DESIGN, SYNTHESIS, CHARACTERIZATION & BIOLOGICAL ACTIVITIES OF FEW HETEROCYCLIC COMPOUNDS

A THESIS SUBMITTED TO THE

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IN

CHEMISTRY

By

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UNDER THE GUIDANCE OF

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RAJKOT – 5 (GUJARAT, INDIA)

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

The work included in the thesis is done by me under the supervision of Dr. Yogesh T. Naliapara and the contribution made thereof is my own work.

Date:

Place: Rajkot **Chirag V. Bhuva**

Certificate

This is to certify that the present work submitted for the Ph. D. degree of Saurashtra University, Rajkot, Gujarat (India) by Mr. Chirag V. Bhuva has been the result of work carried out under my supervision and is a significant contribution in the field of synthetic organic medicinal chemistry.

Date:
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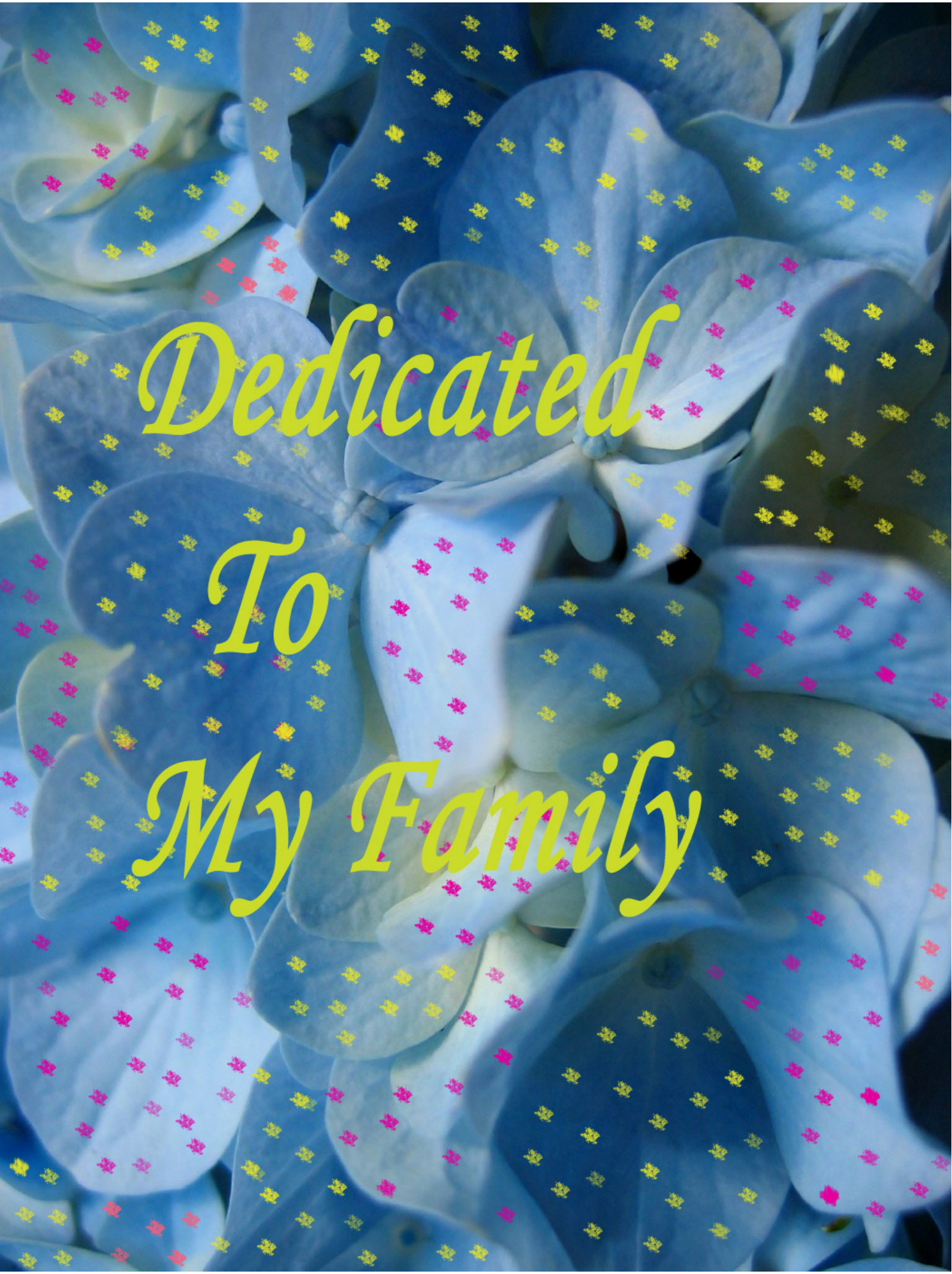
Dedicated
To
My Family

ACKNOWLEDGEMENT

First and foremost I wish to make devote supplication to Almighty God, “the great scientist of this lovely world” without whose blessings and benevolence my endeavors wouldn’t have reached to the zenith of success. My head bows with rapturous dedication from within my heart to the omnipotent Lord shiva, Ma AdhyaSakti and Shreenathjibapu.

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Chirag V. Bhuva

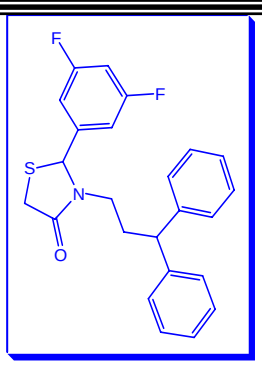
CONTENT

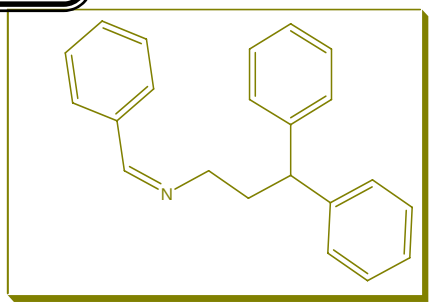
ABBRIVIATIONS

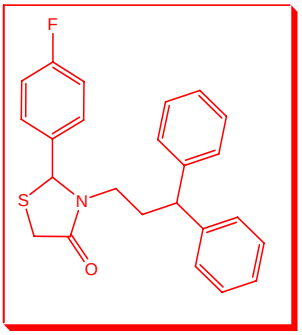
FSH	Follicle stimulating hormone
DNA	Deoxyribonucleic acid
COX	Cyclooxygenase
PGs	Prostaglandins
HIV	Human immunodeficiency virus
NSAIDs	Nonsteroidal anti-inflammatory drugs
AZT	Azidothymidine
ODN	Oligodeoxynucleotide
PDT	Photodynamic therapeutics
DHODase	Dihydroorotate dehydrogenase
MIC	Minimal inhibitory concentration value
(PCA)	Passive cutaneous anaphylaxis
DHPM	Dihydropyrimidines
EA	Ethyl acetate
rt	Room temperature
TEA	Triethylamine
DMF	Dimethyl formamide
SAR	Structure activity relationship
MF	Molecular formula
MW	Molecular weight
MP	Melting point
i.e.	That is
NMR	Nuclear magnetic resonance
DMSO	Dimethylsulfoxide
Con. / con.	Concentrated
hrs / h	Hours
DCC	Dicyclohexyl carbodiimide
TCCA	Trichloroisocyanuric acid

MCRs	Multi-component reactions
TFA	Trifluoroacetic acid
TSILs	Task Specific room temperature Ionic Liquids
MWI	Microwave irradiation
BPH	Benign prostatic hyperplasia
EDA	Etidronic acid
CUR	Curcumin
ADAMs	Alkenyldiarylmethanes
AIDS	Acquired immunodeficiency syndrome
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
ETM	Electronictopological method
IL	Ionic Liquids

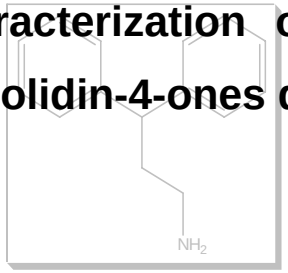
Chapter 1

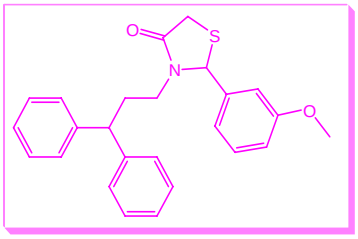


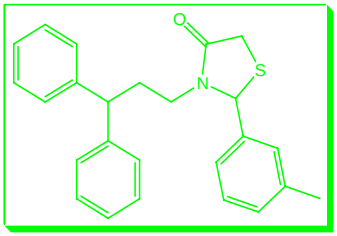


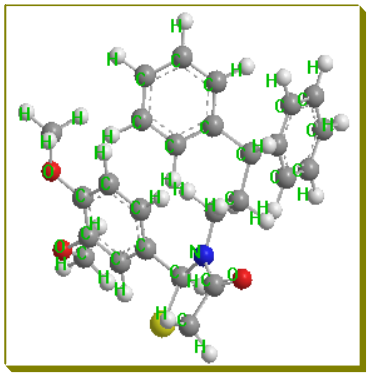


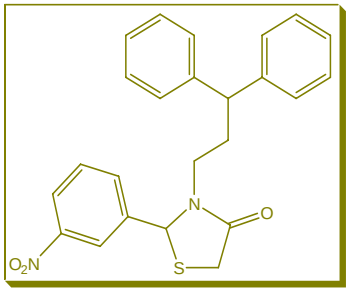
Synthesis and characterization of novel 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones derivatives.





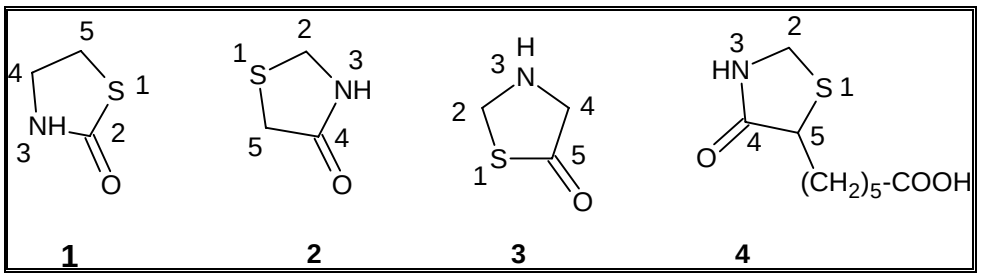






1.1 INTRODUCTION

Thiazolidinones which belong to an important group of heterocyclic compounds have been widely explored for their applications in the field of medicine. Thiazolidinones, with a carbonyl group at position 2 in structure **(1)** and position 4 or 5 in structure **(2, 3)** have been subjected of widespread study in the recent past. Numerous examples have appeared in the literatures which underscore their chemistry and use.[1-9]



Among the 4-thiazolidinone derivatives **(2),** substituents at the 2, 3 and 5 positions may be varied, but the greatest different in structure and properties is exerted by the groups attached to carbon atom at the 2-position and to nitrogen atom at the 3-position. The cyclic structure was assigned after recognition of mercaptoacetic acid as a primary product of hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinones.[10] A well known antibiotic, actithiazic acid **(4)**, isolated from a species of streptomyces showed specific in vitro activity against M. tuberculosis belongs to this class of agents.[11-12]

1.2 Synthetic methods for thiazolidinones

In General, the thiazolidinone motif can be prepared by one pot reaction of aldehyde, primary amine and mercaptoacetic acid.[13-22] several methods for the preparation of 4-thiazolidinone are narrated in literature described as follows.

1. Hongyu Zhou et al.[23] have synthesized a library of microwave-assisted 2-aryl-substituted 4-thiazolidinone and 4-thiazinanone derivatives (**Figure 1**).

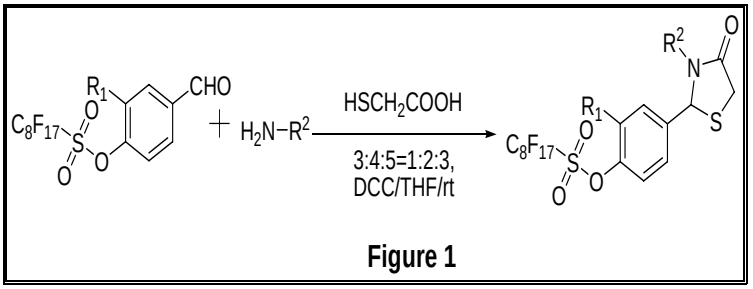


Figure 1

2. Ravindra K. Rawal et al.[24] have reported a series of compounds bearing isothiourea or thiourea functional group and have shown high anti-HIV-1 activity. Furthermore, a series of 2-aryl-3-heteroaryl-1,3-thiazolidin-4-ones was also reported by this group (**Figure 2**).

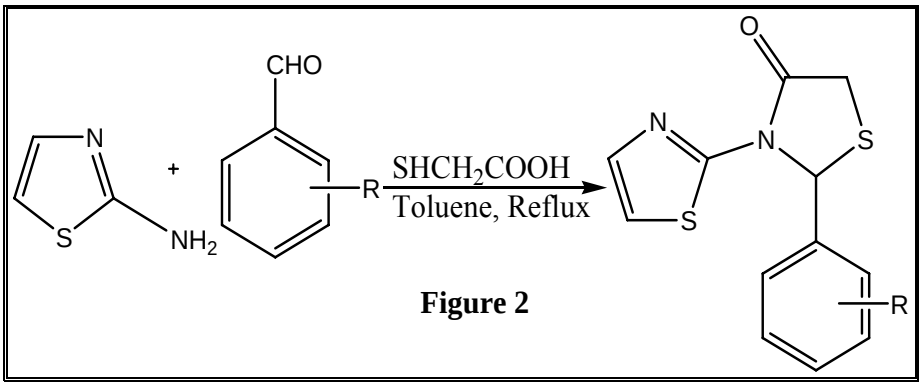


Figure 2

3. Tumul Srivastava et al.[25] have synthesized some new 4-thiazolidinones assembled by DCC mediated three-component reaction of amines, aldehyde and mercaptoacetic acid (**Figure 3**).

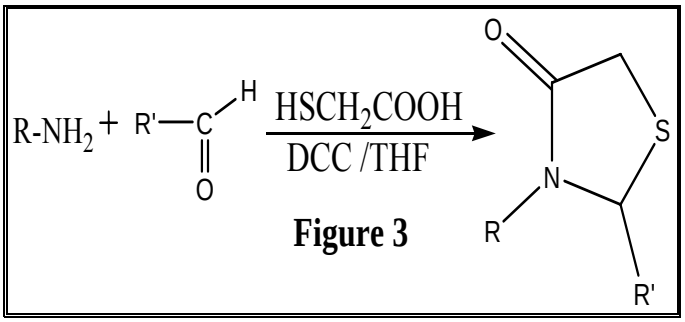


Figure 3

4. Zhong-Zheng Zhou et al.[26] have prepared a one-pot liquid-phase combinatorial synthesis of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones bearing diverse substituents at the 3-position under microwave irradiation using 3-formyl chromone, primary amine, and mercaptoacetic acid as reactants (**Figure 4**).

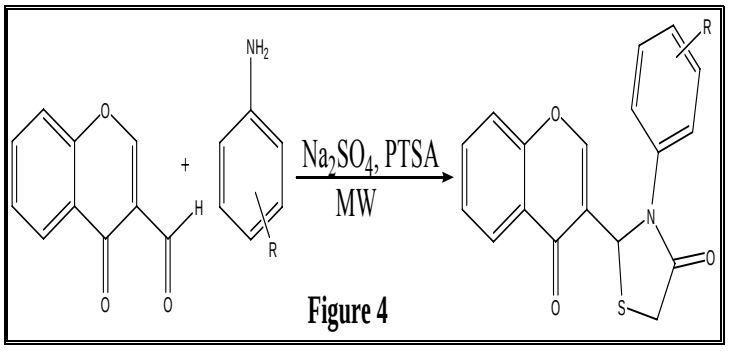


Figure 4

5. Christopher J. Hobbs et al.[27] have synthesized some new *N*-type (Cav2.2) calcium channel blockers derived from the 'hit' structures 2-(3-bromo-4-fluorophenyl)-3-(2-pyridin-2-ylethyl)thiazolidin-4-one and its 2-[4-(4-bromophenyl)pyridin-3-yl]-3-isobutyl analogues (**Figure 5**).

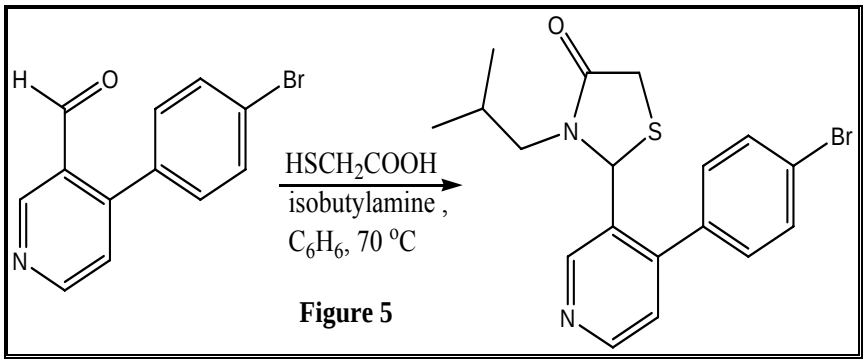


Figure 5

6. Adele Bolognese et al.[28] have described mechanistic and synthetic aspects of the formation of thiazolidine-4-one by the reaction of imines and mercaptoacetic acid under microwave and conventional heating (**Figure 6**).

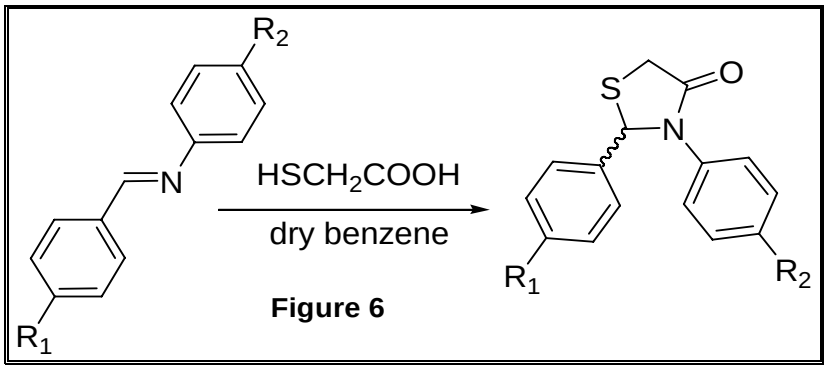


Figure 6

7. Joan Fraga-Dubreuil et al[29] have reported the efficient combination of task specific ionic liquid and microwave dielectric heating applied to one-pot three component synthesis of a small library of 4-thiazolidinones (**Figure 7**).

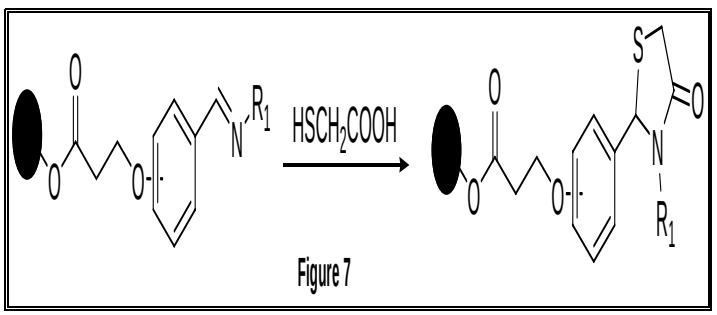


Figure 7

8. Bioactive venlafaxine analogs such as 2,3-disubstituted-1,3-thiazolidinones (**Figure 8**) have been synthesized and reported as antimicrobial agent by C. V. Kavitha and coworkers.[30]

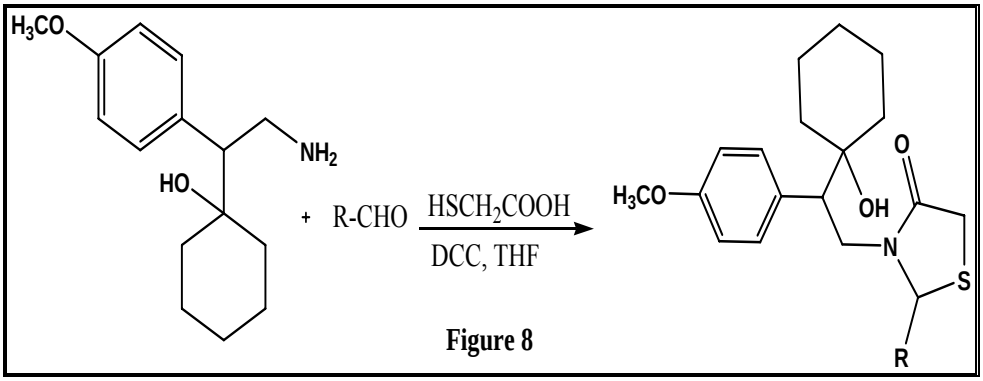


Figure 8

9. Denis R. St. Laurent et al.[31] have synthesized 4-thiazolidinone derivatives by the cyclization of unsymmetrical thiourea. H. S. Joshi and co-workers[32] has synthesized thiazolidinones bearing benzo[*b*]thiophene nucleus from *N*-arylaminothoxomethyl derivatives with chloroacetic acid in ethanol (**Figure 9**).

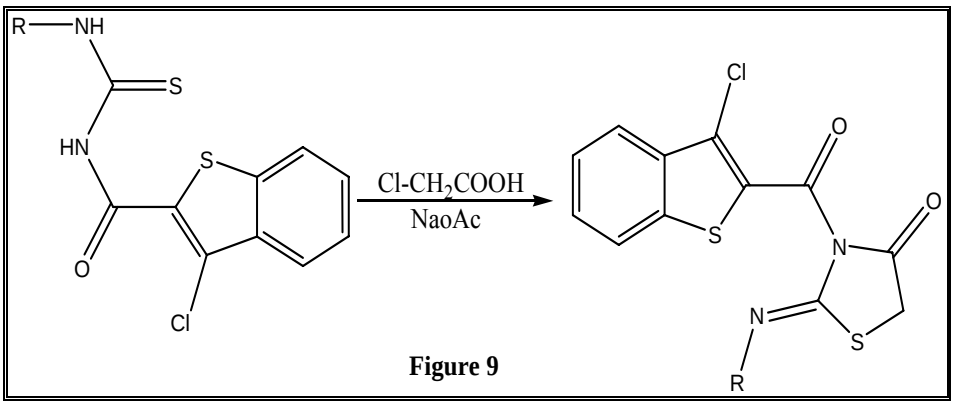


Figure 9

10. M. Shrinivas et al.[33] have reported some new thiazolidinones from isoxazolyl thiourea by treatment with chloroacetic acid and fused anhydrous sodium acetate in ethanol (**Figure 10**).

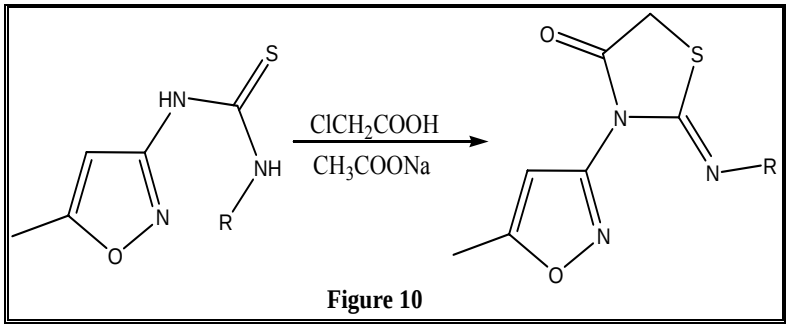


Figure 10

1.3 Mechanism

The reaction mechanisms of the formation of 4-thiazolidinones are well studied by[34] It was shown that the construction of 4-thiazolidinones proceeds by the attacks of the mercaptoacetic acid upon the C=S group, the tautomerism takes place with removal of water and subsequent cyclization (**Figure 11**).

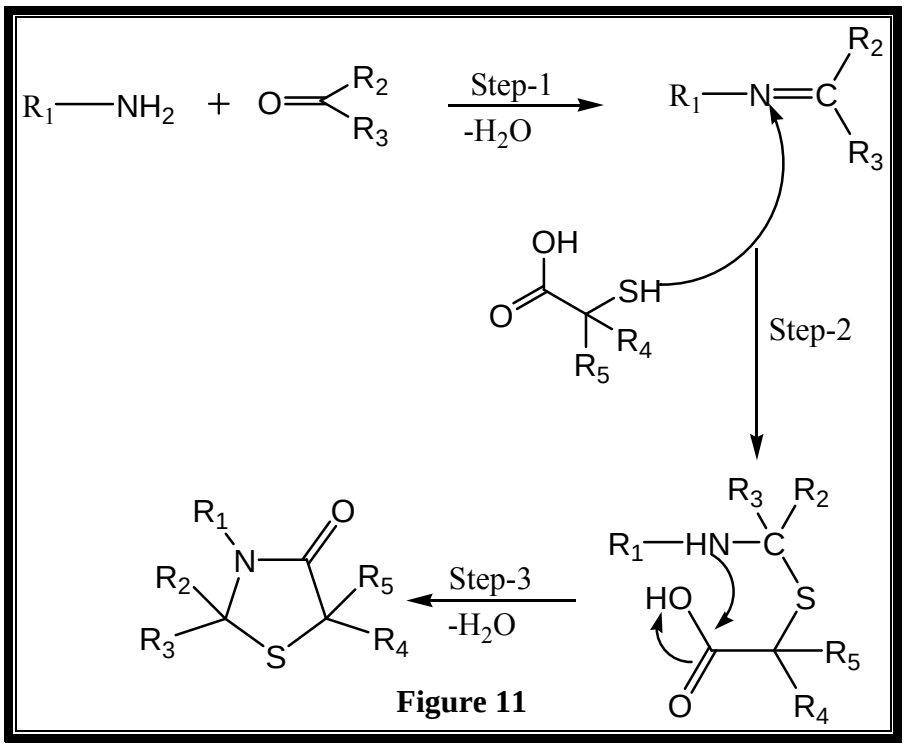


Figure 11

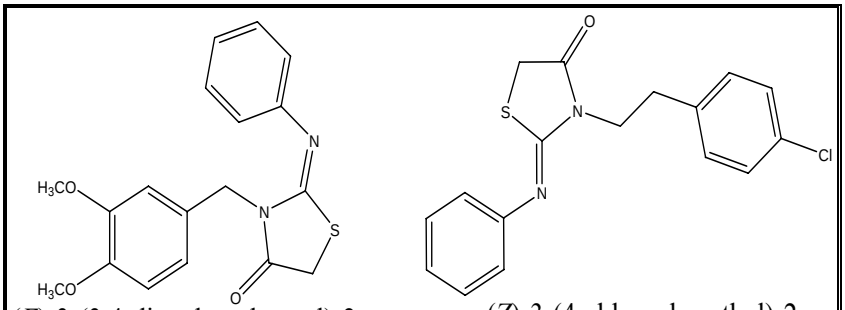
1.4 Biological activity of 4-thiazolidinones

As mentioned above, the 4-thiazolidinone derivatives possessed diverse biological activities such as anticonvulsant activity, Hypnotic activity, antitubercular activity, anthelmintic activity, cardiovascular effects, antibacterial activity, anticancer activity, antihistaminic activity (H1-antagonist), antifungal activity, antiviral activity, Anti-inflammatory activity (COX-inhibitors), Follicle stimulating hormone (FSH) receptor agonist activities which are described briefly as follows.

1.4.1 Anticonvulsant activity

The anticonvulsant activity of several series of 2-(arylimino)/(arylhydrazono)-3-aryl/(alkylaryl)/furfuryl/2-pyrimidyl/cycloalkyl/(substitutedamino)/(3-(*N*-morpholi-*n*-4-yl-propyl)-4-thiazolidinones (**Figure 12**) has been studied against pentylenetetrazol induced seizures [35-38] in albino mice of either sex ata dose of 100 mg/kg. Most of the compounds were found to exhibit protection against pentylenetetrazol-induced seizures,

and the degree of protection ranged up to 80%. However, no definite structure-activity relationship could be observed regarding the anticonvulsant activity possessed by thiazolidinones.



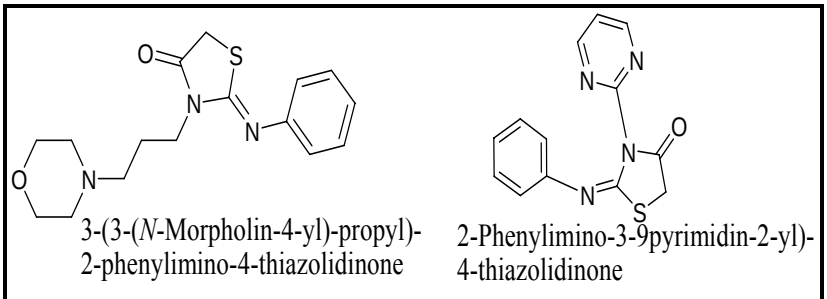
(*E*)-3-(3,4-dimethoxybenzyl)-2-(phenylimino)thiazolidin-4-one

(*Z*)-3-(4-chlorophenethyl)-2-(phenylimino)thiazolidin-4-one

Figure 12

1.4.2 Hypnotic activity

Several 3-(3-(*N*-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones[39] and 2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones[40] were also evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg (**Figure 13**). All thiazolidinones were found to potentiate pentobarbital sleeping time. The increase in the duration of sleep ranged from 10± 3 min in untreated control to 98.6± 10 min in mice pretreated with substituted thiazolidinones.



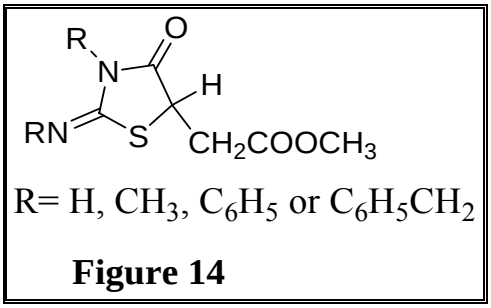
3-(3-(*N*-Morpholin-4-yl)-propyl)-2-phenylimino-4-thiazolidinone

2-Phenylimino-3-9pyrimidin-2-yl)-4-thiazolidinone

Figure 13

1.4.3 Antitubercular activity

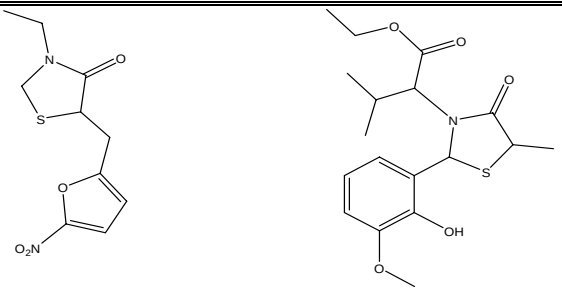
The 4-thiazolidinones also found to be effective against the multi-drug resistant tuberculosis, coupled with the increasing overlap of AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern.[41]



R= H, CH_3, C_6H_5 or $C_6H_5CH_2$

Figure 14

A few derivatives were found to inhibit the growth of human tubercle bacilli, H37Rv strain, in a concentration of 12.5 mg/mL (**Figure 15**).[41] Several other derivatives of thiazolidinones have also been found to inhibit the growth of *Mycobacterium tuberculosis* H37Rv strain (**Figure 15**).[42-44] In an attempt to find new inhibitors of the enzymes in the essential rhamnose biosynthetic pathway, a virtual library of 2,3,5 trisubstituted-4-thiazolidinones was created (**Figure 15**). These compounds were developed as diphosphate surrogates and inhibitors of MurB that bind at the nucleotide sugar site. It was found that the 4-thiazolidinone scaffold mimicked the diphosphate and specificity was generated through the different R-groups placed around the ring. These compounds were then docked into the active site cavity of 60 hydroxyl; dTDP-6-deoxy-D-xylo-4-hexulose 3,5-epimerase (RmlC) from *Mycobacterium tuberculosis*. Those, 30 (32%) have >50% inhibitory activity (at 20 mM) in the coupled rhamnose synthetic assay. This work proposed a hypothesis that the thiazolidinone scaffold can act as a diphosphate mimetic.[45] The effects of thiazolidinone derivatives on other Mycobacterium strains had also been found.[46-48]



3-ethyl-5-((5-nitrofuran-2-yl)methyl)thiazolidin-4-one

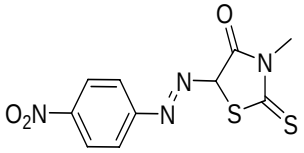
ethyl 2-(2-(2-hydroxy-3-methoxyphenyl)-5-methyl-4-oxothiazolidin-3-yl)-3-methylbutanoate

Figure 15

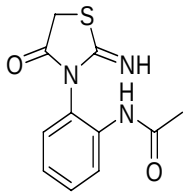
1.4.4 Anthelmintic activity

3-Methyl-5-[(4-nitrophenyl)azo]rhodanin, nitrodan (**Figure 16**), was reported as a potent anthelmintic compound.[49-51] which was effective when administered in feed against *Hymenolepsis nana* and *Syphacia obvelata* infections in mice, *Asceridia galli*

infections in chickens, and *Toxocera canis*, *Ancylostoma caninum*, and *Uncinaria stenocephala* infections in dogs, pigs and horses. 2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives have been found to be effective in vitro against horse Strongyloids at concentration of 10^{-3}–10^{-6} M.[52] Various 2-thiono-3-substituted-5-[(2-methyl-4-nitrophenyl)azo]-4-thiazolidinones and 2-thiono-3-methyl-5-[(2,4-dinitrophenyl)azo]-4-thiazolidinone as potent anthelmintic agents, which were not only effective alone but also showed activity with other parasiticides.[53-54]



3-methyl-5-[(4-nitrophenyl)azo] rhodanin

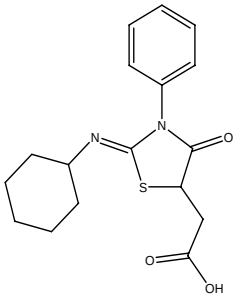


2-imino-3-(2-acetamidophenyl)-4-thiazolidinone

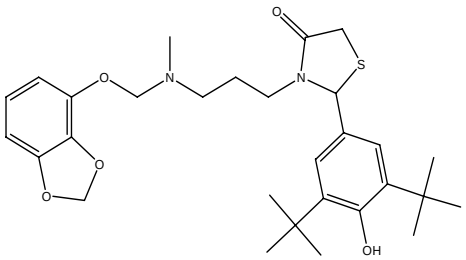
Figure 16

1.4.5 Cardiovascular effects

Cardiovascular effects of a series of 2-cyclopentyl/(cyclohexylimino)- 3-aryl-4-thiazolidinone-5-ylacetic acids (**Figure 17**) on adult cats of either sex were reported.[55] All substituted 4-thiazolidinones induced hypotension of varying degree. The duration of hypertensive activity observed with most of these compounds was less than 15 min.



2-(cyclohexylimino)-3-phenyl-4-thiazolidinone-5-ylacetic acid



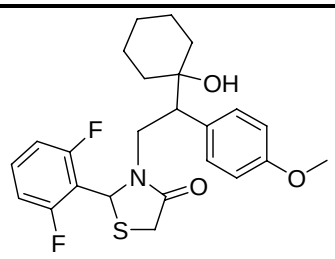
3-{3-[(Benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]-propyl}-2-(3,5-di-tert-butyl-4-hydroxy-phenyl)-thiazolidin-4-one

Figure 17

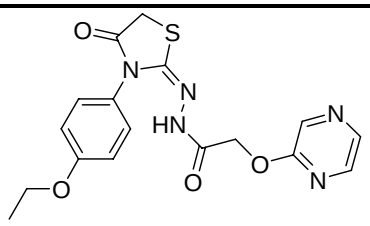
Suzuki et al. examined the effects of CP-060S (3-{3-[(Benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]-propyl}-2-(3,5-di-tert-butyl-4-hydroxy-phenyl)-4-thiazolidinone) (**Figure 17**) on cardiac function and myocardial oxygen consumption (MVO_2) in anesthetized dogs.[56] CP-060S (10-300 mg/kg IV) decreased heart rate, increased aortic flow and decreased mean blood pressure in a dose-dependent manner. The PR (pulse rate) interval was significantly prolonged by administration of CP-060S

(300 mg/kg IV). It increased coronary blood flow in a dose-dependent manner (10-300 mg/kg IV). Its effect on cardiac function and MVO_2 were qualitatively similar to those of diltiazem, a typical Ca-channel blocker.

1.4.6 Antibacterial activity



2-(2,6-Difluoro-phenyl)-3-[2-(1-hydroxycyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-4-thiazolidinone



(Pyrazin-2-yloxy)-acetic acid[3-(4-ethoxy-phenyl)-4-oxothiazolidin-2-ylidene]-hydrazide

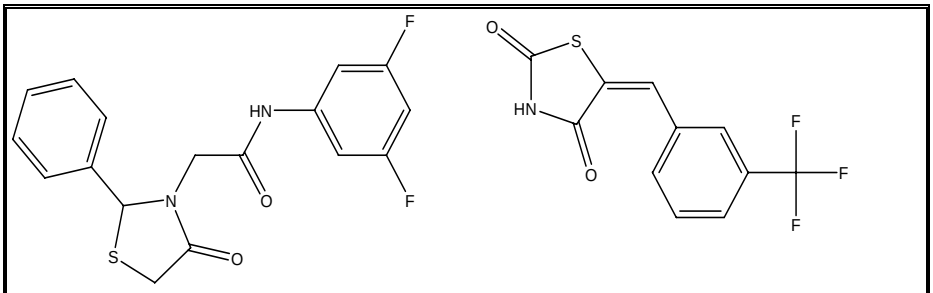
Figure 18

Several 2-[(dichlorophenyl)imino]-4-thiazolidinones and 2-(arylhydrazino)-4-thiazolidinones and their corresponding 5-arylidine derivatives were tested against *Staphylococcus aureus* (**Figure 18**). The antibacterial activity of 5-arylidine derivatives of both 2-[(dichlorophenyl)imino]/2-(arylhydrazino)-4-thiazolidinones was found greater than that of the parent compound.[57] The screening data of more than 50 thiazole and thiazolidinone derivatives against some common bacteria revealed that the thiazolidinones were more active than the thiazoles.[58] An enhancement in the activity was observed with mercurated thiazolidinone derivatives as compared to nonmercurated derivatives. Novel 2,3-disubstituted-1,3-thiazolidin-4-one derivatives which are venlafaxine analogs were tested against *Bacillus subtilis and Escherichia coli*, and found to exhibit potent inhibitory activity compared to that of standard drugs at the tested concentrations. From the results obtained, it was concluded that the presence of two fluorine atoms at 2nd and 6th positions in 2-(2,6-difluorophenyl)-3-[2-(1-hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-4 thiazolidinone might be the reason for the significant inhibitory activity.[59] Different derivatives of *N*-[3,4-disubstituted-1,3-thiazol-2(3*H*)-ylidene]-2-(pyrazin-2-yloxy)acetohydrazide and *N*-[(2)-3-(4-alkyl/arylsubstituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy)-acetohydrazide compounds when evaluated for antibacterial activity against the Gram-positive (*Staphylococcus aureus and Bacillus subtilis*) and Gram-negative (*Escherichia coli and Staphylococcus typhi*) strains of bacteria, showed good antibacterial activity. The structure activity relationship revealed that thiazolidine ring is essential for antibacterial

activity.[60] Bondock et al. reported some new 4-thiazolidinones synthesized from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde for their antimicrobial activity.[61] Thirteen compounds were screened in vitro for their antimicrobial activities against three strains of bacteria *Bacillus subtilis*, *Bacillus megaterium* and *Escherichia coli* by the agar diffusion technique.[62] A 1 mg/mL solution in dimethylformamide was used. The bacteria were maintained on nutrient agar and Czapek's-Dox agar media, respectively. Vicini et al. and other workers also examined some 4-thiazolidinone derivatives for their antimicrobial activity.[63]

1.4.7 Anticancer activity

A series of 2-aryl-4-oxo-thiazolidin-3-yl amides and derivatives were synthesized and evaluated for their ability to inhibit the growth of prostate cancer cells (**Figure 19**). The antiproliferative effects of synthesized compounds were examined in five human prostate cancer cell lines (DU-145, PC-3, LNCaP, PPC-1, and TSU), and in RH7777 cells (negative controls).



N-(3,5-Difluoro-phenyl)-2-(4-oxo-2-phenyl-thiazolidin-3-yl)-acetamide

5-(3-trifluoromethylbenzylidene)-2,4-thiazolidinedione

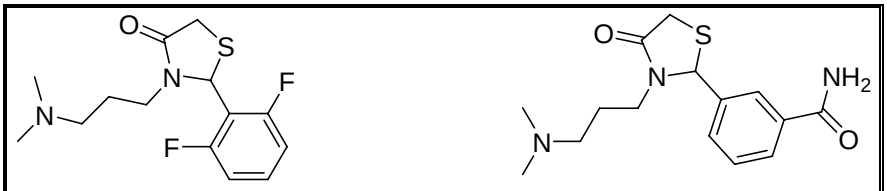
Figure 19

From these studies, few potent compounds were detected, which were effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates (SAPs).[64] Cyclooxygenase (COX) is a well-known enzyme that catalyzes the conversion of arachidonic acid to prostaglandins (PGs) in the cells. However, PGs are also important in cancer pathogenesis. Study reported COX-2 inhibitors as potential drugs aimed at the prevention and treatment of cancer, especially colorectal cancer. Some representative 2-phenylimino-4-thiazolidinones have been investigated as potent inhibitors of the growth of human colon carcinoma cell lines with a different COX-2 expression. The antiproliferative in vitro screening was performed on five cell lines of human colon cancers, such as DLD-1,[65] HCT-116,[66] HT-29,[67] HCT-8,[68] and H-630,[69]

obtained from the American Type Culture Collection (Manassas, VA); among them, HT-29 cell line expresses high COX-2 levels.[70-72] Derivative 5-(3-trifluoromethyl benzylidene)-2,4-thiazolidinedione which does not interact with COX enzymes, inhibited the growth of HT- 29 cells. This compound displayed activity on all cell lines, mainly on the DLD-1.[73]

1.4.8 Antihistaminic activity (H1-antagonist)

Thiazolidinone are also known to show their action on histamine receptors. The geometrical similarity between 2-aryl-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones (**Figure 20**) and different histamine (H1) antagonists such as bamipine, clemastine, cyproheptadine, triprolidine, promethazine, chlorpheniramine, and carbinoxamine [74-75] prompted Diurno et al. to evaluate these compounds for antihistaminic activity.[76] Singh et al. have investigated the antihistaminic (H1-antagonist) activity of 2,3-disubstituted thiazolidin-4-ones and concluded that the hydrophobic substitution at the 4-position of the phenyl ring and cumulative negative polar effects of all the substituents in the phenyl group are advantageous for antihistaminic activity.[77-78]



2-(2,6-Difluoro-phenyl)-3-(3-dimethylamino-propyl)-4-thiazolidinone

2 -(3 -Carbamoyl-phenyl)-3 -[3 -(N,N-dimethylamino)-propyl] -1,3 -thiazolidin-4 -one

Figure 20

In another study, Diurno et al. synthesized, characterized and evaluated a series of 2-(substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-ones for their capacity to inhibit the contraction induced by histamine on guinea pig ileum.[79] 2-(3-Carbamoyl-phenyl)-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-one and derivatives as free bases were converted into the corresponding hydrochlorides for the pharmacological assays (**Figure 20**). The H1-antihistaminic activity of the synthesized compounds was evaluated in vitro by measuring their ability to inhibit the histamine-induced contractions of isolated guinea pig ileum.[80] Results showed that whenever the phenyl moiety of the 4-thiazolidinones interacts with a complementary area of the H1-receptor, the **p** interaction was enhanced by hydrophobic substituents increasing the

HOMO energy and is affected by the size of the 4-alkyl substituents. These studies have highlighted the importance of overall hydrophobicity of the compounds in deciding the antihistaminic activity.[81-82]

1.4.9 Antifungal activity

Rao et al. have reported high fungal activity of some mercurated derivatives of 4-thiazolidinones against Aspergillus niger at a dilution of 1:10,000. Various 2-(40-arylthiazolyl-20-imino)- 3-aryl-4-thiazolidinones have been found to be sufficiently active against *Aspergillus niger* and *Alternaria tenius* at a dilution of 1:10,000.[83] Matolcsy et al. have found very high antifungal activity associated with the derivatives of 2-thiono-4-thiazolidinones against *Alternaria tenius* and *Botrytis allii*. Several 2-[(o-methylphenyl) imino]-3-aryl-4-thiazolidinones and their 5-phenylazo derivatives have been found to be very good fungicidal agents against *Helminthosporium euphorbiae*.[84] 3-ethyl-5-methyl-2-[(4-chlorobenzthiazol-2-yl)imino]-4-thiazolidinone and 3-ethyl-5-methyl-2-[(5-chlorobenzo- thiazol-2-yl)imino]-4-thiazolidinone were found to exhibit 100% inhibition of spore germination of *Alternaria tenius* at concentration of 1:1000, 1:5000 and 1:10,000.[85]

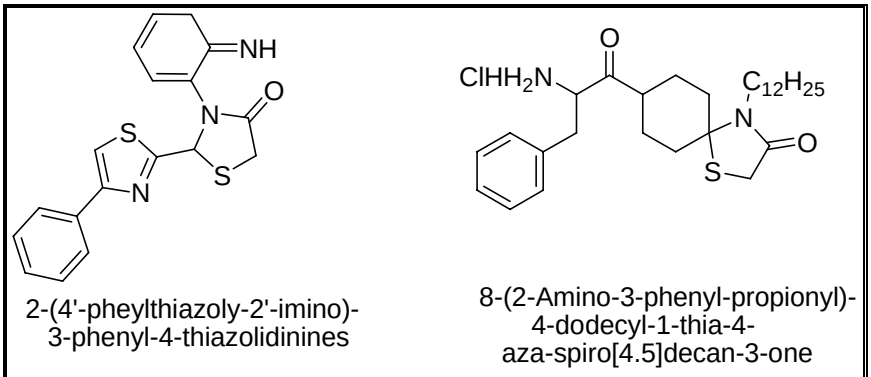


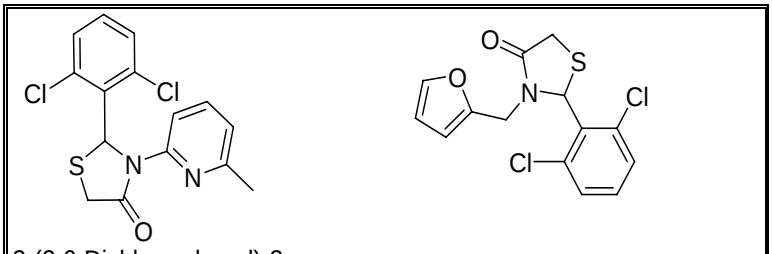
Figure 21

Katti et al. synthesized 8-(2-amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro [4.5] decan-3-one(**Figure 21**) and derivatives and evaluated against two strains of *Candida albicans* and one strain of *Cryptococcus neoformans* in terms of (MIC) in 50 mg/mL, following the Serial Double Dilution reference method[86] and found to possess moderate to good activity against the three fungal strains(**Figure 21**).[87] Recently Dandia et al. screened few microwave synthesized spiro[3*H*-indole-3,2′-thiazolidine]-3′(1,2,4-triazol-3-yl)-2,4′(1*H*)-dione for their antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani*, causing root of okra, *Fusarium oxysporum*, causing wilt of mustard and *Colletotrichum capsici*, causing leaf spot and it was found that all

compounds show good activity against these pathogens, indicating that the incorporation of triazole ring enhances the antifungal activity of compounds (**Figure 21**).[88] Baynate and Thiram, recommended as standard fungicides as seed dressers to control this disease, also have a –N–C–S linkage, similar to the synthesized compounds, which is responsible for their antifungal activity.

1.4.10 Antiviral activity

Recently, there are several reports in the literature have been found regarding the anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones (**Figure 22**). Some derivatives proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentration with minimal cytotoxicity. They act by inhibiting reverse transcriptase enzyme, which plays an essential and multifunctional role in the replication of the human immunodeficiency virus (HIV). Barreca designed and synthesized 2,3-diaryl-1,3-thiazolidin- 4-one derivatives as new NNRTIs.[89]



2-(2,6-Dichloro-phenyl)-3-(6-methyl-pyridin-2-yl) 4-thiazolidinone

2-(2,6-Dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone

Figure 22

Results showed that the compounds were highly potent anti- HIV agents, up to 10-fold more active than the corresponding 1-arylsubstituted 1*H*, 3*H*-thiazolo[3,4-a]benzimidazole derivative (TBZs) lead compounds, probably because conformational changes may allow the correct positioning of the new molecules for a facile attack at the active site residues. Mechanism of action of the compounds was attributed to the inhibition of HIV-1 RT. In addition, these compounds were minimally toxic to MT-4 cells and their selectivity indices were remarkably high. In fact, 6-methylpyridin-2-yl derivatives, particularly compound 2-(2,6-dichlorophenyl)-3-(6-methyl-pyridin-2-yl)-4-thiazolidinone (**Figure 22**), possessed the most promising selectivity index of 6470 and activity with EC_{50} value of 0.044 mM. In terms of SARs, anti-HIV activity was strongly enhanced by introducing a 2-pyridinyl substituent at the *N*-3 atom of the thiazolidinone ring and in particular by two chlorine atoms at 20 and 60 positions of the phenyl rings at

C-2. In another study, Katti et al. in collaboration with E. De Clercq and his group have reported that some novel 2,3-diaryl substituted 4-thiazolidinone derivatives containing *N*-3-substituted furfuryl amine particularly, 2-(2,6-dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone, show promising HIV-RT inhibitory activity by determining their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells with EC_{50} value of 0.204 mM .[90]

1.4.11 Anti-inflammatory activity (COX-inhibitors)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an inhomogeneous family of pharmacologically active compounds used in the treatment of acute and chronic inflammation, pain, and fever. Although several mediators support the inflammatory processes, the main target of NSAIDs is cyclooxygenase (COX),[91] the enzyme involved in the first step of the conversion of arachidonic acid to prostaglandins (PGs). The latter regulate important functions in the gastric, renal, and emetic systems and are known to mediate all inflammatory responses.[92-93] The therapeutic effects are mainly due to the decrease of proinflammatory PGs produced by COX-2, whereas their unwanted side effects result from the inhibition of constitutive COX-1 isoform.

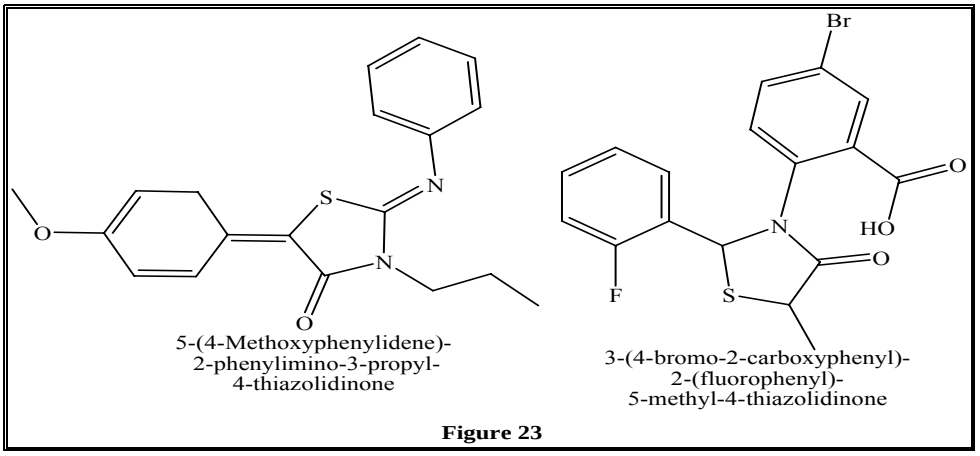
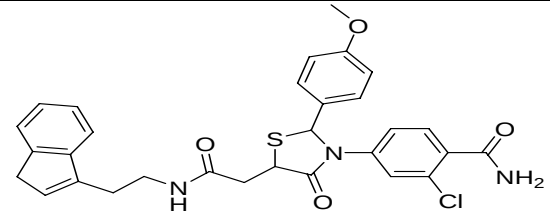


Figure 23

Ottana et al. have investigated 3,3′-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives (**Figure 23**), which showed interesting stereoselective anti-inflammatory/analgesic activities together with better gastrointestinal safety profile than known NSAIDs,[94] suggesting that they might preferentially interact with inducible COX-2 isoform. Synthesized 2-imino-4-thiazolidinones and 5-arylidene-2-imino-4-thiazolidinones were tested for in vivo anti-inflammatory activity in models of acute inflammation such as carrageenan-induced paw edema and pleurisy assays in rats.[95-96] All derivatives exhibited significant activity levels. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoform was assessed in murine

monocyte/macrophage J774 cell line assay.5-(4-Methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone, the most interesting compound, showed promising interaction for COX-2 selectivity at concentration of 1 and 10 mM with 35 and 55% inhibition, respectively. In another study, Kumar et al. synthesized some new anthranilicacid derivatives, 2-substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinones and evaluated them for anti-inflammatory activity against carrageen an-induced edema in albino rats. The most active member of the series, 3-(4-bromo-2-carboxyphenyl)-2-(fluorophenyl)-5-methyl-4-thiazolidinon was compared (**Figure 23**) with phenylbutazone for its relative anti-inflammatory potency at three graded oral doses (25, 50 and 100 mg/kg) and were found nearly equipotent, with ED_{50} =100.0 and 94.4 mg/kg, respectively.[97] Ottana et al. described the anti-inflammatory activity of 5-arylidene-2-imino-4-thiazolidinones.[98] All derivatives exhibited significant activity in models of acute inflammation such as carrageenan-induced paw and pleurisy edema in rats. In particular, 5-(3-methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone displayed high levels of carrageenan-induced paw edema inhibition, comparable to those of indomethacin. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoforms was assessed in murine monocyte/macrophage J774 cell line assay. 5-(4-methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone, the most interesting compound in such an experiment, was docked in the known active site of COX-2 protein and showed that its 4-methoxyarylidene moiety can easily occupy the COX-2 secondary pocket considered as the critical interaction for COX-2 selectivity.

1.4.12 Follicle stimulating hormone (FSH) receptor agonist activity



2-Chloro-4-[5-{[2-(3H-inden-1-yl)-ethylcarbamoyl]-methyl}-2-(4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide

Figure 24

Maclean et al. reported the FSH agonist activity of an encoded 4-thiazolidinone library.[99] Among the hits discovered in these studies was compound 2-chloro-4-[5-{[2-(3*H*-inden-1-yl)-ethylcarbamoyl]-methyl}-2-(4-methoxy-phenyl)-4-oxothiazolidin-3-yl]-benzamide (Figure **24**), which possessed moderate activity as an agonist of FSH, by virtue of its ability to stimulate a reporter cell line expressing the FSH receptor.[100] FSH is

a 31-kDa heterodimeric glycoprotein, and the discovery of a small molecule FSH agonist was an unprecedented achievement.[101] An orally active compound of this class could be a useful addition to the portfolio of drugs available for the alleviation of female infertility.

1.5 Aim of current work

As described above, the thiazolidinone and its derivatives are an important class of heterocyclic compounds because of their broad spectrum of biological activities, such as COX-1 inhibition, [2] anti-inflammatory, [102] antiproliferative, [73, 103] antihistaminic,[5] and anti-HIV activities.[104-105]

The search for new synthetic analgesics has led to the preparation of diphenyl-propylamine derivatives. A comprehensive survey of this work has been given. Lindner[106] and Kochsiek, *et al.,*[107] reported on a new therapeutic action of one member of this group. The novel 3,3-diphenylpropylamine (**Figure 25**), is a coronary dilator of prolonged action. Moreover, 3,3-diphenylpropylamine is a key intermediate of lercanidipine drug[108] (**Figure 26**).

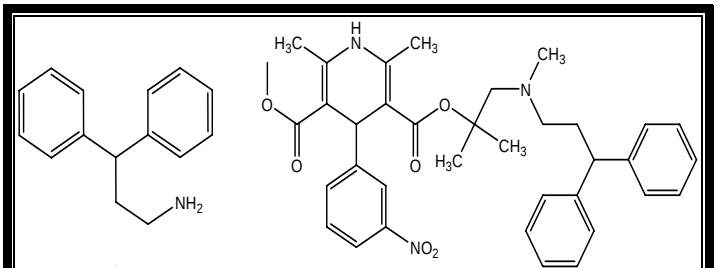


Figure 25 **Figure 26**

In view of the above observations, the synthesis of novel 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones derivatives has been developed starting from 3,3-diphenylpropylamine and various substituted aromatic aldehyde with the aim of investigating their biological activities.

1.6 Chemistry

The synthetic strategies adopted to obtain the target compounds are depicted in **Schemes 1**. The key intermediate **3** was prepared in an moderate yield in two consequence steps by condensing 3,3diphenylpropylamine **(1)** with various benzaldehyde **(2)** to afford Schiff's base **3** , which was reacted with mercaptoacetic acid in toluene. Thus, refluxing **3** in toluene in the presence of catalytic amount of AcOH furnished 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones. However, the yields were moderate.

To find better reaction conditions, next we investigated the application of fuller's earth in a two-step reaction sequence for preparation of 4-thiazolidinones. We found that the 4-thaizolidinones can be prepared in excellent yield by microwave-assisted fuller's earth-catalyzed reaction of various benzaldehydes with amines and mercaptoaceticacid. The results are reported herein.

1.7 Results and discussion

The synthesis of substituted thiazolidin-4-ones **4a–r** (**Scheme 1**) was performed using a microwave irradiation and conventional procedure. All the reactions were performed in closed vessels and the microwave program was composed of appropriate ramping and holding steps. Identification of the optimum profile power at 350W and time for the experiments is reported in **Table 1**.

We first performed conventional method in the reaction using 3,3diphenylpropyl amine **1** as a starting material for a three-component reaction. 3,3diphenylpropylamine **1** was first reacted with appropriate aldehyde **2a-r** in toluene at reflux temperature followed by reaction with mercaptoacetic acid in presence of catalytic amount of AcOH yielded compounds **4a**–**r** in moderate yields (**Table 1**).

Table 1: Yields of the thiazolidinones 4a–r by conventional and microwave-irradiation method

Entry	R_1	Conventional Method		Microwave Method	
		Time(hr)	Yield (%)*	Time(min)	Yield (%)*
4a	H	25	50	3.4	92
4b	4-OCH_3	21	53	3.5	95
4c	4-F	23	60	3.0	92
4d	3-Cl	29	52	3.6	89
4e	4-NO_2	30	50	4.5	90
4f	4-Cl	28	55	3.8	87
4g	2-NO_2	30	43	4.0	85

4h	3-NO_2	25	46	3.9	85
4i	2-Cl	27	48	3.6	88
4j	3,5 di-fluoro	30	37	6.8	87
4k	2-OH	26	35	7.2	85
4l	3-OH	22	41	7.5	86
4m	4-OH	20	45	6.8	89
4n	2-Br	24	36	5.3	85
4o	3-Br	25	43	6.0	88
4p	4-Br	24	45	6.2	90
4q	4-OH, 3-OCH_3	28	38	7.4	87
4r	5- NO_2, 4-OH, 3-OCH_3	30	30	7.5	85

*Isolated yield

Preliminary experiments to examine the reaction time, the solvent, and irradiation power were performed using 3,3-diphenylpropylamine **1** (0.01 mol) and appropriate aldehydes **2a-r** (0.01 mol), mercaptoacetic acid (0.01 mol) and fuller's earth (100 mg) catalyzed was irradiated under microwave oven for 3 to 7.5 min at 350W as a model system to synthesize the compound **4a** and **4b** (**Table 2)**. Various reaction times and irradiation power were tested using various solvent (**Table 2**). All comparative reactions were conducted under optimized conditions, and compound **4a** and **4b** was obtained under MW irradiation. The best yield of **4b** (95%) was obtained by carrying out the reaction in DMF under MW irradiation (350 W) for 3.5 min. Compare to the other solvents including methanol (MeOH), acetonitrile (MeCN), and tetrahydrofuran (THF) (Table 2), the use of DMF resulted in a faster reaction with a higher yield, in contrast to a reaction in less polar THF. When the reaction was carried out with conventional heating (**Table 1**), it requires extended heating time (24-30 h), providing the product in a lower yield (30–60%).

Table: 2 Reaction of 4a and 4b in various solvents using in microwave Irradiation

Entry	Solvent	Mode of Activation	Time	Power	Yield (%)*
4a	DMF	MW	3.4 min	350 W	92
4a	THF	MW	5.0 min	350 W	55
4a	MeOH	MW	5.5 min	350 W	61
4a	MeCN	MW	7.0 min	350 W	60
4b	DMF	MW	3.5 min	350 W	95
4b	THF	MW	4.5 min	350 W	56
4b	MeOH	MW	5.5 min	350 W	60
4b	MeCN	MW	7.5 min	350 W	58

*Isolated yield

These results confirm that the focused microwave irradiation is a very effective technique for accelerating thermal organic reactions. Thus, it has been found that reaction of substituted aldehyde (**2a-r**) derivatives (**Scheme 1**) with 3,3diphenylpropylamine in the presence of fuller's earth followed by the cyclocondensation with mercaptoacetic acid gives the novel 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones (**4a-r**), the corresponding thiazolidinones **4a–r** was obtained in 85 to 95% yield.

The structures of **4a-r** were established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR, and ^{13}C NMR). For example, compound **4a** showed molecular peak at m/z: 374[M + 1], 373[M^{+}], which agrees with its molecular formula $C_{24}H_{23}NOS$. The structure of **2-phenyl-3-(3,3-diphenylpropyl)thiazolidin-4-one (4a)** was assigned to the transient species **4a** on the basis of ^{1}H NMR resonances. The C2–H signal appears as a doublet at 5.49 δ long range coupled (d, 1H, J =1.76 Hz, SCHPh) with the higher field proton of the C5 geminal system at 3.79 δ (dd, 1H, J =1.92, 2.28 Hz, SCH_{α}) and 3.82 δ (d, 1H, J = 7.84 Hz, SCH_{β}) in accordance with the cyclic structure **4a** reported in **Scheme 1**. On the basis of this evidence, it seems reasonable to attribute the structure of a cyclic *gem*-diol to the transient species **4a**, in which the two long-range coupled protons participate in a W-arrangement, an observation consistent with the literature.[109-112] The ^{13}C NMR displayed peaks at 41.27 (SCH_2), 61.21 (NCHPh), 160.90

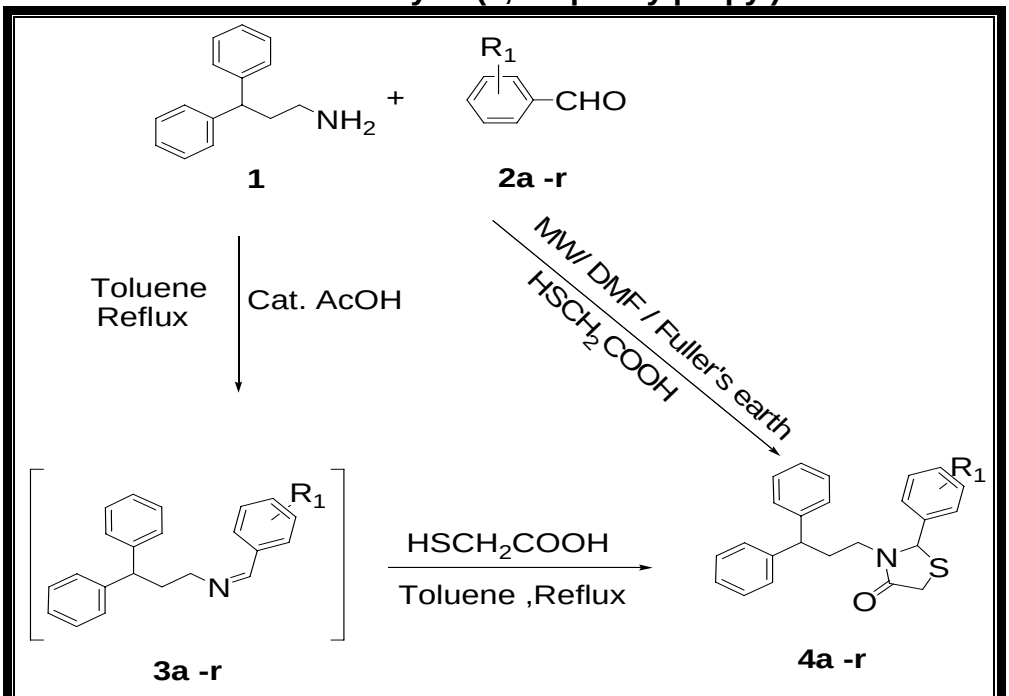
(PhC-F) and 170.25 (C=O), which account for all the carbon atoms in the molecule. In the IR spectra, bands in the 3064-3063 cm^{-1} and 1666-1662 cm^{-1} regions attributed to (C-H, Ar-H) and C=O stretching of the compounds **4a-r** respectively. New C=O bands (1666-1662 cm^{-1}) in the IR spectra of thiazolidin-4-ones provided confirmatory evidence for ring closure.[113-115]

Comparison of the results for 18 compounds showed that microwave-assisted irradiation improved the yields by 20% to 60% compared to those obtained using conventional heating technique. Although the yield of compound **4j** and **4r** was moderate, it was still greater then that achieved under conventional heating, and was obtained in a reaction time of 3 to 7.5 min rather than 30 h (**Table 1**).

1.8 Conclusion

In summary, we have established a rapid and economical procedure for constructing novel 2-aryl-3-(3,3diphenylpropyl)thiazolidin-4-ones using fuller's earth as a catalyst. Comparison of the proposed method with conventional syntheses of the same compound showed that the microwave-assisted syntheses were characterized by much shorter reaction times and higher product yields. The newly developed protocol is efficient for the rapid synthesis of 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones *via* one-pot three-component strategy under microwave irradiation.

1.9 Reaction scheme of 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones



Scheme 1: Synthesis of Thiazolidinones 4a-r

1.10 Experimental procedure

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator.

1.10.1 By conventional heating

A mixture of 3,3-diphenylpropylamine (**1**, 0.01 mol) and appropriate aldehydes (**2a-r**, 0.01 mol) in dry toluene (25 ml) was refluxed until no more water was collected in a Dean–Stark water separator. The reaction being monitored by TLC. To this crude mixture, mercaptoacetic acid (0.01 mol) was added dropwise and the reaction mixture was heated at reflux temperature for 10-15 h. The reaction mixture was cooled to room temperature and evaporated to dryness under *vaccuo*. The crude compound (**4a-r**) obtained was taken up in chloroform (200 mL). The organic layer was washed with 5% aq. citric acid (100 mL), followed by water (200 mL), 5% aqueous sodium hydrogen carbonate (100 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography (SiO_2) using hexane–ethyl acetate (8:2) as an eluent. The fraction containing main products were combined and evaporated to dryness under reduce pressure. The residue was crystallized from ethanol to give pure product **4a-r**.

1.10.2 By microwave heating

A well stirred mixture of 3,3-diphenylpropylamine (**1**, 0.01 mol) in 25 ml dimethylformamide, appropriate aldehyde (**2a-r**, 0.01 mol), mercaptoacetic acid (0.01 mol) and fuller's earth (100 mg) was irradiated under microwave oven for 3 to 7.5 min at 350W. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was taken up in chloroform and extracted with water. The organic layer was washed with 5% aqueous citric acid (100 mL), followed by water (200 mL), 5% aqueous

sodium hydrogen carbonate (100 mL) and brine (100 mL). And dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2) using hexane–ethyl acetate (8:2) as an eluent. The fraction containing the main products were combined and evaporated to dryness under reduce pressure. The crude product thus obtained was crystallized from ethanol to afford the targeted 4-thiazolidinones (**4a-r)**.

Similarly, other 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones were prepared.

2-phenyl-3-(3,3-diphenylpropyl)thiazolidin-4-one (4a). This compound was obtained as yellow solid in 92% yield. mp 114–116 °C; Anal. Calcd for $C_{24}H_{23}NOS$: C, 77.18; H, 6.21; N, 3.75; Found: C, 77.03; H, 6.08; N, 3.60; m/z: 373[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.15-2.30 (m, 2H, CH_2), 2.69–2.76 (m, 1H, CH), 3.49–3.64 (m, 2H, CH_2), 3.74–3.83 (m, 2H, CH_2), 5.49 (d, *J*=1.70 Hz, 1H, CH), 7.07–7.23 (m, 10H, Ar), 7.24 (s, 2H, Ar), 7.34–7.36 (m, 3H, Ar), IR (KBr) (cm^{-1}): 3060-3024, 1660, 1610, 1520, 1340, 1268, 1225, 1150.

2-(4-methoxyphenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4b). This compound was obtained as white solid in 95% yield. mp 135–134 °C; Anal. Calcd for $C_{25}H_{25}NO_2S$: C, 74.41; H, 6.24; N, 3.47; Found: C, 74.25; H, 6.08; N, 3.32; m/z: 403[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.09–2.26 (m, 2H, CH_2), 2.68–2.76 (m, 1H, CH), 3.45–3.59 (m, 2H,CH_2), 3.72–3.81 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 5.47 (d, *J*=1.40 Hz, 1H, CH), 6.85 (d, *J*=8.72 Hz, 2H, Ar), 7.07 (m, 12H, Ar), IR (KBr) (cm^{-1}): 3060-3028, 1666, 1608, 1524, 1348, 1268, 1218, 1148.

2-(4-fluorophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4c). This compound was obtained as off-white solid in 92% yield. mp 98–100°C; Anal. Calcd for $C_{24}H_{22}FNOS$: C, 73.63; H, 5.66; N, 3.58; Found: C, 73.50; H, 5.52; N, 3.41; m/z: 391[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.18–2.31 (m, 2H, CH_2), 2.65–2.72 (m, 1H, CH), 3.52-3.63 (m, 2H, CH_2), 3.74–3.84 (m, 2H, CH_2), 5.47 (d, *J*=1.84 Hz, 1H, CH), 7.05–7.22 (m, 10H, Ar), 7.23–7.33 (m, 4H, Ar), IR (KBr) (cm^{-1}): 3063-3026, 1666, 1597, 1492, 1406, 1330, 1220, 1197; ^{13}C NMR (400 MHz, DMSO): 31.43, 31.98, 41.27, 48.15, 61.21, 115.55, 155.75, 126.18, 128.43, 136.32, 144.28, 160.90.

2-(3-chlorophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4d). This compound was obtained as white solid in 89% yield. mp 119–121°C; Anal. Calcd for $C_{24}H_{22}ClNOS$: C, 70.66; H, 5.44; N, 3.43; Found: C, 70.49; H, 5.28; N, 3.28; m/z: 407 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.12–2.15 (m, 1H, CH), 2.22–2.26 (m, 1H, CH), 2.64–2.71 (m, 1H, CH), 3.48–3.55 (m, 1H, CH), 3.60–3.64 (m, 1H, CH), 3.72–3.83 (m, 2H, CH_2), 5.47 (d, *J*=1.64 Hz, 1H, CH), 6.99–7.21 (m, 10H, Ar), 7.21–7.24 (m, 4H, Ar), IR (KBr) (cm^{-1}): 3064-3026, 1662, 1600, 1523, 1346, 1269, 1220, 1155.

2-(4-nitrophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4e). This compound was obtained as yellow solid in 90% yield. mp 153–155°C; Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69; Found: C, 68.70; H, 5.15; N, 6.57; m/z: 418 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.23–2.29 (m, 2H, CH_2), 2.57–2.65 (m, 1H, CH), 3.61–3.68 (m, 2H, CH_2), 3.75–3.84 (m, 2H, CH_2), 5.53 (d, *J*=1.76 Hz, 1H, CH), 7.12–7.28 (m, 10H, Ar), 7.31 (d, *J*=8.72 Hz, 2H, Ar), 8.17 (d, *J*=8.72 Hz, 2H, Ar), IR (KBr) (cm^{-1}): 3073-3036, 1667, 1587, 1482, 1416, 1340, 1230, 1187.

2-(4-chlorophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4f). This compound was obtained as yellow solid in 87% yield. mp 128–130°C; Anal. Calcd for $C_{24}H_{22}ClNOS$: C, 70.66; H, 5.44; N, 3.43; Found: C, 70.48; H, 5.30; N, 3.30; m/z: 407 [M^+]; IR (KBr) (cm^{-1}): 3064-3036, 1668, 1610, 1525, 1340, 1267, 1225, 1158.

2-(2-nitrophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4g). This compound was obtained as yellow solid in 85% yield. mp 118–120°C; Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69; Found: C, 68.71; H, 5.14; N, 6.55; m/z: 418 [M^+]; IR (KBr) (cm^{-1}): 3066-3022, 1661, 1598, 1511, 1340, 1264, 1223, 1145.

2-(3-nitrophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4h). This compound was obtained as yellow solid in 85% yield. mp 140–142°C; Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69; Found: C, 68.69; H, 5.16; N, 6.56; m/z: 418 [M^+]; IR (KBr) (cm^{-1}): 3068-3029, 1667, 1605, 1528, 1354, 1264, 1221, 1153.

2-(2-chlorophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4i). This compound was obtained as off-white solid in 88% yield. mp 105–107°C; Anal. Calcd for $C_{24}H_{22}ClNOS$:

C, 70.66; H, 5.44; N, 3.43; Found: C, 70.44; H, 5.27; N, 3.24; m/z: 407 [M^+]; IR (KBr) (cm^{-1}): 3064-3026, 1660, 1615, 1528, 1340, 1260, 1230, 1145.

2-(3,5-difluorophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4j). This compound was obtained as off-white solid in 87% yield. mp 104–106°C; Anal. Calcd for $C_{24}H_{21}F_2NOS$: C, 70.39; H, 5.17; N, 3.42; Found: C, 70.23; H, 5.01; N, 3.28; m/z: 409 [M^+]; IR (KBr) (cm^{-1}): 3064-3025, 1660, 1620, 1528, 1344, 1266, 1222, 1153.

2-(2-hydroxyphenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4k). This compound was obtained as white solid in 85% yield. mp 108–110°C; Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60; Found: C, 73.87; H, 5.80; N, 3.47; m/z: 389 [M^+]; IR (KBr) (cm^{-1}): 3070-3030, 1666, 1610, 1518, 1340, 1263, 1225, 1165.

2-(3-hydroxyphenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4l). This compound was obtained as white solid in 86% yield. mp 126–128°C; Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60; Found: C, 73.84; H, 5.83; N, 3.45; m/z: 389 [M^+]; IR (KBr) (cm^{-1}): 3068-3036, 1669, 1610, 1533, 1356, 1259, 1230, 1145.

2-(4-hydroxyphenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4m). This compound was obtained as white solid in 89% yield. mp 142–144°C; Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.60; Found: C, 73.85; H, 5.81; N, 3.46; m/z: 389 [M^+]; IR (KBr) (cm^{-1}): 3054-3016, 1652, 1690, 1513, 1336, 1259, 1210, 1145.

2-(2-bromophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4n). This compound was obtained as brown solid in 85% yield. mp 58–60°C; Anal. Calcd for $C_{24}H_{22}BrNOS$: C, 63.72; H, 4.90; N, 3.10; Found: C, 63.58; H, 4.73; N, 2.96; m/z: 453 [M^+]; IR (KBr) (cm^{-1}): 3065-3024, 1660, 1612, 1518, 1345, 1276, 1212, 1145.

2-(3-bromophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4o). This compound was obtained as brown solid in 88% yield. mp 78–80°C; Anal. Calcd for $C_{24}H_{22}BrNOS$: C, 63.72; H, 4.90; N, 3.10; Found: C, 63.55; H, 4.77; N, 2.94; m/z: 453 [M^+]; IR (KBr) (cm^{-1}): 3044-3016, 1672, 1630, 1533, 1336, 1279, 1230, 1135.

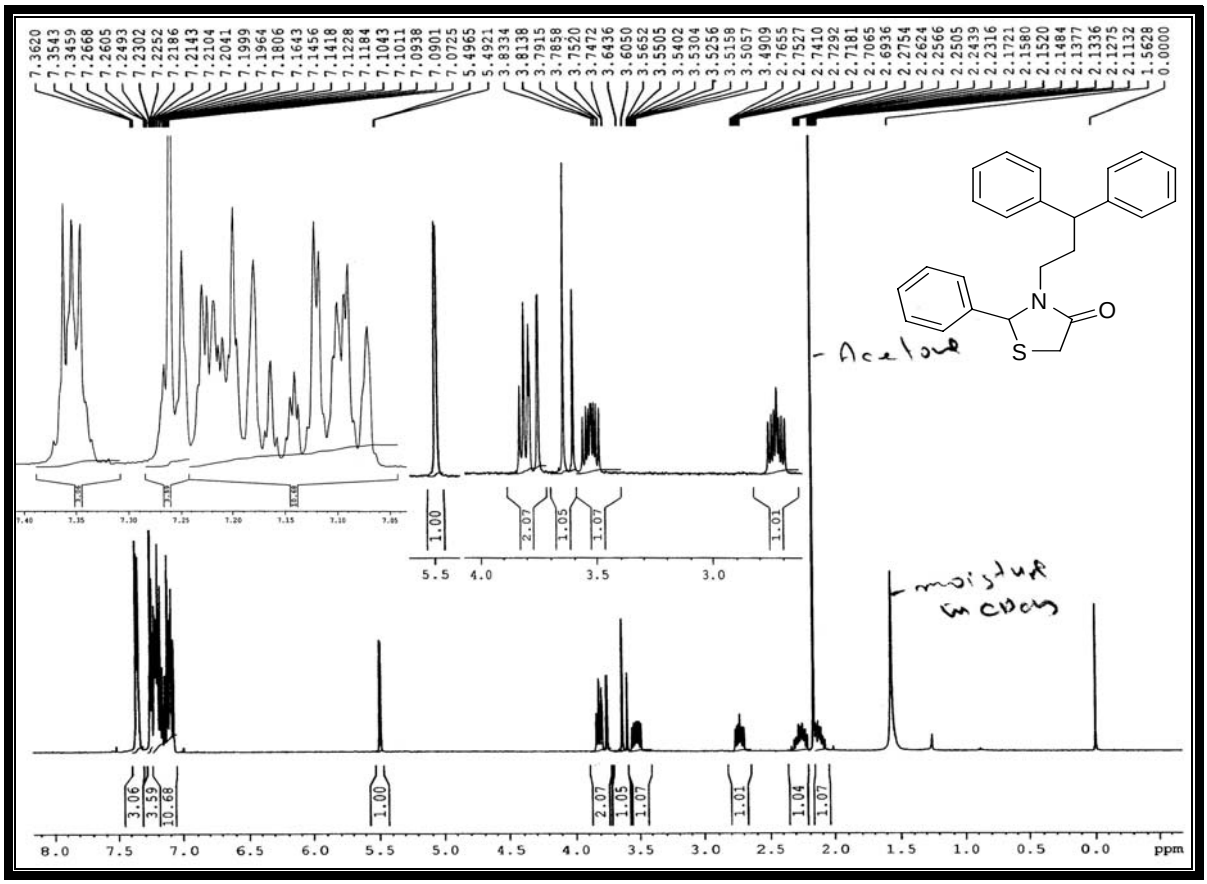
2-(4-bromophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4p). This compound was obtained as brown solid in 90% yield. mp 94–96°C; Anal. Calcd for $C_{24}H_{22}BrNOS$: C, 63.72; H, 4.90; N, 3.10; Found: C, 63.59; H, 4.76; N, 3.00; m/z: 453 [M^+]; IR (KBr) (cm^{-1}): 3054-3036, 1652, 1610, 1519, 1356, 1259, 1229, 1148.

2-(4-hydroxy-3-methoxyphenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4q). This compound was obtained as pale yellow solid in 87% yield. mp 118–120°C; Anal. Calcd for $C_{25}H_{25}NO_3S$: C, 71.57; H, 6.01; N, 3.34; Found: C, 71.43; H, 5.88; N, 3.20; m/z: 419 [M^+]; IR (KBr) (cm^{-1}): 3068-3021, 1658, 1598, 1515, 1336, 1258, 1218, 1140.

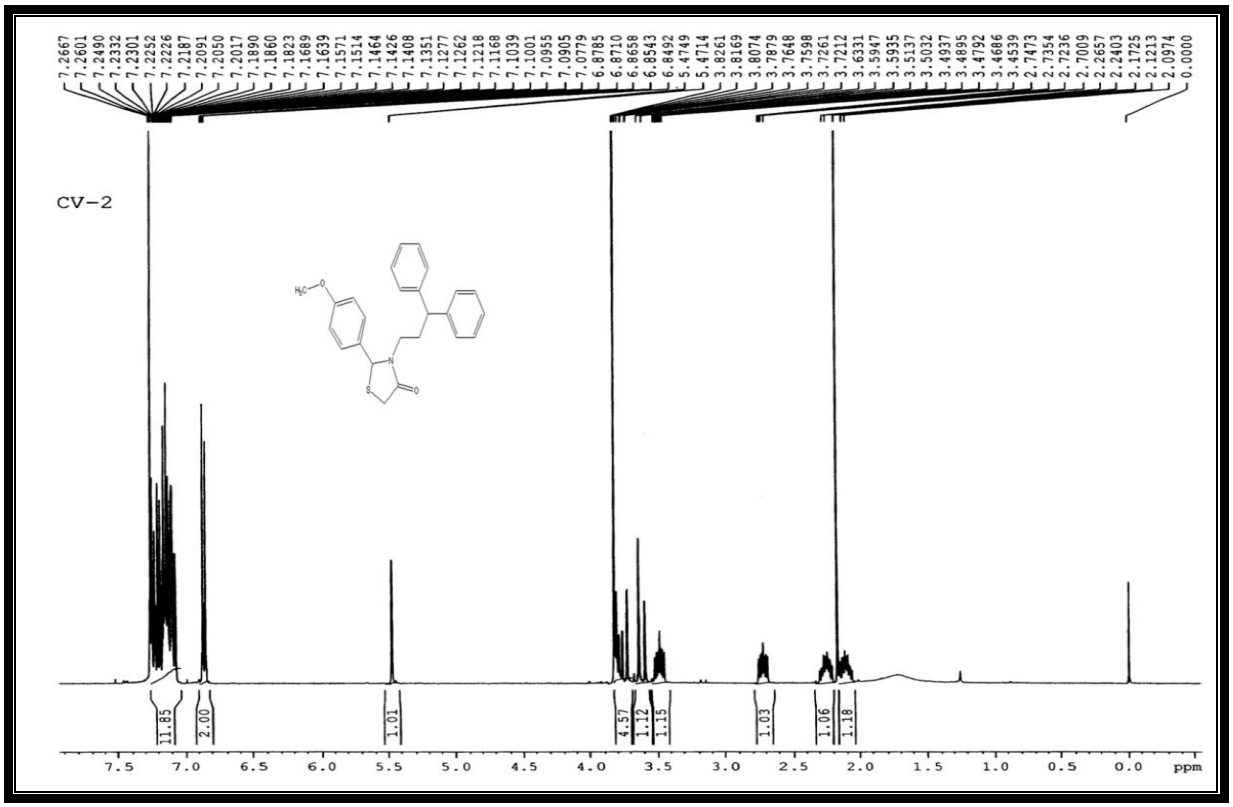
2-(4-hydroxy-3-methoxy-5-nitrophenyl)-3-(3,3-diphenylpropyl)thiazolidin-4-one (4r). This compound was obtained as pale yellow solid in 85% yield. mp 124–126°C; Anal. Calcd for $C_{25}H_{24}N_2O_5S$: C, 64.64; H, 5.21; N, 6.03; Found: C, 64.50; H, 5.08; N, 5.88; m/z: 464 [M^+]; IR (KBr) (cm^{-1}): 3070-3029, 1660, 1611, 1533, 1356, 1255, 1222, 1161.

1.11 spectral representation of synthesized compounds

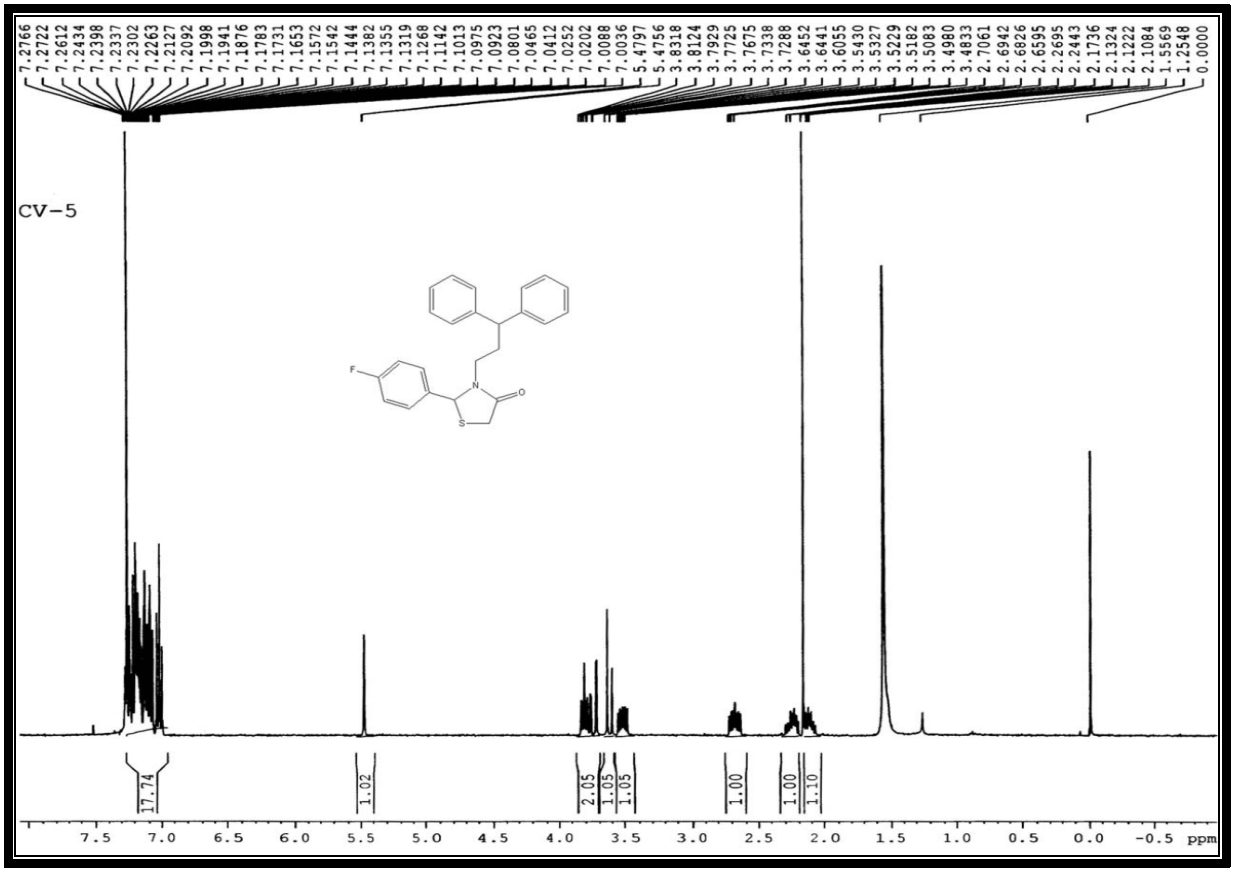
1.11.1 ^{1}H NMR spectrums compound of 4a



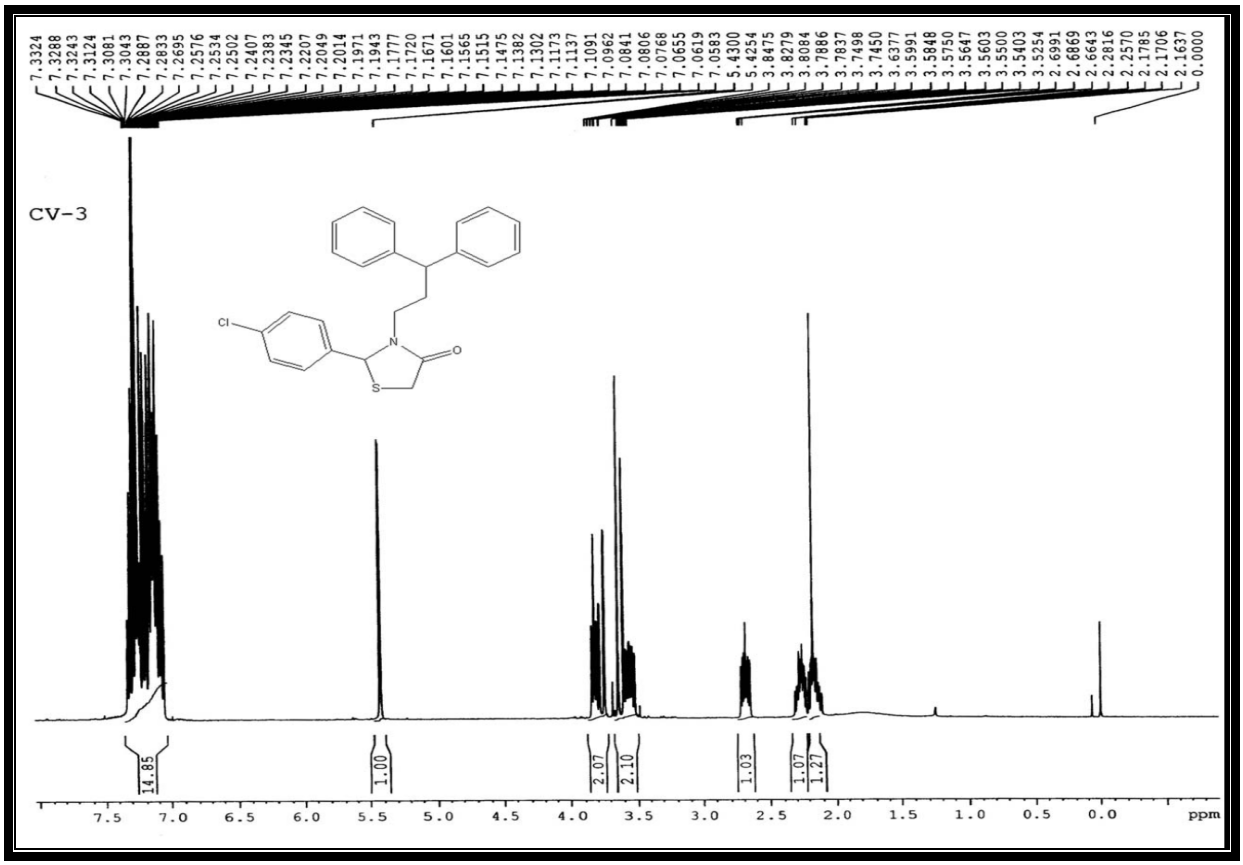
1.11.2 ^{1}H NMR spectrums of compound 4b



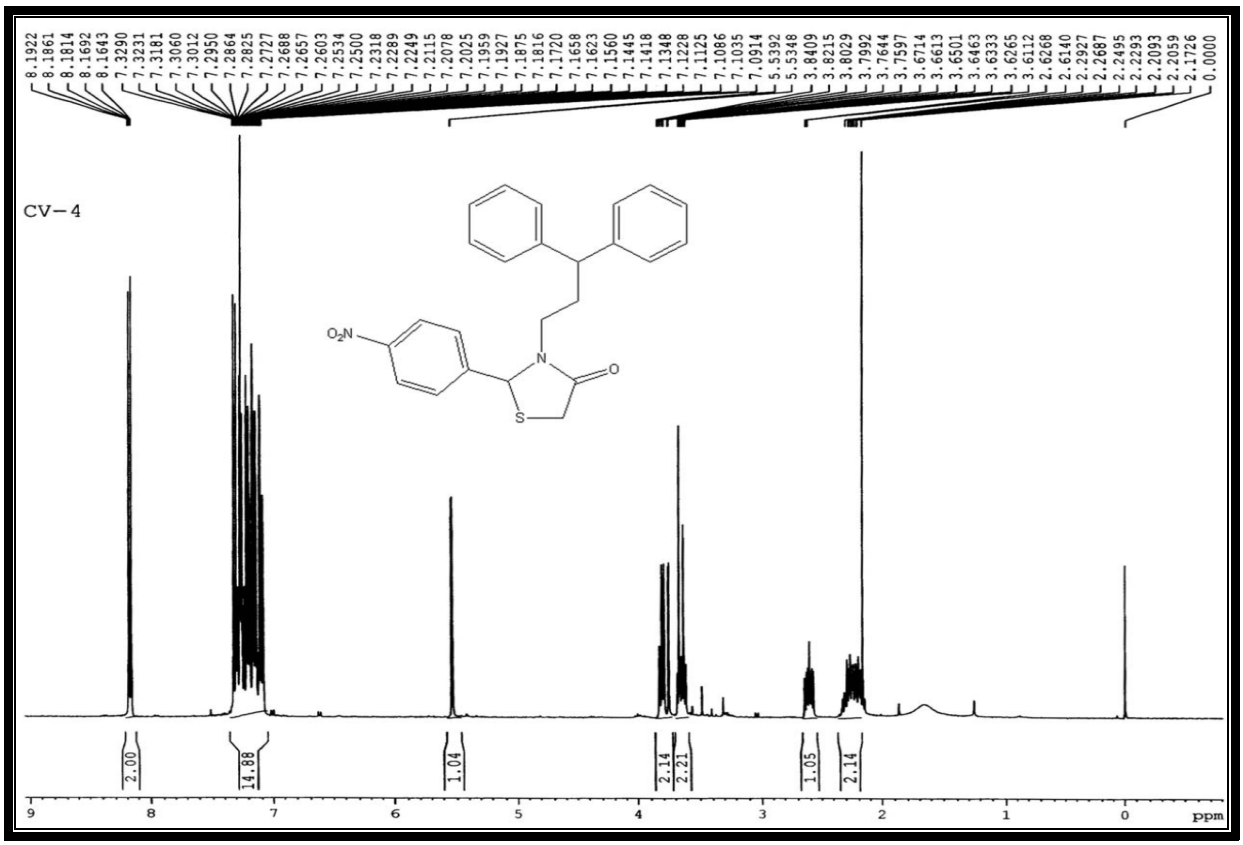
1.11.3 ^{1}H NMR spectrums of compound 4c



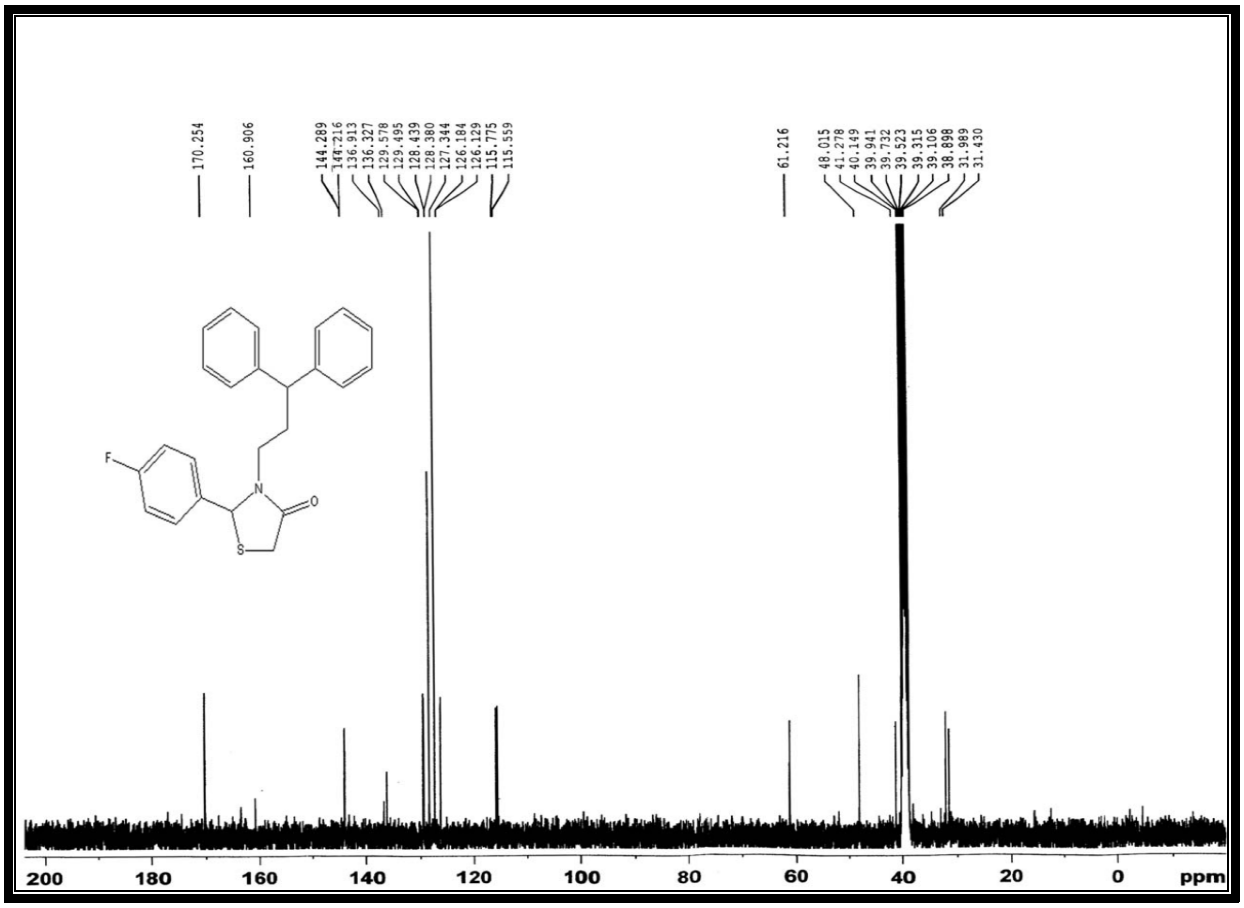
1.11.4 ^{1}H NMR spectrums of compound 4d



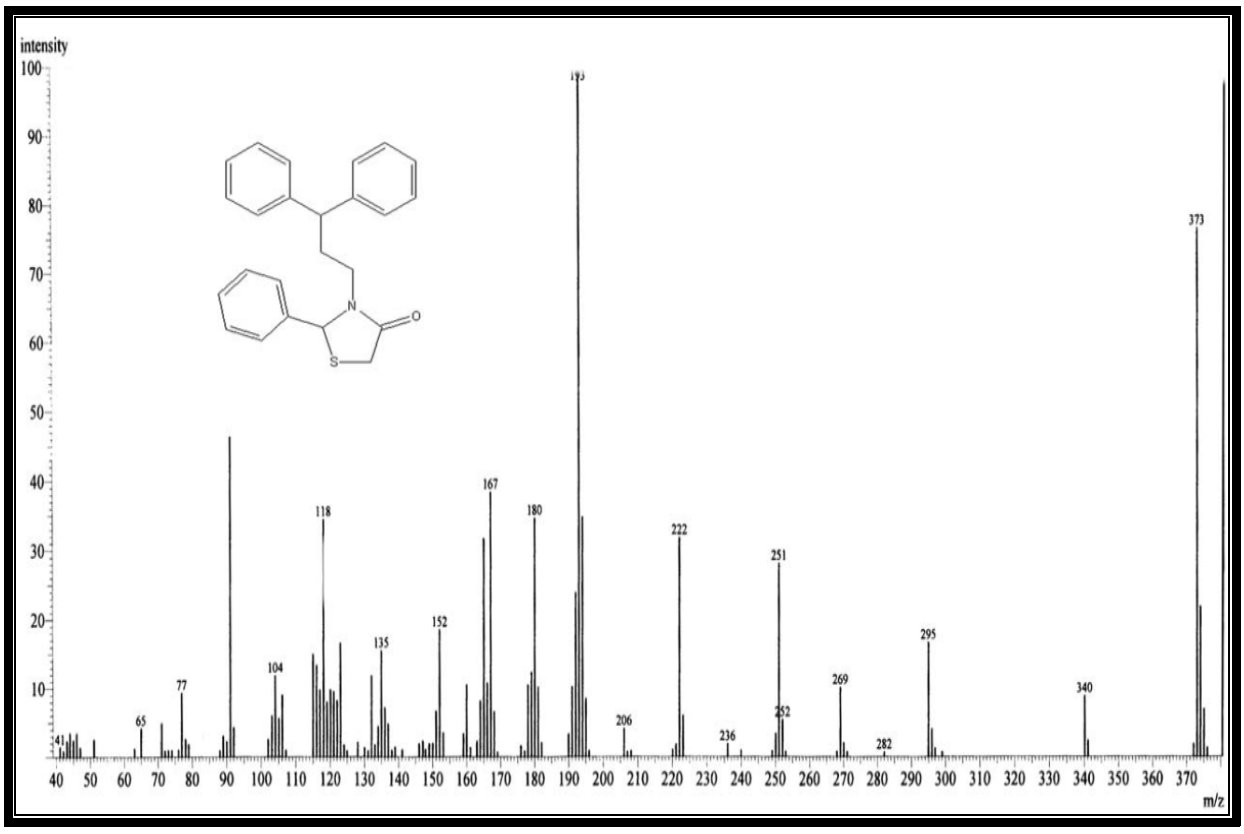
1.11.5 ^{1}H NMR spectrums of compound 4e



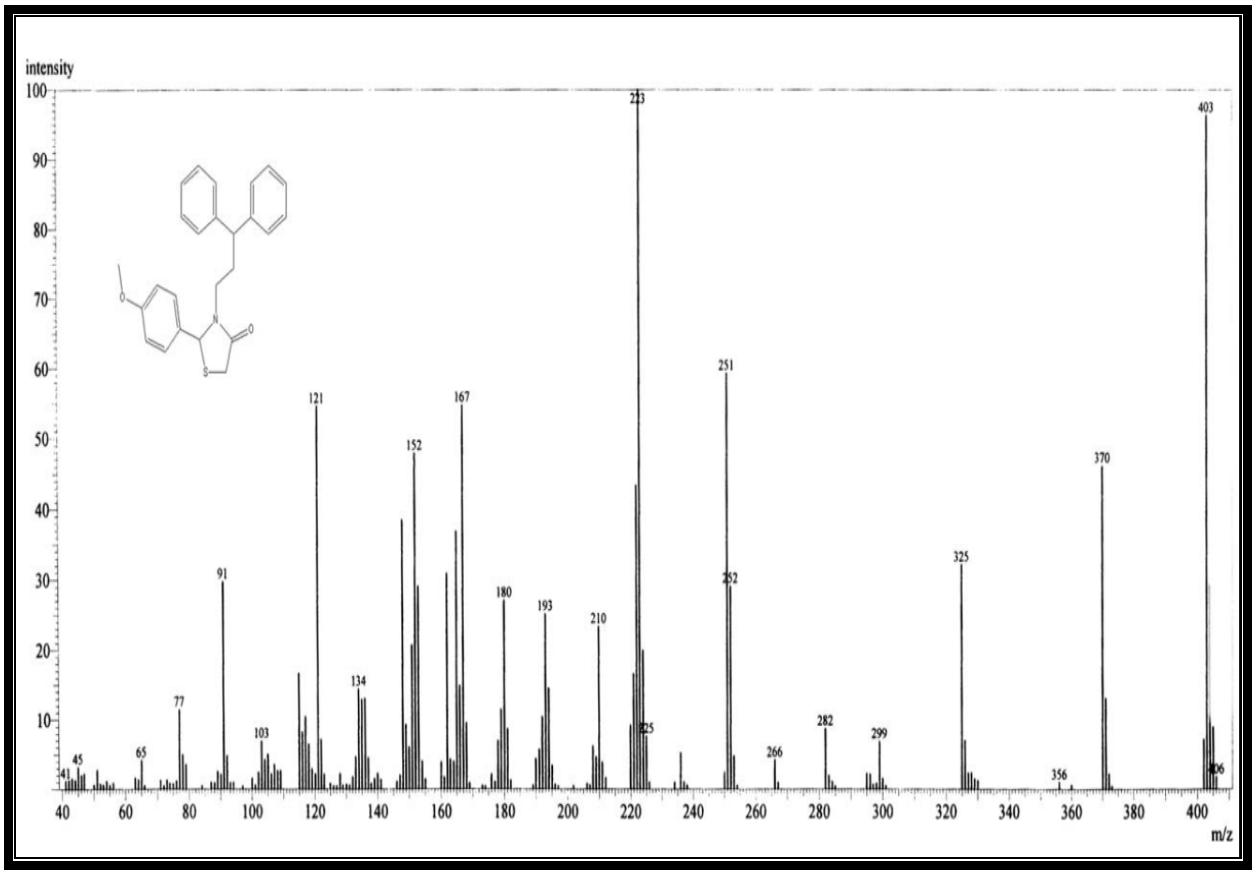
1.11.6 ^{13}C NMR spectrum of compound 4c



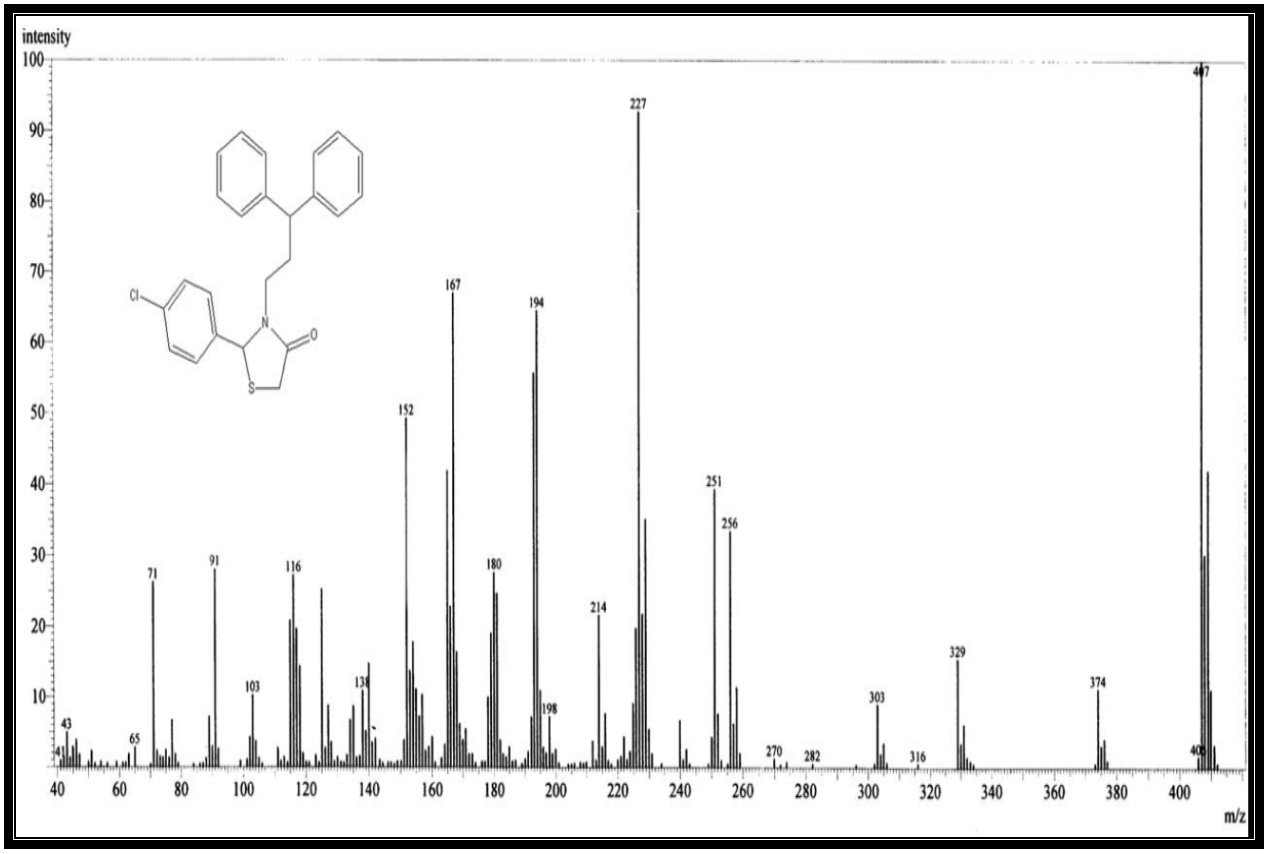
1.11.7 Mass spectrum of compound 4a



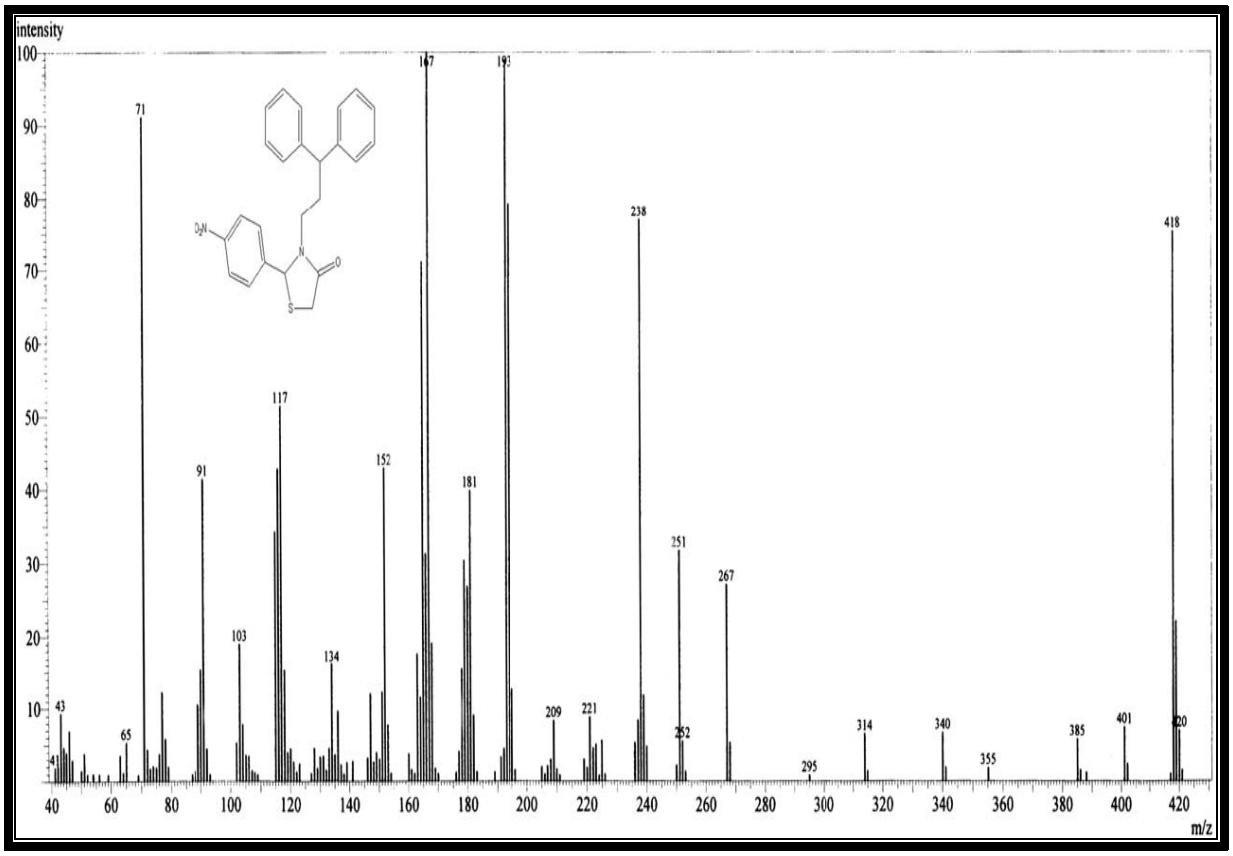
1.11.8 Mass spectrum of compound 4b



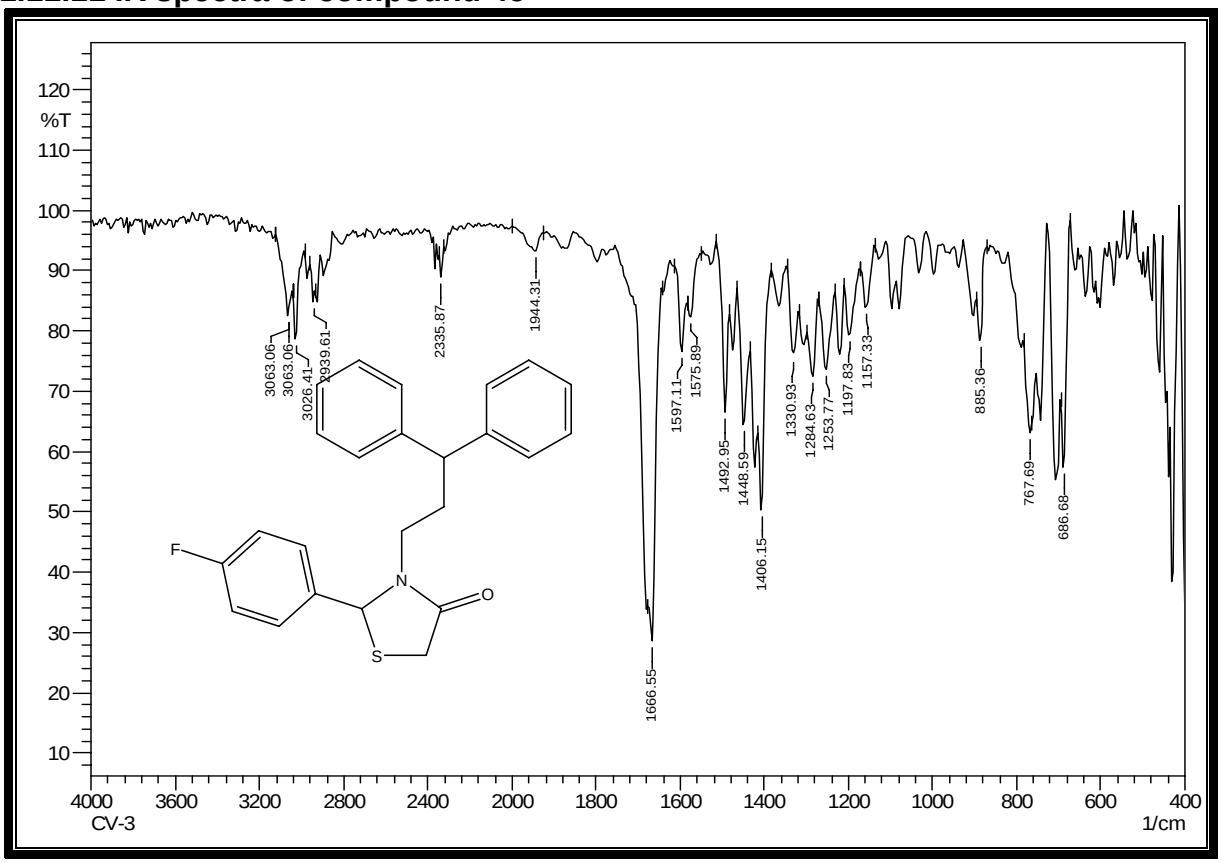
1.11.9 Mass spectrum of compound 4d



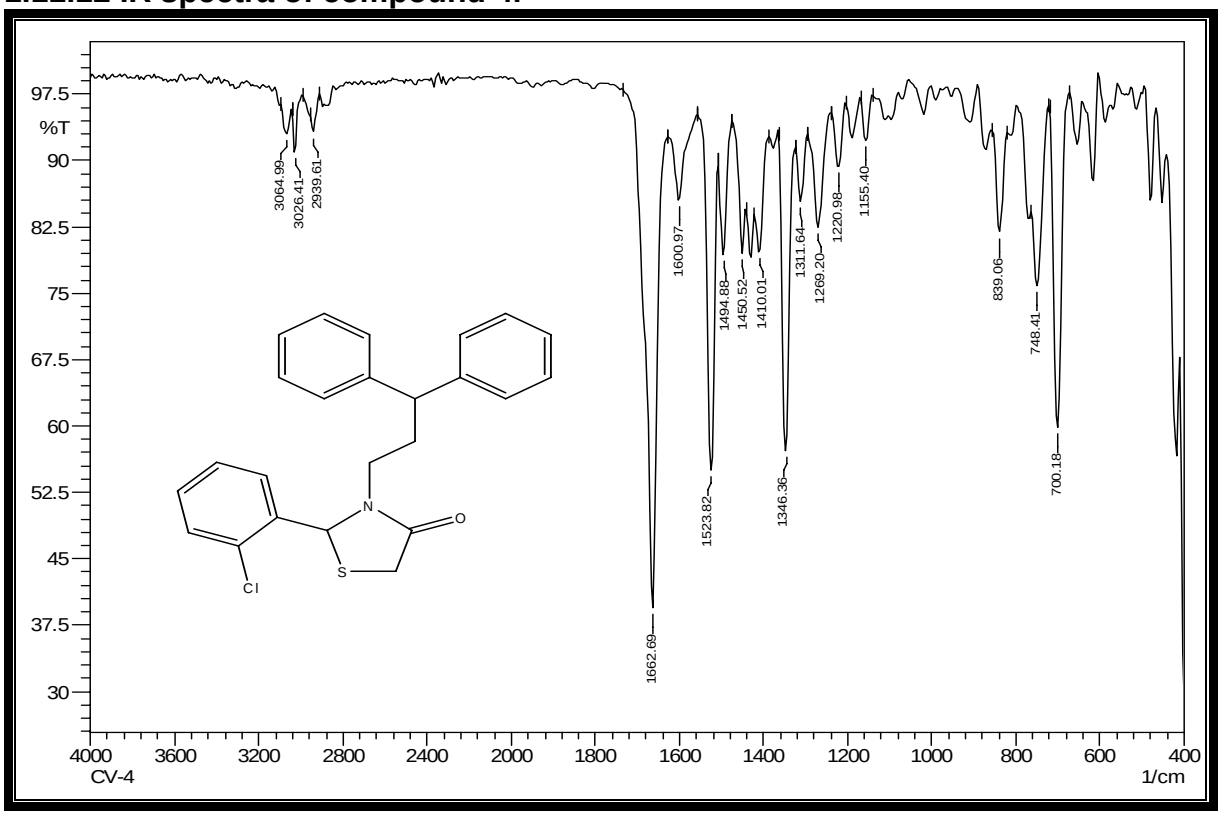
1.11.10 Mass spectrum of compound 4e



1.11.11 IR spectra of compound 4c



1.11.12 IR spectra of compound 4i



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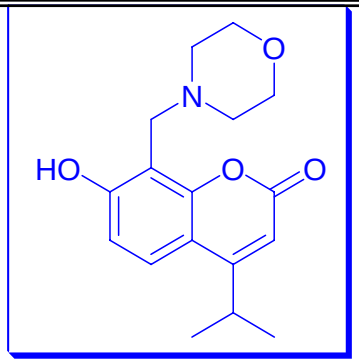
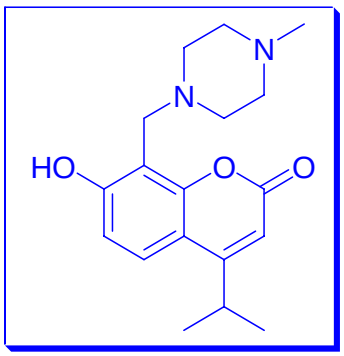
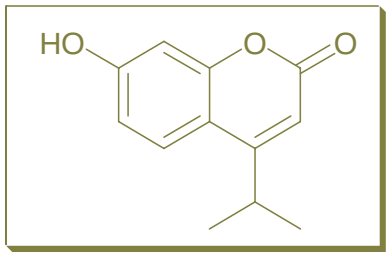
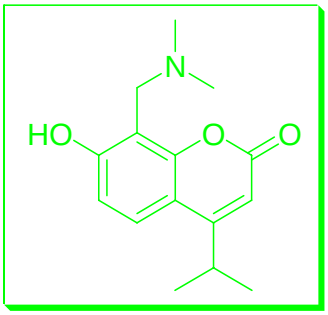
Chapter 2

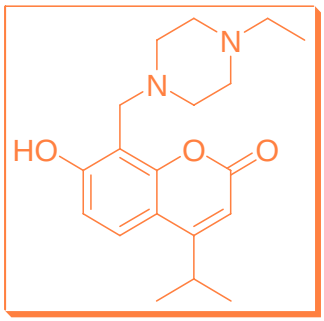


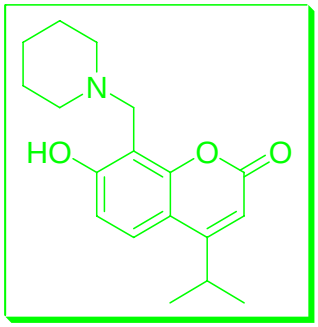




Etidronic acid-catalyzed synthesis of novel Mannich base derivatives of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one.







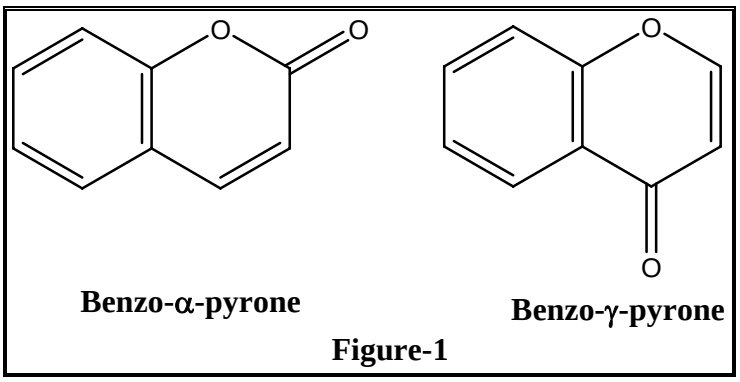
2.1. Introduction

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 chromone 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.

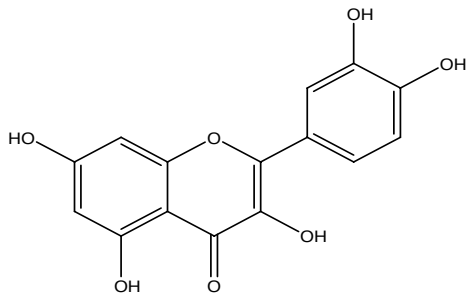
Coumarins, the parent substance of the benzo-α-pyrone group, was first isolated from Tonka beans in 1820.[1] A number of naturally occurring and synthetic monomeric coumarin derivatives are used in drugs and dyes.[2]

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-pyrone, 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**).

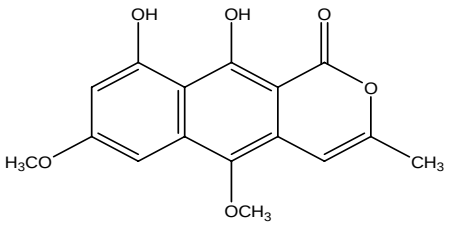


Benzo-α-pyrone **Benzo-γ-pyrone**

Figure-1



Alloxanthoxyletin



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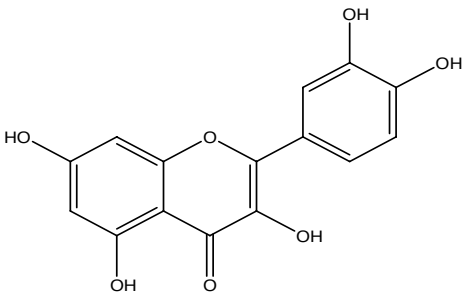

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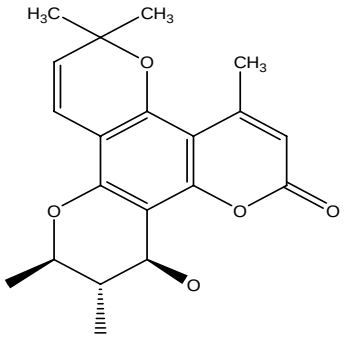

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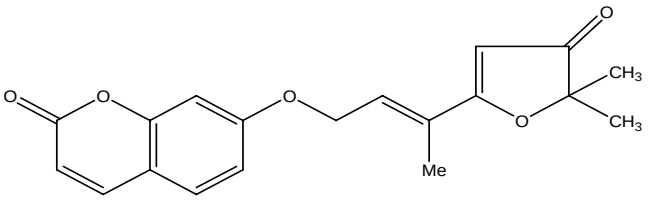


Geiparvarin

Figure-2: Few naturally occurring coumarins

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 also 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]

2.2 Synthetic methods for coumarin and Mannich coumarin

Several various methods for the preparation of coumarin and Mannich coumarin are narrated in literature.[5-18]

1. Babak Karimi et al.[19] have synthesized a highly efficient and water-tolerant sulfonic acid nanoreactor based on tunable ordered porous silica for the von Pechmann reaction (**Figure 3**).

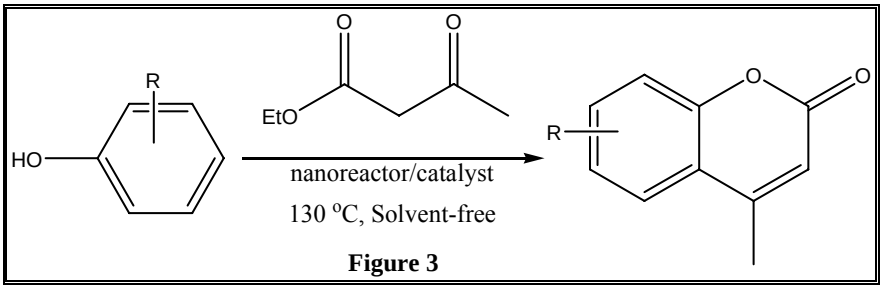


Figure 3

2. Mauro Mazzei et al[20] have reported some Mannich bases of 7-hydroxycoumarin and their simple derivatives were prepared and tested against viruses containing single-stranded, positive-sense RNA genomes (ssRNA) (**Figure 4**).

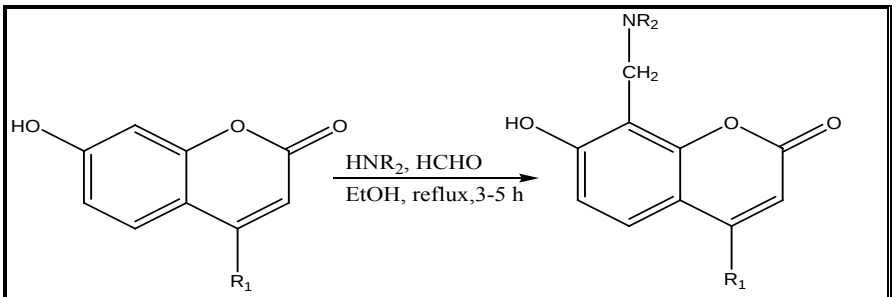


Figure 4

R_1= H, CH_3

R_2=Various secondary amine

3. Rodolfo Quevedo et al[21] have synthesized new macrocyclic compounds having two benzoxazine subunits joined by two ethylene bridges have been prepared by Mannich condensation of the appropriate 4-hydroxyphenylethylamine with an excess of formaldehyde. This is a general method for synthesizing a new family of heterocyclophanes (**Figure 5**).

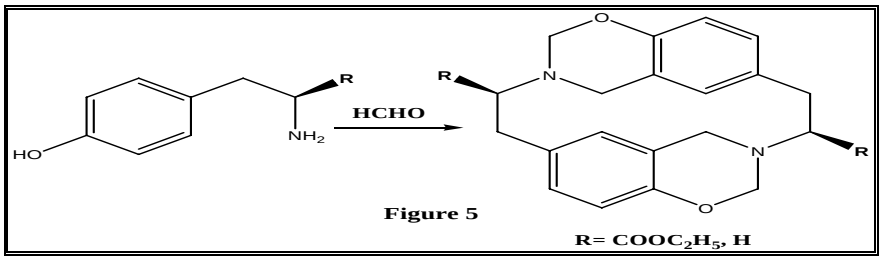


Figure 5

R= $COOC_2H_5$, H

4. Hui Mao et al[22] have synthesized facile and diastereoselective synthesis of *β*-acetamido ketones and keto esters via direct Mannich-type reaction (**Figure 6**). A Mannich type three-component reaction involving aldehydes, acetamide, and enolizable ketones or *β*-keto esters for the preparation of *β*-acetamido carbonyl compounds in the presence of TMSCl is described. This newly developed protocol is operationally convenient, widely applicable, and highly diastereoselective.

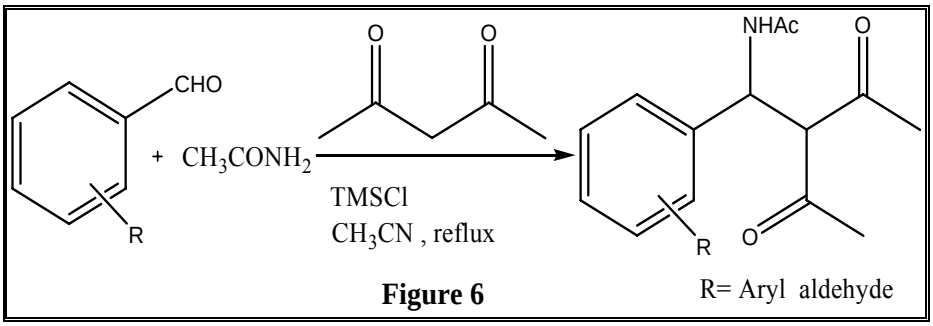


Figure 6 R= Aryl aldehyde

5. Rosaria Villano et al[23] have synthesized a convenient approach to *α*-amino-*β*-ketoester by vinylogous Mannich reaction of masked acetoacetate (**Figure 7**). $SiCl_4$ showed an efficient and selective catalyst for the vinylogous Mannich reaction of linear and cyclic synthetic equivalents of acetoacetate dianion, leading to *α*-amino-*β*-ketoesters in moderate to high yields and complete γ-selectivity; anti-diastereoselective was observed by using a γ -methyl-substituted cyclic silyloxydiene.

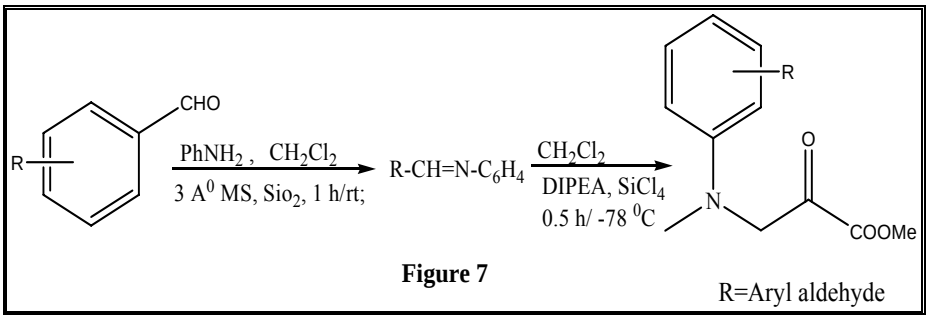


Figure 7 R=Aryl aldehyde

6. M. M. Garazd et al[24] have synthesized modified coumarins with Mannich reaction of substituted 4-phenylcoumarine (**Figure 8**).

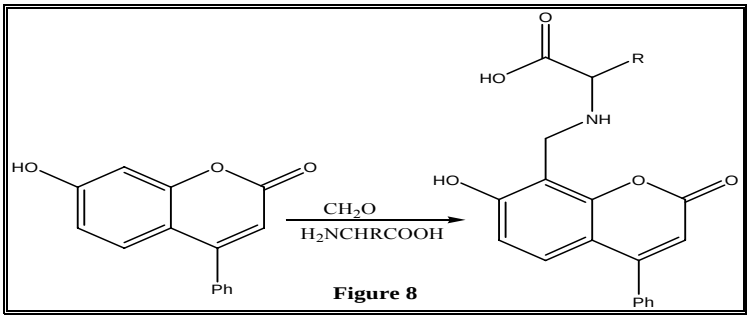


Figure 8

7. Wen-Juan Hao et al[25] have synthesized a new mild base-catalyzed Mannich reaction of heteroarylamines in water highly efficient stereoselective synthesis of β-aminoketones under microwave heating (**Figure 9**).

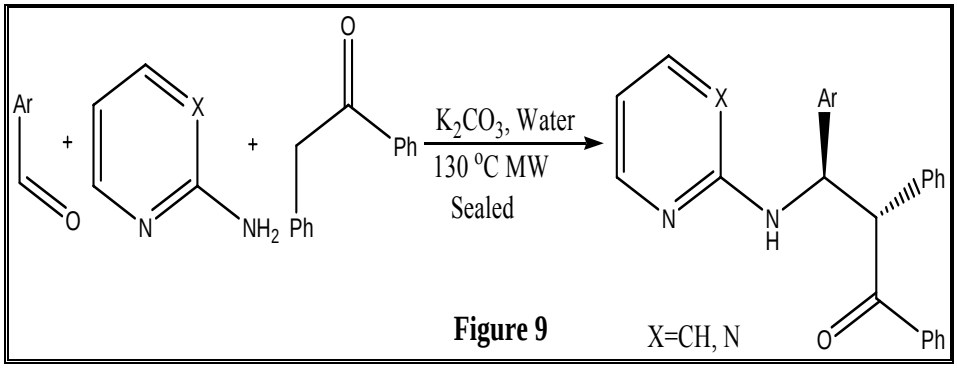


Figure 9

8. Hua Yang et al[26] have synthesized enantioselective Mannich reactions with the practical proline mimetic *N*-(*p*-dodecylphenyl-sulfonyl)-2-pyrrolidinecarboxamide (**Figure 10**).

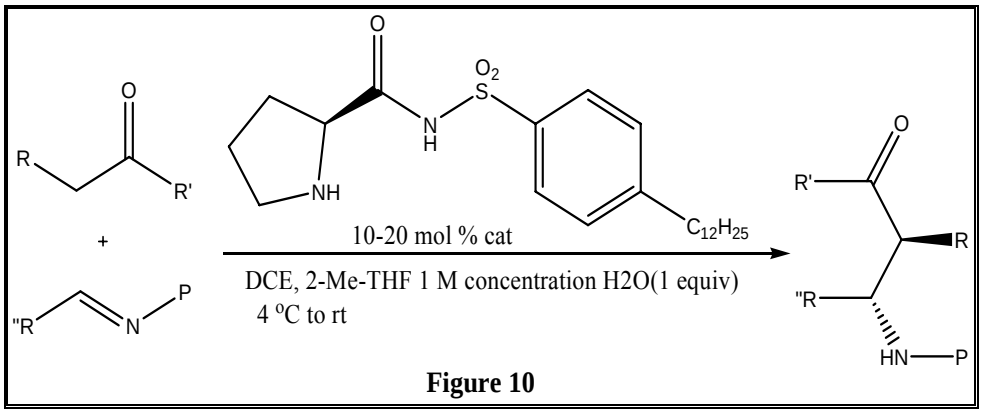


Figure 10

9. Shou-Ri Sheng et al[27] have synthesized novel traceless liquid-phase synthesis of coumarin derivatives on poly (Ethylene Glycol) support (**Figure 11**). Coumarin derivatives were prepared by the von Pechmann reaction of PEG-bound acetoacetate reagent with phenols in the presence of TiCl in excellent yield and purity with a facile workup procedure. The polymer reagent could be recycled two to four times without diminishing the yield or purity.

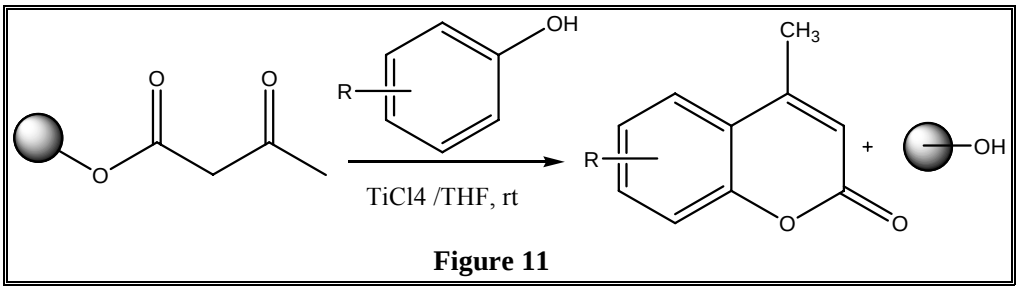


Figure 11

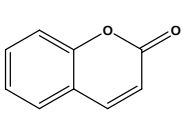
2.3 Biological activities of coumarin derivatives

2.3.1 Coumarins as cytotoxicity agents

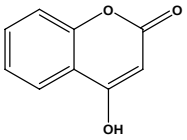
Coumarins have attracted intense interest in recent years because of their diverse pharmacological properties. The cytotoxic coumarins represent an exploitable source of new anticancer agents, which might help addressing cytotoxicity and resistance phenomena. These natural compounds have served as valuable 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.[28]

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.*[29] Coumarins have shown cytotoxicity with derivatives containing *o*-dihydroxy substituents as reported by Kolodziej *et. al.*[30]. 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.[31]

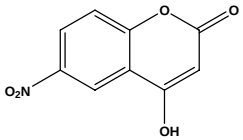
Figure-12: Structures of cytotoxic coumarins[30]



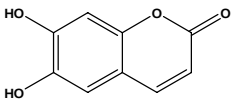
Coumarin



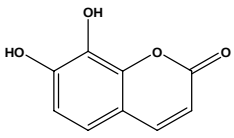
4-Hydroxycoumarin



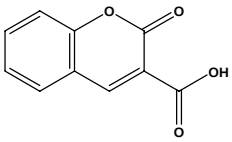
6-Nitro-7-hydroxy coumarin



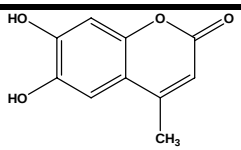
6,7-Dihydroxy coumarin (Esculetin)



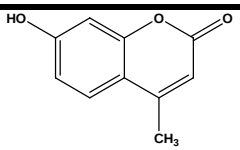
7,8-dihydroxycoumarin (Daphnetin)



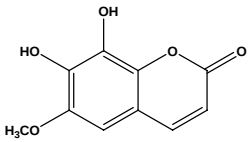
Coumarin-3-carboxylic acid



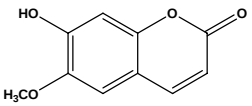
4-Methyl-6,7-dihydroxy coumarin



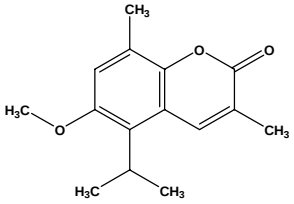
4-Methyl-7-hydroxy coumarin (Mendiaxon)



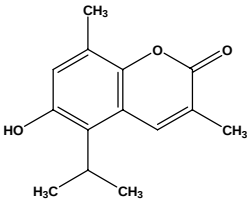
Fraxetin



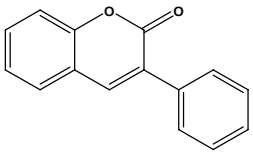
Scopoletin



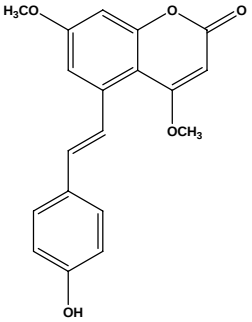
3,8-Dimethyl-5-isopropyl-6-methoxycoumarin (Mansonrin A)



3,8-Dimethyl-5-isopropyl-6-hydroxycoumarin (Mansorin B)



Pervilleanine



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

Figure-12

The aminocoumarin antibiotics novobiocin, clorobiocin and coumermycin A1 are known as potent inhibitors of gyrase.[32] Their equilibrium dissociation constants are in the range of 10 nM, [33.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*[34] (**Figure 13**).

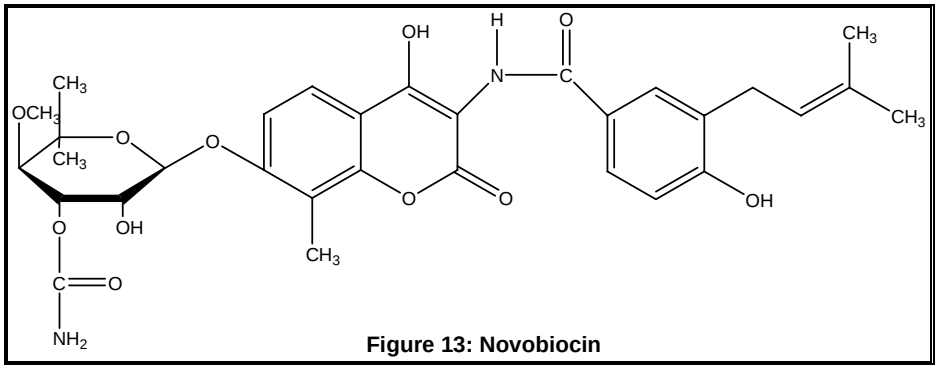


Figure 13: Novobiocin

Novobiocin is produced by *Streptomyces spheroides* (syn. *S. caeruleus*)[35]CIMB 11891, Clorobiocin (**Figure 14**) is produced by *S. roseochromogenes var. oscitans* DS12.976 and coumermycin A1 (**Figure 15**) is produced by *S. rishiriensis* DSM 40489.[36] Obviously, these organisms must protect their gyrases from the inhibitory effect of aminocoumarin during antibiotic formation.

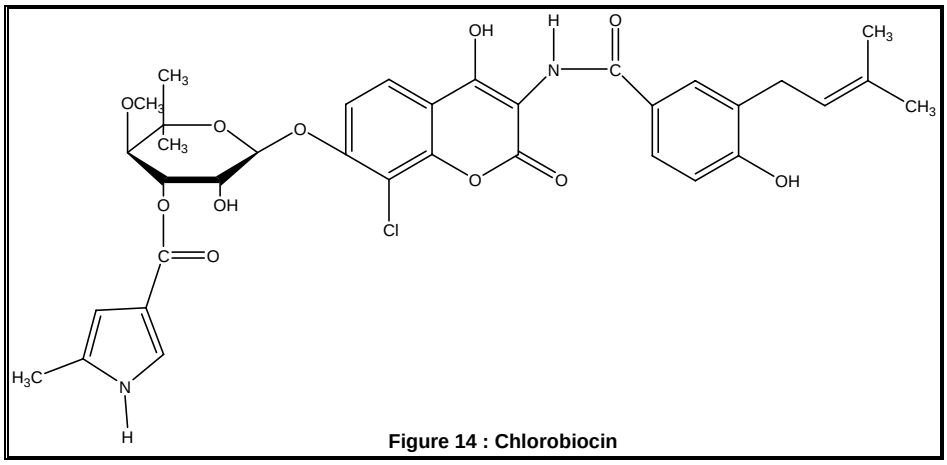


Figure 14 : Chlorobiocin

Thiara and Cundliffe[37-39] have 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.[37] Mitchell *et. al.*[34] 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.*[32]

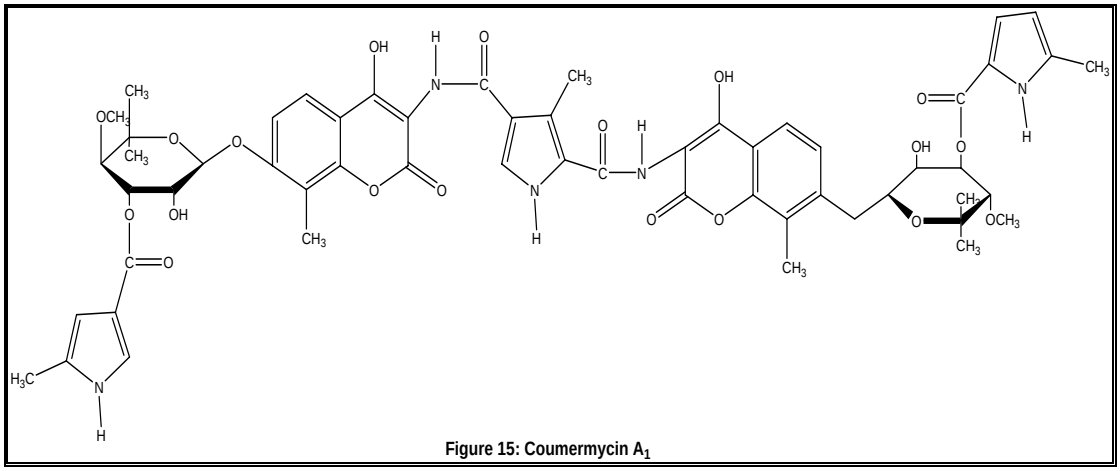


Figure 15: Coumermycin A_1

2.3.2 Coumarin 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.[40,41]Some phenyl coumarins 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.[42]

(+)-Calanolide A, a natural dipyranocoumarin, currently undergoing anti-AIDS clinical trials,[43] has also proven to be an effective antimycobacterial against drug-sensible and drug-resistant *Mycobacterium tuberculosis* strains (**Figure 16**).

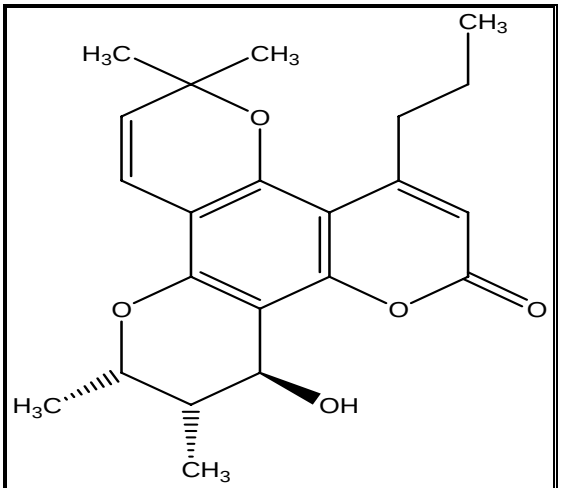


Figure 16: (+)-Calanolide A

It has been reported that mesuol and isomesuol, (**Figure 17**) two 4-phenyl coumarins, isolated from the tree *Marila pluricostata*, suppress HIV-1 replication in Jurkat T cells.[44] 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.

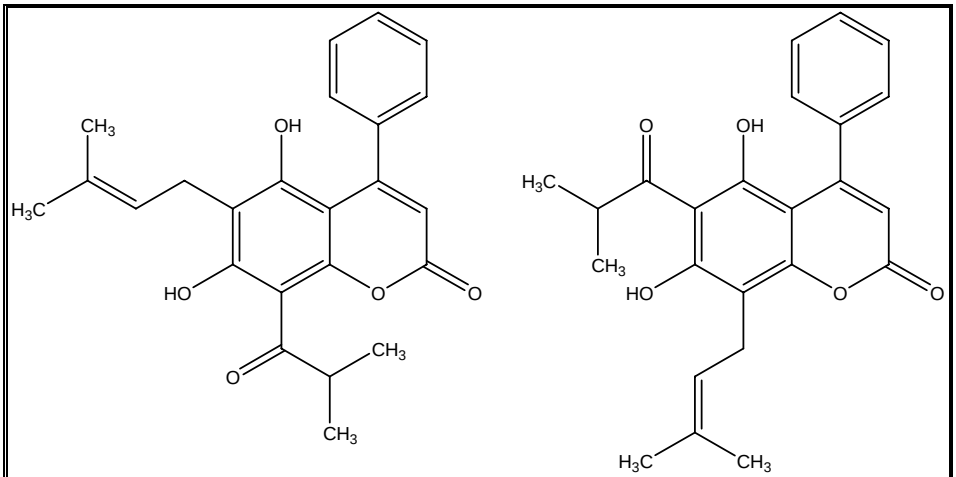


Figure 17: Chemical structures of the 4-phenylcoumarins Isomesuol and Mesuol.

2.3.3 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 18**).

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.[45] 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.[46]

PD099560 is also identified as a non-peptide competitive HIV-1 protease inhibitor[47] (**Figure 18**).

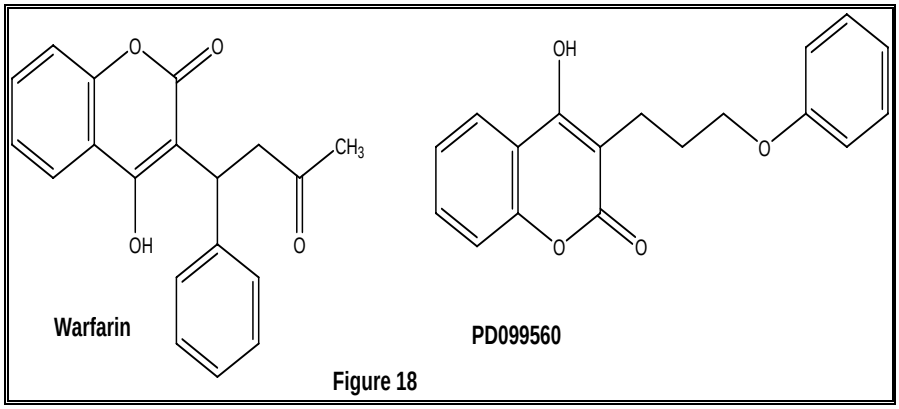


Figure 18

2.3.4 Integrase inhibitors

In addition to HIV RT and protease, HIV integrase is also a major chemotherapeutic target;[48] 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} = 0.8 μM for integration and 1.5 μM for 30-processing)[49] (**Figure-19**).

Increasing the number of aryl rings on the central linker enhanced potency; the rigid stilbene analog[50] is the most potent (integration 3.7 μM, 30-processing 5.5 μM) among the compounds synthesized (**Figure-20**). 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.

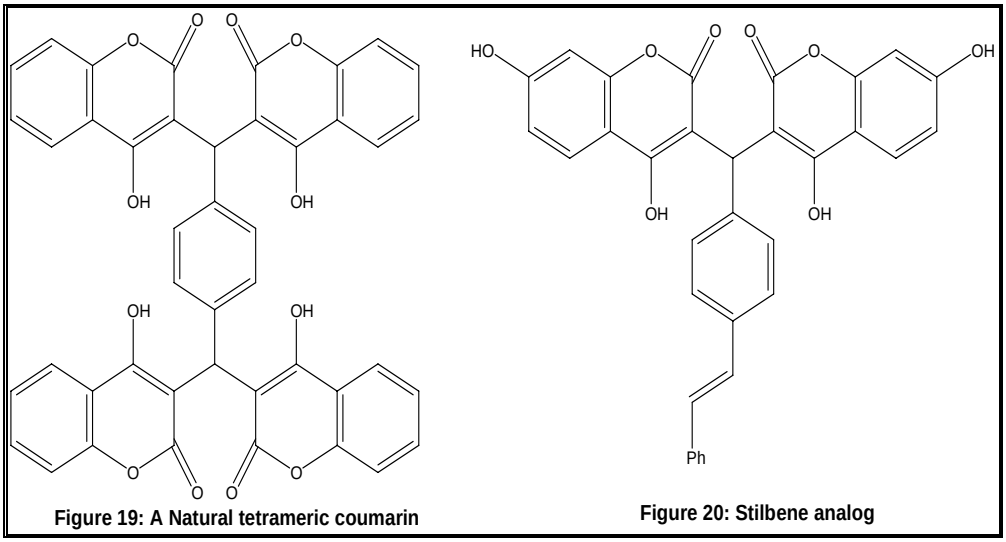


Figure 19: A Natural tetrameric coumarin

Figure 20: Stilbene analog

2.3.5 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 (**Figure 21**).[51]

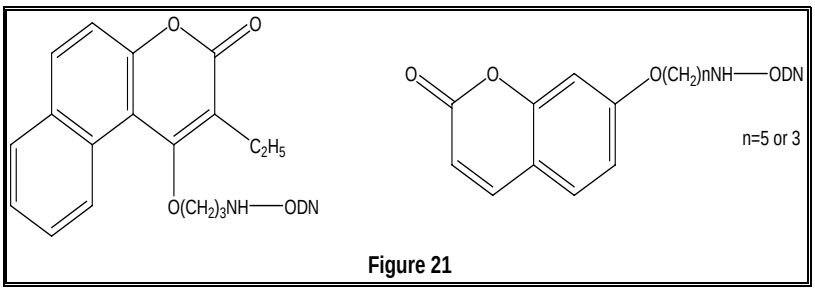


Figure 21

2.3.6 Coumarins as photodynamic therapeutics (PDT) agents

Furancoumarins, 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,[52] 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.[53 (a)]

Most of the dialkylaminoalkyl coumarin-4-acetates showed a local anesthetic activity[53 (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.

2.4 Aim of current work

The Mannich reaction is a fundamentally important carbon–carbon bond forming reaction in organic synthesis, and it has been widely utilized in the syntheses of nitrogen-containing drugs, natural products and biologically active compounds.[54]

Following our interest in benzopyrans, [55-57] this chapter devoted to exploring the activity of some Mannich bases of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one and their simple derivatives in position 8 as secondary amine against Flaviviridae. It is well known that natural and synthetic coumarins have multiple biological activities.[58]

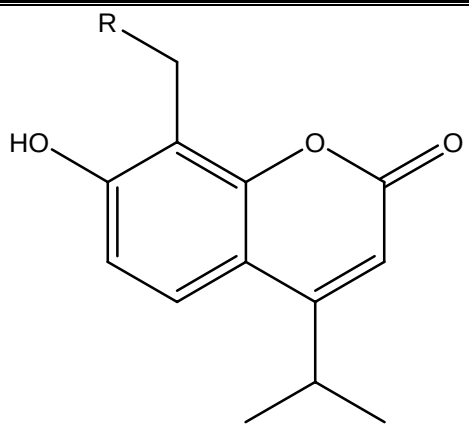


Figure 22 **R= Secondary amine**

Mannich bases can be synthesized by Mannich reaction on nitrogen of secondary amine having hydrogen atom with pronounced activity using simplified methodology and easy work up and this inspired us to develop some new 7-hydroxy-4-isopropyl-2H-chromen-2-one derivatives by Mannich reaction (**Figure 22**). Literature also revealed that secondary amines *viz.* morpholine, piperidine, pyrrolidine, piperazine derivatives.

2.5 Chemistry

The requisite 7-hydroxy-4-isopropyl-2*H*-chromen-2-one were prepared by Pechmann condensation of polyphenols and methylisobutyralacetate in the presence of trifluoroacetic acid (TFA).[59-63] **(Scheme 1).** The Mannich bases **4a-i** were synthesized from 7-hydroxy-4-isopropyl-2*H*-chromen-2-one (**3**) with 40% form aldehyde and suitable secondary amines in absolute dioxane. The final products (**5a-i**) were treated with dry HCl to prepare their corresponding hydrochloride salts.

To find better reaction conditions, next we investigated the application of etidronic acid in a one-pot multicomponent reaction sequence for preparation of Mannich

base. We found that the Mannich base can be prepared in excellent yield by microwave-assisted etidronic acid catalyzed reaction of various secondary amines with formaldehyde and 7-hydroxy-4-isopropyl-2*H*-chromen-2-one. The results are reported herein.

2.6 Results and discussion

Etidronic acid [(1-hydroxyethylidene) bisphosphonic acid] (**Figure 23**) is one of the bisphosphonic acid derivative and also known as bisphosphonate having molecular formula $C_2H_8O_7P_2$. The two PO_3 (phosphonate) groups covalently linked to carbon atom.

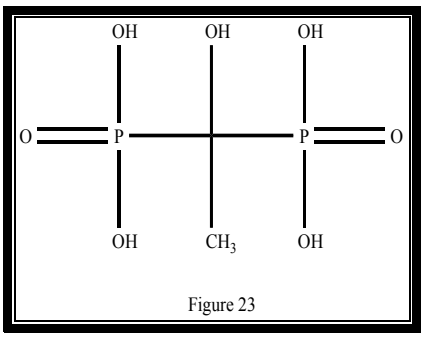


Figure 23

It is differ from polyphosphate ester and polyphosphoric acid. Various bisphosphonic acids are known.[64-65] Etidronic acid is mild enough as compare to another strong acid such as polyphosphoric acid etc. moreover, the catalyst did not affect acid sensitive aldehydes.

We first performed classical method in the reaction using 7-hydroxy-4-isopropyl-2*H*-chromen-2-one as a starting material for a three-component reaction. 7-hydroxy-4-isopropyl- 2*H*-chromen-2-one was first reacted with formaldehyde in dioxane at reflux temperature followed by reaction with appropriate secondary amine to gave yielded compounds **4a**–**i** in moderate yields (**Table 1**).

Table 1: One-pot three-component synthesis of Mannich base derivatives of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one by conventional method

Entry	R	Time / hr	Yield %
4a	Morpholine	3.5	48
4b	Piperidine	3.5	49
4c	4-methylpiperazin	3.0	52
4d	Piperazin	3.2	55
4e	4-methylpiperidin	4.5	60
4f	3-methylpiperidin	4.5	51
4g	Pyrrolidine	5.5	49
4h	Dimethylamine	3.5	53
4i	Diethylamine	3.5	51

Our recent interest has been in the development of new synthetic methods on using etidronic acid catalyst under microwave irradiation. In a typical reaction, the 7-hydroxy-4-isopropyl-2*H*-chromen-2-one, formaldehyde, appropriate secondary amine and etidronic acid catalyzed was irradiated under microwave oven for a specified time period (**Table 2**). After completion of the reaction, extraction with organic solvent followed by aqueous work-up afforded pure Mannich base in 80-90 % yield. The etidronic acid is water-soluble and therefore goes into the aqueous layer.

Table 2. Etidronic acid catalyzed one-pot three-component synthesis of Mannich base derivatives of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one by microwave irradiation method

Entry	R	Time / min	Yield %
4a	Morpholine	14	93
4b	Piperidine	15	91
4c	4-methylpiperazin	10	94
4d	Piperazin	13	90
4e	4-methylpiperidin	11	95
4f	3-methylpiperidin	13	91
4g	Pyrrolidine	15	90
4h	Dimethylamine	12	91
4i	Diethylamine	14	90

Results are summarized in **Table 1** and **Table 2**. In all of the studied examples, the reaction proceeded smoothly; formaldehyde having either electron-withdrawing or electron-releasing substituents, including 7-hydroxy-4-isopropyl-2*H*-chromen-2-one, reacted efficiently to give very good to excellent yields of the desired Mannich base. As an example, the reaction between 7-hydroxy-4-isopropyl-2*H*-chromen-2-one, formaldehyde, and morpholine in the presence of etidronic acid gave the corresponding Mannich base **4a** in 93% yield (**Table 2, entry 1**), also **4a** gives extremely poor yields in the classical method, yielded 48% (**Table 1**, **entry 1**)

According to the literature, the position *ortho* to the hydroxyl is most preferred for attack in a Mannich reaction for all phenolic derivatives. This is explained by the reaction mechanism, according to which a H-bond is formed first between the Mannich reagent and the substrate. This is followed by attack at the *ortho* position.[66] The C-aminomethylation reaction was performed by boiling 7-hydroxy-4-isopropyl-2*H*-

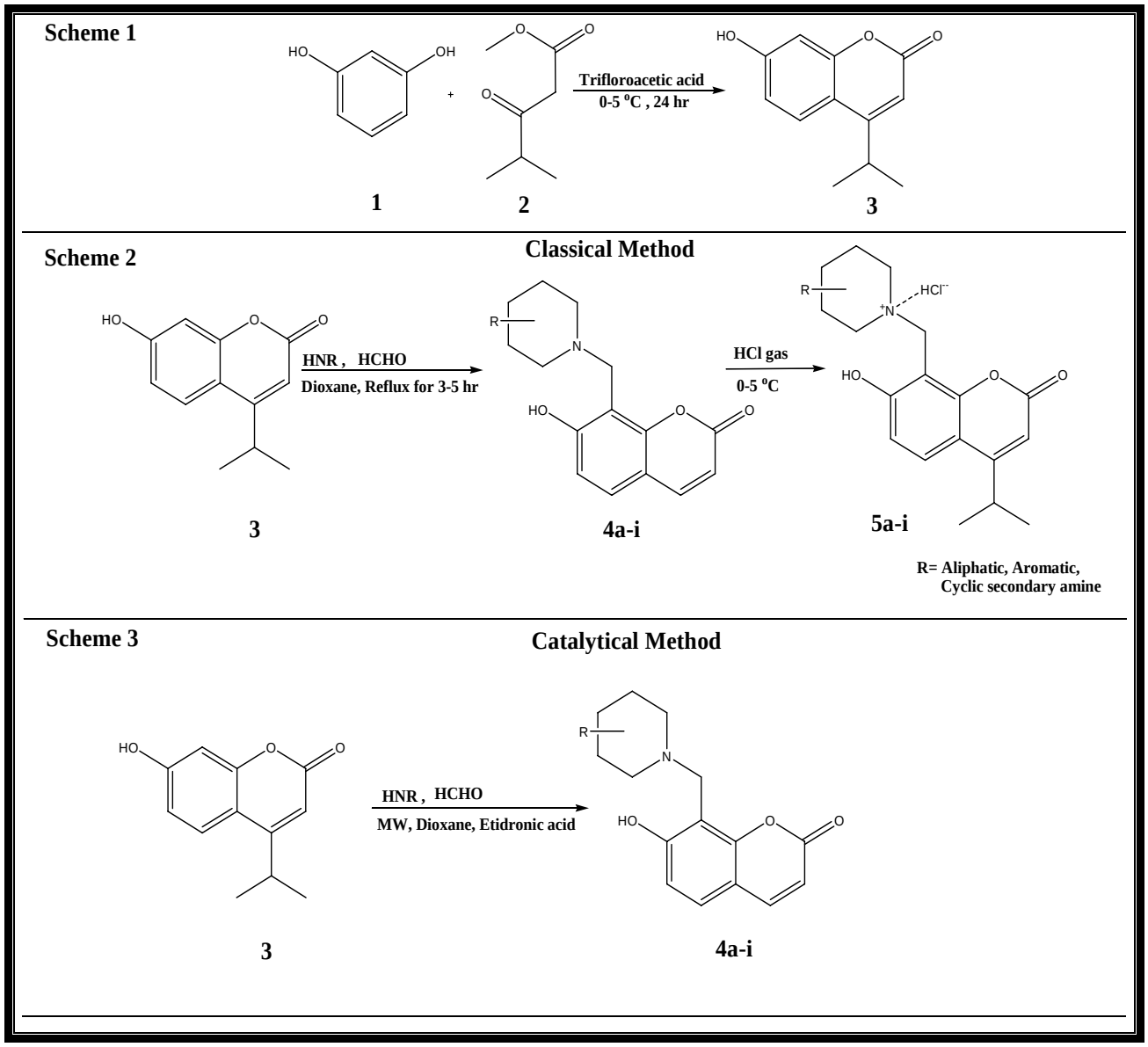
chromen-2-one with substituted amine in absolute dioxane. The amino methyl group occupies the 8-position of the coumarin system.[67]

The formation of Mannich bases **(4a–i)** was confirmed by recording ^{1}H NMR, ^{13}C NMR, and mass spectra. The IR spectrum of 4a–i displayed bands at 3686–3676 and 1722–1708 cm^{-1} due to -OH and –C=O stretching frequencies, respectively. On the other hand, the absorption bands were observed in the region 1599– 1660 cm−1 for (C-N). The aromatic stretching bending vibrations were observed as a sharp medium to strong band at 3072-3070 cm^{-1} in compounds **(4a–i)**. The PMR spectra of compounds **(4a-i)** also contain signals for a methylene at 4.1-4.2 ppm and signals characteristic peak for amine substituents. The hydroxyl protons of 7-OH resonate at weak field (9.97 ppm) because they are involved in an intramolecular H-bond with the N of the secondary amine group. The ^{13}C NMR of compound 4a displayed peaks at 21.64 (2 × ^{i}PrCH3), 27.91 (^{i}PrCH), 57.14-51.55 (morpholine 8CH), 106.15 (pyron C-3), 112.69 (coumarin C-6), 124.65 (coumarin C-5), and 162.95 (C=O), which account for all the carbon atoms in the molecule. The PMR spectra of **(5a-i)** lack signals at 6.12 ppm for H-3 of the pyron system. Protons in the 5- and 6-positions resonate as doublets with 8 to 9 Hz at 7.6 and 7.07 ppm, respectively (**5a-i**). The spectra of compounds **(5a-i)** also contain signals for a methylene at 4.40 ppm and signals characteristic for secondary amine substituents. The hydroxyl protons of 7-OH resonate at weak field (11.38 ppm) because they are involved in an intramolecular H-bond with the *N* of the secondary amine group. Structure **4a** was supported by its mass (m/z 303), which agrees with its molecular formula $C_{17}H_{21}NO_4$. Other prominent peaks appeared at m/z 286, 272, 256, 216, 188, 173 and 86.

2.7 Conclusion

In conclusion, a convenient synthesis of Mannich base has been achieved through a one-pot multicomponent reaction involving a etidronic acid-catalyzed Mannich reaction of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one, with moderate to good yield. We have reported a new simple, economical and environmental friendly multicomponent approach for the one-pot synthesis of heteroatom compounds with microwave irradiation.

2.8 Reaction scheme of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one and (4a-i & 5a-i)



2.9 Experimental Procedure

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator.

2.9.1 General synthesis of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one (See reference no. 59 to 63)

2.9.2 General procedure for conventional synthesis of Mannich bases 4a-i

A solution or suspension of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one (20 mmol) in absolute dioxane (20-25 ml) was treated with the appropriate amine (20 mmol) and 2.0 ml of 40% formaldehyde were added. The resulting mixture was refluxed for 4–6 h. (completion of the reaction was determined by TLC). The solvent was removed under *vaccuo* when the reaction was completed. The solid or oil was crystallized from hexane-diethyl ether (1:1) to give pure product.

2.9.3 General procedure for microwave-assisted synthesis of Mannich bases 4a-i

A well stirred mixture of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one (20 mmol) in absolute dioxane (20-25 ml), appropriate amine (20 mmol), 2.0 ml of 40% formaldehyde and etidronic acid (20 mg/20 mmol) was irradiated under microwave oven for 5 to 10 min at 300W. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was taken up in chloroform and extracted with water. The organic layer was washed with 5% aq. hydrochloric acid (100 mL), followed by water (200 mL), and brine (100 mL). And dried over anhy.sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2) using hexane–ethyl acetate (8:2) as an eluent. The fraction containing the main products were combined and evaporated to dryness under reduce pressure. The crude product thus obtained was crystallized from hexane—diethyl ether (1:1) to afford the targeted Mannich base derivatives.

2.9.4 General procedure for synthesis of Mannich bases hydrochloride salt 5a-i

As above prepare Mannich base **4a-i** was dissolved in ethyl acetate (20 ml) and treated with 2.5M HCl in EA (7 ml) at 0 ^{o}C. The solid separated was filtered to give **5a-i**

Similarly, other Mannich bases were prepared.

2.10 Spectral data of synthesized compounds (3, 4a-i and 5a-i)

7-hydroxy-4-isopropyl-2H-chromen-2-one (3). Off-white solid, yield 90%, mp 118–120°C; Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92; Found: C, 70.53; H, 5.90. m/z: 204[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.29-1.31 (d, J=6.76 Hz, 6H, $2CH_3$), 3.22–3.27 (m, 1H, CH), 6.07 (s, 1H, H-3), 6.79–6..83 (m, 2H, CH), 7.51–7.53 (t, J=6.04 & 2.56 Hz, 1H, CH), 9.97 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3686, 2823, 1722, 1600, 1498, 1388.

7-hydroxy-4-isopropyl-8-(morpholinomethyl)-*2H*-chromen-2-one (4a). white solid, yield 88%, mp 208–210°C; Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62; Found: C, 67.30; H, 6.95; N, 4.58; m/z:303[M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.22-1.24 (d, J=6.8 Hz, 6H, $2CH_3$), 2.59 (s, 4H, morpholine-CH_2 bridge), 3.14-3.21 (m, 1H, CH), 3.66-3.71 (s, 4H, morpholine-CH_2 bridge), 4.0 (s, 1H, CH_2), 6.06 (s, 1H, H-3), 6.70-6.72(d, J=8.84 Hz , 1H, H-6), 7.42-7.44(d, J=8.88 Hz , 1H, H-5); IR (KBr), ν(cm^{-1}): 3688, 2823, 1722, 1610, 1496, 1385; ^{13}C NMR (400 MHz, DMSO): 21.64, 27.91, 51.57, 52.62, 57.14, 66.02, 79.16, 95.41, 106.15, 108.70, 110.42, 112.69, 152.99,160.86, 162.95

7-hydroxy-4-isopropyl-8-((piperidin-1-yl)methyl)-*2H*-chromen-2-one (4b). off-white solid, yield 85%, mp 215–218°C; Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65; Found: C, 71.70; H, 7.65; N, 4.62; m/z:301[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.22-1.24 (d, J=6.8 Hz, 6H, $2CH_3$), 1.96-1.37 (m, 6H, piperidine CH_2), 2.85-2.27 (m, 4H, piperidine CH_2), 3.13-3.20 (m, 1H, CH), 4.05 (s, 2H, CH_2 bridge), 6.09 (s, 1H, H-3), 6.68-6.70 (d, J=9.08 Hz 1H, H-6), 7.46 (d, 1H, H-5), 12.39 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3680, 2828, 1720, 1620, 1498, 1380.

7-hydroxy-4-isopropyl-8-((4-methylpiperazin-1-yl)methyl)-*2H*-chromen-2-one (4c). off-white solid, yield 89%, mp 235–238°C; Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85; Found: C, 68.30; H, 7.68; N, 8.80; m/z:316[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.18-1.22 (d, 6H, 2CH3), 3.11-3.20 (m, 1H, CH), 3.25 (s, 3H, –N–CH_3), 4.00–4.37 (m, 8H, –N–CH_2), 4.99 (s, 2H, CH_2 bridge), 6.68 (s, 1H, H-3), 7.30 (d, J = 9 Hz 1H, H-6), 8.02 (d, J = 9 Hz, 1H, H-5); IR (KBr), ν(cm^{-1}): 3686, 2958, 2823, 1722, 1600, 1498, 1388.

7-hydroxy-4-isopropyl-8-((piperazin-1-yl)methyl)-*2H*-chromen-2-one (4d). white solid, yield 90%, mp 205–208°C; Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26; Found: C, 67.46; H, 7.38; N, 9.20; m/z:302[M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.22-1.23 (d, 6H, 2CH3), 2.69 (m, 1H, CH), 2.89-3.18 (m, 8H, –N–$(CH_2)_4$), 4.03 (s, 2H, CH_2), 6.06-6.05 (d, J=5.2 Hz 1H, H-3), 6.68-6.70 (d, J=8.8 Hz 1H, H-6), 7.40-7.42 (d, J=9.2 Hz 1H, H-5), 12.39 (s, 1H, brs,exchangeable NH); IR (KBr), ν(cm^{-1}): 3690, 2825, 1730, 1620, 1490, 1395.

7-hydroxy-4-isopropyl-8-((4-methylpiperidin-1-yl)methyl)-*2H*-chromen-2-one (4e). White solid, yield 87%, mp 245–248°C; Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44; Found: C, 72.30; H, 7.98; N, 4.40; m/z:315 [M^+]; IR (KBr), ν(cm^{-1}): 3692, 2968, 2833, 1723, 1610, 1492, 1395.

7-hydroxy-4-isopropyl-8-((3-methylpiperidin-1-yl)methyl)-*2H*-chromen-2-one (4f). White solid, yield 84%, mp 231–232°C; Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44; Found: C, 72.30; H, 7.99; N, 4.41; m/z:315 [M^+]; IR (KBr), ν(cm^{-1}): 3691, 2966, 2830, 1720, 1615, 1496, 1399.

7-hydroxy-4-isopropyl-8-((pyrrolidin-1-yl)methyl)-*2H*-chromen-2-one (4g). off-white solid, yield 80%, mp 160-162°C; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; Found: C, 71.00; H, 7.37; N, 4.40. m/z:287 [M^+]; IR (KBr), ν(cm^{-1}): 3670, 2980, 2850, 1730, 1625, 1476, 1369.

8-((dimethylamino)methyl)-7-hydroxy-4-isopropyl-*2H*-chromen-2-one (4h). off-white solid, yield 74%, mp 192-195°C; Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; Found: C, 68.90; H, 7.33; N, 5.30; m/z:261 [M^+]; IR (KBr), ν(cm^{-1}): 3680, 2978, 2866, 1745, 1655, 1486, 1379.

8-((diethylamino)methyl)-7-hydroxy-4-isopropyl-*2H*-chromen-2-one (4i). off-white solid, yield 70%, mp 172-175°C; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; Found: C, 71.00; H, 7.37; N, 4.40; m/z:287 [M^+]; IR (KBr), ν(cm^{-1}): 3690, 2970, 2860, 1740, 1635, 1496, 1389.

7-hydroxy-4-isopropyl-8-(morpholinomethyl)-*2H*-chromen-2-onehydrochloride (5a). white solid, yield 95%; Anal. Calcd for $C_{17}H_{22}ClNO_4$: C, 60.09; H, 6.53; N, 4.12; Found: C, 60.00; H, 6.50; N, 4.10; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.31-1.32 (d, J=6.8 Hz, 6H, $2CH_3$), 3.22-3.31 (m, 5H, 1H & morpholine 4H), 3.98 (s, 4H, morpholine-CH_2 bridge), 4.40 (s, 2H, CH_2), 6.12 (s, 1H, H-3), 7.05-7.07(d, J=8.84 Hz , 1H, H-6), 7.59-7.64(d, J=8.88 Hz , 1H, H-5), 11.38 (s, 1H, brs,exchangeable, OH); IR (KBr), ν(cm^{-1}): 3688, 2823, 1722, 1610, 1496, 1385.

7-hydroxy-4-isopropyl-8-((piperidin-1-yl)methyl)-*2H*-chromen-2-one-hydrochloride (5b). Off-white solid, yield 92%; Anal. Calcd for $C_{18}H_{24}ClNO_3$: C, 63.99; H, 7.16; N, 4.15; Found: C, 63.90; H, 7.13; N, 4.10; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.32-1.34 (d, J=6.8 Hz, 6H, $2CH_3$), 1.90-1.35 (m, 6H, piperidine CH2), 2.85-2.30 (m, 4H, piperidine CH_2), 3.14-3.20 (m, 1H, CH), 4.90 (s, 2H, CH_2 bridge), 6.15 (s, 1H, H-3), 7.06-7.08 (d, J=9.08 Hz 1H, H-6), 7.66 (d, 1H, H-5), 12.39 (s, 1H, brs, exchangeable, OH); IR (KBr), ν(cm^{-1}): 3680, 2828, 1720, 1620, 1498, 1380.

7-hydroxy-4-isopropyl-8-((4-methylpiperazin-1-yl)methyl)-*2H*-chromen-2-one hydrochloride (5c). white solid, yield 90%; Anal. Calcd for $C_{18}H_{24}ClNO_3$: C, 61.27; H, 7.14; N, 7.94; Found: C, 61.15; H, 7.02; N, 7.10; IR (KBr), ν(cm^{-1}): 3686, 2958, 2823, 1722, 1600, 1498, 1388.

7-hydroxy-4-isopropyl-8-((piperazin-1-yl)methyl)-*2H*-chromen-2-one hydrochloride (5d). off-white solid, yield 92%; Anal. Calcd for $C_{17}H_{22}ClN_2O_3$: C, 60.44; H, 6.56; N, 8.29; Found: C, 60.40; H, 7.48; N, 8.20; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.18-1.23 (d, 6H, 2CH3), 2.69 (m, 1H, CH), 2.89-3.20 (m, 8H, –N–$(CH_2)_4$), 4.88 (s, 2H, CH_2), 6.82 (d 1H, H-3), 7.68-7.70 (d, J=8.8 Hz 1H, H-6), 8.40-8.42 (d, J=9.2 Hz 1H, H-5); IR (KBr), ν(cm^{-1}): 3690, 2825, 1730, 1620, 1490, 1395.

7-hydroxy-4-isopropyl-8-((4-methylpiperidin-1-yl)methyl)-*2H*-chromen-2-one hydrochloride (5e). Off-white solid, yield 95%; Anal. Calcd for $C_{19}H_{26}ClNO_3$: C, 64.85; H, 7.45; N, 3.98; Found: C, 64.75; H, 7.35; N, 3.90; IR (KBr), ν(cm^{-1}): 3692, 2968, 2833, 1723, 1610, 1492, 1395.

7-hydroxy-4-isopropyl-8-((3-methylpiperidin-1-yl)methyl)-*2H*-chromen-2-one hydrochloride (5f). white solid, yield 94%; Anal. Calcd for $C_{19}H_{26}ClNO_3$: C, 64.85; H, 7.45; N, 3.98; Found: C, 64.75; H, 7.35; N, 3.90; IR (KBr), ν(cm^{-1}): 3691, 2966, 2830, 1720, 1615, 1496, 1399.

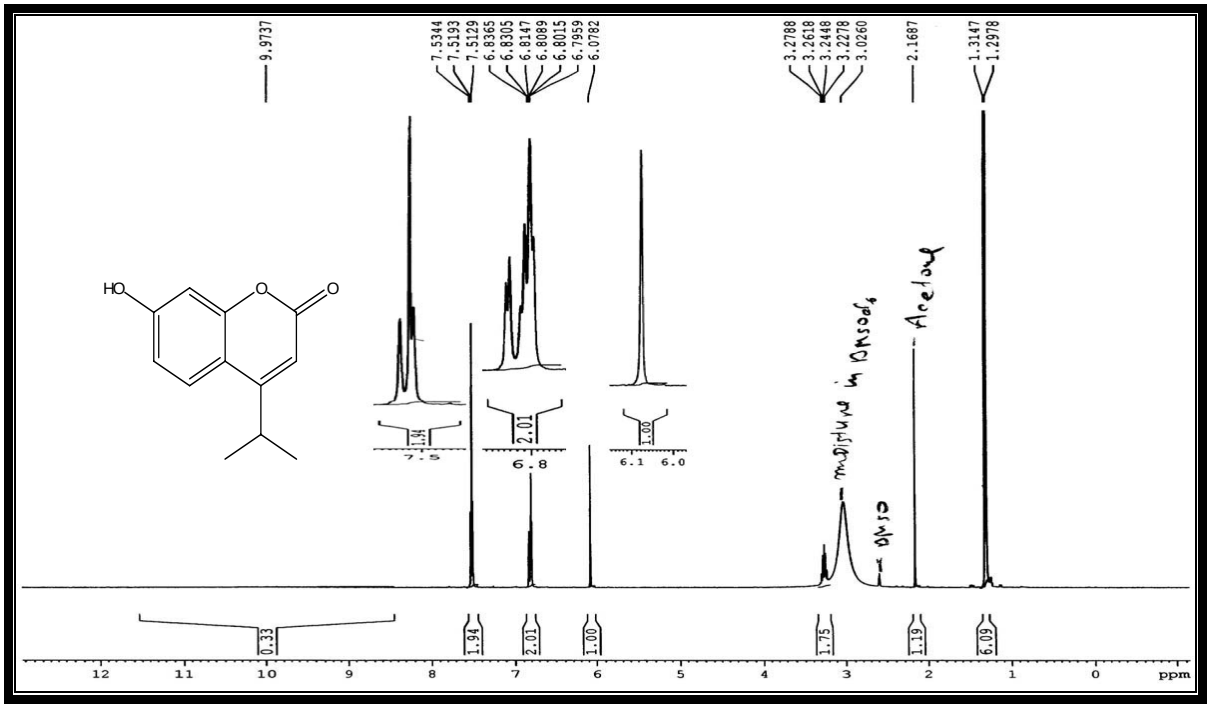
7-hydroxy-4-isopropyl-8-((pyrrolidin-1-yl)methyl)-*2H*-chromen-2-one hydrochloride (5g). white solid, yield 92%; Anal. Calcd for $C_{19}H_{26}ClNO_3$: C, 63.06; H, 6.85; N, 4.33; Found: C, 63.02; H, 6.77; N, 4.24; IR (KBr), ν(cm^{-1}): 3670, 2980, 2850, 1730, 1625, 1476, 1369.

8-((dimethylamino)methyl)-7-hydroxy-4-isopropyl-*2H*-chromen-2-onehydrochloride (5h). off-white solid, yield 94%; Anal. Calcd for $C_{15}H_{20}ClNO_3$: C, 60.50; H, 6.77; N, 4.70; Found: C, 60.40; H, 6.70; N, 7.60; IR (KBr), ν(cm^{-1}): 3680, 2978, 2866, 1745, 1655, 1486, 1379.

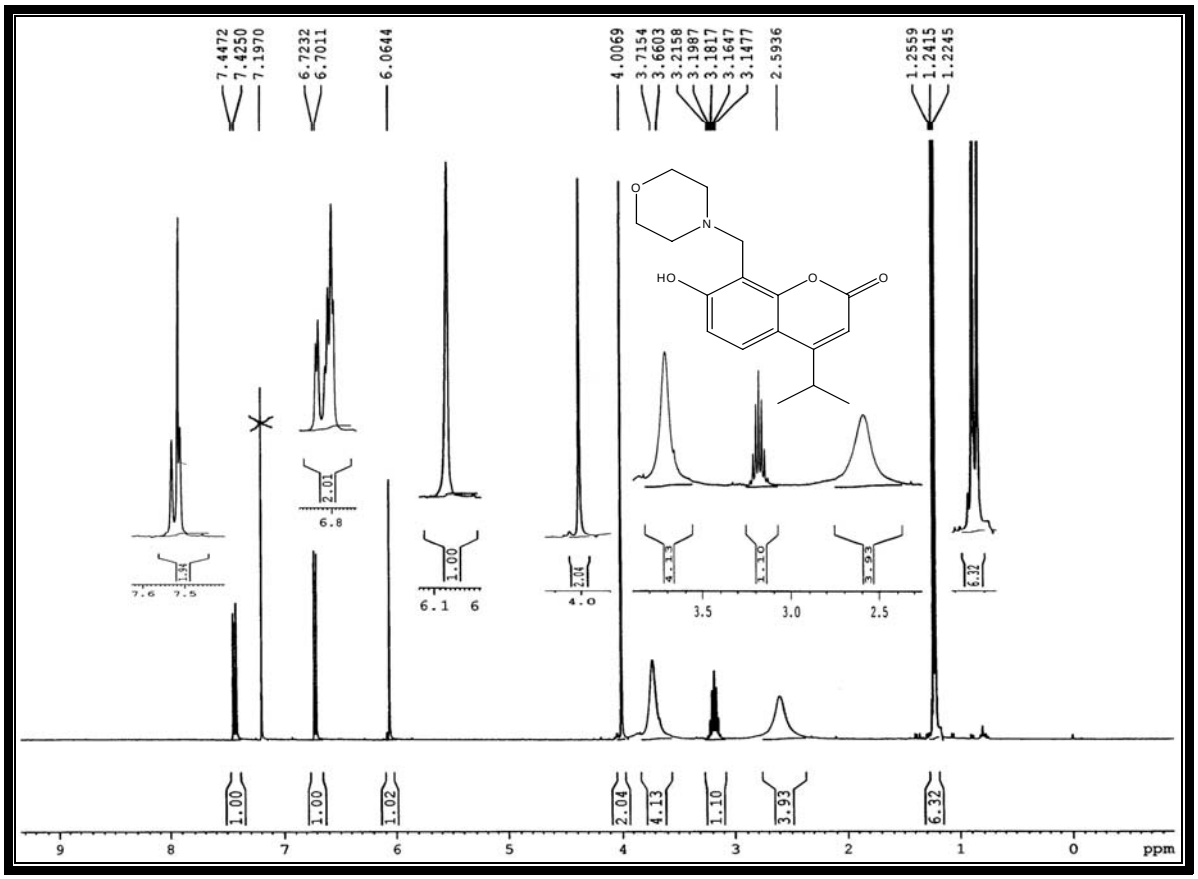
8-((diethylamino)methyl)-7-hydroxy-4-isopropyl-*2H*-chromen-2-one hydrochloride (5i). off-white solid, yield 90%; Anal. Calcd for $C_{17}H_{24}ClNO_3$: C, 62.67; H, 7.42; N, 4.30; Found: C, 62.60; H, 7.33; N, 4.24; IR (KBr), ν(cm^{-1}): 3690, 2970, 2860, 1740, 1635, 1496, 1389.

2.11 Spectral representation of synthesized compounds

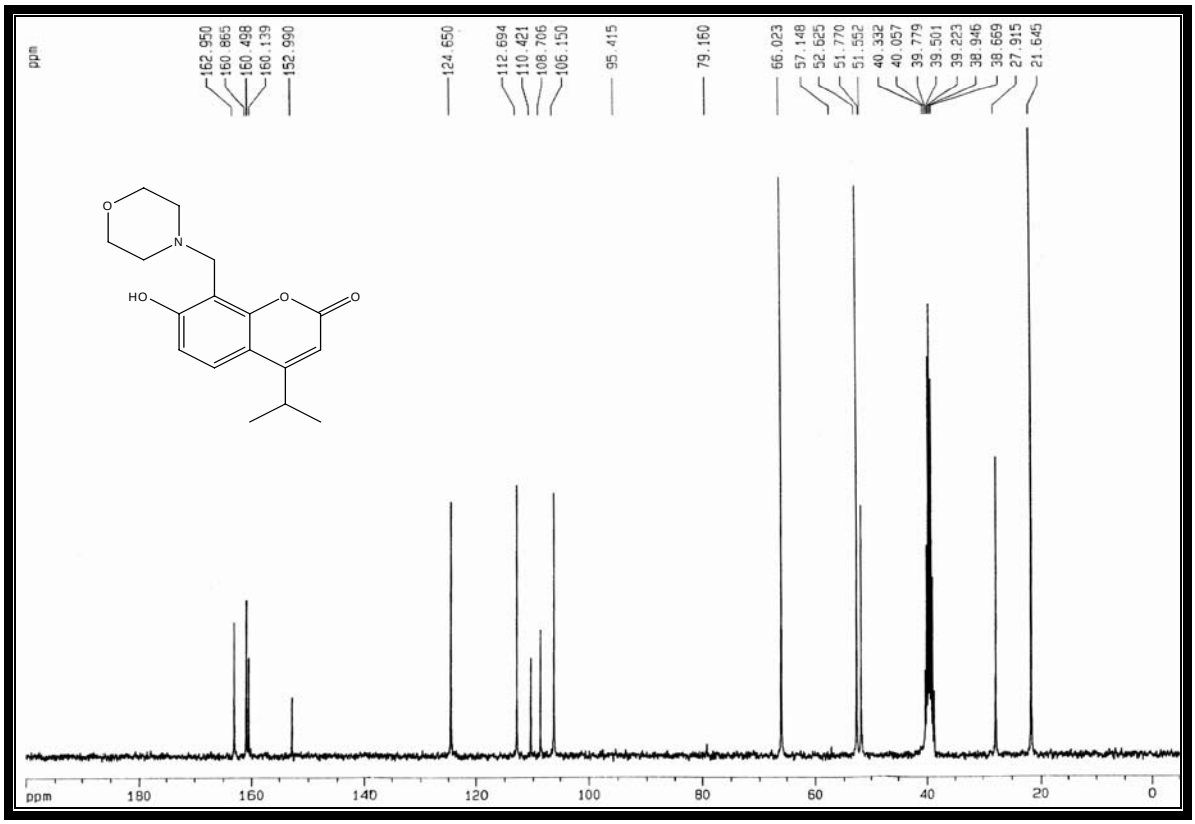
2.11.1 ^{1}H NMR spectrums of 7-hydroxy-4-isopropyl-2H-chromen-2-one (3)



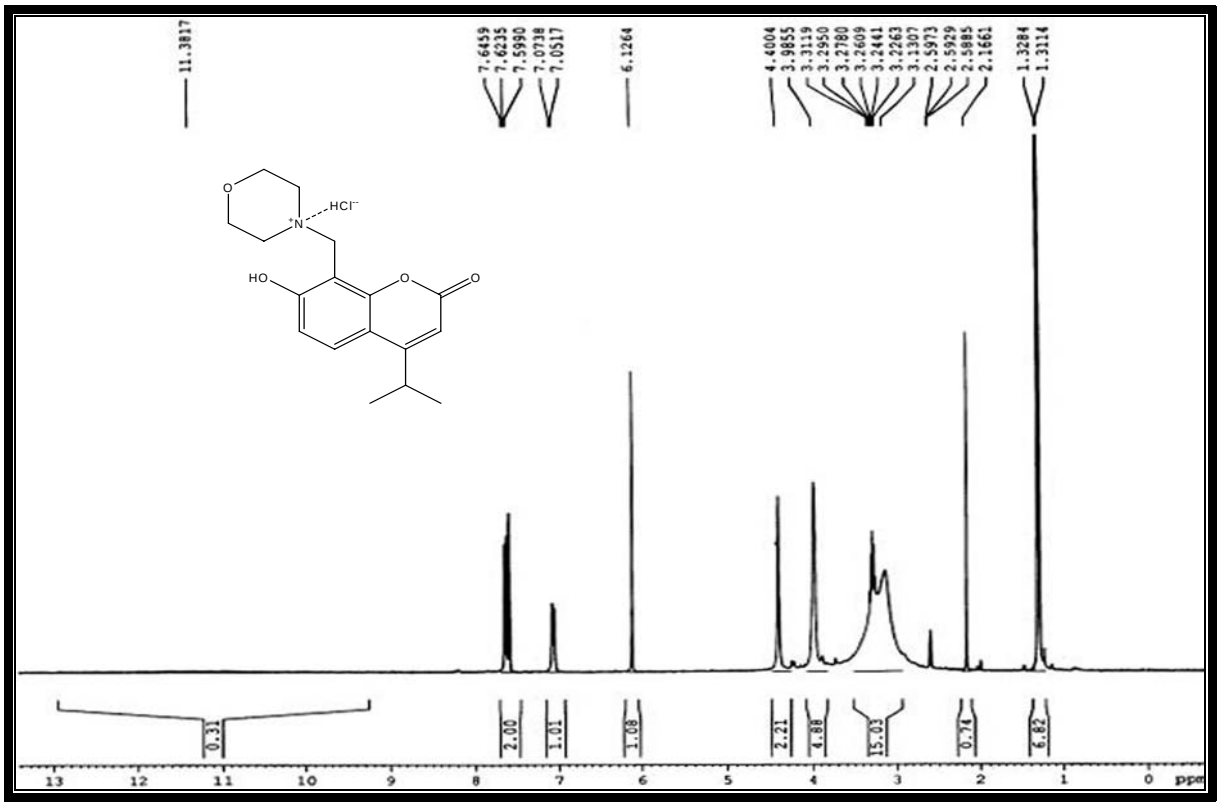
2.11.2 ^{1}H NMR spectrums of 4a



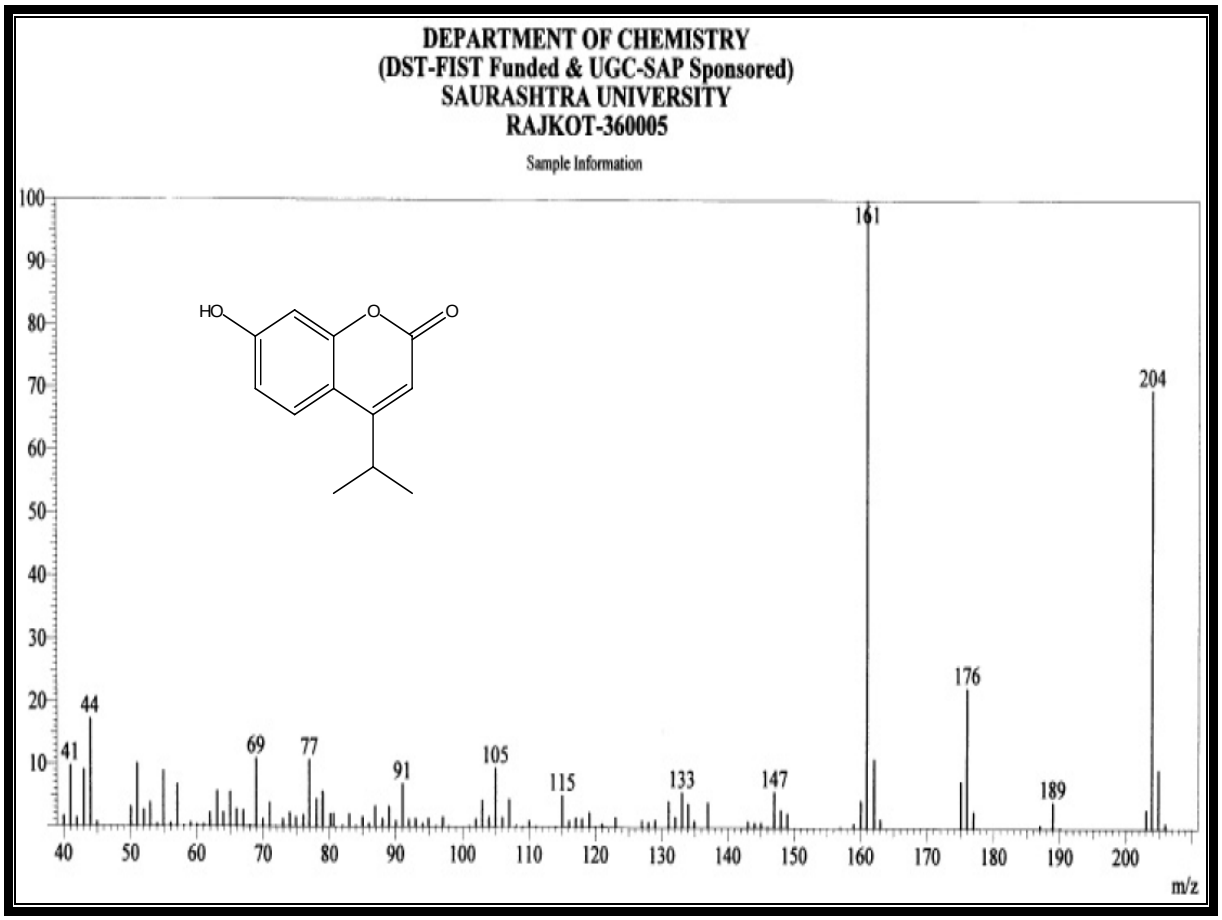
2.11.3 ^{13}C NMR spectrums of 4a



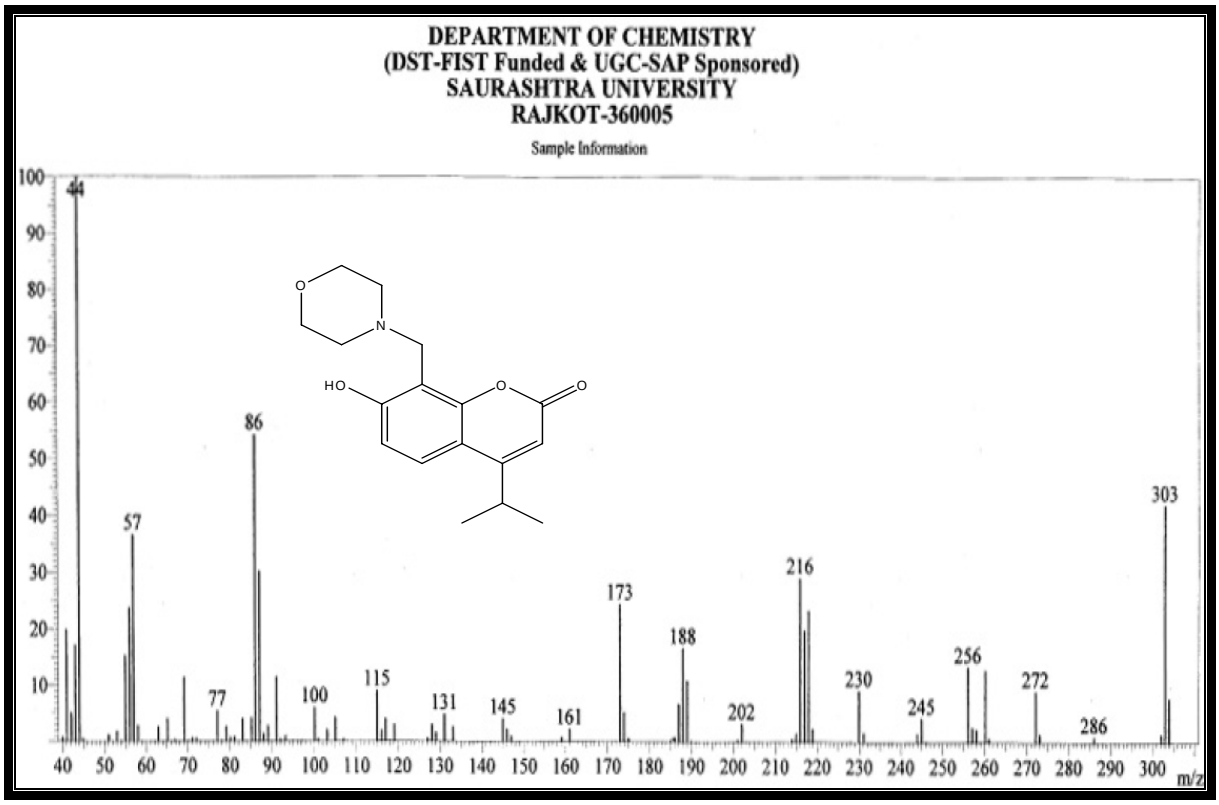
2.11.4 ^{1}H NMR spectrums of 5a



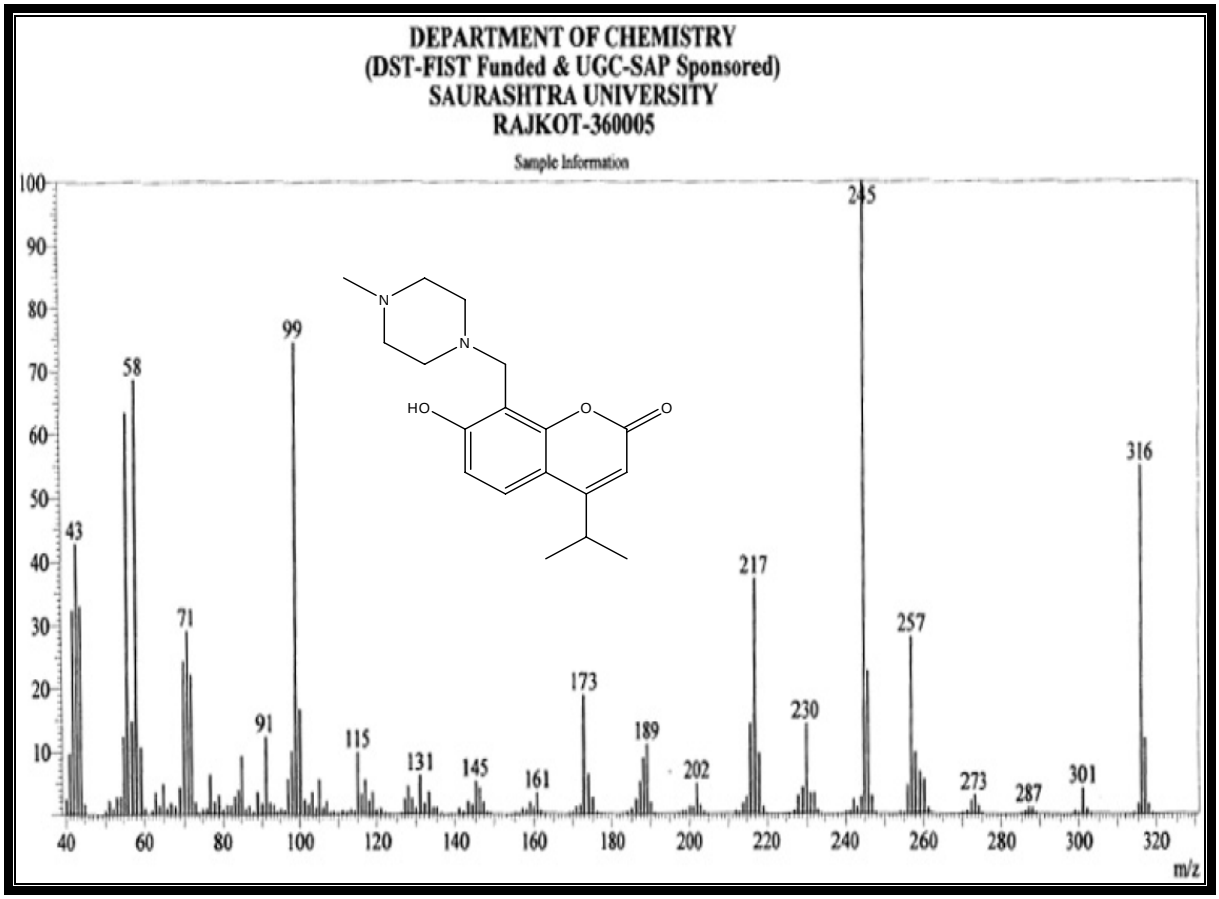
2.11.5 Mass spectrums of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one (3)



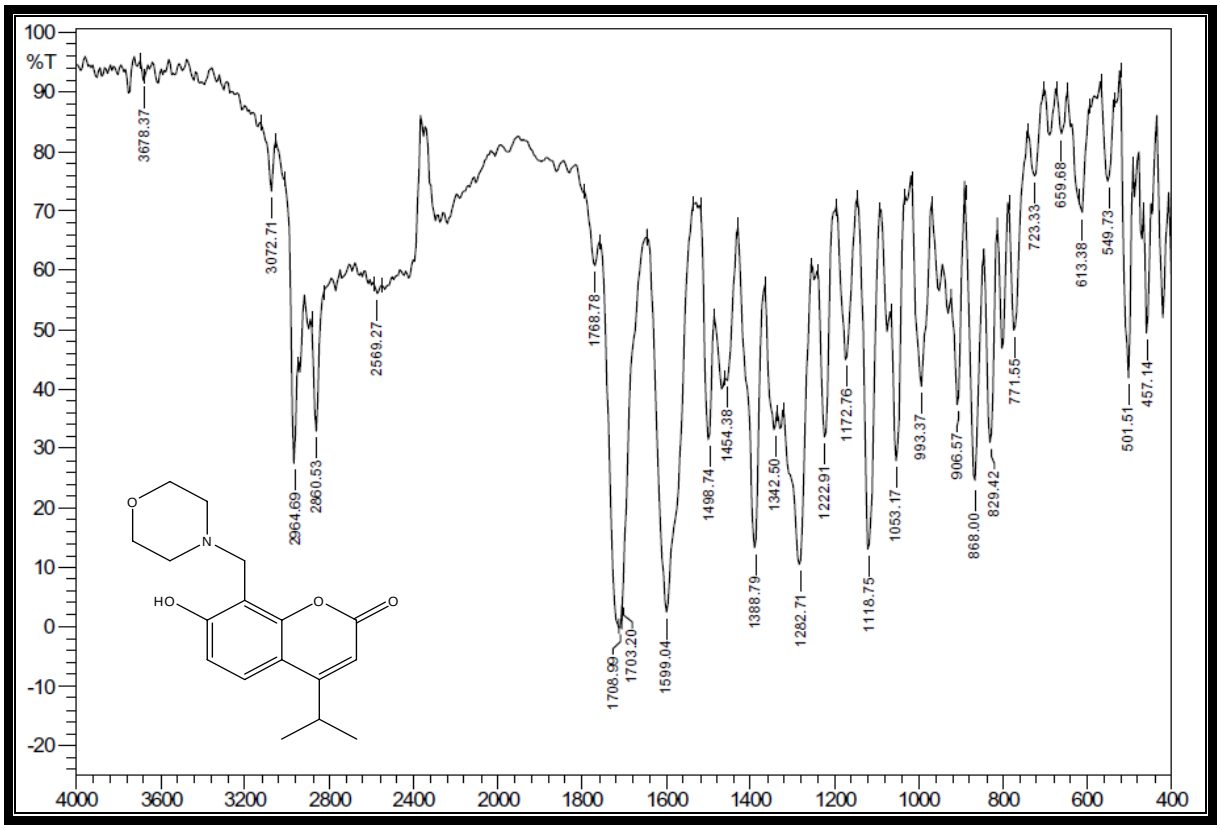
2.11.6 Mass spectrums of 4a



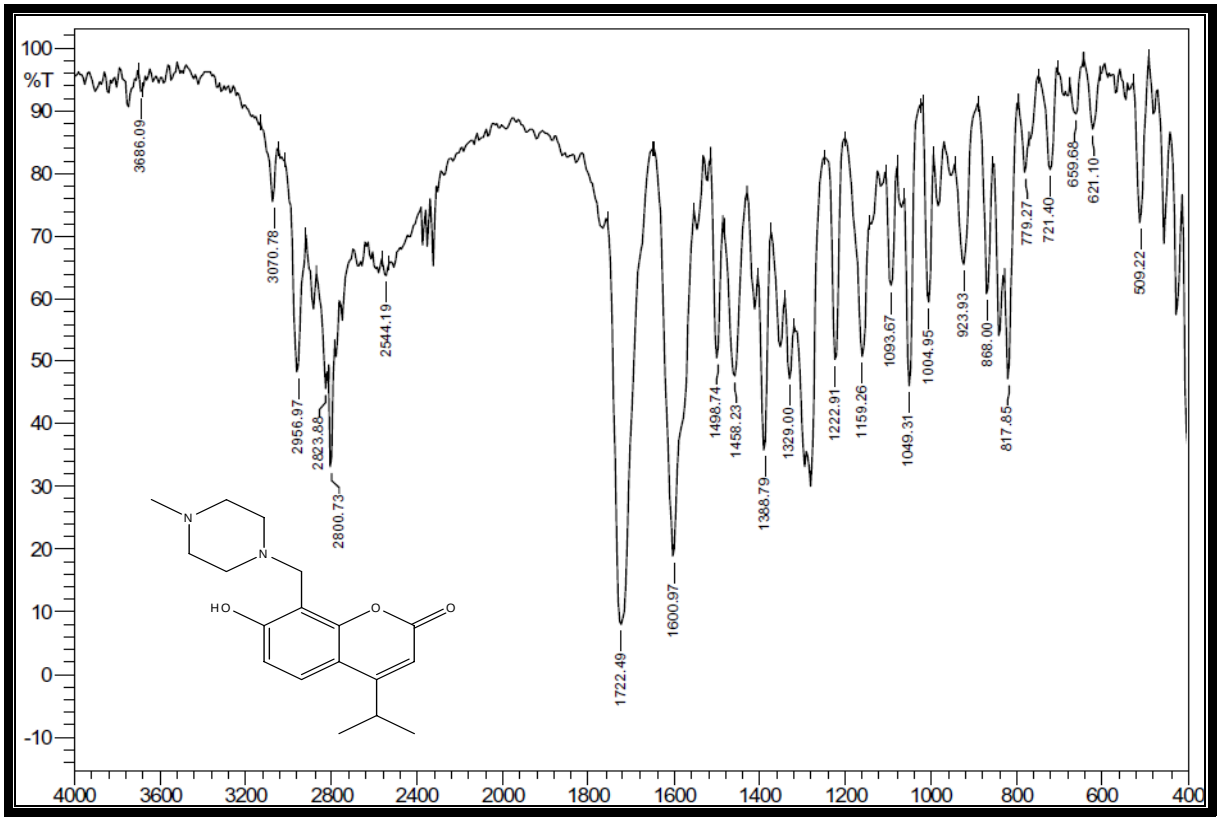
2.11.7 Mass spectrums of 4c



2.11.8 IR spectrums of 4a



2.11.9 IR spectrums of 4c



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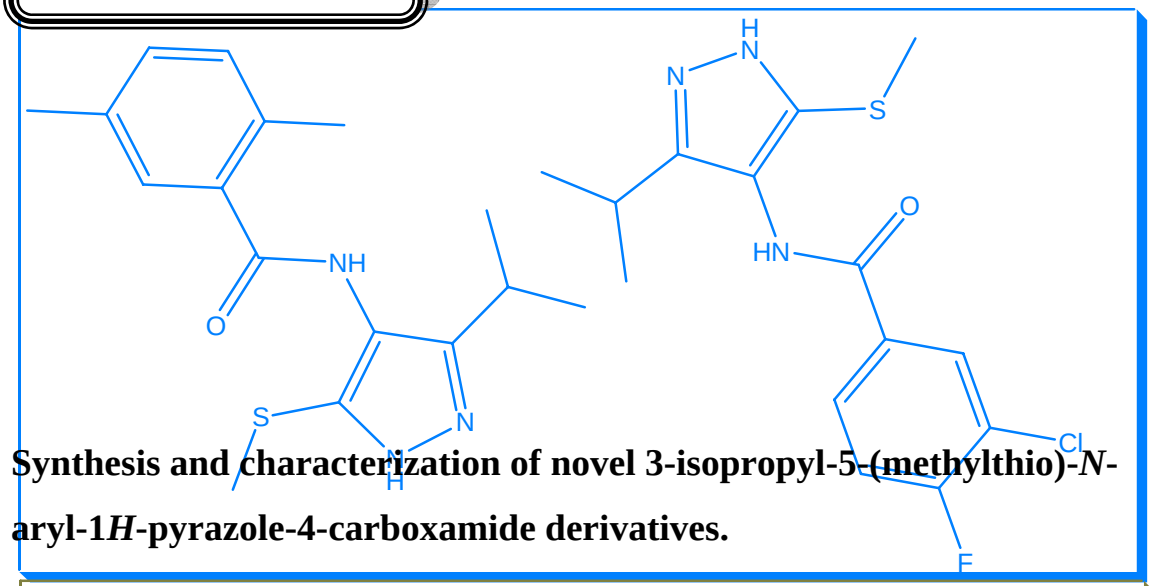
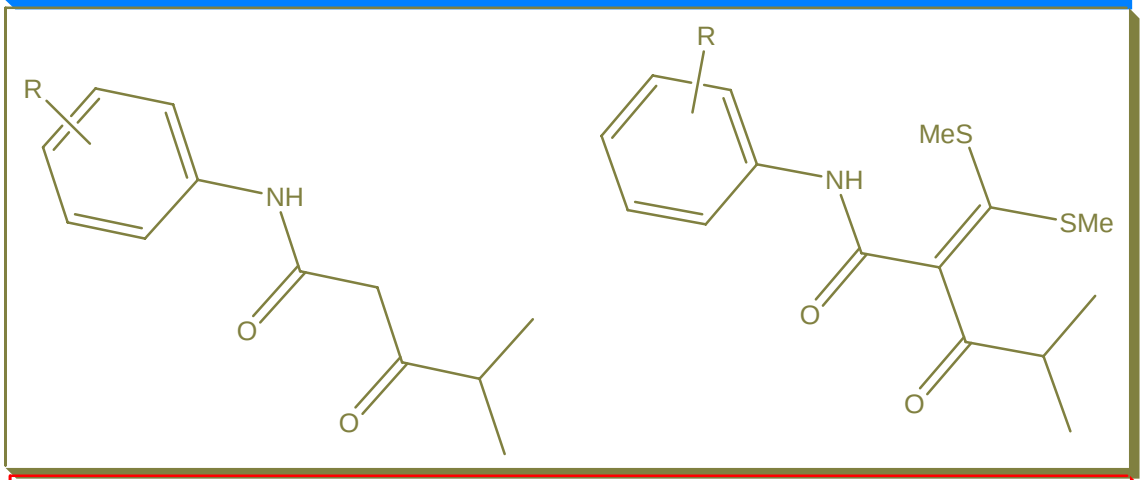
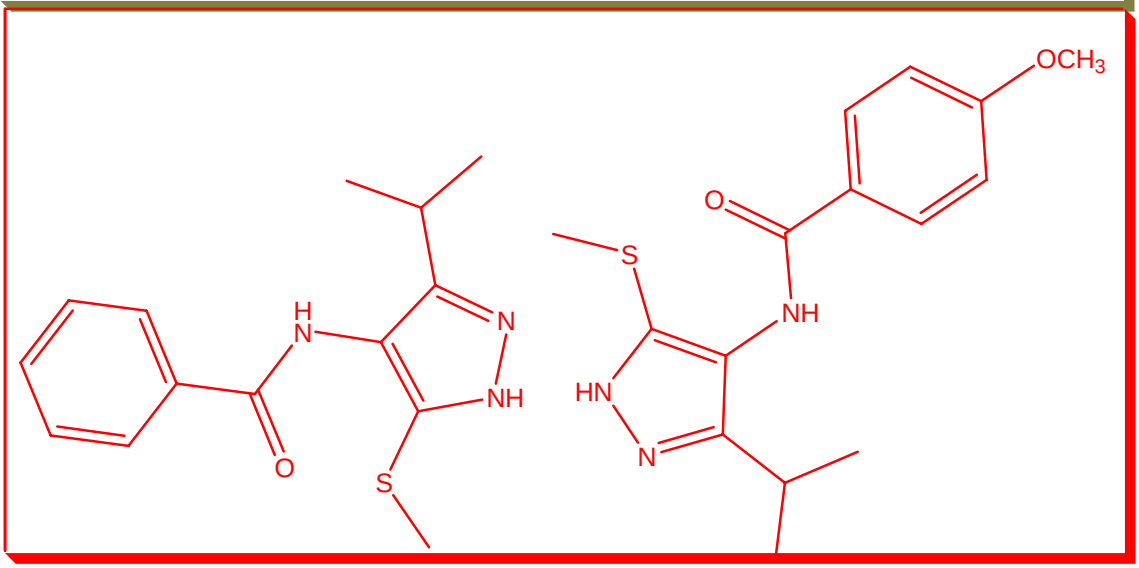
Chapter 3



Synthesis and characterization of novel 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives.





3.1 Introduction

Synthesis of pyrazole and its *N*-aryl analogues has been a subject of consistent interest because of the wide applications of such heterocycles in pharmaceutical as well as in agrochemical industry.[1,2] Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, and sedative-hypnotic activity.[2d-f] The 1-phenylpyrazole motif is present in several drug candidates for treatment of various diseases such as cyclooxygenase-2 (Cox-2) inhibitors, IL-1 synthesis inhibitors, and protein kinase inhibitors etc.[3] Similarly a few of the 1,5-diarylpyrazole derivatives have been shown to exhibit non-nucleoside HIV-1 reverse transcriptase inhibitory activities[4] along with Cox-2 inhibitor.[2g-h] The corresponding 1,3,5-triaryl-4-alkylpyrazoles have been recently identified as efficient ligands for estrogen receptor, displaying high binding affinities and selective transcriptional efficacy for ERR subtype.[5] Therefore continuous efforts have been devoted to the development of more general, efficient, and regioselective methods for the synthesis of this class of compounds.

Pyrazoles are well known five member heterocyclic compounds and several procedures for its synthesis have been extensively studied (**Figure 1**). Such studies have been stimulated by various promising applications, especially in the case of *N*-substituted pyrazole derivatives. In fact, certain *N*-substituted pyrazole are used as analgesic, anti-inflammatory, antipyretic, agrochemicals whereas some others are being studied for their medicinal interest. The knowledge of such applications has pointed out that *N*-substituted pyrazole are important target to be prepared to our interest on synthesis and molecular structure determination of some types of pyrazole. The pyrazole ring system consists of a doubly unsaturated five member ring containing two adjacent nitrogen atoms.

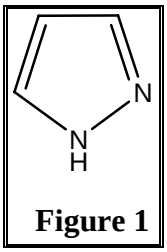


Figure 1

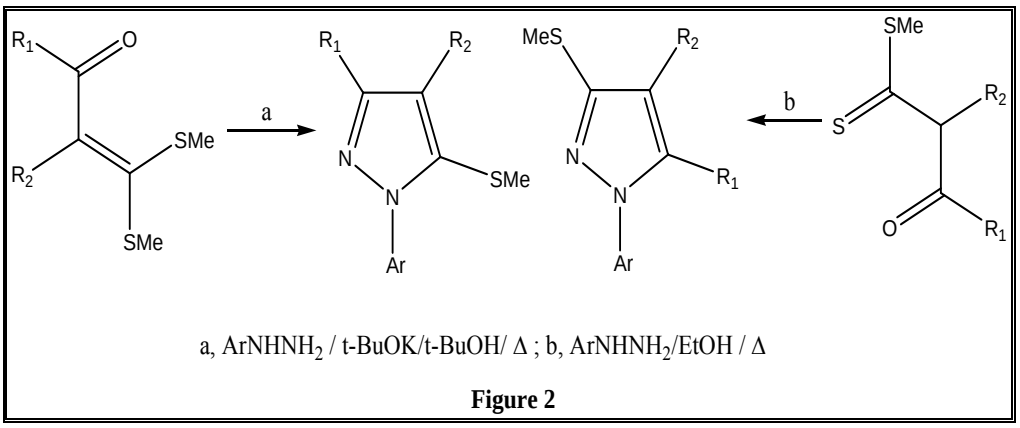
The discovery of pyrazole derivatives as antipyretic agents dates back to 1884, when the German chemist Ludwig Knorr[6] attempted to synthesize quinoline derivatives with antipyretic activity and accidentally obtained antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one), which has analgesic, antipyretic and antirheumatic activity.

Aminopyrine, a more potent analogue was synthesized there after and these drugs were widely used in market as antipyretics.

3.2 Synthetic methods for pyrazole

Different methods are reported in literature for the preparation of pyrazole some are as under.

1. S. Peruncheralathan et al.[7] have synthesized highly efficient and regioselective synthesis of 1-aryl-3,4-substituted/annulated-5-(methylthio)-pyrazoles and 1-aryl-3-(methylthio)-4,5-substituted/annulated pyrazoles has been reported via cyclocondensation of arylhydrazines with either α-oxoketene dithioacetals or α-oxodithioesters.(**Figure 2**)



a, $ArNHNH_2$ / t-BuOK/t-BuOH/ Δ ; b, $ArNHNH_2$/EtOH / Δ

Figure 2

2. Xuemei Wang et al.[8] have synthesized the pyrazole analogs (**Figure 3**) were prepared from a common aryl isocyanides intermediate. Cyclization with the oxime or the BOC-protected hydrazones of ethyl bromopyruvate generated the pyrazole carboxy esters, respectively.

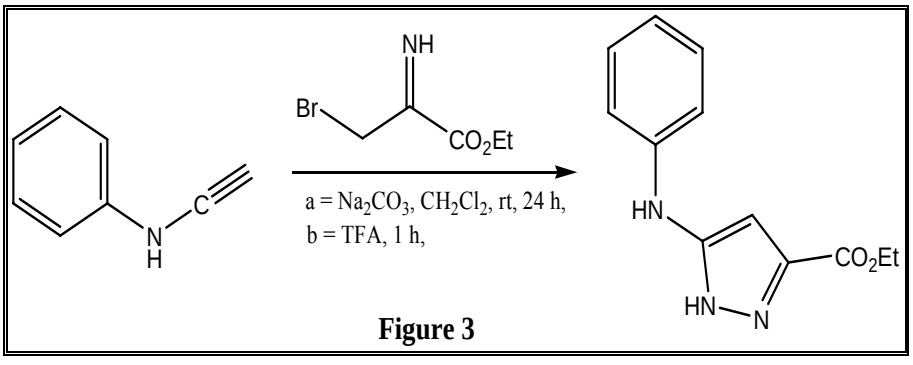


Figure 3

3. Pranab K. Mahata et al[9] have been synthesized 3-(dimethoxymethyl)-5-(methylthio) pyrazole derivative (**Figure 4**) shown to be useful three carbon synthon for

efficient regiospecfic synthesis of a varity of five (pyrazole) with mask or unmask aldehyde functionality by cyclocondensation with bifunctional heteronucleophiles such as hydrazine.

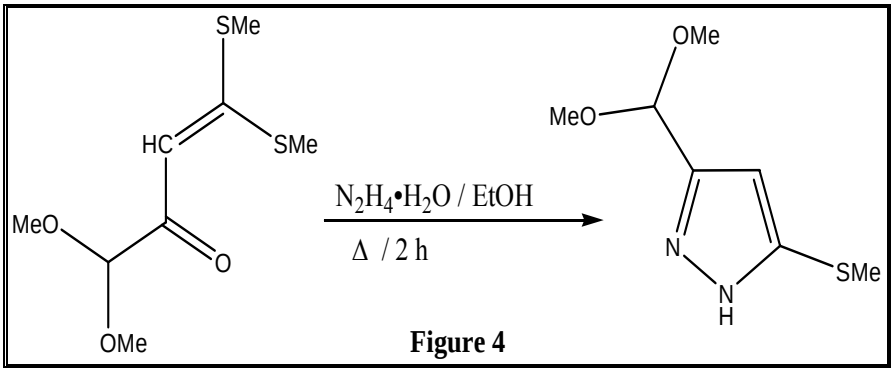


Figure 4

4. Lidia De Luca et al.[10] has been developed the synthesis of libraries of substituted pyrazole via in situ generation of polymer-bound enaminones (**Figure 5**). The synthetic protocol makes use of commercially available aniline cellulose, a low-cost and versatile biopolymer, under very mild conditions. This new support allowed us to carry out reactions in polar solvents under both conventional heating and MW irradiation without degradation of the polymer. The reaction between cellulose-bound enaminones and hydroxylamine or hydrazine to afford the target heterocycles in high yields directly in solution is the key step. The support can be conveniently recycled.

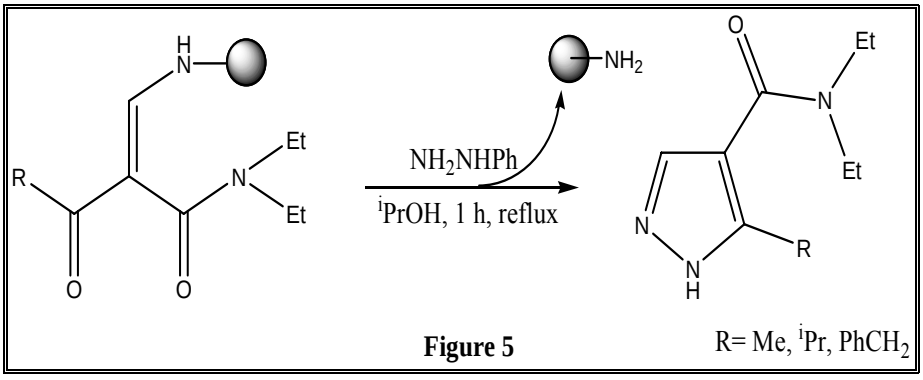


Figure 5 R= Me, ^{i}Pr, $PhCH_2$

5. Sabine Kuettel et al.[11] have been synthesized 4-(3-phenylisoxazol-5-yl)morpholine derrivatives (**Figure 6**) prepared by two synthetic routes, in which substituted acetophenones were reacted with carbon disulfide and methyl iodide in the presence of sodium hydride to give 4-phenoxyphenyl-2,2- bis(methylthio)vinyl ketones, followed by in situ cyclization of the resulting *N*,*S*-acetals with hydrazine hydrate.

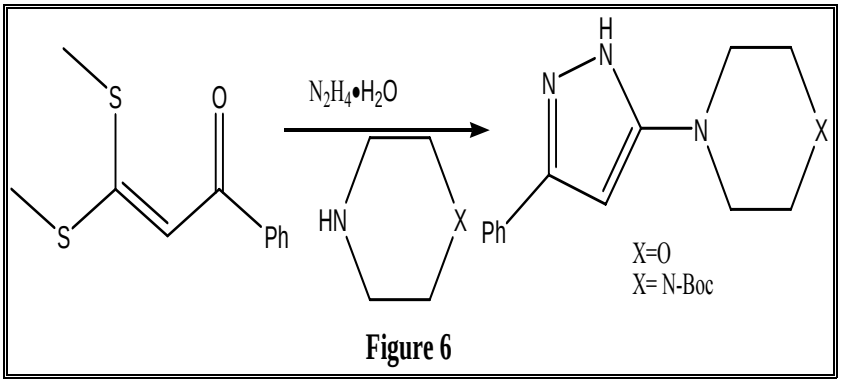


Figure 6

6. Scott R. Tweedie et al.[12] synthesized a palladium-catalyzed couplings of heteroaryl amines with aryl halides using sodium phenolate as the stoichiometric base (**Figure 7**).

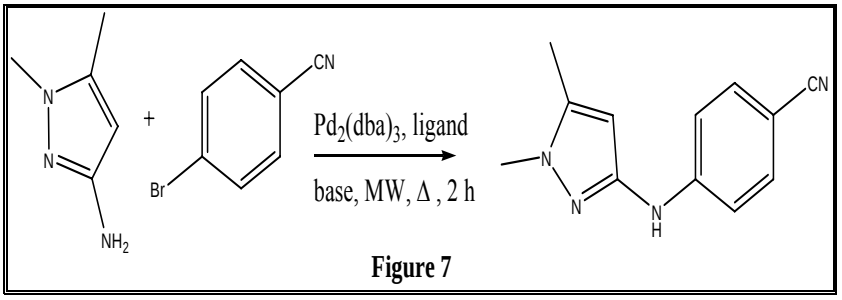


Figure 7

7. HooSook Kim et al[13] have reported on the regio-selective synthesis of 1,3,4,5-tetrasubstituted pyrazole derivatives from the reaction of Baylis-Hillman adducts of alkyl vinyl ketone and hydrazine derivatives (**Figure 8**). During the continuous studies on the chemical transformations of Baylis-Hillman adducts including the synthesis of pyrazole.

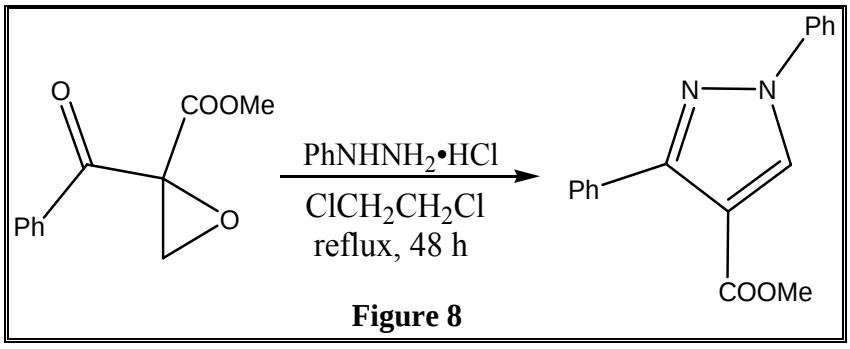


Figure 8

8. Kewei Wang et al.[14] synthesized of efficient and divergent one-pot synthesis of fully substituted 1*H*-pyrazoles (**Figure 9**) from cyclopropyl oximes based on reaction conditions selection is reported. Under Vilsmeier conditions ($POCl_3$/DMF), substituted 1*H*-pyrazoles were synthesized from 1-carbamoyl, 1-oximyl cyclopropanes via sequential ring-opening, chlorovinylation, and intramolecular aza-cyclization.

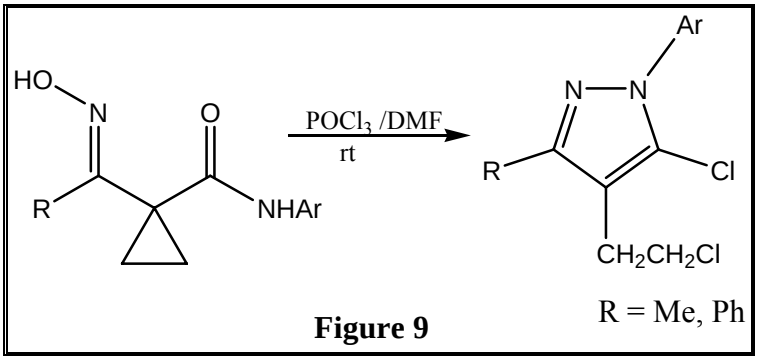


Figure 9

9. Galal H. Elgemeie et al[15] have reported novel ketene *N,S*-acetals were readily prepared by the reaction of cyanoacetamide or cyanothioacetamide with phenylisothiocyanate in the presence of potassium hydroxide, followed by alkylation of the produced salts with methyl iodide. The reaction of ketene *N,S*-acetals with hydrazine afforded different substituted pyrazole (**Figure 10**).

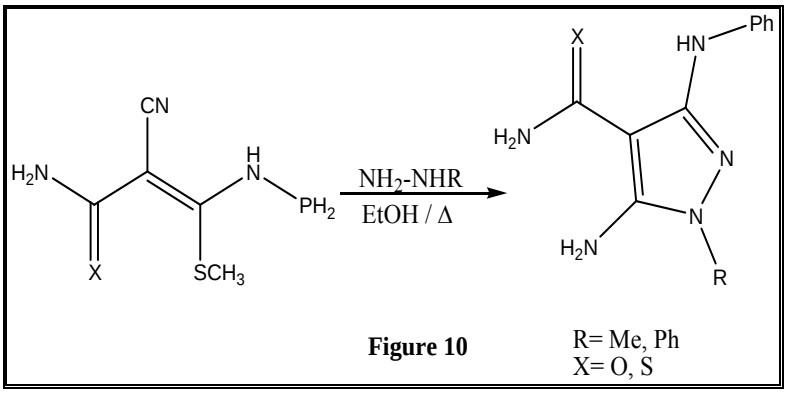


Figure 10

10. Wenli Ma et al.[16] has been developed an efficient three-component, two-step "catch and release" solid-phase synthesis of 3,4,5-trisubstituted pyrazole (**Figure 11**). The first step involves a base-promoted condensation of a 2-sulfonyl or a 2-carbonyl-acetonitrile derivative with an isothiocyanate and in situ immobilization of the resulting thiolate anion on Merrifield resin. Reaction of the resin-bound sulfonyl intermediate with hydrazine, followed by release from the resin and intramolecular cyclization, affords 3,5-diamino-4-(arylsulfonyl)-1*H*-pyrazoles (**Figure 11**), respectively. Reaction of the resin-bound carbonyl intermediate with hydrazine, on the other hand, leads to 3-(aryl amino)-5-aryl-1*H*-pyrazole-4- carbonitriles.

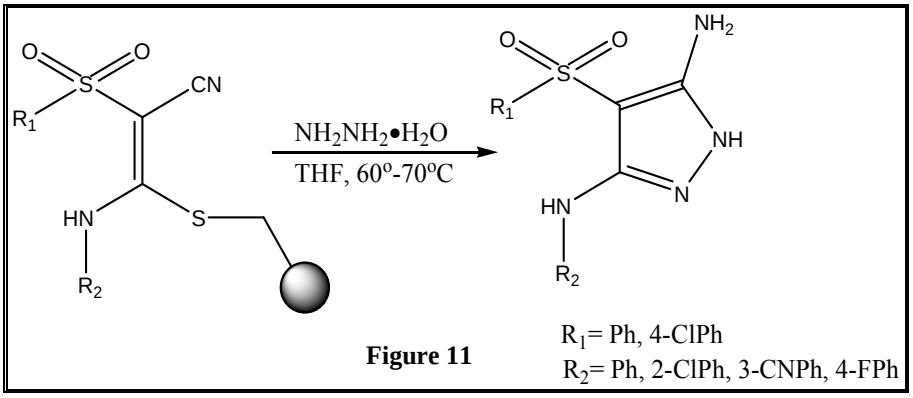


Figure 11

11. Daniel G. Rivera et al[17] have been synthesized steroidal heterocycles containing the pyrazole ring fused to the 16,17-position of the steroid nucleus is reported. Androstenolone acetate reacted with carbon disulfide, iodomethane and sodium hydride to furnish 3*β*-acetoxy-16-[bis(methylthio)methylene]-5-androst-5-en-17-one. The reactions of 3*β*-acetoxy-16-[bis(methylthio)methylene]-5-androst-5-en-17-one with hydrazine hydrate afforded the 5-methylthio-pyrazole[4, 3 :16, 17]androst-5-en-3*β*-ols respectively (**Figure 12**).

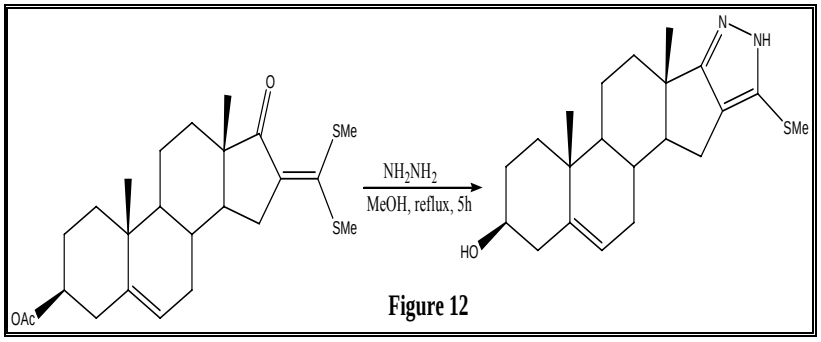


Figure 12

12. Geoffroy L. Sommen et al[18] synthesized variously substituted pyrroles in two steps by reacting a primary or secondary amine and a ketene dithioacetals in a basic medium in moderate to good yield. Ketene dithioacetals are readily prepared from acetylaceton or malononitrile, carbon disulfide, and methyl iodide (**Figure 13**).

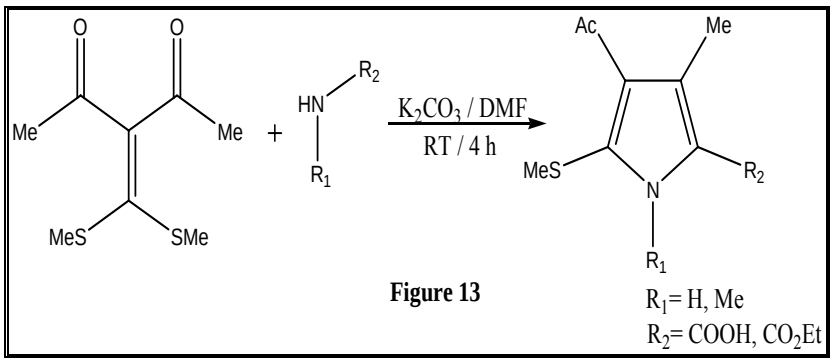


Figure 13

13. Thomas Kurz et al[19] synthesized novel fluorinated ketene *N,S*-acetals were readily prepared by the reaction of fluorosubstituted cyanoacetamide derivatives with arylisothiocyanate in the presence of potassium hydroxide, followed by the alkylation of the produced salts with methyl iodide. The reaction of fluorinated ketene *N,S*-acetals with hydrazine afforded different fluorosubstituted pyrazole (**Figure 14**).

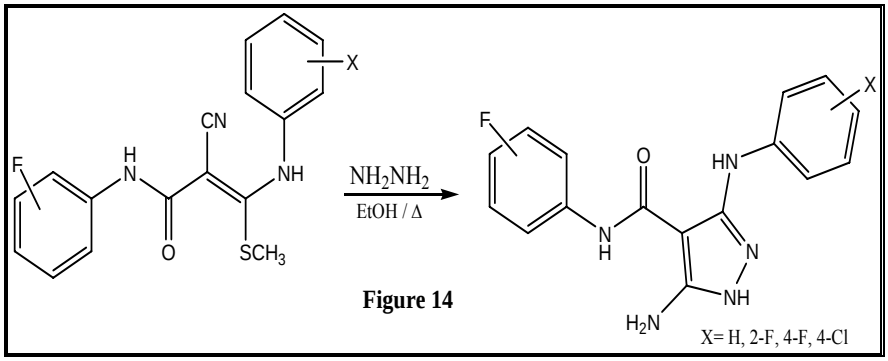


Figure 14

14. Galal H. Elgemeie et al[20] synthesized variety of novel *α*-cyanoketene *S,S*-acetals, readily prepared by the reaction of cyanoacetanilides or cyanothioacetamide with carbon disulfide, followed by alkylation, react smoothly with nucleophile to afford variously substituted methylthio derivatives of pyrazole (**Figure 15**).

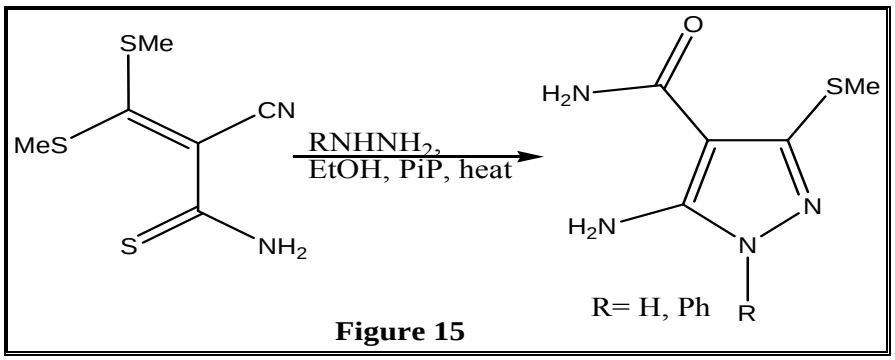


Figure 15

15. Maria T. Di Parsia et al.[21] synthesized several monopyrazole series which was prepared by the ketones were treated with ethyl format in dry pyridine or benzene utilizing sodium methoxide as catalyst, to afford the corresponding hydroxymethylene ketones. These intermediates without further purification were treated with hydrazine hydrate in refluxing methanol or ethanol to afford the final monopyrazole (**Figure 16**).

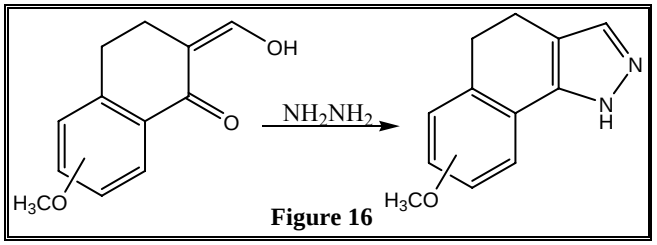


Figure 16

3.3 Mechanism

In ketene dithioacetals systems the carbonyl carbon and β-carbon atoms can also be regarded as hard and soft electrophilic centers, since the carbonyl is adjacent to the hard-base oxygen while the β-carbon is flanked by the soft-base thiomethyl groups[22] (**Figure 17**). Thus, the nucleophile of hydrazine hydrate attack on β-carbon of systems and formed heterocyclic product by removal of thiomethyl group as good leaving group.

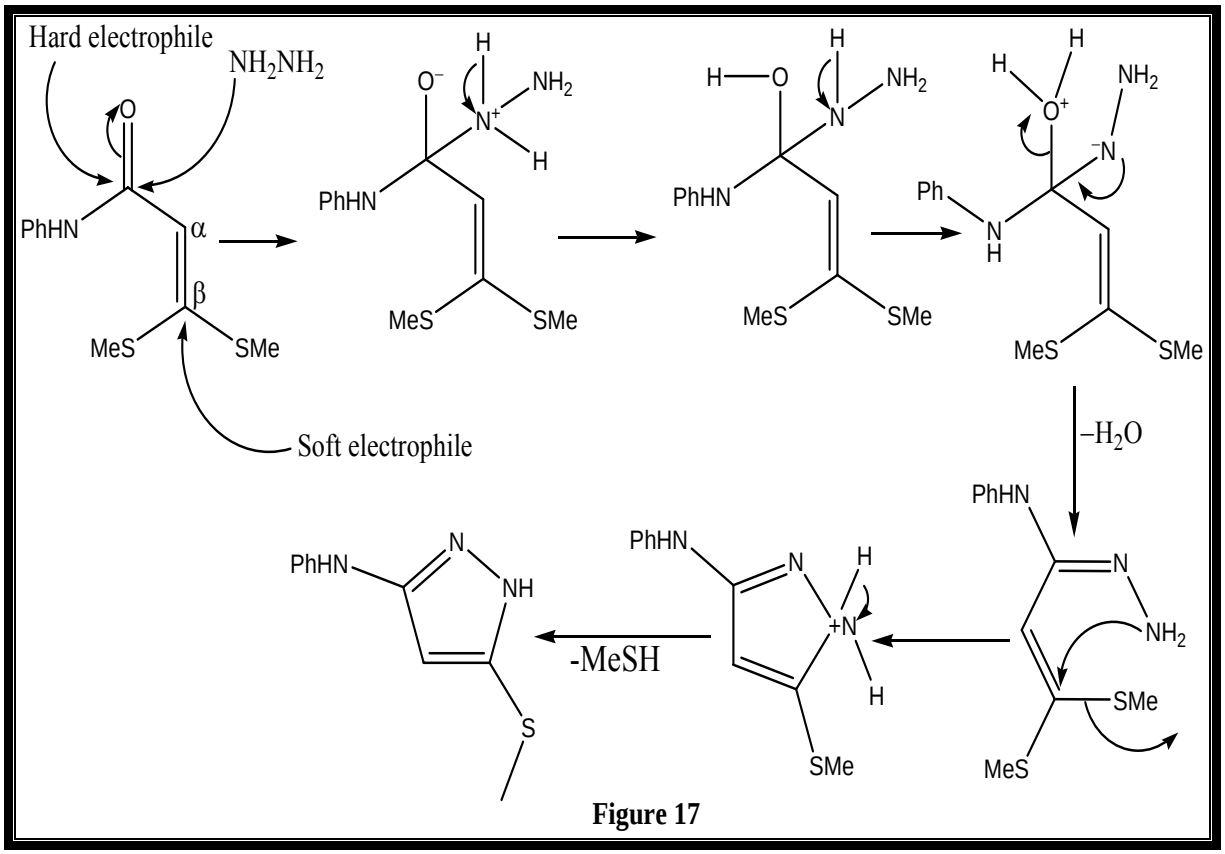


Figure 17

3.4 Biological activity of 1*H*-pyrazole

As mentioned above, the 1*H*-pyrazole derivatives possessed diverse biological activities such as antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, and sedative-hypnotic activity, cyclooxygenase-2 (Cox-2) inhibitors, IL-1 synthesis inhibitors, protein kinase inhibitors which are described briefly as follows. Similarly a few of the 1,5-diarylpyrazole derivatives have been shown to exhibit non-nucleoside HIV-1 reverse transcriptase inhibitory activities[4] along with Cox-2 inhibitor.[2g-h] The corresponding 1,3,5-triaryl-4-alkylpyrazoles have been recently identified as efficient ligands for estrogen receptor, displaying high binding affinities and selective transcriptional efficacy for ERR subtype.[5]

3.4.1 Anti-inflammatory activity

Anti-inflammatory preparations are widely used in the modern clinic, as pathogenetic agents in the treatment of many illnesses and pathological processes, alone or more frequently in combination with other drugs. However many of the known anti-inflammatory agents cause a range of side phenomena and complications in addition to the main effect. Consequently the search for and study of new more active anti-inflammatory agents of low toxicity is one of the urgent problems of contemporary science (**Figure 17**).[23]

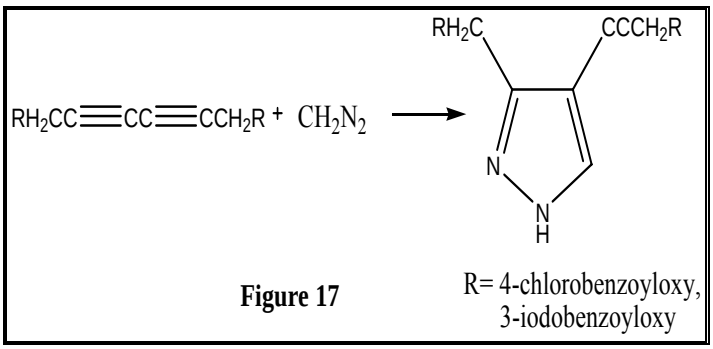


Figure 17

Toxicity was studied in 150 white mice of both sexes of weigh t 18-23 g. preparations were administered at 1-10% in oil solutions subcutaneously. Preparations were tested in not less than six animals at each dose. The volume of introduced solution did not exceed 1 ml. The value of the mean lethal dose (LDso) was determined by the method of Litchfield and Wilcoxon at p = 0.05. It was established that the synthesized compounds were of low toxicity. Even at doses of 1500 mg/kg they did not cause death of animals. Experiments on the study of anti-inflammatory activity were carried out on 250 white rats of both sexes of weight 120- 200 g. Inflammation was caused by formalin. Substances were administered subcutaneously as an oil solution 1 h before formalin. Tile activity of a preparation was compared with that of the widely known preparation amidopyrine.

3.4.2 Cyclooxygenase-2 (COX-2) Inhibitors

Celecoxib and rofecoxib analogues (**Figure 18**), in which the respective SO_2NH_2 and SO_2Me hydrogen-bonding pharmacophores were replaced by dipolar azido bioisosteric substituents, were investigated. Molecular modeling (docking) studies showed that the azidosubstituent of these two analogues (**Figure 18**) was inserted deep into the secondary pocket of the human COX-2 binding site where it undergoes electrostatic interaction with Arg513. The azido analogue of rofecoxib (Figure 18), the

most potent and selective inhibitor of COX-2 (COX-1 IC_{50}= 159.7 μM; COX-2 IC_{50}= 0.196 μM; COX-2 selectivity index = 812), exhibited good oral anti-inflammatory and analgesic activities.[24]

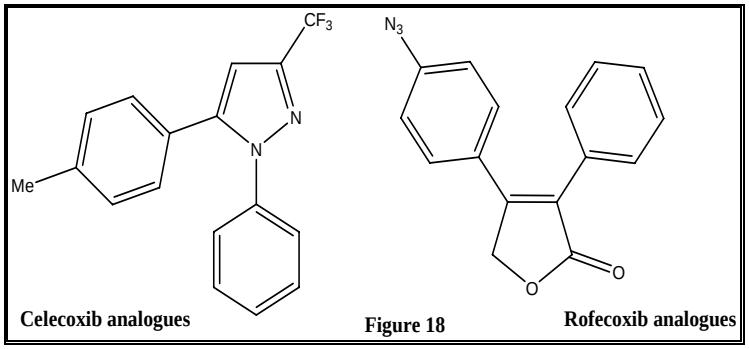


Figure 18

3.4.3 Helicobacter pylori DHODase

The identification of several potent pyrazole-based inhibitors of bacterial dihydroorotate dehydrogenase (DHODase) via a directed parallel synthetic approach is described below (**Figure 19**). The initial pyrazole-containing lead compounds were optimized for potency against Helicobacter pylori DHODase.[25] Using three successive focused libraries, inhibitors were rapidly identified with the following characteristics: *K*i <10 nM against H. pylori DHODase, sub-*μ*g/mL H. pylori minimum inhibitory concentration activity, low molecular weight, and >10 000-fold selectivity over human DHODase.

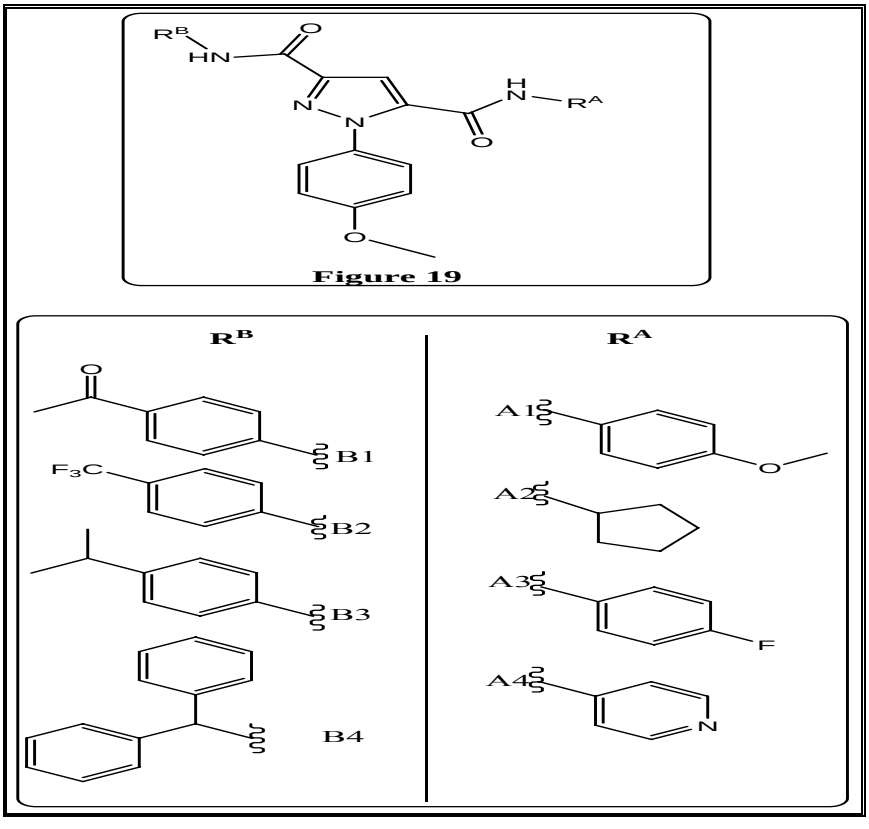


Figure 19

Helicobacter pylori is a Gram-negative microaerophilic bacterium that infects up to 50% of the world's human population.[26] *H.* pylori resides in the acidic surroundings of the stomach, utilizing a high urease enzyme activity to provide a locally alkaline environment. *H. pylori* has been implicated in numerous gastrointestinal disorders and is associated with gastric ulcers, gastritis, and gastric cancer.[27] The current treatment of *H. pylori* infections typically utilizes a multiple drug therapy involving at least one broad spectrum antibiotic (antimicrobial therapy) and a proton pump inhibitor (antisecretory therapy). However, a *H. pylori* specific antimicrobial would be very desirable; a specific agent should avoid many of the negative gastrointestinal side effects associated with a broad spectrum antibacterial resulting from eradication of the normal gastrointestinal flora.

A number of potent *H. pylori* DHODase inhibitors based upon a pyrazole core were identified. Directed parallel synthesis enabled the rapid optimization of lead compounds via three focused libraries. All of the libraries discussed above were developed, synthesized, and purified. The most potent DHODase inhibitors are very selective (>10000-fold) for *H. pylori* over human DHODase enzymes. The inhibitors display low μg/mL to sub-μg/mL antibacterial activity against *H. pylori*. However, no antibacterial activity is seen against a variety of other Gram-positive and Gram-negative organisms (*Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *E. coli*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Psuedomonas aeruginosa*).

3.4.4 Antibacterial activity

Akihiko Tanitame et al.[28] have synthesized a pyrazole derivative (**Figure 20**) possesses antibacterial activity and inhibitory activity against DNA gyrase and topoisomerase IV. They have synthesized new pyrazole derivatives and found that 5-[(*E*)-2-(5-chloroindol-3-yl)vinyl]pyrazole (**Figure 21**) possesses potent antibacterial activity and selective inhibitory activity against bacterial topoisomerases. Many of the synthesized pyrazole derivatives were potent against clinically isolated quinolone coumarin-resistant Gram-positive strains and had minimal inhibitory concentration values against these strains equivalent to those against susceptible strains.

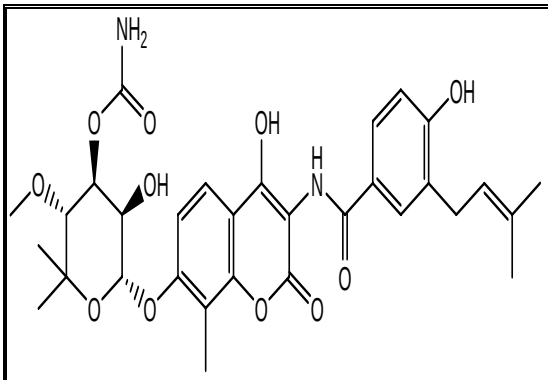


Figure 20

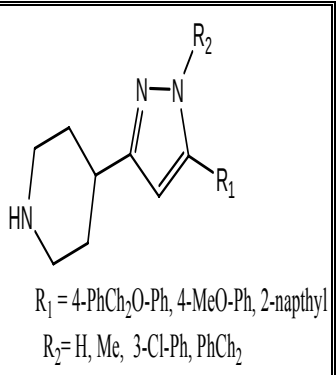


Figure 21

Among them, the pyrazole derivative (**Figure 21**) was identified as an interesting lead candidate. **Figure 21** showed the same minimal inhibitory concentration value (MIC) against clinically isolated multidrug resistant Gram-positive bacteria as against susceptible strains. However, the antibacterial activity of (**Figure 21**) was weak (MIC) 64 μg/mL) because it only slightly inhibited DNA gyrase and topoisomerase IV (IC50) 128 μg/mL). In this study was to optimize the lead compound (**Figure 21**) and to find new, potent DNA gyrase inhibitors with antibacterial activity against MRSA, PRSP, and VRE. They report herein the synthesis and structure-activity relationships of a series of pyrazole derivatives. In addition, pyrazole derivatives showed a more potent antibacterial activity against clinically isolated quinolone and coumarin-resistant Gram-positive bacteria than sparfloxacin and novobiocin, respectively. We are pursuing further modifications of this novel pyrazole scaffold that can potently inhibit DNA gyrase and topoisomerase IV.

3.4.5 Antiproliferative activity

Chih Y. Ho et al[29] have repoted a series of (6,7-dimethoxy-2,4-dihydroindeno[1,2-*c*]pyrazol-3-yl)phenylamines (**Figure 22**) has been optimized to preserve both potent kinase inhibition activity against the angiogenesis target, the receptor tyrosine kinase of Platelet-Derived Growth Factor-BB (PDGF-BB), and to improve the broad tumor cell antiproliferative activity of these compounds. This series culminates in the discovery of (Figure 22) (JNJ-10198409), a compound with anti-PDGFR-α kinase activity (IC_{50} = 0.0042 μM) and potent antiproliferative activity in six of eight human tumor cell lines (IC_{50} = 0.033 μM).

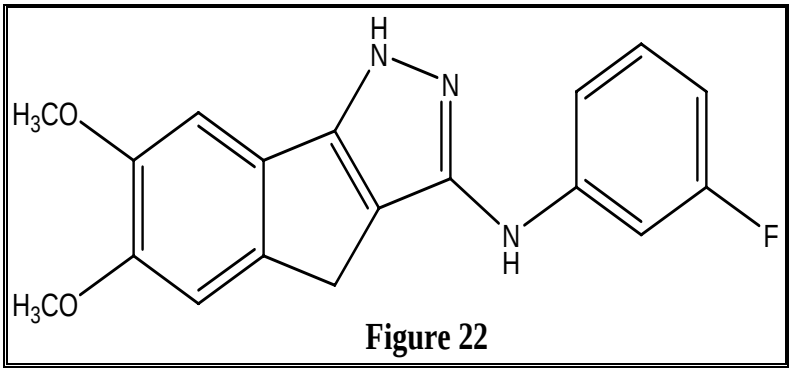


Figure 22

Chih Y. Ho has developed antiangiogenic compounds with an additional antiproliferative activity capable of inhibiting tumor progression by controlling both the vascularization and proliferation of the tumor mass. Tumors may be regarded as a two-compartment system consisting of the vasculature supporting tumor growth composed of 'normal' homogeneous vascular endothelial cells, smooth muscle cells, and pericytes that are surrounded by colonies of neoplastic cancer cells. To find molecules that would affect both the vascular and transformed compartments, we identified several compounds with the potential to inhibit the PDGFR-β kinase-mediated angiogenic effect and then assayed them for collateral antiproliferative activity against a panel of human tumor cell lines.

3.4.6 Antiallergic activity

The synthesis and study of the oral antiallergic activity of a series of monopyrazole derivatives (**Figure 23**) considered as analogues of active bis pyrazole are described.[30] None of the compounds showed significant inhibition of the rat passive cutaneous anaphylaxis (PCA), with the exception of the already known 5-aminoindazole (Figure 23).

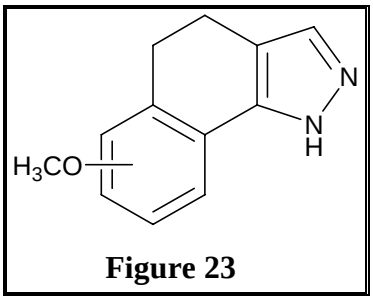


Figure 23

The biological assay was performed as reported previously for compound (**Figure 24**).[31] All the compounds were given orally at a single dose of 200 mg/kg. Anti-PCA activity was measured 1 and 3 h after oral administration. When compared to the 77 and 55% inhibition produced by compound (**Figure 24**), the monopyrazole synthesized showed no significant inhibition of the PCA reaction in rats either at 1 or 3 h after administration.

With the methoxy-substituted compounds, only the 6 and 8 isomers show some degree of activity against the PCA reaction 1 h after oral administration with inhibition values of 15 and 32%, respectively. After 3 h, however, the activity of the 7-isomer begins to approximate that of the other isomers after 1 h (27%), but still the level of activity is rather low to allow any sort of correlation. Surprisingly, with the corresponding hydroxyl compounds the anti-PCA activity is even lower, and after 3 h one of the isomers (9) tends to become a weak potentiator of the PCA reaction. The rest of the compounds can likewise be regarded as inactive, with the exception of **Figure 23** (54%, 3 h). Compound (**Figure 23**) shows the type of prolonged activity characteristic of **Figure 24**. It is interesting that it becomes a better inhibitor with time and thus represents a new "core" structure upon which one can design a potentially interesting structure-activity study.

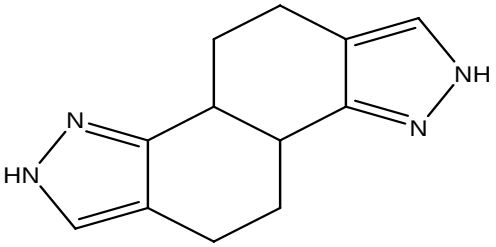


Figure 24

3.4.7 Antimalarial activity

Pyrazole derivatives are known to possess various kinds of biological activity. For example, the pyrazole-[3,4-b]pyrimidine derivative, an isostere of caffeine, is indistinguishable from caffeine in its diuretic properties and is also a strong CNS[32] stimulant.

Robert G. Stein et al[33] have combined the features of the pyrazole ring, a substituted quinoline, and an "antimalarial" side chain in one molecule for antimalarial testing. The key intermediate required was a 4-chloro-1*H*-pyrazolo [3,4-*b*]quinoline (**Figure 25**), in which the active C1 could be replaced with suitable amines expected to impart antimlalarial activity to the final products.

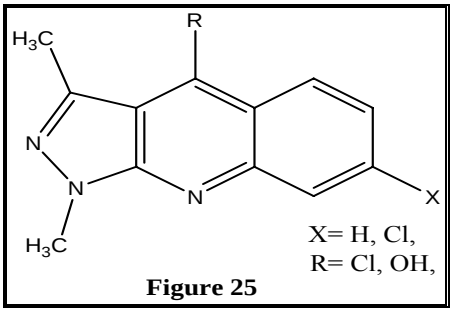


Figure 25

3.5 Aim of current work

The pyrazole nucleus is present in a wide variety of biologically interesting compounds, which exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic activity.[1-5] Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies to this class of compounds.[1-5]

Ketene dithioacetals bearing the cyano, amide, thioamide, or alkoxycarbonyl group at the α-position are extremely interesting eletrophilic reagents for the introduction of three or two carbon units into the ring of heterocyclic compounds.[34, 35]

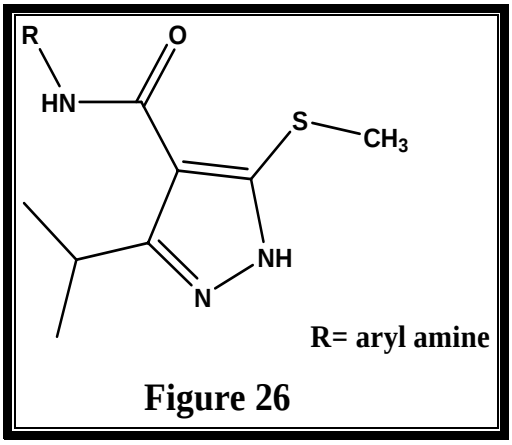


Figure 26

We have recently developed different successful approaches for synthesis of new ketene *S,S*-acetals as starting from acetoacetanilides (**2a-s**). In an extension of this work, we are now reporting a synthesis of some novel ketene *S,S*-acetals and their use in the synthesis of functionalized pyrazole derivatives (**4a-s**) (**Figure 26**).

3.6 Chemistry

α-Oxoketene dithioacetals (**Figure 27, 28, 29**) especially the dimethyl thioacetals have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic compounds.[36, 37] Ketene dithioacetals, in the presence of various regents, undergo different types of reactions to yield other heterocyclic compounds, e.g., pyrazole, thiophene, pyrimidines, pyridines, etc. Consequently we were interested in surveying the synthetic utility of ketene dithioacetals.

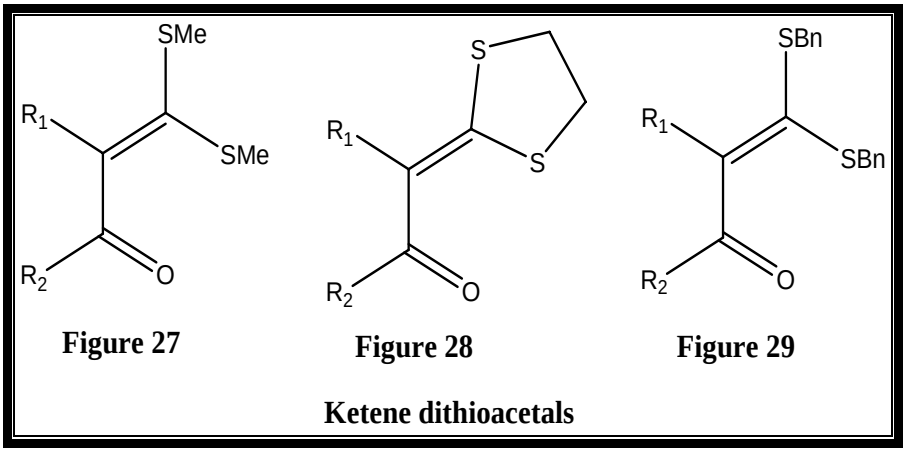


Figure 27 **Figure 28** **Figure 29**

Ketene dithioacetals

The method for preparation of α-oxoketene dithioacetals is common, the combination of an active methylene/methyl substrate, CS_2, RX, and a suitable base. Lawesson and Larsson,[38-40] Junjappa and Ila[41] have reported the synthesis of mixed dialkylketene dithioacetals from dithioesters which were prepared from ketone and dimethyl trithiocarbonate.[42]

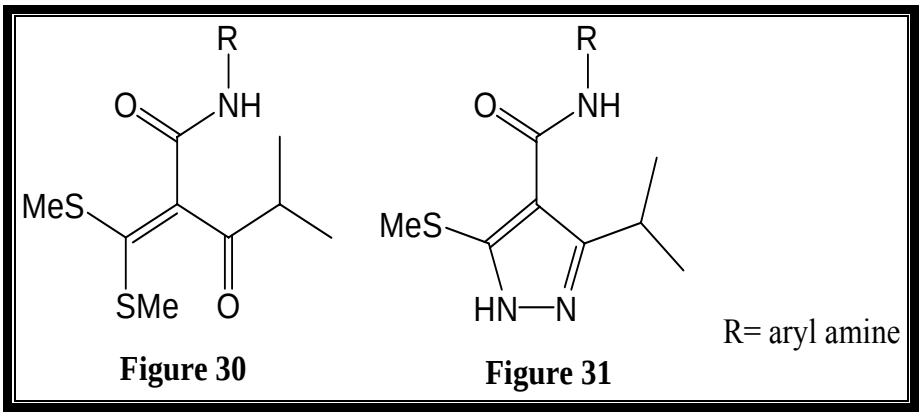


Figure 30 **Figure 31**

In an extension to this work, we now report a novel synthesis of functionalized 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives by the reaction of ketene dithioacetals with acetoacetanilide derivatives. Thus, it has been found that reaction of substituted acetoacetanilide derivatives with carbon disulfide in the presence of potassium carbonate followed by the alkylation with methyl iodide gives the novel ketene dithioacetals (**Figure 30**), the structures of which have been established on the basis of their elemental analysis and spectral data. Ketene dithioacetals with hydrazine in refluxing isopropyl alcohols gave the pyrazole derivatives (**Figure 31**).

3.7 Results and discussion

Various substituted 4-methyl-3-oxo-*N*-phenylpentanamide (**2a-s**) were prepared by reacting substituted amines and methyl-4-methyl-3-oxopentanoate in toluene with a

catalytic amount of NaOH or KOH (**Scheme 1**). The reaction mixture was reflux for 15-20 h. Fifteen different acetoacetanilide were synthesized bearing various electron donating and electron withdrawing groups like 2,3-diCH3; 3,4-diCH3; 4-CH3; H; 2,5-diCH3; 2,4-diCH3; 3-Cl-4-F; 4-F; 4-Cl; 2-Cl; 2-F; 4-OCH3; 2,5-diCl and 3-NO2 on the phenyl ring.

Thus, it has been found that reaction of substituted acetoacetanilide (**2a-s**) derivatives **(Scheme 1)** with carbon disulfide in the presence of potassium carbonate followed by the alkylation with methyl iodide gives the novel ketene dithioacetals **3a-s**, when **3a-s** was reacted with hydrazine hydrate in refluxing isopropyl alcohol, the corresponding 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives **4a-s** was obtained in 85 to 90% yield.

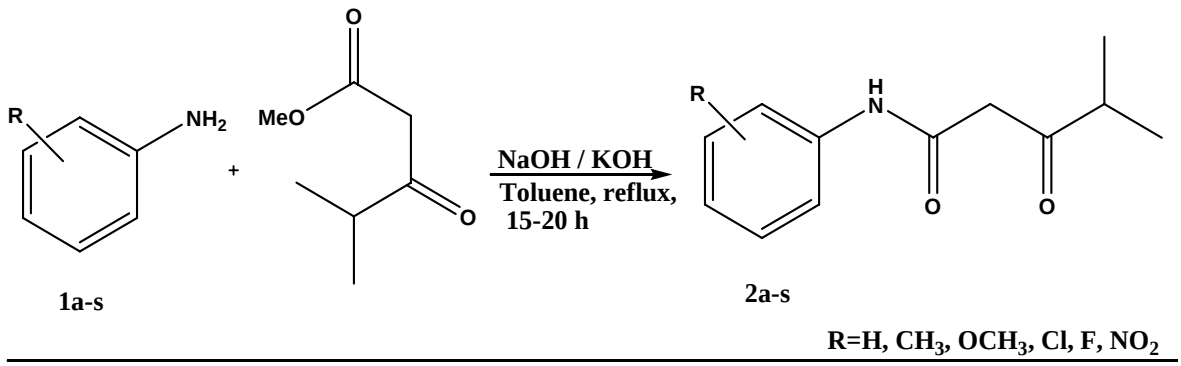
The structures of **4a-s** were established on the basis of their elemental analysis and spectral data (MS, IR, and ^{1}H NMR). The analytical data for **3a** revealed a molecular formula $C_{16}H_{21}NO_2S_2$ (*m/z* 323). The ^{1}H NMR spectrum revealed a two singlet at δ = 1.18-1.20 ppm assigned to isopropyl-CH_3, a singlet at δ = 1.57 ppm assigned to the –CH_3 protons, a singlet at δ = 2.44 ppm assigned to (2 × SCH_3), a multiplet at δ = 3.17-3.24 ppm assigned to the isopropyl-CH protons, a multiplet at δ = 6.99–7.54 ppm assigned to the aromatic protons, and one broad singlets at δ = 8.38 ppm assigned to -CONH groups. Reaction of compounds **3a-s** with hydrazine in refluxing isopropyl alcohol gave the corresponding 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives **4a-s.** The structures of **4q** were established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR, and ^{13}C NMR). Structure **4q** was supported by its mass (*m/z* 327), which agrees with its molecular formula $C_{14}H_{15}ClFN_3OS$; its ^{1}H NMR spectrum had signals at δ= 1.29-1.31ppm (2 × CH_3), δ= 2.53ppm (SCH_3), a multiplet at δ = 3.84-3.87 ppm assigned to the isopropyl-CH protons, a signal at δ = 7.12–7.98 ppm (m, 3H, Ar) related to the aromatic protons, 9.61 (br, s, -CONH) and 12.94 (br s, pyrazole NH).

3.8 Conclusion

In summary, we have achieved a novel synthesis of interesting 4-methyl-3-oxo-*N*-phenylpentanamide (acetoacetanilide, 2a-s), ketene *S,S*-acetals and their conversions to several 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives, compounds which have both chemical and biological potential.

3.9 Reaction scheme of 2-(bis (methylthio)methylene)-4-methyl-3-oxo-*N*-arylpentanamide (2a-s), dithioacetals(3a-s) and 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives (4a-s)

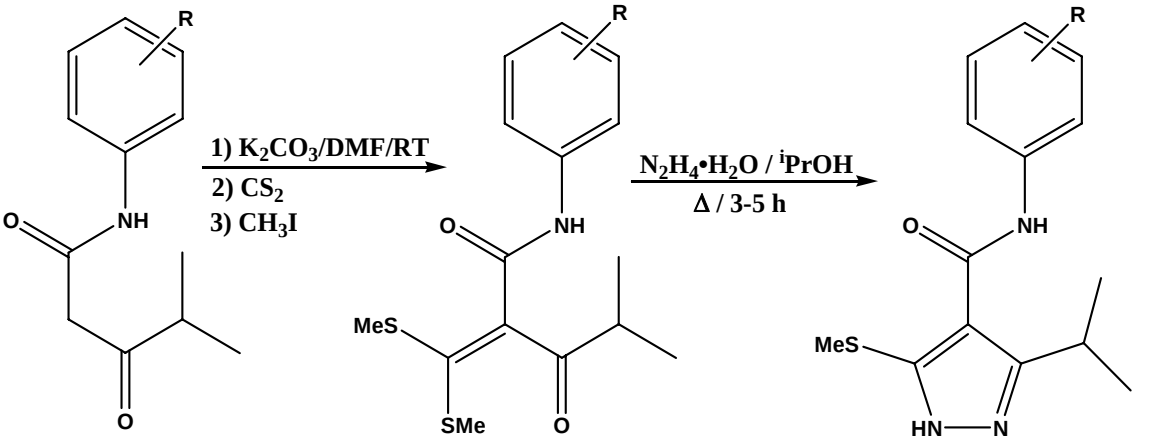
Scheme 1



1a-s **2a-s**

R=H, CH_3, OCH_3, Cl, F, NO_2

Scheme 2



2a-s **3a-s** **4a-s**

3.10 Experimental procedure

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator.

3.10.1 General synthesis of 4-methyl-3-oxo-*N*-phenylpentanamide (2a-s)

A mixture containing the primary amine (10 mmol), methyl isobutyrylacetate (10 mmol), and catalytic amount of sodium or potassium hydroxide lie (10 %) was reflux at 110 ^{o}C for the approximately 15-20 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under *vaccuo* when the reaction was completed. The solid or oil was crystallized from methanol to give pure product (**2a-s**).

3.10.2 General synthesis of ketene dithioacetals (3a-s)

A 100mL conical flask equipped with magnetic stirrer and septum was charged with a solution of 4-methyl-3-oxo-N-phenylpentanamide (**2a-o**, 10 mmol) in DMF (10 mL). Dried K_2CO_3 (10 mmol) was added and the mixture was stirred for 2 h at room temperature. CS_2 (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Methyl iodide (20 mmol) was then added and the mixture was stirred for 4 h before being poured onto water (40 mL). The precipitated crude product was purified by filtration followed by crystallization from EtOH. When the product was oil, the organic phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated in *vaccuo* to afford ketene dithioacetals directly used for the next step.

3.10.3 General synthesis of 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives (4a-s)

A 100mL round-bottom flask equipped with condenser and septum was charged with a solution of ketene dithioacetals (**3a-o**, 10.0 mmol) in isopropyl alcohol (30 mL), followed by the hydrazine hydrate (10.0 mmol) was added and the mixture was reflux for 4 h at 90 ^{o}C. The reaction was monitored by TLC, after complete the reaction mixture was then cooled down to room temperature, poured into crushed ice and stirred for 1 h before usual standard work-up. When the product was oil, the organic phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), concentrated in *vaccuo*, and purified on silica gel with ethyl acetate-hexane (9:1) as eluant. When precipitated, the product is filtered, washed with water, and purified by recrystallization from ethanol to give pure product (**4a-s**).

3.11 Spectral data of synthesized compounds (3a-s & 4a-s):

2-(bis(methylthio) methylene)-4-methyl-3-oxo-*N*-*p*-tolylpentanamide 3a. yellow solid, yield 90%, mp 155-158°C; Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33; Found: C, 59.33; H, 6.45; N, 4.23; m/z:323 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.18-1.20 (m, 6H, 2 × ^{i}prCH**$_3$**), 1.57 (s, 3H, CH_3), 2.44 (s, 6H, 2 × SCH_3), 3.17-3.24 (m, 1H, ^{i}prCH), 6.99–7.54 (m, 4H, Ar), 8.38 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

2-(bis(methylthio)methylene)-*N*-(4-methoxyphenyl)-4-methyl-3-oxopentanamide 3p. yellow solid, yield 92%, mp 169-171°C; Anal. Calcd for $C_{16}H_{21}NO_3S_2$: C, 56.61; H, 6.24; N, 4.13; Found: C, 56.53; H, 6.14; N, 4.06; m/z:339 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.18-1.20 (m, 6H, 2 × ^{i}prCH**$_3$**), 2.44 (s, 6H, 2 × SCH_3), 3.17-3.24 (m, 1H, ^{i}prCH), 3.75 (s, 3H, OCH_3), 6.99–7.54 (m, 4H, Ar), 8.38 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3439, 3007, 2928, 2808, 1599, 1462, 1327, 1255.

3-isopropyl-5-(methylthio)-*N*-*p*-tolyl-*1H*-pyrazole-4-carboxamide 4a. yellow solid, yield 80%, mp 195–198°C; Anal. Calcd for $C_{15}H_{19}N_3OS$: C, 62.25; H, 6.62; N, 14.52; Found: C, 62.10; H, 6.53; N, 14.43; m/z:289 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.29-1.31(d, *J* = 6.88 Hz, 6H, 2 × ^{i}prCH$_3$) 2.32 (s, 3H, PhCH$_3$), 2.45 (s, 3H, SCH_3), 3.89-3.96 (m, 1H, ^{i}prCH), 7.17–7.55 (m, 4H, Ar), 9.24 (br, s, 1H, -CONH) and 12.85 (br, s, 1H, pyrazole NH); IR (KBr), ν(cm^{-1}): 3298, 3167, 2980, 2881, 2825, 1697, 1641, 1408, 1307, 1213.

***N*-(4-fluorophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4b.** white solid, yield 88%, mp 185–188°C; Anal. Calcd for $C_{14}H_{16}FN_3OS$: C, 57.32; H, 5.50; N, 14.32; Found: C, 57.25; H, 5.43; N, 14.22; m/z:293 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3019, 2859, 2882, 1698, 1630, 1481, 1343, 1298.

3-isopropyl-*N*-(2,3-dimethylphenyl)-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4c. off white solid, yield 85%, mp 201–202°C; Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85; Found: C, 63.22; H, 6.88; N, 13.73; m/z:303 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3074, 2894, 2829, 1694, 1638, 1482, 1343, 1298.

3-isopropyl-*N*-(2,4-dimethylphenyl)-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4d. white solid, yield 83%, mp 211–212°C; Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85; Found: C, 63.22; H, 6.88; N, 13.73; m/z:303 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3072, 2895, 2828, 1690, 1635, 1482, 1343, 1298.

3-isopropyl-*N*-(2,5-dimethylphenyl)-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4e. white solid, yield 84%, mp 218–220°C; Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85; Found: C, 63.22; H, 6.88; N, 13.73; m/z:303 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.33 (d, J = 7.08 Hz, 6H, 2 × ^{i}prCH$_3$), 2.16-2.32 (s, 6H, ArCH$_3$), 2.53 (s, 3H, SCH$_3$), 3.84-3.87 (m, 1H, ^{i}prCH), 6.84–7.86 (m, 3H, Ar), 9.61 (br, s, -CONH) and 12.94 (br, s, pyrazole NH); IR (KBr), ν(cm-1): 3292, 3167, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(2-chlorophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4f.** white solid, yield 80%, mp 175–178°C; Anal. Calcd for $C_{14}H_{16}ClN_3OS$: C, 54.27; H, 5.21; N, 13.56; Found: C, 54.15; H, 5.12; N, 13.46; m/z:309 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(3-chlorophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4g.** white solid, yield 82%, mp 185–188°C; Anal. Calcd for $C_{14}H_{16}ClN_3OS$: C, 54.27; H, 5.21; N, 13.56; Found: C, 54.15; H, 5.12; N, 13.46; m/z:309 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3071, 2894, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(4-chlorophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4h.** white solid, yield 85%, mp 198–200°C; Anal. Calcd for $C_{14}H_{16}ClN_3OS$: C, 54.27; H, 5.21; N, 13.56; Found: C, 54.15; H, 5.12; N, 13.46; m/z:309 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.21-1.22 (d, J = 6.92 Hz, 6H, 2 × ^{i}prCH$_3$), 2.43 (s, 3H, SCH$_3$), 4.05-4.31 (m, 1H, ^{i}prCH), 7.23–7.67 (m, 4H, Ar), 9.78 (br, s, 1H, -CONH) and 12.99 (br, s, 1H, pyrazole NH); IR (KBr), ν(cm^{-1}): 3292, 3167, 3078, 2896, 2829, 1694, 1637, 1482, 1343, 1298.

***N*-(2,6-dichlorophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4i.** white solid, yield 74%, mp 245–248°C; Anal. Calcd for $C_{14}H_{15}Cl_2N_3OS$: C, 48.84; H,

4.39; N, 12.21; Found: C, 48.78; H, 4.31; N, 12.11; m/z:344 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3071, 2895, 2828, 1694, 1635, 1481, 1343, 1298.

***N*-(2-bromophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4j.** Off-white solid, yield 85%, mp 222-223°C; Anal. Calcd for $C_{14}H_{16}BrN_3OS$: C, 47.46; H, 4.55; N, 11.56; Found: C, 47.35; H, 4.46; N, 11.76; m/z:353 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3077, 2895, 2824, 1694, 1635, 1482, 1343, 1298.

***N*-(3-bromophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4k.** Off-white solid, yield 87%, mp 232-233°C; Anal. Calcd for $C_{14}H_{16}BrN_3OS$: C, 47.46; H, 4.55; N, 11.56; Found: C, 47.35; H, 4.46; N, 11.76; m/z:353 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3073, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(4-bromophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4l.** Off-white solid, yield 85%, mp 240-241°C; Anal. Calcd for $C_{14}H_{16}BrN_3OS$: C, 47.46; H, 4.55; N, 11.56; Found: C, 47.35; H, 4.46; N, 11.76; m/z:353 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3071, 2894, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(2-nitrophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4m.** Off-white solid, yield 71%, mp 217-219°C; Anal. Calcd for $C_{14}H_{16}N_4O_3S$: C, 52.49; H, 5.03; N, 17.49; Found: C, 52.36; H, 4.96; N, 17.38; m/z:320 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3072, 2899, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(3-nitrophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4n.** Off-white solid, yield 75%, mp 227-230°C; Anal. Calcd for $C_{14}H_{16}N_4O_3S$: C, 52.49; H, 5.03; N, 17.49; Found: C, 52.36; H, 4.96; N, 17.38; m/z:320 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3071, 2895, 2827, 1693, 1635, 1482, 1343, 1298.

***N*-(4-nitrophenyl)-3-isopropyl-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4o.** Off-white solid, yield 78%, mp 237-239°C; Anal. Calcd for $C_{14}H_{16}N_4O_3S$: C, 52.49; H, 5.03; N, 17.49; Found: C, 52.36; H, 4.96; N, 17.38; m/z:320 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3071, 2894, 2828, 1694, 1635, 1482, 1343, 1298.

3-isopropyl-*N*-(4-methoxyphenyl)-5-(methylthio)-*1H*-pyrazole-4-carboxamide 4p. white solid, yield 80%, mp 217-220°C; Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; Found: C, 58.86; H, 6.17; N, 13.68; m/z:305 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.23-1.25 (d, *J* = 8 Hz, 6H, 2 × ^{i}prCH$_3$), 2.47 (s, 3H, SCH_3), 3.77 (s, 3H, OCH_3), 4.10-4.35 (m, 1H, ^{i}prCH), 7.30–7.68 (m, 4H, Ar), 9.85 (br, s, 1H, -CONH) and 13.10 (br, s, 1H, pyrazole NH); IR (KBr), ν(cm^{-1}): 3292, 3167, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

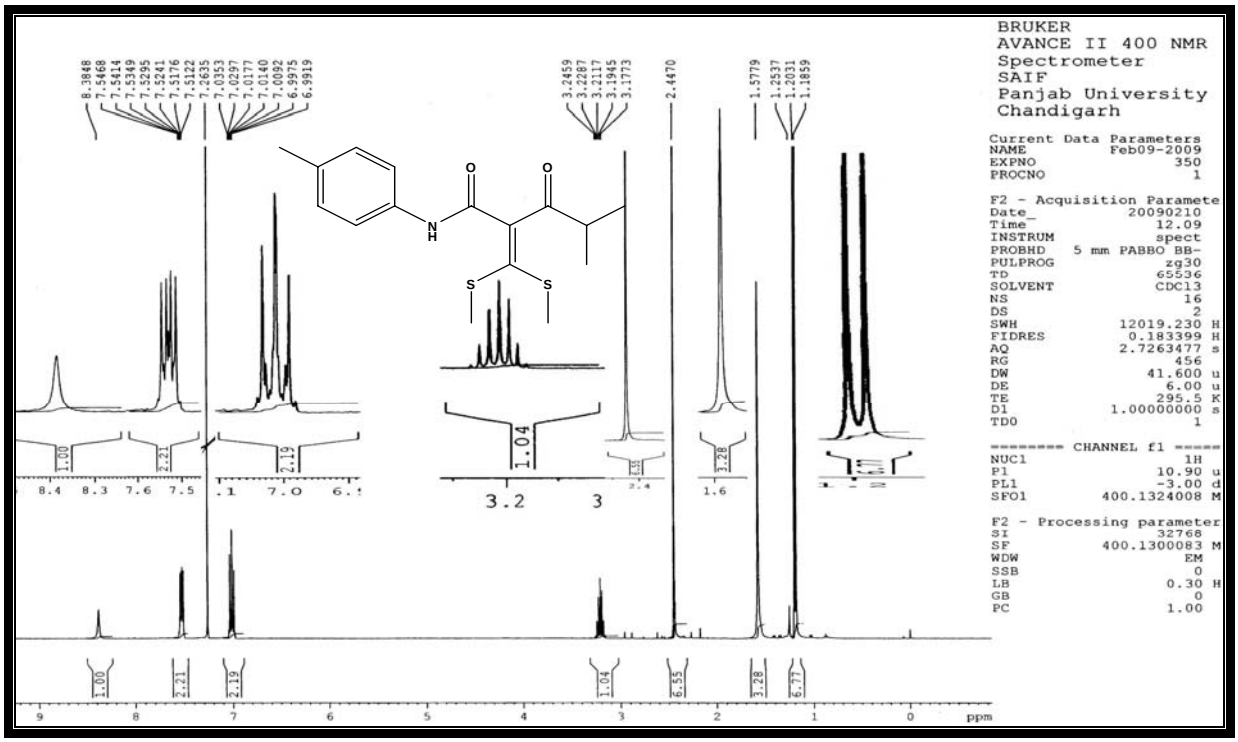
***N*-(3-chloro-4-fluorophenyl)-3-isopropyl-5(methylthio)-*1H*-pyrazole-4-carboxamide 4q.** white solid, yield 82%, mp 207-209°C; Anal. Calcd for $C_{14}H_{15}ClFN_3OS$: C, 51.30; H, 4.61; N, 12.82; Found: C, 51.16; H, 4.51; N, 12.71; m/z:327 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.29-1.31 (d, 6H, 2 × ^{i}prCH**3**), 2.53 (s, 3H, SCH_3), 3.84-3.87 (m, 1H, ^{i}prCH), 7.12–7.98 (m, 3H, Ar), 9.61 (br, s, -CONH) and 12.94 (br s, pyrazole NH); IR (KBr), ν(cm^{-1}): 3292, 3167, 3065, 2894, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(3,4-difluorophenyl)-3-isopropyl-5(methylthio)-*1H*-pyrazole-4-carboxamide 4r.** Off-white solid, yield 81%, mp 205-207°C; Anal. Calcd for $C_{14}H_{15}F_2N_3OS$: C, 54.01; H, 4.86; N, 13.50; Found: C, 53.91; H, 4.73; N, 13.43; m/z:311 [M^+]; IR (KBr), ν(cm^{-1}): 3292, 3167, 3072, 2895, 2828, 1694, 1635, 1481, 1343, 1298.

***N*-(4-ethylphenyl)-3-isopropyl-5(methylthio)-*1H*-pyrazole-4-carboxamide 4s.** White solid, yield 90%, mp 135-137°C; Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85; Found: C, 63.23; H, 6.87; N, 13.73; m/z:303 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.18 (t, 3H, $PhCH_2CH_3$), 1.34-1.36 (d, *J* = 7.08 Hz, 6H, 2 × ^{i}prCH$_3$), 2.56 (s, 3H, SCH_3), 3.89-3.96 (m, 1H, ^{i}prCH), 7.17–7.55 (m, 4H, Ar), 9.22 (br, s, 1H, -CONH) and 10.85 (s, 1H, pyrazole NH); IR (KBr), ν(cm^{-1}): 3292, 3167, 2964, 1633, 1591, 1518, 1411, 1311, 1259; ^{13}C NMR (400 MHz, $CDCl_3$): 15.69, 18.08, 21.43, 25.83, 28.33, 112.60, 120.17, 128.32, 135.76, 140.25, 155.80, 160.93.

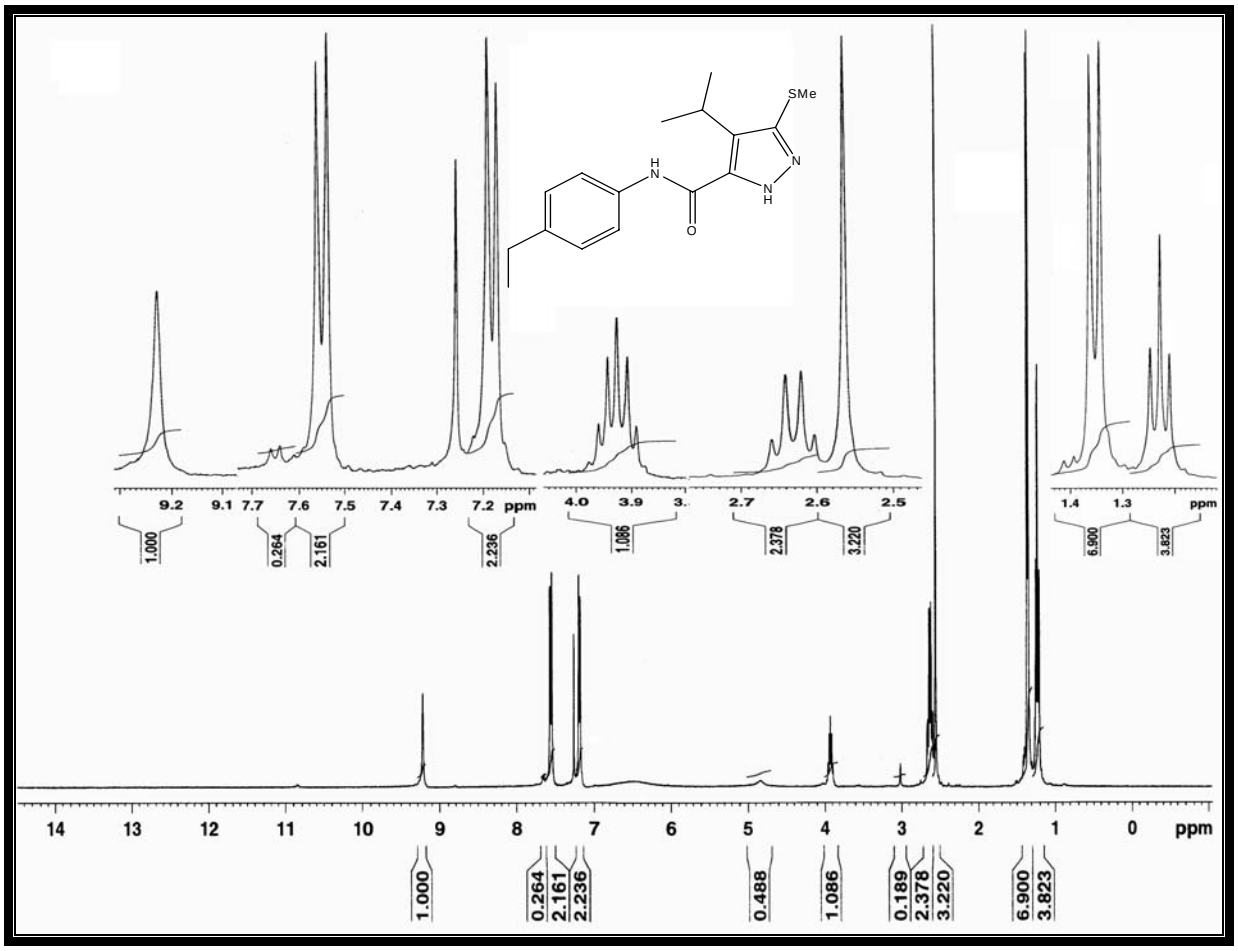
3.12 Spectral representation of synthesized compounds

3.12.1 ^{1}H NMR spectrums compound of 3a

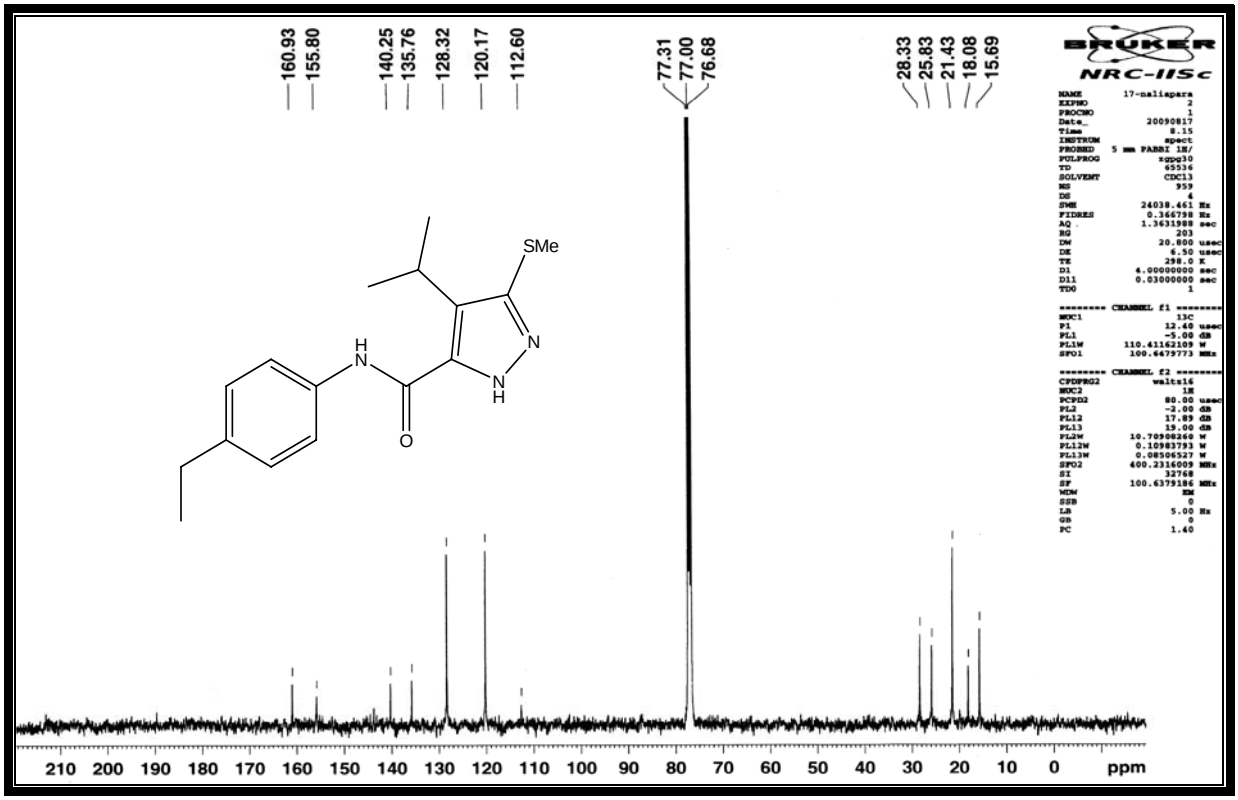


3.12. 2 ^{1}H NMR spectrums compound of 3p

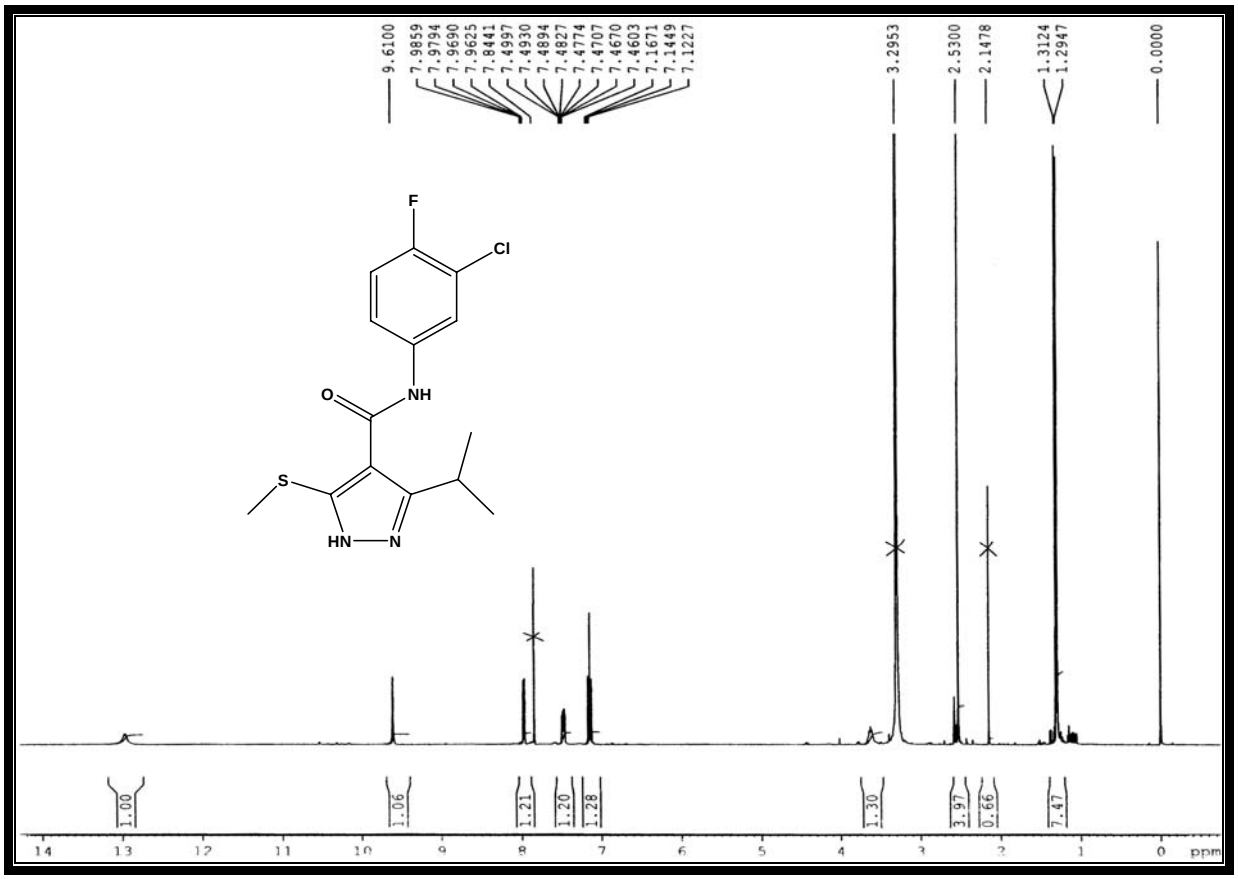
3.12. 3 ^{1}H NMR spectrums compound of 4s



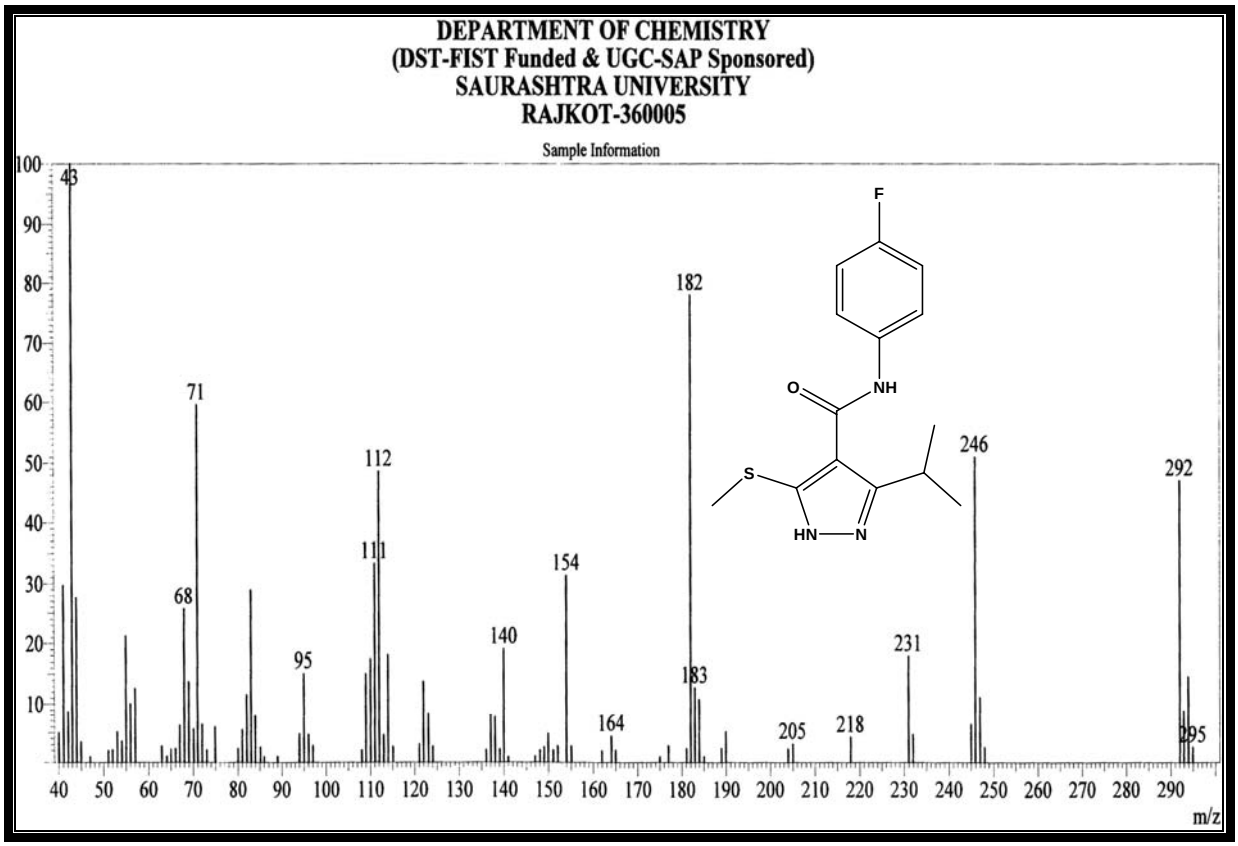
3.12. 4 ^{13}C NMR spectrums compound of 4s



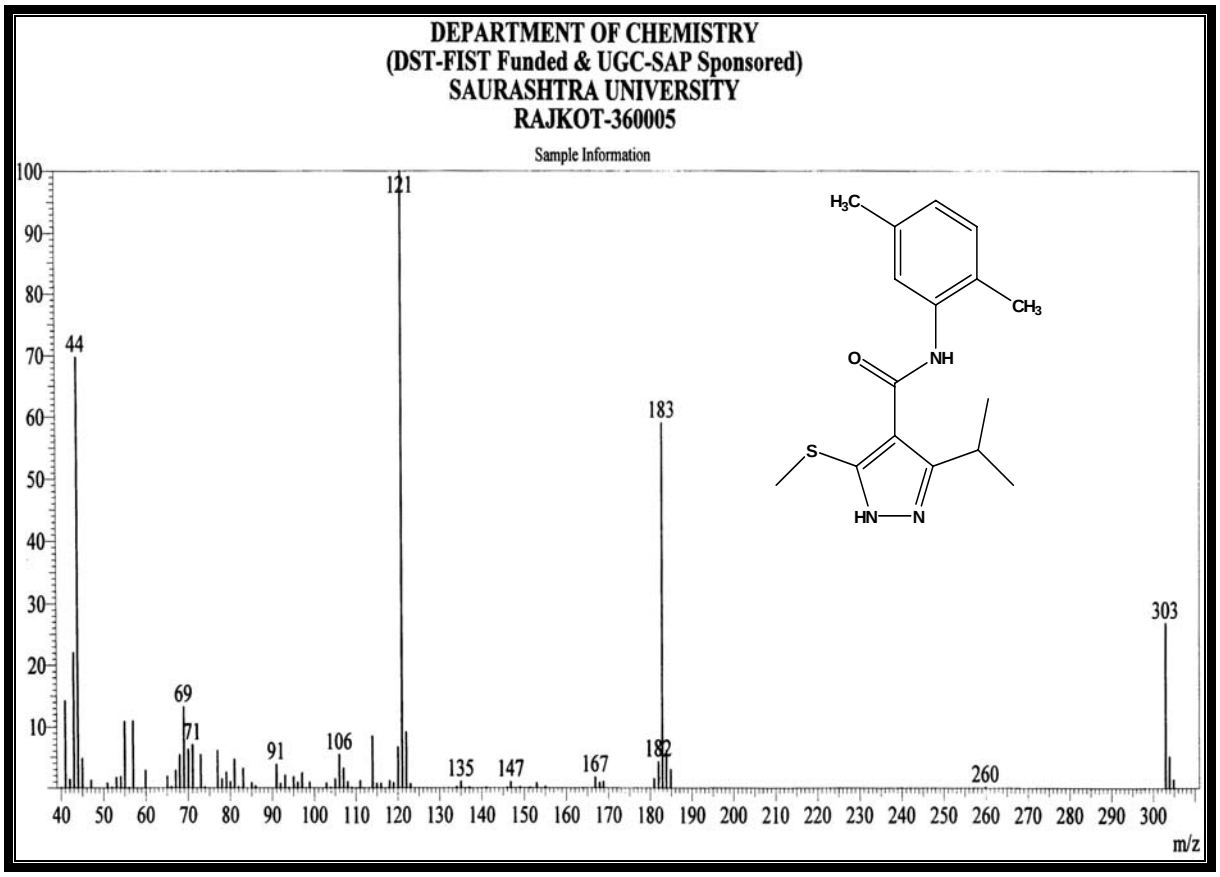
3.12. 5 ^{1}H NMR spectrums compound of 4q



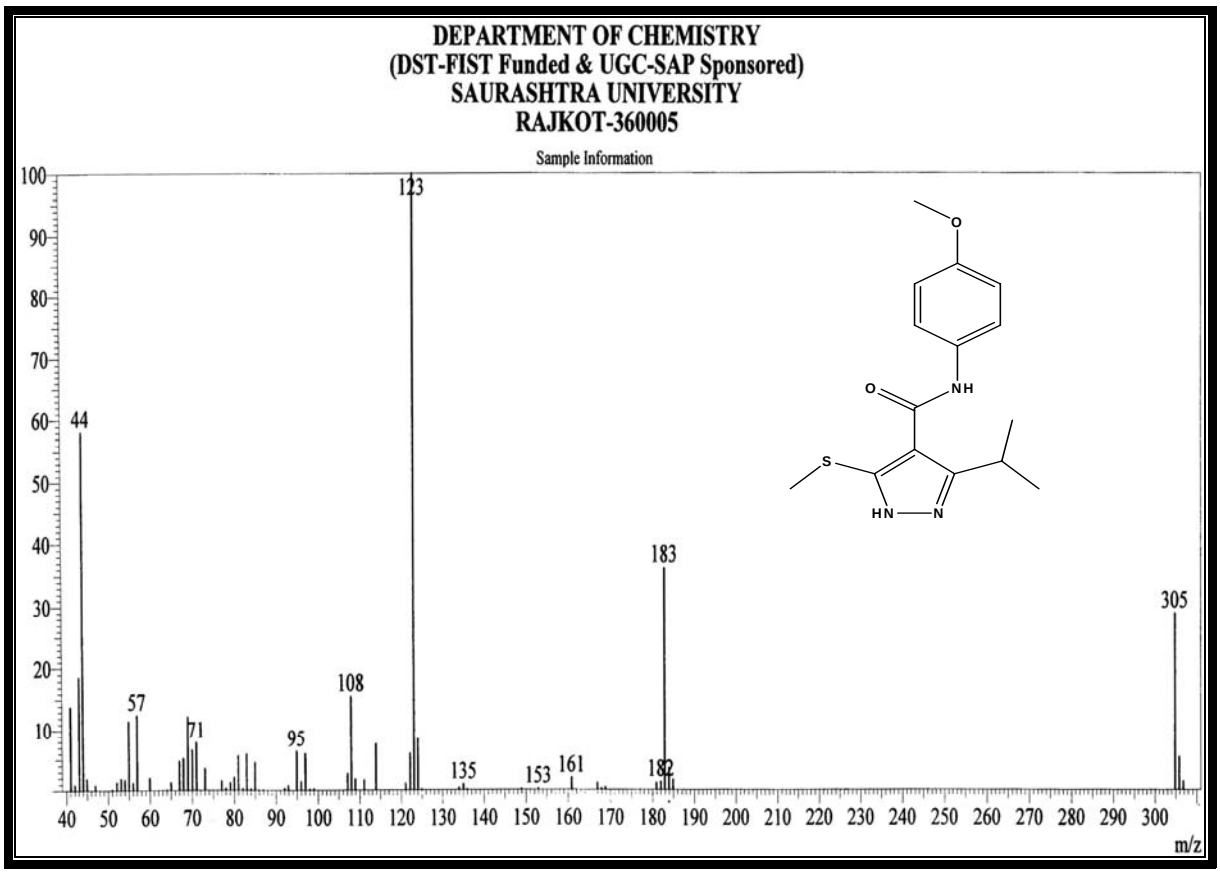
3.12. 6 Mass spectrum of compound 4b



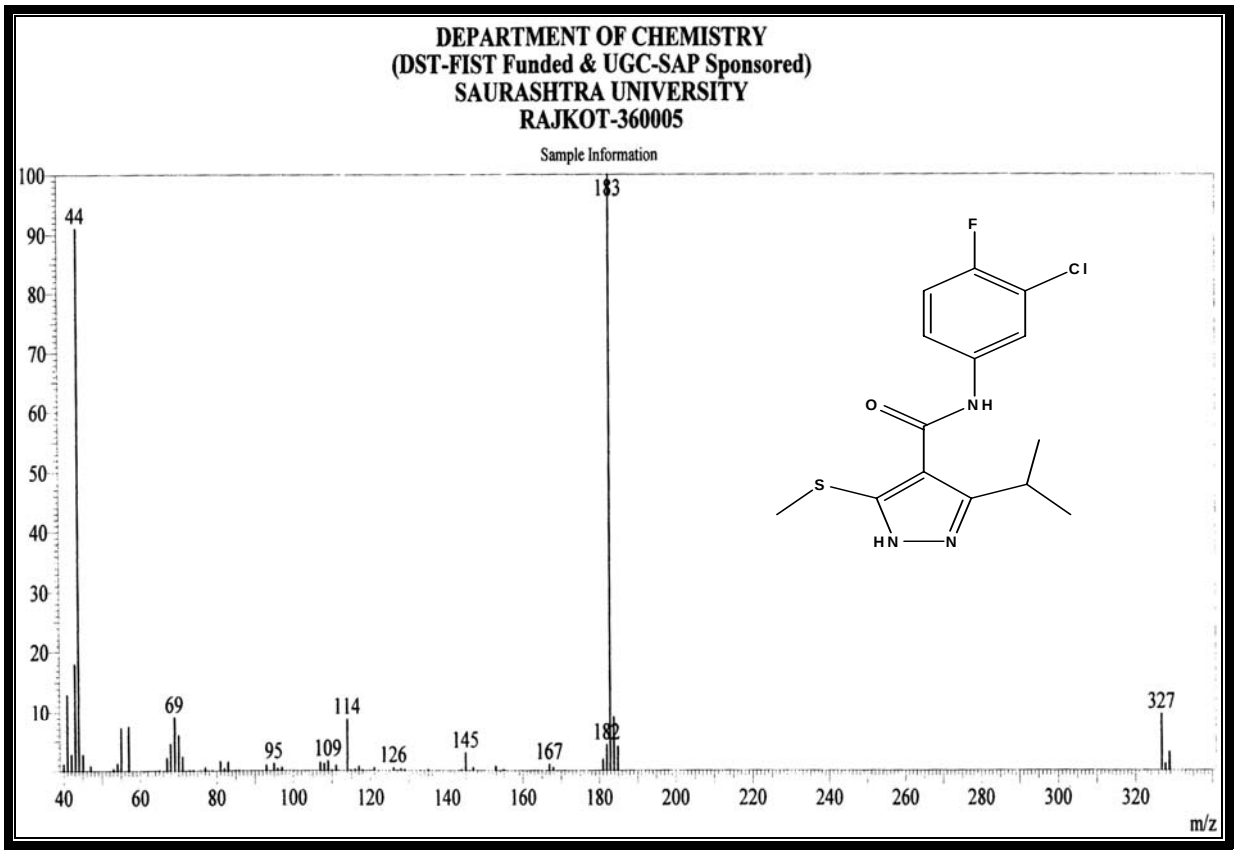
3.12. 7 Mass spectrum of compound 4e



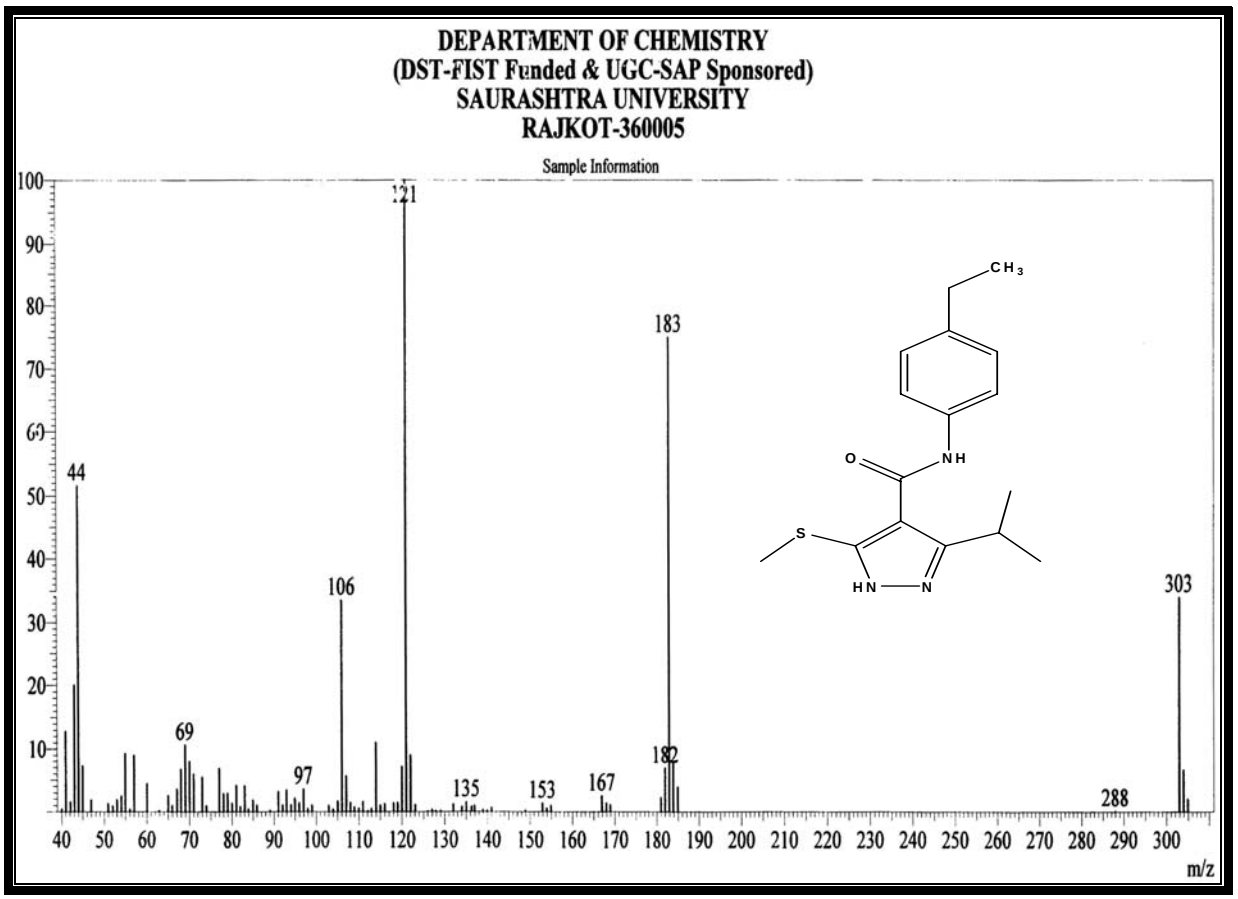
3.12. 8 Mass spectrum of compound 4p



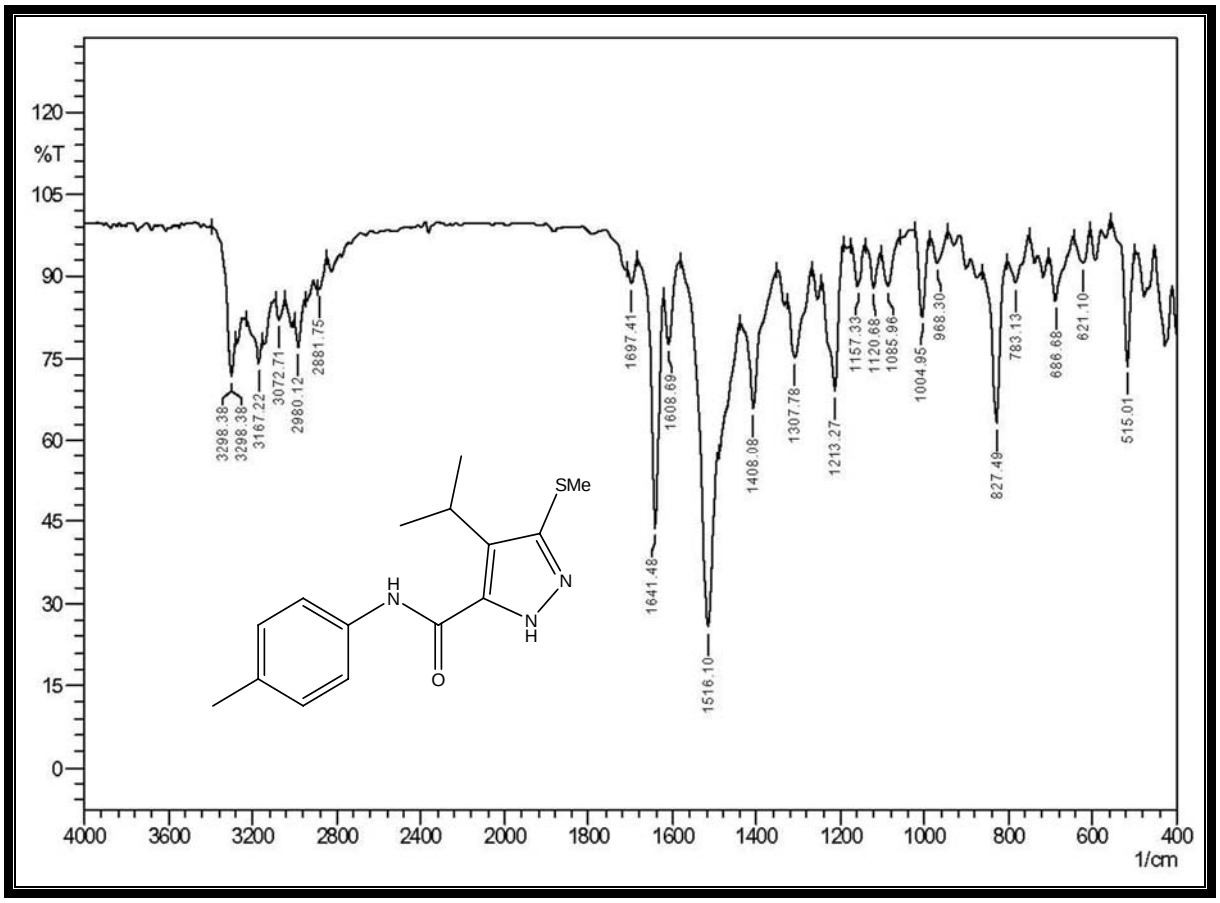
3.12. 9 Mass spectrum of compound 4q



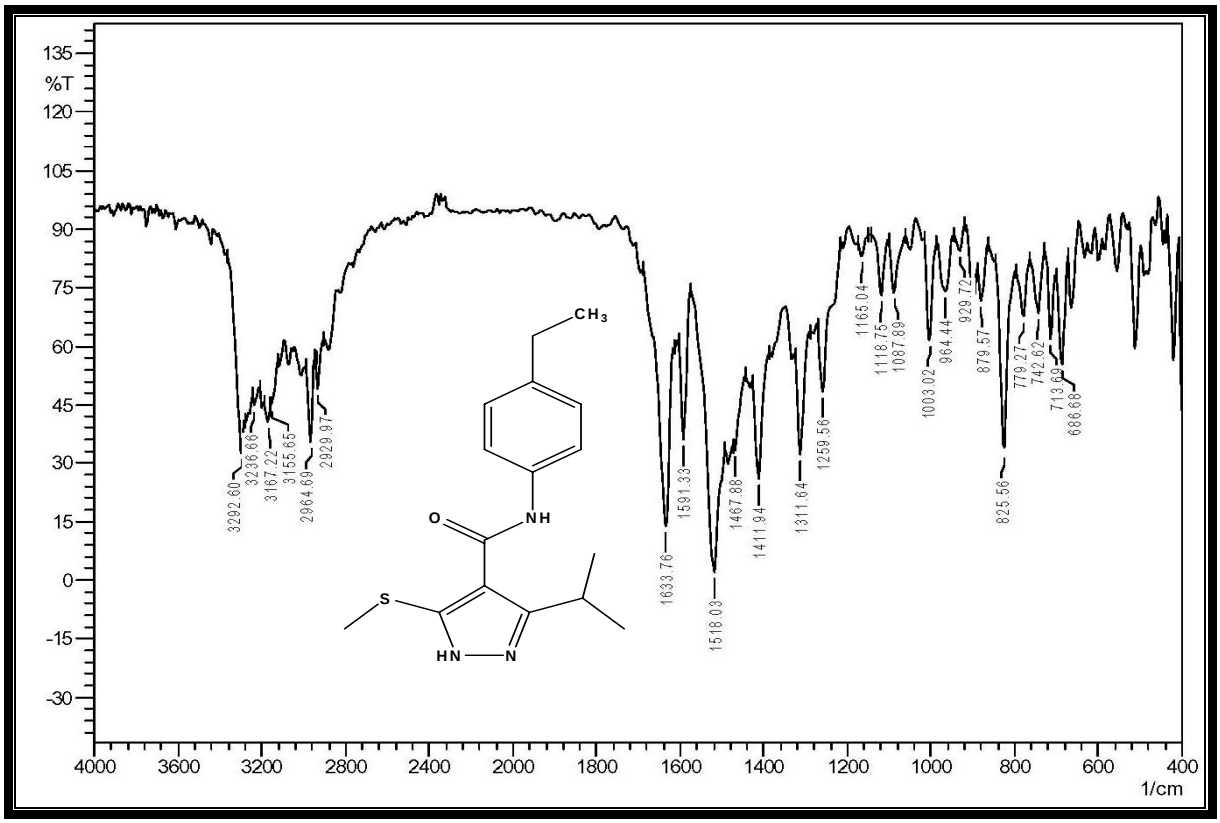
3.12. 10 Mass spectrum of compound 4s



3.12. 11 IR spectrum of coumpound 4a



3.12. 12 IR spectrum of coumpound 4s



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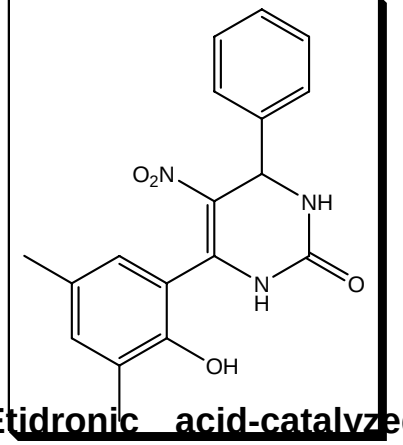
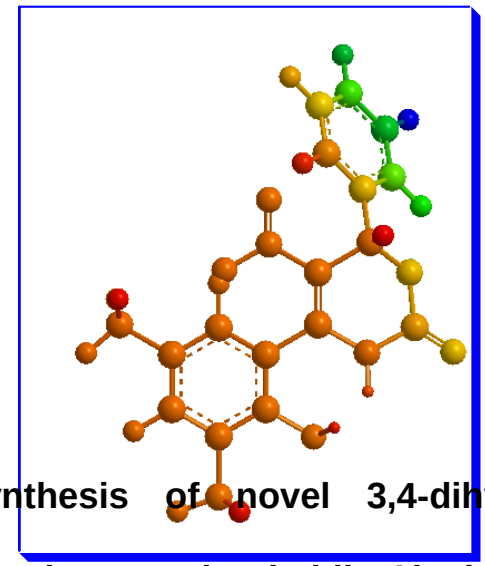
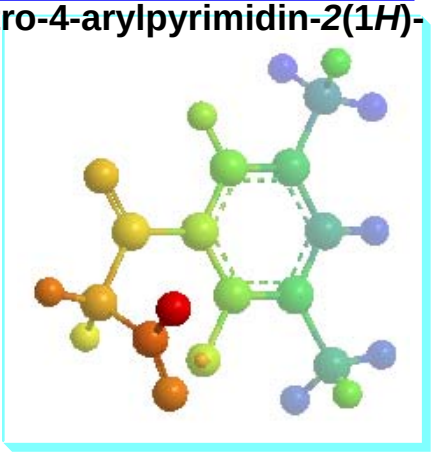
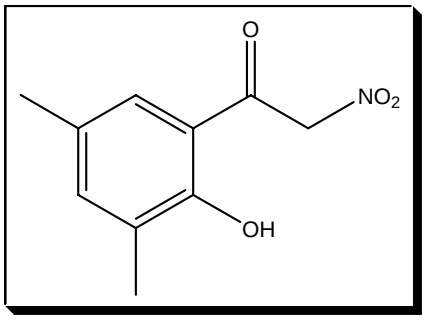
Chapter 4

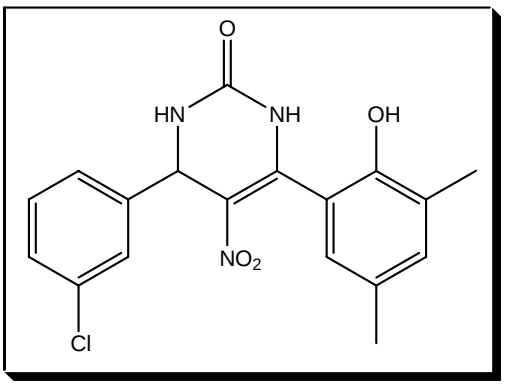


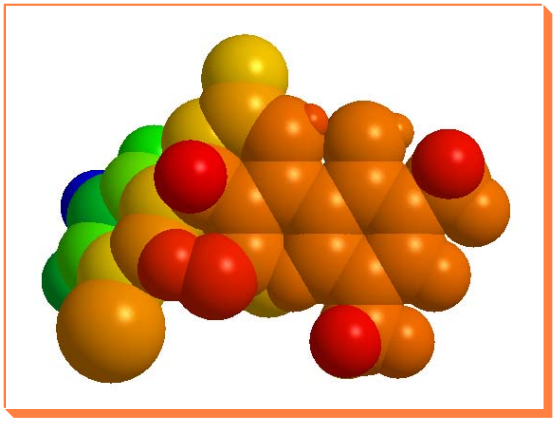


Etidronic acid-catalyzed synthesis of novel 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-*2*(1*H*)-one derivatives









4.1 Introduction

The pyrimidine fragment is present of a series of biologically active compounds, many of which have found use in medical practice (soporific, anti-inflammatory, antitumor, and other products).[1,2] In this connection, great attention has recently been paid to derivatives of pyrimidine, including their hydrogenation products. The first investigations into the synthesis of such compounds appeared more than a hundred years ago (e.g., the Biginelli reaction),[3] and for a long time they remained unused. Only in the last decade have methods been developed specifically for the production of hydrogenated pyrimidine systems and their physicochemical properties been studied. This is explained by the high reactivity and by the wide range of biological activity in these derivatives. Thus, for example, 2-substituted 5-alkoxycarbonyl-4-aryl-l,4-dihydropyrimidines, which are structural analogs of hantsch esters, are modulators of the transport of calcium through membranes.[4-7] Recently, non-nucleoside inhibitors of reverse transcriptase, which have high activity against HIV-1, have been found among hydrogenated quinazolines.[8-10] Many hydrogenated pyrimidines exhibit antimicrobial,[11] hypoglemic,[12] herbicidal,[13] and pesticidal[14] activity. Publications devoted to these problems have been summarized in a number of reviews.[12-17]

Of great interest among the investigated compounds are the nitro-substituted dihydropyrimidines. They readily undergo various chemical transformations, among which the unique ability to undergo recyclization to heterocyclic and carbocyclic compounds should be noted in particular. The interest in the nitrodihydropyrimidines is also due to the fact that these compounds represent the active principle or act as metabolites responsible for the physiological action of nitropyrimidines. Recently, products having antimicrobial[18] and antiviral[19-21] activity and also products suitable for the treatment of cardiovascular diseases[22-25] have been found among them.

5-Nitrodihydropyrimidines can be described by five structures, having one (1,4-, 1,6-, and 1,2-) or two (2,5- and 4,5-dihydropyrimidine systems) geminal centers, the carbon atoms of which are characterized by sp^3 hybridization (**Figure 1**).

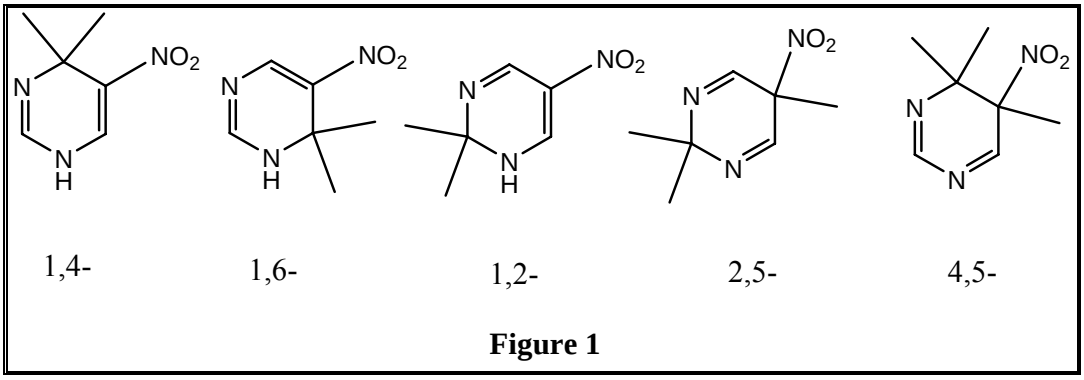


Figure 1

The 5-nitro-l,2-, 5-nitro-l,4-, and 5-nitro-l,6-dihydropyrimidines are cyclic enamines, in which the electron pair of the sp^3-hybridized nitrogen atom is in conjugation with the four π electrons of the C = C and C = N double bonds. On account of the mobility of the hydrogen atom of the *NH* group, the 5-nitro-1,4- and 5-nitro-1,6-dihydropyrimidines can be in tautomeric equilibrium. At the same time the 5-nitro-2,5- and 5-nitro-4,5-dihydropyrimidines are cyclic imines, in which there is no conjugation.[26]

4.2 Methods for the preparation of nitrodihydropyrimidines

The methods for the production of dihydropyrimidines described in the literature can be divided into two main groups such as: synthesis from acyclic compounds and transformations based on pyrimidine derivatives (**Figure 2**). Analysis of the published data makes it possible to conclude that the first methods have advantages over the other. However, the second methods are used more widely if an electron withdrawing group, and particularly a nitro group, is introduced into the pyrimidine molecule. (One of the acyclic compounds contains a nitro group.)

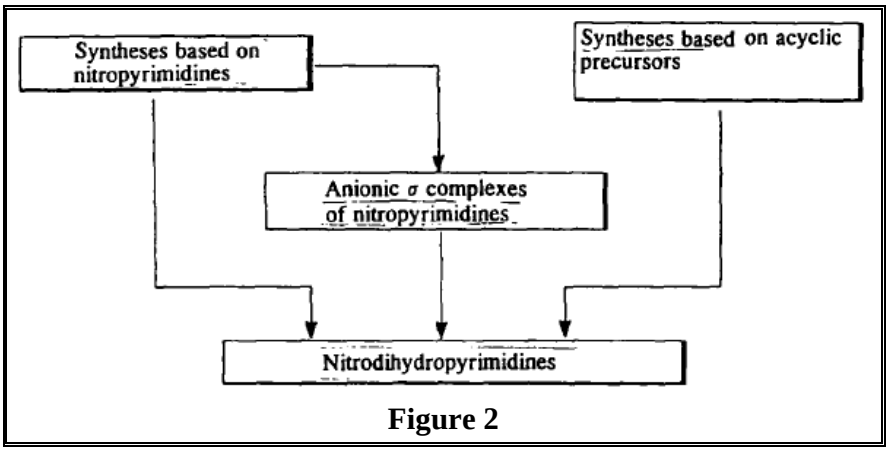


Figure 2

4.2.1 Synthesis from acyclic compounds

Only derivatives of 5-nitro-l,4-dihydropyrimidine have been obtained from acyclic compounds (**Figure 3**). Three-component (**A**) and two-component (**B**, **C**) versions of cyclocondensation, based on the Biginelli reaction,[17, 27-29] and also intramolecular cyclization of the already prepared six-membered chain (version **D**) have been used for this. Nitro ketones (versions **A**, **C**) and 1-arylidene-l-nitropropan-2-ones (version **B**) are used as nitro components in these reactions and derivatives of urea, arninopyrazole, and amidines are used as N-C-N fragments.

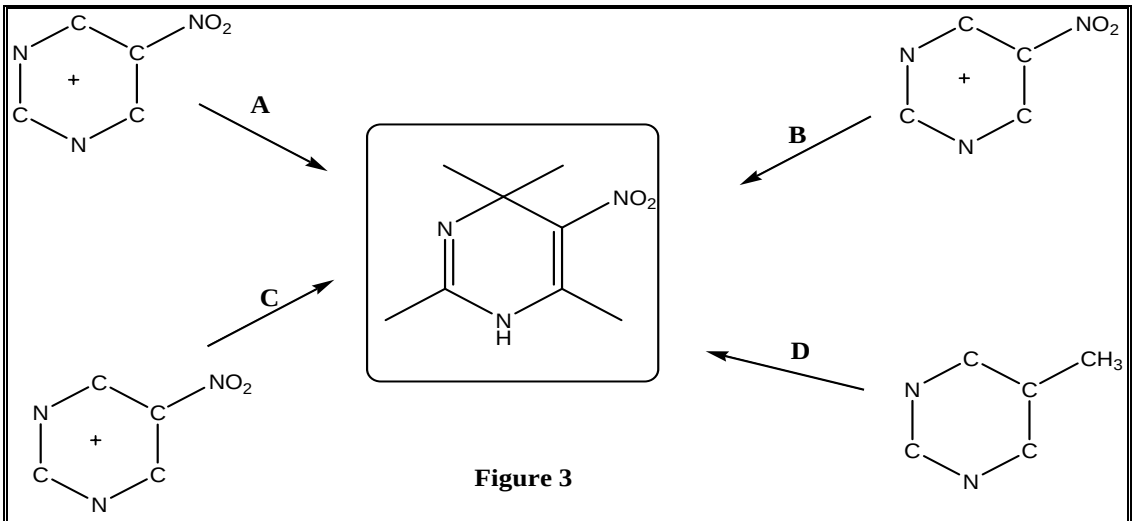


Figure 3

Methods for the synthesis of 5-nitro-l,4-dihydropyrimidines from acyclic compounds

The proposed methods of cyclocondensation are interrelated. As a rule, realization of the reactions by one of the methods leads not to the final product but to an intermediate compound, which is in turn the starting compound for another method of cyclization.

The formation of 5-nitro-4,6-diphenyl-l,4-dihydropyrimidin-2(1*H*)-one (**Figure 4**) from benzylidenebisurea and α-nitroacetophenone was first described in 1972.[30] According to the mechanism of the Biginelli reaction,[28] at the first stage the urea fragment is clearly substituted by the nitroketone residue, and this is followed by cyclization of the six-membered intermediate in the acidic medium.

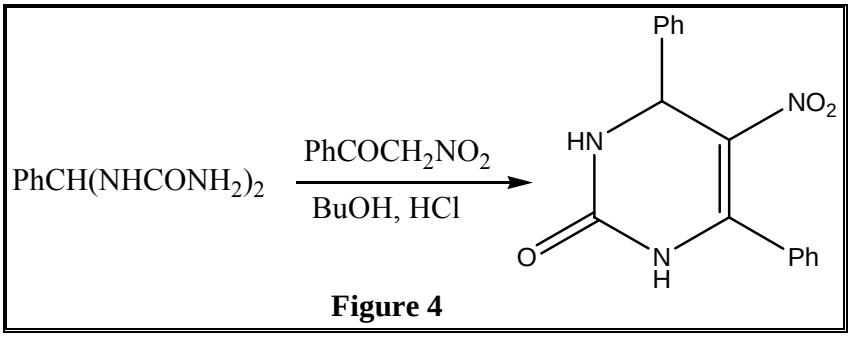


Figure 4

In the reaction of aromatic aldehydes with nitro acetone and a two-fold excess of urea or *N*-methyl urea in boiling ethanol in the presence of HCI 4-aryl-6-methyl- or 4-aryl-l,6-dimethyl-5-nitro-l,4-dihydropyrimidin-2(1*H*)-ones (**Figure 5**).[25, 31] The latter are also formed as a result of the two-component cyclization of the respective 1-arylidene-l-nitropropan-2-ones with urea or *N*-methyl urea.

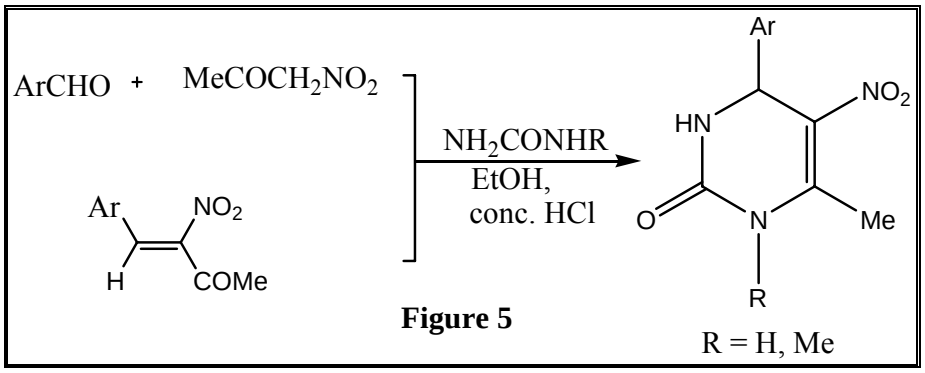


Figure 5

By analysis of the spectral characteristics it is possible to assign compounds (**Figure 5**) the 1,2,3,4-tetrahydropyrimidine structure. It should be noted that almost any aromatic aldehydes enter into the described transformations. This is important during comparison of the pharmacological activity of compounds of this series with the corresponding derivatives of 4-aryl-l,4-dihydropyridines.

4.2.2 Synthesis based on nitropyrimidines

Owing to their reactivity, nitropyrimidines, which contain accepting nitro groups and "pyrimidines" nitrogen atoms, have been found to be a useful synthon for the production of various derivatives of pyrimidine and also various other types of organic compounds whose synthesis by other methods is difficult or practically impossible.[32-34]

4.2.3 Alternative synthetic routes for better yield, shorter reaction time to synthesize new analogs

Various modifications have been applied to Biginelli reaction to get better yield and to synthesize biologically active analogs. Different catalysts have been reported to increase the yield of the reaction. Microwave synthesis strategies have also been applied to shorten the reaction time. Solid phase synthesis and combinatorial chemistry has made possible to generate library of DHPM analogs. The various modifications are discussed in the following section.

Catalysts

Min Yang and coworkers[35] have synthesized the different DHPMs by using different inorganic salts as a catalyst (**Figure 6**). They found that the yields of the one-pot Biginelli reaction can be increased from 20-50 % to 81-99 %, while the reaction time shorted for 18-24 hr to 20-30 min. This report a new and simple modification of the Biginelli type reaction by using $Yb(OTf)_3$ and $YbCl_3$ as a catalyst under solvent free conditions. One additional important feature of this protocol is the catalyst can be easily recovered and reused.

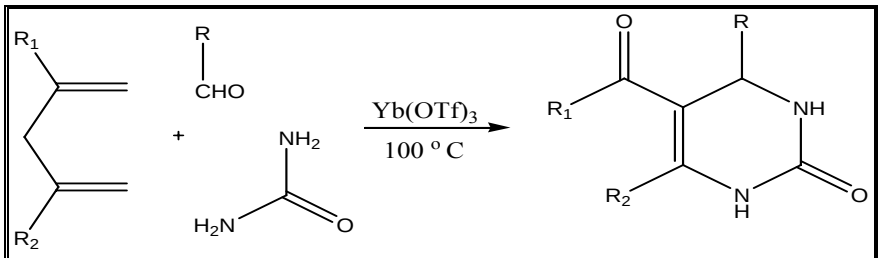


Figure 6

Indium(III)chloride was emerged as a powerful Lewis catalyst imparting high region and chemo selectivity in various chemical transformations. B. C. Ranu and co-workers[36] reported indium(III) chloride ($InCl_3$) as an efficient catalyst for synthesis of 3,4-dihydropyrimidn-2(1*H*)-ones (**Figure 7**). A variety of substituted aromatic, aliphatic and heterocyclic aldehydes have been subjected to this condensation very efficiently. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1*H*)-thiones.

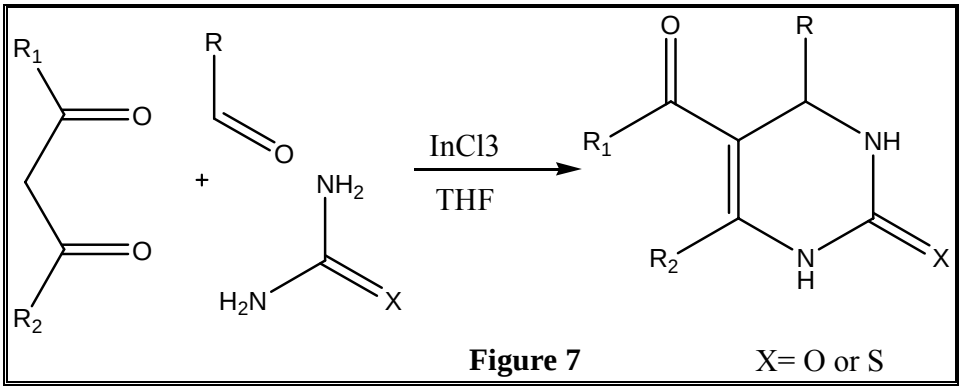


Figure 7

Majid M. Heravi et al. have reported a simple, efficient and cost-effective method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones by one pot three-component cyclocondensation reaction of a 1,3-dicarbonyl compound, an aldehyde and urea or thiourea using 12-tungstophosphoric acid[37] and 12-molybdophosphoric acid[38] as a recyclable catalyst (**Figure 8**).

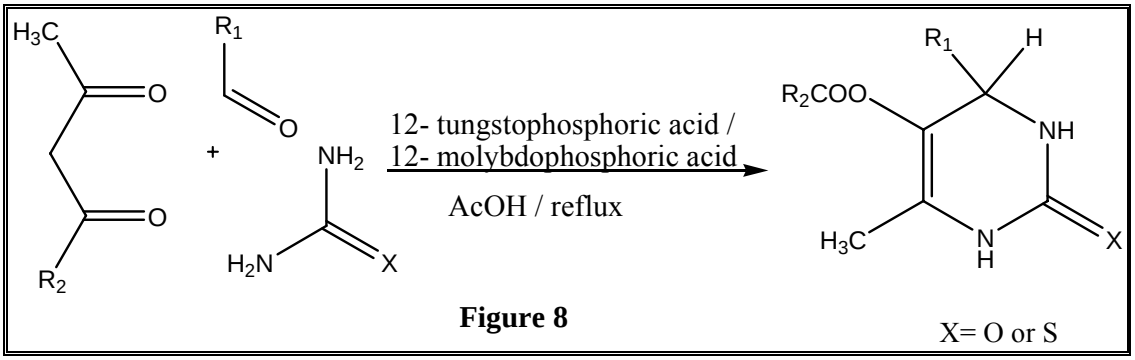


Figure 8

A novel covalently anchored sulfonic acid onto the surface of silica was prepared and investigated for the Biginelli reaction by Satya Paul and co-workers (**Figure 9**).[39] The catalyst is highly stable, completely heterogeneous and recyclable for several times. The workup procedure is very simple and Biginelli compounds were obtained in good to excellent yields (**Figure 10**).

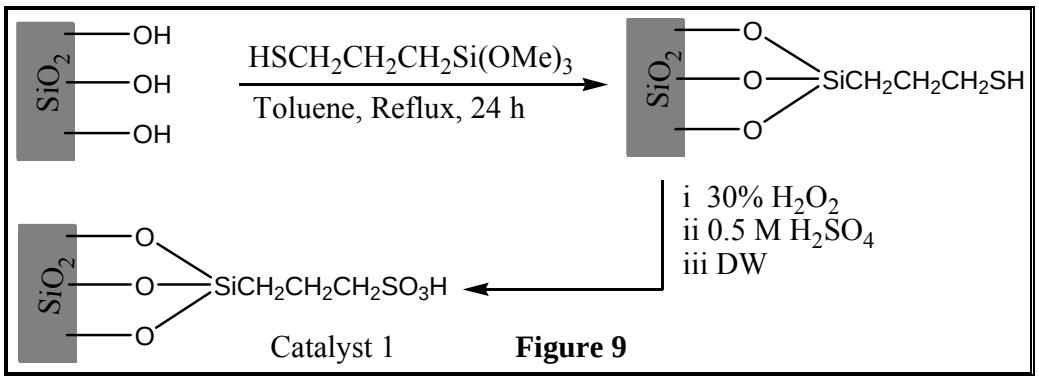


Figure 9

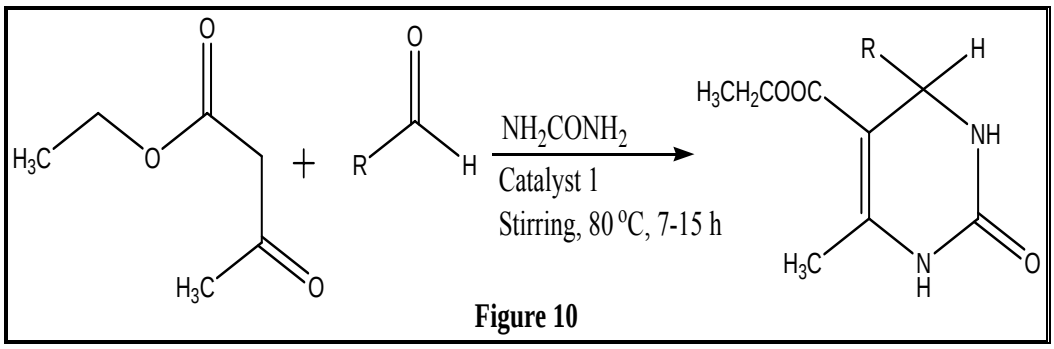


Figure 10

An efficient three-component synthesis of 3,4-dihydropyrimidinones using trichloroisocyanuric acid (TCCA) as mild, homogeneous and neutral catalyst for Biginelli reaction in ethanol or DMF under reflux condition.[40] Many researchers[41-47] have investigated an efficient Biginelli reaction under solvent-free conditions for one-pot synthesis of 3,4-dihydropyrimidi-2-(1*H*)ones/thiones using various catalyst as described under.

Solid phase synthesis

The generation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery and lead optimization in pharmaceutical research. Multi-component reactions (MCRs)[29, 48-53] leading to heterocycles are particularly useful for the creation of diverse chemical libraries, since the combination of any 3 small molecular weight building blocks in a single operation leads to high combinatorial efficiency. Therefore, solid phase modifications of MCRs are rapidly become the cornerstone of combinatorial synthesis of small-molecule libraries.

The first solid-phase modification of the Biginelli condensation was reported by Wipf and Cunningham[54] in 1995 (**Figure11**). In this sequence, γ-aminobutyric acid derived urea

was attached to Wang resin using standard procedures. The resulting polymer-bound urea was condensed with excess *β*-ketoester and aromatic aldehydes in THF at 55 °C in the presence of a catalytic amount of HCl to afford the corresponding immobilized DHPMs. Subsequent cleavage of product from the resin by 50 % trifluoroacetic acid (TFA) provided DHPMs in high yields and excellent purity.

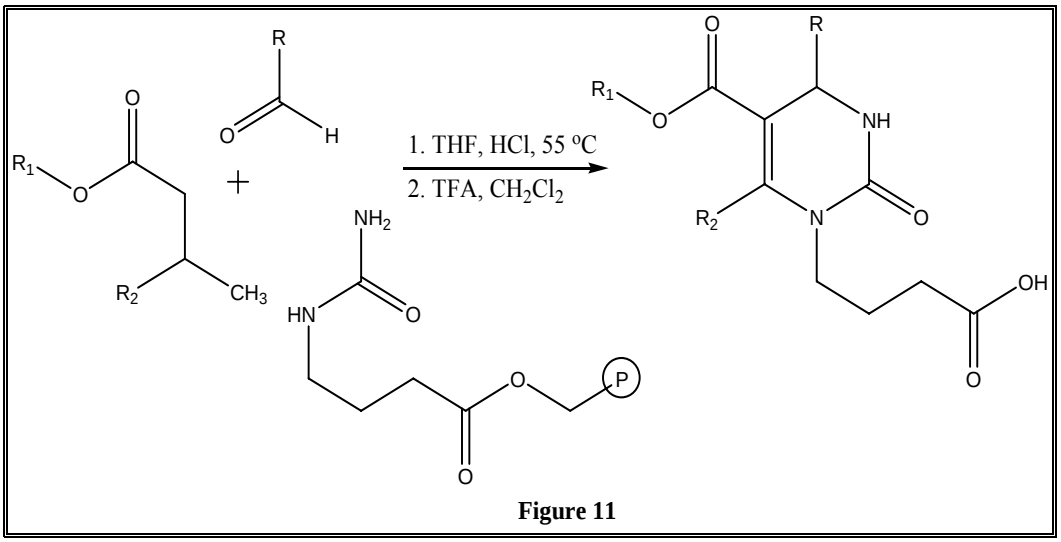


Figure 11

Weiwei Li and Yulin Lam[55] described the synthesis of 3,4-dihydropyrimidin-2-(1*H*)ones/thiones using sodium benzenesulfinate as a traceless linker (**Figure 12**). The key steps involved in the solid-phase synthetic procedure include sulfinate acidification, condensation of urea or thiourea with aldehydes and sulfinic acid and traceless product release by a one-pot cyclization-dehydration process. Since a variety of reagents can be used, the overall strategy appears to be applicable to library generation.

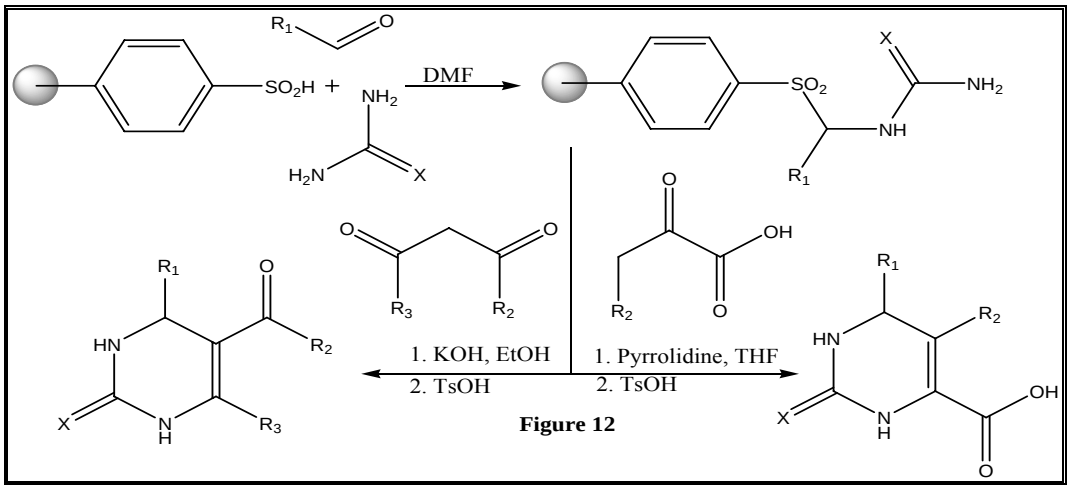


Figure 12

Gross et al.[56] developed a protocol for based on immobilized α-ketoamides to increase the diversity of DHPM (**Figure 13**). The resulting synthetic protocol proved to be suitable for the preparation of a small library using different building blocks. They found that the expected DHPM derivatives were formed in high purity and yield, if aromatic aldehyde and α-ketoamide building blocks were used. The usage of an aliphatic aldehyde leads to an isomeric DHPM mixture. Purities and yields were not affected if thiourea was used instead of urea.

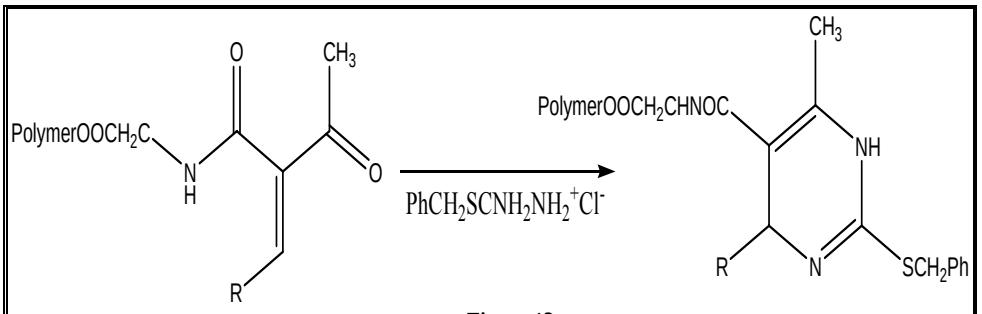


Figure 13

Liquid phase synthesis

In the solid phase synthesis there are some disadvantages of this methodology compared to standard solution-phase synthesis, such as difficulties to monitor reaction progress, the large excess of reagents typically used in solid-phase supported synthesis, low loading capacity and limited solubility during the reaction progress and the heterogeneous reaction condition with solid phase.[57] Recently, organic synthesis of small molecular compounds on soluble polymers, i.e. liquid phase chemistry has increasingly become attractive field.[58] It couples the advantages of homogeneous solution chemistry with those of solid phase chemistry.

Moreover owing to the homogeneity of liquid-phase reactions, the reaction conditions can be readily shifted from solution-phase systems without large changes and the amount of excessive reagents is less than that in solid-phase reactions. In the recent years, Task Specific room temperature Ionic Liquids (TSILs) has emerged as a powerful alternative to conventional molecular organic solvents or catalysts. Liu Zuliang et al.[59] reported cheap and

reusable TSILs for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones via one-pot three component Biginelli reaction.

Ionic liquid-phase bound acetoacetate reacts with thiourea and various aldehydes with a cheap catalyst to afford ionic liquid-phase supported 3,4-dihydropyrimidin-2(1*H*)-thiones by Jean Pierre Bazureau and co-workers (**Figure 14**).[60] 3,4-Dihydropyrimidinones was synthesized in one-pot of aldehydes, *β*-dicarbonyl compounds and urea, catalyzed by non-toxic room temperature ionic liquid 1-*n*-butyl-3-methylimidazolium saccharinate (BMImSac).[61]

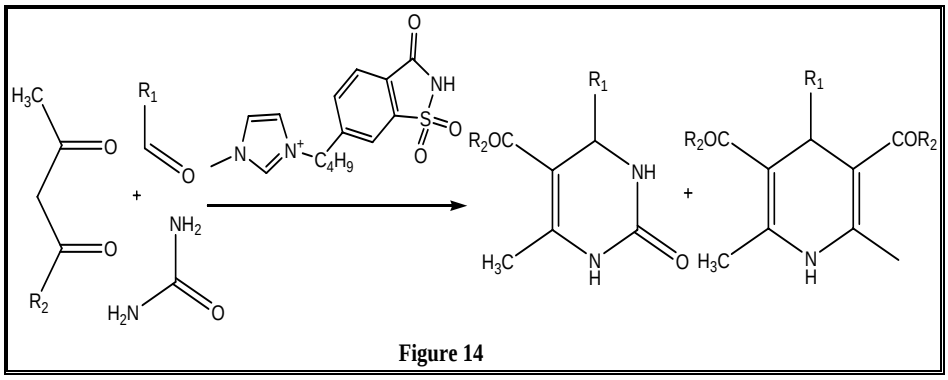


Figure 14

Microwave assisted synthesis

In general, the standard procedure for the Biginelli condensation involves one pot condensation of the three building blocks in a solvent such as ethanol using a strongly acidic catalyst that is hydrochloric acid.[58] One major drawback of this procedure, apart from the long reaction times involving reflux temperatures, are the moderate yields frequently observed when using more complex building blocks. Microwave irradiation (MWI) has become recognized tool in organic synthesis, because the rate enhancement, higher yields and often, improved selectivity with respect to conventional reaction conditions.[62] The publication by Anshu Dandia et al.[63] described microwave-enhanced solution-phase Biginelli reactions employing ethyl acetoacetate, thiourea and a wide variety of aromatic aldehydes as building blocks (**Figure 15**). Upon irradiation of the individual reaction mixtures (ethanol, catalytic HCl) in an open glass beaker inside the cavity of a domestic microwave oven the reaction times were reduced from 2–24 hours of conventional heating 80 °C, reflux to 3–11 minutes under microwave activation (ca. 200 –300 W). At the same time the yields of

DHPMs obtained were markedly improved compared to those reported earlier using conventional conditions.

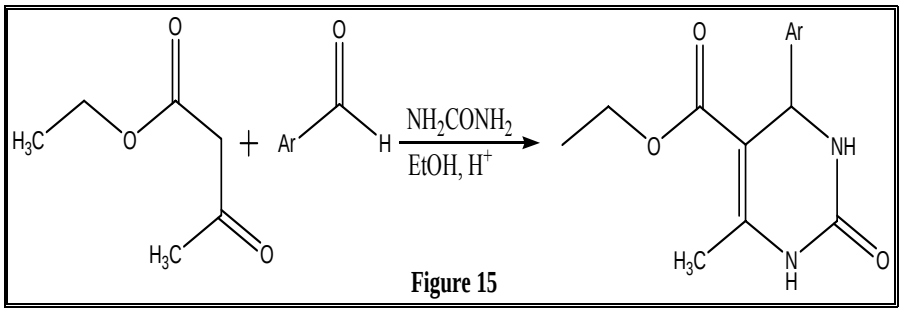


Figure 15

In recent years, solvent free reactions using either organic or inorganic solid supports have received increasing attention.[64] There are several advantages to performing synthesis in dry media: (i) short reaction times, (ii) increased safety, (iii) economic advantages due to the absence of solvent. In addition, solvent free MWI processes are also clean and efficient. M. Gopalakrishnan and co-workers have reported Biginelli reaction under microwave irradiation in solvent-free conditions using activated fly ash as a catalyst, activated fly ash, an industrial waste (pollutant) is an efficient and novel catalyst for some selected organic reactions in solvent free conditions under microwave irradiation.[65]

Ultrasound assisted synthesis

Ultrasound as a green synthetic approach has gradually been used in organic synthesis over the last three decades. Compared with the traditional methods, it is more convenient, easier to be controlled, and consumes less power. With the use of ultrasound irradiation, a large number of organic reactions can be carried out in milder conditions with shorter reaction time and higher product yields.[66] Ultrasound irradiated and amidosulfonicacid (NH_2SO_3H) catalyzed synthesis of 3,4-dihydropyrimidi-2-(1*H*)ones have reported by Ji-Taai Li and co-workers[67] using aldehydes, β-ketoester and urea.

Chenjiang Liu et al.[68] have synthesized a novel series of 4-substituted pyrazolyl- 3,4-dihydropyrimidin-2(1*H*)-thiones under ultrasound irradiation using magnesium perchlorate [$Mg(ClO_4)_2$] as catalyst (**Figure 16**), by the condensation of 5-chloro/phenoxyl-3-methyl-1-phenyl-4-formylpyrazole, 1,3-dicarbonyl compound and urea or thiourea in moderate yields. The catalyst exhibited remarkable reactivity and can be recycled.

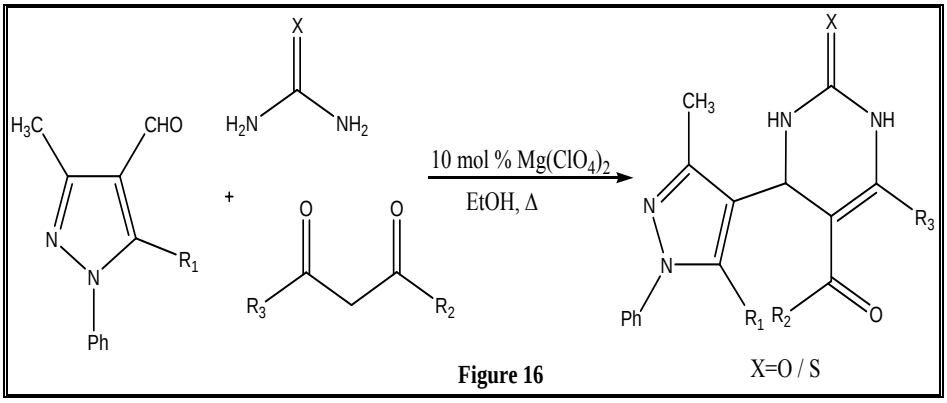


Figure 16

Sonication of aromatic aldehydes, urea and ethyl acetoacetate in presence of solvent (ethanol) or solvent-less dry media (bentonite clay) by supporting-zirconium chloride ($ZrCl_4$) as catalys at 35 kHz gives 6-methyl-4-substitutedphenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl esters proficiently in high yields reported by Harish Kumar et al. (**Figure 17**).[69]

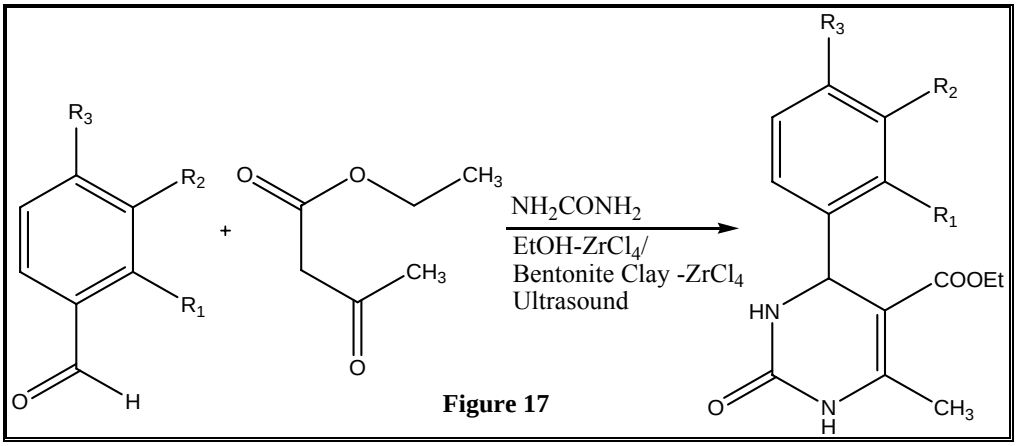


Figure 17

4.3 Mechanistic studies

Since the 1930s several mechanistic pathways have been proposed for the Biginelli reaction. In 1933, Folkers and Johnson reported that one of three intermediates (**Figure 18, 19, 20**) was likely to be present in this reaction.[70]

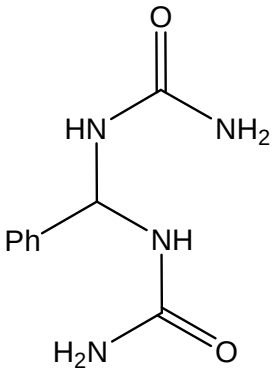


Figure 18

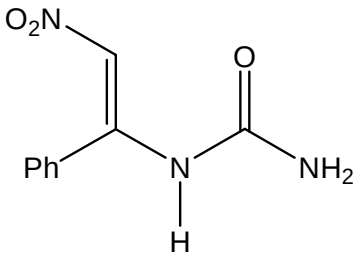


Figure 19

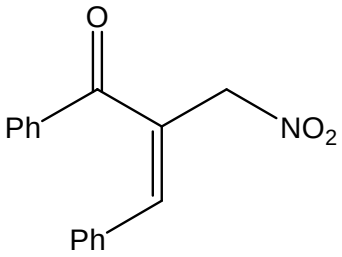
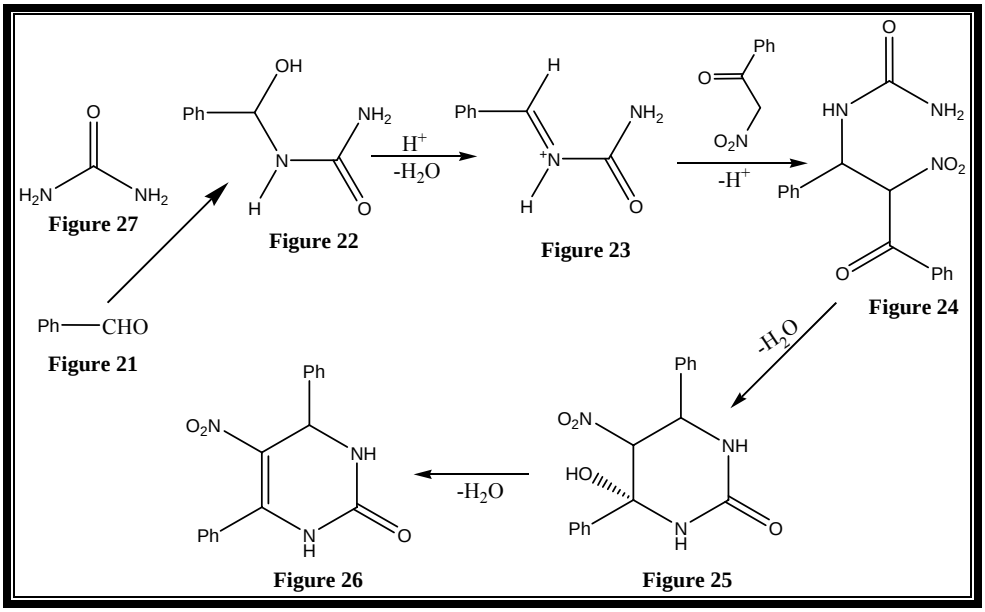


Figure 20

Forty years after the initial proposal, Sweet and Fissekis proposed a more detailed pathway involving a carbonium ion species.[29] After 25 years of second proposed mechanism by Sweet and Fissekis, Kappe[71] reexamined the same mechanism in 1997 using ^{1}H and ^{13}C NMR spectroscopy to support the argument that the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type (**Figure 22**) from the aldehyde (**Figure 21**) and urea (**Figure 27**) precursors. Interception of the iminium ion (**Figure 24**) by α-nitroacetophenone, presumably through its active methelene produces an open chain ureide which subsequently cyclizes to hexahydropyrimidine(**Figure 25**). Acid-catalyzed elimination of water from (**Figure 25**) ultimately leads to the final DHPM product (**Figure 26**).



4.4 Biological activity of 4-aryl-1,4-dihydropyridines and 5-nitro DHPM

4.4.1 Calcium channel modulators

4-Aryl-1,4-dihydropyridines (DHPs, e.g. nifedipine,) are the most studied class of organic calcium channel modulators. More than 30 years after the introduction of nifedipine many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market.[72,73]

In recent years interest has also focused on aza-analogs such as dihydropyrimidines (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[5-7, 74-78] Over the past few years several lead-compounds were developed (*i.e.* SQ 32,926) that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compare favorable with second-generation analogs such as amlodipine and nicardipine (**Figure 28**).[79]

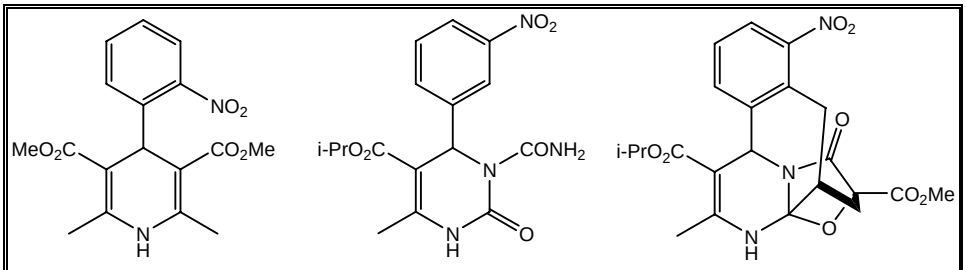


Figure 28

4.4.2 Potent and selective r1A receptor antagonists

Barrow et al reported *in vitro* and *in vivo* evaluation of dihydropyrimidinone C-5 amides as potent and selective r1A receptor antagonists for the treatment of benign prostatic hyperplasia (**Figure 29**). R1 Adrenergic receptors mediate both vascular and lower urinary tract tone, and R1 receptor antagonists such as terazosin are used to treat both hypertension and benign prostatic hyperplasia (BPH). Recently, three different subtypes of this receptor have been identified, with the R1A receptor being most prevalent in lower urinary tract tissue. Barrow et al reported 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective R1A receptor subtype antagonists. In receptor binding assays, these types of compounds generally display *K*i values for the R1a receptor subtype <1 nM while being greater than 100-fold selective versus the R1b and R1d receptor

subtypes. Many of these compounds were also evaluated in vivo and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure. While many of the compounds tested displayed poor pharmacokinetics, one compound was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs. Due to its selectivity for the R1a over the R1b and R1d receptors as well as its favorable pharmacokinetic profile, it has the potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system.[80-84]

The 4-aryldihydropyrimidinone heterocycles attached to an aminopropyl-4-arylpiperidine via a C-5 amide has proved to be an excellent template for selective R1A receptor subtype antagonists. These types of compounds are exceptionally potent in both cloned receptor binding studies as well as in vivo pharmacodynamic models of prostatic tone.

Compounds exhibited high binding affinity and subtype selectivity for the cloned human R1a receptor. Systematic modifications led to identification of highly potent and subtype-selective compounds with high binding affinity (*K*i) 0.2 nM) for R1a receptor and greater than 1500- fold selectivity over R1b and R1d adrenoceptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues. They exhibited excellent selectively to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood pressure (DBP) in mongrel dogs (*K*b(DBP)/*K*b(IUP))suggesting uroselectivity for R1a-selective compounds (**Figure 30**).[85]

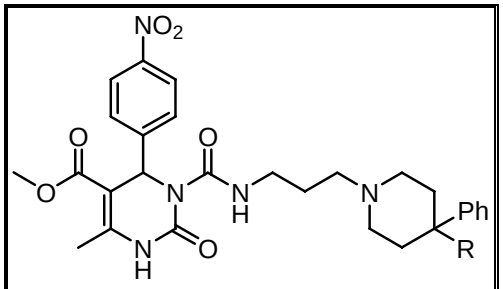


Figure 30

Cho et. al. reported 3-*N*-substituted-3,4-dihydropyrimidine and 3-*N*-substituted-dihydropyrimidin-2(1*H*)-ones as calcium channel antagonist (**Figure 31**). Compounds [especially [R_1=$(CH_2)_2$*N*(benzyl)(2-naphthylmethyl) R_2= i-Pr, X=o-N0$_2$] and [R'= $(CH_2)_2$*N*(benzyl)(3,4-dichlorobenzyl) R_2= i-Pr, X=o-NO_2]] exhibited not only more potent

and longer lasting vasodilative action but also a hypertensive activity with slow onset as compared with dihydropyridines. Moreover, some dihydropyrimidines [R' $=(CH_2)_2N$(benzyl)(3-phenylpropyl), R_2 = CH_2(cyclopropyl), X = o-NO_2] were weaker in blocking atrioventricular conduction in anesthetized open-chest dogs and less toxic than the dihydropyridines.[5]

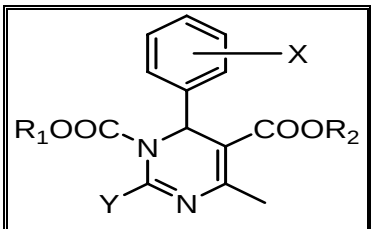


Figure 31

Atwal et al examined a series of novel dihydropyrimidine calcium channel blockers that contain a basic group attached to either C5 or N3 of the heterocyclic ring (**Figure 32**). Structure-activity studies show that l-(phenylmethyl)-4-piperidinyl carbamate moiety at N3 and sulfur at C2 are optimal for vasorelaxant activity in vitro and impart potent and long-acting antihypertensive activity in vivo. One of these compounds was identified as a lead, and the individual enantiomers were synthesized. Two key steps of the synthesis were (1) the efficient separation of the diastereomeric ureido derivatives and (2) the high-yield transformation of 2-methoxy intermediate to the (*p*-methoxybenzyl)thio intermediates. Chirality's was demonstrated to be a significant determinant of biological activity, with the dihydropyridine receptor recognizing the enamines ester moiety but not the carbamate moiety. Dihydropyrimidine is equipotent to nifidepine and amlodipine in vitro. In the spontaneously hypertensive rat, dihydropyrimidine is both more potent and longer acting than nifidepine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine has the potential advantage of being a single enantiomer.[76]

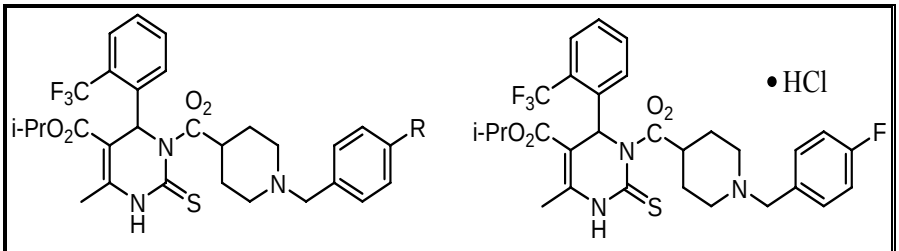


Figure 32

In order to explain the potent antihypertensive activity of the modestly active (ICw = 3.2 pM) dihydropyrimidine calcium channel blocker**,** Atwal et al carried out drug metabolism studies in the rat and found it is metabolized. Two of the metabolites (ICw = 16 nM) and (ICw = 12 nM), were found to be responsible for the antihypertensive activity of compound**.** Potential metabolism in vivo precluded interest in pursuing compounds related to it. Structure-activity studies aimed at identifying additional aryl-substituted analogues led to comparable potential in vivo, though these compounds were less potent in vitro. To investigate the effects of absolute stereochemistry on potency, authors resolved via diastereomeric ureas, prepared by treatment with (R)-α-methylbenzylamine. The results demonstrate that the active R-(-)-enantiomer is both more potent and longer acting than nifedipine as an antihypertensive agent in the SHR. The in vivo potency and duration is comparable to the long-acting dihydropyridine amlodipine. The superior oral antihypertensive activity compared to that of previously described carbamates (R_2=COOEt) could be explained by its improved oral bioavailability, possibly resulting from increased stability of the urea functionality (Figure 33).[6]

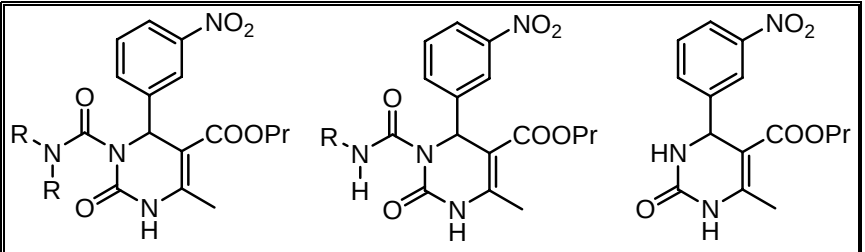


Figure 33

Authors modified the structure of previously described dihydropyrimidine i.e. 3-substituted 1,4-dihydropyrimidines**.** Structure-activity studies using potassium-depolarized rabbit aorta show that ortho, meta-disubstituted aryl derivatives are more potent than either ortho or meta-monosubstituted compounds. While vasorelaxant activity was critically dependent on the size of the **C5** ester group, isopropyl ester being the best, a variety of substituents (carbamate, acyl, sulfonyl, and alkyl) were tolerated at N_3. The results show dihydropyrimidines are significantly more potent than corresponding 2- heteroalkyl-l,4-dihydropyrimidines and only slightly less potent than similarly substituted 2-heteroalkyl-1-4-dihydropyridines (**Figure 34**). Where as dihydropyridine enantiomer usually show 10-15-

fold difference in activity, the enantiomer of dihydropyrimidine show more than a 1000-fold difference in activity. These results strengthen the requirement of an enaminoester for binding to the dihydropyridine receptor and indicate a nonspecific role for the N3-substituent.

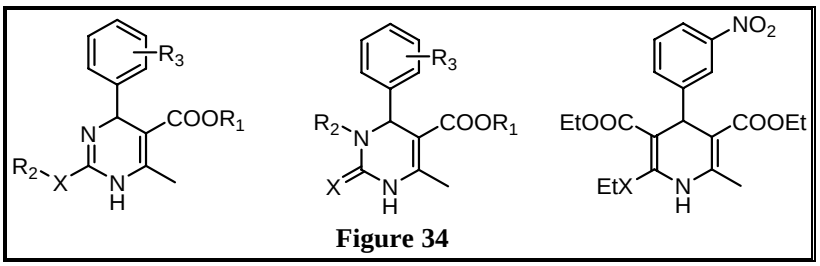


Figure 34

2-Heterosubstituted-4-aryl-l,4-dihydro-6-methyl-5-pyrimidinecarboxylicesters (**Figure 35**), which lack the potential symmetry of dihydropyridine calcium channel blockers, were prepared and evaluated for biological activity. Biological assays using potassium-depolarized rabbit aorta and radio ligand binding techniques showed that some of these compounds are potent mimics of dihydropyridine calcium channel blockers.[75]

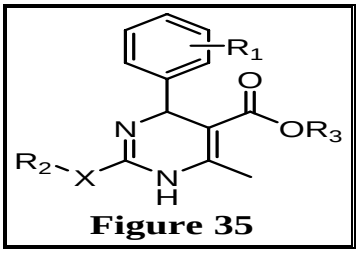


Figure 35

4.4.3 Antiarrhythmic activity

Arkadiy O. Bryzgalov et. al. reported the antiarrhythmic activity of 4,6-di(het)aryl-5-nitro-3,4-dihydropyrimidin-(1*H*)-2-ones toward two types of experimental rat arrhythmia has been studied (**Figure 36**). With $CaCl_2$ induced arrhythmia model, several agents have demonstrated high Antiarrhythmic activity and the lack of influence on arterial pressure of rats.[86]

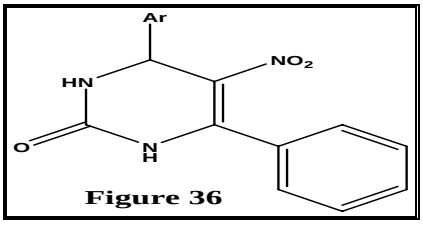


Figure 36

4.5 Aim of current work

Much interest has been focused around 5-nitro dihydropyrimidine derivatives because of their wide variety of pharmacological properties and industrial applications. In view of these findings we were interested to prepare some new 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-phenylpyrimidin-*2(1H)*-one (**Figure 37**) by using 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone instead of *β*-dicarbonyl compound in the Biginelli reaction with substituted benzaldehydes and urea under standard conditions (EtOH, HCl).

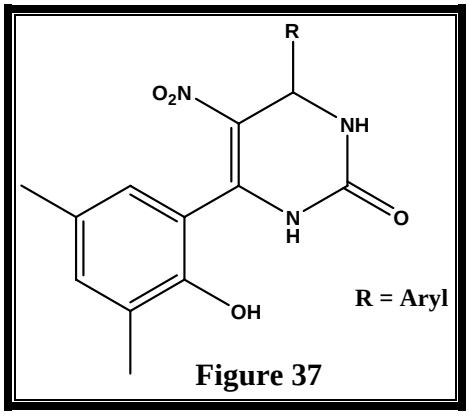


Figure 37

In extension of work, the same molecules when synthesized through green chemistry approach by utilizing Etidronic acid through microwave irradiation technique resulted in formation of all newly synthesized compounds with higher yields and also reaction hours are reduced to a great extent in comparison with conventional synthetic methods as mentioned in literature.

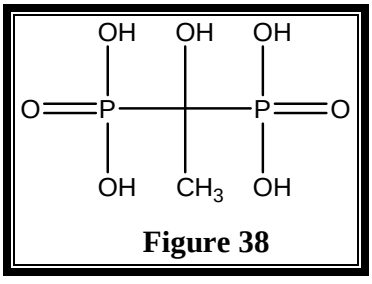


Figure 38

Etidronic acid [(1-hydroxyethylidene)bisphosphonic acid] (**Figure 38**) is a phosphonic acid and is also known as a bisphosphonate having a molecular formula $C_2H_8O_7P_2$. The two PO_3 (phosphonate) groups are covalently linked to a single carbon atom.[87] It is different from PPE and polyphosphoric acid (PPA). As a result we found increased yield

about 20-25% more than conventional method. All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. The antiviral screening of the compounds synthesized with this modification to DHPM skeleton is under investigation.

4.6 Chemistry

The synthesis of 4-Hydroxy-6,8-dimethyl-3-nitro-*2H*-chromen-2-one is outline in **(Scheme 1)**. The requisite 4-Hydroxy-6,8-dimethyl-*2H*-chromen-2-one were prepared by Pechmann condensation of polyphenols (resorcinol)[88] and equimolar malonic acid with 2 moles of $POCl_3$ and 3 moles of $ZnCl_2$. The nitration of 4-Hydroxy-6,8-dimethyl-*2H*-chromen-2-one in concentrated nitric acid in glacial acetic acid on steam bath yielded the 4-Hydroxy-6,8-dimethyl-3-nitro-*2H*-chromen-2-one. The above 4-Hydroxy-6,8-dimethy-3-nitro-2*H*-chromen-2-one was dissolved in 5% sodium hydroxide solution and the reaction mixture was kept at room temperature for 24 hr then acidified with hydrochloric acid to give 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone **(3)** (**Scheme 1**). Thus obtained compound 3 was subjected to Biginelli reaction with substituted benzaldehydes and urea under standard conditions (EtOH, HCl) to furnish the desired 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-*2*(1*H*)-one **(Figure 37)**.

With a view to elucidate whether analogous modifications could be applied to the synthesis of 5-nitrodihydropyrimidine (**Figure 37**) to raise their yields, we examined three-component condensation of 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone **(3)** with aromatic aldehydes **(4a-v)** and urea in the presence of etidronic acid as a catalyst (**Scheme 3**), in boiling ethanol and isolated desired product of 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one **(5a-v).**

4.7 Results and discussion

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-*2*(1*H*)-one have been synthesized in excellent yields in short reaction time at ambient temperature in the presence of etidronic acid catalyst by the reaction of aromatic or aliphatic aldehydes with 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone **(3)** and urea in ethanol under microwave irradiation. The overall synthetic strategy for the preparation of compounds **(5a-v)** is based

on the modification of classical three component Biginelli condensation. The process involves (includes) the one-pot cyclocondensation of a 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone (1.0 equiv) with an aryl aldehyde (1.5 equiv) and urea (1.5 equiv) in ethanol in the presence of etidronic acid. That is outlined in (**Scheme 3**).

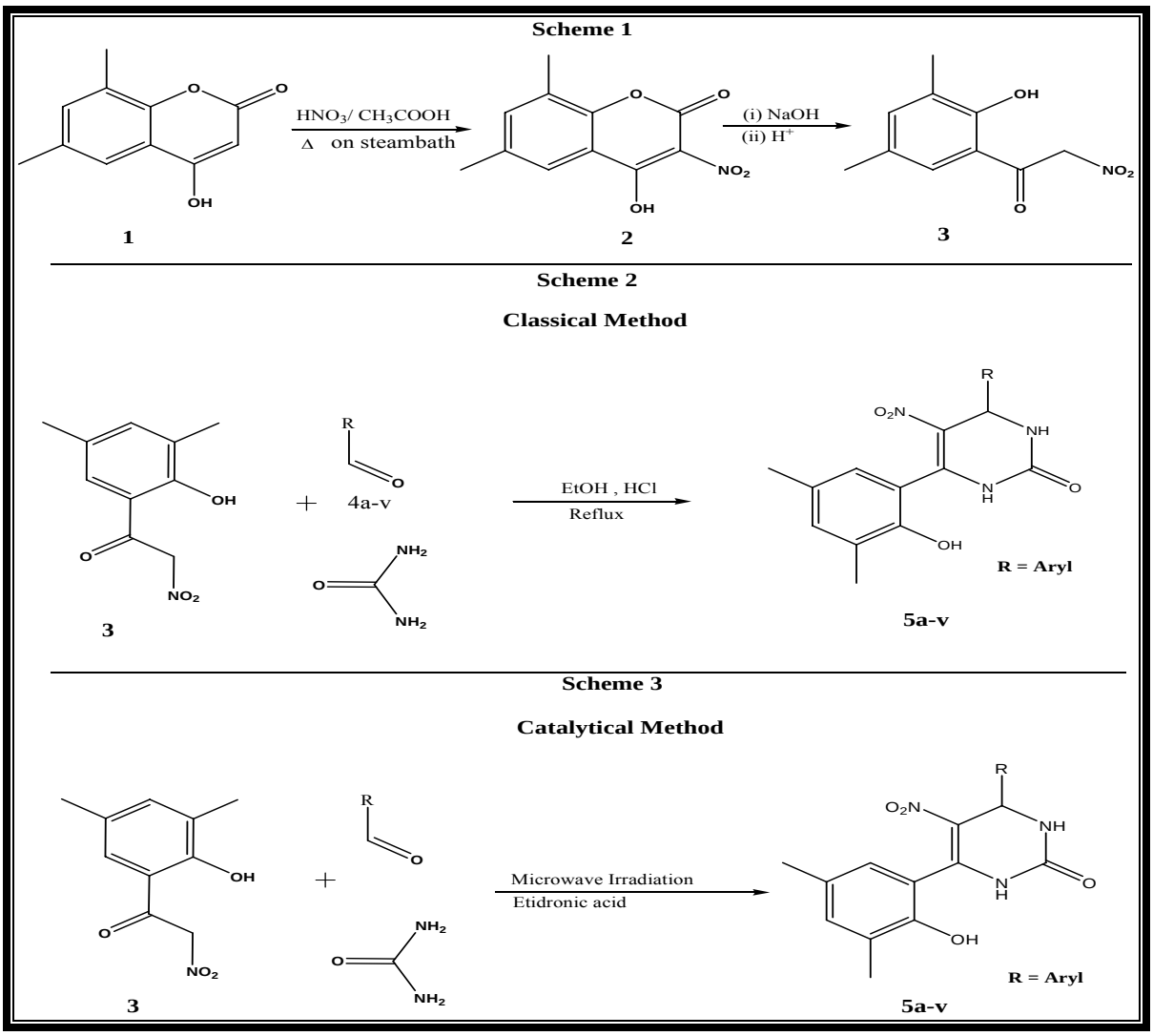
The structures of the resulting 5-nitro DHPM were confirmed by quantitative elemental analysis and PMR spectroscopy. The spectra of compounds **(5a-v)** contain two signals for a two methyl at 2.24-2.26 ppm and signals characteristic for 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone.The pyrimidine ring system –CH proton appear at 5.15-5.76 ppm and both –NH signals at 7.77 and 8.29 ppm. The aryl ring and 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone proton was overlapped shows at 7.0-7.60 ppm. The hydroxyl protons of -OH resonate at weak field 9.0-12.0 ppm. The IR spectrum of **5a–v** displayed bands at 3369–3336 and 1699-1681 cm^{-1} due to -NH and cyclic ketone stretching frequencies, respectively. On the other hand, the absorption bands were observed in the region 1641–1627cm^{-1} for (C-N). The aromatic stretching bending vibrations were observed as a sharp medium to strong band at 3097-3069 cm^{-1} in compounds **(5a–v)**. The mass spectrum of **5a** exhibited a molecular ion peak at m/z 339 (5%) in accordance with its molecular formula $C_{18}H_{17}N_3O_4$. Other prominent peaks appeared at m/z 293, 276, 250, 199, 160, 106, 91 and 77.

4.8 Conclusion

In summary, we have established a rapid and economical procedure for constructing a novel 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-*2(1H)*-one **(5a-v)** by combining microwave irradiation with a catalytically amount of etidronic acid. Comparison of the proposed method with conventional syntheses of the same compound showed that the microwave-assisted syntheses were characterized by much shorter reaction times and higher product yields. The specific advantages offered by the use of etidronic acid as new catalyst in microwave irradiation in organic synthesis are the following: (1) the routine product isolation is very simple because the side product is removed by washings from the appropriate solvent/eluent, (2) the product was obtained with high purity after column chromatography, we are reported of the rapid synthesis of 3,4-dihydro-6-(2-

hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one **(5a-v)** using a catalytically amount of etidronic acid one-pot three-component strategy under microwave irradiation.

4.9 Reaction scheme of 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one



4.10 Experimental procedure

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE

II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator.

4.10.1 General procedure for conventional synthesis of 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one (5a-v)

This title compound is prepared following the method as describe by P. Biginelli[3]

4.10.2 General procedure for microwave-assisted synthesis of 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one (5a-v)

A well stirred mixture of 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone **(3)** (0.01 mol) in 10-20ml ethanol, appropriate aldehyde **(4a-v)** (0.01 mol), and urea (0.01 mol) in the presence of etidronic acid (100 mg/0.01 mol) was irradiated under microwave oven for 5.0 to 10.0 min at 300W. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was taken up in chloroform and extracted with water. The organic layer was washed with 5% aq. sodium bisulphite (100 mL), followed by water (200 mL) and brine (100 mL) and dried over anhy.sodium sulphate. The solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2) using hexane–ethyl acetate (8:2) as an eluent. The fraction containing the main products were combined and evaporated to dryness under reduce pressure. The crude product thus obtained was crystallized from ethanol to afford the targeted 5-nitroDHPM.

Similarly, other 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one (5a-v) were prepared.

4.11 Spectral data of synthesized compounds (3, and 5a-v)

1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone (3) Pale yellow solid, yield 92%, mp 135–137°C; Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70; Found: C, 57.32; H, 5.15; N, 6.56; m/z:209 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.10-2.30 (s, 6H, $2CH_3$), 6.45 (s, 2H, CH_2NO_2), 7.30-7.50 (s, 2H, Ar), 10.95 (s, 1H, OH).

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimidin-2(1*H*)-one 5a. Pale yellow solid, yield 88%, mp 235–237°C; Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.98; Found: C, 63.65; H, 4.99; N, 12.92; m/z:339 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.24 (s, 3H CH_3), 2.26 (s, 3H, CH_3), 5.75 (s, 1H, Pyrm-CH), 6.90-7.00 (s, 2H, 2-OH-phenyl ring), 7.38-7.57 (m, 5H, Ar), 7.44 (s, 1H, Pyrm-NH), 8.16 (s, 1H, Pyrm-NH), 8.46 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3485, 3369, 3068, 2895, 2818, 1699, 1627, 1491, 1319, 1286.

4-(4-fluorophenyl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5b. yellow solid, yield 90%, mp 245–247°C; Anal. Calcd for $C_{18}H_{16}FN_3O_4$: C, 60.50; H, 4.51; N, 11.76; Found: C, 60.45; H, 4.46; N, 11.70; m/z:357 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.16 (s, 3H CH_3), 2.20 (s, 3H, CH_3), 5.60 (s, 1H, Pyrm-CH), 6.85-6.98 (s, 2H, 2-OH-phenyl ring), 7.02-7.54 (m, 4H, Ar), 8.27 (s, 1H, Pyrm-NH), 8.75 (s, 1H, Pyrm-NH), 9.83 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3483, 3372, 3066, 2890, 2822, 1695, 1630, 1488, 1325, 1280.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(2,5-dimethoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5c. yellow solid, yield 85%, mp 252–254°C; Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52; Found: C, 60.10; H, 5.20; N, 10.46; m/z:399 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.26 (s, 3H CH_3), 2.28 (s, 3H, CH_3), 5.96 (s, 1H, Pyrm-CH), 6.80-6.83 (s, 2H, 2-OH-phenyl ring), 6.89-6.91 (m, 3H, Ar), 8.54 (s, 1H, Pyrm-NH), 9.39 (s, 1H, Pyrm-NH), 10.40 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3485, 3375, 3060, 2892, 2824, 1690, 1633, 1485, 1327, 1283.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(3,4-dimethoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5d. yellow solid, yield 80%, mp 242–244°C; Anal. Calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52; Found: C, 60.10; H, 5.20; N, 10.46; m/z:399 [M^+]; IR (KBr), ν(cm^{-1}): 3484, 3374, 3062, 2893, 2825, 1691, 1634, 1486, 1328, 1284.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(2-hydoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5e. yellow solid, yield 75%, mp 192–194°C; Anal. Calcd for $C_{18}H_{17}N_3O_5$: C,

60.84; H, 4.82; N, 11.83; Found: C, 60.80; H, 4.80; N, 11.78; m/z:355 [M^+]; IR (KBr), ν(cm^{-1}): 3483, 3372, 3063, 2890, 2828, 1691, 1630, 1480, 1326, 1285.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(3-hydoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5f. yellow solid, yield 78%, mp 202–204°C; Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83; Found: C, 60.82; H, 4.81; N, 11.79; m/z:355 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3064, 2891, 2827, 1690, 1631, 1481, 1327, 1286.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(4-hydoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5g. yellow solid, yield 80%, mp 212–214°C; Anal. Calcd for $C_{18}H_{17}N_3O_5$: C, 60.84; H, 4.82; N, 11.83; Found: C, 60.79; H, 4.78; N, 11.77; m/z:355 [M^+]; IR (KBr), ν(cm^{-1}): 3484, 3375, 3066, 2893, 2829, 1692, 1633, 1482, 1329, 1288.

4-(2-chlorophenyl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5h. yellow solid, yield 82%, mp 188–190°C; Anal. Calcd for $C_{18}H_{16}ClN_3O_4$: C, 57.84; H, 4.31; N, 11.24; Found: C, 57.79; H, 4.28; N, 11.19. m/z:373 [M^+]; IR (KBr), ν(cm^{-1}): 3488, 3379, 3076, 2898, 2833, 1697, 1638, 1487, 1333, 1293.

4-(3-chlorophenyl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5i. yellow solid, yield 84%, mp 208–210°C; Anal. Calcd for $C_{18}H_{16}ClN_3O_4$: C, 57.84; H, 4.31; N, 11.24; Found: C, 57.78; H, 4.29; N, 11.18; m/z:373 [M^+]; IR (KBr), ν(cm^{-1}): 3486, 3377, 3077, 2896, 2831, 1695, 1635, 1482, 1330, 1290.

4-(4-chlorophenyl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5j. yellow solid, yield 85%, mp 222–225°C; Anal. Calcd for $C_{18}H_{16}ClN_3O_4$: C, 57.84; H, 4.31; N, 11.24; Found: C, 57.79; H, 4.27; N, 11.20; m/z:373 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.30 (s, 3H CH_3), 2.35 (s, 3H, CH_3), 5.66 (s, 1H, Pyrm-CH), 6.85-6.94 (s, 2H, 2-OH-phenyl ring), 7.02-7.20 (m, 4H, Ar), 8.60 (s, 1H, Pyrm-NH), 8.65 (s, 1H, Pyrm-NH), 10.40 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3480, 3370, 3070, 2890, 2825, 1690, 1630, 1480, 1333, 1295.

4-(2,4-dichlorophenyl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5k. yellow solid, yield 80%, mp 242–245°C; Anal. Calcd for $C_{18}H_{15}Cl_2N_3O_4$: C, 52.96; H, 3.70; N, 10.29; Found: C, 52.90; H, 3.67; N, 10.20; m/z:373 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-(2-nitrophenyl)pyrimidin-2(1*H*)-one 5l. pale yellow solid, yield 75%, mp 178–180°C; Anal. Calcd for $C_{18}H_{16}N_4O_6$: C, 56.25; H, 4.20; N, 14.58; Found: C, 56.20; H, 4.12; N, 14.54; m/z:384 [M^+]; IR (KBr), ν(cm^{-1}): 3488, 3379, 3076, 2898, 2833, 1697, 1638, 1487, 1333, 1293.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-(3-nitrophenyl)pyrimidin-2(1*H*)-one 5m. pale yellow solid, yield 77%, mp 198–200°C; Anal. Calcd for $C_{18}H_{16}N_4O_6$: C, 56.25; H, 4.20; N, 14.58; Found: C, 56.22; H, 4.11; N, 14.50; m/z:384 [M^+]; IR (KBr), ν(cm^{-1}): 3490, 3389, 3070, 2899, 2832, 1692, 1640, 1485, 1335, 1291.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-(4-nitrophenyl)pyrimidin-2(1*H*)-one 5n. pale yellow solid, yield 77%, mp 198–200°C; Anal. Calcd for $C_{18}H_{16}N_4O_6$: C, 56.25; H, 4.20; N, 14.58; Found: C, 56.20; H, 4.15; N, 14.49; m/z:384 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 2.36 (s, 3H CH_3), 2.38 (s, 3H, CH_3), 5.70 (s, 1H, Pyrm-CH), 6.88-6.98 (s, 2H, 2-OH-phenyl ring), 7.35-8.10 (m, 4H, Ar), 8.75 (s, 1H, Pyrm-NH), 8.88 (s, 1H, Pyrm-NH), 12.52 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3490, 3389, 3070, 2899, 2832, 1692, 1640, 1485, 1335, 1291.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(2-methoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5o. light yellow solid, yield 87%, mp 215–218°C; Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38; Found: C, 61.70; H, 5.09; N, 11.31; m/z:369 [M^+]; IR (KBr), ν(cm^{-1}): 3491, 3379, 3079, 2890, 2831, 1690, 1645, 1480, 1330, 1292.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(4-methoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5p. yellow solid, yield 90%, mp 225–228°C; Anal. Calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38; Found: C, 61.71; H, 5.10; N, 11.30; m/z:369 [M^+]; ^{1}H NMR (400

MHz, DMSO): δ ppm 2.34 (s, 3H CH_3), 2.38 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3) 5.98 (s, 1H, Pyrm-CH), 6.60-6.75 (s, 2H, 2-OH-phenyl ring), 6.84-6.95 (m, 4H, Ar), 8.72 (s, 1H, Pyrm-NH), 8.81 (s, 1H, Pyrm-NH), 12.42 (s, 1H, OH); IR (KBr), ν(cm^{-1}): 3490, 3389, 3069, 2880, 2835, 1680, 1640, 1470, 1320, 1282; ^{13}C NMR (400 MHz, $CDCl_3$): 15.43, 20.38, 50.86, 80.64, 91.79, 114.48, 118.22, 125.02, 126.02, 127.45, 128.77, 132.01, 139.87, 182.42.

3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(4-hydroxy-3-methoxyphenyl)-5-nitropyrimidin-2(1*H*)-one 5q. yellow solid, yield 71%, mp 251–254°C; Anal. Calcd for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90; Found: C, 59.17; H, 4.90; N, 10.87; m/z:385 [M^+]; IR (KBr), ν(cm^{-1}): 3491, 3382, 3066, 2889, 2845, 1682, 1643, 1473, 1324, 1286.

4-(3,5-difluorophenyl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5r. yellow solid, yield 75%, mp 251–252°C; Anal. Calcd for $C_{18}H_{15}F_2N_3O_4$: C, 57.60; H, 4.03; N, 11.20; Found: C, 57.55; H, 3.96; N, 11.11; m/z:375 [M^+]; IR (KBr), ν(cm^{-1}): 3483, 3372, 3066, 2890, 2822, 1695, 1630, 1488, 1325, 1280.

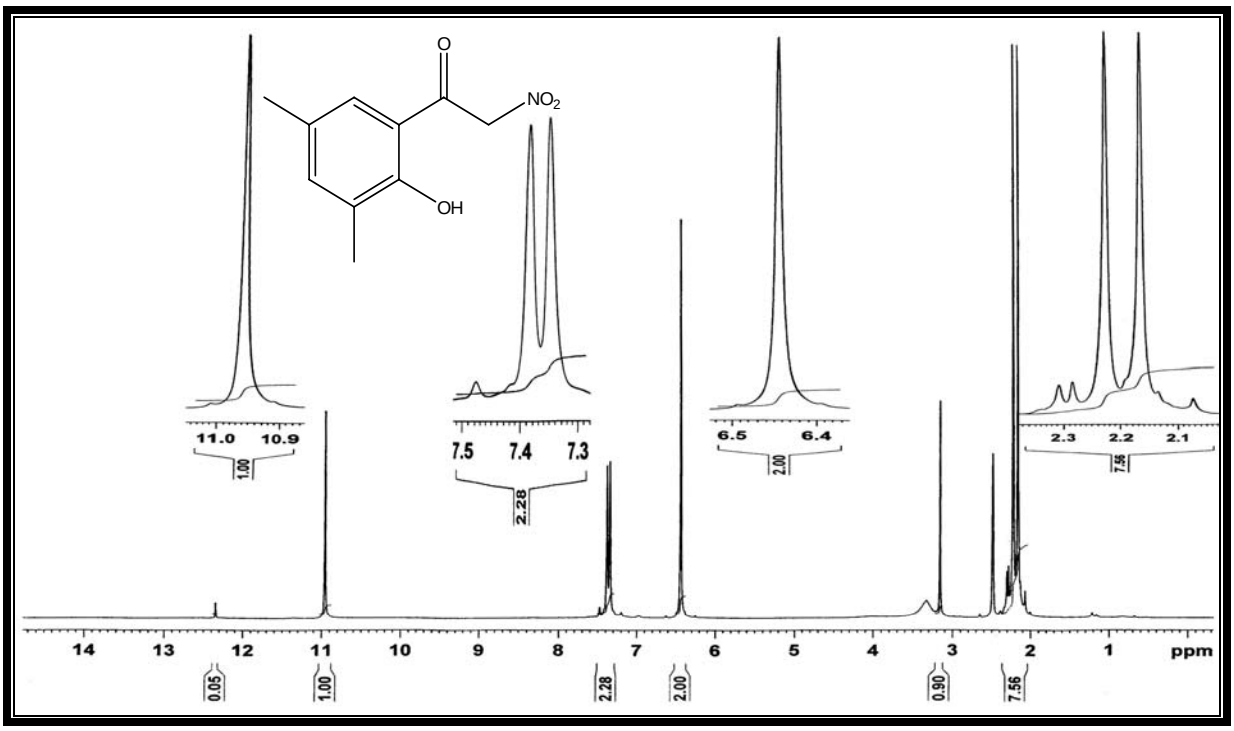
3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-*p*-tolylpyrimidin-2(1*H*)-one 5s. yellow solid, yield 85%, mp 195–198°C; Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89; Found: C, 64.50; H, 5.38; N, 11.81; m/z:369 [M^+]; IR (KBr), ν(cm^{-1}): 3491, 3379, 3079, 2890, 2831, 1690, 1645, 1480, 1330, 1292.

4-(furan-2-yl)-3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitropyrimidin-2(1*H*)-one 5t. yellow solid, yield 75%, mp 251–252°C; Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76; Found: C, 58.30; H, 4.52; N, 12.71; m/z:375 [M^+]; IR (KBr), ν(cm^{-1}): 3481, 3371, 3065, 2892, 2824, 1693, 1632, 1480, 1320, 1288.

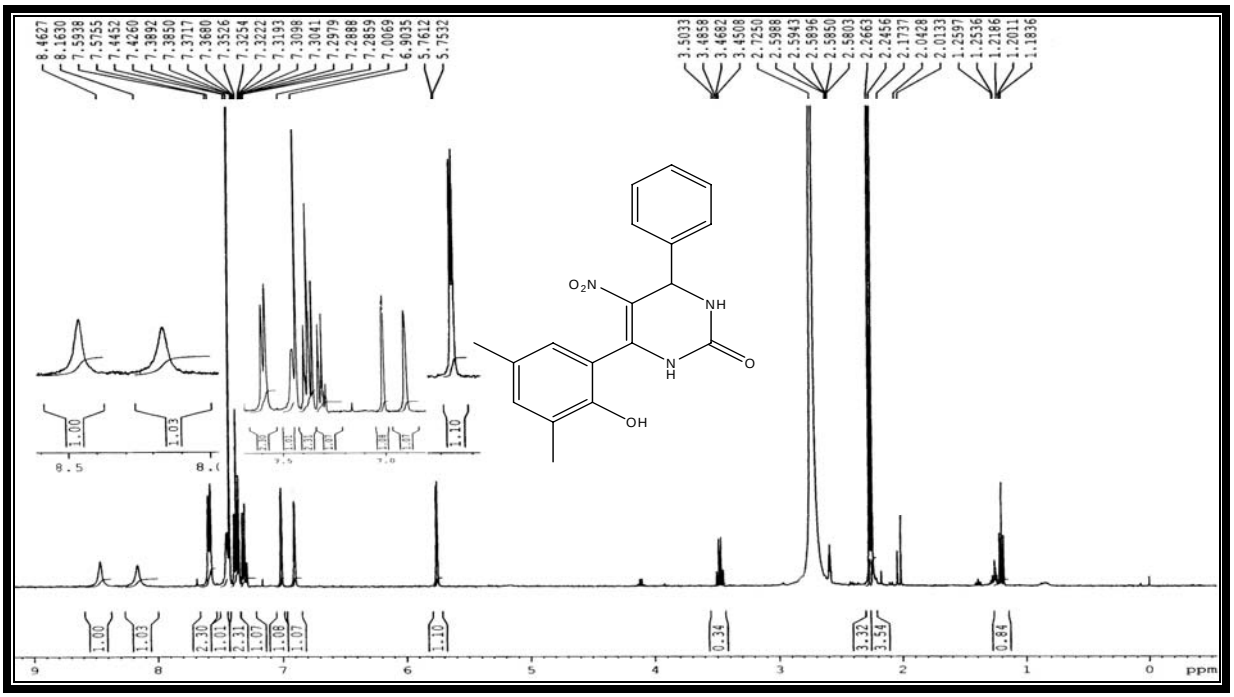
3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-4-(3-hydroxy-4-methoxyphenyl-5-nitrophenyl)-5-nitropyrimidin-2(1*H*)-one 5u. yellow solid, yield 73%, mp 261–263°C; Anal. Calcd for $C_{19}H_{19}N_4O_8$: C, 53.03; H, 4.22; N, 13.02; Found: C, 52.97; H, 4.17; N, 12.97; m/z:430 [M^+]; IR (KBr), ν(cm^{-1}): 3490, 3388, 3064, 2887, 2848, 1681, 1644, 1478, 1327, 1287.

4.12 Spectral representation of synthesized compounds

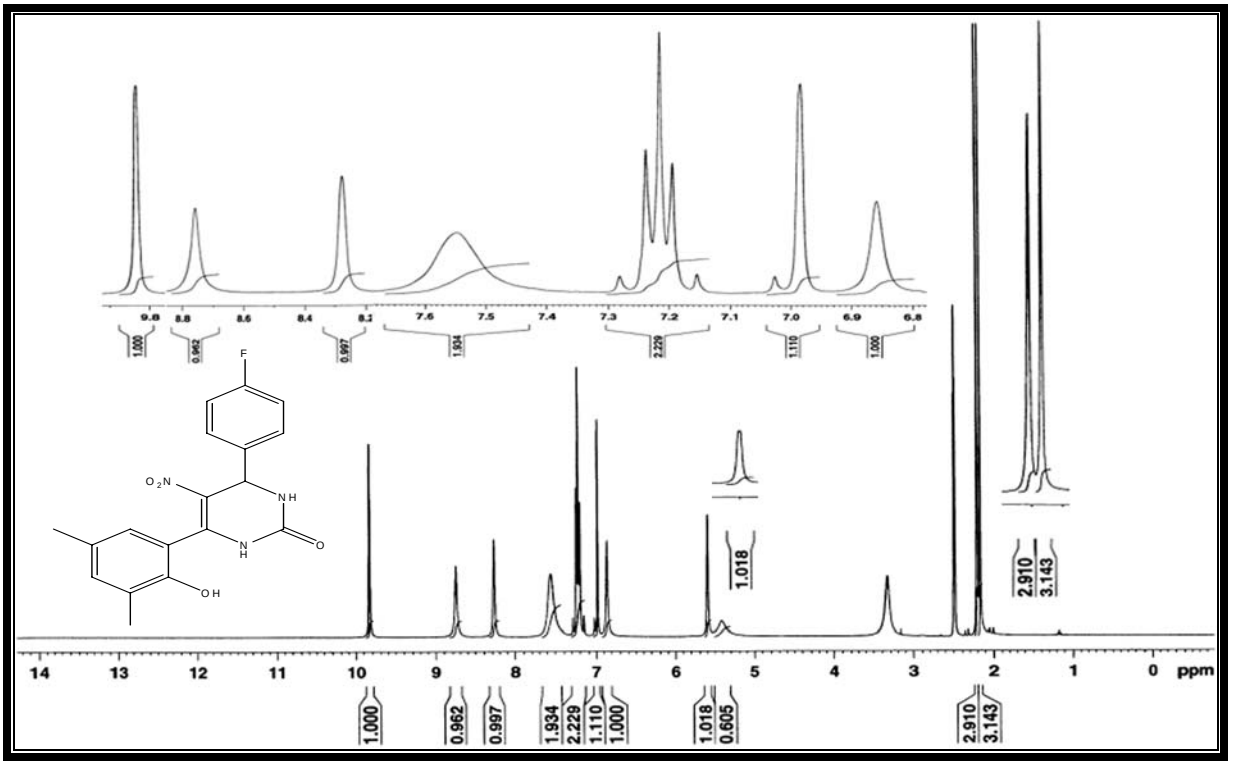
4.12.1 ^{1}H NMR spectrums of 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone (3)



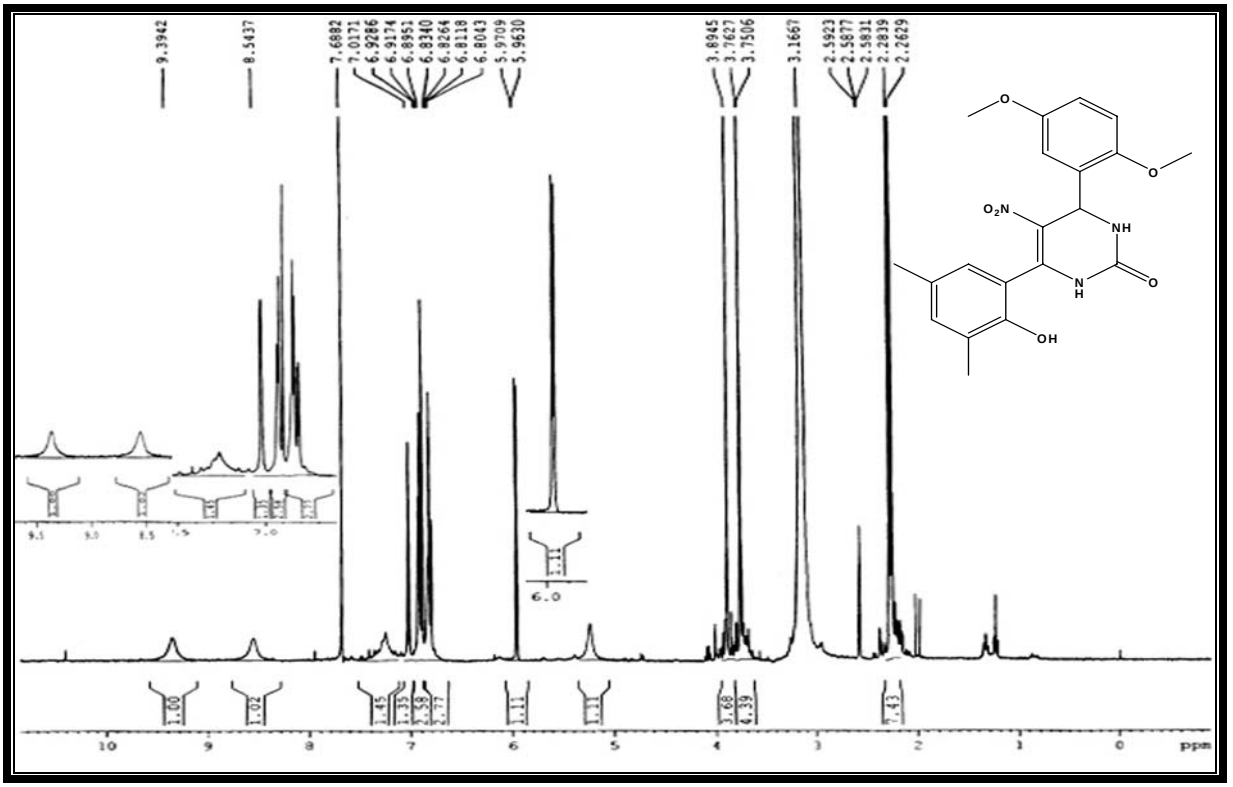
4.12.2 ^{1}H NMR spectrums of compound 5a



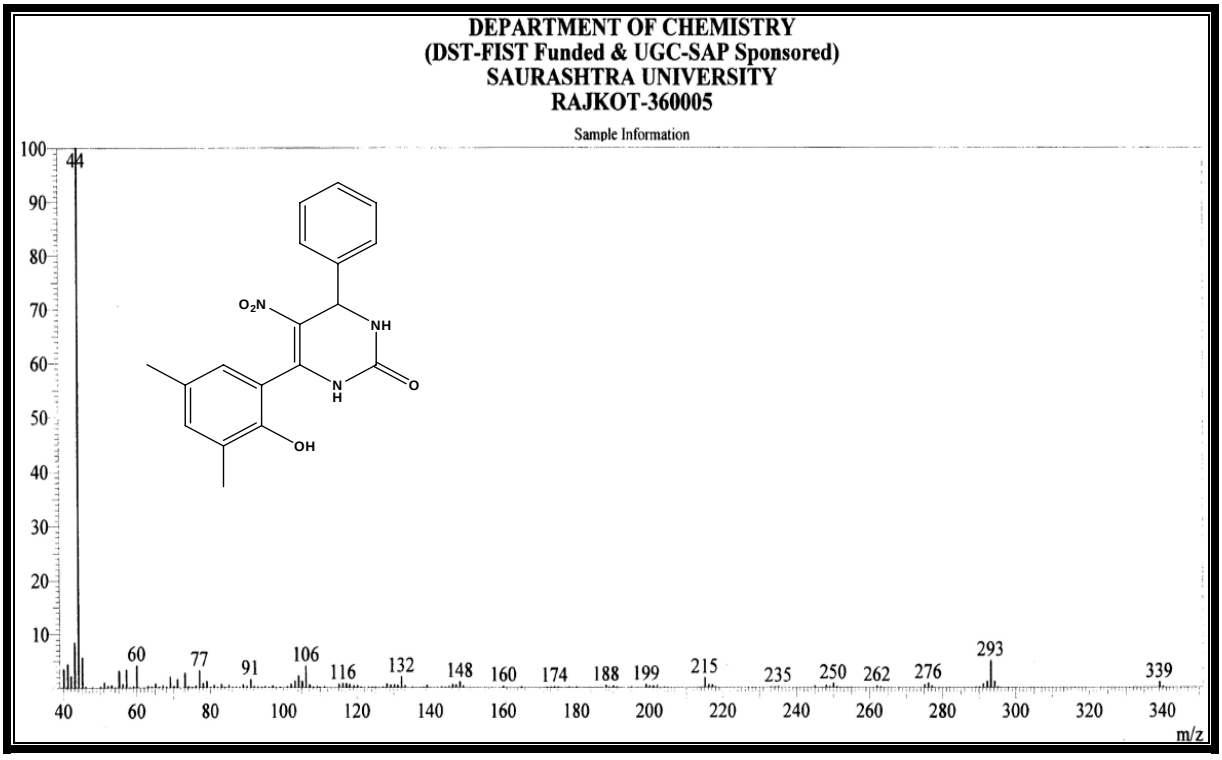
4.12.3 ^{1}H NMR spectrums of compound 5b



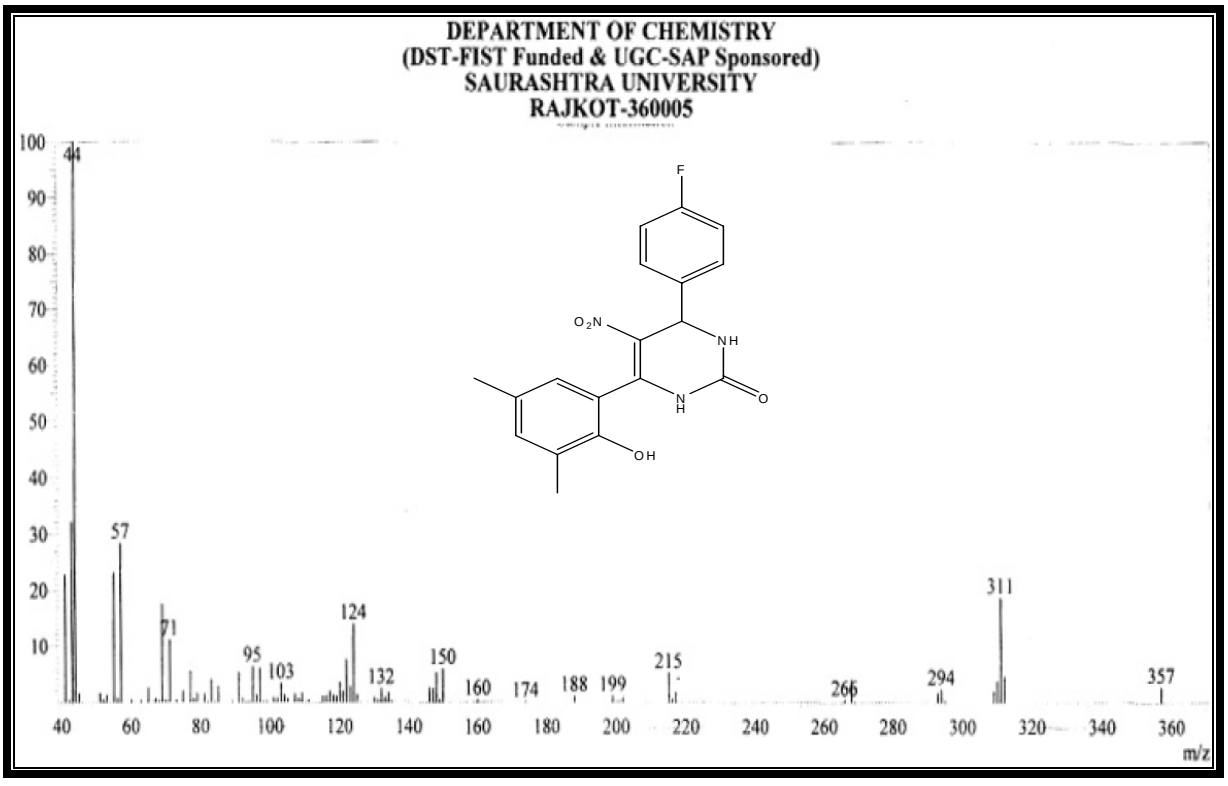
4.12.4 ^{1}H NMR spectrums of compound 5c



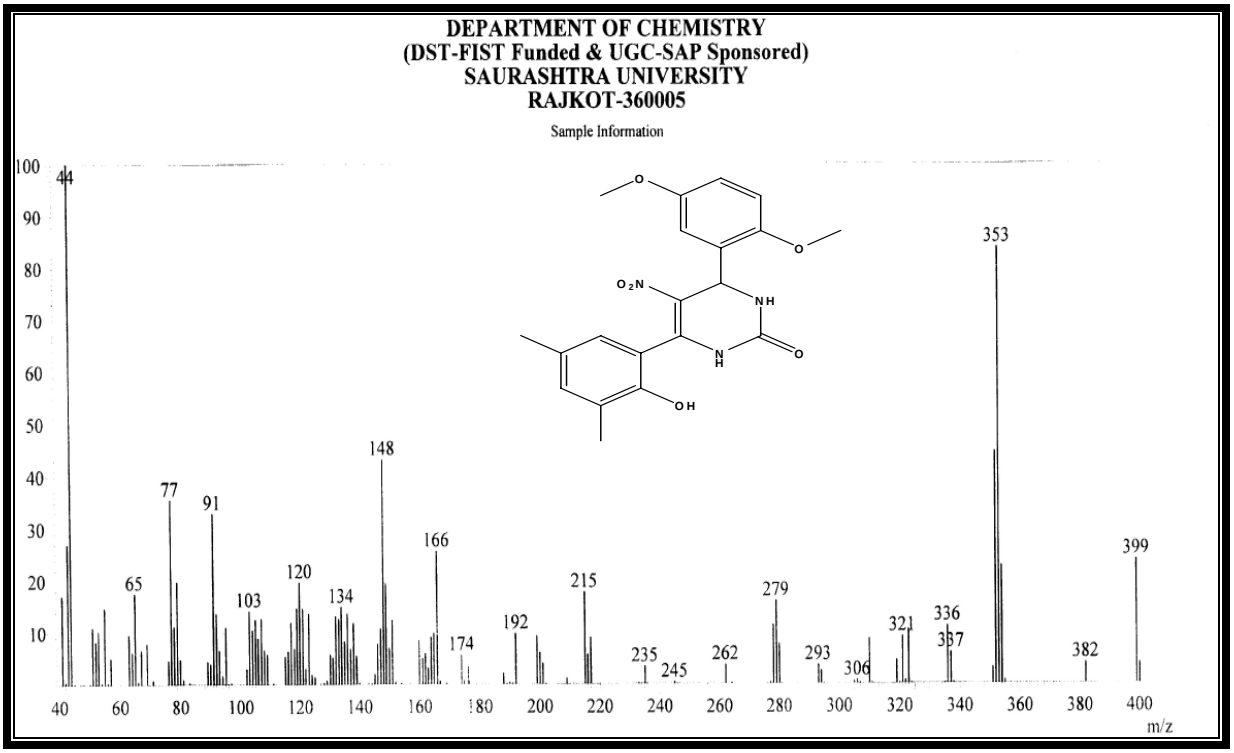
4.12.5 mass spectra of compound 5a



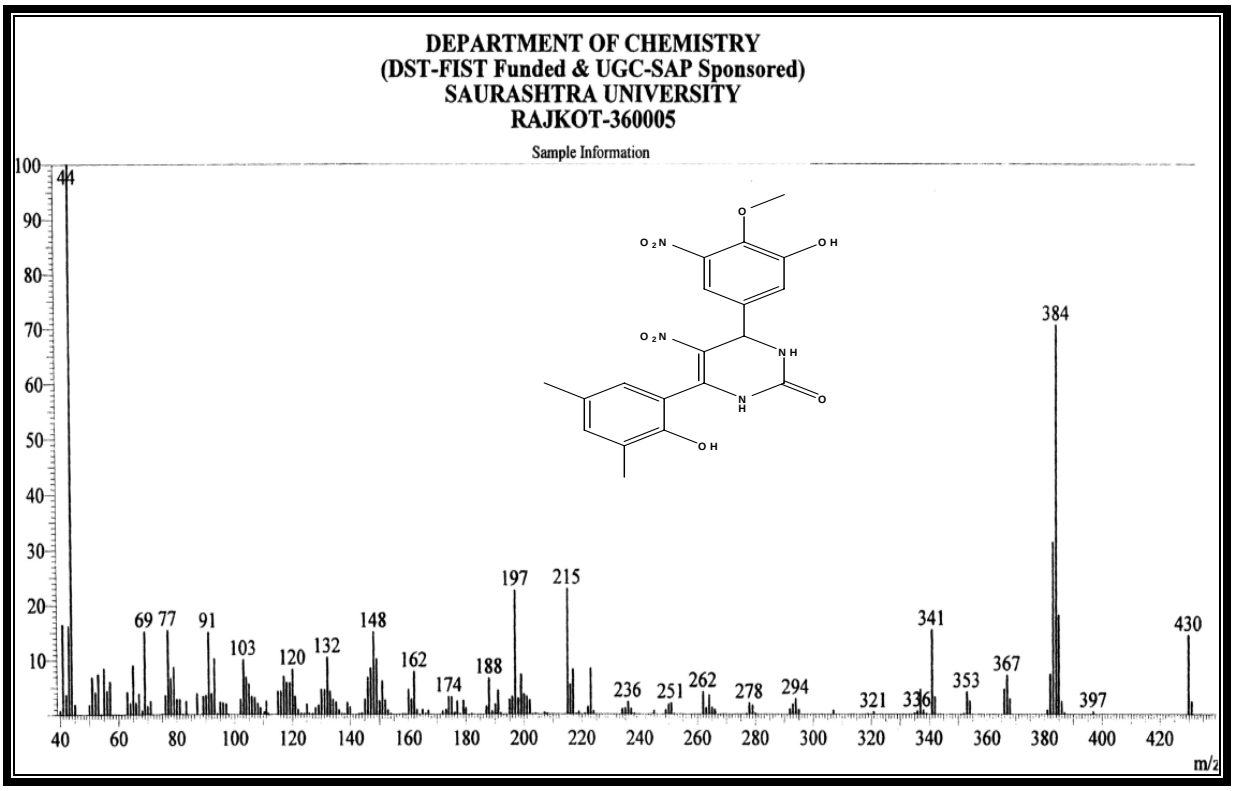
4.12.6 mass spectra of compound 5b



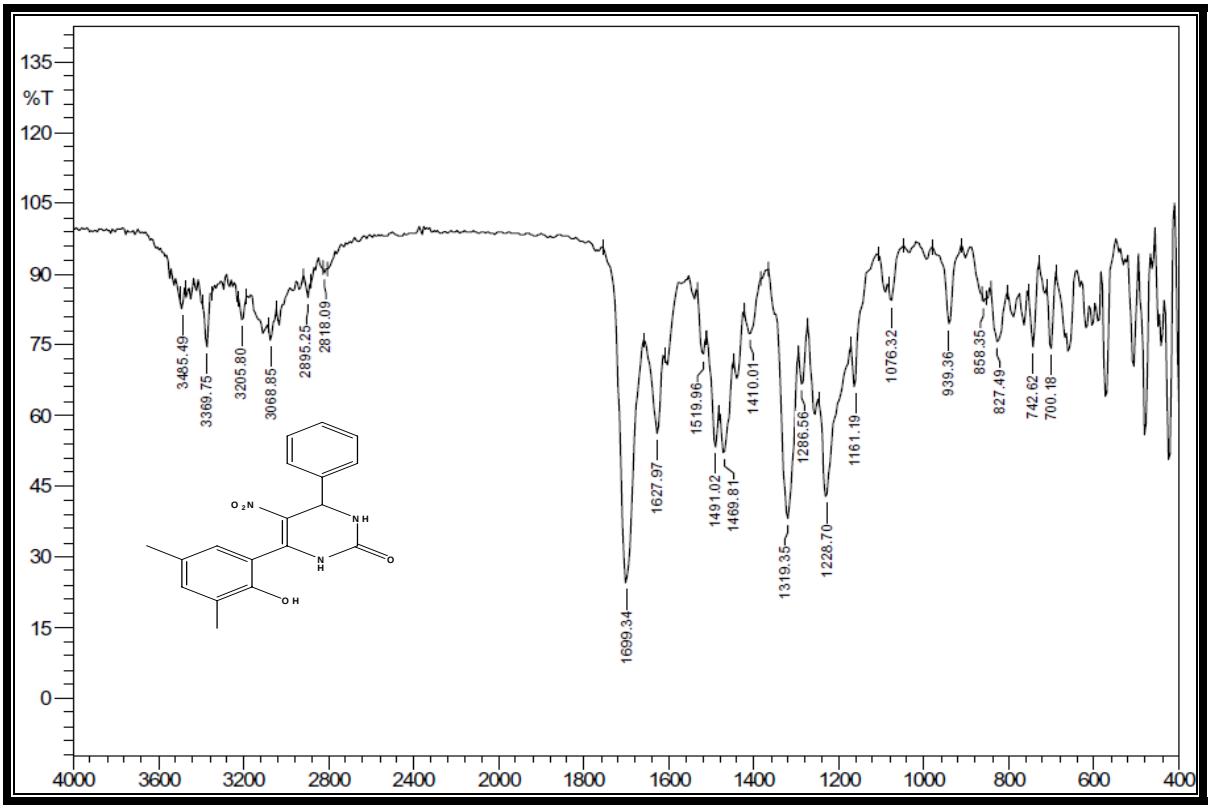
4.12.7 mass spectra of compound 5c



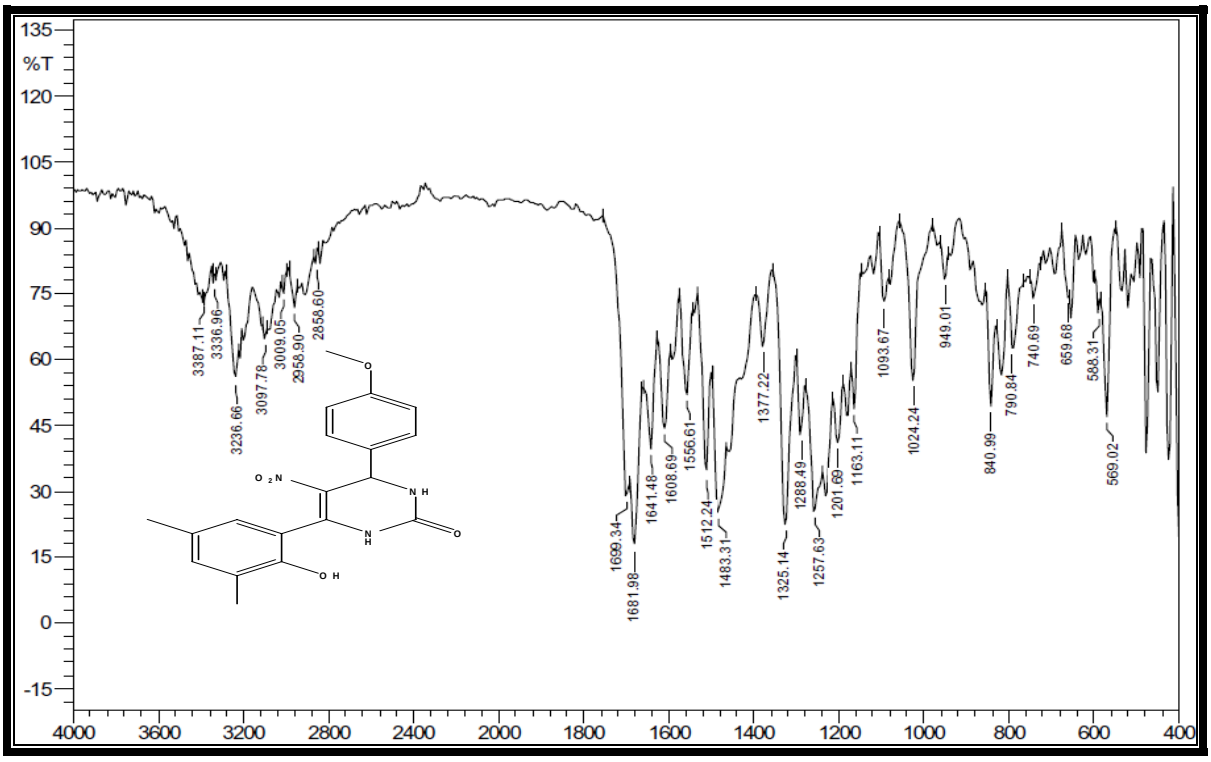
4.12.8 mass spectra of compound 5u



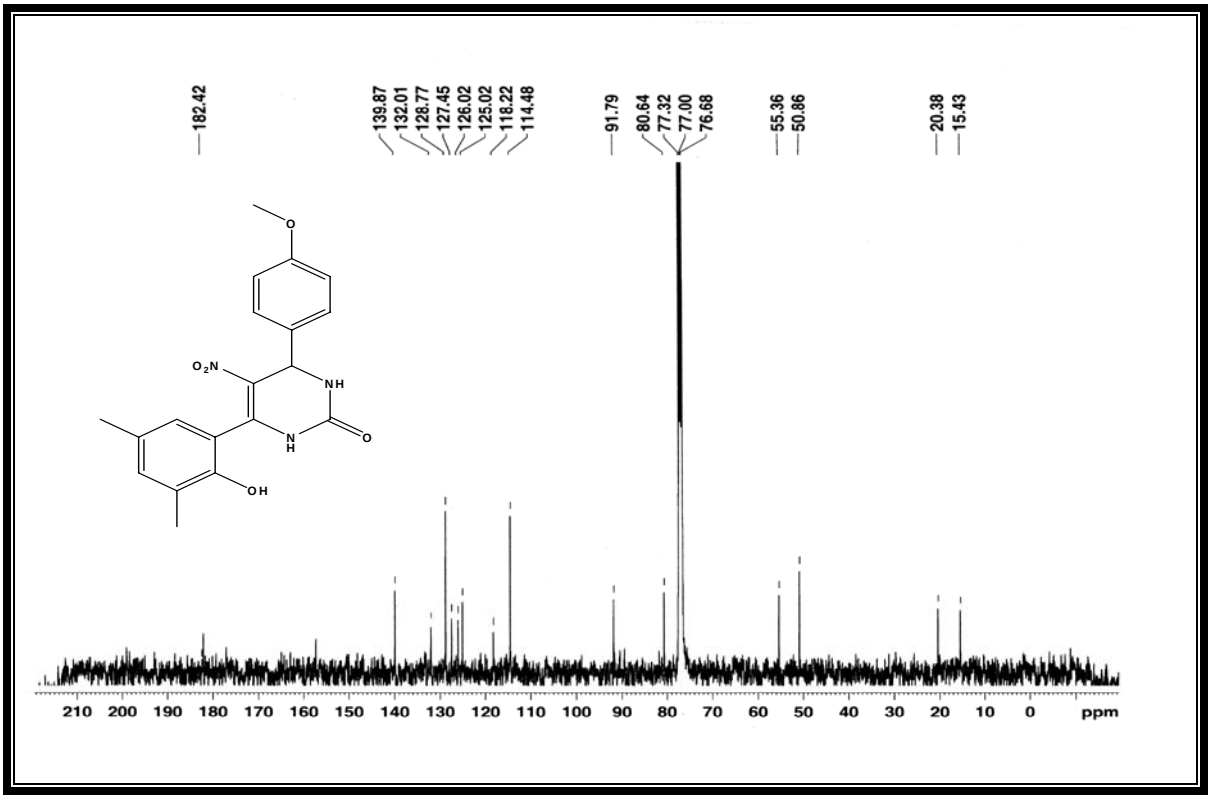
4.12.9 IR spectra of compound 5a



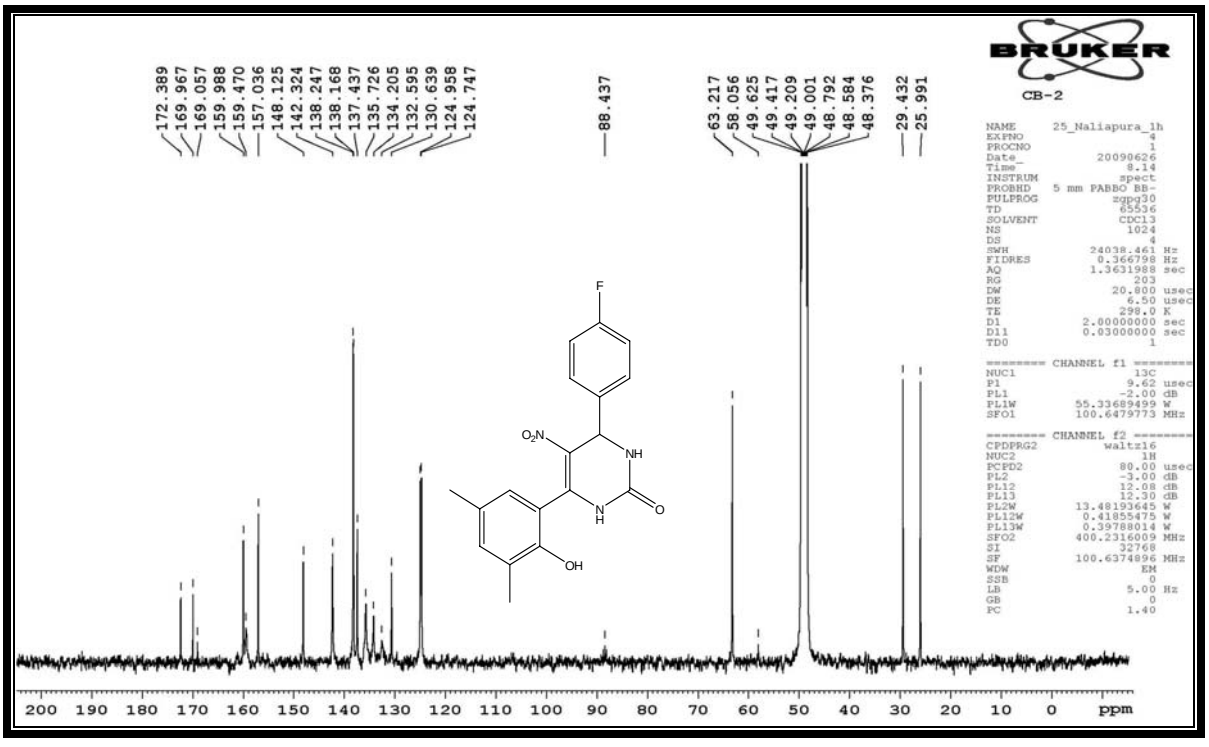
4.12.10 IR spectra of compound 5p



4.12.11 ^{13}C NMR spectrums of compound 5p



4.12.12 ^{13}C NMR spectrums of compound 5b



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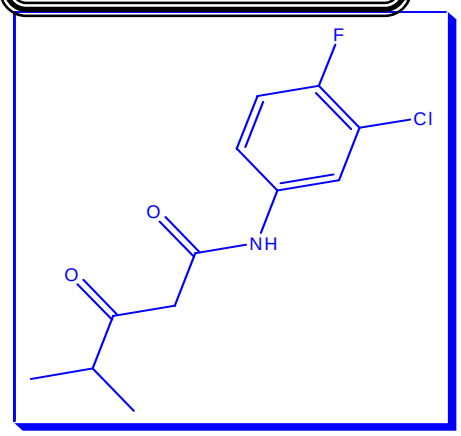
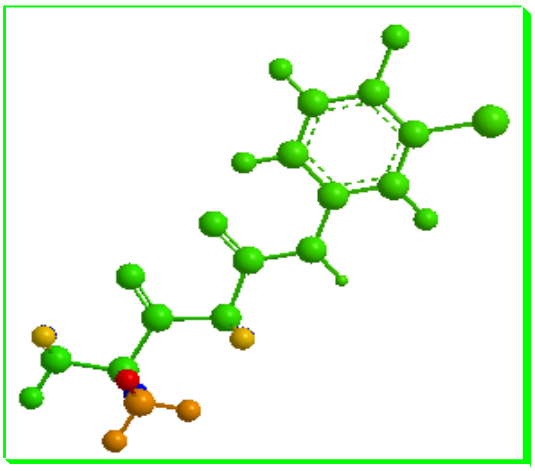
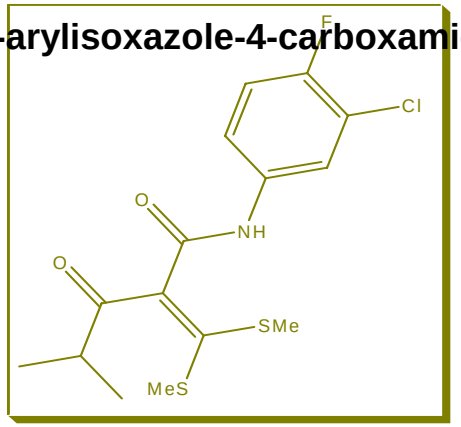
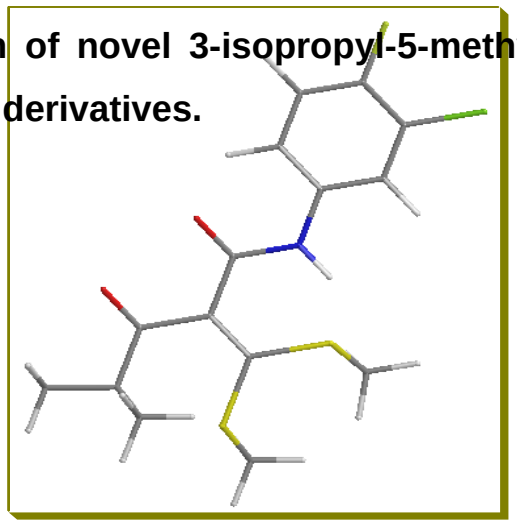
Chapter 5

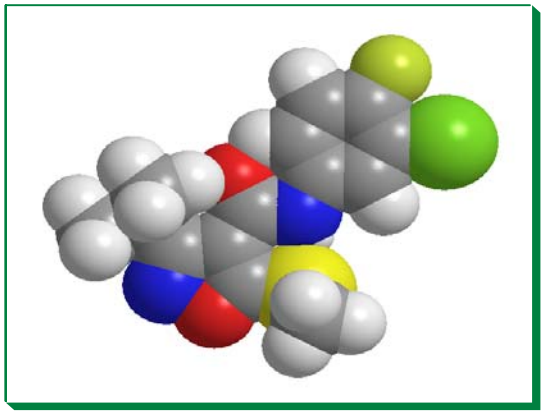


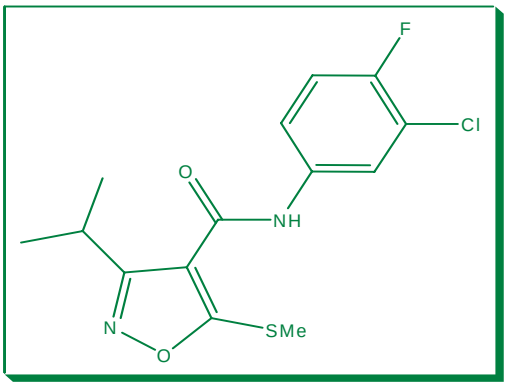


Synthesis and characterization of novel 3-isopropyl-5-methylthio-*N*-arylisoxazole-4-carboxamide derivatives.









5.1 INTRODUCTION

Isoxazole is a five member heterocyclic compound having two hetero atoms oxygen at position 1 and nitrogen at position 2. In 1888, Claisen have been first reported an isoxazole (**Figure 1**) for a product from the reaction of 1,3-diketone with hydroxylamine.[1] Subsequently a solid foundation for the chemistry of isoxazole was laid down by Claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions. Particularly in reducing or basic media, it becomes very highly labile.

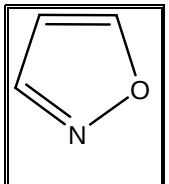


Figure 1

The next important contribution to the chemistry of isoxazoles was made by Quelico.[2] in 1945, when he began to study the formation of isoxazoles from nitrile *N*-oxide and unsaturated compounds.

5.2 Synthetic methods for isoxazoles

Isoxazoles can be synthesized by various methods, which are described as under.

1. Sabine Kuettel et al.[3] have been synthesized 4-(3-phenylisoxazol-5-yl)morpholine derivatives (**Figure 2**) by two synthetic routes, in which substituted acetophenones were reacted with carbon disulfide and methyl iodide in the presence of sodium hydride to give 4-phenoxyphenyl-2,2-bis(methylthio)vinylketones, followed by in situ cyclization of the resulting *N*,*S*-acetals with hydroxylamine.

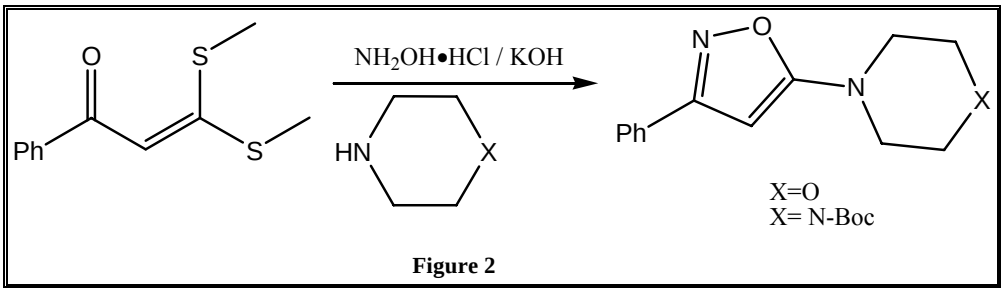


Figure 2

2. Pranab K. Mahata et al[4] have been synthesized 3-dimethoxymethyl-5-(methylthio) isoxazole derivative (**Figure 3**) shown to be useful three carbon synthon for efficient regiospecfic synthesis of a varity of five (isoxazole) with mask or unmask aldehyde functionality by cyclocondensation with bifunctional heteronucleophiles such as hydroxylamine.

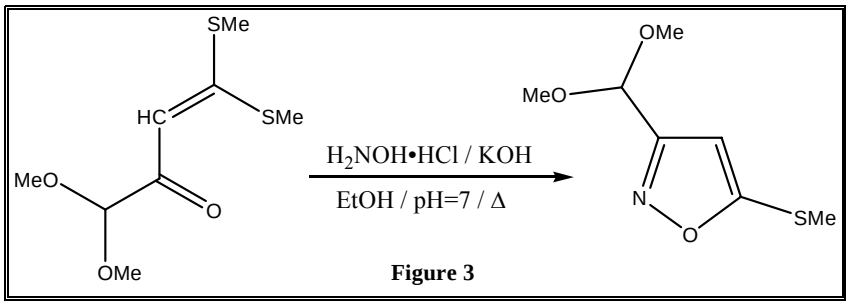


Figure 3

3. Scott R. Tweedie et al.[5] synthesized a palladium-catalyzed couplings of heteroaryl amines with aryl halides using sodium phenolate as the stoichiometric base. (**Figure 4**)

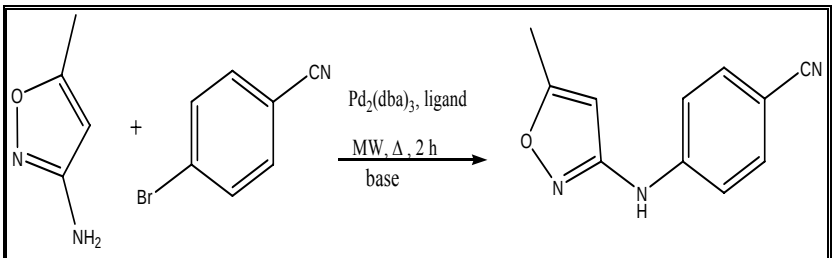


Figure 4

4. Issa Yavari et al.[6] synthesized of isoxazoles (**Figure 5**) through the reaction of activated acetylenes and alkyl 2-nitroethanoates in the presence of triphenylphosphine.

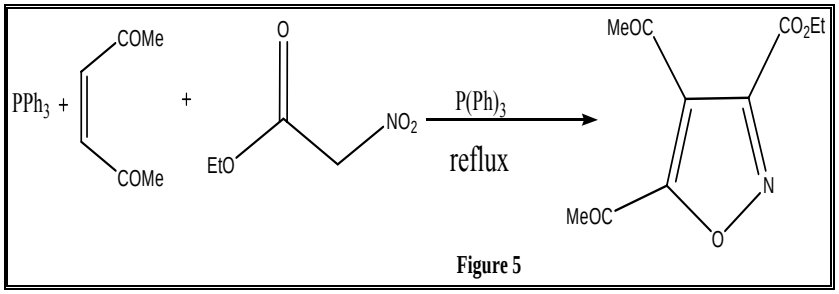


Figure 5

5. Jesse P. Waldo et al.[7] have been synthesized of isoxazoles (**Figure 6**) via electrophilic cyclization under mild reaction conditions by the reaction of 2-alkyn-1-one *O*-methyl oximes with ICl, I_2, Br_2, or PhSeBr.

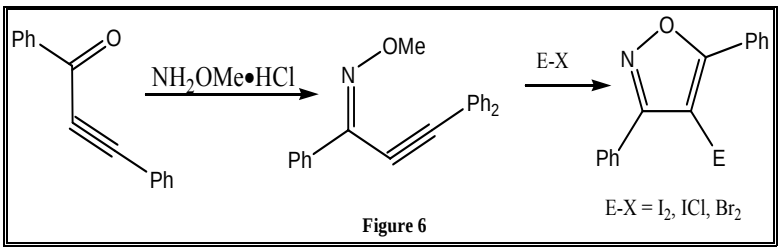


Figure 6

6. David J. Burkhart et al.[8] synthesized ethyl 4-acetyl-5-methyl-3-isoxazoyl carboxylate was smoothly lithiated at the 5-methyl position. The anion was quenched with a varity of electrophiles such as alkyl halides, aldehyde, TMSCl and Me_3SnCl in good to excellent yields.

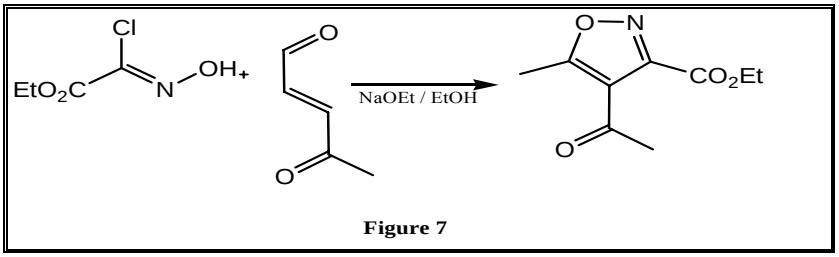


Figure 7

7. Keisuke Suzuki et al.[9] have synthesized functionalized isoxazole derivatives (**Figure 8**) by cyclocondensation of *C*-chlorooximes with cyclic 1,3-diketones.

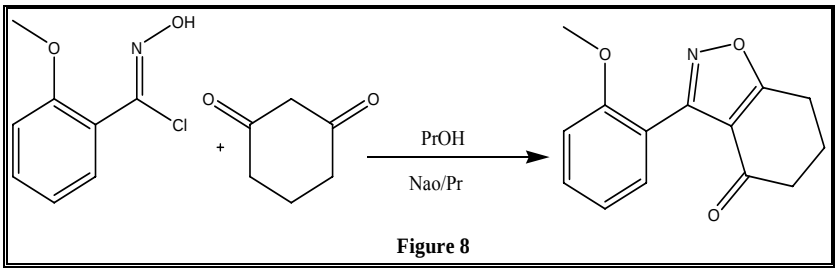


Figure 8

8. Solid phase synthesis of isoxazole derivatives based on amino acids was reported by Lidia De Luca and co-workers[10] in the presence of basic catalyst and dichloromethane used as a solvent. One-pot syntheses of polyfunctionalized isoxazoles[11] have been reported by the

reaction of dipyrrolidinium 3, 3-dimethylpentanedinitrile- 2, 4-dinitronate and acetyl chloride in benzene.

9. Mark Lauten et al.[12] have been prepared highly functionalized isoxazoles (**Figure 9**) by the reaction of *N*-acetoacetyl derivatives and hydroxyl amine hydrochloride in methanol.

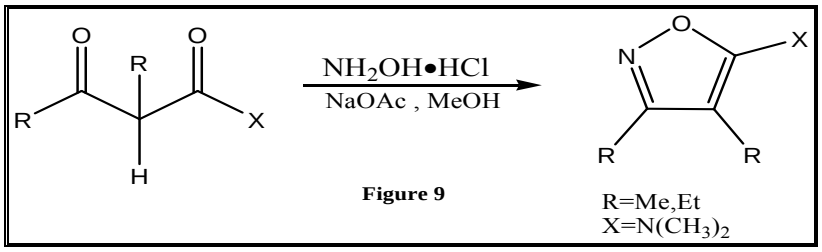


Figure 9

10. V. P. Kislyi et al.[13] were prepared 4-amino-5-benzoyl (acetyl) isoxazole-3-carboxamides (**Figure 10**) by cyclization of *α*-hydroxyimino nitriles *O*-alkylated with bromoaceto-phenones (bromoacetone). The purity of the target 4-aminoisoxazoles can be substantially increased by treating *O*-alkylated oximes with $LiClO_4$ before cyclization.

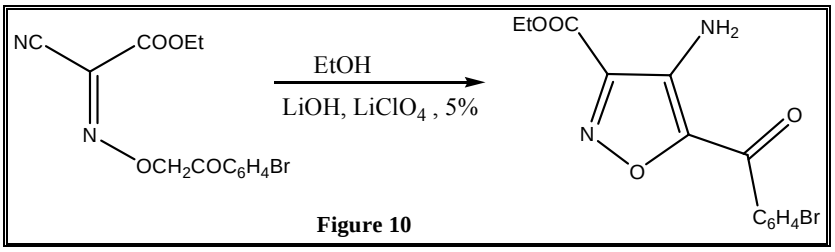


Figure 10

11. Wolfgang Holzer et al.[14] have synthesized 1,3-disubstituted 4-benzoyl-5-hydroxypyrazoles with phosphorusoxytrichloride affords the corresponding 4-benzoyl-5-chloropyrazoles. Reaction of the latter with hydroxylamine leads to oximes, which can be cyclized to novel 3-phenyl-6*H*-pyrazolo [4, 3-*d*] isoxazoles (**Figure 11**) by treatment with sodium hydride in dimethylformamide.

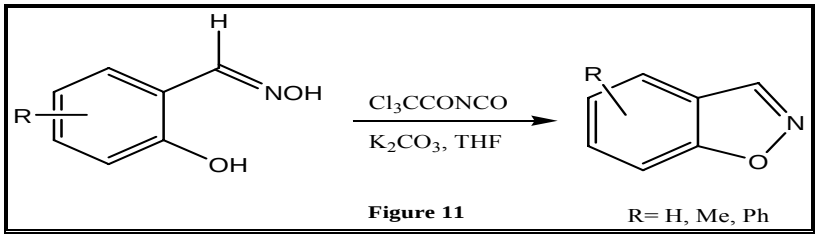


Figure 11

12. Matthew P. Bourbeau et al.[15] have been synthesized series of 4-alkyl-5-aminoisoxazoles (**Figure 12**) in high yield by nucleophilic addition of lithiated alkyl nitriles to α-chlorooximes. The scope and limitations of this reaction were examined by varying the nature of the nitrile and chloride oxime.

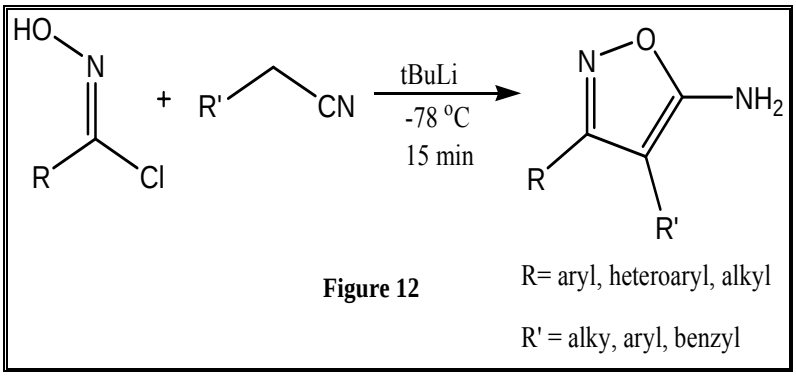


Figure 12

13. Kewei Wang et al.[16] synthesized of efficient and divergent one-pot synthesis of fully substituted isoxazoles in the presence of $POCl_3/CH_2Cl_2$, (**Figure 13**) were obtained from the cyclopropyl oximes via ring-opening and intramolecular nucleophilic vinylic substitution (S_NV) reactions.

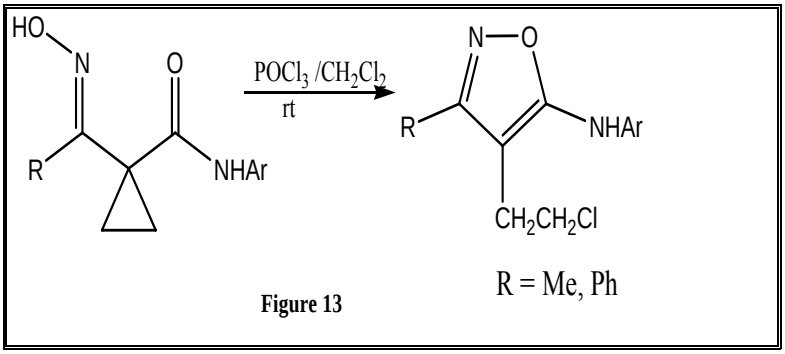


Figure 13

14. Haifeng Duan et al.[17] synthesized of a catalytic cascade synthesis of isoxazoline-*N*-oxide (**Figure 14**) was developed through proline-catalyzed nitroalkene activation. A large substrate scope was obtained with good to excellent yields. Mechanistic studies revealed intramolecular cyclization as the rate-determining step, giving only *trans* isomers in all cases.

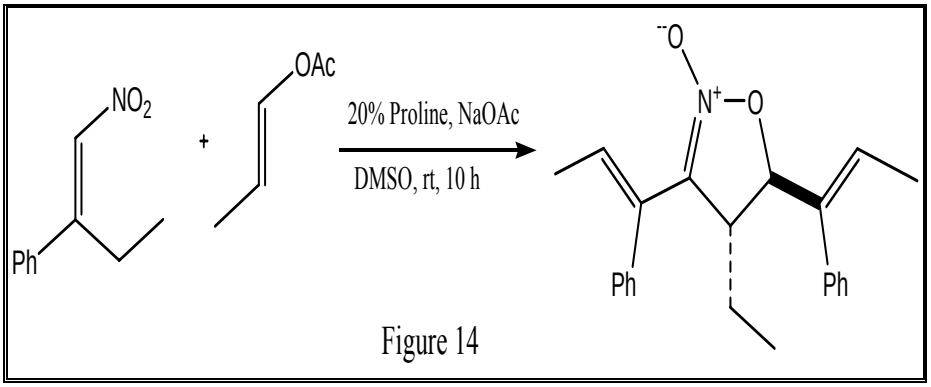


Figure 14

15. Giuseppe Daidone et al.[18] have synthesized several new 3-(isoxazol-3-yl)-quinazolin-4(3*H*)-one derivatives (**Figure 15**). Thus, synthesized starting from the 2-nitroaroyl chlorides and 3-amino-5-methylisoxazole in anhydrous chloroform. When compounds were treated with stannous chloride in aqueous hydrochloric acid the corresponding *N*-(5-methylisoxazol-3-yl)-2-aminobenzamide derivatives (**Figure 15**) were obtained.

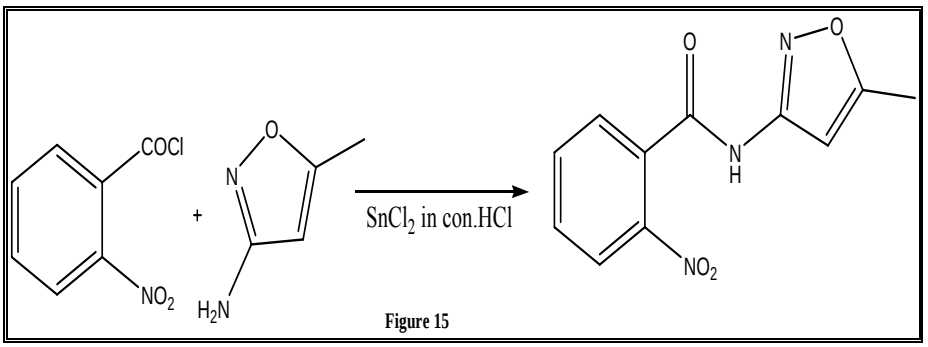


Figure 15

16. Okram Mukherjee Singh et al.[19] have synthesized the regioselective synthesis of isomeric isoxazoles 3-(2-arylcyclopropyl)-5-methylthio and 5-(2-arylcyclopropyl)-3-methylthio-isoxazoles is described (**Figure 16**).

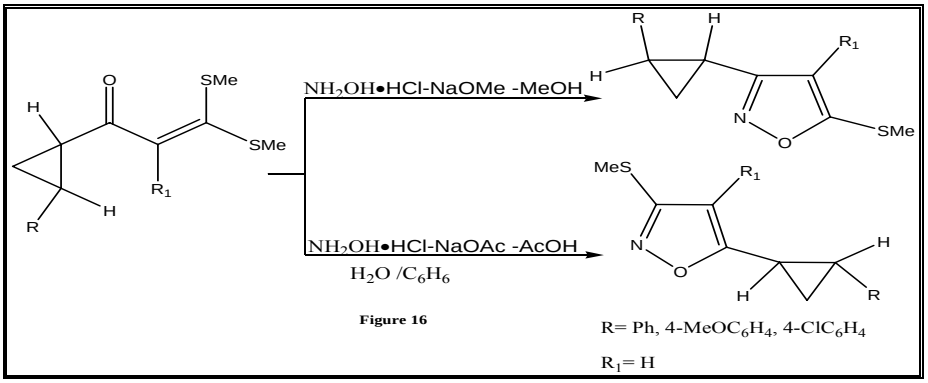


Figure 16

R= Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4

R_1= H

5.3 Mechanism

In dioxoketene dithioacetals systems the carbonyl carbon and *β*-carbon atoms can also be regarded as hard and soft electrophilic centers, since the carbonyl is adjacent to the hard-base oxygen while the *β*-carbon is flanked by the soft-base thiomethyl groups[20] (**Figure 17**). Thus, the nucleophile of hydroxylamine hydrochloride attack on *β*-carbon of systems and formed heterocyclic product by removal of thiomethyl group as good leaving group.

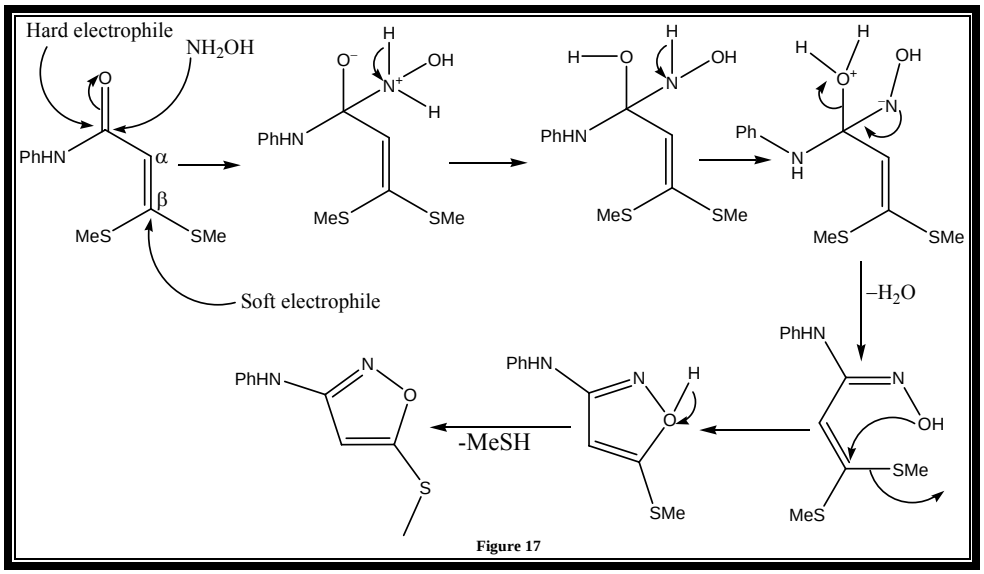


Figure 17

5.4 Biological activity of isoxazole

The biological activity of substituted isoxazoles[21] has made them a focus of medicinal chemistry over the years. Isoxazoles are potent, selective agonists at human cloned dopamine D4 receptors[22] and exhibit $GABA_A$ antagonist,[23] analgesic,[24] antiinflammatory,[24] ulcerogenic,[24] antimicrobial,[25] antifungal,[25] COX-2 inhibitory,[26] antinociceptive,[27] and anticancer[28] activity.

5.4.1 Cyclooxygenase-2 (COX-2) inhibitors

Some *N*-phenyl and *N*-benzyl-substituted (Figure 18) amido analogs of cyclooxygenase (COX-2) selective tricyclic non-steroidal anti-inflammatory drugs have been synthesized with the aim to obtain information on the structural requirements for the COX-inhibitory activity[29]. Compounds were tested in vitro for their inhibitory properties only towards COX-2 enzyme by measuring prostaglandin E2 (PGE2) production on activated

J774.2 macrophages. Some of the new compounds showed a modest activity, with percentage inhibition values near 30% at a concentration of 10 μM. These data have been tentatively explained by a conformational study which indicates that at least the *N*-phenyl-substituted amides present steric hindrances which may prevent a good interaction with COX-2 active site.

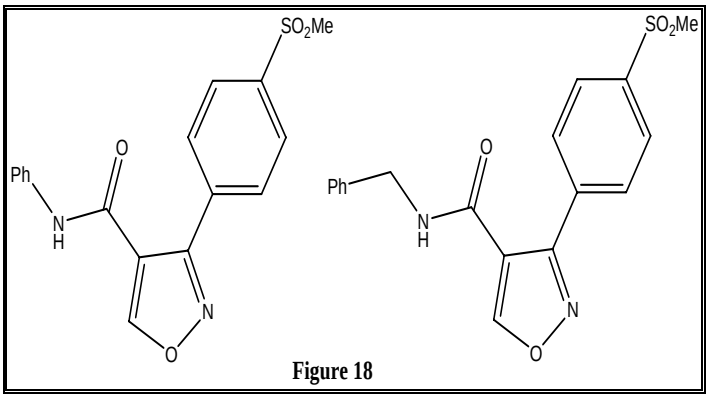


Figure 18

For the new compounds (**Figure 18)** the inhibitory activity towards COX-2, which constitutes the ideal target of an anti-inflammatory drug, was evaluated in vitro by measuring the PGE2 production on activated J774.2 macrophages. The results were reported in Table 1 together with those obtained in the same type of test with Celecoxib and with the previously studied cyclopentenyl and thienyl oxime-ethers. As it can be seen, only compounds **(Figure 18)** at a concentration of 10 μM showed a modest activity, with percentage inhibition values close to 30%, while the other analogs resulted practically inactive. In the same experimental conditions, the benzyloxyimino-ethers showed IC_{50} values in the μM range. These data indicate that in the field of the analogs of the tricyclic anti-inflammatory drugs, an amidic group, either *N*-phenyl or *N*-benzyl-substituted, as the ones present in (**Figure 18)** is less effective than MAOMM in replacing the aryl lacking of sulfurated moiety of compounds.

Aldo Balsamo et al[30] have repotted several heteroaromatic analogues of (2-aryl-1-cyclopentenyl-1-alkylidene)-(arylmethyloxy)amine COX-2 inhibitors (**Figure 19**), in which the cyclopentene moiety was replaced by pyrazole, thiophene or isoxazole ring, were synthesized, in order to verify the influence of the different nature of the central core on the COX inhibitory properties of these kinds of molecules. Among the compounds tested, only the 3-(*p*-methylsulfonylphenyl) substituted thiophene derivatives, showed a certain COX-2 inhibitory activity, accompanied by an appreciable COX-2 versus COX-1 selectivity. Only one of the 1-(*p*-methylsulfonylphenyl)pyrazole compounds displayed a modest inhibitory

activity towards both type of isoenzymes, while the pyrazole 1-(p-aminosulfonylphenyl) substituted 12 proved to be significantly active only towards COX-1. All the isoxazole derivatives were inactive on both COX isoforms.

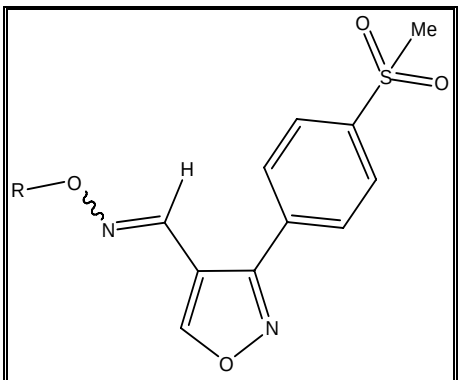


Figure 19

Amgad G. Habeeb et al[31] also repotted a 4,5-diphenyl-4-isoxazolines **(Figure 20)** possessing a variety of substituents (H, F, MeS, $MeSO_2$) at the para position of one of the phenyl rings were synthesized for evaluation as analgesic and selective cyclooxygenase-2 (COX-2) inhibitory anti-inflammatory (AI) agents. Although the 4,5-phenyl-4-isoxazolines **(Figure 20)**, which do not have a C-3 Me substituent, exhibited potent analgesic and AI activities, those compounds evaluated were not selective inhibitors of COX-2. In contrast, 2,3-dimethyl-5-(4-methylsulfonylphenyl)-4-phenyl-4-isoxazoline exhibited excellent analgesic and AI activities, and it was a potent and selective COX-2 inhibitor (COX-1, IC_{50}) 258 μM; COX-2, IC_{50}) 0.004 μM).

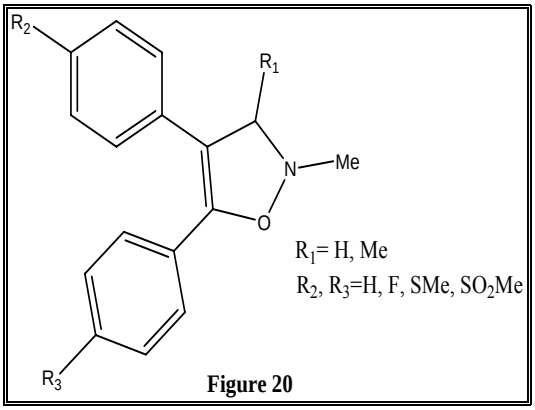


Figure 20

A related compound **(Figure 20)** having a F substituent at the para position of the 4-phenyl ring was also a selective (SI =3162) but less potent (IC_{50} =0.0316 μM) inhibitor of COX-2 than 2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole. A

molecular modeling (docking study) for 4-(4-fluorophenyl)-2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole showed that the S atom of the $MeSO_2$ substituent is positioned about 6.46 Å inside the entrance to the COX-2 secondary pocket (Val^{523}) and that a C-3 Me (2,3-dihydro-2,3-dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole, 4-(4-fluorophenyl)-2,3-dihydro-2,3dimethyl-5-(4-(methylsulfonyl)phenyl)-4-phenylisoxazole) central isoxazoline ring substituent is crucial to selective inhibition of COX-2 for this class of compounds.

John J. Talley et al[32] have repotted *N*-[[(5-Methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonyl]propanamide, sodium Salt, parecoxib sodium: A potent and selective inhibitor of COX-2 for parenteral administration.

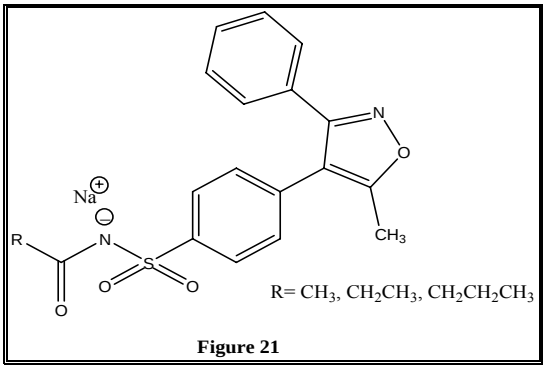


Figure 21

Among the most potent and selective COX-2 inhibitors that have been identified is the isoxazole sulfonamide valdecoxib (**Figure 21**). Against recombinant human cyclooxygenase isoforms, showed the following activity: hCOX-1 IC_{50}= 140 μM and hCOX-2 IC_{50}= 0.005 μM. In addition, sulfonamide valdecoxib possesses exceptional anti-inflammatory activity in vivo.[33] our strategy to develop an injectable COX-2 inhibitor commenced with the idea of identifying a water-soluble prodrug of sulfonamide valdecoxib that would undergo biotransformation in vivo. To test whether an acylated sulfonamide[34,35] would serve as a prodrug for sulfonamide valdecoxib. Against the recombinant isoforms of human cyclooxygenase, sodium salt of isoxazole was found to show very weak inhibitory activity, hCOX-1 IC_{50} →100 μM and hCOX-2 IC_{50} → 20 μM. However, in the carrageen an air pouch model of inflammation,[36] showed potent anti-inflammatory activity after intravenous, intramuscular, or oral administration, ED_{50} = 0.5 mg/kg.

5.4.2 Antitumor and chemosensitizing activities

Curcumin (CUR) can be considered as a good lead compound for the design of new anticancer drugs. Further, structure–activity relationship studies may clarify the importance of the redox activities in the antitumor effects of the drug. We have elaborated the *α,β*-unsaturated 1,3-diketone moiety of CUR into the isoxazole (ISO) derivatives (**Figure 22**).[37] These derivatives should be much less prone to nucleophilic addition than CUR and benzyl mercaptan addition analyses showed that indeed they do not form isolable conjugated products. When compared with CUR, ISO exhibited increased cell growth inhibitory and pro-apoptotic effects in liver cancer HA22T/VGH cells as well as in other tumor cell types; in contrast to CUR, the antitumor effects of ISO were not influenced by concomitant administration of *N*-acetylcysteine, as a source of -SH groups, or buthionine sulfoximine, as an inhibitor of glutathione synthesis. Further, treatment with CUR, but not with ISO, significantly decreased the content of reduced glutathione in the HA22T/VGH cells. Finally, ISO lacked the ability of the parent compound to sensitize the HA22T/VGH cells to cisplatin (CIS), an effect which appeared to occur through an interaction of CUR and CIS at the level of the –SH groups. Thus, the ability of interacting with cell thiols might not be requested for the more potent antitumor activities of new diketone modified CUR derivatives, which might rely on other mechanisms, though possibly devoid of chemosensitization capabilities.

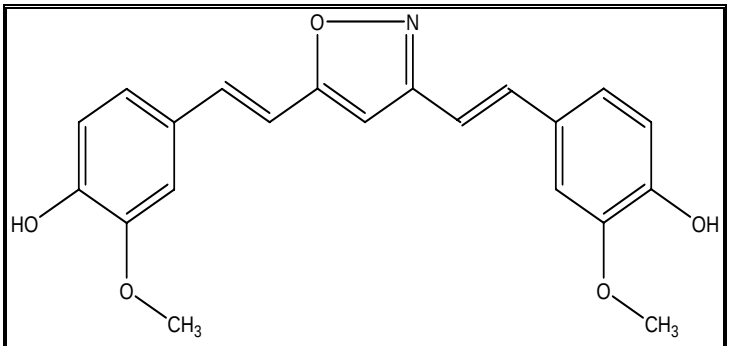


Figure 22

Curcumin (diferuloylmethane) (CUR), a polyphenoliccompound extracted from *Curcuma longa L*. and present in curry spice, has a long story of use in Indian medicine for anti-inflammatory and other therapeutic purposes; it has exhibited definite tumor preventive and suppressive activities inmany in vitro or in vivo models.[38] CUR is endowed with a diketone function, which appears to be important for its antitumor activity:[39-41] also depending on the dose, the compound may show complex either pro-oxidant or anti-oxidant

effects, which both may, at least in part, be linked to this structural moiety.[42-43] In the lower concentration, 'chemo preventive', range, CUR behaves mainly as an anti-oxidant, although this activity may possibly provide negative interactions with other chemotherapeutic agents.[44-45] At higher concentrations, the *α,β*-unsaturated 1,3-diketone, as a Michael acceptor, can form adducts with the –SH groups and generate reactive oxygen species.[46] This may lead to induction of apoptosis through different possible mechanisms involving loss of mitochondrial membrane potential, endoplasmic reticulum stress, activation of terminal caspases or also other mitochondria- and caspase-independent pathways.[47-50]

5.4.3 Anti-HIV activity

As a continuation of efforts to replace the metabolically labile methyl esters of lead alkenyldiarylmethanes(ADAMs) with stable bioisosteres, compounds bearing benzo[*d*]isoxazole and oxazolidine-2- one rings were designed and evaluated as a new series of potent HIV-1 non-nucleoside reverse transcriptase inhibitors with anti-HIV activity. All of the resulting ADAMs were found to inhibit HIV-1 RT with poly (rC) oligo(dG) as the template primer. The most promising compound in this series was ADAM (Figure 23), with EC_{50} values of 40 nM (vs HIV-1_{RF}) and 20 nM (vs HIV-1_{IIIB}).[51] Methyl 5-((*Z*)-5-(methoxycarbonyl)-1-(3-methoxy-7-methylbenzo[d]isoxazole-5-yl)pent-1-enyl-2-methoxy-3-methylbenzoate also inhibited HIV-1 reverse transcriptase with an IC_{50} of 0.91 μM. ADAM 4 has an antiviral EC_{50} of 0.6 μM in CEM-SS cells and a plasma half-life of 51.4 min.

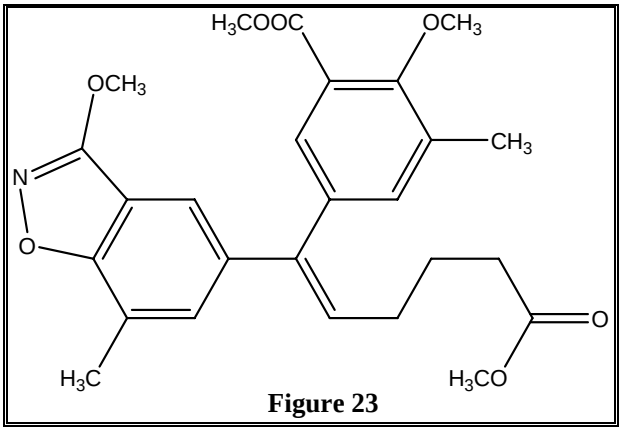


Figure 23

Human immunodeficiency virus type 1 (HIV-1) is the etiological agent of acquired immunodeficiency syndrome (AIDS), one of the world's most serious health problems with about 33 million people infected worldwide in 2007. The reverse transcriptase (RT) of HIV-1

is an essential enzyme in HIV replication and has been a key target in anti-AIDS drug discovery. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, and efavirenz have been approved by the Food and Drug Administration (FDA) for the treatment of AIDS.[52] They are very useful drugs in combination therapy with nucleoside analogues (NRTIs) and protease inhibitors (PIs)[53-54] for the treatment of AIDS. However, a number of problems still remain with these agents. In particular, significant resistance has developed against these drugs. Therefore, considerable effort has been expended to develop new NNRTIs that would overcome the current drug resistance. More than 30 structurally different classes of molecules have been reported as NNRTIs.[52-54] Recently, the NNRTI etravirine was approved by the FDA for treatment of antiretroviral drug-resistant HIV infections. The cytotoxicities of the newly synthesized ADAMs were determined along with their abilities to inhibit the cytopathic effect of HIV-1 in cell culture. The inhibition of HIV-1 RT by the ADAMs, and their metabolic stabilities in rat plasma were also investigated.

5.4.4 $GABA_A$ antagonists

A series of 4-aryl-5-(4-piperidyl)-3-isoxazolol $GABA_A$ antagonists have been synthesized and pharmacologically characterized.[55] The *meta*-phenyl-substituted compounds and the *para*-phenoxy-substituted compound (Figure 24) all display high affinities (K_i = 10-70 nM) and antagonist potencies in the low nanomolar range (K_i = 9-10 nM). These potencies are significantly higher than those of previously reported 4-PIOL antagonists and considerably higher than that of the standard GABAA antagonist SR 95531.

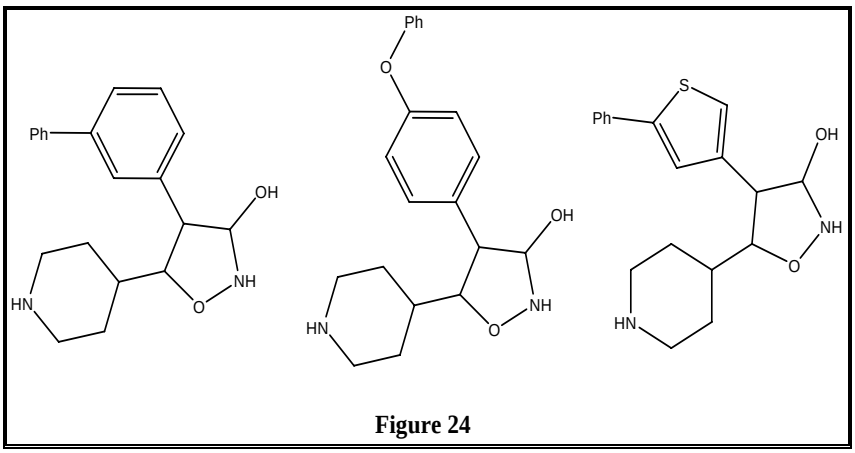


Figure 24

4-Aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system, exerts its effect in the central nervous system through two different classes of receptors, the ion tropic $GABA_A$ and $GABA_C$ receptors and the metabotropic $GABA_B$ receptors. Especially the $GABA_A$ receptors have attracted much attention as therapeutic targets for the treatment of conditions such as anxiety, epilepsy, and sleep disorders.[56]

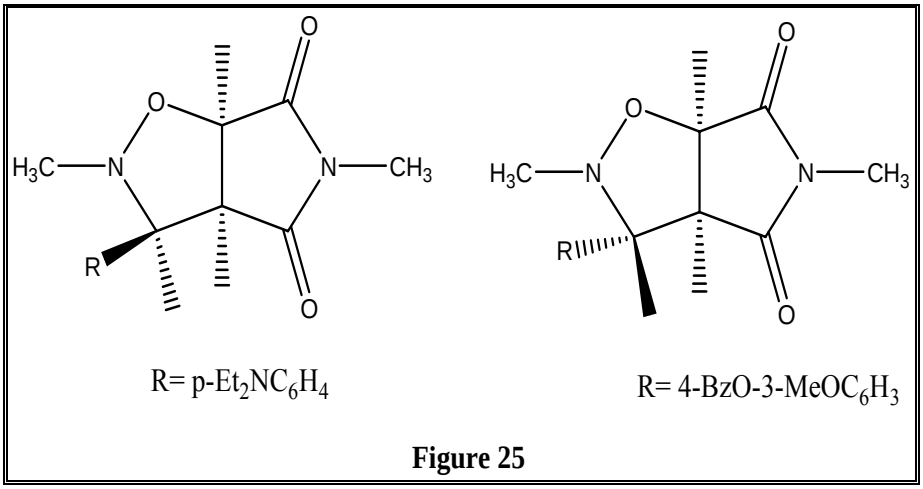
The $GABA_A$ receptor is a member of a super family of ligandgated ion channels, which also comprises the nicotinic acetylcholine, the glycine, and the serotonin ($5\text{-}HT_3$) receptors. The $GABA_A$ receptor is a heteropentameric transmembrane allosteric protein complex, and in addition to the GABA recognition site, it contains a considerable number of separate but allosterically interacting binding sites. This is reflected in the structural diversity of compounds acting at the $GABA_A$ receptors, including important drugs such as benzodiazepines, neurosteroids, and barbiturates.

In contrast to the allosteric modulatory sites, the GABA binding site has very distinct and specific structural requirements for recognition and activation. Thus, very few different classes of structures have been reported. Within the series of compounds showing agonist activity at the $GABA_A$ receptor site are the selective $GABA_A$ agonists muscimol[57] and 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol,[57-58] which have been used for the characterization of the $GABA_A$ receptors (Figure 24).[59] Recently, 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol has been shown to be functionally selective for a subpopulation of $GABA_A$ receptors and is currently in clinical trials as a therapeutic for the regulation of sleep.

5.4.5 Antibacterial activity

The synthesis of 2,3,5-substituted perhydropyrrolo[3,4-*d*]isoxazole-4,6-diones has been accomplished by the cycloaddition reaction of *N*-methyl-*C*-arylnitrones with *N*-substituted maleimides.[60] The compounds were screened for their antibacterial activities and most of them exhibited activity against *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (ATCC 25923). Figure 25 were found fairly effective against *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (ATCC 25923) with MIC values of 25 and 50 μg/ml. With the changes of *cis* isomers of the compounds to *trans*, their antibacterial activities also changed against the bacteria studied. First, pharmacophoric

fragments had been calculated in accordance with the rules of the electronictopological method (ETM). Next, both active compounds and pharmacophores had been projected to the nodes of Kohonen's self-organizing maps (SOM) to obtain the weights of pharmacophore fragments as numerical descriptors, that were used after this for the associative neural networks (ASNN) training. A model for the activity prediction was developed as the result of training the ASNNs.



R= p-$Et_2NC_6H_4$ R= 4-BzO-3-$MeOC_6H_3$

Figure 25

5.4.6 Anticonvulsant activity

Due to the exceptional anticonvulsant activity displayed by substituted aniline enaminones, related pyridine derivatives[61] and phenothiazines synthesized, the further investigation of various aromatic heterocycles was undertaken. Condensation of cyclic 1,3-diketo esters with 3 and 5 aminoisoxazole derivatives led to a series of potent anti-maximal electroshock (MES) analogues, three of which occurred in the 3-amino series: ethyl ester, orally (po) active in rats [ED_{50} 68.9 mg kg^{-1}, TD50 > 500 mg kg^{-1}, protective index ($PI=TD_{50}/ED_{50}$) > 49.6]; methyl ester, ED_{50} 68.9 mg kg^{-1} intraperitoneally (ip) in mice, TD_{50} >500 mg kg^{-1}, PI >7.3, and *tert*-butyl ester, ED_{50} 28.1 mg kg^{-1} po in rats, TD_{50} > 500 mg kg^{-1}, PI > 17.8. Sodium channel binding studies, as well as evaluations against pentylenetetrazol, bicuculline, and picrotoxin on isoxazole were all negative, leading to an unknown mechanism of action. X-ray diffraction patterns of a representative of the 3-amino series (**Figure 26**) unequivocally display the existence of intramolecular hydrogen bonding of the nitrogen to the vinylic proton in the cyclohexene ring, providing a pseudo three ring structure which was also shown previously with the vinylic benzamides. Physicochemical-

permeability across the BBB suggested an efflux mechanism for the previously synthesized aniline enaminones, but not with isoxazole.

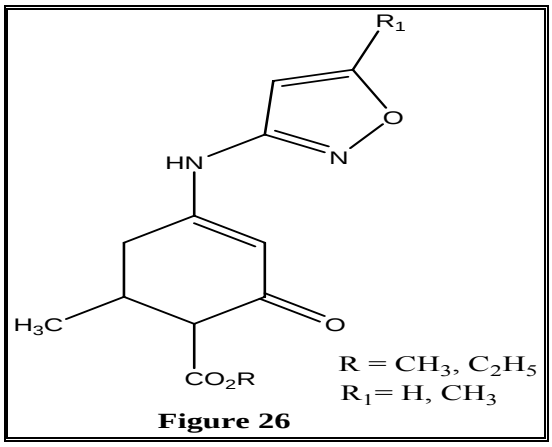


Figure 26

5.4.7 Antithrombotic activity

The 3-substituted phenyl-5-isoxazolecarboxaldehydes[62] has been identified as activated aldehydes for the generation of isoxazole-based combinatorial libraries on solid phase through automation. Three highly functionalized isoxazole-based libraries comprising of (**Figure 27**) compounds each have been synthesized in parallel format using Baylis Hillman reaction, Michael addition, reductive amination and alkylation reactions. With an objective of lead generation all the three libraries were evaluated for their antithrombin activity in vivo.

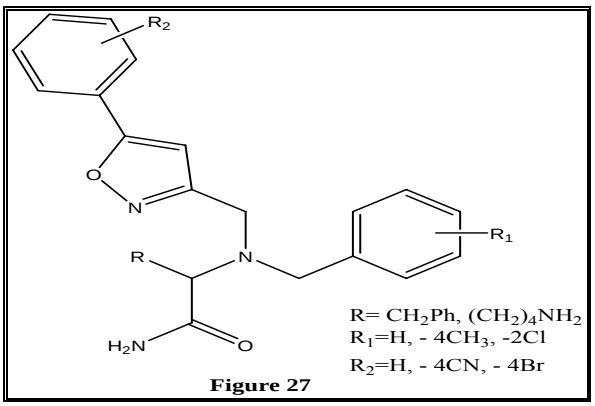


Figure 27

Some of the biological activities ascribed to isoxazole derivatives includes antithrombotic, PAF antagonist, hypolipidemic, nootropic, immunomodulator, antiviral, antiobesity and CNS modulation.[63] The substituted isoxazoles, are also considered to be important synthons due to their versatility towards chemical transformations to useful

synthetic intermediates such as 1,3-dicarbonyl, 1,3-iminocarbonyl and γ-amino alcohols. The significance of this class of molecules gets further impetus due to their involvement as intermediates in the synthesis of various natural products.[64] All the compounds obtained were evaluated for their antithrombotic activity in vivo. Swiss mice (20–25 g, from CDRI animal colony) were used in a group of at least 10 animals each. Thrombosis was induced by infusion of a mixture of 15 mg collagen and 5 mg adrenaline in a volume of 100 mL into the tail vein of each mouse. This resulted either death or hind limb paralysis of 100% animals. The compounds were administered at 30 μmol/kg by oral route 1 h prior to the thrombotic challenge. The antithrombotic effects of these compounds were assessed by the percentage protection offered by these agents to mice from death or paralysis following thrombotic challenge using aspirin as a standard.

5.4.8 Antinociceptive activity

A number of arylpiperazinylalkylpyridazinones[65] structurally related to the previously described lead A (**Figure 28**) (5-{[4-(3-chlorophenyl)piperazin-1-yl]-propyl}-3-methyl-7-phenylisossazolo[4,5-*d*]pyridazin-4-(5*H*)-one) were synthesized and tested for their analgesic activity. Many of the tested molecules, at the dose of 20 mg kg^{-1} p.o., showed high antinociceptive activity, in particular, substituted lead a compound which was able to reduce the number of abdominal constrictions by more than 50% in writhing test. The pharmacological investigation of lead (**Figure 28**) led us to clarify the mechanism of action of this compound, showing that it carries out its analgesic action through the inhibition of reuptake of noradrenaline. The antinociception of some of the most interesting new molecules was completely prevented by pretreatment with α_2-antagonist yohimbine, suggesting the involvement of α_2-adrenoceptors, as with prototype (Figure 28).

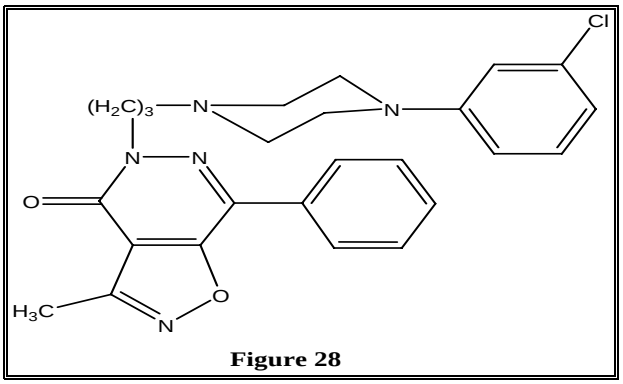


Figure 28

The present results indicate the involvement of α_2-adrenoceptor and, in particular, of the subtype α_2A. (**Figure 28**) increases the pain threshold, and this effect is imputable to an amplification of adrenergic neurotransmission due to an inhibition of noradrenaline uptake.

5.4.9 Potent dual inhibitor of *p*38*α*

Christian Peifer et al[66] reported on the discovery of isoxazole (**Figure 29**) as a potent dual inhibitor of *p*38*α* (IC_{50}= 0.45 μM) and CK1*δ* (IC_{50}= 0.23 μM). Because only a few effective small molecule inhibitors of CK1 have been described so far, we aimed to develop this structural class toward specific agents. Molecular modeling studies comparing p38*α*/CK1*δ* suggested an optimization strategy leading to design, synthesis, biological characterization, and SAR of highly potent compounds including possessing differentiated specificity. Selected compounds were profiled over 76 kinases and evaluation of their cellular efficacy showed 18 (CKP138) to be a highly potent and dual-specific inhibitor of CK1δ and p38α.

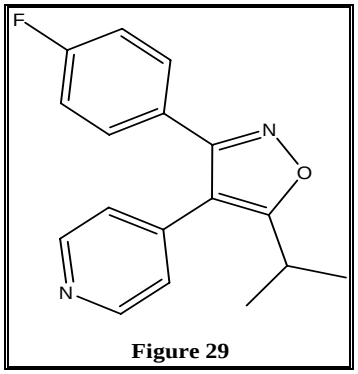


Figure 29

Small molecule inhibitors of various protein kinases are utilized extensively in research and drug development. The human kinome consists of more than 500 protein kinases, and kinase inhibitors typically bind in the highly conserved ATP pocket of these enzymes.[67] Thus the specificity of ATP competitive kinase inhibitors is of significant interest and represents a crucial factor for their use in, e.g., signal transduction research or therapeutic applications.

5.5 Aim of current work

The biological activity of substituted isoxazoles[21] has made them a focus of medicinal chemistry over the years. Isoxazole are potent, selective agonists at human cloned dopamine

D4 receptors[22] and exhibit GABAA antagonist,[23] analgesic,[24] antiinflammatory,[24] ulcerogenic,[24] antimicrobial,[25] antifungal,[25] COX-2 inhibitory,[26] antinociceptive,[27] and anticancer[28] activity.

Many synthetic methods have been employed in the synthesis of isoxazoles,[68] including reactions of hydroxylamine with 1,3-dicarbonyl compounds,[69] *α,β*-unsaturated carbonyl compounds,[70] and *α,β*-unsaturated nitriles.[71] The reaction of an oxime-derived dianion and an ester[72] or amide[73] also provides isoxazoles. [3 + 2] Cycloaddition reactions between alkynes and nitrile oxides have also been developed.[74] Ketene dithioacetals bearing the cyano, amide, thioamide, or alkoxycarbonyl group at the *α*-position are extremely interesting electrophilic reagents for the introduction of three or two carbon units into the ring of heterocyclic compounds.[75, 76]

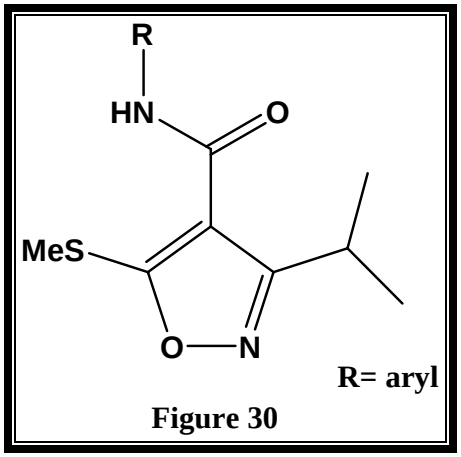


Figure 30

We have recently developed different successful approaches for synthesis of new ketene *S,S*-acetals as starting from acetoacetanilides (**2a-s**). In an extension of this work, we are now reporting a synthesis of some novel ketene *S,S*-acetals and their use in the synthesis of functionalized isoxazole derivatives (**4a-s**) (**Figure 30**).

5.6 Chemistry

α-Oxoketene dithioacetals (**Figure 31, 32, 33**) especially the dimethylthioacetals have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic compounds.[77, 78] Ketene dithioacetals, in the presence of various regents, undergo different types of reactions to yield other heterocyclic compounds, e.g., isoxazole, pyrazole, thiophenes, pyrimidines, pyridines,

etc. Consequently we were interested in surveying the synthetic utility of ketene dithioacetals.

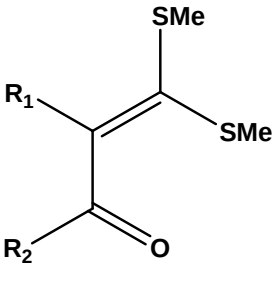


Figure 31

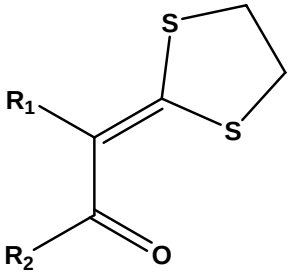


Figure 32

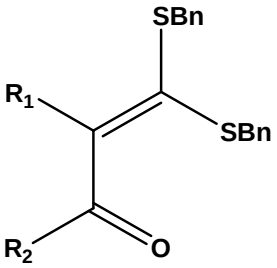


Figure 33

Ketene dithioacetals

The method for preparation of α-oxoketene dithioacetals is common, the combination of an active methylene/methyl substrate, CS_2, RX, and a suitable base. Lawesson and Larsson,[79-81] Junjappa and Ila[82] have reported the synthesis of mixed dialkylketene dithioacetals from dithioesters which were prepared from ketone and dimethyl trithiocarbonate.[83]

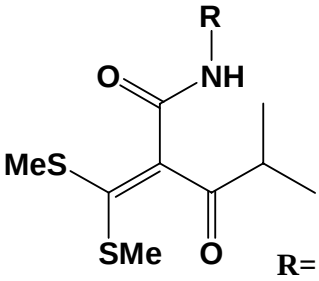


Figure 34

R= aryl amine

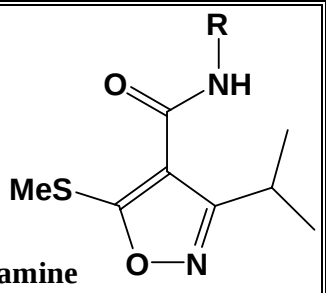


Figure 35

5.7 Result and discussion

Various substituted 4-methyl-3-oxo-*N*-phenylpentanamide **(2a-s)** were prepared by reacting substituted amines and methyl-4-methyl-3-oxopentanoate in toluene with a catalytic amount of NaOH or KOH (**Scheme 1**). The reaction mixture was reflux for 15-20 h. Fifteen different acetoacetanilide were synthesized bearing various electron donating and electron withdrawing groups like 2,3-*di*CH_3; 3,4-diCH_3; 4-CH_3; H; 2,5-*di*CH_3; 2,4-*di*CH_3; 3-Cl-4-F; 4-F; 4-Cl; 2-Cl; 2-F; 4-OCH_3; 2,5-*di*Cl and 3-NO_2 on the phenyl ring.

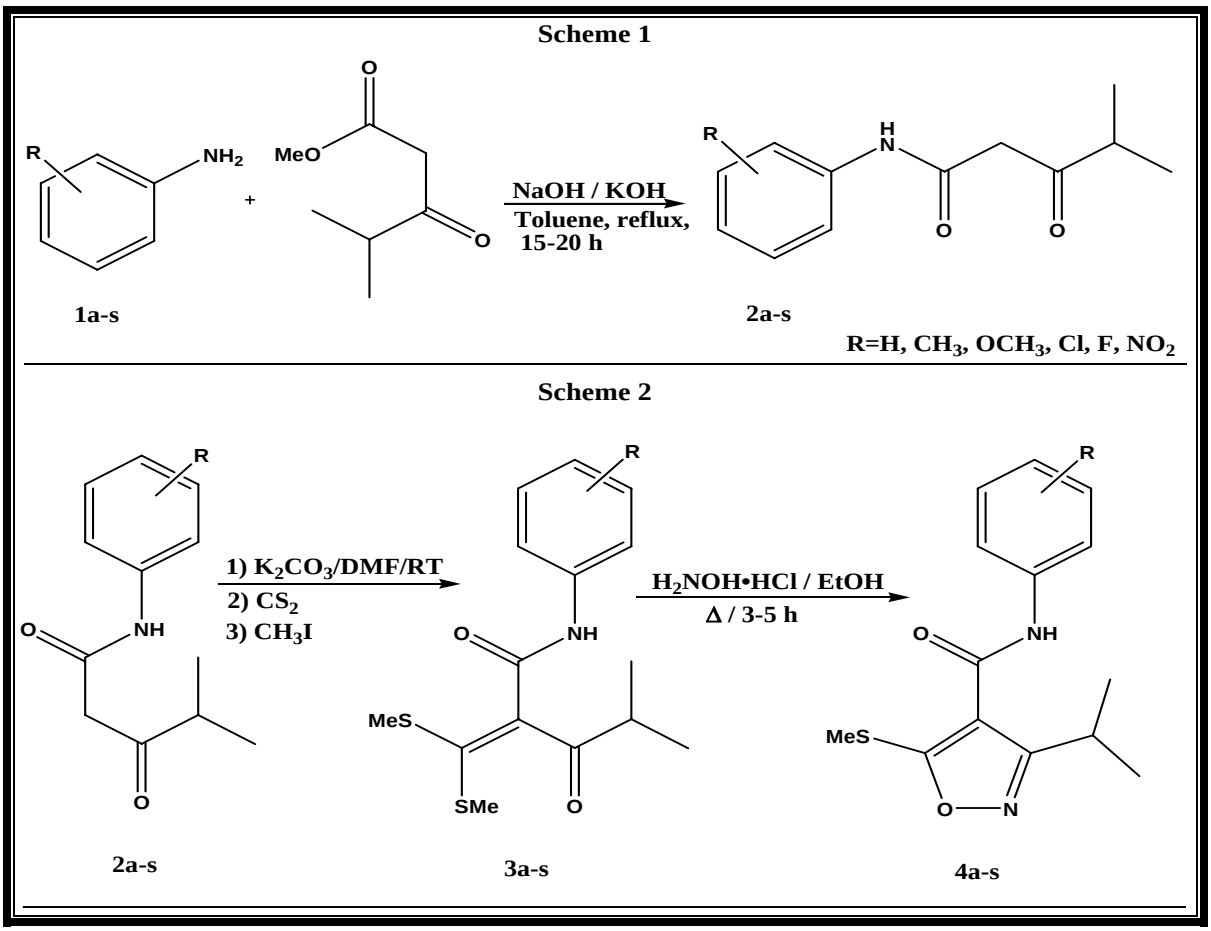
Thus, it has been found that reaction of substituted acetoacetanilide **(2a-s)** derivatives **(Scheme 1)** with carbon disulfide in the presence of potassium carbonate followed by the alkylation with methyl iodide gives the novel ketene dithioacetals (**Figure 34**, **3a-s**), when **3a-s** was reacted with hydroxylamine hydrochloride in refluxing ethanol, the corresponding 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide derivatives (**Figure 35, 4a-s**) was obtained in 85 to 90% yield.

The structures of 4a-s were established on the basis of their elemental analysis and spectral data (MS, IR, and ^{1}H NMR). The analytical data for **3a** revealed a molecular formula $C_{16}H_{21}NO_2S_2$ (m/z 323). The ^{1}HNMR spectrum revealed a doublet at δ = 1.18-1.20 ppm assigned to isopropyl-CH_3, a singlet at δ = 1.57 ppm assigned to the –CH_3 protons, a two singlet at δ = 2.44 ppm assigned to (2 × SCH_3), a multiplet at δ = 3.17-3.24 ppm assigned to the isopropyl-CH protons, a multiplet at δ = 6.99–7.54 ppm assigned to the aromatic protons, and one broad singlet at δ = 8.38 ppm assigned to -CONH groups. Reaction of compounds 3a-s with hydroxylamine hydrochloride in refluxing ethanol gave the corresponding 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide derivatives 4a-s. The structures of **4b** were established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR, and ^{13}C NMR). Structure **4a** was supported by its mass (m/z 294), which agrees with its molecular formula $C_{14}H_{15}FN_2O_2S$; its ^{1}H NMR spectrum had signals at δ= 1.22-1.23 ppm (2 × CH_3), δ= 2.62 ppm (SCH_3), a multiplet at δ = 4.04-4.08 ppm assigned to the isopropyl-CH protons, a signal at δ = 7.14–7.64 ppm (m, 4H, Ar) related to the aromatic protons, 10.21 (br, s, -CONH).

5.8 Conclusion

In summary, we have achieved a novel synthesis of interesting 4-methyl-3-oxo-*N*-phenylpentanamide (acetoacetanilide, **2a-s**), ketene *S,S*-acetals and their conversions to several 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide derivatives **(4a-s)** which have both chemical and biological potential.

5.9 Reaction scheme of 2-(bis (methylthio)methylene)-4-methyl-3-oxo-*N*-arylpentanamide(2a-s), dithioacetals(3a-s) and 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide derivatives (4a-s).



5.10 Experimental procedure

Melting points were determined on an electro thermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H NMR spectra were recorded on a Bruker AVANCE II (400 MHz) spectrometer in DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator.

5.10.1 General synthesis of 4-methyl-3-oxo-*N*-phenylpentanamide (2a-s)

A mixture containing the primary amine (10 mmol), methyl isobutyrylacetate (10 mmol), and catalytic amount of sodium or potassium hydroxide lie (10 %) was reflux at 110 ^{o}C for the approximately 15-20 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under *vaccuo* when the reaction was completed. The solid or oil was crystallized from methanol to give pure product **(2a-s)**.

5.10.2 General Synthesis of ketene dithioacetals (3a-s)

A 100mL conical flask equipped with magnetic stirrer and septum was charged with a solution of 4-methyl-3-oxo-*N*-phenylpentanamide (2a-s, 10 mmol) in DMF (10 mL). Dried K_2CO_3 (10 mmol) was added and the mixture was stirred for 2 h at room temperature. CS_2 (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Methyl iodide (20 mmol) was then added and the mixture was stirred for 4 h before being poured onto water (40 mL). The precipitated crude product was purified by filtration followed by crystallization from EtOH. When the product was oil, the organic phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated in *vaccuo* to afford ketene dithioacetals directly used for the next step.

5.10.3 General synthesis of 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide derivatives (4a-s)

A 100mL round-bottom flask equipped with condenser and septum was charged with a solution of ketene dithioacetals (3a-s, 10.0 mmol) in isopropyl alcohol (30 mL), followed by the hydroxylamine hydrochloride (10.0 mmol) was added and the mixture was reflux for 4 h at 90 ^{o}C. The reaction was monitored by TLC, after completion the reaction mixture was then cooled down to room temperature, poured into crushed ice and stirred for 1 h before usual standard work-up. When the product was oil, the organic phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), concentrated in *vaccuo*, and purified on silica gel with ethyl acetate-hexane (9:1) as eluant. When precipitated, the product was filtered, washed with water, and purified by recrystallization from ethanol to give pure product (4a-s).

5.11 Spectral data of synthesized compounds (3a-s & 4a-s)

2-(bis(methylthio) methylene)-4-methyl-3-oxo-*N*-*p*-tolylpentanamide 3a. yellow solid, yield 90%, mp 155-158°C; Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54; N, 4.33; Found: C, 59.33; H, 6.45; N, 4.23; m/z:323 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.18-1.20 (m, 6H, 2 × ^{i}prCH**$_3$**), 1.57 (s, 3H, CH_3), 2.44 (s, 6H, 2 × SCH_3), 3.17-3.24 (m, 1H, ^{i}prCH), 6.99–7.54 (m, 4H, Ar), 8.38 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3370, 3071, 2895, 2820, 1693 1635, 1480, 1340, 1298.

2-(bis(methylthio)methylene)-*N*-(4-methoxyphenyl)-4-methyl-3-oxopentanamide 3p. yellow solid, yield 92%, mp 169-171°C; Anal. Calcd for $C_{16}H_{21}NO_3S_2$: C, 56.61; H, 6.24; N, 4.13; Found: C, 56.53; H, 6.14; N, 4.06; m/z:339 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.18-1.20 (m, 6H, 2 × ^{i}prCH**$_3$**), 2.44 (s, 6H, 2 × SCH_3), 3.17-3.24 (m, 1H, ^{i}prCH), 3.75 (s, 3H, OCH_3), 6.99–7.54 (m, 4H, Ar), 8.38 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

3-isopropyl-5-(methylthio)-*N*-*p*-tolylisoxazole-4-carboxamide 4a. white solid, yield 82%, mp 178–180°C; Anal. Calcd for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65; Found: C, 61.93; H, 6.14; N, 9.53; m/z:290 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.21-1.22 (d, J = 6.92 Hz, 6H, 2 × ^{i}prCH$_3$), 2.34 (s, 3H, CH_3), 2.73 (s, 3H, SCH_3), 3.80-3.90 (m, 1H, ^{i}prCH), 7.10–7.80 (m, 4H, Ar), and 8.0 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3439, 3007, 2928, 2808, 1599, 1462, 1327, 1255, ^{13}C NMR (400 MHz, $CDCl_3$): 15.00, 20.16, 20.88, 20.98, 26.83, 27.57, 50.86, 109.62, 111.20, 120.18, 129.60, 134.82, 156.49, 158.93, 165.97, 169.45, 182.80.

***N*-(4-fluorophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4b.** Off-white solid, yield 85%, mp 188–190°C; Anal. Calcd for $C_{14}H_{15}FN_2O_2S$: C, 57.13; H, 5.14; N, 9.52; Found: C, 57.01; H, 5.00; N, 9.45; m/z:294 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.22-1.23 (d, J = 6.92 Hz, 6H, 2 × ^{i}prCH$_3$), 2.62 (s, 3H, SCH_3), 4.04-4.08 (m, 1H, ^{i}prCH), 7.15–7.64 (m, 4H, Ar), and 10.21 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

3-isopropyl-*N*-(2,3-dimethylphenyl)-5-(methylthio)isoxazole-4-carboxamide 4c. off white solid, yield 84%, mp 191–192°C; Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; Found: C, 63.05; H, 6.54; N, 9.13; m/z:304 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

3-isopropyl-*N*-(2,4-dimethylphenyl)-5-(methylthio)isoxazole-4-carboxamide 4d. Off-white solid, yield 81%, mp 201–202°C; Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; Found: C, 63.05; H, 6.54; N, 9.13; m/z:304 [M^+]; IR (KBr), ν(cm^{-1}): 3382, 3070, 2897, 2827, 1698, 1638, 1480, 1342, 1291.

3-isopropyl-*N*-(2,5-dimethylphenyl)-5-(methylthio)isoxazole-4-carboxamide 4e. Off-white solid, yield 79%, mp 213–215°C; Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; Found: C, 63.05; H, 6.54; N, 9.13; m/z:304 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(2-chlorophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4f.** white solid, yield 80%, mp 187–188°C; Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01; Found: C, 54.01; H, 4.72; N, 8.91; m/z:310 [M^+]; IR (KBr), ν(cm^{-1}): 3480, 3373, 3071, 2895, 2828, 1694, 1638, 1481, 1343, 1298.

***N*-(3-chlorophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4g.** white solid, yield 74%, mp 202–204°C; Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01; Found: C, 54.01; H, 4.72; N, 8.91; m/z:310 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(4-chlorophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4h.** white solid, yield 75%, mp 212–214°C; Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01; Found: C, 54.01; H, 4.72; N, 8.91; m/z:310 [M^+]; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.21-1.22 (d, J = 6.92 Hz, 6H, 2 × ^{i}prCH$_3$), 2.63 (s, 3H, SCH$_3$), 4.04-4.11 (m, 1H, ^{i}prCH), 7.16–7.64 (m, 4H, Ar), and 10.20 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3488, 3371, 3078, 2896, 2827, 1694, 1637, 1481, 1342, 1298.

***N*-(2,6-dichlorophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4i.** white solid, yield 71%, mp 228–230°C; Anal. Calcd for $C_{14}H_{14}Cl_2N_2O_2S$: C, 48.70; H, 4.09; N, 8.11; Found: C, 48.58; H, 4.0; N, 8.01; m/z:344 [M^+]; IR (KBr), ν(cm^{-1}): 3382, 3373, 3172, 2995, 2928, 1694, 1635, 1482, 1343, 1298.

***N*-(2-bromophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4j.** Off-white solid, yield 80%, mp 202-204°C; Anal. Calcd for $C_{14}H_{15}BrN_2O_2S$: C, 47.33; H, 4.26; N, 7.89; Found: C, 47.23; H, 4.18; N, 7.79; m/z:355 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3018, 2895, 2829, 1694, 1635, 1482, 1343, 1298.

***N*-(3-bromophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4k.** Off-white solid, yield 77%, mp 212-213°C; Anal. Calcd for $C_{14}H_{15}BrN_2O_2S$: C, 47.33; H, 4.26; N, 7.89; Found: C, 47.23; H, 4.18; N, 7.79; m/z:355 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3020, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(4-bromophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4l.** Off-white solid, yield 74%, mp 230-232°C; Anal. Calcd for $C_{14}H_{15}BrN_2O_2S$: C, 47.33; H, 4.26; N, 7.89; Found: C, 47.23; H, 4.18; N, 7.79; m/z:355 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1698, 1635, 1482, 1343, 1298.

***N*-(2-nitrophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4m.** Off-white solid, yield 71%, mp 205-207°C; Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08; Found: C, 52.26; H, 4.61; N, 13.00; m/z:321 [M^+]; IR (KBr), ν(cm^{-1}): 3374, 3072, 2895, 2830, 1694, 1631, 1486, 1348, 1298.

***N*-(3-nitrophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4n.** Off-white solid, yield 72%, mp 220-221°C; Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08; Found: C, 52.26; H, 4.61; N, 13.00; m/z:321 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(4-nitrophenyl)-3-isopropyl-5-(methylthio)isoxazole-4-carboxamide 4o.** Off-white solid, yield 72%, mp 225-227°C; Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70; N, 13.08; Found: C, 52.26; H, 4.61; N, 13.00; m/z:321 [M^+]; IR (KBr), ν(cm^{-1}): 3381, 3072, 2865, 2828, 1694, 1635, 1482, 1343, 1298.

3-isopropyl-*N*-(4-methoxyphenyl)-5-(methylthio)isoxazole-4-carboxamide 4p. white solid, yield 80%, mp 213-216°C; Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14; Found: C, 58.79; H, 5.83; N, 9.03; m/z:306 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3073, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

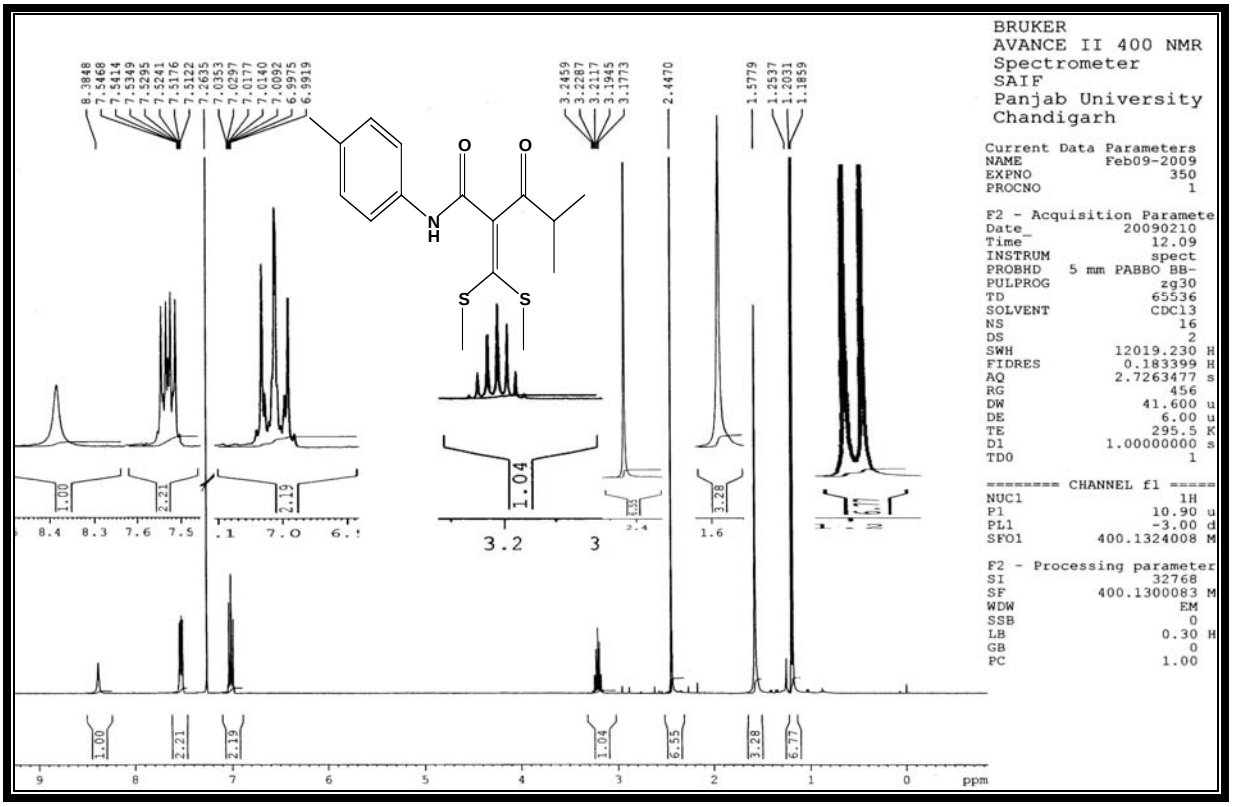
***N*-(3-chloro-4-fluorophenyl)-3-isopropyl-5(methylthio)isoxazole-4-carboxamide 4q.** white solid, yield 76%, mp 227-228°C; Anal. Calcd for $C_{14}H_{14}ClFN_2O_2S$: C, 51.14; H, 4.29; N, 8.52; Found: C, 51.01; H, 4.19; N, 8.43; m/z:305 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2895, 2828, 1694, 1635, 1482, 1343, 1298.

***N*-(3,4-difluorophenyl)-3-isopropyl-5(methylthio)isoxazole-4-carboxamide 4r.** Off-white solid, yield 78%, mp 222-224°C; Anal. Calcd for $C_{14}H_{14}F_2N_2OS$: C, 53.84; H, 4.52; N, 8.97; Found: C, 53.75; H, 4.43; N, 8.90; m/z:312 [M^+]; IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2898, 2842, 1694, 1635, 1481, 1343, 1298.

***N*-(4-ethylphenyl)-3-isopropyl-5(methylthio)isoxazole-4-carboxamide 4s.** White solid, yield 82%, mp 209-211°C; Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; Found: C, 63.03; H, 6.53; N, 9.13; m/z:304 [M^+]; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.22 (t, 3H, $PhCH_2CH_3$), 1.36-1.38 (d, J = 7.08 Hz, 6H, 2 × ^{i}prCH_3), 2.62 (s, 3H, SCH_3), 3.99-4.06 (m, 1H, ^{i}prCH), 7.27–7.65 (m, 4H, Ar), and 10.65 (br, s, 1H, -CONH); IR (KBr), ν(cm^{-1}): 3482, 3373, 3072, 2894, 2827, 1694, 1634, 1482, 1343, 1298.

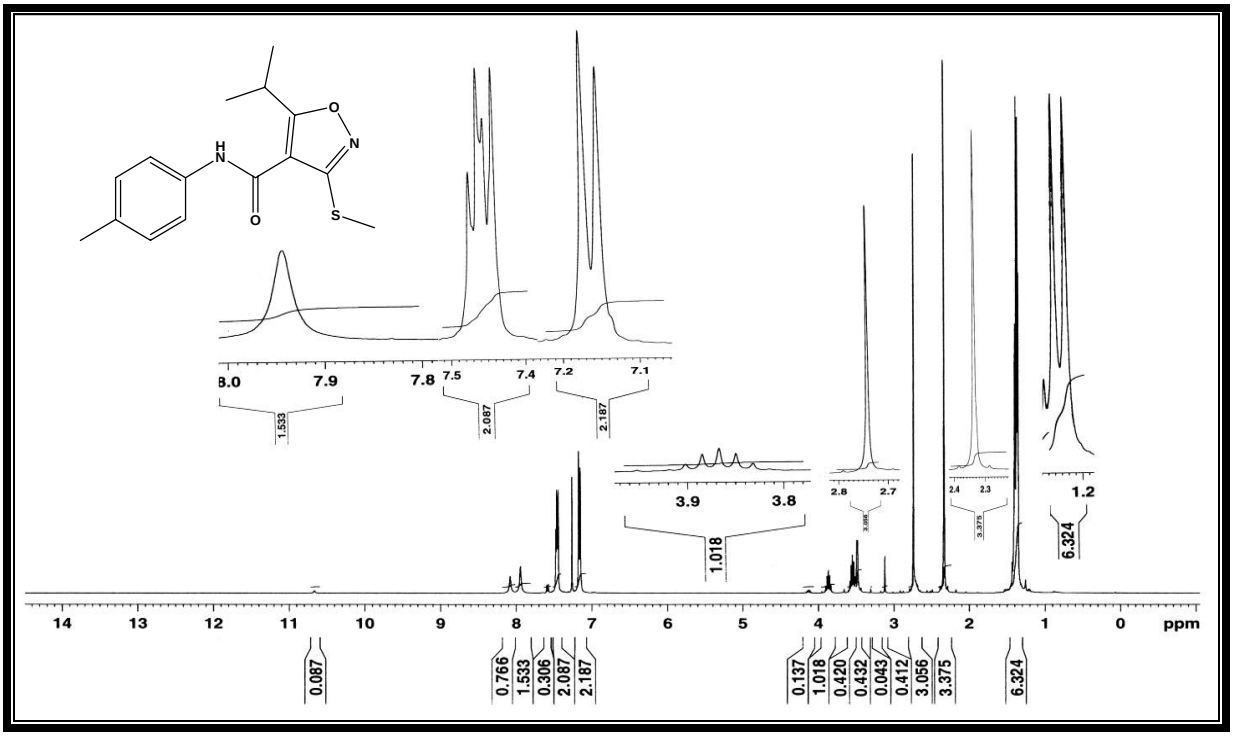
5.12 Spectral representation of synthesized compounds

5.12.1 ^{1}H NMR spectrums compound of 3a

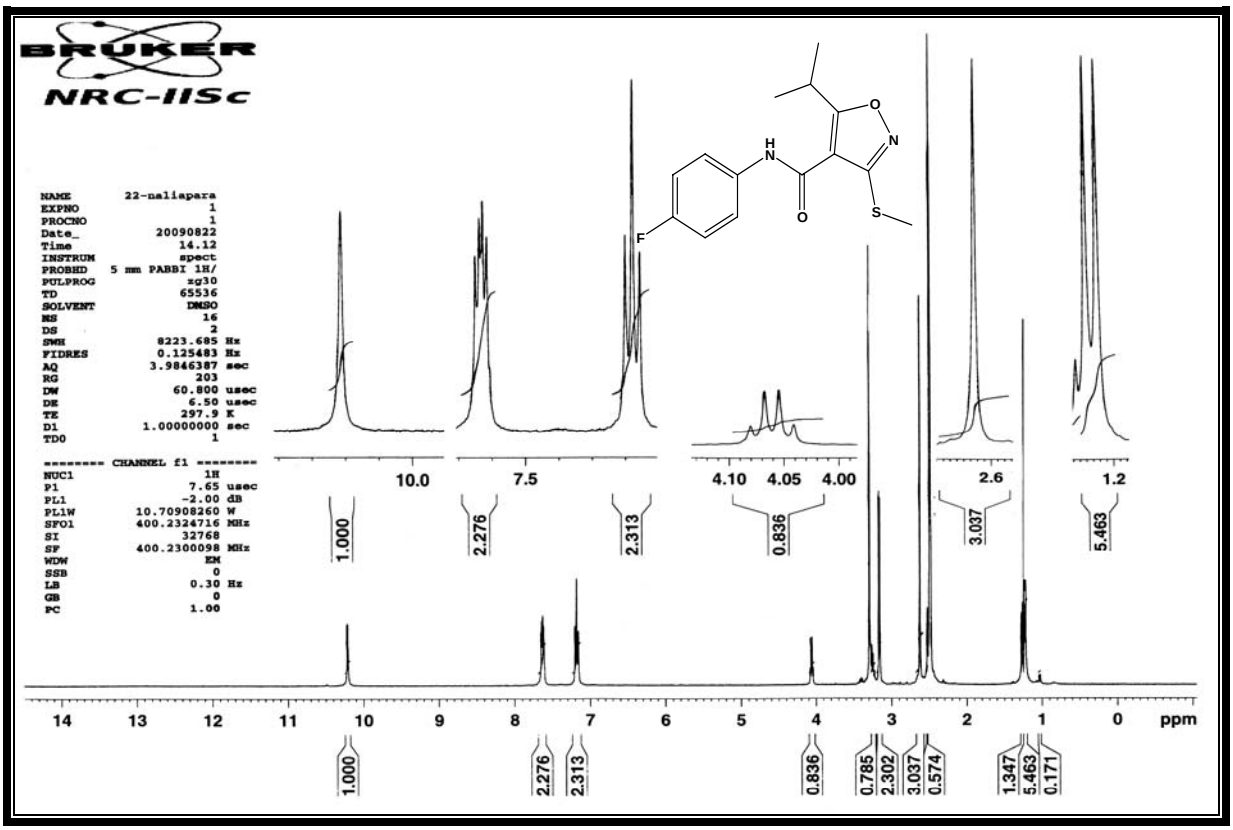


5.12.2 ^{1}H NMR spectrums compound of 3p

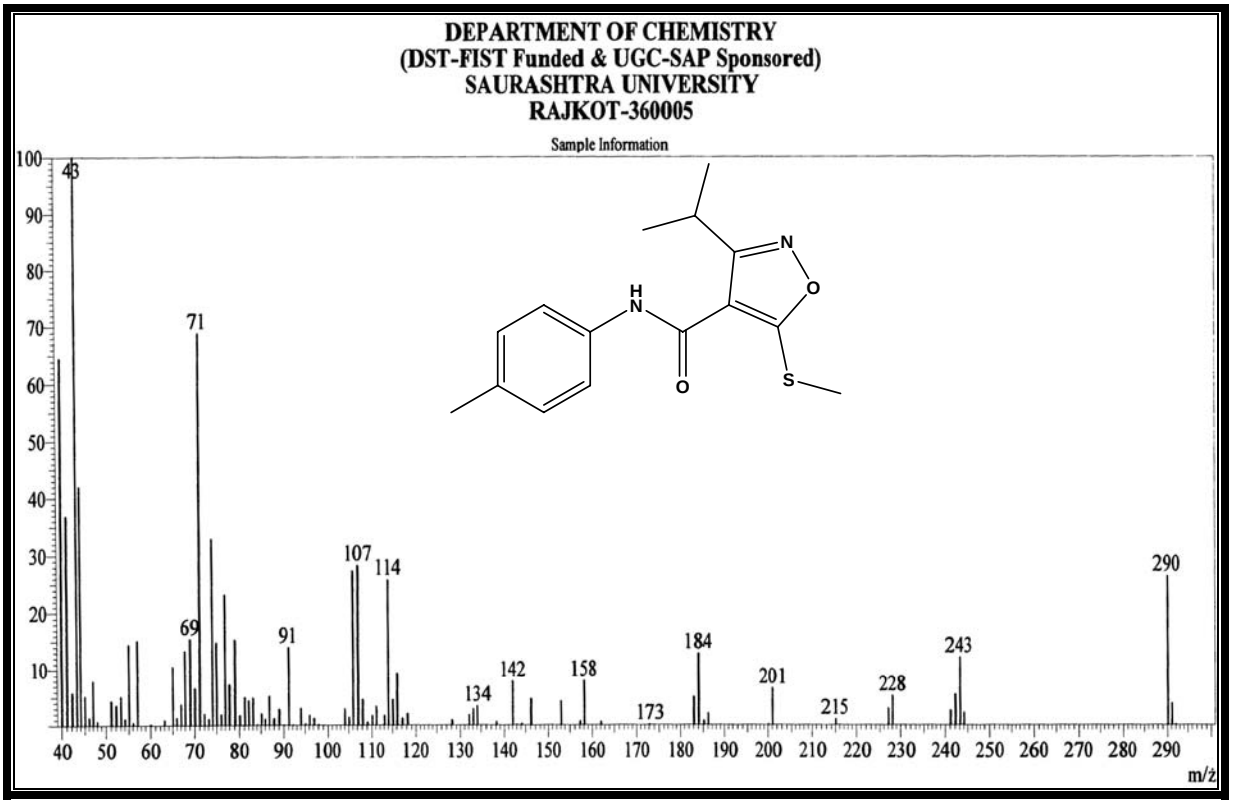
5.12.3 ^{1}H NMR spectrums compound of 4a



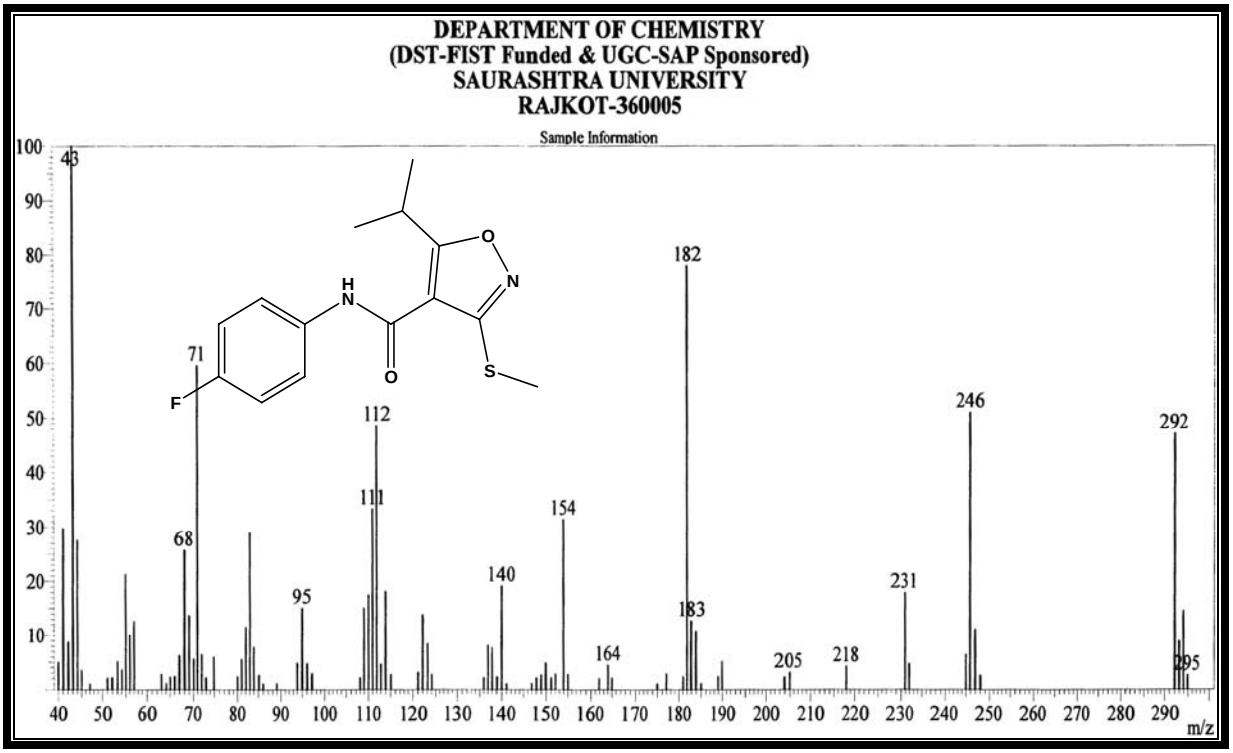
5.12.4 ^{1}H NMR spectrums compound of 4b



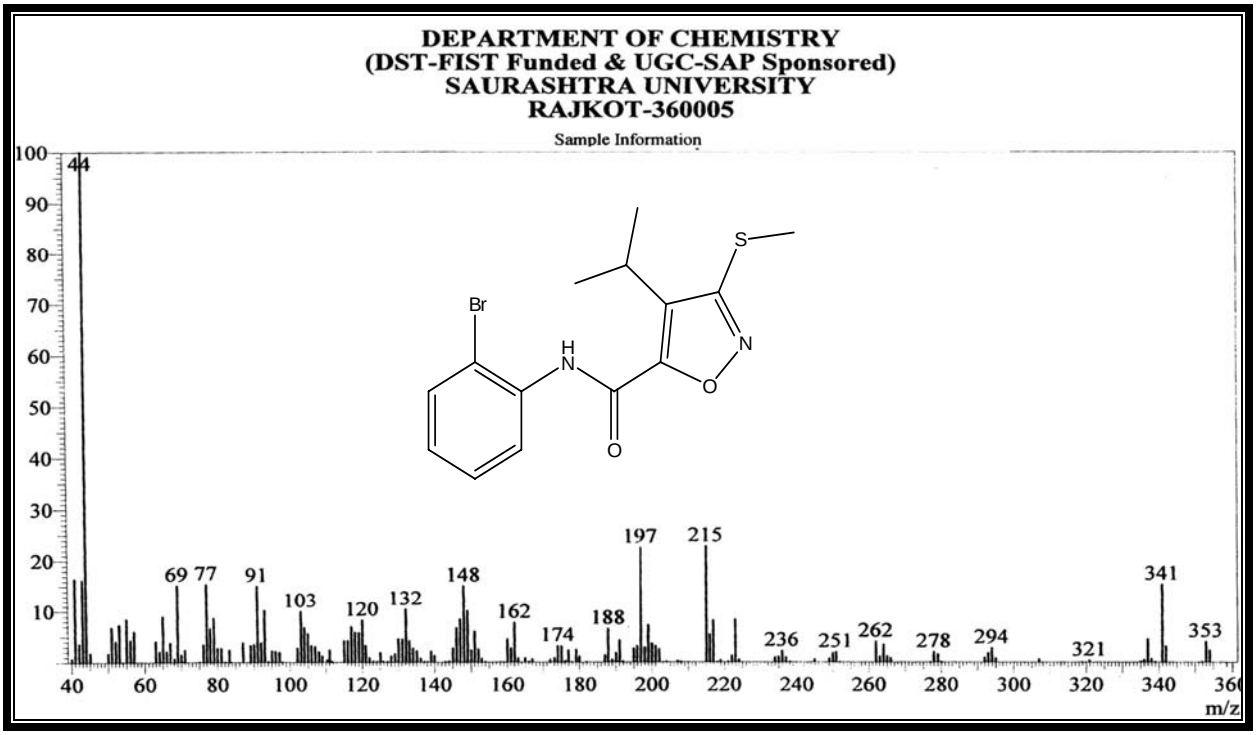
5.12.5 Mass spectra of compounds 4a



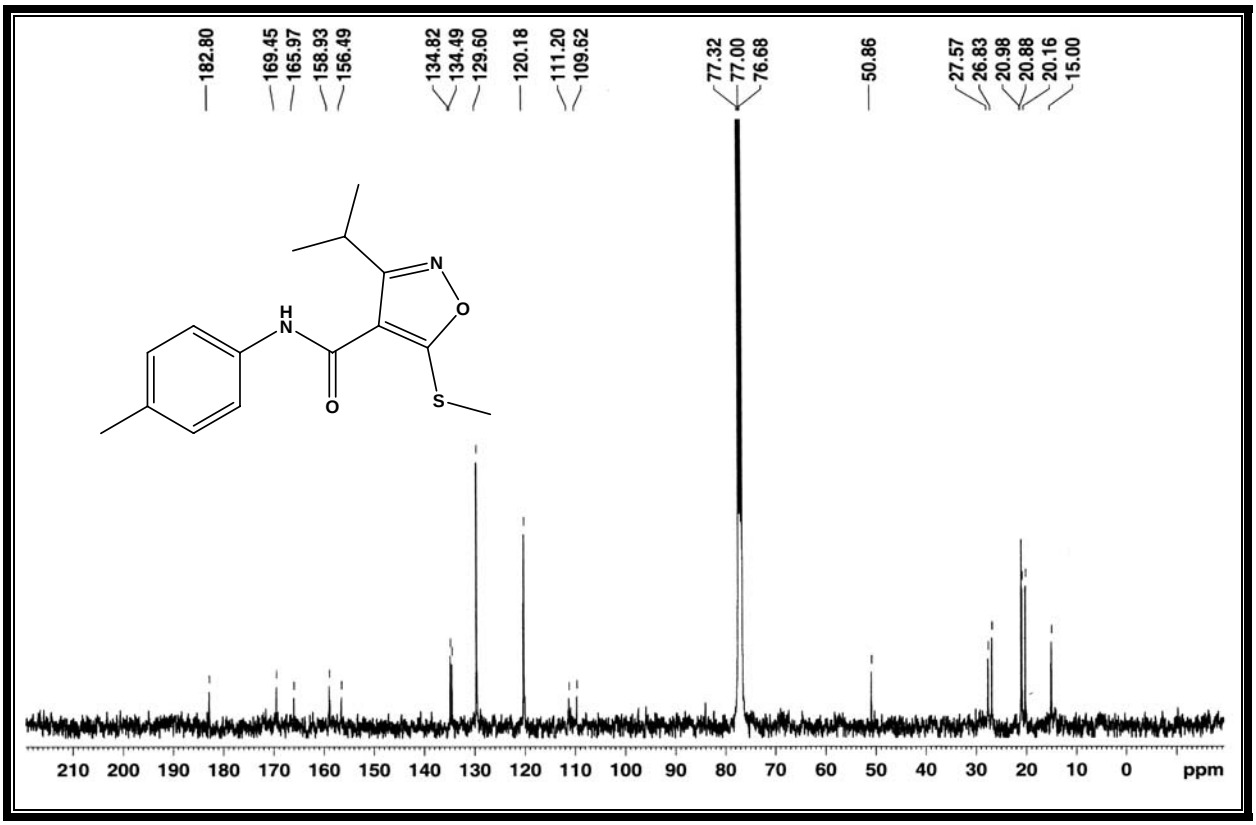
5.12.6 Mass spectra of compounds 4b



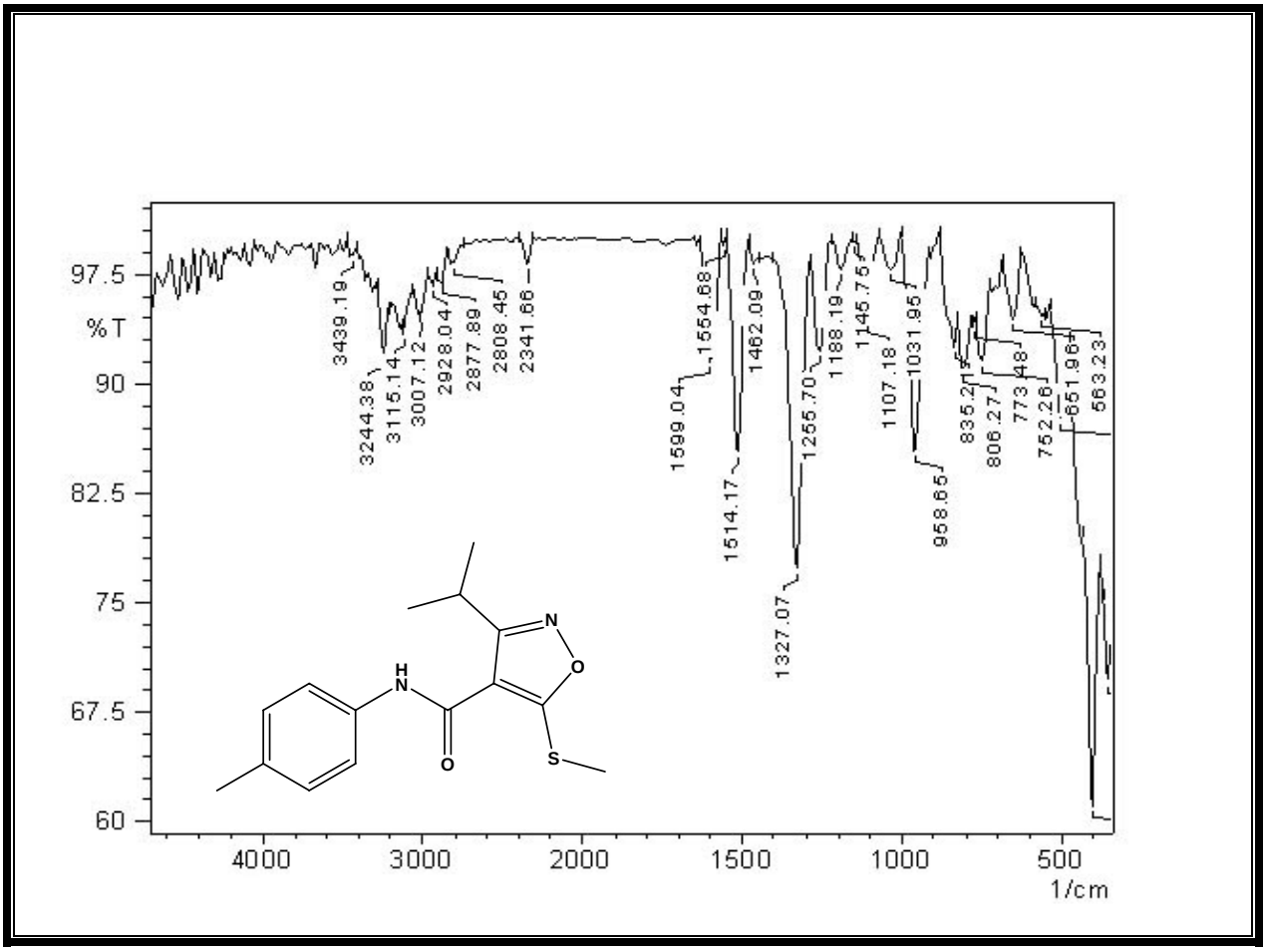
5.12.7 Mass spectra of compounds 4j



5.12.8 ^{13}C NMR spectrums compound of 4a



5.12.9 IR spectrums compound of 4a



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Summary of the present work

The work to be presented in the thesis entitled ***"DESIGN, SYNTHESIS, CHARACTERIZATION & BIOLOGICAL ACTIVITIES OF FEW HETEROCYCLIC COMPOUNDS"*** is divided into five chapters.

In **Chapter-1**, Synthesis and characterization of novel 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones derivatives is reported. This chapter deals with the thiazolidinones and its derivatives are an important class of heterocyclic compounds because of their broad spectrum of biological activities, such as COX-1 inhibition, anti-inflammatory, antiproliferative, antihistaminic, and anti-HIV activities.

In the present chapter, efforts have been made for the synthesis of novel 2-aryl-3-(3,3-diphenylpropyl)thiazolidin-4-ones derivatives. The targeted compounds were prepared by three component one pot reaction of 3,3-diphenyl propylamine, mercaptoacetic acid and appropriate aldehyde under conventional methods. We also found that the targeted compound can be synthesized in excellent yields through green chemistry approach by utilizing Fuller's earth as solid support through microwave irradiation technique. The newly prepared compounds were characterized by Mass, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Chapter-2, Etidronic acid-catalyzed Synthesis of novel Mannich Base derivatives of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one. The Mannich reaction is a fundamentally important carbon–carbon bond forming reaction in organic synthesis, and it has been widely utilized in the synthesis of nitrogen-containing drugs, natural products and biologically active compounds. Following our interest in benzopyrans, this chapter devoted to exploring the activity of some Mannich bases of 7-hydroxy-4-isopropyl-2*H*-chromen-2-one.

A convenient synthesis of Mannich base has been achieved through a one-pot multicomponent reaction involving etidronic acid as catalyst. Thus, 7-hydroxy-4-isopropyl-2*H*-chromen-2-one was reacted with formaldehyde and appropriate amines in presence of etidronic acid. The targeted compounds were isolated in moderate to good

yields. The newly synthesized compounds were characterized by Mass, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Chapter-3, Synthesis and characterization of novel 3-isopropyl-5-(methylthio)-*N*-aryl-1*H*-pyrazole-4-carboxamide derivatives. The pyrazole moiety is present in a wide variety of biologically interesting compounds, which exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic activity. Thus, continuous efforts have been devoted to the development of more general and versatile synthetic methodologies to this class of compounds.

The synthesis of novel functionalized pyrazole derivatives has been achieved from the reaction of dithioacetals and hydrazine hydrate. The requisite dithioacetals were prepared from various acetoacetanilide by reacting with carbon disulfide in the presence of potassium carbonate followed by the alkylation with methyl iodide. Thus obtained, ketene dithioacetals were further reacted with hydrazine in isopropyl alcohols under reflux to generated corresponding pyrazole derivatives. All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Chapter-4, Etidronic acid-catalyzed Synthesis of novel 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-arylpyrimid in-2(1*H*)- one derivatives. Recently, much interest has been focused around 5-nitro dihydropyrimidine derivatives because of their wide variety of pharmacological properties and industrial applications. In view of these, we were interested to prepare some new 3,4-dihydro-6-(2-hydroxy-3,5-dimethylphenyl)-5-nitro-4-phenylpyrimidin-2(1*H*)-one. To achieve the targeted compounds, 1-(2-hydroxy-4,6-dimethylphenyl)-2-nitroethanone was reacted with substituted benzaldehydes and urea in presence of etidronic acid as catalyst under microwave irradiation.

We found that the reaction proceeded smoothly under this protocol leading to the formation of pyrimidin-2(1*H*)-one in excellent yields. The chemical structure of newly synthesized compounds were established by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Chapter-5, Synthesis and characterization of novel 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide derivatives. Isoxazoles are potent, selective agonists at human cloned dopamine D4 receptors and exhibit GABAA antagonist, analgesic, anti-inflammatory, ulcerogenic, antimicrobial, antifungal, COX-2 inhibitory, antinociceptive, and anticancer activity. Many synthetic methods have been employed in the synthesis of isoxazoles, including reactions of hydroxylamine with 1,3-dicarbonyl compounds, *α,β*-unsaturated carbonyl compounds, and *α,β*-unsaturated nitriles.

In this chapter a new synthetic approach for the novel isoxazoles utilizing ketene *S,S*-acetals as synthon is described. Various dithioacetals prepared from various acetoacetanilide, were reacted with hydroxylamine hydrochloride in ethanolic KOH under reflux condition to afford 3-isopropyl-5-(methylthio)-*N*-arylisoxazole-4-carboxamide in good yields. All newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

All the newly synthesized compounds are under investigation for antiviral and antimicrobial screening.

Publication

1. Akshay M. Pansuriya, Mahesh M. Savant, **Chirag V. Bhuva**, Jyoti Singh, Yogesh T. Naliapara. One-pot synthesis of 5-carboxanilidedihydropyrimidinones using etidronic acid. ***ARKIVOC***, 2009, vii, 79–85.

2. Akshay M. Pansuriya, Mahesh M. Savant, **Chirag V. Bhuva**, Jyoti Singh, Yogesh T. Naliapara. Use of cyclic aliphatic ketones for spiro 2-amino-3-cyano pyrano[3,2-*c*]chromene formation. ***ARKIVOC***, 2009, xii, 254–260.

3. Mahesh M. Savant, Akshay M. Pansuriya, **Chirag V. Bhuva**, Yogesh T. Naliapara. Synthesis and evaluation of antimicrobial activity of some new 5-imidazolinone derivatives. ***Organic chemistry: An Indian Journal***, 2009, 5(2), 237–242.

4. Akshay M. Pansuriya, Mahesh M. Savant, **Chirag V. Bhuva**, Jyoti Singh, Yogesh T. Naliapara. Tetraethylammoniumbromide mediated Knoevenagel condensation in water: Synthesis of 4-arylmethylene-3-methyl-5-pyrazolone. ***E-Journal of Chemistry***, Accepted.

5. Mahesh M. Savant, Akshay M. Pansuriya, **Chirag V. Bhuva**, Naval P. Kapuriya, Yogesh T. Naliapara. Etidronic acid: A new and efficient catalyst for the synthesis of novel 5-nitro-3,4-dihydropyrimidine-2(1*H*)-ones. ***Catalysis Letter***, 2009, 132, 281–284.

6. Akshay M. Pansuriya, Mahesh M. Savant, **Chirag V. Bhuva**, Jyoti Singh, Naval Kapuriya, Yogesh T. Naliapara. Construction of 3,4-dihydro-1,2-diazete ring through 4π electron cyclization of 4-hydroxy-2-oxo-2*H* chromene-3-carbaldehyde [(1*E*)-arylmethylene] hydrazone. ***Journal of Heterocyclic Chemistry***, Accepted.

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12. **Chirag V. Bhuva**, Akshay M. Pansuriya, Mahesh M. Savant, Anil S. Patel, Piyush V. Pipaliya, Vipul B. Audichya, Yogesh T. Naliapara. Water mediated and etidronic acid catalyzed synthesis of coumarins *via* Pechmann condensation under microwave irradiation. ***Tetrahedron Letter***, Submitted.

Paper /Conferences / Symposium / Workshop Attended

- International Conference on "Bioactive Heterocycles and Drug Discovery Paradigm" Jointly organized by Department of Chemistry, Saurashtra University and ISCB at Rajkot, India (January 8-10, 2005)

- **Chirag Bhuva**, Akshay Pansuriya, Jyoti Singh, & Naval Kapuria, "Synthesis, X-Ray Crystallography and Biological Activity of Bis Indole Dimers." International Conference on "Advances in Drug Discovery Research" Organized by ISCB at Aurangabad, India (24-26 Feb, 2007)

- "11th CRSI National Symposium in Chemistry" Jointly Organized by National Chemical Laboratory, Pune, Indian Institute of Science Education & Research, Pune and University of Pune (February 6-8, 2009)

- "Two Days National Workshop on Updates in Process & Medicinal Chemistry" Jointly Organized by Department of Chemistry, Saurashtra University, Rajkot and National Facility for Drug Discovery Through NCE's Development & Instrumentation Support to Small Manufacturing Pharma Enterprises and Think Pharma USA (March 3-4, 2009)

- "National Conference on Spectroscopy & Stereochemistry" Organized by Department of Chemistry, Saurashtra University, Rajkot Sponsored by UGC, New Delhi and GUJCOST, Gandhinagar (March 18-20, 2009)