"STUDIES ON BIOACTIVE HETEROCYCLES AND OTHER MOIETIES"

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BY

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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: Shailesh A. Thakrar

CERTIFICATE

This is to certify that the present work submitted for the Ph.D. degree of Saurashtra University by Mr. Shailesh A. Thakrar 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 FAMILY

ACKNOWLEDGEMENT

It is moment of gratification and pride to look back with a sense of contentment at the long traveled path, to be able to recapture some of the fine moments, to be think of the infinite number of people, some who were with me from the beginning, some who joined me at different stages during this journey, whose kindness, love and blessings has brought me to this day. I wish to thank each of them from the bottom of my heart.

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SUMMARY

CONGERENCES/SEMINARS/WORKSHOPS ATTENDED

GNERAL REMARKS

1. Melting points were recorded by open capillary method and are uncorrected.

2. Infrared 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 Spectra were recorded on Bruker Avance II 400 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 scale. The standard abbreviations s, d, t, q, m, dd, dt, brs refer to singlet doublet, triplet, quartet, multiplet, doublet of a doublet, doublet of a triplet, ab quartet and broad singlet respectively.

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. Visulization 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 fro Spectrochem, Sisco Research Laboratories (SRL), Thomas baker, Sd fine chemicals, Loba chemie and SU-Lab.

7. All the reactions were carried out in Samsung MW83Y Microwave Oven which was locally modified for carrying out chemical reactions.

8. All evaporation of solvents was carried out under reduced pressure on Heidolph LABOROTA-400-efficient.

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 ChemBio Draw Ultra 10.0.

11. Elemental analysis was carried out on Vario EL Carlo Erba 1108.

ABBREVIATIONS

CH_3COOH	Acetic acid
Ar	Aromatic
Av.	Average
NH_4OAC	Ammonium acetate
AOA	Antioxidant activity
BP	Boiling point
BF_4	Boron tetra fluoride
BF_3	Boron triflouride
CAN	Ceric ammonium nitrate
CS_2CO_3	Cesium carbonate
CNS	Central Nervous System
Conc.	Concentrated
DMF	Dimethyl Formamide
DHP	Dihydropyridine
DMSO	Dimethyl Sulfoxide
Me_2CO	Dimethyl Carbonate
$NH(CH_3)_2$	Dimethyl amine
D.M.	Demineralized Water
EtOH	Ethanol
Equiv.	Equivalent
EAA	Ethylacetoacetate
FT-IR	Fourier Transform Infrared
GC-MS	Gas Chromatography Mass spectra
GCC	Glycinium chlorochromate
HSC	Human squamous cell carcinoma
HCl	Hydrochloric acid
Hr.	Hour

Hz	Hertz
I_2	Iodine
ILC	Isoliquiritigenin chaldone
MCRs	Multicomponent reactions
CH_3MgI	Methyl magnesium Iodide
MDR	Multidrug resistance
MF	Molecular Formula
MW	Molecular Weight
MP	Melting point
MeOH	Methanol
MAA	Methylacetoacetate
Mw	Microwave
MIC	Minimum inhibition concentration
$CH_2(CN)_2$	Malononitrile
CH_3CN	Methyl cyanide
NCEs	New Chemical Entities
HNO_3	Nitric acid
NADH	Nicotinamide dinucleotide
Nm	Nanometer
O	Ortho
P	Para
PCC	Pyridinium chloro chromate
PhMe	Toluene
$KMnO_4$	Potassium Permanganate
$POCl_3$	Phosphorous oxychloride
Pgp	P-glycoprotein
KBr	Potassium Bromide
KOH	Potassium Hydroxide
K_2CO_3	Potassium Carbonate

R_4NBrO_3	Quartarnary ammonium bromated
R.T.	Room temperature
Rf	Retention Factor
NaCN	Sodium Cyanide
$NaHCO_3$	Sodium bi carbonate
$NaBH_4$	Sodium boro hydride
$NaHSO_4$	Sodium hydrogen sulphate
NaOH	Sodium hydroxide
SD	Standard Deviation
NaH	Sodium hydride
TMS	Tetramethylsilane
TBAHS	Tetrabutylammonium hydrogen sulphate
TLC	Thin layer chromatography
$SOCl_2$	Thionyl chloride
TFA	Triflouro acetic acid
$TiCl_4$	Titanium Chloride
UV	Ultra Violet
VH Reagent	Vilsmeier-Haack reagent
V_2O_5	Vanadium pentoxide
ZnO	Zinc Oxide
$ZnCl_2$	Zinc chloride

Chapter-1

Rapid synthesis and X-ray crystallographic study of 1,4-dihydro-2,6-dimethyl-4-(1,3-substituted diphenyl-1H-pyrazol-4-yl)pyridine-3,5-dicarbonitriles.

1.1 INTRODUCTION

1,4-dihydropyridines contribute as an important class of compounds in medicinal chemistry, leading to several new drugs currently widely used especially as calcium channel blockers and in other cardiovascular disease also.

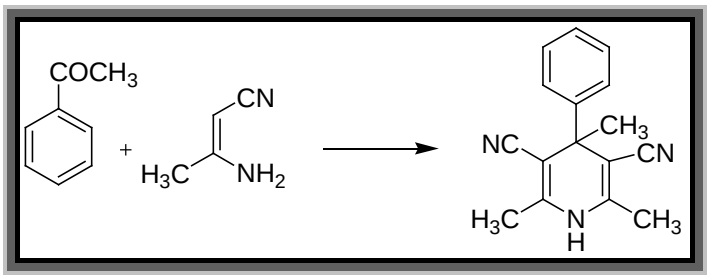
Dihydropyridine chemistry began in 1882 when Hantzsch[1] published the synthesis, which now bears his name Hantzsch reaction and the work was limited to symmetric diesters at C_3 & C_5 position. Then the synthesis was modified for Unsymmetric 1, 4-dihydropyridines also and last few years more than 10,000 papers, reviews and patents were published on these molecules.

Some recent work is summarized as under.

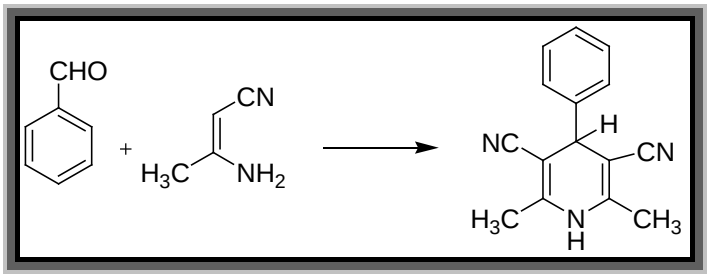
1.2 LITERATURE REVIEW

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.

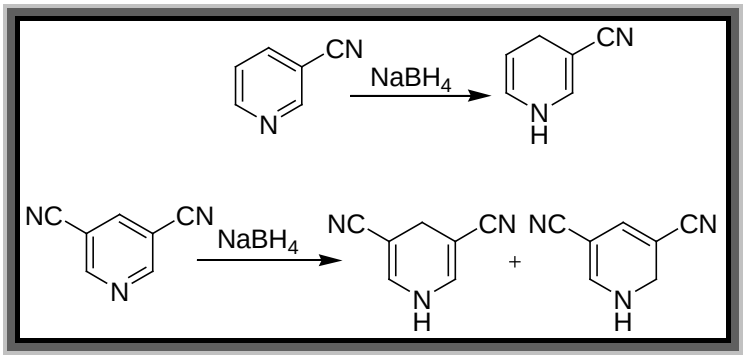
Acetophenone when reacted[3] with 3-amino crotononitrile gave symmetric 3,5-dicyano-2,4,6-trimethyl-4-phenyl-1,4-dihydropyridine.



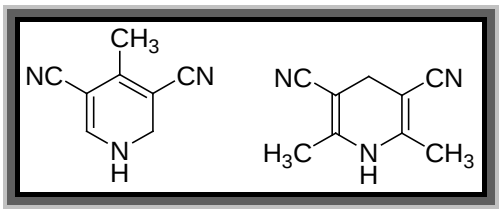
While symmetric 3,5-dicyano-1,4-dihydropyridine was prepared by the condensation of aldehyde with 3-amino crotononitrile in suitable acidic medium like acetic acid[4-6] or hydrochloric acid.[7]



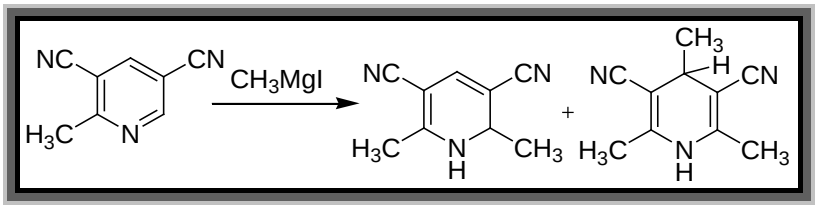
A number of dihydropyridine derivatives have been prepared by reduction[8,9] of the corresponding pyridines or pyridinium salts with complex metal hydrides.



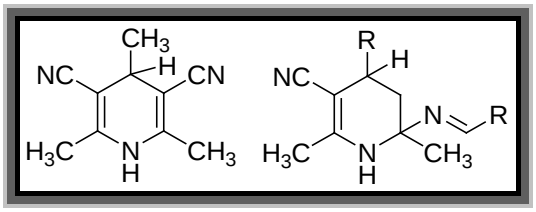
3,5-Dicyano-4-methyl pyridine[9] and 3,5-dicyano-2,6-dimethyl pyridines[9,10] afforded to give the dihydropyridine.



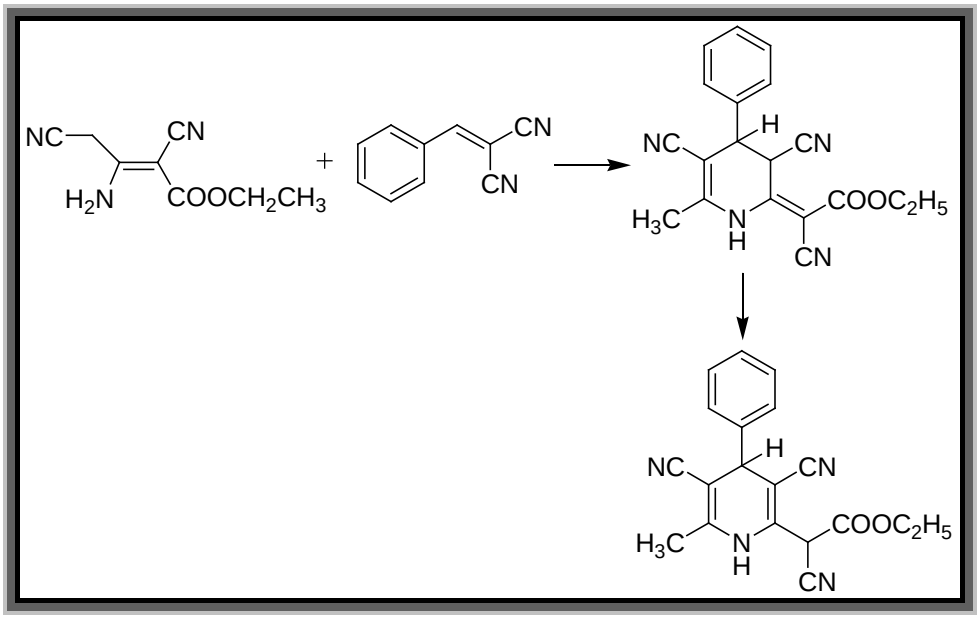
The conversion of pyridine to dihydropyridine was carried out by employing Grignard reagent such as methyl magnesium iodide.[11,12]



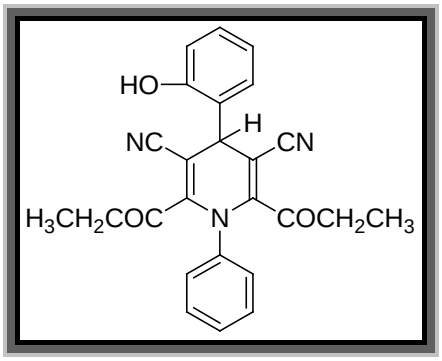
The preparation of Hantzch type 3,5-dicyano-1,4-dihydropyridine is sometimes reported via formation of tetrahyropyridine, which are isolated at room temperature in the presence of ammonium acetate.[13]



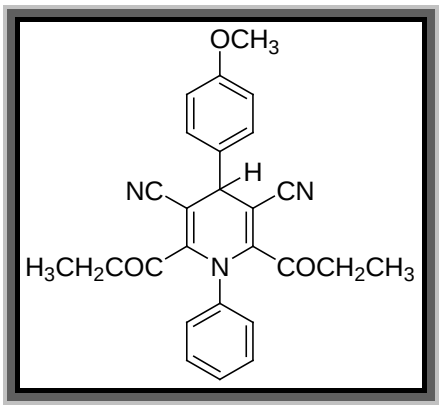
A novel synthesis of polyfunctionally-substituted pyridine was reported by Famhy *et al.*[14] During this reaction, sometimes the formation of tautomer was also reported.



Shah *et al.*[15] prepared many cyano-1,4-dihydropyridines. Out of many 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 1mg/kg and 5 mg/kg.



Another compounds showed moderate hypotensive activity.

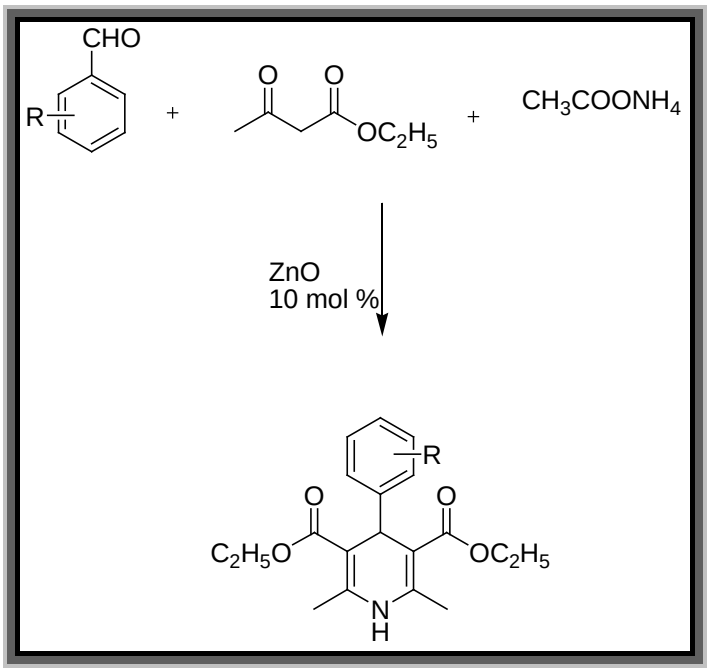


Mustafa *et al.*[16] developed an efficient synthesis method for 1,4-dihydropyridines. It has been developing using 3 or 4 component condensation reactions of aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate in the presence of aluminium sulfuric acid catalyst in minimum methanol at reflux temperature. This procedure offers several advantages including high yields, an environment friendly procedures, short reaction times, and a simple work-up procedure.

1,4-Dihydropyridines (DHPs) are class of nitrogen containing heterocycles having a 6-membered ring. 1,4-DHPs, which are the most potent calcium antagonists or calcium channel blockers, have received much attention due to their wide range of pharmaceutical and biological properties such as inhibition of human cytochrome P450 enzyme,[17] angiotensine-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies.[18] 1,4-DHP compounds play important roles in medicinal chemistry, for example nifedipine, amlodipine, felodipine, and

nicardipine, which are the best selling drugs used in the treatment of cardiovascular diseases.[19]

Matloubi *et al.*[20] has synthesized 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 and polyhydroquinoline derivatives *via* the Hantzsch condensation is described. The present methodology offers several advantages such as simple procedure, excellent yields, and short reaction time.

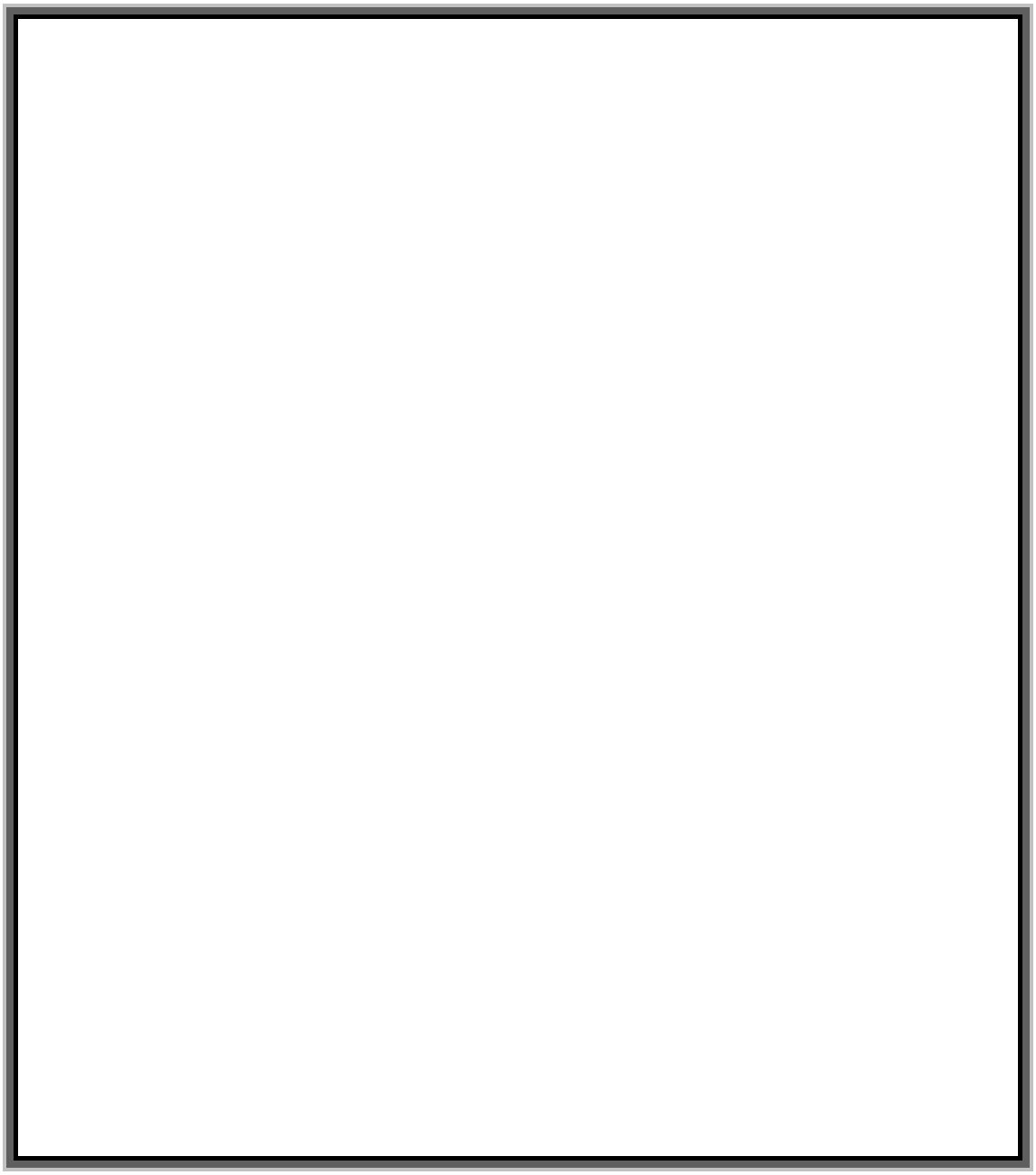


Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot reaction. Clearly, for multi-step synthetic procedures, the number of reactions and purification steps are among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Therefore, in the last decade, research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[21]

Catalysts such as Sc(OTf)3,[22] Silica gel/NaHSO4,[23] heteropolyacid,[24] I_2,[25] CAN,[26] $Yb(OTf)_3$[27] and Baker's yeast [28] have also been used in this reaction.

Domestic microwave ovens as well as laboratory reactors have been successfully employed to prepare dialkyl 1,4-dihydropyridine-3,5-dicarboxylates and to induce the synthesis of the corresponding aromatic derivatives. In that latter particular case, unexpected results have been reported.

Described more than one century ago by Hantzsch,[29] dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (1,4-DHP) have now been recognized as vital drugs in the treatment of angina and hypertension. Some of them (Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine, Nifedipine, Nimodipine, Nitrendipine) have been commercialized and it has been proven that their therapeutic success is related to their efficacy to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart.[30-32]



The usefulness of those calcium antagonists has led to the development of novel synthetic strategies to improve classical methods of preparation[33-35] and microwave activation stands among the alternative routes proposed the past decade.

Aromatization of 1,4-DHP has also attracted considerable attention in recent years as Böcker[36] has demonstrated that metabolism of those drugs involves a cytochrome P-450 catalyzed oxidation in the liver. The so-obtained pyridines are devoid of the pharmacological activity of the parent heterocycles and are further

transformed by additional chemical modifications. Due to the biological importance of the oxidation step of 1, 4-DHP, that reaction has been the subject of a large number of studies and a plethora of reagents has been utilized to mimic the in vivo transformation. In that field, surprising results have been collected when the reactions are performed under microwave irradiation.

The pioneering report on the use of microwave activation to obtain Hantzsch 1,4-DHP was published by Alajarin et al. in 1992.[37]This group prepared a series of 4-aryl derivatives in a domestic oven by the classical multicomponent method (aldehyde: 15 mmol; alkyl acetoacetate: 43 mmol; ammonia: 30 mmol; ethanol: 3 mL). Yields ranged from 15 to 52 % for a reaction time of 4 minutes. The authors claim that classical protocols for the formation of the same compounds require a reflux period of 12 hours but they did not notice any yield improvement when microwave irradiation was applied. Three years later the same group extended its work[38] to the preparation of 3,5-unsymmetrically substituted 1,4-DHP starting from arylmethyleneacetoacetate (8 mmol) and 3-aminocrotonate (4 mmol) in ethanol (4.5 mL). This report again emphasizes that the rapidity of the microwave-assisted syntheses does not affect the isolated yields. The same year Zhang[39] obtained four 4-aryl 1,4-DHP from 3-aminocrotonate (20 mmol), methyl acetoacetate (20 mmol) and arylaldehydes (20 mmol) in a domestic oven. For the first time, the preparations were conducted in the absence of solvent. Yields ranging from 59 to 77 % are reported and optimized heating periods do not exceed 10 minutes. To avoid any loss of volatile material, the reaction flasks were fitted with a condenser containing xylene. Also in 1995, Khadilkar[40] used the same building blocks as Zhang but in the presence of a solvent (ethanol, volume not reported; 3-aminocrotonate: 10 mmol; methyl acetoacetate: 14 mmol; arylaldehyde: 10 mmol). The heterocycles were prepared in a domestic oven within 3 to 5 minutes in 32 to 80 % yield.

Interestingly, Khadilkar[41] also described the formation, in a domestic oven, of 1,4-DHP in an aqueous hydrotrope solution (50% butylmonoglycolsulphate : 5 ml). The experiments were performed with 3-aminocrotonate (10 mmol), methyl acetoacetate (14 mmol) and aliphatic or aromatic aldehydes (10 mmol). The final products were obtained within 3 to 6 minutes in 35 to 97 % yield. All reactions

described by Khadilkar [40,41] were carried out by exposing the reactants to microwaves in containers equipped with a condenser charged with precooled carbon tetrachloride. The coupling of microwave heating (in a domestic oven) with the use of a mineral solid support (alumina: 2 g) has later been exploited by Suarez [42] to synthesize, within 6 minutes and with a yield higher than 85 %, an unsymmetrical 1,4-DHP from methyl 3-aminocrotonate (3 mmol), ethyl acetoacetate (3 mmol) and benzaldehyde (3 mmol).

A catalytic amount of DMF (0.5 ml), as an energy transfer medium to attain higher temperatures, was added to the reaction mixture.

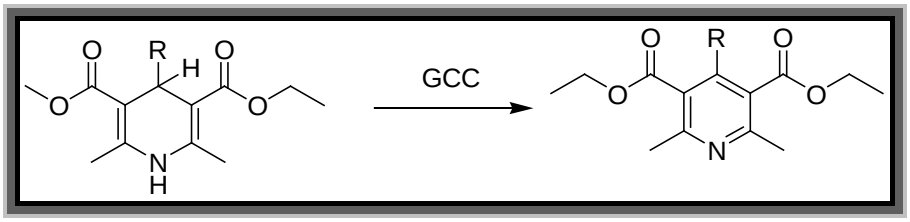
In 2001, a single-mode microwave reactor (SmithSyntheziser from Personal Chemistry, Uppsala, Sweden) was used for the first time to accelerate the preparation of series of 1,4-DHP from various alkyl acetoacetates (12.5 mmol), aldehydes (2.5 mmol) and 25 % aqueous ammonium hydroxide (10.0 mmol).[43] In comparison with experiments performed in domestic ovens, use of a laboratory synthesizer does not appear to provide improved results.

Oxidation of 1,4-DHP under microwave irradiation was reported for the first time in 1991 by Alvarez *et al.* [44,45] They oxidized a series of 1,4-DHP (0.5 g) in a domestic oven by treatment on a mixture of manganese dioxide and Mexican bentonite clay (5.0 g, prepared from 1:2 or 1:4 mixtures of potassium permanganate and clay) in the absence of solvent. The procedure is characterized by short reaction times (10 minutes) and fair to quantitative yields (47-100 %). The most noticeable results were observed when starting from 1,4-DHP bearing a methyl, ethyl, or propyl group in position 4. Indeed those reactions afforded, unexpectedly, mixtures of 4-alkylpyridines and 4-unsubstituted pyridine. In contrast, the same group related,[46] two years later, that those 4-alkyl 1,4-DHP (0.25 g) do not undergo the dealkylation process when they are treated for 1 minute in a domestic microwave oven in the presence of a HNO_3/Mexican bentonite clay system (2.5 g; prepared from a 1:1 mixture of the components). Aromatization of 1,4-DHP has also been studied by Varma.[47] He observed that solid state oxidation of 1, 4-DHP (1mmol) using elemental

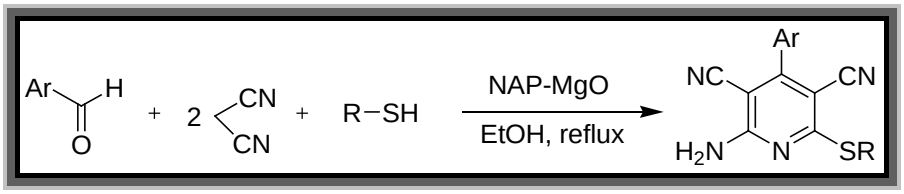
sulfur (1.3 mmol) and microwave activation in a domestic oven affords the dehydro derivatives, whichever the 4-substituent is.

Glycinium chlorochromate[48] (GCC) supported onto silica gel was used as an effective oxidizing agent for the aromatization of 1,4-dihydropyridine.

Many of the reported reagents involve the use of strong oxidants such as $KMno_4$,[49] CrO_3,[50] HNO_3,[51] Pyridinium chlorochromate (PCC),[52] Ceric ammonium nitrate (CAN),[53] bentonite clay-supported manganese dioxide,[54] Sulphar,[55] Palladium/Charcoal dehydrogenations[56] and bismuth nitrate.[57] How ever this aromatization reaction with most of these reagents leads to dealkylation at the 4-position or formation of side products.

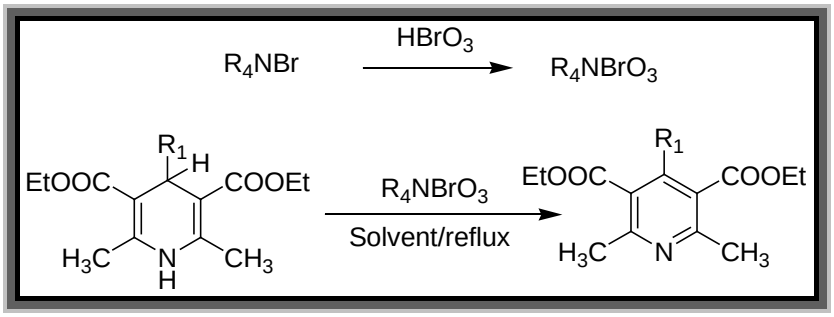


Lakshmi kantam *et al.*[58] has reported the one pot, three component synthesis of 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines and the corresponding 1,4-dihydropyridines are from readily accessible starting materials. Heating of an ethanolic solution of structurally diverse aldehydes with various 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.

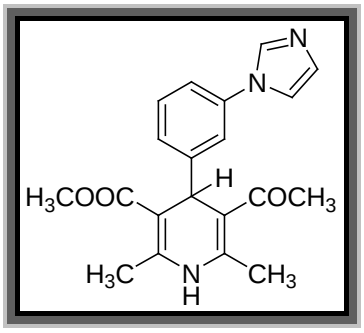


Gunaras *et al.*[59] investigated 1,4-dihydropyridine structure as a less harmful alternative to synthetic phenolic antioxidants in liposomes under conditions simulating food storage. The antioxidant activities (AOA) of 2,6-dimethyl-3,5-dialkoxycarbonyl- 1,4-dihydropyridines possessing various side chain length alkyls (CH_3 - $C_{16}H_{33}$) in ester moiety were tested in transition metalion catalyzed liposome peroxidation and compared with AOA of Trolox™ and Probucol™. The compounds with ethyl - butyl residues in the 3,5-position ester moieties exert the most pronounced AOA. The AOA of tested compounds is associated with their ability to incorporate into liposomes.

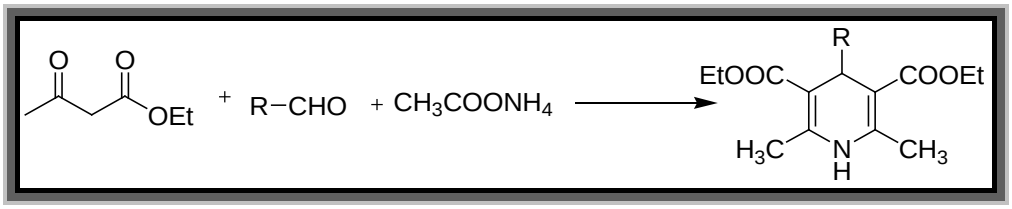
Quaternary ammonium bromate have been prepared from the corresponding bromide and use as a mild and efficient oxidizing agent for the aromatization of Hantzsch esters and related compounds to pyridine derivatives.[60]



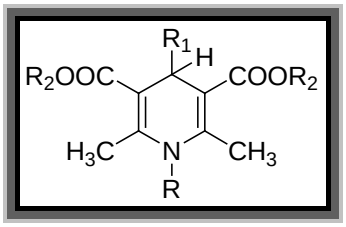
Cozzi *et al.*[61] prepared unsymmetric 4-[3-(1H-imidazol-1-yl-) Phenyl]-1,4-dihydropyridines and studied their antitumor activity. They correlated activity with Letrozole, Anastrozole and other aromatase inhibitors.



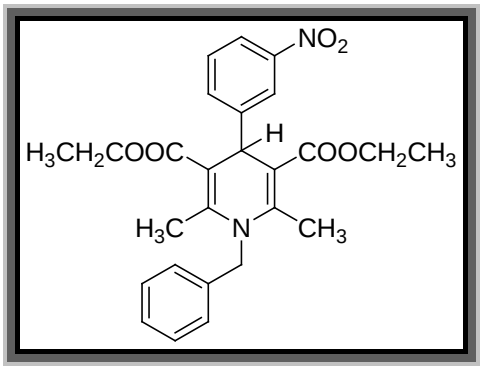
Mohammad *et al.*[62] had prepared 1,4-dihydropyridine under solvent free condition. Ethyl acetoacetate and a range of aldehydes in the presence of ammonium acetate were converted into 1,4-dihydropyridines under mild and solvent free conditions with good to excellent yields.



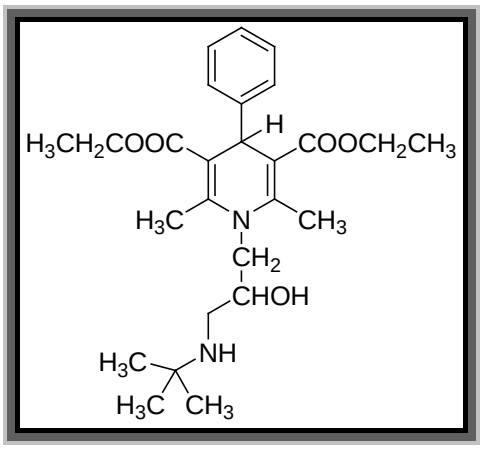
Bossert *et al.*[63-66] prepared many N-substituted 1,4-dihydropyridine derivative by Hantzsch reaction of an amine, acetoacetic ester and an aldehyde, where the condensation also proceeded in ethyl alcohol instead of pyridine.



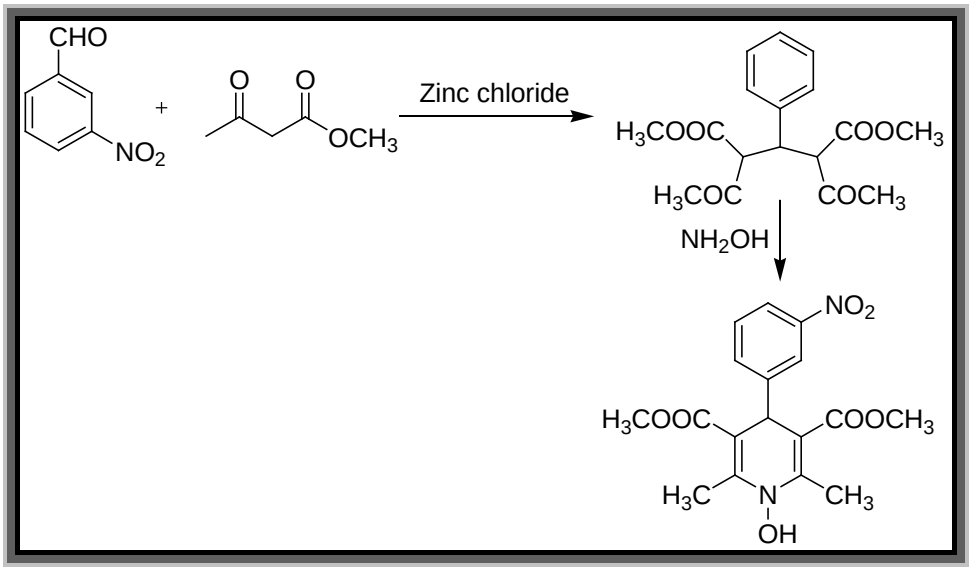
Duburs *et al.*[67] prepared N-benzyl-2,6-dimethyl-4-(3-nitro phenyl)- 3,5-dicarbethyoxy-1,4-dihydropyridine by the condensation of m-nitro benzaldehyde with ethyl acetoacetate and benzyl amine using pyridine as a solvent.



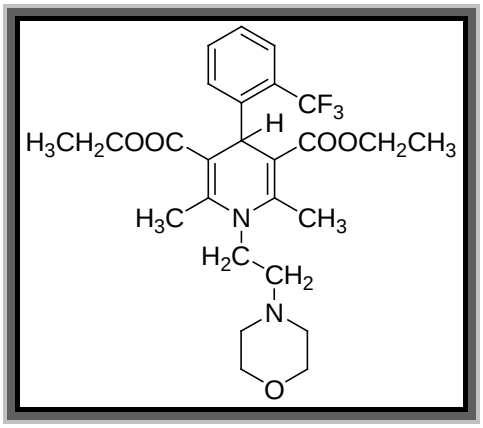
Michael *et al.*[68] prepared antihypertensive and coronary vasodilator N-substituted -1,4-dihydropyridine.



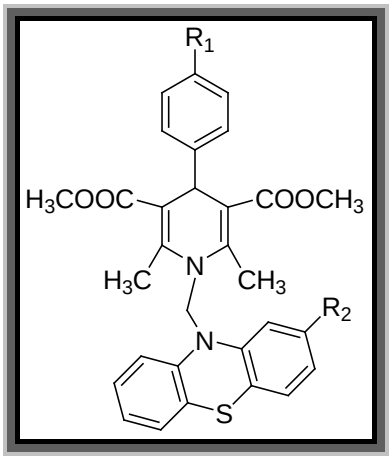
Minoru *et al.*[69] prepared N-phenoxy-1,4-dihydropyridine by the reaction of m-nitro benzaldehyde and methyl acetoacetate in presence of zinc chloride in ethyl acetate at room temperature for 65 min, then at 60-65^{O}C for 6 hrs to give heptadione, which was cyclized with hydroxylamine in methanol at room temperature.



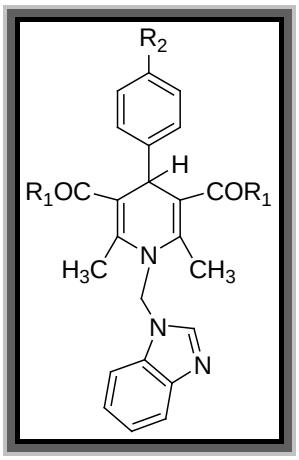
Hung *et al.*[70] were successful in synthesizing antihypertensive model of Flordipine, contrary to the belief proposed by Triggle that N-substituted 1,4-dihydropyridine will not give good antihypertensive activity, probably the concept of prodrug would not have been predicted at that time and –NH was believed to be essential for calcium channel antagonism.



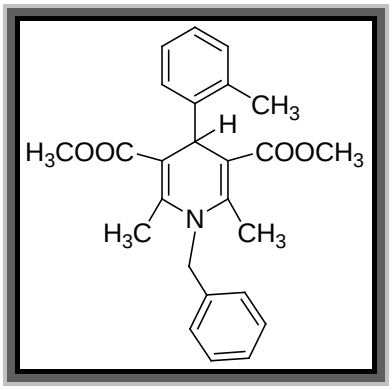
Shah *et al.*[71] also prepared some Mannich Compounds and studied their antimicrobial profile.



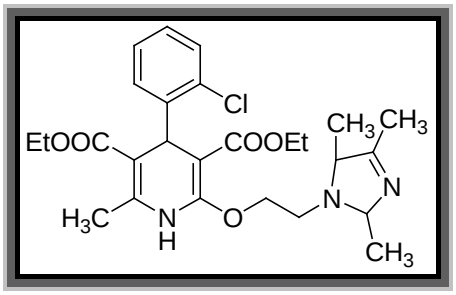
1,4-dihydropyridines were subjected to Mannich reaction to get new 2-alkyl-1-(1'-dihydropyridinyl methyl) benzimidazole as hybrid molecule and was expected to give promising biological active molecules. They were reported to have good antimicrobial activity[72] instead of usual cardiovascular profile.



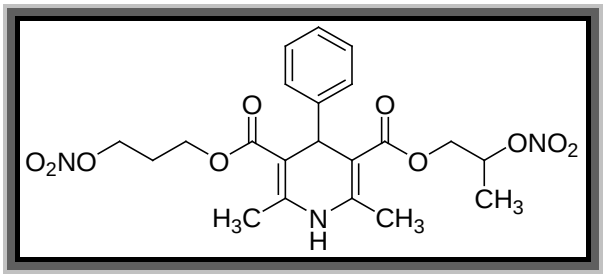
Pitzenberger *et al.*[73] investigated similar analogs in which benzyl amine reacted with acetoacetic ester and via formation as titan amine complex, leading to usual Hantzsch synthesis.



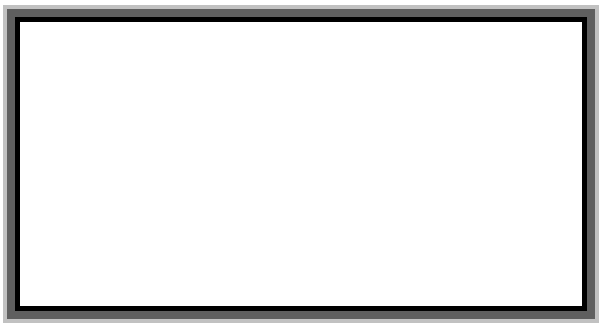
Alkaer *et al.*[74] converted Amlodipine into a derivative as potent vasodilator.



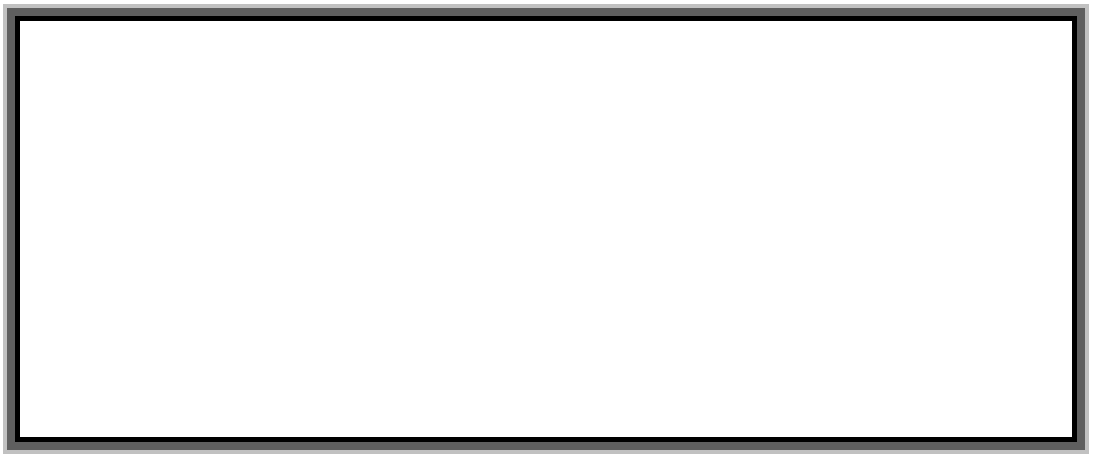
Tsuchida *et al.*[75] has shown that CD-349 can be appeared to be a potent cerebrovasodilator in dogs and could be useful in the treatment of cerebrovascular disorders in human.



Another class of 1,4-DHPs having a cyano group at 3 and 5 position was prepared by Court *et al.*[76] 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.



At this laboratory, the researchers of our group have reported the Tumor-specific Cytotoxicity and MDR-reversal activity of dihydropyridines.[77]



Gaveriya *et al.*[78] have reported the synthesis and MDR reversal activity in Tumor cells.

1.3 BIOLOGICAL PROFILE

Dihydropyridine (DHP) chemistry began in 1882 when Hantzch published the synthesis. The DHP nucleus is common to numerous bioactive compounds which include various vasodilaor, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, eroprotective and antidiabetic agents.[77-82]

DHP have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine,[83] Nitrendipine[84] and Nimodipine.[85] Second generation calcium antagonists include DHP derivatives with improved bioavailability, tissue selectivity, and/or stability such as the antihypertensive, antianginal drugs like Elgodipine,[86] Furnidipine,[87-88] Darodipine,[89] Pranidipine,[90] Lemildipine,[91] Dexniguldipine,[92] Lacidipine[93] and Benidipine.[94] Number of DHP calcium agonists has been introduced as potential drug candidates for treatment of congestive heart failure.[95-96]

The key characteristic of calcium channel blockers is their inhibition of entry of calcium ions via a subset of channels, thereby leading to imairment of contractin. There are three main groups of calcium channel blockers, i.e. dihydropyridines, phenylalkylamines and benzothiazepines, typical examples of which are nifedipine, verapamil and diltiazem respectively.[97-100] Each has a specific receptor on the calcium channel and a different profile of pharmacological activity. Dihydropyridines have a less negative inotropic effect than phenylalkylamines and benzothiazepines but can sometimes cause reflex tachycardia.Dihydropyridines are able to reduce peripheral resistance, generally without clinically significant cardiodepression.

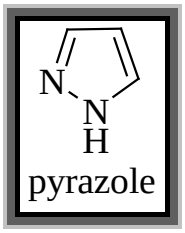
Among DHPs with other types of bioactivity, Cerebrocrast[101] has been recently introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered.[102] These recent examples highlights the level of ongoing interest toword new DHP derivatives and have prompted us to explore this pharmacophoric scaffold to develop a fertile source of bioactive molecules.

1,4-DHPs posses different pharmacological activities such as antitumor,[103] vasodilator,[104] coronary vasodilator and cardiopathic,[105] antimayocardiac ischemic, antiulcer,[106] antiallergic,[107] antiinflammatory[108] and antiarrhythmic,[109] PAF antagonist,[110] Adenosine A3 receptor antagonist[111] and MDR reversal activity.[112-113]

In particular, DHP-CA (calcium channel antagonist DHP) are extensively used for the treatment of hypertension,[114] subarachnoid hemorrhage,[115-116] myocardial infarction[117-120] and stable[121-122] and unstable angina[123-124] even though recently their therapeutic efficacy in myocardial infarction and angina has been questioned.[125] This class of compounds is also under clinical evaluation for the treatment of heart failure,[126] ischemic brain damage[127] nephropathies and atherosclerosis.[128]

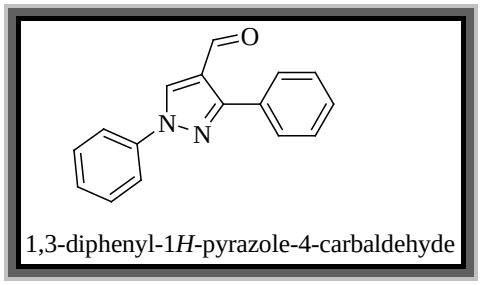
1.4 PYRAZOLS : A VERSATILE SYNTHON

Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a five-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature.



pyrazole

The synthesis of pyrazoles remains of great interest owing to the wide applications in pharmaceutical and agrochemical industry due to their herbicidal, fungicidal, insecticidal, analgesic, antipyretic and anti-inflammatory properties[129-130]. Some methods have been developed in recent years, though the most important method is the reaction between hydrazones and β-dicarbonyl compounds[131] This reaction involves the double condensation of 1, 3-diketones or α, β-unsaturated ketones with hydrazine or its derivatives.[132-133] However, the appealing generality of this method is somewhat vitiated by the severe reaction conditions or the multistep sequences usually required to access the starting materials.[134] Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies for this class of compound. [135]



1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde

The application of Vilsmeier–Haack (VH) reagent ($POCl_3$ / DMF) for formylation of a variety of both aromatic and heteroaromatic substrates is well

documented.[136] Besides this, the reagent has also been extensively used for effecting various chemical transformations from other classes of compounds. Many of these reactions have led to novel and convenient routes for the synthesis of various heterocyclic compounds.[137] A notable example that finds significant application in heterocyclic chemistry is the synthesis of 4-formylpyrazoles from the double formylation of hydrazones with Vilsmeier-Haack (VH) reagent.[138-139] These observations, coupled with the recent developments on the simple synthesis of pyrazole derivatives, [140] especially 4-functionalized 1, 3-diphenylpyrazoles as antibacterial, anti-inflammatory,[141-142] antiparasitic[143] and antidiabetic[144] drugs, prompted chemistry research to undertake the synthesis of pyrazole-4-carboxldehyde derivatives using Vilsmeier-Haack (VH).[145-146] The study is particularly aimed at developing a one-pot synthesis of pyrazole-4-carboxaldehyde oximes starting from acetophenone phenylhydrazones.

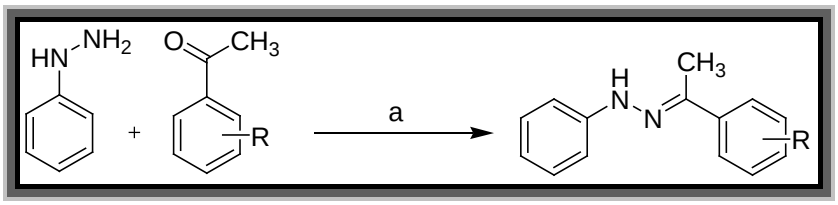
1.5 AIM OF CURRENT WORK

The aim of current work was to prepare a small series of 1,4-dihydropyridine bearing the cyano group having a pyrazole heterocyclic ring in place of the conventional phenyl ring.

1.6 REACTION SCHEMES

1.6.1 PREPARATION OF PYRAZOLE ALDEHYDES :

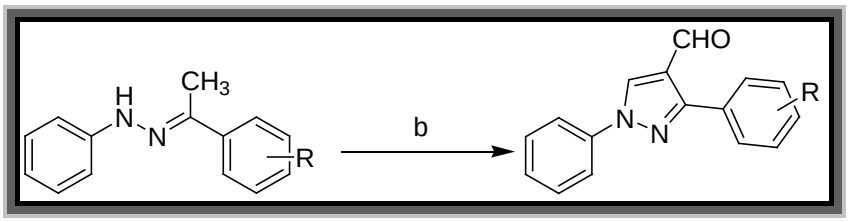
STEP – 1



Reagents / Reaction Condition (a): Glacial acetic acid, Ethanol / Reflux, 5-6 hours.

Where, R = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2

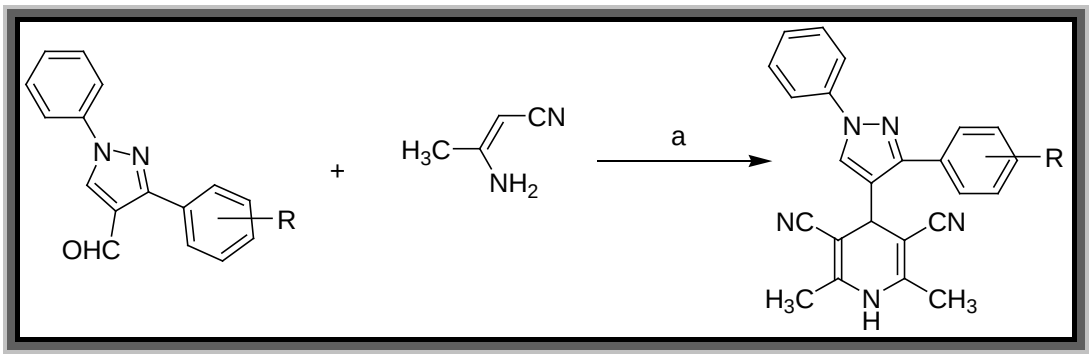
STEP – 2



Reagents / Reaction Condition (b): DMF – $POCl_3$ / 70-80°C, 5-6 hours.

Where, R = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2

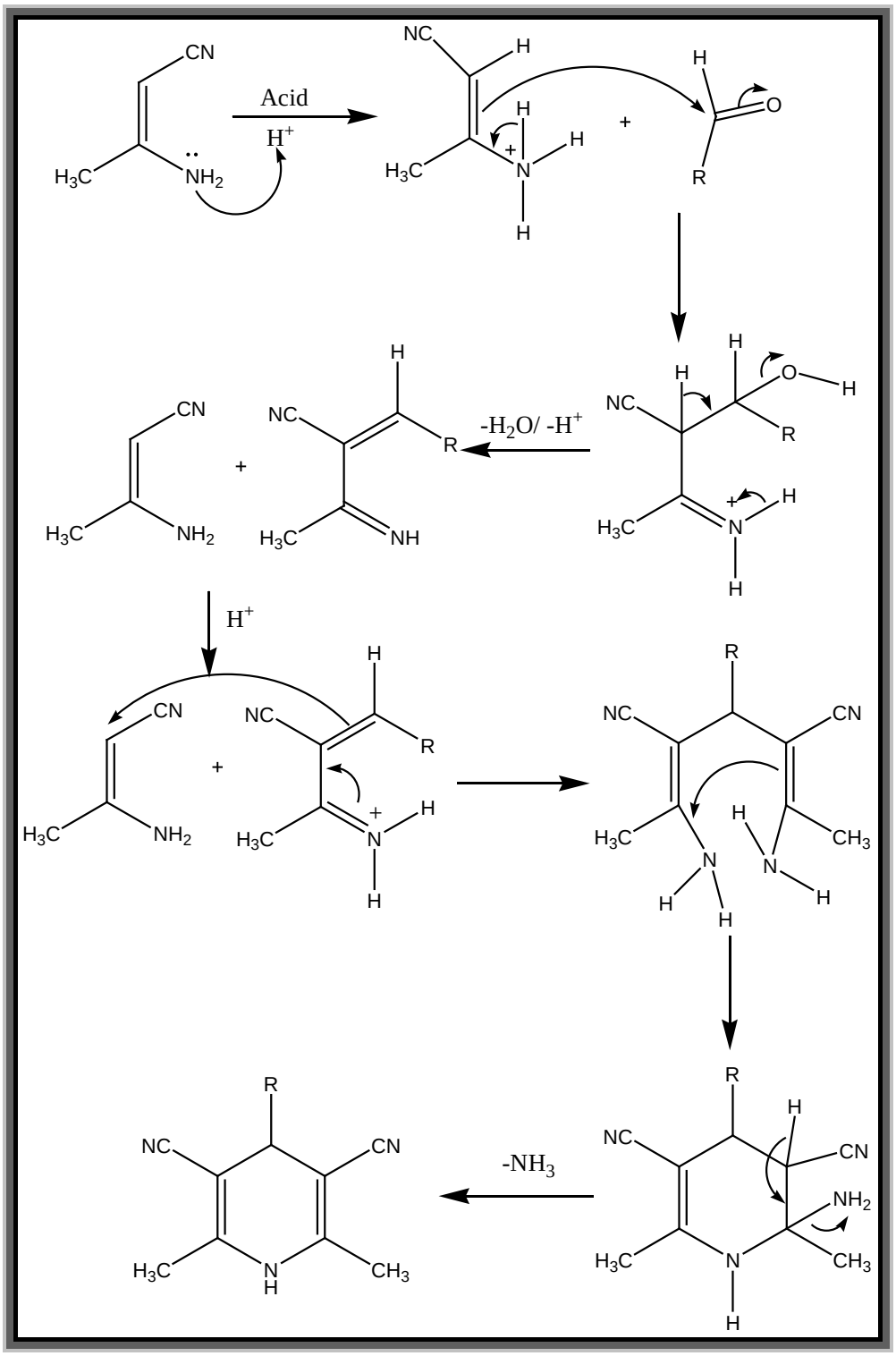
1.6.2 PREPARATION OF 4-(1,3-(SUBSTITUTED) DIPHENYL-1H-PYRAZOL-4-YL)-2,6-DIMETHYL-1,4-DIHYDROPYRIDINE-3,5-DICARBONITRILE



Reagents / Reaction Condition (a): Glacial Acetic acid / 60-70°C, 1 hours.

Where, R = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2

1.7 PLAUSIBLE REACTION MECHANISM



1.8 EXPERIMENTAL

1.8.1 MATERIALS AND METHODS

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 pellet 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 solution on a **Bruker Ac 400 MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model and the results are in agreements with the structures assigned.

1.8.2 PREPARATION OF PYRAZOLE ALDEHYDE: GENERAL METHOD

STEP – 1 PREPARATON OF ACETOPHENONE PHENYL HYDRAZONES.

Appropriately substituted Acetophenone (0.1 mole) was dissolved in 50 ml of ethanol into 250 ml beaker. Phenyl hydrazine (0.1 mole) was added to above flask along with 3-4 drops of glacial acetic acid. The reaction mixture was stirred for 1 hours at room temperature. The progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate : hexane (6 :4) as a mobile phase. After the completion of the reaction, the reaction mixture was kept to room temperature for 1 hours and the crystalline product was separated by filtration. The product was washed with ethanol and dried to give substituted acetone phenyl hydrazone in good yield which was pure enough to use as such for the next step.

TABLE – 1.1

Code No.	Substitution	MF	MW (g/m)	MP (°C)	% Yield
PA-01	H	$C_{14}H_{14}N_2$	210	126-128	78
PA-02	4-CH_3	$C_{15}H_{16}N_2$	224	134-136	80
PA-03	4-NO_2	$C_{14}H_{13}N_3O_2$	255	136-138	76
PA-04	2-OH	$C_{14}H_{14}N_2O$	226	142-144	79
PA-05	2-OCH_3	$C_{15}H_{16}N_2O$	240	158-160	76
PA-06	4-Cl	$C_{14}H_{13}ClN_2$	244	144-146	82
PA-07	3-NO_2	$C_{14}H_{13}N_3O_2$	255	136-138	78
PA-08	4-F	$C_{14}H_{13}FN_2$	228	148-150	84

STEP – 2 PREPARATION OF PYRAZOLE ALDEHYDES

Dimethylformamide (0.32 mole) was transferred into 25 ml flat bottom flak. Phosphorous oxychloride (0.032 mole) was added drop wise to above flask under stirring at 0-5^{O}C. After completion of the addition, the mixture was stirred at this temperature for 10-15 min. freshly prepared acetophenone hydrazone 0.03 mole was added to above mixture and the content was heated on water bath for 5-6 hours. The progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using toluene: ethyl acetate (6: 4) as a mobile phase. After the reaction to be completed, the reaction mixture was cooled to room temperature and the content of the flask was poured on crushed ice to isolate the product. The separated product was filtered off and it was washed with cold water to remove acidity. It was dried at 65^{O}C and recrystallized from the mixture of DMF-Methanol to give crystalline pyrazole aldehyde in good yield.

Similarly other compounds are also prepared

TABLE – 1.2

Code No.	Substitution	MF	MW (g/m)	MP (°C)	% Yield
PY-01	H	$C_{16}H_{12}N_2O$	248	162-164	75
PY-02	4-CH_3	$C_{17}H_{14}N_2O$	262	176-178	70
PY-03	4-NO_2	$C_{16}H_{11}N_3O_3$	293	144-146	82
PY-04	2-OH	$C_{16}H_{12}N_2O_2$	264	142-144	78
PY-05	2-OCH_3	$C_{17}H_{14}N_2O_2$	278	148-150	72
PY-06	4-Cl	$C_{16}H_{11}ClN_2O$	282	164-166	70
PY-07	4-NO_2	$C_{16}H_{11}N_3O_3$	293	154-156	82
PY-08	4-F	$C_{16}H_{11}FN_2O$	266	148-150	68

1.8.3 PREPARATION OF 4-(1,3-(SUBSTITUTED) DIPHENYL-1H-PYRAZOL-4-YL)-2,6-DIMETHYL-1,4-DIHYDROPYRIDINE-3,5-DICARBONITRILE.

GENERAL METHOD

A mixture of pyrazole aldehyde (0.01 mol), 3-amino crotononitrile (0.02 mol) in glacial CH_3COOH was stirred for 1 hrs at 60-70^OC in a stoppered flask. The reaction mixture was kept at room temperature for half an hour. During the reaction the 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 reaction to be completed, the reaction mixture was kept to room temperature for 1 hours and the crystalline product was separated by filtration. The solid product was obtained after cooling and then filtered and washed with first acetic acid and then with hexane.

Similarly other compounds are also prepared.

The physical constant of newly synthesized compounds are given in Table No.1.3

1.9 PHYSICAL DATA

Physical data of 4-(1,3-(Substituted) diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarbonitrile.

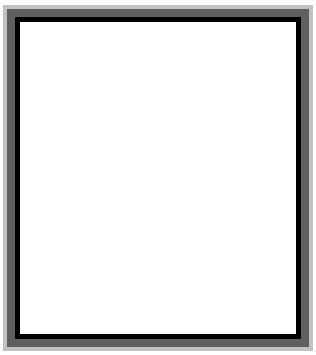


TABLE – 1.3

Code	Substitution R	MF	MW	MP ^{O}C	Rf Value
STAB-01	H	$C_{24}H_{19}N_5$	377	208-210	0.40
STAB-02	4-CH_3	$C_{25}H_{21}N_5$	391	198-200	0.43
STAB-03	4-Cl	$C_{24}H_{18}ClN_5$	411	178-180	0.43
STAB-04	4-NO_2	$C_{24}H_{18}N_6O_2$	422	228-230	0.42
STAB-05	2-OH	$C_{24}H_{19}N_5O$	393	212-214	0.44
STAB-06	2-OCH_3	$C_{25}H_{21}N_5O$	407	238-240	0.43
STAB-07	3-NO_2	$C_{24}H_{18}N_6O_2$	422	196-198	0.47
STAB-08	4-F	$C_{24}H_{18}FN_5$	395	218-220	0.42

R_f value was determined using solvent system = Ethyl Acetate : Hexane (3 : 2)

1.10 SPECTRAL DISCUSSION

1.10.1 IR SPECTRA

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

The characteristic bands of Hydroxyl groups were obtained for streching at 3400-3650 cm^{-1} and those for bending were obtained at 1050-1250 cm^{-1}.The stretching vibrations N-H group showed in the region of 3200 to 3500 cm^{-1} with a deformation due to in plane bending at 1650-1580 cm^{-1}. It gives aromatic C-H stretching frequencies between 3000-3200 cm^{-1} and bending vibration near 1300-1500 cm^{-1} respectively. C-H stretching frequencies for methyl and methylene group were obtained near 2950 cm^{-1} to 2850 cm^{-1}. Characteristic frequency of C-N stretching showed near 2100-2200 cm^{-1} and bending vibration near 1300-1400 cm^{-1}.

1.10.2 MASS SPECTRA

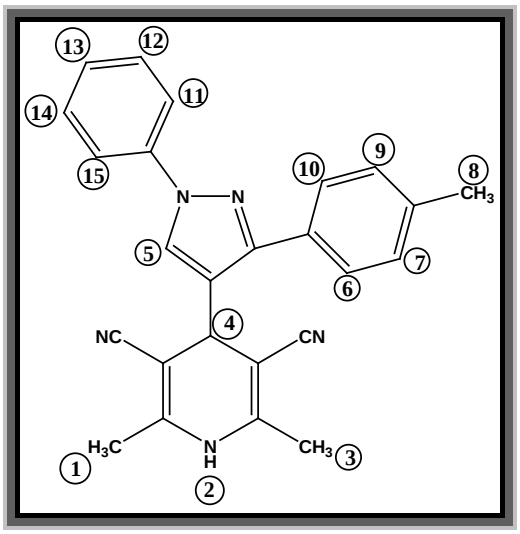
Mass spectra of the synthesized compounds were recorded on **Shimadzu GC-MS QP-2010** model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom.

1.10.3 ^{1}H NMR SPECTRA

^{1}H NMR spectra of the synthesized compounds were recorded on **Bruker Avance II 400 spectrometer** by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons and carbons identified from ^{1}H NMR spectrum 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.

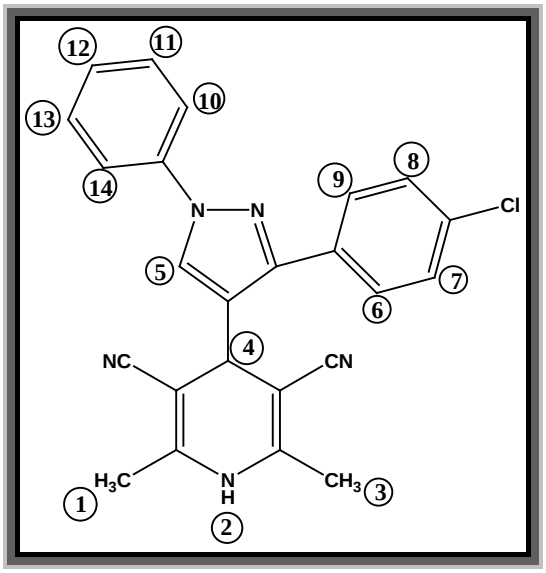
^{1}H NMR of 1,4-Dihydro-2,6-dimethyl-4-(1-phenyl-3-p- tolyl-1H-pyrazol-4-yl)-pyridine-3,5-dicarbonitrile. (STAB-02)



1. Proton no. 1 and 3 of total 6H gave a singlet at 1.95 δ ppm.
2. Proton no. 8 of total 3H gave a singlet at 2.39 δ ppm.
3. Proton no. 4 became deshielded and gave a characteristic singlet at 4.57 δ ppm.
4. Proton no. 7 and 9 of 2H gave a Doublet at 7.22 δ ppm -7.24 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
5. Proton no. 13 of 1H gave a triplet at 7.26 δppm- 7.29 δppm.
6. Proton no. 11, 12, 14 and 15 of 4H gave a multiplet at 7.43 δppm – 7.50 δppm.
7. Proton no. 6 and 10 of 2H gave a dublet at 7.76 δ ppm -7.80 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
8. Proton no. 5 of pyrazol ring gave a singlet at 8.09 δ ppm.
9. Proton no. 2 of pyridine ring gave a singlet at 9.05 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 no. STAB-02 has been confirmed. The spectrum is given on page no. 35.

^{1}H NMR of 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile. (STAB-03)



1. Proton no. 1 and 3 of total 6H gave a singlet at 1.86 δ ppm.
2. Proton no. 4 become deshielded and gave a characteristic signal at 4.48 δ ppm.
3. Proton no. 12 of 1H gave a triplet at 7.18-7.22 δ ppm.
4. Proton no. 6 and 9 of 2H gave a Doublet at 7.31 δ ppm -7.33 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
5. Proton no. 11 and 13 of 2H gave a triplet at 7.34 δ ppm – 7.38 δ ppm.
6. Proton no. 7 and 8 of 2H gave a Doublet at 7.48 δ ppm – 7.51 δ ppm and J value of this proton is 8.0Hz. It suggest ortho coupling.
7. Proton no. 10 and 14 of 2H gave a double dublet at 7.66 δ ppm -7.68 δ ppm.
8. Proton no. 5 of 1H gave a singlet at 7.95 δ ppm.
9. Proton no. 2 of 1H gave a singlet at 8.90 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 no. STAB-03 has been confirmed. The spectrum is given on page no. 37.

1.10.4 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 spectral and elemental analysis data are for individual compounds synthesized in this chapter is mentioned below.

1.11 ANALYTICAL DATA

1,4-Dihydro-2,6-dimethyl-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyridine-3,5-dicarbonitrile. (STAB-02)

Yield: 82% IR (cm^{-1}): 3296 (N-H stretching), 3126 (Aromatic C-H stretching), 2993 (Aliphatic -CH_3 stretching), 2839 (Aliphatic -CH_2 stretching), 2198(C-N stretching), 1662-1595 (N-H bending), 1508, 1448, 1354 (C-H bending), 1292 (C-N bending) 756 (disubstituted), 686 (monosubstituted) ^{1}H NMR (DMSO-d_6) δ ppm: 1.95 (s, 6H), 2.39 (s, 3H), 4.57 (s, 1H), 7.22-7.24 (d, 2H, J=8.0 Hz), 7.26-7.29 (t, 1H), 7.43-7.50 (m, 4H),7.76-7.80 (d,2H, J=8.0Hz) 8.09 (s, 1H), 9.05 (s, 1H), MS: *m/z* = 391 (M^+) ; Anal. Calcd. for $C_{25}H_{21}N_5$: C, 76.70; H, 5.41; N,17.89; Found: C, 76.66; H, 5.36; N, 17.81.

4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethyl pyridine-3,5-dicarbonitile. (STAB-03)

Yield: 85%IR (cm^{-1}): 3290 (N-H stretching), 3126, 3016 (Aromatic C-H stretching), 2993 (Aliphatic -CH_3 stretching), 2839 (Aliphatic -CH_2 stretching), 2200 (C-N Stretching), 1662-1599 (N-H bending), 1545,1446 ,1357 (C- H bending), 1294(C-N bending), 754 (disubstituted), 690 (monosubstituted) ^{1}H NMR (DMSO-d_6) δ ppm: 1.86 (s, 6H), 4.48 (s, 1H), 7.18-7.22 (t, 1H), 7.31-7.33 (d, 2H), 7.34-7.38 (t, 2H), 7.48-7.51 (d, 2H, J=8.0Hz), 7.66-7.68 (d,2H), 7.95 (s, 1H) , 8.90 (s, 1H) MS: *m/z* = 411 (M^+), 413 (M^{+2}) ; Anal. Calcd. for $C_{24}H_{18}ClN_5$: C, 69.98; H, 4.40; Cl,8.61; N, 17.00 ; Found: C, 69.89; H, 4.40; Cl, 8.59; N, 16.98.

1,4-Dihydro-2,6-dimethyl-4-(1,3-diphenyl-1H-prazol-4-yl)pyridine-3,5-dicarbonitrile. (STAB-01)

Yield: 80% IR (cm^{-1}): 3286 (N-H stretching), 3109, 3012 (Aromatic C-H stretching), 2841 (Aliphatic -CH_2 stretching), 2195 (C-N stretching), 1664-1597 (N-H bending), 1518, 1448, 1329 (C-H bending), 1284(C-N bending), 705 (mono substituted), MS: *m/z* = 377 (M^+) ; Anal. Calcd. for $C_{24}H_{19}N_5$: C, 76.37; H, 5.07; N, 18.55; Found: C, 76.29; H, 5.04; N, 18.50.

1,4-Dihydro-2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) pyridine-3,5-dicarbonitrile. (STAB-04)

Yield: 84% IR (cm^{-1}): IR (cm^{-1}): 3296 (N-H stretching), 3129 (Aromatic C-H strething), 2998 (Aliphatic -CH_3 stretching), 2836 (Aliphatic -CH_2 stretching), 2210(C-N stretching), 1668-1599 (N-H bending), 1540,1365 (C-NO_2 stretching), 1510,1458, 1356 (C-H bending), 1296(C-N bending), 758 (disubstituted), 688 (monosubstituted) MS: *m/z* = 422 (M^+) ; Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89; O, 7.57 Found: C, 68.14; H, 4.25; N, 19.80; O, 7.49.

1,4-Dihyro-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3,5-dicarbonitrile. (STAB-05)

Yield: 82% IR (cm^{-1}): 3610 (-OH stretching), 3294 (N-H stretching), 3124 (Aromatic C-H stretching), 2990 (Aliphatic -CH_3 stretching), 2830 (Aliphatic -CH_2 stretching), 2208(C-N stretching), 1661-1592 (N-H bending), 1508,1456, 1360 (C-H bending) , 1240 (-OH bending), 1298(C-N bending), 752(1,2-disubstituted), 678 (monosubstituted) MS: *m/z* = 393 (M^+) ; Anal. Calcd. for $C_{24}H_{19}N_5O$: C, 73.27; H, 4.87; N, 17.80; O, 4.07 Found: C, 73.23; H, 4.79; N, 17.73; O, 4.03.

1,4-Dihydro-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylyridine -3,5-dicarbonitrile. (STAB-06)

Yield: 81% IR (cm^{-1}): 3298 (N-H stretching), 3120 (Aromatic C-H stretching), 2996 (Aliphatic -CH_3 stretching), 2832 (Aliphatic -CH_2 stretching), 2210(C-N stretching), 1660-1582 (N-H bending), 1518,1466, 1361 (C-H bending), 1310 (C-O-C), 1299 (C-N bending), 751(disubstituted), 670 (monosubstituted) MS: *m/z* = 407 (M^+) ; Anal. Calcd. for $C_{25}H_{21}N_5O$: C, 73.69; H, 5.19; N, 17.19; O, 3.93 Found: C, 73.61; H, 5.17; N, 4.05; O, 3.90.

1,4-Dihydro-2,6-dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-3,5-dicarbonitrile. (STAB-07)

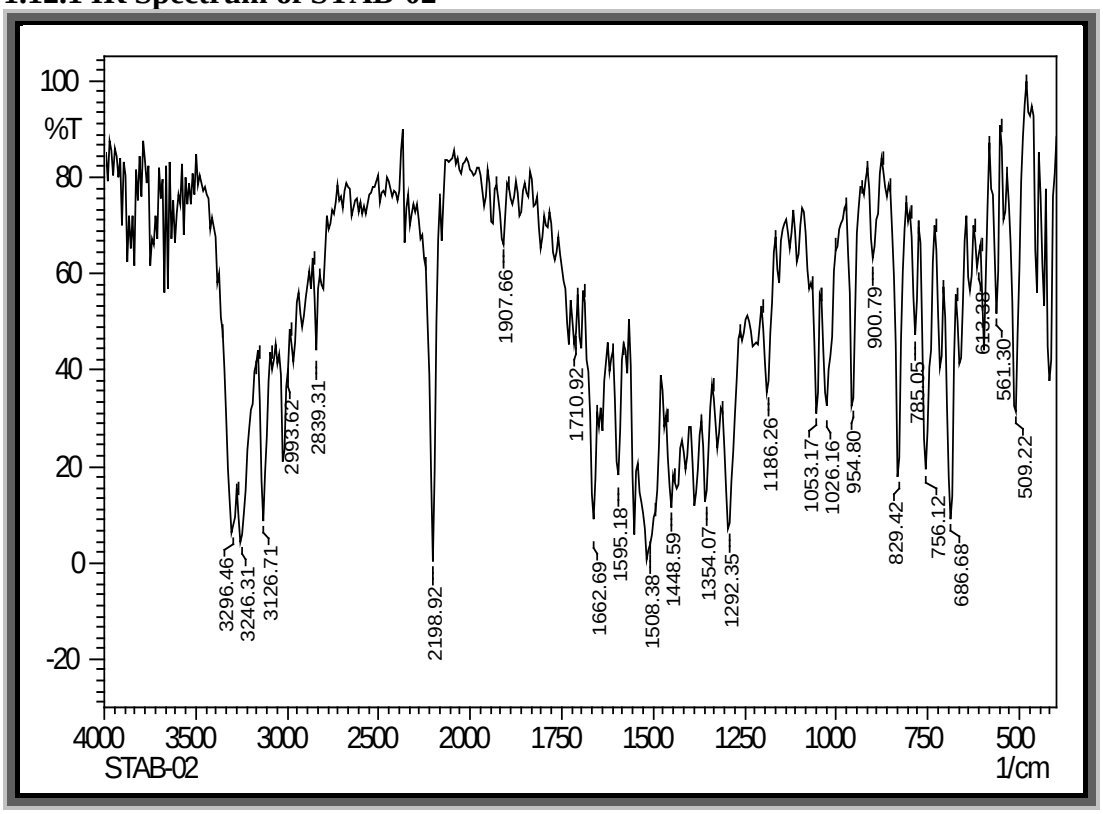
Yield: 80% IR (cm^{-1}): 3292 (N-H stretching), 3121 (Aromatic C-H stretching), 2986 (Aliphatic -CH_3 stretching),2842 (Aliphatic -CH_2 stretching), 2201(C-N stretching), 1662-1572 (N-H bending), 1542 (C-NO_2 stretching) 1508,1476,1360 (C-H bending), 1289(C-N bending), 750(disubstituted), 671(monosubstituted), MS: *m/z* = 422 (M^+) ; Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89; O, 7.57 Found: C, 68.14; H, 4.16; N, 19.81; O, 7.47.

4-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile. (STAB-08)

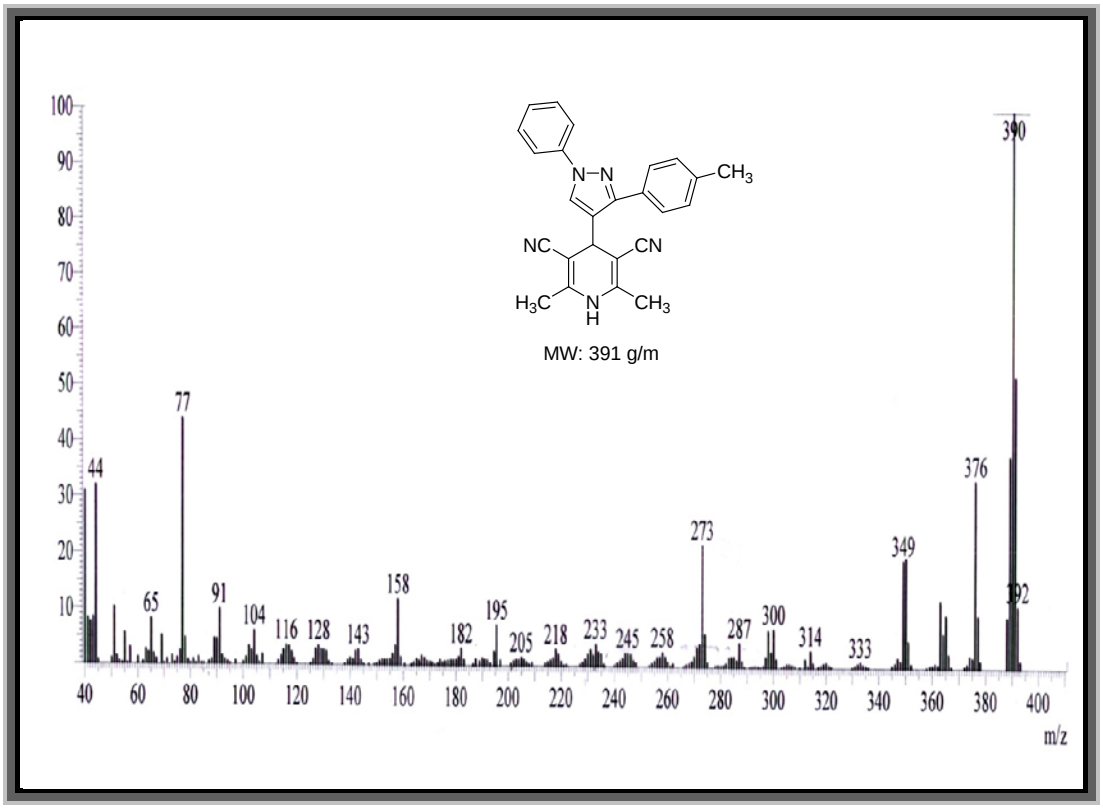
Yield: 86% IR (cm^{-1}): 3298 (N-H stretching), 3124 (Aromatic C-H stretching), 2996 (Aliphatic -CH_3 stretching), 2852 (Aliphatic -CH_2 stretching), 2208(C-N stretching), 1666-1582 (N-H bending), 1518,1486,1360 (C-H bending) , 1299(C-N bending), 753 (disubstituted), 672(monosubstituted) MS: *m/z* = 395 (M^+) , 397 (M^{+2}) ; Anal. Calcd. for $C_{24}H_{18}FN_5$: C, 72.90; H, 4.59; F, 4.80; N, 17.71 Found: C, 72.83; H, 4.51; F, 4.77.

1.12 REPRESENTATIVE SPECTRAS

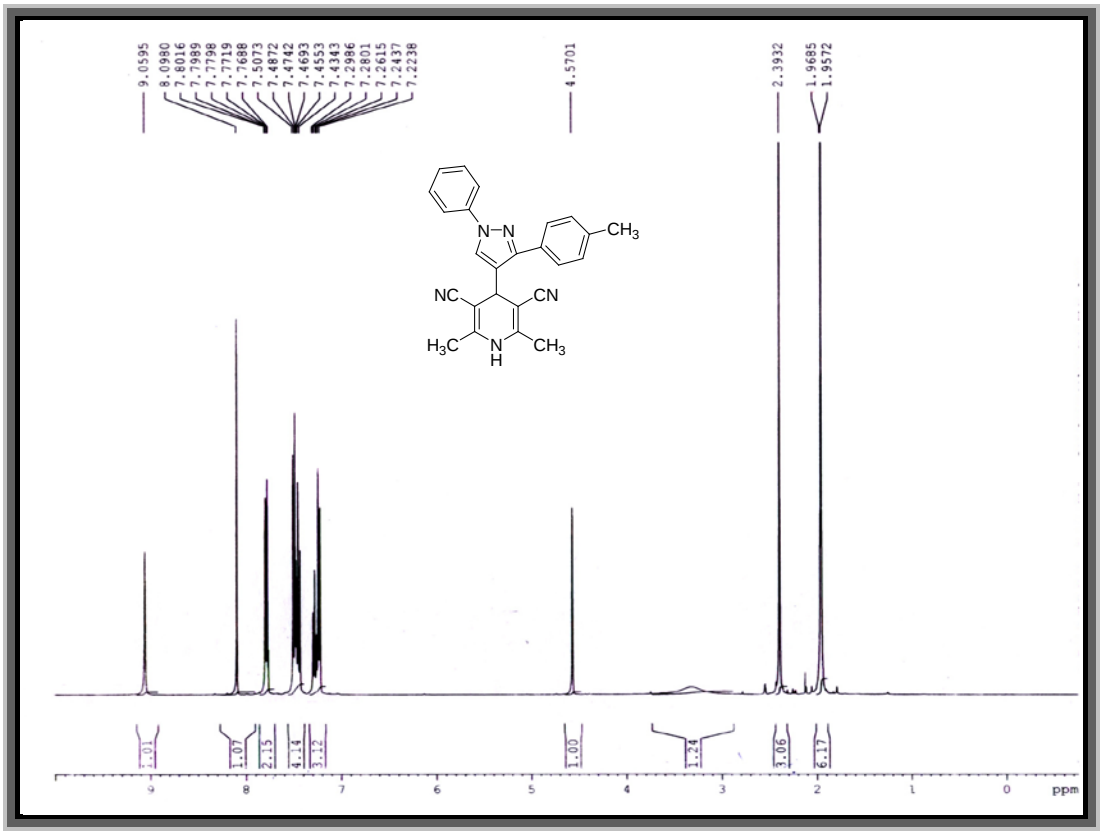
1.12.1 IR Spectrum of STAB-02



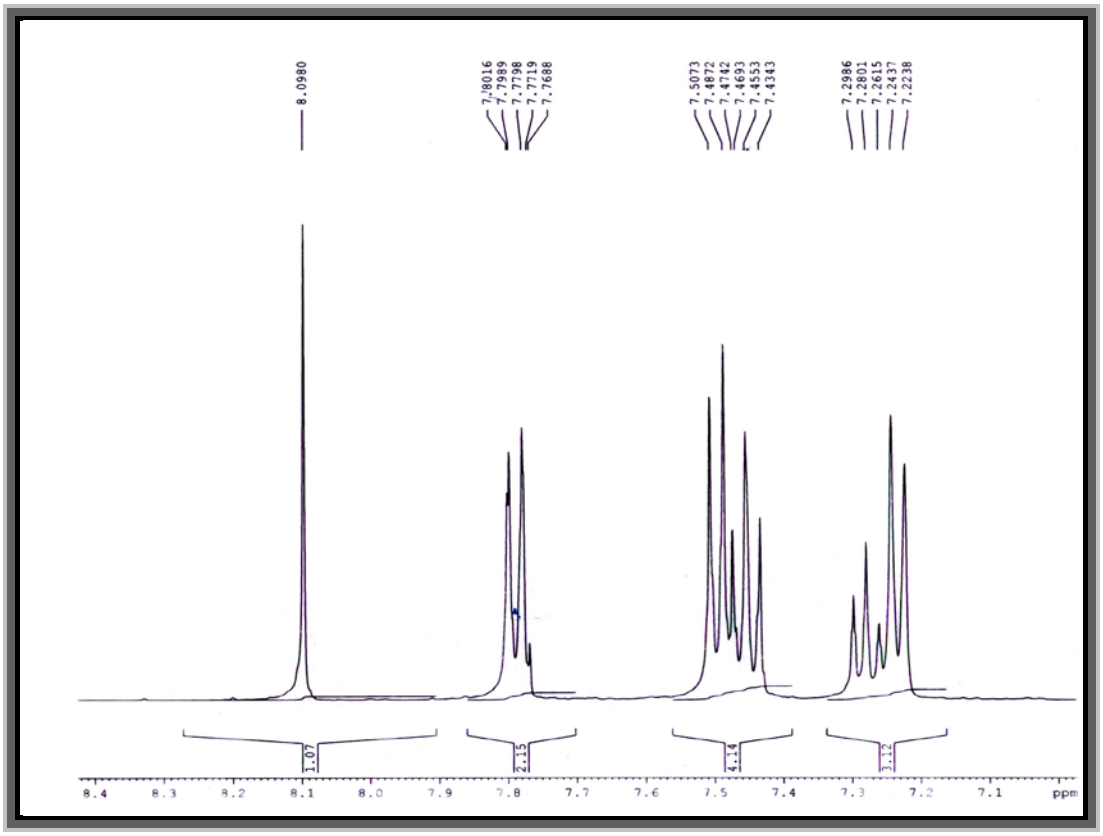
1.12.2 Mass Spectrum of STAB-02



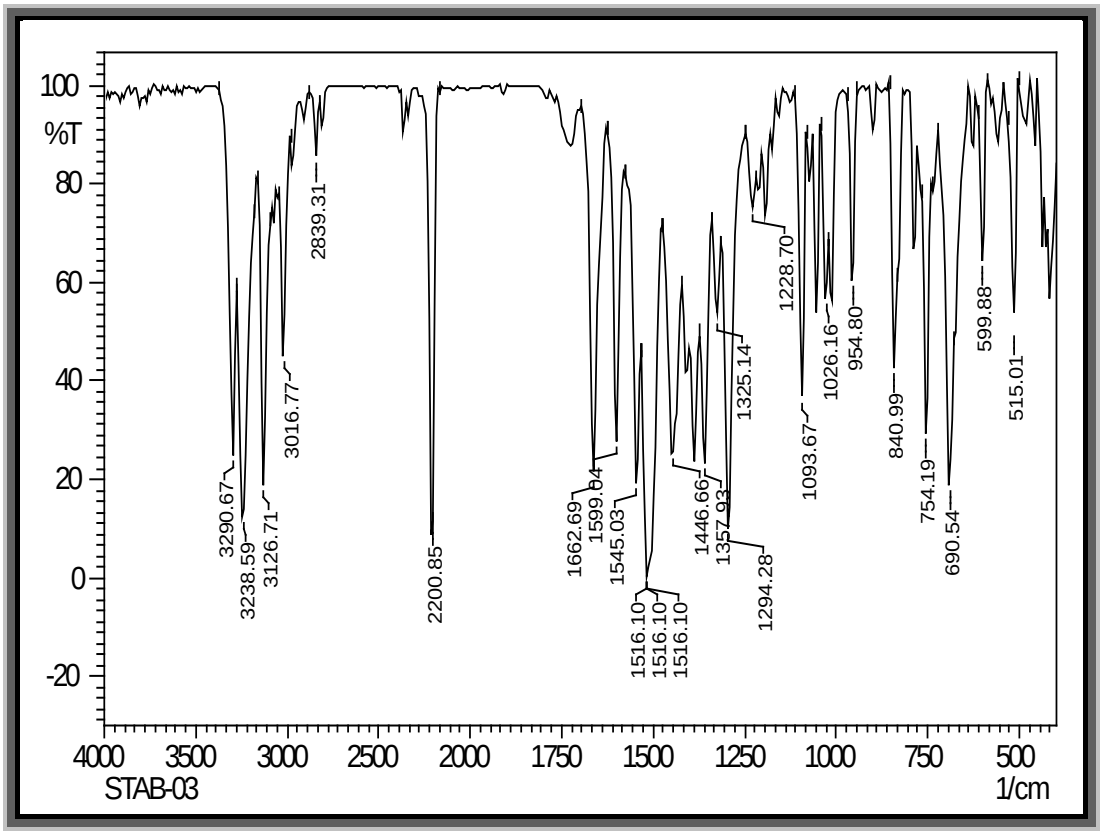
1.12.3 ^{1}H NMR Spectrum of STAB-02



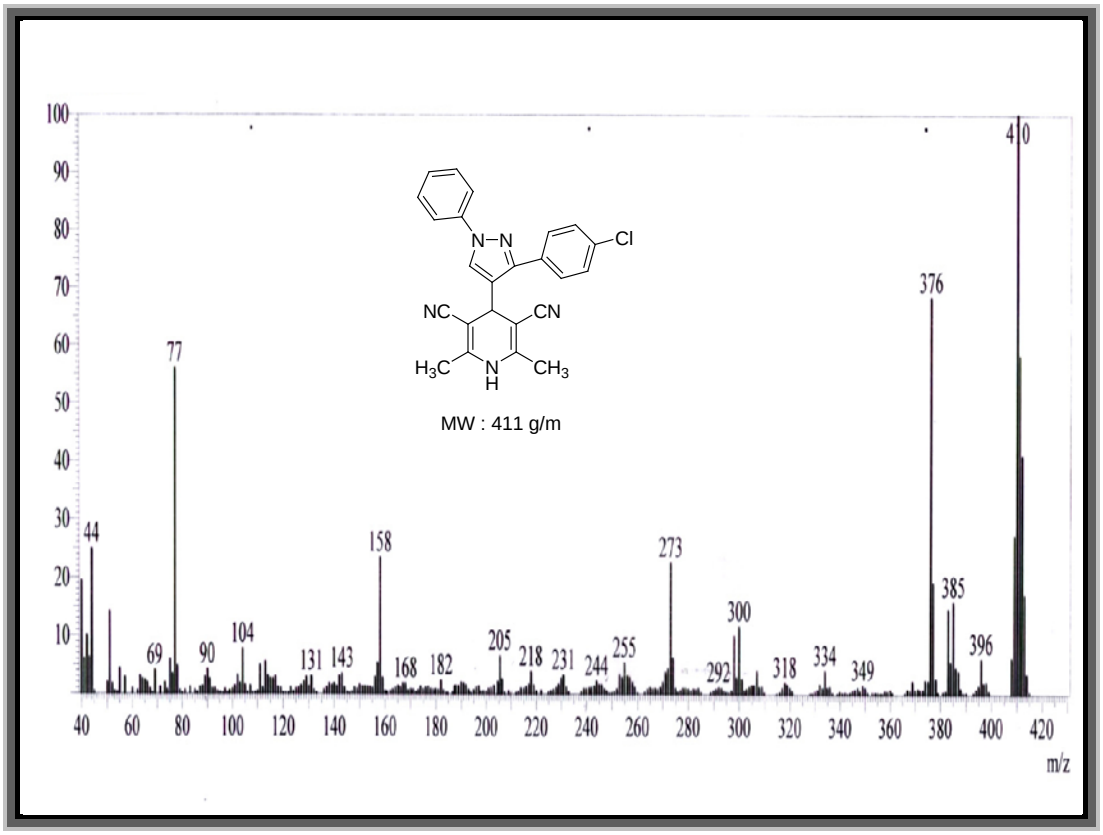
1.12.4 Expanded ^{1}H NMR Spectrum of STAB-02



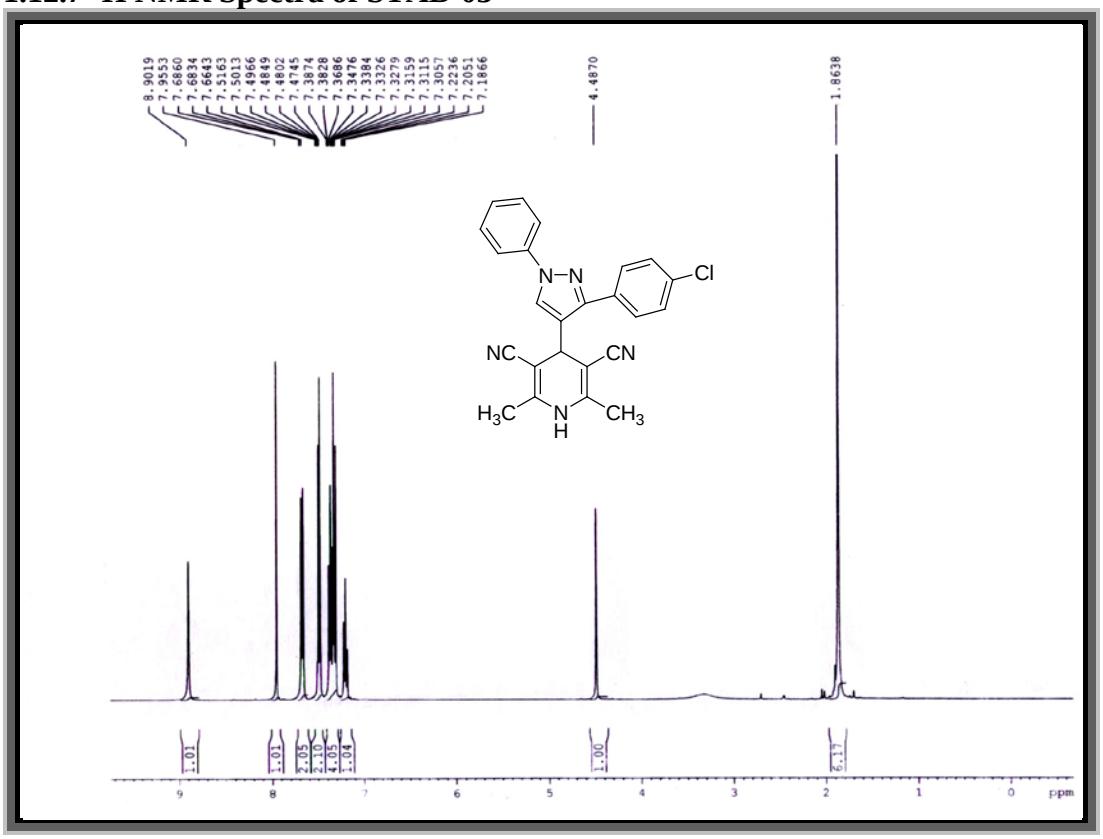
1.12.5 IR Spectrum of STAB-03



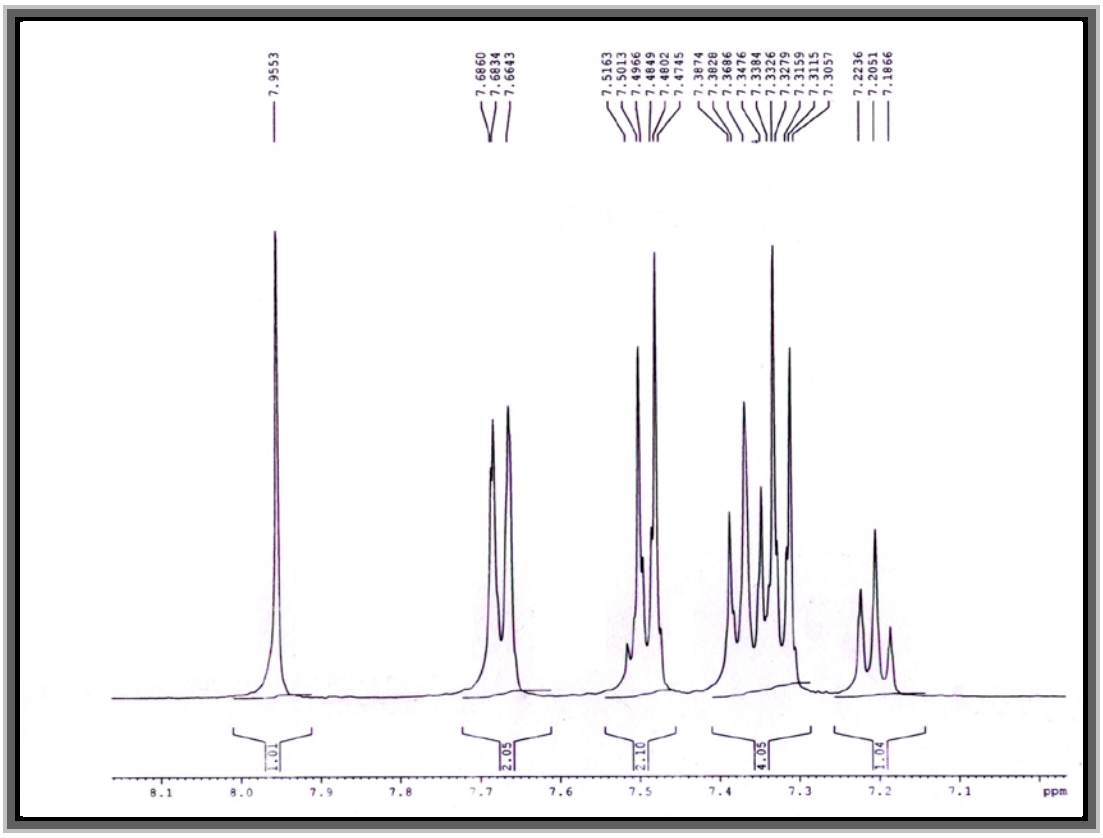
1.12.6 Mass Spectrum of STAB-03



1.12.7 ^{1}H NMR Spectra of STAB-03

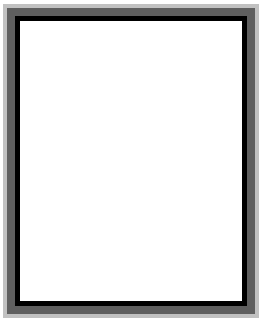


1.12.8 ^{1}H Expanded NMR Spectra of STAB-03

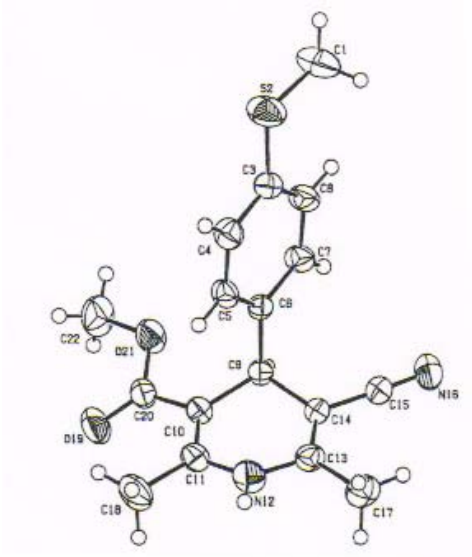


1.13 X-ray crystallographic study

Earlier, Crystal structure of 2,6-dimethyl-3-cyanide-5-methyl acetate-4-(4'-methylthiophenyl)-1,4-dihydropyridine and crystallographic characterization was carried out.[156] This compounds was obtained by the substitution of cyanide group at C_3 and acetyl group at C_5 position of 1,4-dihydropyridine. A schematic diagram of the molecule is shown in figure.



A single crystal of $C_{17}H_{18}N_2O_2S$ having dimensions of 0.2×0.3×0.25 mm was chosen for X-ray diffractions studies. The measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated radiation (Mo Kα). The data were collected by the ω-2Θ scan technique and reduced using the teXsan data reduction program. Lorents and Polarisation corrections were applied. The structure was solved using a direct method and refined by least-squares method.



[ORTEP diagram of 2,6-dimethyl-3-cyanide 5-methyl acetate-4-(4'-methylthiophenyl)-1,4-dihydropyridine]

The ORTEP diagram of the molecule with thermal ellipsoids at 50% probability is given in previous page. Table. No.1 gives the details of the crystal and the experimental data. Table No.2 gives the fractional atomic coordinates and the equivalent thermal parameters for all the refined atoms. Hydrogen atoms were placed at chemically acceptable positions. Tables 3 and 4 give the bond distances and angles of the non-hydrogen atoms, respectively. The bond distances and angles are in good agreement with the those of reported structures. The packing of the molecules shows a layered arrangement along b axis. The structure adopts a flat boat conformation. The phenyl ring (C_3, C_4, C_5, C_6, C_7, C_8) is planner with the maximum deviation of 0.005(2) A^o for C8. The torsion angles connecting between the phenyl and dihydropyridine rings determine the conformation around the C-C bind. The observed angles are C_7-C_6-C_9-C_{14}(83.09(14)^o), C_7-C_6-C_9-C_{10}(155.08(12)^o), C_5-C_6-C_9-C_{14}(92.65(14) ^{o}) and C_5-C_6-C_9-C_{10}(29.19(16) ^{o}). The dihedral angle found between the planes 1(C_9-C_{14}) and 2(C_3-C_8) is 83.26(6)^o. The structure exhibits intra and intermolecular hydrogen bonds of the type C-H$^{\cdots}$O and N-H$^{\cdots}$N. The intra and intermolecular hydrogen bonds are: C(18)-H(8A)$^{\cdots}$O(19) (2.873(2) A^o, 126) and N(12)-H(1)$^{\cdots}$N(16) (3.131(2) $A^{o,}$ 151^o), C(7)-H(13)$^{\cdots}$O(19) (3.225(2) A^o, 132^o) with symmetry codes (-1/2 + x, 3/2-y,z) and (1/2+ x, ½-y,z) and (1/2+x, ½-y,z), respectively.

Table-1 : Crystal and experimental data

Formula formula : $C_{17}H_{18}N_2O_2S$	
Formula weight = 314.39	
Crystal system : monoclinic	
Space group : $P2_1/a$	z=4
a=14.2499(14) A^o	b=8.191(2) A^o
c=14.5527(16) A^o	ß=107.059(8) ^{o}
Volume = 1623.9(5) A^{o3}	
Density(Calculated)= 1.296 Mg/m^3	
$\Theta_{max = 32.49}{}^o$ with Mo Kα	
No. of reflections used = 3601[I>2σ(I)]	
R= 0.0473	
$(\Delta/\sigma)_{max}$= 0.001	
$(\Delta/\rho)_{max}$= 0.428e A^{o3}	

$(\Delta/\rho)_{min}$ = -0.305 e A^{o3}	
Measurement : RIgaku AFC7S	
Program system : teXsan	
Structure determination : SHELXS-97	
Refinement : full matrix	
H atoms : geometrically fixed	

Table-2 : Atomic coordinates and equivalent thermal parameters

Atom	X	Y	Z	Ueq
C_1	0.30816(16)	0.7344(3)	0.47490(16)	0.0678(6)
S_1	0.17978(3)	0.73927(7)	0.45911(3)	0.06156(17)
C_3	0.16862(10)	0.66112(17)	0.56833(10)	0.0372(3)
C_4	0.07322(10)	0.64499(18)	0.57462(10)	0.0403(3)
C_5	0.05622(9)	0.57931(17)	0.65612(9)	0.0365(3)
C_6	0.13383(8)	0.52805(14)	0.73377(8)	0.0292(2)
C_7	0.22856(9)	0.54539(18)	0.72712(9)	0.0370(3)
C_8	0.24645(10)	0.6119(2)	0.64595(10)	0.0418(3)
C_9	0.11863(8)	0.46531(14)	0.82696(8)	0.0292(2)
C_{10}	0.01970(9)	0.38369(15)	0.81463(9)	0.0327(2)
C_{11}	-0.05524(10)	0.46349(18)	0.83458(10)	0.0380(3)
N_{12}	-0.04015(9)	0.61673(16)	0.87585(10)	0.0461(3)
C_{13}	0.05162(10)	0.68315(16)	0.91317(10)	0.0372(3)
C_{14}	0.12947(9)	0.60856(15)	0.89595(9)	0.0317(2)
C_{15}	0.22485(11)	0.67622(18)	0.93357(10)	0.0404(3)
N_{16}	0.30304(12)	0.7278(2)	0.96154(13)	0.0631(4)
C_{17}	0.05525(14)	0.83733(19)	0.96835(13)	0.0516(4)
C_{18}	-0.15986(11)	0.4076(2)	0.81302(15)	0.0562(4)
O_{19}	-0.05690(9)	0.12061(15)	0.78261(10)	0.0577(3)
C_{20}	0.00688(10)	0.21506(17)	0.77834(10)	0.0371(3)
C_{21}	0.07859(9)	0.17118(14)	0.74021(10)	0.0533(3)
C_{22}	0.07135(16)	0.0071(2)	0.70254(17)	0.0669(5)

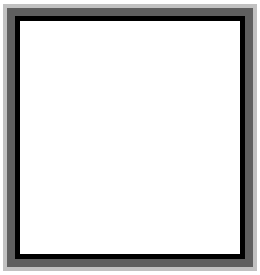
Table-3 : Bond lengths (A^o)

Atoms	Length	Atoms	Length
S_2-C_3	1.763(1)	N_{12}-C_{11}	1.381(2)
S_2-C_1	1.776(2)	C_5-C_4	1.387(2)
C_6-C_7	1.389(2)	C_7-C_8	1.391(2)
C_6-C_5	1.394(2)	C_3-C_8	1.391(2)
C_6-C_9	1.524(2)	C_3-C_4	1.395(2)
C_9-C_{14}	1.522(2)	C_{13}-C_{17}	1.489(2)
C_9-C_{10}	1.523(2)	O_{19}-C_{20}	1.209(2)
C_{10}-C_{11}	1.354(2)	C_{11}-C_{18}	1.502(2)
C_{10}-C_{20}	1.471(2)	C_{20}-O_{21}	1.347(2)
C_{14}-C_{13}	1.353(2)	C_{15}-C_{16}	1.149(2)
C_{14}-C_{15}	1.420(2)	C_{22}-O_{21}	1.444(2)
N_{12}-C_{13}	1.373(2)		

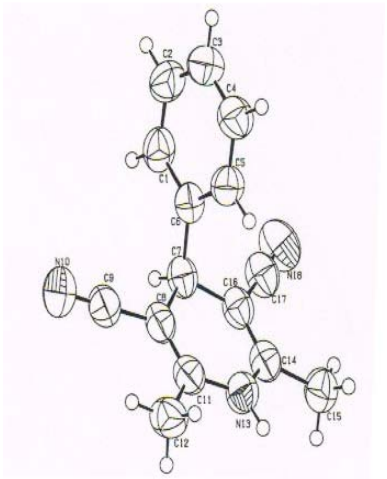
Table-4 : Bond lengths (^{o})

Atoms	Angle	Atoms	Angle
C_3-S_2-C_1	103.72(8)	C_8-C_3-C_4	118.65(12)
C_7-C_6-C_5	117.97(12)	C_8-C_3-S_2	125.18(10)
C_7-C_6-C_9	119.42(11)	C_4-C_3-S_2	116.15(11)
C_5-C_6-C_9	122.47(10)	C_{14}-C_{13}-N_{12}	119.05(12)
C_{14}-C_9-C_{10}	109.11(9)	C_{14}-C_{13}-C_{17}	125.61(14)
C_{14}-C_9-C_6	108.27(10)	N_{12}-C_{13}-C_{17}	115.33(12)
C_{10}-C_9-C_6	114.30(10)	C_{10}-C_{11}-N_{12}	120.01(12)
C_{11}-C_{10}-C_{20}	120.50(12)	C_{10}-C_{11}-C_{18}	127.22(14)
C_{11}-C_{10}-C_9	121.59(12)	N_{12}-C_{11}-C_{18}	112.72(13)
C_{20}-C_{10}-C_9	117.89(10)	O_{19}-C_{20}-C_{21}	121.54(13)
C_{13}-C_{14}-C_{15}	119.76(12)	O_{19}-C_{20}-C_{10}	126.76(13)
C_{13}-C_{14}-C_9	122.70(11)	O_{21}-C_{20}-C_{10}	111.67(11)
C_{15}-C_{14}-C_9	117.09(11)	C_3-C_8-C_7	120.16(12)
C_{13}-N_{12}-C_{11}	122.75(11)	C_5-C_4-C_3	120.72(13)
C_4-C_5-C_6	120.93(12)	N_{16}-C_{15}-C_{14}	177.51(15)
C_6-C_7-C_8	121.56(12)	C_{20}-C_{21}-C_{22}	115.25(13)

In order to study the unsubstituted structures of DHP at C_4 position, synthesis and crystal structure of 3,5-dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine was undertaken.[157]



`The title compound was synthesized by the Hantzch method and characterized by the X-ray diffraction method. It crystallized in monoclinic space group $P2_{1/c}$ with cell parameters a = 8.722(7) A^o, b= 11.420 (1), A^o, c= 13.307(1) A^o and Z = 4. The structure has N-H···N type intermolecular hydrogen bonds and exhibits a flattened boat conformation.



[ORTEP diagram of 3,5-dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine

Table-5 : Crystal and experimental data]

Formula	$C_{15}H_{13}N_3$
Formul Weight	235.28
Crystal system	Monoclinic
Space group	$P2_{1/c,}Z=4$
A	8.722(7) A^o
B	11.420(1) A^o
C	13.307(1) A^o
ß	104.101(5) A^o

Γ	1285.5(2) A^o
D_x	1.210 Mg/m^3
$2\Theta_{max}$	64.8^o
R	0.0625
$(\Delta/\sigma)_{max}$	0.000
$(\Delta\rho)_{max}$	0.373 e A^{o3}
$(\Delta\rho)_{min}$	-0.330e A^{o3}
Measurement	DipLabo Kappa
Program system	Denzo
Structure determination	SHELXs-97
Refinement	Fullmatrix : SHELXL-97

Table-6 : Atomic coordinates and equivalent temperature factors (A^{o2})

Atom	X	Y	Z	Ueq
N_{13}	0.8655(2)	0.78752(14)	0.02215(12)	0.0679(4)
C_7	0.8071(2)	0.97909(15)	0.12403(14)	0.0598(4)
C_8	0.7615(2)	0.97578(15)	0.02075(14)	0.0604(4)
C_{14}	0.9281(2)	0.78180(16)	0.06265(14)	0.0621(5)
C_6	0.6639(2)	0.98761(14)	0.21567(13)	0.0561(4)
C_{11}	0.7856(2)	0.88537(16)	0.04464(14)	0.0617(5)
C_1	0.6409(3)	1.08230(16)	0.28316(16)	0.0689(5)
C_{16}	0.9061(2)	0.87090(16)	0.13110(15)	0.0612(4)
C_5	0.5531(2)	0.89846(16)	0.23507(15)	0.0658(5)
C_9	0.6853(2)	1.07891(18)	0.00436(15)	0.0691(5)
C_{17}	0.9700(2)	0.86490(18)	0.21969(16)	0.0699(5)
C_{12}	0.7358(3)	0.8798(2)	0.14394(16)	0.0783(6)
C_2	0.5119(3)	1.08631(19)	0.36767(16)	0.0794(6)
C_{15}	1.0193(3)	0.67317(19)	0.07043(17)	0.0774(6)
C_4	0.4248(2)	0.90351(19)	0.31988(17)	0.0766(6)
C_3	0.4045(3)	0.9969(2)	0.38603(17)	0.0790(6)
N_{18}	1.0157(2)	0.8649(2)	0.29337(16)	0.0930(6)
N_{10}	0.6271(3)	1.16323(18)	0.02184(17)	0.0923(6)

Table-7 : Selected bondlengths (A^o) and angles (^{o})

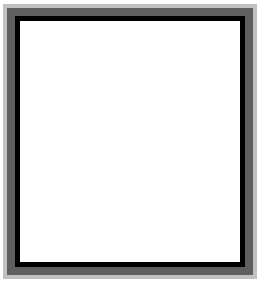
N_{13}-C_{14}	1.370(3)	N_{13}-C_{11}	1.387(2)
C_{11}-C_{12}	1.490(3)	C_7-C_6	1.521(3)
C_7-C_8	1.522(2)	C_{16}-C_{17}	1.423(3)
C_7-C_{16}	1.523(2)	C_5-C_4	1.383(3)
C_8-C_{11}	1.333(3)	C_9-C_{10}	1.139(3)
C_8-C_9	1.431(3)	C_{17}-C_{18}	1.145(3)
C_{14}-C_{16}	1.348(2)	C_{14}-C_{15}	1.491(3)
C_{14}-N_{13}-C_{11}	122.5(2)	C_8-C_{11}-N_{13}	119.4(2)
C_6-C_7-C_8	112.4(1)	C_8-C_{11}-C_{12}	125.3(2)
C_6-C_7-C_{16}	111.7(2)	N_{13}-C_{11}-C_{12}	115.3(2)
C_8-C_7-C_{16}	108.2(2)	C_2-C_1-C_6	120.8(2)
C_{11}-C_8-C_9	119.6(2)	C_{14}-C_{16}-C_{17}	120.2(2)
C_{11}-C_8-C_7	125.1(2)	C_{14}-C_{16}-C_7	124.1(2)
C_9-C_8-C_7	115.4(2)	C_{17}-C_{16}-C_7	115.6(2)
C_{16}-C_{14}-N_{13}	120.1(2)	C_6-C_5-C_4	120.7(2)
C_{16}-C_{14}-C_{15}	124.7(2)	N_{10}-C_9-C_8	177.5(2)
N_{13}-C_{14}-C_{15}	115.1(2)	N_{18}-C_{17}-C_{16}	176.2(2)

A single crystal of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile 0.2×0.3×0.2mm was chosen for X-ray differaction studies. The measurements were made on a DIPLabo Kappa Imaging Plate system with graphite monochromated radiation (Mo Kα). Thirty six frames of data were collected by using the oscillation method. Successive frames were scanned in steps of 5^OC/min with an oscillation range of 5^O for an exposure of 400 s/frame. Image processing and data reduction were done by using Denzo. All the frames could be indexed with monoclinic primitive lattice. The experimental crystallographic details are given in Table No.5. The structure was solved by direct methods and refined by full-matrix least square methods with anisotropic temperature factors for the non-H atoms. All H atoms were placed at chemically acceptable positions and were refined with isotropic temperature factors. The final coordinates and equivalent thermal parameters of non-H atoms are listed in Table No 6. Table No. 7 gives selected bond distance and bond angles; they agree with their standard values. Figure 4 represents the ORTEP diagram

of the molecule with thermal ellipsoids at 50% probability. Both the phenyl ring and the DHP ring are independentyly planner with a maximum deviation of 0.055 A^o for C7, and are almost perpendicular hydrogen bonds of the type N-H···N. The intermolecular distance between atoms is as follows N13-N13···N18 has length 3.034(3) A^o and an angle of 147^O, with symmetry code (x, 3/2-y, 1/2+z). The molecular packing exhibits a linear chain structure (when viewed down b axis).

The value of the torsion angle C5-C6-C7-C16 i.e.,59.1(2) determines the conformation around the inter-ring bond. The closer this angle is to 60.0, the closer the aryl group comes to bisecting the DHP ring. The other structure aspect characteristic of this compound is the confirmation of cyano groups. Each cyano group can be oriented in synperiplanar (cis) or in antiperiplanar (trans) conformation with respect to the adjacent C=C of the 1,4-DHP ring. The DHP ring adopts a flattened boat conformation. The crystal structure shown that the substitutions of 2,6-dimethyl and electron-withdrawing 3,5-dicyano groups in dihydropyridine ring may have an opposite effect on calcium channels, such as agonist and antagonist activity.

In continuation of this, crystal structure of 3,5-dicyano-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine was studied.



A single crystal of dimensions 0.2×0.3×0.25 mm was chosen for x-ray diffraction studies.

The final positional coordinates with equivalent isotropic temperature factors for all nonhydrogen atoms are given in Table No.9. Table No. 10 give the bond distance and angles of the non-hydrogen atoms, respectively. The bond lengths and angles are in good agreement with their standard values. Figure 6 represents the ORTEP diagram of the molecule with thermal ellipsoids at 50% probability. The packing of the molecule shows layered stacking when viewed along the b axis. The 1,4-dihydropyridine ring is planner with a maximum deviation of 0.166 A^o for C8 and 0.121 A^o for N14. The dihedral angle found between the planes 1(C2,C3,C4,C5,C6,C7) and 2(C8,C9,C13,N14,C15, C19) is 78.65^o. The structure has

an intermolecular hydrogen bond of the type N-H···N, and follows accordingly; N14-H14···N11(2.984(7)A^o, 168 ^{o}) with symmetry code x, 3/2-y, +z.

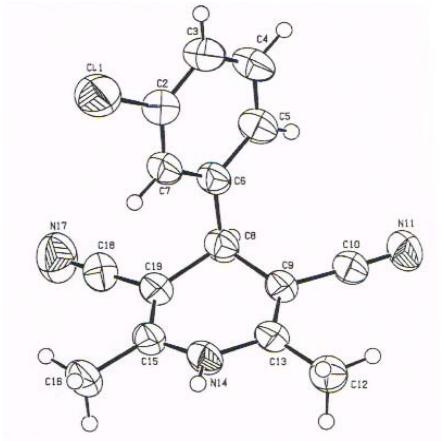


Table-8 : Crystal and experimental data

Formula : $C_{15}H_{12}ClN_3$	
Formula weight = 269.73	
Crystal system : monoclinic	
Space group : $P2_{1/c}$	Z=4
a=13.173(2) A^o	
b=8.0298(18) A^o	ß= 112.376(13)
c=13.8547(17) A^o	
γ=1355.2(4) A^o	
D_x= 1.322 Mg/m^3	
$2\Theta_{max}$ = 46.5^{o}with Mo Kα	
No. of reflections used = 1425[I>2σ(1)]	
R = 0.0737	
$(\Delta/\sigma)_{max}$ = 0.042	
$(\Delta\rho)_{max}$ = 0.388 e A^{o-3}	
$(\Delta\rho)_{min}$ = - 0.533 e A^{o-3}	
Measurement : Rigaku AFC7S	
Program system : teXsan[5]	
Structure determination : SHELXS-97 (Sheldrick, 1990)	
Refinement : SHELXL- 97 (Sheldrick, 1997)	
H atoms : geometrically fixed	

Table-9 : Atomic coordinates and equivalent thermal parameters

Atom	X	y	Z	U_{eq}
C_{11}	0.4886(14)	0.0425(2)	0.20850(13)	0.0849(8)
C_2	0.5602(5)	0.1765(7)	0.1560(4)	0.0580(14)
C_3	0.5173(5)	0.2060(8)	0.0509(4)	0.0689(16)
C_4	0.5741(6)	0.3110(8)	0.0112(4)	0.0730(18)
C_5	0.6726(5)	0.3831(8)	0.0759(4)	0.0640(15)
C_6	0.7148(4)	0.3528(6)	0.1826(3)	0.0490(13)
C_7	0.6565(4)	0.2478(6)	0.2221(4)	0.0556(14)
C_8	0.8200(4)	0.4392(6)	0.2529(4)	0.0495(13)
C_9	0.7983(4)	0.6169(6)	0.2756(3)	0.0465(12)
C_{10}	0.7813(5)	0.7385(7)	0.1957(4)	0.0540(13)
N_{11}	0.7687(5)	0.8312(6)	0.1294(4)	0.0737(15)
C_{12}	0.7580(5)	0.8325(7)	0.3886(4)	0.0619(15)
C_{13}	0.7892(4)	0.6631(6)	0.3656(3)	0.0499(13)
N_{14}	0.8134(4)	0.5486(5)	0.4456(3)	0.0527(12)
C_{15}	0.8655(4)	0.4019(6)	0.4452(3)	0.0494(13)
C_{16}	0.9089(5)	0.3114(7)	0.5476(4)	0.646(15)
N_{17}	0.9887(5)	0.0894(7)	0.3556(5)	0.0865(17)
C_{18}	0.9386(5)	0.2052(7)	0.3577(4)	0.0603(14)
C_{19}	0.8770(4)	0.3508(6)	0.3569(3)	0.0508(13)

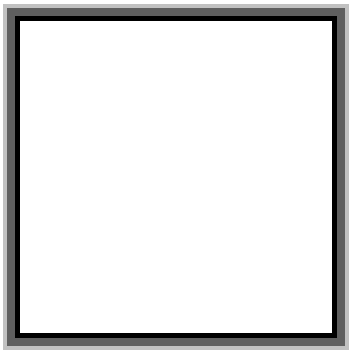
Table-10 : Bond lengths (A^o) and bond angles(^{o})

Atom	Length	Atoms	Length
C_{13}-C_9	1.350(6)	C_{19}-C_{18}	1.420(8)
C_{13}-N_{14}	1.381(6)	C_{15}-N_{14}	1.364(7)
C_{13}-C_{12}	1.490(7)	C_{15}-C_{16}	1.500(7)
C_9-C_{10}	1.428(7)	C_7-C_2	1.376(8)
C_9-C_8	1.511(7)	C_2-C_3	1.368(8)
C_6-C_7	1.368(7)	C_2-C_{11}	1.760(6)
C_6-C_5	1.389(7)	C_5-C_4	1.392(9)

C_6-C_8	1.524(7)	C_3-C_4	1.373(9)
C_8-C_{19}	1.524(7)	C_{18}-N_{17}	1.147(7)
C_{19}-C_{15}	1.352(7)	C_{10}-N_{11}	1.145(6)
C_9-C_{13}-N_{14}	118.9(5)	C_{18}-C_{19}-C_8	117.7(4)
C_9-C_{13}-C_{12}	125.3(4)	C_{19}-C_{15}-N_{14}	119.7(4)
N_{14}-C_{13}-C_{12}	115.7(4)	C_{19}-C_{15}-C_{16}	125.1(5)
C_{13}-C_9-C_{10}	119.0(5)	N_{14}-C_{15}-C_{16}	115.2(4)
C_{13}-C_9-C_8	122.9(4)	C_2-C_7-C_6	119.9(4)
C_{10}-C_9-C_8	118.1(4)	C_7-C_2-C_3	122.7(5)
C_7-C_6-C_5	118.0(5)	C_7-C_2-C_{11}	118.8(4)
C_7-C_6-C_8	122.0(4)	C_3-C_2-C_{11}	118.5(4)
C_5-C_6-C_8	119.9(5)	C_4-C_5-C_6	120.7(6)
C_9-C_8-C_6	111.4(4)	C_4-C_3-C_2	117.7(5)
C_9-C_8-C_{19}	107.9(4)	C_3-C_4-C_5	121.0(5)
C_6-C_8-C_{19}	113.1(4)	N_{17}-C_{18}-C_{19}	177.9(6)
C_{15}-C_{19}-C_{18}	120.2(5)	N_{11}-C_{10}-C_9	177.2(5)
C_{15}-C_{19}-C_8	122.0(5)	C_{15}-N_{14}-C_{13}	122.3(4)

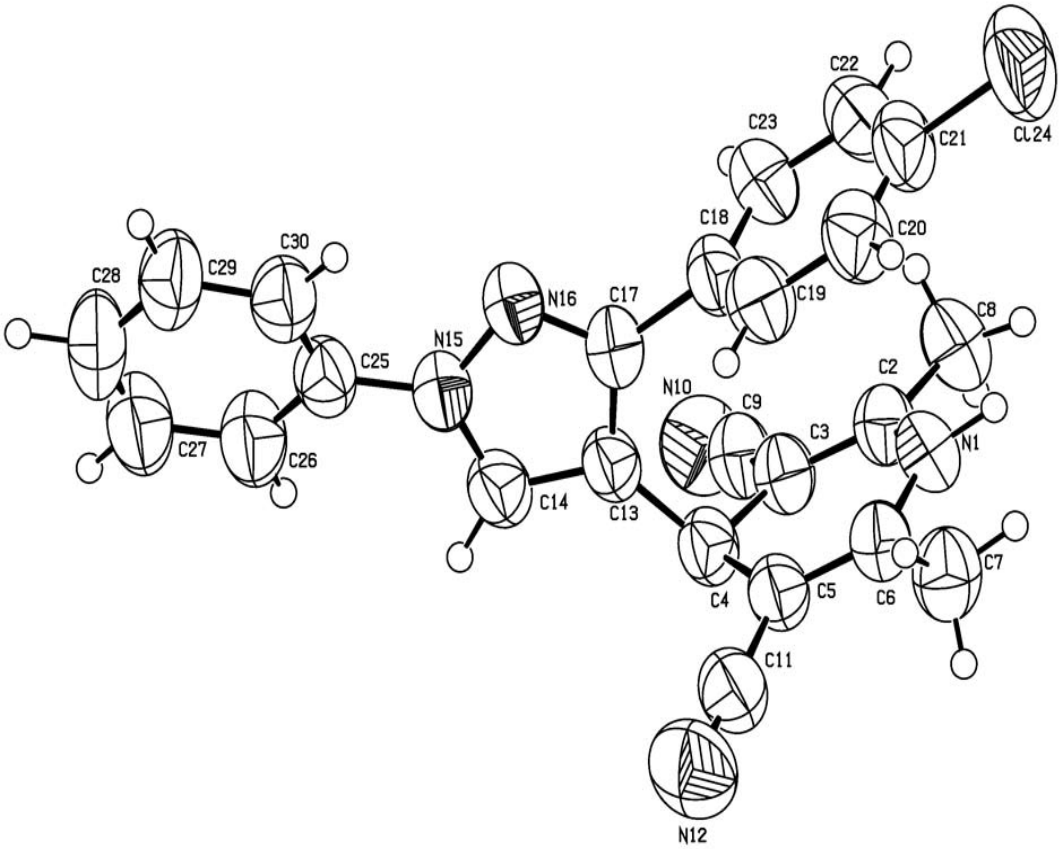
Current study on novel 1,4-dihydropyridine (STAB-03) :

In continuation of our previous work on 3,5-dicyano 1,4-dihydropyridines, we have undertaken to study the crystal structure of 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile.



Preparation of Crystal:

0.5 gms of the sample of 1,4-dihydropyridine was taken in a beaker and dissolved in mimimum quantity of methanol at room temperature. To the solution, add 0.1 gm of activated charcoal and heated to boil. The solution was filtered using wattmann filter paper in a 25 ml standard conical flask and corked. The solvent was allowed to evaporate by thin layer evaporation and the single crystals were observed after 16 days. The crystals were filtered and washed with chilled methanol. Please refer for the XRD analysis data, ORTEP and packing structures below.



[ORTEP diagram of 4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile.]

Table 11: Crystal Structure and Refinement Table of STAB-03

Formula	$C_{24}\ H_{17}\ Cl\ N_5$
Formula Weight	410.88
Wavelength	0.71073 Å
Temperature	293 K
Crystal System	Monoclinic
Space Group	$P2_1/c$
Cell dimensions	a = 6.9730(6) Å
	b = 22.225(4) Å
	c = 13.966(2) Å
	α = 103.759(8)°
Volume	2102.3(5) Å^3
Z	4
Density(calculated)	1.298 g/cm^3
Data / Restraints / Parameters	3230 / 0 / 272
F_{000}	852
Absorption Co-efficient	0.202 mm^{-1}
Index ranges	$-7 \le h \le 7$
	$-26 \le k \le 26$
	$-15 \le l \le 14$
Goodness-of-fit on F^2	1.51
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.1458, wR_2 = 0.4026
Largest diff. peak and hole	0.83 and -.070 e/Å^3

The crystal structure studies have shown that it is a monoclinic structure and the cell dimentions are in the tune of approximately (a) 6.9730(6) A°, (b) 22.335 (4)A°, (c) 13.966(2) A°. The X-ray crystal structure determination of the compounds in this series has proved the synthetic methodology adopted and has led to structure confirmation.

The crystal structure and further refinement and comparative study with other molecules in this series is under study.

1.14 RESULTS AND DISCUSSION

The chemical entities enlisted above in this chapter, especially the 1,4-dihydropyridines involving the pyrazole aldehydes, are novel and have been prepared by a new synthetic methodology.

1.15 CONCLUSION

In this chapter, along with yield optimization of the 1,4-Dihydropyridines, simple, easy and fast method was adopted. Exploration of unreported chemistry and their biological activity was the aim behind the work done in this chapter.

The crystallography study of 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-yl)-1,4-dihydro-2,6-dimehylpyridine-3,5-dicarbonitrile confirmed the structure of compounds which are of biological interest.

1.16 REFERENCES

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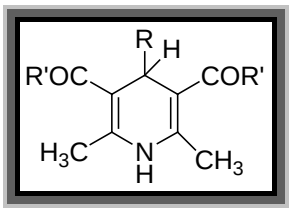
Chapter-2

Synthesis of new dihydropyridines structurally related to MDR reverting agents.

2.1 INRODUCTION

1,4-dihydropyridines are well established as heterocycles having tremendous application and still further scope for its pronounced drug activity like calcium channel antagonism and antihypertensive action. Many other cardiovascular activities are associated with such compounds and they can be presented structure wise as 2, 6-dimethyl-3, 5-diacetyl or dicarboxylate 1, 4-dihydropyridines substituted at 4-position.



All these drugs can be classified into categories:

(a) Symmetrical compounds having esteric linkage both at 3 and 5 position of dihydropyridine.

(b) Structure having different ester linkage at 3 and 5 position or positional variation at 2 or 3.

(c) Symmetrical compounds having atleast one ester group.

(d) Symmetrical structure without ester group or having two acyl group at 3 and 5 position respectively.

As already known original Hantsch[1,2] pyridine synthesis consists of the reaction of ethyl acetoacetate with different aldehydes and ammonia. This method has been widely used for the preparation of dihydropyridines, where at 4-position, an aliphatic chain, aromatic or heterocyclic ring is present. α-β-unsaturated aldehydes and 1,3-Diketones have occasionally been used instead of ethyl acetoacetate or methyl acetoacetate to give 3,5-diacyl 1,4-dihydropyridine derivatives.

Arthur Phillips[3] of Welcome research laboratories, in his well recognized work, used Hantzsch synthesis to get symmetrical compound for the curare like activity that was the first time reported possible pharmacological activity of these

compounds and also reported that such compounds are devoid of undesirable side effect during clinical trials.

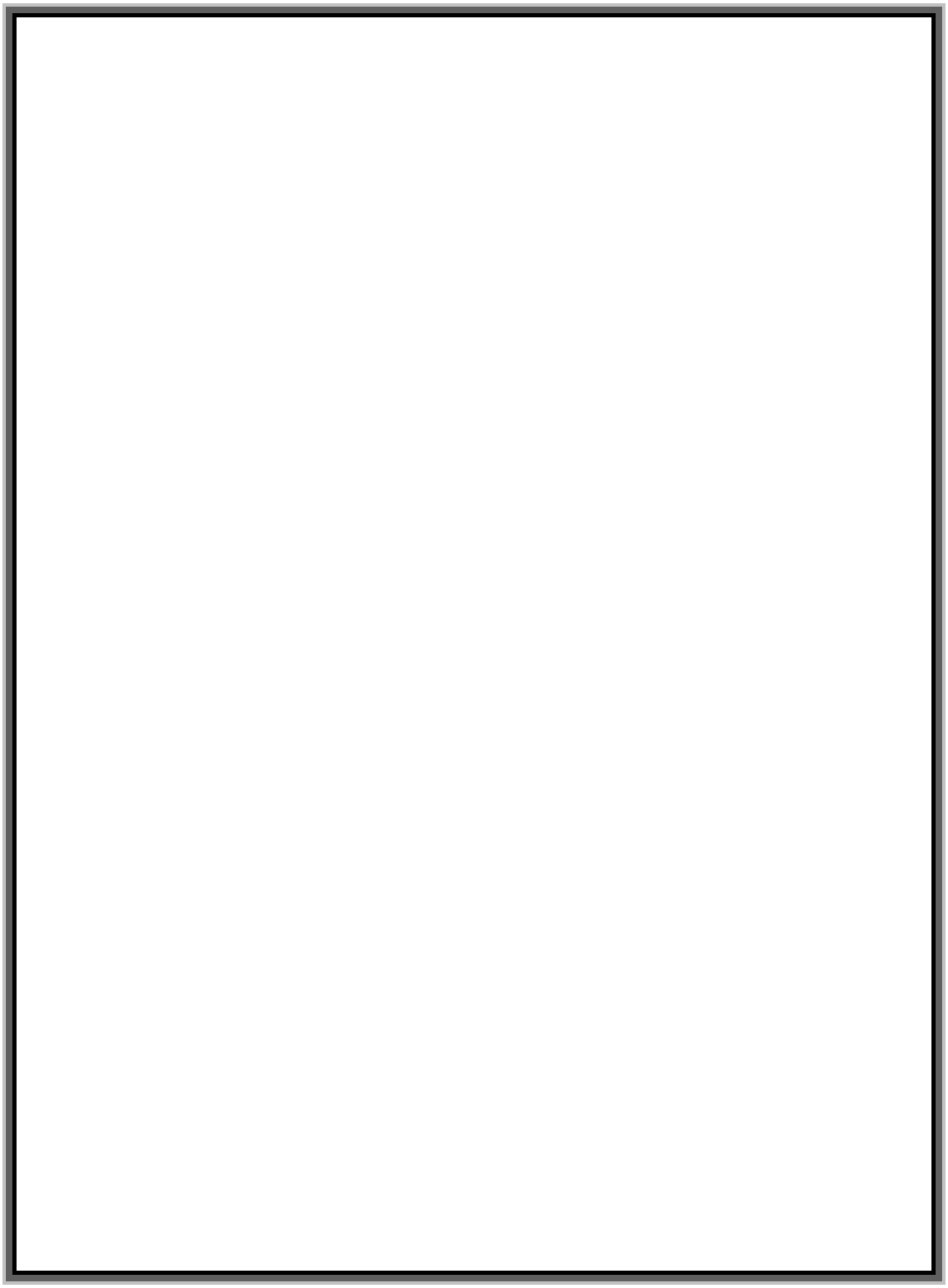
Court *et al.*[4] made successful attempt to prepare 3,5-dicyano-1,4-dihydro-4-(2-nitrophenyl)-2,6-diphenyl pyridine as well as 3,5-dicyano-2,6-dimethyl-(2-nitrophenyl)-1,4-dihydropyridine and other similar compounds. They initiated application of 1,3-diketones likes acetyl acetone and 4-aminopent-3-enl-2-one and also a few aldehydes.

Berson *et al.*[5] has originally prompted the idea involving the condensation of an aldehyde, acetoacetic ester and 1,3-dicarbonyl compounds with ammonia on basis of the earlier work done by Bayer and Knovenegal, who synthesized 2,6-dimethyl-3,5-diacetyl-4 (substituted phenyl)-1,4-dihydropyridine. The important of asymmetric nature of C4 carbon atom of DHP draw the attention and absolute asymmetric synthesis was also studied in detail without the knowledge of it's pharmacological properties, which was discovered in 80's.

Love *et al.*[6] investigated thoroughly structure and activity study of Hantzsch type dihydropyridines for its potent hypotensive activity. As a result Nifedipine came out as a promising compound which exerted its cardiovascular effects through a direct action on vascular smooth muscles. Love and other workers of SKF laboratories studied the possibility of symmetrical structure and they were found moderately active for its hypotensive activity.

Much work is done in last two decade and many molecules having more specific cardiovascular activity have come out as new drug molecules like Amlodipine,[7] Barnidipine,[8] Benidipine,[9] Felodipine,[10] Flordipine,[11] Furaldipine,[12] Nilvodipine, Nimodipine,[13] Nitrendipine,[14] Riodipine,[15] Sagandipine,[16] Taludipine.[17]

The structures of many drugs not covered in the first chapter are presented here.

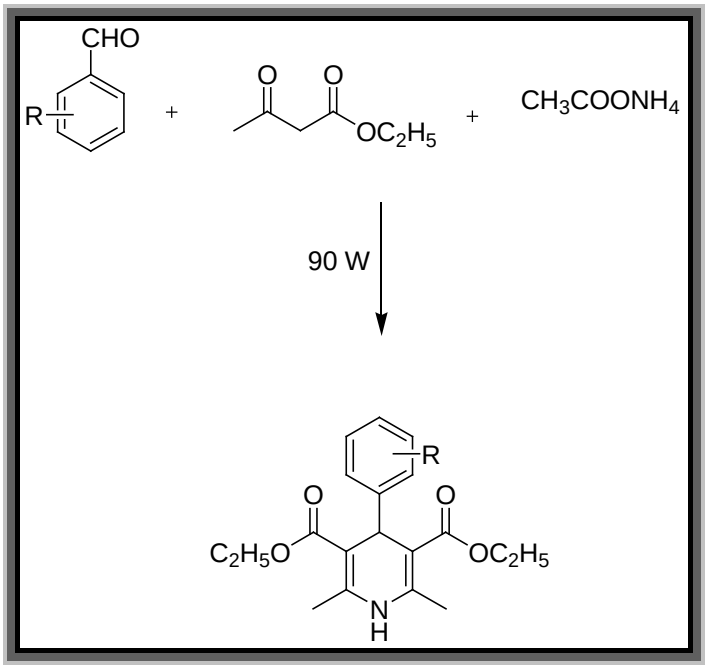


It has been observed in some recent drug like pranidine, lacidipine that a center for unsaturation created either at C_4-phenyl ring or at C_3-position of carbon chain, noteworthy change is marked in cardiovascular activity.

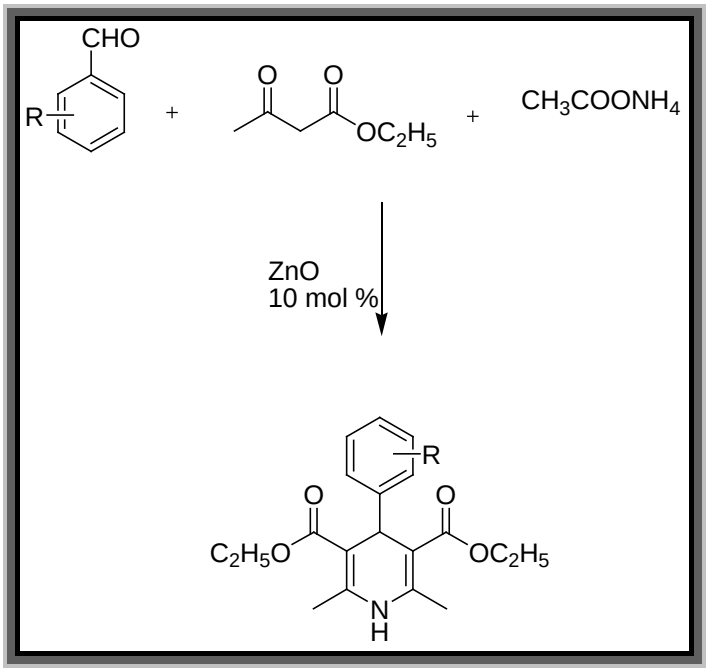
2.2 LITERATURE REVIEW

Few recent methods leading to 1,4-dihydropyridines are summarized below.

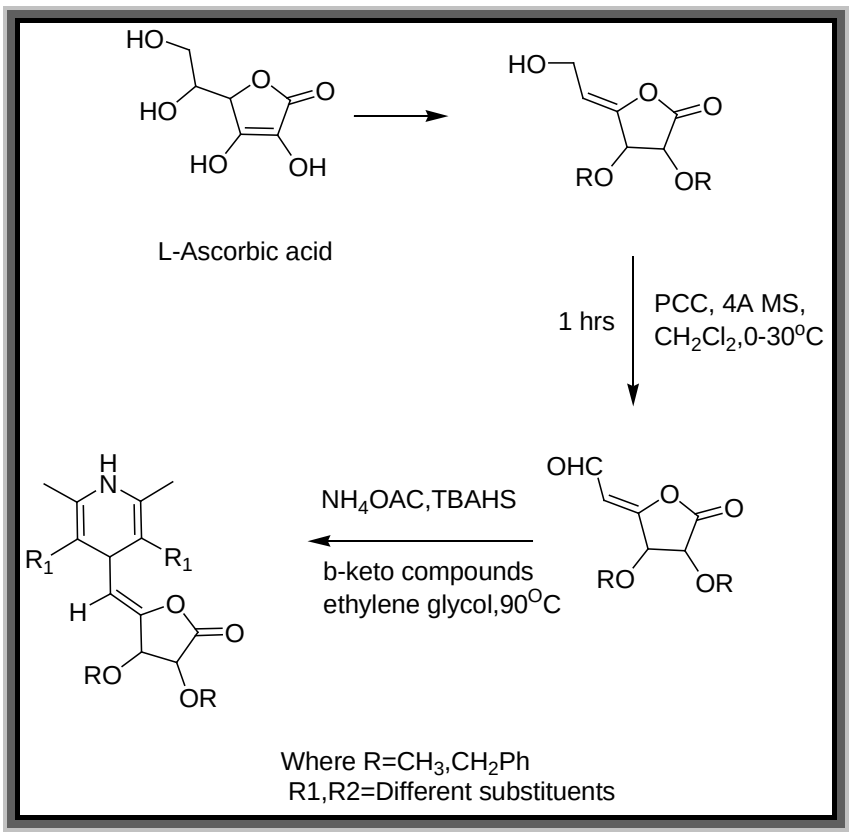
Sandeep *et al.*[18] discovered a novel method, which is eco-friendly, cost effective, solvent free and it was developed for the synthesis of 1,4-dihydropyridines from ethyl acetoacetate, aldehyde and ammonium acetate under domestic microwave oven. It was facile one-pot synthesis of 1,4-dihydropyridine in which reaction time was less with good yields.



Matloubi *et al.*[19] 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 and polyhydroquinoline derivatives *via* the Hantzsch condensation is described. The present methodology offers several advantages such as simple procedure, excellent yields, and short reaction time.

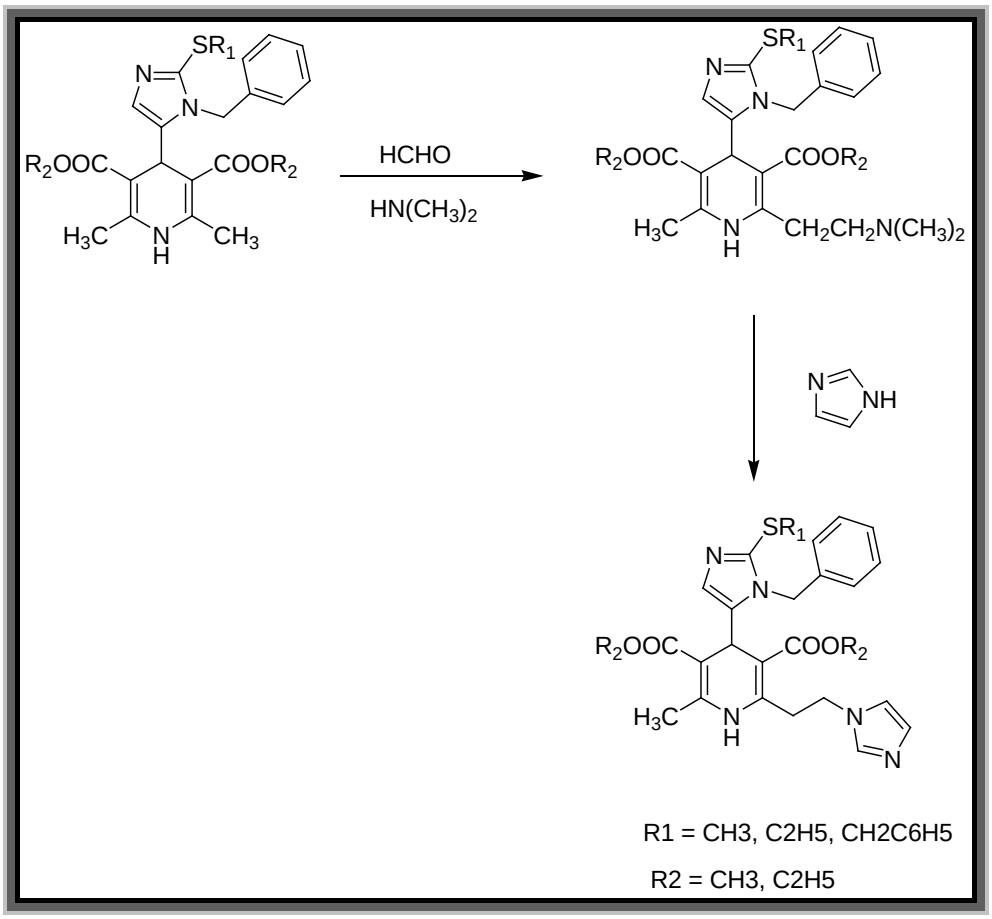


Surendra *et al.*[20] developed an efficient synthesis of 4-(butenolide-5-methylidenyl)-1,4-dihydropyridines has been achieved via a three-component reaction of β-keto esters or ketones, ammonium acetate and vinylic aldehydes from ascorbic acid in the presence of tetrabutylammonium hydrogen sulphate in ethylene glycol.

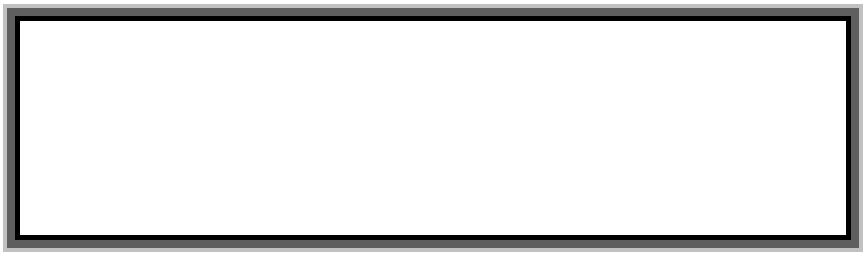


The prominent biological activities associated with 1,4-dihydropyridines are Ca++ channel blockers and as drugs for the treatment of cardiovascular diseases and hypertension.[21] The dihydropyridine skeleton is common in many vasodilator, bronchiodilator, anti-atherosclerotic, antitumor, hepatoprotective and anti-diabetic agents.[22,23] They are also known as neuroprotectants, as anti-platelet treatment of aggregators and are important in Alzheimer's disease, as antiischemic agents[24]. Interest in 1,4-dihydropyridines also relates to nicotinamide dinucleotide (NADH), a co-enzyme, and its unique ability to reduce many functional groups in biological systems. Although 1,4-dihydropyridines with various aromatic, heteroaromatic, aliphatic and sugar substituents at C-4 have been reported,[25,26] there is no report of 1,4-dihydropyridines bearing a (5-ethylidene tetranolactonyl) substituent at C-4.

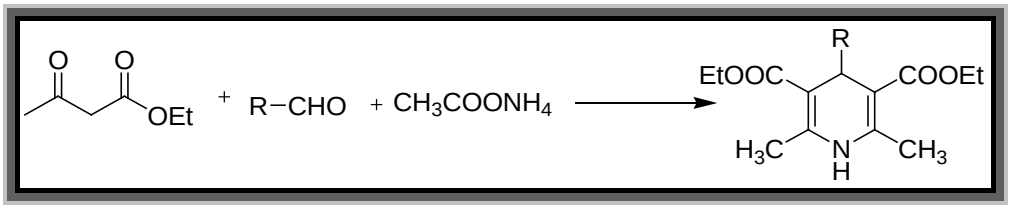
Farzin *et al.*[2] reported the synthesis and antihypertensive activity of newly synthesized 1,4-dihydropyridines.They prepared symmetric DHP by conventional Hantzch condensation as described previously.



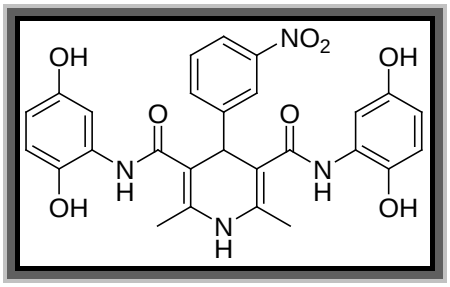
A facile and convenient method was developed by Mohammad Nikpassand *et al.*[27] for the fast and high yielding (70-90 %) synthesis of fused 1,4-dihydropyridines from dimedone in the presence of HY-zeolite as an efficient recyclable heterogeneous catalyst.



Mohammad *et al.*[28] 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.

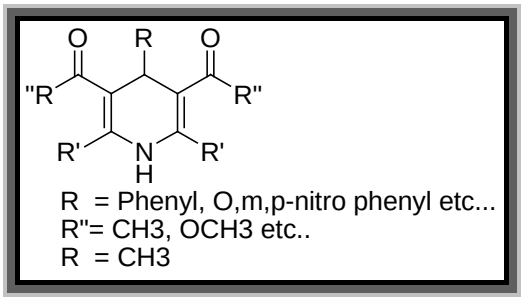


Neamati *et al.*[29] reported that 1,4-dihydropyridine molecule came out with its anti-HIV activity, which has opened up the synthetic as well as pharmacological importance in antiviral area also.

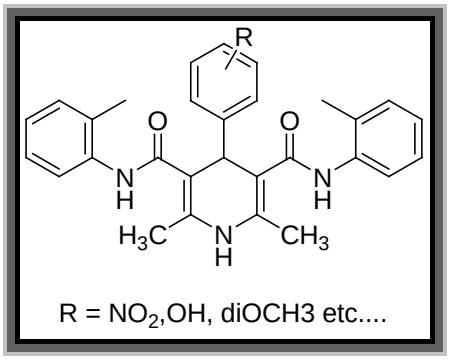


Recently Mosti *et al.*[30] prepared 2-substituted-5-acetyl-1,6-dihydro-6-oxo-3-pyridinecarboxylic acid for its positive inotropic as well as cardiotonic activity and structure activity relationship was also studied.

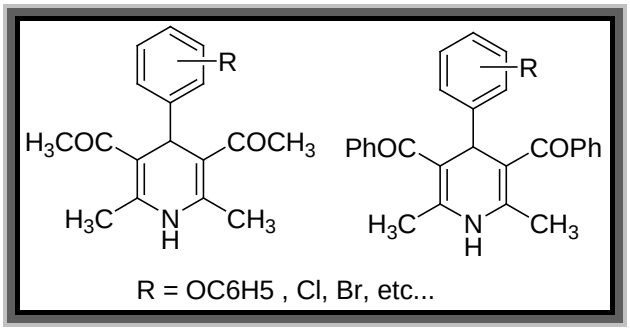
Very Recently Shingare *et al.*[31] in a almost parallel work to this laboratory has came out with biological activity of a few 1,4-dihydropyridines. Many new compounds are prepared using few aldehydes and acetyl acetone for getting Hantzsch type dihydropyridines.



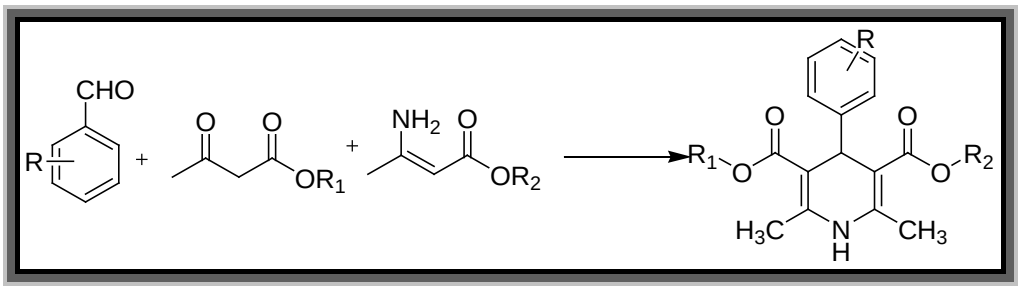
Reddy *et al.*[32] synthesized 4-aryl hetroaryl-2,6-dimethyl-yl-3,5-bis-N-(2-methyl phenyl) carbamoyl-1,4-dihydropyridines (A) through one-pot synthesis using appropriate aromatic aldehydes and liquid ammonia. Pharmacological screening of the new 1,4-dihydropyridines were also carried out for CNS depresent (anticonvulsant and analgesic) and cardiovascular (inotropic and blood pressure) activities by standard methods.



Earlier Shah *et al.*[33-35] synthesized 3,5-diacetyl-4-(substituted phenyl)-1,4-dihydropyridine and 3,5-dibenzoyl-4-substituted phenyl-1,4-dihydro pyridine and studied their MDR reversal activity in tumor cells.



Waldo *et al.*[36] reported a Solvent-free, two-step synthesis of some unsymmetrical 4-aryl-1,4-dihydropyridines.

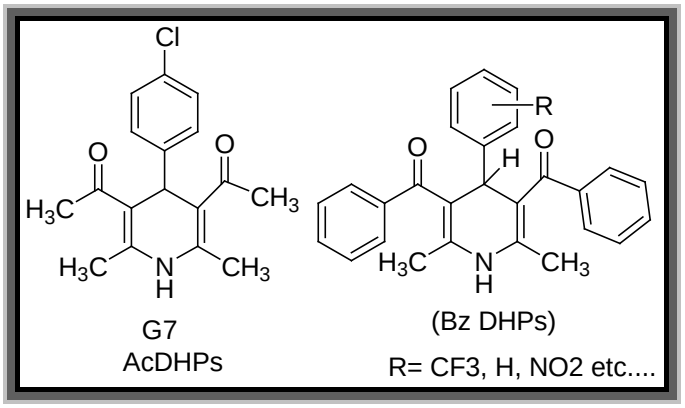


2.3 1,4-DIHYDROPYRIDINE IN MDR REVERSAL

The development of multidrug resistance (MDR) tumor cell population is a major problem in the chemotherapy of human cancer[37]. When tumor cells become resistant to anticancer agents such as vinca alkaloids or anthracylines, they often show resistance to other antitumor agents with different structures and mechanisms of action. Once of the MDR types was proved to involve a membrance bound protein, P-glycoprotein (Pgp) in MDR cancer cells, Protozoa and bacteria. This protein acts as a efflux pump for anticancer drugs[38].

Recently various compounds have been shown to inhibit Pgp mediated drug efflux[39]. These compounds include ion channel blockers such as verapamil[40], dihydropyridines (DHPs), Propafenone[41], antipsychotic drugs like phenothazines[42], quinolones[43]. Among them DHPs calcium antagonists have been studied extensively for the analogy to verapamil. In a combination treatment with antitumor agents, such as vinca alkaloids or anthracyclines, calcium antagonist verapamil caused cardiovascular side effects. It is very important finding that DHPs, which do not have any calcium antagonist activity, possess MDR reversal activity.

Shah *et al.*[44-45] have synthesized 4-phenyl-3,5-diacetyl -1,4-dihydropyridines (AcDHPs) and 4-phenyl-3,5-dibenzoly-1,4-dihydropyridines (Bz DHPs) substituted at the phenyl ring and compared for their cytotoxic activity and multidrug resistance (MDR) reversing activity in in vitro assay systems. Among their synthesized compounds (G7), in AcDHPs and compounds having 2-CF_3, 2-Cl and 3-Cl showed the highest cytotoxic activity against human promyelocytic leukemia HL-60 and human squamous cell carcinoma HSC-2 cells.



Saponara *et al.*[46] have investigated the effects of AcDHPs and BzDHPs on vascular functions in vitro, by comparing their mechanical and electrophysiological actions, as well as quantify their MDR reversal properties.

In earlier chapter, an approach was to synthesize symmetric 3,5-dicyano 1,4-DHPs while in this chapter, 3,5-dibenzoyl 1,4-DHPs synthesized possess symmetric structures with respects to C_3 & C_5 position of the ring.

2.4 AIM OF CURRENT WORK

The structure of many 1,4-Dihydropyridines are important for the treatment of cardiovascular diseases,[47] multidrug resistance (MDR) during cancer chemotherapy,[48] as possible thromboxane synthetase inhibitors,[49] PAF-acether antagonists,[50] and antithrombotic-antihypertensive agents.[51] An alternative to the usual means for the synthesis of 1,4-dihydropyridines2 is the partial reduction[52] of pyridinium salts.

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.

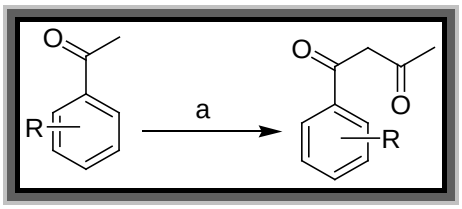
2.5 REACTION SCHEMES

2.5.1 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

2.5.2 PREPARATION OF 1,4- DIHYDROPYRIDINES :

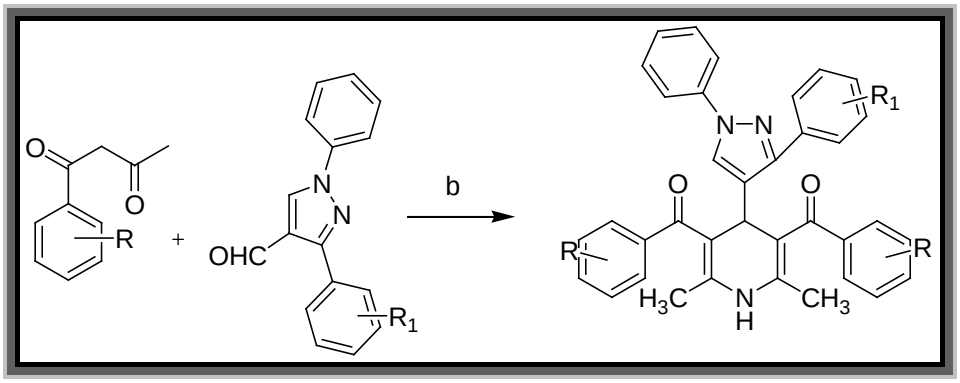
STEP-1 PREPARATION OF BENZOYL ACETONES :



Reagents / Reaction Condition (a): Ethyl Acetate, C_2H_5ONa/ 0-5°C, 2 hours.

Where, R = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2 etc....

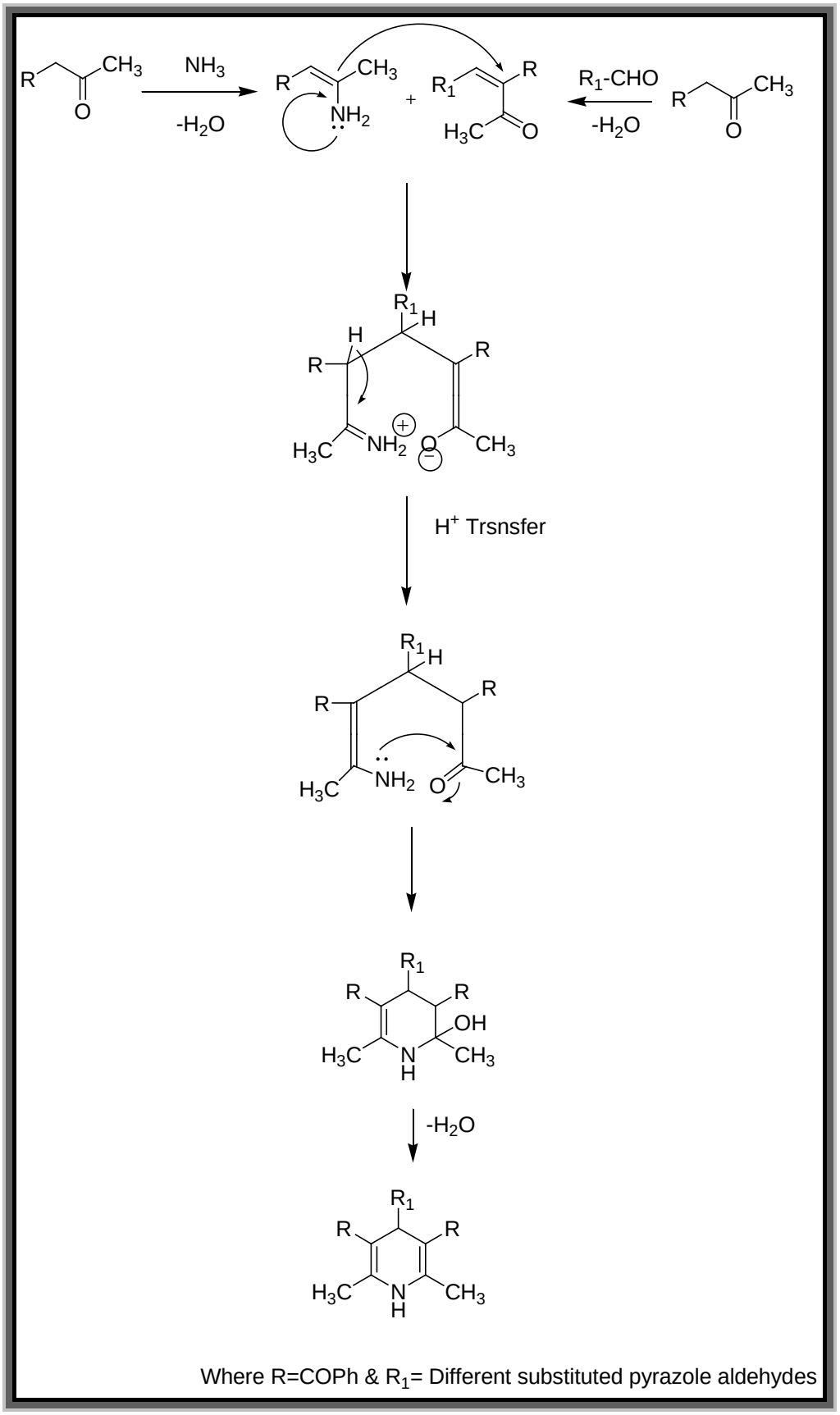
STEP-2 PREPARATION OF 1,4-DIHYDROPYRIDINES :



Reagents / Reaction Condition (b): Methanol, Ammonium carbonate/reflux, 12 hours.

Where, R = 4-H, 4-Cl, & R_1=4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2 etc....

2.6 PLAUSIBLE REACTION MECHANISM



Where R=COPh & R_1= Different substituted pyrazole aldehydes

2.7 EXPERIMENTAL

2.7.1 MATERIALS AND METHODS

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. Formation of all compounds was purified by using **column chromatography.** IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr pellet 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 solution on a **Bruker Ac 400 MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model and the results are in agreements with the structures assigned.

2.7.2 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

2.7.3 PREPARATION OF 1,4-DIHYDROPYRIDINES :

STEP-1 PREPARATION OF BENZOYL ACETONES :

Method-(1): 10 gm of acetophenone, 18 gm of ethylacetate and 60 ml of absolute ether were taken in 250 mls RBF and finely cut metallic sodium (2 gm) is added.

The ether starts boiling somewhat later. When boiling rate was reduced, the flask further was heated for 45 minutes in a water bath. After completion of the reaction, the reaction mixture was cooled. The sodium benzoyl acetone formed was filtered, washed with dry ether and dried immediately. The sodium benzoyl acetone was then dissolved in water and filtered off. The filterate was acidified with glacial acetic acid while simultaneously cooled with ice and benzoyl acetone was precipitated. It was filtered, dried and recrystallized from methanol.

Similarly other compounds are also prepared.

Method-(2): A mixture of Sodium Ethoxide (0.2 moles), Ethyl acetate (0.2 moles) were taken in 250 ml RBF then slowely add (0.05 moles) of aceto phenone to the mixture below 5^{O}C. After addition of acetophenone to it allow it for one day in freeze and pour it to ice water mixture. Then acidify it by glacial acetic acid to get product. After that filter the product and wash with chilled to remove acidity and dry it.

STEP-2 PREPARTION OF (4-(SUBSTITUTED)1,3-DIPHENYL-1H-PYRAZOL-4-YL)-2,6-DIMETHYL-1,4-DIHYDROPYRIDINE-3,5-DIYL)BIS(PHENYLMETHANONE)

GENERAL METHOD

To a mixture of benzoyl acetone (0.01 mole), pyrazole aldehyde (0.005) and 25 ml of methanol, ammonium carbonate (1.2 gm) was added. The mixture was refluxed for 12-14 hrs on water bath. During the reaction the progress and the completion of reaction were checked by silica gel-G F_{254} thin layer chromatography using ethyl acetate: Hexane (4:6) as a mobile phase. And kept it for room temperature for one day. Then filter it under reduced pressure. Finally, it was purified by column chromatography using hexane and ethyl acetate as eluents.

Similarly other compounds are also prepared.

The physical constants of newly synthesized compounds are given in Table No.2

2.8 PHYSICAL DATA

Physical data of (4-(substituted)1,3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanones)

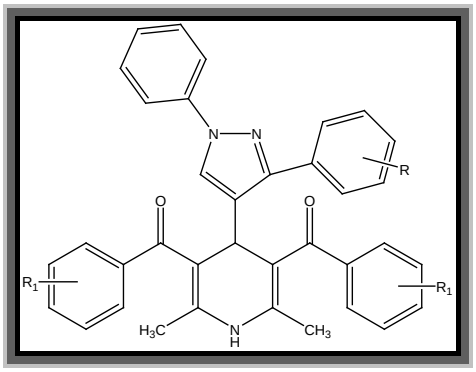


TABLE - 2

Code	Substitution		MF	MW	MP^{O}C	Rf value
	R	R_1				
STAB-031	H	H	$C_{36}H_{29}N_3O_2$	535	220-222	0.50
STAB-032	4-CH_3	H	$C_{37}H_{31}N_3O_2$	549	198-200	0.49
STAB-033	4-Cl	H	$C_{36}H_{28}ClN_3O_2$	570	178-200	0.47
STAB-034	4-NO_2	H	$C_{36}H_{28}N_4O_4$	580	186-188	0.43
STAB-035	2-OH	H	$C_{36}H_{29}N_3O_3$	551	202-204	0.44
STAB-036	2-OCH_3	H	$C_{37}H_{31}N_3O_3$	565	166-168	0.45
STAB-037	3-NO_2	H	$C_{36}H_{28}N_4O_4$	580	208-210	0.44
STAB-038	4-F	H	$C_{36}H_{28}FN_3O_2$	553	222-224	0.48
STAB-039	H	Cl	$C_{36}H_{27}Cl_2N_3O_2$	604	238-240	0.43
STAB-040	4-CH_3	Cl	$C_{37}H_{29}Cl_2N_3O_2$	618	214-216	0.48
STAB-041	4-Cl	Cl	$C_{36}H_{26}Cl_3N_3O_2$	639	228-230	0.45
STAB-042	4-NO_2	Cl	$C_{36}H_{27}Cl_2N_3O_2$	649	232-234	0.39
STAB-043	2-OH	Cl	$C_{36}H_{27}Cl_2N_3O_3$	620	218-220	0.48
STAB-044	2-OCH_3	Cl	$C_{37}H_{29}Cl_2N_3O_3$	634	214-216	0.47
STAB-045	3-NO_2	Cl	$C_{36}H_{26}Cl_2N_4O_4$	649	196-198	0.48
STAB-046	4-F	Cl	$C_{36}H_{26}Cl_2FN_3O_2$	622	188-190	0.44

R_f value was determined using solvent system = Ethyl Acetate : Hexane (2 : 3)

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 pallet method. Various functional groups present were identified by characteristic frequency obtained for them.

The characteristic bands of Hydroxyl groups were obtained for streching at 3400-3650 cm^{-1} and those for bending were obtained at 1050-1250 cm^{-1}.The stretching vibrations N-H group showed in the region of 3200 to 3500 cm^{-1} with a deformation due to in plane bending at 1650-1580 cm^{-1}.It gives aromatic C-H stretching frequencies between 3000-3200 cm^{-1} and bending vibration near 1300-1500 cm^{-1} respectively. C-H stretching frequencies for methyl and methylene group were obtained near 2950 cm^{-1} to 2850 cm^{-1}.

2.9.2 MASS SPECTRA

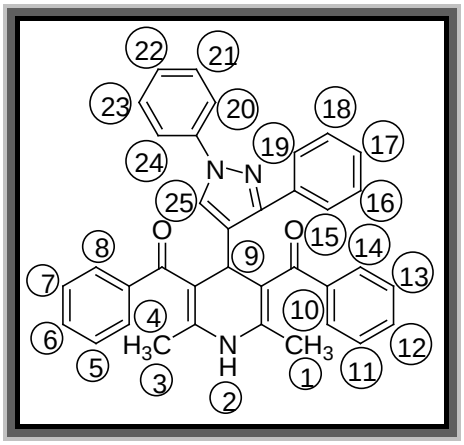
Mass spectra of the synthesized compounds were recorded on **Shimadzu GC-MS QP-2010** model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. Fragmentation pattern can be observed to be particular for these compounds and the characteristic peaks obtained for each compound.

2.9.3 ^{1}H NMR SPECTRA

^{1}H NMR spectra of the synthesized compounds were recorded on **Bruker Avance II 400 spectrometer** by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons and carbons identified from NMR spectrum 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. ^{1}H spectral interpretation can be discussed as under.

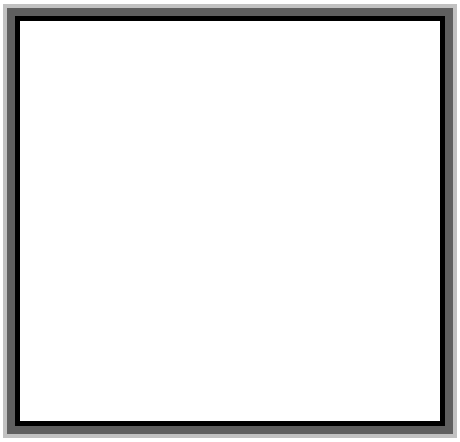
^{1}H NMR of (4-1,3-Diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-031)



1. Proton no. 1 and 3 of total 6H gave a singlet at 2.35 δ ppm.
2. Proton no. 9 of 1H gave a singlet at 4.48 δ ppm.
3. Proton no. 5,6,7,11,12 and 13 total 6H gave a multiplate at 7.46 - 7.54 δ ppm.
4. Proton no. 15,16,17,18,19,20,21,22,23 and 24 of total 10H gave a multiplet at 7.58 - 7.63 δ ppm.
5. Proton no. 25 of 1H gave a singlet at 7.73 δ ppm.
6. Proton no. 2 of 1H gave a singlet at 7.86 δ ppm.
7. Proton no. 4,8,10 and 14 of total 4H gave a doublet at 7.98 - 8.00 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 no. STAB-031 has been confirmed. The spectrum is given on page no. 87.

^{1}H NMR of (2,6-Dimethyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-032)



1. Proton no. 1 and 3 of total 6H gave a singlet at 2.36 δ ppm.
2. Proton no. 17 of 3H gave a singlet at 2.43 δ ppm.
3. Proton no. 9 of 1H gave a singlet at 4.57 δ ppm.
4. Proton no. 16 and 18 of 2H gave a double at 7.25 δ ppm - 7.27 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
5. Proton no. 20,21,22,23 and 24 total 5H gave a multiplate at 7.33 δ ppm – 7.40 δ ppm.
4. Proton no. 15 and 19 of 2H gave a doublet at 7.47 δ ppm -7.49 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
6. Proton no. 5,6,7,11,12 and 13 of total 6H gave a multiplet at 7.52 δ ppm -7.59 δ ppm.
7. Proton no. 25 of 1H gave a singlet at 7.79 δ ppm.
8. Proton no. 2 of 1H gave a singlet at 7.86 δ ppm.
9. Proton no. 4,8,10 and 14 of total 4H gave a doublet at 7.98 δ ppm – 8.00 δ ppm.

Thus, by observing and assigning the signal 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 no. STAB-032 has been confirmed. The spectrum is given on page no. 89.

2.9.4 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 spectral and elemental analysis data are for all individual compounds synthesized in this chapter are mentioned below.

2.10 ANALYTICAL DATA

(4-1,3-Diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-031)

Yield: 78% IR (cm^{-1}): 3498, 3419 (N-H stretching), 3128, 3070 (Aromatic C-H stretching), 2945 (Aliphatic -CH_3 stretching), 2899, 2843 (Aliphatic -CH_2 stretching), 1728 (C=O stretching), 1678-1602 (N-H bending), 1496, 1452, 1340 (C-H bending), 684, 729 (monosubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 2.35 (s, 6H), 4.48 (s, 1H), 7.46-7.54 (m, 6H), 7.58-7.63(m,10H), 7.73 (s, 1H), 7.86 (s, 1H), 7.98-8.00 (d,4H), MS: *m/z* = 535.23 ; Anal. Calcd. for $C_{36}H_{29}N_3O_2$: C, 80.72; H, 5.46; N,7.84;O, 5.97; Found: C, 80.66; H, 5.36; N, 7.81; O, 5.89.

(2,6-Dimethyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-032)

Yield: 85% IR (cm^{-1}): 3439 (N-H stretching), 3169, 3078 (Aromatic C-H stretching), 2994 (Aliphatic -CH_3 stretching), 1718 (C=O stretching), 1666-1639 (N-H bending), 1446, 1411, 1356 (C-H bending), 738 (disubstituted), 700(monosubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 6H), 2.43 (s, 3H), 4.57 (s,1H), 7.25-7.27 (d, 2H, J=8.0Hz), 7.33-7.40 (m, 5H), 7.47-7.49 (d, 2H, J=8.0Hz), 7.52-7.59 (m, 6H), 7.79 (s, 1H), 7.98 – 8.00 (d,4H) MS: *m/z* = 549.66 ; Anal. Calcd. for $C_{37}H_{31}N_3O_2$: C, 80.85; H, 5.68; N,7.64; O, 5.82 ; Found: C, 80.81; H, 5.60; N, 7.59; O, 5.78.

(4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-033)

Yield: 81% IR (cm^{-1}): 3419 (N-H stretching), 3109, 3068 (Aromatic C-H stretching), 2984 (Aliphatic -CH_3 stretching), 2864 (Aliphatic -CH_2 stretching), 1721 (C=O stretching), 1676-1649 (N-H bending), 1456, 1421, 1366 (C-H bending), 748 (disubstituted), 701 (monosubstituted), MS: *m/z* = 570(M^+), 572(M^{+2}) ; Anal. Calcd. for $C_{36}H_{28}ClN_3O_2$: C, 75.85; H, 4.95; N, 7.37; O, 5.61; Found: C, 75.79; H, 4.84; N, 7.30; O,5.59.

(2,6-Dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-034)

Yield: 69% IR (cm^{-1}): 3416 (N-H stretching), 3109, 3012 (Aromatic C-H stretching), 2959 (Aliphatic -CH_3 stretching), 2866 (Aliphatic -CH_2 stretching), 1729 (C=O stretching), 1666-1599 (N-H bending), 1570 (C-NO_2 stretching), 1481, 1368 (C-H bending), 754 (disubstituted), 705 (mono substituted), MS: *m/z* = 580.63; Anal. Calcd. for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65; O, 11.02; Found: C, 74.39; H, 4.74; N, 9.55; O, 11.01.

(4-(3-(2-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-035)

Yield: 82% IR (cm^{-1}): 3560 (-OH stretching), 3416 (N-H stretching), 3119, 3002 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2841 (Aliphatic -CH_2 stretching), 1726 (C=O stretching), 1663-1607 (N-H bending), 1458, 1339 (C-H bend),1320 (-OH bend.), 751 (disub.)701 (mono sub.), MS: *m/z:* 551.63 ; Anal. Calcd. for $C_{36}H_{29}N_3O_3$: C, 78.38; H, 5.30; N, 7.62, O, 8.70; Found: C, 78.29; H, 5.24; N, 7.50, O, 8.61.

***(4-(3-(2-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone*)**. **(STAB-036)**

Yield: 71% IR (cm^{-1}): 3494, 3429 (N-H stretching), 3122, 3070 (Aromatic C-H stretching), 2955 (Aliphatic -CH_3 stretching), 2891 (Aliphatic -CH_2 stretching), 1728 (C=O stretching), 1671-1612 (N-H bending), 1486, 1462, 1342 (C-H bending), 751(disubstituted), 694 (monosubstituted), MS: *m/z* = 565.66 ; Anal. Calcd. for

$C_{37}H_{31}N_3O_3$: C, 78.56; H, 5.52; N, 7.43; O,8.49; Found: C, 78.51; H, 5.44; N, 7.40; O, 8.41.

(2,6-Dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-4-yl)-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-037)

Yield: 76% IR (cm^{-1}): IR (cm^{-1}): 3446 (N-H stretching), 3119, 3002 (Aromatic C-H stretching), 2969 (Aliphatic -CH_3 stretching), 2876 (Aliphatic -CH_2 stretching), 1719 (C=O stretching), 1666-1599 (N-H bending), 1570 (C-NO_2 stretching), 1481, 1368 (C-H bending), 754 (disubstituted), 705 (mono substituted), MS: *m/z* = 580.63 ; Anal. Calcd. for $C_{36}H_{28}N_4O_4$: C, 74.47; H, 4.86; N, 9.65; O, 11.02; Found: C, 74.39; H, 4.84; N, 9.60; O, 10.99.

(4-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(phenylmethanone). (STAB-038)

Yield: 82% IR (cm^{-1}): 3436 (N-H stretching), 3119, 3002 (Aromatic C-H stretching), 2961 (Aliphatic -CH_3 stretching), 2842 (Aliphatic -CH_2 stretching), 1720 (C=O stretching), 1661-1596 (N-H bending), 1445, 1379 (C-H bending), 755 (disubstituted), 707 (mono substituted), MS: *m/z* = 553(M^+), 555(M^{+2}) ; Anal. Calcd. for $C_{36}H_{28}N_3O_2$: C, 78.10; H, 5.10; N,7.59; O,5.78; Found: C, 78.02; H, 5.04; N, 7.50; O, 5.71.

(4-(1,3-Diphenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis((4-chlorophenyl)methanone). (STAB-039)

Yield: 68% IR (cm^{-1}): 3491 (N-H stretching), 3110, 3010 (Aromatic C-H stretching), 2991 (Aliphatic -CH3 stretching), 2851 (Aliphatic -CH_2 stretching), 1724 (C=O stretching), 1664 (N-H bending), 1458, 1329 (C-H bending), 761 (disubstituted), 715 (mono substituted), MS: *m/z* = 377.44; Anal. Calcd. for $C_{36}H_{27}Cl_2N_5O_2$: C, 71.52; H, 4.50; N, 6.95; O, 5.27; Found: C, 71.49; H, 4.44; N, 6.90; O, 5.21.

(2,6-Dimethyl-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-diyl)((4-chlorophenyl)methanone). (STAB-040)

Yield: 74% IR (cm^{-1}): 3406 (N-H stretching), 3108, 3002 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2841 (Aliphatic -CH_2 stretching), 1722 (C=O

stretching), 1654-1567 (N-H bending), 1445, 1339 (C-H bending), 751 (disubstituted), 709 (mono substituted), MS: *m/z* = 618.55; Anal. Calcd. for $C_{37}H_{29}Cl_2N_3O_2$: C, 71.84; H, 4.73; N, 6.79;O, 5.17; Found: C, 71.81; H, 4.64; N, 6.70; O, 5.15.

(4-(3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis((4-chlorophenyl)methanone*). *(STAB-041)

Yield: 85% IR (cm^{-1}): 3416 (N-H stretching), 3119, 3013 (Aromatic C-H stretching), 2931(Aliphatic -CH_3 stretching), 2844 (Aliphatic -CH_2 stretching), 1731 (C=O stretching), 1654-1557 (N-H bending), 1448, 1329(C-H bending), 756 (disubstituted), 702 (mono substituted), MS: *m/z* = 639(M^+), 641(M^{+2}); Anal. Calcd. for $C_{36}H_{26}Cl_3N_3O_2$: C, 67.67; H, 4.10; N, 6.58; O, 9.85; Found: C, 67.59; H, 4.04; N, 6.50; O, 9.81.

(2,6-Dimethyl-4-(3-(4-nitrophenyl)-phenyl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-diyl)bis((4-chlorophenyl)methanone). (STAB-042)

Yield: 73% IR (cm^{-1}): 3398 (N-H stretching), 3101, 3019 (Aromatic C-H stretching), 2942 (Aliphatic -CH_3 stretching), 2844 (Aliphatic -CH_2 stretching), 1720 (C=O stretching), 1654-1591 (N-H bending), 1552 (C-NO_2 stretching), 1458, 1339 (C-H bending), 761(disubstituted), 705 (mono substituted), MS: *m/z* = 649.52; Anal. Calcd. for $C_{36}H_{26}Cl_2N_5O_4$: C, 66.57; H, 4.03; N, 8.63; O, 9.85; Found: C, 66.49; H, 4.01; N, 8.60; O, 9.81.

(4-(3-(2-Hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis((4-chlorophenyl)methanone). (STAB-043)

Yield: 71% IR (cm^{-1}): 3510 (-OH stretching), 3431 (N-H stretching), 3119, 3017 (Aromatic C-H stretching), 2991 (Aliphatic -CH_3 stretching), 2851 (Aliphatic -CH_2 stretching), 1719 (C=O stretching), 1654-1598 (N-H bending), 1458, 1343 (C-H bending), 1325 (-OH bending), 761(disubstituted), 710 (mono substituted), MS: *m/z* = 620.52 ; Anal. Calcd. for $C_{36}H_{27}Cl_2N_3O_3$: C, 69.68; H, 4.39; N, 6.77; O, 7.74; Found: C, 69.59; H, 4.24; N, 6.70; O, 7.72.

(4-(3-(2-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis(4-chlorophenyl)methanone). (STAB-044)

Yield: 84% IR (cm^{-1}): 3406 (N-H stretching), 3129 (Aromatic C-H stretching), 2978(Aliphatic -CH_3 stretching), 2841 (Aliphatic -CH_2 stretching), 1718(C=O stretching), 1664 (N-H bending), 1442, 1349 (C-H bending), 753 (disubstituted), 715 (mono substituted), MS: *m/z* = 634.55; Anal. Calcd. for $C_{37}H_{29}Cl_2N_3O_3$: C, 70.03; H, 4.61; N, 6.62; O, 7.56; Found: C, 70.02; H, 4.54; N, 6.56; O, 7.51.

(2,6-Dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-diyl)bis((4-chlorophenyl)methanone). (STAB-045)

Yield: 70% IR (cm^{-1}): 3409 (N-H stretching), 3149, 3012 (Aromatic C-H stretching), 2941 (Aliphatic -CH_3 stretching), 1711 (C=O stretching), 1665-1587 (N-H bending), 1562 (C-NO_2 stretching), 1448, 1329 (C-H bending), 763(disubstituted), 709 (mono substituted), MS: *m/z* = 649.52 ; Anal. Calcd. for $C_{36}H_{26}Cl_2N_4O_4$: C, 66.57; H, 4.03 ; N, 8.63; O, 9.85; Found: C, 66.49; H, 4.01; N, 8.50; O, 9.81.

(4-(3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)bis((4-chlorophenyl)methanone). (STAB-046)

Yield: 73% IR (cm^{-1}): 3386 (N-H stretching), 3119, 3021 (Aromatic C-H stretching), 2981(Aliphatic -CH_3 stretching), 2841 (Aliphatic -CH_2 stretching), 1731 (C=O stretching), 1668-1597 (N-H bending), 1458, 1339 (C-H bending), 759 (disubstituted), 709 (mono substituted), MS: *m/z* = 622.51(M^+), 624(M^{+2}); Anal. Calcd. for $C_{36}H_2Cl_2FN_3O_2$: C, 69.46; H, 4.21; N, 6.75; O, 5.14; Found: C, 69.39; H, 4.14; N, 6.60; O, 5.11.

2.11 RESULTS AND DISCUSSION

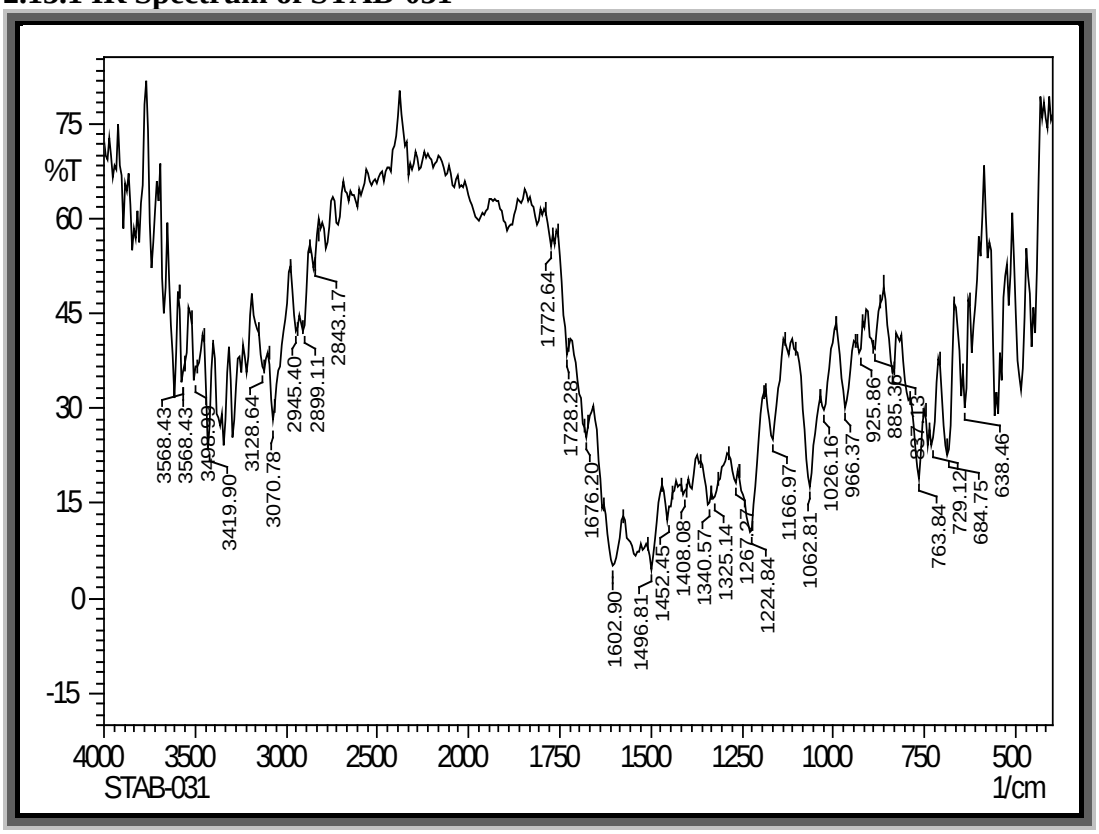
Several dihydropyridines were prepared by reactiong the benzoyl acetone with different substituted pyrazol aldehydes. The compounds prepared in this chapter possess 1,4-dihydropyridine(DHP) nucleus and are basically pyrazole core structure at C_4 position.

2.12 CONCLUSION

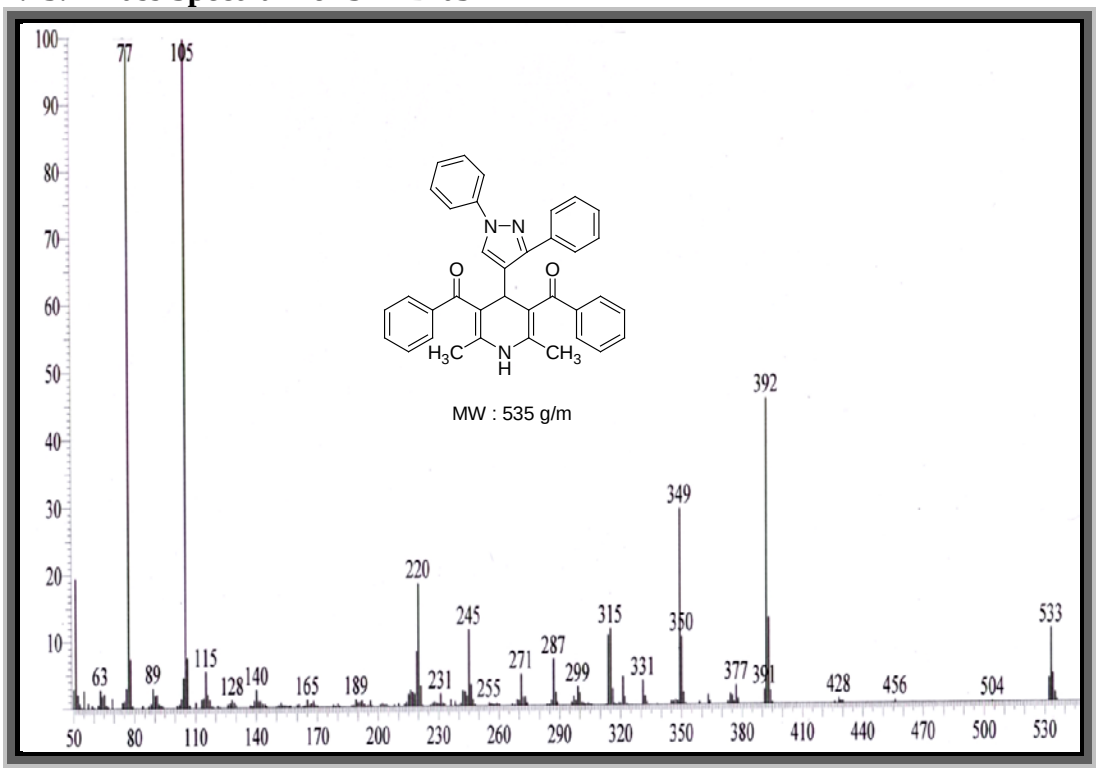
In conclusion, 16 compounds enlisted in this chapter are newly synthesized bioactive compounds for various biological activities.

2.13 REPREENTATIVE SPECTRAS

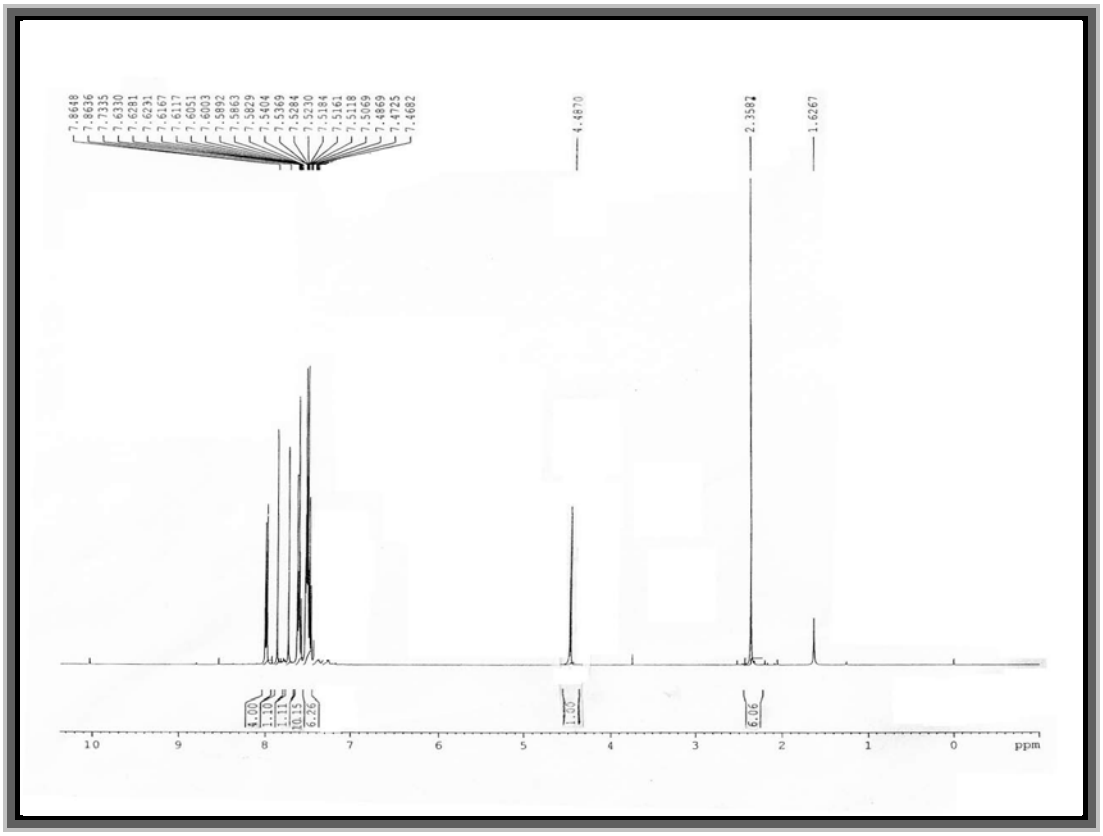
2.13.1 IR Spectrum of STAB-031



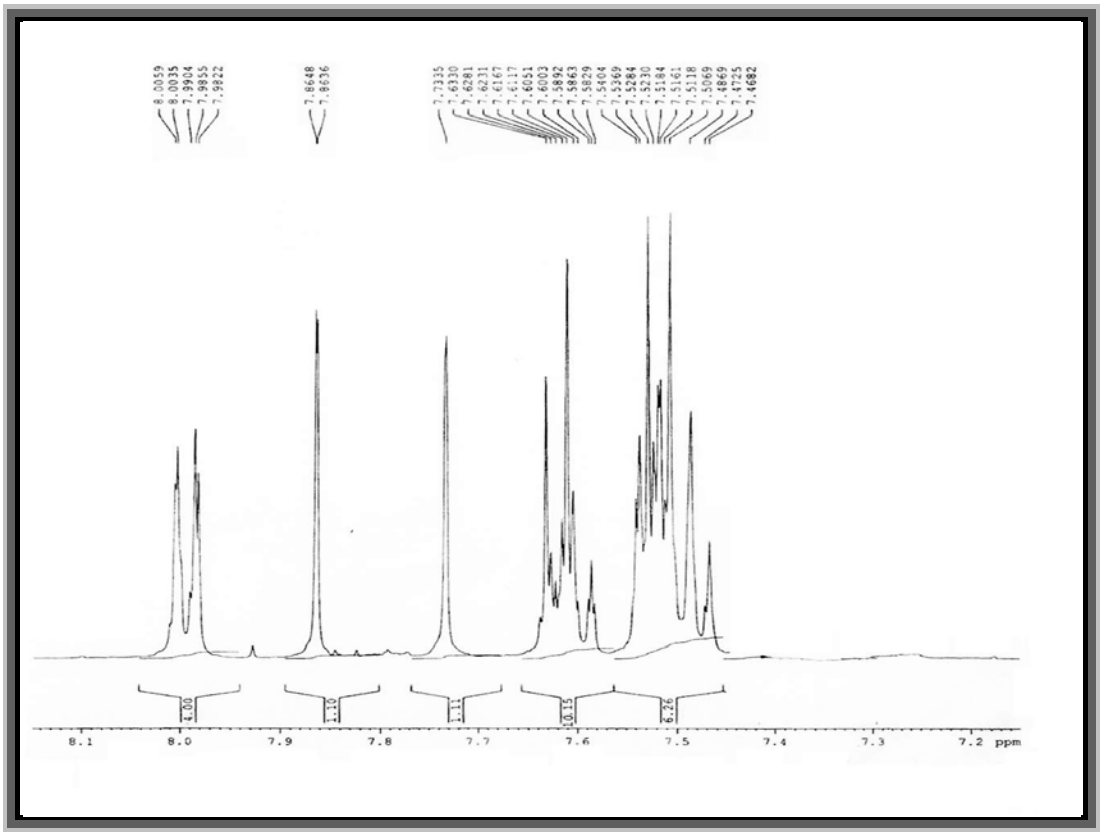
2.13.2 Mass Spectrum of STAB-031



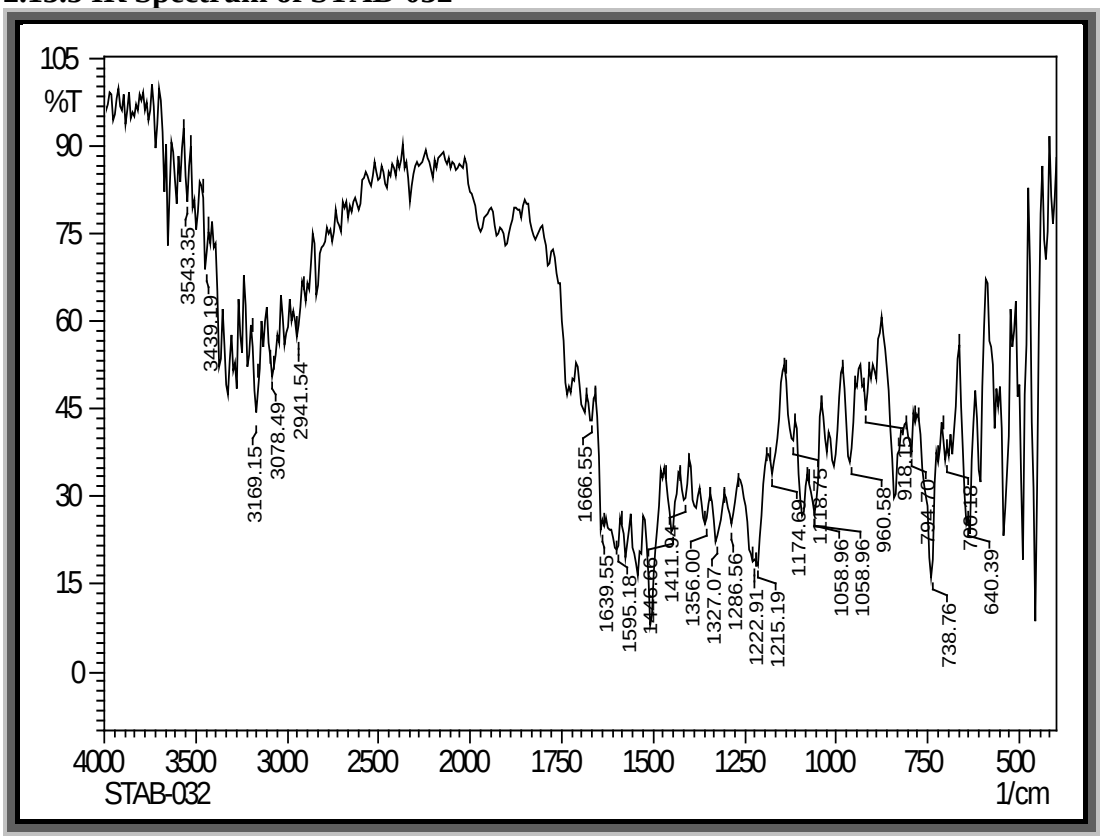
2.13.3 ^{1}H NMR Spectrum of STAB-031



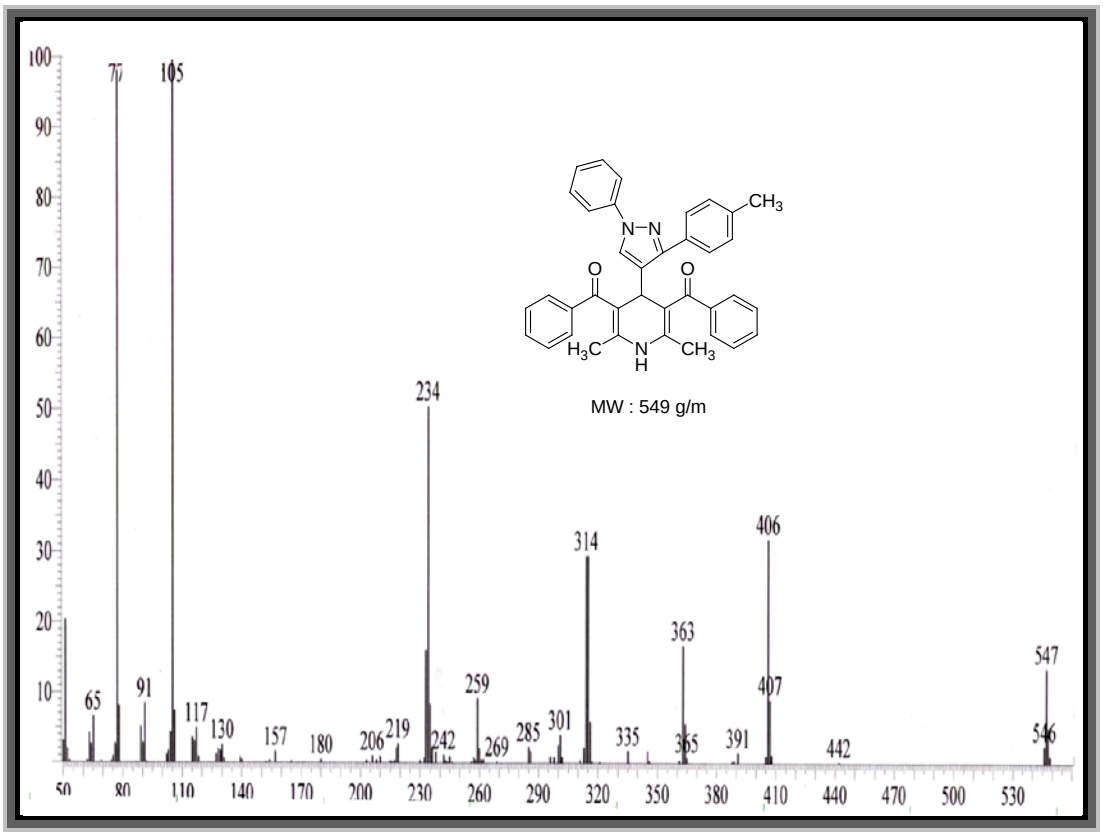
2.13.4 Expanded ^{1}H NMR Spectrum of STAB-031



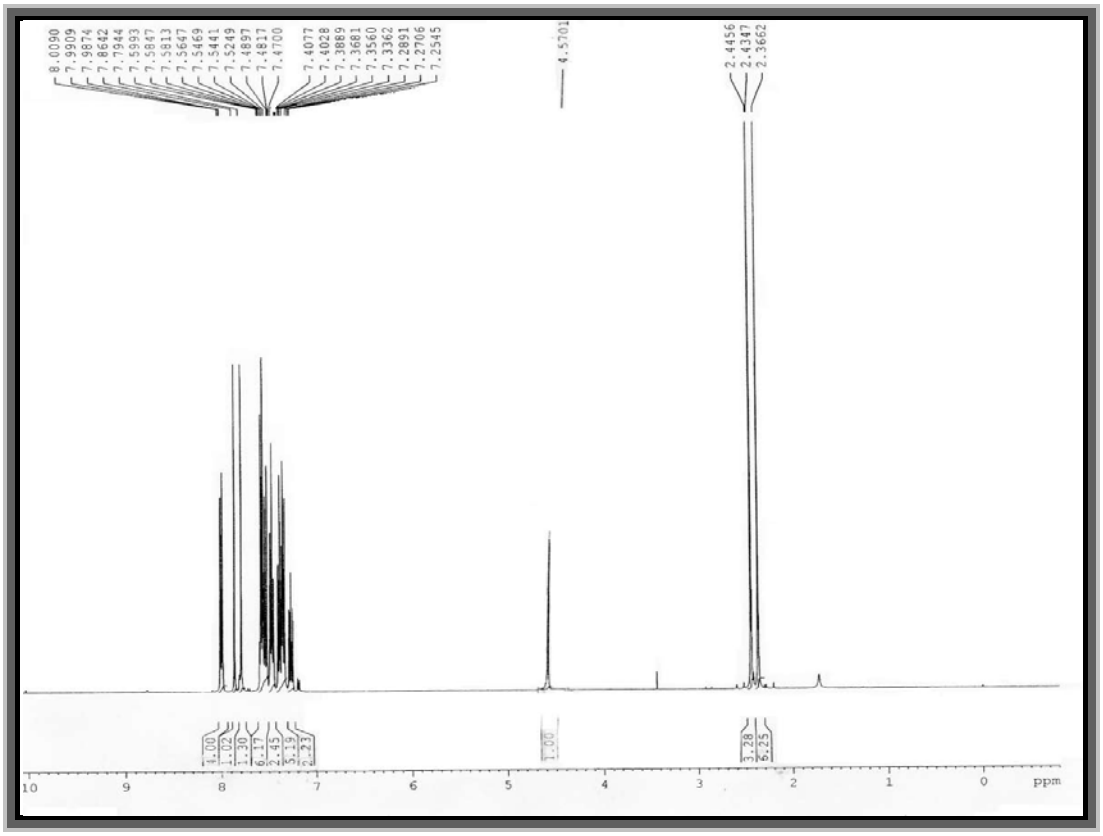
2.13.5 IR Spectrum of STAB-032



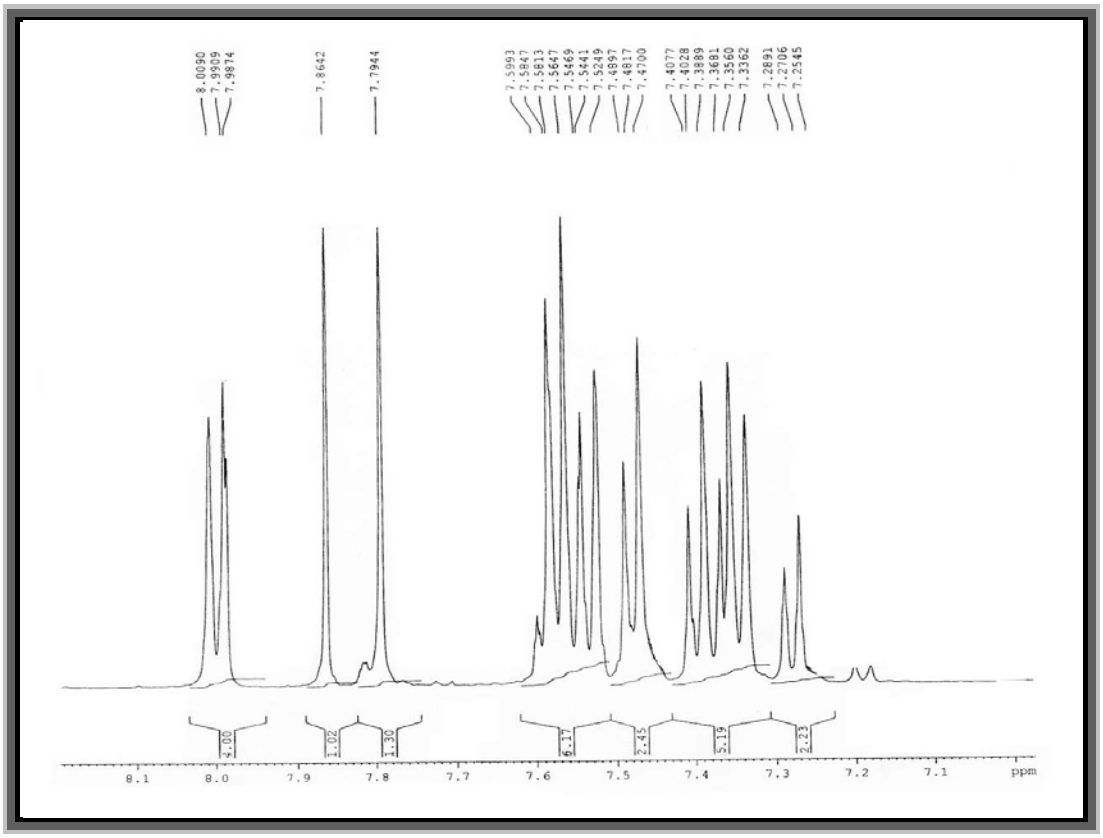
2.13.6 Mass Spectrum of STAB-032



2.13.7 ^{1}H NMR Spectrum of STAB-032



2.13.8 Expanded ^{1}H NMR Spectrum of STAB-032



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Chapter-3

Synthesis of ethyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(1,3(substituted)-diphenyl-1H-pyrazol-4-yl)pyridine-3-carboxylates.

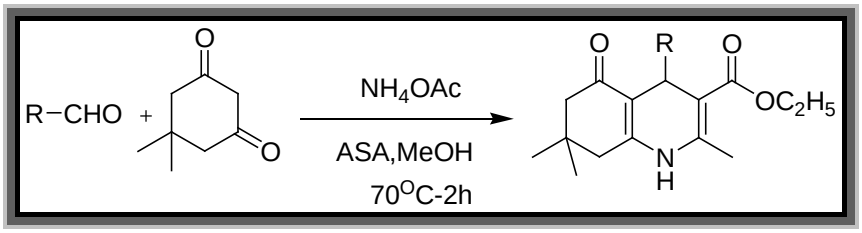
3.1 INRODUCTION

Dihydropyridines are the largest and most studied class of drugs calcium channel blocker. In addition to their proven clinical utilities in cardiovascular medicine, dihydropyridines are employed extensively as biological tools for the study of voltage-activated calcium channel.

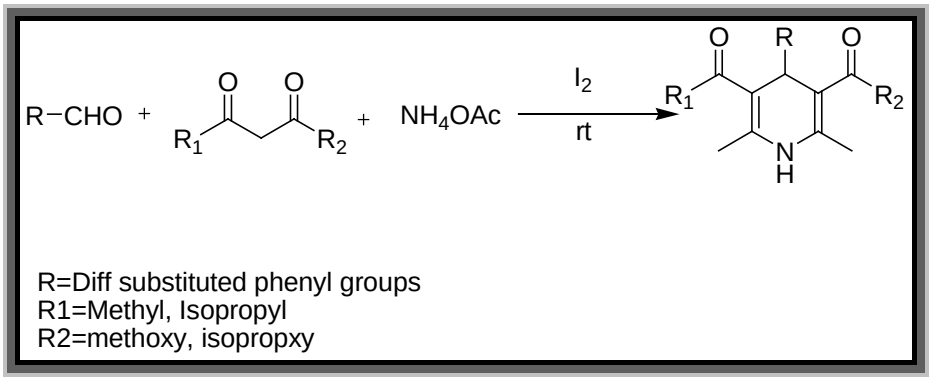
Many 1,4-dihydropyridine derivatives have been synthesized and developed as calcium channel antagonists which inhibit smooth and cardiac muscle contractions blocking the influx of Ca^{+2} through calcium channels and antihypertensive action .

3.2 LITERATURE REVIEW

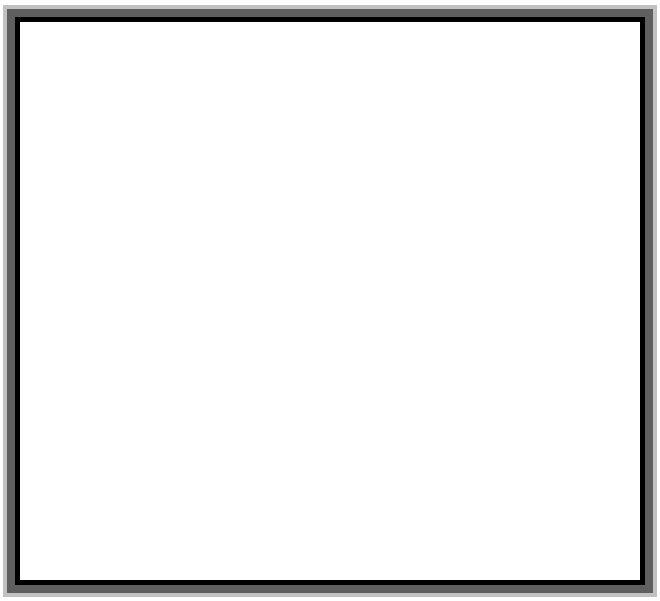
Recently much effort has been expended to develop more efficient methods for the preparation of 1,4-DHPs such as using microwave[1], metal triflates as catalyst[2], reaction in ionic liquid[3], p-TSA[4], HY-Zeolite[5], and $HClO_4$ -SiO_2[6]. 1,4-DHPs are synthesized by the Hantszch method, which involves cyclocondensation of aldehyde, *β*-ketoester, and ammonia either in acetic acid at room temperature or refluxing in alcohol for a long time.



Joshi *et al.*[7] has used molecular iodine as a catalyst for the preparation of 1,4-dihydropyridine. Molecular iodine[8-11] 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. It has been used as a mild Lewis acid in the dehydration of tertiaryalcohols to alkenes, in the formation of ethers, as well as β-keto enol ethers,[12-14] for esterification,[15] transesterification,[16] acetylation[9] and benzothiophene[17] formation, but there are only a few reports about its use for the synthesis of 1,4-DHPs. Its use for the synthesis of 1,4-DHPs.[18-19]



Xin Ying Zhang *et al.*[20] developed an efficient and green method for the synthesis of 1, 4-dihydropyridine derivatives mediated in an ionic liquid, [bmim][BF_4], through a four-component condensation process of aldehydes, 1, 3-dione, Meldrum's acid and ammonium acetate.

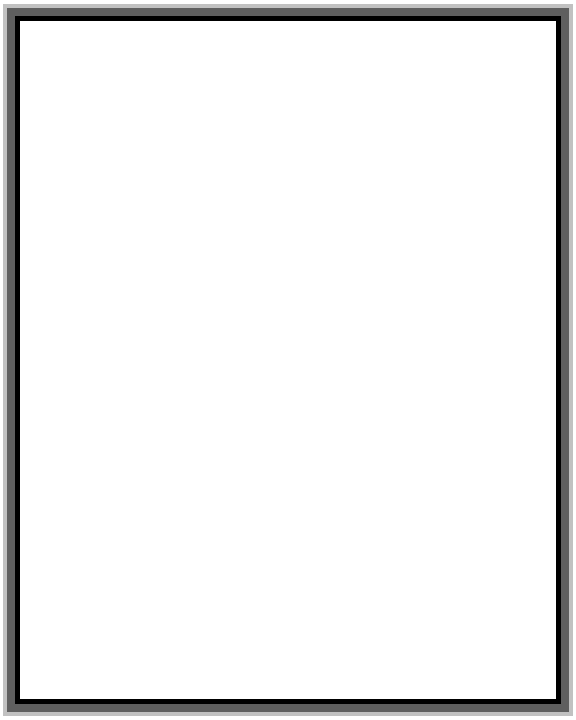


By this investigation they showed that not only aromatic aldehydes, but also heterocyclic and aliphatic aldehydes could undergo the above reaction effectively to afford the corresponding products in good yields.

Further more, 1, 3-cyclohexanedione and an acyclic 1, 3-dione, pentane-2, 4-dione were also tried in place of 5, 5-dimethyl-1, 3-cyclohexanedione for this multi-

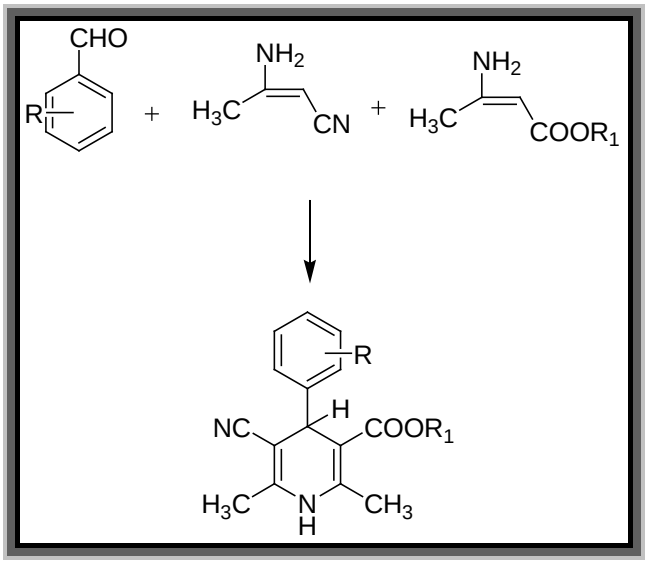
component condensation process, respectively and it also gives the good results in preparation of DHP.

Nandkishor *et al.*[21] 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.

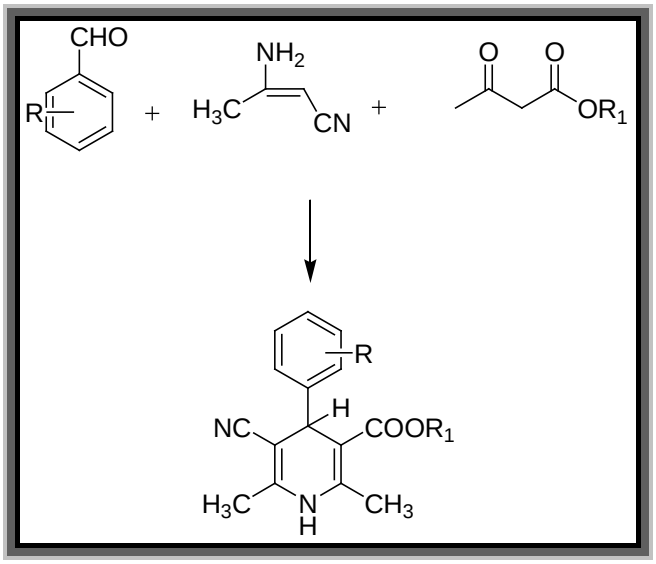


Many MCR for synthesis of DHP and it's aza analog dihydropyridines are revieved by several authors.[22] The multicomponent reaction often affords the target compounds in good yields and this experimental method remains the most widely used protocol to access to 1,4-DHP differently substituted in position 4. Some modified procedures have later been proposed and they involve the use of preformed Knoevenagel adducts between the aldehyde and the keto ester or the use of preformed enaminoesters (represented in the E form to clarify the scheme).

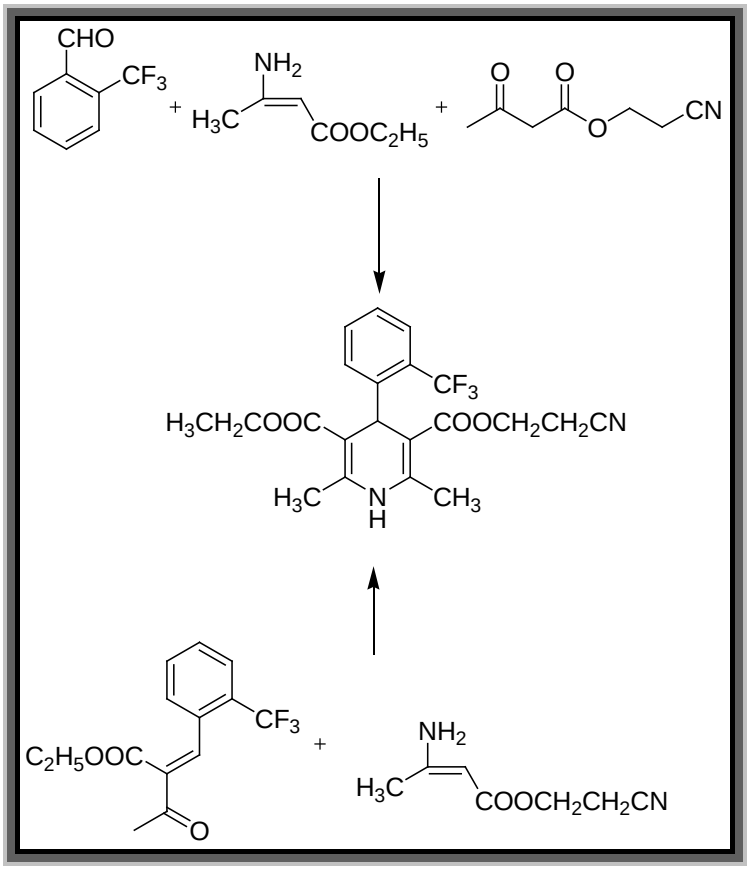
The Unsymmetric[23-27] 3-cyano-5-carboxy ester 1,4-diydrpyridine was prepared by condensation of aldehyde, 3-aminocrotononitrile with alkyl 3-aminocrotonate.



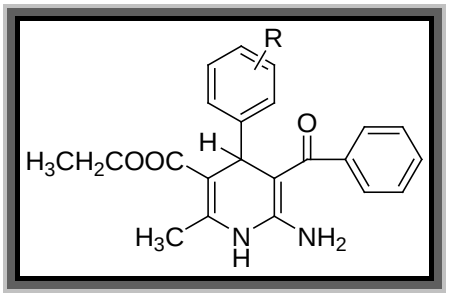
The other methods for the preparation[28] of unsymmetric cyano 1,4-dihydropyridine are reported as under.



Two different routes of synthesis in single step are reported[29] for 3-cyano ethoxycarbonyl-2,6-dimethyl-4-(2-trifluromethyl 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-triflouromethyl phenyl benzylidene) acetoacetate was carried out with 2-cyanoethyl(2Z)-3-aminobut-2-enoate.

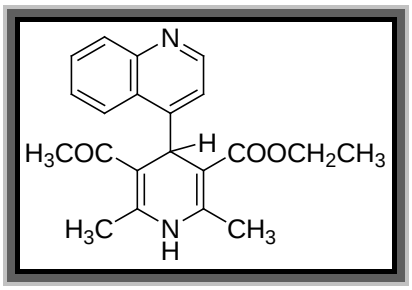


Bossert *et al.*[30] have prepared anti-inflammatory agents such as 2-amino-3-benzoyl cyano-1,4-dihydropyridine.

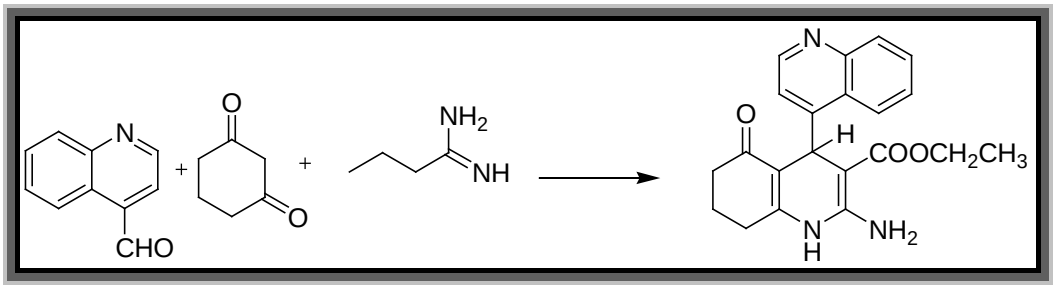


Scoane *et al.*[31] reported a facile method for synthesis of 3,5-dicyano-2,6-diphenyl-1,4-dihydropyridine(compound-1).When 3,5-dicyano-6-aminopyran was reacted with ammonium acetate in acetic acid gave the. While 3-cyano-5-carethoxy-6-aminopyran afforded to give fully aromatized pyridine.

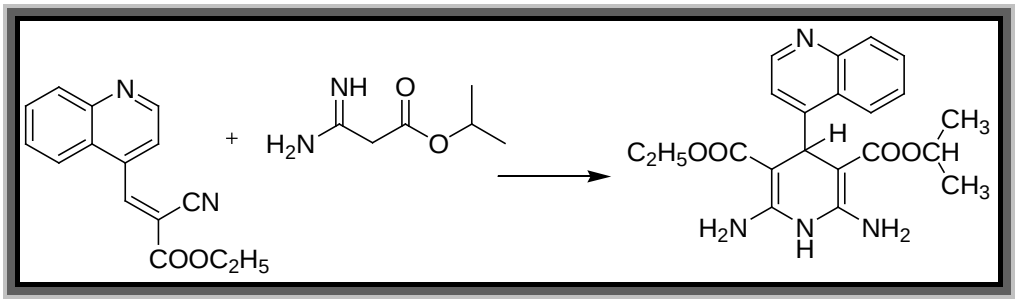
Berson *et al.*[32] reported earlier for first time the synthesis of a quinoline containing unsymmetrical compound 4-(4-quinolyl)-2,6-dimethyl-3-carbethylxy-5-acetyl-1,4-dihydropyridne.



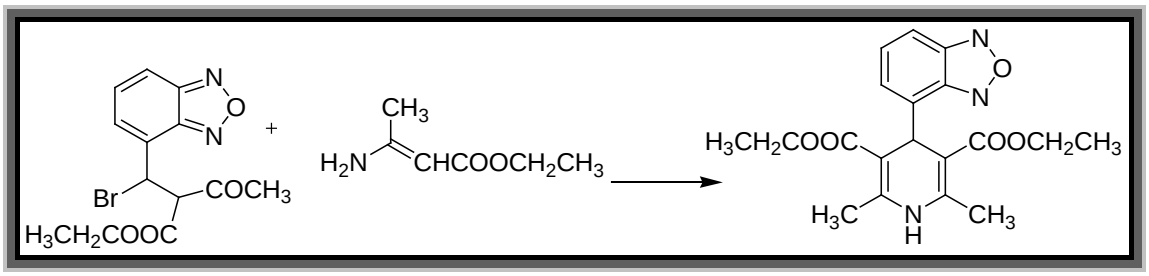
Bossert *et al.*[33] also put in their efforts to preparing coronary dilator and antihypertensive 1,4-dihydropyridines containing a quinoline group at C_4 position. Ethyl 2-amino-4-(4-quinolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate have been prepared by the cyclization of 1,3-cyclohexanedione with aldehyde and CH_3-CH_2-CH_2-C(NH)-NH_2.



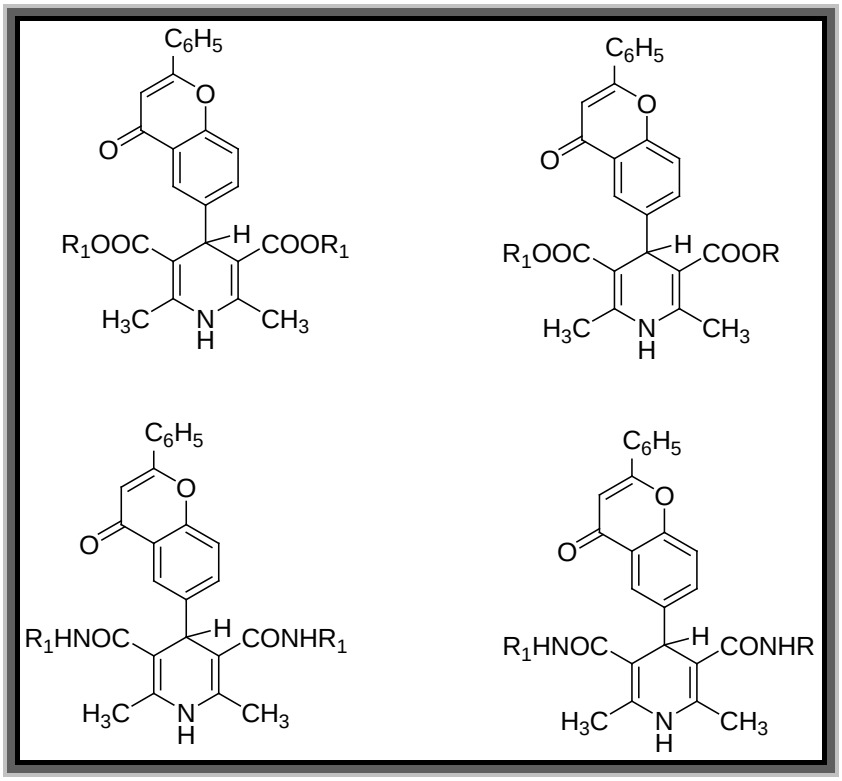
Other unsymmetric 2,6-diamino-4-(4-quinolyl)-1,4-dihydropyridine was synthesized by a different route.[34]



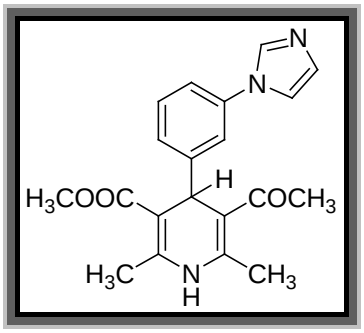
Sachio *et al.*[35] prepared antihypertensive 1,4-dihydropyridine containing a benzo furazanyl moiety at C_4 Position.



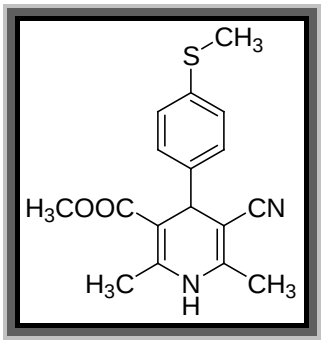
Ozbey *et al.*[36] synthesized some 1,4-dihydropyridine derivatives containing the flavones ring system.



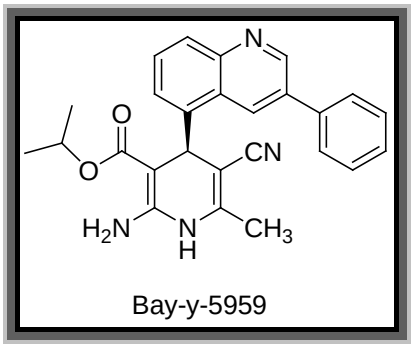
Cozzi *et al.*[37] prepared unsymmetric 4-[3-(1H-imidazol-1-yl-) Phenyl]-1,4-dihydropyridines and studied their antitumor activity.



Shah *et al.*[38] has reported a unsymmetrical 1,4-dihydropyridines having cyano and ester group in it's 3 & 5 position respectively and the compounds were synthesized adopting the Hantzsch synthesis.

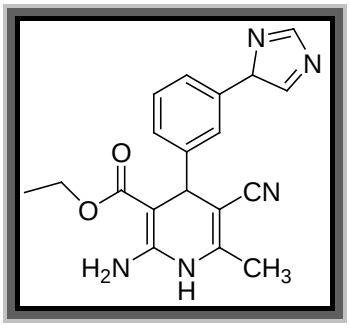


A new positive inotropic agent with high cardio selectivity, found in Bay-y-5959[39] with calcium channel-modulating activity and devoid of vasoconstricting effects. Compound increased dP/dt max by up to 300% at 30-1000mcg/kg i.v. in dogs, and it increased coronary blood flow at all doses was reported and currently undergoing phase II trials for the treatment of congestive heart failure.



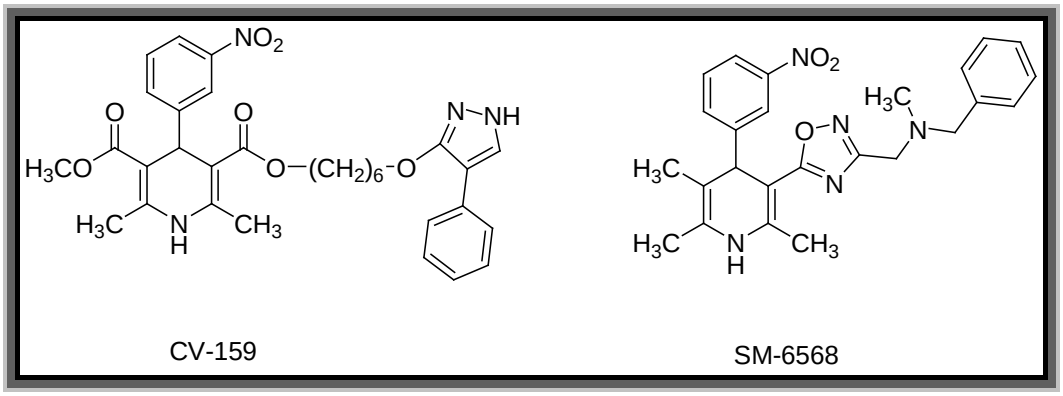
Bay-y-5959

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[40].



Christiaans *et al.*[41] studied new molecules like CV-159 SM-6586 for possible variation at 3-position. CV-159 shows an increase in coronary flow, aortic flow and

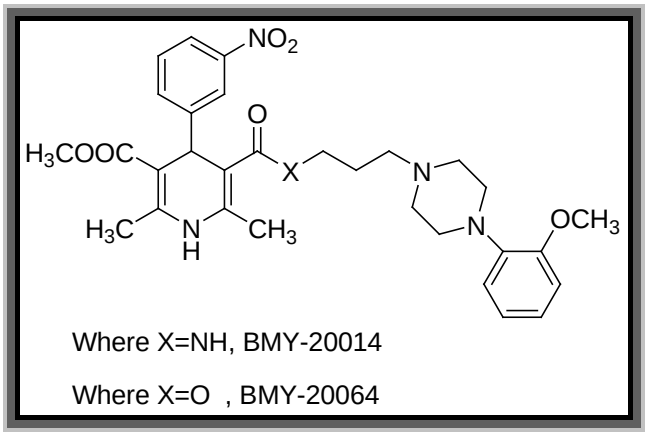
heart rate and decrease in mean blood pressure as incardipine after intravenous administration in anaesthetized open chest dogs.



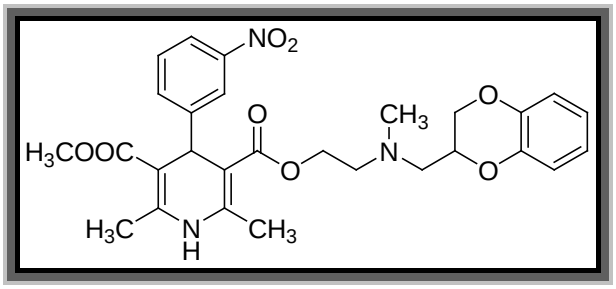
Shah *et al.*[42] synthesized some newly unsymmetrical 1,4-DHP derivatives as potent antitubercular agents and also reported some unsymmetrical 1,4-dihydropyridine derivatives as potent antitubercular agents.

In last few years, researchers of our 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[43].

Another examples of hybrid molecule which combine 1,4-DHP and piperazine are BMY 20064 and BMY 20014. The compound BMY 20064 has potent antihypertensive effects in both normotensive and spontaneously hypotensive rats and is effective against myocardial ischemia, being more potent than Nifedipine. Furthermore BMY 20064 is a selective α–adrenergic antagonist.



A hybrid molecule which combines 1, 4-DHP with benzodioxan moiety has been synthesized by Marciniak et al.[44] which also appeared as α_1 – adrenergic blockers. The most potent hybrid molecule shown in figure consists of four stereo isomers.



Carlos *et al*.[45] reported 1,4-dihydropyridines with a 1,2-benzothiazol-3-One 1-sulphoxide group, linked through an alkylene bridge to the C-3 carboxylete of the DHP ring, with both vasoconstricting and vasorelaxant properties were obtained. In blocking Ca+2 evoked contractions of K+ depolarized rabbit aortic strips. Many compounds were 10 times more potent than Nifedipine. Their vascular versus cardiac selectivity was very pronounced.

Schramm *et al*.[46] have proved that phenyl carbamoyl moiety in dihydropyridine either cardiovascular selective activity.

3.3 AIM OF CURRENT WORK

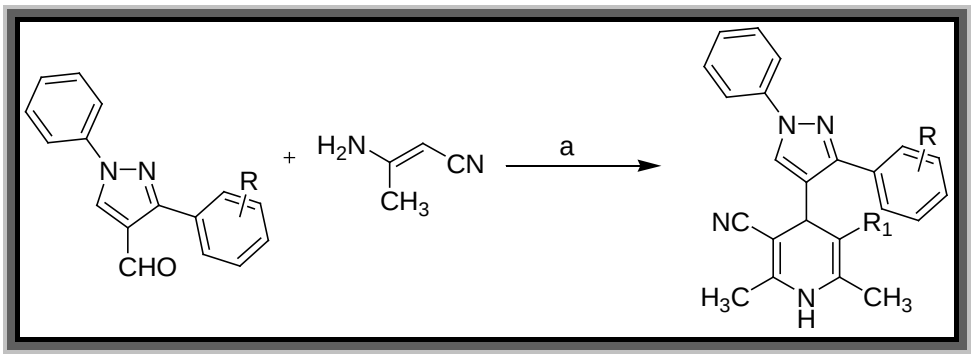
The aim of current work was to prepare the dihydropyridine which have a hybrid 'motif' where at C_3- position possess a cyano group, while at C_5 position various esteric groups are present. This will ultimately give structural and molecular diversity of unsymmetric nature.

3.4 REACTION SCHEMES

3.4.1 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

3.4.2 PREPARATION OF ALKYL 5-CYANO-4-(1,3-DIPHENYL-1H-PYRAZOL-4-YL)-2,6-DIMETHYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLATES :

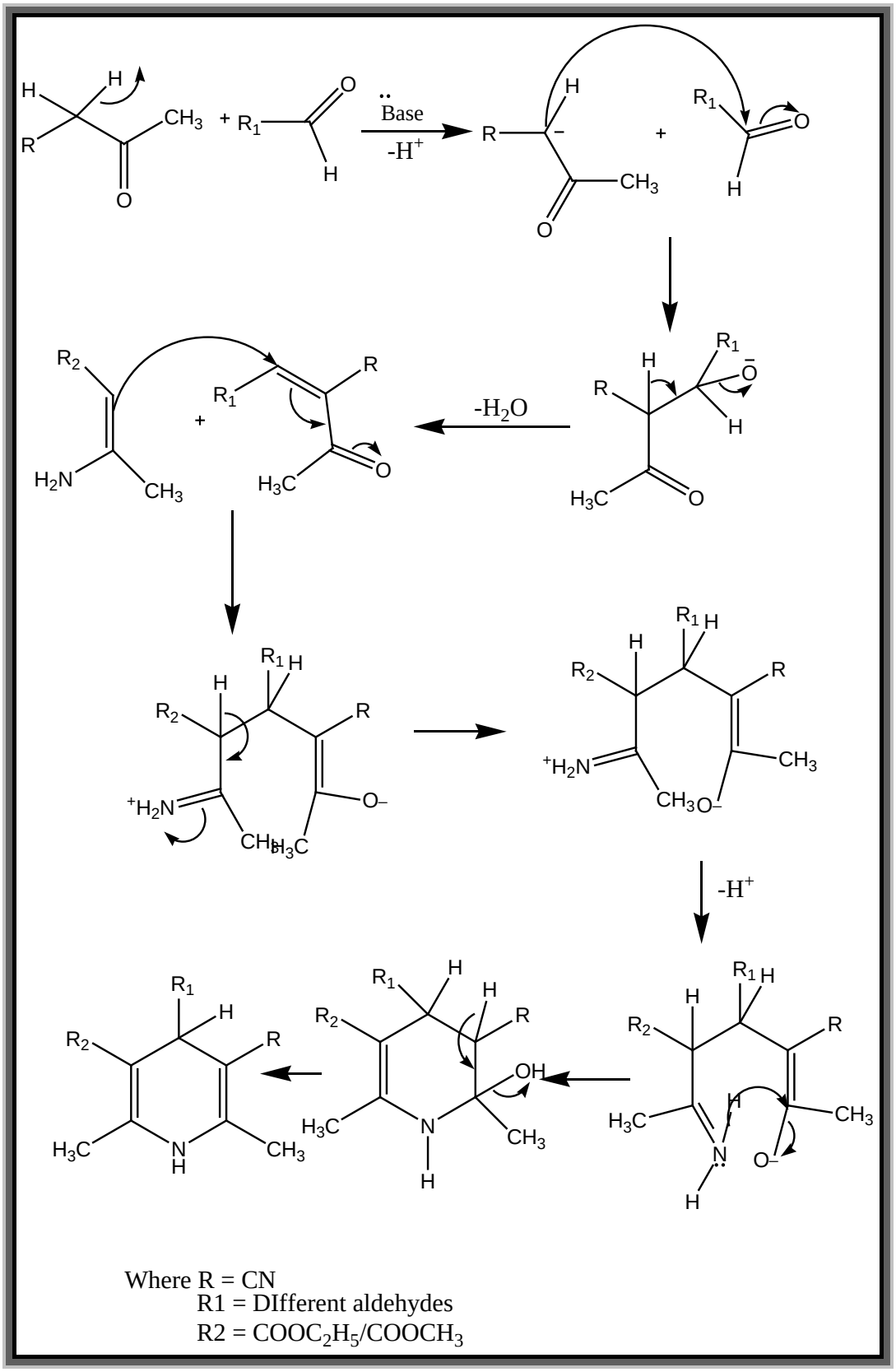


Reagents/ Reaction Condition (a): EAA/MAA, Glacial Acetic acid / 60-70°C, 1 hours.

Where R1= $COOCH_3$/$COOC_2H_5$ &

R = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2 etc.....

3.5 PLAUSIBLE REACTION MECHANISM



Where R = CN
R1 = DIfferent aldehydes
R2 = $COOC_2H_5$/$COOCH_3$

3.6 EXPERIMENTAL

3.6.1 MATERIALS AND METHODS

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 pellet 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 solution on a **Bruker Ac 400 MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model and the results are in agreements with the structures assigned.

3.6.2 PREPARATION OF PYRAZOLE ALDEHYDE :

It was prepared according to method described in Chapter-1

3.6.3 PREPARATION OF 5-CYANO-4-(1-PHENYL, 3(SUBSTITUTED)-PHENYL-1H-PYRAZOL-4-YL)-2,6-DIMETHYL-1,4-DIHYDROPYRIDINE-3-CARBOXYLATE

GENERAL PROCEDURE

A mixture of pyrazole aldehyde (0.01 mol), 3-amino crotononitrile (0.01 mol) and Methyl acetoacetate or Ethyl acetoacetate (0.01 mol) in 10 ml glacial CH_3COOH was stirred at 60-70^{O}C for 1 hrs in a flat bottom stoppered flask. The 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. The solid product was obtained after cooling and then filtered and washed with hexane.

Similarly other compounds are also prepared.

The Physical constants of newly synthesized compounds are given in Table No.3

3.7 PHYSICAL DATA

Physical data of 5-Cyano-4-(1-phenyl, 3(Substituted)phenyl-1H-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3-carboxylates.

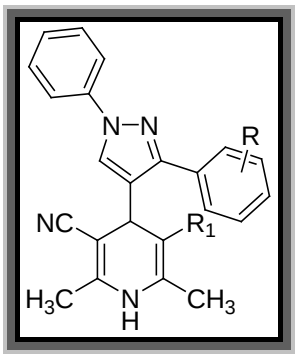


TABLE – 3

Code	Substitution		MF	MW	MP ^{O}C	Rf Value
	R	R1				
STAB-051	H	$COOCH_3$	$C_{25}H_{22}N_4O_2$	410	182-184	0.40
STAB-052	4-CH_3	$COOCH_3$	$C_{26}H_{24}N_4O_2$	424	198-200	0.43
STAB-053	4-Cl	$COOCH_3$	$C_{25}H_{21}ClN_4O_2$	444	178-180	0.43
STAB-054	4-NO_2	$COOCH_3$	$C_{25}H_{21}N_5O_4$	455	202-204	0.46
STAB-055	2-OH	$COOCH_3$	$C_{25}H_{22}N_4O_3$	426	208-210	0.44
STAB-056	2-OCH_3	$COOCH_3$	$C_{26}H_{24}N_4O_3$	440	192-194	0.43
STAB-057	3-NO_2	$COOCH_3$	$C_{25}H_{21}N_5O_4$	455	188-190	0.47
STAB-058	4-F	$COOCH_3$	$C_{25}H_{21}FN_4O_2$	428	172-174	0.42
STAB-061	H	$COOC_2H_5$	$C_{26}H_{24}N_4O_2$	424	206-208	0.44
STAB-062	4-CH_3	$COOC_2H_5$	$C_{27}H_{26}N_4O_2$	438	222-224	0.43
STAB-063	4-Cl	$COOC_2H_5$	$C_{26}H_{23}ClN_4O_2$	458	212-214	0.47
STAB-064	3-NO_2	$COOC_2H_5$	$C_{26}H_{23}N_5O_4$	469	188-190	0.42
STAB-065	4-NO_2	$COOC_2H_5$	$C_{26}H_{23}N_5O_4$	469	192-194	0.42
STAB-066	2-OH	$COOC_2H_5$	$C_{26}H_{24}N_4O_3$	440	178-180	0.43
STAB-067	2-OCH_3	$COOC_2H_5$	$C_{27}H_{26}N_4O_3$	454	192-194	0.44
STAB-068	4-F	$COOC_2H_5$	$C_{26}H_{23}FN_4O_2$	442	202-204	0.46

R_f value was determined using solvent system = Ethyl Acetate : Hexane (3 : 2)

3.8 SPECTRAL DISCUSSION

3.8.1 IR SPECTRA

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

The characteristic bands of -OH groups were obtained for streching at 3400-3650 cm^{-1} and those for bending were obtained at 1050-1250 cm^{-1}.The stretching vibrations N-H group showed in the region of 3200 to 3500 cm^{-1} with a deformation due to in plane bending at 1650-1580 cm^{-1}. It gives aromatic C-H stretching frequencies between 3000-3200 cm^{-1} and bending vibration near 1300-1500 cm^{-1} respectively. C-H stretching frequencies for methyl and methylene group were obtained near 2950 cm^{-1} to 2850 cm^{-1}. Characteristic frequency of C-N stretching showed near 2100-2300 cm^{-1} and bending vibration near 1250-1400 cm^{-1}.

3.8.2 MASS SPECTRA

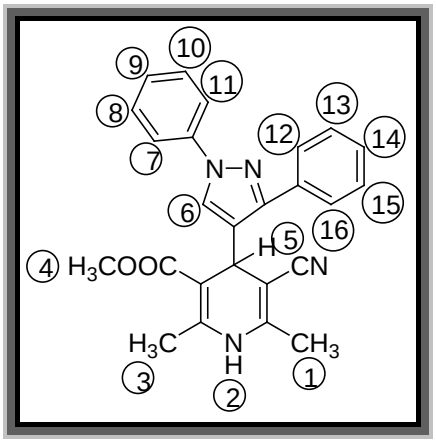
Mass spectra of the synthesized compounds were recorded on **Shimadzu GC-MS QP-2010** model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. Fragmentation pattern can be observed to be particular for these compounds and the characteristic peaks obtained for each compound.

3.8.3 ^{1}H NMR SPECTRA

^{1}H & NMR spectra of the synthesized compounds were recorded on **Bruker Avance II 400 spectrometer** by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons and carbons identified from NMR spectrum 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. ^{1}H spectral interpretation can be discussed as under.

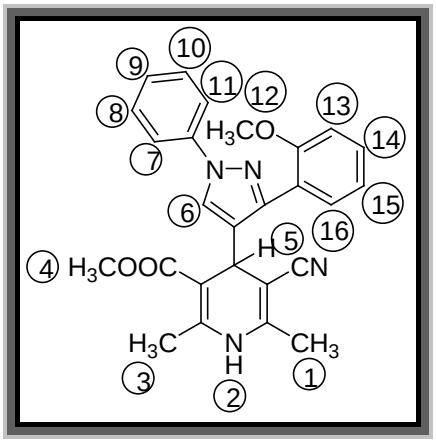
^{1}H NMR of Methyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate.(STAB-051)



1. Proton no. 1 and 3 of 6H gave singlet at 2.14 δ ppm.
2. Proton no. 4 of 3H gave a singlet at 2.58 δ ppm.
3. Proton no. 5 of 1H gave a singlet at 4.91 δ ppm.
4. Proton no. 8 and 10 of 2H gave a doublet and triplet at 6.91 δ ppm - 6.99 δ ppm.
5. Proton no. 7 and 11 of 2H gave a triplet at 7.20 δ ppm - 7.22 δ ppm
6. Proton no. 9 of 1H gave a triplet at 7.29 δ ppm - 7.31 δ ppm.
7. Proton no. 13 and 15 of 2H gave a triplet at 7.45 δ ppm - 7.49 δ ppm.
8. Proton no.14 of 1H gave a doublet at 7.60 δ ppm - 7.62 δ ppm.
9. Proton no. 12 and 16 of 2H gave a doublet at 7.71 δ ppm - 7.73 δ ppm.
10. Proton no. 6 of 1H gave a singlet at 7.95 δ ppm.
11. Proton no. 2 of 1H gave a singlet at 8.74 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 no. STAB-051 has been confirmed. The spectrum is given on page no. 120.

^{1}H NMR of Methyl 5-cyano-1,4-dihydro-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3-carboxylate. (STAB-056)



1. Proton no. 1 and 3 of 6H both gave a singlet at 1.83 δ ppm.
2. Proton no. 4 of 3H gave a singlet at 3.34 δ ppm.
3. Proton no. 12 of 3H gave a singlet at 3.72 δ ppm.
4. Proton no. 5 of 1H gave a singlet at 4.32 δ ppm.
5. Proton no. 13 and 15 of 2H gave multiplate at 6.98 δ ppm - 7.08 δ ppm.
6. Proton no. 16 of 1H gave a doublet at 7.21 δ ppm - 7.24 δ ppm.
7. Proton no. 9 of 1H gave a triplet at 7.27 - 7.32 δ ppm.
8. Proton no.14 of 1H gave a triplet at 7.37 - 7.42 δ ppm.
9. Proton no. 8 and 10 of 2H gave a triplet at 7.47 δ ppm - 7.52 δ ppm.
10. Proton no. 7 and 11 of 2H gave a doublet at 7.86 - 7.88 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
11. Proton no. 6 of 1H gave a singlet at 8.52 δ ppm.
12. Proton no. 2 of 1H gave a singlet at 9.11 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 no. STAB-56 has been confirmed. The spectrum is given on page no. 122.

3.8.4 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 spectral and elemental analysis data are all for individual compounds synthesized in this chapter are mentioned below.

3.9 ANALYTICAL DATA

Methyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-051)

Yield : 79 % IR (cm^{-1}): 3489,3367 (N-H stretching), 3198 (Aromatic C-H stretching), 2974 (Aliphatic -CH_3stretching), 2897 (Aliphatic -CH_2 stretching), 2260,2332 (C-N stretching), 1707(C=O stretching), 1660-1587 (N-H bending), 1519,1435,1356 (C-H bending) ,1282 (C-N bending), 744-688 (disubstituted), MS: *m/z* = 426.17; Anal. Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14; O, 11.25 Found: C, 70.33; H, 5.19; N, 13.13; O, 11.13. ^{1}H NMR (DMSO-d_6) δ ppm: 2.14 (s, 6H), 2.58(s, 3H), 4.91 (s, 1H), 6.91-6.99 (d, 2H), 7.20 - 7.22 (t, 2H), 7.29 - 7.31(t, 1H), 7.45 - 7.49 (t, 2H), 7.60 - 7.62(d, 1H), 7.71 - 7.73(d, 2H), 7.95(s, 1H),8.74 (s, 1H), MS: *m/z:* 410.17; Anal. Calcd. for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N,13.65; O,7.80; Found: C, 73.06; H, 5.36; N, 13.61; O,7.79.

Methyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4yl)pyridine-3-carboxylate. (STAB-052)

Yield : 79 % IR (cm^{-1}): 3469,3307 (N-H stretching), 3191 (Aromatic C-H stretching), 2984 (Aliphatic -CH_3 stretching), 2857 (Aliphatic -CH_2 stretching), 2250,2312 (C-N stretching), 1727(C=O stretching), 1650-1577 (N-H bending), 1509,1455,1366 (CH bending) ,1289 (CN bending), 749 (disubstituted), 698 (monosubstituted) MS: *m/z* = 424.49; Anal. Calcd. for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20; O,7.54 Found: C, 73.49; H, 5.60; N, 13.19; O, 7.48.

Methyl 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-cyano-1,4-dihydro-2,6-dimethylpyridine-3-carboxylate. (STAB-053)

Yield : 77 % IR (cm^{-1}): 3459,3347 (N-H stretching), 3190 (Aromatic -C-H stretching), 2984 (Aliphatic -CH_3 stretching) 2898 (Aliphatic -CH_2 stretching), 2262,2342 (C-N stretching), 1707(C=O stretching), 1662-1587 (N-H bending), 1509,1455,1346 (C-H bending) ,1292 (C-N bend.), 1241,1108 (-OH bend.), 745-689 (disub.), MS: *m/z* = 444(M^+), 446(M^{+2}) ; Anal. Calcd. for $C_{25}H_{21}ClN_4O_2$: C, 67.49; H, 4.76; N, 12.59; O, 7.19 Found: C, 76.29; H, 5.04; N, 18.50.

Methyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-054)

Yield : 87 % IR (cm^{-1}): 3459,3347 (N-H stretching), 3188 (Aromatic C-H stretching), 2954 (Aliphatic -CH_3 stretching), 2857 (Aliphatic -CH_2 stretching), 2240,2342 (C-N stretching), 1717(C=O stretching), 1669-1581 (N-H bending), 1545 (C-NO_2 stretching), 1518,1445,1366 (C-H bending) ,1272 (C-N bending), 749 (disubstituted), 689 (monosubstituted) MS: *m/z* = 455.47; Anal. Calcd. for $C_{25}H_{21}N_5O_4$: C, 65.93; H, 4.65; N, 15.38; O, 14.05 Found: C, 65.84; H, 4.55; N, 15.30; O, 14.01.

Methyl 5-cyano-1,4-dihydro-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3-carboxylate. (STAB-055)

Yield : 81 % IR (cm^{-1}): 3611,3581 (OH stretching), 3489,3367 (N-H stretching), 3198 (Aromatic C-H stretching), 2974 (Aliphatic -CH_3stretching), 2897 (Aliphatic -CH_2 stretching), 2260,2332 (C-N stretching), 1707(C=O stretching), 1660-1587 (N-H bending), 1519,1435,1356 (C-H bending) , 1282 (C-N bending), 1250,1117 (-OH bending), 744 (disubstituted), 688(monosubstituted) MS: *m/z* = 426.17; Anal. Calcd. for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14; O, 11.25 Found: C, 70.33; H, 5.19; N, 13.13; O, 11.13.

Methyl 5-cyano-1,4-dihydro-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3-carboxylate. (STAB-056)

Yield : 83 % IR (cm^{-1}): 3574,3473,3429,3402 (N-H stretching), 3203,3097 (Aromatic C-H stretching), 2999 (Aliphatic -CH_3 stretching), 2347,2196 (C-N stretching), 1780 (C=O stretching), 1658-1508 (N-H bending), 1464,1375,1323 (C-H bending) ,1247 (CN bending), 1134,1022 (-OH bending), 758(disubstituted), 709 (monosubstituted),

^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (s, 6H), 3.34 (s, 3H), 3.72 (s, 3H), 4.32 (s, 1H), 6.98 - 7.08 (m, 2H),7.21-7.24 (d, 1H), 7.27 - 7.32 (t, 1H), 7.37 - 7.42 (t, 1H), 7.47 - 7.52 (t, 2H),7.86 - 7.88 (d, 2H, J= 8.0 Hz), 8.52 (s, 1H), 9.11 (s, 1H), MS: *m/z* = 440.49; Anal. Calcd. for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72; O, 10.90 Found: C, 70.71; H, 5.47; N, 12.65; O, 10.90.

Methyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-057)

Yield : 79 % IR (cm^{-1}): 3479,3368 (N-H stretching), 3192 (Aromatic C-H stretching), 2934 (Aliphatic -CH_3 stretching), 2893 (Aliphatic -CH_2 stretching), 2261,2331 (C-N stretching), 1717(C=O), 1661-1577 (N-H bending), 1530 (C-NO_2 stretching), 1518,1445,1354 (C-H bending) ,1283 (C-N bending), 1241,1101 (-OH bending), 745(disubstituted), 689 (monosubstituted), MS: *m/z* = 455.16; Anal. Calcd. for $C_{25}H_{21}N_5O_4$: C, 65.93; H, 4.65; N, 15.38; O, 14.05 Found: C, 65.84; H, 4.56; N, 15.31; O, 14.07.

Methyl 5-cyano-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3-carboxylate. (STAB-058)

Yield : 69 % IR (cm^{-1}): 3509,3357 (N-H stretching), 3190 (Aromatic C-H stretching), 2984 (Aliphatic -CH_3 stretching), 2898 (Aliphatic -CH_2 stretching), 2261,2330 (C-N stretching), 1717(C=O stretching), 1661-1589 (N-H bending), 1518,1434,1354 (C-H bending),`1281 (C-N bending), 1241,1108 (-OH bending), 745(disubstituted), 689 (monosubstituted), MS: *m/z* = 428 (M^+), 430 (M^{+2}) ; Anal. Calcd. for $C_{25}H_{21}FN_5O_2$: C, 70.08; H, 4.94; N, 13.08; O,7.47 Found: C, 70.03; H, 4.91; N, 13.07; O,7.41.

Ethyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-061)

Yield : 78 % IR (cm^{-1}): 3479,3368 (N-H stretching), 3188 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2887 (Aliphatic -CH_2 stretching), 2250,2342 (C-N stretching), 1727(C=O stretching), 1665-1581 (N-H bending), 1529,1425,1346 (C-H bending) ,1272 (C-N bend.), 1245,1117 (-OH bending), 689 (monosubstituted), MS: *m/z* = 424.19; Anal. Calcd. for $C_{26}H_{24}N_4O_2$: C,73.56; H, 5.70; N, 13.20; O, 7.54 Found: C, 73.43; H, 5.61; N, 13.07; O,7.49.

Ethyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-062)

Yield : 76 % IR (cm^{-1}): 3479,3387 (N-H stretching), 3158 (Aromatic C-H stretching), 2975 (Aliphatic -CH_3 stretching), 2877(Aliphatic -CH_2 stretching), 2268,2352 (C-N stretching), 1717(C=O stretching), 1669-1589 (N-H bending), 1529,1445,1346 (C-H bending) ,1283 (C-N bending), 1244,1109 (-OH bending), 748(disubstituted), 689 (monosubstituted), MS: *m/z* = 438.52; Anal. Calcd. for $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78; O, 7.30 Found: C, 73.83; H, 5.91; N, 12.77; O,7.29.

Ethyl 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-cyano-1,4-dihydro-2,6-dimethylpyridine-3-carboxylate. (STAB-063)

Yield : 79 % IR (cm^{-1}): 3489,3389 (N-H stretching), 3159 (Aromatic C-H stretching), 2979 (Aliphatic -CH_3 stretching), 2879(Aliphatic -CH_2 stretching), 2288,2332 (C-N stretching), 1707(C=O stretching), 1679-1569 (N-H bending), 1529,1455,1356 (C-H bending) ,1282 (C-N bending), 1245,1119 (-OH bending), 749 (disubstituted), 687 (monosubstituted), MS: *m/z* = 458 (M^+), 460 (M^{+2}); Anal. Calcd. for $C_{26}H_{23}ClN_4O_2$: C, 68.04; H, 5.05; N, 12.21; O, 6.97 Found: C, 68.03; H, 5.01; N,12.17; O,6.94.

Ethyl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-064)

Yield : 89 % IR (cm^{-1}): 3489,3397 (N-H stretching), 3168 (Aromatic C-H stretching), 2985 (Aliphatic -CH_3 stretching), 2878(Aliphatic -CH_2 stretching), 2278,2352 (C-N stretching), 1707(C=O stretching), 1689-1586 (N-H bending), 1520 (C-NO_2 stretching), 1539,1435,1345 (C-H bending) ,1284 (C-N bending), 1245,1108 (-OH bending), 749(disubstituted), 687 (monosubstituted), MS: *m/z* = 469.18; Anal. Calcd. for $C_{26}H_{23}N_5O_4$: C,66.51; H, 4.94; N, 14.92; O, 13.63 Found: C, 66.43; H, 4.91; N, 14.87; O,13.59.

Ethayl 5-cyano-1,4-dihydro-2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-3-carboxylate. (STAB-065)

Yield : 81 % IR (cm^{-1}): 3459,3377 (N-H stretching), 3058 (Aromatic C-H stretching), 2976 (Aliphatic -CH_3 stretching), 2878(Aliphatic -CH_2 stretching), 2261,2322 (C-N stretching), 1727(C=O stretching), 1689-1588 (N-H bending), 1551 (C-NO_2 stretching), 1539,1435,1343 (C-H bending) ,1273 (C-N bending), 1234,1101 (-OH

bending), 738(disubstituted), 679 (monosubstituted), MS: *m/z* = 469.18; Anal. Calcd. for $C_{26}H_{23}N_5O_4$: C,66.51; H, 4.94; N, 14.92; O, 13.63 Found: C, 66.43; H, 4.91; N, 14.87; O,13.59.

Ethyl 5-cyano-1,4-dihydro-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3-carboxylate. (STAB-066)

Yield : 78 % IR (cm^{-1}): 3611,3581 (OH stretching), 3479,3347 (N-H stretching), 3108 (Aromatic C-H stretching), 2974 (Aliphatic -CH_3 stretching), 2897 (Aliphatic -CH_2 stretching), 2260,2332 (C-N stretching), 1707(C=O stretching), 1660-1587 (N-H bending), 1519,1435,1356 (C-H bending) ,1282 (C-N bending), 1240,1107 (-OH bending), 744 (disubstituted), 688(monosubstituted, MS: *m/z* = 440.49; Anal. Calcd. for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72; O, 10.90 Found: C, 70.83; H, 5.51; N, 12.77; O,10.89.

Ethyl 5-cyano-1,4-dihydro-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3-carboxylate. (STAB-067)

Yield : 76 % IR (cm^{-1}): 3489,3357 (N-H stretching), 3118 (Aromatic C-H stretching), 2984 (Aliphatic -CH_3 stretching), 2887 (Aliphatic -CH_2 stretching), 2261,2342 (C-N stretching), 1717(C=O stretching), 1661-1581 (N-H bending), 1518,1445,1346 (C-H bending) ,1281 (C-N bending), 1241,1117 (-OH bending), 744(disubstituted), 689 (monosubstituted), MS: *m/z* = 454.52; Anal. Calcd. for $C_{27}H_{26}N_4O_3$: C, 71.35; H, 5.77; N, 12.33; O, 10.56 Found: C, 71.31; H, 5.61; N, 12.27; O,10.49.

Ethyl 5-cyano-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1,4-dihydro-2,6-dimethylpyridine-3-carboxylate. (STAB-068)

Yield : 89 % IR (cm^{-1}): 3419,3307 (N-H stretching), 3101 (Aromatic C-H stretching), 2970 (Aliphatic -CH_3 stretching), 2890 (Aliphatic -CH_2 stretching), 2261,2322 (C-N stretching), 1707(C=O stretching), 1669-1586 (N-H bending), 1509,1425,1326 (C-H bending) ,1283 (C-N bending), 1241,1117 (-OH bending), 745 (disubstituted), 685 (monosubstituted), MS: *m/z* = 442 (M^+), 444 (M^{+2}); Anal. Calcd. for $C_{26}H_{23}FN_4O_2$: C, 70.57; H, 5.24; N, 12.66; O, 7.23 Found: C, 70.53; H, 5.21; N, 12.77; O,7.19.

3.10 RESULTS AND DISCUSSION

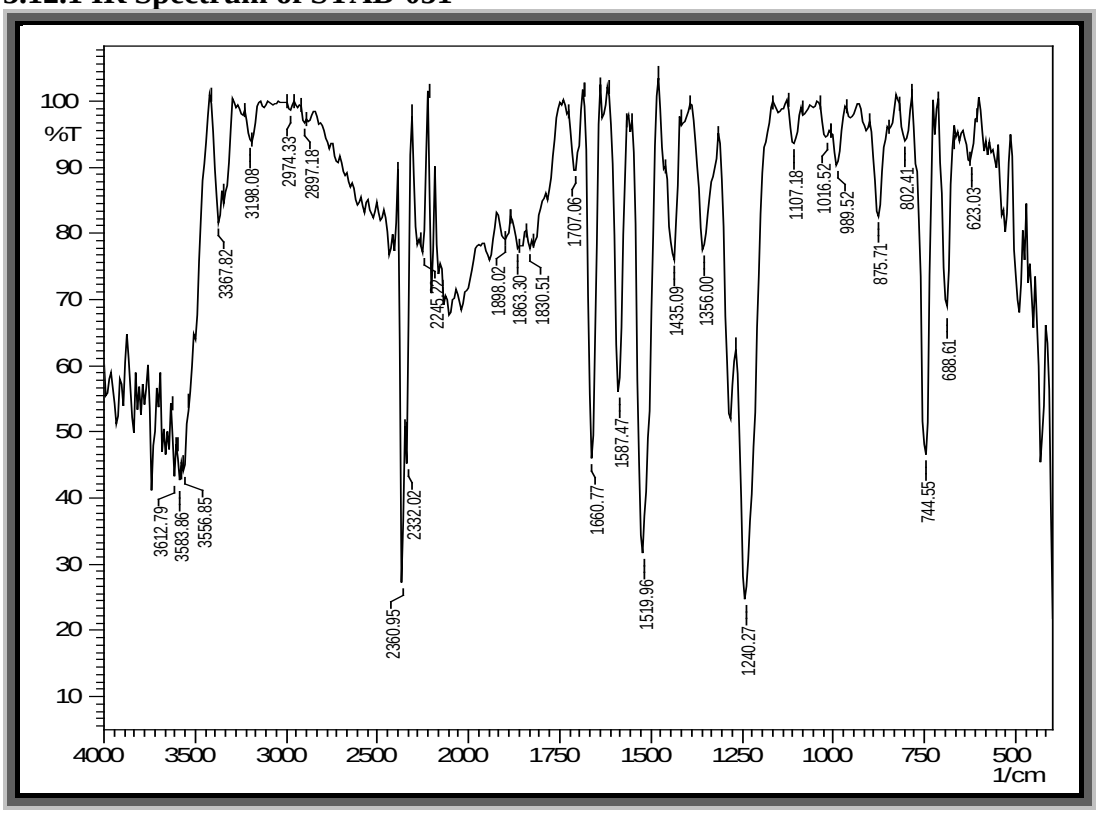
This chapter deals with the preparation of unsymmetric dihydropyridine by three component reaction using normal conventional methodologies. Ethyl acetoacetate/Methyl acetoacetate, methyl 3-aminocrotonate and Pyrazole aldehydes have been employed to synthesize these DHPs. Under normal conditions, the DHPs were prepared by refluxing the aldehydes, 3-aminocrotononitrile and Methyl acetyoacetate/Ethyl acetoacetate more than 10 hrs.

3.11 CONCLUSION

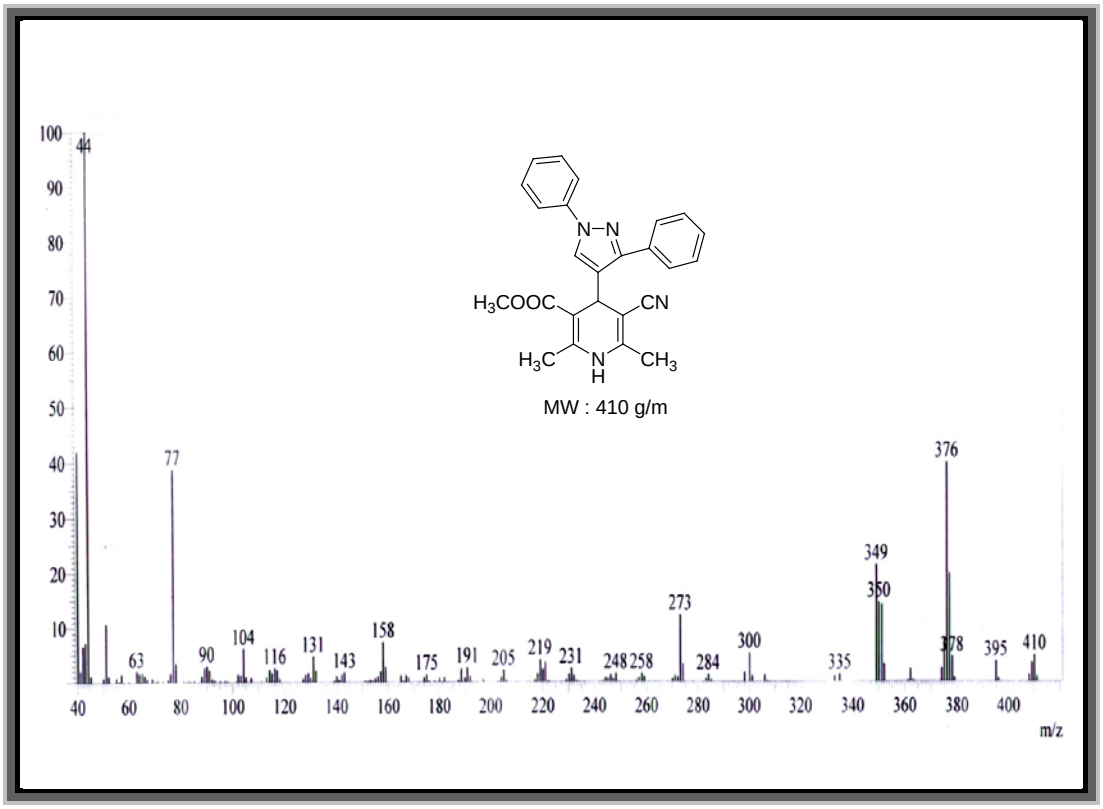
Our experimental protocols have developed an easy, faster and most convenient optimized conditions for preparing new dihydropyridines.

3.12 REPRESENTATIVE SPECTRAS

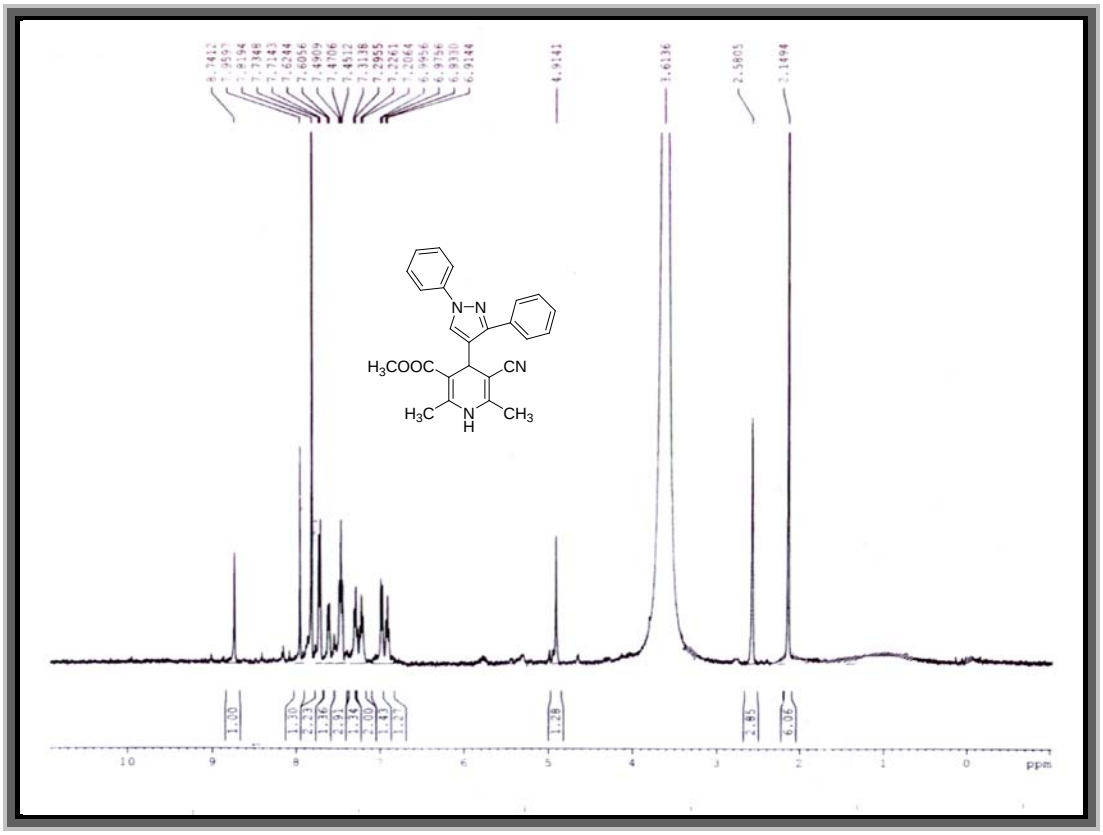
3.12.1 IR Spectrum of STAB-051



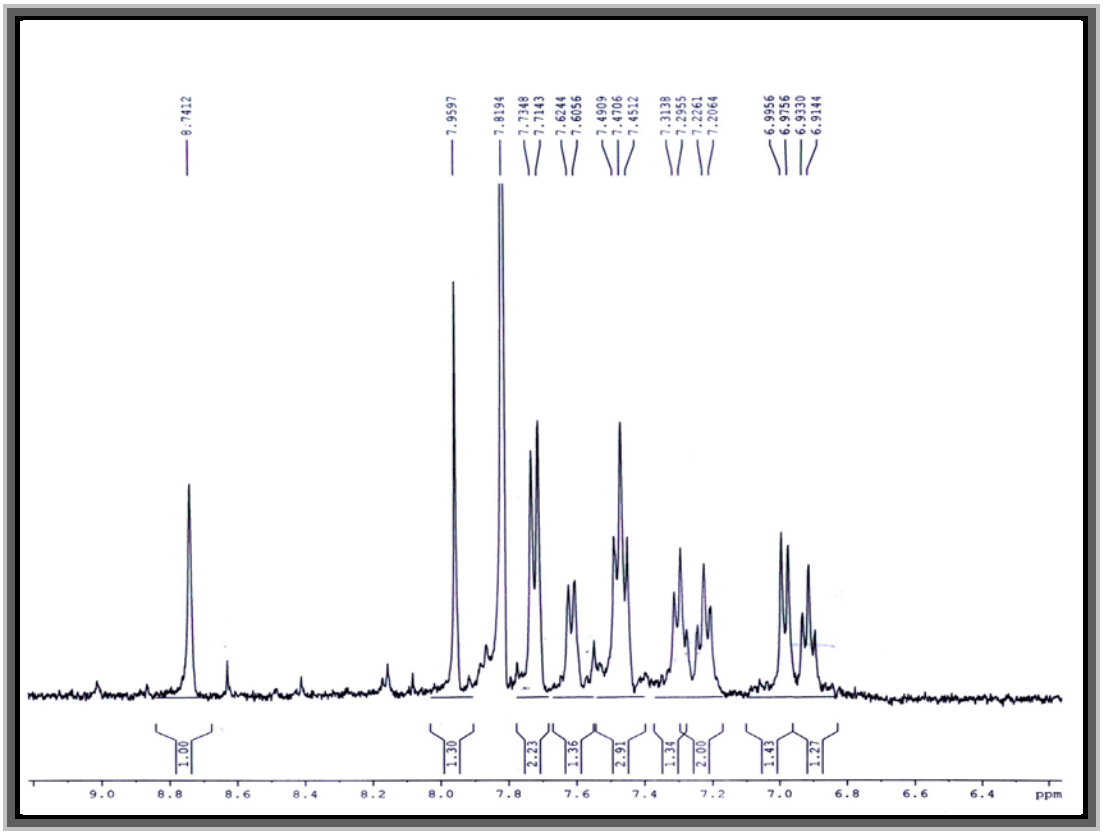
3.12.2 Mass Spectrum of STAB-051



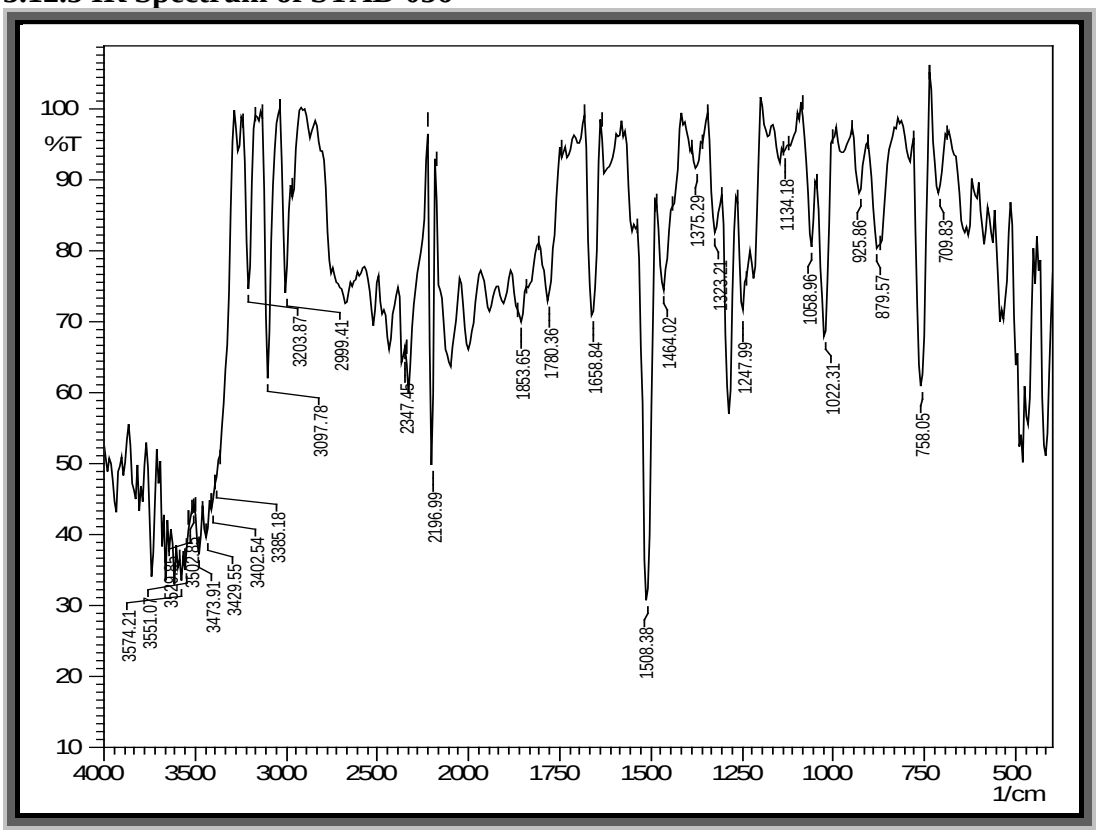
3.12.3 ^{1}H NMR Spectrum of STAB-051



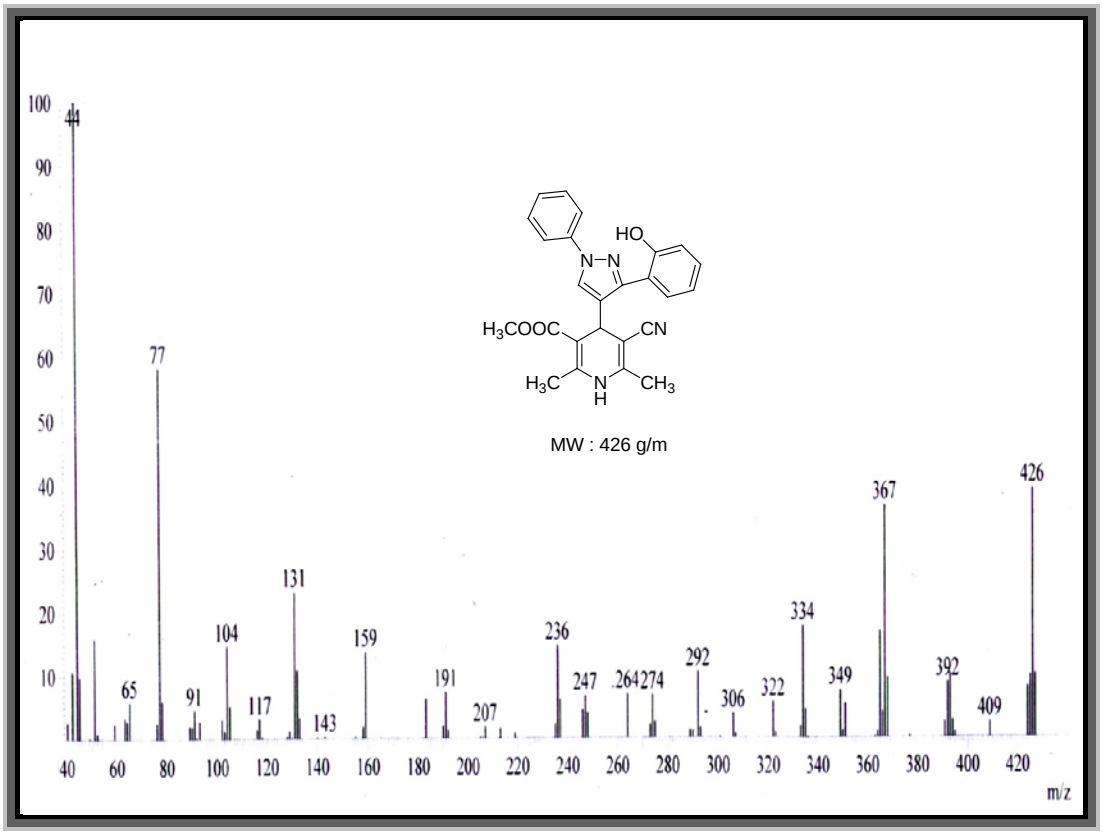
3.12.4 Expanded ^{1}H NMR Spectrum of STAB-051



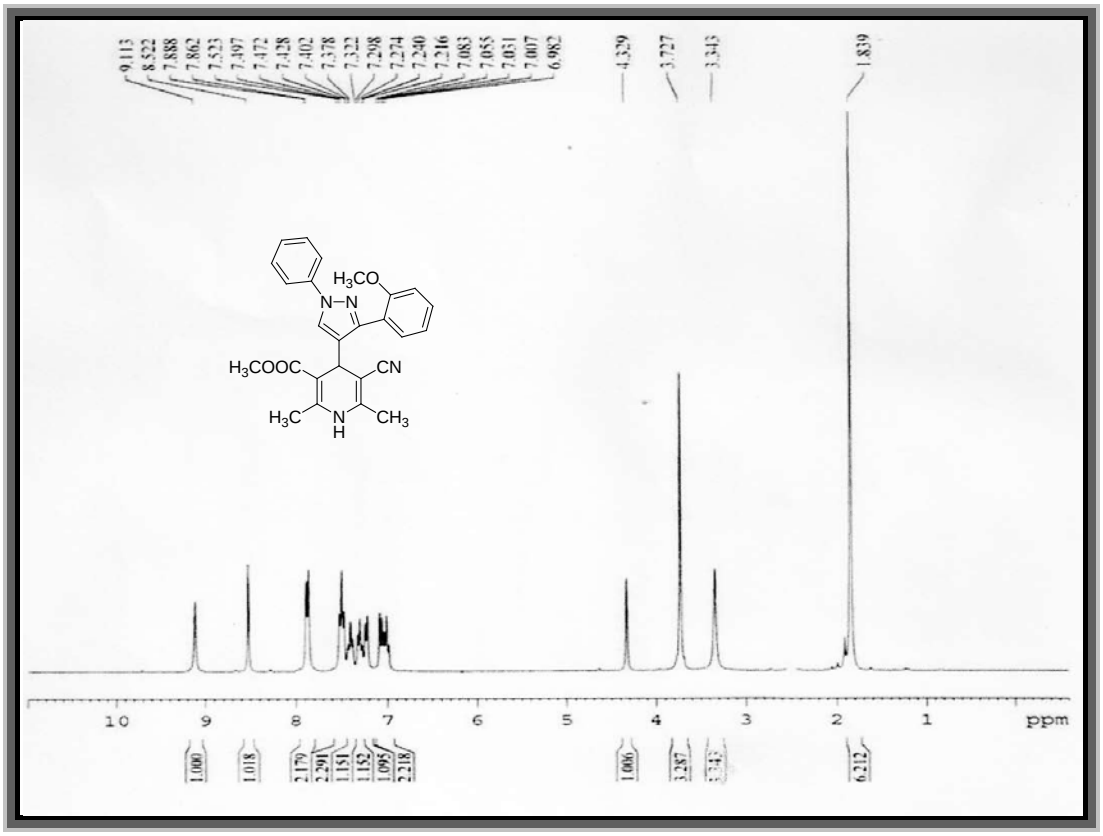
3.12.5 IR Spectrum of STAB-056



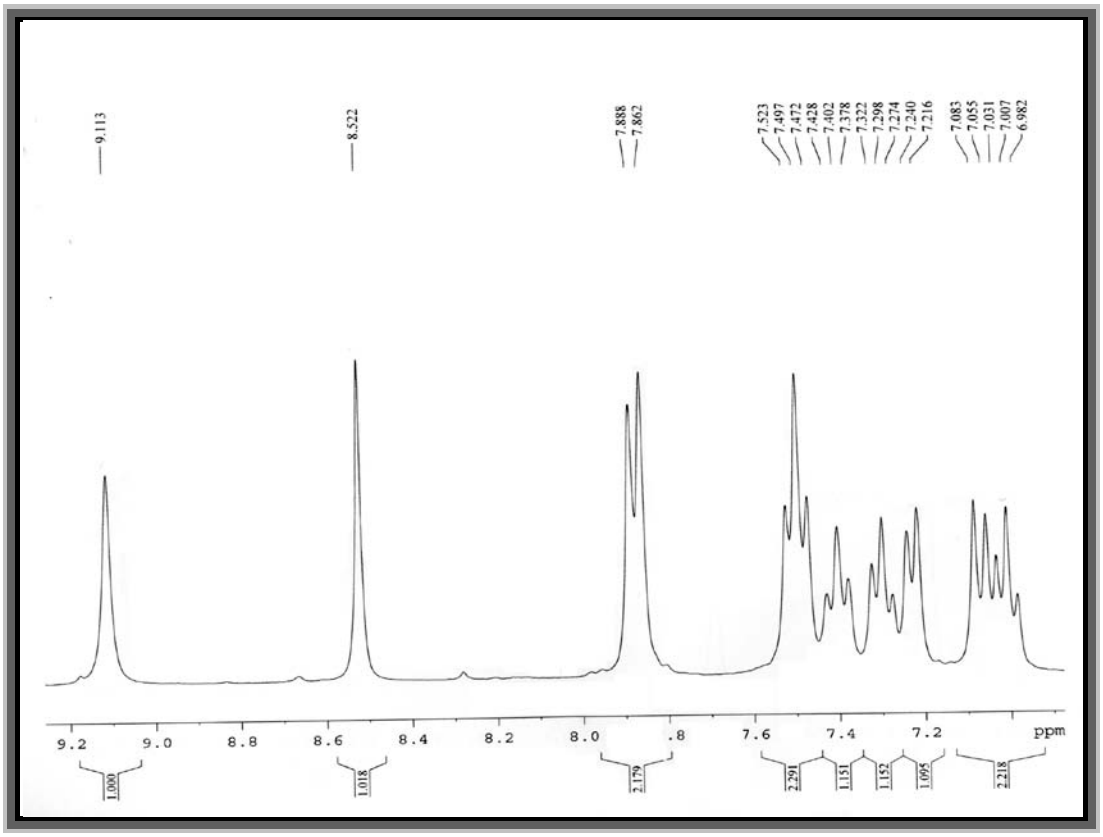
3.12.6 Mass Spectrum of STAB-055



3.12.7 ^{1}H NMR Spectrum of STAB-056



3.12.8 Expanded ^{1}H NMR Spectrum of STAB-056



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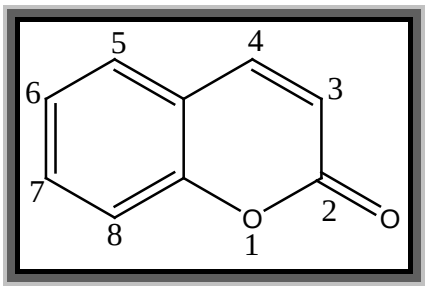
Chapter-4

A Rapid Microwave assisted synthesis of new coumarinyl chalcones.

4.1 INTRODUCTION

Coumarin is a chemical compound (2*H*-chromen-2-one, 1-benzopyran-2-one, benzopyrone; $C_9H_6O_2$); a toxin found in many plants, notably in high concentration in the tonka bean, vanilla grass, woodruff, mullein, and bison grass. It has a sweet scent, readily recognized as the scent of newly-mown hay, and has been used in perfumes since 1882. It has clinical medical value as the precursor for several anticoagulants, notably warfarin, and is used as a gain medium in some dye lasers.



The isolation of coumarin was first reported by Vogel [1] in 1820. He isolated coumarin from tonka beans, bearing the characteristic aroma of cutted grass. The name of coumarin originates [2] from a Caribbean word "*coumarou*" for the tonka tree, which was known botanically at one time as *Coumarouna odorta Aubl*, coumarin is now the accepted trival name. Coumarin was first synthesized in 1868 on treatment of sodium salt of o-hydroxy benzaldehyde with acetic anhydride.[3a, 3b] Compounds containing coumarin subunit possess a wide range of activities and show an interesting reactivity.[4-7] This is consequence of the rich electronic structure of coumarin which offers abundant possibilities for diversified activity and reactivity of the system.

4.1.1 SYNTHESIS OF 4-HYDROXY COUMARINS

Perkin [3] synthesized coumarin and then several methods are reported for the synthesis of 4-hydroxy coumarins and their 4-hydroxy substituted derivatives namely:

1 Anschutz method [8]

2 Pauli Lockemann synthesis [9]

3 Sonn's synthesis [10]

4 Mentzer's synthesis [11]

5 Robertson synthesis [12]

6 Ziegler and Junek method [13]

7 Garden's method [14]

8 Shah, Bose and Shah's method [15]

9 Kaneyuki method [16]

10 Resplandy's method [17]

11 Jain, Rohatagi and Sheshadri's method [18]

12 Shah, Bhatt and Thakor's method [19]

Shah and *et al.*[15, 19] have prepared 4-hydroxy coumarin derivatives in good yield by condensation of different phenols with malonic acid in the presence of zinc chloride and phosphorous oxychloride. The method is useful as single step preparation of 4-hydroxy coumarin derivatives substituted in benzenoid part.

Recently many researchers [20-51] have reported synthetic strategies for 4-hydroxy coumarin.

4.1.2 BIOLOGICAL ACTIVITIES

Numerous biological activities have been associated with coumarins and its analogues. Among them, antimicrobial, antiviral, anticancer, enzyme inhibition, anti-inflammatory, antioxidant, anticoagulant and effect on central nervous system are most prominent. Coumarin nucleus possesses diversified biological activities that can be briefly summarized as under:

1 Antimicrobial and Molluscicidal [52-73]
2 Antiviral [74-78]
3 Anticancer [79-89]
4 As Enzyme Inhibition [90-95]
5 Antioxidant [96-99]
6 Anti-inflammatory [100-104]
7 Anticoagulant and Cardiovascular [105-108]
8 Effect on Central Nervous System [109-111]

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 heterocycles. The synthetic versatility of 4-hydroxycoumarin has led to the extensive use of this compound in organic synthesis. 4-hydroxy coumarin shows diversified chemical reactivity. Preparation of 3-acetyl-4-hydroxycoumarinyl chalcones, condensation reaction of 4-hydroxycoumarin with aldehydes and use of 4-hydroxycoumarin as a β-keto ester in dihydropyrimidine synthesis have been discussed herein.

4.1.3 COUMARINYL CHALCONES

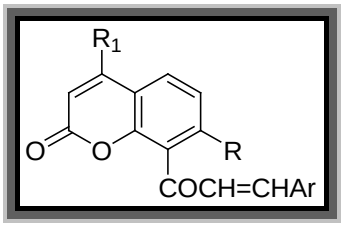
The compound 1, 3–diphenyl-2-propene-1-one is known by its trivial name chalcone. Many naturally occurring flavonoids share structural features with chalcone and are referred by the generic term “chalcones”. This is well illustrated by benzal-acetophenone or phenyl styryl ketone or phenyl acreloacetophenone named first time as chalcones by Kostanecki and Tambor. [112] Certain flavonoids also include chalcone subunit and found to have anticancer activity and chemopreventive activity in some tumors.

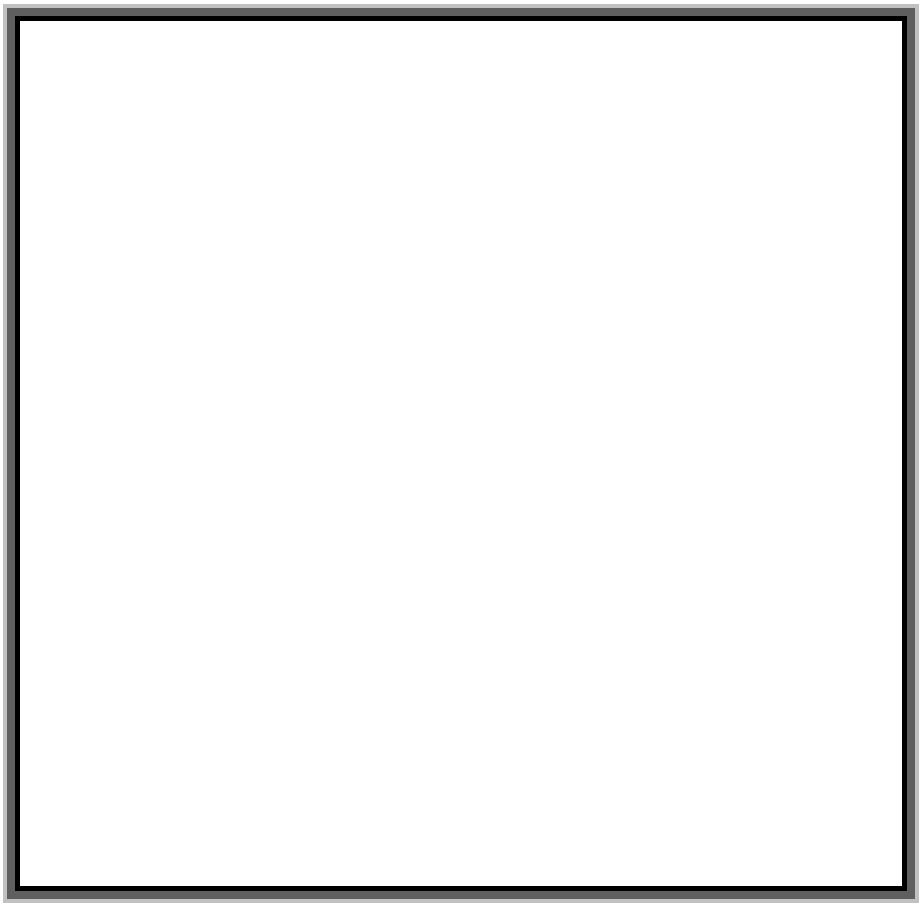
Additionally, some natural or synthetic chalcones are proved to have significant antiproliferation activity on different cell lines. Though the mechanism of antiproliferative activity of flavonoids and Chalcones is still unknown, it is believed to be linked with the interaction of type II estrogen receptors.

The *in vivo* action of these polyphenol substances is certainly much more complicated. All these compounds are generally characterized by an almost complete solubility in water and, *in vivo*, by a very poor bioavailability linked to a rapid metabolism of phenols and a marked affinity for lipids and proteins. It has now been found that certain novel chalcones, chalcone derivatives and chalcone analogues, in particular ones in which the phenyl ring at the 1st position is substituted or replaced by the rings containing one or more heteroatoms, possess greater antiproliferation activity both on sensitive cancer cells or on cells which are resistant to common chemotherapeutic drugs, including the latest generation of anti-neoplastic agents, pacitaxel and docetaxel.

In recent patent literature, compounds of the general formula shown in Fig. 4.10 are a pharmaceutically acceptable salt or solvate there of wherein Ar represents a substituted or unsubstituted, (preferably aromatic), carbocycilc or heterocyclic group, said carbocyclic or heterocyclic group containing from 5 to 10 ring atoms, said ring atoms forming one or two rings, wherein each ring contains 5 or 6 ring atoms, any heteroatoms being selected from N, O and S, any substituents on the Ar group being independently selected from the group consisting of: (a) Cl, (b) Br, (c) F, (d) OH, (e)

NO_2, (f) CF_3, (g) C_{1-4} lower alkyl (in particular CH_3), (h) SCH_3, (i) $NHCOCH_3$, (j) $N(R)(R_1)$ wherein R and R_1 are the same or different and each represents H or lower C_{1-4} alkyl.





Several 2'-hydroxy chalcones are found to exist as pigments. The natural chalcones are found to contain phloroglucinol, pyraogallol, catechol and hydroquinone nuclei. [113-117]

Chalcones contain keto-ethylenic linkage and therefore reactive towards reagents like phenyl hydrazine, hydrazine hydrate and ethyl acetoacetate to produce heterocyclic derivatives. Chalcones have close relationship to flavones, flavanones, flavanols and dihydroflavanols. They are useful as intermediates in the synthesis of certain heterocyclic compounds like flavones, anthocyanins and benzal coumarones. [118-121] Butein, phloretin and hissopin are found to be naturally occurring chalcones. Sometimes, chalcones are found to occur in nature as glycosides like carthamin and isocarthamin present in *Carthamus tinctorious*. [122]

2'-Hydroxy chalcones are used as starting material to synthesize naturally occurring flavanones, flavones, flavonols, etc. The chalcones are also natural biocides [123-125] and are well known intermediates in the synthesis of heterocyclic compounds exhibiting various biological activities like antimalarial, [126] antiviral, [127] antitumor, [128] herbicidal [129] and also bactericidal [130, 131] activities. They are also identified as antioxidants. [132]

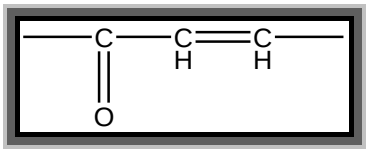
Curcumin is a yellow pigment isolated from the rhizome of the perennial herb *Curcuma longa L* (turmeric). The chemical structure of curcumin was elucidated by Lampe *et. al.* [133]

Curcumin has several biological activities. It possesses anti-inflammatory, antioxidant, antibacterial, antihepatotoxic, hypotensive and hypocholesterolemic properties. [134-137] Tonneses [138] describes curcumin as a non-toxic compound even at high dosages. It has a dual effect in oxygen radical reactions, thus it can act as a scavenger of hydroxyl radicals or catalyse the formation of hydroxyl radicals depending on the experimental conditions. [138, 139]

Curcumin inhibits *in vitro* lipid peroxide formation by liver homogenates of oedemic mice. [140] The inflammatory response induced experimentally in animals appeared to be correlated with disturbances of the regulation of cellular oxidative process, as is evident from the anti-inflammatory action of well known antioxidants. There is evidence of a parallel between the inhibition of aedema formation in mice induced by carrageenan and the decrease in the production of lipid peroxides in liver homogenate. [140] Modification of groups on the terminal aromatic rings of curcumin

reveals that electron donating groups increase anti-inflammatory activity. [141] The structural similarity of chalcone like molecules is expected to exhibit either antagonize or potentiate the biological activity in question and therefore it was very essential to study further, the coumarin derivatives possessing such ethylenic linkages-discussed earlier.

The Chalcones or Phenyl styryl ketones are α:β unsaturated ketones, containing the reactive keto-ethylenic group :



These compounds are also known as a benzylideneacetophenones or benzalacetophenones, which are named "Chalcones" by Kostanecki and J.Tambor [142],In American chemical society Abstracts, they are also termed as 3-phenyl acrylophenones, while 2'–hydroxyl – chalcones are known as O-cinnamoylphenols.

The presence of a keto-ethylenic linkage in general and in vicinity to a hydroxyl group in particular, has given these compounds a great synthetic importance.

The 2'-hydroxy chalcones are used as starting compounds to synthesize naturally occurring flavanones , flavones , flavanols etc.,and the unambiguous methods of synthesis are useful in arriving at the constitution of these naturally occurring pigments. The structure of chrysin, galangin, apegenin, lutionlin, kaempferol, morin and quercetrol were established by their synthesis from suitably substituted chalcone.[143]

Thus, Chalcones are intermediate compound useful for the synthesis of various heterocyclic compounds such as flavanones, flavanols, flavones anthocyanins, banzal coumaranones, phlobathannins as well as certain compounds like deoxybenzoins and hydantoins, which are of some therapeutic value.

Chalcones are natural boicides[144] and are well known intermediates in the synthesis of herterocyclic compounds exhibiting various biological activities[145]. The coumarins also show activity such as antifungal[146], anticoagulant[147], antibactarial[148] and insecticidal.[149]

Some flavanones and flavanols are reported to have stabilizing effect on vitamin A.[150] Setnikar *et al.*[151] reported that 3-methyl-6-diethylaminomethyl flavones are highly antispasmodic (about 14 times more active than papavarine).

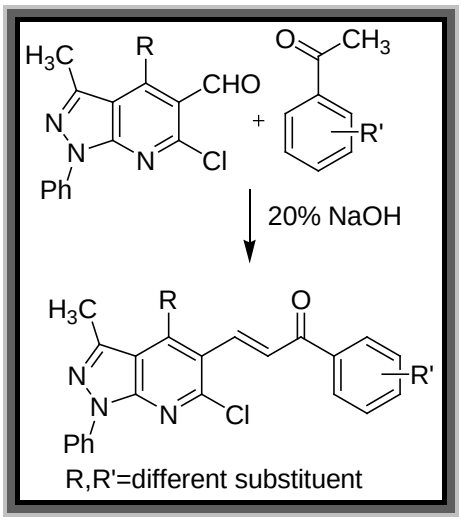
Schraufstatter *et al.*[152] who observed the bacterostatic activities of chalcones against S.Aureus, have tested a number of natural and synthetic chalconesm,flavanones,flavones and flavanols, and have concluded that the activity is due to their unsaturation.

α-Methyl chalcone and 4-chlorochalcones are patented as light stabilizing agents for polyvinylidene chloride or polyvinylidene polymers.[153]

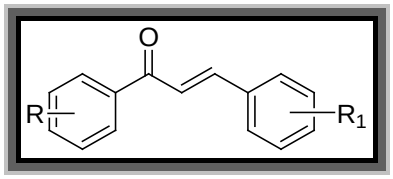
Berger *et al.*[154] have panted a preparation of light fast, water disperisible wood stain obtained from chalcones and flavanoid derivatives like hesperdin and narignain by the action of aluminium chloride in carbon disulphide. Enagaki and Hisada[155] have measured the anhelmintic coefficient of chalcones and their derivatives.

4.2 PREPARATION METHODS OF CHALCONES

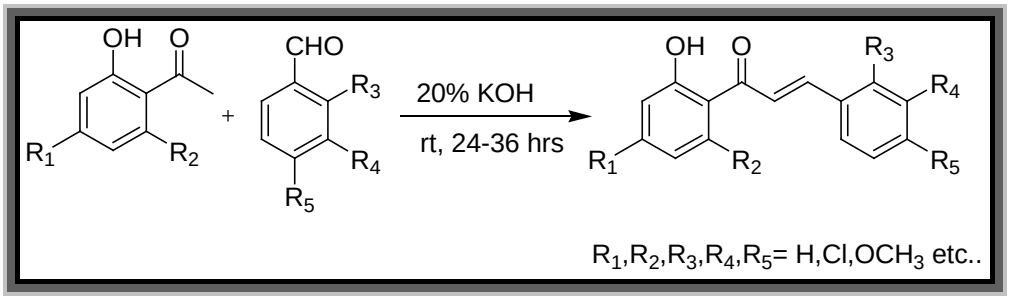
Jairo Quiroga *et al.*[156] reported the method for preparation of chalcones.



Daniela Batovska *et al.*[157] synthesized a large number chalcones and studied against Staphylococcus aureus and scherichia coli.



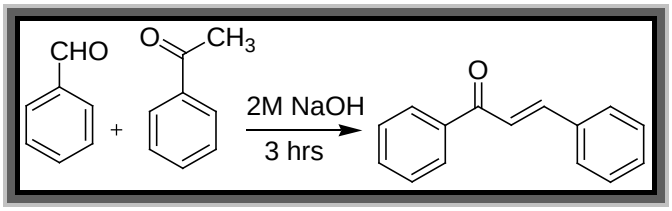
Anastasia Detsi *et al.*[158] reported method for synthesis of chalcones and also reported its antioxidant activity.



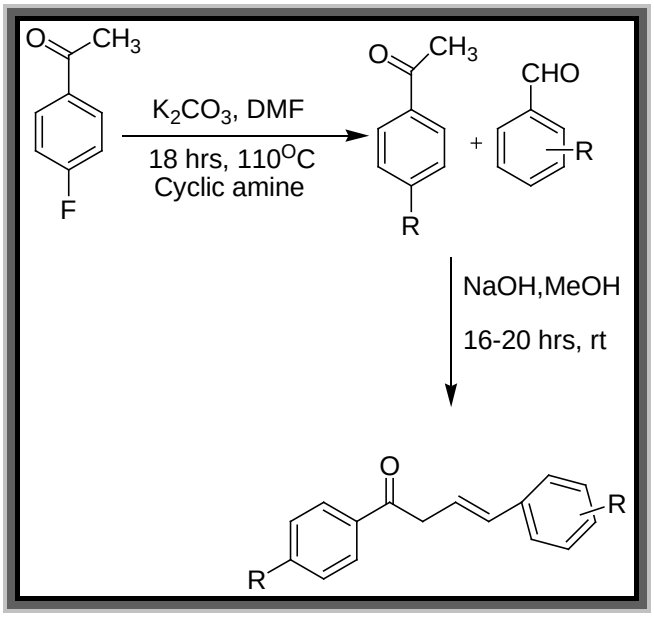
Bandgar *et al.*[159] reported a series of β-chloro vinyl chalcones which have been synthesized by Claisen–Schmidt condensation. All the compounds were

evaluated for their anti-inflammatory activity (against TNF-a and IL-6) and antimicrobial (antibacterial and antifungal) activity.

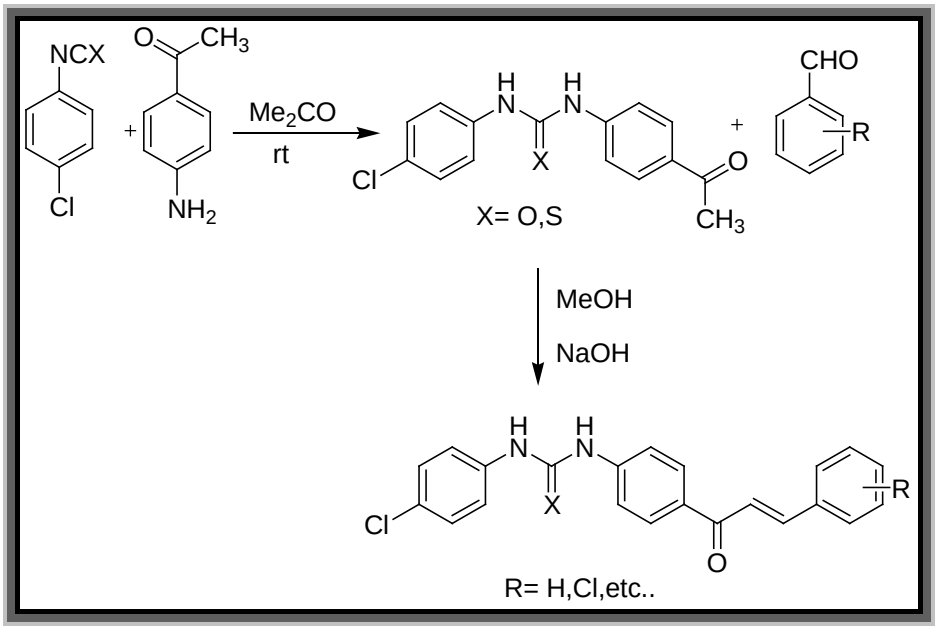
Shiva kumar *et al.*[160] reported the method and antimycobacterial activity for the synthesis of chalcones.



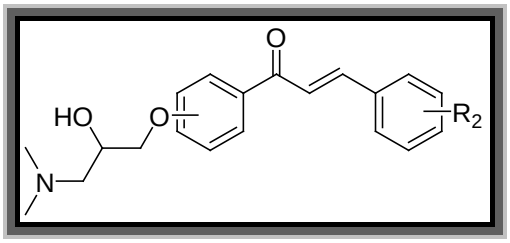
Nidhi Mishra *et al.*[161] have reported the Synthesis of novel substituted 1,3-diaryl propenone derivatives and their antimalarial activity in vitro.



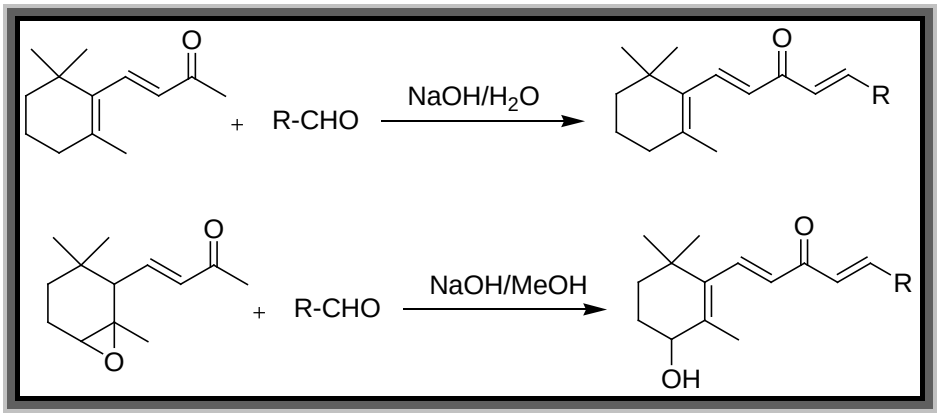
Lorena *et al.*[162] reported the Synthesis of new 1-phenyl-3-{4-[(2E)-3-phenylprop-2-enoyl]phenyl}-thiourea and urea derivatives with anti-nociceptive activity.



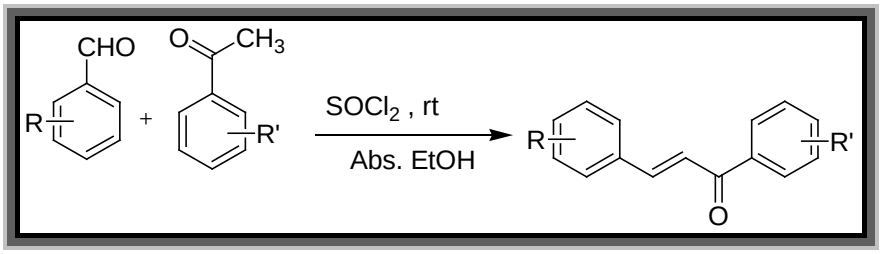
Satyanarayana *et al.*[163] have reported the Synthesis and antihyperglycemic activity of chalcone based aryloxypropanolamines.



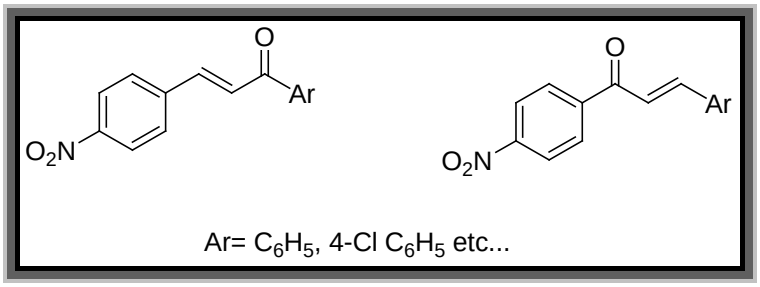
Jinming Zhou *et al.*[164]reported synthesis and potential anti-prostate cancer activities of ionone-based chalcones.



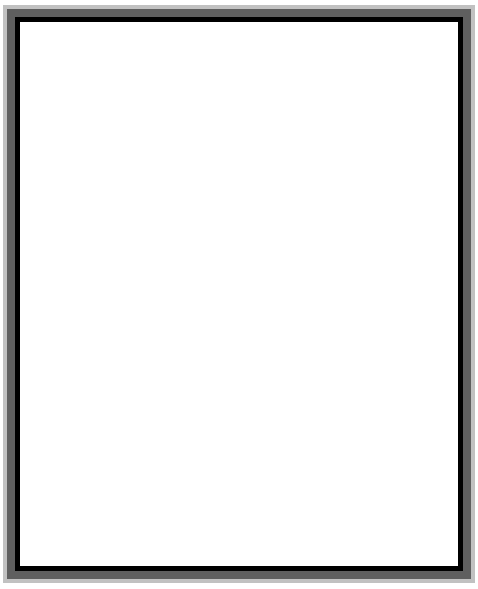
In the presence of $SOCl_2$/EtOH as a catalyst, various substituted chalcones are synthesized by aldol condensation. The HCl is generated in situ by the reaction of $SOCl_2$ with absolute ethanol[165].



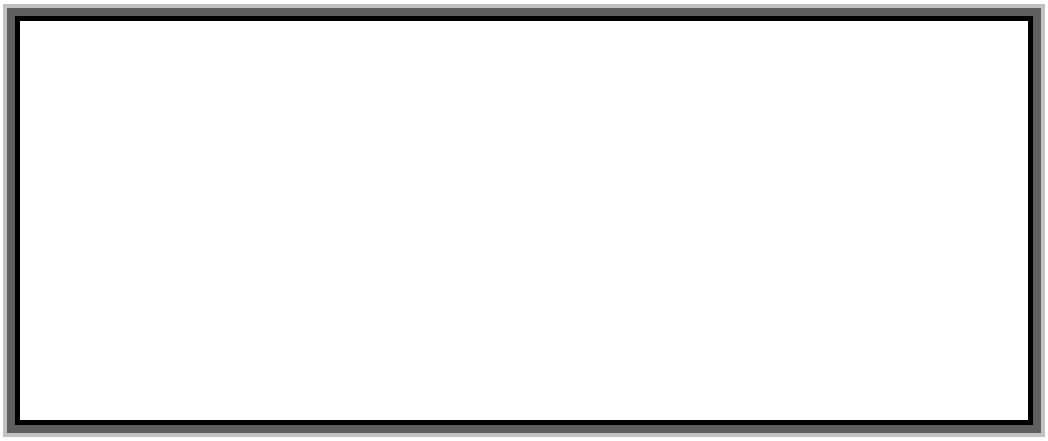
Romeo Romagnoli *et al.*[166] reported the synthesis of Hybrid α-bromoacryloylamido chalcones.



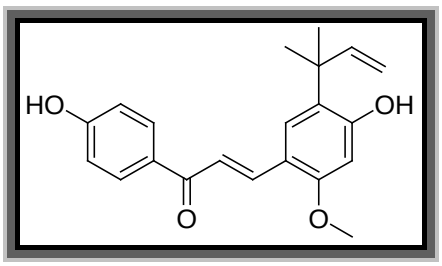
Said Eddarir *et al.*[167] reported an efficient synthesis of chalcones by Suzuki reaction.



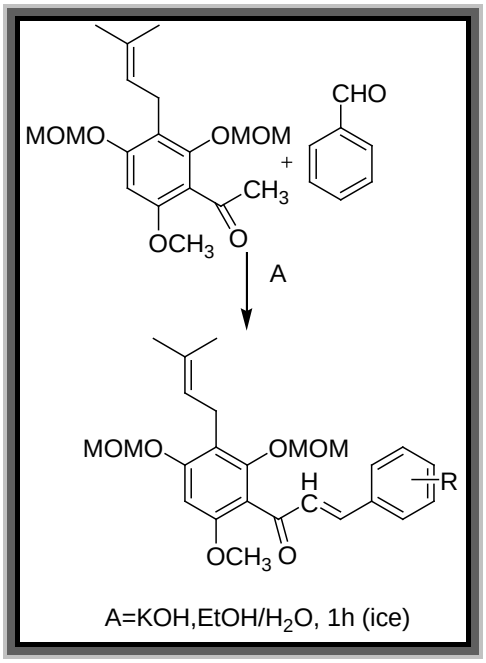
Narender *et al.*[168] reported a simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate. Chalcones are secondary metabolites of terrestrial plants, precursors for the biosynthesis of flavonoids and exhibit various biological activities. Condensation of substituted acetophenones with various aromatic aldehydes in the presence of BF_3–Et_2O at room temperature gave chalcones in good yields.



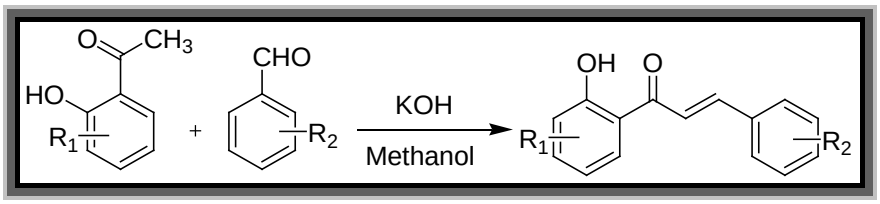
New series of chalcones have been synthesized by reacting 1-(4-piperazin-1-yl-phenyl) ethanone and 1-(2,5-dichloro-3-thienyl)-1-ethanone with different substituted benzaldehydes in turn by Claisen–Schmidt condensation. All the synthesized compounds have been evaluated for antimicrobial activity. Some of these derivatives are potentially active against Gram-positive bacteria[169].



Susanne *et al.*[170] reported a synthesis of chalcones. and also reported cytotoxicity and anti-oxidative activity.

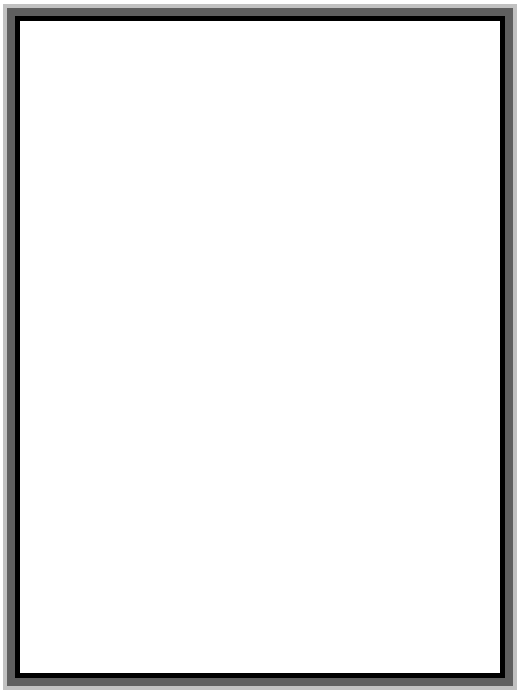


Hyun-Mo Yang *et al.*[171] reported the method for the synthesis of chalcone.



The inhibition of tyrosinase is one of the major strategies to treat hyperpigmentation. Various limitations are associated with many of these inhibitors, such as high cytotoxicity, poor skin penetration and low stability in formulations. In continuation of study, showing that isoliquiritigenin chalcone (ILC) is a potent tyrosinase inhibitor.

At this laboratory, the researchers of our group have reported the improved and rapid synthesis of new coumarinyl chalcones derivatives and their antiviral activity.[172]



4.3 TEST FOR CHALCONES

The Chalcones can be tested with simple chemical test. Few of them are listed as under.

(A) By Sulfuric Acid :- It develops red or bright orange colouration with concentrated sulfuric acid.

(B) By Ethanolic Ferric Chloride Solution :- Chalcones develops a red brown colouration with ethanolic ferric chloride.

(C) By Wilson Test :- A Solution of a Chalcone in dry acetone is first treated with citric acid and then boric acid is added in the absence of moisture. The addition of the latter develops gradually a deep red or orange colouration which is destroyed by a traces of water.

(D) Dibromo Derivatization :- The Chalcones are also well confirmed by their dibromo derivatives formed on treatment with bromine in acetic acid.

4.4 AIM OF CURRENT WORK

Microwave assisted organic synthesis has drawn a remarkable attention of researchers towards its advantages. There are many reactions reported involving microwave assisted organic synthesis. Microwave chemistry is one of the best tools to carry out different reactions on desired molecules with lesser reaction time, lesser energy, easy work up and higher yield with better purity.

In this chapter, the coumarinyl chalcones were aimed at using microwave assisted method.

4.5 REACTION SCHEMES

4.5.1 PREPARATION OF PYRAZOLE ALDEHYDES :

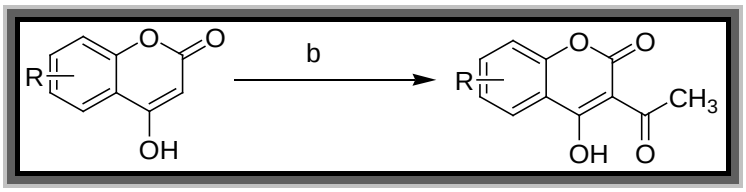
It was prepared according to method described in Chapter-1

4.5.2 PREPARATION OF 3-ACETYL 4-HYDROXY COUMARINS :

STEP-1 :

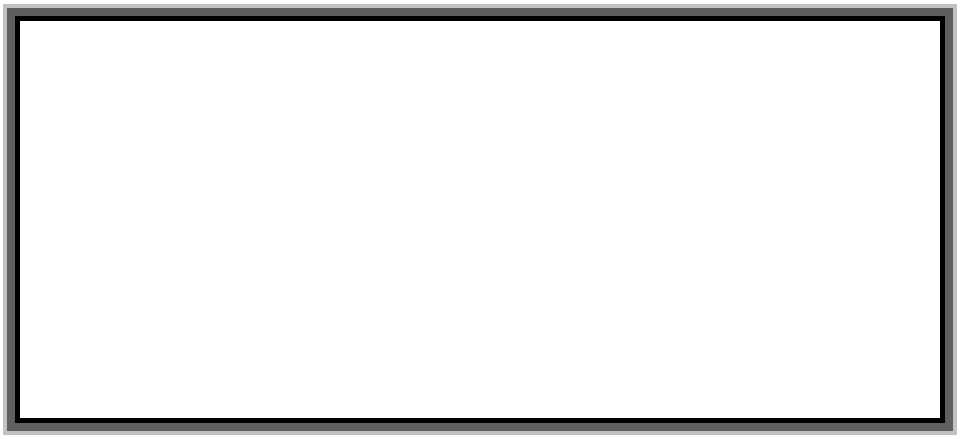
Reagents / Reaction Condition (A): Anhydrous $ZnCl_2$, $POCl_3$ / 70°C, 36 hours.

STEP-2 :



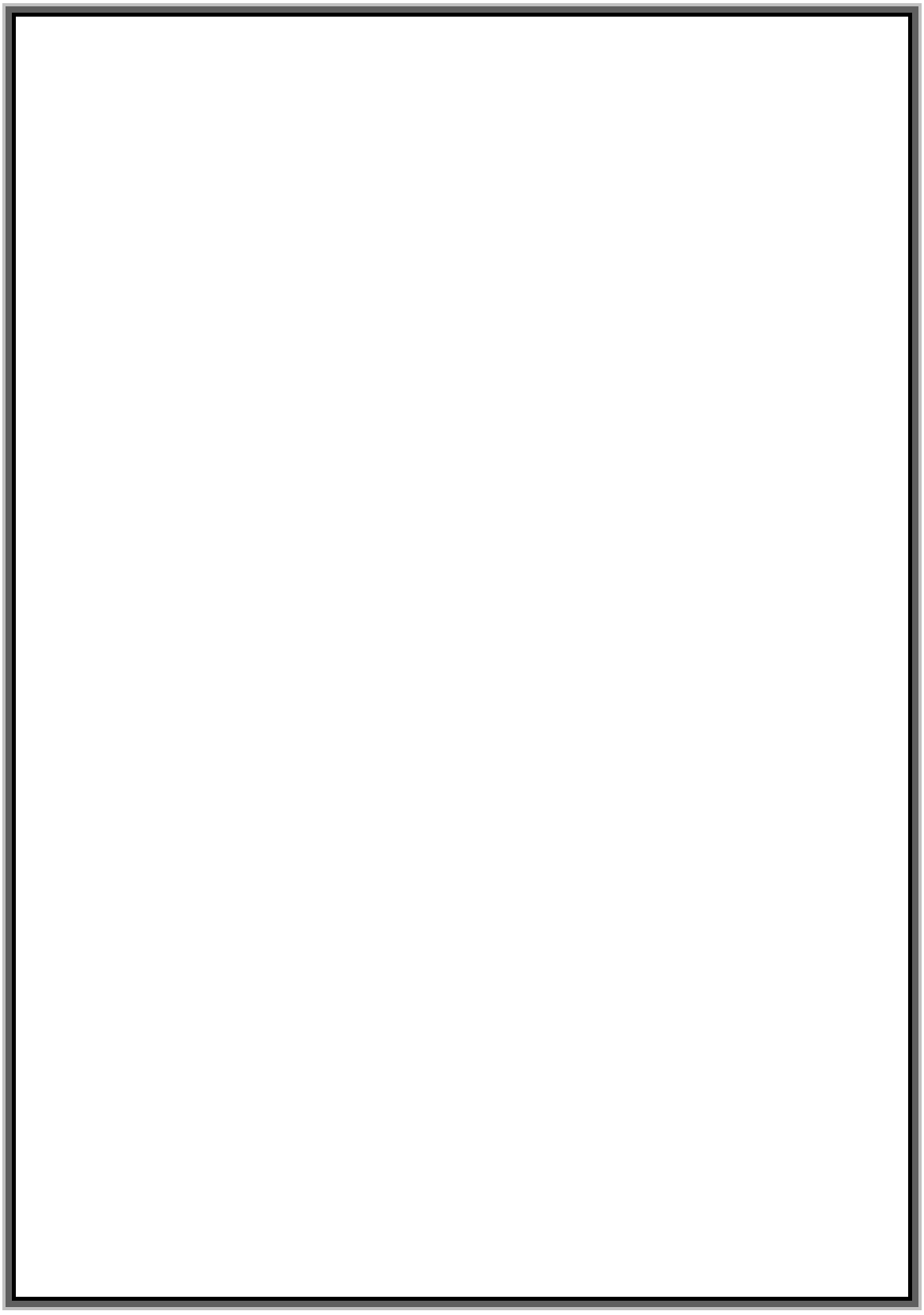
Reagents / Reaction Condition (b) : $POCl_3$, Glacial acetic acid / Reflux, 2-3 hrs.

4.5.3 PREPARATION OF 4-HYDROXY-3-((E)-3-(1-PHENYL-3-(SUBSTITUTED)-1H-PYRAZOL-4-YL) ACRYLOYL)-2H-CHROMEN-2-ONES.



Reagents / Reaction Condition (c): MW (320 Wt),Piperidine, Chloroform, 10-15 min.

4.6 PLAUSIBLE REACTION MECHANISM



4.7 EXPERIMENTAL

4.7.1 MATERIALS AND METHODS

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. All the reactions were carried out in **Q-pro microwave synthesizer.** IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr pellet 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 solution on a **Bruker Ac 400 MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model and the results are in agreements with the structures assigned.

4.7.2 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

4.7.3 PREPARATION OF 3-ACETYL 4-HYDROXY COUMARINS :

GENERAL METHOD

STEP-1

Phenol (0.01mole) and malonic acid (0.01mole) were added to a mixture of phosphorous oxychloride (40ml) and anhydrous zinc chloride (30gm) which is preheated to $600^{O}C$ and the reaction mixture was heated on a water bath at $70^{O}C$ for 36 hrs. It was cooled and decomposed with ice and water to afforded solid mass, which was filtered and washed with water. It was then treated with 10% sodium bicarbonate and filtered. The filterate was slowly acidify with dilute hydrochloric acid. At the neutral point, some oily product was separated which was filtered and washed with water, dried and recrystallized from ethanol as colourless needles. Yield. 60% m.p. $210^{O}C$.

Similarly other compounds are also prepared.

STEP-2

4-hydroxy coumarin (0.017 mole) was mixed with glacial acetic acid (15 ml), and phosphorous oxychloride (14ml) was added slowly, the mixture was further reflux for 2-3 hrs. and then poured on crushed ice with stirring. The solid separated out was filtered, washed with water and crystallize from alcohol. Yield.65% m.p. $117^{O}C$

Similarly other compounds are also prepared.

4.7.4 PREPARATION OF 4-HYDROXY-3-((E)-3-(1-PHENYL-3-(SUBSTITUTED)-1H-PYRAZOL-4-YL) ACRYLOYL)-2H-CHROMEN-2-ONE

GENERAL METHOD

A mixture of 3-Acetyl 4-hydroxy coumarin (0.01mole) and substituted aromatic aldehyde (0.01mole) were dissolved in 30 ml of chloroform. The catalytic amount of piperidine (0.02 ml) was added and the reaction mixture was subjected to microwave for a specific time (see Physical data table) at lower power (320W).The progress of the reaction was monitored by TLC examination at an interval of every minutes. On completion of reaction distilled out excess of chloroform and cool it and add methanol to it, filter it and wash with methanol, dried.

Similarly other compounds are also prepared.

The physical constants of newly synthesized compounds are given in the Table No. 4

4.8 PHYSICAL DATA

Physical data of 4-Hydroxy-3-((E)-3-(1-phenyl-3-(substituted)-1H-pyrazol-4-yl) acryloyl)-2H-chromen-2-ones.

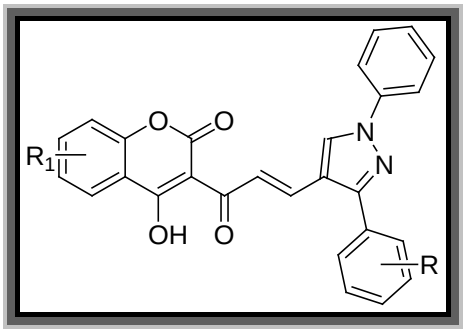


TABLE - 4

Code	Substitution		MF	MW	M.P.	Rf Value	Time
	R	R_1					
SAT-01	H	H	$C_{27}H_{18}N_2O_4$	434	186-188	0.40	8
SAT-02	4-CH_3	H	$C_{28}H_{20}N_2O_4$	448	172-174	0.43	5
SAT-03	2-OCH_3	H	$C_{27}H_{18}N_2O_5$	450	198-200	0.43	9
SAT-04	4-NO_2	H	$C_{27}H_{17}N_3O_6$	479	174-176	0.42	7
SAT-05	2-OCH_3	H	$C_{28}H_{20}N_2O_5$	464	172-174	0.44	11
SAT-06	4-Cl	H	$C_{27}H_{17}ClN_2O_4$	468	184-186	0.43	14
SAT-07	3-NO_2	H	$C_{27}H_{17}N_3O_6$	479	202-204	0.47	7
SAT-08	4-F	H	$C_{27}H_{17}FN_2O_4$	452	192-194	0.42	9
SAT-09	H	8-CH_3	$C_{28}H_{20}N_2O_4$	448	218-220	0.44	8
SAT-10	4-CH_3	8- CH_3	$C_{29}H_{22}N_2O_4$	462	178-180	0.47	7
SAT-11	4-Cl	8- CH_3	$C_{28}H_{19}ClN_2O_4$	482	212-214	0.42	5
SAT-12	4-NO_2	8- CH_3	$C_{28}H_{19}N_3O_6$	493	166-168	0.45	5
SAT-13	2-OH	8- CH_3	$C_{28}H_{20}N_2O_5$	464	158-160	0.43	3
SAT-14	2-OCH_3	8- CH_3	$C_{29}H_{22}N_2O_5$	478	192-194	0.40	7
SAT-15	3-NO_2	8- CH_3	$C_{28}H_{19}N_3O_6$	493	200-202	0.40	8
SAT-16	4-F	8- CH_3	$C_{28}H_{19}FN_2O_4$	466	218-220	0.43	5
SAT-17	H	5,8-di CH_3	$C_{29}H_{22}N_2O_4$	462	188-190	0.43	9
SAT-18	4-CH_3	5,8-di CH_3	$C_{30}H_{24}N_2O_4$	476	210-212	0.42	6
SAT-19	4-Cl	5,8-di CH_3	$C_{29}H_{21}ClN_2O_4$	496	204-206	0.44	8
SAT-20	4-NO_2	5,8-di CH_3	$C_{29}H_{21}N_3O_6$	507	186-188	0.43	7
SAT-21	2-OH	5,8-di CH_3	$C_{29}H_{22}N_2O_5$	478	176-178	0.47	5
SAT-22	2-OCH_3	5,8-di CH_3	$C_{30}H_{24}N_2O_5$	492	192-194	0.42	9
SAT-23	3-NO_2	5,8-di CH_3	$C_{29}H_{21}N_3O_6$	507	196-198	0.48	7
SAT-24	4-F	5,8-di CH_3	$C_{29}H_{21}FN_2O_4$	480	202-204	0.49	8

R_f value was determined using solvent system = Hexane : Ethyl Acetate (2 : 3)

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 pallet method. Various functional groups present were identified by characteristic frequency obtained for them.

The characteristic bands of Hydroxyl groups were obtained for streching at 3400-3650 cm^{-1} and those for bending were obtained at 1050-1250 cm^{-1}. It gives aromatic C-H stretching frequencies between 3000-3200 cm^{-1} and bending vibration near 1300-1500 cm^{-1} respectively. C-H stretching frequencies for methyl and methylene group were obtained near 2950 cm^{-1} to 2850 cm^{-1}. The Characteristic frequency of C=C (Vinyl) stretching showed near 900-1000 cm^{-1}.

4.9.2 MASS SPECTRA

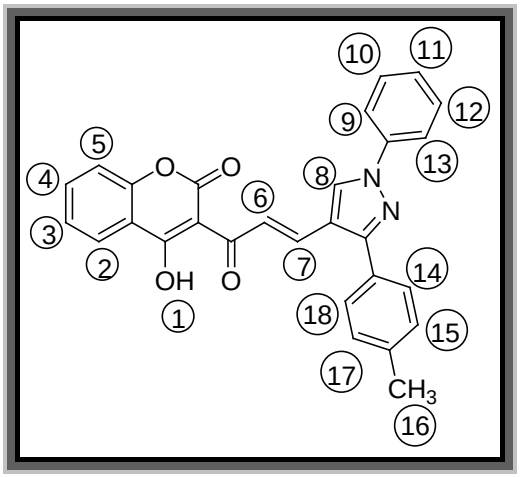
Mass spectra of the synthesized compounds were recorded on **Shimadzu GC-MS QP-2010** model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. Fragmentation pattern can be observed to be particular for these compounds and the characteristic peaks obtained for each compound.

4.9.3 ^{1}H NMR SPECTRA

^{1}H NMR spectra of the synthesized compounds were recorded on **Bruker Avance II 400 spectrometer** by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons and carbons identified from NMR spectrum 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 and it gives approximately 8.0 Hz which indicates the presence of **cis isomers** of compounds. In some cases, aromatic protons were obtained as multiplet. ^{1}H spectral interpretation can be discussed as under.

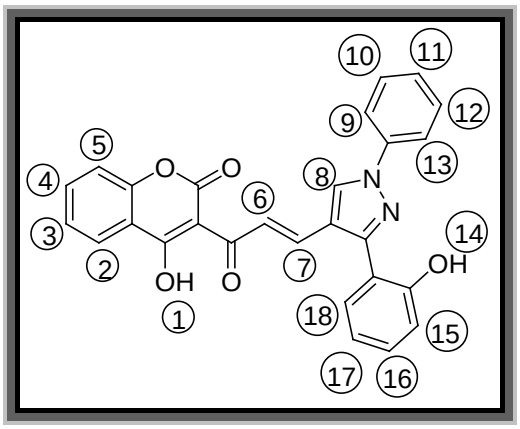
^{1}H NMR of 4-Hydroxy-3-((E)-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-02)



1. Proton no. 16 of 1H gave a singlet at 2.16 δ ppm.
2. Proton no. 3 of 1H gave a doublet at 7.04 δ ppm – 7.07 δ ppm.
3. Proton no. 6 and 7 of 2H gave a doublet at 7.08 δ ppm and 7.09 δ ppm respectively which shows the presence of CH=CH cis isomer.
4. Proton no.10, 11 and 12 of 3H gave a multiplate at 7.23 δ ppm – 7.27 δ ppm
5. Proton no. 9 and 13 of 2H gave a triplet at 7.38 δ ppm- 7.40 δ ppm.
6. Proton no. 15 and 17 of 2H gave a doublet at 7.44 δ ppm and 7.46 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
7. Proton no.5 of 1H gave a triplet at 7.51 δ ppm- 7.56 δ ppm.
8. Proton no. 3 of 1H gave a doublet at 7.59 δ ppm - 7.63 δ ppm.
9. Proton no. 14 and 18 of 2H gave a doublet at 7.70 δ ppm -7.72 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
10. Proton no. 2 of 1H gave a doublet at 8.08 δ ppm – 8.10 δ ppm.
11 Proton no. 8 of pyrazol ring of 1H gave a singlet at 8.46 δ ppm.
12. Proton no. 1 of 1H is become highest deshielded and did not appear till 10 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 no. SAT-02 has been confirmed. The spectrum is given on page no. 159.

^{1}H NMR of 4-Hydroxy-3-((E)-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-03)



1. Proton no. 14 of 1H gave a singlet at 7.14 δ ppm.
2. Proton no. 3 of 1H gave a triplet at 7.16 δ ppm – 7.19 δ ppm.
3. Proton no. 10, 11 and 12 of 3H gave a multiplate at 7.21 – 7.36 δ ppm.
4. Proton no. 6 and 7 of 2H gave a doublet at 7.45 δ ppm – 7.47 δ ppm.
5. Proton no. 4 of 1H gave a triplet at 7.48 δ ppm – 7.50 δ ppm.
6. Proton no. 15,16,17 and 18 of 4H gave a multiplate at 7.58 δ ppm – 7.76 δ ppm.
7. Proton no. 9 and 13 of 2H gave a doublet at 7.77 δ ppm – 7.79 δ ppm.
8. Proton no. 5 of 1H gave a doublet at 7.95 δ ppm – 7.99 δ ppm.
9. Proton no. 2 of 1H gave a doublet at 8.06 δ ppm – 8.08 δ ppm.
10. Proton no. 8 of 1H gave a singlet at 8.42 δ ppm.
11. Proton no. 1 of 1H is become highest deshielded and did not appear till 10 δ ppm.

Thus, by observing and assigning the signal 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 no. SAT-03 has been confirmed. The spectrum is given on page no. 161.

4.9.4 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 spectral and elemental analysis data for individual compounds synthesized in this chapter are mentioned below.

4.10 ANALYTICAL DATA

4-Hydroxy-3-((E)-3-(1,3-di phenyl-1H-pyrazol-4-yl) acryloyl)-2H-chromen-2-one. (SAT-01)

Yield: 84 % IR (cm^{-1}): 3587 (OH stretching), 3101, 3015 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2898 (Aliphatic -CH_2 stretching), 1708 (C=O Stretching), 1497, 1433, 1363 (C-H bending), 1291, 1236, 1215, 1134 (OH bending), 987,933 (C=C stretching), 690(monosubstituted), MS: *m/z:* 434.44(M^+); Anal. Calcd. for $C_{27}H_{18}N_2O_4$: C, 74.64; H, 4.18; N,6.45; O,14.73; Found: C, 74.60; H, 4.06; N, 6.31; O,14.69.

4-Hydroxy-3-((E)-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4yl)acryloyl)-2H-chromen-2-one. (SAT-02)

Yield: 72% IR (cm^{-1}): 3581,3522 (OH stretching), 3001 (Aromatic C-H stretching), 2968 (Aliphatic -CH_3 stretching), 2897 (Aliphatic -CH_2 stretching), 1707 (C=O Stretching), 1498,1431,1383 (C-H bending),1290, 1226,1205,1139 (OH bending), 997,923 (C=C stretching), 731(disubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 2.16 (s, 1H), 7.04-7.07 (d, 1H) 7.08-7.09 (d, 2H), 7.23-7.27 (m, 3H), 7.38-7.40 (t, 2H), 7.44-7.46 (d,2H, J=8.0Hz), 7.51-7.56 (t, 1H), 7.59-7.63(d, 1H), 7.70-7.72 (d, 2H, J=8.0Hz), 8.08-8.10 (d, 1H), 8.46 (s, 1H), MS: *m/z:* 448.47(M^+); Anal. Calcd. for $C_{28}H_{20}N_2O_4$: C, 74.99; H, 4.50; N,6.25; O, 14.27 ; Found: C, 74.89; H, 4.40; N, 6.19; O, 14.18.

4-Hydroxy-3-((E)-3-(3-(2-hydroxypenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-03)

Yield: 68% IR (cm^{-1}): 3581,3477 (OH stretching), 3194,3084 (Aromatic C-H stretching), 3003 (Aliphatic -CH_3 Stretching), 2899 (Aliphatic -CH_2 Stretching), 1705 (C=O Stretching), 1454,1429,1294 (C-H bending),1226,1138,1062 (OH bending), 819,761 (C=C stretching), 756(disubstituted), 690(monosubstituted), ^1H NMR (DMSO-d_6) δ ppm: 7.14 (s, 1H), 7.16 - 7.19 (t, 1H), 7.21 - 7.36 (m, 3H), 7.45 - 7.47 (d, 2H), 7.58 -7.76 (m, 4H), 7.77 - 7.79 (d, 2H), 7.95 – 7.99(d, 1H) , 8.06 – 8.08(d, 1H), 8.42(s, 1H), MS: *m/z:* 450.44(M^+); Anal. Calcd. for $C_{27}H_{18}N_2O_5$: C, 71.99; H, 4.03; N, 6.22; O,17.76 Found: C, 71.89; H, 4.01; N, 6.10; O,17.66.

4-Hydroxy-3-((E)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-04)

Yield: 58% IR (cm^{-1}): 3582, 3532 (OH stretching), 3031,3010 (Aromatic C-H stretching), 2966 (Aliphatic -CH_3 stretching), 2887 (Aliphatic -CH_2 stretching), 1717 (C=O Stretching), 1545 (C-NO_2 stretching), 1499, 1433, 1373 (C-H bending), 1291, 1236,(OH bending), 996 (C=C stretching), 745(disubstituted), 689 (monosubstituted), MS: *m/z:* 479.44(M^+); Anal. Calcd. for $C_{27}H_{17}N_3O_6$: C, 67.64; H, 3.57; N, 8.76; O, 20.02 Found: C, 67.54; H, 3.45; N, 8.70; O, 20.00.

4-Hydroxy-3-((E)-3-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-05)

Yield: 83% IR (cm^{-1}): 3571 (OH stretching), 3101, 3010 (Aromatic C-H stretching), 2961 (Aliphatic -CH_3stretching), 2891 (Aliphatic -CH_2 stretching), 1727 (C=O Stretching), 1497, 1432, 1384 (C-H bending), 1291, 1227,1215,1149 (OH bending), 987,913 (C=C stretching), 731(disubstituted),705 (monosubstituted), MS: *m/z:* 464.47(M^+); Anal. Calcd. for $C_{28}H_{20}N_2O_5$: C, 72.41; H, 4.34; N, 6.03; O,17.22 Found: C, 72.23; H, 4.29; N, 6.00; O, 17.13.

3-((E)-3-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-4-hydroxy-2H-chromen-2-one. (SAT-06)

Yield: 64% IR (cm^{-1}): 3582, 3532 (OH stretching), 3011 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2887 (Aliphatic -CH_2 stretching), 1707 (C=O Stretching), 1498, 1432, 1393 (C-H bending), 1291, 1236, 1215, 1149 (OH bending), 987,925 (C=C stretching), 755(disubstituted),715 (monosubstituted), MS: *m/z:* 468 (M^+), 470 (M^{+2}); Anal. Calcd. for $C_{27}H_{17}ClN_2O_4$: C, 69.16; H, 3.65; N, 5.97; O, 13.65 Found: C, 69.11; H, 3.57; N, 5.85; O, 13.60.

4-Hydroxy-3-((E)-3-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-07)

Yield: 84% IR (cm^{-1}): 3561, 3532 (OH stretching), 3121 (Aromatic C-H stretching), 2969 (Aliphatic -CH_3 stretching), 2890 (Aliphatic -CH_2 stretching), 1717 (C=O Stretching), 1551 (C-NO_2 stretching), 1499, 1432, 1373 (C-H bending), 1291, 1236, 1215, 1149 (OH bending), 998,943 (C=C stretching), 731(disubstituted), 688(monosubstituted), MS: *m/z:* 479.44(M^+); Anal. Calcd. for $C_{27}H_{17}N_3O_6$: C, 67.64; H, 3.57; N, 8.76; O, 20.02 Found: C, 67.54; H, 3.46; N, 8.71; O, 20.00.

3-((E)-3-(3-(4-flourophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-4-hydroxy-2H-chromen-2-one. (SAT-08)

Yield: 73% IR (cm^{-1}): 3566, 3542 (OH stretching), 3021 (Aromatic C-H stretching), 2989 (Aliphatic -CH_3 stretching) 2898 (Aliphatic -CH_2 stretching), 1707 (C=O stretching), 1489, 1442,1372 (C-H bending), 1281, 1246, 1205, 1159 (OH bending), 988,942 (C=C stretching), 739(disubstituted), 712(monosubstituted), MS: *m/z:* 452(M^+), 454 (M^{+2}) ; Anal. Calcd. for $C_{27}H_{17}FN_2O_4$: C,71.68; H, 3.79; N,6.19; O,14.15 Found: C, 71.63; H, 3.59; N, 6.17; O,14.10.

4-Hydroxy-8-methyl-3-((E)-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-09)

Yield: 84% IR (cm^{-1}): 3606, 3540 (OH stretching), 3026 (Aromatic C-H stretching), 2980 (Aromatic -CH_3 stretching), 2891 (Aliphatic -CH_2 stretching), 1717 (C=O stretching), 1479, 1443, 1371 (C-H bending), 1282, 1236, 1215 (OH bending), 998, 962 (C=C stretching), 704(monosubstituted), MS: *m/z:* 448.47(M^+); Anal. Calcd. for $C_{28}H_{20}N_2O_4$: C,74.99; H, 4.50; N, 6.25; O,14.27 Found: C, 74.83; H, 4.41; N, 6.17; O,14.18.

4-Hydroxy-8-methyl-3-((E)-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-10)

Yield: 78% IR (cm^{-1}): 3616, 3560 (OH stretching), 3036 (Aromaticd C-H stretching), 2981 (Aliphatic -CH_3stretching), 2892 (Aliphatic -CH_2 stretching), 1707 (C=O Stretching), 1489, 1453, 1372 (C-H bending), 1281, 1246, 1205 (OH bending), 997,961 (C=C stretching), 735 (disubstituted), MS: *m/z:* 462.50(M^+); Anal. Calcd. for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06: O,13.84 Found: C, 75.23; H, 4.71; F, 6.01; O,13.79.

3-((E)-3-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-4-hydroxy-8-methyl-2H-chromen-2-one. (SAT-11)

Yield: 66% IR (cm^{-1}): 3616, 3560 (OH stretching), 3036 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2892 (Aliphatic -CH_2 stretching), 1707 (C=O Stretching), 1489, 1453, 1372 (C-H bending), 1281, 1246, 1205 (OH bending), 997,961 (C=C stretching), 735 (disubstituted), MS: *m/z:* 482(M^+), 484(M^{+2}) ; Anal. Calcd. for $C_{28}H_{19}ClN_2O_4$: C, 69.64; H, 3.97; Cl, 7.34; N, 5.80 ;O, 13.25 Found: C, 69.63; H, 3.81; Cl,7.27; N,579; O,13.19.

4-Hydroxy-8-methyl-3-((E)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-wH-chromen-2-one. (SAT-12)

Yield: 81% IR (cm^{-1}): 3536, 3561 (OH stretching), 3046 (Aromatic C-H stretching), 2991 (Aliphatic -CH_3stretching), 2890 (Aliphatic -CH_2 stretching), 1717 (C=O Stretching), 1541 (C-NO_2 stretching), 1481, 1451, 1382 (C-H bending), 1291, 1266, 1215 (OH bending), 996, 966 (C=C stretching), 731 (disubstituted), MS: *m/z:* 493(M^+); Anal. Calcd. for $C_{28}H_{19}N_3O_6$: C,68.15; H, 3.88; N, 8.52; O,19.45 Found: C,68.13; H, 3.81; N,8.47; O,19.41.

4-Hydroxy-3-((E)-3-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazolyl-4-yl)acrylolyl)-8-methyl-2H-chromen-2-one. (SAT-13)

Yield: 72% IR (cm^{-1}): 3546, 3521 (OH stretching), 3056 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2891 (Aliphatic -CH_2 stretching), 1707 (C=O Stretching), 1471, 1461, 1372 (C-H bending), 1292, 1276, 1205 (OH bending), 997,

965 (C=C stretching), 745 (disubstituted), MS: *m/z:* 464.47(M^+); Anal. Calcd. for $C_{28}H_{20}N_2O_5$: C,72.41; H, 4.34; N, 6.06; O,17.22 Found: C, 72.33; H, 4.31; N, 6.01; O,17.11.

4-Hydroxy-3-((E)-3-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-8-methyl-2H-chromen-2-one. (SAT-14)

Yield: 83% IR (cm^{-1}): 3556, 3541 (OH stretching), 3016 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2892 (Aliphatic -CH_2 stretching), 1707 (C=O Stretching), 1491, 1461, 1392 (C-H bending), 1282, 1281, 1225 (OH bending), 997 (C=C), 735 (disubstituted), 698(monosubstituted), MS: *m/z:* 478.50(M^+); Anal. Calcd. for $C_{29}H_{22}N_2O_5$: C, 72.79; H, 4.63; N, 5.85; O, 16.72 Found: C, 72.73; H, 4.61; N, 5.77; O,16.69.

4-Hydroxy-8-methyl-3-((E)-3-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-15)

Yield: 73% IR (cm^{-1}): 3576, 3521 (OH stretching), 3016 (Aromatic C-H stretching), 2996 (Aliphatic -CH_3 stretching), 2881 (Aliphatic -CH_2 stretching), 1711 (C=O Stretching), 1556 (C-NO_2 stretching), 1491, 1442, 1372 (C-H bending), 1272, 1256, 1235 (OH bending), 986 (C=C stretching), 741 (disubstituted), 701(monosubstituted), MS: *m/z:* 493.47(M^+); Anal. Calcd. for $C_{28}H_{19}N_3O_6$: C,68.15; H, 3.88; N, 8.52; O,19.45 Found: C, 68.13; H, 3.71; N, 4.77; O, 19.41.

3-((E)-3-(3-(4-flourophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-4-hydroxy-8-methyl-2H-chromen-2-one. (SAT-16)

Yield: 85% IR (cm^{-1}): 3606, 3561 (OH stretching), 3006 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2891 (Aliphatic -CH_2 stretching), 1701 (C=O stretching), 1498, 1452, 1371 (C-H bending), 1273, 1246, 1215 (OH bending), 996 (C=C stretching), 745(disubstituted), 702 (monosubstituted), MS: *m/z:* 466(M^+), 468(M^{+2}) ; Anal. Calcd. for $C_{28}H_{19}FN_2O_4$: C,72.10; H, 4.11; N, 6.01; O, 13.72 Found: C, 72.03; H, 4.05; N,5.98; O,13.69.

4-Hydroxy-5,8-dimethyl-3-((E)-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-17)

Yield: 89% IR (cm^{-1}): 3616, 3501 (OH stretching), 3016 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2892 (Aliphatic -CH_2 stretching), 1711 (C=O stretching), 1488, 1381 (C-H bending), 1272, 1256, 1225 (OH bending), 997 (C=C stretching), 715 (monosubstituted), MS: *m/z:* 462.50(M^+) ; Anal. Calcd. for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06; O,13.84 Found: C, 75.23; H, 4.71; N, 6.01; O,13.79.

4-Hydroxy-5,8-dimethyl-3-((E)-3-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)acryloyl-2H-chromen-2-one. (SAT-18)

Yield: 82% IR (cm^{-1}): 3661, 3521 (OH stretching), 3046 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2899 (Aliphatic -CH_2 stretching), 1715 (C=O Stretching), 1498, 1382 (C-H bending), 1271, 1257, 1235 (OH bending), 987 (C=C stretching), 732 (disubstituted), MS: *m/z:* 476.52(M^+) ; Anal. Calcd. for $C_{30}H_{24}N_2O_4$: C, 75.61; H, 5.08; N, 5.88; O, 13.43 Found: C, 75.58; H, 5.01; N, 5.77; O,13.39.

3-((E)-3-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (SAT-19)

Yield: 85% IR (cm^{-1}): 3651, 3591 (OH stretching), 3041 (Aromatic C-H stretching), 2991 (Aliphatic -CH_3 stretching), 2879 (Aliphatic -CH_2 stretching), 1705 (C=O stretching), 1488, 1392 (C-H bending), 1281, 1267, 1245 (OH bending), 989 (C=C stretching), 744 (disub.), 701 (monosubstituted), MS: *m/z:* 496(M^+), 498(M^{+2}); Anal. Calcd. for $C_{29}H_{21}ClN_2O_4$: C,70.09; H, 4.26; N, 5.64; O,12.88 Found: C, 70.03; H, 4.11; N, 5.57; O,12.81.

4-Hydroxy-5,8-dimethyl-3-((E)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-20)

Yield: 78% IR (cm^{-1}): 3601, 3581 (OH stretching), 3011 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2899 (Aliphatic -CH_2 stretching), 1715 (C=O stretching), 1542 (C-NO_2), 1498, 1382 (C-H bending), 1282, 1245 (OH bending), 979 (C=C stretching), 755(disubstituted), 701 (monosubstituted), MS: *m/z:* 507.49(M^+) ; Anal. Calcd. for $C_{29}H_{21}N_3O_6$: C, 68.63; H, 4.17; N, 8.28; O, 18.92 Found: C, 68.56; H, 4.11; N, 4.07; O,18.90.

4-Hydroxy-3-((E)-3-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-5,8-dimethyl-2H-chromen-2-one. (SAT-21)

Yield: 83% IR (cm^{-1}): 3611, 3561 (OH stretching), 3021 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2889 (Aliphatic -CH_2 stretching), 1717 (C=O Stretching), 1497, 1392 (C-H bending), 1292, 1255 (OH bending), 989 (C=C stretching), 749 (disubstituted), 711(monosubstituted), MS: *m/z:* 478.50 (M^+); Anal. Calcd. for $C_{29}H_{22}N_2O_5$: C, 72.79; H, 4.63; N, 5.85; O, 16.72 Found: C, 72.73; H, 4.51; N, 5.77; O,16.68.

4-Hydroxy-3-((E)-3-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-5,8-dometyl-2H-chromen-2-one. (SAT-22)

Yield: 86% IR (cm^{-1}): 3610, 3551 (OH stretching), 3031 (Aromatic C-H stretching), 2989 (Aliphatic -CH_3 stretching), 2879 (Aliphatic -CH_2 stretching), 1712 (C=O stretching), 1498, 1362 (C-H bending), 1299, 1265 (OH bending), 979 (C=C stretching), 741(disubstituted), 698 (monosubstituted), MS: *m/z:* 492.52 (M^+); Anal. Calcd. for $C_{30}H_{24}N_2O_5$: C, 73.16; H, 4.91; N, 5.69; O, 16.24 Found: C, 73.13; H, 4.81; N, 5.67; O,16.20.

4-Hydroxy-5,8-dimethyl-3-((E)-3-(3-(-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-2H-chromen-2-one. (SAT-23)

Yield: 68% IR (cm^{-1}): 3610, 3541 (OH stretching), 3041 (Aromatic C-H stretching), 2928 (Aliphatic -CH_3 stretching), 2859 (Aliphatic -CH_2 stretching), 1727 (C=O stretching), 1551 (C-NO_2 stretching), 1491, 1390 (C-H bending), 1293, 1235 (OH bending), 979 (C=C stretching), 739(disubstituted), MS: *m/z:* 507.49 (M^+); Anal. Calcd. for $C_{29}H_{21}N_3O_6$: C,68.63; H, 4.17; N, 8.28; O, 18.92 Found: C, 68.53; H, 4.11; N, 8.17; O, 18.88.

3-((E)-3-(3-(4-flourophenyl)-1-phenyl-1H-pyrazol-4-yl)acryloyl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (SAT-24)

Yield: 81% IR (cm^{-1}): 3591, 3521 (OH stretching), 3071 (Aromatic C-H stretching), 2985 (Aliphatic -CH_3 stretching), 2829 (Aliphatic -CH_2 stretching), 1727 (C=O stretching), 1487, 1362 (C-H bending), 1252, 1225 (OH bending), 969 (C=C stretching), 749(disubstituted), 689 (monosubstituted), MS: *m/z:* 480 (M^+), 482 (M^{+2})

; Anal. Calcd. for $C_{29}H_{21}FN_2O_4$: C, 72.49; H, 4.41; N, 5.83; O, 13.32 Found: C, 72.43; H, 4.31; N, 5.77; O,13.28.

4.11 RESULTS AND DISCUSSION

This chapter is related to modification in the previous work done by our group as well as others but the scaffolds reported here are new. It is very well known that C_3 position of 4-hydroxycoumarin is highly reactive. 3-acetyl-4-hydroxycoumarin was synthesized by acetylation on 4-hydroxycoumarin adopting cited literature method. The importance of chalcones was discussed in the introduction of this chapter.

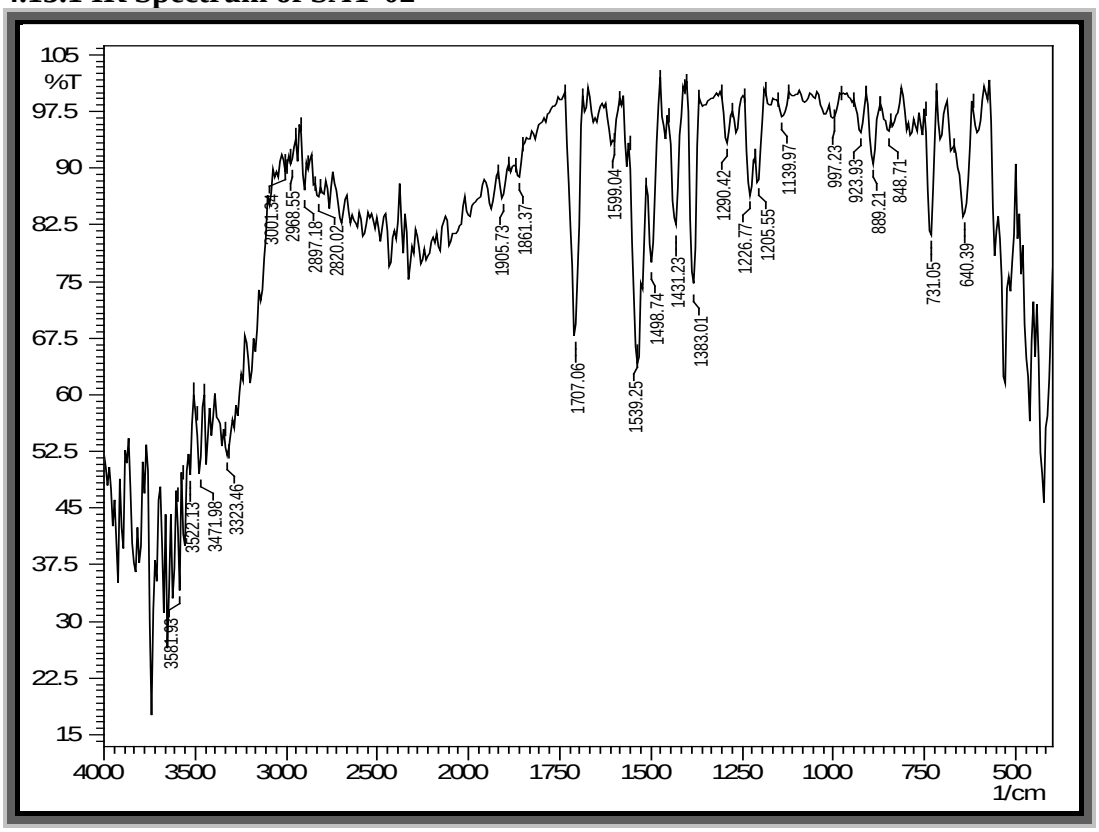
Earlier chalcones were prepared by previous workers in the presence of piperidine using conventional methods which takes almost 36-48 hrs. It was further modified by reducing reaction time drastically upto 1 hrs only in conventional method. However, in this chapter, the compounds were prepared by microwave method below 15 min.

4.12 CONCLUSION

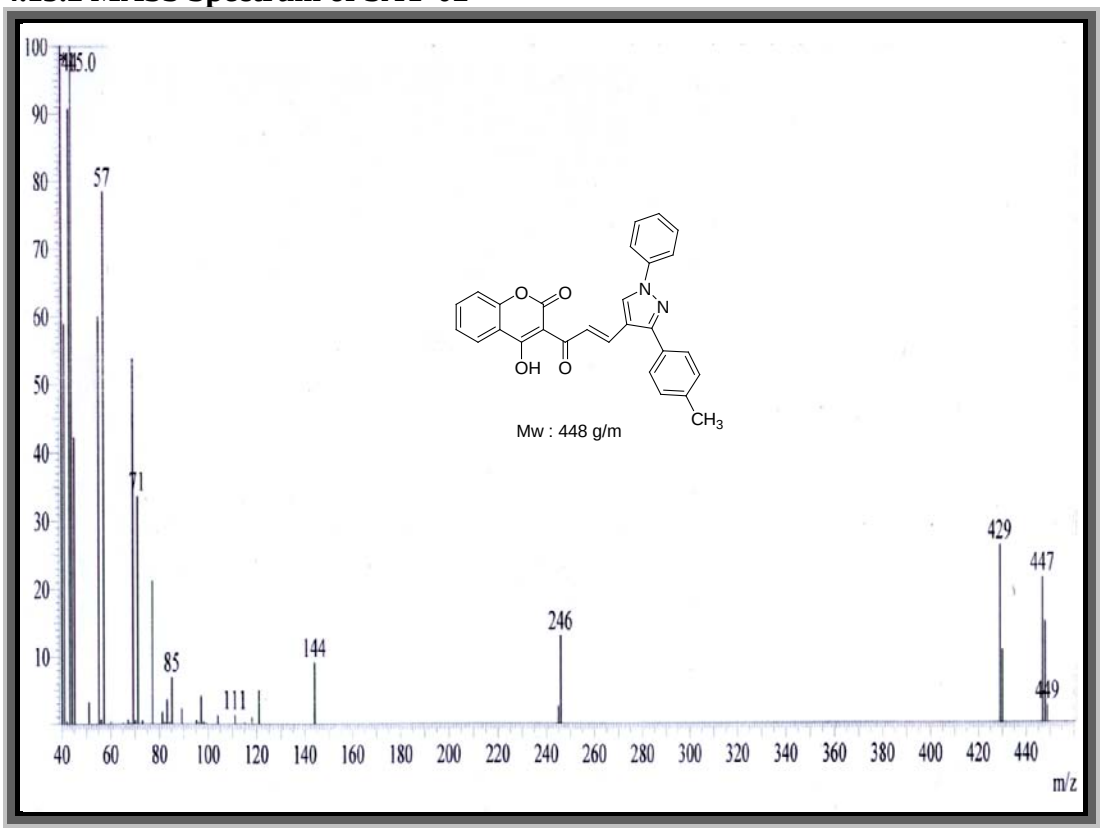
The chemical entities enlisted above in this chapter, especially the chalcone involving the pyrazole aldehydes have been prepared by a microwave methodology and it is much faster giving very good yields.

4.13 REPRESENTATIVE SPECTRAS

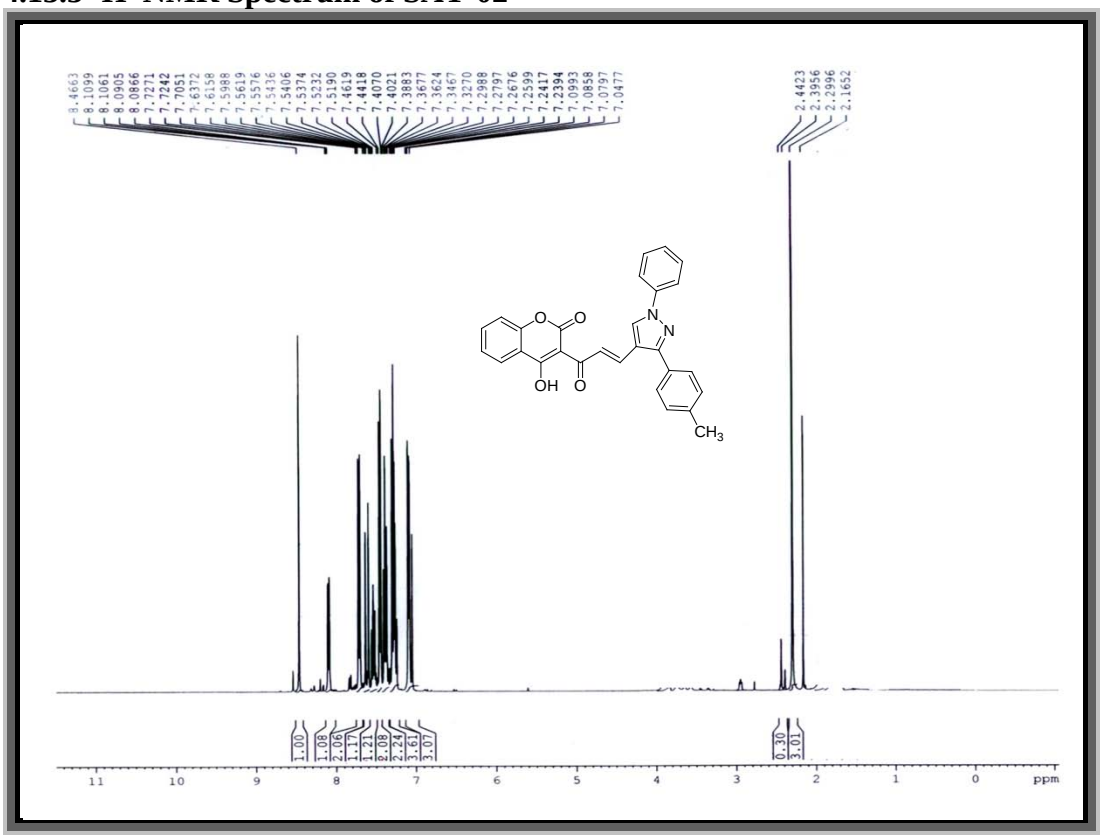
4.13.1 IR Spectrum of SAT-02



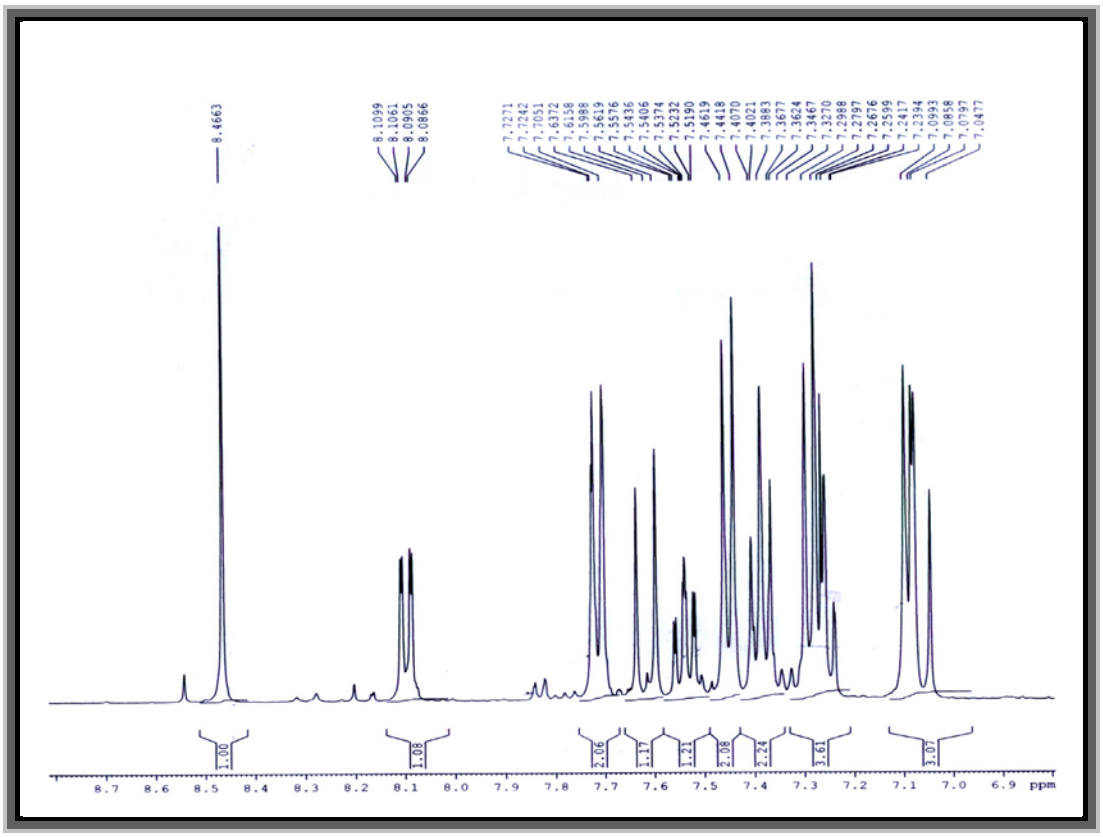
4.13.2 MASS Spectrum of SAT-02



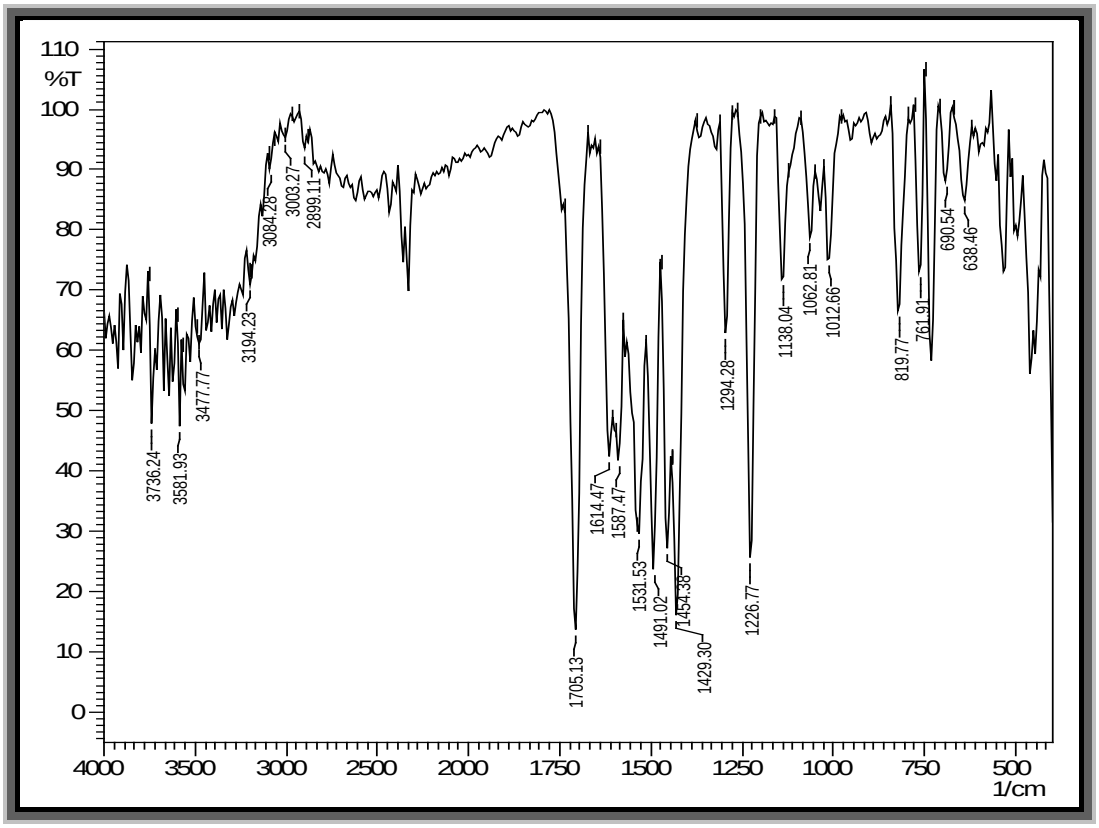
4.13.3 ^{1}H NMR Spectrum of SAT-02



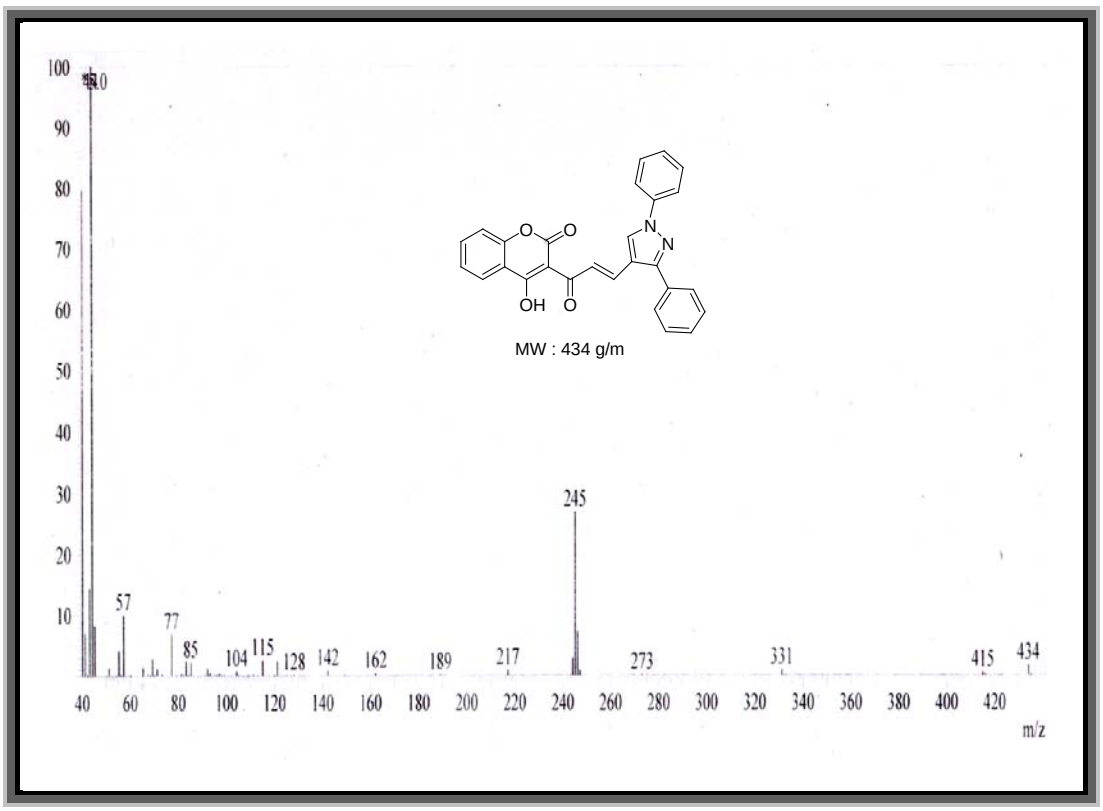
4.13.4 Expanded ^{1}H NMR Spectrum of SAT-02



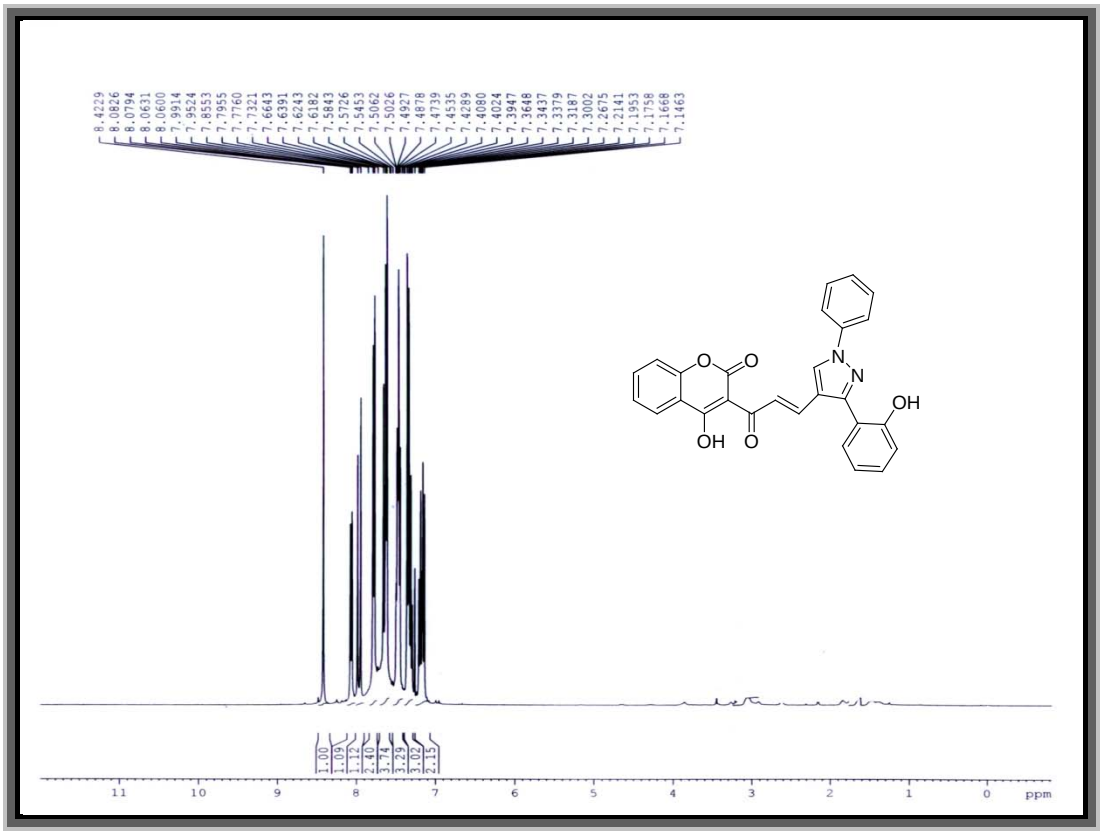
4.13.5 IR Spectrum of SAT-03



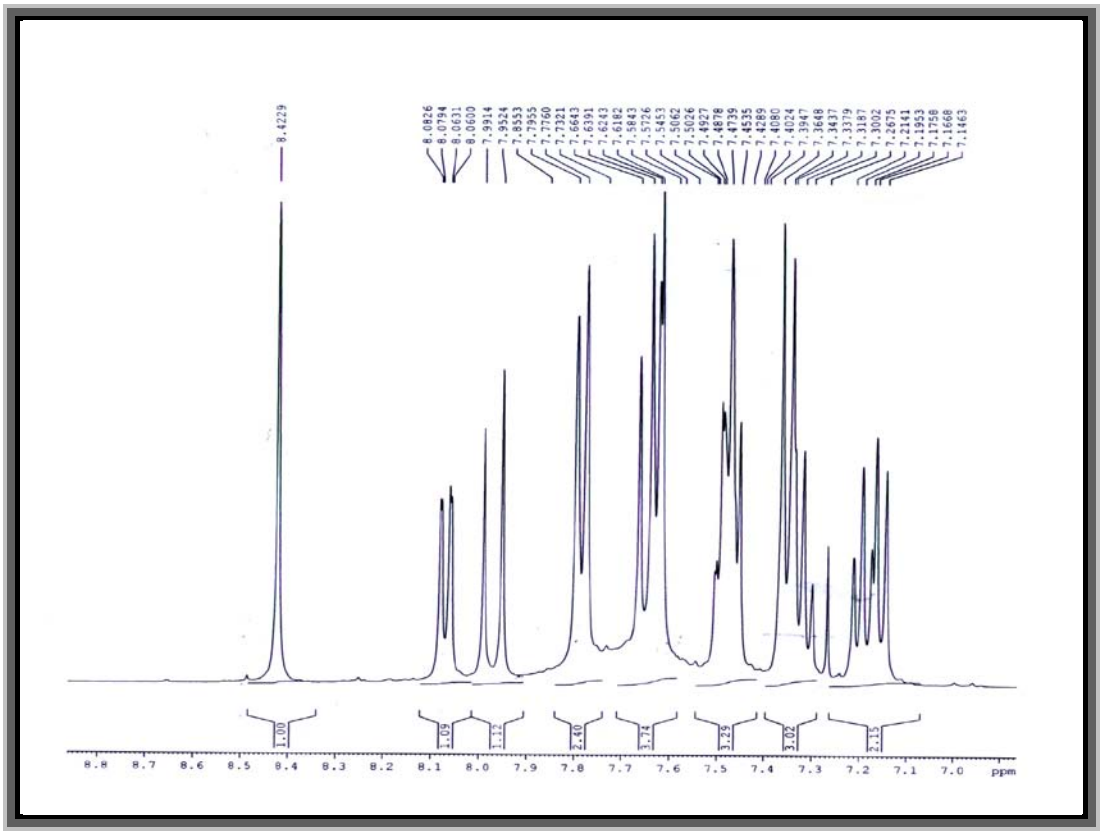
4.13.6 MASS Spectrum of SAT-01



4.13.7 ^{1}H NMR Spectrum of SAT-03



4.13.8 Expanded ^{1}H NMR Spectrum of SAT-03



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Chapter-5

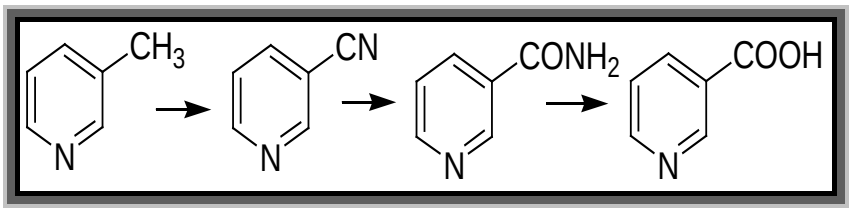
Conventional and microwave assisted synthesis of novel cyano pyridines.

5.1 INRODUCTION

Pyridine has its own importance in the field of Chemistry, Agriculture, Medicine and Industrial chemistry. Although many polysubstituted pyridine compounds like other heterocyclic compounds are synthesized with their functional group present from acyclic compounds, most derivatives are prepared by manipulatin of pyridine and it's simple homologues in a manner similar to the chemistry of the benzenoid chemistry. However, the simple pyridine compounds are prepared by the cyclization of aliphatic raw materials.

The availability of 3-Cyanopyridines, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

Among all Cyanopyridines 3-cyanopyridine is the most important commercially since partial hydrolysis occurs radily with base catalysis to give nicotinamide (Niacinamide) which could be further hydrolyzed to nicotinic acid.



The availability of 2-cyanopyridines, nicotinamide and nicotinic acid makes possible their use as synthetic intermediate.

5.2 REVIEW OF LITERATURE

Synthesis methods of Cyanopyridines

Different methods for preparation of 3-cyanopyridines are as follows:

(1) 3-cyanopyridine can be prepared by the vapour phase air oxidation of nicotine over V_2O_5[1] or alkenyl substituted pyridines in presence of ammonia.[2]

(2) Oxley and co-worker[3] synthesized pyridine benzenesulphonate by heating nicotinicacid benzensulphonate and $PhSO_2NH_2$ at 23^0C for 40 min.

(3) 3-cyanopyridines can be synthesized by the reaction of an alkali cyanide with 3-pyridine sulphonate[4] or 3-bromopyridine.[5]

(4) Taylor and Crovetti[6] synthesized by the reaction of an alkali cyanide with 3-pyridine sylphonate[4] or 3-bromopyridine.[5]They also synthesized 2-amino 3-cyanopyridine from pyridine-1-oxide.[6]

(5) Pyridine-3-carboxylic acid is converted to 3-cyanopyridine when it is mixed with ammonia and heated in the present presence of dehydrating catalyst at 275-450^{O}C.[7-8]

(6) 3-Cyanopyridine can be synthesized by heating the potassium salt of 3-pyridine sulphonic acid with sodium cyanide at 350-400^{O}C.[9]

(7) Dornow and Nense[10] synthesized substituted 3-cyanopyridine by boiling ethylcyanoacetate and ethylacetoacetate with ammonia.

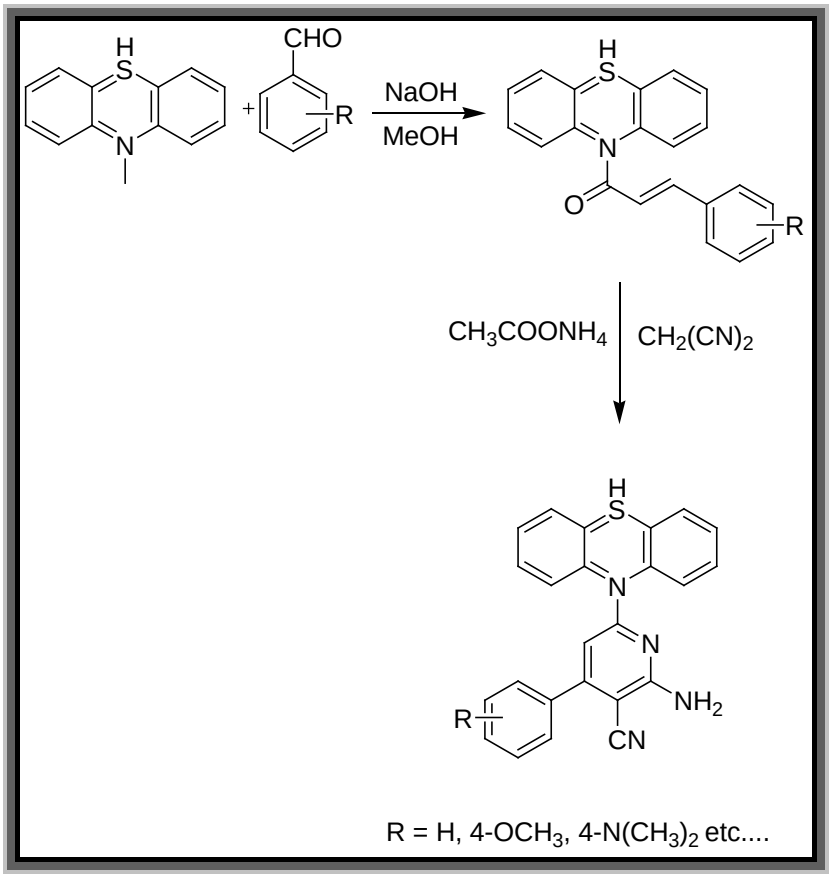
(8) Aromatic nitriles[11] can be prepared from the corresponding primary carboxylic acid amine in presence of $TiCl_4$ an a base like triethylamine at 0^OC.

(9) Sumour and co-workers[12] prepared substituted Cyanopyridines by the condensation of Chalcones with ethylcyanoacetate and Malononitrile in the ammonium acetate.

(10) Sukari and Midorikawa[13-14] have reported that Malononitrile reacts with alpha, beta-unsatutated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines.

Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules such as cyanopyridines[15] and triazolopyridines[16] and have played an important role in medicinal chemistry. They are reported to possess a broad spectrum of biological activity such as potential cardiovascular agents antiviral[17], CNS depressant[18], bactericidal[19], ulcer inhibitors[20] etc. Furthermore researchers have also revealed that cyanopyridine derivatives constitute an important class of compounds possessing diverse type of biological properties including antiviral,[21] antiparasitic,[22] antiparkinsonian,[23] anticonvulsant,[24] antihistaminic[25] as well as anthelmintic[26] properties.

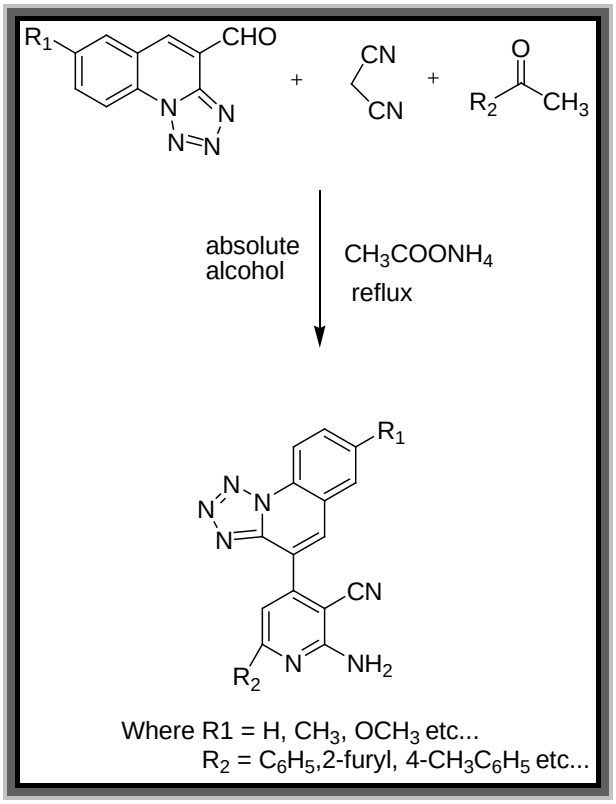
Raval *et al.*[27] have reported the synthesis and antimicrobial activity of new triazolopyridinyl phenothiazines through cyanopyridine ring.



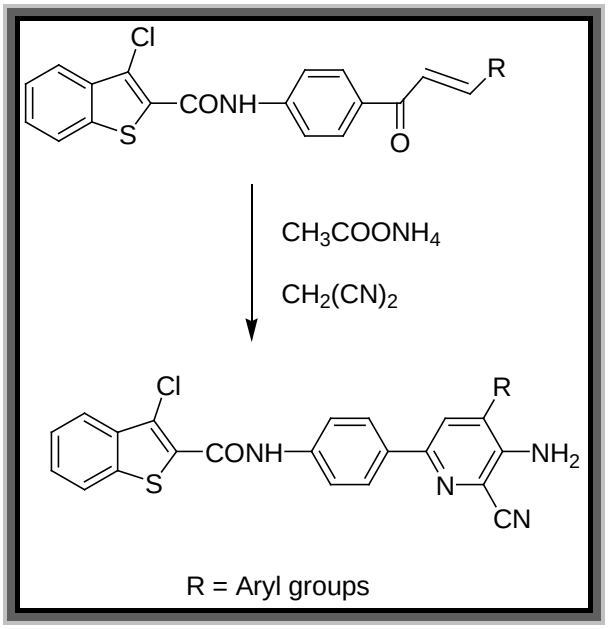
Many naturally occurring and synthetic compounds bearing pyridine scaffold possess interesting biological properties.[28] 2-amino-3-cyanopyridine derivatives have been identified as IKK-β inhibitors.[29-30] Various routes for the synthesis of 2-amino-3-

cyanopyridine derivatives have been reported using two-component as well as three-component reactions.[31-35] Tu and coworkers[31] have reported a facile synthesis of 2-amino-3-cyanopyridine derivatives in a one-pot reaction using aromatic aldehyde, methyl ketone, malononitrile and ammonium acetate.

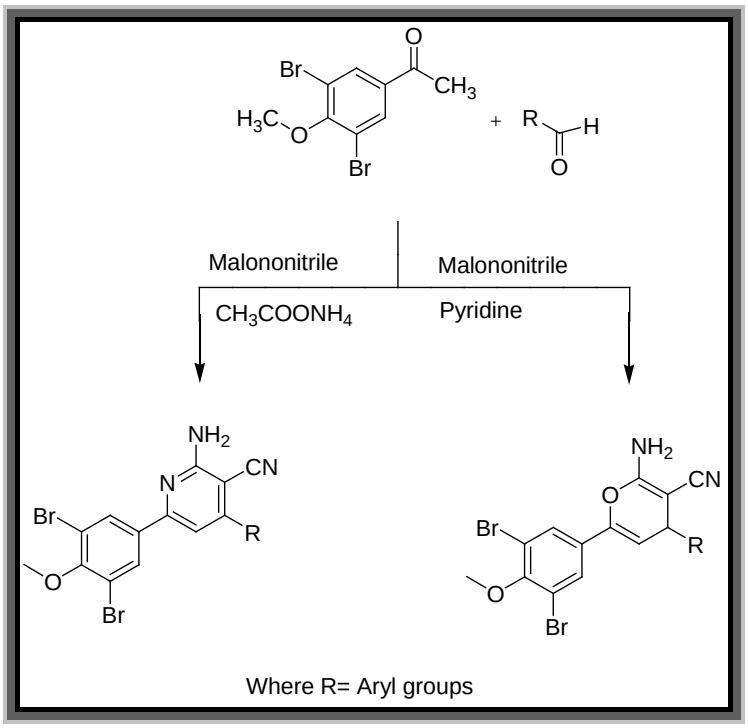
Mungra *et al.*[36] have reported an efficient one-pot multicomponent synthesis of 2-amino-3-cyanopyridine derivatives having tetrazoloquinoline nucleus which have also been recognized as promising new scaffold to endow good biological properties[37,38] such as anti-inflammatory and antimicrobial activity.[39-42]



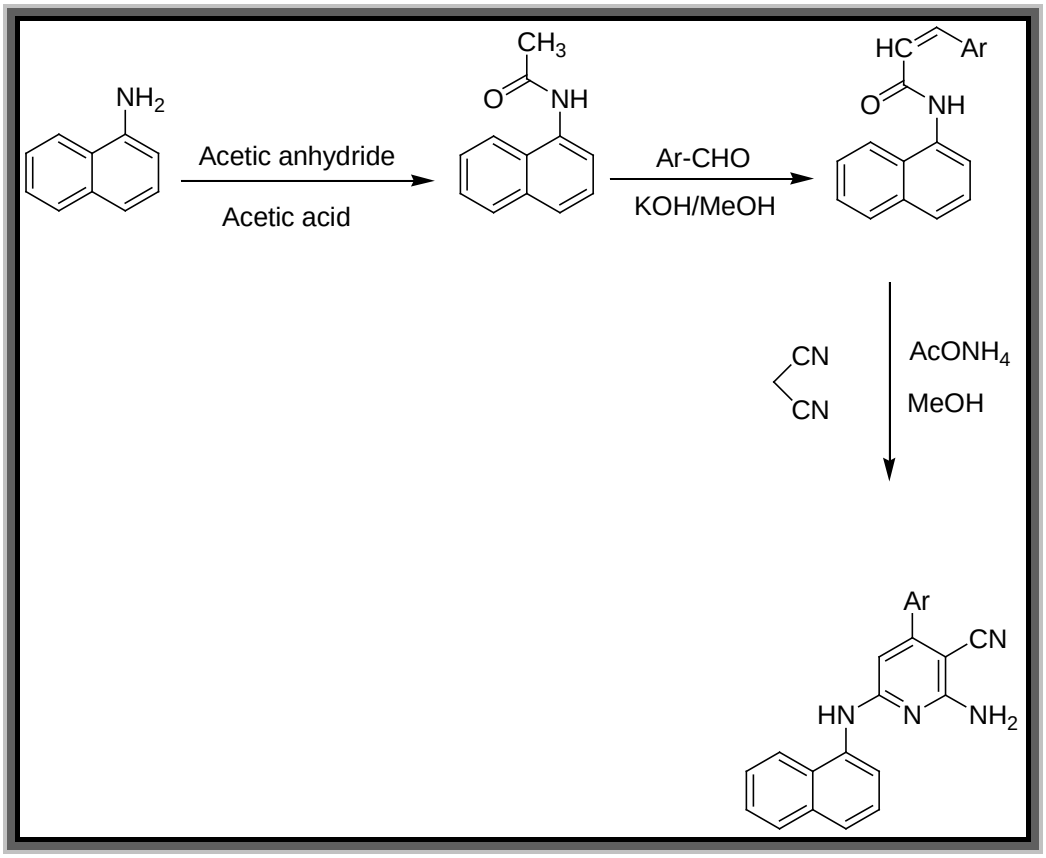
Kachhadia *et al.*[43] have reported the Synthesis of cyanopyridines bearing benzo thiophene nucleus as potential antitubercular and antimicrobial agents.



Vyas *et al.*[44] have extended studied on cyanopyridine and reported the synthesis and antimicrobial activity of some new cyanopyridines and cyanopyrans towards mycobacterium tuberculosis and other microorganism.

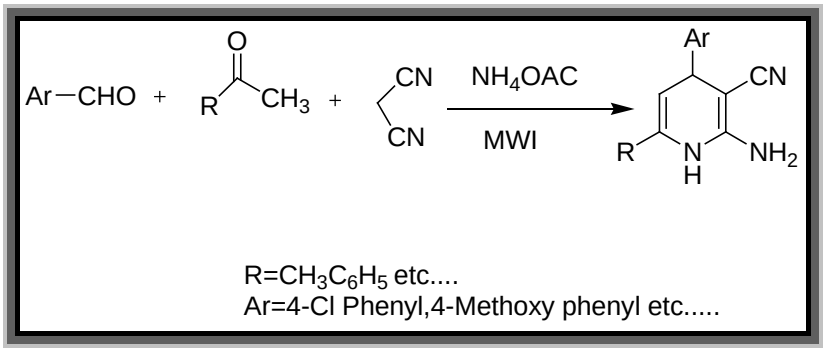


Konda *et al.*[45] reported the synthesis and antibacterial activities of some new cyanopyridines.



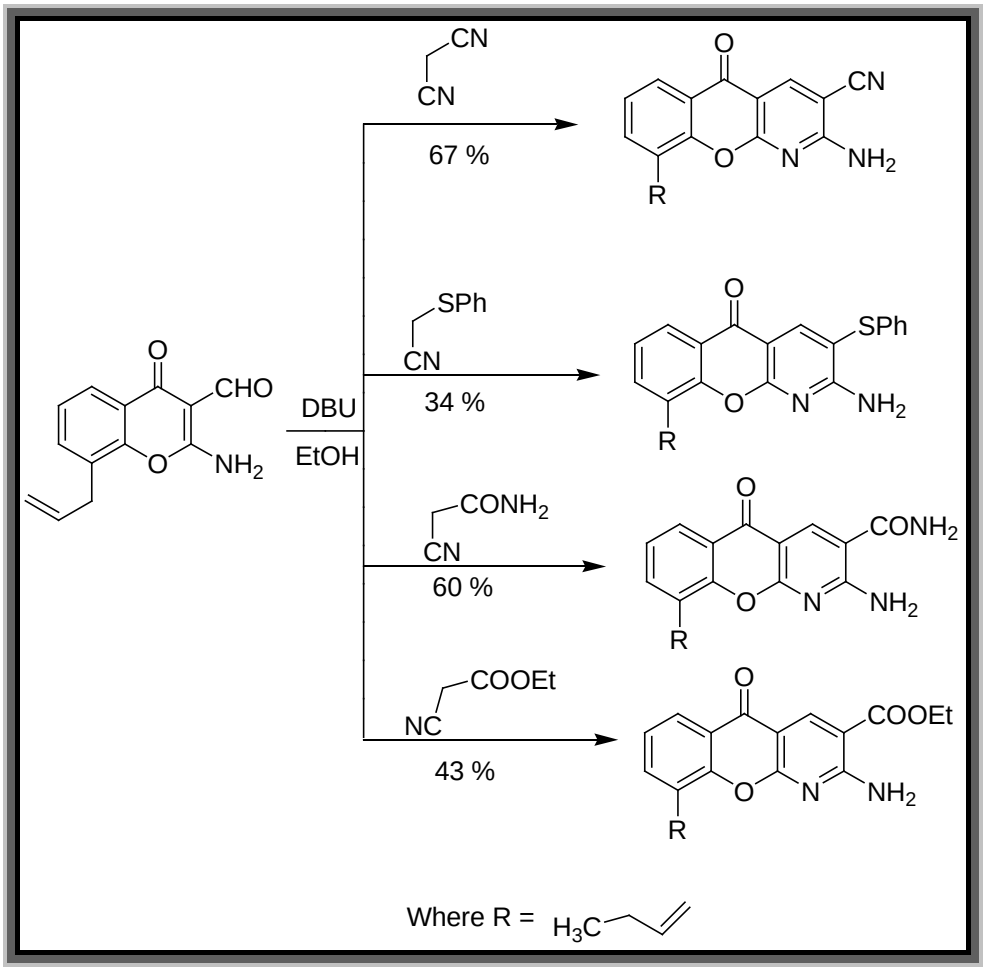
2-amino-6-aryl-3-cyano-4-piperidinylpyridine core structure can be constructed using a one-pot coupling reaction of acetophenone, piperidine, malononitrile and ammonium acetate in conventional heating mode.[46] In addition to that, Microwave activation as a non-conventional energy source has become an important method that can be used to carry out a wide range of reactions within short time and with high yields, especially in the absence of solvents[47-50]. Satya *et al.* has also prepared 2-amino-3-cyanopyridines from arylidene malononitrile, ketone and ammonium acetate under microwave irradiation.[51] However, arylidene malononitriles as one of the starting materials must be synthesized from malononitrile and aromatic aldehyde.

Feng *et al.*[52] have reported the synthesic method of 2-amino-3-cyanopyridine derivatives by one-pot condensation from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate under microwave irradiation without solvent. This method has the advantage of short routine, high yields and being environmentally-friendly.

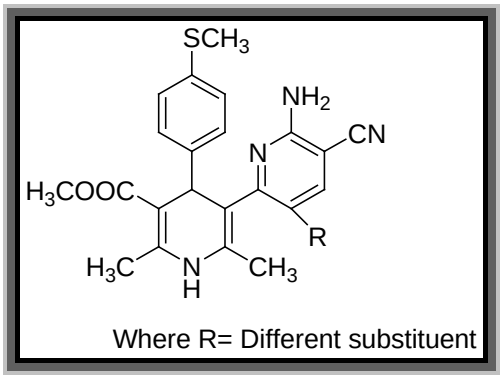


Chromone derivatives drew much attention because of their activity against the human immunodeficiency virus (HIV-1)[53-55] and their broad anti-inflammatory[56], antitumor,[57] antibacterial,[58] antimicrobial,[59] antifungal,[61,61] antibiotic,[62] and insecticidal activities.[63] Chromones bearing an allyl group at position 8 have a special medicinal importance; 8-allyl-2-styrylchromones were used as inhibitors for the growth of tumors.[64] Also, the 8-allyl derivatives were used as a precursor for the synthesis of the 8-acetic acid derivatives which exhibit anticancer properties.[65-67] eteroannulated chromones showed significant biological activity including pharmacological,[68] anti-inflammatory and antiplatelet activities.[69]

Salah *et al.*[70] have reported the Synthesis of 8-allylchromone-3-carboxaldehyde and further they studied its reaction with malononitrile, cyanoacetamide, ethyl cyanoacetate, phenylthioacetonitrile, ethyl acetoacetate, ethyl benzoylacetate and barbituric acid.



At this laboratory previous work on Cyanopyridine moiety is reported.[71] The synthesized compounds were screened for their antimicrobial, antifungal activity against various strains of bacteria and fungi.



The Cyanopyridines were explored for other biological activities too.

5.3 Biological Profile

Cyanopyridine derivatives have been found to possess wide range of therapeutic activities as shown below.

1. Antiviral[72]
2. CNS depressant[73]
3. Bactericial[74]
4. Ulcer inhibitors[75]
5. Antiparasitic[76]
6. Antiparkinsonian[77]
7. Anticonvulsant[78]
8. Antihistaminic[79]

It also possess antibacterial[80-82], antifungal[83-84], antidiabatic, anticholestrimic and antihypertensive activities. They are also used as dyes for cotton and polyester fabrics. Substituted-3-cyanopyridines are useful as chemical buffer. Francis and coworkers studied the effect of some substituted pyridines on the growth of the walker carcinosarcome-256 in tissue culture. Streightoff[80] and seydel[81-82] have studied the bacteriostatic effect of some substituted 3-cyanopyridines.

Kadlac *et al.*[83] showed that 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridines caused occupational health hazard like eczema. Rigterink *et al.*[84] studied the Pesticidal activity of 3-cyano-pyridine derivatives. Hoefling and *et al.*[85] prepared 3 and 4-cyanpyridines, which possess antitubercular activity.

Barton *et al.*[86] prepared 2-substituted-3-cyano-5-nitro-pyridines which possess fungicidal and insecticidal properties.

Kurt *et al.*[87] studied the antiphogistic and analgestic properties of substituted 3-cyanopyridines. Latif *et al.*[88] have reported the antibacterial and antifungal activity of 2-amino-3-cyano-4,6disubstituted pyridines. Scott and Joseph[89-90] have prepared 2-

aminopyridine derivatives, which were found to be useful as antipsoriasis pharmaceuticals. Baldwin[91-93] studied antihypertensive activity of Cyanopyridines.

Taylor *et al.*[94] have prepared N-substituted-2-aminopyridines which possess anticonvulsant activity. Engel and Benenburg[95] synthesized 2-amino-3,6-disubstitued pyridine derivatives as antiepileptic agents. 3-cyanopyridine derivative synthesized by Castedo et al.[96] had a MIC of 1.56 µg/ml against S.aureus.

5.4 AIM OF CURRENT WORK

In recent years, environmentally benign synthesis methods have received considerable attention. In present work, multistep synthesis in which the final step is performed by using microwave synthesizer for rapid synthesis.

5.5 REACTION SCHEMES

5.5.1 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

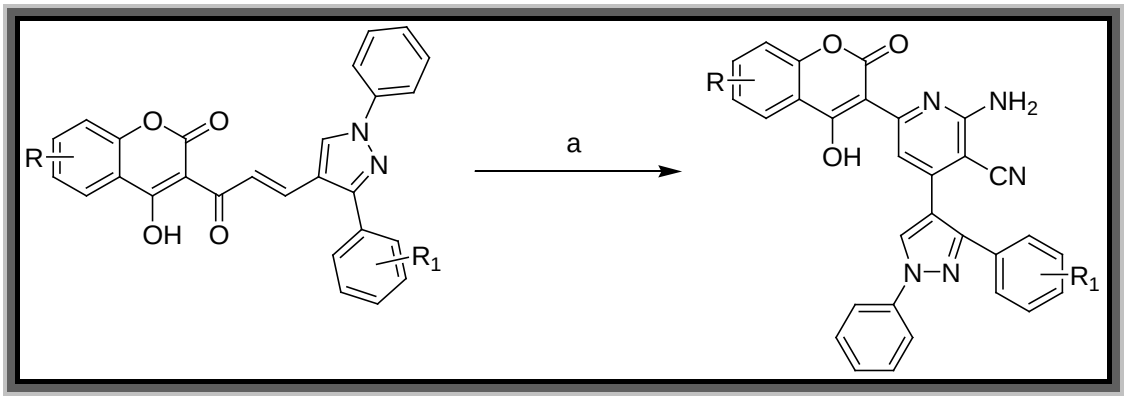
5.5.2 PREPARATION OF 3-ACETYL 4-HYDROXY COUMARINS :

It was prepared according to method described in Chapter-4

5.5.3 PREPARATION OF CHALCONES :

It is prepared according to method described in Chapter-4

5.5.4 PREPARATION OF 3 AMINO-4-(3-(SUBSTITUTED) PHENYL)-1-PHENYL-1H-PYRAZOL-4-YL)-6-(4-HYDROXY-2-OXO-2H-CHROMEN-3-YL) PYRIDINE-2-CARBONITRILE:

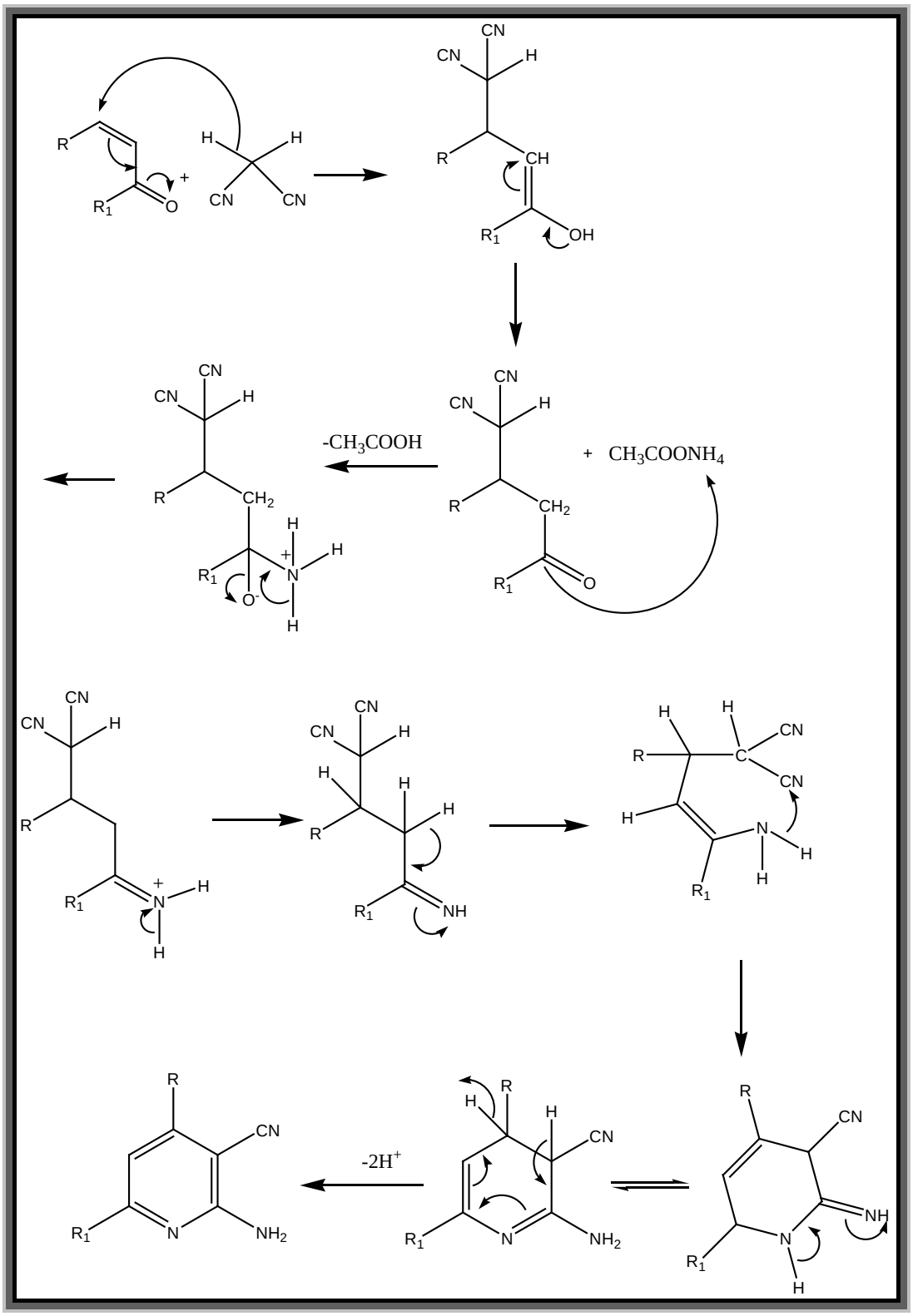


Reagents/ Reaction Condition (a): Mw, 400Wt, $CH_2(CN)_2$, CH_3COONH_4, MeOH,.

Where R= H, 5-CH_3, 5, 8-diCH_3 &

R_1 = 4-H, 4-Cl, 4-F, 4-NO_2, 3-NO_2 etc.....

5.6 PLAUDIBLE REACTION MECHANISM



5.7 EXPERIMENTAL

5.7.1 MATERIALS AND METHODS :

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. All the reaction were carried out in **Q-pro microwave synthesizer.** IR spectra were recorded in **Shimadzu FT-IR-8400** instrument using KBr pellet 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 solution on a **Bruker Ac 400 MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model and the results are in agreements with the structures assigned.

5.7.2 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

5.7.3 PREPARATION OF 3-ACETYL 4-HYDROXY COUMARINS :

It was prepared according to method described in Chapter-4

5.7.4 PREPARATION OF CHALCONES :

It was prepared according to method described in Chapter-4

5.7.5 PREPARATION OF 3 AMINO-4-(3-(SUBSTITUTED) PHENYL)-1-PHENYL-1H-PYRAZOL-4-YL)-6-(4-HYDROXY-2-OXO-2H-CHROMEN-3-YL) PYRIDINE-2-CARBONITRILE:

GENERAL METHOD

(A) CONVENTIONAL METHOD :

A mixture of Chalcone (0.01 mole) , Malononitrile (0.01 mole), ammonium acetate (0.08 mole) and 20 mls of methanol was refluxed for 4-6 hrs. The progress and the completion of the reaction were checked at interval of every one min. by silica gel-G F_{254} thin layer chromatography using hexane : ethyl acetate (2 : 3) as a mobile phase. After that it was cool to room temperature and filtered it and wash with methanol. Dry it.

Similarly other compounds are also prepared using different methods.

(B) MICROWAVE METHOD :

A mixture of chalcone (0.01 mole), Malononitrile (0.01 mole), ammonium acetate (0.08 mole) and 20 mls of methanol were taken in 100 ml microwave flask. The reaction mixture was irradiated under microwave irradiation using Qpro-M microwave synthesizer for the desired time at 400 Watt. The progress and the completion of the reaction were checked at interval of every one minute by using silica gel-G F_{254} thin layer chromatographic plates using hexane : ethyl acetate (2 : 3) as a mobile phase. It was then cooled to room temperature and filtered, washed with chilled methanol and dried.

Similarly other compounds are also prepared using different methods.

Comparative Results of conventional method (A) and microwave method (B)

TABLE – 5.1

Code No.	Reaction Condition					% Yield	
	Conventional Method (A)		Microwave Method (B)			Method (A)	Method (B)
	Temp. (°C)	Time (hrs.)	Watt (W)	Temp. (°C)	Time (min.)		
STAB-1001	70-75	4.0	400	110	6.0	62	76
STAB-1002	70-75	5.0	400	110	5.0	72	78
STAB-1003	70-75	4.0	400	110	5.0	68	81
STAB-1004	70-75	5.0	400	110	6.0	66	79
STAB-1005	70-75	5.0	400	110	7.0	62	78
STAB-1006	70-75	5.0	400	110	8.0	72	81
STAB-1007	70-75	4.0	400	110	8.0	74	82
STAB-1008	70-75	5.0	400	110	6.0	66	81
STAB-1009	70-75	5.0	400	110	8.0	70	78
STAB-1010	70-75	4.0	400	110	7.0	71	80
STAB-1011	70-75	4.5	400	110	9.0	73	82
STAB-1012	70-75	4.0	400	110	6.0	60	71
STAB-1013	70-75	5.0	400	110	7.0	72	76
STAB-1014	70-75	5.0	400	110	9.0	69	74
STAB-1015	70-75	4.0	400	110	8.0	67	79
STAB-1016	70-75	4.5	400	110	5.0	64	72
STAB-1017	70-75	4.5	400	110	8.0	64	74
STAB-1018	70-75	5.5	400	110	6.0	71	83
STAB-1019	70-75	5.5	400	110	9.0	66	80
STAB-1020	70-75	4.5	400	110	4.0	70	79
STAB-1021	70-75	6.0	400	110	6.0	62	72
STAB-1022	70-75	5.5	400	110	5.0	71	78
STAB-1023	70-75	5.5	400	110	6.0	68	72
STAB-1024	70-75	6.0	400	110	6.0	72	74

5.8 PHYSICAL DATA

Physical data of 3-Amino-4-(3-(substituted)phenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile.

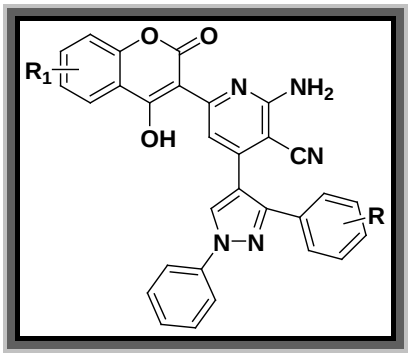


TABLE – 5.2

Code	Substitution		MF	MW	MP ^{O}C	Rf Value
	R	R_1				
STAB-1001	4-Cl	H	$C_{30}H_{18}ClN_5O_3$	531	178-180	0.46
STAB-1002	4-CH_3	H	$C_{31}H_{21}N_5O_3$	511	192-194	0.52
STAB-1003	H	H	$C_{30}H_{19}N_5O_3$	497	202-204	0.44
STAB-1004	4-NO_2	H	$C_{30}H_{18}N_6O_5$	542	238-240	0.48
STAB-1005	2-OH	H	$C_{30}H_{19}N_5O_4$	513	222-224	0.50
STAB-1006	2-OCH_3	H	$C_{31}H_{21}N_5O_4$	527	216-218	0.40
STAB-1007	3-NO_2	H	$C_{30}H_{18}N_6O_5$	542	168-170	0.44
STAB-1008	4-F	H	$C_{30}H_{18}FN_5O_3$	515	198-200	0.48
STAB-1009	H	8- CH_3	$C_{31}H_{21}N_5O_3$	511	224-228	0.42
STAB-1010	4-CH_3	8- CH_3	$C_{32}H_{23}N_5O_3$	525	236-238	0.46
STAB-1011	4-Cl	8- CH_3	$C_{31}H_{20}ClN_5O_3$	545	180-182	0.42
STAB-1012	4-NO_2	8- CH_3	$C_{31}H_{20}N_6O_5$	556	178-180	0.54
STAB-1013	2-OH	8- CH_3	$C_{31}H_{21}N_5O_4$	527	192-194	0.50
STAB-1014	2-OCH_3	8- CH_3	$C_{32}H_{23}N_5O_4$	541	222-224	0.48
STAB-1015	3-NO_2	8- CH_3	$C_{31}H_{20}N_6O_5$	556	212-214	0.40
STAB-1016	4-F	8- CH_3	$C_{31}H_{20}FN_5O_3$	529	232-234	0.46
STAB-1017	H	5,8-di CH_3	$C_{32}H_{23}N_5O_3$	525	244-246	0.44
STAB-1018	4-CH_3	5,8-di CH_3	$C_{33}H_{25}N_5O_3$	539	166-168	0.48
STAB-1019	4-Cl	5,8-di CH_3	$C_{32}H_{22}ClN_5O_3$	559	212-214	0.40
STAB-1020	4-NO_2	5,8-di CH_3	$C_{32}H_{22}N_6O_5$	570	232-234	0.42
STAB-1021	2-OH	5,8-di CH_3	$C_{32}H_{23}N_5O_4$	541	178-180	0.48
STAB-1022	2-OCH_3	5,8-di CH_3	$C_{33}H_{25}N_5O_4$	555	192-194	0.46
STAB-1023	3-NO_2	5,8-di CH_3	$C_{32}H_{22}N_6O5$	570	180-182	0.52
STAB-1024	4-F	5,8-di CH_3	$C_{32}H_{22}FN_5O_3$	543	212-214	0.42

R_f value was calculated using solvent system = Hexane : Ethyl Acetate (2 : 3)

5.9 SPECTRAL DISCUSSION

5.9.1 IR SPECTRA

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

The characteristic bands of Hydroxyl groups were obtained for streching at 3400-3650 cm^{-1} and those for bending were obtained at 1050-1250 cm^{-1}.The stretching vibrations N-H group showed in the region of 3200 to 3500 cm^{-1} with a deformation due to in plane bending at 1650-1580 cm^{-1}. It gives aromatic C-H stretching frequencies between 3000-3200 cm^{-1} and bending vibration near 1300-1500 cm^{-1} respectively. C-H stretching frequencies for methyl and methylene group were obtained near 2950 cm^{-1} to 2850 cm^{-1}. Characteristic frequency of C-N stretching showed near 2100-2400 cm^{-1} and bending vibration near 1300-1400 cm^{-1}.

5.9.2 MASS SPECTRA

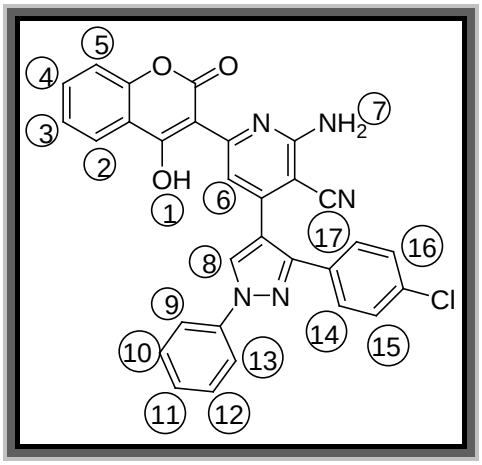
Mass spectra of the synthesized compounds were recorded on **Shimadzu GC-MS QP-2010** model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. Fragmentation pattern can be observed to be particular for these compounds and the characteristic peaks obtained for each compound.

5.9.3 ^{1}H NMR SPECTRA

^{1}H NMR spectra of the synthesized compounds were recorded on **Bruker Avance II 400 spectrometer** by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons and carbons identified from NMR spectrum 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. ^{1}H spectral interpretation can be discussed as under.

^{1}H NMR of 3-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile (STAB-1001)

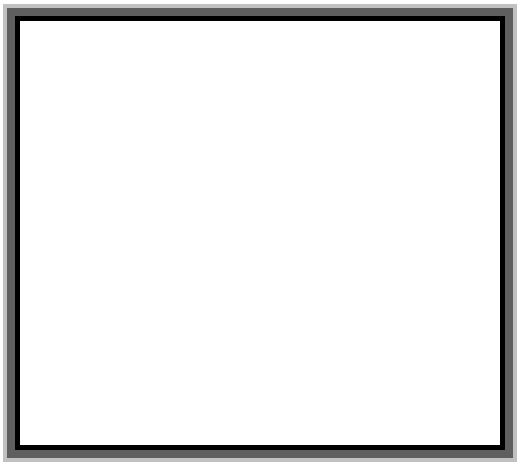


1. Proton no. 7 of total 2H gave a Broad singlet at 3.74 δ ppm.
2. Proton no. 11 of 1H gave a doublet at 7.21 δ ppm - 7.23 δ ppm.
3. Proton no. 4 of 1H gave a triplet at 7.26 δ ppm - 7.30 δ ppm.
4. Proton no. 15 and 16 of 2H gave a doublet at 7.34 δ ppm -7.36 δ ppm and J value of this proton is 8.0 Hz it suggest ortho coupling.
5. Proton no. 5 of 1H gave a doublet at 7.38 δ ppm -7.40 δ ppm.
6. Proton no. 3 of 1H gave a doublet at 7.51 δ ppm.
7. Proton no. 9,13,10 and 12 of 4H gave a triplet at 7.55 δ ppm - 7.60 δ ppm.
8. Proton no. 14 and 17 of 2H gave a doublet at 7.78 δ ppm -7.85 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
9. Proton no. 2 of coumarin ring gave a doublet at 8.03 δ ppm - 8.05 δ ppm.
10. Proton no. 6 of pyridine ring of 1H gave a singlet at 8.27 δ ppm.
11. Proton no. 8 of pyrazol ring of 1H gave a singlet at 8.50 δ ppm.
12. Proton no. 1 of 1H gave a singlet at 18.35 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 no. STAB-1001 has been confirmed. The spectrum is given on page no.201.

^{1}H NMR of 3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl) pyridine-2-carbonitrile
(STAB-1002)



1. Proton no. 18 of total 3H gave a singlet at 2.36 δ ppm.
2. Proton no. 7 of total 2H gave a Broad singlet at 3.76 δ ppm.
3. Proton no. 10 and 12 of 2H gave a doublet at 7.16 δ ppm – 7.18 δ ppm.
4. Proton no. 3 of 1H gave a doublet at 7.20 δ ppm.
5. Proton no. 11 of 1H gave a triplet at 7.25 δ ppm -7.27 δ ppm.
6. Proton no. 4 of 1H gave a Triplet at 7.34 δ ppm -7.38 δ ppm.
7. Proton no. 9 and 13 of 2H gave a dublet at 7.44 δ ppm -7.46 δ ppm.
8. Proton no. 15 and 17 of 2H gave a doublet at 7.50 δ ppm – 7.52 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
9. Proton no. 5 of 1H gave a triplet at 7.59 δ ppm – 7.77 δ ppm.
10. Proton no. 14 and 16 of 2H gave a doublet at 7.86 δ ppm – 7.88 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
11. Proton no. 2 of 1H gave a doublet at 8.02 δ ppm – 8.05 δ ppm.
12. Proton no. 6 of pyridine ring of 1H gave a singlet at 8.25 δ ppm.
13. Proton no. 8 of pyrazole ring of 1H gave a singlet at 8.50 δ ppm.
14. Proton no. 1 of 1H gave a singlet at 18.30 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 no. STAB-1002 has been confirmed. The spectrum is given on page no.203.

5.9.4 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 spectral and elemental analysis data are for individual compounds synthesized in this chapter is mentioned below.

5.10 ANALYTICAL DATA

3-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile. (STAB-1001)

IR (cm^{-1}): 3645,3562 (OH Stretching), 3475,3400,3317 (N-H stretching), 3082,3014 (Aromatic C-H stretching), 2974,2901 (Aliphatic -CH_3 stretching), 2829 (Aliphatic -CH_2 Stretching.), 2424,2322 (C-N Stretching), 1768(C=O Stretching),1560 (N-H bending), 1429,1381 (C-H bending) , 1253 (C-N bending), 1159 (OH bending), 762 (disubstituted), 715(monosubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 3.74 (s, 2H), 7.21-7.23 (d, 1H), 7.26-7.30 (t, 1H), 7.34-7.36 (d, 2H, J=8.0 Hz), 7.38-7.40 (d, 1H), 7.51 (d, 1H), 7.55-7.60 (t, 4H), 7.78-7.85(d, 2H, J=8.0 Hz), 8.03-8.05(d, 1H), 8.27 (s, 1H), 8.50 (s, 1H),8.35 (s, 1H) MS: *m/z* = 531(M^+), 533(M^{+2}) ; Anal. Calcd. for $C_{30}H_{18}ClN_5O_3$: C, 75.56; H, 4.61; N,10.68; O, 9.15; Found: C, 75.46; H, 4.56; N, 10.68; O, 9.09.

3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyrimidine-2-carbonitrile. (STAB-1002)

IR (cm^{-1}): 3626,3568 (OH Stretching), 3421,3392,3275 (N-H stretching), 3189,3086 (Aromatic C-H stretching), 2908,(Aliphatic -CH_3 stretching), 2891 (Aliphatic -CH_2 Stretching), 2424,2333 (C-N Stretching), 1782(C=O Stretching), 1668,1618 (N-H bending), 1554,1379 (C-H bending) , 1165 (OH bending), 790 (disubstituted),

717(monosubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 2.36 (s, 3H), 3.76 (s, 2H), 7.16-7.18 (d, 2H), 7.20 (d, 1H), 7.25-7.27 (t, 1H), 7.34-7.38 (t, 1H), 7.44-7.46 (d, 2H), 7.50-7.52 (d, 2H, J=8.0 Hz), 7.59-7.77(t, 1H),7.86-7.88 (d, 2H, J=8.0Hz), 8.02-8.05 (d, 2H), 8.25 (s, 1H), 8.50 (s, 1H), 8.30 (s, 1H) MS: *m/z* = 511.16; Anal. Calcd. for $C_{34}H_{26}N_4O_3$: C, 75.82; H, 4.87; N, 10.40; O, 8.91; Found: C, 75.81; H, 4.80; N, 10.38; O,8.81.

3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1003)

IR (cm^{-1}): 3635,3542 (OH Stretching), 3465,3401 (N-H stretching), 3032,3024 (Aromatic C-H stretching), 2984 (Aliphatic -CH_3 stretching), 2823 (Aliphatic -CH_2 Stretching), 2332 (C-N Stretching), 1778(C=O Stretching), 1570 (N-H bending), 1428,1382 (C-H bending), 1263 (C-N bending), 1158 (OH bending), 793 (disubstituted), 716(monosubstituted), MS: *m/z* = 497.50; Anal. Calcd. for $C_{30}H_{19}N_5O_3$: C, 72.43; H, 3.85; N, 14.08; O,9.65, Found: C, 72.34; H, 3.75; N, 14.00; O,9.59.

3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1-(4-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1004)

IR (cm^{-1}): 3552 (OH Stretching), 3450,3417 (N-H stretching), 3062,3034 (Aromatic C-H stretching), 2984,2901 (Aliphatic -CH_3 stretching), 2839 (Aliphatic -CH_2 Stretching), 2332 (C-N Stretching), 1767(C=O Stretching), 1562 (N-H bending), 1560 (C-NO_2 stretching), 1439,1382 (C-H bending), 1263 (C-N bending), 1160 (OH bending), 794(disubstituted), 717(monosubstituted), MS: *m/z* = 542.50; Anal. Calcd. for $C_{30}H_{18}N_6O_5$: C,66.42; H, 3.34; N, 15.49; O,14.75 Found: C, 66.40; H, 3.29; N, 15.33; O,14.73.

3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1-(2-hydroxyphenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1005)

IR (cm^{-1}): 3602 (OH stretching), 3451,3427 (N-H stretching), 3032,3014 (Aromatic C-H stretching), 2974,2961 (Aliphatic -CH_3 stretching), 2838 (Aliphatic -CH_2 stretching), 2342 (C-N stretching), 1769(C=O stretching), 1572 (N-H bending), 1438,1381 (C-H bending), 1262 (C- N bending), 1161 (OH bending), 795 (disubstituted), 716 (monosubstituted), MS: *m/z* = 513.14; Anal. Calcd. for

$C_{30}H_{19}N_5O_4$: C, 70.17; H, 3.73; N, 13.64; O,12.46 Found: C, 70.13; H, 3.69; N, 13.53; O,12.43.

3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(2-methyoxyphenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1006)

IR (cm^{-1}): 3562 (OH stretching), 3456,3427 (N-H stretching), 3072,3024 (Aromatic C-H stretching), 2983,2911 (Aliphatic -CH_3 stretching), 2849(Aliphatic -CH_2 Stretching), 2342 (C-N stretching), 1768(C=O stretching), 1552(N-H bending), 1449,1372 (C-H bending), 1262 (C-N bending), 1161 (OH bending), 792 (disubstituted), 715 (monosubstituted), MS: *m/z* = 542.50; Anal. Calcd. for $C_{30}H_{18}N_6O_5$: C, 66.42; H, 3.34; N, 15.49; O, 14.75 Found: C, 70.51; H, 3.99; N, 13.15; O, 12.06.

3-Amino-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)-4-(1-(3-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1007)

IR(cm^{-1}): 3552 (OH stretching), 3450,3417 (N-H stretching), 3062,3034 (Aromatic C-H stretching), 2984,2901 (Aliphatic -CH_3 stretching), 2839 (Aliphatic -CH_2 stretching), 2332 (C-N stretching), 1767(C=O stretching), 1562 (N-H bending), 1565 (C-NO2 stretching), 1439,1382 (C-H bending), 1263 (C- N bending), 1154 (OH bending), 794 (disubstituted), 717(monosubstituted), MS: *m/z* = 569.57; Anal. Calcd. for $C_{33}H_{23}N_5O_5$: C, 69.59; H, 4.07; N, 12.30; O,14.05 Found: C, 69.54; H, 4.06; N, 12.21; O, 14.02.

3-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile. (STAB-1008)

IR (cm^{-1}): 3602 (OH stretching), 3430,3407 (N-H stretching), 3061,3024 (Aromatic C-H stretching), 2994,2911 (Aliphatic -CH_3 stretching), 2849 (Aliphatic -CH_2 stretching), 2339 (C-N stretching), 1777(C=O stretching), 1560 (N-H bending), 1449,1389 (C-H bending), 1253 (C-N bending), 1169 (OH bend.), 790 (disub.), 710(monosub.) MS: *m/z* = 515(M^+), 517(M^{+2}); Anal. Calcd. for $C_{30}H_{18}FN_5O_3$: C, 69.90; H, 3.52; N, 10.33; O, 8.85 Found: C, 69.80; H, 3.41; N, 10.23; O, 8.75.

3-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1009)

IR (cm^{-1}): 3562 (OH stretching), 3421,3402 (N-H stretching), 3042,3014 (Aromatic C-H stretching), 2984 (Aliphatic -CH_3 stretching), 2819 (Aliphatic -CH_2 stretching), 2232 (C-N stretching), 1760(C=O stretching), 1572 (N-H bending), 1429,1372 (C-H bending), 1269 (C-N bending), 1161 (OH bending), 792 (disubstituted), 707(monosubstituted), MS: *m/z* = 511.53; Anal. Calcd. for $C_{34}H_{26}N_4O_3$: C,72.79; H, 4.14 ; N, 13.69; O, 9.38 Found: C, 72.83; H, 4.11; N,13.59 ; O,9.39 .

3-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1010)

IR (cm^{-1}): 3602 (OH stretching), 3431,3407 (N-H stretching), 3012 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2829 (Aliphatic -CH_2 stretching), 2331 (C-N stretching), 1768(C=O stretching), 1572 (N-H bending), 1419,1381 (C-H bending), 1261 (C-N bending), 1161 (OH bending), 764 (disubstituted), 727(monosubstituted), MS: *m/z* = 525(M^+) ; Anal. Calcd. for $C_{32}H_{23}N_5O_3$: C, 73.13; H, 4.41; N, 13.33; O, 9.13 Found: C, 73.03; H, 4.31; N, 13.17; O,9.10.

3-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile. (STAB-1011)

IR (cm^{-1}): 35562 (OH stretching), 3420, (N-H stretching), 3069 (Aromatic C-H stretching), 2991 (Aliphatic -CH_3 stretching), 2849 (Aliphatic -CH_2 stretching), 2342 (C-N stretching), 1777(C=O stretching), 1582 (N-H bending), 1429,1372 (C-H bending), 1273 (C-N bending), 1140 (OH bending), 758 (disubstituted), 719(monosub.) MS: *m/z* = 545(M), 547(M^{+2}); Anal. Calcd. for $C_{31}H_{20}ClN_5O_3$: C, 68.20; H, 3.69; N, 12.83; O, 8.79 Found: C, 68.23; H, 3.51; N,12.71; O,8.89.

3-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1012)

IR (cm^{-1}): 3550 (OH stretching), 3470,3407 (N-H stretching), 3092 (Aromatic C-H stretching), 2974,2921 (Aliphatic -CH_3 stretching), 2859 (Aliphatic -CH_2 stretching), 2322 (C-N stretching), 1787(C=O stretching), 1563 (N-H bending), 1571 (C-NO_2) 1432,1381 (C-H bending), 1262 (C-N bending), 1168 (OH bending), 751

(disubstituted), 711(monosub.) MS: *m/z* = 556.15; Anal. Calcd. for $C_{31}H_{20}N_6O_5$: C, 66.90; H, 3.62; N, 15.10; O,14.37 Found: C, 66.83; H, 3.61; N, 15.07; O,14.49.

3-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1013)

IR (cm^{-1}): 3552 (OH stretching), 3452,3407 (N-H stretching), 3063,3014 (Aromatic C-H stretching), 2983,2911 (Aliphatic -CH_3 stretching), 2890 (Aliphatic -CH_2 stretching), 2330 (C-N stretching), 1787(C=O stretching), 1561 (N-H bending), 1429,1382 (C-H bending), 1253 (C-N bending), 1161 (OH bending), 761 (disubstituted), 717 (monosubstituted) MS: *m/z* = 527.16; Anal. Calcd. for $C_{31}H_{21}N_5O_4$: C,70.58; H, 4.01; N, 13.28; O,12.13 Found: C, 70.53; H, 4.01; N, 13.17; O,12.11.

3-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1014)

IR (cm^{-1}): 3651 (OH stretching), 3420,3407 (N-H stretching), 3052,3014 (Aromatic C-H stretching), 2994,2921 (Aliphatic -CH_3 stretching), 2829 (Aliphatic -CH_2 stretching), 2341 (C-N stretching), 1787(C=O stretching), 1562 (N-H bending), 1433,1372 (C-H bending) ,1262 (C-N bending), 1161 (OH bending), 764 (disubstituted), 714(monosubstituted) MS: *m/z* = 541.56; Anal. Calcd. for $C_{32}H_{23}N_5O_4$: C, 70.97; H, 4.28; N, 12.93; O, 11.82 Found: C, 70.83; H, 4.21; N, 12.87; O,11.75.

3-Amino-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-4-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1015)

IR (cm^{-1}): 3602 (OH stretching), 3490,3457 (N-H stretching), 3012,3031 (Aromatic C-H stretching), 2994,2981 (Aliphatic -CH_3 stretching), 2829 (Aliphatic -CH_2 stretching), 2382 (C-N stretching), 1777(C=O stretching), 1563 (N-H bending), 1560 (C-NO_2), 1429,1381 (C-H bending), 1253 (C-N bending), 1161 (OH bending), 755 (disubstituted), 702(monosubstituted), MS: *m/z* = 556.53; Anal. Calcd. for $C_{31}H_{20}N_6O_5$: C, 66.90; H, 3.62; N, 15.10; O, 14.37 Found: C, 66.91; H, 3.51; N, 15.07; O,14.39.

3-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-8-methyl-2-oxo-2H-chromen-3-yl)-pyridine-2-carbonitrile. (STAB-1016)

IR (cm^{-1}): 3552 (OH stretching), 3450,3417 (N-H stretching), 3062,3034 (Aromatic C-H stretching), 2984,2901 (Aliphatic -CH_3 stretching), 2839 (Aliphatic -CH_2 stretching), 2332 (C-N stretching), 1767(C=O stretching), 1562 (N-H bending), 1439,1382 (C-H bending), 1263 (C-N bending), 1160 (OH bending), 754 (disubstituted), 717(monosubstituted), MS: *m/z* = 529(M^+), 531(M^{+2}); Anal. Calcd. for $C_{31}H_{20}FN_5O_3$: C, 70.31; H, 3.81; N, 13.23; O,9.06 Found: C, 70.21; H, 3.71; N,13.21; O,9.01.

3-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(1,3-diphenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1017)

IR (cm^{-1}): 3642 (OH stretching), 3451,3427 (N-H stretching), 3069,3014 (Aromatic C-H stretching), 2994 (Aliphatic -CH_3 stretching) 2831 (Aliphatic -CH_2 stretching), 2334 (C-N stretching), 1787(C=O stretching), 1564 (N-H bending), 1439,1382 (C-H bending), 1269 (C-N bending), 1159 (OH bending), 759 (disubstituted), 711(monosubstituted), MS: *m/z* = 525.56; Anal. Calcd. for $C_{33}H_{23}N_5O_3$: C, 73.13; H, 4.41; N, 13.33; O, 9.13 Found: C, 73.05; H, 4.31; N,13.27; O,9.08.

3-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(3-phenyl-1-p-tolyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1018)

IR (cm^{-1}): 3602 (OH stretching), 3460,3417 (N-H stretching), 3068,3024 (Aromatic C-H stretching), 2989,2911 (Aliphatic -CH_3 stretching)d 2829 (Aliphatic -CH_2 stretching), 2342 (C-N stretching), 1747(C=O stretching), 1532 (N-H bending), 1439,1382 (C-H bending), 1268 (C-N bending), 1169 (OH bending), 748 (disubstituted), 719(monosubstituted), MS: *m/z* = 539.58; Anal. Calcd. for $C_{33}H_{25}N_5O_3$: C,73.46; H, 4.67; N, 12.98; O, 8.90 Found: C, 73.33; H, 4.61; N, 12.97; O,8.84.

3-Amino-4-(1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile.(STAB-1019)

IR (cm^{-1}): 3552 (OH stretching), 3450,3417 (N-H stretching), 3061,3031 (Aromatic C-H stretching), 2974,2911 (Aliphatic -CH_3 stretching), 2839 (Aliphatic -CH_2 stretching), 2332 (C-N stretching), 1767(C=O stretching), 1561 (N-H bending),

1438,1381 (C-H bending), 1262 (C-N bending), 1162 (OH bending), 795 (disubstituted), 717(monosub.) MS: *m/z* = 559(M^+), 561(M^{+2}); Anal. Calcd. for $C_{32}H_{22}ClN_5O_3$: C, 68.63; H, 3.96; N, 12.51; O,8.57 Found: C, 68.53; H, 3.91; N,12.41; O,8.47.

3-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(1-(4-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1020)

IR (cm^{-1}): 3556 (OH stretching), 3456,3467 (N-H stretching), 3162,3024 (Aromatic C-H stretching), 2994,2981 (Aliphatic -CH_3 stretching), 2829 (Aliphatic -CH_2 stretching), 2331 (C-N stretching), 1768(C=O stretching), 1562 (N-H bending), 1560 (C-NO_2 stretching), 1429,1392 (C-H bending), 1253 (C-N bending), 1161 (OH bending), 754 (disubstituted), 707(monosubstitute), MS: *m/z* = 570.55; Anal. Calcd. for $C_{32}H_{22}N_6O_5$: C, 67.36; H, 3.89; N, 14.73; O,14.02 Found: C, 67.33; H, 3.81; N, 14.67; O,14.06.

3-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(1-(2-hydroxyphenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1021)

IR (cm^{-1}): 3612 (OH stretching), 3460,3427 (N-H stretching), 3065,3014 (Aromatic C-H stretching), 2994,2911 (Aliphatic -CH_3 stretching), 2839 (Alipharic -CH_2 strething), 2332 (C-N stretching), 1767(C=O stretching), 1562 (N-H bending), 1449,1383 (C-H bending), 1253 (C-N bending), 1169 (OH bending), 759 (disubstituted), 717(monosubstituted), MS: *m/z* = 541.56; Anal. Calcd. for $C_{32}H_{23}N_5O_4$: C,70.97; H, 4.28; N, 12.93; O, 11.82 Found: C, 70.83; H,4.17; N, 12.77; O,11.74.

3-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4(1-(2-methoxyphenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1022)

IR (cm^{-1}): 3552 (OH stretching), 3458, (N-H stretching), 3034 (Aromatic C-H stretching), 2901 (Aliphatic -CH_3 stretching), 2849 (Aliphatic -CH_2 stretching), 2342 (C-N stretching), 1777(C=O stretching), 1561 (N-H bending), 1439,1382 (C-H bending),1261 (C-N bending), 1161 (OH bending), 758 (disubstituted), 712(monosub.) MS: *m/z* = 555.19; Anal. Calcd. for $C_{33}H_{25}N_5O_4$: C, 71.34; H, 4.54; N, 12.61; O,11.52 Found: C, 71.23; H, 4.41; N, 12.57; O,11.41.

3-Amino-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)-4-(1-(3-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)pyridine-2-carbonitrile. (STAB-1023)

IR (cm^{-1}): 3612 (OH stretching), 3455,3447 (N-H stretching), 3062,3014 (Aromatic C-H stretching), 2974, (Aliphatic -CH_3 stretching), 2849 (Aliphatic -CH_2 stretching), 2334 (C-N stretching), 1769(C=O stretching), 1569 (N-H bending), 1561 (C-NO_2 stretching), 1449,1384 (C-H bending), 1264 (C-N bending), 1164 (OH bending), 769 (disubstituted), 719(monosubstituted), MS: *m/z* = 570.55; Anal. Calcd. for $C_{32}H_{22}N_6O_5$: C,67.36; H, 3.89; N, 14.73; O,14.02 Found: C, 67.23; H, 3.81; N, 14.67; O,14.01.

3-Amino-4-(1-(4-fluorophenyl)-3-phenyl-1H-pyrazol-4-yl)-6-(4-hydroxy-5,8-dimethyl-2-oxo-2H-chromen-3-yl)pyridine-2-carbonitrile. (STAB-1024)

IR (cm^{-1}): 3562 (OH stretching), 3456,3427 (N-H stretching), 3092,3084 (Aromatic C-H stetching), 2901 (Aliphatic -CH_3 stretching), 2899 (Aliphatic -CH_2 stretching), 2342 (C-N stretching), 1787(C=O stretching), 1563 (N-H bending), 1449,1342 (C-H bending), 1264 (C-N bending), 1164 (OH bending), 768 (disubstituted), 707(monosubstituted), MS: *m/z* = 543(M^+), 545(M^{+2}); Anal. Calcd. for $C_{32}H_{22}FN_5O_3$: C, 70.71; H, 4.08; N, 12.88; O,8.83 Found: C, 70.65; H, 4.02; N,12.79; O,8.72.

5.11 RESULTS AND DISCUSSION

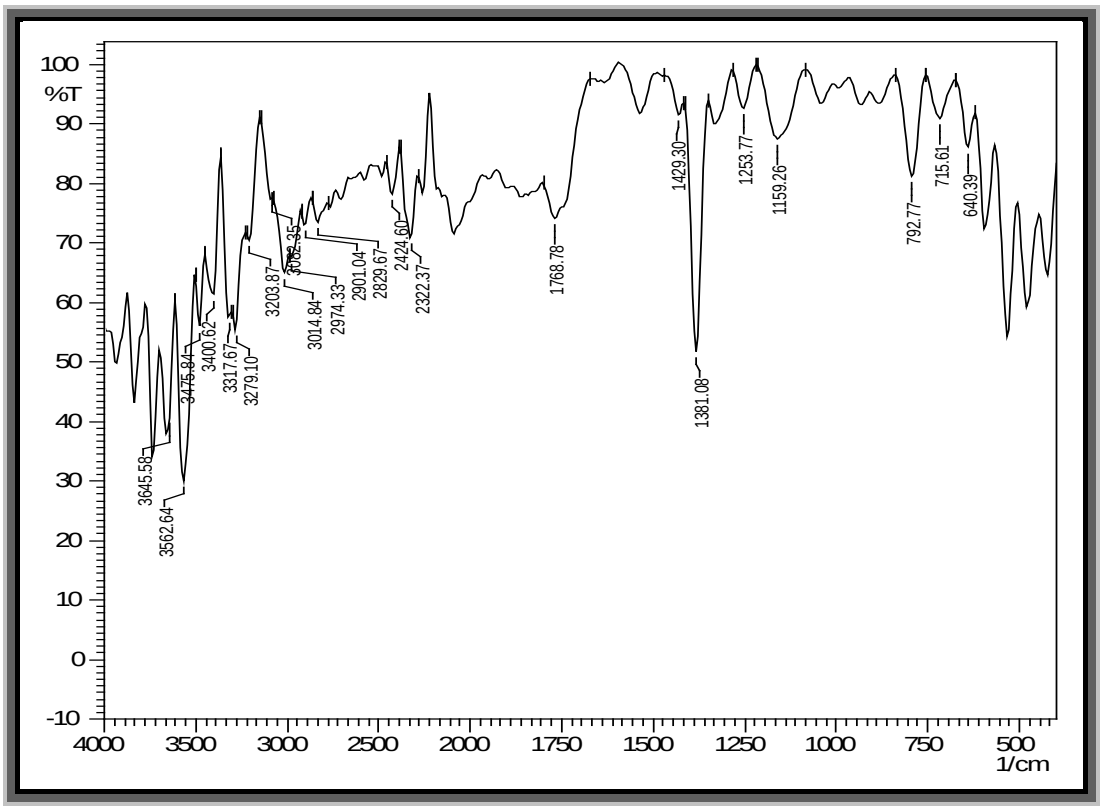
24 cyanopyridine derivatives were prepared in 60 to 70 percentage yield by conventional method and 70 to 80 percentage yield were obtained by microwave method. Thus the later is found to be superior method.

5.12 CONCLUSION

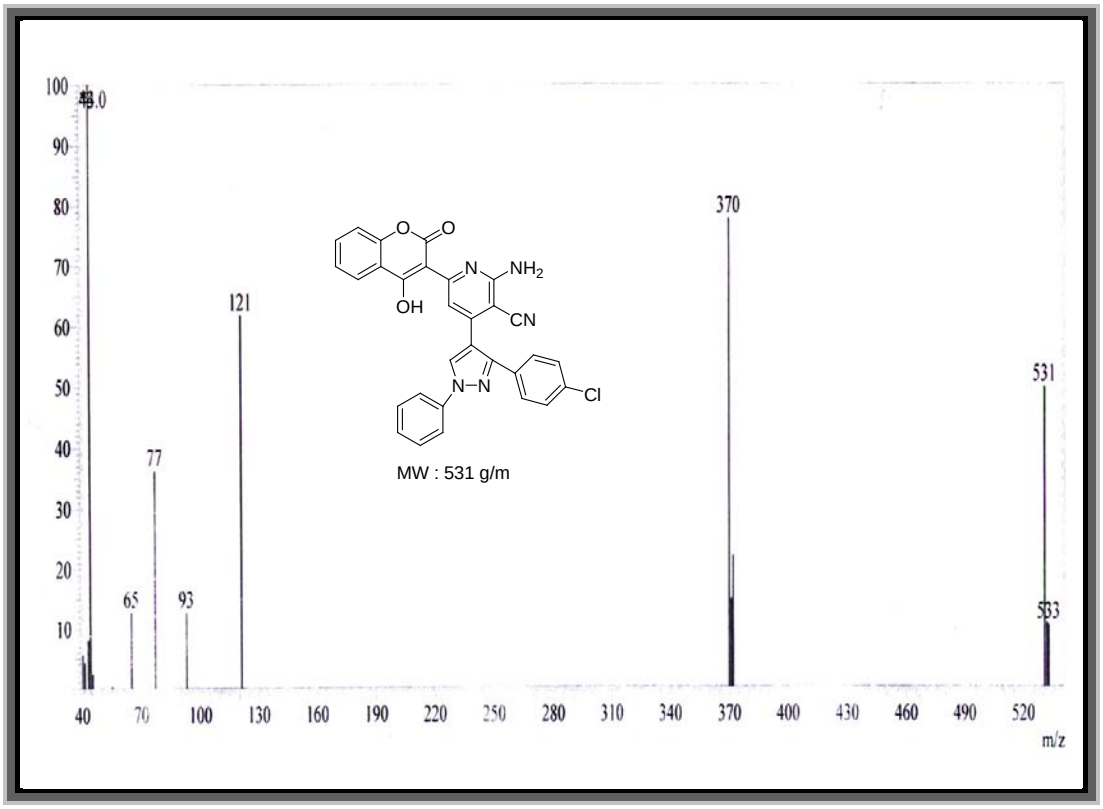
A comparative study of conventional and microwave assisted methods reveals that the time taken by the microwave method is approximately 5-10 minutes in compare to conventional method which takes minimum 5-6 hrs. The yield of the products also increases 10-15% by the microwave method.

5.13 REPRESENTATIVE SPECTRAS

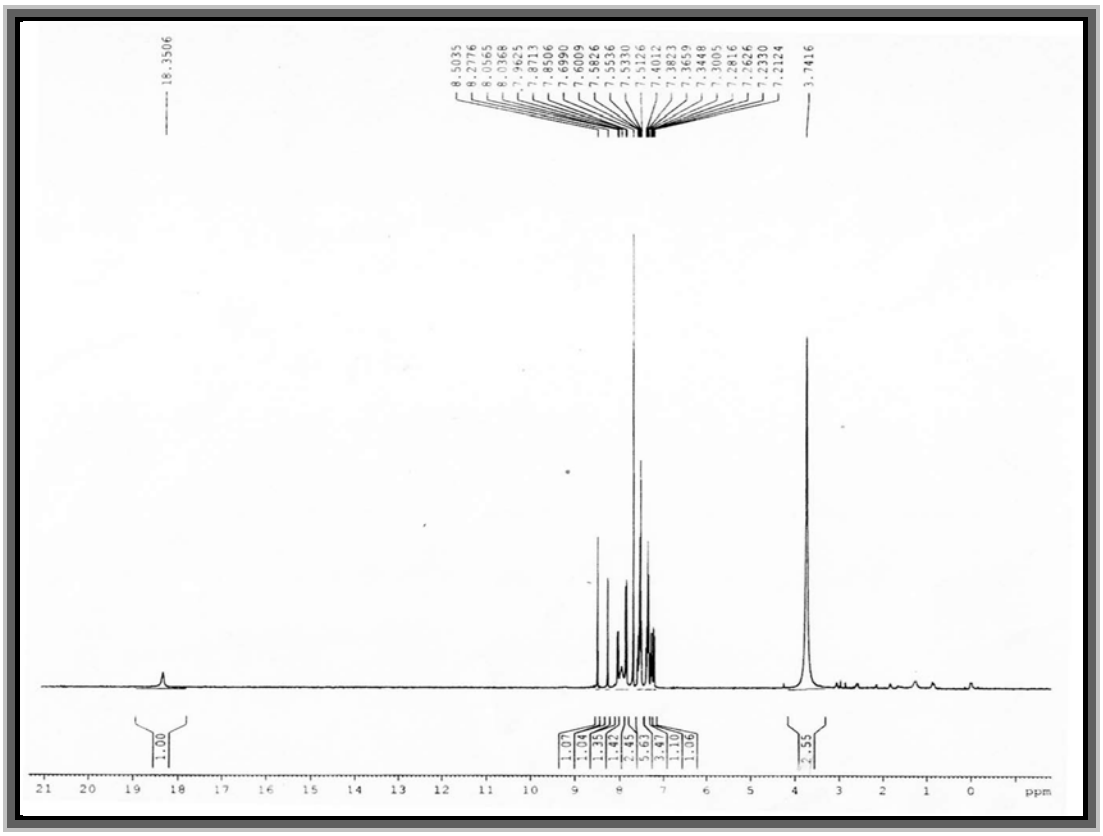
5.13.1 IR Spectrum of STAB-1001



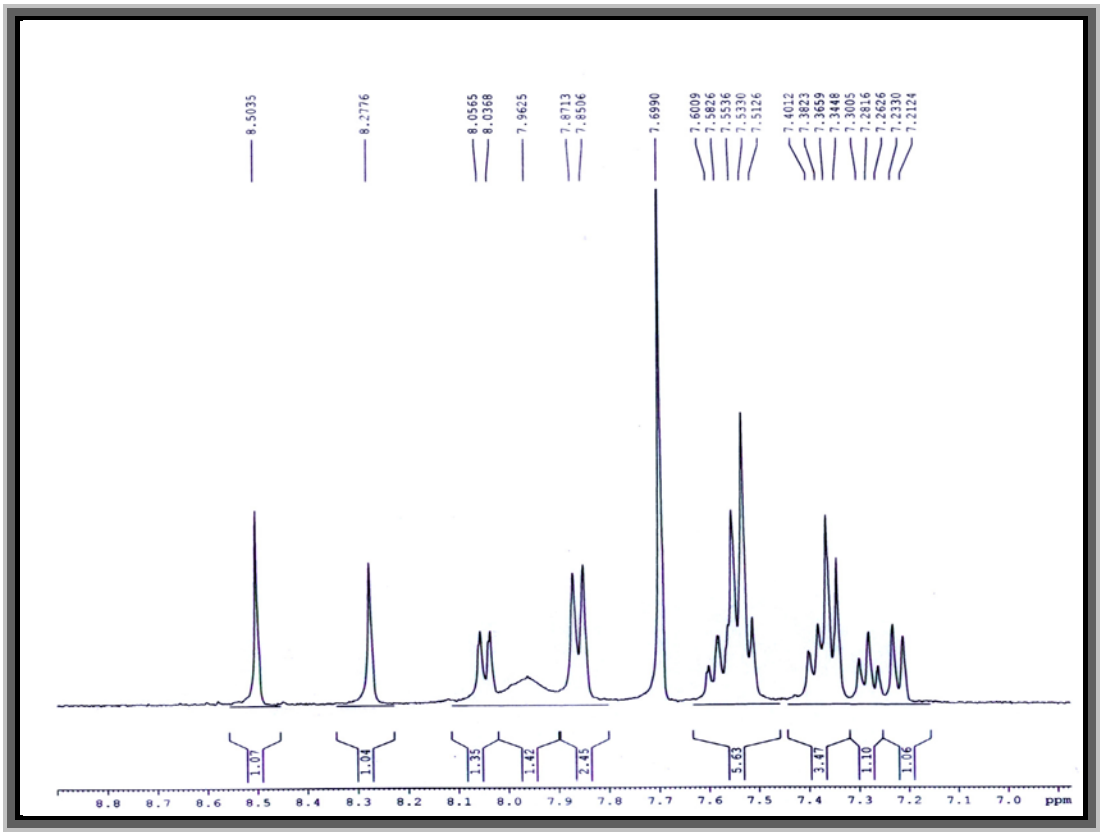
5.13.2 Mass Spectrum of STAB-1001



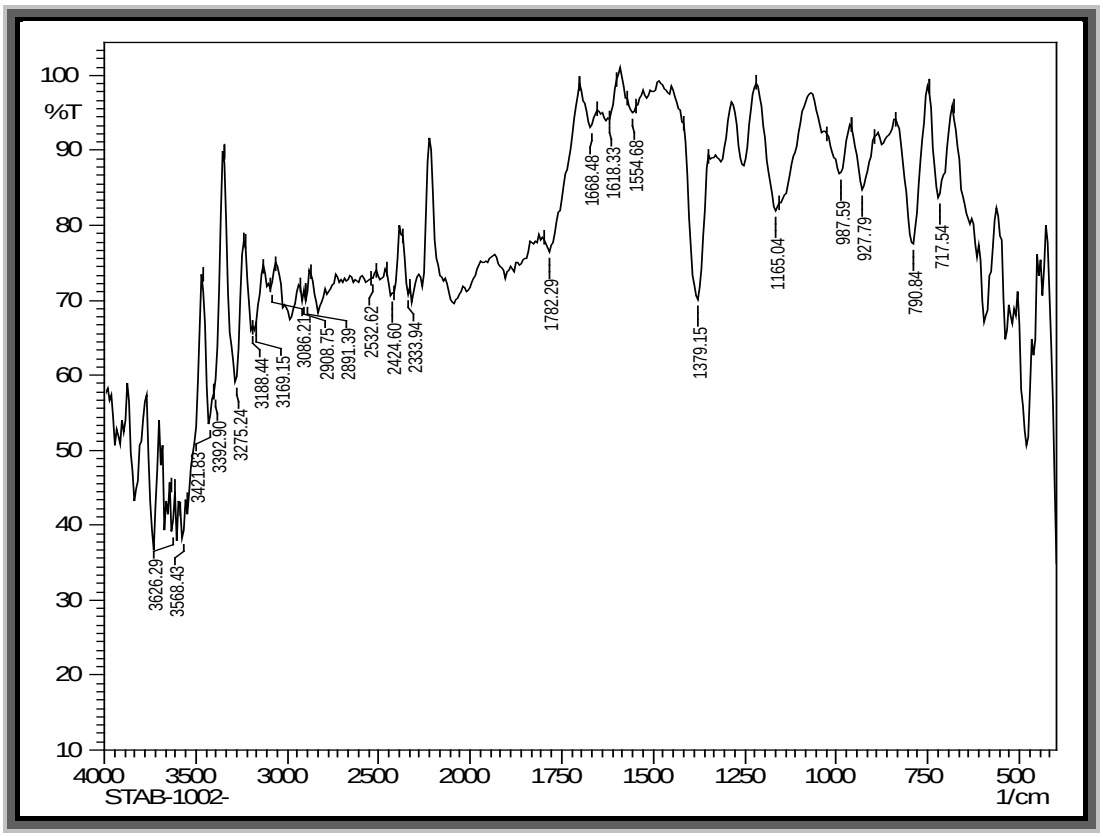
5.13.3 ^{1}H NMR Spectrum of STAB-1001



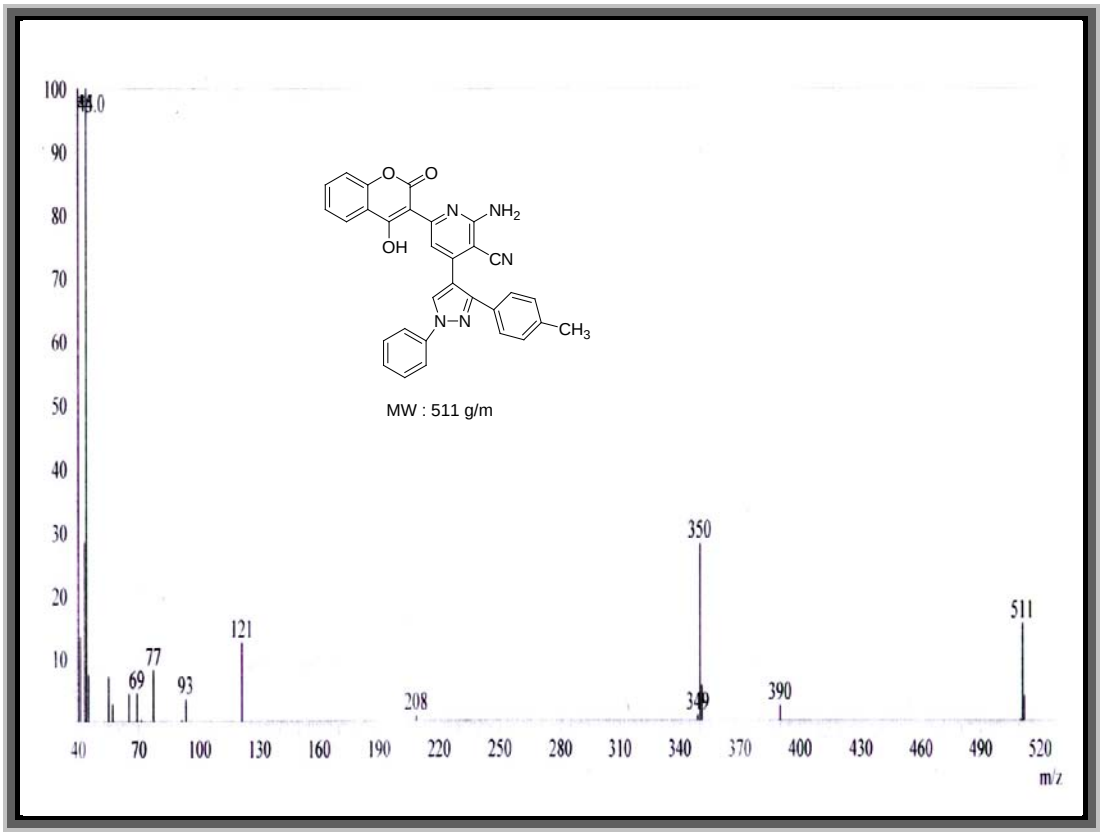
5.13.4 Expanded ^{1}H NMR Spectrum of STAB-1001



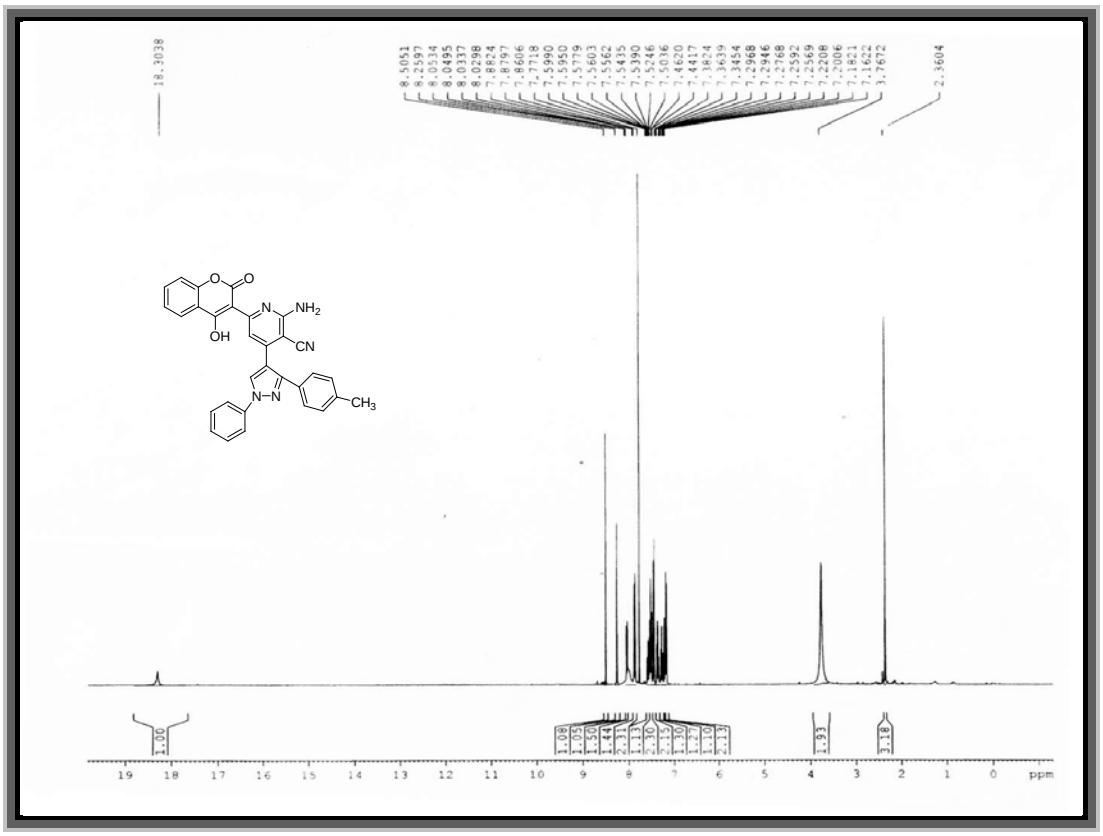
5.13.5 IR Spectrum of STAB-1002



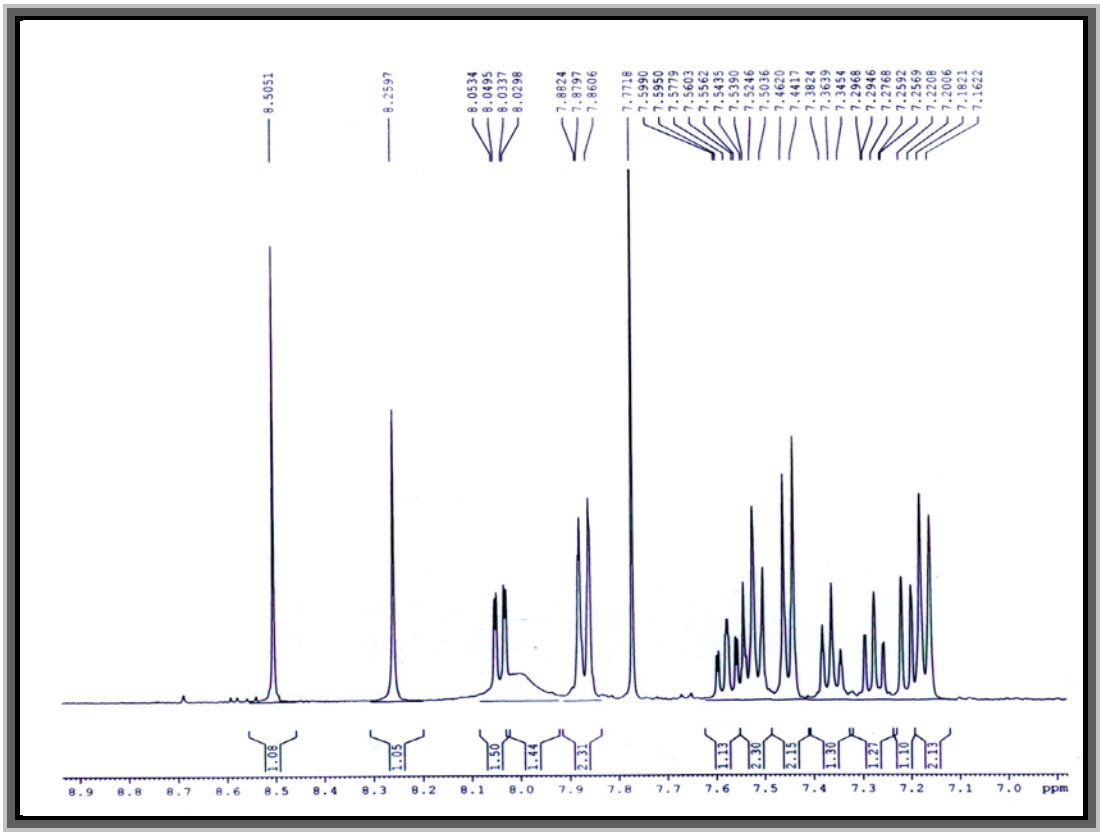
5.13.6 Mass Spectrum of STAB-1002



5.13.7 ^{1}H NMR Spectrum of STAB-1002



5.13.8 Expanded ^{1}H NMR Spectrum of STAB-1002



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Chapter-6

Synthesis of benzopyran clubbed 1,5-benzodiazepines appended to pyrazoles.

6.1 INRODUCTION

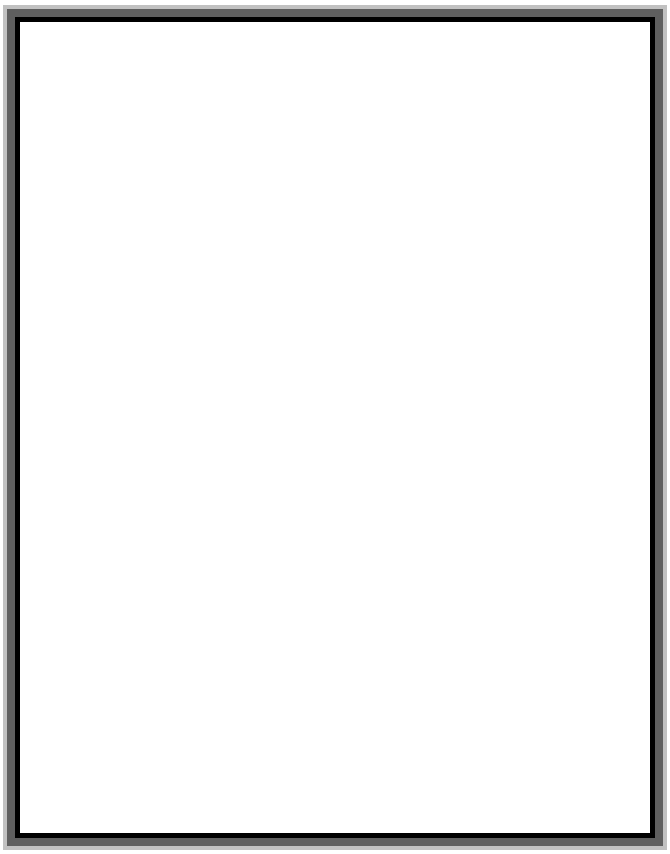
Coumarin system is an important heterocyclic skeleton which lead to number of synthetic drugs like dicoumarol, warfarin, acenocoumarin etc. Recently researchers introduced coumarin derivatives as inhibitors of lipoxygenase and cyclooxygenase in the arachidonic acid cascade[1-3] of serine protease[4-8] and of tyrosine kinase.[9] Many coumarin derivatives have also been found to inhibit peroxidation[9] and to possess vasorelaxant,[9] anticoagulant,[10] anti-inflammatory and antioxidant activities.[11-14] Coumarins have been evaluated in vitro, for their inhibitory activity towards bovine α-chymotrypsin, human leukocyte elastase[15-17] and thrombin, plasmin and tissue ploaminogen activators. 4-hydroxy coumarin and its derivatives are also reported to possess significant antibacterial,[18] coronary dialatory,[19] hypothermal[20-23] and antiviral,[24] antimicrobial,[25-26] antitubercular,[27] MDR reversal[28] and cytotoxic activities[29] too.

On the other hand, are the examples of the serendipitous discovery of new drugs based on an almost random screening of chemicals synthesized in the laboratory is striking. Since 1960, when chlordiazepoxide (Librium) entered in the market, efforts to discover new biologically active compounds with limited side effects in benzodiazepines are going on which are reflected by the important number of publication focused in this subject.[30-34]

Benzodiazepines have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, antianxiety, analgesic, sedative, anti-depressive, hypnotic agents[35] as well as anti-inflammatory agents.[36] Other than their biological importance, benzodiazepine derivatives are also commercially used as dyes for acrylic fibres.[37] Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be used in preparation of other fused ring compounds such as triazolo, oxadiazolo, oxazino or furano-benzodiazepines.[38] Research in this area is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. Generally, these compounds are synthesized by the condensation of *o*-

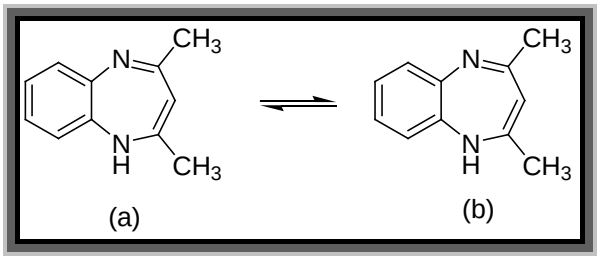
phenylenediamines with α, β-unsaturated carbonyl compounds,[39] β-haloketones, or ketones.[40]

Among all types of benzodiazepines (1,2-,1,3-, 1,4-, 1,5-, 2,3-, & 2,4-) only 1,4- and 1,5-benodiazepines have found wide applications in medicines, during one of the most important classes of the therapeutic agents with wide spread biological activities[41] including hypnotics, sedatives, anxiolytics and antianxiety etc. Effects range from their well-documented anticonvulsive or tranquilizing properties, through pesticidal[42] or antitumor[43] action and to their more recently described peptidomimetic activity.[44]



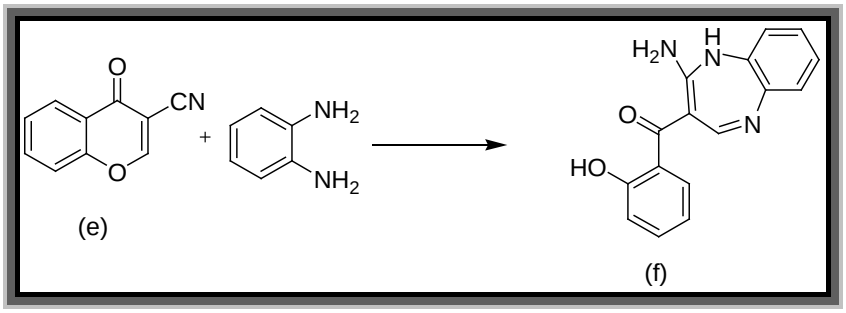
6.2 SYNTHETIC METHODS

The most widely used method for the synthesis of 3H-1,5-benzodiazepines is condensation of 1,2-diaminobenzene and 1,3-diketones or their enols, in presence of acid catalyst to yield violet 2,5-dialkyl-1,5-benzodiazepinium chlorides as primary product. Upon neutralization with sodium hydroxide will give yellow coloured diazepine tautomer (a, b).[45]



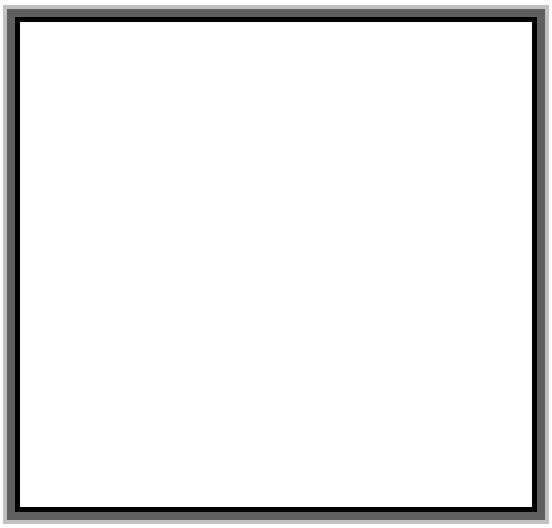
Augustin *et al.*[46] has synthesized 2-aryl substituted 2,5-dihydro-1H-1,5-benzodiazepine (d) in 25-94% yield by condensation of (Z/E)-1-aryl-4-arylmethylene pyrrolidine-2,3,5-triones(c) with O-phenylene diamine.

Risitano *et al.*[47] have discovered versatile method from chromone derivative as starting material. Thus, 3-cyano chromone (e), when reacts with O-phenylene diamine afforded 1H-1,5-benzodiazepine (f).

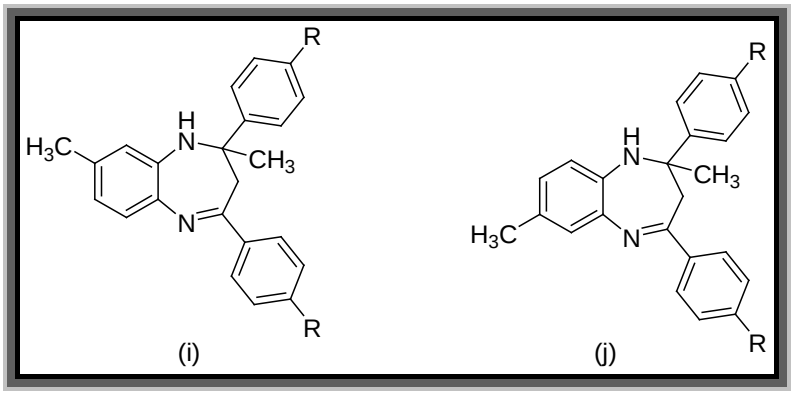


(e) (f)

Cohen *et al.*[48] used crotonic acid or methacrylic acid (g) as a new starting material for preparation of substituted 1,5-benzodiazepine-2-ones (h) when it reacts with substituted 1,2-phenylene diamine.

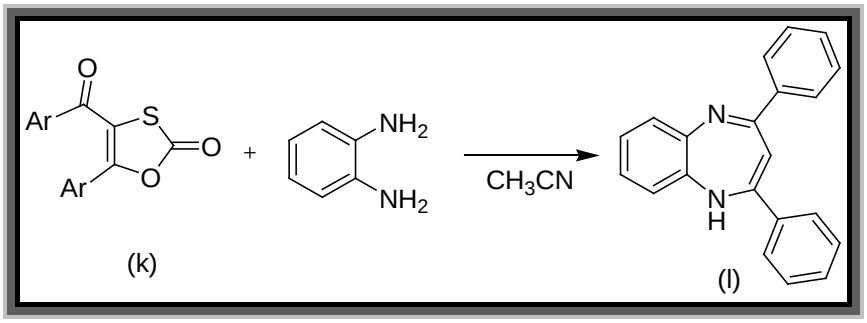


Insuasty *et al.*[49] had suggested that 1,2-diamino-4-methylbenzene reacts in the presence of sulphuric acid with 4-substituted acetophenones yielding 2,4-diaryl-2,3-dihydro-2,8-dimetyl 1H-1,5-benzodiazepines(i) and as minor components 2,4-diaryl-2,3-dihydro-2,7-dimethyl-1H-1,5-benzodiazepines(j).

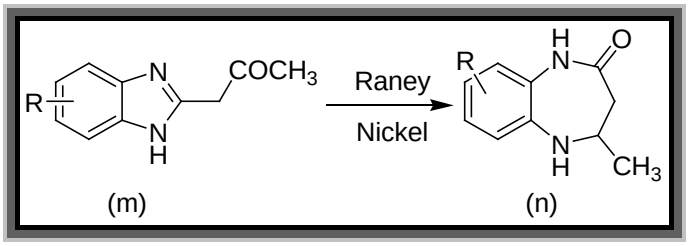


(i) (j)

He-Xi *et al.* [50] synthesized 2,4-diphenyl-1,5-benzodiazepine (k) via reaction of 4-benzoyl-5-phenyl-1,3-oxathiol-2-ones (l) with 1,2-aminobenzene (Orthophenylene diamine).

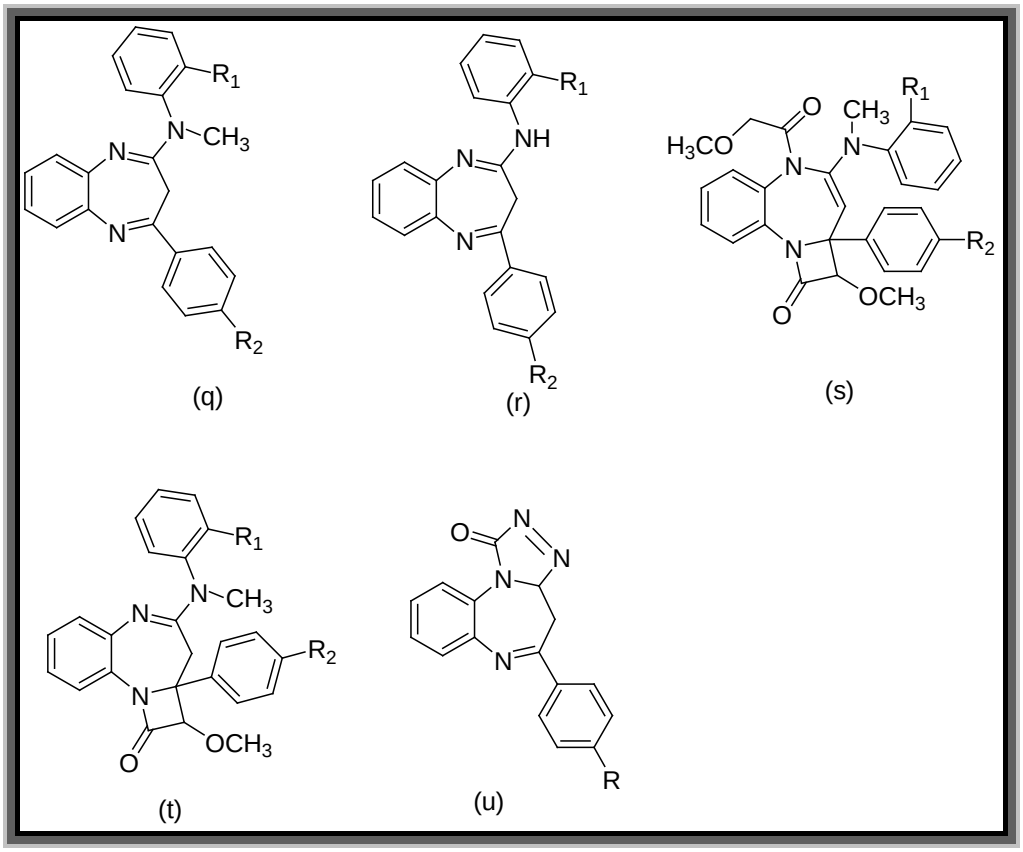


O-Nitro acetoacetanilide are reduced by iron in alcoholic hydrochloric acid to give 2-acetonyl benzimidazole(m). Catalytic hydrogenation of these anilides in presence of Raney Nickel yields the diazepinone derivative(n).[51]

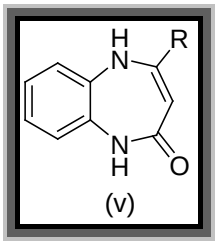


Hamdi *et al.*[52] has established a new method of synthesis of 1,5-benzodiazepine-2-one (p) from 4-hydroxy coumarin(o) and substituted 1,2-phenylenediamines by heating in xylene or acetic acid-ethanol.

Eduardo *et al.*[53-54] Cortes and his group have focused their efforts on search for superior central nervous system agent. They have studied heterocyclic varients of the 1,5-benzodiazepine system specially derivatives like (q), (r), (s), (t), (u).

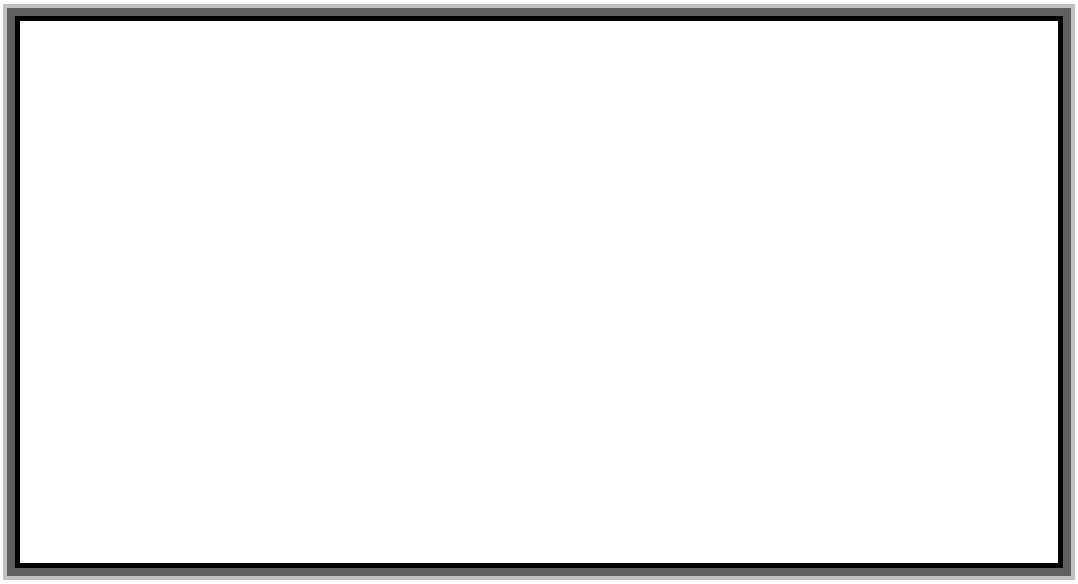


Bougrin *et al.*[55] has carried out a reaction of O-β-arylenediamines with β-ketoesters in xylene under microwave irradiation to prepare substituted 1,5-benzodiazepines(v). Here, the specific effects of microwave are evidenced as no reaction occurs by classical heating in the same reaction.

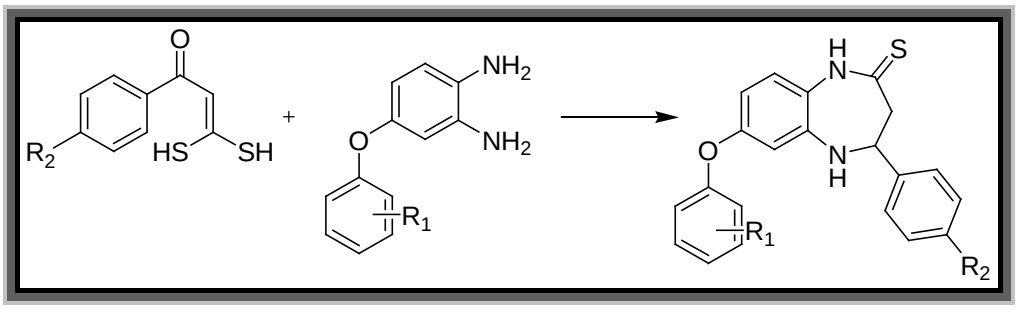


Reaction of 4-Chloro-1,2-diaminobenzene with 3,3-dimercapro-1-phenyl-2-propen-1-one afforded a mixture of 7-chloro and 8-chloro-1,3-dihydro-4-phenyl-2H-1,5-benzodiaze-2-thione. On separation of these two products, 7-chloro compound is

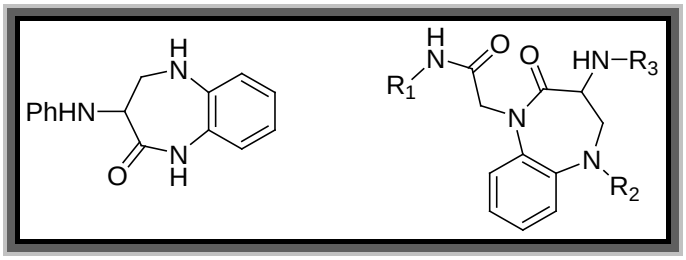
treated with NaH and N,N-diethyl amino ethyl chloride which on further chemical reaction gives 7-Chloro-2-(2-diethylaminoethylthio)-4-phenyl-3H-1,5-benzodiazepine.[56]



2,3-Dihydro-4-(p-substituted phenyl)-7-[(o, m and p-substituted) phenoxy]-1H-1,5-benzodiazepine-2-thiones has been synthesized by condensing the 3,3-dimercapto-1-(Para substituted phenyl)-2-propen-1-one with 3,4-diaminophenyl-R-phenyl ethers.[57]

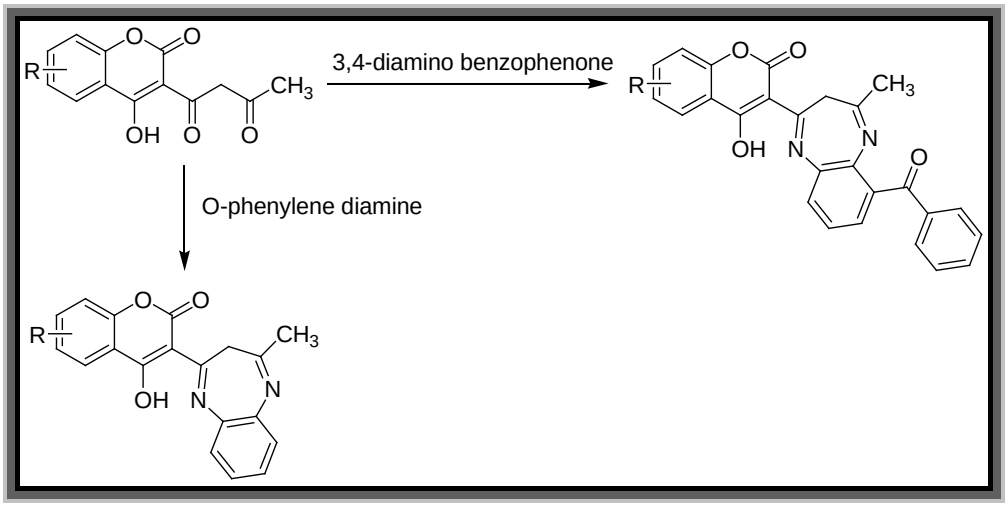


The strategy, the design and the constraints for a lead discovery library are radically different than for a hit optimization library. Examples of both types of libraries and solid-phase chemistry to prepare 1,5-benzodiazepine-2-one and its derivatives were presented.[58]



Various heterocycles including 1,5-diazepines were prepared from 3-acetoacetyl-4-hydroxy coumarin and 1,2-phenylene diamine/3,4-diamino benzophenone using reported method.[59-60] They also studied antimicrobial[61], antifungal,[62] anti-HIV[63-64] and antitubercular activity of these compounds.

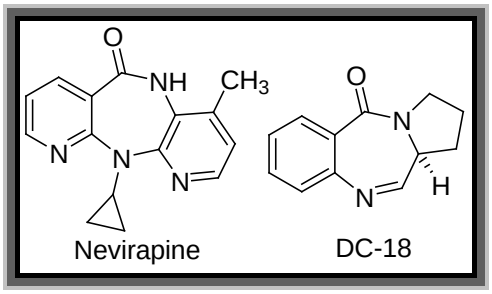
In many compounds,[65,66] MIC were observed >6.25 µg/ml bearing >70% inhibition against mycobacterium tuberculosis (H_{37} Rv strain), when compared of Rifampicin (99% inhibition).



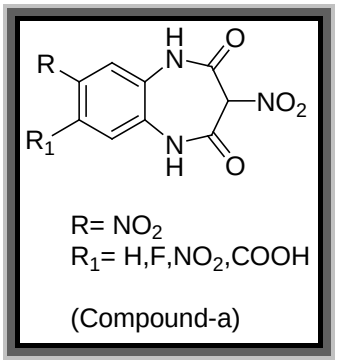
Gopalakrishna *et al.*[67] reported the three component Mannich reaction of 1,5-benzodiazepine catalyzed by a tetranitrile-silver complex.

6.3 BIOLOGICAL PROFILE

More recent analogues of the Benzodiazepines have attracted interest as anti HIV compounds, such as the clinically used nevirapine and as anticancer compounds, such as the pyrrolo fused antitumor antibiotic DC-18, analogues of which are in clinical development as anticancer agents.[68]



Buckle *et al.*[69] prepared 1H-benzo-1,5-diazepine-2,4-(3H,5H)- diones(compound-a) from 4,2-$R_2(NH_2)C_6H_3$ NH_2(R_2= H, Cl, F, COOH) by refluxing with malonic acid in 4N HCl for half an hour followed by nitration with fuming HNO_3 which is antiallergic substance useful in the treatment of rhinitis, hay fever and certain type of asthma.

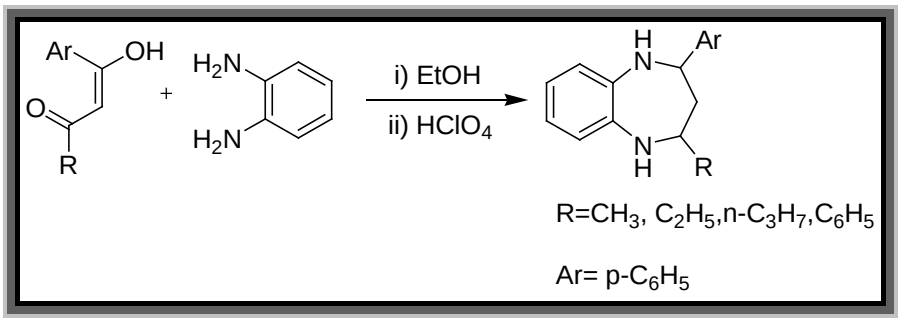


The a-β-unsaturated ketones of 3-arylsydnones were treated with 1,2-phenylenediamine to obtain the 3-Aryl-4-[2'-aryl-2',4',6',7'-tetrahydro-(1'H)-1',5'-benzodiazepine-4'-yl] sydnones in high yield. All the new compounds synthesized were screened for antibacterial and antifungal activities.[70]

Rubin *et al.*[71] al have synthesized 4-phenyl-2-trichloromethyl-3H-1,5-benzodiazepine hydrogen sulphate and examined its pharmacological effects in mice,

keeping diazepam as reference. The data suggest that this recently synthesized compound possesses anxiolytic activity and produces motor in co-ordination similar to those observed with diazepam.

4-Alkyl/aryl-2-fluoroaryl-1H-1,5-benzodiazepines exhibits excellent gastric acid secretion pylorus ligation, passaive cutaneous and parasitological activities in rats and monkeys.[72]



6.4 AIM OF CURRENT WORK

The current work is aimed as preparing some new hybrid derivatives of benzodiazepines clubbed with coumarin skeleton to arrive at small library of “drug like” substances. Since benzodiazepine is a priviledge structure, the possibility of diversed pharmacological activities are expected from compounds synthesized in this chapter.

6.5 REACTION SCHEMES

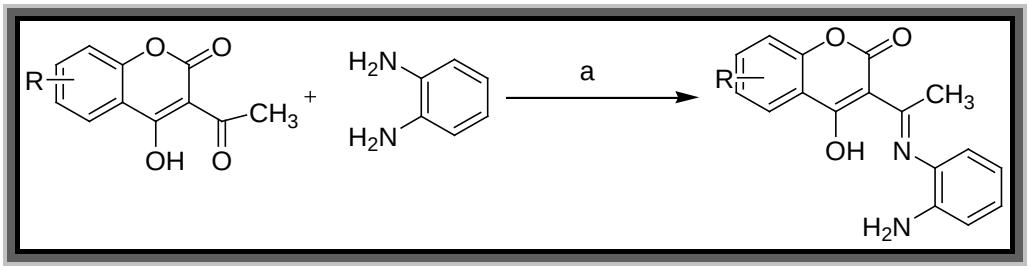
6.5.1 PREPARATION OF PYRAZOLE ALDEHYDES :

It was prepared according to method described in Chapter-1

6.5.2 PREPARATION OF 3-ACETYL 4-HYDROXY COUMARINS :

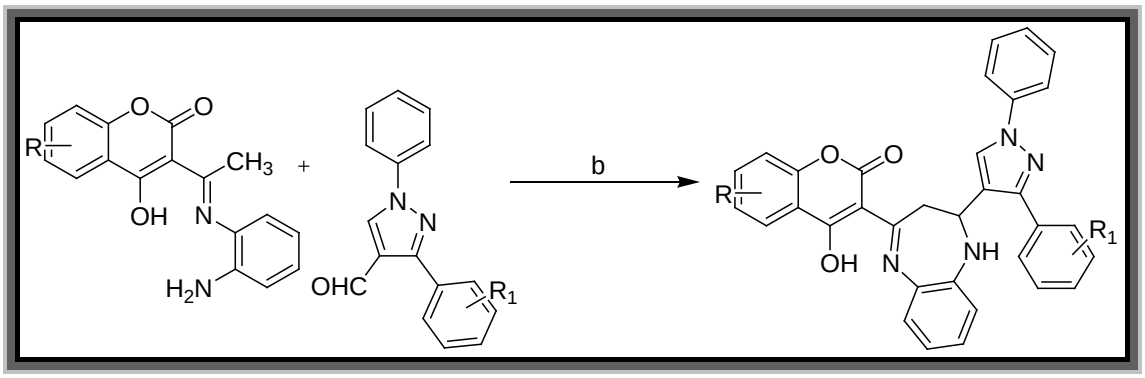
It was prepared according to method described in Chapter-4

6.5.3 PREPARATION OF 3-[(1E)-N-(2- AMINOPHENYL) ETHANIAMIDOYL]-4-HYDROXYL-2H-CHROMENE-2-ONE :



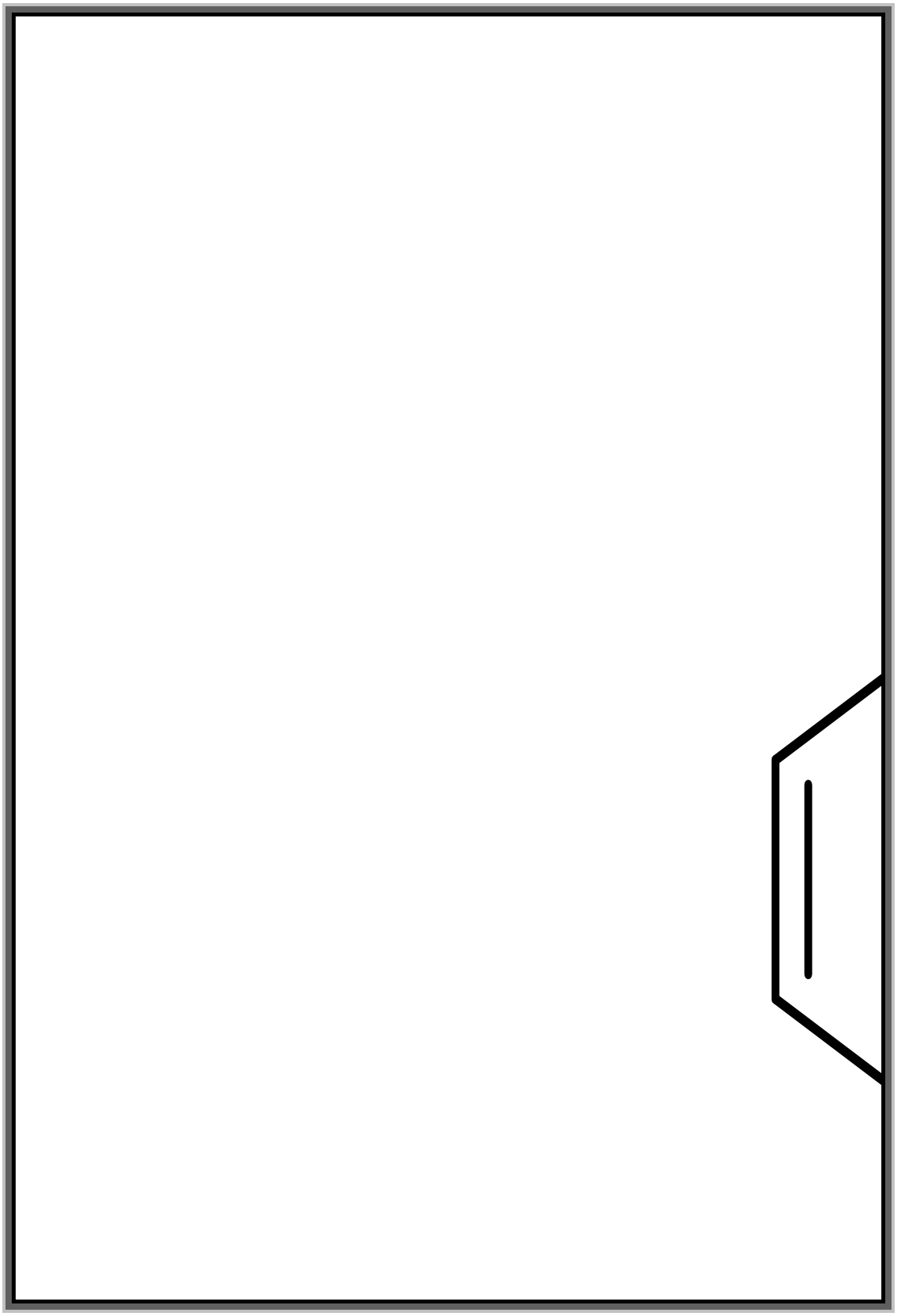
Reagents / Reaction Condition (a) :,Ethanol / Reflux, 8-10 hrs.

6.5.4 PREPARATION OF 4-HYDROXY-3-[2-(4-N,N-DIMETHYLPHENYL)-2,3-DIHYDRO-1,5-BENZODIAZEPIN-4-YL]-2H-CHEOMEN-2-ONE :



Reagents / Reaction Condition (a) :,Ethanol + DMF, TFA / Reflux, 4-6 hrs.

6.6 PLAUSIBLE REACTION MECHANISM



6.7 EXPERIMENTAL

6.7.1 MATERIALS AND METHODS

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 pellet 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 solution on a **Bruker Ac 400 MHz spectrometer**. Elemental analysis of the all the synthesized compounds was carried out on Elemental **Vario EL III Carlo Erba 1108** model and the results are in agreements with the structures assigned.

6.7.2 PREPARATION OF PYRAZOLE ALDEHYDE :

It was prepared according to method described in Chapter-1

6.7.3 PREPARATION OF 3-ACETYL 4-HYDROXY COUMARIN :

It was prepared according to method described in Chapter-4

6.7.4 PREPARATION OF 3-[(1E)-N-(2-AMINOPHENYL) ETHANIMIDOYL]-4-HYDROXYL-2H-CHROMEN-2-ONE :

3-Acetyl-4-hydroxy coumarin (0.01mole) and O-phenylene diamine (0.01mole) was dissolved in 30ml ethanol and refluxed the content for 8-10 hrs. Solid separated out is to be filtered and washed with chilled methanol, recrystallize it from mixture of methanol–DMF.

Similarly other compounds are also prepared.

6.7.5 PREPARATION OF 4-HYDROXY-3-[2-(4-N,N-DIMETHYLPHENYL)-2,3-DIHYDRO-1,5-BENZODIAZEPIN-4-YL]-2H-CHROMEN-2-ONE :

3-[(1E)-N-(2-Aminophenyl) ethanimidoyl]-4-hydroxy-2H-chromen-2-one (0.01mole) and substituted pyrazole aldehydes (0.01mole) was dissolved in a mixture of ethanol-dimethyl formamide and refluxed in an oil-bath at 115-120^{O}C with catalytic amount of triflouroacetic acid for 4-5 hrs. During the reaction the 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. Pour the content into crushed ice. The solid separated out was filtered, washed, dried and recrystallized it from methanol.

Similarly other compounds are also prepared.

The physical constant of newly synthesized compounds are given in the Table No.6

6.8 PHYSICAL DATA

Physical data of *3((E)-2,3-dihydro-2-(3-(substituted)phenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]dizepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one.*

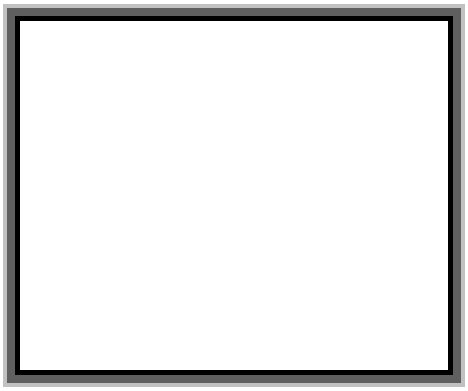


TABLE - 6

Code	Substitution		MF	MW	MP	Rf Value
	R	R_1				
TAP-01	H	H	$C_{33}H_{24}N_4O_3$	524	180-182	0.46
TAP-02	4-CH_3	H	$C_{34}H_{26}N_4O_3$	538	204-206	0.52
TAP-03	4-NO_2	H	$C_{33}H_{23}N_5O_5$	569	226-228	0.44
TAP-04	2-OH	H	$C_{33}H_{24}N_4O_4$	540	208-210	0.48
TAP-05	2-OCH_3	H	$C_{34}H_{26}N_4O_4$	554	196-198	0.50
TAP-06	4-Cl	H	$C_{33}H_{23}ClN_4O_3$	559	188-190	0.40
TAP-07	3-NO_2	H	$C_{33}H_{23}N_5O_5$	569	210-212	0.44
TAP-08	4-F	H	$C_{33}H_{23}FN_4O_3$	542	178-180	0.48
TAP-09	H	8-CH_3	$C_{34}H_{26}N_4O_3$	538	186-188	0.42
TAP-10	4-CH_3	8-CH_3	$C_{35}H_{28}N_4O_3$	552	168-170	0.46
TAP-11	4-Cl	8-CH_3	$C_{34}H_{25}ClN_4O_3$	573	194-196	0.42
TAP-12	4-NO_2	8-CH_3	$C_{34}H_{25}N_5O_5$	583	206-208	0.54
TAP-13	2-OH	8-CH_3	$C_{34}H_{26}N_4O_4$	554	178-180	0.50
TAP-14	2-OCH_3	8-CH_3	$C_{35}H_{28}N_4O_4$	568	166-168	0.48
TAP-15	3-NO_2	8-CH_3	$C_{34}H_{25}N_5O_5$	583	218-220	0.40
TAP-16	4-F	8-CH_3	$C_{34}H_{25}FN_4O_3$	556	208-210	0.46
TAP-17	H	5,8-di CH_3	$C_{35}H_{28}N_4O_3$	552	178-180	0.44
TAP-18	4-CH_3	5,8-di CH_3	$C_{36}H_{30}N_4O_3$	566	212-214	0.48
TAP-19	4-Cl	5,8-di CH_3	$C_{35}H_{27}ClN_4O_3$	586	202-204	0.40
TAP-20	4-NO_2	5,8-di CH_3	$C_{35}H_{27}N_5O_5$	597	182-184	0.42
TAP-21	2-OH	5,8-di CH_3	$C_{35}H_{28}N_4O_4$	568	176-178	0.45
TAP-22	2-OCH_3	5,8-di CH_3	$C_{36}H_{30}N_4O_4$	582	218-220	0.49
TAP-23	3-NO_2	5,8-di CH_3	$C_{35}H_{27}N_5O_5$	597	192-194	0.52
TAP-24	4-F	5,8-di CH_3	$C_{35}H_{27}FN_4O_3$	570	188-190	0.48

R_f value was determined using solvent system = Ethyl Acetate : Hexane (3 : 2)

6.9 SPECTRAL DISCUSSION

6.9.1 IR SPECTRA

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

The characteristic bands of Hydroxyl groups were obtained for streching at 3400-3650 cm^{-1} and those for bending were obtained at 1050-1250 cm^{-1}.The stretching vibrations N-H group showed in the region of 3200 to 3500 cm^{-1} with a deformation due to in plane bending at 1650-1580 cm^{-1}. It gives aromatic C-H stretching frequencies between 3000-3200 cm^{-1} and bending vibration near 1300-1500 cm^{-1} respectively. C-H stretching frequencies for methyl and methylene group were obtained near 2950 cm^{-1} to 2850 cm^{-1}. Characteristic frequency of C-N stretching showed near 2100-2200 cm^{-1} and bending vibration near 1300-1400 cm^{-1}.

6.9.2 MASS SPECTRA

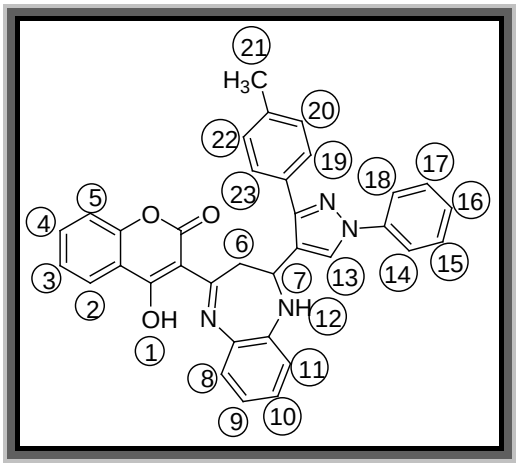
Mass spectra of the synthesized compounds were recorded on **Shimadzu GC-MS QP-2010** model using direct injection probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. Fragmentation pattern can be observed to be particular for these compounds and the characteristic peaks obtained for each compound.

6.9.3 ^{1}H NMR SPECTRA

^{1}H NMR spectra of the synthesized compounds were recorded on **Bruker Avance II 400 spectrometer** by making a solution of samples in $CDCl_3$ solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned. Numbers of protons and carbons identified from NMR spectrum 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 and it gives approximately 8.0 Hz which indicates the presence of **cis isomers** of compounds. In some cases, aromatic protons were obtained as multiplet. ^{1}H spectral interpretation can be discussed as under.

^{1}H NMR of 3-((E)-2,3-dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one (TAP-02)

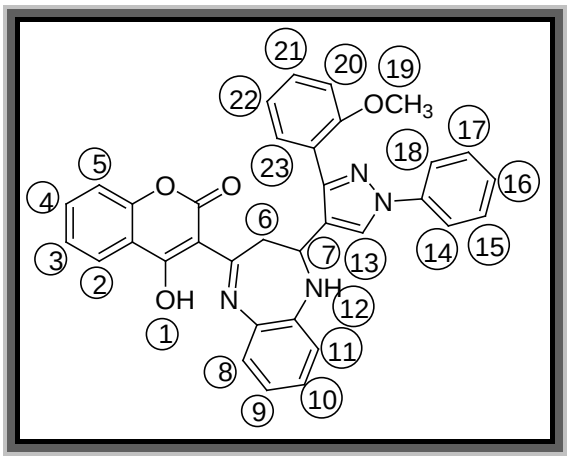


1. Proton no. 21 of total 3H gave a singlet at 2.39 δ ppm.
2. Proton no. 6 of total 2H gave a doublet 3.1 δ ppm - 3.2 δ ppm.
3. Proton no.12 of 1H gave a singlet at 4.5 δ ppm.
4. Proton no. 7 of diazepine ring became deshielded and gave a characteristic doublet at 5.55 δ ppm.
5. Proton no. 16 of 1H gave a doublet 6.90 δ ppm - 6.93 δ ppm.
6. Proton no.11 of 1H gave a triplet at 7.07 δppm- 7.11 δppm. .
7. Proton no. 20 and 22 gave a doublet at 7.21 δppm - 7.23 δppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
8. Proton no. 3,4,8,9 and 10 gave a multiplate at 7.23 - 7.30 δppm.
9. Proton no. 15 and 17 of 2H gave a triplet at 7.40 δ ppm - 7.45 δppm.
10. Proton no. 5 of 1H gave a triplet at 7.56 - 7.60 δ ppm.
11. Proton no.19 and 23 gave a doublet at 7.66 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
12. Proton no. 14 and 18 gave a doublet at 7.72 δ ppm -7.75 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
13. Proton no. 13 of pyrazol ring gave a doublet at 8.00 δ ppm.

14. Proton no. 2 of 1H gave a doublet at 8.06 δ ppm - 8.09 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
15. Proton no. 1 of 1H gave a singlet at 15.7 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 no. TAP-02 has been confirmed. The spectrum is given on page no. 238.

^{1}H NMR of 3-((E)-2,3-dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]dizepin-4-yl)-4-hydroxy-2H-chromen-2-one (TAP-05)



1. Proton no. 6 of 2H gave a quartet at 2.85 δ ppm – 3.00 δ ppm.
2. Proton no. 19 of total 3H gave a singlet at 3.83 δ ppm.
3. Proton no. 12 of total H gave a singlet at 4.49 - 4.52 δ ppm.
4. Proton no. 7 of 1H became deshielded and gave a characteristic doublet at 5.23 δ ppm - 5.26 δ ppm.
5. Proton no. 16 of 1H gave a doublet at 6.56 δ ppm - 6.58 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
6. Proton no. 5 and 11 of 2H gave a doublet at 6.97 δppm - 7.02 δppm.
7. Proton no. 3 and 4 of 2H gave a multiplate at 7.06 δppm - 7.15 δppm.
8. Proton no. 20, 21, 22 and 23 of 4H gave a multiplate at 7.17 δ ppm -7.26 δ ppm.
9. Proton no. 8,9 and 10 of 3H gave a multiplate at 7.36 δppm - 7.41 δppm.
10. Proton no. 15 and 17 2H gave a triplet at 7.49 δ ppm - 7.53 δ ppm.

11. Proton no. 14 and 18 of 2H gave a doublet at 7.64 – 7.66 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
12. Proton no. 13 of 1H gave a singlet at 7.83 δ ppm.
13. Proton no. 2 of 1H gave a doublet at 8.03 δ ppm – 8.05 δ ppm and J value of this proton is 8.0 Hz. It suggest ortho coupling.
14. Proton no. 1 of 1H gave a singlet at 15.59 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 no. TAP-05 has been confirmed. The spectrum is given on page no.240.

6.9.4 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 spectral and elemental analysis data are for all individual compounds synthesized in this chapter are mentioned below.

6.10 ANALYTICAL DATA

3-((E)-2,3-dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-01)

Yield : 68% IR (cm^{-1}): 3606 (OH stretching), 3425(N-H stretching), 3090, 3061 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2823 (Aliphatic -CH_2 stretching), 1776 (C=O stretching), 1606,1562 (N-H bending), 1454,1429,1374 (C-H bending), 1221 (OH bending), 766 (Disubstituted), 692,702 (monosubstituted), MS: *m/z* = 524.18; Anal. Calcd. for $C_{33}H_{24}N_4O_3$ C, 75.56; H, 4.61; N,10.68; O, 9.15; Found: C, 75.46; H, 4.56; N, 10.68; O, 9.09.

3-((E)-2,3-dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4 diazepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-02)

Yield : 76% IR (cm^{-1}): 3576, 3556 (OH stretching), 3525(N-H stretching), 3190, 3161 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2833 (Aliphatic -CH_2 stretching), 1766 (C=O stretching), 1676,1606,1562 (N-H bending), 1492,1464,1419,1354 (C-H bending), 1211 (OH bending), 756 (Disubstituted), 681,701 (monosubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 2.39 (s, 3H), 3.1-3.2 (d, 2H), 4.5 (s, 1H), 5.55 (d, 1H), 6.90-6.93 (d, 1H), 7.07-7.11 (t, 1H), 7.21-7.23 (d, 2H, J=8.0 Hz) , 7.23-7.30 (m, 5H), 7.40-7.45 (t, 2H), 7.56-7.60 (t, 1H), 7.66 (d, 2H, J=8.0 Hz), 7.72-7.75(d, 2H, J=8.0 Hz), 8.00(d, 1H), 8.06-8.09 (d, 2H, J=8.0 Hz), 15.70 (s, 1H), MS= *m/z* = 538.20; Anal. Calcd. for $C_{34}H_{26}N_4O_3$: C, 75.82; H, 4.87; N, 10.40; O, 8.91; Found: C, 75.81; H, 4.80; N, 10.38; O,8.81.

3-((E)-2,3-dihydro-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-03)

Yield : 88% IR (cm^{-1}): 3616 (OH stretching), 3435(N-H stretching), 3043, 3021 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2820 (Aliphatic -CH_2 stretching), 1756 (C=O stretching), 1616,1582 (N-H bending), 1545 (C-NO_2), 1444,1419,1364 (C-H bending) , 1211 (OH bending), 756 (Disubstituted), 691,709 (monosub.), MS: *m/z* = 569.57; Anal. Calcd. for $C_{33}H_{23}N_5O_5$: C, 69.59; H, 4.07; N, 12.30; O, 14.05, Found: C, 69.49; H, 4.04; N, 12.21; O,14.01.

3-((E)-2,3-dihydro-2-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-04)

Yield : 72% IR (cm^{-1}): 3601,3523(OH stretching), 3383,3221 (N-H stretching), 3115, 3051,3014 (Aromatic C-H stretching), 2945 (Aliphatic -CH_3 stretching), 2879 (Aliphatic -CH_2 stretching), 1786 (C=O stretching), 1674,1604,1566 (N-H bending), 1483,1462,1415,1346 (C-H bending), 1242,1205 (-OH bending), 1159,1126,1085 (C-N bending), 761,750 (Disubstituted), 682,709 (monosubstituted), MS: *m/z* = 540.57; Anal. Calcd. for $C_{33}H_{24}N_4O_4$: C, 73.32; H, 4.48; N, 10.36; O,11.84, Found: C, 73.24; H, 4.45; N, 10.30; O,11.79.

3((E)-2,3-dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]dizepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-05)

Yield : 69% IR (cm^{-1}): 3668 (OH stretching), 3468 (N-H stretching), 3271, 3097, 3012 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2901 (Aliphatic -CH_2 stretching), 1766 (C=O stretching), 1697,1604, (N-H bending), 1467,1423,1340 (C-H bending), 1290,1236 (-OH bending), 1201,1120,1022 (C-N bending), 765 (Disubstituted), 688,708 (monosubstituted), ^{1}H NMR (DMSO-d_6) δ ppm: 2.85 - 3.00 (q, 2H), 3.83 (s, 3H), 4.49 - 4.52 (s, 1H), 5.23 - 5.26 (d, 1H), 6.56 - 6.58 (d, 1H, *J*=8.0 *Hz*), 6.97 - 7.02 (d, 2H),7.06 - 7.15 (m, 2H), 7.17 - 7.26 (m, 4H), 7.36 - 7.41(m, 3H), 7.49 - 7.53 (t, 2H), 7.64 - 7.66 (d, 2H, J=8.0 Hz), 7.83 (s, 1H), 8.03 - 8.05 (d, 1H), 15.59 (s, 1H), MS: *m/z* = 554.59; Anal. Calcd. for $C_{34}H_{26}N_4O_4$: C, 73.63; H, 4.73; N, 10.10; O,11.54 Found: C, 73.43; H, 4.59; N, 10.03; O,11.43.

3-((E)-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one.(TAP-06)

Yield : 78% IR (cm^{-1}): 3568 (OH stretching), 3448 (N-H stretching), 3071, 3037 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2891(Aliphatic -CH_2 stretching), 1746 (C=O stretching), 1687,1624, (N-H bending), 1453,1440 (C-H bending), 1236,1286 (-OH bending), 1201,1120 (C-N bending), 755 (Disubstituted), 688,702 (monosubstituted), MS: *m/z* = 559(M^+), 562(M^{+2}); Anal. Calcd. for $C_{33}H_{23}ClN_4O_3$: C, 70.90; H, 4.15; Cl, 6.34; N, 10.02; O, 8.59 Found: C, 70.81; H, 4.07; Cl,6.30; N, 10.05; O, 8.46.

3-((E)-2,3-dihydro-2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-07)

Yield : 75% IR(cm^{-1}): 3623(OH stretching), 3323 (N-H stretching), 3115, 3041 (Aromatic C-H stretching), 2935 (Aliphatic -CH_3 stretching), 2869 (Aliphatic -CH_2 stretching), 1776 (C=O stretching), 1675,1634 (N-H bending), 1560 (C-NO_2 stretching), 1482,1425,1326 (C-H bending), 1232,1215 (-OH bending), 1169,1136,1075 (C-N bending) 771,760 (Disubstituted), 672,719 (monosub.) MS: *m/z* = 569.57; Anal. Calcd. for $C_{33}H_{23}N_5O_5$: C, 69.59; H, 4.07; N, 12.30; O,14.05 Found: C, 69.54; H, 4.06; N, 12.21; O, 14.02.

3-((E)-2-(3-(4-flourophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihylro-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-2H-chromen-2-one. (TAP-08)

Yield : 86% IR (cm^{-1}): 3523(OH stretching), 3343 (N-H stretching), 3015, 3011 (Aromatic C-H stretching), 2945 (Aliphatic -CH_3 stretching), 2879 (Aliphatic -CH_2 stretching), 1786 (C=O stretching), 1685,1644 (N-H bending), 1472,1435 (C-H bending), 1282,1245 (-OH bending), 1210,1136, (C-N bending), 761,750 (Disubstituted), 692,709 (monosubstituted), MS: *m/z* = 542, 544(M^{+2}); Anal. Calcd. for $C_{33}H_{23}FN_4O_3$: C, 73.05; H, 4.27; F, 3.50; N, 10.33; O, 8.85 Found: C, 73.00; H, 4.21; F, 3.42; N, 10.23; O, 8.75.

3-((E)-2,3-dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-09)

Yield : 78% IR (cm^{-1}): 3616 (OH stretching), 3445(N-H stretching), 3110, 3051 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2833 (Aliphatic -CH_2 stretching), 1786 (C=O stretching), 1696,1602 (N-H bending), 1464,1439,1364 (C-H bending), 1291,1236 (OH bending), 1211,1146, (C-N bending), 765 (Disubstituted), 692,719 (monosubstituted), MS: *m/z* = 538.60; Anal. Calcd. for $C_{34}H_{26}N_4O_3$: C,75.82; H, 4.87 ; N, 10.40; O, 8.91 Found: C, 72.83; H, 4.81;O, 8.89 .

3-((E)-2,3-dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4] diazepin-4-yl)-4-hydroxy-8-mehyl-2H-chromen-2-one. (TAP-10)

Yield : 69% IR (cm^{-1}): 3609 (OH stretching), 3435(N-H stretching), 3190, 3051 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching) , 2843 (Aliphatic -CH_2 stretching), 1777 (C=O stretching), 1616,1572 (N-H bending), 1439,1384 (C-H

bending), 1211 (OH bending), 1212,1146, (C-N bending), 756 (Disubstituted), 681,701 (monosubstituted) MS: *m/z:* 552.62; Anal. Calcd. for $C_{35}H_{28}N_4O_3$: C, 76.07; H, 5.11; N, 10.14; O, 8.69 Found: C, 76.03; H, 5.01; N, 10.07; O,8.60.

3-((E)-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-11)

Yield: 82% IR (cm^{-1}): 3599 (OH stretching), 3445(N-H stretching), 3090, 3052 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2853 (Aliphatic -CH_2 stretching), 1767 (C=O stretching), 1606,1562 (N-H bending), 1449,1374 (C-H bending), 1221 (OH bending), 1201,1126, (C-N bending), 776 (Disubstituted), 689,703 (monosubstituted), MS: *m/z* = 573, 575(M^{+2}); Anal. Calcd. for $C_{34}H_{25}ClN_4O_3$: C, 71.26; H, 4.40; Cl, 6.19; N, 9.78; O, 8.38 Found: C, 71.23; H, 4.31; Cl, 6.77; O,8.31.

3-((E)-2,3-dihydro-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-12)

Yield : 76% IR (cm^{-1}): 3589 (OH stretching), 3435(N-H stretching), 3190, 3062 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2863 (Aliphatic -CH_2 stretching), 1787 (C=O stretching) 1616,1542 (N-H bending), 1560 (C-NO_2 stretching), 1469,1382 (C-H bending) , 1221 (OH bending), 1212,1146, (C-N bending) , 766 (Disubstituted), 692,701 (monosubstituted), MS: *m/z* = 583.59; Anal. Calcd. for $C_{34}H_{25}N_5O_5$: C, 69.97; H, 4.32; N, 12.00; O,13.71 Found: C, 69.83; H, 4.31; N, 11.77; O,13.69.

3-((E)-2,3-dihydro-2-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-13)

Yield : 83% IR (cm^{-1}): 3609 (OH stretching), 3445(N-H stretching), 3090, 3072 (Aromatic C-H stretching), 2998 (-CH_3 stretching), 2873 (Aliphatic -CH_2 stretching), 1777 (C=O stretching), 1626,1532 (N-H bending), 1489,1372 (C-H bending), 1320,1281 (OH bending), 1219,1116, (C-N bending) 766(Disubstituted), 692,719 (monosubstituted), MS: *m/z* = 554.59; Anal. Calcd. for $C_{24}H_{18}FN_5$: C, 73.63; H, 4.73; N, 10.10; O,11.54 Found: C, 73.53; H, 4.61; N, 9.77; O,11.41.

3((E)-2,3-dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]dizepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-14)

Yield : 68% IR (cm^{-1}): 3609 (OH stretching), 3445(N-H stretching), 3090, 3072 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2873 (Aliphatic -CH_2 stretching), 1777 (C=O stretching), 1626,1532 (N-H bending), 1489,1372 (C-H bending), 1320,1281 (OH bending), 1219,1116 (C-N bending), 766 (Disubstituted), 692,719 (monosubstituted), MS: *m/z* = 568.62; Anal. Calcd. for $C_{35}H_{28}N_4O_4$: C, 73.93; H, 4.96; N, 9.85; O, 11.25 Found: C, 73.83; H, 4.81; N, 9.67; O,11.15.

3-((E)-2,3-dihydro-2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-15)

Yield : 86% IR (cm^{-1}): 3619 (OH stretching), 3415(N-H stretching), 3091, 3071 (Aromatic C-H stretching), 2978 (Aliphatic -CH_3 stretching), 2872 (Aliphatic -CH_2 stretching), 1787 (C=O stretching), 1616,1531 (N-H bending), 1561 (C-NO_2 stretching), 1488,1371 (C-H bending), 1321,1271 (OH bending), 1209,1106, (C-N bending), 776 (Disubstituted), 691,709 (monosubstituted), MS: *m/z* = 583.59; Anal. Calcd. for $C_{34}H_{25}N_5O_5$: C, 69.97; H, 4.32; N, 12.00; O, 13.71 Found: C, 69.91; H, 4.31; N, 10.77; O,13.69.

3-((E)-2-(3-(4-flourophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihylro-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-8-methyl-2H-chromen-2-one. (TAP-16)

Yield : 77% IR (cm^{-1}): 3589 (OH stretching), 3455(N-H stretching), 3098, 3082 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2883 (Aliphatic -CH_2 stretching), 1778 (C=O stretching), 1636,1522 (N-H bending), 1479,1382 (C-H bending), 1321,1282 (OH bending), 1209,1110 (C-N bending), 767 (Disubstituted), 691,709 (monosubstituted), MS: *m/z* = 556, 558(M^{+2}); Anal. Calcd. for $C_{34}H_{25}FN_4O_3$: C, 73.37; H, 4.53; F, 3.41; N, 10.07; O,8.62 Found: C, 73.31; H, 4.51; F, 3.37; O,10.01.

3-((E)-2,3-dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-17)

Yield : 89% IR (cm^{-1}): 3601 (OH stretching), 3435(N-H stretching), 3080, 3062 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2883 (Aliphatic -CH_2 stretching), 1776 (C=O stretching), 1636,1542 (N-H bending), 1479,1382 (C-H

bending), 1321,1271 (OH bending), 1219,1117 (C-N bending), 767 (Disubstituted), 691,709 (monosubstituted), MS: *m/z* = 552.62; Anal. Calcd. for $C_{35}H_{28}N_4O_3$: C, 76.07; H, 5.11; N, 10.14; O, 8.69 Found: C, 76.05; H, 5.01; N,10.07; O,8.58.

3-((E)-2,3-dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4] diazepin -4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-18)

Yield : 82% IR (cm^{-1}): 3619 (OH stretching), 3455(N-H stretching), 3091, 3082 (Aromatic C-H stretching), 2997 (Aliphatic -CH_3 stretching), 2871 (Aliphatic -CH_2 stretching), 1767 (C=O stretching), 1616,1542 (N-H bending), 1499,1371 (C-H bending), 1310,1271 (OH bending), 1218,1106, (C-N bending), 776 (Disubstituted), 682,709 (monosubstituted), MS: *m/z* = 566.65; Anal. Calcd. for $C_{36}H_{30}N_4O_3$: C,76.31; H, 5.34; N, 9.89; O, 8.47 Found: C, 76.23; H, 5.31; N, 9.77; O,8.44.

3-((E)-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-19)

Yield : 84% IR (cm^{-1}): 3639 (OH stretching), 3455(N-H stretching), 3099, 3071 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2883 (Aliphatic -CH_2 stretching), 1778 (C=O stretching), 1616,1542 (N-H bending), 1499,1382 (C-H bending), 1321,1271 (OH bending), 1229,1106 (C-N bending), 776 (Disubstituted), 682,729 (monosubstituted), MS: *m/z* = 587, 589(M^{+2}) ; Anal. Calcd. for $C_{35}H_{27}ClN_4O_3$: C, 71.61; H, 4.64; Cl, 6.04; N, 9.54; O,8.18 Found: C, 71.53; H, 4.51; Cl, 6.01; N,9.51; O,8.17.

3-((E)-2,3-dihydro-2-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-20)

Yield : 69% IR (cm^{-1}): 3602 (OH stretching), 3435(N-H stretching), 3190, 3072 (Aromatic C-H stretching), 2988 (Aliphatic -CH_3 stretching), 2863 (Aliphatic -CH_2 stretching), 1776 (C=O stretching), 1636,1531 (N-H bending), 1570 (C-NO_2 stretching), 1479,1378 (C-H bending), 1320 (OH bending), 1209 (C-N bending), 769 (Disubstituted), 719 (monosubstituted), MS: *m/z* = 597.62; Anal. Calcd. for $C_{35}H_{27}N_5O_5$: C, 70.34; H, 4.55; N, 11.72; O,13.39 Found: C, 70.33; H, 4.51; N, 11.67; O,13.26.

3-((E)-2,3-dihydro-2-(3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-21)

Yield : 87% IR (cm^{-1}): 3612 (OH stretching), 3455(N-H stretching), 3191, 3032 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2861 (Aliphatic -CH_2 stretching), 1786 (C=O stretching), 1646,1541 (N-H bending), 1479,1378 (C-H bending), 1321(OH bending), 1219 (C-N bending), 759 (Disubstituted), 709 (monosubstituted), MS: *m/z* = 568.62; Anal. Calcd. for $C_{35}H_{28}N_4O_4$: C,73.93; H, 4.96; N, 9.85; O, 11.25 Found: C, 73.83; H,9.81; N, 9.77; O,11.24.

3((E)-2,3-dihydro-2-(3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo [b][1,4]dizepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-22)

Yield : 82% IR (cm^{-1}): 3612 (OH stretching), 3455(N-H stretching), 3110, 3012 (Aromatic C-H stretching), 2981 (Aliphatic -CH_3 stretching), 2861 (Aliphatic -CH_2 stretching), 1778 (C=O stretching), 1632,1533 (N-H bending), 1478,1379 (C-H bending), 1320 (OH bending), 1208 (C-N bending), 768 (Disubstituted), 718 (monosubstituted), MS: *m/z* = 582.65; Anal. Calcd. for $C_{36}H_{30}N_4O_4$: C, 74.21; H, 5.19; N, 9.62; O,10.98 Found: C, 74.13; H, 5.11; N, 9.57; O,10.91.

3-((E)-2,3-dihydro-2-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-23)

Yield : 86% IR (cm^{-1}): 3582 (OH stretching), 3445(N-H stretching), 3120, 3071 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2863 (Aliphatic -CH_2 stretching), 1776 (C=O stretching), 1636,1531 (N-H bending), 1570 (C-NO_2 stretching), 1479,1378 (C-H bending), 1320 (OH bending), 1209 (C-N bending), 769 (Disubstituted), 719 (monosubstituted), MS: *m/z* = 597.62; Anal. Calcd. for $C_{35}H_{27}N_5O_5$: C, 70.34; H, 4.55; N, 11.72; O,13.39 Found: C, 70.23; H, 4.51; N, 11.67; O,13.31.

3-((E)-2-(3-(4-flourophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,3-dihylro-1H-benzo [b][1,4]diazepin-4-yl)-4-hydroxy-5,8-dimethyl-2H-chromen-2-one. (TAP-24)

Yield : 89% IR (cm^{-1}): 3612 (OH stretching), 3445(N-H stretching), 3191, 3082 (Aromatic C-H stretching), 2998 (Aliphatic -CH_3 stretching), 2861 (Aliphatic -CH_2 stretching), 1786 (C=O stretching), 1626,1521 (N-H bending), 1478,1388 (C-H bending), 1321 (OH bending), 1201 (C-N bending), 768 (Disubstituted),718

(monosubstituted), MS: *m/z* = 570, 572(M^{+2}); Anal. Calcd. for $C_{35}H_{27}FN_4O_3$: C, 73.67; H, 4.77; F, 3.33; N, 9.82; O,8.41 Found: C, 73.65; H, 4.59; F, 3.27; N,9.79; O,8.32.

6.11 RESULTS AND DISCUSSION

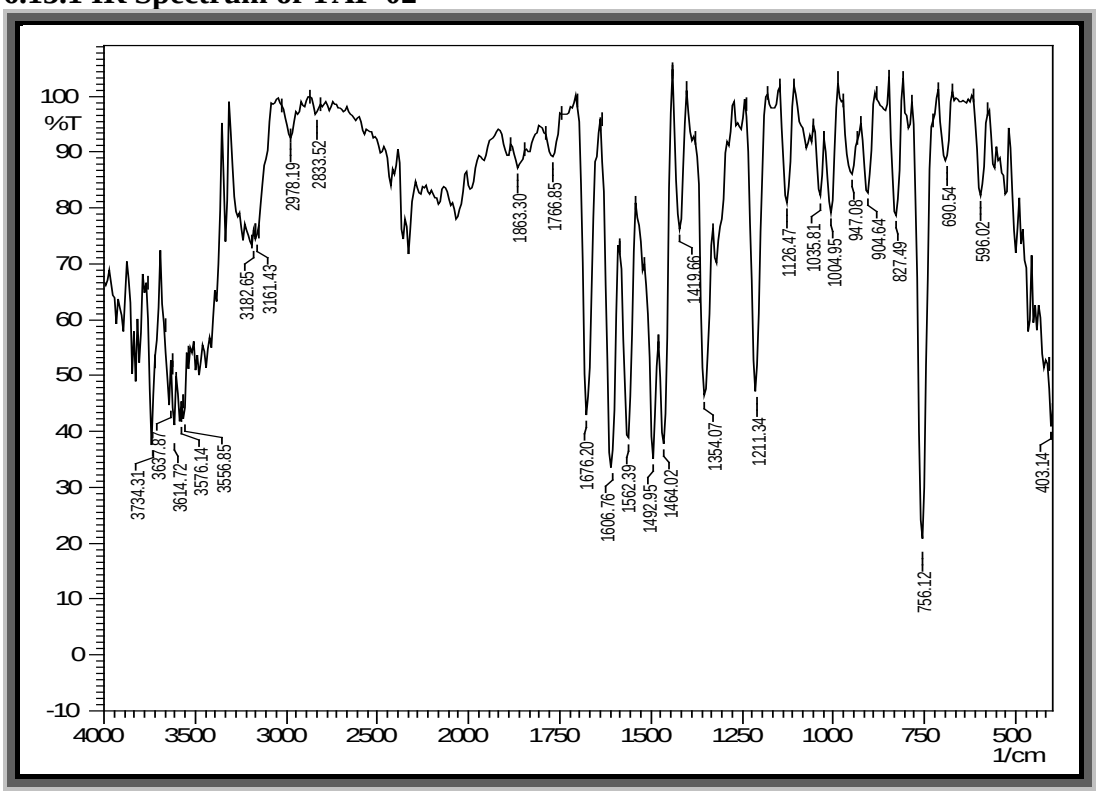
In the current chapter, condensation of coumarinyl chalcones with pyrazole aldehydes led to several new benzodiazepines coumarins possessing pyrazole hybrid structures. 24 new molecules are prepared and charecterized. The yield of these compounds are approximetaly 70-80 percentage.

6.12 CONCLUSION

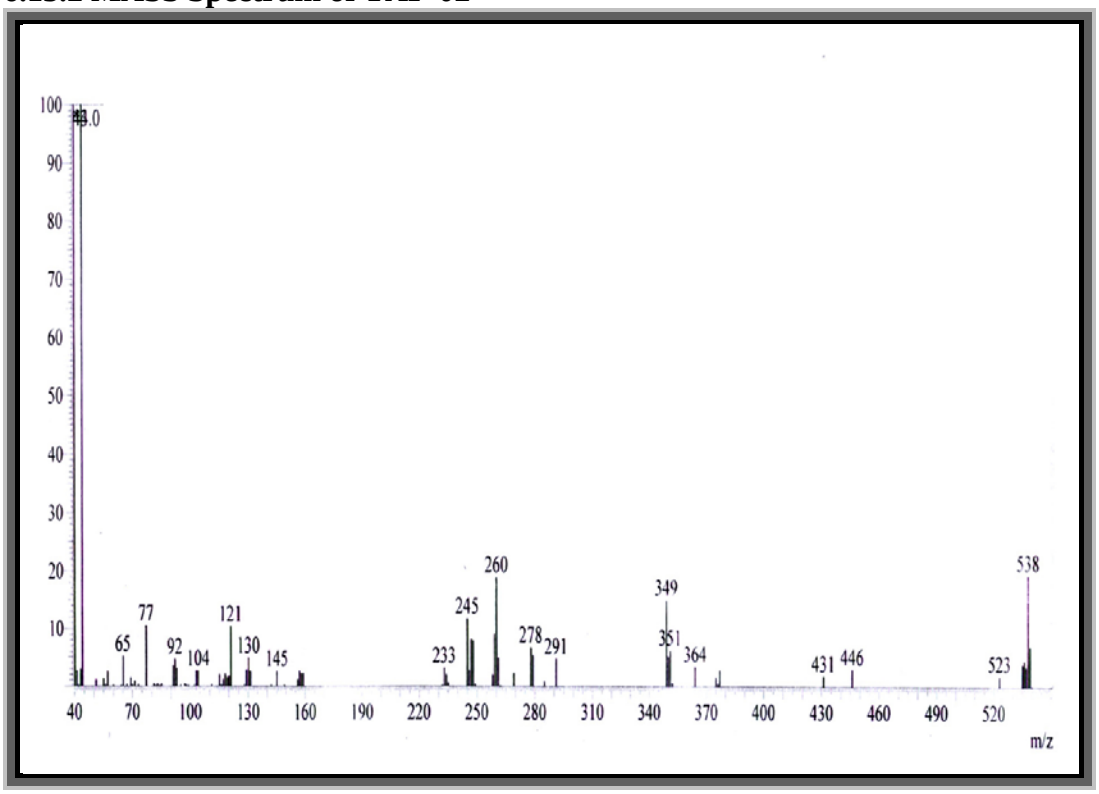
The synthetic methodology adopted led to considerable inprovement in the reaction hours. The reaction completion time reduced from 8-10 hours to 4 to 5 hours. It was observed that the nitro bearing moiety will take longer reaction time.

6.13 REPRESENTATIVE SPECTRAS

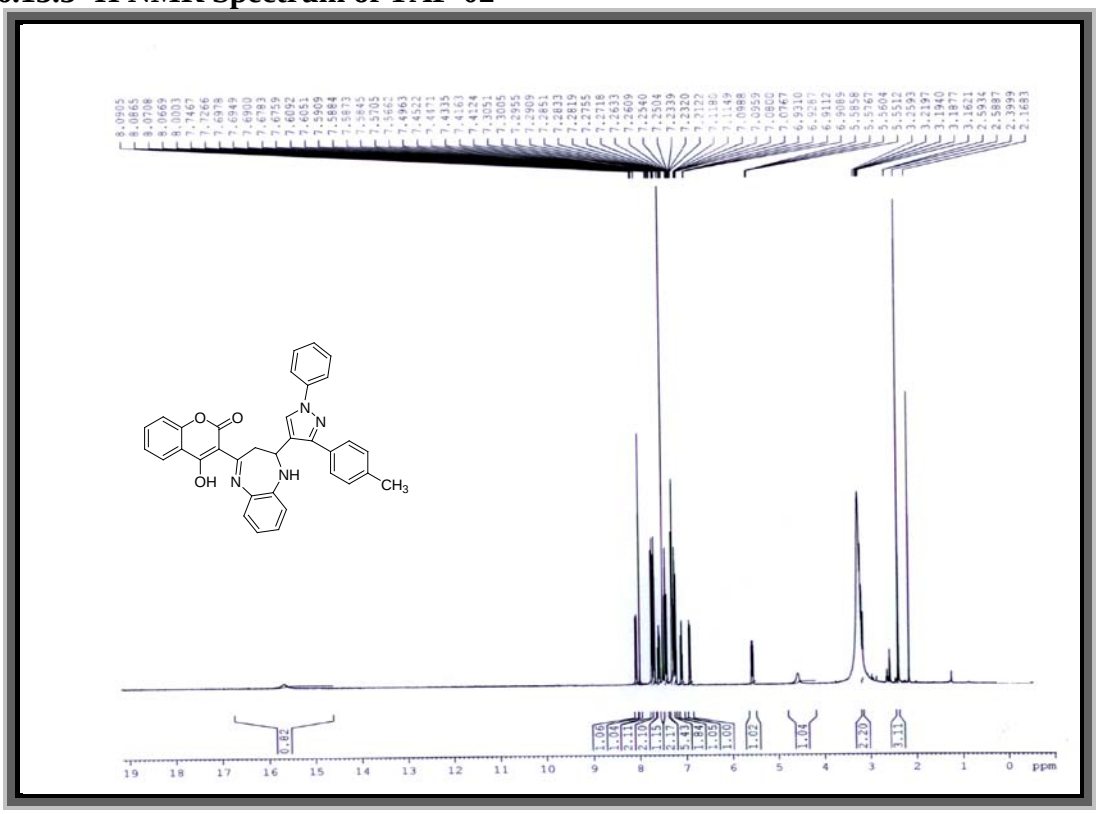
6.13.1 IR Spectrum of TAP-02



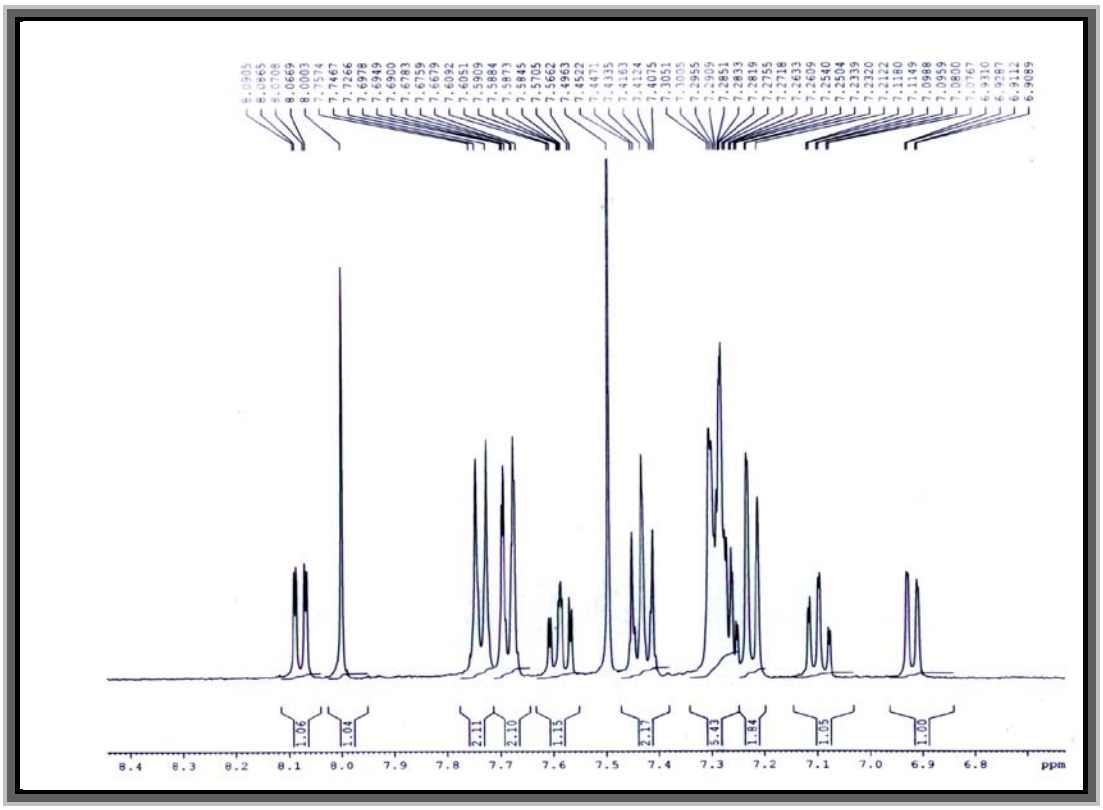
6.13.2 MASS Spectrum of TAP-02



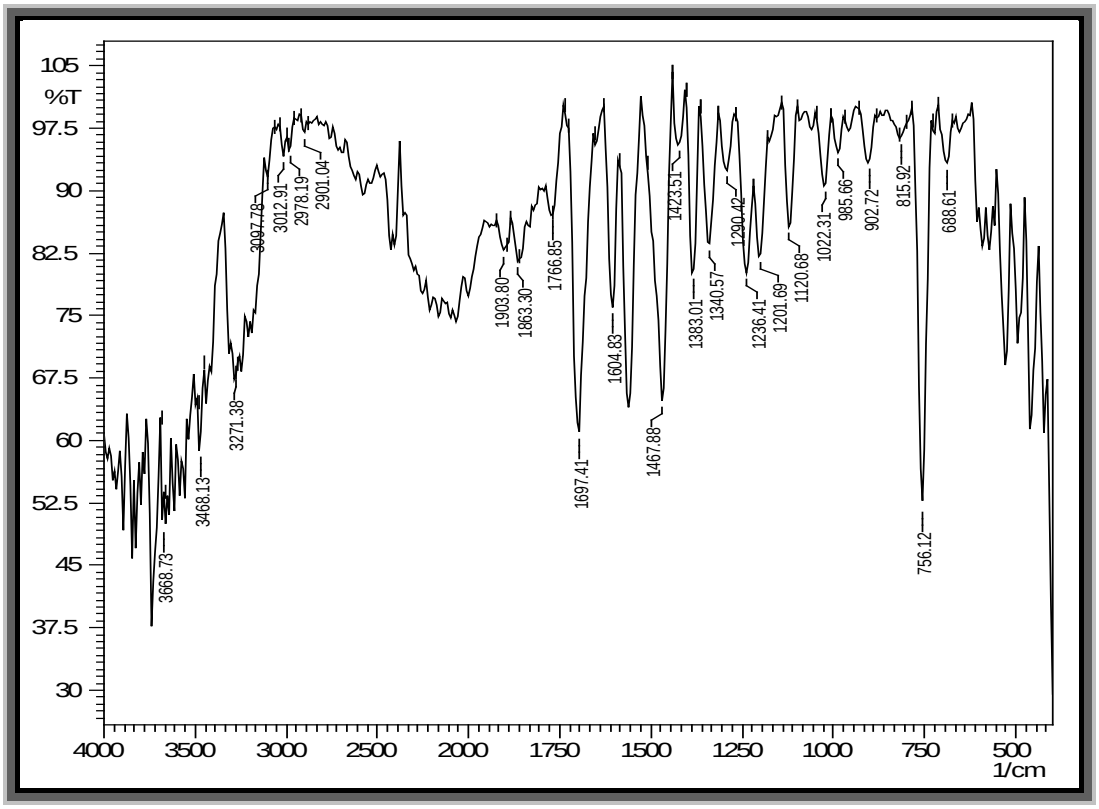
6.13.3 ^{1}H NMR Spectrum of TAP-02



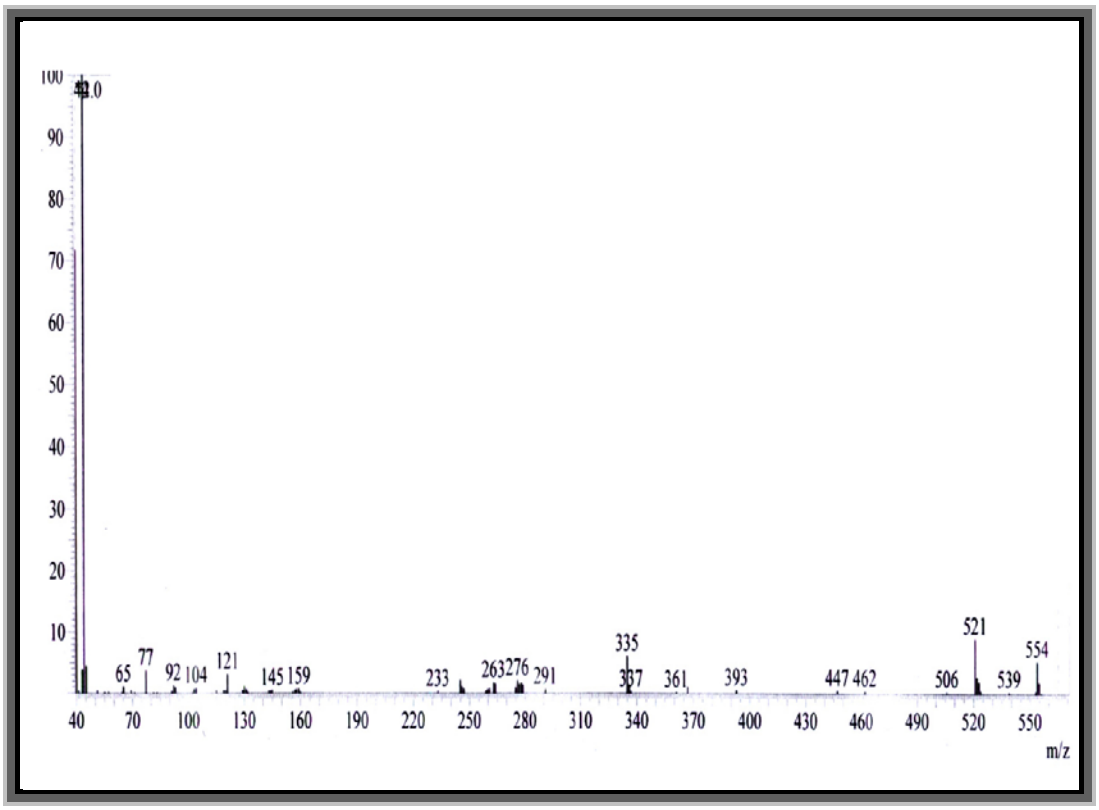
6.13.4 Expanded ^{1}H NMR Spectrum of TAP-02



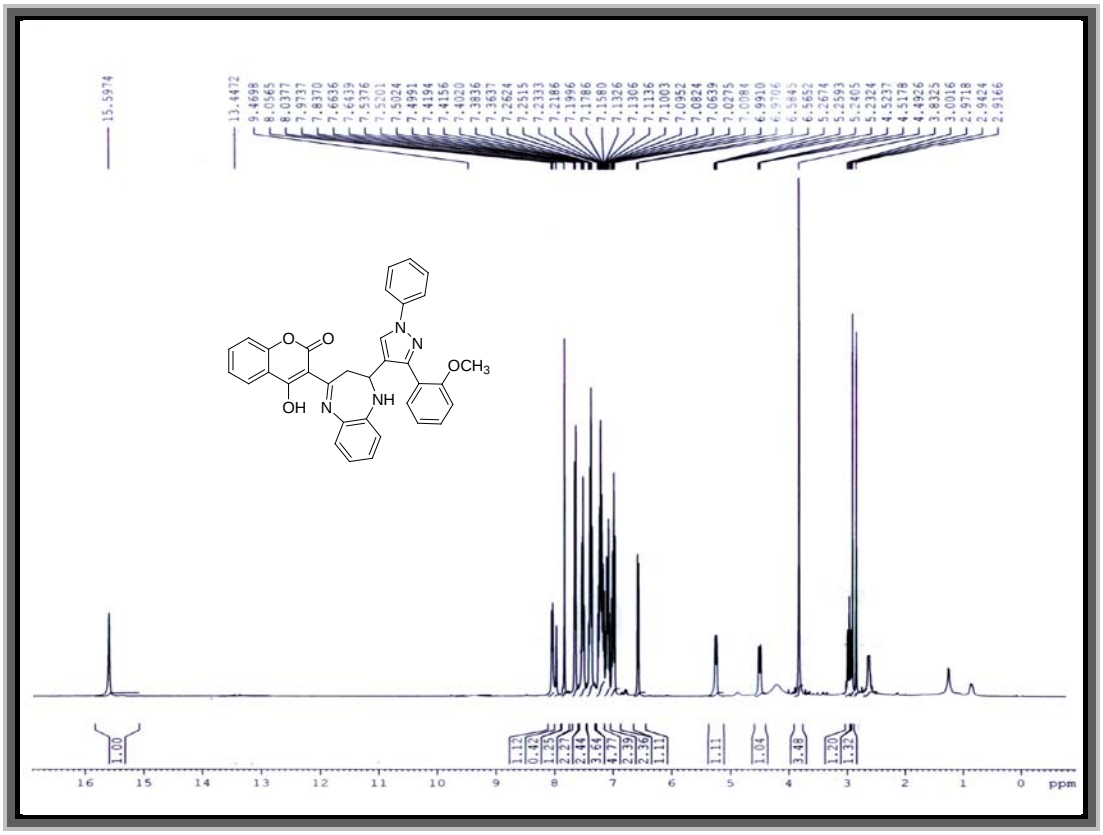
6.13.5 IR Spectrum of TAP-05



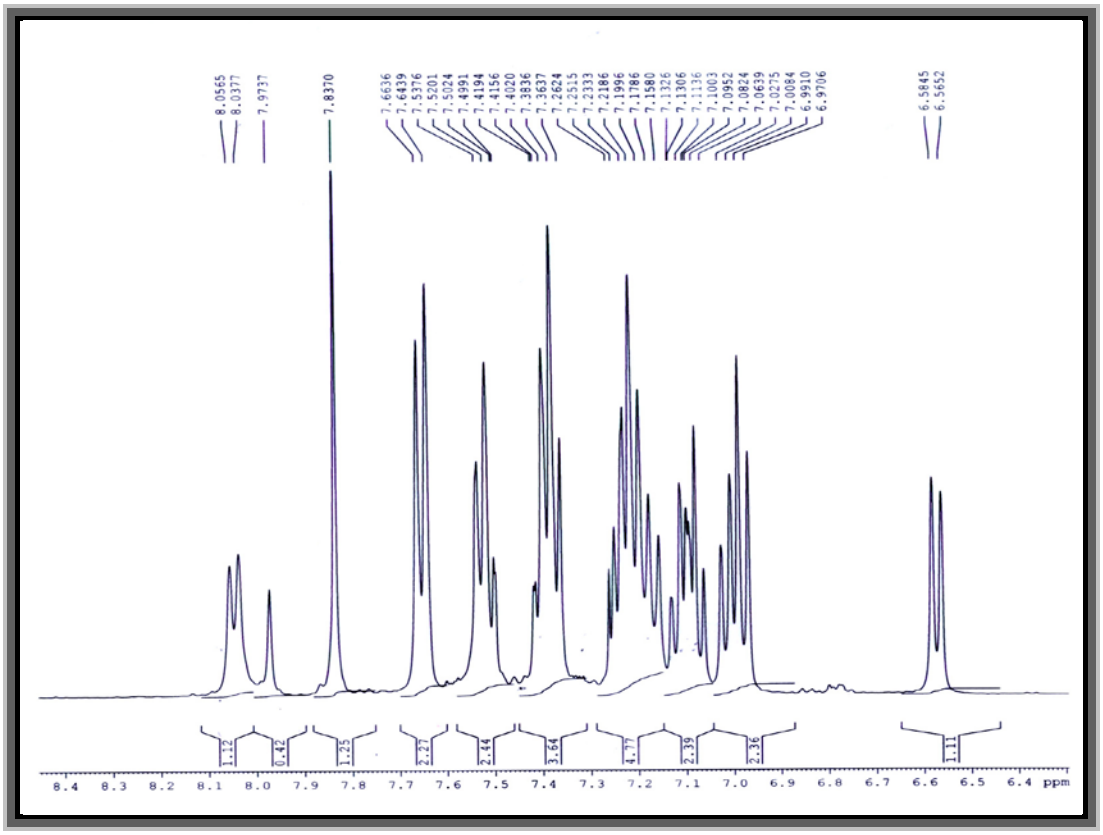
6.13.6 Mass Spectrum of TAP-05



6.13.7 ^{1}H NMR Spectrum of TAP-05



6.13.8 Expanded ^{1}H NMR Spectrum of TAP-05



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Chapter-7

Biological activity of synthesized compounds.

7.1 INTRODUCTION

An **anti-microbial** is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbistatic). Disinfectants are antimicrobial substances used on non-living objects.

Antibiotic resistance is a serious concern worldwide as it would result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either gram-positive or gram-negative pathogens. Antibiotics compounds with effective activity against both gram-positive and gram-negative pathogens are generally regarded as having a broad spectrum of activity. The synthesized compounds were preliminary screened gram-positive and gram-negative pathogens.

Gram-positive pathogens, for example staphylococci, Enterococci, Streptococci and Micobacteria bacteria are particular because of the development of resistant strains which is difficult to eradicate from the hospital environment once established. Example of such strains are methicilline resistance Staphylococcus (MRSA), methicillin resistance coagulase negative. Staphylococci (MRCNS), penicillin resistance Streptococcus pnumaniae and multiplied resistance Enteocouccus faecium, community acquired pathogens (CAP) and so on.

BACTERIA:-

In 1928, a German scientist C.E. Chrenberg first used the term “Bacterium” to denote small microscopic organism with a relatively simple and primitive form of the cellular organization known as “Prokaryotic”.

danish physician, Gram in peculiarity, Bacteria are generally unicellular E.G. Cocci, Bacilli, Etc… Filamentous, Eg.Actinomycetes, some being sheathed having certain cells specialized for reproduction. The microorganisms are capable of producing diseases in host are known as ‘Pathogenic’. Most of the microorganisms present on the skin and mucous membrane are non pathogenic and are often referred to as “Commensals” or if they live on food residues as in intestine,

they may be called “Saprophytes”. Generally, the pathogenic Cocci and Bacilli are gram positive and the pathogenic coco bacilli are gram negative.

Fro evaluation of antibacterial activity in our case, we have used staphylococcus aureus and streptococcus pyogenes from gram positive group of bacteria and escherichia coli and pseudomonas aeruginosa from gram negative Group of bacteria.

STAPHYLOCOCCUS AUREUS : -

Genus: Staphylococcus [Microccaceae]

Staphylococci are differentiated from micrococcus, a genus of the same family by its ability to utilize glucose, mannitol and pyruvate anaerobically. Cells of staphylococci are usually to be found on the skin or mucous membranes of the animal body, especially of the nose and mouth where they occur in large numbers even under normal conditions.

Species: Staphylococcus Aureus

The individual cells of S.Aureus are 0.8 To 0.9 micro in diameter. They are ovoid or spherical, non motile, non capsulated, non sporing stain with ordinary aniline dyes and gram positive, typically arranged in groups of irregular clusters like branches of groups found in pus, singly or in pairs. The optimum temperature for the growth us 37^0 C, optimum PH is 7.4 to 7.6. They produce golden yellow pigment, which develops best at room temperature. They cause pyoregenic of pus forming [Suppurative] conditions, mastitis of women and cows, boils, carbuncles infantile impetigo, internal abscess and food poisoning.

ESCHERICHIA COLI : -

Genus: Escherichia [Enterobacteriaceae]

This genus comprises escherichia and several variants and are of particular interest to the sanitarian since they occur commonly in the formal intestinal tract of man and animals. Their presence in foods or in drinking water may indicates faecal pollution. E.Coli is the most distinctively recognized feacal species.

Species: Escherichia coli

E.Coli is the most important type in this species, which contains a number of other types.escherichia in 1885 discovered in from the faces of the newborn and showed the organisms in the intesting within three days after birth. It is a commensals of the human intesting and found in the intestinal tract of men and animals and is also found in the sewage water, land, soil contaminated by feacal matters. The gram negative rods are 2 to 4 micro by 0.4 micro in size, commonly seen in coccobacillary form and rarely in filamentous form. They are facultative anaerobes and grow in all laboratory media. Colonies are circular, raised, and smooth and emit a faecal odour. E.Coli are generally non pathogenic and are incriminated as pathogens because in certain instances some strains have been found to produce septicemia, inflammations of liver and gall bladder, appendix, meningitis, pneumonia and other infections and this species is a recognized pathogen in the veterinary field.

STREPTOCOCCUS PYOGENES:-

Genus: Streptococcus

The term Streptococcus was first introduced by Bilroth [1874] and the term Streptococcus Pyogenes was used by Rosenbach [1884]. These are spherical or ovoid cells; divide in one axis and form chains; nonmotile and nonsporing. The growth is absence of native proteins in the medium; they produce characteristic haemolytic changes in media containing blood; produce acid only by fermentation of carbohydrates; often fail t liquefy gelatin; some strains produce exotoxin and extracellular products; a few of them are anaerobic.

Species: Streptococcus Pyogenes

Streptococcus pyogenes is pathogenic to human and found in sore throat, follicular tonsillitis, septicemia, acute or malignant ulcerative endocarditis etc. These are spherical Cocci 0.5 to 0.75 micro in diameter, arranged in moderately long chains of round Cocci and easily differentiated from Enterococci that from short chains of 2 to 4 spheres. Streptococcus Pyogenes is recently isolated from throat or other lesions; they show either mucoid or matt colonies. On keeping in the laboratory, they undergo varation to a glossy type. Streptococci are susceptible to destructive agents, and to penicillin and sulphomamides.

PSEUDOMONAS AERUGINOSA:-

Genus: Pseudomonas

Genus Pseudomonas is characterized by gram negative motile rods, nonsporing aerobes, oxidase positive, bluish green or yellowish pigment diffusing into the medium. Out of 140 species, only one is pathogenic to human.

Species: Pseudomonas aeruginosa

Ps.aeruginosa occurs as a commensal in the intestine of human and animal's but, when the defensive mechanism of the body is poor. It acts as a minor pathogen producing Suppurative wound, otitis media, peritonitis, cystitis, bronchopneumonia and empyema. In children it causes diarrhea and septicemia. The pus produced by p.aeruginosa is greenish blue. These are gram negative, actively motile, non sporing organisms 1.5-3 micro by 0.5 micro with rounded ends and bipolar flagella. They occur singly or in pair, of short chains. They grow well in ordinary media under aerobic conditions, producing diffusible pigment.

METHODS USED FOR PRIMARY AND SECONDARY SCREENING:

Each synthesized drug was diluted obtaining 2000 microgram /ml concentration, as a stock solution.

Primary screen: In primary screening 1000 micro/ml, 500 micro/ml, and 250 micro/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The drugs found active in primary screening were similarly diluted to obtain 200 micro/ml 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, 6.250 micro/ml, and concentrations.

Reading Result:-

The highest dilution showing at least 99 % inhibition zone is taken as MIC. The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 organism/ml.

7.2 MINIMUM INHIBITION CONCENTRATION (MIC)

In microbiology, MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation. Minimum inhibitory concentration are important in diagnostic laboratories to confirm resistance of microorganisms to an antimicrobial agent and also to monitor the activity of new antimicrobial agents. An MIC is generally regarded as the most basic laboratory measurement of the activity of an antimicrobial agent against an organism.

MIC can be determined by agar or broth dilution dilution methods usually following the guidelines of a reference body such as the CLSI, BSAC or EUCAST. There are several commercial methods available, incliuding the well established Etest strips and the recently launched Oxiod MIC Evaluator method.

The Etest system comprises a predefined and continuous concentration gradient of different antimicrobial agents, which when applied to inoculated agar plates and incubated, create ellipses of microbial inhibition. The MIC is determined where the ellipse of inhibition intersects the strip and is easily read off the MIC reading scale on the strip.

Clinically, the minimum inhibitory concentrations are used not only to determine the amount of antibiotic that the patient will receive but also the type of antibiotic used, which in turn lowers the opportunity for microbial resistance to specific antimicrobial agents.

TABLE- 7.1 MIC VALUE(µg/ml) OF NEWLY SYNTHESIZED COMPOUNDS

CHAPTER -1

COMPOUND CODE	STRUCTURE	MIC VALUE (µg/ml)			
		S.TYPHI MTCC-98	VI.CHOLERAE MTCC-3906	S.PYOGENUS MTCC-442	C.ALBICANS MTCC-227
STAB-01		500	500	250	500
STAB-02		500	500	500	500
STAB-03		250	250	250	250
STAB-04		250	200	200	500
STAB-05		100	200	250	1000
STAB-06		100	100	200	1000
STAB-07		250	250	500	250
STAB-08		500	500	500	250

TABLE- 7.2 MIC VALUE(µg/ml) OF NEWLY SYNTHESIZED COMPOUNDS

CHAPTER -5

COMPOUND CODE	STRUCTURE	MIC VALUE(µg/ml)			
		S.TYPHI MTCC-98	VI.CHOLERAE MTCC-3906	S.PYOGENUS MTCC-442	C.ALBICANS MTCC-227
STAB-1001		100	100	250	1000
STAB-1002		250	250	1000	1000
STAB-1003		250	250	250	250
STAB-1004		200	200	250	1000
STAB-1005		200	200	500	500
STAB-1007		250	250	500	250
STAB-1009		500	250	250	500
STAB-1010		500	200	250	250

STAB-1012		100	250	500	500
STAB-1015		200	200	200	100
STAB-1016		200	250	500	500
STAB-1017		250	250	200	1000
STAB-1018		250	250	250	1000
STAB-1020		500	250	250	500
STAB-1021		500	200	500	500
STAB-1023		200	250	250	500

TABLE- 7.3 MIC VALUE(µg/ml) OF NEWLY SYNTHESIZED COMPOUNDS

CHAPTER -6

COMPOUND CODE	STRUCTURE	MIC VALUE(µg/ml)			
		S.TYPHI MTCC-98	VI.CHOLERAE MTCC-3906	S.PYOGENUS MTCC-442	C.ALBICANS MTCC-227
TAP-01		500	200	250	500
TAP-02		250	250	500	250
TAP-03		250	500	500	250
TAP-04		500	200	200	1000
TAP-05		200	200	200	1000
TAP-09		250	100	250	250
TAP-10		200	250	500	250
TAP-11		250	250	500	500
TAP-13		200	250	1000	1000

TAP-14		500	200	250	1000
TAP-16		500	200	500	1000
TAP-17		250	500	250	>1000
TAP-18		250	200	200	500
TAP-19		100	200	500	500
TAP-20		200	250	250	200
TAP-21		200	250	500	200
TAP-23		62.5	250	250	1000
TAP-24		100	250	200	1000

TABLE 7.4 STANDATDS DRUGS

MINIMUM INHIBITION CONCENTRATION(µg/ml) :

DRUG	S.TYPHI	VI.CHOLERAE	S.PYOGENUS
	MTCC-98	MTCC-3906	MTCC-442
AMPICILLIN	100	100	100
CHLORAMPHENICOL	50	50	50

MINIMUM FUNGICIDAL CONCENTRATION :

DRUG	C.ALBICANS
	MTCC-227
NYSTATIN	100
GRESEOFULVIN	500

7.3 RESULT AND DISCUSSION

Antimicrobial activity is shown by STAB-05, STAB-06, TAP-09, TAP-19, TAP-23, TAP-24, STAB-1001, STAB-1012, STAB-1015 and these compounds are moderately active. The rests of the compounds are poorly active.

TABLE 7.5

Sr. No.	Code	Structure
1	STAB-05	
2	STAB-06	
3	TAP-09	
4	TAP-19	
5	TAP-23	
6	TAP-24	
7	STAB-1001	
8	STAB-1012	

9	STAB-1015	

7.4 CONCLUSION

As mentioned in Table No. 7.5, among the synthesized compounds, two compounds from dihydropyridines, four from diazepines and three from Cyano pyridine analogues have shown good activity. Coumarin bearing DHPs, Diazepines and Cyano pyridine are good scaffold for anti microbial activity. On the basis of the above interesting results, new synthetic programmes can be planned to develop more active compounds.

SUMMARY

The work represented in the thesis entitled ***"Studies on Bioactive Heterocycles and other moieties"*** is divided into seven chapters which can be summarized as under.

Chapter-1 The synthesis of pyrazole aldehydes and dihydropyridines remains of great interest owing to the wide applications in pharmaceutical for their analgesic, antipyretic, antibacterial, multidrug resistance and anti inflammatory properties. Synthesis and yield optimization of 1,4-dihydropyridines was carried out in this chapter by modified simple and fast conventional method. Eight (8) compounds were synthesized and studied for Antimicrobial activity. To confirm the structure of 1,4-dihydropyridine, single crystal was developed and data were collected.

Chapter-2 deals with the introduction and preparation of dihydropyridines. Dihydropyridines were prepared by reacting the benzoylactone with different substituted pyrazol aldehyde. The compounds synthesized in this chapter possess the DHP nucleus and are basically pyrazole core structure at C-4 position. In this chapter, 16 compounds enlisted which are newly synthesized bioactive compounds for various biological activities.

Chapter-3 covers the preparation of 16 Unsymmetric dihydropyridines by three component reaction. Under normal conditions the DHPs were prepared by refluxing the aldehydes, 3-aminocrotononitrile and methyl acetoacetate/ethyl acetoacetate more than 10 hours, but by newer protocols, it takes only one hour. Thus, a simple, easy and fast method for preparation of dihydropyridine is developed.

Chapter-4 encompasses the rapid microwave assisted synthesis of different chalcones. Charting out the important of coumarin and chalcone nucleus, the chapter starts with the introduction to the chalcone systems and the previous synthetic routes thereof. Different Pyrazole aldehydes and 3-acetyl 4-hydroxy coumarin were taken using microwave irradiation as the nonconventional source of energy and a green

synthetic approach. Again the inclusion of two bioactive motifs like coumarin and pyrazole aldehyde nucleus into a single skeleton to arrive at “drug like” structure.

Chapter-5 deals with the preparation of 24 different Cyanopyridines by conventional as well as microwave irradiation method and comparative study thereof. The yield of the compound synthesized in this chapter by microwave method is more than the conventional method. The study reveals that the time taken by the microwave method is approximately 5-10 minutes only in compare to conventional method which it takes 5-6 hours.

Chapter-6 covers the condensation reaction of coumarinyl chalcones with pyrazole aldehyde led to several new benzodiazepines clubbed coumarins possessing pyrazole hybrid structure. 24 new molecules are prepared and characterized in this chapter. The yield of these compounds is approximately 70-80 percentage. The compounds synthesized in this chapter are screened for antimicrobial activity.

Chapter-7 narrates the biological activity study of the synthesized compounds which have been screened for Antimicrobial activity against four strains namely *S.TYPHI, VI.CHOLERAE, S.PYOGENUS* as well as *C.SLBICANS*. The protocol by which the activity study has been carried out is also discussed in brief in the chapter. Some preliminary results were found and only few compounds are moderately active either against all strains or against any single strains. The standard antimicrobial drugs like Ampicillin, Chloramphenicol, Nystatin as well as Greseofluvin were used as reference standards for the screening. Moderate to weak antimicrobial compounds as the drugs have a significantly lower MIC value. The details of specific active compounds are given in Table No. 7.5.

The synthesized compounds are also under screening for Anticancer, Anti-tubercular as well as multi drug resistance reversal (mdr) activity study, the results of which are awaited.

CONFERENCES, SEMINARS & WORKSHOPS ATTENDED*:*

- ISCB Conference **"International conference on chemical biology for discovery: perspectives and Challenges"** at CDRI, Lucknow, 15-18 Jan., 2010.
- ISCB Conference **"Interplay of Chemical and Biological Sciences: Impact on Health and Environment"** at Delhi University, on 26th February - 1st March 2009
- **"International Seminar on Recent Developments in Structure and Ligand based Drug Design"** jointly organized by Schrodinger LLC, USA; National Facility for Drug Discovery through New Chemicals Entities Development & Instrumentation support to Small Manufacturing Pharma Enterprises and DST FIST, UGC-SAP & DST-DPRP Funded Department of Chemistry, Saurashtra University, Rajkot, dated December, 23rd, 2009.
- **"National seminar on Alternative Synthetic Strategies for Drugs & Drug Intermediates"** at Institute of Pharmacy, Nirma University, Ahmedabad on 13th November, 2009.
- **"Two Days National Workshop on Patents & Intellectual Property Rights Related Updates"** Sponsored by TIFAC & GUJCOST and Organized by DST-FIST, UGC-SAP & DST-DPRP Funded Department of Chemistry, Saurashtra University, Rajkot, dated September, 19-20, 2009.
- DST-FIST, UGC (SAP) supported and GUJCOST sponsored **"National Conference on Selected Topics in Spectroscopy and Stereochemistry"** organized by the Department of Chemistry, Saurashtra University, Rajkot, dated March, 18-20, 2009.
- **"A National Workshop On Updates In Process and Medicinal Chemistry"** jointly organized by National Facility for Drug Discovery through New Chemicals Entities Development & Instrumentation support to Small Manufacturing Pharma Enterprises and DST FIST, UGC-SAP & DST-DPRP Funded Department of Chemistry, Saurashtra University, Rajkot dated March, 3-4, 2009.

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- ***PAPER/POSTER PRESENTED AT THE INTERNATIONAL CONFERENCE:***

- **"Invitro cytotoxic evaluation of indoline based anticancer compounds against MCF (breast cancer) celllines"**
  Shailesh Thakrar, Manu Jaggi, Anu singh **Anamik Shah***
  Poster presented at 13th ISCB International Conference was organized on "Interplay of Chemical and Biological Sciences: Impact on Health and Environment" at Delhi University, Delhi on 26th February - 1st March 2009

- **"Synthesis of Hybrid Structures : Thiazole linked coumarin derivatives"**
  Shailesh Thakrar and Arun Mishra*

  Poster presented at 14th ISCB International conference on chemical biology for discovery: perspectives and challenges, CDRI, Lucknow, 15-18 Jan., 2010.

- **"Synthesis and Anticoagulant activity of dimeric 4-hydroxycoumarins having indole and chromone as central linkers"**
  Shrey Parekh and Shailesh Thakrar, **Anamik Shah***

  Poster presented at 14th ISCB International conference on chemical biology for discovery: perspectives and challenges, CDRI, Lucknow, 15-18 Jan., 2010.