STUDIES ON SOME IMPORTANT HETEROCYCLIC MOIETIES

A
THESIS
SUBMITTED TO
THE SAURASHTRA UNIVERSITY
IN
THE FACULTY OF SCIENCE
FOR
THE DEGREE
OF

Doctor of Philosophy

IN
CHEMISTRY
BY

Miss Jalpa C. Trivedi

Supervisor

Prof. Anamik Shah
(FIST-DST Funded & UGC-SAP Sponsored)
Department of Chemistry
Saurashtra University
Rajkot – 360 005 (India)
FEBRUARY – 2008

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

The work included in the thesis is my own work under the supervision of **Prof. Anamik Shah** and leads to some contribution in the field of Synthetic Organic Chemistry and is supported by recent references.

Date: 4th February 2008
Place: Rajkot

Jalpa C. Trivedi

Certificate

This is to certify that the present work submitted for the Ph.D. Degree of Saurashtra University by Miss Jalpa C. Trivedi has been the result of work carried out under my supervision and is a good contribution in field of Chemistry of "Coumarin-4-acetic acids, 2-Imidazolone-4-carboxylic acid, Amide linkage synthesis, 1.4-Dihydropyridines, Dihydropyrimidines and related heterocycles" with a special emphasis on synthetic aspects.

Date: 4th February 2008
Place: Rajkot

Prof. Anamik Shah
Department of Chemistry
Saurashtra University
Rajkot-360 005

Dedicated

To My Parents

Acknowledgement

*I pay my homage to "**The Almighty**", who controls the whole universe, without whose blessings this task would have not been accomplished.*

*It is my privilege to express my deep sense of gratitude to **Prof. Anamik Shah**, for suggesting this very interesting work and for his unique guidance during the course of my research. He constantly encouraged me to remain focused on achieving my goal. His observations and comments helped me to establish the overall direction of the research and also move forward expeditiously with investigation in depth. I thank him for providing me the opportunity to work with numerous local and global peers.*

I am greatful to Dr. P. H. Parsania, Professor and Head, Department of Chemistry for providing all the necessary facilities in carrying out my research work. I am also thankful of Dr. H. S. Joshi, Dr. V. H. Shah, Dr. Shipra Baluja, Dr. Y. T. Naliapara and Dr. M. K. Shah to provide their full co-operation during my work. I extend my gratitude to the teaching and non teaching staff of my department for their constant help.

I would like to express my special thanks to Dr. H. H. Parekh, former Professor and Head, Department of Chemistry, Saurashtra University, Rajkot, for guiding me in my dissertation work during my M.Sc. and Dr. Natubhai Chauhan, former Professor, for his constant encouragement throughout the course of my studies.

I am unable to find adequate words to express my feelings for my lab mates & friends. I take this opportunity to thank my dearest friend & my lab mate Mr. Jitender Bariwal for his tremendous support in my ups and downs, his constant encouragement and helping me throughout my research work.

I acknowledge what I have learned from working with my seniors Dr. Kuldip Updhyay, Dr. Chintan Dholakiya, Dr. Priti Adlakha, Dr. Mausami Chavda, Dr. Dinesh Manvar, Dr. Kena Raval, Dr. Hrishikesh Acharya and Dr. Arun Mishra.

I would like to thank my colleagues and Ms. Jyoti Singh, Mr. Atul Manvar, Mr. Rupesh Khunt, Mr. Rajesh Kakadiya, for their help and my jouniors Sachin, Ravi, Manisha, Bharat, Bhavin, Nilay, Shrey, Shailesh and Punit for their support. My special thanks to my friends Gaurang Dubal, Dhaval Joshipura, and Anchal Kulshereshtha for being with me and helping me throughout my research work.

I am equally thankful to Dr. Vimal Bhuva, Bhavin Thanki, Bhavin Shukla, Viren Patel, Vrajesh Aghera, Manoj Dhaduk, Jignesh Akbari, Satish Tada, Pranav Vachhrajani, Pankaj Kachhadiya, Nilesh Godhwani, Akshay Pansuriya, Chirag Bhuva, Janak Surani, Samir Jarsania, Hitesh Mathukiya, Bharat Bhuva and Pankaj Mer for their constant help.

I am thankful to Ms. Ranjan Khunt for guiding me and helping me in my research work and Mrs. Chetna Upadhyay, Department of Biosciences, Saurashtra University, Rajkot for encouraging me throughout.

I am thankful to Sophisticated Analysis Instrumentation Facilities, Punjab University, Chandigarh for the spectral analysis such as ^{1}H NMR as well as ^{13}C NMR.

I am also thankful to Nicholas Piramal, Mumbai, for their support in evaluating the anti-inflammatory and anti-cancer activities.

I am indebted to Dr. Ranjan Shah and Aditya for making me feel homely throughout my research tenure.

I express my deep sense of gratitude and heartfelt emotions for my dearest daddy, mummy and my dearest younger brother Bhargav who provided me with time, greatest support and inspiration needed for my synthetic work and preparing my thesis.

Jalpa C. Trivedi

Contents

Chapter-1: Synthesis of some (2-Oxo-2*H*-chromen-4-yl) Acetic Acids

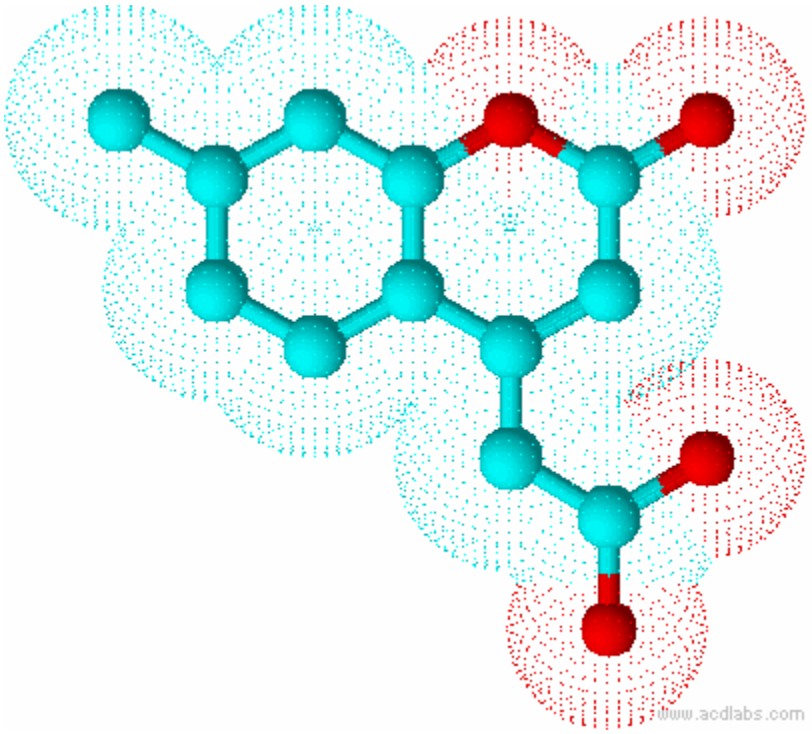
Chapter-2: Preparation of *N*-1, 3-Benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)-Acetamide Derivatives

Chapter-3: Synthesis, Anti-inflammatory and Anti-cancer Activity of *N*-(4, 6-Diphenylpyrimidin-2-yl)-2-oxo-2, 3-Dihydro-1*H*-Imidazole-4-Carboxamides

Chapter-4: Synthesis of Some (5-Carboxymethyl-2, 4, 6-triphenyl-1, 4-Dihydropyridine-3-yl)-Acetic Acids

Chapter-5: Synthesis of 5-Benzoyl-6-methyl-4-(substituted) phenyl-3,4-Dihydropyrimidin-2(1*H*)-ones

CHAPTER-1



Synthesis and Characterization of Some (2-Oxo-2H-chromen-4-yl) Acetic Acid Derivatives

Synthesis and Characterization of Some (2-Oxo-2*H*-chromen-4-yl) Acetic Acid Derivatives

1.1. Introduction

The chemistry of coumarins

Benzo-2-pyrones, commonly known as coumarins, are a fascinating group of compounds occurring widely in nature, both in free and combined states. Benzo-2-pyrones and benzo-4-pyrones are known as coumarins and chromones respectively. They occur in plants of the families *Orchideceae, Leguminaceae, Rutaceae, Umbellifereae* and *Labiateae*. Most red and blue flower petals contain anthocyanine derivatives of the benzo-2-pyrones and benzo-4-pyrones are widely distributed. Coumarins form a distinct class of oxygen containing heterocycles that are widely distributed in nature.

Coumarin, the parent substance of the benzo-α-pyrone group, was first isolated from Tonka beans in 1820.[1] A number of naturally occurring and synthetic monomeric coumarin derivatives are used in drugs and dyes.[2]

The fusion of a pyrone ring with a benzene nucleus gives rise to heterocyclic compounds known as benzopyrones, of which two distinct types are recognized as benzo-α-pyrones, commonly called coumarins, and benzo-γ-pyrones, called chromones, the latter differing from the former only in the position of the carbonyl group in the heterocyclic ring.[3] (Figure-1).

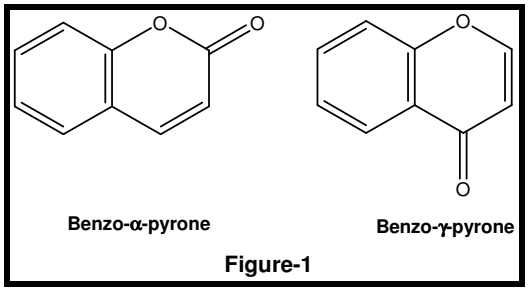
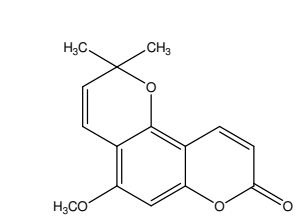
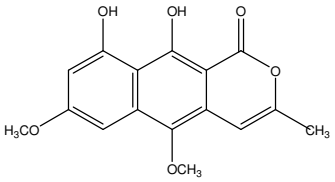


Figure-1

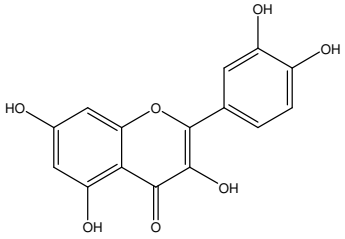
Figure-2: Few Naturally occurring coumarins



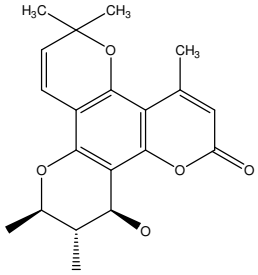
Alloxanthoxyletin



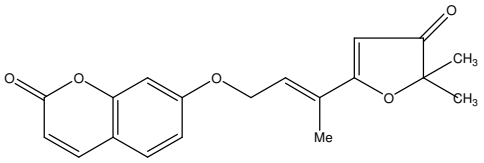
Paepalantine



Quercetin



Calanolide-A



Geiparvarin

Figure-2

The coumarins have diverse biological properties and various effects on the different cellular systems. Coumarins have important effects in plant biochemistry and physiology, acting as antioxidants, enzyme inhibitors and precursors of toxic substances. In addition, these compounds are involved in the actions of plant growth hormones and growth regulators, the control of respiration, photosynthesis, as well as defense against infection.

The coumarins have long been recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral and anticarcinogenic activities. The coumarins are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence in their biological activity.[4]

A number of natural and synthetic coumarin (2-oxo-2*H*-chromene) derivatives have been reported for their notably antimicrobial,[5,6] antifungal[7,8] and tuberculostatic[9] activity.

The α-benzopyran-2-one moiety the structural core of coumarins, is often found in more complex natural products[2] and is frequently associated with biological activity, such as anti-cancer,[10] antifungal[11,12] anti-HIV,[13] and anti-clotting.[14] For example, carbochromen is a potent specific coronary vasodilator used for many years in the treatment of angina pectoris.[15]

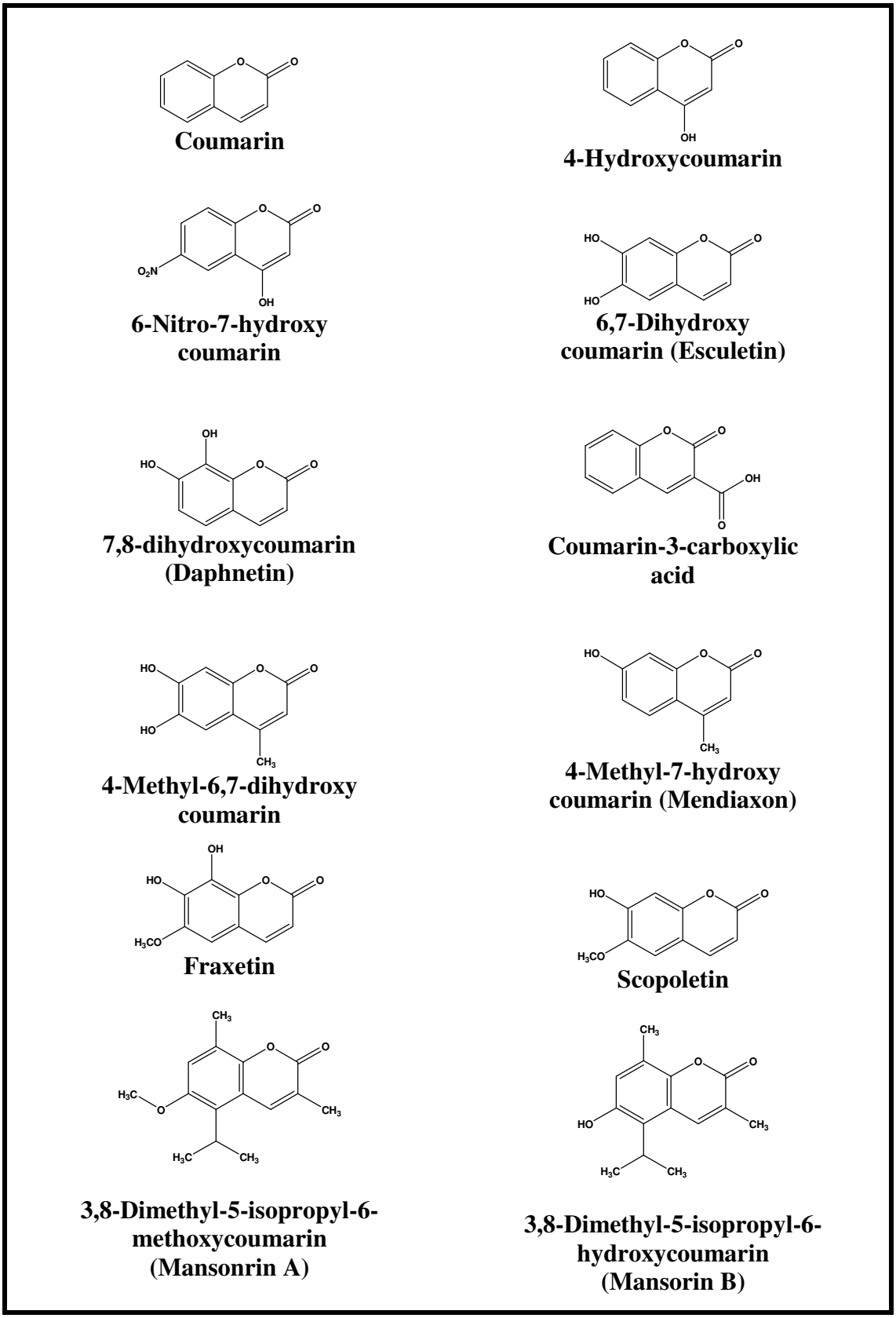
1.2. Pharmacology

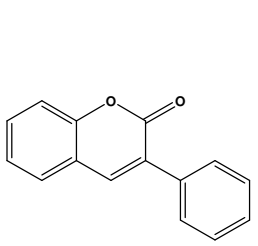
Coumarins as cytotoxic agents

Coumarins have attracted intense interest in recent years because of their diverse pharmacological properties. The cytotoxic coumarins represent an exploitable source of new anticancer agents, which might help addressing cytotoxicity and resistance phenomena. These natural compounds have served as valuable leads for further design and synthesis of more active analogues. Promising data have been reported for a series of different coumarins used as cytotoxic agents.[16]

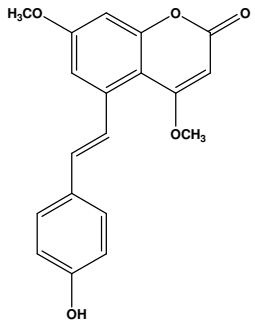
A large number of structurally novel coumarin derivatives have ultimately been reported to show substantial cytotoxic and anti-HIV activity *in vitro* and *in vivo.*[17] Coumarins have shown cytotoxicity with derivatives containing *o*-dihydroxy substituents as reported by Kolodziej *et. al.*[14]. The chemical structure and biological activity study of the coumarins showed that the addition of a catecholic group to the basic structure induced increased cytotoxic activity in tumor cell lines.[18]

Figure-3: Structures of cytotoxic coumarins[14]





Pervilleanine



5-(4-Hydroxyphenethenyl)-4,7-dimethoxycoumarin

Figure-3

The aminocoumarin antibiotics novobiocin, clorobiocin and coumermycin A1 are known as potent inhibitors of gyrase.[19] Their equilibrium dissociation constants are in the range of 10 nM,[20] i.e., their affinity for gyrase is considerably higher than that of modern fluoroquinolones. Novobiocin is licensed as an antibiotic for clinical use (Albamycin; Pharmacia-Upjohn) and is used for the treatment of infections with multi resistant gram-positive bacteria, e.g. *Staphylococcus aureus*[21] (Figure-4).

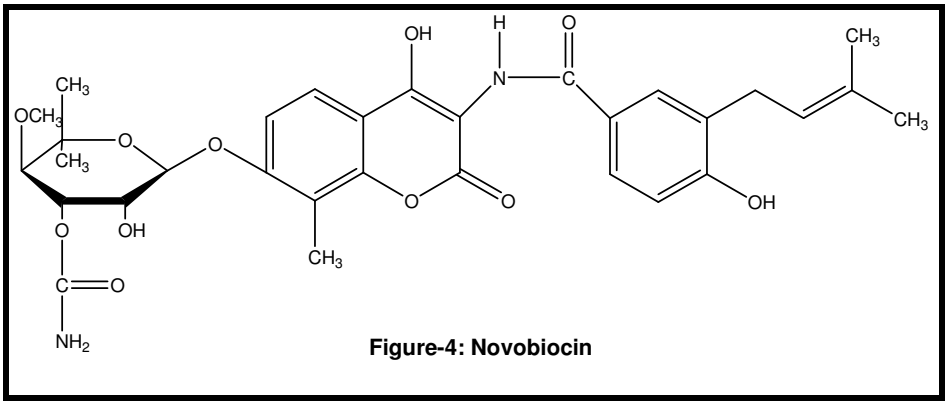


Figure-4: Novobiocin

Novobiocin is produced by *Streptomyces spheroides* (syn. *S. caeruleus*)[22] NCIMB 11891, Clorobiocin (Figure-5) is produced by *S. roseochromogenes var. oscitans* DS12.976 and coumermycin A1 (Figure-6) is produced by *S. rishiriensis* DSM 40489.[23] Obviously, these organisms must protect their gyrases from the inhibitory effect of aminocoumarin during antibiotic formation.

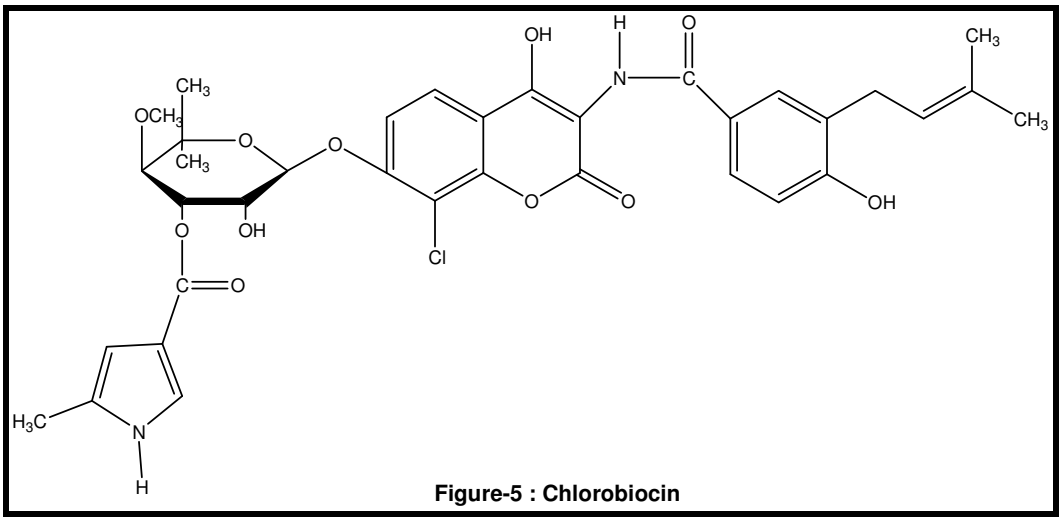


Figure-5 : Chlorobiocin

Thiara and Cundliffe[24-26] reported that the principal resistance mechanism of the novobiocin producer *S. sphaeroides* is the *de novo* synthesis of a coumarin-resistant gyrase B subunit, which replaces the sensitive GyrB subunit in the active (GyrA)2(GyrB)2 heterotetramer. Thus, this novobiocin producer contains two *gyrB* genes, a constitutively expressed *gyrB*S, encoding the coumarin-sensitive protein and the *gyrB*R gene, encoding the resistant protein and expressed in the presence of novobiocin. The promoter of *gyrBR* appears to be regulated by changes in the superhelical density of DNA.[24] Mitchell *et. al.*[21] supplied evidence that additional genes may contribute to novobiocin resistance. They used the novobiocin producer *S. niveus*, which has recently been identified as a subjective synonym for *S. spheroids.*[19]

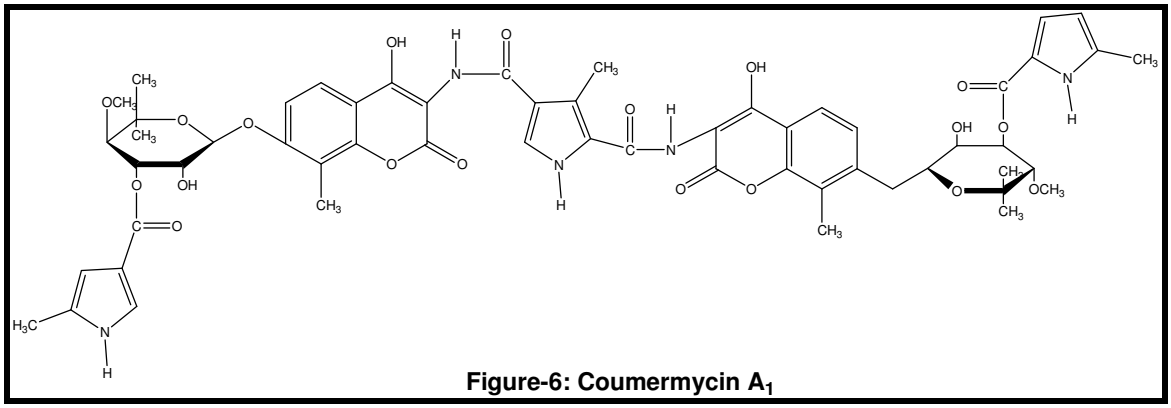


Figure-6: Coumermycin A_1

Coumarins as potent anti-HIV compounds

Natural coumarins and their derivatives can display anti-HIV activity through different mechanisms, including blockade of viral entry, inhibition of reverse transcriptase and interference with viral integration.[27,28] Some phenylcoumarins and chalcones, as well as tannins and lignins, have been proposed as suppressors of LTR-dependent transcription, but the mechanism of action has not been fully characterised.[29]

(+)-Calanolide A, a natural dipyranocoumarin, currently undergoing anti-AIDS clinical trials,[30] has also proven to be an effective antimycobacterial against drug-sensible and drug-resistant *Mycobacterium tuberculosis* strains (Figure-7).

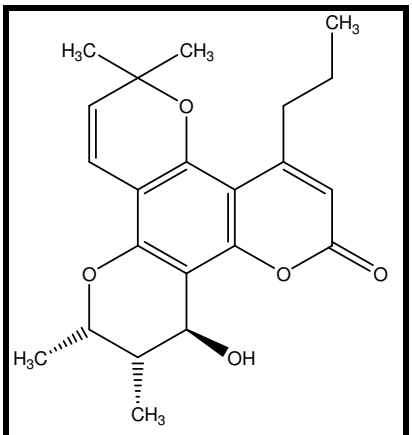


Figure-7: (+)-Calanolide A

It has been reported that mesuol and isomesuol, (Figure-8) two 4-phenyl coumarins, isolated from the tree *Marila pluricostata*, suppress HIV-1 replication in Jurkat T cells.[31] These coumarins do not affect the reverse transcription and intregration steps of the viral cycle and their antiviral effect is additive with that of azidothymidine (AZT). In addition, mesuol inhibits TNFα-induced HIV-1-LTR transcriptional activity by targeting the nuclear factor-κB (NF-κB) pathway. While mesuol does not prevent either the binding of NF-κB to DNA or the phosphorylation and degradation of NF-κB inhibitory protein, IκBα, it inhibits the phosphorylation and the transcriptional activity of the NF-κB p65 subunit in TNFα-stimulated cells. These results highlight the potential of the NF-κB transcription factor as a target for anti-HIV-1 compounds such as 4-phenyl coumarins,

which could serve as lead compounds for the development of additional therapeutic approaches against AIDS.

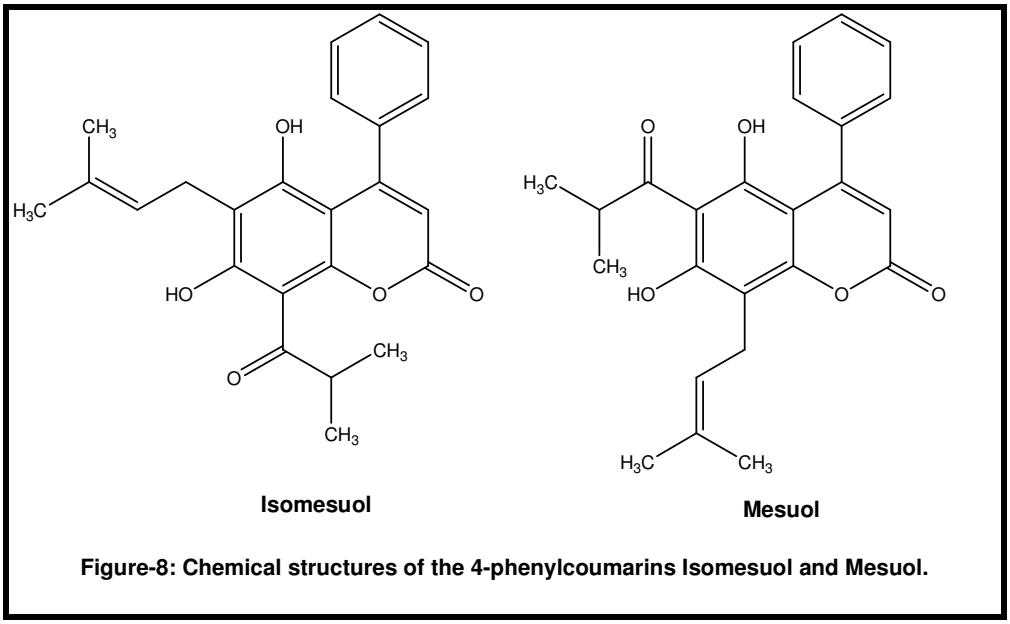


Figure-8: Chemical structures of the 4-phenylcoumarins Isomesuol and Mesuol.

Table-1: A review of EC_{50} values and TIs (defined as LD_{50}/IC_{50}) for some coumarins

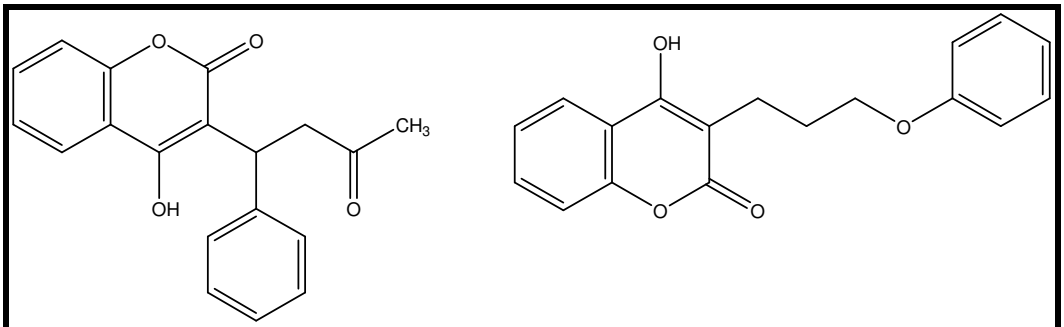
Sr. No.	Compound	EC_{50}	TI	Ref.
1	Suksdorfin	1.3 µM	> 40	32
2	3', 4' Di-*o*-(-)-camphanoyl-(+)-cis-khellacetone	4×10^{-4} µM*	136.719	33
3	4-Methyl-DCK lactum	0.00024 µM	119.333	34
4	5-Methoxy-4-methyl DCK	7.21×10^{-6} µM	$> 2.08 \times 10^{7}$	35
5	3-Hydroxymethyl-4-methyl-DCK	0.004 µM in H9 cells 0.024 µM in PBMC**		36
6	3-Methyl-, 4-methyl-, and 5-methyl-3',4'-di-*o*-(S)-camphanoyl-(3'R, 4'R)-(+)-*cis*-khellactone	5.25×10^{-5} µM	2.15×10^{6}	37
7	3-Hydroxymethyl DCK	1.87×10^{-4} µM	1.89×10^{5}	38
8	4-Methyl-3',4'-di-*o*-(-)-camphanoyl-(+)-*cis*-khelthiolactone	0.00718 µM	> 21000	32
9	3-Bromomethyl-4-methyl-DCK	0.00011 µM	189600	36

* Here IC_{50} but not EC_{50} is reported
** Peripheral Blood Mononuclear Cells

A. Protease inhibitors

Warfarin is believed to inhibit the vitamin K dependent conversion of prothrombin and serine protease activity of thrombin. A 100 μM dose of warfarin is inhibitory toward HIV aspartyl protease. In view of the four remarkable properties of warfarin, *i.e.*, inhibition of serine protease, aspartyl protease, reverse transcriptase and integrase, all of which are essential for HIV replication, this drug deserves clinical testing in a larger population of HIV-positive individuals (Figure-9).

Two large pharmaceutical companies, Parke-Davis, a division of Warner Lambert and Pharmacia & Upjohn confirmed that warfarin and related coumarin compounds were HIV protease inhibitors.[39] Warfarin, the first non-peptide derived protease inhibitor, was proclaimed to be a modest PI (IC_{50} of 18 or 30 μM) and coumarin derivatives with better specificity were provided. Inhibitors of HIV-1 protease, the pyran-2-one group, 4 hydroxyl group, and substitution at the 3-position are all necessary for activity.[40] PD099560 is also identified as a non-peptide competitive HIV-1 protease inhibitor[41] (Figure-9).



Warfarin **PD099560**

Figure-9

B. Integrase inhibitors

In addition to HIV RT and protease, HIV integrase is also a major chemotherapeutic target;[42] integrase inhibitors mainly includes biscatechols and coumarins. Because catechols are cytotoxic, partly due to *in situ* oxidation to quinone species, coumarins have

clinical advantages. A natural tetrameric coumarin showed high anti-integrase activity (IC_{50} ¼ 0.8 μM for integration and 1.5 μM for 30-processing)[43] (Figure-10).

Increasing the number of aryl rings on the central linker enhanced potency; the rigid stilbene analog[44] is the most potent (integration 3.7 μM, 30-processing 5.5 μM) among the compounds synthesized (Figure-11). 7-Hydroxylation was beneficial in a wide range of dimeric 4,7-hydroxycoumarins and led to a simplified coumarin integrase inhibitor without greatly sacrificing the potency of the tetrameric compound.

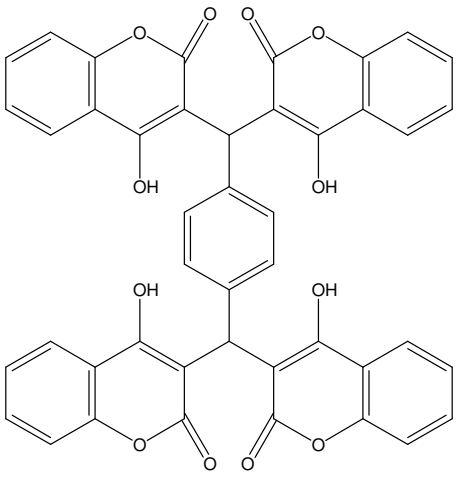


Figure-10: A Natural tetrameric coumarin

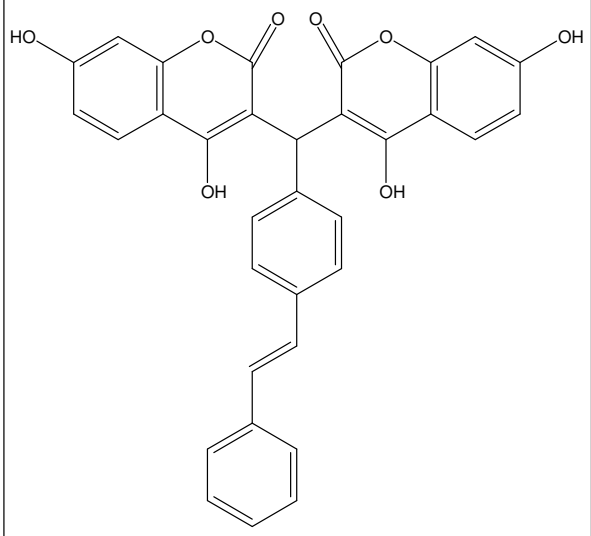


Figure-11: Stilbene analog

C. Reverse trancriptase inhibitors

HIV-1 RT interacts with complementary oligodeoxynucleotide (ODN) primers at the 50-end of the tRNA binding site as well as at the 30-end of the primer. ODN derivatives can form specific, more stable complexes with complementary nucleic acids. When several chromone and coumarin structures were conjugated to the 50-end of ODNs affinity toward HIV-1 RT is increased, suggesting that these compounds may be functioning as primers. This action was confirmed when protection of RT by tRNA lys3 decreased the complex formation between the enzyme and the conjugated ODN. The same ODNs conjugated to chromone or coumarin did change the polymerization rate: either inhibition

or slight activation followed by inhibition depending on the concentration. When ‘‘chain terminator’’ 30ddT was added, the ligand-ODN complex was easily converted to a strong inhibitor[45] (Figure-12).

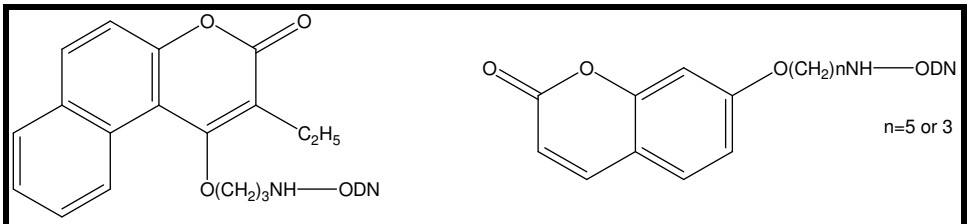


Figure-12

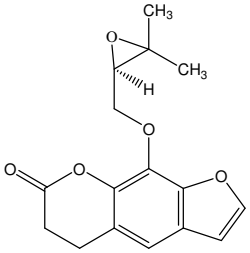
D. Coumarins as photodynamic therapeutics (PDT) agents

Furanocoumarins, such as the psoralene and angelicin, are common constituents of many members of the *Rutaceae* and *Apriaceae* plant families. They are commonly UV phototoxic toward cells, bacteria, fungi, and viruses. Photomodified viral genomes can not be transcribed into RNA/DNA,[46] thus, the furanocoumarins inhibit viral replication. Coriandrin, a furanoisocoumarin from coriander, is much more photoreactive than psoralen but does not cross-link with DNA nor photosensitize human skin.[47(a)]

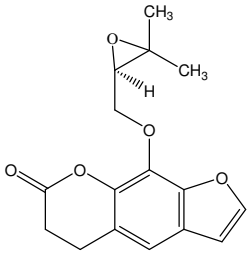
Most of the dialkylaminoalkyl coumarin-4-acetates showed a local anesthetic activity[47(b)] by infiltration approaching that of procaine. In contrast to procaine, they were also found to be topically active. For example, 3-(2-methylpiperidyl-1)-propyl 7-methylcoumarin-4-acetate hydrochloride was equal in activity to procaine by infiltration (external canthus of the rabbit's eye) and about one-half as active as cocaine topically. Its toxicity was about onehalf that of cocaine. In general, the coumarin-4-acetic acid derivatives were much less toxic than the corresponding coumarin-3-carboxylic acid derivatives.

Figure-13: Some natural furo- and pyranocoumarins

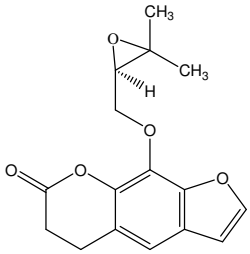
Furo Coumarins



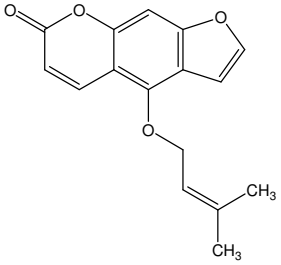
Heraclenin



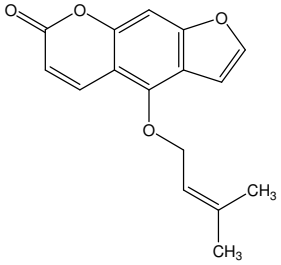
Heraclenin



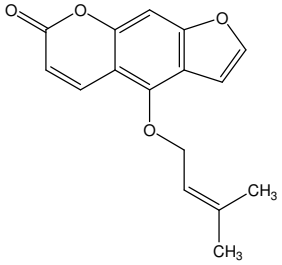
Heraclenin



Isoimperatorin

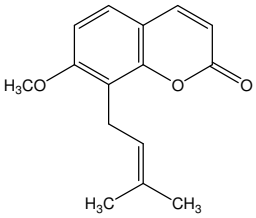


Isoimperatorin

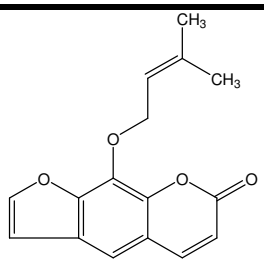


Isoimperatorin

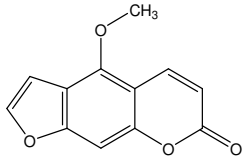
Pyranocoumarins



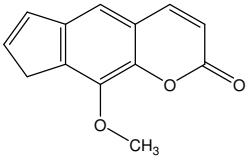
Osthol



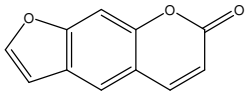
Imperatorin



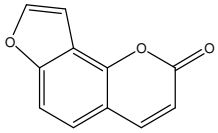
Bergapten



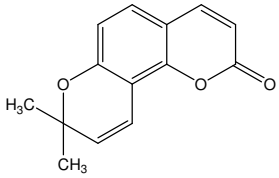
Xanthotoxin



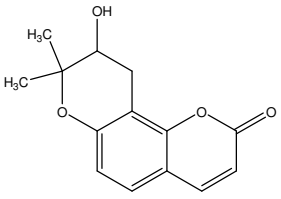
Psoralen



Angelicin



Seselin

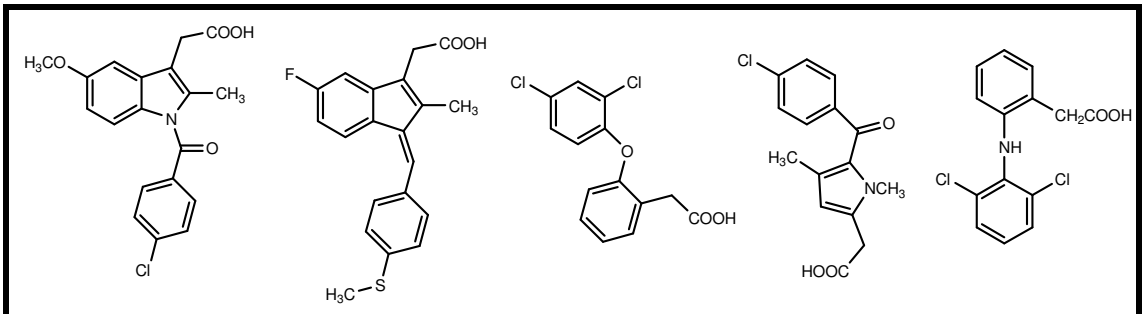


Lomatin

Figure-13

Known drugs with alkanoic (acetic acid) as a core fragment

NSAIDs used as starting points for the design of selective CRTH2 antagonists. Several non-steroidal anti-inflammatory drugs (NSAIDs) (Figure-14) showed moderate binding affinity for CRTH2 (chemoattractant receptor-homologous molecule expressed on T_H2 cells), such as fenclofenac and sulindac sulphide (4,953 nM and 3,450 nM respectively), but were also active on DP_1. Indomethacin, however, demonstrated selective binding for CRTH2 (binding values vary between 25 nM and 8.000 nM depending on assay conditions) and was shown to be a potent agonist of the receptor (15-50 nM) in functional assays. Zomepirac was subsequently shown to have antagonistic activity *in vitro.*[48]



Indomethacin **Sulindac sulphide** **Fenclofenac** **Zomepirac** **Diclofenac sodium**

Figure-14: NSAIDs used as starting points for the design of selective CRTH2 antagonists

Important leads containing acetic acid chain

1. Ramatroban analogues with CRTH2 antagonist activity.

Moving the amide nitrogen present in ramatroban into the core ring structure led to compound 1, which demonstrated potent (3 nM) antagonistic activity *in vitro*. By transposing fused benzene and cyclohexyl rings, a series of compounds were identified with moderate binding activity and selectivity. CRTH2 (chemo attractant receptor-homologous molecule expressed on TH2 cells. Further modification of compound 2, by shortening the propionic acid group to an acetic acid group gave compound 3, a more potent and selective analogue. Acetic-acid group is a strongly preferred group as compared to propionic-acid group in potent CRTH2 antagonists. By simple N methylation the sulphonamide NH (TM30642) or by truncating the propionic-acid group

to an acetic-acid group (TM30643) or a combination of both modifications (TM30089), three potent CRTH2 binding compounds with high selectivity over TP binding were modified with improved selectivity over ramatroban[48] (Figure-15).

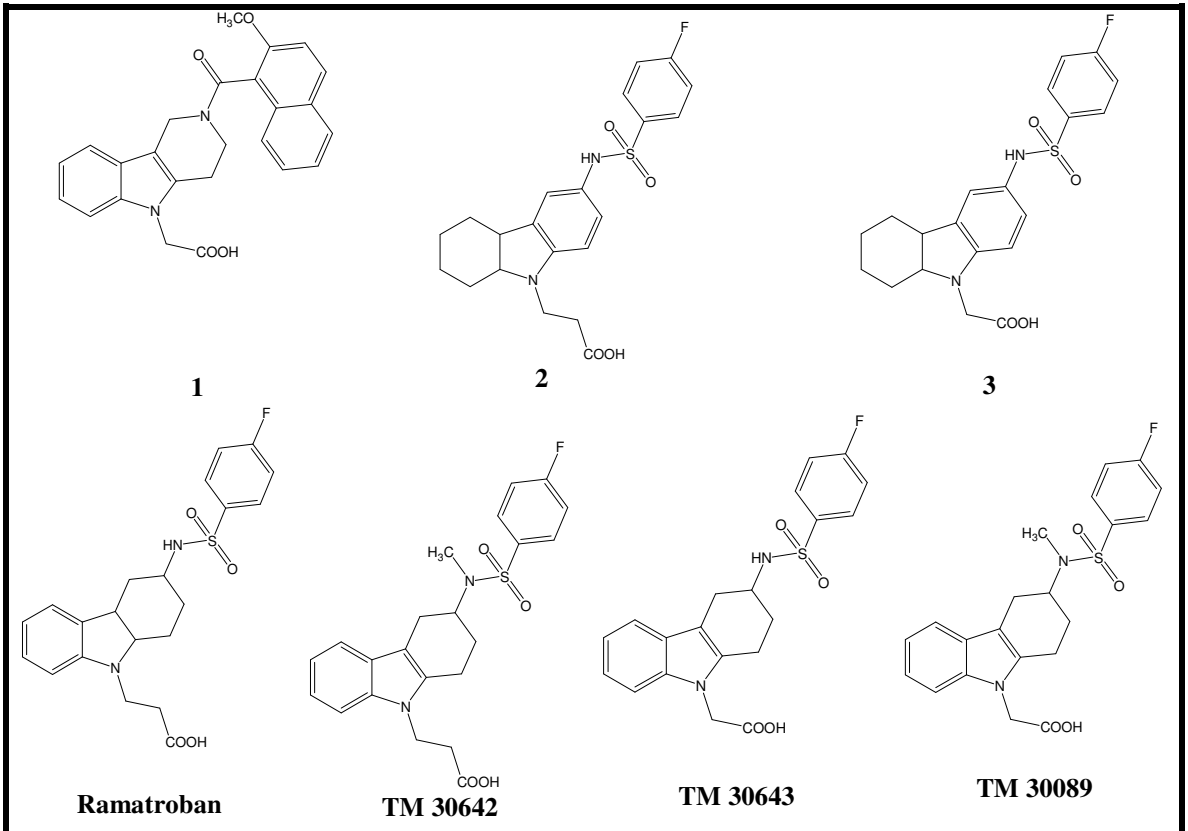


Figure-15: Ramatroban analogues with CRTH2 antagonist activity.

2. Physicogenetically identified CRTH2 antagonists.

A physicogenetically based method that classifies seven transmembrane receptors with respect to the physicochemical properties of the key amino-acid residues located in a common core ligand-binding site to CRTH2 (chemo attractant receptor-homologous molecule expressed oil TH2 cells) identified angiotensin II receptor type 1 (AGTR1) and AGTR2 receptors as likely to share similar binding properties to CRTH2. Screening of a focused compound library led to the identification of TM27632 and TM3170 as CRTH2 ligands with low micromolar affinity, whereas selected screening of AGTR1 and AGTR2 ligands identified Candesaetan as the most potent (2.100 nM) ligand for CRTH2[48] (Figure-16).

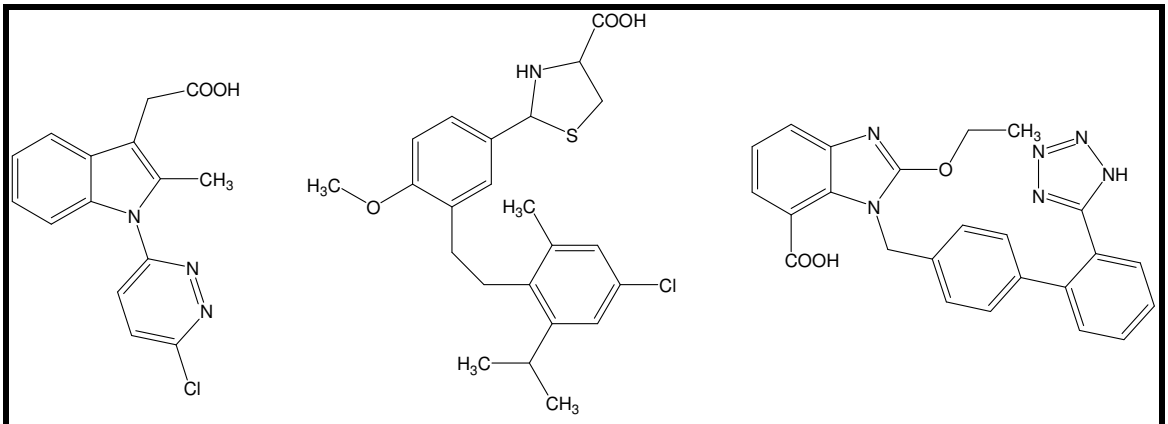


Figure-16: Physicogenetically identified CRTH2 antagonists.

Aryl acetic acid CRTH2 antagonists

The biaryl thioether, 1, was first identified as CRTH2 (chemoattractant receptor-homologus molecule expressed on TH2 cells) antagonists within this structural class with 40 fold functional selectivity for CRTH2 over DP_1. Biaryl-acetic acid derivatives such as compound, 2, with a CRTH2 binding pIC_{50} of 8.2 and biaryl-ether-acetic-acid derivatives such as compound, 3, with a CRTH2 binding pIC_{50} of 9.0 have been patented[49-52] (Figure-17).

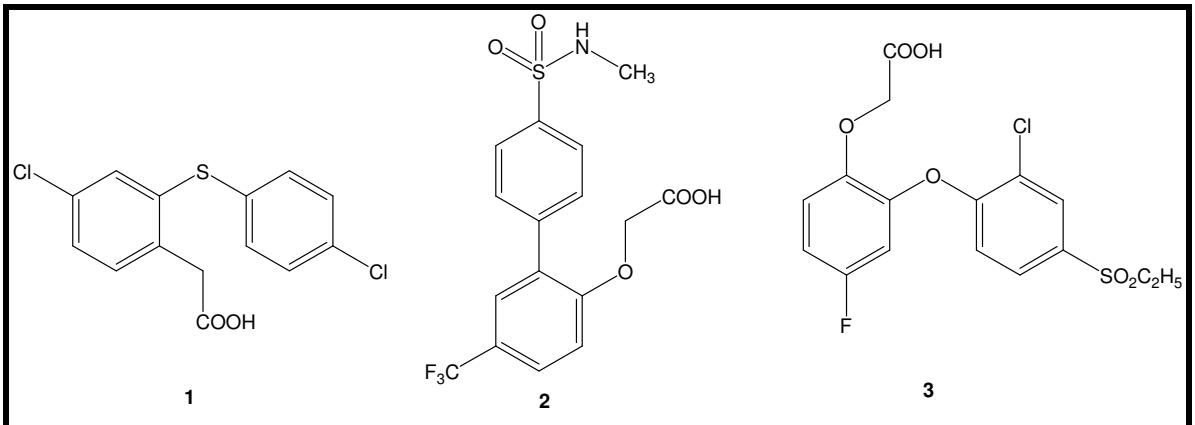


Figure-17: Aryl acetic acid CRTH2 antagonists

Prostaglandin D_2 (PD_2) is an important mediator of allergic responses. The high contraction produced in response to an allergic stimulation combined with its highly potent activity result in PGD_2, having a dominant role in mediating mast-cell dependent

activation of TH2 lymphocytes, all effect mediated by CRTH2. Therefore, PGD_2, produced by mast cells might provide all essential link between the early phase and late-phase allergic responses. Such antagonism of PGD_2, provides an attractive target for therapeutic intervention. There are a number of potent and selective CRTH2 antagonist series identified with drug -like properties and results of ongoing clinical trials in asthma and allergic rhinitis are awaited.

Coumarin-3-and coumarin-4-acetates are written in hypothetical non-cyclic forms (I, II), it is apparent that they are, respectively, a substituted Phenylvinylacetic ester and a substituted pheny1 propionic ester[53] (Figure-18).

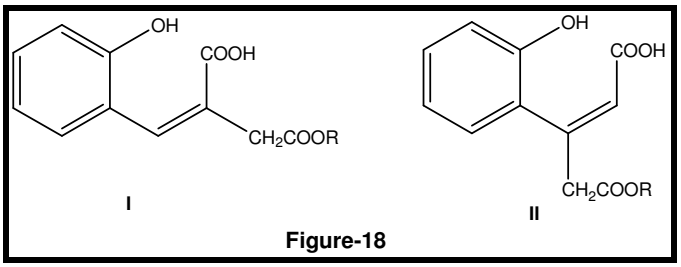
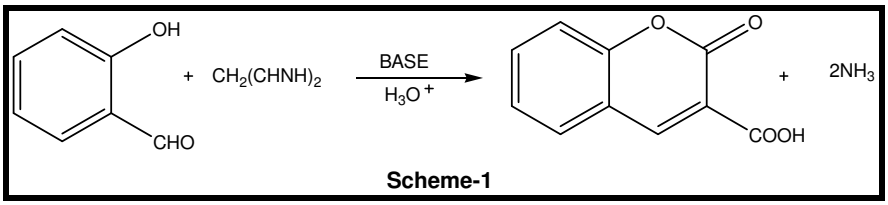


Figure-18

The literature contains no references to basic derivatives of coumarin-3-or -4-acetic acids, other than a single benzene derivative, *viz.* 7-dimethylaminocoumarin-4-acetic acid. No pharmacological investigations appear to have been made in these series.[54]

1.3. Synthetic aspects

Coumarin-3-carboxylic acids can be synthesized by the conventional Knoevenagel method,[55] from a substituted salicylaldehyde and malonic ester. The ethyl esters were saponified by refluxing with an excess of dilute sodium hydroxide solution for several hours, followed by acidification with hydrochloric acid. Therapeutic assay of the coumarin-3-carboxylic acid derivatives for local anesthetic activity has been carried out by Becker and Luduena[56] (Scheme-1).



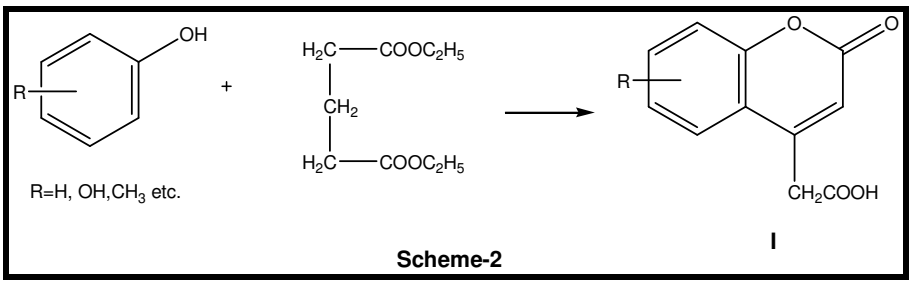
Scheme-1

Werder *et. al.*[57] have synthesized more than 100 derivatives of coumarin-3-carboxylic acid, which were found to be sedative in low doses and hypnotic in large doses. Among the derivatives of these acids, the diethyl amide proved to be a good drug in general nervous disease and in various neuro anaesthetic and hysterical ailments. It has also been found that some oxygenated coumarins possessing the power of absorbing UV rays which were extensively used as medicines in skin desieses.[58]

1.4. Present Work

The present work aims at preparation of coumarin-4-acetic acids of different substitutions, to find out optimum reaction conditions and also to study their anticancer properties as a core scaffold.

The coumarin-4-acetic acids were prepared by the von Pechmann reaction[59] from a *m*-substituted phenol and acetone dicarboxylic acid (prepared *in situ* from citric acid). Biginelli[6] condensed quinol with ethyloxalacetate in presence of sulfuric acid to obtain 6-hydroxy-coumarin-4-acetic acid. Pechmann and Kraft[60] extended this reaction to other phenols. Gokhle and Ghosh,[61] Chakravarti[62] and Banerjee[63] have studied the formation of coumarin-4-acetic acid from substituted phenol and acetone dicarboxylic acid using sulfuric acid as condensing agent. Limaye[64] found that phenol when condenced with citric acid, gave coumarin-4-acetic acid. Dey,[65] Dixit,[66] Fries[67] have studied the reaction of phenol with acetonedicarboxilic acid and also using citric acid. Burton and Muller[68, 69a] have found that condensation of resorcinol with diethylacetone dicarboxylate afforded 7-hydroxy coumarin-4-acetic acid. Ghia and co-workers[69b] also studied these compounds for bromination of styryl derivatives (Scheme-2).



Scheme-2

In general, these syntheses offered no difficulty, although in certain cases the yields were poor. However, the von Pechmann reaction failed with *m*-thiocresol, *m*-trifluoromethylphenol and *p*-hydroxydiphenyl and the synthesis of pharmacologically interesting 7-methylthiocoumarin and 7-trifluoromethylcoumarin-4-acetic acids was failed.

Drawback of reaction conditions

The complication in this reaction arises from the extreme case of decarboxylation observed in the coumarin-4-acetic acid series.[53] A similar phenomenon was observed in the related esterification reaction between a coumarin-4-acetic acid and a basic alcohol. In both reactions the chief product was the 4-methylcoumarin. Dey[70] attempted to prepare coumarin-4-acetyl chlorides from the acids and phosphorus pentachloride, which failed, instead, only deeply colored decomposition products were obtained. Acyl chlorides were successfully isolated from the reaction between coumarin-4-acetic acids and thionyl chloride, but the acyl chlorides, contained a second chlorine atom (Figure-19).

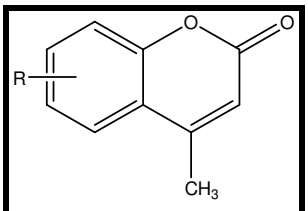
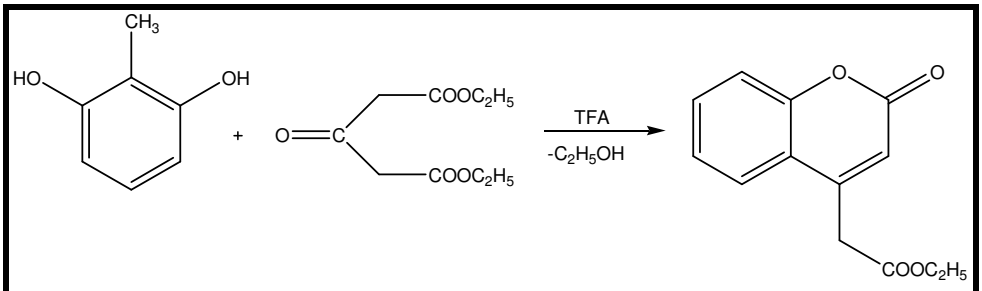


Figure-19

Gardner *et. al.*[71] prepared basic esters and amides of coumarin-4-acetic acids, *via* ω-haloalkyl coumarin-4-acetates, which were readily obtained by esteritication of the acids with an α-haloalkanol. Replacement of the ω-halogen group by reaction with a secondary

amine gave excellent results if the condensations were carried out in an appropriate solvent (toluene with bromo esters and xylene with chloro esters). The coumarin-4-acetamides were easily prepared by amination of the corresponding ethyl coumarin-4-acetates with a primary amine in boiling xylene.

Woods and co-workers[72] have reported a new one-step method of preparing substituted coumarins in which phenols were condensed with various β-keto esters under the influence of trifluoroacetic acid. The ethyl esters of coumarin-4-acetic acids can be prepared if diethyl acetone dicarboxylate is the β-ketonic ester component. The fact that coumarin-4-acetic acids are subject to easy dehydration to an internal ester, makes the ester a more satisfactory compound for consistent syntheses. Further, since the free acid is a malonic acid vinylog, methods of isolation and purification often cause considerable decarboxylation (Scheme-3).



Scheme-3

Applications

Ultrafast transient absorption spectroscopy has been employed by Ramakrishna and co-workers[73] to understand the effect of molecular structure on interfacial electron transfer (ET) dynamics of 7-*N*, *N*-dimethyl amino coumarin 4-acetic acid (DMACA) and 7-hydroxy coumarin 4-acetic acid (HCA) sensitized TiO_2 and ZrO_2 nanoparticles. Electron injection is confirmed by observing the cation radical of the dye molecules as well as the conduction band electron in the visible and near-IR regions. Electron injection efficiency has been found to be higher for the HCA/TiO_2 system as compared to the DMACA/TiO_2 system. Both dyes are structurally similar except that HCA has a hydroxyl group at the 7-position while DMACA has a dimethyl amino group at the 7-position (Figure-20).

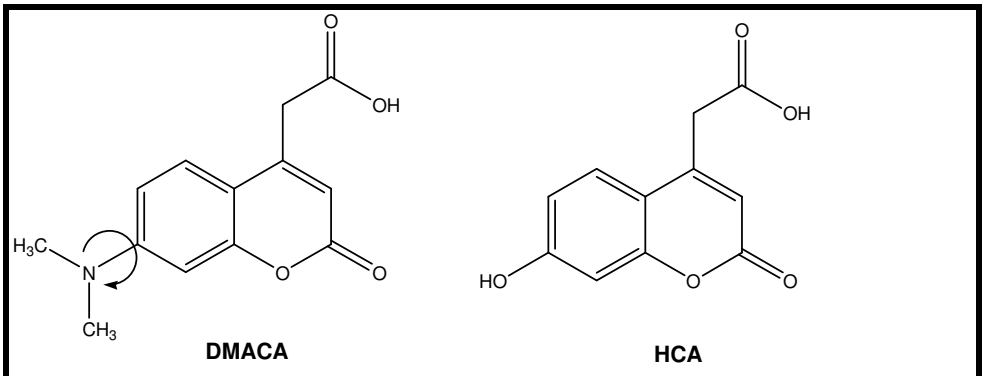


Figure-20: Molecular Structure of 7-*N,N*-Dimethyl Coumarin-4-acetic Acid (DMACA) and 7-Hydroxy Coumarin-4-acetic Acid (HCA)

The steady-state and time-resolved fluorescence measurements confirmed that, in highly polar solvent, the excited state of DMACA dye exists both in twisted intramolecular charge transfer (TICT) and intramolecular charge transfer (ICT) states, whereas excited HCA exists only in the ICT state (figure-21).

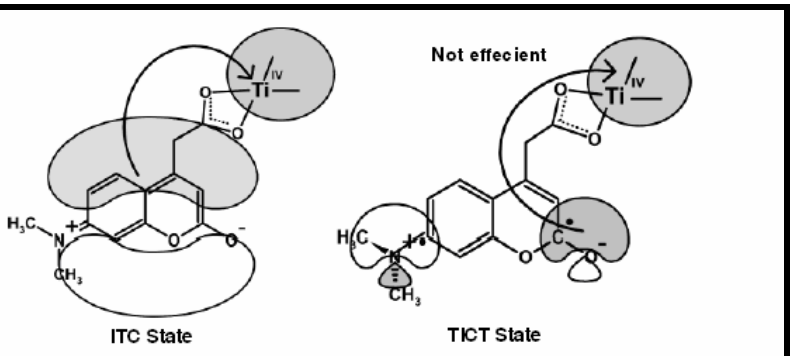


Figure-21: Orbital scheme showing Electron Injection from ICT and TICT state of 7-N,N-Dimethyl coumarin-4-acetic acid (DMACA) into TiO2 nanoparticles

Sarges *et. al.*[74] synthesized some coumarin-4-acetic acids contain the preapations of substituted and unsubstitutred coumarin-4-carboxylic or acetic acid derivatives which has been proved as aldose reducatase inhibitors and as therapeautic agents for the treatment of chronic diabetic complications. Sarges *et. al.*[74] synthesized certain novel carboxylic acid derivatives which are useful in the treatment of certain chronic complications arising from diabetis mellitus, such as diabetic cataracts and neuropathy. Aldose reduatase inhibitors such as 1,3-dioxo-1*H*-benz[-*d,e*]-isoquinoline-2(3*H*)-acetic acid and its

derivatives are useful in this regard. Such compounds inhibit the enzymatic reduction of aldoses, such as glucose and galactose, to the corresponding polyols, such as sorbitol and galactol, thus preventing or reducing the harmful and unwanted accumulations of polyols in the diseased organs of the body (Figure-22).

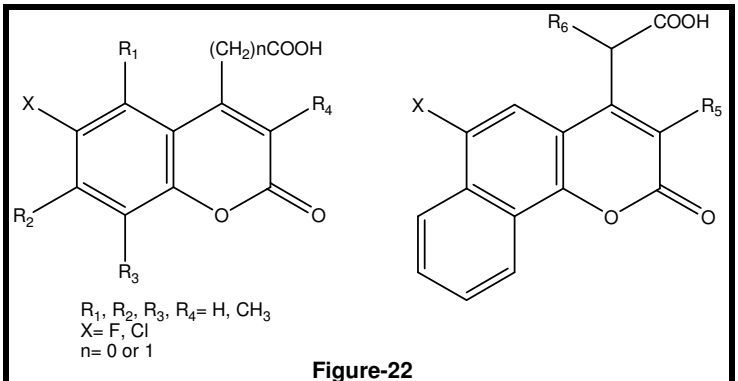


Figure-22

The derivatives are easily prepared by condensing an acetonedicarboxilic acid or ketosuccinic acid with the approproiate phenol compound. The ability of these active ingredients of the derivatives, to control chronic diabetic complications and enzymatic reduction of aldoses has been determined by a number of standared biological or pharmacological tests.

These tests include:

1. Measuring the ability to inhibit the enzyme activity or isolated aldose reductase.
2. Measuring the ability to reduse or inhibit sorbitol accumulation in th sciatic nerve or acutely diabetic rats.
3. Measuring the ability to reverse already-elevated sorbitol levels in the sciatic nerve and lens of chronic streptozocin-induced diabetic rats.
4. Measuring the ability to prevent or inhibit glactitol formation in the lens of acutely glactosemic rats.
5. Measuring the ability to delay cataract formation and reduse the severity of lens opacities in chronic galctosemic rats.

The derivatives were tested for their ability to reduce or inhibit aldose reductase enzyme activity, based on the procedure of Hayman *et. al*.[75] The drugs were tested at a level of 10^{-4} M to determine the degree of inhibition of enzyme activity relative to untreated controls.

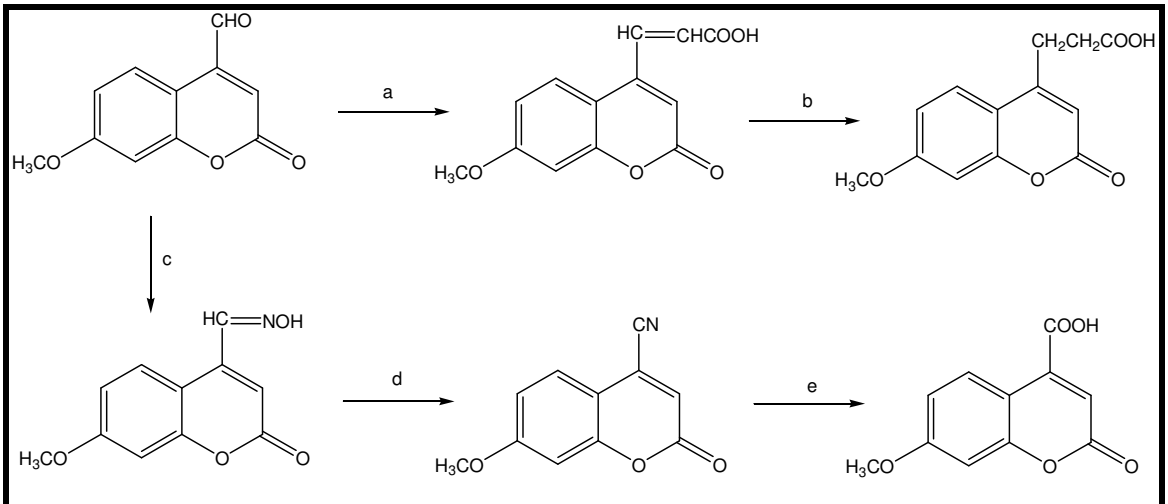
The compound useful for prophylactic or remedial treatment of diabetic cataracts, retinopathy, nephropathy or neuropathy in a diabetic patient should comprise of a pharmaceutical carrier and a therapeutic amount of a coumarin carboxylic acid derivative selected from the group consisting of the above structures: Where, R^1, R^2, R^3 and R^4 must be H, CH_3 and X must be either F or Cl, n can be either 0 or 1 (Figure-22).

Clinton *et. al.*[76] synthesized basic esters and amides derived from 7-substituted coumarin-4-acetic acids, which were found effective as local anesthetics. Basic esters and amides were prepared by the general method of Pechman and Duisberg.

Profit *et. al*.[77] demonstrated that 7-hydroxy-coumarin-4-acetic acid linked to the *N*-terminus of pTyr-Glu-Glu-Ile-amide significantly enhances the affinity of this peptide for the SH_2 domain of Lck (lymphoid T cell kinase).[78] Although this effect appears to be quite specific for Lck, we do observe a modest enhancement for the SH_2 domain of Fyn (Fgr and Yes-related kinase) as well.

Brubaker *et. al.*[79] synthesized a number of 4,7-disubstituted benzopyran-2-ones and evaluated them for crude rat lens aldose reductase inhibitory activity. The 3-oxo-3*H*-naphtho[2,1-*b*]pyran-l-acetic acid, 2-oxo-2*H*-naphtho[l,2-*b*]pyran-4-acetic acid, and 1-naphthylacetic acids. The structure-activity relationships reveal that optimal enzyme inhibitory activity is displayed by those compounds possessing the acetic acid moiety. The most potent derivative, 3-oxo-3*H*-naphtho-[2,1-*b*]pyran-l-acetic acid with an IC_{50} of 0.020 pM, is as potent as sorbinil (IC_{50} = 0.017 pM) in the crude rat lens aldose reductase assay.

DeRuiter and co-workers[80] described the aldose reductase inhibitory activity of some quinazolinones containing acetic acid moiety. The most potent aldose reductase inhibitor of the series, 6,7-dimethoxy-2- [(4-carboxyphenyl)amino]-4(3*H*)-quinazolinone, suggested that the presence of an acidic moiety on the quinazolinone nucleus contributed significantly to the inhibitory potency of the quinazolinones.[81] The potent inhibitory activity demonstrated for an extensive series of 2-oxo-ω-benzopyran-4-acetic acids in which the electronic nature of the substituent on the aromatic ring is varied, suggested that these compounds could serve as excellent probes to investigate the steric and electronic requirements of the common inhibitor binding site[82] present on aldose reductase (Scheme-4).



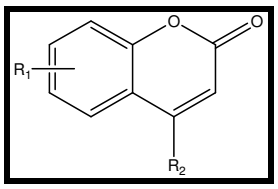
Where, (a) $CH_2(COOH)_2/C_5H_5N/C_5H_{11}N$; (b) $H_2/Pd/C/EtOH$; (c) $NH_2OH/EtOH$; (d) Ac_2O; (e) 50% H_2SO_4.

Scheme-4

The compounds listed in the table-2 below were screened for their ability to inhibit crude aldose reductase obtained from rat lens[83] as described previous1y. The IC_{50} values were determined for those compounds displaying greater than 50% inhibition at 100 µM by least-squares analysis of log dose-response curves. These data suggest two basic SAR points.[84]

a) An ionizable carboxyl moiety is necessary for optimal aldose reductase inhibitory activity.
b) The number of atoms between the carboxyl group and benzopyran-2-one ring is a critical determinant of potency.

Table: Aldose reductase inhibitory activity of 2*H*-1-benzopyran-2-ones[80]

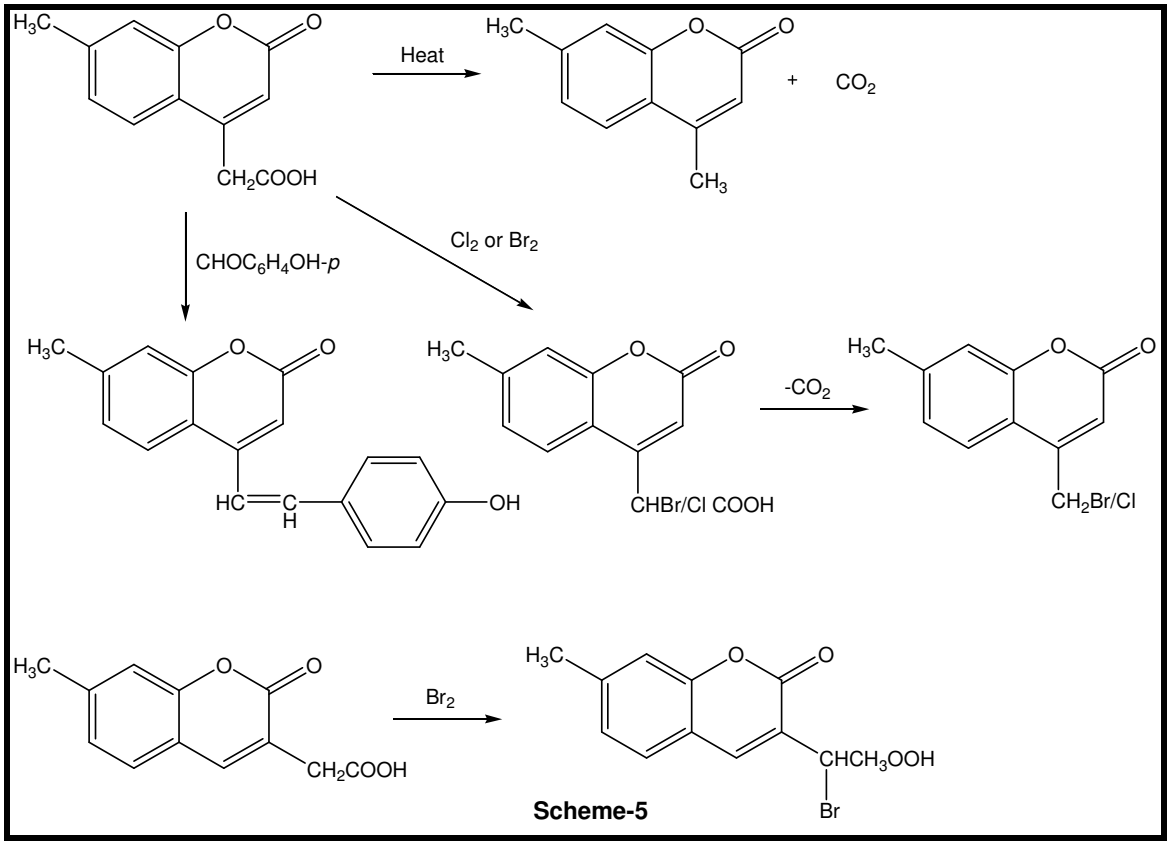


R_1	R_2	Inhibition type[a]	Inhibition[b] % (SEM)	IC_{50}[c] µM
H	CH_3		19 (4.12)	
6-OH	CH_3		22 (2.00)	
7-OH	CH_3	noncomp		62
7-OCH_3	CH_3		21 (3.25)	
7-OAC	CH_3		13 (0.75)	
7-CH_2CH_3	CH_3		16 (0.0)	
7-Cl	CH_3		10 (2.10)	
5,7-$(OH)_2$	CH_3	noncomp		17
7,8-$(OH)_2$	CH_3	noncomp		10
H	CH_2COOH	noncomp		0.60
7-OH	CH_2COOH	noncomp		0.15
		noncomp (NADPH)		
7-OH	CH_2COOCH_3	noncomp		38
7-OH	CH_2CONH_2	noncomp		10
7-OAc	CH_2COOH	noncomp		61
7-OCH_3	CH_2COOH	noncomp		0.37
7-OCH_3	COOH	noncomp		11
7-OCH_3	CH=CHCOOH	noncomp		4.4
7-OCH_3	CH_2CH_2COOH	noncomp		2.1
7-Cl	CH_2COOH	noncomp		0.56
7-CH_2CH_3	CH_2COOH	noncomp		0.24
5,7-$(OH)_2$	CH_2COOH	noncomp		0.26
5,6-$(CH)_4$	CH_2COOH	noncomp		0.020
		noncomp (NADPH)		
7,8-$(CH)_4$	CH_2COOH	noncomp		0.41
1-Napthylacetic acid		noncomp		32
Sorbinil		noncomp		0.017

(a) Double-reciprocal plots were linear, and the significance level for the least-squares was < 0.01 unless indicated otherwise. **(b)** Present inhibition produced at 10^{-4} M followed by the standard error of the mean (SEM). **(c)** IC_{50} values represent the concentration required to produce 50% inhibition.

1.5. Chemistry and synthesis of coumarin-3- and -4-acetic acids

Coumarin-3- and 4-acetic acids comprise within their molecules a double bond between carbon atoms 3 and 4 in the pyrone ring and a reactive methylene group attached to either of these atoms. Dey and Row[85] and Dey and Seshadri[86] have shown that coumarin-4-acetic acids resemble malonic acid in decomposing smoothly and quantitatively into 4-methylcoumarins and carbon dioxide. Further, coumarin-4-acetic acids and their esters readily condense with aromatic aldehydes both by Perkin's and by Knoevenagel's methods, giving rise to 4-coumarylphenylethylene and 4,3-dicoumaryl derivatives. Coumarin-3-acetic acids, on the other hand, are more stable and do not decompose even on heating at high temperatures; they are less reactive, as they do not undergo the Knoevenagel reaction (Scheme-5).



Scheme-5

Dey and Radhabai[87] have studied the action of halogens on the above acids. They found that halogen does not attack the double bond in the pyrone ring, but substitutes one of the methylene hydrogen atoms, a considerable amount of decarboxylation taking place.

Dey[88] condensed various phenols with acetonedicarboxylic acid ester and observed that the methylene group in the side chain in the 4-position was attacked and that 4-halogeno coumarin acetic acids were obtained. Addition of the halogen to the double bond of the pyrone ring was observed in the case of l,2-naphthopyrone-4-acetic acid only.

Bartosova *et. al.*[89] studied some new coumarin derivatives *i.e.* 3-(2-oxo-2*H*-chromen-4-yl)-2-oxo-2*H,* 5*H*-pyrano-[3,2-*c*]chromen-5-yl esters of ethanoic acid and their reaction with nucleophiles and rearrangement in acetic acid. 3-Formylchromones were prepared by Vilsmeier-Haack reaction.[90] They are attractive intermediates for preparation of new heterocycles.[91,92] Microwave irradiation was used for the preparation of coumarins such as compounds a, b, c.[93] (Figure-23) .

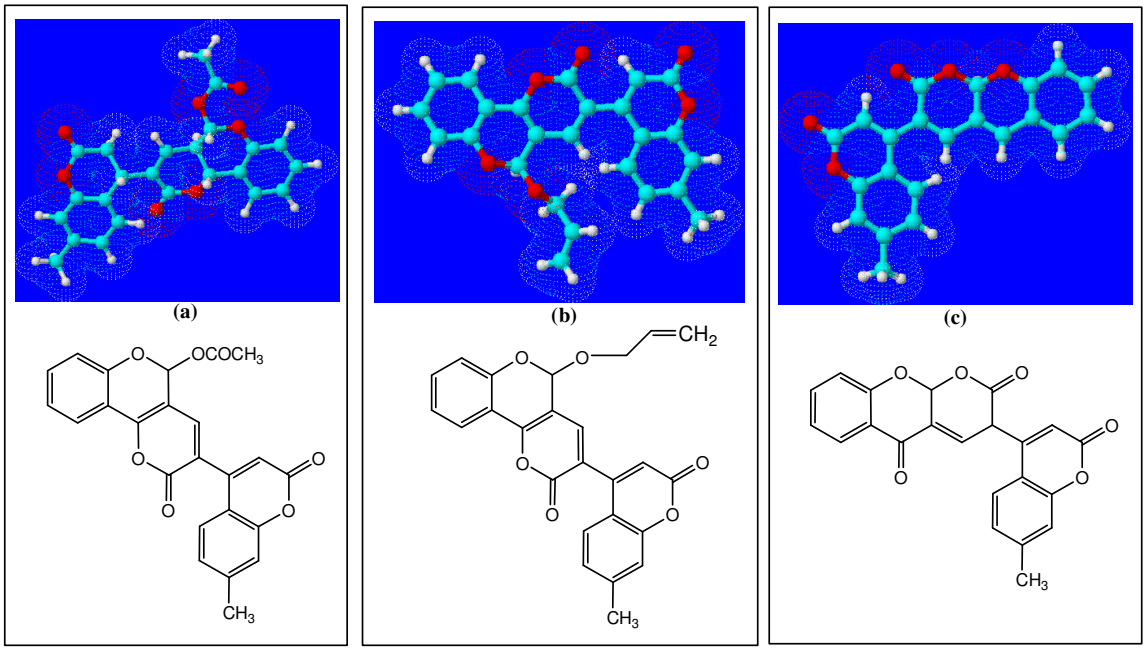
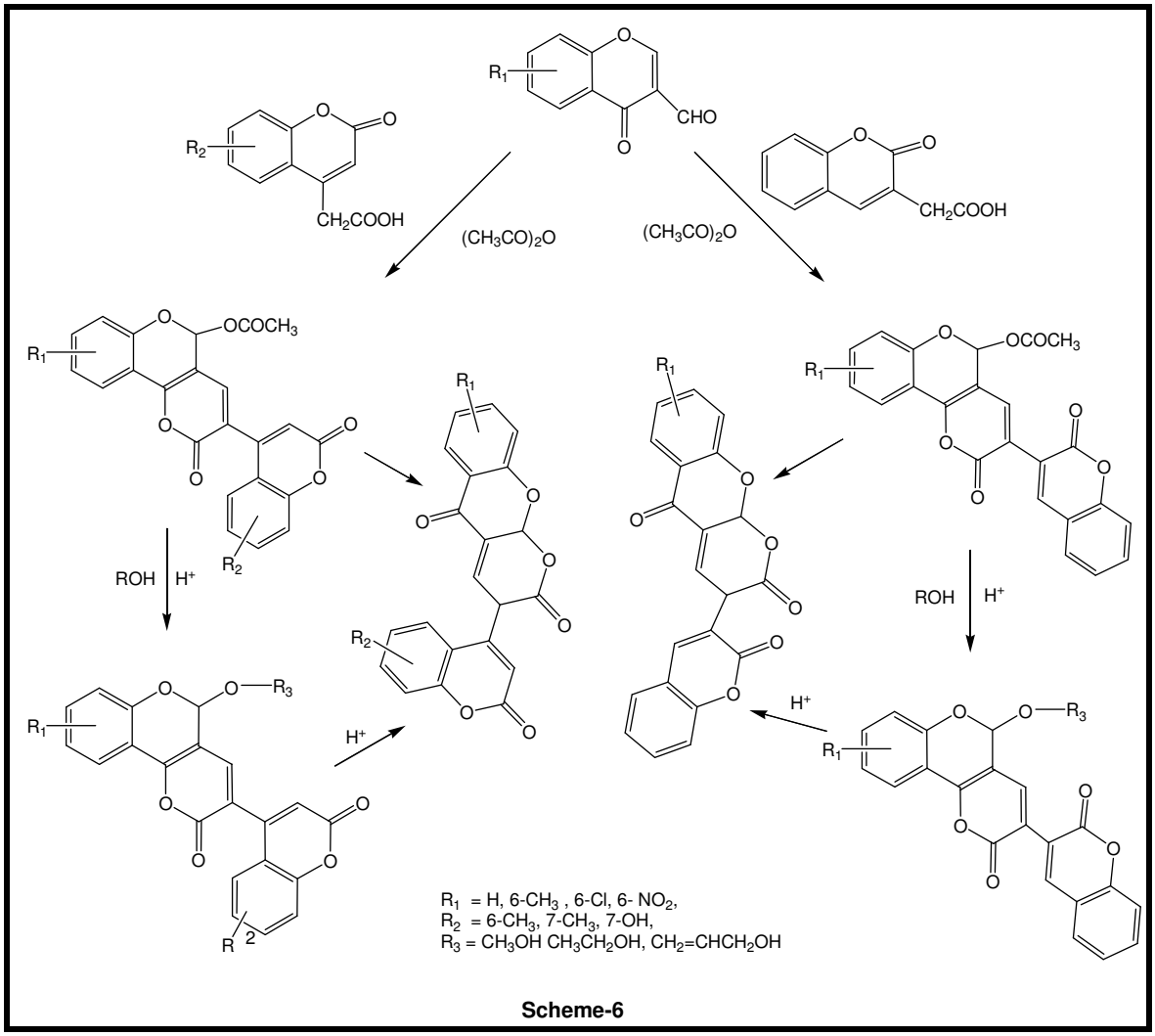


Figure-23

3-Formylchromones were reacted with 3-coumarin- or 4-coumarin- acetic acids in acetic anhydride at reflux temperature and gave 3-(2-oxo-2*H*-chromen-4-yl)-2-oxo-2*H,*5*H*-pyrano[3,2-*c*]chromen-5-yl acetate and 3-(2-oxo-2*H*-chromen-3-yl)-2-oxo-2*H,*5*H*-pyrano[3,2-*c*]chromen-5-yl acetate. The reaction were carried out in acetic anhydride in the presence of potasium acetate as a catalyst under microwave irradiation conditions.

Above products were obtained after ten minutes irradiation in a microwave oven at 400W. The subsequent nucleophile reaction (alcoholysis) of above compounds producted ethers, *i.e.* alkyloxy-3-(-2-oxo-2*H*-chromen-4-yl)-5*H*-pyrano[3,2-*c*] chromen-2-ones) and alkyloxy-3-(2-oxo-2*H*-chromén-3-yl)-5*H*-pyrano[3,2-*c*]chromen-2-ones), in the presence of catalytic amount of *p*-toluenesolfonic acid in various alcohols at 60-100ºC. It was found that the synthesized compounds shown in scheme-6 underwent a rearrengment by treatment with acetic acid at 60-80ºC without another part of reaction medium and yielded compounds 3-(2-oxo-2*H*-chromen-4-yl)-3,10*a*-dihydro-pyrano[2,3-*b*] chromene-2,5-diones and 3-(2-oxo-2*H*-chromen-3-yl)-3,10*a*-dihydro-pyrano[2,3-*b*] chromene-2,5-diones.[94]



Scheme-6

Vida and co-workers[95] did the selective reduction of 3,4-dihydrocoumarin-4-acetic acid which leads to 2-*o*-hydroxyphenyl-4-hydroxybutane-I-carboxylic acid lactone. Lactonization of the intermediate 4-hydroxycarboxylic acid to form the above & carboxylic acid lactone is preferred over the formation of the phenolic lactone 3,4-dihydro-4-(α-hydroxyethyl)coumarin. Electrophilic reagents convert α-hydroxyphenyl-4-hydroxybutane-l-carboxylic acid lactone into 4-substituted 3,4-dihydrocoumarins. The phenolic lactone 3,4-dihydro-4-(*p*-bromoethyl)coumarin, reacts with primary or secondary amine to form 4-substituted chroman derivatives.

3, 4-Dihydrocoumarin-4-acetic acid, upon treatment with diazomethane, was converted into the methyl ester which was brominated and dehydrobrominated to yield 4-carbomethoxymethylcoumarin.[96] Coumarin-4-acetic acids are vinyl analogs of malonic acid; when the methyl ester was hydrolyzed in boiling aqueous dioxane with hydrochloric acid, 4-methyl coumarin was obtained. Similarly, the latter compound was obtained from bromination, followed by dehydrobromination of coumarin-4-acetic acid.

Cleavage of the carboxylic acid lactone ring and the subsequent ring closure to form the dihydrocoumarin ring system can be affected with electrophilic reagents, *e.g.*, trifluoroacetic anhydride, thionylchloride in benzene,[97] and gaseous hydrobromic acid in chloroform[98] (Figure-24).

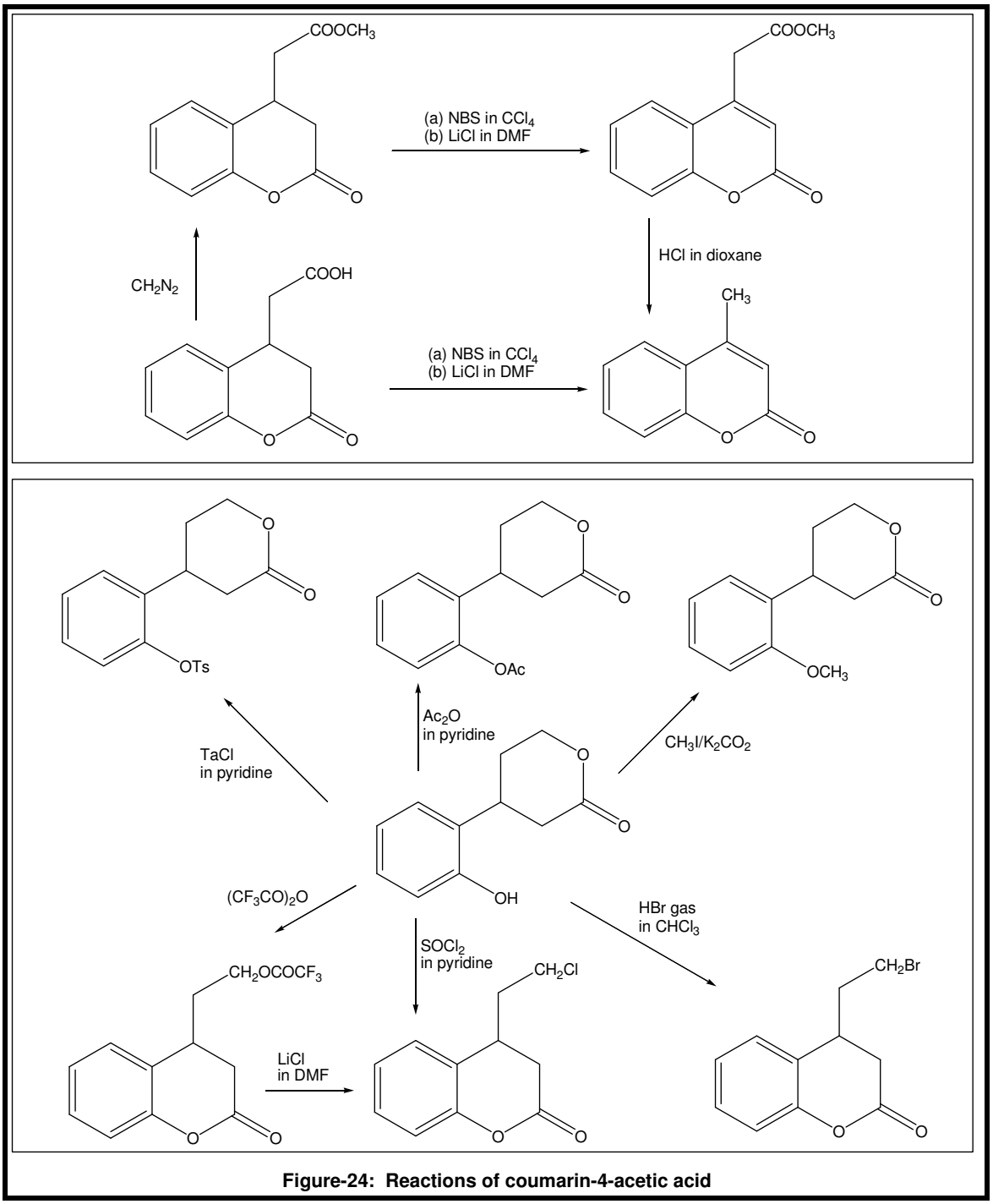


Figure-24: Reactions of coumarin-4-acetic acid

Zhu *et. al.*[99] synthesized various coumarin-4-acetic acids and their its basic esters as well as amides. The following compounds were synthesized and were used in the solution-based microplate assays (Figure-25).

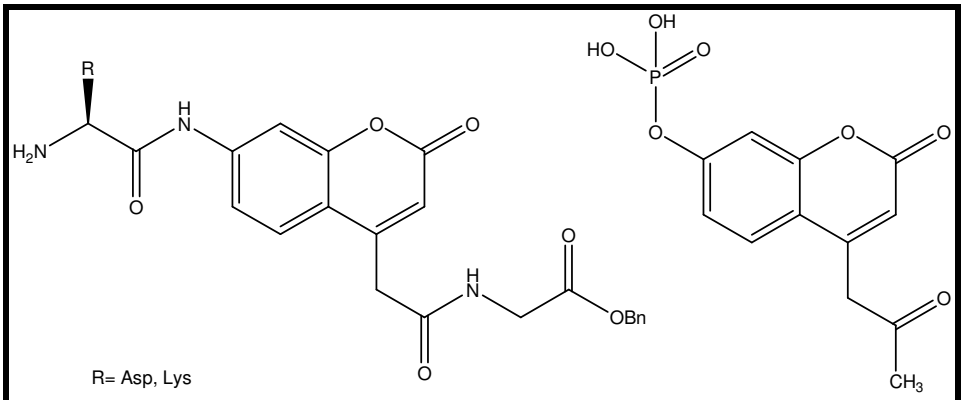
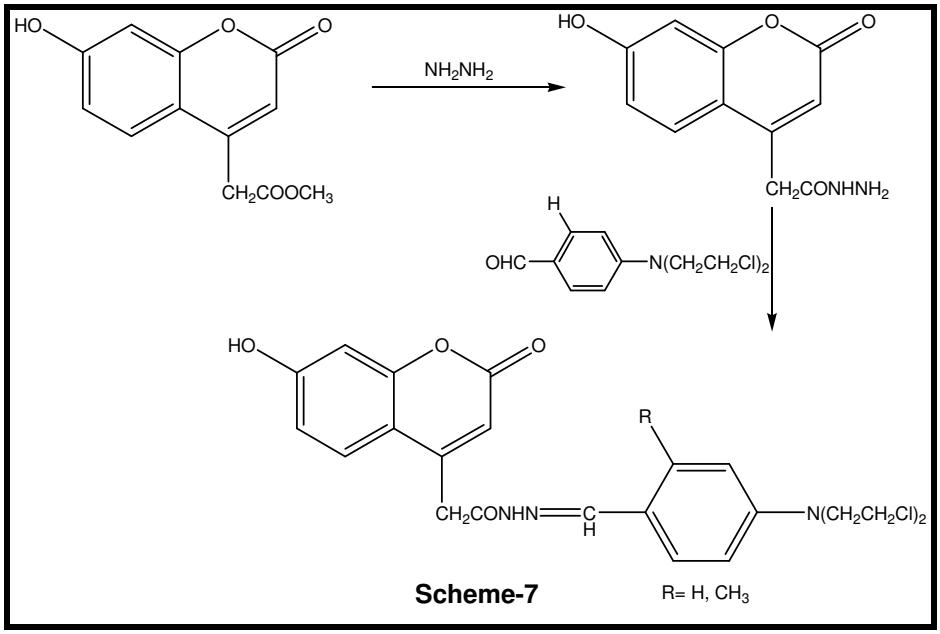


Figure-25

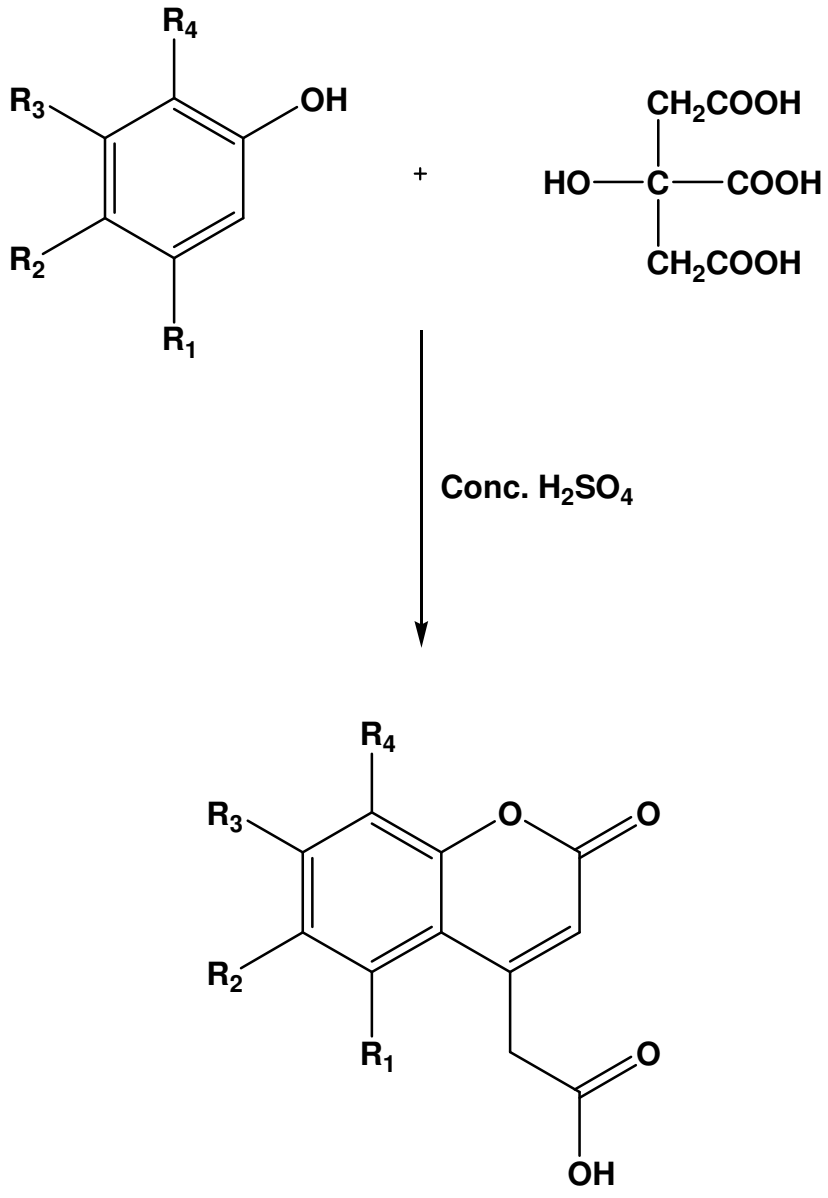
Ahmed Mustafa and co-workers[100] synthesized some new styryl derivatives by condensing 4-coumarin acetic acid derivatives with the appropriate aldehyde in the presence of pyridine and a few drops of piperidine[101].

Elderfield *et. al.*[102] reported the synthesis of nitrogen mustards derived from 7-hydroxycoumarins from 7-hydroxycoumarin-4-acetic acid (Scheme-7).



Scheme-7

1.6. REACTION SCHEME



Where, R_1, R_2, R_3, R_4= OH, CH_3, H, C_6H_5, NH_2.

Synthesis of coumarin-4-acetic acid

1.7. Experimental

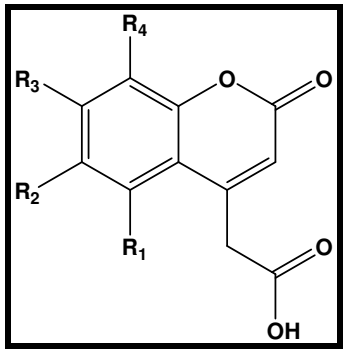
General method of preparation of coumarin-4-acetic acid

A mixture of citric acid monohydrate (0.1 M) and 28 ml of concentrated sulphuric acid was stirred at room temperature for sixty minutes, and then slowly heated to 70^{o}C. After half an hour at this temperature, with stirring throughout, the evolution of carbon monoxide had slackened and the clear yellow coloured solution was rapidly cooled to 0^{o}C. To this stirred solution, was added phenol (0.08 M) and 11.2 ml of concentrated sulphuric acid, each in three equal portions, at a rate that the temperature does not exceed 10^{o}C. The resulting was stored at 0^{o}C for sixteen hours, poured into ice and the resulting crystalline precipitates were filtered off and washed thoroughly with water. It was then treated with 10% sodium bicarbonate solution and then filtered. The filterate, on acidification gave coumarin-4-acetic acids. The bicarbonate insoluble portion is 4-methyl coumarin. The purity of the compound is checked by TLC. (Acetone: Benzene :: 5:5).

Several substituted coumarin 4-acetic acids were similarly prepared by using different phenols.[49]

The physical data and Rf value of various coumarin 4-acetic acids were recorded in the Table No. 3.

1.8. Table 3: Physical data of coumarin-4-acetic acids



Codes	Substitution				Moleular formula	Molecular weight	Melting point (^oC)	Rf value	Colour	% Yield
	R_1	R_2	R_3	R_4						
JCT-10	H	H	OH	H	$C_{11}H_8O_5$	220.18	202-204[a]	0.43	White	68
JCT-11	H	H	-Benzo-		$C_{15}H_{10}O_4$	254.24	210-212	0.46	Brown	59
JCT-12	-Benzo-		H	H	$C_{15}H_{10}O_4$	254.24	208-210	0.55	Yellow	61
JCT-13	H	H	H	CH_3	$C_{12}H_{10}O_4$	218.21	202-204	0.41	White	54
JCT-14	H	H	CH_3	H	$C_{12}H_{10}O_4$	218.21	204-206	0.51	Off white	58

TLC solvent system: Acetone: Benzene = 5:5

Ref.: (a= Reported m. p.: 204-206^{o}C) (1) Laskowski, S. C.; Clinton, R. O. Coumarins. II. Derivatives of Coumarin-3- and -4-Acetic Acids, *J. Am. Chem. Soc*. **1950**, 72, 3987-3991. (2) Dey, B. B. *J. Organic Chem.* **1915**, 107, 1606-1651.

1.8. Table 3 (contd.): Physical data of coumarin-4-acetic acids

Codes	Substitution				Moleular formula	Molecular weight	Melting point (^oC)	Rf value	Colour	% Yield
	R_1	R_2	R_3	R_4						
JCT-15	H	CH_3	H	H	$C_{12}H_{10}O_4$	218.21	184-185	0.49	Pale white	63
JCT-16	H	H	CH_3	CH_3	$C_{13}H_{12}O_4$	232.23	205-206	0.50	White	69
JCT-17	H	CH_3	H	CH_3	$C_{13}H_{12}O_4$	232.23	206-208	0.47	Off white	58
JCT-18	H	CH_3	CH_3	H	$C_{13}H_{12}O_4$	232.23	168-170	0.53	Pale yellow	53
JCT-19	CH_3	H	CH_3	H	$C_{13}H_{12}O_4$	232.23	202-206	0.54	White	52
JCT-20	H	C_6H_5	H	H	$C_{17}H_{12}O_4$	280.27	184-185	0.48	Off white	36
JCT-21	OH	H	OH	H	$C_{11}H_8O_6$	236.18	166-168	0.52	Brown	67
JCT-22	H	H	NH_2	H	$C_{11}H_9NO_4$	219.19	172-176	0.55	Brown	46
JCT-23	H	H	H	naphtyl	$C_{21}H_{14}O_4$	330.09	156-158	0.47	Off white	22

1.9. Spectral study

Infra Red spectra

Infra Red spectra of 2-(2-oxo-2*H*-chromen-4-yl)acetic acids were taken on SHIMADZU 8400 FT-IR-435 Spectrometer using KBr Pellet method. The characteristic carbonyl group in coumarin moiety is observed at 1710-1680 cm^{-1}. The carboxylic acid group in 2-(2-oxo-2*H*-chromen-4-yl) acetic acids was observed between the values 1794-1844 cm^{-1}. The coumarin moiety showed the ring skeleton vibrations at 1600-1645, 1550-1590, 1550-1520, 1470-1495 cm^{-1}. The methylene group was observed between the values 1396-1458 cm^{-1}. The ether (C-O-C) was observed at 1275-1235 cm^{-1} and 1085-1025 cm^{-1}. Mono, *ortho* as well as *meta* substitution at C_6, C_7 as well as C_8 of coumarin ring showed the absorbance frequency between 830-890 cm^{-1}, 760-780 cm^{-1}, 720-760 cm^{-1}.

^{1}H NMR spectra

^{1}H NMR spectra of 2-(2-oxo-2*H*-chromen-4-yl)acetic acids were recorded on Bruker AC 400 MHz FT-NMR Spectrometer using TMS (Tetramethyl Silane) as an internal standard and DMSO-d_6 as a solvent. In the NMR spectra of 2-(2-oxo-2*H*-chromen-4-yl)acetic acid, various proton values like methylene ($-CH_2$), methyl ($-CH_3$), aromatic protons (Ar-H) were observed. The values for methyl ($-CH_3$) protons are seen between 2.3-2.6 δ ppm and for methylene ($-CH_2$) protons between 3.5-4 δ ppm. The aromatic protons (Ar-H) shows doublets or multiplets between 6.4-7.8 δ ppm. The carboxylic proton (-COOH) in coumarin 4-acetic acid in one of the spectra (JCT-24) was observed very broad at 10 δ ppm but the broad peak in all other compounds was not observed in the ^{1}H NMR spectra.

^{13}C NMR spectra

^{13}C NMR spectra were recorded on Bruker AC 400 MHz instrument using DMSO as the solvent with TMS (Tetramethyl Silane) as respective internal standard. As the carboxylic acid group in most of substituted coumarin-4-acetic acid is not observed in ^{1}H NMR spectra, ^{13}C NMR spectra of the coumarin-4-acetic acids clearly shows the presence of carboxylic acid group from 170-170 δppm.

Mass spectra

The mass spectrum of compounds was recorded by GCMS-QP2010 spectrometer (EI method). The mass spectrum of compounds were obtained by positive chemical ionization mass spectrometry. The molecular ion peak and the base peak in all compounds were clearly obtained in mass spectram study. The molecular ion peak (M^+) values are in good agreement with molecular formula of all the compounds synthesized. .

C, H, N analysis

Elemental analysis of the compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

1.10. Spectral characterization

2-(7-Hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-10)

IR (KBr) cm^{-1}: 3335 (-OH), 2960 (C-H str.), 1812 (-COOH), 1732 (-C-O-O, ester), 1712 (>C=O), 1612, 1548, 1507, 1436 (ring skeleton), 1449 (CH_2), 1273, 1057 (C-O-C), 887 (mono substd.).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 3.69 (s, 2H, -CH_2), 6.17 (s, 1H, OH), 6.7-7.4 (m, 4H, Ar-H), 9.95 (s, br, 1H, OH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 38.9 (CH_2), 102-125 (Ar), 160 (C=O), 170 (COOH).

Mass [m/e (%)], M. Wt.: 220, 202, 192, 176, 148, 131, 120, 91, 74, 65, 44.

C, H, N analysis, Calculated: C, 60.00; H, 3.66. **Found:** C, 60.23; H, 3.54.

2-(2-Oxo-2*H*-benzo[*h*]chromen-4-yl)acetic acid (JCT-11)

IR (KBr) cm^{-1}: 3362 (-OH), 2960 (C-H str.), 1834 (-COOH), 1746 (-C-O-O, ester), 1685 (>C=O), 1591, 1545, 1508, 1473 (ring skeleton), 1473 (CH_2), 1268, 1089 (C-O-C).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 3.86 (s, 2H, -CH_2), 8.52 (s, 1H, OH), 6.46 (s, 1H, CH), 6.49-7.8 (m, 7H, Ar-H).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 38.03 (CH_2), 114-135 (Ar), 159 (C=O), 170 (COOH).

Mass [m/e (%)], M. Wt.: 254, 210, 181, 152, 139, 115, 91, 76, 63, 44.

C, H, N analysis, Calculated: C, 70.86; H, 3.96. **Found:** C, 70.57; H, 3.89.

2-(3-Oxo-3*H*-benzo[*f*]chromen-1-yl)acetic acid (JCT-12)

IR (KBr) cm^{-1}: 3113 (-OH), 2935 (C-H str.), 1907 (-COOH), 1746 (-C-O-O, ester), 1701 (>C=O), 1624, 1537, 1477, 1452 (ring skeleton), 1477 (CH_2), 1278, 1145 (C-O-C).

Mass [m/e (%)], M. Wt.: 254, 210, 181, 152, 139, 115, 91, 76, 63, 44.

C, H, N analysis, Calculated: C, 70.86; H, 3.96. **Found:** C, 70.57; H, 3.58.

2-(8-Methyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-13)

IR (KBr) cm^{-1}: 3335 (-OH), 2956 (C-H str.), 1824 (-COOH), 1737 (-C-O-O, ester), 1745 (>C=O), 1615, 1517, 1476, 1438 (ring skeleton), 1413 (CH_2), 1369 (CH_3), 1255, 1016 (C-O-C), 883 (mono substd.).

Mass [m/e (%)], M. Wt.: 218, 200, 190, 174, 162, 145, 131, 115, 103, 91, 77, 65, 44.

C, H, N analysis, Calculated: C, 60.05; H, 4.62. **Found:** C, 65.98; H, 4.32.

2-(7-Methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-14)

IR (KBr) cm^{-1}: 3394 (-OH), 3043 (C-H str.), 1832(-COOH), 1745 (-C-O-O, ester), 1680 (>C=O), 1618, 1558, 1500, 1413 (ring skeleton), 1424 (CH_2), 1332 (CH_3), 1255, 1059 (C-O-C), 815 (mono substd.).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 2.45 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 6.33 (s, 1H, 0H), 7.1-7.5 (m, 3H, Ar-H).

400 MHz ^{13}C NMR (DMSO-d_6, δ ppm): 37.56 (CH_2), 115-125 (Ar), 142 (C=O), 170 (COOH).

Mass [m/e (%)], M. Wt.: 218, 174, 145, 131, 115, 103, 91, 77, 63, 44.

C, H, N analysis, Calculated: C, 60.05; H, 4.62. **Found:** C, 65.78; H, 4.57.

2-(6-Methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-15)

IR (KBr) cm^{-1}: 3514 (-OH), 2951 (C-H str.), 1811 (-COOH), 1720 (-C-O-O, ester), 1672 (>C=O), 1587, 1546, 1516, 1440 (ring skeleton), 1440 (CH_2), 1323 (CH_3), 1276, 1014 (C-O-C), 858 (mono substd.).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 2.41 (s, 3H, CH_3), 3.74 (s, 2H, -CH_2), 6.38 (s, 1H, CH), 6.7-7.4 (m, 3H, Ar-H).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 37.54 (CH_2), 116-151 (Ar), 160 (C=O), 170 (COOH).

Mass: [m/e (%)], M. Wt.: 218, 200, 190, 174, 162, 145, 131, 115, 103, 77, 65, 44.

C, H, N analysis, Calculated: C, 66.05; H, 4.62. **Found:** C, 65.76; H, 4.13.

2-(7,8-Dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-16)

IR (KBr) cm^{-1}: 3477 (-OH), 2939 (C-H str.), 1865 (-COOH), 1726 (-C-O-O, ester), 1687 (>C=O), 1604, 1558, 1510, 1431 (ring skeleton), 1431 (CH_2), 1342 (CH_3), 1249, 1093 (C-O-C), 764 (ortho substd.).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 2.36 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.74 (s, 2H, -CH_2), 6.32 (s, 1H, CH), 7.11 (d, 1H, Ar-H, *J*=8.12), 7.38 (d, 1H, Ar-H, *J*=8.16).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 37.7 (CH_2), 114-125 (Ar), 160 (C=O), 170 (COOH).

Mass: [m/e (%)], M. Wt.: 232, 204, 188, 173, 145, 128, 115, 103, 91, 77, 65, 44, 41.

C, H, N analysis, Calculated: C, 67.23; H, 5.21. **Found:** C, 67.07; H, 4.79.

2-(6,8-Dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-17)

IR (KBr) cm^{-1}: 3500 (-OH), 2879 (C-H str.), 1834 (-COOH), 1718 (-C-O-O, ester), 1668 (>C=O), 1608, 1566, 1419 (ring skeleton), 1419 (CH_2), 1419 (CH_3), 1203, 1051 (C-O-C), 744 (meta substd.).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 2.37 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.74 (s, 2H, -CH_2), 6.37 (s, 1H, CH), 7.23 (d, 2H, Ar-H, *J*=10.52).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 37.65 (CH_2), 115-133 (Ar), 160 (C=O), 170 (COOH).

Mass: [m/e (%)], M. Wt.: 232, 214, 204, 188, 176, 159, 145, 128, 115, 103, 91, 77, 65, 44, 41.

C, H, N analysis, Calculated: C, 67.23; H, 5.21. **Found:** C, 67.14; H, 4.69.

2-(6,7-Dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-18)

IR (KBr) cm^{-1}: 3564 (-OH), 2934 (C-H str.), 1821 (-COOH), 1735 (-C-O-O, ester), 1723 (>C=O), 1612, 1586, 1557, 1459 (ring skeleton), 1454 (CH_2), 1265, 1042 (C-O-C), 754 (ortho substd.).

Mass: [m/e (%)], M. Wt.: 232, 214, 204, 188, 176, 159, 145, 128, 115, 103, 91, 77, 65, 44, 41.

C, H, N analysis, Calculated: C, 67.23; H, 5.21. **Found:** C, 67.08; H, 5.03.

2-(5,7-Dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-19)

IR (KBr) cm^{-1}: 3492 (-OH), 2945 (C-H str.), 1834 (-COOH), 1767 (-C-O-O, ester), 1723 (>C=O), 1601, 1561, 1503, 1452 (ring skeleton), 1457 (CH_2), 1379 (CH_3), 1268, 1046 (C-O-C), 734 (meta substd.).

Mass: [m/e (%)], M. Wt.: 232, 214, 204, 188, 176, 159, 145, 128, 115, 103, 91, 77, 65, 44, 41.

C, H, N analysis, Calculated: C, 67.23; H, 5.21. **Found:** C, 66.96; H, 5.16.

2-(2-Oxo-6-phenyl-2*H*-chromen-4-yl) acetic acid (JCT-20)

IR (KBr) cm^{-1}: 3534 (-OH), 2934 (C-H str.), 1814 (-COOH), 1756 (-C-O-O, ester), 1715 (>C=O), 1606, 1587, 1502, 1458 (ring skeleton), 1451 (CH_2), 1269, 1048 (C-O-C).

Mass: [m/e (%)], M. Wt.: 280, 256, 232, 214, 204, 188, 176, 159, 145, 128, 115, 103, 91, 72.

C, H, N analysis, Calculated: C, 72.85; H, 4.32. **Found:** C, 71.95; H, 3.97.

2-(5,7-Dihydroxy-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-21)

IR (KBr) cm^{-1}: 3519 (-OH), 2964 (C-H str.), 1811 (-COOH), 1722 (-C-O-O, ester), 1666 (>C=O), 1598, 1583, 1521, 1457 (ring skeleton), 1411 (CH_2), 1253, 1128 (C-O-C), 862 (meta substd.).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 2.94 (s, 2H, -CH_2), 5.19(s, 1H, 0H), 5.36 (s, 1H, 0H), 6.27 (d, 2H, Ar-H, *J*= 2.48), 9.8 (br. s, 2H, 2 x OH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 38.9 (CH_2), 102-125 (Ar), 160 (C=O), 170 (COOH).

Mass: [m/e (%)], M. Wt.: 284, 258, 230, 218, 202, 190, 162, 147, 134, 120, 105, 95, 77, 69, 44.

C, H, N analysis, Calculated: C, 55.94; H, 3.41. **Found:** C, 55.37; H, 3.13.

2-(7-Amino-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-22)

IR (KBr) cm^{-1}: 3535 (-OH), 3419 (N-H str.), 2954 (C-H str.), 1825 (-COOH), 1734 (-C-O-O, ester), 1715 (>C=O), 1613, 1584, 1524, 1448 (ring skeleton), 1437 (CH_2), 1267, 1058 (C-O-C), 789 (mono substd.).

Mass: [m/e (%)], M. Wt.: 219, 190, 162, 134, 120, 109, 80, 69, 44.

C, H, N analysis, Calculated: C, 60.27; H, 4.14; N, 6.39. **Found:** C, 60.04; H, 3.69; O, 28.99; N, 6.43.

2-(8-(Naphthalene-1-yl)-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-23)

IR (KBr) cm^{-1}: 3523 (-OH), 2942 (C-H str.), 1835 (-COOH), 1731 (-C-O-O, ester), 1724 (>C=O), 1596, 1557, 1508, 1468 (ring skeleton), 1433 (CH_2), 1275, 1064 (C-O-C), 753 (mono substd.).

Mass: [m/e (%)], M. Wt.: 330, 306, 280, 256, 232, 214, 204, 188, 176, 159, 145, 128, 115, 103, 91, 77, 65, 44, 41.

C, H, N analysis, Calculated: C, 76.35; H, 4.27. **Found:** C, 76.26; H, 3.77.

2-(2-Oxo-2*H*-chromen-4-yl) acetic acid (JCT-24)

IR (KBr) cm^{-1}: 2836 (C-H str.), 1823 (-COOH), 1726 (-C-O-O, ester), 1738 (>C=O), 1623, 1582, 1502, 1493 (ring skeleton), 1458 (CH_2), 1236 (C-O-C).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 3.97 (s, 2H, -CH_2), 6.47 (s, 1H, -CH), 6.80-7.66 (m, 4H, Ar-H), 10.01 (br. s, 1H, COOH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 39.50 (CH_2), 115.25-130.70 (Ar), 165.40 (C=O), 171.90 (COOH).

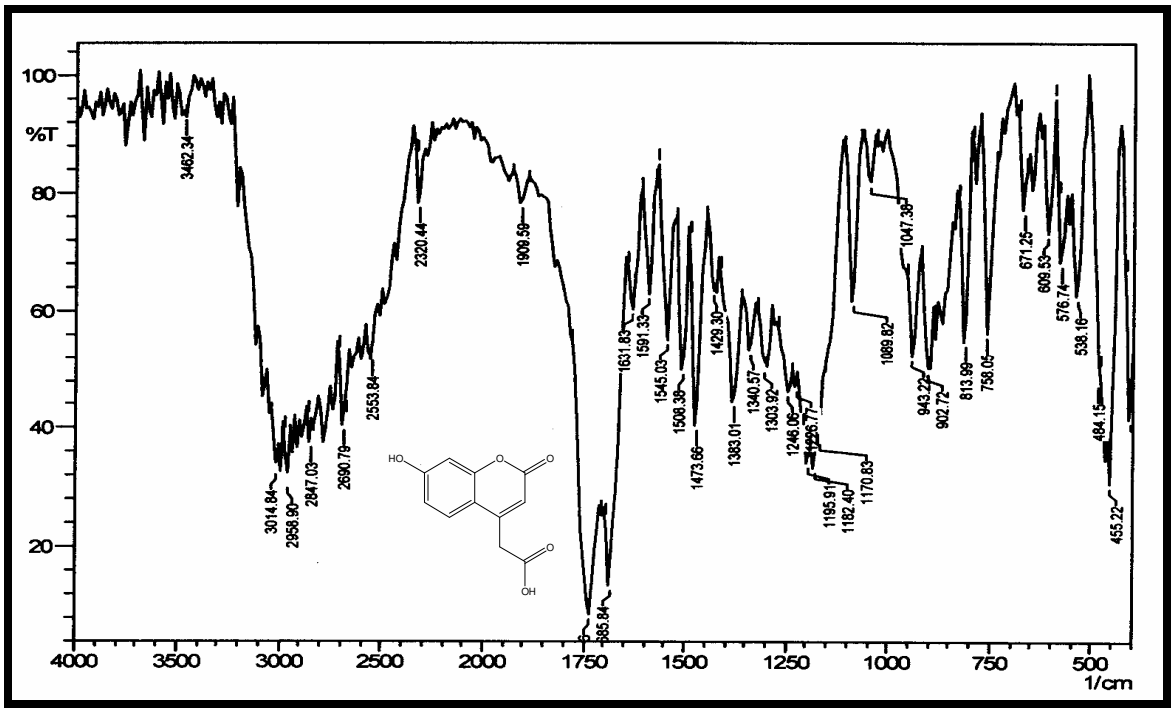
C, H, N analysis, Calculated: C, 64.71; H, 3.95. **Found:** C, 64.43; H, 3.56.

1.11. Conclusion

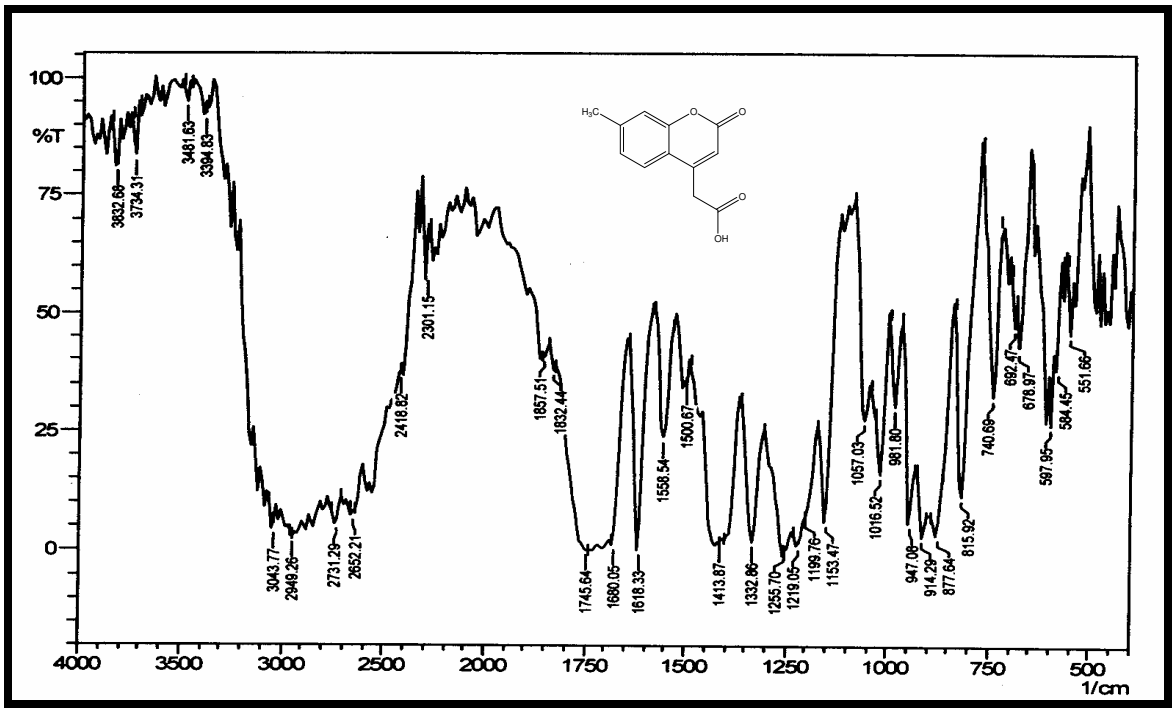
Total 15, 2-(2-oxo-2*H*-chromen-4-yl) acetic acids were synthesized in this chapter and in few cases process development was also undertaken to improve the yield, compared to the earlier reported methods. The compounds were characterized by IR, NMR, Mass spectral data and elemental analysis. All the synthesized compounds have been sent for anti-cancer activity and the results are awaited.

1.12. Spectra of (2-oxo-2*H*-chromen-4-yl)acetic acid derivatives

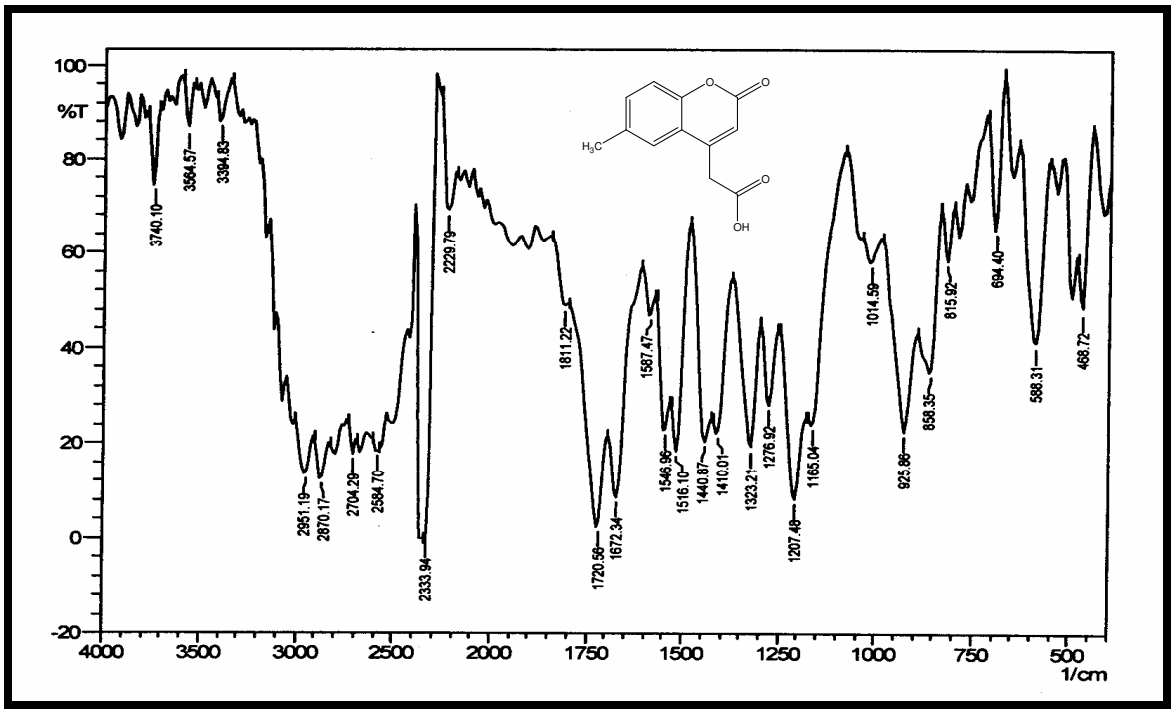
Infra Red spectrum of 2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-10)



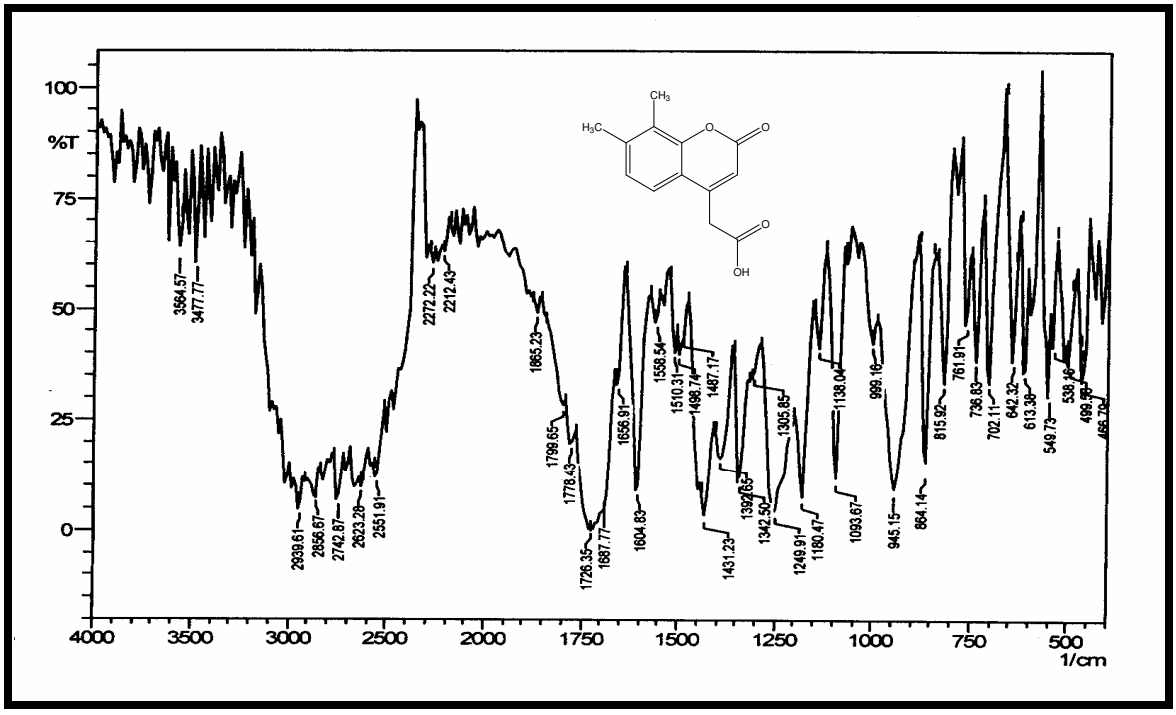
Infra Red spectrum of 2-(7-methyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-14)



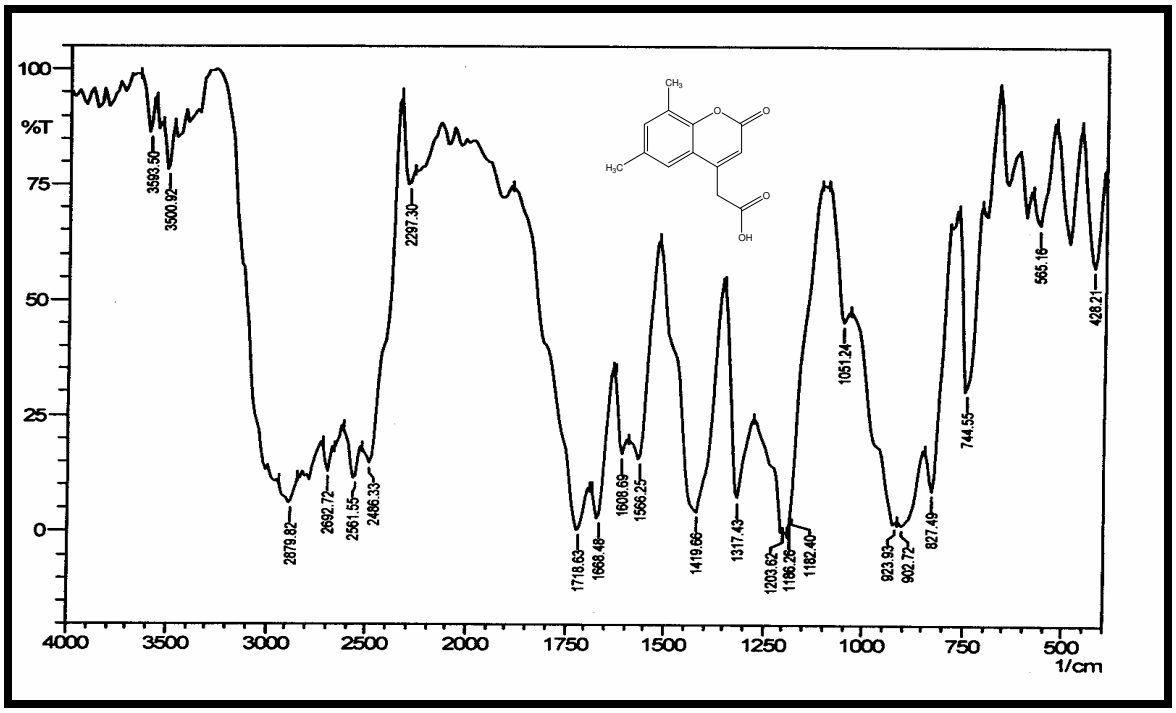
Infra Red spectrum of 2-(6-methyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-15)



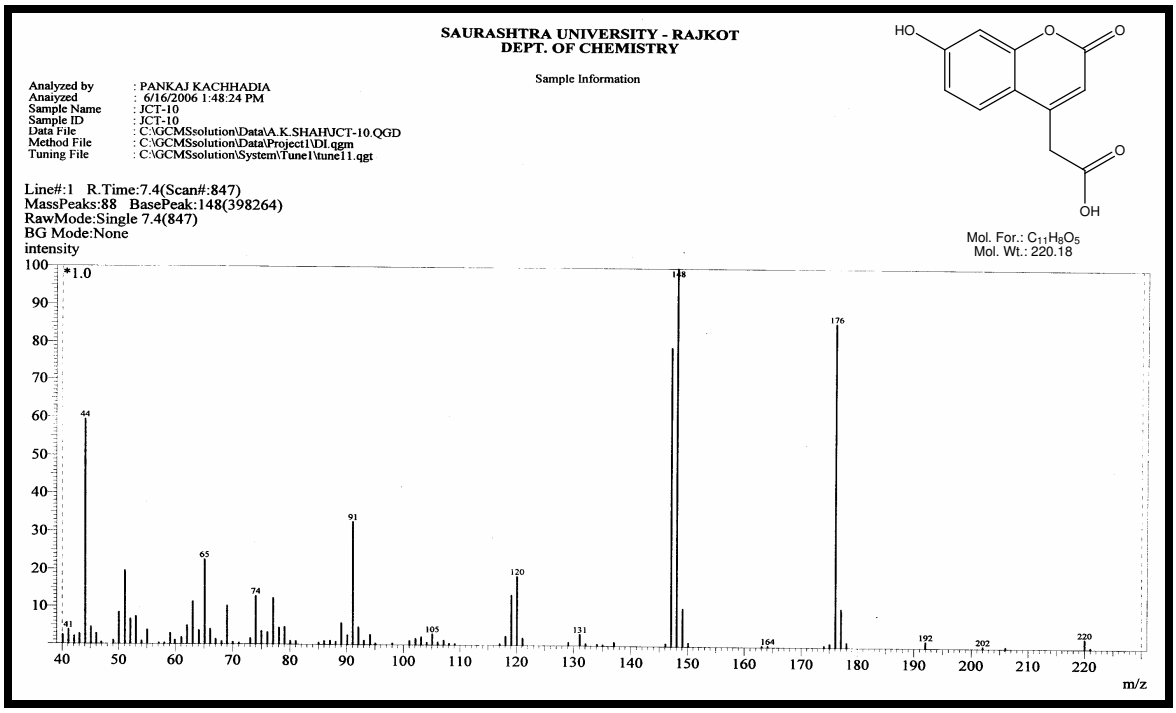
Infra Red spectrum of 2-(7,8-dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-16)



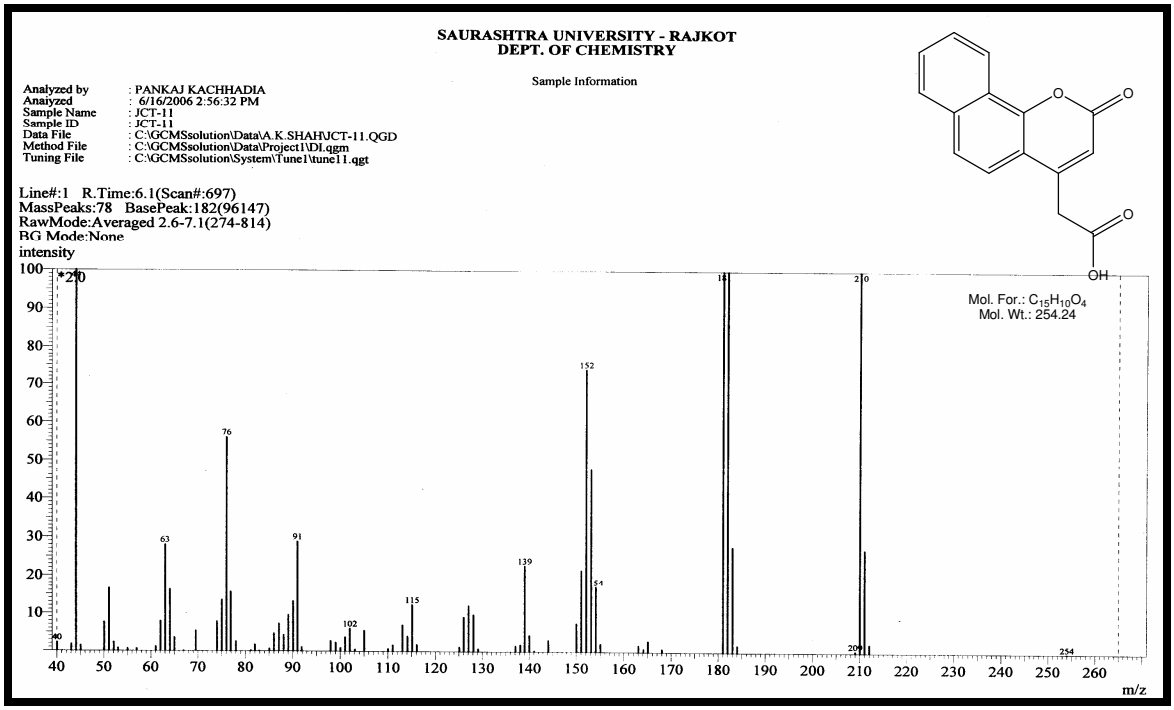
Infra Red spectrum of 2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-17)



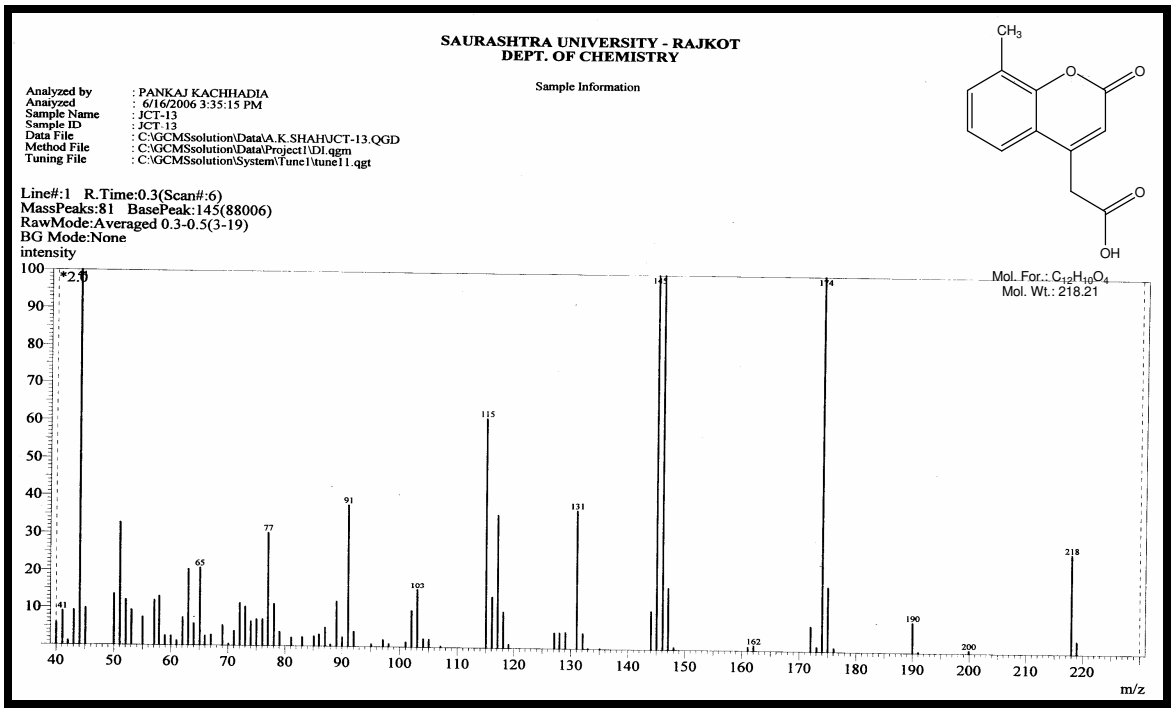
Mass spectrum of 2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-10)



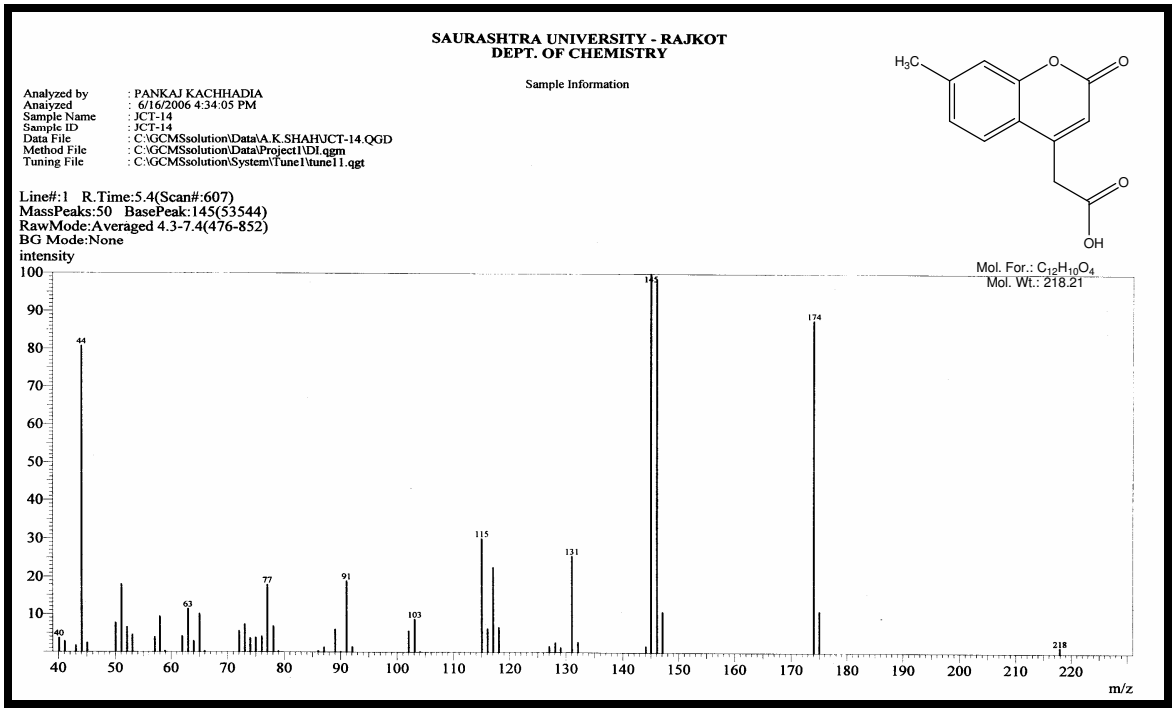
Mass spectrum of 2-(2-oxo-2*H*-benzo[*h*]chromen-4-yl) acetic acid (JCT-11)



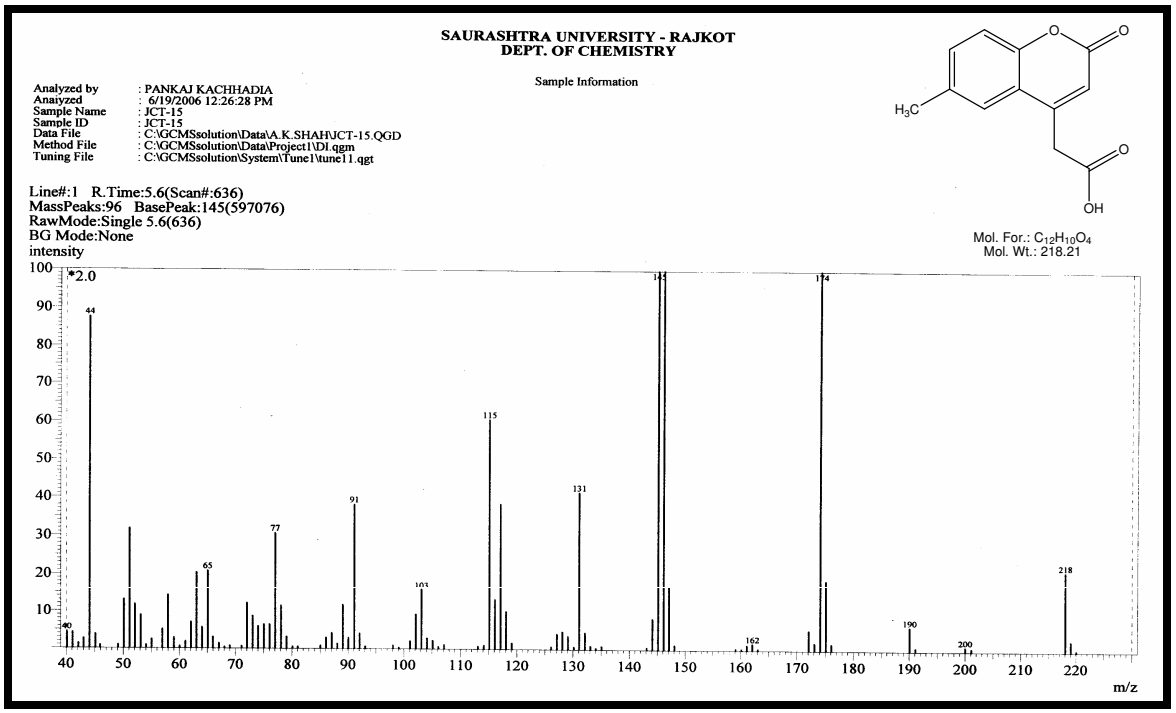
Mass spectrum of 2-(8-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-13)



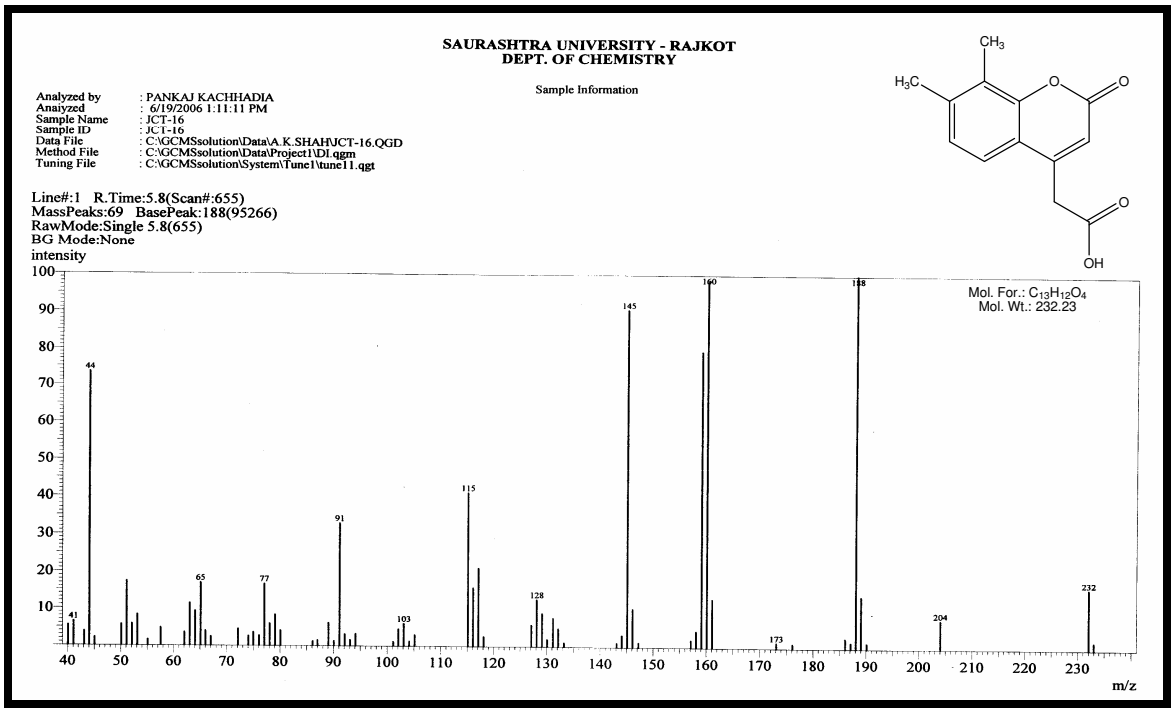
Mass spectrum of 2-(7-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-14)



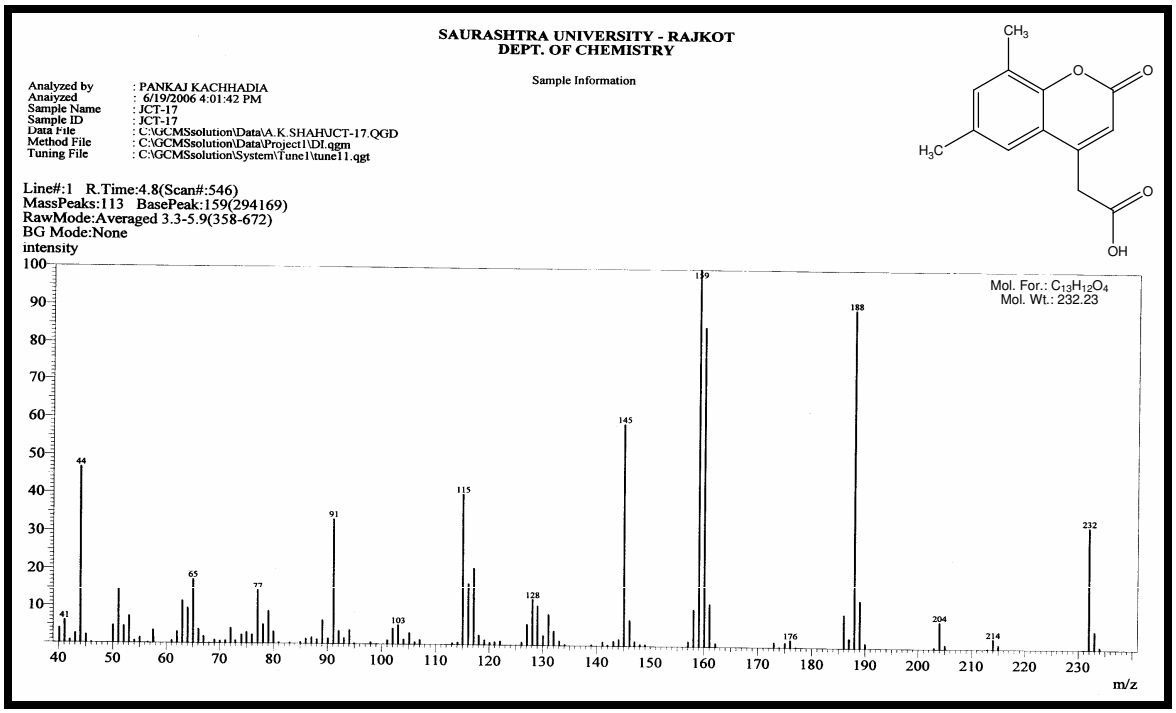
Mass spectrum of 2-(6-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid



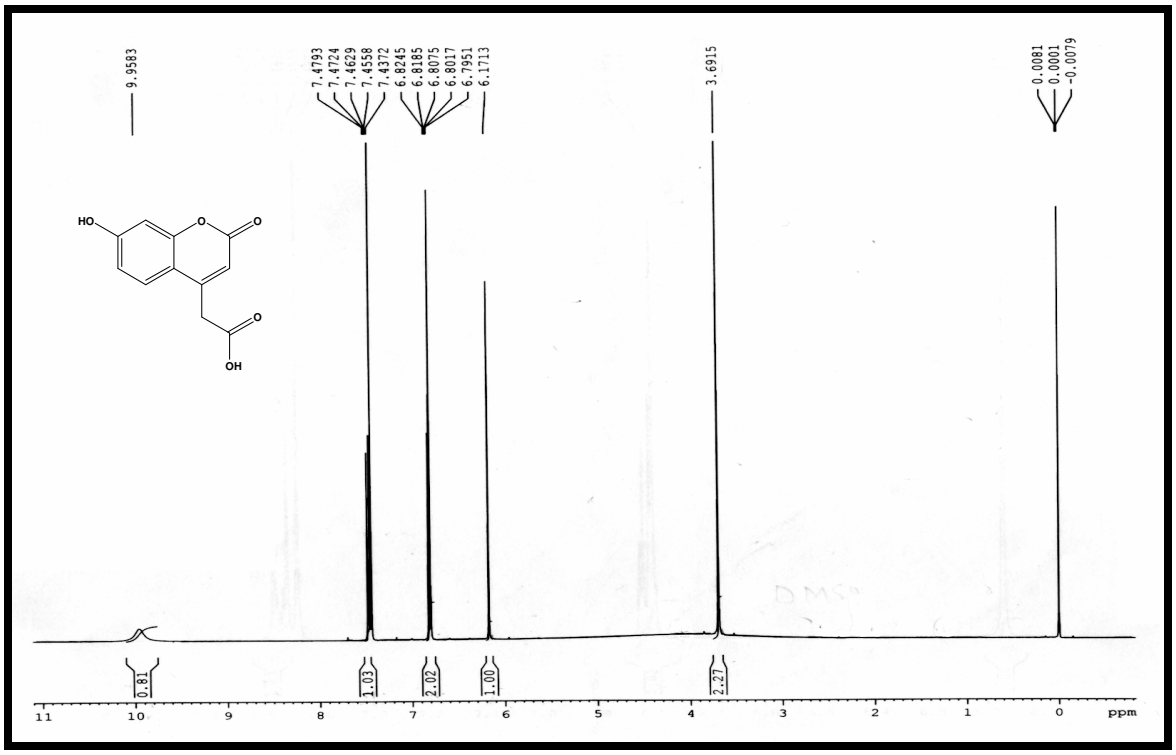
Mass spectrum of 2-(6-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-16)

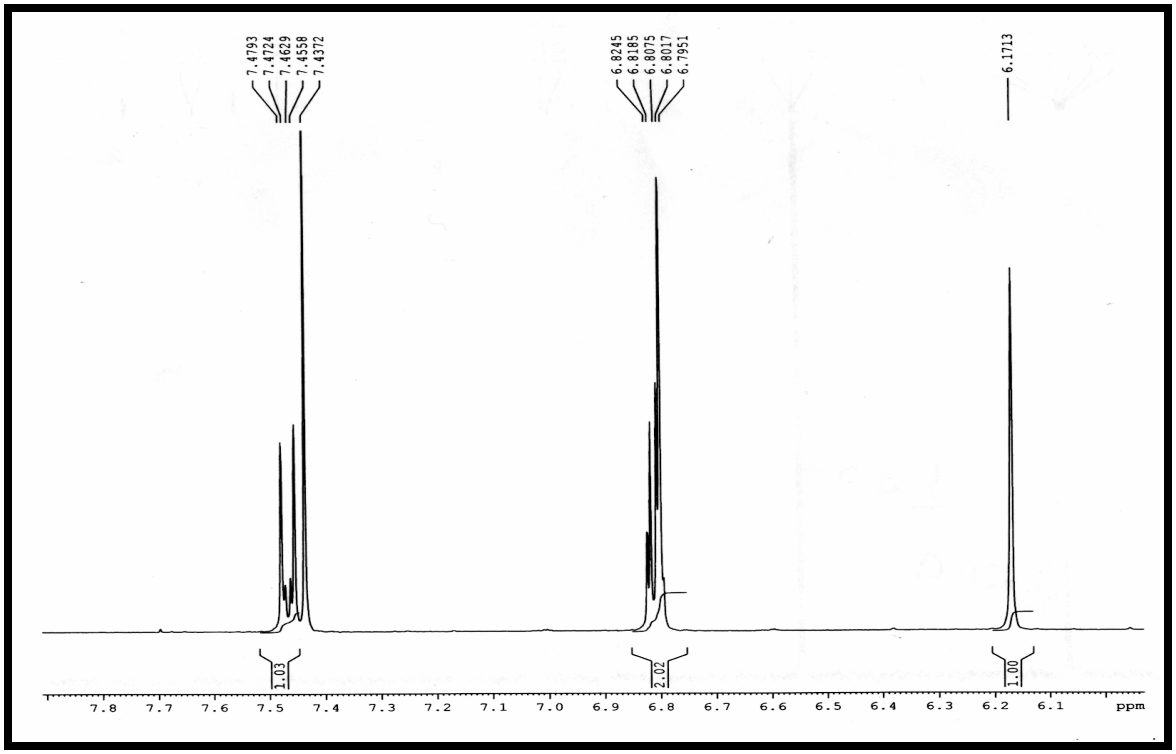


Mass spectrum of 2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-17)

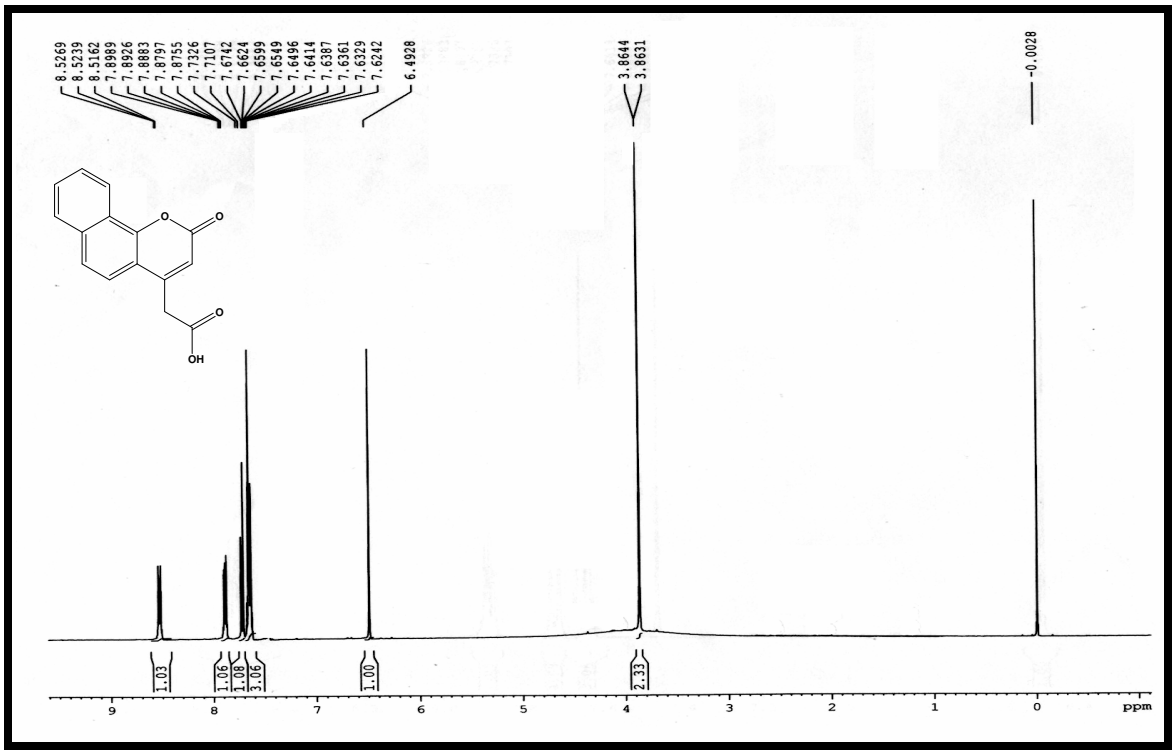


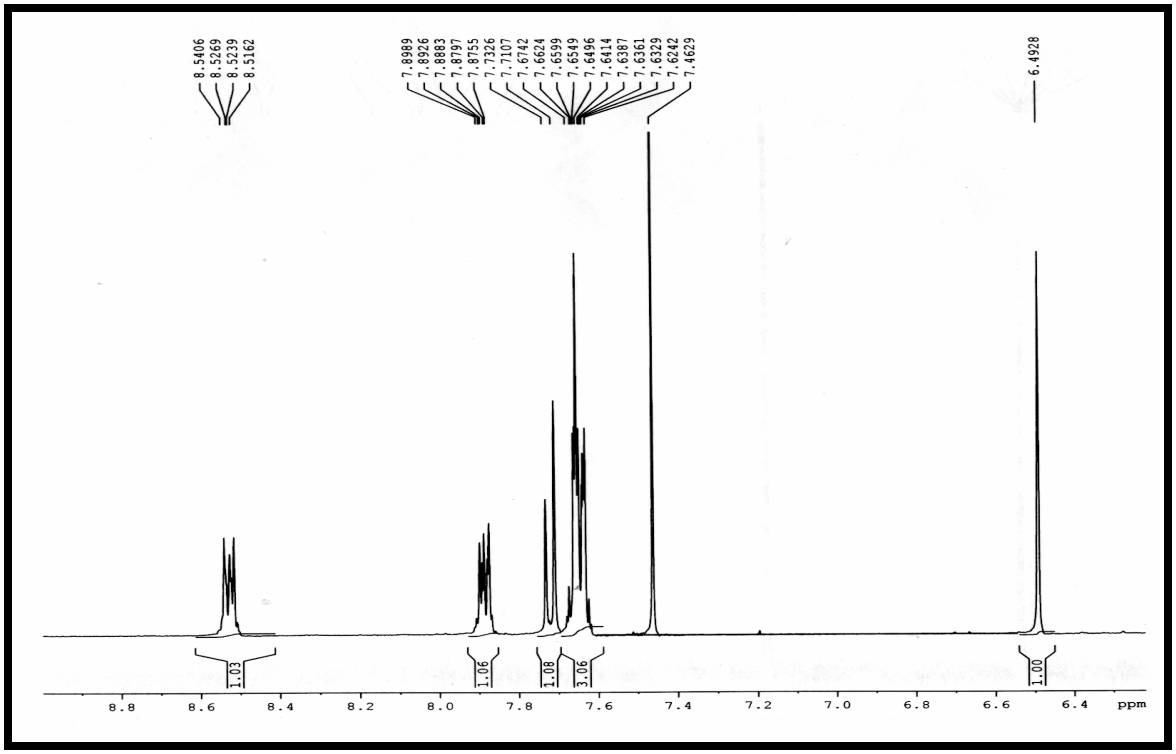
^{1}H NMR spectrum of 2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-10)



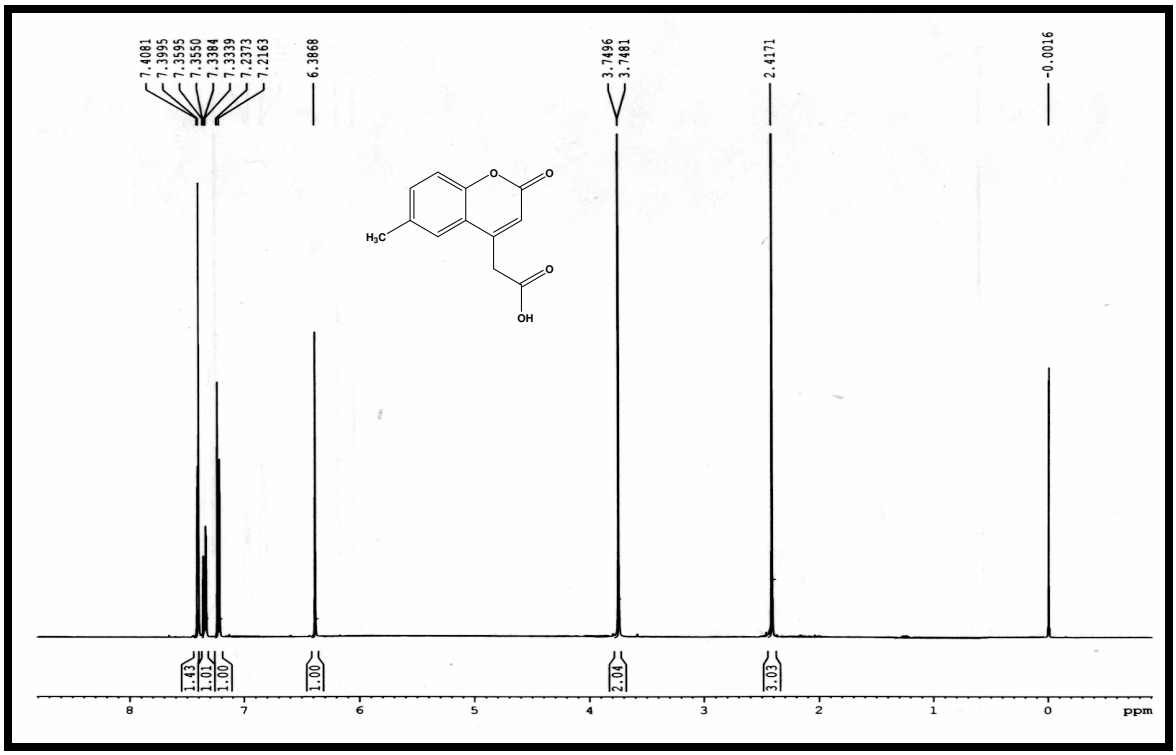


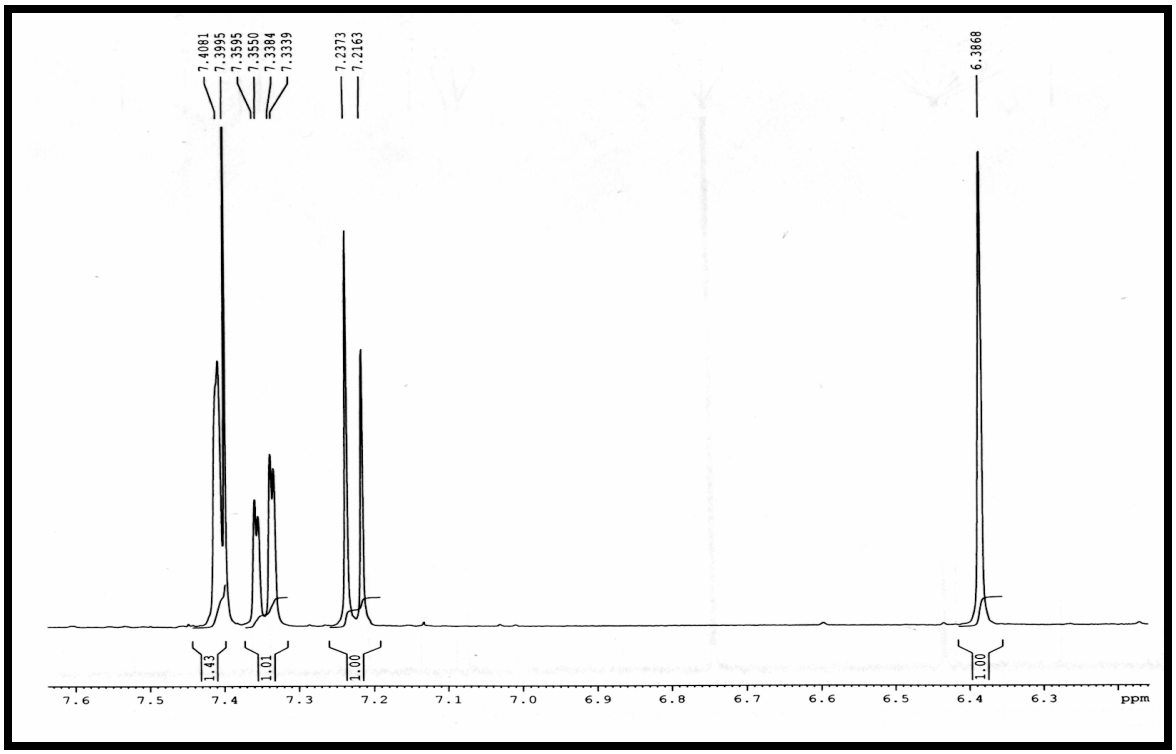
^{1}H NMR spectrum of 2-(2-oxo-2*H*-benzo[*h*]chromen-4-yl)acetic acid (JCT-11)



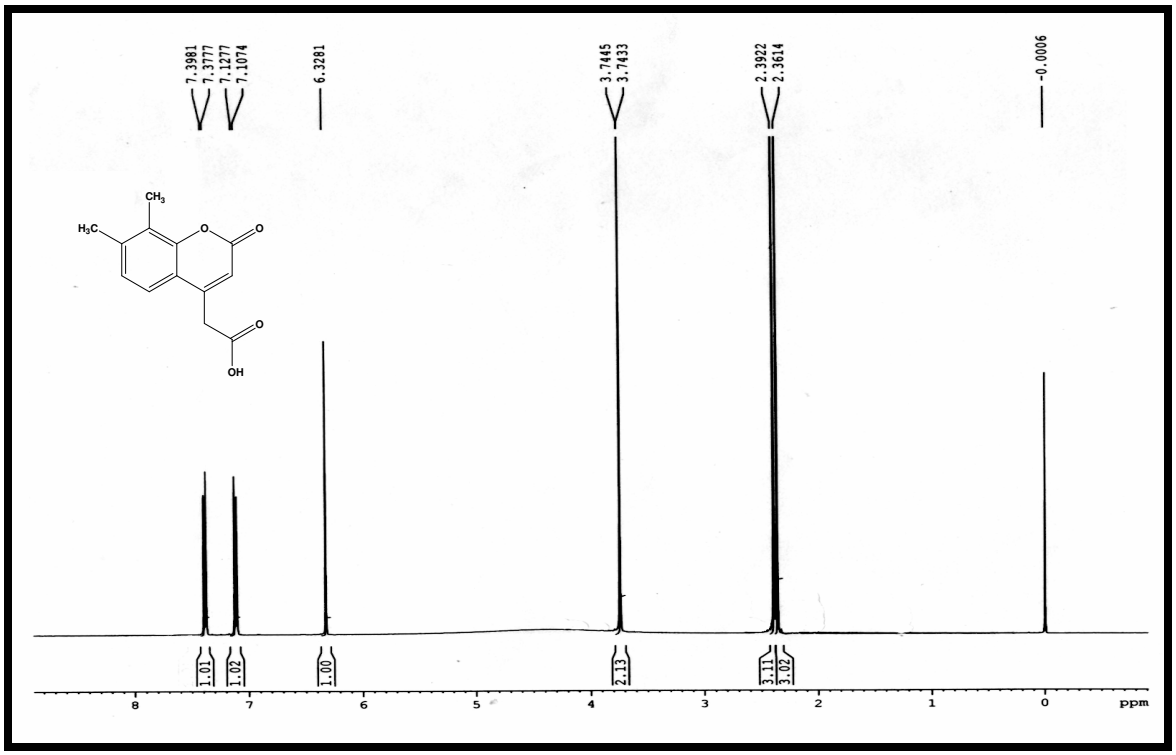


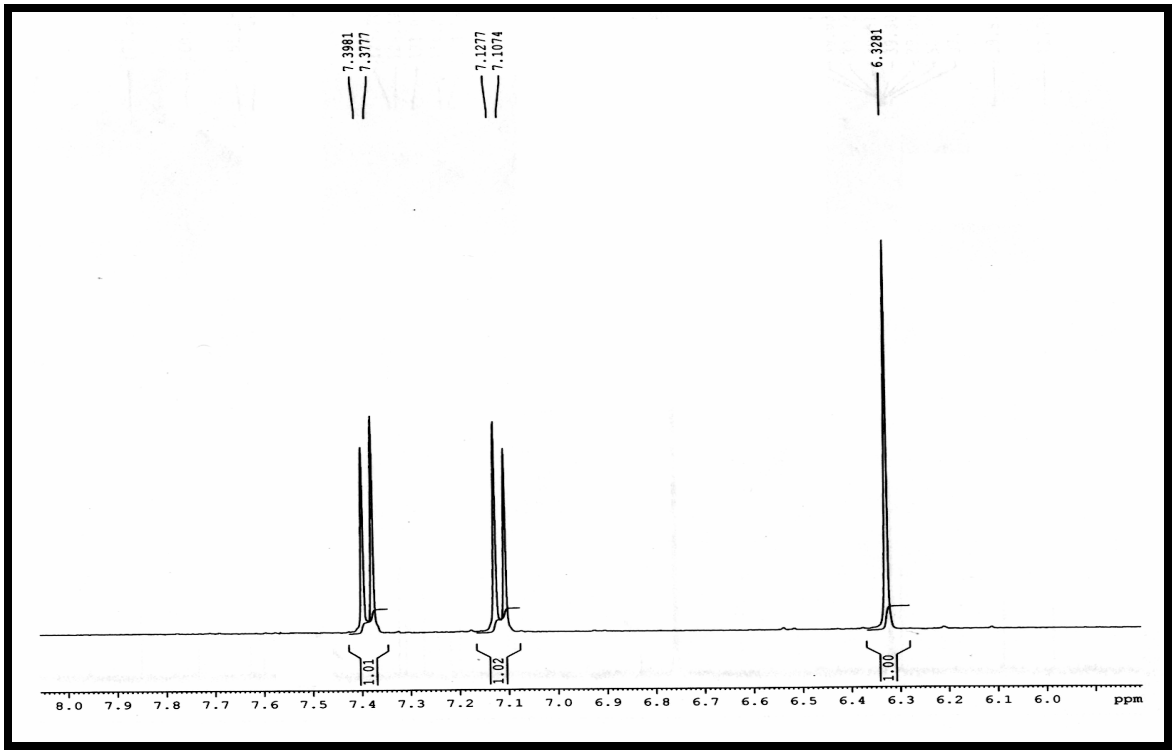
^{1}H NMR spectrum of 2-(6-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-15)



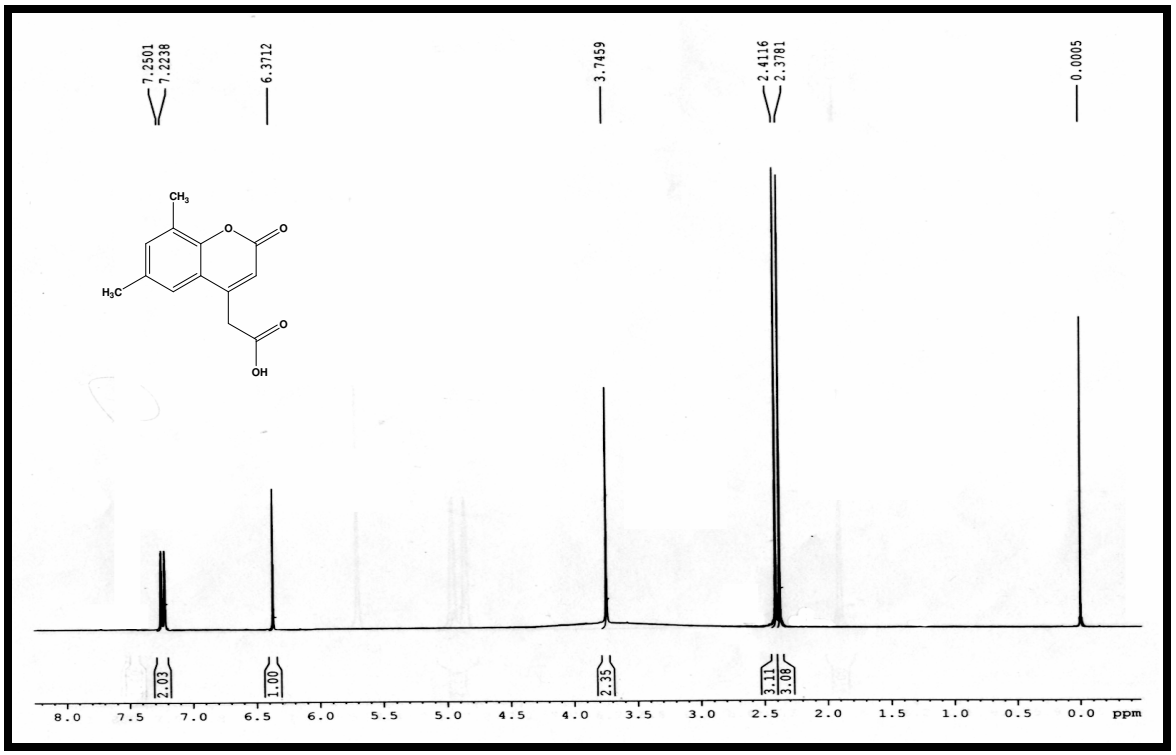


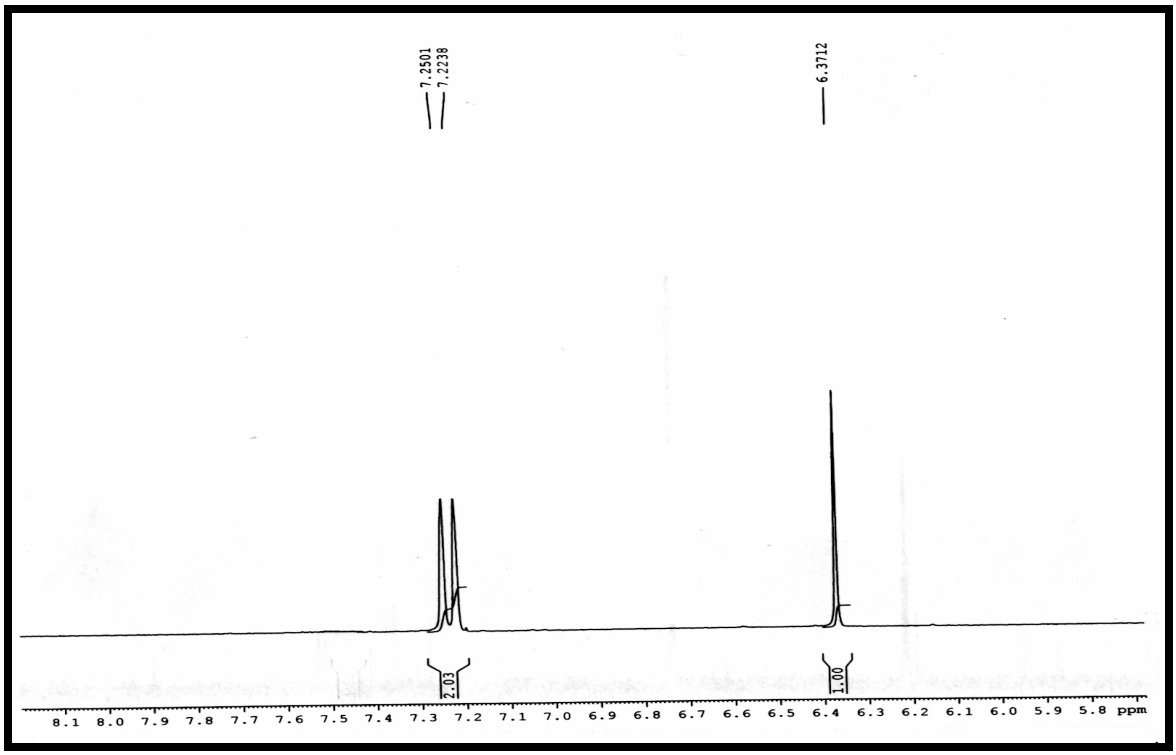
^{1}H NMR spectrum of 2-(7,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-16)



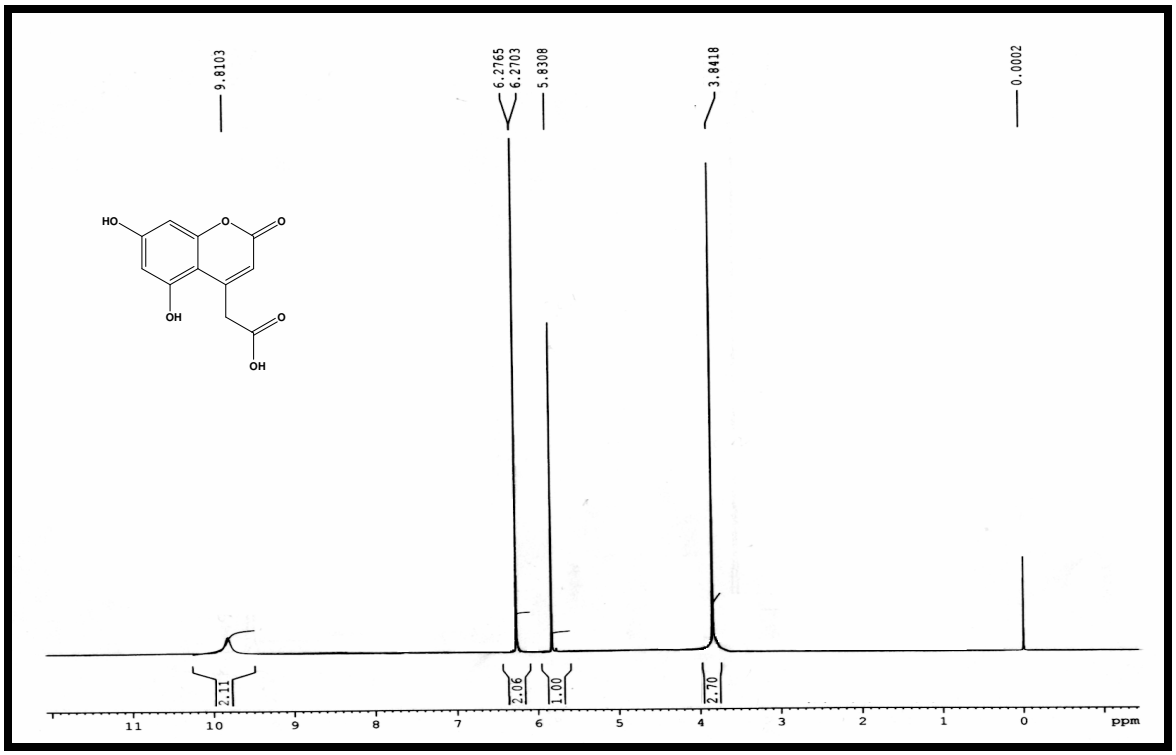


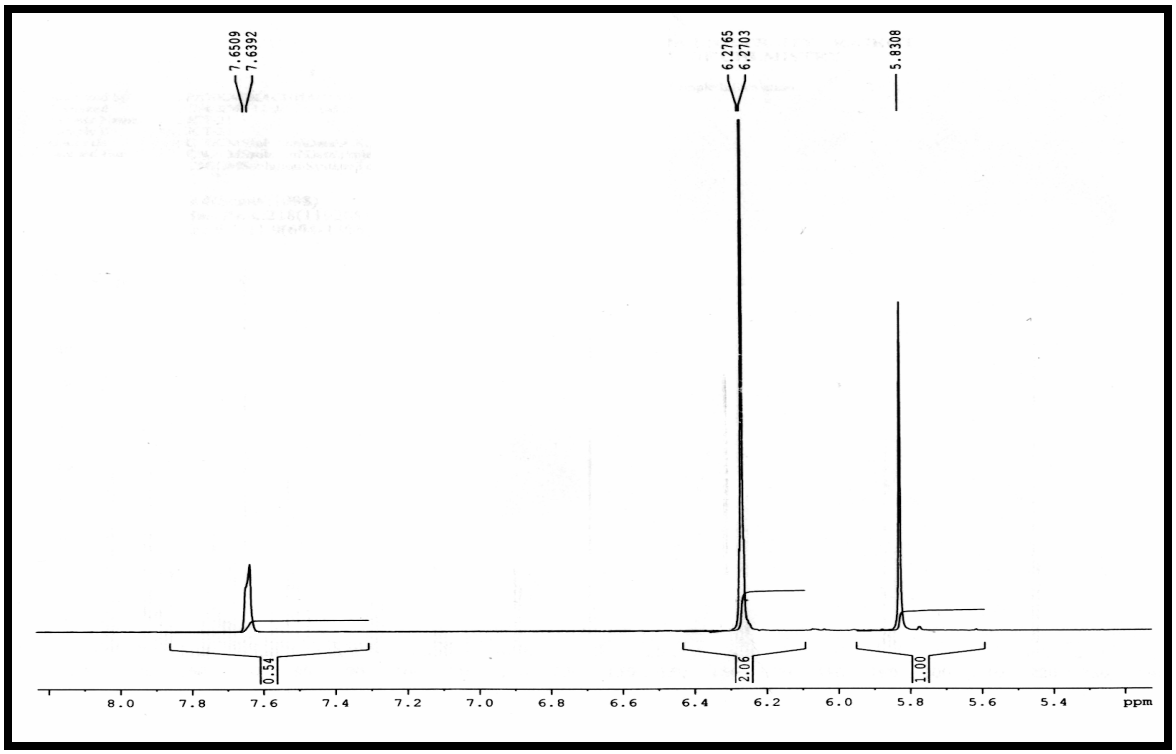
^{1}H NMR spectrum of 2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-17)



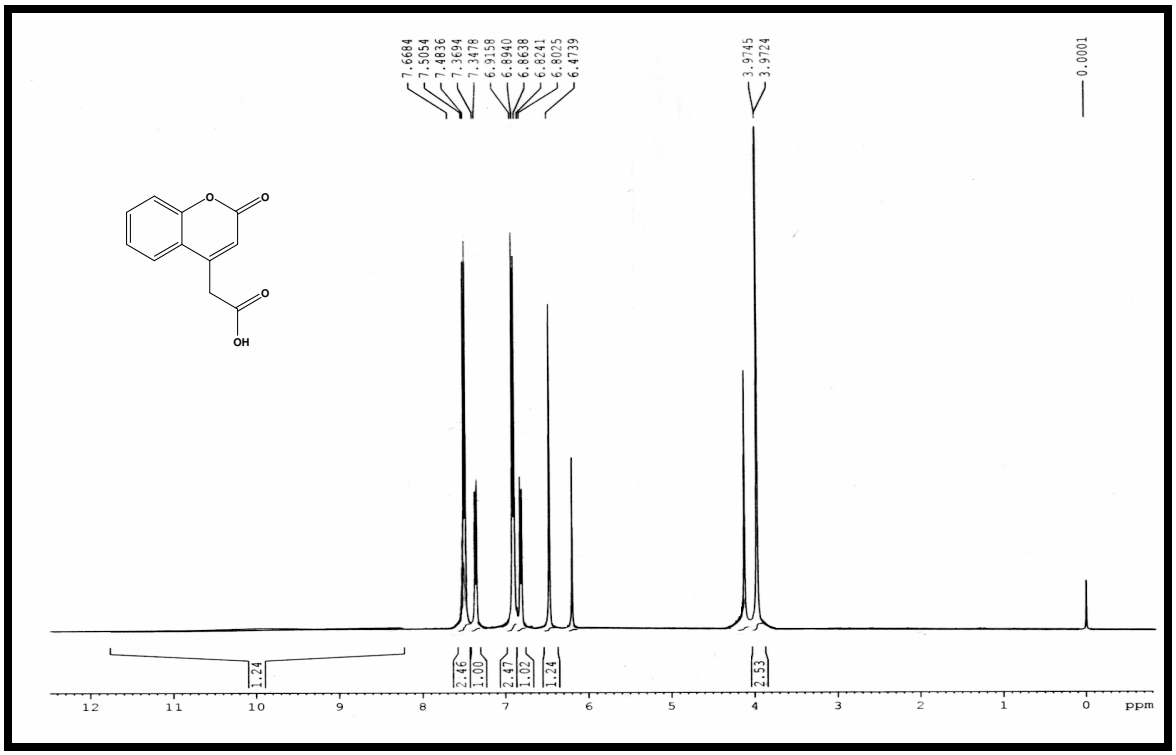


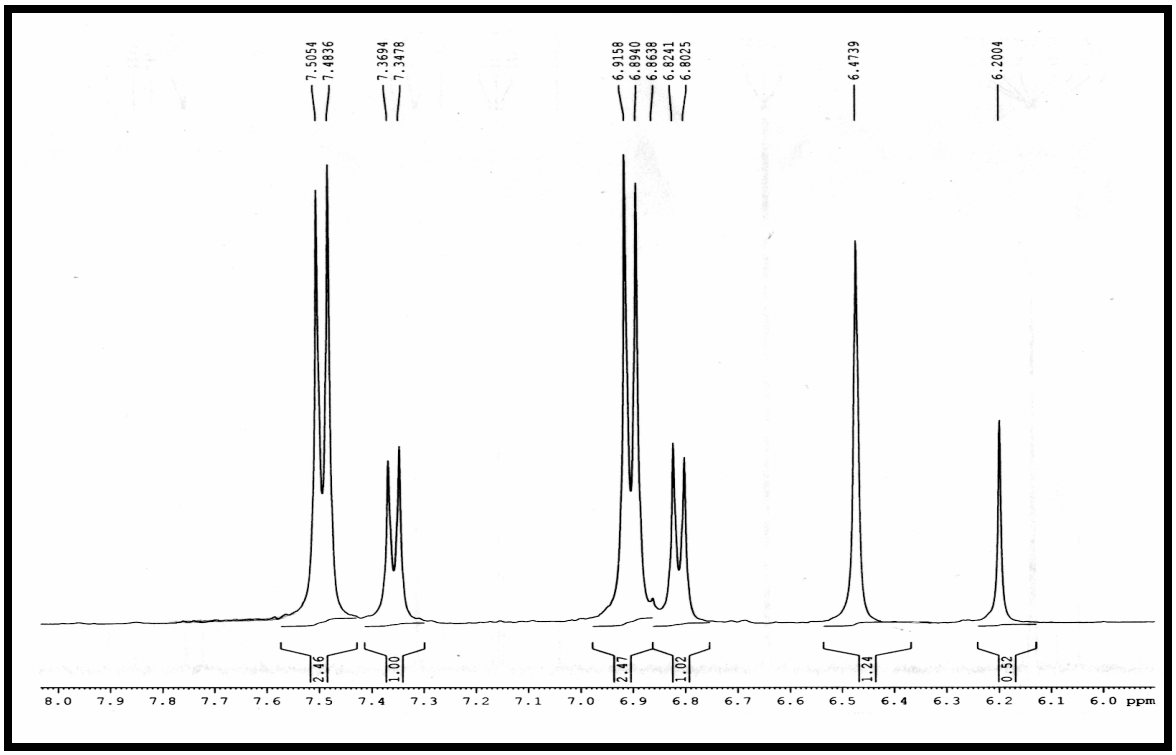
^{1}H NMR spectrum of 2-(5,7-dihydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-21)



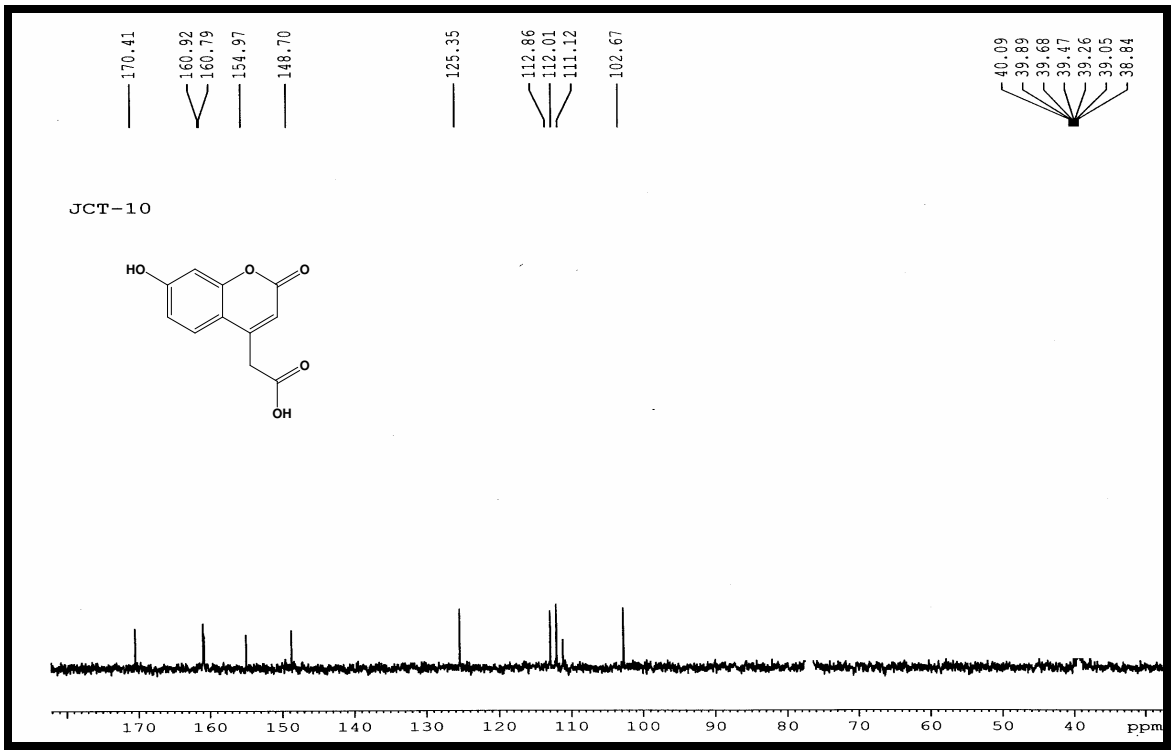


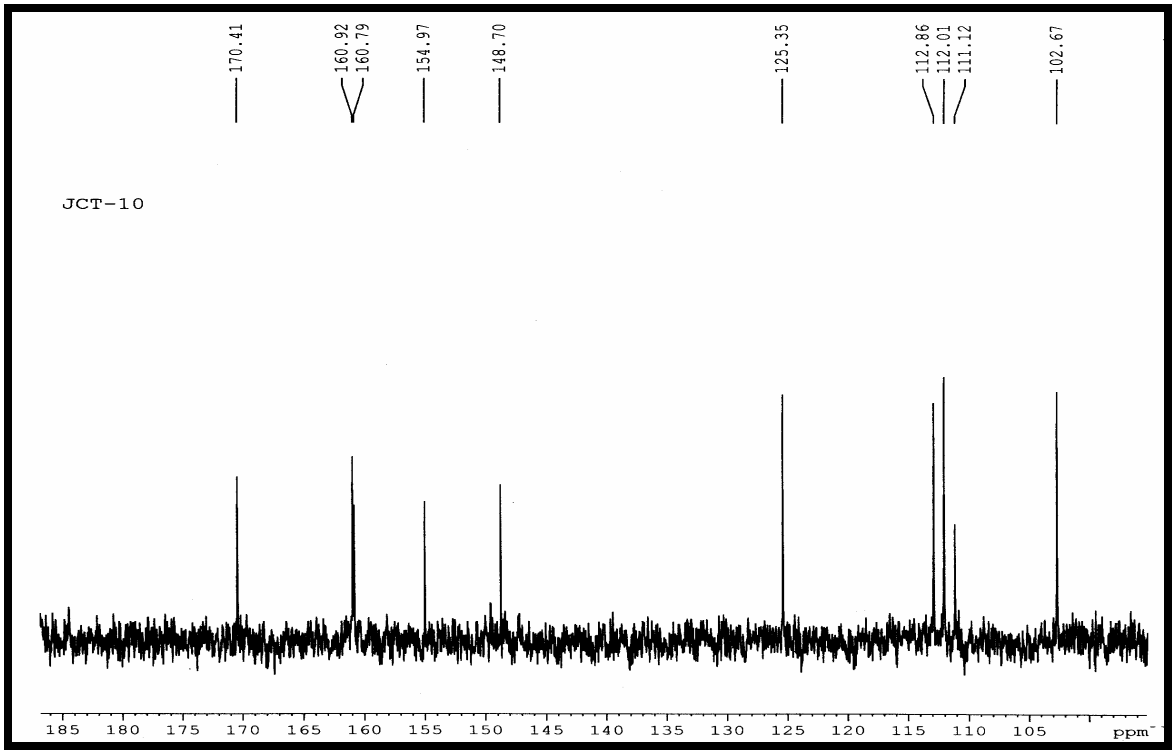
^{1}H NMR spectrum of 2-(2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-24)



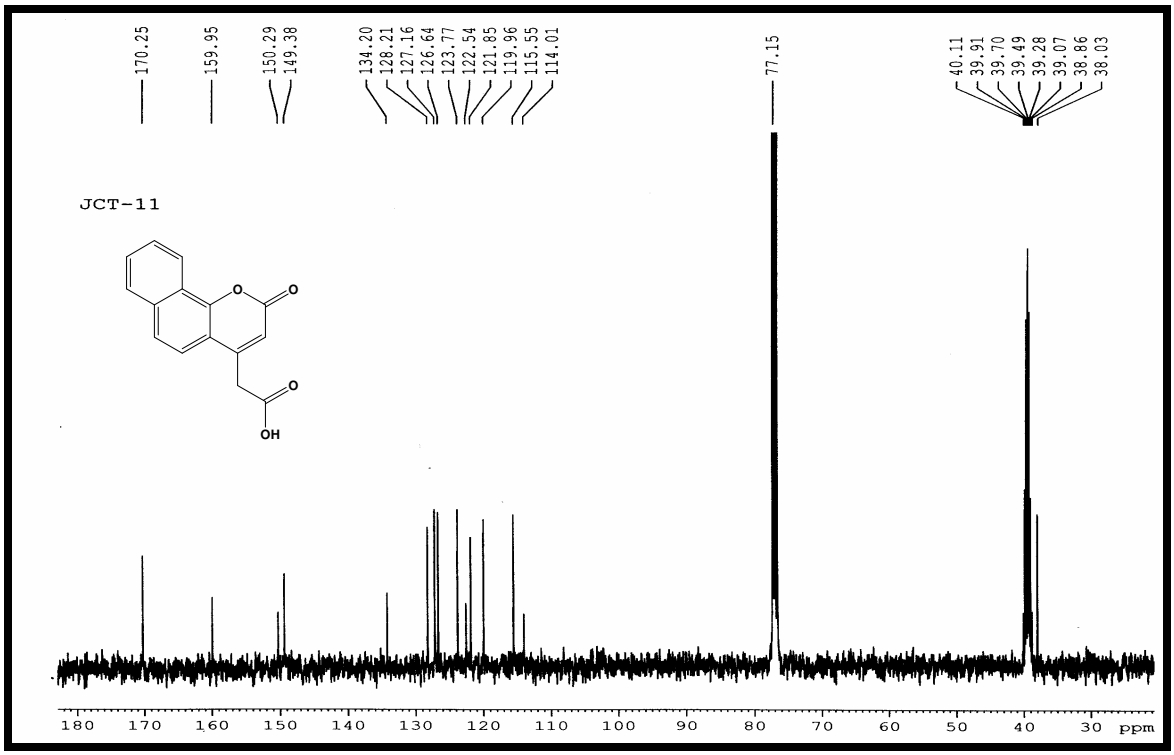


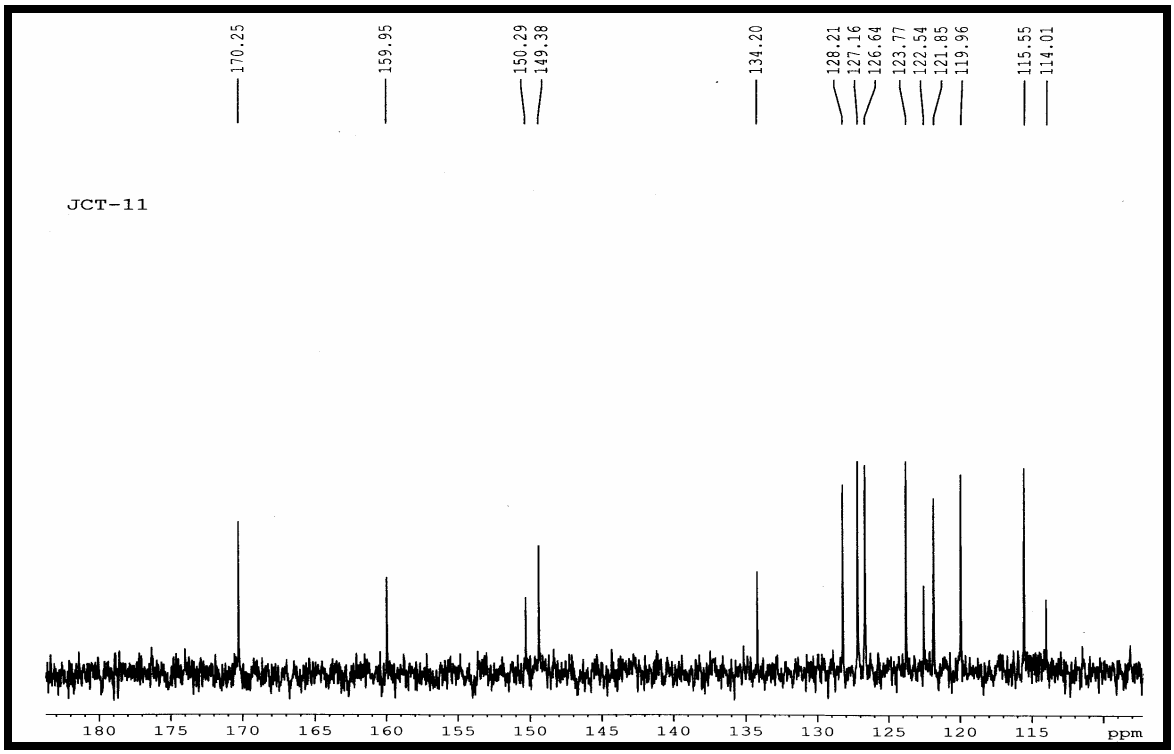
^{13}C NMR spectrum of 2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-10)



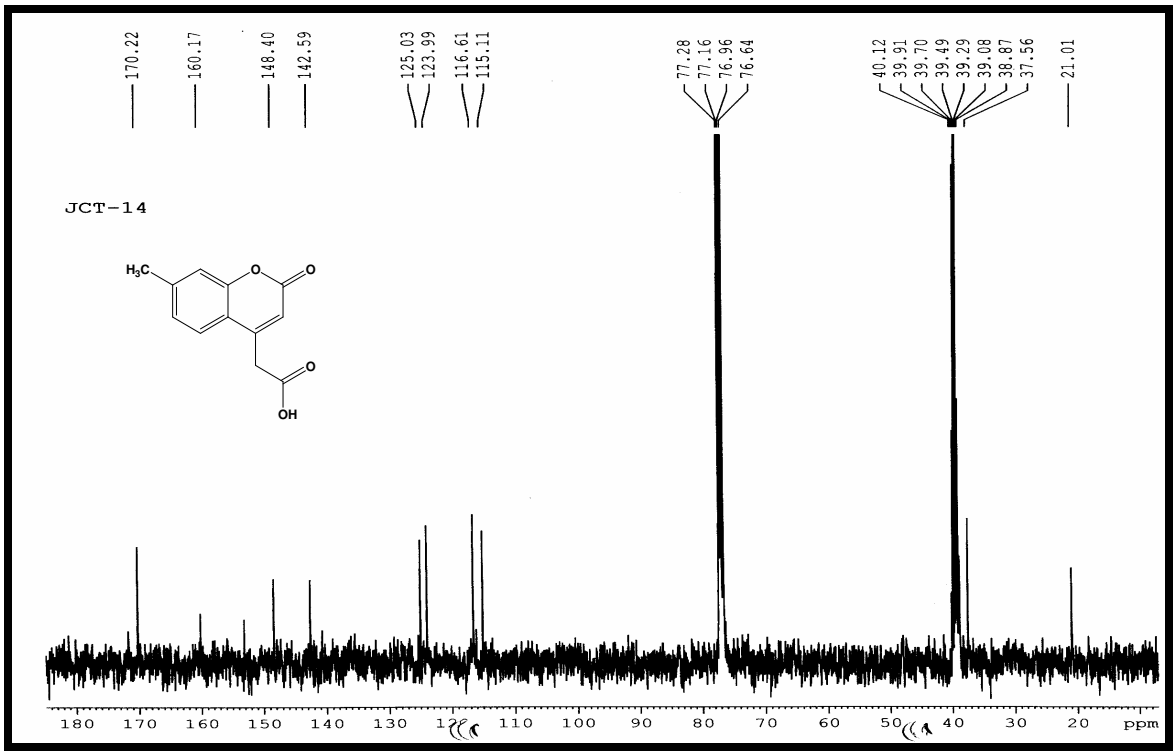


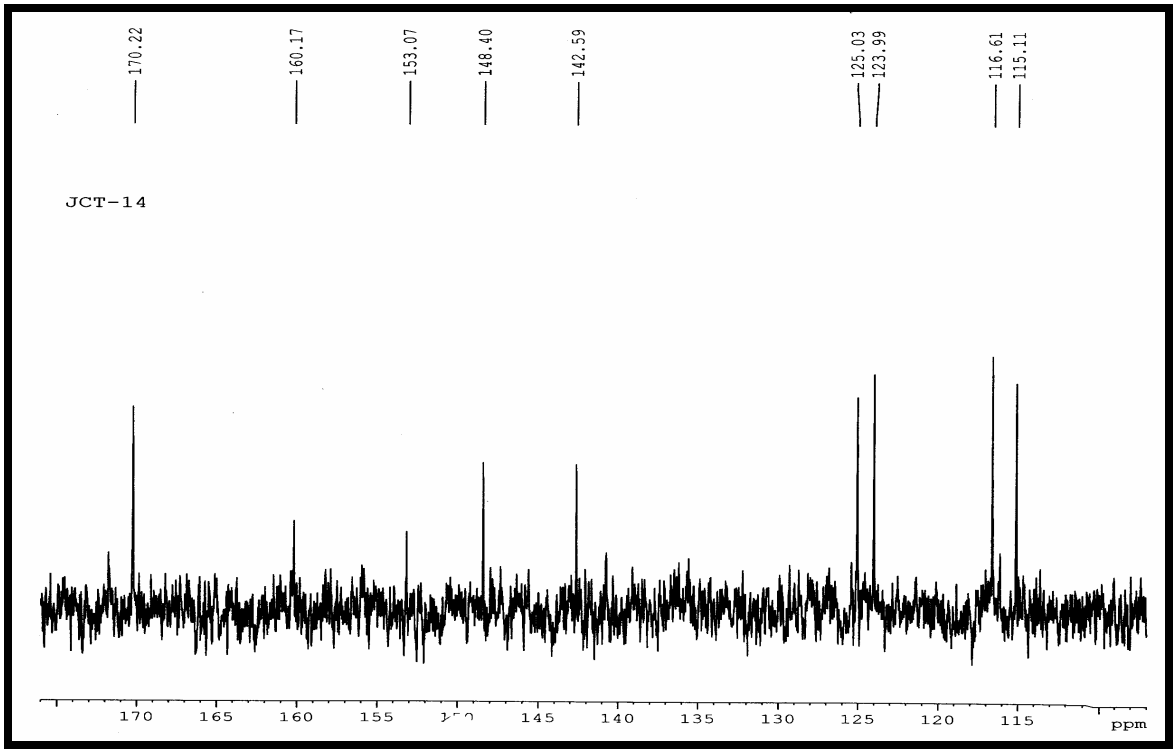
^{13}C NMR spectrum of 2-(2-oxo-2*H*-benzo[*h*]chromen-4-yl) acetic acid (JCT-11)



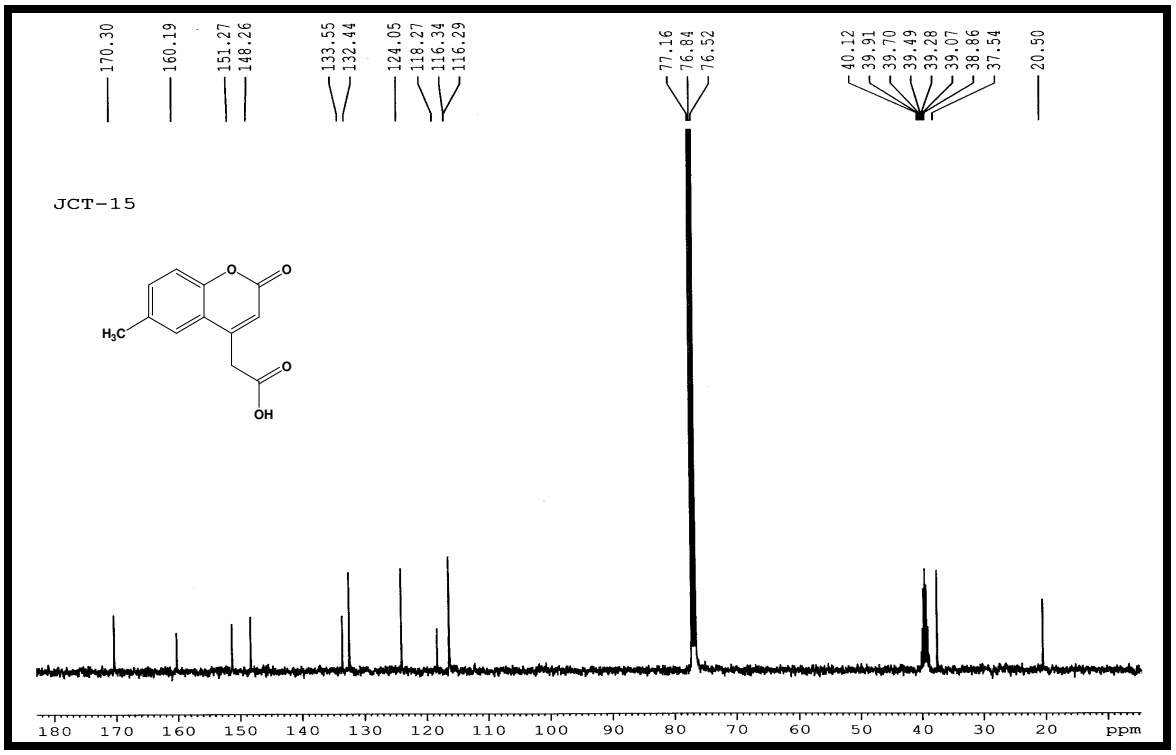


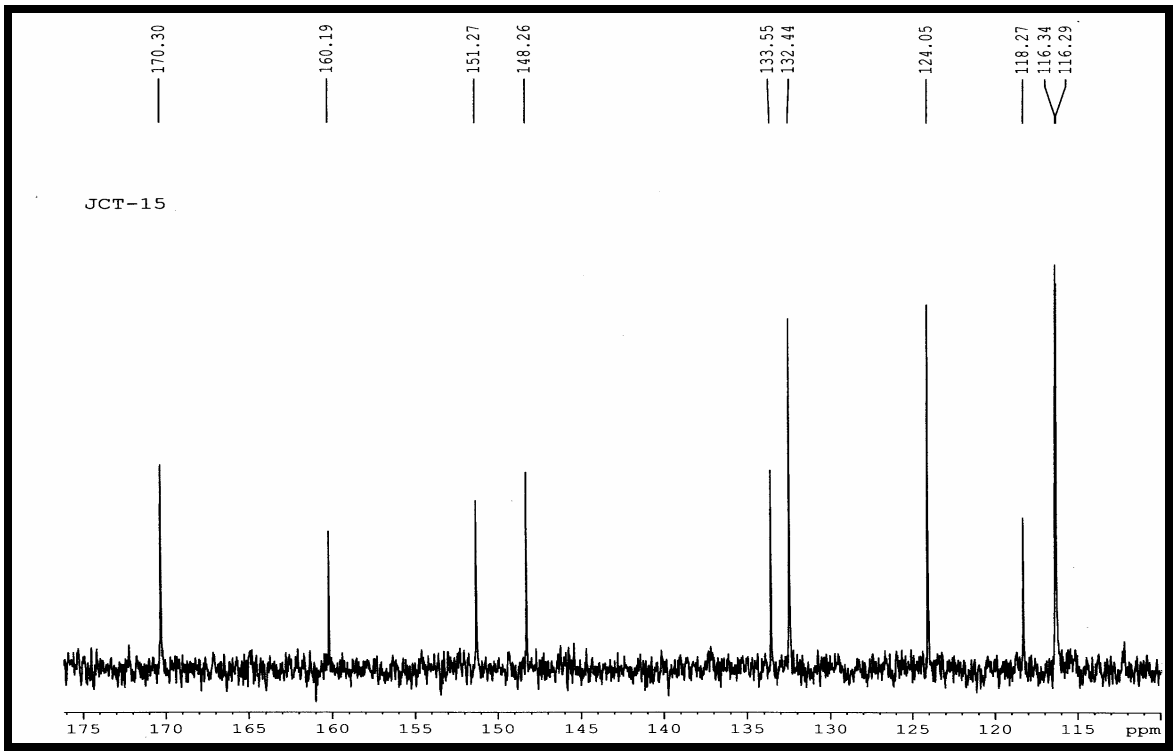
^{13}C NMR spectrum of 2-(7-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-14)



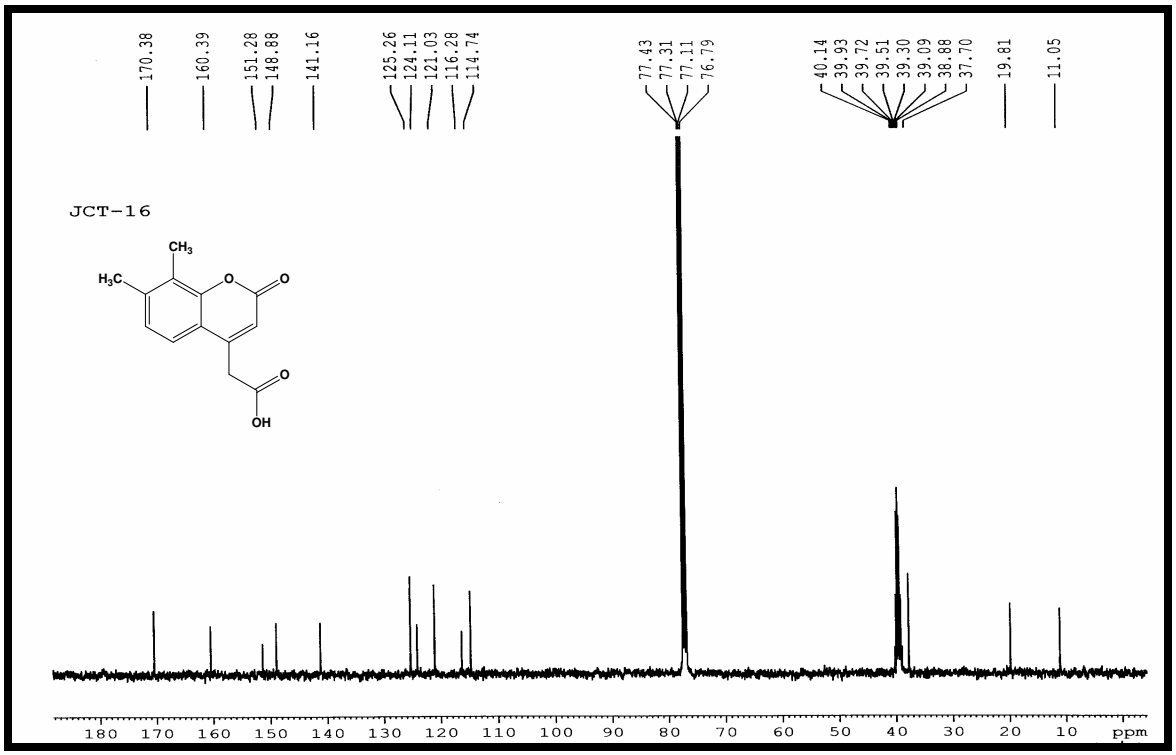


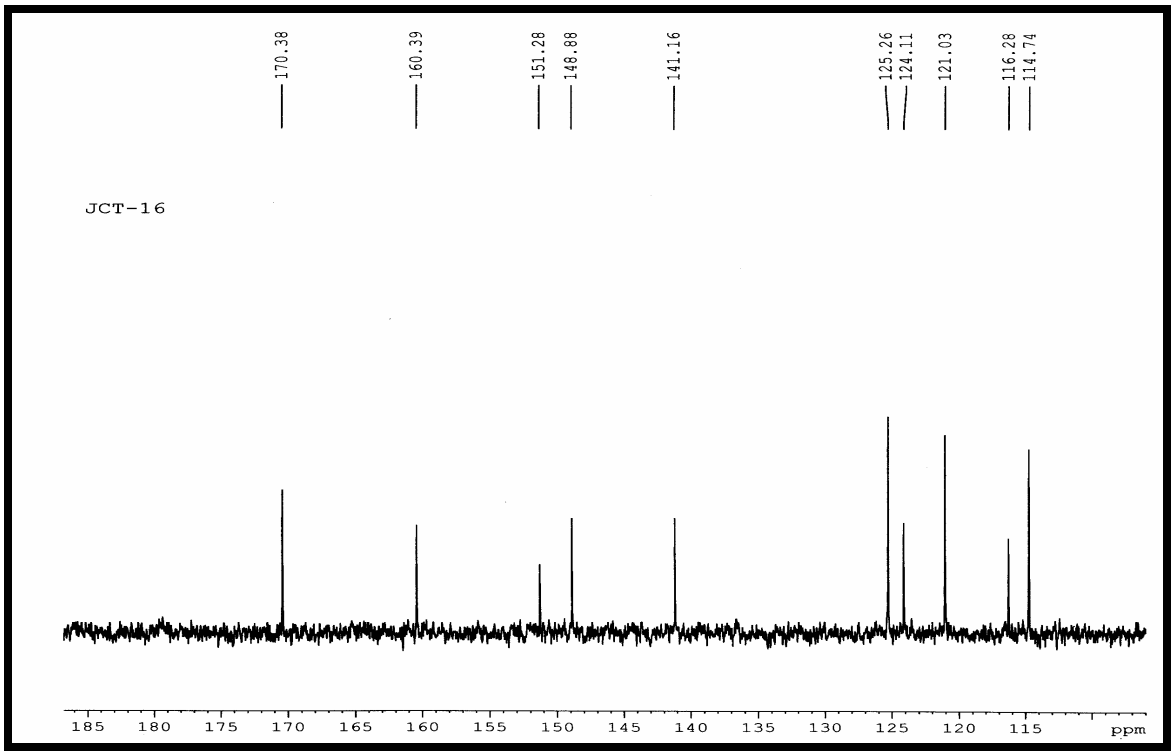
^{13}C NMR spectrum of 2-(6-methyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-15)



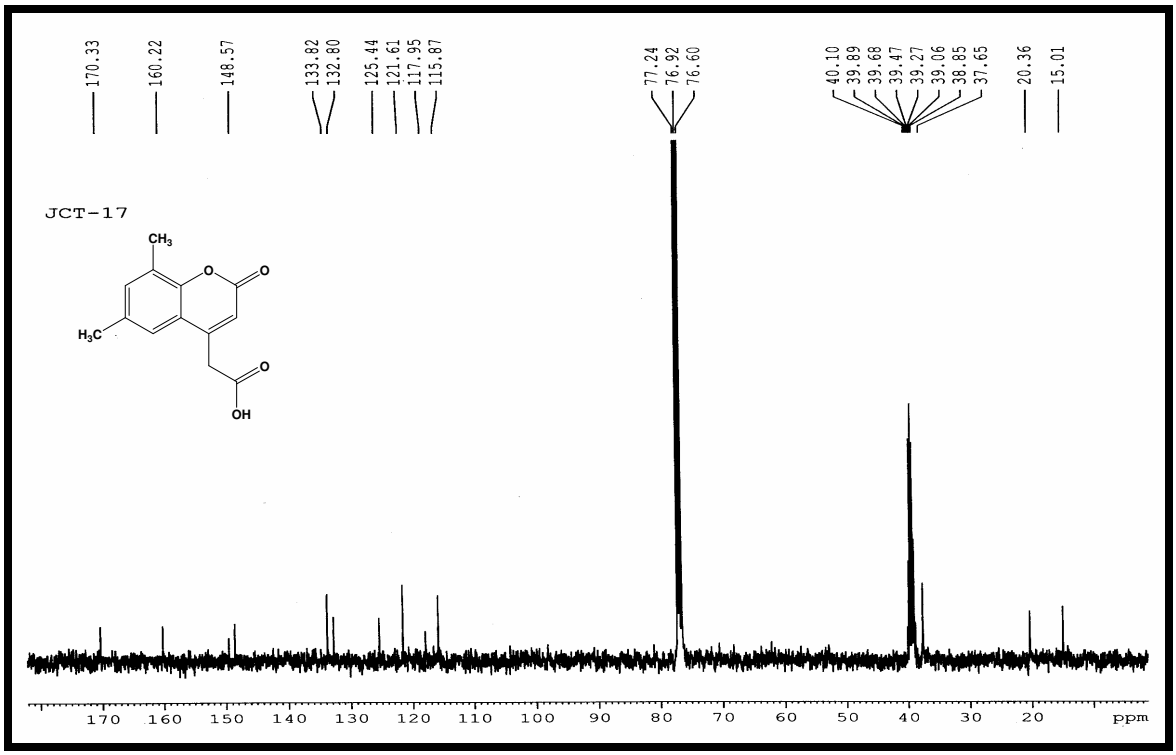


^{13}C NMR spectrum of 2-(7,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetic acid (JCT-16)

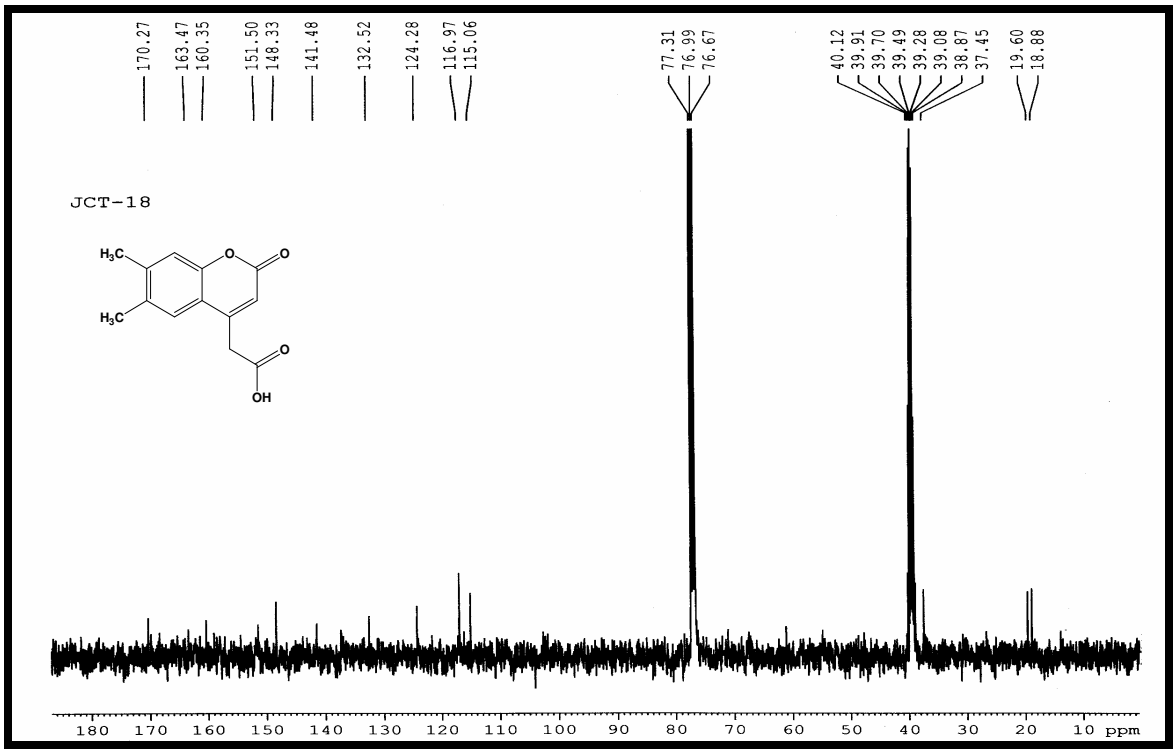




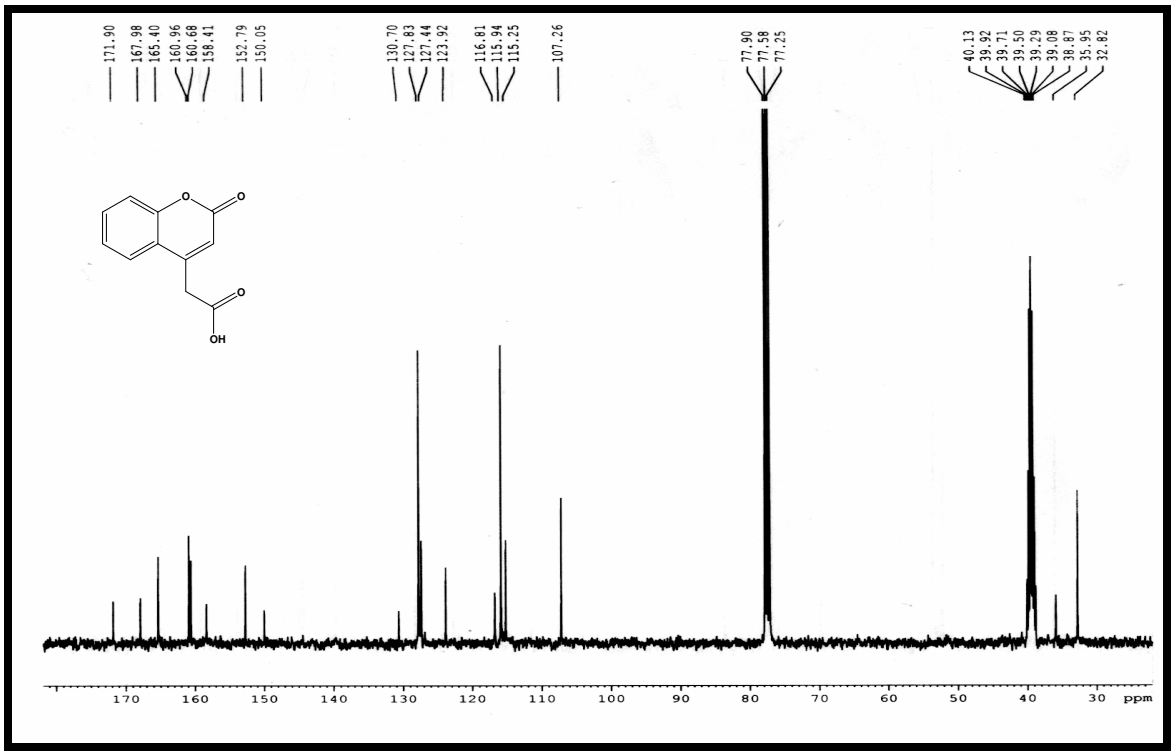
^{13}C NMR spectrum of 2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-17)

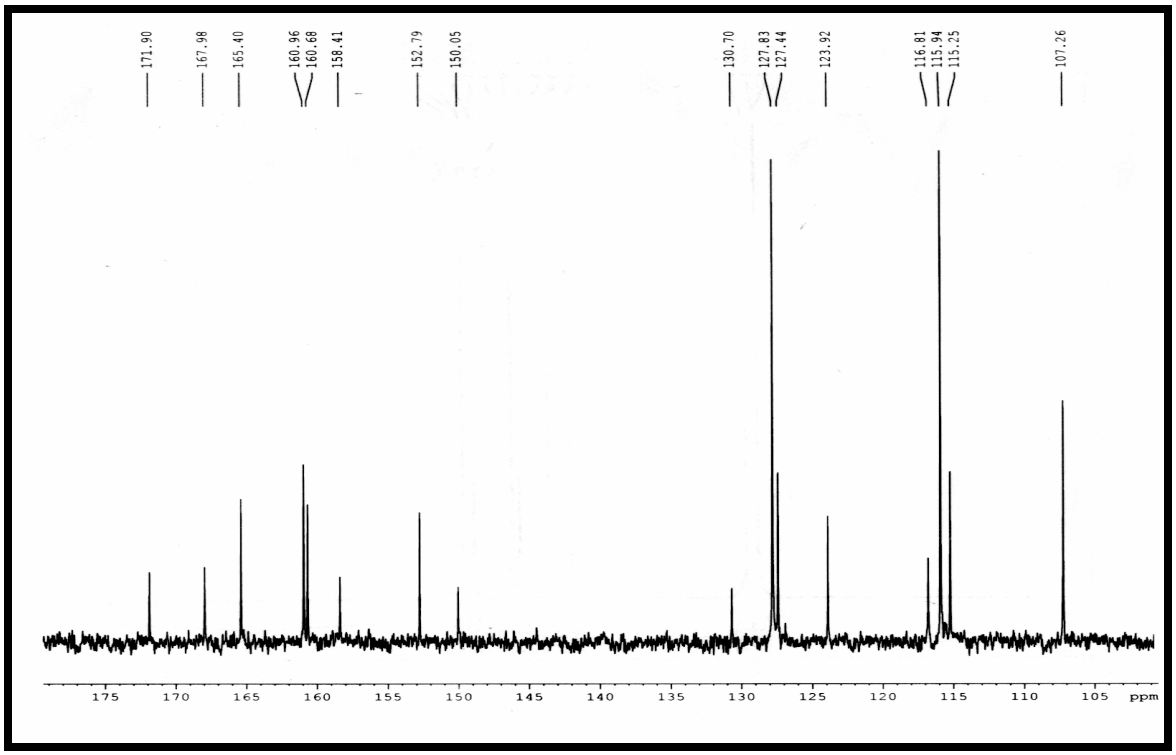


^{13}C NMR spectrum of 2-(6,7-dimethyl-2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-18)



^{13}C NMR spectrum of 2-(2-oxo-2*H*-chromen-4-yl)acetic acid (JCT-24)





1.13. References

1. Vogel, A. *Gibb. Ann. Physik*, 1820, 64, 161.
2. Brahmbhatt, D. I.; Raolji, G. B.; Patel, C. N.; Pandya, V. P. Synthesis and characterization of Polycoumarin Ethylenes/Propylenes, *International Journal of Polymeric Materials*, **2005,** 54, 667–674**.**
3. Sethna, S.; Shah, N. The Chemistry of Coumarins, *Chem. Re.* **1945,** 36, 1.
4. Kostova, I.; Raleva, S.; Genova, P.; Argirova, R. Structure-Activity Relationships of Synthetic Coumarins as HIV-1 Inhibitors, *Bioinorg. Chem. Appl.* **2006**, 2006, 1–9.
5. Czerpack, R.; Skolska, S. Effect of selected synthetic regulators on Pseudomonas aeruginosa growth in liquid culture. *Med. Dosw. Microbiol.* **1982**, 34, 37-50; *Chem. Abstr*. **1983**, 98, 50232.
6. Jund, L.; Corse, J.; King, A. S.; Bayne, H.; Mihrag, K. Antimicrobial properties of 6,7-dihydroxy-7,8-dihydroxy-6-hydroxy-and8-hydroxycoumarins, *Phytochem.* **1971**, 10, 2971-2974.
7. El-Ansary, S. L.; Aly, E. I.; Halem, M. A. New coumarin derivatives as antibacterial agents. *Egypt. J. Pharm. Sci*. **1992**, 33, 379-390.
8. Reddy, Y. D.; Somayojulu, V. V. Synthesis, spectra and physiological activity of 7*H*-pyrano[3,2-c]benzoxazole-7-one. *J. Ind. Chem. Soc.* **1981**, 58, 599-601.
9. Abdullah, O. A. Synthesis and biological studies of some benzopyrano[2,3-c]pyrazole derivatves. *Al Farmaco*, **2000**, 55, 641-649.
10. Lacy, A.; O'Kennedy, R. *Curr. Pharm. Des.* **2004**, 10, 3797.
11. (a) Murray, R. D. H.; Mendez, J.; Brown, S. A. The Natural Coumarins: Occurrence, Chemistry and Biochemistry; *Wiley & Sons: New York,* 1982. (b) Banerji, A.; Mallick, B.; Chatterjee, A.; Budzikiewicz, H.; Breuer, M. *Tetrahedron Lett*. **1988**, 29, 1557. (c) Gustafson, K. R.; Bokesch, H. R.; Fuller, R. W.; Cardellina, J. H.; Kadushin, M. R.; Soejarto, D. D.; Boyd, M. R. *Tetrahedron Lett.* **1994**, 35, 5821. (d) O'Kennedy, R.; Thornes, R. D. Coumarins: Biology, Applications and Mode of Action; *Wiley & Sons: Chichester*, **1997**. (e) Asomaning, W. A.; Otoo, E.; Akoto, O.; Oppong, I. V.; Addae-Mensah, I.; Waibel, R.; Achenbach, H. *Phytochem.* **1999**, 51, 937. (f) Choudhary, M. I.; Azizuddin; Khalid, A.; Sultani, S. Z.; Atta-Ur-Rahman *Planta Med*. **2002**, 68, 81. (g) Atta-ur-Rahman; Sultana, N.; Khan, M. R.; Choudhary, M. I. *Nat. Prod. Lett*. **2002**, 16, 305. (h) Chen, K.; Wu, C.; Chang, F.; Chia, Y.; Chiang, M. Y.; Wang, W.; Wu, Y. *Planta Med*. **2003**, 69, 654. (i) Nunes, F. M.; Barros-Filho, B. A.; de Oliveira, M. C. F.;

Andrade-Neto, M.; de Mattos, M. C.; Mafezoli, J.; Pirani, J. R. *Magn. Reson. Chem.* **2005**, 43, 864.

12. Sardari, S.; Nishibe, S.; Daneshatalab, M. *Stud. Nat. Prod. Chem*. **2000**, 23, 335.
13. (a) Hariprassad, V.; Talele, T. T.; Kulkarni, V. M. *Pharm. Pharmacol. Commun.* **1998**, 4, 365. (b) Kaye, P. T.; Musa, M. A.; Nichinda, A. T.; Nocanda, X. W. *Synth. Commun*. **2004**, 34, 2575.
14. (a) O'Kennedy, R.; Thomas, R. D.; Coumarins: Biology, Applications, and Mode of Action. *Eds. Wiley: Chichester, UK*, **1997**. (b) Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev*. **2003**, 23, 322. (c) Murray, R. D. H.; Mendez, J.; Brown, S. A. The Natural Coumarins; *Wiley: Chichester, UK*, **1982**.
15. (a) Fiedler, V. B.; Scholtholt, J. *J. Pharmacol. Exp. Ther*. **1981**, 217, 306. (b) Opherk, D.; Schuler, G.; Waas, W.; Dietz, R.; Kubler, W. *Eur. Heart J*. **1990**, 11, 342.
16. Raleva, S.; Savov, A.; Froloshka, L.; Dundarova, D.; Manolov, I.; Argirova, R. Examination For Anti Human Immunodeficiency Virus – Type 1 (HIV-1) Effect of three 4-Hydroxycoumarin (4-Hc) Derivatives, *Biotechnol. & Biotechnol. Eq*., **2005**, 24, 11-17.
17. Kostova, I. Synthetic and Natural Coumarins as Cytotoxic Agents, *Curr. Med. Chem. - Anti-Cancer Agents,* **2005***, 5,* 29-46.
18. Kolodziej, H.; Kayser, O.; Woerdenbag, H. J.; van Uden, W.; Pras, N. *Z. Naturforsch*, **1997**, 52, 240.
19. Maxwell, A. DNA gyrase as a drug target. *Biochem. Soc. Trans*. **1999**, 27, 48–53.
20. Gormley, N. A.; Orphanides, G.; Meyer, A.; Cullis, P. M.; Maxwell. A. The interaction of coumarin antibiotics with fragments of DNA gyrase B protein. *Biochemistry*, **1996**, 35, 5083–5092.
21. Mitchell, J. I.; Logan, P. G.; Cushing, K. E.; Ritchie. D. A.; Novobiocin-resistance sequences from the novobiocin-producing strain *Streptomyces niveus*. *Mol. Microbiol*. **1990**, 4, 845–849.
22. Lanoot, B.; Vancanneyt, M.; Cleenwerck, I.; Wang, L.; Li, W.; Liu, Z.; Swings. J. *Int. J. Syst. Evol. Microbiol*. **2002**, 52, 823–829.
23. Berger, J.; Batcho. A. D. Coumarin-glycoside antibiotics. *J. Chromatogr. Libr*. **1978**, 15, 101–158.
24. Thiara, A. S.; Cundliffe. E. Cloning and characterization of a DNA gyrase B gene from *Streptomyces sphaeroides* that confers resistance to novobiocin. *Emb. J.* **1988**, **7,** 2255–2259.

25. Thiara, A. S.; Cundliffe. E. Interplay of novobiocin-resistant and -sensitive DNA gyrase activities in self-protection of the novobiocin producer *Streptomyces sphaeroides*. *Gene*. **1989**, 81, 65–72.

26. Thiara, A. S.; Cundliffe. E. Expression and analysis of two *gyrB* genes from the novobiocin producer *Streptomyces sphaeroides*. *Mol. Microbiol*. **1993**, 8, 495–506.

27. Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med*. **1998**, 64, 97.

28. Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev*. **2003**, 23, 322.

29. Uchiumi, F.; Hatano, T.; Ito, H.; Yoshida, T.; Tanuma, S. I. *Antiviral Res*. **2003**, 58, 89.

30. De Clercq, E. *J. Clin. Virol.* **2004**, 30, 115.

31. M´arquez, N.; Sancho, R.; Bedoya, L. M.; J.; Alcam´ı, L´opez-P´erez, J.; L.; San Feliciano, A.; Fiebich, B. L.; Mu˜noz, E. Mesuol, A natural occurring 4-phenylcoumarin, inhibits HIV-1 replication by targeting the NF-κB pathway. *Antiviral Research*, 2005, 66, 137–145.

32. Lee, K-H.; Natschke, M. S. Recent advances in the discovery and development of plant-derived natural products and their analogs as anti-HIV agents. *Pure and Applied Chemistry.* **1999**, 71(6),1045–1052.

33. Huang, L.; Kashiwada, Y.; Cosentino L. M. et al. Anti-AIDS agents. 15. Synthesis and anti-HIV activity of dihydroseselins and related analogs. *J. Med. Chem.***1994**, 37(23), 3947–3955.

34. Yang, Z-Y.; Xia, Y.; Xia, P./; Brossi, A.; Cosentino, L. M.; Lee, K. H. Anti-AIDS agents. Part 41: synthesis and anti-HIV activity of 3_,4_-di-*o*-(−)-camphanoyl-(+)-*cis*-khellactone (DCK) lactam analogues. *Bioorg. Med. Chem. Lett.* **2000**, 10(10), 1003–1005.

35. Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K. H. Anti-AIDS agents. 42. Synthesis and anti-HIV activity of disubstituted (3'R,4'R)-3',4'-Di-O-(S)-camphanoyl-(+)-cis-khellactone analogues. *J. Med. Chem.* **2001**, 44(5), 664–671.

36. Xie, L.; Yu, D.; Wild, C. *et al.* Anti-AIDS agents. 52. Synthesis and anti-HIV activity of hydroxymethyl (3'R,4'R)-3',4'-Di-O-(*S*)-camphanoyl-(+)-*cis*-khellactone derivatives. *J. Med. Chem.* **2004**, 47(3), 756–760.

37. Xie, L.; Takeuchi, Y.; Cosentino, L. M.; Lee, K-H. Anti-AIDS agents. 37. Synthesis and structure-activity relationships of (3'R,4'R)-(+)-*cis*-khellactone derivatives as novel potent anti-HIV agents. *J. Med. Chem.* **1999**, 42(14), 2662–2672.

38. Xie, L.; Allaway, G.; Wild, C.; Kilgore, N.; Lee, K-H. Anti-AIDS agents. Part 47: Synthesis and anti-HIV activity of 3-substituted 3',4'-Di-O-(*S*)-camphanoyl-(3_*R*,4_*R*)-(+)-*cis*khellactone derivatives. *Bioorg. Med. Chem. Lett.* **2001**, 11(17), 2291–2293.

39. Thaisrivongs, S,; Tomich, P. K.; Watenpaugh, K. D.; Chong, K. T.; Howe, W. J.; Yang, C. P.; Strohbach, J. W.; Turner, S. R.; McGrath, J. P.; Bohanon, M. J.; *J. Med. Chem.* **1994**, 37, 3200-3204.

40. Tummino, P. J.; Ferguson, D.; Hupe, D. Competitive inhibition of HIV-1 protease by warfarin derivatives. *Biochem. Biophys. Res. Commun*. **1994**, 201, 290–294.

41. Lunney, E. A.; Hagen, S. E.; Domagala, J. M.; Humblet, C.; Kosinski, J.; Tait, B. D.; Warmus, J. S.; Wilson, M.; Ferguson, D.; Hupe, D.; Tummino, P. J.; Baldwin, E. T.; Bhat, T. N.; Liu, B.; Erickson, J. W. A novel nonpeptide HIV-1 protease inhibitor: Elucidation of the binding mode and its application in the design of related analogs. *J. Med. Chem*. **1994**, 37, 2664–2677.

42. D'angelo, J.; Mouscadet, J. F.; Desmaele, D.; Zouhiri, F.; Leh, H. HIV-1 integrase: The next target for AIDS therapy. *Pathol. Biol.* **2001**, 49, 237–246.

43. Mazumder, A.; Wang, S.; Neamati, N.; Nicklaus, M.; Sunder, S.; Chen, J.; Milne, G. W. A.; Rice, W. G.; Burke, T. R. Jr., Pommier, Y. Antiretroviral agents as inhibitors of both human immunodeficiency virus type I integrase and protease. *J. Med. Chem.* **1996**, 39, 2472–2481.

44. Zhao, H.; Neamati, N.; Hong, H.; Mazumder, A.; Wang, S.; Sunder, S.; Milne, G. W. A.; Pommier Y.; Burke T. R, Jr. Coumarin-based inhibitors of HIV integrase. *J. Med. Chem.* **1997**, 40, 242–249.

45. Clinton, Salvador, Laskowski. *ibid.* **1949,** *72,* 3366.

46. Martyanov, N.; Zakharova, O. D.; Sottofattori, E.; Pyshnyi, D. V.; Yurchenko, E. Y.; Babbi, P.; Mazzei, M.; Balbi, A.; Andreola, M. L.; Litvak.; S, Tarrago-Litvak L.; Nevinsky, G. A. Interaction of oligonucleotides conjugated to substituted chromones and coumarins with HIV-1 reverse transcriptase. *Antisense Nucleic Acid Drug Dev.* **1999**, 9, 473–480.

47. (a) Miolo, G.; Tomanin, R.; De Rossi, A.; Dall'Acqua, F.; Zacchello, F.; Scarpa, M. Antiretroviral activity of furocoumarins plus UVA light detected by a replication-defective retrovirus. *J. Photochem. Photobil. Biol*. **1994**, 26, 241–247. (b) Hudson, J. B.; Graham, E. A.; Harris, L.; Ashwood-Smith, M. J. The unusual UVA-dependent antiviral properties of the furoisocoumarin, coriandrin. *Photochem. Photobiol*. **1993**, 57, 491–496.

48. Pettipher, R.; Hansel, T.; T. Armer, R. Antagonism of the prostaglandin D_2 receptors DP_1 and CRTH2 as an approach to treat allergic diseases, *Drug Discovery, Nature Reviews*, **2007**, 6 , 313-325.

49. Pairaudeau, G.; Rasul, R.; Thom, S. Novel compounds. World Patent *WO2004089884*, **2004**.

50. Bonnert, R.; *et al*. Novel compounds World Patent, *W02004089885*, **2004**.

51. Luker, T. J.; Birkinshaw, T. N.; Mohammed, R. T.; Biphenyloxyacetic acid derivatives for the treatment of respiratory disaese. World Patent *W02006021759*, **2006**.

52. Bonnert, R. V.; Luker, T. J.; Pairaudeau, G.; Thom, S. Novel compounds. World Patent *WO2006037982*, **2006**.

53. Laskowski, S. C.; Clinton, R. O. Coumarins. II. Derivatives of Coumarin-3- and -4-Acetic Acids, *J. Am. Chem. Soc*. **1950**, 72, 3987-3991.

54. Dey, B. B.;*J. Chem. Soc.* **1915**, 107, 1606.

55. Knoevenagel, *Ber*. 1898, 91, 2585.

56. Werder, F.; *Mercks Jahresbericht*, **1936**, 50, 88.

57. Foye, W. O.; Lemke, T. L.; Williams, D. A. *Principles of Medicinal Chemistry*, 4th Edi. 1995, 895.

58. Clinton, R. O.; Laskowski, S. C. Coumarins. I. Derivatives of Coumarin-3- and 4-carboxylic acids, *J. Am. Chem. Soc*. **1949**, *71*, 3602-3606.

59. Pechmann, *Ber*. **1901**, 34, 378,.

60. Pechmann, Kraft, E. *Ber*. **1901**, 34, 421.

61. Chakravarti, D.; Ghosh, B. *J. Ind. Chem. Soc*. **1935**, 12, 622.

62. Chakravarti, D.; Mukherjee, H. *J. Ind. Chem. Soc*. **1937**, 14, 725.

63. Chakravarti, D.; Banerjee, H. *J. Ind. Chem. Soc*. **1936**, 13, 619.

64. Limaye, D. *J. Ind. Chem. Soc*. **1927**, 4, 159.

65. Dey, B. B. *J. Chem. Soc.* **1915**, 107, 1606.

66. Dixit, V.; Gokhle G.; *J. Uni. Bombay (Pt-2)*, **1934**, 3, 95-105; *C. A.* **1935**, 29, 4753.

67. Fries, K.; Volk, W. *Ann*. **1911**, 379, 90.

68. Burton, H.; Pechmann. *Ann*. **1891**, 261, 166.

69. (a) Muller, D. *Ber*. **1925.** 58, 2202. (b) Ghia, B. J., Gharde, A. D., *J. Ind. Chem. Soc*. **1992**, 69, 397-398.

70. Dey, Sankaranarayanan. *J. Indian Chem. Soc.*1931, ***8,*** 817.

71. Gardner, J. H.; Clarke, D. V.; Semb, J. Some new local Anesthetics containing the morpholine ring . II. *J. Am. Chem. Soc*. **1933**, 55, 2999.

72. Woods, L. L.; Sapp, J. Ethyl Esters of Coumarin-4-Acetic Acids, *J.Chem. And Eng. Data,* **1963**, 8(2), 235-236.

73. Ramakrishna, G.; Singh, A. K.; Palit, D. K.; Ghosh, H. N. Effect of Molecular Structure on Interfacial Electron Transfer Dynamics of 7-*N*,*N*-Dimethyl Coumarin 4-Acetic Acid (DMACA) and 7-Hydroxy Coumarin 4-Acetic Acid (HCA) Sensitized TiO_2 and ZrO_2 Nanoparticles, *J. Phys. Chem. B,* **2004**, *108,* 12489-12496.

74. Sarges, R; Conn, M.; Belletire, J.; Wis, M; Schnur, R; Conn, N; Pharmaceautical preparations containing coumarin carboxylic acid derivatives, *US Patent 4,210,667*, **1980**, July,1.

75. Hayman, *J. Biolo. Chem*. **1965**, 240, 877.

76. Clinton, R.; County, R.; Laskowski, S. Basic esters and amides of 7-substituted coumarin-4-acetic acids and salts and processes of preparation, *US patent 2,615,024,* **1952**, Oct. 21.

77. Profit, A. A.; Lee, T. R.; Lawrence, D. S. Bivalent Inhibitors of Protein Tyrosine Kinases, *J. Am. Chem. Soc.* **1999**, *121,* 280-283.

78. Lee, T. R.; Lawrence, D. S., unpublished results.

79. Brubaker, A. N.; DeRuiter, J.; Whitmer, W. L. Synthesis and Rat Lens Aldose Reductase Inhibitory Activity of Some Benzopyran-2-ones, *J. Med. Chem.* **1986**, 29, 1094-1099.

80. DeRuiter, J.; Brubaker, A. N.; Millen, J.; Riley, T. N. *J. Med. Chem.,* in press.

81. Kador, P. F.; Sharpless, N. E. *Mol. Pharmacol.* **1983**, 24, 521.

82. Kador, P. F.; Kinoshita, J. H.; Sharpless, N. E. *J. Med. Chem.* **1985,** *28,* 841.

83. Bowden, K.; Hanson, M. J.; Taylor, *G.* R. *J. Chem. SOC. B* **1968**, 174.

84. Kador, P. F.; Sharpless, N. E. *Biophys. Chem.* **1978,** 8, 81.

85. Dey, B. B., Row, K. K. *J. Indian Chem. Soc.* **1924**, 1, 107.

86. Dey, B. B., Seshadri, T. R. *J. Indian Chem. Soc.* **1931**, 8, 247.

87. Dey, B. B., Radhabai, K. *J. Indian Chem. Soc.* **1934**, 11, 635.

88. Dey, B. B.: *J. Chem. Soc.* **1916**, 1606.

89. Bartosova, B.; Lacova, M.; Gaplovsky, A.; Chovancova, J.; Pronayova, N.; Simunek, P.; Loos, D. The Atypical Condensations of 4-Oxo-4*H*-Benzopyran-3-Carbaldehydes with Derivatives Coumarin-3-acetic- and Coumarin-4-acetic Acids by Microwave Irradiation and Classical Methods , ***Sixth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-6),*** **2003, September 1-30**.

90. Nohara, A.; Ishiguto, T.; Sanno, Y., *Tetrahedron,* **1974**, 13, 1183.

91. Stankovicova, H.; Lacova, M.; Gaplovsky, A.; Chovancova J.; Pronayova, N., *Tetrahedron,* **2001**, 57, 3455.

92. Sabitha, G., *Aldrichimica Acta.* **1996**, 29, 15.

93. Lacova, M.; Gasparova, M.; Loos, D.; Liptay, T.; Pronayova, N., *Molecules,* **2000**, *5*,167.

94. Galema, A. S.; *Chem. Soc. Rev.* **1997**, 26, 233.

95. Vida, J. A.; Gut, A. I. Investigations in the 3,4-Dihydrocoumarin Melilotic Acid Series, *J. Org. Chem.* **1968**, 33 (3), 1202-1209.

96. Woodruff, E. H.; "Organic Syntheses," *Coll. Vol. III*, Horning, E. C. *Ed. J. Wiley and Sons, Inc., New York, N. Y.*, **1955**, 581.

97. Wheelock, C. E.; *J . Am. Chem. Soc.* **1959**, 81, 1348.

98. Lukes, R.; Zobaoova, A. *Collection Czech. Chem. Commun.* **1957**, 1649.

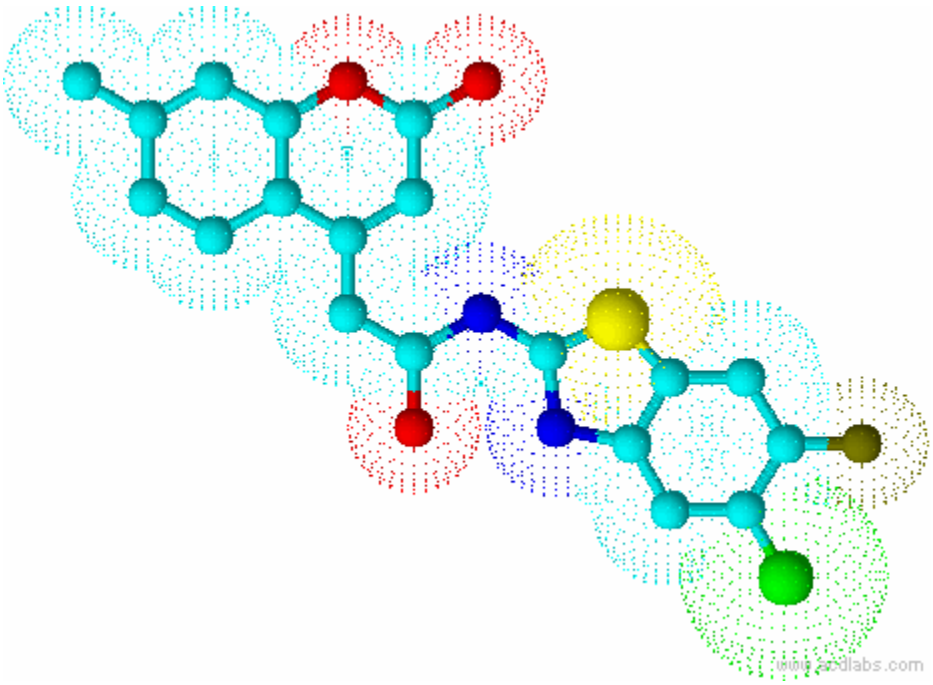
99. Zhu, Q.; Uttamchandani, M.; Li, D.; Lesaicherre, M. L.; Yao, S. Q.; "An Enzymatic Profiling System in a Small-Molecule Microarray", *Org.c lett.* **2002**, 5, 1257-1259.

100. Mustafa, A.; Kamel, M.; Allam, M. A. 4-Styrylcoumarins in Diene Syntheses. II, *J. Am. Chem. Soc.* **1956**, 78, 4692-4694.

101. Mustafa M.; Kamel, *J. Am. Chem. Soc.* **1965**, 77, 1828.

102. Elderfield, R. C.; Mehta, A. C. Synthesis of Potential Anticancer Agents. XIX. Nitrogen Mustards from 7-Hydroxycoumarin derivatives, *J. Med. Chem.* **1967**, 10, 921-923.

CHAPTER-2



Preparation of N-1, 3-benzo[d]thiazol-2-yl-2 (2-oxo-2H-chromen-4-yl) acetamide derivatives

Preparation of *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl) acetamide derivatives

2.1. Introduction

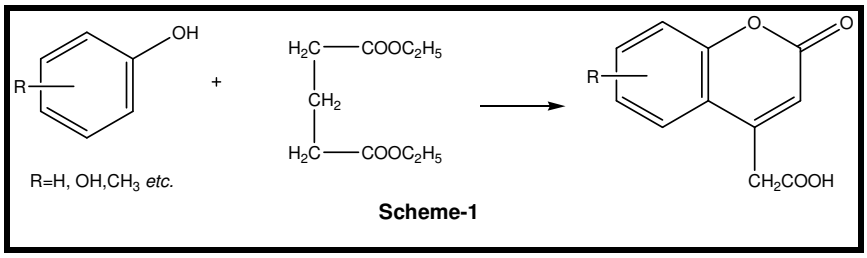
Coumarin,[1(a)] the parent substance of the benzo-α-pyrone group, was first isolated from Tonka beans in 1820. Their derivatives have been found to be widely distributed in plant kingdom.[1(b-e)] The three classical methods were adopted for the preparation of coumarin derivatives.

i. Perkin[2] synthesized coumarins from salisaldehyde with acetic anhydride and anhydrous sodium acetate.

ii. Pechmann[3] prepared coumarins from phenol and malic acid when heated in concentrated sulfuric acid.

iii. Knoevenagel[4] developed coumarin from 2-hydroxyaldehyde with diethyl malonate in presence of piperidine.

Pechmann reaction has been studied by many researchers, using various substituted phenols and different β-ketonic esters. Biginelli[5] condensed quinol with ethyloxalacetate in presence of sulfuric acid and obtained 6-hydroxy-coumarin-4-acetic acid. Pechmann, Kraft,[6] and Graeger[7] extended this reaction to other phenols (Scheme-1).



Scheme-1

Limaye[8] found that phenol when condensed with citric acid, gave coumarin-4-acetic acid. Dey[9], Dixit[10], Fries[11] and Radhabai[12] had studied the reaction of phenol with acetone dicarboxylic acid and citric acid. Gokhle, Ghosh,[13] Chakravarti[14] and Banerjee[15] have studied the formation of coumarin-4-acetic acid from substituted phenol and acetone dicarboxyllic acid using sulfuric acid as condensing agent. Burton and Muller[16,17] have found that condensation of resorcinol with diethylacetone dicarboxylate afforded 7-hydroxy coumarin-4-acetic acid. Ghiya and co-workers[18a] also studied these compounds for bromination of styryl derivatives.

Werder[18b] have synthesized more than 100 derivatives of coumarin-3-carboxylic acid, which were found to be sedative in small doses and hypnotic in large doses. Among the derivatives of these acids, the diethyl amide proved to be a good drug in general nervous disease and in various neuro anaesthetic and hysterical ailments. It has been further found that some oxygenated coumarins possessing the power of absorbing UV rays were extensively used as medicines in skin desieses[18c].

A number of natural and synthetic coumarin (2-oxo-2*H*-chromene) derivatives have been reported to exert notably antimicrobial[19,20] as well as antifungal[21,22] and tuberculostatic[23] activity. Moreover, the antibiotic novobiocin belongs to the hydroxy coumarin series (Figure-1).

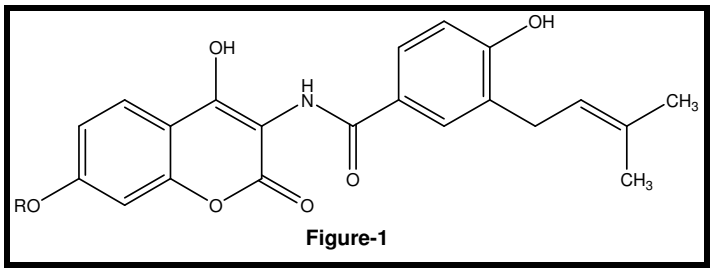


Figure-1

Aryl alkanoic acids

A phenyl ring or aryl ring attached with acetic or propionic acid gave phenyl acetic acid derivatives. It was found that when a heterocyclic system was introduced in place of aromatic ring, the resulting alkanoic acid derivatives showed therapeutic importance such as analgesics, anti-inflammatory and antiarthritic. Many aryl alkanoic acids are classified as non-steroidal antiinflamatory drugs (NSAIDS).

Figure-2: Some of the aryl alkanoic acids and their biological activity profile

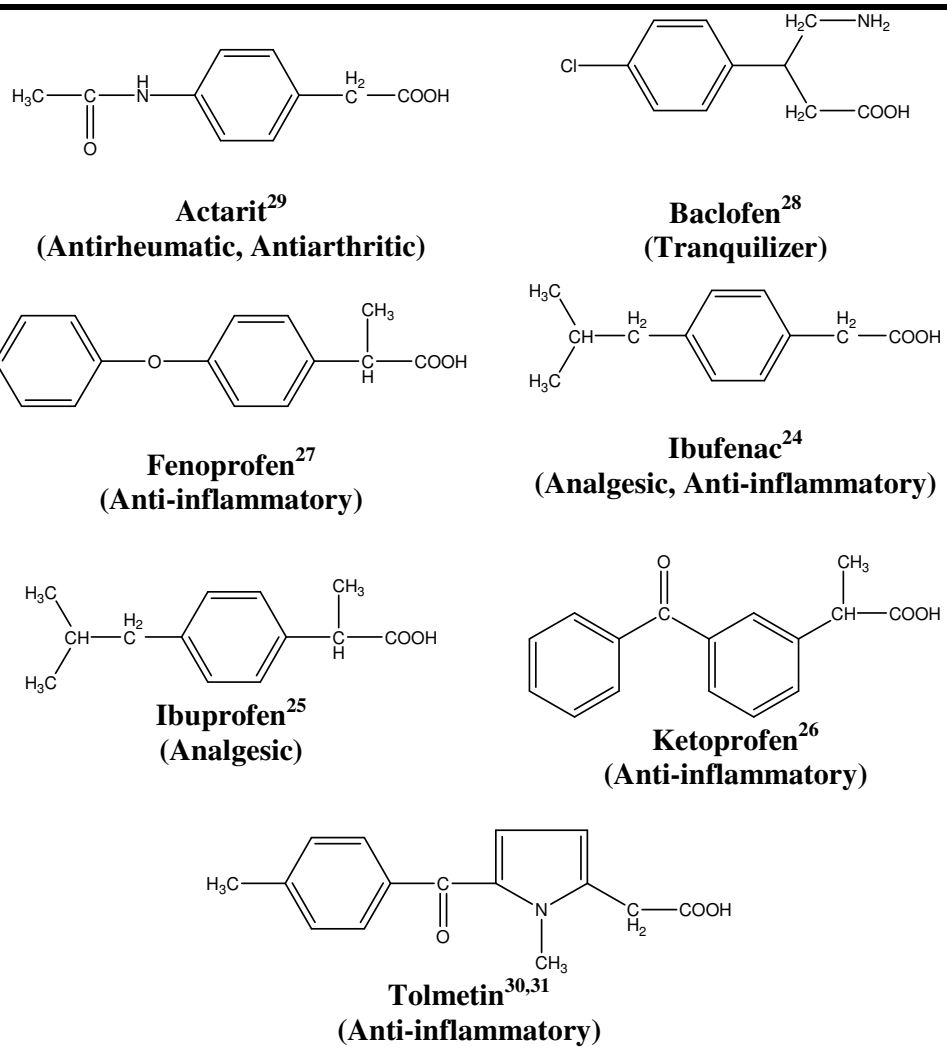


Figure-2

Benzothiazole containing analogues

Benzothiazoles are heterocyclic compounds with multiple applications and, have been known from long ago as biologically active.[32-34] Their varied biological features are still of much scientific interest. 2-Aminobenzothiazoles are oxygen sensitive and therefore used as acid salts, alkaline salts, zinc salts and di-sulphides which generate free 2-aminobenzothiazoles under reducing conditions. 2-Aminobenzothiazoles are appreciably reactive and react with a number of compounds to produce benzothiazoles (Figure-3).

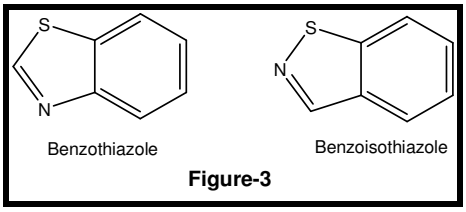


Figure-3

They show very potent antitumor activity, especially the phenyl-substituted benzothiazoles,[35-37] while condensed pyrimido[2,1-*b*]benzothiazoles and benzothiazolo[2,3-*b*]-quinazolines exert antiviral activity.[38]

Recently, Racane *et. al.*[39] have described the synthesis of bis-substituted amidinobenzothiazoles as potential anti-HIV agents. Substituted benzamido- and phenylacetamido-substituted 2-phenylbenzothiazoles,[40-42] 2-substituted 6-nitro- and 6-aminobenzothiazoles,[43] fluorobenzothiazoles[44] and Schiff bases derived from benzothiazoles[45] had also shown anti-microbial activity (Figure-4).

Benzothiazole derivatives show other biological activities, too. 2-Amino-substituted benzothiazoles are reported as inhibitors of Src family kinases .[46, 47]

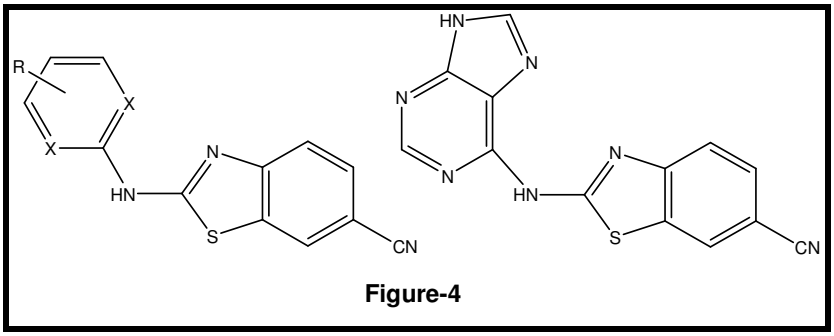


Figure-4

During last 50 years, number of 2-benzothiazolamines was intensively studied as central muscle relaxants.[48] Biologist's attention was drawn to this series when the pharmacological profile of riluzole was discovered. Riluzole, 6-(trifluoromethoxy)-2-benzothiazolamine, was found to interfere with glutamate neurotransmission in biochemical, electrophysiological and behavioral experiments. Riluzole is the most active compounds displaying *in vivo* "antiglutamate" activity (Figure-5).

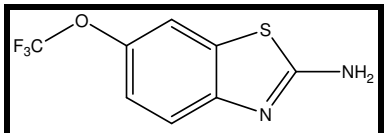
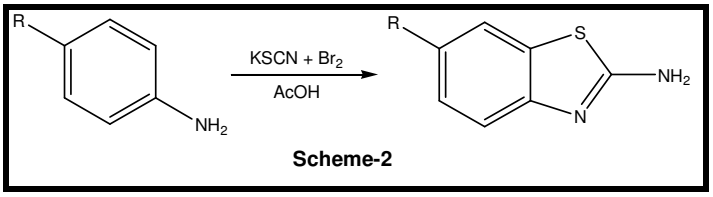


Figure-5

Two series of analogues of riluzole, *i.e.* mono-substituted 2-benzothiazolamines and 3-substituted derivatives, have been synthesized by Jimonet and co-workers.[49] Of all the compounds synthesized, only 2-benzothiazolamines bearing alkyl, polyfluoroalkyl, or polyfluoroalkoxy substituents in the 6-position showed potent anticonvulsant activity against administration of glutamic acid in rats.

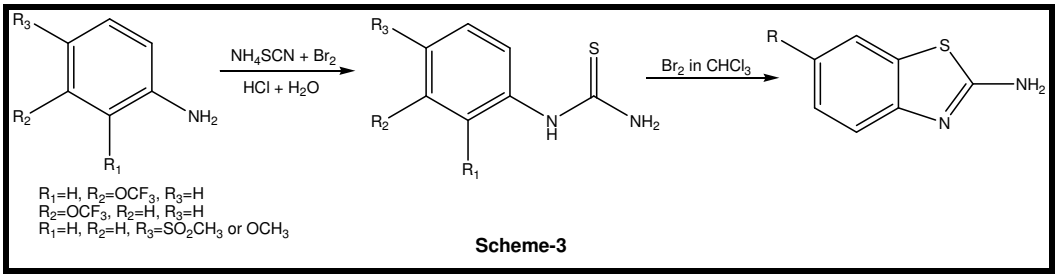
Synthetic aspects and biological profiles of benzothiazoles

6-Substituted-2-benzothiazolamines bearing various substituents in the 6-position (scheme-2) shows the classical synthetic route[50] used for the preparation of various derivatives 6-substituted-2-benzothiazolamines. One-pot reaction of the appropriate aniline with thiocyanogen generated from bromine and alkaline thiocyanate in acetic acid medium led to formation of the desired products in good to moderate yields.



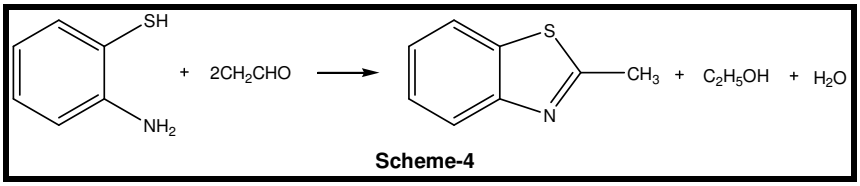
Scheme-2

Another classical way[51] previously used for the preparation of 2-aminobenzothiazoles is cyclization of phenylthioureas with bromine in chloroform (Scheme-3)**.**



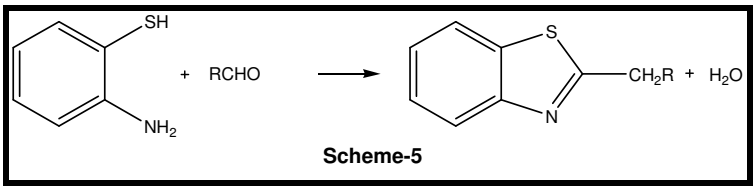
Scheme-3

Hofmann[52] obtained benzothiazoles by the action of acids, acid chlorides and acid anhydrides upon *o*-aminothiophenol. Upon condensing certain aldehydes with *o*-aminothiophenol, also obtained were benzothiazoles[53] (Scheme-4).



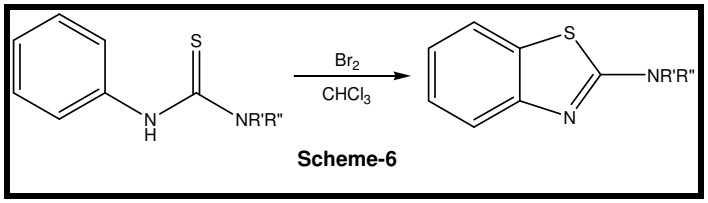
Scheme-4

Green and Perkin[54] also obtained a benzobisthiazole by condensing benzaldehyde with p-phenylenediamine-2,5-di-(thiosulfonic acid). Claasz[55] condensed a number of aldehydes with *o*-aminothiophenol hydrochloride and obtained benzothiazolines (Scheme-5).



Scheme-5

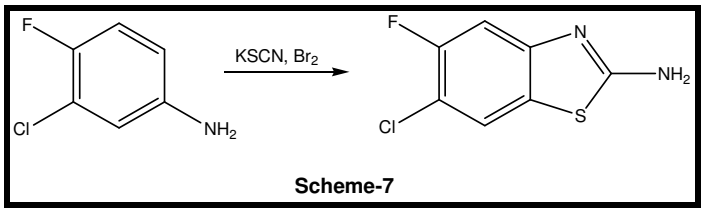
Investigations for the preparation of 2-aminobenzothiazoles can be traced to the early 1900s with the work of Hugerschoff,[56] who found that an arylthiourea can be cyclized with bromine solution in chloroform to form an 2-aminobenzothiazoles.[57] This reaction usually proceeds efficiently at room temperature. Hugerschoff reaction is a well known reaction for the production of 2-aminobenzothiazoles by the reaction of molecular bromine (Br_2) with arylthioureas (Scheme-6).



Scheme-6

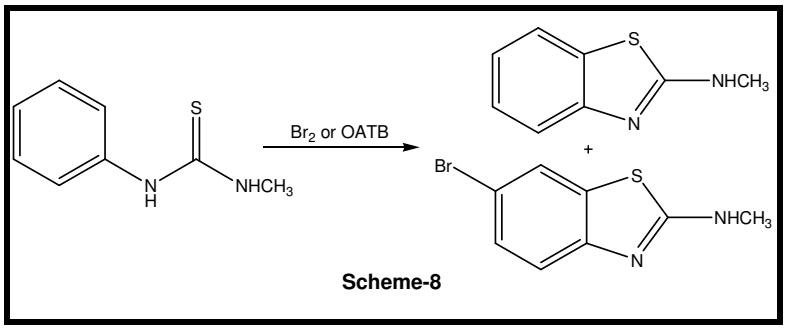
Cecchetti and co-workers[58] synthesized substituted 2-aminobenzothiazoles and carried out successive cyclocondensation with 1-bromo-2-chloroethane. Few of the

pyridobenzothiazine acids showed potent antibacterial activities against Gram-positive and Gram-negative pathogens (Scheme-7).



Scheme-7

However, Jordan *et. al.*[59] synthesized 2-aminobenzothiazoles by using benzyltrimethylammonium tribromide ($PhCH_2NMe_3Br_3$), a stable, crystalline organic ammonium tribromide (OATB), which can be readily utilized as an alternative electrophilic bromine source. It is easier to control the stoichiometry of addition with an OATB, which minimizes aromatic bromination caused by excess reagent. They developed a direct procedure from isothiocyanates and amines using tetrabutylammonium thiocyanate and benzyltrimethylammonium tribromide to afford functionalized 2-aminobenzothiazoles (Scheme-8).



Scheme-8

Benzothiazoles of biological interest

A new series of 2-(4-aminophenyl) benzothiazoles substituted in the phenyl ring and benzothiazole moiety has been synthesized by Shi and co-workers[60] by simple, high-yielding routes. The parent molecule 4-(benzo[*d*]thiazol-2-yl)benzenamine (figure-6) shows potent inhibitory activity *in vitro* in the nanomolar range against a panel of human breast cancer cell lines, activity against the sensitive breast lines MCF-7 and MDA 468 is characterized by a biphasic dose-response relationship.

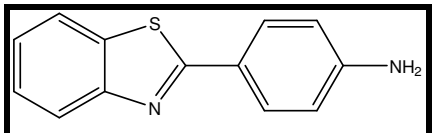
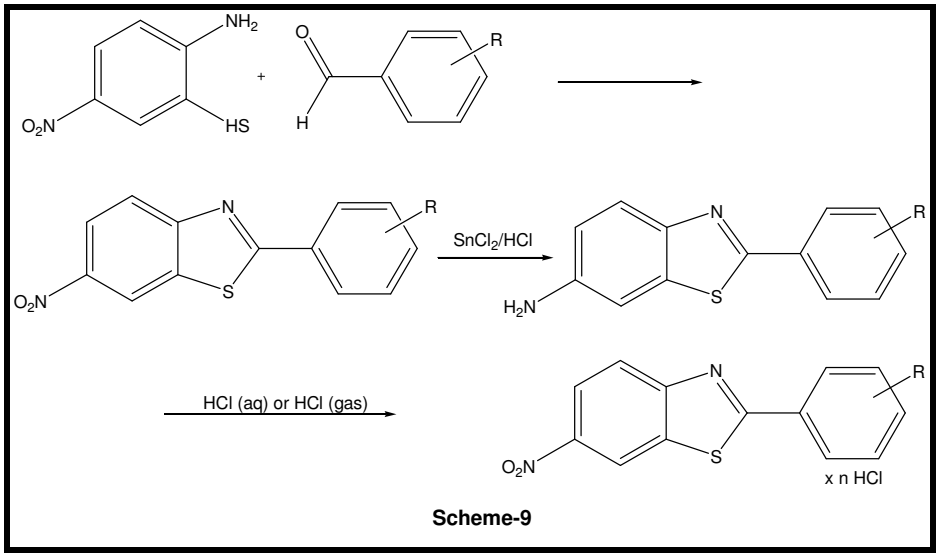


Figure-6

Racane *et. al.*[61] synthesized 6-nitro-2-(substituted-phenyl)benzothiazoles by condensation reactions of substituted benzaldehydes with 2-amino-5-nitrothiophenol. Few compounds were found to exert cytostatic activities against malignant human cell lines such as cervical (HeLa), breast (MCF-7), colon (CaCo-2), laryngeal carcinoma (Hep-2) and normal human fibroblast cell lines (WI-38). An efficient synthesis of 2-phenylbenzothiazole derivatives was carried out by the reactions outlined in scheme-9.



Scheme-9

Mackie *et. al.*[62] reported the paralysant and lethal action of some benzothiazole compounds toward *Ascaris lumbricoides* and *Fasciola hepatica.* In view of the important physiological properties[63 (a-c)] possessed by the 2-amino-6-substituted benzothiazoles, it appeared of interest to prepare the condensation products of these compounds with chloral,[64] incorporating a lipid-solubilizing group (trichloromethyl) which might assist the penetration of the compounds through the cuticle of *Ascaris lumbricoides* and thereby have a deleterious effect on the neuromuscular system of the intestinal nematodes and on other trematodes. Condensation products of aromatic and heterocyclic amines with chloral had previously been reported by Sumerford *et.*

al.[65] and Nelson *et. al.*[66] (figure-7) but no work in this respect seems to have been done with the 2-amino-6-substituted benzothiazoles.

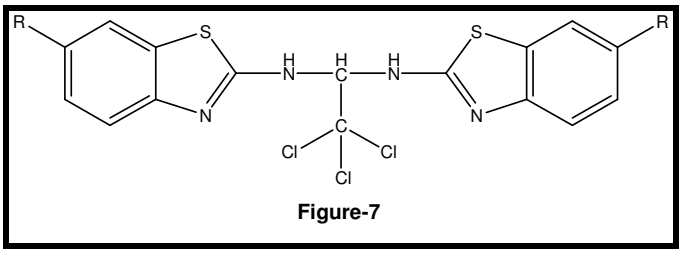
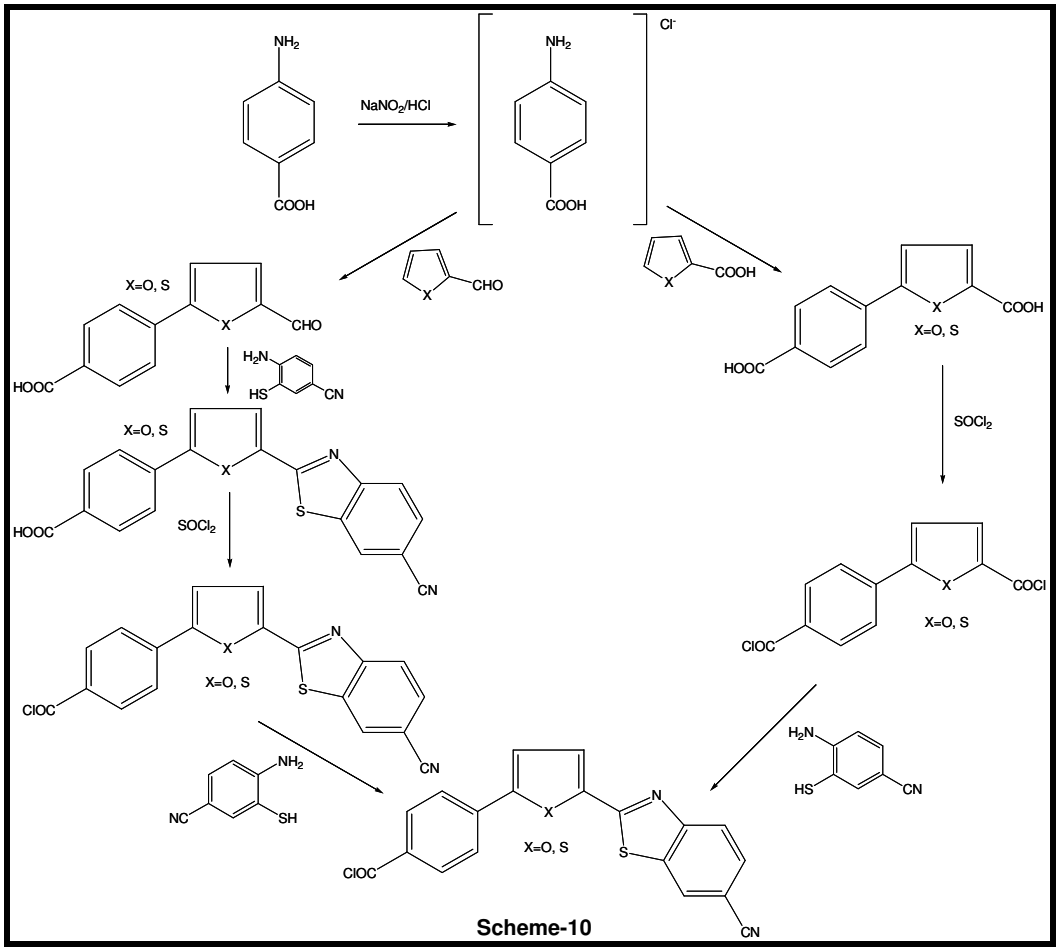


Figure-7

On the other hand, bis-benzothiazoles and substituted bis-benzothiazoles are frequently fluorescent compounds and therefore convenient for fluorimetric measurements, which could serve as a potential method for detection of binding the biologically active compounds on DNA.[67] (Scheme-10) However, there is little data describing compounds containing two benzothiazole rings attached *via* a heterocyclic system.[68]



Scheme-10

Several lines of evidence support the hypothesis that c-Jun N-terminal kinase (JNKs) plays a critical role in a wide range of diseases including cell death (apoptosis)-related disorders (neurodegenerative diseases, brain, heart, and renal ischemia, epilepsy) and inflammatory disorders (multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases). The c-Jun N-terminal kinases (JNKs) (also known as "stress-activated protein kinases") are members of the mitogen-activated protein kinase (MAPK) family along with p38 mitogen-activated protein kinases (p38 kinases) and extracellular signal-regulated kinases (ERKs).

Recently,[69] the identification of (benzoylaminomethyl) thiophene sulfonamide inhibitors such as AS600292 (figure-8) as the first potent and selective JNK inhibitor of this class that demonstrates a protective action against neuronal cell death induced by growth factor and serum deprivation.[70]

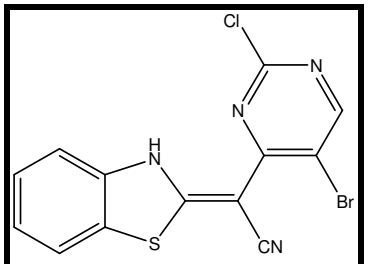
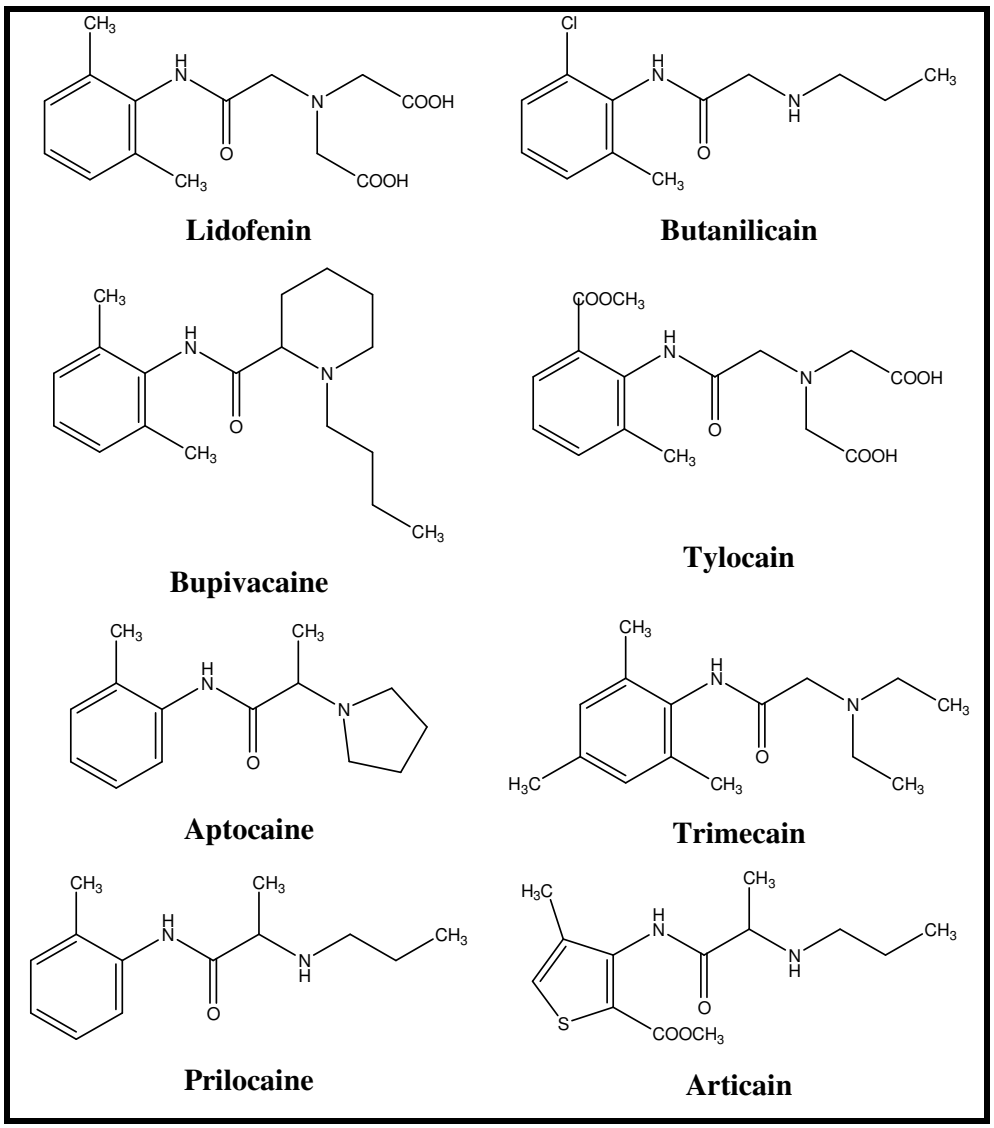
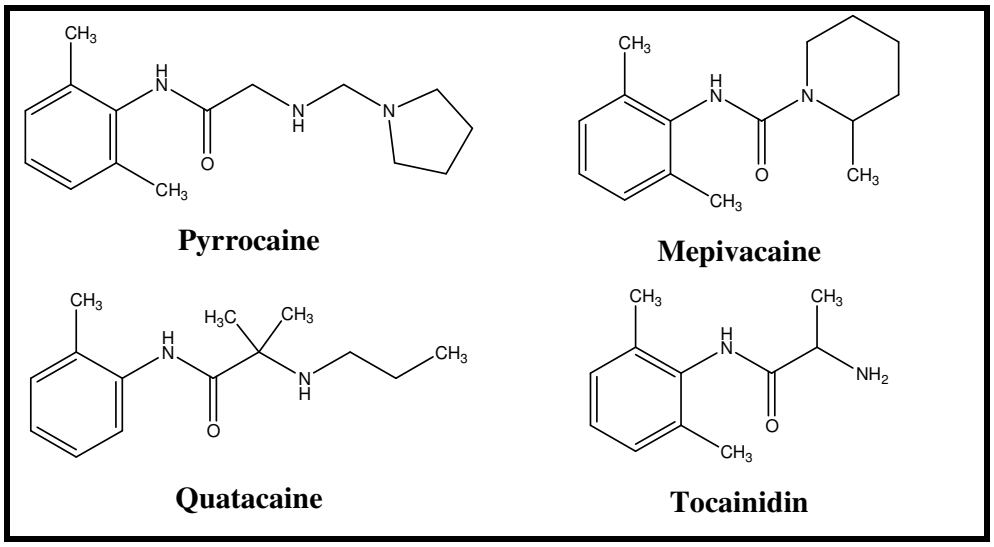


Figure-8: AS007149

Figure-9: Amide linkage containing analogues: A collection of commercial analogues based on α-aminoamide structure:[71]





A number of drugs and drug like compounds have amide linkages. Coumarin carboxamide[72] has been prepared from the corresponding coumarin carboxylic acid and 2-amino-4-phenylthiazole[73] and tested for anti-fungal and antibacterial activity.[74] (Figure-10).

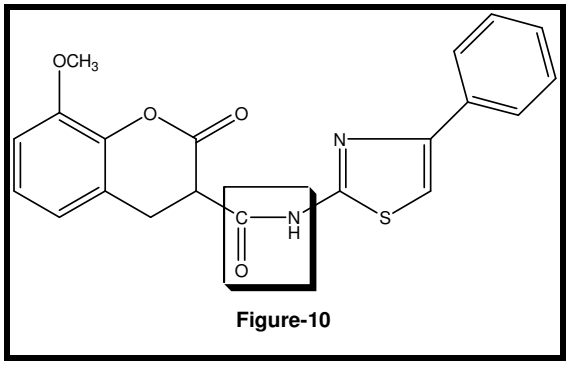


Figure-10

Mayaux and Soler *et. al.* have reported that RPR 103611, the most promising betulinic acid derivative in their studies, interfered with virus replication specifically at syncytium formation.[75,76] RPR 103611, a triterpene derivative, has been identified as a fusion inhibitor (Figure-11).

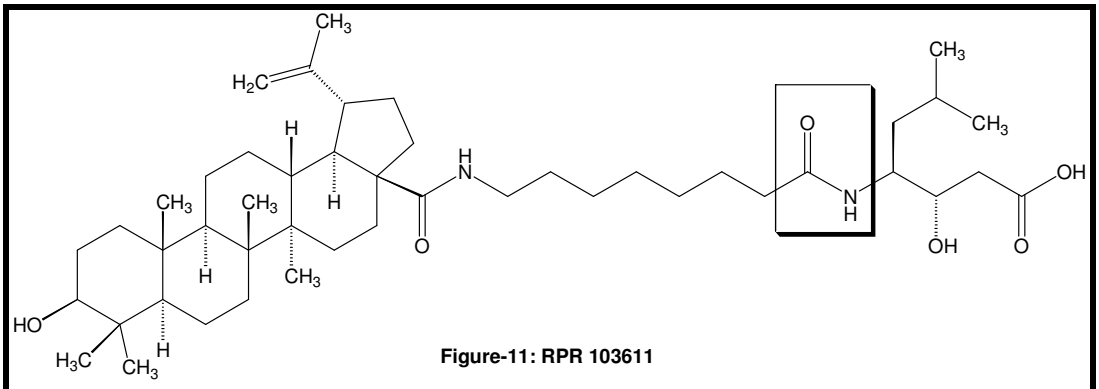
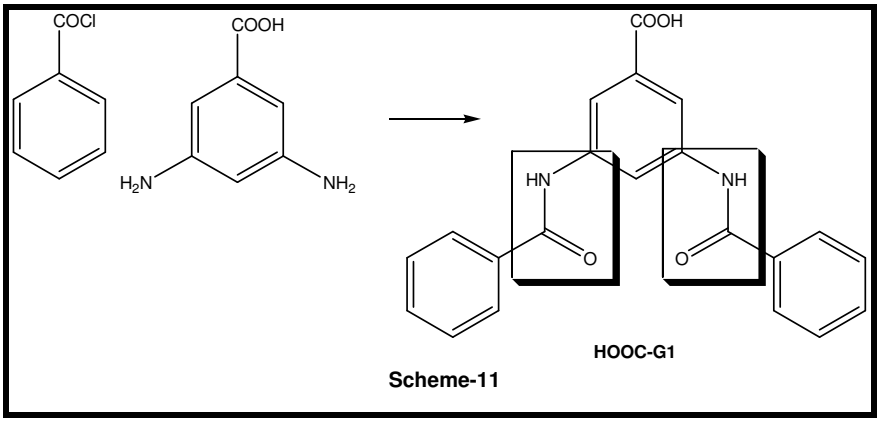


Figure-11: RPR 103611

Aromatic polyamide dendrons HOOC-G1, were synthesized by Ishida *et. al.*[77] by an orthogonal approach, which utilizes the direct condensation reaction and palladium catalyzed carbon monoxide insertion reaction in an alternating fashion to form amide linkages (Scheme-11).



HOOC-G1

Scheme-11

Nevirapine,[78] consisting of amide linkage, is used for inhibition of RT enzyme (Figure-12).

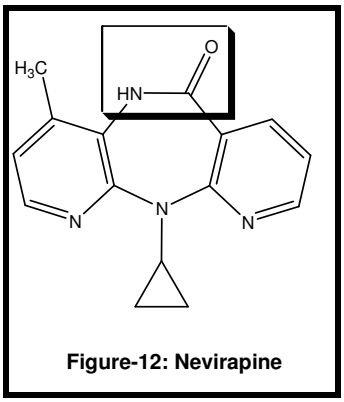


Figure-12: Nevirapine

2.2. Pharmacology

Biologically active heterocycles containing amide linkage

Guanidinothiazolecarboxamides are a novel class of antitumor agents found to be systemically active against experimental pulmonary metastates of 3LL Lewis lung carcinoma (Figure-13).

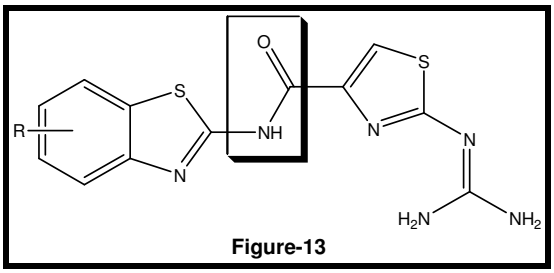
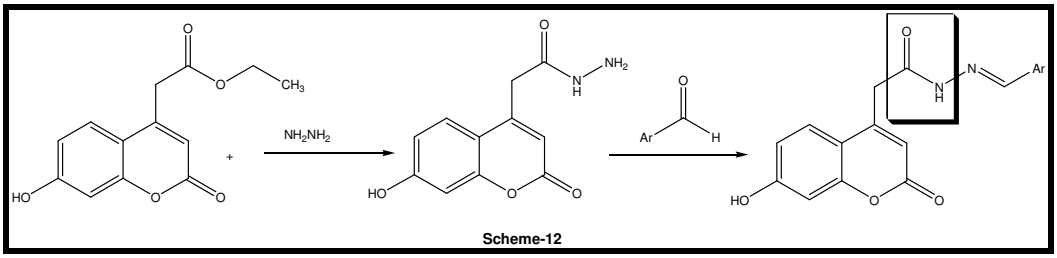


Figure-13

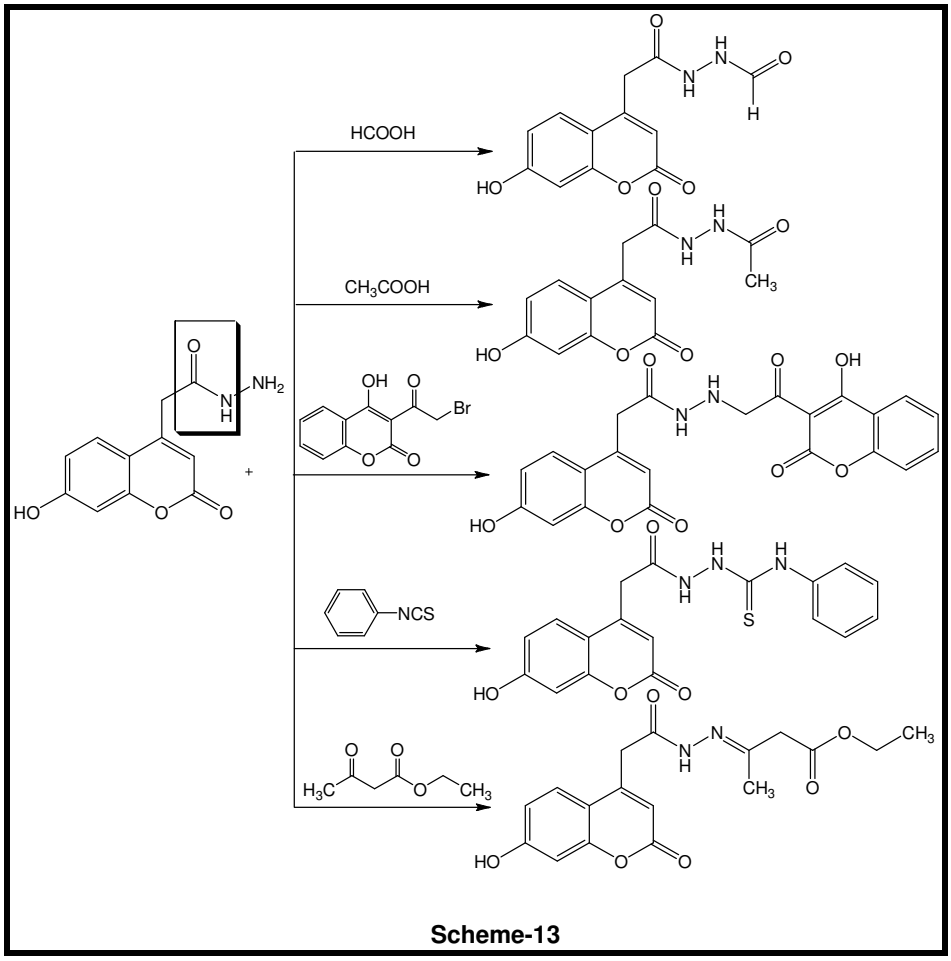
Schnur and co-workers[79] found that a series of substituted benzothiazole GTCs enhances the survival in this model by using 8 days of intraperitoneal dosing, initiated 2 days after intravenous tumor challenge. Quantitative structure-activity relationships have been studied in the GTC series with survival enhancement correlated to substituent parameters.

A large number of hydrazides have been reported to be of biological interest[80,81] while oxadiazole derivatives and thiosemicarbazides have been reported to possess antibacterial,[82,83] antifungal[84,85] and other biological activities. Furthermore, a number of substituted thiazolines and thiazolidinones were found to exhibit appreciable antimicrobial and antifungal activities[86-90] (Scheme-12).

It was therefore thought worthwhile to incorporate the hydrazide, thiosemicarbazide and oxadiazole moieties into the coumarin nucleus[91] (Scheme-13).



Scheme-12



Scheme-13

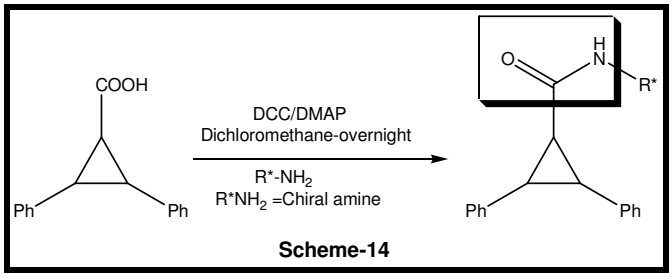
Synthesis of amide derivatives

There are number of approaches for carrying out amide bond formation from a carboxylic acid and an amine.

i. Use of an acid and an amine with direct heating to eliminate water.
ii. Use of acid chloride and an amine with the use of catalytic acid scavenger.
iii. Use of Dicyclohexyl Carbodiimide (DCC) at room temperature.

Following are the few examples:

Hassner and co-workers[92] synthesized amide linkage coupling 2,3-diphenylcyclopropane-1-carbobxylic acid with the corresponding chiral amine using DCC/DMAP (Scheme-14).



Scheme-14

Khunnawutmanotham *et. al.*[93] developed an efficient synthetic route to prepare 2-chloro-5,11-dihydro-11-ethyl-8- (phenylthio)methyl-6*H*-dipyrido[3,2-*b:*2',3'-*e*][1,4]diazepin-6-one (T1) and 2-chloro-5,11-dihydro-11- ethyl-8-(3-methoxy-phenylthio)methyl-6*H*-dipyrido[3,2-*b:*2',3'-*e*][1,4]diazepin-6-one (T2) and to evaluate their anti-HIV-1 activity.

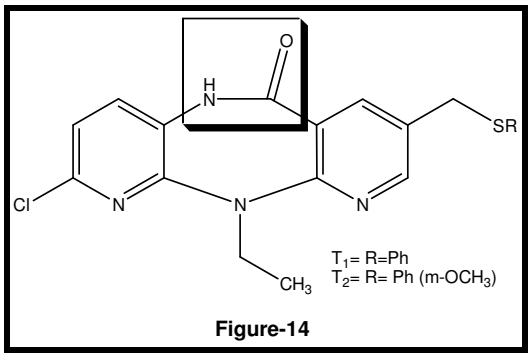
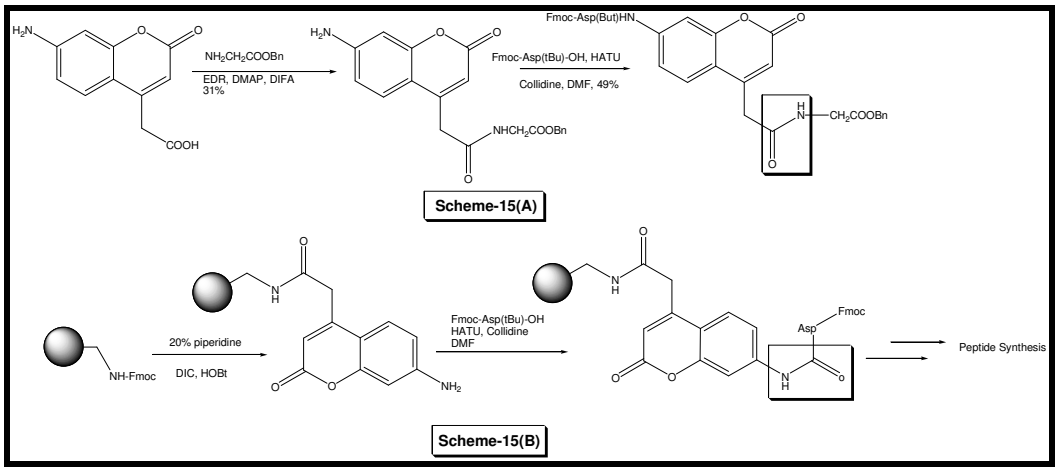


Figure-14

The use of 7-amino-4-methyl coumarin (AMC) peptide substrates for the assay of protease activity is a well established.[94] Upon conjugation of its aromatic amino group to the C-terminal carboxyl group of a peptide, however, the fluorescence of the molecule is essentially quenched, thereby rendering the resulting peptide–AMC conjugate practically non-fluorescent. Incubation of an AMC-containing peptide substrate with a protease leads to specific cleavage of the anilide bond between AMC and the conjugated peptide, which liberates the fluorogenic AMC leaving group, allowing for the simple determination of cleavage rates for individual substrates. Libraries of fluorogenic AMC peptide substrates have also been synthesized to investigate the substrate specificity of proteases.[95,96] This was accomplished by the use of a bifunctional fluorophore, 7-amino-4-carbamoylmethyl coumarin (ACC), to replace the original AMC in the library synthesis.[97]

The bifunctional fluorophore, ACC without any protection groups, was regioselectively attached to different solid supports functionalized with a primary amino group. The resulting resins were used to synthesize fluorogenic protease substrates with high yields and purity[98] (Figure-15).



Planarity of the CONH linkage

The XC(CO)NHY linkage, under the assumption Y=H called the amide linkage, or referred to as the peptide linkage, is generally assumed to have a planar structure[99] (Figure-15).

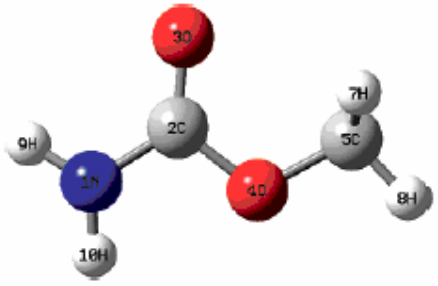


Figure-15: Conformation and atomic numbering of syn-methyl carbamate

It is shown that formamide, considered prototype for the amide linkage, is not typical as it has a planar equilibrium amide linkage corresponding to a single-minimum inversion potential around N. In contrast, several molecules containing the CONH linkage seem to have pyramidal nitrogen at equilibrium and a double-minimum inversion potential with a very small inversion barrier allowing for an effective planar ground-state structure.[100]

Many of the molecules containing the XC(CO)NHY linkage are not planar at equilibrium. The simple molecules containing the C(CO)NH linkage can be divided into three groups:

(i) All of the atoms of the molecule lie in a plane, *i.e.*, the point-group symmetry of the molecule is *Cs*.

(ii) All of the atoms of the molecule lie in a plane except pairs of hydrogen atoms which are situated symmetrically about the plane of symmetry, *i.e.*, the point-group symmetry of the molecule is *Cs.*

(iii) Molecules which do not have a plane of symmetry.

Coumarin ring linked through -CH_2-NH group with benzothiazoles were also studied and gave very good antimicrobial activity. Bhawsar *et. al.*[101] have proved that the

Mannich bases of 4-methyl-7-hydroxy coumarins with various aliphatic amines[102] and those derived from benzoxazoles have been found to possess antimicrobial and also CNS stimulating activity.

Antifungal activity of 4-methyl-7-hydroxy/acetoxy coumarins and substituted amino benzothiazoles have been reported.[103,104] (Figure-16).

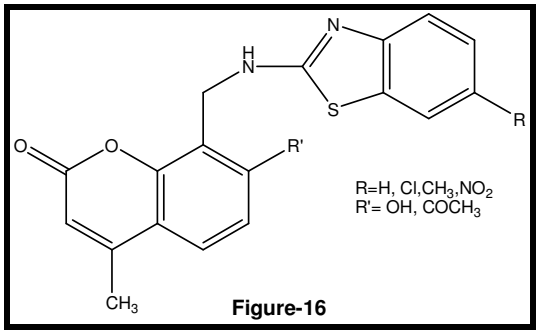


Figure-16

Adityavardhan *et. al.*[105,106] synthesized 3-(2-aminothiazolyl) derivatives of coumarins with open chain functionalities and heterocyclic systems possessing thiazole at 2-position and 3-(2-amino-4-thiazolyl) coumarin from 3-acetyl coumarin and thiourea (Figure-17) .

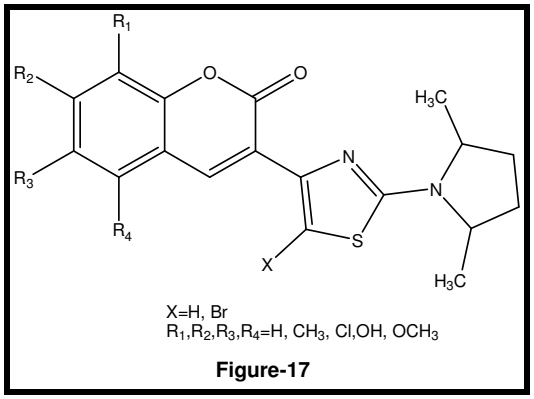


Figure-17

Various pharmacological properties have been observed in different heterocyclic moieties having -CH_2COOH group or -CH_2-CO-NH linker. They can be categorized as under:

A. Aldose reductase inhibitors

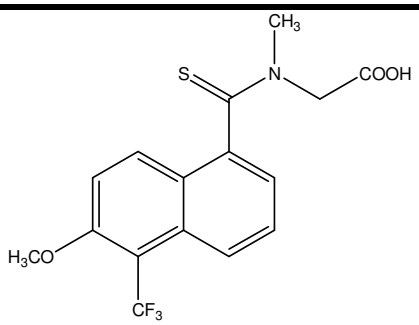
Aldose reductase has become a prime target for the development of compounds for preventing or treating chronic complications of diabetes mellitus. Experimental results generated during last few years suggest that diabetic pathology may be partly controlled through inhibition of the enzyme *aldose reductase*.[107]

Specific structural and electronic similarities of apparently diverse aldose reductase inhibitors have been observed through basic studies and the presence of an acidic proton appears to be of prime importance in inhibiting the enzyme.

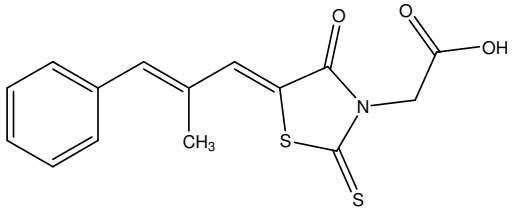
The search for aldose reductase inhibitors, which has been underway for more than 25 years, culminated in 1989 with the launch of the first aldose reductase inhibitor Tolrestat,[108] for the treatment of diabetic neuropathy, retinopathy and nephropathy.

The second aldose reductase inhibitor to reach the market was Epalrestat in 1992. Alrestatin,[109] a carboxylic acid type aldose reductase inhibitor was discovered, had an IC_{50} values between 10^{-5} to 10^{-6} against bovine lense aldose reductase. While 5, 6-benzocoumarin-4-acetic acid, being the most potent representative[110] had IC_{50} of 20 mM against bovine ladose reductase.[111] Repaglinide, oral hypoglycemic agent have a $–CH_2$-NH-CO-CH_2- linkage between two benzene ring showing antidiabetic property[112] (Figure-18).

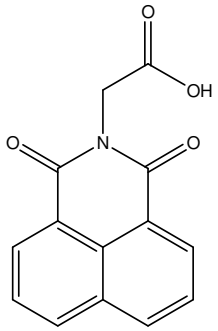
Figure-18: Aldose reductase inhibitors under clinical trials[113]



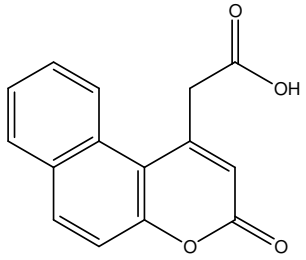
Tolrestat



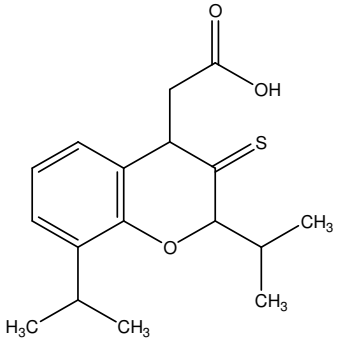
Epalrestat



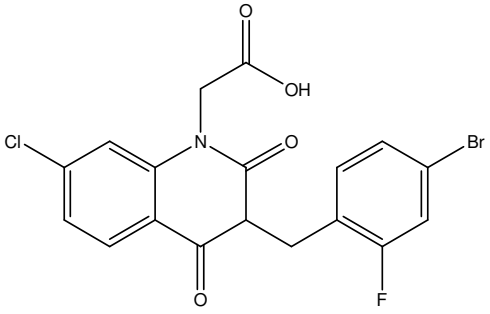
Alrestatin



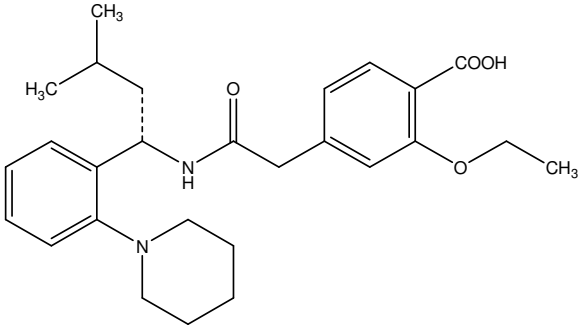
5,6–Benzocoumarin 4–aceticacid



AD - 5467



Zenarestat



Repaglinide

Figure-18

B. Antioxidant activity

Oxidants such as hydrogen peroxide and oxygen derived free radicals may play an important role in the physiopathology of tissue damage. Studies have shown that diabetes causes a thrombotic tendency in patients with increased oxidative stress.[114] Recently, it appeared that new threpeautic approaches for the prevention of diabetic complications may be found in free radical scavengers in order to limit the damage caused by oxidant stress.[115,116] Antioxidant compounds often possess an acidic proton in their chemical structures. The structures of the synthetic antioxidant derivatives, oxypurinol and nifedipine contain an acidic or related function.[117, 118].

2.3. Synthetic aspects

Coumarin-4-acetic acids were synthesized by many researchers using different methods. Limaye[8] synthesized coumarin-4-acetic acid from phenol and citric acid using conc. sulfuric acid. Dixit and Gokhle[10] condenced phenols with acetone dicarboxilic acids in presence of concentrated sulfuric acid to afford coumarin-4-acetic acids. Dixit and Padukone[119,120] prepared 6-hydroxy coumarin-4-acetic acid from citric acid and hydroquinone. 7-Hydroxy coumarin-4-acetic acid was prepared from resorcinol and acetone-dicarboxylic acid in presence of different Lewis catalysts like alluminium chloride, phosphporous oxychloride, phosphorous pentoxide or thionyl chloride under different reaction time and temperature conditions.

2.4. Present work

Several coumarin-4-acetic acids were prepared by Pechmann condensation of appropriate phenols and citric acid using sulfuric acid as a condensing agent (Figure-19).

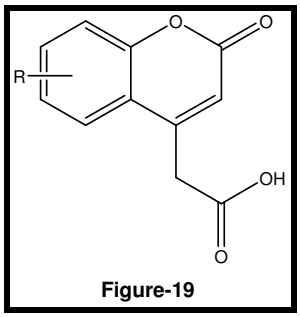


Figure-19

In the present work, mono-methyl as well as di-methyl coumarin-4-acetic acids were synthesized. Moreover, 7-hydroxylation in coumarin systems found to possess excellent pharmacodynamic properties.[121] While 5,6-benzocoumarin-4-acetic acid and 7,8-benzocoumarin-4-acetic acid were synthesized particularly to correlate with the pharmacological study. It is interesting to note the pronounced anti-diabetic nature of the later compound in light of former's activity results.

In well known Hantzsch synthesis,[122] a reaction of 2-haloketone with thiourea and alcohol gave thiazole. 4-(Substituted phenyl)-2-amino thiazoles were also prepared by using acetophenone, thiourea and Iodine. Straley and Adams[123] used β-ketoesters for the preparation of thiazoles. The 5th position of aminothiazole is highly reactive towards electophilic substitution reaction.

Taking into account, pharmacological active pharmacophores like coumarin and benzothiazole, few heterocycles of the type below were prepared by direct fusion of coumarin-4-acetic acid with 2-amino benzothiazoles at high temperature (Figure-20).

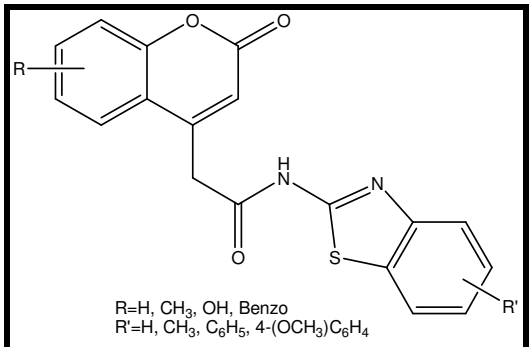


Figure-20

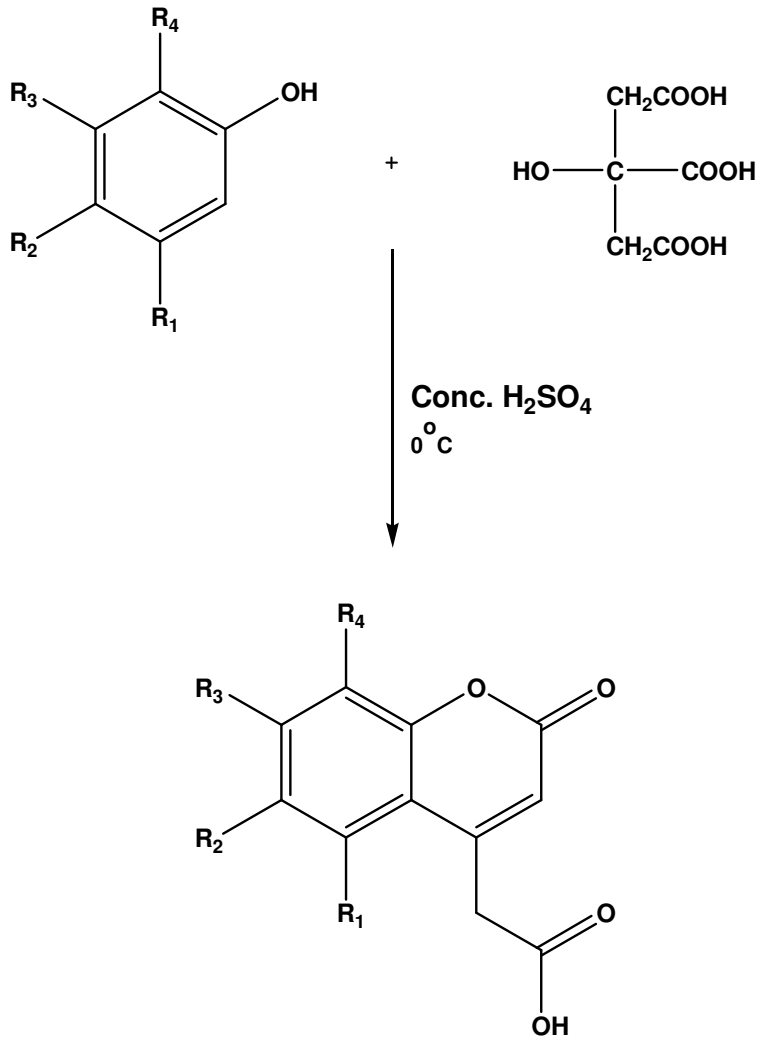
Modifications

Method-1: *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl) acetamides were synthesized in three steps.

1. The formation of coumarin-4-acetic acids.
2. The formation of coumarin-4-acetic acids into acid chlorides by using excess thionyl chloride. It was taken without further purification in next step.
3. The condensation of coumarin-4-acetic acid chlorides and 2-aminobenzothiazoles in presence of pyridine using benzene as a solvent.

Method 2: An alternate method is a single step method, where a mixture of coumarin-4-acetic acid and 2-amino benzothiazole were heated at high temperature on sand bath. In both the methods, the purity of compounds were monitered by TLC (Acetone:Benzene:: 1:1). The purity as well as the yields were found better in the later method and thus, this has been found to be very quick and efficient method for the condensation reactions between 2-amino thiazoles and coumarin-4-acetic acids.

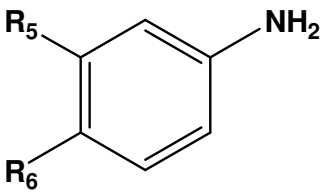
2.5. REACTION SCHEME-I



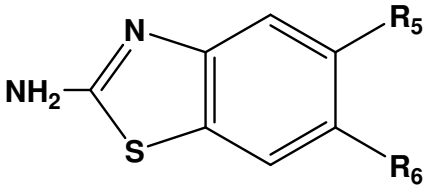
Where, R_1, R_2, R_3, R_4= OH, CH_3, H, C_6H_5, NH_2.

Synthesis of coumarin-4-acetic acid

REACTION SCHEME-II



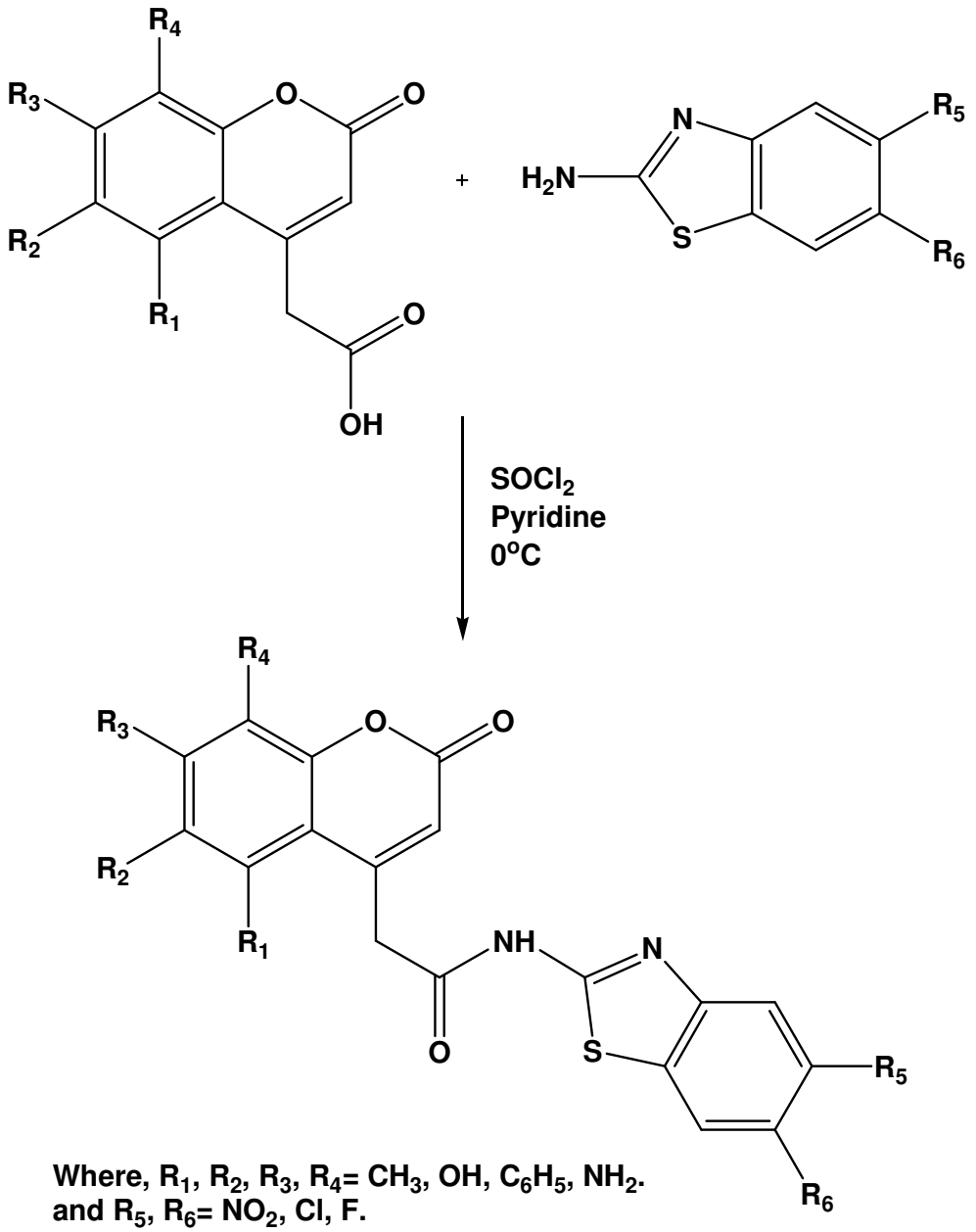
KSCN
Br_2 in gl. acetic acid
0^0C



Where R_5, R_6= NO_2, Cl, F.

Synthesis of 2-amino benzothiazole

REACTION SCHEME-III



Where, R_1, R_2, R_3, R_4= CH_3, OH, C_6H_5, NH_2.
and R_5, R_6= NO_2, Cl, F.

Condensation of coumarin-4-acetic and 2-amino benzothiazole

2.6. Experimental

General method for preparation of coumarin-4-acetic acid

A mixture of citric acid monohydrate (0.1 M) and 28 ml of conc. sulphuric acid was stirred at room temperature for sixty minutes and then slowly heated to 70^{o}C. After half an hour at this temperature, with stirring throughout, the evolution of carbon monoxide had slackened and the clear yellow coloured solution was rapidly cooled to 0^{o}C. To this stirred solution, phenol (0.08 M) was added and 11.2 ml of conc. sulphuric acid, each in three equal portions, at a rate that the temperature does not exceed 10^{o}C. The resulting solution was stored at 0^{o}C for sixteen hours, poured into ice, and the resulting crystalline precipitate was filtered off and washed thoroughly with water. It was then treated with 10% sodium bicarbonate solution and then filtered. The filterate, on acidification gave coumarin-4-acetic acids. The bicarbonate insoluble portion is 4-methyl coumarin. The purity of the compound is checked by TLC. (Acetone: Benzene :: 1:1). The coumarin 4-acetic acid derivatives were similarly prepared by using different phenols. The physical data and Rf value of various coumarin 4-acetic acids are recorded in the Table No. 1.

General method for preparation of coumarin-4-acetic acid chloride

A mixture of coumarin-4-acetic acid (0.1 M) and thionyl chloride (0.5 M) was refluxed for 6-8 hours in water bath. Excess of thionyl chloride was distilled off and crude coumarin-4-acetic acid chloride obtained, was used immediately for further reaction without purification.

General method for preparation of 2-amino benzothiazole

Aniline (0.2 M), potassium thiocyanate (0.4 M) and 500 ml of glacial glacial acetic acid were taken in a flask and stirred continuously with mechanical stirring. Bromine (0.3 M) in 500 ml of glacial glacial acetic acid was added dropwise to this mixture, the temperature being kept below 30-35^{o}C. Stirring was continued for an additional 1 hr after the bromine addition. The solution was filtered and the filterate was then basified with NH_4OH and the precipitated solid was collected and washed with water, to give the desired 2-amino benzothiazole. It was finally recrystallized with methanol. The purity of the compounds was checked by TLC. (Acetone: Benzene :: 1:1).

The physical data and Rf value of various 2-amino benzothialole were recorded in the Table No. 2.

Preparation of 2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo [*d*]thiazole-2-yl)-2-(2-oxo-2*H*-benzo[*h*]chromen-4-yl)acetamide (JT-17)

Method-1: The reaction of coumarin-4-acetic acid chloride and 2-aminothiazole
Method-2: The fusion of coumarin-4-acetic acid and 2-aminothiazole.

Method-1

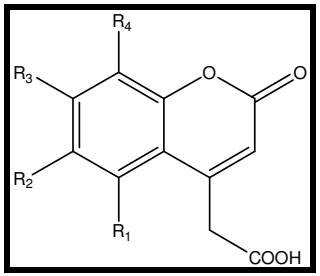
6-Nitro-2-aminobenzothiazole (0.1 M) was taken in pyridine (10-12 ml) and was stirred at 0^0C. 6,8-dimethyl coumarin-4-acetic acid chloride (0.1 M) was added dropwise to the above solution within 30 minutes. The colour of the solution changes and becomes dark, which was further stirred for two hours. The resultant mass was poured into crushed ice to get crude 2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-netribenzo[*d*]thiazole-2-yl)-2-(2-oxo-2*H*-benzo[*h*]chromen-4-yl)acetamide,which was washed with diethyl ether, filtered and dried. It was finally recrystallized from ethanol. M.p. 112-114^{o}C, Yield 56 %. Elemental analysis: [Calcd: C, 58.67; H, 3.69; N, 10.26. Found C, 58.63; H, 3.66; N, 10.21].
Similarly, the other compounds were also prepared by using different coumarin-4-acetic acids and 2-aminobenzothiazoles.

Method-2

The 6, 8-dimethyl coumarin-4-acetic acid (0.005 M) and 6-nitro-2-amino benzothiazole (0.005 M) were thoroughly mixed together and fused at 180-200^{o}C for one hour on a sand bath. The reaction mass was cooled, some water (25-30 ml) was added to the reaction mass and further heated for one hour in a boiling water bath. The crude mass separated, filtered, dried and purified by first washing with 5% sodium bicarbonate solution to remove unreacted coumarin-4-acetic acid and then by distilled water. It was further washed with 5% hydrochloric acid and again with distilled water. It was filtered, dried and recrystallized from ethanol. m.p. 112-114^{o}C, Yield 56 %.

Similarly, the other compounds have also been prepared using various 2-amino benzothiazoles. The purity of the compounds was checked by TLC.

2.7. Table 1: Physical data of coumarin-4-acetic acids

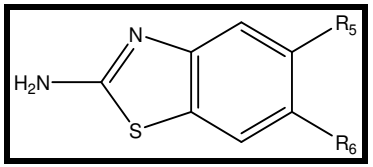


Sr. No.	Substitution				Moleular formula	Molecular weight	Melting point (^oC)	Rf value	Colour	% Yield
	R_1	R_2	R_3	R_4						
1	H	H	OH	H	$C_{11}H_8O_5$	220.18	206-208[a]	0.58	White	68
2	H	H	H	CH_3	$C_{12}H_{10}O_4$	218.21	202-204	0.56	White	54
3	H	H	CH_3	H	$C_{12}H_{10}O_4$	218.21	204-206	0.53	Off white	58.5
4	H	CH_3	H	H	$C_{12}H_{10}O_4$	218.21	184-185	0.55	Pale white	63.8
5	H	H	CH_3	CH_3	$C_{13}H_{12}O_4$	232.23	205-206	0.52	Pink	69
6	H	CH_3	H	CH_3	$C_{13}H_{12}O_4$	232.23	206-208	0.49	Off white	58
7	--Benzo--		H	H	$C_{15}H_{10}O_4$	254.24	208-210	0.48	Dull yellow	61
8	H	H	--Benzo--		$C_{15}H_{10}O_4$	254.24	210-212	0.46	Carrot pink	59

TLC Solvent system: Acetone: Benzene = 1:1

Ref.: (1) Laskowski, S. C.; Clinton, R. O. Coumarins. II. Derivatives of Coumarin-3- and -4-Acetic Acids, *J. Am. Chem. Soc*. **1950**, 72, 3987-3991. (2) Dey, B. B. *J. Chcm. Soc.* **1915**, 107, 1606. (a= Reported m. p.: 204-206^{o}C)

2.7. Table 2: Physical data of 2-amino benzothiazoles

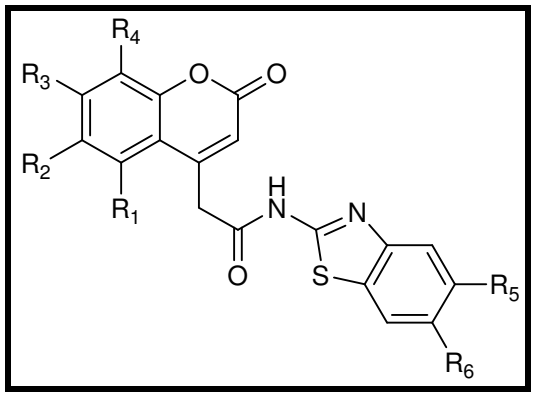


Sr. No.	Substitution		Molecular formula	Molecular weight	Melting point (^oC)	Rf value	Colour	% Yield
	R_5	R_6						
1	H	NO_2	$C_7H_5N_3O_2S$	195	174-176	0.52	Orange	42
2	H	Cl	$C_7H_5ClN_2S$	184	186-188	0.54	Pale yellow	64
3	H	F	$C_7H_5FN_2S$	168	168-170	0.48	Greenish white	57
4	Cl	F	$C_7H_4ClFN_2S$	202	194-196[b]	0.58	Pale white	68
5	H	OCH_3	$C_8H_8N_2OS$	180	152-154	0.46	Brownish black	46

TLC Solvent system: Acetone: Benzene = 5:5

Ref.: Cecchetti, V. et al. *J. Med Chem.* **1987***,* 30, 465-473.
(b= Reported m.p.: 189-192^{o}C)

2.7. Table 3: *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)acetamides



Code	Substitution						Molecular formula	Molecular weight	Melting point (^{o}C)	Rf value	% Yield
	R_1	R_2	R_3	R_4	R_5	R_6					
JT-1	H	H	H	CH_3	H	NO_2	$C_{19}H_{13}N_3O_5S$	395.38	130-132	0.58	54
JT-2	H	H	H	CH_3	H	Cl	$C_{19}H_{13}ClN_2O_3S$	384.83	160-162	0.55	58
JT-3	H	H	H	CH_3	H	F	$C_{19}H_{13}FN_2O_3S$	368.38	106-108	0.54	61
JT-4	H	H	H	CH_3	Cl	F	$C_{19}H_{12}ClFN_2O_3S$	402.82	140-142	0.57	63
JT-5	H	H	CH_3	H	H	NO_2	$C_{19}H_{13}N_3O_5S$	395.38	192-194	0.48	58

2.7. Table 3 (contd.): *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)acetamides

Code	Substitution						Molecular formula	Molecular weight	Melting point (^oC)	Rf value	% Yield
	R_1	R_2	R_3	R_4	R_5	R_6					
JT-6	H	H	CH_3	H	H	Cl	$C_{19}H_{13}ClN_2O_3S$	384.83	118-120	0.49	56
JT-7	H	H	CH_3	H	H	F	$C_{19}H_{13}FN_2O_3S$	368.38	136-138	0.56	51
JT-8	H	H	CH_3	H	Cl	F	$C_{19}H_{12}ClFN_2O_3S$	402.82	188-190	0.61	48
JT-9	H	CH_3	H	H	H	NO_2	$C_{19}H_{13}N_3O_5S$	395.38	110-112	0.59	43
JT-10	H	CH_3	H	H	H	Cl	$C_{19}H_{13}ClN_2O_3S$	384.83	118-120	0.60	63
JT-11	H	CH_3	H	H	H	F	$C_{19}H_{13}FN_2O_3S$	368.38	98-100	0.46	61
JT-12	H	CH_3	H	H	Cl	F	$C_{19}H_{12}ClFN_2O_3S$	402.82	116-118	0.62	59

2.7. Table 3 (contd.): *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)acetamides

Code	Substitution						Molecular formula	Molecular weight	Melting point (^oC)	Rf value	% Yield
	R_1	R_2	R_3	R_4	R_5	R_6					
JT-13	H	H	CH_3	CH_3	H	NO_2	$C_{20}H_{15}N_3O_5S$	409.41	124-128	0.61	54
JT-14	H	H	CH_3	CH_3	H	Cl	$C_{20}H_{15}ClN_2O_3S$	398.86	152-158	0.55	58
JT-15	H	H	CH_3	CH_3	H	F	$C_{20}H_{15}FN_2O_3S$	382.40	148-154	0.53	60
JT-16	H	H	CH_3	CH_3	Cl	F	$C_{20}H_{14}ClFN_2O_3S$	416.85	142-146	0.58	61
JT-17	H	CH_3	H	CH_3	H	NO_2	$C_{20}H_{15}N_3O_5S$	409.41	112-114	0.62	63
JT-18	H	CH_3	H	CH_3	H	Cl	$C_{20}H_{15}ClN_2O_3S$	398.86	96-98	0.60	56
JT-19	H	CH_3	H	CH_3	H	F	$C_{20}H_{15}FN_2O_3S$	382.40	136-138	0.62	58

2.7. Table 3 (contd.): *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)acetamides

Code	Substitution						Molecular formula	Molecular weight	Melting point (^oC)	Rf value	% Yield
	R_1	R_2	R_3	R_4	R_5	R_6					
JT-20	H	CH_3	H	CH_3	Cl	F	$C_{20}H_{14}ClFN_2O_3S$	416.85	104-106	0.53	49
JT-21	H	H	OH	H	H	NO_2	$C_{18}H_{11}N_3O_6S$	397.36	186-188	0.57	55
JT-22	H	H	OH	H	H	Cl	$C_{18}H_{11}ClN_2O_4S$	386.80	184-186	0.59	52
JT-23	H	H	OH	H	H	F	$C_{18}H_{11}FN_2O_4S$	370.35	188-190	0.52	56
JT-24	H	H	OH	H	Cl	F	$C_{18}H_{10}ClFN_2O_4S$	404.79	208-210	0.49	58
JT-25	H	H	--Benzo--		H	OCH_3	$C_{23}H_{16}N_2O_4S$	416.66	122-124	0.52	67
JT-26	--Benzo--		H	H	H	OCH_3	$C_{23}H_{16}N_2O_4S$	416.66	136-138	0.57	74

2.8. Spectral study

Infra Red spectra

Infra Red Spectra were taken on SHIMADZU IR-435 Spectrometer using KBr Pellet method. The characteristic carbonyl group in coumarin moiety is observed at 1710-1720 cm^{-1}, while carbonyl value of –CONH- peaks are observed in the range 1630-1690 cm^{-1}. In some of the compounds, the moisture showed a broad peak between 3000-3200 cm^{-1}. Secondary amine (> NH) observed a broad peak between 3000-3200 cm^{-1}, -OH appeared at 3440 cm^{-1} as a broad band. A (>C=N) str. is observed at 1620 cm^{-1} while (>C=S) str. Was observed at 1132-1178 cm^{-1}. The ether (C-O-C) and thioether (C-S-C) were observed at 1262-1283 str., 1065-1069 str. and 746-773 cm^{-1}, repectively. Monosubstitution at C_6 as well as C_7 of coumarin ring showed the frequency between 860-880 cm^{-1}.

^{1}H NMR spectra

^{1}H NMR Spectra were recorded on a Bruker AC 400 MHz FT-NMR Spectrometer using TMS (Tetramethyl Silane) as an internal standard and DMSO-d_6 as a solvent. In the NMR spectra of *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)acetamides various proton values of methylene (-CH_2), methyne (-CH), methoxy (-OCH_3), methyl (-CH_3) and aromatic protons (Ar-H) etc. were observed as under.

The values for methylene (-CH_2) proton is observed between δ 4,45-4.55 ppm. In some cases, the value of methylene proton differs to δ 5.20 and 5.43 ppm. The C6 protons of methoxy group of benzothiazole observed at δ 3.61 ppm. Aromatic protons shows the multiplet between δ 6.71-8.54 δ ppm. The signal due to NH proton of (>C=O-NH) group was observed at 8.5 δ ppm value.

Mass spectra

The mass spectrum of compounds were recorded by GCMS-QP2010 spectrometer (EI method). The mass spectrum of compounds was obtained by positive chemical ionization mass spectrometry. The molecular ion peak and the base peak in all compounds were clearly obtained in mass spectral study. The molecular ion peak (M^+) values are in good agreement with molecular formula of all the compounds synthesized.

C, H, N analysis

Elemental analysis of the compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

2.9. Spectral characterization

2-(8-Methyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*]thiazole-2-yl)acetamide (JT-1)

IR (KBr) cm^{-1}: 3155 (-NH), 1714 (>C=O), 1680 (-CONH), 1666 (C=N), 1450 (CH_2), 1334 (-CH_3, str.), 1273, 1067 (C-O-C), 1112 (>C=S), 872 (o.o.p.), 887 (mono substd.), 751 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.35 (s, 3H, -CH_3), 2.85 (s, 2H, -CH_2), 6.04 (s, 1H, CH), 6.9-8.5(m, 6H, Ar-H).

Mass: [m/e (%)], M. Wt.: 395.38, 395, 381, 351, 348, 316, 266, 244, 238, 222, 196, 188, 176, 165, 145, 134, 122, 102, 89, 79, 63, 44.

C, H, N analysis, Calculated: C, 57.72; H, 3.31; N, 10.63. **Found:** C, 57.67; H, 3.26; N, 10.61.

***N*-(6-Chlorobenzo[*d*]thiazole-2-yl)-2-(8-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-2)**

IR (KBr) cm^{-1}: 3080 (-NH), 1735 (>C=O), 1709 (-CONH), 1498 (CH_2), 1356 (-CH_3, str.), 1264, 1170 (C-O-C), 1139 (>C=S), 819(o.o.p.), 861 (mono substd.), 670 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.55 (s, 3H, -CH_3), 2.89 (s, 2H, -CH_2), 6.04 (s, 1H, CH), 7.0-8.5 (m, 6H, Ar-H).

Mass: [m/e (%)], M. Wt.: 385, 340, 266, 256, 250, 226, 222, 201, 184, 169, 160, 145, 134, 122, 102, 89, 79, 6, 44.

C, H, N analysis, Calculated: C, 59.30; H, 3.40; N, 7.28. **Found:** C, 59.26; H, 3.39; N, 7.25.

***N*-(6-Fluorobenzo[*d*]thiazole-2-yl)-2-(8-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-3)**

IR (KBr) cm^{-1}: 3068 (-NH), 1748 (>C=O), 1690 (-CONH), 1472 (CH_2), 1368 (-CH_3, str.), 1258, 1184 (C-O-C), 1156 (>C=S), 835(o.o.p.), 872 (mono substd.), 676 (C-S-C).

C, H, N analysis, Calculated: C, 61.95; H, 3.56; N, 7.60. **Found:** C, 61.92; H, 3.54; N, 7.59.

***N*-(5-Chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(8-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-4)**

IR (KBr) cm^{-1}: 3067 (-NH), 1717 (>C=O), 1680 (-CONH), 1623 (C=N), 1452 (CH_2), 1385 (-CH_3, str.), 1242, 1123 (C-O-C), 1135 (>C=S), 720(o.o.p.), 750 (mono substd.), 670 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.35 (s, 3H, -CH_3), 2.85 (s, 2H, -CH_2), 6.5 (s, 1H, CH), 7.2-8.9 (m, 5H, Ar-H).

Mass: [m/e (%)], M. Wt.: 403, 351, 293, 212, 210, 184, 174, 157, 145, 127, 122, 111, 73, 69, 44.

C, H, N analysis, Calculated: C, 56.65; H, 3.00; N, 6.95. **Found:** C, 56.62; H, 2.96; N, 6.91.

2-(7-Methyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*]thiazole-2-yl)acetamide (JT-5)

IR (KBr) cm^{-1}: 3438 (-NH), 1728 (>C=O), 1669 (-CONH), 1572 (C=N), 1451 (CH_2), 1335 (-CH_3, str.), 1250, (C-O-C), 1044 (>C=S), 750 (o.o.p.), 669 (mono substd.), 825 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.45 (s, 3H, -CH_3), 2.98 (s, 2H, -CH_2), 6.94 (s, 1H, CH), 7.1-8.9 (m, 6H, Ar-H).

Mass: [m/e (%)], M. Wt.: 395, 381, 351, 348, 316, 266, 244, 238, 222, 196, 188, 176, 165, 145, 134, 122, 102, 89, 79, 63, 44.

C, H, N analysis, Calculated: C, 56.65; H, 3.00; N, 6.95. **Found:** C, 56.62; H, 2.96; N, 6.91.

***N*-(6-Chlorobenzo[*d*]thiazole-2-yl)-2-(7-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-6)**

IR (KBr) cm^{-1}: 3424 (-NH), 1736(>C=O), 167469 (-CONH), 1578 (C=N), 1462 (CH_2), 1378 ($-CH_3$, str.), 1258, (C-O-C), 1046 (>C=S), 756 (o.o.p.), 672 (mono substd.), 832 (C-S-C).

C, H, N analysis, Calculated: C, 59.30; H, 3.40; N, 7.28. **Found:** C, 59.26; H, 3.39; N, 7.25.

***N*-(6-Fluorobenzo[*d*]thiazole-2-yl)-2-(7-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-7)**

IR (KBr) cm^{-1}: 343255 (-NH), 1742 (>C=O), 1662 (-CONH), 1646 (C=N), 1444 (CH_2), 1385 ($-CH_3$, str.), 1264, 1067 (C-O-C), 1124 (>C=S), 678 (o.o.p.), 891 (mono substd.), 755 (C-S-C).

C, H, N analysis, Calculated: C, 61.95; H, 3.56; N, 7.60. **Found:** C, 61.92; H, 3.54; N, 7.59.

***N*-(5-Chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(7-methyl-2-oxo-2*H*-chromen-4-yl) acetamideb (JT-8)**

IR (KBr) cm^{-1}: 3230 (-NH), 1729 (>C=O), 1680 (-CONH), 1695 (C=N), 1452 (CH_2), 1305 ($-CH_3$, str.), 1278, 1083 (C-O-C), 1112 (>C=S), 817 (o.o.p.), 888 (mono substd.), 644 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.2 (s, 3H, $-CH_3$), 2.85 (s, 2H, $-CH_2$), 6.9 (s, 1H, CH), 7.2-8.4 (m, 5H, Ar-H).

Mass: [m/e (%)], M. Wt.: 402, 387, 373 (100), 357, 343, 327, 297, 281, 280, 254, 248, 236, 221, 206, 195, 175, 160, 147, 133, 122, 107, 95, 78, 63, 44.

C, H, N analysis, Calculated: C, 56.65; H, 3.00; N, 6.95. **Found:** C, 56.62; H, 2.96; N, 6.91.

2-(6-Methyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*]thiazole-2-yl)acetamide (JT-9)

IR (KBr) cm^{-1}: 3332 (-NH), 1731 (>C=O), 1677 (-CONH), 1667 (C=N), 1448 (CH_2), 1333 ($-CH_3$, str.), 1277, 1048 (C-O-C), 1126 (>C=S), 817 (o.o.p.), 849(mono substd.), 749(C-S-C).

C, H, N analysis, Calculated: C, 56.65; H, 3.00; N, 6.95. **Found:** C, 56.62; H, 2.96; N, 6.91.

***N*-(6-Chlorobenzo[*d*]thiazole-2-yl)-2-(6-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-10)**

IR (KBr) cm^{-1}: 3418 (-NH), 1718 (>C=O), 1664 (-CONH), 1665 (C=N), 1448 (CH_2), 1383 (-CH_3, str.), 1294, 1082 (C-O-C), 1124 (>C=S), 778 (o.o.p.), 848 (mono substd.), 812(C-S-C).

Mass: [m/e (%)], M. Wt.: 387, 360, 346, 325, 296, 294, 228, 215, 202, 193, 176, 160, 145, 125, 111, 93, 81, 69, 4, 41.

C, H, N analysis, Calculated: C, 59.30; H, 3.40; N, 7.28. **Found:** C, 59.26; H, 3.39; N, 7.25.

***N*-(6-Fluorobenzo[*d*]thiazole-2-yl)-2-(6-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-11)**

IR (KBr) cm^{-1}: 3498 (-NH), 1718 (>C=O), 1671 (-CONH), 1649 (C=N), 1457 (CH_2), 1383 (-CH_3, str.), 1252 (C-O-C), 1124 (>C=S), 78 (o.o.p.), 843 (mono substd.), 818(C-S-C).

C, H, N analysis, Calculated: C, 61.95; H, 3.56; N, 7.60. **Found:** C, 61.92; H, 3.54; N, 7.59.

***N*-(5-Chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(6-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-12)**

IR (KBr) cm^{-1}: 3230 (-NH), 1729 (>C=O), 1680 (-CONH), 1695 (C=N), 1452 (CH_2), 1305 (-CH_3, str.), 1278, 1083 (C-O-C), 1112 (>C=S), 817 (o.o.p.), 888 (mono substd.), 644(C-S-C).

Mass: [m/e (%)], M. Wt.: 403, 351, 293, 217, 207, 184, 174 (100), 159, 145, 131, 115, 103, 91, 77, 65, 44.

C, H, N analysis, Calculated: C, 56.65; H, 3.00; N, 6.95. **Found:** C, 56.62; H, 2.96; N, 6.91.

2-(7,8-Dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*]thiazole-2-yl)acetamide (JT-13)

IR (KBr) cm^{-1}: 3417 (-NH), 1732 (>C=O), 1676 (-CONH), 1674 (C=N), 1459 (CH_2), 1383 (-CH_3, str.), 1276, 1088 (C-O-C), 1127 (>C=S), 814 (o.o.p.), 783 (mono substd.), 659(C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.32 (s, 3H, -CH_3), 2.68 (s, 2H, -CH_2), 6.25 (s, 1H, CH), 7.1-8.5 (m, 5H, Ar-H).

Mass: [m/e (%)], M. Wt.: 411, 383, 368, 353, 326, 311, 298, 285, 257, 239, 236, 211, 201, 183, 171, 152, 123, 98, 97, 71, 57, 44.

C, H, N analysis, Calculated: C, 58.67; H, 3.69; N, 10.26. **Found:** C, 58.63; H, 3.66; N, 10.21.

***N*-(6-Chlorobenzo[*d*]thiazole-2-yl)-2-(7,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetamide (JT-14)**

IR (KBr) cm^{-1}: 3398 (-NH), 1705 (>C=O), 1696 (-CONH), 1670 (C=N), 1471 (CH_2), 1305 (-CH_3, str.), 1305, 1023 (C-O-C), 1097 (>C=S), 817 (o.o.p.), 758 (mono substd.), 743(C-S-C).

C, H, N analysis, Calculated: C, 60.22; H, 3.79; N, 7.02. **Found:** C, 60.20; H, 3.78; N, 7.00.

***N*-(6-Fluorobenzo[*d*]thiazole-2-yl)-2-(7,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetamide (JT-15)**

IR (KBr) cm^{-1}: 3450 (-NH), 2917 (-CH aromatic), 1699 (>C=O), 1679 (-CONH), 1611 (C=N), 1474 (CH_2), 1350 (-CH_3, str.), 1220, 1096 (C-O-C), 1024 (>C=S), 819 (o.o.p.), 920 (mono substd.), 611(C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.4 (s, 3H, -CH_3), 2.6 (s, 2H, -CH_2), 6.4 (s, 1H, CH), 6.9-8.5 (m, 6H, Ar-H).

C, H, N analysis, Calculated: C, 62.82; H, 3.95; N, 7.33. **Found:** C, 62.76; H, 3.86; N, 7.32.

***N*-(5-Chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(7,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetamide (JT-16)**

IR (KBr) cm^{-1}: 3317 (-NH), 1708 (>C=O), 1677 (-CONH), 1678 (C=N), 1436 (CH_2), 1378 (-CH_3, str.), 1256, (C-O-C), 1117 (>C=S), 914 (o.o.p.), 764 (mono substd.), 680 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.4 (s, 3H, -CH_3), 2.8 (s, 2H, -CH_2), 8.0 (s, 1H, -NH), 7.1-8.5 (m, 4H, Ar-H).

Mass: [m/e (%)], M. Wt.: 417, 402, 387, 374, 357, 456, 320, 290, 280, 263, 251, 228, 202, 187, 175, 148, 129, 115, 111, 95, 79, 6, 44.

C, H, N analysis, Calculated: C, 57.63; H, 3.39; N, 6.72. **Found:** C, 57.62; H, 3.37; N, 6.69.

2-(6,8-Dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*] thiazole-2-yl)acetamide (JT-17)

IR (KBr) cm^{-1}: 33OO (-NH), 2948 (-CH aromatic), 1728 (>C=O), 1695 (-CONH), 1664(C=N), 1452 (CH_2), 1333 (-CH_3, str.), 1250, (C-O-C), 1O25 (>C=S), 858 (o.o.p.), 752 (mono substd.), 684 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.4 (s, 3H, -CH_3), 2.8 (s, 2H, -CH_2), 8.5 (s, 1H, -NH), 7.3-8.8 (m, 5H, Ar-H).

Mass: [m/e (%)], M. Wt.: 410, 401, 382, 373, 352, 338, 327, 292, 260, 231, 214, 195, 165, 149, 138, 122, 105, 95, 78, 63, 44.

C, H, N analysis, Calculated: C, 58.67; H, 3.69; N, 10.26. **Found:** C, 58.63; H, 3.66; N, 10.21.

***N*-(6-Chlorobenzo[*d*]thiazole-2-yl)-2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetamide (JT-18)**

IR (KBr) cm^{-1}: 341O (-NH), 2916 (-CH aromatic), 1724 (>C=O), 1681 (-CONH), 1669(C=N), 1472 (CH_2), 1320 (-CH_3, str.), 1244, (C-O-C), 1025 (>C=S), 858 (o.o.p.), 670 (mono substd.), 552 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.9 (s, 3H, -CH_3), 2.8 (s, 2H, -CH_2), 8.0 (s, 1H, -NH), 7.0-8.5 (m, 5H, Ar-H).

Mass: [m/e (%)], M. Wt.: 400, 361, 319, 300, 292, 278, 261, 234, 210, 194, 174, 168, 145, 131, 115, 108, 91, 77, 69, 44.

C, H, N analysis, Calculated: C, 60.22; H, 3.79; N, 7.02. **Found:** C, 60.20; H, 3.78; N, 7.00.

***N*-(6-Fluorobenzo[*d*]thiazole-2-yl)-2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl) acetamide (JT-19)**

IR (KBr) cm^{-1}: 3076 (-CH aromatic), 1748 (>C=O), 1680 (-CONH), 1648(C=N), 147O (CH_2), 1313 (-CH_3, str.), 1245 (C-O-C), 1024 (>C=S), 838 (o.o.p.), 674 (mono substd.), 562 (C-S-C).

C, H, N analysis, Calculated: C, 62.82; H, 3.95; N, 7.33. **Found:** C, 62.76; H, 3.86; N, 7.32.

***N*-(5-Chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-20)**

IR (KBr) cm^{-1}: 3372 (-NH), 2917 (-CH aromatic), 1718(>C=O), 1669 (-CONH), 1653 (C=N), 1457 (CH_2), 1369 (-CH_3, str.), 1243, (C-O-C), 1O25 (>C=S), 861 (o.o.p.), 845 (mono substd.), 669 (C-S-C).

C, H, N analysis, Calculated: C, 57.63; H, 3.39; N, 6.72. **Found:** C, 57.62; H, 3.37; N, 6.69.

2-(7-Hydroxy-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*]thiazole-2-yl)acetamide (JT-21)

IR (KBr) cm^{-1}: 3690 (free –OH str.), 341O (-NH), 3074 (-CH aromatic), 1714 (>C=O), 1681 (-CONH), 1629 (C=N), 1453 (CH_2), 1360 (-CH_3, str.), 1256 (C-O-C), 1023 (>C=S), 851 (o.o.p.), 751 (mono substd.), 763 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.25 (s, 2H, -CH_2), 6.05 (s, 1H, -OH), 8.0 (s, 1H, -NH), 6.7-8.8 (m, 6H, Ar-H).

Mass: [m/e (%)], M. Wt.: 397, 379, 369, 351 (100), 350, 324, 310, 295, 289, 276, 258, 245, 224, 211, 197, 184, 175, 159, 142, 130, 122, 107, 95, 82, 63, 44.

C, H, N analysis, Calculated: C, 54.41; H, 2.79; N, 10.57. **Found:** C, 54.38; H, 2.76; N, 10.55.

***N*-(6-Chlorobenzo[*d*]thiazole-2-yl)-2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl)acetamide (JT-22)**

IR (KBr) cm^{-1}: 3742 (free –OH str.), 3083 (-CH aromatic), 1743 (>C=O), 1715 (-CONH), 1539 (C=N), 1476 (CH_2), 1386 (-CH_3, str.), 1218 (C-O-C), 1023 (>C=S), 842 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.25 (s, 2H, -CH_2), 6.8 (s, 1H, -CH), 8.6 (s, 1H, -OH), 8.0 (s, 1H, -NH), 6.9-7.9 (m, 6H, Ar-H).

Mass: [m/e (%)], M. Wt.: 387 (100), 372, 360, 346, 325, 319, 296, 294, 244, 228, 213, 202, 193, 175, 160, 148, 126, 113, 108, 93, 81, 69, 44.

C, H, N analysis, Calculated: C, 55.89; H, 2.87; N, 7.24. **Found:** C, 55.87; H, 2.85; N, 7.21.

***N*-(6-Fluorobenzo[*d*]thiazole-2-yl)-2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl)acetamide (JT-23)**

IR (KBr) cm^{-1}: 3608 (free –OH str.), 3061 (-CH aromatic), 1744 (>C=O), 1699 (-CONH), 1668 (C=N), 1457(CH_2), 1314 (-CH_3, str.), 1255(C-O-C), 1157(>C=S), 845(C-S-C).

C, H, N analysis, Calculated: C, 58.37; H, 2.99; N, 7.56. **Found:** C, 58.36; H, 2.97; N, 7.53.

***N*-(5-Chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl)acetamide (JT-24)**

IR (KBr) cm^{-1}: 3643 (free –OH str.), 3030 (-CH aromatic), 1732 (>C=O), 1696 (-CONH), 1672 (C=N), 1436 (CH_2), 1390 (-CH_3, str.), 1252 (C-O-C), 1157(>C=S), 841(C-S-C).

C, H, N analysis, Calculated: C, 53.41; H, 2.49; N, 6.92. **Found:** C, 53.36; H, 2.48; N, 6.87.

***N*-(6-Methoxybenzo[*d*]thiazole-2-yl)-2-(2-oxo-2*H*-enzo[*h*]chromen-4-yl)acetamide (JT-25)**

IR (KBr) cm^{-1}: 3430 (-NH str.), 3078 (-CH aromatic), 1714 (>C=O), 1634 (-CONH), 1678 (C=N), 1602, 1587, 1534, 1486 (ring skeleton), 1423 (CH_2), 1378 (-CH_3, str.), 1245 (C-O-C), 1143 (>C=S), 836(C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.55 (s, 2H, -CH_2), 3.88 (s, 3H, -CH_3), 6.36 (s, 1H, -CH), 8.0 (s, 1H, -NH), 7.6-8.5 (m, 9H, Ar-H).

C, H, N analysis, Calculated: C, 66.33; H, 3.87; N, 6.73. **Found:** C, 66.32; H, 3.83; N, 6.69.

***N*-(6-Methoxybenzo[*d*]thiazole-2-yl)-2-(3-oxo-3*H*-benzo[*f*]chromen-1-yl)acetamide (JT-26)**

IR (KBr) cm^{-1}: 3486 (-NH str.), 3035 (-CH aromatic), 1693 (>C=O), 1624 (-CONH), 1657 (C=N), 1636, 1596, 1554, 1474 (ring skeleton), 1453 (CH_2), 1393 (-CH_3, str.), 1234 (C-O-C), 1165 (>C=S), 822 (C-S-C).

^{1}H NMR 400 MHz: (DMSO-d_6, δ ppm): 2.9 (s, 2H, -CH_2), 3.85 (s, 3H, -CH_3), 6.48 (s, 1H, -CH), 8.0 (s, 1H, -NH), 7.0-8.6 (m, 9H, Ar-H).

Mass: [m/e (%)], M. Wt.: 416, 397, 379, 351 (100), 350, 324, 310, 295, 289, 276, 258, 245, 224, 211, 197, 184, 175, 159, 142, 130, 122, 107, 95, 82, 63, 44.

C, H, N analysis, Calculated: C, 66.33; H, 3.87; N, 6.73. **Found:** C, 66.29; H, 3.85; N, 6.70.

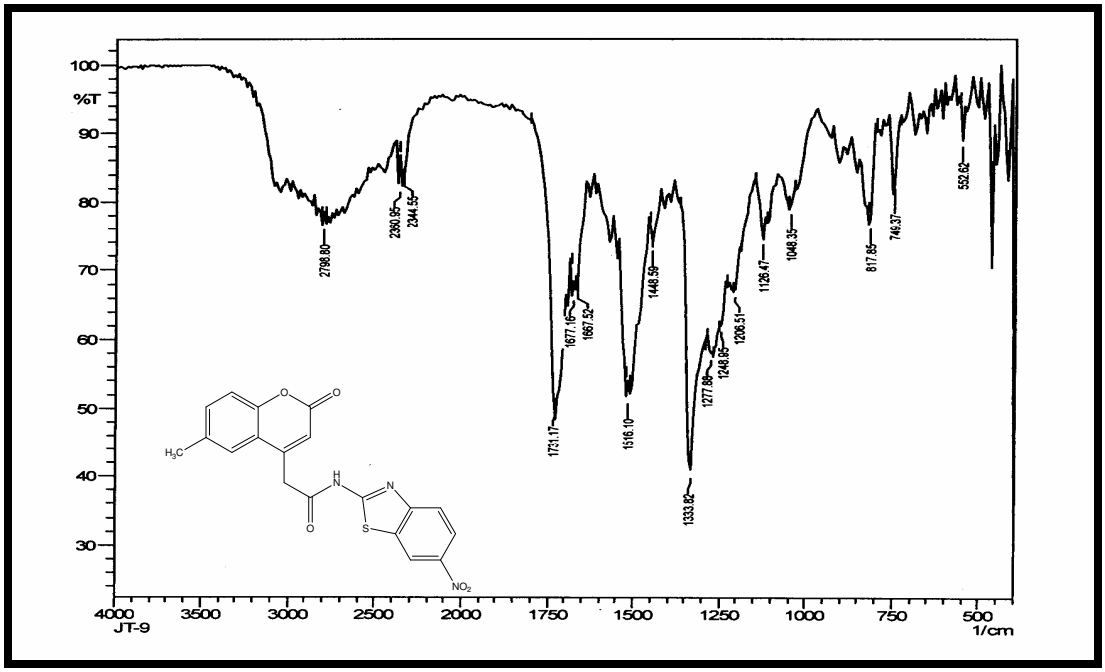
2.10. Conclusion

Total 26 *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl)acetamides were synthesized in this chapter and in few cases, process development was also undertaken to improve the yields. The compounds are characterized by IR, ^{1}H NMR, Mass spectral data and elemental analysis.

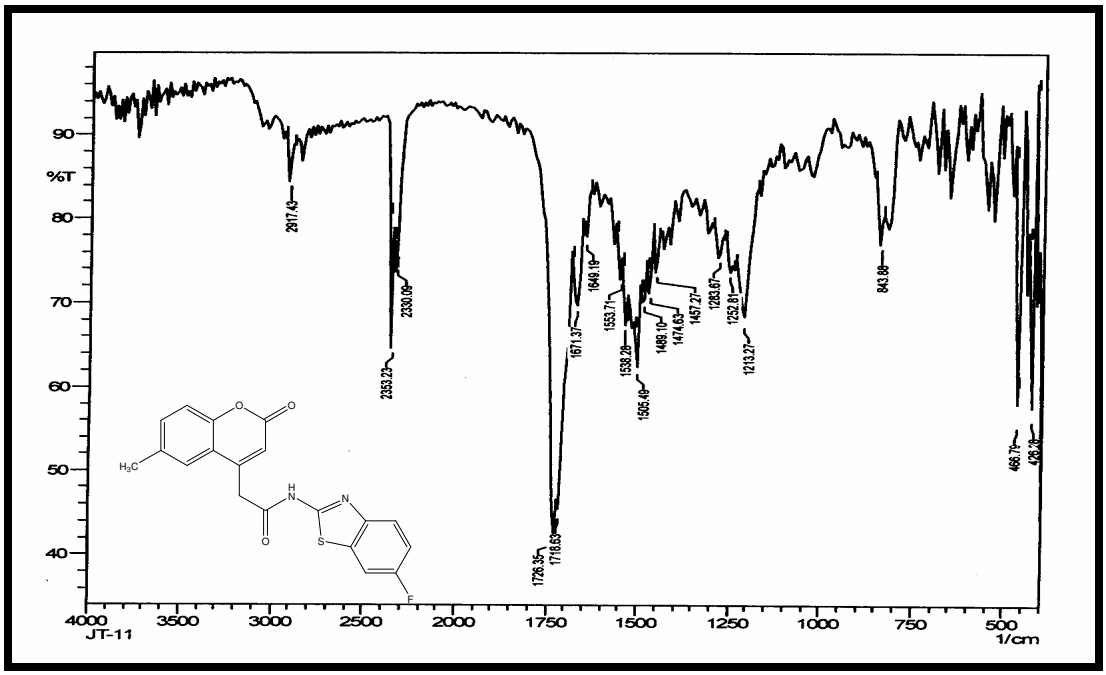
All the newly synthesized compounds have been sent for anti-viral activity and the results are awaited.

2.11. Spectra of some *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl) acetamide derivatives

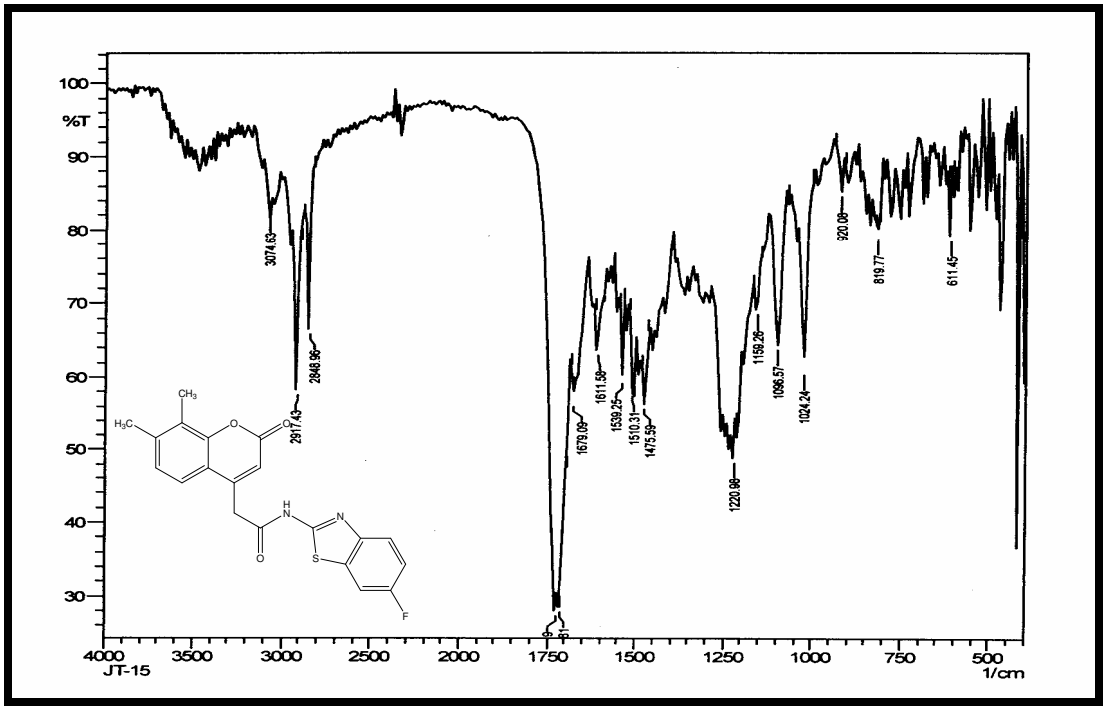
Infra Red spectrum of 2-(6-methyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*] thiazole-2-yl) acetamide (JT-9)



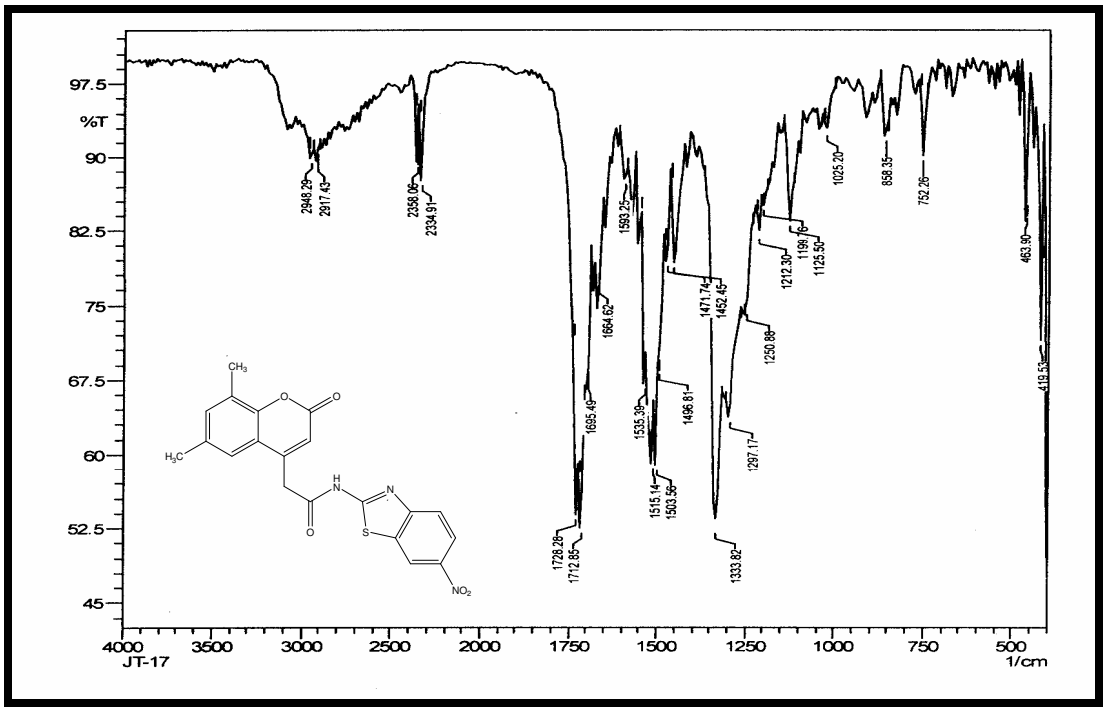
Infra Red spectrum of N-(6-fluorobenzo[*d*]thiazole-2-yl)-2-(6-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-11)



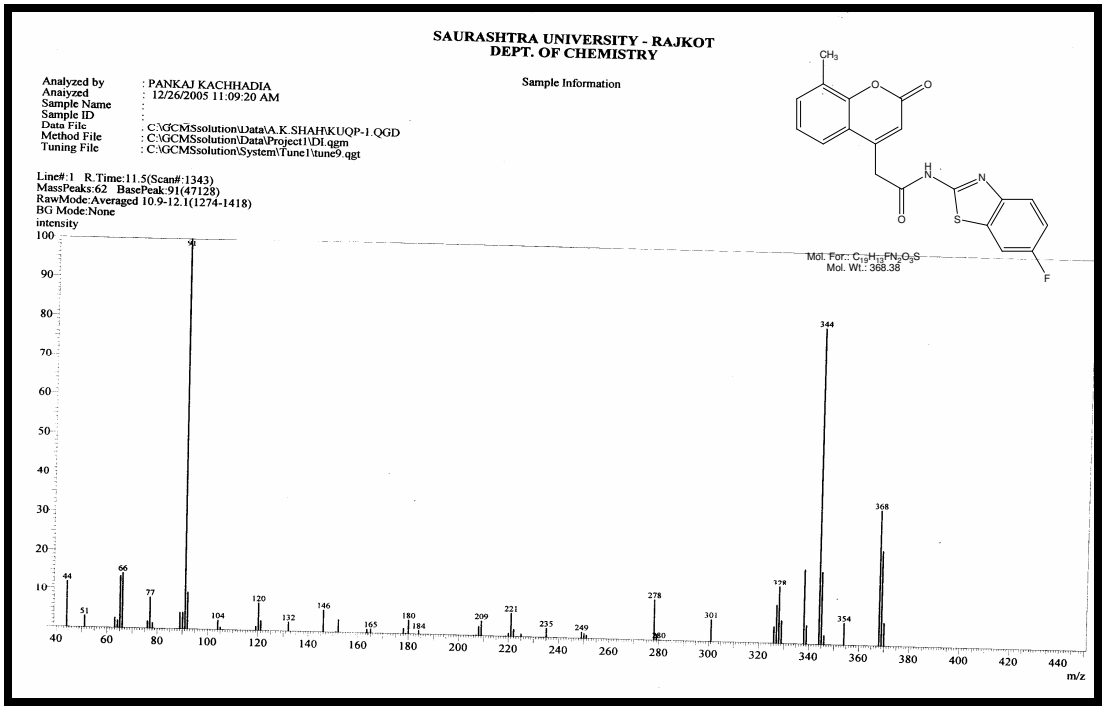
Infra Red spectrum of *N*-(6-fluorobenzo[*d*]thiazole-2-yl)-2-(7,8-dimethyl -2-oxo-2*H*- chromen-4-yl)acetamide (JT-15)



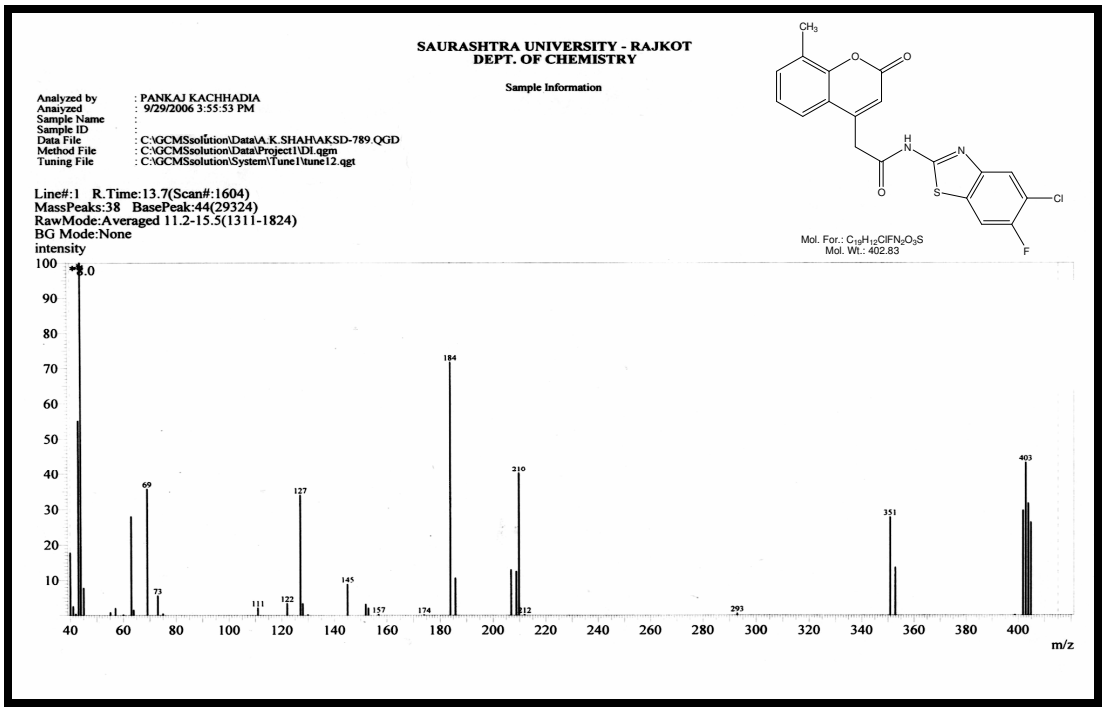
Infra Red spectrum of 2-(6, 8-dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*] thiazole-2-yl)acetamide (JT-17)



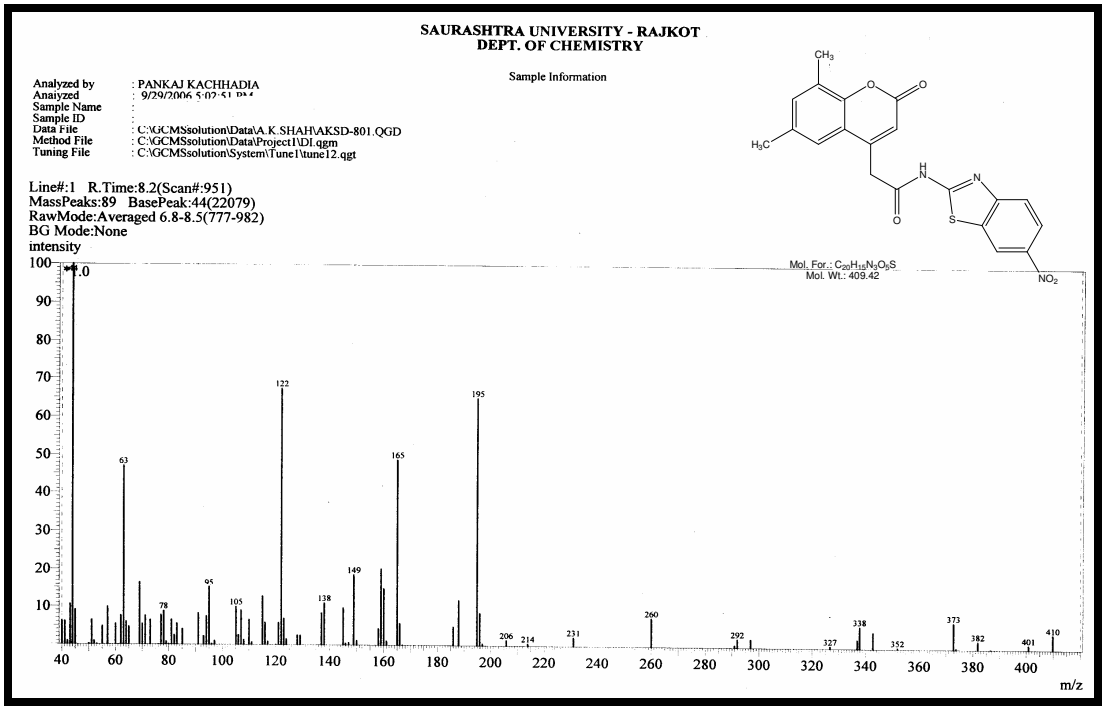
Mass spectrum of *N*-(6-fluorobenzo[*d*]thiazole-2-yl)-2-(8-methyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-3)



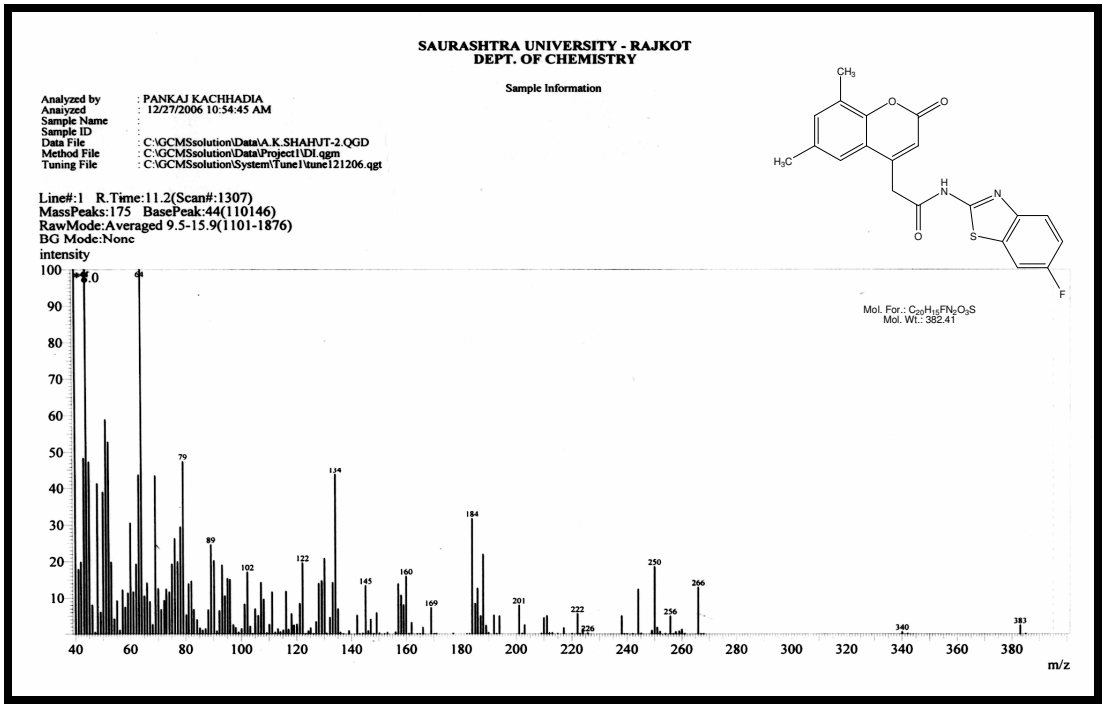
Mass spectrum of *N*-(5-chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(8-methyl-2-oxo-2*H*- chromen-4-yl)acetamide (JT-4)



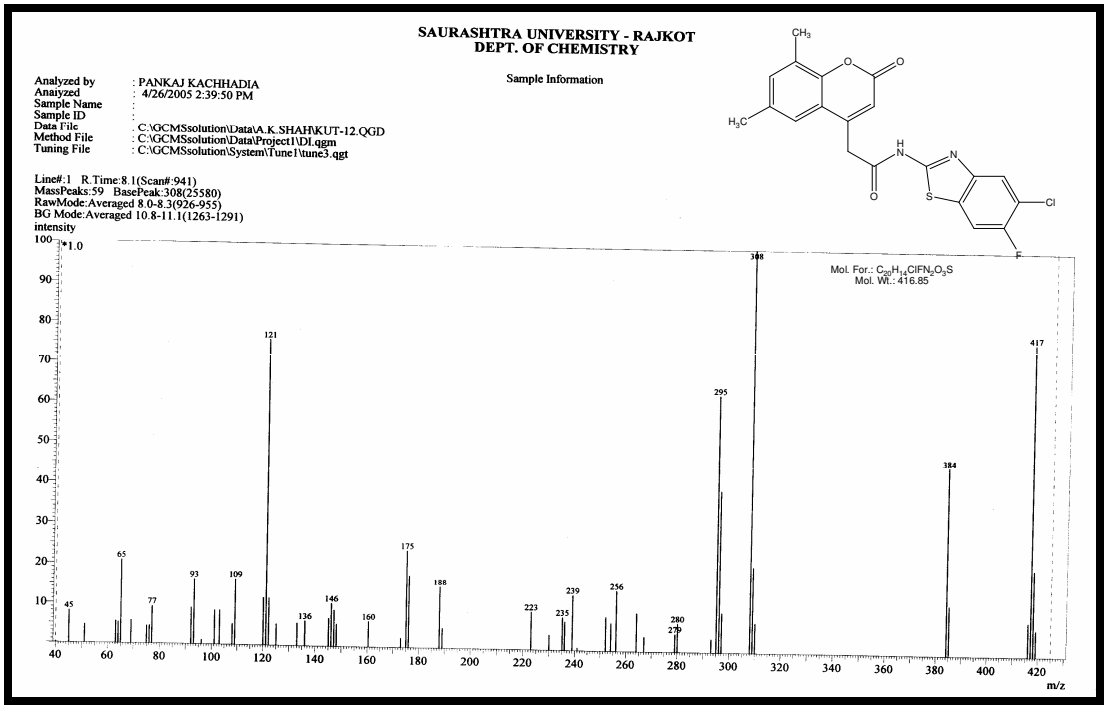
Mass spectrum of 2-(6, 8-dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*] thiazole-2-yl)acetamide (JT-17)



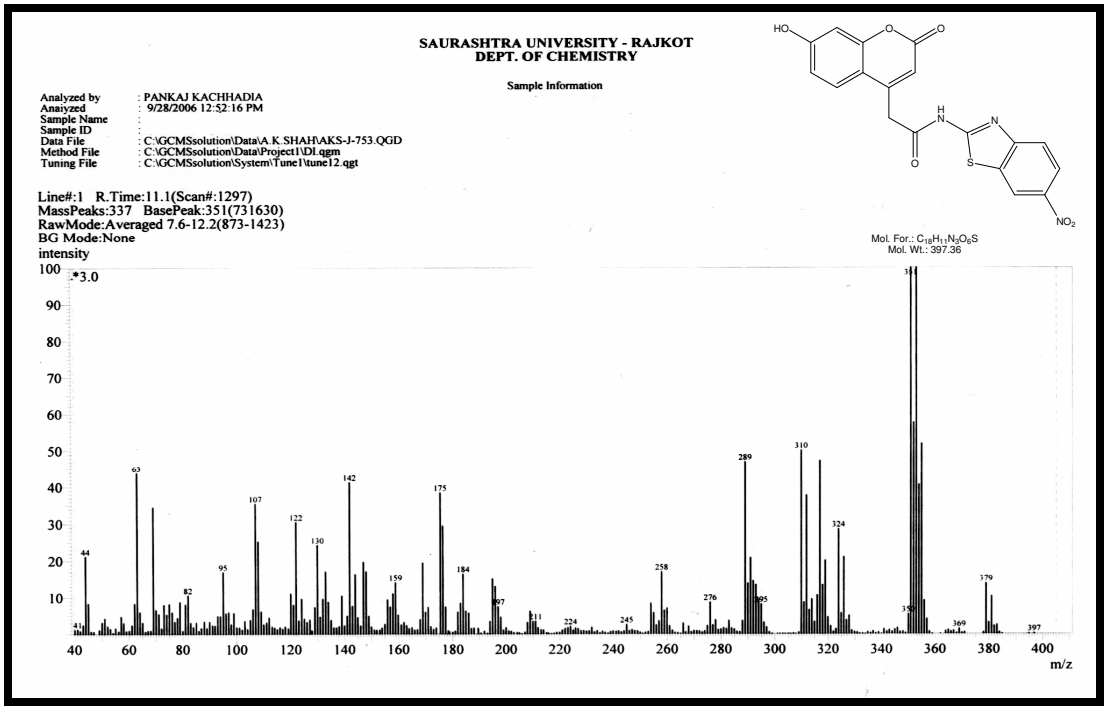
Mass spectrum of *N*-(6-fluorobenzo[*d*]thiazole-2-yl)-2-(6,8-dimethyl -2-oxo-2*H*-chromen-4-yl)acetamide (JT-19)



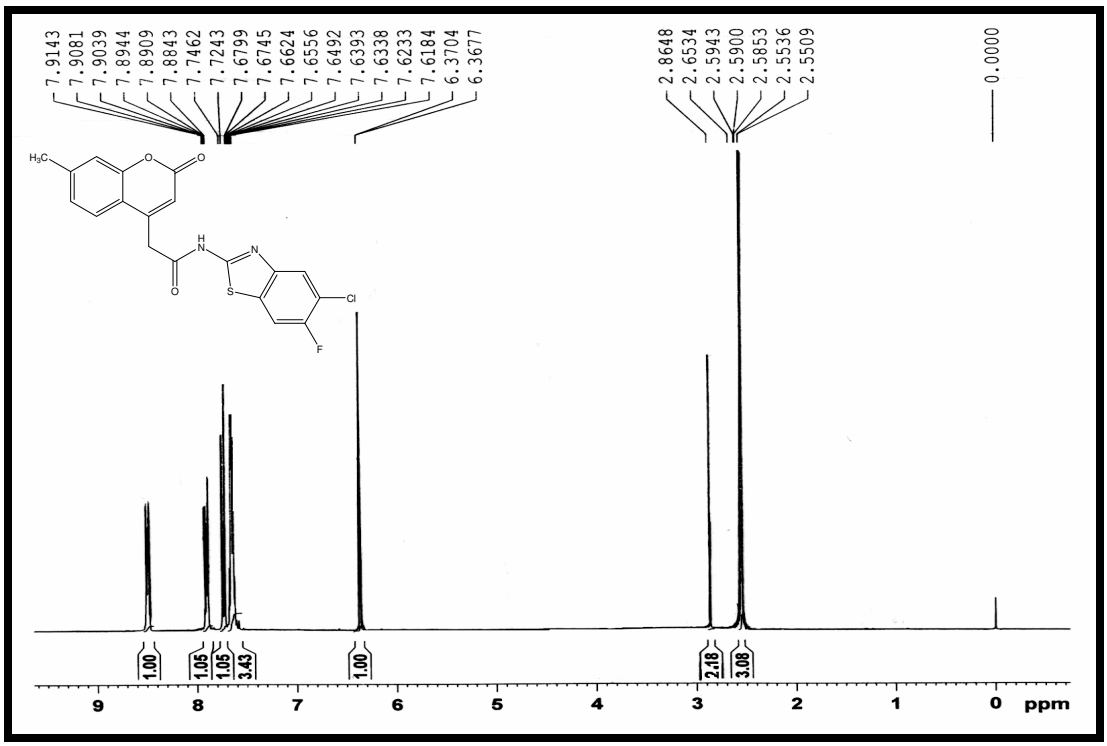
Mass spectrum of *N*-(5-chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(6,8-dimethyl-2-oxo-2*H*-chromen-4-yl)acetamide (JT-20)

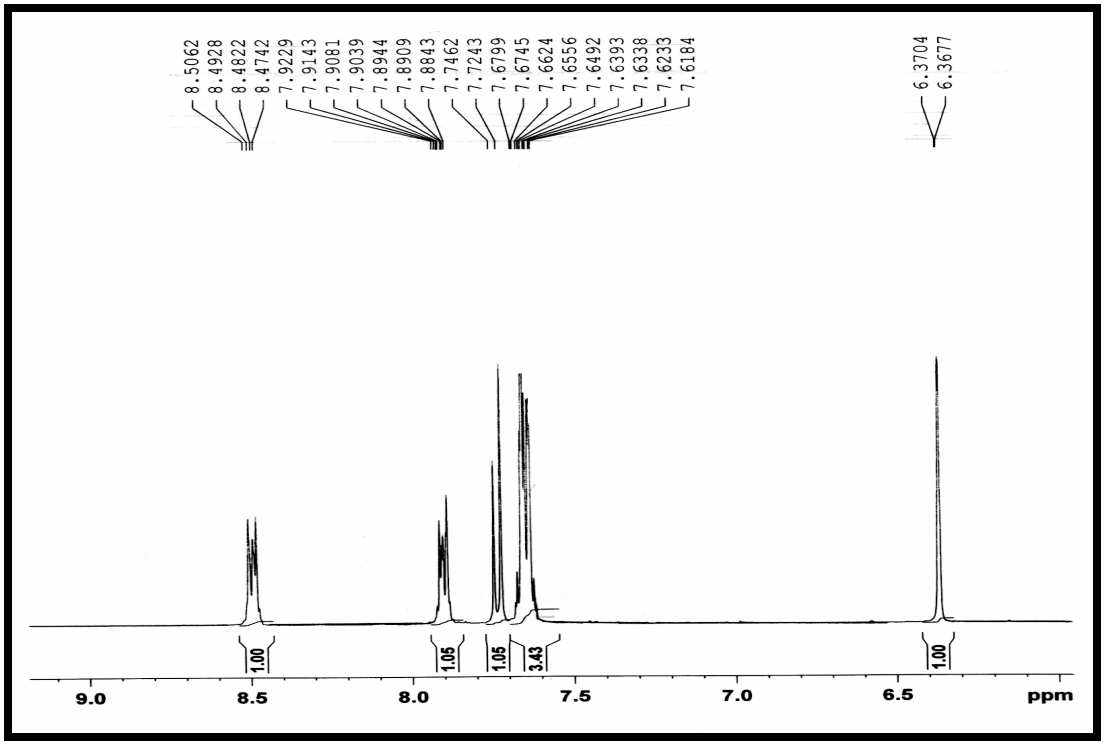


Mass spectrum of 2-(7-hydroxy-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*] thiazole-2-yl)acetamide (JT-21)

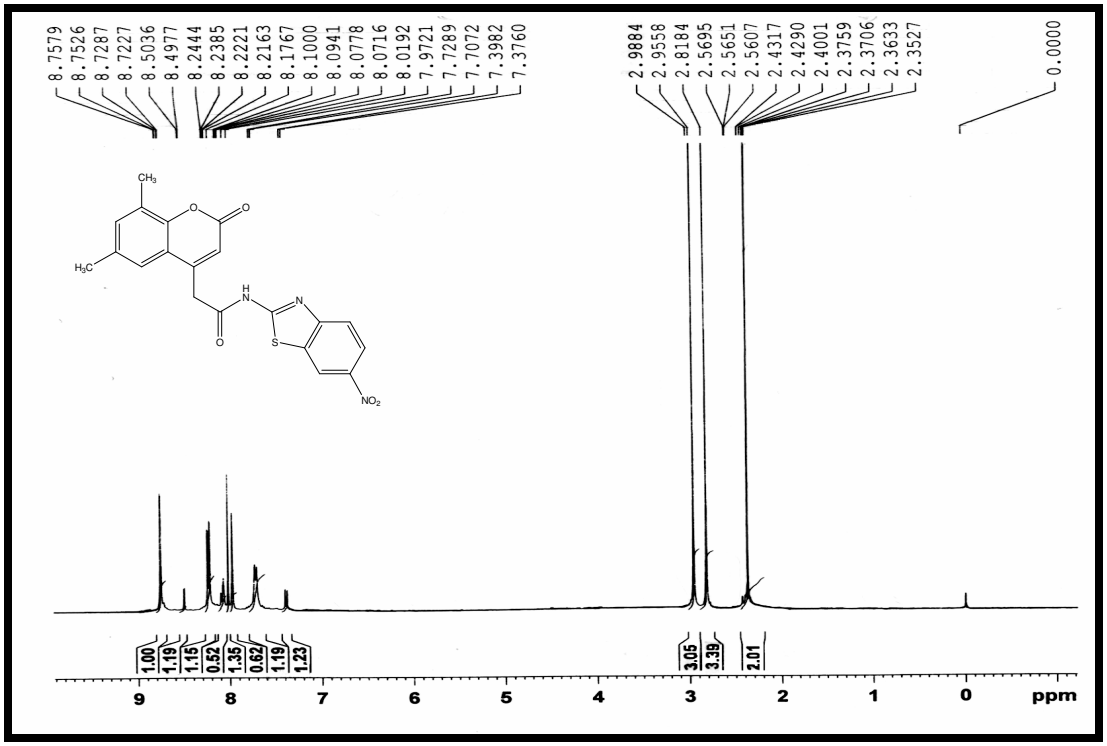


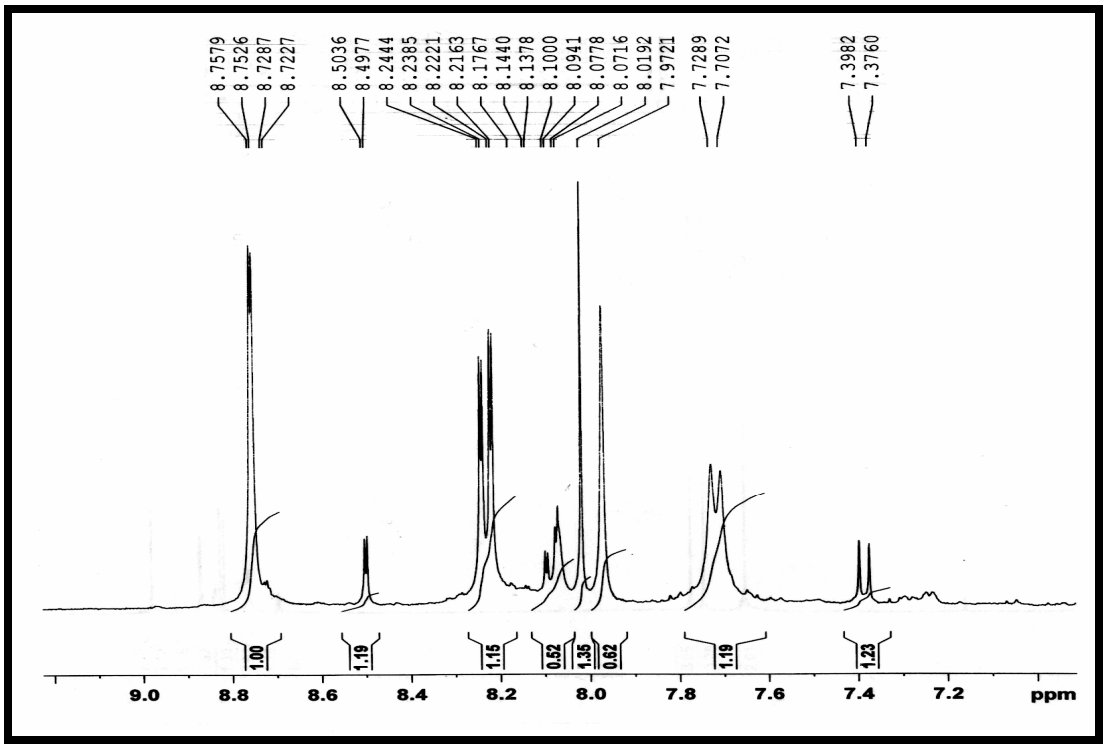
^{1}H NMR spectrum of *N*-(5-chloro-6-fluorobenzo[*d*]thiazole-2-yl)-2-(7-methyl-2-oxo-2*H*- chromen-4-yl)acetamide (JT-8)



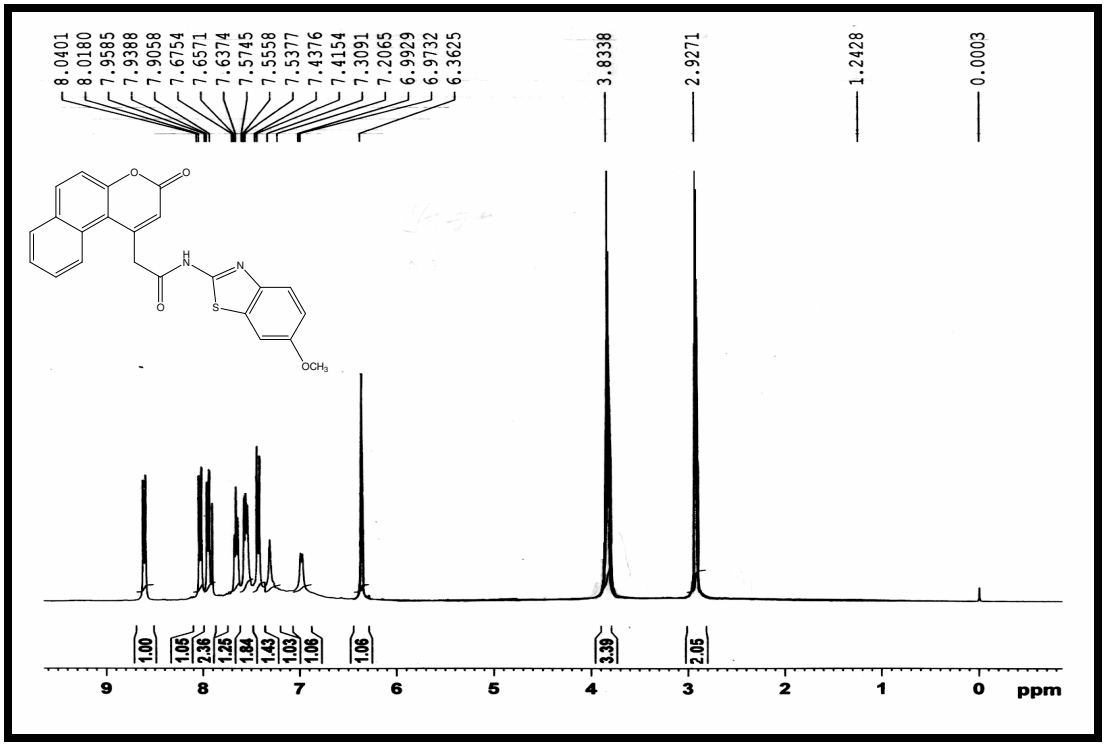


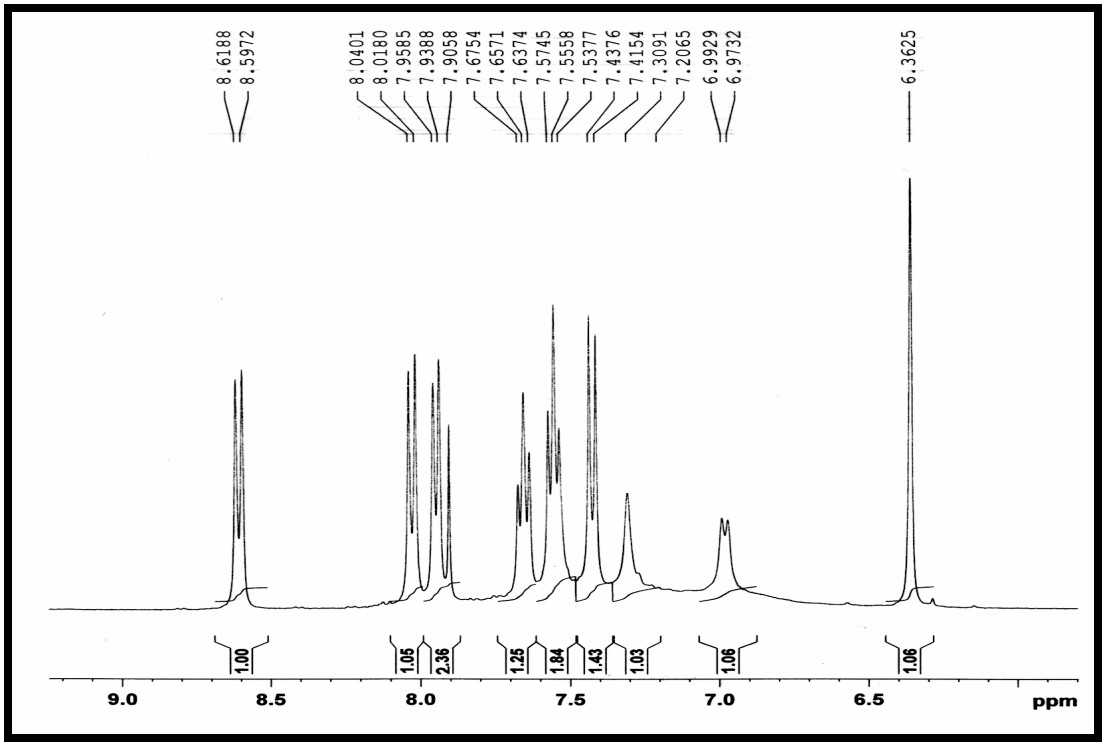
^{1}H NMR spectrum of 2-(6, 8-dimethyl-2-oxo-2*H*-chromen-4-yl)-*N*-(6-nitrobenzo[*d*] thiazole-2-yl)acetamide (JT-17)





^{1}H NMR spectrum of *N*-(6-methoxybenzo[*d*]thiazole-2-yl)-2-(3-oxo-3*H*-benzo[*f*]chromen-1-yl)acetamide (JT-26)





2.12. References:

1. (a) Vogel, A. *Gibb. Ann. Physik.* **1820**, 64, 161. (b) Wawzonek, S. Heterocyclic Compounds (*Elerfield R. C. ed.*), Wiley, Newyork, **1951**, 2, 173-216. (c) Sethna, S. M.; Phadke, R. *Org Reactions*, 7, John Wiley and Sons, Newyork, **1953**, 1-58. (d) Dean, F. M. *Naturally occuring oxygen ring compounds, Butterworths, London*, **1963**. (e) Murray, R. D. H.; Mendez, J.; Brown, S. A. The natural coumarins, *John Wiley and Sons, Newyork,* **1982**.
2. Perkin, W. H. *Ann.* **1868,** 147, 229.
3. Pechmann, V. *Ber.* **1884**, 17, 929.
4. Knoevenagel, E. Ber. 1895, 31, 2585-2595; 1904, 37, 4461.
5. Biginelli, P. *Gazetta.* **1894**, 24, 391.
6. Pechmann, H.; Kraft, E. *Ber.* **1901**, 34, 421.
7. Pechmann, H.; Graeger, E. *Ber.* **1901**, 34, 378.
8. Limaye, D. *J. Ind. Chem. Soc*. **1927**, 4, 159.
9. Dey, B. B.;*J. Chcm. SOC.* **1915**, 107, 1606.
10. Dixit, V.; Gokhle G.; *J. Uni. Bombay (Pt-2)*, **1934**, 3, 95-105; *C. A.* **1935**, 29, 4753.
11. Fries, K.; Volk, W. *Ann*. **1911**, 379, 90.
12. Dey, B. B.; Radhabai, K. J. *J. Ind. Chem. Soc.* **1934**, 11, 635.
13. Chakravarti, D.; Ghosh, B. *J. Ind. Chem. Soc*. **1935**, 12, 622.
14. Chakravarti, D.; Mukherjee, H. *J. Ind. Chem. Soc*. **1937**, 14, 725.
15. Chakravarti, D.; Banerjee, H. *J. Ind. Chem. Soc*. **1936**, 13, 619.
16. Burton, H.; Pechmann. *Ann*. **1891**, 261, 166.
17. Muller, D. *Ber*. **1925.** 58, 2202.
18. (a) Ghia, B. J., Gharde, A. D., *J. Ind. Chem. Soc*. **1992**, 69, 397-398. (b) Werder, F.; *Mercks Jahresbericht*, **1936**, 50, 88. (c) Foye, W. O.; Lemke, T. L.; Williams, D. A. *Principles of Medicinal Chemistry*, 4th Edi. **1995,** 895.
19. Czerpack, R.; Skolska, S. Effect of selected synthetic regulators on Pseudomonas aeruginosa growth in liquid culture. *Med. Dosw. Microbiol.* **1982**, *34*, 37-50; *Chem. Abstr*. **1983**, *98*, 50232.
20. Jund, L.; Corse, J.; King, A. S.; Bayne, H.; Mihrag, K. Antimicrobial properties of 6,7-dihydroxy-, 7,8-dihydroxy-, 6-hydroxy- and 8-hydroxycoumarins. *Phytochemistry,* **1971**, *10*, 2971-2974.
21. El-Ansary, S. L.; Aly, E. I.; Halem, M. A. New coumarin derivatives as antibacterial agents. *Egypt. J. Pharm. Sci*. **1992**, *33*, 379-390.

22. Reddy, Y. D.; Somayojulu, V. V. Synthesis, spectra and physiological activity of 7*H*-pyrano[3,2- c]benzoxazole-7-one. *J. Ind. Chem. Soc.* **1981**, *58*, 599-601.
23. Abdullah, O. A. Synthesis and biological studies of some benzopyrano[2,3-c]pyrazole derivatves. *Al Farmaco*, **2000**, *55*, 641-649.
24. Nicholson, J. S.; Adams, S. S.; *Brit. Pat*. **1964**, 971, 700, *Corresp. to U.S. Pat*. 3,385,887, **1968**.
25. Shiori, T.; Kawai, N. *J. Org. Chem.* **1978**, 43, 2936.
26. Farge, D. S. *Afr. Pat* 6,800,524, **1968**, *Corresp. to U.S. Pat.* 3,642,127,**1972**.
27. Marshall, W. S. *Fr. Pat*. 2,015,718, **1970**; *Corresp. to U.S. Pat.* 3,600,437, **1971**.
28. *Neth. Pat. Appl.* **1965**, 6, 407,755; Keberle, H.; *U. S. Pat.* 3,471,548, **1969**.
29. Gabriel, S. *Chem. Ber*. **1882,** 15, 834.
30. Carson, J. R. *Fr. Pat*. 1,574,570, **1969**; *C.A.* **1969**, 72, 100498y.
31. Carson, J. R. *J. Med. Chem.* **1971**, 14, 646.
32. Lácová, M.; Chovancová, J.; Hýblová, O.; Varkonda, S. Synthesis and Pesticidal Activity of Acyl Derivatives of 4-chloro-2-aminobenzothiazole and the Products of their Reduction. *Chem. Pap,* **1991**, 45, 411-418.
33. Chulák, I.; Sutorius, V.; Sekerka, V. Benzothiazole compound XXXV. Synthesis of 3-substituted 2-benzylbenzothiazolium Salts and their Growth-regulating Effect on Triticum Aestivum L. *Chem. Pap.* **1990**, 44, 131-138.
34. Papenfuhs, T. Preparation of Benzothiazoles as Intermediates for Dyes, Plant Protectants and Pharmaceuticals. *Ger. Offen. DE 3,528,032*.**1987**.
35. Bradshaw, T. D.; Bibby, M. C.; Double, J. A.; Fichtner, I.; Cooper, P.A.; Alley, M. C.; Donohue, S.; Stinson, S.F.; Tomaszewjski, J. E.; Sausville, E.A.; Stevens, M. F. G. Preclinical Evaluation of Amino Acid Prodrugs of Novel Antitumor 2-(4-amino-3-methylphenyl)benzothiazoles. *Mol. Cancer Therapeutics*. **2002**, 1, 239-246.
36. Bradshaw, T. D.; Chua, M. S.; Browne, H. L.; Trapani, V.; Sausville, E. A.; Stevens, M. F. G. In Vitro Evaluation of Amino Acid Prodrugs of Novel Antitumor 2-(4-amino-3-methylphenyl)benzothiazoles. *Br. J. Cancer*. **2002**, 86, 1348-1354.
37. Hutchinson, I.; Jennings, S. A.; Vishnuvajjala. B. R.; Westwell, A. D.; Stevens, M. F. G. Antitumor Benzothiazoles: Synthesis and Pharmacutical Properties of Antitumor 2-(4-aminophenyl)benzothiazole Amino Acid Prodrugs. *J. Med. Chem.* **2002**, 45, 744-747.
38. El-Sherbeny, M. A.; Synthesis of Certain Pyrimido[2,1-b]benzothiazole and Benzothiazolo[2,3-b]quinazoline Derivatives for in Vitro Antitumor and Antiviral Activities. *Arzeneim. Forsch*. **2000**, 50, 848-853. Racanè, L.; Tralić-Kulenović, V.; Fišer-Jakić, L.; Boykin, D. W.; Karminski-Zamola, G. Synthesis of *bis*-Substituted

Amidinobenzothiazoles as Potential Anti-HIV Agents. *Heterocycles*. **2001**, 55, 2085-2098.

39. Racanè, L.; Tralić-Kulenović, V.; Fišer-Jakić, L.; Boykin, D. W.; Karminski-Zamola, G. Synthesis of *bis*-Substituted Amidinobenzothiazoles as Potential Anti-HIV Agents. *Heterocycles*. **2001**, 55, 2085-2098.
40. Sener, E. A.; Arpaci, O. T.; Yalcin, I.; Altanlar, N. Synthesis and Microbiological Activity of Some Novel 5-benzamido- and 5-phenylacetamido- Substituted 2-phenylbenzoxazole Derivatives. *Farmaco*. **2000**, 55, 397-405.
41. Mruthyunjayaswamy, B. H. M.; Shanthaveerappa, B. K. Synthesis and Pharmacological Evaluation of 3,5-disubstituted indole-2-[N beta-(substituted benzopyran-2'-one-3'-carboxyl)]carboxy hydrazides and 2H-3-(various substituted indol-3'-yl)methyl-1,3-benzothiazoles. *Indian J. Chem. Sect. B.* **2000**, 39, 433-439.11.
42. Temiz-Arpaci, O.; Aki-Sener, E.; Yalcin, I.; Altanlar, N. Synthesis and Antimicrobial Activity of Some 2-[p-substituted-phenyl]benzoxazol-5-yl-arylcarboxyamides. *Arch. Pharm.* **2002**, 335, 283-288.
43. Delmas, F.; Di Giorgio, C.; Robin, M.; Azas, N.; Gasquet, M.; Detang, C.; Costa, M.; Timon-David, P.; Galy, J.P. In Vitro Activities of Position 2 Substitution–bearing 6-nitro and 6-amino-benzothiazoles and their Corresponding Anthranilic Acid Derivatives Against Leishmania Infantum and Trichomonas Vaginalis. *Antimicrob. Ag. Chemother*. **2002**, 46, 2588-2594.
44. Pattan, S. R.; Babu, S. N. N.; Angadi, J. Synthesis and Biological Activity of 2-amino [5'-(4'-sulphonylbenzylidene)-2,4-thiazolidine dione]-7-(substituted)-6-fluoro benzothiazoles. *Ind. J. Het. Chem.* **2002**, 11, 333-334.
45. Mahmood-ul-Hasan.; Chohan, Z. H.; Supuran, C. T. Antibacterial Zn(II) Compounds of Schiff Bases Derived from Some Benzothiazoles. Main Group *Met. Chem*. **2002**, 25, 291-296.
46. Bradshaw, T. D.; Stevens, F. G.; Westwell, A. D. *Current Med. Chem.* **2001**, 8, 203-208.
47. Das, J.; Moquin, R. V.; Lin, J.; Liu, C.; Doweyko, A. M. *et al.*, *Bioorg.& Med. Chem. Lett*. **2003**, 13, 2587-2590.
48. Domino, E. F.; Unna, K. R.; Kerwin, J. Pharmacological properties of benzazoles. I. Relationship between structure and paralyzing action. *J. Pharmacol. Exp. Ther.* **1952**, *105*, 486-497.
49. Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J.; Boireau, A.; Bour, Y.; Cole´no, M.; Doble, A.; Doerflinger, G.; Do Huu, C.; Donat, M.; Duchesne, J.; Ganil, P.; Gue´re´my, C.; Honore´, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; Le Blevec, J.; Meunier, M.; Miquet, J.; Nemecek, C.; Pasquet, M.; Piot, O.;

Pratt, J.; Rataud, J.; Reibaud, M.; Stutzmann, J.; Mignani, S. Riluzole Series. Synthesis and in Vivo "Antiglutamate" Activity of 6-Substituted-2-benzothiazolamines and 3-Substituted-2-imino-benzothiazolines, *J. Med. Chem.* **1999**, 42, 2828-2843.

50. Kaufmann, H. P.; Die Bildung von Thiazol-Derivaten bei der Rhodanierung von Aminen. *Archiv. Pharm.* **1928**, 266, 197-218.
51. Hugerschoff, A.; Einwirkung von Brom auf aromatische Thioharnstoffe, *Chem. Ber.* **1903**, 36, 3121-3134.
52. Hofmann, *Ber.* **1879**, 12, 2359; **1880**, 13, 8.
53. Hofmann, *ibid.,* **1880**, 13, 1236.
54. Green, Perkin, *J. Chem. Soc.* **1903**, 83, 1207.
55. Claasz, *Ber*. 1912, 45, 1031; **1916**, 49, 1141.
56. (a) Hugerschoff, H. *Chem. Ber.* **1901**, *34,* 3130. (b) Hugerschoff, H. *Chem. Ber.* **1903**, *36,* 3121.
57. Sprague, J. M.; Land, A. H. *J. Heterocyclic Compounds*, **1957**, 5, 484-721.
58. Cecchetti, V.; Fravolini, A.; Fringuelli, R.; Mascellani, G.; Pagella, P.; Palmioli, M.; Segre, G.; Ternit, P. Quinolone carboxylic Acids. 2. Synthesis and Antibacterial Evaluation of 7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-de][1,4]benzothiazine-6-carboxylic Acids, *J. Med. Chem.* **1987**, 30, 465-473.
59. Jordan, A. D.; Luo, C.;Reitz, A. B. Efficient Conversion of Substituted Aryl Thioureas to 2-Aminobenzothiazoles Using Benzyltrimethylammonium Tribromide, *J. Org. Chem.* **2003**, 68, 8693-8696.
60. Shi, D.; Bradshaw, T. D.; Wrigley, S.; McCall, C. J.; Lelieveld, P.; Fichtner, I.; Stevens, M. F. G. Antitumor Benzothiazoles. 3. Synthesis of 2-(4-Aminophenyl)benzothiazoles and Evaluation of Their Activities against Breast Cancer Cell Lines *in Vitro* and *in Vivo, J. Med. Chem.* **1996**, 39, 3375-3384.
61. Racane, L.; Stojkovic, R.; Tralic-Kulenovic, V.; Zamola, G. K. Synthesis and Antitumor Evaluation of Novel Derivatives of 6-Amino-2-phenylbenzothiazoles, *Molecule,* **2006**, 11, 325-333.
62. Mackie, A.; Stewart G. M.; Misra A. L. *Arch .int. Phaimaeodyn.,* **1955**, 103, 187.
63. *(a)* Domino, E. F.; Unna, K.; Kerwin, J. *J. Pharm. Exptl. Therap.* **1951**, 101, 9; **1952**, 105, 486. *(b)* Funderburk, W. H.; King, E. E.; Domino, E. F.; Unna, K. *J. Pham. Exptl. Therap.* **1953**, 107, 350 *(e)* Funderburk, W. H;. King, E. E.; Unna, K. *J. Pharm. Exptl. Therap.* **1 953**, 108, 94.
64. Anand, L.; Misra, M. 2-Amino-6-substituted Benzothiazoles as Potential Anthelmintics, **1958**, 23, 1388-1389.
65. Sumerford, W. T. Dalton, D. N. *J. Org. Chem.* **1944**, 9, 81.

66. Nelson, J. W.; Edwards, L. D.; Christian, J. E.; Jenkins, G. L. *J. Am. Pharm. Assoc., Sci. Ed.,* **1947**, 36, 349.

67. Akyama, S.; Ochiai, T.; Nakatsuji, S.; Nakashima, K.; Ohkura, Y. Preparation and Evaluation of Fatty Acid Esters of Fluorescent p-Substituted Phenols as Substrates for Measurement of Lipase Activity. *Chem. Pharm. Bull*. **1987**, 35, 3029-3032.

68. Racanè, L.; Kulenović, V. T.; Boykin, D. W.; Zamola, G. K. Synthesis of New Cyano-Substituted *bis*-Benzothiazolyl Arylfurans and Arylthiophenes, *Molecules,* **2003**, *8*, 342-349.

69. Gaillard, P.; Jeanclaude-Etter, I.; Ardissone, V.; Arkinstall, S.; Cambet, Y.; Camps, M.; Chabert, C.; Church, D.; Cirillo, R.; Gretener, D.; Halazy, S.; Nichols, A.; Szyndralewiez, C.; Vitte, P. A.; Gotteland, J. P. Design and Synthesis of the First Generation of Novel Potent, Selective, and in Vivo Active (Benzothiazol-2-yl)acetonitrile Inhibitors of the c-Jun N-Terminal Kinase, *J. Med. Chem.* **2005**, 48, 4596-4607.

70. Ruckle, T.; Biamonte, M.; Grippi-Vallotton, T.; Arkinstall, S.; Cambet, Y.; Camps, M.; Chabert, C.; Church, D. J.; Halazy, S.; Jiang, X.; Martinou, I.; Nichols, A.; Sauer, W.; Gotteland, J. P. Design, synthesis, and biological activity of novel, potent, and selective (benzoylaminomethyl)thiophene sulfonamide inhibitors of c-Jun-N-terminal kinase. *J. Med. Chem.* **2004**, 47, 6921-6934.

71. Alaxender Domling and Ivar Ugi, *Angew. Chem,* Int. Ed., **2000,** 39, 3168-3210.

72. Shah, S.; Mehta, R. H. *J. Indian Chem. Soc.*, **1987**, 64(11), 708.

73. Metwally, M. A.; Abdel-latif, E.; Amer F. A.; Kaupp, G. Versatile 2-amino-4-substituted-1,3-thiazoles: synthesis and reactions, Review**,** *J. Sulfur Chemistry,* **2004**, 25, 63–85.

74. Dodson, R. M.; King, L. C. *J. Am. Chem. Soc.*, **1945**, 67, 2242.

75. Mayaux, J. F.; Bousseau, A.; Pauwels, R.; Huet, T.; He´nin, Y.; Dereu, N.; Evers, M.; Soler, F.; Poujade, C.; De Clercq, E.; Le Pecq, J.-B. Triterpene Derivatives That Block Entry of Human Immunodeficiency Virus Type 1 into Cells. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, 91, 3564-3568.

76. Soler, F.; Poujade, C.; Evers, M.; Carry, J. C.; He´nin, Y.; Bousseau, A.; Huet, T.; Pauwels, R.; De Clercq, E.; Mayaux, J. F.; Le Pecq, J. B.; Dereu, N. Betulinic Acid Derivatives: a New Class of Specific Inhibitors of Human Immunodeficiency Virus Type 1 Entry. *J. Med. Chem.* **1996**, 39, 1069-1083.

77. Ishida, Y.; Jikei, M.; Kakimoto, M. Rapid Synthesis of Aromatic Polyamide Dendrimers by an Orthogonal and a Double-Stage Convergent Approach, *Macromolecules,* **2000**, *33,* 3202-3211.

78. Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase. 1. Tricyclic pyridobenzo- and dipyridodiazepinones. *J. Med. Chem.* **1991**, 34, 2231-2241.

79. Schnur, R. C.; Gallaschun, R. J.; Singleton, D. H.; Grissom, M.; Sloan, D. E.; Goodwin, P.; McNiff, P. A.; Fliri, A. F. J.; Mangano, F. M.; Olson, T. H.; Pollack V. A. Quantitative Structure-Activity Relationships of Antitumor Guanidinothiazolecarboxamides with Survival Enhancement for Therapy in the 3LL Lewis Lung Carcinoma Model, *J. Med. Chem.* **1991**, 34, 1975-1982.

80. Wkrner, W. Antitubercular Agents. Derivatives of pyridinecarboxylic acid hydrazides. *J. Org. Chem.* **1953**, 18, 1333-1337.

81. Parmer, S. S.; Kumar, R. Substituted quinazolinone hydrazides as possible antituberculous agents. *J. Med. Chem.* **1963**, 11, 635-636.

82. Bhamaria, R. P.; Bellare, R. A.; Deliwala, C. V. In intro effect of 1-acyl-4-alkyl-(or aryl)- thiosemicarbazides 1-(5-chlorosalicylidine)-4-alkyl-(or aryl)-thiosemicarbazones and some hydrazones of 5-chlorosalicylaldehyde against pathogenic bacteria including Mycobacterium tuberculosis (H37Rv). *Indian J. Exp. Biol.* **1968**, 6, 62-63.

83. Abdel-Al, E. H.; Al-Ashamawi, M. I.; Abd El-Fattah, B. Synthesis and antimicrobial testing of certain oxadiazoline and triazole derivatives. *Die Pharmazie* **1983**, 38, 833-838.

84. Gupta, A. K. S.; Garg, M.; Chandra, U. Synthesis of some new Mannich bases derived from substituted benzimidazole, benzoxazol-2-one, benzoxazol-2-thione, oxadiazol-2-thiones and their biological activities. *J. Indian Chem. Soc*. **1979**, 56, 1230-1232.

85. Mansour, A. K.; Eid, M. M.; Khalil, N. S. A. M. Synthesis and reactions of some new heterocyclic carbohydrazides and related compounds as potential anticancer agents. *Molecules,* **2003**, 8, 744- 755.

86. Dutta, M. M.; Goswani, B. N.; Kataky, J. C. S. Studies on biologically active heterocycles. Part I. Synthesis and antifungal activity of some new aroyl hydrazones and 2,5-disubstituted-1,3,4- oxadiazoles. *J. Heterocyclic Chem.* **1986**, 23, 793-795.

87. Sharma, S.C. Synthesis of new fungicides. 2-(4'-arylthiazolyl-2'-imino)-3-aryl-4-thiazolidones. *Bull. Chem. Soc. Japan*, **1967**, 40, 2422-2424.

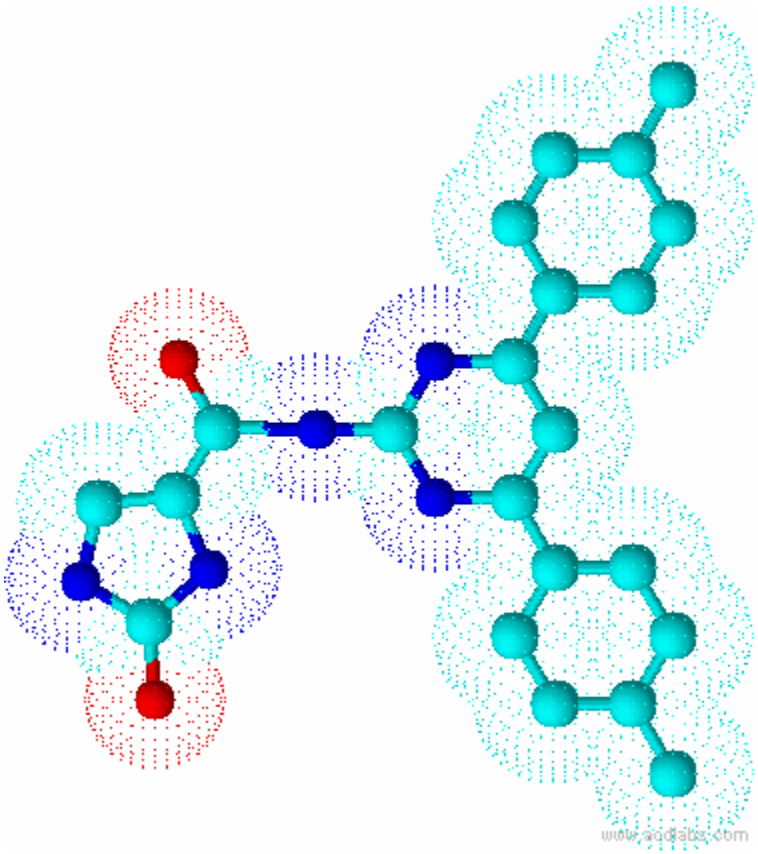
88. Chaubey, V. N.; Singh, H. Synthesis of some new fungicides. *Bull. Chem. Soc. Japan*, **1970**, 43, 2233-2236.

89. Foye, W. O.; Tovivich, P. N-Glucopyranosyl-5-aralkylidenerhodanines: Sinthesis and antibacterial and antiviral activities. *J. Pharm. Sci.* **1977**, 66, 1607-1611.

90. Akerblom, E. B. Synthesis and structure-activity relations of a series of antibacterially active 5-(5- nitro-2-furfurylidene)thiazolones, 5-(5-nitro-2-furylpropenylidene)thiazolones, and 6-(5-nitro-2- furyl)-4*H*-1,3-thiazinones. *J. Med. Chem*. **1974**, 17, 609-615.
91. Cacic, M.; Trkovnik, M.; Cacic, F.; Has-Schon, E. Synthesis and Antimicrobial Activity of Some Derivatives of (7-Hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic Acid Hydrazide *Molecules,* **2006**, *11*, 134-147.
92. Hassner, A.; Alexanian, V. *Tetrehedron Lett*. **1978**, 46, 4475.
93. Khunnawutmanotham, N.; Chimnoi, N.; Saparpakorn, P.; Pungpo, P.; Louisirirotchanakul, S.; Hannongbua, S.; Techasakul, S. Novel 2-Chloro-8-arylthiomethyldipyridodiazepinone Derivatives with Activity against HIV-1 Reverse Transcriptase, *Molecules,* **2007**, 12, 218-230.
94. Zimmerman, M.; Ashe, B.; Yurewicz, E.; Patel, G. *Anal. Biochem.* **1977**, 78, 47.
95. Rano, T. A.; Timkey, T.; Peterson, E. P.; Rotonada, J.; Nicholson, D. W.; Becker, J. W.; Chapman, K. T.; Thornberry, N. A. *Chem. Biol.* **1997**, 4, 149.
96. Thornberry, N. A.; Rano, T. A.; Peterson, E. P.; Rasper, D. M.; Timkey, T.; Garcia-Calvo, M.; Houtzager, V. M.; Nordstrom, P. A.; Roy, S.; Vaillancourt, K. T.; Chapman, K. T.; Nicholson, D. W. *J. Biol. Chem.* **1997,** 272, 17907.
97. Beckes, B. J.; Harris, J. L.; Leonetti, F.; Craik, C. S.; Ellman, J. A. *Nat. Biotechnol*. **2000**, 18, 187.
98. Zhu, Q.; Li, D. B.; Uttamchandani, M.; Yao, S. Q. Facile Synthesis of 7-Amino-4-carbamoylmethylcoumarin (ACC)-Containing Solid Supports and Their Corresponding Fluorogenic Protease Substrates, *Bioorg. Med. Chem. Lett.* **2003,** 13, 1033–1036.
99. (a) Wheland, G. Resonance in Organic Chemistry; *Wiley: New York,* **1955**, 345. (b) Pauling, L. *Nature of the Chemical Bond*, 2nd ed.; Cornell University Press: Ithaca, NY, **1960**, 276.
100. Demaison, J.; Csaszar, A. G.; Kleiner, I.; Møolendal, H. Equilibrium vs Ground-State Planarity of the CONH Linkage, *J. Phys. Chem. A,* **2007**, 111, 2574-2586.
101. Bhawsar, S. B.; Mane, D. V.; Shinde, D. B.; Shingare, M, S.; Deokate, A. S.; Gaangawane, L.V.; *Ind. J. Het. Chem.* **1996**, 6,135-138.
102. Gupta, V. N.; Sharma B. R.; Arora, R. B. *J. Sci. Ind. Res.* **1961**, 20B, 300.
103. Khan, M. H.; Giri, S. Ind. J. Chem, 32B, 1993, 984.
104. Sengupta, A. K.; Garg, M.; Chandra, V. *J. Ind. Chem. Soc.* **1979**, 56, 1230.
105. Veerbhadraiah, V.; Rajeshwarrao, V.; Padmabha Rao, T. V.; *Coll. Czech. Chem. Commun*. **1990**, 55, 535.
106. Adityavardhan, V.; Rajeshwar Rao, V. *Ind. J. Chem*. **1997**, 36B, 1085-88.
107. Kador, P. F.; *Med. Res. Rev*. **1988**, 8, 325-352.

108. Sestanj, K. *Eur. Pat. Appl.* **1982**, 59, 596, *J. Med. Chem*. **1984**, 27, 255.
109. Terashima, H. J. *Pharmacol. Exp. Therp.* **1983**, 229, 226.
110. Hayman, S.; Kinoshita, J. *J. Biol. Chem.* **1965**, 240, 877-882.
111. Brubaker, A.; Deruiter, J.; Whitmer, W. *J. Med. Chem.* **1986**, 29, 1094-1099.
112. Ampudia, F.; Blasco. *J. Diabetologia*. **1994**, 37, 703.
113. Drugs of Future, **1996**, 21(3), 261-265.
114. Jennings, P. E.; Barnett, A. H.; *Diabet. Med.* **1988**, 5, 111-117.
115. Ceriello, A.; Quatraro, A.; Giugliano, D. *Diabet. Med.* **1992**, 9, 297-299.
116. Jennings, P. E.; Scott, N. A; Saniabadi, A. R.; Belch, J. J. F.; *Metabolism*, **1992**, 41(1), 36-39.
117. Spector, T. *Biochem. Pharmacol.* **1988**, 37, 349-352.
118. Engineer, F.; Shridhar, R. *Biochem. Pharmacol.* **1989**, 38, 1279-1285.
119. Dixit, V .M.; Padukone,V. V. *J. Ind. Chem. Soc.* **1950**, 27, 127-130; *C. A*. **1951**, 45, 8515.
120. Dixit, V. M.; Kankundti, A. M.; Mulay, L. M. *J. Ind. Chem. Soc.* **1945**, 22, 207-213; C. A. **1946**, 40, 4045; C. A. **1952**, 6, 11188c.
121. Zhao, H.; Neamati, N.; Hong, H.; Mazumder, A.; Wang, S.; Sunder, S.; George, W. A.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **1997,** 40, 242-249.
122. Hantzsch, A. *Ber.* **1890**, 23, 1474.
123. Straley, J. M.; Adams, A.C. *Organic Synthesis Vol IV* Edited by Rabjohn, John Wiley & Sons, **1963**, p 415.

CHAPTER-3



Synthesis, Anti-inflammatory and Anti-cancer Activity of N-(4, 6-Diphenyl Pyrimidin-2-yl)-2-oxo-2, 3-Dihydro-1H-imidazole-4-Carboxamides

Synthesis, Anti-inflammatory and Anti-cancer Activity of *N*-(4,6-Diphenylpyrimidin-2-yl)-2-oxo-2,3-Dihydro-1*H*-Imidazole-4-Carboxamides

3.1. Introduction

The imidazole core is an important unit in heterocyclic chemistry. It occurs in different natural products and in a variety of synthetic compounds. Imidazole is a nitrogen containing five membered heterocyclic system. It is an aromatic molecule with a pyrrole-type and pyridine-type annular nitrogen. The systematic name 1, 3-diazole is seldom used, but the IUPAC names of these type of aromatic systems are generally taken as follows: imidazole 1, benzimidazole 2, 2*H*-imidazole 3, imidazolines 4-6, and imidazolidine,7 (Figure-1).

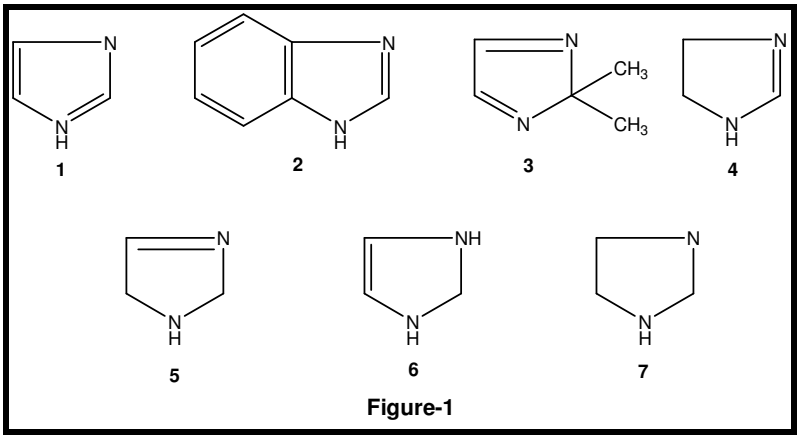
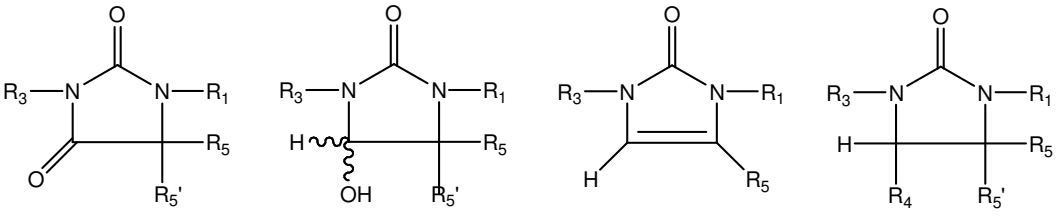


Figure-1

Some examples of imidazole-containing compounds in living organisms are the essential amino acids histidine and histamine. A lot of imidazoles show different biological activities.[1(a-d)] Some known imidazole based drugs are ketoconazole, which has antifungal properties and losartan, a drug against hypertension. Recently, interest in imidazoles is still increasing due to applications as green solvents by means of ionic liquids[2] and in organometallic chemistry as *N*-heterocyclic carbenes.[3]

Cortes and co-workers[4] reported selectively substituted hydantoins 8, 4-hydroxy-2-imidazolidinones 9, 2-imidazolones 10, 2-imidazolidinones 11, have been prepared and evaluated in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole seizure threshold (sc Met) and rotorod (Tox) tests. The medium effective doses (ED_{50}) and the medium toxic dose (TD_{50}) for the most active compounds were reported. The most pronounced activity was observed for hydantoins (Figure-2)**.**



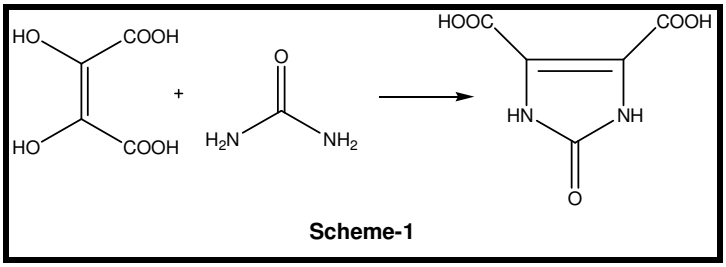
8 **9** **10** **11**

Figure-2

The most active compounds observed were the two 2-imidazolones 4-methyl-l-(phenylmethyl)-l,3-dihydro-2*H*-imidazol-2-one and l-phenyl-l,3-dihydro-2*H*-imidazol-2-one. Among the most important members of this class of compounds are the hydantoins.[5] The effect of structural modification of the hydantoin ring system on biological activity has been a subject of considerable intererest.[6] Many hydantoins served as anticonvulsants for years which disappeared in use only after advent of new drugs in this therapeautic area.

Many procedures have been developed to generate a broad range of differentl substituted imidazoles.[7] Several synthetic approaches are reported in literature for single step to multistep synthesis of imidazole skeleton.

Davidson and Baudisch[8] have utilized the von Pechmann reaction[9] for a novel synthesis of uracil by treating malic acid and urea with fuming sulfuric acid. Hilbert and co-workers [10] synthesized uracil-4-acetic acid from citric acid and urea (Scheme-1).



Scheme-1

Hilbert[11] reported 2-imidazolone-4-carboxilic acid, synthesized by the reaction of tartaric acid, with urea in sulfuric acid. The initial product formed in a reaction between tartaric and sulfuric acids would be α, β-dihydroxyacrylic acid (formylglycolic acid) which upon

subsequent reaction with sulfuric acid would yield glyoxal. The condensation of urea with the citric acid and α or β-hydroxy groups of would be expected to yield 2-imidazolone-4-carboxylic acid (Figure-3).

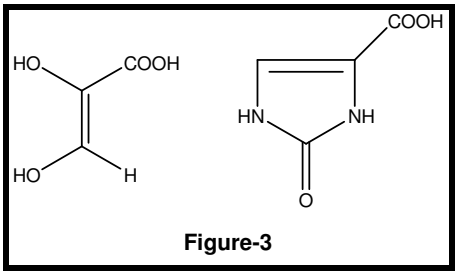
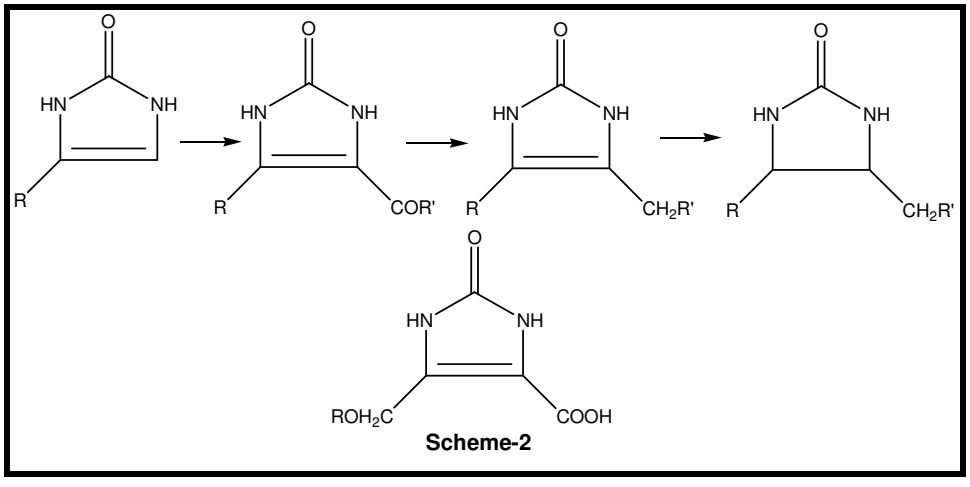


Figure-3

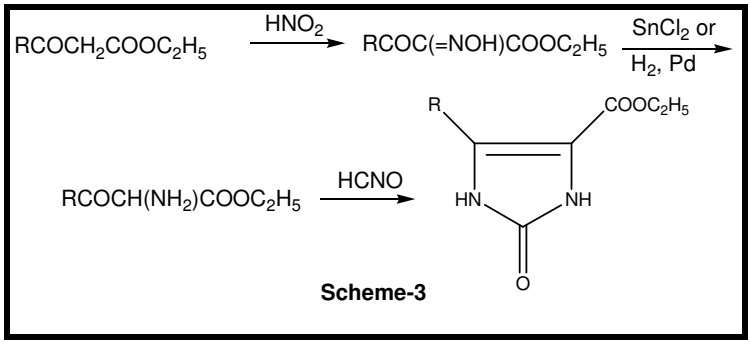
Duschinsky[12] reported that Friedel-Crafts acylations of 4-methyl-2-imidazolone (R = CH_3), followed by hydrogenation of the obtained ketones, lead to imidazolidone compounds, the keto group being first reduced to methylene. It was then reported that 2-imidazolone (R = H) and 4-ethyl-2-imidazolone (R = C_6H_6) react in a similar manner. The compounds having different properties were described in the literature as 2-imidazolones.

In 1892, Marckwald[13] reported the synthesis of imidazolone from amino acetal *via* ureido acetal, and described it as a substance not melting at the boiling point of sulfuric acid. Duschinsky[14] then reported the analogue of 2-imidazolone-4,5-dicarboxilic acid (Scheme-2).



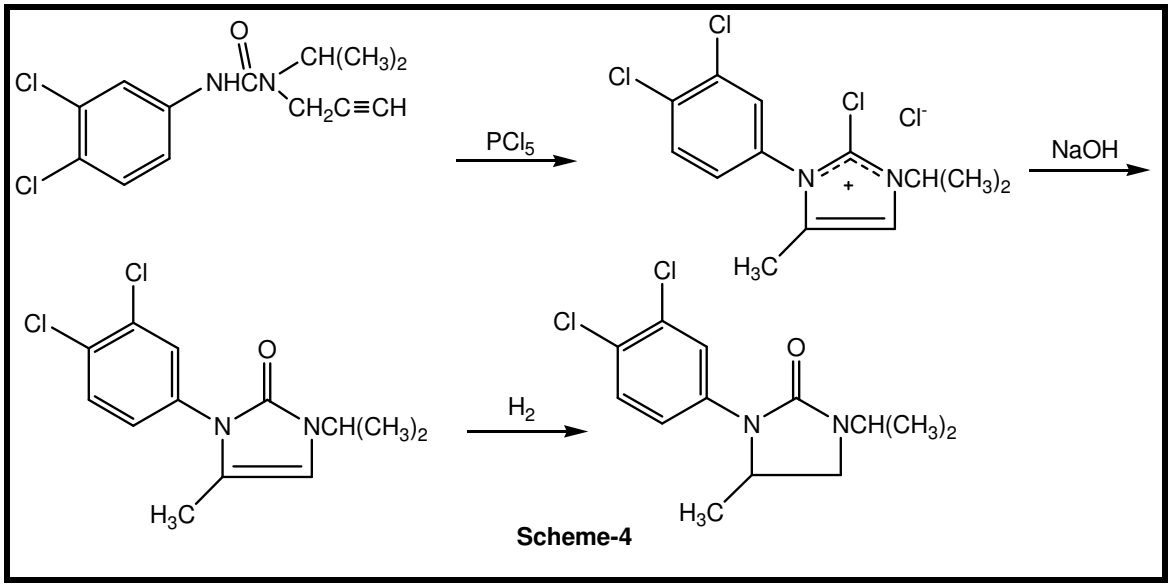
Scheme-2

Later, Fenton and Wilks[15] prepared the same from dihydroxymaleic acid a substance melting at 245°C, which they found to be not identical with Marckwald's preparation and therefore called iso-imidazolone. Finally Hilbert[16] obtained imidazolone by heating 2-imidazolone-4-carboxylic acid *in vacuo* at 230°C (Scheme-3).



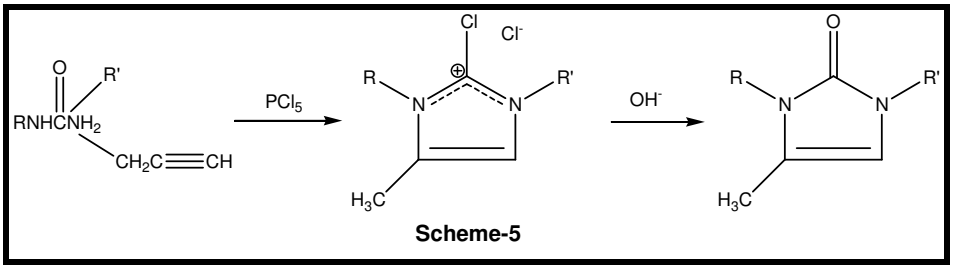
Scheme-3

Stoffel *et. al.*[17] reported a novel ring closure effected by treating a propynyl urea with phosphorus pentachloride. A stable imidazolium chloride was obtained which on treatment with base was converted to an imidazolone. The propynyl urea with PCl_5 in refluxing benzene gave the cyclized imidazolium chloride. On reaction with sodium hydroxide gave 1-(3,4-dichlorophenyl)-3-isopropyl-5-methyl-1*H*-imidazol-2(3*H*)-one which on reduction obtained 3-(3,4-dichlorophenyl)-1-isopropyl-4-methylimidazolidin-2-one (Scheme-4).



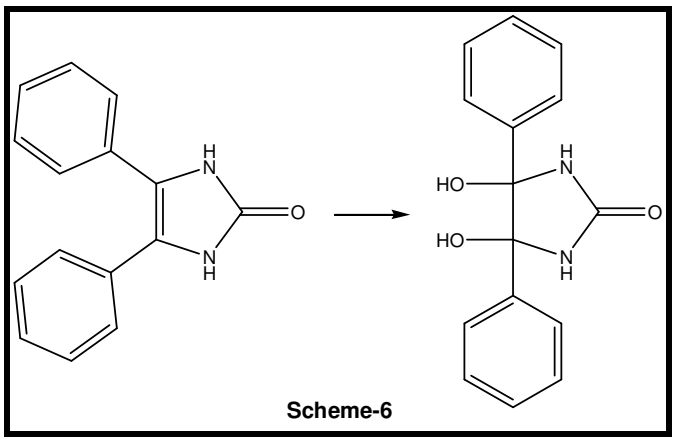
Scheme-4

Stoffel[18] then reported the closure affected by treating a suitable propynylurea with phosphorus pentachloride. A 2-imidaxolone is obtained *via* a stable isolable imidazolium chloride. Recent reports show[19-22] the formation of stable acylic amido chlorides and carbamido chlorides from the corresponding amides (Scheme-5).



Scheme-5

The oxidation of 4,5-diphenyl-2-imidazolone to 4,5-diphenyl-4,5-dihydroxy-2-imidazolone was reported by Dunnavant *et. al.*[24] which utilized concentrated nitric acid as the oxidant (Scheme-6). The nitric acid was cooled at 0^{o}C before addition to a slurry of propynylurea in glacial acetic acid. This unusual nitric acid hydroxylation method may also be applicable to other carbon-carbon double bonds with adjacent amide linkages.



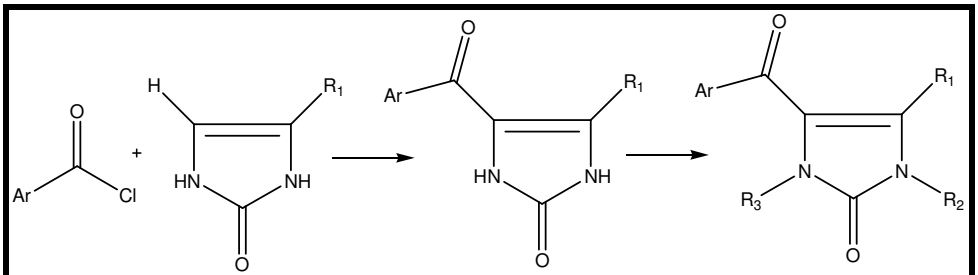
Scheme-6

3.2. Pharmacology

Schnettler[23] reported a series of 4-aroyl-l,3-dihydro-2*H*-imidazol-2-ones which were synthesized and evaluated for pharmacological activity in the anesthetized dog. Most members of this series produced dose-related increases in cardiac contractile force as well as relatively minor increases in heart rate and decreases in systemic arterial blood

pressure. The 4-methoxy or 4-methylthiobenzoyl substitution afforded compounds of greatest inotropic potency. The 1,3-dihydro-4-(4-methoxybenzoyl)-6-methyl-2-imidazol-2-one was shown to produce a dose-related positive inotropic effect and reverse the depressant effect of pentobarbital on cardiac pump function in the dog heart-lung preparation. The cardiotonic activity of this series may have important utility in the treatment of congestive heart failure. The 1,3-dihydro-4-[4-(methylthio)benzoyl]-5-methyl-2*H*-imidazol-2-one was chosen for human studies and is currently undergoing clinical trials.

The 2*H*-imidazol-2-one, an inhibitor of cyclic nucleotide phosphodiesterases,[24] was reported to produce positive inotropic and chronotropic effects and peripheral vasodilation in dogs.[25] In isolated tissue preparations at low Ca^{2+} concentrations, substituted 2*H*-imidazol-2-one increased cardiac contractile force in a manner similar to the effect of increasing Ca^{2+} concentration. Chemical changes that would increase the chelation potential might also increase the inotropic effect. Compounds that would appear to offer greater metal binding or chelating potential are the 4-aroylimidazol-2-ones (Scheme-7).



Scheme-7

Table-1: Effect of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazole-2-one in the Dog Heart-Lung preparation[a].

Measurement	Dose, µg/kg	n	Control	Change[b]	% Change
	0.3	5	71.8±6.8	62.0±4.4[c]	88±7
Cardiac contractile force,g	1.0	8	80.1±1.6	96.7±6.2[c]	121±7
	3.0	5	74.2±4.7	128.9±7.7[c]	179±19
	0.3	5	154±7	22±1[c]	14±0.3
Heart rate, beats/min	1.0	8	154±4	35±3[c]	23±1
	3.0	5	150±3	41±5[c]	28±4
	0.3	5	1088±31	37±7[c]	3±1
Cardiac output, ml/min	1.0	8	1079±34	28±11[c]	3±1
	3.0	5	1019±74	46±10[c]	4±1
	0.3	5	7.1±0.3	-0.7±0.1c	-10±1
Stroke control, ml	1.0	8	7.0±0.3	-1.1±0.1[c]	-16±2
	3.0	5	6.8±0.5	-1.2±0.2[c]	-18±3
	0.3	5	3.1±0.5	-1.6±0.6[c]	-49±14
Left atrial pressure, mmHg	1.0	8	2.8±1.0	-1.2±0.4[c]	-31±10
	3.0	5	3.2±0.7	-1.1±0.7	-43±23

[a]Means and standard errors. [b]Measurements made 10 min after addition of 6 to the blood reservoir. [c]A significant change from control by paired Student's *t* test, $p < 0.05$. Additionally, there was a significant linear dose-response curve for cardiac force and heart rate by regression analysis.

In continuing search for new cardiotonic agents, Knope *et. al.*[26] synthesized imidazole and Ro 7-2956 (Figure-4) which were recently reported to increase myocardial contractility. It was suggested that imidazole may act upon calcium tissue 1evels.[27] 2-Imidazole exerted a positive inotropic effect on spontaneously beating rabbit atria and isolated hearts. It was suggested that the 2-imidazole was making more Ca^{2+} available to the contractile mechanism. Pharmacological evaluation showed these compounds have strong cardiotonic activity.[28-32]

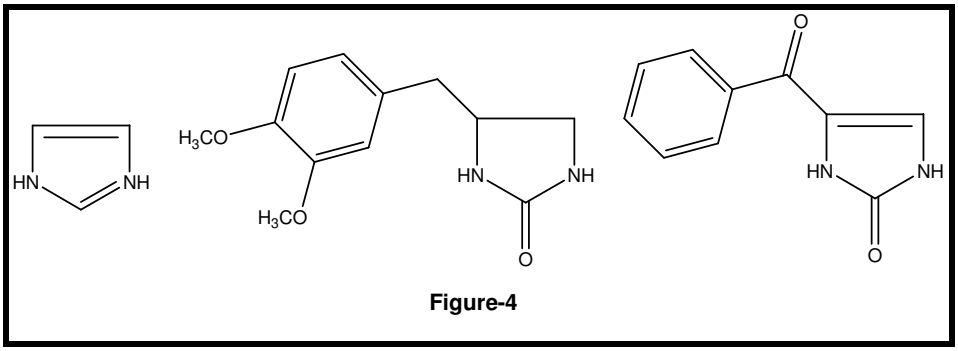


Figure-4

However, one of the derivative of 2-imidazolone (Figure-5) has been reported to be a potent inhibitor of a CAMP phosphodiesterase isozyme.[33]

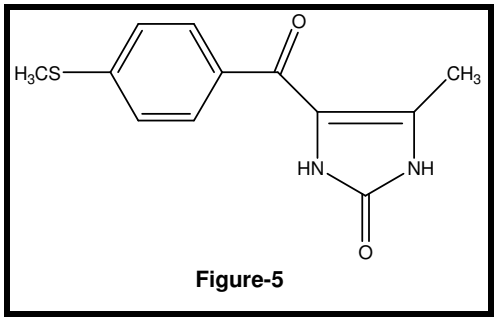
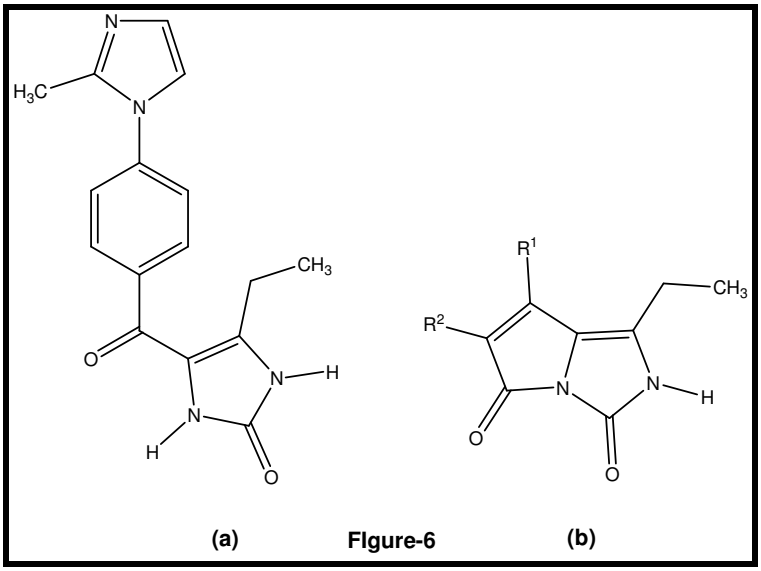


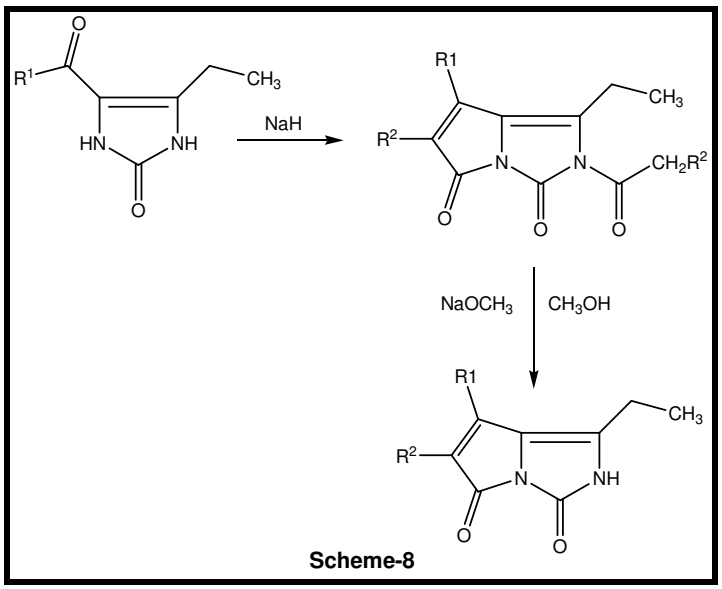
Figure-5

Shaw and co-workers[34,35] aimed toward the development of nitrogen acylated prodrugs of cardiotonic agents[36] (a) and obtained some novel fluorescent compounds which were determined to be 3*H*-pyrrolo[1,2-*c*]imidazole-3,5(2*H*)-diones[37] (b) (Figure-6) .



(a) **FIgure-6** **(b)**

Several of the pyrrolo[1,2-*c*]imidazoledione derivatives derived, displayed cardiotonic properties similar to the parent [4-(1*H*-imidazol-l-yl)benzoyl]-imidazolones.[38(a,b)] imidazolone was prepared in an 87% yield by Friedel-Craft reaction of 5-ethyl-2-oxoimidazole-4-carboxylic acid[39] (Scheme-8).



Scheme-8

Bovy *et. al.*[40] invented the derivatives of 2-imidazolones (figure-7) which inhibited platelet aggregation in mammals. Fibrinogen is a glycoprotein present as a normal component of blood plasma which participates in platlet aggregation and fibrin formation in the blood clotting mechanism.

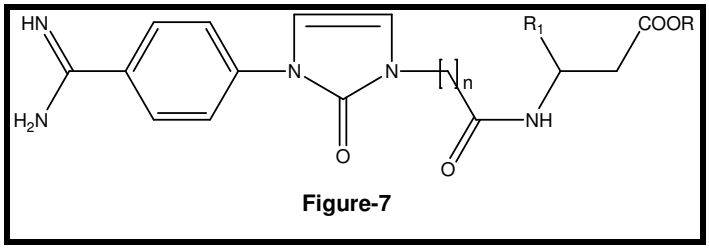


Figure-7

Potent anticonvulsant activity has been demonstrated by Walker *et. al.*[41] for a large number of l-(naphthyl)-3-l*H*-imidazoles containing a variety of functional groups in the alkylene bridge. The presence of a small oxygen function in the bridge, in general, confers a high therapeutic index between anticonvulsant and depressant activity. Clinical expectations are discussed for 1-(2-naphthoylmethyl)imidazole hydrochloride, which is undergoing development for testing in humans (Figure-8).

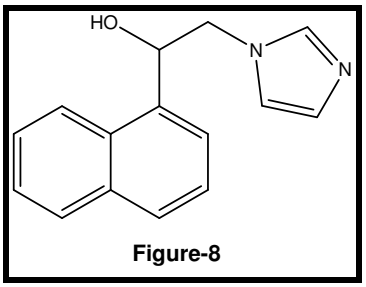
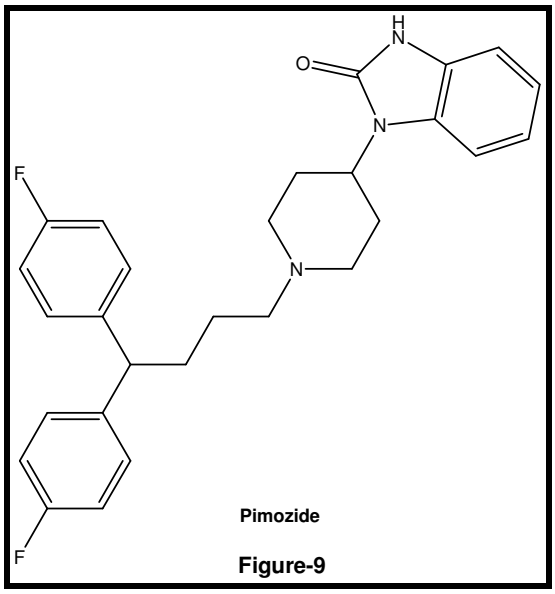


Figure-8

The Ca^{2+} channel blockers such as pimozide demonstrate potent sodium channel binding activity and are used for treatment of chronic pain.[42] The mechanism of action for all these compounds could perhaps be related to their common effects on a particular subtype of neuronal Na^{+} channel (Figure-9).



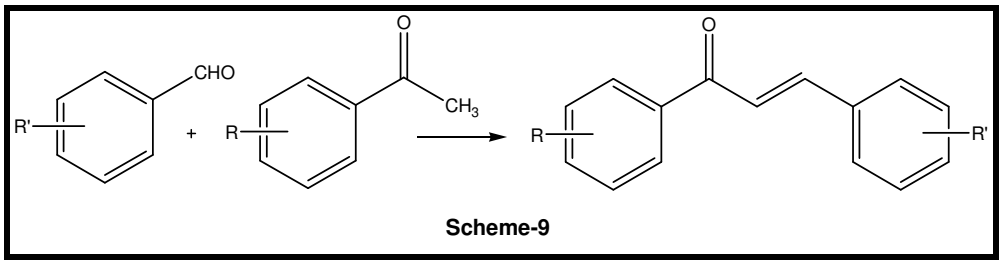
Pimozide

Figure-9

The importance of oxygenated imidazoles in the metabolism of histidine led Beiler[43] to synthesize 2-imidazolone-propionic acid and the corresponding imidazolidone for metabolic studies. The method involved the synthesis of 5-aminolevulinic acid and its condensation with potassium cyanate. High pressure reduction of the imidazolone was unnecessary; the solubility of the imidazolidone in acetic acid facilitated smooth reduction with Adam's catalyst at atmospheric pressure.

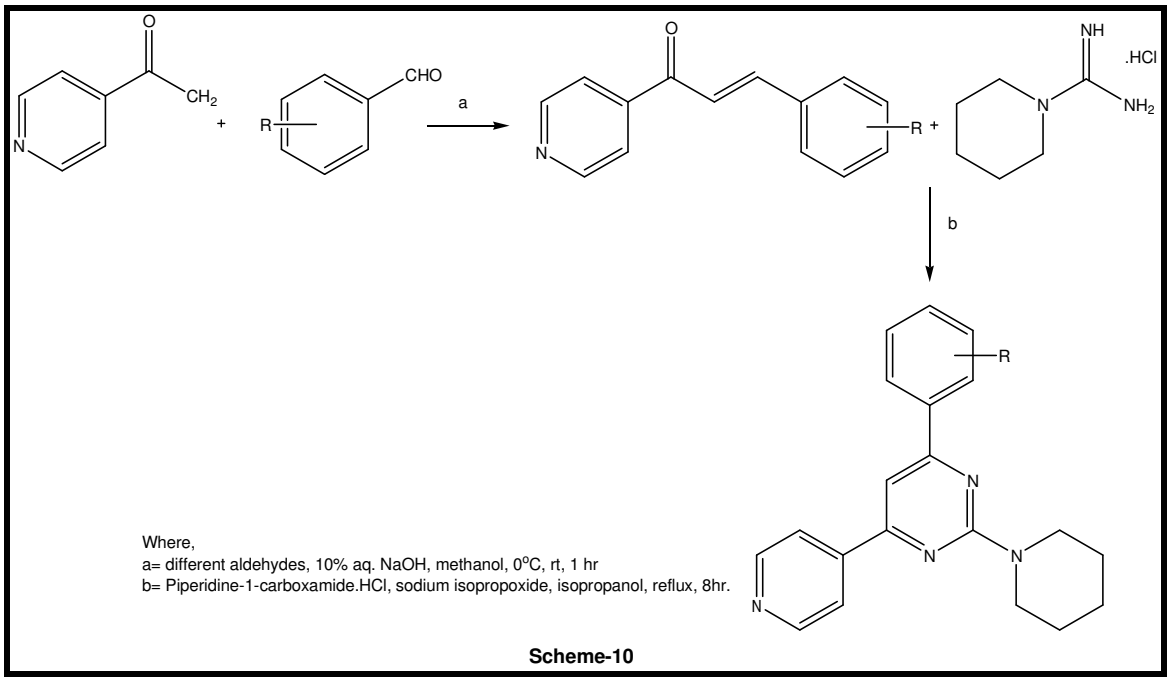
A series of chalcones and their derivatives have been identified as novel potential antimalarials using both molecular modeling and *in vitro* testing against the intact parasite. Some chalcone derivatives have been synthesized by Rongshi and co-workers[44] and were screened *in vitro* against both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falsiparum* and shown to be active at concentrations in the nanomolar range. The most active chalcone derivative, l-(2,5-dichlorophenyl)-3-(4-quinolinyl)-2-propen-l-one, had an IC_{50} value of 200 nM against both a chloroquine-resistant strain (W2) and a chloroquine sensitive strain (D6).

A series of chalcones was evaluated as antimitotic agents. One of these, (*E*)-l-(2,5-dimethoxyhenyl)-3-[4-(dimethylamino) phenyl]-2-methyl-2-propen-l-one), was found to be an effective antimitotic agent at a concentration of 4 nM in an in vitro HeLa cell test system, exhibited antitumor activity against L1210 leukemia and BI6 melanoma in experimental tumor models *in vivo*[45] (Scheme-9).



Scheme-9

Chauhan and co-workers[46] synthesized a series of 2,4,6-trisubstituted-pyrimidines and evaluated for their *in vitro* antimalarial activity agaist *P. falciparum*. The 2,4,6-trisubstituted-pyrimidines were synthesized by reacting 4-acetylpyridine with different aldehydes in NaOH and methanol to yield the corresponding chalcones (Scheme-10). The chalcones were further cyclized with imidine hydrochlorides in the presence of sodium isopropoxide to afford pyrimidines. It has been found that the chloro group in the aromatic ring system did not affected the activity of the compounds but the presence of methoxy group in the phenyl ring increased the activity. These compounds found out to be 5-40 times more potent than pyrimethamine. These identified pyrimidines are new lead in antimalarial chemotherapy.



Scheme-10

Laufer *et. al.*[47] reported a series of polysubstituted pyridin-4-yl imidazole inhibitors of p38 MAP (mitogen-activated protein) kinase which was prepared as small molecular anticytokine agents and drug candidates for the treatment of chronic inflammatory diseases. The contribution of substituents at the pyridinyl and imidazole moiety to selective inhibition of p38 without concomitant cytochrome P450 interaction was evaluated. Placement of a 1-phenylethyl (p38: IC_{50} 0.38 *t*M) or acetyl substituent at the exocyclic nitrogen of several 2-aminopyridine imidazoles led to the identification of potent p38 inhibitors which exceeded the starting lead ML 3375 (p38: IC_{50} 0.63 *t*M) in potency (Figure-10).

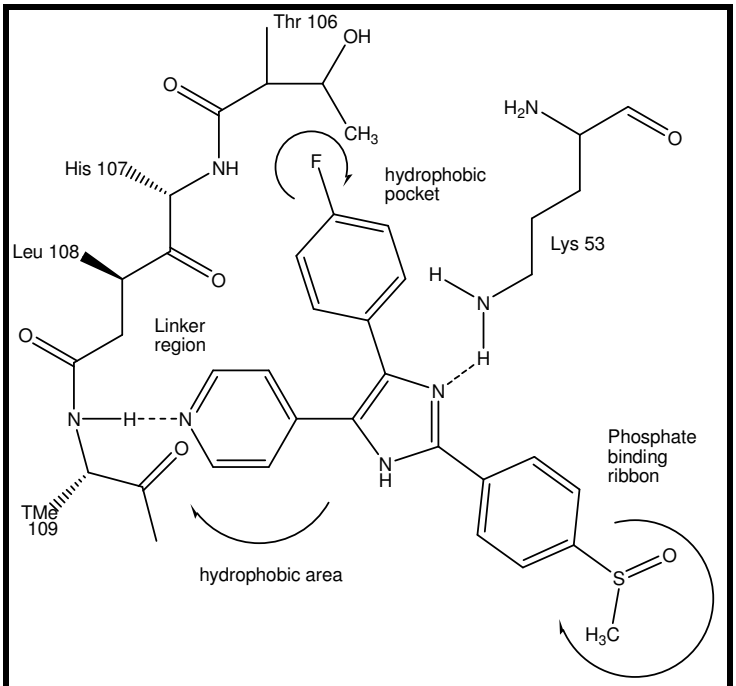


Figure-10: Schemetic drawing of important interactions between the prototypical pyridine-4-yl imidazole inhibitor SB 203580 and the ATP binding site of p38.

A preliminary modeling study related the enhanced bioactivity of 1-phenylethyl substituent to a novel interaction between its 1-phenylethylamino side chain and a hydrophobic pocket close to the linker region of p38. The most active p38 inhibitors in this series maintained their efficacy in functional PBMC (peripheral blood mononuclear cells) and whole blood assays (Figure-11).

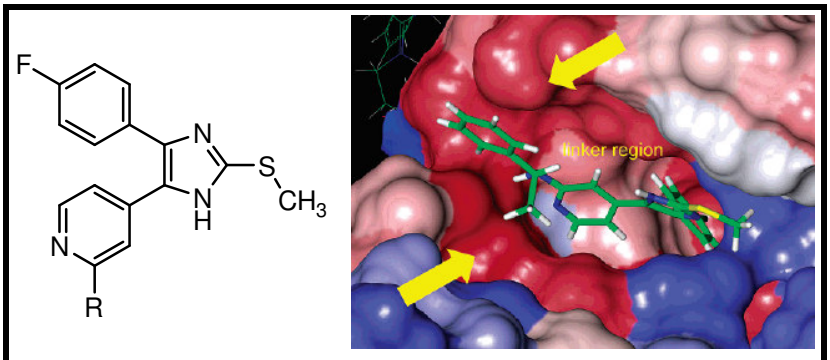


Figure-11: Banzylsulfulfanylimdazoles and Modeling of 7g into the ATP cleft of p38 MAP kinase. The arrows denote the hydrophobic area in close proximity to the linker region which stretches both above and below the pyridine ring.

Laufer and co-workers[48] then prepared novel 1,2,4,5-tetrasubstituted imidazole derivatives with high anti-inflammatory activity. Systematic optimization of the imidazole *N*-1 substituent resulted in a compound that potently inhibited the mitogen activated protein kinase p38 (p38 IC_{50}) 0.218 *i*M) as well as the release of the proinflammatory cytokines interleukin-1α (^{1}L-1α) and tumor necrosis factor R (TNFR) from human whole blood after stimulation with LPS. Furthermore, this compound exhibited reduced cytochrome P450 interaction in comparison with SB203580. This result is particularly important, since cytochrome P450 interaction is observed for some p38 inhibitors and in turn can potentially cause drug-drug interaction or lead to other hepatic changes such as P450 enzyme induction (Figure-12).

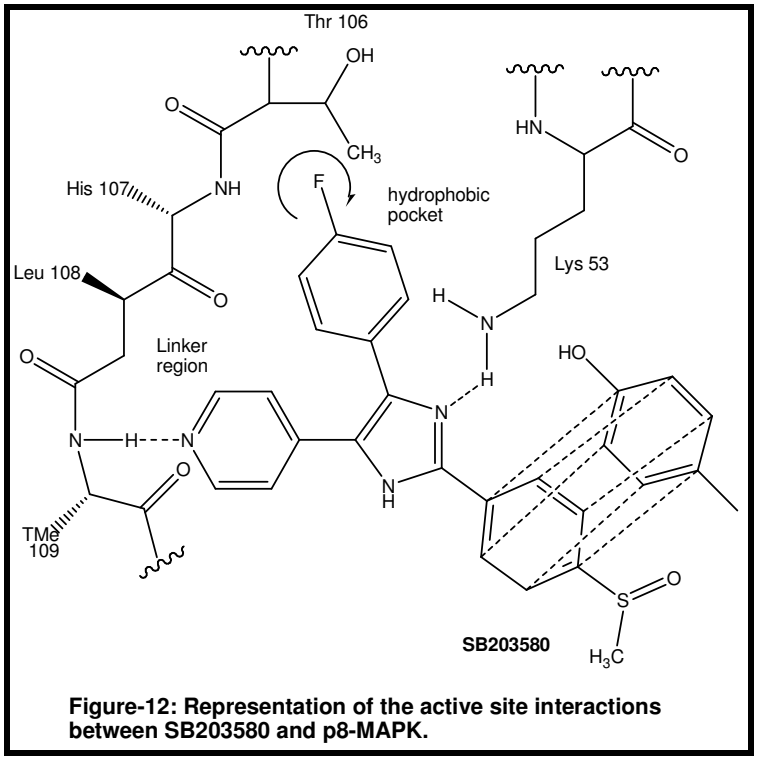


Figure-12: Representation of the active site interactions between SB203580 and p8-MAPK.

A new therapeutic drug target for the treatment of inflammatory disorders is the mitogen-activated protein kinase (MAPK) p38.[49-52] P38 is a serine/threonine kinase that is part of the stress-activated signal transduction cascade that transduces extracellular signals to intracellular response, *e.g.* cytokine production.[53,54] Activated p38 phosphorylates other

kinases or transcription factors, leading to mRNA stabilization or expression of certain target genes.[55-57]

Pyridinylimidazoles (*i.e.* SB203580) are potent and selective inhibitors of p38-MAPK7,[58,59] by competing with ATP for binding to the ATP pocket[60-62] This small hydrophobic pocket near the ATP-binding site is responsible for the selectivity of SB203580 for p38 compared to most other kinases[63,64] The pyridin-4-yl moiety is essential for the inhibitory potency and generates a pivotal hydrogen bond with the amino backbone of Met109 through its pyridinium nitrogen[65] (Figure-13).

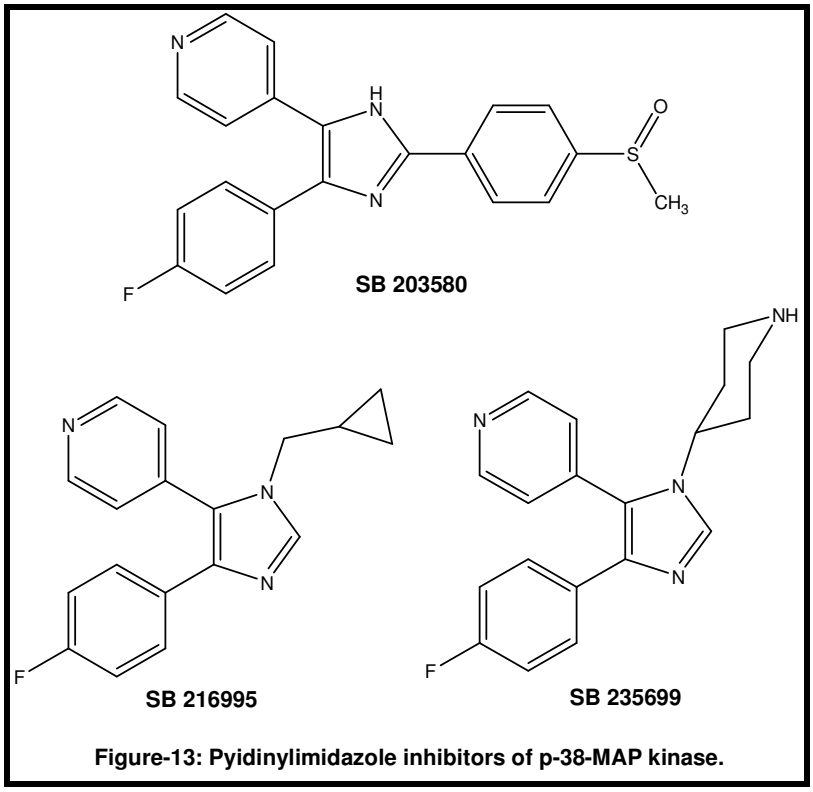
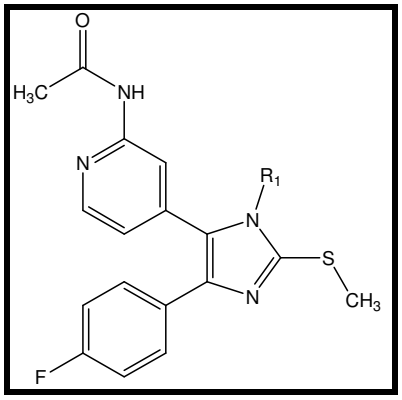
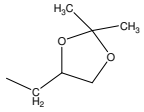
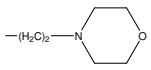
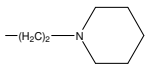
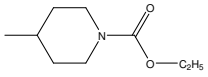


Figure-13: Pyidinylimidazole inhibitors of p-38-MAP kinase.

Table-2: Inhibition of p-38-MAP kinase by acetylaminopyridines.



Compd	R^1	IC_{50} ± (µM)
		P38α
1	-(CH_2)-OH	0.398±0.037 (n=3)
2	-$(CH_2)_2$-O-CH_3	0.218±0.010 (n=3)
3	-$(CH_2)_3$-OH	0.813±0.040 (n=3)
4	-$(CH_2)_3$-O-CH_3	0.205±0.027 (n=3)
5	-$(CH_2)_2$O-$(CH_2)_2$-OH	8.479±0.384 (n=2)
6	-(CH_2)-CH-(CH_3)-OH	8.692±0.188 (n=2)
7	-$(CH_2)_2$-NH-COCH	7.29 (n=1)
8	-$(CH_2)_2$-N$(CH_3)_2$	2.409±0.145 (n=3)
9	-$(CH_2)_2OCH_2CH{=}CH_2$	1.85±0.753 (n=3)
10	-$(CH_2)_2OCH_2C{\equiv}CH$	0.666±0.148 (n=3)
11	-$(CH_2)_2$-S-CH_3	0.431±0.1 (n=3)
12	-(CH_2)-CH$(OCH_3)_2$	4.099±1.690 (n=2)
13		3.732±2.116 (n=2)
14		2.029±0.686 (n=2)
16		1.343±0.576 (n=2)
17		> 10
SB 203580		0.462±0.025 (n=6)

[α] Results are given as mean of two independent experiments except stated otherwise.

3.3. Synthetic approach & present work

Over the years there have been many attempts to design and develop adenosine receptor antagonists and over the past decade the search for ligands that show selectivity toward individual receptors has intensified as the role of the receptors in many therapeutic areas expands.[66] Adenosine A1 receptors are in abundance in the mammalian brain and play role in important functions, such as in the modulation of neurotransmitter release, sleep regulation and cognition enhancement, has been thoroughly investigated.[67-69] For this reason, it is essential that a compound targeted at these therapeutic areas is able to cross the blood brain barrier (BBB). Research into the BBB and the ability of a compound to cross it has become a highly investigated topic in recent years.

In the wider field of adenosine receptor ligands, (dihydro) pyrimidines have been developed and explored as A3 receptor antagonists by Jacobson *et. al.*[70-72] and as adenosine receptor agonists by Bayer.[73] Adenosine receptor antagonists usually possess a bi- or tricyclic heteroaromatic structure at their core with varying substitution patterns to achieve selectivity and/or greater affinity.

Chang and co-workers[74] synthesized two novel series of pyrimidines, A & B, possessing good potency at the adenosine A1 receptor and desirable PSA values (Figure-14). LUF 5735 displayed excellent A1 affinity (Table-3).

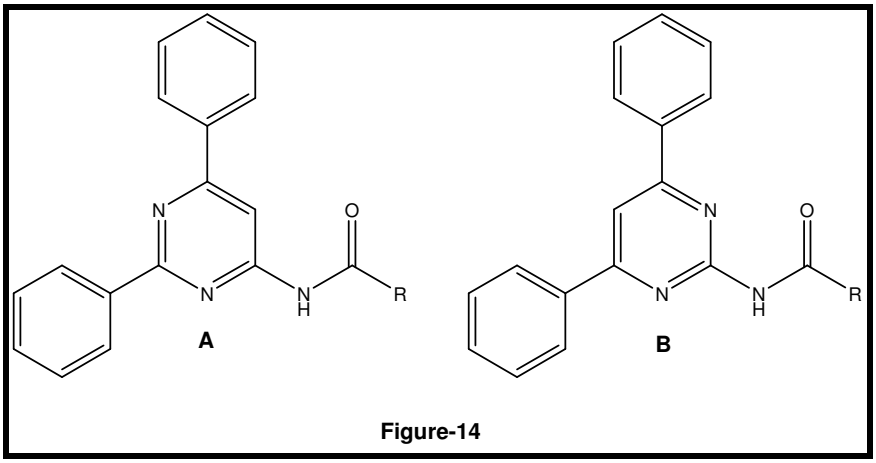
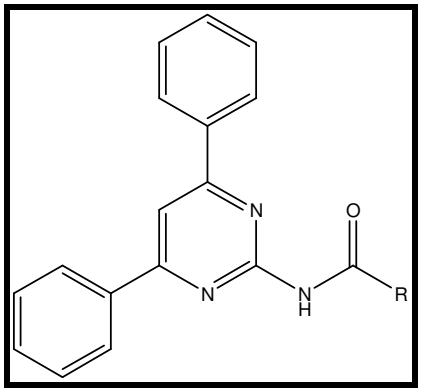


Figure-14

Al-Hajjar and Sabri[75] described a method in which guanidine was reacted with benzylideneacetophenone. This 2-aminopyrimidine was then reacted with the respective acid chlorides in the presence of triethylamine to give the desired 2-amido compounds. With the alkyl amides, significant improvements were made over the phenyl substituents at the L1 pocket. In the straight-chained alkyls, from methyl to pentyl (7-10) a distinct optimum is apparent for a two-carbon chain at the A1 receptor, with an affinity of 9.5 nM. This pattern is repeated at the adenosine 2A receptor, with a *Ki* of 82 nM. At the A3 receptor, however, the methyl substituted derivative, with an affinity of 7 nM, was the better compound. In terms of selectivity, compound 7 was 5-fold more selective for the A3 receptor than for the A1 receptor, while, in a slight reversal of this, compound 8 showed a 2-fold selectivity in favor of the A1 adenosine receptor over the A3 receptor. Better selectivity for the A1 adenosine receptor came with the *n*-propyl derivative with an almost 7-fold better affinity over the A2A receptor.

Based on these observations, a new series of 24 compounds have been synthesized by taking 2-imidazolone-4-carboxylic acid and various 2-amino-4,6-di-sibstituted pyrimidines and making an amide linkage between them.

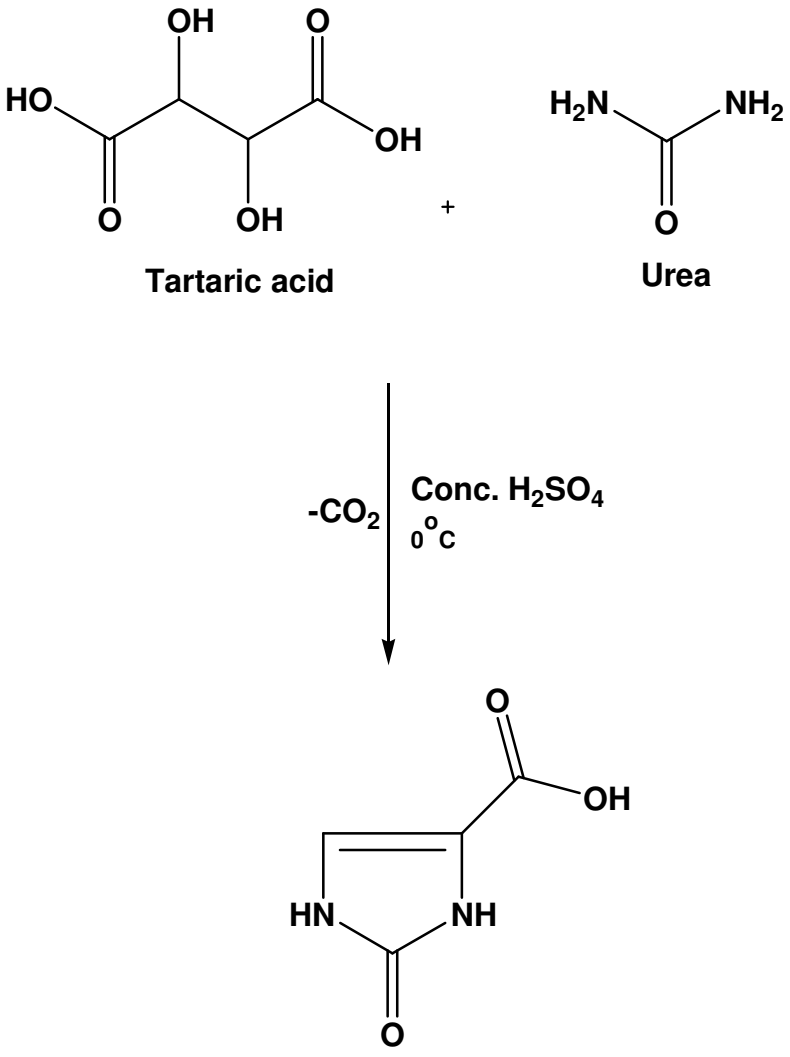
Table-3: Affinities and PSA values of the 4,6-diphenyl-substituted-2-amidopyrimidines 22-40 in radioligand binding assays at the human adenosine receptors.



Compd	R	Calcd. PSA values (aÅ^2)	Ki (nM) or % displacement [a]			
			hA_1 [b]	hA_{2A} [c]	hA_{2B} [d]	hA_3 [e]
1	Ph	53	309±73	5%		38%
2	4-Cl-Ph	53	0%	0%		3280±1700
3	4-MeOPh	64	31%	45%		41%
4	4-Me-Ph	53	37%	0%		13%
5	3,4-DiCl-Ph	53	0%	0%		30%
6	3-Cl-Ph	53	368±66	22%		41%
7	Me	53	483±90	31%		237±150
8	Et	53	46.4±2.5	893±160		547±47
9 (LUF 5735)	Pr	53	3.70±1.9	7%	54%	38%
10	Bu	53	27.6±10	0%		23%
11	Pent	52	28%	0%		24%
12 (LUF 5737)	I-Pr	51	8.87±4.2	44%	79%	45%
13	T-Bu	50	224±120	0%		4%
14	CH_2CHMe_2	51	25.1±6.6	42%		23%
15	$CHEt_2$	51	27.1±5.7	11%		27%
16	C-Prop	52	24.9±4.9	228±95		676±120
17	C-But	53	107±36	33%		18%
18 (LUF 5751)	C-Pent	51	11.4±2.4	11%	42%	39%
19	C-Hex	51	119±42	31%		9%

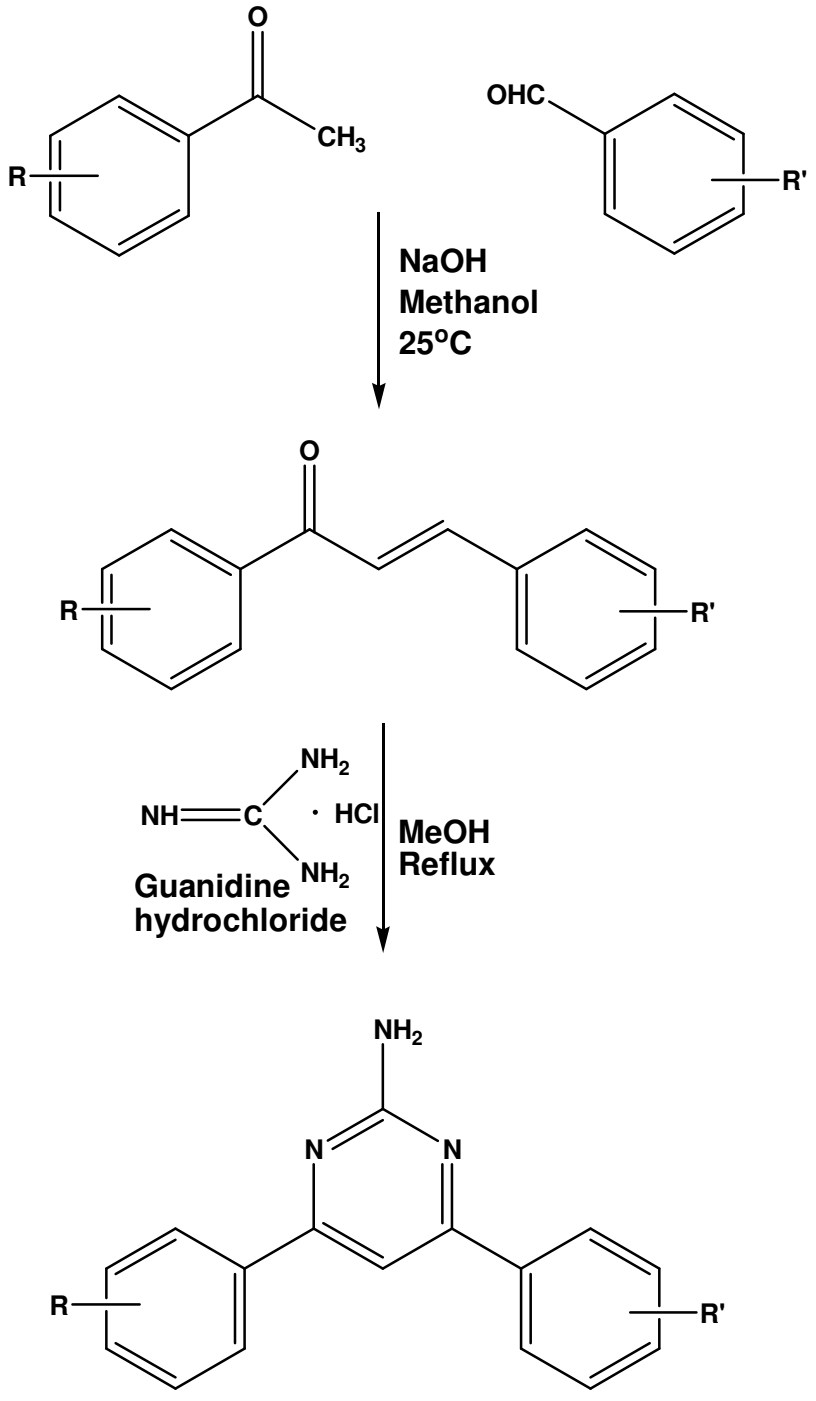
[a] *K*i ± SEM (n=3), % displacement (n=2). [b] Displacement of specific [^{3}H]DPCPX binding in CHO cell membranes expressing human adenosine A_1 receptors or % displacement of specific binding at 1µM concentrations. [c]Displacement of specific [^{3}H]ZM241385 binding in HEK 293 cell membranes expressing human adenosine A_{2A} receptors or % displacement of specific binding at 1µM concentrations. [d] % Displacement of specific [^{3}H]MRS1754 binding in CHO cell membranes stably transfected with the human adenosine A_{2B} receptor at 1 µM concentrations. [e] Displacement of specific [^{125}I]AB-MECA binding in HEK 293 cell membrane expressing human adenosine A_3 receptors or % displacement of specific binding at 1µM concentrations.

3.4. REACTION SCHEME-I



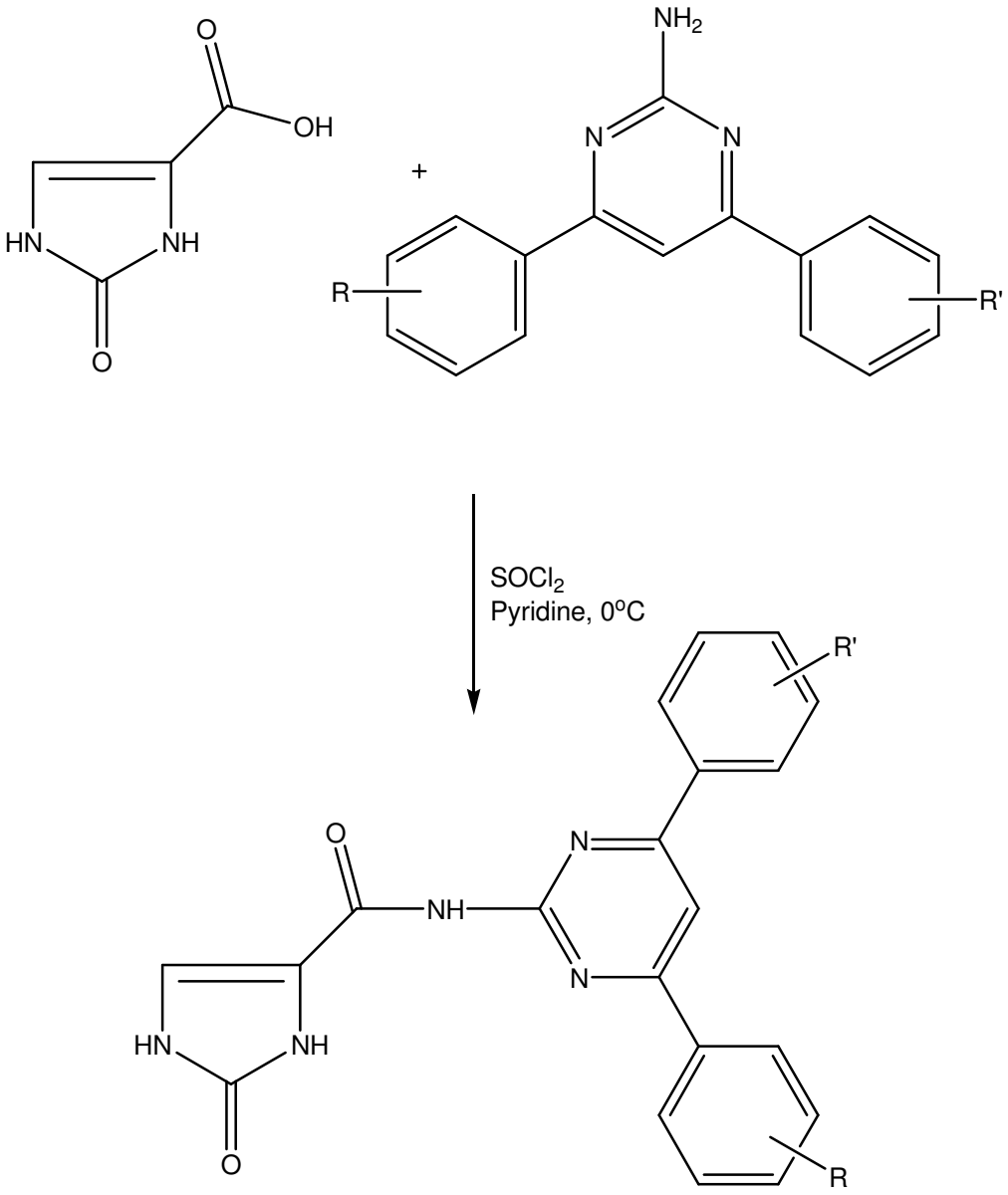
Synthesis of-2-Imidazolone-4-carboxylic acid

REACTION SCHEME-II



Synthesis of 2-amino-4,6-disubstituted phenyl pyrimidine

REACTION SCHEME-III



Synthesis of *N*-(4, 6-diphenylpyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamide

3.5. Experimental

Method for preparation of 2-imidazolone-4-carboxylic acid[11]

To a 2 liter three-necked flask fitted with a stirrer, 400 cc of 13% fuming sulfuric acid was added. After cooling this to 0°C, 11g of finely powdered anhydrous tartaric acid was added at such a rate that the temperature did not rise above 10°C, which required 10 minutes. The ice-bath was removed and 100g of urea was then added. The temperature during this operation rose rapidly and was finally held with the aid of a burner at 80°C for 30 min. A vigorous reaction ensued with the concomitant evolution of carbon monoxide and carbon dioxide the reaction mixture rapidly turned black. After completion of the reaction, the contents of the flask were cooled and poured on 1200 g of ice. An amorphous chocolate colored precipitate immediately separated. This, having stood in the icebox overnight, was filtered, yield of crude dry product 35 g. It was decolorized by boiling a water solution with large portions of bone black and finally recrystallizing from water from which it was separated as colorless needles, it melted with vigorous effervescence at 260°C (Reported m.p. 261°C), 2-imidazolone-4-carboxyllic acid is slightly soluble in boiling water and insoluble in organic solvents.

General method for the preparation of chalcones[45]

A mixture of methanol (50 ml), acetophenone (0.015 mol), benzaldehyde (0.015 mol) and 50% aqueous NaOH (1 ml) was stirred for 18 hr at ambient temperature. The resulted solid was filtered, dried and recrystalized with methanol to give the product as pure white needles. m.p. 96-98°C (Reported m.p. 94-96°C)

General method for preparation of 2-amino-4,6-disubstituted phenyl pyrimidines[74,76]

A mixture of chalcone (1.1 equiv) and guanidine hydrochloride (1 equiv) was refluxed in methanol (150 ml). Sodium hydroxide (3.2 equiv) was dissolved in a minimum amount of water (40 ml) and added drop wise to the refluxing mixture. The reaction mixture was then stirred at reflux for a further 6 h and poured into 250 ml of cold water. The product

obtained was filtered, washed with water and crystallized from ethyl acetate to give orange coloured needles. Yield, 31%.

General method for preparation of *N*-(4, 6-diphenylpyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamide[153]

Method I

A mixture of 2-imidazolone-4-carboxylic acid (0.1 M) and 2-amino-4,6-disubstituted phenyl pyrimidine (0.1 M) was taken in pyridine (10 ml) and was stirred at 0^0C. Thionyl chloride (10 ml) was added drop wise to the above solution within 30 minutes. After the color of the solution changed to dark, it was further stirred for two hours. The resultant mass was poured into crushed ice to get crude amide, which was washed, filtered and dried. It was thoroughly washed with hot water and ethyl acetate and was finally recrystalized with dimethyl formamide to obtain the corresponding amide in crystalline form.

Method II

To a mixture of the amino-diphenylpyrimidine (0.202 mM, 1 equiv) in 1,4-dioxane (5 ml) was added triethylamine (0.223 mM, 1.1 equiv) , followed by the appropriate acid chloride (0.304 mM, 1.5 equiv). This was stirred at reflux until no starting material was identified. The progress of the reaction was monitered by TLC. Upon completion, the reaction mixture was washed with ethyl acetate and finally recrystallized with petroleum ether-ethyl acetate to yield the corresponding amide in crystalline form.

The same procedure was followed for the preparation of all the amides listed in Table 4.

3.6. Protocol for determination of TNF-α mRNA[77]

Plasma was collected from ACD blood after the cells were pelleted at 1,000 x *g* for 10 min. The cell pellet was resuspended in Dulbecco's phosphate-buffered saline (PBS) and peripheral blood mononuclear cells (PBMC) were prepared by centrifugation through Ficoll-Hypaque and resuspended in fresh plasma at approximately 2×10^7 /ml. Plasma was distributed in 250-µl aliquots into 4 ml polypropylene tubes and incubated in 5% CO_2 at 37°C. Lipopolysaccharide (LPS) (2.5 ml of a solution at 100 × final concentration) was added at intervals so that all reactions could be terminated together. To detect bioactive LPS, 50 µl of the PBMC-plasma suspension was added, and the reaction mixtures were incubated an additional 30 min. Cells were harvested, and TNF-α mRNA expression was analyzed by Reverse Transcriptase-PCR (RT-PCR) by pelleting the cells at 1,000 x *g* for 7 min at 4°C. The supernatant liquid was carefully aspirated, with care taken not to disturb the soupy pellet. Total RNA was prepared from the cells by using a kit on the basis of the method of Chomczynski and Sacchi, by lysing the pelleted cells in 0.5 ml of solution D (4 M guanidine thiocyanate, 20 mM sodium citrate [pH 7.0], 0.5% Sarkosyl, 0.1 M β-mercaptoethanol). Recovery of the RNA precipitates was maximized by increasing the centrifugation times to 60 min. All recovered RNA for each sample was converted to cDNA in a 50-µl reaction mixture with oligo (dT) and 500 U of Moloney murine leukemia virus RT according to recommended conditions. Amplifications were done with 1 µl of cDNA in a final 20-µl reaction mixture volume (10 mM Tris-Cl [pH 8.8], 50 mM KCl, 1.8 mM $MgCl_2$, 0.1% Triton X-100, 0.2 mM deoxynucleoside triphophates, 0.5 µM each primer [with 50,000 to 250,000 cpm of one ^{32}P-5'-end-labelled primer], 0.4 U of *Taq* polymerase). Reaction mixtures were assembled on ice, transferred to a prewarmed block (> 50°C), and cycled at 94.5°C (20 s), 60°C (30 s), and 72°C (60 s) for 22 cycles. Amplification products were separated on 6% polyacrylamide gels, and bands of the appropriate sizes were quantified by using a 400E PhosphoImager. To allow comparison of mRNA expression patterns from different donors, the data for each gene were normalized by the following formula:

$$\textbf{Relative amplified product} = (P/P_{max}) \times 100$$

Where, P is the amount of amplified product obtained at each point and P_{max} is the maximum amount of amplified product obtained in a particular experiment. Results are reported as the mean relative amplified product (± standard errors of the means [SEM]), unless otherwise noted.

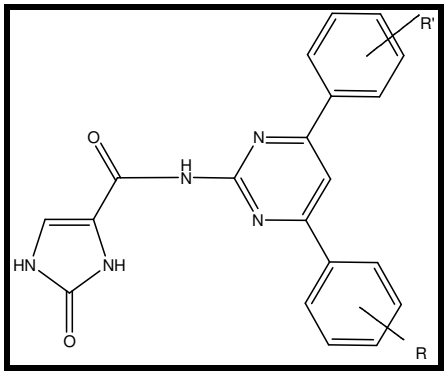
For secreted cytokines, blood was incubated as described for the RT-PCR analysis, but the reactions were stopped by the addition of 0.75 ml of ice-cold RPMI 1640. Protein levels were measured by enzyme-linked immunosorbent assay (ELISA) with kits for TNF-α and IL-1β, following the manufacturers' instructions. Each sample was assayed in triplicate. Again, to compare expression patterns from different donors, the data for each donor were normalized by the following formula:

$$\textbf{Relative secreted product} = (S/S_{max}) \times 100$$

Where, S is the concentration of cytokine measured at each point and Smax is the maximum concentration of cytokine measured in a particular experiment. Results are reported as the mean relative secreted product (6 SEM) for Fig. 5A or the mean relative secreted product.

The result obtained is tabulated in table-5.

3.7. Table 4: Physical data of *N*-(4, 6-diphenylpyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamides



Codes	Substitution		Molecular formula	Molecular weight	Melting point (^{O}C)	Rf value	% of Yield
	R	R'					
JT-51	H	H	$C_{20}H_{15}N_5O_2$	357.36	146-148	0.43	43
JT-52	4-F	4-F	$C_{20}H_{13}F_2N_5O_2$	393.34	212-214	0.47	54
JT-53	4-Cl	4-Cl	$C_{20}H_{13}ClN_5O_2$	426.25	226-228	0.40	46
JT-54	4-F	4-CH_3	$C_{21}H_{16}FN_5O_2$	389.38	196-198	0.52	48
JT-55	4-F	4-OCH_3	$C_{21}H_{16}FN_5O_3$	409.38	144-148	0.54	52

TLC Solvent system: Dichloromethane: Methanol :: 6:40.48

Ref.: Chang, L. C. W.; Spanjersberg, R. F.; Frijtag Drabbe Kunzel, J. K.; Mulder-Krieger, T.; Hout, G.; Beukers, M. W.; Brussee, J.; IJzerman, A. P. 2,4,6-Trisubstituted pyrimidines as a new class of selective adenosine A_1 receptor antagonists, *J. Med. Chem.* **2004**, 47, 6529-6540.

3.7. Table 4 (contd.): *N*-(4, 6-diphenylpyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamides

Codes	Substitution		Molecular formula	Molecular weight	Melting point (^{O}C)	Rf value	% of Yield
	R	R'					
JT-56	4-Br	4-CH_3	$C_{21}H_{16}BrN_5O_2$	450.28	246-248	0.61	55
JT-57	H	4-OCH_3	$C_{22}H_{19}N_5O_4$	387.39	212-216	0.55	46
JT-58	4-OCH_3	4-OCH_3	$C_{21}H_{17}N_5O_3$	398.36	166-168	0.57	48
JT-59	H	3,4,5-tri-OCH_3	$C_{23}H_{21}N_5O_5$	447.44	136-138	0.47	53
JT-60	4-F	H	$C_{20}H_{14}FN_5O_2$	375.35	208-212	0.63	54
JT-61	4-Cl	H	$C_{20}H_{14}ClN_5O_2$	391.81	186-188	0.46	41
JT-62	4-Br	H	$C_{20}H_{14}BrN_5O_2$	436.26	162-164	0.32	56
JT-63	4-CH_3	H	$C_{21}H_{17}N_5O_2$	371.39	188-190	0.49	47
JT-64	4-OCH_3	H	$C_{21}H_{17}N_5O_3$	387.39	234-236	0.44	44
JT-65	4-OCH_3	2-Cl	$C_{21}H_{16}ClN_5O_3$	421.83	266-268	0.54	53

3.7. Table 4 (contd.): *N*-(4, 6-diphenylpyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamides

Codes	Substitution		Molecular formula	Molecular weight	Melting point (^{O}C)	Rf value	% of Yield
	R	R'					
JT-66	3-NO_2	2-Cl	$C_{20}H_{13}ClN_6O_4$	36.80	156-158	0.49	45
JT-67	4-OCH_3	4-F	$C_{21}H_{16}FN_5O_3$	405.38	142-144	0.52	39
JT-68	4-Cl	2-OH	$C_{20}H_{14}ClN_5O_3$	407.80	210-212	0.50	46
JT-69	2-Cl	2,5-di-OCH_3	$C_{22}H_{18}ClN_5O_4$	451.86	234-236	0.56	53
JT-70	4-Cl	2,5-di- OCH_3	$C_{22}H_{18}ClN_5O_4$	452.86	230-234	0.58	57
JT-71	3-NO_2	2,5-di- OCH_3	$C_{22}H_{18}N_6O_6$	462.41	198-200	0.41	43
JT-72	4-Br	4-OCH_3	$C_{21}H_{16}BrN_5O_3$	466.28	256-258	0.63	48
JT-73	H	4-CN	$C_{21}H_{14}N_6O_2$	382.37	178-180	0.47	51
JT-74	4-OCH_3	4-CN	$C_{22}H_{16}N_6O_3$	412.42	172-174	0.53	56

3.8. Biological activity results

Table-5 : *In-vitro* activity for IL-6 and TNF-α in monocytes at three concentration (0.3, 3, 30) uM in human monocytes assay.

Sr. No.	Sample code	IC_{50} for IL-6 Inhibition (µM)	IC_{50} for TNF-α Inhibition (µM)	Toxicity (µM)
1	JT-51	3	ND	> 100
2	JT-52	< 0.3	ND	> 100
3	JT-53	< 0.3	ND	> 100
4	JT-54	3	ND	> 100
5	JT-55	< 0.3	ND	> 100
6	JT-56	3	ND	> 100
7	JT-57	30	ND	> 100
8	JT-58	3	ND	> 100
9	JT-59	30	ND	> 100
10	JT-60	30	ND	> 100
11	JT-61	< 0.3	ND	> 100
12	JT-62	30	ND	> 100

3.8. Table-5 (contd.) : *In-vitro* activity for IL-6 and TNF-α in monocytes at three concentration (0.3, 3, 30) uM in human monocytes assay.

Sr. No.	Sample code	IC_{50} for IL-6 Inhibition (µM)	IC_{50} for TNF-α Inhibition (µM)	Toxicity (µM)
13	JT-63	< 0.3	ND	> 100
14	JT-64	30	ND	> 100
15	JT-65	3	ND	> 100
16	JT-66	30	ND	> 100
17	JT-67	30	ND	> 100
18	JT-68	30	ND	> 100
19	JT-69	3	ND	> 100
20	JT-70	30	ND	> 100
21	JT-71	0.3	ND	> 100
22	JT-72	30	ND	> 100
23	JT-73	3	ND	> 100
24	JT-74	30	ND	> 100

From the above results, it has been concluded that the synthesized compounds are inactive at the selected dose.

3.9. Spectral study

Infra Red spectra

IR Spectra were taken on SHIMADZU IR-435 Spectrometer using KBr Pellet method. The N-H stretch in *N*-(4,6-diphenylpyrimidin-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamides was observed at 3500-3400 cm^{-1}. In some cases, free hydroxyl group (OH) was observed at 3550-3580 cm^{-1}. The characteristic carbonyl group (>C=O) was observed between 1660-1735 cm^{-1}. The compounds showed the ring skeleton vibrations at 1600-1660, 1550-1590, 1550-1520, 1470-495 cm^{-1}. The methoxy groups were observed between 1780-1850 cm^{-1}. The amide groups were observed between 1620-1650 cm^{-1}. The methyl groups were observed between 1350-1380 cm^{-1}. The holagen groups were observed between 720-840 cm^{-1}.

^{1}H NMR spectra

^{1}H NMR Spectra were recorded on a Bruker AC 400 MHz FT-NMR Spectrometer using TMS (Tetramethyl Silane) as an internal standard and DMSO-d_6 as a solvent. In the NMR spectra of 5-benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-ones, various proton values like methyl (-CH_3), aromatic protons (Ar-H), N-H protons and sometimes, hydroxyl (-OH) were observed and recorded in individual compound details.

The values for methyl (-CH_3) proton is seen between 1.12-1.96 δ ppm. as well as methoxy proton (-OCH_3)was observed between 3.2-3.9 δ ppm respectively. The aromatic protons (Ar-H) showed multiplets between 6.00-8.20 δ ppm. The N-H protons were observed between value 4.0-10.0 δ ppm.

^{13}C NMR spectra

^{13}C NMR spectra were recorded on Bruker AC 400 MHz instrument using DMSO as the solvent with TMS (Tetramethyl Silane) as respective internal standard.

Mass spectra

The mass spectrum of compounds was recorded by GCMS-QP2010 spectromeyter (EI method). The mass spectrums of compounds were obtained by positive chemical ionization mass spectrometry. The molecular ion peak and the base peak in all compounds were clearly obtained in spectra. The molecular ion peak (M^+) values are in good agreement with molecular formula of all the compounds synthesized. The probable mass fragmentation of *N*-(4,6-diphenylpyrimidin-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamides is shown in the spectra.

C, H, N analysis

Elemental analysis of the compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

3.10. Spectral characterization

***N*-(4,6-Diphenylpyrimidin-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-51)**

IR (KBr) cm^{-1}: 3403, 3435 (N-H str.), 2857 (C-H str.), 1678, 1720 (>C=O), 1692 (CONH), 1589, 1488, 1442, 1417 (ring skeleton).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 6.49 (s, 1H, -CH), 7.63 (s, 1H, NH), 7.64 (s, 1H, NH), 7.20-7.84 (m, 11H, Ar-H), 9.84 (s, 1H, CONH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 21.40, 47.26, 48.04, 50.81, 54.44, 82.48, 109.54, 119.40, 127.07, 132.95, 136.99, 154.67, 176.84, 198.10.

Mass: [m/e (%)], M. Wt. :357, 343, 328, 313, 301, 285, 273, 258, 230, 191, 171, 164, 150, 135, 122, 110, 95, 80, 69, 44.

C, H, N analysis, Calculated: C, 67.22; H, 4.23; N, 19.60. **Found:** C, 67.18; H, 4.22; N, 19.56.

***N*-[4,6-Bis(4-fluorophenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-52)**

IR (KBr) cm^{-1}: 3412, 3443 (N-H str.), 2756 (C-H str.), 1686, 1732 (>C=O), 1678 (CONH), 723 (C-F).

C, H, N analysis, Calculated: C, 61.07; H, 3.33; N, 17.80. **Found:** C, 61.02; H, 3.26; N, 17.77.

***N*-[4,6-Bis(4-chlorophenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide(JT-53)**

IR (KBr) cm^{-1}: 3356, 3424 (N-H str.), 2855 (C-H str.), 1655, 1712 (>C=O), 1645 (CONH), 729 (C-Cl).

C, H, N analysis, Calculated: C, 56.35; H, 3.07; N, 16.43. **Found:** C, 56.31; H, 3.02; N, 16.40.

***N*-[4-(4-Fluorophenyl)-6-(4-methylphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-54)**

IR (KBr) cm^{-1}: 3378, 3402 (N-H str.), 2823 (C-H str.), 1658, 1727 (>C=O), 1635 (CONH),1328 (CH_3), 745 (C-Cl).

C, H, N analysis, Calculated: C, 64.78; H, 4.14; N, 17.99. **Found:** C, 64.76; H, 4.11; N, 17.97.

***N*-[4-(4-Fluorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-55)**

IR (KBr) cm^{-1}: 3424, 3467 (N-H str.), 2824 (C-H str.), 1678, 1724 (>C=O), 1649 (CONH), 1864 (OCH_3), 734 (C-F).

C, H, N analysis, Calculated: C, 62.22; H, 3.98; N, 17.28. **Found:** C, 62.24; H, 3.90; N, 17.24.

***N*-[4-(4-Bromophenyl)-6-(4-methylphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-56)**

IR (KBr) cm^{-1}: 3534, 3487 (N-H str.), 2865 (C-H str.), 1698, 1734 (>C=O), 1658 (CONH), 1574, 1465, 1437, 1417 (ring skeleton), 1339 (CH_3), 787 (C-Br).

C, H, N analysis, Calculated: C, 56.01; H, 3.58; N, 15.55. **Found:** C, 55.97; H, 3.53; N, 15.51.

***N*-[4-(4-Methoxyphenyl)-6-phenylpyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-57)**

IR (KBr) cm^{-1}: 3512, 3487 (N-H str.), 2838 (C-H str.), 1673, 1727 (>C=O), 1569, 1441, 1479, 1438 (ring skeleton), 1638 (OCH_3).

C, H, N analysis, Calculated: C, 65.11; H, 4.42; N, 18.08. **Found:** C, 65.03; H, 4.37; N, 18.02.

***N*-(4,6-bis(4-Methoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-58)**

IR (KBr) cm^{-1}: 3436, 3449 (N-H str.), 2828 (C-H str.), 1683, 1725 (>C=O), 1635 (CONH), 1669, 1635 (OCH_3).

C, H, N analysis, Calculated: C, 63.30; H, 4.59; N, 16.78. **Found:** C, 63.28; H, 4.54; N, 16.76.

2,3-Dihydro-*N*-(4-(3,4,5-trimethoxyphenyl)-6-phenylpyrimidine-2-yl)-2-oxo-1*H*-imidazole-5-carboxamide (JT-59)

IR (KBr) cm^{-1}: 3514, 3479 (N-H str.), 2828 (C-H str.), 1682, 1722 (>C=O), 1654 (CONH), 1568, 1468, 1432, 1401 (ring skeleton), 1657, 1645, 1632 (OCH_3).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 3.00 (s, 9H, 3×OCH_3), 5.48 (s, 1H, -CH), 7.35, 7.35 (s, 1H, NH), 7.36 (s, 1H, NH), 7.20-7.58 (m, 8H, Ar-H), 9.19 (s, 1H, CONH).

C, H, N analysis, Calculated: C, 61.74; H, 4.73; N, 15.65. **Found:** C, 61.72; H, 4.68; N, 15.62.

***N*-[4-(4-Fluorophenyl)-6-phenylpyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-60)**

IR (KBr) cm^{-1}: 3510, 3486 (N-H str.), 2836 (C-H str.), 1684, 1715 (>C=O), 1638 (CONH), 1567, 1484, 1446, 1427 (ring skeleton), 748 (C-F).

C, H, N analysis, Calculated: C, 61.74; H, 4.73; N, 15.65. **Found:** C, 61.71; H, 4.70; N, 15.64.

***N*-[4-(4-Chlorophenyl)-6-phenylpyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-61)**

IR (KBr) cm^{-1}: 3519, 3483 (N-H str.), 2837 (C-H str.), 1683, 1734 (>C=O), 1648 (CONH), 1569, 1425, 1469, 1403 (ring skeleton), 724 (C-Cl).

Mass: [m/e (%)], M. Wt. : 391, 362, 341, 286, 256, 218, 192, 160, 128, 115, 79, 64, 44.

C, H, N analysis, Calculated: C, 61.31; H, 3.60; N, 17.87. **Found:** C, 61.28; H, 3.59; N, 17.84.

***N*-(4-(4-Bromophenyl)-6-phenylpyrimidin-2-yl)-2,3-dihydro-2-oxo-1H-imidazole-4-carboxamide (JT-62)**

IR (KBr) cm^{-1}: 3509, 3485 (N-H str.), 2848 (C-H str.), 1682, 1717 (>C=O), 1675 (CONH), 1557, 1489, 1443, 1406 (ring skeleton), 716 (C-Br).

Mass: [m/e (%)], M. Wt. : 435, 368, 354, 344, 328, 301, 278, 249, 235, 221, 209, 180, 165, 16, 132, 120, 104, 91, 77, 66, 44.

C, H, N analysis, Calculated:C, 55.06; H, 3.23; N, 16.05. **Found:** C, 55.01; H, 3.20; N, 16.02.

2,3-Dihydro-2-oxo-*N*-(4-phenyl-6-*p*-tolylpyrimidin-2-yl)-1*H*-imidazole-4-carboxamide (JT-63)

IR (KBr) cm^{-1}: 3435, 3426 (N-H str.), 2879 (C-H str.), 1657, 1706 (>C=O), 1583, 1485, 1443, 1456 (ring skeleton), 1346 (CH_3).

C, H, N analysis, Calculated: C, 67.91; H, 4.61; N, 18.86. **Found:** C, 67.89; H, 4.56; N, 18.82.

***N*-[4-(4-Methoxyphenyl)-6-phenylpyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-64)**

IR (KBr) cm^{-1}: 3494, 3456 (N-H str.), 2859 (C-H str.), 1659, 1723 (>C=O), 1622 (CONH), 1569, 1474, 1457, 1427 (ring skeleton), 1857 (OCH_3).

C, H, N analysis, Calculated: C, 65.11; H, 4.42; N, 18.08. **Found:** C, 65.03; H, 4.37; N, 18.03.

***N*-[4-(2-Chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-65)**

IR (KBr) cm^{-1}: 3456, 3424 (N-H str.), 2878 (C-H str.), 1684, 1702 (>C=O), 1658 (CONH), 1635 (OCH_3), 739 (C-Cl).

Mass: [m/e (%)], M. Wt. :423, 357, 340, 332, 280, 266, 251, 237, 213, 209, 180, 163, 146, 132, 120, 104, 91, 77, 65, 44.

C, H, N analysis, Calculated: C, 59.79; H, 3.82; N, 16.60. **Found:** C, 59.74; H, 3.76; N, 16.56.

***N*-[4-(2-Chlorophenyl)-6-(3-nitrophenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-66)**

IR (KBr) cm^{-1}: 3485, 3450 (N-H str.), 2868 (C-H str.), 1691, 1700 (>C=O), 1673 (CONH), 768 (C-Cl).

C, H, N analysis, Calculated: C, 54.99; H, 3.00; N, 19.24. **Found:** C, 54.93; H, 2.87; N, 19.16.

***N*-[4-(4-Fluorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-67)**

IR (KBr) cm^{-1}: 3445, 3426 (N-H str.), 2826 (C-H str.), 1695, 1716 (>C=O), 1758 (OCH_3), 1636 (CONH), 745 (C-Cl).

C, H, N analysis, Calculated: C, 62.22; H, 3.98; N, 17.28. **Found:** C, 62.16; H, 3.94; N, 17.23.

***N*-[4-(4-Chlorophenyl)-6-(2-hydroxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-68)**

IR (KBr) cm^{-1}: 3601 (OH), 3429, 3416, 3502 (N-H str.), 2736 (C-H str.), 1697, 1717 (>C=O), 1644 (CONH), 744 (C-Cl).

C, H, N analysis, Calculated: C, 58.90; H, 3.46; N, 17.17. **Found:** C, 58.87; H, 3.36; N, 17.14.

***N*-(4-(2-Chlorophenyl)-6-(2,5-dimethoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-69)**

IR (KBr) cm^{-1}: 3424, 3419 (N-H str.), 2825 (C-H str.), 1680, 1716 (>C=O), 1623 (CONH), 728 (C-Cl).

C, H, N analysis, Calculated: C, 58.48; H, 4.02; N, 15.50. **Found:** C, 58.46; H, 4.00; N, 15.46.

***N*-(4-(4-Chlorophenyl)-6-(2,5-dimethoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-70)**

IR (KBr) cm^{-1}: 3456, 3425 (N-H str.), 2868 (C-H str.), 1635, 1719 (>C=O), 1825, 1797 (OCH_3), 1589 (CONH), 723 (C-Cl).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 3.69, 3.72 (d, 6H, 2×OCH_3), 4.22 (s, 1H, CONH), 6.65 (s, 1H, -CH), 6.67 (s, 1H, NH) , 6.65 (s, 1H, NH), 6.96-7.52 (m, HH, Ar-H).

400 MHz 13 C NMR (DMSO-d$_6$, δ ppm): 31.92, 38.88-40.13, 42.40, 54.92, 55.16, 77.01, 77.34, 77.66, 111.80, 114.50, 128.17, 138.49, 150.56, 197.06.

Mass: [m/e (%)], M. Wt. : 456, 438, 423, 407, 343, 317, 303, 285, 271, 261, 249, 228, 178, 164, 141, 139, 111, 91, 75, 65, 44.

C, H, N analysis, Calculated: C, 58.48; H, 4.02; N, 15.50. **Found:** C, 58.44; H, 3.93; N, 15.47.

2,3-Dihydro-*N*-(4-(2,5-dimethoxyphenyl)-6-(3-nitrophenyl)pyrimidine-2-yl)-2-oxo-1*H*-imidazole-5-carboxamide (JT-71)

IR (KBr) cm^{-1}: 3435, 3414 (N-H str.), 2846 (C-H str.), 1657, 1703 (>C=O), 1757, 1742 (OCH_3), 1592 (CONH).

Mass: [m/e (%)], M. Wt.:463, 450, 448, 432, 415, 402, 387, 374, 357, 346, 320, 290, 280, 263, 251, 220, 202, 187, 175, 148, 129, 115, 111, 95, 64, 44.

C, H, N analysis, Calculated: C, 57.14; H, 3.92; N, 18.17. **Found:** C, 57.12; H, 3.86; N, 18.14.

***N*-[4-(4-Bromophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-72)**

IR (KBr) cm^{-1}: 3436, 3428 (N-H str.), 2934 (C-H str.), 1680, 1712 (>C=O), 1826 (OCH_3), 1613 (CONH), 748(C-Br).

Mass: [m/e (%)], M. Wt.:466, 451, 322, 256, 224, 197, 180, 165, 152, 137, 120, 105, 93, 78, 64, 52, 44.

C, H, N analysis, Calculated: C, 54.09; H, 3.46; N, 15.02. **Found:** C, 54.02; H, 3.43; N, 14.98.

***N*-(4-(4-Cyanophenyl)-6-phenylpyrimidin-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-73)**

IR (KBr) cm^{-1}: 3413, 3443 (N-H str.), 2835 (C-H str.), 2169 (C≡N), 1668, 1704 (>C=O), 1639 (CONH), 1557, 1479, 1447 (ring skeleton).

C, H, N analysis, Calculated: C, 65.96; H, 3.69; N, 21.98. **Found:**
C, 65.93; H, 3.66; N, 21.97.

***N*-(4-(4-Cyanophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-74)**

IR (KBr) cm^{-1}: 3443, 3418 (N-H str.), 2813 (C-H str.), 2146 (C≡N), 1689, 1716 (>C=O), 1893 (OCH_3), 1635 (CONH).

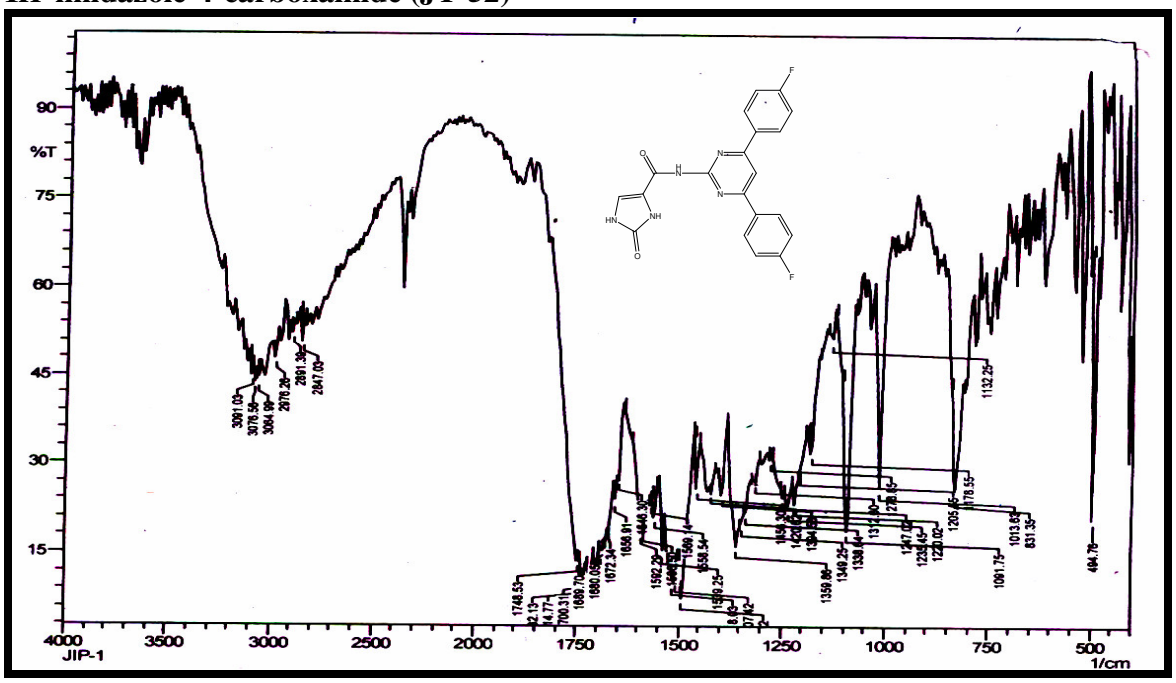
C, H, N analysis, Calculated: C, 64.07; H, 3.91; N, 20.38. **Found:** C, 64.06; H, 3.88; N, 20.34.

3.11. Conclusion

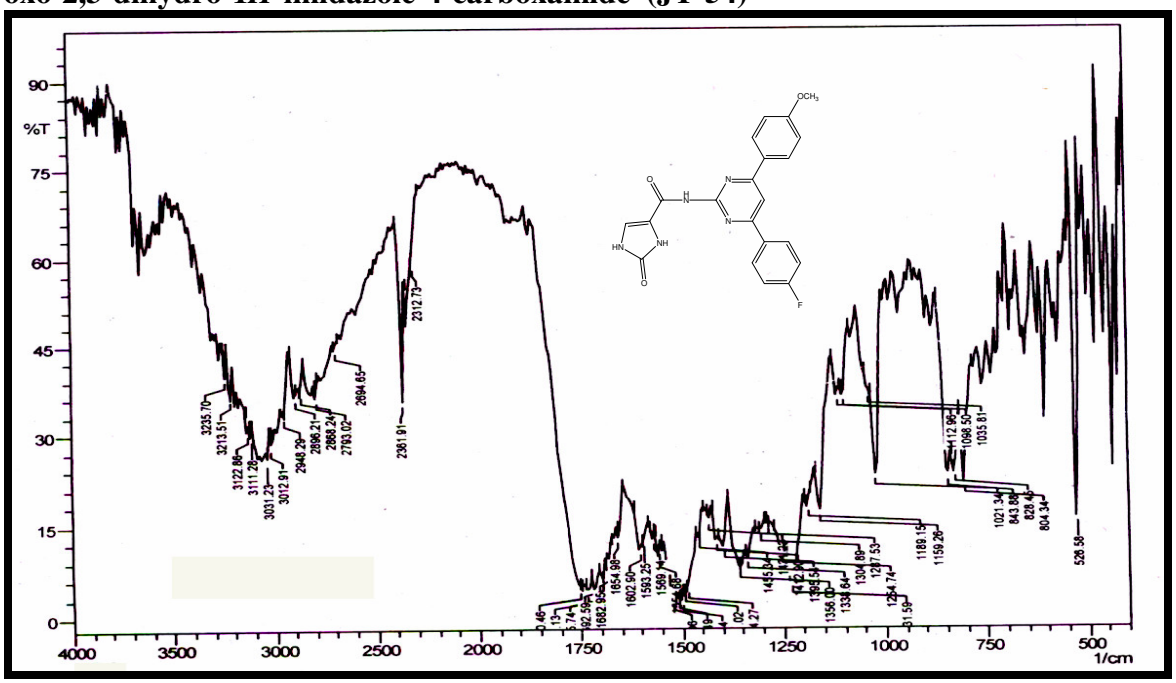
Total 24, of *N*-(4, 6-diphenyl pyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamides were synthesized in this chapter. The compounds were characterized by IR, NMR, Mass spectral data and elemental analysis. The synthesized compounds were screened for anti-inflammatory and anti-cancer activity. Unfortunalely, none of the compound was found active.

3.12. Spectra of some *N*-(4, 6-diphenyl pyrimidin-2-yl)-2-oxo-2, 3-dihydro-1*H*-imidazole-4-carboxamides

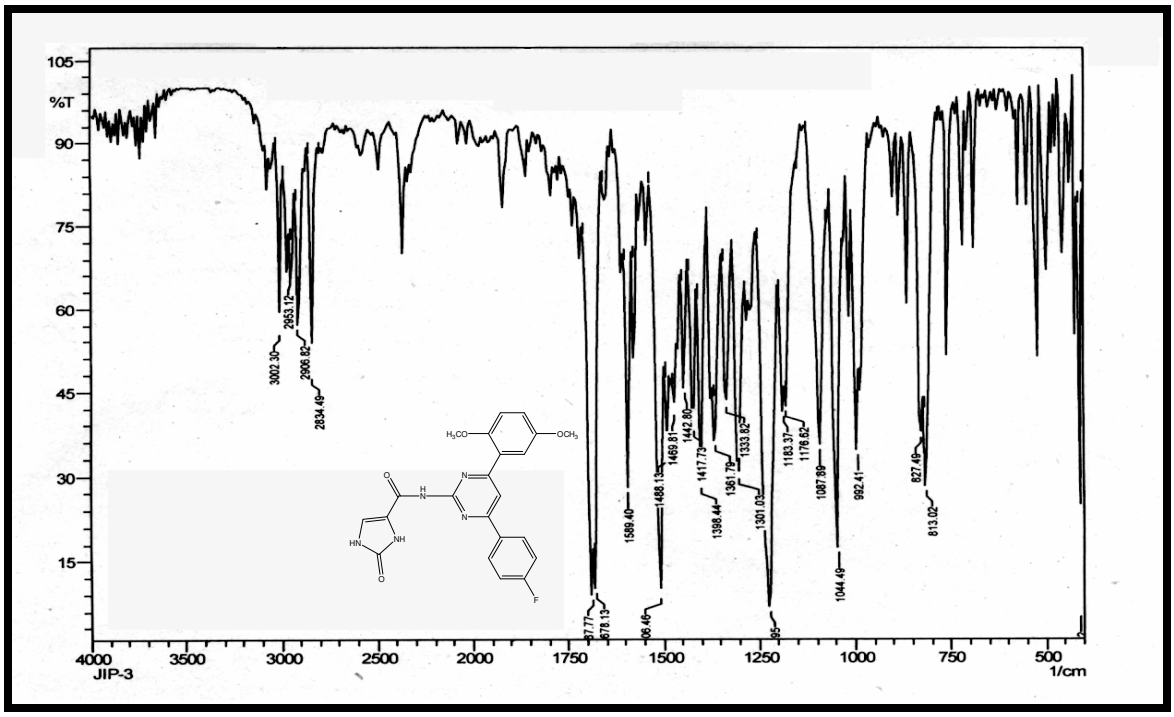
Infra Red spectra of *N*-[4,6-bis(4-fluorophenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-52)



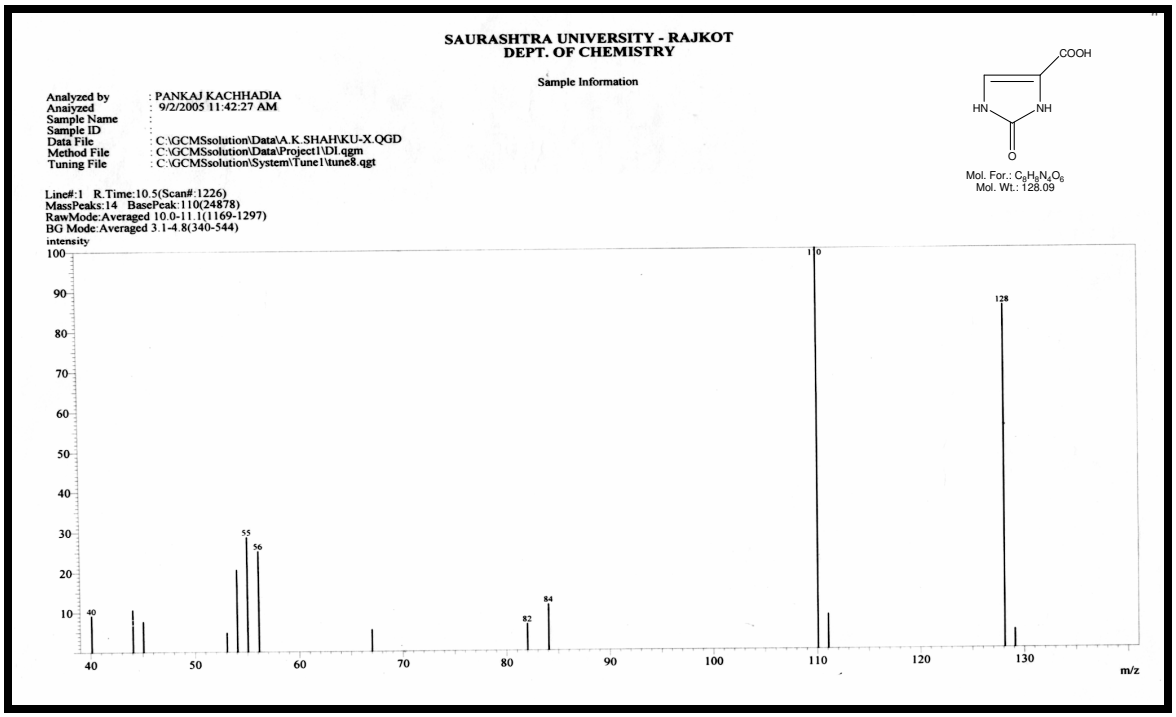
Infra Red spectra of *N*-[4-(4-fluorophenyl)-6-(4-methylphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-54)



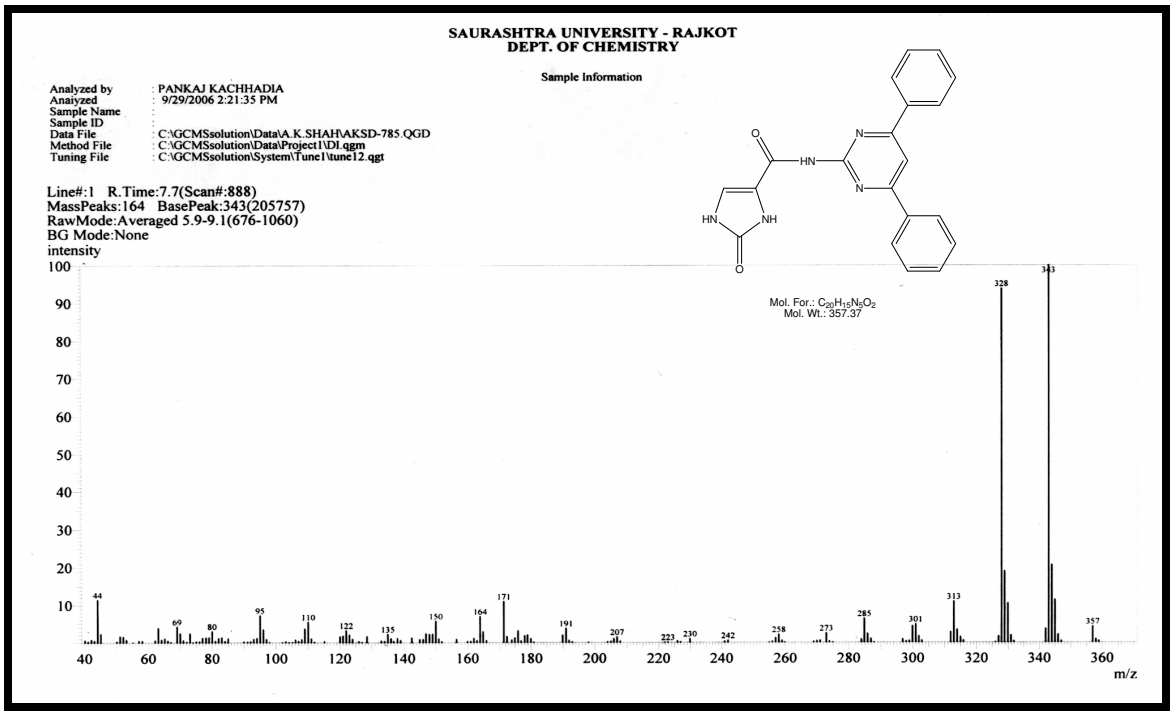
Infra Red spectra of *N*-(4-(4-chlorophenyl)-6-(2,5-dimethoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-70)



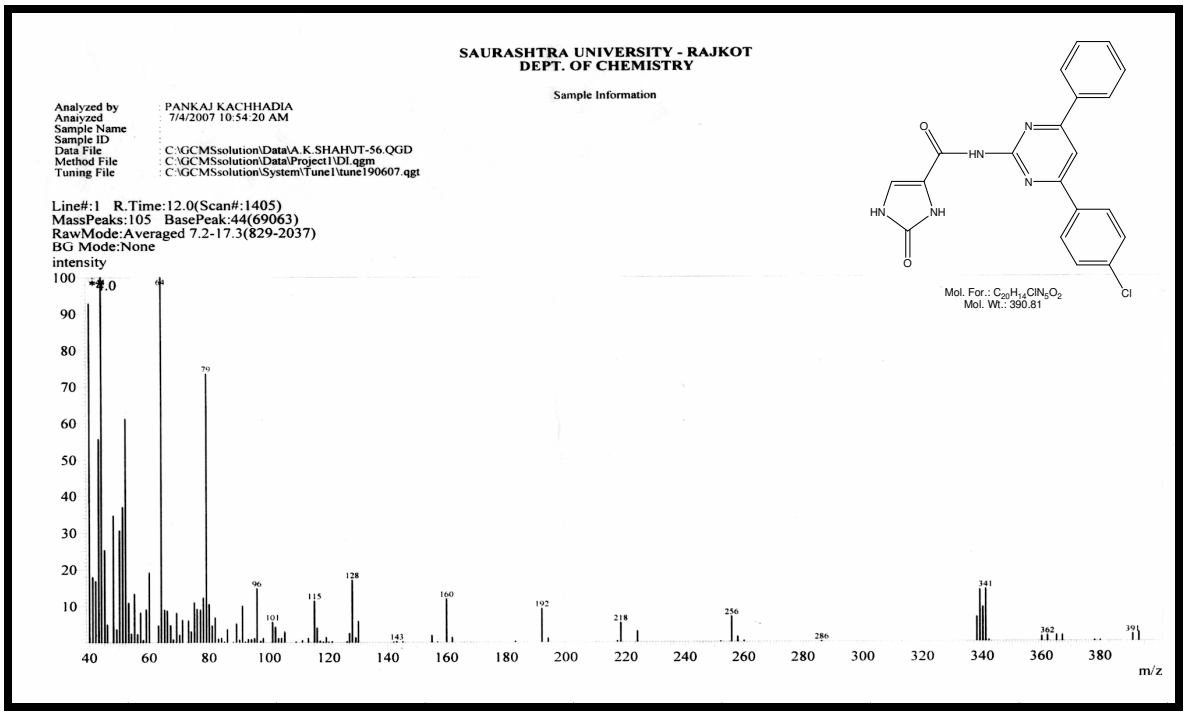
Mass spectrum of 2-Imidazolone-4-carboxylic acid



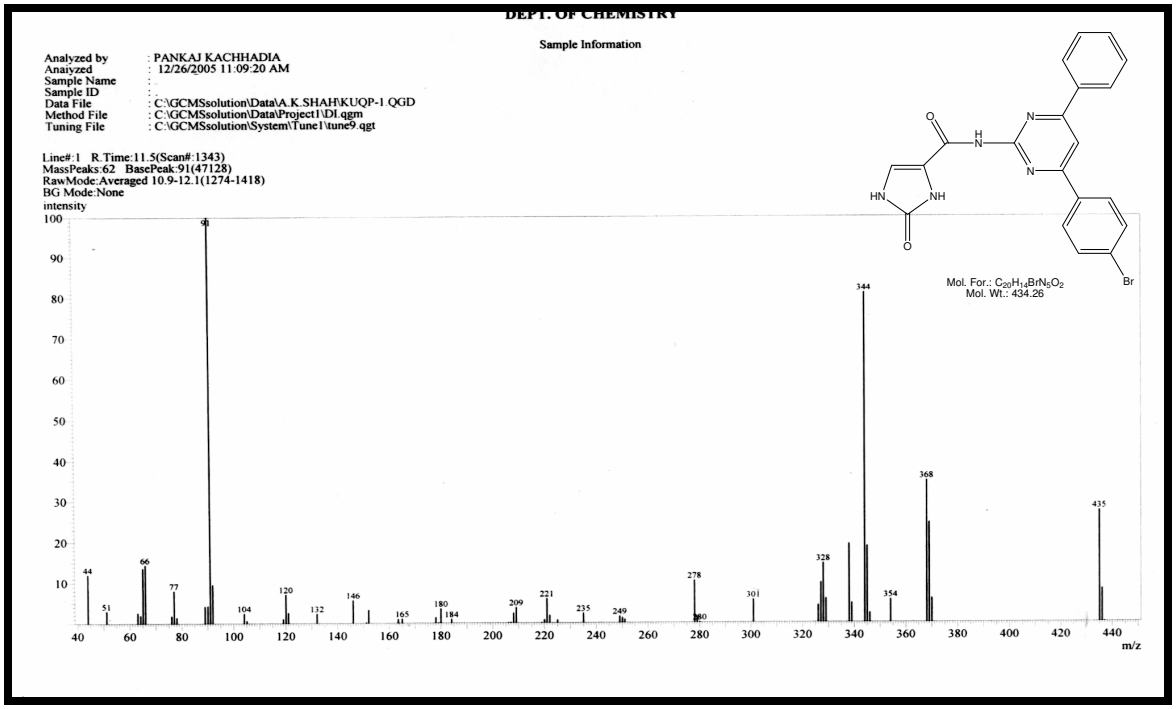
Mass spectrum of *N*-(4,6-diphenylpyrimidin-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-51)



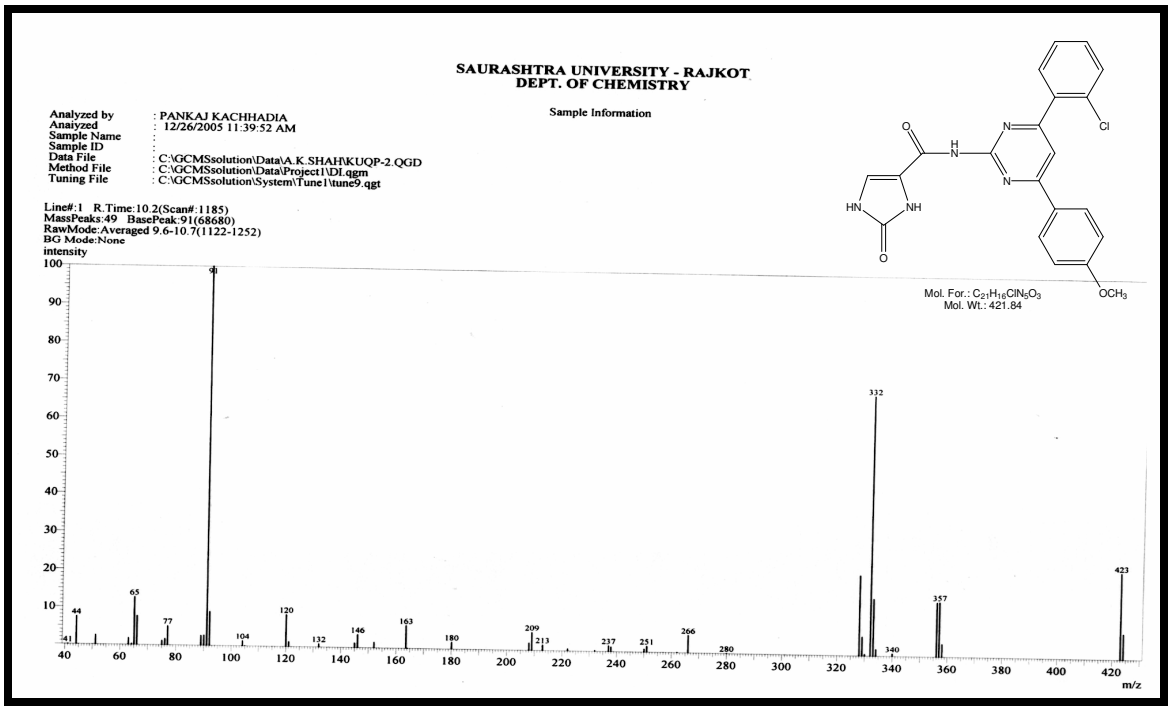
Mass spectrum of *N*-[4-(4-chlorophenyl)-6-phenylpyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-61)



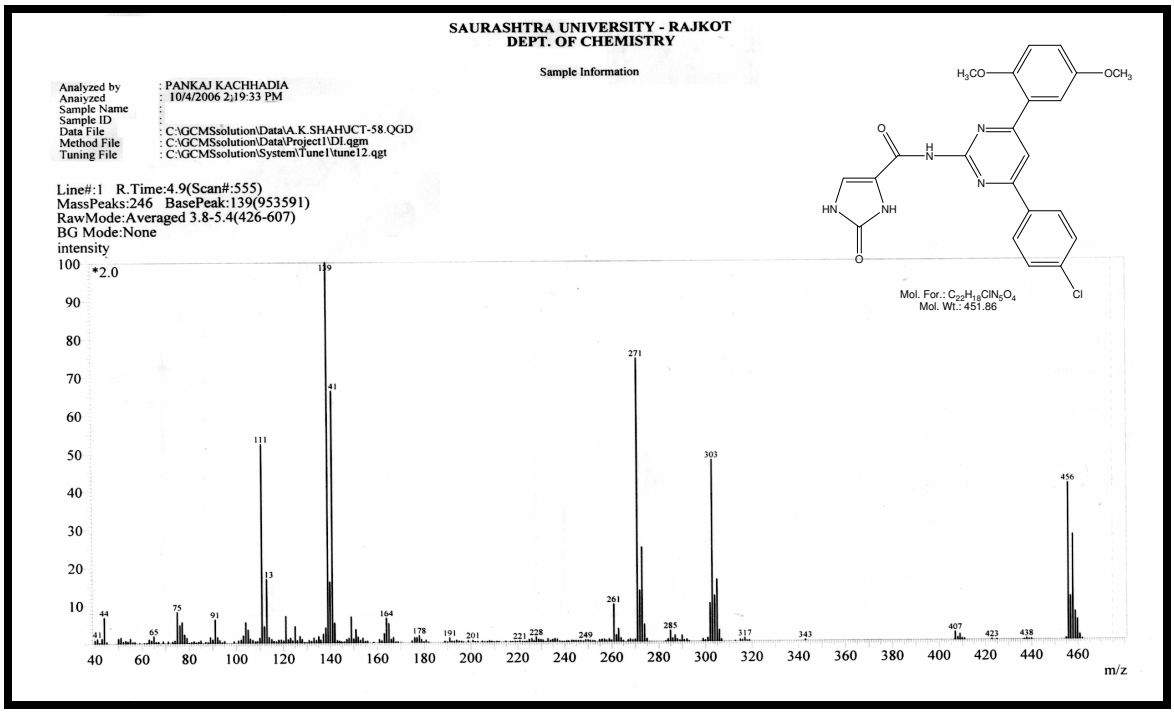
Mass spectrum of N-(4-(4-bromophenyl)-6-phenylpyrimidin-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-62)



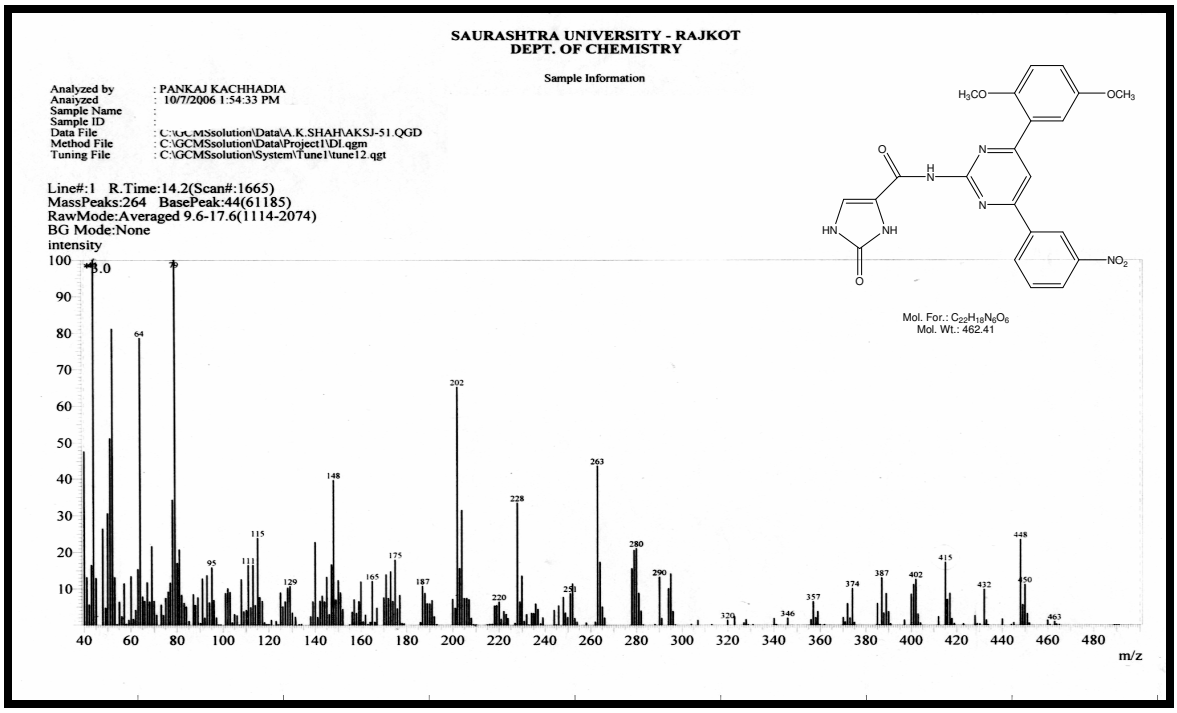
Mass spectrum *N*-[4-(2-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-65)



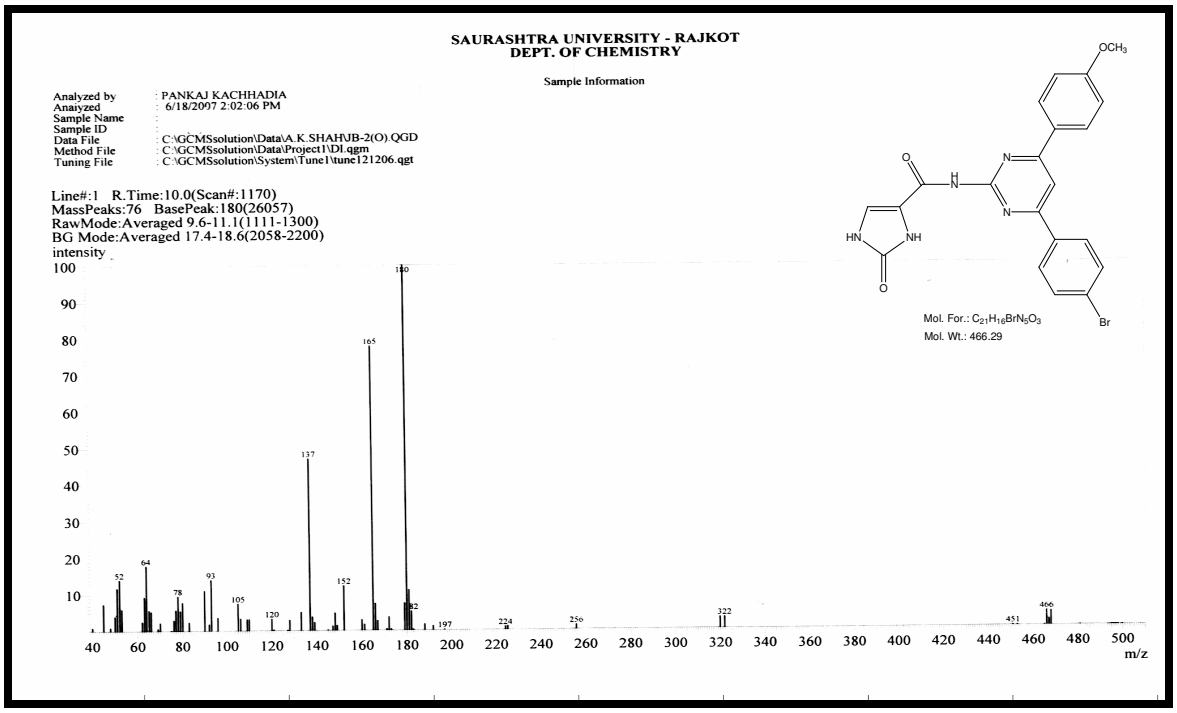
Mass spectrum of *N*-(4-(4-chlorophenyl)-6-(2,5-dimethoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-70)



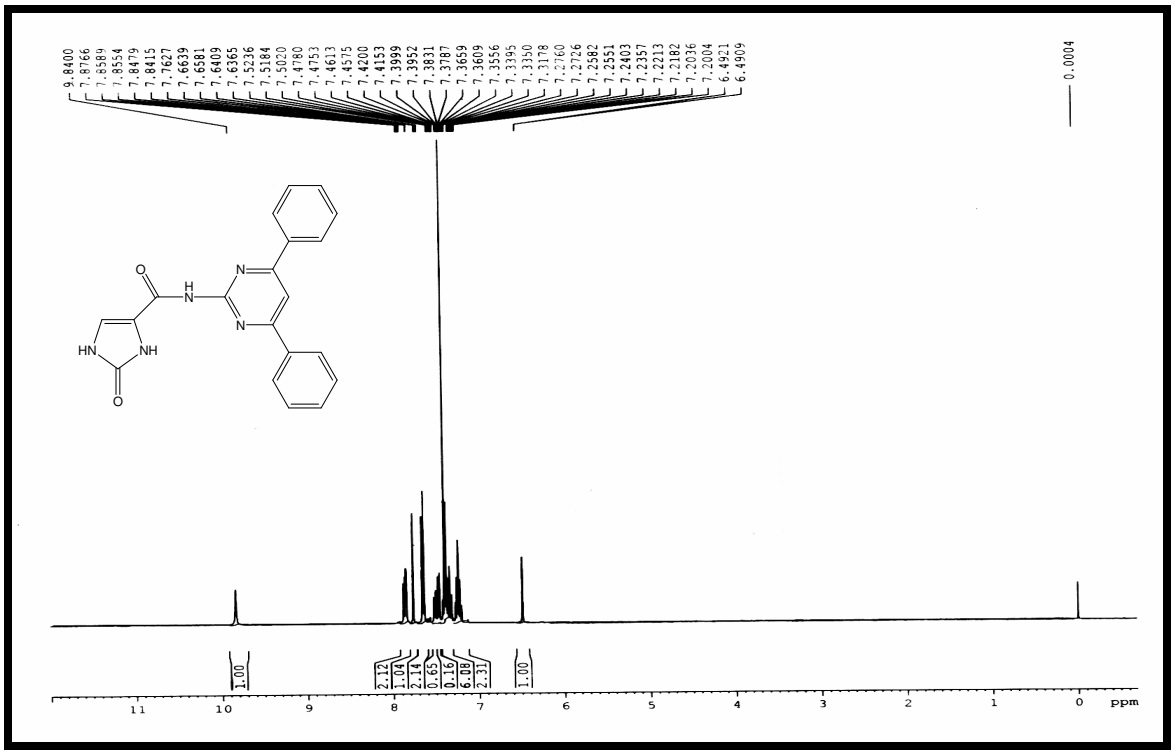
Mass spectrum of 2,3-dihydro-*N*-(4-(2,5-dimethoxyphenyl)-6-(3-nitrophenyl) pyrimidine-2-yl)-2-oxo-1*H*-imidazole-5-carboxamide (JT-71)

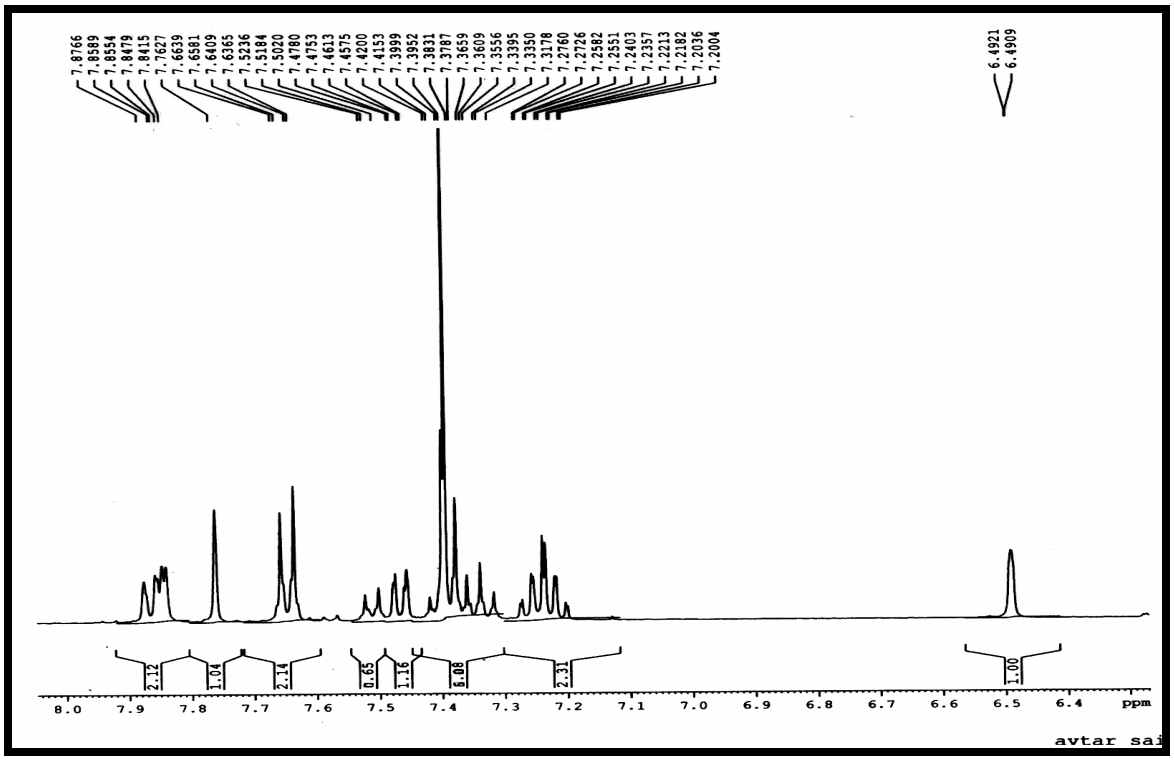


Mass spectrum *N*-[4-(4-bromophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-72)

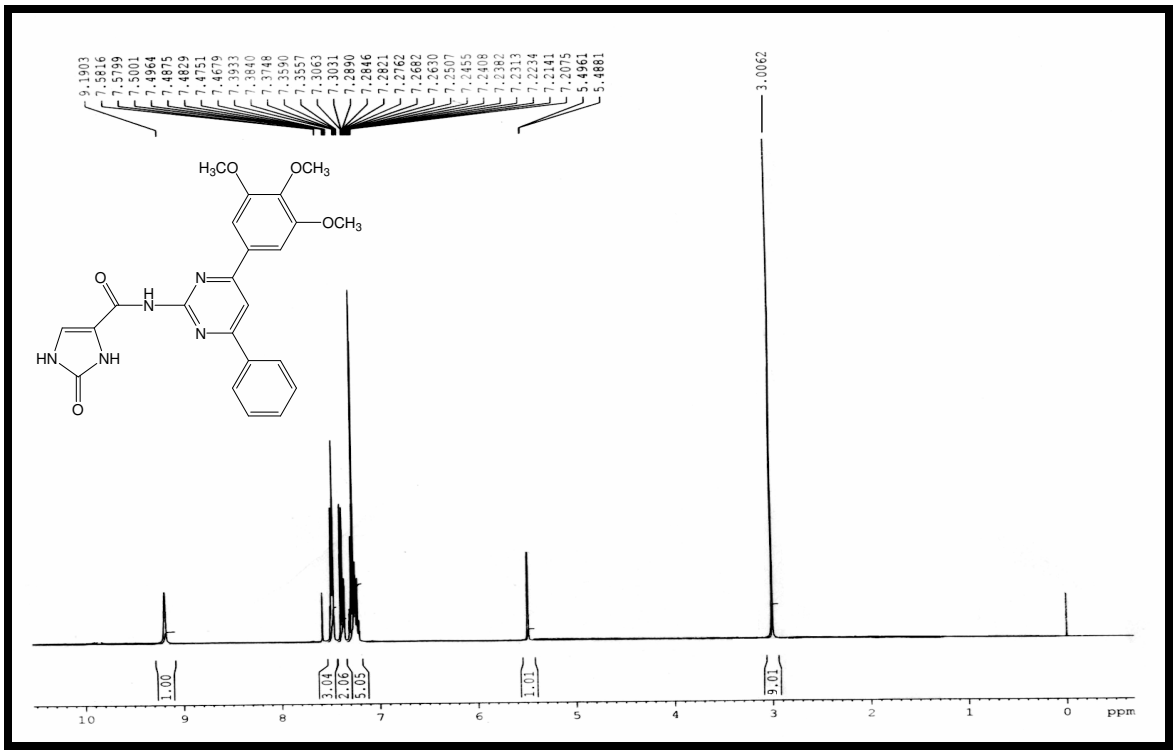


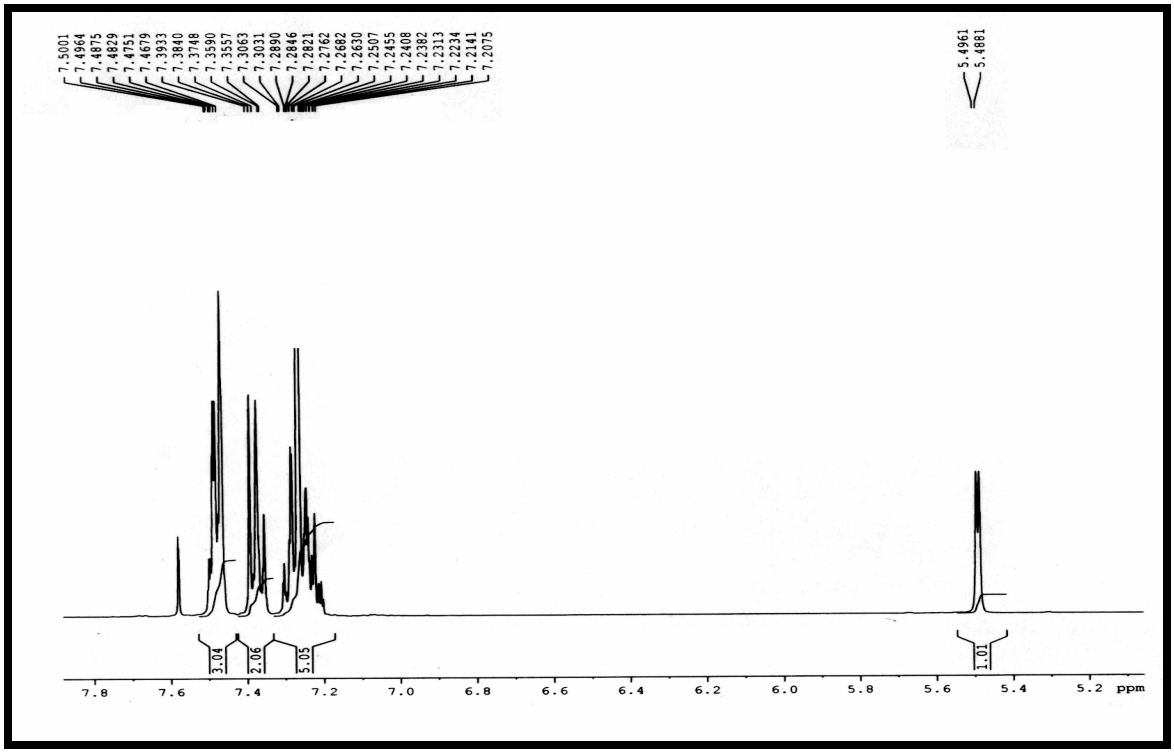
^{1}H NMR spectrum *N*-(4,6-diphenylpyrimidin-2-yl)-2-oxo-2,3-dihydro-1*H*-imidazole-4-carboxamide (JT-51)



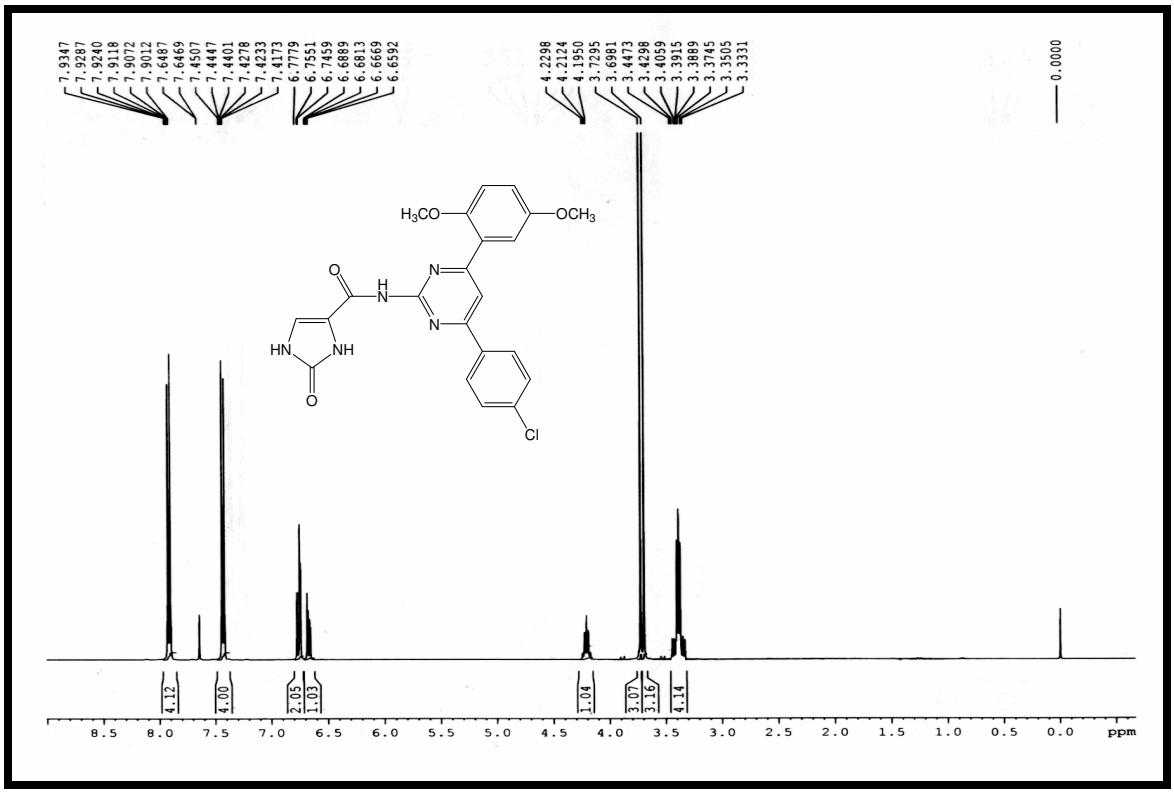


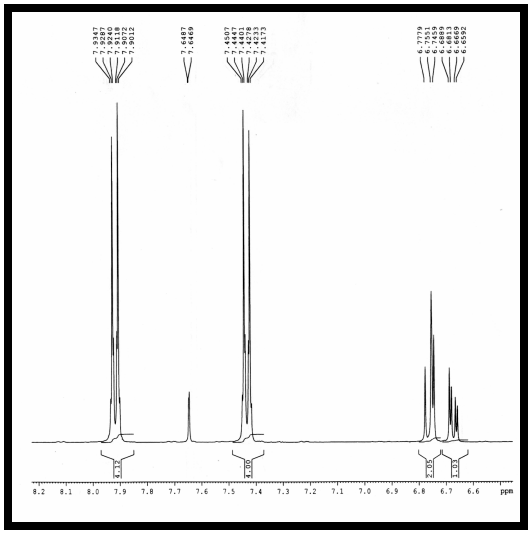
^{1}H NMR spectrum of 2,3-dihydro-*N*-(4-(3,4,5-trimethoxyphenyl)-6-phenylpyrimidine-2-yl)-2-oxo-1*H*-imidazole-5-carboxamide (JT-59)

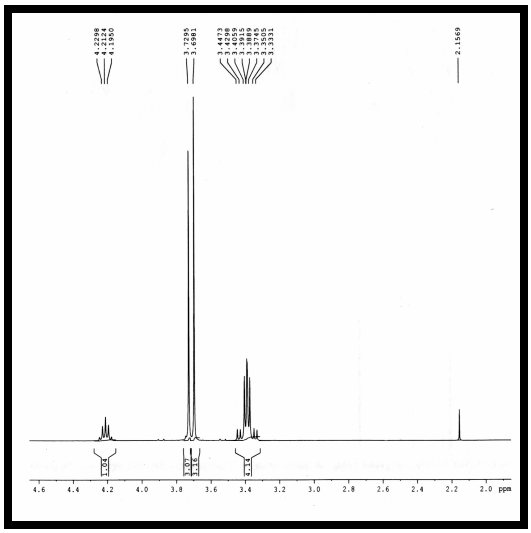




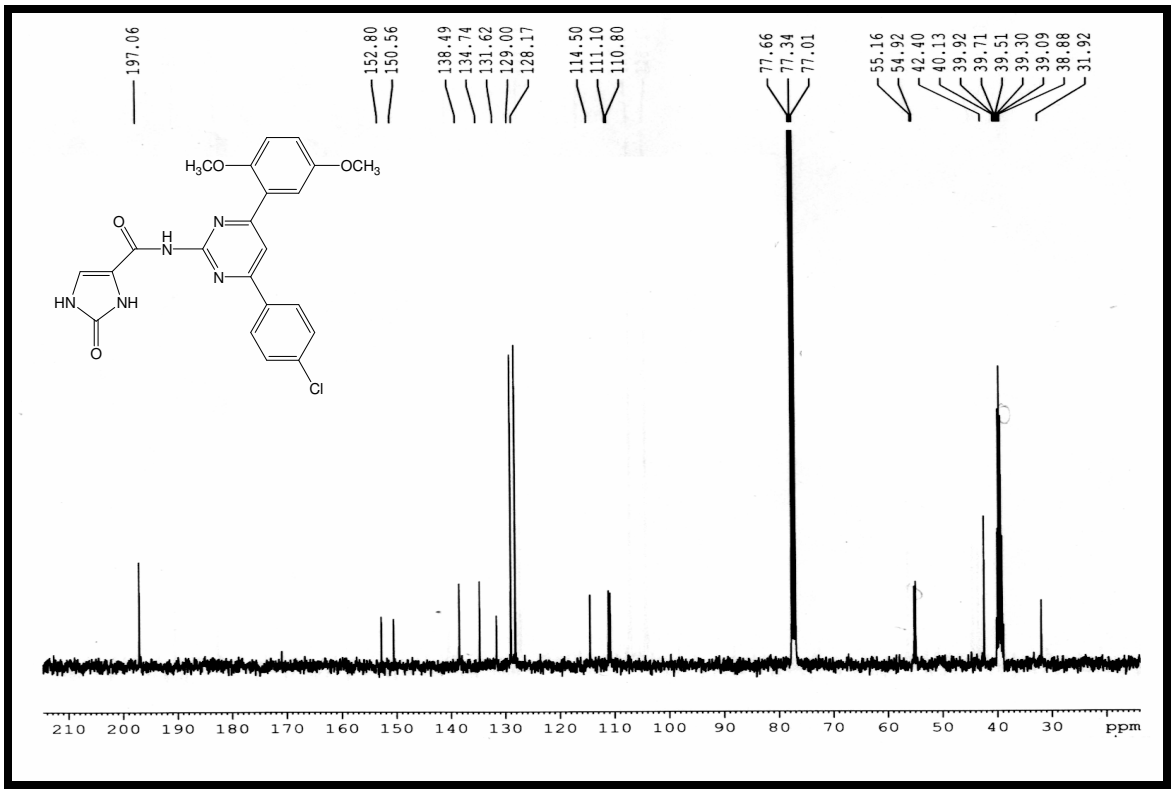
^{1}H NMR spectrum of *N*-(4-(4-chlorophenyl)-6-(2,5-dimethoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-70)

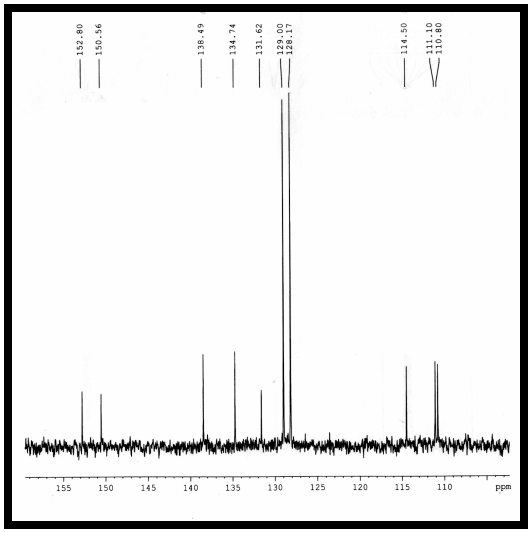


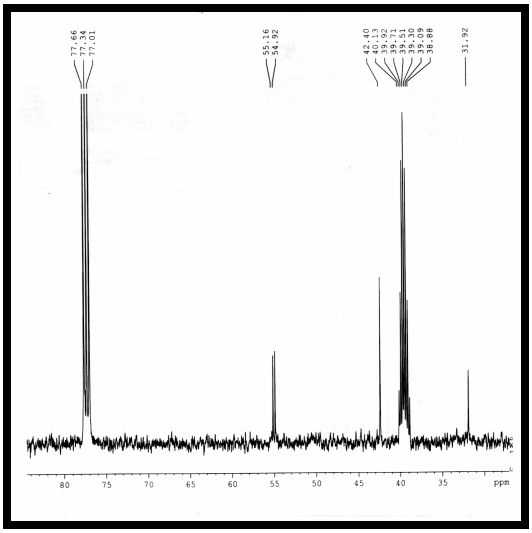




^{13}C NMR spectrum of *N*-(4-(4-chlorophenyl)-6-(2,5-dimethoxyphenyl)pyrimidine-2-yl)-2,3-dihydro-2-oxo-1*H*-imidazole-4-carboxamide (JT-70)







3.13. References

1. (a) Laufer, S.A.; Zimmermann, W.; Ruff, K.J. *J. Med. Chem.* **2004**, 47, 6311. (b) Mjalli, A.; Sarshar, S. *U.S. Patent* **1997**, US 5,700,826, 19. (c) Cheung, D.W.; Daniel, E.E. *Nature* **1980**, 283, 485. (d) Black, J.W.; Durant, G.J.; Emmett, J.C.; Ganellin, C.R. *Nature,* **1974**, 248, 65.
2. Welton, T. *Chem. Rev.* **1999**, 99, 2071.
3. Herrmann, W.A. *Angew. Chem. Int. Ed.*. **2002**, 41, 1290.
4. Cortes, S.; Liao, Z-K.; Watson, D.; Kohn, H. Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity, *J. Med. Chem.* **1985**, 28, 601-606.
5. Jones, G. L.; Woodbury, D. M. *Drug Dev. Res.* 1982, 2, 333-355.
6. Poupaert, J. H.; Vandervorst, D.; Guiot, P.; Moustafa, M. M. M.; Dumont, P. *J. Med. Chem.* 1984, 27, 76-78.
7. Gribble, G.W.; Joule, J.A.; Gilchrist, T.L. (Eds.) Progress in Heterocyclic Chemistry, volume 13 - 17, Elsevier, Oxford, **2001-2005**.
8. Davidson, Baudisch. *J. Am. Chem. Soc.*, **1926**, 48, 2379.
9. Von Pechmann, *Ber.*, **1884**, 17*,* 936; *Ann.,* **1891**, 264, 261.
10. Hilbert, *J. Am. Chem. Soc.*, **1932**, 54, 2076.
11. Guido, E.; Hilbert. The syntheses of 2-imidazolone-4-carboxylic acid and 2-imidazolone, *J. Am. Chem. Soc.*, **1932**, 54, 3413-3419.
12. Duschinsky, Dolan. *J. Am. Chem. Soc.*, **1946**, 67, 2069.
13. Marckwald, *Em.,* **1892**, 96, 2357.
14. Duschinsky, R.; Dolan A. Studies in the Imidazolone Series. The Synthesis of a Lower and a Higher Homolog of Desthiobiotin and of Related Substances I, *J. Am. Chem. Soc.*, **1946**, 68, 2350-2355.
15. Fenton and Wilks, *J.* Chem. *Soc.* **1909**, 96, 1329.
16. Hilbert, *J. Am. Chem. Soc.*, **1932**, 64, 3414.
17. Stoffel, P. J.; Speziale, A. J. The Preparation of 2-Imidazolones: A Novel Ring Closure of Propynyl Ureas with Phosphorus Pentachloride-I, *J. Am. Chem. Soc.*, **1962,** 84, 501-504.
18. The Preparation of 2-Imidazolones. A Novel Ring Closure of Propynylureas with Phosphorus Pentachloride-II, Stoffel, P. J.; Speziale, A. *J. Am. Chem. Soc.*, **1962**, 84, 3079-3083.
19. Ugi, I.; Steinbruckner, C. *Angew. Chem.,* **1960**, 72, 267.
20. Eilingsfeld, H.; Seefelder, M.; Weidinger, H. *ibid.,***1909***,* 72, 836.
21. Klages, F.; Grill, W. *Ann.,* **1955**, 694, 21.
22. Steindorff, A. *Ber.,* **1904**, 37, 964.

23. Schnettler, R. A.; Dage, R. C.; Grisar J. M. 4-Aroyl-l,3-dihydro-2H-imidazol-2-ones, a New Class of Cardiotonic Agents, *J. Med. Chem.* **1982**, 25, 1477-1481.
24. Dalton, C.; Quinn, J. B.; Burkhart, C. R.; Sheppard, H. *J. Exp. Ther.,* 1971, 1976, 174.
25. Osborne, M. W.; Wenger, J. J.; Moe, R. A. *J. Pharmacol.* 1972, 399.
26. Knope, R.; Moe, G. K.; Saunders, J.; Tuttle, R. *J. Pharmacol. Exp. Ther*., **1970**, 173, 270.
27. Knope, R.; Moe, G. K.; Saunders, J.; Tuttle, R. *J. Pharmacol. Exp. Ther*., **1973**, 186, 29.
28. Dage, R. C.; Hsieh, C. P.; Wiech, N. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **1980**, 39, 1105.
29. Hsieh, C. P.; Dage, R. C. *Fed. Proc., Fed. Am. Soc. Exp. Biol.,* **1980**, 39, 1106.
30. Roebel, L. E.; Cheng, H. C.; Lucas, R. W.; Hodgeman, R. J.; Reavis, O. K. Woodward, J. K. *Pharmacologist*, **1980**, 22, 287.
31. Dage, R. C;. Roebel, L. E.; Hsieh, C. P.; Weiner, D. L.; Woodward, J. K. *J. Cardiovasc. Pharmacol.,* **1982**, 4, 500.
32. Roebel, L. E.; Dage, R. C.; Cheng, H. C.; Woodward, J. K. *J. Cardiovasc. Pharmacol.* in press.
33. Kariya, T.; Wille, L. J.; Dage, R. C. *J. Cardiovasc. Pharmacol.,* **1982**, 4, 509.
34. Shaw, K. J.; Vartanian, M. Synthesis of 3H-Pyrrolo [1,2-c] imidazole-3,5(2H)-diones, *J. Org. Chem.* **1991**, 56, 858-861.
35. Shaw, K. J. US patent 4,937,258, **1990**.
36. Erhardt, P. W.; Hagedorn, A. A. U.S. Patent 4,743,612, **1988**.
37. Hagedorn, A. A,; Erhardt, P. W.; Lumma, W. C.; Jr.; Wohl, R. A,; Cantor, E.; Chou, Y.-L.; Ingebretsen, W. R.; Lampe, J. W.; Pang, D.; Pease, C. A.; Wiggins, J. *J. Med. Chem.* **1987**, 30, 1342.
38. (a) Butler, D. E.; Leonard, J. D. U.S. Patent 4,582,838, **1986**. (b) Condensed Imidazoles, 5-5 Ring Systems. Preston, P. N. In *The Chemistry of Heterocyclic Compounds;* Wiley: New York, **1986**, 42.
39. Erhardt P. W.; Hagedorn, A. A.; Davey, D.; Pease, C. A.; Venepalli, B. R.; Griffin, C.W.; Gomez, R. P.; Wiggins, J. R.; Ingebretsen, W. R.; Pang, D.; Cantor, E. *J. Med. Chem*., **1989**, 32, 1173.
40. Bovy, Philippe, Roger, Cupertino, EP 0715 623 B1, 1998, 37.
41. Keith, A. M.; Walker, Marshall, B.; Wallach, Hirschfeld, D. R. 1-(Naphthylalky1)-1 H-imidazole Derivatives, a New Class of Anticonvulsant Agents, *J. Med. Chem.* **1981**, 24, 67-74.

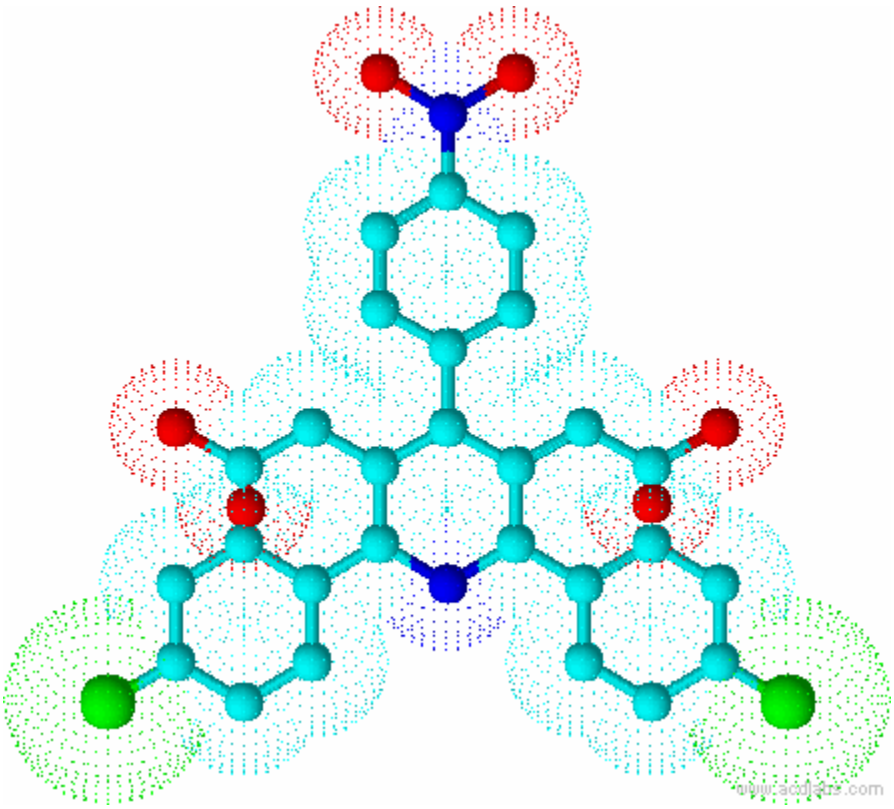
42. Deffois, A.; Fage, D.; Carter, C. Inhibition of Synaptosomal Veratridine-Induced Sodium Influx by Antidepressants and Neuroleptics Used in Chronic Pain, *Neurosci. Lett.* **1996**, 220 (2), 117-20.
43. Beiler, T. W.; Plato, C. H.; Shepard, K. E. 2-Imidazolone and 2-Imidazolidonepropionic Acids, *J. Org. Chem.,* **1960**, 25, 2236-2237.
44. Li, R.. Kenyon, G. L Cohen, F. E. Chen, X. Gong, B. Dominguez, J. N. Davidson, J E. Kurzban, G. Miller, R. E. Nuzum, E. Philip, O. Rosenthal, J. Mckerrowisa, J. H. *In Vitro* Antimalarial activity of Chalcones and their Derivatives, *J. Med. Chem.* **1995**, 38, 5031-5037.
45. Edwards, M. L.; Stemerick, D. M.; Sunkara, P. S. Chalcones: A New Class of Antimitotic Agents, *J. Med. Chem.* **1990**, 33, 1948-1954.
46. Agrawal, A.; Srivastava, K.; Puri, S. K.; Chauhan, P. M. S. Synthesis of 4-pyrido-6-aryl-2-substituted amino pyrimidines as a new class of antimalarial gents, *Bioorg. Med. Chem.,* **2005**, 13 (22), 6226-6232.
47. Laufer, S. A.; Wagner, G. K.; Kotschenreuther, D. A.; Albrecht. W. Novel substituted Pyridinyl Imidazoles as Potent Anticytokine agents with low activity against Hepatic Cytochrome P450 Enzymes, *J. Med. Chem.* **2003**, 46, 3230-3244.
48. Laufer, S. A.; Zimmermann, W.; Ruff, K. J. Tetrasubstituted Imidazole Inhibitors of Cytokine Release: Probing Substituents in the N-1 Position, *J. Med. Chem.* **2004**, 47, 6311-6325.
49. Lee, J. C.; Kumar, S.; Griswold, D. E.; Underwood, D. C.; Votta, B. J.; Adams, J. L. Inhibition of p38 MAP kinase as a therapeutic strategy. *Immunopharmacology,* **2000**, 47, 185-201.
50. Lee, J. C.; Laydon, J. T.; McDonnell, P. C.; Gallagher, T. F.; Kumar, S.; Green, D.; McNulty, D.; Blumenthal, M. J.; Heyes, J. R. A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. *Nature (London)* **1994**, 372, 739-746.
51. Young, P.; McDonnell, P.; Dunnington, D.; Hand, A.; Laydon, J.; Lee, J. Pyridinyl imidazoles inhibit IL-1 and TNF production at the protein level, *Agents Actions,* **1993**, 39, 67-9.
52. Pearson, G.; Robinson, F.; Gibson, T. B.; Xu, B. E.; Karandikar, M.; Berman, K.; Cobb, M. H. Mitogen-activated protein (MAP) kinase pathways: Regulation and physiological functions. *Endocr. Rev.* **2001**, 22, 153-183.
53. Beyaert, R.; Cuenda, A.; Vanden Berghe, W.; Plaisance, S.; Lee, J. C.; Haegeman, G.; Cohen, P.; Fiers, W. The p38/RK mitogenactivated protein kinase pathway regulates interleukin-6 synthesis response to tumor necrosis factor, *EMBO J.* **1996**, 15, 1914-1923.

54. Raingeaud, J.; Gupta, S.; Rogers, J. S.; Dickens, M.; Han, J.; Ulevitch, R. J.; Davis, R. J. Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J. Biol. Chem.* **1995**, 270, 7420-7426.
55. Lee, J. C.; Kassis, S.; Kumar, S.; Badger, A.; Adams, J. L. p38 mitogen-activated protein kinase inhibitors Mechanisms and therapeutic potentials. *Pharmacol. Ther.* **1999**, 82, 389-397.
56. Henry, J. R.; Cavender, D. E.; Wadsworth, S. A. p38 Mitogenactivated protein kinase as a target for drug discovery. *Drugs Future,* **1999**, 24, 1345-1354.
57. Salituro, F. G.; Germann, U. A.; Wilson, K. P.; Bemis, G. W.; Fox, T.; Su, M. S. S. Inhibitors of p38 MAP kinase: Therapeutic intervention in cytokine-mediated diseases. *Curr. Med. Chem.* **1999**, 6, 807-823.
58. Boehm, J. C.; Adams, J. L. New inhibitors of p38 kinase. *Expert Opin. Ther. Patents* **2000**, 10, 25-37.
59. Mclay, L. M.; Halley, F.; Souness, J. E.; McKenna, J.; Benning, V.; Birrell, M.; Burton, B.; Belvisi, M.; Collis, A.; Constan, A.; Foster, M.; Hele, D.; Jayyosi, Z.; Kelley, M.; Maslen, C.; Miller, G.; Ouldelhkim, M. C.; Page, K.; Phipps, S.; Pollock, K.; Porter, B.; Ratcliffe, A. J.; Redford, E. J.; Webber, S.; Slater, B.; Thybaud, V.; Wilsher, N. The discovery of RPR 200765A, a p38 MAP kinase inhibitor displaying a good oral antiarthritic efficacy. *Bioorg. Med. Chem.* **2001**, 9, 537-554.
60. Tong, L.; Pav, S.; White, D. M.; Rogers, S.; Crane, K. M.; Cywin, C. L.; Brown, M. L.; Pargellis, C. A. A highly specific inhibitor of human p38 MAP kinase binds in the ATP pocket. *Nat. Struct. Biol.* **1997**, 4, 311-316.
61. Wang, Z.; Canagarajah, B. J.; Boehm, J. C.; Kassisa, S.; Cobb, M. H.; Young, P. R.; Abdel-Meguid, S.; Adams, J. L.; Goldsmith, E. J. Structural basis of inhibitor selectivity in MAP kinases. *Structure,* **1998**, 6, 1117-1128.
62. Wilson, K. P.; McCaffrey, P. G.; Hsiao, K.; Pazhinisamy, S.; Galullo, V.; Bemis, G. W.; Fitzgibbon, M. J.; Caron, P. R.; Murcko, M. A.; Su, M. S. S. The structural basis for the specificity of pyridinylimidazole inhibitors of p38 MAP kinase. *Chem. Biol.* **1997**, 4, 423-431.
63. Gum, R. J.; McLaughlin, M. M.; Kumar, S.; Wang, Z.; Bower, M. J.; Lee, J. C.; Adams, J. L.; Livi, G. P.; Goldsmith, E. J.; Young, P. R. Acquisition of sensitivity of stress-activated protein kinases to the p38 inhibitor, SB 203580, by alteration of one or more amino acids within the ATP binding pocket. *J. Biol. Chem.* **1998**, 273, 15605-15610.

64. Lisnock, J.; Tebben, A.; Frantz, B.; O'Neill, E. A.; Croft, G.; O'Keefe, S. J.; Li, B.; Hacker, C.; de Laszlo, S.; Smith, A.; Libby, B.; Liverton, N.; Hermes, J.; LoGrasso, P. Molecular basis for p38 protein kinase inhibitor specificity. *Biochemistry,* **1998**, 37, 16573-16581.
65. Wang, Z.; Canagarajah, B. J.; Boehm, J. C.; Kassisa, S.; Cobb, M. H.; Young, P. R.; Abdel-Meguid, S.; Adams, J. L.; Goldsmith, E. J. Structural basis of inhibitor selectivity in MAP kinases. *Structure (London)* **1998**, 6, 1117-1128.
66. Fredholm, B. B.; IJzerman, A. P.; Jacobson, K. A.; Klotz, K.-N.; Linden, J. M. International Union of Pharmacology. XXV. Nomenclature and Classification of Adenosine Receptors. *Pharmacol. Rev.* **2001**, 53, 527-552.
67. Porkka-Heiskanenm, T.; Strecker, R. E.; Thakkar, M.; Bjørkum, A. A.; Greene, R. W.; McCarley, R. W. Adenosine: A Mediator of the Sleep-Inducing Effects of Prolonged Wakefulness. *Science,* **1997**, 276, 1265-1268.
68. Porkka-Heiskanenm, T.; Alanko, L.; Kalinchuk, A.; Stenburg, D. Adenosine and Sleep. *Sleep Med. Rev.* **2002**, 6, 321-332.
69. Dunwiddle, T. V.; Masino, S. A. The Role and Regulation of Adenosine in the Central Nervous System. *Annu. Rev. Neurosci.* **2001**, 24, 31-55.
70. Li, A-H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X.-d.; Jacobson, K. A. Synthesis, CoMFA Analysis, and Receptor Docking of 3,5- Diacyl-2,4-Dialkylpyridine Derivatives as Selective A3 Adenosine Receptor Antagonists. *J. Med. Chem.* **1999**, 42, 706-721.
71. Li, A-H.; Moro, S.; Melman, N.; Ji, X.-d.; Jacobson, K. A. Structure-Activity Relationships and Molecular Modeling of 3,5- Diacyl-2,4-dialkylpyridine Derivatives as Selctive A3 Adenosine Receptor Antagonists. *J. Med. Chem.* **1998**, 41, 3186-3201.
72. van Rhee, M.; Jiang, J.-L.; Melman, N.; Olah, M. E.; Stiles, G. L.; et al. Interaction of 1,4-dihydropyridines and pyridine derivatives with adenosine receptors: selectivity for A3 Receptors. *J. Med. Chem.* **1996**, 39, 2980-2989.
73. Aktiengesellschaft, B. WO 0125210, 2001. Aktiengesellschaft, B. DE 10115922A1, 2002.
74. Chang, L. C. W.; Spanjersberg, R. F.; von Frijtag Drabbe Kunzel, J. K.; Mulder-Krieger, T.; van den Hout, G.; Beukers, M. W.; Brussee, J.; IJzerman, A. P. 2,4,6-Trisubstituted Pyrimidines as a New Class of Selective Adenosine A1 Receptor Antagonists, *J. Med. Chem.* **2004**, 47, 6529-6540.
75. Al-Hajjar, F. H.; Sabri, S. S. Reaction of α, β-Unsaturated ketones with Guanidine. Substituent Effects on the Protonation Constants of 2-Amino-4,6-diarylpyrimidines. *J. Heterocycl. Chem.* **1982,** 19, 1087-1092.

76. Pasha, T. Y.; Udupi, R. H.; Bhat, A. R. Synthesis and antimicrobial screening of some pyrimidine derivatives, *Indian J. Het. Chem*. **2005**, 15, 149-152.
77. Dedrick, R. L.; Conlon, P. J. Prolonged Expression of Lipopolysaccharide (LPS)-Induced Inflammatory Genes in Whole Blood Requires Continual Exposure to LPS. *Infection and Immunity*, **1995**, 63, 1362-1368.

CHAPTER-4



Synthesis and Characterization of Some (5-Carboxymethyl-2,4,6-triphenyl-1,4-Dihydropyridine-3-yl)-Acetic Acids

Synthesis and Characterization of Some (5-Carboxymethyl-2, 4, 6-Triphenyl-1, 4-Dihydropyridine-3-yl)-Acetic Acids

4.1. Introduction

The study of dihydropyridines began early in 1882, when Hantzsch disclosed the first synthesis of these compounds.[1] Afterwards, the research was focused on NADH (reduced nicotinamide adenine dinucleotide) mimics and on the synthetic aspects of these heterocyclic systems, especially with regard to natural products and bioactive agents.

Dihydropyridine chemistry[2] is of interest not only from the point of view of pure research on heterocyclic compounds but especially because of expanding practical applications of dihydropyridine derivatives as pharmaceuticals,[3] plating bath components[4] photographic materials[5-7] and different antioxidants and stabilizers of unstable organic substances.[8-13] Certain dihydropyridine derivatives appear to be effective, such as fertility, milk productivity and growth stimulators for cows[14] stabilizers of fishmeal for broiler chicks,[15,16] ingredients in hog, calf and cattle feed[17-19] as well as agents for antiradiation protection of plants.[20] Dihydropyridine compounds are important intermediates in the synthesis of benmorphane,[21-25] thienomorphane[26-28] and cephalosporine [29,30] derivatives, biosynthesis of indole alkaloids,[31] nicotine[32] and in the biotransformations of elastine.[33] Two alkaloids possessing a dihydropyridine skeleton has been identified.[34] It is well known that the reduced coenzyme forms of NAD(P)H are dihydropyridine derivatives[35] and through these compounds dihydropyridine chemistry in all living organisms enters fundamental biochemical processes.

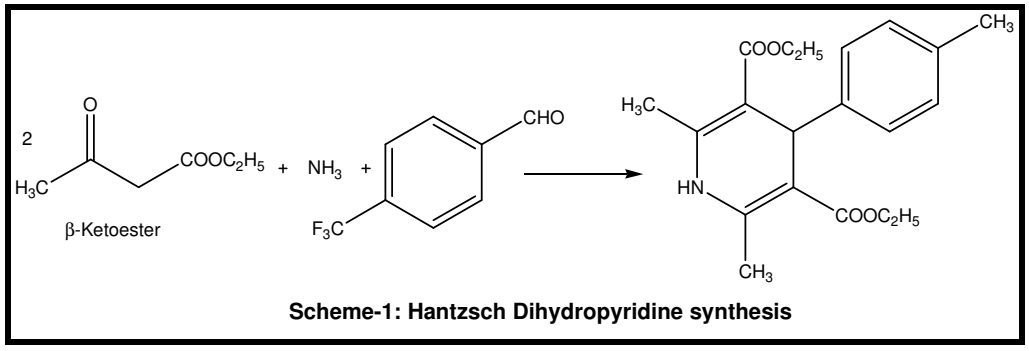
Dihydropyridine derivatives, such as nifedipine, nitrendipine and nimodipine, have been found to be commercially useful molecules as Ca^{2+} channel blockers.[36-38] A number of dihydropyridine Ca^{2+} channel (Ca^{2+}) antagonists have been introduced as potential drugs for the treatment of congestive heart failure.[39,40]

Cerebrocrast, a dihydropyridine derivative, has been introduced as a neuroprotective agent.[41] Together with Ca^{2+} channel blocker and neuroprotective activity, a number of dihydropyridine derivatives have been found as vasodilators, antihypertensive,

bronchodilators, antiatherosclerotic, hepatoprotective, antitumour, antimutagenic, antidiabetic and antiplatelet aggregation agents.[42-46]

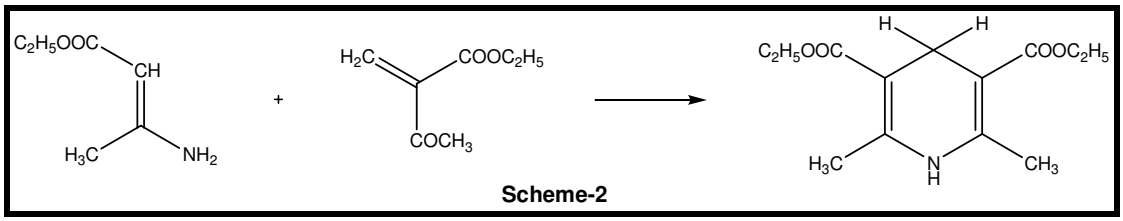
Hantzsch dihydropyridine syntheses

The first synthesis of a dihydropyridine is attributed to Arthur Hantzsch for work done a century ago[47]. Interestingly, the product from the condensation of two mols of ethyl acetoacetate, one mole of aldehyde and one mole of ammonia was assigned the dihydropyridine structure by Hantzsch (Scheme-1). Recent interest in the Hantzsch dihydropyridine has focused on substituents in the 2, 4, and 6 positions of the ring and on condensations involving compounds other than the β-keto esters. The first report of a Hantzsch ester unsubstituted at the 1, 2, and 6 positions involved the reaction of methyl propionate with an aromatic aldehyde and ammonium acetate in acetic acid.[48]



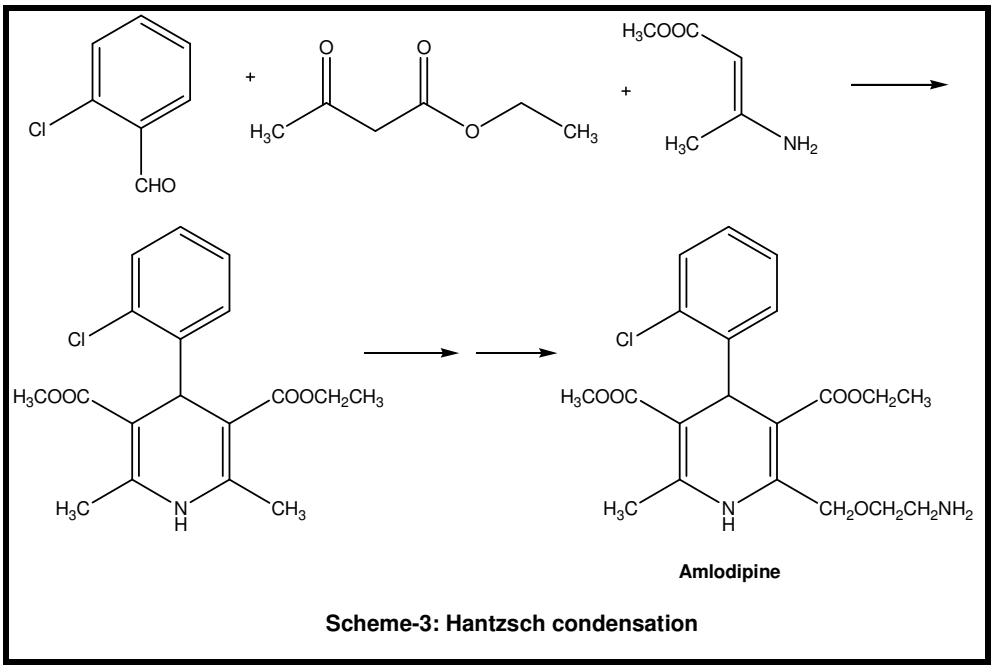
Scheme-1: Hantzsch Dihydropyridine synthesis

Jerome and co-workers[49] reported the classical Hantzsch synthesis[50] of dihydropyridines, involving the condensation of an aldehyde, ammonia and acetoacetic ester or other β-dicarbonyl compound, which was previously modified by Beyer[51] and later by Knoevenagel[52]. The symmetrical 1,4-dihydropyridines were hence prepared by condensation of formaldehyde, ammonia and ethyl acetoacetate which lead to 2,6-dimethyl-3,5-dicarbethoxy-l,4- dihydropyridine. The mechanism of the condensation was represented by involving preliminary formation of ethyl o-aminocrotonate and methyleneacetoacetic ester followed by Michael condensation and cyclization (Scheme-2).



Scheme-2

The 1,4-dihydropyridine[53] Ca^{2+} channel antagonists are clinically significant antihypertensive drugs and are immensely valuable as molecular tools with probe structural and functional aspects of Ca^{2+} channel function.[1,2] Amlodipine[5] consists of o-substituted phenyl ring because it is one of the most widely used drugs in 1,4-dihydropyridine family. Aza Diels-Alder reaction approach can be taken to construct highly substituted 1,4-dihydropyridine moiety focused on Amlodipine (Scheme-3).



Amlodipine

Scheme-3: Hantzsch condensation

4.2. Pharmacology

DHP as multi drug resistant reverting agents

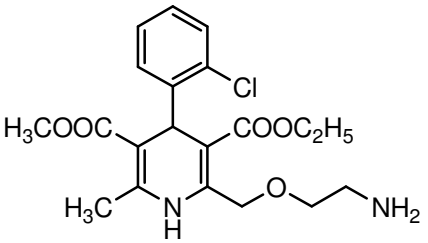
The 1,4-dihydropyridine,[54] blockers of L-type Ca^{2+} channels are used extensively in the treatment of cardiovascular disorders as dilators of coronary arteries. In addition to binding to Ca^{2+} channels, 1,4-dihydropyridines tends to bind to three subtypes of adenosine receptors, *i.e.* A_1, A_{2A}, and A_3[55,56]. For example, nifedipine binds these three

adenosine receptors with micromolar affinity, although it is much more potent at L-type Ca^{2+} channels. A newer generation Ca^{2+} channel blocker, nicardipine,[57] within the family of adenosine receptors is actually selective for the A_3 subtype. The (*S*)-enantiomer of niguldipine, which is the more potent enantiomer at L-type Ca^{2+} channels, binds to human A_3 adenosine receptors with a *K*i value of 2.8 μM and is totally inactive at A_1 and A_{2A} receptors. Thus, with respect to adenosine receptors alone it is highly specific for the A_3 subtype.

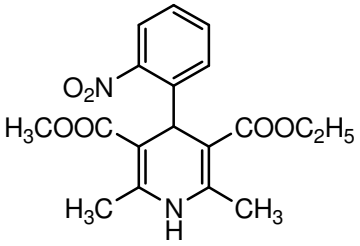
Some of the other dihydropyridines, such as amlodipine**,** felodipine**,** isradipine**,** lacidipine**,** nifedipine**,** nimodipine and nitrendipine have been commercialized and it has been proven that their therapeutic success is related to their efficacy to bind to Ca^{2+} channels and consequently to decrease the passage of the transmembrane Ca^{2+} current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart. [58-60]

Jiang and co-workers[61] designed and synthesized some dihydropyridines that bind to adenosine receptors without binding to L-type Ca^{2+} channels. 1, 4-Dihydropyridine derivatives substituted with α-styryl or phenylethanyl groups at the 4-position and aryl groups at the 6-position were synthesized and found to be selective for human A_3 receptors.

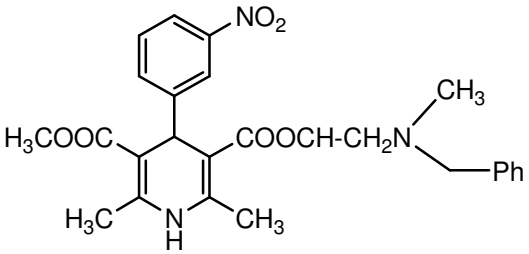
Table-1: Some important 1, 4-dihydropyridines as Ca^{2+} channel antagonists:



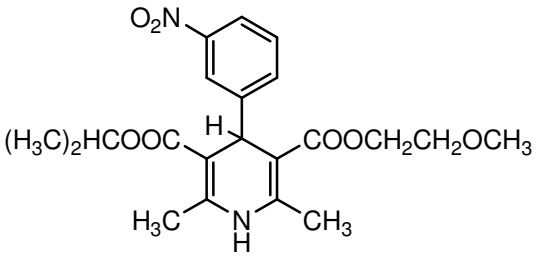
Amlodipine



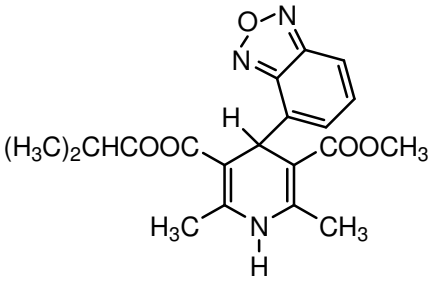
Nifedipine



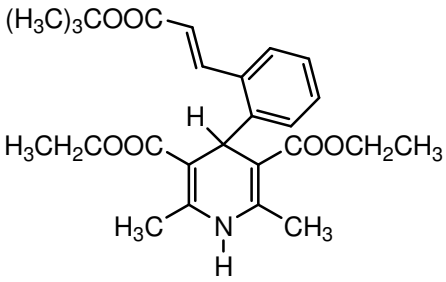
Nicardipine



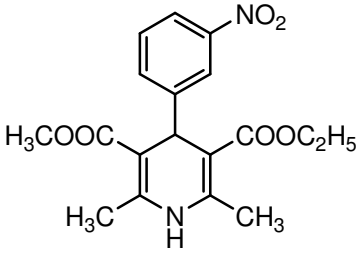
Nimodipine



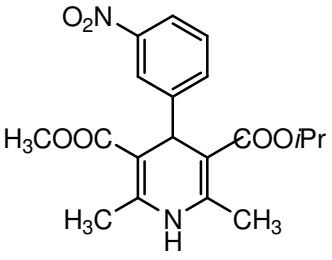
Isradipine



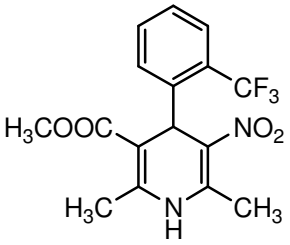
Lacidipine



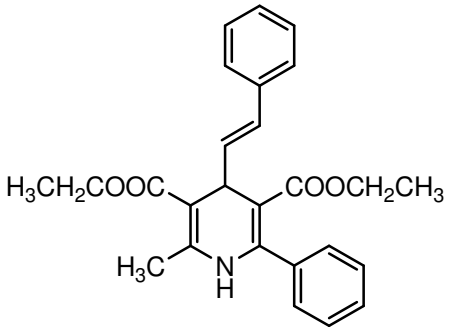
Nitrendipine



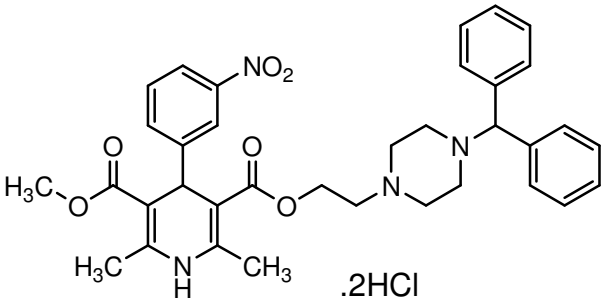
(R) –Nilvadipine



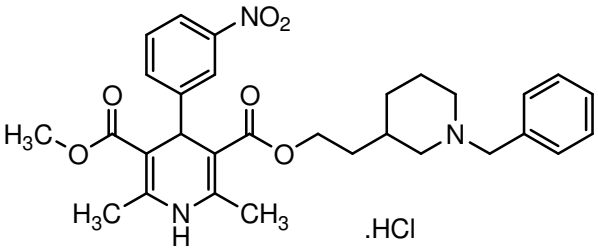
Bay K-8644



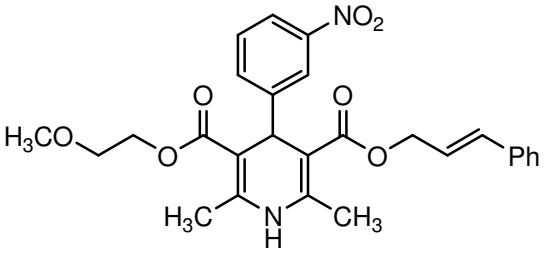
MRS 1097



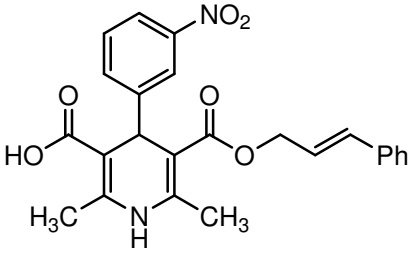
Manidipine dihydrocholride



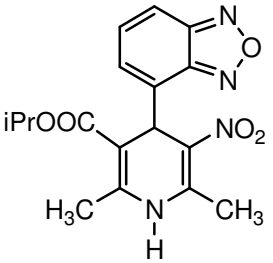
Benidipine hydrocholride



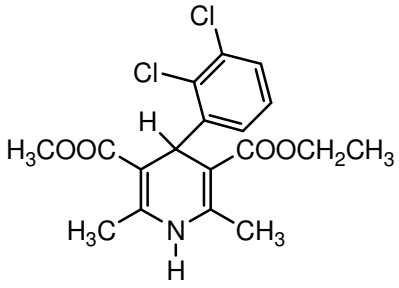
Clinidipine



APJ2708



202-791

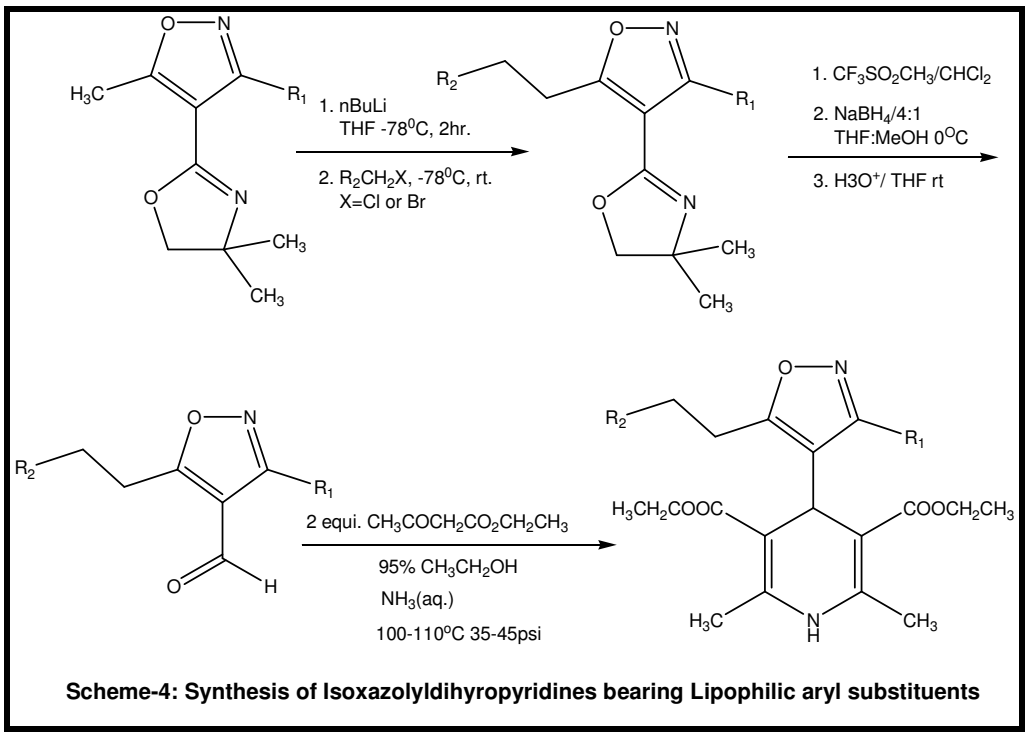


Felodipine

Cilnidipine is a 1,4-dihydropyridine derived L/N-type Ca^{2+} channel dual antagonist possessing neuro protective and analgesic effects which are related to its N-type Ca^{2+} channel inhibitory activity.[62, 63] It is currently used for the treatment of essential hypertension in Japan.[64] Its inhibitory effect for N-type Ca^{2+} channel can be clinically observed in the reduction of white coat effect, cold presser stress-induced platelet aggregation, urinary catecholamine excretion, and cardiac sympathetic overactivity in hypertensive patients.[65] Moreover, N-type Ca^{2+} channel-blocking profile of cilnidipine contributes to its neuroprotective action in the animal focal brain ischemia model and its intrathecal analgesic effect in rat formalin-induced pain model.[66]

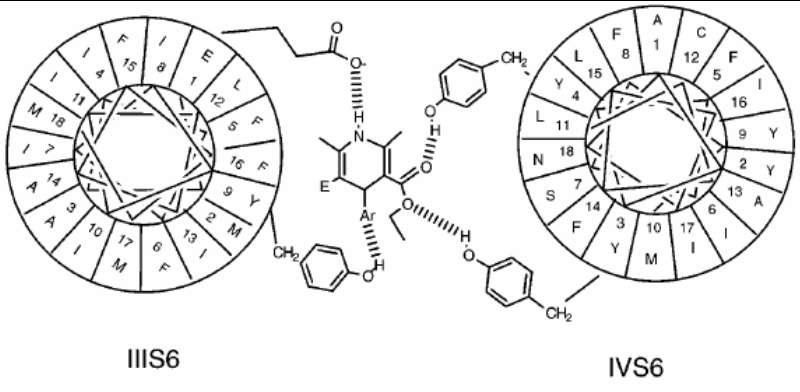
In order to find specific N-type Ca^{2+} channel antagonists with the effects on cardiovascular system, Yamamota and co-workers[67] performed structure–activity relationship study on APJ2708, which is a derivative of cilnidipine, and found a promising N-type Ca^{2+} channel blocker possessing analgesic effect *in vivo* with a 1600-fold lower activity against L-type Ca^{2+} channels than that of cilnidipine. APJ2708, which is a carboxylic acid derivative of cilnidipine, has almost the same inhibitory activity against N-type Ca^{2+} channels with far lower activity against L-type channels than that of cilnidipine. As a consequence of this L-type activity, APJ2708 showed a weak hemodynamic effect and needed more than 100-fold intravenously administered dose for decreasing the same amount of blood pressure as cilnidipine *in vivo*. It is assumed that the carboxylic acid moiety of APJ2708 was the key structure for this selectivity and hence APJ2708 was optimized with the aim of discovering N-type Ca^{2+} channel blockers with low activity against L-type channels which have lesser influence on the cardiovascular systems.

Natale and co-workers[68] prepared a series of 4-isoxazolyl-1,4-dihydropyridines bearing lipophilic side chains at the C-5 position of the isoxazole ring (Scheme-4). The Ca^{2+} channel antagonistic activity of these compounds has been evaluated.



Scheme-4: Synthesis of Isoxazolyldihyropyridines bearing Lipophilic aryl substituents

A hypothetical model for binding of these compounds in the Ca^{2+} channel is proposed and the validity of this model is evaluated based on the SAR of this series of Ca^{2+} binding, especially for the two most active derivatives (Figure-1). The solid state structure for the most active compound, has also been determined, and its important features were reported.

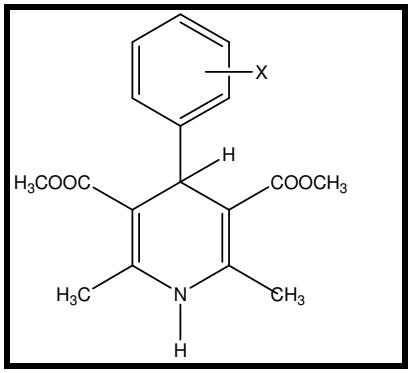


The IVS6 is positioned to interact with the starboard ester functional group of the DHP.

Figure-1: Edmundson helical wheel representation of the binding model, based on covalent effinity labeling data, of the hypothetical role of the IVS6 portion of the Ca^{2+} channel in DHP binding.

Si and co-workers[69] used gene expression programming, a novel machine learning algorithm, to develop quantitative model as a potential screening mechanism for a series of 1,4-dihydropyridine Ca^{2+} channel antagonists. The heuristic method was used to search the descriptor space and select the descriptors responsible for activity. A nonlinear, six-descriptor model based on gene expression programming with mean-square errors 0.19 was set up with a predicted correlation coefficient (R_2) 0.92. A new and effective method for drug design and screening was hence established (Table-2).

Table-2: Experimental and predicted activities [-log (IC_{50})] of 1, 4-dihydropyridine Ca^{2+} channel antagonists



Antagonist	X	Log (I/IC_{50})		
		Experimental	HM	GEP
1	2'-NO_2	8.89	8.22	8.76
2[a]	2'-CF_3	8.82	8.74	9.25
3	2'Cl	8.66	8.02	8.10
4	3'-NO_2	8.40	8.20	8.23
5[a]	2'-$CH=CH_2$	8.35	8.33	7.96
6	2'-NO_2	8.29	7.95	8.16
7	2'-CH_3	8.22	7.71	7.67
8[a]	2'-CH_2CH_3	8.19	8.05	8.63
9	2'-Br	8. 12	7.45	7.68
10	2-CN	7.80	8.37	8.64
11[a]	3'-Cl	7.80	7.54	8.31
12	3'-F	7.68	7.78	7.81
13	H	7.68	7.95	7.66
14[a]	3'-CN	7.46	7.78	7.75
15	3'-I	7.38	7.21	7.09
16	2'-F	7.37	7.59	7.63
17[a]	2'-I	7.33	7.19	7.31
18	2'-OCH_3	7.24	6.63	7.14
19	3'-CF_3	7.13	7.37	7.64
20[a]	3'-CH_3	6.96	6.70	6.43
21	2'-OCH_2CH_3	6.96	7.19	7.53
22	3'-OCH_3	6.72	6.59	6.76
23[a]	3'-$N(CH_3)_2$	6.05	5.98	6.06
24	3'-OH	6.00	6.15	6.06
25	3'-NH_2	5.70	5.05	5.60
26[a]	3'-OAc	5.22	5.46	5.49
27	3'-OCOPh	5.20	4.57	5.64
28	2'-NH_2	4.40	5.43	4.86
29[a]	4'-F	6.89	6.62	6.53
30	4'-Br	5.40	5.69	5.74
31	4'-I	4.64	4.53	5.05
32[a]	4'-NO_2	5.50	5.00	5.34
33	4'-NMe_2	4.00	3.97	4.25
34	4'-CN	5.46	5.99	5.85

[a]Test Set

Budriesi and co-workers[70] synthesized novel, substituted 1,4-dihydropyridines with a 3-methoxy-flavone moiety. Structural modifications of the substituents in the dihydropyridine ring of nifedipine were carried out in order to find tissue specific compounds. The negative inotropic, chronotropic and vasorelaxant effects were investigated on guinea-pig left, right atria and aortic strips, respectively. The introduction of an heteroaromatic ring in 4-position of the 1,4-dihydropyridine nucleus led to compounds selective for cardiac tissues. Moreover, different residues in the 1,4-dihydropyridine ring could modulate the chronotropic versus inotropic activity (Figure-2).

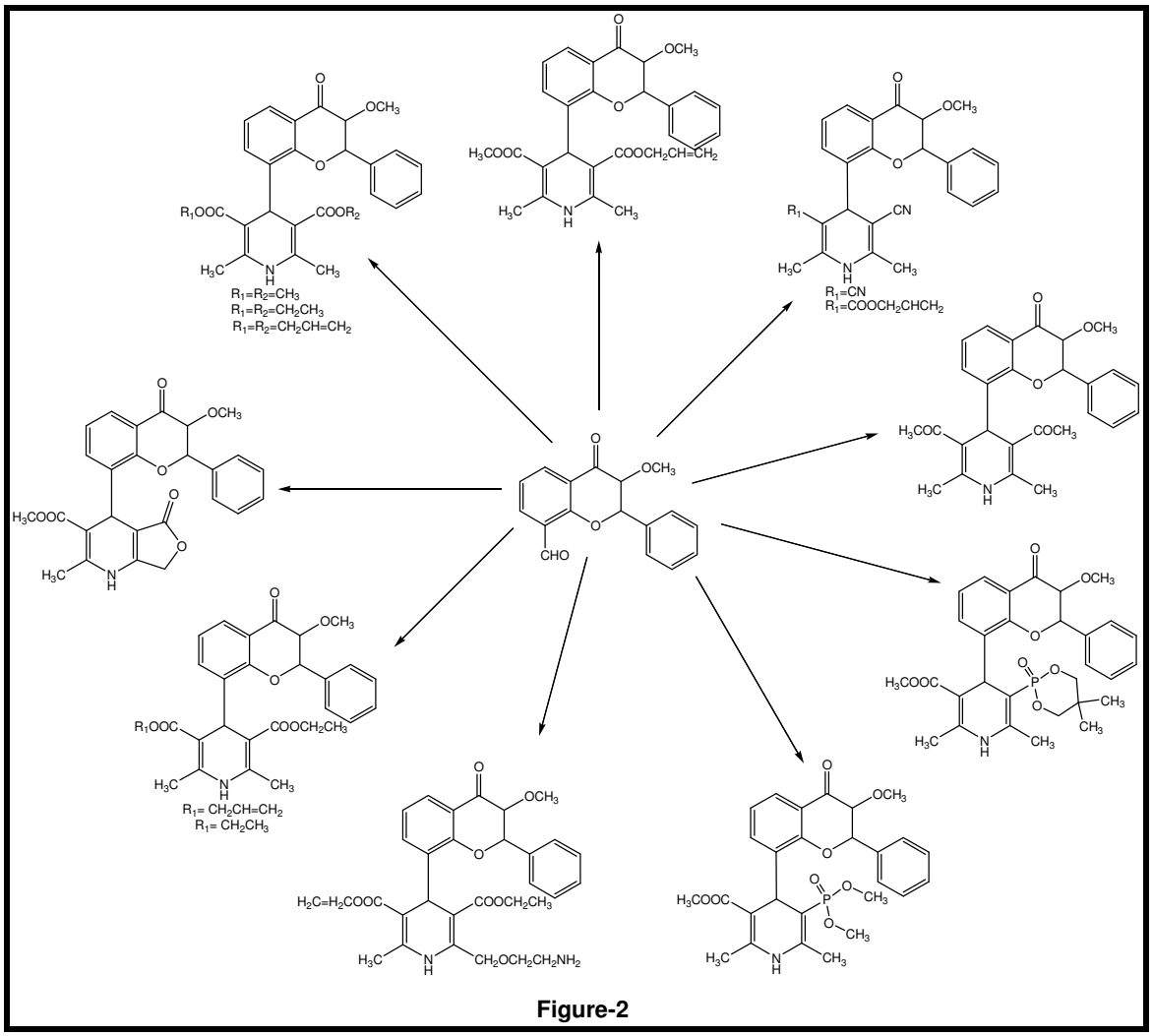
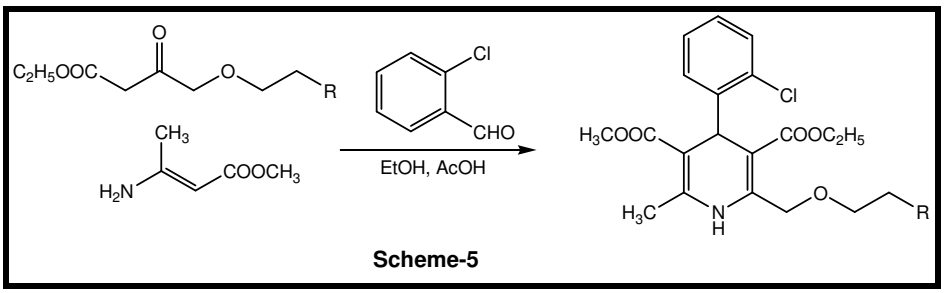


Figure-2

Several derivatives of 4-aryl-1,4-dihydropyridines are widely used as therapeutic agents for the treatment of hypertension, angina,[71] and other cardiovascular diseases. The DHPs have also proven to be powerful probes of the molecular basis of antagonism and the site of action in the Ca^{2+} channel.[72] The bioisosteric replacement of the 4-aryl moiety with a 4-isoxazolyl group yields analogous 4-isoxazolyl-1,4-dihydropyridines which retain potent Ca^{2+} antagonist activity.[73] Some dihydropyridines were prepared with pharmacological activity equal to or greater than that of currently used therapeutic agents, such as nifedipine. Ideally, new drug development arise from the detailed study of drug-receptor complexes both in the solid state (X-ray diffractometry) and in the solution phase (NMR spectroscopy). In the absence of such detailed information, drug development must proceed based on lead compounds and information on the nature of drug receptor or interactions gathered from the best-available methodology.

Alker and co-workers[74] reported the synthesis of a series of 1,4-dihydropyridines which had N-linked heterocycles at the terminus of an ethoxymethyl chain at the 2-position. The Ca^{2+} antagonist activity on rat aorta of this class of DHPs was compared with their negative inotropic activity as determined by using a Langendorff-perfused guinea pig heart model. The compounds examined showed a wide range of selectivity for vascular over cardiac tissue, with those analogues which possess an amide group at the terminus of the 2-substituent proved to be the most selective. From the *in vitro* data obtained for a series of 1, 2, 3-triazoles, it was concluded that the SARs for binding to the Ca^{2+} channels in vascular and cardiac tissue are different. One of the compounds, 2-amino-1-[2-[[4-(2,3-dichlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-4-dihydropyrid-2-y1]methoxy]ethyl]-4(3*H*)-imidazolone was identified as a potent (ICw = 8 X 10^4 M) Ca^{2+} antagonist which is 40-fold selective for vascular over cardiac tissue and which has a significantly longer duration of action (>3 h) than nifedipine in the anesthetized dog on intravenous administration (Scheme-5).

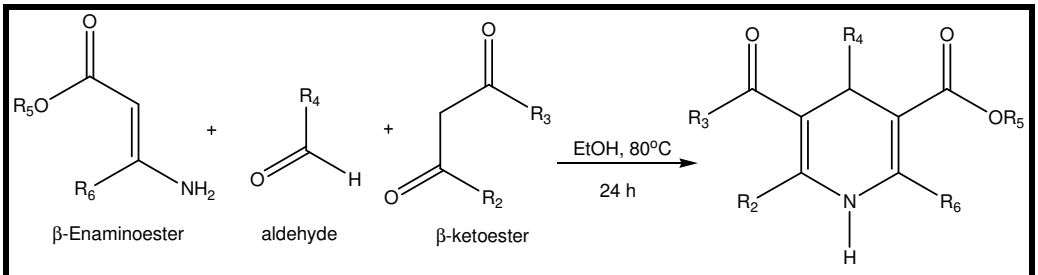


Scheme-5

Other pharmacollogical properties of 1,4-dihydrpyridines

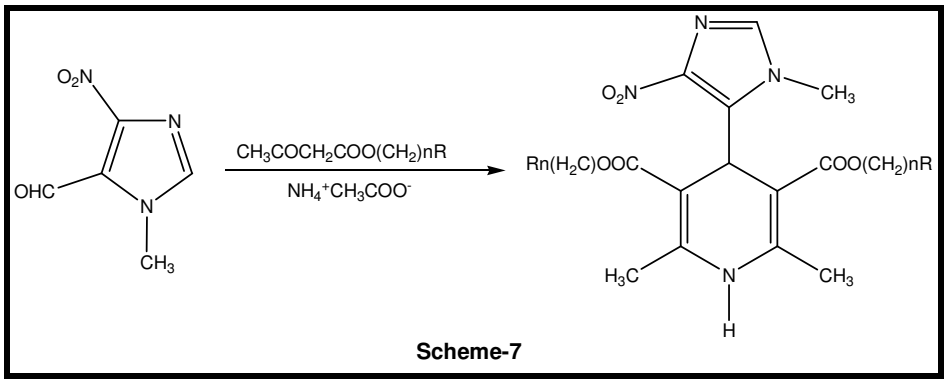
Dihydropyridine drugs such as nifedipine, nicardipine, amlodipine and others are effective cardiovascular agents for the treatment of hypertension.[75] The 4-aryl-1,4-dihydropyridines have been explored for their Ca^{2+} channel activity and the heterocyclic rings are found in a variety of bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumour, antidiabetic, geroprotective and heptaprotective agents.[76] Moreover, studies have discovered that these compounds exhibit diverse medical functions such as neuroprotectants, compounds with platelet antiaggregators, cerebral anti-ischaemic agents and chemosensitizers.[77]

Li *et. al.*[78] reported some novel 1,4-dihydropyridines which were tested for their affinity in radioligand binding assays at adenosine receptors. The Hantzsch condensation, which involved condensing three components, a 3-amino-2-propenoate ester, an aldehyde, and a β-ketoester, was used for synthesizing 1,4-dihydropyridine derivatives.



Scheme-6: Synthesis of substituted 1,4-dihydropyridines using the Hantzsch reaction

Shafiee *et. al.* [79] carried out anticonvulsant activity of alkyl, cycloalkyl and arylalkyl ester analogues of nifedipine in which the *o*-nitro phenyl group at position 4 was replaced by 1-methyl-4-nitro-5-imidazolyl substituent, were determined against pentylenetetrazole-induced seizures in mice. The anticonvulsant effects of the compounds were evaluated by the measurement of seizure potency and duration. Significant differences were observed between treated animals with control group and nifedipine in seizure duration. The results had shown that most of the compounds had similar activity to the reference drug nifedipine. In addition, some of the compounds were more active than the reference drug nifedipine (Scheme-7).



Scheme-7

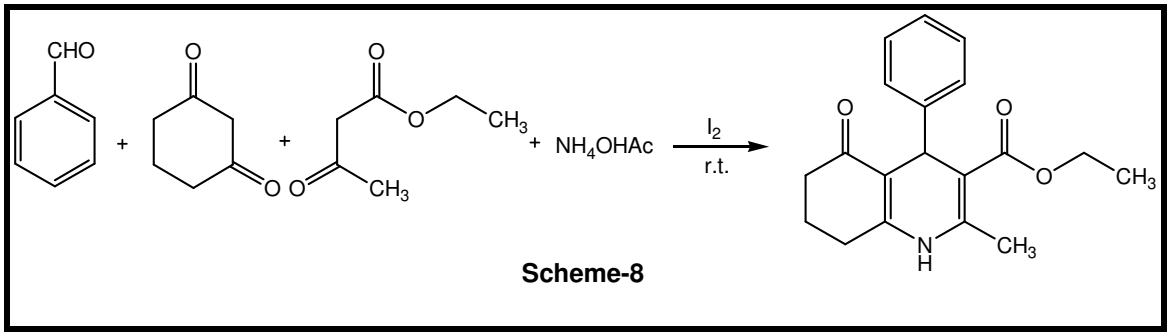
4.3. Synthetic approaches

Multiple synthesis of 1, 4-dihydropyridines

It has been reported that there are many methods to synthesize 1,4-dihydropyridine derivatives, in view of the biological importance associated with these compounds. The classical method involves the mixing of aldehyde with ethyl acetoacetate and ammonia in acetic acid or in refluxing alcohol.[80] Starting from Hantzsch,[81] more than a century ago, there are several efficient methods developed for the synthesis of 1,4-dihydropyridines, which comprise the use of microwave,[82] ionic liquids,[83] at high temperature in refluxing solvent, TMSCl–NaI and metal triflates.[84] The development of a simple, efficient and versatile method for the preparation of 1,4-dihydropyridine derivatives is an active area of research and there is a scope for further improvement towards milder reaction conditions and higher product yields.

The 4-aryl-1, 4-dihydropyridines are used in the treatment of cardiovascular disease, one of the world's leading causes of death. Its synthesis is typical of those in organic chemistry that usually involve more than one step, reagents and solvents and overall low atom efficiencies. The 4-aryl-1, 4-dihydropyridines are efficiently synthesized by Correa and co-workers[85] under solvent-free conditions in high yield. The use of volatile solvents was restricted to recrystallisation of the product, which, due to the high degree of conversion, kept to a minimum. Optimization of reaction conditions by careful consideration of the reaction rate and extent of conversion was demonstrated. This is yet another example of how readily solvent-free reactions may be implemented in the highly reproducible and efficient preparation of pure therapeutic agents with minimal production of waste and optimised use of energy.

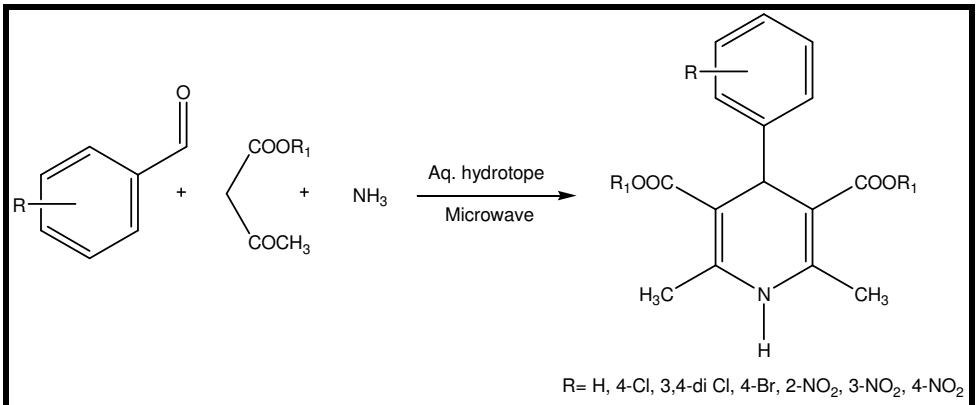
Sastry and co-workers[86] carried out a simple, inexpensive and efficient one-pot synthesis of 1,4-dihydropyridine derivatives at room temperature using catalytic amount of iodine with excellent product yields. Various substituted 1,4-dihydropyridine derivatives were synthesized using commercially available iodine as a catalyst. A novel synthesis of 1,4-DHPs using catalytic amount of iodine under ambient conditions with excellent yields was carried out by stirring benzaldehyde, 1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate at room temperature in a few drops of ethanol (Scheme-8).



Scheme-8

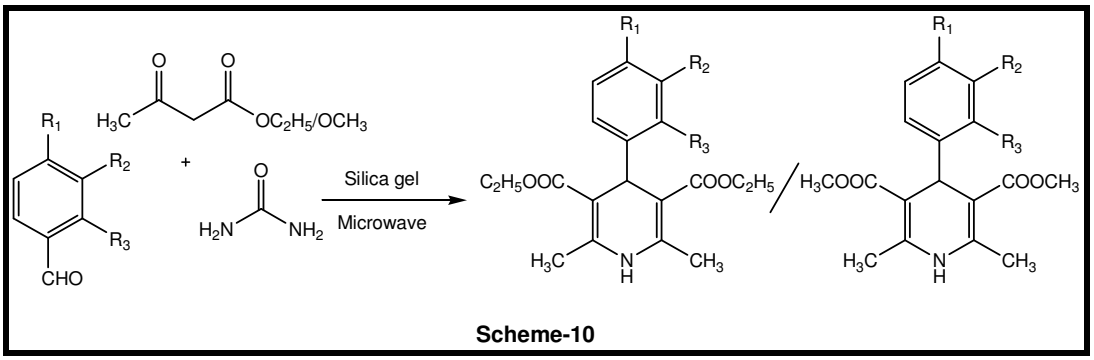
Khadilkar *et. al.*[87] described the scaling up of clinically important dihydropyridine by using a continuous microwave reactor (CMR). The use of aqueous hydrotrope solution as a cheap, safe and green alternative to organic solvent was was carry out for homogeneous reactions under microwave heating. Different aqueous hydrotrope solutions were studied for the reaction in batch as well as continuous-flow process.

The Hantzsch ester synthesis was performed using the hydrotrope solution by taking the mixture of benzaldehyde, methyl 3-aminocrotonate, and ethyl/methyl acetoacetate. The contents were solublized in the aqueous hydrotrope solution of sodium *p*-toluene sulphonate and circulated through the microwave oven cavity to obtain dihydropyridines in high yield and of excellent quality. A continuous microwave reactor (CMR) was prepared to carry out DHP synthesis reaction at a larger scale. 50% NaPTSA hydrotrope solution was used to carry out reaction under CMR (Scheme-9).



Scheme-9

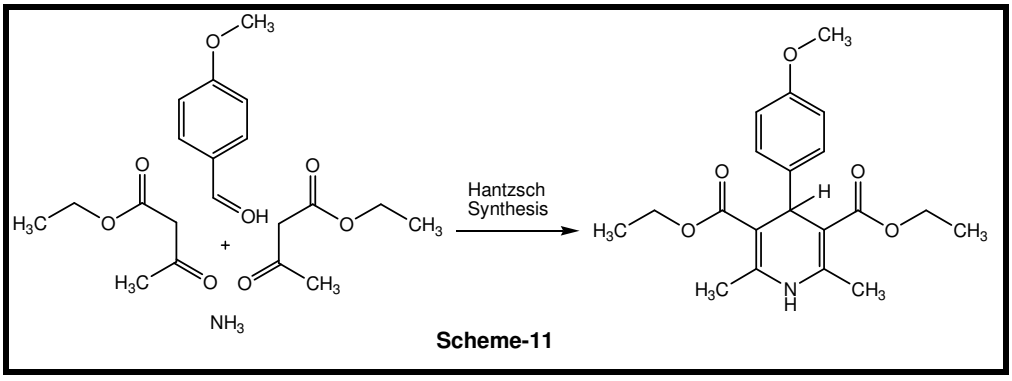
Chhillar and co-workers[88] synthesized 4-aryl-1,4-dihydropyridine and some 4-aryl-1,2,3,4-tetrahydropyrimidin-2-one derivatives and examined for their activity against pathogenic strains of *Aspergillus fumigatus* and *Candida albicans*. Two of the compounds of the dihydropyridine series, that is, diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate and dimethyl 4-(4-methoxyphenyl)- 2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate, exhibited significant activity against *A. fumigatus* in disc diffusion, microbroth dilution and percent spore germination inhibition assays. The diethyl dicarboxylate derivative of dihydropyridine also exhibited appreciable activity against *C. albicans*. The *in vitro* toxicity of the most active diethyl dihydropyridine derivative was evaluated using haemolytic assay, in which the compound was found to be non-toxic to human erythrocytes even at a concentration of 625 µg/ml. The standard drug amphotericin B exhibited 100% lysis of erythrocytes at a concentration almost 16 times less than the safer concentration of the most active dihydropyridine derivative (Scheme-10).



Scheme-10

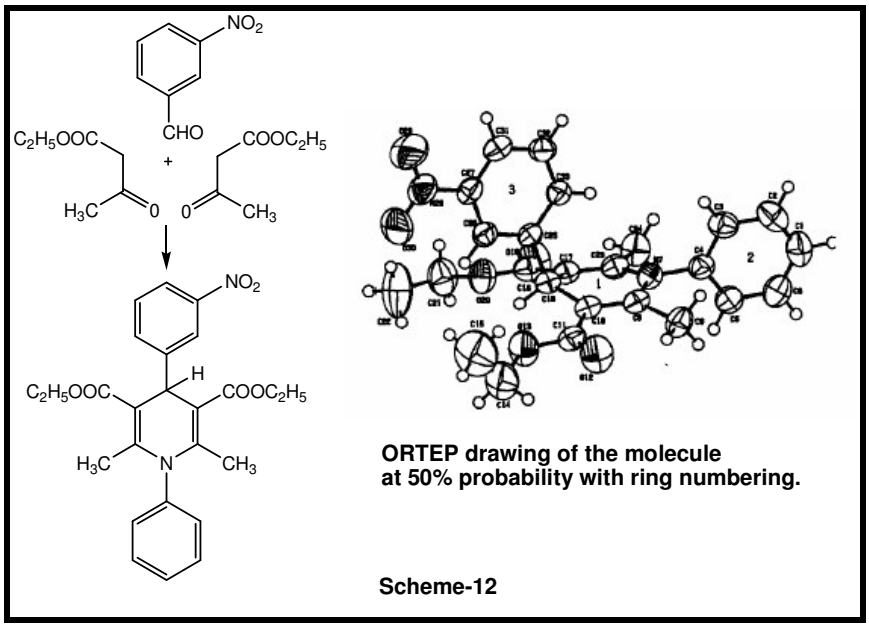
X-Ray crystallographic study of 1,4-dihydrpyridines

X-ray crystallographic studies of molecules of dihydropyridine have established the fact that majority of 1,4-dihydropyridine rings have a boat type conformation with varying degree of puckering at C_4 position. To synthesize the analogs of known drugs like flordipine, felodipine, darodipine, modifications to the C_4 part of 1,4 dihydropyridine moiety have been carried out. Some DHP molecules were synthesized with different electron donating groups (EDG) such as methoxy group at C4 position[89]. The title compound was prepared by Hantzsch (dihydro) pyridine synthesis (Scheme-11).



Scheme-11

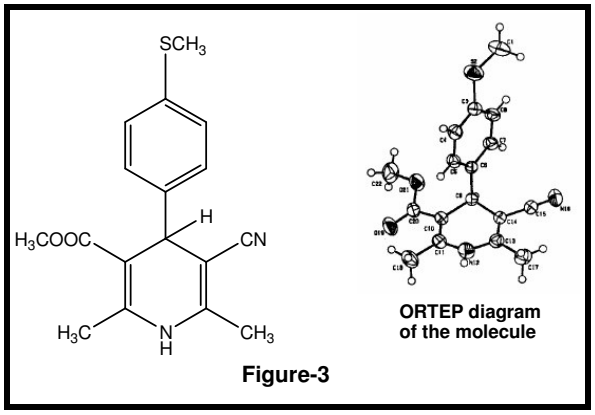
An *N*-substituted 1,4-dihydropyridine derivative has been synthesized by reacting ethyl acetoacetate, 3-nitro benzaldehyde and aniline in methanol and the X-ray structure was proved[90] (Scheme-12). The OPTEP drawing of the molecule at 50% probability with the ring numbering is also shown (Scheme-12).



ORTEP drawing of the molecule at 50% probability with ring numbering.

Scheme-12

A 1, 4-dihydropyridine has been synthesized by varing the substituents at the phenyl ring without disturbing the novel carbamoyl group at C_3 and C_5 positions of 1,4-dihydropyrimidine ring. The crystallographic characterization of the title compound was carried out. This compound is obtained by the substitution of cyanide group at C_3 and acetyl group at C_5 position of 1,4-dihydropyridine[91] (Figure-3).

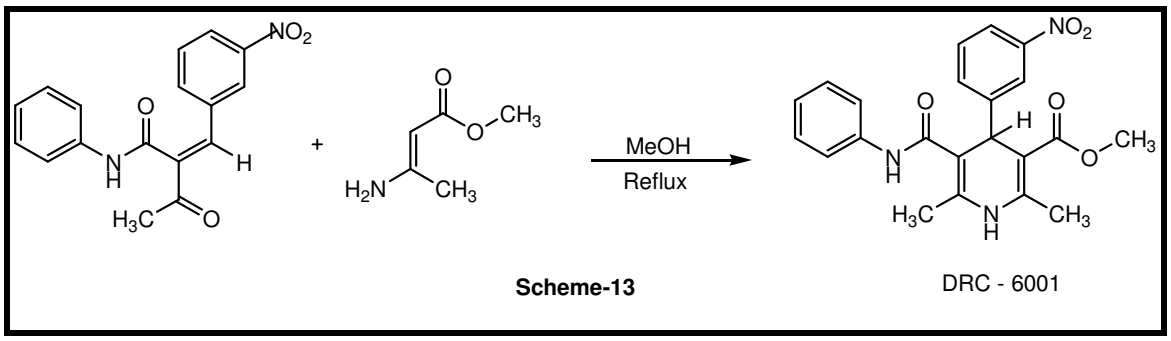


ORTEP diagram of the molecule

Figure-3

A series of potent unsymmetrical DHPs[92] were synthesized in our laboratory. Among the synthesized compounds, the compound DRC-6001, in which carbamoyl functionality and the esteric part in the C_3 and C_5 positions was introduced, respectively. This type of

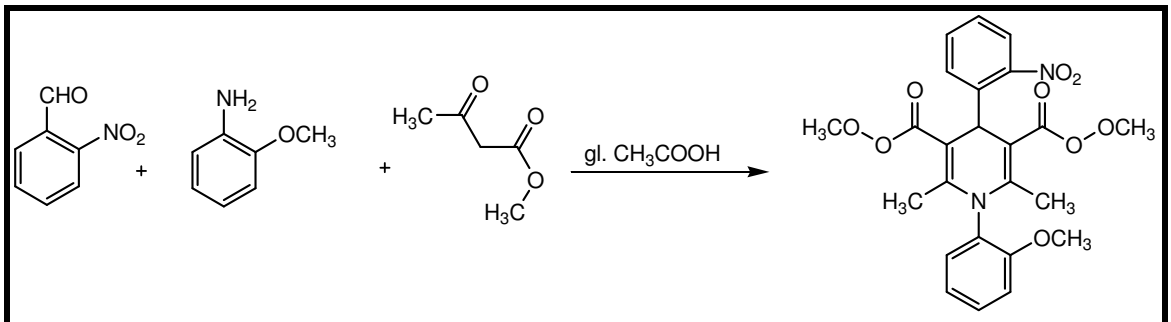
hybrid structure was confirmed by X-ray diffraction cryastallography method (Scheme-13).



Scheme-13

DRC - 6001

A potent[93] *N*-substituted 1,4-dihydropyridine, AKS-751, dimethyl-2,6-dimethyl-4-(2-nitrophenyl)–*N*-(2-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate,was synthesiz -ed and the crystal structure was proved by X-ray crysatallographic study. The compound was synthesized by heating methyl acetoacetate, 2-anisidine and 2-nitro benzaldehyde in glacial acetic acid (Scheme-14).



Scheme-14

AKS-751

Goldmann *et. al.*[94] synthesized 4,4-disubstituted 1,4-dihydropyridines which show a loss of Ca^{2+} antagonistic potency of 10^3 times both *in vitro* on aortic rings and *in vivo* on anaesthetized dogs as compared to examples that are mono-substituted at the 4-position of the DHP ring. The X-ray structure shows, the 4-aryl substituent is present not in the accustomed axial conformation, but in an equatorial one. This dramatic change in conformation could be the reason for the major loss of activity and would indicate the

need for axial conformation of the aryl residue in pharmacologically active 1,4-dihydropyridines (Figure-4).

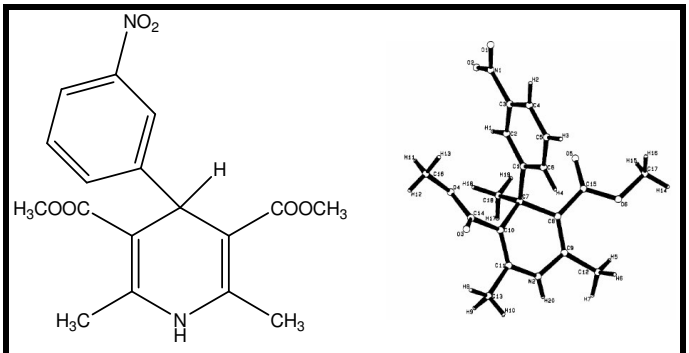


Figure-4

Work carried out at our laboratory:

The development of multidurg resestance (MDR)-tumor cell populations is a major problem in the chemotherapy of human cancer[95]. When tumor cells become resistant to anticancer agents such as *vinca* alkaloids or anthracyclines, they often show resistance to other antitumor agents with different structures and mechanisms of actions. One of the MDR types was proved to involve a membrane-bound protein, P-glycoprotein (Pgp) in MDR cancer cells, protozoa and baceteria. This protein acts as an efflux pump for the anticancer drugs[96]. Recently, various compounds have been shown to inhibit Pgp-mediated drug efflux[97]. These compounds include ion cannel blockers such as verapamil, dihydropyridines,[98] propafenone,[99] etc. Among them, DHPs, Ca^{2+} antagonists, have been studied extensively for the analogy to verapamil. It is very important finding that those DHPs which do not have any Ca^{2+} channel antagonistic, activity possess MDR reversal activity[100].

Shah *et al.*[101]. investigated the cytotoxic and the MDR-reversal activites of 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine derivatives against mouse lymphoma cells transfected with MDR1 gene. Among the synthesized compounds, G7 showed highest cytotoxic activity against human promyelocytic leukemia HL-60 and human squamous cell carcinoma HSC-2 cells (Figure-5).

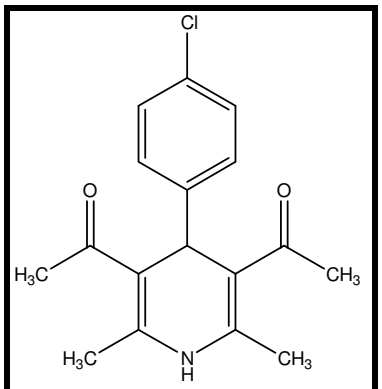


Figure-5: G-7

On these basis of these[102(a)] observations, some 4-substituted phenyl-2,6-dimethyl-3,5-bis-*N*-(substituted phenyl)carbamoyl-1,4-dihydropyridines were synthesized and tested against *M. tuberculosis* H37Rv.[102(b)]

Three-dimensional quantitative structure-activity relationship (3D QSAR) methods, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA), were applied on a series of 1,4-dihydropyridines possessing antitubercular activity.[103]

The 3, 5-dibenzoyl-1,4-dihydropyridines[104] (nifedipine analogues) were synthesized and the compounds were tested on three different *E. coli.* strains. Among all the synthesized compounds, GB12 was the most active in enhancing the activity of erythromycin, and was selected for plasmid elimination studies (Figure-6).

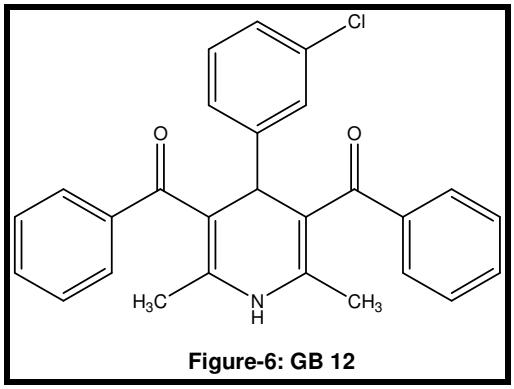


Figure-6: GB 12

Few of the DHPs of above series[105] showed synergistic interactions with ampicillin and erythromycin on *E. coli.* K12LE140/F'lac. With a sensitive clinical isolate of *E. coli.* Gy-1/Ap_{sens} Er_{res}, compound G1 antagonized the antibacterial effect of Ap and a synergistic effect was found in the combination of Er with other compounds (Figure-7).

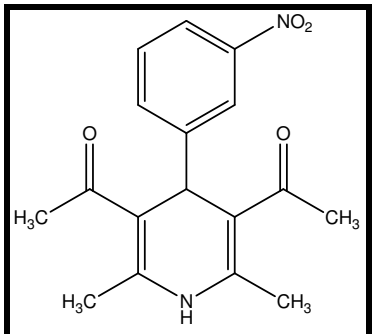


Figure-7: G-1

Three different series of 1,4-diphenyl-1,4-dihydropyridine derivatives were synthesized[106] and were tested to inhibit the transport activity of P-gp and were studied by flow cytometry in a MDR human colon cancer cell line (COLO320) and in human MDR 1 gene-transfected mouse lymphoma cells (L 5178 Y). The cytoxicities of these compounds were also examined against human normal and cancer cell lines. The majority of the tested compounds were proved to be effective inhinbitors of rhodamine 123 outward transport. Some dihydropyridines derivatives displayed cytotoxic activity against four human oral tumor cell lines and against three normal human oral cell lines (Figure-8).

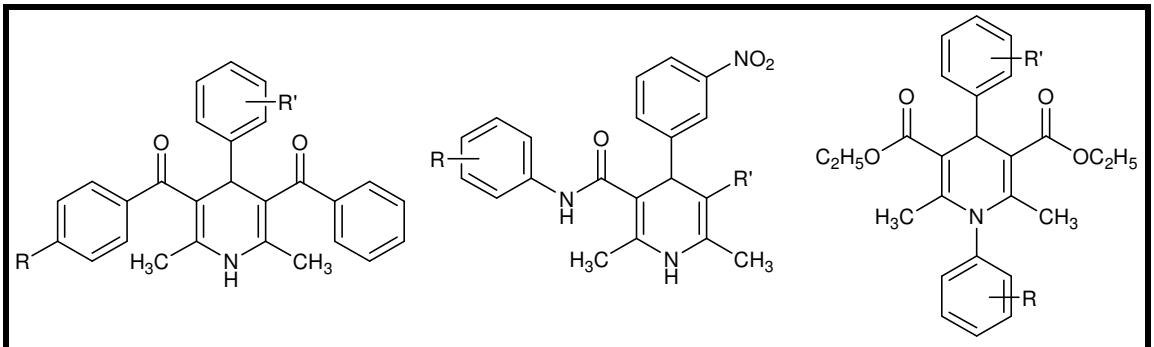


Figure-8

DP7, a novel dibenzoyl-1,4-dihydropyridine compound[107], synthesized in our laboratory has been shown to be a powerful P-gp inhibitor, almost devoid of cardiovascular effects, but capable of inhibiting liver CYP3A. DP7 is considered a lead compound for the development of novel dihydropyridines which do not effect CYP enzyme but still remains active towards ABC-efflux transporters (Figure-9).

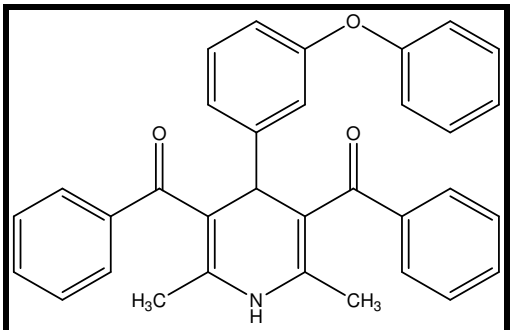
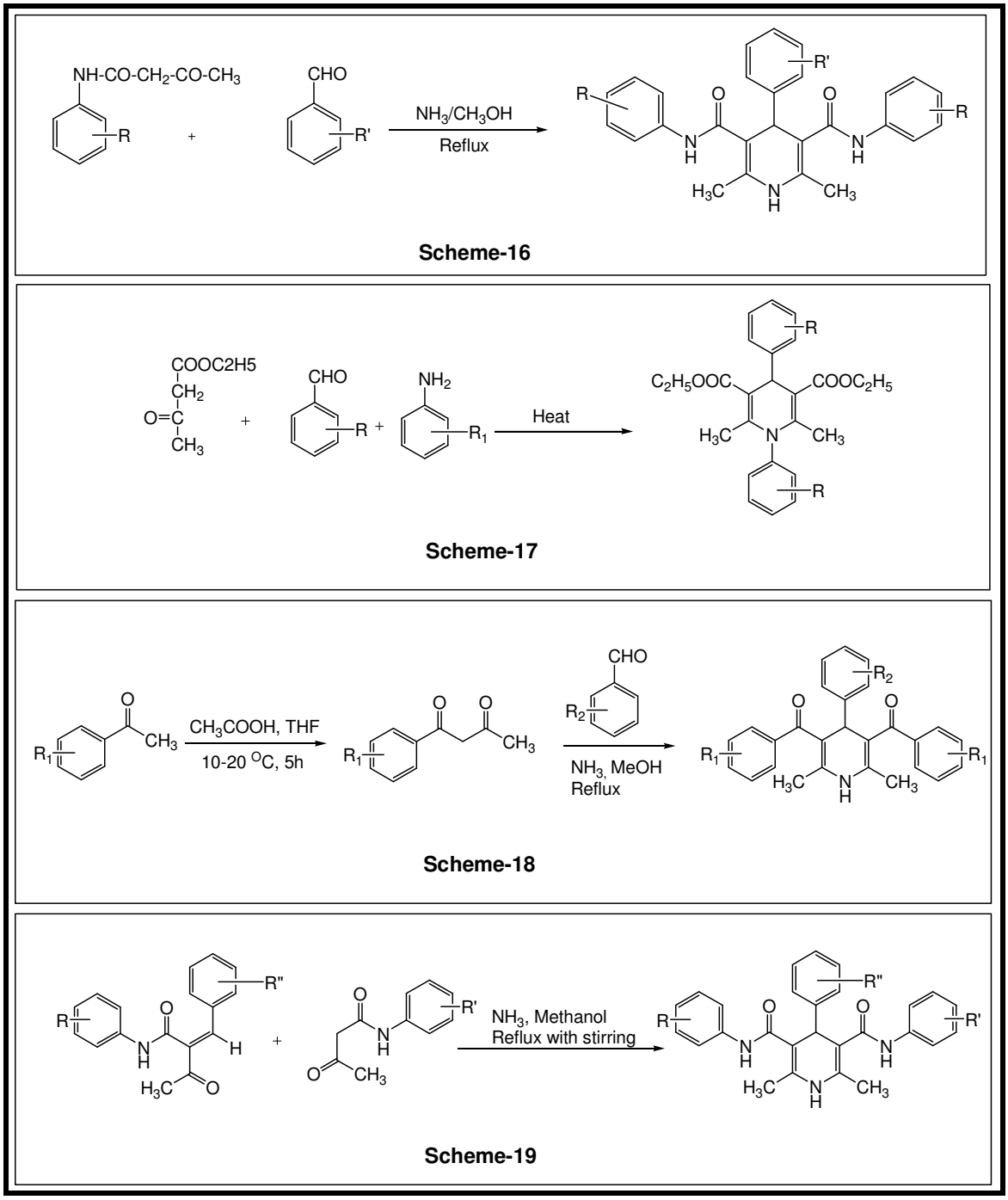


Figure-9: DP7

The compound, DP7, has also found out as a new multidrug resistance reveting agent devoid on vascular smooth muscle contractility. DP7 inhibited L-type Ca^{2+} ion current recorded in artery myocytes in a concentration dependant manner, with IC_{50} values ranging between 1.12×10^{-6} and $2.23\times10^{-5.}$ In L5187 MDR cell line, DP7 exhibited an MDR-reversing activity, with IC_{50} values ranging between 3.02×10^{-7} and 4.27×10^{-5}, being the most potent. The K^+ channel opener cromakalim inhibited the Ca^{2+} ion induced contraction in K30 but not that evoked in K60. But DP7, on the contrary was ineffective in both experimental conditions[108].

A series of 4-substituted phenyl-2,6-dimethyl-3,5-bis-*N*-(substituted phenyl) carbamoyl-1,4-dihydropyridines were synthesized and the compounds were emerged as potential antitubercular agents[109]. These compounds may act as precursors and after penetration into the cell wall may lead to the 3,5-carboxylate anions by enzymatic hydrolysis. All the derivatives were screened for their anti-tubercular activity against *M. Tuberculosis* H_{37} Rv (ATCC 27294; American type culture collection, Rockville, MD). Among them, some of the derivatives showed > 90% inhibition comparable to rifampicin.

A few compounds synthesized in out laboratory having 1,4-dihydropyridine as a core structure

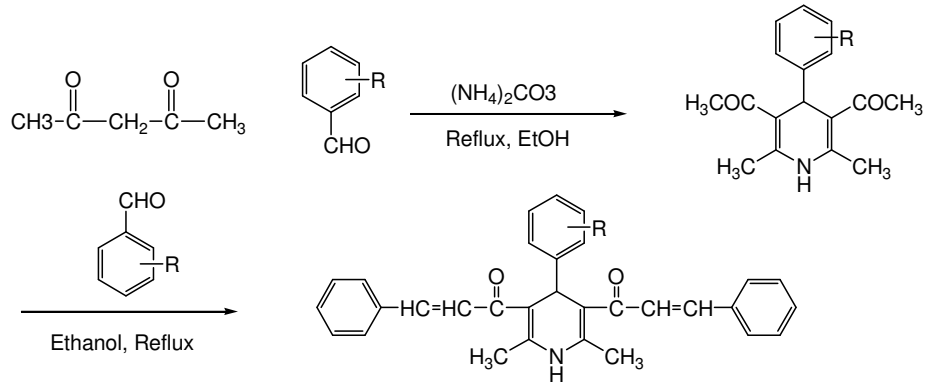


Scheme-16

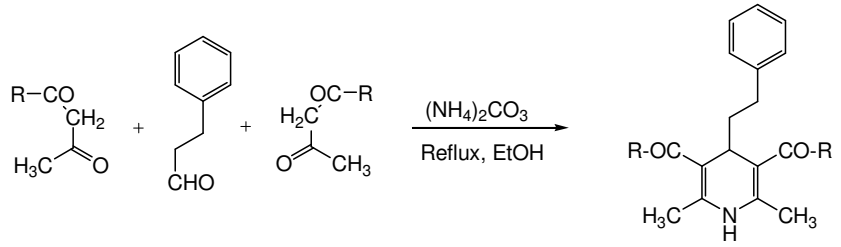
Scheme-17

Scheme-18

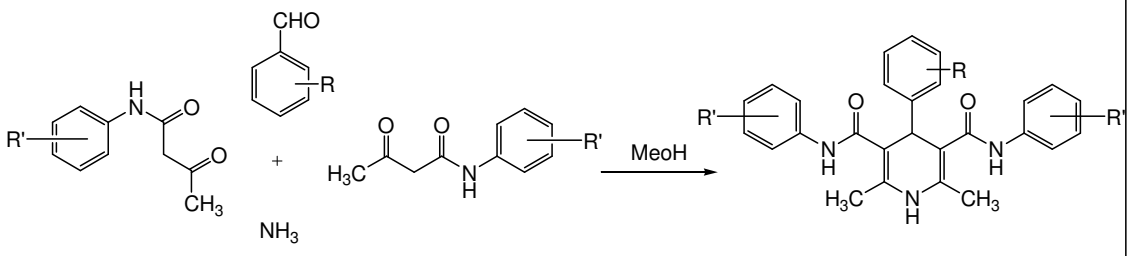
Scheme-19



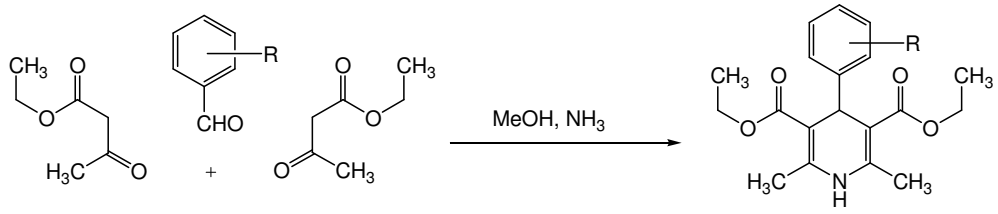
Scheme-20



Scheme-21



Scheme-22



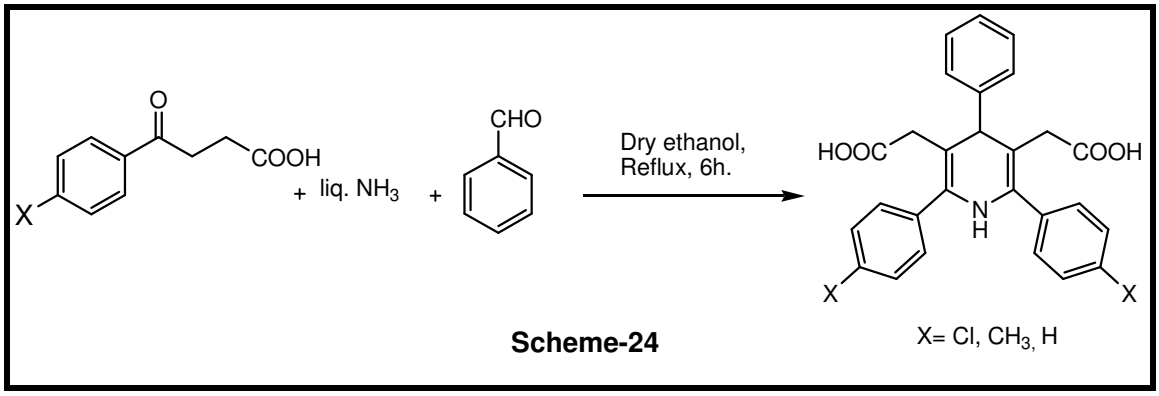
Scheme-23

4.4. Present work

A large number of heterocyclic alkanoic acids and related compounds have been reported for their anti-inflammatory activity.[110-113] Some new work is also reported so far on the anti-inflammatory activity of 1,4-dihydropyridines possessing analgesic,[114] hypotensive,[115] anti-tumor,[116] and coronary dialating activities[117]. These results promted us to synthesize the title compounds. The synthesized compounds belongs to heteroaryl alkanoic acids, which are well known as NSAIDs. A series of 26, 1,4-dihydropyridines have been synthesized by treating different aromatic aldehydes with β–aroylpropanoic acid and ammonia in ethanol (Scheme-24).

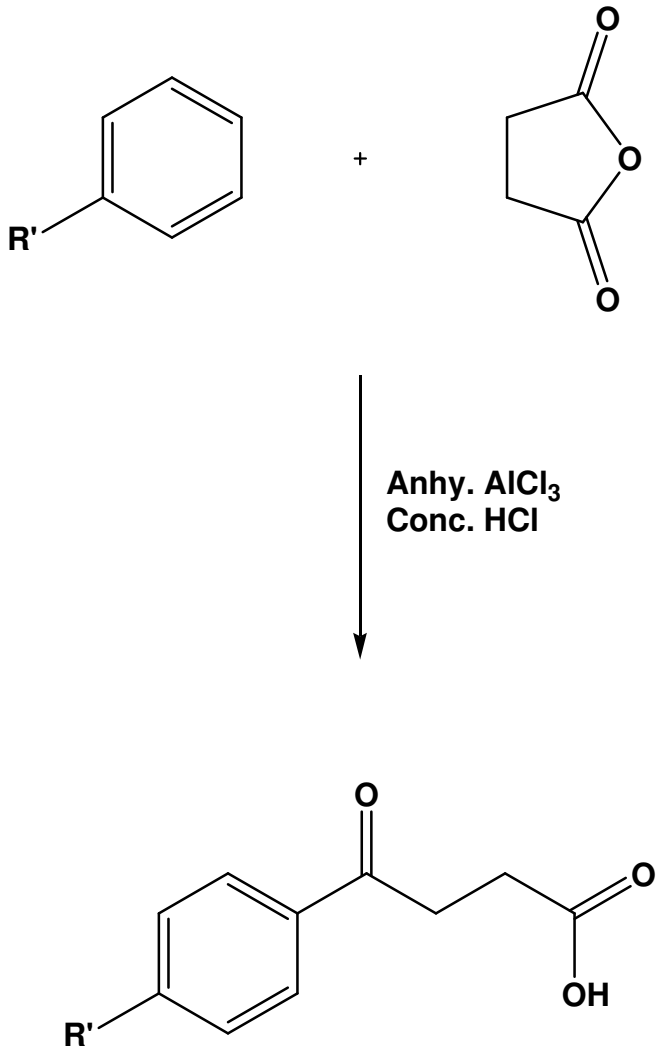
Bahekar and Shinde[118] synthesized a series of [5-carboxymethyl-2,6-bis-(4-substituted-phenyl)-4-aryl 1,4-dihydropyridine-3-yl]–acetic acids by reacting different aromatic aldehydes with β–aroylpropanoic acid and ammonia in ethanol.

The compounds were subjected to preliminary testing for their anti-inflammatory activity. The percentage of reduction in inflammation 3 hr after administration of carrageenin was recorded. Compared to the reference standard, diclofenac sodium, all the compounds showed a tendency to reduce the edema. The (5-carboxymethyl-4-phenyl-(2, 6-(di-4-chlorophenyl))-1, 4-dihydropyridine-3-yl)-acetic acid showed the enhanced activity among all the other synthesized compounds.



Scheme-24

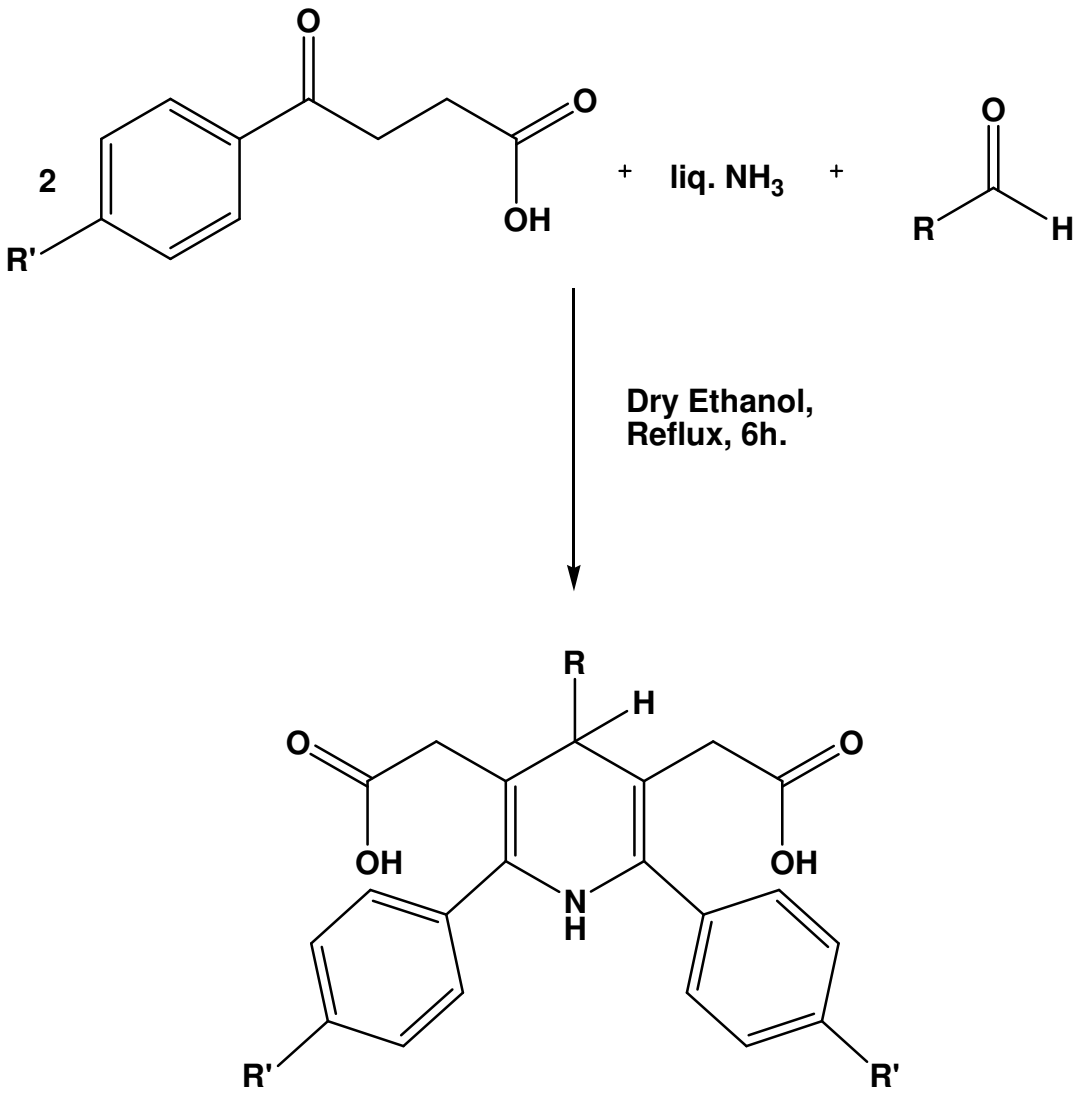
4.5. REACTION SCHEME-I



Where, R'= Cl, CH_3, H.

Synthesis of β-benzoyl propionic acid

REACTION SCHEME-II



Where, R= aryl
R'= Cl, CH_3, H.

Syntrhesis of 1,4-dihydropyridines

4.6. Experimental

General method for preparation of β-benzoyl propionic acid[100]

Succinic anhydride (6 g, 0.06 mole), is added to a 500 ml three necked round bottom flask equipped with a mechanical stirrer and a reflux condenser. Pure dry benzene (35 ml) was added and the mixture was stirred. Powdered anhydrous aluminium chloride (17.6 g, 0.13 mole) is added in one lot. Hydrogen chloride gas is evolved and the mixture becomes hot. It is stirred and heated in a boiling water bath for 30 min. The reaction mixture is cooled to room temperature and water (25 ml) was added. Concentrated hydrochloric acid (8.3 ml) is added and benzene was removed by steam distillation. The mixture is cooled and the separated oil solidified. It was then filtered, washed with dilute hydrochloric acid (25 ml, 1:3) and cold water (50 ml). The solid was purified by dissolving in sodium bicarbonate solution and acidifying the clear filterate. The precipitates were filtered and dried. Yield 10.0 g (94%). m.p.115^{o}C (Reported m.p.117^{o}C).[100]

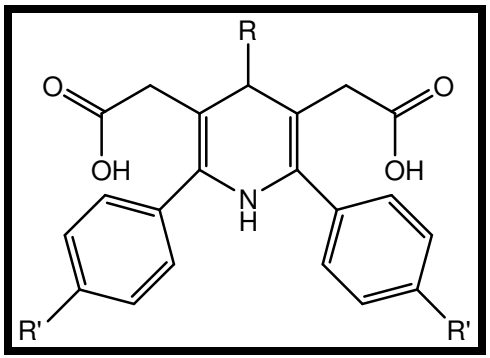
Similarly, other substituted β-aroyl propionic acids were prepared.

General method for preparation of (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acid[118]

To a solution of β-benzoyl propionic acid (0.02 mol) in dry ethanol, benzaldehyde (0.01 mol) and liquid ammonia (0.01 mol) were added. The mixture was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature. The solid obtained was filtered off, washed with cold ethanol and upon recrystallization with ethanol afforded the pure (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids.

The physical data and Rf value of various (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids were recorded in the Table 1.

4.7. Table 3: (5-Carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids



Codes	Substitution		Moleular formula	Molecular weight	Melting point (^oC)	Rf value	% Yield
	R	R'					
JT-101	4-NO_2 phenyl	Cl	$C_{27}H_{20}Cl_2N_2O_6$	539.36	158-160	0.363	61
JT-102	4-OH phenyl	Cl	$C_{27}H_{21}Cl_2NO_5$	510.37	136-138	0.333	46
JT-103	4-CN phenyl	Cl	$C_{28}H_{20}Cl_2N_2O_4$	519.38	168-170	0.38	48
JT-104	4-OCH_3 phenyl	Cl	$C_{28}H_{23}Cl_2NO_5$	524.39	162-164	0.378	72

Solvent system: Ethyl acetate: Hexane :: 6:4

Ref: (a)Bahekar S, and Shinde, Synthesis and anti-inflammatory activity of 1,4-dihydropyridines, *Acta Pharm.*, 52, 281-287, **2002.** (b) Kentoro H.; Hirohito S.; Synthesis of 2-substituted-amino-4-aryl-5-ylalkanoic acids, *Chem. Pharm Bull*. **1977**, 25, 2292-2299.

4.7. Table 3 (contd.): (5-Carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids

Codes	Substitution		Moleular formula	Molecular weight	Melting point (^oC)	Rf value	% Yield
	R	R'					
JT-105	2,5-$(OCH_3)_2$ phenyl	Cl	$C_{29}H_{25}Cl_2NO_6$	554.42	182-184	0.469	51
JT-106	3,4-$(OCH_3)_2$ phenyl	Cl	$C_{29}H_{25}Cl_2NO_6$	554.42	156-158	0.48	58
JT-107	3,4,5-$(OCH_3)_3$ phenyl	Cl	$C_{30}H_{27}Cl_2NO_7$	584.44	140-142	0.41	70
JT-108	Cinnamyl	Cl	$C_{29}H_{23}Cl_2NO_4$	520.40	126-128	0.40	74
JT-109	4-$N(CH_3)_2$ phenyl	Cl	$C_{29}H_{26}Cl_2N_2O_4$	537.43	118-120	0.47	72
JT-110	2-Pyridyl	Cl	$C_{26}H_{20}Cl_2N_2O_4$	595.35	88-90	0.51	68
JT-111	3-Indolyl	Cl	$C_{29}H_{22}Cl_2N_2O_4$	533.40	122-124	0.54	62
JT-112	1-Naphthayl	Cl	$C_{31}H_{23}Cl_2NO_4$	544.42	136-138	0.47	57
JT-113	4-NO_2 phenyl	CH_3	$C_{29}H_{26}N_2O_6$	498.53	120-122	0.43	73
JT-114	4-OH phenyl	CH_3	$C_{30}H_{26}N_2O_4$	469.53	158-160	0.47	49
JT-115	4-CN phenyl	CH_3	$C_{30}H_{26}N_2O_4$	478.54	126-128	0.38	56
JT-116	4- OCH_3 phenyl	CH_3	$C_{30}H_{29}NO_5$	483.55	162-168	0.51	77

4.7. Table 3 (contd.): (5-Carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids

Codes	Substitution		Moleular formula	Molecular weight	Melting point (^oC)	Rf value	% Yield
	R	R'					
JT-117	2,5-$(OCH_3)_2$ phenyl	CH_3	$C_{31}H_{31}NO_6$	513.58	156-158	0.43	58
JT-118	3,4-$(OCH_3)_2$ phenyl	CH_3	$C_{31}H_{31}NO_6$	513.58	158-160	0.51	53
JT-119	3,4,5--$(OCH_3)_3$ phenyl	CH_3	$C_{32}H_{33}NO_7$	543.61	124-126	0.56	71
JT-120	Cinnamyl	CH_3	$C_{31}H_{29}NO$	479.57	98-100	0.42	58
JT-121	4- $N(CH_3)_2$ phenyl	CH_3	$C_{31}H_{32}N_2O_4$	496.60	116-118	0.49	68
JT-122	2-Pyridyl	CH_3	$C_{28}H_{26}N_2O_4$	454.52	82-84	0.48	64
JT-123	3-Indolyl	CH_3	$C_{31}H_{28}N_2O_4$	492.57	102-104	0.46	62
JT-124	1-Naphthayl	CH_3	$C_{23}H_{29}NO_4$	503.59	116-118	0.47	55
JT-125	4-NO_2 phenyl	H	$C_{27}H_{22}N_2O_6$	470.47	128-130	0.46	74
JT-126	4- OCH_3 phenyl	H	$C_{28}H_{25}NO_5$	455.5	142-144	0.58	63

4.8. Spectral study

Infra Red spectra

IR spectra were taken on SHIMADZU 8400 FT-IR-435 Spectrometer using KBr Pellet method. The free hydroxyl group (-OH) is observed between the value 3605-3560 cm^{-1}. The NH stretching was observed between 3430-3460 cm^{-1}. The –CH stretching frequency was observed between the values 2846-2963 cm^{-1}. The characteristic acid group (COOH of carboxylic acid) in dihydropyridine moiety is observed at 1790-1830 cm^{-1}, The dihydropyridine moiety showed the ring skeleton vibrations at 1600-1630, 1550-1590, 1550-1520, 1470-1495 cm^{-1}. The frequency of the methyl as well as methylene group in the compounds showed the value between 1436-1468 cm^{-1}, as well as 1358-1394 cm^{-1} respectively. The value of C-Cl frequency in some compounds was observed between 712-756 cm^{-1}.

.

^{1}H NMR spectra

^{1}H NMR spectra were recorded on Bruker AC 400 MHz FT-NMR Spectrometer using TMS (Tetramethyl Silane) as an internal standard and DMSO-d_6 as a solvent. In the ^{1}H NMR spectra of (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids, various proton values like methylene (-CH_2), methyl (-CH_3), aromatic protons (Ar-H) and hydroxyl protons (of carboxylic acid) of carboxylic acid were observed as under.

The values for methyl (-CH_3) proton is observed between 2.3-2.6 δ ppm and for methylene (-CH_2) proton, between 3.5-4.0 δ ppm. The aromatic protons (Ar-H) shows doublets or multiplets between 6.4-7.8 δ ppm. The value for hydroxyl proton (-OH) in carboxylic acid group was observed after 8.0 δ ppm.

Individual ^{1}H NMR data of synthesized compounds are mentioned in spectral data analysis.

Mass spectra

The mass spectrum of compounds was recorded by GCMS-QP2010 spectromeyter (EI method). The molecular ion peak (M^+) and the base peak in all compounds were clearly

obtained in mass spectral study. The molecular ion peak (M^+) values are in good agreement with molecular weight of all the compounds synthesized.

C, H, N analysis

Elemental analysis of the compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

4.9. Spectral characterization

(5-Carboxymethyl-4-(4-nitrophenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-101)

IR (KBr) cm^{-1}: 3437 (N-H str.), 2973 (C-H str.), 1802 (COOH), 1447 (CH_2), 723 (C-Cl).

C, H, N analysis, Calculated: C, 60.12; H, 3.74; N, 5.19. **Found:** C, 60.10; H, 3.72; N, 5.17.

(5-Carboxymethyl-4-(4-hydroxyphenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-102)

IR (KBr) cm^{-1}: 3593 (free OH str.), 3500 (N-H str.), 2879 (C-H str.), 1815 (COOH), 1419 (CH_2 str.), 744 (C-Cl).

C, H, N analysis, Calculated: C, 63.54; H, 4.15; N, 2.74. **Found:** C, 63.46; H, 4.13; N, 2.73.

(5-Carboxymethyl-4-(4-cyanophenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-103)

IR (KBr) cm^{-1}: 3457 (N-H str.), 2863 (C-H str.), 2235 (C≡N), 1826 (COOH), 1436 (CH_2), 722 (C-Cl).

Mass: [m/e (%)], M. Wt.: 518, 484, 463, 426, 415, 397, 379, 351, 324, 310, 289, 258, 224, 184, 175, 142, 130, 122, 107, 95, 63, 44.

C, H, N analysis, Calculated: C, 64.75; H, 3.88; N, 5.39. **Found:** C, 64.72; H, 3.87; N, 5.32.

(5-Carboxymethyl-4-(4-methoxy-phenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-104)

IR (KBr) cm^{-1}: 3453 (N-H str.), 2894 (C-H str.), 1821 (COOH), 1447 (CH_2), 1350 (OCH_3), 715 (C-Cl).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 1.71 (s, 3H, OCH_3), 3.25 (s, 4H, 2 × –CH_2), 4.30 (s, 1H, -CH), 5.57 (s, 1H, -NH), 7.37-8.15 (m, 12H, Ar-H), 9.25 (s, 2H, 2 × -COOH).

C, H, N analysis, Calculated: C, 64.13; H, 4.42; N, 2.67. **Found:** C, 64.10; H, 4.39; N, 2.64.

(5-Carboxymethyl-4-(2,5-dimethoxyphenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-105)

IR (KBr) cm^{-1}: 3478 (N-H str.), 2959 (C-H str.), 1825 (COOH), 1447 (CH_2), 1350, 1369 (OCH_3), 723 (C-Cl).

C, H, N analysis, Calculated: C, 62.82; H, 4.55; N, 2.53. **Found:** C, 62.77; H, 4.54; N, 2.51.

(5-Carboxymethyl-4-(3,4-dimethoxyphenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-106)

IR (KBr) cm^{-1}: 3447 (N-H str.), 2937 (C-H str.), 1822 (COOH), 1426 (CH_2), 1342, 1348 (OCH_3), 743 (C-Cl).

C, H, N analysis, Calculated: C, 62.82; H, 4.55; N, 2.53. **Found:** C, 62.74; H, 4.54; N, 2.50.

(5-Carboxymethyl-4-(3,4,5-tri-methoxyphenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-107)

IR (KBr) cm^{-1}: 3494 (N-H str.), 2892 (C-H str.), 1814 (COOH), 1425 (CH_2), 1326, 1348, 1363 (OCH_3), 726 (C-Cl).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 1.71 (s, 3H, OCH_3), 3.25 (s, 4H, 2 × –CH_2), 4.30 (s, 1H, -CH), 5.57 (s, 1H, -NH), 7.37-8.15 (m, 12H, Ar-H), 9.25 (s, 2H, 2 × -COOH).

C, H, N analysis, Calculated: C, 61.65; H, 4.66; N, 2.40. **Found:** C, 61.62; H, 4.61; N, 2.35.

(5-Carboxymethyl-4-(3,4,5-tri-methoxy-phenyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-108)

IR (KBr) cm^{-1}: 3483(N-H str.), 2869 (C-H str.), 1823 (COOH), 1603, 1585, 1516, 1486 (ring skeleton), 1426 (CH_2), 936 (R-CH=CH-R), 742 (C-Cl).

C,H,N analysis, Calculated: C, 66.93; H, 4.45; N, 2.69. **Found:** C, 66.84; H, 4.42; N, 2.66.

(5-Carboxymethyl-4-(cinnamyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-109)

IR (KBr) cm^{-1}: 3483 (N-H str.), 2892 (C-H str.), 1802 (COOH), 1456 (CH_2), 1346, 1378 (CH_3), 767 (C-Cl).

C, H, N analysis, Calculated: C, 64.81; H, 4.88; N, 5.21. **Found:** C, 64.78; H, 4.83; N, 5.19.

(5-Carboxymethyl-4-(2-pyridinyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-110)

IR (KBr) cm^{-1}: 3456 (N-H str.), 2937 (C-H str.), 1812 (COOH), 1467 (CH_2), 735 (C-Cl).

C, H, N analysis, Calculated: C, 63.04; H, 4.07; N, 5.66. **Found:** C, 63.02; H, 4.01; N, 5.63.

(5-Carboxymethyl-4-(3-indolyl)-(2,6-di-(4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-111)

IR (KBr) cm^{-1}: 3445, 3482 (N-H str.), 2956 (C-H str.), 1814 (COOH), 1576, 1513, 1502, 1458 (ring skeleton), 1436 (CH_2), 742 (C-Cl).

C, H, N analysis, Calculated: C, 65.30; H, 4.16; N, 5.25. **Found:** C, 65.24; H, 4.13; N, 5.22.

(5-Carboxymethyl-4-(1-naphthyl)-(2,6-(di-4-chlorophenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-112)

IR (KBr) cm^{-1}: 3467 (N-H str.), 2972 (C-H str.), 1814 (COOH), 1577, 1523, 1546, 1486 (ring skeleton), 1423 (CH_2), 756 (C-Cl).

C, H, N analysis, Calculated: C, 68.39; H, 4.26; N, 2.57. **Found:** C, 68.33; H, 4.25; N, 2.52.

(5-Carboxymethyl-4-(4-nitrophenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-113)

IR (KBr) cm^{-1}: 3496 (N-H str.), 2924 (C-H str.), 1836 (COOH), 1414 (CH_2 str.), 1335, 1352, 1345 (-CH_3 str.).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 3.29 (s, 6H, 2 × CH_3), 3.65 (s, 4H, 2 × –CH_2), 4.39 (s, 1H, -CH), 5.63 (s, 1H, -NH), 6.82-7.57 (m, 12H, Ar-H), 9.00 (s, 2H, 2 × -COOH).

C, H, N analysis, Calculated: C, 69.87; H, 5.26; N, 5.626. **Found:** C, 69.82; H, 5.24; N, 5.58.

(5-Carboxymethyl-4-(4-hydroxyphenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-114)

IR (KBr) cm^{-1}: 3601 (free OH str.), 3500 (N-H str.), 2935 (C-H str.), 1907 (COOH), 1452 (CH_2 str.), 1332, 1346 (-CH_3 str.).

C, H, N analysis, Calculated: C, 74.18; H, 5.80; N, 2.98. **Found:** C, 74.17; H, 5.77; N, 2.95.

(5-Carboxymethyl-4-(4-cyanophenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-115)

IR (KBr) cm^{-1}: 3467 (N-H str.), 2911 (C-H str.), 2224 (C≡N), 1923, 1934 (COOH), 1413 (CH_2 str.), 1378, 1383 (-CH_3 str.).

Mass: [m/e (%)], M. Wt.: 478, 475, 440, 425, 383, 341, 315, 301, 263, 238, 203, 175, 163, 139, 125, 111, 84, 75, 64, 44.

C, H, N analysis, Calculated: C, 75.30; H, 5.48; N, 5.85. **Found:** C, 75.24; H, 5.44; N, 5.82.

(5-Carboxymethyl-4-(4-methoxyphenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-116)

IR (KBr) cm^{-1}: 3479 (N-H str.), 2923 (C-H str.), 1836 (COOH), 1423 (CH_2 str.), 1378 (OCH_3), 1378 (-CH_3 str.).

C, H, N analysis, Calculated: C, 74.52; H, 6.04; N, 2.90. **Found:** C, 74.50; H, 6.01; N, 2.86.

(5-Carboxymethyl-4-(2,5-dimethoxyphenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-117)

IR (KBr) cm^{-1}: 3489 (N-H str.), 2913 (C-H str.), 1867 (COOH), 1425 (CH_2 str.), 1365 (OCH_3), 1378, 1383 (-CH_3 str.).

C, H, N analysis, Calculated: C, 72.50; H, 6.08; N, 2.73. **Found:** C, 72.48; H, 6.04; N, 2.71.

(5-Carboxymethyl-4-(3,4-dimethoxyphenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydro pyridine-3-yl)-acetic acid (JT-118)

IR (KBr) cm^{-1}: 3497 (N-H str.), 2912 (C-H str.), 1836 (COOH), 1445 (CH_2 str.), 1334, 1352 (-CH_3 str.).

Mass: [m/e (%)], M. Wt. : 515, 403, 351, 293, 217, 207, 184, 174, 159, 145, 131, 115, 103, 91, 77, 65, 44.

C, H, N analysis, Calculated: C, 72.50; H, 6.08; N, 2.73. **Found:** C, 72.48; H, 6.02; N, 2.67.

(5-Carboxymethyl-4-(3,4,5-tri-methoxyphenyl)-(2,6-di-(4-methylphenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-119)

IR (KBr) cm^{-1}: 3487 (N-H str.), 2912 (C-H str.), 1812 (COOH), 1421 (CH_2 str.), 1323 (OCH_3), 1367, 1373 (-CH_3 str.).

C, H, N analysis, Calculated: C, 70.70; H, 6.12; N, 2.58. **Found:** C, 70.68; H, 6.03; N, 2.55.

(5-Carboxymethyl-4-(3,4,5-tri-methoxy phenyl)-(2,6-di-(4- methyl phenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-120)

IR (KBr) cm^{-1}: 3496 (N-H str.), 2863 (C-H str.), 1830 (COOH), 1602, 1586, 1526, 1484 (ring skeleton), 1449 (CH_2 str.), 1359, 1364 (-CH_3 str.).

C, H, N analysis, Calculated: C, 77.64; H, 6.10; N, 2.92. **Found:** C, 77.61; H, 6.07; N, 2.89.

(5-Carboxymethyl-4-(cinnamyl)-(2,6-di-(4-methylphenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-121)

IR (KBr) cm^{-1}: 3497 (N-H str.), 2913 (C-H str.), 1836 (COOH), 1447 (CH_2 str.), 1397, 1399 (-CH_3 str.).

Mass: [m/e (%)], M. Wt.: 496, 481, 466, 451, 322, 256, 224, 197, 180, 165, 152, 137, 120, 105, 93, 78, 64, 52, 44.

C, H, N analysis, Calculated: C, 74.98; H, 6.50; N, 5.64. **Found:** C, 74.94; H, 6.48; N, 5.62.

(5-Carboxymethyl-4-(2-pyridinyl)-(2,6-di-(4-methylphenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-122)

IR (KBr) cm^{-1}: 3435 (N-H str.), 2924 (C-H str.), 1846 (COOH), 1423 (CH_2 str.), 1332, 1342 (-CH_3 str.).

C, H, N analysis, Calculated: C, 73.99; H, 5.77; N, 6.16. **Found:** C, 73.94; H, 5.75; N, 6.12.

(5-Carboxymethyl-4-(3-indolyl)-(2,6-di-(4-methylphenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-123)

IR (KBr) cm^{-1}: 3487, 3546 (N-H str.), 2926 (C-H str.), 1893 (COOH), 1434 (CH_2 str.), 1332, 1342 (-CH_3 str.).

C, H, N analysis, Calculated: C, 75.59; H, 5.73; N, 5.699. **Found:** C, 75.54; H, 5.71; N, 5.66.

(5-Carboxymethyl-4-(1-naphthyl)-(2,6-di-(4-methylphenyl))-1,4-dihydropyridine-3-yl)-acetic acid (JT-124)

IR (KBr) cm^{-1}: 3468 (N-H str.), 2912 (C-H str.), 1848 (COOH), 1623, 1579, 1514, 1476 (ring skeleton), 1423 (CH_2 str.), 1336, 1342 (-CH_3 str.).

C, H, N analysis, Calculated: C, 78.71; H, 5.80; N, 2.78. **Found:** C, 78.68; H, 5.78; N, 2.73.

(5-Carboxymethyl-2,6-diphenyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-125)

IR (KBr) cm^{-1}: 3473 (N-H str.), 2868 (C-H str.), 1823 (COOH), 1616, 1578, 1524, 1496 (ring skeleton), 1428 (CH_2 str.).

C, H, N analysis, Calculated: C, 68.93; H, 4.71; N, 5.95. **Found:** C, 68.91; H, 4.67; N, 5.93.

(5-Carboxymethyl-2,6-diphenyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-126)

IR (KBr) cm^{-1}: 3483 (N-H str.), 2857 (C-H str.), 1827 (COOH), 1623, 1594, 1559, 1469 (ring skeleton), 1456 (CH_2 str.).

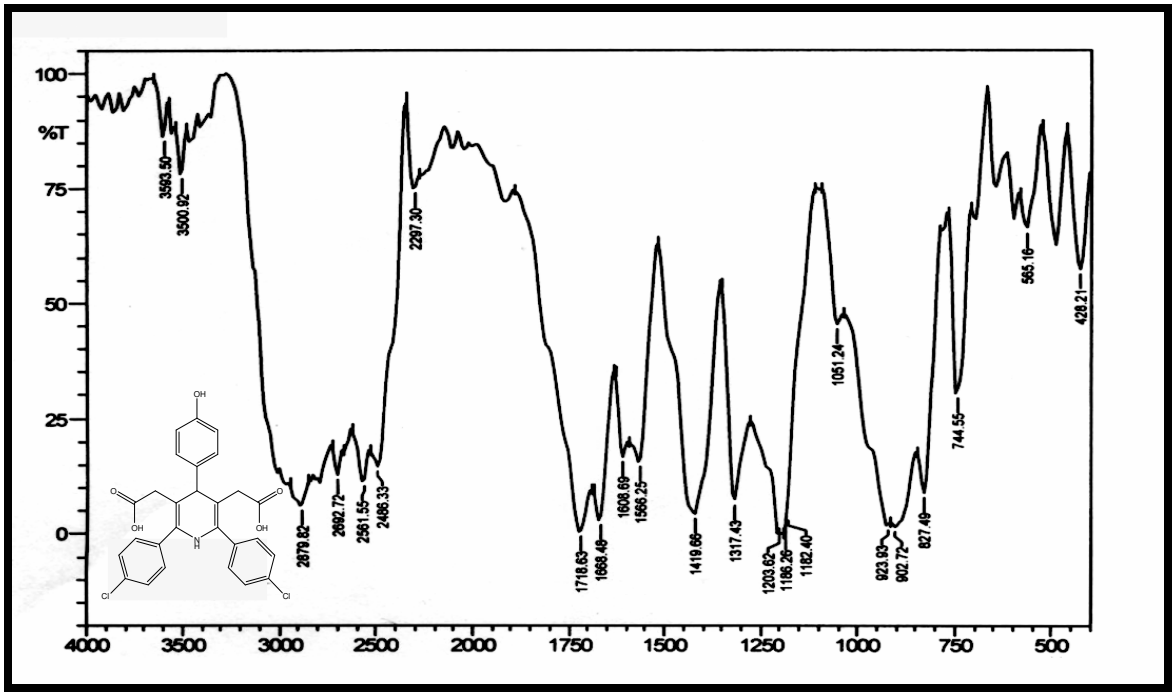
C, H, N analysis, Calculated: C, 73.83; H, 5.53; N, 3.08. **Found:** C, 73.81; H, 5.48; N, 3.04.

4.10. Conclusion

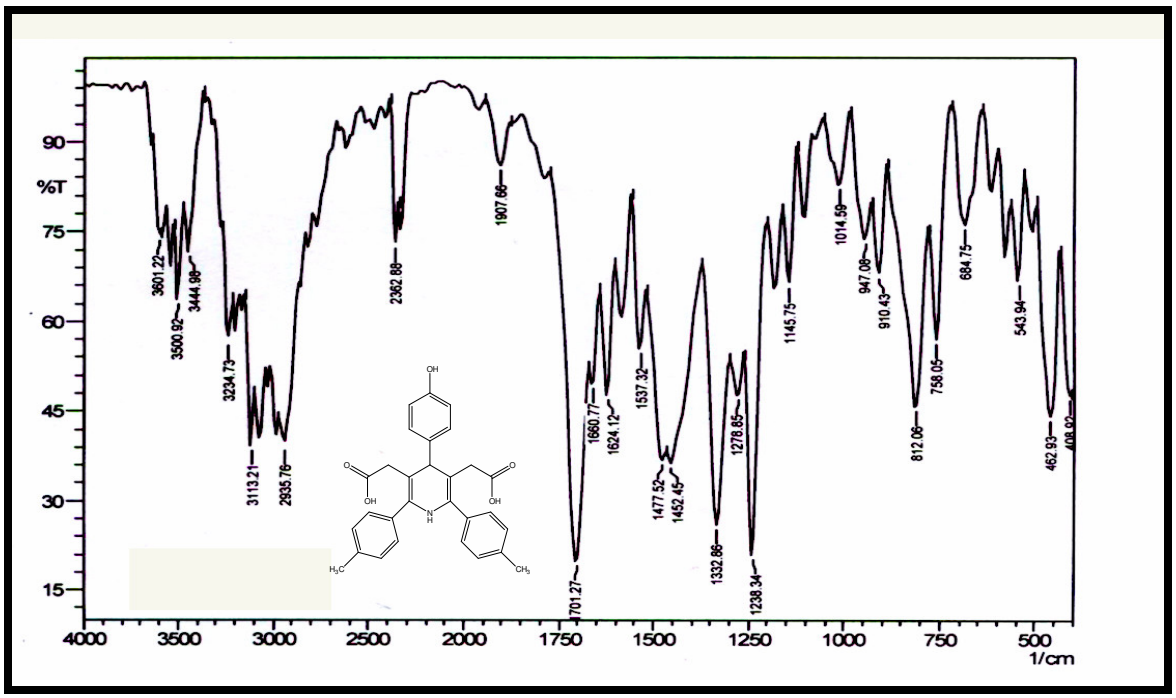
Total 26 (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids were synthesized in this chapter. The compounds are characterized by IR, NMR, Mass spectral data and elemental analysis. All spectral data are in well agreement with the assigned structures. All the newly synthesized compounds have been sent for anti-tubercular activity and the results are awaited.

4.11. Spectra of some (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids

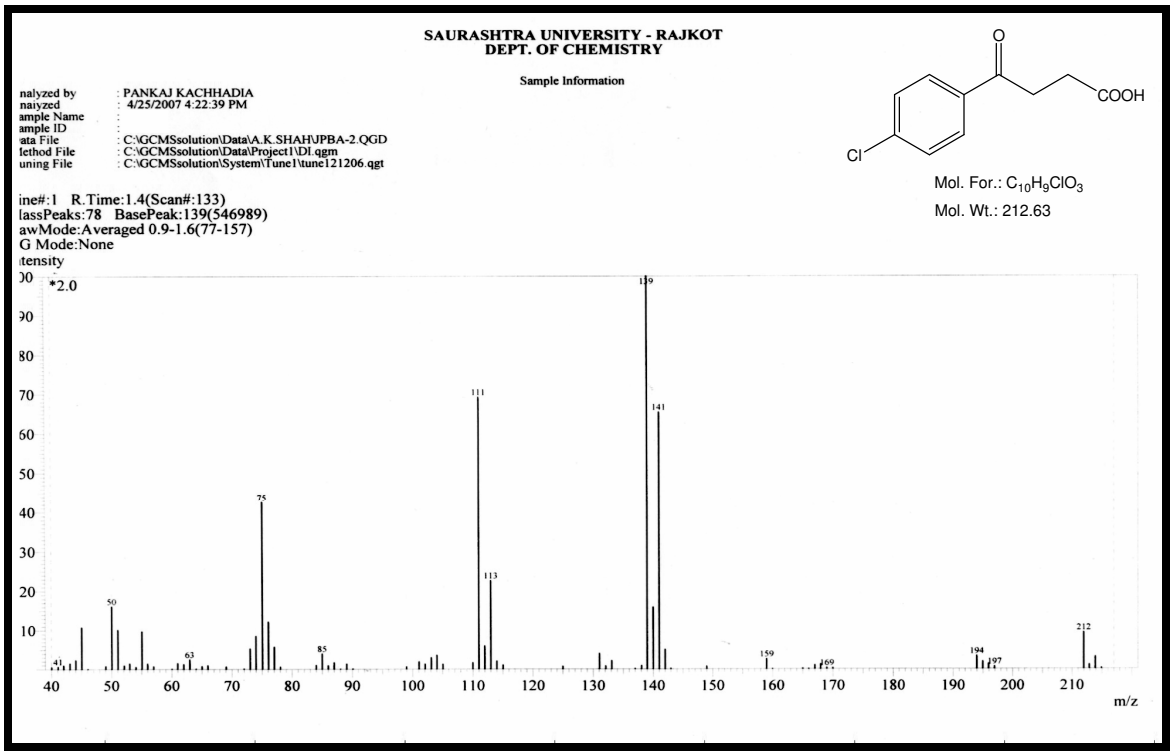
Infra Red spectrum of (5-carboxymethyl-4-(4-hydroxy phenyl)-(2, 6-di-4-chloro phenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-102)



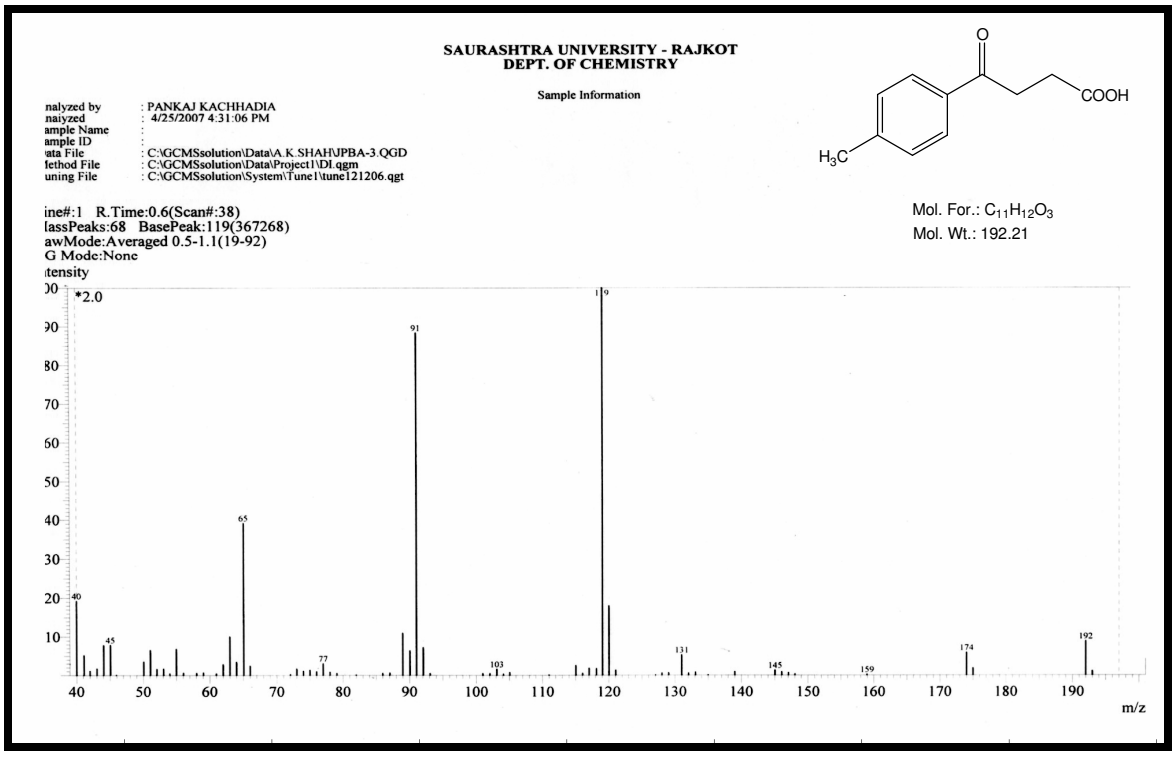
Infra Red Spectrum of (5-Carboxymethyl-4-(4-hydroxy phenyl)-(2, 6-di-4-methyl phenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-114)



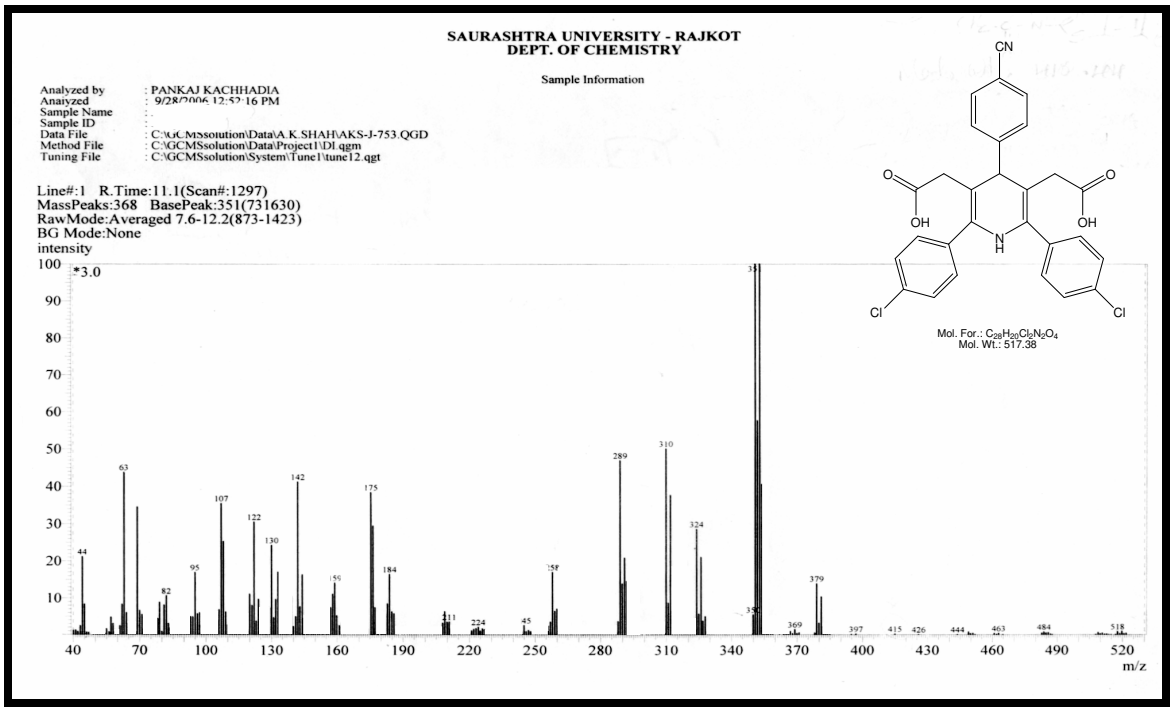
Mass spectrum of 4-(4-chlorophenyl)-4-oxobutanoic acid



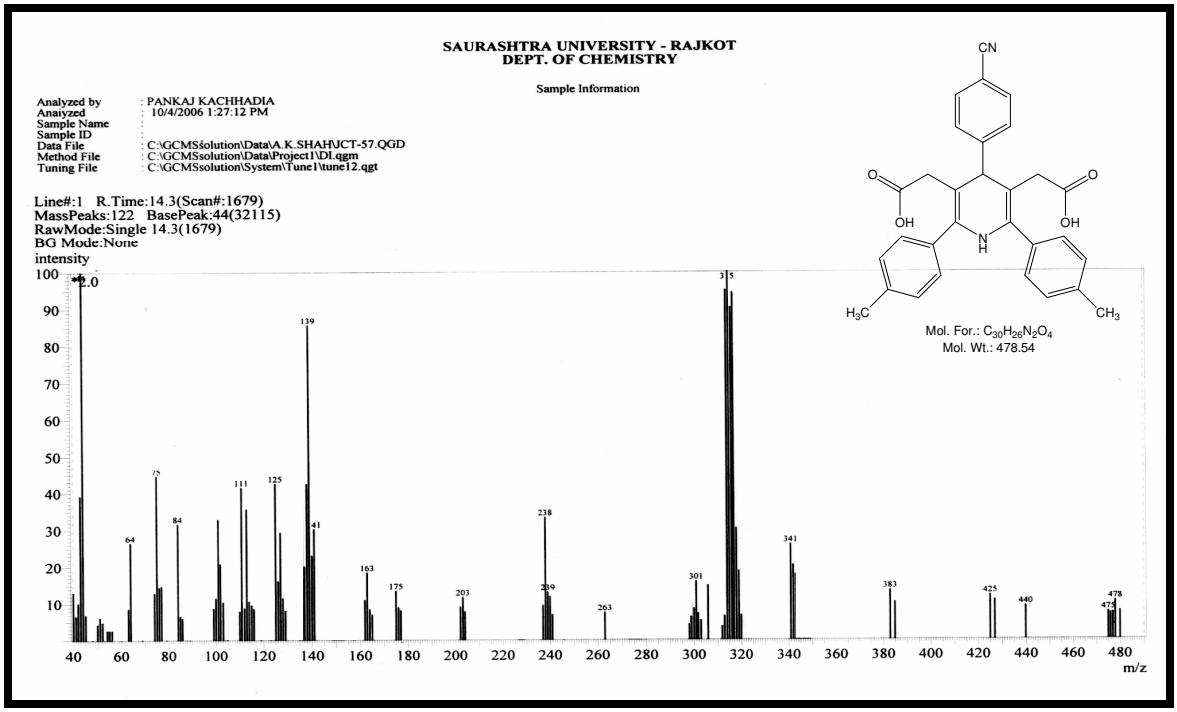
Mass spectrum of 4-oxo-4-p-tolylbutanoic acid



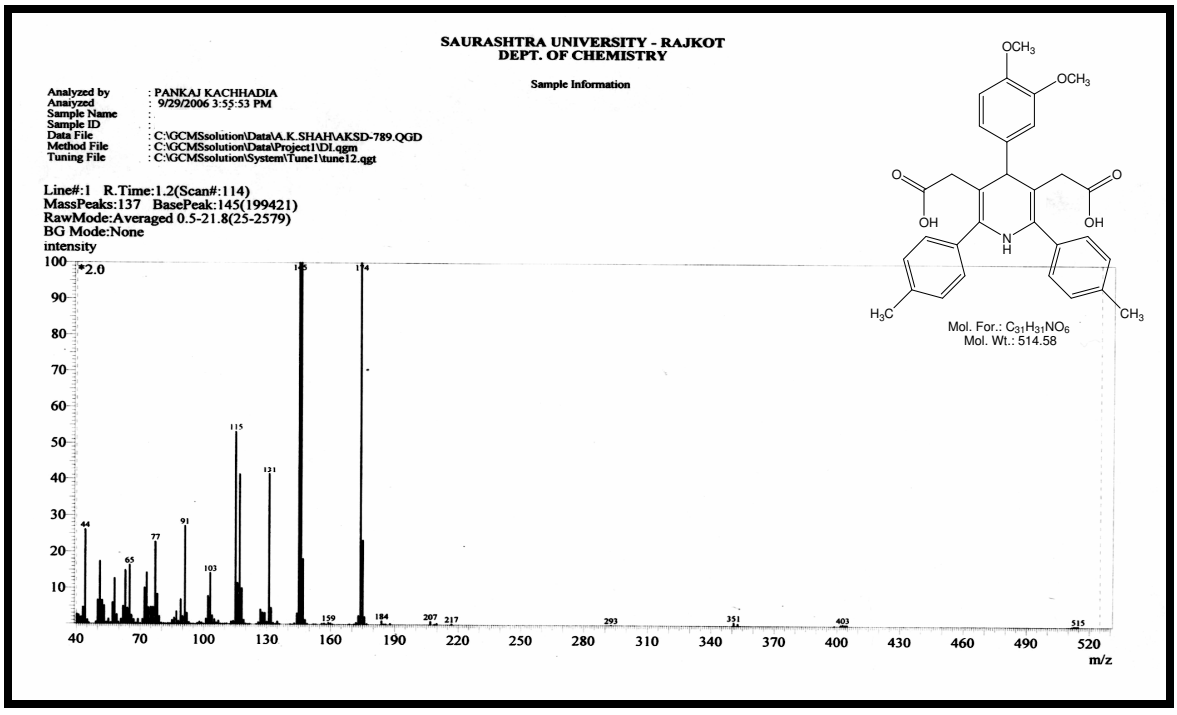
Mass spectrum of (5-carboxymethyl-4-(4-cyanophenyl)-(2,6-di-4-chlorophenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-103)



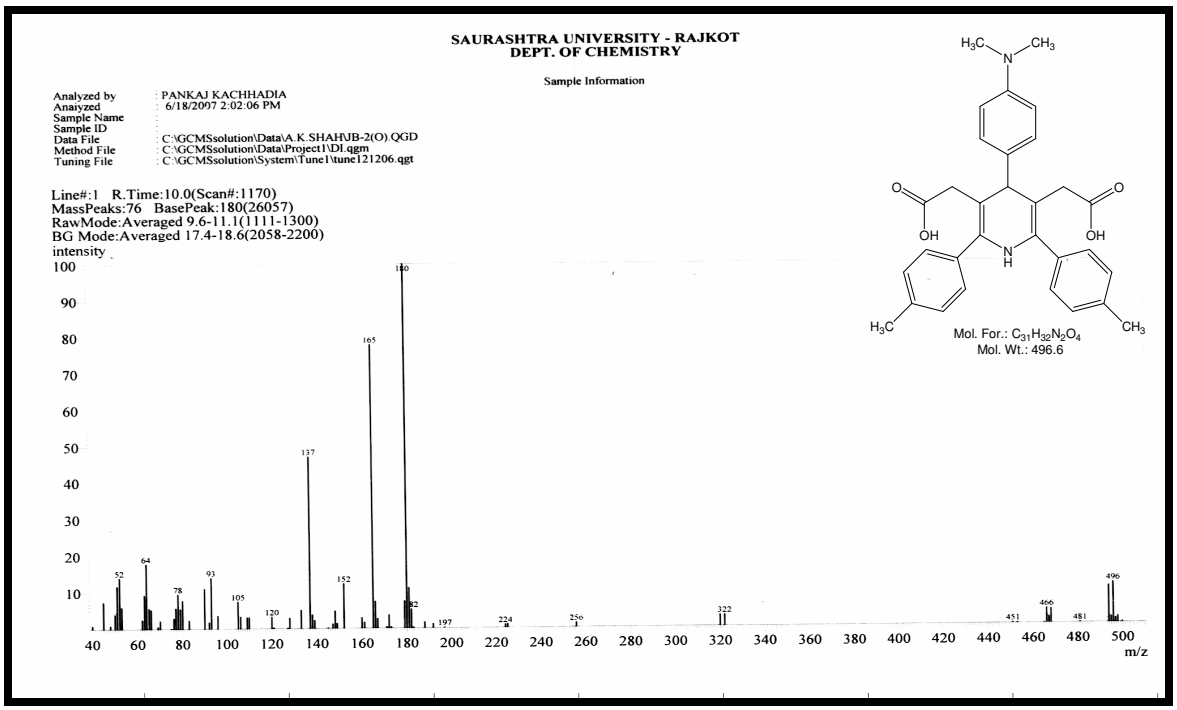
Mass spectrum of (5-carboxymethyl-4-(4-cyano phenyl)-(2,6-di-4-methylphenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-115)



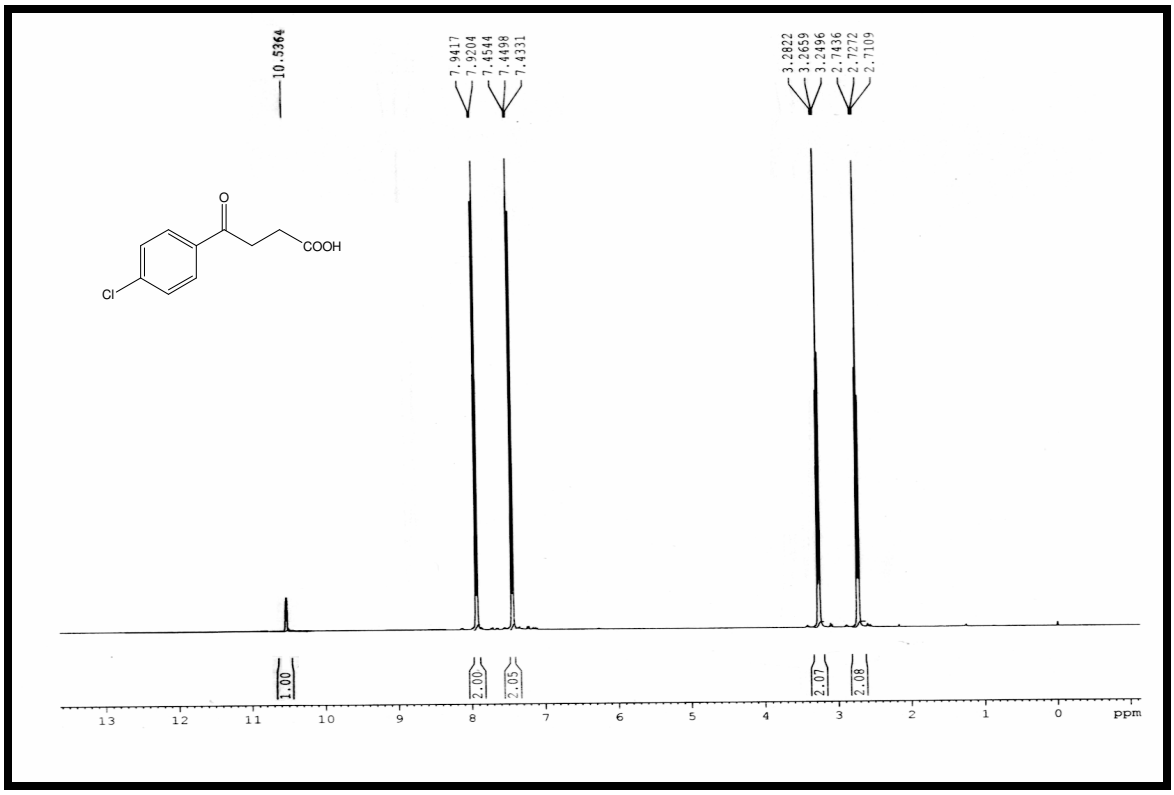
Mass spectrum of (5-carboxymethyl-4-(3,4-dimethoxyphenyl)-(2,6-di-4-methyl phenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-118)

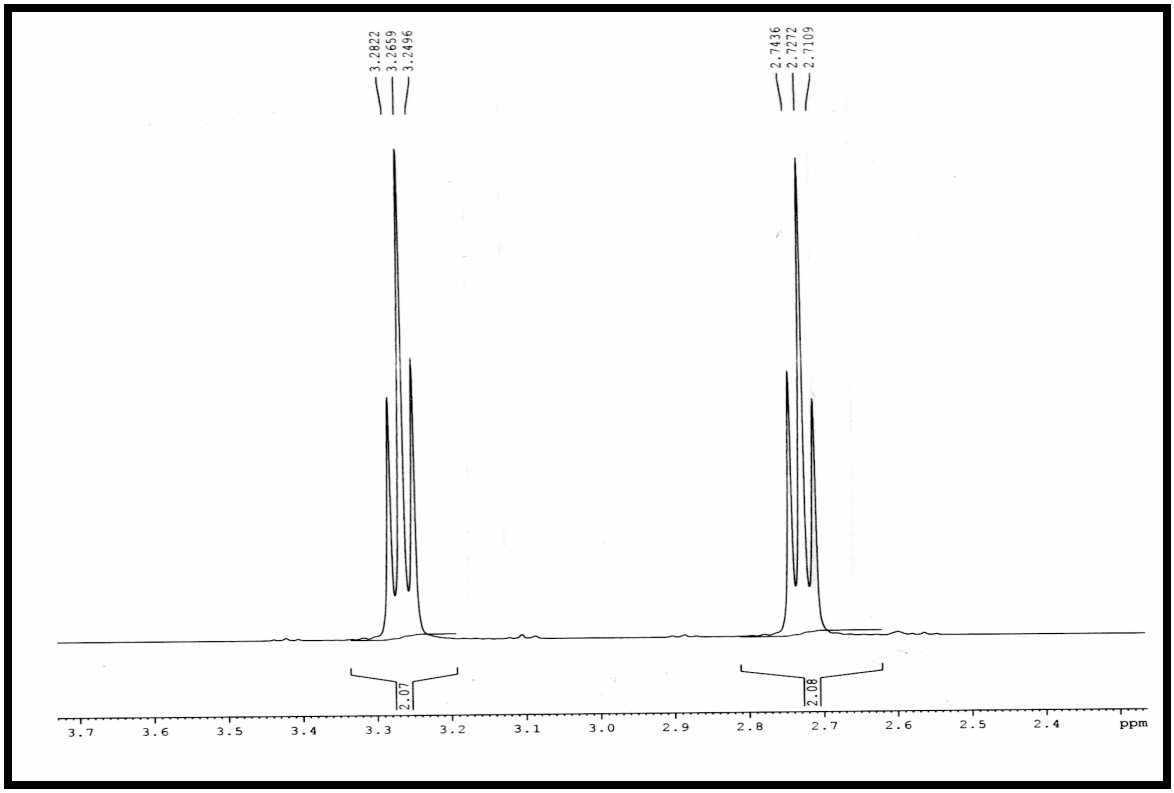


Mass spectrum of (5-carboxymethyl-4-(cinnamyl)-(2, 6-di-4-methylphenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-121)

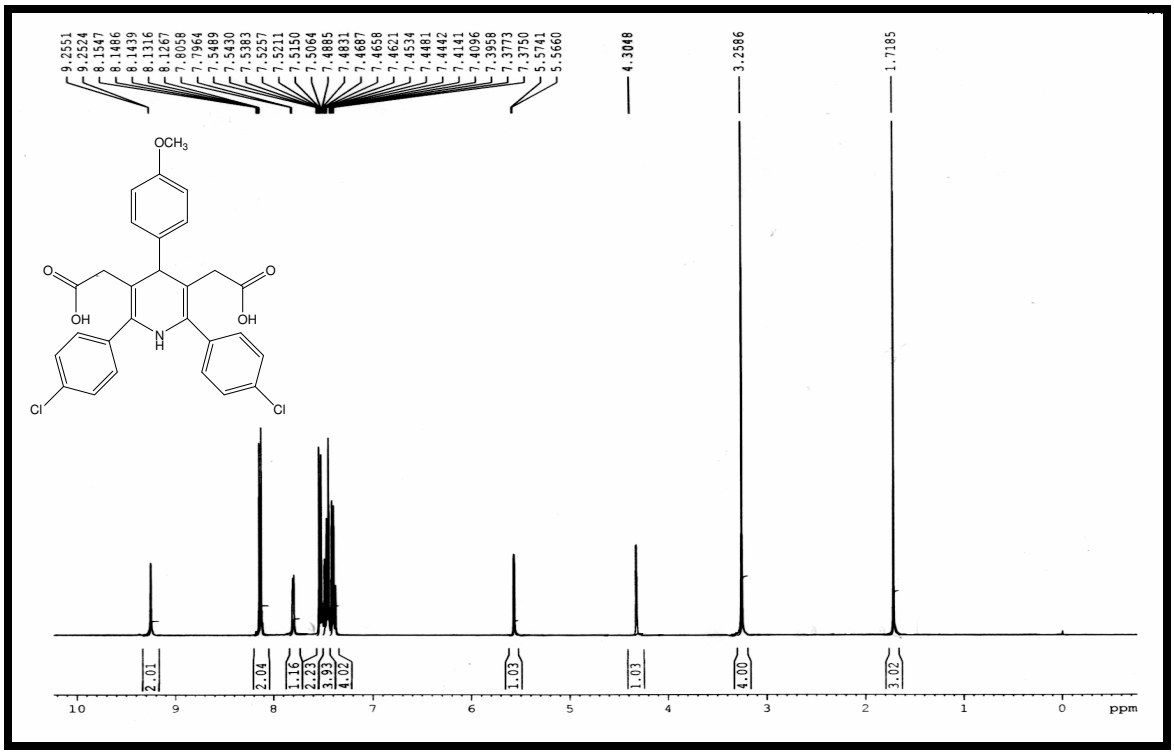


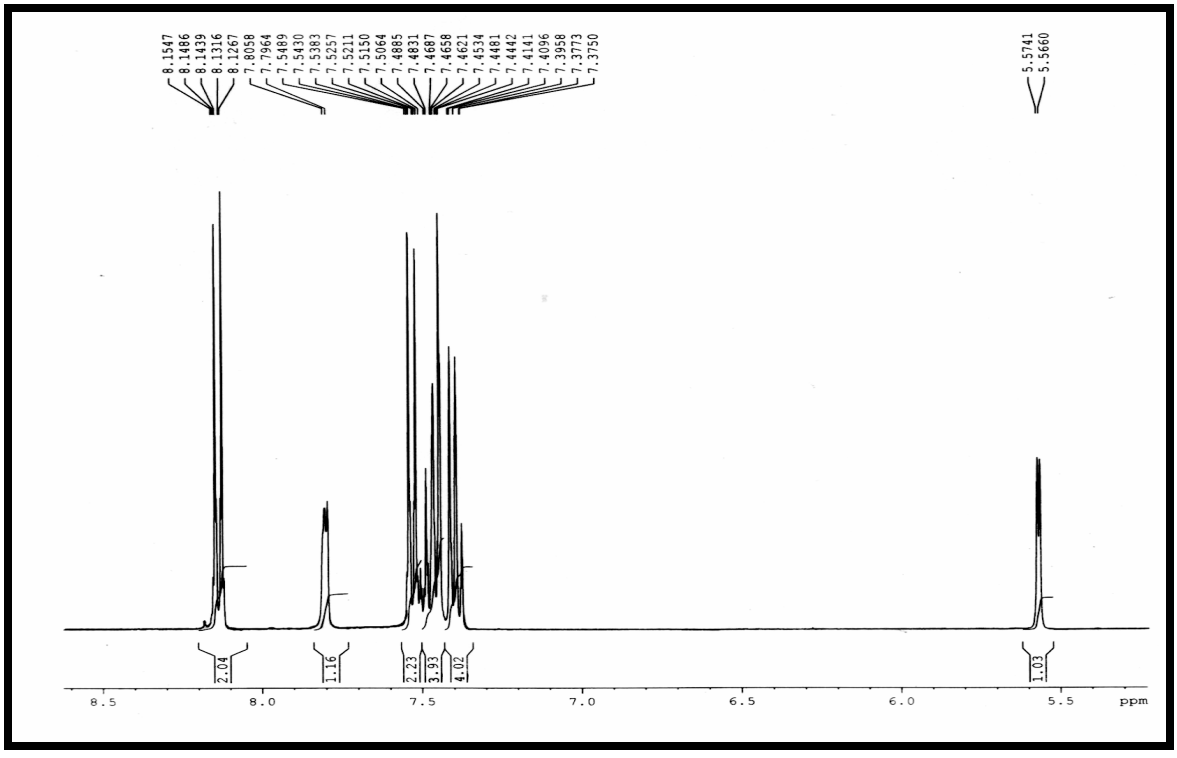
^{1}H NMR of 4-(4-chlorophenyl)-4-oxobutanoic acid



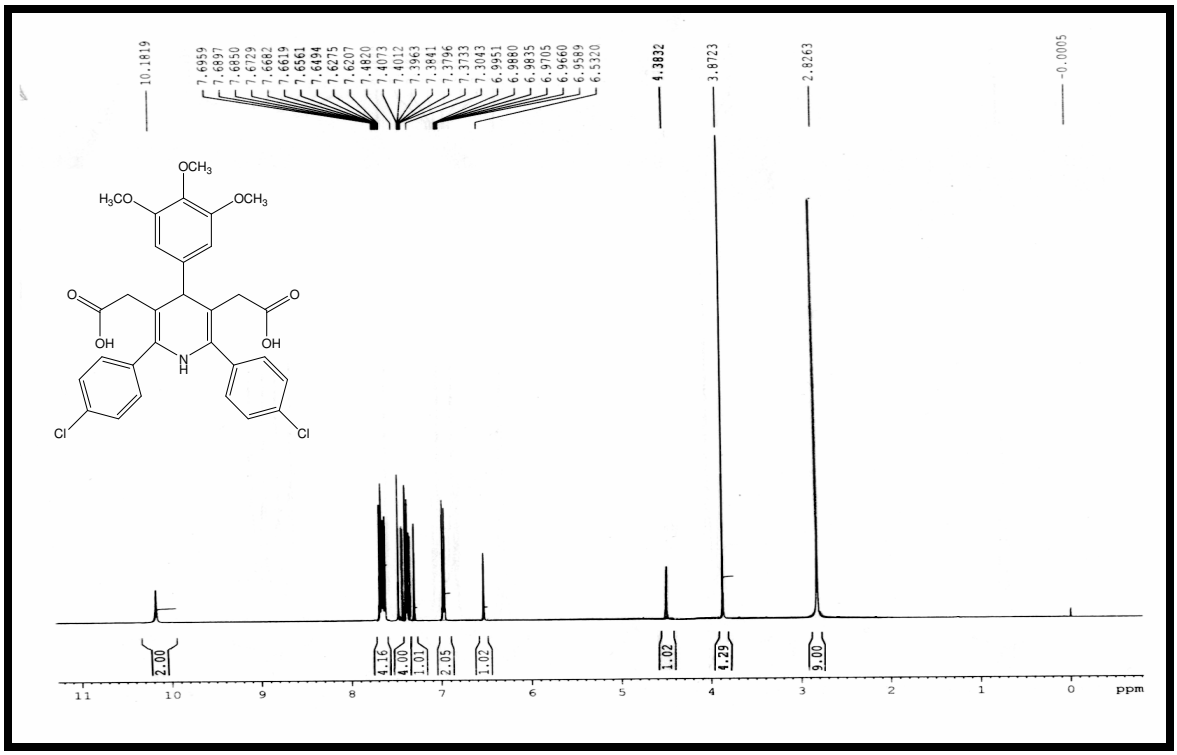


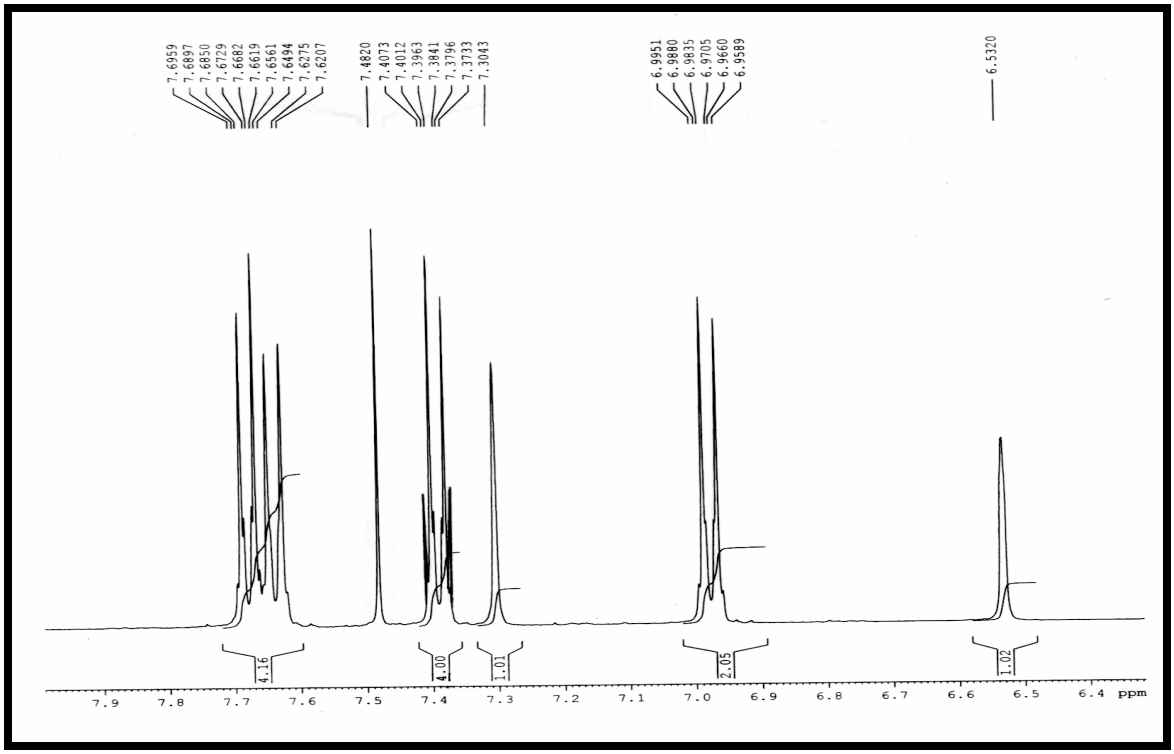
^{1}H NMR spectrum of (5-carboxymethyl-4-(4-methoxyphenyl)-(2,6-di-4-chlorophenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-104)



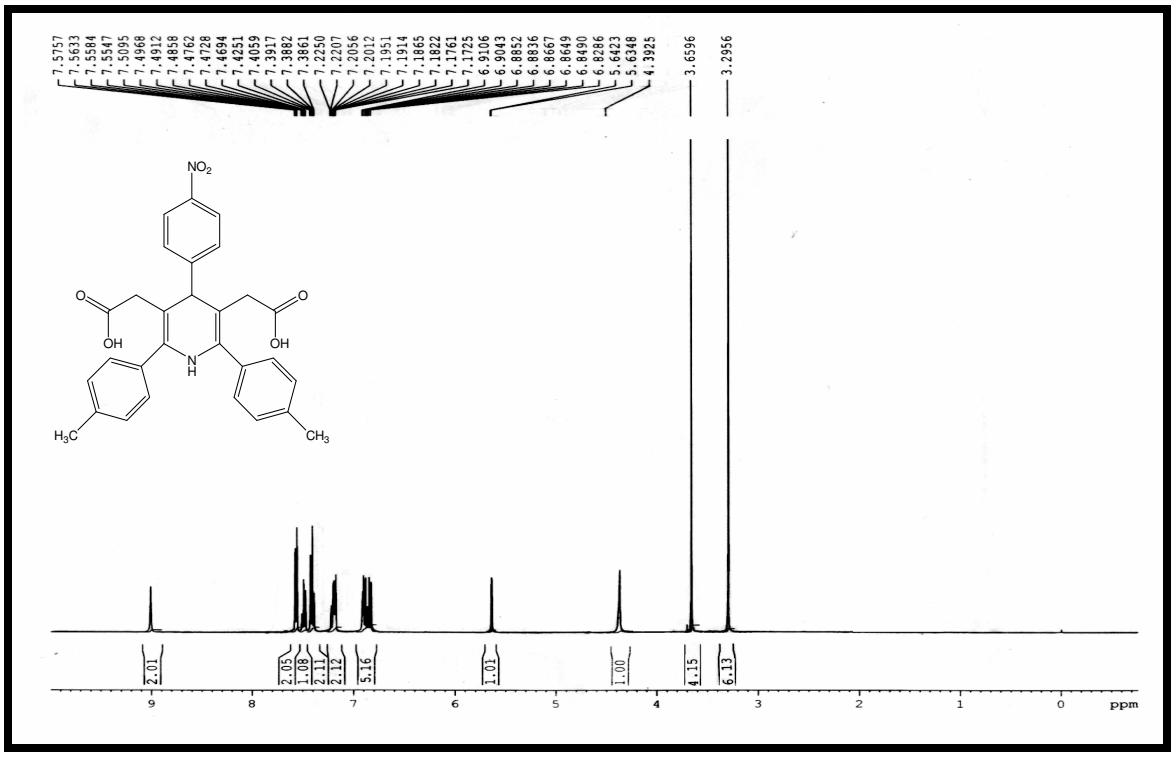


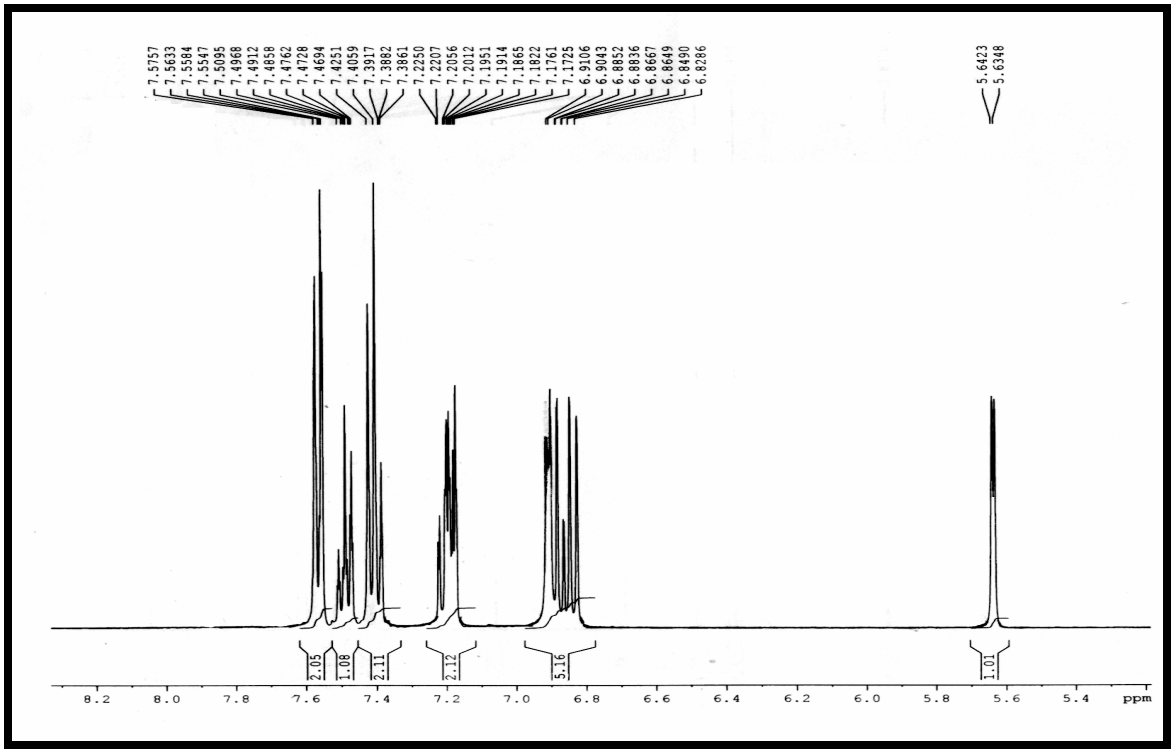
^{1}H NMR spectrum of (5-carboxymethyl-4-(3, 4, 5-tri-methoxy phenyl)-(2,6-di-4-chlorophenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-107)





^{1}H NMR spectrum of (5-carboxymethyl-4-(4-nitrophenyl)-(2,6-di-4-methyl phenyl)-1,4-dihydropyridine-3-yl)-acetic acid (JT-113)





4.12. References

1. Lavilla, R. Recent developments in the chemistry of dihydropyridines. *J. Chem. Soc. Perkin Trans*. 1, **2002**, 1141–1156.
2. Kuthan, J.; Kurfurst, A. Development In Dihydropyridine Chemistry, *I &. Eng. Chem. Prod Res. Dev.* **1882,** 21, 191-261.
3. Redmore, D. *U.S. Patent 3998833*, **1976**; *Chem. Abstr.* **1977**, 87, 84823.
4. Cope, R. P., Jr. *U.S. Patent 3755097*, **1973**; *Chem. Abstr.* **1973,** 79, 142347.
5. Abele, W.; Orosse, M.; Pllz, 0. *Ger. Offen. 2758210,* **1979.** *Chem. Abstr.* **1980**, 2, 155, 899.
6. Ranz, E.; Bossert, F.; Schuetz, H. 0.; Von Rintelen, H.; Deizenne, G. A.; De Jaeger, A. A. *Ger. Offen. 2246106*, **1974**; *Chem. Abstr.* **1974,** 81, 56670.
7. Stout, D. M. *Diss. Abstr. Int*. 6, **1975,** 36, 247; *Chem. Abstr.* **1975.** 83, 163957.
8. Tlrzitis, G. D.; Duburs, G. Ya. *Khlm. Geterofsikl. Soedln.* **1972**, 133; *Chem. Abstr.* **1972**, 77, 33760.
9. Tirzitls, O. D.; Duburs, G. *Chem. Abstr.* **1977**, 87, 5767.
10. Tirzkis, O. D.; Krustina. B.; Duburs, O. Ye. *Lafv. fSR Zinaf. Akad. Vestls, Kim. Ser.* **1978**, 603; *Chem. Abstr.* **1979**, 90, 2007.
11. Veinberga,.; Velena, A.; Andersons, P.; Duburs, G. Ya. *Flshche. I. Vsas. Zhiv. Riga*, **1979**, 165; *Chem. Abstr.* **1980,** 92, 213926.
12. Velena. A.; Qrlnberga, S.; Vlkane, V.; Duburs, G. Ya. *Mafer. Blokhim. Konf. frlball. Resp*. 6 SSR, 5fh **1976**, 42; *Chem. Abstr.* **1978**, 89, 38624.
13. Velena, A.; Rubene, D. Slnt. Issfed. Biol. Soedin., *Tezisy fokl. Konf. Molodvkh Uch.* 6th **1978**, 71; *Chem. Abstr*. **1980**. 92, 106398.
14. Spruzs, Ya. Ya.; Lutinskli, S. Ya.; Duburs, G. Ya.; Uldrikis, Ya. R. *U.S.S.R. Patent 594980*, **1978**, *Chem. Abstr.* **1978**, 88, 158502.
15. Dvinskaya, L. M.; Manukhin, B. D.; Reshetova, L. V.; Naslrdinov, U. *TI. Vses. Nauchno-Issled. Inst. Fizish ., Biokhim . Pitan ., S-KZhivotn.* **1977,** 77, 68; *Chem. Abstr.* **1978**, 89, 12847.
16. Stroza, I.; Vevere, L. Pishchevarenie I. Vsasyvanie U. *Zhivotnych* **1979,** 226; *Chem. Abstr.* **1980**, 93, 6508.
17. Spruzs, Ya. Ya. Bioi. Uki. Dobovki Korml. S. *Zh. Zivotn. Ptitsy.* **1978**, 48; *Chem. Abstr.* 1979, 90, 120059.
18. Valdmanis, A. R.; Duburs, G. Ya.; Spruzs, Ya. Ya. *Lafv. fSR Zinaf. Akad. Vesfls* **1977**, 43; *Chem. Abstr*. **1978**, 88, 5211.

19. Zakharchenko, S. A. *Latv. Lanksaimn. Akad. Raksti* **1978**, 155, 44 *Chem. Abstr.* **1879**, 90, 5004.

20. Hlllers, S. A.; Millers, A. T.; Sharkovskii, P. A.; Duburs, G. Ya.; Magone, Yu. O.; Tlrzitis, G. D.; Uldrikis, Ya. R. *U.S.S.R. Patent 515423*, **1978**; *Chem. Abstr.* **1978**, 88, 186171.

21. Atsuml. T.; Kobayashl, K.; Takebayashi, Y.; Yamamoto, H. *Ger. Offen.* **1966,** 179; *Chem. Abstr.* **1972**, 76, 99532.

22. Atsumi, T.; Kobayashi. K.; Takebayashi, Y.; Yamamoto. H. *Ger. Offen. 2128525*, **1972**; *Chem. Abstr.* **1972**, 76, 99532.

23. Atsumi, T.; Kobayashl, K.; Takebayashi, Y.; Yamamoto, H. J*apanese Kokal 7319315,* **1973**; *Chem. Abstr*. **1973.** 79, 92035.

24. Fukumaru, T.; Kobayashi, K.; Mizote, H.; Inaba, S.; Yamamoto. H. *Japan. Kokai 7541 869,* **1975**; *Chem. Abstr.* **1975**, 83, 206127.

25. Kikazawa, K.; Tsuchiki, M.; Hayasaka, T.; Azuma. N.; Wakisaka, K. *Japan Patent 7300718*, **1973**; *Chem. Abstr*. **1973**, 78, 124467.

26. Granados, R.; Alvarez, M.; Bosch, J.; Martinez, C.; Rabadan, F. *Ger. Offen. 2750197*, **1978**; *Chem. Abstr*. **1978**, 89, 54679.

27. Granados, R.; Akarez, M.; Bosch, J.; Martinez, C.; Rabadan, F. *Ger. Offen. 2805443*, **1978**; *Chem. Abstr.* **1979**, 90. 54928.

28. Archer, S. *U.S. Patent 4 105659*, **1978**; *Chem. Abstr.* **1979,** 90, 54847.

29. Mlchne, W. F. *U.S. Patent 4 100164*, **1978**; *Chem. Abstr*. **1979**, 90, 137700.

30. Ochlal, M.; Akl, 0.; Morlmoto, A.; Okada, T. *Japan. Kokal 7431894*, **1974**; *Chem. Abstr.* **1074**, 81, 77943.

31. Stables, H. C.; Atherton, J.; Michan, M. J. *Ger. Offen. 2142424*, **1972**; *Chem. Abstr.* **1972**, 77, 60056.

32. Kutney, J. P. *Heterocycles*, **1977**, 7, 593.

33. Leete, E. Biomimetic synthesis of nicotine. *J. Chem. Soc., Chem. Commun*. **1972**, 1091a.

34. Par. M. A.; Pereyra, 6; Gallop, P. M.; Slefter, S. J. *Mechanochem. Cell. Motil*. **1074**, 2, 231.

35. Levesque, J.; Pousset, J. L.; Cave, A. *Acad. Sci., Ser. C* **1974**, 278, 959.

36. Janis, R. A.; Triggle, D. J. New developments in calcium ion channel antagonists. *J. Med. Chem.* **1983**, 26, 775.

37. Bocker, R. H.; Guengerich, E. P. Oxidation of 4-aryl- and 4-alkyl-substituted 2,6-dimethyl-3,5-bis(alkoxycarbonyl)-1,4-dihydropyridines by human liver microsomes and

immunochemical evidence for the involvement of a form of cytochrome P-450. *J. Med. Chem.* **1986**, 29, 1596.

38. Gordeev, M. F.; Patel, D. V.; Gordon, E. M. Approaches to Combinatorial Synthesis of Heterocycles: A Solid-Phase Synthesis of 1,4-Dihydropyridines . *J. Org. Chem*. **1996**, 61, 924.
39. Sunkel, C. E.; Fau de Casa-Juana, M. F.; Santos, L.; Garcia, A. G.; Artalijero, C. R.; Villarroya, M.; Gonzalez-Morales, M. A.; Lopez, M. G.; Cillero, J.; Alonso, S.; Priego, J. G. Synthesis of 3-[(2,3-dihydro-1,1,3-trioxo-1,2-benzisothiazol-2-yl)alkyl] 1,4-dihydropyridine-3,5-dicarboxylate derivatives as calcium channel modulators. *J. Med. Chem.* **1992**, 35, 2407.
40. Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, N.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. *Eur. J. Med. Chem*. **1995**, 38, 2851.
41. Klusa, V. Cerebrocrast. Neuroprotectant, cognition enhancer. *Drugs Fut.* **1995**, 20, 135.
42. Godfraind, T.; Miller, R.; Wibo, M. Calcium antagonism and calcium entry blockade**.** *Pharmacol. Rev.* **1986**, 38, 321.
43. Sausins, A.; Duburs, G. *Heterocycles* **1988**, 27, 269.
44. Gaudio, A. C.; Korolkovas, A.; Takahata, Y. *J. Pharm. Sci.* **1994**, 83, 1110.
45. Cooper, K.; Fray, M. J.; Parry, M. J.; Richardson, K.; Steele, J. 1,4-Dihydropyridines as antagonists of platelet activating factor. 1. Synthesis and structure-activity relationships of 2-(4-heterocyclyl)phenyl derivatives. *J. Med. Chem*. **1992**, 35, 3115.
46. Yadav, J. S.; Reddy, V. S.; Reddy, P. T. Unprecedented Synthesis of Hantzsch 1,4-Dihydropyridines Under Biginelli Reaction Conditions. *Synth. Commun.* **2001**, 31, 425.
47. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882,** 215, 1.
48. Chennat, T.; Eisner, V. J. Reduction of 3,5-disubstituted pyridines to dihydropyridines. *Chem. SOC., Perkin Trans. 1* **1975**, 926.
49. Jerome, N.; Rerson, M.; E. Brown, Studies on Dihydropyridines. I. The Preparation of Unsymmetrical 4-Aryl-l,4-dihydropyridines by the Hantzsch-Beyer Synthesis 1, *J. Am. Chem. Soc.* **1955**, 77, 444-447.
50. Iiantzsch, A. *Ber.,* **1884,** 17, 1515.
51. Beyer, C. *ibid,* **1891,** 24, 1002.
52. Knoevenagel, E.; Ruschhauyt, W. *ibid.* 1898, 81, 1025.
53. Kim, S-C.; Choi, K-M.; Cheong, C-S. Synthesis of Amlodipine Using Aza Diels-Alder Reaction, *Bull. Korean Chem. Soc*. **2002**, 23, 143-144.
54. Emmett, J. C., Ed.; Pergamon, *Press: London,* **1985**; 3, 1047-1099.

55. Hu, P. S.; Lindgren, E.; Jacobson, K. A.; Fredholm, B. B. Interaction of dihydropyridine calcium channel agonists and antagonists with adenosine receptors. *Pharmacol. Toxicol*. **1987**, 61, 121-125.

56. Van Rhee, A. M.; Jiang, J-I.; Melman, N.; Olah, M. E.; Stiles, G. L.; Jacobson, K. A. Interaction of 1,4-dihydropyridine and pyridine derivatives with adenosine receptors: selectivity for A3 receptors. *J. Med. Chem.* **1996**, 39, 2980-2989.

57. Sorkin, E. M.; Clissold, S. P. Nicardipine: A review of its pharmacological and pharmacokinetic properties and therapeutic efficacy, in the treatment of angina pectoris, hypertension, and related cardiovascular disorders. *Drugs* **1987**, 33, 296-345.

58. Loev, B.; Goodman, M.; Snader, K.; Tedeschi, R.; Macko, E. "Hantzsch-type" dihydropyridine hypotensive agents. *J. Med. Chem.* **1974**, *17*, 956-965.

59. Bossert, F.; Meyer, H.; Wehinger, E. 4-Aryldihydropyridines, a new class of highly active calcium antagonists. *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 762-769.

60. Katzung, B.G. In *Basic & Clinical Pharmacology* **1998,** Appleton & Lange, Stamford, CT (USA).

61. Ji-long Jiang, A. Michiel van Rhee, Neli Melman, Xiao-duo Ji, and Kenneth A. Jacobson, 6-Phenyl-1,4-dihydropyridine Derivatives as Potent and Selective A3 Adenosine Receptor Antagonists. *J. Med. Chem.* **1996,** 39*,* 4667-4675.

62. Oike, M.; Inoue, Y.; Kitamura, K.; Kuriyama, H. Dual action of FRC8653, a novel dihydropyridine derivative, on the Ba^{2+} current recorded from the rabbit basilar artery. *Circ. Res*. **1990**, 67, 993.

63. Takahara, A.; Fujita, S.; Moki, K.; Ono, Y.; Koganei, H.; Iwayama, S.; Yamamoto, H. Neuronal Ca^{2+} Channel Blocking Action of an Antihypertensive Drug, Cilnidipine, in IMR-32 Human Neuroblastoma Cells. *Hypertens. Res.* **2003**, 26, 743.

64. (a) Uneyama, H.; Uchida, H.; Konda, T.; Yoshimoto, R. Cilnidipine: Preclinical Profile and Clinical Evaluation. *Cardiovasc. Drug Rev*. **1999**, 17, 341; (b) Rose, G. W.; Kanno, Y.; Ikebukuro, H.; Kaneko, M.; Kaneko, K.; Kanno, T.; Ishida, Y.; Suzuki, H. Cilnidipine Is As Effective As Benazepril for Control of Blood Pressure and Proteinuria in Hypertensive Patients with Benign Nephrosclerosis. *Hypertens. Res.* **2001**, 24, 377.

65. (a) Tomiyama, H.; Kimura, Y.; Kuwabara, Y.; Maruyama, C.; Yoshida, Y.; Kuwata, S.; Kinouchi, T.; Yoshida, H.; Doba, N. Cilnidipine More Highly Attenuates Cold Pressor Stress-Induced Platelet Activation in Hypertension than Does Amlodipine. *Hypertens. Res.* **2001**, 24, 679; (b) Takeda, S.; Ueshiba, H.; Hattori, Y.; Irie, M. Cilnidipine, the N- and L-type calcium channel antagonist, reduced on 24-h urinary catecholamines and C-

peptide in hypertensive non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.* **1999**, 44, 197; (c) Sakata, K.; Shirotani, M.; Yoshida, H.; Nawada, R.; Obayashi, K.; Togi, K.; Miho, M. Effects of Amlodipine and Cilnidipine on Cardiac Sympathetic Nervous System and Neurohormonal Status in Essential Hypertension. *Hypertension,* **1999**, 33, 1447.

66. (a) Takahara, A.; Konda, T.; Enomoto, A.; Kondo, N. *Biol. Pharm. Bull.* **2004**, 27, 1388. (b) Konda, T.; Takeda, T.; Takahara, A.; Uneyama, H. J. *Hypertens.* **2003**, 21, 82.

67. Yamamoto, T.; Niwa, S.; Ohno, S.; Onishi, T.; Matsueda, H.; Koganei, H.; Uneyama, H.; Fujita, S-I.; Takeda, T.; Kito, M.; Ono, Y.; Saitou, Y.; Takahara, A.; Iwata, S.; Shoji, M.; Structure–activity relationship study of 1,4-dihydropyridine derivatives blocking N-type calcium channels *Bioorg. Med. Chem. Lett.* **2006**, 16, 798–802.

68. Natale, N. R.; Rogers, M. E.; Staples, R.; Triggle, D. J.; Rutledge, A. Lipophilic 4-Isoxazolyl-1,4-dihydropyridines: Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **1999,** 42, 3087-3093.

69. Si, H- Z.; Wang, T.; Zhang, K. J.; Hua, Z. D.; Fane, B. T. QSAR study of 1,4-dihydropyridine calcium channel antagonists based on gene expression programming, *Bioorg. Med. Chem.* **2006**, 14, 4834–4841.

70. Budriesi, R.; Bisi, A.; Ioan, P.; Rampa, A.; Gobbi, S.; Belluti, F.; Piazzi, L.; Valenti, P.; Chiarini, A. 1,4-Dihydropyridine derivatives as calcium channel modulators: the role of 3-methoxy-flavone moiety, *Bioorg. Med. Chem.,* **2005**, 13, 3423–3430.

71. Triggle, D. J.; Langs, D. A.; Janis, R. A. Ca^{2+} Channel Ligands: Structure-Function-Relationships of the 1,4-Dihydropyridines. *Med. Res. Rev.* **1989**, 9*,* 123-180.

72. (a) Striessnig, J.; Murphy, B. J.; Catterall, W. A. Dihydropyridine Receptor of L-Type Calcium Channels: Identification of Binding Domains for 3H-PN-200-110 and 3H-azidopine Within the Alpha 1 Subunit. *Proc. Natl. Acad. Sci. U.S.A*. **1991**, 88, 10769-10773. (b) Nakayama, H.; Taki, M.; Striessnig, J.; Glossmann, H.; Catterall, W. A.; Kanaoke, Y. Identification of 1,4-Dihydropyridine Binding Regions Within the Alpha 1 Subunit of Skeletal Muscle Ca^{2+} Channels by Photoaffinity Labeling with Diazepine. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, 88, 9203-9207. (c) Bangalore, R.; Baindur, N.; Rutledge, A.; Triggle, D. J.; Kass, R. S. L-Type Calcium Channels: Asymmetrical Intramembrane Binding Domain Revealed byVariable Length, Permanently Charged 1,4-Dihydropyridines. *Mol. Pharmacol*. **1994**, 46, 660-666. (d) Tang, S.; Yatani, A.; Bahinski, A.; Mori, Y.; Schwartz, A. Molecular Localization of Regions in the L-Type Calcium Channel Critical for Dihydropyridine Action. *Neuron* **1993**, 11, 1013-1021.

73. (a) Mirzaei, Y. R.; Simpson, B. M.; Triggle, D. J.; Natale, N. R. Diastereoselectivity in the Metalation and Electrophilic Quenching of Isoxazolyloxazolines. *J. Org. Chem*. **1992**, 57, 6271-6279. (b) Natale, N. R.; Triggle, D. J.; Palmer, R. B.; Lefler, B. J.; Edwards, W. D. 4-Isoxazolyl-1,4-dihydropyridines: Biological, Theoretical, and Structural Studies. *J. Med. Chem*. **1990**, 33, 2255-2259. (c) McKenna, J. I.; Schlicksupp, L.; Natale, N. R.; Maryanoff, B. E.; Flain, S. F.; Willet, R. D. Cardioactivity and Solid State Structure of Two 4-isoxazolyl-1,4-dihydropyridines Related to the 4-aryldihydropyridine Calcium Channel Blockers. *J. Med. Chem.* **1988**, 31, 473-476.

74. Alker, D.; Simon F.; Campbell I.; Peter E. Cross, R.; Burges, A. Carter, A. J.; Gardiner D. G. Long-Acting Dihydropyridine Calcium Antagonists. Synthesis and Structure-Activity Relationships for a Series of 2-[(N-Substituted- heterocyclic)methoxy]methyl-1 ,4-dihydropyridine Calcium Antagonists, *J. Med. Chem.* **1990**,33, 1805-1811.

75. (a) Buhler, F. R.; Kiowski, W. J. *Hypertens.* **1987**, S3, 5; (b) Reid, J.; Meredith, P. A.; Pasanisi, F. *J. Cardiovasc. Pharmacol.* **1985,** 18, 7.

76. (a) Godfraid, T.; Miller, R.; Wibo, M. Calcium antagonism and calcium entry blockade**.** *Pharmacol. Rev*. **1986**, 38, 321; (b) Sausins, A.; Duburs, G. *Heterocycles* **1988,** 27, 269; (c) Mager, P. P.; Coburn, R. A.; Solo, A. J.; Triggle, D. J.; Rothe, H. *Drug Des. Dis.* **1992**, 8, 273; (d) Mannhold, R.; Jablonka, B.; Voigdt, W.; Schoenafinger, K.; Schravan, K. Calcium- and calmodulin-antagonism of elnadipine derivatives: comparative SAR. *Eur. J. Med. Chem*. **1992**, 27, 229.

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

78. An-Hu Li, Stefano Moro, Neli Melman, Xiao-duo Ji, and Kenneth A. Jacobson, Structure-Activity Relationships and Molecular Modeling of 3,5-Diacyl-2,4-dialkylpyridine Derivatives as Selective A3 Adenosine Receptor Antagonists, *J. Med. Chem.* **1998**, 41, 3186-3201

79. Shafiee, A.; Rastkari, N.; Sharifzadeh, M.; Anticonvulsant activities of new 1,4-dihydropyridine derivatives containing 4-nitroimidazolyl substituents. DARU, 2004, 12(2), 81-86.

80. Loev, B.; Sander, K. M. The Hantzsch Reaction. I. Oxidative Dealkylation of Certain Dihydropyridines. *J. Org. Chem.* **1965**, 30, 1914.

81. (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1888**, 21, 942; (b) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, 23, 1747; (c) Wiley, R. H.; England, D. C.; Behr, L. C. *In Organic Reactions; John Wiley*, **1951**; 6, 367; (c) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Multicomponent Hantzsch cyclocondensation as a route to highly functionalized 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their N-oxides: preparation via a polymer-assisted solution-phase approach. *Tetrahedron*, **2004**, 60, 2311.

82. (a) Khadikar, B. M.; Gaikar, V. G.; Chitnavis, A. A. 1,3 acyclic control in free radical reactions: Threo—selective additions. *Tetrahedron Lett.* **1995**, 36, 8083; (b) Ohberg, L.; Westman, J. An Efficient and Fast Procedure for the Hantzsch Dihydropyridine Synthesis under Microwave Conditions. *Synlett* **2001**, 1296; (c) Agarwal, A.; Chauhan, P. M. S. Solid supported synthesis of structurally diverse dihydropyrido[2,3-d]pyrimidines using microwave irradiation. *Tetrahedron Lett.* **2005,** 46, 1345.

83. (a) Ji, S.-J.; Jiang, Z.-Q.; Lu, J.; Loh, T.-P. Facile Ionic Liquids-Promoted One-Pot Synthesis of Polyhydroquinoline Derivatives under Solvent Free Conditions. *Synlett* **2004**, 831; (b) Sridhar, R.; Perumal, P. T. A new protocol to synthesize 1,4-dihydropyridines by using 3,4,5-trifluorobenzeneboronic acid as a catalyst in ionic liquid: synthesis of novel 4-(3-carboxyl-1H-pyrazol-4-yl)-1,4-dihydropyridines. *Tetrahedron* **2005**, 61, 2465.

84. (a) Phillips, A. P. Hantzsch's Pyridine Synthesis. *J. Am. Chem. Soc*. **1949**, 71, 4003; (b) Anderson, G. J. R.; Berkelhammer, G. A Study of the Primary Acid Reaction on Model Compounds of Reduced Diphosphopyridine Nucleotide[1,2] . *J. Am. Chem. Soc*. **1958**, 80, 992; (c) Singh, H.; Chimni, D. S. S.; Kumar, S. Acid catalysed enamine induced transformations of 1,3-dimethyl-5-formyluracil. A unique annulation reaction with enaminones. *Tetrahedron* **1995,** 51, 12775; (d) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. Approaches to Combinatorial Synthesis of Heterocycles: A Solid-Phase Synthesis of 1,4-Dihydropyridines. *J. Org. Chem.* **1996**, 61, 924; (e) Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett.* **2000**, 41, 4311; (f) Liang, J.-C.; Yeh, J.-L.; Wang, C.-S.; Liou, S.-F.; Tasi, C.-H.; Chen, I. The new generation dihydropyridine type calcium blockers, bearing 4-phenyl oxypropanolamine, display α-/β-Adrenoceptor antagonist and long-Acting antihypertensive activities. *Bioorg. Med. Chem.* **2002**, 10, 719; (g) Miri, R.; Niknahad, H.; Vesal, Gh.; Shafiee, A. *IL Farmaco* **2002**, 57, 123; (h) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertoasi, V. Model Studies toward the Synthesis of Dihydropyrimidinyl and Pyridyl α-Amino Acids via Three-Component Biginelli and Hantzsch Cyclocondensations. *J. Org. Chem.* **2003**, 68, 6172; (i) Tewari, N.; Dwivedi,

N.; Tripathi, R. P. Tetrabutylammonium hydrogen sulfate catalyzed eco-friendly and efficient synthesis of glycosyl 1,4-dihydropyridines. *Tetrahedron Lett*. **2004**, 45, 9011; (j) Moseley, J. D. Alternative esters in the synthesis of ZD0947. *Tetrahedron Lett.* 2005, 46, 3179. Sabitha, G.; Reddy, G. S. K. K.; Reddy, Ch. S.; Yadav, J. S. A novel TMSI-mediated synthesis of Hantzsch 1,4-dihydropyridines at ambient temperature. *Tetrahedron Lett.* **2003**, 44, 4129. (k) Wang, L.-M.; Sheng, J.; Zhang, L.; Han, J.-W.; Fan, Z.; Tian, H.; Qian, C.-T. *Tetrahedron* **2005**, 61, 1539.

85. Correa, W. H.; Scott J. L. Solvent-free, two-step synthesis of some unsymmetrical 4-aryl-1,4-dihydropyridines. *Green Chemistry,* **2002**, 56,184-186.

86. Shengkai Ko, M. N. V. Sastry, Chunchi Lin and Ching-Fa Yao, Molecular iodine-catalyzed one-pot synthesis of 4-substituted-1,4-dihydropyridine derivatives via Hantzsch reaction. *Tetrahedron Lett.,* **2005**, 46, 5771–5774.

87. B. M.; Khadilkar, V. R. Madyar Scaling Up of Dihydropyridine Ester Synthesis by Using Aqueous Hydrotrope Solutions in a Continuous Microwave Reactor *Org. Pro. Res. & Dev.* **2001**, 5*,* 455-458.

88. Chhillar, A. K.; Arya, P.; Mukherjee, C.; Kumar, P.; Yadav, Y.; Sharma, A.; K. Yadav, V.; Gupta, J.; Dabur, R.; Jha, H. N. Watterson, A. C.; Parmar, V. S.; Prasad A. K.; Sharma G. L. Microwave-assisted synthesis of antimicrobial dihydropyridines and tetrahydropyrimidin-2-ones: Novel compounds against aspergillosisq. *Bioorg. Med. Chem.* **2006**, 14, 973–981.

89. Lakshmi, S.; Sridhar, M. A.; Shashidhara Prasad, J.; Manvar, D.; Parecha, A.; Patel, G.; Shah, A. Crystal and molecular structure of 3,5-dicarbethoxy-2,6-dimethyl-4-(4-methoxyphenyl)-1,4-dihydropyridine*, J. Anal. Sci*. **2005**, 21, X93-X94.

90. Mahendra, M.; Doreswamy, B. H.; Parecha, A. R.; Patel, J. A.; Shah, A.; Sridhar, M. A.; Shashidhara Prasad, J. Synthesis and Structure of N-substituted 1,4-dihydropyridine derivative. *Analytical Sciences*, **2004**, 20, X19.

91. Devaru, V. B.; Devarajegowda, H. C.; Doreswamy, B. H.; Mahendra, M.; Shah, A.; Anandalwar, S. M.; Prasad J. S. Crystal structure of 2,6-dimethyl-3-cyanide-5-methylacetate-4-(4'-methyl thiophenyl)-1,4-dihydropyridine, *Analytical Sciences*, **2004**, 20, X45.

92. Naveen, S.; Ananandalwar, SM.; Shashidhara, Prasad J.; Manvar, D.; Mishra, A.; Shah, A. Synthesis and structural confirmation studies of a potent unsymmetical 1,4-dihydropyridine. *J. Chem. Crystall.* **2007**, 6-8.

93. Kakadiya, R.; Bariwal, J.; Virsodia, V.; Karia, D.; Shah, A. Crystal structure of dimethyl-2,6-dimethyl-4-(2-nitrophenyl)–N-(2-methoxyphenyl)-1,4-dihydro-pyridine-3,5-dicarboxylate, *Mol. Cryst. Liq. Cryst.*, **2007**.

94. Goldmann, S.; Born, L.; Kazda, S.; Pittel, B.; Schramm, M.; Synthesis, Pharmacological Effects, and Conformation of 4,4-Disubstituted 1,4-Dihydropyridines, *J. Med. Chem.* **1990**, 33(5), 1413-1418.

95. Raderer, M.; Scheithauer, W. Clinical trials of gents that reverse multidrug resistance. *Cancer*, **1993**, 72, 3553-3563.

96. Aszalos, A.; Pine, P. S.; Pandey, R.; Gottesman, M. M. Behaviour of N-acylated daunorubincins in *mdr* 1 gene trensfected and parental cells. *Biochem. Pharm*. **1995**, 50, 889-892.

97. Ford, J. M, Hait, W. Pharmacology of drugs that alter multidrug resistance in cancer, *Pharmacol. Rev*. **1990**, 42, 155-199.

98. Tsuruo, T.; Iida, H.; Tsukagoshi, S.; Sakurai, Y. Overcomming of vincristine resistance in P388 leukemia *in vivo* and *in vitro* through enhanced cytoxicity of vincristine and vinblastine by verapamil. *Cancer Res.* **1981**, 41, 1967-1972.

99. Nogae, I.; Kohno, K.; Kikuchi, J.; Kuwano, M.; Akiyama, S.; Kiue, A.; Suzuki, K.; Yoshida, Y.; Cornwell, M. M.; Pastan, I.; Gettesman, M. M. Analysis of structural features of dihydropyridine analogues needed to reverse multidrug resistance and to inhibit photoaffinity labeling of P-glycoprotein. *Biochem Pharmacol*, **1989**, 38, 519-527.

100. Chiba, P.; Ecker, D.; Schmid, J.; Drach, J.; Tell, B.; Goldenberg, S.; Gekeler, V. Structural requirements for activity of propafenone-type modulators in P-glycoprotein-mediated miltidrug resistance. *Mol. Pharmacol.* **1996**, 49, 1122-1130.

101. Shah, A.; Gaveriya, H.; Motohashi, N.; Kawase, M.; Saito, S.; Sakagami, H.; Satoh, K.; Tada, Y.; Solymosi, A.; Walfard, K.; Molnar, J. 3,5-Diacetyl-1,4-dihydropyridines : Synthesis and MDR reversal in tumor cells, *Anticancer Res.*, **2000**, 20, 373-378.

102. (a) Kharkar, P. S.; Desai, B.; Gaveria, H.; Varu, B.; Loriya, R.; Naliapara, Y.; Shah, A.; Kulkarni, V. M. Three-Dimensional Quantitative Structure-Activity Relationship of 1,4-Dihydropyridines As Antitubercular Agents *J. Med. Chem.* **2002,** 45, 4858-4867. (b) Desai, B.; Sureja, D.; Naliapara, Y.; Shah, A.; Saxena, A. Synthesis and QSAR Studies of 4-Substituted phenyl-2,6-dimethyl-3,5-bis-N-(substituted phenyl)-carbamoyl-1,4-dihydropyridines as Potential Antitubercular Agents. *Bioorg. Med. Chem.* **2001**, 4, 1993-1997.

103. Kharkar, P. S.; Desai, B.; Gaveria, H.; Naliapara, Y. T.; Loriya, R. M.; Varu, B. V.; A, Shah.; Kulkarni, V. M. Three Dimentional Quantitative Structure Activity Relationship of Antitubercular Agents. *J. Med. Chem.*, **2002,** 45(22), 4858-4867.

104. Gunics, G.; Motohashi, N.; Molnar, J.; Farkas, S.; Kawase, M.; Saito, S.; Shah, A. Enhanced antibacterial effect of erythromycin in the presence of 3,5-dibenzoyl-1,4-dihydropyridines, *Anticancer Res.* **2001**, 21, 269-274.

105. Gunics, G.; Farkas, S.; Motohashi, N.; Shah, A.; Gevariya, H.; Kawase, M.; Molnar, J. Interaction between 3,5-diacetyl-1,4-dihydropyridines and ampicillin, and erythromycin on different E. coli. Strains, *International Journal of Antimicrobial Agents,* **2002**, 20, 227-229.

106. Engi H.; Sakagami H.; Kawase M.; Parecha A.; Manvar D.; Kothari H.; Adlakha P.; Shah A.; Motohashi N.; Ocsovszki I.; Molanr J. Tomor-specific cytotoxicity and MDR-reversal activity of Dihydropyridiens, *In vivo*, **2006,** 20, 637-644.

107. Fusi, F.; Saponara S.; Valoti M.; Dragoni S.; D'Elia P.; Sgaragli T, Alderighi D.; Sgaragli G.; Shah A. Cancer cell pearmeability-Glycoprotein as a target of MDR reverters: Possible role of novel dihydropyridine derivatives, *Curr. Drug Targets*, **2006**, 7, 949-959.

108. Saponara, S.; Kawase M.; Shah A.; Motohashi N.; Molnar J.; Ugocsai k.; Sgaraghi G.; Fusi F. 3,5-dihenzoyl-4-(3-phenoxyphenyl)-1,4-dihydro-2,6-dimethylpyridien (DP7) as a new multidrug resistance reverting agent devoid of effects on vascular smooth muscle contractility. *Br. J. Pharmacol*, **2004**, 141, 415-422.

109. Desai B.; Sureja D.; Naliapara Y.; Shah A.; Saxena A K. Synthesis and QSAR studies of 4-substituted phenyl-2,6-dimethyl-3,5-Bis-N-(sunstituted phynyl) carbamoyl-1,4-dihydropyridines as potential antitubercular agents, *Bioorg. Med. Chem.* **2001**, 9, 1993-1998.

110. Imming P.; Graf M.; Tries S.; Hirschelmann R.; Krause E.; Pawlitzki G. Anti-Inflammatory planar chiral [2.2] paracyclophaneacetic acid enantiomers, *Inflamm. Res.* **2001**, 50, 371-374.

111. Agudoawu, S.A.; Yiu, SH,; Wallace, J.L.; Knaus, E.E. Synthesis and analgesic activity of 2-methyl-2-[1-(3-benzoyl-4-substituted-1,4-dihydropyridyl)] acetic acid methyl esters, acetic acids and acetamides, *Arch. Pharm. (Weinheim)* **1999**, 332, 213-218.

112. Shi, K. H.; Lim, S. S.; Jung, S. H.; Ji, J.; Lee, E. B.; Kim, D. C.; Shin, K. J.; Kim, D. J.; Park, S. W. Synthesis and anti-inflammatory and alalgesic activities of pyridyloxy-and phenoxyalkanoic acid derivatives, *Arch. Pharm. Res.* **2000**, 23, 17-21.

113. Gred, D.; Warner, K. Cyclooxygenase inhibitors-current status and future prospects, *Eur. J. Med. Chem.* **2001,** 36, 109-126.

114. Figueiredo, J. M.; Camara, C. A.; Amarante, E. G.; Miranda, A. L. P.; Santos, F. M.; Rodrigues, C. R.; Fraga, C. A. M.; Barreiro, E. J. Design and synthesis of novel potent antinociceptive agents methyllimidazoyl-N-acylhydrazone derivatives, *Bioorg. Med. Chem.* 2000, 8, 2243-2238.

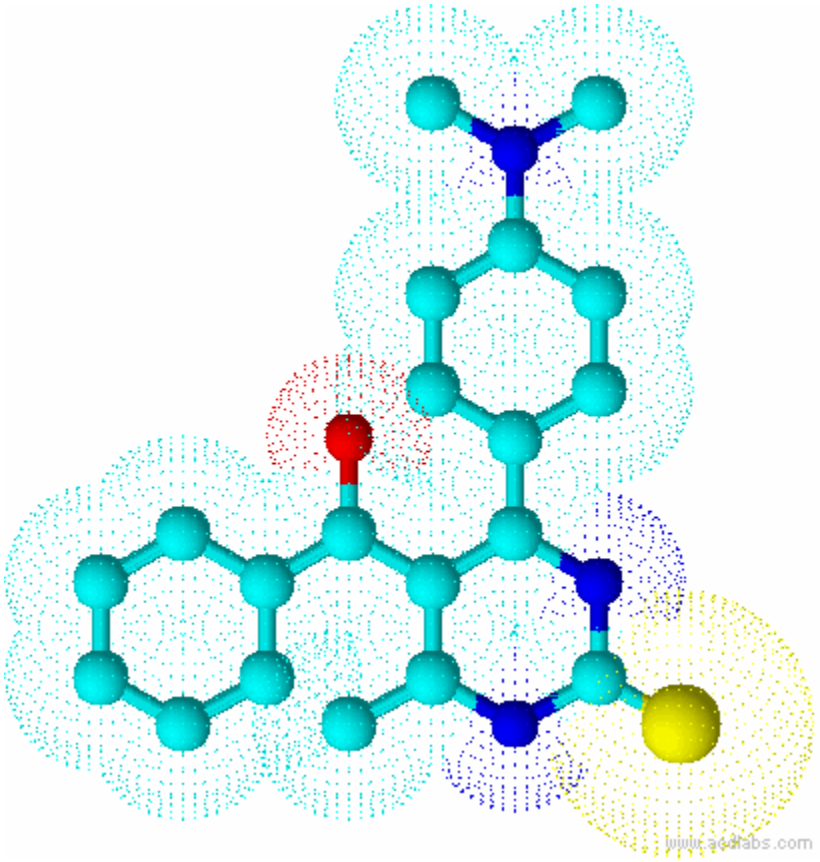
115. Shinde, D.B.; Shinde, N.D.; Shingare, M.S.; Synthesis of 1,4-dyhydropyridines and their hypotensive activity. *Indian J. Chem.* **1995**, 34B, 920-922.

116. Shah, A.; Gaveriya, H.; Motohashi, N.; Kawase, M.; Saito, S.; Sakagami, H.; SatohTada, Y.; Solmosi, A.; Walfard, K.; Molnar, J. 3,5-Diacetyl-1,4-dihydropyridines synthesis and MDR reversal in tumor cells, *Anticancer. Res*. **2000**, 20, 373-377.

117. Di Donato, M.; Maioli, M.; Venturi.; Burgisser, C.; Fantini, F.; Biamino, G.; Marchionni, N. Acute hemodynamic effects of intravenous diperdipine, a new dihydropyridine derivative, in coronary heart disease. *Am. Heart J.* **1991**, 121, 776-781.

118. Bahekar, S.; Shinde, D. Synthesis and anti-inflammatory activity of 1,4-dihydropyridines, *Acta. Pharm.* **2002**, 52, 281-287.

CHAPTER-5



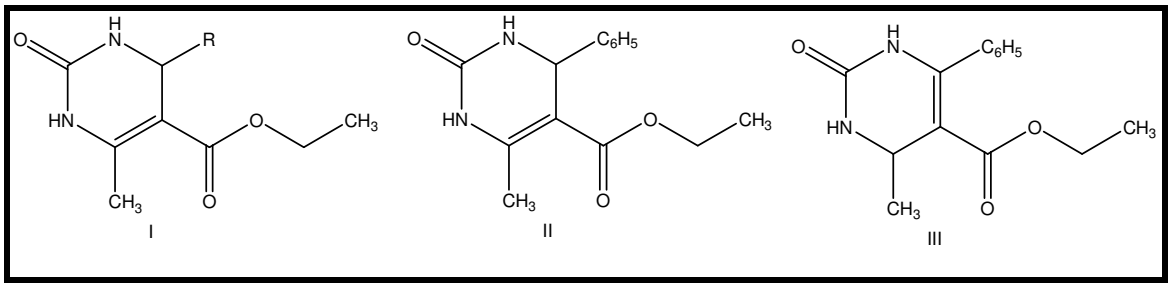
Synthesis and Characterization of 5-Benzoyl-6-methyl-4-(Subtituted) phenyl-3,4-Dihydro-pyrimidin-2(1H)-ones

Synthesis and Characterization of 5-Benzoyl-6-methyl-4-(substituted) phenyl -3,4-Dihydropyrimidin-2(1*H*)-ones

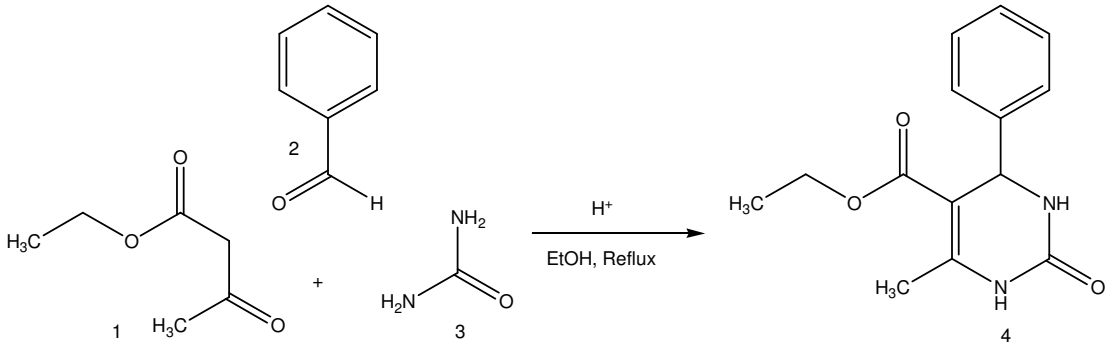
5.2. Introduction

In 1893, Pietro Biginelli[1] reported the synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) *via* three-component condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate. Since then, the "Biginelli reaction" has been known as an efficient one-pot reaction protocol to prepare 3, 4-dihydropyrimidine-2(1*H*)-one (DHPM) derivatives.

Biginelli formulated structure I, which is used to represent these tetrahydropyrimidines, in which R is the grouping joined to aldehyde of the particular aryl, alkyl or arylalkyl aldehyde employed in conjunction with urea and ethyl acetoacetate. Accordingly, when benzaldehyde was used, Biginelli obtained a pyrimidine which he considered to be represented by structure II, namely, 2-keto-4-phenyl-5-carbethoxy-6-methyl-1, 2, 3, 4-tetrahydropyrimidine. Biginelli's structure II was apparently accepted by Hinkel and Hey[2].



The original Biginelli protocol for the preparation of the DHMPs consisted of heating a mixture of the three components (aldehyde **1**, β-keto-ester **2**, and urea **3**) in ethanol containing a catalytic amount of HCl.[3] This procedure leads in one step-one pot to the desired DHPM[4] (Scheme-1).



Scheme-1: Biginell Dihydropyrimidine synthesis

Multi-componant reactions (MCRs) & dihydropyrimidine synthesis:

Definition

Multicomponent Reactions (MCRs) are those reactions in which three or more reactants come together in a single reaction vessel to form a new product which contains portions of all the components.[5]

"MCRs convert more than two adducts directly into their product by one-pot reaction."

Importance

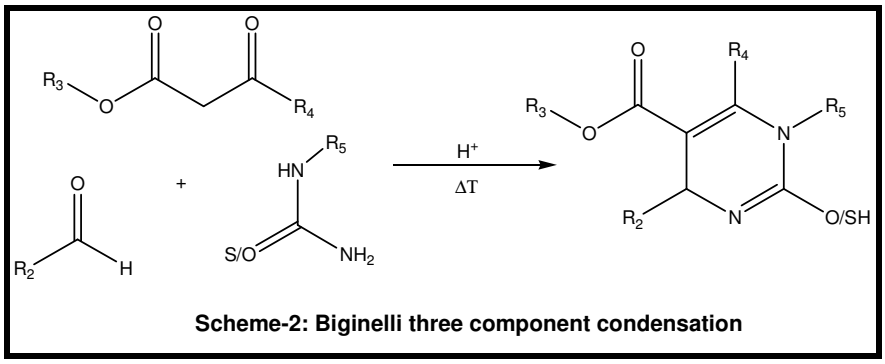
MCRs occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry and diversity-oriented synthesis.[6] MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations.

MCRs are providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques. MCRs leading to interesting heterocyclic scaffolds that are particularly useful for the creation of diverse chemical libraries of "drug-like" molecules for biological screening, since the

combination of three or more small-molecular-weight building blocks in a single operation leads to high combinatorial efficacy.

Over the last decade, industrial and academic researchers have made such powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial and parallel synthesis.[7(a-i)] One prominent MCR that produces an interesting class of nitrogen heterocycles is the Biginelli dihydropyrimidine synthesis.

The Biginelli reaction, one-pot cyclocondensation of aldehyde, 1,3-ketoester, and urea or thiourea, is inarguably one of the most useful MCRs.[1,8(a,b)] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified as 3,4-dihydropyrimidin-2(1*H*)-one (Scheme-2), and this reaction is referred to as "Biginelli reaction", "Biginelli condensation", or as "Biginelli dihydropyrimidine synthesis."[9-11]

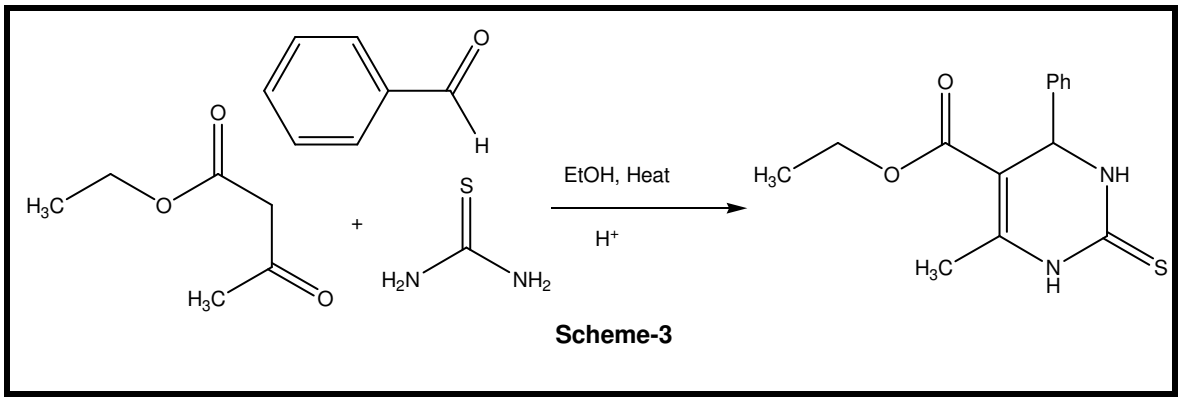


Scheme-2: Biginelli three component condensation

5.2. Synthetic aspects of dihydropyrimidines

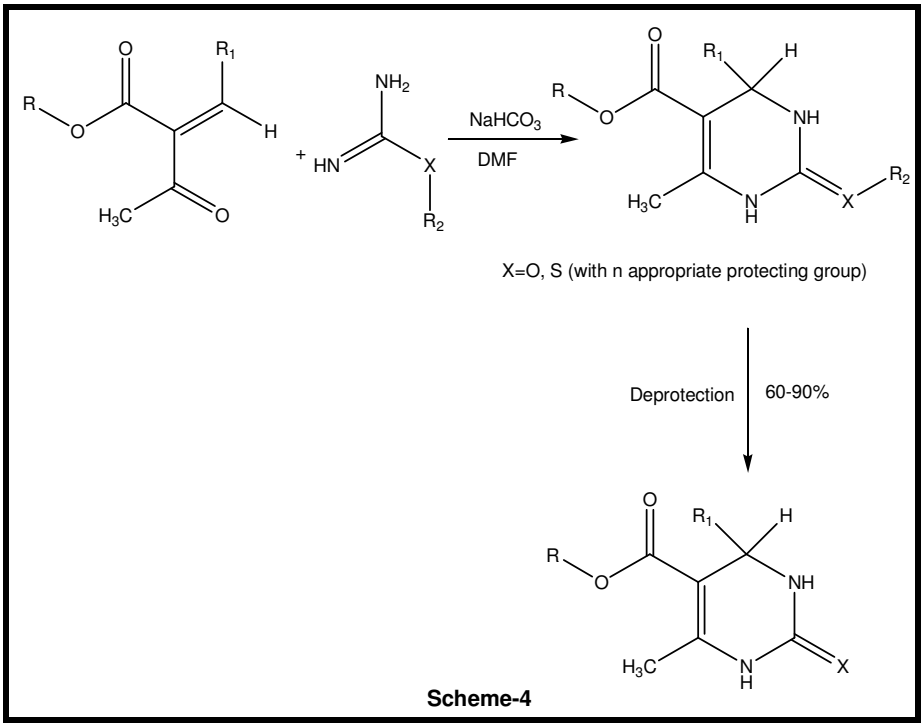
To make diversed DHPM derivatives available for drug discovery, appropriate synthetic protocols are needed.

Biginelli dihydropyrimidine synthesis: The standard procedure for the Biginelli condensation[1] involves one-pot condensation of the three building blocks in a solvent such as ethanol using a strongly acidic catalyst, *i.e.* hydrochloric acid[12] (Scheme-3).



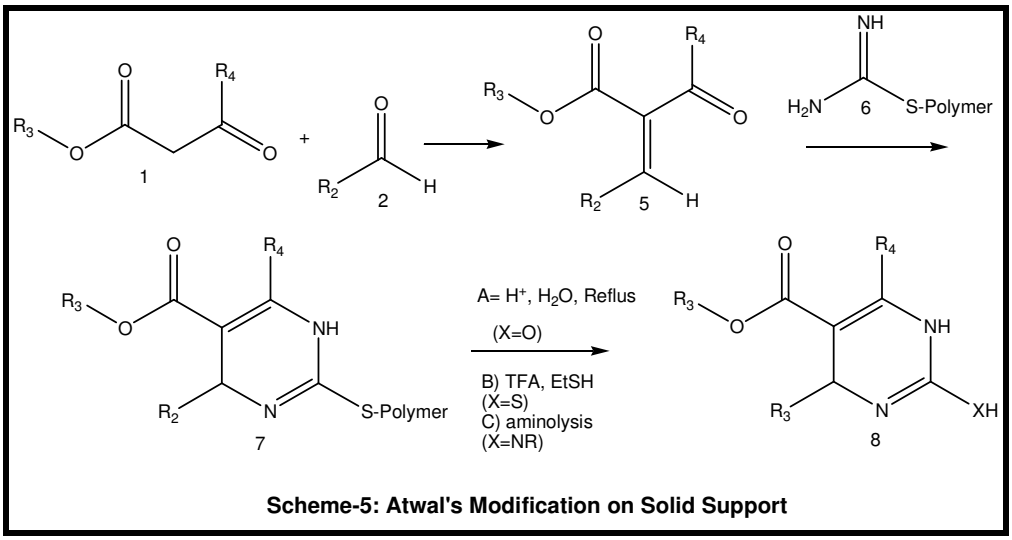
Scheme-3

Atwal's Modification: Atwal[13] modified the synthesis of dihydropyrimidine for better yield. He took o-substituted aryl aldehydes as well as aliphatic aldehydes for the synthesis of dihydropyrimidines and observed that R_1 can be significantly varied with little effect on the yield (Scheme-4).



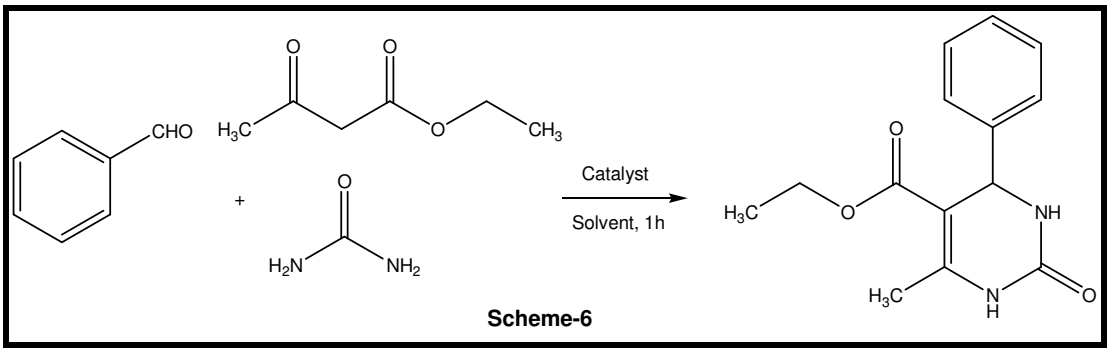
Scheme-4

The first one makes use of immobilized urea or thiourea moieties. The second uses an immobilized β-ketoester, and the third one uses an S-linked isothiouronium isothiouranium salt (Scheme-5).



Scheme-5: Atwal's Modification on Solid Support

Rafiee and co-workers[14] described an efficient synthesis of 3,4-dihydropyrimidinones or thiones (DHPMs), using silica-supported heteropoly acid $H_3PW_{12}O_{40}/SiO_2$ (PW/SiO_2) for the first time as the catalyst from an aldehyde, β-keto ester and urea or thiourea in acetonitrile. Compared to the classical Biginelli reaction conditions, this method consistently has the advantage of excellent yields, mild reaction conditions, easy workup, survival of different functional groups, and short reaction times (Scheme-6).

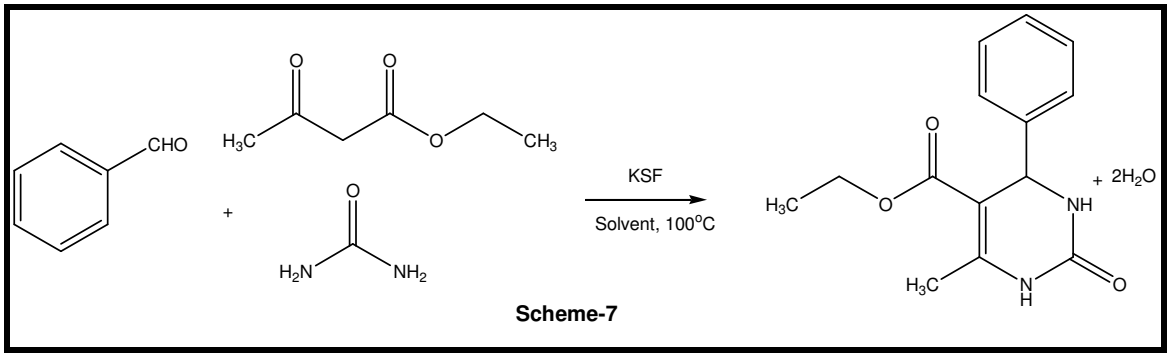


Scheme-6

It has been reported that Lewis acids (such as BF_3OEt_2)[15] in combination with transition metals and a proper proton source were effective catalyst for this reaction. Dihydropyrimidinones were also synthesized by using various protic acids such as HCl,[16] and acetic acid[17] under microwave irradiation. More recently, ionic liquids,[25] montmorillonite KSF, polyphosphate ester (PPE),[18-19] and lanthanide triflate,[20] as

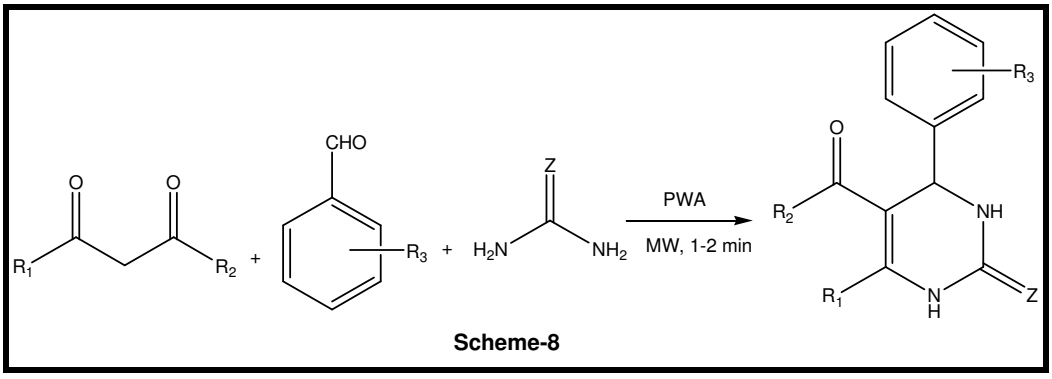
catalysts for the one-pot solvent-free synthesis of dihydropyrmidinones have also been reported.

Bigi[21] and co-workers synthesized various dihydropyridinesin the presence of the acidic clay montmorillonite KSF 7 taking the mixture of benzaldehyde, ethyl acetoacetate and urea with or without water or toluene as solvent, at 100°C (Scheme-7).



Scheme-7

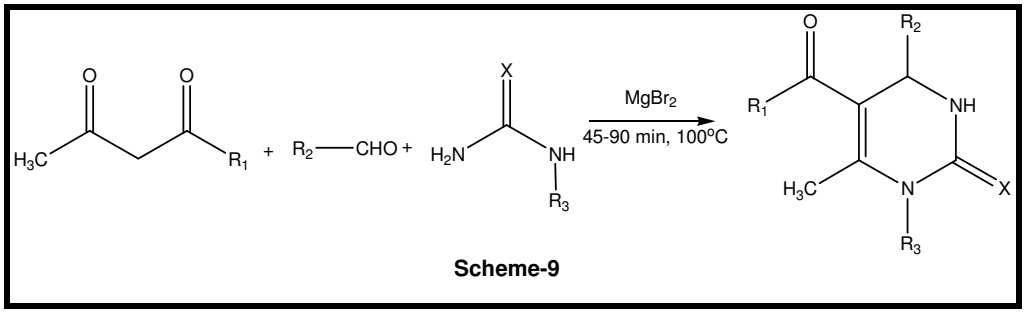
Phosphotungstic acid (0.05 mol%) catalyzed one-pot condensation[22] of aryl aldehydes, urea derivatives and β-diketones under microwave irradiation rapidly affords substituted 3,4-dihydropyrimidin-2(1*H*)-ones in excellent yields and high purity. The low cost catalyst has exhibited remarkable reactivity and reusability (Scheme-8).



Scheme-8

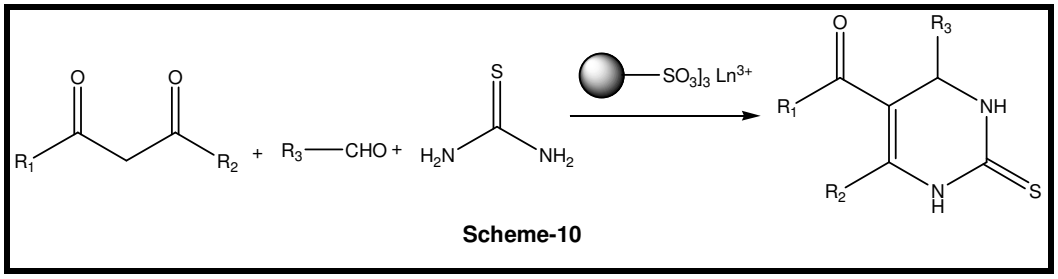
Salehi and co-workers[23] reported a facile and efficient method for the one-pot synthesis of dihydropyrimidinones using magnesium bromide as catalyst under solvent free conditions. Magnesium bromide efficiently catalyzes the three-component condensation reaction of aldehyde, β-di-ketone and urea/thiourea under solvent free conditions to

afford the corresponding dihydropyrimidinones in high yields and short reaction time (Scheme-9).



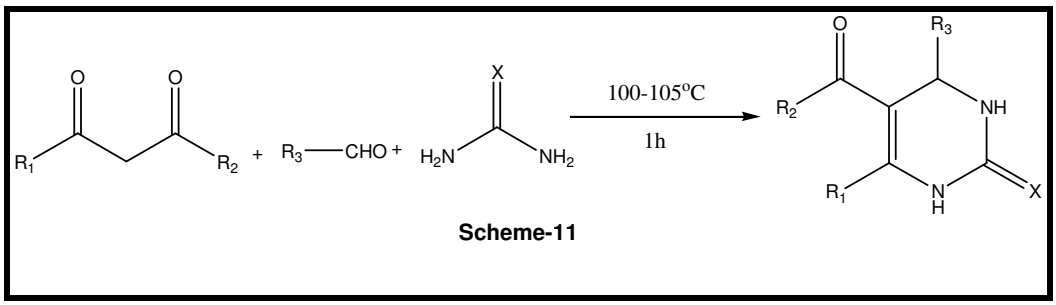
Scheme-9

One-pot synthesis of a library of 3,4-dihydropyrimidine-2(1*H*)-thiones and quinazolin-4(3*H*)-ones were described by Zhidong1[24] and co-workers. Ytterium reagent supported on ion exchange resin is applied to the multicomponent condensation reactions under solvent-free conditions. The advantages of easy separation and recyclability of the catalysts were demonstrated (Scheme-10).



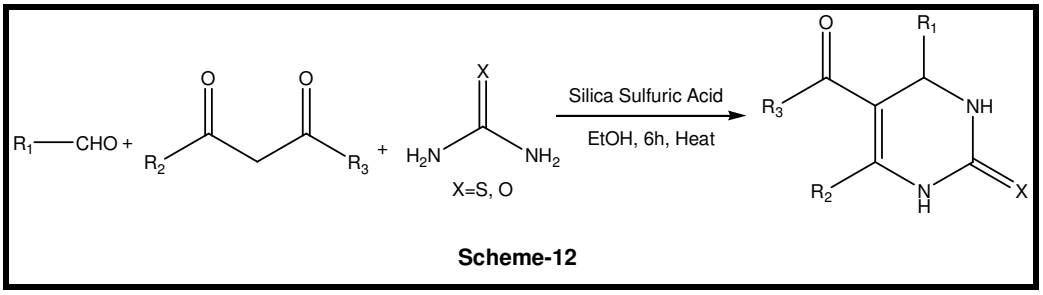
Scheme-10

A simple, efficient, green and cost-effective procedure has been developed for the synthesis of dihydropyrimidinones by a solvent-free and catalyst-free Biginelli's condensation of 1,3-dicarbonyl compound, aldehyde and urea. This approach[25] of direct reaction in neat without solvent and catalyst shows a new direction in green synthesis (Scheme-11).



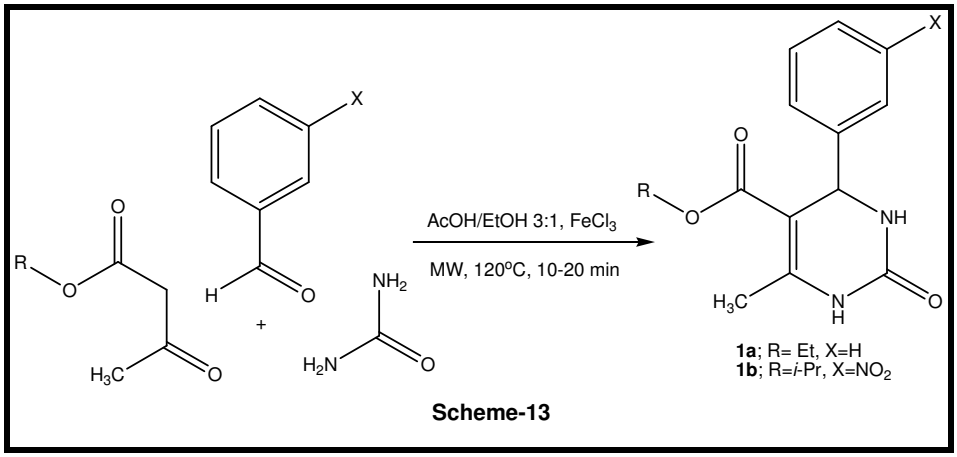
Scheme-11

Peyman Salehi[26] and co-workers also observed that Silica sulfuric acid efficiently catalyzes the three-component Biginelli reaction between an aldehyde, and a dicarbonyl compound and urea or thiourea in refluxing ethanol to afford the corresponding dihydropyrimidinones in high yields. The catalyst is reusable and can be applied several times without any decrease in the yields of the reactions (Scheme-12).



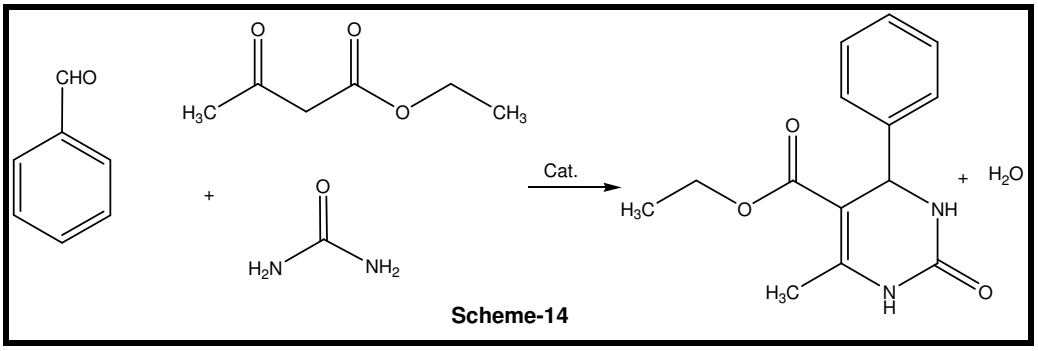
Scheme-12

Stadler *et. al.*[27] have recently described a high yielding and rapid microwave-assisted protocol that allows the synthesis of gram quantities of DHPMs utilizing controlled single-mode microwave irradiation[28] (Scheme-13).



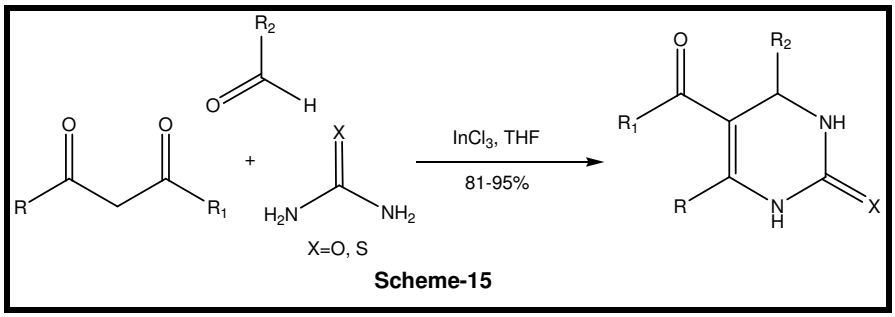
Scheme-13

Yun Ma and co-workers,[29] have tested a variety of reaction conditions with the model reaction using lanthanide trifluoromethanesulfonates as a catalyst and obtained the dihydropyrimidines in higher yields (Scheme-14).



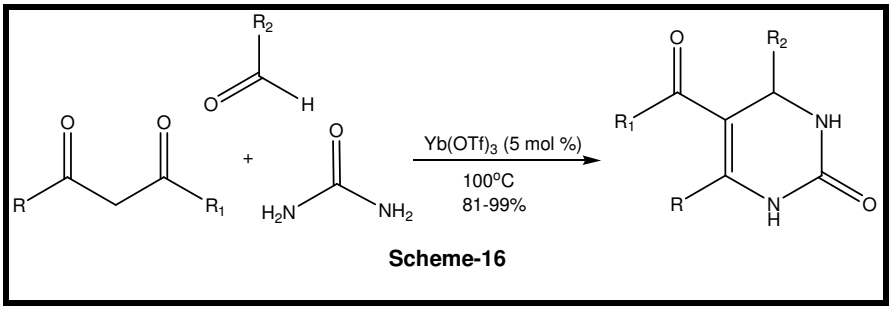
Scheme-14

Brindaban Ranu *et. al.*[30] synthesized Indium (III) chloride mediated Biginelli reactions (Scheme-15).



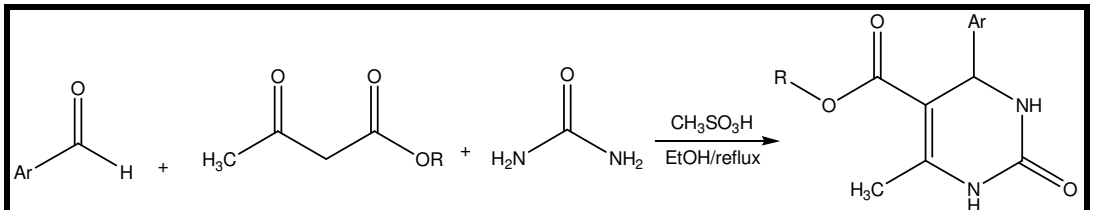
Scheme-15

Ma and co-workers[31] synthesized dihydropyrimidines using heavy metal catalysis (Scheme-16).



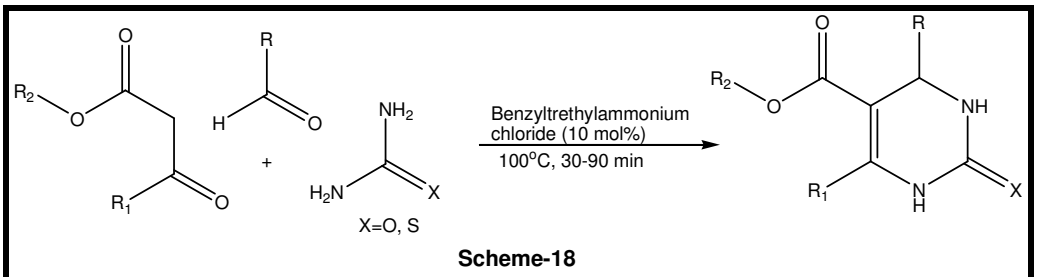
Scheme-16

An efficient synthesis of 3,4-dihydropyrimidin-2-ones from the aldehydes, β-ketoesters and urea in ethanol using methanesulfonic acid (CH_3SO_3H) as the catalyst is described by Jin and co-workers.[32] Compared with the classical Biginelli reaction conditions, this method has the advantage of excellent yields and short reaction time (Scheme-17).



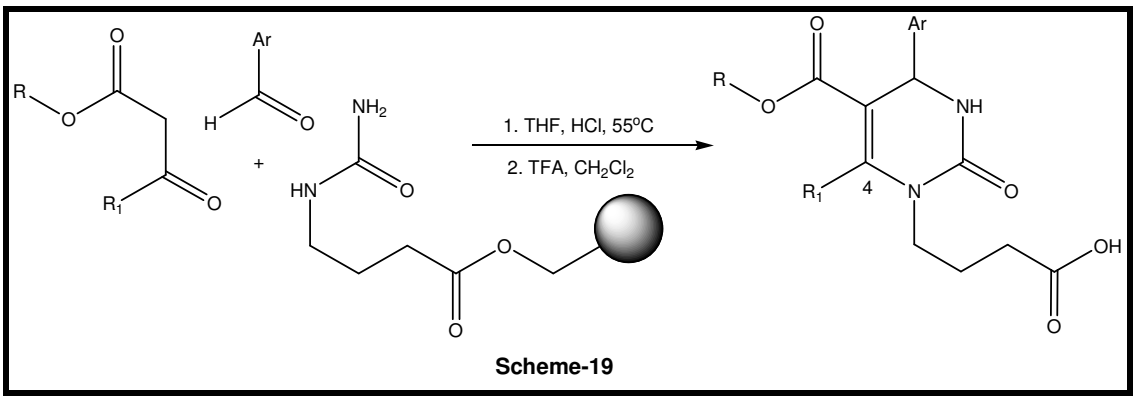
Scheme-17

A simple, efficient and cost-effective method[33] has been developed for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by a one-pot three component cyclocondensation reaction of 1,3 dicarbonyl compound, aldehyde and urea using benzyltriethylammonium chloride as the catalyst, under solvent-free conditions. The scope of this protocol is utilized for the synthesis of mitotic Kinesin EG5 inhibitor monastrol (Scheme-18).



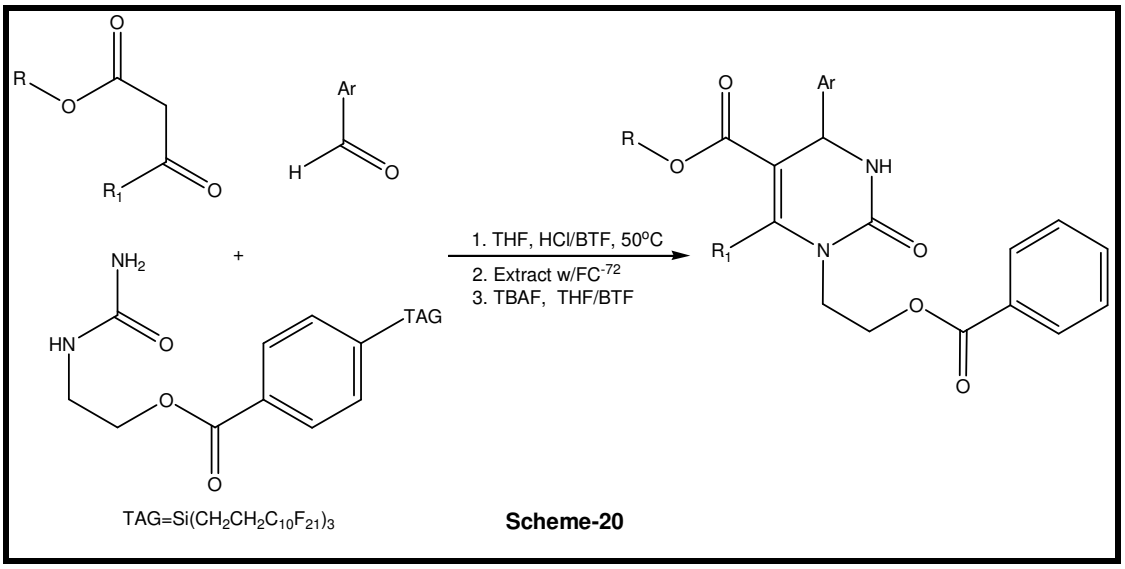
Scheme-18

Wipf *et. al.*[34] reported the solid phase synthesis for combinatorial scaffolds of Biginelli compounds (Scheme-19).



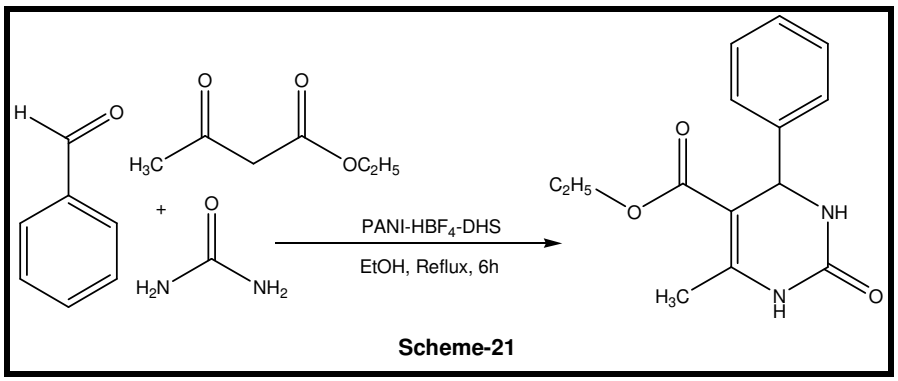
Scheme-19

Studer *et. al.*[35] reported the florous phase modifications for the dihydropyrimidine synthesis (Scheme-20).



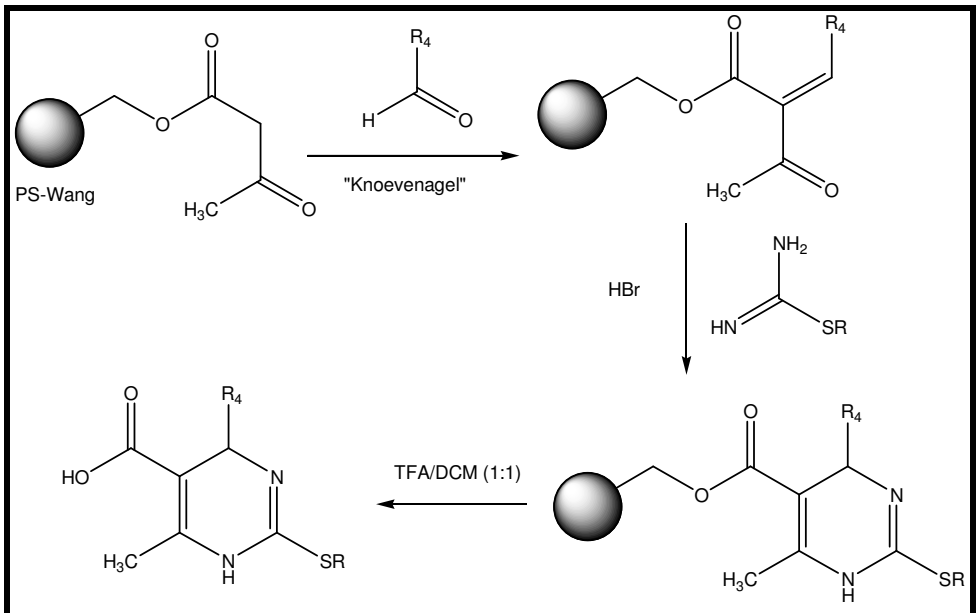
Scheme-20

Srinivasan and co-workers[36] synthesized dihydropyrimidinones by refluxing benzaldehyde, ethyl acetoacetate and urea with 5 wt.% of PANI–HBF4–DHS salt in ethanol for 6 h and obtained the products in more than 97% yields (Scheme-21).



Scheme-21

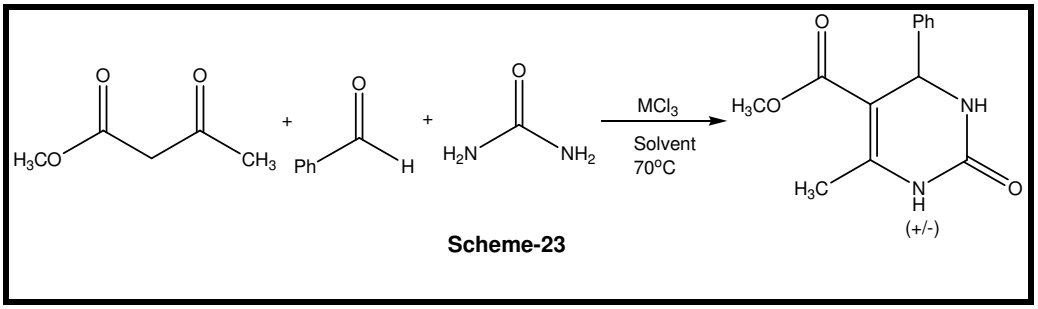
A closely related approach has been reported by Robinett *et. al.*[37] Here, the supported acetoacetate was first subjected to a Knoevenagel condensation on the resin[38] with a variety of aldehydes, followed by reaction with S-alkylisothioureas to produce 1,4-dihydropyrimidines on solid support. Rather than hydrolyzing the protected urea/thiourea functionality, these intermediates were directly cleaved with TFA/DCM 1:1 to furnish a 648 member combinatorial library 26[37] (Scheme-22).



Scheme-22: Solid phase synthesis of 1, 4-dihydropyrimidine-5-carboxilic acids employing the Atwal modification of the Biginelli condensation.[25]

Recently, cerium (III) chloride and indium (III) chloride have emerged as powerful catalysts imparting high regio and chemoselectivity in various chemical

transformations.[39(a-c)] Munoz-Muniz and co-workers[40(a-c)] performed enantioselective Biginelli condensation reactions catalyzed with $InCl_3$ or $CeCl_3$ in the presence of chiral ligands (Scheme-23).



Scheme-23

5.3. Pharmacology

Biologically active dihydropyrimidines

The biological activity makes these pyrimdines such attractive targets especially because of the following activities:

- Calcium channel blockers[41a]
- Antiviral activity[42a]
- Antibacterial activity[42c]
- Antitumor[12]
- Anti-inflammatory[42b]
- Analgesic[43]
- Blood platelet aggregation inhibitor[41b]
- Cardiovascular effects[44]

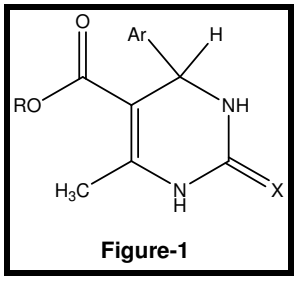


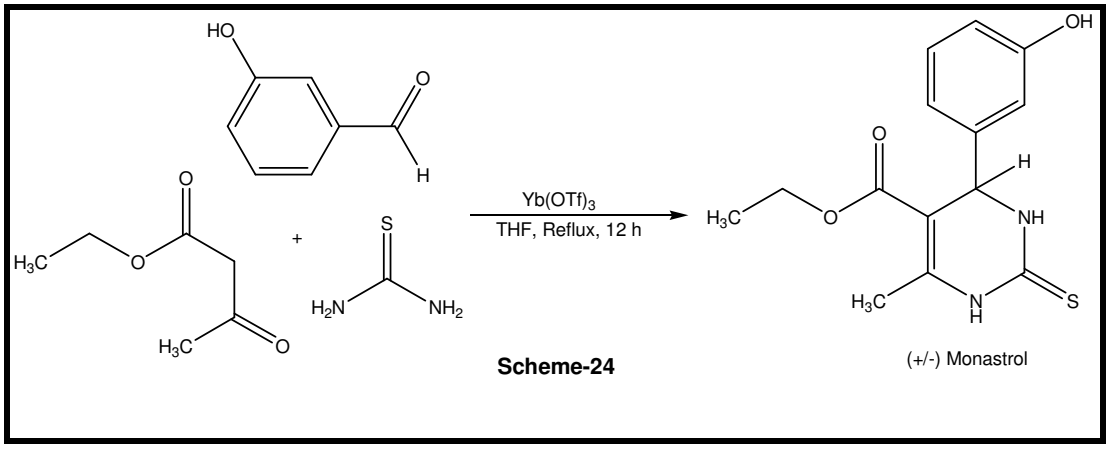
Figure-1

3,4-Dihydropyrimidin-2(1*H*)-ones and their synthetic analogues are of considerable importance because of their promising biological activities such as antibacterial, antiviral, anti-inflammatory and antitumor.

For example, aryl derivatives of dihydropyrimidones, SQ32926 and SQ32547 has been found to possess similar biological properties as that of dihydropyridines, a class of compounds showing remarkable pharmacological properties.[45] Other biological activities of DHPMs include α_{1A} adrenergic receptor antagonists as drug candidates for the treatment of benign prostatic hyperplasia. Recently, monastrol has been identified as a lead compound of a new class of anticancer agents acting as cell division (mitosis) blockers.[46]

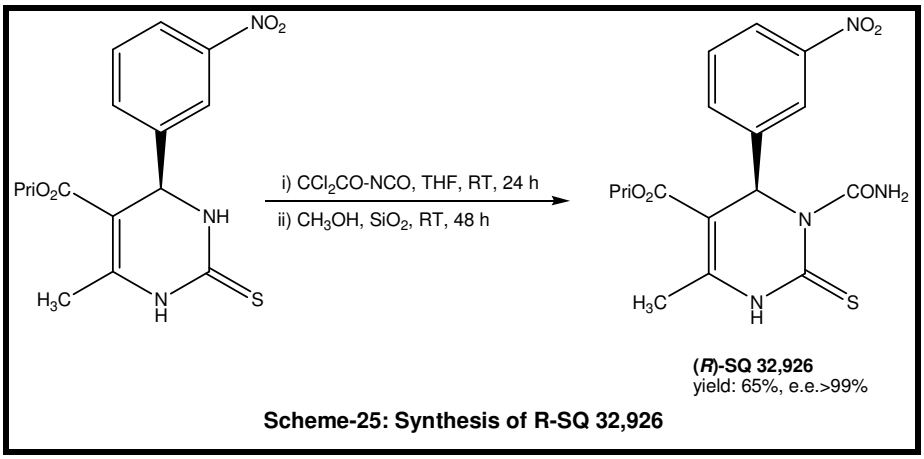
Dihydropyrimidine derivatives are known as interesting heterocyclic scaffolds for drug research. Polyfunctionalized dihydropyrimidines represent a heterocyclic system of remarkable pharmacological efficiency and many exhibit antiviral,[12a] antitumor,[12b] antibacterial and anti-inflammatory properties.[12c] The DHPM core structure was found to possess Channel modulating, adrenergic agonistic, mitotic kinesin inhibiting, antibacterial, fungicidal and other pharmacological properties. In addition, the dihydropyrimidine-5-carboxylate core has been found in several marine natural products.

Monastrol, the only cell-permeable molecule is currently known to specifically inhibit mitotic kinase Eg5 and is considered a lead for the development of new anticancer drugs.[13] (Scheme-24).



Scheme-24

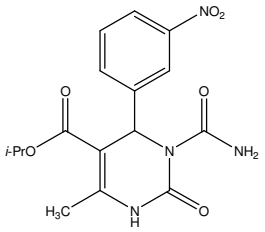
(*R*)-SQ 32,926, a potent orally active antihypertensive agent. Several marine natural products containing the dihydropyrimidine-5-carboxylate core were found to be potent HIVgp-120-CD4 inhibitors.[48(a-c)] Pharmacological studies concerning the absolute configuration at the C_4 stereogenic center were well documented and in some cases, individual enantiomers perform opposing biological activities.[49(a,b)] Nevertheless, only a few examples of asymmetric synthesis of this heterocyclic target have been reported.[50(a,b)] Chemical resolution and enzymatic strategies have thus far been the methods of choice to obtain optically active DHPMs.[51(a-d)] Access to highly enantiomerically pure DHPMs by catalytic asymmetric synthesis is therefore of considerable current interest and a formidable task, too (Scheme-25).



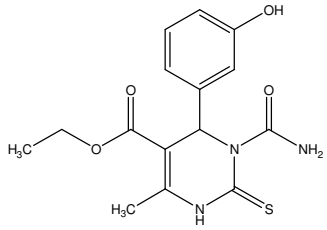
(*R*)-SQ 32,926
yield: 65%, e.e.>99%

Scheme-25: Synthesis of R-SQ 32,926

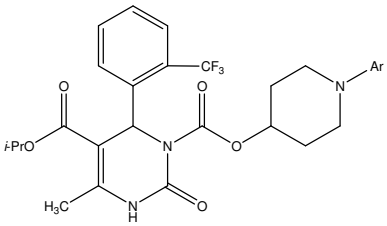
Table-1: Biologically active dihydropyrimidines under clinical trial at various stages [52]:



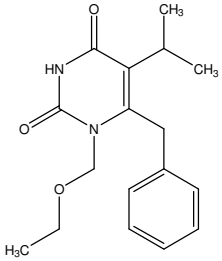
SQ32926 (Anti-viral)



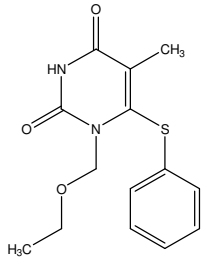
Monastrol (Anticancer)



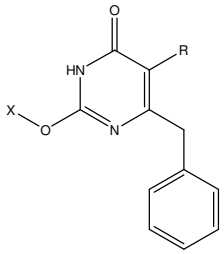
SQ32547 (Antitumor)



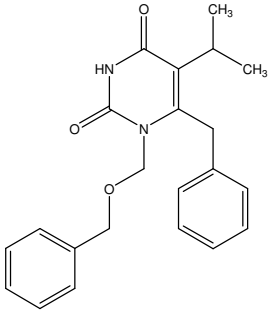
MKC-442 (NNRTI)



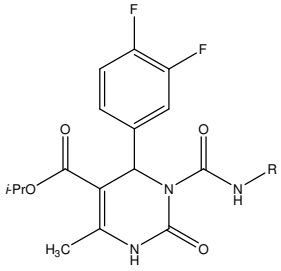
HETP (NNRTI)



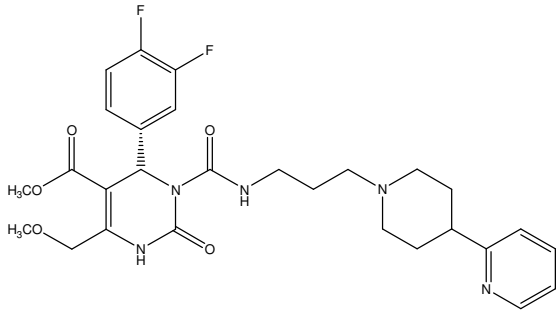
DABOs (NNRTI)



TNK—651 (NNRTI)



Merk-Synaptic product
(α-1A-adrenergic receptor antagonist)



L-771,668
(β_{1A}-selective adrenoceptor antagonist)

The preparation of enantiomerically enriched 4-phenyl-dihydropyrimidinone derivative[53] was achieved in moderate enantioselectivity (8-40%) by a modified one-pot Biginelli condensation procedure in the presence of the chiral ligands (*R*,*R*)-**A** or (*S*,*S*)-**B** (Figure-2).

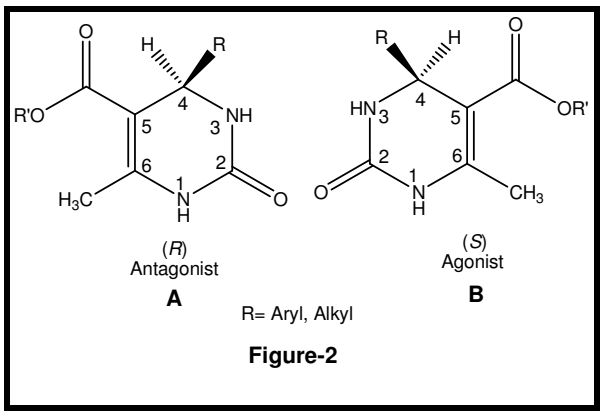


Figure-2

It was recently proposed that calcium channel modulation (antagonist *vs.* agonist activity) is dependent on the absolute configuration at C_4, whereby the orientation of the 4-aryl group (*R*- versus *S*-enantiomer) acts as a "molecular switch" between antagonist and agonist activity.[54] In the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyridine ring, with the 4-aryl substituent (X) prefering the synperiplanar (sp) orientation relative to C_4-H (Figure-3).

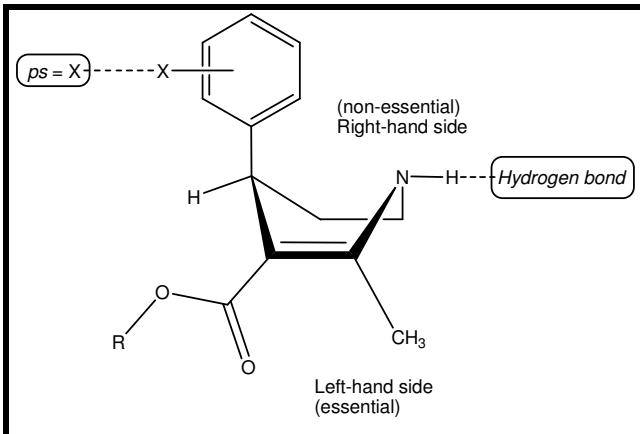


Figure-3: Proposed receptor-bound conformation of DHPM calcium channel modulator.

Over the years, research interest in multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones *viz*. the Biginelli scaffold, has surged rapidly, owing to the pharmacological properties associated with many derivatives of this privileged heterocyclic core.[55-58] Reports describe several DHPMs that have been identified, for example, Ca^{2+} channel modulators,[56(a-c)] or small molecules targeting the mitotic machinery.[57(a-c)] Notably, 4-aryldihydropyrimidinone heterocycles attached to an aminopropyl-4-piperidine moiety *via* a C_5 amide linkage have proven to be excellent templates for selective α-1A-receptor subtype antagonists to warrant further consideration for the treatment of Benign Prostatic Hyperplasia (BPH).[58(a,b)] In the synthesis of these DHPM-5-carboxamides.

Zhang and co-workers[59] reported a solid-phase organic synthesis protocol to introduce carboxamido acid functionality on the C_5 position of the DHPMs using amino acids.

Oliver Kappe and co-workers,[60] synthesized the amide bond formation between the requisite amines and the corresponding DHPM acids was performed using standard solution phase amide coupling chemistry involving carbodiimide coupling reagents (Figure-4).

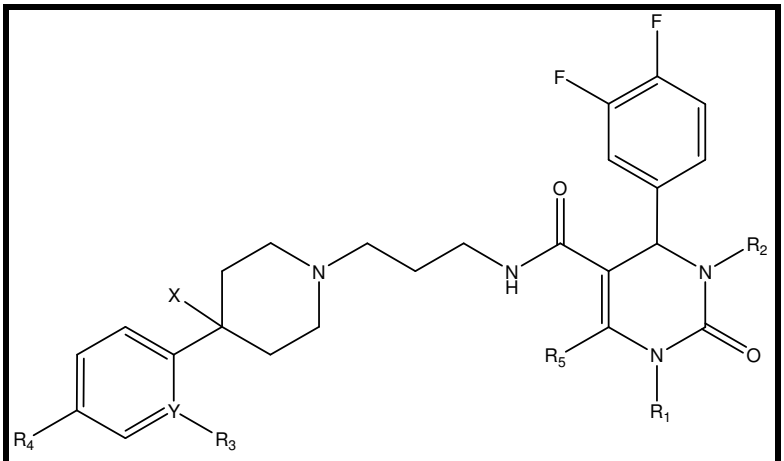
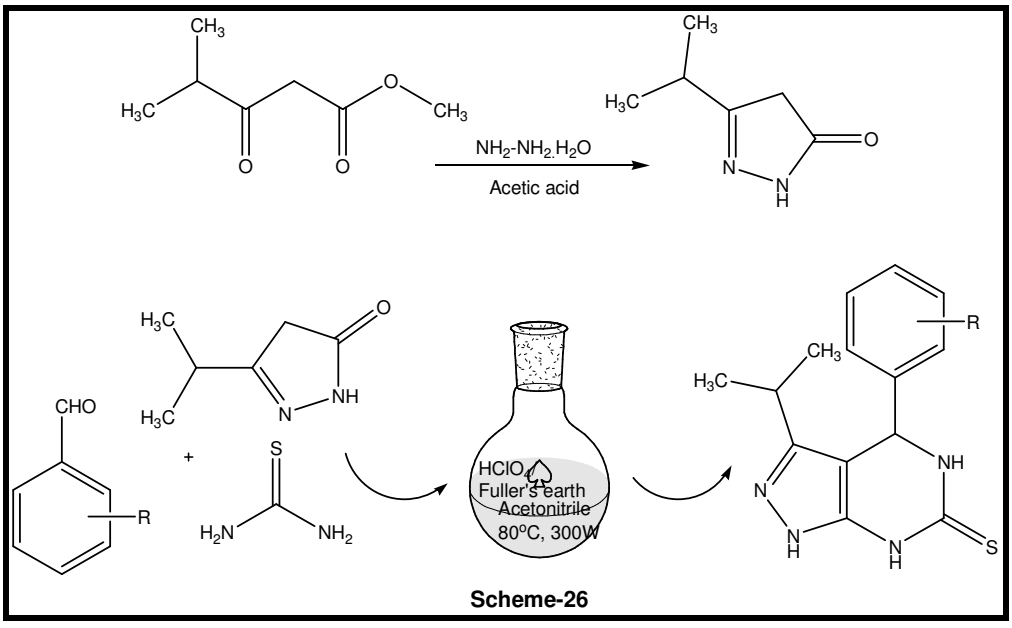


Figure-4

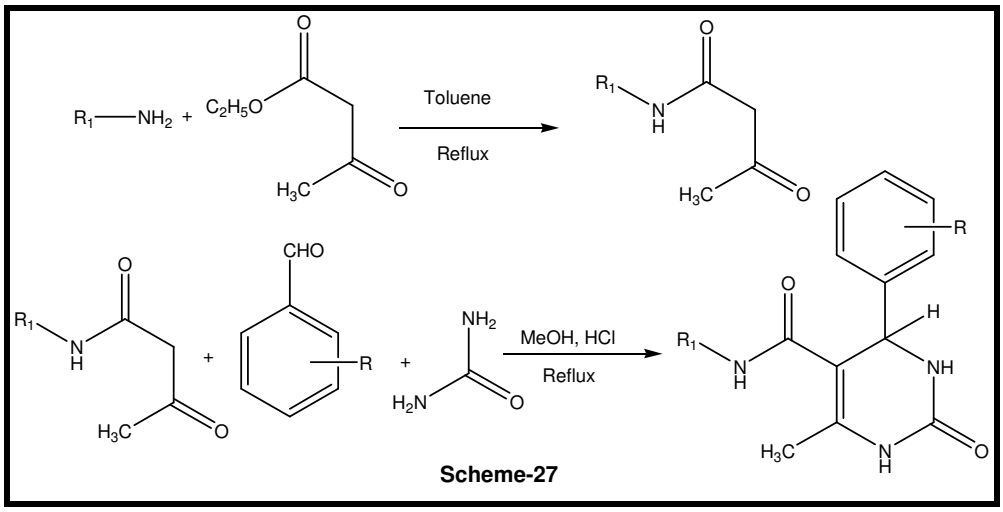
A few compounds synthesized in our laboratory having 1,4-dihydropyrimidine as a core structure

The following work deals with the multi-component reactions of aldehydes, thiourea and pyrazolone by classical heating using conc. HCl as the acid catalyst and by microwave assisted synthesis employing $HClO_4$-Fuller's earth as the novel heterogeneous acid catalyst. To our best knowledge, this is the first report of $HClO_4$-Fuller's earth as the heterogeneous catalyst. The synthesis of the catalyst is shown in the experimental section. The introduction of phenyl ring at position-4 of the core structure is itself novel by employing one pot reaction condition *i.e.* Biginelli type reaction. In fact, current protocol is the novel protocol for the solution-phase synthesis of pyrazolo[3,4-*d*]pyrimidine by classical heating as well as Microwave Assisted Organic Synthesis (MAOS). In MAOS, the overall yields of the products are higher than the conventional counterparts (Scheme-26).



Scheme-26

Another series of tetrahydropyrimidine was synthesized by two step synthesis. Substituted aniline and ethyl acetoacetate were heated at reflux in presence of toluene as a solvent to obtain substituted acetoacetanilides. Acetoacetanilide, substituted aldehydes and urea were taken in a round bottom flask and was heated at reflux in presence of methanol as a solvent. Few drops of conc. HCl was added to obtain substituted 6-methyl-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides (Scheme-27).



Scheme-27

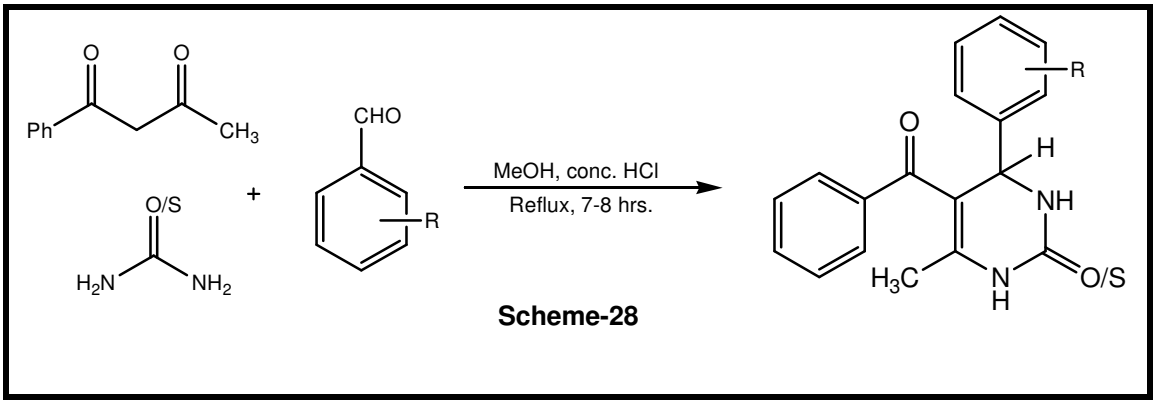
5.4. Present work

Multi-component condensation strategies are capable of providing in a single step durable core structures and highly variable side chains from simple starting materials. In the Biginelli dihydropyrimidine synthesis, the one-pot cyclocondensation of β-keto esters, aldehydes, and ureas provides DHPMs (Biginelli compounds) of well-established pharmacological potential.

In a typical general experimental procedure, equivalent amounts of aldehyde, benzoyl acetone and urea/thiourea were taken in a round bottom flask, adding 2-3 drops of conc. HCl and methanol was taken as solvent. The mixture was refluxed for 7-8 h to obtain dihydropyrimidinones.

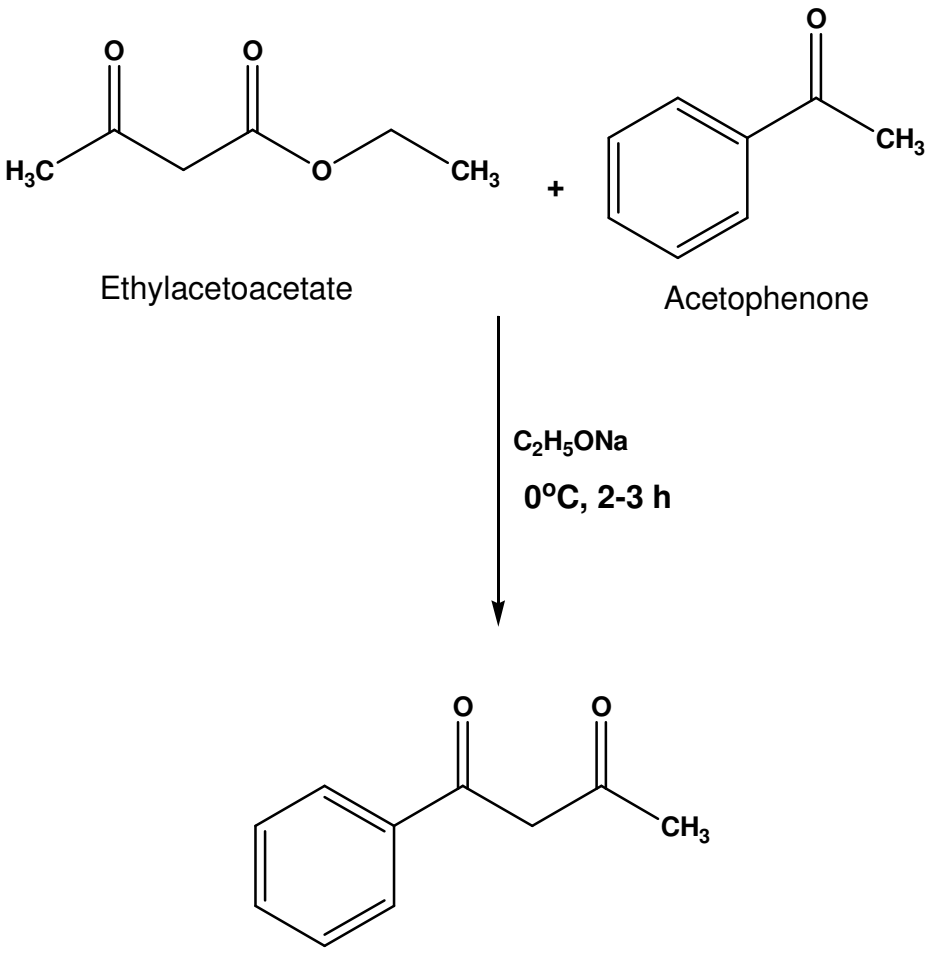
A wide range of substituted aldehydes and several β-diketones and urea/thiourea were subjected to this procedure to produce the corresponding DHPMs. The procedure gave the products in good to excellent yields. Urea and thiourea have been used with success to provide the corresponding dihydropyrimidinones, which are also of much interest with regard to the biological activity. Another important aspect of this procedure is survival of a variety of functional groups, such as CH_3, OCH_3, OH, and CN under the experimental conditions. Furthermore, aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents all worked well, giving good to excellent yields. In addition,

acid sensitive aldehydes, such as furfural reacted well without any side products. The adopted procedure is convenient, involves simple experimental procedure and product isolation; hence, it is a useful addition to the existing methods (Scheme-28).



Scheme-28

5.5. REACTION SCHEME-I



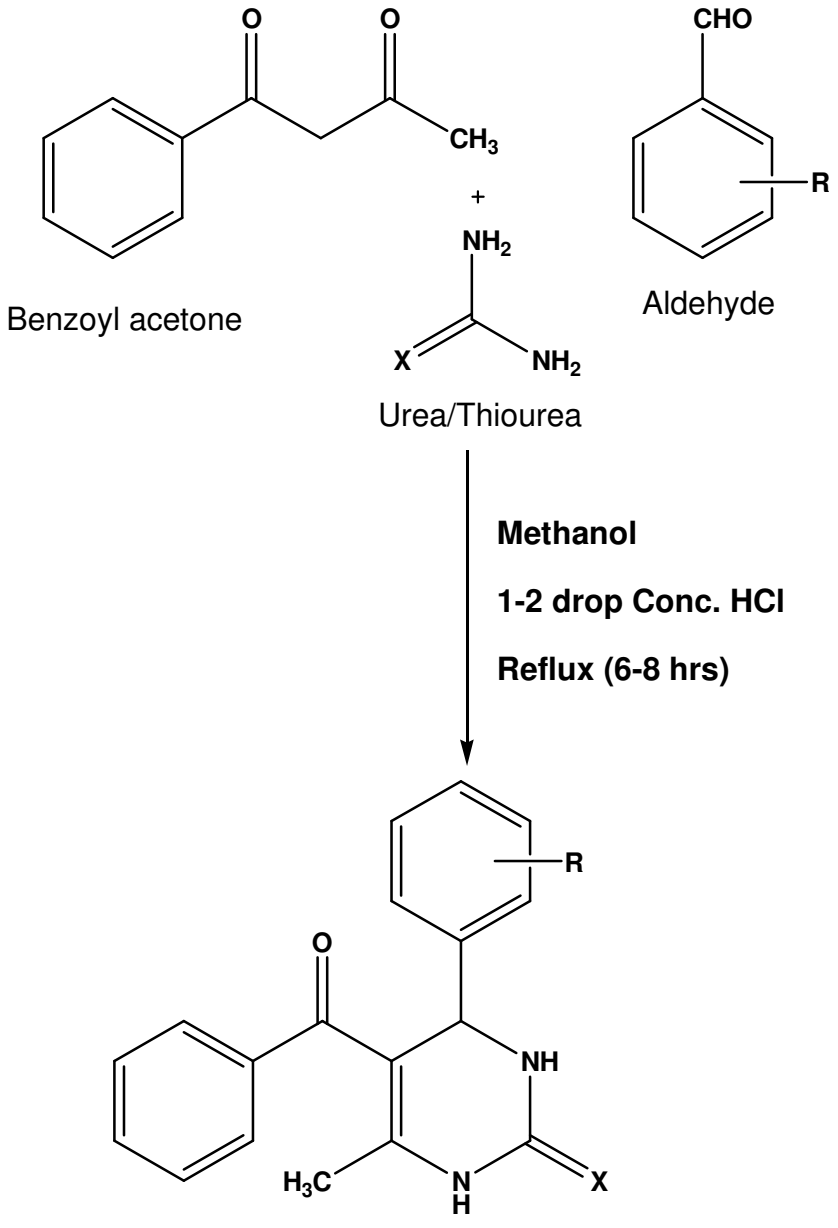
Ethylacetoacetate

Acetophenone

Benzoyl acetone

Synthesis of Benzoyl acetone

REACTION SCHEME-II



X= S, O

Synthesis of Dihydropyrimidine

5.6. Experimental

Method for preparation of benzoylacetone[61]

A suspension of 0.5 mol of granulated sodium metal in dry xylene was prepared and was transferred to a 1-litre three neck flask and the xylene was decanted. The flask was kept in water bath with a stirrer and 100 ml of ethanol was added to the flask. The mixture was continued to reflux till all the sodium was reacted. The residual sodium ethoxide containing flask was then surrounded with ice and 2.0 mol of pure, dry ethyl acetate was added. The stirring was started and 0.5 mol of acetophenones was added dropwise. The reaction commences with the precipitation of sodium salt of benzoylacetone. The stirring was continued for 2 h and was kept in ice box overnight, the precipates were filtered and dried. The dried solid was dissolved in cold water and finally acidified with glacial acetic acid. Crude benzoylacetone was finally purified by distillation under reduced pressure and obtained as colourless crystalline needles. m.p. 61^{o}C, (reported m.p.62^{o}C), yield 62%.

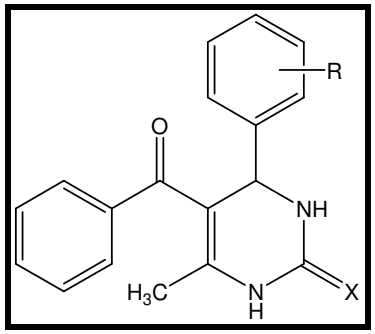
General method of preparation of 5-benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-one

A neat mixture of benzoylacetone (10 mmol), benzaldehyde (10 mmol), urea/thiourea (15 mmol), were taken in a round bottom flask. Ethanol (10 ml) was added to the flask and the contents were dissolved by gently heating the flask. Conc. HCl (1-2 drops)was added to the flask and was then refluxed for 6-8 hours. After cooling at room temperature, the product was filtered and washed with methanol and then recrystallized from ethanol to afford to yield 5-benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-ones.

All the products were characterized by m.p., spectral and analytical data.

The same procedure was followed for the preparation of all the dihydropyrimidinones listed in Table 2.

5.7. Table 2.: Physical data of 5-benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-ones



Codes	Substitution		Molecular formula	Molecular weight	Melting point (^{o}C)	Rf value	% of Yield
	R	X					
JT-151	2-OCH_3	S	$C_{19}H_{18}N_2O_2S$	338.42	218-220	0.57	63
JT-152	2-NO_2	S	$C_{18}H_{15}N_3O_3S$	353.39	120-122	0.49	71
JT-153	4-NO_2	S	$C_{18}H_{15}N_3O_3S$	353.39	152-154	0.51	74
JT-154	4-F	S	$C_{18}H_{15}FN_2OS$	326.39	198-200	0.43	86
JT-155	3-OH	S	$C_{18}H_{16}N_2O_2S$	324.4	158-160	0.62	56

TLC solvent system: Ethyl acetate: Hexane :: 6:4

Ref.: *(a) Kappe, C. O. Tetrahedron **1993**, 49, 6937-6963. (b) Kappe, C. O. Acc. Chem. Res. **2000**, 33, 879-888. (c) Kappe, C. O. Eur. J. Med. Chem. **2000**, 35, 1043-1052*

5.7. Table 2 (contd.): 5-Benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-ones

Codes	Substitution		Molecular formula	Molecular weight	Melting point (^oC)	Rf value	% of Yield
	R	X					
JT-156	4-OH	S	$C_{18}H_{16}N_2O_2S$	324.4	224-226	0.47	52
JT-157	4-CH_3	S	$C_{19}H_{18}N_2OS$	322.42	232-234	0.64	53
JT-158	4-OCH_3	S	$C_{19}H_{18}N_2O_2S$	338.42	200-202	0.53	69
JT-159	4-CN	S	$C_{19}H_{15}N_3OS$	333.41	204-206	0.56	51
JT-160	2,5-Di OCH_3	S	$C_{20}H_{20}N_2O_3S$	368.45	210-212	0.59	64
JT-161	C_4-Furfural	S	$C_{16}H_{14}N_2O_2S$	298.36	240-242	0.44	42
JT-162	C_4-N-Indolyl	S	$C_{20}H_{17}N_3OS$	347.43	120-122	0.41	49
JT-163	4-*N,N*-Di CH_3	S	$C_{20}H_{21}N_3OS$	351.47	200-204	0.68	76
JT-164	3-OCH_3, 4-OH	S	$C_{19}H_{18}N_2O_3S$	354.42	188-190	0.64	79
JT-165	3,5-Di Br, 4-OH	S	$C_{18}H_{14}Br_2N_2O_2S$	482.19	208-210	0.58	82

5.7. Table 2 (contd.): 5-Benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-ones

Codes	Substitution		Molecular formula	Molecular weight	Melting point (^{o}C)	Rf value	% of Yield
	R	X					
JT-166	2-OCH_3	O	$C_{19}H_{18}N_2O_3$	322.36	216-218	0.55	83
JT-167	4-F	O	$C_{18}H_{15}FN_2O_2$	310.32	202-20	0.63	78
JT-168	4-NO_2	O	$C_{18}H_{15}N_3O_4$	337.33	238-240	0.66	74
JT-169	4-OH	O	$C_{18}H_{16}N_2O_3$	308.33	186-188	0.68	58
JT-170	4-CH_3	O	$C_{19}H1_8N_2O_2$	306.36	232-234	0.48	54
JT-171	4-*N,N*-Di CH_3	O	$C_{20}H_{21}N_3O_2$	335.4	238-240	0.61	73
JT-172	Vanillin	O	$C_{19}H_{18}N_2O_4$	338.36	228-230	0.53	84
JT-173	3-OCH_3, 4-OH	O	$C_{19}H_{18}N_2O_4$	338.36	234-236	0.50	75
JT-174	3,5-Di Br, 4-OH	O	$C_{18}H_{14}Br_2N_2O_3$	466.12	190-200	0.52	71

5.8. Spectral study

Infra Red spectra

IR Spectra were recorded on SHIMADZU IR-435 Spectrometer using KBr Pellet method. The N-H stretch in dihydropyrimidines was onserved at 3400-3520 cm^{-1}. In some cases, free hydroxyl group (OH) was observed at 3550-3640 cm^{-1}. The characteristic carbonyl group (C=O) was observed between 1660-1720 cm^{-1}. The dihydropyrimidines showed the ring skeleton vibrations at 1600-1630, 1550-1590, 1550-1520, 1470-1495 cm^{-1}. The methyl groups were observed between 1356-1395 cm^{-1}.

^{1}H NMR spectra

^{1}H NMR Spectra were recorded on a Bruker AC 400 MHz FT-NMR Spectrometer using TMS (Tetramethyl silane) as an internal standard and DMSO-d_6 as a solvent. In the NMR spectra of 5-benzoyl-6-methyl-4-(substituted)phenyl-3,4-dihydropyrimidin-2(1*H*)-ones, various proton values of methyl (-CH_3), aromatic protons (Ar-H), N-H protons and were recorded and in few synthesized compounds, hydroxyl (-OH) were also observed.

The values for methyl (-CH_3) proton is observed between 1.71-1.79 δ ppm .The aromatic protons (Ar-H) shows doublets or multiplets between 6.02-8.24 δ ppm. N-H protons were observed between value 7.8-9.8 δ ppm. The value for hydroxyl proton (-OH) was observed between 8.6-10.3 δ ppm.

^{13}C NMR spectra

^{13}C NMR spectra were recorded on Bruker AC 400 MHz instrument using DMSO as the solvent with TMS (Tetramethyl silane) as respective internal standard.

Mass spectra

The mass spectrum of compounds was recorded by GCMS-QP2010 spectromeyter (EI method). The mass spectrums of compounds were obtained by positive chemical ionization mass spectrometry. The molecular ion peak and the base peak in all compounds were clearly obtained in mass spectral study. The molecular ion peak (M^+) values are in good agreement with molecular formula of all the synthesized compounds.

C, H, N analysis

Elemental analysis of the compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model at CDRI, Lucknow and the results are in agreement with the structures assigned.

5.9. Spectral characterization

4-(2-Methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-151)

IR (KBr) cm^{-1}: 3437 (N-H str.), 2968 (C-H str.), 1680 (>C=O), 1577, 1518, 1506, 1456 (ring skeleton), 1357 (CH_3), 1210 (C=S).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 1.19 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.79 (s, 1H, CH), 6.8-8.02 (m, 9H, Ar-H), 8.43 (s, 1H, NH), 8.60 (s, 1H, NH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 21.40, 47.26, 48.04, 50.81, 54.44, 82.48, 109.54, 119.40, 127.07, 132.95, 136.99, 154.67, 176.84, 198.10.

C, H, N analysis, Calculated: C, 67.43; H, 5.36; N, 8.28. **Found:** C, 67.37; H, 5.23; N, 8.17.

[6-Methyl-4-(2-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-152)

IR (KBr) cm^{-1}: 3447 (N-H str.), 2973 (C-H str.), 1689 (>C=O), 1589, 1519, 1512, 1464 (ring skeleton), 1379 (CH_3), 1168 (C=S).

Mass: [m/e (%)], M. Wt.: 220, 202, 192, 176, 148, 131, 120, 91, 74, 65, 44.

C,H,O analysis, Calculated: C, 60.00; H, 3.66; O, 36.33. **Found:** C, 60.23; H, 3.54; O, 36.24.

[6-Methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-153)

IR (KBr) cm^{-1}: 3468 (N-H str.), 2979 (C-H str.), 1696 (>C=O), 1593, 1552, 1515, 1473 (ring skeleton), 1384 (CH_3), 1206 (C=S).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 1.27 (s, 3H, CH_3), 4.76 (s, 1H, CH), 6.6-7.89 (m, 9H, Ar-H), 8.46 (2s, 2H, 2NH).

C, H, N analysis, Calculated: C, 61.18; H, 4.28; N, 11.89. **Found:** C, 61.12; H, 4.24; N, 11.82.

4-(4-Fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-154)

IR (KBr) cm^{-1}: 3414 (N-H str.), 2986 (C-H str.), 1675 (>C=O), 1579, 1536, 1516, 1487 (ring skeleton), 1377 (CH_3), 1186 (C=S), 780 (C-F).

C, H, N analysis, Calculated: C, 66.24; H, 4.63; F, 5.82; N, 8.58. **Found:** C, 66.18; H, 4.62; F, 5.78.

[4-(3-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-155)

IR (KBr) cm^{-1}: 3606 (free OH), 3457 (N-H str.), 2957 (C-H str.), 1678 (>C=O), 1602, 1580, 1503, 1484 (ring skeleton), 1379 (CH_3), 1176 (C=S).

C, H, N analysis, Calculated: C, 66.64; H, 4.97; N, 8.64. **Found:** C, 66.56; H, 4.92; N, 8.61.

[4-(4-Hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-156)

IR (KBr) cm^{-1}: 3586 (free OH), 3465 (N-H str.), 2984 (C-H str.), 1676 (>C=O), 1592, 1523, 1499, 1456 (ring skeleton), 1364 (CH_3), 1194 (C=S).

C, H, N analysis, Calculated: C, 66.64; H, 4.97; N, 8.64. **Found:** C, 66.54; H, 4.91; N, 8.58.

[6-Methyl-4-(4-methylphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-157)

IR (KBr) cm^{-1}: 3496 (N-H str.), 2983 (C-H str.), 1669 (>C=O), 1565, 1520, 1524, 1468 (ring skeleton), 1379, 1380 (CH_3), 1063 (C=S).

C, H, N analysis, Calculated: C, 70.78; H, 5.63; N, 8.69. **Found:** C, 70.75; H, 5.61; N, 8.66.

[4-(4-Methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-158)

IR (KBr) cm^{-1}: 3489 (N-H str.), 2944 (C-H str.), 1678 (>C=O), 1613, 1580, 1503, 1456 (ring skeleton), 1423 (OCH_3), 1379 (CH_3), 1123 (C=S).

C, H, N analysis, Calculated: C, 67.43; H, 5.36; N, 8.28. **Found:** C, 67.43; H, 5.36; N, 8.28.

4-(5-Benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzonitrile (JT-159)

IR (KBr) cm^{-1}: 3437 (N-H str.), 2943 (C-H str.), 1714 (>C=O), 2229 (C=N), 1593, 1562, 1500, 1460 (ring skeleton), 1383 (CH_3), 900 (mono substd.), 1204 (C=S).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 1.74 (s, 3H, CH_3), 5.48 (s, 1H, CH), 7.3-7.9 (m, 9H, Ar-H), 9.76 (s, 1H, NH), 10.35 (s, 1H, NH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 18.09, 39.9, 77.88, 110.60, 118.05, 126.95, 131.41, 139.92, 142.61, 147.69, 174.76, 194.24.

Mass: [m/e (%)], M. Wt.: 333, 318, 300, 273, 231, 201, 169, 144, 105, 77, 67, 42.

C, H, N analysis, Calculated: C, 68.45; H, 4.53; N, 12.60. **Found:** C, 68.36; H, 4.7; N, 12.57.

[4-(2,5-Dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl)methanone (JT-160)

IR (KBr) cm^{-1}: 3459 (N-H str.), 2935 (C-H str.), 1689 (>C=O), 1602, 1585, 1506, 1466 (ring skeleton), 1423, 1457 (OCH_3), 1374 (CH_3), 1208 (C=S).

C, H, N analysis, Calculated: C, 65.20; H, 5.47; N, 7.60. **Found:** C, 65.16; H, 5.43; N, 7.47.

[4-(2-Furyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-161)

IR (KBr) cm^{-1}: 3509 (N-H str.), 2923 (C-H str.), 1689 (>C=O), 1601, 1581, 1553, 1486 (ring skeleton), 1392 (CH_3), 1256 (C-O-C, ether linkage), 1192 (C=S).

C, H, N analysis, Calculated: C, 64.41; H, 4.73; N, 9.39. **Found:** C, 64.34; H, 4.70; N, 9.33.

[4-(1*H*-Indol-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl) methanone (JT-162)

IR (KBr) cm^{-1}: 3513, 3478 (N-H str.), 2936 (C-H str.), 1698 (>C=O), 1600, 1584, 1521, 1476 (ring skeleton), 1397 (CH_3), 1123 (C=S).

C, H, N analysis, Calculated: C, 69.14; H, 4.93; N, 12.09. **Found:** C, 69.12; H, 4.87; N, 12.03.

{4-[4-(Dimethylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl}(phenyl) methanone (JT-163)

IR (KBr) cm^{-1}: 3560 (N-H str.), 3049 (C-H str.), 1651 (>C=O), 1593, 1568, 1554, 1429 (ring skeleton), 1398, 1386, 1379 (CH_3), 1212 (C=S).

^{1}H NMR 400 MHz (DMSO-d_6, δ ppm): 1.73 (s, 3H, CH_3), 3.07 (s, 6H, CH_3), 4.40 (d, 1H, CH, *J*= 3.48), 7.2-7.8 (m, 9H, Ar-H), 9.52 (s, 1H, NH), 10.18 (s, 1H, NH).

^{13}C NMR 400 MHz (DMSO-d_6, δ ppm): 17.93, 43.59, 54.69, 110.05, 117.46, 127.59, 131.39, 139.91, 141.73, 174.34, 194.44.

Mass: [m/e (%)], M. Wt.: 351, 334, 291, 246, 187, 120, 105, 77, 44.

C, H, N analysis, Calculated: C, 68.35; H, 6.02; N, 11.96. **Found:** C, 68.32; H, 5,99; N, 11.92.

[4-(4-Hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl)methanone (JT-164)

IR (KBr) cm^{-1}: 3603 (OH str), 3491 (N-H str.), 2976 (C-H str.), 1723 (>C=O), 1606, 1578, 1514, 1489 (ring skeleton), 1428 (OCH_3), 1399 (CH_3), 1162 (C=S).

C, H, N analysis, Calculated: C, 64.39; H, 5.12; N, 7.90. **Found:** C, 64.34; H, 5.07; N, 7.68.

[4-(3,5-Dibromo-4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl)methanone (JT-165)

IR (KBr) cm^{-1}: 3598 (OH str), 3503 (N-H str.), 2986 (C-H str.), 1711 (>C=O), 1592, 1576, 1512, 1489 (ring skeleton), 1409 (CH_3), 1153 (C=S).

C, H, N analysis, Calculated: C, 44.84; H, 2.93; N, 5.81. **Found:** C, 44.77; H, 2.89; N, 5.79.

5-Benzoyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-166)

IR (KBr) cm^{-1}: 3519 (N-H str.), 2946 (C-H str.), 1763, 1672 (>C=O), 1605, 1582, 1515, 1459 (ring skeleton), 1432 (OCH_3), 1383 (CH_3).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 1.80 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 5.63 (d, 1H, CH, *J* = 3.0), 6.82-7.57 (m, 9H, Ar-H), 6.91 (s, 1H, NH), 9.00 (s, 1H, NH).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 17.81, 50.53, 54.53, 108.06, 110.16, 119.92, 127.92, 131.06, 140.03, 144.24, 153.32, 155.79, 194.07.

C, H, N analysis, Calculated: C, 70.79; H, 5.63; N, 8.69. **Found:** C, 70.73; H, 5.61; N, 8.64.

5-Benzoyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-167)

IR (KBr) cm^{-1}: 3508 (N-H str.), 2931 (C-H str.), 1685 (>C=O), 1591, 1556, 1508, 1487 (ring skeleton), 1344 (CH_3), 732 (C-F).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 1.71 (s, 3H, CH_3), 5.43 (d, 1H, CH, *J* = 2.96), 6.9-7.49 (m, 9H, Ar-H), 7.63 (s, 1H, NH), 9.10 (s, 1H, NH).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 18.42, 54.76, 109.50, 114.78, 127.90, 131.03, 139.94, 140.75, 144.81, 152.37, 160.07, 162.48, 194.40.

Mass: [m/e (%)], M. Wt.: 310, 295, 266, 248, 233, 215, 205, 185, 172, 162, 146, 133, 122, 105, 95, 95, 77, 67, 42

C, H, N analysis, Calculated: C, 69.67; H, 4.87; N, 9.03. **Found:** C, 69.63; H, 4.82; N, 9.00.

5-Benzoyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-168)

IR (KBr) cm^{-1}: 3487 (N-H str.), 2982 (C-H str.), 1723, 1691 (>C=O), 1608, 1562, 1512, 1482 (ring skeleton), 1386 (CH_3).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 1.71 (s, 3H, CH_3), 5.57 (d, 1H, CH, *J* = 3.24), 7.37-8.15 (m, 9H, Ar-H), 7.80 (d, 1H, NH, *J* = 3.76), 9.26 (s, 1H, NH).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 18.69, 54.76, 108.64, 123.19, 127.35, 131.10, 140.63, 146.37, 150.98, 152.31, 194.19.

C, H, N analysis, Calculated: C, 64.09; H, 4.48; N, 12.46. **Found:** C, 64.03; H, 4.43; N, 12.42.

5-Benzoyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-169)

IR (KBr) cm^{-1}: 3601 (OH str.), 3497 (N-H str.), 2944 (C-H str.), 1721, 1689 (>C=O), 1602, 1580, 1523, 1469 (ring skeleton), 1367 (CH_3).

C, H, N analysis, Calculated: C, 68.35; H, 6.02; N, 11.96. **Found:** C, 68.31; H, 5.89; N, 11.93.

5-Benzoyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-170)

IR (KBr) cm^{-1}: 3500 (N-H str.), 2935 (C-H str.), 1701, 1695 (>C=O), 1624, 1537, 1477, 1452 (ring skeleton), 1379, 1332 (CH_3).

^{1}H NMR 400 MHz (DMSO-d$_6$, δ ppm): 1.71 (s, 3H, CH_3), 2.27, (s, 3H, CH_3), 5.41 (d, 1H, CH, *J* = 2.8), 7.05-7.48 (m, 9H, Ar-H), 7.48 (s, 1H, NH), 9.02 (d, 1H, NH, *J* = 1).

^{13}C NMR 400 MHz (DMSO-d$_6$, δ ppm): 18.31, 20.56, 55.29, 109.84, 128.62, 131.01, 136.33, 140.88, 144.00, 152.60, 194.57.

C, H, N analysis, Calculated: C, 74.49; H, 5.92; N, 9.14. **Found:** C, 74.45; H, 5.88; N, 9.12.

5-Benzoyl-4-[4-(dimethylamino)phenyl]-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-171)

IR (KBr) cm^{-1}: 3566 (N-H str.), 2032 (C-H str.), 1765, 1687 (>C=O), 1602, 1596, 1545, 1479 (ring skeleton), 1383, 1334, 1313 (CH_3).

C, H, N analysis, Calculated: C, 71.62; H, 6.31; N, 12.53. **Found:** C, 71.57; H, 6.27; N, 12.48.

5-Benzoyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-172)

IR (KBr) cm^{-1}: 3609 (OH str.), 3486 (N-H str.), 2965 (C-H str.), 1766, 1689 (>C=O), 1597, 1586, 1523, 1467 (ring skeleton), 1443 (OCH_3), 1390 (CH_3).

C, H, N analysis, Calculated: C, 67.44; H, 5.36; N, 8.28. **Found:** C, 67.38; H, 5.32; N, 8.25.

5-Benzoyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-173)

IR (KBr) cm^{-1}: 3600, 1583 (OH str.), 3453 (N-H str.), 2977 (C-H str.), 1763, 1659 (>C=O), 1599, 1546, 1490, 1430 (ring skeleton), 1436 (OCH_3), 1380 (CH_3).

C, H, N analysis, Calculated: C, 66.66; H, 4.97; N, 8.64.**Found:** C, 66.62; H, 4.93; N, 8.62.

5-Benzoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-174)

IR (KBr) cm^{-1}: 3593 (OH str.), 3454 (N-H str.), 2881 (C-H str.), 1699 (>C=O), 1618, 1564, 1462 (ring skeleton), 1386 (CH_3).

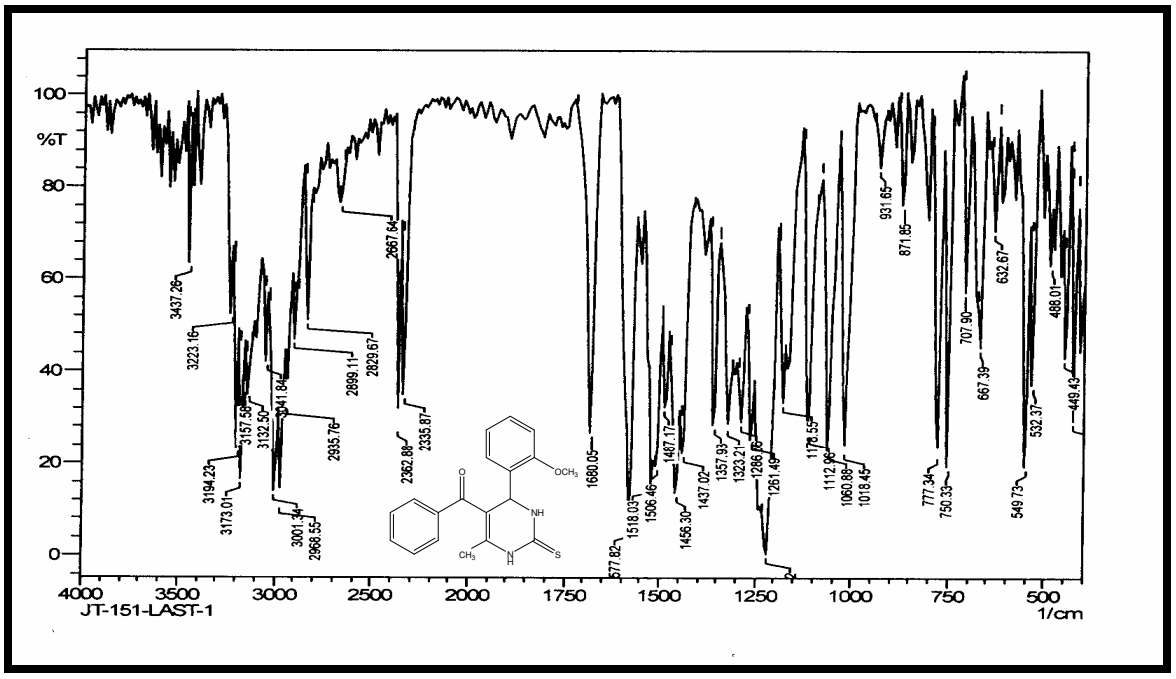
C, H, N analysis, Calculated: C, 46.38; H, 3.03; N, 6.01. **Found:** C, 46.32; H, 3.00; N, 5.97.

5.10. Conclusion

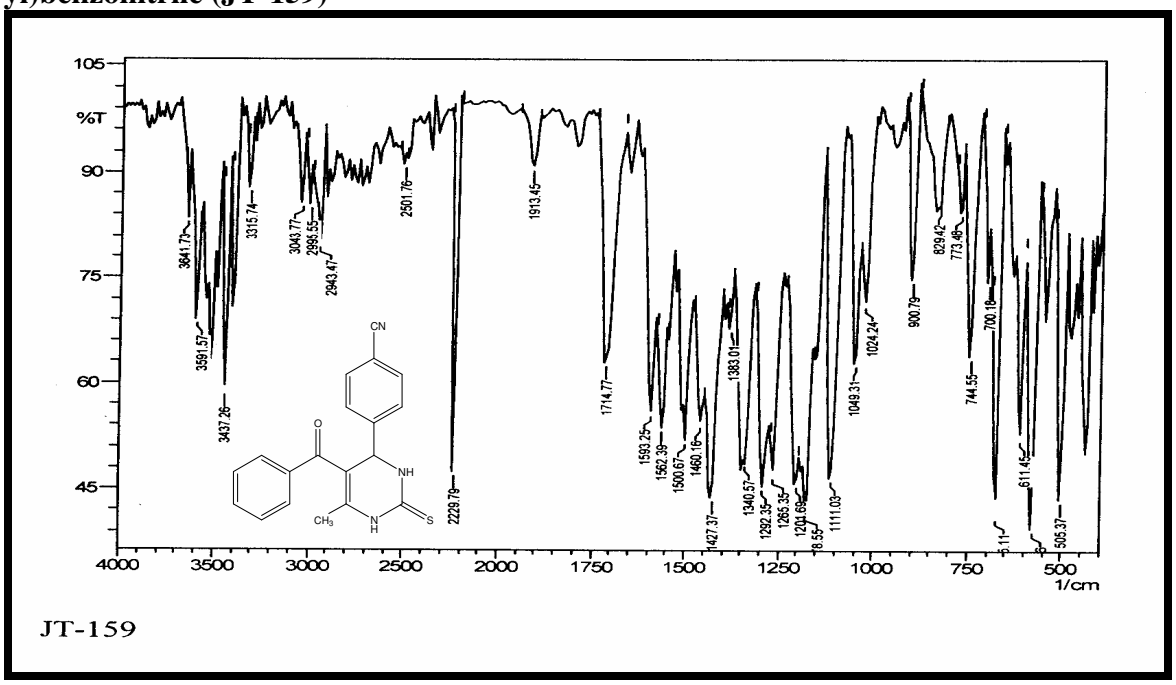
Total 24 5-benzoyl-6-methyl-4-(substituted)phenyl -3,4-dihydropyrimidin-2(1*H*)-ones were synthesized in this chapter. The compounds are characterized by IR, ^{1}H NMR, Mass spectral data and elemental analysis. All the compounds have been sent for anti-cancer activity and the results are awaited.

5.11. Spectra of some 5-benzoyl-6-methyl-4-(substituted)phenyl -3,4-dihydropyrimidin-2(1*H*)-ones

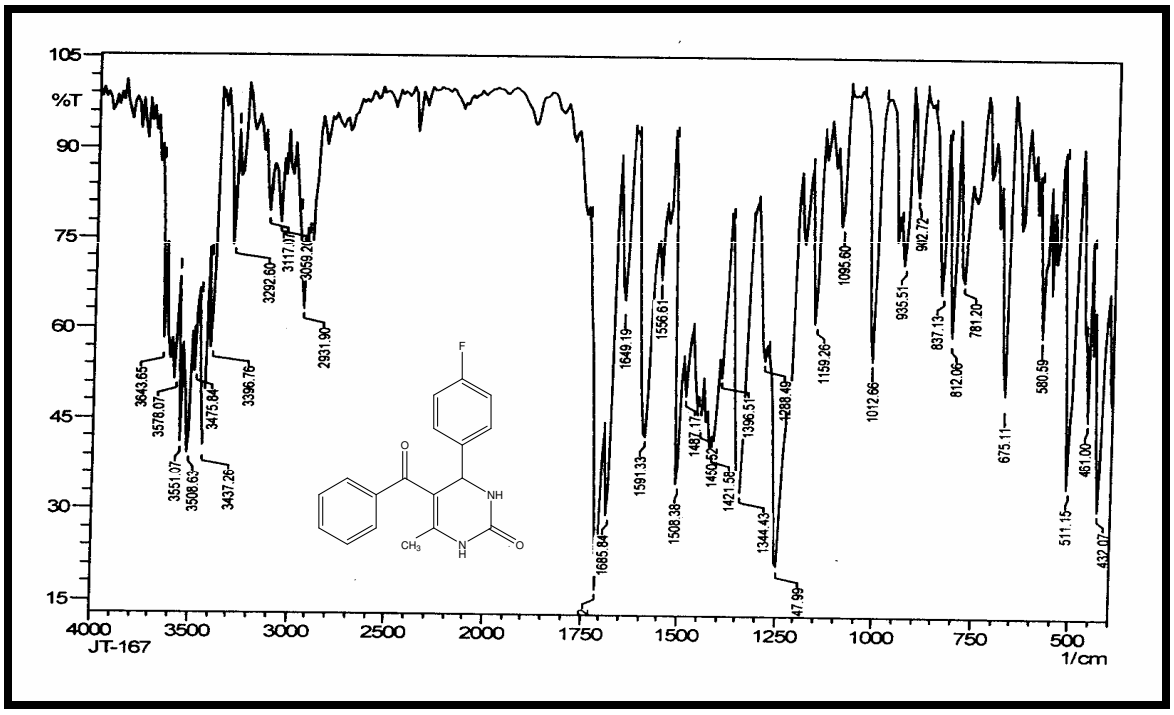
Infra Red spectrum of 4-(2-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl)methanone (JT-151)



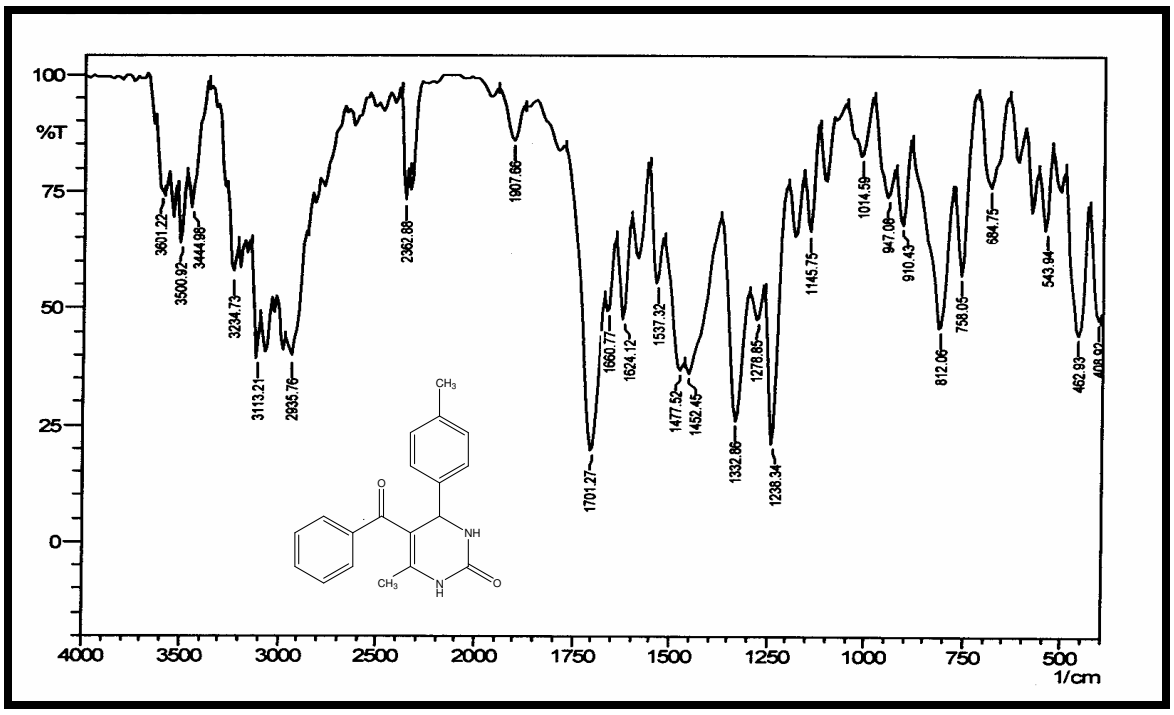
IR spectrum of 4-(5-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzonitrile (JT-159)



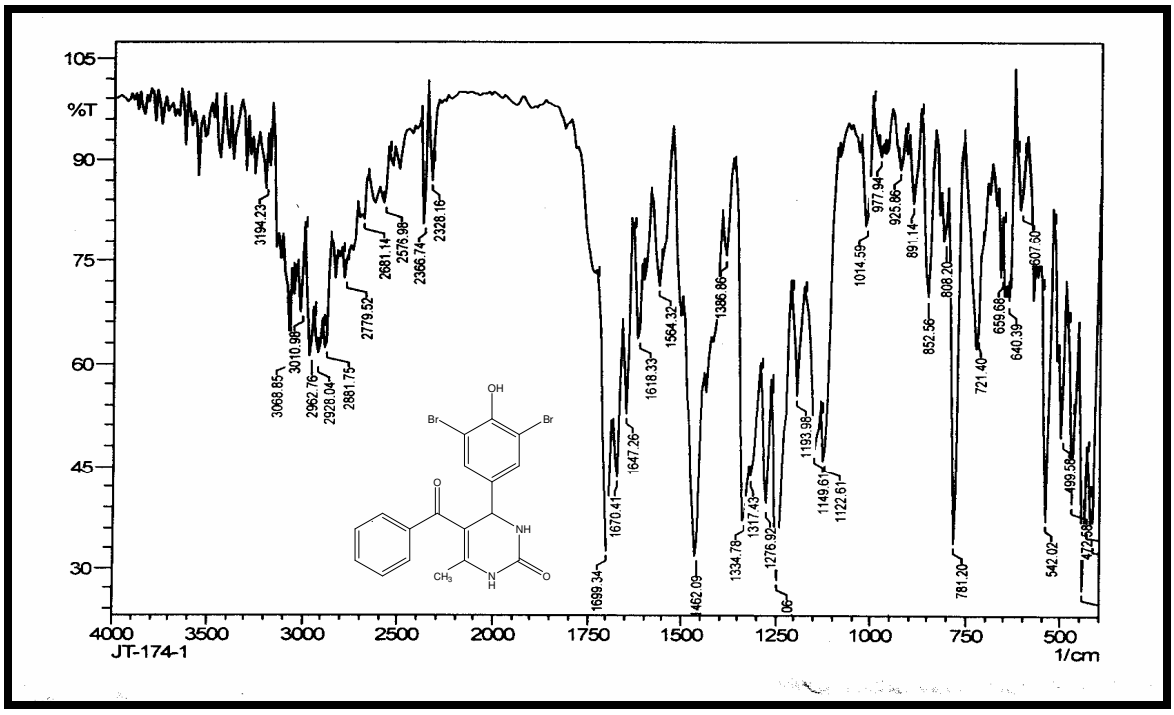
IR spectrum of 5-benzoyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-167)



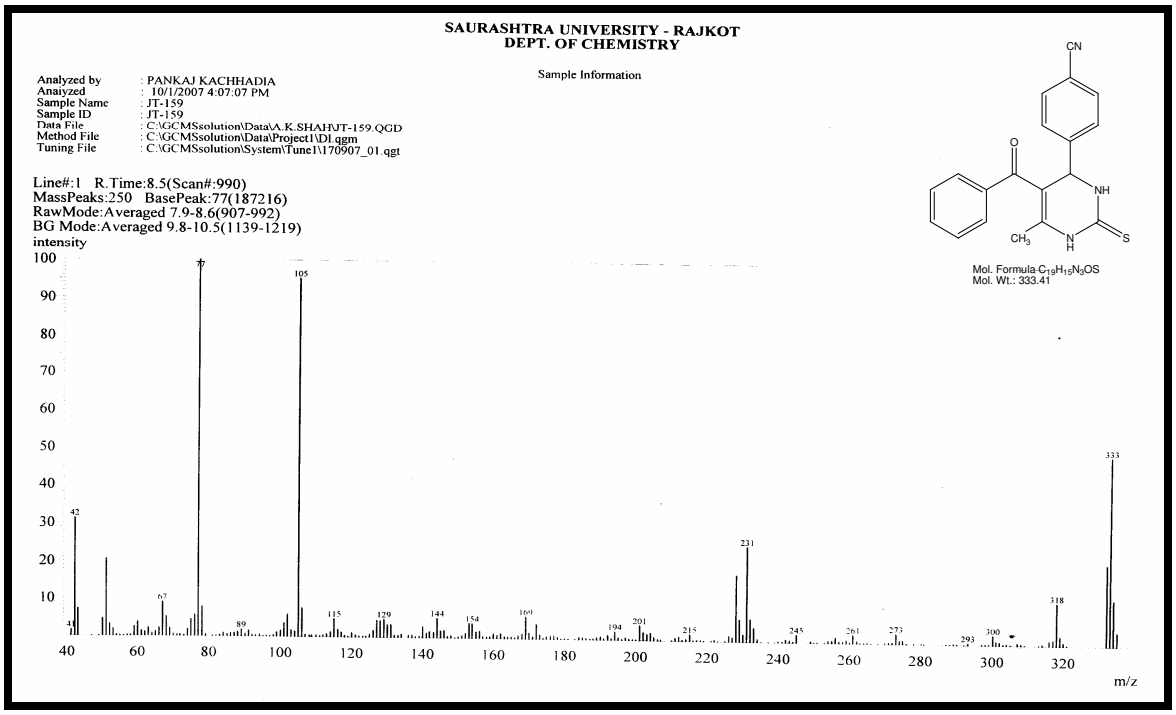
IR spectrum of 5-benzoyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-170)



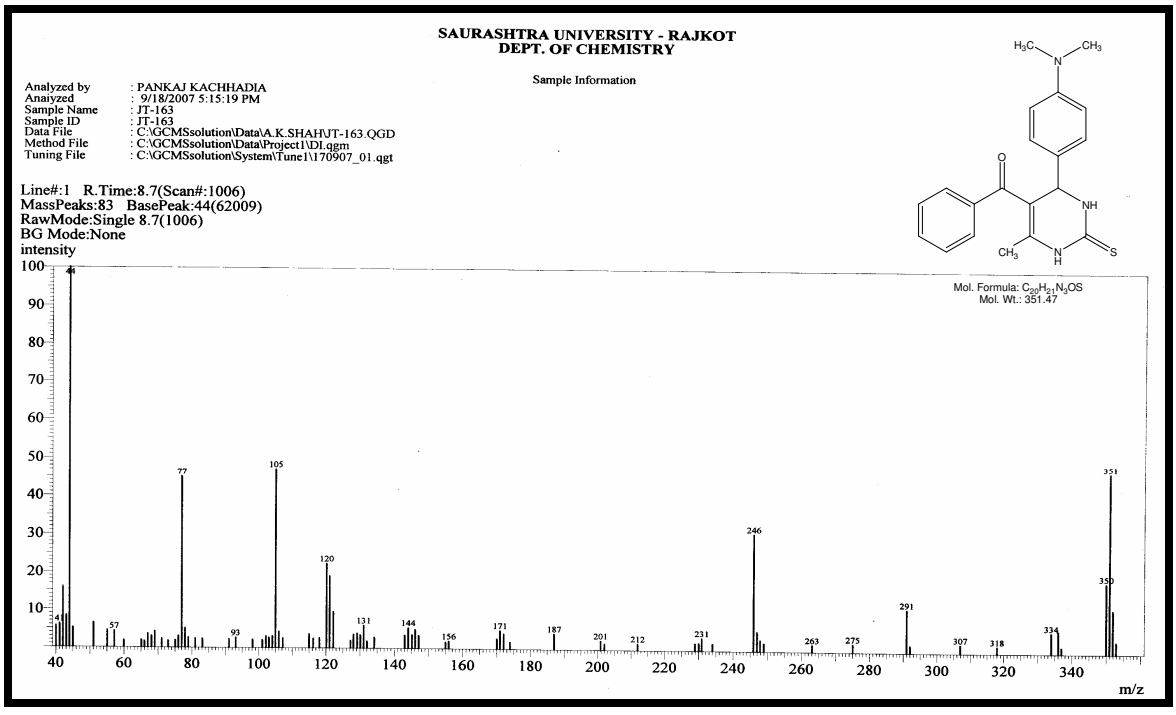
IR spectrum of 5-benzoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-174)



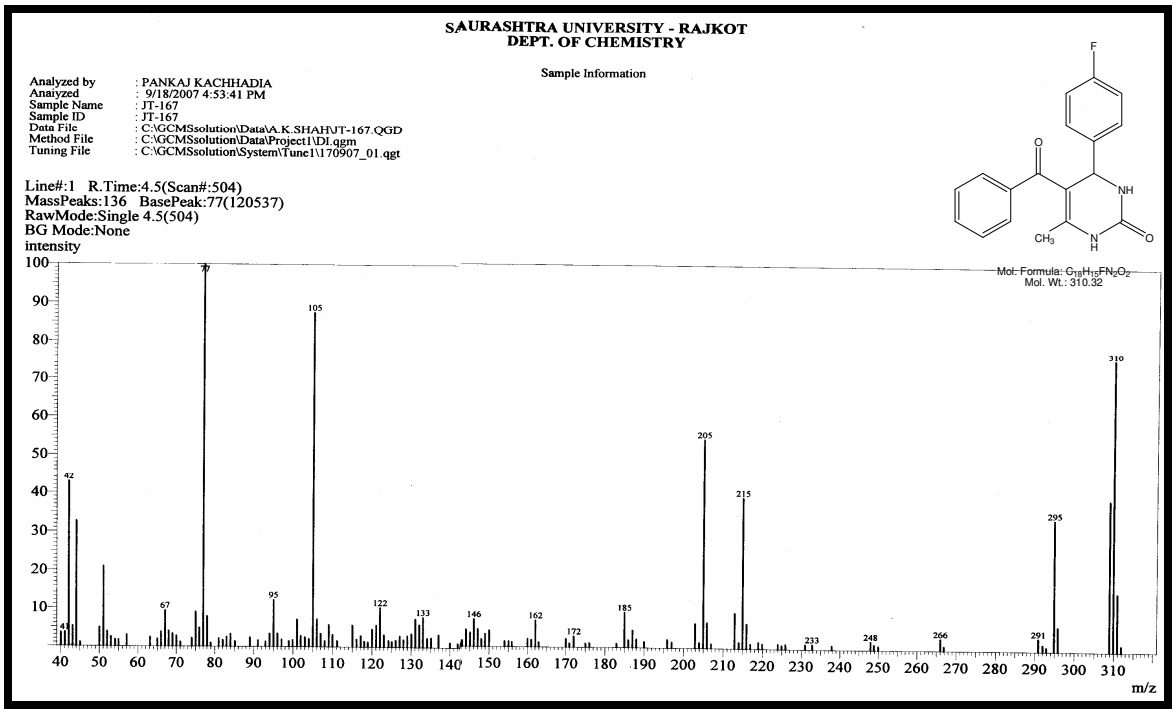
Mass spectrum of 4-(5-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzonitrile (JT-159)



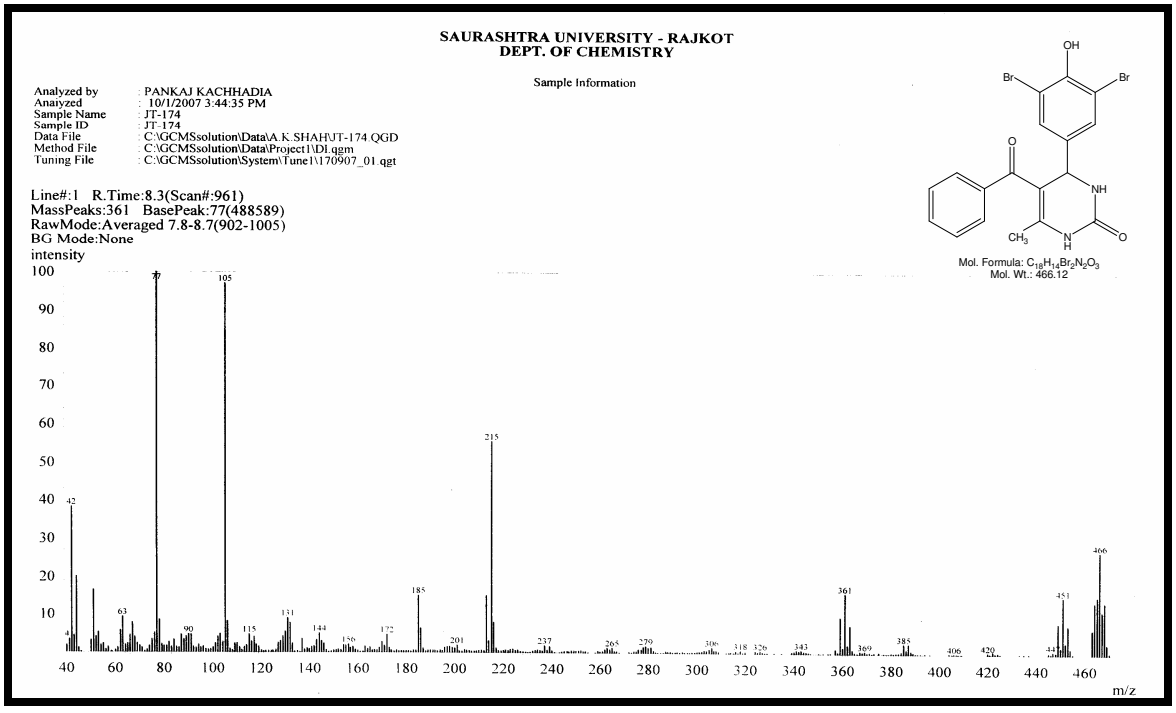
Mass spectrum of {4-[4-(dimethylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl}(phenyl)methanone (JT-163)



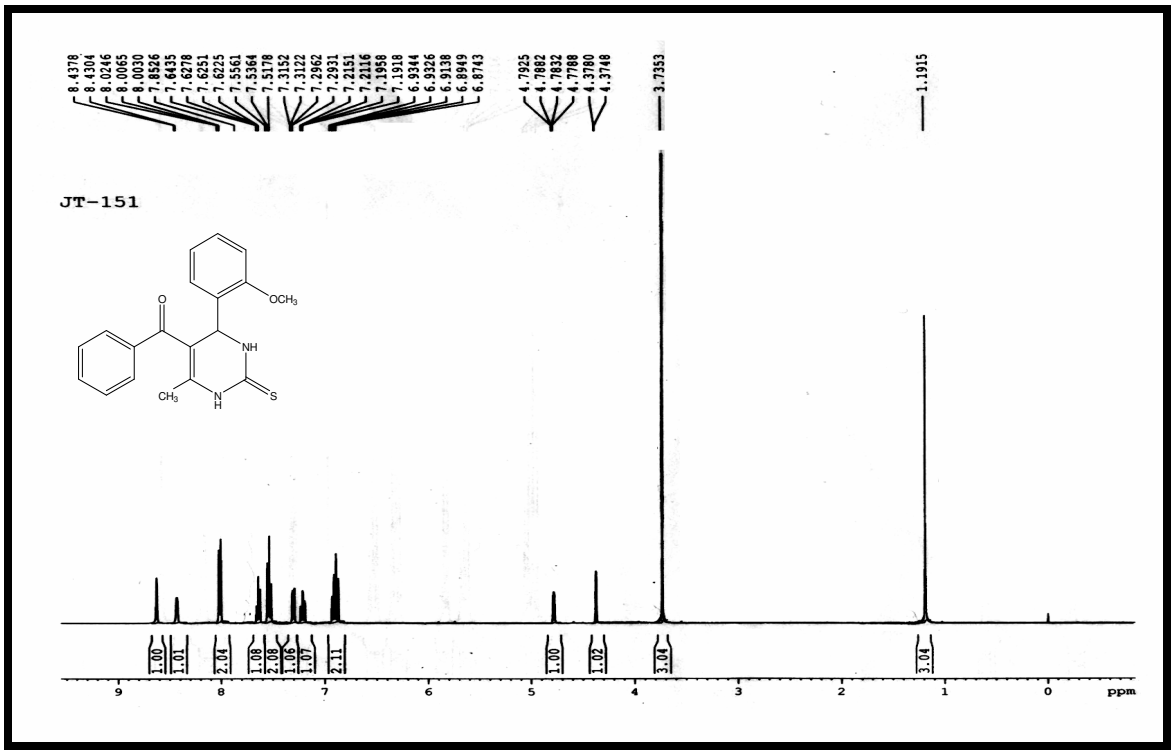
Mass spectrum of 5-benzoyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-167)

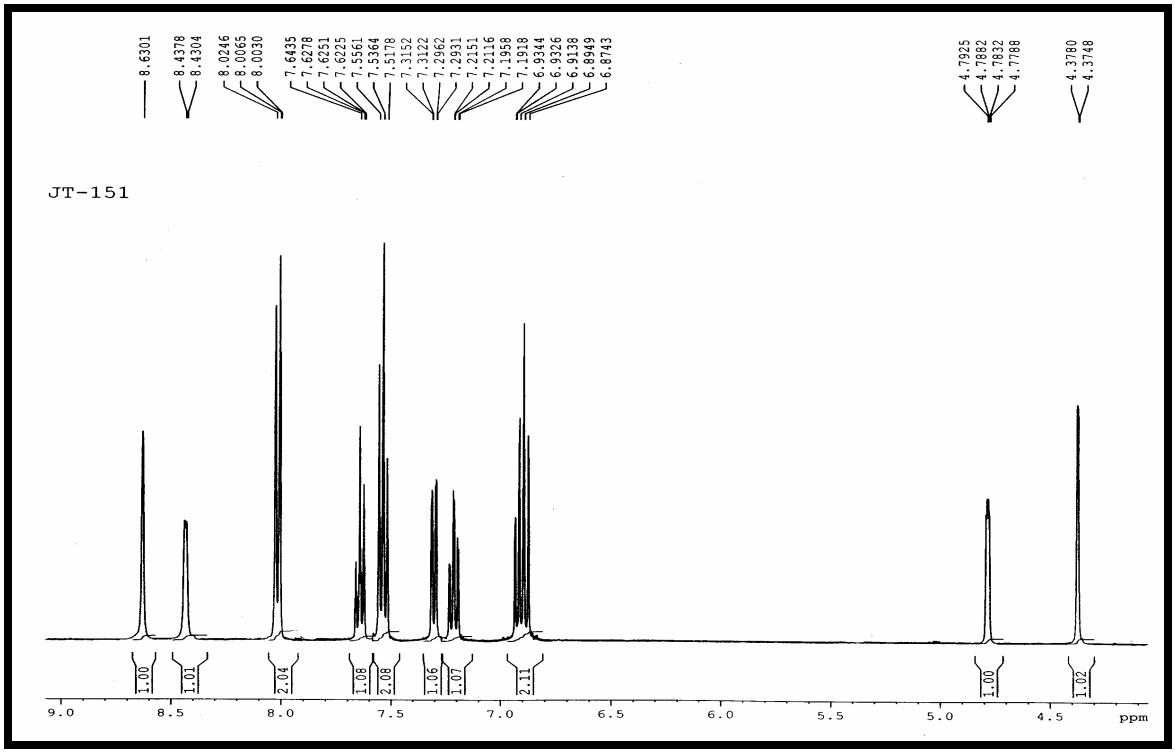


Mass spectrum of 5-benzoyl-4-(3,5-dibromo-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-174)

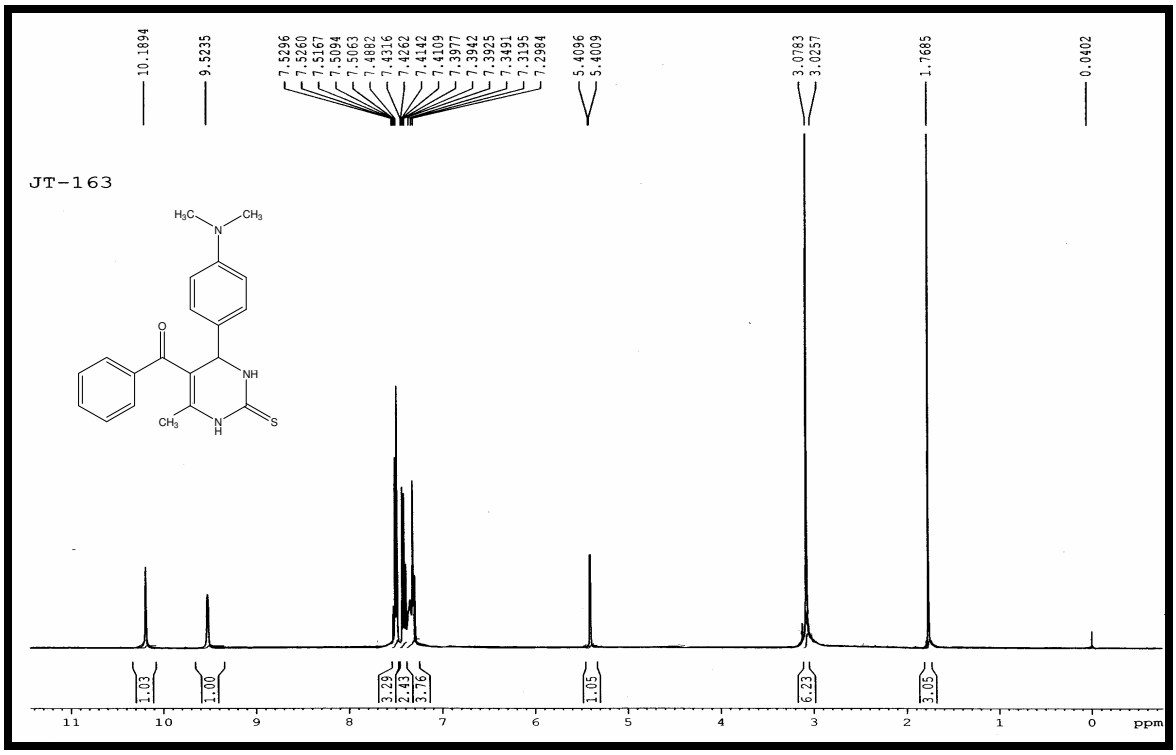


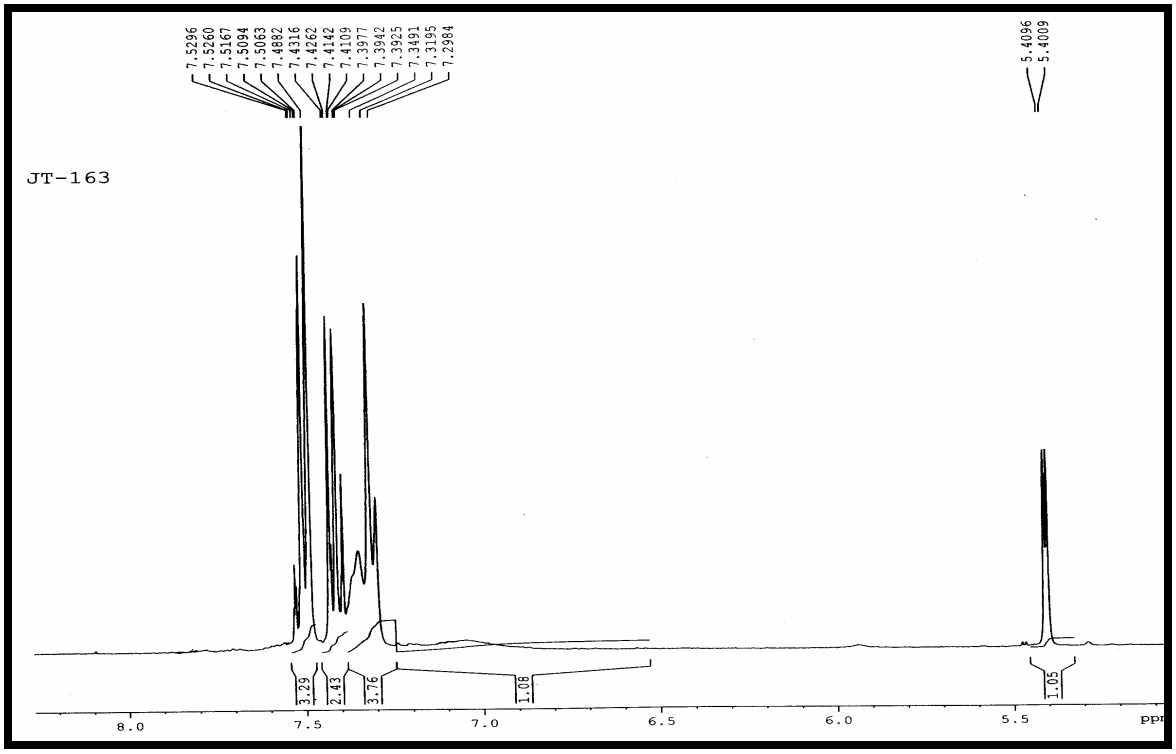
^{1}H NMR spectrum of 4-(2-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl)methanone (JT-151)



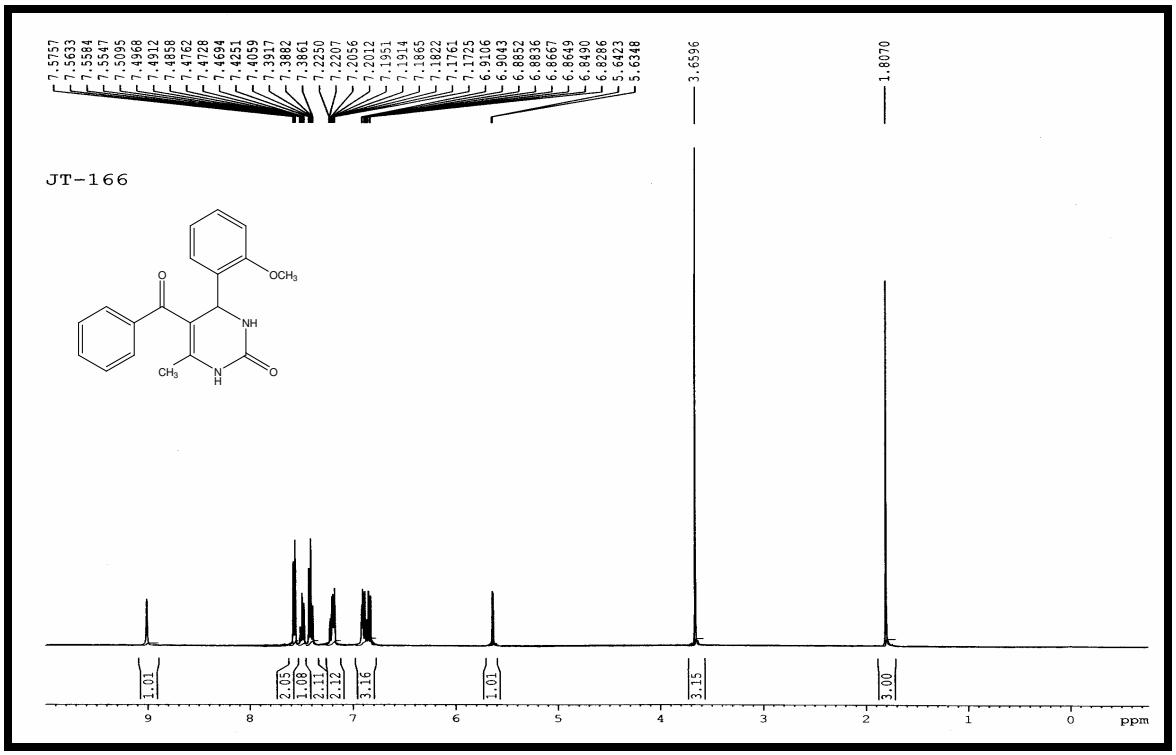


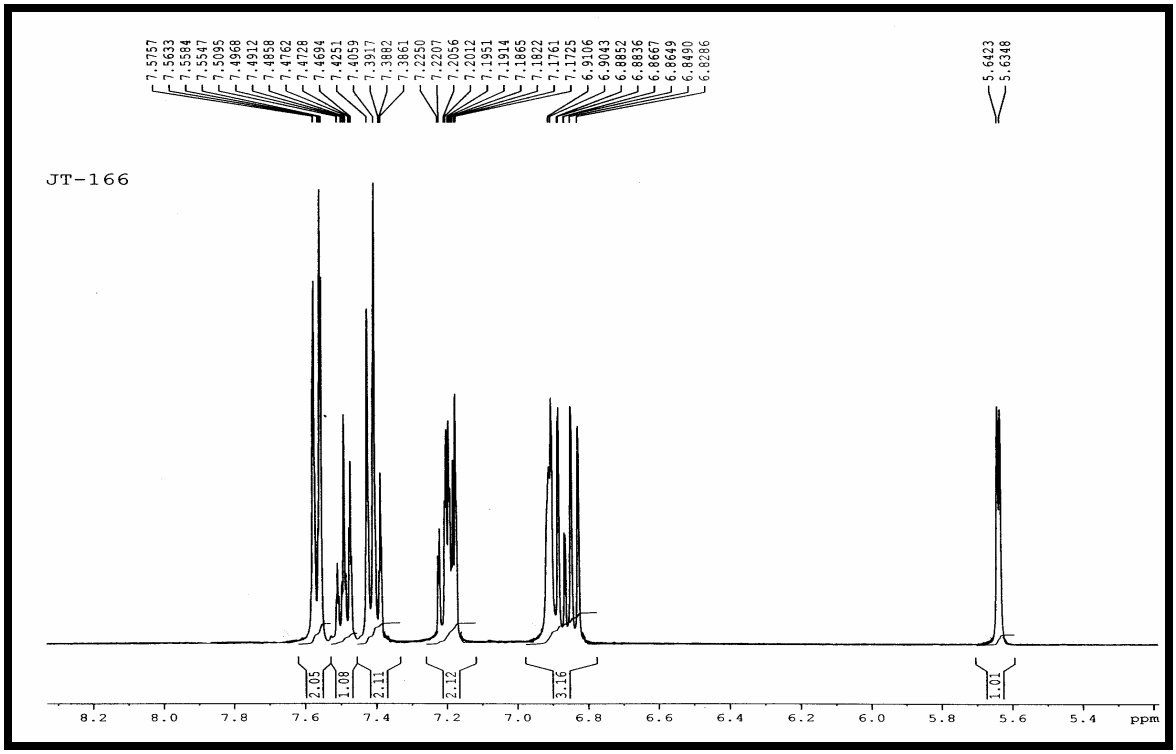
^{1}H NMR spectrum of {4-[4-(dimethylamino)phenyl]-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl}(phenyl)methanone (JT-163)



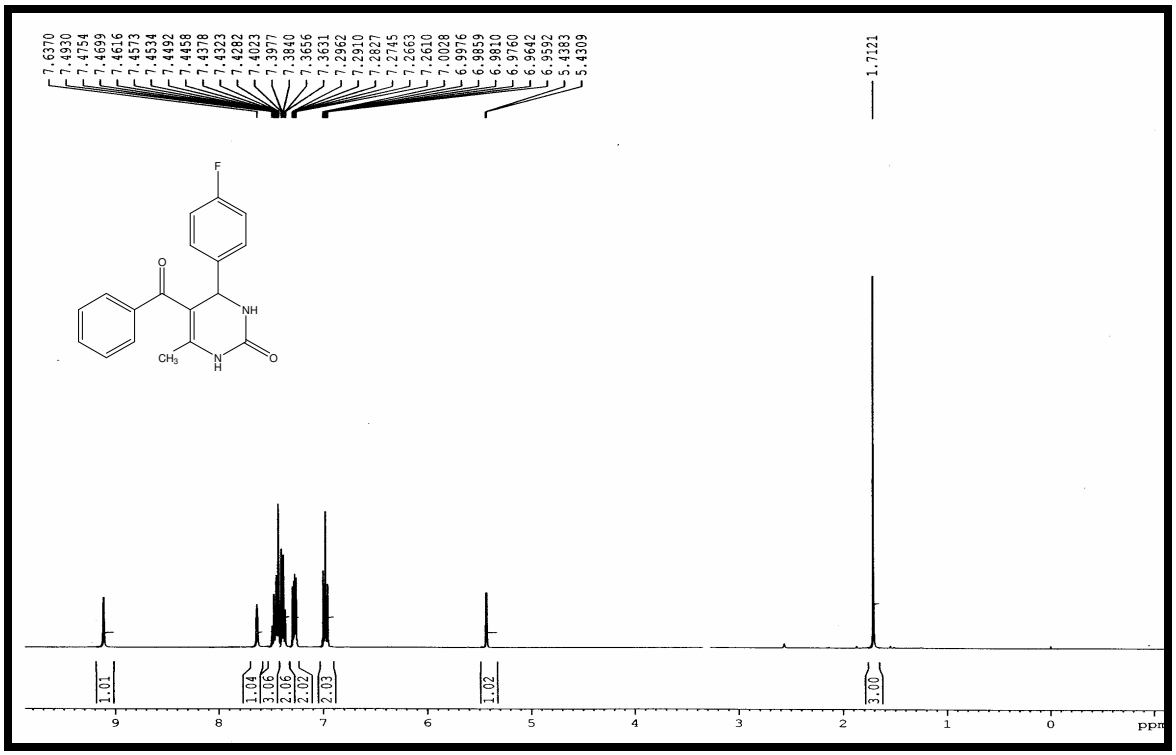


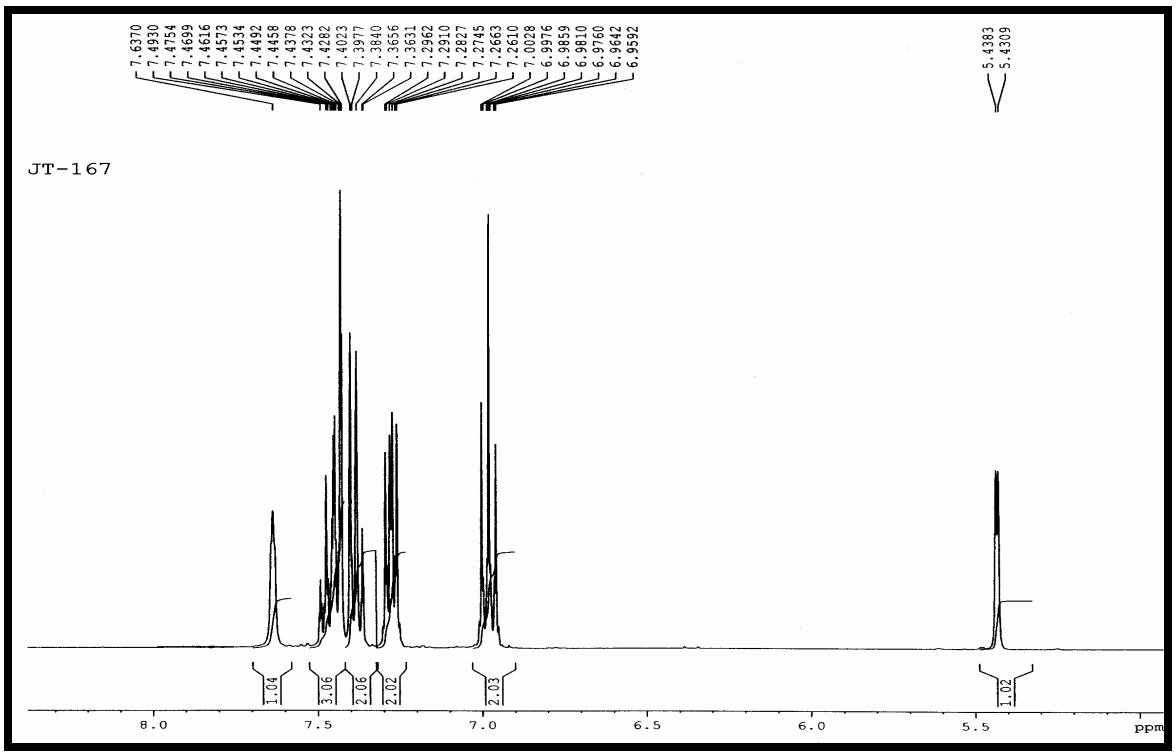
^{1}H NMR spectrum of 5-benzoyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-166)



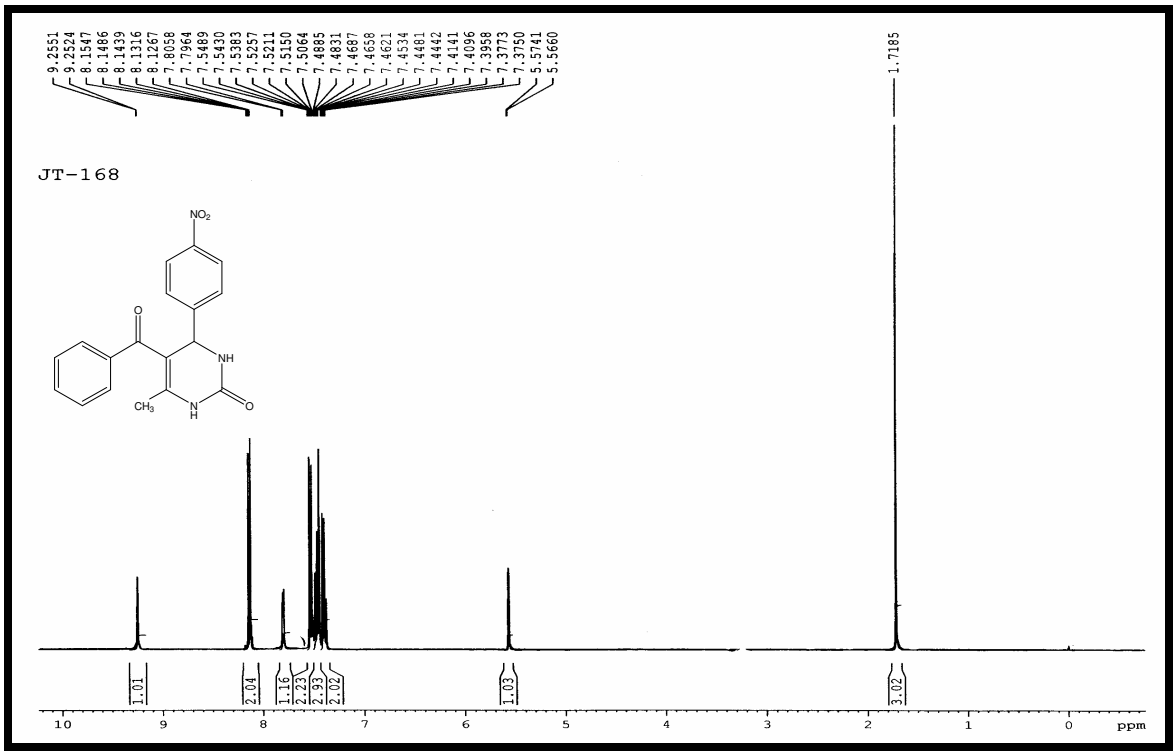


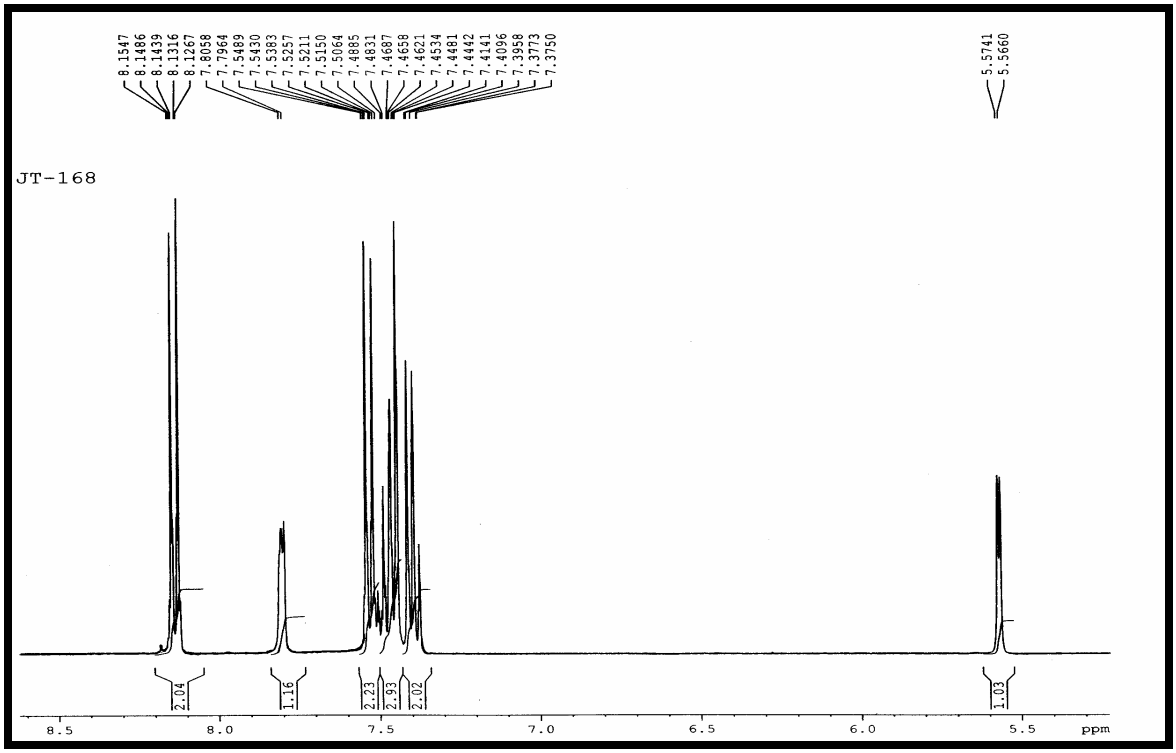
^{1}H NMR spectrum of 5-benzoyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-167)



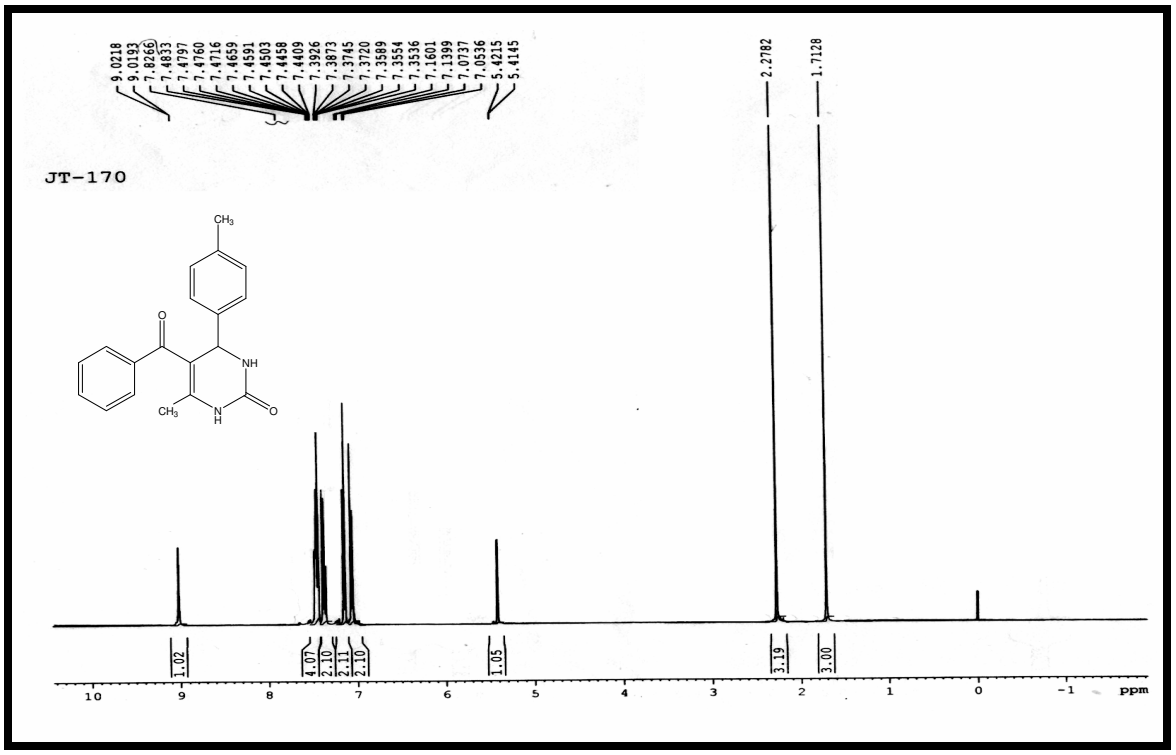


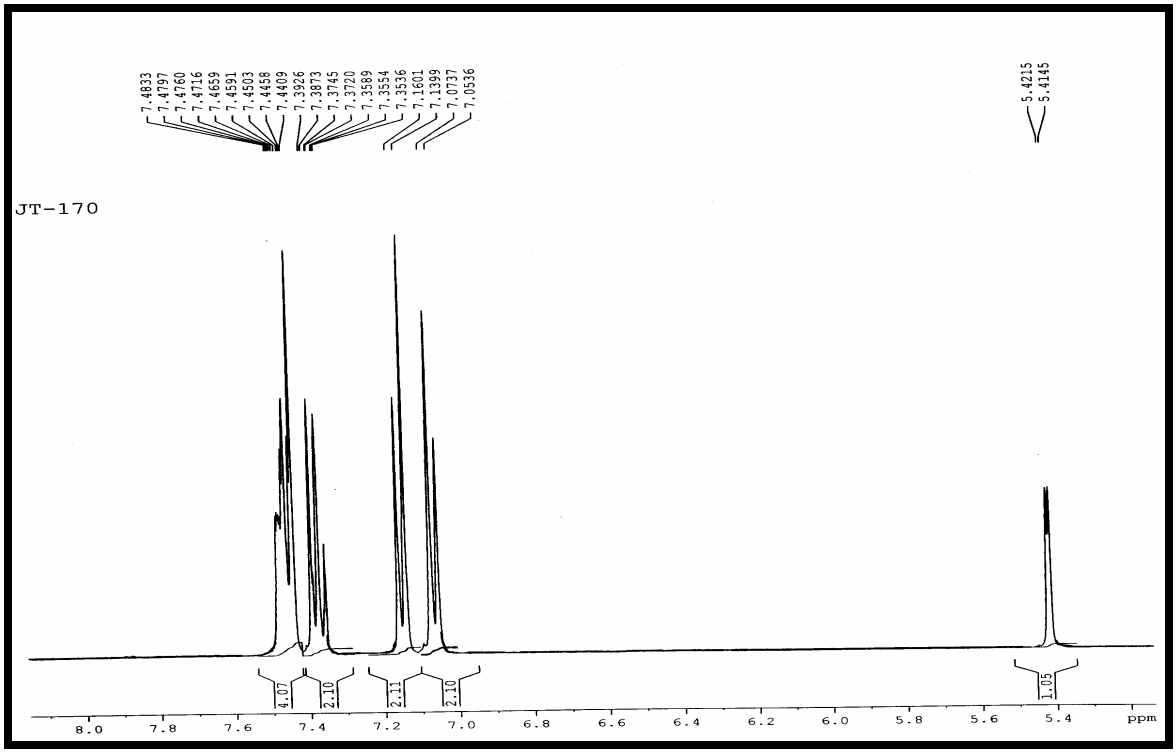
^{1}H NMR spectrum of 5-benzoyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-168)



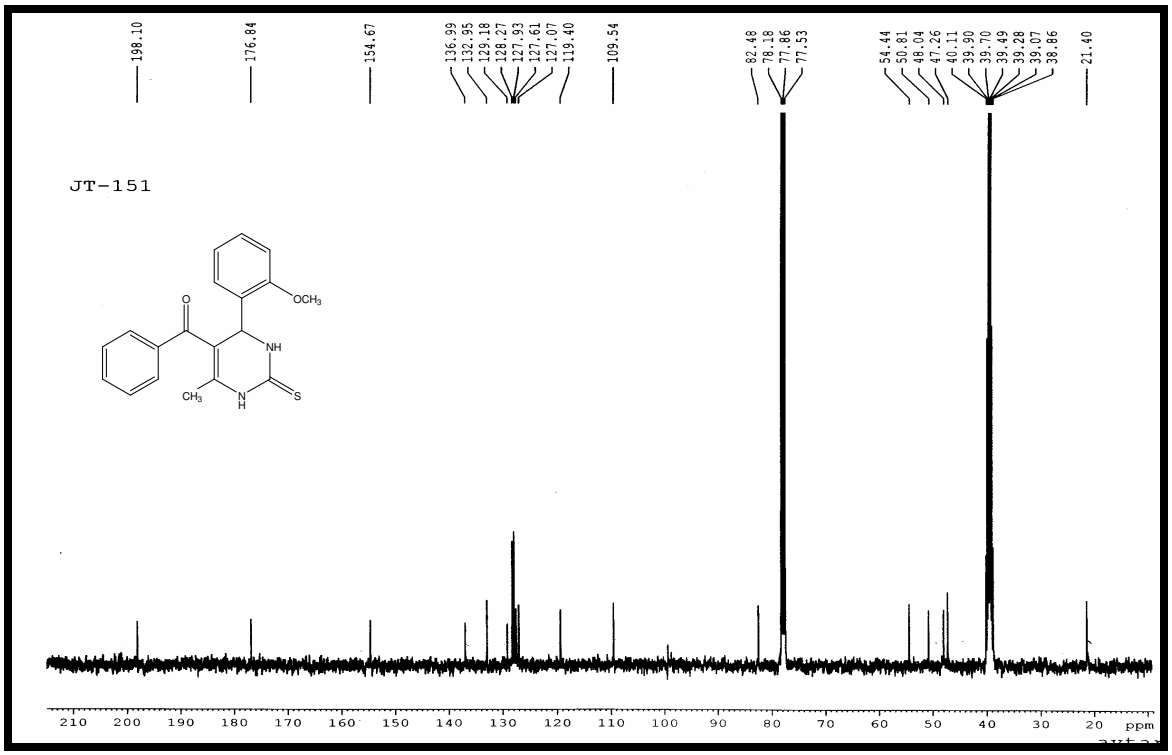


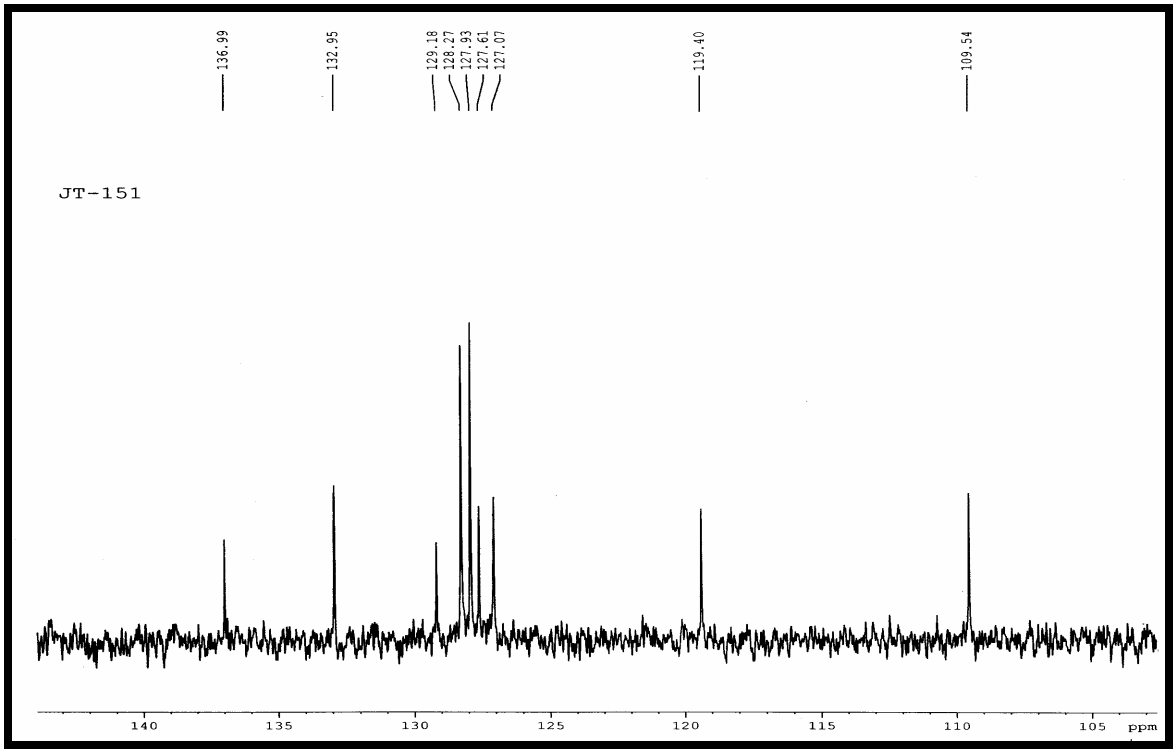
^{1}H NMR spectrum of 5-benzoyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-170)



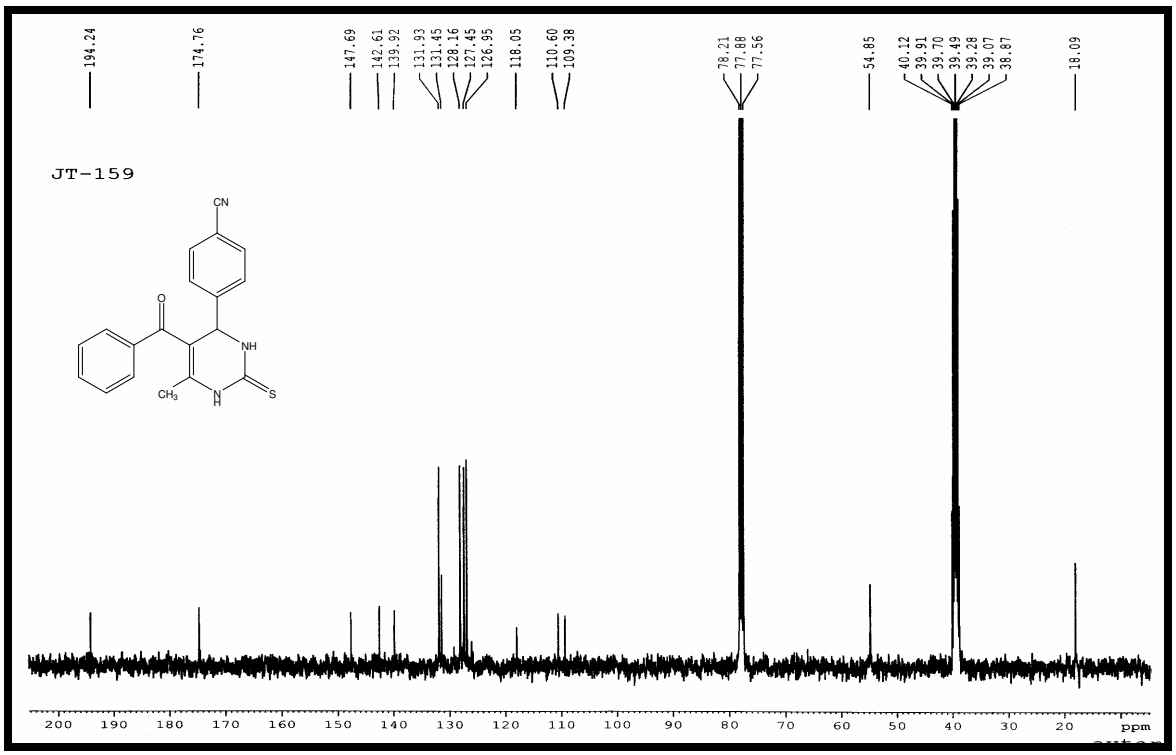


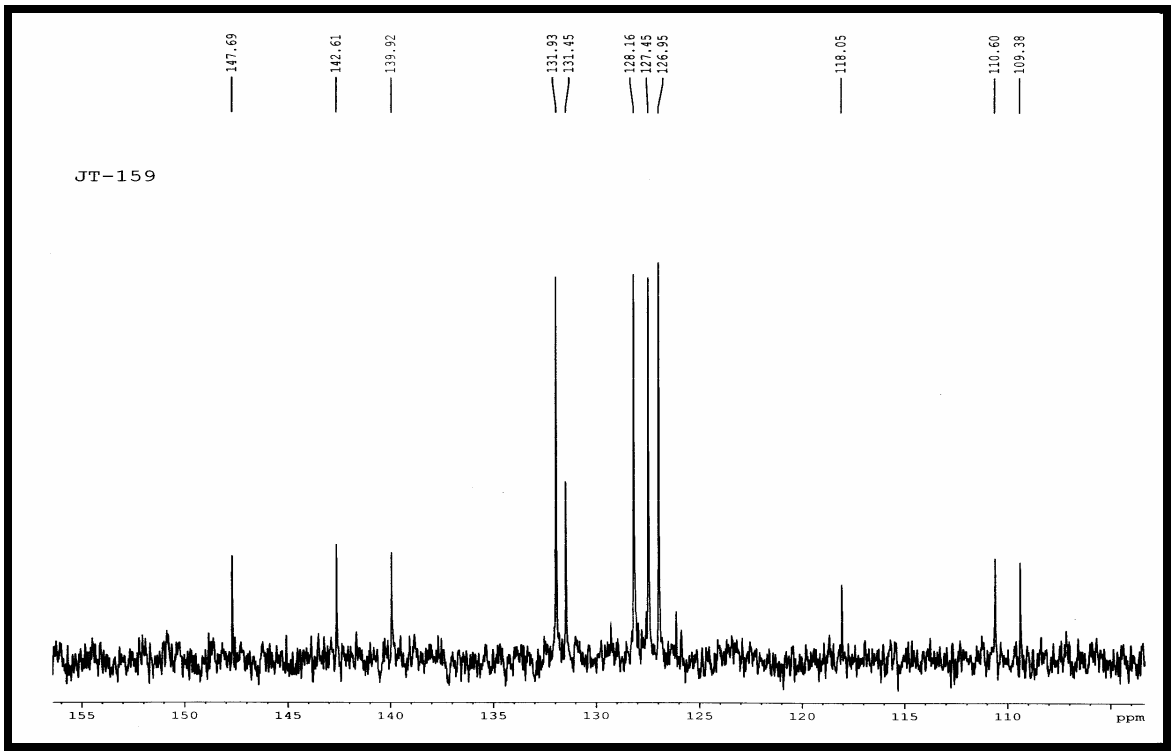
^{13}C NMR spectrum of 4-(2-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl](phenyl)methanone (JT-151)



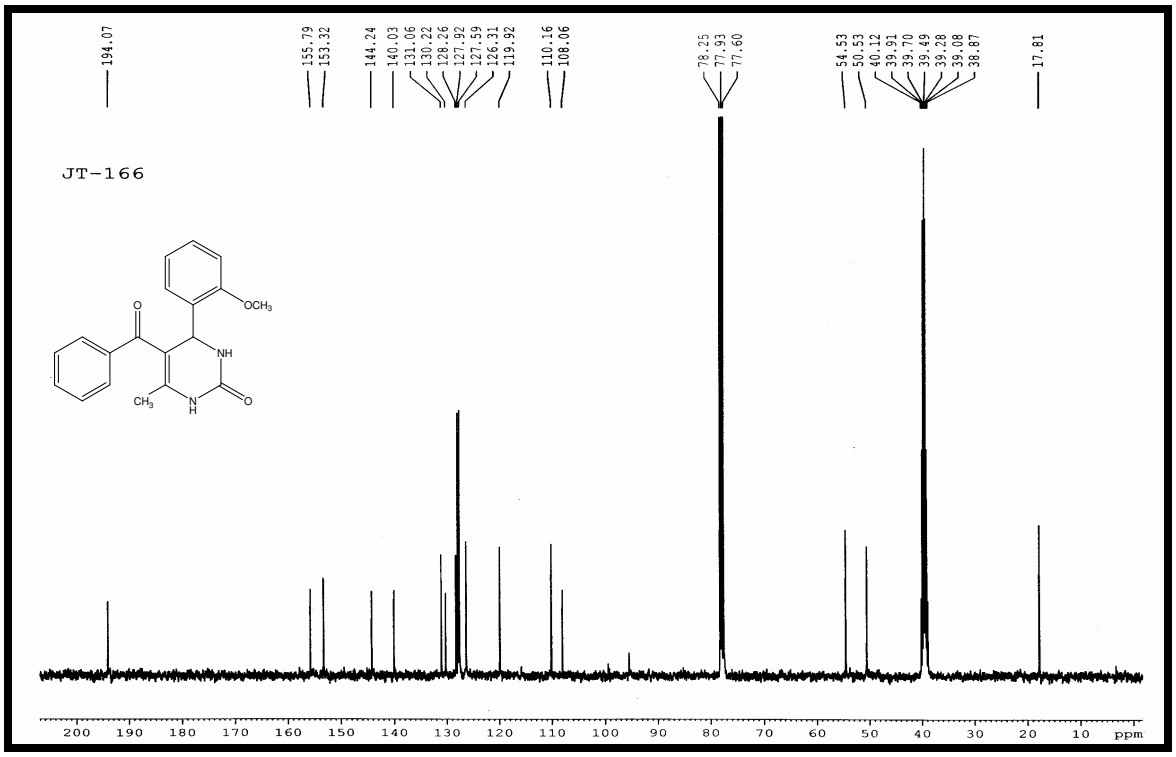


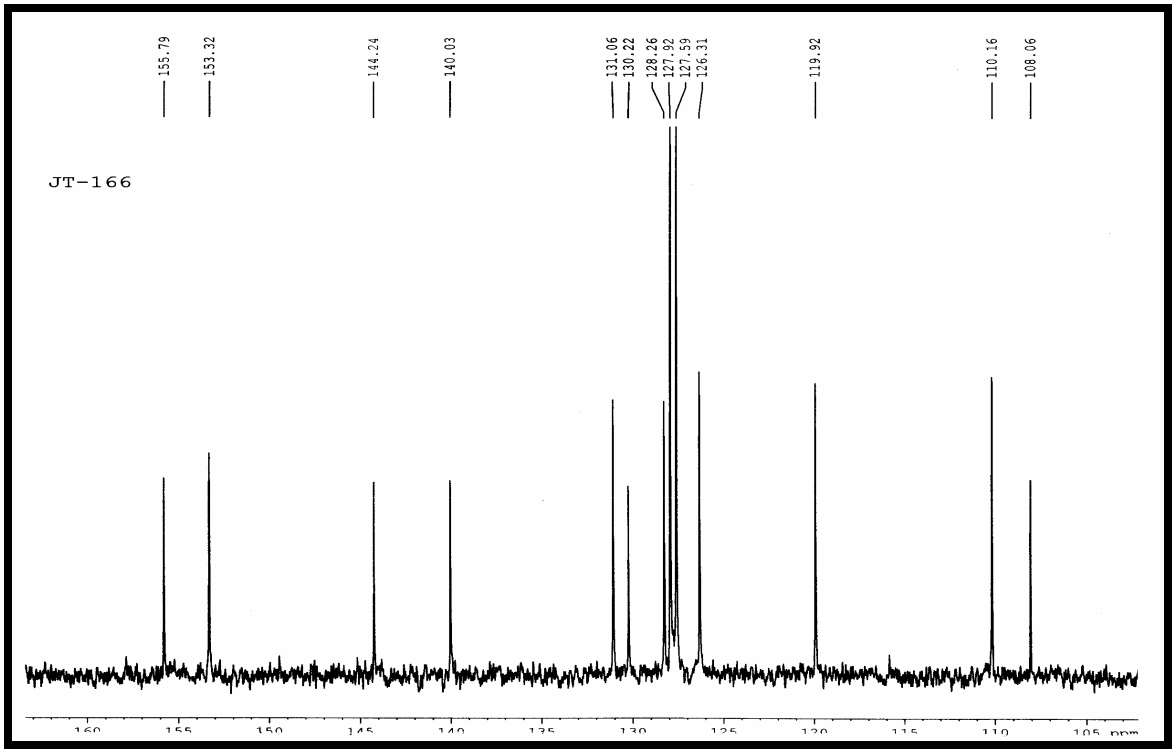
^{13}C NMR spectrum of 4-(5-benzoyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)benzonitrile (JT-159)



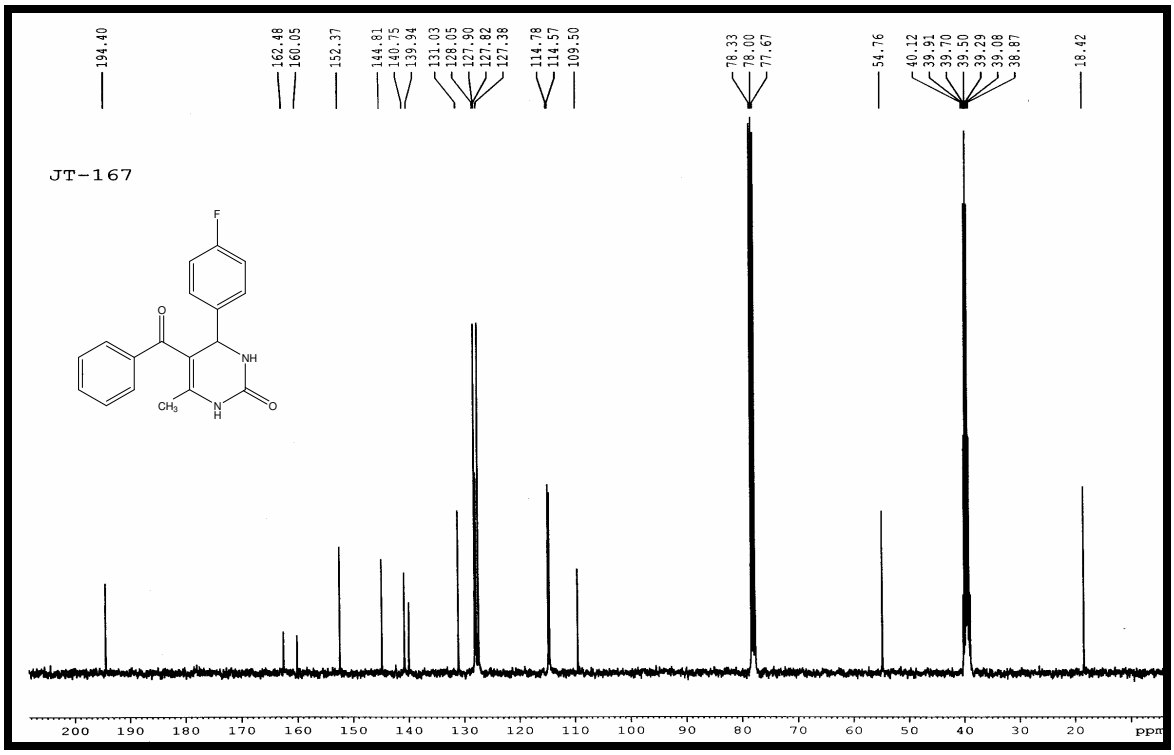


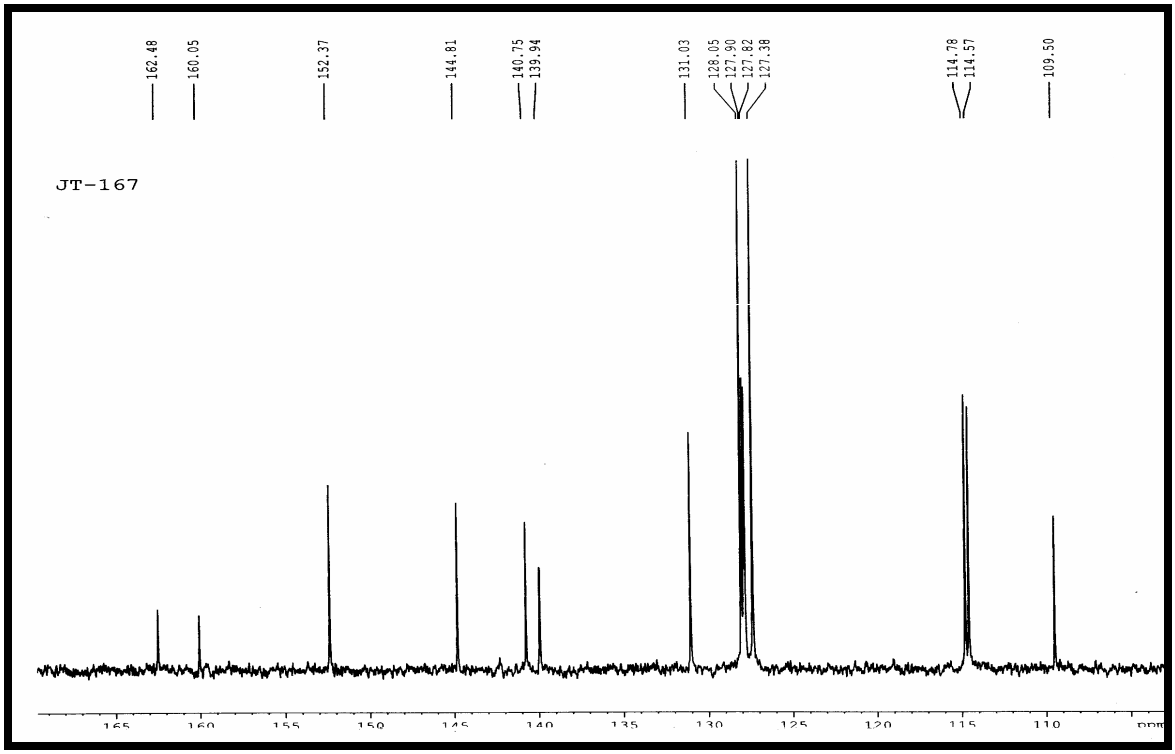
^{13}C NMR spectrum of 5-benzoyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-166)



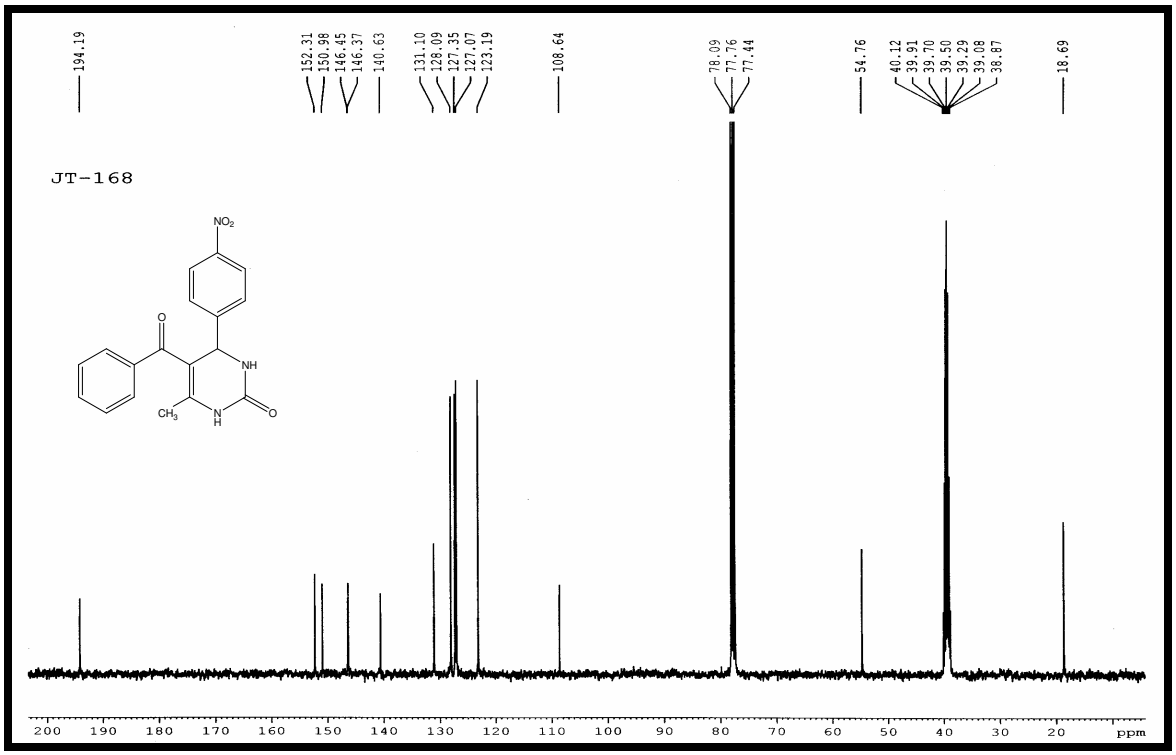


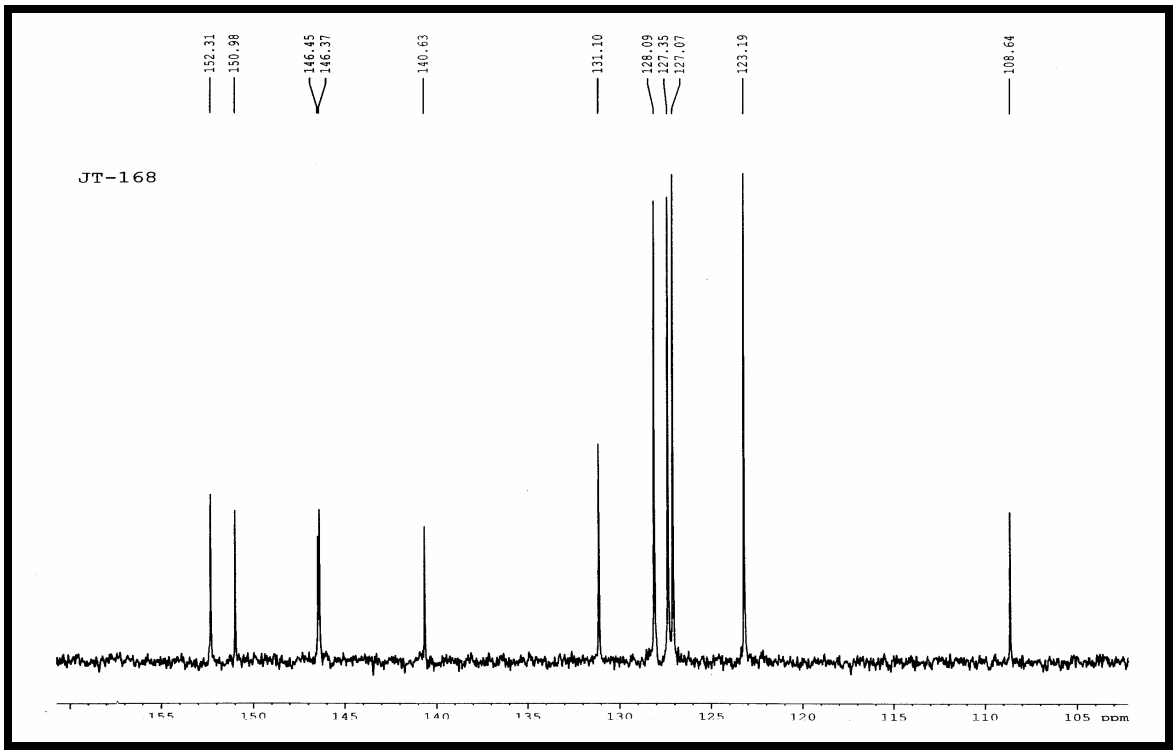
^{13}C NMR spectrum of 5-benzoyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-167)



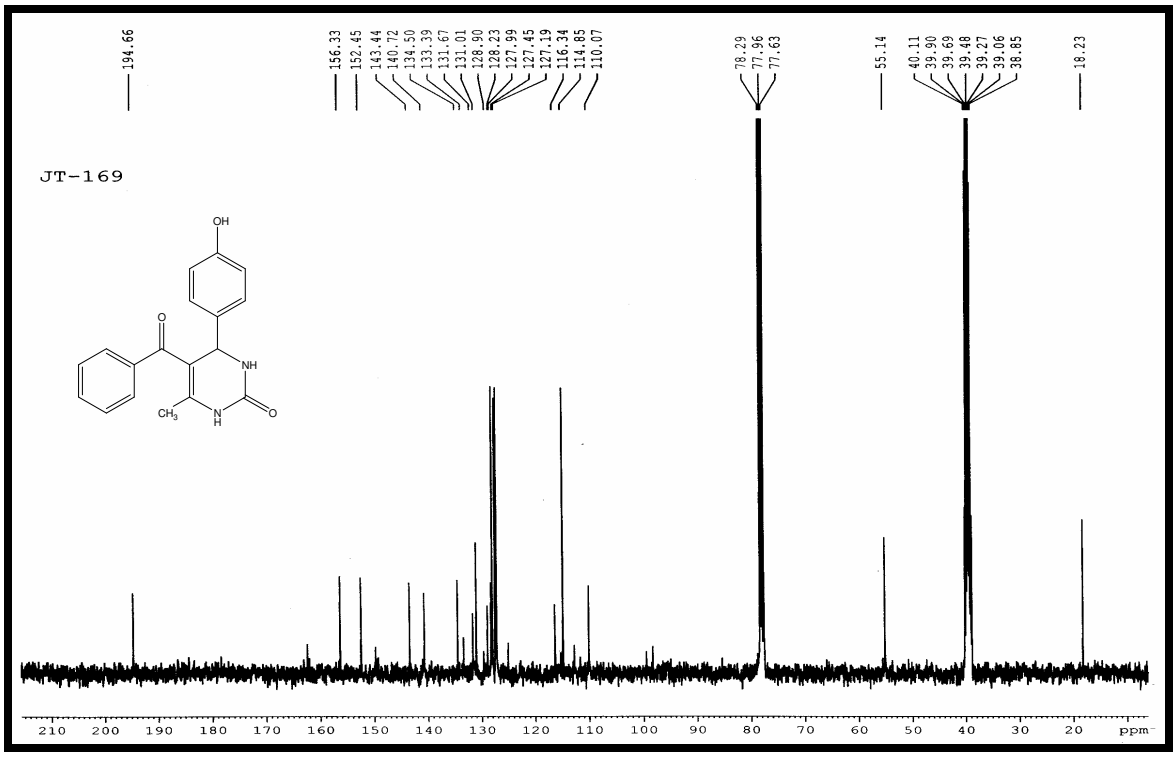


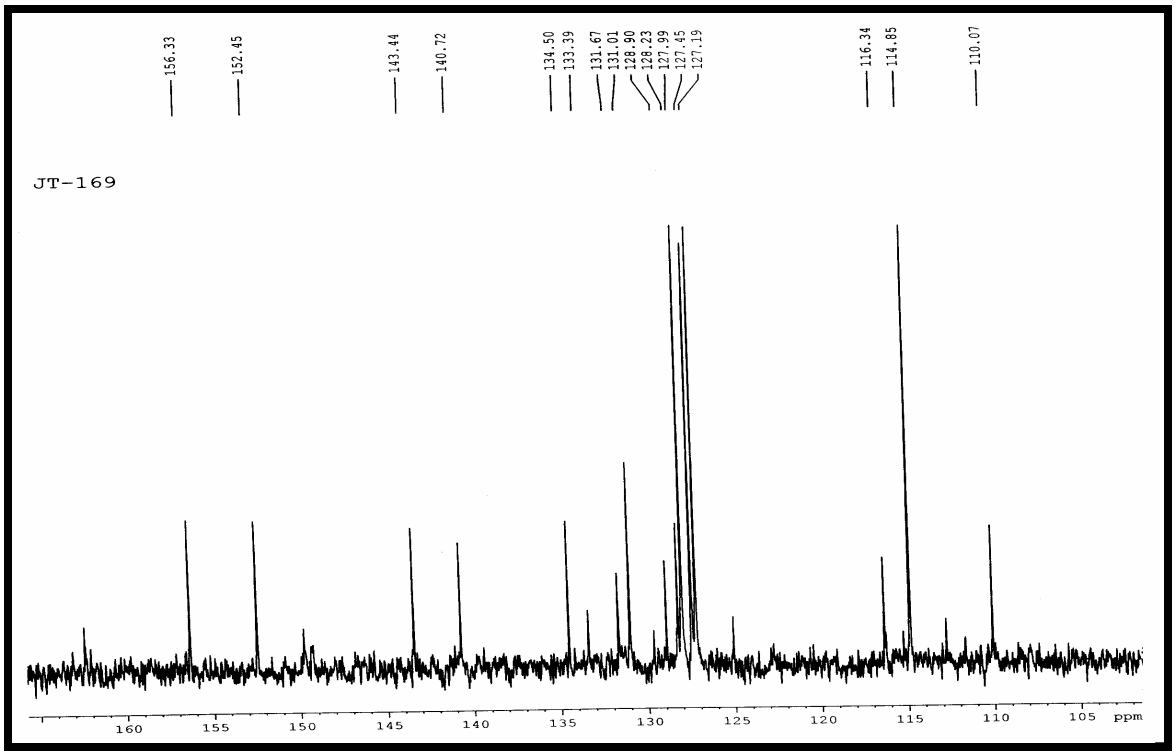
^{13}C NMR spectrum of 5-benzoyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-168)



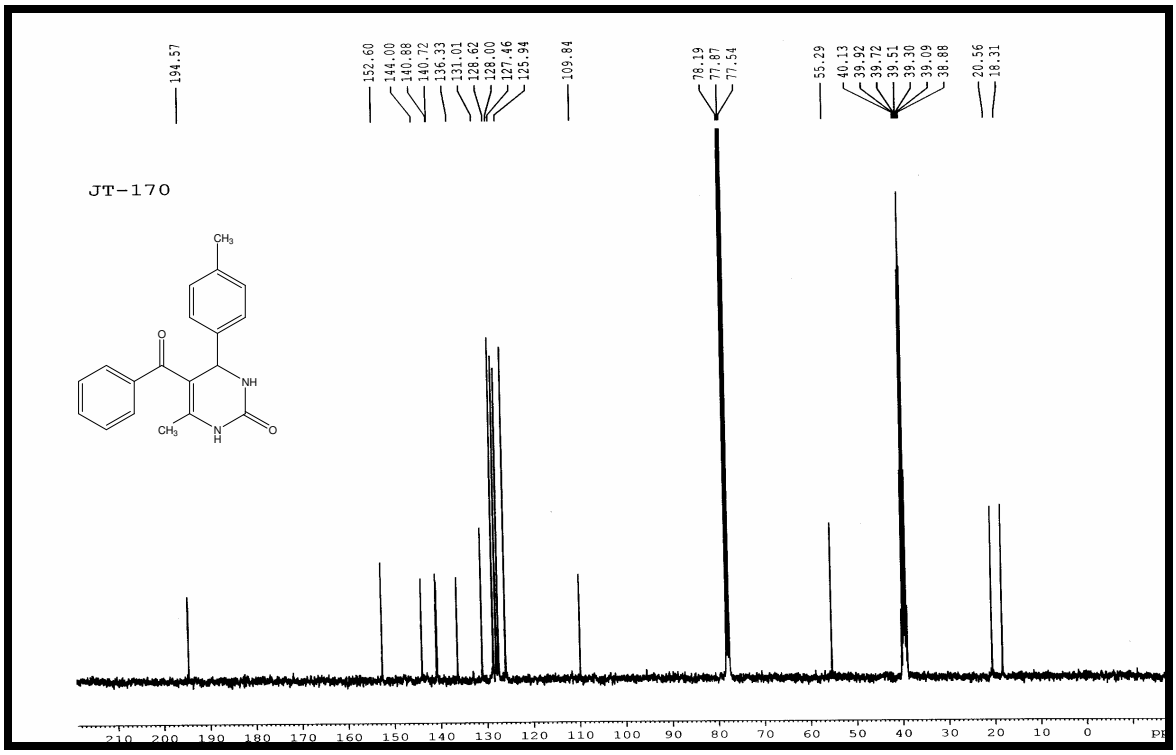


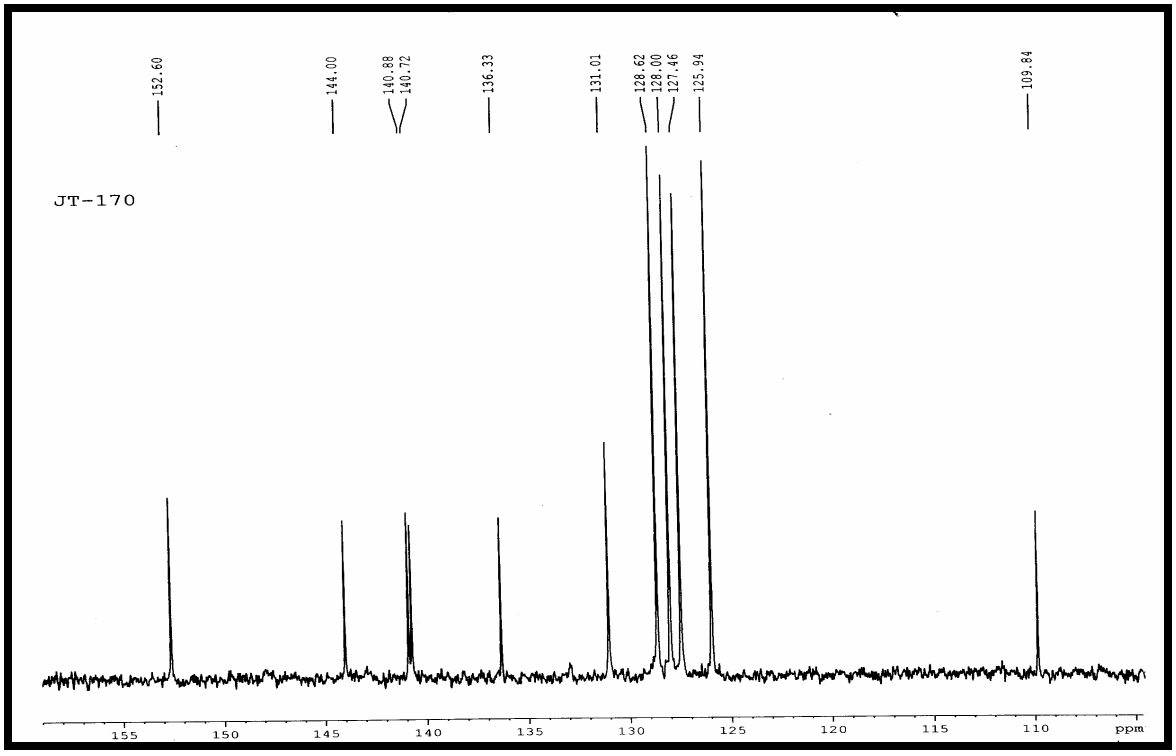
^{13}C NMR spectrum of 5-benzoyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (JT-169)





^{13}C NMR spectrum of 5-benzoyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (JT-170)





5.12. References

1. Biginelli, P. *Ber.* **1891**, 24, 1317, *Gazz. Chim. Ital*. **1893**, 23, 360.
2. Hinkel, Hey, *Rec. Trav. Chim*. **1929**, 48, 1280.
3. (a) Kappe, C. O. 100 years of the biginelli dihydropyrimidine synthesis. *Tetrahedron,* **1993**, 49, 6937-6963. (b) Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res.* **2000**, 33, 879.
4. (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. Substituted 1,4-dihydropyrimidines. 3. Synthesis of selectively functionalized 2-hetero-1,4-dihydropyrimidines *J. Org. Chem.* **1989**, 54, 5898. (b) Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. 1,4-Cycloaddition of 1,3-diazabutadienes with enamines: An efficient route to the pyrimidine ring. *Tetrahedron Lett.* **1989**, 30, 4573.
5. Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res.* **2000**, 33, 879.
6. (a) Ramo´n, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem., Int. Ed.* **2005**, 44, 1602. (b) Ramachary, D. B.; Barbas, C. F. towards Organo-Click Chemistry: Development of Organocatalytic Multicomponent Reactions through Combinations of Aldol, Wittig, Knoevenagel, Michael, Diels-Alder and Huisgen Cycloaddition Reactions**.** *Chem. Eur. J.* **2004**, 10, 5323. (c) Denmark, S. E.; Fan, Y. *J.* The First Catalytic, Asymmetric α-Additions of Isocyanides. Lewis-Base-Catalyzed, Enantioselective Passerini-Type Reactions. *Am. Chem. Soc.* **2003**, 125, 7825. (d) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. Stereochemical Control of the Passerini Reaction. *Org. Lett.* **2004**, 6, 4231. (e) Cozzi, P. G.; Rivalta, E. Highly Enantioselective One-Pot, Three-Component Imino-Reformatsky Reaction. *Angew. Chem., Int. Ed*. **2005**, 44, 3600. (f) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. *Acc. Chem. Res.* **1996**, 29, 123. (g) Burke, M. D.; Schreiber, S. L. A Planning Strategy for Diversity-Oriented Synthesis. *Angew. Chem., Int. Ed*. **2004**, 43, 46.
7. (a) Ugi, I.; Dömling, A.; Hörl. W. Multicomponent reactions in organic chemistry. *Endeavour*, **1994**, 18, 115–122. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating. T. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. *Acc. Chem. Res.* **1996**, 29, 123–131. (c) Dömling, A. Isocyanide Based Multi Component Reactions in Combinatorial Chemistry. *Comb. Chem. High Throughput Screen.* **1998**, 1, 1–22. (d) Dax, S. L.; McNally, J. J.; Youngman, M. A. Multi-Component Methodologies in Solid-Phase Organic Synthesis. *Curr. Med. Chem.* **1999**, 6, 255–270. (e)

Tietze, L. F.; Modi, A**.** Multicomponent domino reactions for the synthesis of biologically active natural products and drugs. *Med. Res. Rev.* **2000**, 20, 304–322. (f) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. Maximizing Synthetic Efficiency: Multi-Component Transformations Lead the Way. *Chem. Eur. J.* **2000**, 6, 3321–3329. (g) Ugi, I.; Heck, S. The Multicomponent Reactions and their Libraries for Natural and Preparative Chemistry. *Comb. Chem. High Throughput Screen.* **2001**, 4, 1–34. (h) Weber, L. Multi-component reactions and evolutionary chemistry. *Drug Disc. Today,* **2002**, 7, 143–147. (i) Dömling, A. Recent advances in isocyanide-based multicomponent chemistry. *Curr. Opin. Chem. Biol.* **2002**, 6, 306–313.

8. (a) Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res.* **2000**, 33, 879. (b) Lusch, M. J.; Tallarico, J. A. Demonstration of the Feasibility of a Direct Solid-Phase Split-Pool Biginelli Synthesis of 3,4-Dihydropyrimidinones. *Org. Lett.* **2004**, 6, 3237.
9. Kappe, C. O. 100 years of the biginelli dihydropyrimidine synthesis. *Tetrahedron,* **1993**, 49, 6937–6963. (For an extensive review of the first 100 years of the Biginelli reaction)
10. Kappe, C. O. A Reexamination of the Mechanism of the Biginelli Dihydropyrimidine Synthesis. Support for an *N*-Acyliminium Ion Intermediate. *J. Org. Chem.* **1997**, 62, 7201–7204.
11. Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog *Acc. Chem. Res.* **2000**, *33*, 879–888. (For a more recent update on the Biginelli reaction)
12. Kappe, C. O. Biologically active dihydropyrimidones of the Biginelli-type — a literature survey. *Eur. J. Med. Chem.* **2000**, 35, 1043.
13. Atwal, K. S. Karnail S. Atwal, George C. Rovnyak, Brian C. O'Reilly, Joseph Schwartz. Substituted 1,4-dihydropyrimidines. 3. Synthesis of selectively functionalized 2-hetero-1,4-dihydropyrimidines. *J. Org. Chem.* **1989**, 54, 5898.
14. Rafiee, E.; Shahbazi, F. One-pot synthesis of dihydropyrimidones using silica-supported heteropoly acid as an efficient and reusable catalyst: Improved protocol conditions for the Biginelli reaction, *J. of Mol. Cat. A: Chem.* 2006, 250, 57–61.
15. Hu, E. H.; Sidler, D. R.; Dolling, U. H. Unprecedented catalytic three component one-pot condensation reaction: an efficient synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones. *J. Org. Chem.* **1998**, 63, 3454–3457.

16. Gupta, R.; Gupta, A. K.; Paul, S.; Kachroo, P. L. Improved synthesis of some ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one/thion-5-carboxylates by microwave irradiation. *Ind. J. Chem.* **1995**, 34B, 151.
17. Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramalingam, T. J. Microwave assisted efficient synthesis of dihydropyrimidines: Improved high yielding protocol for the Biginelli reaction. *Chem. Res.* **2000**, 7, 354.
18. Peng, J.; Deng, Y. Ionic liquids catalyzed Biginelli reaction under solvent-free conditions. *Tetrahedron Lett*. **2001**, 42, 5917.
19. Kappe, C.O.; Kumar, D.; Varma, R.S. Microwave-assisted high-speed parallel synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-ones using a solventless Biginelli condensation protocol. *Synthesis*, **1999,** 10, 1799.
20. Yun, M.; Changtao, Q.; Limin, W.; Min, Y. Lanthanide triflate catalyzed Biginelli reaction. One-pot synthesis of dihydropyrimidinones under solvent-free conditions. *J. Org. Chem.* **2000**, 65, 3864–3868.
21. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. A Revision of the Bigineili Reaction Under Solid Acid Catalysis. Solvent-free Synthesis of Dihydropyrimidines Over Montmorilionite KSF, *Tetrahedron Lett.* 1999, 40 3465-3468.
22. Mishra, B. G.; Kumar, D.; Rao, V. S. $H_3PW_{12}O_{40}$ catalyzed expeditious synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions, *Cataly. Communi.* **2006**, 7, 457–459.
23. Salehi H.; Guo, Q. X. A Facile and Efficient One-Pot Synthesis of Dihydropyrimidinones Catalyzed by Magnesium Bromide under Solvent-Free Conditions, *Synth. Commun.* **2004**, 34(1), 171–179.
24. Jiang, Z.; Chen, R. Synthesis of 3,4-Dihydropyrimidine-2(1H)-thiones and Quinazolin-4(3H)-ones over Yb(III)-Resin Catalyst Under Solvent-free Conditions, *Synth. Commun.* **2005**, 35, 503–509.
25. Ranu, B. C.; Hajra, A. S.; Dey, S. A Practical and Green Approach towards Synthesis of Dihydropyrimidinones without Any Solvent or Catalyst Organic *Process Research & Development*, **2002**, 6, 817-818.
26. Salehi, P.; Dabiri, M.; Zolfigolc M. A.; Bodaghifard, M. A. Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, *Tetrahedron Lett.* **2003**, 44, 2889–2891.

27. Stadler, A.; Kappe, C. O. Automated Library Generation Using Sequential Microwave-Assisted Chemistry. Application toward the Biginelli Multicomponent Condensation. *J. Comb. Chem.* **2001**, 3, 624-630.
28. Stadler, A.; Behrooz, H.; Dallinger, Y. D.; Walla, P.; Eycken, E. V.; Kaval, N.; Kappe, C. O. Scalability of Microwave-Assisted Organic Synthesis. From Single-Mode to Multimode Parallel Batch Reactors, *Org. Pro Res.Dev.* **2003**, 7, 707-716.
29. Ma, Y.; Qian, C.; Wang, L.; Yang M. Lanthanide Triflate Catalyzed Biginelli Reaction. One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Conditions *J. Org. Chem.* **2000,** 65, 3864-3868.
30. Ranu, B. C.; Hajra, A.; Jana, U. Indium(III) Chloride-Catalyzed One-Pot Synthesis of Dihydropyrimidinones by a Three-Component Coupling of 1,3-Dicarbonyl Compounds, Aldehydes, and Urea: An Improved Procedure for the Biginelli Reaction. *J. Org. Chem.* **2000**, 65, 6270.
31. Ma, Y.; Qian, C.; Wang, L.; Yang, M. Lanthanide Triflate Catalyzed Biginelli Reaction. One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Conditions. *J. Org. Chem.* **2000**, 65, 3864.
32. Jin, T. S.; Wang, H. X.; Xing, C. Y.; Li, X. L.; Li, T. S. An Efficient One-Pot Synthesis of 3,4-Dihydropyrimidin-2-ones Catalyzed by Methanesulfonic Acid, *Synth. Commun,* **2004**, 34(16), 3009–3016.
33. Bose, D. S.; Sudharshan, M.; Chavhan, S. W. New protocol for Biginelli reaction-a practical synthesis of Monastrol, *Arkivoc*, **2005,** (iii), 228-236.
34. Wipf, P., Cunningham, A. A solid phase protocol of the biginelli dihydropyrimidine synthesis suitable for combinatorial chemistry. *Tetrahedron. Lett.* **1995**, 36, 7819.
35. Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P., Fluorous Synthesis: Fluorous Protocols for the Ugi and Biginelli Multicomponent Condensations. *J. Org. Chem.*, **1997**, 62*,* 2917.
36. Palaniappan, S.; John, A.; A novel polyaniline-fluoroboric acid-dodecylhydrogensulfate salt: A versatile reusable polymer based solid acid catalyst for organic transformations, *J. Mol. Cat. A: Chem.* **2005**, 2339-15.
37. Robinett, L. D.; Yager, K. M.; Phelan, J. C. *11th National Meeting of the American Chemical Society, New Orleans,* 1996; American Chemical Society: Washington, DC, **1996**; ORGN 122.
38. Strohmeier, G. A.; Kappe, C. O. Rapid Parallel Synthesis of Polymer-Bound Enones Utilizing Microwave-Assisted Solid-Phase Chemistry. *J. Comb. Chem.* **2002**, 4, 154-161.

39. (a) Mukaiyama, T.; Ohno, T. Han, J. S.; Kobayashi, S. Reversal Phenomena of the Preferential Activation of Aldehydes to the Corresponding Acetals under Non-Basic Conditions. The Chemoselective Aldol Reaction of Aldehydes with *t*-Butyldimethylsilyl Enol Ethers Using TBSCl–$INCl_3$ as a Catalyst. *Chem. Lett.* **1991**, 949. (b) Loh, T-P.; Chua, G-L.; Vittal, J. J.; Wong, M-W. Highly stereoselective indium trichloride-catalysed asymmetric aldol reaction of formaldehyde and glucose-derived silyl enol ether in water**.** *Chem. Commun.* **1998**, 861. (c) Teck-Peng Loh and Xu-Ran Li. Clay montmorillonite K10 catalyzed aldol-type reaction of aldehydes with silyl enol ethers in water. *Tetrahedron, 1999*, *55*, 10789.

40. (a) Munoz-Muniz, O.; Quintanar-Audelo, M.; Juaristi, E. Reexamination of $CeCl_3$ and $InCl_3$ as Activators in the Diastereoselective Mukaiyama Aldol Reaction in Aqueous Media. *J. Org. Chem*. **2003**, 68, 1622-1625. (b) Ranu, B. C.; Hajra, A.; Jana, U. General Procedure for the Synthesis of α-Amino Phosphonates from Aldehydes and Ketones Using Indium(III) Chloride as a Cat. *Org. Lett.* **1999**, 1, 1141. (c) Ranu, B. C.; Hajra, A.; Jana, U. General Procedure for the Synthesis of α-Amino Phosphonates from Aldehydes and Ketones Using Indium(III) Chloride as a Cat. *J. Org. Chem.* **2000**, 65, 6270.

41. (a) Atwal, K. S.; Rovnyak, G. C.; O. Reilly, B. C.; Schwartz, J. Substituted 1,4-dihydropyrimidines. 3. Synthesis of selectively functionalized 2-hetero-1,4-dihydropyri. *J. Org.Chem*. **1989**, 54, 5898. (b) C. Oliver Kappe, Walter M. F. Fabian and Marcus A. Semones; Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators. A comparison of ab initio, semiempirical and X-ray crystallographic studies. *Tetrahedron,* **1997**, 53, 2803.

42. (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. Dihydropyrimidine calcium channel modulators, *J. Med. Chem.* **1991**, 34, 806. (b) Kappe, C. O. The Generation of Dihydropyrimidine Libraries Utilizing Biginelli Multicomponent Chemistry. *QSAR Comb. Sci.* **2003**, 22, 630.

43. Hurst, E. W.; Hull, R. *J. Med. Pharm. Chem.* **1961**, 3, 215.

44. Khania, E. L.; Sillinietse, *G.* O.; Dabur, G.; Ya, Y.; Kimenis, A. A. *Khim. Pharm. Zh.* **1978**, 78, 1321.

45. Jauk, B.; Belaj, F.; Kappe, C. O. Synthesis and reactions of Biginelli-compounds. Part 14.[1] A rhodium-induced cyclization–cycloaddition sequence for the construction of conformationally rigid calcium channel modulators of the dihydropyrimidine type**.** *J. Chem. Soc. Perkin Trans. 1*, **1999**, 307.

46. Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Small Molecule Inhibitor of Mitotic Spindle Bipolarity Identified in a Phenotype-Based Screen. *Science*, **1999**, 286, 971.

47. Dondoni, A.; Massi, A.; Sabbatini, S. Improved synthesis and preparative scale resolution of racemic monastrol. *Tetrahedron Lett.* **2002**, 43, 5913.

48. (a) Heys, L.; Moore, C. G.; Murphy, P. *J. Chem. Soc. Rev.* The guanidine metabolites of *Ptilocaulis spiculifer* and related compounds; isolation and synthesis**.** **2000**, 29, 57. (b) Barluenga, J.; Tomas, M.; Rubio, V.; Gotor, V. J. *Chem. Commun*. **1995**, 1369. (c) Aron, Z. D.; Overman, L. E. The tethered Biginelli condensation in natural product synthesis**.** *Chem. Commun*. **2004**, 253.

49. (a) Mayer, T. M.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Small Molecule Inhibitor of Mitotic Spindle Bipolarity Identified in a Phenotype-Based Screen. *Science* **1999**, 286, 971. (b) Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. X-Ray Structure, Conformational Analysis, Enantioseparation, and Determination of Absolute Configuration of the Mitotic Kinesin Eg5 Inhibitor. Monastrol. *Tetrahedron,* **2000**, 56, 1859.

50. (a) Munoz-Muniz, O.; Juaristi, E. *Arkivoc,* **2003**, 11, 16. (b) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. Asymmetric Mannich Reactions of β-Keto Esters with Acyl Imines Catalyzed by Cinchona Alkaloids. *J. Am. Chem. Soc.* **2005**, 127, 11256.

51. (a) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. Three-Component Biginelli Cyclocondensation Reaction Using *C*-Glycosylated Substrates. Preparation of a Collection of Dihydropyrimidinone Glycoconjugates and the Synthesis of *C*-Glycosylated Monastrol Analogues. *J. Org. Chem.* **2002**, 67, 6979. (b) Schnell, B.; Strauss, U. T.; Verdino, P.; Faber, K.; Kappe, C. O. Synthesis of enantiomerically pure 4-aryl-3,4-dihydropyrimidin-2(1H)-ones via enzymatic resolution: preparation of the antihypertensive agent (R)-SQ 32926. *Tetrahedron: Asymmetry,* **2000**, 11, 1449. (c) Alessandro Dondoni, Alessandro Massi and Simona Sabbatini. Improved synthesis and preparative scale resolution of racemic monastrol. *Tetrahedron Lett.* **2002**, *43*, 5913. (d) Schnell, B.; Krenn, W.; Faber, K.; Kappe, C. O. Synthesis and reactions of Biginelli-compounds. Part 23. Chemoenzymatic syntheses of enantiomerically pure 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones**.** *J. Chem. Soc., Perkin Trans. 1,* **2000**, 4382.

52. Ragno, R.; Mai, A.; Sbardella, G.; Artico, M.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; La Colla, P. Computer-Aided Design, Synthesis, and Anti-HIV-1 Activity in Vitro of 2-Alkylamino-6-[1-(2,6-difluorophenyl)alkyl]-3,4-dihydro-5-

alkylpyrimidin-4(3*H*)-ones as Novel Potent Non-Nucleoside Reverse Transcriptase Inhibitors, Also Active Against the Y181C Variant, *J. Med. Chem.* **2004**, 47, 928-934.

53. Munoz-Muniz, O.; Juaristi, E. An enantioselective approach to the Biginelli dihydropyrimidinone condensation reaction using $CeCl_3$ and $InCl_3$ in the presence of chiral ligands. *Arkivoc.* **2003**, 11, 16-26.
54. (a) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators. *J. Med. Chem*. **1995**, 38, 119. (b) Triggle, D. J.; Padmanabhan, S. *Chemtracts: Org. Chem.* **1995**, 8, 191.
55. Kappe, C. O. The Generation of Dihydropyrimidine Libraries Utilizing Biginelli Multicomponent Chemistry. *QSAR Comb. Sci.* **2003**, 22, 630.
56. (a) Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. Dihydropyrimidine calcium channel blockers: 2-heterosubstituted 4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines. *J. Med. Chem.* **1990**, 33, 1510. (b) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. *J. Med. Chem.* **1992**, 35, 3254. (c) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Gucinotta, G.; DiMarco, J. D.; Gougoutas, J. C.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. Calcium Entry Blockers and Activators: Conformational and Structural Determinants of Dihydropyrimidine Calcium Channel Modulators. *J. Med. Chem*. **1995**, 38, 119.
57. (a) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Small Molecule Inhibitor of Mitotic Spindle Bipolarity Identified in a Phenotype-Based Screen *Science*, **1999**, 286, 971; (b) Haggarty, S. J.; Mayer, T. U.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L**.** Dissecting cellular processes using small molecules: identification of colchicine-like, taxol-like and other small molecules that perturb mitosis. *Chem. Biol.* **2000**, 7, 275; (c) Maliga, Z.; Kapoor, T. M.; Mitchison, T. J. Evidence that Monastrol Is an Allosteric Inhibitor of the Mitotic Kinesin Eg5. *Chem. Biol.* **2002**, 9, 989.
58. (a) Lagu, B.; Tian, D.; Chiu, G.; Nagarathnam, D.; Fang, J.; Shen, Q.; Forray, C.; Ransom, R.; Chang, R. S. L.; Vyas, K. P.; Zhang, K.; Gluchowski, C. Synthesis and evaluation of

furo[3,4-d]pyrimidinones as selective α_{1a}-adrenergic receptor antagonists. *Bioorg. Med. Chem. Lett*. **2000**, 175; (b) Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Rittle, K. E.; Gilbert, K. F.; Steele, T. G.; Homnick, C. F.; Freidinger,T.W.; Ransom, R.W.; Kling, P.; Reiss, D.; Broten,T. P.; Schorn, T.W.; Chang, R. S. L.; O'Malley, S. S.; Olah, T. V.; Ellis, J. D.; Barrish, A.; Kassahun, K.; Leppert, P.; Nagarathnam, D.; Forray, C. In Vitro and in Vivo Evaluation of Dihydropyrimidinone C-5 Amides as Potent and Selective α_{1A} Receptor Antagonists for the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem.* **2000**, 43, 2703.

59. Zhang, L.; Rana, T. M. Solid-Phase Synthesis of α-(2-(Benzylthio)- 1,4-dihydro-6-methyl-4-*p*-tolylpyrimidine-5- carboxamido) Acids: a New Strategy To Create Diversity in Heterocyclic Scaffolds. *J. Comb. Chem.* **2004**, 6, 457.
60. Desai, B.; Dallinger D.; Kappe, C. O. Microwave-assisted solution phase synthesis of dihydropyrimidine C5 amides and esters, *Tetrahedron*, **2006**, 62, 4651–4664.
61. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's text book of practical organic chemistry*, 5th edition, Addison-Wesley Longman, Harlow, **1998**, 634-635.

Summary of the present work

The work presented in this thesis, entitled "**Studies on Some Important Heterocyclic Moieties**." is divided into five chapters.

In **Chapter-1**, synthesis and characterization of some (2-oxo-2*H*-chromen-4-yl) acetic acid derivatives is reported. This chapter deals with the synthesis of coumarin-4-acetic acid derivatives. The coumarin skeleton has been associated with different types of pharmacological activities. The brief review about coumarins, especially derivatives of coumarin-4-acetic acid is given which covers synthesis & pharmacological activities of different types of coumarin derivatives. The series of 15 compounds have been synthesized by the reaction of citric acid and various substituted phenols in presence of conc. H_2SO_4. The structure of the synthesized compounds has been confirmed by IR, NMR and Mass spectroscopy. All the synthesized compounds have been sent for anti-cancer activity and the results are awaited.

Chapter-2, deals with the synthesis of *N*-1, 3-benzo[*d*]thiazol-2-yl-2-(2-oxo-2*H*-chromen-4-yl) acetamide derivatives. Total 26 title compounds are prepared by forming an amide linkage between various substituted coumarin-4-acetic acids and 2-amino benzothiazoles. The coumarin ring linked with amide group is a moiety of biological interest. The structures of the newly synthesized compounds have been confirmed by IR, NMR and Mass spectroscopy. All the newly synthesized compounds have been sent for anti-viral activity and the results are awaited.

Chapter-3 covers a detailed study of imidazoles, 2-imidazolones, 2-amino pyrimidines and synthesis of amide linkage between 2-imidazolone-4-carboxylic acid and 2-amino-4,6-disubstituted pyrimidines. Total 24 compounds have been synthesized and screened for anti-inflammatory as well as anti-cancer activities. The structures of the newly synthesized compounds have been confirmed by IR, NMR and Mass spectroscopy.

Chapter-4, synthesis and characterization of some (5-carboxymethyl-2, 4, 6-triphenyl-1, 4-dihydropyridine-3-yl)-acetic acids. A series of 26 compounds have been synthesized by reacting different aromatic aldehydes with β–aroylpropanoic acid and ammonia in ethanol. The synthesized compounds belong to heteroaryl alkanoic acids, which are well known as NSAIDs. The structures of the newly synthesized compounds have been confirmed by IR, NMR and Mass spectroscopy. All the newly synthesized compounds have been sent for anti-tubercular activity and the results are awaited.

Chapter-5 encompasses synthesis and characterization of 5-benzoyl-6-methyl-4-(substituted) phenyl -3,4-dihydropyrimidin-2(1*H*)-ones. Total 24 dihydropyrimidines are prepared. Urea and thiourea have been used successfully to provide the corresponding dihydropyrimidinones, which are also of much interest with regard to the biological activity. This protocol gave the products in good to excellent yields. Another important aspect of this procedure is survival of a variety of functional groups, such as CH_3, OCH_3, OH, and CN under the experimental conditions. The structures of the newly synthesized compounds have been confirmed by IR, NMR and Mass spectroscopy. All the newly synthesized compounds have been sent for anti-cancer activity and the results are awaited.

Research Publications

1. **Jalpa C. Trivedi**, Jitender B. Bariwal, Kuldip D. Upadhyay, Yogesh T. Naliapara, Sudhir K. Joshi, Christophe C. Pannecouque, Erik De Clercq and Anamik K. Shah, Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity, *Tetrahedron Lett.* **2007**, 48, 8472–8474.
2. Jitender B. Bariwal, Kuldip D. Upadhyay, Atul, T. Manvar, **Jalpa C. Trivedi**, Jyoti S. Singh, Kishor S. Jain and Anamik Shah, 1,5-Benzothiazepine a Versatile Pharmacophore: A review. (Communicated in *Eur. J. Med. Chem.*).

Paper presentation at National / International Conferences

1. Bariwal J., **Trivedi J**., Upadhayay K., Manver A., Joshi S., Naliyapara Y., Mungra N. and Shah A, "Synthesis and Characterization of 4-Hydroxy-3-(-2-(un)substituted phenyl-2,5-dihydro-1,5-benzothiazepine-4yl) 2*H*-chromen-2-one", Abstract no. 165, International Conference on "Building Bridges, Forging Bonds" for 21st Century Organic Chemistry and Chemical Biology (ACS CSIR OCCB 2006) Jan 4-6, 2006, NCL, Pune.
2. Bariwal J., **Trivedi J**., Upadhayay K., Vekariya N., Bochiya P. and Shah A, "Synthesis and Biological Activity of N-substituted amino acid from substituted chromen-2-one", Abstract no. 42, International Conference on " Advance in Organic Chemistry and Chemical Biology (AOCCB 2006)", Jan. 11-12, 2006, IICT, Hydrabad.
3. **Jalpa Trivedi**, Hrishikesh Acharya, Nikhil Vekariya, Arun Mishra, Dinesh Manvar, Denish Karia, Nimish Mungara and Anamik Shah, "Synthesis and Biological activity of some Pyrano[2',3':4,5]Pyrano[3,2-*c*] Quinoline-2-Carbonitriles 10th International Conference of ISCB on "Drug Discovery: Prospective and Challenges", Feb 24-25, 2006, CDRI, Lucknow, India.

Conferences / Symposium / Workshop Attended

1. Joint International Conference on Advances in Organic Chemistry and Chemical Biology, AOCCB-2006, by the Indian Institute of Chemical Technology & American Chemical Society, Hyderabad, India, during January 11-12, 2006.
2. Joint International Conference on Building Bridges, Forging Bonds for 21st Century Organic Chemistry and Chemical Biology at National Chemical Laboratory, Pune, India, during 6-9th January 2006.
3. 9th National Conference on "Bioactive Heterocycles and Drug Discovery Paradigm" held at Rajkot organized by Indian Society of Chemists and Biologists (ISCB) and Department of Chemistry, Saurashtra University, Rajkot, Gujarat, India on 8-10th January, 2006.
4. DST workshop on "Green Chemistry"- Organized by Institute of Pharmacy, Nirma University of Science and Technology, Ahmedabad on 25-26th November, 2005.
5. A National Workshop on "Nanotechnology: Opportunities & Challenges" on 17th October, 2005 held at Saurashtra University, Rajkot, jointly organized by Saurashtra University, Gujarat Council of Science and Technology (GUJCOST), Gandhinagar.
6. 2-Days National Workshop on "E-resources in Chemical Synthesis and natural Products" held at Department of Chemistry, Saurashtra University, Rajkot, on 2-3rd march, 2006.
7. One day GUJCOST Sponsored Workshop on "Current Drug Patent Regime" at S. J. Thakkar Pharmacy College, Rajkot on 5th March, 2006.