- and 7-hydroxycoumarins, also biologically active and very important for the synthesis of other coumarin derivatives. Some of hydroxylated coumarins are demonstrated in Figure 2.2 & 2.3. [24]

Figure 2.2

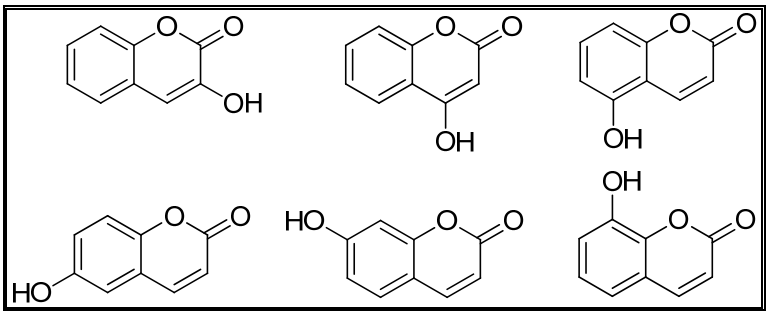
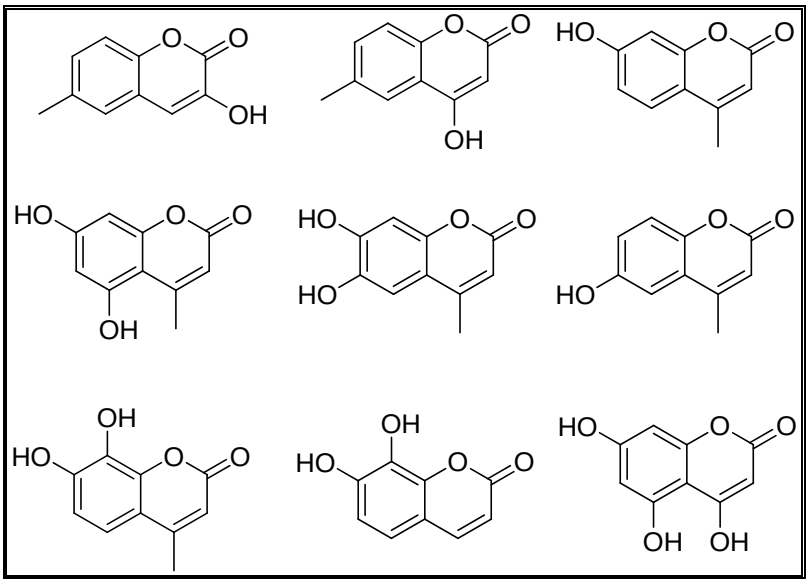


Figure 2.3



2.2 LITERATURE REVIEW

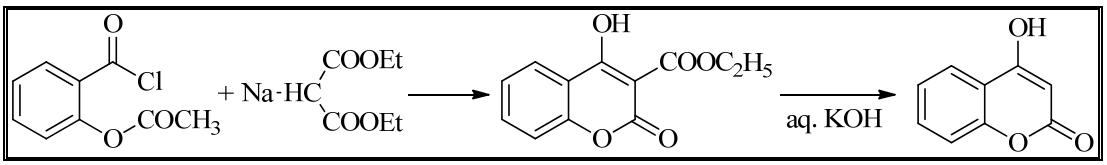
A) 4-Hydroxy Coumarins

4-Hydroxycoumarin is a versatile scaffold and is being consistently used as a building block in organic chemistry as well as in heterocyclic chemistry for the synthesis of different heterocyclic compounds. The nucleus of 4-hydroxycoumarin is very susceptible to electrophilic substitution, so they are very easy to synthesize and substitute by other functional groups to enhance their biological activities. [25]

The chemistry of 4-hydroxycoumarin has gained importance since the discovery of dicoumarol. A number of publications describing physiologically active 4-hydroxycoumarins have appeared in the literature. Pharmacologically earlier 4-hydrooxycoumarin is well established acting as anticoagulant as well as rhodenticide (long acting anticoagulant), but in recent studies numerous potential antibiotic, antitubercular, antiallergic, anthelmintic, central nervous system depressant, hypotensive, coronary dilator, antibacterial, antipsychotic, psychotropic and antifertility agents have been synthesized using 4-hydroxycoumarin. [26]

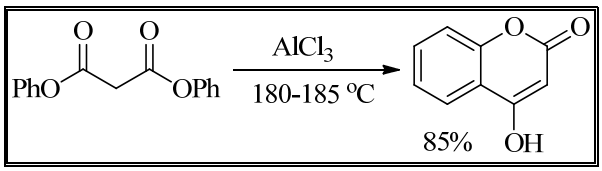
Anschutz first synthesized 4-hydroxycoumarin, by treating acetylsalicylyl chloride with the sodium derivative of malonic ester to form 3-carboethoxy-4-hydroxycoumarin, on treatment with alkali this compound was decarboxylated to form 4-hydroxycoumarin. [27]

Scheme 2.1



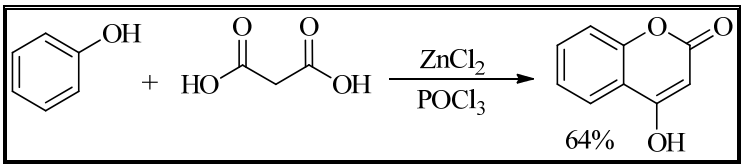
Zeigler and co-worker [28] cyclized malonic acid diphenyl ester in the presence of $AlCl_3$ using Friedle Craft's alkylation to give 4-hydroxycoumarin in 85% yield.

Scheme 2.2



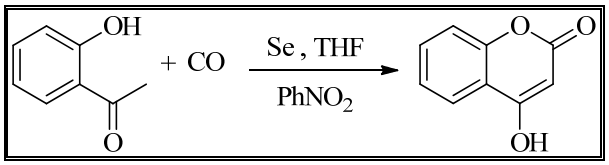
Shah *et al.* [29] have evolved a simple process for the synthesis of 4-hydroxycoumarins in which a substituted phenol was treated with malonic acid in the presence of anhydrous zinc chloride and phosphorus oxychloride at 60-75 ºC. The method is useful as single step preparation of 4-hydroxycoumarin derivatives substituted in benzenoid part.

Scheme 2.3



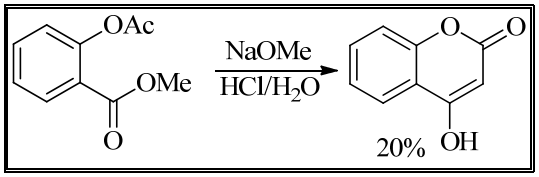
Selenium catalyzed carbonylation of 4-hydroxy acetophenone in THF containing nitro benzene under carbon monoxide atmosphere at 90 ºC for 30 hours giving 68% yield. [30]

Scheme 2.4



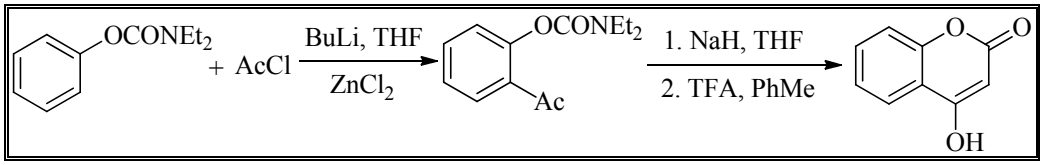
Intramolecular Claisen condensation of methyl acetylsalicylate with NaOMe in liquid paraffin at 160-260 ºC for 5 hours gave 20% of 4-hydroxycoumarin. [31]

Scheme 2.5



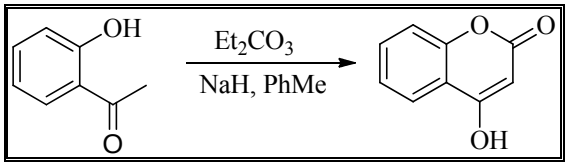
Substituted 4-hydroxycoumarin was synthesized via new Baker-Venkatraman rearrangement. [32]

Scheme 2.6



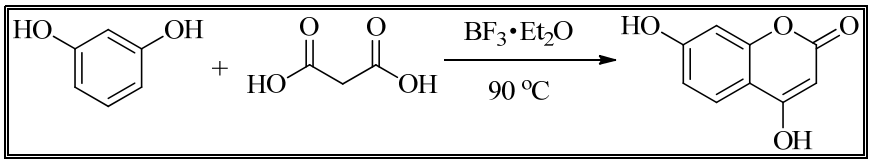
One-pot synthesis of 4-hydroxycoumarin by reacting 2-hydroxyacetophenone with acylating agents in the presence of base was reported. [33]

Scheme 2.7



4,7-Dihydroxycoumarin was synthesized from resorcinol and malonic acid in boron trifluoride-diethyl etherate complex (BF_3•Et_2O) at 90 ºC. [34]

Scheme 2.8



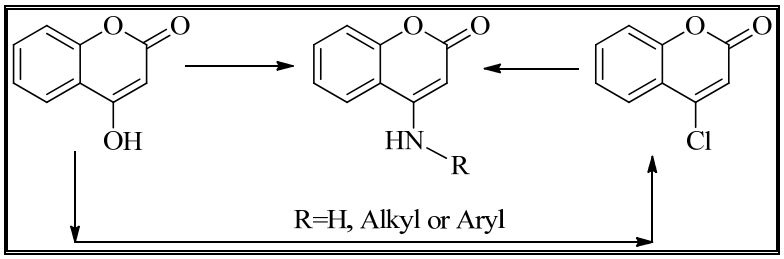
B) 4-Amino Coumarins

Aminocoumarin is a class of antibiotics that act by an inhibition of the DNA Gyrase enzyme involved in the cell division in bacteria. They are derived from *Streptomyces* species, [35] whose best-known representative - *Streptomyces coelicolor* - was completely sequenced in 2002. [36] From the group of aminocoumarins, 3-aminocoumarin and 7-aminocoumarin derivatives are well studied. The 3-aminocoumarin moiety can be recognized in the molecular structure of several natural antibiotics, such as Novobiocin, Chlorobiocin, Coumermycin, etc. These antibiotics and their derivatives are in the research focus. [37] In addition, some simple N-acylderivatives of 3-aminocoumarin exhibit an anti-inflammatory activity [38] and antimicrobial activity against the gram-positive bacteria. [39] Most of the publications for 7-aminocoumarin derivatives present interesting photochemical behavior of these compounds [40] and many of them can be used as fluorescent markers. [41] Furthermore, some platinum complexes of 7-aminocoumarins have been synthesized and evaluated for their *in vitro* cytotoxicity against Caco-2T cells. [42]

4-Aminocoumarins can be prepared from 4-hydroxy or 4-chlorocoumarin derivatives by different synthetic routes which are described below.

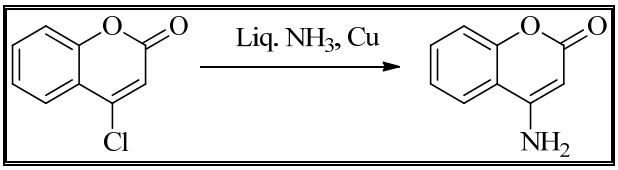
Apparently it is found that 4-aminocourmarin is prepared by direct method by removing acidic hydroxyl group with amino group in one step only, but alternate route is to convert the hydroxyl group into chloro group and then convert it into amino group by appropriate reagent for substitution.

Scheme 2.9



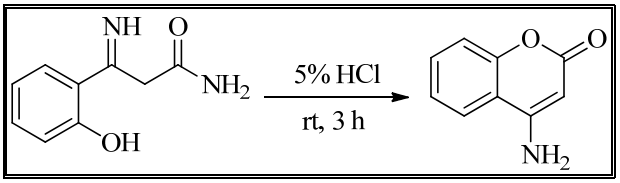
Zagorevskii V. A. and Dudykina N. V. [43] reported that the action of liquor ammonia on 4-chloro coumarin in the presence of copper powder exclusively afforded the 4-aminocoumarin.

Scheme 2.10



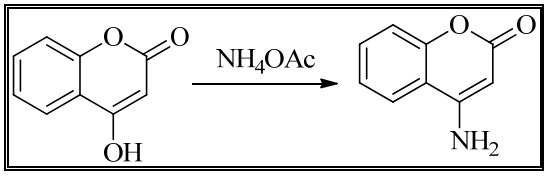
3-(2-Hydroxyphenyl)-3-iminopropanamide treated with 5% HCl at room temperature for 3 hours to yield 4-aminocoumarin. [44]

Scheme 2.11



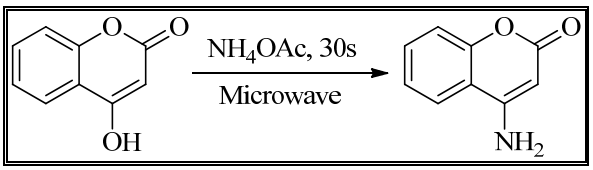
Ivanov I. *et al.* [45] demonstrated the amination of 4-hydroxycoumarin using ammonium acetate or the corresponding primary amine in AcOH.

Scheme 2.12



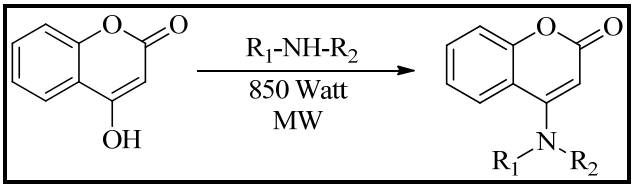
Abhijit Chavan gave microwave assisted synthesis of 4-aryl/alkyl amino coumarins using various amines including ammonium acetate in solvent free condition with good yield. [46]

Scheme 2.13



Ivanov and co-worker [47] have prepared 4-arylamino coumarin without any solvent in molar ratio of 1:1:2 under microwave irradiation with 90-98% yield.

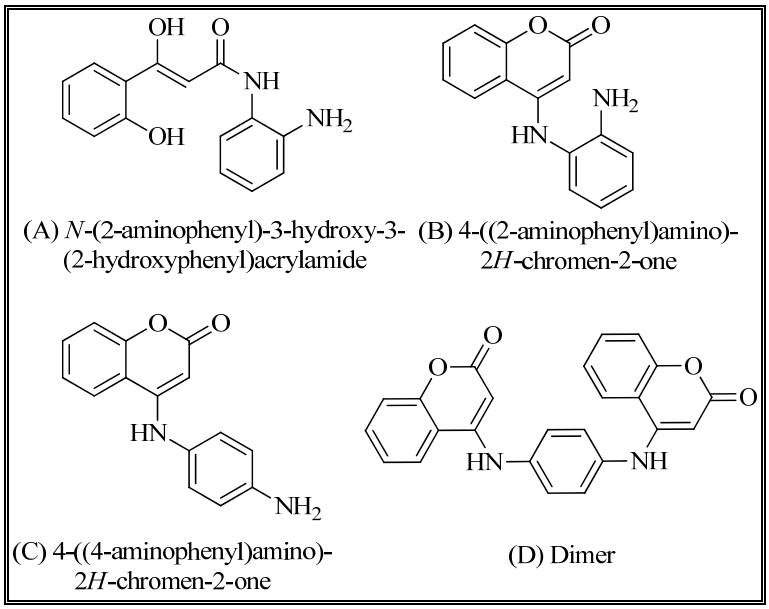
Scheme 2.14



Checchi and Vettori [48] synthesized 4-aminocoumarin-3-sulphonamide and its derivatives. Sulphonation of 4-hydroxycoumarin in the absence of any solvent, with an excess of chlorosulphonic acid yielded 3-sulphonic acid, which was converted to its potassium salt and on further chlorination with phosphorous oxychloride, afforded 4-chlorocoumarin sulphochloride. The treatment of either ammonia or primary aliphatic and aromatic amines led to the formation of 4-aminocoumarin-3-sulphonamide and its derivatives.

Hamdi *et al.* [49] demonstrated that heating 1, 2-phenylenediamine with the 4-hydroxycoumarin in ethanol, two products were obtained, one was *N*-(2-aminophenyl)-3-hydroxy-3-(2-hydroxyphenyl) acrylamide (A) and another was 4-[(2-aminophenyl)amino]-2*H*-chromen-2-one (B). While 1,4-phenylenediamine was refluxed in xylene with 4-hydroxycoumarin, it also gave two products, one was 4-[(4-aminophenyl) amino]-2*H*-chromen-2-one (C) and another was the dimer (D).

Figure 2.4

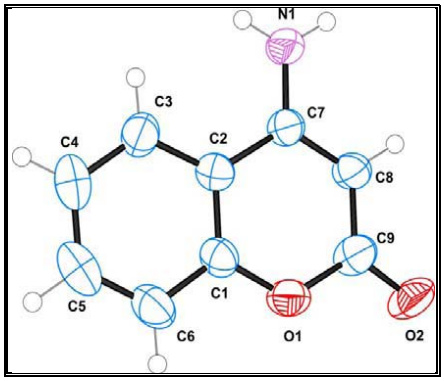


(A) *N*-(2-aminophenyl)-3-hydroxy-3-(2-hydroxyphenyl)acrylamide (B) 4-((2-aminophenyl)amino)-2*H*-chromen-2-one

(C) 4-((4-aminophenyl)amino)-2*H*-chromen-2-one (D) Dimer

B. Stamboliyska and co-workers [50] reported experimental and theoretical investigation of the structure and nucleophilic properties of 4-aminocoumarin. Structure of 4-aminocoumarin was elucidated by single crystal x-ray crystallography.

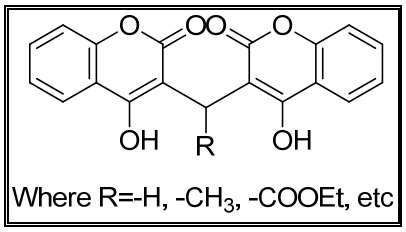
Figure 2.5



C) Coumarin Dimers

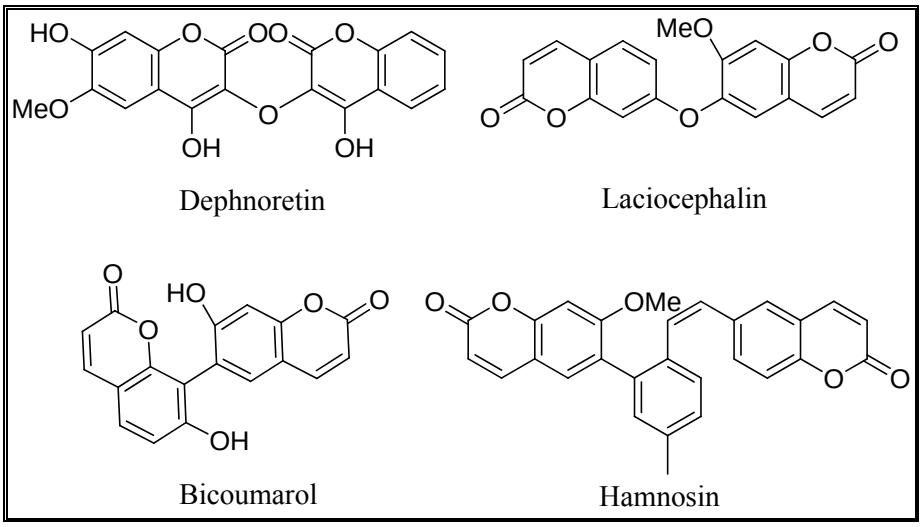
For the first time, Link and co-workers discovered that the substance responsible for producing hemorrhages in cattle feeding on spoilt sweet clover hay is dimer 3,3'-methylene-bis-(4-hydroxycoumarin), commonly known as dicoumarol. Dicoumarol was later used as anticoagulant activity in drug therapy. [51,52]

Figure 2.6



Dimeric coumarins which exist naturally are Dephnoretin, [53] Hamnosin, [54] Laciocephalin [55] and Bicoumarol. [56]

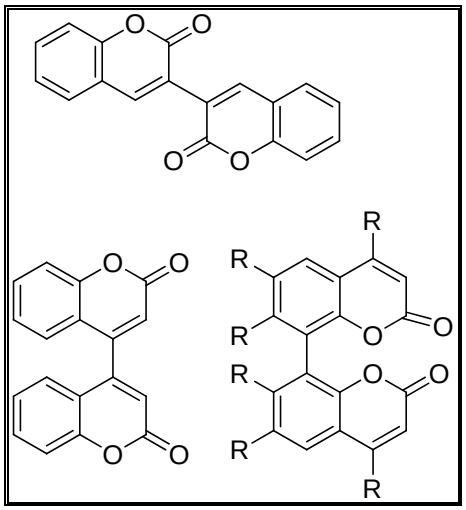
Figure 2.7



Some of the dicoumarols which were studied for their potential drug like properties are summarized as below.

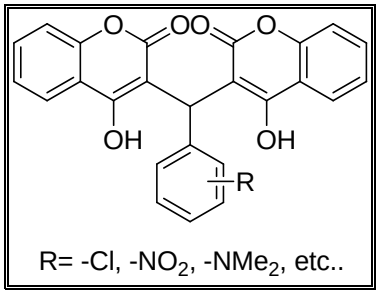
Trivedi and co-workers prepared biscoumarinoxymethanes. [57] Mentzer synthesized Daphnoretin tosylate by reacting 2,4-dihydroxyanisole and 7-coumarinyl malonate over three steps. [58] Huebner *et al.* [59] and Lele *et al.* [60] also synthesized dicoumarins of the type below. Efforts were made to study dimers by forming C-C bonds in coumarin unit at C_3, C_4 and C_8 positions.

Figure 2.8



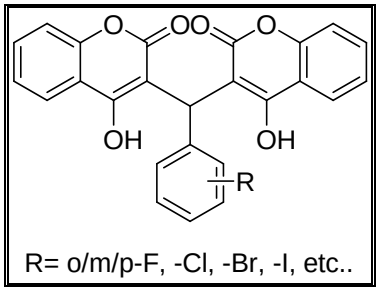
Arora and his team synthesized various substituted dicoumarins and tested its anticoagulant activity in comparison to dicoumarol. [61]

Figure 2.9



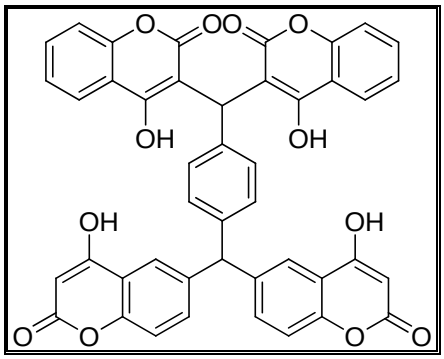
Further, Guminska *et al.* [62] studied anticoagulant activity of 3,3'-(halobenzylidene)bis-4-hydroxycoumarins as compared with that of dicoumarol in rabbits. They concluded that in general, all p-halo substituted derivatives were more active anticoagulants than o- and m-substituted compounds and specifically chloro analogs were better than fluoro and iodo.

Figure 2.10



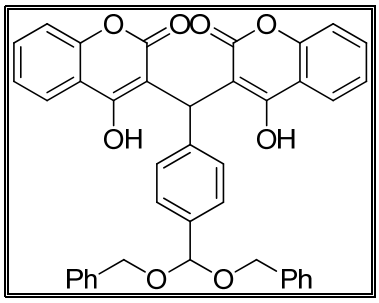
Mazumder *et al.* [63] investigated many dimeric coumarin containing moieties for potential antiviral, antiprotease and anti integrase activity. They concluded that NSC 158393, which contains four 4-hydroxycoumarin residues, was the most effective in micromolar concentrations. Hence, NSC 158393 may represent essential elements of the antiintegrase coumarin pharmacophore.

Figure 2.11



The structures of a large number of HIV-1 integrase inhibitors have in common two aryl units separated by a central linker. Frequently, at least one of these aryl moieties must contain 1,2- dihydroxy substituents in order to exhibit high inhibitory potency. Replacement of this central phenyl ring by more extended aromatic systems having higher lipophilicity improved potency, as did the additions of 7-hydroxy substituents to the coumarin rings gave the same potency. [64]

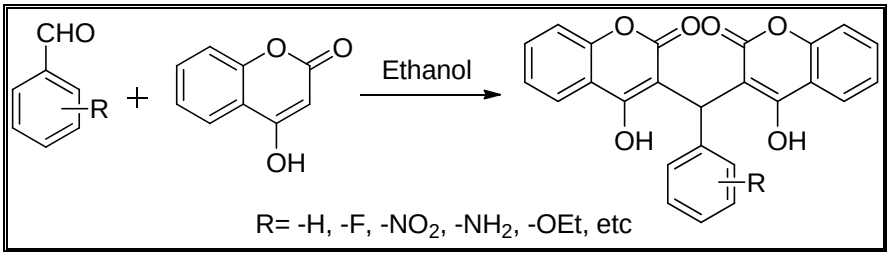
Figure 2.12



Many synthetic routes have been applied for the preparation of dicoumarins. Some important methodologies are outlined here.

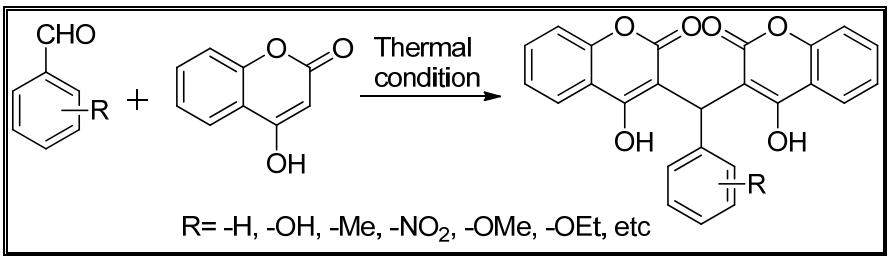
Dicoumarins were prepared by the condensation of 4-hydroxycoumarin and substituted benzaldehydes. The compounds were evaluated for antiplatelet aggregation and cytotoxicity to human cancer cells. [65]

Scheme 2.15



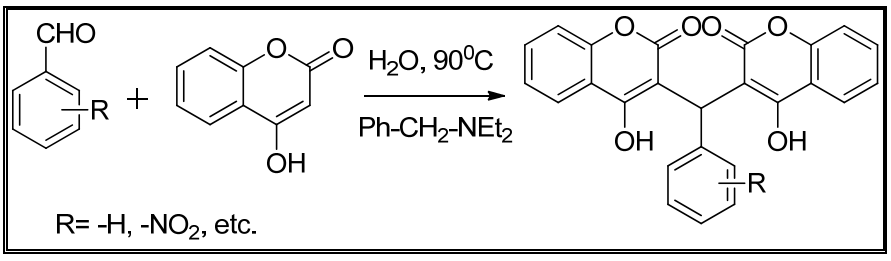
Shaterian Hamid Reza [66] reported uncatalyzed, one-pot synthesis of 3,3'-(benzylene)bis(4-hydroxy-2H-chromen-2-one) derivatives under thermal solvent-free conditions. This environmentally friendly synthesis is uncatalyzed and affords the desired products in excellent yields.

Scheme 2.16



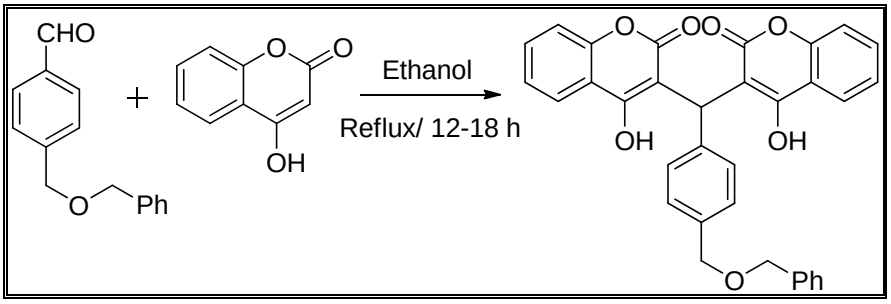
Use of phase transfer catalyst TEBA (triethylbenzylammonium chloride) reported to condense aromatic aldehydes with 4-hydroxycoumarin in the presence of aqueous media. [67]

Scheme 2.17



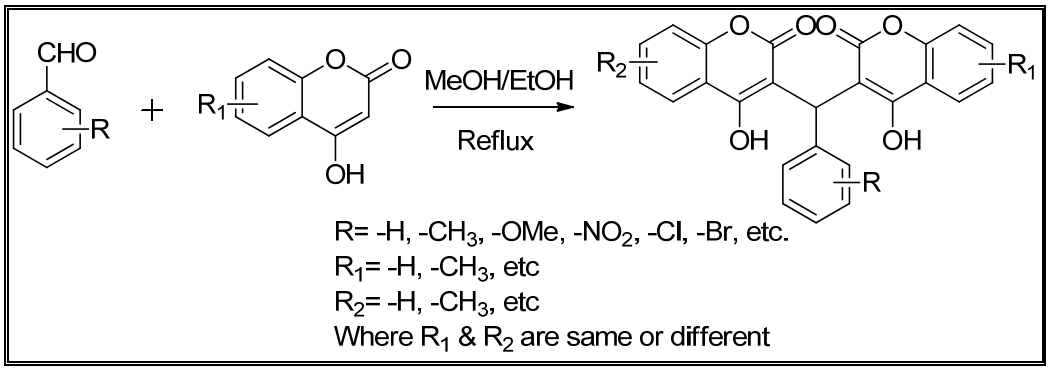
A series of coumarin dimers were synthesized by Shah & co-workers and tested for their inhibitory activity against HIV-1 integrase. The authors concluded that a hydrophobic moiety on the linker display potent inhibitory activities. [68]

Scheme 2.18



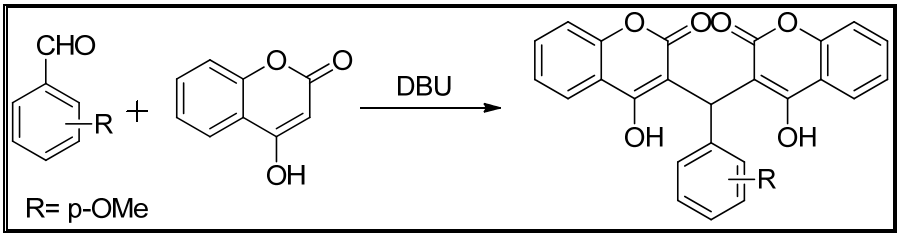
Besides these, Shah *et al.* [69-77] synthesized several coumarin as well as quinoline dimers and tested them for various biological activities.

Scheme 2.19



Ilia I. Manolov [78] has synthesized methylenebis(4-hydroxycoumarin) derivatives by reaction of 4-hydroxycoumarin with aromatic aldehydes by organic solid-state reaction.

Scheme 2.20

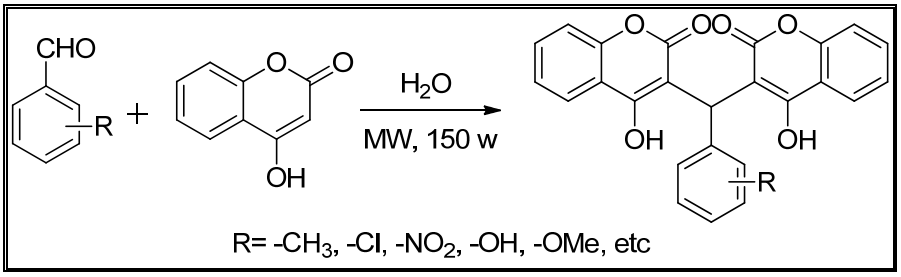


Prashant Singh *et al.* [79] demonstrated that phosphotungstic acid provided a simple, efficient and environmentally benign route in a two-component one-pot domino Knoevenagel-type condensation/Michael reaction between 4-hydroxycoumarin and an aldehyde in water as a solvent in shorter duration with high yields.

A simple, efficient and ecofriendly procedure has been developed by Jitender M. Khurana & co-workers [80] using tetrabutylammonium bromide (TBAB) as catalyst for the synthesis of biscoumarin and dihydropyrano[c]chromene derivatives in water and solvent-free neat conditions. The present methodology offers several advantages such as excellent yields, short reaction time, and environmentally benign milder reaction conditions.

Gui-Xia & co-workers [81] have developed an efficient catalyst-free synthesis of α,α-bis(4-hydroxycoumarin-3-yl)toluene. The reaction of 4-hydroxycoumarin with aromatic aldehydes in aqueous media was performed by microwave irradiation. The reaction was completed in short reaction time of 8-10 minutes with high yields of 76-94%. This method is environmentally benign and has easy workup.

Scheme 2.21



Qadir Saima *et al.* [82] gave a convenient synthesis of various biscoumarins by condensing a series of aldehydes with 4-hydroxycoumarin under microwave irradiation and also carried out a comparative assessment of percentage yield under thermal and microwave-assisted conditions.

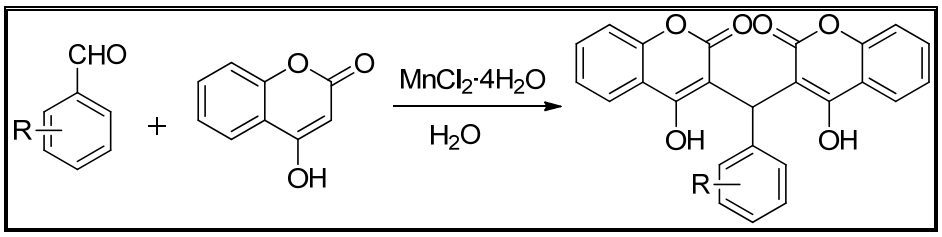
M. Kidwai & co-workers [83] reported molecular iodine as a versatile catalyst for the synthesis of bis(4-hydroxycoumarin)methanes in water.

Zhou Jianfeng *et al.* [84] synthesized a series of 3,3-arylidene bis(4-hydroxycoumarins) by the reaction of aromatic aldehydes with 4-hydroxycoumarin using sulfamic acid as catalyst in aqueous media under microwave irradiation.

Heravi M. Majid *et al.* [85] developed reaction of aldehydes and 4-hydroxycoumarin in the presence of catalytic amount of silica-supported Preyssler nano-particles led to synthesis of bis-coumarins in excellent yields.

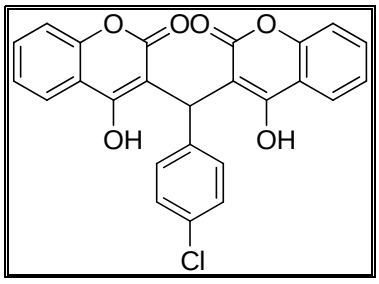
Sangshetti Jaiprakash N. *et al.* [86] have performed water mediated efficient one-pot synthesis of various aromatic and heteroaromatic aldehydes with 4-hydroxycoumarin to afford bis-(4-hydroxycoumarin)methanes. Manganese chloride ($MnCl_2 \cdot 4H_2O$) has been used as an efficient catalyst for an improved and rapid one-pot synthesis of bis-(4-hydroxycoumarin)methanes in excellent yields using water as a reaction medium.

Scheme 2.22



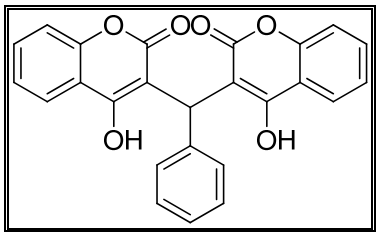
Ilia Manolov *et al.* [87] have synthesized twenty 4-hydroxycoumarin derivatives and five of them were described for the first time. The X-ray crystal structure analysis of 3,3'-(2,3,4-trimethoxyphenylmethylene)bis-(4-hydroxy-2H-1-benzopyran-2-one) and 3,3'-(3,5-dimethoxy-4-hydroxyphenylmethylene)bis-(4-hydroxy-2H-1-benzopyran-2-one) confirmed the structure of these compounds. A comparative pharmacological study of the anticoagulant effect with respect to Warfarin showed that the synthesized compounds had different anticoagulant activities. The most prospective compound was 3,3'-(4-chlorophenylmethylene)bis-(4-hydroxy-2H-1-benzopyran-2-one) with low toxicity, very good index of absorption and dose dependent anticoagulant activity.

Figure 2.13



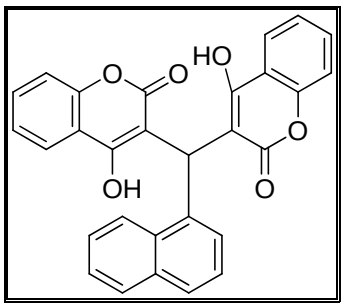
Valente J. Edward and co-workers [88] determined the Structure of (phenyl) bis-(4-hydroxybenzo-2H-pyran-2-one-3-yl)-methane.

Figure 2.14



The crystal structure of 3,3'-(-naphthylmethylene) bis-(4-hydroxycoumarin) was successfully studied by Eckstein and Csoregh. [89]

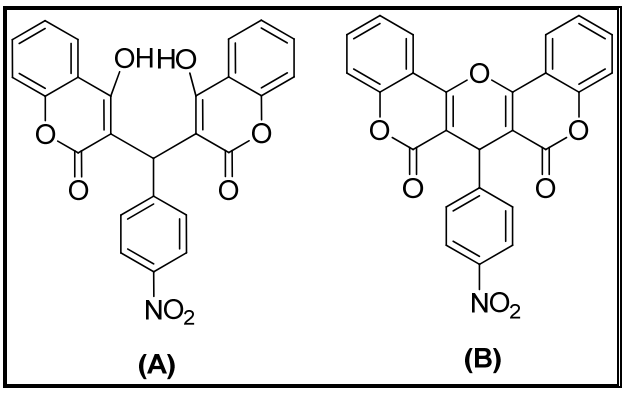
Figure 2.15



Hamdi Naceur *et al.* [90] gave synthesis, structure, antimicrobial and antioxidant investigations of dicoumarol and related compounds. Different substituted 3,3'-arylidenebis-4-hydroxycoumarins, e.g., (A), and a tetrakis-4-hydroxycoumarin derivatives are the final products when 4-hydroxycoumarin and aromatic aldehydes containing different groups in ortho, meta or para positions condense in boiling ethanol or acetic acid. Upon heating the 3,3'-arylidenebis-4-hydroxycoumarins and tetrakis-4-hydroxycoumarin derivatives in acetic anhydride, the epoxydicoumarins,

e.g., (B), were formed. From a study of NMR and IR spectra, intramolecularly hydrogen-bonded structures are proposed for the dicoumarols, e.g., (A). A possible relationship between such hydrogen-bonded structures and the antimicrobial and the antioxidant activities of compounds such as (A) is suggested.

Figure 2.16



2.3 PHARMACOLOGICAL SIGNIFICANCE

Coumarins comprise a group of natural compounds found in a variety of plant sources. The very long association of plant coumarins with various animal species and other organisms throughout evolution may account for the extraordinary range of biochemical and pharmacological activities of these chemicals inmammalian and other biological systems. The coumarins have diverse biological properties and various effects on the different cellular systems. A lot of biological parameters should be evaluated to increase our understanding of mechanisms by which these coumarins act. Coumarins have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors, and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection. [21]

The coumarins have long been recognized to possess anticoagulant, antipsoriasis, anti-inflammatory, antioxidant, antibacterial, antiallergic, hepatoprotective, antithrombotic, antiviral and anticarcinogenic activities. [91]

Considerable progress has been made in recent years in the field of drug development against HIV. The discovery and development of coumarins as anti-HIV agents has expanded in the past two decades. Most of the studies have been focused on the inhibitory activity of reverse transcriptase, but anti-integrase and antiprotease activities were also described. [92]

Coumarin derivatives were prepared as γ-secretase inhibitors for treating or preventing neurodegenerative diseases such as Alzheimer's disease. [93]

Dicoumarol, a natural anticoagulant drug chemically designated as 3,3-methylenebis[4-hydroxycoumarin], is metabolized from coumarin in the sweet clover (*Melilotus alba* and *Melilotus officinalis*) by molds, such as *Penicillium nigricans* and *Penicillium jensi*. [94]

Dicoumarol analogs are prepared as inhibitors of human NAD(P)H quinone oxidoreductase-1 (NQO1), an enzyme overexpressed in several types of tumor cell. [95]

Inhibition of HIV integrase by 4-hydroxycoumarin dimer bearing aniline mustard moiety are described by Mao Pili Chih-Min and co-workers. [96]

Dicoumarins were also investigated for potential herbicidal activity as growth inhibitors of Mimosa pigra Linn (giant mimosa). The hydroxy or methoxy groups as substituent(s) on the benzylidene ring had higher activity. [97]

2.4 AIM OF CURRENT WORK

In today's world, synthetic chemists in both academia and industry are constantly challenged to consider more environmentally benign methods for generation of the desired target molecules. Among the 12 principles of green chemistry, the desire for to utilize ''safer solvents'' and to ''design for energy efficiency'' can be considered two key principles of relevance to synthetic chemists.

Microwave irradiation has been utilized as one of the most convenient and efficient ways to promote organic reactions. In particular, the use of microwave energy to directly heat chemical reactions has become an increasingly popular technique in the scientific community. On the other hand, microwave (MW) promoted reactions have the advantages such as atom economy, high efficiency, greater selectivity, enhance reaction rate as well as environmental friendly nature. [81-98]

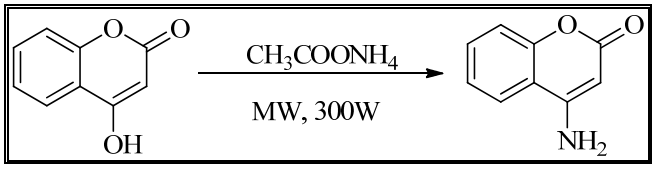
On the other hand, the use of toxic and expensive organic solvents can be avoided by solvent free reaction condition. Such reactions not only reduce the amount of waste solvent generated, but also reduce the cost. The product obtained by this often need very little or no purification.

Moreover, multicomponent reactions have become very popular in the discovery of biologically active novel compounds due to the intrinsic atom economy and selectivity underlying such reactions, simpler procedures and equipment, time and energy savings, as well as environmental friendliness have all led to a sizable effort to design and implement MCRs in both academia and industry. [99]

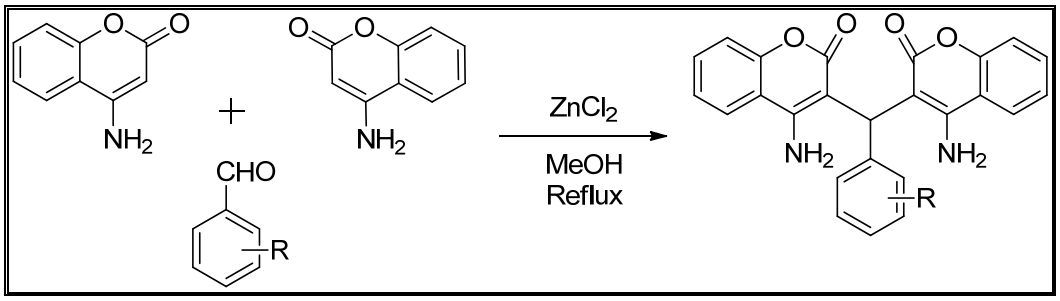
In continuation with our previous work related to coumarin and 4-hydroxy coumarin dimer and biological importance of coumarin dimers prompted us to synthesize some new, possibly more potent and pharmacologically active 4-amino coumarin dimers. Aim of current work is to synthesize some novel 3,3'-((substituted phenyl) methylene) bis (4-amino-2H-chromen-2-one) derivatives using green chemistry protocol.

2.5 REACTION SCHEME

2.5.1 Preparation of 4-Aminocoumarin (MNP-061)

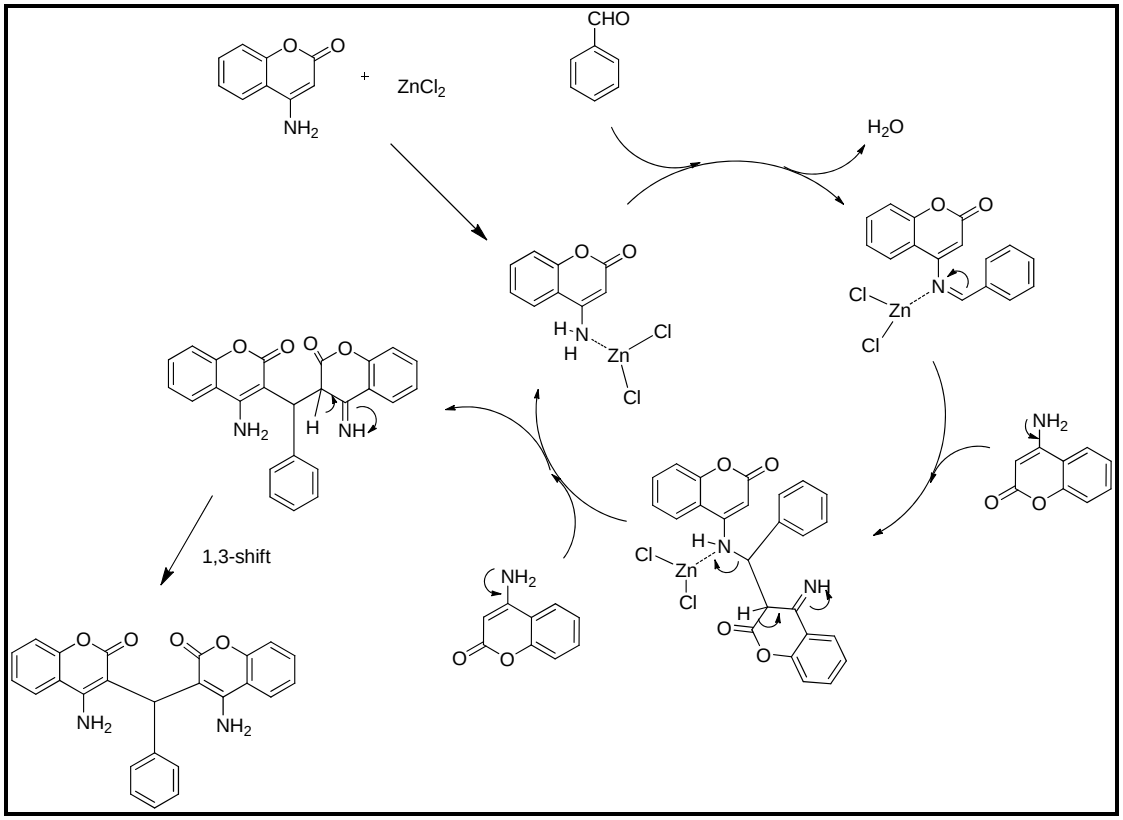


2.5.2 Preparation of 3,3'-((Substituted phenyl) methylene) bis (4-amino-*2H*-chromen-2-one) (MNP-062 to 080)



Where R= -H, -F, -Cl, -Br, $-OCH_3$, $-NO_2$, etc.

2.6 PLAUSIBLE REACTION MECHANISM



2.7 EXPERIMENTAL

2.7.1 Analysis Protocol

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr Powder method. Mass spectra were recorded on **Shimadzu GC-MS-QP-2010** model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$/DMSO-d_6 solution on a **Bruker Avance II 400 NMR MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model. All the results are in agreements with the structures assigned.

2.7.2 Preparation of 4-Aminocoumarin

A mixture of 4-hydroxycoumarin **(**0.01 mole) and ammonium acetate (0.03 mole) was taken in a 250 mL round bottom flask and placed in **Samsung MW83Y Microwave Oven** which was locally modified for carrying out chemical reactions and irradiated at 300 watt for 10 minutes. The progress and the completion of the reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (5: 5) as a mobile phase. After completion of the reaction it was allowed to cool and the crude product was poured into 50 mL 10% $NaHCO_3$ solution to remove unreacted 4-hydroxycoumarin and allowed to stir for an hour, filtered and washed with water. The product was recrystallized from methanol to yield pure 4-aminocoumarin. Slight yellow in colour with 161 ºC MP and 75 % yield.

2.7.3 Preparation of 3,3'-((Substituted phenyl) methylene) bis (4-amino-*2H*-chromen-2-one) (General Procedure)

A mixture of substituted aldehyde (0.01 mole), 4-amino coumarin (0.02 mole) and anhydrous zinc chloride (0.001 mole) was taken in 250 mL round bottom flask. The

reaction mixture was fused at 110 ºC temperature for 15 minutes followed by addition of 25 mL methanol and reaction mixture was refluxed with stirring for 1-2 hour. The progress and the completion of the reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After completion of the reaction, the product was separated out automatically. The product was filtered and washed with hot methanol. Similarly other compounds were also prepared.

There are many factors which affect the reaction time, yield & purity of the final product, which are enlisted below.

1) $ZnCl_2$: Catalytic amount of Zinc Chloride affect very strongly by means of reaction time, yield and purity of the final product. It decreases reaction time from about 40 hours to 2-3 hours.

2) Molar ratio is also one of the key factors which affect the yield and purity of the final product.

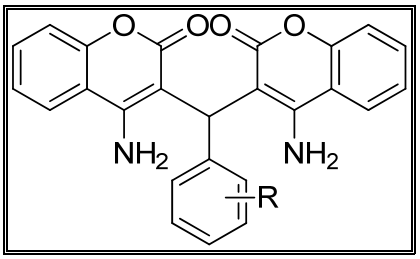
3) Variety of aldehyde which possesses o, m or p substituted group also affect the reaction time, yield and purity of the final compound. e.g. o-nitro benzaldehyde gave low yield in comparison with m-/p-nitro benzaldehyde.

4) There is a least possibility of the formation of Schiff base of $-NH_2$ group while synthesizing dimer of 4-amino coumarin.

The physical data of the newly synthesized compounds are given in Table No. 2.8.1

2.8 PHYSICAL DATA

2.8.1 Physical Data Table of 3,3'-((Substituted phenyl) methylene) bis (4-amino-2H-chromen-2-one)



Sr. No.	Sample Code	Substitution R	Molecular Formula	M. Wt	MP °C	Yield %
1	MNP-061*	4-Amino Coumarin	$C_9H_7NO_2$	161	161-162	75
2	MNP-062	H	$C_{25}H_{18}N_2O_4$	410	284-286	64
3	MNP-063	2-NO_2	$C_{25}H_{17}N_3O_6$	455	280-282	62
4	MNP-064	3-NO_2	$C_{25}H_{17}N_3O_6$	455	288-290	73
5	MNP-065	4-NO_2	$C_{25}H_{17}N_3O_6$	455	276-278	68
6	MNP-066	4-Cl	$C_{25}H_{17}ClN_2O_4$	444	295-297	67
7	MNP-067	3-Cl	$C_{25}H_{17}ClN_2O_4$	444	300-302	70
8	MNP-068	3-Br	$C_{25}H_{17}BrN_2O_4$	489	297-299	78
9	MNP-069	3-F	$C_{25}H_{17}FN_2O_4$	428	284-286	62
10	MNP-070	4-F	$C_{25}H_{17}FN_2O_4$	428	313-315	70
11	MNP-071	4-OH	$C_{25}H_{18}N_2O_4$	426	264-266	65
12	MNP-072	3-OH	$C_{25}H_{18}N_2O_4$	426	271-273	60
13	MNP-073	3,4-di OH	$C_{25}H_{18}N_2O_6$	442	278-280	62
14	MNP-074	3-OCH_3	$C_{26}H_{20}N_2O_5$	440	275-277	61
15	MNP-075	4-OCH_3	$C_{26}H_{20}N_2O_5$	440	266-268	64
16	MNP-076	3,4-di -OCH_3	$C_{27}H_{22}N_2O_6$	470	281-283	63
17	MNP-077	2,5-di-OCH_3	$C_{27}H_{22}N_2O_6$	470	286-288	60
18	MNP-078	3,4,5-tri-OCH_3	$C_{28}H_{24}N_2O_7$	500	265-267	68
19	MNP-079	3- OCH_3, 4-OH	$C_{27}H_{22}N_2O_6$	470	283-285	60
20	MNP-080	3- OC_2H_5, 4-OH	$C_{26}H_{20}N_2O_6$	456	270-272	65

NB: '*' Indicating the compound is reported. Ref. No. [43-48, 100]

2.9 SPECTRAL DISCUSSION

2.9.1 IR Spectra

IR spectra of the synthesized compounds were recorded on Shimadzu FT-IR 8400 model using KBr powder method. Various functional groups present were identified by characteristic frequency obtained for them.

The characteristic bands of N-H group showed in the region of 3400-3200 cm^{-1} with a deformation due to in plane bending at 1680-1650 cm^{-1}. Aromatic C-H stretching and bending vibration showed near 3070-3030 cm^{-1} and 1600-1400 cm^{-1} respectively. Alkane C-H stretching and bending frequencies for methylene group appeared at 2920-2870 cm^{-1} and 1450-1350 cm^{-1} respectively. Characteristic C=O stretching frequency of coumarin ring showed at 1740-1690 cm^{-1}. C-O stretching showed at 1200-1150 cm^{-1}. C-N stretching of primary amine showed near 1350-1250 cm^{-1}.

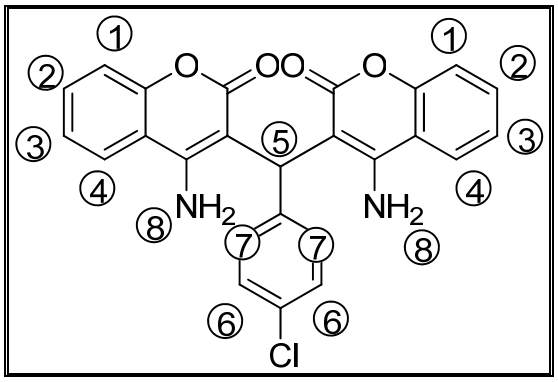
2.9.2 Mass Spectra

Mass spectra of the synthesized compounds were recorded on Shimadzu GC-MS QP-2010 model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak are observed in case of compounds having chloro substituent, while in case of bromo derivatives, both M^{+1} and M^{+2} molecular ion peaks are observed.

2.9.3 ^{1}H NMR Spectra

^{1}H NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR spectrometer by making a solution of samples in $CDCl_3$/DMSO-d_6 solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Number of protons identified from ^{1}H NMR spectra and their chemical shift (δ ppm) were in the agreement of the structure of the molecule. *J* values were calculated to identify o, m and p coupling. In some cases, aromatic protons were obtained as multiplet. Interpretation of representative spectrum is discussed here.

2.9.3.1 ^{1}H NMR of 3,3'-((4-Chlorophenyl) methylene) bis (4-amino-*2H*-chromen-2-one) (MNP-066)



1. Proton no. 1 of total 2H gave a multiplet at 7.54-7.58 δ ppm due to ortho and meta coupling with proton no. 2 and 3.

2. Proton no. 2 and 3 of total 4H gave a multiplet at 7.28-7.32 δ ppm.

3. Proton no. 4 became deshielded and gave a characteristic double doublet at 8.05-8.07 δ ppm due to ortho coupling with proton no. 3 (*J*=7.12) and meta coupling with proton no. 2 (*J*=1.32) as well *J* value confirmed the coupling of this proton.

4. Proton no. 5 of 1H gave a characteristic singlet at 5.99 δ ppm.

5. Proton no. 6 and 7 of total 2H and 2H gave a typical para di substituted pattern of doublet of doublet at 7.22 δ ppm-7.14 δ ppm.

6. Proton no. 8 of total 4H gave a typical broad singlet of amino group at 7.79 δ ppm.

Thus, by observing and assigning the signals in the NMR spectrum and by the calculation of the *J* values for above proton, we can clearly suggest that the proposed structure for compound MNP-066 has been confirmed. The spectrum is given on page no. 105.

2.9.4 ^{13}C NMR Spectra

^{13}C NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in DMSO-*d6*/$CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Types of carbons identified from NMR spectrum and their chemical shifts (δ ppm) were in the agreement with the structure of the molecule.

2.9.5 Elemental Analysis

Elemental analysis of the synthesized compounds was carried out on Vario EL Carlo Erba 1108 which showed calculated and found percentage values of Carbon, Hydrogen and Nitrogen in support of the structure of synthesized compounds.

The analytical data for individual compounds synthesized in this chapter is mentioned as follow.

2.10 ANALYTICAL DATA

1) 4-Amino-2H-chromen-2-one (MNP-061)

Yield: 75%; **IR** (cm^{-1}): 3390-3210 (N-H str.), 3070-3030 (Ar C=C-H str.), 1722 (C=O str.), 1668 (N-H def), 1600, 1548, 1500 (Ar C=C str.), 1265 (C-N str. pri amine), 1195 (C-O str.); **^{1}H NMR** ($CDCl_3$) δ ppm: 4.89 (s, 2H), 5.52 (s, 1H), 7.27-7.31 (m, 1H), 7.35-3.37 (d, 1H), 7.44-7.46 (d, 1H), 7.55-7.59 (m, 1H); **MS**: *m/z* = 161 (100%); Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69; O, 19.86; Found: C, 67.35; H, 4.20; N, 8.54.

2) 3,3'-(Phenylmethylene)bis(4-amino-2H-chromen-2-one) (MNP-062)

Yield: 64%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1600, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 750-700 (C-H oop def); **MS**: *m/z* = 410.42 (100%); Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.83; O, 15.59; Found: C, 73.28; H, 4.33; N, 6.48.

3) 3,3'-((2-Nitrophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-063)

Yield: 62%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1600, 1545, 1500 (Ar C=C str.), 1550-1510 (N=O str. NO_2), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 750-750 (C-H oop def); **MS**: *m/z* = 455.42 (100%); Anal. Calcd. for $C_{25}H_{17}N_3O_6$: C, 65.93; H, 3.76; N, 9.23; O, 21.08; Found: C, 65.25; H, 3.84; N, 9.55.

4) 3,3'-((2-Nitrophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-064)

Yield: 73%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1600, 1545, 1500 (Ar C=C str.), 1550-1510 (N=O str. NO_2), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 800-780 (C-H oop def); **^{1}H NMR** (DMSO-d_6) δ ppm: 6.09 (s, 1H), 7.32-7.35 (m, 4H), 7.49-7.53 (t, 1H, *J*=7.96), 7.58-7.65 (m, 3H), 7.88 (s,b, 4H), 7.95 (s, 7.95), 8.03-8.04 (t, 1H); **^{13}C NMR** (DMSO-d_6) δ ppm: 37.21, 93.4,

114.43, 116.51, 120.35, 121.31, 123.23, 123.55, 128.80, 131.87, 133.24, 140.84, 147.80, 152.11; **MS**: *m/z* = 455.42 (100%); Anal. Calcd. for $C_{25}H_{17}N_3O_6$: C, 65.93; H, 3.76; N, 9.23; O, 21.08; Found: C, 65.46; H, 3.58; N, 9.70.

5) 3,3'-((2-Nitrophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-065)

Yield: 68%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1600, 1545, 1500 (Ar C=C str.), 1550-1510 (N=O str. NO_2), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 810-800 (C-H oop def); **^{1}H NMR** (DMSO-d_6) δ ppm: 6.05 (s, 1H), 7.32-7.36 (m, 4H), 7.40-7.42 (d, 1H, *J*=8.32), 7.59-7.63 (m, 2H), 7.88 (s, b, 4H), 8.10-8.12 (d, 4H); ^{13}C NMR (DMSO-d_6) δ ppm: 37.69, 93.53, 114.46, 116.57, 122.92, 123.29, 123.99, 127.68, 130.44, 132.01, 139.90, 145.47, 147.04, 152.11, 154.46, 164.13; **MS**: *m/z* = 455.42 (100%); Anal. Calcd. for $C_{25}H_{17}N_3O_6$: C, 65.93; H, 3.76; N, 9.23; O, 21.08; Found: C, 65.86; H, 3.47; N, 9.63.

6) 3,3'-((4-Chlorophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-066)

Yield: 67%; **IR** (cm^{-1}): 3388-3215 (N-H str.), 3064 (Ar C=C-H str.), 2900 (C-H str. -CH), 1690 (C=O str.), 1658-1650 (N-H def), 1572, 1533, 1500 (Ar C=C str.), 1435 (C-H bend -CH), 1278 (C-N str. pri amine), 1205 (C-O str.), 821 (C-H oop def), 756 (C-Cl str.); **^{1}H NMR** (DMSO-d_6) δ ppm: 5.99 (s, 1H), 7.14-7.16 (d, 2H, *J*=8.36), 7.20-7.22 (d, 2H, *J*=8.56), 7.28-7.32 (m, 4H), 7.54-7.58 (m, 2H), 7.79 (s, b, 4H), 8.05-8.07 (d, 2H); **^{13}C NMR** (DMSO-d_6) δ ppm: 37.21, 93.90, 111.90, 112.11, 113.24, 114.51, 116.54, 122.40, 123.23, 129.38, 131.90, 132.01, 139.90, 141.46, 152.11, 154.28, 164.01; **MS**: *m/z* = 444.87 (100%); Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50; H, 3.85; Cl, 7.97; N, 6.30; O, 14.39; Found: C, 67.38; H, 3.90; N, 6.98.

7) 3,3'-((3-Chlorophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-067)

Yield: 70%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 800-780 (C-H oop def), 790 (C-Cl str.); **MS**: *m/z* = 444.87 (100%); Anal. Calcd. for $C_{25}H_{17}ClN_2O_4$: C, 67.50; H, 3.85; Cl, 7.97; N, 6.30; O, 14.39; Found: C, 67.63; H, 3.47; N, 6.18.

8) 3,3'-((3-Bromophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-068)

Yield: 78%; **IR** (cm^{-1}): 3378-3204 (N-H str.), 3076-3027 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1670 (C=O str.), 1658 (N-H def), 1640, 1541, 1500 (Ar C=C str.), 1338 (C-H bend -CH), 1273 (C-N str. pri amine), 1205 (C-O str.), 800-780 (C-H oop def), 757 (C-Br str.); **^{1}H NMR** (DMSO-d_6) δ ppm: 5.97 (s, 1H), 7.14-7.21 (m, 2H), 7.26 (s, 1H), 7.31-7.35 (m, 5H), 7.58-7.62 (m, 2H), 7.84 (s, b, 4H), 8.09-8.11 (dd, 2H, *J*=1.2, *J*=7.44); **^{13}C NMR** (DMSO-d_6) δ ppm: 37.09, 93.75, 114.49, 116.53, 121.55, 123.23, 123.55, 125.50, 128.18, 129.17, 131.86, 141.14, 152.10, 154.32, 164.03; **MS**: *m/z* = 489.32 (100%); Anal. Calcd. for $C_{25}H_{17}BrN_2O_4$: C, 61.36; H, 3.50; Br, 16.33; N, 5.72; O, 13.08; Found: C, 61.29; H, 3.40; N, 5.88.

9) 3,3'-((4-Fluorophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-069)

Yield: 62%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 1020 (C-F str.), 810 (C-H oop def); **MS**: *m/z* = 428.41 (100%); Anal. Calcd. for $C_{25}H_{17}FN_2O_4$: C, 70.09; H, 4.00; F, 4.43; N, 6.54; O, 14.94; Found: C, 69.89; H, 4.40; N, 6.68.

10) 3,3'-((3-Fluorophenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-070)

Yield: 70%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 1100-1060 (C-F str.), 800-780 (C-H oop def); **^{1}H NMR** (DMSO-d_6) δ ppm: 5.97 (s, 1H), 6.86-6.94 (m, 2H), 6.97-6.99 (d, 1H, *J*=7.8), 7.23-7.29 (m, 1H), 7.32-7.36 (m, 4H), 7.58-7.63 (m, 2H), 7.84 (s, b, 4H), 8.09-8.10 (d, 2H, *J*=7.52); **^{13}C NMR** (DMSO-d_6) δ ppm: 37.21, 93.98, 111.90, 112.11, 113.24, 114.51, 116.54, 122.40, 123.23, 129.38, 131.90, 132.01, 139.90, 141.46, 152.11, 154.28, 164.01; **MS**: *m/z* = 428.41 (100%); Anal. Calcd. for $C_{25}H_{17}FN_2O_4$: C, 70.09; H, 4.00; F, 4.43; N, 6.54; O, 14.94; Found: C, 70.15; H, 4.10; N, 6.59.

11) 3,3'-((4-Hydroxy phenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-071)

Yield: 65%; **IR** (cm^{-1}): 3600-3500 (O-H str.), 3400-3200 (N-H str.), 3075-3030 (Ar

C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 426.42 (100%); Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 70.42; H, 4.25; N, 6.57; O, 18.76; Found: C, 70.46; H, 4.20; N, 6.60.

12) 3,3'-((3-Hydroxy phenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-072)

Yield: 60%; **IR** (cm^{-1}): 3600-3500 (O-H str.), 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 800-780 (C-H oop def); **MS**: *m/z* = 426.42 (100%); Anal. Calcd. for $C_{25}H_{18}N_2O_4$: C, 70.42; H, 4.25; N, 6.57; O, 18.76; Found: C, 70.56; H, 4.37; N, 6.48.

13) 3,3'-((3,4-Dihydroxy phenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-073)

Yield: 62%; **IR** (cm^{-1}): 3600-3500 (O-H str.), 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2900-2880 (C-H str. -CH), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 442.42 (100%); Anal. Calcd. for $C_{25}H_{18}N_2O_6$: C, 67.87; H, 4.10; N, 6.33; O, 21.70; Found: C, 67.83; H, 4.25; N, 6.23.

14) 3,3'-((3-Methoxy phenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-074)

Yield: 61%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2900-2880 (C-H str. -CH), 2870 (Sym C-H str. $-CH_3$), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1260-1200 (Ar-O-Al str.), 1180 (C-O str.), 800-780 (C-H oop def); **MS**: *m/z* = 440.45 (100%); Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36; O, 18.16; Found: C, 70.63; H, 4.47; N, 6.38.

15) 3,3'-((4-Methoxy phenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-075)

Yield: 64%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2900-2880 (C-H str. -CH), 2870 (Sym C-H str. -CH_3), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1260-1200 (Ar-O-Al str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 440.45 (100%); Anal. Calcd. for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36; O, 18.16; Found: C, 70.84; H, 4.65; N, 6.30.

16) 3,3'-((3,4-Dimethoxyphenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-076)

Yield: 63%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2900-2880 (C-H str. -CH), 2870 (Sym C-H str. -CH_3), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1260-1200 (Ar-O-Al str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 470.47 (100%); Anal. Calcd. for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.71; N, 5.95; O, 20.40; Found: C, 68.78; H, 4.47; N, 5.88.

17) 3,3'-((2,5-Dimethoxyphenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-077)

Yield: 60%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2900-2880 (C-H str. -CH), 2870 (Sym C-H str. -CH_3), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1260-1200 (Ar-O-Al str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 470.47 (100%); Anal. Calcd. for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.71; N, 5.95; O, 20.40; Found: C, 68.90; H, 4.69; N, 5.91.

18) 3,3'-((3,4-Dimethoxyphenyl) methylene) bis (4-amino-2H-chromen-2-one) (MNP-078)

Yield: 68%; **IR** (cm^{-1}): 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2900-2880 (C-H str. -CH), 2870 (Sym C-H str. -CH_3), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1260-1200 (Ar-O-Al str.), 1180 (C-O

str.), 810 (C-H oop def); **MS**: *m/z* = 500.50 (100%); Anal. Calcd. for $C_{28}H_{24}N_2O_7$: C, 67.19; H, 4.83; N, 5.60; O, 22.38; Found: C, 67.03; H, 4.77; N, 5.75.

19) 3,3'-((3-Ethoxy-4-hydroxyphenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-079)

Yield: 60%; **IR** (cm^-1): 3600-3500 (O-H str.), 3400-3200 (N-H str.), 3075-3030 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2900-2880 (C-H str. -CH), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740-1690 (C=O str.), 1680-1650 (N-H def), 1580, 1545, 1500 (Ar C=C str.), 1450 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1345 (C-H bend -CH), 1280-1260 (C-N str. pri amine), 1260-1200 (Ar-O-Al str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 470.47 (100%); Anal. Calcd. for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.71; N, 5.95; O, 20.40; Found: C, 68.79; H, 4.84; N, 6.08.

20) 3,3'-((4-hydroxy-3-methoxyphenyl)methylene)bis(4-amino-2H-chromen-2-one) (MNP-080)

Yield: 65%; **IR** (cm^{-1}): 3632 (O-H str.), 3368-3208 (N-H str.), 3085 (Ar C=C-H str.), 2984 (Asy C-H str. -CH_3), 2900-2880 (C-H str. -CH), 2843 (Sym C-H str. -CH_3), 1695 (C=O str.), 1634 (N-H def), 1591, 1543, 1512 (Ar C=C str.), 1413 (C-H bend -CH_3), 1341 (C-H bend -CH), 12780 (C-N str. pri amine), 1205 (Ar-O-Al str.), 1180 (C-O str.), 800 (C-H oop def); **^{1}H NMR** (DMSO-d_6) δ ppm: 3.68 (s, 3H), 5.93 (s, 1H), 6.57-6.59 (d, 1H, *J*= 8.16), 6.66-6.70 (m, 2H), 7.28-7.31 (m, 4H), 7.54-7.58 (m, 2H), 7.76-7.79 (s, b, 4H), 8.05-8.07 (dd, 2H, *J*=0.88, *J*=7.48), 8.48 (b, 1H); **^{13}C NMR** (DMSO-d_6) δ ppm: 36.83, 55.54, 11.99, 114.61, 114.67, 116.35, 118.56, 123.02, 123.30, 128.72, 131.42, 144.17, 147.13, 152.09; **MS**: *m/z* = 456.45 (100%); Anal. Calcd. for $C_{26}H_{20}N_2O_6$: C, 68.42; H, 4.42; N, 6.14; O, 21.03; Found: C, 68.29; H, 4.68; N, 6.25.

2.11 RESULTS AND DISCUSSION

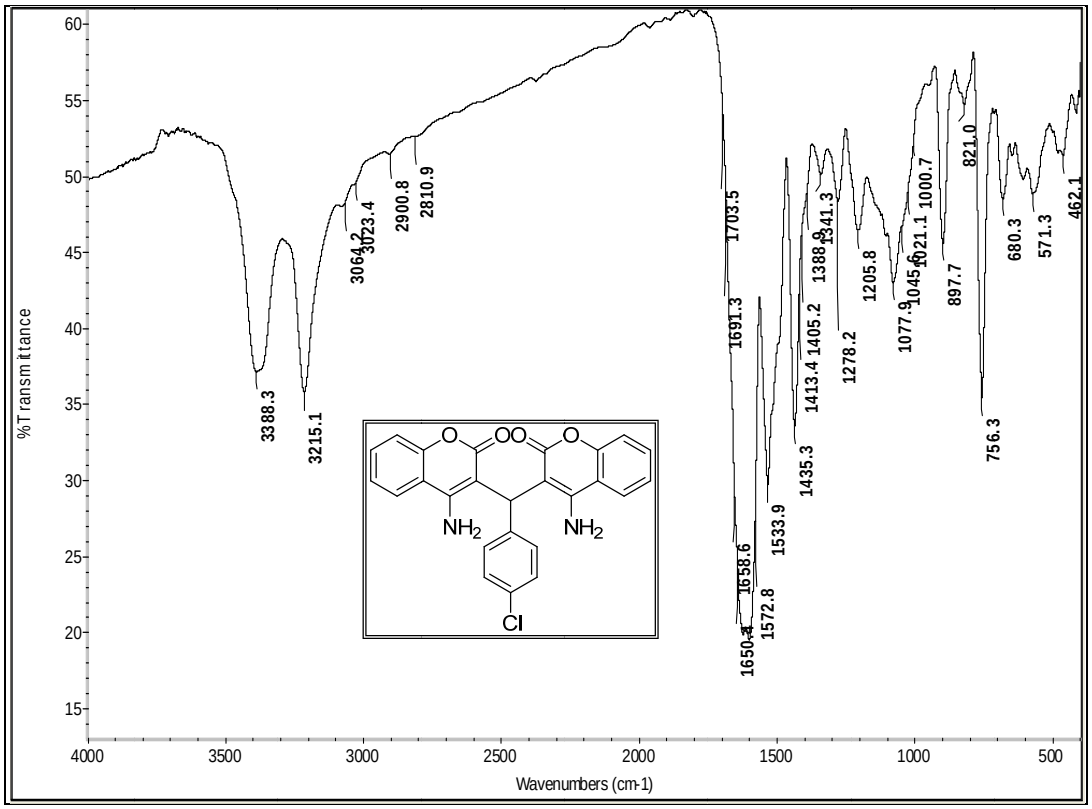
This chapter deals with the dimerization of 4-amino coumarin using green chemistry approach. Some novel 3,3'-((Substituted phenyl)methylene)bis(4-amino-2H-chromen-2-one) derivatives have been synthesized to evaluate for various biological as well as pharmacological interest. The synthesized compounds were well characterized by IR, ^{1}H and ^{13}C NMR and Mass Spectrometry.

2.12 CONCLUSION

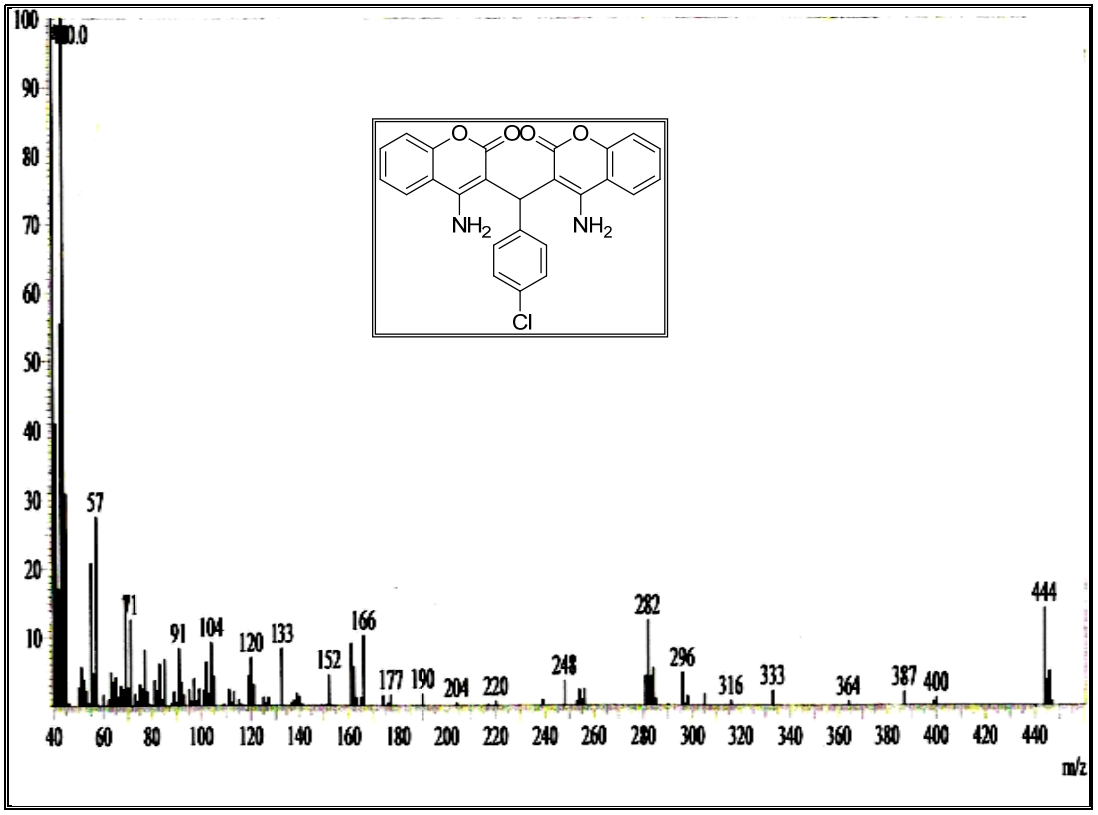
We have developed a very simple, efficient and rapid dimerization of 4-amino coumarin in the presence of catalytic amount of zinc chloride. Presence of catalytic amount zinc chloride enhanced reaction rate exclusively. Apart from these, this method has advantageous by means of almost devoid of hazardous chemicals as well as expensive solvents. A very less amount of methanol has been used for the isolation of the final products. Easy work up procedure with better yield and purity is the main benefit of this method. To the best of our knowledge, this is the first report of direct synthesis of dimeric 4-aminocoumarins.

2.13 REPRESENTATIVE SPECTRA

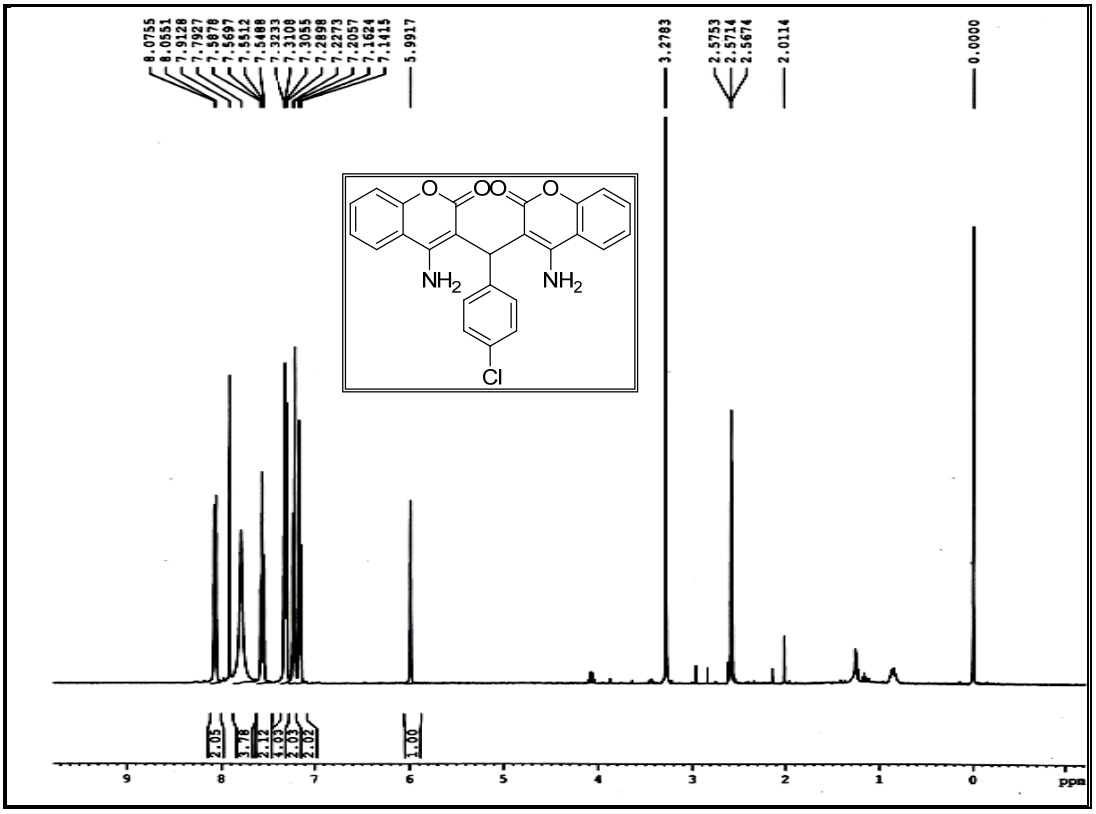
2.13.1 IR Spectrum of MNP-066



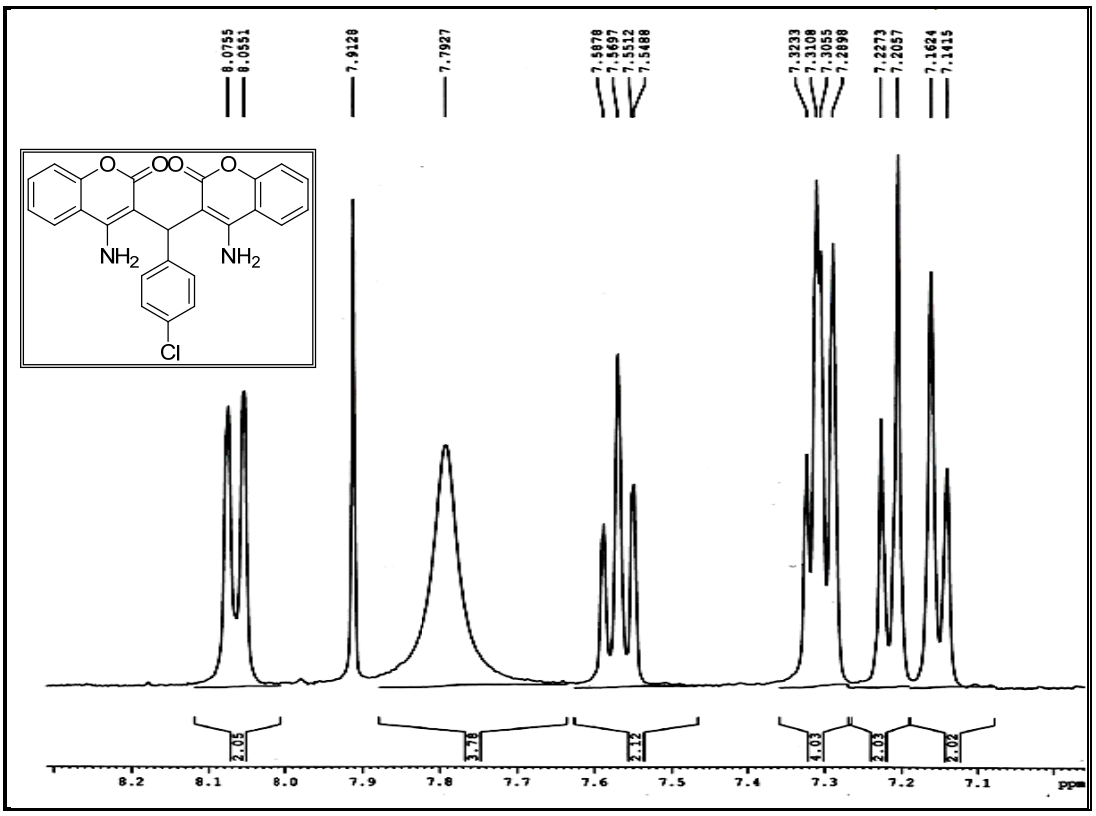
2.13.2 Mass Spectrum of MNP-066



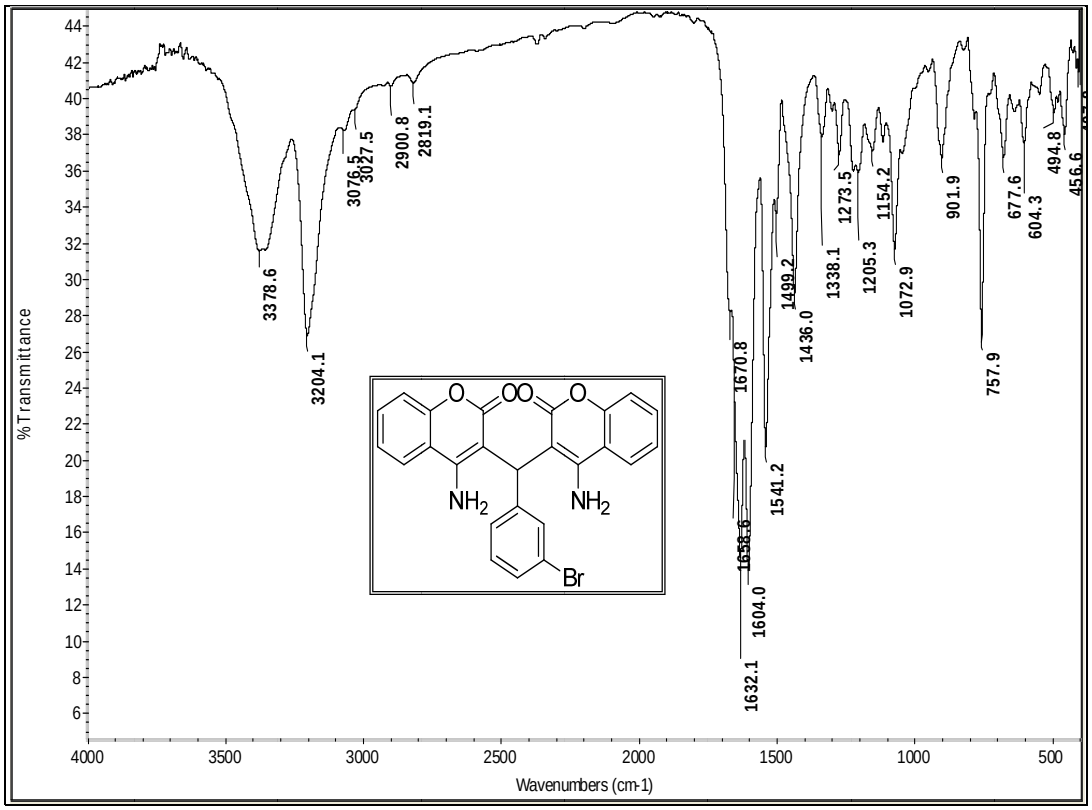
2.13.3 ^{1}H NMR Spectrum of MNP-066



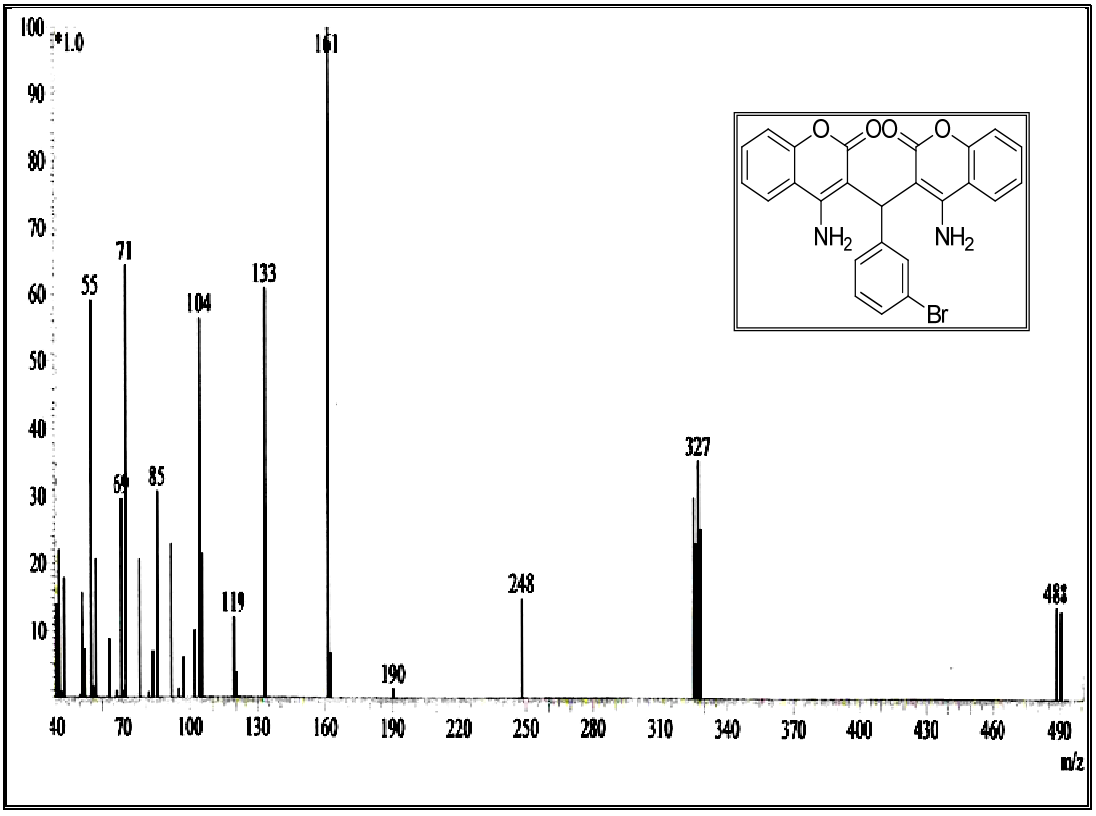
2.13.4 Expanded ^{1}H NMR Spectrum of MNP-066



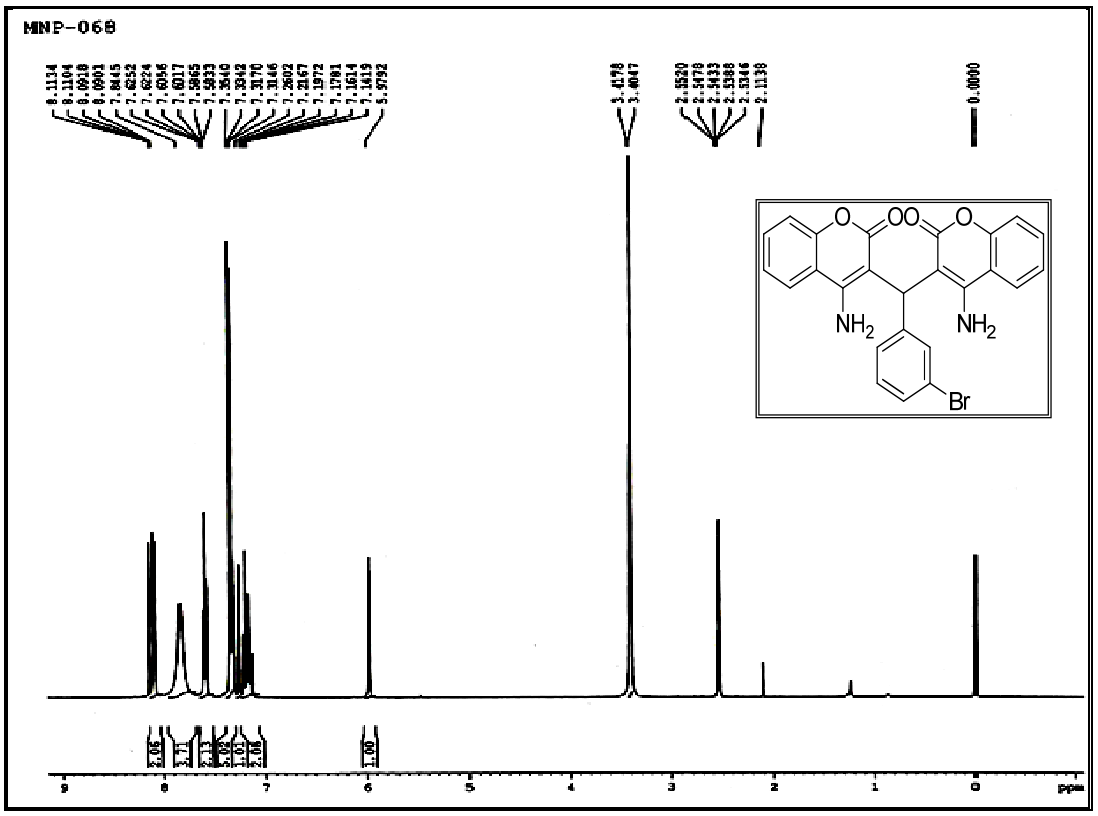
2.13.5 IR Spectrum of MNP-068



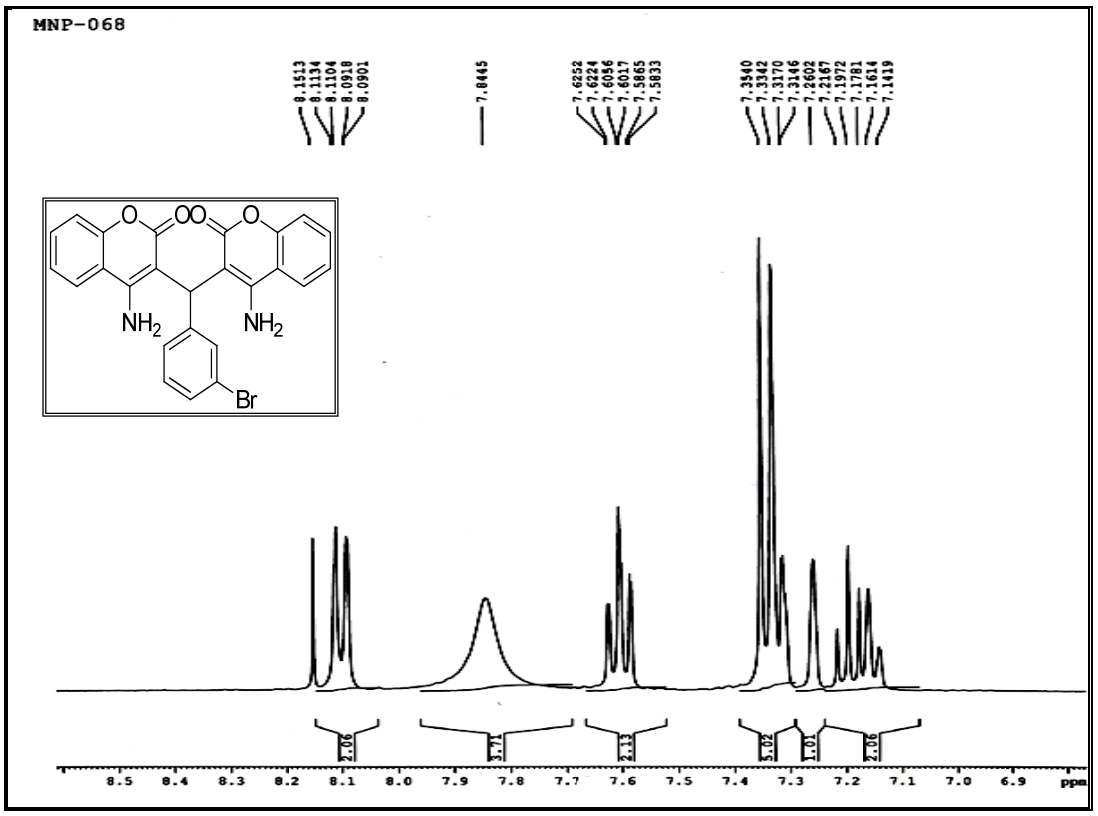
2.13.6 Mass Spectrum of MNP-068



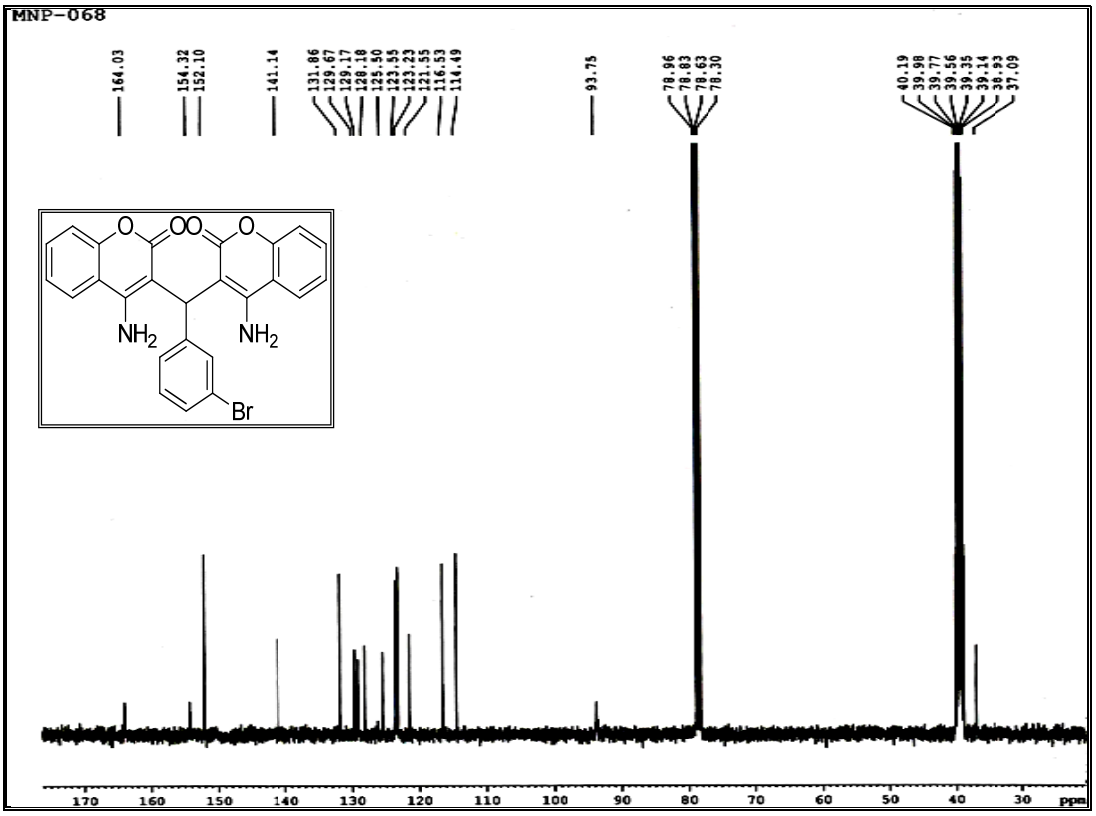
2.13.7 ^{1}H NMR Spectrum of MNP-068



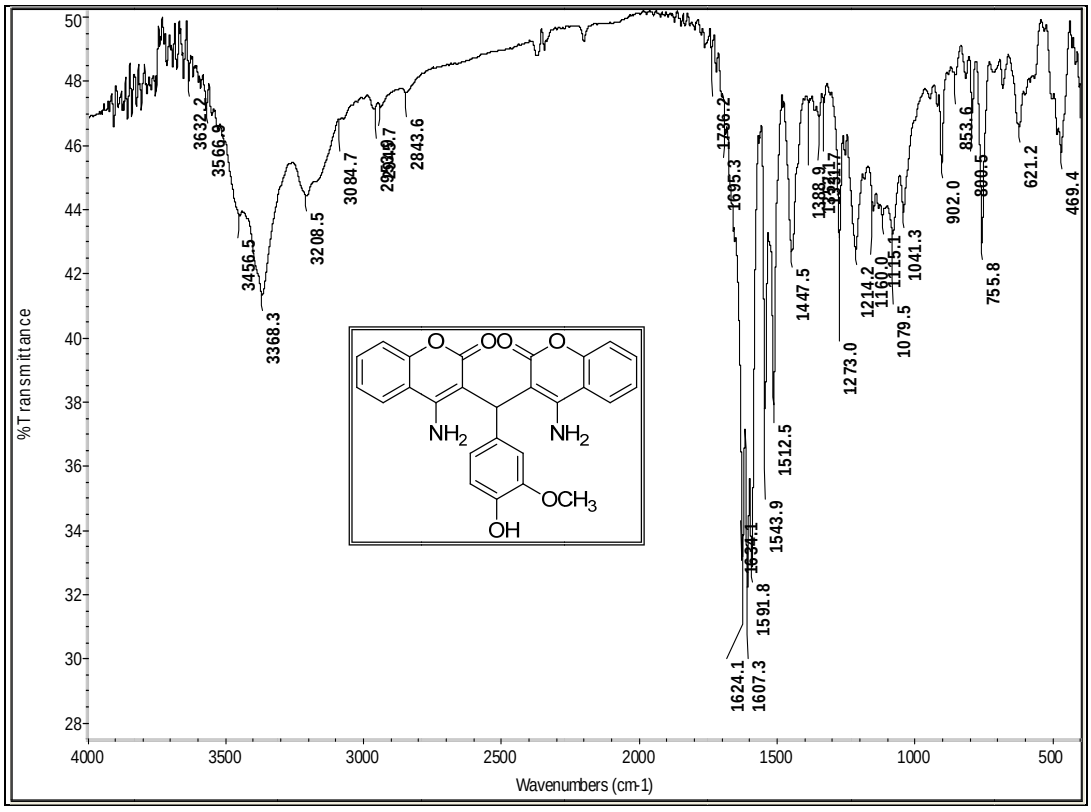
2.13.8 Expanded ^{1}H NMR Spectrum of MNP-068



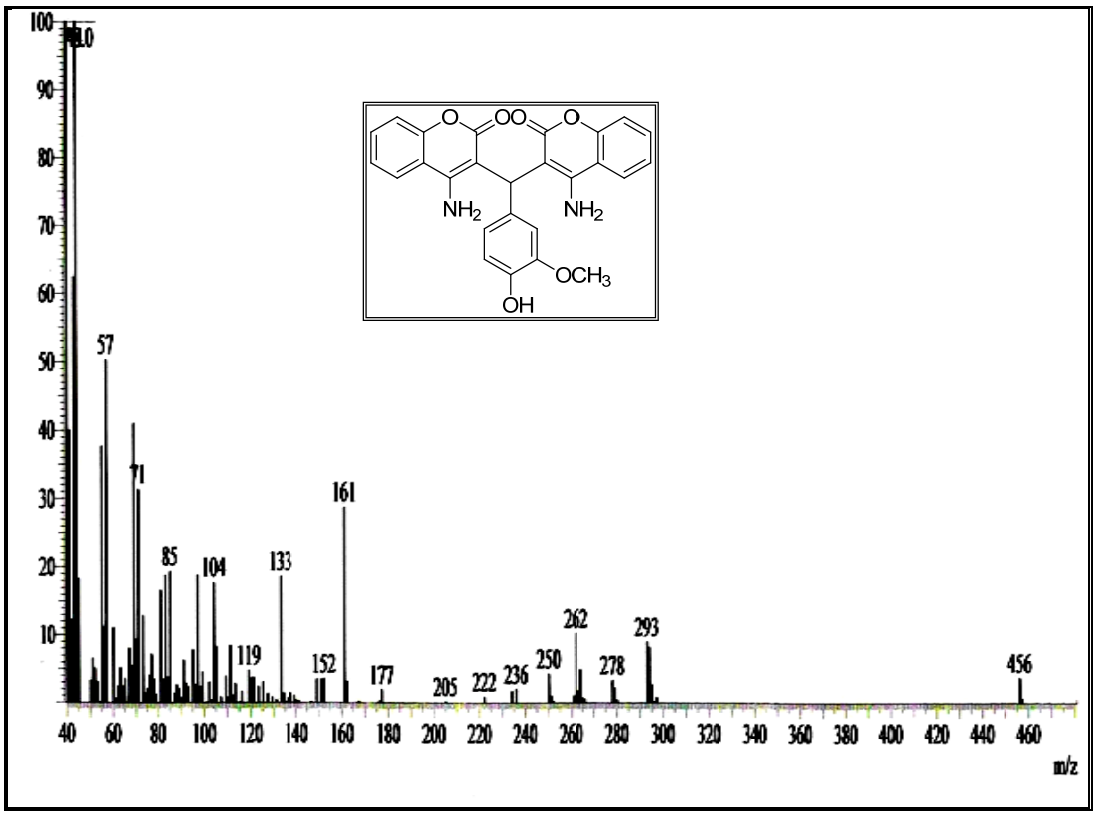
2.13.9 ^{13}C NMR Spectrum of MNP-068



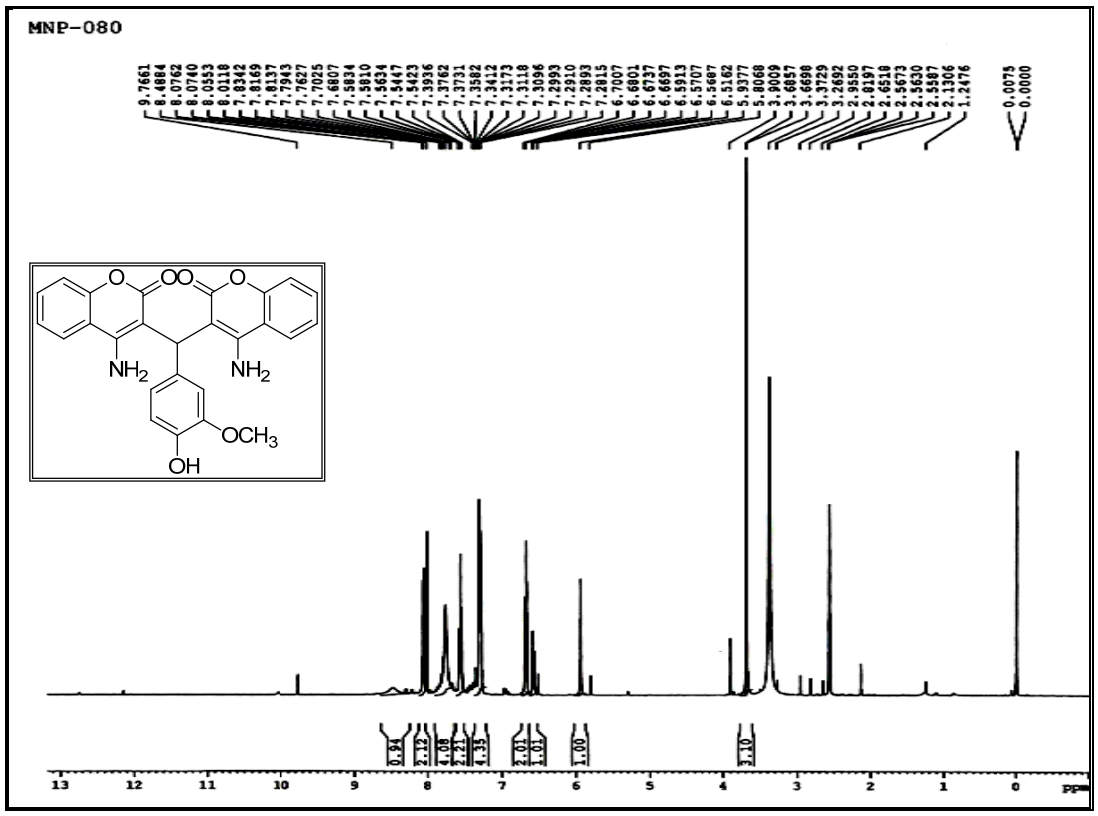
2.13.10 IR Spectrum of MNP-080



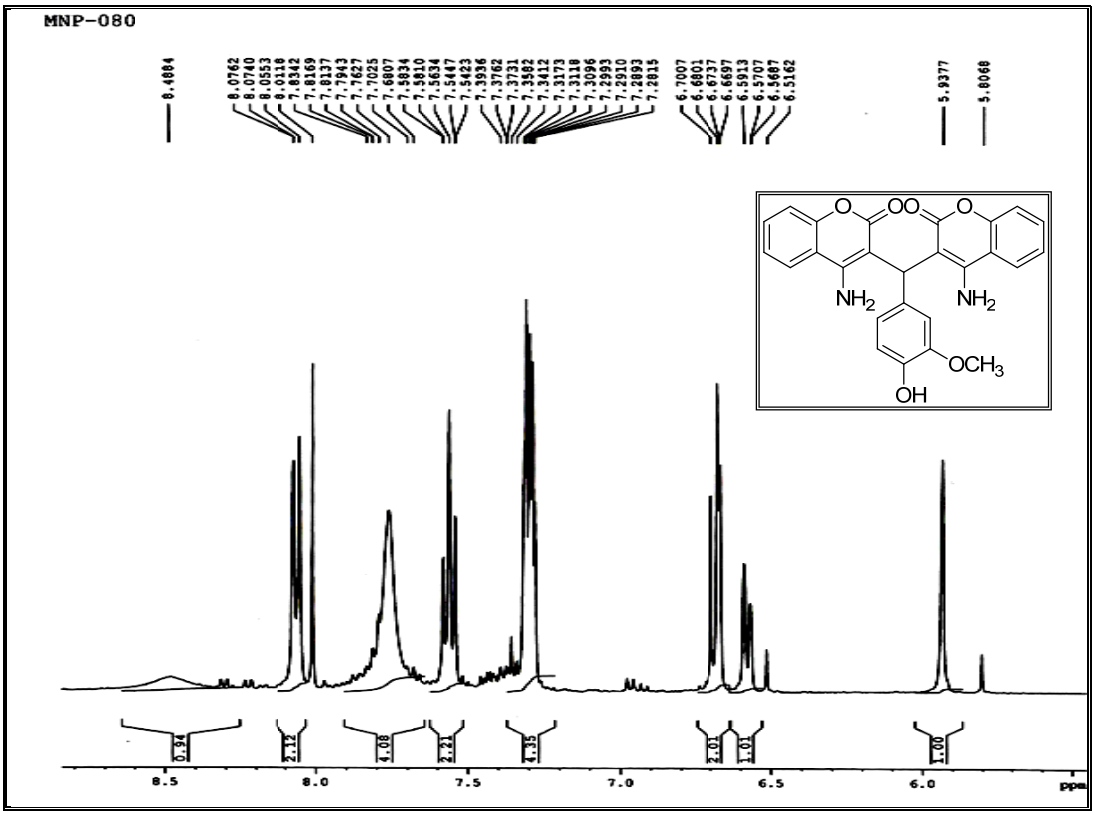
2.13.11 Mass Spectrum of MNP-080



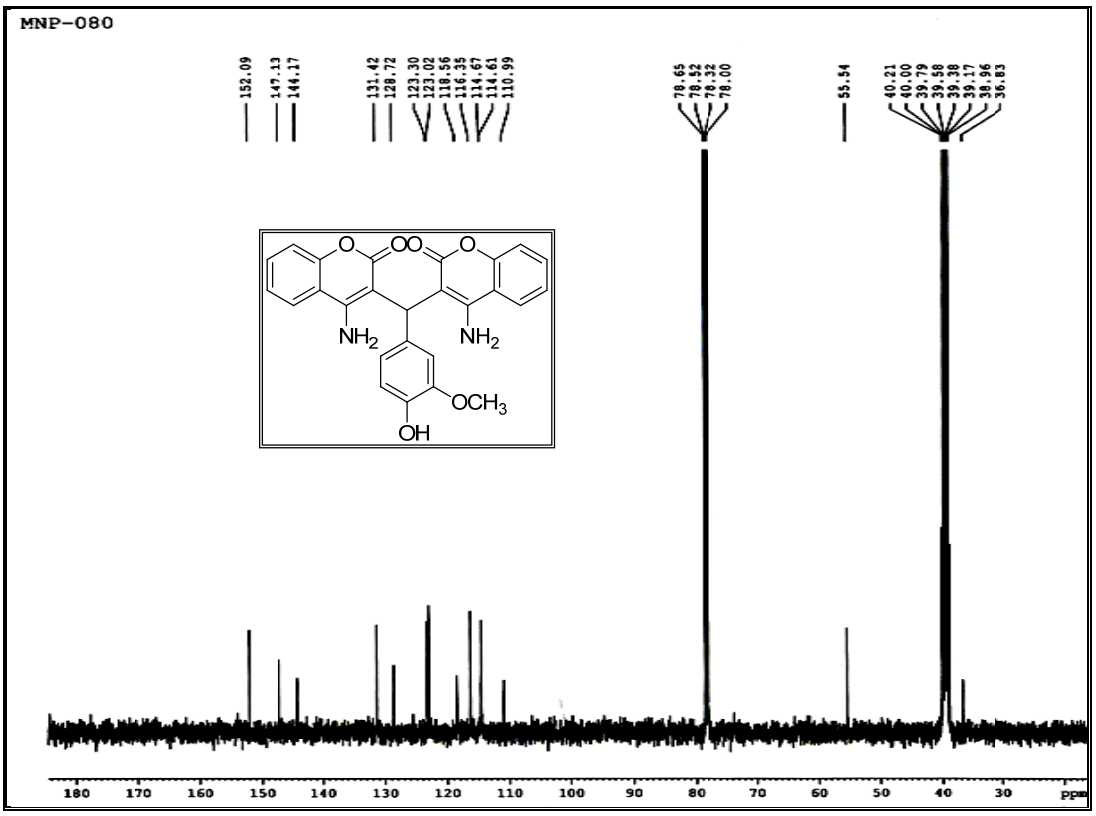
2.13.12 ^{1}H NMR Spectrum of MNP-080



2.13.13 Expanded ^{1}H NMR Spectrum of MNP-080



2.13.14 ^{13}C NMR Spectrum of MNP-080



2.14 REFERENCES

1. S. Sen and V. Srivastava; *J. Ind. Chem. Soc*.; 66, 166, **1989**.
2. A. Vogel; Gilbert's *Ann. Phys*.; 64, 161, **1820**.
3. A. Guillemette and J. Leibigs; *Ann. Chem.*; 14, 324, **1835**.
4. F. Von Werder; *Merck's Jahresber*; 50, 88, **1936.**
5. P. K. Bose; *J. Ind. Chem. Soc.*; 35, 367, **1958**.
6. T. O. Soine; *J. Pharm. Sci*.; 53, 231, **1964**.
7. D. H. Murray and A. Stewart; "The Natural Coumarins", John Wiley & Sons, **1982.**
8. L. Schio, F. Chatreaux and M. Klich.; *Tetrahedron Lett*.; 41, 1543, **2000**.
9. R. Robinson; "The structural relation of natural products"; *Oxford,* **1955.**
10. A. M. El-Agrody, M. S. Abd El-Latif, N. A. El-Hady, A. H. Fakery and A. H. Bedair; *Molecules*; 6, 519, **2001**.
11. T. Patonay, G. Y. Litkei, R. Bognar, J. Erdei and C. Misztic; *Pharmazie*; 39, 86, **1984**.
12. R. M. Shaker; *Pharmazie*; 51, 148, **1996**.
13. A. F. El-Farargy; *Egypt. J. Pharm. Sci.*; 32, 625, **1991**.
14. I. Manolov and N. D. Danchev; *Eur. J. Med. Chem*.; 30, 531, **1995**.
15. A. A. Emmanuel-Giota, K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas and D. N. Nicolaides; *J. Het. Chem*.; 38, 717, **2001**.
16. L. L. Raev, E. Voinova, I. C. Ivanov and D. Popov; *Pharmazie*; 45, 696, **1990**.
17. Z. M. Nofal, M. El-Zahar and S. Abd El-Karim; *Molecules*; 5, 99, **2000**.
18. L. Xie, Y. Takeuchi, L. M. Consentino and K.H. Lee; *J. Med. Chem*.; 42, 2662, **1999**.
19. R. O'Kennedy and R. D. Thornes; John Wiley & Sons Ltd.; Chichester, UK, **1997**.
20. M. Zahradnik; John Wiley & Sons Ltd.; Chichester, England, **1992**.
21. N. S. Dighe, S. R. Pattan, S. S. Dengale, D. S. Musmade, M. Shelar, V. Tambe and M. B. Hole; *Arch. Appl. Sci. Res*.; 2 (2), 65, **2010.**
22. I. Kostova, S. Raleva, P. Genova, and R. Argirova; Bioinorg. Chem. & Appl.; 68274, 19, **2006.**
23. I. Kostava; *Curr. Med. Chem.- Anti Cancer Agents*; 5, 29, **2005.**

24. H. Suzuki, Funabashi-shi and T. Tamura, Funabashi-shi; US 0130755 A1; **2010.**

25. H. K. Vala, Ph.D. Thesis, Saurashtra University, **2011.**

26. A. J. Bavishi, Ph.D. Thesis, Saurashtra University, **2011.**

27. R. Anschutz; *Br*.; 36, 465, **1903**; *Ann.*; 867, 169, **1909**.

28. E. Ziegler and H. Junek; *Monatshefte fur Chemie*; 86, 29, **1955**.

29. V. R. Shah, J. L. Bose and R. C. Shah; *J. Org. Chem*.; 25, 677, **1960**.

30. A. Ogawa, K. Kondo, S. Murai and N. Sonoda; *Chem.Comm*.; 21, 1283, **1982;** *Tetrahedron;* 41, 4813, **1985**.

31. Ye Dingyue, Zhou Yushen and Su Qiang; Chinese Patent, CN, 1101045.

32. A. V. Kalinin, A. J. M. Da Silva, C. C. Lopes, R. S. C. Lopes, V. Snieckus; *Tetrahedron Lett*.; 39, 4995, **1998**.

33. J. C. Jung, Y. J. Jung and O. S. Park; *Synth. Comm*.; 31, 1195, **2001**.

34. L. Pisani, G. Muncipinto, T. F. Miscioscia, O. Nicolotti, F. Leonetti, M. Catto, C. Caccia, P. Salvati, R. Soto-Otero, E. Mendez-Alvarez, C. Passeleu and A. Carotti; *J. Med. Chem*.; 52, 6685, **2009**.

35. L. Heide; Chapter 18, Aminocoumarins Mutasynthesis, Chemoenzymatic synthesis and Metabolic Engineering; 459, 437, **2009**.

36. S. D. Bentley, K. F. Chater, , A. M. Cerdeno-Tarraga, G. L.Challis, N. R. Thomson, K. D. James, D. E. Harris, M. A. Quail, H. Kieser; Nature; 417, 141, **2002.**

37. (a) L. Heide; *Methods Enzymol*.; 459, 437, **2009**. (b) C. Anderle, M. Stieger, M. Burrell, S. Reinelt, A. Maxwell, M. Page and L. Heide; *Antimicrob. Agents Chemother*.; 52,1982, **2008**. (c) C. Anderle, S. Li, B. Kammerer, B. Gust and L. Heide; *J. Antibiot*.; 60 (8), 504, **2007**. (d) M. Fridman, C. J. Balibar, T. Lupoli, D. Kahne and C. T. Walsh; S. Garneau-Tsodikova; *Biochemistry*; 46 (28), 8462, **2007**. (e) A. A. Kudale, J. Kendall, C. C. Warford, N. D. Wilkins and G. J. Bodwell; *Tetrahedron Lett*.; 48, 5077, **2007**. (f) S. Li and L. Heide; *Curr. Med. Chem*.; 12, 419, **2005**. (g) A. Freitag, U. Galm, S. Li and L. Heide; *J. Antibiot*.; 57, 205, **2004**. (h) H. Xu, L. Heide and S. Li; *Chem. Biol*.; 11, 655, **2004**.

38. V. Maddi, S. N. Mamledesai, D. Satyanarayana and S. Swamy; *Indian J. Pharm. Sci*.; 69, 847, **2007**.

39. M. A. Al-Haiza, M. S. Mostafa and M. Y. El-Kady; *Scientific Journal of King Faisal University (Basic and Applied Sciences)*; 6, 1426, **2005**.
40. (a) B. R. Naik, B. H. S. Naik, H. N. Harish Kumar, K. M. Hosamani and K. M. Mahadevan; *Arkivoc*; 2, 11, **2009**. (b) B. D. Wagner; *Molecules*; 14, 210, **2009**. (c) J. Y. Choi, E. J. Park, S. H. Chang and T. J. Kang; *Bull. Korean Chem. Soc*.; 30, 1452, **2009**.
41. (a) J. Li and S. Q. Yao; *Org. Lett*.; 11, 405, **2009**. (b) E. K. Lewis, W. C. Haaland, F. Nguyen, D. A. Heller, M. J. Allen, R. R. MacGregor, C. S. Berger, B. Willingham, L. A. Burns, G. B. I. Scott, C. Kittrell, B. R. Johnson, R. F. Curl and M. L. Metzker; *PNAS*; 102, 5346, **2005**.
42. G. Kokotos, V. Theodoru, C. TzougrakiDieter, L. D. Deforce and E. G. Van den Eeckhout; *Bioorg.& Med. Chem. Lett*.; 7, 2165, **1998**.
43. V. A. Zagorevskii and N. V. Dudykina; *Zhurnal Obshchei Khimii*.; 32, 2384, **1962**.
44. H. Uno, M. Kurokawa and H. Nishimura; *Chem. Pharm. Bull*.; 24, 644, **1976**.
45. I. C. Ivanov, S. K. Karagiosov and I. Manolov; *Arch. Pharm*.; 324, 61, **1991**.
46. A. P. Chavan; *J. Chem. Res*.; 3, 179, **2006**.
47. E. V. Stoyanov and I. C. Ivanov; *Molecules*; 9, 627, **2004.**
48. S. Checchi, L. P. Vettori and M. B. Alberti; *Gazz. Chim. Ital*.; 97, 1749, **1967**.
49. M. Hamdi, O. Grech, R. Sakellariou and V. Spéziale; *J. Het. Chem*.; 31,509, **1994**.
50. B. Stamboliyska, V. Janevska, B. Shivachev, R. P. Nikolova, G. Stojkovic, B. Mikhova and E. Popovski; *Arkivoc*; 10, 62, **2010.**
51. K. P. Link; *Harvey Lectures*; 39, 162, **1944.**
52. M. A. Stahmann, C. F. Hubner and K. P. Link; *J. Biol Chem*.; 138, 513, **1941.**
53. R. Tschesche, U. Schacht and G. Legler; Liebigs Ann. Chem.; 662, 113, **1963.**
54. J. P. Kutney, T. Inaba and D. L. Dreyer; *Tetrahedron*; 26 (13), 3171, **1970.**
55. A. K. Bhattacharya and S. C. Das; *Chemistry and Industry (London, U. K.)*; (31), 885, **1971.**
56. R. R. Spencer, S. C. Witt, R. E. Lundin and E. M. Bickoff; *Journal of Agricultural and Food Chemistry*; 15 (3), 536, **1967.**
57. (a) K. N. Trivedi, M. G. Parekh and N. H. Pardanani; *J. Indian Chem. Soc.*; 47 (1), 36, **1970;** (b) S. K. Joshi, Ph.D. Thesis, Saurashtra University, **1999.**

58. C. Mentzer, J. Riboullean, C. Deschanpsvallet and D. Molho; *Bulletin de la Societe Chimique de France*; (8-9), 3138, **1970.**

59. C. F. Huebner and K. P. Link; *J. Am. Chem. Soc.*; 67, 99, **1945.**

60. S. S. Lele, M. G. Patel and S. Shethna; *J. Chem. Soc.*; 969, **1961.**

61. R B. Arora, N R. Krishnaswamy, T R. Seshadri, S. D. S. Seth and B. R. Sharma; *J. Med. Chem.*; 10 (1), 121, **1967**.

62. M. Guminska, M. Eckstein and B. Stachurska; *ssertationes Pharmaceuticae et Pharmacologicae*; 20 (2), 157, **1968**.

63. A. Mazumder, S. Wang, N. Neamati, M. Nicklaus, S. Sunder, J. Chen, G.W. A. Milne, R. G. William, T. R. Burke, Jr. and Y. Pommier; *J. Med. Chem.*; 39 (13), 2472, **1996**.

64. H Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G. W. A. Milne, Y. Pommier and T. R. Burke, Jr.; *J. Med. Chem.*; 40 (2), 242, **1997.**

65. H. Hagiwara, N. Fujimoto, T. Suzuki and M. Ando; *Heterocycles*; 53 (3), 549, **2000.**

66. S. R. Hamid and M. Honarmand; *Chinese Journal of Chemistry*; 27 (9), 1795, **2009.**

67. G. V. P. Chandramouli, P. Naveen Kumar and V. P. Reddy; *Het. Comm.*; 10 (2-3), 223, **2004.**

68. M. Chavda, D. Karia and A. Shah; *Indian J. Chem. Section B: Org. Chem. Including Med. Chem.*; 41B (10), 2197, **2002.**

69. D. Sureja, Ph.D. Thesis, Saurashtra University, **1997.**

70. A. Saravani, Ph.D. Thesis, Saurashtra University, **1997.**

71. H. Gevariya, Ph.D. Thesis, Saurashtra University, **1999.**

72. N. Dodia, Ph.D. Thesis, Saurashtra University, **1999.**

73. V.B. Vora, Ph.D. Thesis, Saurashtra University, **2000.**

74. D. Karia, Ph.D. Thesis, Saurashtra University, **1999.**

75. M. Chavda, Ph.D. Thesis, Saurashtra University, **2000.**

76. A. Parecha, Ph.D. Thesis, Saurashtra University, **2002.**

77. J. Singh, Ph.D. Thesis, Saurashtra University, **2008.**

78. I. I. Manolov; *Tetrahedron Lett.*; 39 (19), 3041, **1998.**

79. P. Singh, P. Kumar, A. Katyal, R. Kalra, S. K. Dass, S. Prakash and R. Chandra; *Catal Lett.*; 134 (3-4), 303, **2010.**

80. J. M. Khurana and Sanjay Kumar; *Tetrahedron Lett.*; 50 (28), 4125, **2009.**

81. Gong Gui-Xia, Zhou Jian-Feng, An Li-Tao, Duan Xiu-Li and Ji Shun-Jun; *Synth. Comm*.; 39 (3), 497, **2009**.

82. Qadir Saima, Dar Aijaz Ahmad and Khan Khaliquz Zaman; *Synth. Comm*.; 38 (20), 3490, **2008.**

83. M. Kidwai, V. Bansal, P. Mothsra, S. Saxena, R. K. Somvanshi, S. Dey and T. P. Singh; *J. Mol. Catal. A: Chem*; 268 (1-2), 76, **2007.**

84. Zhou Jianfeng, Gong Guixiab, An Litaoa, Sun Xiaojuna and Zhu Fengxiaa; 29 (12), 1988, **2009.**

85. H. Majid, N. Fatemeh, S. Samaheh, O. Hossein, B. Fatemeh; *Synth. Comm*.; 40 (4), 498, **2010.**

86. J. N. Sangshetti, N. D. Kokare and D. B. Shinde; *Green Chem. Lett. & Rev*.; 2 (4), 233-235, **2009.**

87. I. Manolov, C. Maichle-Moessmer and N. Danchev; *Eur. J. Med. Chem*.; 41 (7), 882, **2006.**

88. V. J. Edward and E. S. Drake; *Acta Crystallographica, Section C: Crystal Structure Comm*.; C45 (5), 785, **1989**.

89. M. Eckstein and I. Csoregh; *Acta Cryst.*, *Section B: Structural Crystallography and Crystal Chemistry*; B35 (2), 389, **1979.**

90. N. Hamdi, C. Puerta and P. Valerga; *Eur. J. Med. Chem*.; 43 (11), 2541, **2008.**

91. Y. Jacquot, I. Laïos, A. Cleeren, D. Nonclercq, L. Bermont, B. Refouvelet, K. Boubekeur, A. Xicluna, G. Leclercq and G. Laurent; *Bioorg. & Med. Chem*.; 15 (6), 2269, **2007.**

92. I. Kostova and J. Mojzis; *Future HIV Therapy*; 1 (3), 315, **2007.**

93. Zhu Lei, Djaballah Hakim, Li Yueming and Shelton Christopher Chad; PCT Int. Appl. WO; 075280 A2 20100701, **2010.**

94. H. Madari, D. Panda and L. Wilson and R. S. Jacobs; *Cancer Res.*; 63, 1214, **2003.**

95. N. A. Karen, D. R. Jeremy, D. S. Mark, S. A. Katherine, F. A. David, S. David, R. David, B. John, L. Colin and L. David; *J. Med. Chem*.; 52 (22), 7142, **2009**.

96. M. Pili Chih-Min, M. Jean-Francois, L. Herve, A. Christian and H. Ling-Yih; *Heterocycles*; 55 (7), 1263, **2001.**

97. W. Chavasiri, S. Deesamer, U. Kokpol, C. Thipnoisanga, S. Wattanasereekul and S. Zungsontiporn; *Thai Journal of Agricultural Science*; 34 (1-2), 81, **2001.**

98. N. Pandya, Ph.D. Thesis, Saurashtra University, **2010.**

99. N. M. Evdokimov, I. V. Magedov, A. S. Kireev and A. Kornienko; *Org. Lett*.; 8 (5), 899, **2006.**

100. R. Livingstone; Rodd's Chemistry of Carbon Compounds; Vol. IV E, N.Y., **1977**.

PART- II

CHAPTER-3 ONE POT HIGH PURITY SYNTHESIS OF SOME NEW DIHYDROPYRIDINES STRUCTURALLY RELATED TO MDR REVERTING AND ANTIHYPERTENSIVE AGENTS

CHAPTER-4 A RAPID AND FACILE SYNTHESIS OF SOME NOVEL MANNICH BASES OF DIHYDROPYRIDINES

CHAPTER-5 A RAPID AND FACILE SYNTHESIS OF SOME METHOXYLATED 3,5-DICYANO DIHYDROPYRIDINES & THEIR NOVEL MANNICH BASES

CHAPTER- 3

ONE POT HIGH PURITY SYNTHESIS OF SOME NEW DIHYDROPYRIDINES STRUCTURALLY RELATED TO MDR REVERTING AND ANTIHYPERTENSIVE AGENTS

3.1 INTRODUCTION

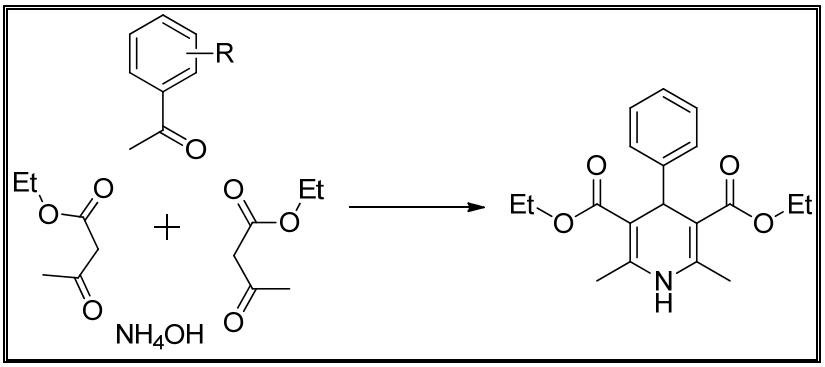
The 1,4-dihydropyridines (DHPs), a class of drugs, possess a wide variety of biological and pharmacological actions, have represented one of the most important groups of calcium-channel modulating agents and have experienced widespread use in the treatment of cardiovascular disease. Moreover, it has been demonstrated that DHPs could prove to be highly important as multidrug-resistance-reverting agents in cancer chemotherapy. Recent reports suggest that this class also has other notable activities, particularly as antimycobacterial and anticonvulsant agents. Finally, it might be possible for the DHP motif to serve as a scaffold for other pharmacological applications. [1]

Some of important work is summarized as under.

3.2 LITERATURE REVIEW

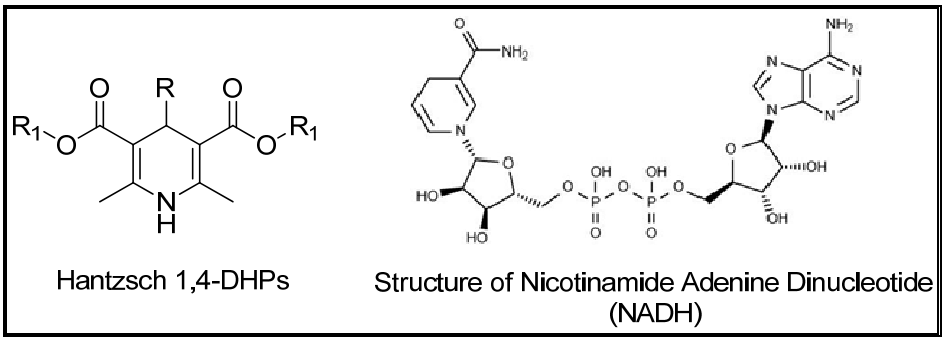
Arthur Hantzsch described preparation of 1,4- dihydropyridine more than a century ago. [2,3] These pyridines are called Hantzsch pyridines and reaction as Hantzsch reaction (HR). Original synthesis reported by Hantzsch is three components (acetoacetic ester, benzaldehyde and ammonia or ammonium salts) coupling reaction in refluxing ethanol (Scheme 3.1).

Scheme 3.1



Exploration of 1,4-dihydropyridine initially were quite slow, later it picked up very fast because of their structural resemblance to reduced Nicotinamide Adenine Dinucleotide (NADH, Figure 3.1), which is an established hydrogen transferring agent in biological processes. [4] Hantzsch pyridines are a subset of the coenzyme NADH.

Figure 3.1



After Hantzsch synthesis, successive structural modifications involving additions, reductions and condensations, mainly at the 1, 2 and 6 positions of the dihydropyridine ring were performed. Later in 1977, modifications in positions 1, 3, 4 and 5, resulted in the Bayer [5] group synthesizing the drug Nifedipine, revolutionizing the pharmaceutical market due to its antihypertensive properties.

1,4-DHPs, such as Nifedipine, Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine, Nimodipine, Nisoldipine, Nitredipine and others have been found to be useful as calcium channel blockers, [6-8] and are used most frequently as cardiovascular agents for the treatment of hypertension **(**Figure 3.2**)**. [9] A number of dihydropyridine calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure and angina pectoris. [10-12] Their therapeutic success is related to their efficiency to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current associated in smooth muscle with a longtasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart. [13-15]

Much work is done in last two decade and many molecules having more specific cardiovascular activity have come out as new drug molecules like Barnidipine, [16]

Benidipine, [17] Flordipine, [18] Riodipine, [19] Nilvadipine, Niguldipine, pranidine, lacidipine, [20,21] which are demonstrated in Figure 3.3.

Figure 3.2

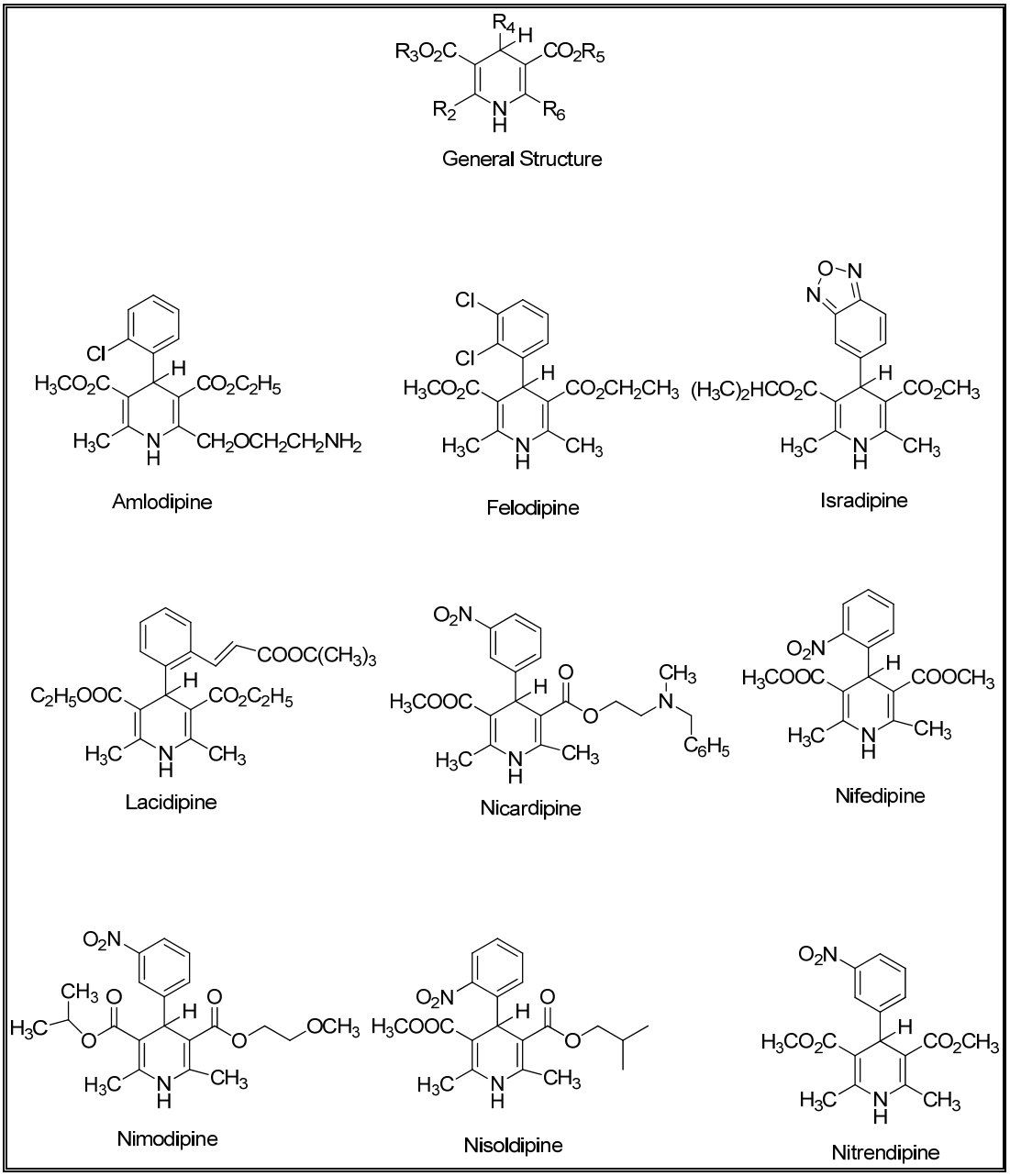
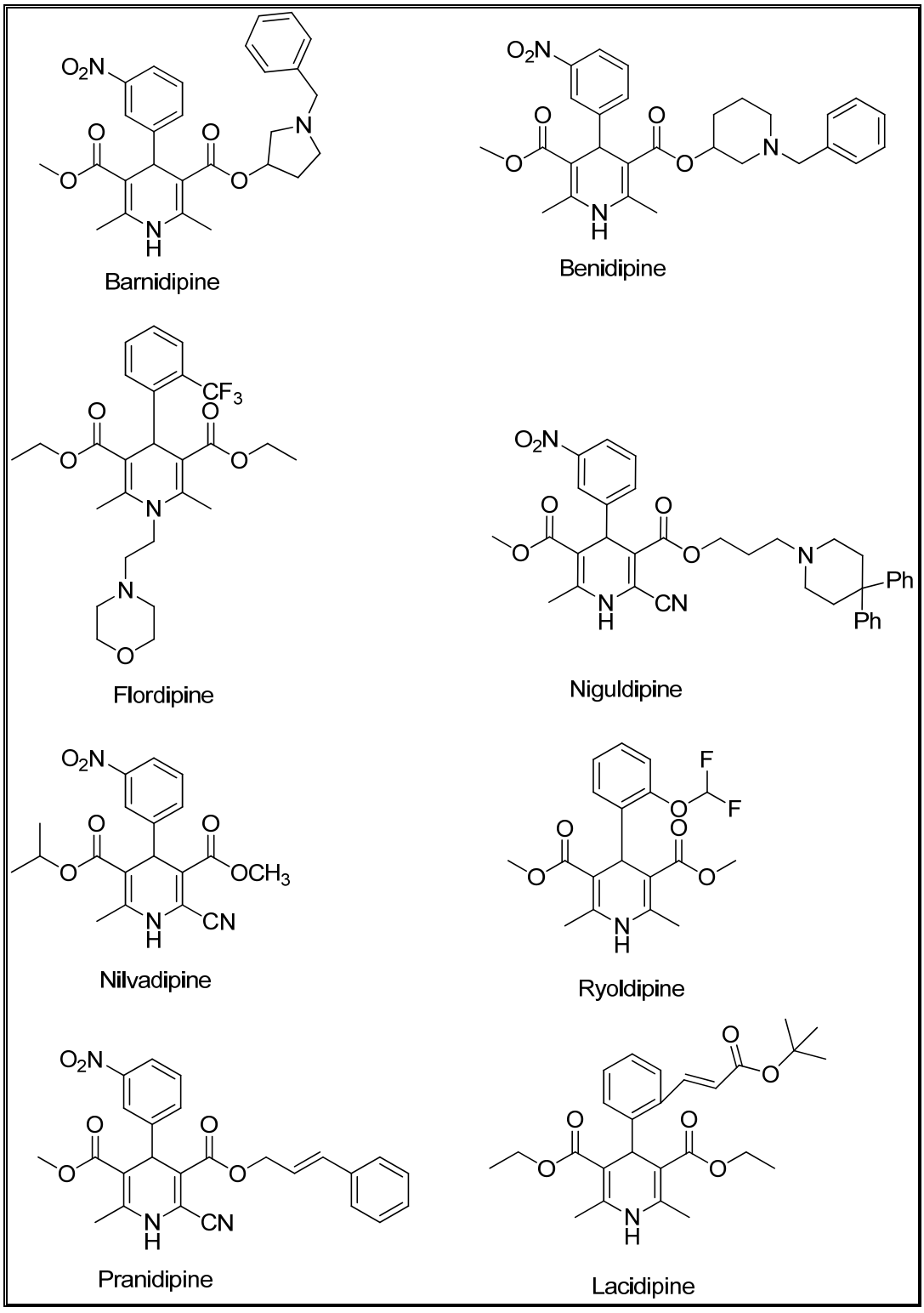


Figure 3.3

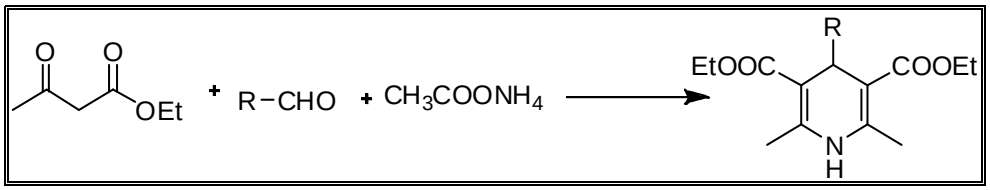


Few recent methods leading to symmetric, asymmetric and N-substituted 1,4-dihydropyridines are summarized as follow.

A) Synthesis of Symmetric 1,4-dihydropyridines containing same group at 2,6 & 3,5 position.

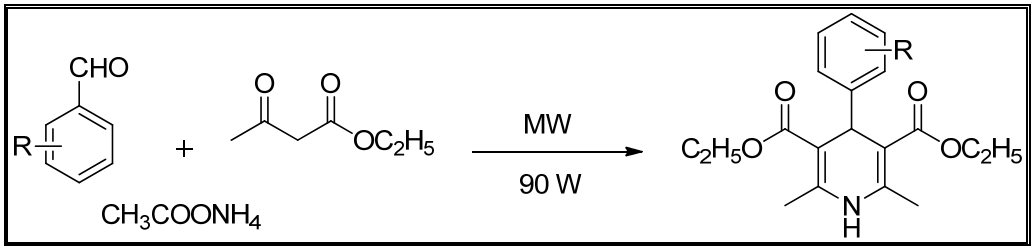
Mohammad *et al.* [22] had prepared 1,4-dihydropyridine under solvent free condition. Ethyl acetoacetate and a range of aldehydes in the presence of ammonium acetate were converted into 1,4-dihydropyridines under mild and solvent free conditions with good to excellent yields.

Scheme 3.2



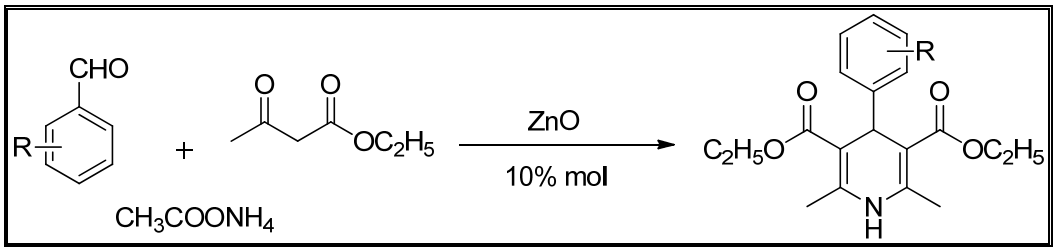
Sandeep *et al.* [23] discovered a novel method, which is eco-friendly, cost effective, solvent free and it was developed for the synthesis of 1,4-dihydropyridines from ethyl acetoacetate, aldehyde and ammonium acetate under domestic microwave oven. It was facile one-pot synthesis of 1,4-dihydropyridine in which reaction time was less with good yields.

Scheme 3.3



Matloubi *et al.* [24] synthesized an one-pot four-component reaction of aldehydes, ethyl acetoacetate/5,5-dimethyl-1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate in the presence of 10 mol% of ZnO as a heterogeneous catalyst for the synthesis of corresponding 1,4- dihydropyridine. The present methodology offers several advantages such as simple procedure, excellent yields and short reaction time.

Scheme 3.4



Liselotte *et al.* [25] synthesized 24 symmetric 1,4-dihydropyridines by using 6 different aldehydes, 4 different 1,3-diketones and ammonium hydroxide. Reaction assisted with microwave dielectric heating, to give shorter reaction time and often higher yields as compared to conventional method.

Scheme 3.5

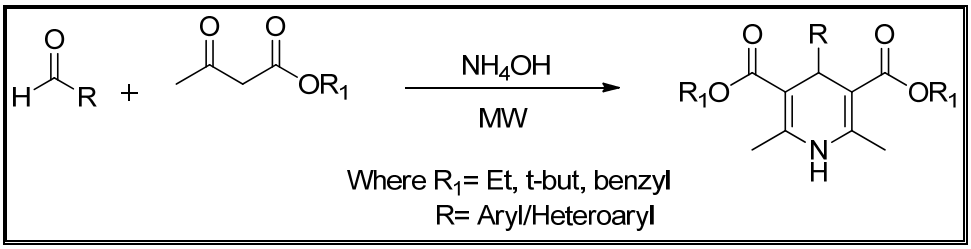
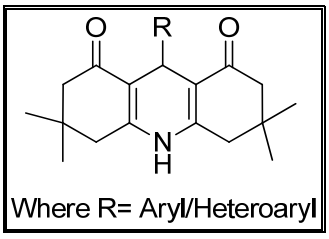
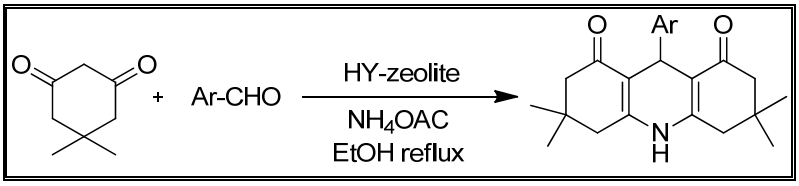


Figure 3.4



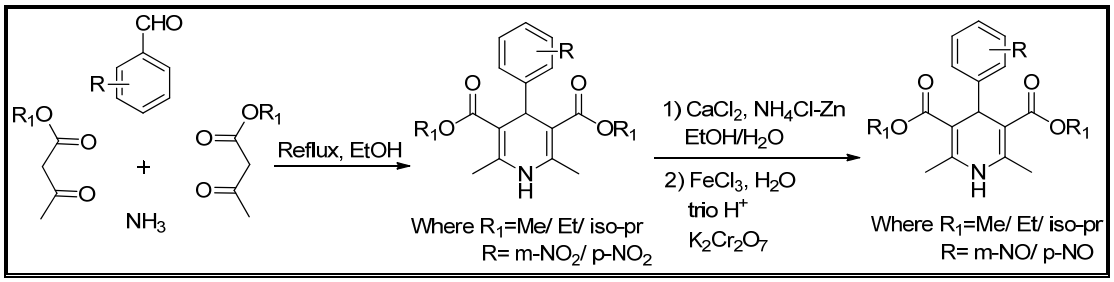
A facile and convenient method was developed by Mohammad Nikpassand *et al.* [26] for the fast and high yielding (70-90 %) synthesis of fused 1,4-dihydropyridines from dimedone in the presence of HY-zeolite as an efficient recyclable heterogeneous catalyst.

Scheme 3.6



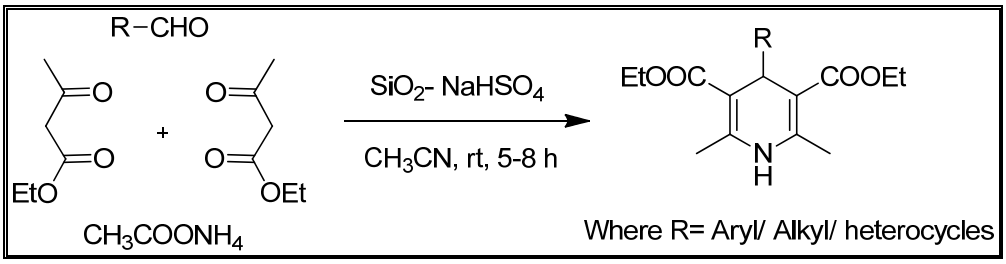
Santander-G *et al.* [27] synthesized nitroso-substituted derivatives of 1,4-dihydropyridine to search for new compounds with potential toxic effects on parasites or tumoral cells. The synthetic pathway was based on the classical Hantzsch synthesis of 1,4-dihydropyridines using nitrobenzaldehyde as starting material and a subsequent reduction of the nitro group.

Scheme 3.7



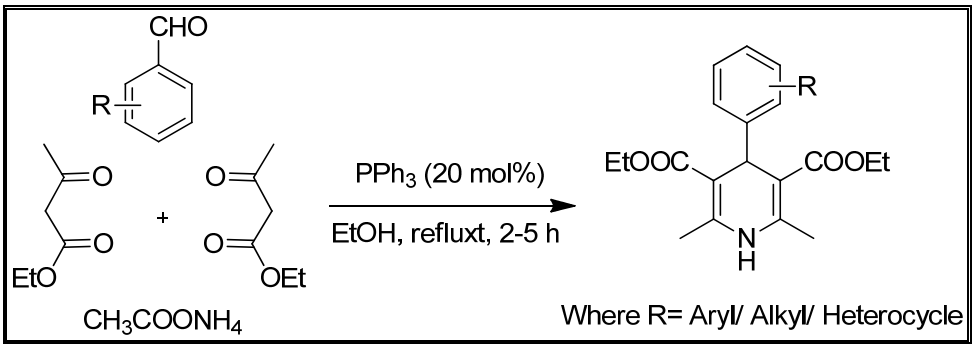
M. Adharvana Chari *et al.* [28] reported the synthesis of 1,4-DHPs in the presence of $NaHSO_4$–SiO_2 at ambient temperature by following Hantzsch procedure, which has advantages of low cost, ease of preparation and catalyst recycling.

Scheme 3.8



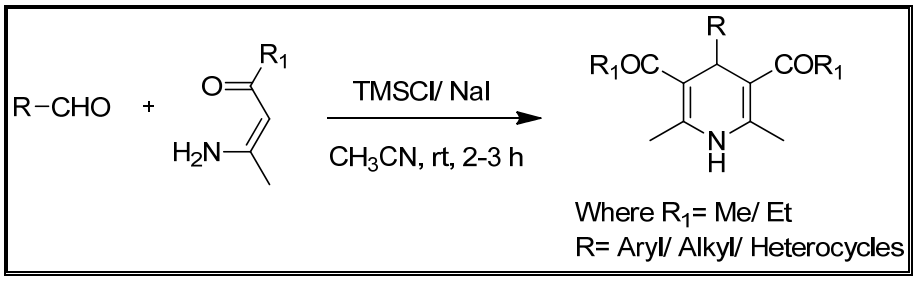
Abdelmadjid Debache *et al.* [29] reported that triphenylphosphine is a highly efficient catalyst for the synthesis of a variety of 4-substituted- 1,4-dihydropyridines in one pot. This method is applicable to a wide range of substrates, including aromatic and heterocyclic aldehydes and provides the corresponding 1,4-dihydropyridines in good to excellent yields. The present methodology offers advantages such as reduced reaction times and economic viability of the catalyst, compared with conventional methods and other catalysts.

Scheme 3.9



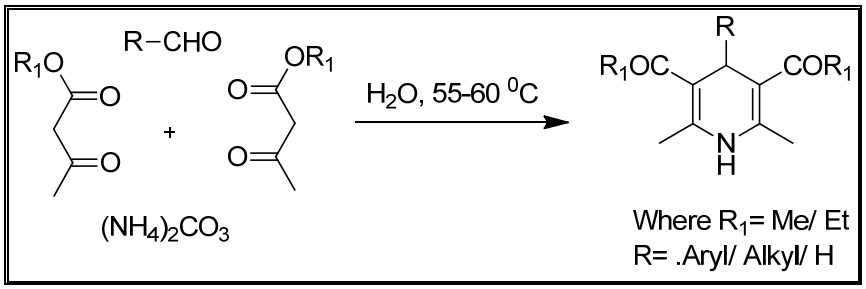
Gowravaram Sabitha *et al.* [30] reported a novel and efficient synthesis of Hantzsch 1,4-dihydropyridines by a modified Hantzsch procedure using TMSI in CH_3CN at ambient temperature.

Scheme 3.10



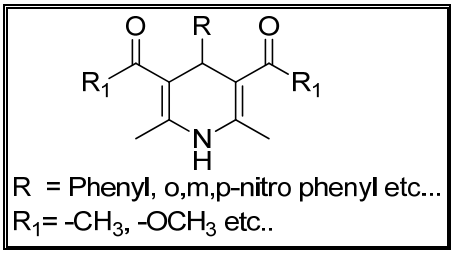
Fatemeh Tamaddon et al. [31] reported 1,4-dihydropyridines in water via Hantzsch reactions using ammonium carbonate as a solid ammonia source. The products were obtained in high yields and purities compared with previous methods without the use of a catalyst or an organic solvent.

Scheme 3.11



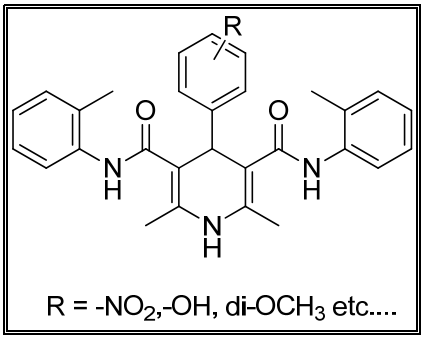
Very recently Shingare *et al.* [32] has came out with biological activity of a few 1,4-dihydropyridines. Many new compounds are prepared using few aldehydes and acetyl acetone for getting Hantzsch type dihydropyridines.

Figure 3.5



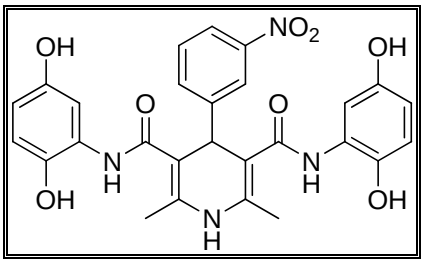
Reddy *et al.* [33] synthesized 4-aryl heteroaryl-2,6-dimethyl-yl-3,5-bis-N-(2-methyl phenyl) carbamoyl-1,4-dihydropyridines through one-pot synthesis using appropriate aromatic aldehydes and liquid ammonia. Pharmacological screening of the new 1,4-dihydropyridines were also carried out for CNS depressant (anticonvulsant and analgesic) and cardiovascular (inotropic and blood pressure) activities by standard methods.

Figure 3.6



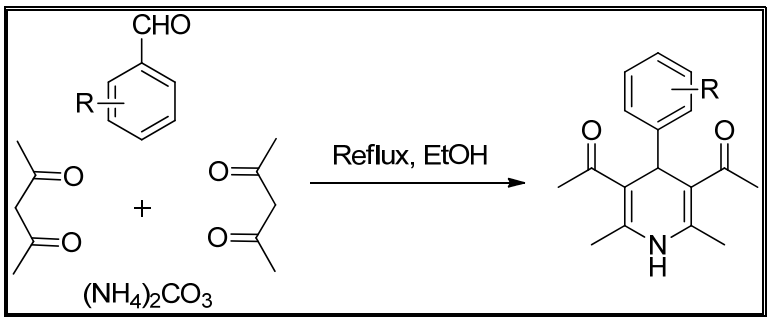
Neamati *et al.* [34] reported that 1,4-dihydropyridine molecule came out with its anti-HIV activity, which has opened up the synthetic as well as pharmacological importance in antiviral area also.

Figure 3.7

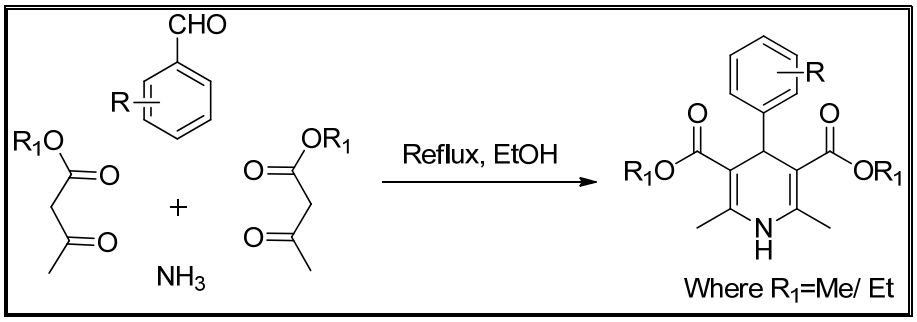


Earlier Shah *et al.* synthesized library of symmetric 1,4-dihydropyridines containing 3,5-diacetyl-2,6-dimethyl-4-(substituted phenyl) -1,4-dihydropyridine, [35,36] 3,5-dicarboxylate-2,6-dimethyl-4-(substituted phenyl)-1,4-dihydro pyridine, [37] 3,5-dibenzoyl-2,6-dimethyl-4-(substituted phenyl)-1,4-dihydropyridine, [38-44] 3,5-dicarbamoyl-2,6-dimethyl-4-(substituted phenyl)-1,4-dihydropyridine [45,46] and 3,5-dicarboxylic acid-2,6-diaryl-4-(substituted phenyl)-1,4-dihydro pyridine, [47] to investigate various biological activity like MDR reversal, anti-TB, anti-tumor and antimicrobial activity for the synthesized compounds.

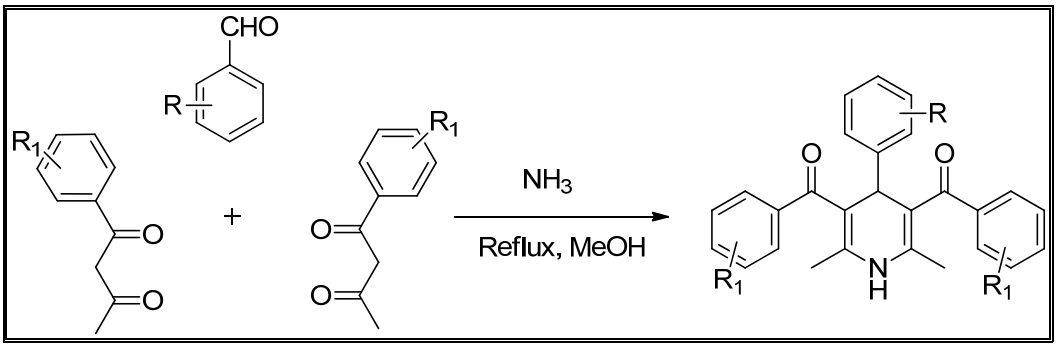
Scheme 3.12



Scheme 3.13



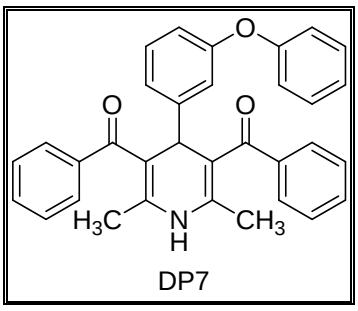
Scheme 3.14



From these 3,5- dibenzoyl 1,4-dihydropyridines, DP7, a novel dibenzoyl-1,4-dihydropyridine compound, synthesized in our laboratory has been shown to be a powerful Pgp inhibitor, almost devoid of cardiovascular effects, but capable of inhibiting liver CYP3A. DP7 is considered a lead compound for the development of novel dihydropyridiens which do not affect CYP enzyme but still remains active towards ABC-efflux transporters.

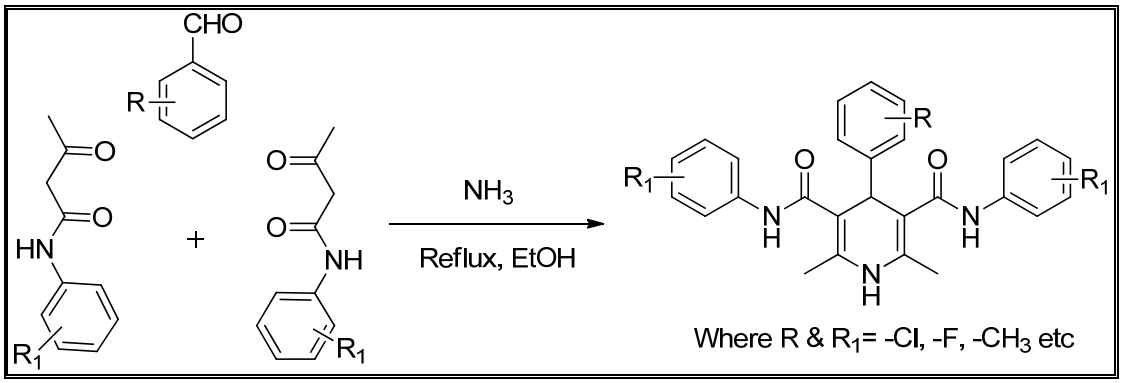
DP7 has also found out as a new multidrug resistance reverting agent devoid of vascular smooth muscle contractility. DP7 inhibited L-type Ca^{2+} current recorded in artery myocytes in a concentration –dependant manner, with IC50 values ranging between 1.12×10^{-6} and 2.23×10^{-5}. In L5187 MDR cell line, DP7 exhibited an MDR-reversing activity, with IC50 values ranging between 3.02×10^{-7} and 4.27×10^{-5}, being the most potent. The K^+ channel opner cromakalim inhibited the Ca^{2+} induced contraction in K30 but not that evoked in K60. But DP7, on the contrary was ineffective in both experimental conditions.

Figure 3.8

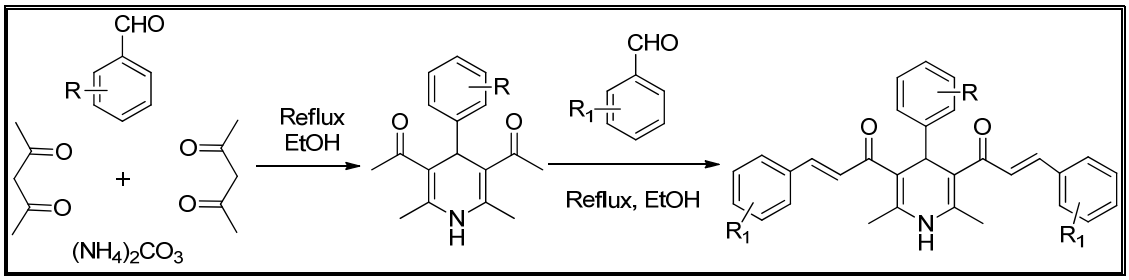


DP7

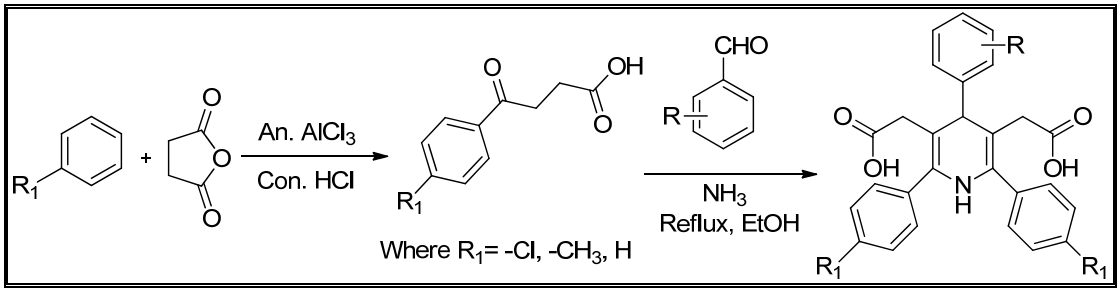
Scheme 3.15



Scheme 3.16



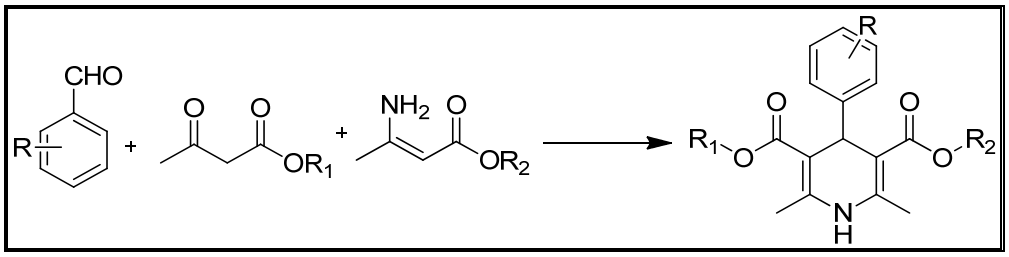
Scheme 3.17



B) Synthesis of Asymmetric 1,4-dihydropyridines containing different group at 2,6 and/or 3,5 position

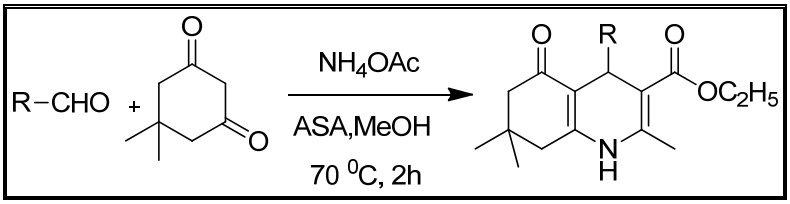
Waldo *et al.* [48] reported a solvent-free, two-step synthesis of some unsymmetrical 4-aryl-1,4-dihydropyridines.

Scheme 3.18



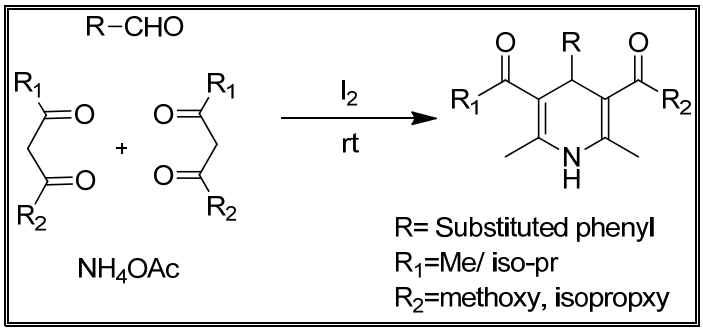
Recently much effort has been expended to develop more efficient methods for the preparation of 1,4-DHPs using microwave, [49] metal triflates as catalyst, [50] reaction in ionic liquid, [51] p-TSA, [52] HY-Zeolite, [53(a)] K7[PW11CoO40]-catalyzed [53(b)]and $HClO_4$ -SiO_2. [54] 1,4-DHPs were synthesized by the Hantszch method, which involves cyclocondensation of aldehyde, *β*-ketoester, and ammonia either in acetic acid at room temperature or refluxing in alcohol for a long time.

Scheme 3.19



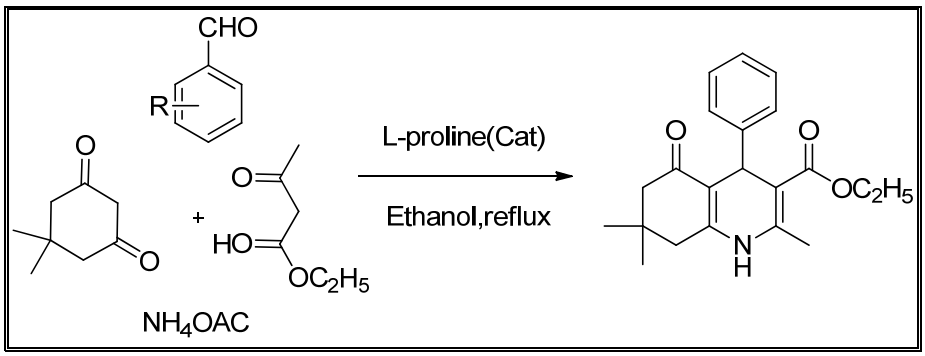
Joshi *et al.* [55] has used molecular iodine as a catalyst for the preparation of 1,4-dihydropyridine. Molecular iodine [56-61] has attracted attention as an inexpensive, non toxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity.

Scheme 3.20



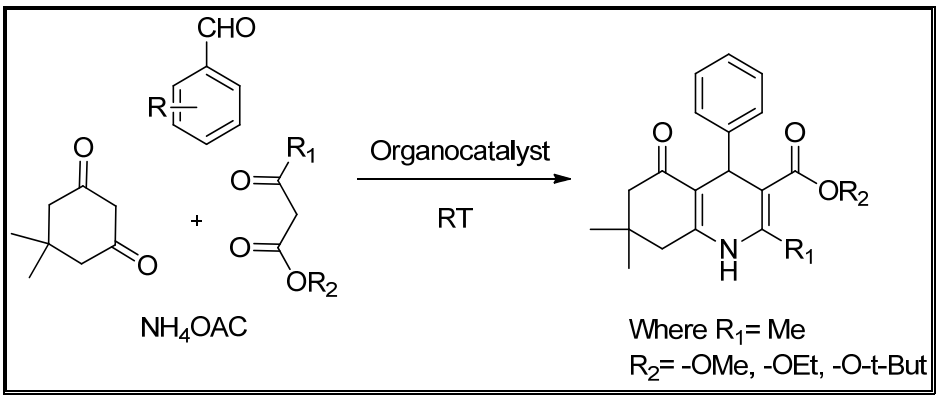
Nandkishor *et al.* [62] found that *L*-Proline has been found as an effective catalyst for the one pot synthesis of polyhydroquinoline derivatives via four component Hantzsch reaction. This method provides several advantages such as being environmentally benign, possessing high yields with increased variations of the substituents in the product and preparative simplicity.

Scheme 3.21



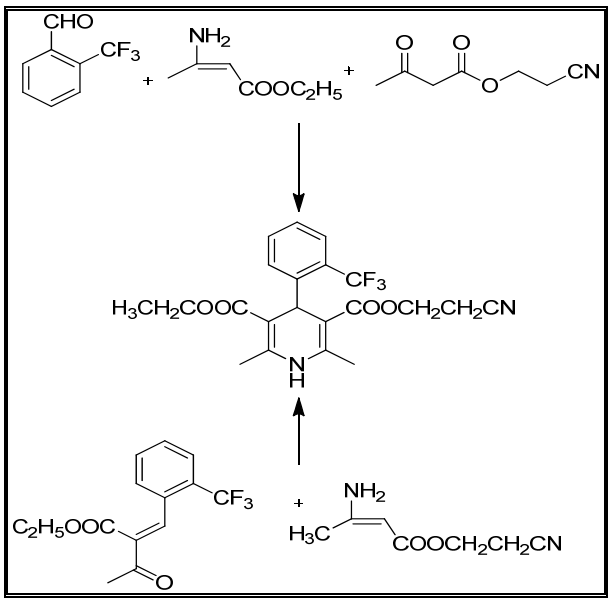
Atul Kumar *et al.* [63] described Synthesis of polyhydroquinoline derivatives through unsymmetric Hantzsch reaction using organocatalysts.

Scheme 3.22



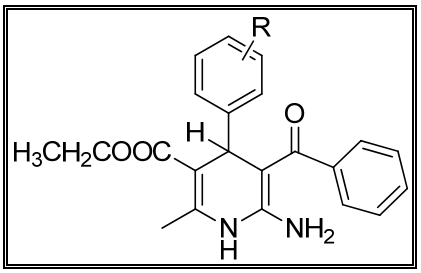
Two different routes of synthesis in single step are reported for 3-cyano ethoxycarbonyl-2,6-dimethyl-4-(2-trifluoro methyl phenyl)- 1,4-dihydropyridine. Firstly, the condensation of aldehyde with ethyl-3-aminocrotonate and 2-cyanoethyl-3-oxobutanoate. In another method, the condensation of ethyl-2-(2-trifluoromethyl phenyl benzylidene) acetoacetate was carried out with 2-cyanoethyl (2*Z*)-3-aminobut-2-enoate. [64]

Scheme 3.23



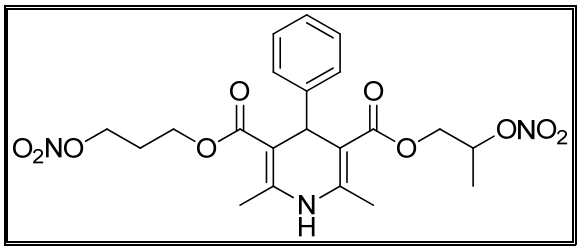
Meyer *et al.* [65] have prepared anti-inflammatory agents such as 2-amino-3-benzoyl cyano-1,4-dihydropyridine.

Figure 3.9



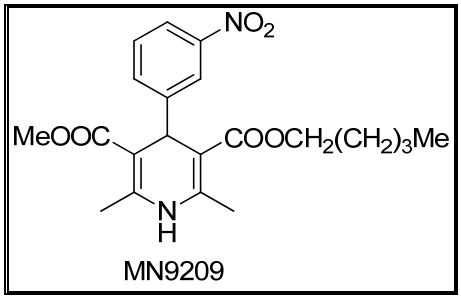
Tsuchida *et al.* [66] has shown that CD-349 can be appeared to be a potent cerebrovasodilator in dogs and could be useful in the treatment of cerebrovascular disorders in human.

Figure 3.10



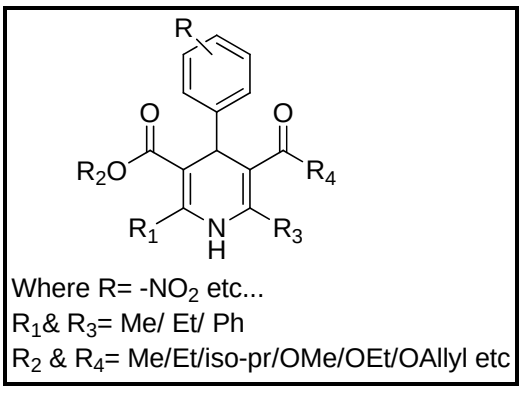
Bang-le Zhang *et al.* [67] reported an efficient total synthesis of (R) and (S)-3-methyl 5-pentyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine- 3,5-dicarboxylate in high optical purities.

Figure 3.11



Mikhail F. Gordeev *et al.* [68] described method enables simple and expedient solid-phase syntheses of 1,4-dihydropyridines in good overall yields and is well suited for the combinatorial split and pool protocols.

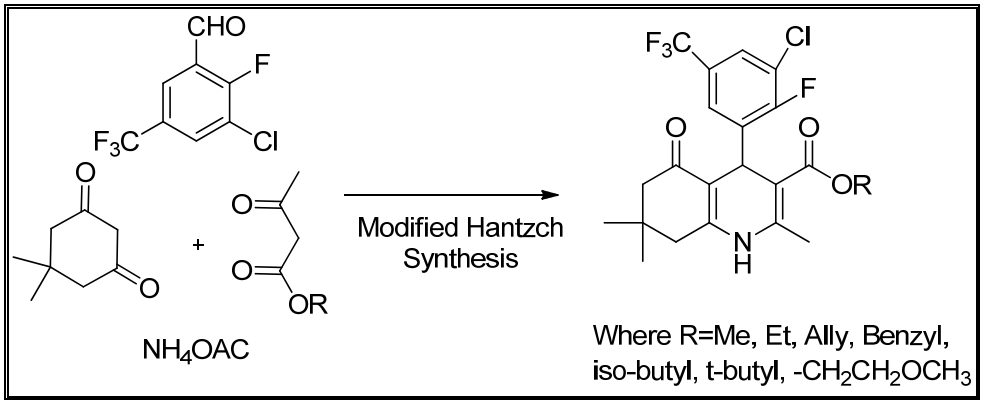
Figure 3.12



Bahadir Bulbul *et al.* [69] reported new condensed 1,4-DHP derivatives, synthesized by the reaction of substituted cyclohexanedione derivatives, various alkyl acetoacetate

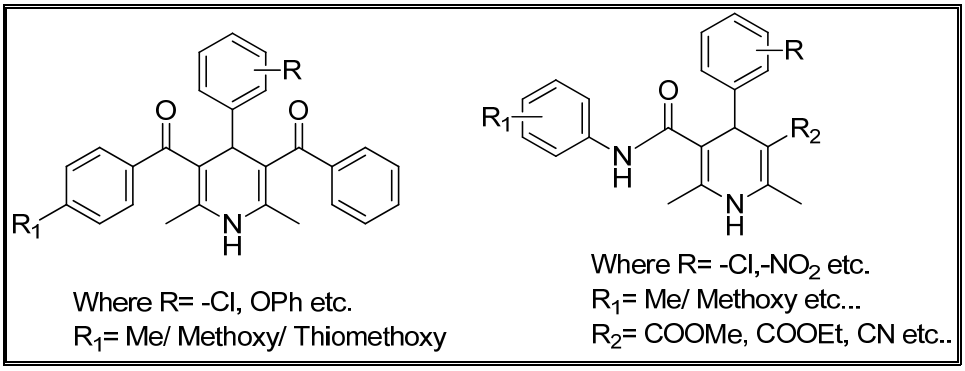
esters and trisubstituted aromatic aldehydes according to modified Hantzsch synthesis. In pharmacological screening tests, the obtained results showed that condensed 1,4-DHP derivatives exerted calcium channel blocking effects.

Scheme 3.24



Shah *et al.* [70] synthesized several asymmetric 1,4-dihydropyridines to evaluate their various pharmacological activities, like anti-TB, tumor specific cytotoxicity, Pgp inhibitor, anti viral and antimicrobial activity.

Figure 3.13

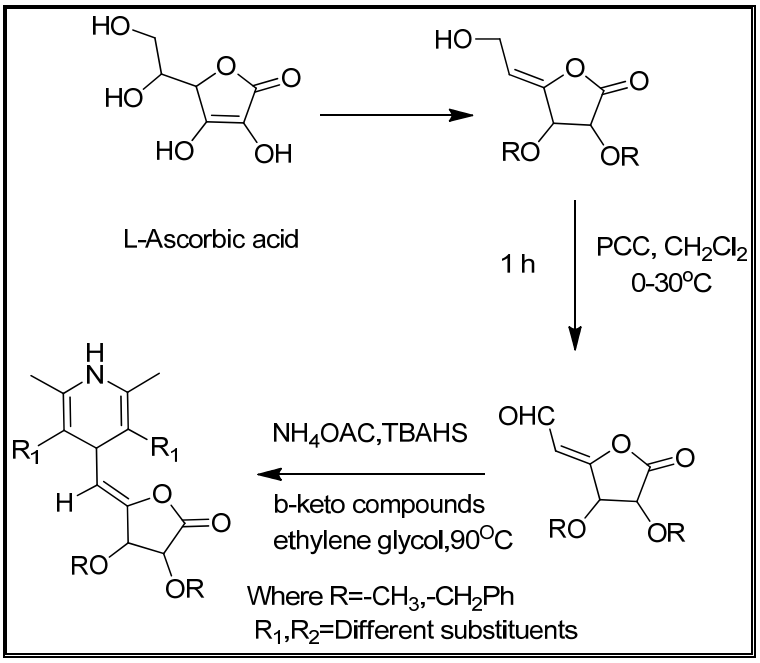


Apart from these, many 1,4-dihydropyridines with various substituents like heteroaromatic/ aliphatic/ sugar/ coumarin/ quinoline/ flavone at C_4 position have been reported, which are also covered under asymmetric 1,4-dihydropyridines.

Surendra *et al.* [71] developed an efficient synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines, which has been achieved via a three-component

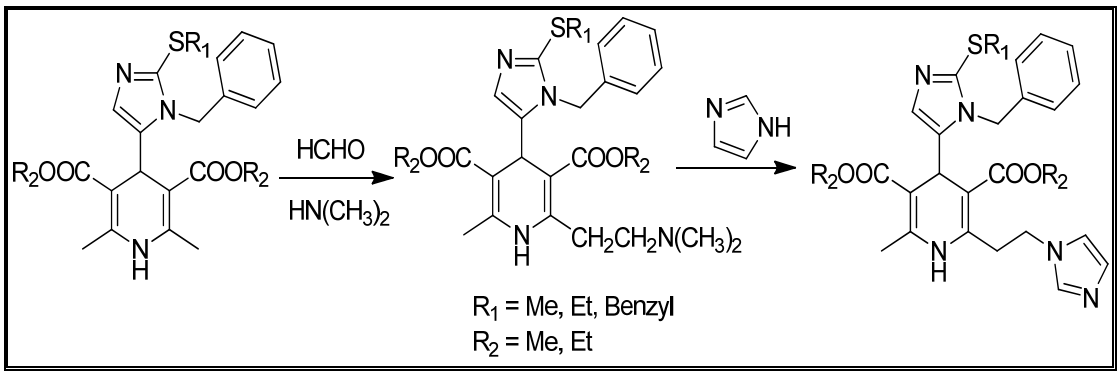
reaction of β-keto esters or ketones, ammonium acetate and vinylic aldehydes from ascorbic acid in the presence of tetrabutylammonium hydrogen sulphate in ethylene glycol.

Scheme 3.25



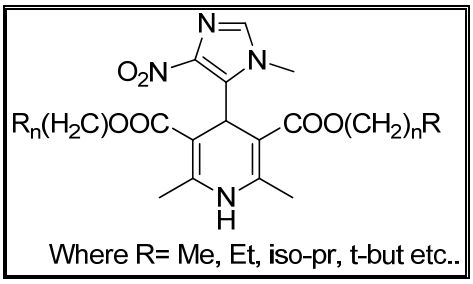
Farzin *et al.* [72] demonstrated the synthesis and antihypertensive activity of newly synthesized 1,4-dihydropyridines. They prepared symmetric DHPs by conventional Hantzch condensation as described previously.

Scheme 3.26



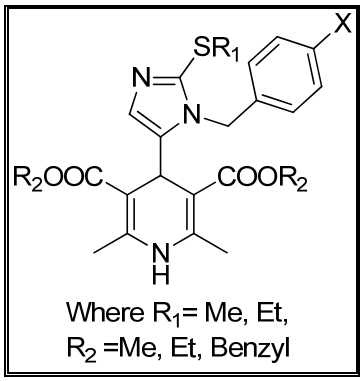
Abbas Shafiee *et al.* [73] described anticonvulsant activities of new 1,4-dihydropyridine derivatives containing 4-nitroimidazolyl substituents.

Figure 3.14



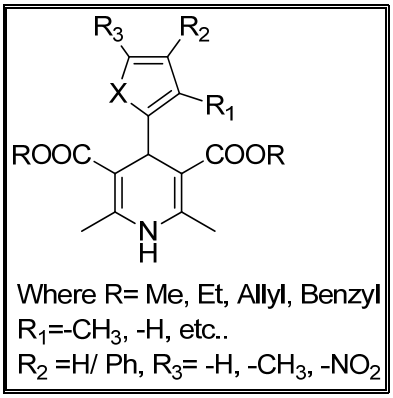
F. Hadizadeh *et al.* [74] synthesized a series of 1,4-dihydropyridine calcium channel blockers bearing 1-(4-X -benzyl)-5-imidazolyl substituent at 4 position (5a-e) (X=H, F) which were tested for antihypertensive activity in desoxycorticosterone acetate (DOCA)-induced hypertension in rats.

Figure 3.15



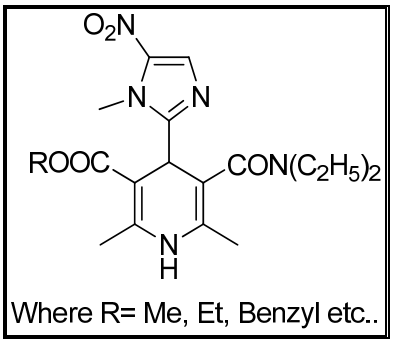
Francesca Cateni *et al.* [75] reported synthesis of 4-thiophen-20-yl-1,4-dihydropyridines as potentiators of the CFTR chloride channel.

Figure 3.16



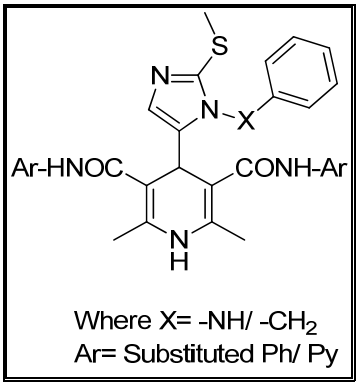
Mehdi Khoshneviszadeh *et al.* [76] described Synthesis and biological evaluation of some new 1,4-dihydropyridines containing different ester substitute and diethyl carbamoyl group as anti-tubercular agents.

Figure 3.17



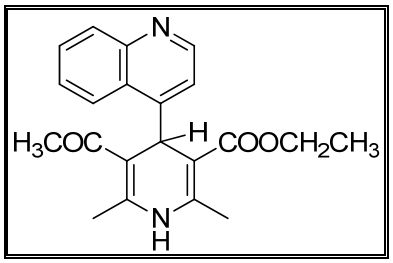
Afshin Fassihi et al [77] reported synthesis and antitubercular activity of novel 4-substituted imidazolyl -2,6- dimethyl- N3,N5-bisaryl-1,4-dihydropyridine -3,5-dicarboxamides.

Figure 3.18



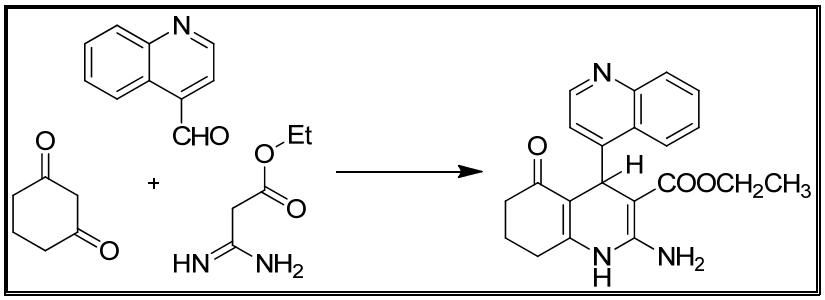
Earlier, Berson *et al.* [78] first time synthesized quinoline containing unsymmetrical compound 4- (4-quinolyl) -2,6- dimethyl-3- carbethylxy- 5-acetyl -1,4-dihydropyridne.

Figure 3.19



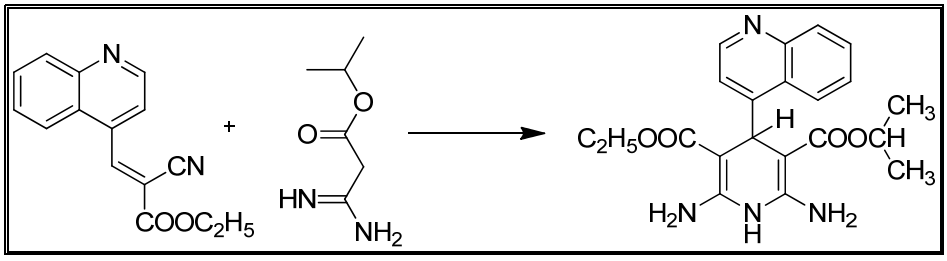
Bossert *et al.* [79] also put in their efforts to preparing coronary dilator and antihypertensive 1,4-dihydropyridines containing a quinoline group at C_4 position. Ethyl 2-amino-4-(4-quinolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate have been prepared by the cyclization of 1,3-cyclohexanedione with aldehyde and CH_3-CH_2-CH_2-C(NH)-NH_2.

Scheme 3.27



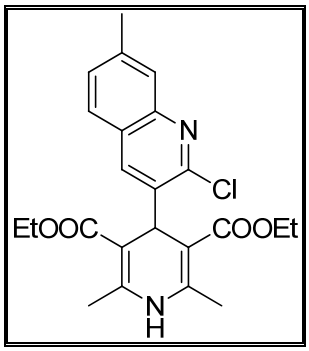
Other unsymmetric 2,6-diamino-4-(4-quinolyl)-1,4-dihydropyridine was synthesized by a different route. [80]

Scheme 3.28



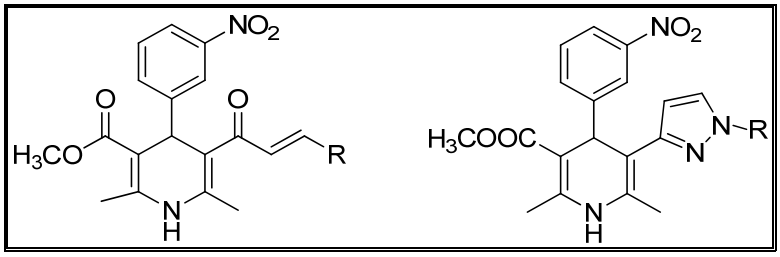
Shah *et al.* [81] also synthesized quinoline containing asymmetric 1,4-dihydropyridines to study its X-ray crystallographic parameters.

Figure 3.20



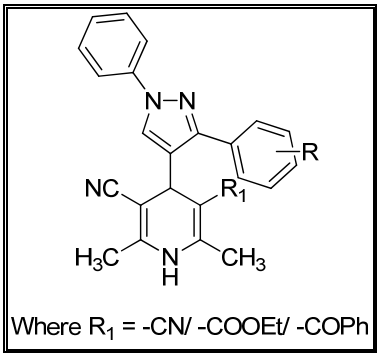
Shah *et al.* [82,83] reported some unsymmetrical 1,4-DHP derivatives as potent antitubercular agents. In last few years, researchers of this laboratory synthesized and studied 1,4-dihydropyridine derivatives bearing pyrazoline, isooxazole at C_3 position. They reported these derivatives as bactericidal, fungicidal and surprisingly antitubercular also.

Figure 3.21



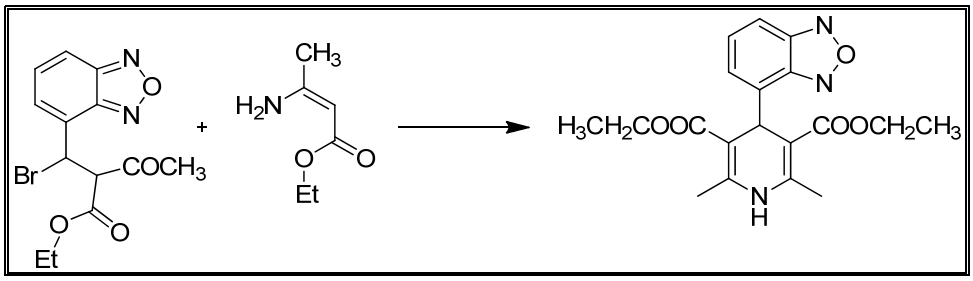
Recently Shah *et al.* [84] synthesized asymmetric 1,4-dihydropyridines containing pyrazole motif at C_4 position to give structural and molecular diversity.

Figure 3.22



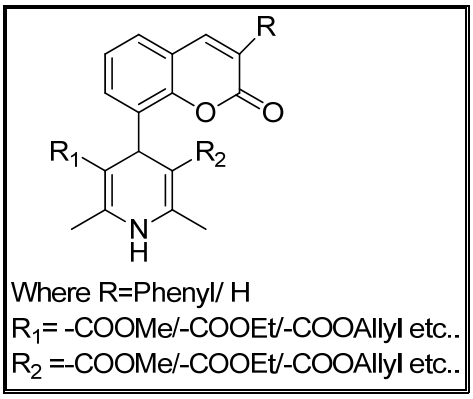
Sachio *et al.* [85] prepared antihypertensive 1,4-dihydropyridine containing a benzo furazanyl moiety at C_4 Position.

Scheme 3.29



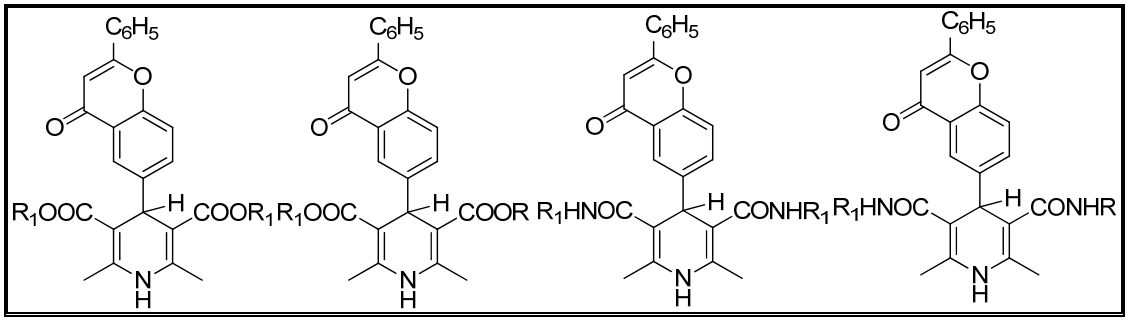
P. Valenti *et al.* [86] synthesized a series of 1,4-dihydropyridines bearing a coumarin moiety in 4-position. The compounds were evaluated for inotropic, chronotropic and calcium antagonist activities.

Figure 3.23



Ozbey *et al.* [87] gave synthesis of some 1,4-dihydropyridine derivatives containing the flavone ring system.

Figure 3.24



C) Synthesis of N-Substituted 1,4-dihydropyridines containing same/ different group at 2,6 & 3,5 position.

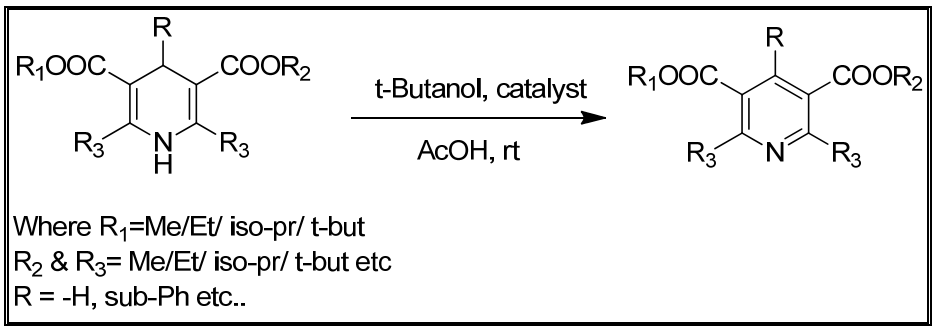
1,4-dihydropyridines containing cyano group at C_3/C_5 position and N-Substituted 1,4-dihydropyridines will be discussed in next chapter.

D) Aromatization of 1,4-dihydropyridines

The oxidation of Hantzsch's 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines has been extensively studied. The relevance of this reaction to the metabolism of Hantzsch's esters as calcium channel blocking drugs is exploited to treat various cardiovascular disorders. For example, 1,4-DHP-derived drugs such as nifedipine, nitrendipine and nimodipine are frequently used as cardiovascular agents (Ca^{2+} channel blockers) in the treatment of hypertension and angina pectoris diseases. The metabolism of these drugs involves the oxidative aromatization of 1,4-DHP nucleus to the corresponding pyridine derivatives, which are catalyzed in the liver by cytochrome P-450. Therefore, numerous studies have been performed on the mimicking of this enzyme.

Numerous reagents have been recommended for the oxidative aromatization of 1,4-DHPs to the pyridines, such as I_2, $KMnO_4$, SeO_2, $KBrO_3/SnCl_45H_2O$, magtrieve, $Pb(OAc)_4$, chloranil, $H_2O_2/Co(OAc)_2$, Co-naphthenate/O_2, nicotinium dichromate, clay or wet-SiO_2 supported oxidants, S-nitrosoglutathione, NO, palladium catalyst, peroxydisulfate–cobalt(II), hypervalent iodine reagents, inorganic acidic salts, and sodium nitrite or nitrate, solid acids, sodium periodate catalyzed by manganese(III) Schiff's base, N,N0-ethylene-bis(benzoylacetoniminato) copper(II), cytochrome P-450, electrochemical methods, K_2FeO_4 by microwave promoted and photooxidation. [88-91]

Scheme 3.30

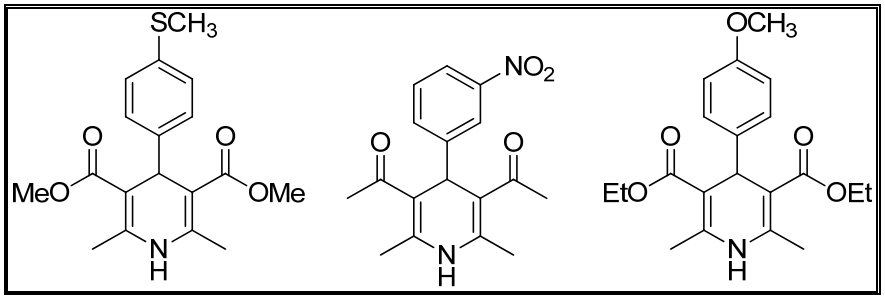


E) X-ray crystallographic study of some 1,4-dihydropyridines

A systematic study of symmetric as well as asymmetric 1,4-dihydropyridines has been carried out by Shah *et al.* [92-105] to investigate their manifold medicinal utility like antihypertensive, anticancer, Pgp-inhibitor, tumor specific, antitubercular, antimicrobial and anti-HIV. Many of the synthesized compounds were well characterized by single crystal x-ray crystallographic study, which is enlisted below.

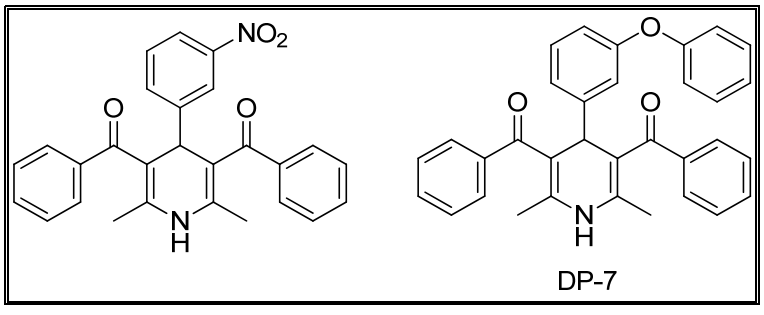
Inhouse synthesized various symmetric 1,4-dihydropyridines like 3,5-diacetyl, 3,5-dicrbmethoxy [106] and 3,5-dicarbethoxy [107] 1,4-dihydropyridines have been confirmed from single crystal x-ray crystallographic studies.

Figure 3.25



Symmetric 3,5-dibenzoyl, 1,4-dihydropyridines were studied by single crystal x-ray crystallography. [108,109]

Figure 3.26



Symmetric 1,4-dihydropyridines containing carbamoyl group at C_3 and C_5 position have been synthesized and well characterized by single crystal x-ray crystallography. [110,111(98,100)]

Figure 3.27

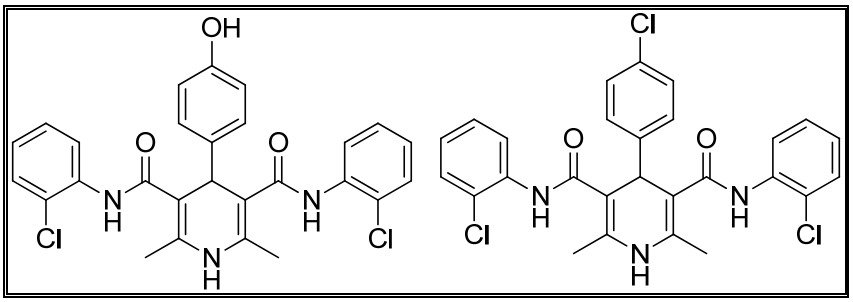
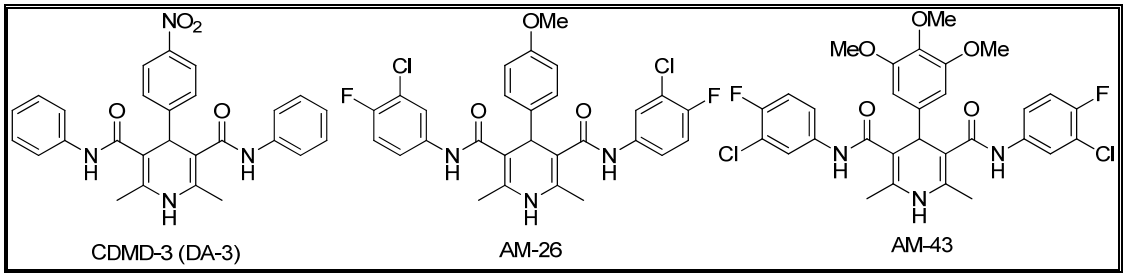
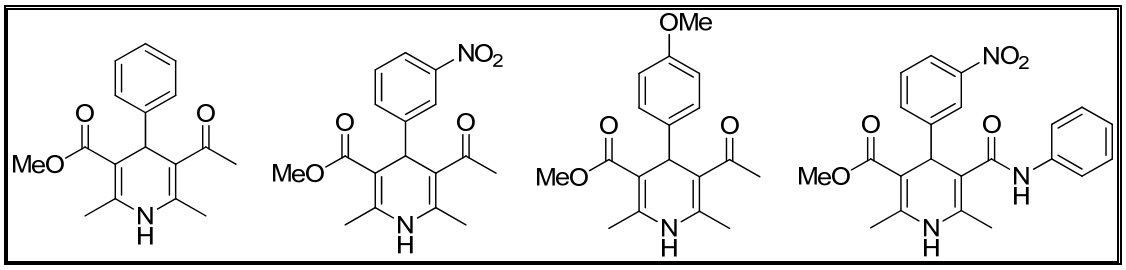


Figure 3.28



While four different asymmetric 1,4-dihydropyridines were confirmed by single crystal x-ray crystallographic study. [112-115]

Figure 3.29



1,4-dihydropyridines containing cyano group at C_3/C_5 position and N-substituted 1,4-dihydropyridines also well characterized by single crystal x-ray crystallographic study, which is described in next chapter.

3.3 PHARMACOLOGICAL SIGNIFICANCE

1,4-Dihydropyridines (1,4-DHPs) belong to a class of nitrogen containing heterocycles having a six-membered ring. Much attention has been devoted to explore their pharmacological activities. A number of bioactivity are associated with 1,4-dihydropyridines. Among several bioactivities, their value as antihypertensive agents is unquestioned and is reported as good calcium channel blocker. On the molecular level, 1,4-DHP compounds cause vasorelaxation by blocking voltage-operated calcium channels in smooth muscle cells and also by increasing NO release from intact endothelium. Among other types of heterocyclic compounds having similar pharmacological activity (verapamil and diltiazem), 1,4-DHPs are the most potent calcium antagonists or calcium channel blockers. [116]

Despite this, 1,4-DHPs are significantly potent in cancer chemotherapy along with clinically used drugs. This family of compounds is potent inhibitors of P-glycoprotein (Pgp), which are the main cause of the efflux of toxins the cells. [117,35,36,38-44]

The DHP ring is a common feature of various bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents. [118] Recent studies have revealed that 1,4-DHPs exhibit several other medicinal applications which include neuroprotectant [119(a)] and platelet anti-aggregratory activity, [119(b)] in addition to acting as a cerebral antiischemic agent in the treatment of Alzheimer's disease [119(c)] and as a chemosensitizer in tumor therapy. [119(d)]

Recent studies have demonstrated that 4-aryl-1,4-DHPs containing lipophilic dicarbamoyl groups on the C_3 and C_5 positions of the DHP ring have considerable antitubercular activity against Mycobacterium tuberculosis H37Rv. [120-122] Other studies developed the new DHP derivatives containing diethyl carbamoyl and ester substituents on C_3 and C_5 and a nitroimidazolyl group on the C-4 position of the DHP ring (nitroimidazolyl derivatives have been demonstrated to be potential antitubercular agents, especially against resistant strains). Aryl ester analogs of these derivatives (especially the 3-phenylpropyl ester analog) exhibited comparable

antitubercular activity against M. tuberculosis H37Rv with the reference drug isoniazid and minimal calcium-channel blocking activity. [123]

Several DHP derivatives have been found to have bronchodilatory, vasculoprotective, hepatoprotective, antiplatelet and antifungal properties. [124] They have also shown analgesic properties, as well as antioxidant activity and inhibition of GABA receptors. [125,126]

DHPs reduced hyperglycemia considerably, improved glucose metabolism and increased insulin sensitivity in diabetic rats. In addition, administration of nisoldipine in streptozocin-induced diabetes lowers the blood glucose level by peripheral vasodilation and increased glucose turn over. Moreover, it was reported that nifidepine has an inhibitory effect on TNF-α-induced neovascularization in streptozocin-induced diabetic rats. [127,128]

Some experiments have shown synergistic effects of DHPs with some anticonvulsant drugs, such as carbamazepine. [129]

1,4-DHPs possess different pharmacological activities such as coronary vasodilator and cardiopathic, [130] antimayocardiac ischemic, antiulcer, [131] antiallergic, [132] anti-inflammatory [133] and antiarrhythmic, [134] PAF antagonist, [135] Adenosine A3 receptor antagonist. [136]

Moreover, studies revealed that 1,4-dihydropyridine derivatives (1,4-DHP) show antimutagenic and anticlastogenic properties and accelerate repair of oxidant and ionising radiation generated DNA damage. [137,138]

Antioxidant activity with 1,4-dihydropyridine structure were investigated as a less harmful alternative to synthetic phenolic antioxidants in liposomes under conditions simulating food storage. [139]

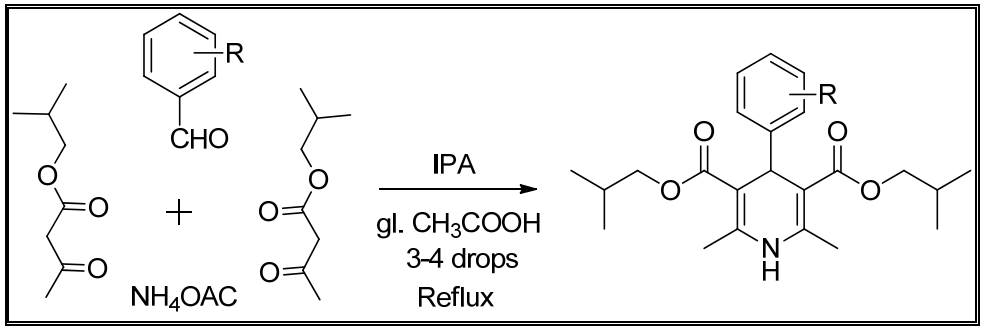
3.4 AIM OF CURRENT WORK

DHPs are the molecules of diverse pharmacological interest mainly in cardiovascular diseases but they are now also established as potent inhibitors of Pgp which is the main cause of chemotherapy failure in cancer. There is lot of scopes in the DHP molecules as at least five main positions are available for modification. Moreover, the particular position can be modified according to structural need. For Pgp inhibitory activity, replacement of C_3 and C_5 ester groups was explored in most of the cases as these positions are responsible for cardiovascular selectivity. Even the C_2 position was studied. Thus, this "privileged structural" class studied extensively and identified in recent years for their very promising other therapeutic activity spectrum such as Pgp inhibitors, MDR modifier and immunomodulators.

Thus, the opportunity to synthesize some new chemical entities as well as to explore their biological activity was the main rational behind initializing the work included in this chapter.

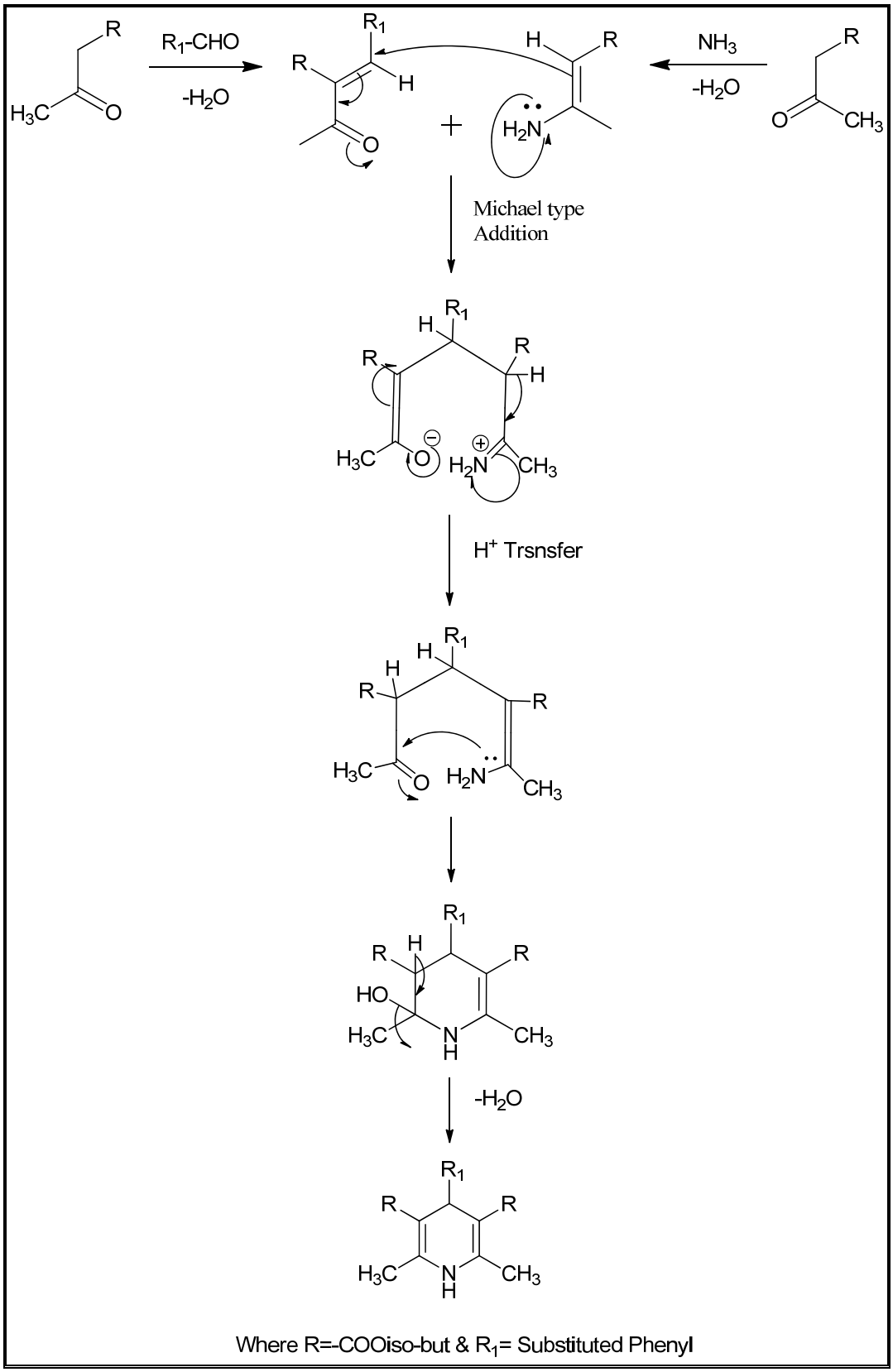
3.5 REACTION SCHEME

3.5.1 Preparation of Diisobutyl 2,6-dimethyl-4-(substituted phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-081 to 099)



Where R= -NO_2, -F, -OCH_3, -Cl, etc.

3.6 PLAUSIBLE REACTION MECHANISM



3.7 EXPERIMENTAL

3.7.1 Analysis Protocol

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr Powder method. Mass spectra were recorded on **Shimadzu GC-MS-QP-2010** model using Direct Injection Probe technique. ^{1}H NMR was determined in $CDCl_3$ solution on a **Bruker Avance II 400 MHz NMR Spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model. Purity of all the compounds was checked by **Shimadzu HPLC** SPD-M 10 A-VP LC-10 ATVP model. All the results are in agreements with the structures assigned.

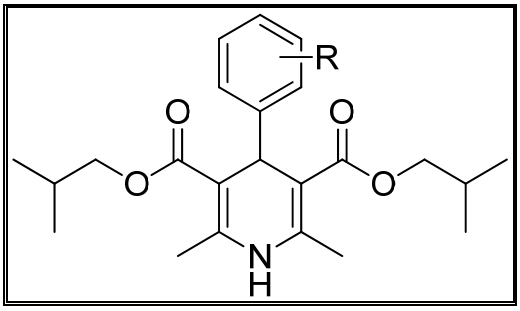
3.7.2 Preparation of Diisobutyl 2,6-dimethyl-4-(substituted phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (General Procedure)

A mixture of substituted aldehyde (0.01 mole), isobutyl acetoacetate (0.02 mole) and ammonium acetate (0.05 mole) were taken in isopropyl alcohol with 3-4 drops of glacial acetic acid. The reaction mixture was refluxed for 12-14 hours at reflux temperature till reaction completed. The progress and the completion of the reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After completion of the reaction, solvent was evaporated under reduced pressure to obtained crude product. Crude product extracted with ether and hexane (70:30). Then ether layer was evaporated to get the solid product. Product was recrystallized from methanol and the crystalline product was separated by filtration. Similarly other compounds are also prepared. All the synthesized compounds were found to pure upto 97-99% by HPLC.

The physical data of newly synthesized compounds are given in Table No. 3.8.1

3.8 PHYSICAL DATA

3.8.1 Physical Data Table of Diisobutyl 2,6-dimethyl-4-(substituted phenyl)-1,4-dihydropyridine-3,5-dicarboxylates



Sr. No.	Sample Code	Substitution R	Molecular Formula	M. Wt	MP °C	Yield %
1	MNP-081	H	$C_{23}H_{31}NO_4$	385	138-140	85
2	MNP-082	2-NO_2	$C_{23}H_{30}N_2O_6$	430	132-134	80
3	MNP-083*	3-NO_2	$C_{23}H_{30}N_2O_6$	430	148-150	93
4	MNP-084	4-NO_2	$C_{23}H_{30}N_2O_6$	430	120-122	90
5	MNP-085	3-F	$C_{23}H_{30}NFO_4$	403	124-126	92
6	MNP-086	4-OH, 3-OC_2H_5	$C_{25}H_{35}NO_6$	445	120-122	70
7	MNP-087	4-OH, 3-OCH_3	$C_{24}H_{33}NO_6$	431	118-119	68
8	MNP-089	2-OCH_3	$C_{24}H_{33}NO_5$	415	114-116	65
9	MNP-090	3-OPh	$C_{29}H_{35}NO_5$	477	121-123	62
10	MNP-091	2-Cl	$C_{23}H_{30}NClO_4$	419	142-144	70
11	MNP-092	3-Cl	$C_{23}H_{30}NClO_4$	419	88-90	55
12	MNP-093	4-Cl	$C_{23}H_{30}NClO_4$	419	120-122	50
13	MNP-097	3,4- di-OCH_3	$C_{25}H_{35}NO_6$	445	102-104	75
14	MNP-098	2,5- di-OCH_3	$C_{25}H_{35}NO_6$	445	98-100	73
15	MNP-099	3,4,5-tri-OCH_3	$C_{26}H_{37}NO_7$	475	124-126	80

NB: '*' indicating that the compound is reported. [140-142]

3.9 SPECTRAL DISCUSSION

3.9.1 IR Spectra

IR spectra of the synthesized compounds were recorded on Shimadzu FT-IR 8400 model using KBr powder method. Various functional groups present were identified by characteristic frequency obtained for them.

The characteristic bands of N-H group showed in the region of 3500-3200 cm^{-1} with a deformation due to in plane bending at 1650-1550 cm^{-1}. Aromatic C-H stretching and bending frequencies showed between 3070-3030 cm^{-1} and 1600-1400 cm^{-1} respectively. C-H stretching and bending frequencies for methyl and methylene group were obtained near 2950-2850 cm^{-1} and 1450-1375 cm^{-1}. Characteristic frequency of C=O stretching of esters showed near 1750-1715 cm^{-1} and C-O stretching showed at 1200-1170 cm^{-1}. Characteristic frequency of C-N stretching showed near 1350-1280 cm^{-1}.

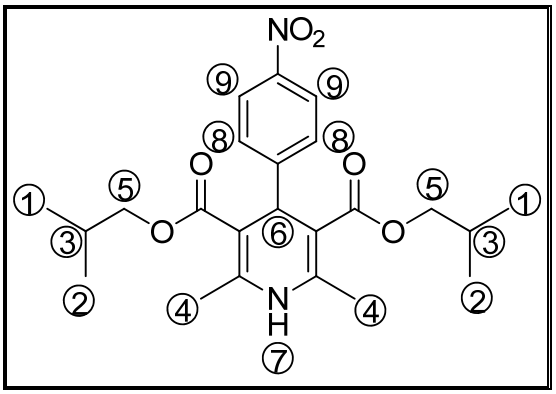
3.9.2 Mass Spectra

Mass spectra of the synthesized compounds were recorded on Shimadzu GC-MS-QP-2010 model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound.

3.9.3 ^{1}H NMR Spectra

^{1}H NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Number of protons identified from ^{1}H NMR spectra and their chemical shift (δ ppm) were in the agreement of the structure of the molecule. *J* values were calculated to identify o, m and p coupling. In some cases, aromatic protons were obtained as multiplet. Interpretation of representative spectrum is discussed as under.

3.9.3.1 ^{1}H NMR of Diisobutyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (MNP-084)



1. Proton no. 1 and 2 of methyl group of total 12 H gave a doublet at 0.86-0.91 δ ppm.

2. Proton no. 3 of total 2H gave a multiplet at 1.86-1.93 δ ppm.

3. Proton no. 4 of methyl group of total 6H gave a characteristic singlet at 2.37 δ ppm.

4. Proton no. 5 of methylene of isobutyl group of total 4H gave a multiplet at 3.82-3.85 ppm.

5. Proton no. 6 of 1H gave a singlet at 5.15 δ ppm.

6. Proton no. 7 of secondary amine of dihydropyridine ring of 1H gave a singlet at 5.79 δ ppm.

7. Proton no. 8 and 9 of total 2H and 2H gave a typical double doublet of para substitution pattern at 7.44-7.47 δ ppm (J=8.72) and 8.07-8.09 δ ppm (J=8.72). J value suggest ortho coupling.

Thus, by observing and assigning the signals in the NMR spectrum and by the calculation of the J values for above proton, we can clearly suggest that the proposed structure for compound MNP-084 has been confirmed. The spectrum is given on page no. 164.

3.9.4 ^{13}C NMR Spectra

^{13}C NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Types of carbons identified from NMR spectrum and their chemical shifts (δ ppm) were in the agreement with the structure of the molecule.

3.9.4 Elemental Analysis

Elemental analysis of the synthesized compounds was carried out on Vario EL Carlo Erba 1108 which showed calculated and found percentage values of Carbon, Hydrogen and Nitrogen in support of the structure of synthesized compounds.

The analytical data for individual compounds synthesized in this chapter is mentioned as follow.

3.10 ANALYTICAL DATA

1) Diisobutyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (MNP-081)

Yield: 85%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **MS**: *m/z* = 385 (100%); Anal. Calcd. for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.11; N, 3.63; O, 16.60; Found: C, 71.56; H, 7.90; N, 3.75.

2) Diisobutyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (MNP-082)

Yield: 80%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1510 (N=O str.), 1460 (C-H bend –CH_2), 1375 (C-H bend -CH_3), 1360 (C-NO_2 str.), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **^{1}H NMR** ($CDCl_3$) δ ppm: 0.76- 0.77 (d, 6H), 0.80-0.81 (d, 6H), 1.87-1.94 (m, 2H), 2.33 (s, 6H), 3.71-3.75 (m, 2H), 3.86-3.90 (m, 2H), 5.75 (s,1H), 5.82 (s, 1H), 7.22-7.26 (m, 1H), 7.43-7.47 (m, 1H), 7.52-7.54 (dd, 1H, *J*=1.44, *J*=7.72), 7.68-7.71 (dd, 1H, *J*=1.28, *J*=6.84); **MS**: *m/z* = 430 (100%); Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51; O, 22.30; Found: C, 64.25; H, 7.10; N, 6.48.

3) Diisobutyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (MNP-083)

Yield: 93%; **IR** (cm^{-1}): 3375 (N-H str.), 3068-3027 (Ar C=C-H str.), 2965 (Asym C-H str. -CH_3), 2941 (Asym C-H str. -CH_2), 2925 (C-H str. ipr), 2891 (Sym C-H str. -CH_3), 2873 (Sym C-H str. -CH_2), 1715 (C=O str. ester), 1652 (N-H bend), 1580, 1519, 1488 (Ar C=C str.), 1519 (N=O str.), 1474 (C-H bend –CH_2), 1379 (C-H bend -

CH_3), 1347 (C-NO_2 str.), 1312 (C-N sec amine vib), 1164 (C-O str.), 1025 (C-H i-p def), 810-750 (C-H oop def); **^{1}H NMR** ($CDCl_3$) δ ppm: 0.86- 0.87 (d, 6H), 0.89-0.91 (d, 6H), 1.87-1.94 (m, 2H), 2.38 (s, 6H), 3.82-3.84 (d, 4H), 5.14 (s,1H), 5.87 (s, 1H), 7.35-7.39 (t, 1H, *J*=7.92), 7.64-7.67 (m, 1H, *J*=1.28, *J*=5.24), 7.99-8.02 (m, 1H), 8.12-8.13 (t, 1H, *J*=1.98); **MS**: *m/z* = 430 (100%); Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51; O, 22.30; Found: C, 64.34; H, 6.95; N, 6.68.

4) Diisobutyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (MNP-084)

Yield: 90%; **IR** (cm^{-1}): 3321 (N-H str.), 3099 (Ar C=C-H str.), 2963 (Asym C-H str. -CH_3), 2950 (Asym C-H str -CH_2), 2917 (C-H str. ipr), 2872 (Sym C-H str. -CH_3), 2867 (Sym C-H str. -CH_2), 1752-1698 (C=O str. ester), 1670 (N-H bend), 1621, 1580, 1487 (Ar C=C str.), 1487 (N=O str.), 1462 (C-H bend –CH_2), 1397 (C-H bend -CH_3), 1380 (C-NO_2 str.), 1302 (C-N sec amine vib), 1212 (C-O str.), 1029 (C-H i-p def), 870-800 (C-H oop def); **^{1}H NMR** ($CDCl_3$) δ ppm: 0.86- 0.88 (d, 6H), 0.89-0.91 (d, 6H), 1.86-1.93 (m, 2H), 2.37 (s, 6H), 3.82-3.85 (2d, 4H), 5.15 (s,1H), 5.79 (s, 1H), 7.44-7.47 (d, 2H, *J*=8.72), 8.07-8.09 (d, 2H, *J*=8.72); **MS**: *m/z* = 430 (100%); Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51; O, 22.30; Found: C, 64.19; H, 7.19; N, 6.60.

5) Diisobutyl 2,6- dimethyl-4-(3-fluoro phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-085)

Yield: 92%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asymm C-H str -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1510 (N=O str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1360 (C-NO_2 str.), 1340 (C-N sec amine vib), 1180 (C-O str.), 1090 (C-F str.), 1050 (C-H i-p def), 750 (C-H oop def); **^{1}H NMR** ($CDCl_3$) δ ppm: 0.87- 0.89 (d, 6H), 0.90-0.91 (d, 6H), 1.88-1.94 (m, 2H), 2.35 (s, 6H), 3.83-3.85 (d, 4H), 5.05 (s,1H), 5.76 (s, 1H), 6.79-6.84 (m, 2H, *J*=5.32), 6.95-6.99 (*J*=6.28), 7.06-7.07 (dd, 1H, *J*=1.12, *J*=5.48), 7.12-7.18 (m, 1H); **MS**: *m/z* = 403 (100%); Anal. Calcd. for $C_{23}H_{30}FNO_4$: C, 68.46; H, 7.49; F, 4.71; N, 3.47; O, 15.86; Found: C, 69.89; H, 4.40; Cl, 8.59; N, 16.98.

6) Diisobutyl 2,6-dimethyl -4-(3-ethoxy-4-hydroxy-phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-086)

Yield: 70%; **IR** (cm^{-1}): 3679-3652 (OH str.), 3314 (N-H str.), 3015 (Ar C=C-H str.), 2959 (Asym C-H str. -CH_3), 2929 (Asym C-H str. -CH_2), 2904 (C-H str. ipr), 2872 (Sym C-H str. -CH_3), 2837 (Sym C-H str. -CH_2), 1740-1719 (C=O str. ester), 1676 (N-H bend), 1596, 1564, 1511 (Ar C=C str.), 1467 (C-H bend -CH_2), 1377 (OH bend), 1346 (C-H bend -CH_3), 1313 (C-N sec amine vib), 1214 (C-O str.), 1045 (C-H i-p def), 850-750 (C-H oop def); **^{1}H NMR** ($CDCl_3$) δ ppm: 0.87- 0.94 (2d, 12H), 1.38-1.41 (t, 3H), 1.87-1.94 (m, 2H), 2.33 (s, 6H), 3.83-3.86 (2d, 4H), 4.01-4.06 (q, 2H), 4.97 (s, 1H), 5.82 (s, 1H), 6.70-6.76 (m, 2H), 6.84-6.85 (d, 1H, *J*=1.48); **MS**: *m/z* = 445 (100%); Anal. Calcd. for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14; O, 21.55; Found: C, 67.66; H, 7.63; N, 3.71.

7) Diisobutyl 2,6-dimethyl-4-(3-methoxy-4-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (MNP-087)

Yield: 68%; **IR** (cm^{-1}): 3550 (OH str.), 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1390 (OH bend), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **MS**: *m/z* = 431 (100%); Anal. Calcd. for $C_{24}H_{33}NO_6$: C, 66.80; H, 7.71; N, 3.25; O, 22.25; Found: C, 66.85; H, 7.53; N, 3.81.

8) Diisobutyl 2,6- dimethyl-4-(2-methoxy phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-089)

Yield: 65%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **^{1}H NMR** ($CDCl_3$) δ ppm: 0.86- 0.91 (2d, 12H), 1.86-1.91 (m, 2H), 2.28 (s, 6H), 3.71-3.78 (m, 5H), 3.80-3.85 (m, 2H), 5.33 (s, 1H), 5.75 (s, 1H), 6.77-6.81 (t, 2H, *J*=7.28, *J*=7.76), 7.08-7.09 (m, 1H), 7.18-7.20 (dd, 1H, *J*=1.6, *J*=5.96); **^{13}C NMR** ($CDCl_3$) δ ppm:

19.24, 19.31, 19.43, 27.75, 35.27, 55.18, 70.05, 77.04, 102.97, 110.68, 120.03, 127.31, 130.15, 134.85, 143.83, 157.16, 168.22; **MS**: *m/z* = 415 (100%); Anal. Calcd. for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37; O, 19.25; Found: C, 69.46; H, 8.36; N, 3.12.

9) Diisobutyl 2,6 -dimethyl-4-(3-phenoxy phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-090)

Yield: 62%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **MS**: *m/z* = 477 (100%); Anal. Calcd. for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39; N, 2.93; O, 16.75; Found: C, 72.90; H, 7.36; N, 2.87.

10) Diisobutyl 2,6 -dimethyl-4-(2-chloro phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-091)

Yield: 70%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str.. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 790 (C-Cl str.), 750 (C-H oop def); **MS**: *m/z* = 419 (100%); Anal. Calcd. for $C_{23}H_{30}NClO_4$: C, 65.78; H, 7.20; Cl, 8.44; N, 3.34; O, 15.24; Found: C, 65.65; H, 7.16; N, 3.29.

11) Diisobutyl 2,6 -dimethyl-4-(3-chloro phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-092)

Yield: 55%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 790 (C-Cl str.), 750 (C-H oop def); **MS**: *m/z* = 419 (100%); Anal. Calcd. for $C_{23}H_{30}NClO_4$: C, 65.78; H, 7.20; Cl, 8.44; N, 3.34; O, 15.24; Found: C, 65.43; H, 7.34; N, 3.28.

12) Diisobutyl 2,6 -dimethyl-4-(4-chloro phenyl) -1,4-dihydropyridine-3,5-dicarboxylate (MNP-093)

Yield: 50%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 790 (C-Cl str.), 750 (C-H oop def); **MS**: *m/z* = 419 (100%); Anal. Calcd. for $C_{23}H_{30}NClO_4$: C, 65.78; H, 7.20; Cl, 8.44; N, 3.34; O, 15.24; Found: C,65.47; H, 7.10; N, 3.43.

13) Diisobutyl 4- (3,4-dimethoxy phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (MNP-097)

Yield: 75%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **MS**: *m/z* = 445 (100%); Anal. Calcd. for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14; O, 21.55; Found: C, 67.30; H, 7.87; N, 3.20.

14) Diisobutyl 4- (2,5-dimethoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (MNP-098)

Yield: 73%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **MS**: *m/z* = 445 (100%); Anal. Calcd. for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14; O, 21.55; Found: C, 67.42; H, 7.98; N, 3.02.

15) Diisobutyl 4- (3,4,5-triimethoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (MNP-099)

Yield: 80%; **IR** (cm^{-1}): 3400-3300 (N-H str.), 3045 (Ar C=C-H str.), 2980 (Asym C-

H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2890 (C-H str. ipr), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 1740 (C=O str. ester), 1650 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend -CH_2), 1375 (C-H bend -CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 1050 (C-H i-p def), 750 (C-H oop def); **MS**: *m/z* = 475 (100%); Anal. Calcd. for $C_{26}H_{37}NO_7$: C, 65.66; H, 7.84; N, 2.95; O, 23.55; Found: C, 65.50; H, 7.81; N, 2.94.

3.11 RESULTS AND DISCUSSION

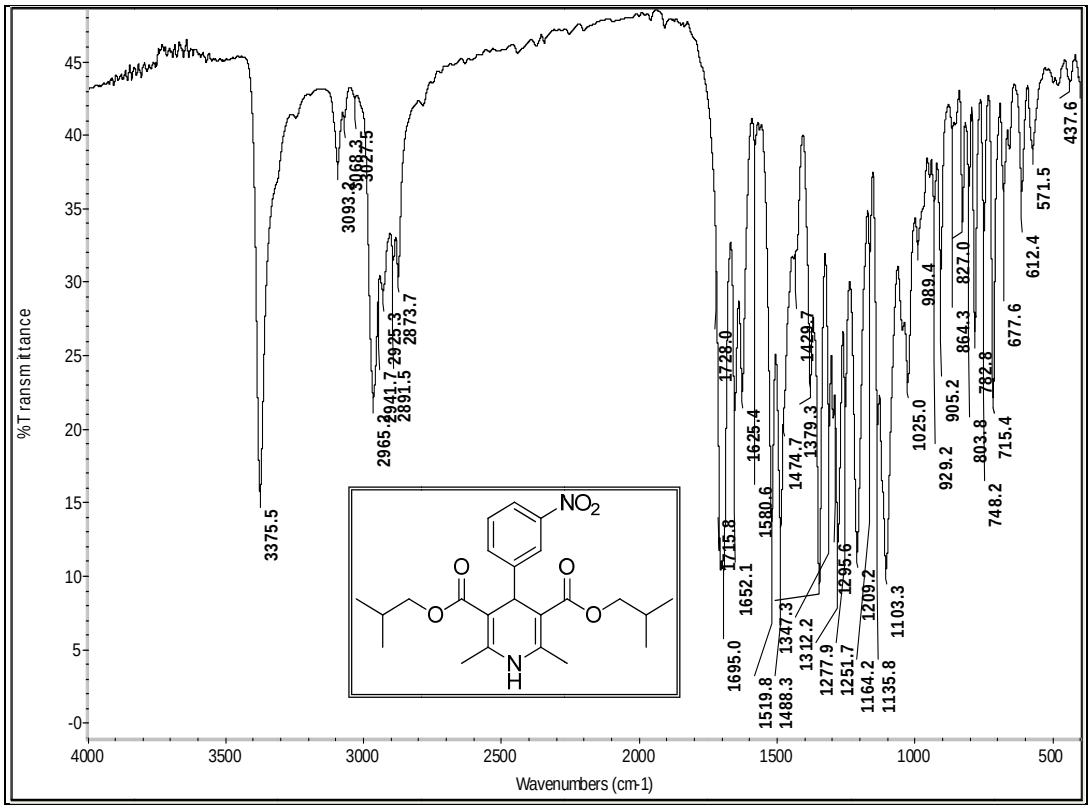
This chapter deals with the preparation of symmetric 1,4-dihydropyridines by one pot high purity Multi Component Reaction (MCR) using normal conventional approach. Isobutyl acetoacetate, substituted aldehydes and ammonium acetate in the presence of catalytic amount of glacial acetic acid forwarded by refluxing the reaction mixture in isopropyl alcohol upto 10-14 hrs to obtained the final products.

3.12 CONCLUSION

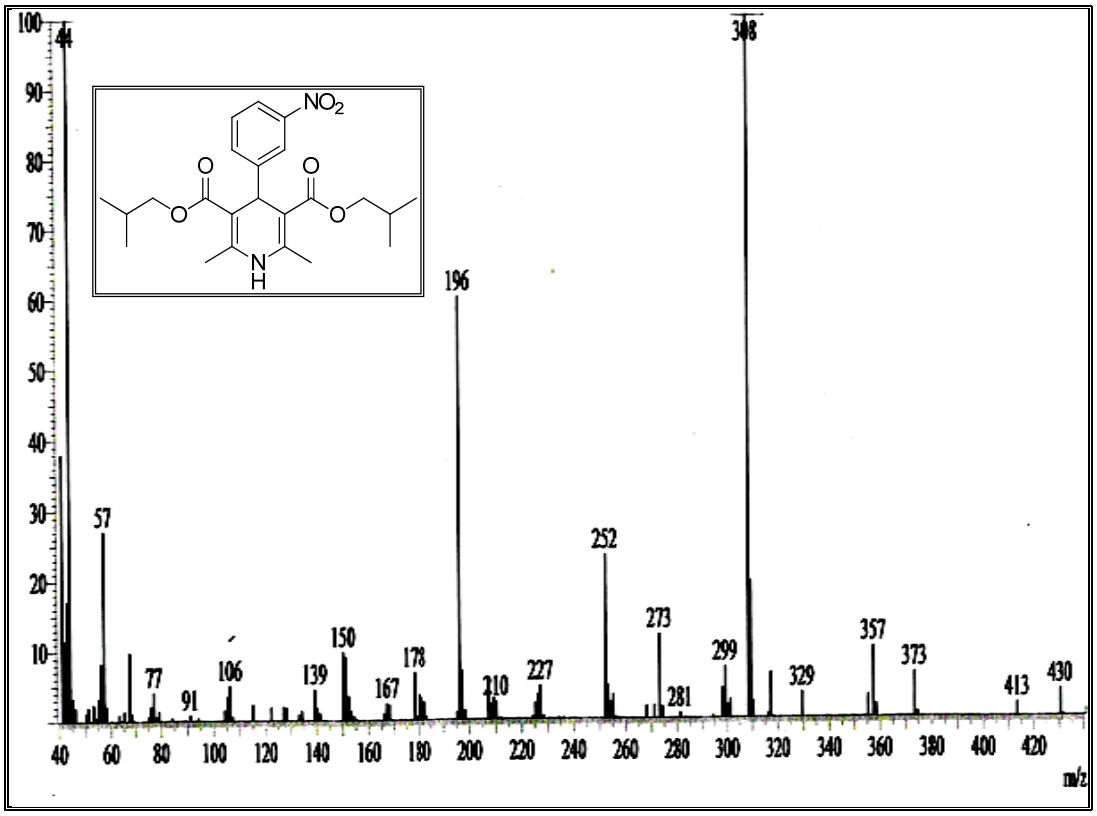
Herein we demonstrated some new symmetric 1,4-dihydropyridines structurally correlated with Nisoldipine, a potent calcium channel antagonist, for the biologically as well as pharmacological interest. All the synthesized compound are highly pure and well characterized by IR, Mass, ^{1}H NMR and ^{13}C NMR.

3.13 REPRESENTATIVE SPECTRA

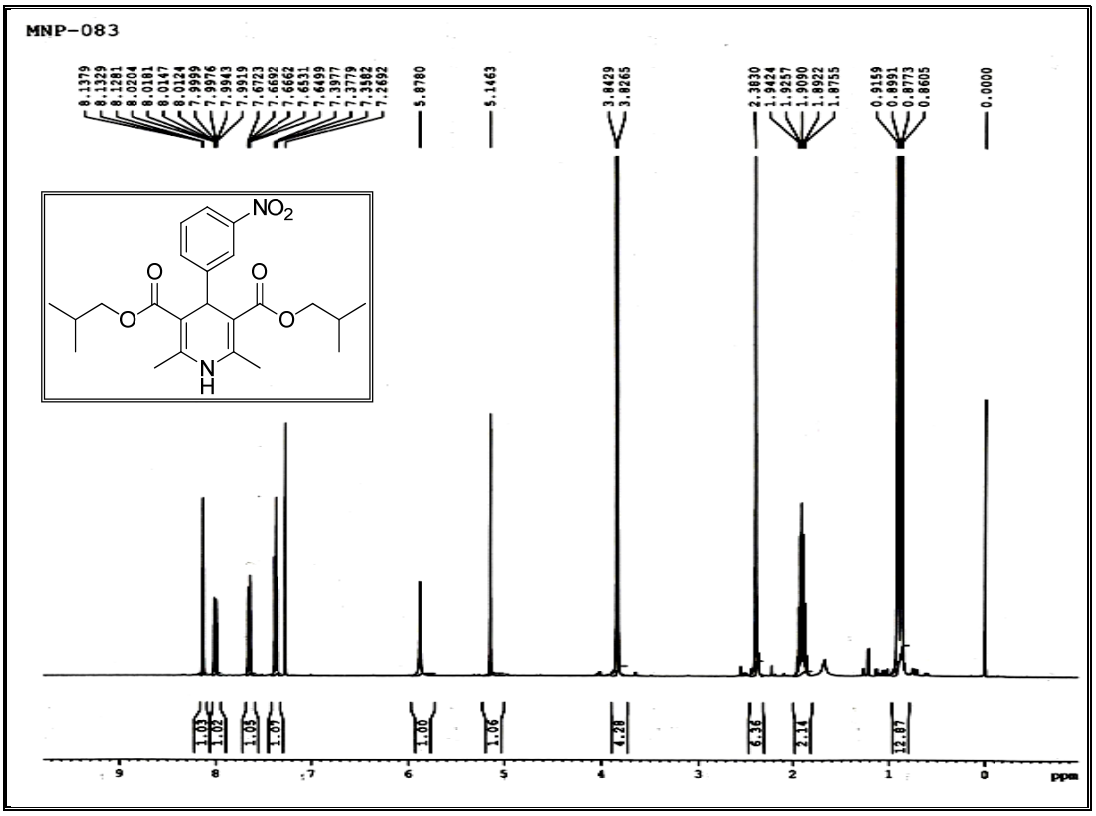
3.13.1 IR Spectrum of MNP-083



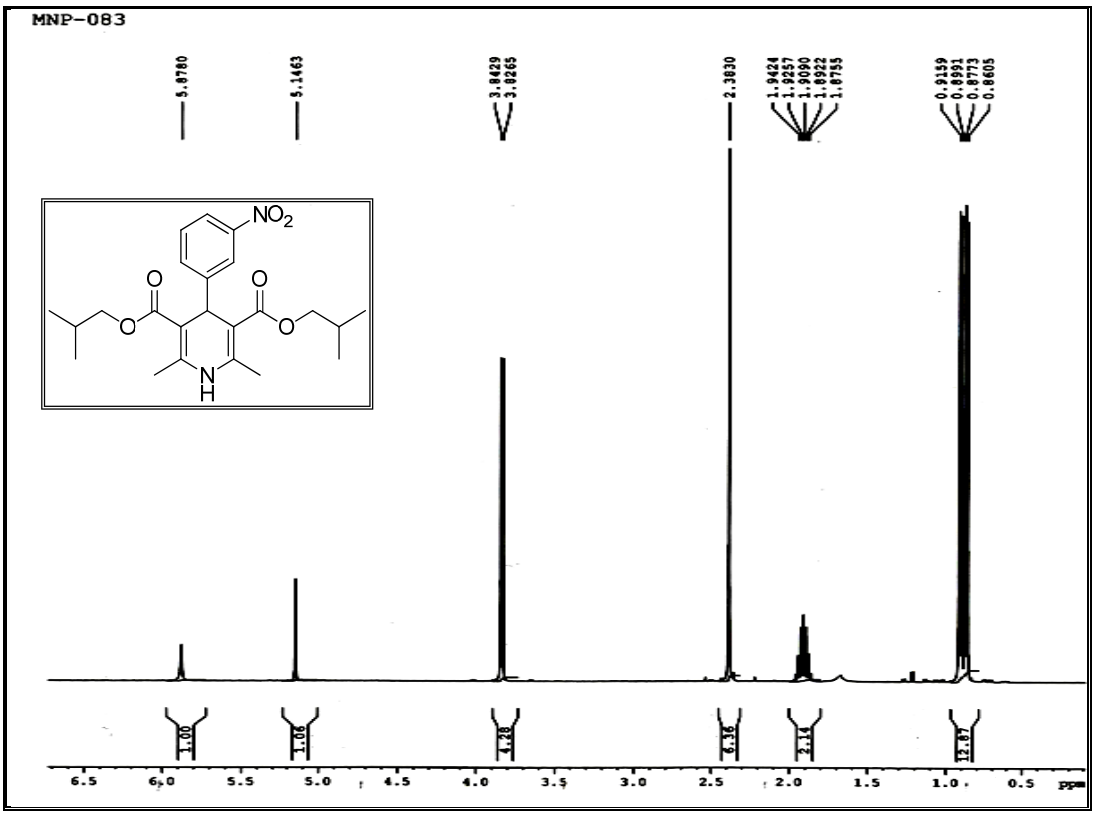
3.13.2 Mass Spectrum of MNP-083



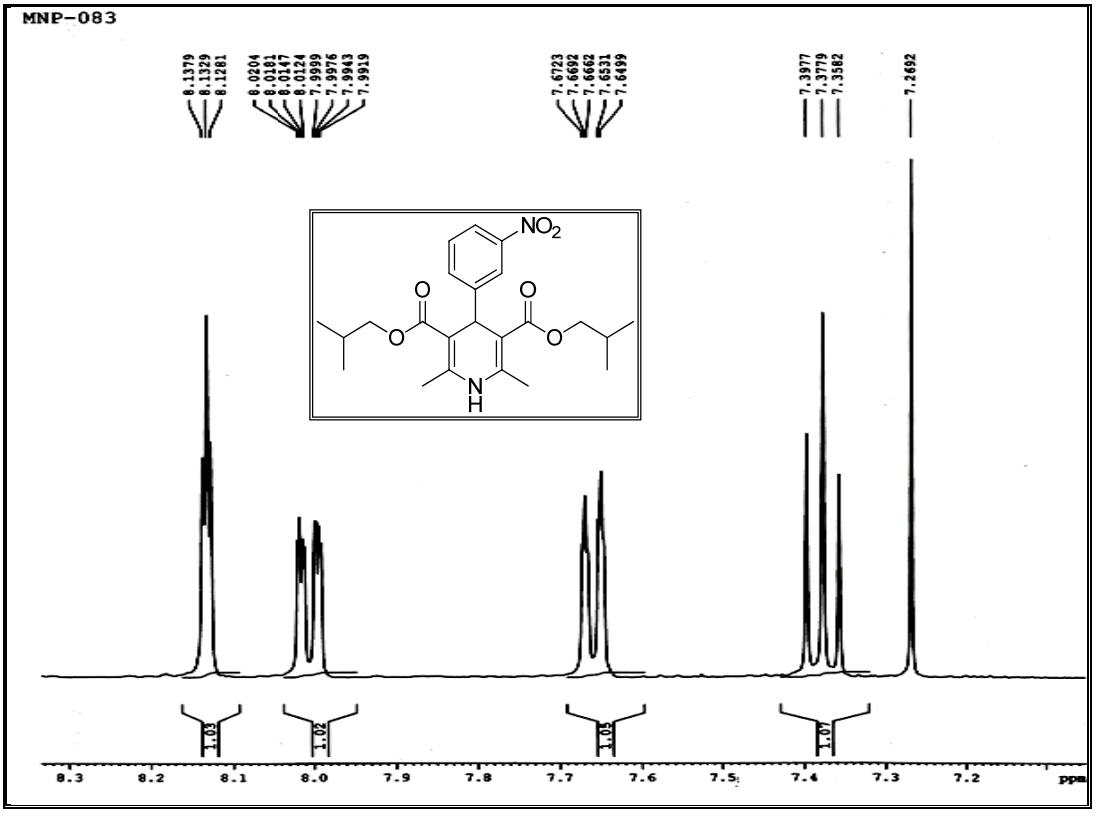
3.13.3 ^{1}H NMR Spectrum of MNP-083



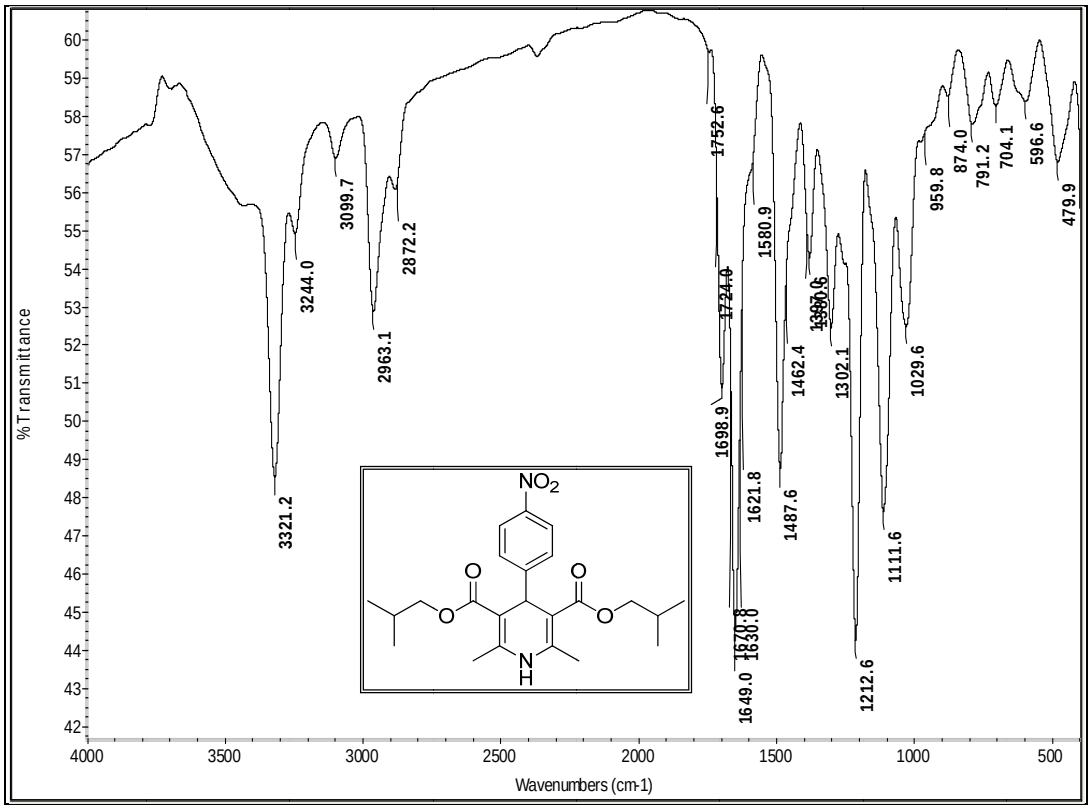
3.13.4 Expanded ^{1}H NMR Spectrum of MNP-083



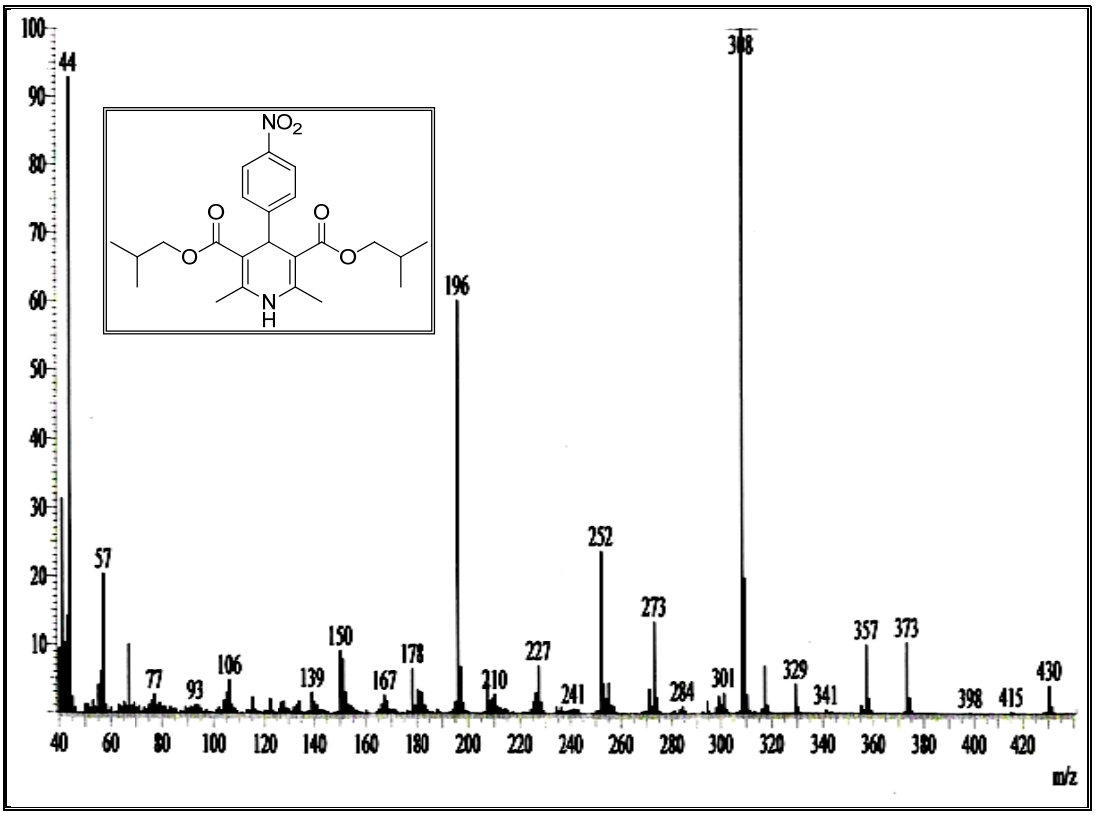
3.13.5 Expanded ^{1}H NMR Spectrum of MNP-083



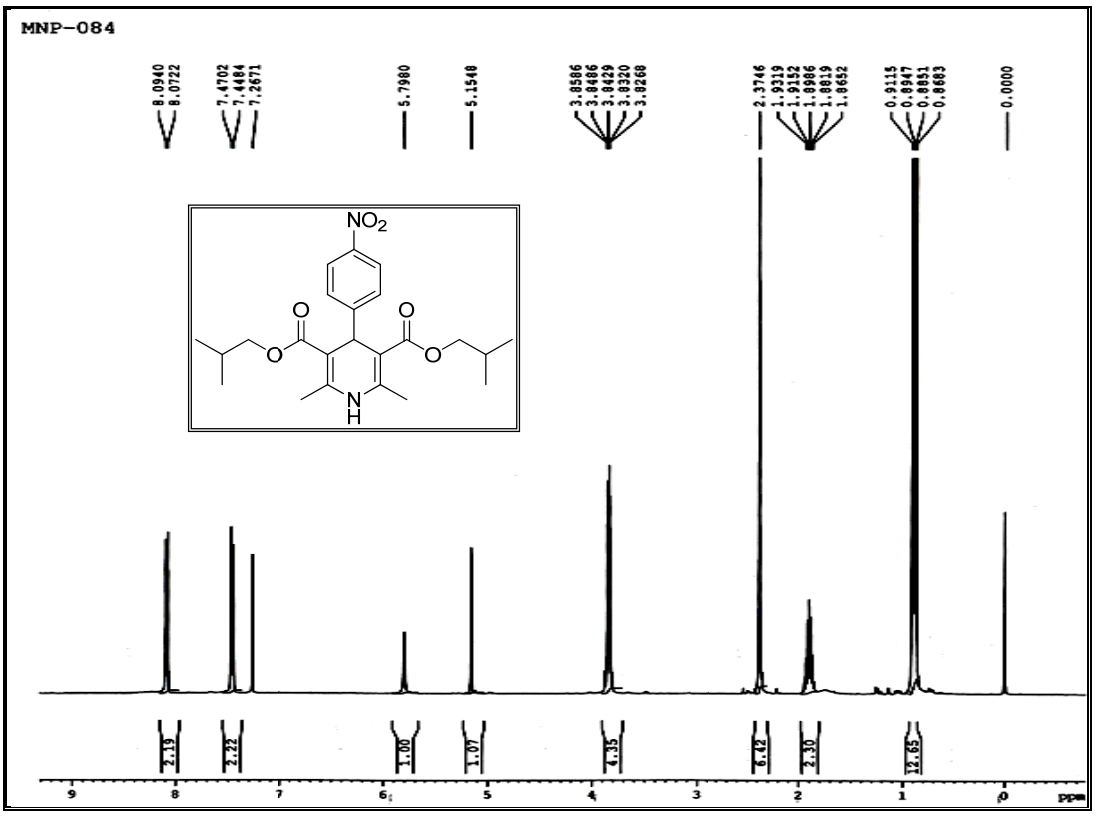
3.13.6 IR Spectrum of MNP-084



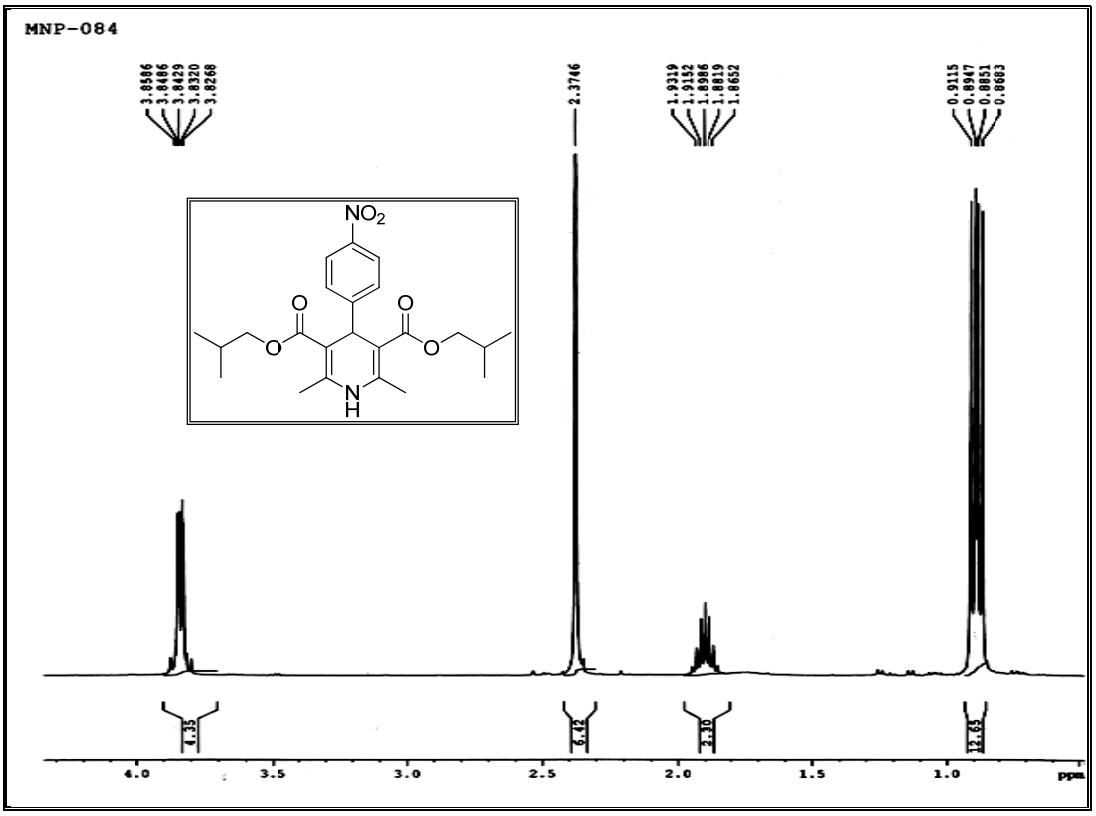
3.13.7 Mass Spectrum of MNP-084



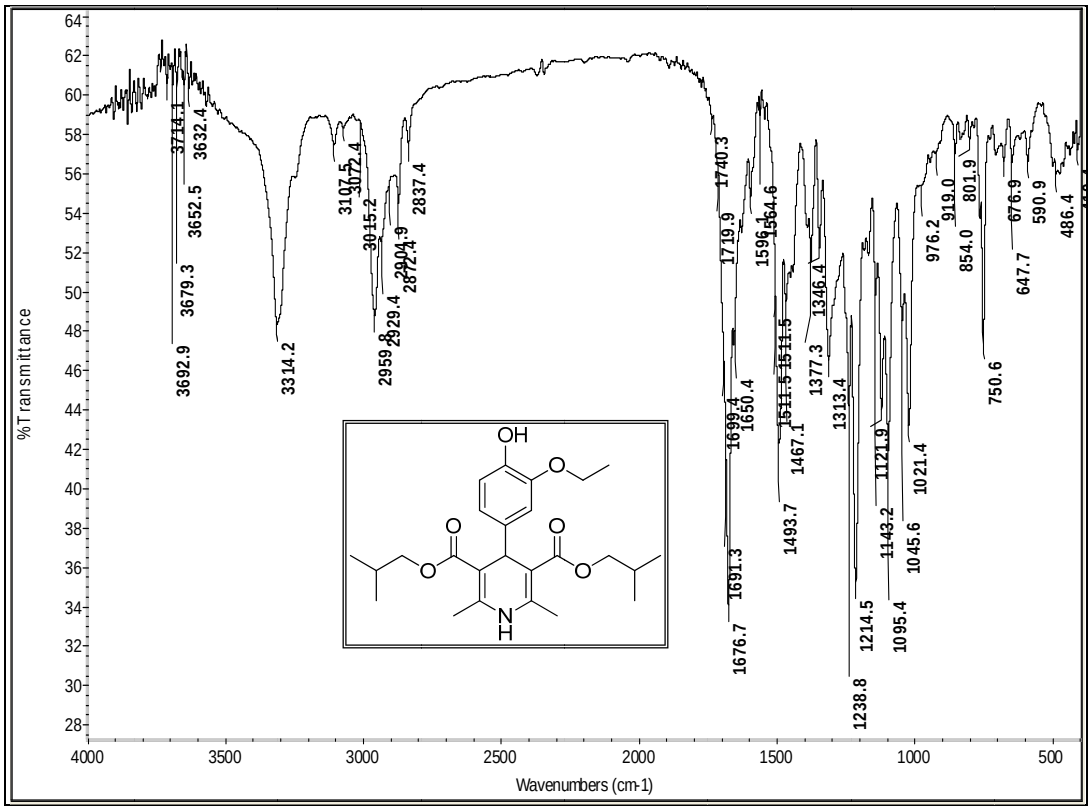
3.13.8 ^{1}H NMR Spectrum of MNP-084



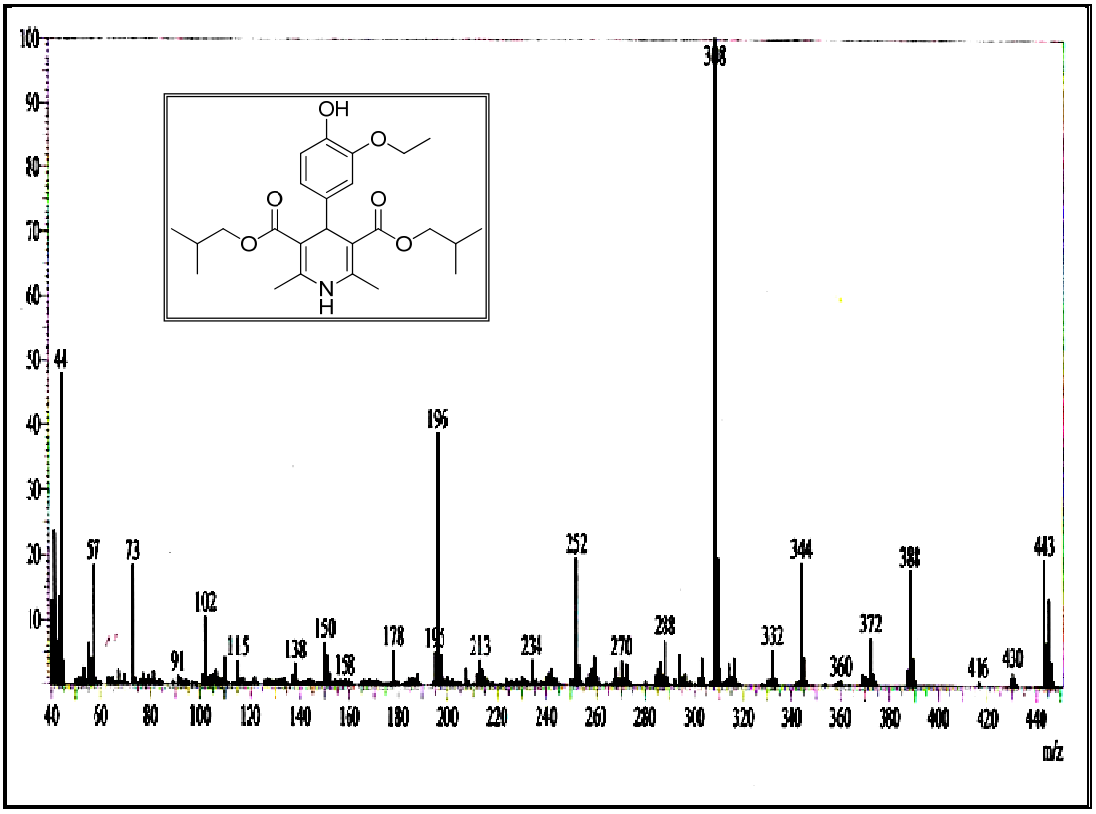
3.13.9 Expanded ^{1}H NMR Spectrum of MNP-084



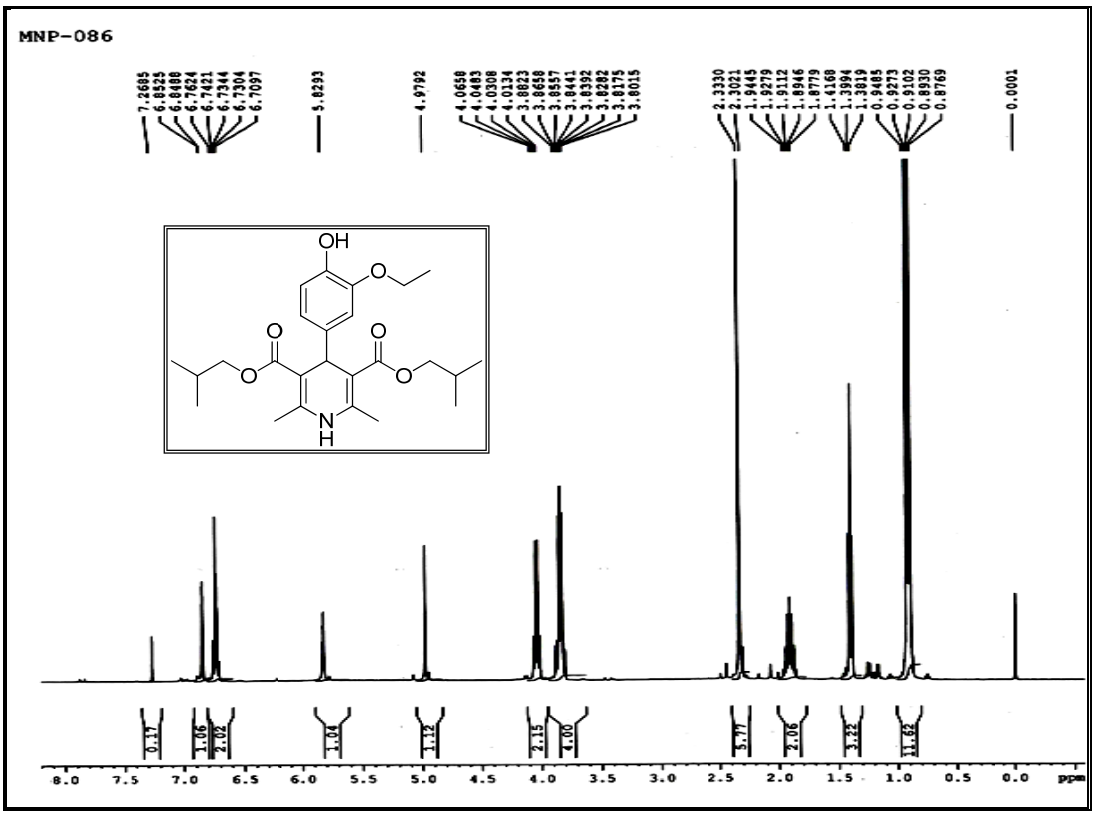
3.13.10 IR Spectrum of MNP-086



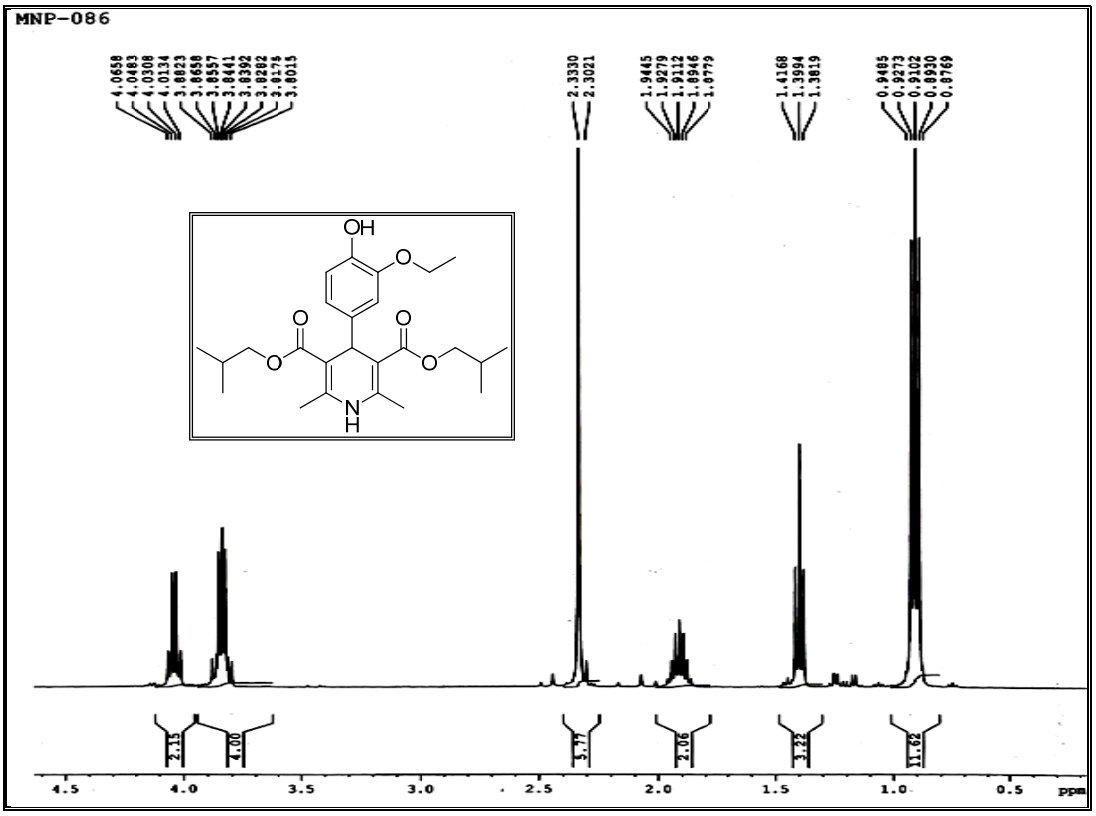
3.13.11 Mass Spectrum of MNP-086



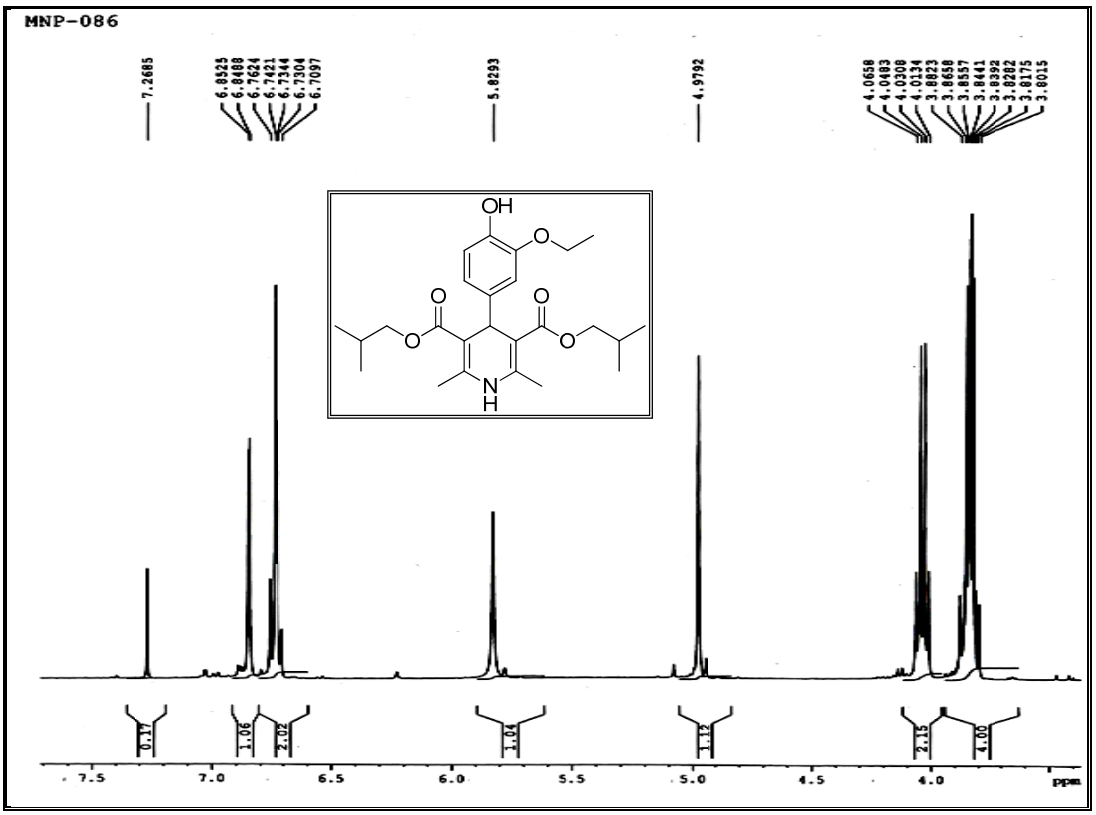
3.13.12 ^{1}H NMR Spectrum of MNP-086



3.13.13 Expanded ^{1}H NMR Spectrum of MNP-086



3.13.14 Expanded ^{1}H NMR Spectrum of MNP-086



3.14 REFERENCES

1. N. Edraki, A. R. Mehdipour, M. Khoshneviszadeh and R. Miri; *Drug Discovery Today*; 14, 21, **2009.**
2. A. Hantzsch; *Ber*.; 14, 1637, **1881**.
3. A. Hantzsch and Justus Liebigs; *Ann. Chem.*; 1, 215, **1882**.
4. M. Schramm, G Thomas and G. Franckowiak; *Nature*; 303, 535, **1983.**
5. D. Stout and A. Meyers; *Chem. Rev.*; 82, 223, **1982**.
6. R. A. Janis and D. J. Triggle; *J. Med. Chem.*; 26, 775, **1983**.
7. R. H. Bocker and E. P. Guengerich; *J. Med. Chem*.; 29, 1596, **1986**.
8. M. F. Gordeev, D. V. Patel and E. M. Gordon; *J. Org. Chem*.; 61, 924, **1996**.
9. (a) F. R. Buhler and W. J. Kiowski; *Hypertens*.; 5, S3 **1987**; (b) J. L. Reid, P. A. Meredith, and F. J. Pasanisi; *Cardiovasc. Pharmacol*.; 7, S18, **1985**.
10. C. E. Sunkel, M. F Fau de Casa-Juana, L. Santos, A. G. Garcia, C. R. Artalijero, M. Villarroya, M. A. Gonzalez-Morales, M. G. Lopez, J. Cillero, S. Alonso and J. G. Priego; *J. Med. Chem*.; 35, 2407, **1992**.
11. D. Vo, W. C. Matowe, M. Ramesh, N. Iqbal, M. W. Wolowyk, S. E. Howlett and E. E. Knaus; *J. Med. Chem*.; 38, 2851, **1995**.
12. S. F. Flaim and R. Zelis; *Fed. Proc.*; 40, 2877, **1981**.
13. B. Love, M. Goodman, K. Snader, R. Tedeschi and E. Macko; *J. Med. Chem*.; 17, 956, 1**974**.
14. F. Bossert, H. Meyer and E. Wehinger; *Angew. Chem., Int. Ed. Engl*.; 20, 762, **1981**.
15. B. G. Katzung; *Basic & Clinical Pharmacology*, (Appleton & Lange, Stamford, CT, USA); **1998**.
16. H. Satoh; *Cardiovasc. Drug. Rev*.; 9(4), 340, **1991**.
17. K. Yoshinaga; *Japan Pharmacol. Ther.*; 18, 103, **1990**.
18. F. C. Huang, G. J. Lin and H. Jones; *Eur. Pat. Appl.*; 109, 049, **1984**.
19. P. Statkow; *Eur. J. Pharmacol.,* 183(4), 173, **1990**.
20. V. V. Kastron, G. J. Dubur, V. D. Shatz and L. M. Yagupolsky; *Arzenim – Forsh.*; 35, 669, **1985**.
21. C. Semeraro, D. Micheli, D. Pieraccioli, G. Gaviraghi and A. D. Borthwick; GB Patent 2,164,336; **1986**; C.A., 105, 97322, **1986**.
22. A. Z. Mohammad and S. Maliheh; *Synlett*; 5, 827, **2004**.

23. A. Sandeep and B. Devanand; *Ukrainica Bioorganica Acta.*; 1, 3, **2006**.
24. M. F. Matloubi, H. Saeidian, Z. Mirjafary and A. Sadeghi; *J. Iran. Chem. Soc.*; 6(2), 317, **2009.**
25. L. Öhberg and J. Westmanb; *Synlett*; 8, 1296, **2001.**
26. M. Nikpassand, M. Mamaghani and K. Tabatabaeian; *Molecule*; 14, 1468, **2009**.
27. I. P. Santander-G., L. J. Núñez-Vergara, J. A. Squella and P. A. Navarrete-Encina; *Synthesis*; 18, 2781, **2003.**
28. M. A. Chari and K. Syamasundar ; *Catalysis Comm.*; 6, 624, **2005**.
29. A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati and B. Carboni; *Tetrahedron Lett.*; 50, 5248, **2009.**
30. G. Sabitha, G. S. Kiran Kumar Reddy, Ch. Srinivas Reddy and J. S. Yadav; *Tetrahedron Lett.*; 44, 4129, **2003.**
31. F. Tamaddon , Z. Razmi and A. A. Jafari; *Tetrahedron Lett.*; 51, 1187, **2010.**
32. D. B. Shinde, N. D. Shinde and M. S. Shingare; *Ind. J. Chem.*; 34B, 920, **1995**.
33. S. K. Swamy, T. M. Reddy and V. M. Reddy; *J. Pharm. Sci.*; 60 (2), 102, **1998.**
34. N. Neamati, H. Hong, A. Mazumderm and Y. Pommier; *J. Med. Chem.*; 40 (6), 942, **1997.**
35. A. Shah, H. Gevariya, N. Motohashi, M. Kawase, H. Sakagami, J. Molnar, and S. Saito; *Anticancer Research*; 20, 373, **2000.**
36. G. Gunics, S. Farkas, N. Motohashi, A. Shah, M. Kawase and J. Molnar; *International Journal of Antimicrobial Agents*; 20, 227, **2002**.
37. A. Manvar, D. Karia, V. Trangadia, N. Vekariya and A. Shah; *Organic Chemistry an Indian Journal*; 3(4), 166, **2007.**
38. G. Gunics, N. Motohashi, J. Molnar, S. Karkas, M. Kawase. S. Saito, H. Gevariya and A. Shah; *Anticancer Research*; 21, 269, **2001.**
39. A. Shah, H. Gevariya, N. Motohashi, M. Kawase, S. Saito, H. Sakagami and J. Molnar; *Bioorg.& Med. Chem.*; 10, 1051, **2002**.
40. Sufi Reza M. D. Morshed, K. Hashimoto, Y. Murotani, M. Kawase, A. Shah, K. Satosh, H. Kikuchi, H. Nishikawa, J. Maki and H. Sakagami; *Anticancer Research*; 25 (3B), 2033, **2005.**

41. S. Saponara, M. Kawase, A. Shah, N. Motohashi, J. Molnar, K. Ugocsai, G. Sgaragli and F. Fusi.; *Br. J. Pharmacol.*; 141 (3), 415, **2004.**

42. F. Fusi, S. Saponara, M. Valoti, S. Dragoni, P. D'Elia, T. Sgaragli, D. Alderighi, M. Kawase, A. Shah, N. Motohashi and G. Sgaragli; *Current Drug Targets*; 7(12), 1729, **2006**.

43. S. Saponara, A. Ferrara, B. Gorelli, A. Shah, M. Kawase, N. Motohashi, J. Molnar, G. Sgaragli and F. Fusi; *Eur. J. Pharmacol*.; 563, 160, **2007.**

44. P D'Elia, F. De Matteis, S. Dragoni, A. Shah, G. Sgaragli and M. Valoti; *Eur. J. Pharmacol*.; 614 (1-3), 7, **2009**

45. B. Desai, D. Sureja, Y. Naliapara, A. Shah and A. K. Saxena; *Bioorg. & Med. Chem.*; 9, 1993, **2001.**

46. P. S. Kharkar, B. Desai, H. Gaveria, Y. T. Naliapara, R. M. Loriya, B. V. Varu, A. Shah and V. M. Kulkarni; *J. Med. Chem.*; 45 (22), 4858, 2**002.**

47. J. Trivedi, Ph. D. Thesis, Saurashtra University, **2007**.

48. W. H. Correa and J. L. Scott; *Green Chemistry*; 3, 296, **2001**.

49. (a) B. M. Khadikar, V. G. Gaikar and A. A. Chitnavis; *Tetrahedron Lett.*; 36, 8083, **1995**. (b) L. Ohberg and J. Westman; *Synlett*; 1296, **2001**. (c) A. Agarwal and P. M. S. Chauhan; *Tetrahedron Lett.*; 46, 1345, **2005.**

50. L. Wang, J. Sheng, L. Zhang, J. W. Han, Z. Y. Fan, H. Tian and C. T. Qian; *Tetrahedron*; 61, 1539, **2005**.

51. (a) S. J. Ji, Z. Q. Jiang, J. Lu and T. P. Loh; *Synlett*; 831, **2004**. (b) R. Sridhar and P. T. Perumal; *Tetrahedron*; 61, 2465, **2005**.

52. S. R. Cherkupally and R. Mekala; *Chem. Pharm. Bull.*; 56, 1002, **2008.**

53. (a) B. Das, B. Ravikant, R. Ramu and B. V. Rao; *Chem. Pharm. Bull.*; 54, 1044, **2006.** (b) Majid M. Heravi, Khadijeh Bakhtiari, Negar M. Javadi, Fatemeh F. Bamoharram, Mina Saeedi and Hossein A. Oskooie; *Journal of Molecular Catalysis A: Chemical*; 264, 50, **2007**.

54. M. Maheswara, V. Siddaiah, G. L. V. Damu and C. V. Rao; *Arkivoc*; 2, 201, **2006.**

55. J. D. Akbari, S. D. Tala, M. F Dhaduk and H. Joshi; *Arkivoc*; 12, 126, **2008.**

56. J. Sun, Y. Dong, X. Wang, S. Wang and Y. Hu; *J. Org. Chem.*; 69, 8932, **2004**.

57. P. Phukan; *Tetrahedron Lett.*; 45, 4785, **2004**.

58. B. Ke, Y. Qin, Q. He, Z. Huang and F. Wang; *Tetrahedron Lett.*; 46, 1751, **2005**.

59. B. K. Banik, M. Fernandez and C. Alvarez; *Tetrahedron Lett.*; 46, 2479, **2005**.

60. S. Ko, M. N. V. Sastry, C. Lin and C. F. Yao; *Tetrahedron Lett.*; 46, 5771, **2005**.

61. M. A. Zolfigol, P. Salehi, A. Khorramabadi-Zad and M. Shayegh; *Journal of Molecular Catalysis A: Chemical*; 261, 88, **2007.**

62. N. N. Karade, V. H. Budhewara, S. V. Shinde and W. N. Jadhav; *Letters in Organic Chemistry*; 4, 16, **2007.**

63. A. Kumar and R. A. Maurya; *Tetrahedron*; 63, 1946, **2007.**

64. E. Wehinger, F. Bossert, W. Vater and K. Stoepel; *Ger. Offen*; 2,847, 236; C.A.; 93, 168138v, **1980.**

65. H. Meyer, F. Bossert, W. Vater, K. Stoepel and R. Towart; *Ger. Offen*; 2,845,530; C.A., 93, 150123b**. 1980**

66. K. Tsuchida, R. Yamazaki, K. Kaneko and H. Aihara; *Arzneim-Forsch. Drug Res.*; 37, 1239, **1987.**

67. B. Zhang, W. He, X. Shi, M. Huan, Q. Huang and S. Zhou; *Bioorg. & Med. Chem. Lett.*; 20, 805, **2010.**

68. M. Gordeev, D. V. Patel and E. M. Gordon; *J. Org. Chem.*; 61, 924, **1996.**

69. B. Bulbul, G. S. Ozturk, M. Vural, R. Simseka, Y. Sarioglu, A. Linden, M. Ulgen and C. Safak; *Eur. J. Med. Chem.*; 44, 2052, **2009.**

70. H. Engi, H. Sakagami, M. Kawase, A. Parecha, D. Manvar, H. Kothari, P. Adlakha, A. Shah, N. Motohashi, I. Ocsovszki and J. Molnar; *in vivo*; 20, 637, **2006.**

71. S. Bisht, N. Dwivedi and R. Tripathi; *Tetrahedron Lett.*; 48, 1187, **2007**.

72. F. Hadizadeh, Z. Fatehi-Hassanabad, M. Bamshad, H. Poorsoghat and M. Fatchi-Hassanabad; *Indian J. Chem. Section B: Org. Chem. Including Med. Chem.*; 44B (11), 2343; **2005.**

73. A. Shafiee, N. Rastkari and M. Sharifzadeh; *DARU*; 12 (2), 81, **2004.**

74. F. Hadizadeh, Z. Fatehi-Hassanabad, M. Fatehi-Hassanabad, A. Beheshtizadeh and F. Nabati; *Research in Pharmaceutical Sciences*; 2(2), 85, **2007.**

75. F. Cateni, M. Zacchigna, N. Pedemonte, L. J. V. Galietta, M. T. Mazzei, P. Fossa, M. Giampieri and M. Mazzei; *Bioorg. & Med. Chem.*; 17, 7894, **2009.**

76. M. Khoshneviszadeh, N. Edraki, K. Javidnia, A. Alborzi, B. Pourabbas, J. Mardaneh and R. Miri; *Bioorg. & Med. Chem.*; 17, 1579, **2009.**

77. A. Fassihi, Z. Azadpour, N. Delbari, L. Saghaie, H. R. Memarian, R. Sabet, A. Alborzi, R. Miri, B. Pourabbas, J. Mardaneh, P. Mousavi, B. Moeinifard and H. Sadeghi-aliabadi; *Eur. J. Med. Chem.*; 44, 3253, **2009.**

78. J. A. Berson and E. Brown; *J. Am. Chem. Soc.*; 77, 444, **1955.**

79. (a) H. Meyer, F. Bossert, W. Vater and K. Stoepl; *U.S. Publ. Appl.*; 13,503,345; C.A.; 84, 164639a, **1976;** (b) H. Meyer, F. Bossert, W. Vater and K. Stoepel; U.S. Publ. Apll.; 13, 515,642; C.A., 84, 164440, **1976;** (c) H. Meyer, F. Bossert, W. Vater and K. Stoepel; U.S. 3,935,223; C.A.,85, 21140, **1976**.

80. H. Meyer, F. Bossert, W. Vater and K. Stoepel; U.S. 3,988,458; C.A., 87, 5816, **1977**.

81. V. B. Devaru, H. C. Devrajgowda, B. H. Doreswamy, M. Mahendra, A. Shah, A. M. Anandalawar and J. S. Prasad; *Analytical Sciences*; 20, 47, **2004.**

82. H. Gaveriya, B. Desai, V. Vora and A. Shah; *Indian J. Pharm. Sci.*; 64(1), 59, **2002.**

83. R. Loriya, Ph.D. Thesis, Saurashtra University, **2001**.

84. S. Thakrar, Ph.D. Thesis, Saurashtra University, **2010.**

85. O. Sachio, M. Seishi, K. Osamu; JP, 61,186,380; **1986**; C.A., 106,32863g, **1987**

86. P. Valenti, A. Rampa, R. Budriesi, A. Bisi and A. Chiarini; *Bioorg. & Med. Chem.*; 6, 803, **1998.**

87. S. Ozbey and E. Kendi; *J. Het. Chem.*; 35, 1485, **1998**.

88. A. C. Shaikh, C. Chen; *Bioorg. & Med. Chem. Lett.*; 20, 3664, **2010.**

89. Atul Kumar, R. A. Maurya and S. Sharma; *Bioorg. & Med. Chem. Lett.*; 19 (15), 4432, **2009**.

90. M. Filipan-Litvic, M. Litvic and V. Vinkovic; *Bioorg. & Med. Chem.*; 16, 9276, **2008**.

91. M. Filipan-Litvic, M. Litvic and V. Vinkovic; *Tetrahedron*; 64, 5649, **2008.**

92. K. Parmar, Ph.D. Thesis, Saurashtra University, **1994.**

93. D. Thaker, Ph.D. Thesis, Saurashtra University, **1994.**

94. D. Sureja, Ph.D. Thesis, Saurashtra University, **1997.**

95. A. Sarvani, Ph.D. Thesis, Saurashtra University, **1997.**

96. A. Hingarajiya, Ph.D. Thesis, Saurashtra University, **1997.**

97. H. Gevariya, Ph.D. Thesis, Saurashtra University, **1999.**

98. A. Mishra, Ph.D. Thesis, Saurashtra University, **2005.**

99. H. Kothari, Ph.D. Thesis, Saurashtra University, **2005.**

100. C. Dholakiya, Ph.D Thesis, Saurashtra University, **2005**.

101. P. Adlakha, Ph.D Thesis, Saurashtra University, **2005**.

102. D. Manvar, Ph.D Thesis, Saurashtra University, **2005**.

103. R. Khunt, Ph.D Thesis, Saurashtra University, **2007**.

104. N. Vekariya, Ph.D Thesis, Saurashtra University, **2007**.

105. V. Virsodiya, Ph.D Thesis, Saurashtra University, **2007.**

106. H. C. Devaraje Gowda, M. A. Sridhar, J. Shashidhara Prasad, H. C. Gevaria and A. Shah; *Mol. Cryst. Liq. Cryst.*; 348, 301, **2000**.

107. S. Lakshmi, M. A. Sridhar, J. Shashidhara Prasad, D. Manvar, A. Parecha, G. Patel and A. Shah; *J. Anal. Sci.*; 21, 93, **2005**.

108. H. C. Devaraje Gowda, M. A. Sridhar, J. Shashidhara Prasad, H. C. Gevaria and A. Shah; *Mol. Cryst. Liq. Cryst.*; 348, 301, **2000.**

109. B. Savaliya, Ph.D. Thesis, Saurashtra University, **2011.**

110. M. Mahendra, B. H. Doreswamy, M. A. Sridhar., J. Shashidhara Prasad, D. Kinnari, M. Dinesh and A. Shah; *Acta Cryst.*; E61, 2567, **2005**.

111. S. Lakshmi, M. A. Sridhar, J. Shashidhara Prasad, D. Manvar, L. Rajesh, P. Gautam and A. Shah; *J. Anal. Sci.*; 21, 189, **2005**.

112. P. Adlakha, S. Naveen, S. Lakshmi, A. Manvar, D. Karia, A. Shah, M. A. Sridhar, J. Shashidhara Prasad; *J. Chem. Crystallography*; 39, 389, **2009.**

113. A. Trivedi, N. Gowda, Y. T. Naliapara, J. Shashidhara Prasad, M. A. Sridhar and A. Shah; *J. Chem. Cryst.*; 41, 774, **2011.**

114. M. Mahendra, B. H. Doreswamy, M. A. Sridhar, J. Shashidhara Prasad, R. P. Gautam, A. P. Jignesh and A. Shah; *J. Chem. Cryst.*; 34, 441, **2004.**

115. M. Mahendra, B. H. Doreswamy, M. Dinesh, P. Gautam, N. Yogesh, D. Kinnari, A. Shah, M.A. Sridhar and J. Shashidhara Prasad; *J. Chem. Res.*; 12, 843, **2004.**

116. A. Saini, S. Kumar and J. S. Sandhu; *J. Sci. & Ind. Res.*; 67, 95, **2008.**

117. A. Shah, J. Bariwal, J. Molnár, M. Kawase and N. Motohashi; Topics in Heterocyclic Chemistry; 15, 201, **2008.**

118. (a) T. Godfraid, R. Miller and M. Wibo; *Pharmocol. Rev.***;** 38, 321, **1986.** (b) A. Sausins and G. Duburs; *Heterocycles*; 27, 269, **1988.** (c) P. P. Mager, R. A. Coburn, A. J. Solo, D. J. Triggle and H. Rothe; *Drug Design Discovery*; 8, 273, **1992.** (d) R. Mannhold, B. Jablonka, W. Voigdt, K. Schoenafinger and K. Schravan; *Eur. J. Med. Chem.*; 27, 229, **1992**.

119. (a) V. Klusa; *Drugs Fut*.; 20, 135, **1995.** (b) R. G. Bretzel, C. C. Bollen, E. Maeser K. F. Federlin; *Am. J. Kidney. Dis.*; 21, 53, **1993**. (c) R. G. Bretzel, C. C. Bollen, E. Maeser and K. F. Federlin; *Drugs Fut.*; 17, 465, **1992.** (d) R. Boer and V. Gekeler; *Drugs Fut.*; 20, 499, **1995.**

120. B. Desai, D. Sureja, Y. Naliapara, A. Shah and A. Saxena; *Bioorg. & Med. Chem.*; 9, 1993, **2001.**

121. P. S. Kharkar, B. Desai H. Gaveria, B. Varu, R. Loriya, Y. Naliapara, A. Shah and V. M. Kulkarni; *J. Med. Chem.*; 45, 4858, **2002**.

122. A. T. Manvar, R. S. Raghuvir, R. Pissurlenkar, V. K. Virsodia, D. R. Manvar, A. K. Mishra, H. D. Acharya, A. R. Parecha, C. D. Dholakia and A. K. Shah; *Molecular Diversity*; 14 (2), 285, **2010.**

123. M. Khoshneviszadeh, N. Edraki, K. Javidnia, A. Alborzi, B. Pourabbas, J. Mardaneh and R. Miri; *Bioorg. & Med. Chem*.; 17, 1579, **2009.**

124. A. K. Chhillar, P. Arya, C. Mukherjee, P. Kumar, Y. Yadav, A. K. Sharma, V. Yadav, J. Gupta, R. Dabur, H. N. Jha, A. C. Watterson, V. S. Parmar, A. K. Prasad and G. L. Sharma; *Bioorg. & Med. Chem*.; 14, 973, **2006.**

125. P. Das, C. L. Bell-Horner, R. Q. Huang, A. Raut, E. B. Gonzales, Z. L. Chen, D. F. Covey and G. H. Dillon; *Neuroscience*; 124, 195, **2004.**

126. J. Briede, M. Stivrina, D. Stoldere, E. Bisenieks, J. Uldrikis, J. Poik˜ans, N. Makarova and G. Duburs; *Cell Biochem. Funct*.; 22, 219, **2004**.

127. S. Kobayashi, M. Fukuta, M. Suzuki, H. Tsuneki and I. Kimura; *Biol. Pharm. Bull*.; 28, 242, **2005.**

128. R. M. Kaminski, M. Mazurek, W. A. Turski, Z. Kleinrok, S. J. Czuczwar; *Pharmacol. Biochem. Behav*.; 68, 661, **2001.**

129. S. H. Yiu and E. E. Knaus; *Drug Devl. Res.*; 48, 26, **1999.**

130. W. E. Wehinger, Horst, M., Andres, K., Yoshiharu.; Ger. Offen; C.A., 107, 217482, **1987**.

131. S. Hachiro, H. Kunizo, S. Tadao, A. Hideyuki and D. Yoshihsru; EP 197, 448, **1986**; JP 68, 649, **1985**; C.A., 106, 328559, **1987**.

132. Z. M. Yan, Y. M. Dong and Y. Xuebao; EP 220, 653, **1987**; JP 253,909, **1985**; C.A., 116, 173968, **1992**.

133. F. Macro, Z. Andrea, G. Carmelo and M. Bermini; EP 272, 693; C.A., 109, 190259, **1998**.

134. R. C. Johnson, D. J. Taylor, Hann Kenneth, V. and S. Sheng; U.S. Patent 4,758,669; C.A., 109, 149366, **1988**.

135. K. Cooper, M. Jonathan Fray, M. John Parry, K. Richardson and J. Steele; *Bioorg. & Med. Chem. Lett.*; 5, 24, 3085, **1995.**

136. K. Copper, M. J. Fray, M. J. Parry, K. Richardson and J. Steele; *J. Med. Chem.*; 35, 3115, **1992.**

137. O. Dalivelya, N. Savina, T. Kuzhir, I. Buraczewska, M. Wojewódzka and I. Szumiel; *Nukleonika*; 51 (3), 141, **2006.**

138. N. I. Ryabokon, R. I. Goncharova, G. Duburs and J. Rze-szowska-Wolny; *Mutat. Res*.; 587, 52, **2005.**

139. G. Tirzitis, D. Tirzite and Z. Hyvonen; *Czech J. Food Sci*.; 19 (3), 81, **2001.**

140. C. Chang, S. Cao, S. Kang, L. Kai, X. Tian, P. Pandey, S. Fernandez Dunne, C. Luan, D. J. Surmeier and R. B. Silverman; *Bioorg. & Med. Chem.*; 18, 3147, **2010.**

141. D. Kong, Z. Yuan, X. Zhang; X. Sheng; N. Wang, S. Xing, Y. Du and L. Zhang; *Chromatographia*; 70(11/12), 1743, **2009.**

142. K. R. Rowan and E. M. Holt; *Acta Crystallographica, Section C: Crystal Structure Communications*; C52 (9), 2207, **1996**.

CHAPTER- 4

A RAPID AND FACILE SYNTHESIS OF SOME NOVEL MANNICH BASES OF DIHYDROPYRIDINES

4.1 INTRODUCTION

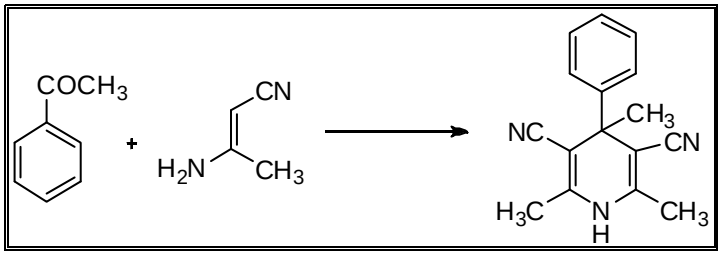
1,4-Dihydropyridine derivatives (1,4-DHPs) are versatile intermediates in organic synthesis. Moreover, compounds based on this heterocycles play key roles in therapeutic and bioorganic chemistry as calcium channel modulators. Many natural products as well as first, second, and third generation calcium channel blockers such as nifedipine, nitrendipine, felodipine, amlodipine and nisoldipine are 1,4-DHPs. [1(a)] Looking to the new findings, it is said that 1,4-DHPs belong to the class of "privileged structures" due its diversified pharmacological profile since it interact at diverse receptors and ion channels. [1(b,c)]

4.2 LITERATURE REVIEW

A) Symmetric or Asymmetric 1,4-dihydropyridines containing cyano group at 3,5 or only at 3 or 5 position

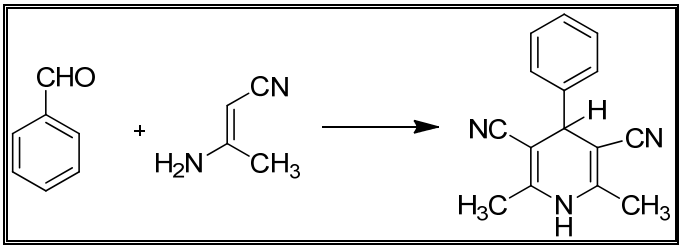
Josef *et al.* [2] prepared 3,5-dicyano-2,6-methyl-1,4-dihydopyridine by the condensation of acetone/cyclopentanone/cyclohexanone with benzoyl acetonitile. In this reaction 2,4,6-triphenyl-2-cyanomethyl-2H-pyran was also obtained in lower yields. Acetophenone when reacted [3] with 3-amino crotononitrile gave symmetric 3,5-dicyano-2,4,6-trimethyl-4-phenyl-1,4-dihydropyridine.

Scheme 4.1



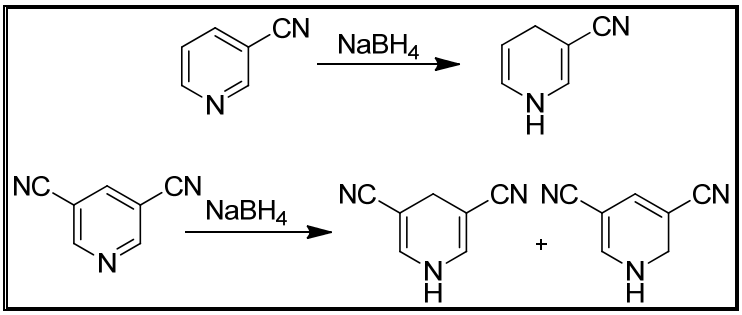
While symmetric 3,5-dicyano-1,4-dihydropyridine was prepared by the condensation of aldehyde with 3-amino crotononitrile in suitable acidic medium like acetic acid [4-6] or hydrochloric acid. [7]

Scheme 4.2



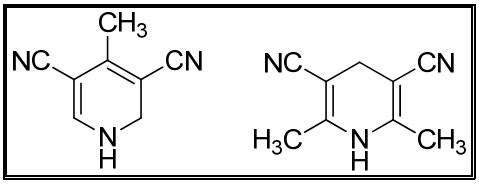
A number of dihydropyridine derivatives have been prepared by reduction of the corresponding pyridines or pyridinium salts with complex metal hydrides. [8,9]

Scheme 4.3



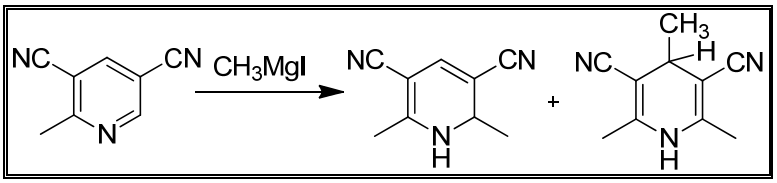
3,5-Dicyano-4-methyl pyridine and 3,5-dicyano-2,6-dimethyl pyridines afforded to give the dihydropyridine. [10]

Figure 4.1



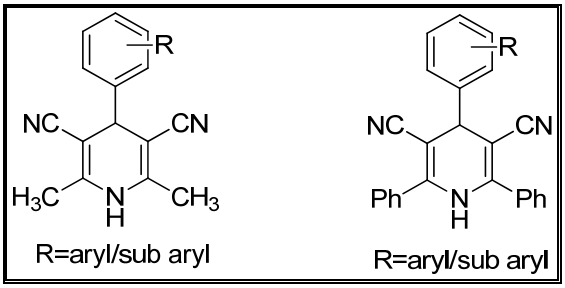
The conversion of pyridine to dihydropyridine was carried out by employing Grignard reagent such as methyl magnesium iodide. [11,12]

Scheme 4.4



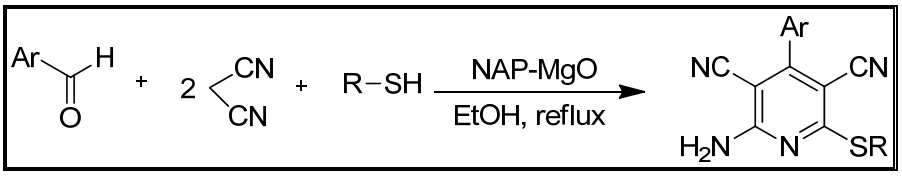
Another class of 1,4-DHPs having a cyano group at C_3 and C_5 position was prepared by Godfraind and co-workers in 1952. They have prepared 3,5-dicyano-2,6-diphenyl-4-(2-nitrophenyl)-1,4-dihydropyridine as well as 3,5-dicyano-2,6-dimethyl-4-(2-nitrophenyl) 1,4-dihydropyridine and other similar compounds. [13]

Figure 4.2



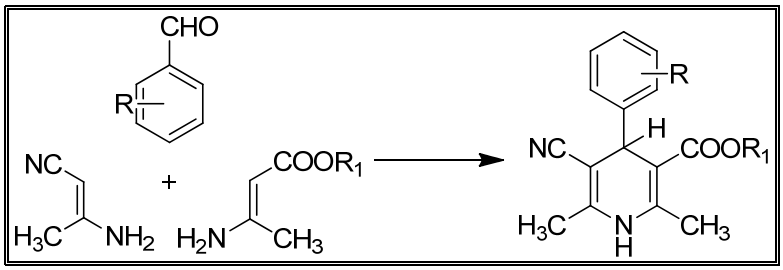
Lakshmi kantam *et al.* [14] has reported the one pot, three component synthesis of 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines and the corresponding 1,4-dihydropyridines are from readily accessible starting materials. Heating of an ethanolic solution of structurally diverse aldehydes with various thiols and malononitrile in the presence of nanocrystalline magnesium oxide provides the highly substituted pyridine derivatives in moderate to high yields, each representing a privileged medicinal scaffold with their structural motif. After completion of the reaction, the catalyst can be recovered efficiently and reused with consistent activity.

Scheme 4.5



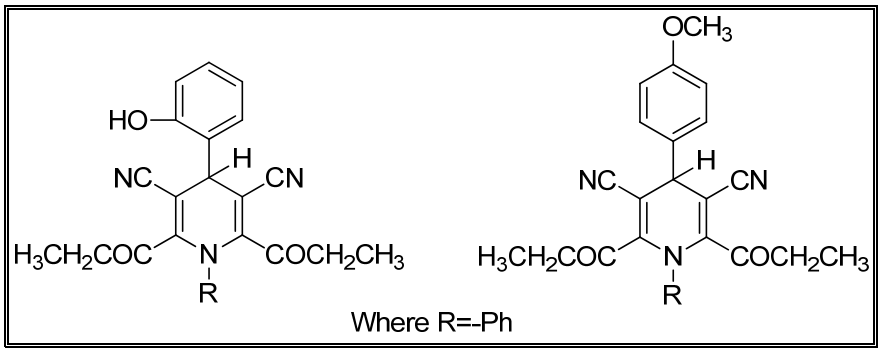
The unsymmetric [15-20] 3-cyano-5-carboxy ester 1,4-diydrpyridine was prepared by condensation of aldehyde, 3-aminocrotononitrile with alkyl 3-aminocrotonate.

Scheme 4.6



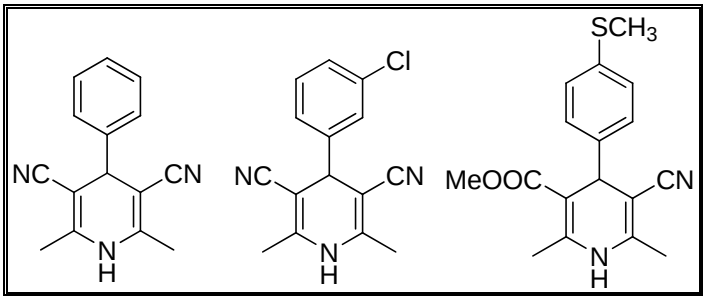
Earlier Shah *et al.* [21] prepared many cyano-1,4-dihydropyridines. From that compounds, 3,5-dicyano-2,6-diethoxy-4-(2-hydroxy phenyl)-N-(2-pyridyl)-1,4-dihydropyridine showed good anti-inflammatory activity and also showed moderated increase in blood pressure at 1 Mg/kg and 5 Mg/kg. Another compounds showed moderate hypotensive activity.

Figure 4.3



Shah *et al.* [22-25] also reported a series of symmetric as well as asymmetric synthesis of 1,4-dihydropyridines containing cyano group at C_3/C_5 position. Some of the synthesized compounds were well characterized by single crystal X-ray crystallographic study.

Figure 4.4



Shah and co-workers have prepared some pyrazole containing 3,5-dicyano as well as asymmetric 1,4-dihydropyridines containing cyano group at C_3/C_5 position. X-ray crystallographic study of 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile has been carried out. [26]

Scheme 4.7

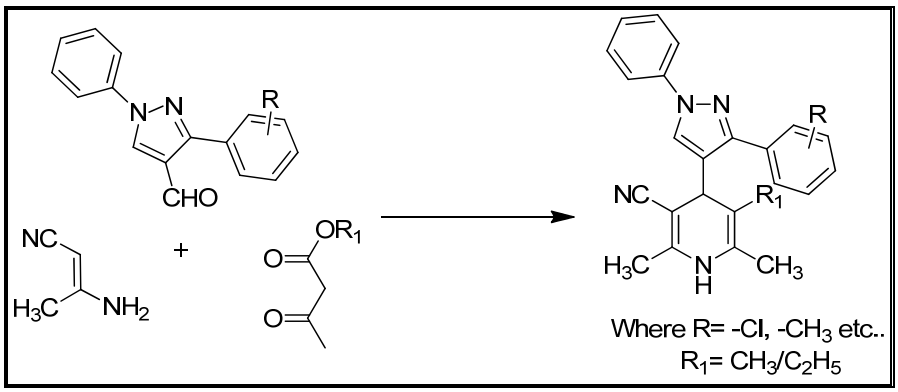
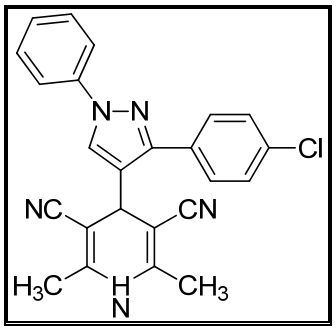
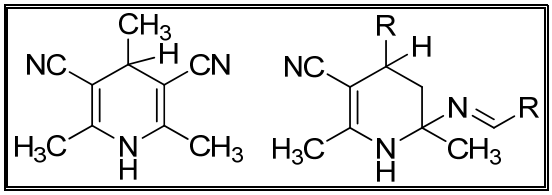


Figure 4.5



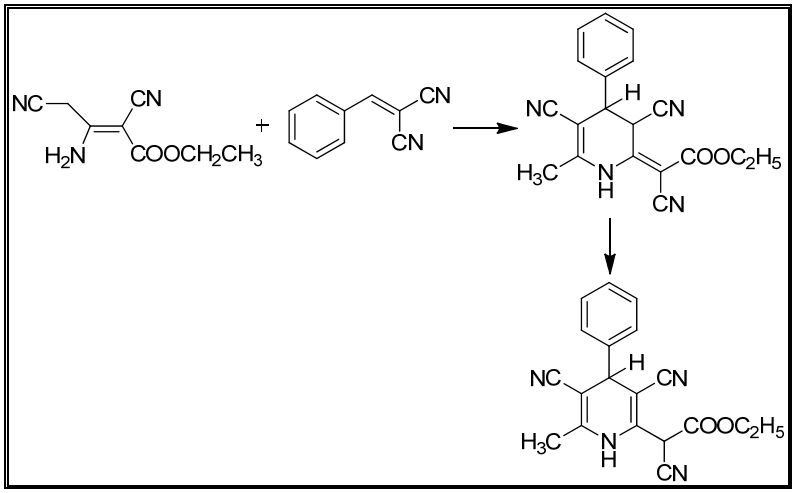
The preparation of Hantzch type 3,5-dicyano-1,4-dihydropyridine is sometimes reported via formation of tetrahydropyridine, which are isolated at room temperature in the presence of ammonium acetate. [27]

Figure 4.6



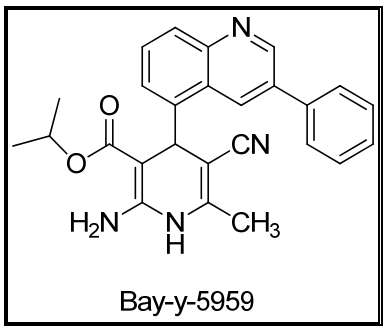
A novel synthesis of polyfunctionally-substituted pyridine was reported by Fahmy and co-workers. [28] During this reaction, sometimes the formation of tautomer was also reported.

Scheme 4.8



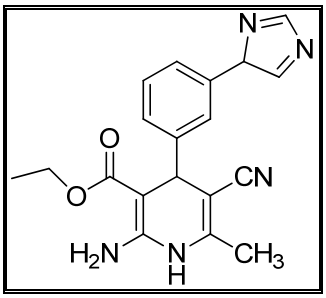
A new positive inotropic agent with high cardio selectivity, found in Bay-y-5959 with calcium channel-modulating activity and devoid of vasoconstricting effects. Compound increased dP/dt max by up to 300% at 30-1000mcg/kg i.v. in dogs, and it increased coronary blood flow at all doses was reported and currently undergoing phase II trials for the treatment of congestive heart failure. [29]

Figure 4.7



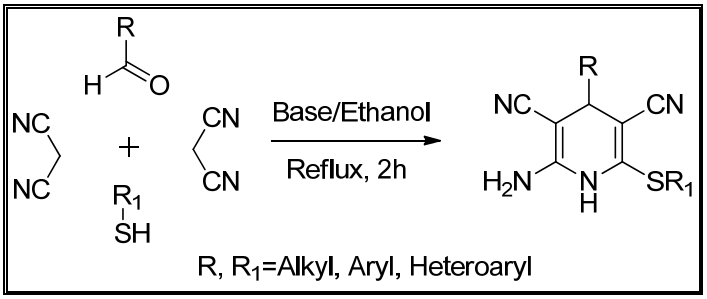
Antineoplastic agent, (FCE-29013) an aromatase inhibitor (IC_{50} = 1.5 nM against human placental enzyme) found to be potentially useful for the treatment of estrogen-dependent tumors and prostatic hyperplasia. [30]

Figure 4.8



Nikolai M. Evdokimov *et al.* [31] reported one step three component synthesis of pyridine and 1,4-dihydropyridines.

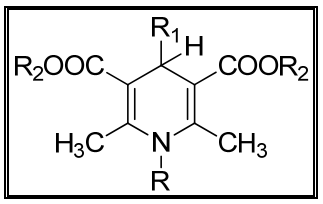
Scheme 4.9



B) N-Substituted 1,4-dihydropyridines

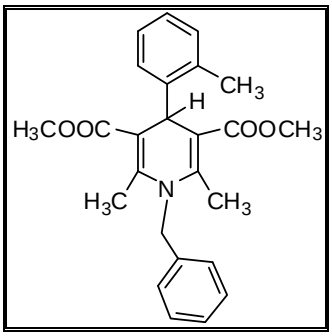
Bossert *et al.* [32-35] prepared many N-substituted 1,4-dihydropyridine derivative by Hantzsch reaction of an amine, acetoacetic ester and an aldehyde, where the condensation also proceeded in ethyl alcohol instead of pyridine.

Figure 4.9



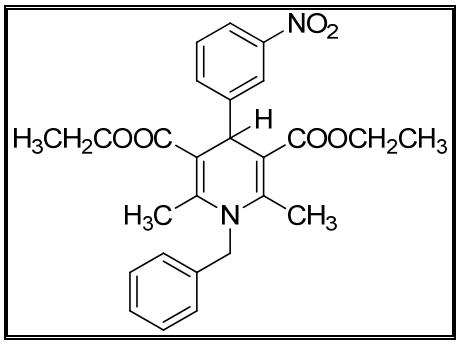
Pitzenberger *et al.* [36] investigated similar analogs in which benzyl amine reacted with acetoacetic ester and via formation as titan amine complex, leading to usual Hantzsch synthesis.

Figure 4.10



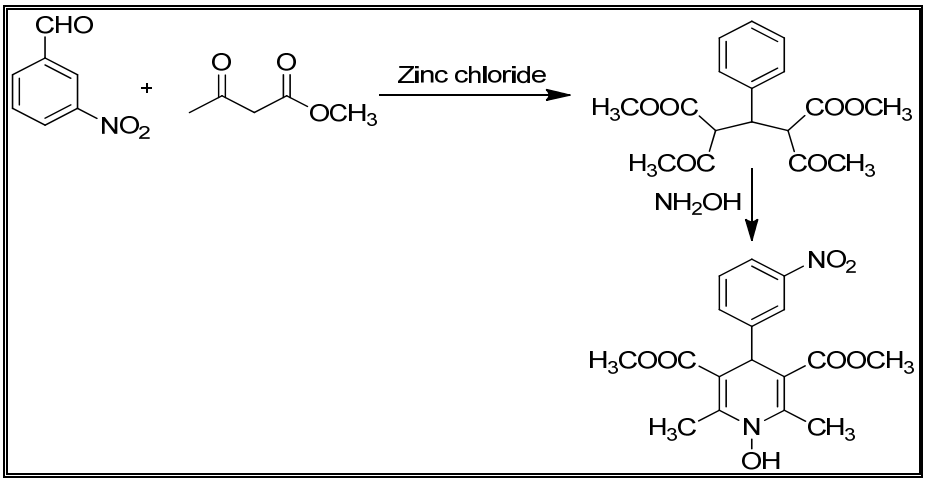
Duburs *et al.* [37] gave synthesis of N-benzyl-2,6-dimethyl-4-(3-nitro phenyl)- 3,5-dicarbethyoxy-1,4-dihydropyridine by the condensation of m-nitro benzaldehyde with ethyl acetoacetate and benzyl amine using pyridine as a solvent.

Figure 4.11



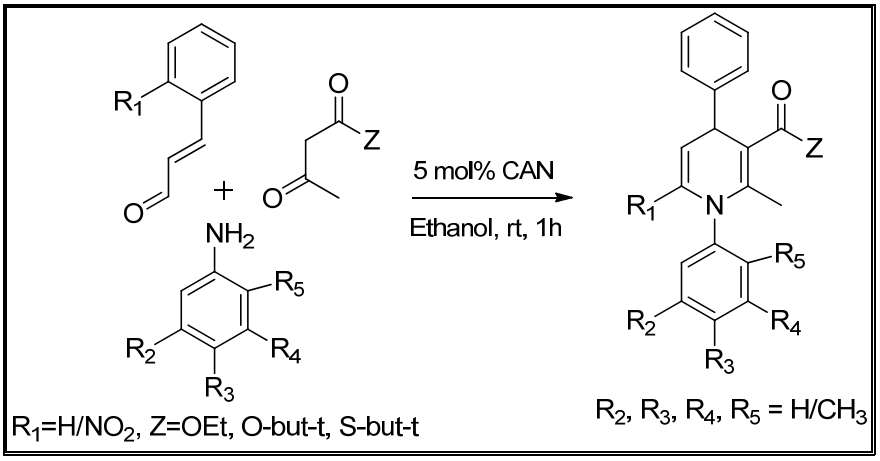
Minoru *et al.* [38] prepared N-phenoxy-1,4-dihydropyridine by the reaction of m-nitro benzaldehyde and methyl acetoacetate in the presence of zinc chloride in ethyl acetate at room temperature for 65 minutes, then at 60-65 ºC for 6 hours to give heptadione, which was cyclized with hydroxylamine in methanol at room temperature.

Scheme 4.10



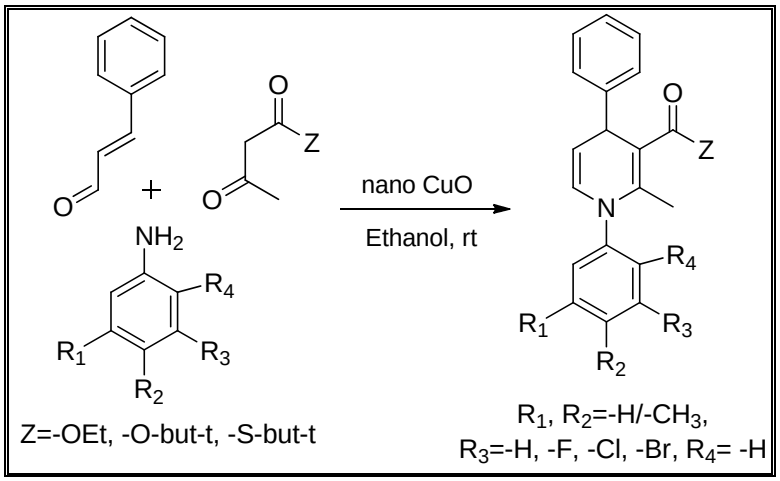
V. Sridharan *et al.* [39] described a new three-component domino synthesis of N-substituted 1,4-dihydropyridines.

Scheme 4.11



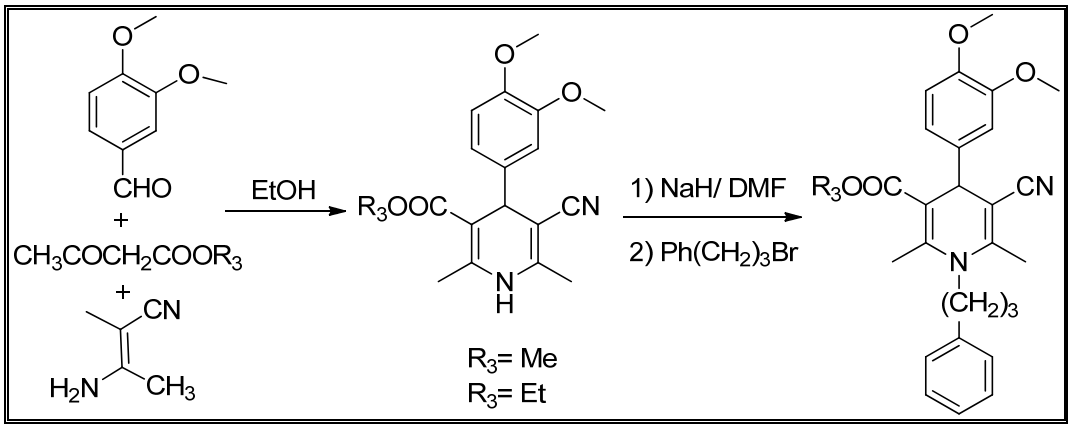
Lakshmi Kantam [40] synthesized 1,4-dihydropyridine derivatives using nano crystalline copper(II) oxide catalyst.

Scheme 4.12



Koji Ohsumi *et al*. [20] also reported N-alkylated 1,4-dihydropyridines and their ability to overcome Multidrug Resistance (MDR) was examined.

Scheme 4.13



Shah *et al.* [41-46] reported various N-substituted 1,4-dihydropyridines to investigate its manifold medicinal utility. Some of them are well characterized by single crystal X-ray crystallographic study also.

Scheme 4.14

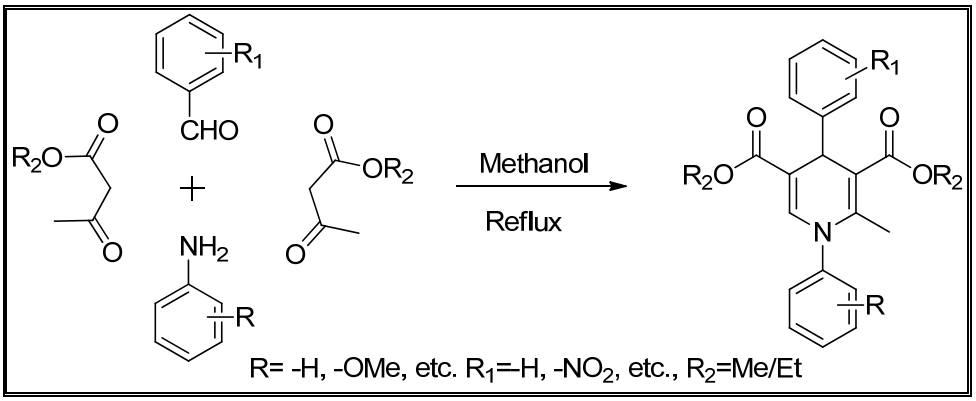
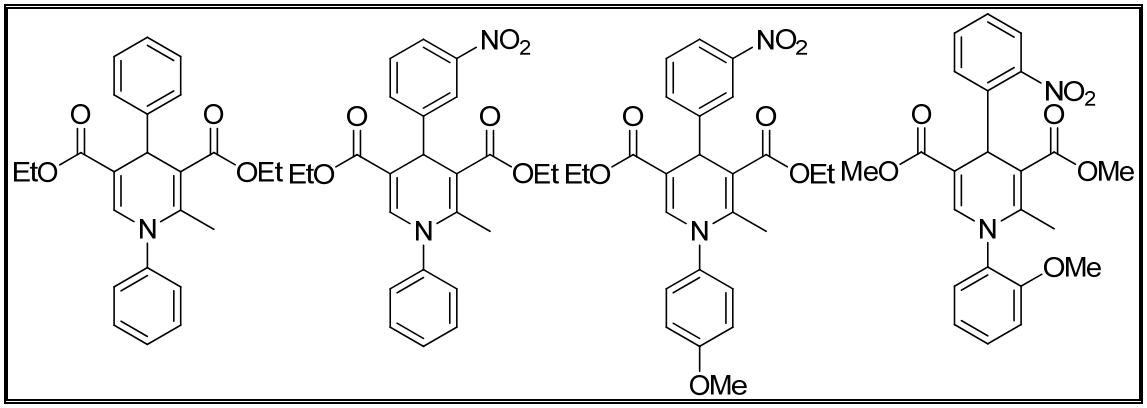


Figure 4.12



C) 1,4-dihydropyridines and Mannich reaction

The **Mannich reaction** is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound also known as a 'Mannich Base'. Mannich bases are of particular in interest due to their application as synthetic building blocks and precursors of biologically active compounds. The reaction is named after chemist Carl Mannich. [47]

The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the schiff base. The schiff base is an electrophile which reacts in the second step in an electrophilic addition with a

compound containing an acidic proton (which is, or had become an enol). [48] The Mannich reaction is also considered a condensation reaction. The Mannich Reaction is an important carbon-carbon-bond forming reaction that is commonly employed in the synthesis of alkaloid natural products and is involved in a number of biosynthetic pathways. Numerous examples of both direct and indirect Mannich reactions have been reported in the literature, some of recent are sited in reference. [49-75]

Few references are found related to Mannich reaction of 1,4-dihydropyridines. Some of them are enlisted below.

Jiro Aritomi *et al.* [76-77] reported Mannich reaction of dialkyl 4-aryl-2,6-dimethyl 1,4-dihydropyridine-3,5-dicarboxylates with secondary amines and found that the reaction proceeds on the 2- and 6- methyl carbon.

Figure 4.13

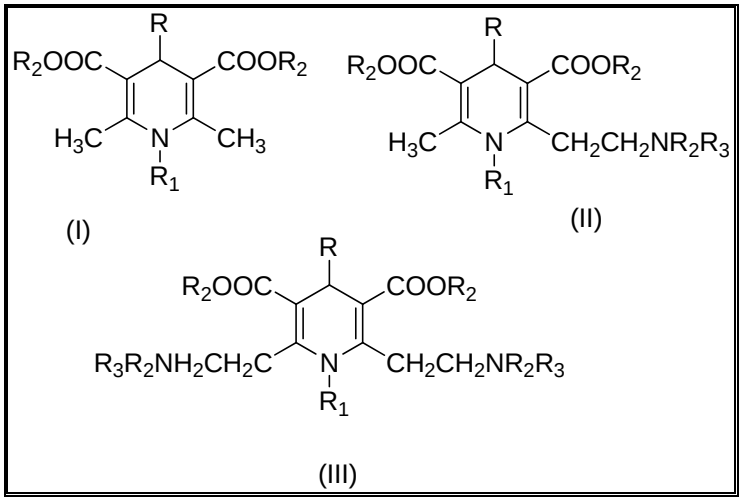
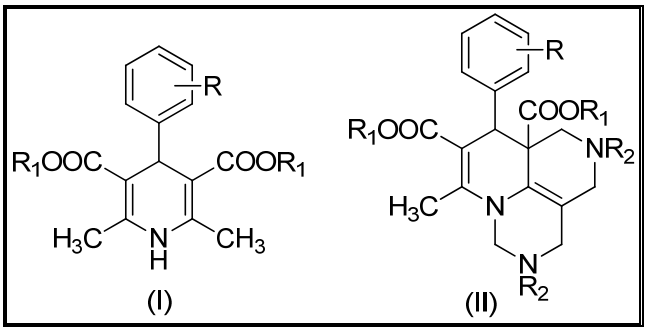


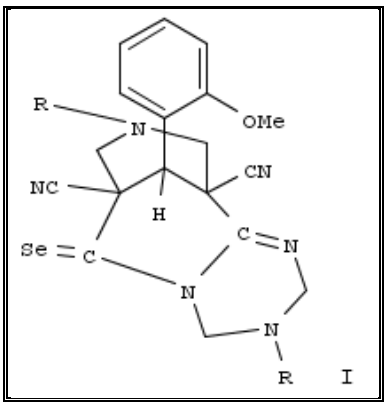
Figure 4.14



V. V. Dotsenko *et al.* [78,79] reported the reactions of *N*-methylmorpholinium 6-amino-3,5-dicyano-1,4-dihydropyridine-2-thiolates with formaldehyde and primary aromatic amines produce 3,5,7,11-tetraaza-tricyclo[7.3.1.02,7]tridec-2-ene-1,9-dicarbonitrile derivatives.

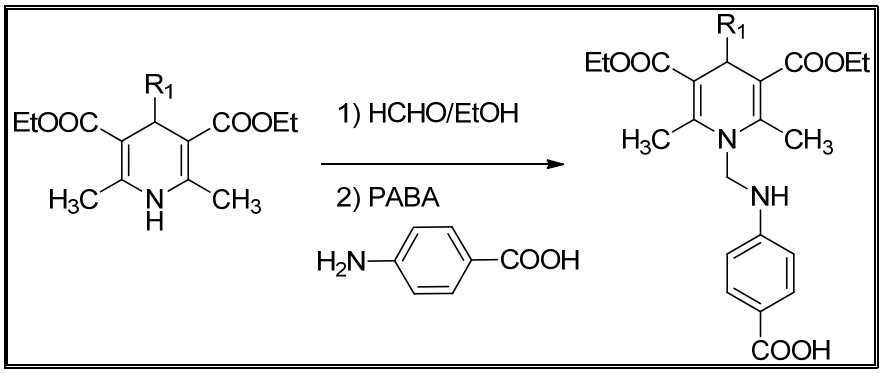
K. A. Frolov *et al.* [80] gave synthesis of derivatives of 3,5,7,11-tetraazatricyclo-[7.3.1.02,7]tridec-2-ene-8-selenone yield by Mannich reaction of N-methyl-morpholinium 6-amino-3,5-di-cyano-4-(2-methoxy phenyl)-1,4-dihydropyridine-2-selenolate with primary amines and excess HCHO.

Figure 4.15



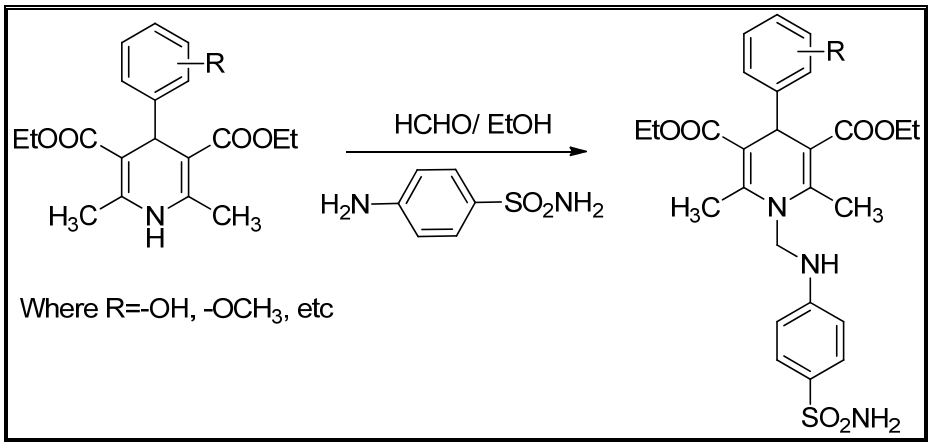
M Vijey Aanandhi *et al.* [81] demonstrated synthesis, characterization and *in-vitro* antioxidant activity of Mannich bases of 1, 4-dihydro pyridines derivatives**.**

Scheme 4.15



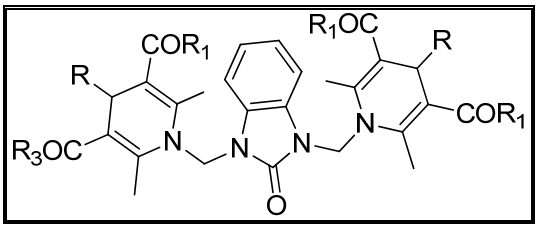
B. B. Subudhi *et al.* [82] reported synthesis and anti-ulcer activity study of 1,4-dihydropyridines and their Mannich bases with sulfanilamides.

Scheme 4.16



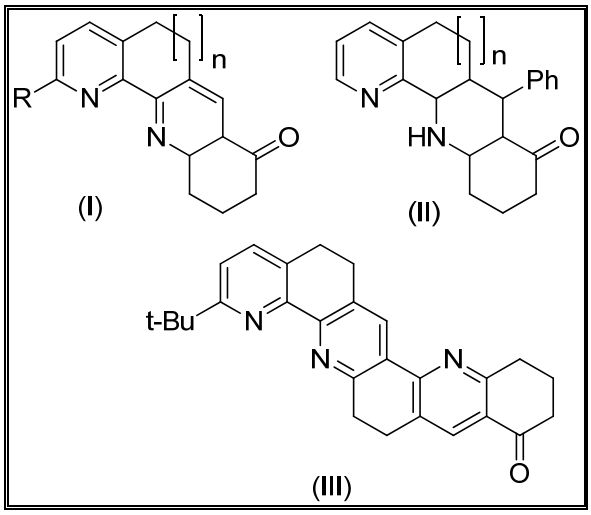
Mane D. V. *et al.* [83] synthesized 1,3-Bis- [N-substituted dihydropyridine methylc]-benzimidazoline-2-thiones I (R= Ph, substituted phenyl; R_1 = Me, OMe, OEt) from benz-imidazoline-2-thione, various dihydropyridines and paraformaldehyde by Mannich reaction and screened for their antimicrobial activities.

Figure 4.16



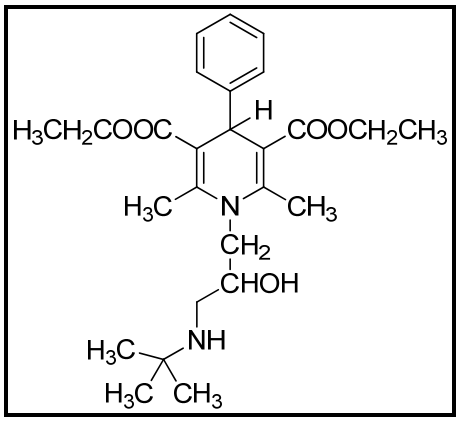
Sielemann Dirk *et al.* [84] gave synthesis of novel functionalized bi- and oligopyridines. An annelation reaction is presented in which 1,3-cyclohexanedione and Mannich bases derived thereof are used for the preparation of functionalized bipyridines I (R = H, n = 1; R = H, n = 0; R = CMe3, n = 1) and dihydropyridine derivatives II (n = 0, 1). All these products possess a keto group which will allow further transformations. The same concept was applied for the synthesis of the S-shaped terpyridine III. The reaction of a Mannich base derived from 1,2,3,4,5,6,7,8-octahydro-4,5-acridinedione with 1,3-cyclohexanedione yielded a heptacyclic terpyridine, which is a key intermediate for the synthesis of torands and other tridentate clefts. Ketone I (R = H, n = 1) was used for the synthesis of a quaterpyridine.

Figure 4.17



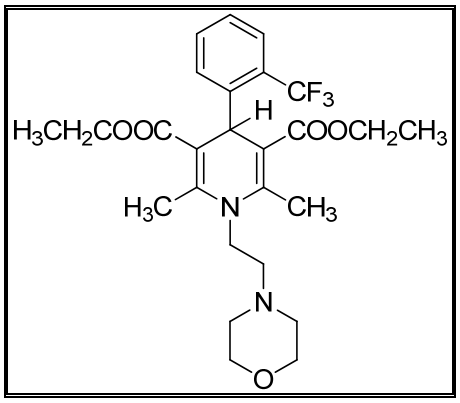
Apart from these, Michael *et al.* [85] prepared antihypertensive and coronary vasodilator Mannich type N-substituted -1,4-dihydropyridine.

Figure 4.18



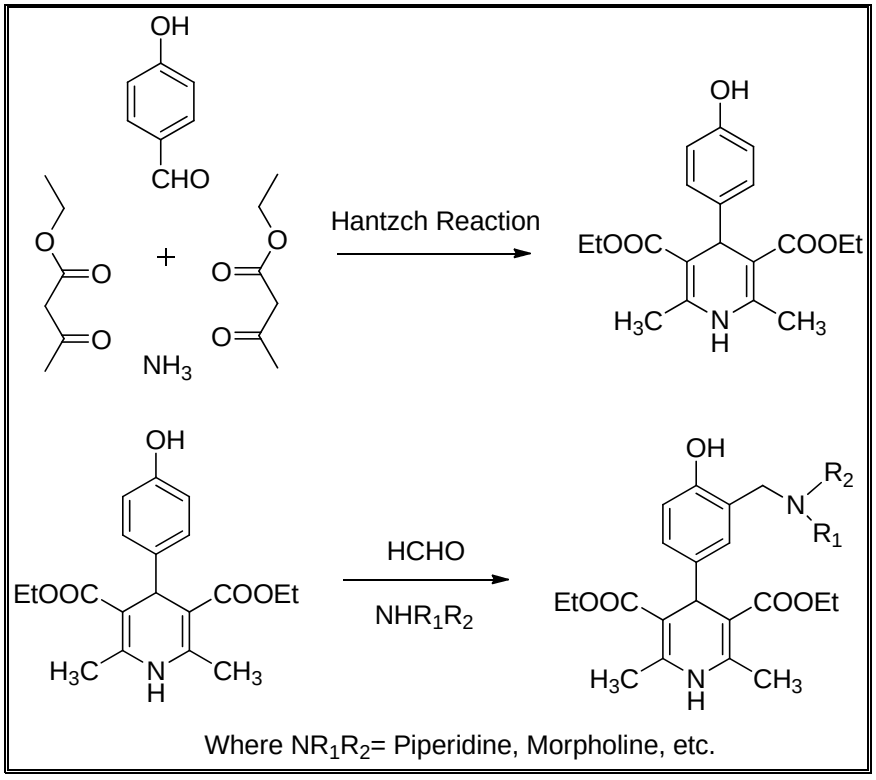
Hung *et al.* [86] were successful in synthesizing antihypertensive model of Flordipine, contrary to the belief proposed by Triggle that N-substituted 1,4-dihydropyridine will not give good antihypertensive activity, probably the concept of prodrug would not have been predicted at that time and –NH was believed to be essential for calcium channel antagonism.

Figure 4.19



Earlier, Arthur P. Philips [87,88] reported Mannich bases derived from a Hantzsch pyridine synthesis products. Use of Mannich reaction on a phenolic Hantzsch synthesis product afforded an alternative type of compound containing a basic chain. [89]

Scheme 4.17



4.3 PHARMCOLOGICAL SIGNIFICANCE

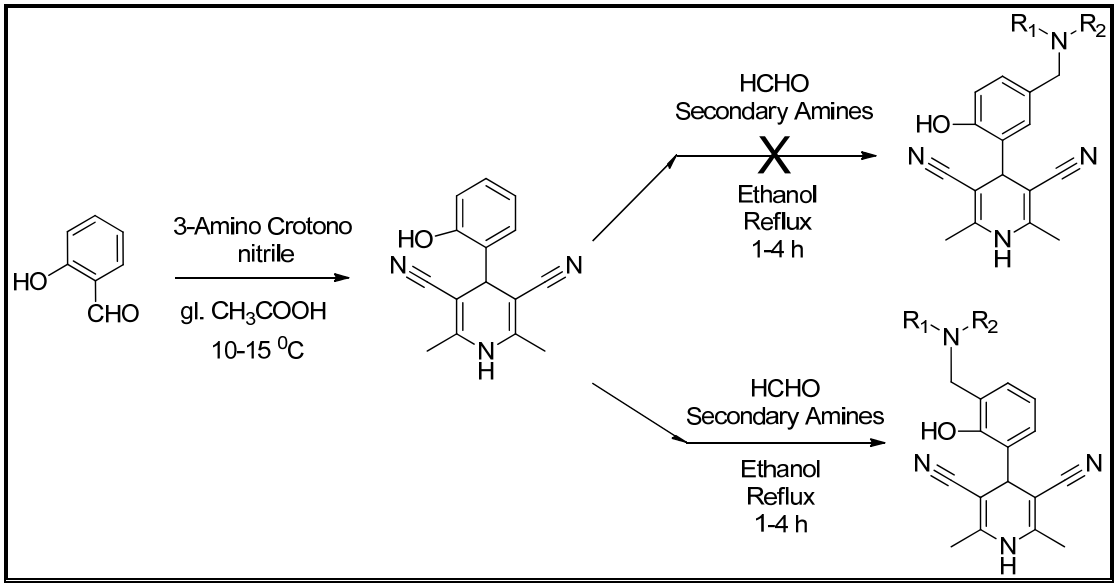
The pharmacological activity of these new Mannich bases will be of immense interest, as these molecules are “Priviledge Structure” class targeting many receptor sites.

4.4 AIM OF CURRENT WORK

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are well known as Ca2+ channel blockers, and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension. The DHP heterocyclic ring is a common feature of various bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, hepatoprotective and antidiabetic agents. Recent studies have revealed that 1,4-DHPs exhibit several other medicinal applications which include neuroprotectant and platelet anti-aggregratory activity, in addition to acting as a cerebral antiischemic agent in the treatment of Alzheimer's disease and as a chemosensitizer in tumor therapy. These examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database found the DHP framework to be among the most prolific chemotypes found. Thus, the synthesis of the New Chemical Entities containing this heterocyclic nucleus is of continuing interest.

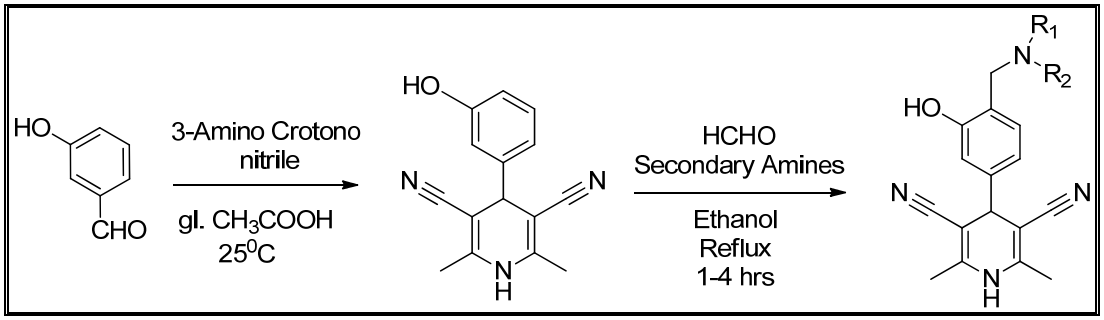
4.5 REACTION SCHEME

4.5.1 Preparation of 4-(2-Hydroxy-3-(substitued-1-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile



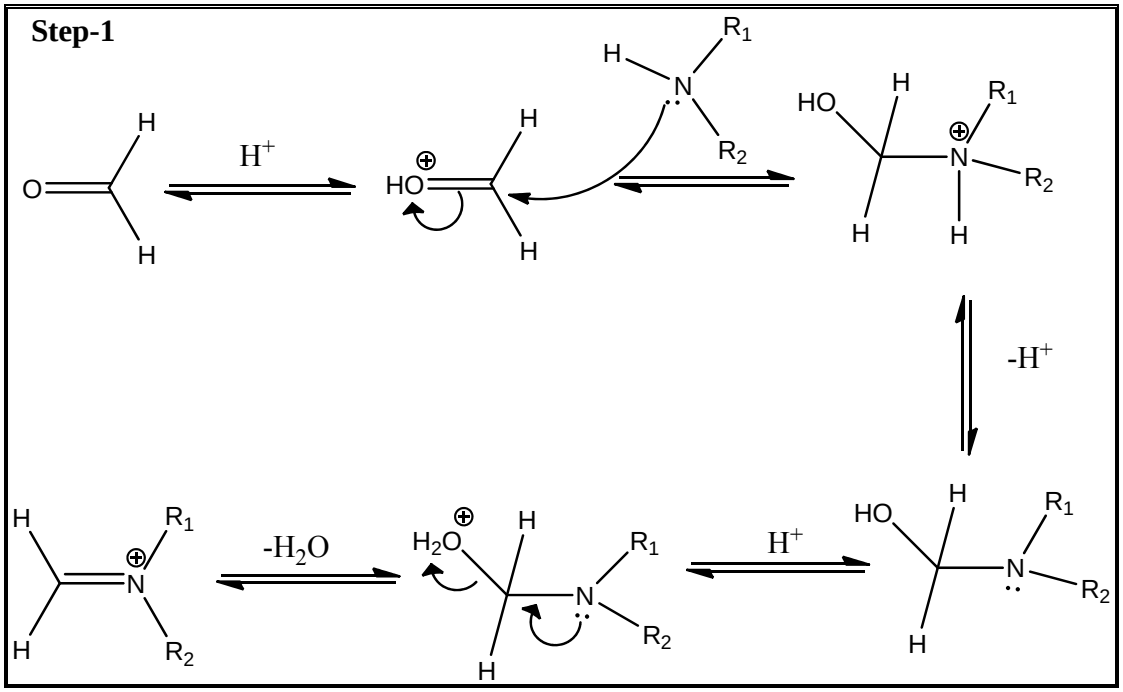
Where NR_1R_2= Secondary amines like piperidine, morpholine etc.

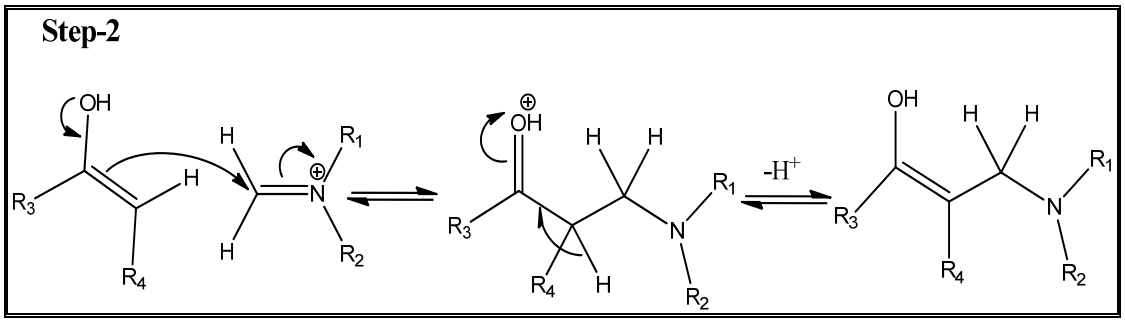
4.5.2 Preparation of 4-(3-Hydroxy-4-(substitued-1-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile



Where NR_1R_2= Secondary amines like piperidine, morpholine etc.

4.6 PLAUSIBLE REACTION MECHANISM





Where, NR_1R_2 = Secondary amines like morpholine, piperidine

R_3 & R_4 = Phenyl ring

4.7 EXPERIMENTAL

4.7.1 Analysis Protocol

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr Powder method. Mass spectra were recorded on **Shimadzu GC-MS-QP-2010** model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6/$CDCl_3$ solution on a **Bruker Avance II 400 MHz NMR Spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model. All the results are in agreements with the structures assigned.

4.7.2 Preparation of 4-(2-Hydroxy phenyl)-2,6-di-methyl-1,4-dihydropyridine-3,5-dicarbonitrile

A mixture of 2-hydroxy benzaldehyde (0.01 mole) and 3-amino crotononitrile (0.02 mole) was taken in glacial acetic acid in a stoppered flask and stirred for 1 hour at 10-15 ºC. During the reaction, progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After the completion of the reaction, the crystalline product was separated out which was filtered and washed with diethyl ether.

4.7.3 Preparation of 4-(2-Hydroxy-3-(substitued-1-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (General Procedure)

A mixture of 4-(2-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (0.01 mole), secondary amine (0.0135 mole) and formaldehyde (0.02 mole) were taken in absolute alcohol in 250 mL round bottom flask. The reaction mixture was refluxed for 1-4 hours at reflux temperature till reaction completed. The progress and the completion of the reaction were checked by silica gel-G F_{254} thin

layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After completion of the reaction, the reaction mixture was allowed to cool at room temperature to obtain the product. When crystalline product was separated out, it was filtered and washed with cold ethanol. Similarly other compounds were also prepared.

The physical data of newly synthesized compounds are given in Table No.4.8.1

4.7.4 Preparation of 4-(3-Hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

A mixture of 3-hydroxy benzaldehyde (0.01 mole) and 3-amino crotononitrile (0.02 mole) was taken in glacial acetic acid in a stoppered flask and stirred for 1 hour at room temperature. During the reaction, progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3: 2) as a mobile phase. After the completion of the reaction, the crystalline product was separated out which was filtered and washed with diethyl ether.

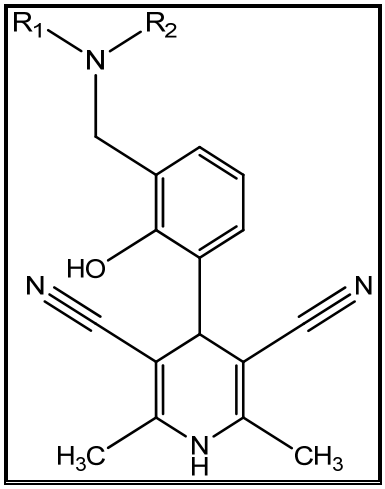
4.7.5 Preparation of 4-(3-Hydroxy-4-(substitued-1-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (General Procedure)

A mixture of 4-(3-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (0.01 mole), secondary amine (0.0135 mole) and formaldehyde (0.02 mole) were taken in absolute alcohol in 250 mL round bottom flask. The reaction mixture was refluxed for 1-4 hours at reflux temperature till reaction completed. The progress and the completion of the reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After completion of the reaction, the reaction mixture was allowed to cool at room temperature to obtain the product. When crystalline product was separated out, it was filtered and washed with cold ethanol. Similarly other compounds were also prepared.

The physical data of newly synthesized compounds are given in Table No.4.8.2

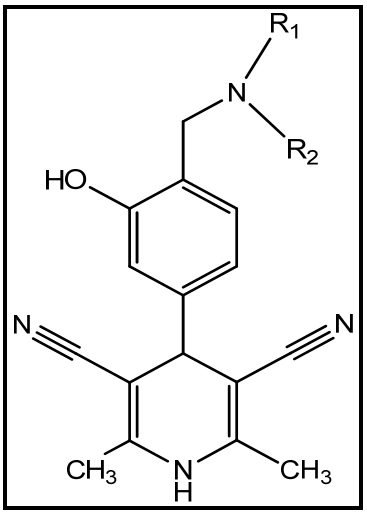
4.8 PHYSICAL DATA

4.8.1 Physical Data Table of 4-(2-Hydroxy-3-(substitued-1-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles



Sr. No.	Sample Code	Substitution NR_1R_2	Molecular Formula	M. Wt	MP °C	Yield %
1	MNP-MB-101	Piperazine	$C_{20}H_{23}N_5O$	349	256-258	62
2	MNP-MB-102	N-Me-piperazine	$C_{21}H_{25}N_5O$	363	242-244	73
3	MNP-MB-103	N-Et-Piperazine	$C_{22}H_{27}N_5O$	377	236-238	75
4	MNP-MB-104	N-phenyl piperazine	$C_{26}H_{27}N_5O$	425	218-220	75
5	MNP-MB-105	N-benszyl piperazine	$C_{27}H_{29}N_5O$	439	150-152	78
6	MNP-MB-106	Morpholine	$C_{20}H_{22}N_4O_2$	350	224-226	78
7	MNP-MB-107	Piperidine	$C_{21}H_{24}N_4O$	348	233-235	65
8	MNP-MB-108	2-methl piperidine	$C_{22}H_{26}N_4O$	362	213-215	63
9	MNP-MB-109	Pyrrolidine	$C_{20}H_{22}N_4O$	334	239-241	65
10	MNP-MB-110	N,N-Diethyl Amine	$C_{20}H_{24}N_4O$	336	180-182	60

4.8.2 Physical Data Table of 4-(3-Hydroxy-4-(substitued-1-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles



Sr. No.	Sample Code	Substitution NR_1R_2	Molecular Formula	M. Wt	MP °C	Yield %
11	MNP-MB-201	Piperazine	$C_{20}H_{23}N_5O$	349	246-248	65
12	MNP-MB-201	N-Me-piperazine	$C_{21}H_{25}N_5O$	363	188-190	75
13	MNP-MB-203	N-Et-Piperazine	$C_{22}H_{27}N_5O$	377	112-114	78
14	MNP-MB-204	N-phenyl piperazine	$C_{26}H_{27}N_5O$	425	216-218	80
15	MNP-MB-205	N-benzyl piperazine	$C_{27}H_{29}N_5O$	439	222-224	82
16	MNP-MB-206	Morpholine	$C_{20}H_{22}N_4O_2$	350	215-217	80
17	MNP-MB-207	Piperidine	$C_{21}H_{24}N_4O$	348	220-222	78
18	MNP-MB-208	2-methl piperidine	$C_{22}H_{26}N_4O$	362	214-216	75
19	MNP-MB-209	Pyrrolidine	$C_{20}H_{22}N_4O$	334	208-210	78
20	MNP-MB-210	N,N-Diethyl Amine	$C_{20}H_{24}N_4O$	336	160-162	65

4.9 SPECTRAL DISCUSSION

4.9.1 IR Spectra

IR spectra of the synthesized compounds were recorded on Shimadzu FT-IR 8400 model using KBr Powder method. Various functional groups present were identified by characteristic frequency obtained for them.

The stretching frequency of OH group showed at 3650-3600 (O-H str.) $cm^{-1}$and bending vibration at 1410-1310 cm^{-1}. The characteristic band of secondary N-H group showed in the region of 3500-3200 cm^{-1} with a deformation due to in plane bending at 1650-1550 cm^{-1}. Aromatic C-H stretching and bending frequencies showed between 3070-3030 cm^{-1} and 1600-1400 cm^{-1} respectively. C-H stretching and bending frequencies for methyl and methylene group were obtained near 2950-2850 cm^{-1} and 1450-1375 cm^{-1}. Characteristic frequency of C≡N showed at 2260-2200 cm^{-1}. Characteristic frequency of C-N stretching showed near 1350-1280 cm^{-1}. C-O stretching frequency showed at 1230-1140 cm^{-1}.

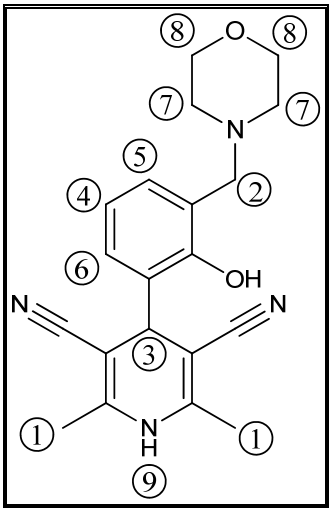
4.9.2 Mass Spectra

Mass spectra of the synthesized compounds were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound.

4.9.3 ^{1}H NMR Spectra

^{1}H NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in DMSO-d_6/$CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Number of protons identified from ^{1}H NMR spectra and their chemical shift (δ ppm) were in the agreement of the structure of the molecule. *J* values were calculated to identify o, m and p coupling. In some cases, aromatic protons were obtained as multiplet. Interpretations of representative spectra are discussed as under.

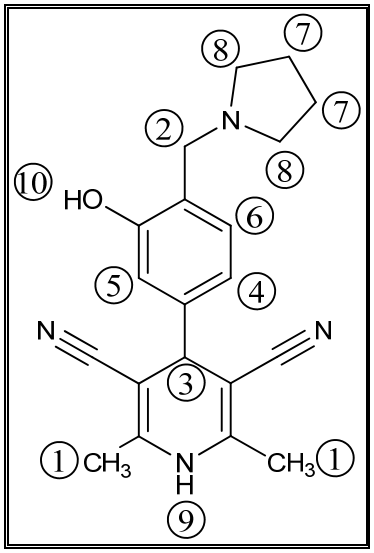
4.9.3.1 ^{1}H NMR of 4-(2-Hydroxy-3-(morpholinomethyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-106)



1. Proton no. 1 of total 6H of methyl group gave a singlet at 2.05 δ ppm.
2. Proton no. 2 of total 2H of methylene group gave a characteristic singlet at 3.73 δ ppm.
3. Proton no. 3 of total 1H gave a singlet at 4.90 δ ppm.
4. Proton no. 4 of total 1H of aromatic ring gave a triplet at 6.80-6.83 δ ppm (J=7.52, J=7.48), which suggest di ortho coupling.
5. Proton no. 5 of total 1H of aromatic ring gave a doublet at 6.92-6.94 δ ppm (J=6.8), which suggest ortho coupling.
6. Proton no. 6 of total 1H of aromatic ring gave a triplet (double doublet type) at 7.11-7.12 δ ppm (J=6.52, J=1.04), which suggest ortho-meta coupling.
7. Proton no. 7 of total 4H of secondary amine of morpholine ring gave a singlet at 2.55 δ ppm.
8. Proton no. 8 of total 4H of secondary amine of morpholine ring gave a singlet at 3.71 δ ppm.
9. Proton no. 9 of total 1H of secondary amine of dihydropyridine ring gave a singlet at 8.99 δ ppm.

Thus, by observing and assigning the signals in the NMR spectrum, we can clearly suggest that the proposed structure for compound MNP-MB-106 has been confirmed. The spectrum is given on page no. 218.

4.9.3.2 ^{1}H NMR of 4-(3-Hydroxy-4- (pyrrolidin-1-yl methyl) phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-209)



1. Proton no. 1 of total 6H of methyl group gave a singlet at 2.01 δ ppm.
2. Proton no. 2 of total 2H of methylene group gave a characteristic singlet at 3.83 δ ppm.
3. Proton no. 3 of total 1H gave a singlet at 4.22 δ ppm.
4. Proton no. 4 and 5 of total 2H of aromatic ring gave a triplet at 6.65-6.68 δ ppm (J=10 and J=1.64) which suggest ortho-meta coupling of both the protons.
5. Proton no. 6 of total 1H gave a doublet at 6.94-6.96 δ ppm (J=7.44), which suggest ortho coupling.
6. Proton no. 7 and 8 of total 4H and 4H of secondary amine of pyrrolydine ring gave a singlet at 1.85 δ ppm and 2.65 δ ppm respectively.
7. Proton no. 9 of total 1H of secondary amine of dihydropyridine ring gave a singlet at 7.46 δ ppm.
8. Proton no. 10 of total of 1H of OH group appeared as singlet at 8.05 δ ppm.

Thus, by observing and assigning the signals in the NMR spectrum and by calculating J value, we can clearly suggest that the proposed structure for compound MNP-MB-209 has been confirmed. The spectrum is given on page no. 225.

4.9.4 ^{13}C NMR Spectra

^{13}C NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in DMSO-*d6*/$CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Types of carbons identified from NMR spectrum and their chemical shifts (δ ppm) were in the agreement with the structure of the molecule.

4.9.5 Elemental Analysis

Elemental analysis of the synthesized compounds was carried out on Vario EL Carlo Erba 1108 which showed calculated and found percentage values of Carbon, Hydrogen and Nitrogen in support of the structure of synthesized compounds.

The analytical data for individual compounds synthesized in this chapter is mentioned as follow.

4.10 ANALYTICAL DATA

1) 4-(2-Hydroxy-3- (piperazin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarbonitrile (MNP-MB-101)

Yield: 62%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 349 (100%); Anal. Calcd. for $C_{20}H_{23}N_5O$: C, 68.74; H, 6.63; N, 20.04; O, 4.58; Found: C, 68.67; H, 6.87; N, 20.12.

2) 4-(2-Hydroxy-3-((4-methyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-102)

Yield: 73%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d_6) δ ppm: 1.08 (s, 3H), 2.04 (s, 6H), 2.41-2.46 (m, b, 8H), 3.72 (s, 2H), 4.95 (s, 1H), 6.44 (s, 1H), 6.78-6.82 (t, 2H, *J*=7.56), 6.91-6.93 (dd, 1H, *J*=6.04, *J*=1.36), 7.06-7.09 (dd, 1H, *J*=6.12, *J*=1.56); **^{13}C NMR** (DMSO-d6) δ ppm: 11.99, 18.43, 33.89, 52.30, 61.26, 77.06, 84.82, 119.03, 19.43, 121.44, 128.36, 128.65, 129.35, 145.36, 154.84; **MS**: *m/z* = 363 (100%); Anal. Calcd. for $C_{21}H_{25}N_5O$: C, 69.40; H, 6.93; N, 19.27; O, 4.40; Found: C, 69.36; H, 6.83; N, 19.17.

3) 4-(3-((4-Ethyl piperazin-1-yl) methyl)-2-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-103)

Yield: 75%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3),

1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.03-1.07 (t, 3H), 2.03 (s, 6H), 2.40-2.44 (q, 2H), 2.59 (s, 2H), 3.43 (s, b, 6H), 6.78-6.82 (t, 2H, *J*=7.56), 6.92-6.94 (dd, 1H, *J*=6.04, *J*=1.36), 7.08-7.11 (dd, 1H, *J*=6.16, *J*=1.48); **^{13}C NMR** (DMSO-d6) δ ppm: 11.84, 17.74, 33.24, 40.18, 51.62, 51.76, 52.13, 60.62, 78.72, 82.77, 99.66, 119.14, 119.22, 127.77, 128.60, 130.34, 146.31, 154.20; **MS**: *m/z* = 377 (100%); Anal. Calcd. for $C_{22}H_{27}N_5O$: C, 70.00; H, 7.21; N, 18.55; O, 4.24; Found: C, 70.11; H, 7.33; N, 18.40.

4) 4-(2-Hydroxy-3-((4-phenyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-104)

Yield: 75%; **IR** (cm^{-1}): 3624-3591 (O-H str.), 3436-3406 (N-H str.), 3056-3007 (Ar C=C-H str.), 2982 (Asym C-H str. -CH_3), 2949 (Asym C-H str. -CH_2), 2891 (Sym C-H str. -CH_3), 2831 (Sym C-H str. -CH_2), 2196 (C≡N str.), 1666-1636 (N-H bend), 1598, 1491, 1454 (Ar C=C str.), 1387 (C-H bend –CH_2), 1371 (C-H bend –CH_3), 1351 (C-N sec amine vib), 1139 (C-O str.), 840-760 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 2.05 (s, 6H), 2.63 (s, 4H), 3.22 (s, 4H), 3.79 (s, 2H), 4.90 (s, 1H), 6.81-6.85 (m, 2H), 6.89-6.91 (d, 2H, *J*=8.16), 6.94-6.96 (d, 1H, *J*=7.24), 7.12-7.14 (d, 1H, *J*=7.6), 7.20-7.24 (t, 2H, *J*=7.52, *J*=8.12), 8.97 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.56, 18.04, 33.22, 40.13, 48.44, 51.67, 60.59, 77.62, 82.68, 115.67, 119.13, 120.67, 127.68, 128.46, 129.98, 146.14, 150.44, 153.98; **MS**: *m/z* = 425 (100%); Anal. Calcd. for $C_{26}H_{27}N_5O$: C, 73.39; H, 6.40; N, 16.46; O, 3.76; Found: C, 73.22; H, 6.29; N, 16.59.

5) 4-(3-((4-Benzylpiperazin-1-yl)methyl)-2-hydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-105)

Yield: 78%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 439 (100%); Anal. Calcd. for $C_{27}H_{29}N_5O$: C, 73.78; H, 6.65; N, 15.93; O, 3.64; Found: C, 73.74; H, 6.48; N, 16.05.

6) 4-(2-Hydroxy-3-(morpholino-methyl) phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-106)

Yield: 78%; **IR** (cm^{-1}): 3632-3630 (O-H str.), 3529-3460 (N-H str.), 3017 (Ar C=C-H str.), 2966 (Asym C-H str. -CH_3), 2913 (Asym C-H str. -CH_2), 2853 (Sym C-H str. -CH_3), 2827 (Sym C-H str. -CH_2), 2201 (C≡N str.), 1663 (N-H bend), 1561, 1521, 1457 (Ar C=C str.), 1439 (C-H bend –CH_2), 1384-1364 (C-H bend –CH_3), 1351-1329 (C-N sec amine vib), 1206 (C-O str.), 860-790 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 2.05 (s, 6H), 2.55 (s, 4H), 3.71 (s, 4H), 3.73 (s, 2H), 4.90 (s, 1H), 6.80-6.83 (t, 1H, *J*=7.50), 6.92-6.94 (d, 1H, *J*=6.8), 7.11-7.13 (t, 1H, *J*=6.52, *J*=1.04), 8.99 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.51, 33.10, 40.12, 52.05, 60.92, 66.06, 82.61, 119.06, 120.35, 127.71, 128.46, 129.97, 146.10, 153.76; **MS**: *m/z* = 350 (100%); Anal. Calcd. for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99; O, 9.13; Found: C, 68.63; H, 6.25; N, 15.84.

7) 4-(2-Hydroxy-3- (piperidin-1-yl methyl) phenyl)- 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-107)

Yield: 65%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def);); **MS**: *m/z* = 348 (100%); Anal. Calcd. for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08; O, 4.59; Found: C, 72.43; H, 6.88; N, 16.21.

8) 4-(2-Hydroxy-3-((2-methyl piperidin-1-yl) methyl)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-108)

Yield: 63%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 362 (100%); Anal. Calcd. for $C_{22}H_{26}N_4O$: C, 72.90; H, 7.23; N, 15.46; O, 4.41; Found: C, 72.99; H, 7.24; N, 15.55.

9) 4-(2-Hydroxy-3- (pyrrolidin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-109)

Yield: 65%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 334 (100%); Anal. Calcd. for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75; O, 4.78; Found: C, 71.74; H, 6.72; N, 16.68.

10) 4-(3-((Diethyl amino) methyl) -2-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-110)

Yield: 60%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 336 (100%); Anal. Calcd. for $C_{20}H_{24}N_4O$: C, 71.40; H, 7.19; N, 16.65; O, 4.76; Found: C, 71.32; H, 7.13; N, 16.58.

11) 4-(3-Hydroxy-4-(piperazin-1-yl methyl) phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-201)

Yield: 65%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 349 (100%); Anal. Calcd. for $C_{20}H_{23}N_5O$: C, 68.74; H, 6.63; N, 20.04; O, 4.58; Found: C, 67.97; H, 6.57; N, 19.74.

12) 4-(3-Hydroxy-4-((4-methyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-202)

Yield: 75%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H

str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 2.05 (s, 6H), 2.52 (s, 3H), 2.54 (s, b, 7H), 3.68 (s, 2H), 4.19 (s, 1H), 6.63-6.67 (t, 2H, *J*=7.68, *J*=5.92), 6.98-6.99 (d, 1H, *J*=7.48), 9.22 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.63, 38.83, 40.09, 41.23, 45.43, 51.93, 60.11, 78.01, 82.89, 114.62, 117.89, 119.09, 120.49, 128.76, 144.04, 146.11, 157.57; **MS**: *m/z* = 363 (100%); Anal. Calcd. for $C_{21}H_{25}N_5O$: C, 69.40; H, 6.93; N, 19.27; O, 4.40; Found: C, 69.26; H, 6.75; N, 19.22.

13) 4-(4-((4-Ethyl piperazin-1-yl) methyl)-3-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-203)

Yield: 78%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.07-1.10 (t, 3H), 2.03 (s, 6H), 2.41-2.47 (q, 2H), 2.60-2.63 (s, b, 5H), 3.71 (s, 2H), 4.22 (s, 1H), 6.6642-6.6684 (d, 1H, *J*=1.68), 6.68-6.70 (dd, 1H, *J*=5.88, *J*=1.72), 6.96-6.98 (d, 1H, *J*=7.6), 7.28 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 11.92, 18.24, 41.80, 52.43, 61.00, 77.08, 84.66, 115.14, 118.61, 118.96, 121.09, 129.09, 143.84, 145.62, 158.19; **MS**: *m/z* = 377 (100%); Anal. Calcd. for $C_{22}H_{27}N_5O$: C, 70.00; H, 7.21; N, 18.55; O, 4.24; Found: C, 70.41; H, 7.13; N, 18.20.

14) 4-(3-Hydroxy-4-((4-phenyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-204)

Yield: 80%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 425 (100%); Anal. Calcd. for $C_{26}H_{27}N_5O$: C, 73.39; H, 6.40; N, 16.46; O, 3.76; Found: C, 73.35; H, 6.59; N, 16.39.

15) 4-(4-((4-Benzyl piperazin-1-yl) methyl)-3-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-205)

Yield: 82%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 2.01 (s, 6H), 2.58-2.71 (s, b, 8H), 3.53 (s, 2H), 3.70 (s, 2H), 4.21 (s, 1H), 6.65-6.66 (d, 1H, *J*=1.60), 6.67-6.69 (dd, 1H, *J*=5.92, *J*=1.68), 6.94-6.96 (d, 1H, *J*=7.56), 7.24-7.33 (m, 5H), 7.38 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 18.26, 41.82, 52.59, 52.82, 61.01, 62.79, 77.12, 84.63, 115.17, 118.61, 119.04, 121.12, 127.28, 128.33, 129.08, 137.55, 143.91, 145.70, 158.24; **MS**: *m/z* = 439 (100%); Anal. Calcd. for $C_{27}H_{29}N_5O$: C, 73.78; H, 6.65; N, 15.93; O, 3.64; Found: C, 73.64; H, 6.58; N, 15.81.

16) 4-(3-Hydroxy-4- (morpholino methyl) phenyl) -2,6-dimethyl -1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-206)

Yield: 80%; **IR** (cm^{-1}): 3630-3620 (O-H str.), 3537-3468 (N-H str.), 3014 (Ar C=C-H str.), 2955 (Asym C-H str. -CH_3), 2913 (Asym C-H str. -CH_2), 2876 (Sym C-H str. -CH_3), 2860 (Sym C-H str. -CH_2), 2199 (C≡N str.), 1659 (N-H bend), 1560, 1523, 1508 (Ar C=C str.), 1465 (C-H bend –CH_2), 1384 (C-H bend –CH_3), 1348 (C-N sec amine vib), 1159 (C-O str.), 870-795 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 2.06 (s, 6H), 2.53 (s, 4H), 3.68 (s, 4H+2H), 4.19 (s, 1H), 6.6429-6.6453 (d, 1H, *J*=0.96), 6.66-6.68 (d, 1H, *J*=7.68), 7.01-7.03 (d, 1H, *J*=7.64), 9.28 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.62, 40.14, 41.20, 52.47, 60.20, 66.12, 77.83, 78.49, 82.85, 114.62, 117.99, 118.98, 120.32, 129.08, 144.17, 146.11, 157.28; **MS**: *m/z* = 350 (100%); Anal. Calcd. for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99; O, 9.13; Found: C, 68.50; H, 6.26; N, 15.79.

17) 4-(3-Hydroxy-4-(piperidin-1-yl methyl) phenyl) -2,6-dimethyl -1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-207)

Yield: 78%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend),

1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $–CH_2$), 1375 (C-H bend $–CH_3$), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 2.02 (s, 6H), 1.63 (s, 6H), 2.50-2.57 (s, b, 4H), 3.68 (s, 2H), 4.21 (s, 1H), 6.63-6.64 (d, 1H, *J*=1.60), 6.66-6.68 (dd, 1H, *J*=5.92, *J*=1.68), 6.92-6.94 (d, 1H, *J*=7.6), 7.60 (s, 1H), 9.02 (s, b, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 18.16, 23.85, 25.87, 41.88, 53.81, 61.72, 77.43, 84.62, 115.00, 118.48, 119.07, 121.48, 128.89, 143.85, 145.76, 158.54; **MS**: *m/z* = 348 (100%); Anal. Calcd. for $C_{21}H_{24}N_4O$: C, 72.39; H, 6.94; N, 16.08; O, 4.59; Found: C, 72.30; H, 6.98; N, 16.10.

18) 4-(3-Hydroxy-4-((2-methyl piperidin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-208)

Yield: 75%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $–CH_2$), 1375 (C-H bend $–CH_3$), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.18 (d, 3H), 1.40-1.42 (t, 2H), 1.59-1.76 (m, b, 4H), 2.06 (s, 6H), 2.16-2.22 (q, 1H), 2.55 (s, 1H), 2.80-2.83 (t, 1H), 3.39 (s, 1H), 4.18 (s, 2H), 6.5707-6.5745 (d, 1H, *J*=1.52), 6.62-6.64 (dd, 1H, *J*=6.04, *J*=1.60), 6.96-6.98 (d, 1H, *J*=7.64), 9.32 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.63, 22.28, 25.21, 33.52, 40.00, 41.14, 50.51, 55.71, 56.28, 78.58, 82.91, 114.55, 117.68, 119.00, 121.36, 128.43, 143.76, 146.02, 146.06, 157.92; **MS**: *m/z* = 362 (100%); Anal. Calcd. for $C_{22}H_{26}N_4O$: C, 72.90; H, 7.23; N, 15.46; O, 4.41; Found: C, 72.95; H, 7.19; N, 15.75.

19) 4-(3-Hydroxy-4- (pyrrolidin-1-yl methyl) phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-209)

Yield: 78%; **IR** (cm^{-1}): 3628-3575 (O-H str.), 3572-3253 (N-H str.), 3007 (Ar C=C-H str.), 2970 (Asym C-H str. $-CH_3$), 2917 (Asym C-H str. $-CH_2$), 2873 (Sym C-H str. $-CH_3$), 2826 (Sym C-H str. $-CH_2$), 2196 (C≡N str.), 1663 (N-H bend), 1543, 1518, 1458 (Ar C=C str.), 1438 (C-H bend $–CH_2$), 1385 (C-H bend $–CH_3$), 1326 (C-N sec amine vib), 1176 (C-O str.), 875-800 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.85 (s, 4H), 2.01 (s, 6H), 2.65 (s, 4H), 3.83 (s, 2H), 4.22 (s, 1H), 6.65-6.68 (t, 2H, *J*=10, *J*=1.64), 6.94-6.96 (d, 1H, *J*=7.44), 7.46 (s, 1H), 8.85 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 18.17, 23.65, 41.84, 53.52, 58.43, 77.10, 84.60, 114.96, 118.34,

119.08, 122.35, 128.30, 143.74, 145.75, 158.57; **MS**: *m/z* = 334 (100%); Anal. Calcd. for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75; O, 4.78; Found: C, 71.64; H, 6.76; N, 16.62.

20) 4-(4-((Diethyl amino) methyl) -3-hydroxy phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-210)

Yield: 65%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2260-2200 (C≡N str.), 1650-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 336 (100%); Anal. Calcd. for $C_{20}H_{24}N_4O$: C, 71.40; H, 7.19; N, 16.65; O, 4.76; Found: C, 71.28; H, 7.33; N, 16.55.

4.11 RESULTS & DISCUSSION

Present work covers the synthesis of some novel Mannich base compounds using hydroxy substituted dihydropyridines and different secondary amines with formaldehyde. The main significance of the present work is the very rapid and easy reaction condition, facile work up method, excellent yield and high chemical purity of the desired compounds for biological as well as pharmacological interest.

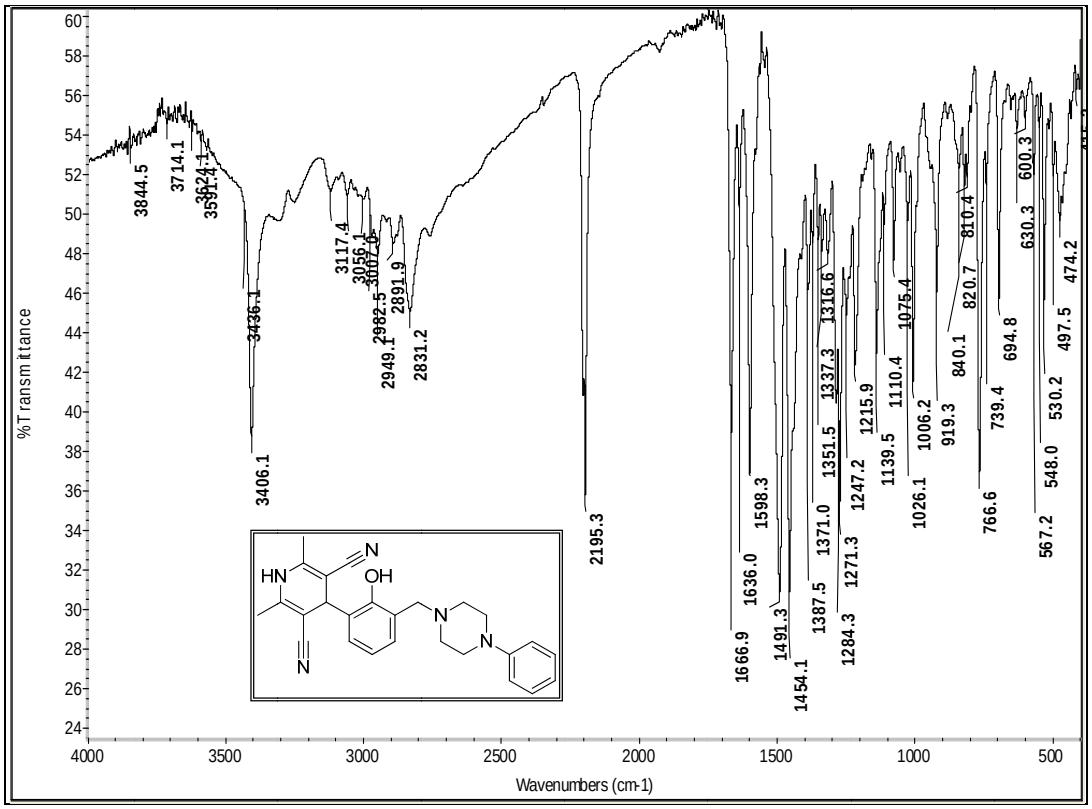
4.12 CONCLUSION

Herein we reported a Mannich reaction of 1,4-dihydropyridines at C_4 phenyl ring containing hydroxyl group, as an alternative of N-1 position of 1,4-dihydropyridines.

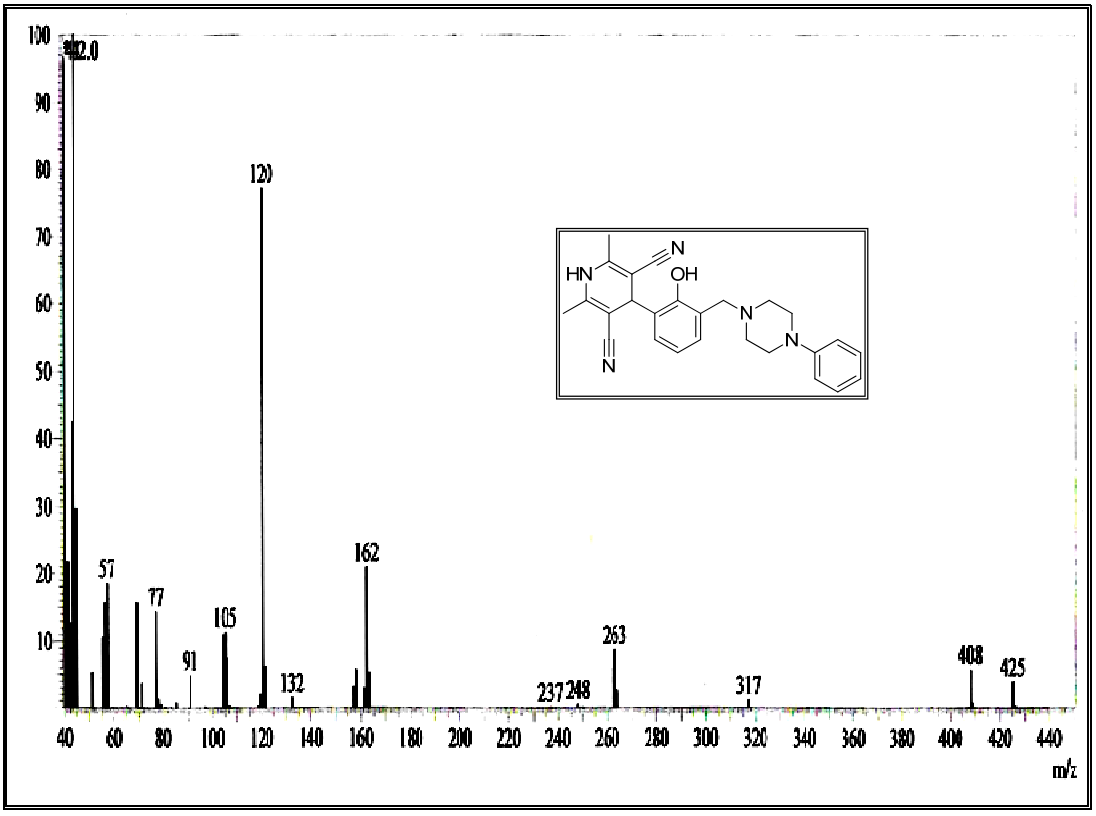
The newly synthesized compounds are well characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR and Elemental analysis.

4.13 REPRESENTATIVE SPECTRA

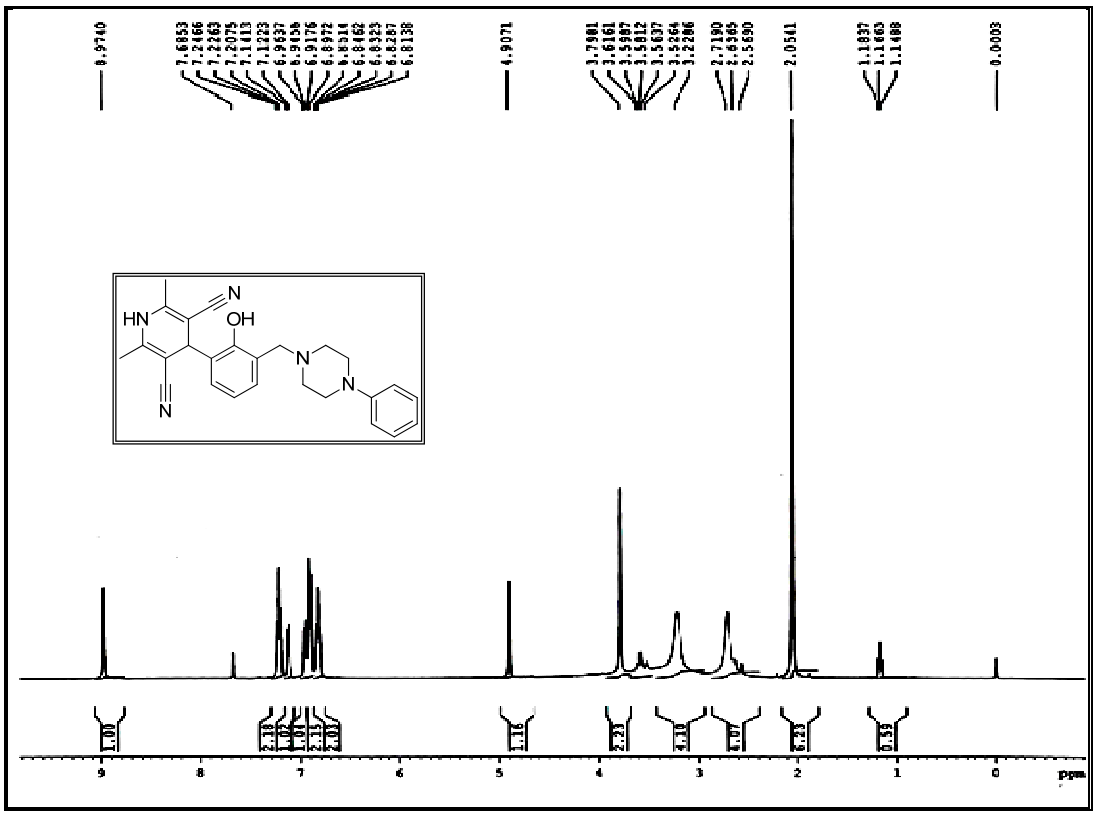
4.13.1 IR Spectrum of MNP-MB-104



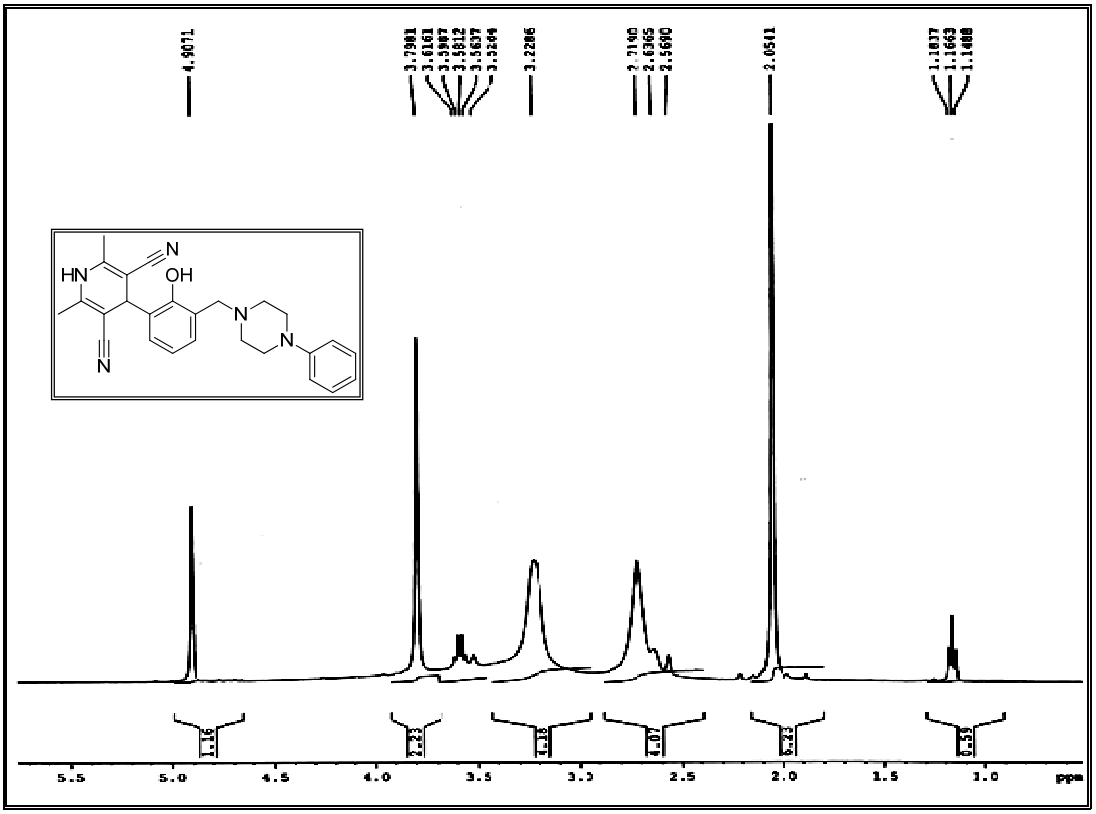
4.13.2 Mass Spectrum of MNP-MB-104



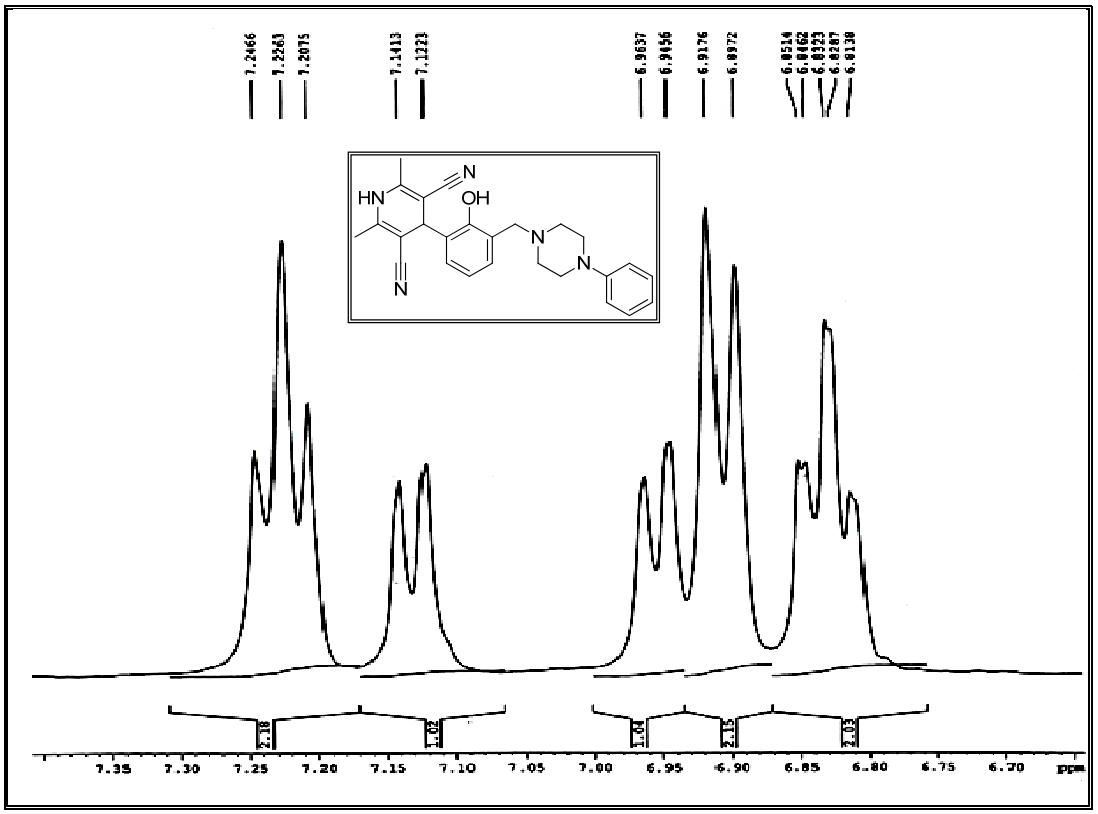
4.13.3 ^{1}H NMR Spectrum of MNP-MB-104



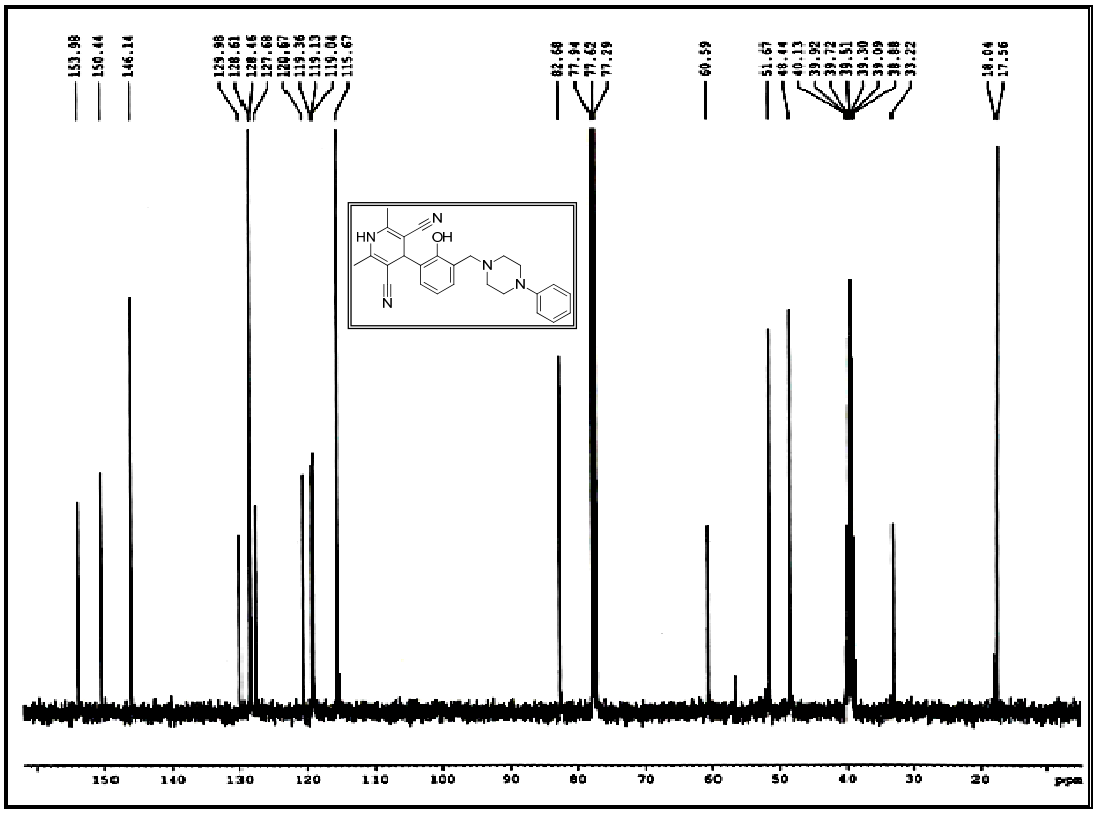
4.13.4 Expanded ^{1}H NMR Spectrum of MNP-MB-104



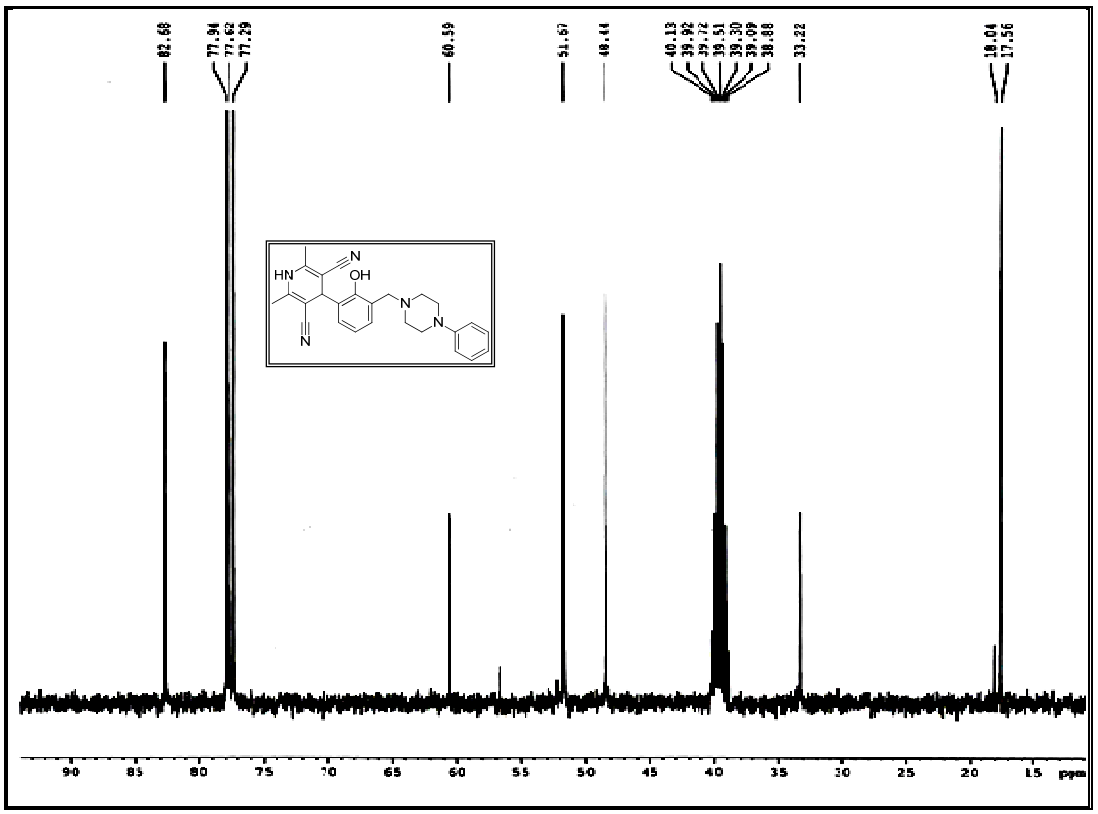
4.13.5 Expanded ^{1}H NMR Spectrum of MNP-MB-104



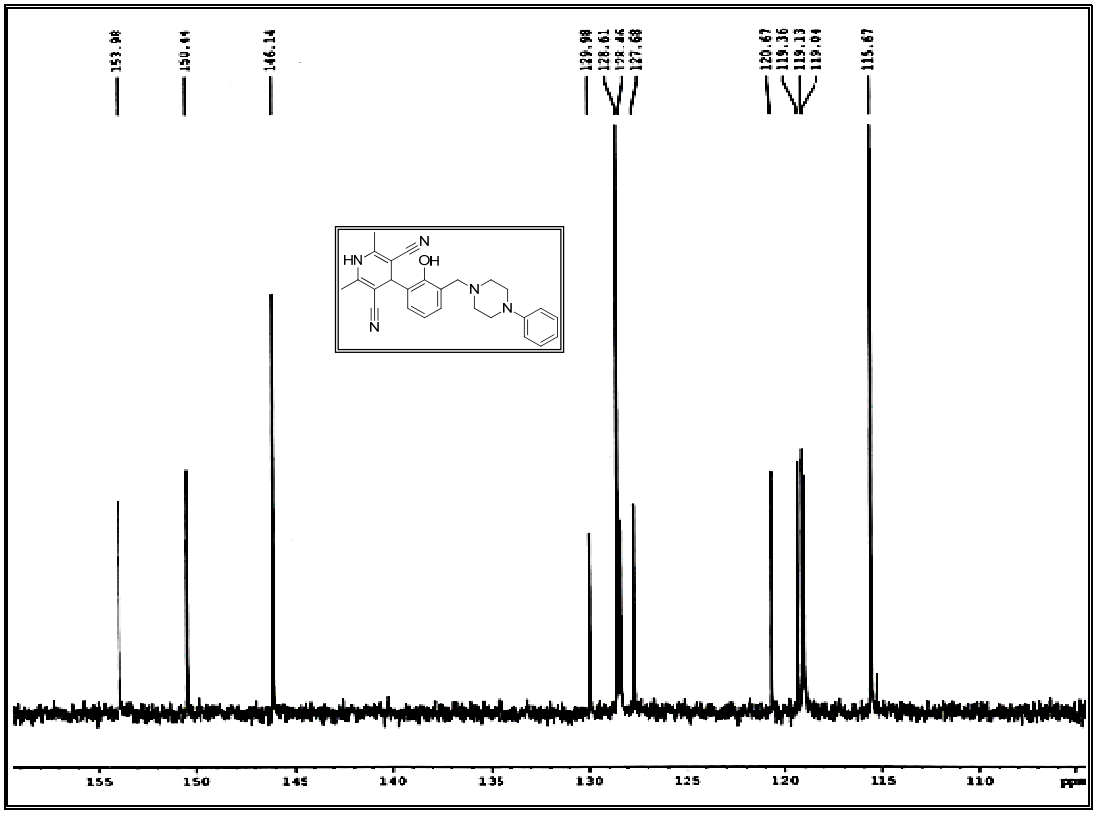
4.13.6 ^{13}C NMR Spectra of MNP-MB-104



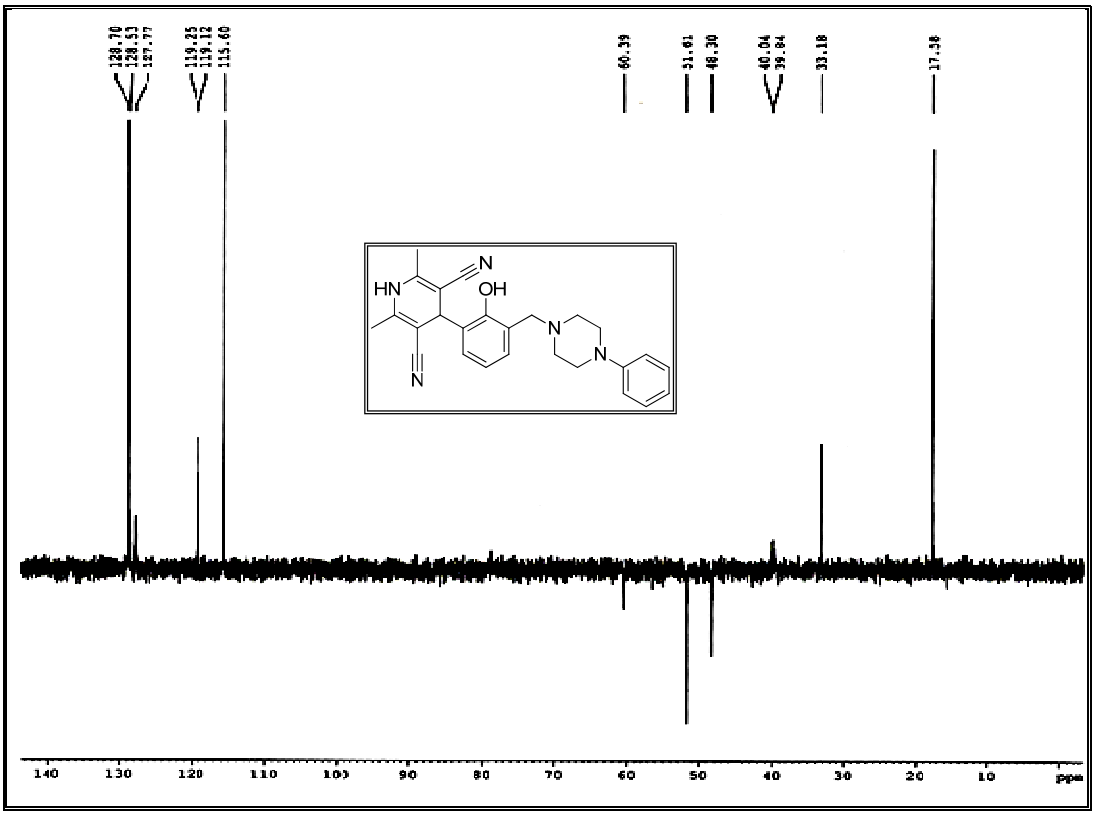
4.13.7 Expanded ^{13}C NMR Spectrum of MNP-MB-104



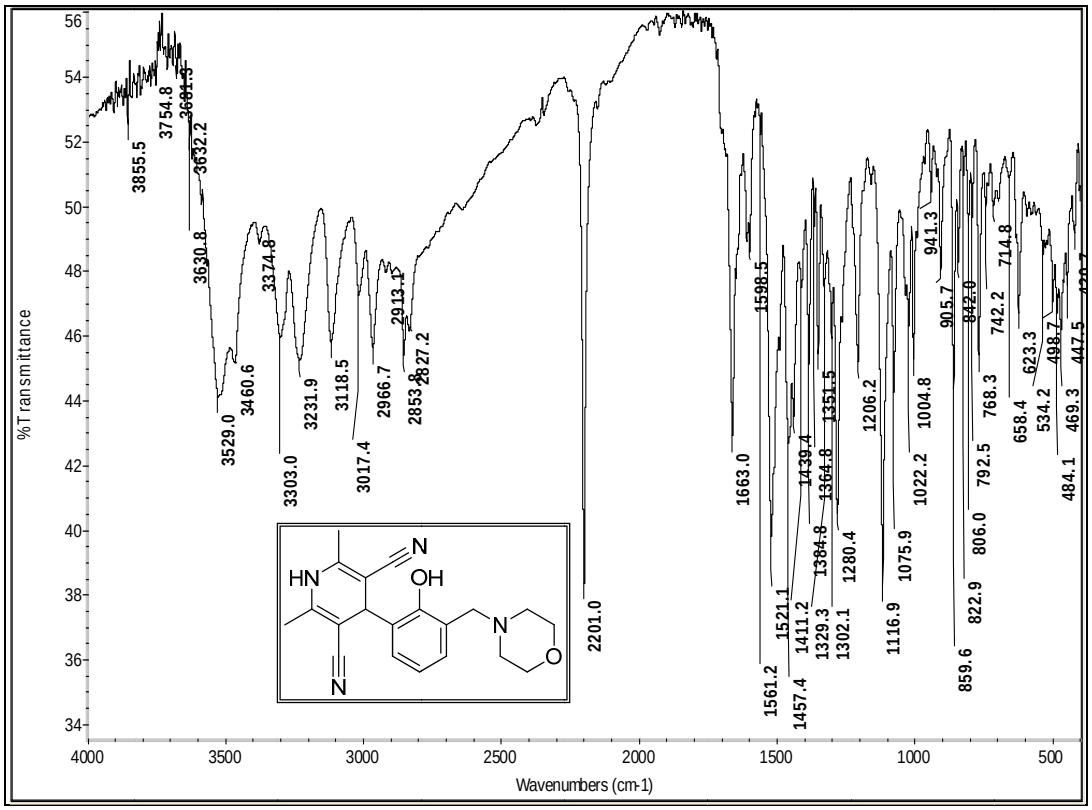
4.13.8 Expanded ^{13}C NMR Spectrum of MNP-MB-104



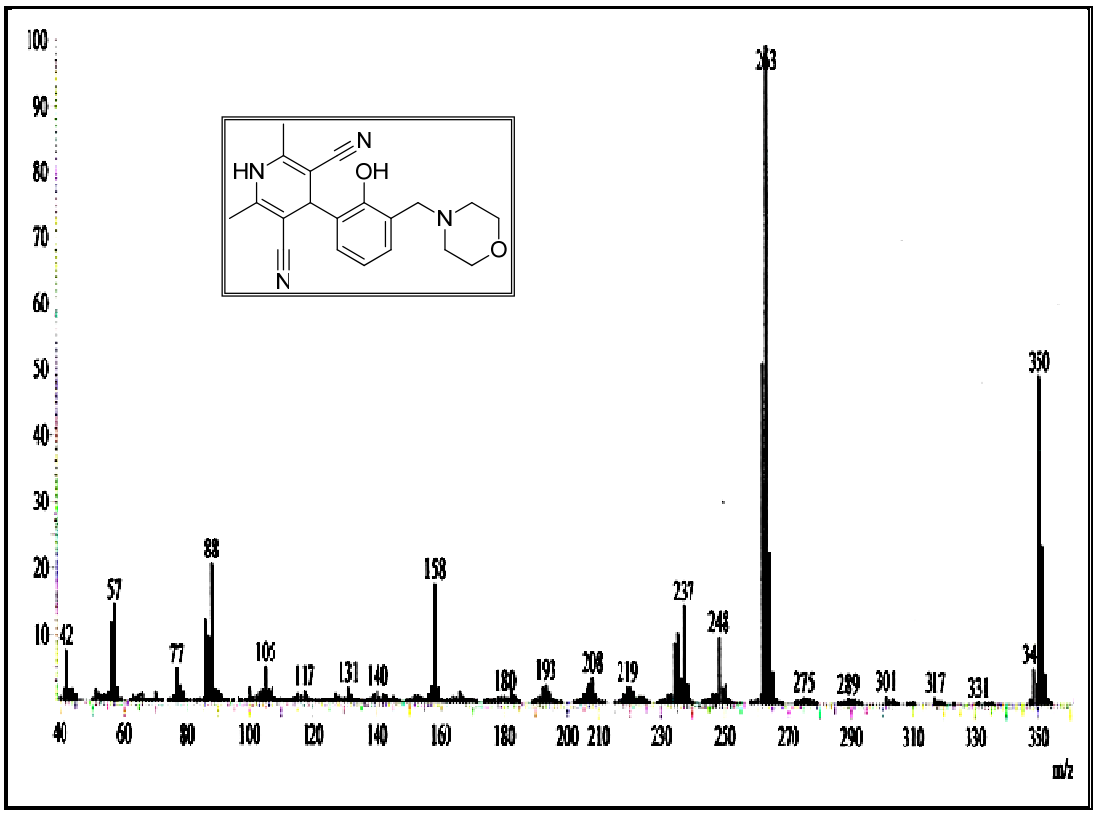
4.13.9 Expanded ^{13}C NMR Spectrum of MNP-MB-104



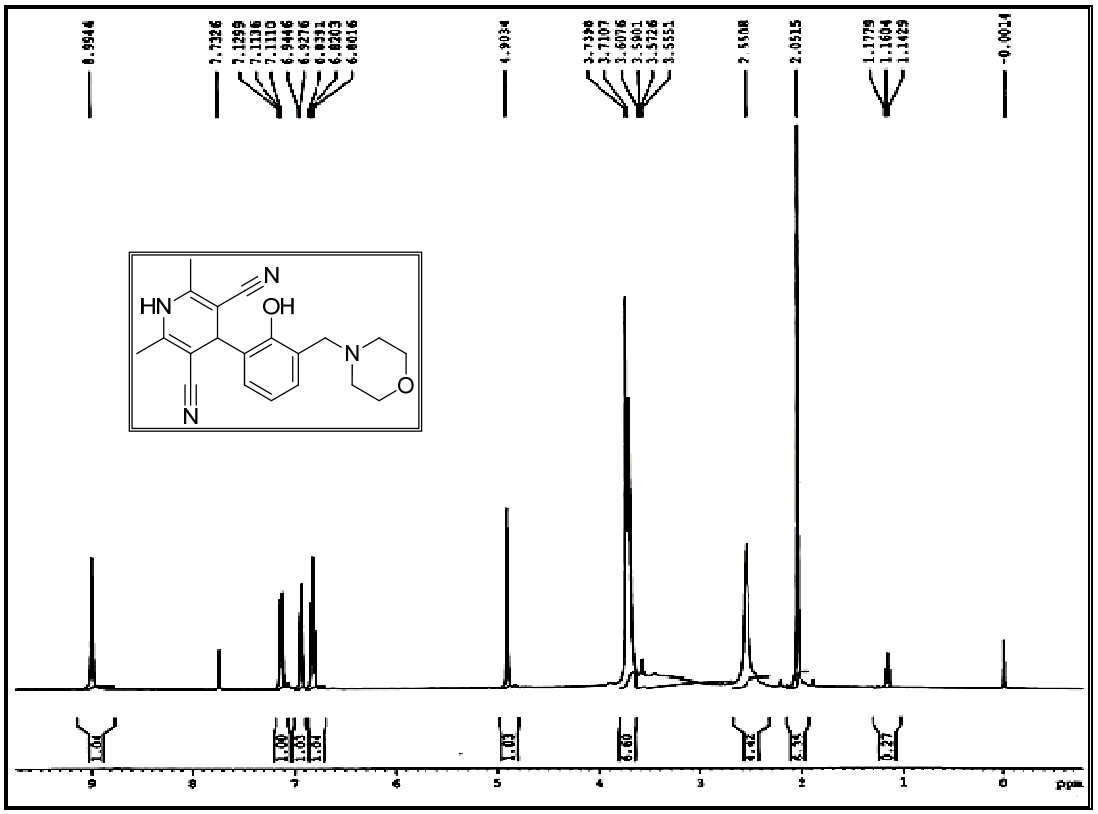
4.13.10 IR Spectrum of MNP-MB-106



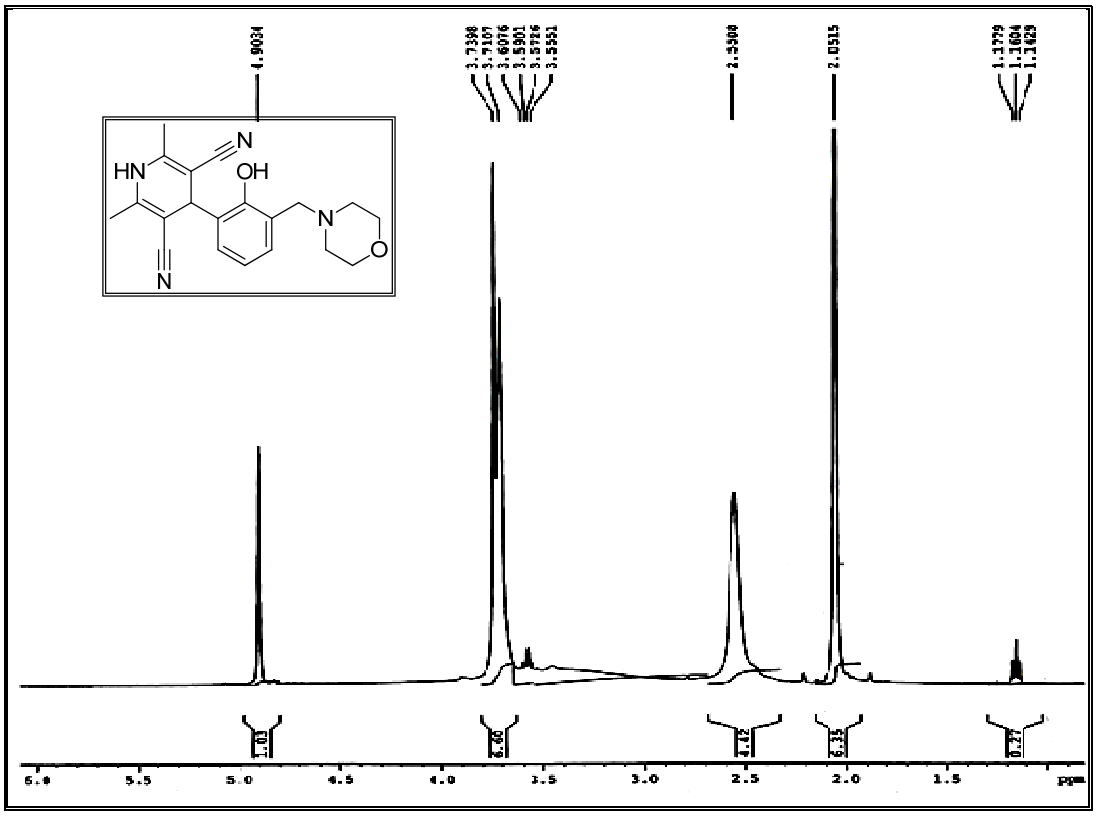
4.13.11 Mass Spectrum of MNP-MB-106



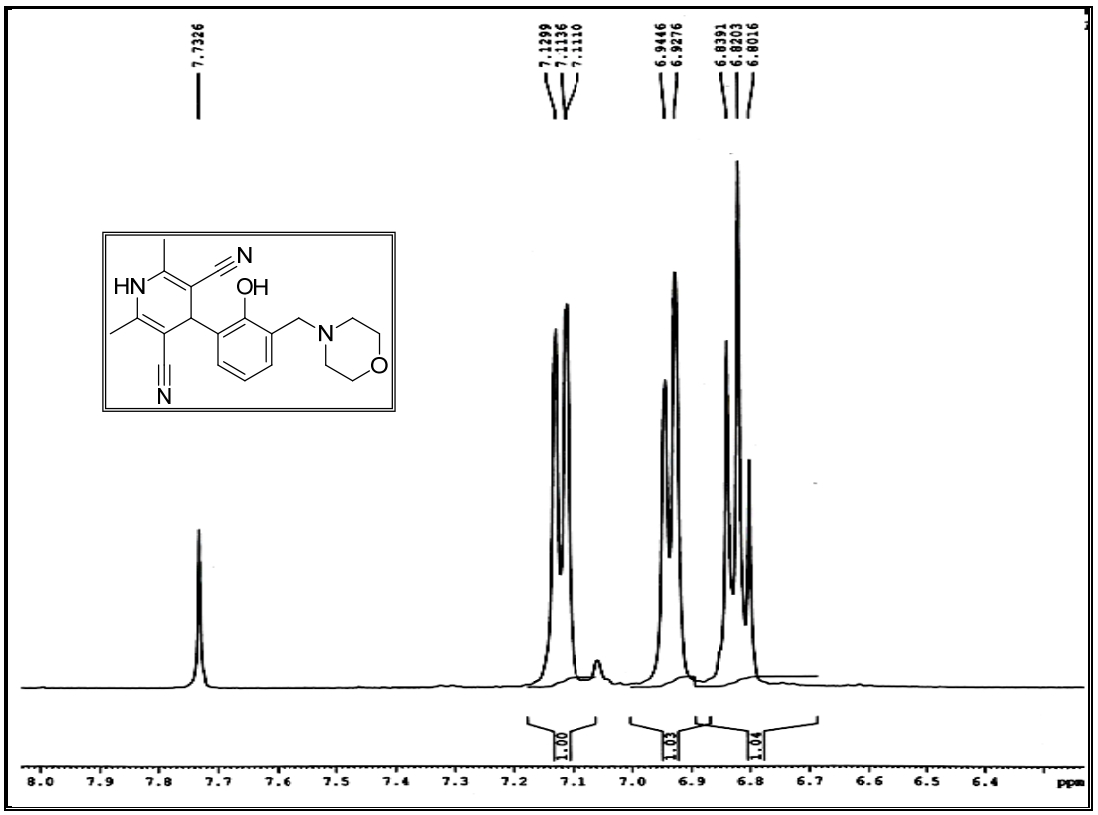
4.13.12 ^{1}H NMR Spectrum of MNP-MB-106



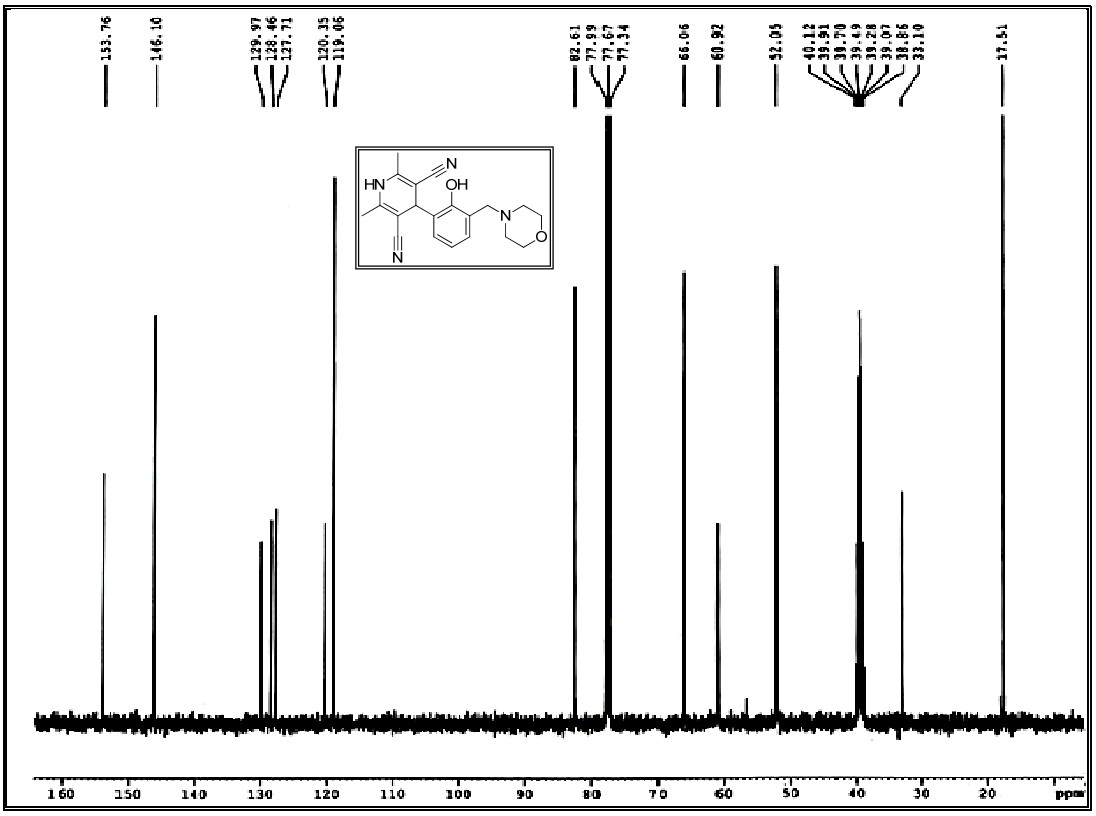
4.13.13 Expanded ^{1}H NMR Spectrum of MNP-MB-106



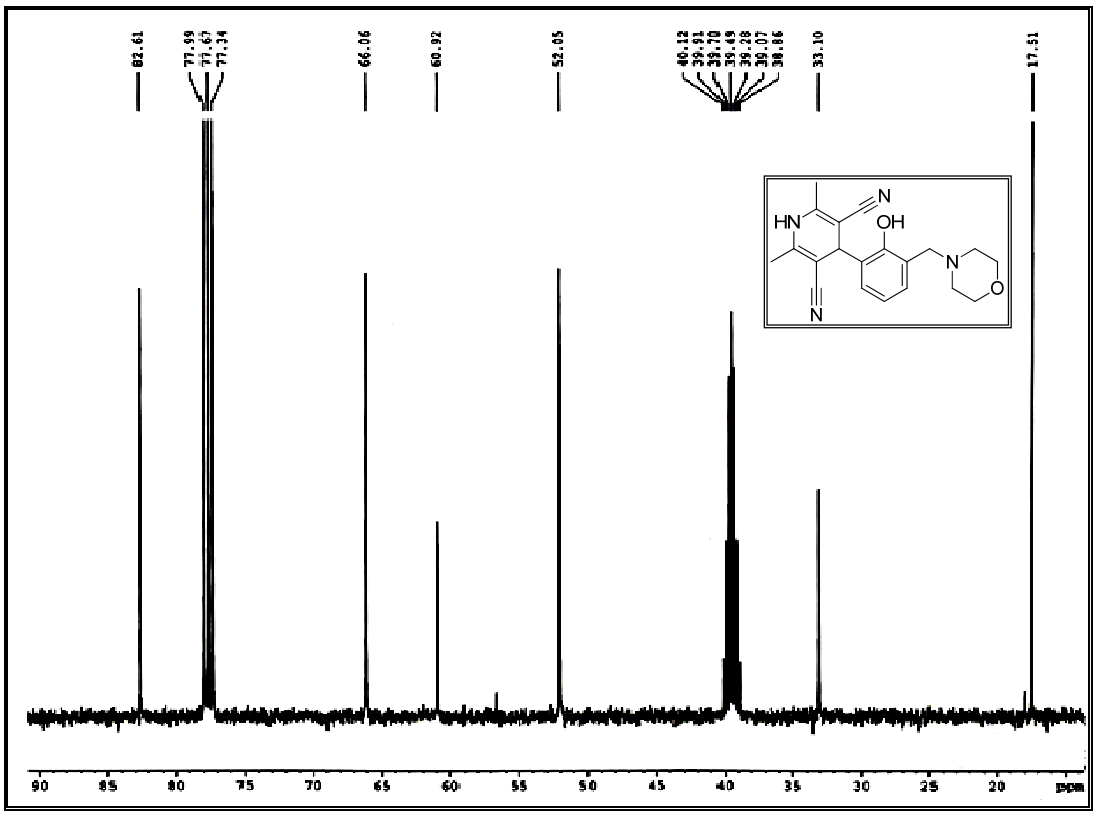
4.13.14 Expanded ^{1}H NMR Spectrum of MNP-MB-106



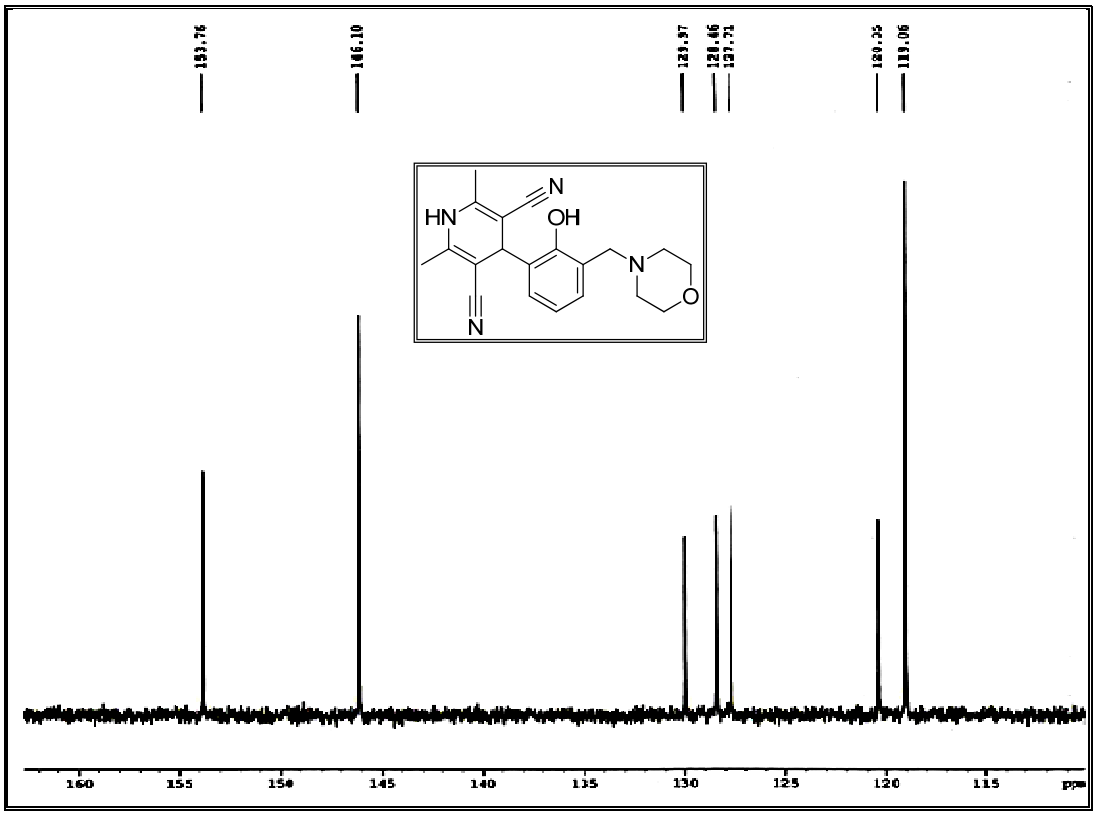
4.13.15 ^{13}C NMR Spectrum of MNP-MB-106



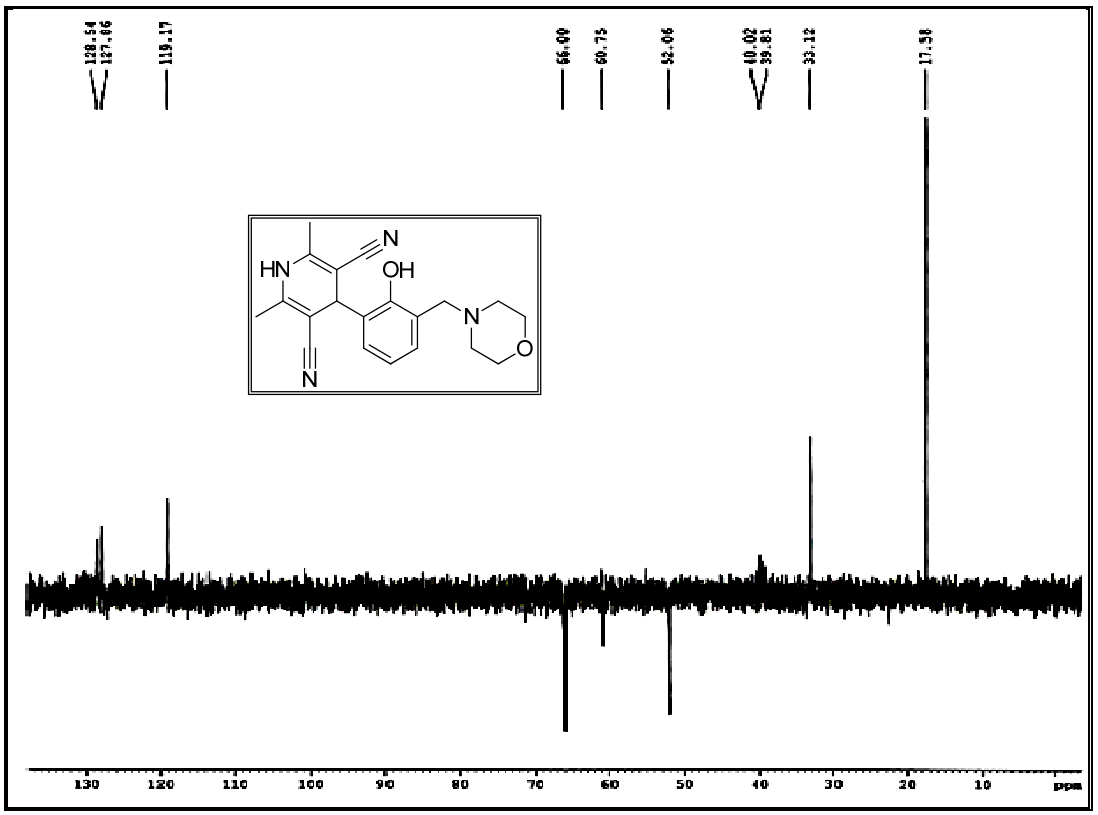
4.13.16 Expanded ^{13}C NMR Spectrum of MNP-MB-106



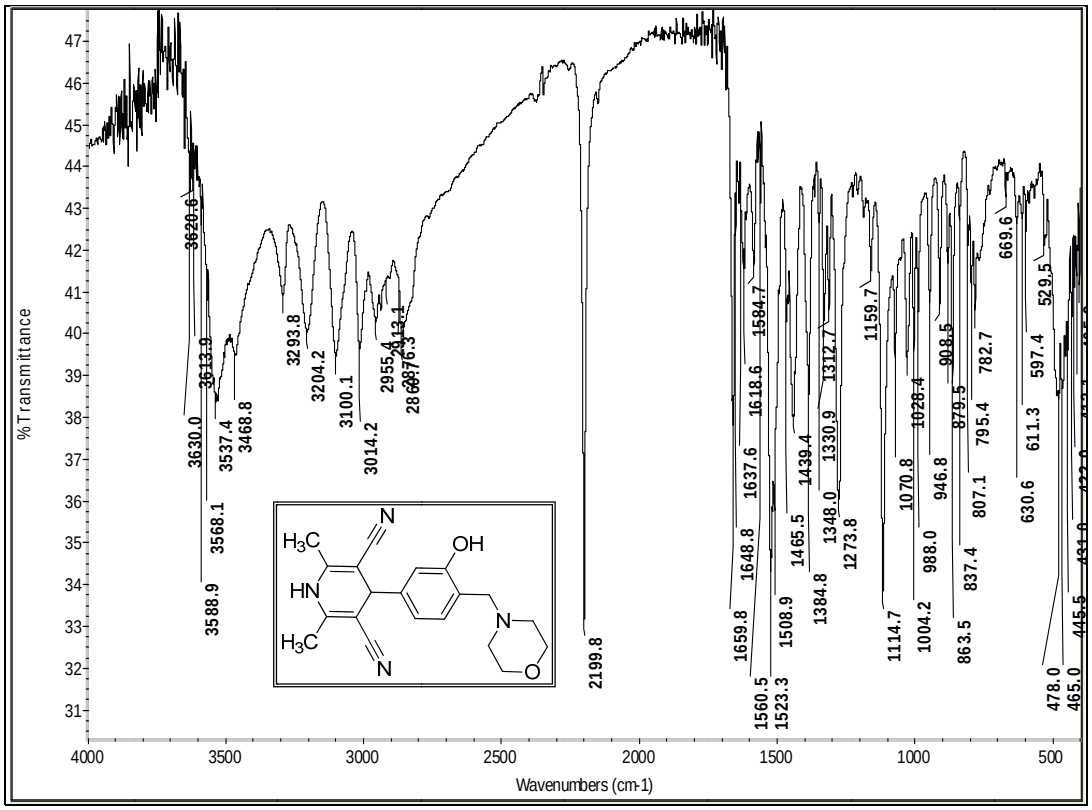
4.13.17 Expanded ^{13}C NMR Spectrum of MNP-MB-106



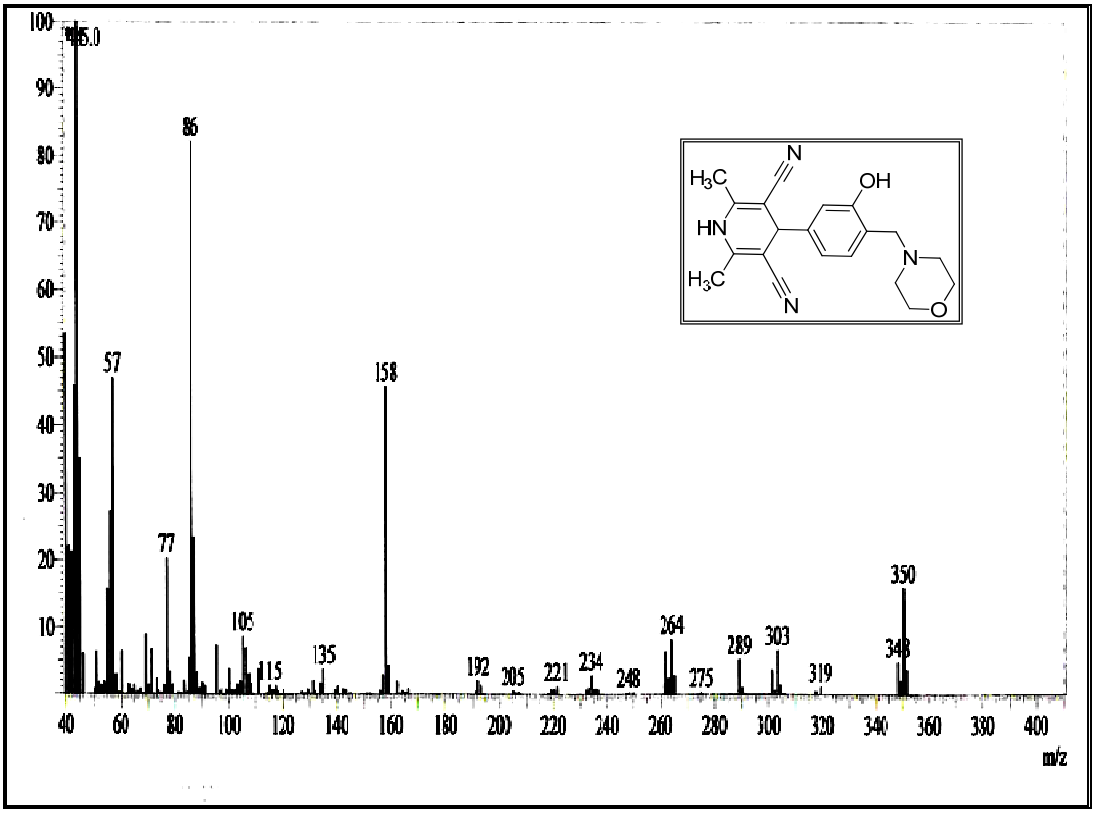
4.13.18 Expanded ^{13}C NMR Spectrum of MNP-MB-106



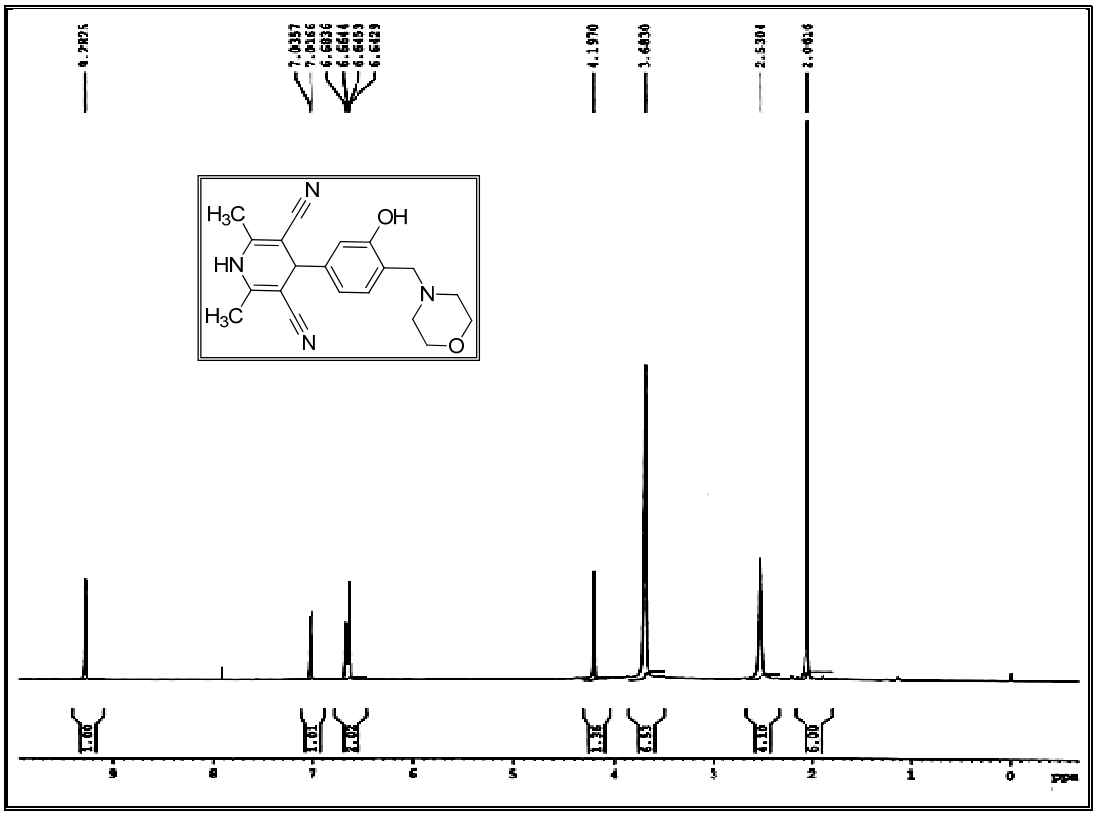
4.13.19 IR Spectrum of MNP-MB-206



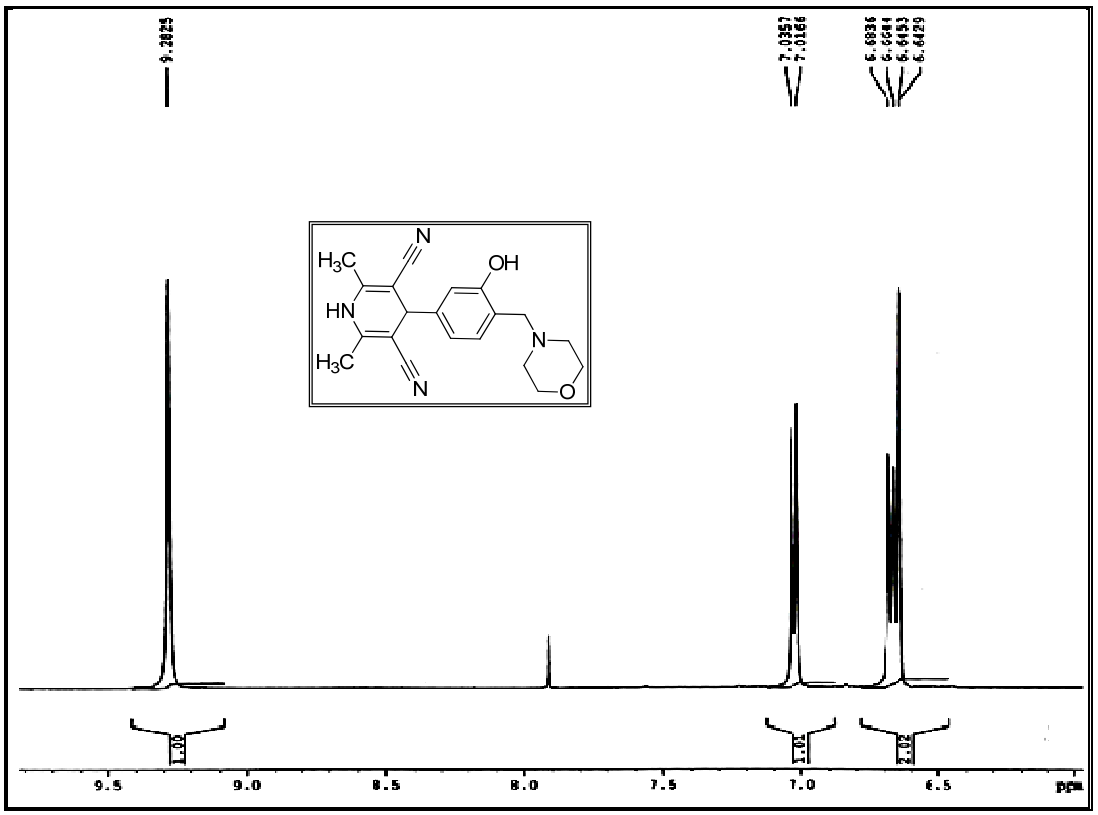
4.13.20 Mass Spectrum of MNP-MB-206



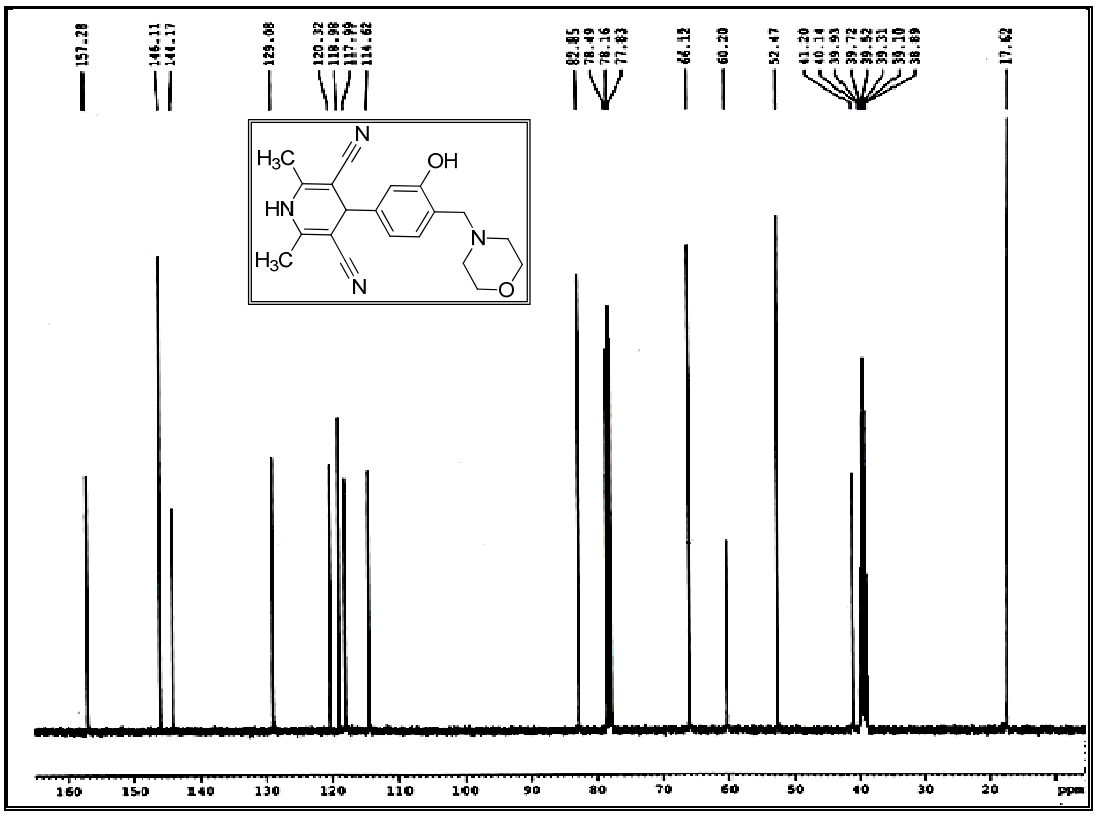
4.13.21 ^{1}H NMR Spectrum of MNP-MB-206



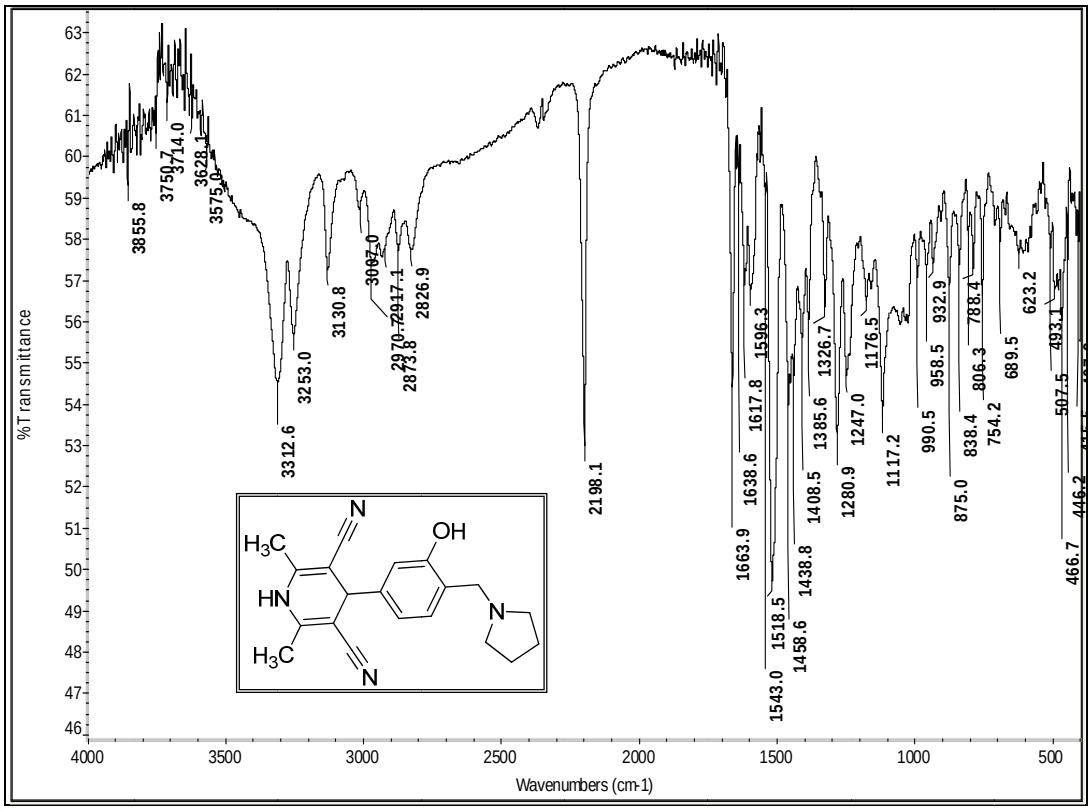
4.13.22 Expanded ^{1}H NMR Spectrum of MNP-MB-206



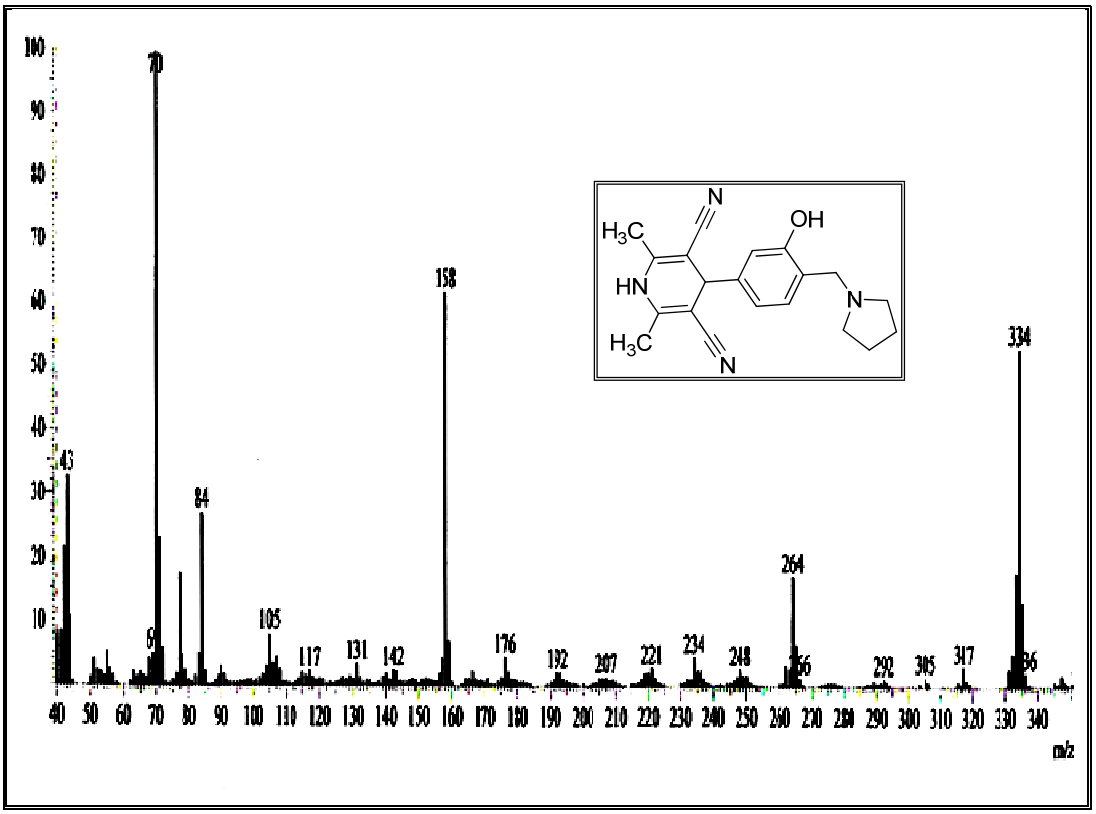
4.13.23 ^{13}C NMR Spectrum of MNP-MB-206



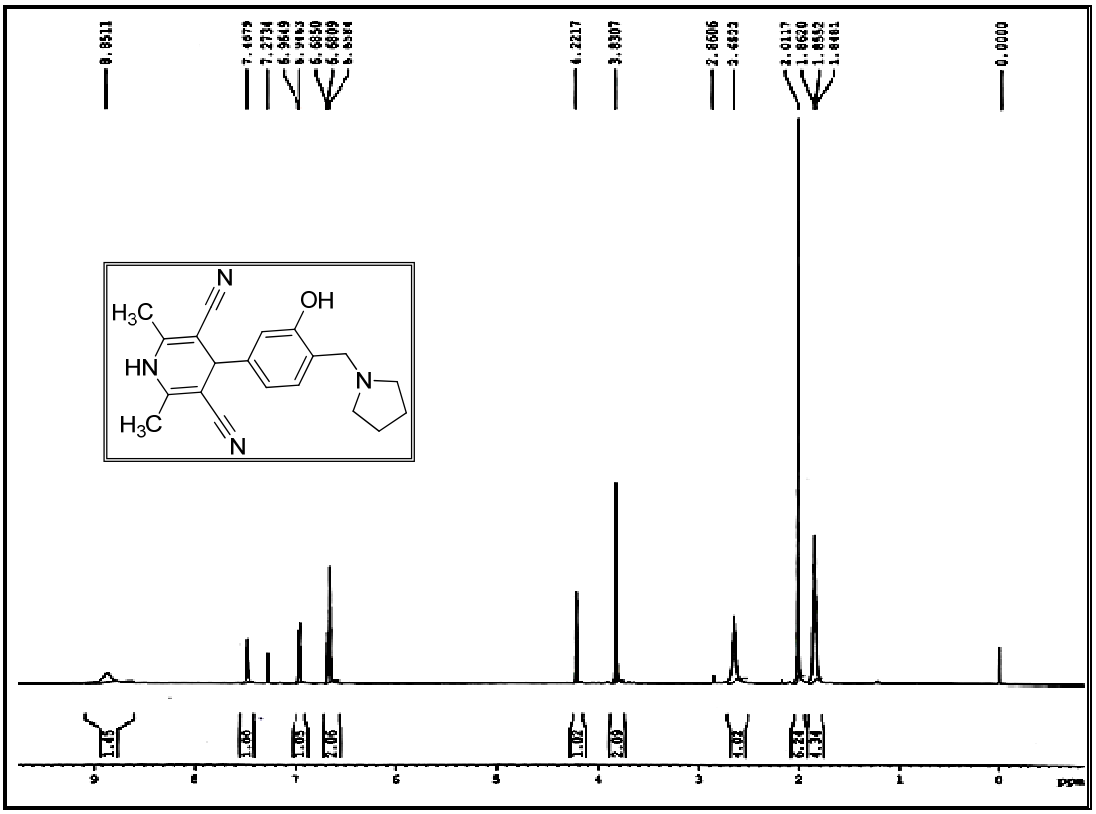
4.13.24 IR Spectrum of MNP-MB-209



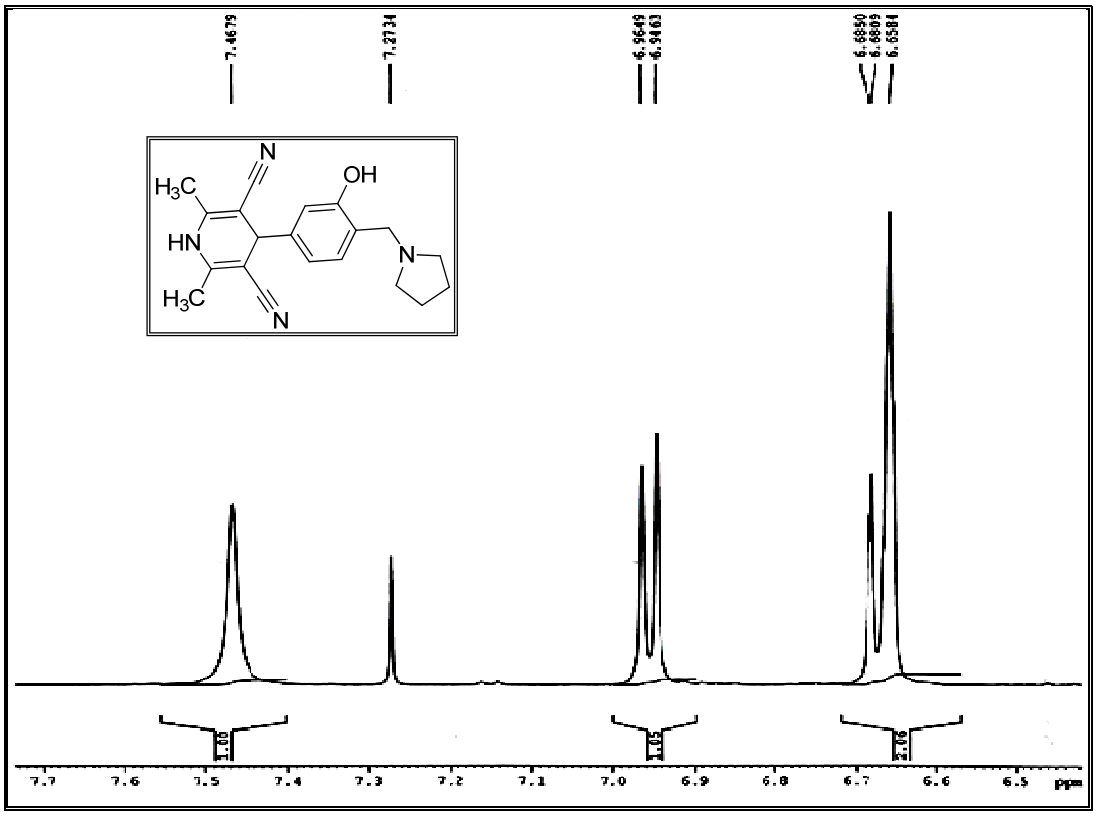
4.13.25 Mass Spectrum of MNP-MB-209



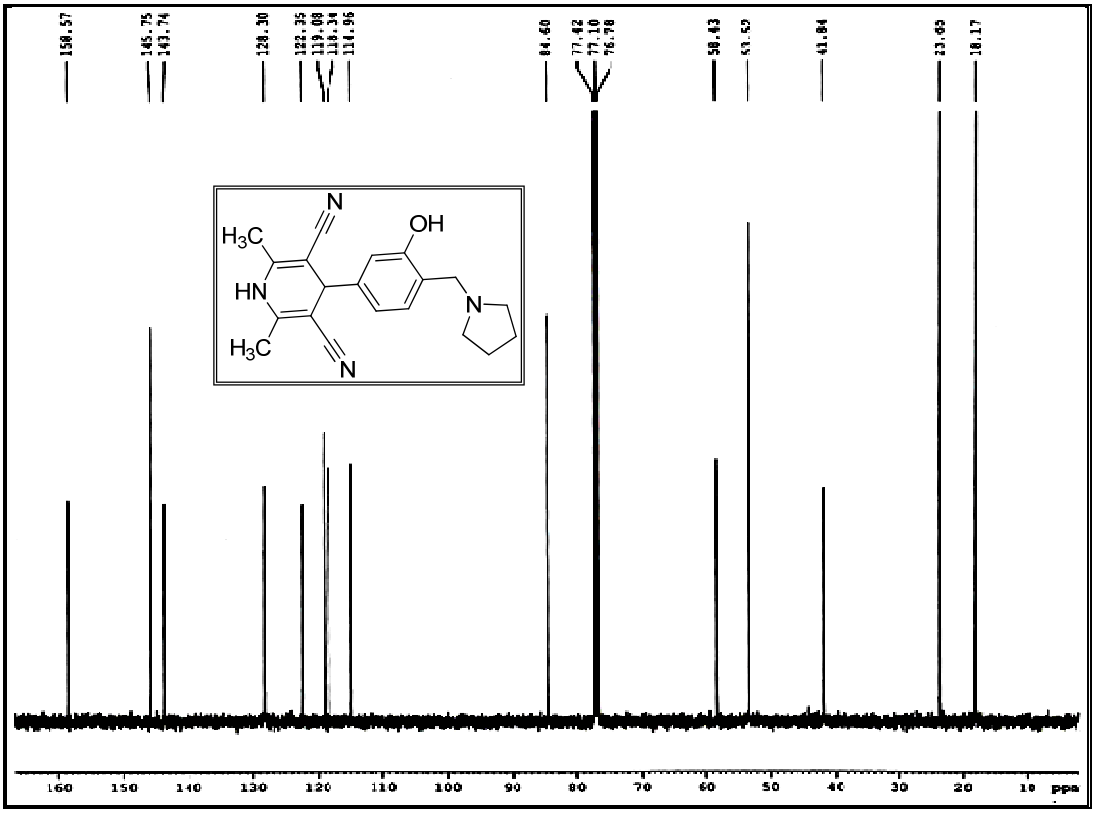
4.13.26 ^{1}H NMR Spectrum of MNP-MB-209



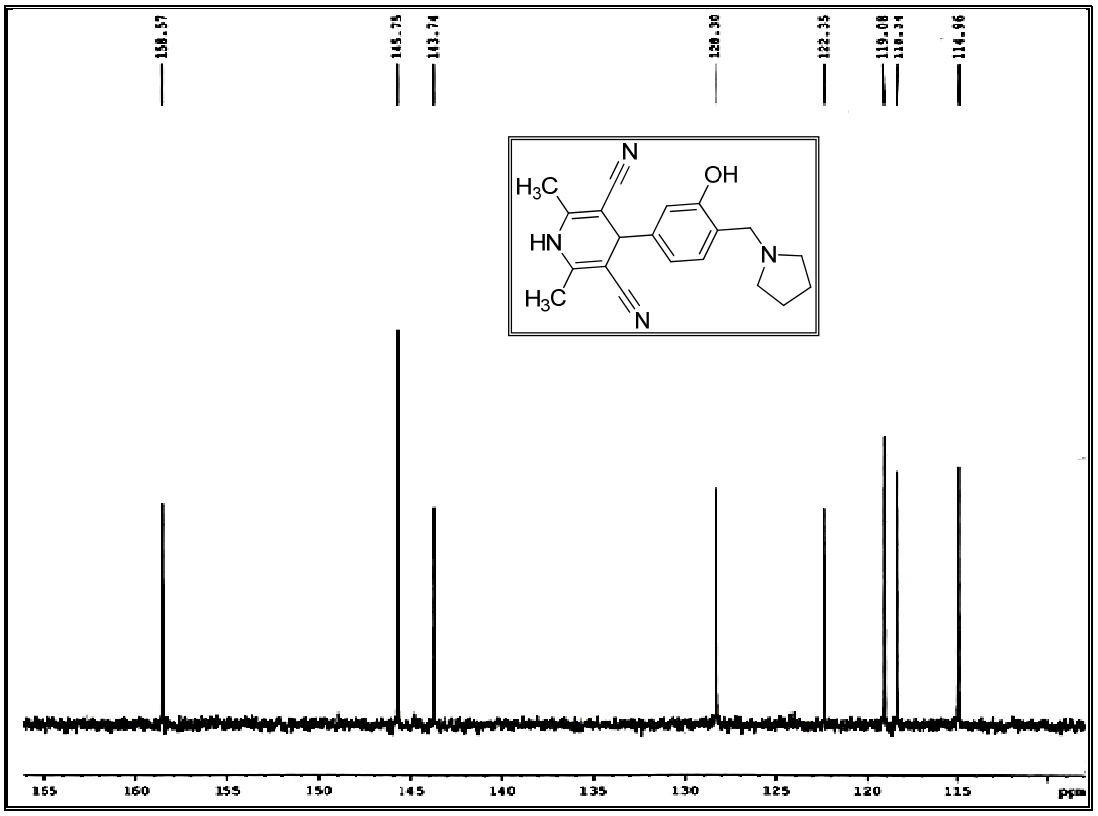
4.13.27 Expanded ^{1}H NMR Spectrum of MNP-MB-209



4.13.28 ^{13}C NMR Spectrum of MNP-MB-209



4.13.29 Expanded ^{13}C NMR Spectra of MNP-MB-209



4.14 REFERENCES

1. (a)F. Palacios, E. Herran, G. Rubiales and C. Alonso; *Tetrahedron*; 63, 523 5669, **2007**. (b) D. Triggle; *Cell Mol. Neurobiol.*; 23, 293, **2003.** (c) A. A. Patchett and R. Nargund; *Annu. Rep. Med. Chem.;* 35, 289, **2000.**
2. J. K. Jaroslav, P. Lubos and C. Czech; *Chem. Comm.;* 39 (3), 854, C.A., 81, 13360q **1974.**
3. W. James, U.S. 3,973,025; Brit.Appl. 74/22,451; C.A. 85, 177262t, **1976.**
4. P. Cozzi, G. Briatico, D. Giudici, A. Rossi and E. D. Salle; *Med. Chem. Res.*; 6, 611, **1996.**
5. K. Ohsumi, K. Ohishi, Y. Morinaga, R. Nakagawa, Y. Suga, T. Sekiyama, Y. Akiyama, T. Tusji and T. Tsuruo; *Chem. Pharm. Bull.*; 43 (5), 818, **1995.**
6. B. Roman, M. Marian and N. Pawl; *Pol.*, 86,477; C.A., 87, 135104d, **1977.**
7. K. Josef, K. Antonin, P. Zdenek and P. Jaroslav; *Collect Czech. Chem. Commun.*; 43 (4), 1068; C.A., 89, 10891u **1978.**
8. S. Yamada, M. Kuramoto and Y. Kikugawa; *Tetrahedron Lett.*; 10, 3101, **1969.**
9. J. Kuthan and E. Janeckova; *Collect. Czech. Chem. Commun.*; 29, 1654, **1964.**
10. S. Yamada and Y. Kikugawa; *Chem. Ind (London*); 52, 2169 **1966.**
11. R. Luke and Y. Kuthan; *Collect. Czech. Chem. Comm.*; 26, 1422, **1961.**
12. J. Kuthan and R. Bartonickova; *Collect. Czech. Chem. Comm.*; 30, 2609, **1965.**
13. T. Godfraind, R. Miller and M. Wibo; *Pharmacol. Rev*,; 38, 321, **1986.**
14. M. Lakshmi and M. Koosam; *J. Chem. Sci.*; 122 (1), 63, **2010.**
15. H. Eberhard, F. Gerhard, J. Edgar, B. Roland, B Ehrenfried, B, Gerhard, E., Werner, F.; Ger. (East) 122, 524; C.A. 87, 23073m. **1977.**
16. M. Carsten and B. Hans; *S. African*, 77 07, 702; C.A. 90, 18681z. **1979.**
17. V. V. Kastron, G. Duburs, R. Vitolis, I. Skrastins and A. Kimenis; *Khim-Farm. Zh.*; 19 (5), 545, **1977;** C.A., 104, 88392d 1986 **1985.**
18. E. Wehinger, F. Bossert, G. Franckowiak and H. Meyer; *Ger. Offen*. 2, 658, 804; C.A., 89, 109133j, **1978.**

19. P. Cozzi, G. Briatico, D. Giudici, A. Rossi and E. D. Salle; *Med. Chem. Res*.; 6, 611, **1996.**
20. K. Ohsumi, K. Ohishi, Y. Morinaga, R. Nakagawa, Y. Suga, T. Sekiyama, Y. Akiyama, T. Tsuji and T. Tsuruo; *Chem. Pharm. Bul*.; 43 (5), 818, **1995.**
21. K. Parmar, Ph. D. Thesis, Saurashtra University **1994**.
22. B. Varu, Ph.D. Thesis, Saurashtra University **2001.**
23. M. Mahendra, B. H. Doreswamy, M. A. Sridhar., J. Shashidhara Prasad, P. Adlakha, K. Raval, B. Varu and A. Shah; J. *Anal. Sci*.; 19, 55, **2003.**
24. B. H. Doreswamy, M. Mahendra, A. Shah, M. A. Sridhar and J. Shashidhara Prasad; *Analytical Sciences*; 20, 13, **2004**.
25. V. B. Devaru, H. C. Devarajegowda, B. .H. Doreswamy, M. Mahendra, A. Shah, M. A Sridhar and J. Shashidhara Prasad.; *J.Anal. Sci*.; 20, 45, **2004**.
26. S. Thakrar, Ph.D. Thesis, Saurashtra University, **2010.**
27. C. N. O'Callaghn and T. B. H. McMurry; *J.Chem. Res, Symop.*; 9, 286, **1988** C.A. 110, 135047f, **1989.**
28. S. M. Fahmy, S. O. Abd Allah, R. M. Mohareb; *Synthesis*; 11**,** 976, **1984,** C.A., 102, 203849f **1985.**
29. Drug Data Report; 17 (1), 48, **1995.**
30. Durg Data Report**;** 19 (6), 557, **1997**.
31. N. M. Evdokimov, I. V. Magedov, A. S. Kireev and A. Kornienko; Org. Lett.; 8 (5), 899, **2006.**
32. F. Bossert and W. Vater; *Ger. Offen.;* 1, 813, 436, **1970**; C.A. 74, 22702k, **1971.**
33. F. Bossert and W. Vater; *Ger. Offen*.; 1963, 188, **1971**; C.A. 75, 63618b **1971.**
34. F. Bossert and W. Vater; *Ger. Offen*.; 2, 005, 166, **1971.** C.A., 75, 15168d **1971.**
35. F. Bossert, A. Heise, S. Kazda., E. Klauke and K. Stoepel; *Ger. Offen*.; 2,753, 946; C.A., 92, 76294u, **1980.**
36. S. M. Pitzenberger and B. M. Trost; Eur. Pat. Appl.; 234776 C.A. 108, 167304, **1988.**
37. G. Duburs, B. Cekavicius, A. Sausins, R. Vitolina and A. Kimenis; *Ger. Offen.*; 2908738; C.A., 92, 58623r, **1980.**

38. W. Minoru, M. Kenji, T. Yoshinori, H. Tako, H. Tamotsu and Y. Koji; *Eur. Pat. Appl.; EP* 93, 945 **1983**. Jp Appl 82/71,425 **1982**; C.A., 100, 120843y **1984**.

39. V. Sridharan, P. T. Perumal, C. Avendan and J. C. Menendez; Tetrahedron; 63, 4407, **2007.**

40. M. L. Kantam, T. Ramani, L. C. Garcoa and B. M. Choudary; *Catal. Comm.*; 10, 370, **2009.**

41. A. Hingarajiya, Ph.D. Thesis, Saurashtra University, **1997.**

42. A. Sarvani, Ph.D. Thesis, Saurashtra University, **1997.**

43. H. Engi, H. Sakagami, M. Kawase, A. Parecha, D. Manvar, H. Kothari, P. Adlakha, A. Shah, N. Motohashi, I. Ocsovszki and J. Molnar; *in vivo*; 20, 637, **2006.**

44. M. Mahendra, B. H. Doreswamy, M. A. Sridhar, Shashidhara Prasad J., A. R. Parecha, J. A. Patel, D. Manvar, K. Dholaria and A. Shah; *Cryst. Res. Tech.*; 41, 92, **2006**.

45. M. Mahendra, B. H. Doreswamy, M. A. Sridhar, Shashidhara Prasad J., A. R. Parecha, J. A. Patel and A. Shah**;** *J. Anal. Sci.*; 20, 19, **2004.**

46. S. Naveen, R. Kakadiya, J. Bariwal, V. Virsodia, D. Karia, A. Shah, M. A. Sridhar and Shashidhara Prasad J.; *Mol. Cryst. Liq. Cryst*.; 474, 55, **2007.**

47. C. Mannich and W. Krosche; *Archiv der Pharmazie*,; 250, 647, **1912.**

48. F. F. Blicke; *Org. React.*; 1, 303, **1942.**

49. M. Arend, B. Westermann and N. Risch; *Angew. Chem., Int. Ed.*; *37*, 1044, **1998.**

50. M. Tramontini and L. Angiolini; *Tetrahedron*; 46, 1791, **1990**..

51. E. F. Kleinman; *Comprehensive Organic Synthesis*; 93, **1991.**

52. T. F. Cummings and J. R. Shelton; *J. Org. Chem.*; 25, 419, **1960.**

53. J. E. Fernandez and G. B. Butler; *J. Org. Chem.*; 28, 3258, **1963.**

54. J. H. Burckhalter, J. N. Wells and W. J. Mayer; *Tetrahedron Lett.*; 21, 1353, **1964.**

55. E. R. Alexander and E. J. Underhill; *J. Am. Chem. Soc.*; 71, 4014, **1949**.

56. B. List; *Tetrahedron*; 58, 5573, **2002.**

57. W. S. Jen, J. J. M. Wiener and D. W. C. MacMillan; *J. Am. Chem. Soc.*; 122, 9874 **2000.**

58. Y. Huang, A. K. Unni, A. N. Thadani and V. H. Rawal; *Nature*; 424, 146, **2003.**

59. D. Uraguchi and M. Terada; *J. Am. Chem. Soc.*; 126, 5356, **2004**.

60. D. Nakashima and H. Yamamoto; *J. Am. Chem. Soc.*; 128, 9626, **2006**.

61. N. Marion, S.Díez-González and S. P. Nolan; *Angew. Chem., Int. Ed.*; 46, 2988, **2007.**

62. D. Bourissou, O. Guerret, F. P. Gabbaie and G. Bertrand; *Chem. Rev.*; 100, 39, **2000.**

63. R. L. Knight and F. J. Leeper; *J. Chem. Soc.,Perkin Trans*.; 1, 1891, **1998.**

64. D. Enders and U. Kallfass; *Angew. Chem., Int. Ed.*; 41, 1743, **2002**.

65. J. Read de Alaniz and T. Rovis; J. *Am. Chem. Soc.*; 127, 6284, **2005.**

66. P. Vachal, E. N. Jacobsen; *J. Am. Chem. Soc*.; 124, 10012, **2002.**

67. D. Seebach, A. K. Beck, M. Brenner, C. Gaul and A. Heckel; *Angew. Chem., Int. Ed.*; 40, 92, **2001.**

68. V. B. Gondi, M. Gravel and V. H. Rawal; *Org. Lett.*; 7, 5657, **2005.**

69. A. K. Unni, N. Takenaka, H. Yamamoto and V. H. Rawal; *J. Am. Chem. Soc.*; 127, 1336, **2005.**

70. T. Akiyama, J. Itoh, K.Yokota and K. Fuchibe; *Angew. Chem., Int. Ed.*; 43, 1566, **2004.**

71. C. H. Cheon and H. Yamamoto, *J. Am. Chem. Soc.*; 130, 9246, **2008**.

72. J. M. M. Verkade, L. J. C. Van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes; *Chem. Soc. Rev.*; 37, 29, **2007**.

73. Y. Omura, Y. Taruno, Y. Irisa, M. Morimoto, H. Saimoto and Y. Shigemasa; *Tetrahedron Lett.*; 42 , 7273, **2001.**

74. Lindsay, Anita, Ph.D. Thesis, Durham University, 2010.

75. M. Minakawa, H. M. Guo and F. Tanaka; *J Org Chem.*; 73 (21), 8669, **2008.**

76. J. Aritomi, S. Ueda and H. Nishimura; *Chem. Pharm. Bull.*; 28 (11), 3163 **1980.**

77. J. Aritomi and H. Nishimura; *Chem. Pharm. Bull.*; 29 (5), 1193, **1981.**

78. V. V. Dotsenko, S. G. Krivokolys ko and V. P. Litvinov; *Russ. Chem. Bull., Int. Ed*; 54 (11), 2692, **2005.**

79. V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov; *Russ. Chem. Bull., Int. Ed*; 56 (5), 1053, **2007.**

80. K. A. Frolov, V. V. Dotsenko, S. G. Krivokolysko and V. P. Litvinov; *Chemistry of Heterocyclic Compounds*; 46 (9), 1142, **2010.**

81. M. V. Aanandhi, S. Kalvikkarasi, K. A. Navamani and P. Shanmugasundaram; *RJPBCS*; 1 (4), 926, **2010.**

82. B. B. Subudhi, P. K. Panda and D. Bhatta; *Indian J. Chem.*; 48 (B), 725, **2009**.

83. D. V. Mane, S. B. Bhawsar, D. B. Shinde and M. S. Shingare; *Indian Journal of Heterocyclic Chemistry*, 4 (4), 311, **1995.**

84. D. Sielemann, R. Keuper and N. Risch; *Eur. J. Org. Chem.*; 3, 543, **2000.**

85. V. Michael, R. Georges and L. Michel; *Ger. Offen.*; 2,405,658; C.A., 81,169440b, **1974.**

86. D. J Triggle; Drugs acting on ion channels and membranes; Comprehensive Medicinal Chemistry; 3, 1047, **1990.**

87. A. P. Phillips; *J. Am. Chem. Soc.*; 71, 4003, **1949.**

88. A. P. Phillips; *J. Am. Chem. Soc.*; 73, 3522, **1951.**

89. R. P. Mariella and E. P. Belcher; *J. Am. Chem. Soc.*; 73, 2616, **1951.**

CHAPTER- 5

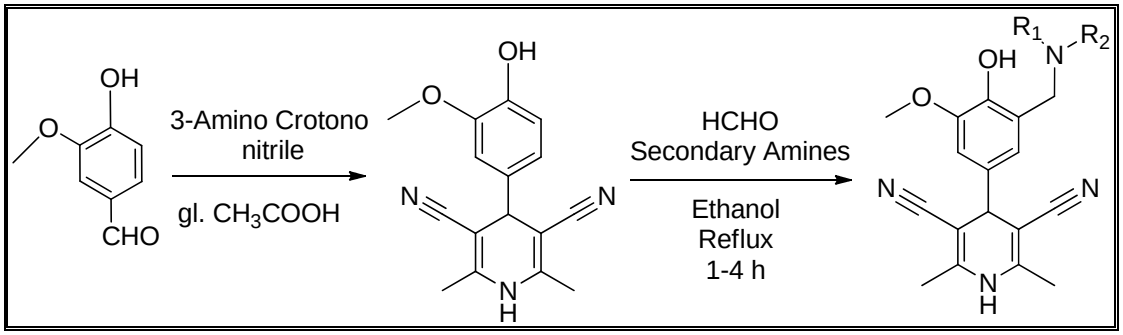
A RAPID AND FACILE SYNTHESIS OF SOME METHOXYLATED 3,5-DICYANO DIHYDROPYRIDINES & THEIR NOVEL MANNICH BASES

5.1 AIM OF CURRENT WORK

Chapter 4 covered Mannich reaction of 1,4-dihydropyridines containing one hydroxyl group on phenyl ring at C_4 position, while herein one methoxy/ethoxy group introduced along with one hydroxyl group on phenyl ring at C_4 position to give structural and molecular diversity to the 1,4-dihydropyridine scaffold for biological interest.

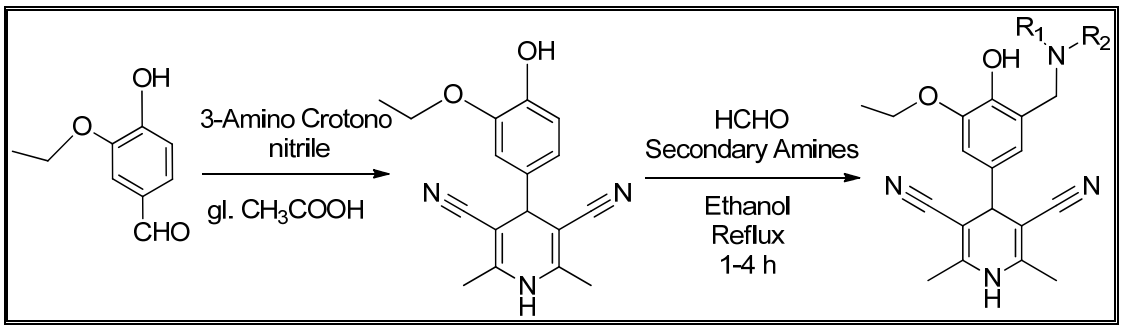
5.2 REACTION SCHEME

5.2.1 Preparation of 4-(4-Hydroxy-3-Methoxy-5-((substituted-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile



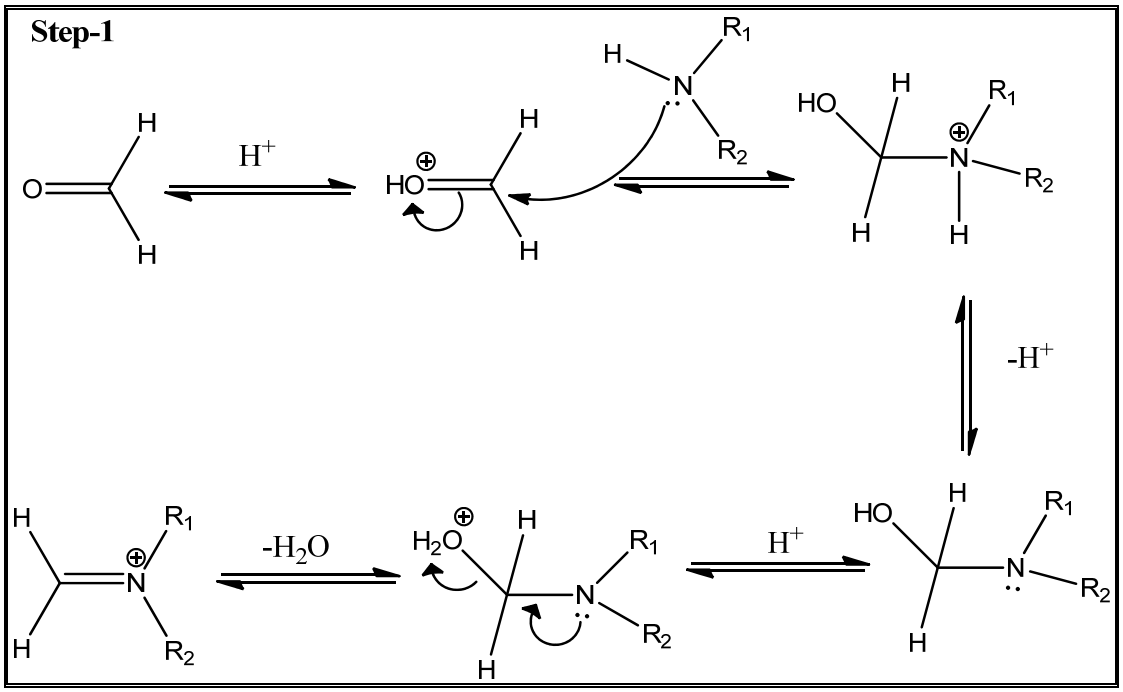
Where NR_1R_2= Secondary amines like piperidine, morpholine etc.

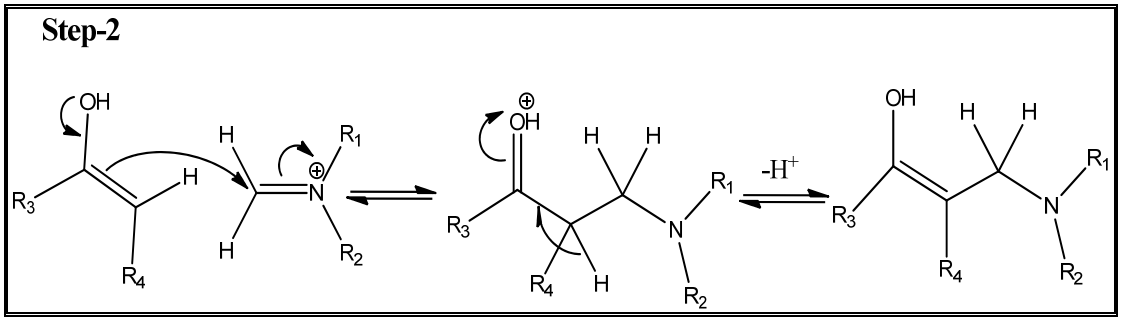
5.2.2 Preparation of 4-(4-Hydroxy-3-Ethoxy-5-((substituted-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile



Where NR_1R_2= Secondary amines like piperidine, morpholine etc.

5.3 PLAUSIBLE REACTION MECHANISM





Where, NR_1R_2 = Secondary amines like morpholine, piperidine

R_3 & R_4 = Phenyl ring

5.4 EXPERIMENTAL

5.4.1 Analysis Protocol

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV. IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr Powder method. Mass spectra were recorded on **Shimadzu GC-MS-QP-2010** model using Direct Injection Probe technique. ^{1}H NMR was determined in DMSO-d_6 solution on a **Bruker Avance II 400 MHz NMR spectrometer**. Elemental analysis of all the synthesized compounds was carried out on **Elemental Vario EL III Carlo Erba 1108** model. All the results are in agreements with the structures assigned.

5.4.2 Preparation of 4- (4-Hydroxy-3-Methoxy phenyl) -2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

A mixture of 4-hydroxy-3-methoxy benzaldehyde (0.01 mole) and 3-amino crotononitrile (0.02 mole) was taken in glacial acetic acid in a stoppered flask and stirred for half an hour at room temperature. During the reaction, progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After the completion of the reaction, the crystalline product was separated out automatically which was filtered and washed with diethyl ether.

5.4.3 Preparation of 4-(4-Hydroxy-3-Methoxy-5-((substituted-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (General Procedure)

A mixture of 4-(4-hydroxy-3-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (0.01 mole), secondary amine (0.0135 mole) and formaldehyde (0.02 mole) was taken in absolute alcohol in 250 mL round bottom flask. The reaction mixture was refluxed for 1-4 hours at reflux temperature till reaction completed. The

progress and the completion of the reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After completion of the reaction, the reaction mixture was allowed to cool at room temperature to obtain the product. When crystalline product was separated out, it was filtered and washed with cold ethanol. Similarly other compounds were also prepared.

The physical data of newly synthesized compounds are given in Table No.5.5.1

5.4.4 Preparation of 4-(4-Hydroxy-3-Ethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile

A mixture of 4-hydroxy-3-ethoxy benzaldehyde (0.01 mole) and 3-amino crotononitrile (0.02 mole) was taken in glacial acetic acid in a stoppered flask and stirred for half an hour at room temperature. During the reaction, progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After the completion of the reaction, the crystalline product was separated out automatically which was filtered and washed with diethyl ether.

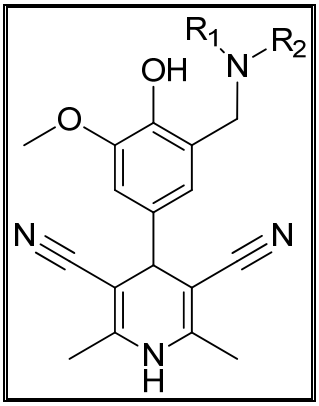
5.4.5 Preparation of 4-(4-Hydroxy-3-Ethoxy-5-((substituted-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (General Procedure)

A mixture of 4-(4-hydroxy-3-ethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (0.01 mole), secondary amine (0.0135 mole) and formaldehyde (0.02 mole) was taken in absolute alcohol in 250 mL round bottom flask. The reaction mixture was refluxed for 1-4 hours at reflux temperature till reaction completed. The progress and the completion of the reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: hexane (3:2) as a mobile phase. After completion of the reaction, the reaction mixture was allowed to cool at room temperature to obtain the product. When crystalline product was separated out, it was filtered and washed with cold ethanol. Similarly other compounds were also prepared.

The physical data of newly synthesized compounds are given in Table No.5.5.2

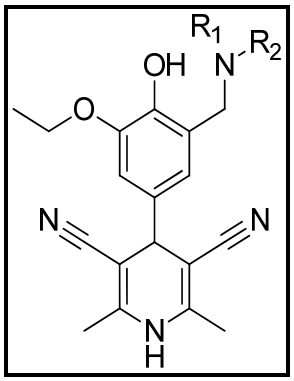
5.5 PHYSICAL DATA TABLE

5.5.1 Physical Data Table of 4-(4-Hydroxy-3-Methoxy-5-((substituted-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles



Sr. No.	Sample Code	Substitution NR_1R_2	Molecular Formula	M. Wt	MP °C	Yield %
1	MNP-MB-1	Piperazine	$C_{21}H_{25}N_5O_2$	379	268-270	66
2	MNP-MB-2	N-Me-piperazine	$C_{22}H_{27}N_5O_2$	393	242-244	73
3	MNP-MB-3	N-Et-Piperazine	$C_{23}H_{29}N_5O_2$	407	246-248	78
4	MNP-MB-4	N-phenyl piperazine	$C_{27}H_{29}N_5O_2$	455	260-262	81
5	MNP-MB-5	N-benzyl piperazine	$C_{28}H_{31}N_5O_2$	469	240-242	83
6	MNP-MB-6	Morpholine	$C_{21}H_{24}N_4O_3$	380	195-197	80
7	MNP-MB-7	Piperidine	$C_{22}H_{26}N_4O_2$	378	244-246	78
8	MNP-MB-8	2-methl piperidine	$C_{23}H_{28}N_4O_2$	392	180-182	75
9	MNP-MB-9	Pyrrolidine	$C_{21}H_{24}N_4O_2$	364	244-246	78
10	MNP-MB-10	N,N-Diethyl Amine	$C_{21}H_{26}N_4O_2$	366	176-178	65

5.5.2 Physical Data Table of 4-(4-Hydroxy-3-Ethoxy-5-((substituted-methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitriles



Sr. No.	Sample Code	Substitution NR_1R_2	Molecular Formula	M. Wt	MP °C	Yield %
1	MNP-MB-11	Piperazine	$C_{22}H_{27}N_5O_2$	393	252-254	65
2	MNP-MB-12	N-Me-piperazine	$C_{23}H_{29}N_5O_2$	407	208-210	75
3	MNP-MB-13	N-Et-Piperazine	$C_{24}H_{31}N_5O_2$	421	226-228	75
4	MNP-MB-14	N-phenyl piperazine	$C_{28}H_{31}N_5O_2$	469	220-222	80
5	MNP-MB-15	N-benzyl piperazine	$C_{29}H_{33}N_5O_2$	483	216-218	82
6	MNP-MB-16	Morpholine	$C_{22}H_{26}N_4O_3$	394	236-238	78
7	MNP-MB-17	Piperidine	$C_{23}H_{28}N_4O_2$	392	214-216	80
8	MNP-MB-18	2-methl piperidine	$C_{24}H_{30}N_4O_2$	406	202-204	73
9	MNP-MB-19	Pyrrolidine	$C_{22}H_{26}N_4O_2$	378	206-208	75
10	MNP-MB-20	N,N-Diethyl Amine	$C_{22}H_{28}N_4O_2$	380	195-197	62

5.6 SPECTRAL DISCUSSION

5.6.1 IR Spectra

IR spectra of the synthesized compounds were recorded on Shimadzu FT-IR 8400 model using KBr Powder method. Various functional groups present were identified by characteristic frequency obtained for them. The stretching frequency of OH group showed at 3650-3600 $cm^{-1}$and bending vibration at 1410-1310 cm^{-1}. The characteristic band of secondary N-H group showed in the region of 3500-3200 cm^{-1} with a deformation due to in plane bending at 1650-1550 cm^{-1}. Aromatic C-H stretching and bending frequencies showed between 3070-3030 cm^{-1} and 1600-1400 cm^{-1} respectively. C-H stretching and bending frequencies for methyl and methylene group were obtained near 2950-2850 cm^{-1} and 1450-1375 cm^{-1}. Characteristic frequency of C≡N showed at 2260-2200 cm^{-1}. Characteristic frequency of C-N stretching showed near 1350-1280 cm^{-1}. Ar-O-R stretching showed at 1260-1200 cm^{-1}. C-O stretching frequency showed at 1230-1140 cm^{-1}.

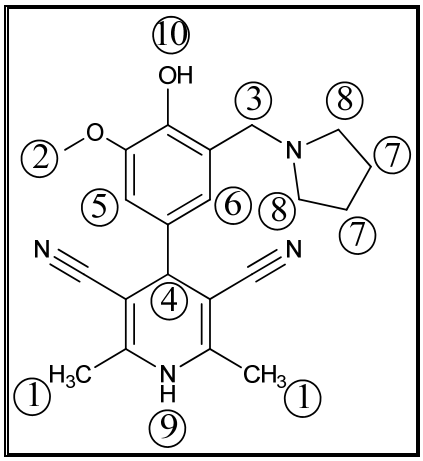
5.6.2 Mass Spectra

Mass spectra of the synthesized compounds were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound.

5.6.3 ^{1}H NMR Spectra

^{1}H NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR spectrometer by making a solution of samples in DMSO-d_6 solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Number of protons identified from ^{1}H NMR spectra and their chemical shift (δ ppm) were in the agreement of the structure of the molecule. *J* values were calculated to identify o, m and p coupling. In some cases, aromatic protons were obtained as multiplet. Interpretation of representative spectra is discussed as under.

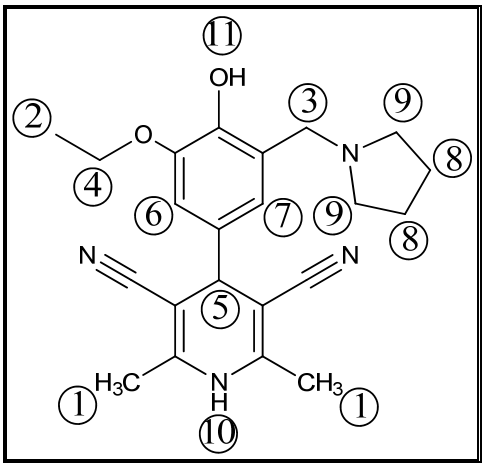
5.6.3.1 ^{1}H NMR of 4-(4-Hydroxy-3-Methoxy-5-(pyrrolidin-1-ylmethyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-9)



1. Proton no. 1 of total 6H of methyl group gave a singlet at 2.08 δ ppm.
2. Proton no. 2 of total 3H of OCH_3 group gave a singlet at 3.85 δ ppm.
3. Proton no. 3 of total 2H of methylene group gave a characteristic singlet at 3.89 δ ppm.
4. Proton no. 4 of total 1H gave a singlet at 4.21 δ ppm.
5. Proton no. 5 and 6 of total 2H of aromatic ring gave a singlet at 6.54 δ ppm and 6.69 δ ppm respectively.
6. Proton no. 7 of total 4H of secondary amine of pyrrolydine ring gave a singlet at 1.86 δ ppm.
7. Proton no. 8 of total 4H of secondary amine of pyrrolydine ring gave a singlet at 2.71 δ ppm.
8. Proton no. 9 of total 1H of secondary amine of dihydropyridine ring gave a singlet at 9.20 δ ppm.
9. Proton no. 10 of total 1H of OH group appeared as broad band at 5.69 δ ppm.

Thus, by observing and assigning the signals in the NMR spectrum, we can clearly suggest that the proposed structure for compound MNP-MB-9 has been confirmed. The spectrum is given on page no. 257.

5.6.3.2 ^{1}H NMR of 4-(4-Hydroxy-3-Ethoxy-5-(pyrrolidin-1-ylmethyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-19)



1. Proton no. 1 of total 6H of methyl group gave a singlet at 2.04 δ ppm.
2. Proton no. 2 of total 3H of ethoxy group gave a triplet at 1.36-1.40 δ ppm.
3. Proton no. 3 of total 2H of methylene group gave a characteristic singlet at 3.81δ ppm.
4. Proton no. 4 of total 2H gave a quartet at 4.00-4.06 δ ppm.
5. Proton no. 5 of total 1H gave a singlet at 4.19 δ ppm.
6. Proton no. 6 of 1H of aromatic ring gave a doublet at 6.5302-6.5460 δ ppm (*J*=1.92) and proton no. 7 of 1H gave a doublet at 6.66-6.67 δ ppm (*J*=1.96), which suggest meta coupling.
7. Proton no. 8 and 9 of total 4H and 4H of secondary amine of pyrrolydine ring gave a singlet at 1.81 δ ppm and 2.53 δ ppm respectively.
8. Proton no. 10 of total 1H of secondary amine of dihydropyridine ring gave a singlet at 9.32 δ ppm.
9. Proton no. 11 of total 1H of OH group appeared as a broad band at 5.8 δ ppm.

Thus, by observing and assigning the signals in the NMR spectrum and by calculating *J* value, we can clearly suggest that the proposed structure for compound MNP-MB-19 has been confirmed. The spectrum is given on page no. 265.

5.6.4 ^{13}C NMR Spectra

^{13}C NMR spectra of the synthesized compounds were recorded on Bruker Avance II 400 MHz NMR Spectrometer by making a solution of samples in DMSO-*d6* solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Types of carbons identified from NMR spectrum and their chemical shifts (δ ppm) were in the agreement with the structure of the molecule.

5.6.5 Elemental Analysis

Elemental analysis of the synthesized compounds was carried out on Vario EL Carlo Erba 1108 which showed calculated and found percentage values of Carbon, Hydrogen and Nitrogen in support of the structure of synthesized compounds.

The analytical data for individual compounds synthesized in this chapter are mentioned as follow.

5.7 ANALYTICAL DATA

1) 4-(4-Hydroxy-3-methoxy-5-(piperazin-1-ylmethyl) phenyl)-2,6-dimethyl -1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-1)

Yield: 66%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 379 (100%); Anal. Calcd. for $C_{21}H_{25}N_5O_2$: C, 66.47; H, 6.64; N, 18.46; O, 8.43; Found: C, 66.40; H, 6.63; N, 18.54.

2) 4-(4-Hydroxy-3-methoxy-5-((4-methyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-2)

Yield: 73%; **IR** (cm^{-1}): 3650-3600 (O-H str..), 3500-3200 (N-H str..), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 393 (100%); Anal. Calcd. for $C_{22}H_{27}N_5O_2$: C, 67.15; H, 6.92; N, 17.80; O, 8.13; Found: C, 67.26; H, 6.97; N, 17.75.

3) 4-(3-((4-Ethylpiperazin-1-yl) methyl) -4-hydroxy -5-methoxyphenyl) -2,6-dimethyl -1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-3)

Yield: 78%; **IR** (cm^{-1}): 3650-3600 (O-H str..), 3500-3200 (N-H str..), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 407 (100%); Anal. Calcd. for $C_{23}H_{29}N_5O_2$: C, 67.79; H, 7.17; N, 17.19; O, 7.85; Found: C, 67.65; H, 7.23; N, 17.15.

4) 4-(4-Hydroxy-3-methoxy-5-((4-phenyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-4)

Yield: 81%; **IR** (cm^{-1}): 3650-3600 (O-H str..), 3500-3200 (N-H str..), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 455 (100%); Anal. Calcd. for $C_{27}H_{29}N_5O_2$: C, 71.19; H, 6.42; N, 15.37; O, 7.02; Found: C, 71.05; H, 6.49; N, 15.29.

5) 4-(3-((4-Benzyl piperazin-1-yl) methyl)-4-hydroxy-5-methoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-5)

Yield: 83%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 469 (100%); Anal. Calcd. for $C_{21}H_{31}N_5O_2$: C, 71.62; H, 6.65; N, 14.91; O, 6.81; Found: C, 71.55; H, 6.74; N, 15.09.

6) 4-(4-Hydroxy-3-methoxy-5-(morpholine methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-6)

Yield: 80%; **IR** (cm^{-1}): 3693-3679 (O-H str.), 3323-3257 (N-H str.), 3027 (Ar C=C-H str.), 2994 (Asym C-H str. -CH_3), 2970 (Asym C-H str. -CH_2), 2941 (Sym C-H str. -CH_3), 2876-2844 (Sym C-H str. -CH_2), 2198 (C≡N str.), 1664-1639 (N-H bend), 1509, 1459, 1440 (Ar C=C str.), 1415 (C-H bend –CH_2), 1385 (C-H bend –CH_3), 1351 (C-N sec amine vib), 1281-1260 (Ar-O-R str.), 1156 (C-O str.), 850-790 (C-H oop def); **^{1}H NMR** (DMSO-d_6) δ ppm: 2.06 (s, 6H), 2.55 (s, 4H), 3.67 (s, 4H), 3.71 (s, 2H), 3.82 (s, 3H), 4.22 (s, 1H), 6.57 (d, 1H, *J*=1.64), 6.69-6.70 (d, 1H, *J*=1.76), 9.29 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.67, 18.27, 41.03, 52.44, 55.5356.29, 59.77, 66.04, 78.63, 83.08, 110.45, 119.0, 120.10, 121.17, 134.24, 145.57, 145.76, 147.33; **MS**: *m/z* = 380 (100%); Anal. Calcd. for $C_{21}H_{24}N_4O_3$: C, 66.30; H, 6.36; N, 14.73; O, 12.62; Found: C, 66.40; H, 6.33; N, 14.54.

7) 4-(4-Hydroxy-3-methoxy-5-(piperidin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-7)

Yield: 78%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def);); **^{1}H NMR** (DMSO-d6) δ ppm: 1.50 (s, 2H), 1.62-1.64 (t, 4H), 2.07 (s, 6H), 2.57-2.58 (b, 2H), 3.71 (s, 2H), 3.85 (s, 3H), 4.19 (s, 1H), 4.80 (b, 3H), 6.48 (d, 1H, *J*=1.60), 6.67(d, 1H, *J*=1.76), 9.16 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.95, 23.60, 25.52, 41.47, 533.50, 55.72, 61.63, 78.34, 83.49, 110.44, 119.32, 119.84, 121.28, 134.04, 145.93, 146.70, 147.61; **MS**: *m/z* = 378 (100%); Anal. Calcd. for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80; O, 8.45; Found: C, 69.80; H, 6.83; N, 14.94.

8) 4-(4-Hydroxy-3-methoxy-5-((2-methyl piperidin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-8)

Yield: 75%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.17-1.19 (d, 3H), 1.37-1.42 (t, 2H), 1.51-1.76 (m, b, 4H), 2.06 (s, 6H), 2.20-2.24 (t, 1H), 2.52-2.56 (b, 1H), 2.83-2.86 (q, 1H), 3.44 (s, 1H), 3.82 (s, 3H), 4.19 (s, 2H), 6.4813-6.4859 (d, 1H, *J*=1.84), 6.65-6.66 (d, 1H, *J*=1.96), 9.24 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.86, 18.42, 22.53, 25.36, 40.20, 41.32, 50.93, 55.64, 56.11, 56.57, 56.87, 78.80, 83.37, 110.27, 119.22, 119.58, 122.01, 134.03, 145.84, 146.67, 147.51; **MS**: *m/z* = 392 (100%); Anal. Calcd. for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.27; O, 8.15; Found: C, 70.30; H, 7.15; N, 14.31.

9) 4-(4-Hydroxy-3-methoxy-5-(pyrrolidin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-9)

Yield: 78%; **IR** (cm^{-1}): 3692-3678 (O-H str.), 3292-3238 (N-H str.), 3023-3011 (Ar C=C-H str.), 2990 (Asym C-H str. -CH_3), 2961 (Asym C-H str. -CH_2), 2900 (Sym C-H str. -CH_3), 2837 (Sym C-H str. -CH_2), 2198 (C≡N str.), 1657 (N-H bend), 1511,

1497, 1462 (Ar C=C str.), 1440 (C-H bend $-CH_2$), 1384 (C-H bend $-CH_3$), 1305 (C-N sec amine vib), 1283 (Ar-O-R str.), 1157 (C-O str.), 850-800 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.86 (s, 4H), 2.08 (s, 6H), 2.71 (s, 4H), 3.85 (s, 3H), 3.89 (s, 2H), 4.21 (s, 1H), 5.69 (b, 1H), 6.54 (s, 1H), 6.69 (s, 1H), 9.20 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 17.67, 23.06, 41.16, 52.89, 55.48, 57.19, 78.14, 83.14, 99.49, 110.30, 119.03, 119.34, 121.64, 133.81, 145.70, 145.17, 147.30; **MS**: *m/z* = 364 (100%); Anal. Calcd. for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37; O, 8.78; Found: C, 69.24; H, 6.53; N, 15.46.

10) 4-(3-((Diethylamino) methyl)-4-hydroxy-5-methoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-10)

Yield: 65%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $-CH_2$), 1375 (C-H bend $-CH_3$), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 366 (100%); Anal. Calcd. for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29; O, 8.73; Found: C, 68.78; H, 7.19; N, 15.26.

11) 4-(3-Ethoxy-4-hydroxy-5-(piperazin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-11)

Yield: 65%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $-CH_2$), 1375 (C-H bend $-CH_3$), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 393 (100%); Anal. Calcd. for $C_{22}H_{27}N_5O_2$: C, 67.15; H, 6.92; N, 17.80; O, 8.13; Found: C, 67.07; H, 6.93; N, 17.74.

12) 4-(3-Ethoxy-4-hydroxy-5-((4-methyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-12)

Yield: 75%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2210-2180 (C≡N str.), 1660-1580 (N-H bend),

1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $-CH_2$), 1375 (C-H bend $-CH_3$), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 407 (100%); Anal. Calcd. for $C_{23}H_{29}N_5O_2$: C, 67.79; H, 7.17; N, 17.19; O, 7.85; Found: C, 67.26; H, 7.25; N, 17.22.

13) 4-(3-Ethoxy-5-((4-ethyl piperazin-1-yl) methyl)-4-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-13)

Yield: 75%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $-CH_2$), 1375 (C-H bend $-CH_3$), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 421 (100%); Anal. Calcd. for $C_{24}H_{31}N_5O_2$: C, 68.38; H, 7.41; N, 16.61; O, 7.59; Found: C, 68.41; H, 7.43; N, 16.20.

14) 4-(3-Ethoxy-4-hydroxy-5-((4-phenyl piperazin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-14)

Yield: 80%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $-CH_2$), 1375 (C-H bend $-CH_3$), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 469 (100%); Anal. Calcd. for $C_{28}H_{31}N_5O_2$: C, 71.62; H, 6.65; N, 14.91; O, 6.81; Found: C, 71.65; H, 6.59; N, 14.95.

15) 4-(3-((4-Benzyl piperazin-1-yl) methyl)-5-ethoxy-4-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-15)

Yield: 82%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. $-CH_3$), 2930 (Asym C-H str. $-CH_2$), 2870 (Sym C-H str. $-CH_3$), 2845 (Sym C-H str. $-CH_2$), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend $-CH_2$), 1375 (C-H bend $-CH_3$), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 483 (100%); Anal. Calcd. for $C_{29}H_{33}N_5O_2$: C, 72.02; H, 6.88; N, 14.48; O, 6.62; Found: C, 72.14; H, 6.84; N, 14.51.

16) 4-(3-Ethoxy-4-hydroxy-5-(morpholine methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-16)

Yield: 78%; **IR** (cm^{-1}): 3677-3651 (O-H str.), 3301-3254 (N-H str.), 3015 (Ar C=C-H str.), 2970 (Asym C-H str. -CH_3), 2950 (Asym C-H str. -CH_2), 2873 (Sym C-H str. -CH_3), 2826 (Sym C-H str. -CH_2), 2197 (C≡N str.), 1664 (N-H bend), 1514, 1492, 1436 (Ar C=C str.), 1436 (C-H bend –CH_2), 1364 (C-H bend –CH_3), 1350 (C-N sec amine vib), 1290-1261 (Ar-O-R str.), 1156 (C-O str.), 860-800 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.40-1.44 (t, 3H), 2.06 (s, 6H), 2.56 (s, 4H), 3.69 (s, 4H), 3.72 (s, 2H), 3.71 (s, 2H), 4.03-4.09 (q, 2H), 4.19 (s, 1H), 6.53 (d, 1H, J=1.32), 6.69 (d, 1H, *J*=1.32), 9.20 (s, 1H), 10.62 (b, 1H); **^{13}C NMR** (DMSO-d6) δ ppm:14.57, 17.66, 41.08, 52.40, 60.38, 63.78, 66.08, 78.35, 83.14, 111.77, 118.98, 119.87, 120.96, 134.12, 145.68, 145.91, 146.54; **MS**: *m/z* = 394 (100%); Anal. Calcd. for $C_{22}H_{26}N_4O_3$: C, 66.99; H, 6.64; N, 14.20; O, 12.17; Found: C, 66.90; H, 6.73; N, 14.24.

17) 4-(3-Ethoxy-4-hydroxy-5-(piperidin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-17)

Yield: 80%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.41-1.46 (t, 3H), 1.50 (s, 2H), 1.61-1.64 (t, 4H), 2.06 (s, 6H), 2.56-2.58 (b, 2H), 3.71 (s, 2H), 4.03-4.08 (q, 2H), 4.18 (s, 1H), 6.48 (d, 1H, *J*=1.60), 6.66-6.67 (d, 1H, J=1.84), 9.19 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 14.82, 17.90, 23.54, 25.43, 41.35, 53.45, 61.20, 63.95, 78.52, 83.42, 111.88, 119.25, 119.84, 121.34, 145.86, 146.77, 146.85; **MS**: *m/z* = 392 (100%); Anal. Calcd. for $C_{23}H_{28}N_4O_2$: C, 70.38; H, 7.19; N, 14.27; O, 8.15; Found: C, 70.40; H, 7.21; N, 14.30.

18) 4-(3-Ethoxy-4-hydroxy-5-((2-methyl piperidin-1-yl) methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-18)

Yield: 73%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -

CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.11-1.18 (t, 3H), 1.37-1.42 (m, 5H), 1.53-1.76 (b, 4H), 2.05 (s, 6H), 2.18-2.23 (q, 1H), 2.54-2.55 (b, 1H), 2.82-2.85 (m, 1H), 3.39-3.43 (d, 1H), 4.01-4.06 (q, 2H), 4.17 (s, 2H), 6.47-6.48 (d, 1H, *J*=1.72), 6.64-6.65 (d, 1H, *J*=1.88), 9.27 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 14.65, 17.67, 18.28, 22.39, 25.15, 33.63, 41.03, 50.85, 55.99, 56.64, 83.16, 111.52, 119.02, 119.41, 121.98, 133.84, 145.64, 146.51, 146.66; **MS**: *m/z* = 406 (100%); Anal. Calcd. for $C_{24}H_{30}N_4O_2$: C, 70.91; H, 7.44; N, 13.78; O, 7.87; Found: C, 70.95; H, 7.39; N, 13.75.

19) 4-(3-Ethoxy-4-hydroxy-5-(pyrrolidin-1-yl methyl) phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-19)

Yield: 75%; **IR** (cm^{-1}): 3658-3624 (O-H str.), 3298-3247 (N-H str.), 3018 (Ar C=C-H str.), 2972 (Asym C-H str. -CH_3), 2919 (Asym C-H str. -CH_2), 2832 (Sym C-H str. -CH_3), 2800 (Sym C-H str. -CH_2), 2198 (C≡N str.), 1660 (N-H bend), 1518, 1497, 1479 (Ar C=C str.), 1458 (C-H bend –CH_2), 1388 (C-H bend –CH_3), 1341 (C-N sec amine vib), 1288-1255 (Ar-O-R str.), 1158 (C-O str.), 880-790 (C-H oop def); **^{1}H NMR** (DMSO-d6) δ ppm: 1.36-1.40 (t, 3H), 1.80-1.81 (d, 4H), 2.04 (s, 6H), 2.61-2.62 (d, 4H), 3.81 (s, 2H), 4.00-4.06 (q, 2H), 4.19 (s, 1H), 6.53 (d, 2H, *J*=2.12), 6.66-6.67 (d, 1H, *J*=1.96), 9.20 (s, 1H); **^{13}C NMR** (DMSO-d6) δ ppm: 14.68, 17.68, 23.17, 40.91, 52.96, 57.21, 63.80, 83.11, 111.88, 119.08, 119.33, 122.69, 133.89, 145.76, 146.36, 146.4; **MS**: *m/z* = 378 (100%); Anal. Calcd. for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80; O, 8.45; Found: C, 69.34; H, 6.53; N, 15.36.

20) 4-(3-((Diethyl amino) methyl)-5-ethoxy-4-hydroxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile (MNP-MB-20)

Yield: 62%; **IR** (cm^{-1}): 3650-3600 (O-H str.), 3500-3200 (N-H str.), 3040 (Ar C=C-H str.), 2980 (Asym C-H str. -CH_3), 2930 (Asym C-H str. -CH_2), 2870 (Sym C-H str. -CH_3), 2845 (Sym C-H str. -CH_2), 2210-2180 (C≡N str.), 1660-1580 (N-H bend), 1580, 1545, 1500 (Ar C=C str.), 1460 (C-H bend –CH_2), 1375 (C-H bend –CH_3), 1340 (C-N sec amine vib), 1260-1200 (Ar-O-R str.), 1180 (C-O str.), 810 (C-H oop def); **MS**: *m/z* = 380 (100%); Anal. Calcd. for $C_{22}H_{28}N_4O_2$: C, 69.45; H, 7.42; N, 14.73; O, 8.41; Found: C, 68.98; H, 7.43; N, 14.66.

5.8 RESULTS & DISCUSSION

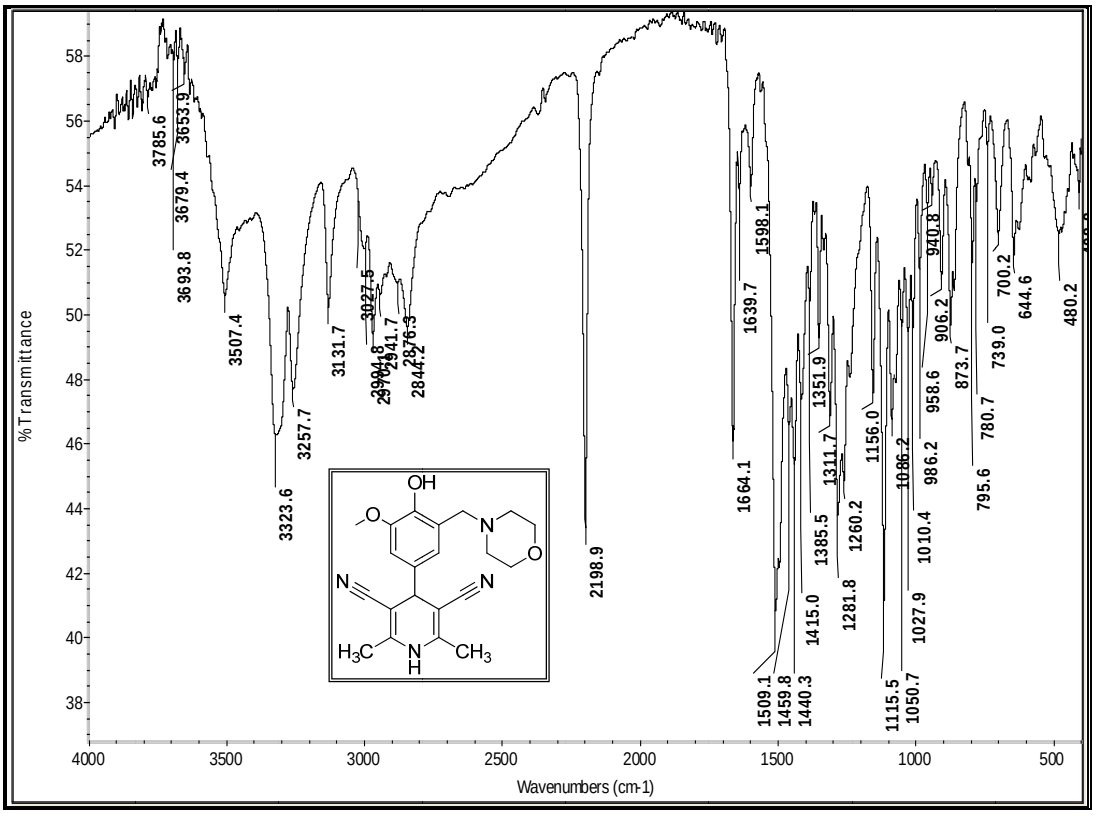
Present work covers the synthesis of Mannich reaction of 1,4-dihydropyridines containing hydroxyl and methoxy/ethoxy groups on phenyl ring at C_4 position. All the synthesized compounds are novel and well characterized by IR, Mass, ^{1}H NMR and ^{13}C NMR.

5.9 CONCLUSION

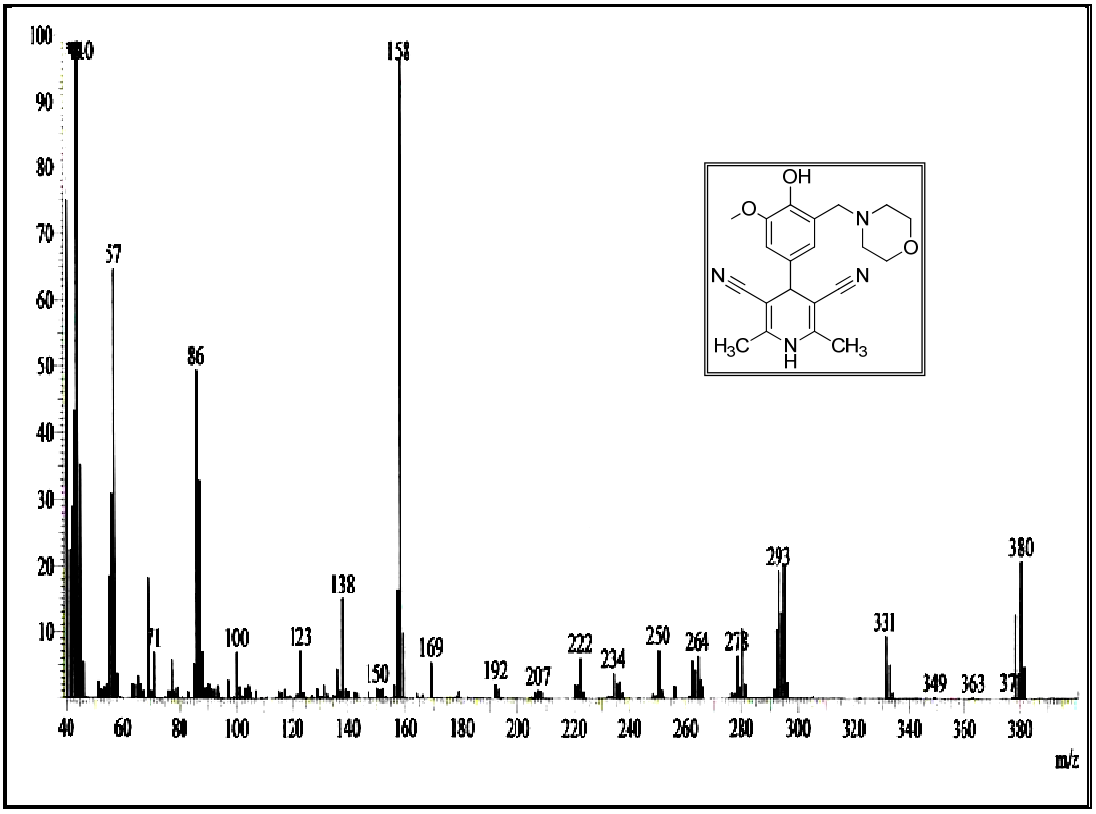
The Mannich bases of 3,5-dicyano-4-(substituted phenyl)-2,6-dimethyl-1,4-dihydropyridines are novel and therefore to evaluate their various biological activities are of interest. The activity is under study.

5.10 REPRESENTATIVE SPECTRA

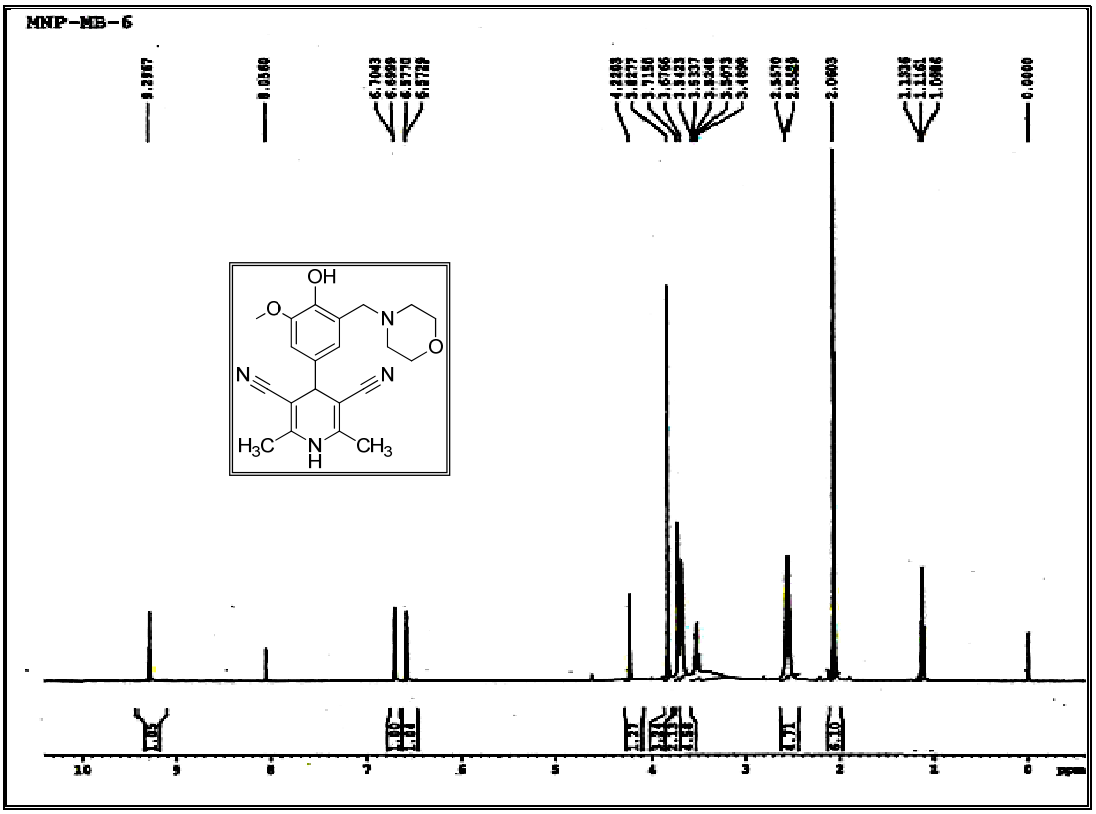
5.10.1 IR Spectrum of MNP-MB-6



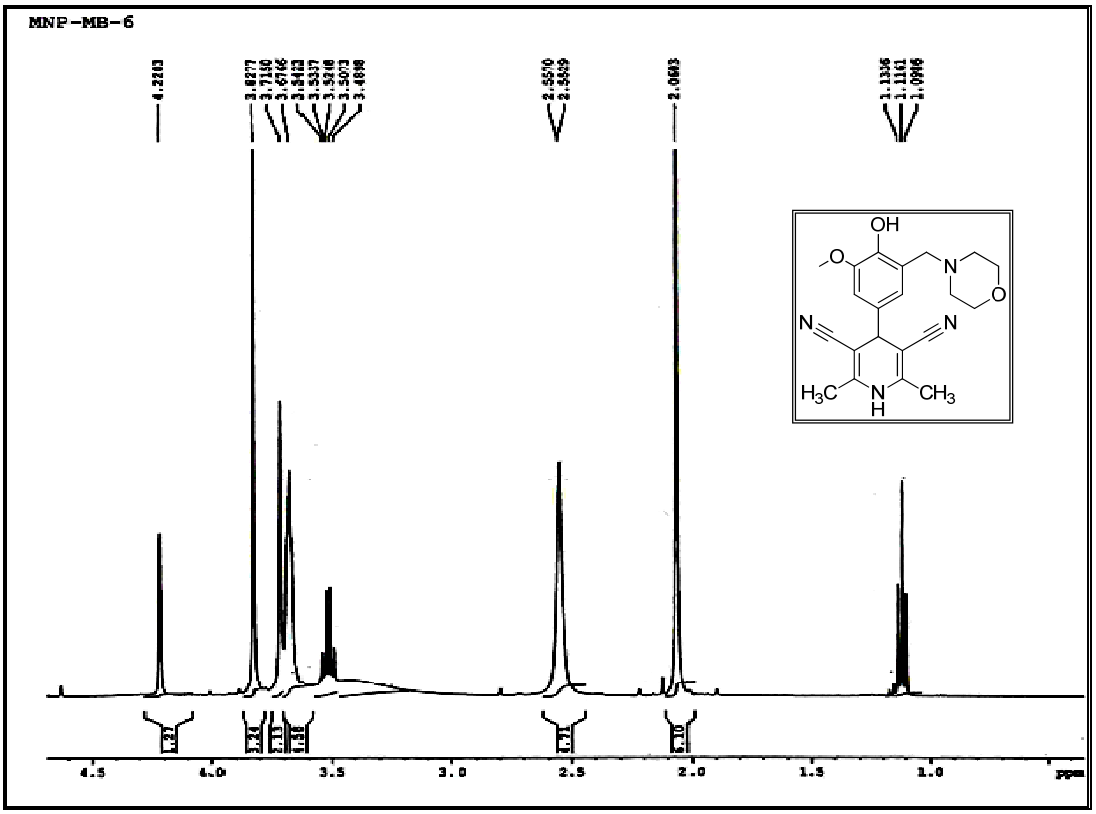
5.10.2 Mass Spectrum of MNP-MB-6



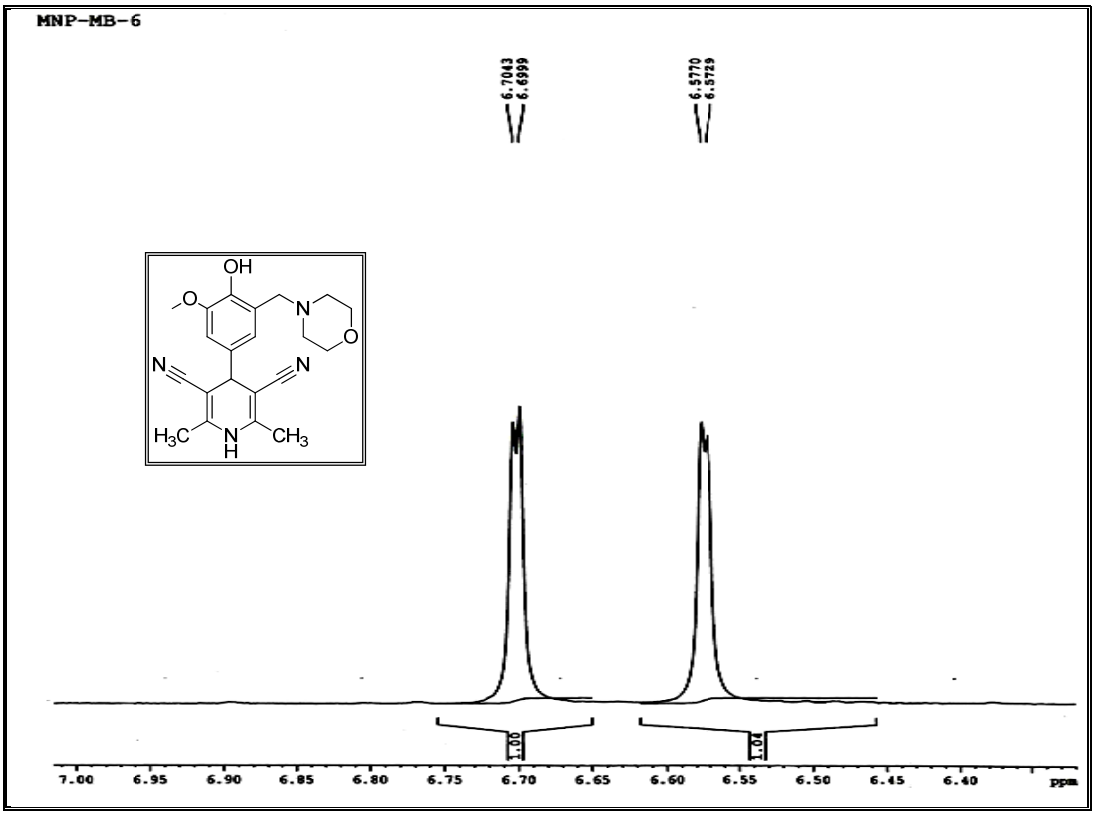
5.10.3 ^{1}H NMR Spectrum of MNP-MB-6



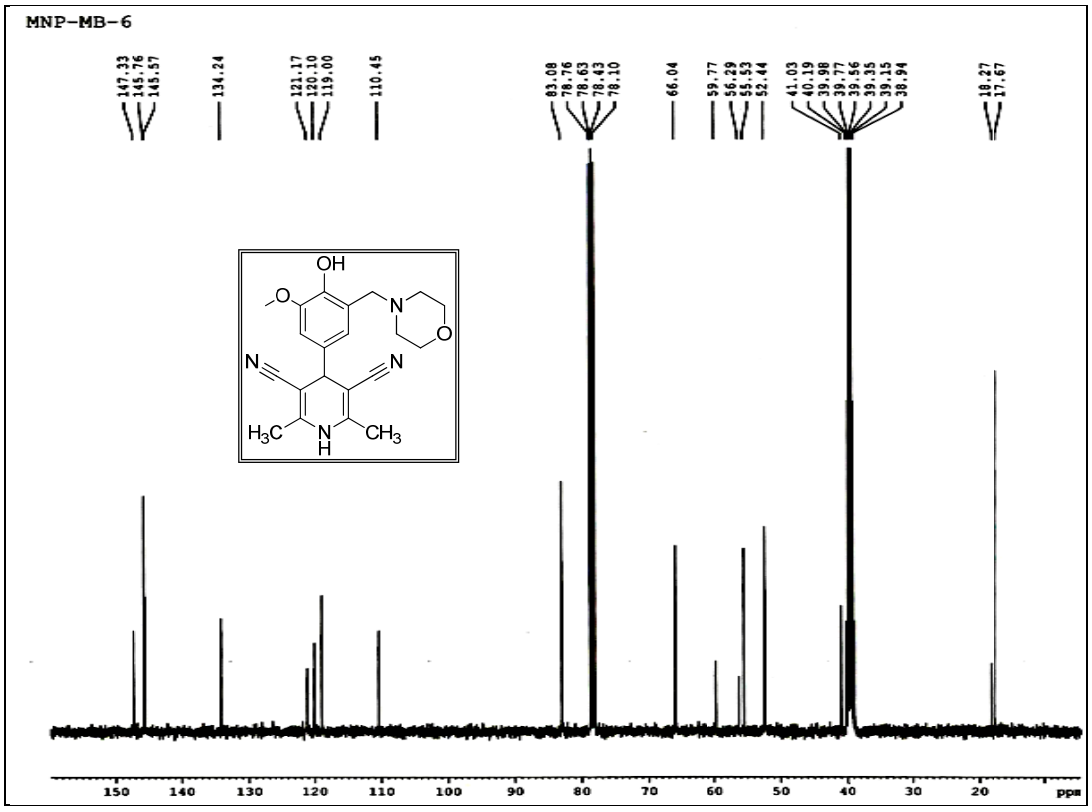
5.10.4 Expanded ^{1}H NMR Spectrum of MNP-MB-6



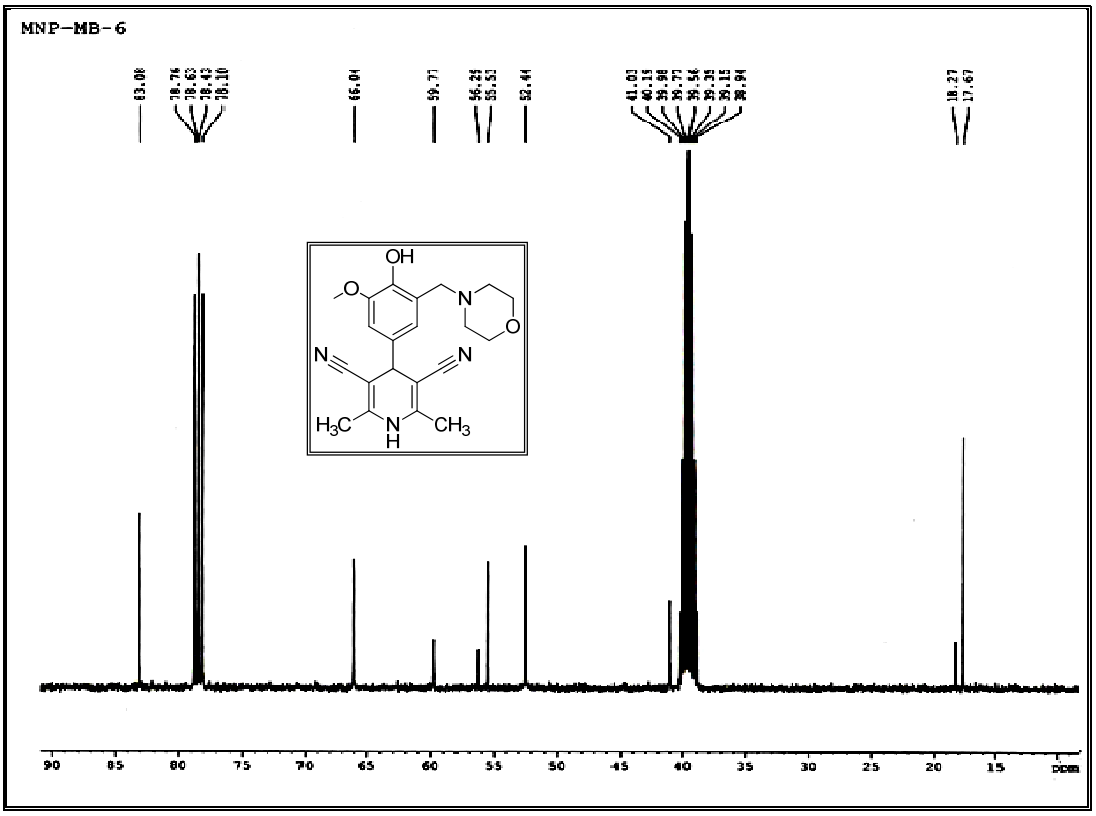
5.10.5 Expanded ^{1}H NMR Spectrum of MNP-MB-6



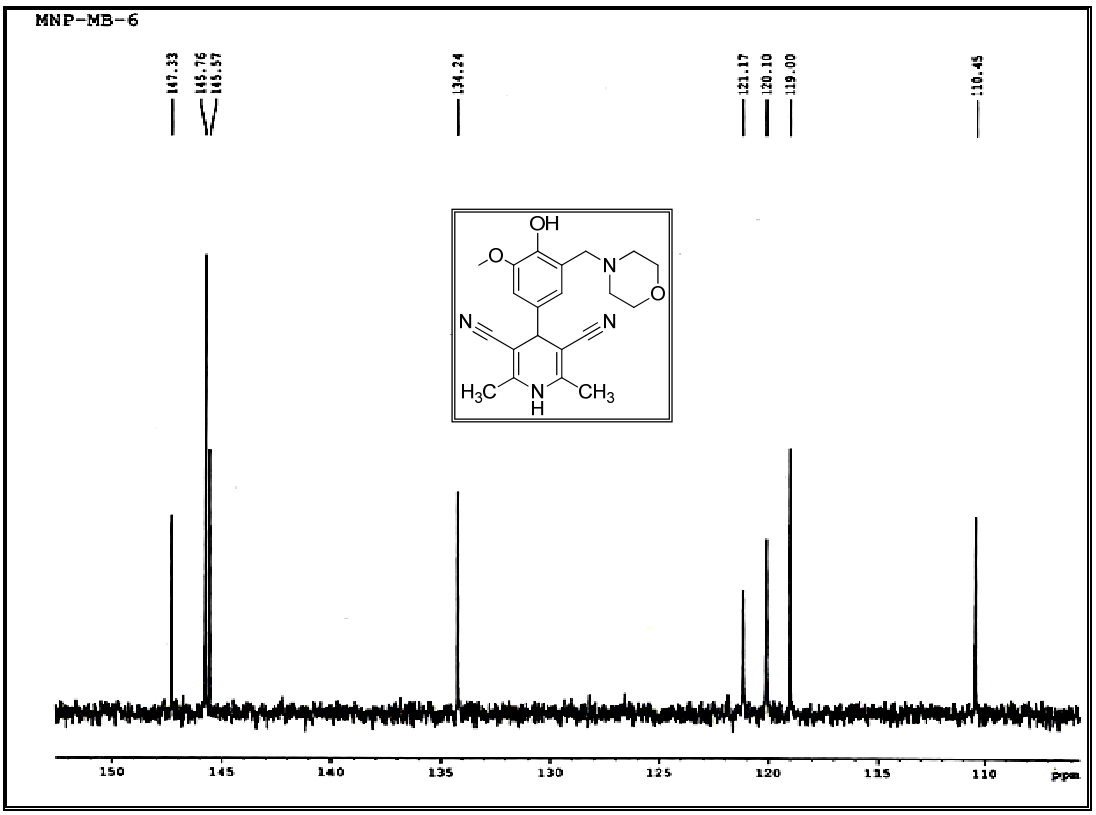
5.10.6 ^{13}C NMR Spectrum of MNP-MB-6



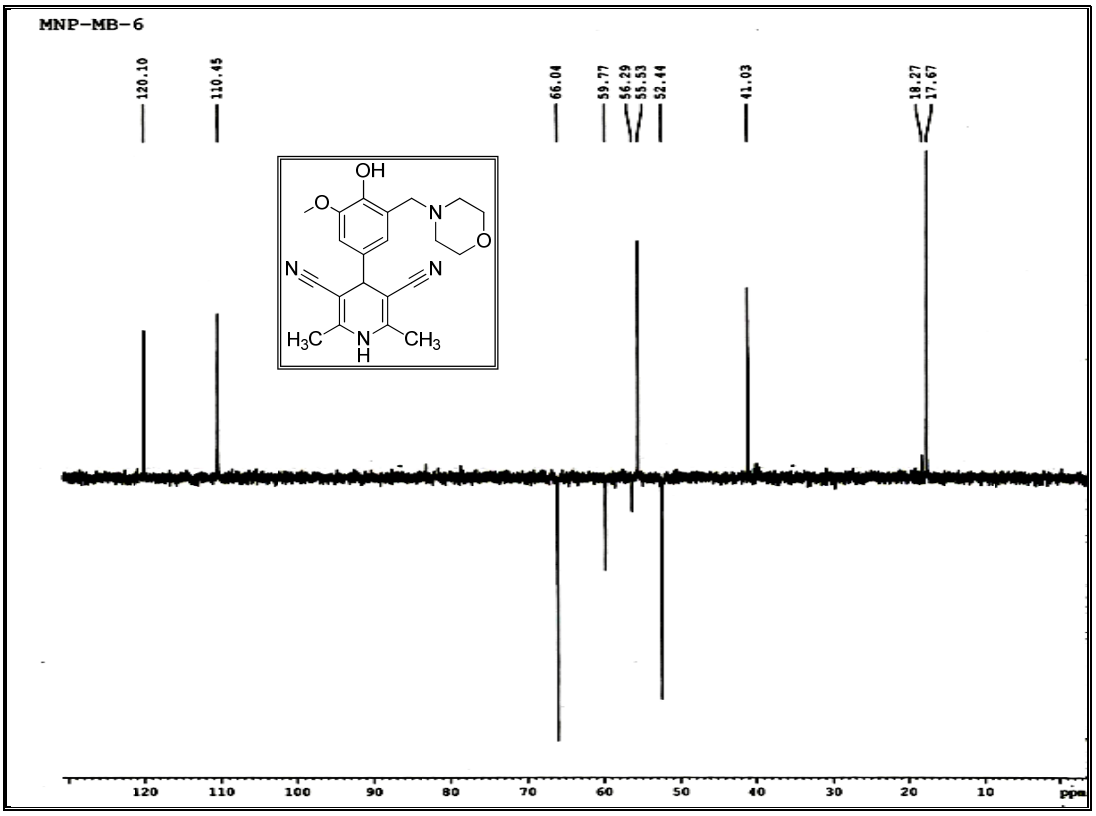
5.10.7 Expanded ^{13}C NMR Spectrum of MNP-MB-6



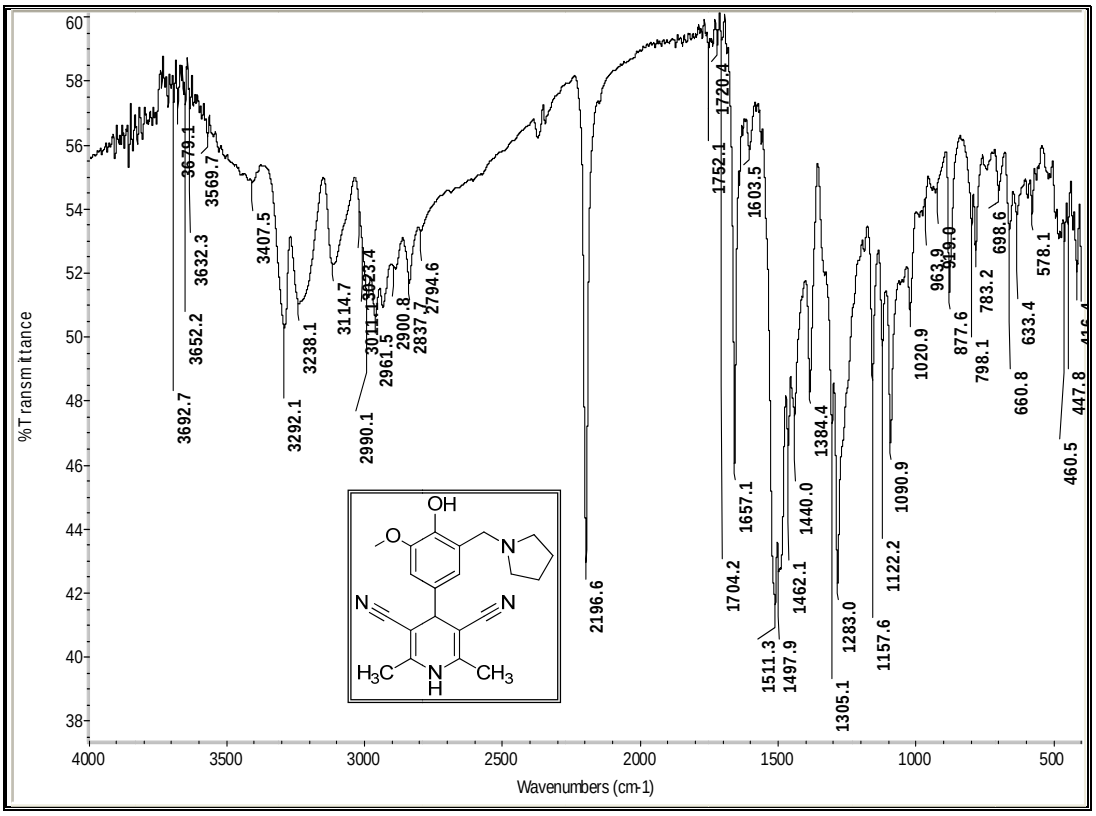
5.10.8 Expanded ^{13}C NMR Spectrum of MNP-MB-6



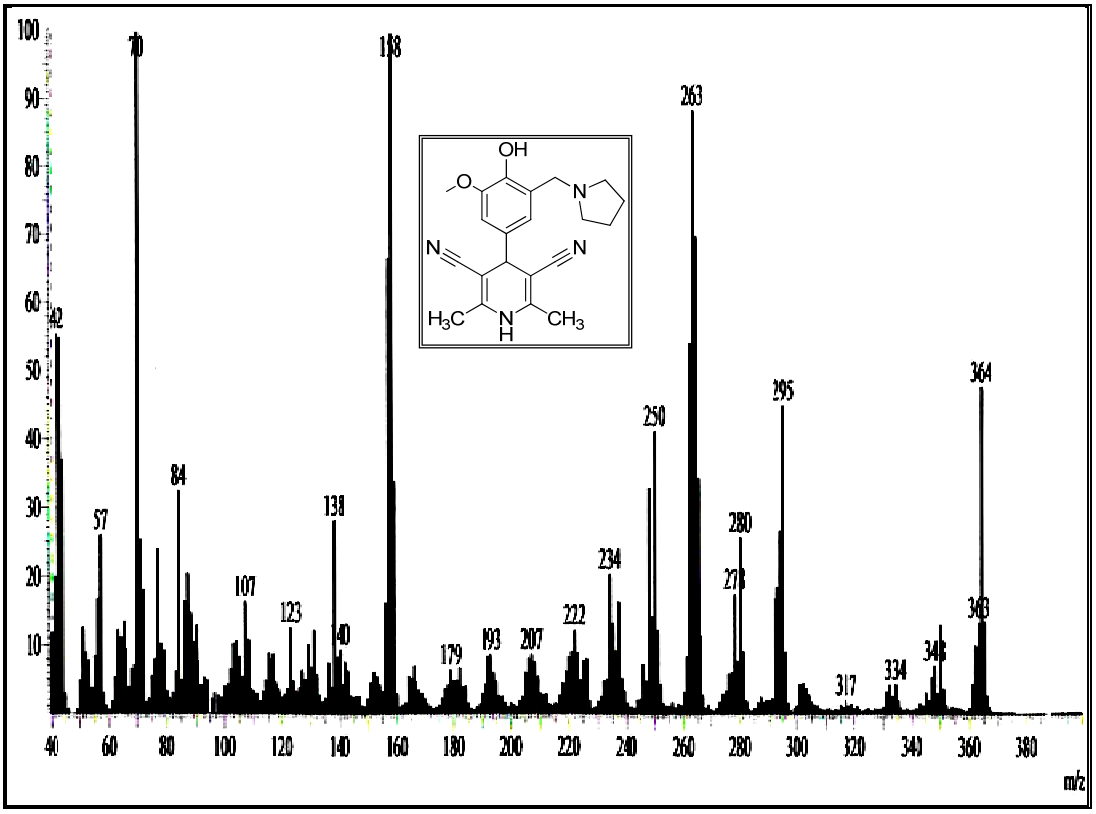
5.10.9 Expanded ^{13}C NMR Spectrum of MNP-MB-6



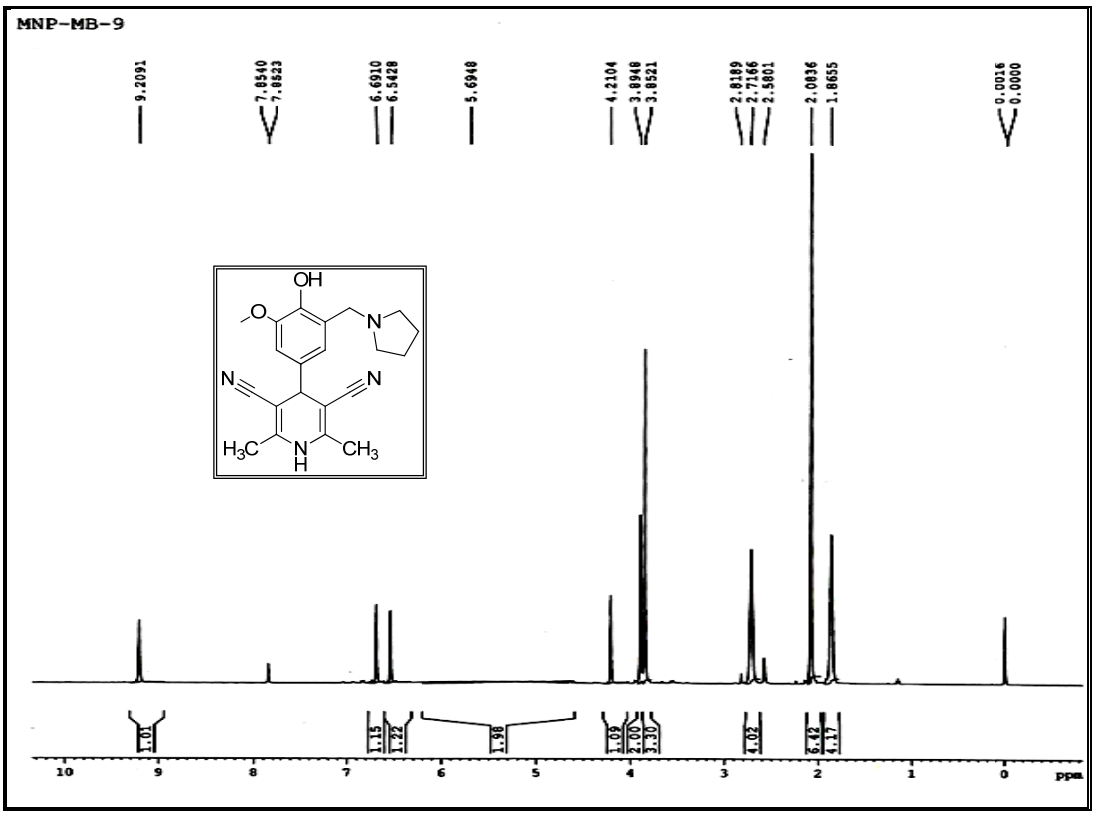
5.10.10 IR Spectrum of MNP-MB-9



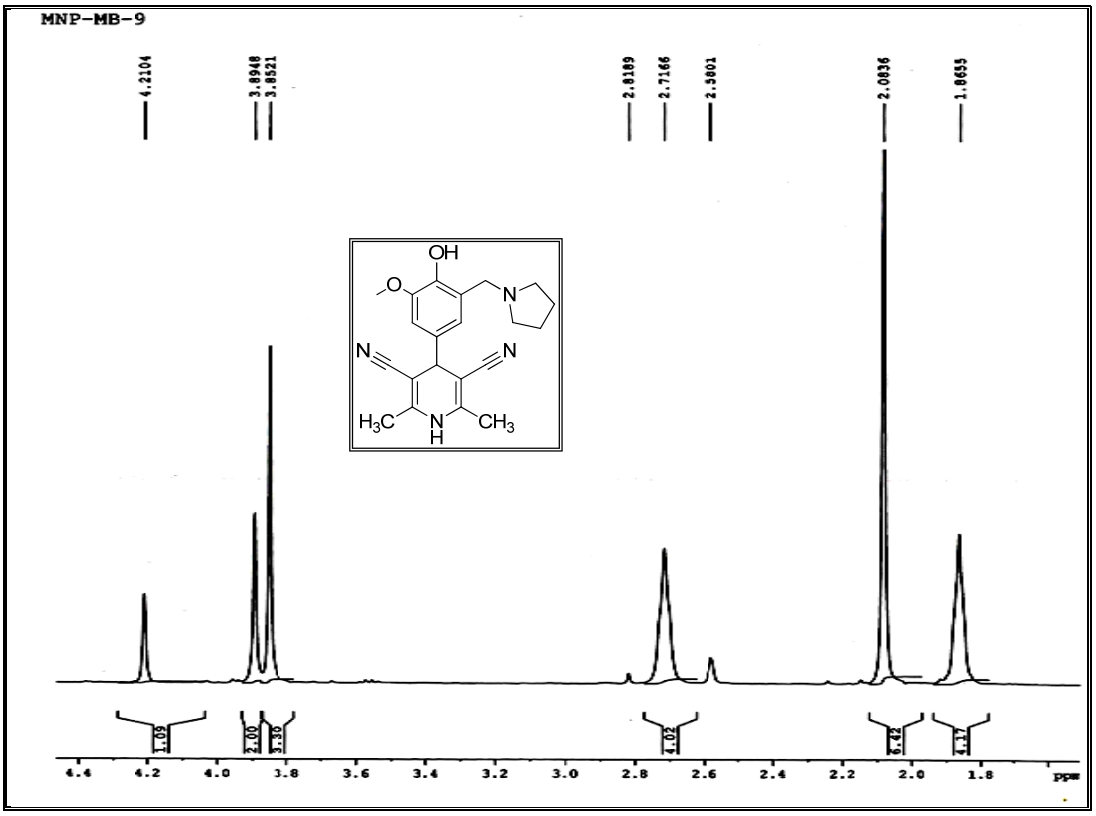
5.10.11 Mass Spectrum of MNP-MB-9



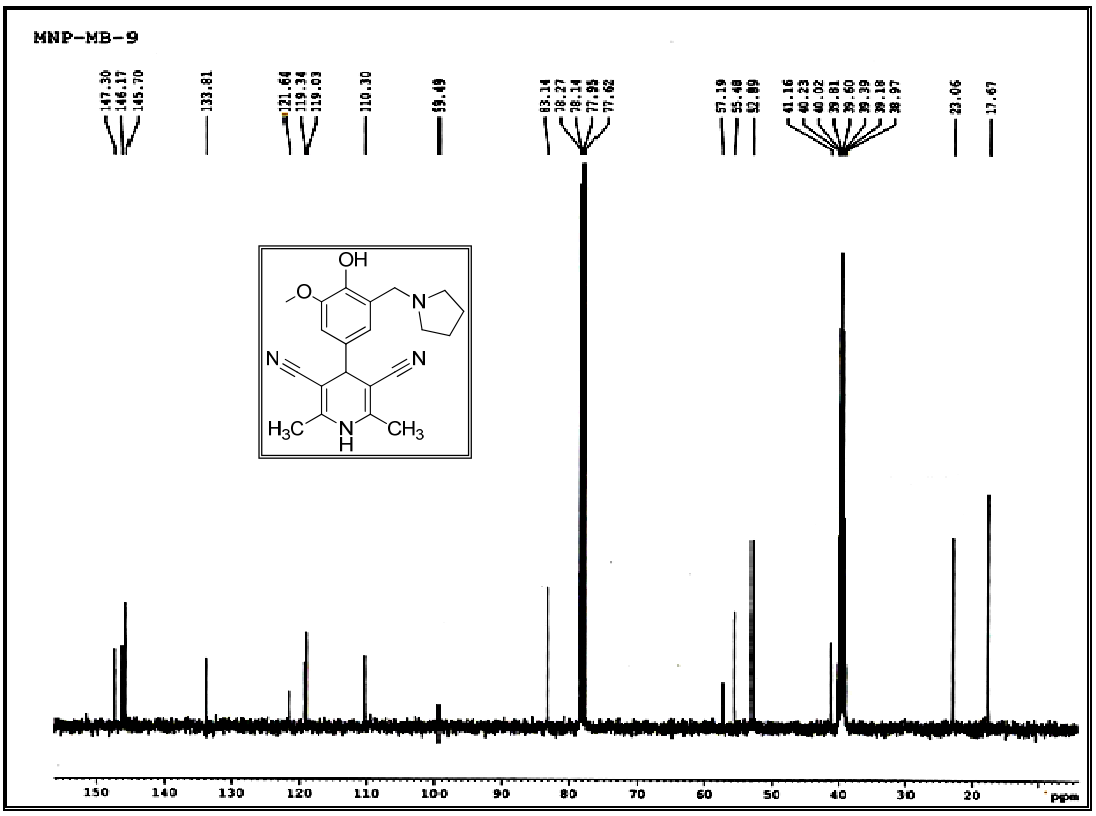
5.10.12 ^{1}H NMR Spectrum of MNP-MB-9



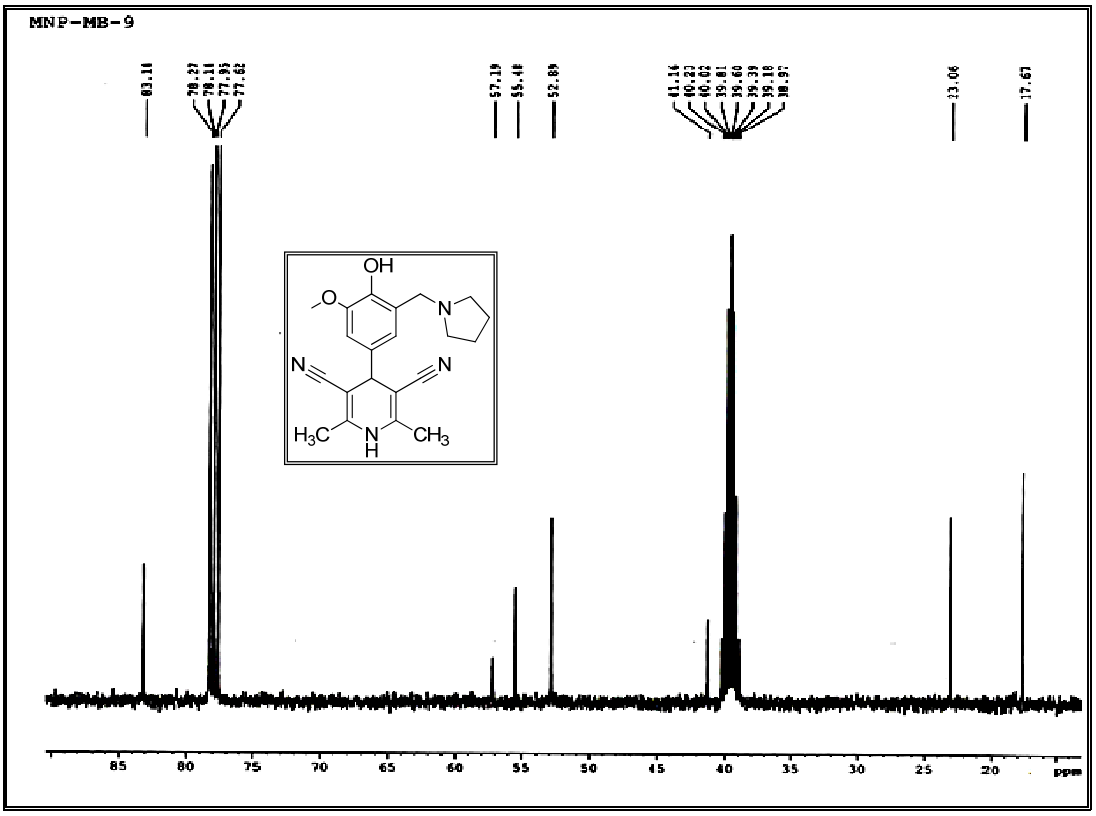
5.10.13 Expanded ^{1}H NMR Spectrum of MNP-MB-9



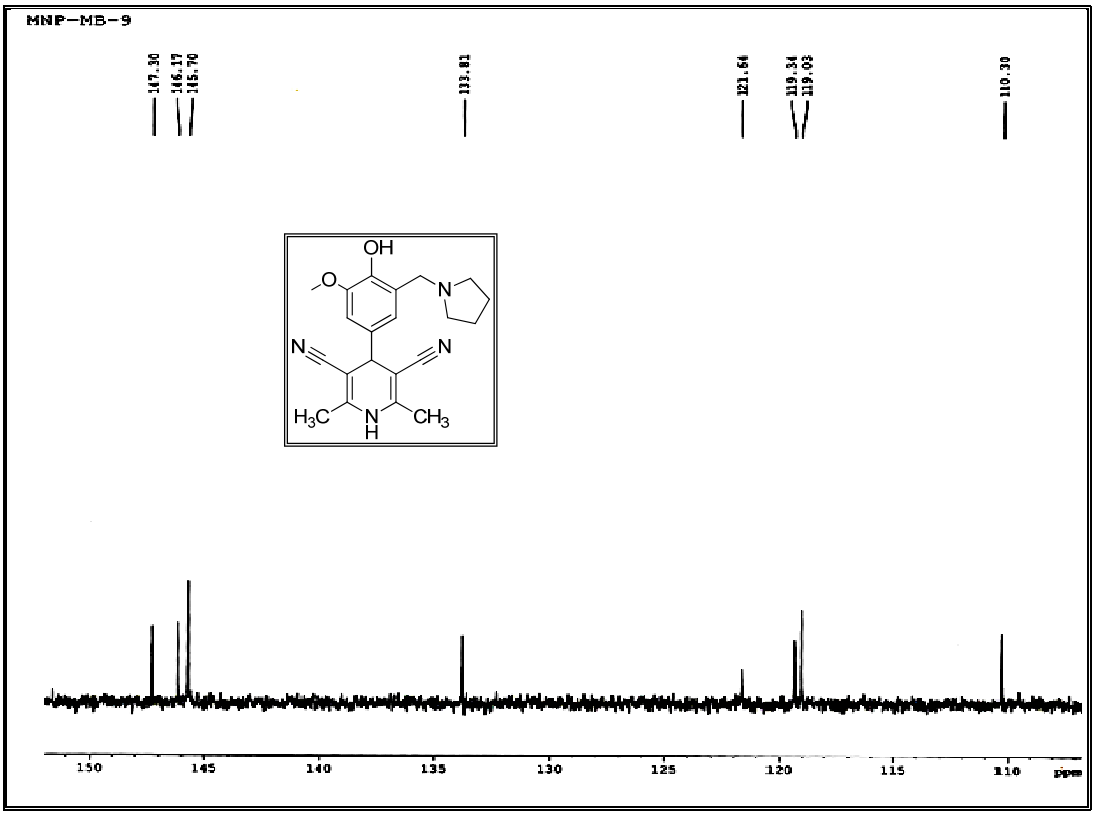
5.10.14 ^{13}C NMR Spectrum of MNP-MB-9



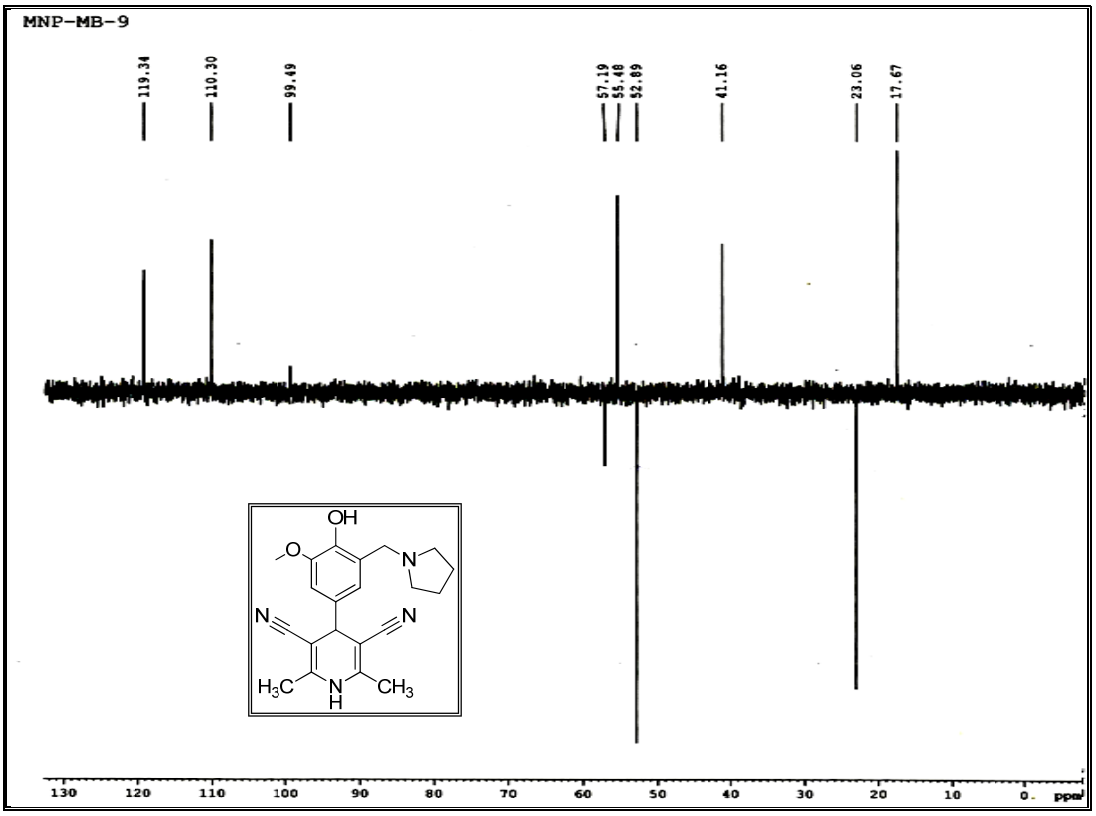
5.10.15 Expanded ^{13}C NMR Spectrum of MNP-MB-9



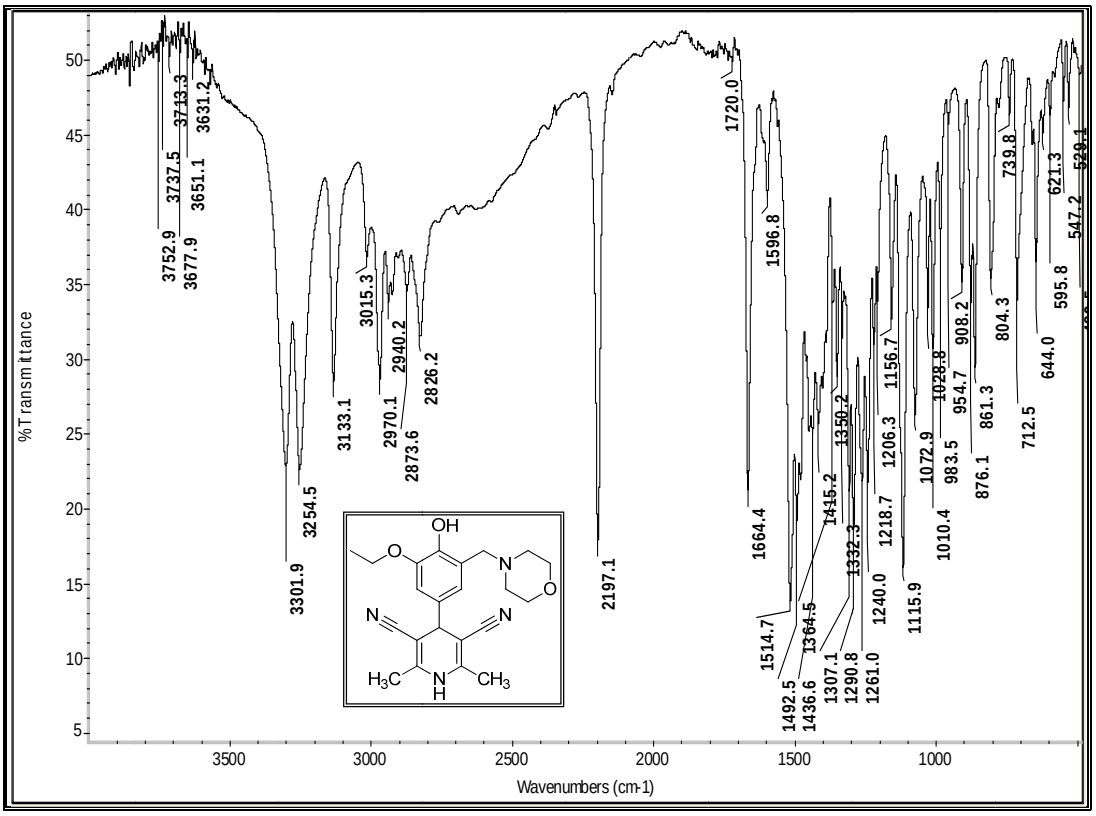
5.10.16 Expanded ^{13}C NMR Spectrum of MNP-MB-9



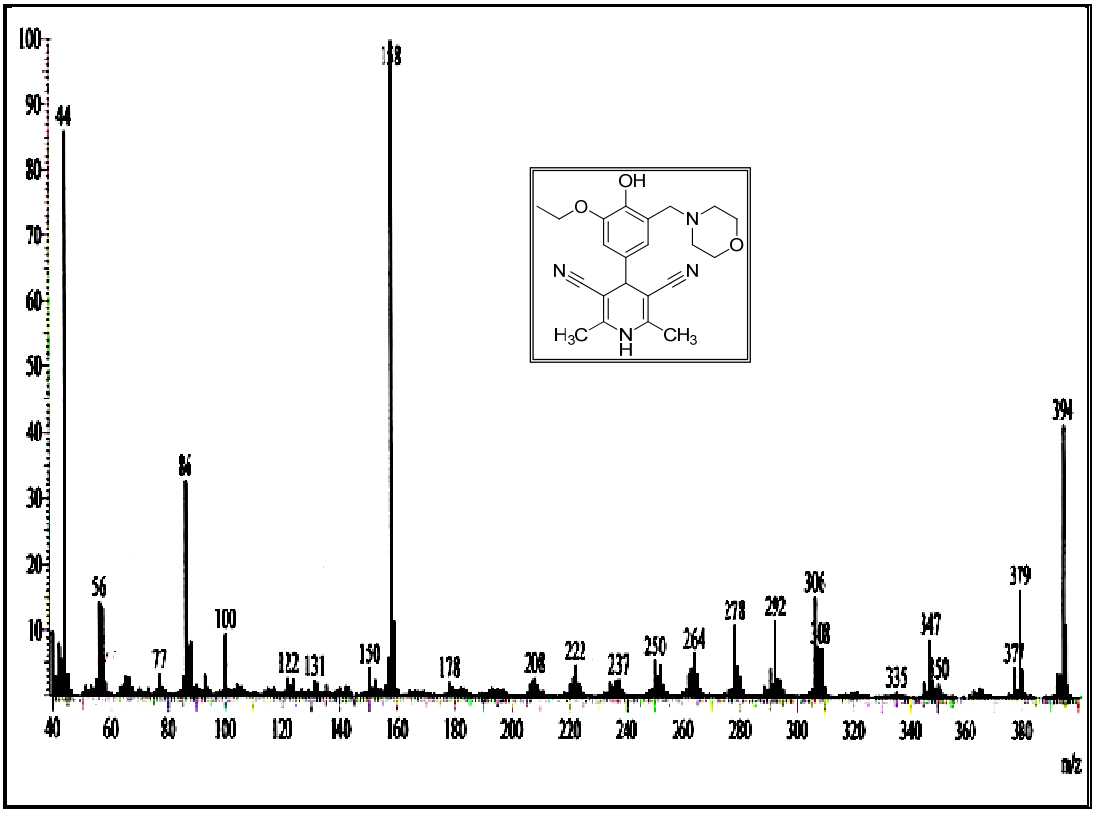
5.10.17 Expanded ^{13}C NMR Spectrum of MNP-MB-9



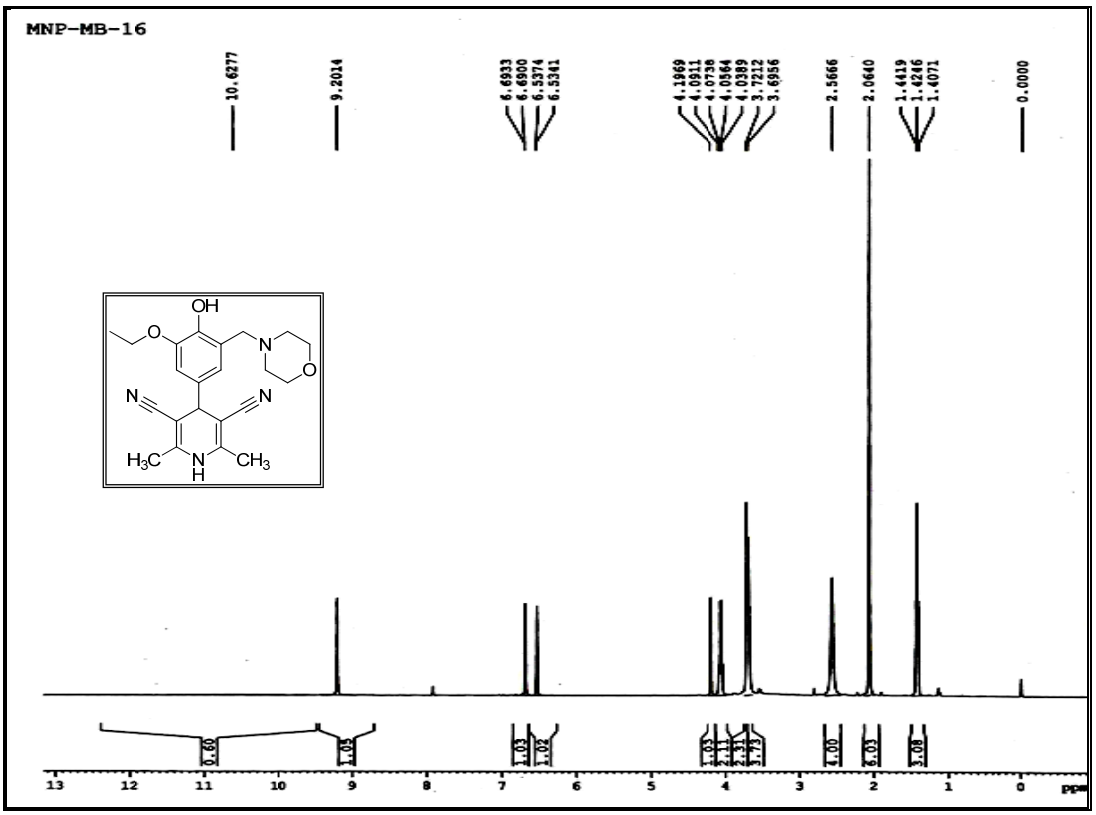
5.10.18 IR Spectrum of MNP-MB-16



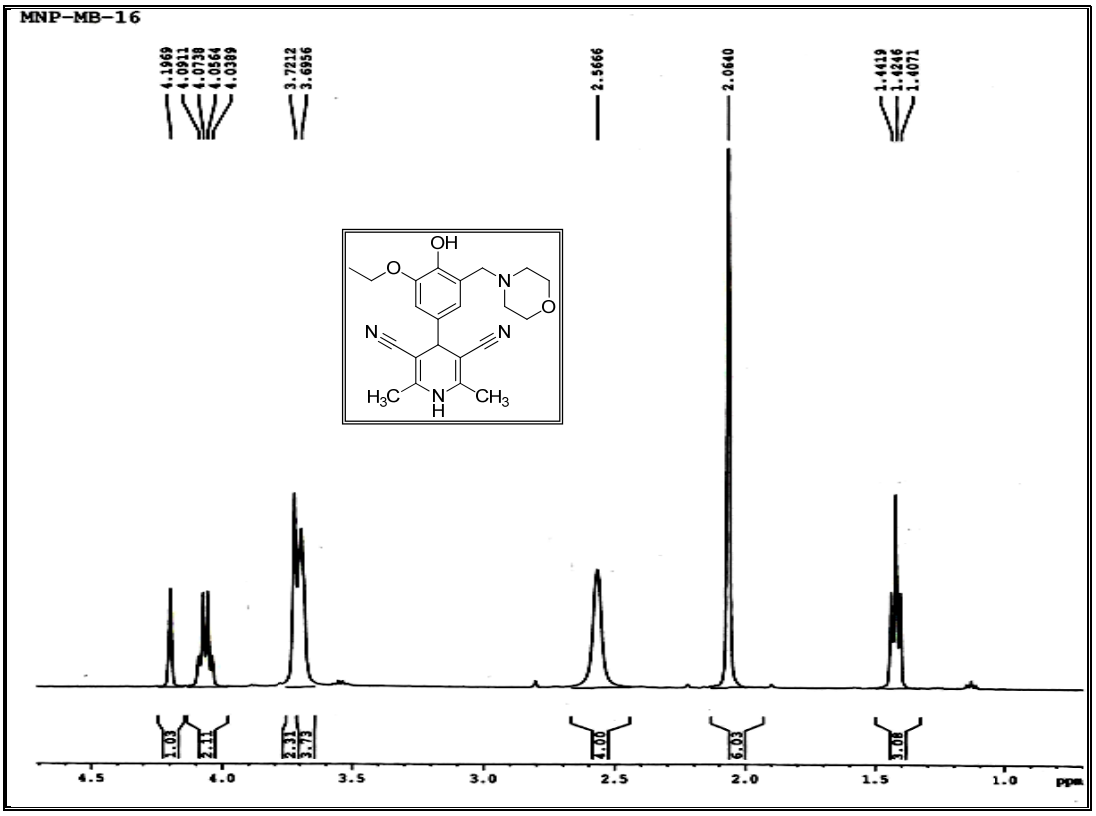
5.10.19 Mass Spectrum of MNP-MB-16



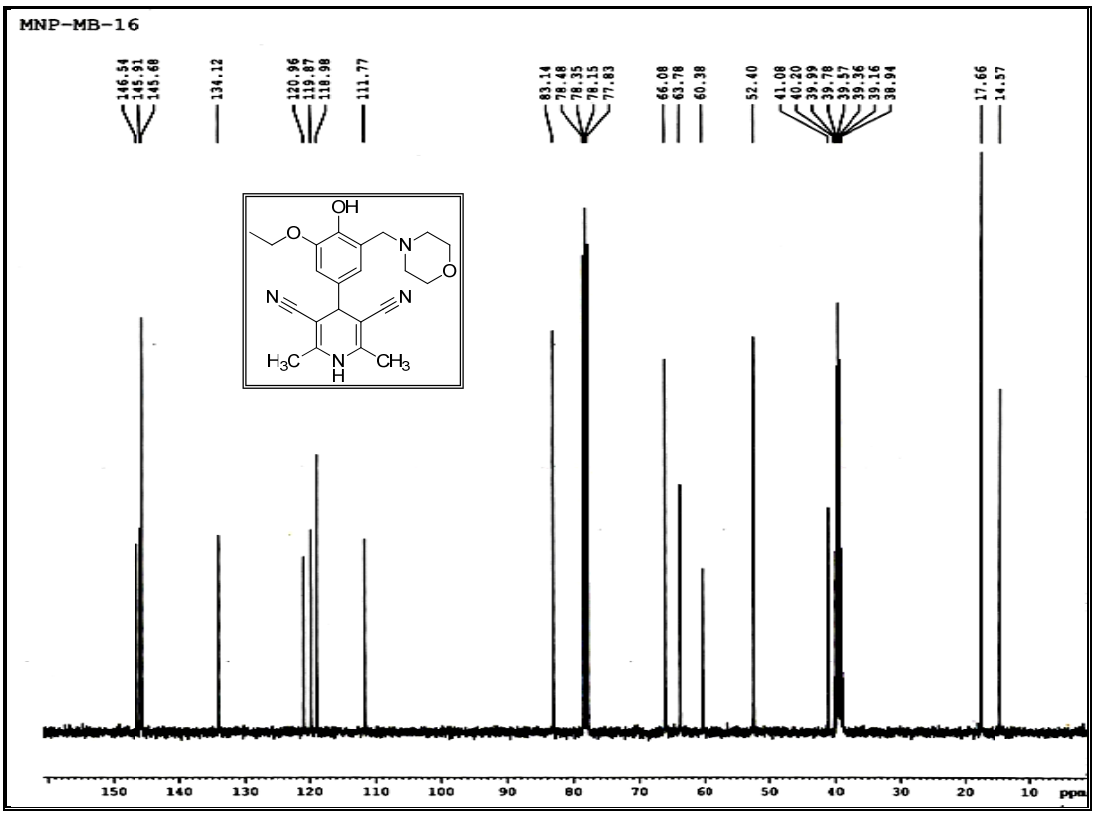
5.10.20 ^{1}H NMR Spectrum of MNP-MB-16



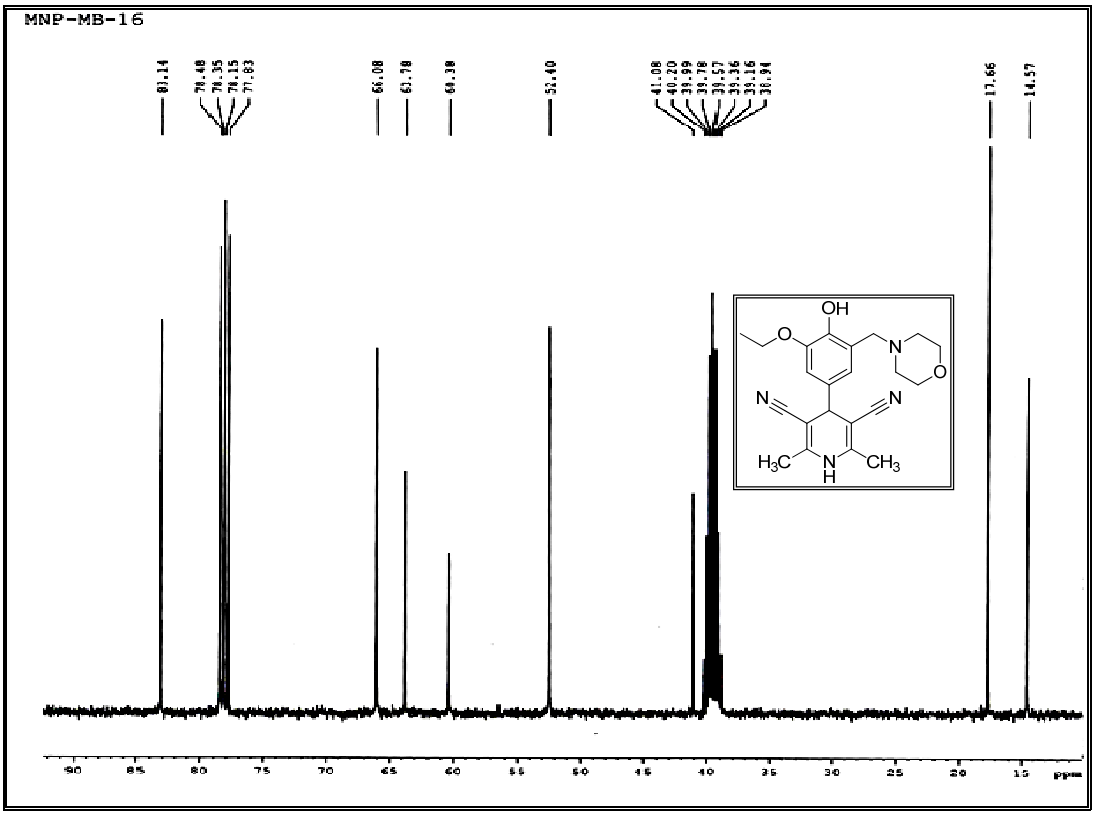
5.10.21 Expanded ^{1}H NMR Spectrum of MNP-MB-16



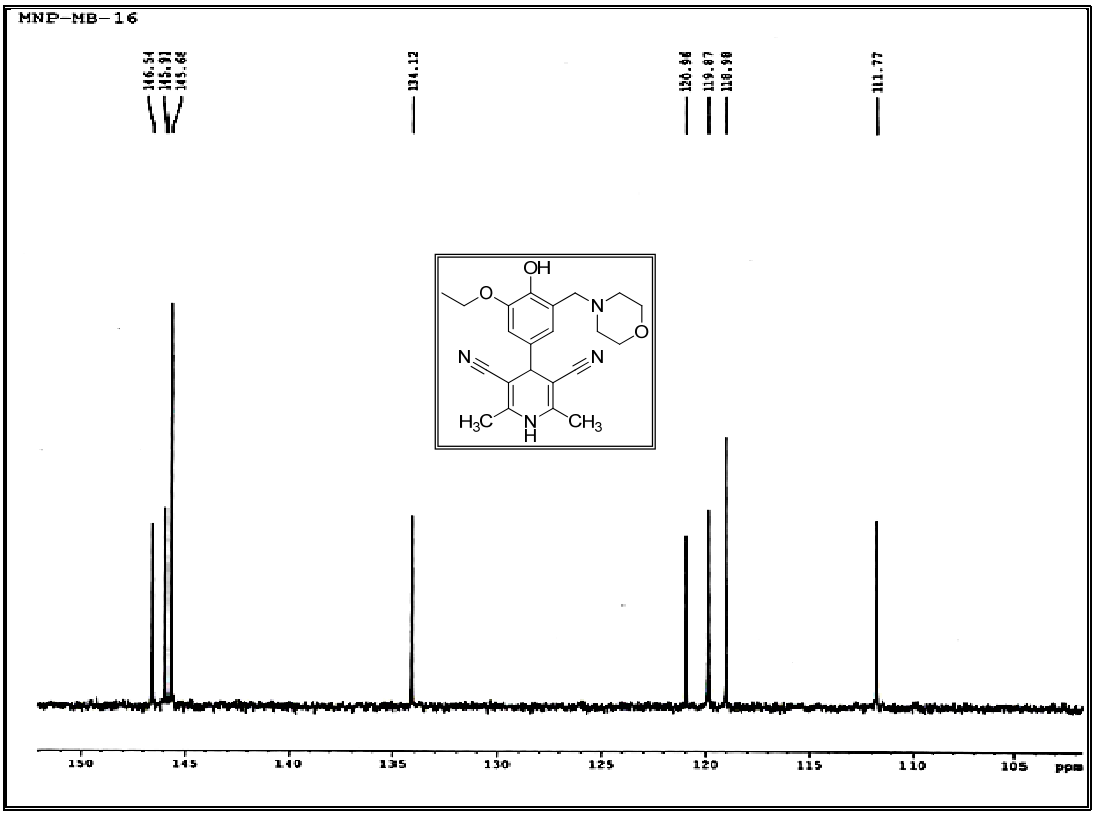
5.10.22 ^{13}C NMR Spectrum of MNP-MB-16



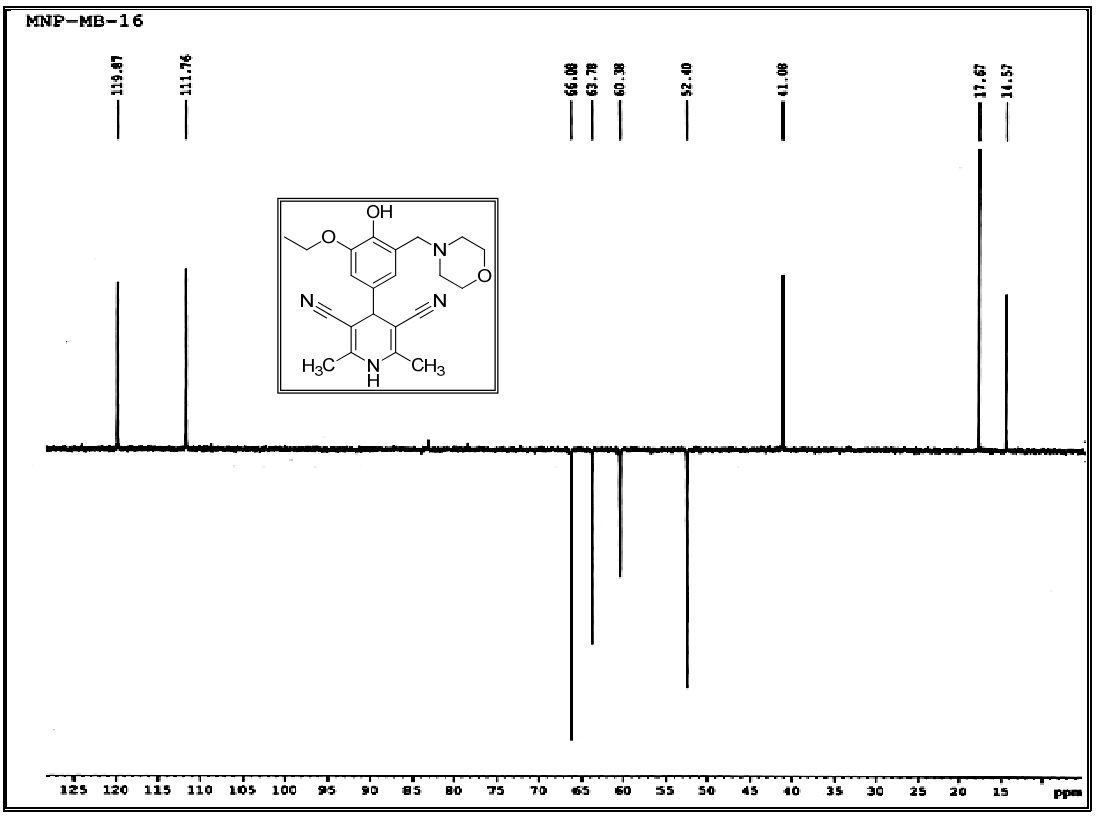
5.10.23 Expanded ^{13}C NMR Spectrum of MNP-MB-16



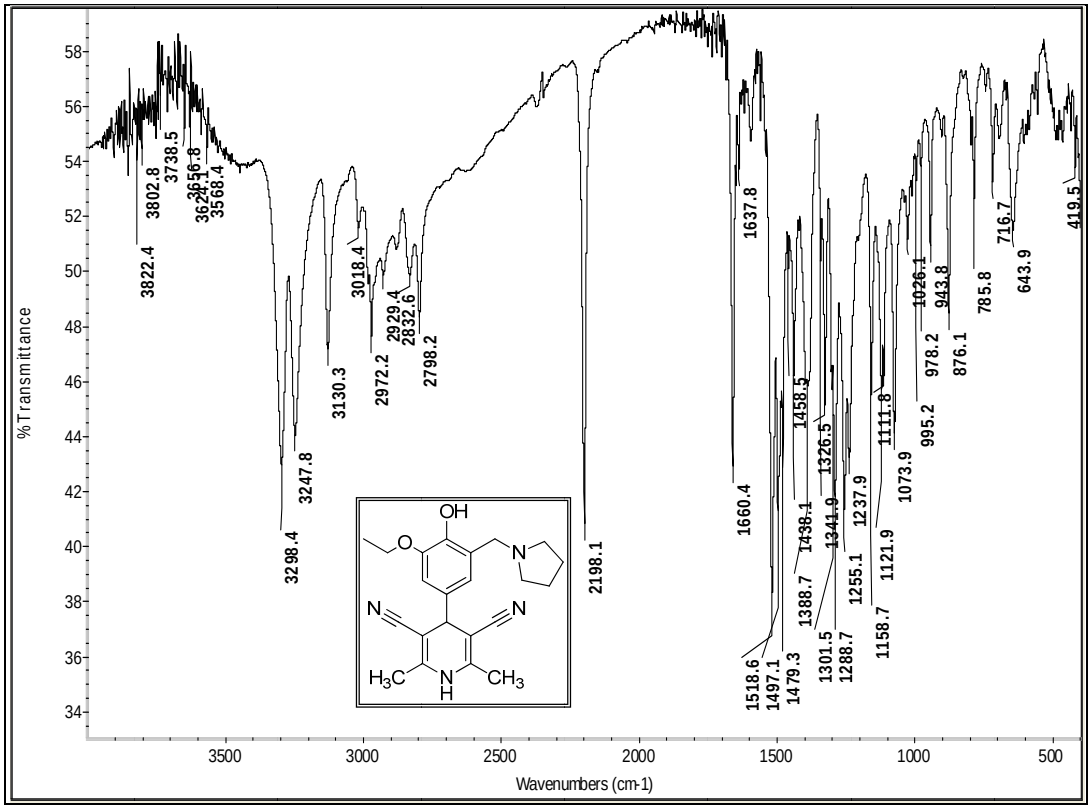
5.10.24 Expanded ^{13}C NMR Spectrum of MNP-MB-16



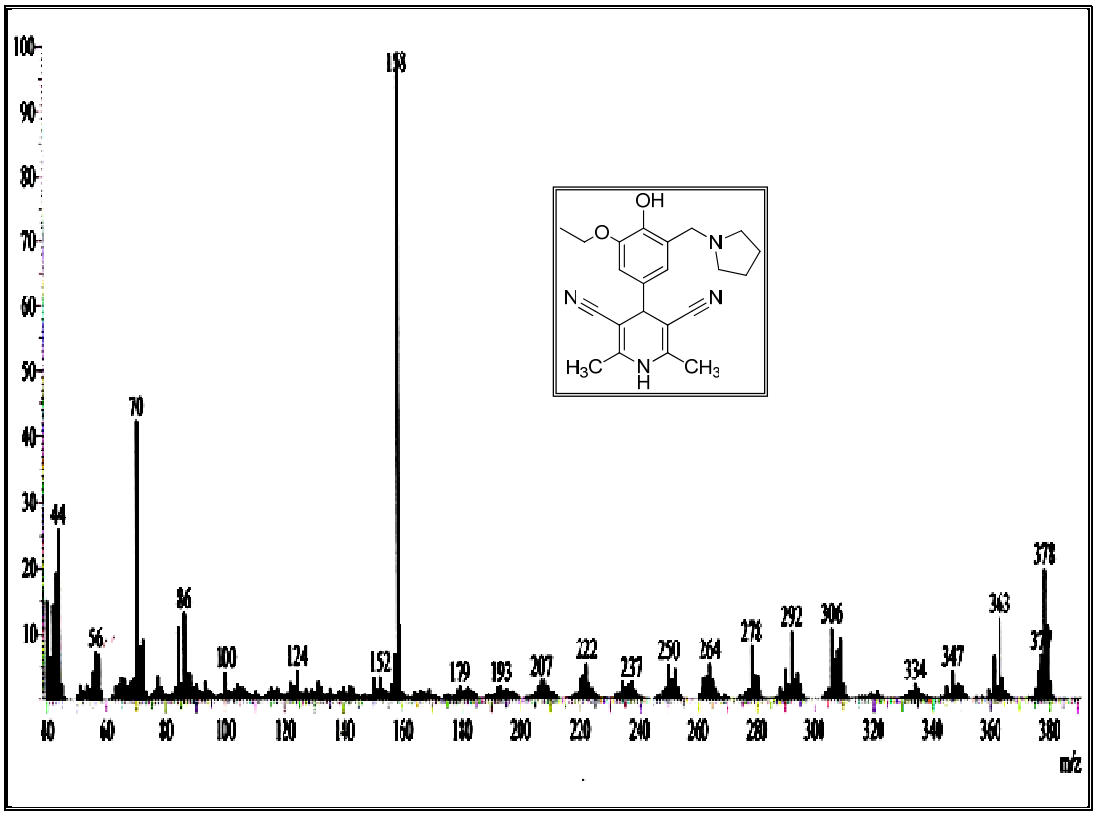
5.10.25 Expanded ^{13}C NMR Spectrum of MNP-MB-16



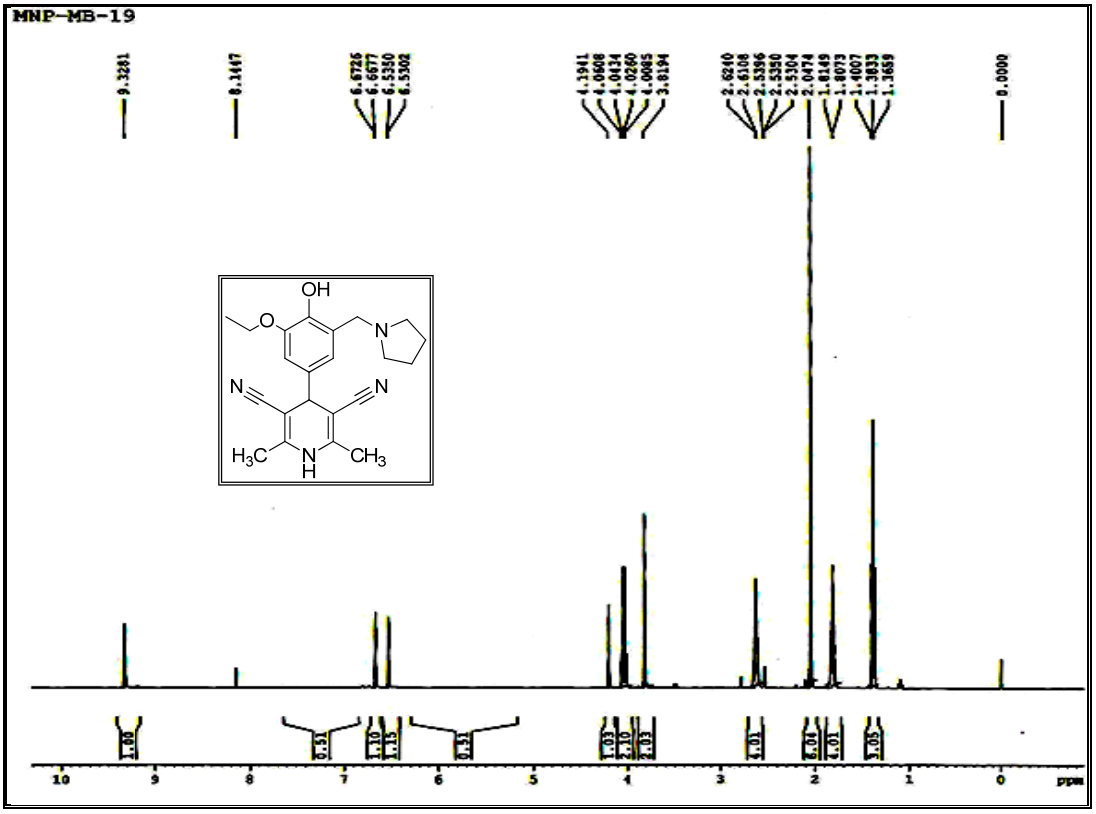
5.10.26 IR Spectrum of MNP-MB-19



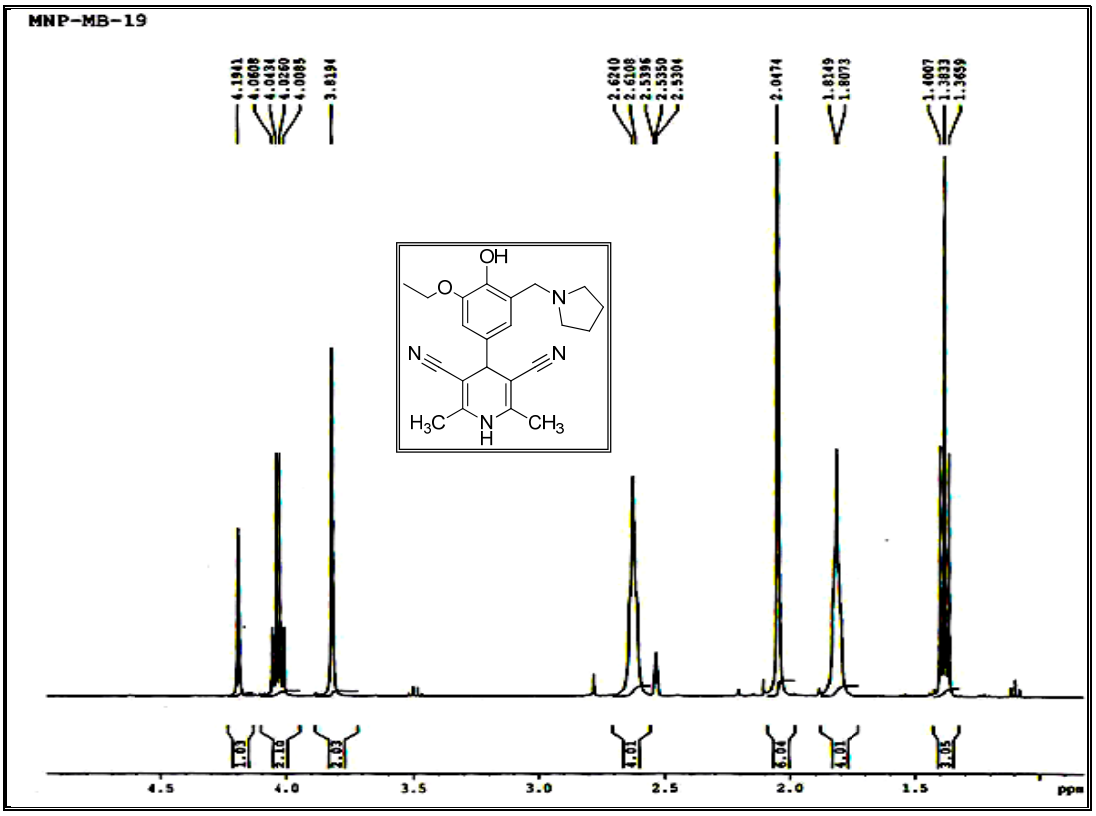
5.10.27 Mass Spectrum of MNP-MB-19



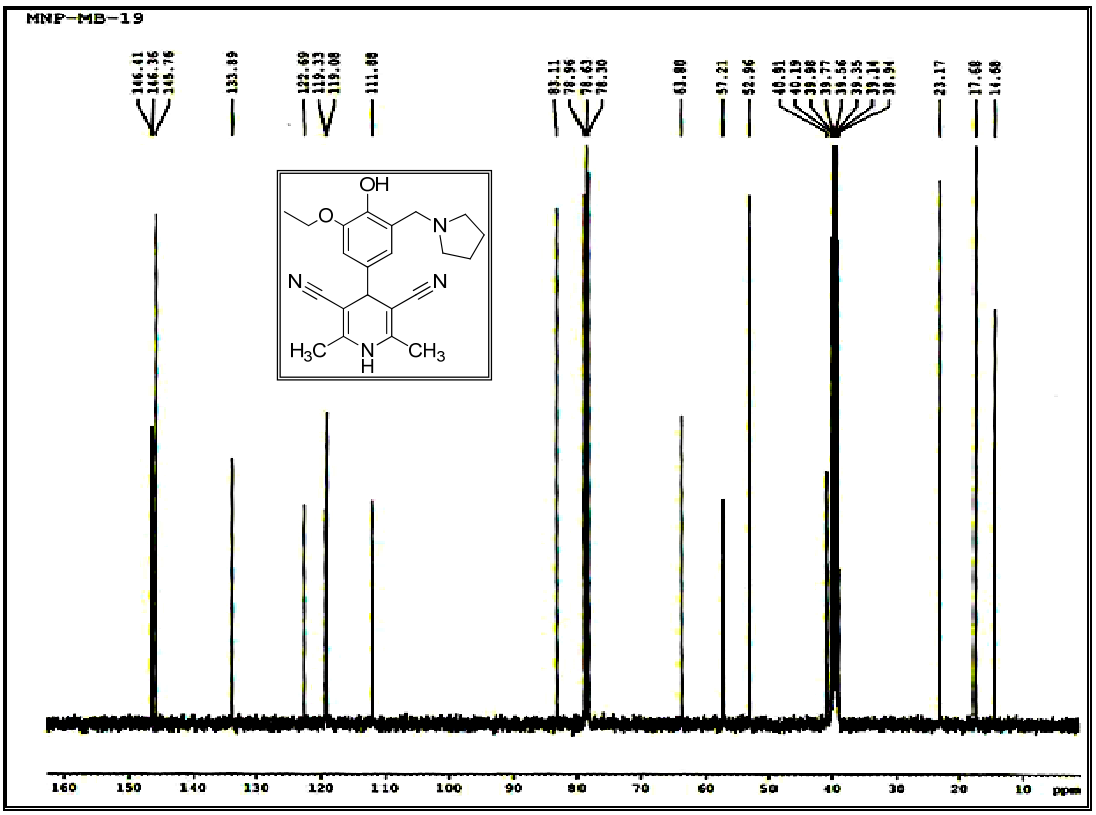
5.10.28 ^{1}H NMR Spectrum of MNP-MB-19



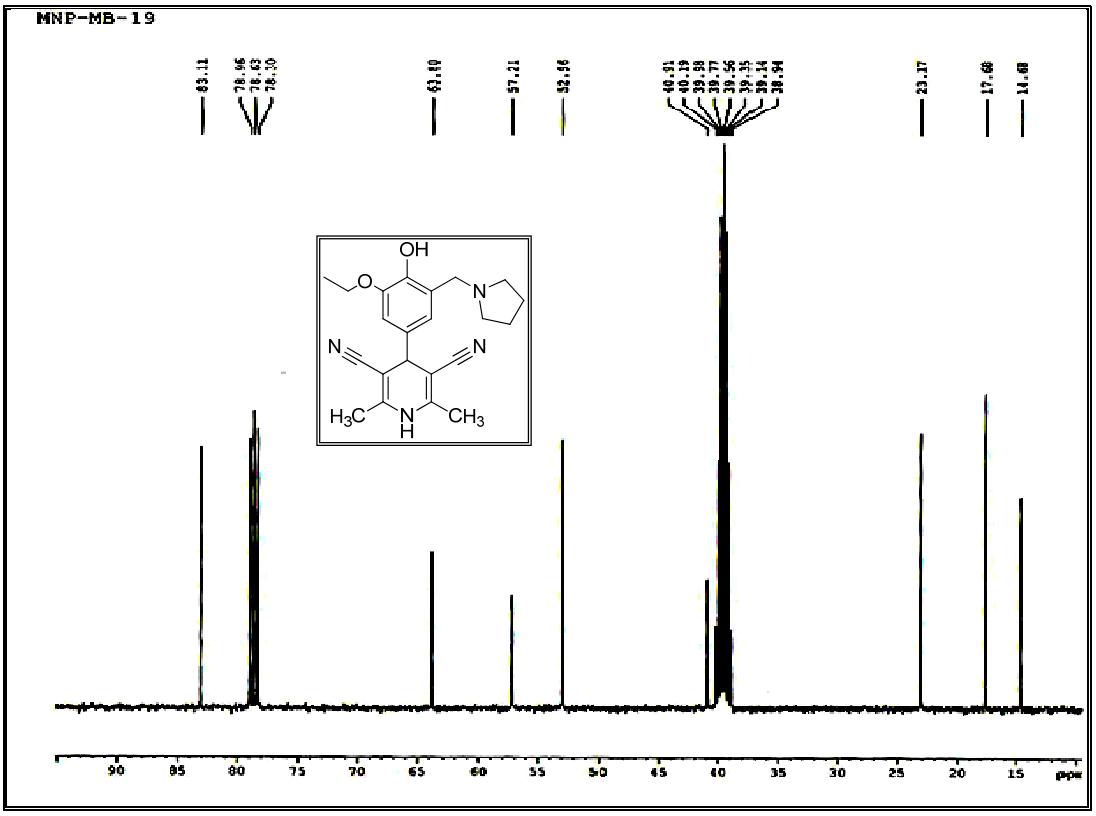
5.10.29 Expanded ^{1}H NMR Spectrum of MNP-MB-19



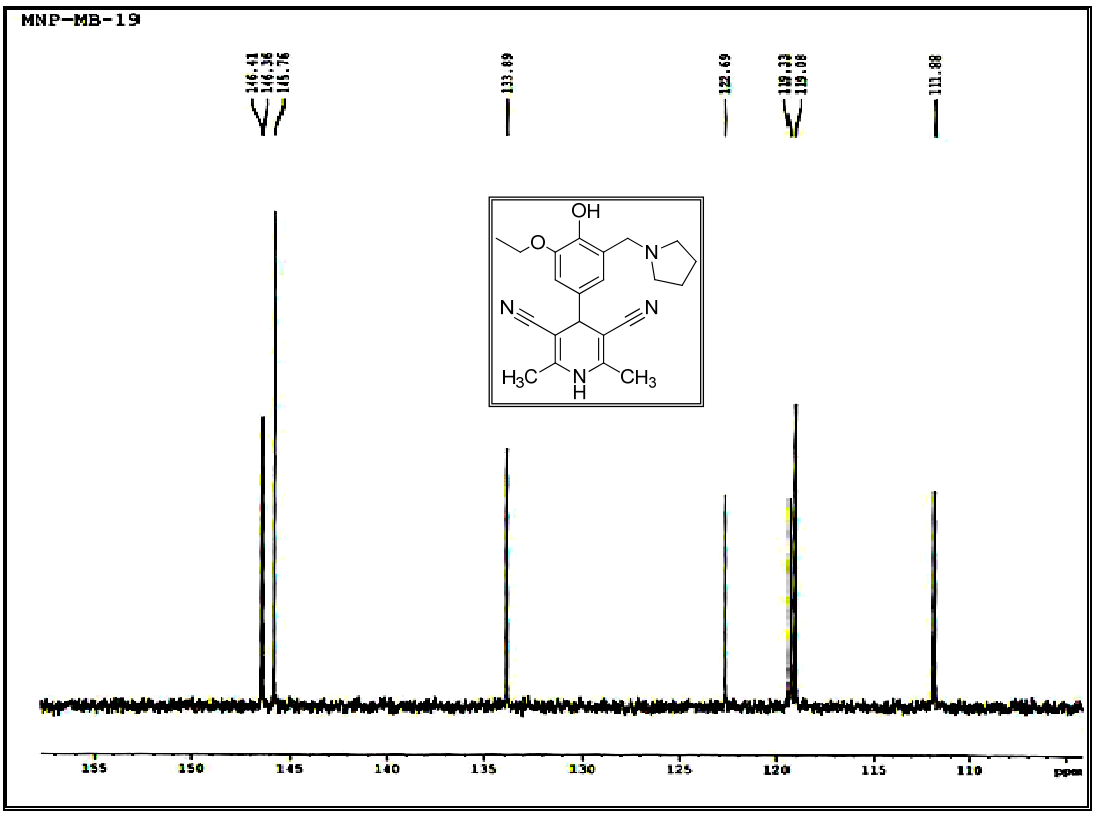
5.10.30 ^{13}C NMR Spectrum of MNP-MB-19



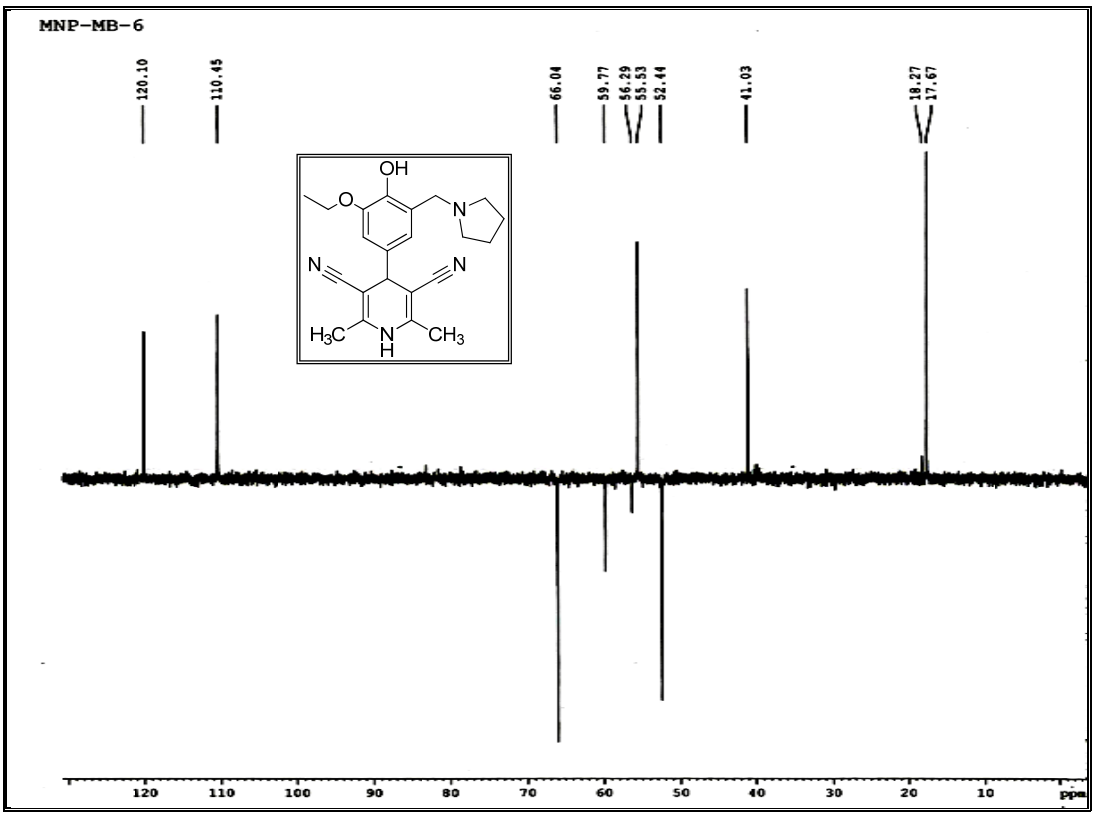
5.10.31 Expanded ^{13}C NMR Spectrum of MNP-MB-19



5.10.32 Expanded ^{13}C NMR Spectrum of MNP-MB-19



5.10.33 Expanded ^{13}C NMR Spectrum of MNP-MB-19



The work represented in the thesis entitled **"A Synthetic Approach Towards Bioactive Molecules and Related Studies"** is divided into two Parts and five chapters which can be summarized as under.

Part-I

Chapter-1 deals with the synthesis of 2, 4-dimethyl benzopyrylium salts using substituted Phenols. Good yield and easy work up are the main significances of this method. The synthesized compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectrometry. The structures were proven by x-ray crystallographic technique, by developing single crystals of three compounds in particular series.

Chapter-2 covers synthesis of some new 4-amino coumarin derivatives using green chemistry protocols. This process involves one pot three component reaction of 4-amino coumarin, aromatic aldehyde and catalytic amount of zinc chloride to form dimeric coumarin compounds. The main advantage of this process is economically viable, environmental benign and less time consuming. The compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectrometry.

Part-II

Chapter-3 represents the preparation of symmetric 1,4-dihydropyridines, structurally correlated with Nisoldipine, a potent calcium channel antagonist by one pot high purity Multi Component Reaction (MCR) using normal conventional approach. Isobutyl acetoacetate, substituted aldehydes and ammonium acetate in the presence of catalytic amount of glacial acetic acid forwarded by refluxing the reaction mixture in isopropyl alcohol to obtain the final products. All the synthesized compounds are highly pure and well characterized by IR, Mass, ^{1}H NMR and ^{13}C NMR.

Chapter-4 involves the synthesis of some novel Mannich base compounds using hydroxy substituted dihydropyridines and different secondary amines with formaldehyde. Very rapid and easy reaction condition, facile work up procedure, excellent yield and high chemical purity of the desired compounds are the main significances. The chapter covers IR, ^{1}H NMR, ^{13}C NMR, DEPT, Mass spectral and other Physical data to support the structure elucidation.

Chapter-5 related with the synthesis of some novel Mannich base compounds using 1,4-dihydropyridines containing one hydroxyl group along with one methoxy/ethoxy group on phenyl ring at C_4 position, to give structural and molecular diversity to the 1,4-dihydropyridine scaffold for biological as well as pharmacological interest. All the synthesized compounds were well characterized by IR, ^{1}H NMR, ^{13}C NMR, DEPT, Mass spectral and other Physical data to support the structure elucidation.

Biological Activity: The newly synthesized chemical entities are under study for various biological activities.

List of Publications

1. **Synthesis and biological evaluation of 4-Styrylcoumarin derivatives as inhibitors of TNF-α and IL-6 with anti-tubercular activity.**
   Kuldip Upadhyay, Abhay Bavishi, Shailesh Thakrar, Ashish Radadiya, Hardev Vala, Shrey Parekh, Dhairya Bhavsar, Mahesh Savant, **Manisha Parmar**, Priti Adlakha, Anamik Shah*
   Bioorganic & Medicinal Chemistry Letters **doi:10.1016/j.bmcl.2011.02.016**

2. **Synthesis of some novel benzofuran-2-yl(4,5-dihyro-3,5-substituted diphenylpyrazol-1-yl) methanones and studies on the antiproliferative effects and reversal of multidrug resistance of human MDR1-gene transfected mouse lymphoma cells in vitro.**
   Shrey Parekh, Dhairya Bhavsar, Mahesh Savant, Shailesh Thakrar, Abhay Bavishi**, Manisha Parmar**, Hardevsinh Vala, Ashish Radadiya, Nilay Pandya, Juliana Serly, Joseph Molnár, Anamik Shah*
   European Journal of Medicinal Chemistry, **46 (5), 1942-1948, 2011.**

3. **Synthesis and In Vitro anti-HIV Activity of N-1,3-benzo[d]thiazol-2-yl-2-(2-oxo-2H-chromen-4-yl) Acetamide Derivatives using MTT method.**
   Dhairya Bhavsar, Jalpa Trivedi, Shrey Parekh, Mahesh Savant, Shailesh Thakrar, Abhay Bavishi, Ashish Radadiya, Hardev Vala, **Manisha Parmar**, Roberta Loddo, Anamik Shah*
   Bioorganic & Medicinal Chemistry Letters. **doi:10.1016/j.bmcl.2011.03.105**.

4. **An efficient and rapid synthesis of highly functionalized novel symmetric 1,4-dihydropyridines using glacial acetic acid as solvent.**
   Shailesh Thakrar, Abhay Bavishi, Dhairya Bhavsar, Shrey Parekh, Hardev Vala, Ashish Radadiya, **Manisha Parmar**, Mahesh Savant, Nilay Pandya and Anamik Shah*
   Synthetic Communication **(Accepted).**

5. **Microwave assisted rapid Synthesis of novel 1,5-benzodiazepines derivatives as potent antimicrobial agent.**
   Shailesh Thakrar, Abhay Bavishi, Shrey Parekh, Dhairya Bhavsar, Hardevsinh Vala, Ashish Radadiya, **Manisha Parmar**, Nilay Pandya and Anamik Shah*
   Journal of heterocyclic chemistry **(Accepted)**

Conferences/Seminars/Workshops attended

1. Poster presented at International conference, 15th ISCBC "International conference on Bridging gaps in discovery and development: Chemical & Biological science for affordable health, wellness & sustainability" held at Department of Chemistry SU, Rajkot, 4-7 February, **2011**.

2. Poster presented at International conference, 14th ISCBC "Chemical biology for discovery: perspectives and Challenges" held at CDRI, Lucknow, 15-18 January, **2010**.

3. National seminar on Alternative Synthetic Strategies for Drugs & Drug Intermediates held at Institute of Pharmacy, Nirma University, Ahmedabad on 13th November, **2009**.

4. Two days National Workshop on Patents & IPR related Updates, Jointly organized by Technology Information, Forecasting Assessment Council (TIFAC) - New Delhi, Gujarat Council on Science and Technology (GUJCOST) Gandhinagar & National Facility for Drug Discovery Programme, Saurashtra University, Rajkot on 19-20th September, **2009**.

5. National workshop on Spectroscopy & Stereo chemistry held at Department of Chemistry, Saurashtra University, Rajkot on 18th- 20th March, **2009**.

6. National workshop on updates in Process & Medicinal Chemistry held at Department of chemistry, Saurashtra University, Rajkot on 3rd- 4th March, **2009**.

7. 11th CRSI & 3rd CRSI-RSC National Symposium in Chemistry held at National Chemical Laboratory (NCL), Pune on 5th -8th February, **2009**.

8. "Management and Use of Chemical databases & Patent Literature" held at the Department of Chemistry, Saurashtra University, Rajkot on 27th-29th February, **2008**.

9. Poster presented at International Conference on the Interface of Chemistry-Biology in Biomedical Research, 12th ISCB Conference held at BITS Pilani, Pilani on 22nd-24th February, **2008**.

10. "National Workshop on E-Resources in Chemical Synthesis & Natural Products" held at Department of Chemistry, Saurashtra University, Rajkot on 2nd-3rd March, **2006**.

11. "National Workshop on Nanotechnology: Opportunities & Challenges" jointly organized by Saurashtra University Rajkot and Gujarat Council of Science & Technology (GUJCOST), Gandhinagar, to be held at Rajkot, 17th October, **2005**.

12. 9th National conference (Inclusive one day International Symposium-ISCB 2005) on "Bioactive Heterocycles and Drug Discovery Paradigm", jointly organized by Department of Chemistry, Saurashtra University, Rajkot & Indian Society of Chemists & Biologist (ISCB), CDRI, Lukhnow, held at Rajkot, 8th-10th January, **2005**.