"STUDIES ON NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS AS BIOACTIVE AGENTS"

A THESIS

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IN

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BY

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UNDER THE GUIDANCE

OF

Prof. H. S. Joshi

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

The work included in the thesis is my own work under the supervision of ***Prof. H. S. Joshi*** and leads to some contribution in chemistry subsidized by a number of references.

Date: - -2011 ***(Piyush B. Vekariya)***
Place: Rajkot

This is to certify that the present work submitted for the Ph.D. Degree of Saurashtra University by ***Piyush B. Vekariya*** **(Reg.No.: 4156/Date: 28/02/2009)** his own work and leads to advancement in the knowledge of chemistry. The thesis has been prepared under my supervision.

Date: - -2011
Place: Rajkot

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Dedicated
to
My Family

ACKNOWLEDGEMENT

First and foremost, I wish to pay my sincere homage to the **Lord Krishna** for making me capable of doing all that I propose, the work leading to my Ph. D. thesis submission is one of them.

I would like to express my sincere gratitude to my supervisor **Prof. H. S. Joshi** for accepting me as his research student and who made this research a success. It is with Dr. Joshi's enthusiasm and integral view on research combined with his willingness to provide quality chemistry and not less that kept me going and I wish to say thank you sir. Besides being a wonderful Supervisor, Dr. Joshi is as close as family and a very good friend and I am deeply honored to have wonderful person like him in my life. I wish to say thank you so much again for all the help you offered over the years both in and out of my academic life.

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(Piyush B. Vekariya)

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Molecular iodine catalyze and classical synthesis, characterization and X-ray crystallographic study of diisopropyl 1, 4-dihydro-1-(4-methoxyphenyl)-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3, 5-dicarboxylate

SYNOPSIS

A comprehensive summary of the work to be incorporated in the thesis entitled "**STUDIES ON NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS AS BIOACTIVE AGENTS**" has been described as under.

PART-A: STUDIES ON PYRAZINE DERIVATIVES

PART-B: STUDIES ON 6-FLUOROCHROMAN-2-CARBOXYLIC ACID DERIVATIVES

PART-C: X-RAY CRYSTALLOGRAPHY STUDY OF DIHYDROPYRIDINE DERIVATIVE

PART-A: STUDIES ON PYRAZINE DERIVATIVES

The primary goal of our research work is to find and develop new chemical entities (NCEs) which can be used against untreatable diseases, or which have superior properties when compared to currently available drugs. In our newly synthesized pyrazine derivatives is a side chain modified derivates. Ligand-free palladium-catalyzed Suzuki-Miyaura cross-couplings between aryl halides and aryl boronic acids performed at reflux temperature are presented.

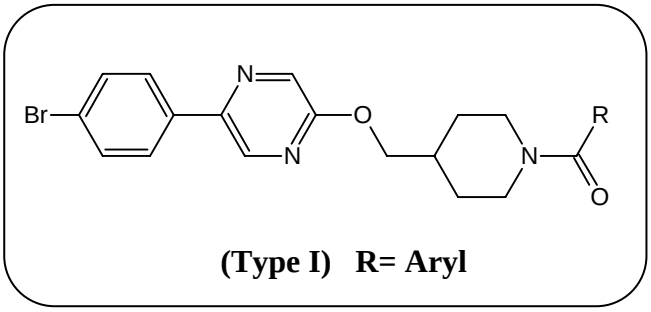
Pyrazine nucleus possesses remarkable pharmaceutical importance and biological activities, some of their derivatives occur as natural products. Many pyrazine derivatives have displayed diverse pharmacological activities like anti-inflammatory, anti tubercular, antitumor, calcium channel blocker etc. Pyrazine play an important role against various biological activities. Pharmaceutical properties of the series are improved via inclusion of hydroxyl-contg.sidechains. In view of our ongoing interest in the synthesis of some new potentially bioactive pyrazine derivatives have been described as under.

PART-I: STUDIES ON 2-(PIPERIDIN-4-YLMETHOXY) PYRAZINE DERIVATIVES

The synthesis of 2-(piperidin-4-ylmethoxy) pyrazine derivatives has been attracted widespread attention due to their diverse pharmacological properties like anti-inflammatory, anti tubercular, antibiotic, antifungal, herbicidal etc. To approach this goal

synthesis of some new 2-(piperidin-4-ylmethoxy) pyrazine derivatives have been undertaken.

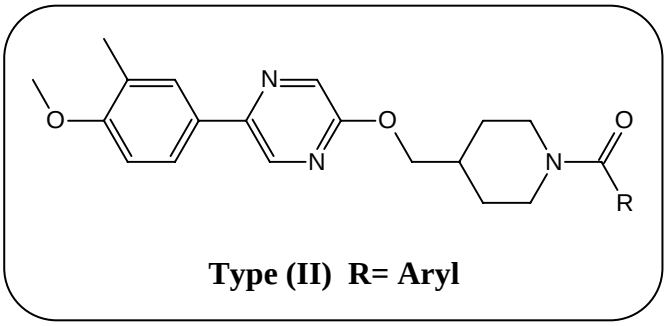
SECTION-I: Synthesis and biological evaluation of (4-(((5-(4-bromophenyl) pyrazine-2-yl)oxy) methyl) piperidin-1-yl) (aryl) methanones.



(Type I) R= Aryl

2-(Piperidin-4-ylmethoxy) pyrazine derivatives of Type (I) have been synthesized by the condensation of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy) pyrazine with various aromatic acids in the presence of DIPEA, HBTU and TEA.

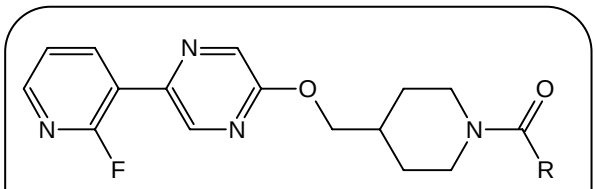
SECTION-II: Synthesis and biological evaluation of (4-(((5-(4-methoxy-3-methyl phenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.



Type (II) R= Aryl

2-(Piperidin-4-ylmethoxy) pyrazine derivatives of Type (II) have been synthesized by the condensation of 2-(4-methoxy-3-methylphenyl)-5-(piperidin-4-ylmethoxy) pyrazine with various aromatic acids in the presence of DIPEA, HBTU and TEA.

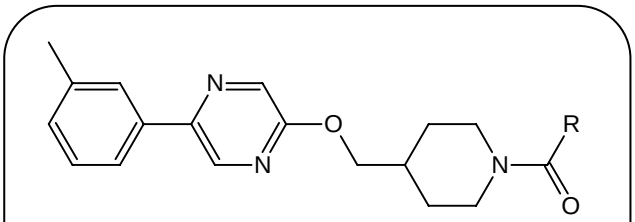
SECTION-III: Synthesis and biological evaluation of (4-(((5-(2-fluoro-Pyridine-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.



Type (III) R= Aryl

2-(Piperidin-4-ylmethoxy) pyrazine derivatives of Type (III) have been synthesized by the condensation of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy) pyrazine with various aromatic acids in the presence of DIPEA, HBTU and TEA.

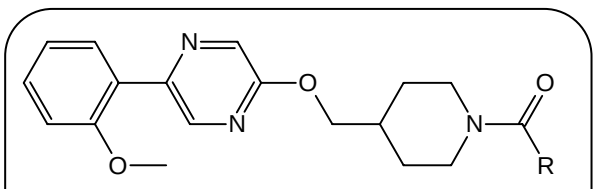
SECTION-IV: Synthesis and biological evaluation of Aryl(4-(((5-*m*-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanones.



Type (IV) R= Aryl

2-(Piperidin-4-ylmethoxy)pyrazine derivatives of Type (IV) have been synthesized by the condensation of 2-(piperidin-4-ylmethoxy)-5-(*m*-tolyl)pyrazine with various aromatic acids in the presence of DIPEA, HBTU and TEA.

SECTION-V: Synthesis and biological evaluation of (4-(((5-(2-methoxyphenyl) pyrazin-2-yl)oxy)methyl) piperidin-1-yl) (aryl) methanones.



Type (V) R= Aryl

2-(Piperidin-4-ylmethoxy) pyrazine derivatives of Type (V) have been synthesized by the condensation of 2-(2-methoxyphenyl)-5-(piperidin-4-ylmethoxy) pyrazine with various aromatic acids in the presence of DIPEA, HBTU and TEA.

PART-B: STUDIES ON 6-FLUOROCHROMAN-2-CARBOXYLIC ACID DERIVATIVES

Our strategy is based on to develop a new bioactive entity especially with pharmacological activities bearing heterocyclic ring system.Chroman is an aromatic heterocyclic organic compound. It has a bicyclic structure consisting of a six-membered benzene ring fused to a six-membered oxygen hetero atom.

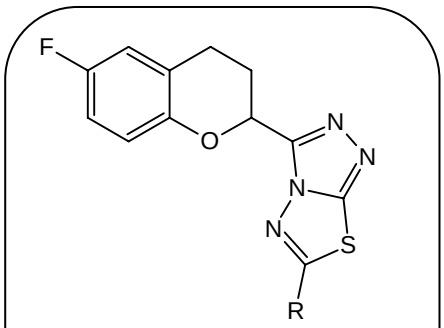
6-Fluorochroman-2-carboxylic acid and their derivatives constitute an important class of organic compounds with diverse agriculture, industrial and biological activities. The synthesis of this moiety has received considerable attention in recent years. 6-Fluorochroman-2-carboxylic acid is also known as nebivolol acid and it's a derivative of nebivolol drug. Nebivolol is an antihypertensive drug.

Considering the increasing importance of chroman nucleus, we have undertaken the synthesis of some new thiadiazoles, oxadiazoles, aryl triazoles, thiazolidinones bearing chroman nucleus, which have been described as under.

PART-I: STUDIES ON 1,3,4-THIADIAZOLE DERIVATIVES.

Literature survey revealed that the synthesis of compounds incorporating 1,3,4 - thiadiazoles have resulted in many potential drugs and are known to exhibit a broad spectrum due to their diverse pharmacological properties like antibiotic, antifungal, herbicidal, antitubercular, antitumor, antiviral, antibacterial, amoebicidal, antagonist agent, antipyretic etc. In thiadiazole ring system one sulphur and two nitrogen atoms are present in a five membered ring. To approach this goal synthesis of some new 1,3,4-thiadiazole have been undertaken, which have been described as under.

SECTION-I: Synthesis and biological evaluation of 3-(6-fluorochroman-2-yl)-6-aryl-[1,2,4]triazolo[3, 4-b][1,3,4]thiadiazoles.



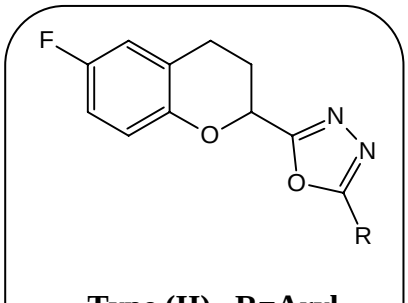
Type (I) R= Aryl

1,3,4-Thiadiazole derivatives of Type (I) have been synthesized by the condensation of 4-amino-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol with different aromatic acids in the presence of $POCl_3$.

PART-II: STUDIES ON 1,3,4-OXADIAZOLE DERIVATIVES.

1,3,4-Oxadiazoles are associated with broad spectrum of pharmacological activity like anesthetic, hypnotic, antibacterial, hypoglycemic and antifungal. These valid observations promoted us to synthesize 1,3,4-oxadiazole derivatives with better therapeutic value which have been described as under.

SECTION-I: Synthesis and biological evaluation of 2-(6-fluorochroman-2-yl)-5-aryl-1, 3, 4-oxadiazoles.



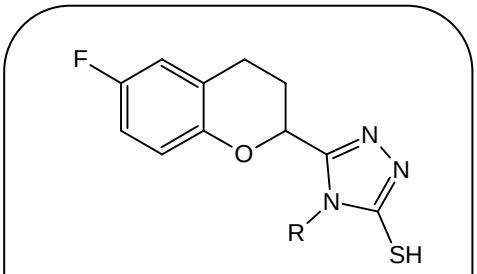
Type (II) R=Aryl

The 1,3,4- oxadiazole derivatives of Type (II) have been synthesized by the condensation of 6-fluorochroman-2-carbohydrazide with various aromatic acids in the presence of $POCl_3$.

PART-III: STUDIES ON 4-ARYLTRIAZOLE DERIVATIVES.

4-Aryltriazole derivatives have been found to be potent drug which possess a wide spectrum of biological activity. Different types of 1,2,4-triazole derivatives shows variety of pharmacological activities such as antidepressant, anti-inflammatory, biocides etc. Considering the increasing importance of compounds bearing 1,2,4-triazole nucleus, some new 1,2,4-triazole derivatives have been synthesized described as under.

SECTION-I: Synthesis and biological evaluation of 5-(6-fluorochroman-2-yl)-4-aryl-4H-1, 2, 4-triazole-3-thiols



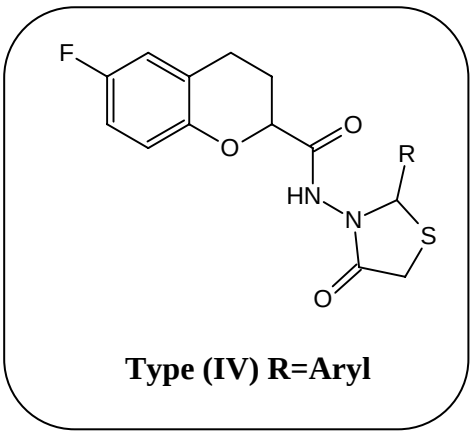
Type (III) R = Aryl

4-Aryltriazole derivatives of Type (III) have been synthesized by reaction of Potassium 2-[(6-fluorochroman-2-yl) carbonyl] hydrazinecarbodithioate with different aromatic amines.

PART-IV: STUDIES ON THIAZOLIDINONE DERIVATIVES

4-Thiazolidinones are derivatives of thiazolidine, which belong to an important group of heterocyclic compounds, have been extensively explored for their applications in the field of medicine. Compound containing thiazolidinone nucleus shows wide range of biological activities such as antitubercular, antitumor, antileprosy, hypnotics, anticonvulsant and anticancer, antibacterial etc. With a view to prepare potential bioactive agents the syntheses of some new thiazolidinones have been undertaken, which have been described as under.

SECTION-I: Synthesis and biological evaluation of 6-fluoro-*N*-(4-oxo-2-arylthiazolidin-3-yl) chroman-2-carboxamides.



Type (IV) R=Aryl

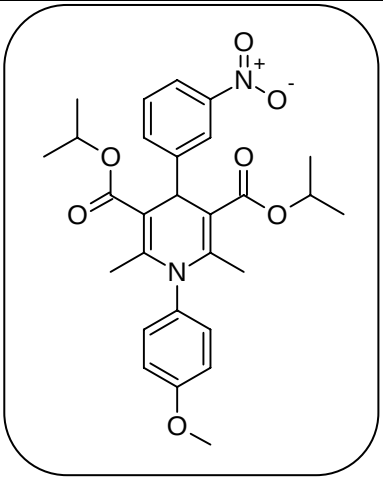
The thiazolidinones of Type-(IV) have been prepared by condensation of 6-fluorochroman-2-carbohydrazide with aryl aldehydes and thioglycolic acid.

PART-C: X-RAY CRYSTALLOGRAPHY STUDY OF DIHYDROPYRIDINE DERIVATIVE

1,4- Dihydropyridines have been known since long as calcium channel blockers. This structural class is also important because of their wide spectrum of biological activities, these include antidiabetic, nurotropic, neuromodulatory, cognition and memory enhancing, neuroprotective and many other properties.

Molecular iodine has been used as a mild and efficient catalyst for various organic syntheses. The classical method for the synthesis of 1,4-dihydropyridine is a one-pot condensation of three component in refluxing alcohol. Development of as efficient and versatile method for the preparation of 1,4-dihydropyridines is an active ongoing research area and there is scope for further improvement toward synthesis of new derivatives of 1,4-dihydropyridines with milder reaction conditions and improved yields. This chapter deals with the synthesis of N-substituted dihydropyridines by molecular iodine catalyze and classical method.

SECTION-1: Molecular iodine catalyze and classical synthesis, characterization and X-ray crystallographic study of diisopropyl 1, 4-dihydro-1-(4-methoxyphenyl)-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.



Single crystal X-ray diffraction is the most common experimental method of obtaining a detailed picture of a small molecule that allows resolution of individual atoms.

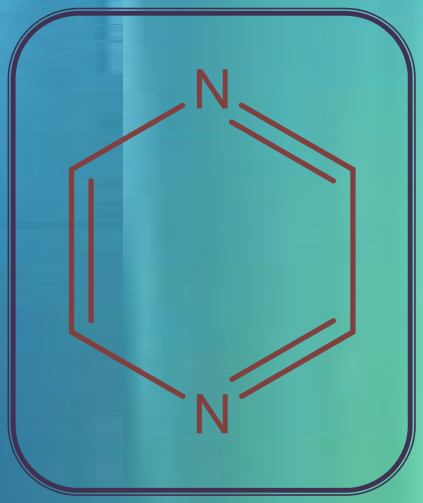
Single crystal of diisopropyl 1, 4-dihydro-1-(4-methoxyphenyl)-2, 6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylate were grown by slow evaporation technique at constant temperature using methanol as a solvent. Good quality single crystals were harvested within 45 days. The crystals are exhibiting photo conducting nature.

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR and ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatography.

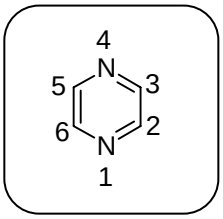
All the compounds have been evaluated for their antibacterial activity towards *Gram +ve* and *Gram -ve* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration 40 μg/ml. The biological activities of the synthesized compounds have been compared with standard drugs.

PART-A

STUDIES ON PYRAZINE DERIVATIVES



Pyrazine contains two nitrogen atoms in its aromatic ring.[1] Pyrazine play an important role as intermediates for perfumes,[2] pharmaceuticals, agricultural chemicals[3] and food spices. Especially, amides and sulfonamides of pyrazines have been used on various topics as anti-tuberculosis, dyes and pigments,[4] oral anti diabetics, nutrition supplement, insecticides and fungicides.

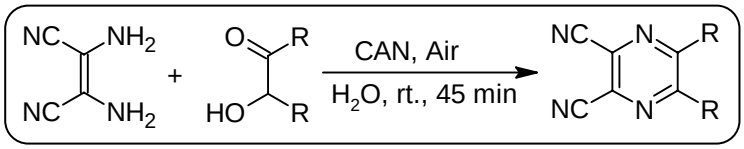


In general pyrazine is prepared by the catalytic reaction of diamines with dioles in a vapour phase, dehydrogenation of piperazine or dealkylation of methyl pyrazine. Pyrazine and their derivatives form an important class of compounds present in several natural flavors and complex organic molecules, it is also responsible for flavor in foodstuffs, like cheese, tea coffee, cooked meats nice aroma etc.[5]

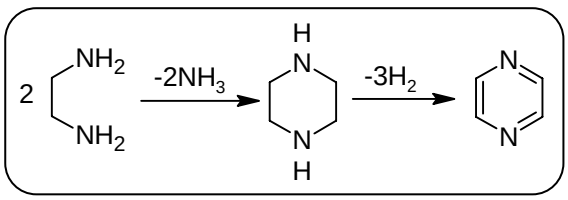
SYNTHETIC ASPECT

Various methods for the preparation of pyrazine derivatives have been cited in literature, some of them are as under.

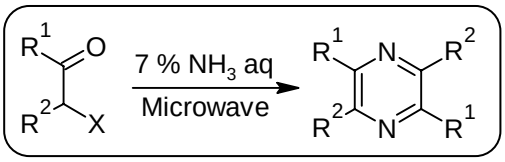
1. The pyrazine derivatives have synthesized by direct conversion of α-hydroxy ketones and α-keto oximes in the presence of a catalytic amount of ceric ammonium nitrate was reported by A. Shaabani et al.[6]



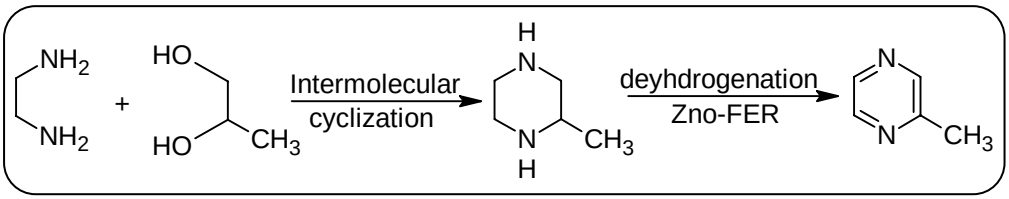
2. B. M. Latha et al.[7] have synthesized pyrazine from ethylenediamine on copper oxide/copper chromite catalysts.



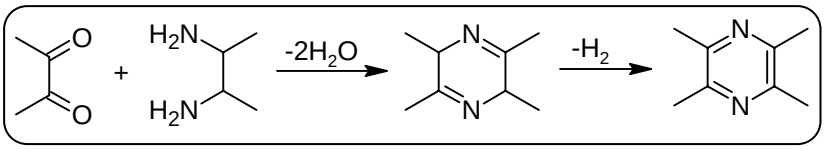
3. Microwave-assisted synthesis of pyrazine derivatives from α-halo ketone in 7% NH_3 solution was given by T. Utsukihara et al.[8]



4. Synthesis of 2-methyl pyrazine from zinc-modified ferrierite (FER) catalysts was documented by R. Anand et al.[9]



5. W. T. Reichle et al.[10] have given the synthesis which involve the reaction of diketones with appropriate diamines, which gave the diazine which readily oxidized to the pyrazines.

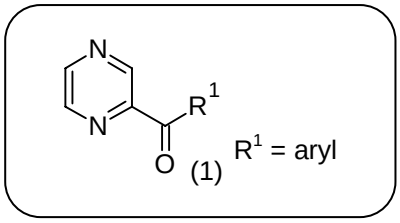


THERAPEUTIC IMPORTANCE

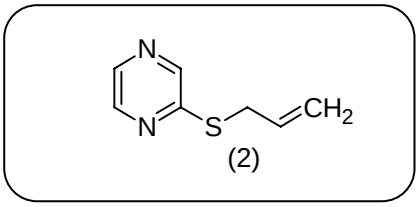
Over recent years there has been an increasing interest in the chemistry of pyrazine derivatives because of their biological significance.

1. Analgesic[11]
2. Antiallergic[12]
3. Antibacterial[13]
4. Anti-inflammatory[14]
5. Antiviral[15]
6. Diuretic[16]
7. Anticancer[17]
8. Anti HIV[18]
9. Anti hypertensive[19]
10. Cardiovascular[20]
11. Antioxidant[21]
12. Antimycobacterial[22]

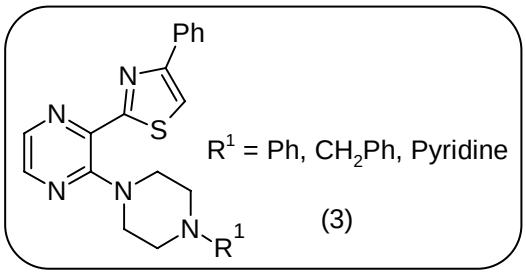
L. E. Seitz et al.[23] have synthesized and evaluated antimycobacterial activity of pyrazine derivatives (1). H. Foks et al.[24] have synthesized and screened antibacterial activity of 1*H*-pyrazolo[3,4-*b*]pyrazine derivatives.



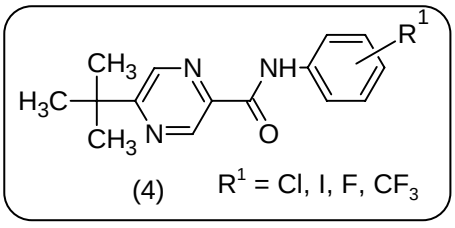
Pyrazine derivative (2) with an allylsulfur moiety have hepatoprotective effects against toxicants. Effect of 2-AP on hepatic tumorigenesis in association with glutathione *S*-transferase (GST) induction was examined in rats exposed to aflatoxin B1 (AFB1) was given by T. G. Ha et al.[25]



H. Foks et al.[26] have synthesized and checked tuberculostatic activity of 4-substituted 3,4,5,6-tetrahydro-2*H*-[1,2']-bis-pyrazine derivatives (3). F. Micheli et al.[27] have synthesized pyrido [2,3-*b*] pyrazine-8-oxide derivatives as selective glycine antagonist with *in vivo* activity.

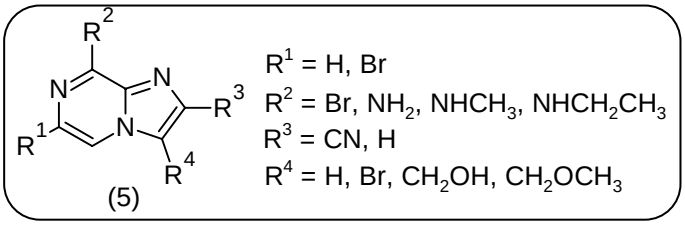


Synthesis and evaluation of substituted *N*-phenylpyrazine-2-carboxamides (4) as herbicides and abiotic elicitors was reported by M. Dolezal et al.[28]

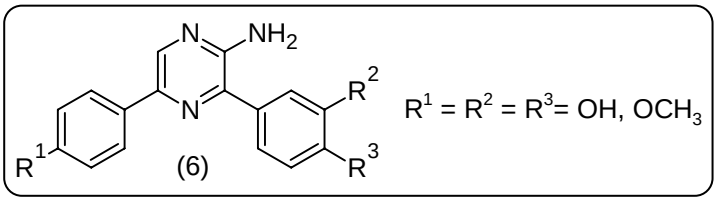


K. Zurbonsen and coworkers[29] have studied antiproliferative, differentiating and apoptotic effects elicited by imidazo[1,2-*a*]pyrazine derivatives (5). T. Yanai et al.[30] have

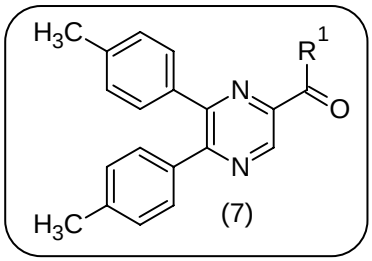
synthesized novel pyrazine compounds produced from chitin by the activity of the enzyme from vibrio alginolyticus TK-24.



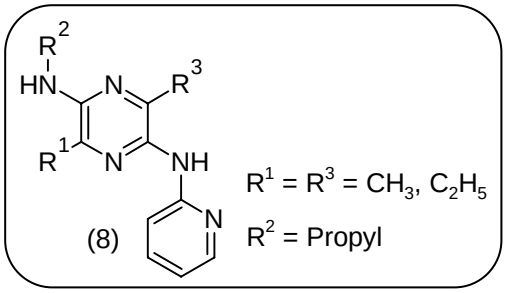
Pyrazine derivatives (6) tested against human keratinocyte cells stressed UVB irradiation showed high anti oxidative properties was given by J. Cavalier et al.[31]



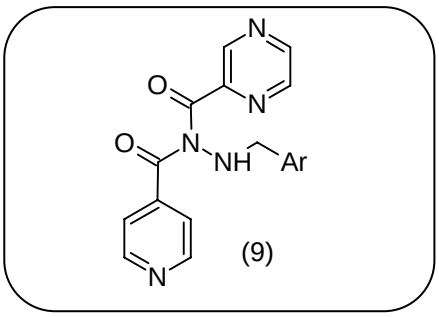
B. A. Ellsworth et al.[32] have studied structure activity relationships for a series of pyrazine carboxamide (7) as CB1 antagonists. Pharmaceutical properties of the series (7) were improved via inclusion of hydroxyl containing side chains. This structural modification sufficiently improved ADME properties of an orally inactive series such that food intake reduction was achieved in rat feeding models.



J. W. Corbett et al.[33] have synthesized indanylpyrazines (8) and reported corticotrophin releasing factor type-1 receptor antagonists.

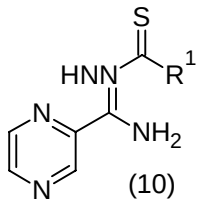


N. Sinha et al.[34] have synthesized and screened antimycobacterial activity of some pyrazine derivatives (9). K. Yoshiizumi et al.[35] have synthesized and studied structure activity relationships of 5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine based hydroxamic acids as HB-EGF shedding inhibitors.



(9)

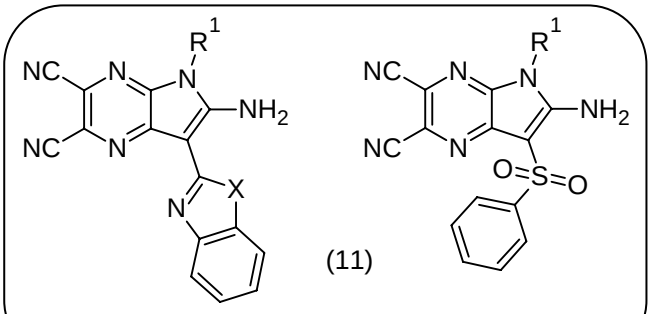
Pyrazin-2-yl-formamide thiosemicarbazones (10) related to their tuberculostatic activity was reported by A. Olczak et al.[36]



R^1 = secondary amine

(10)

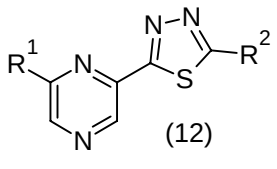
The novel structures 5,7-disubstituted 6-amino-5*H*-pyrrolo[3,2-*b*]pyrazine-2,3-dicarbonitriles (11) and their promising protein kinase inhibitors with antiproliferative activity was given by G. G. Dubinina et al.[37]



(11)

X = NH, N-CH_3, N-CH_2Ph, S

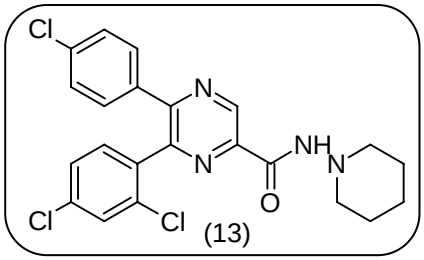
Synthesis and tuberculostatic activity of pyrazinyl substituted derivatives (12) was reported by H. Foksi et al.[38]



R^1 = R^2 = secondary amine

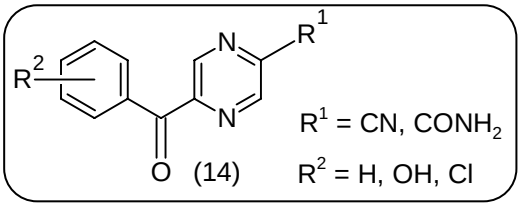
(12)

J. Bostrom et al.[39] have studied scaffold hopping, synthesis and structure activity relationships of 5,6-diaryl-pyrazine-2-amide derivatives (13) of CB1 receptor antagonists.



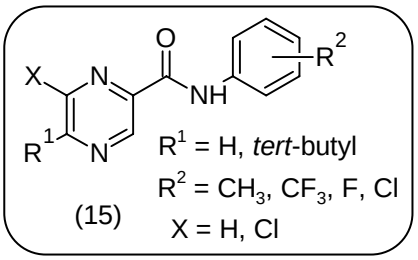
(13)

Synthesis and biological activity of 5-aroylpyrazine-2-carboxylic acid derivatives (14) was given by M. Dolezal et al.[40]



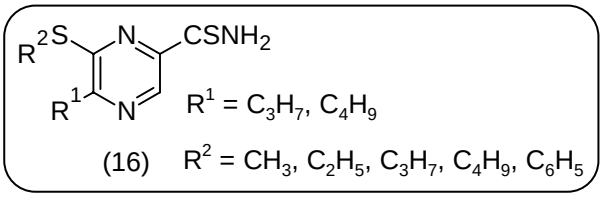
(14)

M. Dolezal et al.[41] have synthesized and reported antimycobacterial evaluation of substituted pyrazine carboxamide derivatives (15).



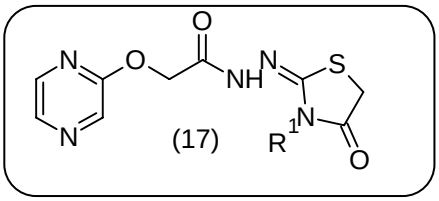
(15)

J. Krinkova et al.[42] have synthesized and evaluated biological activity of 5-alkyl-6-(arylsulfanyl)pyrazine-2- thioamides derivatives (16).



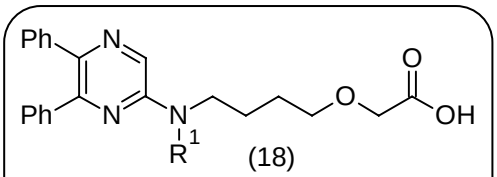
(16)

C. G. Bonde coworkers[43] have synthesized and given preliminary evaluation of some pyrazine derivatives (17) as antimicrobial agents.



(17)

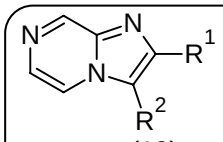
T. Asaki et al.[44] have studied structure activity on diphenylpyrazine derivatives (18) of prostacyclin receptor agonists.



(18)

R^1 = ethyl, allyl, cyclopropyl

Synthesis and antiinflammatory activity of methyl substituted imidazo[1,2-*a*]pyrazine derivatives (19) was reported by M. G. Rimoli et al.[45]



(19)

R^1 = CH_3, CH_2COOH, COOH

R^2 = H, COOH

Synthesis of two new hybrid metal-organic polymers using flexible pyrazine crystal structures were given by C. Zhang et al.[46] Synthesis and biological evaluation of pyrido[2,3-*b*]pyrazine-*N*-oxide as selective glycine antagonists was reported by A. Cugola et al.[47] J. E. Dowling et al.[48] have synthesized of [1,2,4]triazolo[1,5-*a*]pyrazines as adenosine A_{2A} receptor antagonists. C. A. Hargreaves and coworkers[49] have studied tetrahydropyrido[2,3-*b*]pyrazine scaffolds. H. Mukaiyama et al.[50] have synthesized and given C-SRC inhibitory activity of imidazo[1,5-*a*]pyrazine derivatives as an agent for treatment of acute ischemic stroke. D. R. Owen et al.[51] have studied structure activity relationships of pyrazine derivatives as a novel non competitive mGluR1 antagonists. Synthesis and antimycobacterial activity of pyrazine derivatives documented by L. E. Seitz et al.[52] Imidazo[1,2-*a*]pyrazine shows the bronchodilatory and cyclic nucleotide phosphodiesterase inhibitory activities was given by T. O. Vitse et al.[53]

Thus the important role displayed by pyrazine and its derivatives for various therapeutic and biological activities prompted us to synthesize some pyrazine derivatives

in order to achieve compounds having better therapeutic activities, which summarized in this part as under.

STUDIES ON PYRAZINE DERIVATIVES

PART-I: STUDIES ON 2-(PIPERIDINE-4-YLMETHOXY)PYRAZINE DERIVATIVES

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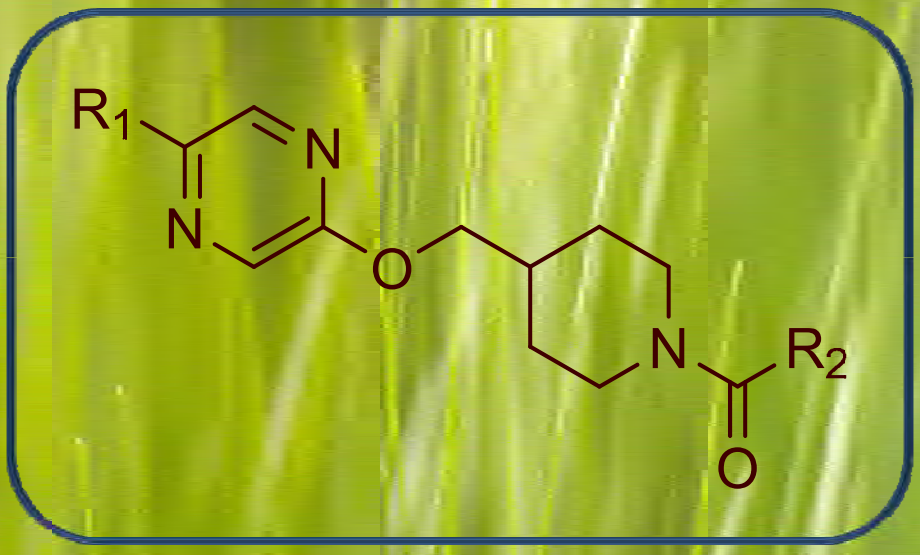
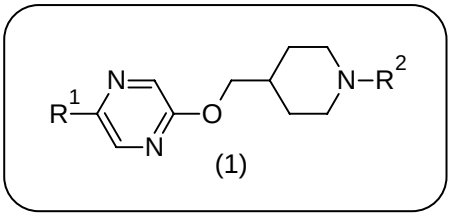
PART-I

STUDIES ON 2-(PIPERIDIN-4-YLMETHOXY)PYRAZINE DERIVATIVES



INTRODUCTION

Pyrazine nucleus possesses remarkable pharmaceutical importance and biological activities, some of their derivatives occur as natural products. In view of our ongoing interest in the synthesis of some new potentially bioactive pyrazine derivatives (1) have been described as under.



(1)

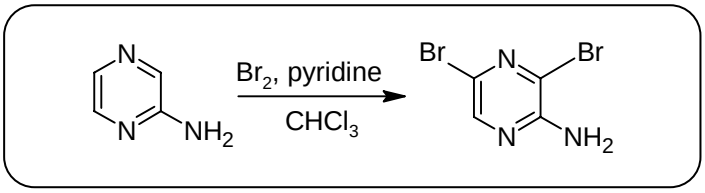
The synthesis of compound 2-(piperidin-4-ylmethoxy)pyrazine derivatives has been attracted widespread attention due to their diverse pharmacological properties like anti-inflammatory, antibiotic, antifungal, herbicidal, antitubercular, etc. To approach this goal synthesis of some new 2-(piperidin-4-ylmethoxy)pyrazine derivatives have been undertaken.

SYNTHETIC ASPECT

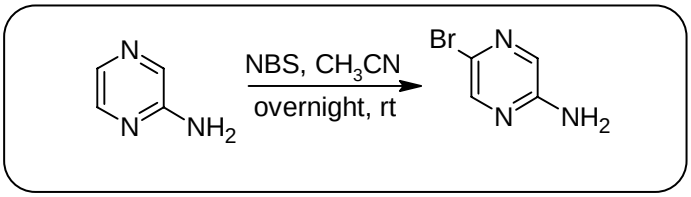
Various methods of bromination, diazotization, mitsunobu reaction, suzuki cross coupling and deprotection of pyrazine derivatives have been cited in literature, some of the methods are as under.

BROMINATION

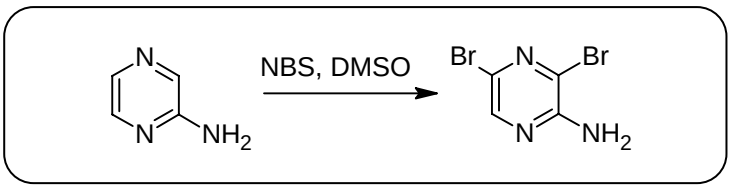
1. Bromination of 2-amino pyrazine in presence of bromine and pyridine in $CHCl_3$ was given by S. Sevilla et al.[1]



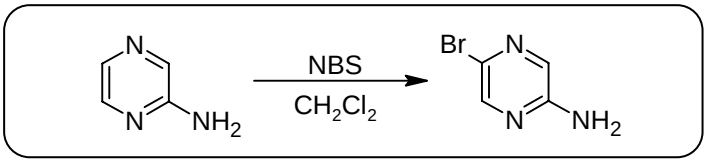
2. F. D. Weal et al.[2] have synthesized 2-amino-5-bromopyrazine from 2-amino pyrazine, *N*-bromosuccinamide in acetonitrile solution.



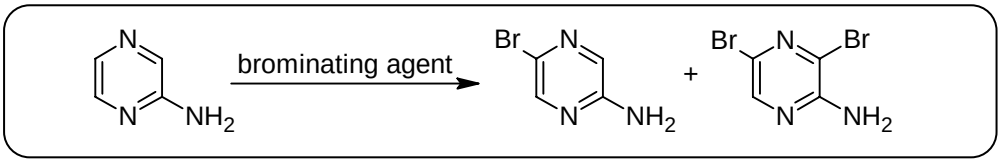
3. 2-Amino pyrazine react with *N*-bromosuccinamide in DMSO solution to give 2-amino-3,5 dibromo pyrazine was reported by B. Jiang et al.[3]



4. A. M. Stadler et al.[4] have synthesized 2-amino-5-bromopyrazine from 2-amino pyrazine, *N*-bromosuccinamide in CH_2Cl_2 solution.

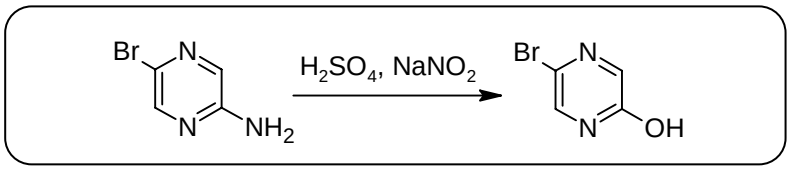


5. T. Itoh et al.[5] have been synthesized 2-amino-5-bromopyrazine from 2-amino pyrazine with brominating agent.

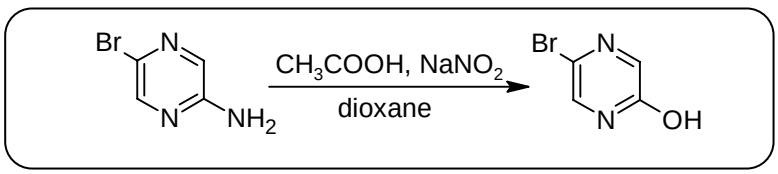


DIAZOTIAZITION

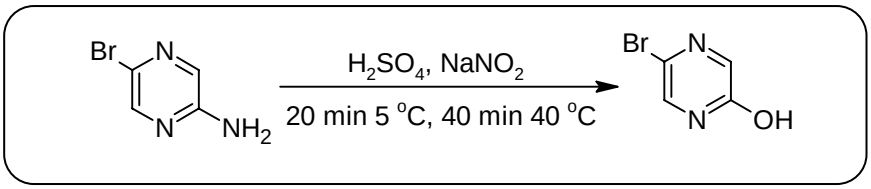
1. Preparation of 5-bromopyrazin-2-ol from 2-amino-5-bromopyrazine, $NaNO_2$ and H_2SO_4 was reported by F. Jing et al.[6]



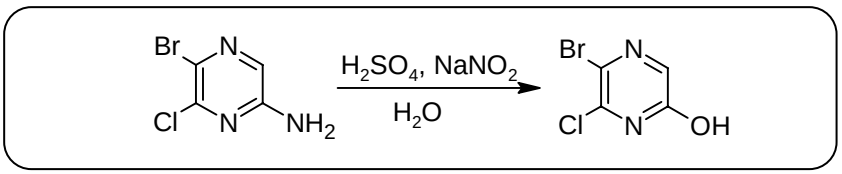
2. H. Mukaiyama et al.[7] have prepared 5-bromopyrazin-2-ol from 2-amino-5-bromopyrazine, $NaNO_2$ and CH_3COOH in dioxane solution.



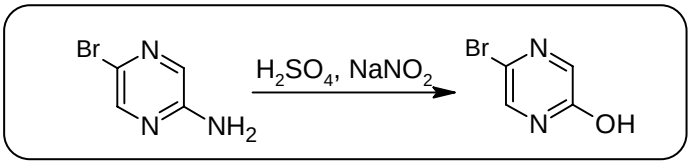
3. S. Nobuhiro et al.[8] have studies diazotization of 2-amino-5-bromopyrazine in sulphuric acid and sodium nitrate.



4. H_2SO_4 and sodium nitrate react with 2-aminopyrazine to give 2-hydroxypyrazine which was given by Y. Jun et al.[9]

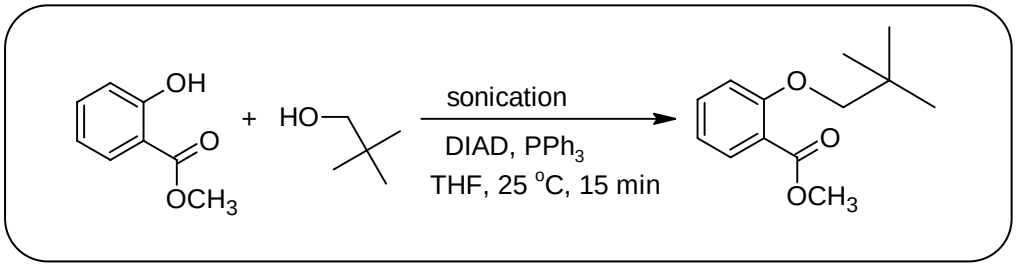


5. A. E. Erickson et al.[10] have synthesized 5-bromopyrazin-2-ol from 2-amino-5-bromopyrazine, $NaNO_2$ and H_2SO_4.

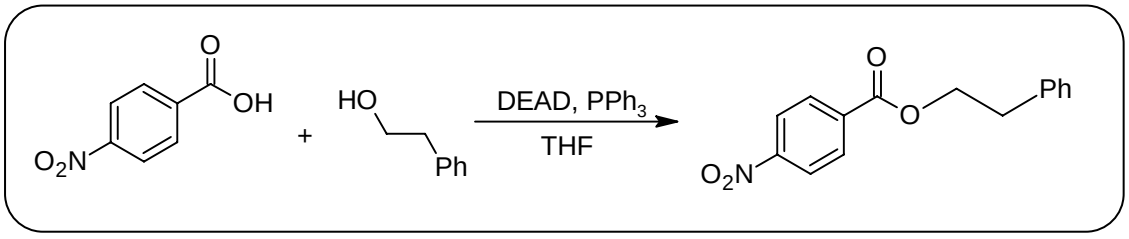


MITSUNOBU REACTION

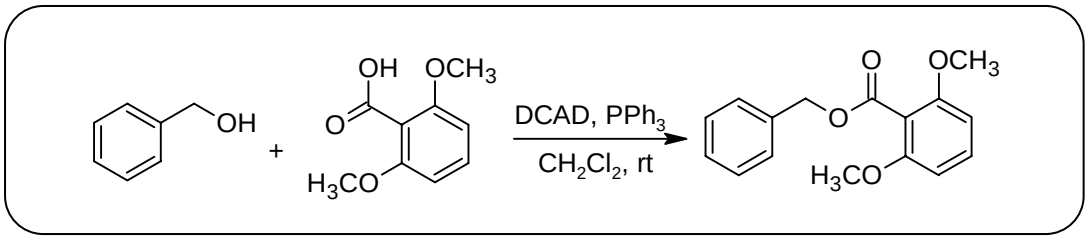
1. Use of sonication for the coupling of sterically hindered substrates in the phenolic mitsunobu reaction was reported by S. D. Lepore et al.[11]



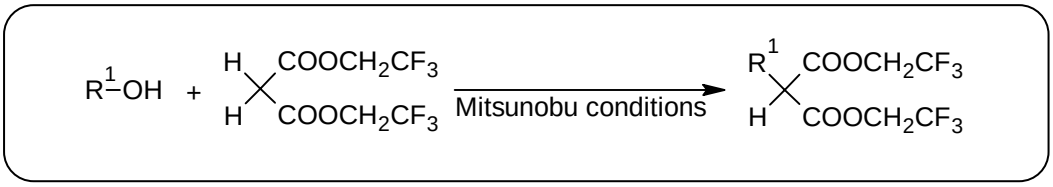
2. Organocatalytic mitsunobu reaction of phenol and acid in THF was documented by T. Y. S. But et al.[12]



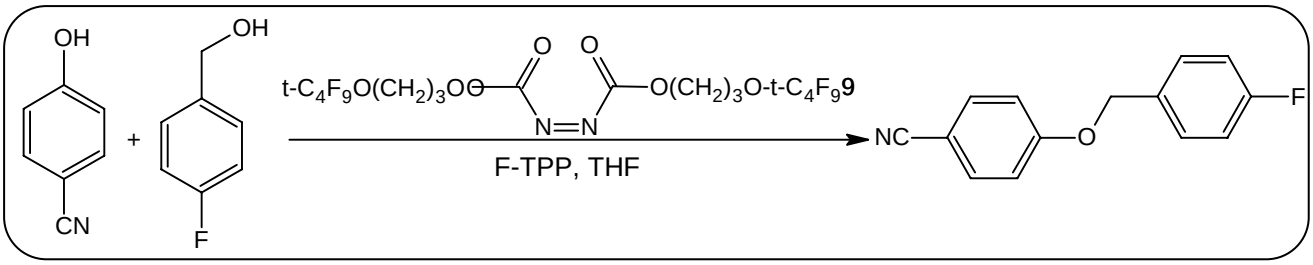
3. Di-p-chlorobenzyl azodicarboxylate (DCAD) was introduced as a novel, stable and solid variety of mitsunobu coupling in CH_2Cl_2 was given by B. H. Lipshutz et al.[13]



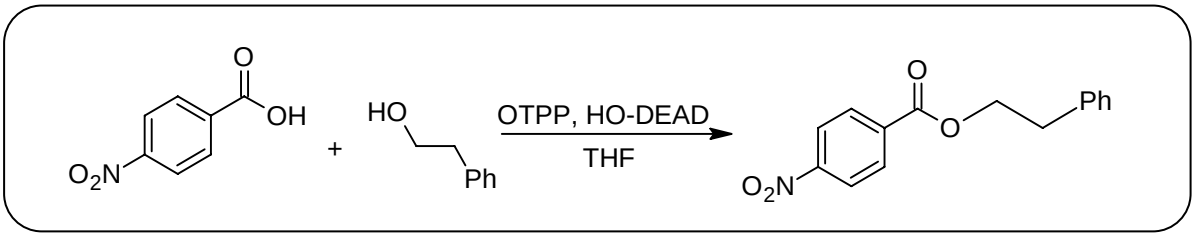
4. Carbon nucleophiles in the mitsunobu reaction, mono- and dialkylation of bis(2,2,2-trifluoroethyl) malonates was given by J. M. Takacs et al.[14]



5. Second-generation tags for fluorous chemistry exemplified with a new fluorous mitsunobu reagent and fluorous triphenylphosphine in THF was reported by Q. Chu et al.[15]



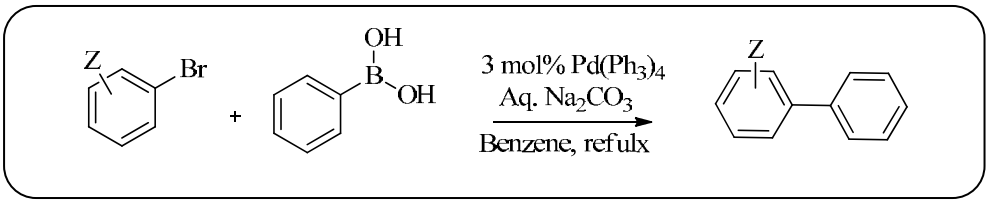
6. Multipolymer solution-phase organocatalytic mitsunobu reaction of phenol and acid in THF was reported by A. M. Harned et al.[16]



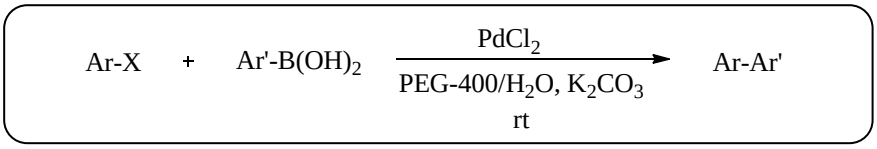
SUZUKI CROSS COUPLING

1. The well known Suzuki reaction[17] is the organic reaction of an aryl or vinyl-boronic acid with an aryl or vinyl-halide catalyzed by a palladium (0) complex forming carbon-carbon bond. Some reported reactions are described as under.

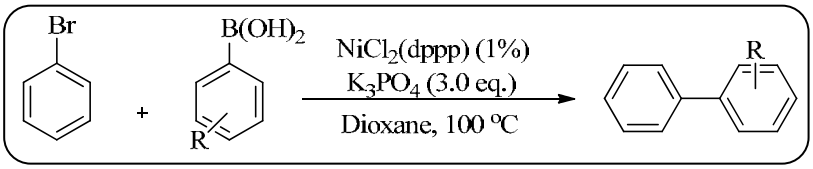
2. In 1981, A.Suzuki and N.Miyaura et al.[18] have made a breakthrough in the methodology for biaryl compounds using aryl boronicacids and aryl bromide under homogeneous palladium catalyzed conditions in the presence of base.



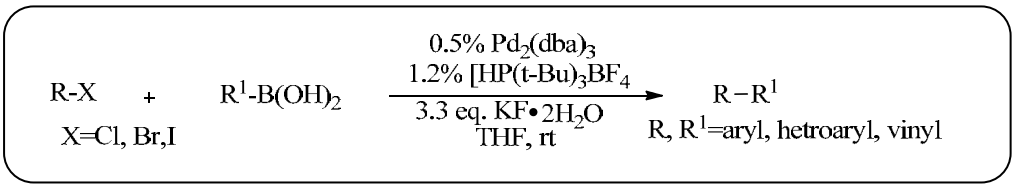
3. Z.Du et al.[19] have reported an ultrafast and highly efficient ligand-free Suzuki-Miyaura cross-coupling reaction between aryl bromides/iodides and aryl boronicacids using palladium chloride as catalyst in PEG-400/H_2O in air at room temperature. TEM showed that palladium nanoparticles were generated in situ from $PdCl_2$/PEG-400/H_2O without use of other reductants. The catalyst system can be recycled to reuse three times with good yields.



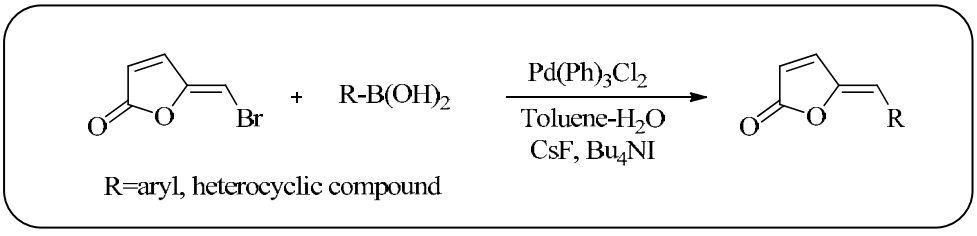
4. Yu-L.Zhao et al.[20] have prepared a highly practical and reliable Nickel catalyst for Suzuki–Miyaura coupling of aryl halides with various aryl boronicacid.



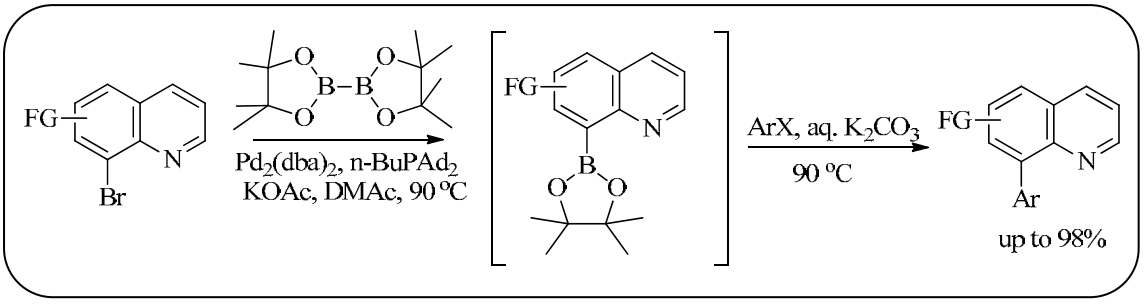
5. S.Lou et al.[21] have developed Palladium/Tris(tert-butyl)phosphine-Catalyzed Suzuki Cross-Couplings of aryl and heteroaryl halides with aryl and heteroaryl boronic acids in the Presence of Water.



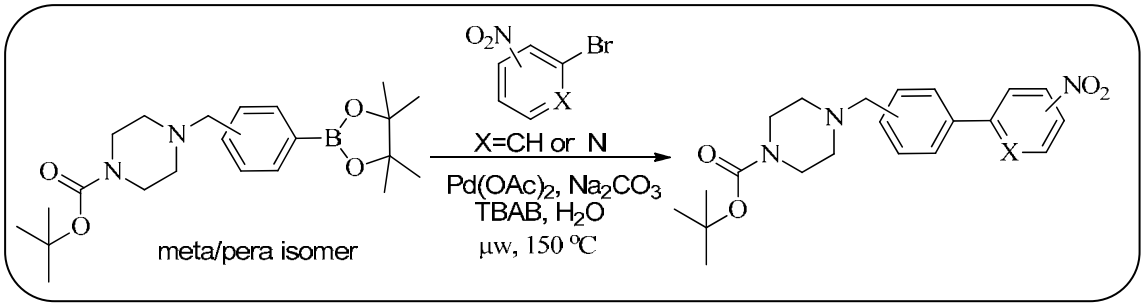
6. R.Zhang et al.[22] have synthesized a series of novel 5-arylidenefuran-2(5*H*)-ones and 5-arylidene-4-arylfuran-2(5*H*)-ones *via* the Suzuki-Miyaura reactions.



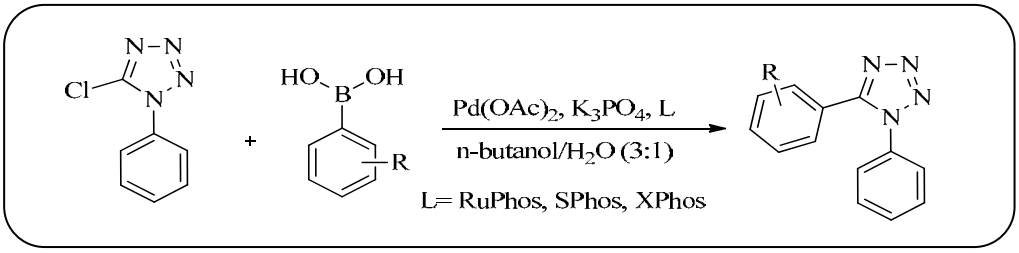
7. Y.Zhang et al.[23] have been developed one-pot process for the synthesis of 8-arylquinolines *via* Pd-catalyzed borylation of quinoline-8-yl halides and subsequent Suzuki-Miyaura coupling with aryl halides using *n*-BuPAd$_2$ as ligand.



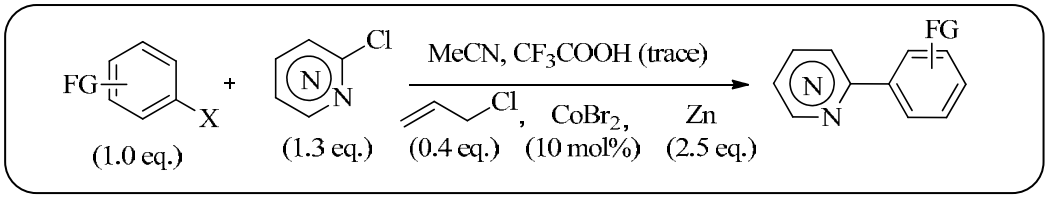
8. J.Spencer et al.[24] have reported synthesis of a (piperazin-1-ylmethyl)biaryl library via microwave-mediated Suzuki–Miyaura cross-couplings.



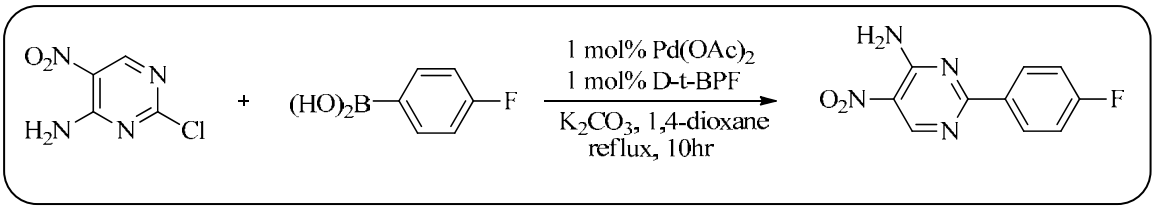
9. Q.Tang et al.[25] have developed Suzuki–Miyaura coupling reactions of 5-chloro-1-phenyl-tetrazole with various functionalized aryl boronicacids in the presence of catalytic amounts of SPhos/Pd(OAc)$_2$ or RuPhos/Pd(OAc)$_2$.



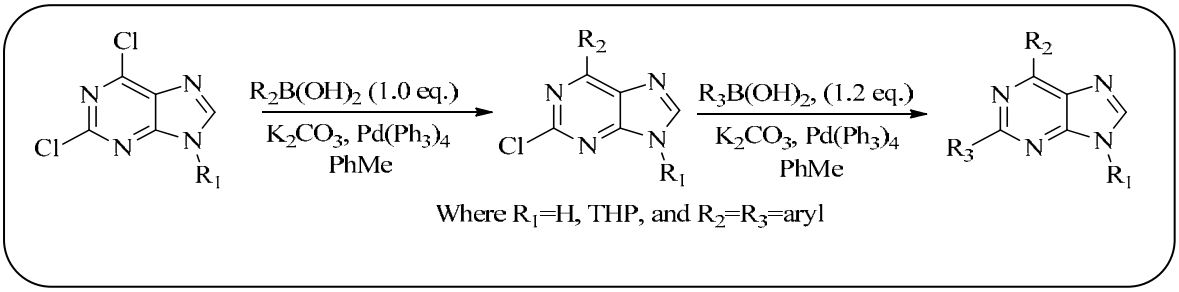
10. J.-M. Begouin et al.[26] have reported cobalt-catalyzed cross-coupling between aryl zinc halides and 2-chloropyrimidine/2-chloropyrazine prepared in situ.



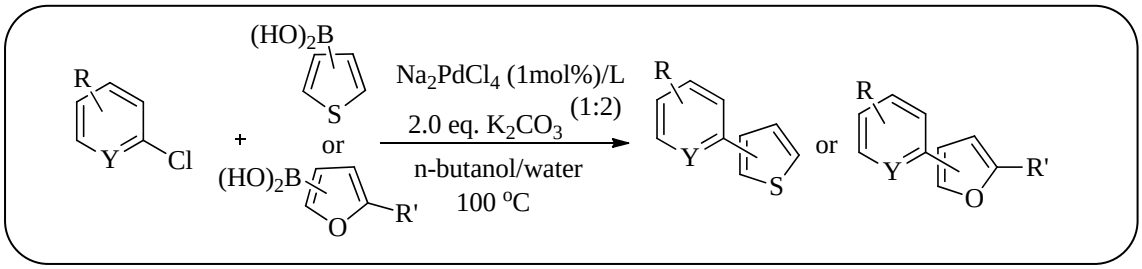
11. T. Itoh et al.[27] have discovered a direct synthesis of hetero-biaryl compounds containing an unprotected NH_2 group *via* Suzuki–Miyaura reaction by using $Pd(OAc)_2$ and D-t-BPF ligand as a catalyst.



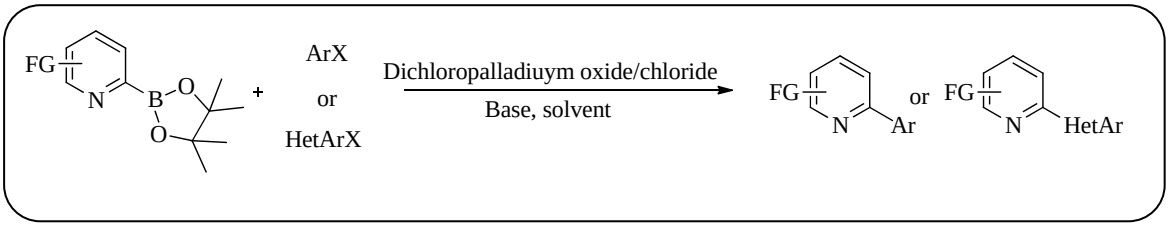
12. L.C.W. Chang et al.[28] synthesized 2,6-disubstituted and 2,6,8-trisubstituted purines as adenosine receptor antagonists *via* Suzuki–Miyaura reaction.



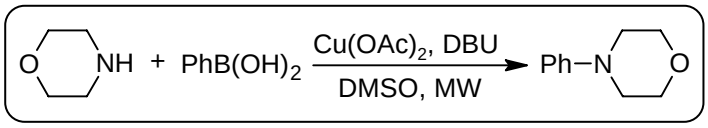
13. C. A.Fleckenstein et al.[29] have reported an efficient Suzuki-Miyaura coupling of (hetero)aryl chlorides with Thiophene- and Furan boronicacids in aqueous *n*-butanol.



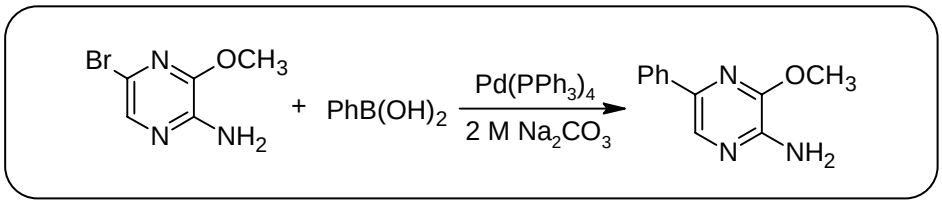
14. D. X. Yang et al.[30] have reported palladium-catalyzed Suzuki-Miyaura coupling of Pyridyl-2-boronic esters with aryl halides using highly active and air-stable phosphine chloride and oxide Ligands.



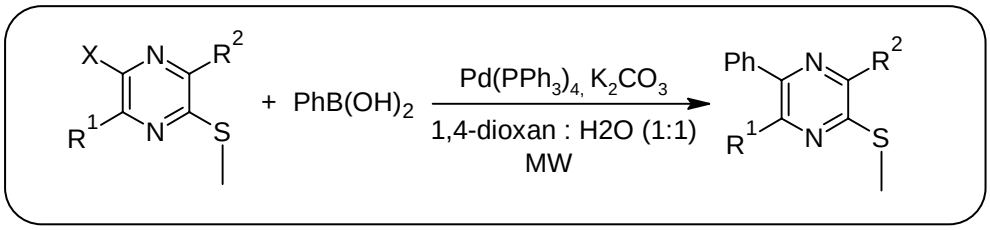
15. Microwave-assisted efficient copper-promoted *N* arylation of amines with arylboronic acids was given by S. Chen et al.[31]



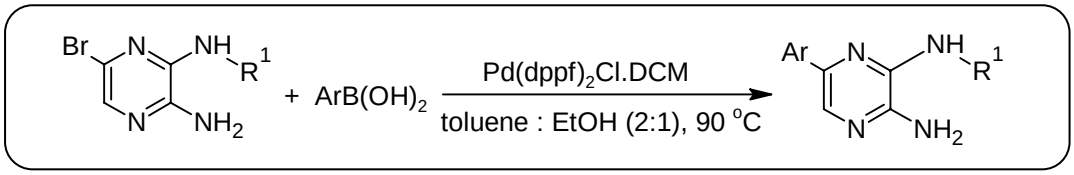
16. Stepwise cross-coupling reactions in pyrazine derivatives was reported by C. Yang et al.[32]



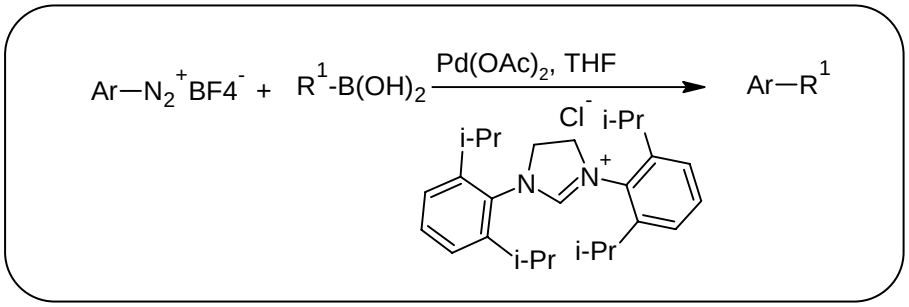
17. A novel and versatile entry to asymmetrically substituted pyrazines was reported by V. P. Mehta et al.[33]



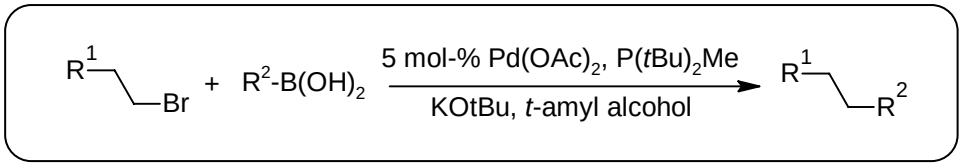
18. Microwave-assisted synthesis C-C bond formation of pyrazine derivatives was documented by S. Sevilla et al.[1]



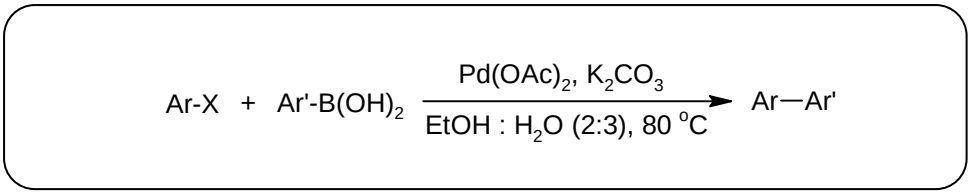
19. Palladium imidazolium carbene catalyzed aryl, vinyl and alkyl suzuki-miyaura cross coupling synthesis was given by M. B. Andrus et al.[34]



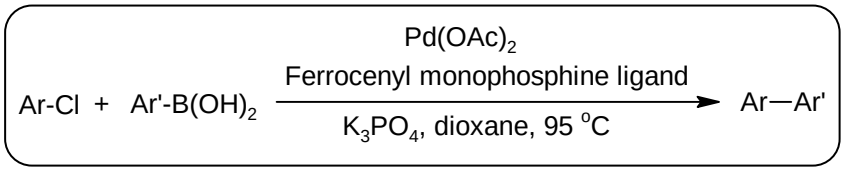
20. New coupling partners in room temperature suzuki reaction of alkyl bromides under remarkable mild conditions was reported by J. H. Kirchhoff et al.[35]



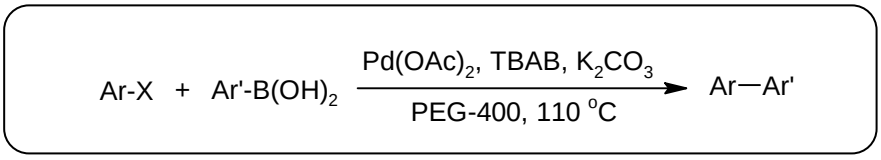
21. S. Li et al.[36] have synthesized $Pd(OAc)_2$-catalyzed room temperature suzuki cross-coupling reaction in aqueous media under aerobic conditions.



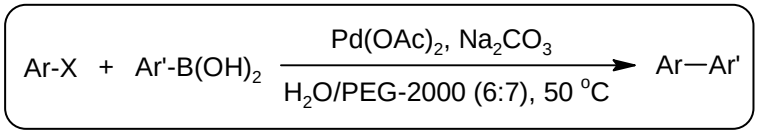
22. C. Baillie et al.[37] have documented and given its applications in the suzuki-miyaura coupling of aryl chlorides in presence of ferrocenyl monophosphine ligand in dioxane.



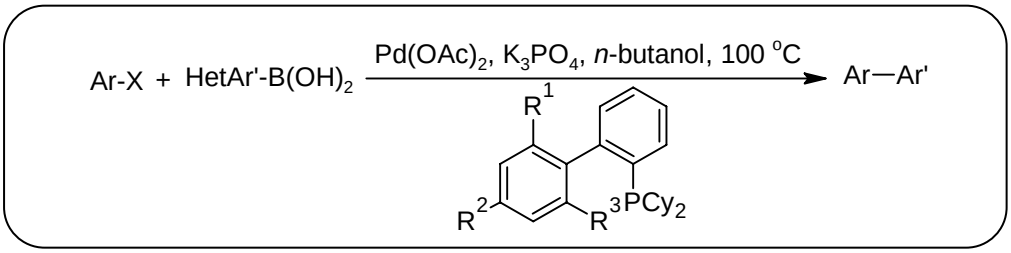
23. Suzuki-miyaura cross-coupling reaction under ligand free conditions was given by W. J. Liu et al.[38]



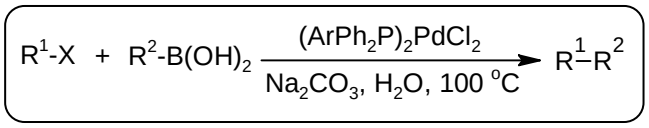
24. Phosphine free palladium acetate catalyzed suzuki reaction in water was given by L. Liu et al.[39]



25. A highly active catalyst for suzuki-miyaura cross coupling reactions of heteroaryl compounds was reported by K. L. Billingsley et al.[40]

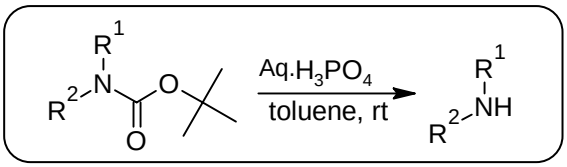


26. Y. M. A. Yamada et al.[41] have prepared highly active catalyst for the heterogeneous suzuki-miyaura reaction by assembled complex of palladium and non-cross-linked amphiphilic polymer.

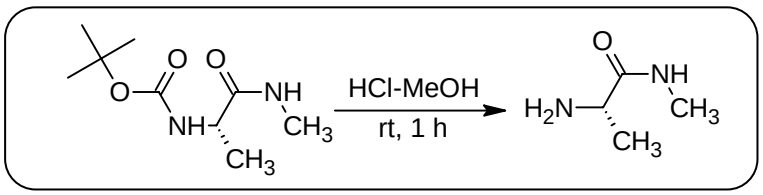


DEPROTECTION

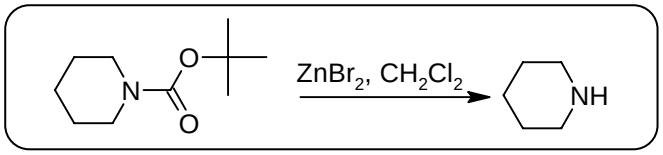
1. B. Li et al.[42] have used aqueous phosphoric acid is an effective, environmentally benign, selective and mild reagent for the deprotection of *tert*-butyl carbamates.



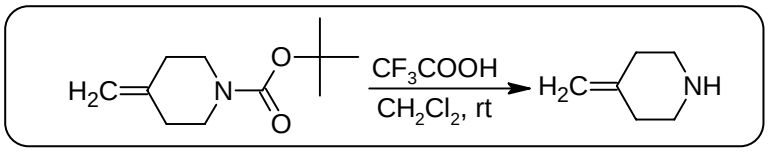
2. A stereo conservative deprotection method of amino groups was reported by D. M. Shendage et al.[43]



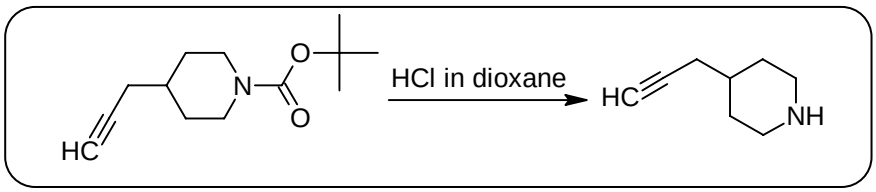
3. Selective removal of the *tert*-butoxycarbonyl group from secondary amines using zinc bromide as the deprotecting reagent was given by S. C. Nigama et al.[44]



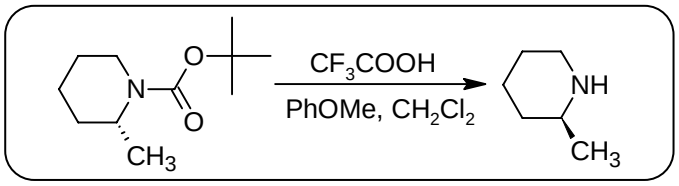
4. N. B. Narasimhulu et al.[45] have studied deprotection of piperidine derivatives from *tert*-butyl piperidine and TFA in chloroform solution.



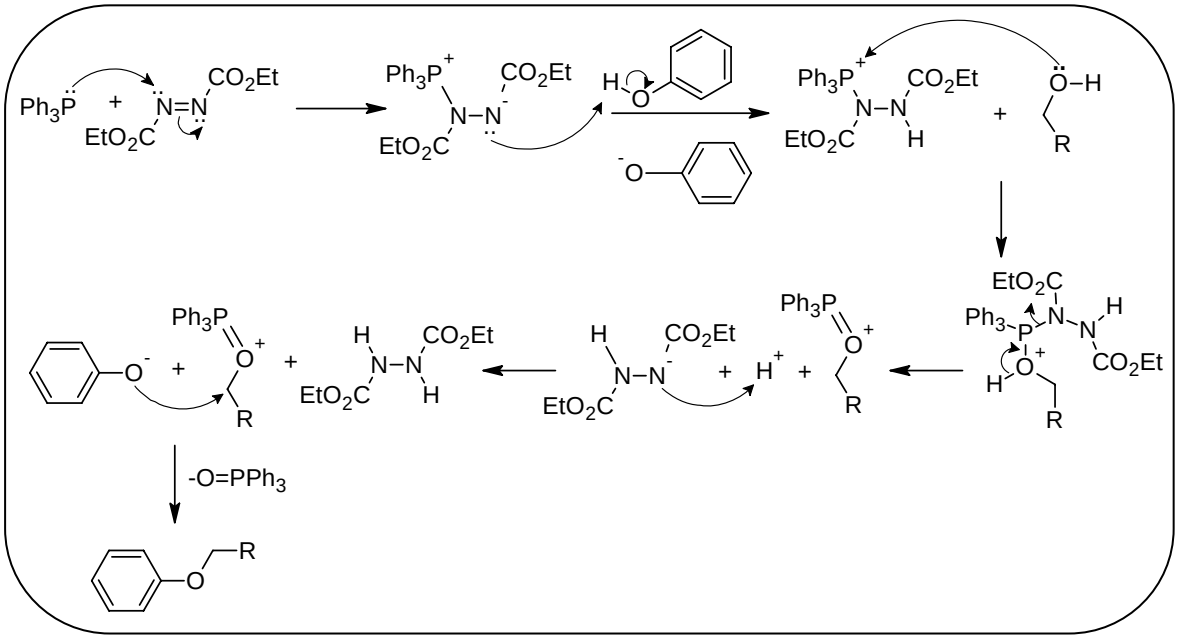
5. Reaction of *tert*-butyl 4-(prop-2-yn-1-yl)piperidine-1-carboxylate in HCl in dioxane solution to gave 4-(prop-2-yn-1-yl)piperidine was carried out by N. D. Waal et al.[46]



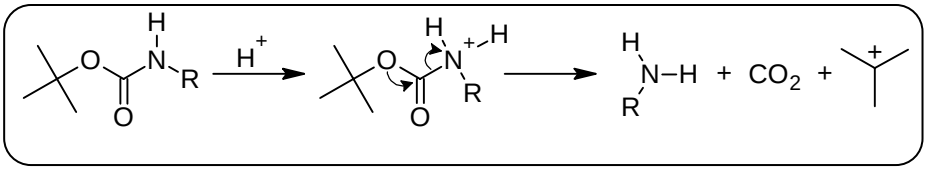
6. F. Bois et al.[47] have studied deprotection of (2*S*)-2-methylpiperidine from *tert*-butyl (2*R*)-2-methylpiperidine-1-carboxylate, CF_3COOH and anisole in dichloromethane solution.



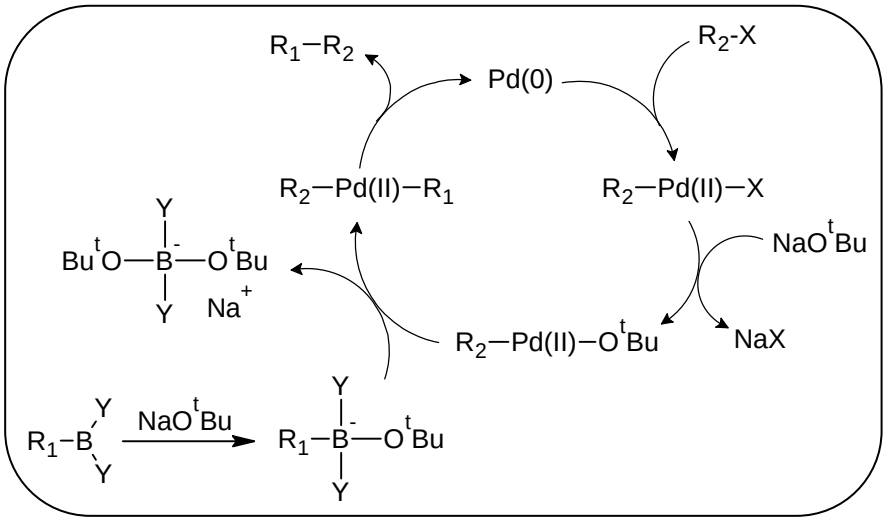
REACTION MECHANISM OF MITSUNOBU



REACTION MECHANISM OF DEPROTECTION



REACTION MECHANISM OF SUZUKI COUPLING

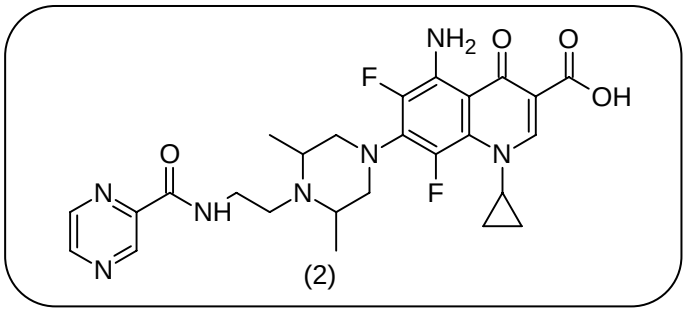


THERAPEUTIC IMPORTANCE

2-(Piperidine-4-yl methoxy)pyrazine derivatives have been tested for various pharmacological activities, which have been summarized as under.

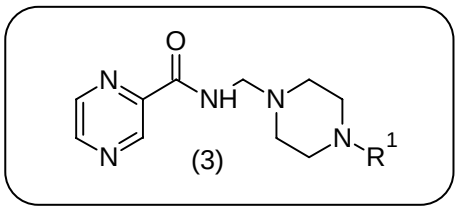
1. Analgesic[48]
2. Antibacterial[49]
3. Antifungal[50]
4. Anti-inflammatory[51]
5. Antiviral[52]
6. Anticancer[53]
7. Anti HIV[54]

A. V. Shindikar et al.[55] have designed, synthesized, and tested *in vivo* activity in mice against *mycobacterium tuberculosis H37Rv* of pyrazine derivatives (2). K. J. French et al.[56] have studied cyclohexyl-octahydro-pyrrolo[1,2-*a*]pyrazine based inhibitors of human *N*-myristoyltransferase-1.



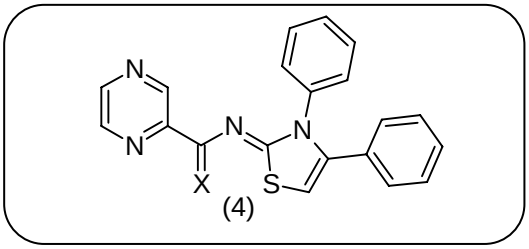
(2)

D. Sriram et al.[57] have synthesized pyrazinamide derivatives (3) and reported antitubercular properties. D. C. Scopes et al.[58] have synthesized new k-receptor agonists based upon a 2-[(alkylamino)methy]piperidine nucleus.



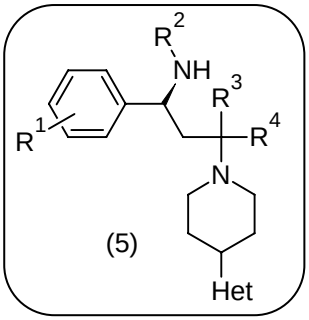
(3)

Synthesis, anticancer, anti-inflammatory and analgesic activity evaluated of some pyrazine derivatives have been (4) reported by S. M. Sondhi et al.[59] B. S. Huegi et al.[60] have synthesized and reported pharmacological studies on 4,4-disubstituted piperidine derivatives as a potent analgesic properties.



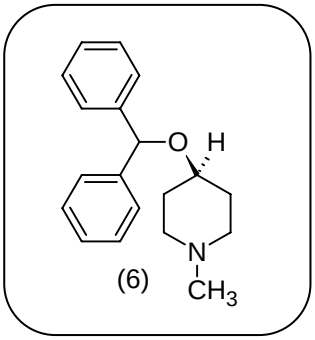
(4)

B. C. Gordon et al.[61] have synthesized pharmaceutical composition containing piperidine derivatives (5) and doccumented their use as modulators of chemokine CCR5 receptors. Synthesis and analgesic activity of some spiro[dibenz[*b,f*]oxepin]-10,4'-piperidine] derivatives was reported by H. H. Ong et al.[62]



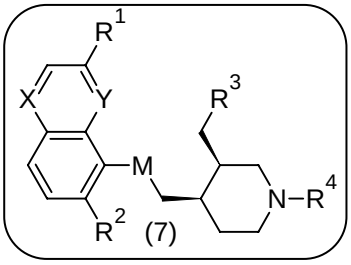
(5)

Antimycobacterial and H^1-antihistaminic activity of 2-substituted piperidine derivatives (6) was given by R. Weis et al.[63] A. Z. Kabdraisova et al.[64] have reported synthesis and biological activity of *N*-(2-thoxyethyl)piperidine derivatives of anabasin. Some piperidine substituted with benzimidazoles was reported by V. Sundari et al.[65] as bioactive substance.A. Seza et al.[66] have studied antimicrobial activity of some piperidine substituted halogenobenzene derivatives.



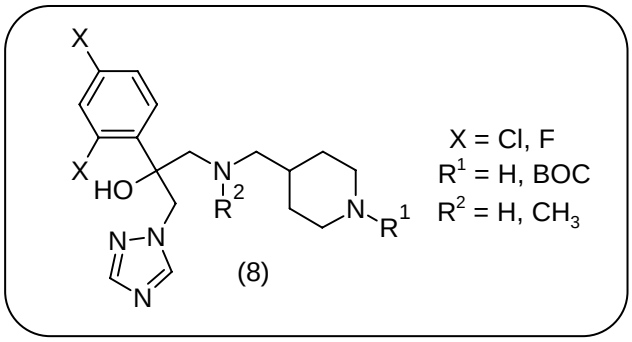
(6)

S. J. Philippe et al.[67] have prepared piperidine derivatives (7) and tested antibiotics activity. Effect of substituents on *N*-(1-piperidinobenzyl)acetamide and their antimicrobial activity was reported by N. Raman et al.[68] M. Yoshifumi et al.[69] have studied antimicrobial and anti-plaque activity of *N*'-alkyl-*N*-(2-aminoethyl)piperidine against dental plaque bacteria.



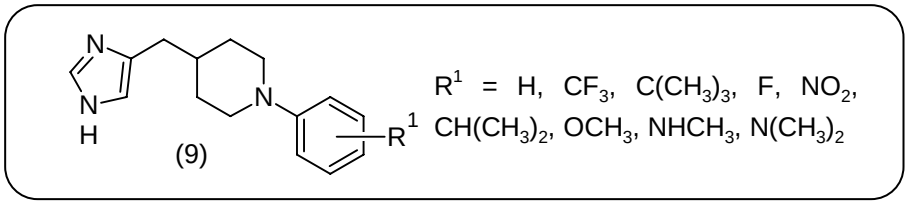
(7)

Synthesis and structure activity relationships of 2-phenyl-1-[(pyridinyland piperidinylmethyl)amino]-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ols (8) as antifungal agents was given by F. Giraud et al.[70] K. K. Goel et al.[71] have synthesized and screened for antimicrobial activity of piperidin-4-one derivatives. K. Canan et al.[72] have synthesized and tested antimicrobial activity of some novel 2-[4-(substituted piperidin-1-ylcarbonyl)phenyl]-1*H*-benzimidazole derivatives.



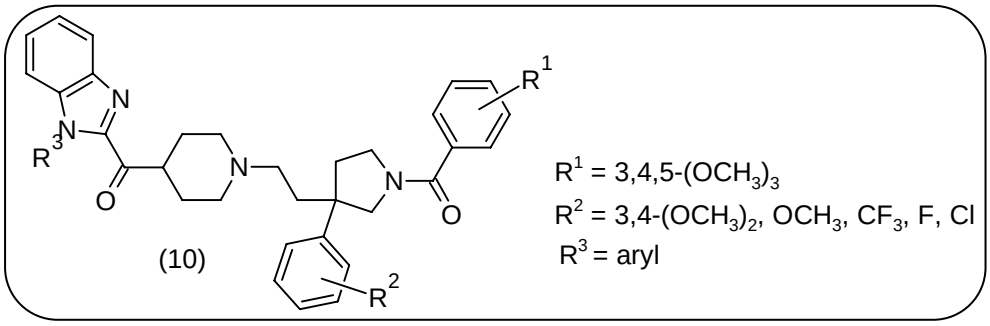
(8)

M. Ishikawa et al.[73] have synthesized and given structure activity relationships of *N*-aryl-piperidine derivatives (9) as potent (partial) agonists for human histamine H3 receptor. M. Tibor et al.[74] have studied histamine H3 receptor antagonists of 1-(4-Phenoxymethyl) benzyl)piperidines derivatives.



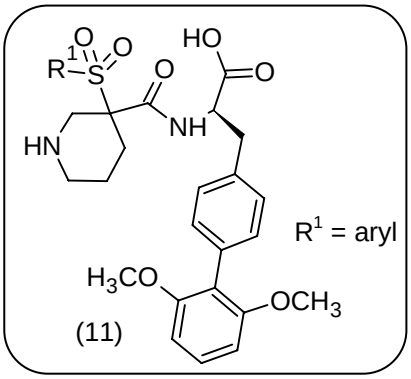
(9)

G. D. Maynard et al.[75] have synthesized and reported SAR of 4-(1*H*-benzimidazole-2-carbonyl)piperidines (10) with dual histamine H_1/tachykinin NK_1 receptor antagonist activity. A. G. Magid et al.[76] have synthesized substituted piperidine derivatives as novel H1-antagonists. V. Claudio et al.[77] studied antinociceptive profile of 2,3,6-trisubstituted piperidine alkaloids.



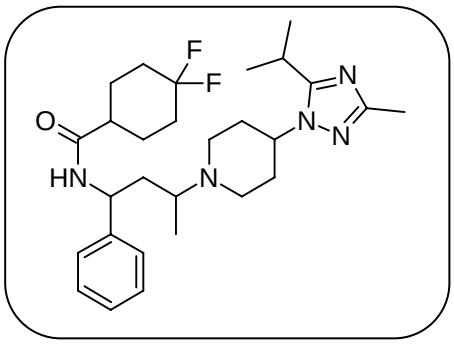
(10)

C. E. Gutteridge et al.[78] have studied *N*-(3-phenylsulfonyl-3-piperidinoyl)-phenylalanine derivatives (11) as potent, selective VLA-4 antagonists. Study of piperidine carboxylic acid derivatives of 10*H*-pyrazino[2,3-*b*][1,4]benzothiazine as orally active adhesion molecule inhibitors investigated by K. Toshihiko et al.[79]

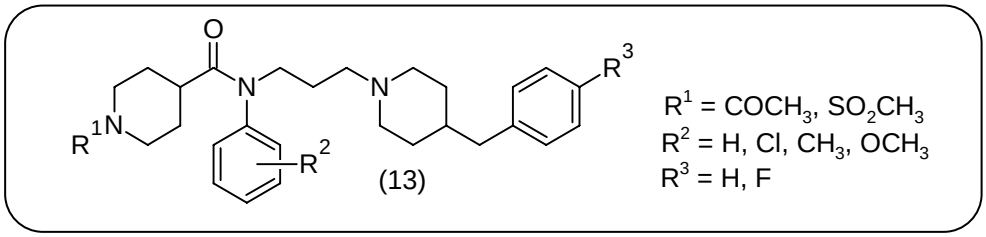


(11)

C. G. Barber et al.[80] have investigated 1-amino-1-phenyl-3-piperidinylbutanes (12) CCR5 antagonists for the treatment of HIV. Analgesic and antiinflammatory activity screening of 6-acyl-3-piperidinomethyl-2(3*H*)-benzoxazolone derivatives was reported by E. D. Demir et al.[81]



S. Imamura et al.[82] synthesized and reported biological evaluation of piperidine-4-carboxamide derivatives (13) as CCR5 antagonists as anti-HIV-1 agents. Synthesis and biological activity of piperidinoaryl carbamides and their derivatives was reported by V. M. Gujrati et al.[83] W. Tao et al.[84] have synthesized diketopiperidine derivatives as HIV attachment inhibitors and reported, pharmaceutical compositions and use in the treatment of HIV infection and AIDS.



(13)

R. H. K. Foster and coworkers[85] have studied piperidine derivatives with morpholine like analgesia activity. Study of (2S)-1-(arylacetyl)-2-(aminomethyl)piperidine derivatives and highly selective kappa opioid analgesics was

given by V. Vecchietti et al.[86] M. Eiichi and coworkers[87] have synthesized and reported antiallergic activity of novel pyrazine derivative. Synthesis and anti mycobacterial evaluation of some pyrazine-2-carboxylic acid hydrazide derivatives was documented by A. A. Mohamed et al.[88] G. Katarzyna et al.[89] have synthesized and screened antibacterial activity of novel pyrazine derivative obtained from amindoximes. Synthesis and antibacterial activity of 6-methoxypyrazine-2-carboxylic acid hydrazide derivatives was reported by G. Katarzyna et al.[90] Synthesis and antimicrobial activity of 2,3-(substituted phenyl)pyrazine dicarboxamide was given by N. S. Rao et al.[91] Pyrazine-2-substituted carboxamide derivatives synthesis, antimicrobial and leuconostoc mesenteroides growth inhibition activity study investigated by A. H. F. Wahab et al.[92] N. B. Patel et al.[93] have synthesized and reported antimicrobial activity of 2-[3-(arylureido)carbonyl]pyrazine derivatives. A study of 2-piperidino-1-ethanol and its derivatives as antimicrobial additives to oils was reported by S. A. Gamzaeva et al.[94]

Looking to the interesting properties of 2-(piperidine-4-ylmethoxy)pyrazine, we have synthesized some new 2-(piperidine-4-ylmethoxy)pyrazine, which have been describe as under.

PART-I: STUDIES ON 2-(PIPERIDINE-4-YLMETHOXY) PYRAZINE DERIVATIVES

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-BROMOPHENYL)PYRAZIN-2-YL)OXY)METHYL) PIPERIDIN-1-YL)(ARYL)METHANONES

SECTION-II: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-METHOXY-3-METHYLPHENYL)PYRAZIN-2-YL)OXY) METHYL)PIPERIDIN-1-YL)(ARYL)METHANONES

SECTION-III: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-FLUOROPYRIDIN-3-YL)PYRAZIN-2-YL)OXY)METHYL) PIPERIDIN-1-YL)(ARYL)METHANONES

SECTION-IV: SYNTHESIS AND BIOLOGICAL EVALUATION OF ARYL(4-(((5-(m-TOLYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)METHANONES

SECTION-V: SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-METHOXYPHENYL)PYRAZIN-2-YL)OXY)METHYL) PIPERI DIN-1-YL)(ARYL)METHANONES

Part – A

[Part – I (Section-i)]

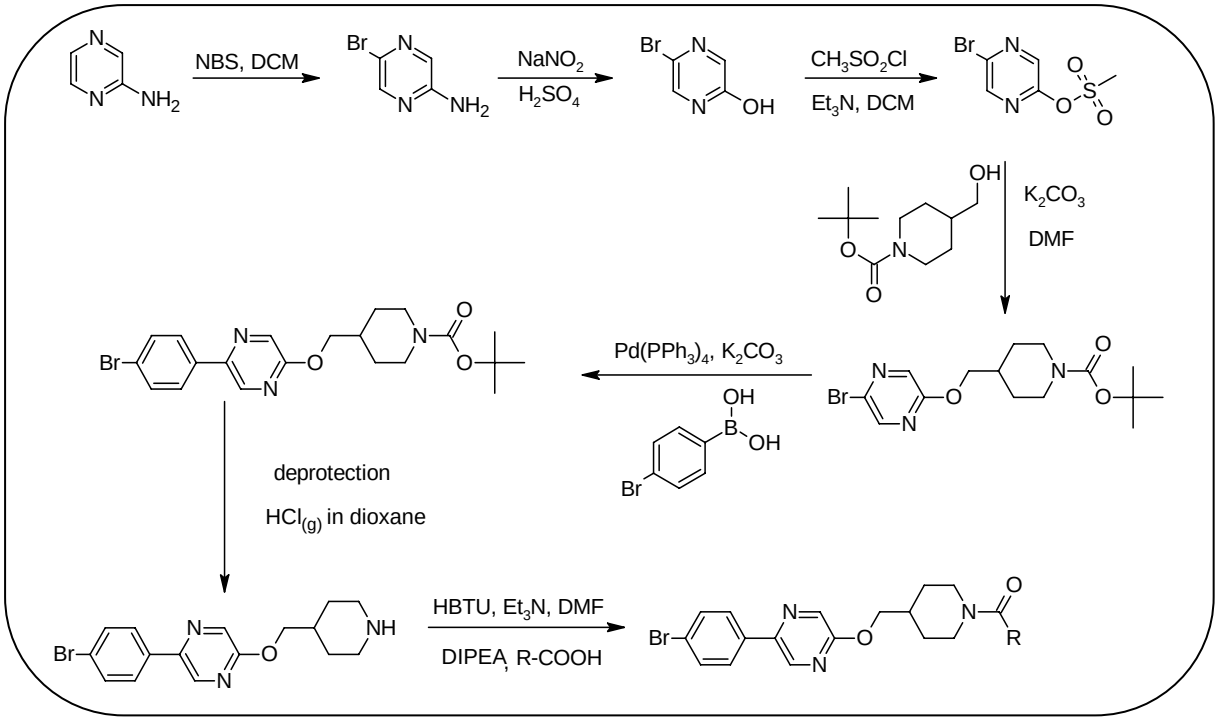
Synthesis and biological evaluation of (4-(((5-(4-(bromophenyl)pyrazin-2-yl)oxy) methyl) piperidin-1-yl)(aryl)methanones

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-BROMOPHEN-YL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL) METHANONES

Pyrazine nucleus possesses remarkable pharmaceutical importance and biological activities, some of their derivatives occur as natural products. In view of these findings, it appeared of interest to synthesize 2-(piperidin-4-ylmethoxy)pyrazines derivatives by the condensation of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA, as shown in reaction scheme.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of 5-Bromopyrazin-2-amine.

To a stirred cooled to 0^oC solution of 2-aminopyrazine (10.0 g, 0.105 mol) in dry DCM (250 ml), *N*-bromosuccinamide (18.72 g, 0.105 mol) was added portion wise. The mixture was stirred at 0^oC for 24 hours. The reaction was monitored on TLC. After completion of the reaction, saturated aqueous solution of sodium carbonate was added (200 ml) to quench the reaction. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the resulting crude product was purified by column chromatography on silica gel (eluent: 2 : 8 = E.A. : Hexane) to obtain pure product. Yield: 70 %, mp 133-135^oC.

[B] Preparation of 5-Bromopyrazin-2-ol.

Sodium nitrite (8.9 g, 0.129 mol) was added portion wise with stirring to concentrated H_2SO_4 (49 ml) at 0^oC and the mixture was warmed to dissolved the solid. The mixture was cooled to 5^oC. To this a solution of 5-bromopyrazin-2-amine (15.0 g, 0.086 mol) in concentrated H_2SO_4 (71 ml) was added slowly. The reaction mixture was stirred bellow 5^oC for 30 minute and warmed to 40^oC for 2 hours. The reaction mixture was poured onto crushed ice. The aqueous solution was extracted with ethyl acetate (250 ml x 3) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*, and the solid product was obtained. Yield: 50 %, mp 80-82^oC.

[C] Preparation of 5-Bromopyrazin-2-yl methanesulfonate.

To a stirred cooled (ice bath) solution of 5-bromopyrazin-2-ol (5.0 g, 0.028 mol) in dry DCM (25 ml), TEA (5.85 ml, 0.042 mol) and CH_3SO_2Cl (2.80 ml, 0.034 mol) was added drop wise in solution at 0^oC. The reaction mixture was stirred for 2 hours at room temperature (monitored by TLC), and the solvent was removed *in vacuo*. The product was filtered, washed with water and dried to give analytical pure product. Yield: 80 %, mp 85-87^oC.

[D] Preparation of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

To a stirred suspension of K_2CO_3 (3.036 g, 0.022 mol) and 5-bromopyrazin-2-yl methanesulfonate (3.0 g, 0.011 mol) in dry DMF (30 ml), *tert*-butyl 4-(hydroxymethyl) piperidine-1-carboxylate (2.54 g, 0.011 mol) was added. The solution was heated on a water bath for 2 hours at 75-80^oC. (monitored by TLC). The reaction mixture was poured onto crushed ice, thus the precipitate obtained, was filtered and washed with water to give pure product. Yield: 68 %, mp 99-101^oC.

[E] Preparation of *tert*-butyl 4-(((5-(4-bromophenyl)pyrazin-2-yl) oxy) methyl) piperidine-1-carboxylate.

A solution of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was further stirred for 5.0 minutes. To this solution (4-bromophenyl)boronic acid(0.880 g, 0.0044 mol), isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K_2CO_3 (10.0 ml, 0.02 mol) in water was added drop wise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 6 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

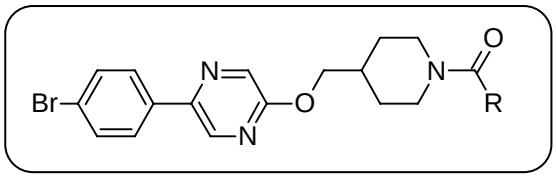
[F] Preparation of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy)pyrazine.

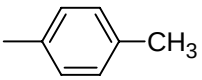
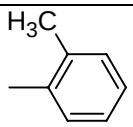
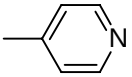
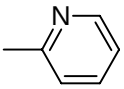
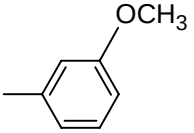
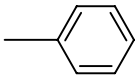
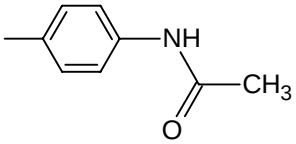
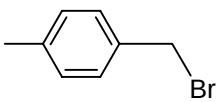
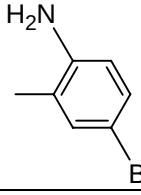
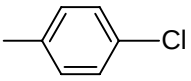
A mixture of $HCl_{(g)}$ in dioxane (10 ml) and *tert*-butyl 4-(((5-(4-bromo phenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate was added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure product. Yield: 63 %, mp 152-154^oC.

[G] General procedure for the preparation of (4-(((5-(4-(bromophenyl)pyrazin-2-yl)oxy)methyl]piperidin-1-yl)(aryl)methanones.

To a cooled mixture of 2-(4-bromophenyl)-5-(piperidin-4-ylmethoxy) pyrazine (0.2 g, 0.570 mmol) and aryl acid (0.570 mmol) in dry DMF (3 ml), HBTU[2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate](0.261 g, 0.690 mmol), DIPEA[di isopropyl ethyl amine] (0.089 g ≅ 0.117 ml,0.690 mmol) and TEA (0.1 ml, 0.850 mmol) was added to basify the content at 0^oC. The reaction mixture was stirred for 10 hours at room temperature (monitored by TLC). The reaction mixture was poured on to crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in **Table-1a.**

Table-1a: Physical constants of (4-(((5-(4-(bromophenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(aryl)methanones.



Sr. No.	Substitution R	MF	MW	Yield (%)	R_f value
1a		$C_{24}H_{24}BrN_3O_2$	466.37	79	0.52
1b		$C_{24}H_{24}BrN_3O_2$	466.37	67	0.51
1c		$C_{22}H_{21}BrN_4O_2$	453.33	76	0.43
1d		$C_{22}H_{21}BrN_4O_2$	453.33	66	0.40
1e		$C_{24}H_{24}BrN_3O_3$	482.36	75	0.46
1f		$C_{23}H_{22}BrN_3O_2$	452.34	84	0.47
1g		$C_{25}H_{25}BrN_4O_3$	509.39	69	0.32
1h		$C_{24}H_{23}Br_2N_3O_2$	545.26	71	0.39
1i		$C_{23}H_{22}Br_2N_4O_2$	546.25	68	0.35
1j		$C_{23}H_{21}BrClN_3O_2$	486.78	82	0.42

TLC solvent system:- E.A. : Hexane = 6 : 4

ANALYTICAL DATA

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl)methanone *(1a).* mp 146-148^{o}C; IR (DRS): 3072, 3031, 2975, 1645, 1563, 1523, 1440, 1352, 1299, 1170, 1054, 883, 835, 749, 695 cm^{-1}; MS: *m/z* = 466 $[M]^{+}$; Anal. Calcd for $C_{24}H_{24}BrN_3O_2$: C, 61.81; H, 5.19; N, 9.01. Found: C, 61.70; H, 5.07; N, 8.90%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone *(1b).* mp 176-178^{o}C;IR (DRS): 3083, 3015, 2982, 2852, 1652, 1586, 1520, 1480, 1365, 1254, 1169, 1063, 878, 826, 743, 699 cm^{-1}; MS: *m/z* = 467 $[M+1]^{+}$; Anal. Calcd for $C_{24}H_{24}BrN_3O_2$: C, 61.81; H, 5.19; N, 9.01. Found: C, 61.40; H, 5.09; N, 8.91%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridine-4-yl) methanone (*1c).* mp 234-236^{o}C; IR (DRS): 3095, 3012, 2930, 2883, 1654, 1593, 1534, 1454, 1356, 1266, 1164,1052, 890, 822, 723, 705 cm^{-1}; MS: *m/z* = 454 $[M+1]^{+}$; Anal. Calcd for $C_{22}H_{21}BrN_4O_2$: C, 58.29; H, 4.67; N, 12.36. Found: C, 58.01; H, 4.50; N, 12.25%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(1d).* mp 167-169 ^{o}C; IR (DRS): 3066(Ar, C-H str.), 3001(Ar, C-H str.), 2935(C-H str.), 1626(amide, C=O str.), 1531(Ar, C=C str.), 1446(Ar, C=C str.), 1346(C-H ben), 1294(C-Br str.), 1172(C-N str.), 1049(C-N str.), 1008(C-O-C str.), 829(C-H o,p, ben), 750(C-H o,p, ben) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm, 1.45-1.56(m, 2H, CH), 1.81-1.85(d, *J*=12.72 Hz, 1H, CH), 1.97-2.01(d, *J*=12.4 Hz, 1H, CH),2.17(m, 1H, CH), 2.84-2.90(t, 1H, CH), 3.10-3.96 (t, 1H, CH), 3.98-4.01(d, *J*=12.16 Hz, 1H, CH), 4.25-4.26(d, *J*=6.48 Hz, 2H, 2CH), 4.80-4.83 (d, *J*=12.24 Hz, 1H, CH), 7.35(m, 1H, ArH), 7.57-7.63(m, 3H, ArH), 7.77-7.83(m, 3H, ArH), 8.26-8.27(d, *J*=1.24 Hz, 1H, ArH), 8.46-8.46(d, *J*= 1.24 Hz, 1H , ArH), 8.60(m, 1H, ArH).). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm, 28.53, 35.93, 42.75, 46.42, 70.40, 114.61, 118.27, 123.07, 127.66, 132.08, 134.93, 135.47, 137.22, 142.38, 144.26, 152.55, 159.10;MS: *m/z* = 452 $[M-1]^{+}$; Anal. Calcd for $C_{22}H_{21}BrN_4O_2$: C, 58.29; H, 4.67; N, 12.36. Found: C, 58.05; H, 4.55; N, 12.23%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl) methanone (*1e*). mp 201-203^{o}C; IR (DRS): 3070, 2999, 2918, 2852, 1726, 1627, 1581, 1531, 1444, 1274, 1173, 1246, 1168, 1045, 987, 889, 831, 800, 752, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm, 1.39-1.42(m, 2H, CH), 1.80-2.01(m, 2H, CH), 2.11-2.14(m,

1H, CH), 2.83(m, 1H, CH), 3.03(m, 1H, CH), 3.82-3.85(d, *J*=11.84 Hz, 4H, OCH_3, CH), 4.17-4.19(d, *J*=6.36 Hz, 2H, 2CH), 4.75-4.78(d, *J*= 11.64 Hz, 1H, CH), 6.94-6.99(m, 1H, ArH), 7.29-7.36(m, 1H,ArH), 7.58-7.60(d, *J*=8.48 Hz, 3H, ArH), 7.77-7.80(d, *J*=8.52 Hz, 3H, ArH), 8.16-8.16(d, *J*=1.08 Hz ,1H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm, 29.71, 35.87, 35.98, 42.35, 46.32, 55.38, 70.36, 112.30, 115.40, 118.91, 123.10, 126.21, 127.67, 128.88, 129.61, 132.09, 134.90, 135.38, 137.23, 142.80, 144.42, 156.59, 159.65, 170.32; MS: *m/z* = 483 $[M+1]^+$; Anal. Calcd for $C_{24}H_{24}BrN_3O_3$: C, 59.76; H, 5.01; N, 8.71. Found: C, 59.55; H, 4.89; N, 8.60%.

(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl) methanone *(1f).* mp 154-156^oC; IR (DRS): 3087, 2958, 2832, 1684, 1585, 1456, 1269, 1175, 1036, 838, 796, 742, 693 cm^{-1}; MS: *m/z* = 452 $[M]^+$; Anal. Calcd for $C_{23}H_{22}BrN_3O_2$: C, 61.07; H, 4.90; N, 9.29. Found: C, 61.01; H, 4.70; N, 9.04%.

N*-(4-(4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl) acetamide *(1g). mp 235-237^oC; IR (DRS): 3445, 3015, 2918, 2823, 1648 1610, 1545, 1445, 1355, 1290, 1115, 1020, 825, 796, 743, 698 cm^{-1}; MS: *m/z* = 509 $[M]^+$; Anal. Calcd for $C_{25}H_{25}BrN_4O_3$: C, 58.95; H, 4.95; N, 11.00. Found: C, 58.19; H, 4.88; N, 10.91%.

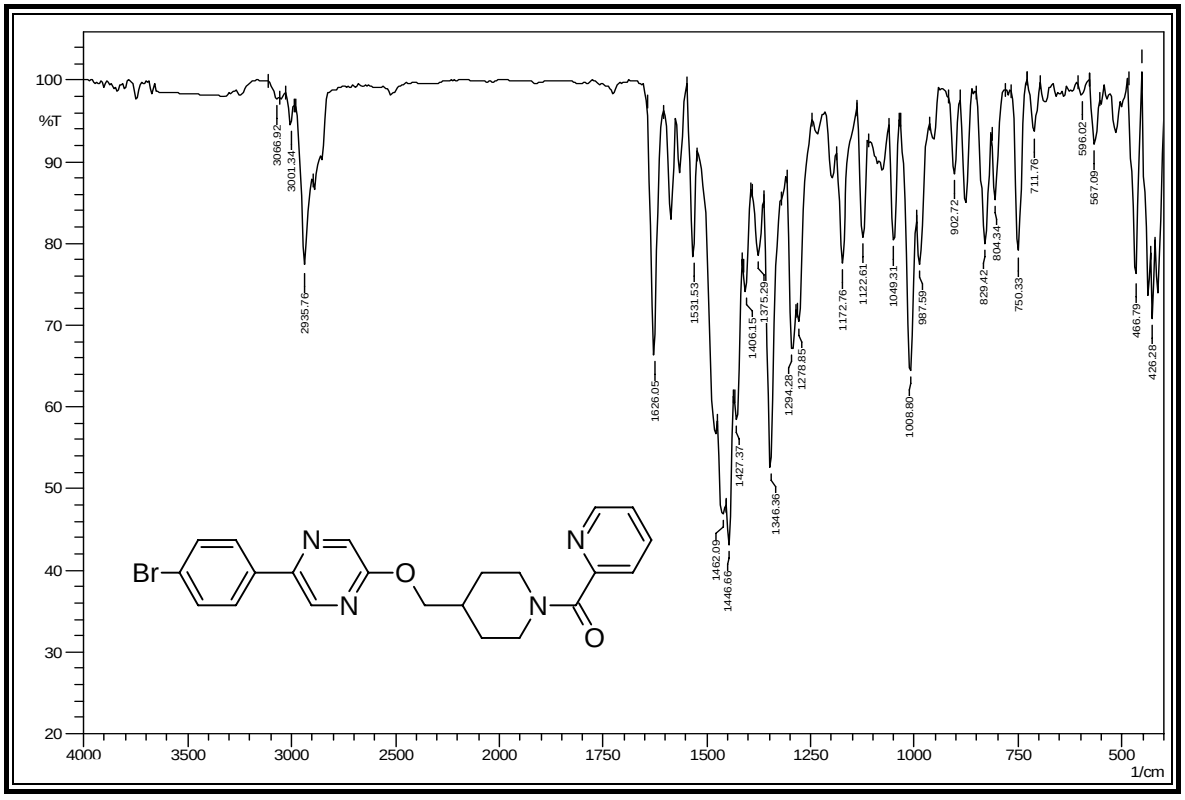
(4-(Bromomethyl)phenyl)(4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone *(1h).* mp 157-159^oC; IR (DRS): 3053, 2968, 2843, 1556, 1503, 1453, 1354, 1258,1135, 1032, 840, 799, 735, 689 cm^{-1}; MS: *m/z* = 546 $[M+1]^+$; Anal. Calcd for $C_{24}H_{23}Br_2N_3O_2$: C, 52.87; H, 4.25; N, 7.71. Found: C, 52.78; H, 4.14; N, 7.49%.

(2-Amino-5-bromophenyl)(4-(((5-(4-bromophenyl)pyrazin-2-yl)oxy)methyl) piperidine-1-yl)methanone *(1i).* mp 196-198^oC; IR (DRS): 3442, 3403, 3085, 2998, 2854, 1636, 1558, 1428, 1322, 1237, 1141, 1052, 835, 769, 733, 680 cm^{-1}; MS: *m/z* = 547 $[M+1]^+$; Anal. Calcd for $C_{23}H_{22}Br_2N_4O_2$: C, 50.57; H, 4.06; N, 10.26. Found: C, 50.38; H, 3.97; N, 10.20%.

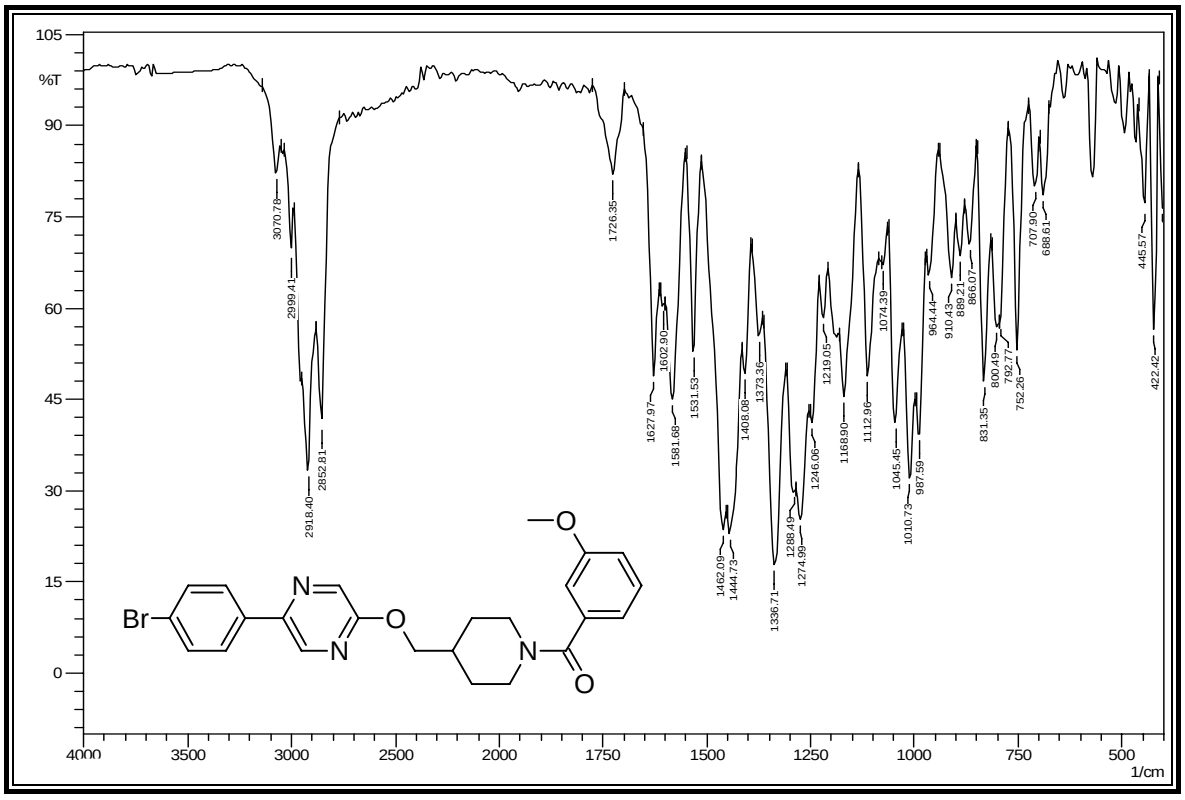
(4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(4-chlorophenyl) methanone *(1j).* mp 127-129^oC; IR (DRS): 3052, 3015, 2963, 2846, 1652, 1563, 1458, 1352, 1236, 1169, 1046, 885, 834, 756, 701 cm^{-1}; MS: *m/z* = 487 $[M+1]^+$; Anal. Calcd for $C_{23}H_{21}BrClN_3O_2$: C, 56.75; H, 4.35; N, 8.63. Found: C, 56.52; H, 4.25; N, 8.53%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

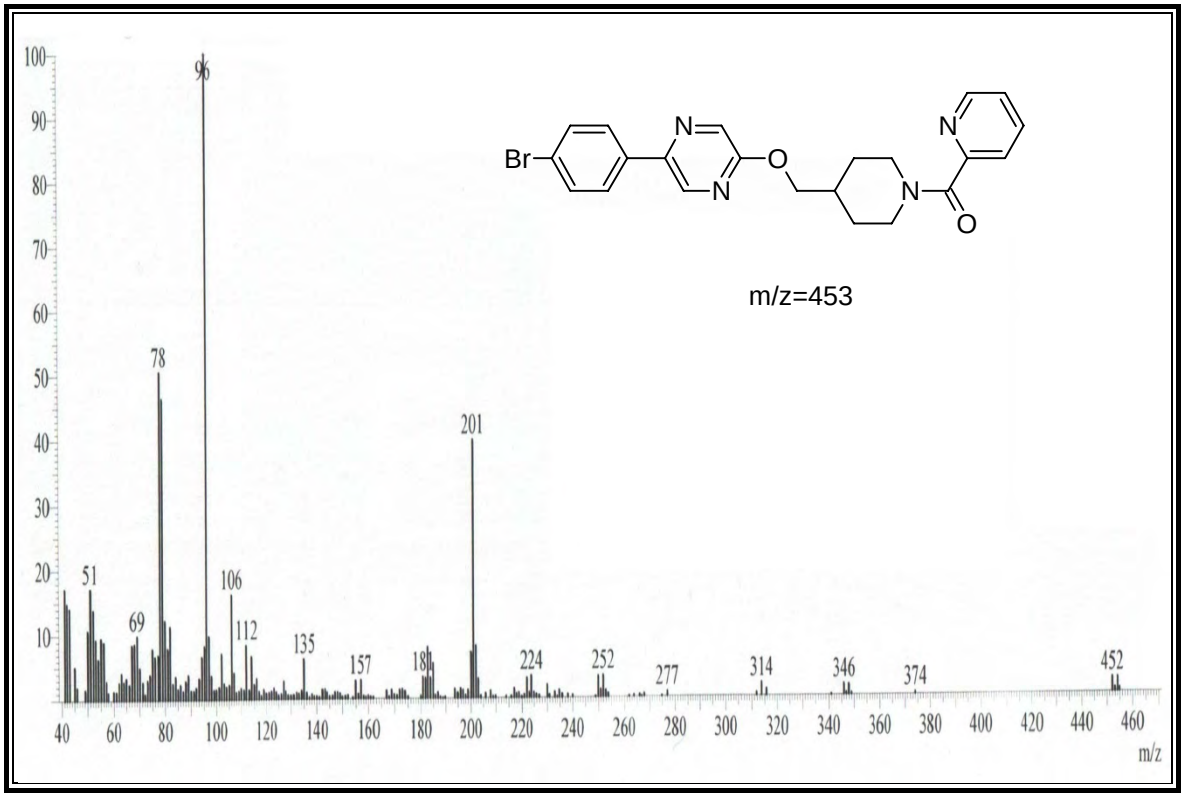
IR Spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(1d)*.



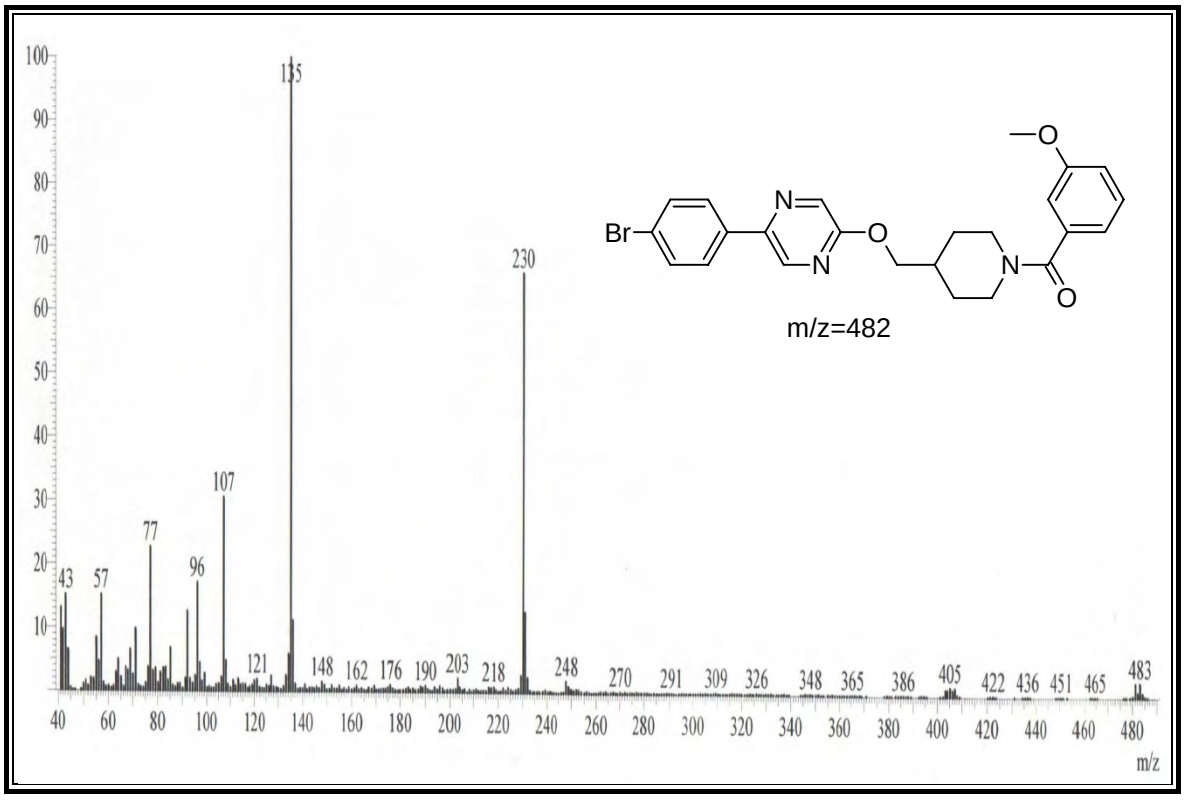
IR Spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(*1e*).



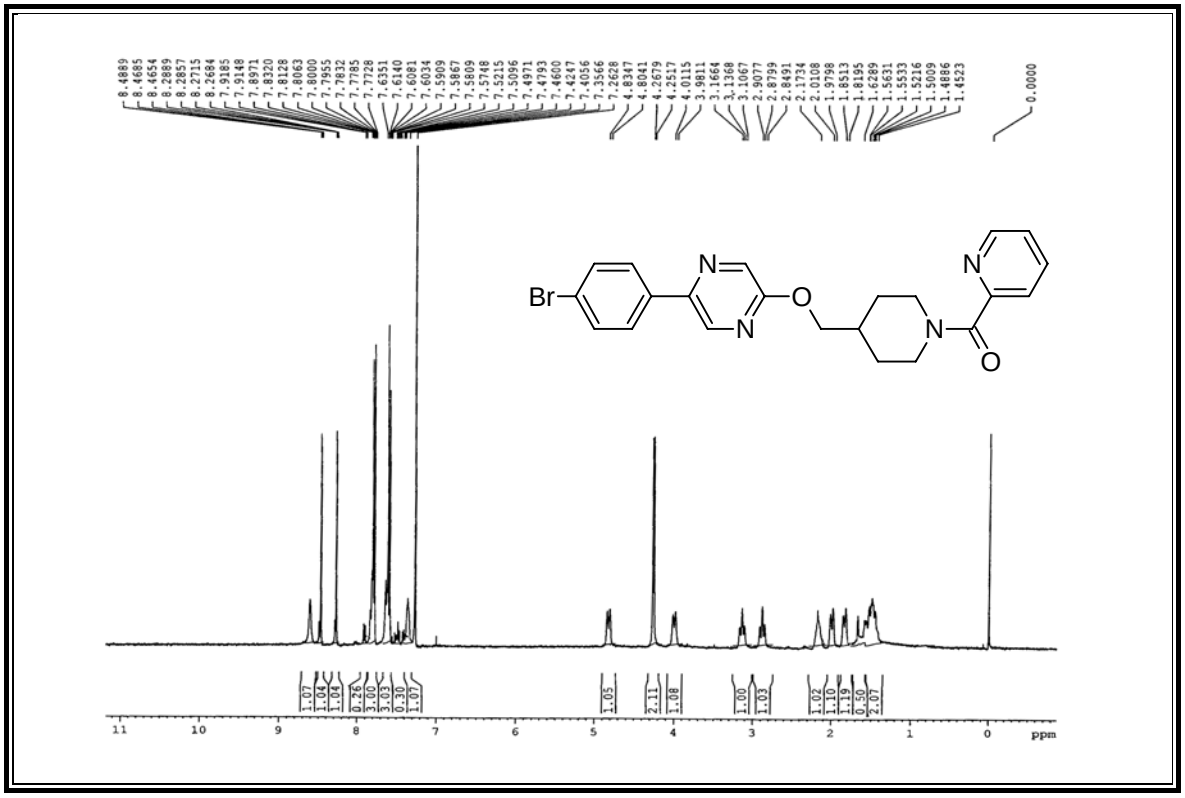
Mass spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(1d)*.



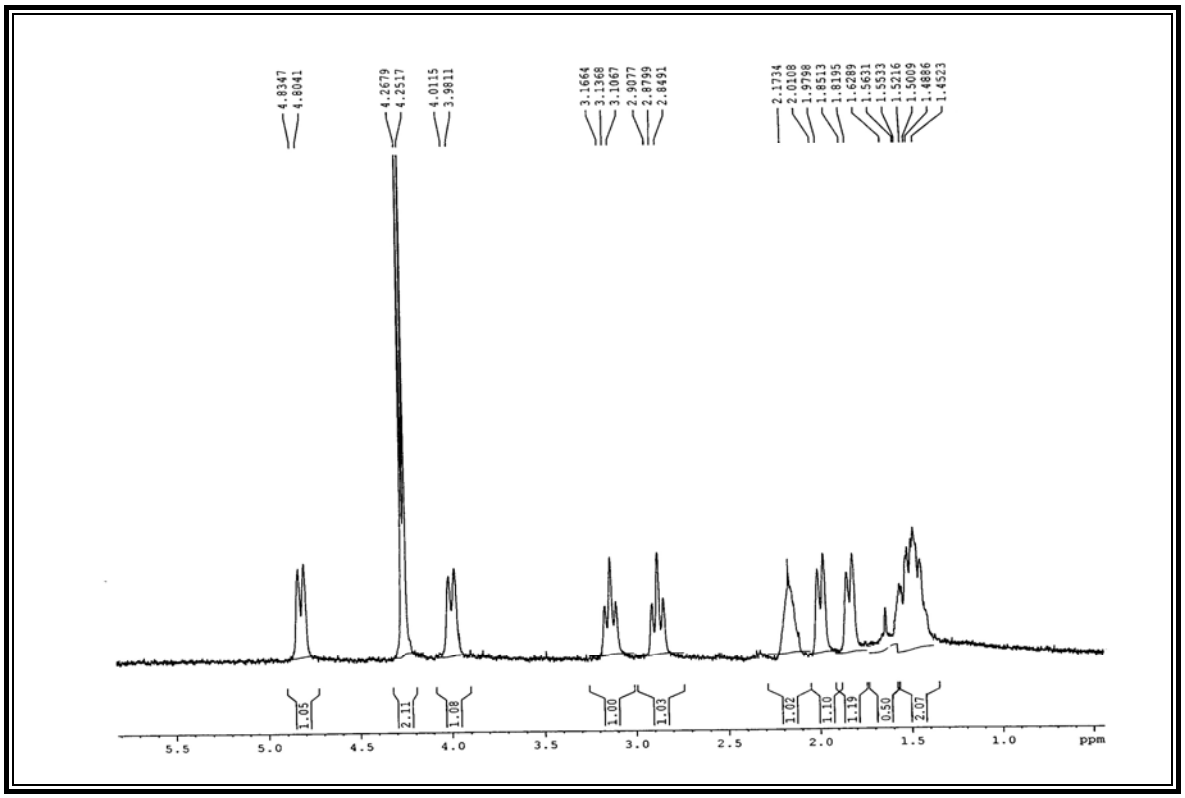
Mass spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(*1e*).



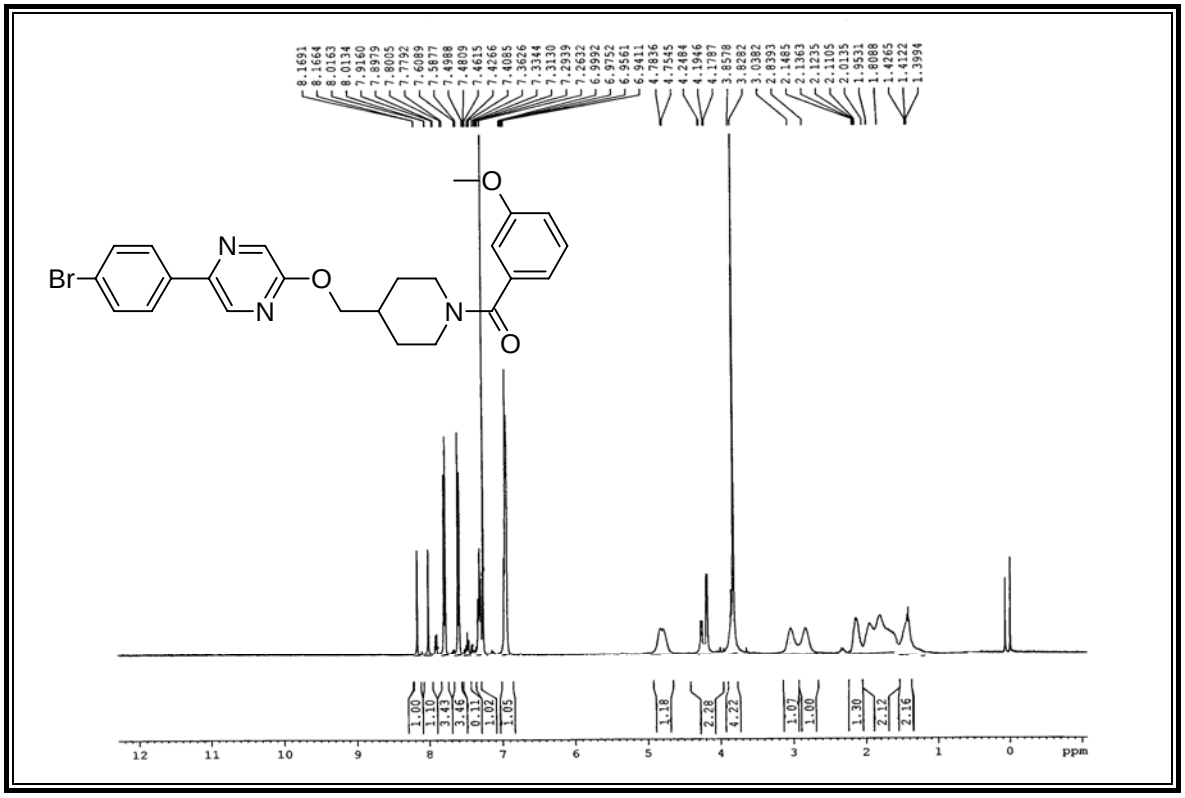
^{1}H NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(1d)*.



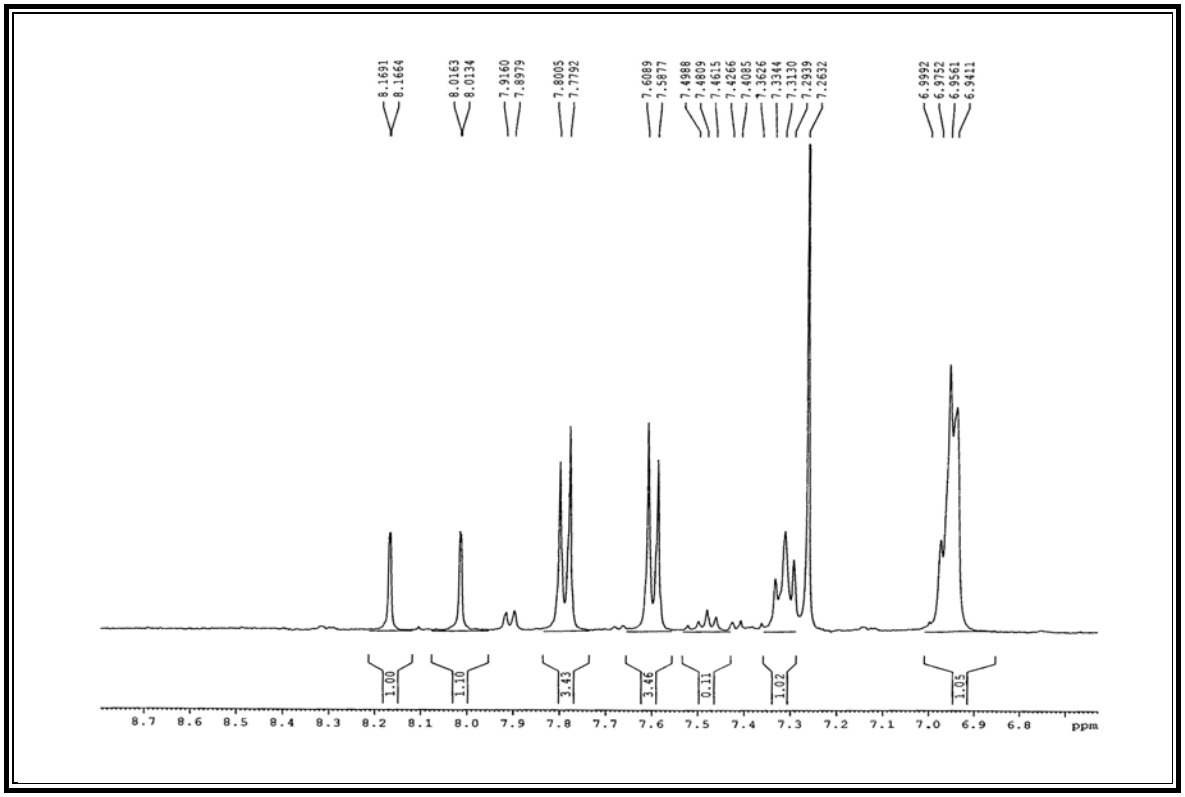
Expanded spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(1d)*.



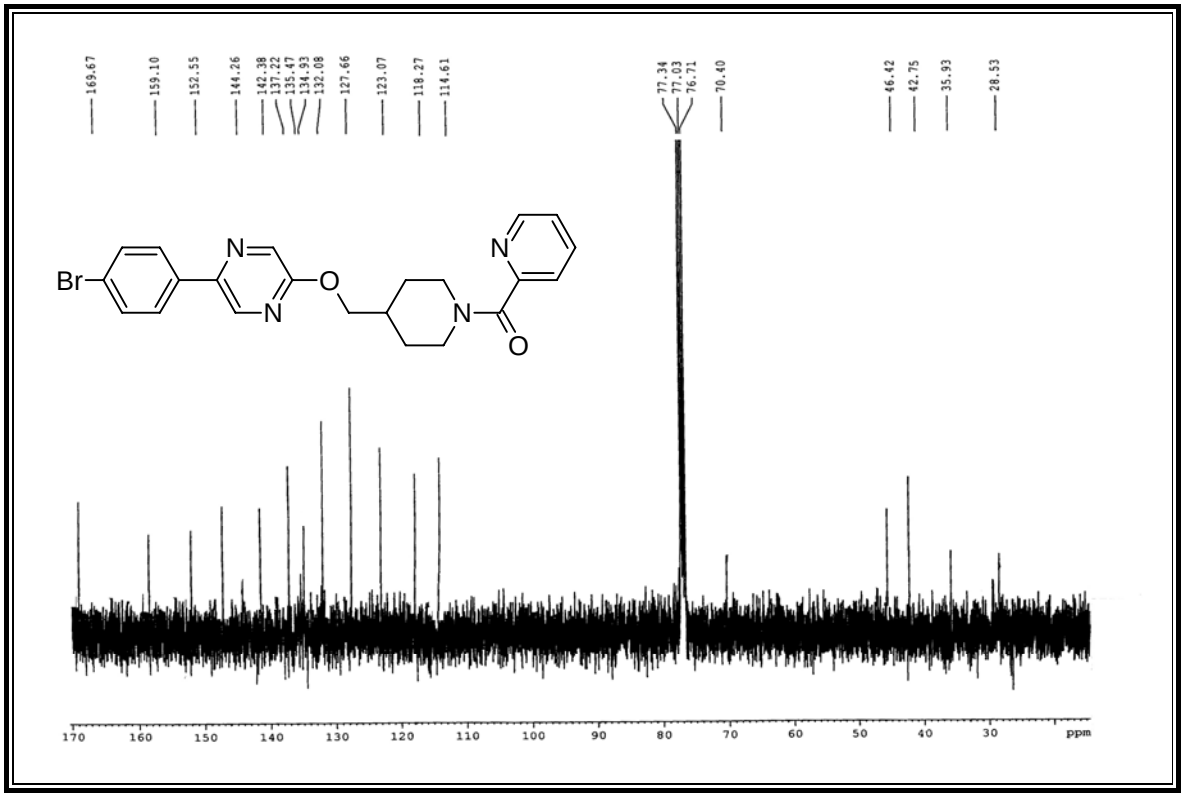
^{1}H NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(*1e*).



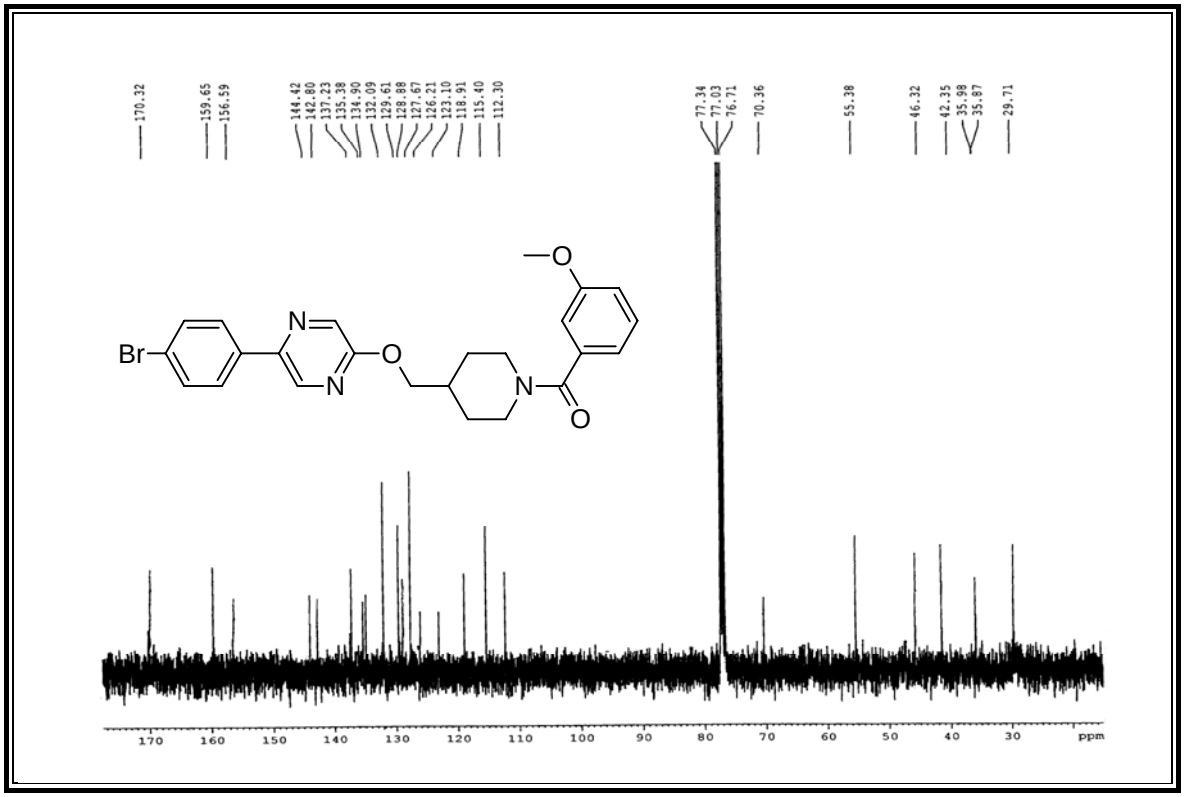
Expanded spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(*1e*).



^{13}C NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(1d)*.



^{13}C NMR spectrum of (4-(((5-(4-Bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone(*1e*).



ANTIMICROBIAL ACTIVITY

Biological evaluation of (4-(((5-(4-(bromophenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

All of the synthesized compounds **(1a-j)** were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method[52-54] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC 442, two Gram-negative bacteria *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.[38]

Minimal Inhibition Concentration [MIC]

The main advantage of the **Broth Dilution Method** for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

1. Serial dilutions were prepared in primary and secondary screening.
2. The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight.
3. The MIC of the control organism is read to check the accuracy of the drug concentrations.
4. The lowest concentration inhibiting growth of the organism is recorded as the MIC.
5. The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

Methods used for primary and secondary screening

Each synthesized compounds were diluted in DMSO to obtain 2000 μg mL^{-1} concentration, as a stock solution. Inoculum size for test strain was adjusted to 10^8 cfu (colony forming unit) per milliliter by comparing the turbidity.

Primary screen: In primary screening 1000 μg mL^{-1}, 500 μg mL^{-1} and 250 μg mL^{-1} concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The compounds found active in primary screening were similarly diluted to obtain 200 μg mL^{-1}, 100 μg mL^{-1}, 50 μg mL^{-1}, 25 μg mL^{-1}, 12.5 μg mL^{-1}, and 6.250 μg mL^{-1} concentrations.

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

The results obtained from antimicrobial susceptibility testing are depicted in **Table 1b**.

Table-1b: Antimicrobial activity of(4-(((5-(4-(bromophenyl)pyrazin-2-yl) oxy) methyl) piperidin-1-yl)(aryl)methanones.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
1a	100	250	250	250	250	1000	1000
1b	125	200	500	500	500	500	500
1c	250	250	500	250	200	500	500
1d	250	250	62.5	100	250	>1000	>1000
1e	500	250	125	200	500	250	1000
1f	250	125	100	250	1000	500	1000
1g	125	500	250	250	250	500	>1000
1h	250	500	100	100	>1000	250	500
1i	200	200	500	125	500	1000	>1000
1j	125	250	100	500	250	>1000	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

Part – A

[Part – I (Section-ii)]

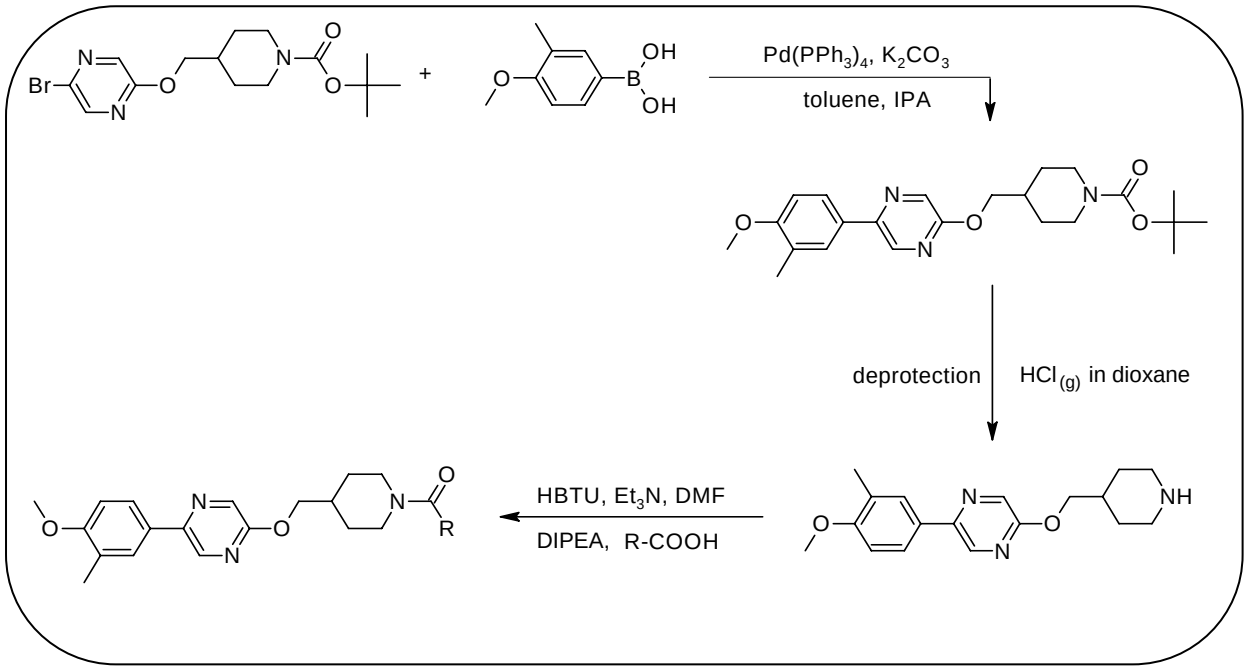
Synthesis and biological evaluation of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl) methanones

SECTION-II

SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(4-METHOXY-3-METHYLPHENYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL) METHANONES

Many pyrazine derivatives have displayed diverse pharmacological activities. In view of our on going interest in the synthesis of some new 2-(piperidin-4-yl methoxy) pyrazine derivatives have been synthesized by the condensation of 2-(4-methoxy-3-methyl phenyl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of *tert*-butyl 4-(((5-(4-methoxy-3-methylphenyl)pyrazine-2-yl) oxy)methyl) piperidine-1-carboxylate.

A solution of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution (4-methoxy-3-methylphenyl)boronic acid (0.660 g, 0.004 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K_2CO_3 (10 ml, 0.02 mol) in water was added dropwise under nitrogen atmosphere and stirred for 5.0 minute. Tetrakis(tripenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 6 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

[C] Preparation of 2-(4-methoxy-3-methylphenyl)-5-(piperidin-4-ylmethoxy) pyrazine.

A mixture of $HCl_{(g)}$ in dioxane (10 ml) and *tert*-butyl 4-(((5-(4-methoxy-3-methyl phenyl)pyrazine-2-yl)oxy)methyl)piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure product. Yield: 66 %, mp 136-138^oC.

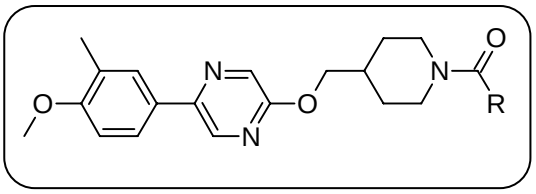
[D] General procedure for the preparation of (4-(((5-(4-methoxy-3-methyl phenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

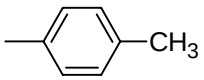
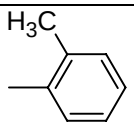
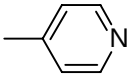
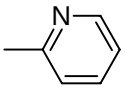
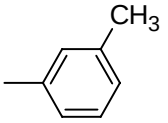
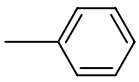
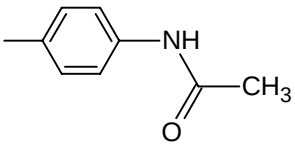
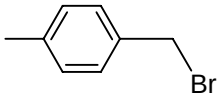
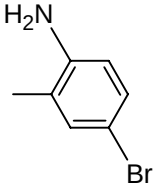
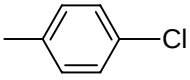
To a cooled mixture of 2-(4-methoxy-3-methylphenyl)-5-(piperidin-4-ylMethoxy)pyrazine (0.2 g, 0.640 mmol) and aryl acid (0.640 mmol) in dry DMF(3ml), HBTU[2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.288 g, 0.760 mmol), DIPEA[diisopropyl ethyl amine], (0.098 g ≅ 0.129 ml,0.760 mmol) and TEA (0.11 ml, 0.960 mmol) was added to basify the content at 0^oC. The reaction mixture was stirred for 10 hour at room temperature (monitored by TLC). The reaction mixture was poured on to crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in **Table-2a.**

[E] Biological evaluation of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-2b**.

Table-2a: Physical constants of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl) oxy)methyl)piperidin-1-yl)(aryl)methanones.



Sr. No.	Substitution R	MF	MW	Yield (%)	R_f value
2a		$C_{26}H_{29}N_3O_3$	431.52	82	0.52
2b		$C_{26}H_{29}N_3O_3$	431.52	72	0.48
2c		$C_{25}H_{26}N_4O_5$	418.48	73	0.43
2d		$C_{25}H_{26}N_4O_5$	418.48	74	0.44
2e		$C_{26}H_{29}N_3O_3$	431.52	80	0.46
2f		$C_{25}H_{27}N_3O_3$	417.50	87	0.46
2g		$C_{27}H_{30}N_4O_4$	474.55	66	0.30
2h		$C_{26}H_{28}BrN_3O_3$	510.42	75	0.36
2i		$C_{25}H_{27}BrN_4O_3$	511.41	69	0.28
2j		$C_{25}H_{26}ClN_3O_3$	451.94	77	0.46

TLC solvent system:- MeOH : $CHCl_3$ = 2 : 8

ANALYTICAL DATA

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl) methanone *(2a).* mp 150-152^{o}C;IR (DRS): 3056, 2985, 2864, 1683, 1625, 1552, 1463, 1352, 1170, 780, 696, cm^{-1}; MS: m/z = 431 $[M]^{+}$; Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.09; H, 6.70; N, 9.66%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone *(2b).* mp 134-138^{o}C; IR (DRS): 2989, 2949, 2856, 1699, 1681, 1629, 1541, 1465, 1340, 1172, 1028, 775, 651 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.17-1.41(m, 2H, CH), 1.71-1.79(m, 1H, CH), 1.94-1.99(m, 1H, CH), 2.11(m, 1H, CH), 2.24 (s, 3H, CH_3), 2.30(s, 3H, CH_3), 2.81(m, 1H, CH), 2.99-3.05(m, 1H, CH), 3.43(d, 1H, CH), 3.85(s, 3H, OCH_3), 4.21-4.23(d, *J*= 6.32 Hz, 2H, 2CH), 4.69-4.72(d, *J*= 12.8 Hz, 1H, CH), 6.93-6.96(d, *J*= 8.36 Hz, 1H, ArH), 7.08-7.29(m, 4H, ArH), 7.74-7.76(d, *J*= 9.68 Hz, 2H, ArH), 8.21(s, 1H, ArH), 8.53(s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ ppm, 16.10, 18.46, 28.23, 28.75, 29.34, 35.29, 45.78, 46.31, 55.06, 69.69, 109.93, 124.44, 125.11, 125.55, 126.05, 127.82, 127.93, 128.30, 129.89, 133.30, 133.66, 136.43, 144.47, 157.83, 158.23, 168.63.MS: m/z = 431 $[M]^{+}$; Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.19; H, 6.56; N, 9.68%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) (pyridine-4-yl)methanone *(2c).* mp 140-144^{o}C; IR (DRS): 3046, 2985, 2846, 1678, 1635, 1546, 1452, 1368,1166, 1045, 880, 835, 780, 754, 703 cm^{-1}; MS: m/z = 418 $[M]^{+}$; Anal. Calcd for $C_{25}H_{26}N_4O_5$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.32; H, 6.21; N, 13.29%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) (pyridine-2-yl)methanone *(2d).* mp 104-106^{o}C; IR (DRS): 3027, 2978, 1835, 1666, 1564, 1456, 1378, 1089, 890, 834, 754, 699 cm^{-1}; MS: m/z = 418 $[M]^{+}$; Anal. Calcd for $C_{25}H_{26}N_4O_5$: C, 68.88; H, 6.26; N, 13.39. Found: C, 68.82; H, 6.18; N, 13.26%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(*m*-tolyl) methanone *(2e).* mp 96-98^{o}C; IR (DRS): 3003(Ar, C-H str.), 2941(C-H str.), 2929(C-H str.), 2883(C-H str.), 2860(C-H str.), 1633(amide, C=O str.), 1533(Ar, C=C str.), 1456(Ar, C=C str.), 1346(C-H ben), 1170(C-N str.), 1066(C-O-C str.), 1026(C-O-C str.), 883(C-H o,p, ben), 812(C-H o,p, ben), 754(C-H o,p, ben), cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.24-1.31(m, 2H, CH), 1.79(m, 1H, CH), 1.91(m, 1H, CH), 2.08-2.13(m,

1H, CH), 2.24(s, 3H, CH_3), 2.36(s, 3H, CH_3), 2.80(m, 1H, CH), 3.06(m, 1H, CH), 3.67-3.71(d, *J*= 19.2 Hz, 1H, CH), 3.85(s, 3H, OCH_3), 4.21-4.23(d, *J*= 6.44 Hz, 2H, 2CH), 4.60-4.65(d, *J*= 19.04 Hz, 1H, CH), 6.94-6.96(d, *J*= 8.32 Hz, 1H, ArH), 7.13-7.17(t, 2H, ArH), 7.21-7.23(d, *J*= 7.56 Hz, 1H, ArH), 7.27-7.31(t, 1H, ArH), 7.75-7.77(d, *J*= 9.32 Hz, 2H, ArH), 8.23-8.23 (d, *J*=0.92 Hz, 1H, ArH), 8.54-8.55(d, *J*= 0.88 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ ppm, 15.60, 20.94, 28.23, 28.75, 29.34, 35.27, 45.78, 46.31, 55.08, 69.73, 109.97, 123.40, 124.46, 126.02, 126.94, 127.83, 127.94, 127.97, 129.72, 133.68, 136.13, 136.30, 137.60, 144.45, 157.83, 158.25, 169.22; MS: m/z = 431 $[M]^+$; Anal. Calcd for $C_{26}H_{29}N_3O_3$: C, 72.37; H, 6.77; N, 9.74. Found: C, 72.17; H, 6.70; N, 9.69%.

(4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl) methanone *(2f)*. mp 101-102^{o}C; IR (DRS): 3083, 3015, 2956, 2863, 1688, 1635, 1525, 1470, 1342, 1162, 1010, 883, 764, 693 cm^{-1}; MS: m/z = 417 $[M]^+$; Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.85; H, 6.25; N, 9.90%.

***N*-(4-(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide *(2g)*.** mp 189-190^{o}C; IR (DRS): 3460, 3028, 2976, 2846, 1647, 1532, 1465, 1323, 1032, 1045, 838, 756, 704 cm^{-1}; MS: m/z = 475 $[M+1]^+$; Anal. Calcd for $C_{27}H_{30}N_4O_4$: C, 68.34; H, 6.37; N, 11.81. Found: C, 68.23; H, 6.33; N, 11.41%.

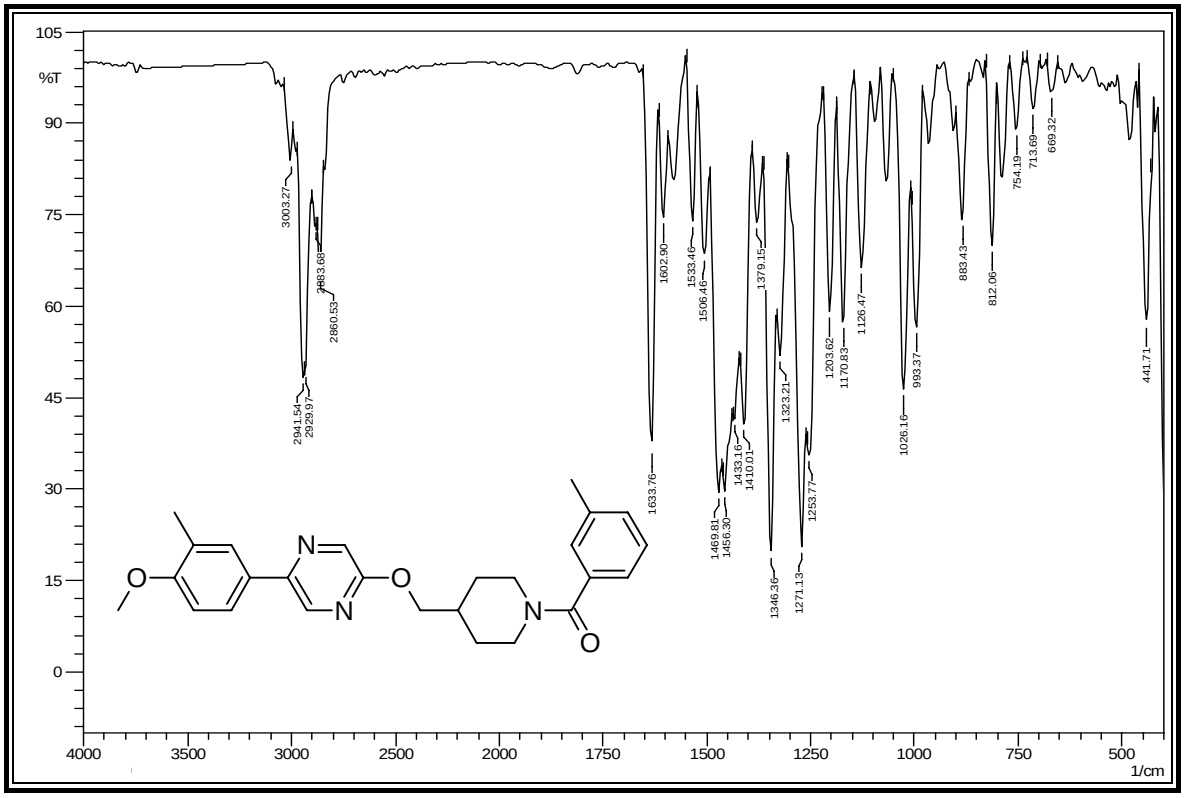
(4-(Bromomethyl)phenyl)(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)methanone *(2h)*. mp 137-139^{o}C; IR (DRS): 3091, 3027, 2923, 2856, 1641, 1523, 1470, 1347, 1056, 830, 745 cm^{-1}; MS: m/z = 510 $[M]^+$; Anal. Calcd for $C_{26}H_{28}BrN_3O_3$: C, 61.18; H, 5.53; N, 8.23. Found: C, 61.11; H, 5.19; N, 8.02%.

(2-Amino-5-bromophenyl)(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)methanone *(2i)*. mp 135-136^{o}C; IR (DRS): 3443, 3383, 3056, 2947, 2856, 1656, 1544, 1426, 1330, 1041, 830, 741, 631 cm^{-1}; MS: m/z = 513 $[M+2]^+$; Anal. Calcd for $C_{25}H_{27}BrN_4O_3$: C, 58.71; H, 5.32; N, 10.96. Found: C, 58.69; H, 5.06; N, 10.43%.

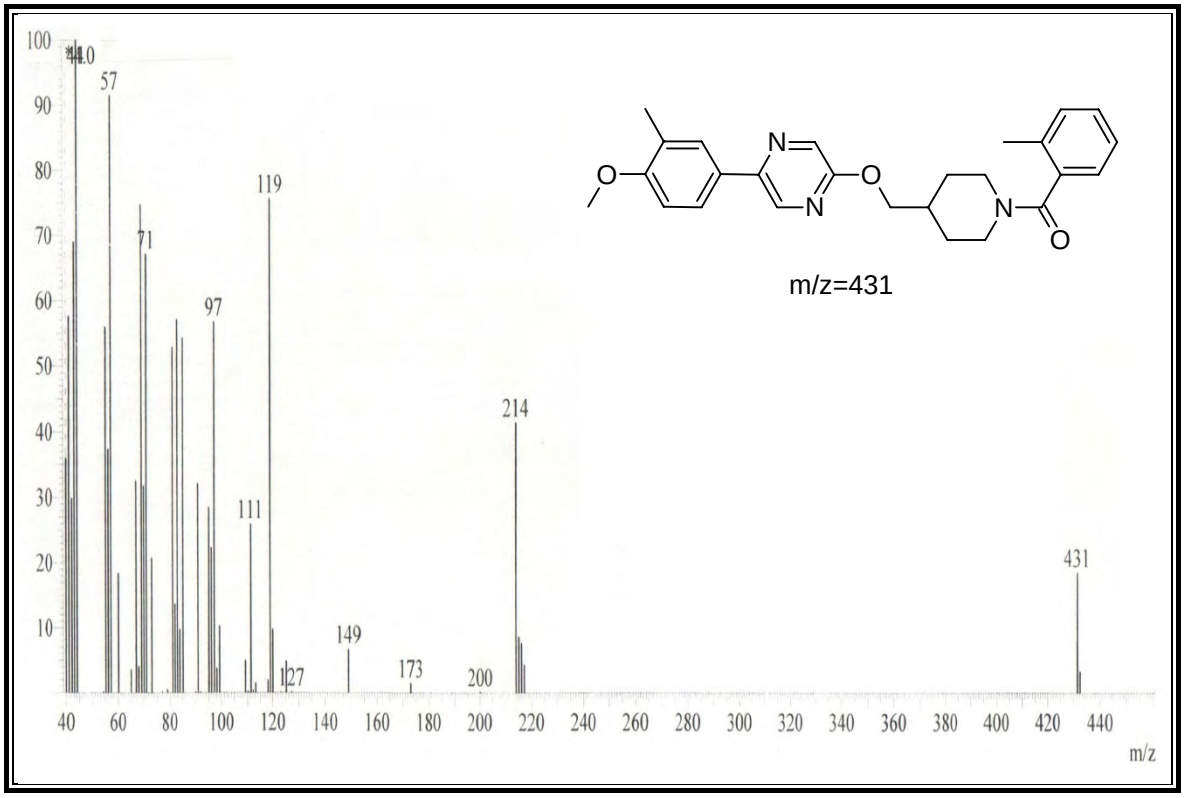
(4-Chlorophenyl)(4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone *(2j)*. mp 208-212^{o}C; IR (DRS): 3074, 3025, 2999, 2840, 1659, 1522, 1466, 1336, 1170, 1054, 887, 838, 756, 703 cm^{-1}; MS: m/z = 452 $[M+1]^+$; Anal. Calcd for $C_{25}H_{26}ClN_3O_3$: C, 66.44; H, 5.80; N, 9.30. Found: C, 66.12; H, 5.81; N, 9.28%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

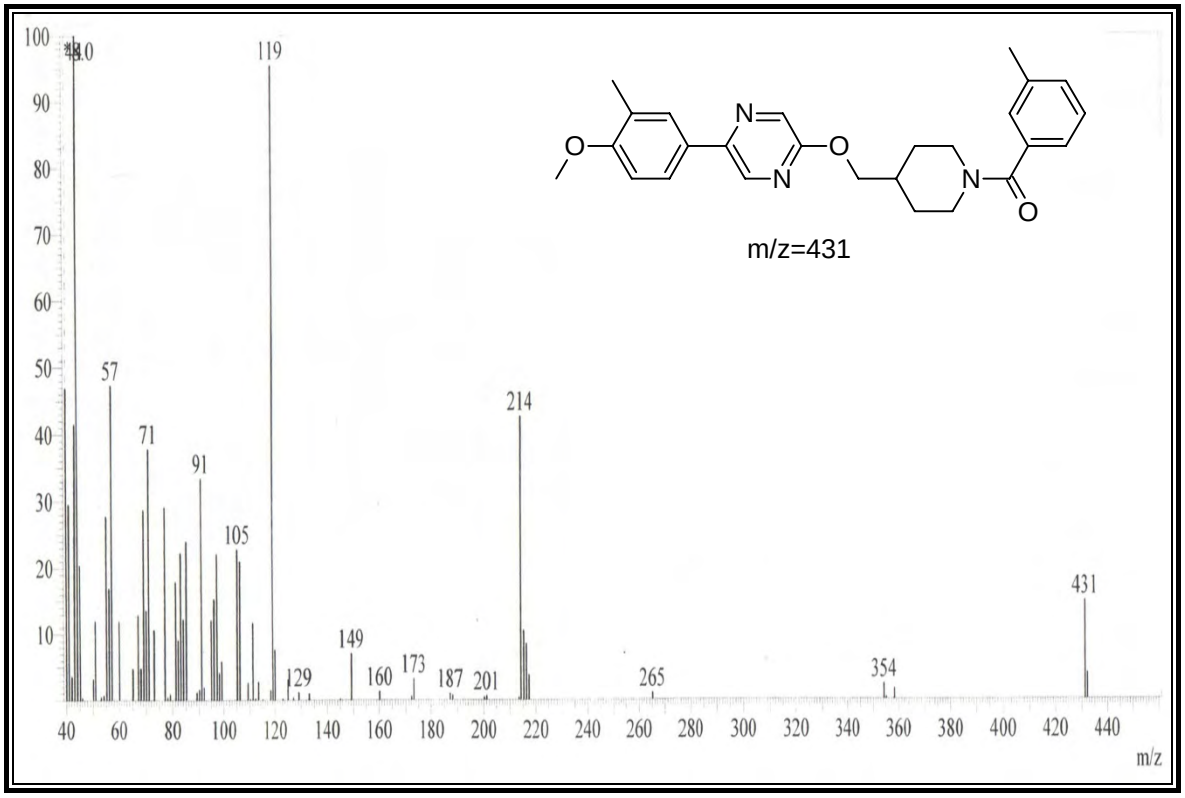
IR Spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(*m*-tolyl)methanone*(2e)*.



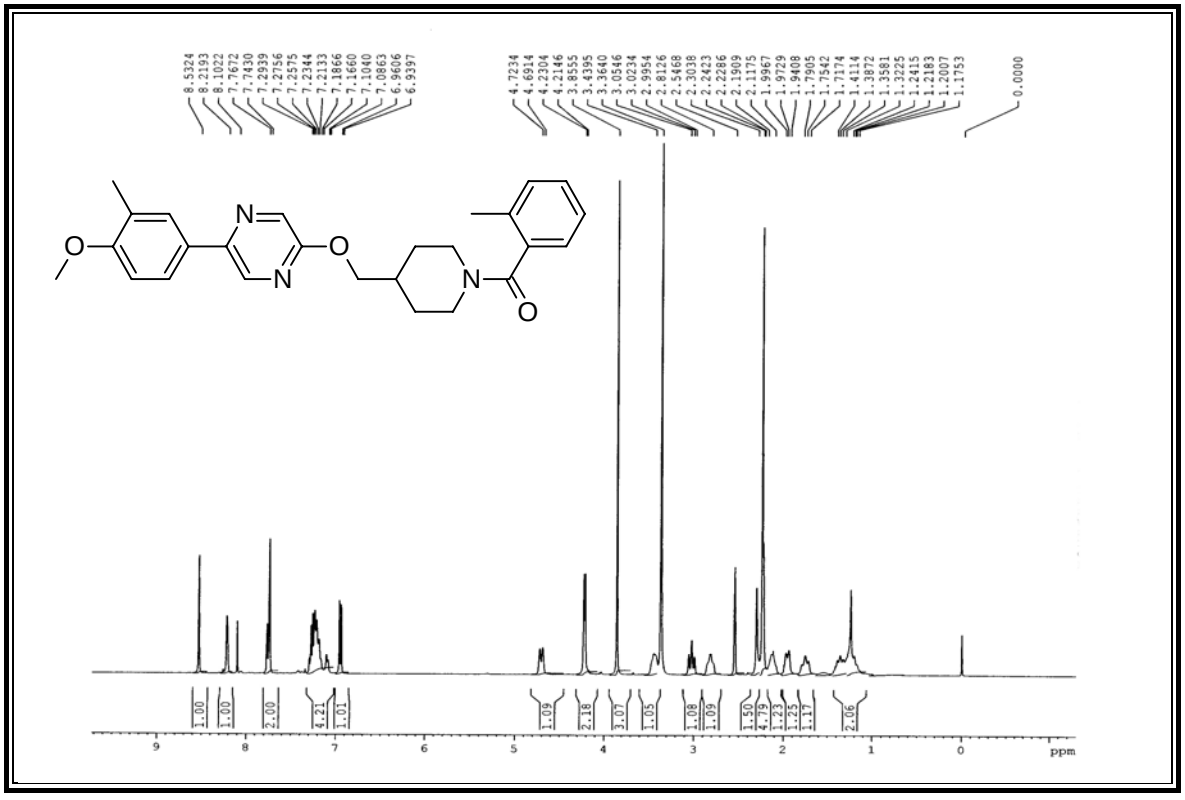
Mass spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(o-tolyl)methanone*(2b)*.



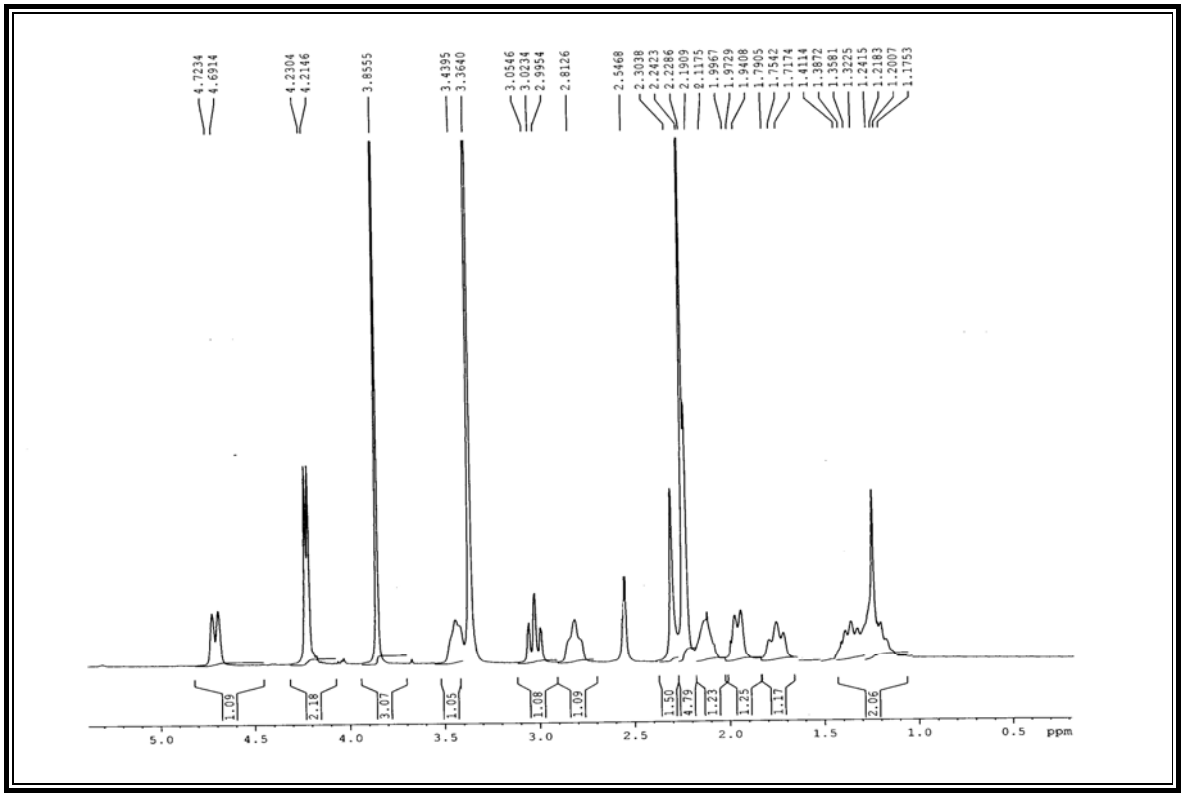
Mass spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(*m*-tolyl)methanone*(2e)*.



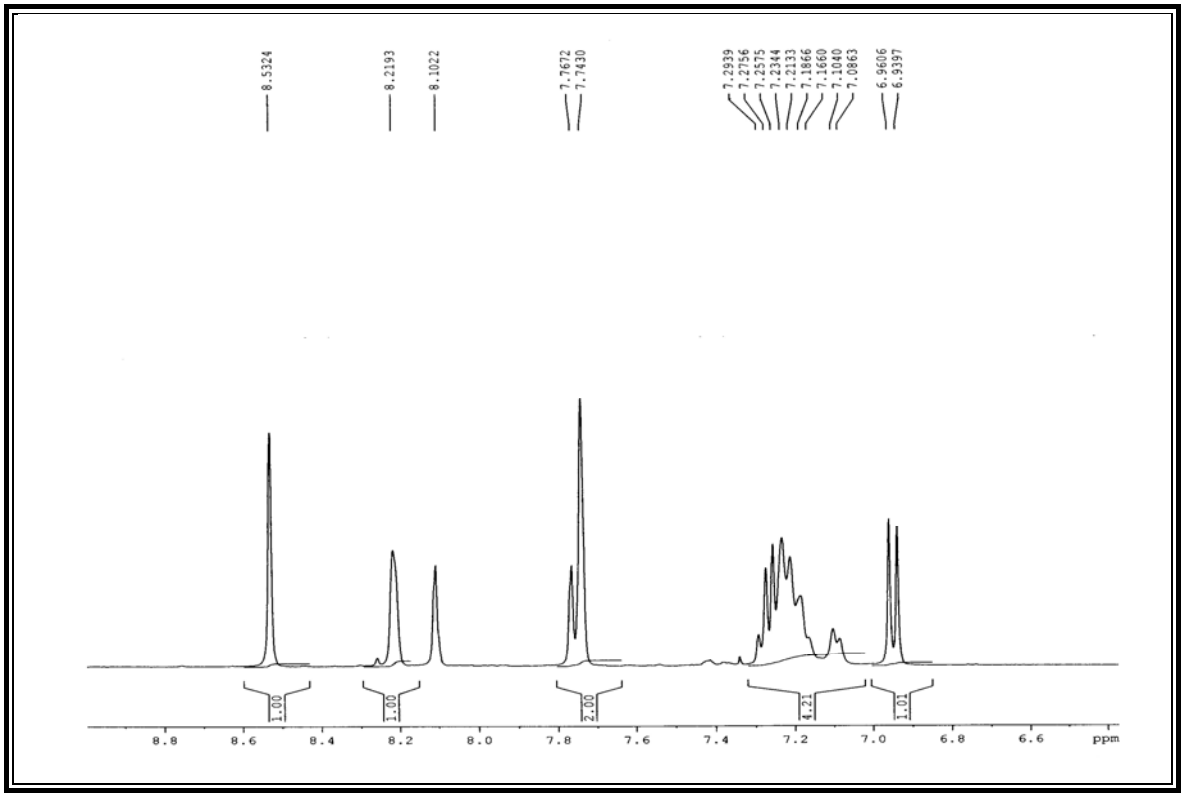
^{1}H NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(o-tolyl)methanone*(2b)*.



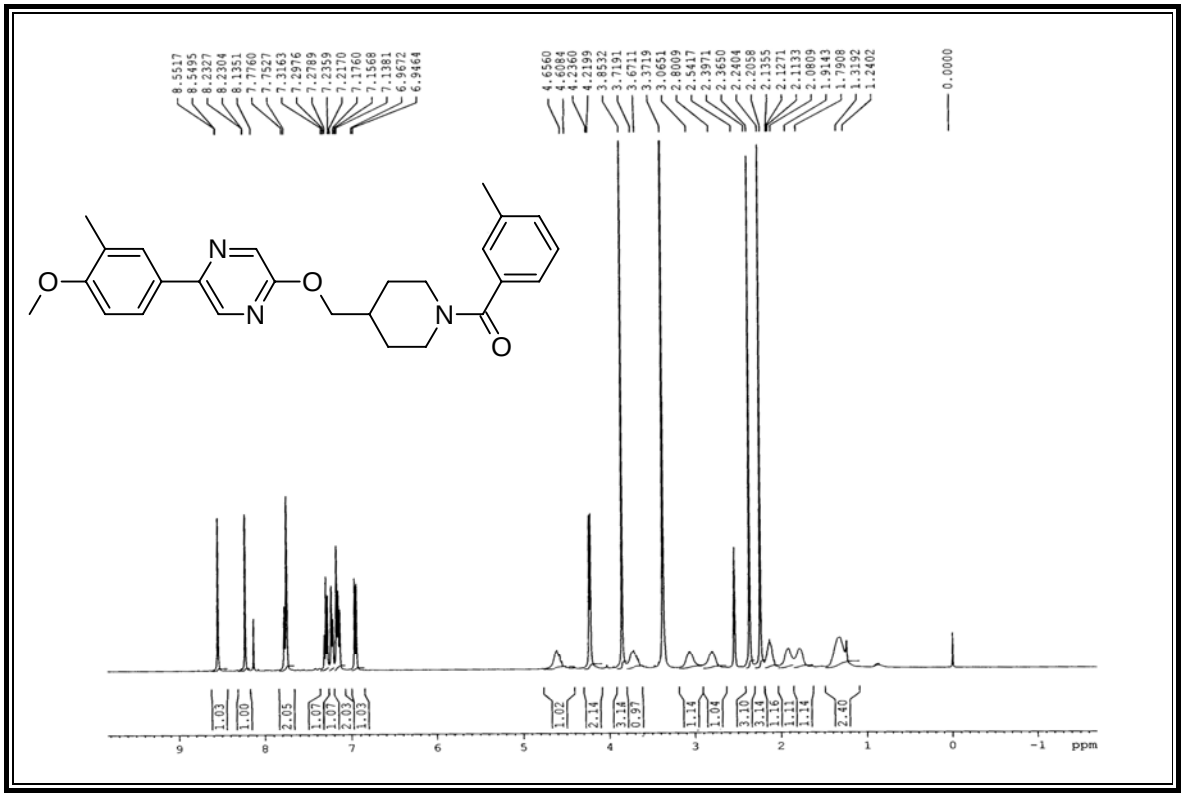
Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(o-tolyl)methanone*(2b)*.



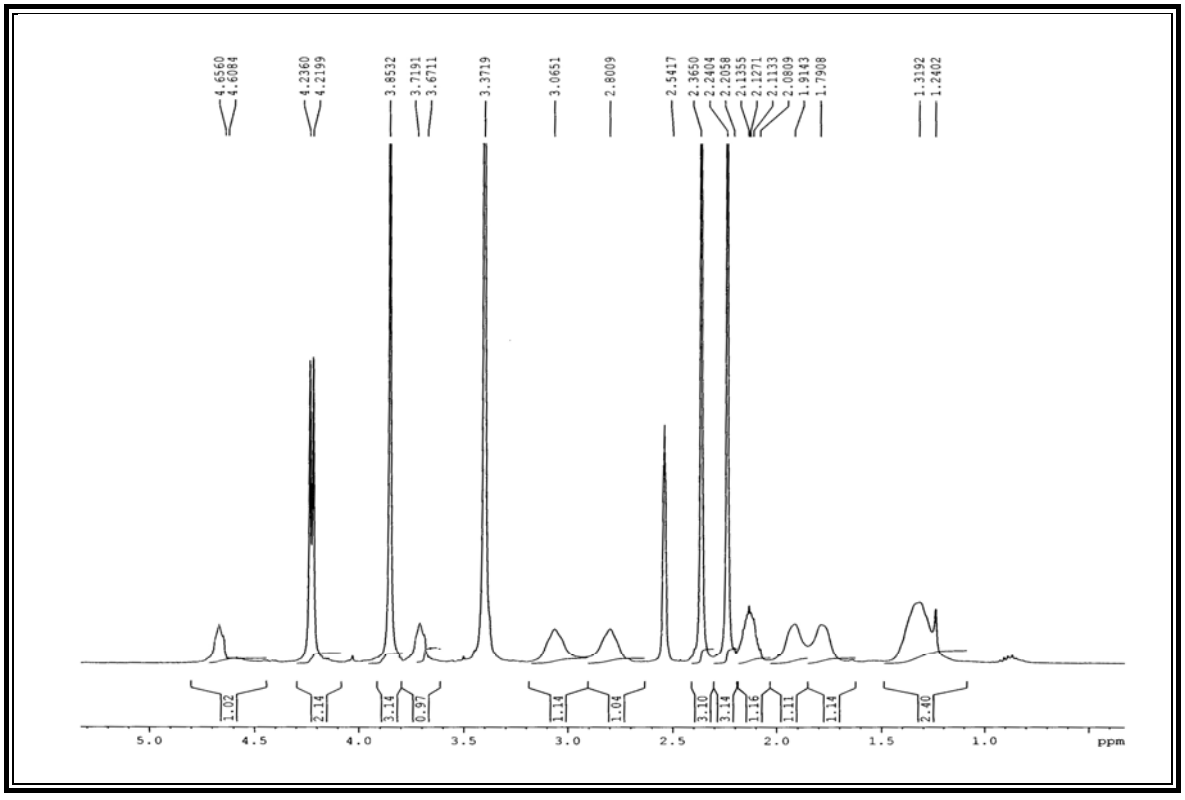
Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(o-tolyl)methanone*(2b)*.



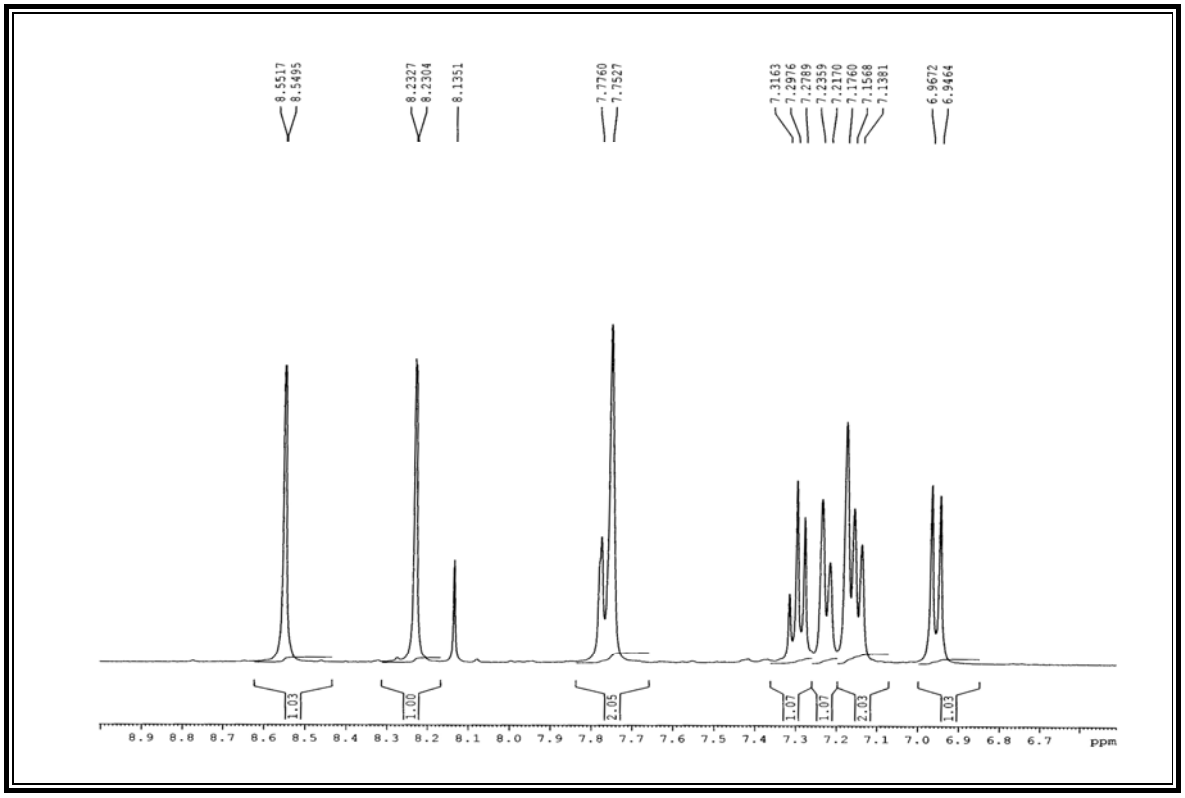
^{1}H NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(*m*-tolyl)methanone*(2e).*



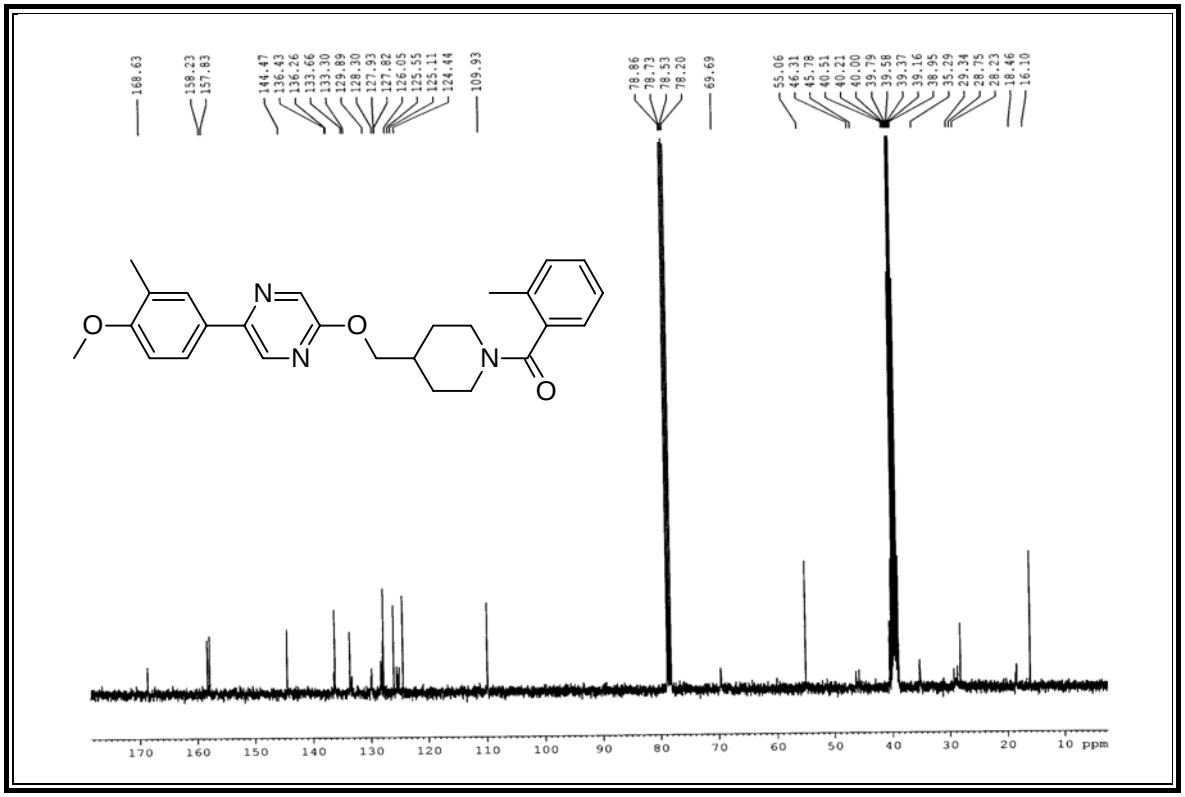
Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(*m*-tolyl)methanone*(2e).*



Expanded spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(*m*-tolyl)methanone*(2e)*.



^{13}C NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(o-tolyl)methanone*(2b)*.



^{13}C NMR spectrum of (4-(((5-(4-Methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)(*m*-tolyl)methanone*(2e)*.

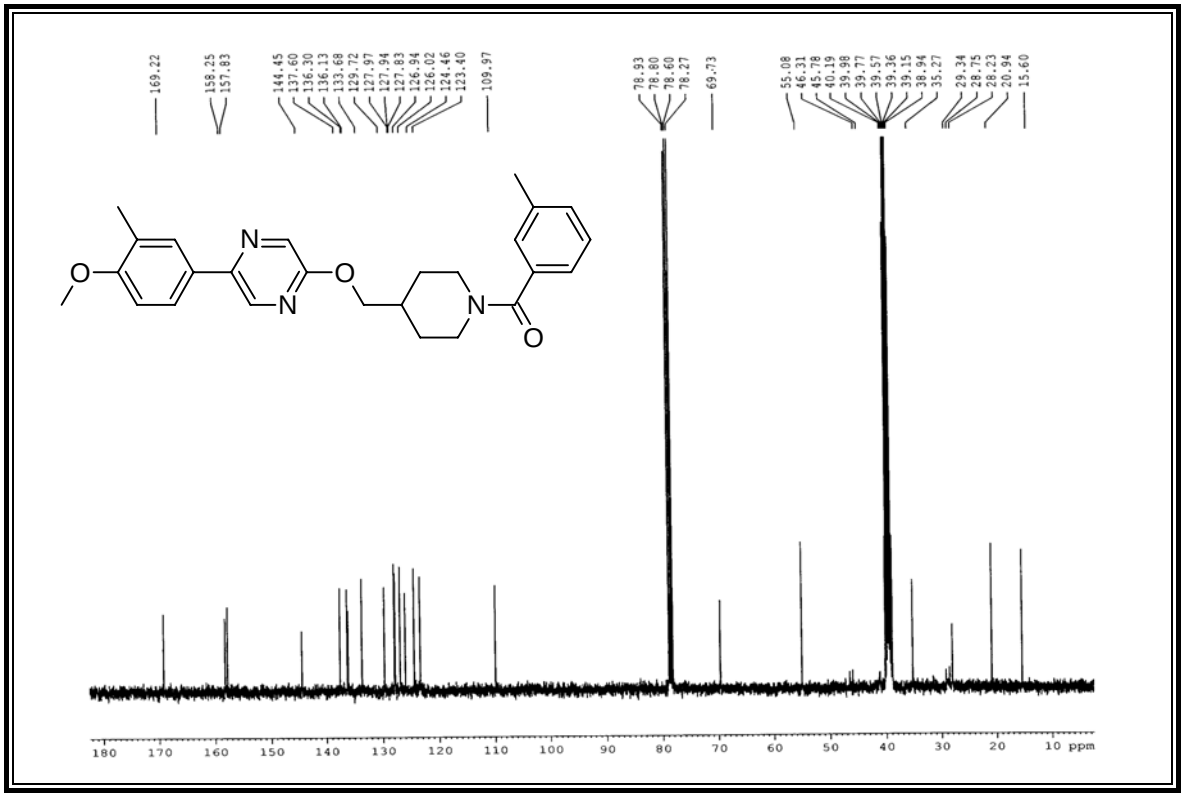


Table-2b: Antimicrobial activity of (4-(((5-(4-methoxy-3-methylphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
2a	200	200	100	125	1000	500	500
2b	500	100	250	200	250	250	500
2c	125	100	200	200	>1000	250	250
2d	125	125	200	200	250	1000	1000
2e	200	200	125	100	500	1000	1000
2f	125	125	250	250	500	500	500
2g	500	500	250	250	1000	250	250
2h	200	200	200	200	250	500	500
2i	125	125	125	200	250	500	500
2j	100	62.5	125	500	500	>1000	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

Part – A

[Part – I (Section-iii)]

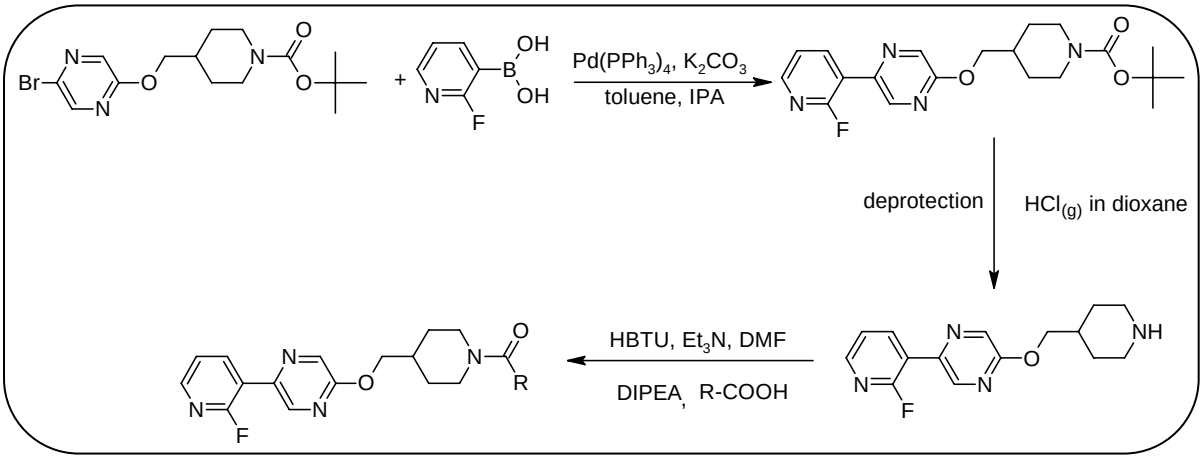
Synthesis and biological evaluation of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl) oxy)methyl)piperidin-1-yl)(aryl) methanones

SECTION-III

SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-FLUORO PYRIDIN-3-YL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL) METHANONES

Pyrazine derivatives have been attracted widespread attention due to their diverse pharmacological properties. Looking to this, the synthesis of 2-(piperidin-4-ylmethoxy) pyrazine derivatives have been under taken by the condensation of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker AC 400 MHz spectrometer. Purity of the synthesized compounds was checked by HPLC Agilent 1100 series. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of *tert*-butyl 4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy) methyl) piperidine-1-carboxylate.

A solution of tert-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution (2-fluoropyridin-3-yl)boronic acid(0.620 g, 0.0044 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K_2CO_3 (10 ml, 0.02 mol) in water was added dropwise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 7 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

[C] Preparation of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazine.

A mixture of $HCl_{(g)}$ in dioxane (10 ml) and *tert*-butyl 4-(((5-(2-fluoropyridin-3-yl) pyrazin-2-yl)oxy)methyl) piperidine-1-carboxylate was stirred at room temperature for overnight (monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3), and the combine organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure product. Yield: 56 %, mp 94-96^oC.

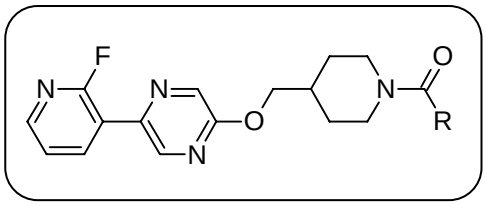
[D] General procedure for the preparation of (4-(((5-(2-fluoropyridin-3-yl) pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

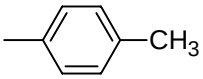
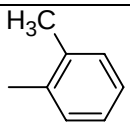
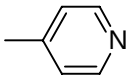
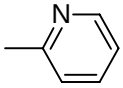
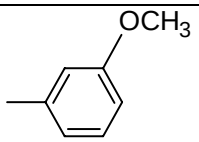
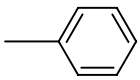
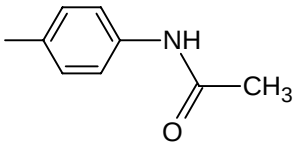
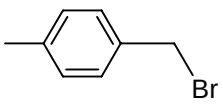
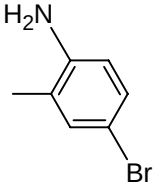
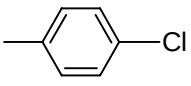
To a cooled mixture of 2-(2-fluoropyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazine (0.2 g, 0.690 mmol) and aryl acid (0.690 mmol) in dry DMF (3 ml), HBTU[2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.314 g, 0.830 mmol),DIPEA[di isopropyl ethyl amine], (0.107 g ≅ 0.141 ml,0.830 mmol) and TEA (0.19 ml, 1.03 mmol) was added to basify the content at 0^oC. The reaction mixture was stirred for 10 hours at room temperature (monitored by TLC). The reaction mixture was poured on to crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in **Table-3a.**

[E] Biological evaluation of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-3b**.

Table-3a: Physical constants of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.



Sr. No.	Substitution R	MF	MW	Yield (%)	R_f value
3a		$C_{23}H_{23}FN_4O_2$	406.45	80	0.51
3b		$C_{23}H_{23}FN_4O_2$	406.45	84	0.49
3c		$C_{21}H_{20}FN_5O_2$	393.41	67	0.37
3d		$C_{21}H_{20}FN_5O_2$	393.41	62	0.38
3e		$C_{23}H_{23}FN_4O_3$	422.45	76	0.42
3f		$C_{22}H_{21}FN_4O_2$	392.42	63	0.46
3g		$C_{24}H_{24}FN_5O_3$	449.47	69	0.30
3h		$C_{23}H_{22}BrFN_4O_2$	485.34	70	0.43
3i		$C_{22}H_{21}BrFN_5O_2$	486.33	78	0.36
3j		$C_{22}H_{20}ClFN_4O_2$	426.87	77	0.43

TLC solvent system:- E.A. : Hexane = 6 : 4

ANALYTICAL DATA

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl) methanone *(3a)*. mp 92-94^{o}C; IR (DRS): 3070, 2948, 2863, 1636, 1521, 1453, 1339, 1158, 1012, 842, 801, 746, 695 cm^{-1}; MS: m/z = 407 $[M+1]^{+}$; Anal. Calcd for $C_{23}H_{23}FN_4O_2$: C, 67.97; H, 5.70; N, 13.78. Found: C, 67.91; H, 5.45; N, 13.58%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone *(3b)*. mp 86-87^{o}C; IR (DRS): 3098, 3048, 2940, 2853, 1628, 1525, 1450, 1329, 1175, 1017, 880, 831,740 cm^{-1}; MS: m/z = 406 [M]+; Anal. Calcd for $C_{23}H_{23}FN_4O_2$: C, 67.97; H, 5.70; N, 13.78. Found: C, 67.88; H, 5.44; N, 13.59%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-4-yl) methanone *(3c)*. mp 164-168^{o}C; IR (DRS): 3044, 2925, 2858, 1627, 1545, 1468, 1316, 1170, 1033, 820, 768,720 cm^{-1}; MS: m/z = 394 $[M+1]^{+}$; Anal. Calcd for $C_{21}H_{20}FN_5O_2$: C, 64.11; H, 5.12; N, 17.80. Found: C, 64.02; H, 4.96; N, 17.64%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(3d)*. mp 260-262^{o}C; IR (DRS): 3087, 3051, 2948, 2891, 1620, 1542, 1478, 1298, 1150, 1031, 880, 804, 721 cm^{-1}; MS: m/z = 394 $[M+1]^{+}$; Anal. Calcd for $C_{21}H_{20}FN_5O_2$: C, 64.11; H, 5.12; N, 17.80. Found: C, 64.05; H, 5.01; N, 17.63%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(3-methoxy-phenyl)methanone *(3e)*. mp 108-110^{o}C; IR (DRS): 3068, 3017, 2930, 2861, 1616, 1541, 1460, 1299, 1131, 1016, 804, 754, 700 cm^{-1}; MS: m/z = 422 $[M]^{+}$; Anal. Calcd for $C_{23}H_{23}FN_4O_3$: C, 65.39; H, 5.49; N, 13.26. Found: C, 65.20; H, 5.39; N, 13.14%.

(4-(((5-(2-Fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl) methanone *(3f)*. mp 95-96^{o}C; IR (DRS): 3078, 3042, 2935, 2860, 1610, 1564, 1488,1250, 1320, 1112, 1007, 810, 768, 737 cm^{-1}; MS: m/z = 392 $[M]^{+}$; Anal. Calcd for $C_{22}H_{21}FN_4O_2$: C, 67.33; H, 5.39; N, 14.28. Found: C, 67.18; H, 5.04; N, 14.27%.

***N*-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl) phenyl)acetamide *(3g)*.** mp 212-214^{o}C; IR (DRS): 3329, 3248, 3024,2914, 2866, 1689, 1645, 1612, 1531, 1448, 1350, 1263, 1176,1010, 879, 765, 711 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm, 1.24-1.36(m, 2H, CH), 1.86-1.92(m, 2H, CH), 2.08(s, 3H, OCH_3), 2.11-2.16(m, 1H, CH), 2.85-3.08(m, 2H,CH), 3.90-3.93(d, *J*= 13.64 Hz, 1H, CH), 4.24-

4.26(d, *J*=6.4 Hz, 2H, 2CH),4.55-4.58(d, *J*=13.6 Hz, 1H, CH), 7.30-7.32(d, *J*= 8.56 Hz, 2H, ArH), 7.40-7.43(d,d, *J*=2.0 Hz, *J*= 2.04 Hz, 1H, ArH), 7.63-7.65(d, *J*= 8.52 Hz, 2H, ArH),8.25-8.26(d, *J*= 1.28 Hz, 1H, ArH), 8.28-8.32(m, 1H. ArH), 8.89-8.90(d, *J*=1.36 Hz, 1H, ArH), 9.35-9.36(d, *J*= 1.36 Hz, 1H ,ArH), 10.04(s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ ppm,13.86, 22.11, 23.94, 28.52, 28.73, 28.88, 29.03, 31.31, 35.27, 69.84, 105.39, 114.16, 118.34, 122.27, 125.21, 127.43, 129.83, 130.27, 133.87, 135.39, 138.81, 139.83, 140.31, 141.14, 158.36, 161.21, 168.38, 169.00.; MS: m/z = 449 $[M]^+$; Anal. Calcd for $C_{24}H_{24}FN_5O_3$: C, 64.13; H, 5.38; N, 15.58. Found: C, 64.02; H, 5.19; N, 15.43%.

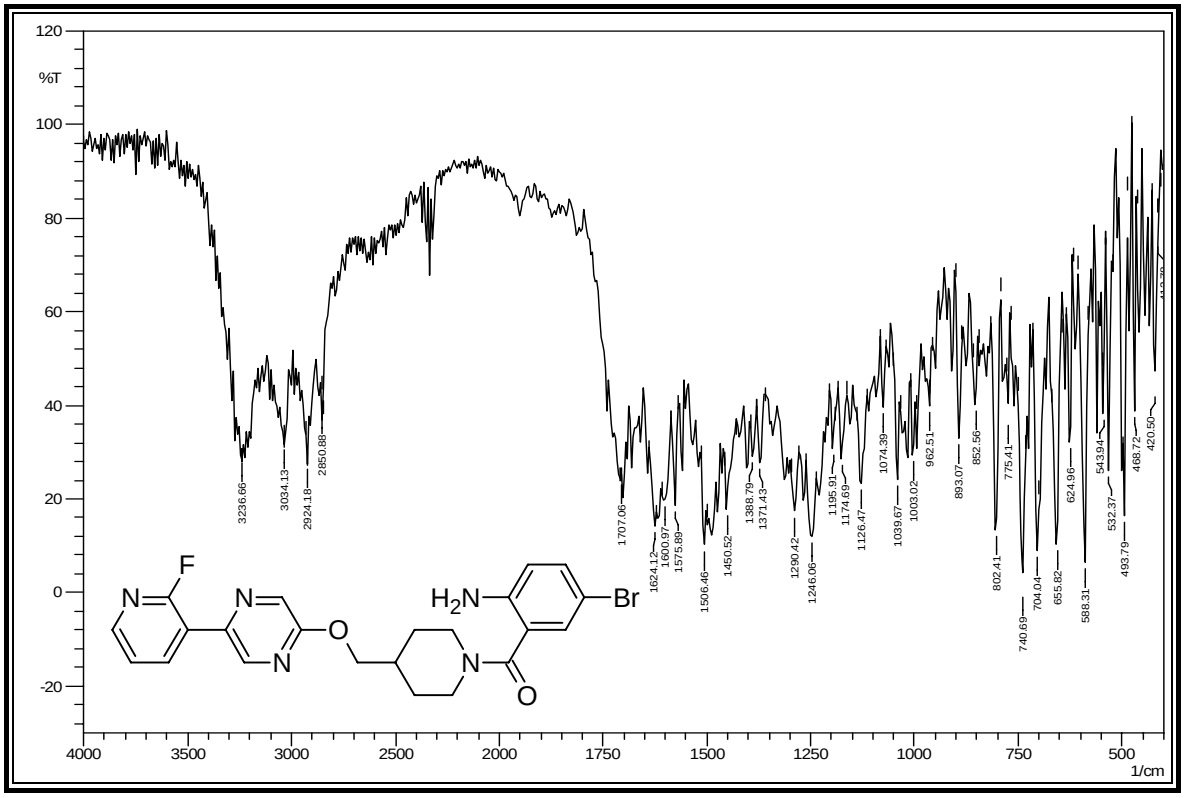
(4-(Bromomethyl)phenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-yl)methanone *(3h).* mp 79-81^{o}C; IR (DRS): 3101, 3038, 2940, 2853, 1618, 1525, 1450, 1329, 1247,1175, 1017, 840, 768, 703, 635 cm^{-1}; MS: m/z = 486 $[M+1]^+$; Anal. Calcd for $C_{23}H_{22}BrFN_4O_2$: C, 56.92; H, 4.57; N, 11.54. Found: C, 56.80; H, 4.48; N, 11.52%.

(2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone *(3i).* mp 245-247^{o}C; IR (DRS): 3236(-NH_2 str.), 3034(Ar,C-H str.), 2924(C-H str.), 2850(C-H str.),1707(amide, C=O str.),1624(amide, C=O str.),1575(Ar, C=C str.),1506(Ar, C=C str.),1450(Ar, C=C str.),1388(C-H ben),1246(C-Br str.),1174(C-F str.),1074(C-N str.),1003(C-O-C str.),893(C-H, o,p, ben), 852(C-H, o,p, ben), 802(C-H, o,p, ben),740(C-H o,p, ben),704(C-C o,p, ben)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.23-1.40 (m, 2H, 2CH), 1.91-1.94 (m, 1H, CH), 2.11-2.14 (m, 1H, CH), 2.48-2.54 (m, 1H, CH), 2.94-2.99 (m, 1H, CH), 3.28-3.37 (m, 1H, CH), 3.68-3.71 (d, *J*=12.48 Hz, 1H, CH), 4.23-4.24 (d, *J*=6.52 Hz, 2H, 2CH), 4.54-4.57 (d, *J*=12.84 Hz, 1H, CH), 5.30 (s, 2H, NH_2), 6.67-6.69 (d, *J*=8.52 Hz, 1H, ArH), 7.20-7.21 (m, 2H, ArH), 7.41-7.43 (m, 1H, ArH), 7.57-7.58 (m, 1H, ArH), 7.79-7.80 (m, 1H, ArH), 8.01-8.02 (d, *J*=1.24 Hz, 1H, ArH), 8.16-8.17 (d, *J*=1.20 Hz, 1H, ArH);MS: m/z = 486 $[M]^+$; Anal. Calcd for $C_{22}H_{21}BrFN_5O_2$: C, 54.33; H, 4.35; N, 14.40. Found: C, 54.06; H, 4.02; N, 14.33%.

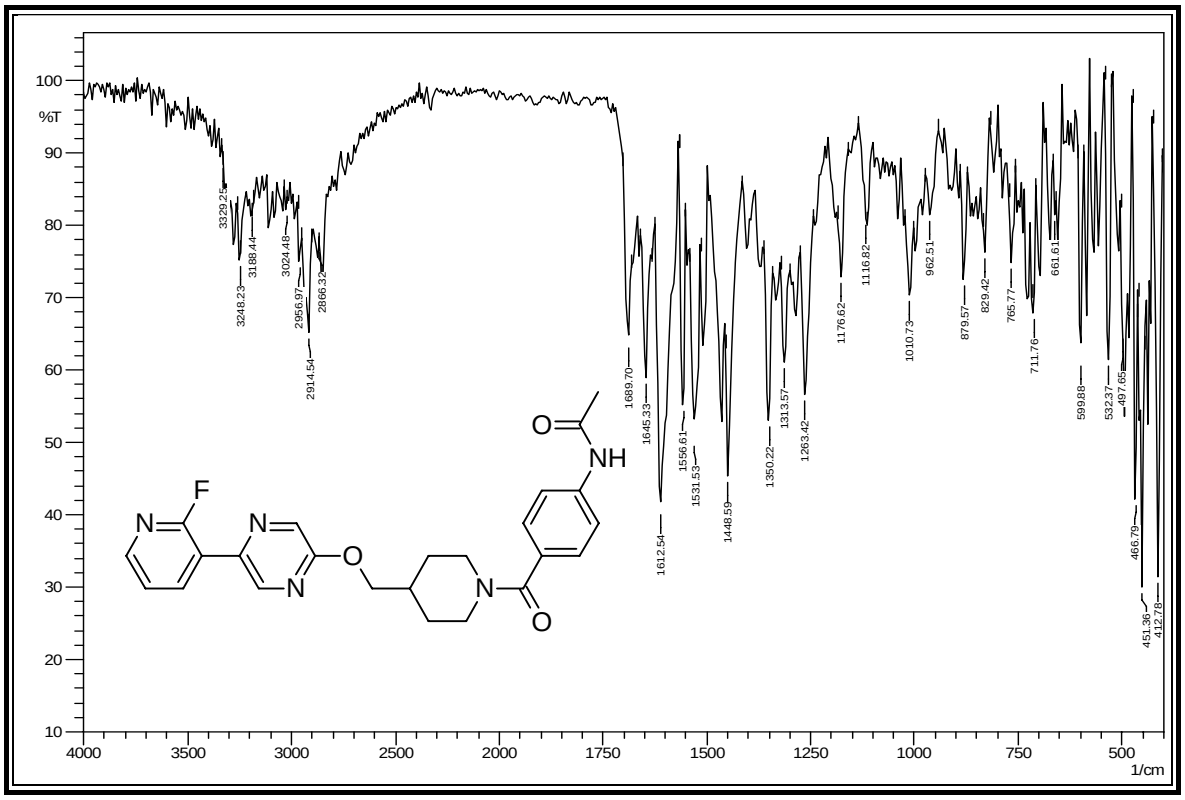
(4-Chlorophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone *(3j).* mp 170-171^{o}C; IR (DRS): 3066, 3053, 2978, 2851, 1622, 1510, 1442, 1346,1245, 1165, 1037, 836, 796, 702 cm^{-1}; MS: m/z = 427 $[M+1]^+$; Anal. Calcd for $C_{22}H_{20}ClFN_4O_2$: C, 61.90; H, 4.72; N, 13.12. Found: C, 61.37; H, 4.65; N, 12.91%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

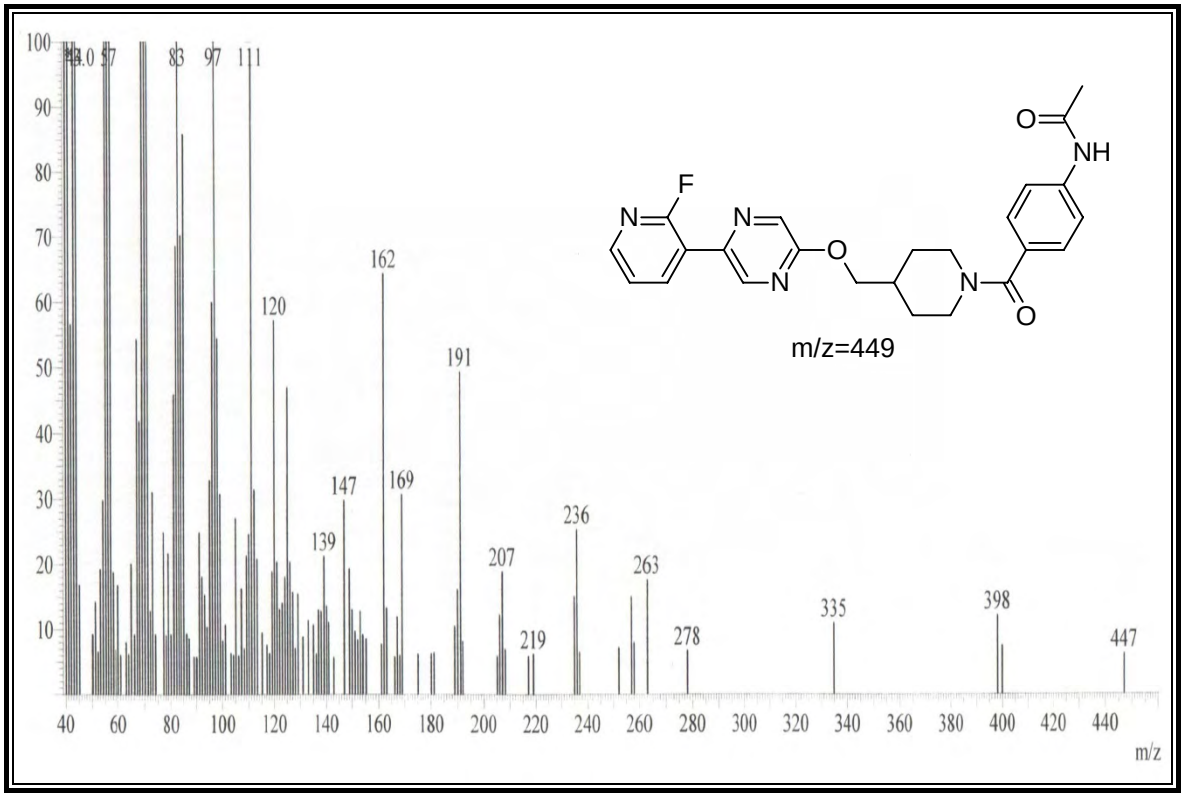
IR Spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(3i)*.



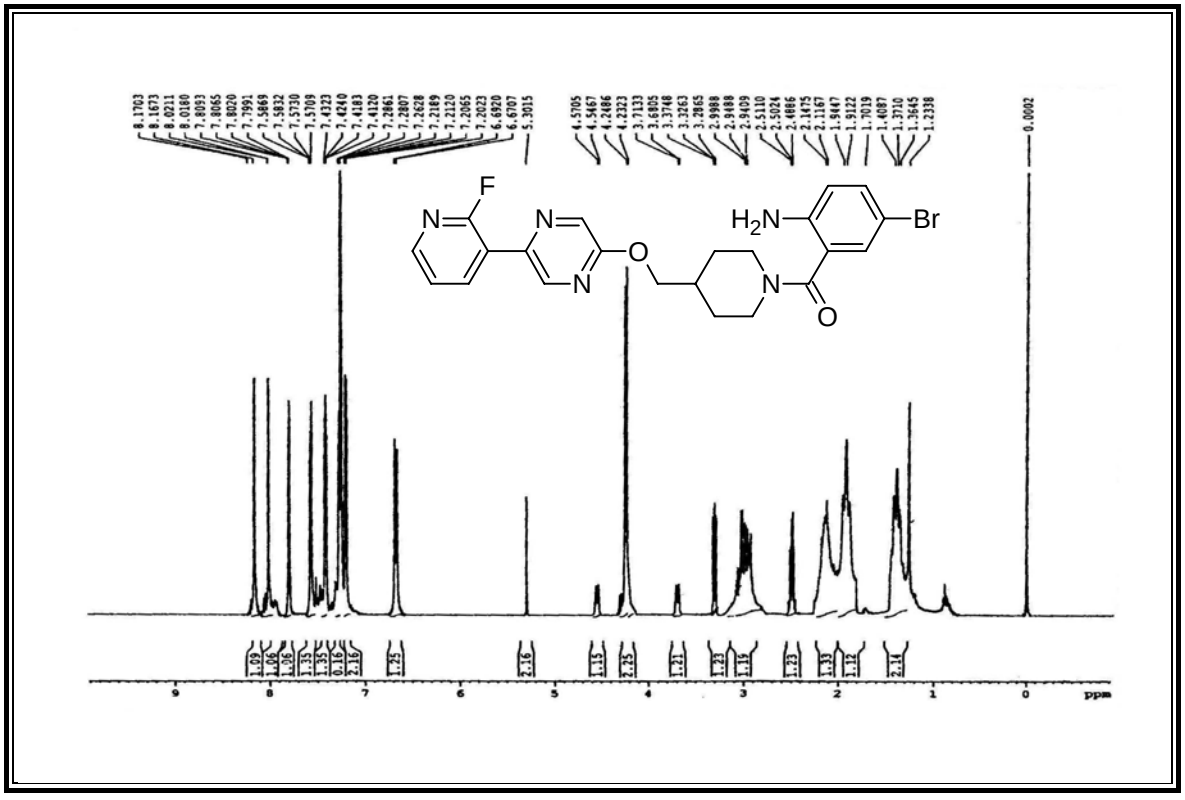
IR Spectrum of *N*-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carbonyl)phenyl)acetamide*(3g)*.



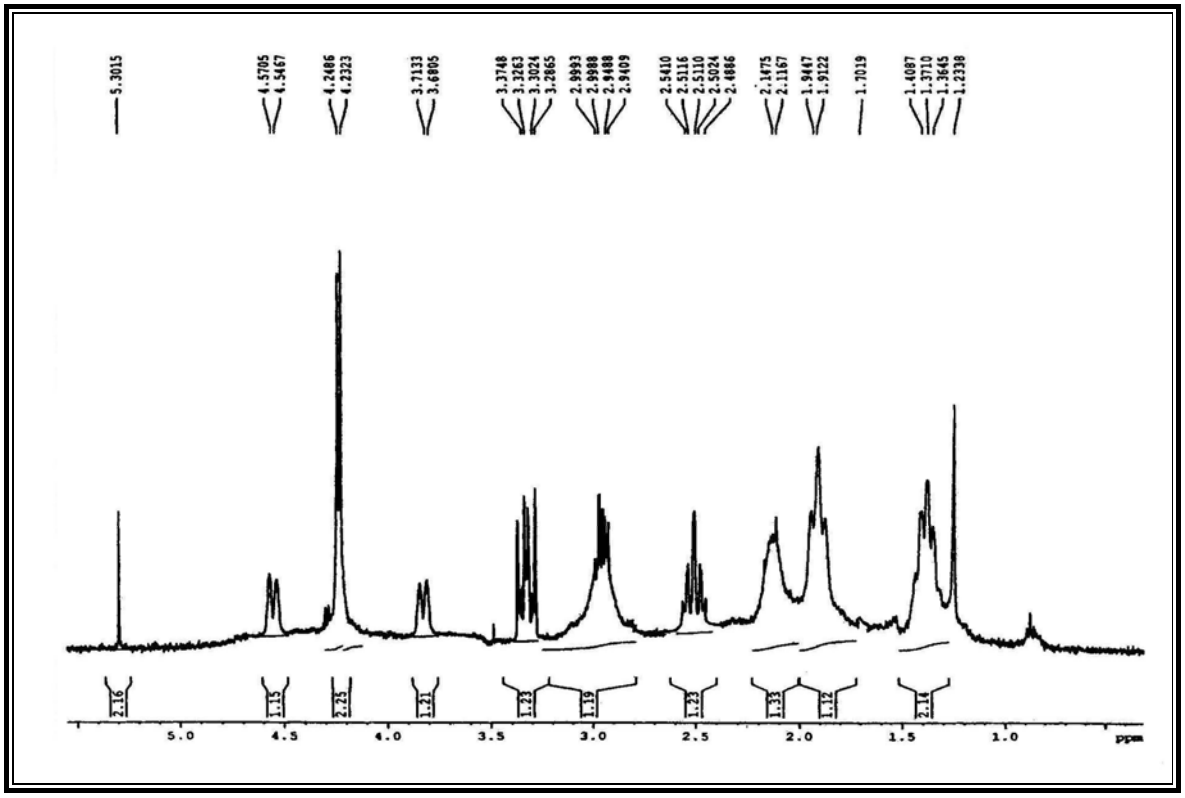
Mass spectrum of *N*-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carbonyl)phenyl)acetamide*(3g)*.



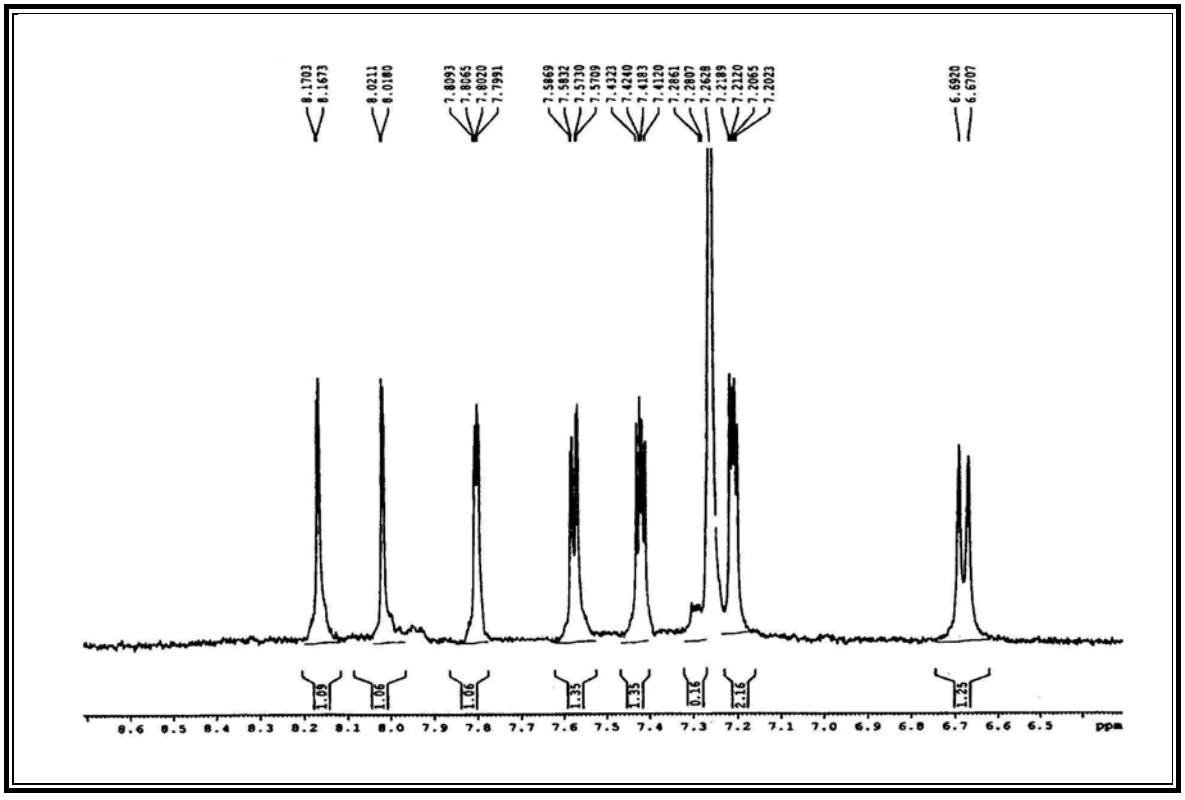
^{1}H NMR spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(3i)*.



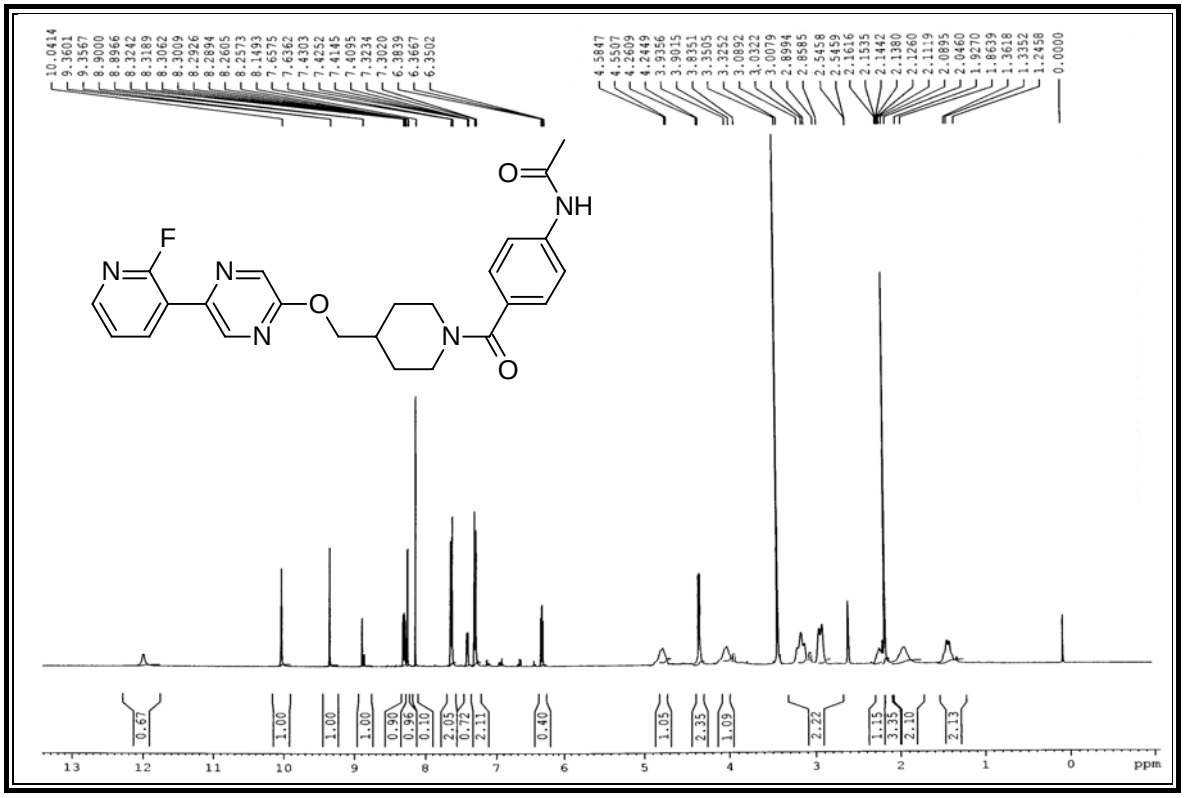
Expanded spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(3i)*.



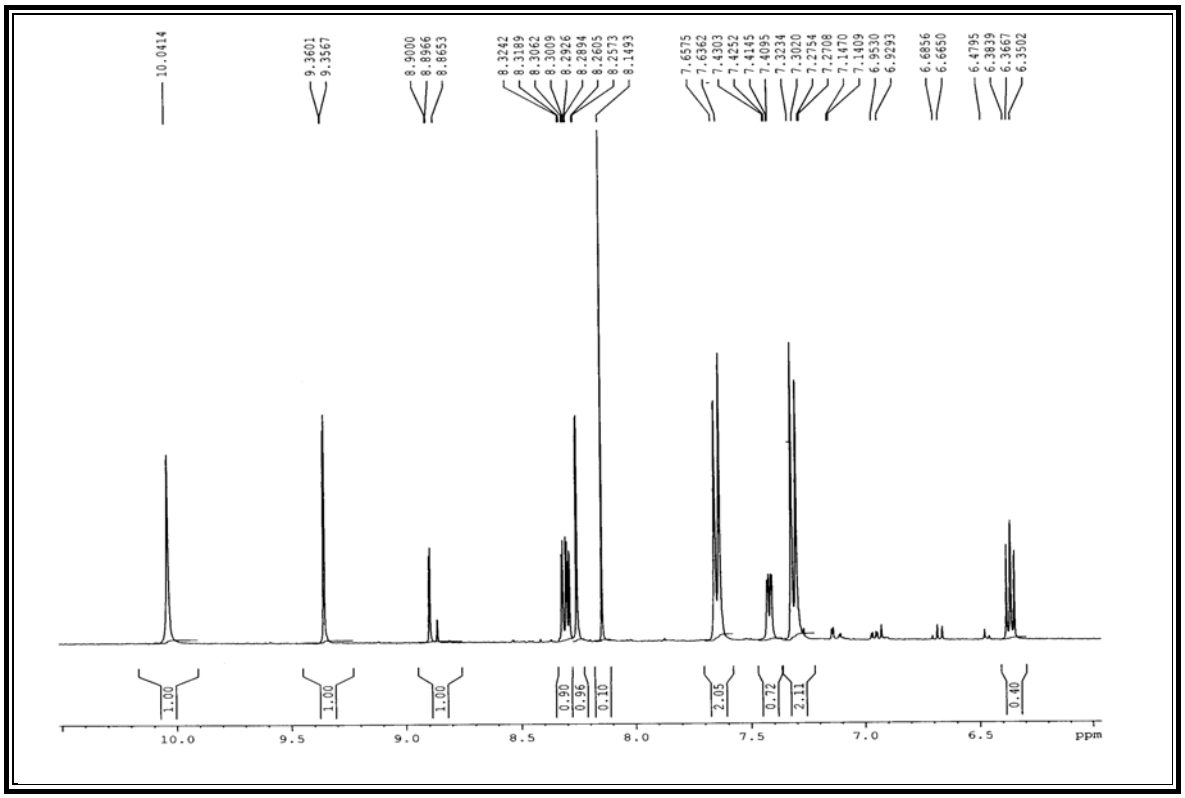
Expanded spectrum of (2-Amino-5-bromophenyl)(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(3i)*.



^{1}H NMR spectrum of *N*-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carbonyl)phenyl)acetamide*(3g)*.



Expanded spectrum of *N*-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carbonyl)phenyl)acetamide*(3g)*.



^{13}C NMR spectrum of *N*-(4-(4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy)methyl) piperidine-1-carbonyl)phenyl)acetamide*(3g)*.

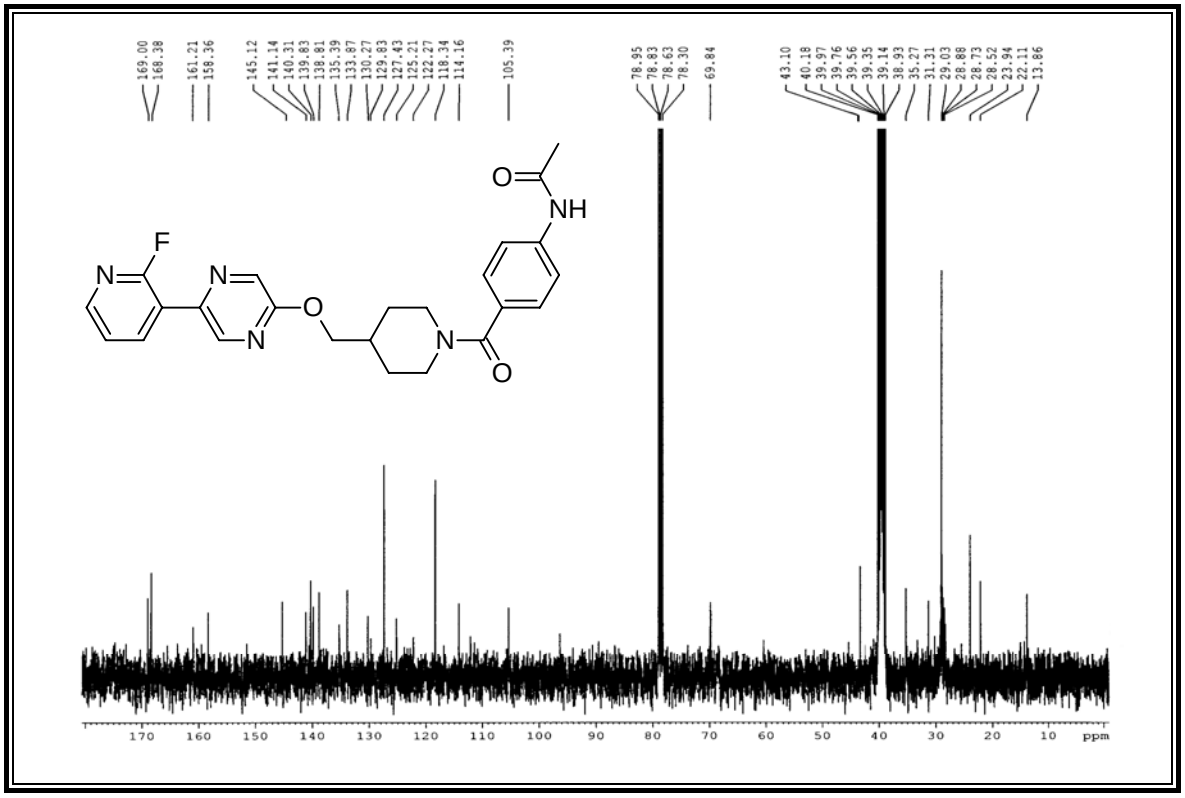


Table-3b: Antimicrobial activity of (4-(((5-(2-fluoropyridin-3-yl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
3a	62.5	100	125	100	>1000	200	250
3b	200	125	250	250	>1000	200	200
3c	125	250	200	100	200	250	500
3d	200	100	250	125	200	500	200
3e	250	250	200	100	500	1000	1000
3f	250	62.5	100	250	250	500	200
3g	125	100	100	200	200	>1000	1000
3h	200	250	250	250	500	1000	1000
3i	125	200	200	200	500	500	500
3j	200	125	100	250	1000	250	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

Part – A

[Part – I (Section-iv)]

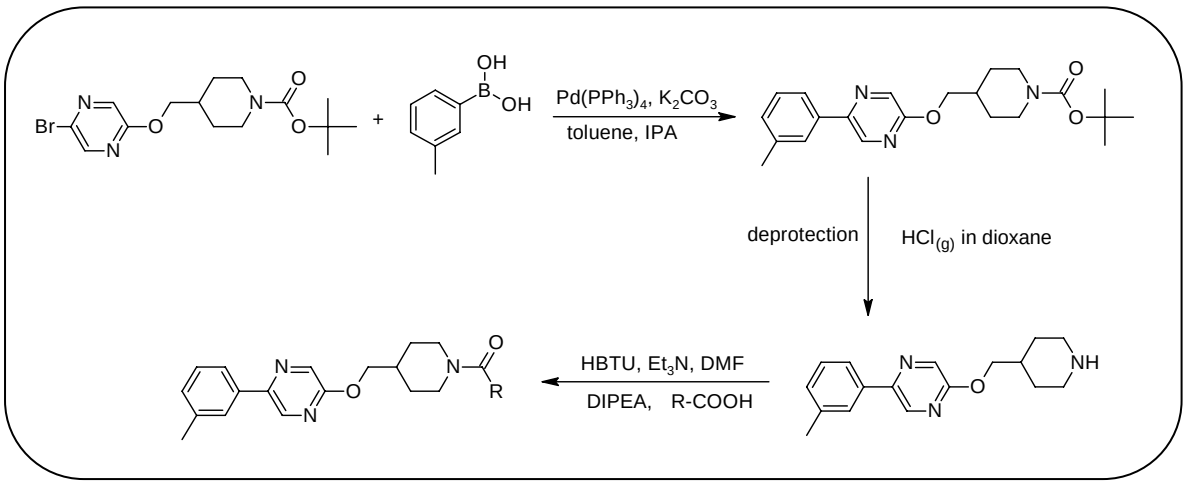
Synthesis and biological evaluation of Aryl(4-(((5-(*m*-tolyl)pyrazin-2-yl)oxy) methyl) piperidine-1-yl)methanones.

SECTION-IV

SYNTHESIS AND BIOLOGICAL EVALUATION OF ARYL(4-(((5-(*m*-TOLYL) PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)METHANONES

Pyrazine play an important role as intermediates for perfumes, pharmaceuticals, agricultural chemicals and food spices. In view of these reports, we have synthesized 2-(piperidin-4-ylmethoxy)pyrazines derivatives by the condensation of 2-(piperidin-4-ylmethoxy)-5-(*m*-tolyl)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of *tert*-butyl 4-(((5-(*m*-tolyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

A solution of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution 1-benzothiophen-3-yl-3-boronic acid (0.594 g, 0.0044 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K_2CO_3 (10 ml, 0.02 mol) in water was added drop wise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 5 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

[C] Preparation of 2-(piperidin-4-ylmethoxy)-5-(*m*-tolyl)pyrazine.

A mixture of $HCl_{(g)}$ in dioxane (10 ml) and *tert*-butyl 4-(((5-(*m*-tolyl)pyrazin-2-yl) oxy)methyl)piperidine-1-carboxylate was stirred at room temperature for over-night

(monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combine organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure product. Yield: 69 %, mp 87-88^oC.

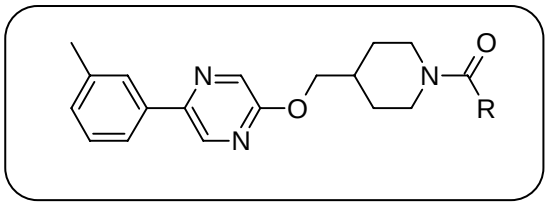
[D] General procedure for the preparation of Aryl(4-(((5-(*m*-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanones.

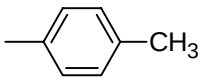
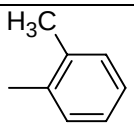
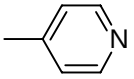
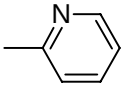
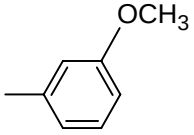
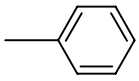
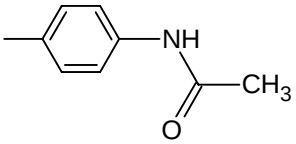
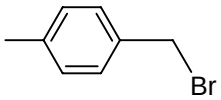
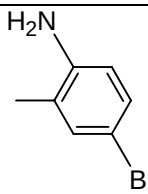
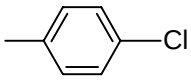
To a cooled mixture of 2-(piperidin-4-ylmethoxy)-5-(*m*-tolyl)pyrazine (0.2 g, 0.700 mmol) and aryl acid (0.700 mmol) in dry DMF (3 ml), HBTU [2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate] (0.318 g, 0.840 mmol), DIPEA[di isopropyl ethyl amine], (0.108 g ≅ 0.142 ml,0.840 mmol) and TEA (0.21 ml, 1.05 mmol) was added to basify the content at 0^oC. The reaction mixture was stirred for 10 hours at room temperature (monitored by TLC).The reaction mixture was poured onto crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in **Table-4a.**

[E] Biological evaluation of Aryl(4-(((5-(*m*-tolyl)pyrazin-2-yl)oxy)methyl) piperidine -1-yl)methanones.

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-4b**.

Table-4a: Physical constants of Aryl(4-(((5-(*m*-tolyl)pyrazin-2-yl)oxy)methyl) piperidine-1-yl)methanones.



Sr. No.	Substitution R	MF	MW	Yield (%)	R_f value
4a		$C_{25}H_{27}N_3O_2$	401.50	74	0.54
4b		$C_{25}H_{27}N_3O_2$	401.50	69	0.52
4c		$C_{23}H_{24}N_4O_2$	488.46	74	0.44
4d		$C_{23}H_{24}N_4O_2$	488.46	71	0.42
4e		$C_{25}H_{27}N_3O_3$	417.50	80	0.45
4f		$C_{24}H_{25}N_3O_2$	387.47	59	0.49
4g		$C_{26}H_{28}N_4O_3$	444.52	64	0.31
4h		$C_{25}H_{26}BrN_3O_2$	480.39	76	0.42
4i		$C_{24}H_{25}BrN_4O_2$	481.38	78	0.36
4j		$C_{24}H_{24}ClN_3O_2$	421.91	84	0.44

TLC solvent system:- E.A. : Hexane = 5 : 5

ANALYTICAL DATA

P*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(4a). mp 124 -126^{o}C; IR (DRS): 3083, 3049, 2953, 2848, 1678, 1531, 1444, 1329, 1176, 1016, 854, 792, 748, 701 cm^{-1}; MS: m/z = 401 $[M]^{+}$; Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.11; H, 6.72; N, 10.40%.

O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(4b). mp 118-120 ^{o}C; IR (DRS): 3049(Ar, C-H Str..), 2914 (C-H Str..), 2860 (C-H Str..),1631 (amide,C=O Str..), 1599 (Ar, C=C Str..) ,1535 (Ar, C=C Str..),1444 (Ar, C=C Str..), 1340 (C-H ben), 1201 (C-N Str..), 1168 (C-N Str..), 1006 (C-O-C Str..), 900 (C-H o,p, ben), 767 (C-H o,p, ben); ^{1}H NMR(400 MHz (DMSO): δ ppm 1.17-1.39(m, 2H, CH), 1.71-1.79(m, 1H, CH), 1.94-1.97(m, 1H, CH), 2.11-2.13(m, 1H, CH), 2.40(s, 3H, CH_3), 2.78-2.81(m, 1H, CH), 2.98-3.05(m, 1H, CH), 3.42-3.43(d, *J*=6.4 Hz, 1H, CH), 4.23-4.24(d, *J*=6.4 Hz, 2H, 2CH), 4.69-4.72(d, *J*=13.04 Hz, 1H, CH), 7.08-7.10(d, *J*= 7.0 Hz, 1H, ArH), 7.16-7.29(m, 5H, ArH), 7.32-7.35(t, 1H, ArH), 7.72-7.77(t, 1H, ArH), 8.26(s, 1H, ArH), 8.60(s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ ppm, 18.46, 18.65, 21.12, 28.22, 28.73, 29.34, 35.15, 35.27, 45.75, 46.30, 69.79, 122.80, 125.13, 125.24, 125.47, 125.56, 126.30, 128.30, 128.46, 129.02, 129.89, 130.03, 133.30, 133.54, 133.99, 135.86, 136.44, 137.09, 137.83, 144.40, 158.73, 168.62.; MS: m/z = 401 $[M]^{+}$; Anal. Calcd for $C_{25}H_{27}N_3O_2$: C, 74.79; H, 6.78; N, 10.47. Found: C, 74.19; H, 6.64; N, 10.36%

Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone *(4c).* mp 84-86 ^{o}C; IR (DRS): 3049 , 2912 , 2852, 1631, 1533, 1464, 1338, 1278, 1168, 1018 , 798, 727 cm^{-1}. ^{1}H NMR (400 MHz $CDCl_3$): δ ppm 1.21-1.28(m, 1H, CH), 1.34-1.43(m, 1H, CH), 1.76-1.79(d, *J*=12.64 Hz, 1H, CH), 2.0 2.09(m, 1H, CH), 2.35(s, 3H, CH_3), 2.74-2.80(t, 1H, CH), 2.98-3.04(t, 1H, CH), 3.59-3.62(d, *J*=12.96 Hz, 1H, CH), 4.17-4.19(d, *J*=6.0 Hz, 2H, 2CH), 4.69-4.72(d, *J*=12.2 Hz, 1H, CH), 7.13-7.15(d, *J*=7.44 Hz, 1H, ArH), 7.26-7.30(m, 1H, ArH), 7.59-7.70(m, 2H, ArH), 8.20(s, 1H, ArH), 8.40(s, 1H, ArH), 8.58-8.63(t, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm, 21.56, 28.48, 29.58, 29.70, 35.87, 35.90, 41.92, 47.34, 70.01, 70.06, 121.09, 123.23, 123.52, 126.92, 128.84, 129.54, 132.00, 134.61, 134.94, 136.37, 137.45, 138.68, 143.84, 145.66, 147.80, 150.31, 150.70, 159.04, 167.71; MS: m/z = 388 $[M]^{+}$; Anal. Calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.09; H, 6.10; N, 14.13%.

Pyridin-2-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone *(4d).* mp 100-102^{o}C; Purity by HPLC: 88 %; IR (DRS): 3078, 3011, 2933, 2908, 1656, 1533, 1465, 1344, 1172, 1010, 888, 831, 748, 699 cm^{-1};; MS: m/z = 489 $[M+1]^{+}$; Anal. Calcd for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 70.86; H, 6.12; N, 14.36%.

(3-Methoxyphenyl)(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone *(4e).* mp 98-99^{o}C; IR (DRS): 3098, 3064, 2954, 2879, 1677, 1556, 1527, 1440, 1327, 1166, 1014, 848, 799, 747, 699 cm^{-1}; MS: m/z = 417 $[M]^{+}$; Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.66; H, 6.40; N, 10.04%.

Phenyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone *(4f).* mp 73-75^{o}C; IR (DRS): 3061, 3025, 2958, 2871, 1668, 1548, 1421, 1314, 1151, 1038, 845, 799, 736 cm^{-1}; MS: m/z = 387 $[M]^{+}$; Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.16; H, 6.28; N, 10.67%.

N*-(4-(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carbonyl)phenyl) acetamide *(4g). mp 114-116^{o}C; IR (DRS): 3457, 3042, 2946, 2821, 1688, 1556, 1443, 1331, 1224, 1157, 1032, 842, 805, 796, 748 cm^{-1}; MS: m/z = 445 $[M+1]^{+}$; Anal. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.60. Found: C, 70.15; H, 6.31; N, 12.44%.

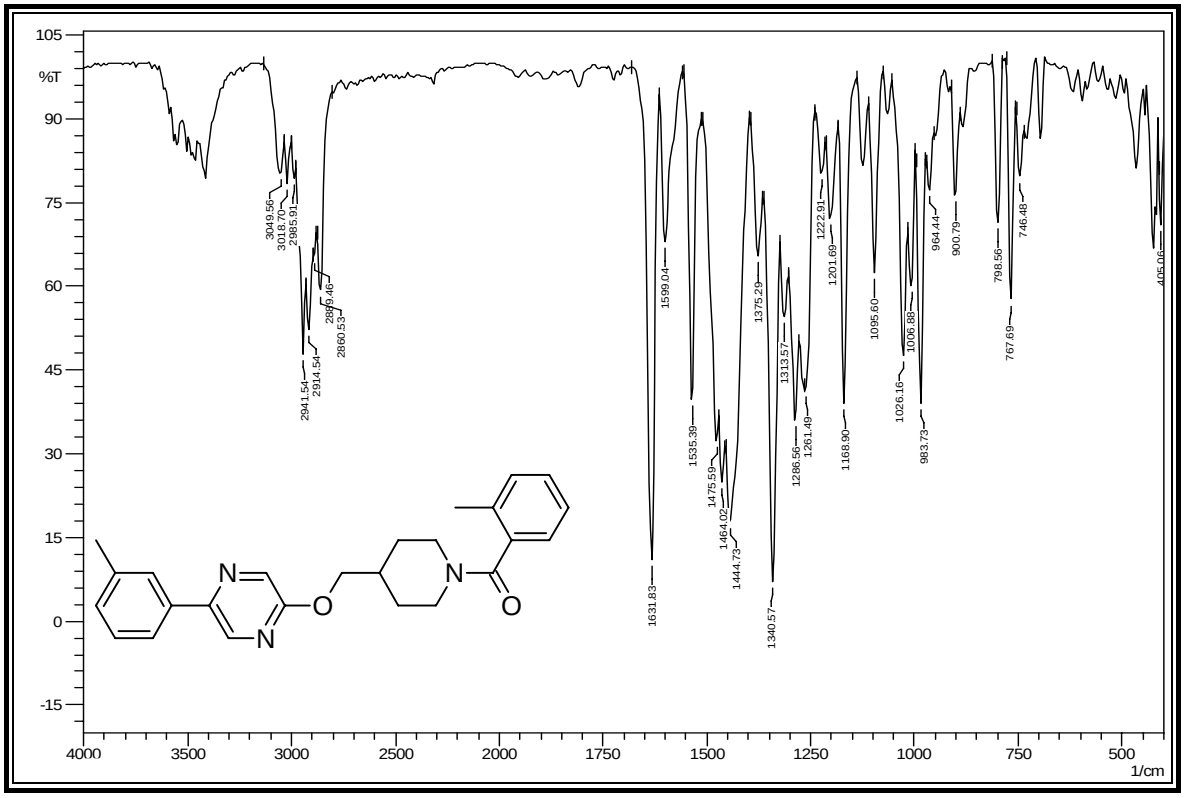
(4-(Bromomethyl)phenyl)(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone *(4h).* mp 69-71^{o}C; IR (DRS): 3105, 3048, 2951, 2820, 1676, 1530, 1455, 1323, 1112, 1041, 834, 769, 698, 621 cm^{-1}; MS: m/z = 481 $[M+1]^{+}$; Anal. Calcd for $C_{25}H_{26}BrN_3O_2$: C, 62.50; H, 5.46; N, 8.75. Found: C, 62.39; H, 5.19; N, 8.54%.

(2-Amino-5-bromophenyl)(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone *(4i).* mp 160-161^{o}C; IR (DRS): 3483, 3450, 3020, 2940, 2843, 1696, 1542, 1450, 1320, 1330, 1116, 1018, 856, 788, 716, 631 cm^{-1}; MS: m/z = 482 $[M+1]^{+}$; Anal. Calcd for $C_{24}H_{25}BrN_4O_2$: C, 59.88; H, 5.23; N, 11.64. Found: C, 59.84; H, 5.20; N, 11.09%.

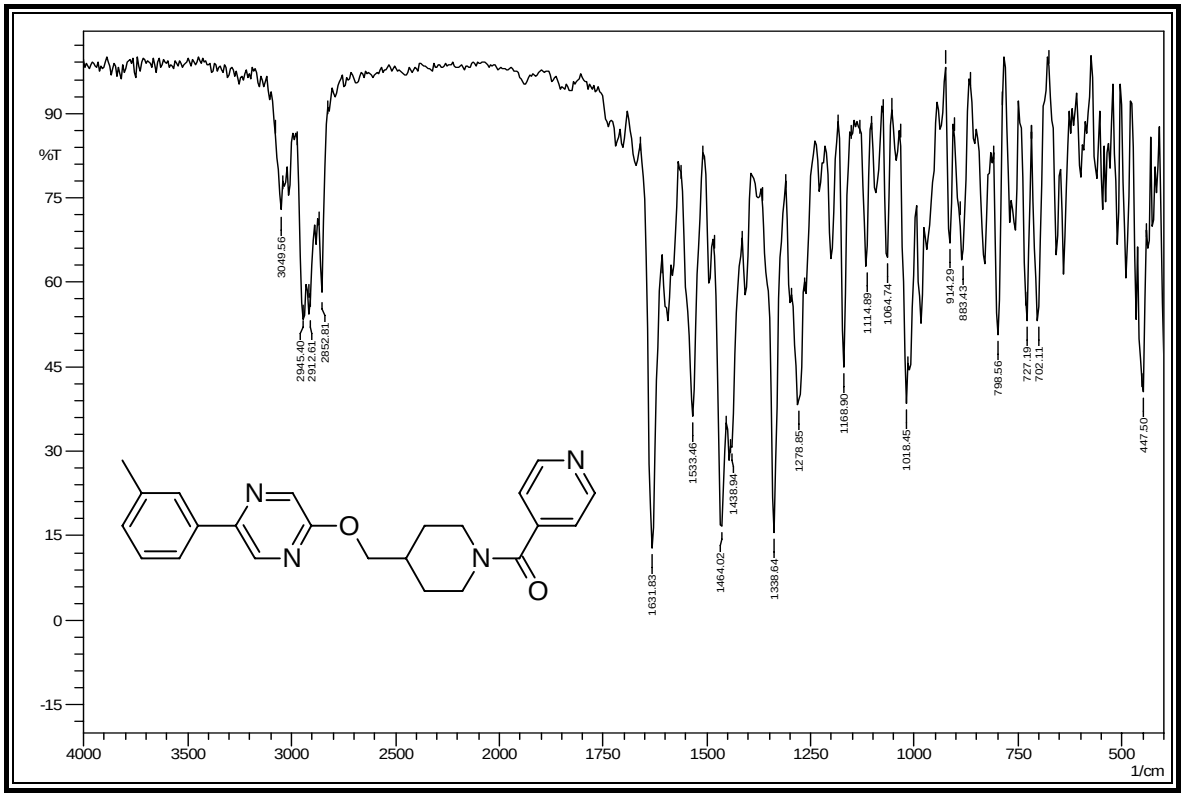
(4-Chlorophenyl)(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone *(4j).* mp 106-108^{o}C; IR (DRS): 3125, 3083, 2910, 2830, 1629, 1515, 1443, 1334, 1241, 1118, 1019, 821, 788, 731, 670 cm^{-1}; MS: m/z = 422 $[M+1]^{+}$; Anal. Calcd for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.10; H, 5.70; N, 9.59%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

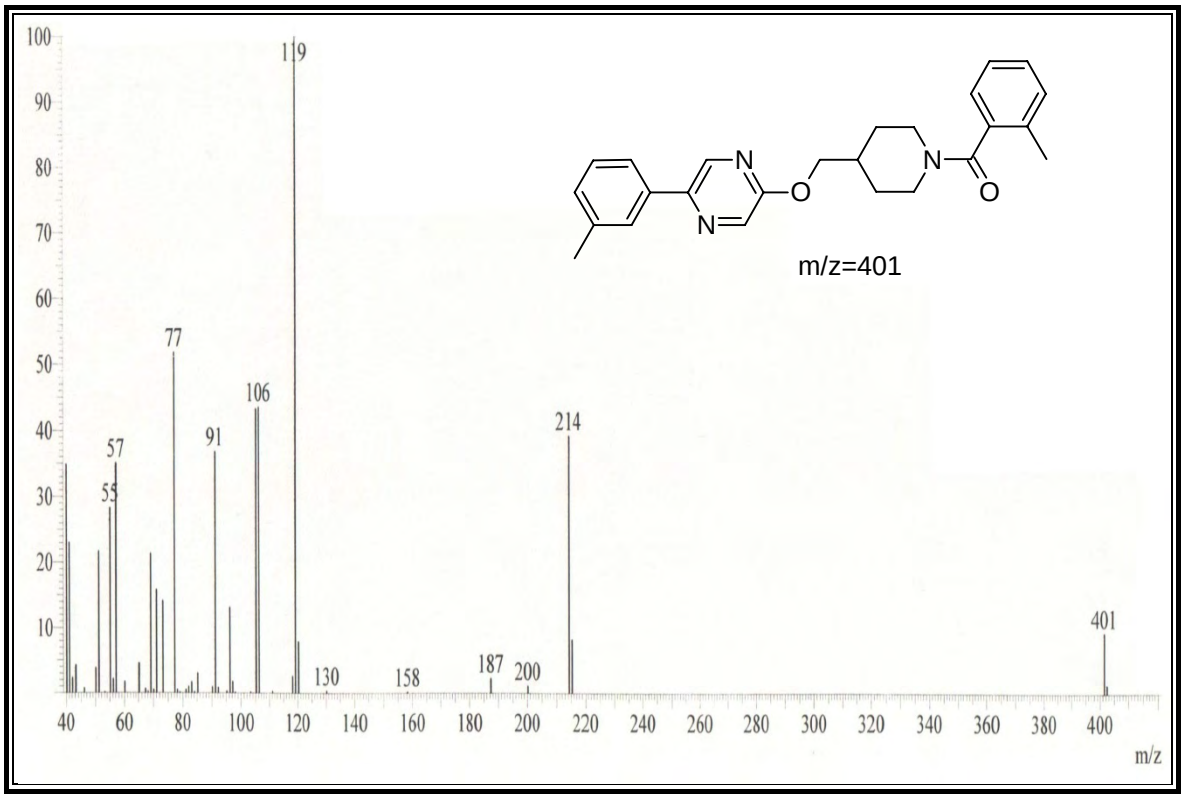
IR Spectrum of *O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone*(4b)*.



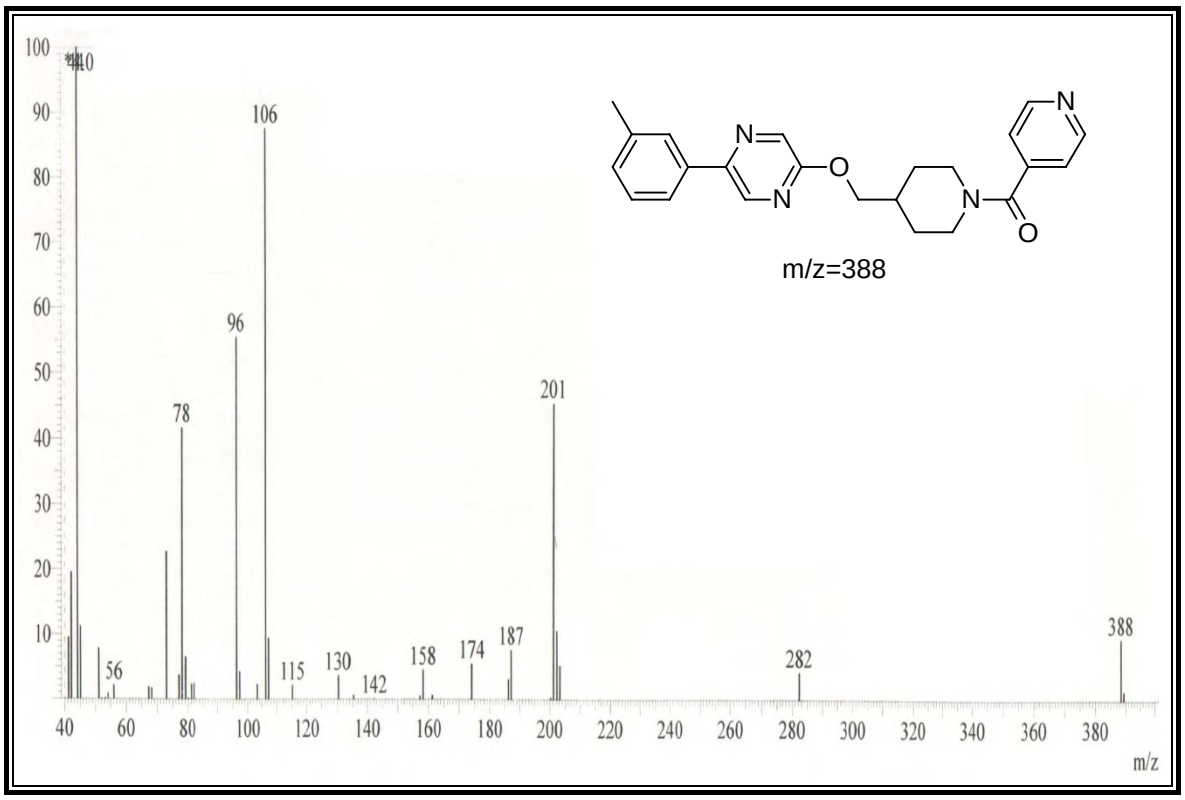
IR Spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(4c)*.



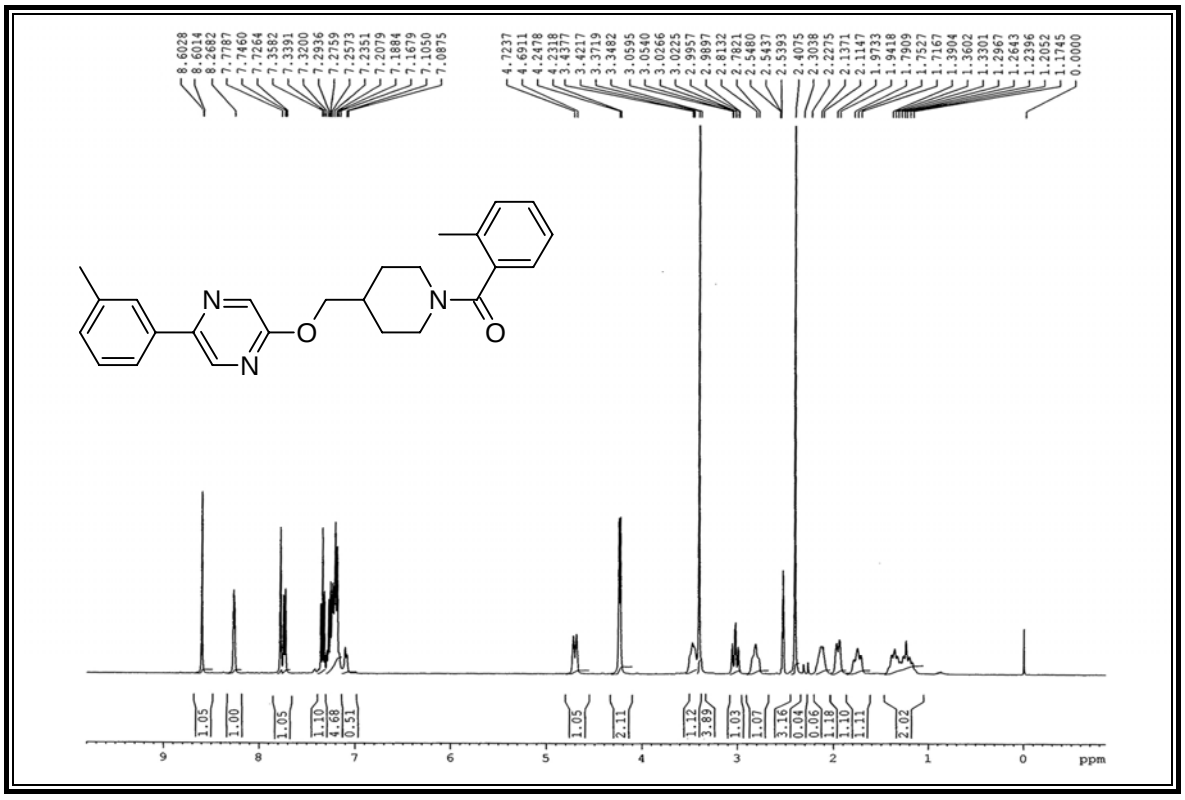
Mass spectrum of *O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone*(4b)*.



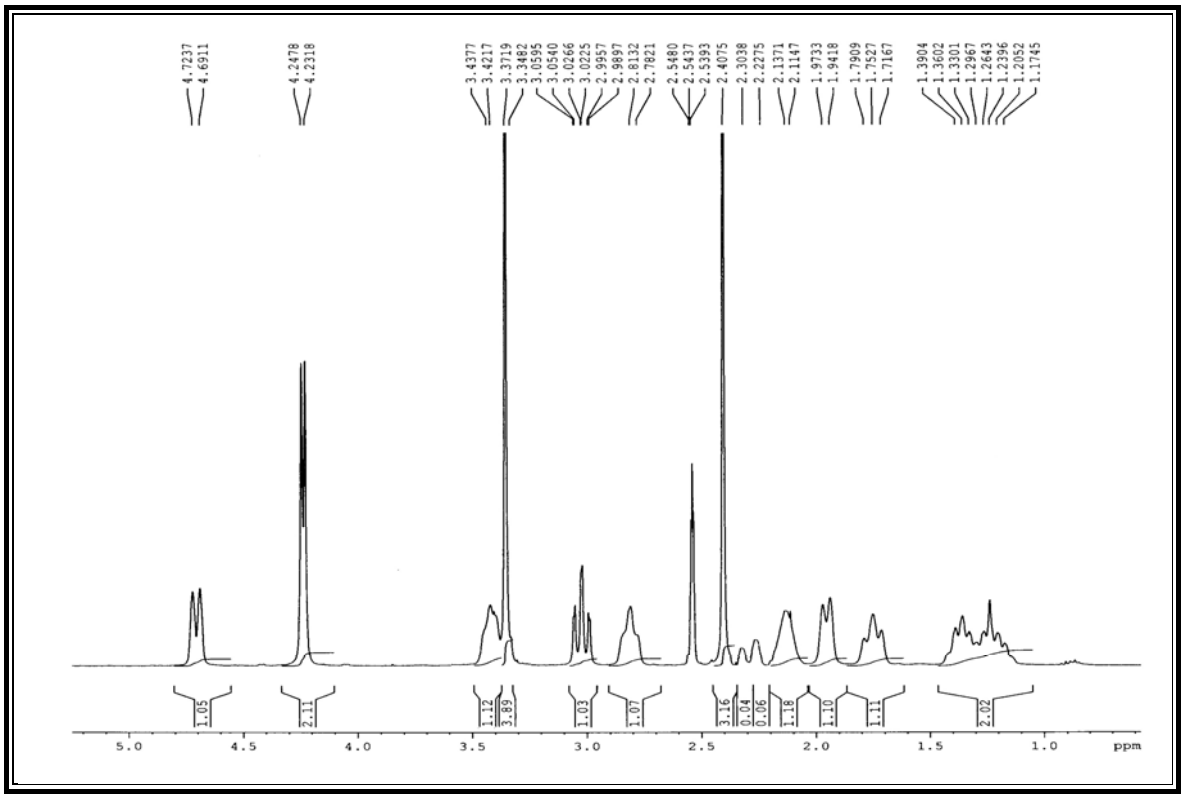
Mass spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)methanone*(4c)*.



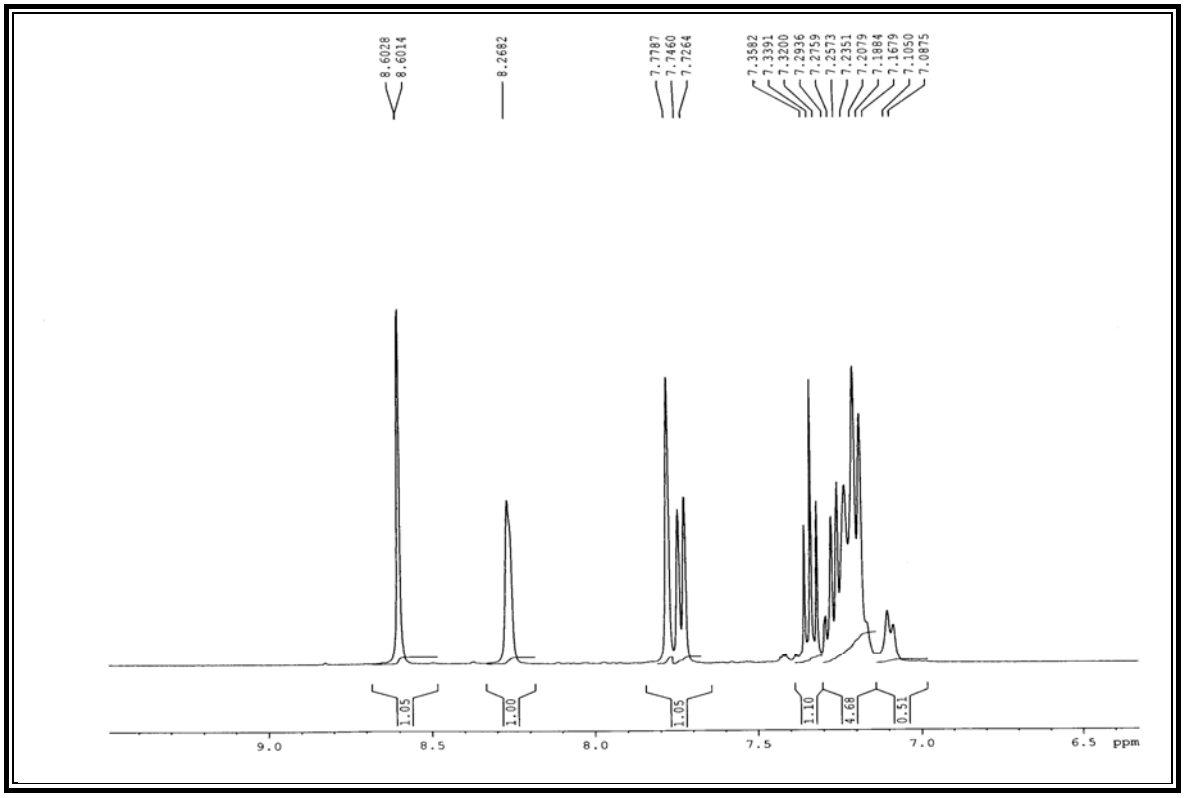
^{1}H NMR spectrum of *O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone*(4b)*.



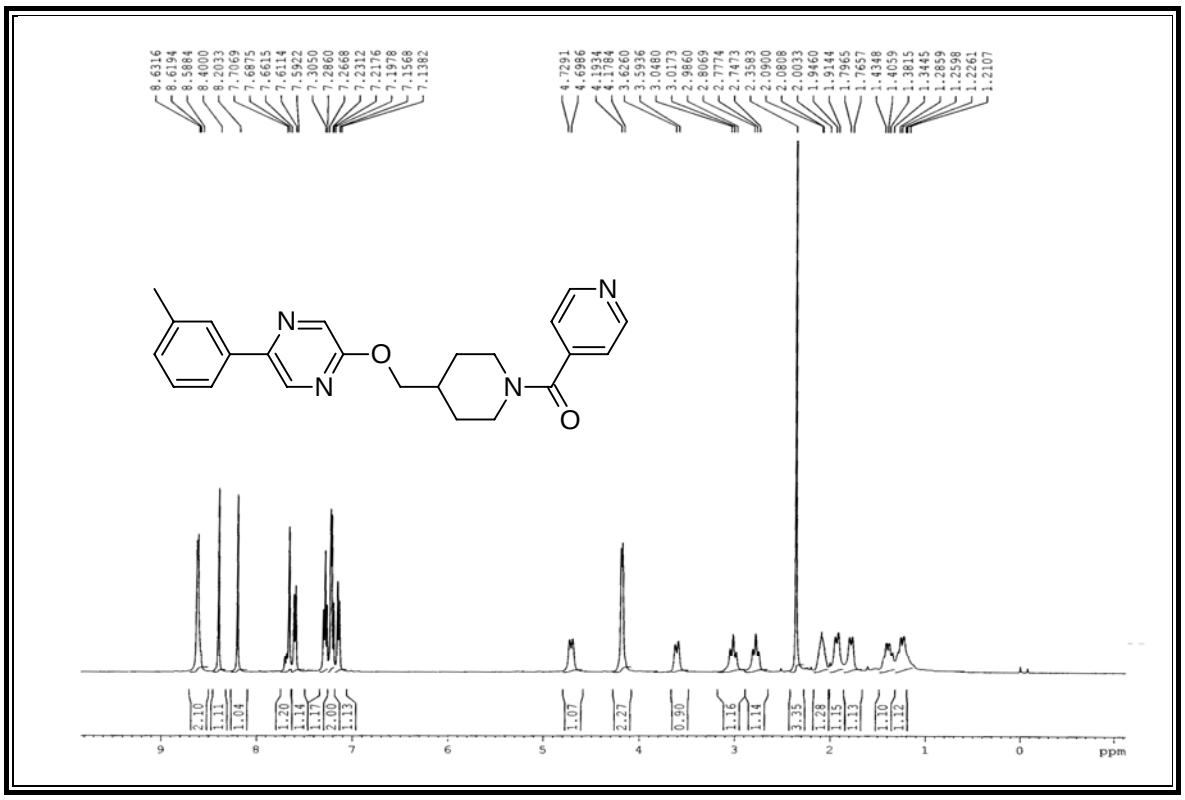
Expanded spectrum of *O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone*(4b)*.



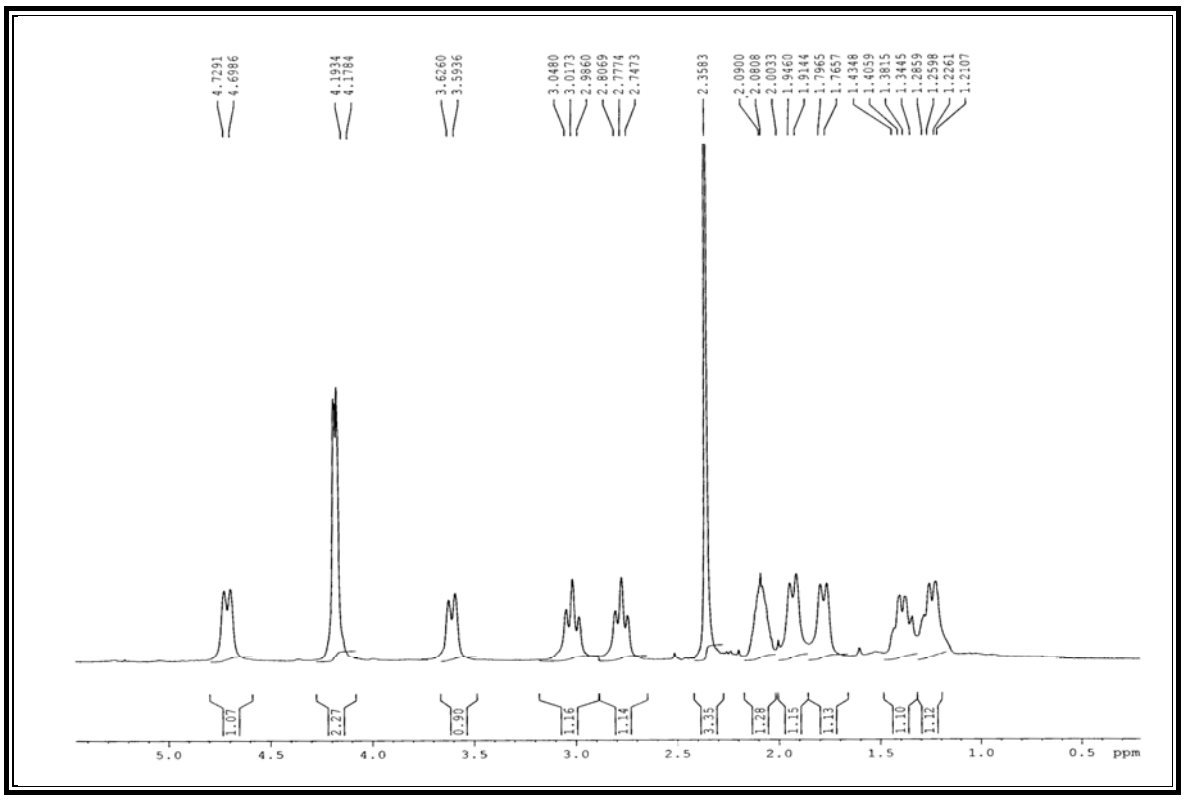
Expanded spectrum of *O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone*(4b).*



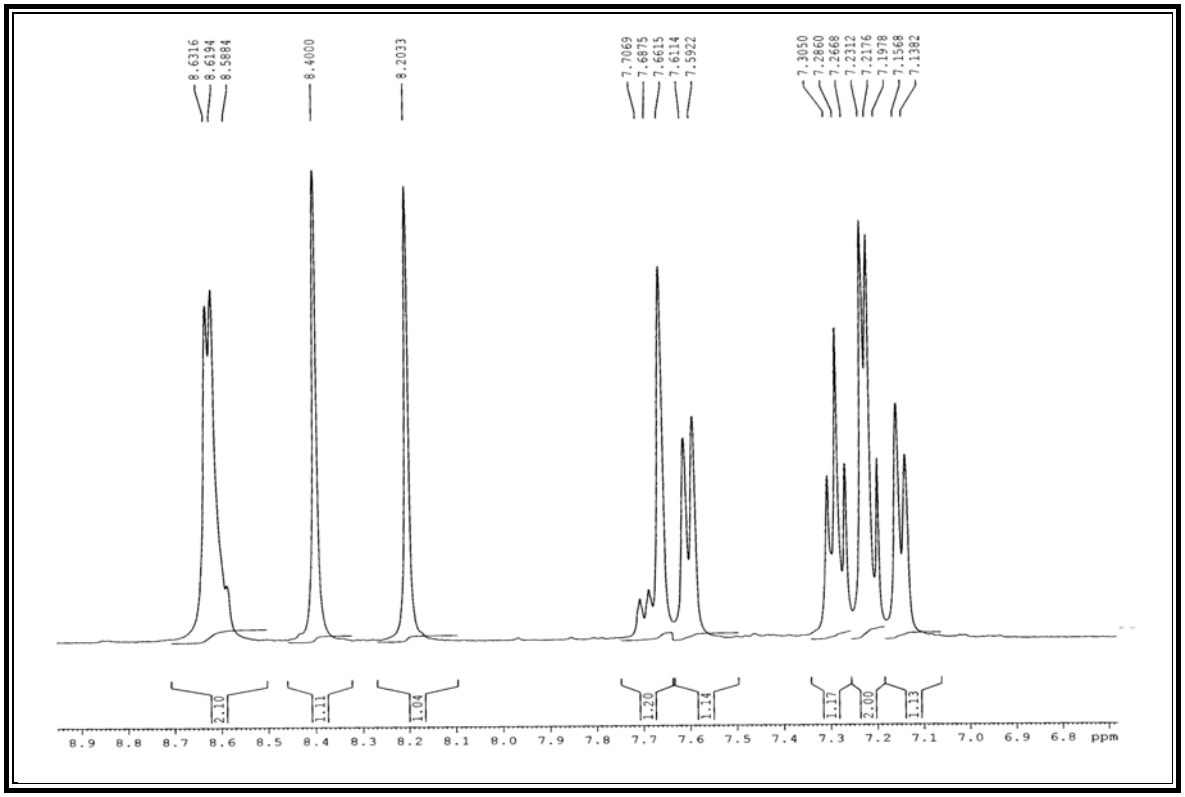
^{1}H NMR spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone*(4c).*



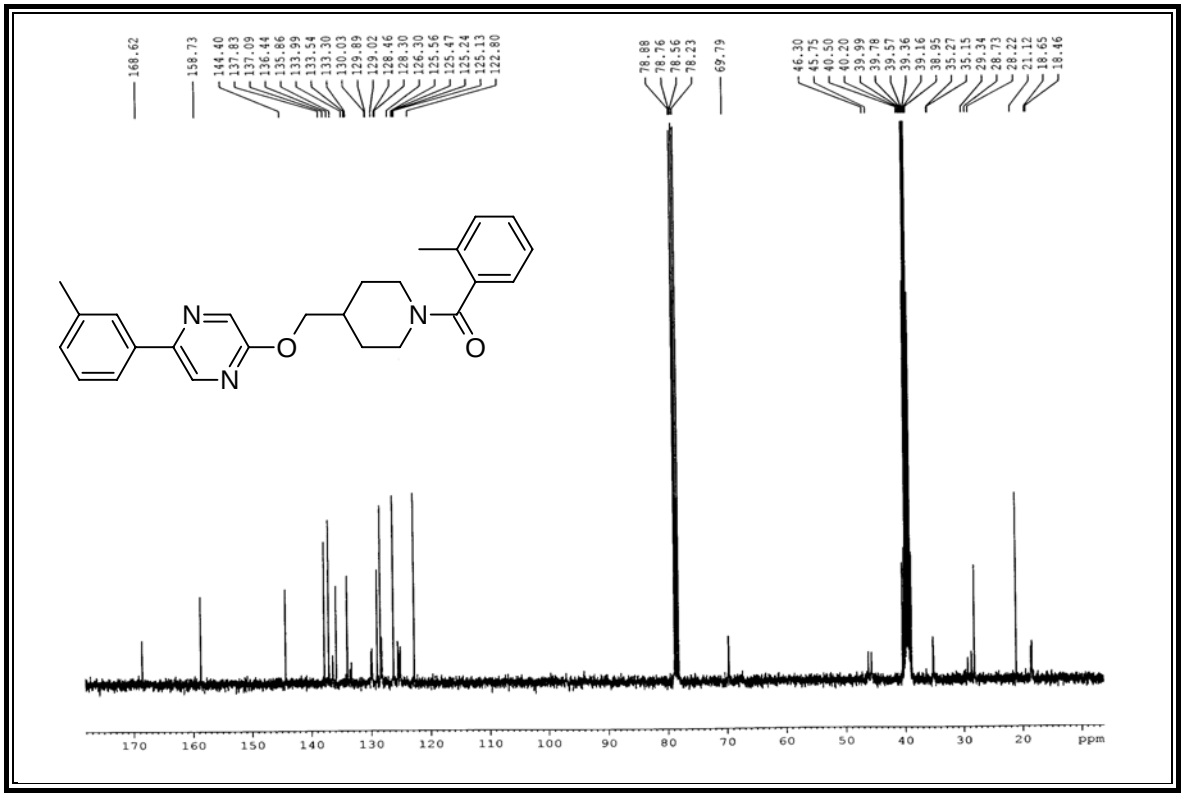
Expanded spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone*(4c)*.



Expanded spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone*(4c)*.



^{13}C NMR spectrum of *O*-tolyl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone*(4b).*



^{13}C NMR spectrum of Pyridin-4-yl(4-(((5-(m-tolyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone*(4c).*

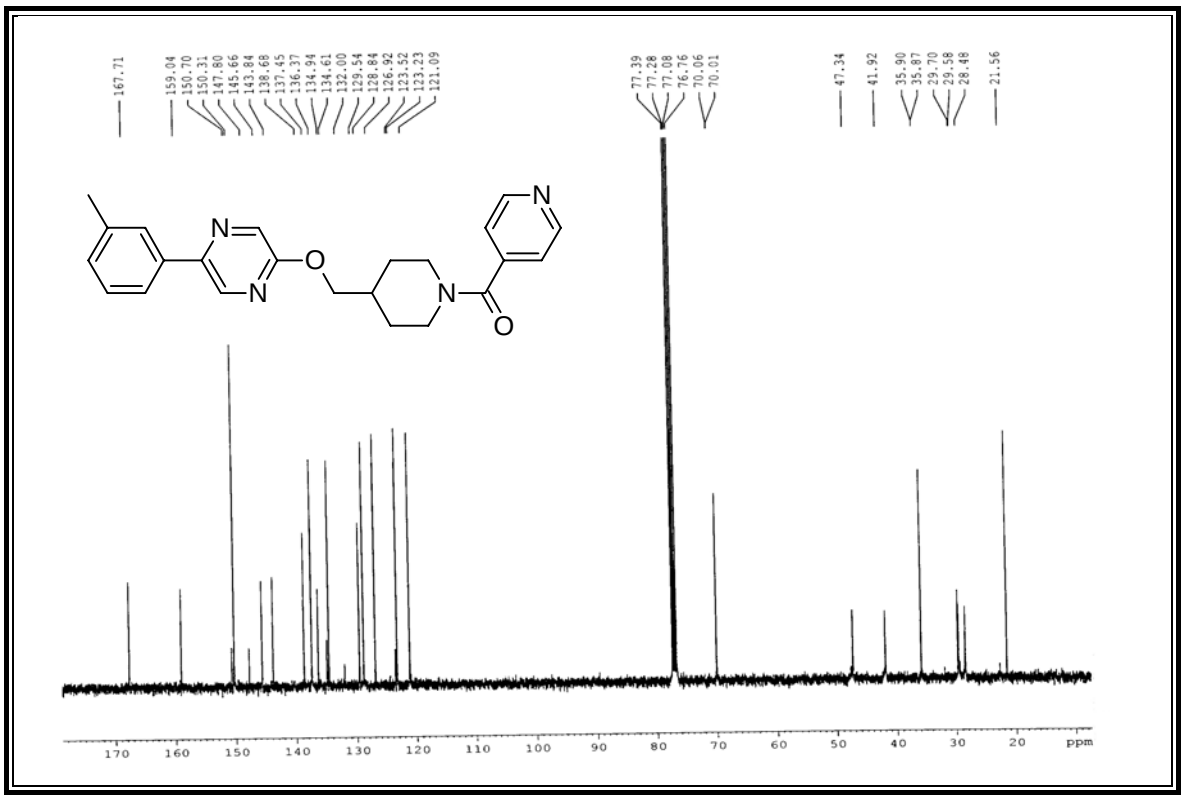


Table-4b: Antimicrobial activity of Aryl(4-(((5-(*m*-tolyl)pyrazin-2-yl) oxy) methyl) piperidin-1-yl)methanones.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
4a	125	200	200	100	>1000	>1000	>1000
4b	100	200	125	250	250	500	1000
4c	200	125	125	100	500	500	500
4d	250	250	250	250	500	1000	1000
4e	100	100	250	125	250	1000	1000
4f	62.5	125	200	100	>1000	500	500
4g	250	100	125	125	1000	250	1000
4h	500	500	250	250	500	500	500
4i	250	125	62.5	200	1000	1000	200
4j	125	500	500	500	200	250	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

Part – A

[Part – I (Section-v)]

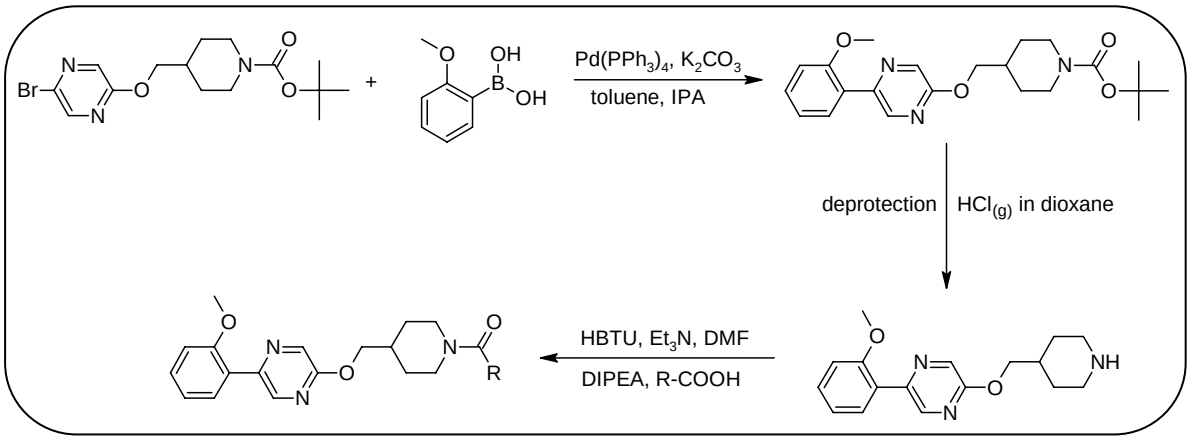
Synthesis and biological evaluation of (4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones

SECTION-V

SYNTHESIS AND BIOLOGICAL EVALUATION OF (4-(((5-(2-METHOXY PHENYL)PYRAZIN-2-YL)OXY)METHYL)PIPERIDIN-1-YL)(ARYL) METHANONES

Pyrazine plays an important role as intermediates for perfumes, pharmaceuticals, agricultural chemicals and food spices. In view of these reports, we have synthesize 2-(piperidin-4-ylmethoxy)pyrazines derivatives by the condensation of 2-(2-methoxy-phenyl)-5-(piperidin-4-ylmethoxy)pyrazine with various aromatic acids in the presence of TEA.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker AC 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate.

See, Part-A, Part-1, Section-I Experimental Section [D].

[B] Preparation of *tert*-butyl 4-(((5-(2-methoxyphenyl)pyrazin-2-yl) oxy) methyl) piperidine-1-carboxilate.

A solution of *tert*-butyl 4-(((5-bromopyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate (1.5 g, 0.004 mol) in toluene (20 ml) was stirred at room temperature under nitrogen atmosphere. The obtained solution was stirred for further 5.0 minutes. To this solution (2-methoxyphenyl)boronic acid(0.664 g, 0.0044 mol) and isopropyl alcohol (20 ml) was added at room temperature. To this content a solution of K_2CO_3 (10 ml, 0.02 mol) in water was added dropwise under nitrogen atmosphere and stirred for 5.0 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.0002 mol) was added in to the above reaction mixture and the reaction mixture was heated to reflux for 5 hours (monitored by TLC). The reaction mixture was added in to the water under stirring. The aqueous layer was extracted with ethyl acetate (100 ml × 3), and the combined organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give crude product. The crude product was used in the next step without further purification.

[C] Preparation of 2-(2-methoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazine.

A mixture of HCl(g) in dioxane (10 ml) and *tert*-butyl 4-(((5-(2-methoxy phenyl) pyrazin-2-yl)oxy)methyl)piperidine-1-carboxilate was stirred at room temperature for

overnight (monitored by TLC), and the solvent was removed *in vacuo*. Water and ethyl acetate were added in to the crude product and stirred well. The organic layer was separated and the major impurities were removed in the organic layer. The aqueous layer was basified using sodium hydroxide solution and the product was extracted with DCM (100 ml × 3). The combine organic layers were washed with water followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to give pure product. Yield: 62 %, mp 71-72 ^oC.

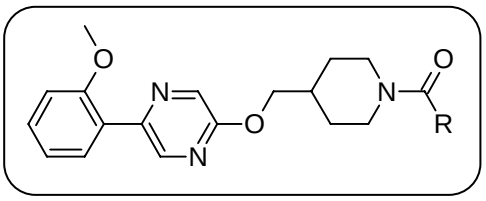
[D] General procedure for the preparation of (4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(aryl)methanones.

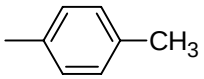
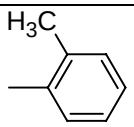
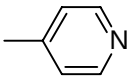
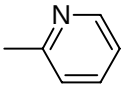
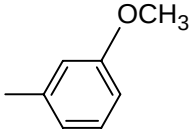
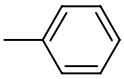
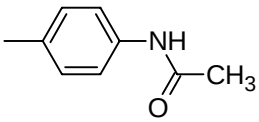
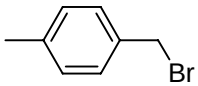
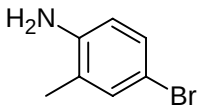
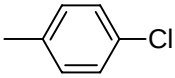
To a cooled mixture of 2-(2-methoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazine (0.2 g, 0.700 mmol) and aryl acid (0.700 mmol) in dry DMF (3 ml), HBTU[2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate](0.318 g, 0.840 mmol), DIPEA[di isopropyl ethyl amine] (0.108 g ≅ 0.142 ml,0.840 mmol) and TEA (0.21 ml, 1.05 mmol) was added to basify the content at 0^oC. The reaction mixture was stirred for 10 hour at room temperature (monitored by TLC). The reaction mixture was poured onto crushed ice, thus the precipitate separated was filtered and washed with water to give pure product. The physical constants of the products are recorded in **Table-5a.**

[E] Biological evaluation of (4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy) methyl) piperidin-1-yl)(aryl)methanones.

Antimicrobial testing was carried out as described in Part-A, Part-1, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-5b**.

Table-5a: Physical constants of (4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy) methyl)piperidin-1-yl)(aryl)methanones.



Sr. No.	Substitution R	MF	MW	Yield (%)	R_f value
5a		$C_{25}H_{27}N_3O_3$	417.50	73	0.53
5b		$C_{25}H_{27}N_3O_3$	417.50	70	0.51
5c		$C_{23}H_{24}N_4O_3$	404.46	71	0.48
5d		$C_{23}H_{24}N_4O_3$	404.46	68	0.44
5e		$C_{25}H_{27}N_3O_4$	433.49	84	0.45
5f		$C_{24}H_{25}N_3O_3$	403.47	59	0.49
5g		$C_{26}H_{28}N_4O_4$	460.52	63	0.30
5h		$C_{25}H_{26}BrN_3O_3$	496.39	75	0.40
5i		$C_{25}H_{27}BrN_4O_2$	495.41	78	0.35
5j		$C_{25}H_{26}ClN_3O_2$	435.94	84	0.46

TLC solvent system:- E.A. : Hexane = 6 : 4

ANALYTICAL DATA

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(p-tolyl) methanone *(5a).* mp 102-104^{o}C; IR (DRS): 3089, 3039, 2933, 2858, 1618, 1531, 1444, 1329, 1211,1176, 1016, 854, 788, 699 cm^{-1}; MS: m/z = 417 $[M]^{+}$; Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.11; H, 6.41; N, 10.01%.

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone *(5b).* mp 147-149^{o}C; IR (DRS): 2989, 2920, 2854, 1631, 1531, 1446, 1340, 1257, 1168, 1097, 1008, 983, 875, 842, 754, 597 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.18-1.40(m, 2H, CH), 1.74-1.77(d, *J*=12.12 Hz, 1H, CH), 1.96-1.99(d, *J*=12.12 Hz, 1H, CH), 2.12-2.15(m, 1H, CH), 2.23(s, 3H, CH_3), 2.82(t, 1H, CH), 3.0-3.06(t, 1H, CH), 3.44-3.46(d, *J*=7.2 Hz, 1H, CH), 3.88(s, 3H, OCH_3), 4.24-4.25(d, *J*= 5.92 Hz, 2H , 2CH), 4.71-4.74(d, *J*= 12.92 Hz, 1H ,CH), 7.03-7.10(m, 2H, ArH), 7.19-7.29(m, 4H, ArH), 7.34-7.38(t, 1H ,ArH), 7.74-7.76(d, *J*=7.32 Hz, 1H, ArH), 8.27 (s, 1H, ArH), 8. 65(s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ ppm,18.46, 18.63, 28.22, 28.73, 29.33, 35.29, 45.77, 55.23, 69.67, 111.19, 120.55, 125.01, 125.53, 128.28, 129.60, 129.87, 130.02, 133.82, 136.34, 141.07, 142.80, 156.26, 158.03, 168.75.MS: m/z = 418 $[M+1]^{+}$; Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.90; H, 6.30; N, 9.88%

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(piridin-4-yl) methanone *(5c).* mp 63-65^{o}C; Purity by HPLC: 89 %; IR (DRS): 3078, 2958, 2858, 1634, 1525, 1478, 1278, 1054, 888, 841, 754, 703 cm^{-1}; MS: m/z = 404 $[M]^{+}$; Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.10; H, 5.90; N, 13.73%.

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(pyridin-2-yl) methanone *(5d).* mp 111-112^{o}C; Purity by HPLC: 88 %; IR (DRS): 3081, 3054, 2933, 2908, 1626, 1533, 1465, 1344, 1172, 1010, 878, 831, 748, 699 cm^{-1}; MS: m/z = 405 $[M+1]^{+}$; Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.27; H, 5.88; N, 13.72%.

(3-Methoxyphenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone *(5e).* mp 116-118^{o}C IR (DRS): 3108, 3064, 3015, 2924, 2879, 1627, 1556, 1527, 1440, 1327, 1166, 1014, 831, 798, 727, 676 cm^{1}; MS: m/z = 433 $[M]^{+}$; Anal. Calcd for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.20; H, 6.23; N, 9.50%.

(4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(phenyl) methanone *(5f).* mp 173-175^{o}C; IR (DRS): 3085, 3047, 2938, 2871, 1636, 1548, 1421, 1314, 1151, 1018, 888, 834, 746, 703 cm^{-1}; MS: m/z = 403 $[M]^{+}$; Anal. Calcd for $C_{24}H_{25}N_3O_3$: C, 71.44; H, 6.25; N, 10.41. Found: C, 71.40; H, 6.18; N, 10.37%.

N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl) phenyl)acetamide *(5g). mp 129-131^{o}C; IR (DRS): 3416(N-H str.), 3173(Ar, C-H str.), 3097(Ar, C-H str.), 3043(Ar, C-H str.), 2937(C-H str.), 2854(C-H str.), 1691(amide, C=O str.), 1599(Ar, C=C str.), 1531(Ar, C=C str.), 1496(Ar, C=C str.), 1338(C-H ben), 1257(C-H ben), 1172(C-N str.), 1020(C-O-C str.), 758(C-H o,p, ben)cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.24-1.36(m, 2H, CH), 1.86-1.92(m, 2H, CH), 2.08(s, 3H, OCH_3), 2.11-2.16(m, 1H, CH), 2.85-3.08(m, 2H, CH), 3.83-3.93(m, 4H, OCH_3, CH), 4.24-4.26(d, *J*=6.4 Hz, 2H, 2CH), 4.55-4.58(d, *J*=13.0 Hz, 1H, CH), 7.03-7.09(m, 2H, ArH), 7.30-7.39(m, 3H, ArH), 7.74-7.76(d,d *J*= 1.56 Hz, 1.48 Hz, 1H, ArH), 8.28-8.29(d, *J*=1.08 Hz, 1H, ArH), 8.65-8.66(d, *J*= 1.16 Hz, 1H, ArH), 10.0(s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): δ ppm, 22.17, 23.92, 35.29, 55.29, 69.75, 111.29, 118.37, 120.57, 125.03, 127.41, 129.64, 130.04, 130.26, 133.87, 140.30, 141.08, 142.79, 156.30, 158.09, 168.38, 169.06. MS: m/z = 460 $[M]^{+}$; Anal. Calcd for $C_{26}H_{28}N_4O_4$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.76; H, 6.02; N, 12.04%.

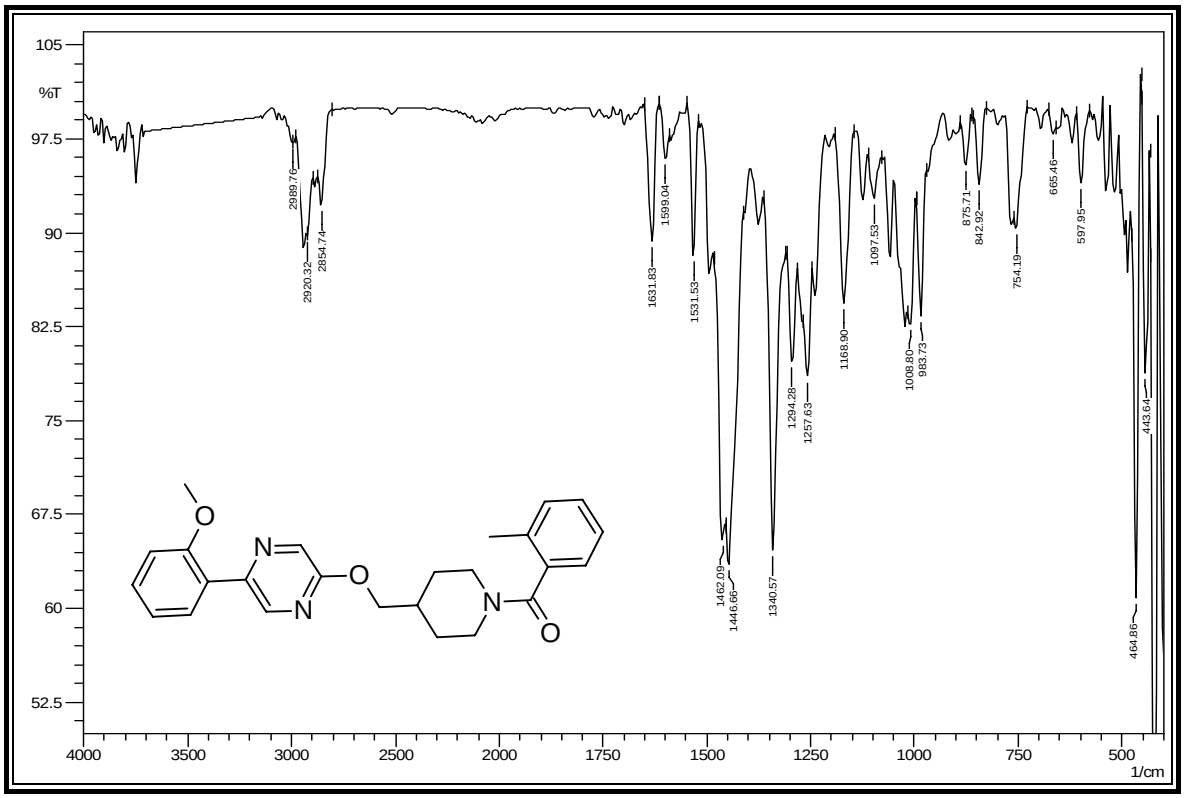
(4-(Bromomethyl)phenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-yl)methanone *(5h).* mp 90-92^{o}C; IR (DRS): 3048, 2951, 2820, 1636, 1530, 1455, 1323, 1112, 1041, 824, 621 cm^{-1}; MS: m/z = 497 $[M+1]^{+}$; Anal. Calcd for $C_{25}H_{26}BrN_3O_3$: C, 60.49; H, 5.28; N, 8.47. Found: C, 60.39; H, 5.19; N, 8.42%.

(2-Amino-5-bromophenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidine-1-yl)methanone *(5i).* mp 239-241^{o}C; IR (DRS): 3483, 3410, 3083, 3043, 2940, 2843, 1616, 1542, 1450, 1320, 1330, 1116, 1018, 780, 703, 631 cm^{-1}; MS: m/z = 498 $[M+1]^{+}$; Anal. Calcd for $C_{25}H_{27}BrN_4O_2$: C, 57.95; H, 5.07; N, 11.26. Found: C, 57.02; H, 5.02; N, 11.22%.

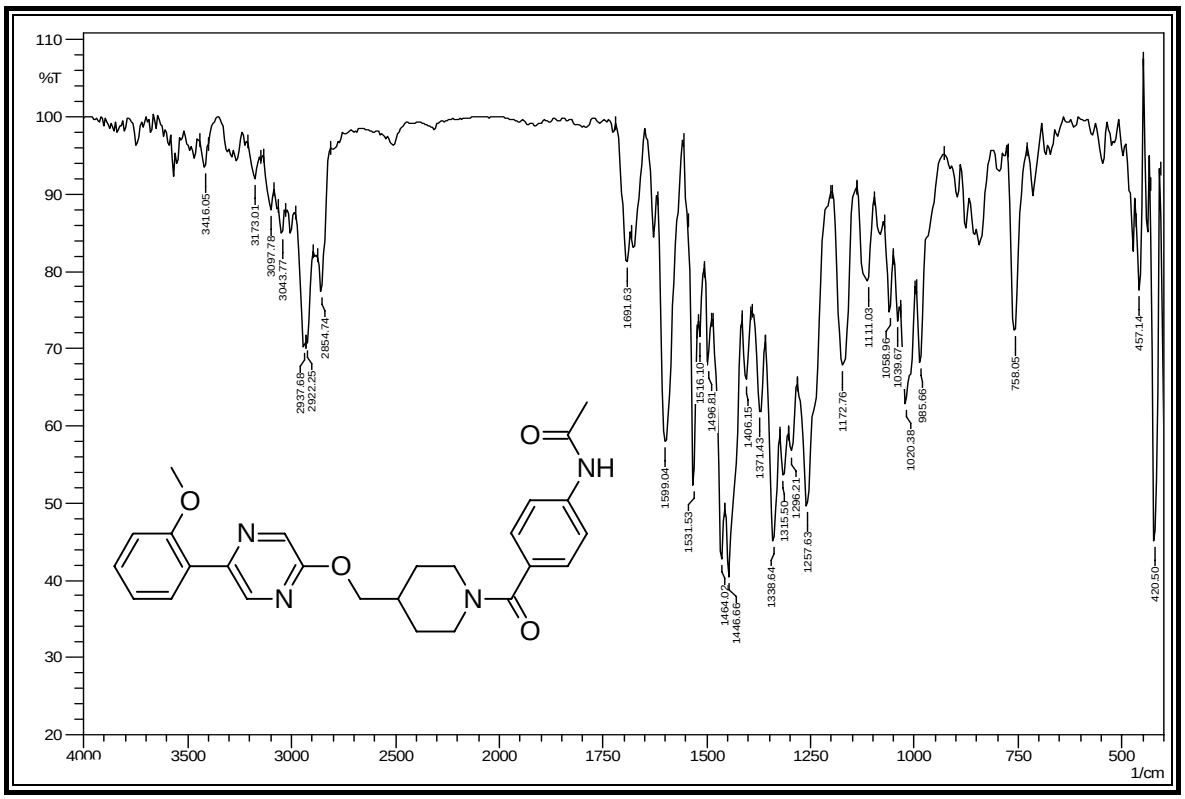
(4-Chlorophenyl)(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl) methanone *(5j).* mp 167-169^{o}C; IR (DRS): 3083, 3010, 2954, 2830, 1629, 1515, 1443, 1334, 1241, 1118, 1019, 841, 768, 690 cm^{-1}; MS: m/z = 464 $[M+1]^{+}$; Anal. Calcd for $C_{25}H_{26}ClN_3O_2$: C, 65.82; H, 5.52; N, 9.60. Found: C, 65.50; H, 5.46; N, 9.59%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

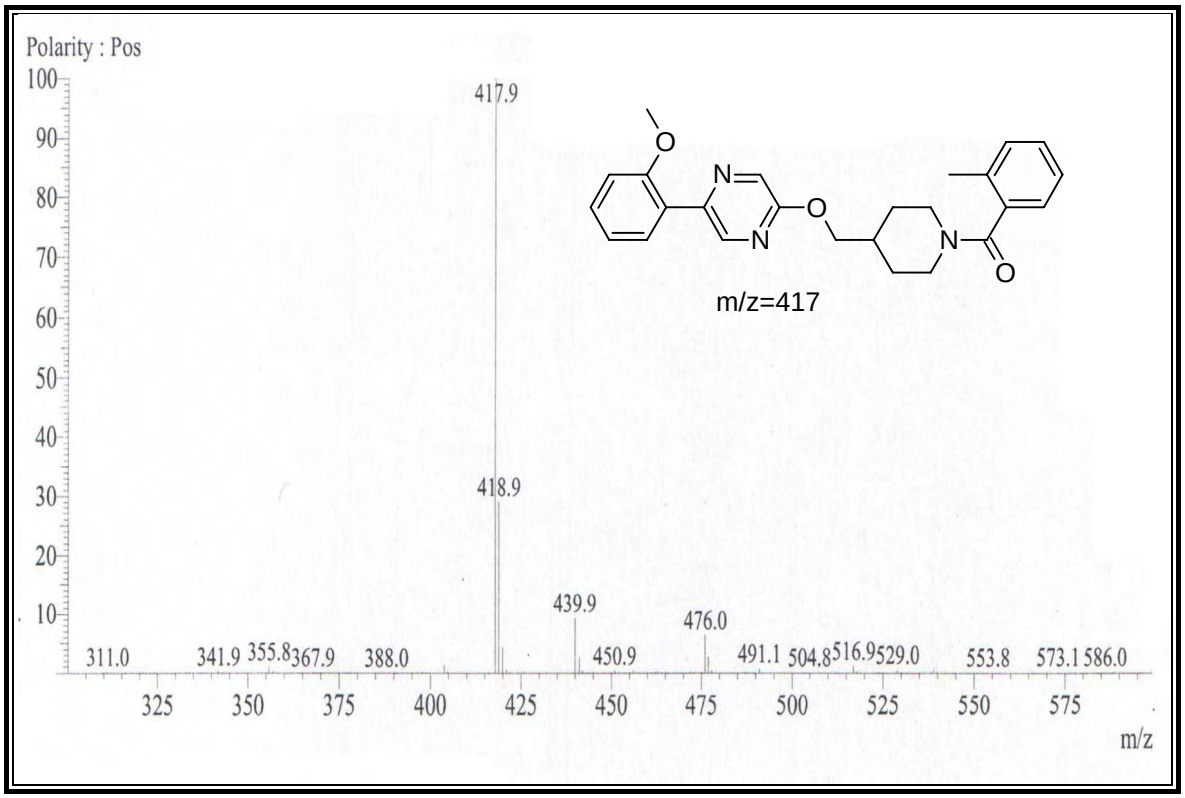
IR Spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone*(5b)*.



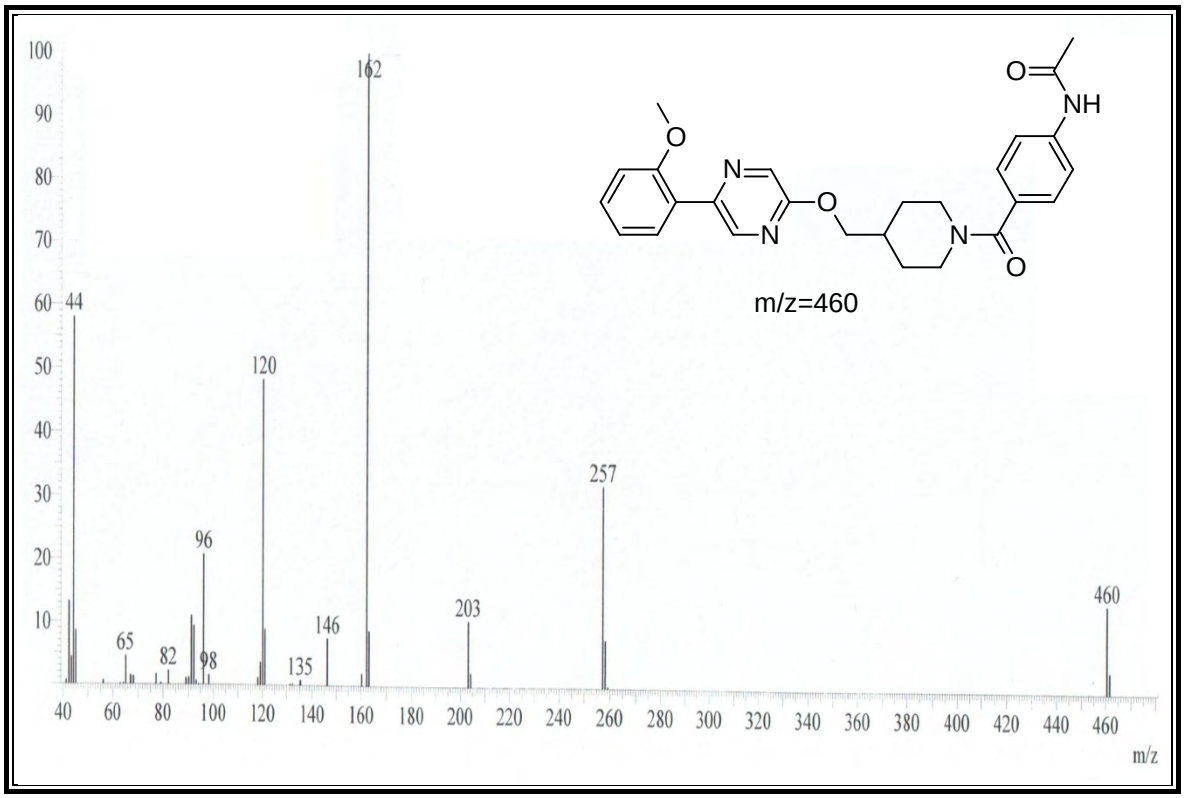
IR Spectrum of *N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-carbonyl)phenyl)acetamide*(5g)*.



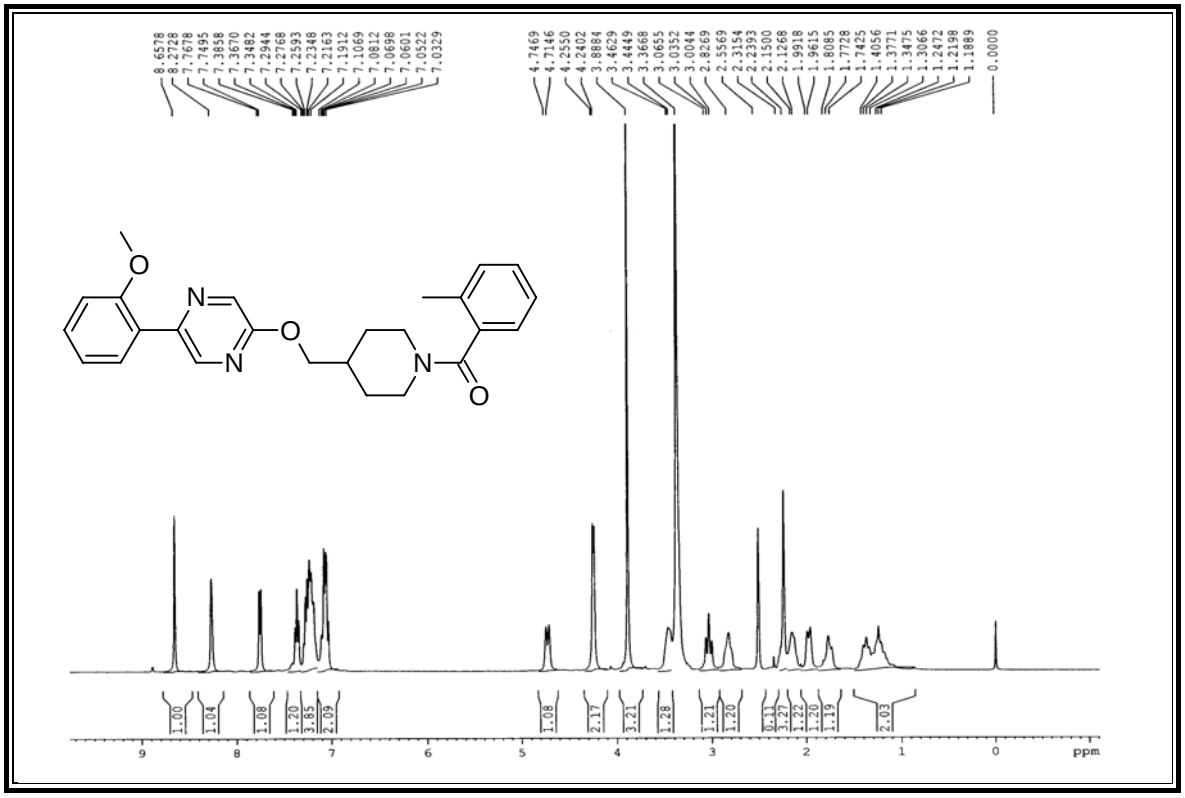
Mass spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone *(5b).*



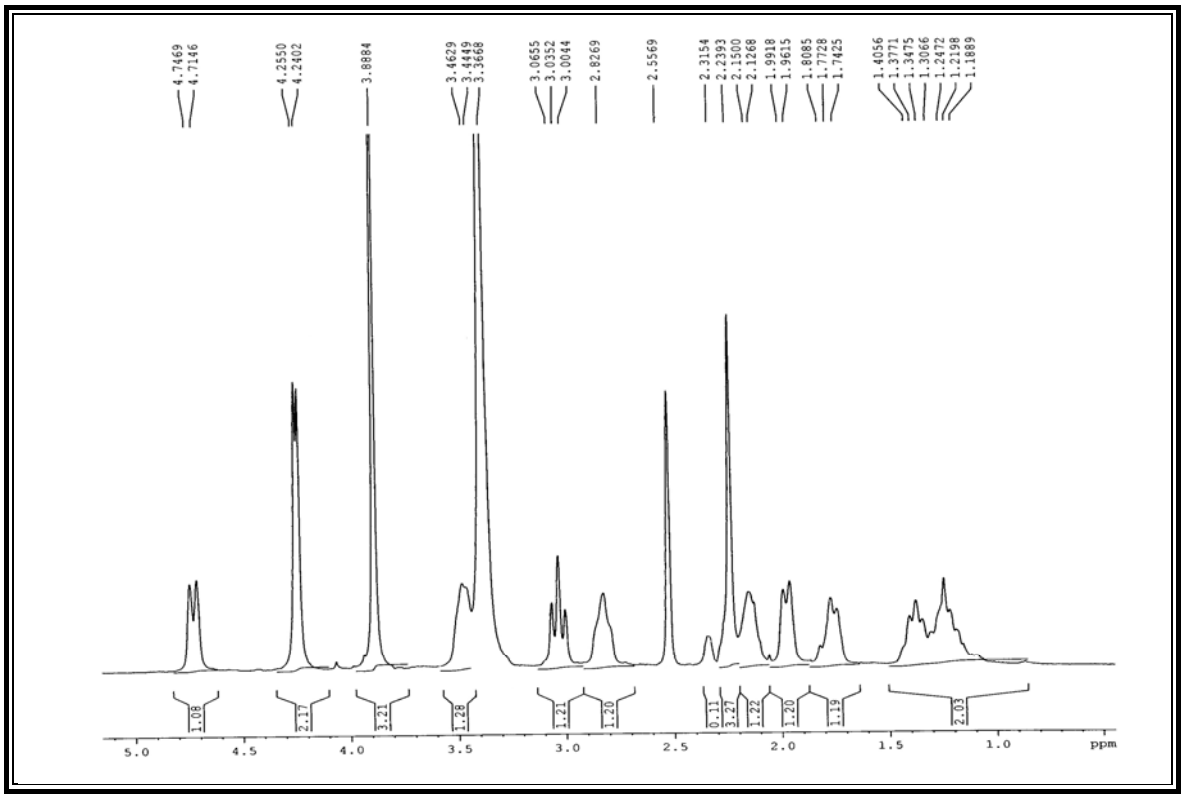
Mass spectrum of *N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-carbonyl) phenyl)acetamide *(5g).*



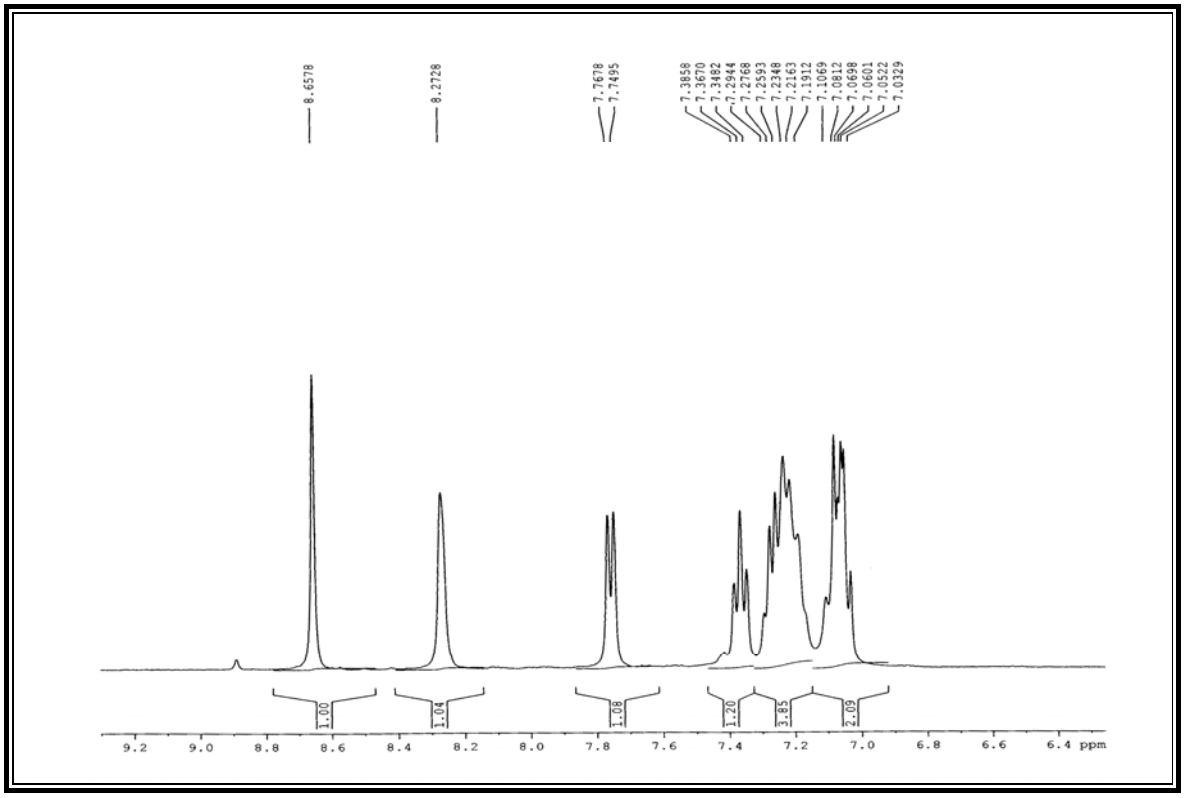
^{1}H NMR spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl) methanone *(5b).*



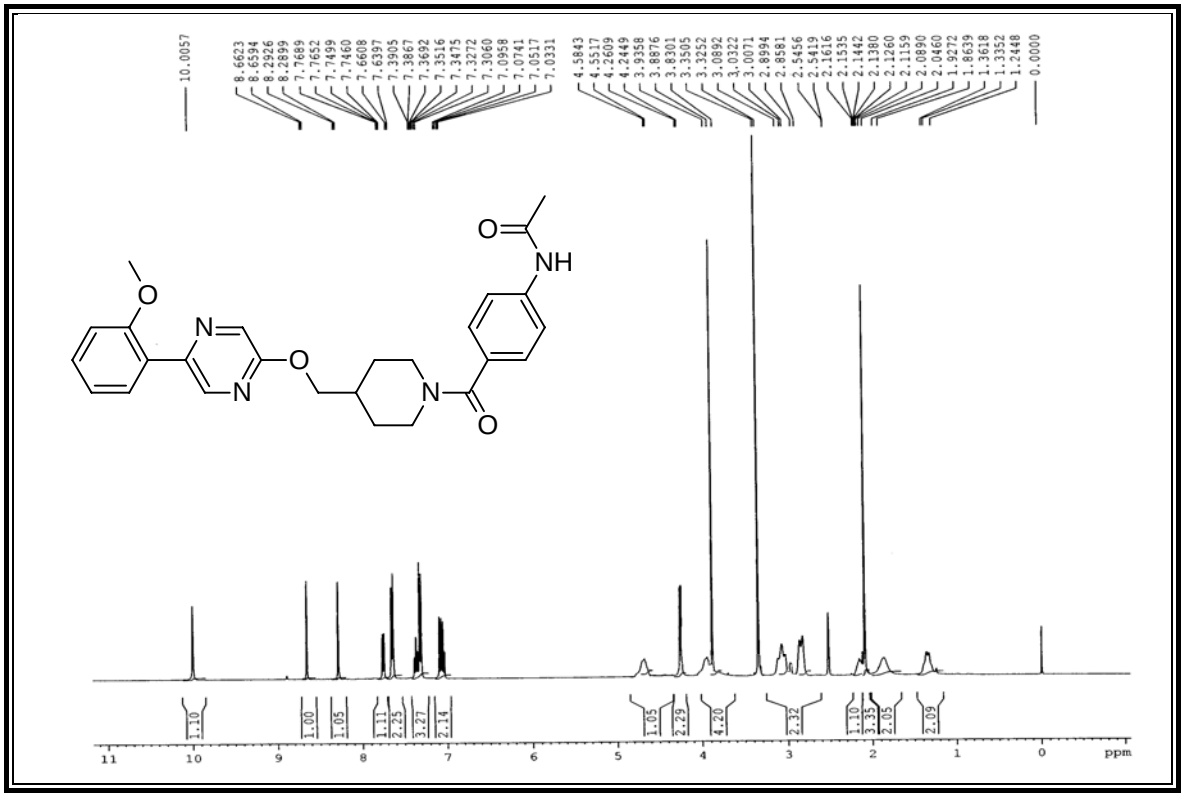
Expanded spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone*(5b).*



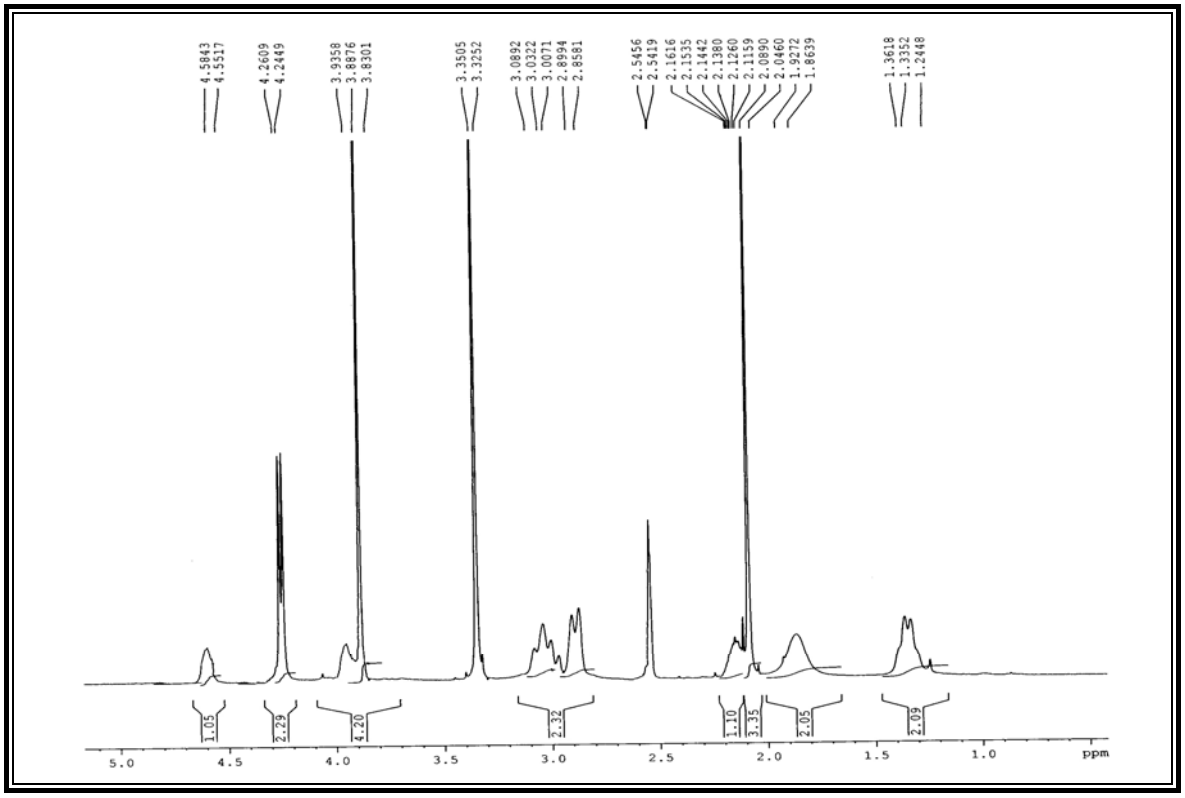
Expanded spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone*(5b).*



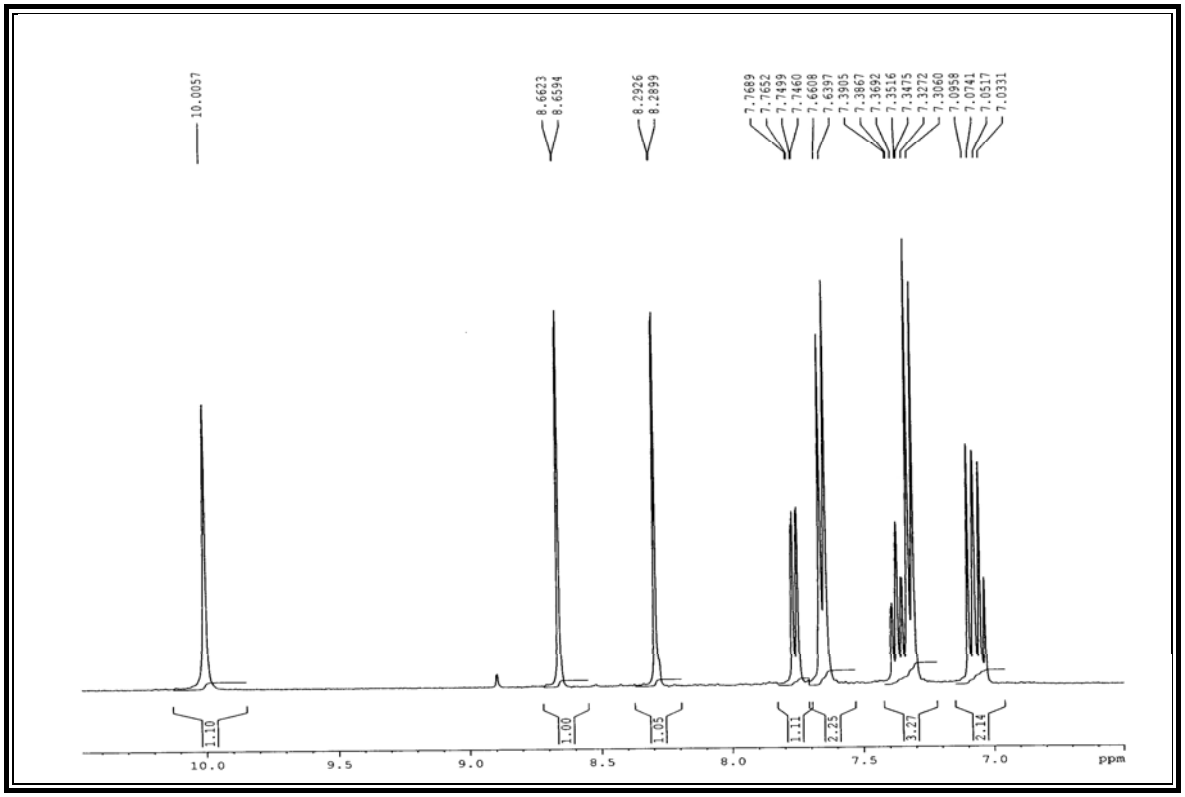
^{1}H NMR spectrum of *N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-carbonyl)phenyl)acetamide*(5g).*



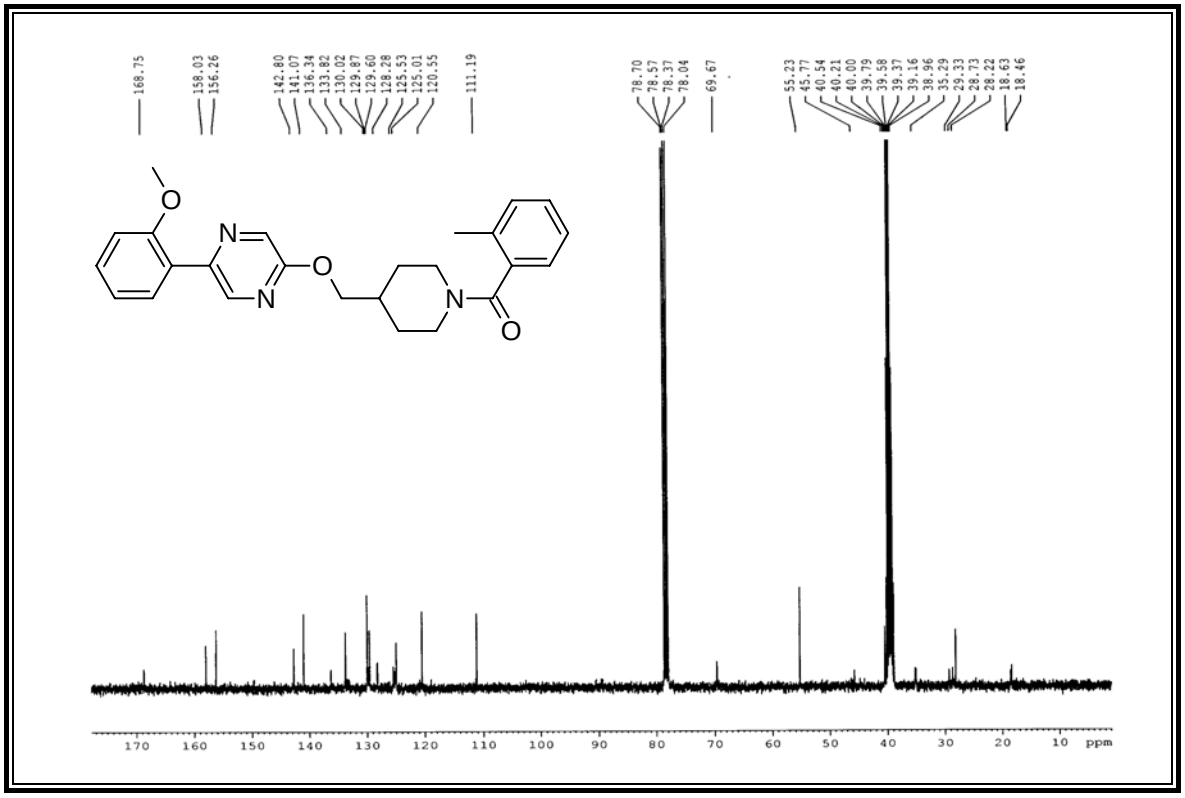
Expanded spectrum of *N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-carbonyl)phenyl)acetamide*(5g)*.



Expanded spectrum of *N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-carbonyl)phenyl)acetamide*(5g)*.



^{13}C NMR spectrum of (4-(((5-(2-Methoxyphenyl)pyrazin-2-yl)oxy)methyl)piperidin-1-yl)(o-tolyl)methanone*(5b)*.



^{13}C NMR spectrum of *N*-(4-(4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy)methyl) piperidin-1-carbonyl) phenyl)acetamide *(5g)*.

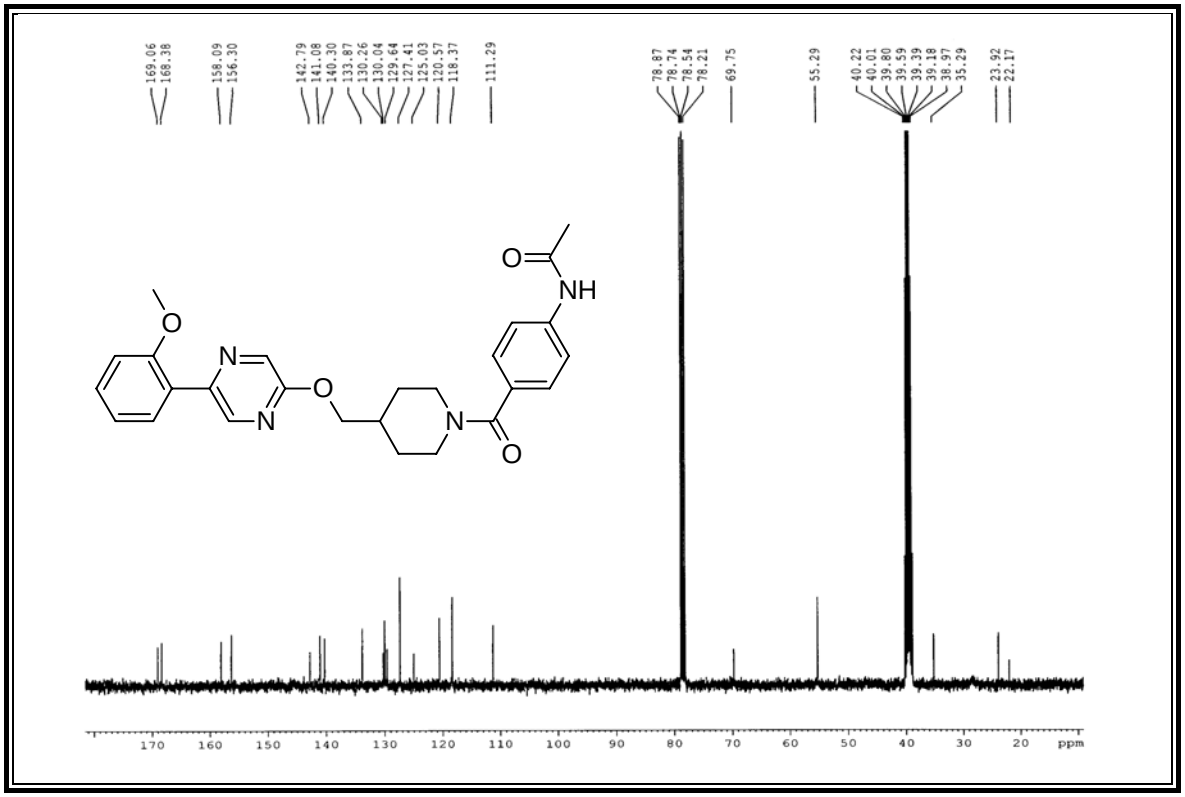


Table-5b: Antimicrobial activity of (4-(((5-(2-methoxyphenyl)pyrazin-2-yl)oxy) methyl) piperidin-1-yl)(aryl)methanones.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
4a	100	200	200	200	1000	500	500
4b	62.5	100	500	500	500	1000	1000
4c	250	250	250	500	250	1000	1000
4d	200	200	200	62.5	>1000	>1000	>1000
4e	100	100	100	125	250	500	500
4f	125	100	200	125	200	500	250
4g	200	500	125	500	500	200	200
4h	250	250	250	200	250	500	500
4i	500	125	125	100	500	1000	1000
4j	500	200	500	250	1000	250	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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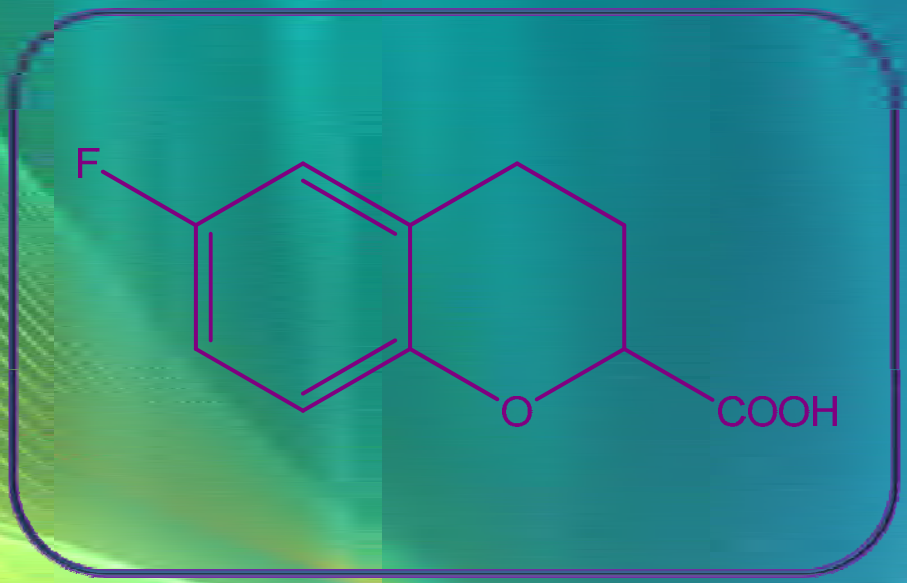
PART-B

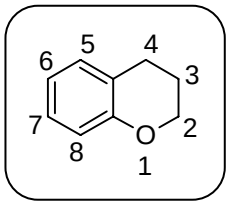
STUDIES ON 6-FLUOROCHROMAN-2-CARBOXYLIC ACID DERIVATIVES



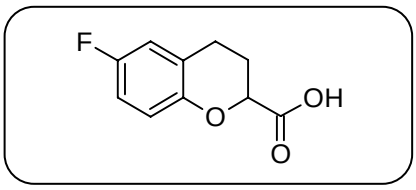
INTRODUCTION

Although chroman was first prepared in 1905, little interest was shown in the compound until studies on the tocopherols (Vitamin-E) began to indicate that they were derivatives of chroman. Same as many derivatives of chroman were prepared like a nebivolol acid and nebivolol drug. The monoalkyl chromans can be divided into two groups-one with the alkyl substituted attacked to the benzene ring and the second with attacked to the heterocyclic ring. The former can be obtained from appropriate derivatives of benzene similar to those used for the preparation of chroman. Chroman is stable to acids and oxidizing agents. It is soluble in common organic solvents[1].

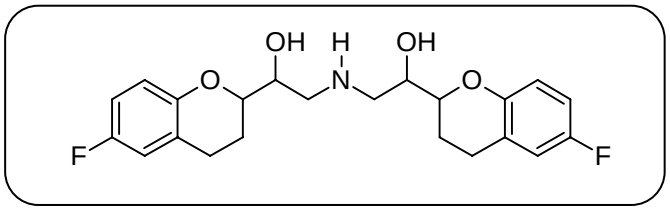
Chroman is an aromatic heterocyclic organic compound. It is a bicyclic structure, consisting of a six-membered benzene ring fused to a six-membered oxygen hetero atom(benzopyrane).



6-Fluorochroman-2-carboxylic acid is a solid at room temperature. And it is a derivative of nebivolol drug. And it is also known as nebivolol acid .Nebivolol is an antihypertensive compound. Nebivolol has been studied in over 3000 patients with hypertension. The use of nebivolol is contraindicated in patients with, cardiogenic shock, uncontrolled heart failure, Sick sinus syndrome, Second and third degree heart block, Asthma, Hypotension, and Pregnancy.etc.



6-FLUOROCHROMAN-2-CARBOXYLIC ACID (NEBIVOLOL ACID)

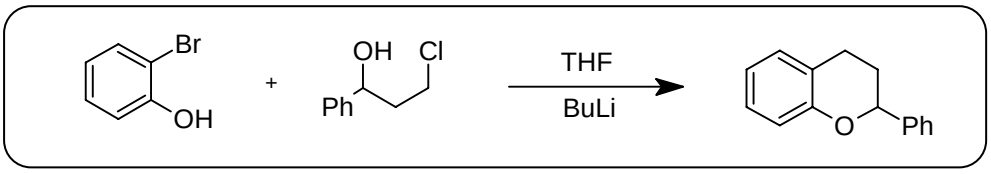


NEBIVOLOL [2,2'-azanediylbis(1-(6-fluorochroman-2-yl)ethanol)]

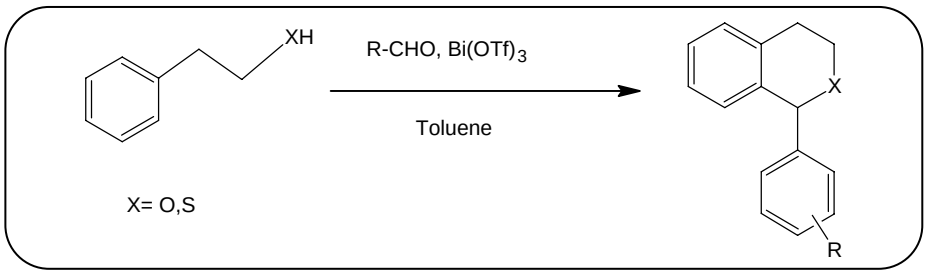
Vitamin E refers to a family of eight molecules having a chromanol ring (chroman ring with an alcoholic hydroxyl group) and a 12-carbon aliphatic side chain containing two methyl groups in the middle and two more methyl groups at the end. Tocotrienols (found in high concentrations in palm oil) are many times more potent as anti-oxidants than are tocopherols, but they are poorly assimilated by digestion, are poorly distributed to tissues in blood and are rapidly metabolized and eliminated from the body. But tocotrienols are well-absorbed by the skin and thus are well suited for use as a Vitamin E cream.

SYNTHETIC ASPECT

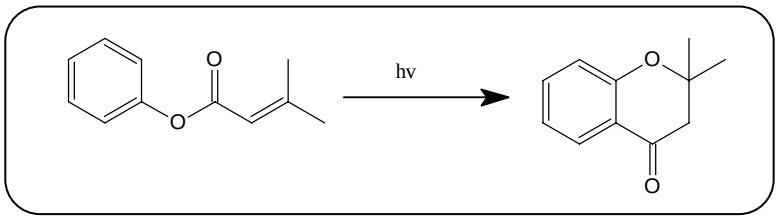
1. K. J. Hodgetts[2] has developed a new method for 2-substituted chroman by intermolecular Mitsunobu reaction of a homochiral halopropanol and 2-bromophenol.



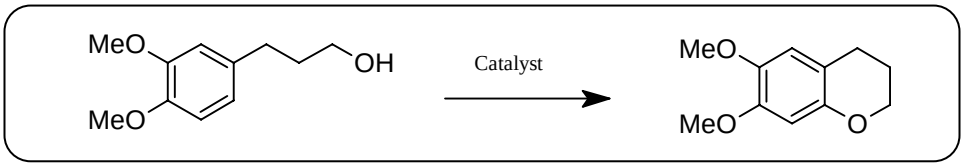
2. C. Lherbet et al .[3] have synthesized isochroman in the one pot-reaction by using different benzaldehydes and phenylethanethiol or phenyl ethanol in presence of bismuth triflate as a catalyst.



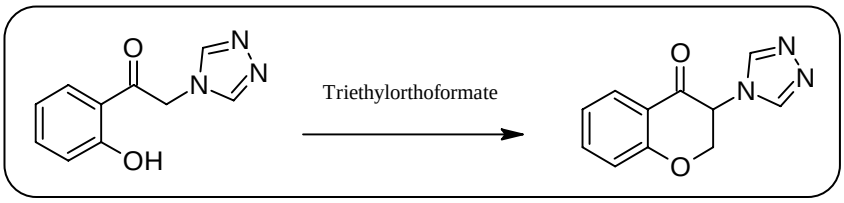
3. C. S. López et al. [4] have developed a mild and convenient one-pot photochemical synthesis of chroman-4-one derivatives.



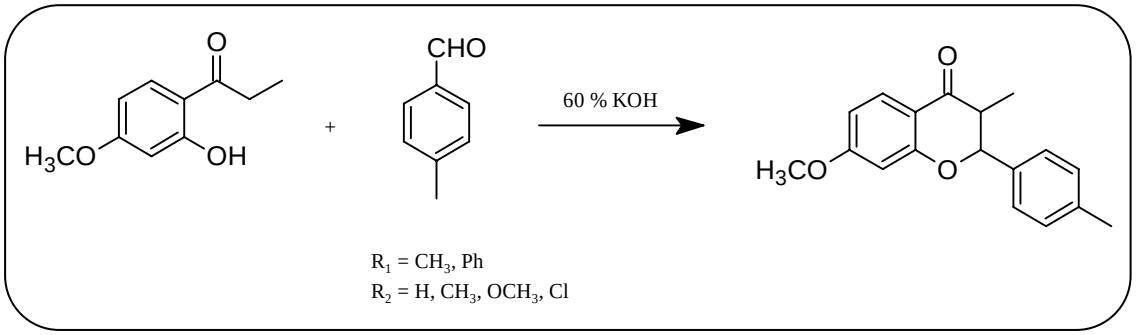
4. H. Hamamoto et al.[5] synthesized chroman by direct aromatic carbon–oxygen bond-formation reaction involving aromatic cation radical intermediates using the hypervalent iodine (III) reagent, phenyl iodine (III) bis(trifluoroacetate) (PIFA).



5. S. Emami et al.[6] have synthesized azolyl chroman derivatives prepared as conformationally constrained analogs of (aryl alkyl) azoles.

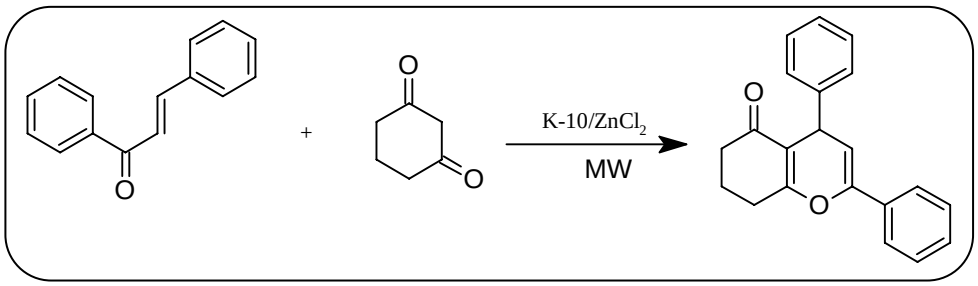


6. M.Venkati et al.[7] have synthesized chroman from substituted o-hydroxy aceto - phenone and substituted benzaldehyde in 60% KOH.

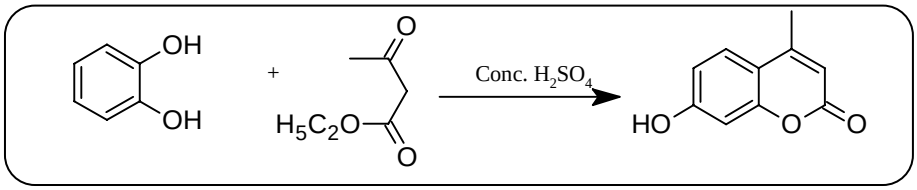


7. R. R. Karimi et al.[8] have developed simple, clean and benign route for synthesis of 2H-chromen-2-ones derivatives through one-pot condensation of β-ketoesters and substituted phenols in the presence of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane. Bistetrafluoroborate is (SelectfluorTMF-TEDA-BF_4) was used as catalyst under solvent free reaction conditions.

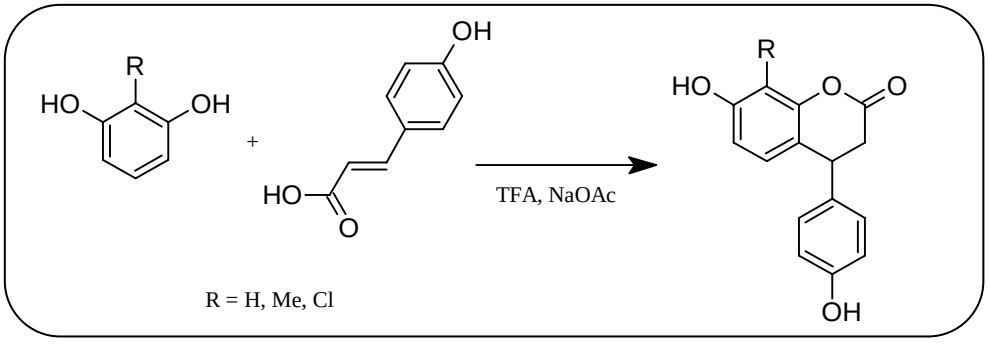
8. S. R. Sarda et al.[9] have synthesized 2,4-diphenyl-4*H*-chromen-5-one from α, β-unsaturated carbonyl compounds and 1,3-cyclohexanedione under microwave irradiation in the presence $ZnCl_2$/montmorillonite K-10.



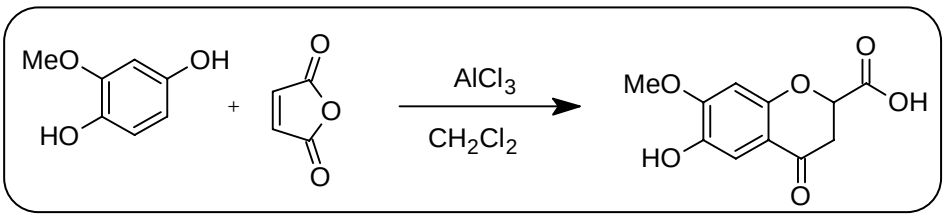
9. D. P. Kardile et al.[10] have synthesized 7-hydroxy-4-methylcoumarin from various phenols like resorcinol, m-cresol etc. condensed with ethylacetoacetate (II) in presence of concentrated sulphuric acid by Pechmann reaction.



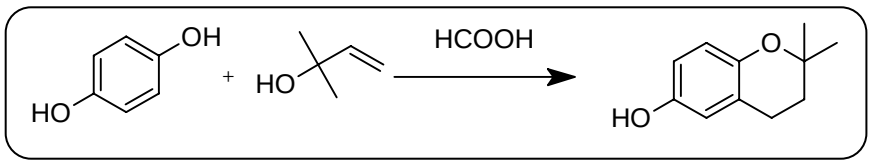
10. R. Suthunuru et al.[11] have developed highly effective, facile, one-pot regioselective synthesis of a series of 4,7-dihydroxy-4-phenyl-chroman-2-ones involves a die none-phenol rearrangement followed by a Michael type reaction.



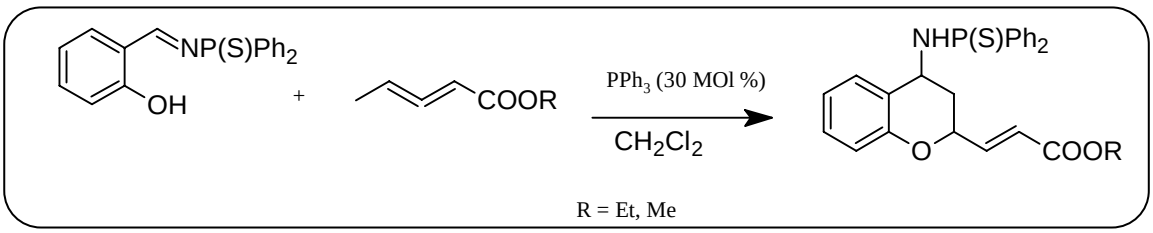
11. H. Lee et al.[12] have synthesized 6-hydroxy-7-methoxy-4-chromanone using aluminum chloride as catalyst.



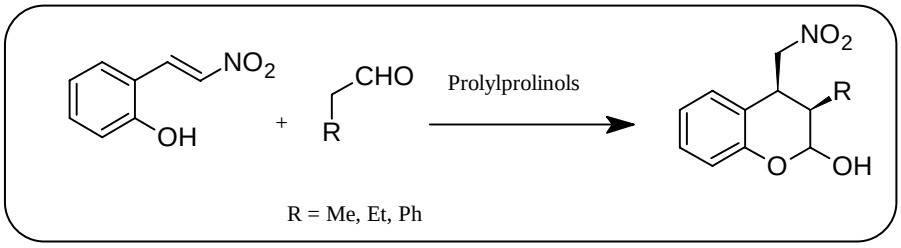
12. Q. Wang et al.[13] have synthesized 6-hydroxy chroman from condensation of 2-methyl-3-butene-2-ol and substituted phenol in the presence of formic acid.



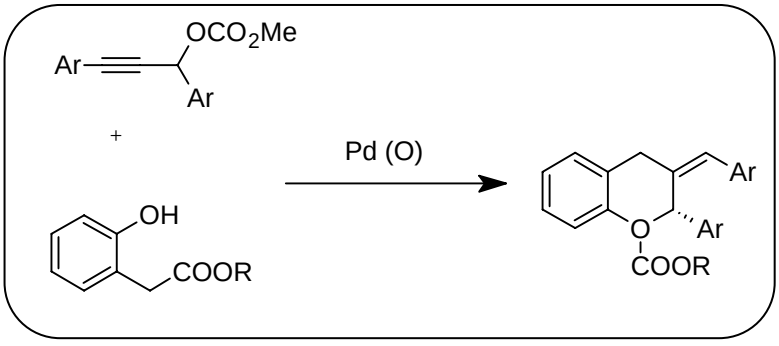
13. X. Meng et al.[14] have developed a novel domino reaction catalyzed by triphenylphosphine for synthesis of the highly functionalized chroman derivatives.



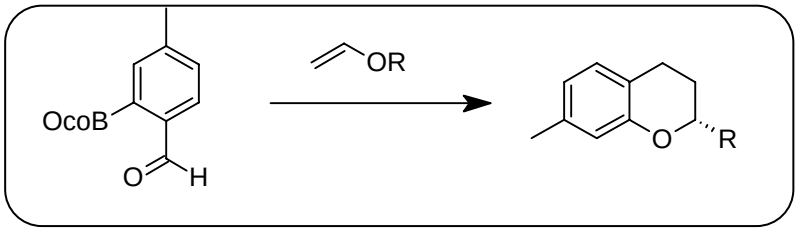
14. D.Lu et al.[15] have developed symmetric tandem Michael addition hemi-acetalization between aliphatic aldehydes and (*E*)-2-(2-nitrovinyl)phenols for constructing chroman backbones



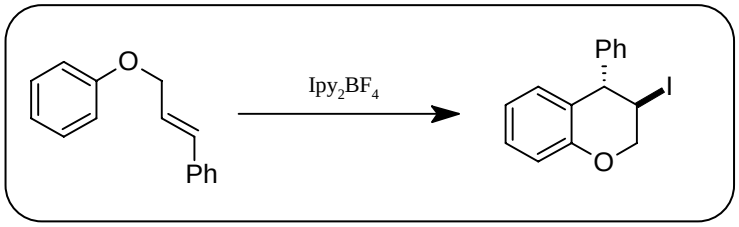
15. M.Yoshida et al.[16] have synthesized chroman in the presence of 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$ and 20 mol % 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) in dioxane at 120 °C for 5 min.



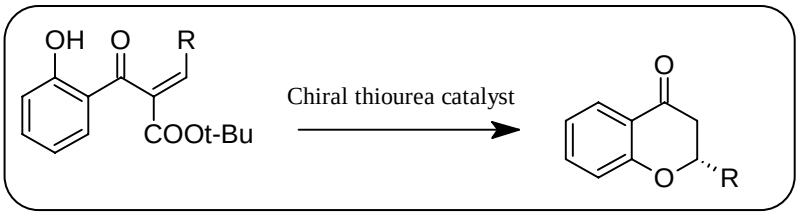
16. C. Selenski et al.[17] have synthesized chroman derivatives as like natural molecule of (+)-mimosifoliol.



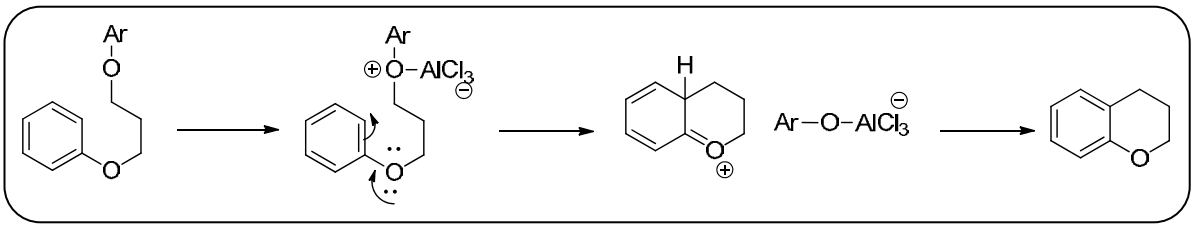
17. J. Barluenga et al.[18] have synthesized chroman derivatives by the reaction of different ally phenyl ethers with Ipy_2BF_4.



18. M. M. Biddle et al.[19] have synthesized flavanones and chromanone using bifunctional thiourea catalysts promote an asymmetric oxo-conjugate addition to a β-ketoester alkylidene.



REACTION MECHANISM

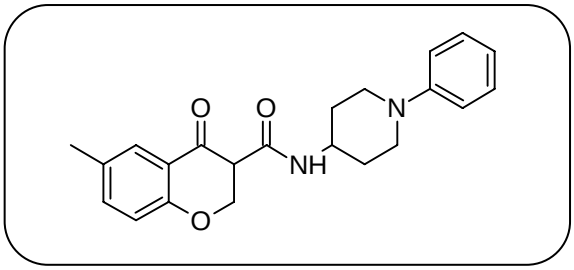


THERAPEUTIC IMPORTANCE

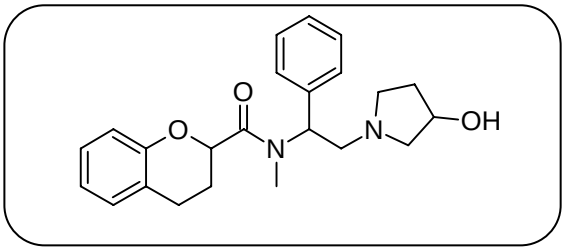
The chroman ring system represents a privileged structure in drug discovery. The number of bioactive compounds containing this ring system is so vast that the complete range of their biological activities can be hardly classified[20-22]

1. Antifungal[23]
2. Antibacterial[24,25]
3. Antioxidant [26]
4. Anti HIV[27]
5. Antiarrythmic[28]
6. antiepileptic agents[29-31]
7. antihypertensive[32]
8. Antiviral[33]
9. Antiallergic[34]
10. Anti-inflammatory[35]
11. Antitumor[36]
12. Antitubercular[37]
13. Antidiabetic[38]
14. Hepatoprotective agents[39]
15. Antiulcer activity[40]

M.C.Patel et al.[41] have synthesized some novel chroman derivative and studied their antibacterial and antifungal activities, using the E. coli, P.aeruginosa, S. aureus, and S.Pyogenus and Candida albicans.

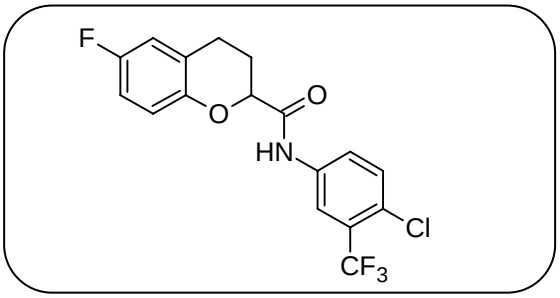


G. Hua et al.[42] have synthesized chroman- and 2,3-dihydrobenzofuran-based constraints as a potent and highly selective kappa opioid receptor agonists

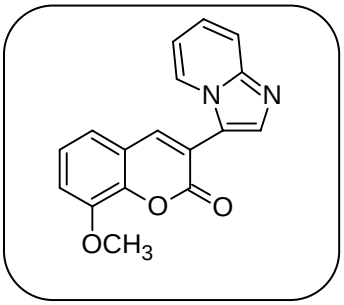


B. S. Priya et al.[43] have synthesized 6-fluoro-chroman-2-carboxamides by using nebulic acid chloride with different amines in presence of triethylamine as acid scavenger and dichloroethane as solvent. These molecules were evaluated for their efficacy as antimicrobials *invitro* by disc diffusion and microdilution method against pathogenic strains such as *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens,*

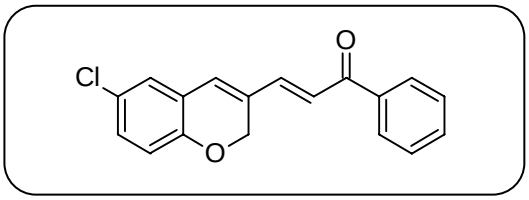
Xanthomonas campestris pvs, X. oryzae, Aspergillus niger, A. flavus, Fusarium oxysporum, Trichoderma species, F. monaliforme, and Penicillum species.



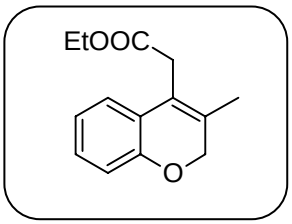
P.V.Kumar et al.[44] have synthesized 3-indolizin-2-yl-chromen-2-one as a antitubercular, antiviral and anticancer activities



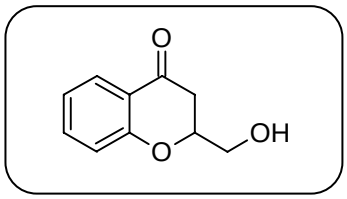
Z. Nazarian et al.[45] have synthesized a chalconoids containing a 6-chloro-2*H*-chromen-3-yl group and showed cytotoxicity assessment against mouse peritoneal macrophage cells.It showed that these compound display antileishmanial activity at non-cytotoxic concentrations.



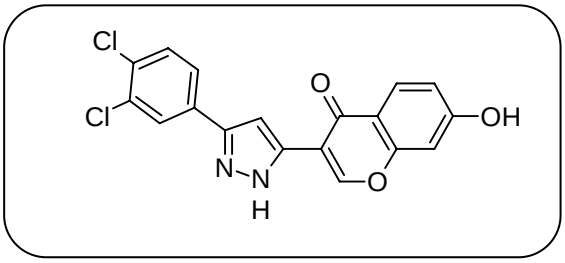
S. Gowrisankar et al.[46] have synthesized 4-substituted 3-*exo*-methylenechroman derivatives and evaluated as a antimicrobial agents.



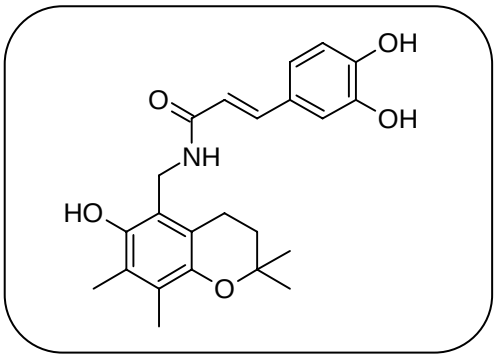
J. G. Kanga et al.[47] have isolated 2-hydroxymethyl-chroman-4-one which exhibited good activities against phytopathogen such as *Pythium ultimum*, *Phytophthora capsici* and *Sclerotinia sclerotiorum*



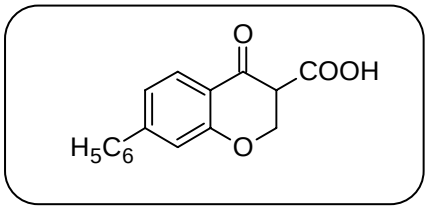
K.Hatzade et al.[48] have synthesized 7-hydroxy-3-pyrazolyl chromones and evaluated for their in vitro antimicrobial and anti-oxidant activity.



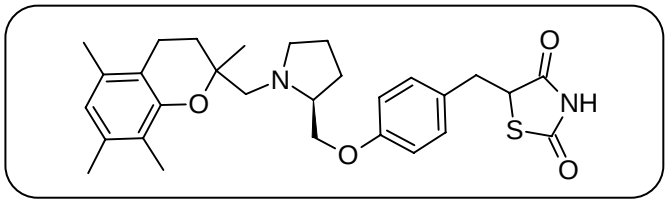
M. Koufaki et al.[49] have synthesized 5-substituted chroman and evaluated as a their activity against oxidative Stress Induced Cellular Damage.



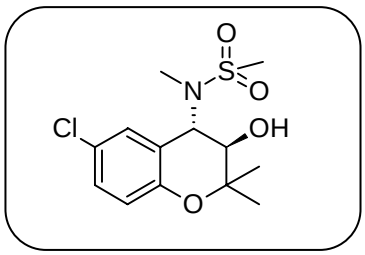
D. T. Witiak et al.[50] have synthesized ethyl 6-substituted-chroman and evaluated as anti-hyperlipidemic agent.



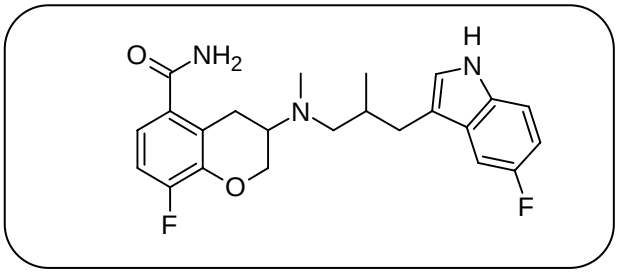
K. A. Reddy et al.[51] have synthesized benzyloxy containing chroman derivatives and evaluated for their euglycemic and hypolipidemic activities.



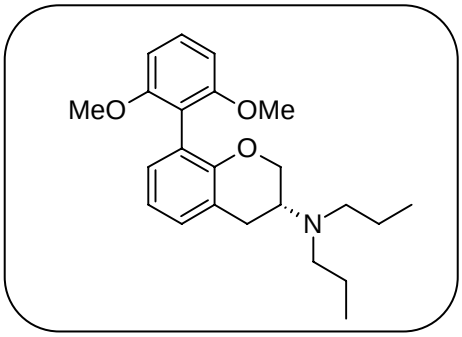
U. Gerlach et al.[52] have synthesized various ethanesulfonamide containing chroman for development as an antiarrhythmic drug



N. T. Hatzenbuhler et al.[53] have worked on combining a 5-HT_{1A} moiety (3-aminochroman scaffold) and a 5-HT transporter (indole analogues) linked through a common basic nitrogen via an alkyl chain attached at the 1- or 3-position of the indole evaluated for dual affinity at both the 5-HT reuptake site and the 5-HT_{1A} receptor.



P. Holmberg et al.[54] have synthesized novel 2-aminotetralin and 3-aminochroman derivatives as selective serotonin 5-HT_7 receptor agonists and antagonists.



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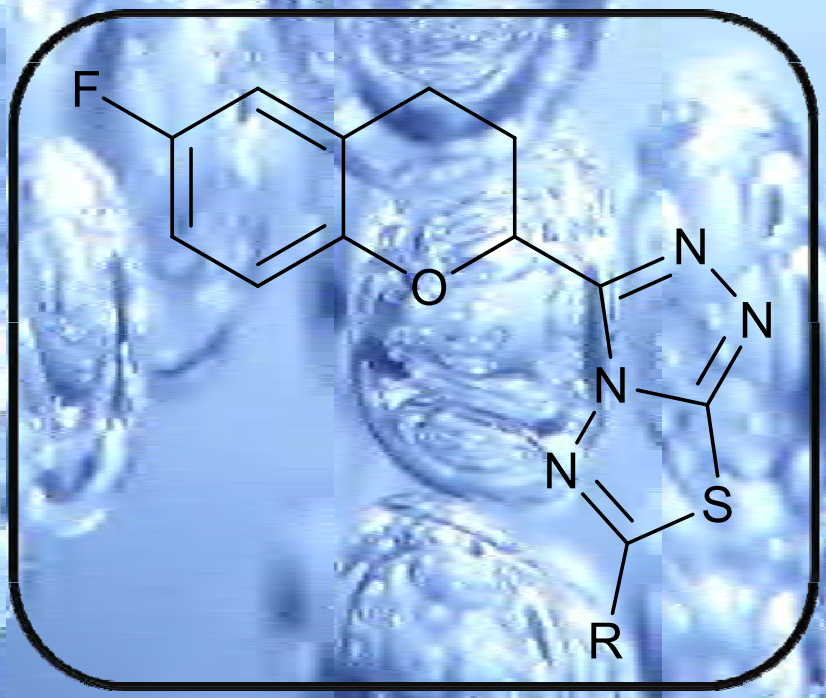
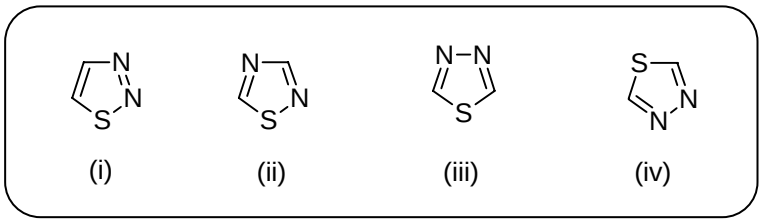
PART-I

STUDIES ON 1,3,4- THIADIAZOLE DERIVATIVES.



INTRODUCTION

Thiadiazole derivatives have played an important role in pharmaceutical industries and exhibited various biological activities due to the presence of –N=C-S group.[1] In thiadiazole ring system one sulphur and two nitrogen atoms are present in a five membered ring. According to their position, thiadiazole systems are classified as 1,2,3-thiadiazole (I), 1,2,4-thiadiazole (II), 1,3,4-thiadiazoles(III) and 1,2,5-thiadiazoles(IV).

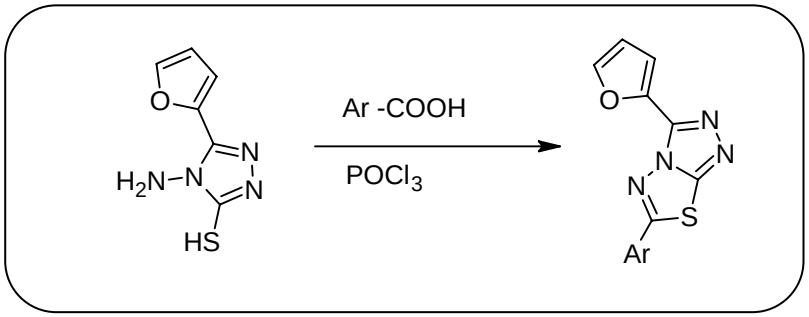


Among these four types of thiadiazoles,1,3,4-thiadiazole is well known. Fischer has described the first 1,3,4-thiadiazole in 1882 and further developed by Buch and co-workers.

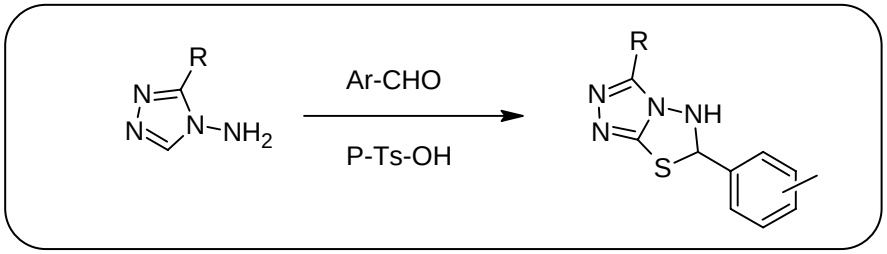
SYNTHETIC ASPECT

Literature survey reveals that several publications and patents[2] described the synthesis of 1,3,4-thiadiazole as under.

1. Li-xue Zhang et al.[3] have synthesized 1,3,4-thiadiazoles by the cyclization of aromatic acid with triazole in presence of $POCl_3$.

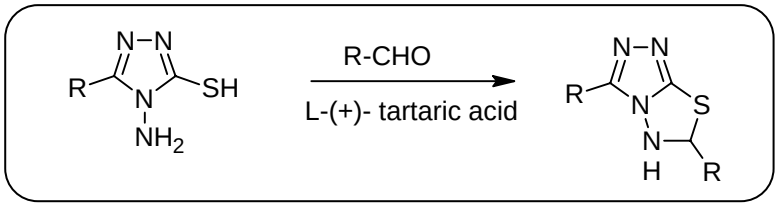


2. J.Mohan et al.[4] have prepared thiadiazole derivatives by the cyclization of amino mercapto triazole and aryl aldehyde in presence of p-Ts-OH

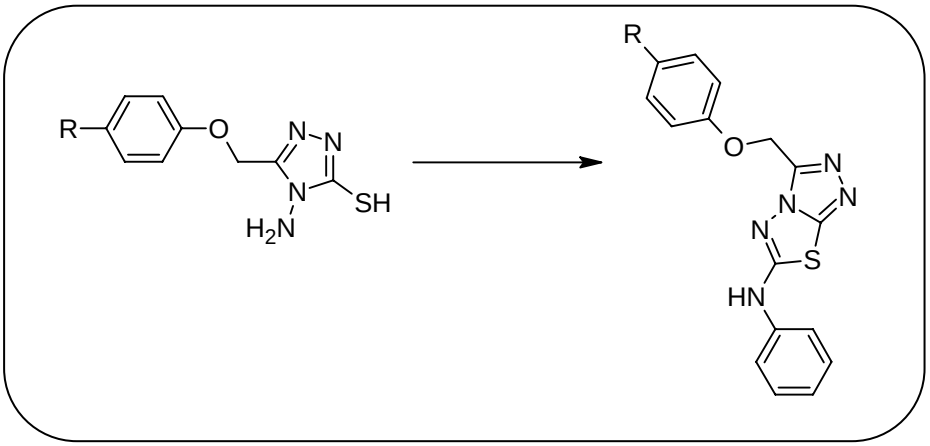


3. Microwave irradiation used for the preparation of thiadiazole using DMF as an energy transfer medium was reported by K. Mazaahir et al.[5]

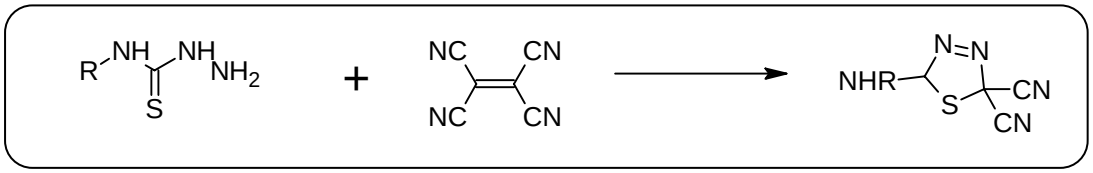
4. Zhong-Yi et al.[6] have been prepared thiadiazole derivatives from amino mercapto triazole and aryl aldehyde in presence of L-(+)-tartaric acid.



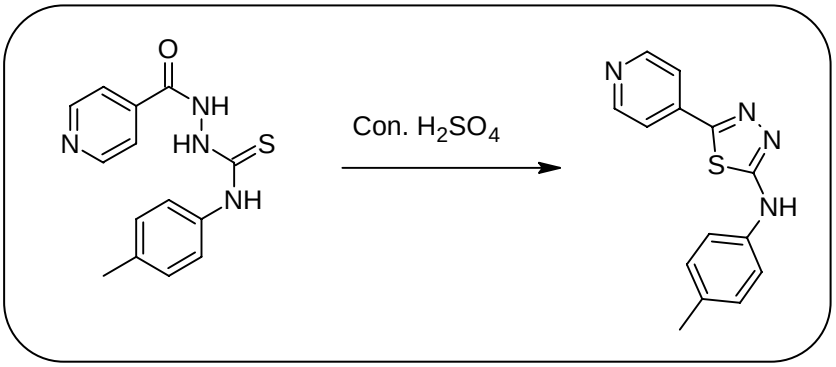
5. Q.Bano and co-workers[7] have been prepared 6-phenyl amino-1,3,4-thiadiazole by reacting triazole with amino acid.



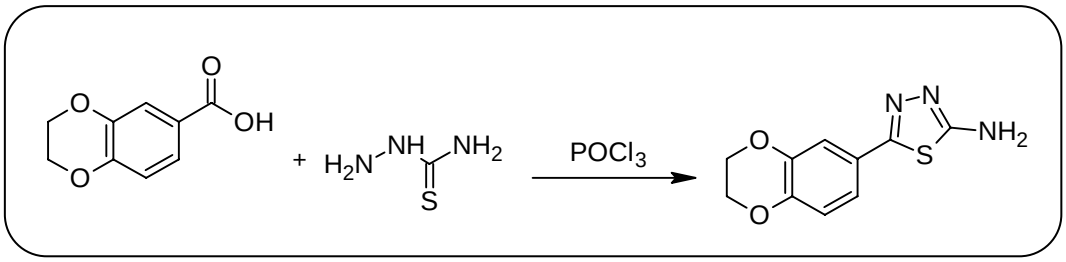
6. A.A.Hassan et al.[8] have prepared 1,3,4-thiadiazoles by the cyclization of tetracyanoethene and 4-phenyl thiosemicarbazides.



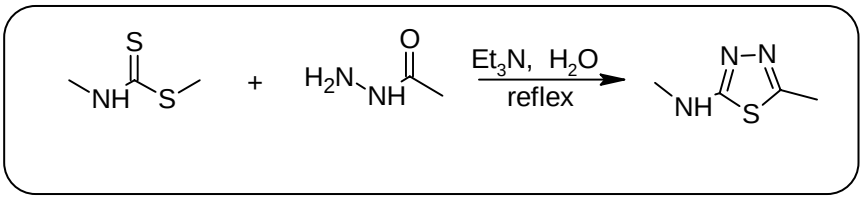
7. K. Zamani et al.[9] have prepared thiadiazole from the thiosemicarbazide by the cyclization in sulphuric acid.



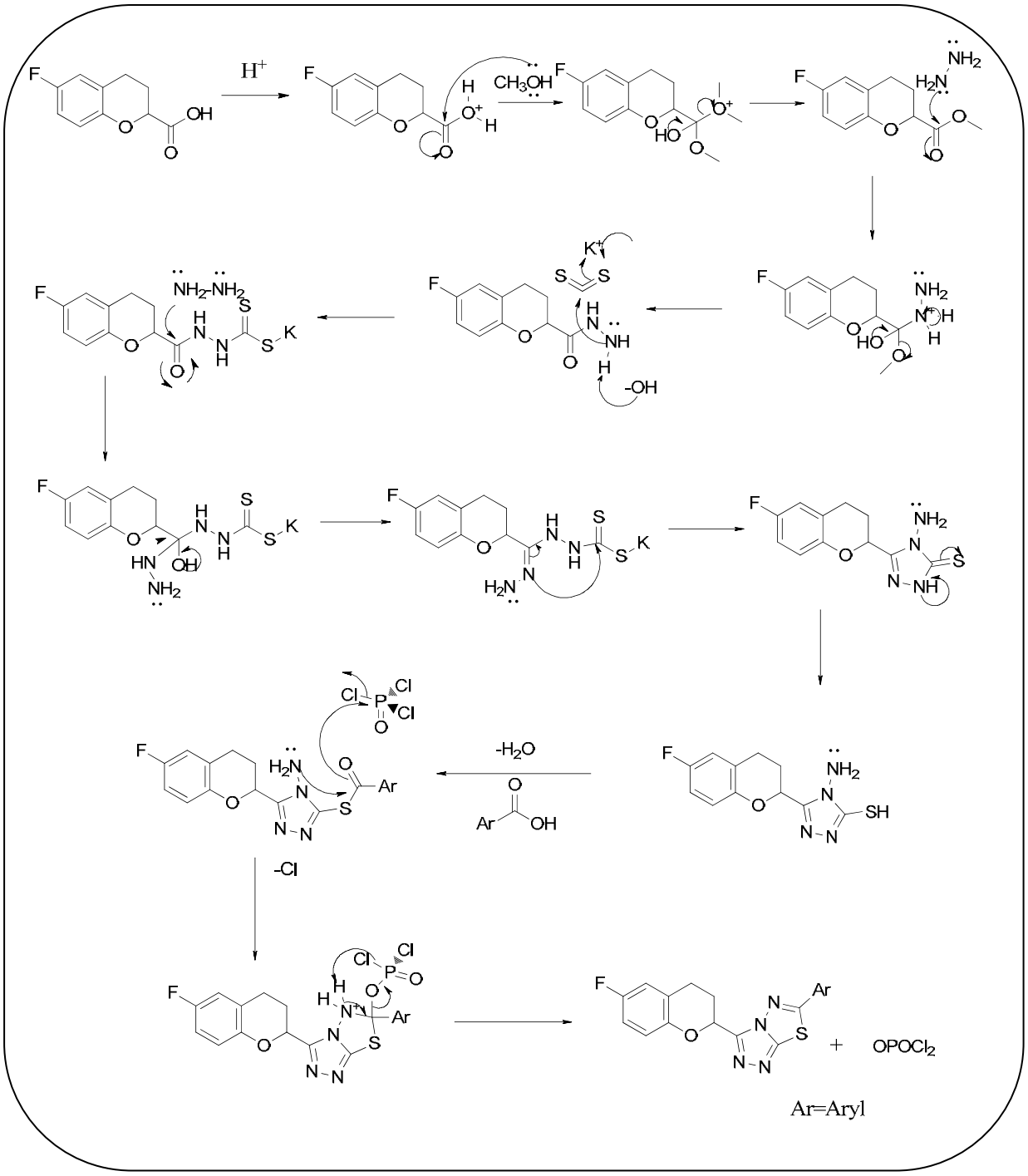
8. J. Sun et al.[10] have synthesized a series of 1,3,4-thiadiazole derivatives from2,3-dihydro benzo[b][1,4] dioxine-6-carboxylic acid on treatment with thiosemicarbazide in presence of phosphoryl chloride.



9. F. Aryanasab et al.[11] have synthesized a series of 2-amino-1,3,4-thiadiazoles in water.



REACTION MECHANISM

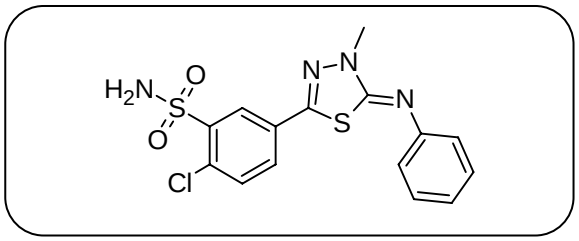


THERAPEUTIC IMPORTANCE

Literature survey revealed that various thiadiazoles have resulted in many potential drugs and are known to exhibit a broad spectrum of pharmacological properties. The specific pharmacological activities associated are as under.

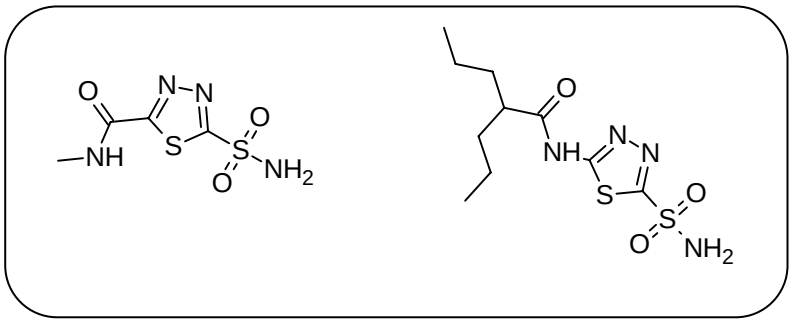
1. Antitumor[12]
2. Antiviral[13]
3. Antibacterial[14]
4. Amoebicidal[15]
5. Antagonist agent[16]
6. Antitubercular[17]
7. Antipyretic[18]
8. Antinelmintic[19]
9. CNS depressant[20]
10. Antischistosomal[21]
11. Herbicidal[22]
12. Insecticidal[23]
13. Pesticidal[24]
14. Hypogycemic[25]

V. Fabrice et al.[26] have synthesized 1,3,4-thiadiazole derivatives and screened for their antiinflammatory, anticancer and anti-HIV activity. U.V. Laddi et al.[27] have discovered thiadiazoles possessing antimicrobial and antituberculosis activity. B.G.Ronald et al.[28] have reported thiadiazoles as antiinflammatory agents. A.Mobinikhaledi et al.[29] have investigated 1,3,4-thiadiazoles and tested for insecticidal activity. Che Chao et al.[30] have prepared thiadiazole derivatives showed antifungal and plant growth regulating effect.



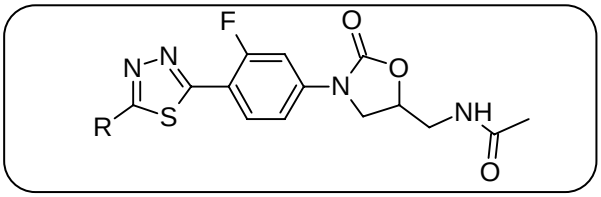
C.Chazalete et al.[31] have synthesized acetazolamide possessing diuretics and antiglaucoma activity. A.Varvareso et al.[32] suggested thiadiazoles and reported them as antidepressant. P.Mishra et al.[33] have screened 1,3,4-thiadiazoles for their potent spasmolytic activity and anti-inflammatory activity. B. Masercel et al.[34] have synthesized 1,3,4-thiadiazoles possessing potent

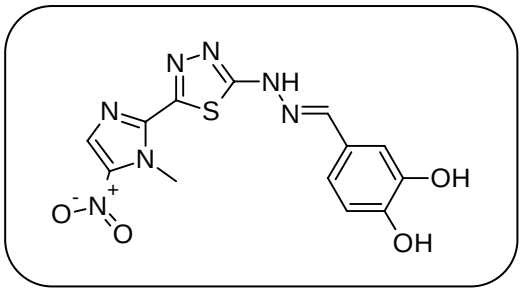
carbonic anhydrase inhibitor properties and also prepared 5-valproyl amino 1,3,4-thiadiazole-2-sulphonamide (XIII) as str.ong anticonvulsant.



C. T. Supuran and Andrea Scozzafava[35] have reported 1,3,4-thiadiazole derivatives as carbonic anhydrase inhibitors and antitumor. E. Palaska et al.[36] synthesized thiadiazoles containing anti-inflammatory activity. J. M. Colacino et al.[37] have documented anti-influenza virus activity of thiadiazoles.

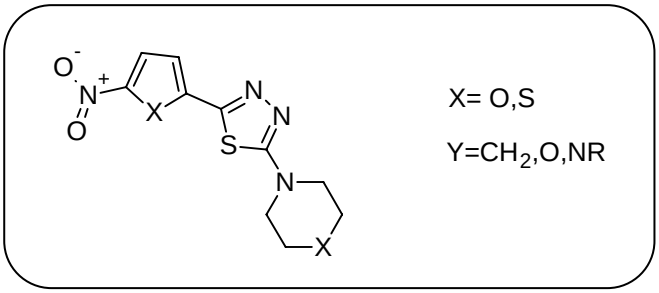
L.M.Thomasco et al.[38] have prepared 1,3,4-thiadiazole possessing potent antibacterial activity against Gram positive and Gram negative organisms. S. A. Carvalho and co-workers[39] have documented antitrypanosomal profile of 1,3,4-thiadiazole derivatives, Z. Kiani et al.[40] have discovered thiadiazoles as antituberculosis agent





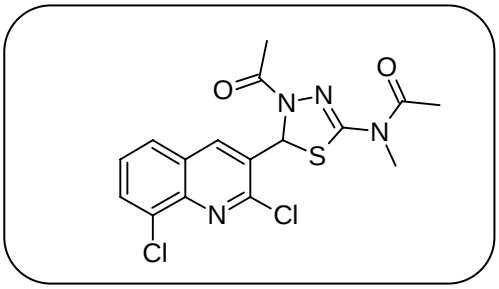
A. faroumadi et al.[41] have synthesized 1,3,4-thiadiazoles (XVI) and studied their leishmanicidal activity. H.N. Dogan et al.[42] have prepared 2,5-disubstituted-1,3,4- thiadiazolo derivatives as anticonvulsant and antimicrobial agent. N. Terzioglv

and A. Gursoy[43] have discovered thiadiazoles and studied their anticancer activity. A. Foroumadi and co-workers[44] have documented antituberculosis activity and cytotoxicityof 1,3,4-thiadiazoles.

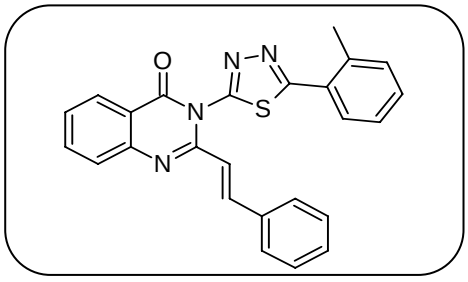


Recently S. Karakus and S. Rollas[45] have screened thiadiazoles for their antituberculosis activity. Jui-Yi Chou et al.[46] have synthesized thiadiazoles and reported them as anticancer agents.

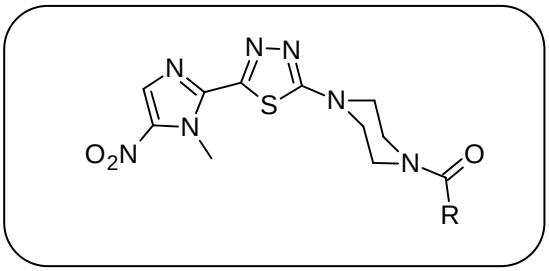
A. R. Bhat et al.[47] have synthesized new series of thiadiazoles evaluated on *in vitro* growth of microorganisms causing microbial infection.



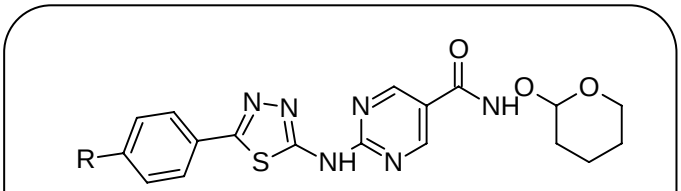
V. Jatav et al.[48] have synthesized a series of 3-[5-substitutedphenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones and evaluated for anticonvulsant, sedative-hypnotic and CNS depression activities.



F. Poorrajab et al.[49] have synthesized 1,3,4-thiadiazole derivatives and evaluated *in vitro* against *Leishmania major*.



H. Rajak et al.[50] have synthesised 2,5-disubstituted-1,3,4-thiadiazole and tested for antitumor activity against Ehrlich ascites carcinoma cells in Swiss albino mice.



R = 4-Cl, 4-NO_2, 4-OH, 2-Cl, 3-Cl

Work done from our laboratory

K.M.Thaker[51] have synthesized 2-(3'5'-dichlorobenzo[b]thiophen-2'-yl)-5-arylamino-1,3,4-thiadiazoles from triazole. S.L.Vasoya[52] have synthesized some new thiosemicarbazide and 1,3,4-thiadiazole heterocycles bearing the benzo[b]thiophene nucleus as potent antituberculer and antimicrobial agents.

In light of wide varieties of therapeutic activities exhibited by thiadiazole, we have embarked upon the synthesis of some new thiadiazole derivatives which have been described in following sections.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-(6-FLUOROCHROMAN-2-YL)-6-ARYL[1,2,4]TRIAZOLO [3,4-b] [1,3,4]THIADIAZOLES.

Part – B

[Part – I (Section-i)]

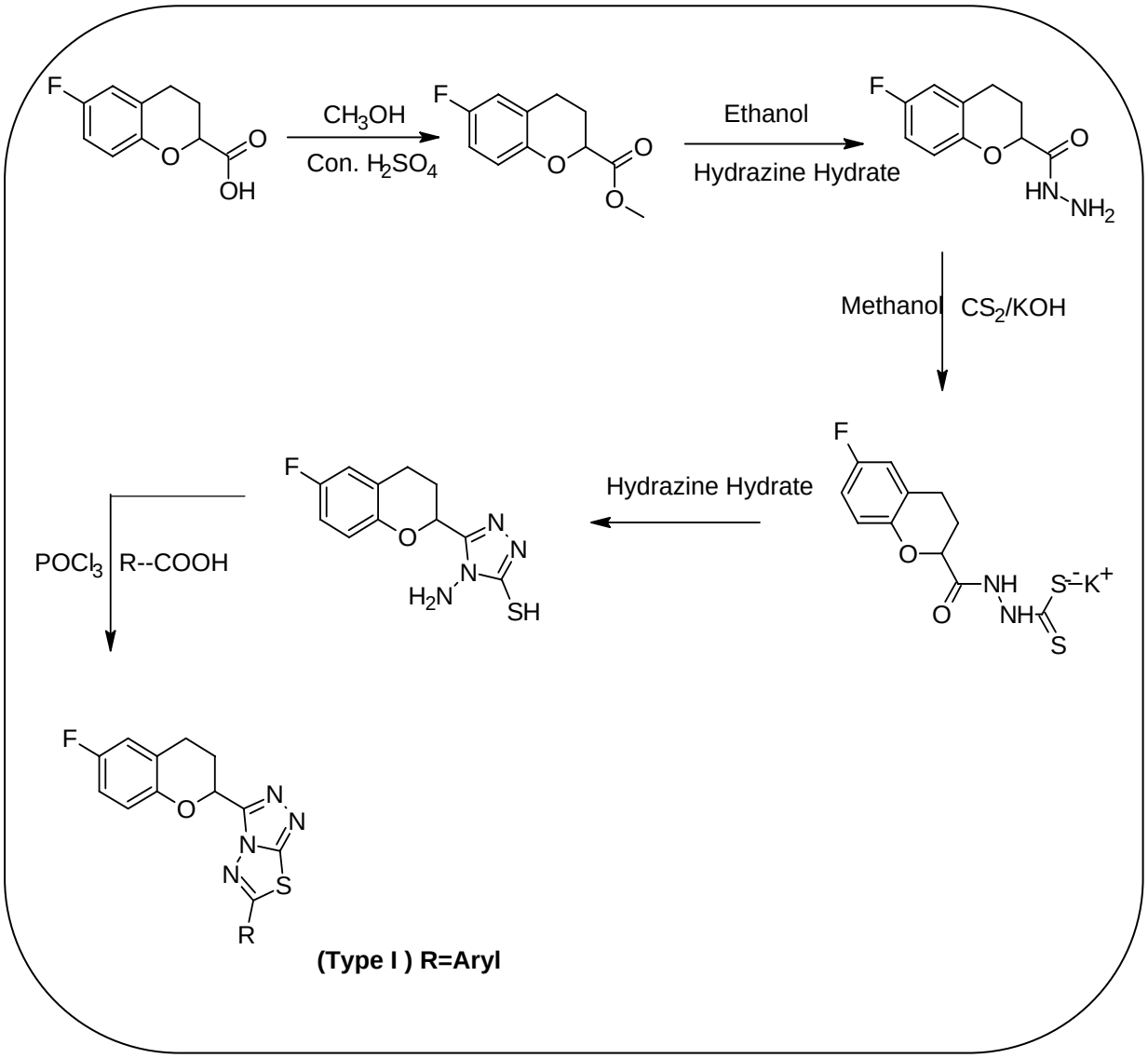
Synthesis and biological evaluation of 3-(6-fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazoles.

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-(6-FLUORO CHROMAN-2-YL)-6-ARYL-[1,2,4]TRIAZOLO[3,4-b][1,3,4] THIADIAZOLES.

Thiadiazole derivatives are associated with broad spectrum of biological activities. In view of these finding it appeared of interest to synthesize some newer thiadiazole derivatives, with better potency. Thiadiazoles of type (I) have been prepared by cyclocondensation of 4-amino-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol with different aromatic acids in presence of phosphorous oxychloride, as shown in reaction scheme.

REACTION SCHEME



(Type I) R=Aryl

The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ and DMSO solution on a Bruker AC 300 MHz, 400 MHz and 100MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Synthesis of Methyl 6-fluorochroman-2-carboxylate.

6-Fluorochroman-2-carboxylic acid (2.0 gm, 0.01 mol) in methanol (10 ml) was stirred at room temperature for 5 minutes then add concentrated H_2SO_4 (0.5 ml, 0.01 mol) and stir the reaction mixture at room temperature for 10 hours.After the completion of the reaction checked by TLC, methanol was removed *in vacuo* and then add methelene dichloride(40 ml) and stir it further for 10 minutes.The resultant mixture was treated with saturatured sodium bicarbonate until pH become neutral. The neutral solution was treated with sodium sulphate and then organic layer was removed in *vacuo.* Collect the crude product and there is no need to purification, the crude ester directly used for further reaction.

[B] Synthesis of 6-Fluorochroman-2-carbohydrazide.

Methyl 6-fluorochroman-2-carboxylate (2.0 g, 0.01 mol) in absolute ethanol (25 ml) was cooled at $0\text{-}(-5)^0$c.To the cooled solution add hydrazine hydrate (4.0 ml, 0.08 mol) and stir the reaction mixture at $0\text{-}(-5)^0$c for 10 hours. After the completion of the reaction (monitored by TLC). The white color solid separated was filtered and washed with cold ethanol and crystallized from ethanol.

[C] Preparation of Potassium 2-[(6-fluorochroman-2-yl)carbonyl] hydrazine carbodithioate.

To a mixture of potassium hydroxide (8.40g, 0.15 mol) and 6- fluorochroman -2-carbohydrazide (17.0 g, 0.1 mol) in methanol (50 ml), carbon disulphide (11.4g, 0.15 mol) was added. This mixture was stirred for 22-24 hours at room temperature. Thus the

solid obtained was filtered and washed with diethyl ether and dried. There is no need to purify the salt for further reaction.

[D] Preparation of 4-Amino-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol.

A suspension of the potassium salt (24.5g, 0.1 mol), hydrazine hydrate (15 ml, 0.3 mol) and water (5 ml) was refluxed with stirring for 30 hours. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odour) and a homogeneous solution was resulted. Dilute the solution with of cold water (100 ml) and neutralized with glacial acetic acid. Thus the white solid precipitates were formed. The product was filtered, washed with cold water and crystallized from dioxane yield 50%, m.p.173^{o}C.

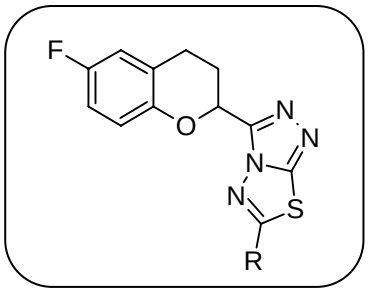
[E] General procedure for the preparation of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.

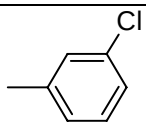
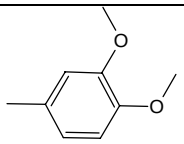
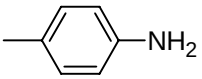
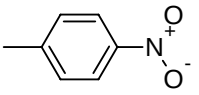
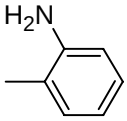
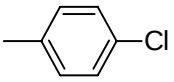
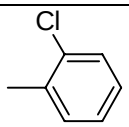
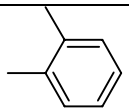
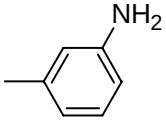
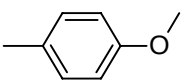
A mixture of 4-amino-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol(2.26g, 0.01 mol) and different aryl acids (0.01 mol) in phosphorous oxychloride (15 ml) was refluxed with continuous stirring. After completion the reaction (15-16 hours monitoring by TLC), the content was cooled to room temperature then add ice cooled water and thus solid separated out was filtered, washed with water and neutralized with sodium bicarbonate solution.Crude product was purified by column chromatography to give the analytical pure compounds. The physical constants of the products are recorded in **Table-6a.**

[F] Biological evaluation of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.

Antimicrobial testing was carried out as described in Part-B, Part-I, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-6b**.

Table-6a: Physical constant of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.



Sr. No	Substitution R	M. F.	M. W.	Yield (%)	R_f value
6a		$C_{18}H_{12}ClFN_4OS$	386.83	95	0.49
6b		$C_{20}H_{17}FN_4O_3S$	412.43	79	0.31
6c		$C_{18}H_{14}FN_5OS$	367.40	87	0.59
6d		$C_{18}H_{12}FN_5O_3S$	397.38	94	0.38
6e		$C_{18}H_{14}FN_5OS$	367.40	82	0.54
6f		$C_{18}H_{12}ClFN_4OS$	386.83	81	0.61
6g		$C_{18}H_{12}ClFN_4OS$	386.83	74	0.51
6h		$C_{19}H_{15}FN_4OS$	366.41	72	0.41
6i		$C_{18}H_{14}FN_5OS$	367.40	86	0.68
6j		$C_{19}H_{15}FN_4O_2S$	382.41	83	0.63

TLC solvent system:- E.A. : Hexane = 9 : 1

ANALYTICAL DATA

6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6a). mp 150-154 °C; IR (DRS): 3073, 3031, 2957, 2847, 1625, 1462, 1442, 1325, 1258, 1140, 1065, 1018, 825, 748, 701, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 2.44-2.48(m, 1H, 2CH), 2.74-2.76(m, 1H, 2CH), 3.04(m, 2H, 2CH), 5.66-5.68(m, 1H, CH), 6.82-6.84(m, 3H, ArH), 7.48-7.50(d, *J*= 5.79 Hz, 1H, ArH), 7.56(m, 1H, ArH), 7.73-7.75(d, *J*= 6.69 Hz, 1H, ArH), 7.90(s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ ppm 23.47, 23.83, 38.97, 68.33, 102.68, 107.14, 113.57, 113.80, 115.01, 115.24, 117.38, 117.46, 122.81, 125.55, 126.44, 130.52, 130.92, 134.66, 146.13, 149.45, 161.22, 165.22, 175.36; MS: *m/z* = 386 $[M]^+$; Anal. Calcd for $C_{18}H_{12}ClFN_4OS$: C, 55.89; H, 3.13; N, 14.48. Found: C, 55.83; H, 3.04; N, 14.08%.

6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (6b). mp 119-121°C; IR (DRS): 3090(Ar, C-H str.), 3020(Ar, C-H str.), 2935(C-H str.), 2839(C-H str.), 1637(Ar, C=C str.), 1492(Ar, C=C str.), 1440(C-H ben), 1363(C-H ben), 1138(C-F str.), 1058(C-N str.), 1020(C-O-C str.), 810(C-H o,p, ben), 756(C-H o,p, ben), 705(C-C o,p, ben), 680(C-C o,p, ben) cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 2.41-2.44(m, 1H, 2CH), 2.58-2.65(m, 1H, 2CH), 3.02-3.19(m, 2H, 2CH), 3.90(s, 6H, OCH_3, OCH_3), 5.70-5.73(d,d, *J*= 4.4 Hz, 3.4 Hz, 1H, CH), 6.78-6.93(m, 3H, ArH), 7.09-7.11(d, *J*=8.44 Hz, 1H, ArH), 7.39(s, 1H, ArH), 7.49-7.51(d, *J*= 7.72 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ ppm 23.88, 38.92, 55.72, 68.23, 102.47, 108.96, 111.54, 113.59, 113.81, 115.04,115.31, 117.47, 121.19, 122.98, 130.42, 130.80, 147.17, 149.14, 152.65, 161.11, 166.12, 166.55, 175.12; MS: *m/z* = 412 $[M]^+$; Anal. Calcd for $C_{20}H_{17}FN_4O_3S$: C, 58.24; H, 4.15; N, 13.58. Found: C, 58.18; H, 3.99; N, 13.49%.

4-(3-(6-Fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-6-yl)aniline (6c). mp 168-170 °C; IR (DRS): 3422, 3378, 3030, 2964, 2853, 1642, 1612, 1581, 1471, 1368, 1247, 1156, 1057, 1014, 819, 744, 710, 678 cm^{-1}; MS: *m/z* = 367 $[M]^+$; Anal. Calcd for $C_{18}H_{14}FN_5OS$: C, 58.84; H, 3.84; N, 19.06. Found: C, 58.69; H, 3.78; N, 18.90%.

3-(6-Fluorochroman-2-yl)-6-(4-nitrophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6d). mp 158-160°C; IR (DRS): 3074, 2987, 2851, 1645, 1612, 1585, 1468, 1345, 1184, 1250, 1061, 1023, 820, 780, 744, 695, 566 cm^{-1}; MS: *m/z* = 397 $[M]^+$; Anal. Calcd for $C_{18}H_{12}FN_5O_3S$: C, 54.40; H, 3.04; N, 17.62. Found: C, 54.28; H, 2.93; N, 17.44%.

2-(3-(6-Fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)aniline (6e). mp 147-149 °C; IR (DRS): 3442, 3091, 3081, 2975, 2844, 1641, 1579, 1556, 1464, 1357, 1242, 1145, 1088, 1017, 832, 750, 687 cm^{-1}; MS: *m/z* = 367 $[M]^+$; Anal. Calcd for $C_{18}H_{14}FN_5OS$: C, 58.84; H, 3.84; N, 19.06. Found: C, 58.41; H, 3.78; N, 18.99%.

6-(4-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6f). mp 116-118°C; IR (DRS): 3080, 2983, 2867, 1629, 1572, 1525, 1462, 1381, 1245, 1196, 1046, 1011, 830, 778, 701, 665, 578 cm^{-1}; MS: *m/z* = 386 $[M]^+$; Anal. Calcd for $C_{18}H_{12}ClFN_4OS$: C, 55.89; H, 3.13; N, 14.48. Found: C, 55.84; H, 2.97; N, 14.17%.

6-(2-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6g). mp 183-185 °C; IR (DRS): 3077, 2978, 2863, 1625, 1609, 1563, 1464, 1331, 1238, 1142, 1038, 1014, 870, 832, 778, 668, 514 cm^{-1}; MS: *m/z* = 386 $[M]^+$; Anal. Calcd $C_{18}H_{12}ClFN_4OS$: C, 55.89; H, 3.13; N, 14.48. Found: C, 55.67; H, 3.01; N, 14.21%.

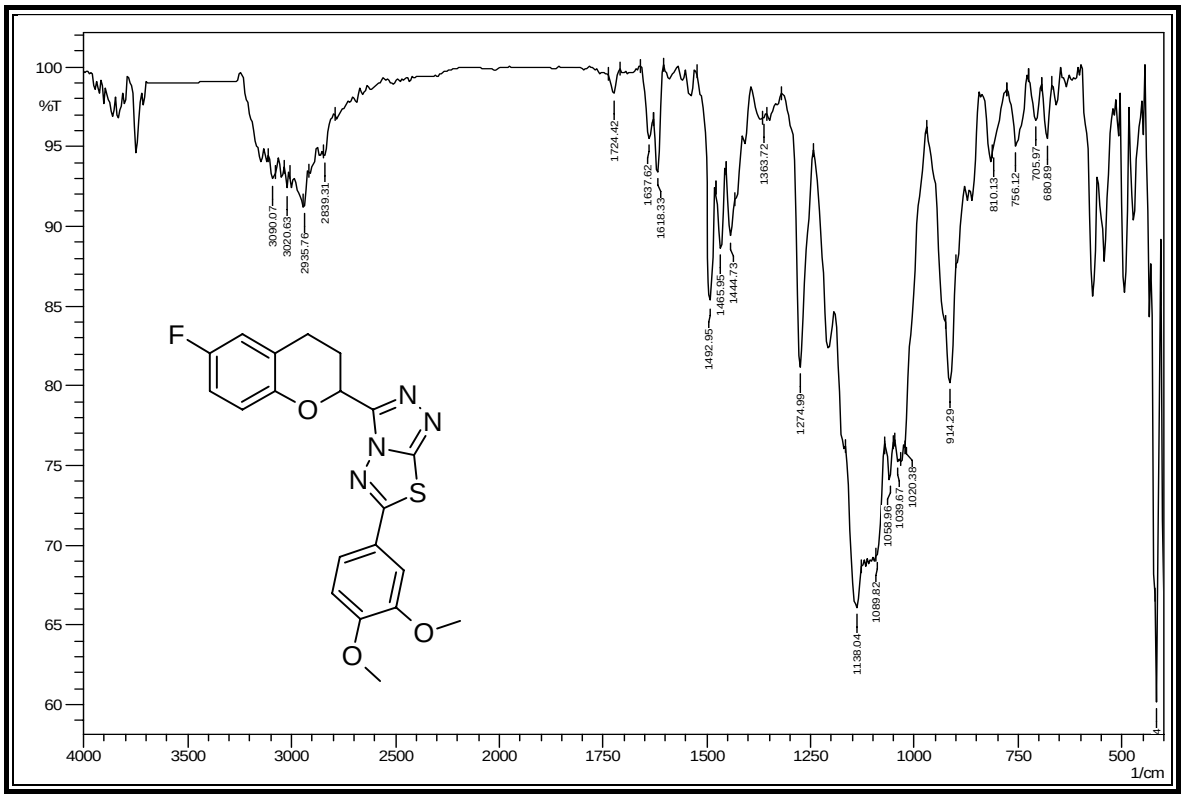
3-(6-Fluorochroman-2-yl)-6-(o-tolyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (6h). mp 160-162°C; IR (DRS): 3063, 2962, 2854, 1603, 1545, 1542, 1452, 1325, 1260, 1146, 1060, 1023, 812, 754, 662, 518 cm^{-1}; MS: *m/z* = 366 $[M]^+$; Anal. Calcd for $C_{19}H_{15}FN_4OS$: C, 62.28; H, 4.13; N, 15.29. Found: C, 62.19; H, 3.97; N, 15.24%.

3-(3-(6-Fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-6-yl)aniline (6i). mp 109-111°C; IR (DRS): 3428, 3392, 3075, 2964, 2853, 1721, 1601, 1581, 1423, 1371, 1241, 1149, 1054, 1026, 888, 848, 766, 720, 665, 578 cm^{-1}; MS: *m/z* = 367 $[M]^+$; Anal. Calcd for $C_{18}H_{14}FN_5OS$: C, 58.84; H, 3.84; N, 19.06. Found: C, 58.53; H, 3.71; N, 18.90%.

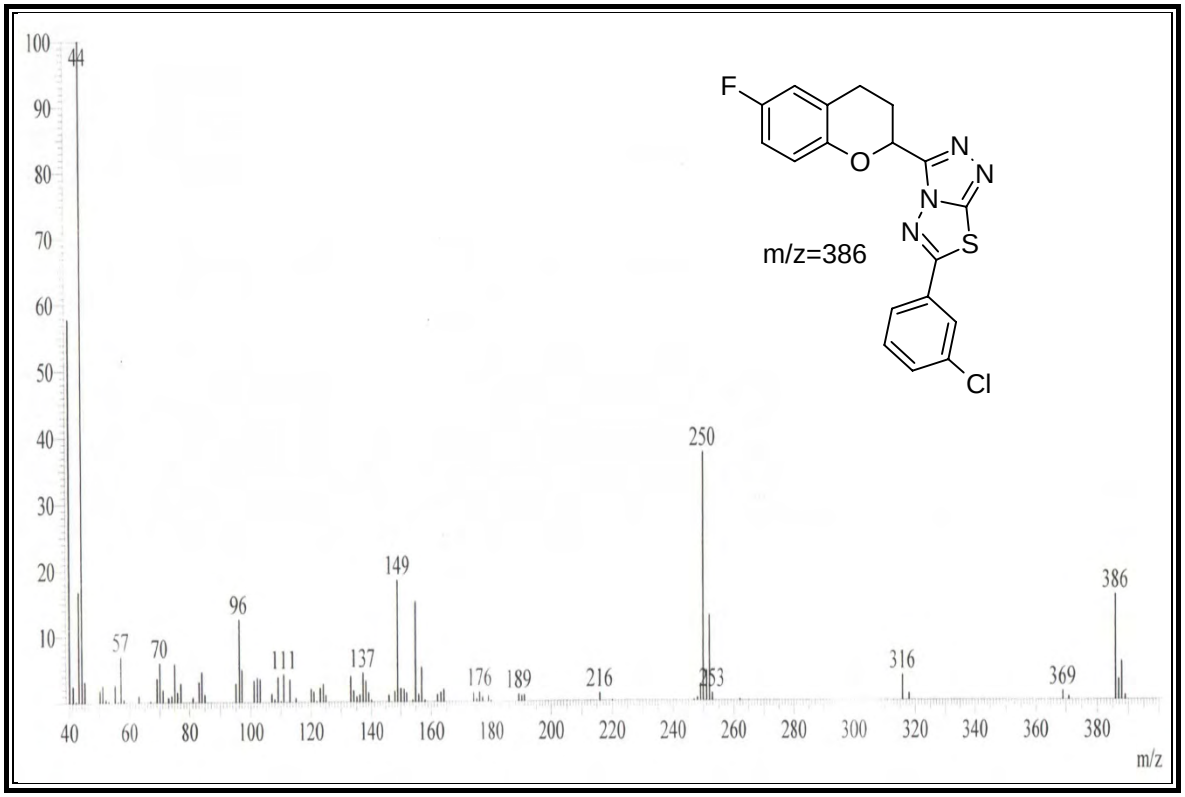
3-(6-Fluorochroman-2-yl)-6-(4-methoxyphenyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazole (6j). mp 224-226°C; IR (DRS): 3061, 2951, 2872, 1689, 1589, 1579, 1462, 1354, 1208, 1135, 1099, 1003, 819, 755, 688 cm^{-1}; MS: *m/z* = 382 $[M]^+$; Anal. Calcd for $C_{19}H_{15}FN_4O_2S$: C, 59.67; H, 3.95; N, 14.65. Found: C, 59.08; H, 3.88; N, 14.62%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

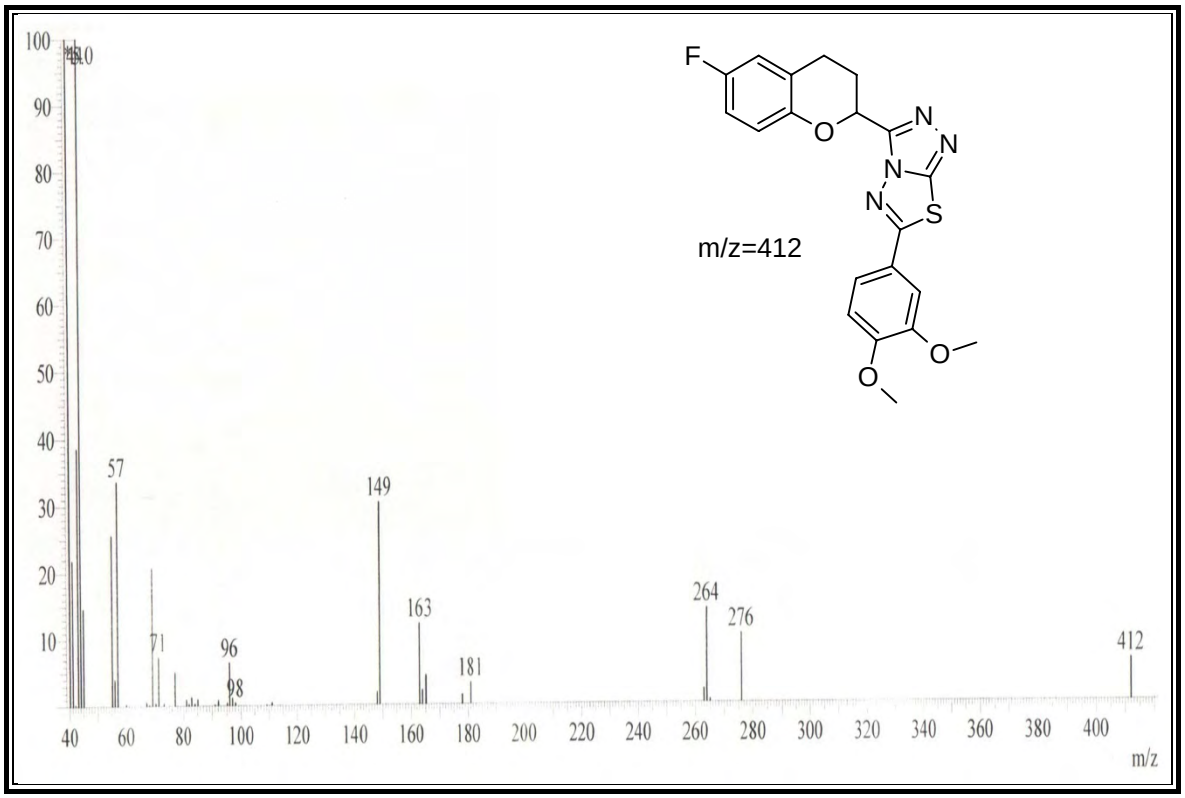
IR Spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).



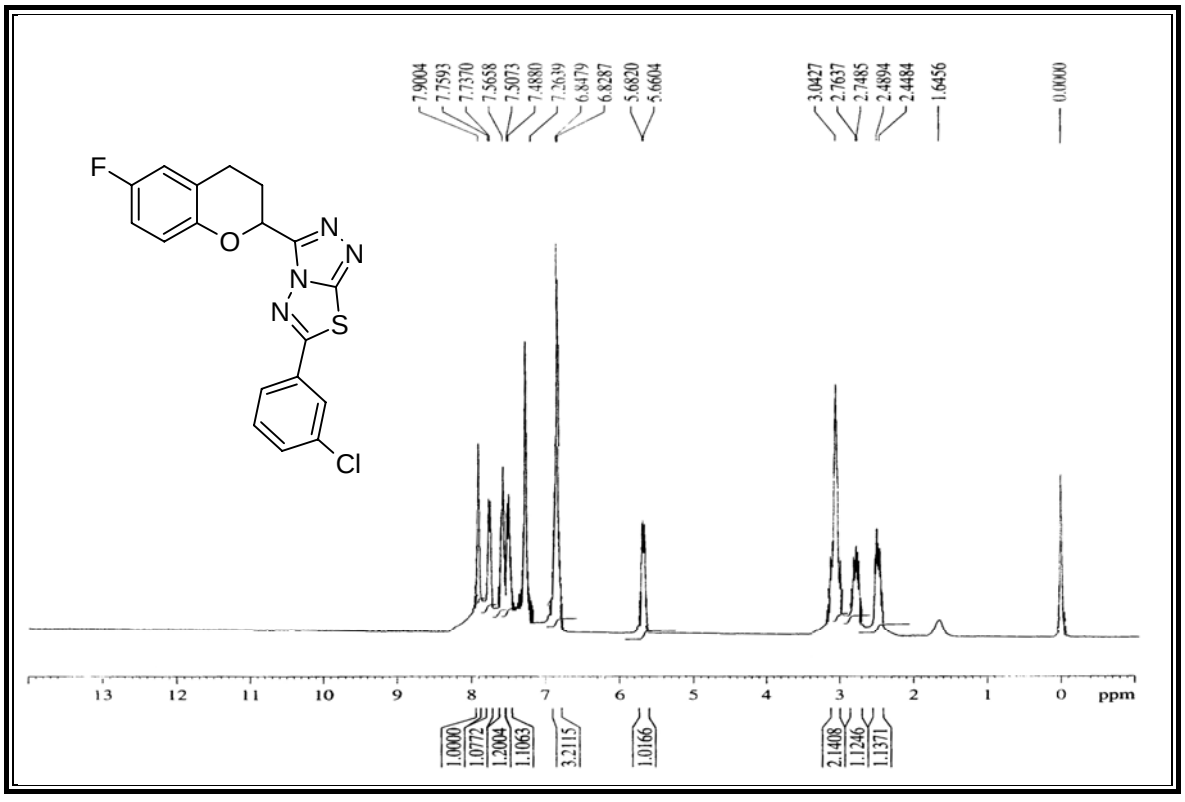
Mass spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(6a).



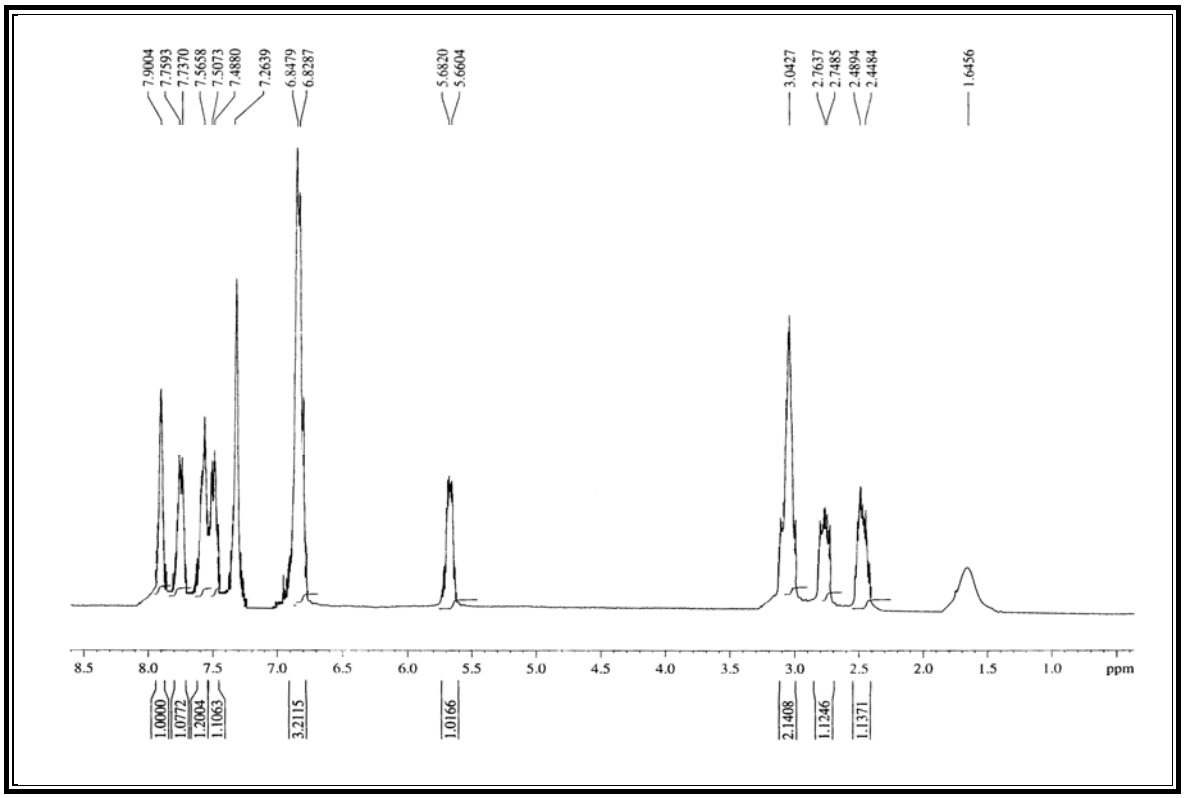
Mass spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).



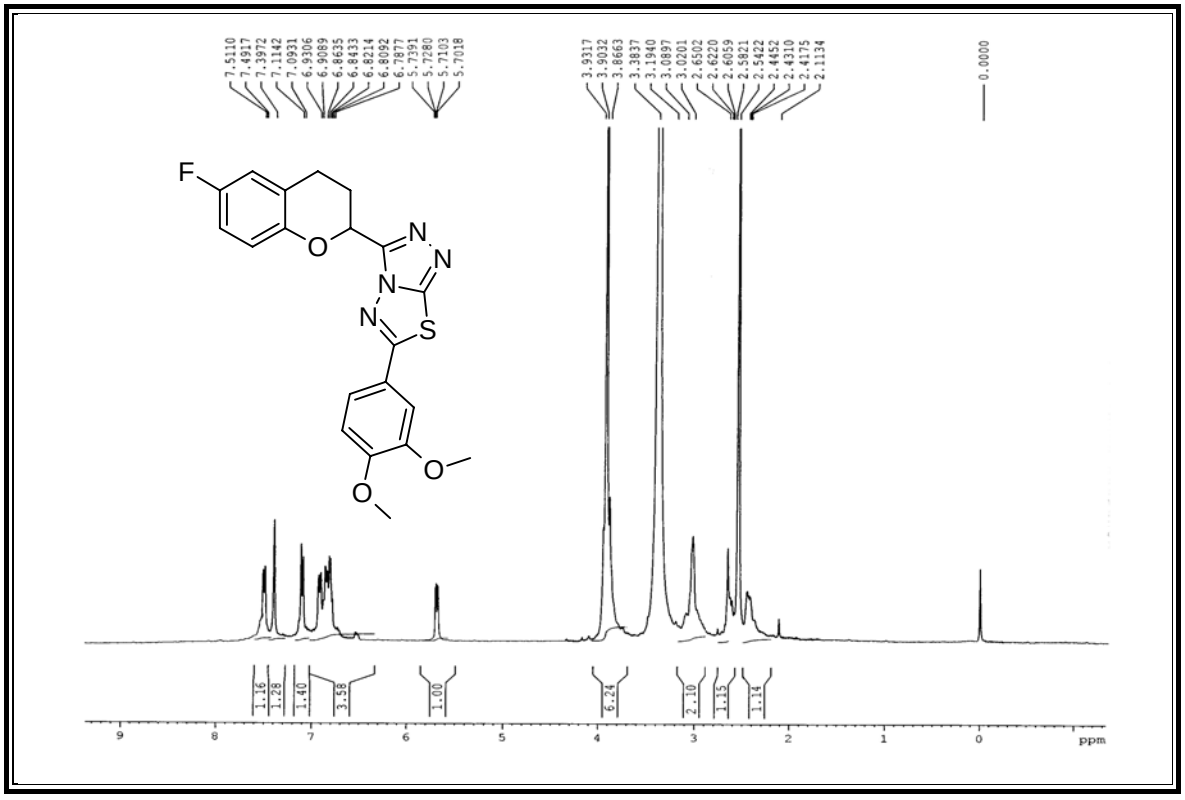
^{1}H NMR spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6a).



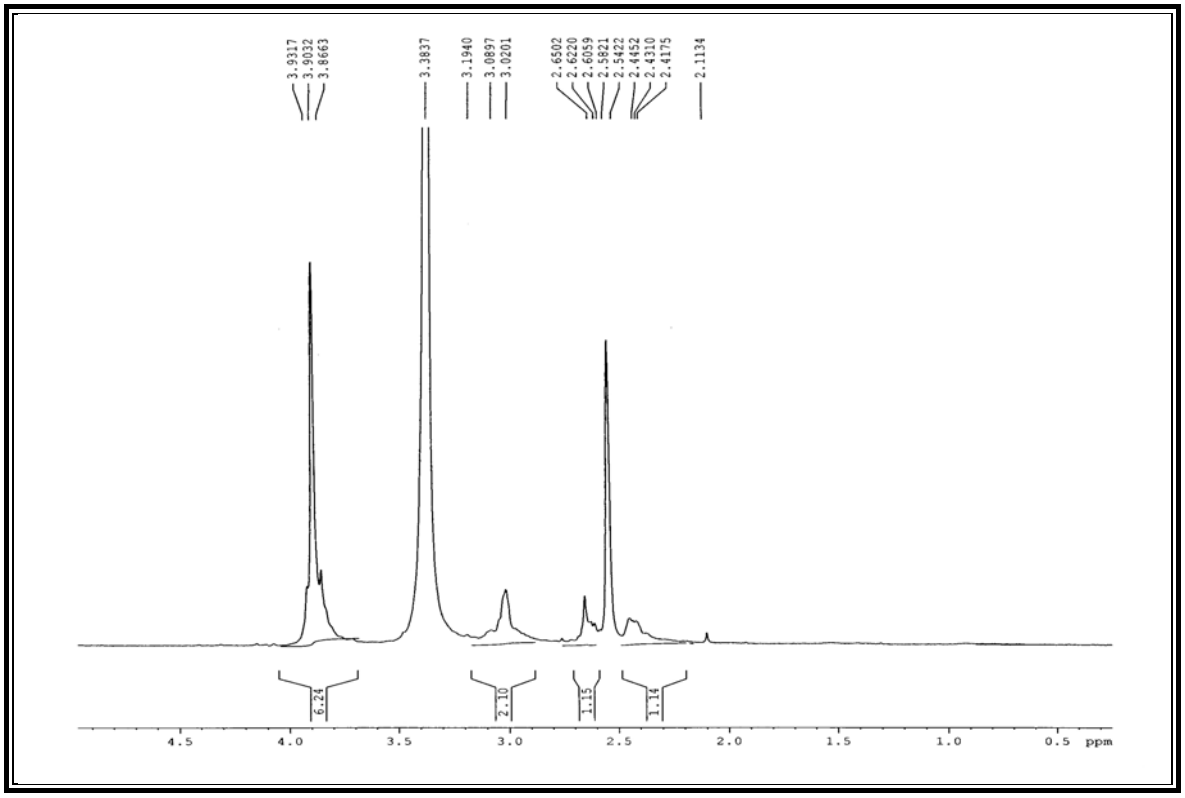
Expanded spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6a).



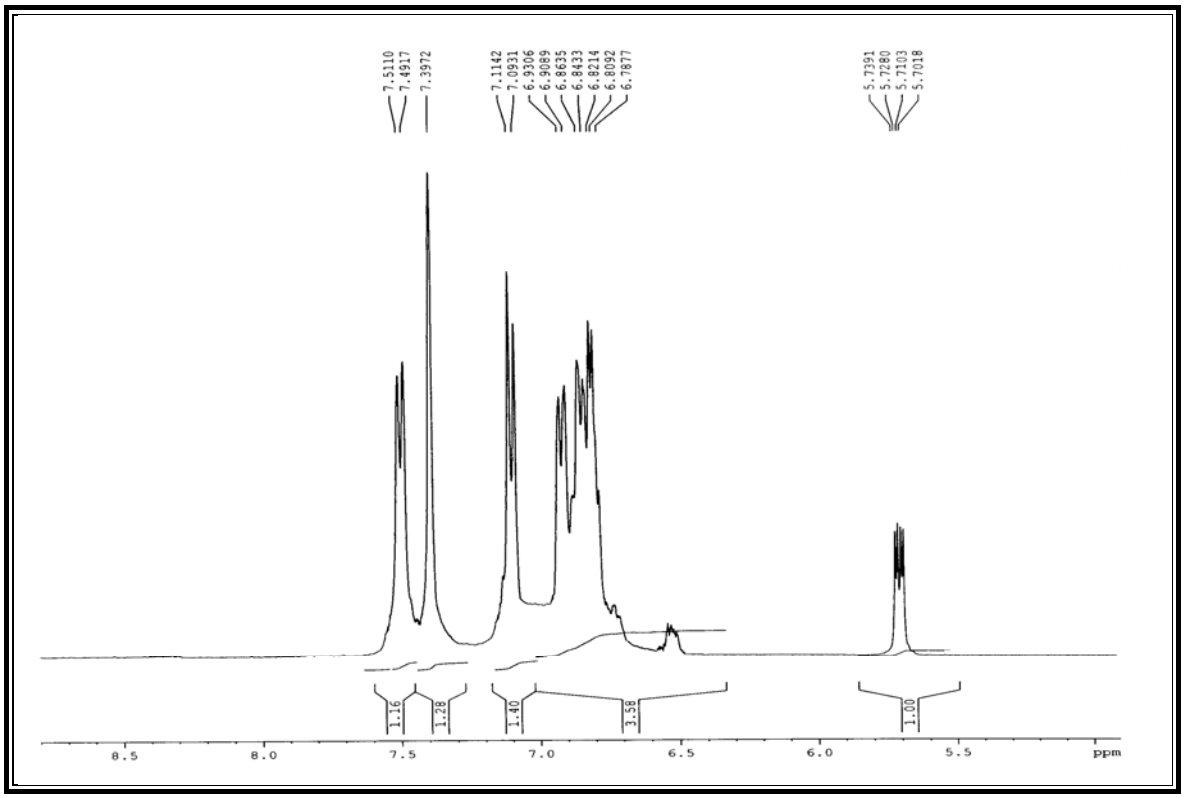
^{1}H NMR spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).



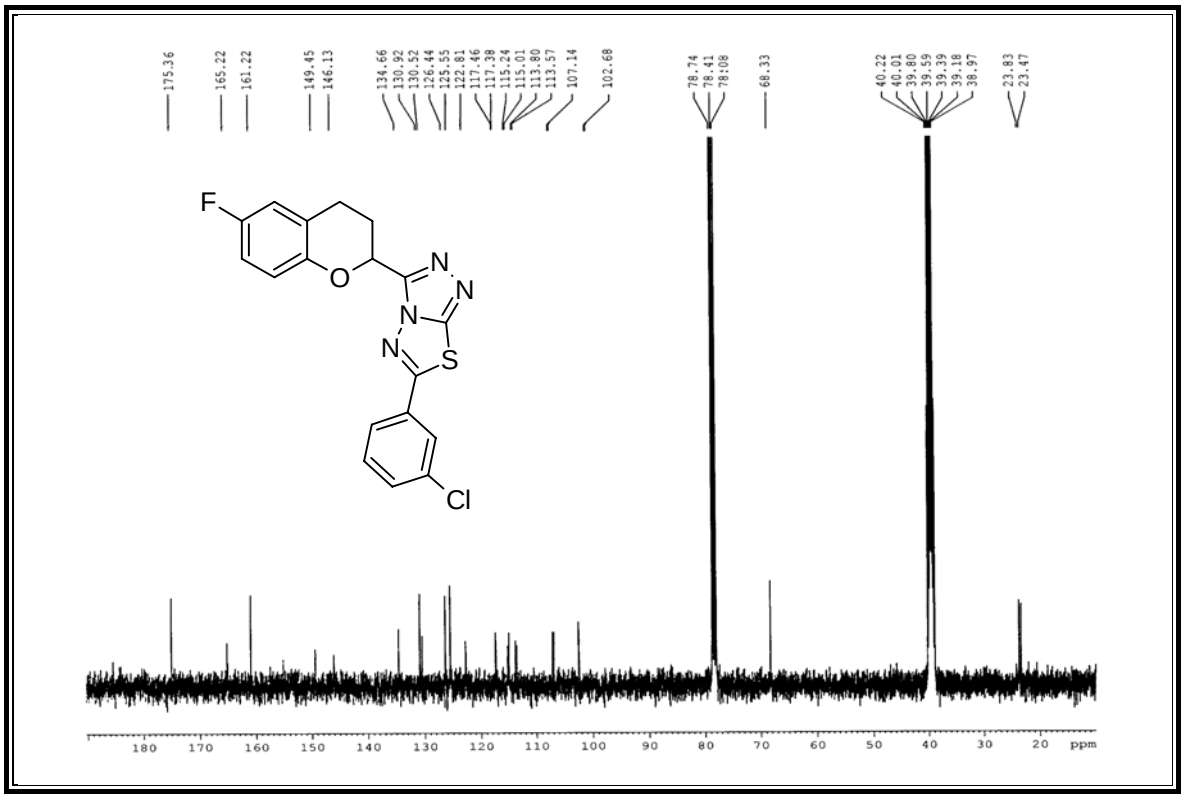
Expanded spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).



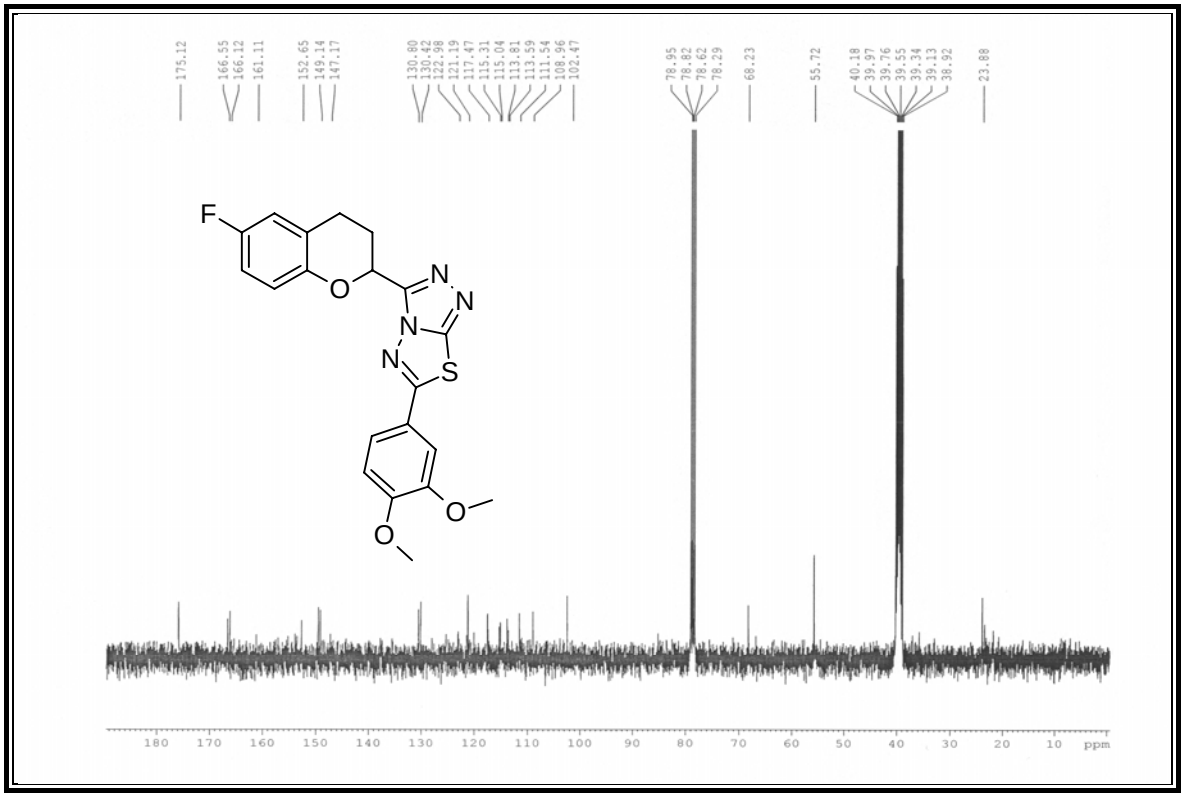
Expanded spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).



^{13}C NMR spectrum of 6-(3-Chlorophenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6a).



^{13}C NMR spectrum of 6-(3,4-Dimethoxyphenyl)-3-(6-fluorochroman-2-yl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazole(6b).



ANTIMICROBIAL ACTIVITY

Biological evaluation of 3-(6-fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.

All of the synthesized compounds **(6a-j)** were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC 442, two Gram-negative bacteria *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using micro dilution broth method according to NCCLS standards.[38]

Minimal Inhibition Concentration [MIC]

The main advantage of the **Broth Dilution Method** for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.

1. Serial dilutions were prepared in primary and secondary screening.
2. The control tube containing no antibiotic is immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight.
3. The MIC of the control organism is read to check the accuracy of the drug concentrations.
4. The lowest concentration inhibiting growth of the organism is recorded as the MIC.
5. The amount of growth from the control tube before incubation (which represents the original inoculums) is compared.

Methods used for primary and secondary screening

Each synthesized compounds were diluted in DMSO to obtain 2000 μg mL^{-1} concentration, as a stock solution. Inoculum size for test str.ain was adjusted to 10^8 cfu (colony forming unit) per milliliter by comparing the turbidity.

Primary screen: In primary screening 1000 μg mL^{-1}, 500 μg mL^{-1} and 250 μg mL^{-1} concentrations of the synthesized compounds were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms.

Secondary screen: The compounds found active in primary screening were similarly diluted to obtain 200 μg mL^{-1}, 100 μg mL^{-1}, 50 μg mL^{-1}, 25 μg mL^{-1}, 12.5 μg mL^{-1}, and 6.250 μg mL^{-1} concentrations.

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

The results obtained from antimicrobial susceptibility testing are depicted in **Table 6b**.

Table-6b: Antimicrobial activity of 3-(6-Fluorochroman-2-yl)-6-aryl-[1,2,4] triazolo [3,4-b][1,3,4]thiadiazoles.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
6a	100	62.5	250	250	1000	>1000	>1000
6b	250	250	250	200	>1000	>1000	>1000
6c	125	100	250	100	>1000	>1000	>1000
6d	200	200	100	200	1000	>1000	>1000
6e	62.5	125	62.5	100	500	1000	1000
6f	125	200	100	125	>1000	250	500
6g	500	500	250	200	500	1000	1000
6h	500	250	200	100	>1000	>1000	>1000
6i	500	500	100	100	1000	250	250
6j	250	500	250	250	500	500	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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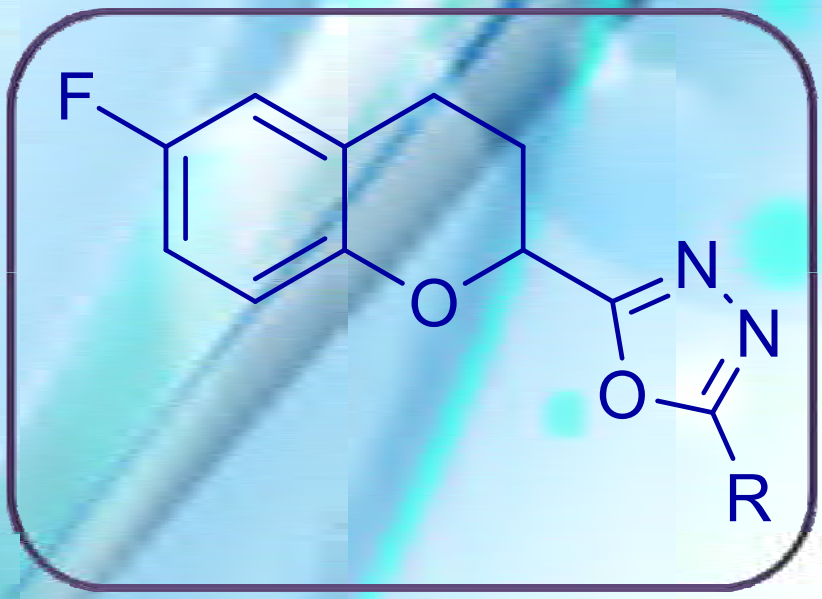
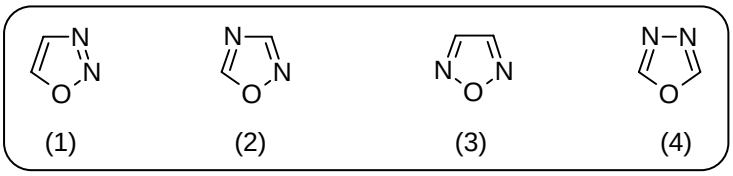
PART-II

STUDIES ON 1,3,4-OXADIAZOLE DERIVATIVES.



INTRODUCTION

Oxadiazoles belong to an important group of heterocyclic compounds having –N=C-O- linkage. It is well documented that oxadiazole system contains the following members which are numbered by designating the hetero atoms at particular position.

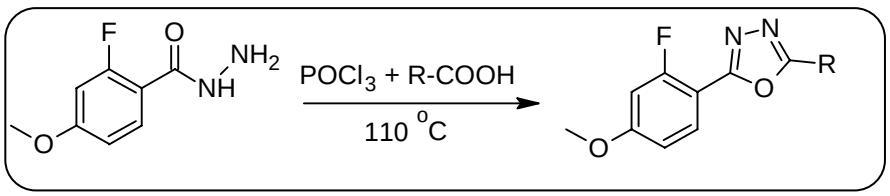


1,3,4-Oxadiazole is a heterocyclic molecule with oxygen atom at 1 and two nitrogen atoms at 3 and 4 position. 1,3,4-Oxadiazole is a thermally stable aromatic molecule.[1] They have been known for about 80 years it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas viz. drug synthesis, dye stuff industry, heat resistant materials, heat resistant polymers and scintillators. Reviews of the relevant literature prior to 1965 are available.[2]

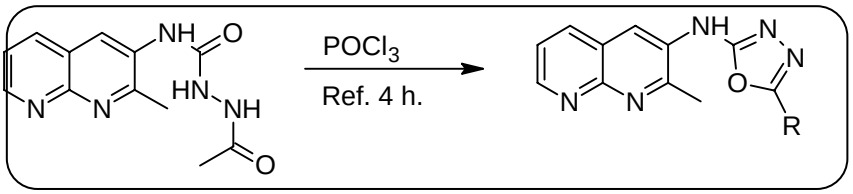
SYNTHETIC ASPECT

Most 1,3,4-oxadiazoles are best obtained by synthesis from acyclic precursors. Such reactions are 'one bond' or 'two bond' cyclization. Different methods for the synthesis have been cited in literature.[3-8]

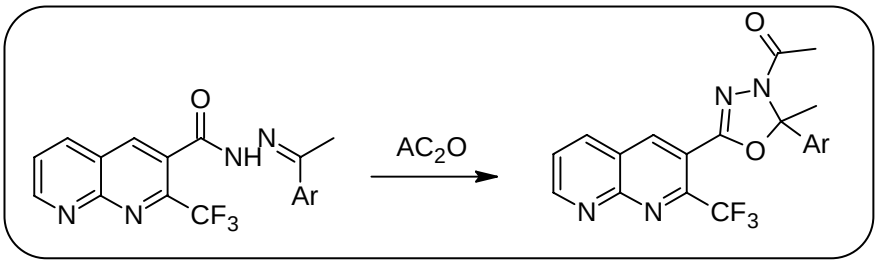
1. B. Chandrakantha et al.[9] have synthesized oxadiazoles by the reaction of hydrazide and aromatic acid in presence of $POCl_3$.



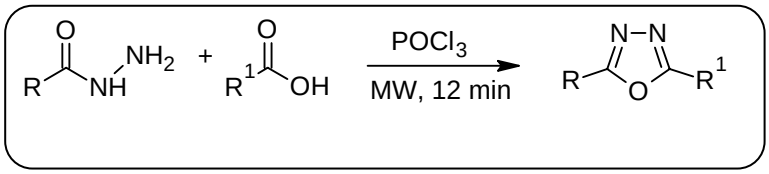
2. D. Ramesh and B. Sreenivasan[10] have synthesized 1,3,4-oxadiazoles from semicarbazide in presense of $POCl_3$.



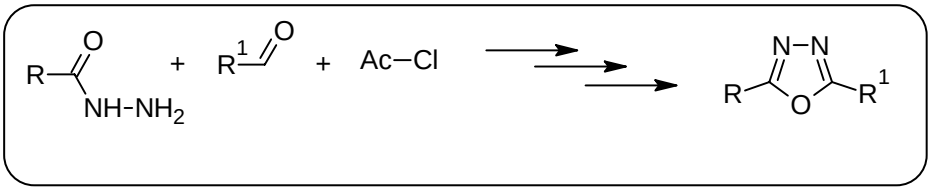
3. K. Mogilaiah and B. Sakram[11] have prepared 1,3,4-oxadiazoles from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.



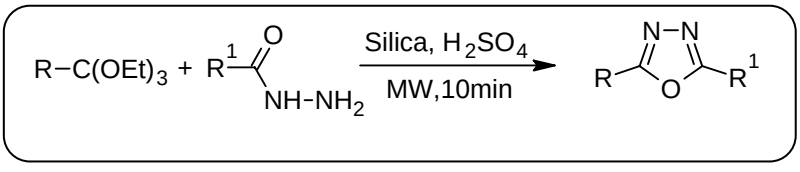
4. Yu Yuve have reported microwave-assisted synthesis protocol of oxadiazoles with 91 % of the yield.[12]



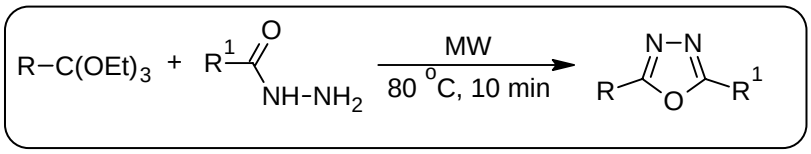
5. L. Somogyi[13] have been synthesized 1,3,4-oxadiazoles from several steps, from aryl hydrazides and aryl aldehydes.



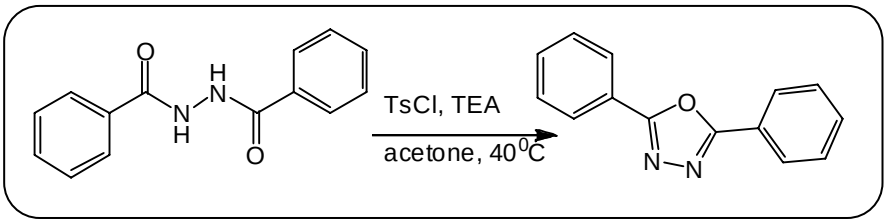
6. Silica sulfuric acid catalyst used for the rapid and ecofriendly synthesis of 1,3,4-oxadiazoles at ambient temperature reported by M. Dabiri et al.[14]



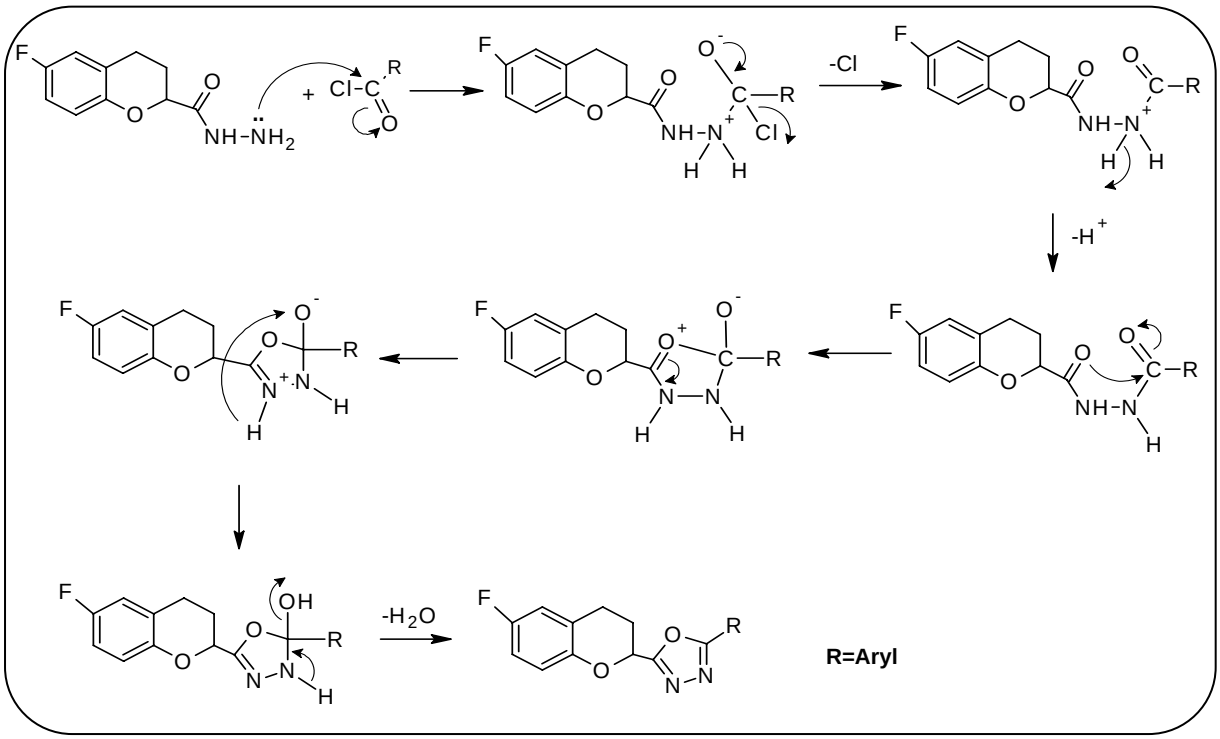
7. Green chemistry and one-pot, solvent-free using microwave mediated synthesis of 1,3,4-oxadiazoles were reported by V. Polshettiwar.[15]



8. A mild, general, convenient, and efficient one-pot synthesis of 2-phenyl-5-substituted-1,3,4-oxadiazoles were reported by P. Stabile.[16]



REACTION MECHANISM



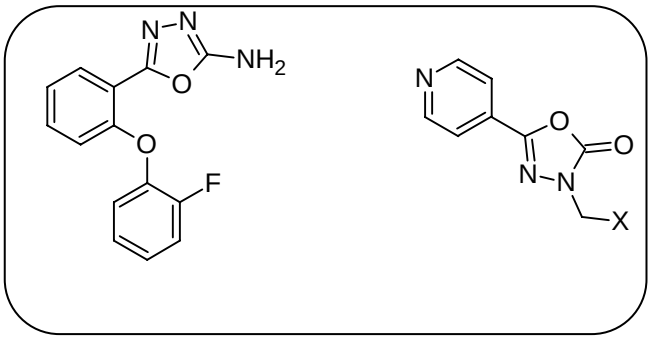
THERAPEUTIC IMPORTANCE

2,5-Disubstituted-1,3,4-oxadiazole derivatives have been tested for various pharmacological activities, which have been summarized as under.

1. Antibacterial[17]
2. Antiinflammatory[18]
3. Analgesic[19]
4. Antiviral and anticancer[20]
5. Antihypertensive[21]
6. Anticonvulsant[22]
7. Antiproliferative[23]
8. Antifungal[24]
9. Cardiovacular[25]
10. Herbicidal[26]
11. Hypoglycemic[27]
12. Hypnotic and Sedative[28]
13. MAO inhibitor[29]
14. Insecticidal[30]

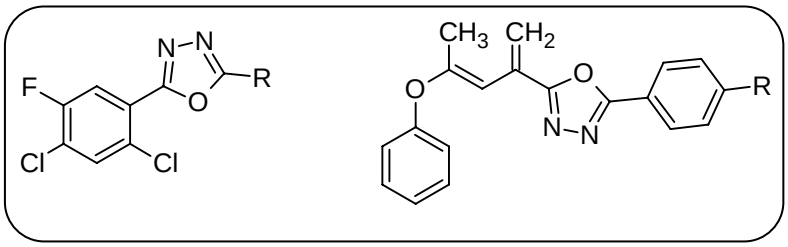
S. R. Bishnoi et al.[31] have screened oxadiazoles for their antimicrobial activity. A. El-Azzouny et al.[32] have synthesized 1,3,4-oxadiazole derivatives and evaluated for their analgesic, anti-inflammatory, ulcerogenic effects and inhibitory activity on plasma prostaglandin E_2 (PGE_2) Level.

S. V. Bhandari et al.[33] have reported 1,3,4-oxadiazoles for their anti-inflammatory activity. Song Cao et al.[34] have investigated some oxadiazoles possessing insecticidal activity. G. V. Suresh Kumar et al.[35] have discovered oxadiazole derivatives and reported their antimycobacterial activity. Ali Almasired et al.[36] have prepared 1,3,4-oxadiazoles of type as anticonvulsant agent. Meria Grazia Mamolo et al.[37] have synthesized 3-substituted-5-(pyridine-4-yl)-3*H*-1,3,4-oxadiazole-2-ones of type and studied their antimycobacterial activity.

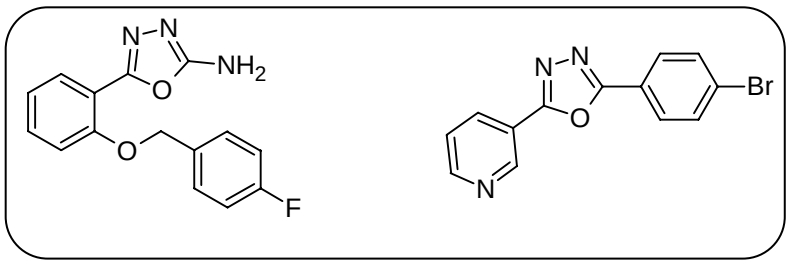


Krishna Kant Jha et al.[38] have reported antimicrobial activity of oxadiazole derivatives. J. A. Christopher et al.[39] have documented human immunodeficiency virus

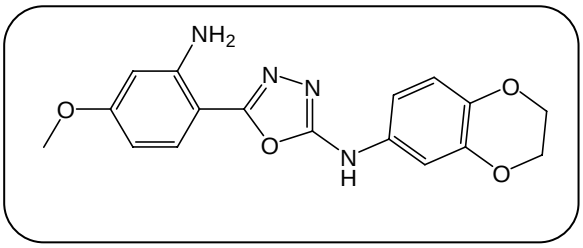
(HIV) infection of 1,3,4-oxadiazole derivatives. S. J. Gilani et al.[40] have synthesized some oxadiazoles as anti-inflammatory and analgesic agents. K. Subrahmanya Bhat et al.[41] have prepared new fluorine containing 1,3,4-oxadiazoles and reported them as potential antibacterial and anticancer agents. T. P. Mohan et al.[42] have synthesized 2,5-disubstituted-1,3,4-oxadiazole derivatives and screened for their insecticidal activity.



Ronald Kim et al.[43] have discovered oxadiazole derivatives useful as protease inhibitors. Mohd Amir and Kumar Shikha[44] have documented anti-inflammatory, analgesic and ulcerogenic activity of some newly synthesized oxadiazoles. A. Ali et al.[45] have investigated some oxadiazole derivatives possessing antimicrobial and anti-HIV-1 activity. A. Sherif et al.[46] have reported oxadiazoles as potential antitumor and anti-HIV agents. A. Zarghi et al.[47] have synthesized R-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles possessing anticonvulsant activity. M. Tareq et al.[48] have synthesized 2,5-disubstituted-1,3,4-oxadiazoles useful as tyrosinase inhibitors.



Kiselyov et al.[49] have synthesized novel derivatives of 1,3,4-oxadiazoles as potent mitostatic agents featuring strong microtubule depolymerizing activity in the sea urchin embryo and cell culture assays.



Work done from our laboratory

K. M. Thaker[50] have synthesized 2-(3',5'-dichlorobenzo[*b*]thiophen-2'-yl)-5-aryl-1,3,4-oxadiazoles in the presence of aromatic acid. S. L. Vasoya[51] reported facile synthesis of some new acetyl oxadiazoles bearing benzo[*b*]thiophene nucleus as a potent biological active agent. Preparation and antimicrobial activity of 2-aryl-5-(5',7'-diiodo-8'-quinolinoxy)-1,3,4-oxadiazoles have been reported by H. S. Joshi.[52]

Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological screening, we have under taken the synthesis of several oxadiazoles which has been described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-(6-FLUOROCHROMAN-2-YL)-5-ARYL-1,3,4-OXADIAZOLES.

Part – B

[Part – II (Section-i)]

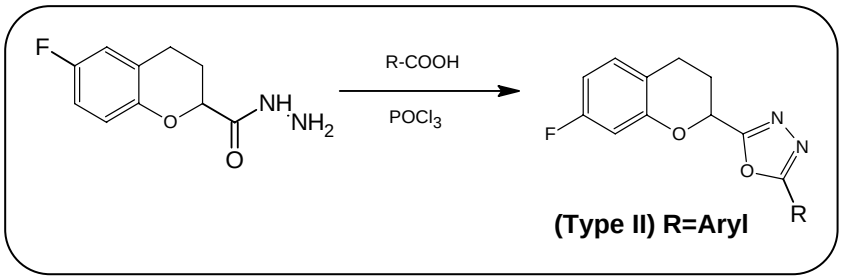
Synthesis and biological evaluation of 2-(6-fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-(6-FLUORO-CHROMAN-2-YL)-5-ARYL-1,3,4-OXADIAZOLES.

Synthesis of 1,3,4-oxadiazole derivatives has attracted considerable attention in view of therapeutic applications. Looking to this, the synthesis of 1,3,4-oxadiazoles was undertaken by the condensation of different aromatic acid with 6-fluorochroman-2-carbohydrazide in presence of phosphorous oxychloride, as shown in reaction scheme.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ solution on a Bruker AC 400 MHz and 100 MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Synthesis of 6-Fluorochroman-2-carbohydrazide.

See PART-B, part-I, section-I [B].

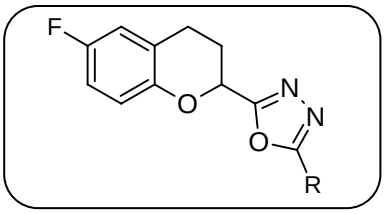
[B] General procedure for the preparation of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

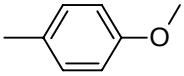
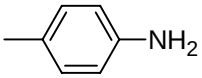
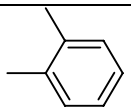
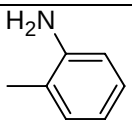
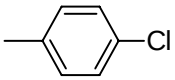
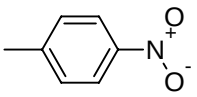
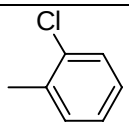
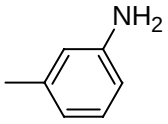
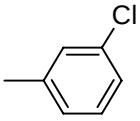
A mixture of 6-fluorochroman-2-carbohydrazide (2.0 g, 0.01mol) and different aryl acids (0.01mol) in phosphorous oxychloride (10 ml) was refluxed with continuous stirring. After completion of the reaction (13-15 hours monitoring by TLC), the content was cooled to room temperature then add ice cooled water and neutralized with sodium bicarbonate solution. Then the mixture was by extracted into ethyl acetate. The organic extracts was washed with water (2 x 10 ml), dried with Na_2SO_4, solvent was removed *in vacuo* and the resulting crude product was purified by column chromatography to give the analytical pure compound. The physical constants of the products are recorded in **Table-7a.**

[C] Biological evaluation of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

Antimicrobial testing was carried out as described in Part-B, Part-II, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-7b**.

Table-7a: Physical constant of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.



Sr. No	Substitution R	M. F.	M. W.	Yield (%)	R_f value
7a		$C_{18}H_{15}FN_2O_3$	326.32	94	0.47
7b		$C_{18}H_{15}FN_2O_2$	310.32	88	0.39
7c		$C_{17}H_{14}FN_3O_2$	311.31	77	0.52
7d		$C_{18}H_{15}FN_2O_2$	310.32	91	0.42
7e		$C_{17}H_{14}FN_3O_2$	311.31	89	0.50
7f		$C_{17}H_{12}ClFN_2O_2$	330.74	72	0.59
7g		$C_{17}H_{12}FN_3O_4$	341.29	76	0.41
7h		$C_{17}H_{12}ClFN_2O_2$	330.74	78	0.38
7i		$C_{17}H_{14}FN_3O_2$	311.31	83	0.67
7j		$C_{17}H_{12}ClFN_2O_2$	330.74	79	0.62

TLC solvent system:- E.A. : Hexane = 7 : 3

ANALYTICAL DATA

2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a). mp 140-142 °C; IR (DRS): 3028, 2974, 2943, 2841, 1616, 1558, 1425, 1303, 1259, 1174,1080,1024, 873, 819, 798, 736, 636, 570 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.42-2.51(m, 2H, 2CH), 2.96-2.99(t, 2H, 2CH), 3.88(s, 3H, OCH_3), 5.39-5.42(d,d, *J*=3.76 Hz, 3.68 Hz, 1H, CH), 6.79-6.87(m, 3H, ArH), 6.99-7.01(d, *J*=8.8 Hz, 2H, ArH), 7.99-8.01(d, *J*=8.76 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 23.59, 24.86, 44.20, 55.49, 68.80, 114.34, 114.50, 114.57, 115.36, 115.58, 116.06, 117.96, 118.04, 122.35, 122.43, 128.90, 149.31, 149.33,156.08, 158.46, 162.53, 164.06, 165.46; MS: *m/z* = 326 $[M]^+$; Anal. Calcd for $C_{18}H_{15}FN_2O_3$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.10; H, 4.56; N, 8.30%.

2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)- 1,3,4-oxadiazole (7b). mp 110-112°C; IR (DRS): 3036(Ar, C-H str.), 2955(C-H str.), 2922(C-H str.), 2852(C-H str.), 1616(Ar, C=C str.), 1570(Ar, C=C str.), 1496(Ar, C=C str.), 1390(C-H ben), 1263(C-H ben), 1178(C-F str.), 1139(C-F str.), 1080(C-N str.), 1016(C-O-C str.), 821(C-H o,p, ben), 767(C-H o,p, ben), 729(C-H o,p, ben), 700(C-C o,p, ben), 561(C-C o,p, ben) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 2.35-2.44(m, 5H, 2CH, 3CH), 2.88-2.91(t, 2H, 2CH), 5.32-5.35(d,d, *J*=3.76 Hz, 3.72 Hz, 1H, CH), 6.72-6.80(m, 3H, ArH), 7.22-7.24(d, *J*=7.96 Hz, 2H, ArH), 7.86-7.88(d, *J*= 8.08 Hz, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.15, 21.68, 22.71, 23.58, 24.87, 29.38, 29.68, 29.72, 31.95, 44.20, 68.80, 114.34, 114.58, 115.36, 115.58, 117.97, 118.05, 120.80, 122.34, 122.42, 127.07, 129.79, 142.61, 149.29, 149.31, 156.09, 158.46, 164.30, 165.66; MS: *m/z* = 310 $[M]^+$; Anal. Calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.18; H, 4.80; N, 8.93%.

4-(5-(6-Fluorochroman-2-yl)-1,3,4-oxadiazol-2-yl)aniline (7c). mp 138-140 °C; IR (DRS): 3452, 3403, 3030, 2964, 2853, 1642, 1612, 1581, 1471, 1378, 1245, 1156, 1077, 1025, 878, 819, 788, 721, 698, 558 cm^{-1}; MS: *m/z* = 311 $[M]^+$; Anal. Calcd for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.57; H, 4.29; N, 13.44%.

2-(6-Fluorochroman-2-yl)-5-(*O*-tolyl)-1,3,4-oxadiazole (7d). mp 114-116 °C; IR (DRS): 3074, 2987, 2851, 1645, 1612, 1585, 1468, 1325, 1281, 1184, 1077, 1034,820, 745, 696, 545 cm^{-1}; MS: *m/z* = 310 $[M]^+$; Anal. Calcd for $C_{18}H_{15}FN_2O_2$: C, 69.67; H, 4.87; N, 9.03. Found: C, 69.28; H, 4.83; N, 8.98%.

2-(5-(6-Fluorochroman-2-yl)-1,3,4-oxadiazol-2-yl)aniline (7e). mp 161-163 °C; IR (DRS): 3419, 3371, 3081, 2975, 2844, 1641, 1579, 1556, 1464, 1362, 1232, 1176, 1060, 1004, 810, 756, 592 cm^{-1}; MS: *m/z* = 311 $[M]^+$; Anal. Calcd for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.41; H, 4.45; N, 13.39%.

2-(4-Chlorophenyl)-5-(6-fluorochroman-2-yl)-1,3,4-oxadiazole (7f). mp 105-107°C; IR (DRS): 3080, 2983, 2867, 1629, 1572, 1525, 1462, 1245, 1196, 1079, 1017, 830 cm^{-1}; MS: *m/z* = 330 $[M]^+$; Anal. Calcd for $C_{17}H_{12}ClFN_2O_2$: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.63; H, 3.58; N, 8.43%.

2-(6-Fluorochroman-2-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (7g). mp 133-135 °C; IR (DRS): 3077, 2978, 2863, 1625, 1609, 1563, 1464, 1384, 1238, 1142, 1058, 1022, 870, 798, 732, 687, 603 cm^{-1}; MS: *m/z* = 341 $[M]^+$; Anal. Calcd $C_{17}H_{12}FN_3O_4$: C, 59.83; H, 3.54; N, 12.31. Found: C, 59.77; H, 3.40; N, 12.21%.

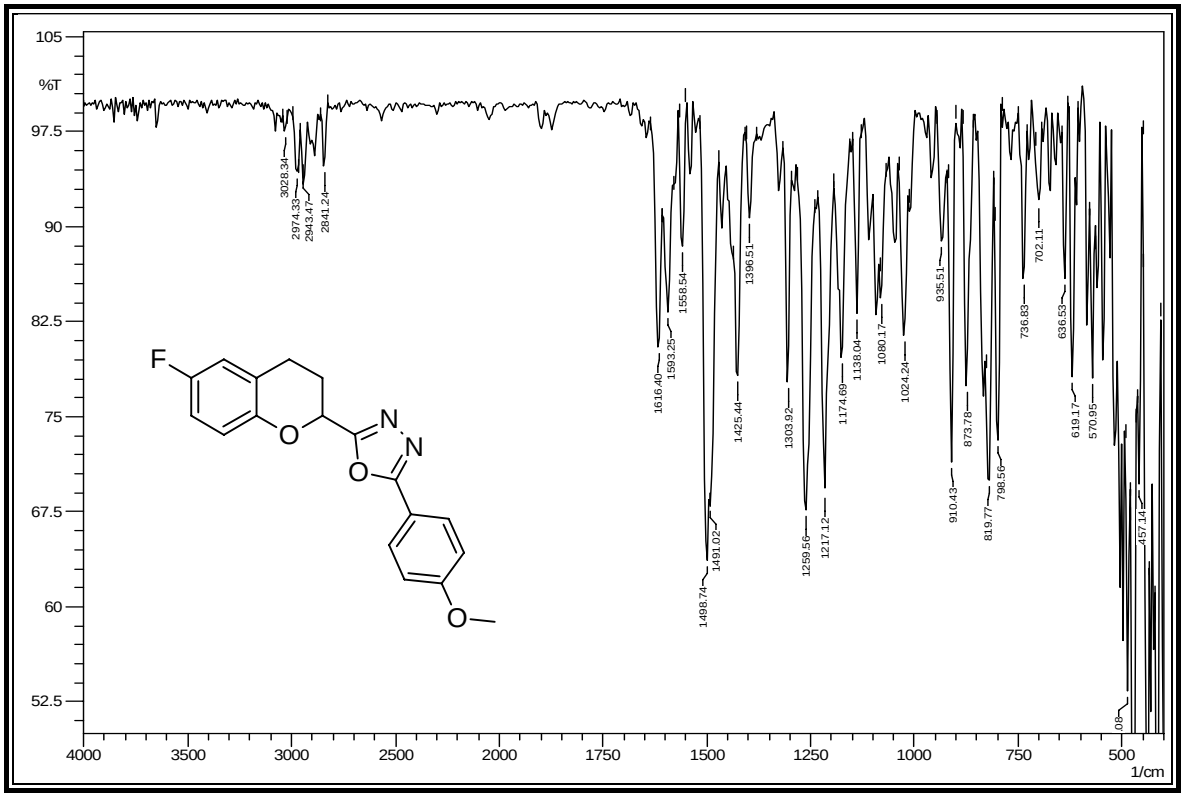
2-(2-Chlorophenyl)-5-(6-fluorochroman-2-yl)-1,3,4- oxadiazole (7h). mp 173-175°C; IR (DRS): 3012, 2962, 2854, 1603, 1545, 1542, 1452, 1345, 1260, 1146, 1082, 1010, 888, 825, 777, 731, 634, 512 cm^{-1}; MS: *m/z* = 330 $[M]^+$; Anal. Calcd for $C_{17}H_{12}ClFN_2O_2$: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.65; H, 3.57; N, 8.34%.

3-(5-(6-Fluorochroman-2-yl)-1,3,4–oxadiazol-2-yl)aniline (7i). mp 169-171°C; IR (DRS): 3443, 3401, 3075, 2964, 2853, 1721, 1601, 1581, 1423, 1392, 1228, 1149, 1054, 1013, 799, 720, 666 cm^{-1}; MS: *m/z* = 311 $[M]^+$; Anal. Calcd for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.25; H, 4.47; N, 13.37%.

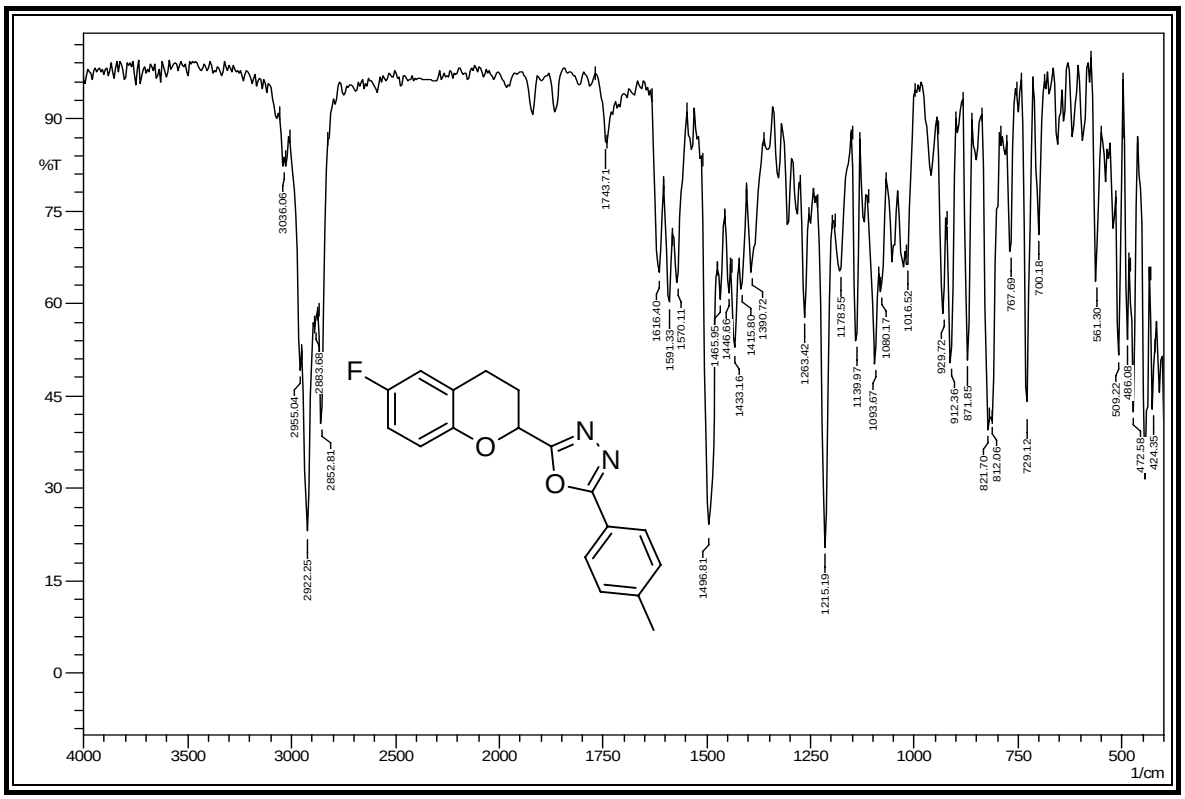
2-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-1,3,4-oxadiazole (7j). mp 181-183°C; IR (DRS): 3061, 2951, 2872, 1689, 1589, 1579, 1462, 1310, 1288, 1175, 1099, 1012, 798, 755, 678 cm^{-1}; MS: *m/z* = 330 $[M]^+$; Anal. Calcd for $C_{17}H_{12}ClFN_2O_2$: C, 61.73; H, 3.66; N, 8.47. Found: C, 61.08; H, 3.61; N, 8.41%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

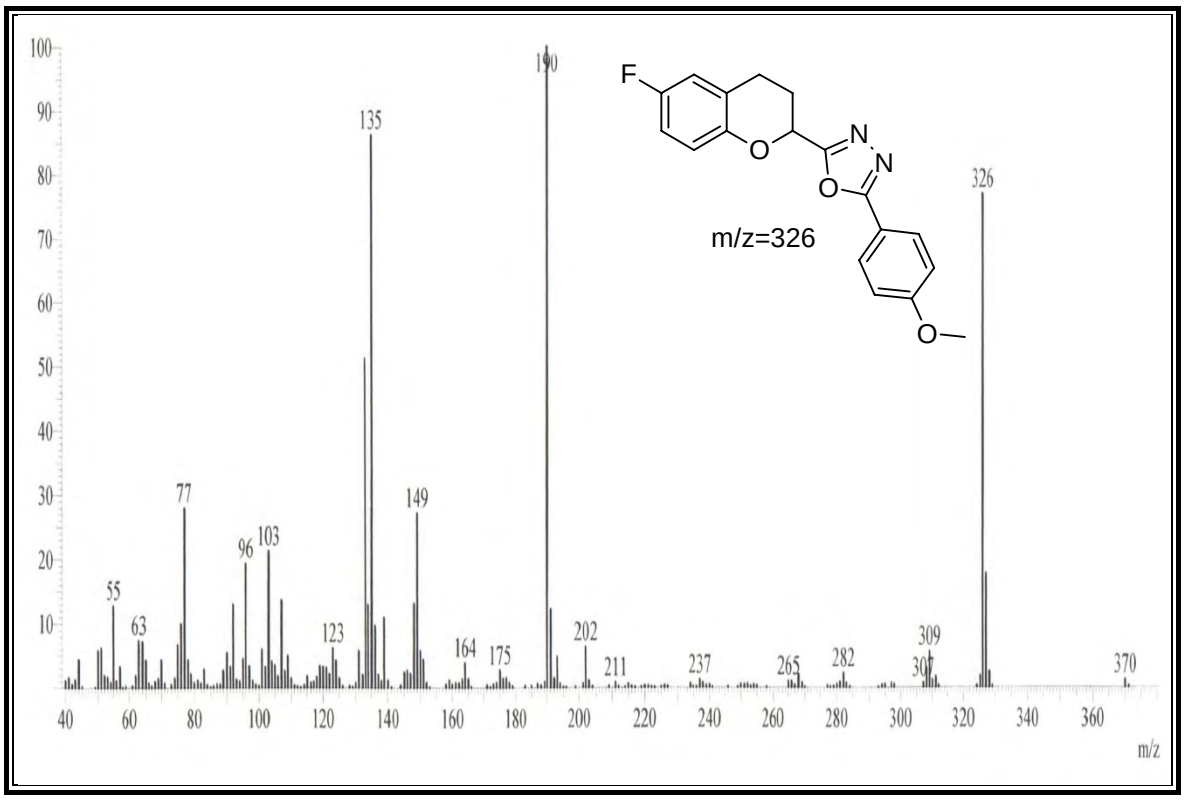
IR Spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a).



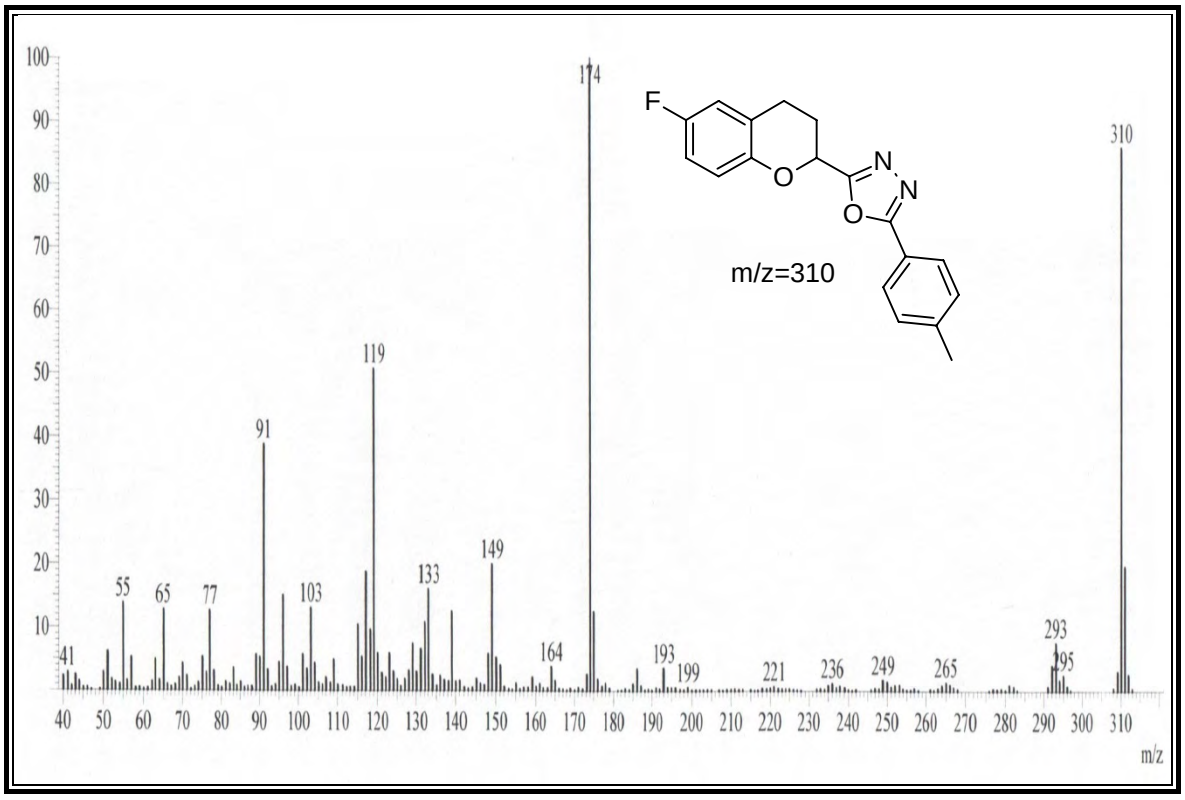
IR Spectrum of 2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)-1,3,4-oxadiazole(7b).



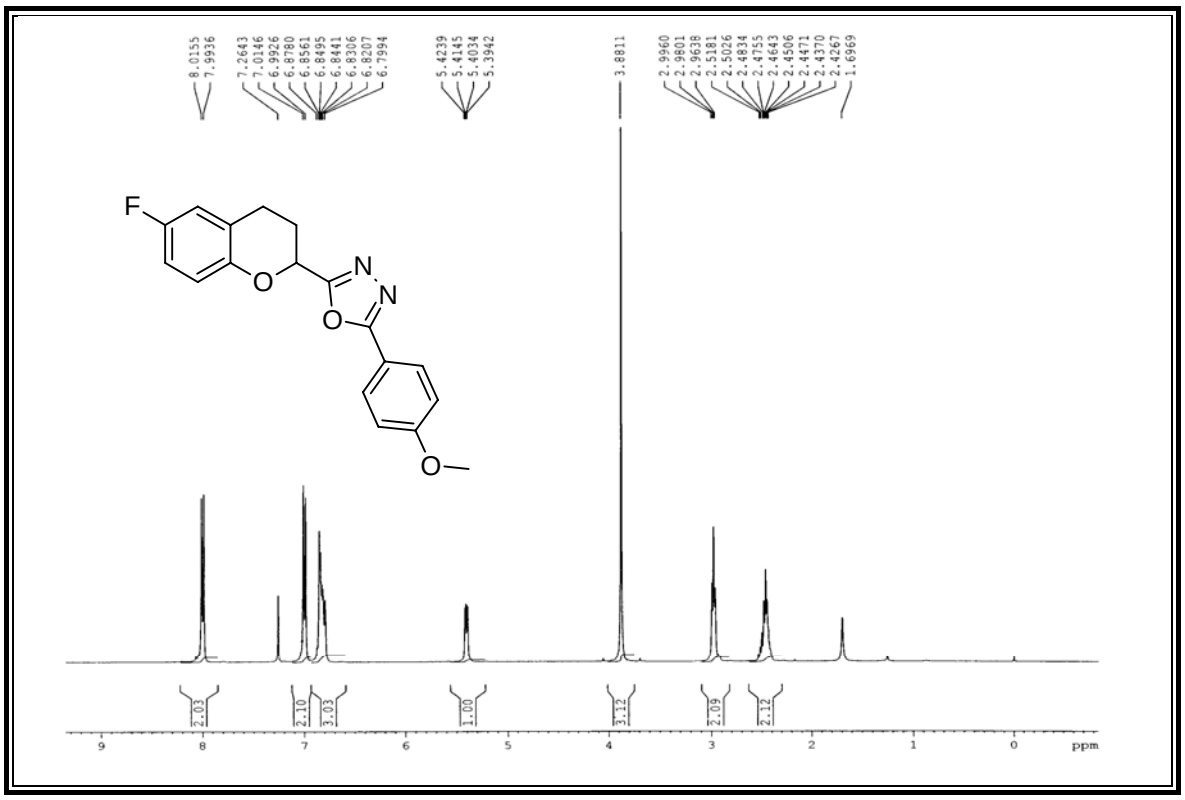
Mass spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (7a).



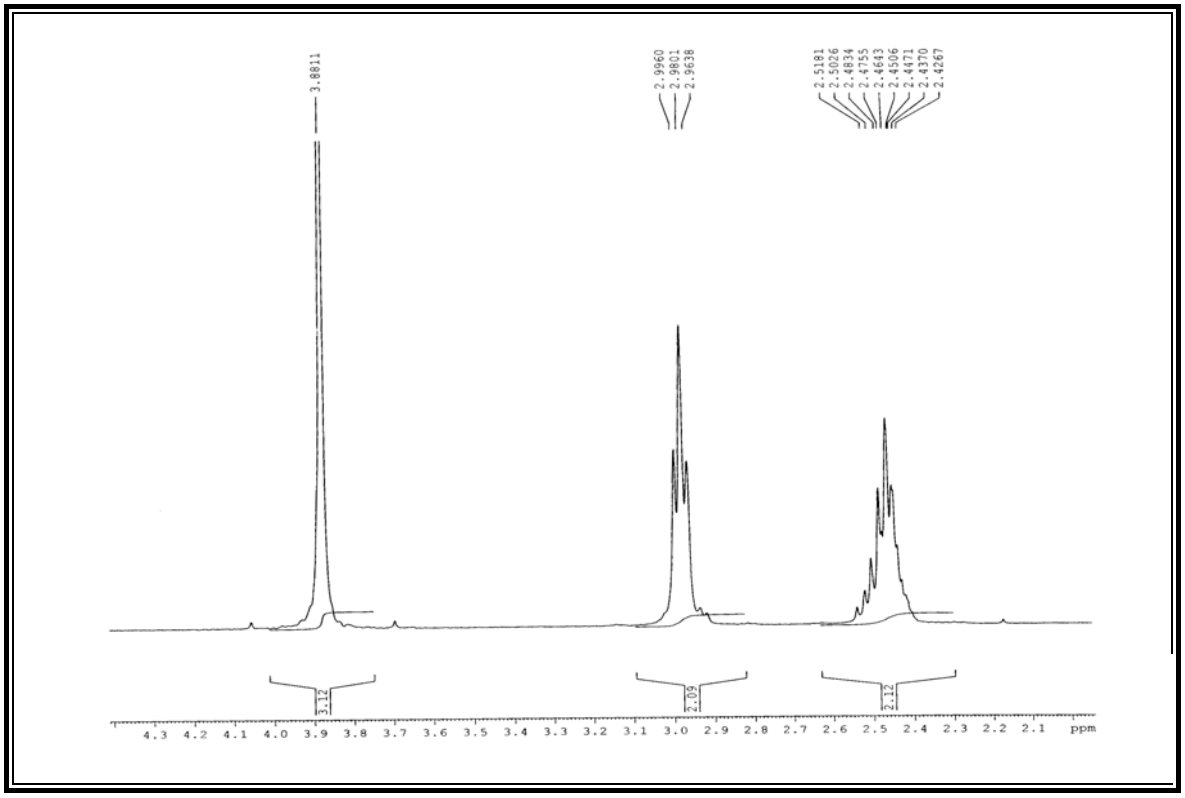
Mass spectrum of 2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)- 1,3,4-oxadiazole (7b).



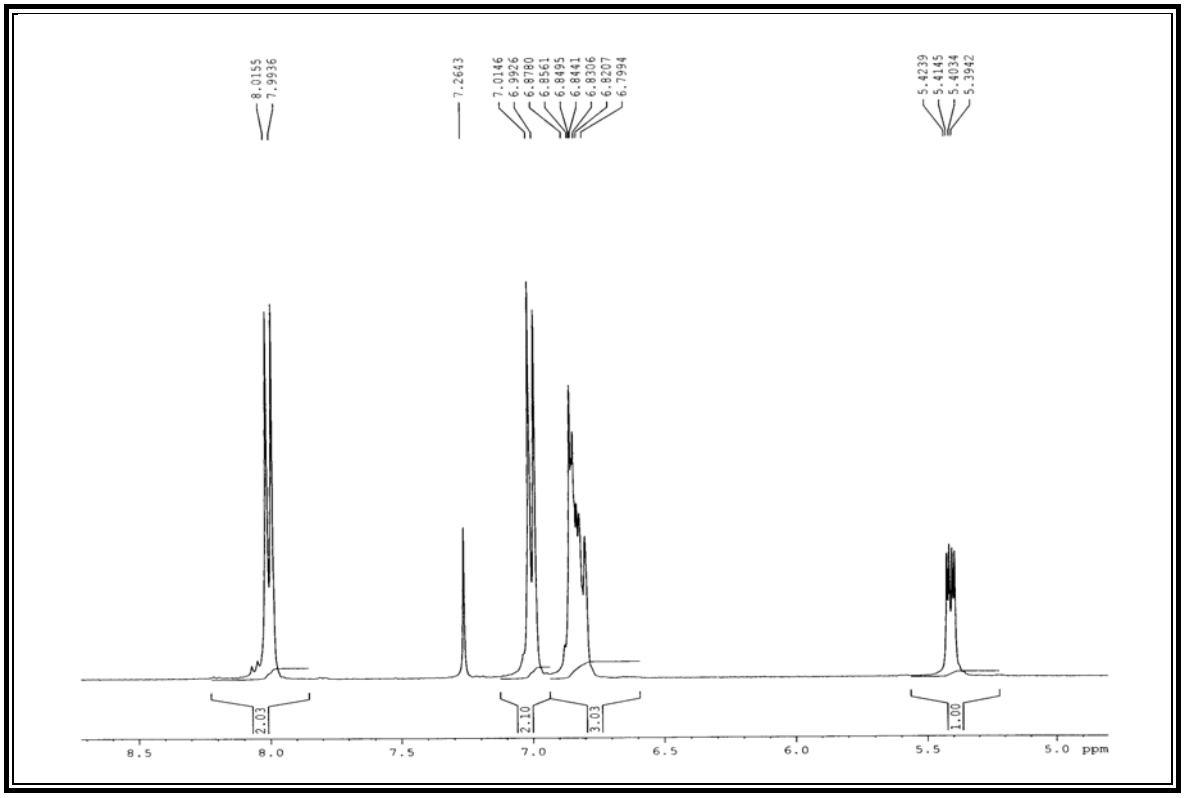
^{1}H NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).



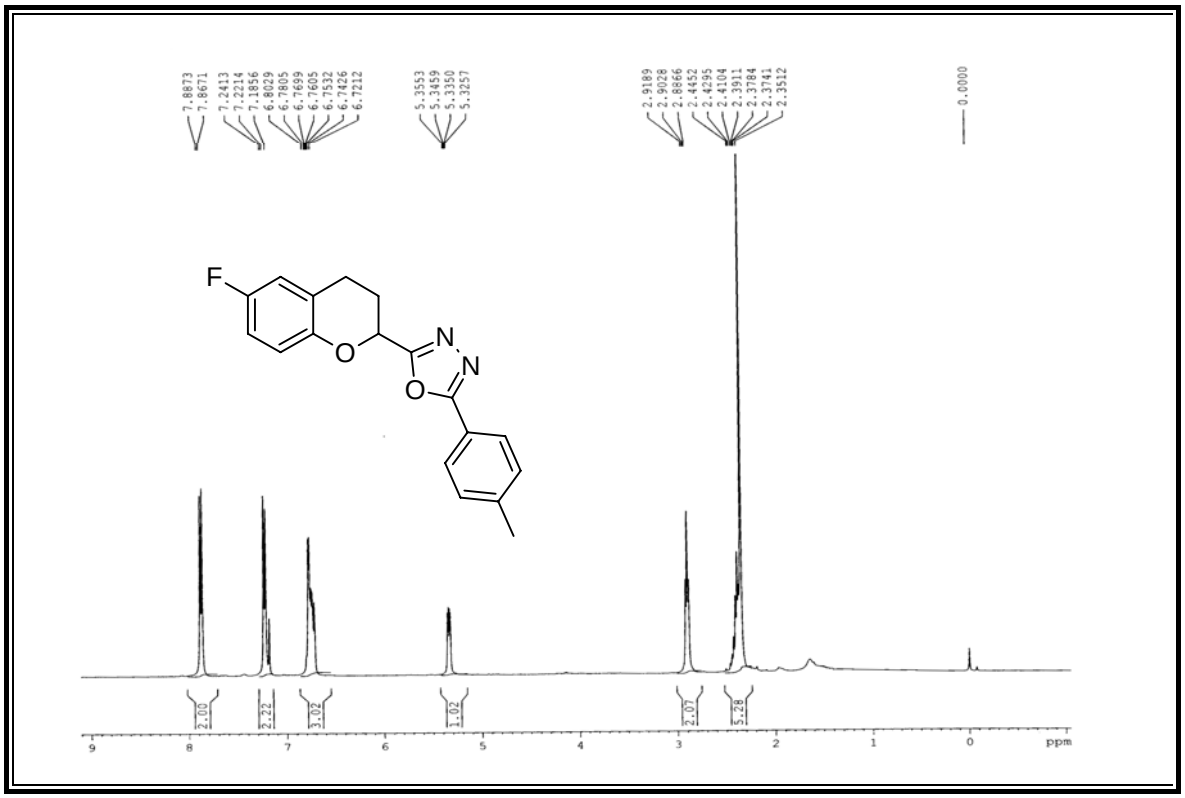
Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).



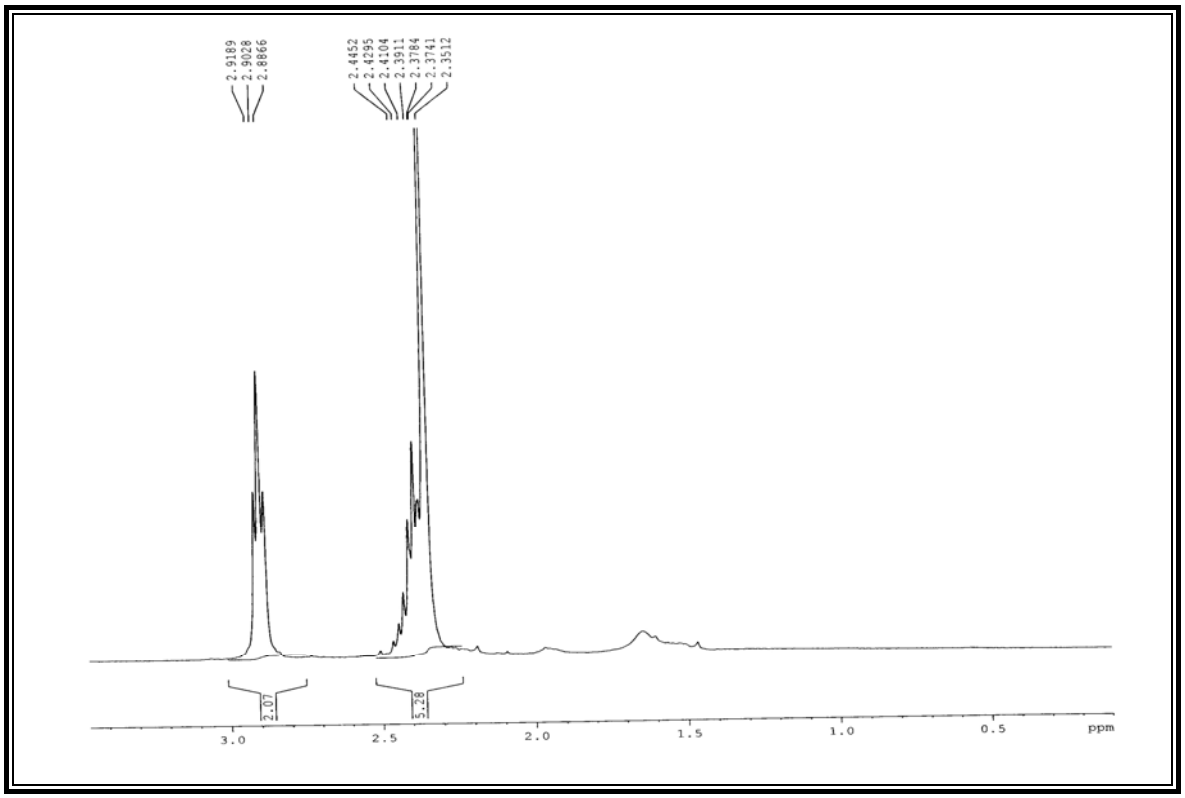
Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).



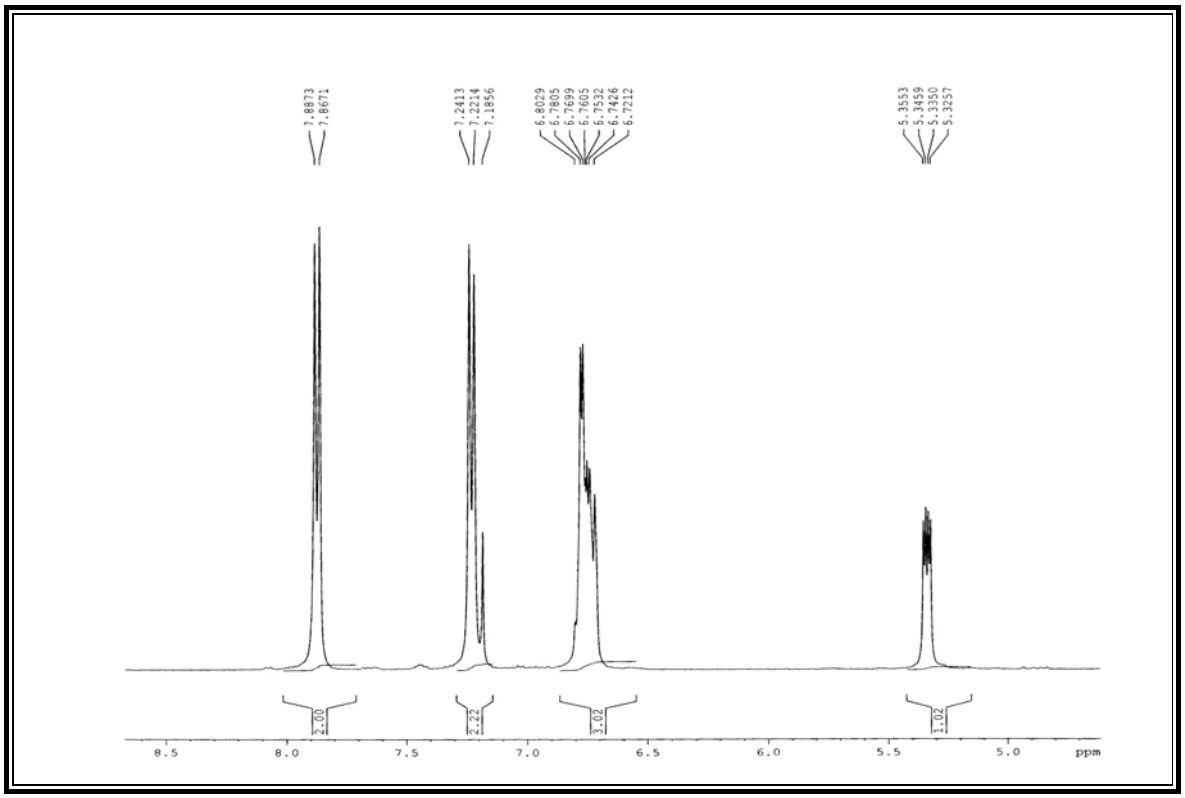
^{1}H NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)- 1,3,4-oxadiazole (7b).



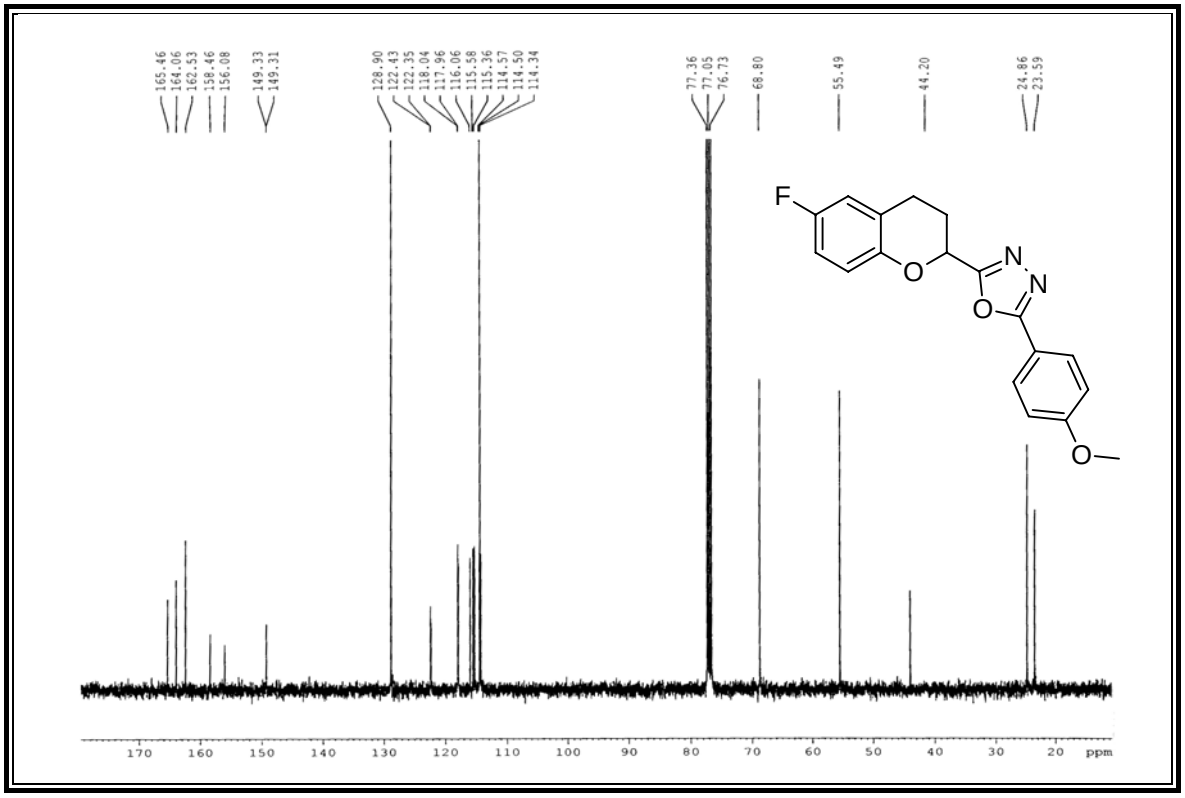
Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)- 1,3,4-oxadiazole (7b).



Expanded spectrum of 2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)- 1,3,4-oxadiazole (7b).



^{13}C NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(7a).



^{13}C NMR spectrum of 2-(6-Fluorochroman-2-yl)-5-(*p*-tolyl)- 1,3,4-oxadiazole (7b).

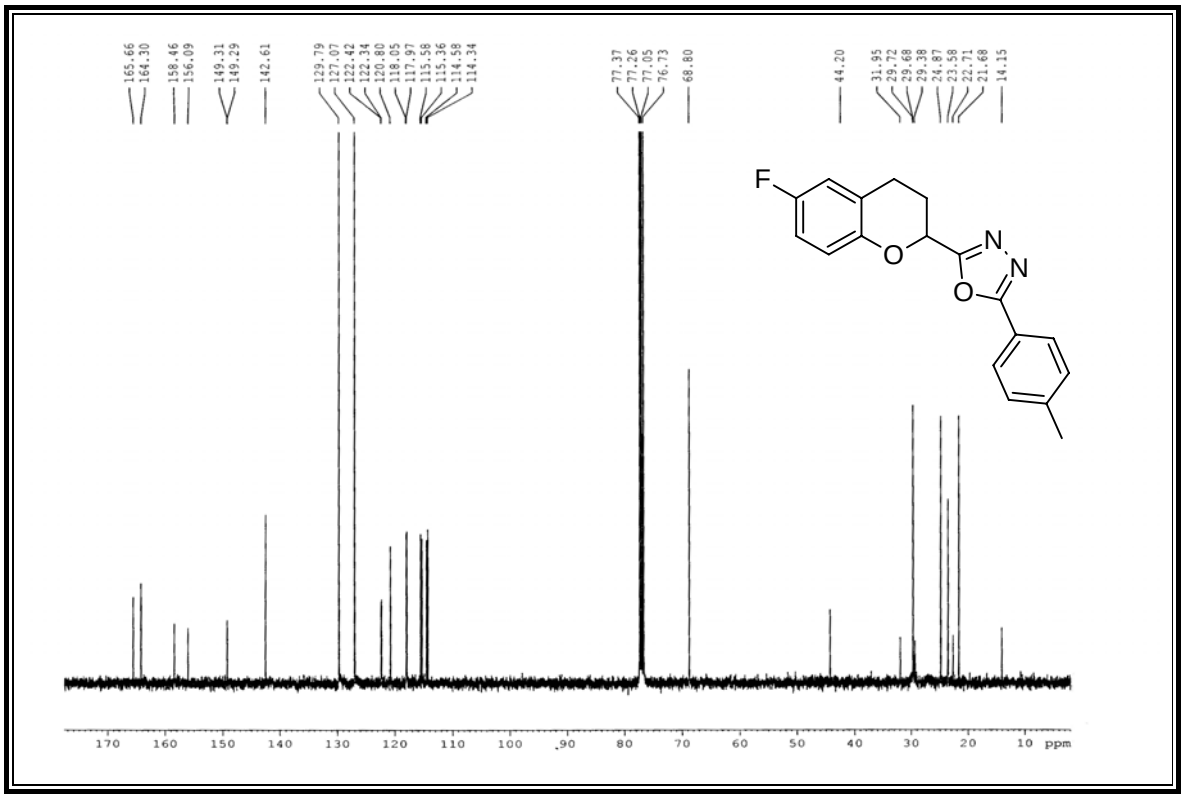


Table-7b: Antimicrobial activity of 2-(6-Fluorochroman-2-yl)-5-aryl-1,3,4-oxadiazoles.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration μg/ml				Minimal fungicidal concentration μg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
7a	500	250	62.5	125	500	500	1000
7b	200	250	125	100	>1000	500	500
7c	250	500	200	62.5	>1000	250	500
7d	125	250	100	200	500	1000	>1000
7e	250	250	250	250	250	500	500
7f	200	125	200	100	1000	>1000	>1000
7g	500	250	100	100	500	>1000	>1000
7h	125	125	200	125	1000	>1000	>1000
7i	100	100	125	200	1000	>1000	>1000
7j	200	200	250	250	>1000	500	500

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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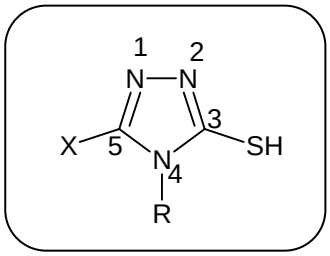
INTRODUCTION

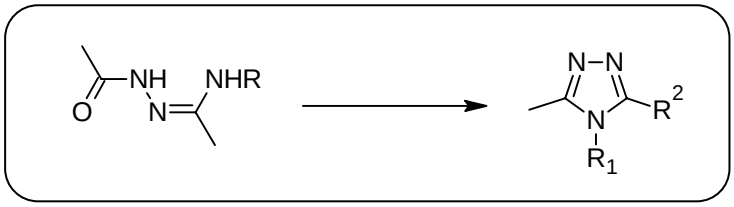
1,2,4-Triazoles have proved to be most useful framework for biological activities among nitrogen containing five membered heterocycles. In five membered heterocyclic ring system 4-aryl triazole (I) have three nitrogen atoms at 1,2 and 4 positions, an aryl group at 4-position and free mercapto group at 3-position.



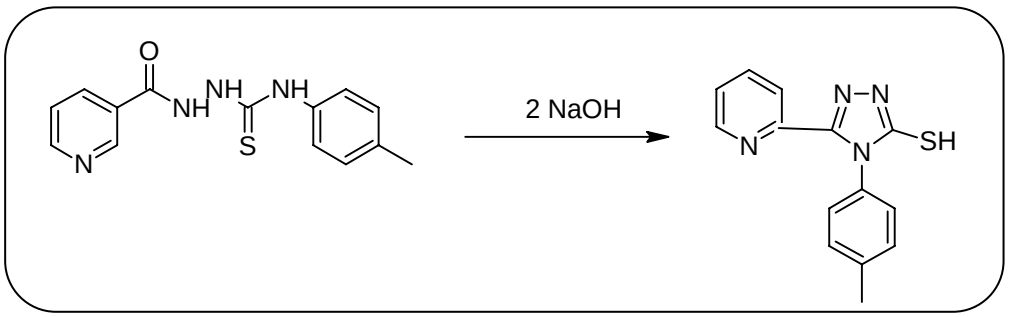
SYNTHETIC ASPECT

Several methods have been reported in the literature for the preparation of 4-aryl triazoles.

1. A.R.Katritzky et al.[1] have synthesized 4- aryltriazoles by the cyclization of semicarbazide.

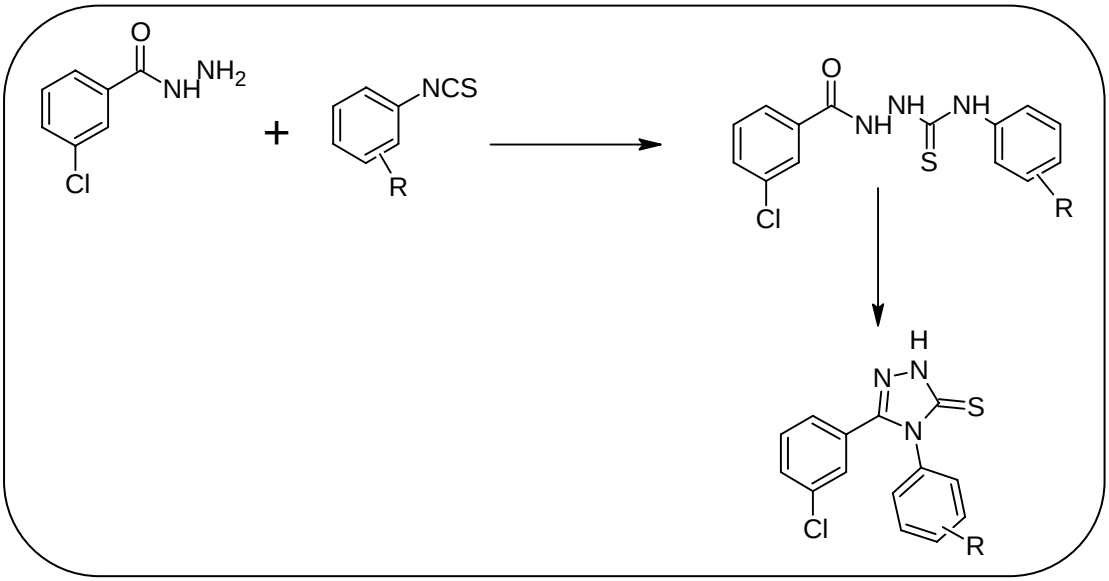


2. K. Zamani et al.[2] synthesized 4-aryltriazole from thiosemicarbazide by ring closure reaction with 2N NaOH.

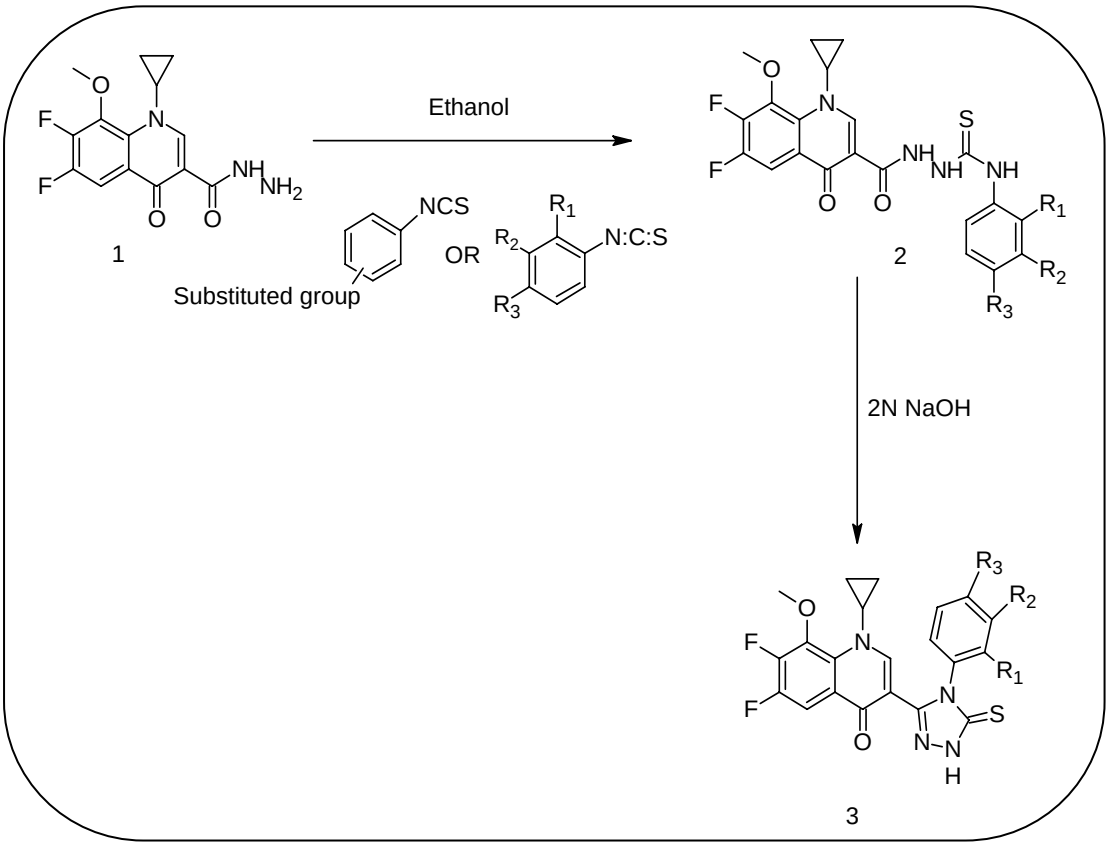


3. T. Plech et al.[3] have synthesized s-triazoles by the reaction of 3- chlorobenzoic acid hydrazide, arylisothiocyanates and 1-[(3- chrophenyl) carbonyl]-4-sustituted thisemicarbazides. The reaction was complete in short time. Which on alkaline

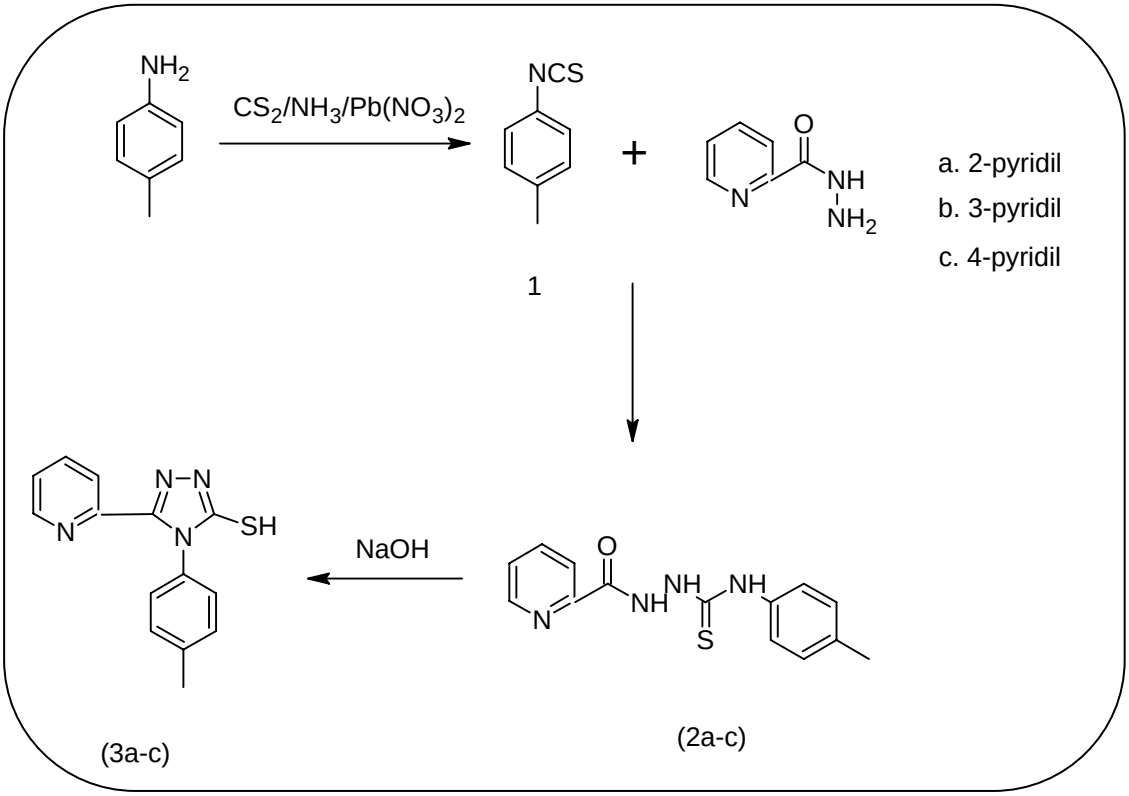
cyclization with 2% solution of soduim hydroxide afforded the corresponding 5-(3- chrophenyl)-4- substituted-2,4- dihydro-3H-1,2,4-triazole-3-thiones.



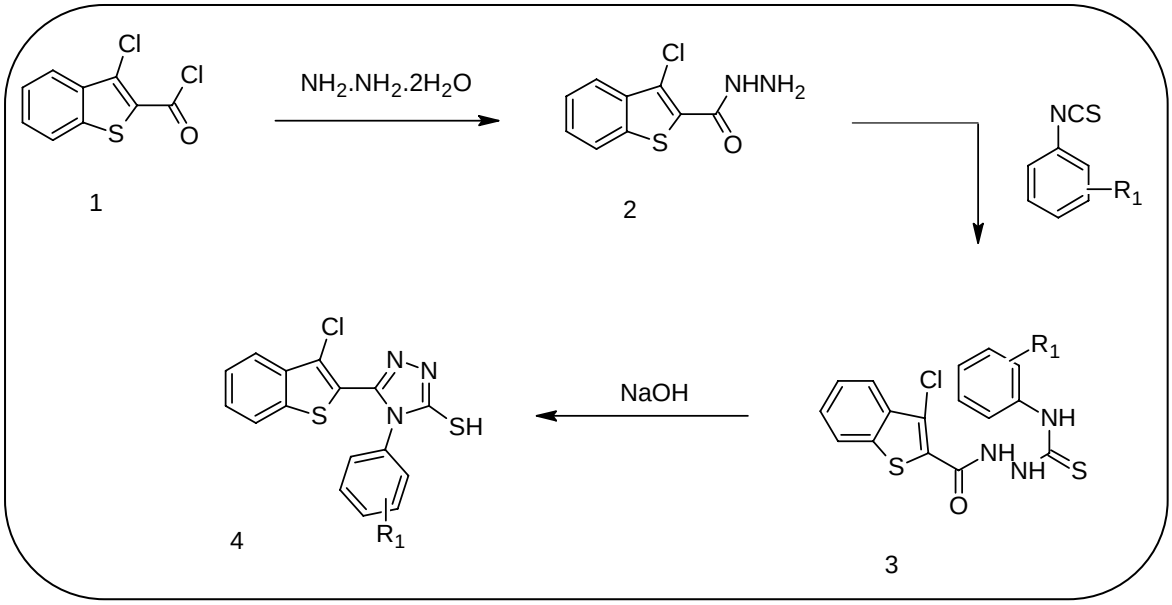
4. S.Shelke et al.[4] have synthesized some novel azoles as antimicrobial agents.Thio-semicarbazides **(2)** have been prepared from acid hydrazide **(1),** and fluorinated aryl isothiocynates. Thiosemicarbazides **(2)** in 1% NaOH to gave compounds **(3).** with 72-88% yield under green technique.



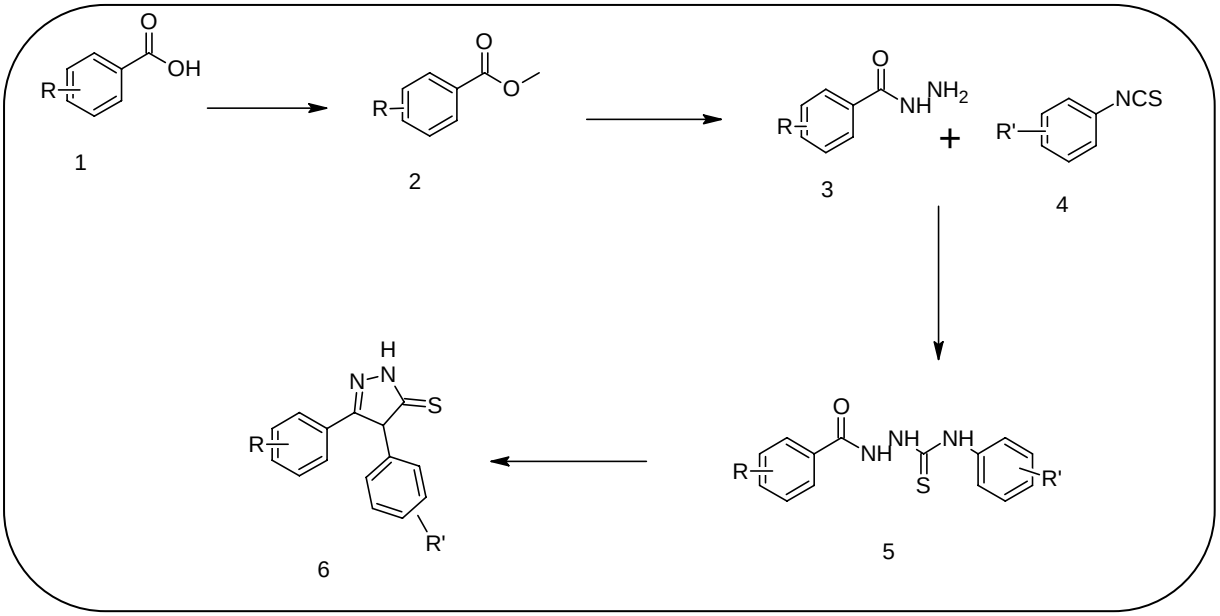
5. R.J.Singh et al.[5] have novel synthesized of some 1,2,4- triazoles as potent bacteriocidal agents with the reaction of 4- methyl phenyl amine, carbon disulphide and ammonia in the methanol as a solvent and leadnitrate as a catalyst and compound **(1)** was obtained.Pyridine carboxylic acid hydrazides**(a-c)** were react with 4-methylphenylisotiocyanate in the presence of ethanol to give compound **(2a-c)** which on reaction with 2M sodium hydroxide solution to give final compounds **(3a-c)** with higer yield (75-85%).



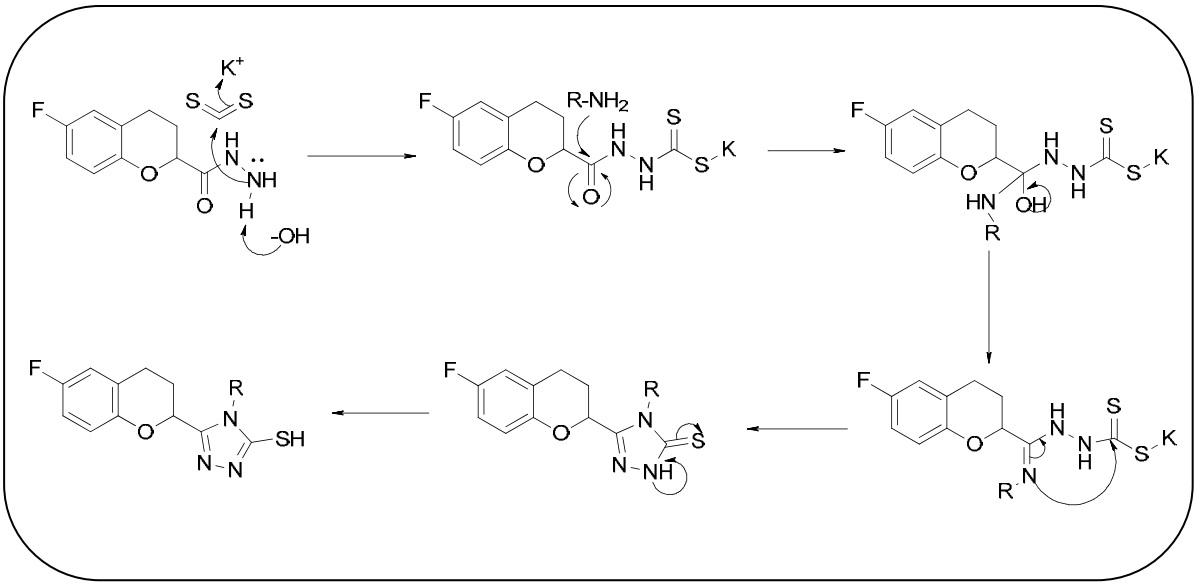
6. G. Naganagowda et al.[6] have been synthesized 5-substituted-4-aryl-3-mercapto-4h-1,2,4-triazoles. The compound **(1)** was treated with hydrazine hydrate to obtaine-3-chloro-1-benzothiophene-2-carbohydrazide**(2)** in good yield.Then condensation of carbo hydrazide **(2)** with aryl isothiocyanates separately afforded thiosemicarbazides (**3)** in good yields. Then the compounds 3a-b upon heating with 4N NaOH in ethanol underwent smooth cyclization through dehydration to form 5-substituted-4-aryl-3-mercapto-4H-1,2,4-triazoles (**4).**



7. I. Khan et al.[7] have been synthesized some new 1,2,4- triazoles with antioxidant activities and urease inhibition.Substituted aromatic esters (2)were synthesized by the reaction of corresponding acids(1) with methanol in the presence of catalyitic amount of sulfuric acid. Esters(2) were converted to the corresponding acid hydrazides(3) by refluxing with hydrazine (80%) and phenylisothiocyanates(4) in methanol and obtained carbothioamides (5). Then compounds (6) were synthesized by intramolecular dehydrative cyclization of carbothioamides(5) when refluxed in 4N NaOH solution , followed by neutralization with concentrated HCl.



REACTION MECHANISM

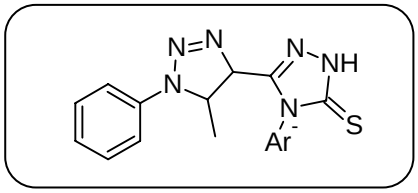


THERAPEUTIC IMPORTANCE

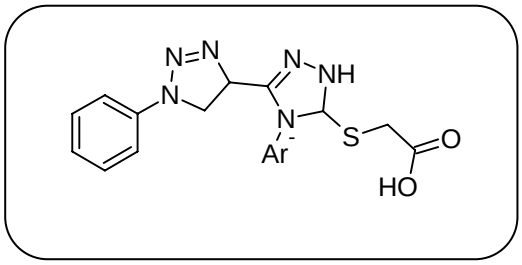
4-Aryltriazoles are reported to exhibit a wide variety of biological activities such as,

1. Antiinflammatory[8]
2. Biocides[9]
3. Cholesteryl ester transfer protein[10]
4. Antidepressant[11]

Chang et al.[12] have synthesized aryltriazoles and reported them as antifungal drugs. O. Crisan et al.[13] have screened antiinflammatory activity of triazoles. A.Varvaresou et al.[14] have synthesized triazoles and reported their antimicrobial potency and antidepressant activities. Papakonstantinou et al.[15] have investigated some triazole derivatives possessing significant antiviral activity. T. Konosu and co-workers[16] have prepared aryltriazoles as fungicides.

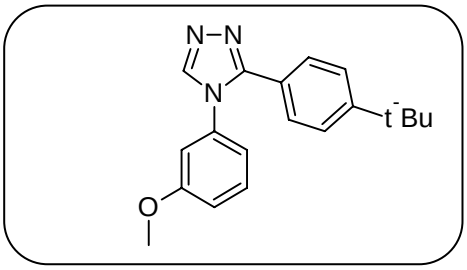


N.Yasuda et al.[17] have discovered aryltriazoles which have been extensively investigated for their antibacterial properties. S.C. Bahel et al.[18] have documented anti- fungal activity of aryl triazoles. Athansia varvaresou et al.[19] have synthesized aryltriazoles possessing antidepressant activity. Chu. Changhu et al.[20] have screened 4-aryltriazoles for their antifungal activity.

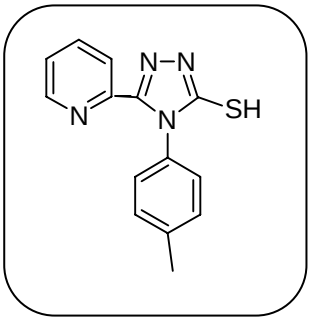


Some aryltriazoles possessing analgesic and diuretic activities have been synthesized by Shrivastava S.K. et al.[21] Wang Sheng et al.[22] have reported triazoles as herbicidal agents.

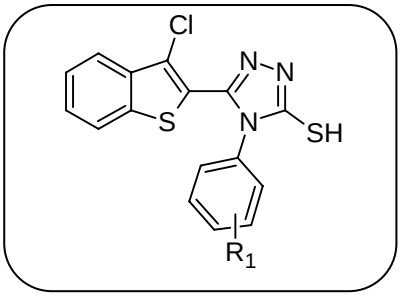
R.F. Lowe and co-workers[23] have reported aryltriazoles as useful antagonists. B.Holla et al.[24] have documented anticancer activity of aryltriazoles. Welsh et al.[25] have discovered aryltriazoles and reported them as analgesic agents.



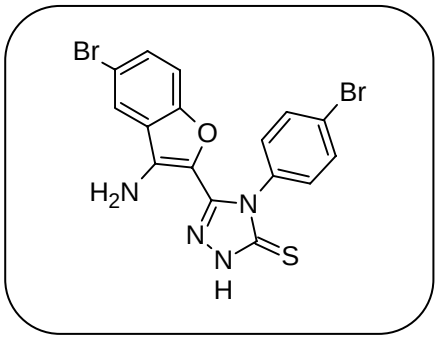
R.J. Singh et al.[5] synthesized some novel 1,2,4-Triazoles as potent bacteriocidal agents



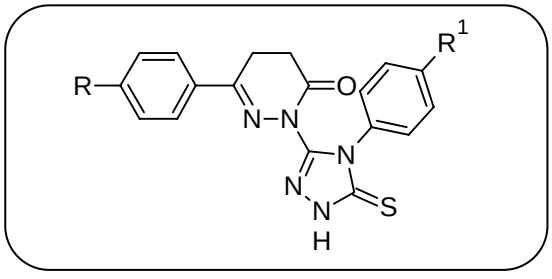
G.Naganagowda et al.[6] have synthesized of some new 3-chlorobenzothiophene-2-carbonylchloride derivatives which shown good activities like antimicrobial and anthelmintic.



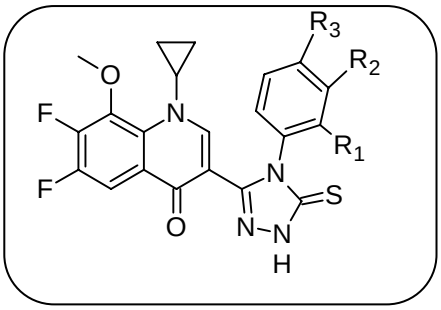
G. Parameshwarappa et al.[26] have been synthesized 5- bromo-3-amino benzofuran nucleus from 5- bromosalicylonitrile which was the shown a good activities of anti-microbial.



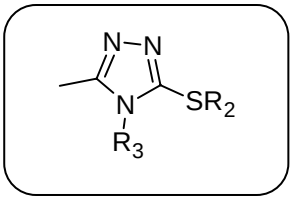
A.A. Siddiqui et al.[27] have designed, synthesized and screened *in vivo* triazole incorporated with pyridazinones as a new class of antihypertensive agents.



S. Shelke et al.[4] have discovered green synthesis of some novel azoles as antimicrobial agents.



M. D. Grandi et al.[28] have synthesized 3,4,5- substituted triazoles derivatives as inhibitors of HIV RT Ribonuclease H



Work done from our laboratory

S.L.Vasoya[29] have synthesized some new thiosemicarbazide and 1,2,4-triazoles heterocycles bearing the benzo[b]thiophene nucleus as potent antituberculer and antimicrobial agents.

In light of wide varieties of therapeutic activities exhibited by aryl triazole, we have embarked upon the synthesis of some new aryl triazole derivatives which have been described in following sections.

SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(6-FLUOROCHROMAN-2-YL)-4-ARYL-4*H* -1,2,4 TRIAZOLE-3- THIOLS.

Part – B

[Part – III (Section-i)]

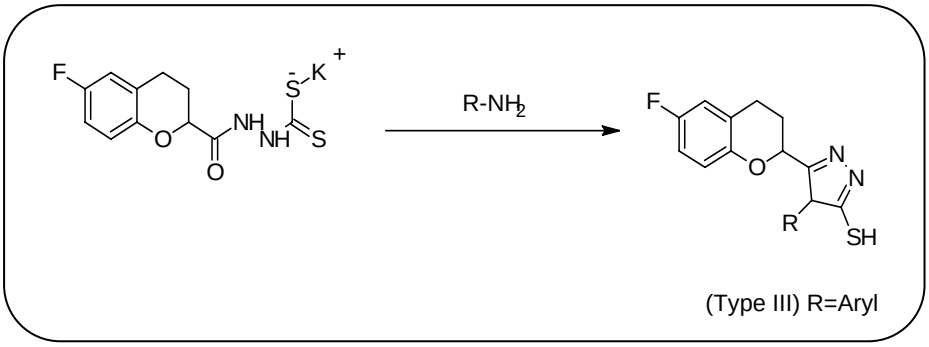
Synthesis and biological evaluation of 5-(6-fluorochroman-2-yl)-4-aryl-4H-1,2,4 - triazole-3-thiols

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 5-(6-FLUORO CHROMAN-2-YL)-4-ARYL-4*H*-1,2,4-TRIAZOLE-3- THIOLS.

4-Aryltriazole derivatives are associated with broad spectrum of pharmacological activity. In views of these findings, it appeared of interest to synthesize 5-(6-fluorochroman-2-yl)-4-aryl-4*H*-1,2,4-triazole-3-thiols. The synthesis of triazole derivatives of type (III) have been undertaken by heating dry potassium 2-[(6-fluorochroman-2-yl)carbonyl]hydrazine carbodithioate with different aromatic amines.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ and DMSO solution on a Bruker AC 300 MHz, 400 MHz and 100MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

[A] Preparation of Potassium 2-[(6-fluorochroman-2-yl) carbonyl] Hydrazinecarbodithioate

See PART-B, part-I, section-I [C].

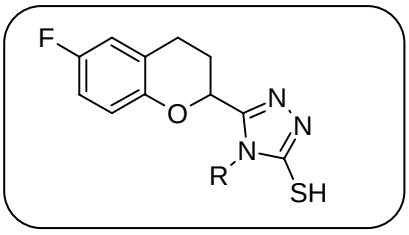
[B] General procedure for the preparation of 5-(6-Fluorochroman-2-yl)-4-aryl-4H-1,2,4-triazole-3-thiols.

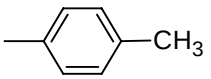
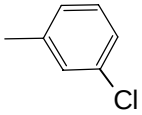
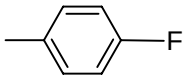
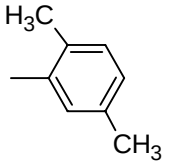
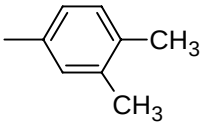
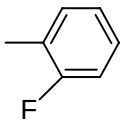
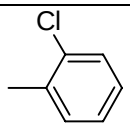
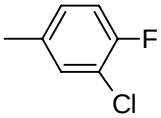
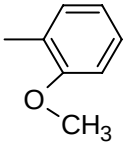
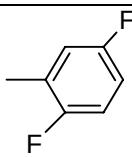
A mixture of potassium 2-[(6-fluorochroman-2-yl) carbonyl] hydrazine carbodithioate (2.85g, 0.01M) and different aromatic amines (0.01M) was heated at 140-150^{O}C until the evolution of H_2S gas ceased (15 hours.). The product was dissolved in DMF (20ml), treated with dilute HCl and then poured in to crushed ice. The product was isolated and crystallized from ethanol. The physical constants of the products are recorded in **Table-8a.**

[C] Biological evaluation of 5-(6-Fluorochroman-2-yl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

Antimicrobial testing was carried out as described in Part-B, Part-III, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-8b**.

Table-8a: Physical constant of 5-(6-Fluorochroman-2-yl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.



Sr. No	Substitution R	M. F.	M. W.	Yield (%)	R_f value
8a		$C_{18}H_{16}FN_3OS$	341.40	89	0.62
8b		$C_{17}H_{13}ClFN_3OS$	361.82	86	0.42
8c		$C_{17}H_{13}F_2N_3OS$	345.36	78	0.37
8d		$C_{19}H_{18}FN_3OS$	355.42	95	0.51
8e		$C_{19}H_{18}FN_3OS$	355.42	84	0.59
8f		$C_{17}H_{13}F_2N_3OS$	345.36	79	0.69
8g		$C_{17}H_{13}ClFN_3OS$	361.82	76	0.44
8h		$C_{17}H_{12}ClF_2N_3OS$	379.81	87	0.31
8i		$C_{18}H_{16}FN_3O_2S$	357.40	90	0.58
8j		$C_{17}H_{12}F_3N_3O_2S$	363.35	75	0.70

TLC solvent system:- E.A. : Hexane = 5 : 5

ANALYTICAL DATA

5-(6-Fluorochroman-2-yl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole-3-thiol *(8a)*. mp 170-172 °C; IR (DRS): 3076, 3039, 2924, 2862, 2773, 2731, 1735, 1699, 1637, 1514, 1429, 1319, 1138, 916,871, 815, 767, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ppm 2.02-2.44 (m, 5H, 2CH, 3CH), 2.65-2.96(m, 2H, 2CH), 4.83-4.90(d,d, *J*=12.6 Hz, 6 Hz, 1H, CH), 6.60-6.69(m, 1H, ArH), 6.73-6.76(m, 2H, ArH), 7.05-7.49(m, 4H, ArH), 11.43(s, 1H, SH). ^{13}C NMR (100 MHz, DMSO): δ 22.87, 22.99, 38.96, 67.72, 113.50, 113.73, 114.98, 115.20, 117.18, 117.26, 122.83, 122.91, 127.92, 129.50, 130.83, 139.07, 148.95, 149.89, 161.80, 168.76; MS: *m/z* = 341 $[M]^+$; Anal. Calcd for $C_{18}H_{16}FN_3OS$: C, 63.32; H, 4.72; N, 12.31. Found: C, 63.23; H, 4.41; N, 12.28%.

4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8b)*. mp 205-207°C; IR (DRS): 3066(Ar, C-H str.), 2914(C-H str.), 2850(C-H str.), 2777(-SH str.), 2533(-SH str.), 1680(Ar, C=C str.), 1647(Ar, C=C str.), 1558(Ar, C=C str.), 1494(Ar, C=C str.), 1375(C-Hben), 1203(C-Cl str.), 1101(C-F str.), 1087(C-N str.), 1072(C-N str.), 1041(C-O-C str.), 815(C-H o,p, ben), 769(C-H o,p, ben), 707(C-C o,p, ben), 663(C-C o,p, ben), 511(C-C o,p, ben)cm^{-1}; ^1H NMR (400 MHz, DMSO): δ ppm 2.27-2.30(m, 2H, 2CH), 2.82-2.95(m, 2H, 2CH), 4.92-4.95(d,d, *J*=6.12 Hz, 12 Hz, 1H, CH), 6.50-6.54(m, 1H, ArH), 6.75-6.79(m, 2H, ArH), 7.41-7.43(m, 1H, ArH), 7.53-7.55(m, 3H, ArH), 14.0 (s, 1H, SH). ^{13}C NMR (100 MHz, DMSO): δ ppm 22.69, 22.85, 38.95, 67.74, 102.75, 108.64, 113.53, 115.05, 117.14, 118.18, 122.91, 127.17, 128.52, 129.64, 130.44, 133.33, 134.77, 140.63, 143.11, 148.80, 149.67, 161.90, 168.71; MS: *m/z* = 361 $[M]^+$; Anal. Calcd for $C_{17}H_{13}ClFN_3OS$: C, 56.43; H, 3.62; N, 11.61. Found: C, 56.18; H, 3.49; N, 11.59%.

5-(6-Fluorochroman-2-yl)-4-(4-fluorophenyl)-4*H*-1,2,4-triazole-3-thiol *(8c)*. mp 188-190 °C; IR (DRS): 3030, 2964, 2853, 2658, 1642, 1612, 1581, 1471, 1378, 1225, 1156, 1045, 819, 777, 696, 513, cm^{-1}; MS: *m/z* = 345 $[M]^+$; Anal. Calcd for $C_{17}H_{13}F_2N_3OS$: C, 59.12; H, 3.79; N, 12.17. Found: C, 59.02; H, 3.53; N, 12.01%.

4-(2,5-Dimethylphenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8d)*. mp 123-125°C; IR (DRS): 3074, 2987, 2851, 2710, 1645, 1612, 1585, 1468, 1330, 1281, 1184, 1074, 820, 766, 692, 587 cm^{-1}; MS: *m/z* = 355 $[M]^+$; Anal. Calcd for $C_{19}H_{18}FN_3OS$: C, 64.21; H, 5.10; N, 11.82. Found: C, 64.16; H, 4.93; N, 11.78%.

4-(3,4-Dimethylphenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8e)*. mp 163-165 °C; IR (DRS): 3081, 2975, 2844, 2687, 1641, 1579, 1556, 1464, 1378, 1282, 1142, 1023, 887, 750, 687, 555 cm^{-1}; MS: *m/z* = 355 $[M]^+$; Anal. Calcd for $C_{19}H_{18}FN_3OS$: C, 64.21; H, 5.10; N, 11.82. Found: C, 64.09; H, 5.03; N, 11.50%.

5-(6-Fluorochroman-2-yl)-4-(2-fluorophenyl)-4*H*-1,2,4-triazole-3-thiol *(8f)*. mp 108-110°C; IR (DRS): 3080, 2983, 2867, 2661, 1629, 1572, 1525, 1462, 1341, 1245, 1196, 1094, 830, 774, 682, 575 cm^{-1}; MS: *m/z* = 345 $[M]^+$; Anal. Calcd for $C_{17}H_{13}F_2N_3OS$: C, 59.12; H, 3.79; N, 12.17. Found: C, 58.96; H, 3.67; N, 12.06%.

4-(2-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8g)*. mp 192-194 °C; IR (DRS): 3077, 2978, 2863, 2712, 1625, 1609, 1563, 1464, 1310, 1238, 1142, 1044, 870, 798, 756, 656, 544 cm^{-1}; MS: *m/z* = 361 $[M]^+$; Anal. Calcd $C_{17}H_{13}ClFN_3OS$: C, 56.43; H, 3.62; N, 11.61. Found: C, 55.97; H, 3.55; N, 11.59%.

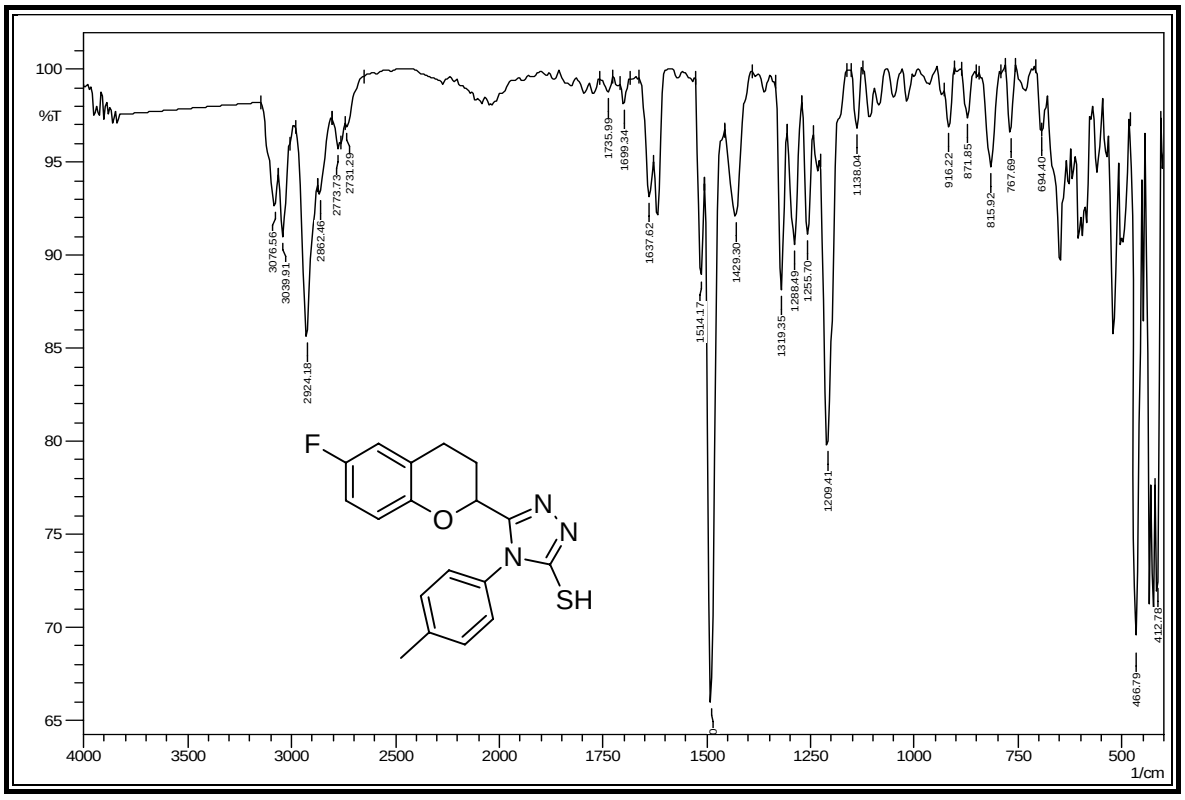
4-(3-Chloro-4-fluorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8h)*. mp 139-141°C; IR (DRS): 3031, 2962, 2854, 2691, 1603, 1545, 1542, 1452, 1332, 1260, 1146, 1042, 878, 831, 778, 631, 542 cm^{-1}; MS: *m/z* = 379 $[M]^+$; Anal. Calcd for $C_{17}H_{12}ClF_2N_3OS$: C, 53.76; H, 3.18; N, 11.06. Found: C, 53.69; H, 3.07; N, 10.90%.

5-(6-Fluorochroman-2-yl)-4-(2-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol *(8i)*. mp 251-253°C; IR (DRS): 3075, 2964, 2853, 2711, 1721, 1601, 1581, 1423, 1355, 1281, 1149, 1075, 740, 602 cm^{-1}; MS: *m/z* = 357 $[M]^+$; Anal. Calcd for $C_{18}H_{16}FN_3O_2S$: C, 60.49; H, 4.51; N, 11.76. Found: C, 60.39; H, 4.29; N, 11.37%.

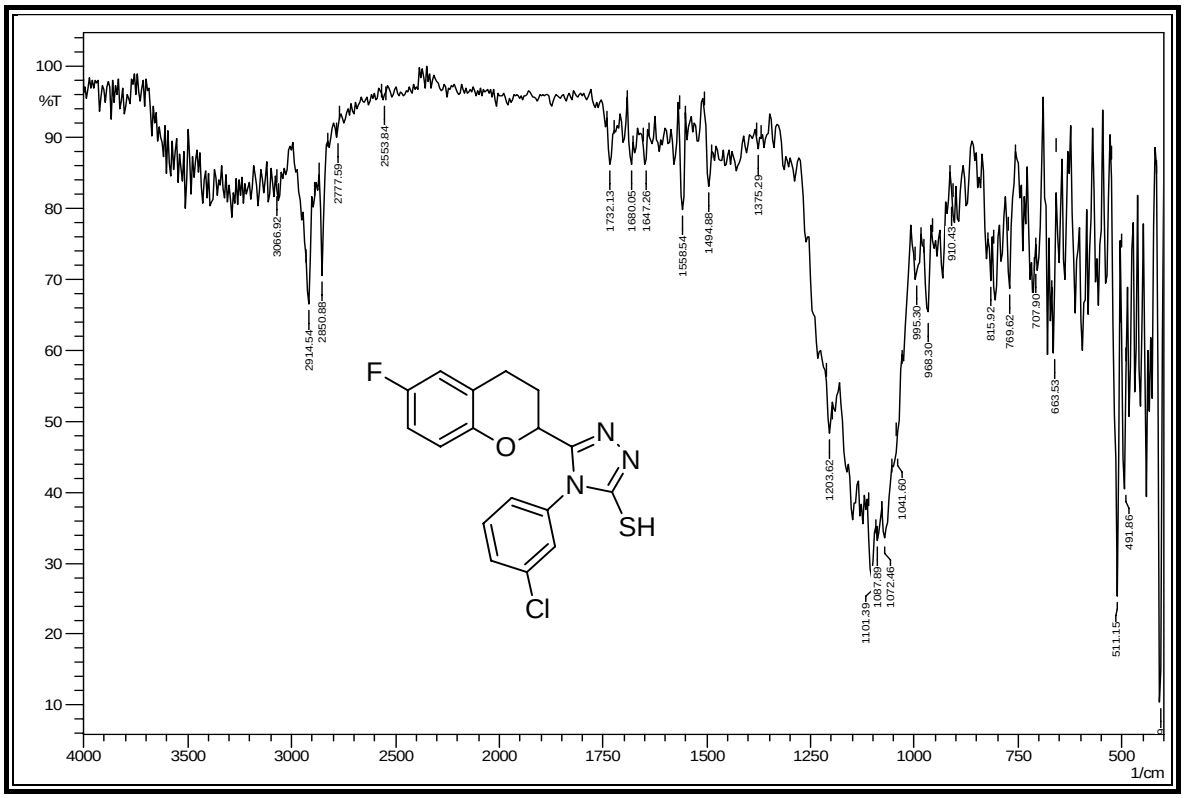
4-(2,5-Difluorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8j)*. mp 229-231°C; IR (DRS): 3061, 2951, 2872, 2635, 1689, 1589, 1579, 1462, 1352, 1099, 831, 755, 621, 510 cm^{-1}; MS: *m/z* = 363 $[M]^+$; Anal. Calcd for $C_{17}H_{12}F_3N_3O_2S$: C, 56.19; H, 3.33; N, 11.56. Found: C, 56.06; H, 3.14; N, 11.32%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

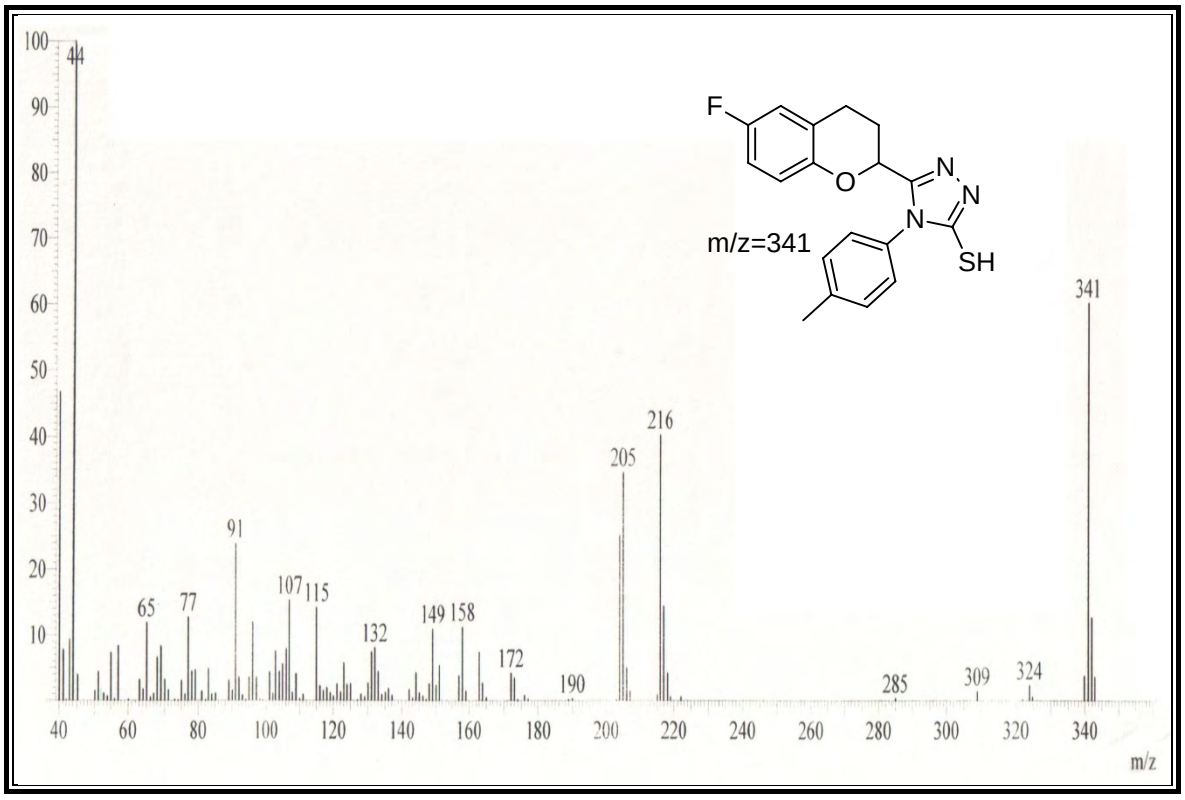
IR Spectrum of 5-(6-Fluorochroman-2-yl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole-3-thiol *(8a)*.



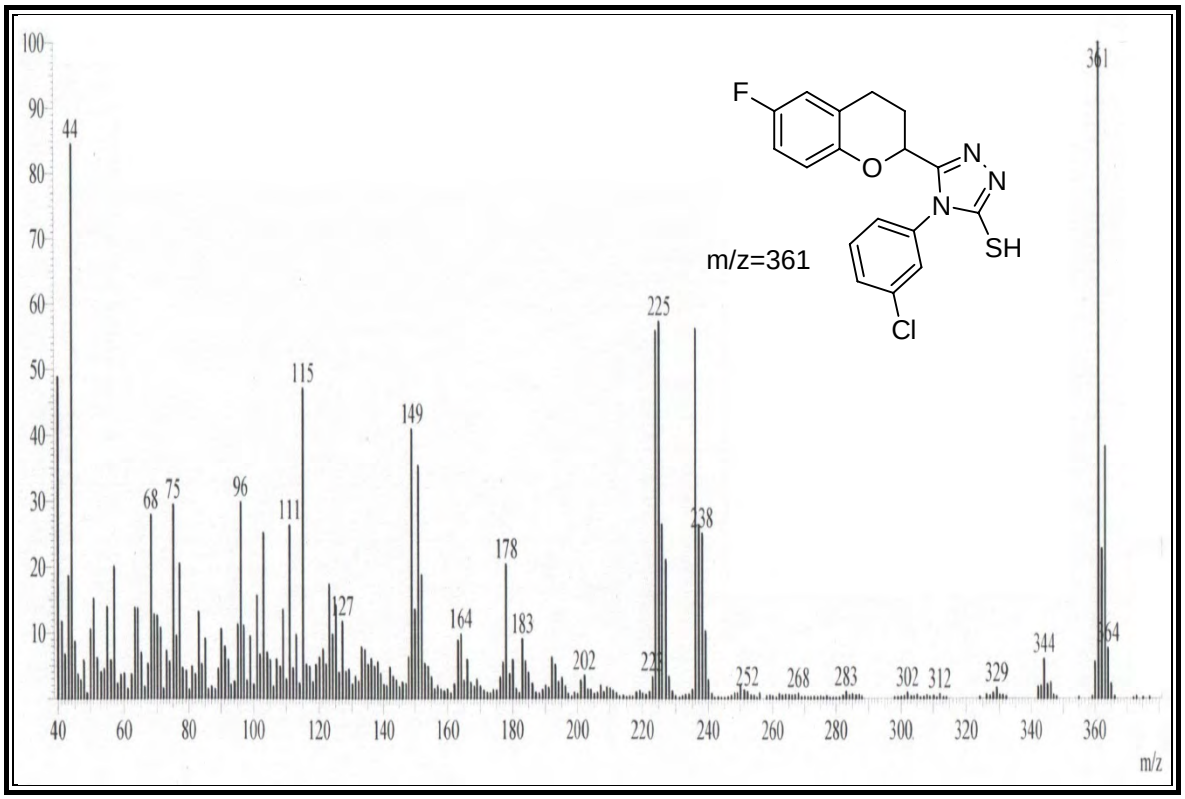
IR Spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8b)*.



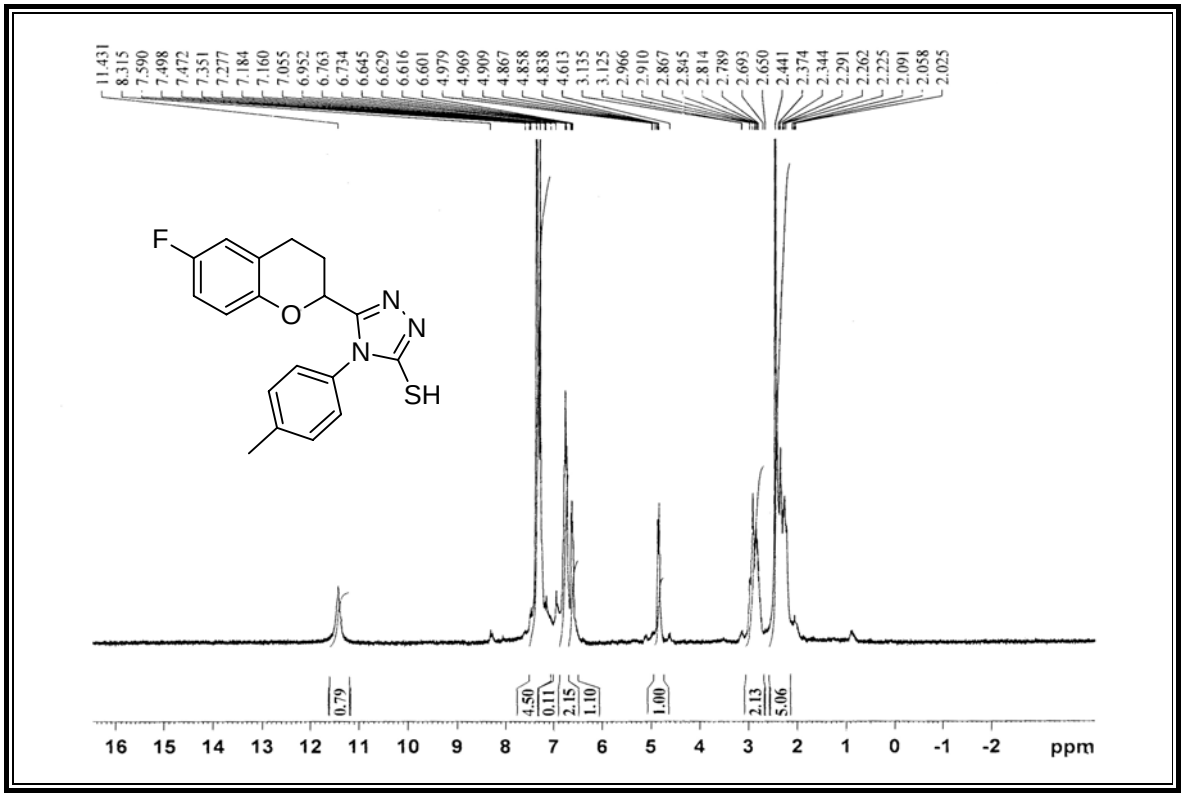
Mass spectrum of 5-(6-Fluorochroman-2-yl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole-3-thiol *(8a)*.



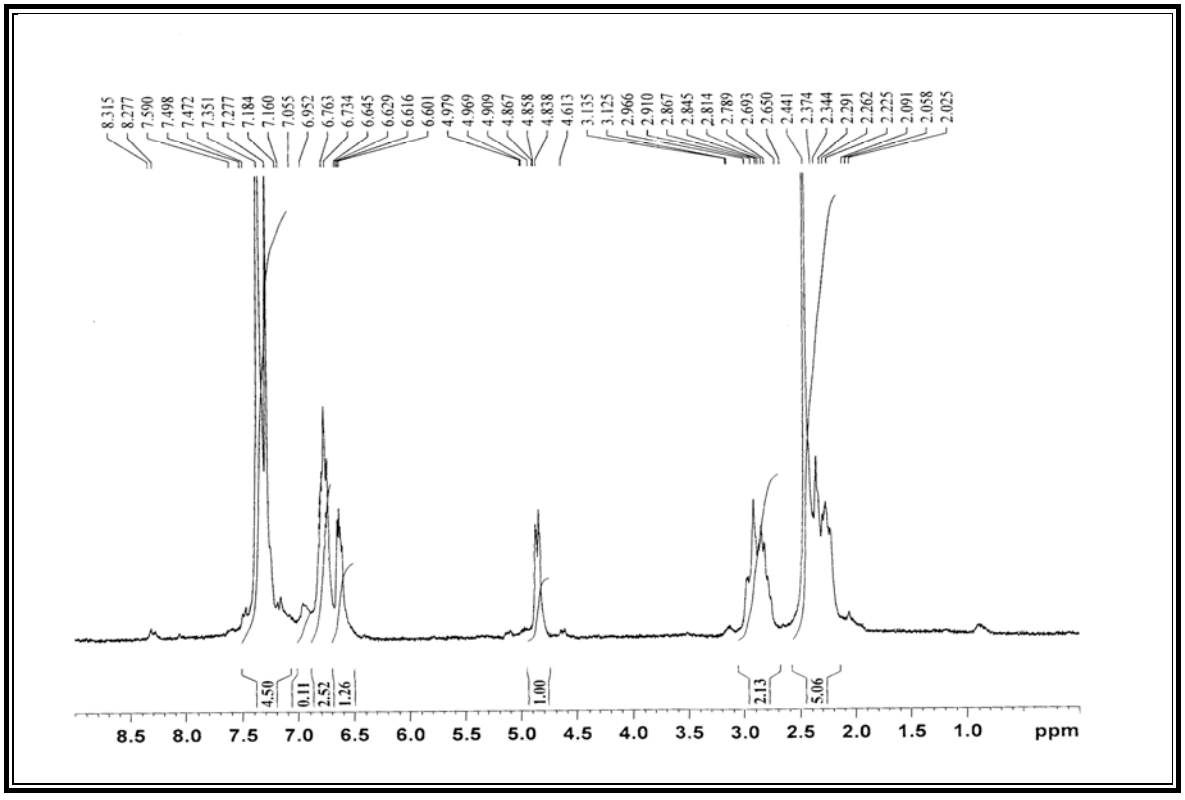
Mass spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol *(8b)*.



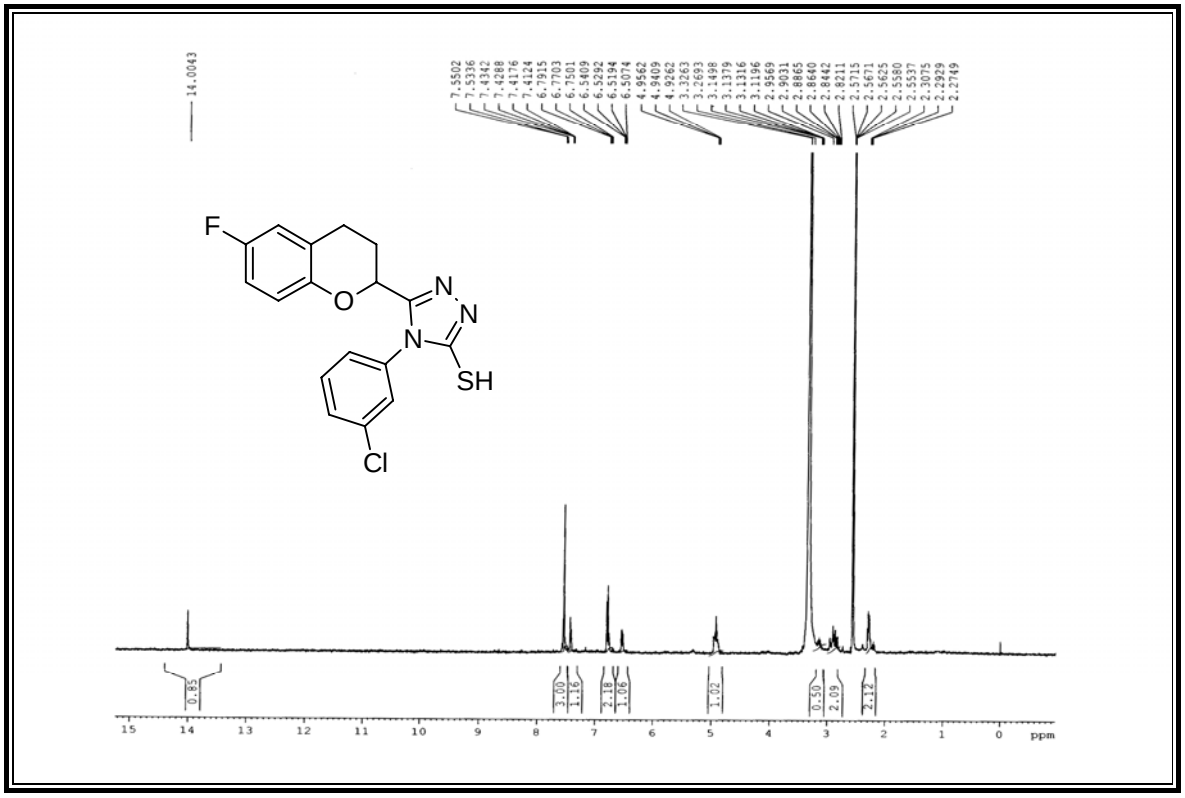
^{1}H NMR spectrum of 5-(6-Fluorochroman-2-yl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole-3-thiol *(8a)*.



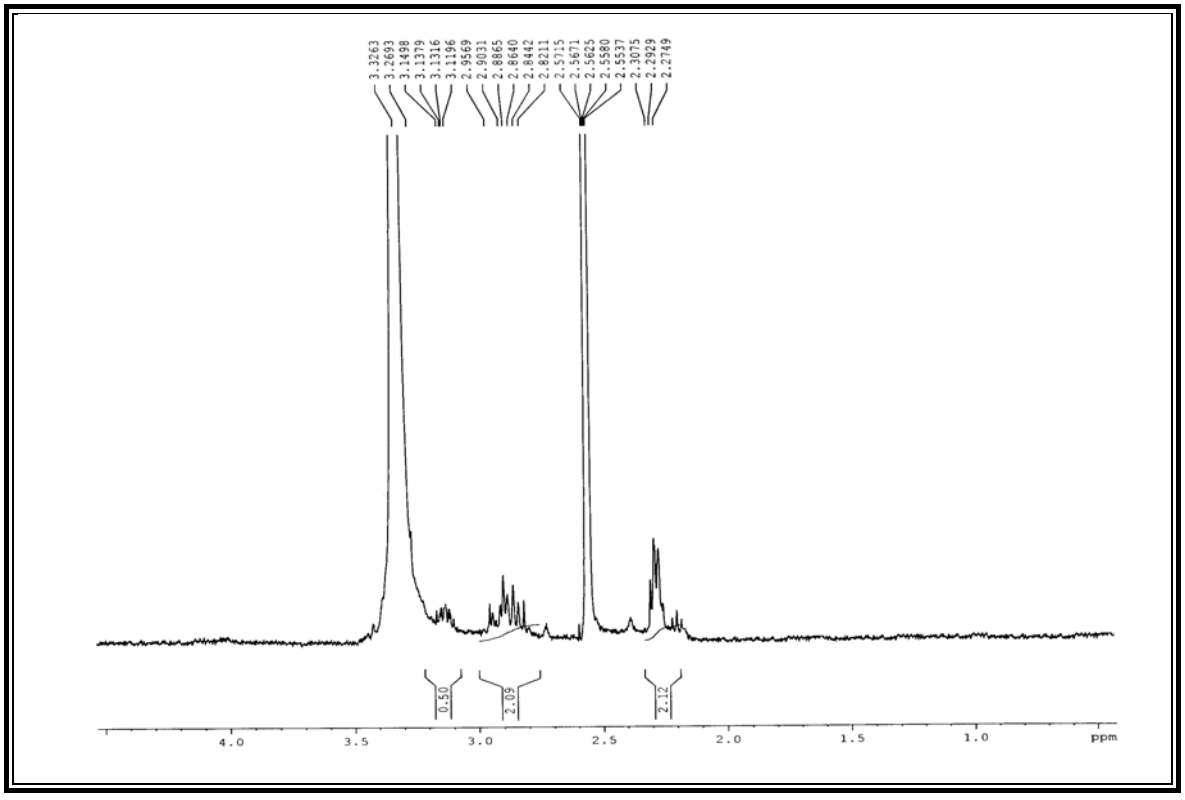
Expanded spectrum of 5-(6-Fluorochroman-2-yl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole-3-thiol *(8a)*.



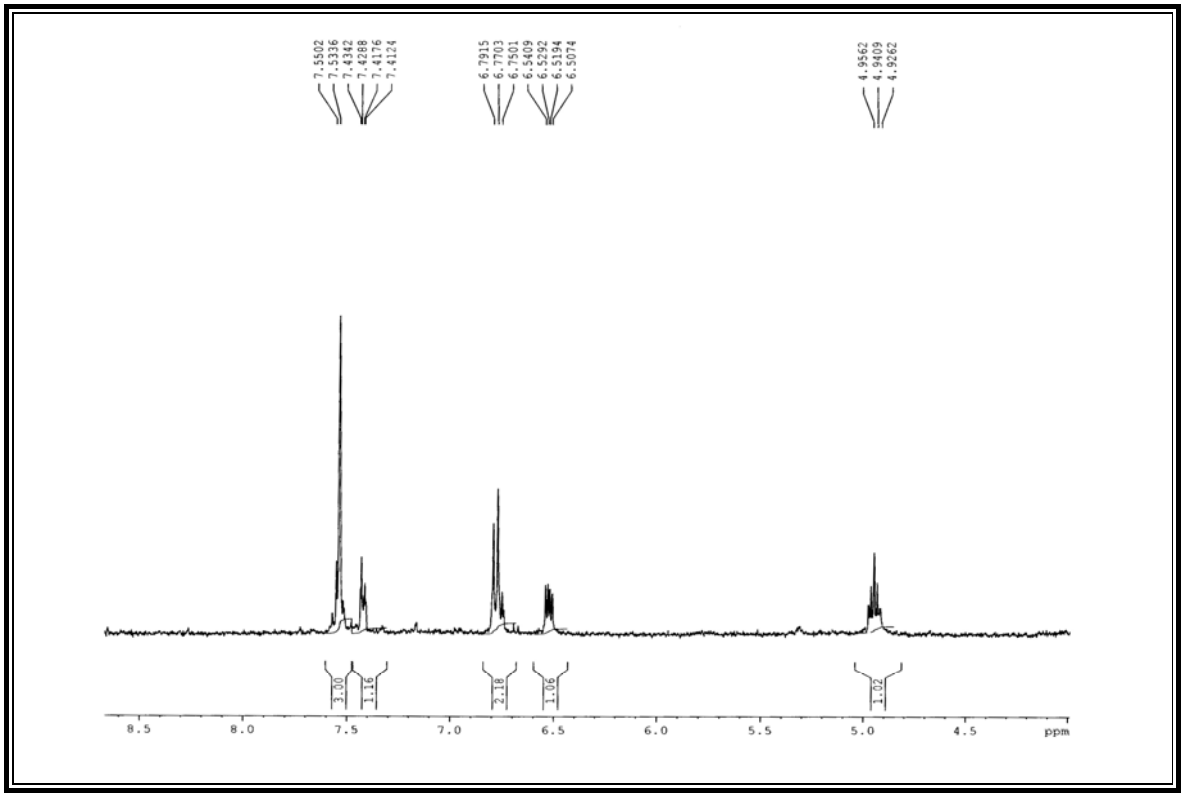
^{1}H NMR spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol*(8b)*.



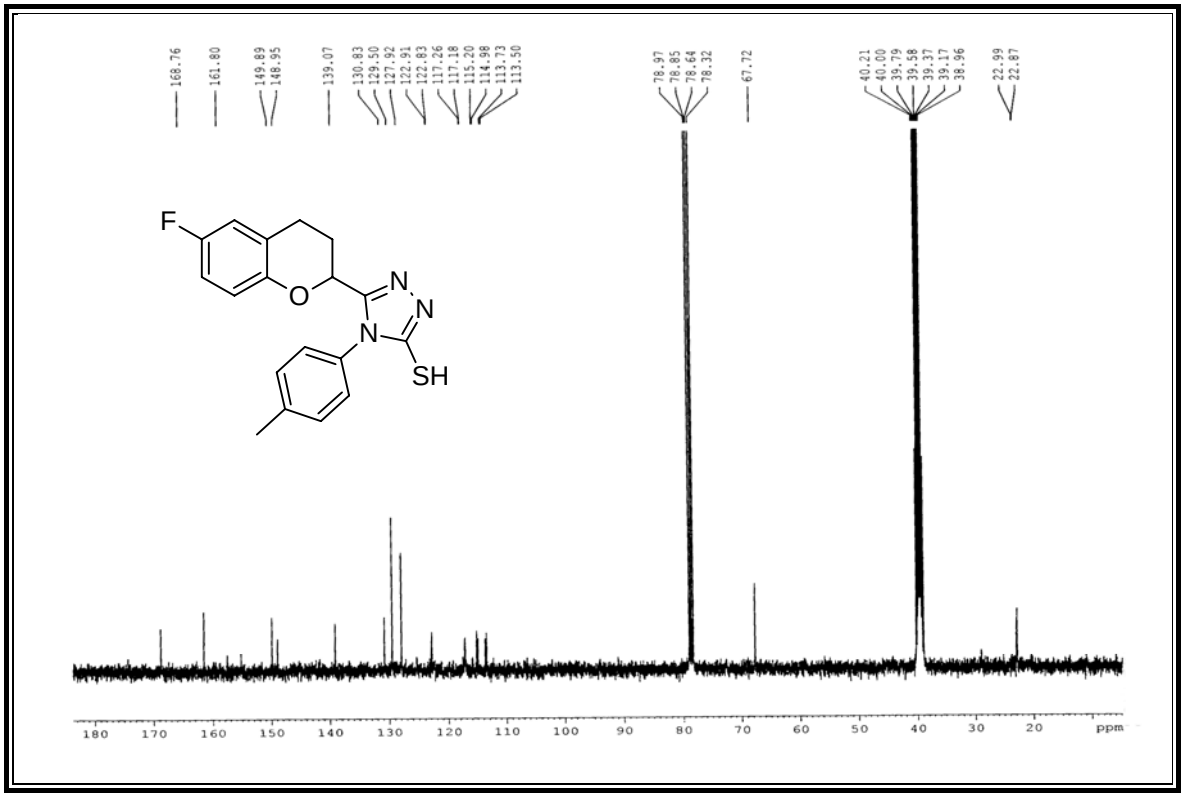
Expanded spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol*(8b)*.



Expanded spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol*(8b)*.



^{13}C NMR spectrum of 5-(6-Fluorochroman-2-yl)-4-(*p*-tolyl)-4*H*-1,2,4-triazole-3-thiol *(8a)*.



^{13}C NMR spectrum of 4-(3-Chlorophenyl)-5-(6-fluorochroman-2-yl)-4*H*-1,2,4-triazole-3-thiol*(8b)*.

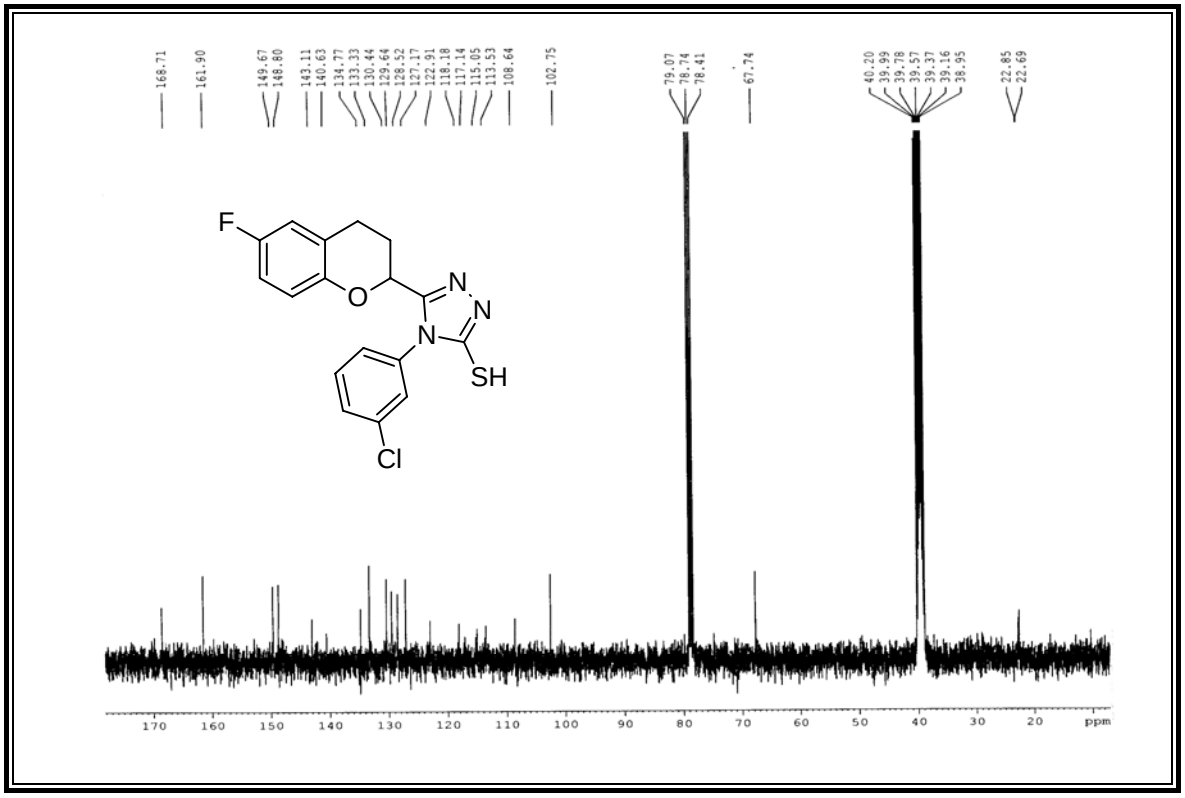


Table-8b: Antimicrobial activity of 5-(6-Fluorochroman-2-yl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
8a	500	250	200	250	1000	500	500
8b	62.5	250	62.5	125	500	1000	1000
8c	200	200	100	200	250	1000	>1000
8d	500	500	125	250	1000	>1000	>1000
8e	250	200	62.5	200	1000	>1000	>1000
8f	200	200	200	125	1000	1000	1000
8g	200	200	125	200	500	500	1000
8h	62.5	100	250	250	1000	1000	1000
8i	125	200	250	250	>1000	500	500
8j	100	62.5	200	200	>1000	>1000	>1000

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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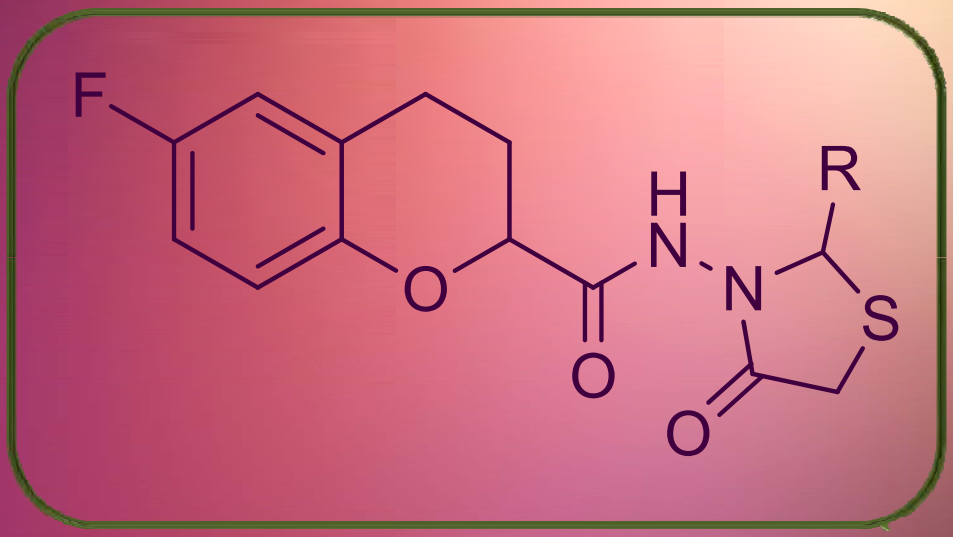
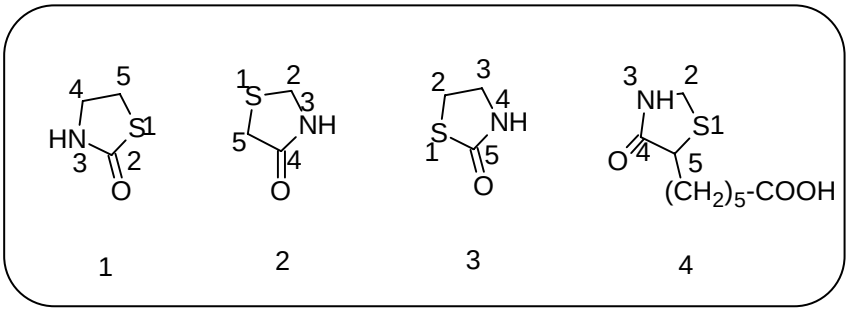
PART-IV

STUDIES ON THIAZOLIDINONE DERIVATIVES



INTRODUCTION

Thiazolidinones, which belongs 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 gossips have appeared in the literatures which underscore their chemistry and use.



1 2 3 4

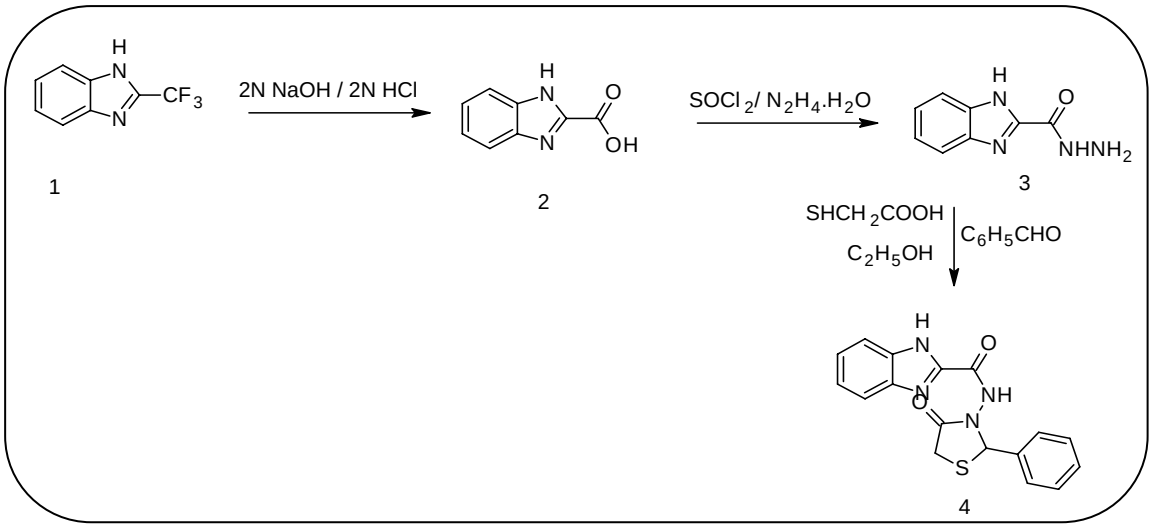
4-Thiazolidinones are derivatives of thiazolidinones with carbonyl group at 4-position **(2).** Substituent in the 2, 3 and 5 positions may be varied, but the greatest different in structure and properties is exerted by the groups attached to carbon atom at the 2-position and to nitrogen atom at the 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.[1] A well known antibiotic, actithiazic acid **(4)**, isolated from a species of *streptomyces* shows specific *in vitro* activity against *M. tuberculosis*, but it is inactive *in vivo* probably due to antagonisation by biotin, bears the 4-thiazolidinone skeleton.

SYNTHETIC ASPECT

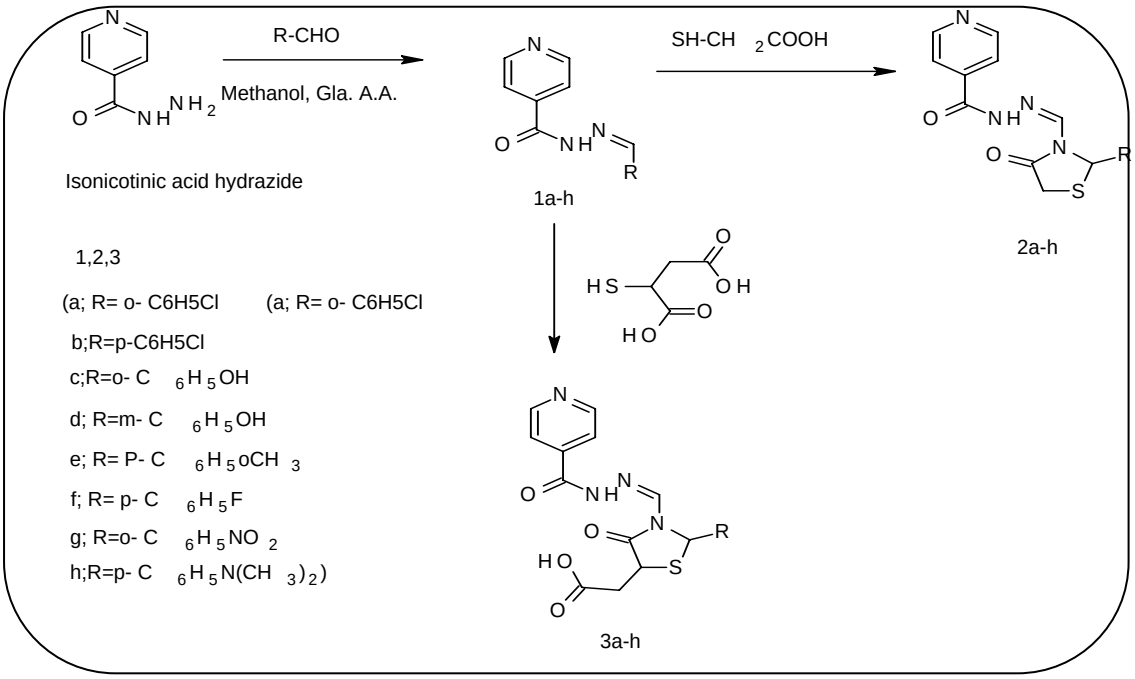
Several methods for the preparation of 4-thiazolidinones are narrated in literature.[2-10]

1. R.S. Harisha et al.[11] have synthesized the one pot synthesis of thiazolidinone, by hydrolysis of 2- (trifluoromethyl)-1H-benzimidazole**(1)** in NaOH/ HCl gives the 1H- benzimidazole-2-carboxylic acid**(2),**which on treatment with thionyl chloride followed by hydrazine hydrate to gave the desired 1H- benzimidazole-2-carboxylic acid hydrazide **(3)**in 90% yield. Then the compound (3) on reaction

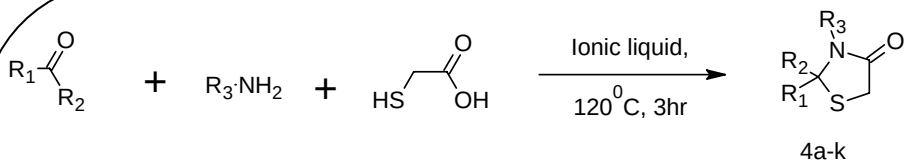
with benzaldehyde and mercapto acetic acid in ethanol as a solvent to give compound**(4).**



2. S.J. Gilani et al.[12] have been synthesized main two types of derivatives of 4-thiazolidinones.To an equimolar methanolic solution of isonicotinic acid hydrazide(0.1 mol) and sustituted benzaldehyde(0.1 mol), a few drops of glacial acetic acid were added. The mixture was refluxed on water bath for 5-6 hours, then allowed to cool and poured on to crushed ice. The product isolated and recrystallisation from methanol yielded compounds **(1a-h)**.A mixture of(1) (0.01 mol) and thioglycolic acid(0.01 mol) was heated on oil-bath at 120-125^{o}C for 12 hours,then treated with sodium bicarbonate to gave compounds(2a-h).Same as reaction carryout in thiomalic acid to gave compounds**(3a-h).**



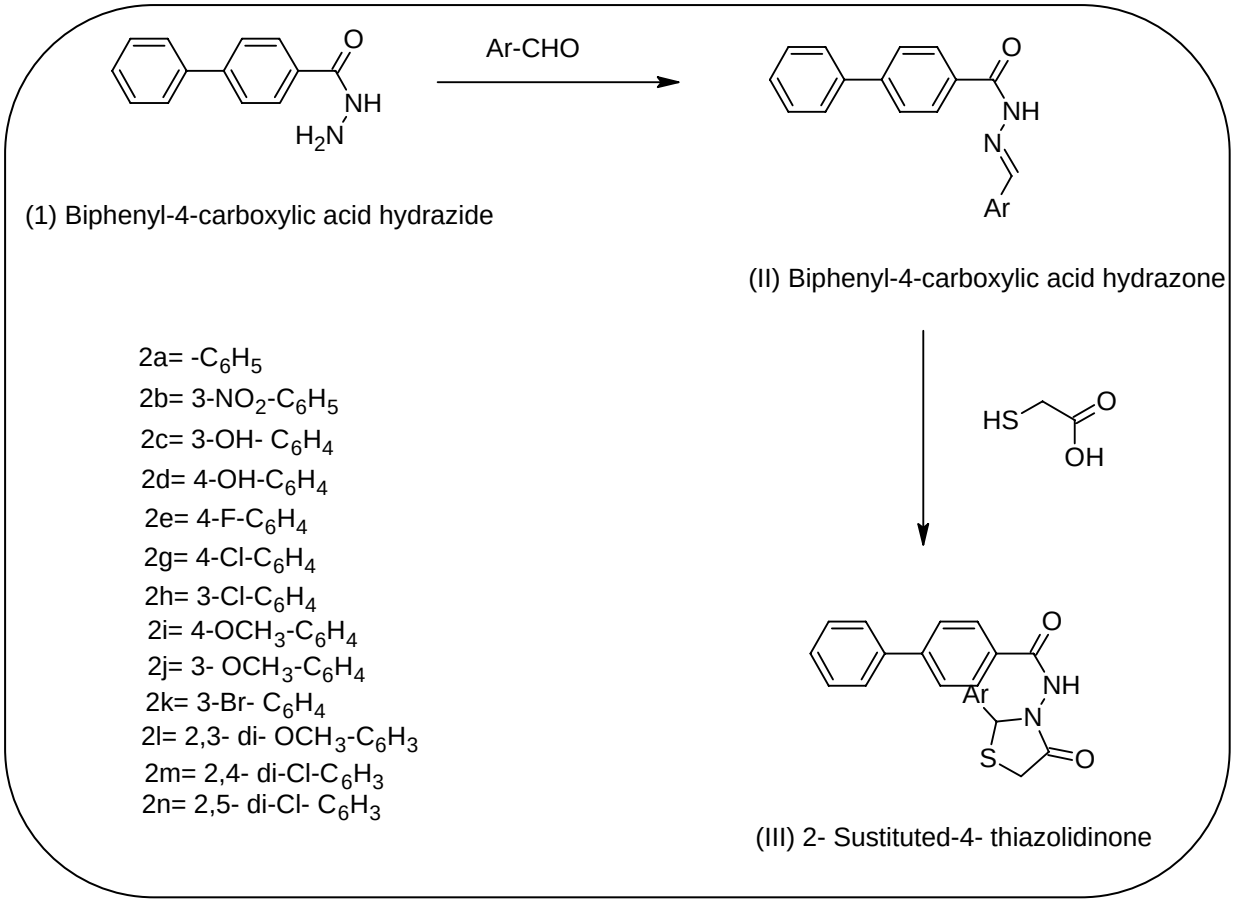
3. D. Lingampalle et al.[13] have synthesized a convenient one-pot ,three-component cyclo condensation mediated by ionic liquid for obtaining 2,3- disustituted-4-thiazolidinones with excellent yields reported.



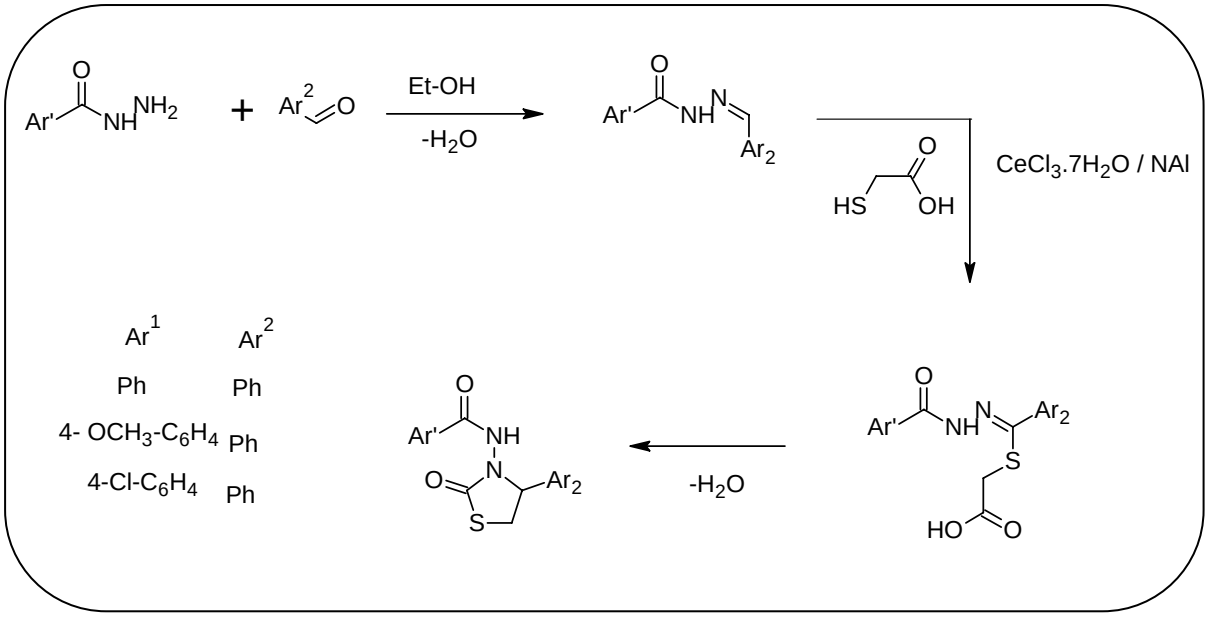
1a-e 2a-e 4a-k

	R_1	R_2	R_3
4a	4-hydroxy ph.	CH_3	4- methoxy ph.
4b	4-hydroxy ph.	CH_3	4- methoxy ph.
4c	Ph.	H	Ph.
4d	4-methyl ph.	H	4-methyl ph.
4e	4-methyl ph.	H	Ph.
4f	Ph.	H	4-methyl ph.
4g	4- Cl-ph.	H	Ph.
4h	Ph.	H	4- Cl-ph.
4i	4- methoxy ph.	H	Isonicotinoyl amino
4j	4- Cl-ph.	H	Isonicotinoyl amino
4k	4- methoxy ph.	H	Isonicotinoyl amino

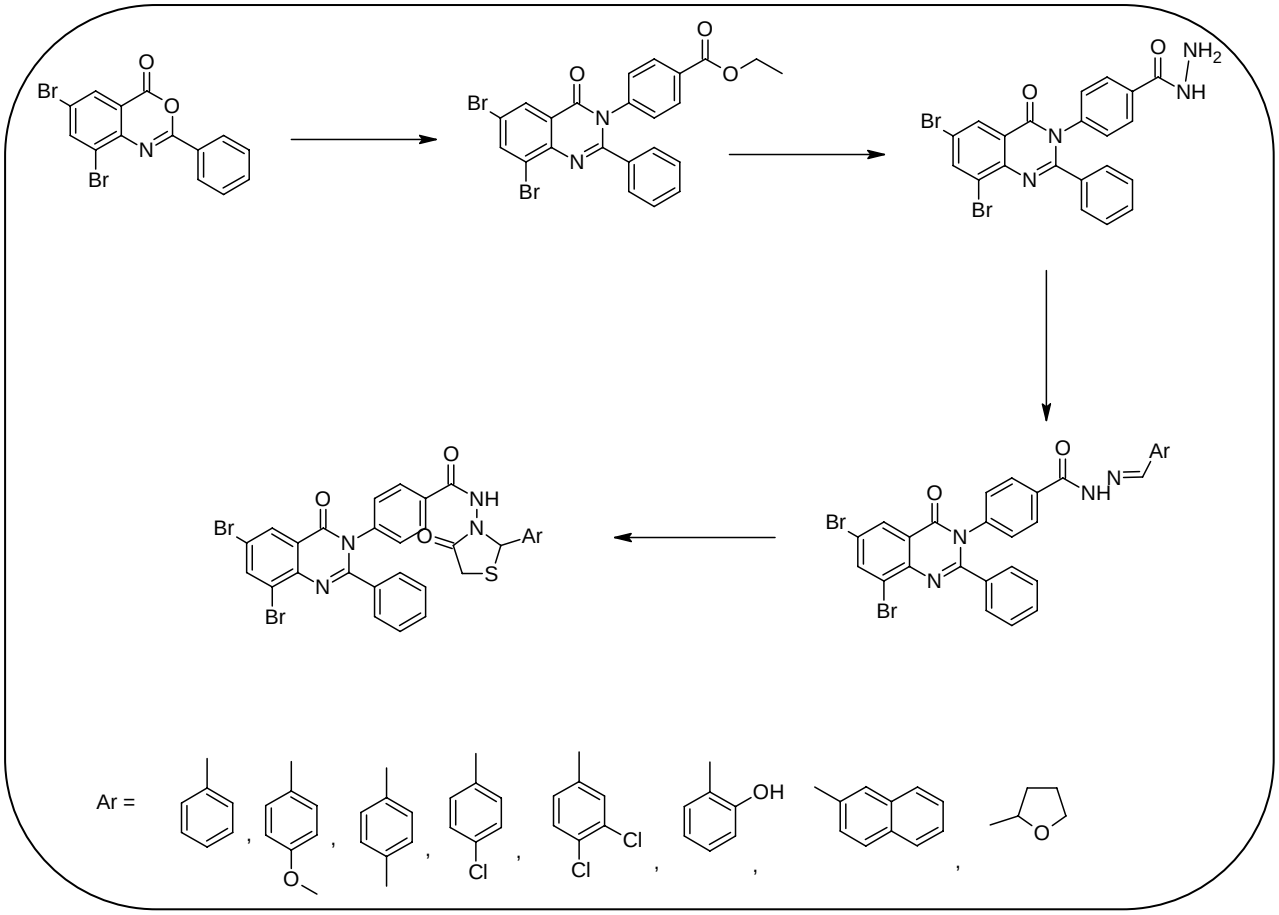
4. A. Madhukar et al.[14] have been synthesized biphenyl-4-carboxylic acid 2-(aryl)-4-oxo- thiazolidin-3-yl-amide.



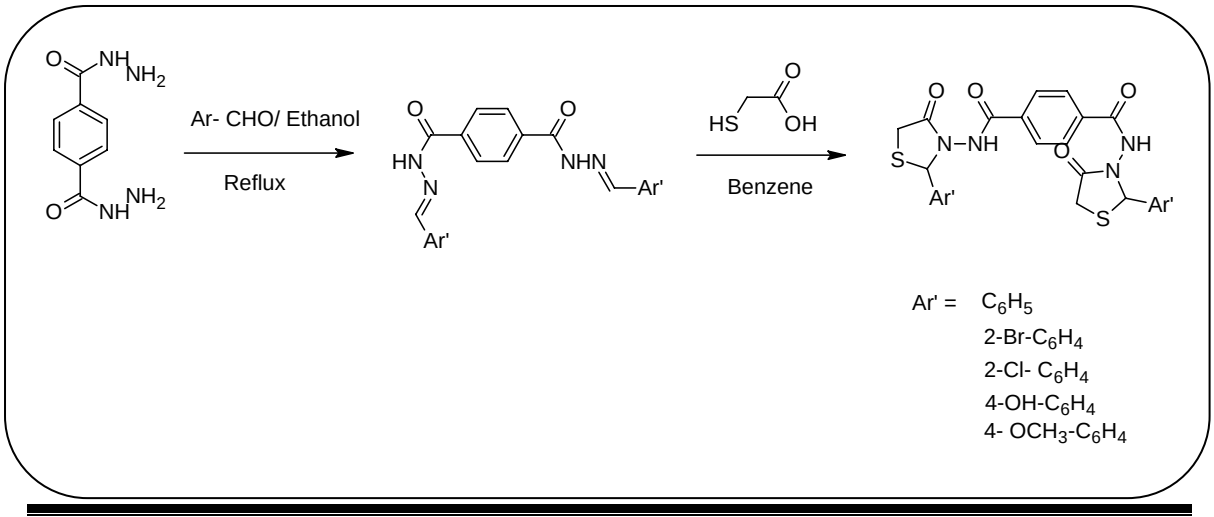
5. L.D.S. Yadav et al.[15] reported a convenient $CeCl_3\_7H_2O$/NAl- promoted structurally novel synthesis of thiazolidinones. Which is describe as under.



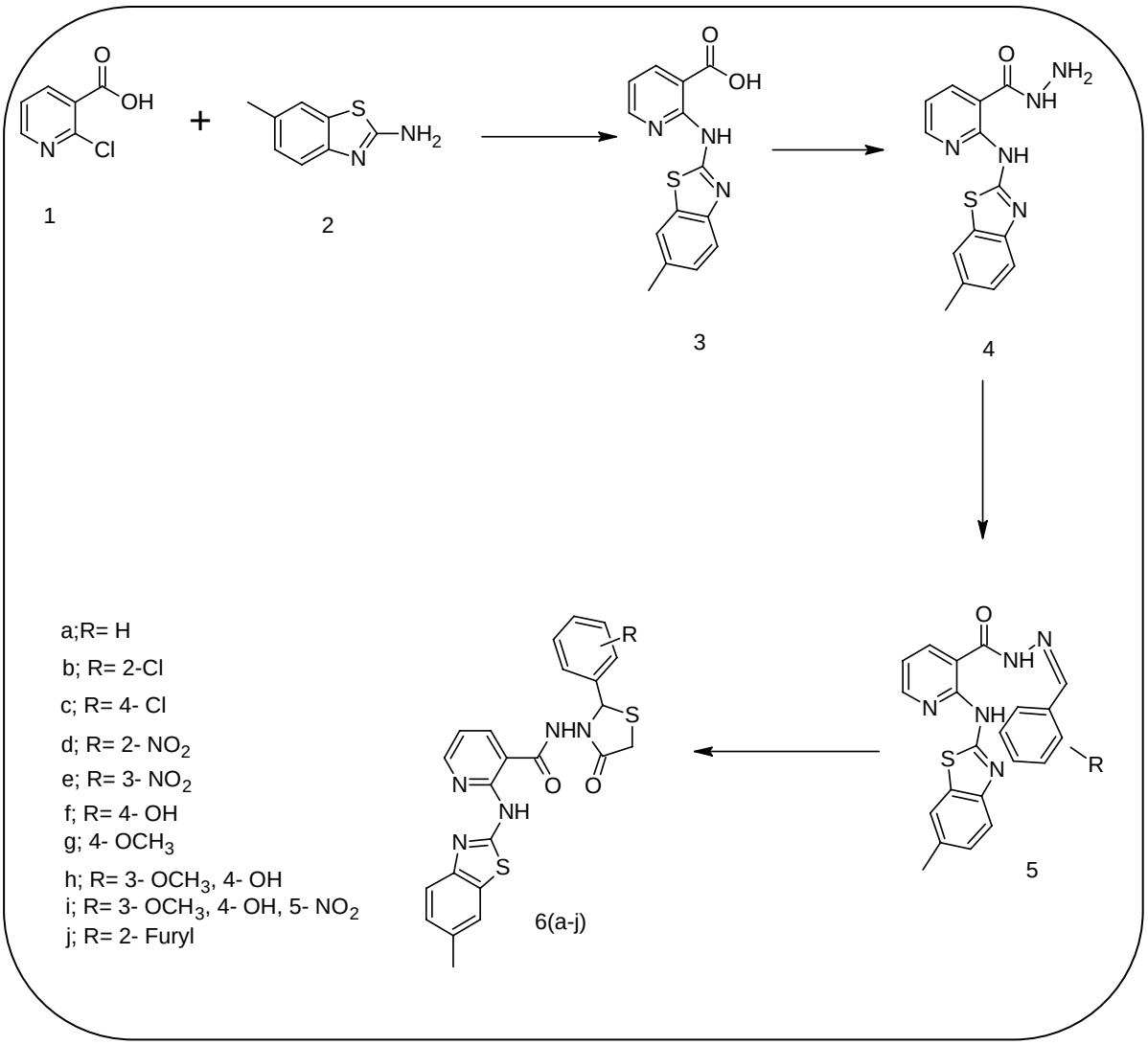
6. M.S. Mohamed et al.[16] synthesized novel thiazolidinones bearing 6,8-dibromo-4(3H) quinazolinone, which shows a very good anti-bactarial and anti-fungal activity. The reaction scheme as under.



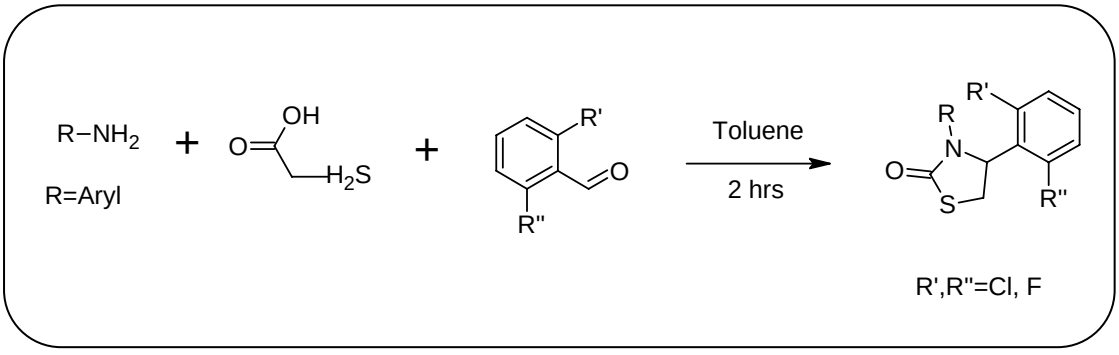
7. V.S. Palekar et al.[17] have been synthesized some novel bis-4- thiazolidinone derivatives from terphthalic dihydrazide.Which shows good anti-bactarial activity.The reaction scheme are as under.



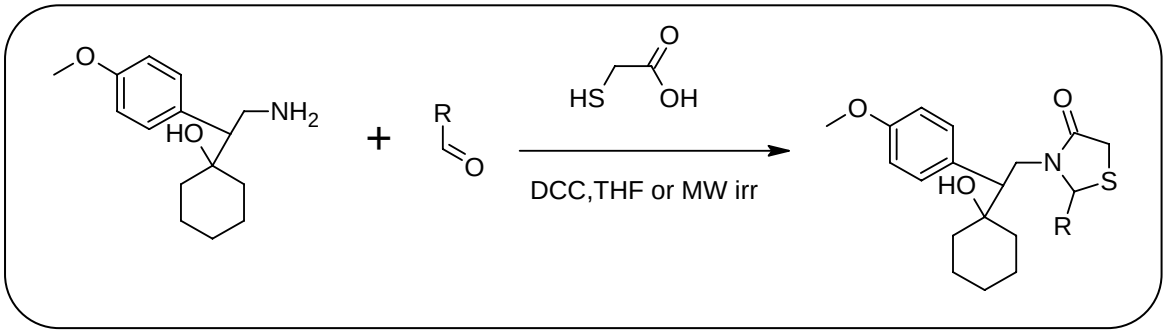
8. N. B. Patel et al.[18] have synthesized some new 4- thiazolidinones of nicotinic acid with 2- amino -6- methyl benzothiazole. Which have been described as under.



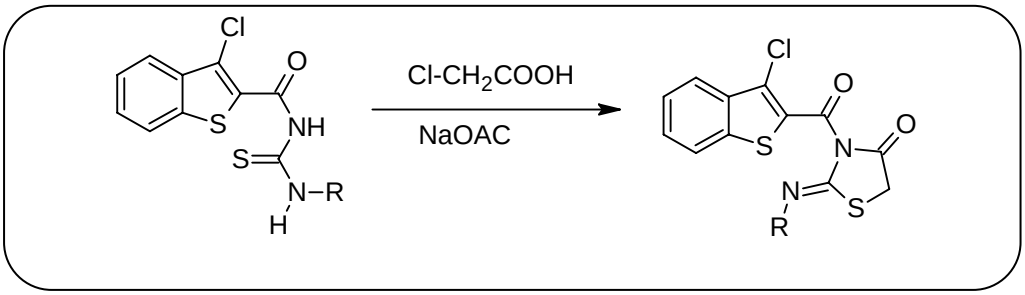
9. M. L. Berreca et al.[19] have synthesized some novel 2,3-diaryl-1,3-thiazolidin-4-one derivatives from 2,3-dihalo substituted benzaldehyde, equivalent amount of aromatic amine and mercaptoacetic acid in refluxing with toluene.



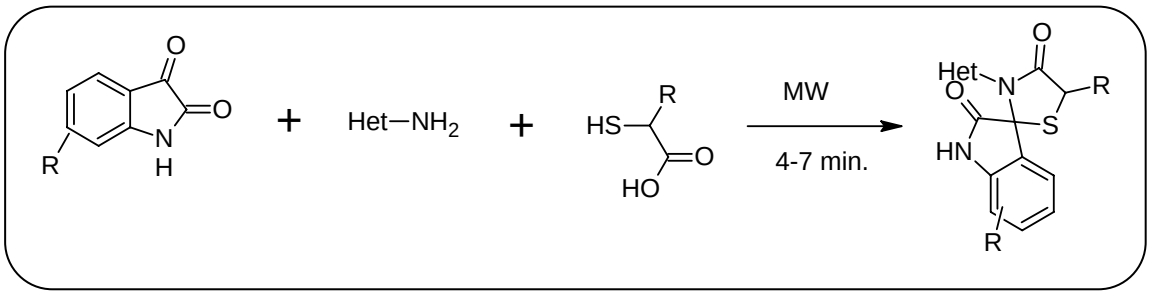
10. Bioactive venlafaxine analogs such as 2,3-disubstituted-1,3-thiazolidinones have been synthesized and reported as antimicrobial agent by C. V. Kavitha and coworkers.[20]



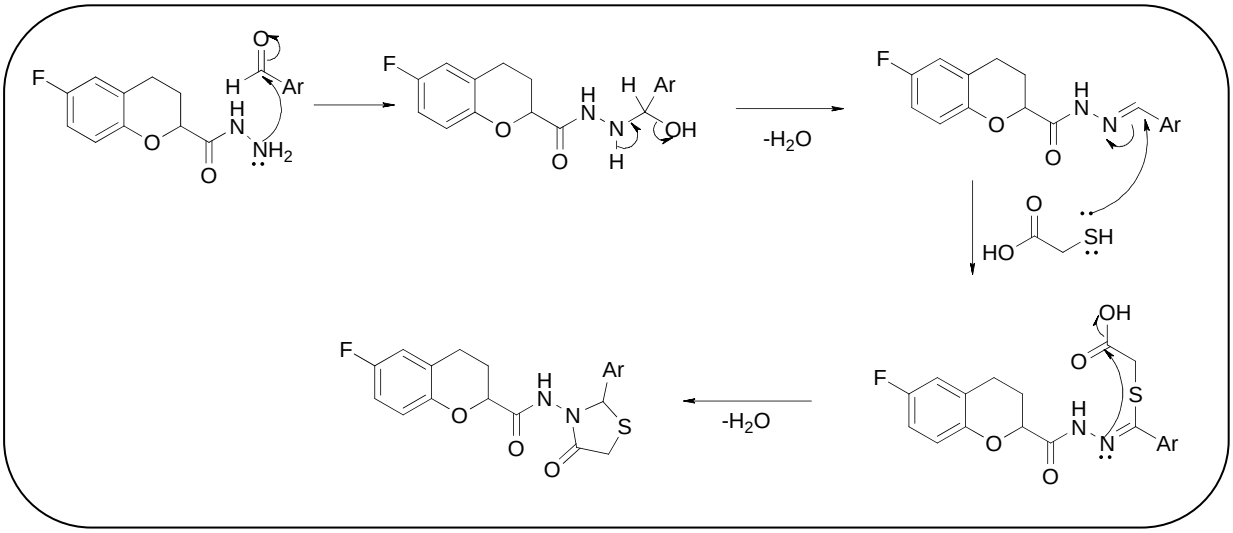
11. D. R. St. Laurent et al.[21] have synthesized 4-thiazolidinone derivatives by the cyclization unsymmetrical thiourea. H. S. Joshi and co-workers[22] have synthesized thiazolidinones bearing benzo[*b*]thiophene nucleus from *N*-arylaminothoxomethyl derivatives with chloroacetic acid in ethanol.



12. A. Dandia and co-workers[23] have synthesized thiazolidinone derivatives and reported their antifungal activity.



REACTION MECHANISM

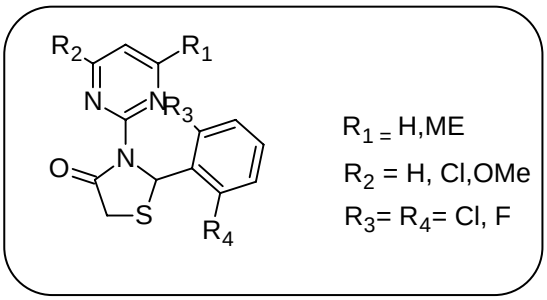


THERAPEUTIC IMPORTANCE

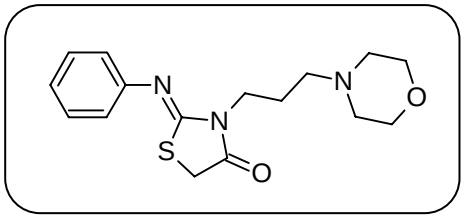
Much research has been accepted with intend to pronouncement therapeutic values of thiazolidinone moiety since their discovery. The thiazolidinones, substituted at 2 and 3 position are reported to demonstr.ate a wide variety of biological activities.

1. Antibacterial.[24, 25]
2. Anticancer.[26]
3. Antiinflammatory.[27]
4. Antitubercular.[28]
5. Antihistaminic.[29]
6. Antimalarial.[30]
7. Anti-HIV[31,32]
8. Antimicrobial[33,34]
9. Antifungal[35]
10. Antioxidant[36]
11. Herbicidal[37]

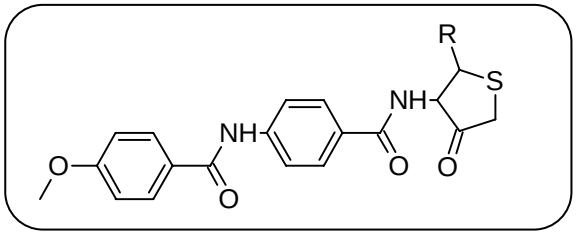
Goel et al.[38] have synthesized thiazolidinone derivatives and compaired their antiinflammatory activity, ulcerogenic liability, cardiovascular and CNS effects.M. Siddique et al.[39] have prepared substituted thiazolidinones and reported their antibacterial, antifungal, antithyroid and amoebicidal properties. S. K. Srivastava et al.[40] have prepared new thiazolidinones as antibacterial, antifungal, analgesic and diuretic agents. A. Rao et al.[41] have been synthesized several 1,3-thiazolidin-4-ones bearing 2,6-dihalophenyl group at C-2 and a substituted pyrimidin-2-yl ring at the N-3 were synthesized and evaluated as anti-HIV agents.



R.Ottana et al.[42] have designed and synthesised 5-arylidene-2-imino-4-thiazolidinone derivatives as novel antiinflammatory agent. A. Tsutoma et al.[43] have synthesized thiazolidinones as a telomeres inhibitors. S. K. Chaudhary et al.[44] have synthesized several 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones and evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg.

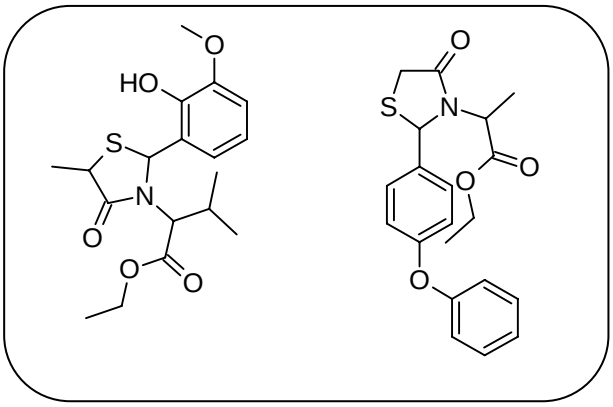


Suzuki et al.[45] have synthesized and examined the effects of CP-060S 3-{3-[(benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]propyl}-2-(3,5-di-tert-butyl-4-hydroxy phenyl)-4-thiazolidinone on cardiac function and myocardial oxygen consumption (MVO2) in anesthetized dogs. V. K. Agraval et al.[46] have investigated 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. In another study, Diurno et al.[47] have synthesized, characterized and evaluated a new series of 2-(substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-ones for their capacity to inhibit contraction induced by histamine on guinea pig ileum. G. Kucukguzel et al.[48] have been synthesized some thiazolidinine derivatives and reported as anti-inflammatory agent.

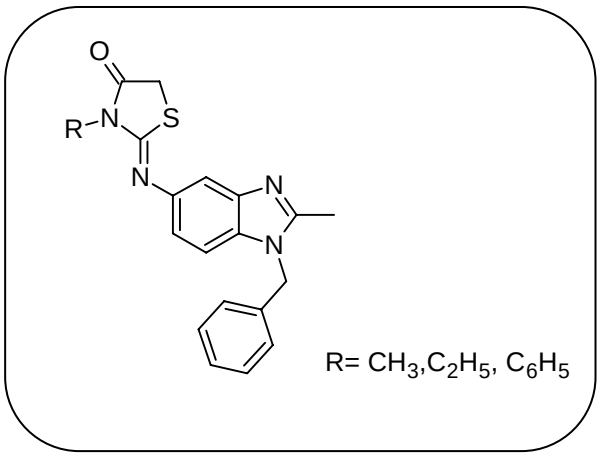


N. Ulusoy et al.[49] have prepared thiazolidinone derivatives as potent antimycobacterial agents. R. Govindarajan et al.[50] have synthesized thiazolidinones as

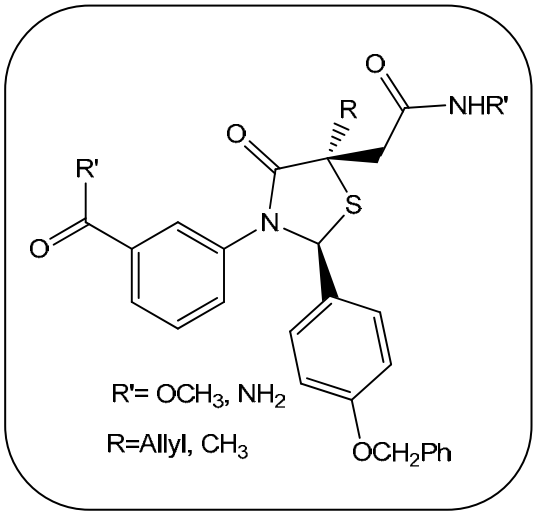
antitubercular, antifungal and antibacterial agent. Hassan et al.[51] have prepared 2-imino-4-thiazolidinones which have been found to possess antimicrobial activity. A. Dandia and co-workers[52] have reported thiazolidinone derivatives as potential antifungal and antitubercular agents. C. Muanprasat et al.[53] have prepared some new thiazolidinone derivatives as CFTR inhibitors. M. G. Vigorita et al.[54] have prepared meso 3,3'-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinones] derivatives as antiinflammatory and analgesic agents. K. Babaoglu et al.[55] have been prepared a virtual library of 2,3,5 trisubstituted- 4-thiazolidinones (12,13) as inhibitors of dTDP-rhamnose synthesis.



C. J. Andres and co-workers[56] have prepared some 4-thiazolidinone derivatives and reported as novel inhibitors of the bacterial enzyme *Mur B* which is a precursor acting during the biosynthesis of peptidoglycan. D. Maclean et al.[57] reported the FSH agonist activity of an encoded 4-thiazolidinone library. M. M. Ramla et al.[58] have been synthesized series of some new derivatives of 2-(1-benzyl-2-methyl-*1H*-benzimidazol-5-ylimino)-3-substituted-thiazolidin-4-ones and studied their inhibitory activity against the *Epstein–Barr Virus-early antigen* (EBV-EA) activation introduced by 12-Otetradecanoylphorbol-13-acetate (TPA).

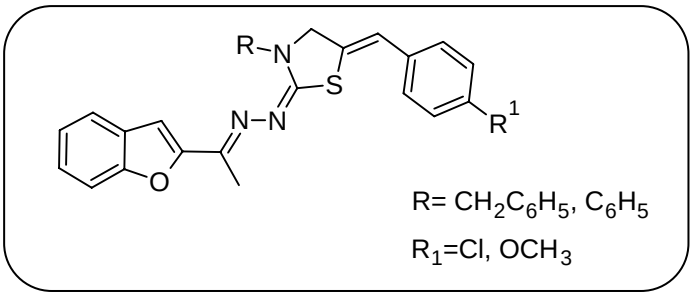


A. Kumar et al.[59] have been synthesized 2-[(4'-oxo-3'-chloro-2'-phenylazetidin-1'-yl) aminomethyl]-3-[4''-(p-chlorophenyl) thiazol-2''-yl]-6-bromoquinazolin-4-ones and screened for their anti-infammatory and analgesic activities at the dose of 50 mg/kg. R. P. Tenorio and co-workers[60] have synthesized 4-thiazolidinones in one and two steps and synthesized compounds were submitted to evaluation against host cells infected with toxoplasma gondii. J. Wrobel et al.[61] have been synthesized 5-alkylated thiazolidinones as follicle-stimulating hormone (FSH) receptor agonists.

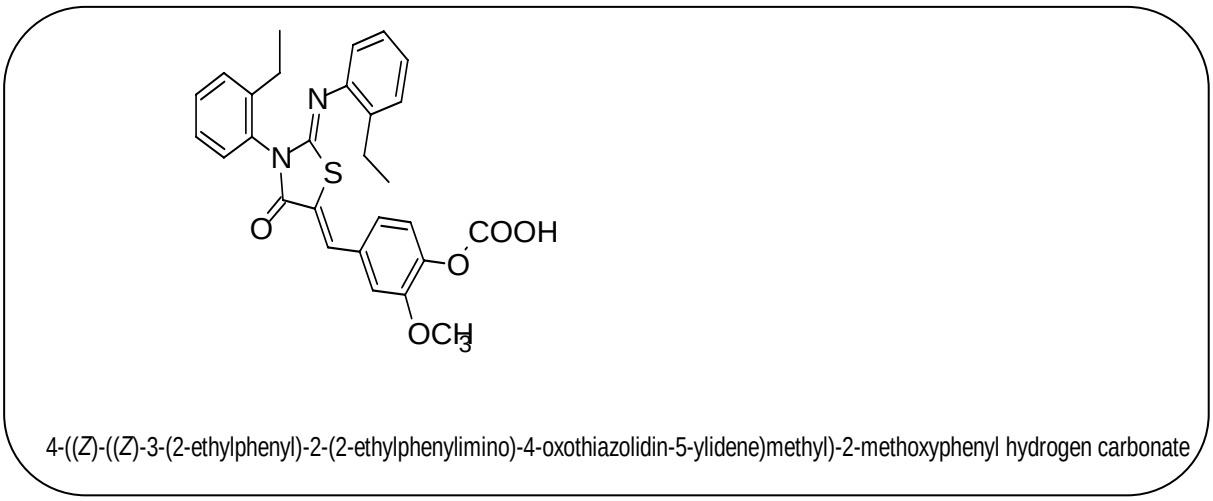


R. Dayam et al.[62] have reported some novel thiazolidinone derivatives as novel class of HIV- integrase inhibitors. N. D. Sonawane et al.[63] have synthesized some new thiazolidinone derivatives as *in vivo* pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents. Antimicrobial activity of some pyrazine containing thiazolidinones have been reported by C. G. Bonda.[64] X. F. Wang et al.[65] have synthesized some novel thiazolidinone derivatives described as new cystic fibrosis transmembrane conductance regulator inhibitor on Cl-conductance in human sweat ducts. F.Ur et al.[66] have constr.ucted some new 6-methylimidazo[2,1-*b*]thiazole-5- carbo hydrazide derivatives and their antimicrobial activities. D. Reigada et al.[67] have reported some new thiazolidinone derivatives as release of ATP from retinal pigment epithelial cells involves both CFTR and vesicular transport. Antiproliferative activities of 2-aryl-4-oxo-thiazolidin-3-yl-amides for prostate cancer have been reported by V. Gududuru et al.[68] D. B. Salinas et al.[69] documented thiazolidinone derivatives as CFTR inhibitor. H. S. Joshi et al.[70] have been reported some thiazolidinones bearing benzo[*b*]thiophene moity as antitubercular and antimicrobial agents. S. M. Rida and co-workers[71] have been

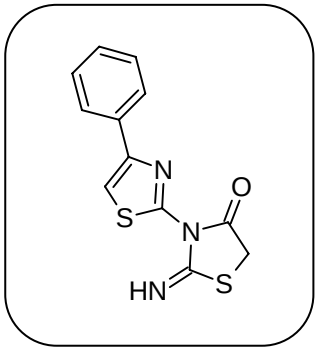
prepared 2-[(1-benzofuran-2-yl-ethylidene)hydrazono]-5-(4-substitutedbenzylidene)-3-substituted-thiazolidin-4-ones as anticancer agents.



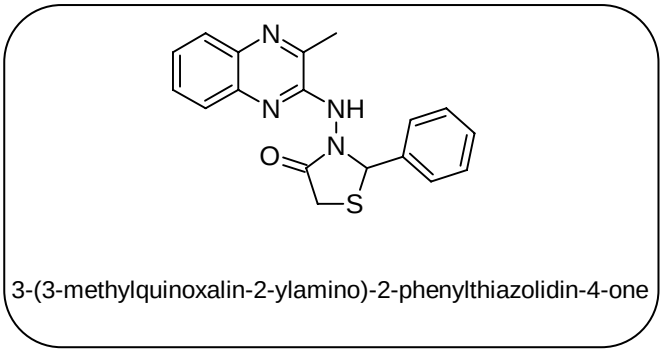
A series of novel 2-arylimino-3-aryl-thiazolidine-4-ones was designed, synthesized and tested for *in vitro* antibiofilm activity against Staphylococcus epidermidis.[72] Among them tested, some compounds with carboxylic acid groups showed good antibiofilm activity. The antibiofilm concentration of 1x was 6.25 lM.



Liu et al.[73] synthesized derivatives of 2-imino-3-(4-arylthiazol-2-yl)thiazolidin-4-ones and series of their 5-arylidene derivatives and tested for antifungal activity against seven agricultural fungi.

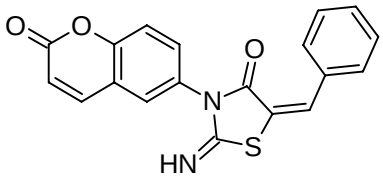


G.C. Sekhar et al.[74] have synthesized compounds and most of them were found to possess moderate activity against fungi.aspergillus flavus and candida albican respectively. The antifungal activities of test compounds were compared with standard salicylic acid (20 - 30 mm) and chlotrimazole (25 - 30 mm).



3-(3-methylquinoxalin-2-ylamino)-2-phenylthiazolidin-4-one

V.V. Mulwad et al.[75] have been screened compounds various thiazolidine derivetives for their antimicrobial activity by cup plate method and have found to exhibit significant activity against *B.Subtilis, E.coli* at different concentration (50 and 100 µg/ml) using DMSO as solvent.



(*E*)-5-benzylidene-2-imino-3-(2-oxo-2*H*-chromen-6-yl)thiazolidin-4-one

Work done from our laboratory

K.M.Thaker et al[76] have synthesized 2-aryl-5H-(3',5'-dichroro-2-benzo(b)thio phenoyl -amino)-4-thiazolidinone bearing the benzo[b]thiophene nucleus as potent antimicrobial agents. S.L.Vasoya et al[77] have synthesized some new2-aryl-5H-(3'-chloro-5'-phenoxybenzo(b)thiophenoyl-2-amino)-4-thiazolidinone nucleus as potent antimicrobial agents.

With an intention of preparing the compounds possessing better therapeutic activity, We have undertaken the synthesis of thiazolidinones bearing chroman nucleas which have been described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-FLUORO-*N*-(4-OXO-2-ARYLTHIAZOLIDIN-3-YL) CHROMAN-2-CARBOXAMIDES.

Part – B

[Part – Ⅳ (Section-i)]

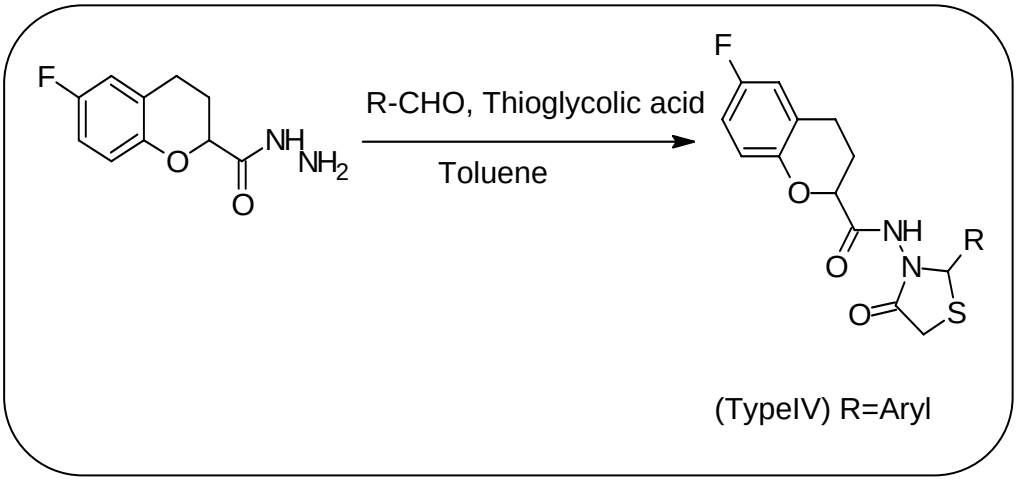
Synthesis and biological evaluation of 6-fluoro-N(4-oxo-2-arylthiazolidin-3-yl) chroman-2-carboxamides.

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-FLUORO-*N*-(4-OXO-2-ARYLTHIAZOLIDIN-3-YL)CHROMAN-2-CARBOXAMIDES.

With a view to getting better therapeutic agents and considering the association of various biological activities of thiazolidinonone heterocycles, the synthesis of thiazolidinones have been undertaken by the condensation of different aryl aldehydes with 6-fluorochroman-2-carbohydrazide and thioglycolic acid(mercapto acetic acid), as shown in reaction scheme.

REACTION SCHEME



The constitution of all the synthesized compounds have been characterized by using elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and further supported by mass spectroscopy. Purity of all the compounds has been checked on thin layer chromatographic plate.

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method with two Gram-positive bacteria, two Gram-negative bacteria and three fungal strains. The biological activities of the synthesized compounds have been compared with standard drugs.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using DRS (diffusive reflectance system) method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR and ^{13}C NMR were determined in $CDCl_3$ and DMSO solution on a Bruker AC 400 MHz and 100MHz spectrometer. Elemental analysis of the all the synthesized compounds were carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned

[A] Synthesis of 6-Fluorochroman-2-carbohydrazide.

See PART-B, part-I, section-I [B].

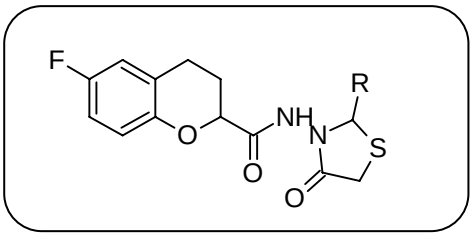
[B] General procedure for the preparation of 6-Fluoro-*N*-(4-oxo-2-aryl thiazolidin-3-yl)chroman-2-carboxamides.

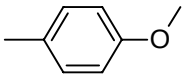
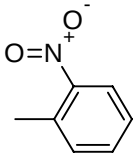
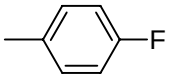
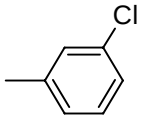
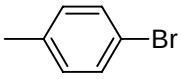
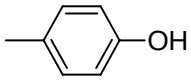
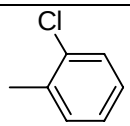
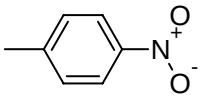
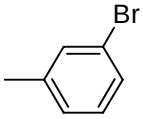
A mixture of 6-fluorochroman-2-carbohydrazide (2.0 g,0.01mol), different aryl aldehydes (0.01 mol) and thioglycolic acid(mercapto acetic acid) (26.7 g≅20.4 ml, 0.29 mol) in toluene (50 ml) was refluxed in a Dean-Stark assembly with continuous stirring. After completion of the reaction (48 hours monitoring by TLC), the content was cooled to room temperature then neutralized with sodium bicarbonate solution.The organic extracts was washed with water (2 x 10 ml), dried with Na_2SO_4, solvent was removed *in vacuo* and the resulting crude product was purified by column chromatography to give the analytical pure compounds. The physical constants of the products are recorded in **Table-9a.**

[C] Biological evaluation of 6-Fluoro-*N*-(4-oxo-2-arylthiazolidin-3-yl)chroman-2-carboxamides.

Antimicrobial testing was carried out as described in Part-B, Part-IV, Section-I, antimicrobial activity. The MIC values of the test compounds are recorded in **Table-9b**.

Table-9a: Physical constant of 6-Fluoro-*N*-(4-oxo-2-arylthiazolidin-3-yl)chroman-2-carboxamides.



Sr. No	Substitution R	M. F.	M. W.	Yield (%)	R_f value
9a		$C_{20}H_{19}FN_2O_4S$	402.43	85	0.55
9b		$C_{19}H_{16}FN_3O_5S$	417.41	95	0.62
9c		$C_{19}H_{16}F_2N_2O_3S$	390.40	89	0.57
9d		$C_{19}H_{16}ClFN_2O_3S$	406.85	77	0.44
9e		$C_{19}H_{16}BrFN_2O_3S$	451.30	90	0.38
9f		$C_{19}H_{17}FN_2O_4S$	388.41	73	0.58
9g		$C_{20}H_{19}FN_2O_3S$	386.43	84	0.49
9h		$C_{19}H_{16}ClFN_2O_3S$	406.85	71	0.33
9i		$C_{17}H_{14}FN_3O_2$	417.41	79	0.71
9j		$C_{19}H_{16}FN_3O_5S$	451.30	88	0.41

TLC solvent system:- E.A. : Hexane = 5 : 5

ANALYTICAL DATA

6-Fluoro-*N*-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9a). mp 98-100 °C; IR (DRS): 3383, 3081, 2858, 1714, 1688, 1542, 1465, 1356, 1278, 1152, 1077, 887, 712, 689, 584 cm^{-1};MS: *m/z* = 402 $[M]^+$; Anal. Calcd for $C_{20}H_{19}FN_2O_4S$: C, 59.69; H, 4.76; N, 6.96. Found: C, 59.23; H, 4.61; N, 6.88%.

6-Fluoro-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9b).mp 190-192°C; IR (DRS): 3392, 3205, 2918, 2850, 1712, 1678, 1523, 1485, 1390, 1259, 1190, 864, 702, 657, 561 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): δ ppm 1.81-2.05(m, 2H, 2CH), 2.61-2.74(m, 2H, 2CH), 3.68-3.72(d, *J*=16.0 Hz, 1H, CH), 3.91-3.95(d, *J*=15.6 Hz, 1H, CH), 4.66-4.69(d,d, *J*=3.6 Hz, 3.2 Hz, 1H, CH), 6.12(s, 1H, CH), 6.72-6.79(m, 1H, ArH), 6.84-6.91(m, 2H, ArH), 7.60-7.63(t, 1H, ArH), 7.78-7.87(m, 2H, ArH), 8.04-8.06(d, *J*= 8.0 Hz, 1H, ArH), 10.43-10.46(d, *J*= 11.6 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm, 22.71, 23.56, 24.14, 29.29, 29.38, 29.71, 30.50, 50.43, 58.29, 75.20, 114.27, 114.51, 115.60, 115.83, 117.60, 123.26, 125.40, 127.95, 129.88, 134.07, 134.28, 148.30, 148.40, 156.16, 162.20, 169.32, 169.47.MS: *m/z* = 417 $[M]^+$; Anal. Calcd for $C_{19}H_{16}FN_3O_5S$: C, 54.67; H, 3.86; N, 10.07. Found: C, 54.58; H, 3.49; N, 9.99%.

6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9c). mp 106-110 °C; IR (DRS): 3487(Ar, C-H str.), 3041(Ar, C-H str.), 2958(C-H str.), 2848(C- H str.), 1710(amide C=O str.), 1676(amide C=O str.), 1537(Ar, C=C str.), 1429(Ar, C=C str.), 1388(C-H ben), 1261(C-F str.), 1190(C-F str.), 1078(C-N str.), 891(C-H o,p, ben), 868(C-H o,p, ben), 813(C-H o,p, ben), 759(C-H o,p, ben), 709(C-C o,p, ben), 673(C-C o,p, ben), 650(C-Co,p, ben), 592(C-C o,p , ben) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.82-2.02(m, 2H, 2CH), 2.56-2.70(m, 2H, 2CH), 3.59-3.78(m, 2H, 2CH), 4.45-4.58(d,d, *J*=10.52 Hz, 11.52 Hz, 1H, CH), 5.79-5.83(d, *J*= 17.32 Hz, 1H, CH), 6.54-6.72(m, 3H, ArH), 6.86-6.90(t, 1H, ArH), 6.99-7.03 (t, 1H,ArH), 7.20-7.22(t, 1H, ArH), 7.33-7.36(t, 1H, ArH), 8.05-8.13(d, *J*= 29.44 Hz, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm,22.71, 23.07, 23.52, 23.87, 24.21, 29.37, 29.71, 30.06, 30.08, 31.94, 50.26, 62.05, 62.48, 74.81, 75.14, 114.23, 114.31, 114.46, 114.54, 115.44, 115.55, 115.67, 115.78, 115.89, 116.11, 117.54, 117.60, 117.68, 122.69, 122.77, 123.20, 123.27, 129.82, 129.90, 130.16, 130.25, 131.95, 131.98, 132.37, 132.40, 148.06, 148.24, 156.10, 158.49, 162.07, 162.17, 164.55, 164.65, 169.15, 169.33, 169.47; MS: *m/z* = 390 $[M]^+$; Anal. Calcd for $C_{19}H_{16}F_2N_2O_3S$: C, 58.45; H, 4.13; N, 7.18. Found: C, 58.02; H, 4.03; N, 7.10%.

***N*-(2-(3-chlorophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9d).** mp 151-153°C; IR (DRS): 3401 , 3284, 3074, 2987, 2851, 1717, 1645, 1612, 1585, 1468, 1352, 1278, 1184,1066, 820, 754, 710, 636, 541 cm^{-1}; MS: *m/z* = 406 $[M]^+$; Anal. Calcd for $C_{19}H_{16}ClFN_2O_3S$: C, 56.09; H, 3.96; N, 6.89. Found: C, 55.90; H, 3.83; N, 6.83%.

***N*-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9e).** mp 118-120 °C; IR (DRS): 3412, 3081, 2975, 2844, 1706, 1641, 1579, 1556, 1464, 1332, 1272, 1045, 831, 750, 592, 545 cm^{-1}; MS: *m/z* = 452 $[M+1]^+$; Anal. Calcd for $C_{19}H_{16}BrFN_2O_3S$: C, 50.56; H, 3.57; N, 6.21. Found: C, 50.45; H, 3.28; N, 6.11%.

6-Fluoro-*N*-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9f). mp 132-134°C; IR (DRS): 3564, 3442, 3080, 2983, 2867, 1705, 1629, 1572, 1525, 1462, 1374, 1245, 1196, 1074, 830, 748, 676 cm^{-1}; MS: *m/z* = 388 $[M]^+$; Anal. Calcd for $C_{19}H_{17}FN_2O_4S$: C, 58.75; H, 4.41; N, 7.21. Found: C, 58.56; H, 4.34; N, 7.06%.

6-Fluoro-*N*-(4-oxo-2-(*p*-tolyl)thiazolidin-3-yl)chroman-2-carboxamide (9g). mp 89-91°C; IR (DRS): 3410, 3077, 2978, 2863, 1714, 1625, 1609, 1563, 1464, 1322, 1238, 1142, 1054, 870, 798, 675, 542 cm^{-1}; MS: *m/z* = 386 $[M]^+$; Anal. Calcd $C_{20}H_{19}FN_2O_3S$: C, 62.16; H, 4.96; N, 7.25. Found: C, 62.07; H, 4.55; N, 7.09%.

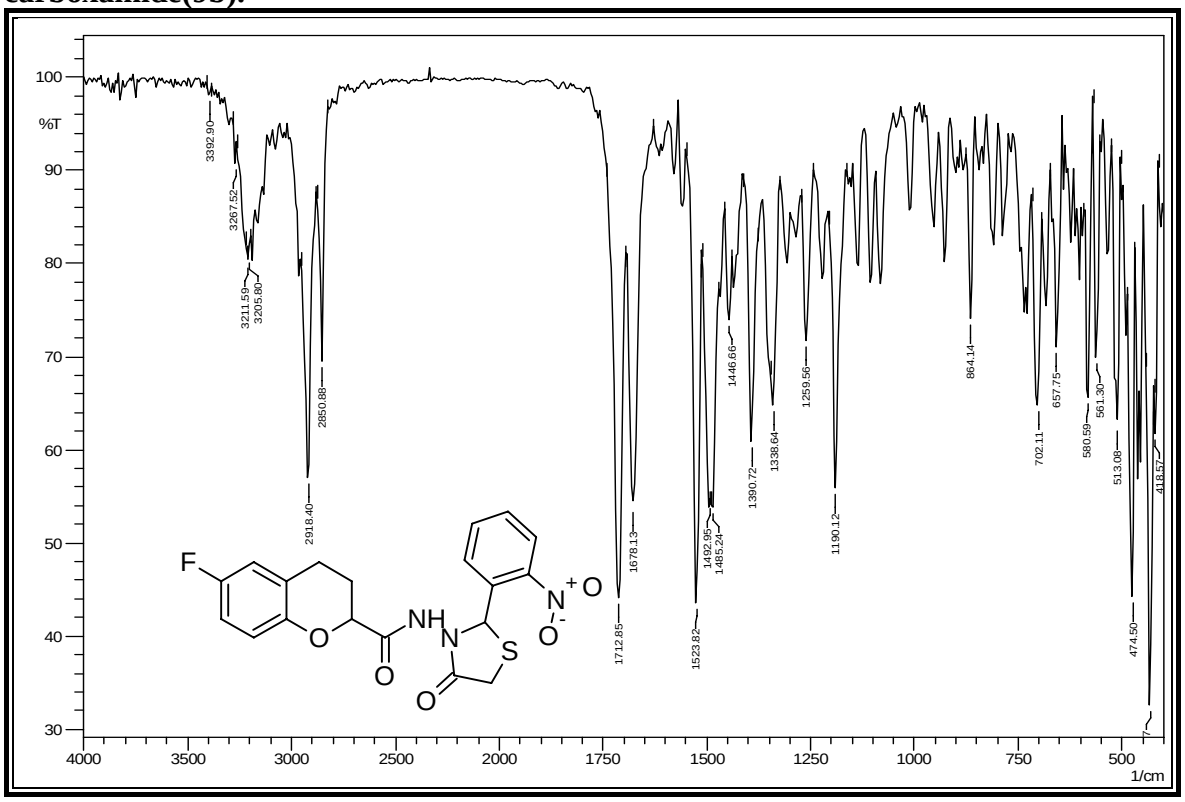
***N*-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9h).** mp 158-160°C; IR (DRS): 3391, 3113, 3054, 2962, 2854, 1702, 1603, 1545, 1542, 1452, 1302, 1260, 1146, 1078, 1021, 841, 798, 756, 674, 651, 531 cm^{-1}; MS: *m/z* = 406 $[M]^+$; Anal. Calcd for $C_{19}H_{16}ClFN_2O_3S$: C, 56.09; H, 3.96; N, 6.89. Found: C, 55.93; H, 3.77; N, 6.84%.

6-Fluoro-*N*-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide (9i). mp 207-209°C; IR (DRS): 3405, 3075, 2964, 2853, 1721, 1601, 1581, 1423, 1385, 1254, 1149, 1021, 878, 754, 720, 678, 531 cm^{-1}; MS: *m/z* = 417 $[M]^+$; Anal. Calcd for $C_{17}H_{14}FN_3O_2$: C, 54.67; H, 3.86; N, 10.07. Found: C, 54.39; H, 3.79; N, 9.89%.

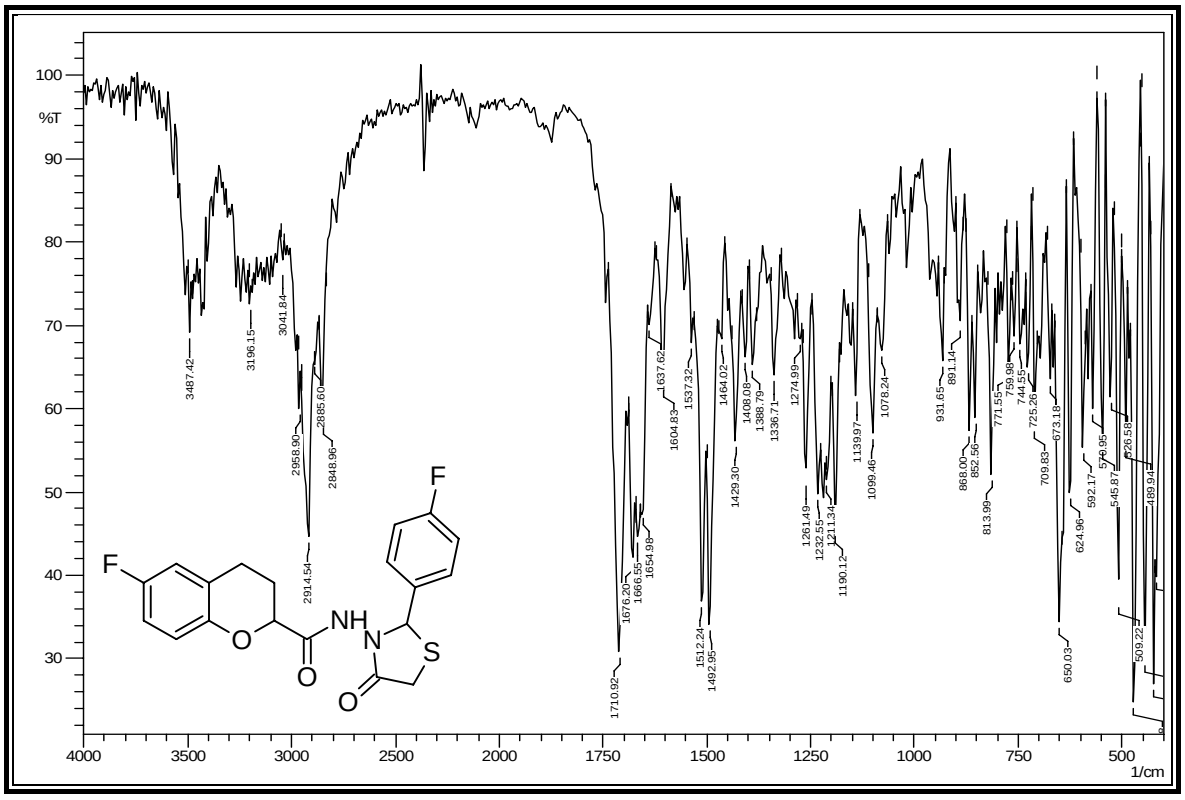
***N*-(2-(3-bromophenyl)-4-oxothiazolidin-3-yl)-6-fluorochroman-2-carboxamide (9j).** mp 166-168°C; IR (DRS): 3395, 3061, 2951, 2872, 1701, 1689, 1589, 1579, 1462, 1356, 1254, 1099, 1041, 881, 755, 692, 565 cm^{-1}; MS: *m/z* = 452$[M+1]^+$; Anal. Calcd for $C_{19}H_{16}FN_3O_5S$: C, 50.56; H, 3.57; N, 6.21. Found: C, 50.17; H, 3.14; N, 6.12%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

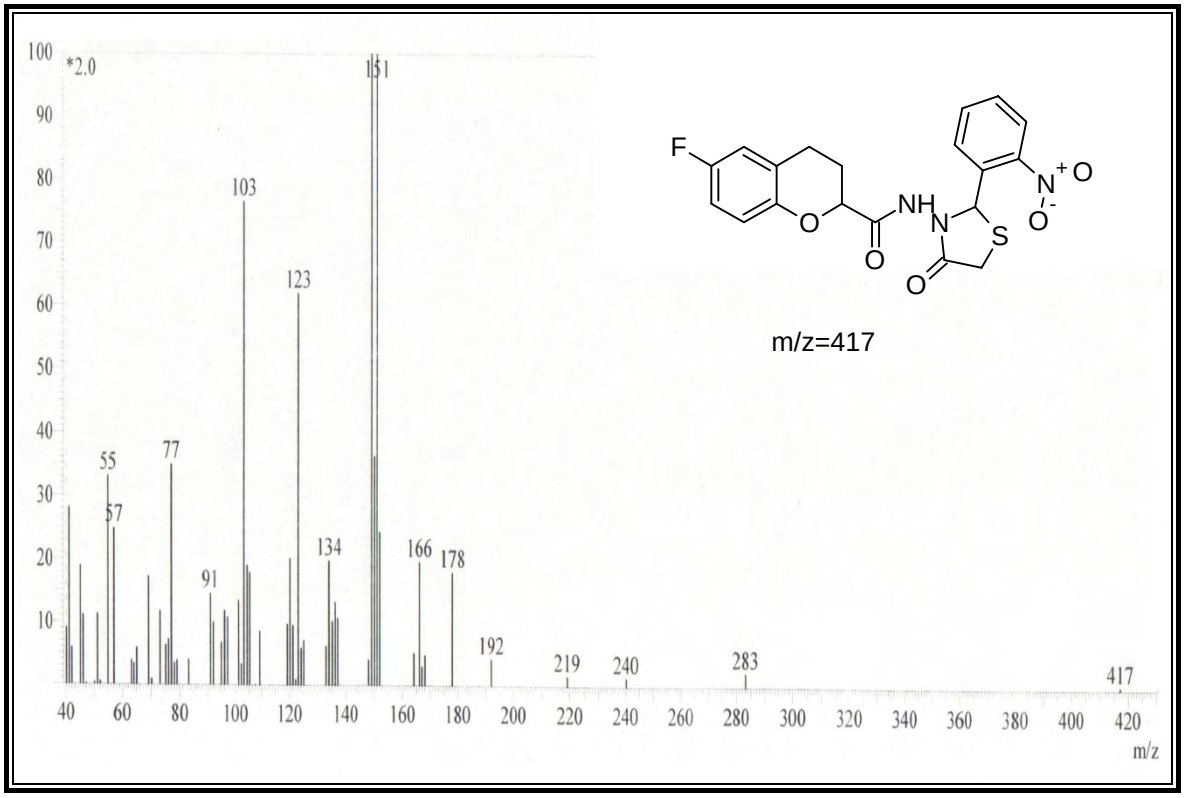
IR Spectrum of 6-Fluoro-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).



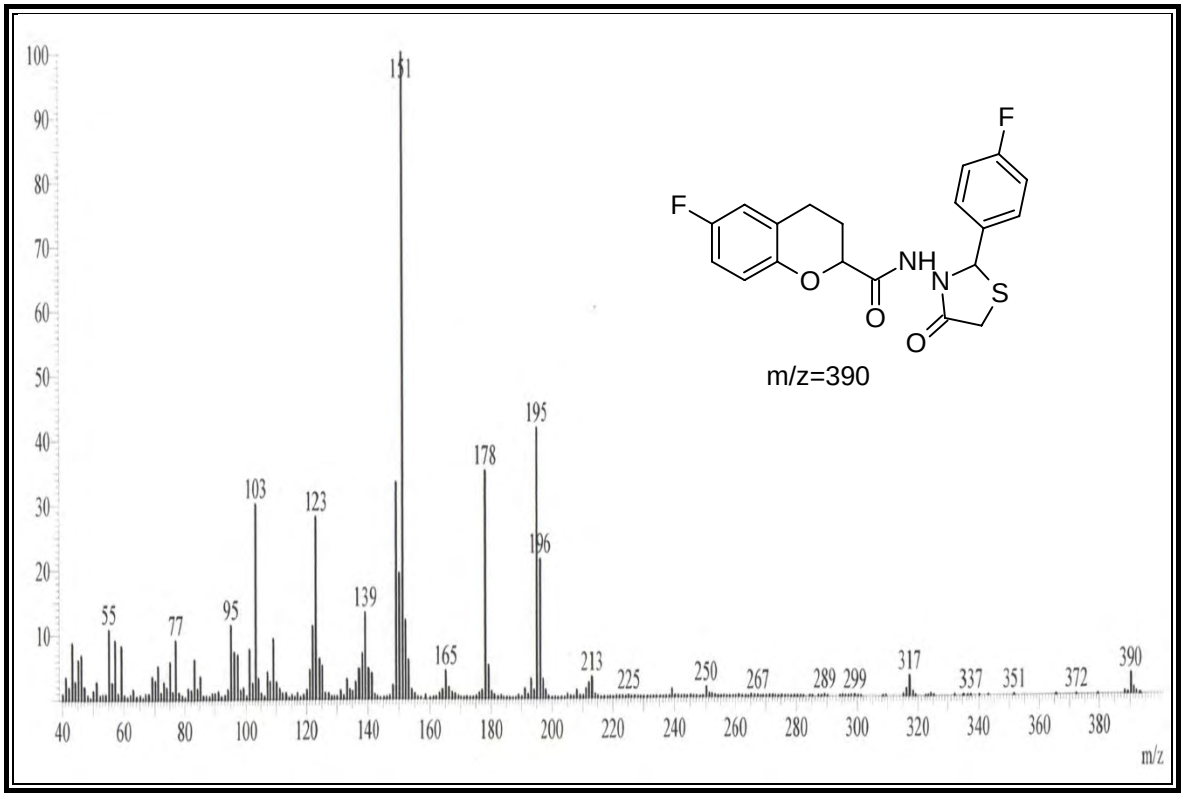
IR Spectrum of 6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).



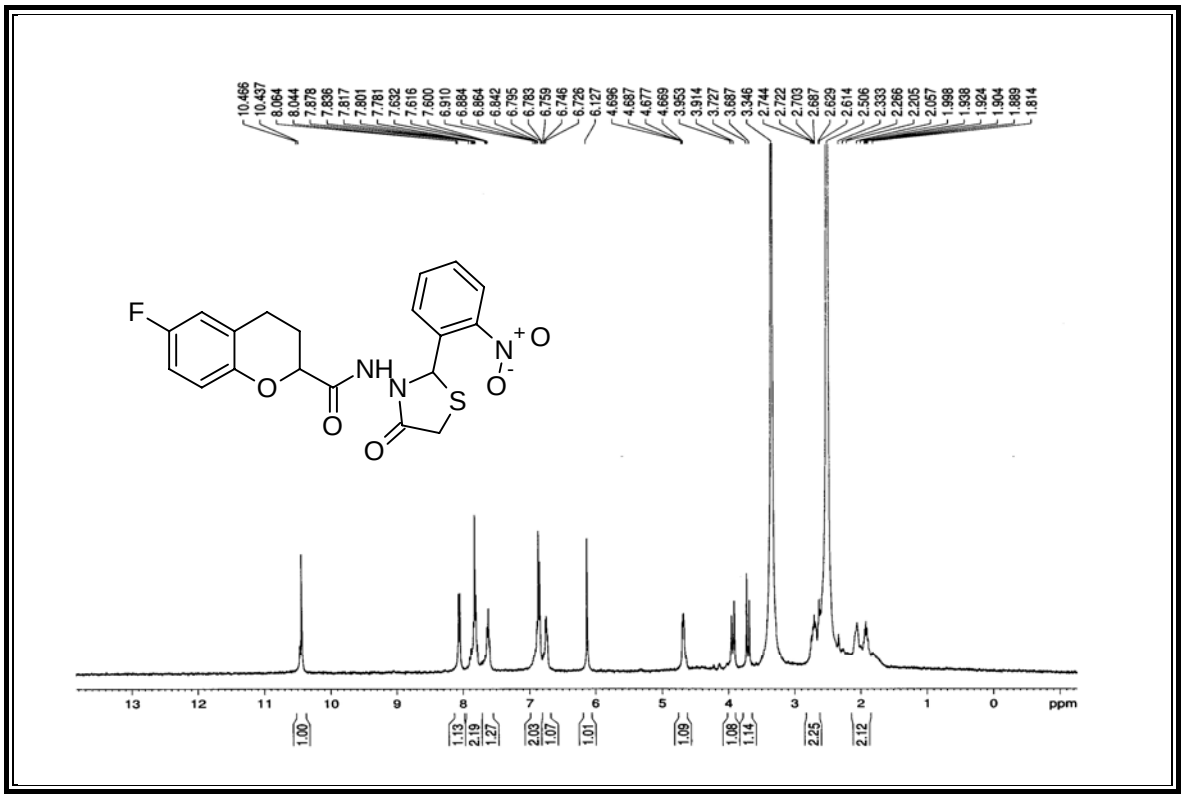
Mass spectrum of 6-Fluoro-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).



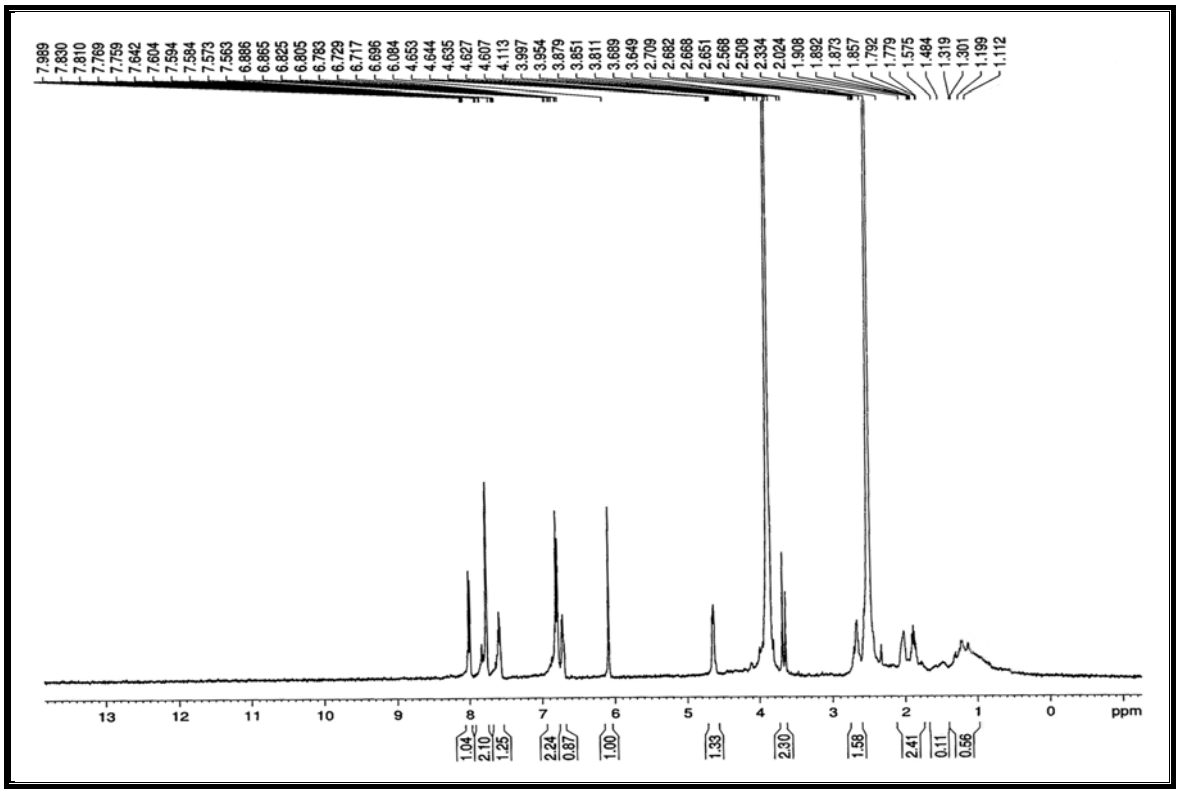
Mass spectrum of 6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).



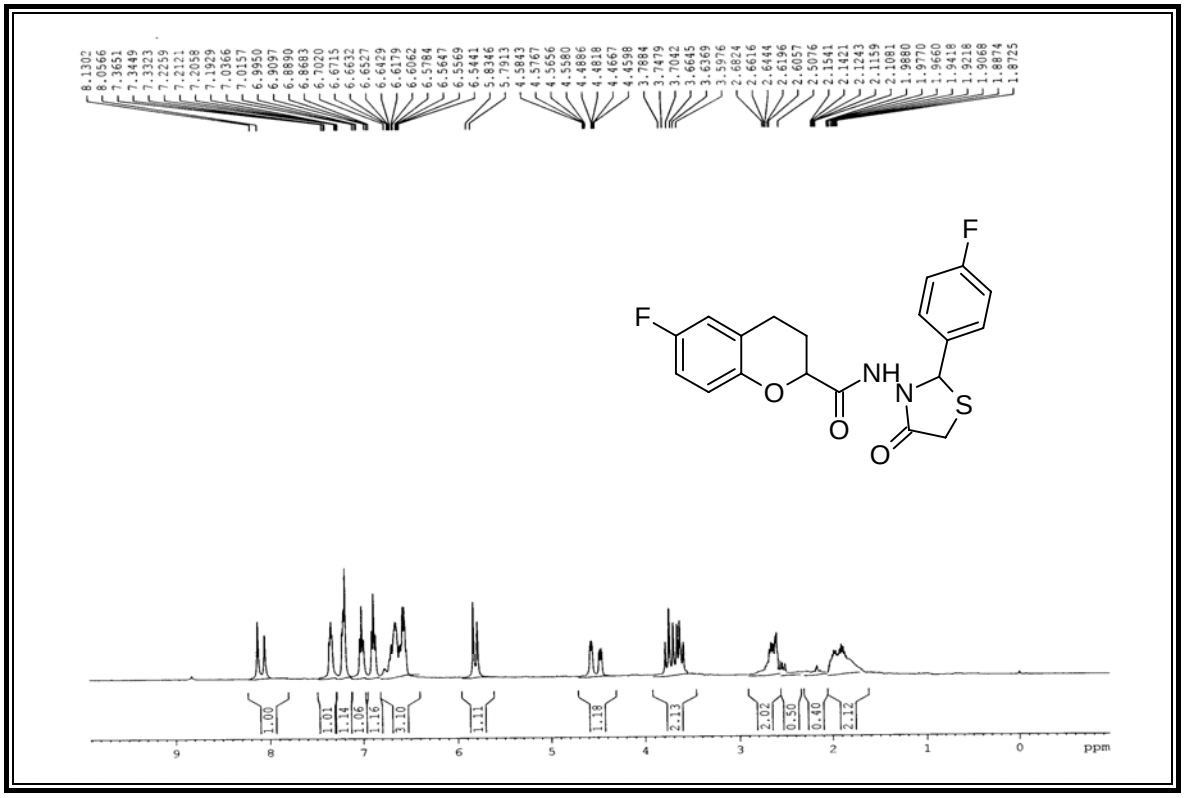
^{1}H NMR spectrum of 6-Fluoro-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).



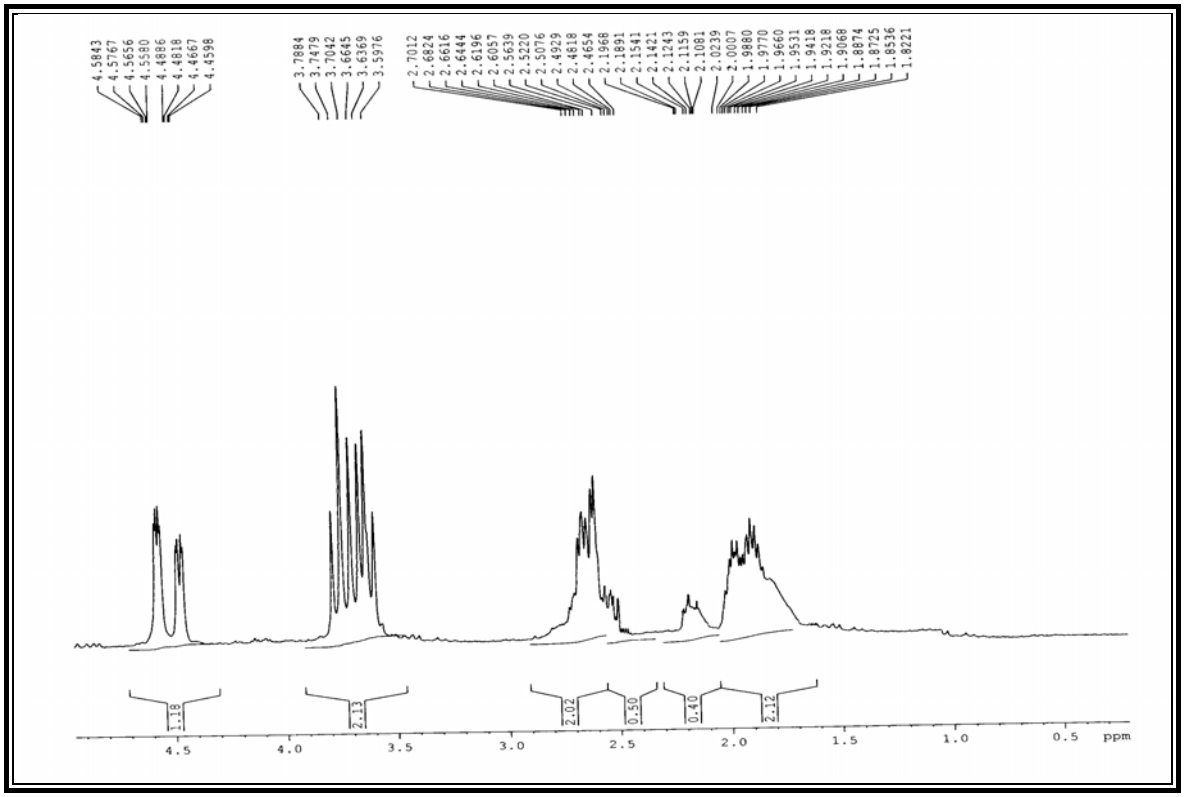
D_2O Exchange ^{1}H NMR spectrum of 6-Fluoro-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl) chroman-2-carboxamide (9b).



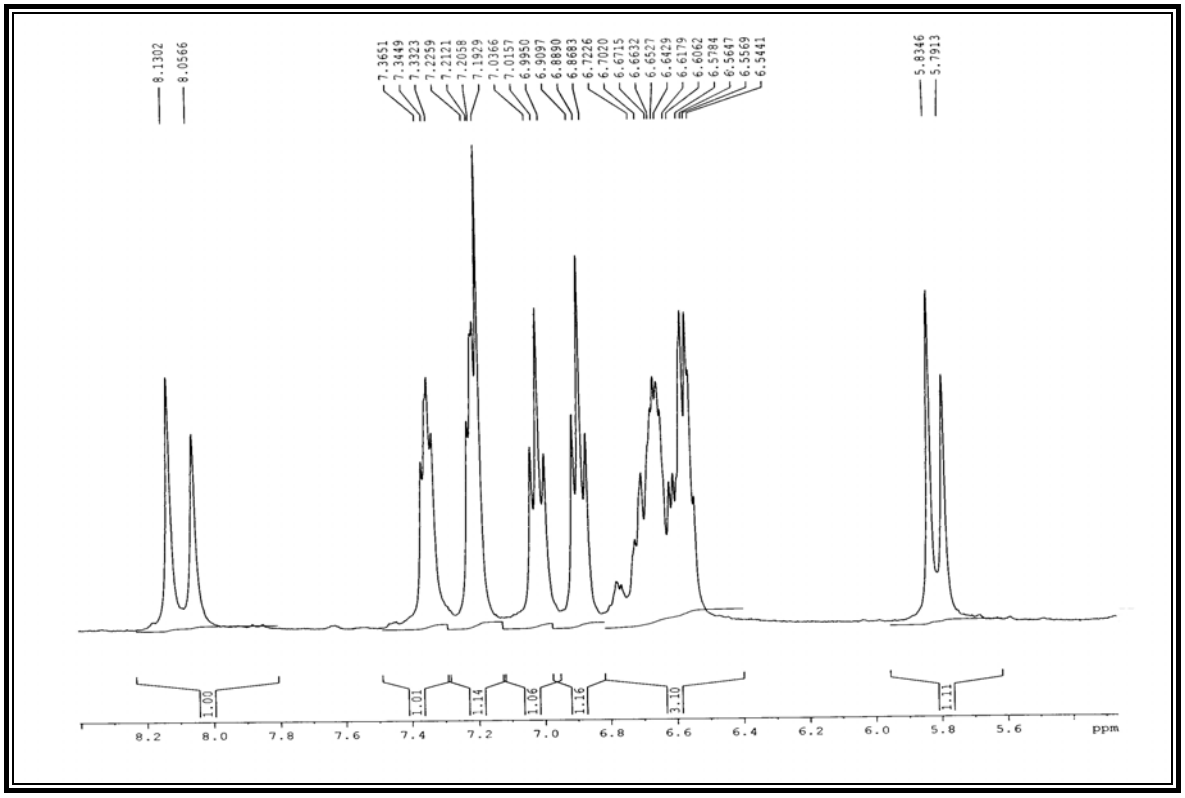
^{1}H NMR spectrum of 6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).



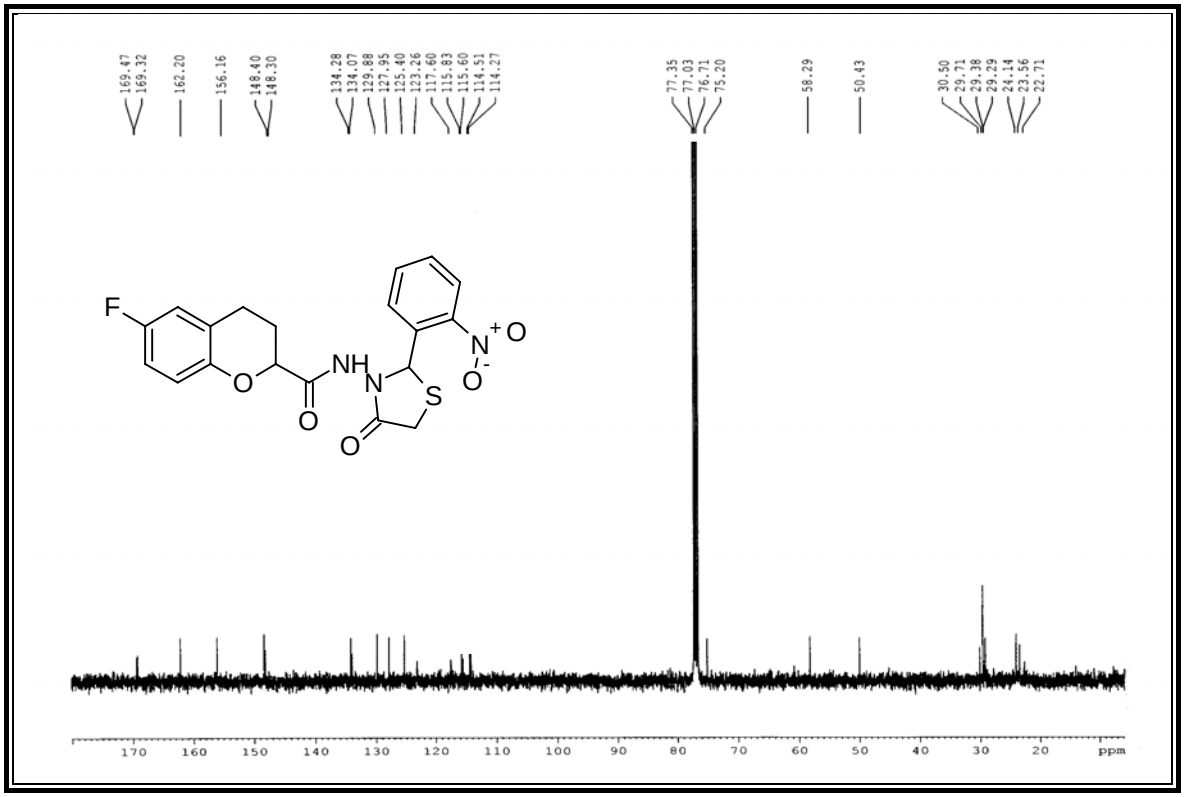
Expanded spectrum of 6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).



Expanded spectrum of 6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).



^{13}C NMR spectrum of 6-Fluoro-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9b).



^{13}C NMR spectrum of 6-Fluoro-*N*-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)chroman-2-carboxamide(9c).

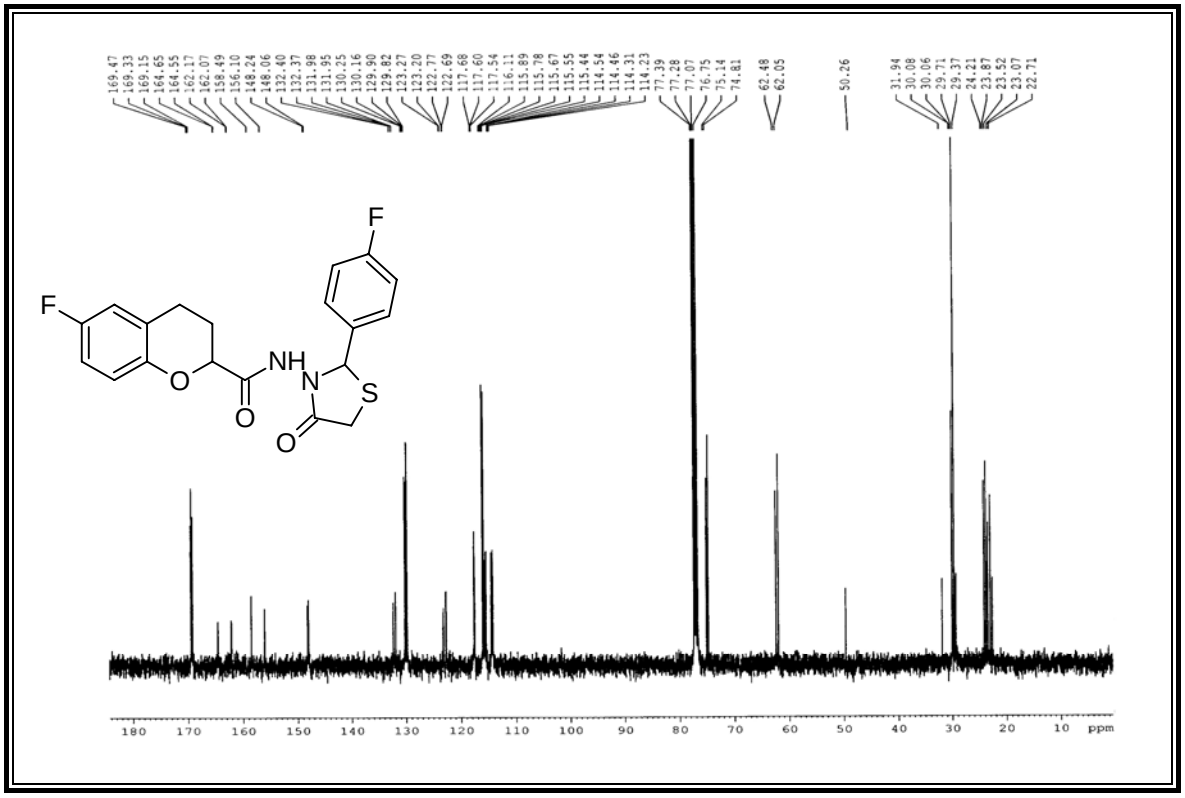


Table-9b: Antimicrobial activity of 6-Fluoro-*N*-(4-oxo-2-arylthiazolidin-3-yl) chroman-2-carboxamides.

Sr. No.	Antibacterial Activity				Antifungal activity		
	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram +*ve* Bacteria		Gram –*ve* Bacteria				
	S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
9a	250	250	125	250	>1000	1000	1000
9b	200	200	200	125	1000	250	500
9c	125	200	200	200	1000	500	500
9d	250	200	125	62.5	1000	500	500
9e	500	250	500	500	1000	1000	1000
9f	250	200	250	250	500	500	500
9g	100	250	62.5	200	1000	250	1000
9h	125	200	200	250	500	1000	1000
9i	250	250	100	125	1000	>1000	>1000
9j	200	200	100	200	>1000	>1000	>1000

MINIMAL INHIBITION CONCENTRATION

Standard Drugs	S.aureus	S.pyogenus	E.coli	P.aeruginosa
	(microgramme/ml)			
Gentamycin	0.25	0.5	0.05	1
Ampicillin	250	100	100	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	50	50	25	25
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

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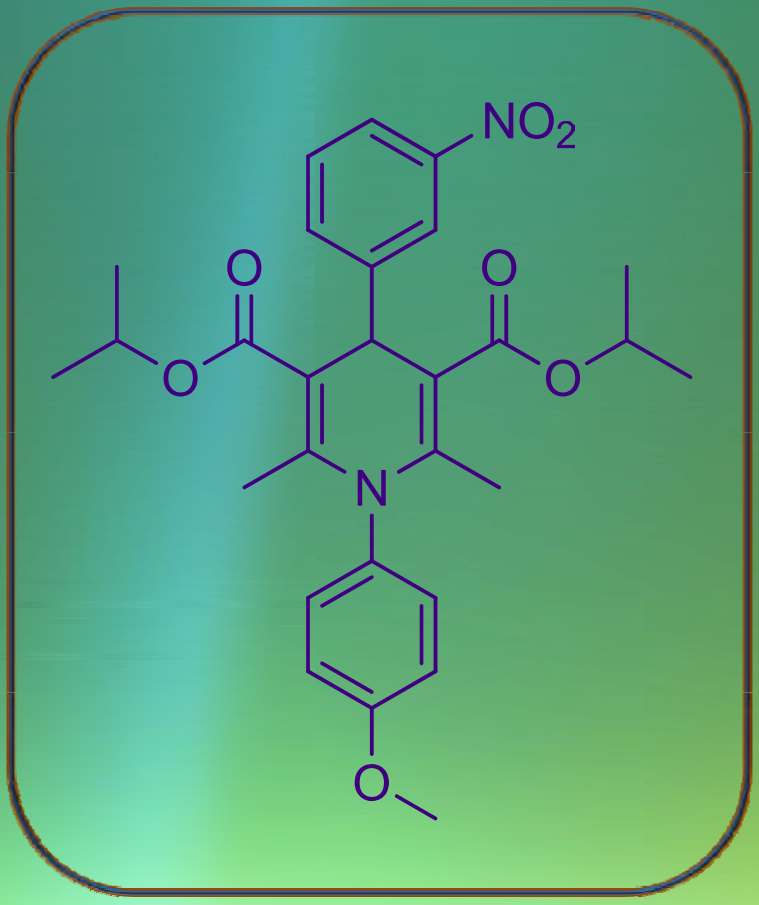
PART-C

X-RAY CRYSTALLOGRAPHY STUDY OF DIHYDROPYRIDINE DERIVATIVE.

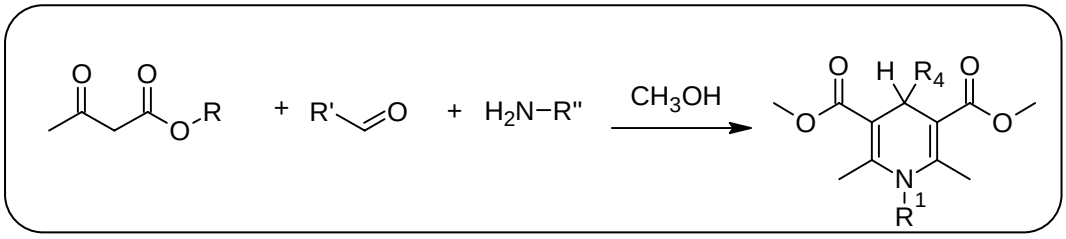


INTRODUCTION

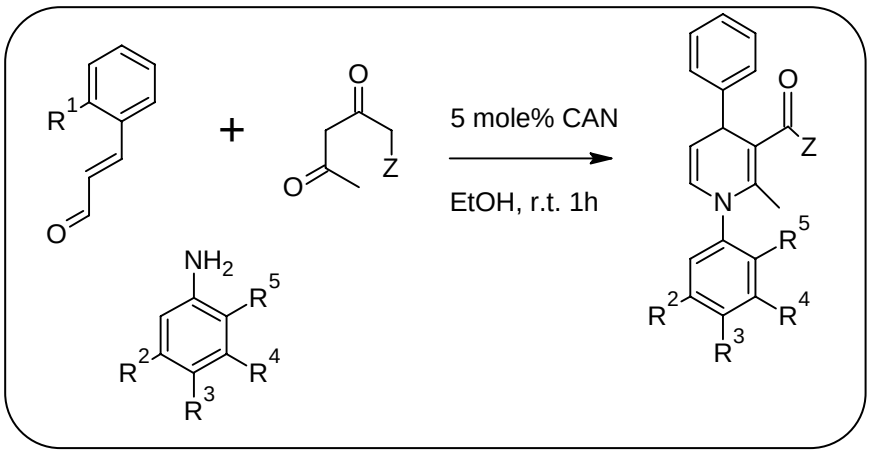
During discovery of Nifedipine, Loev and co-workers[1] reported that the N-phenyl-1,4-dihydropyridine was also formed by reaction of benzalaniline and acetoacetic ester.[2,3] 1,4-Dihydropyridines are versatile compounds because their derivatives play important roles in medicinal chemistry; for example, nifedipine, amlodipine and other antihypertensive agents.[4] Among the numerous methods developed for the synthesis of 1,4-dihydropyridines, Hantzsch reaction is one of the most well-accepted methods and much effort has been made to modify this reaction.[5] However, these classical methods were not enough to make pyridine libraries.

SYNTHETIC ASPECT

A series of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diesters substituted at the N-1 positions of the dihydropyridine **(4)** ring was synthesized by I. O. Donkor et al.[6] The *in vitro* cytotoxicity and *in vitro* and *in vivo* radioprotective efficacy of these agents were evaluated in Chinese hamster (V-79) cells and CD2F1 male mice, respectively.



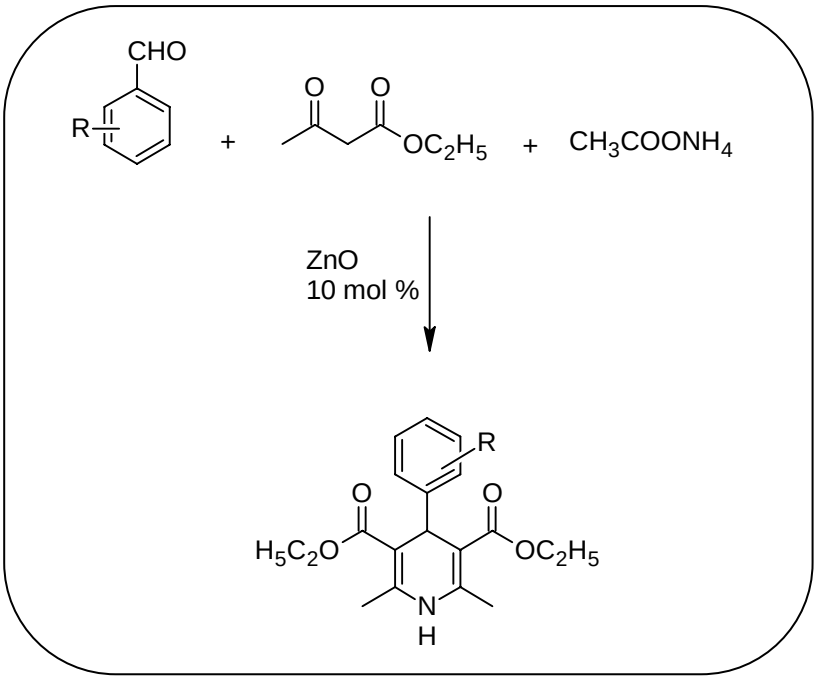
Ceric ammonium nitrate (CAN) catalyzed the three-component domino reaction between aromatic amines, a,â-unsaturated aldehydes, and ethyl acetoacetate, providing an efficient new N-aryl-5,6-unsubstituted dihydropyridines **(9)**.[7]



Mustafa *et al.*[8] developed an efficient synthesis method for 1,4-dihydropyridines. It has been developing using 3 or 4 component condensation reactions of aldehydes, 1,3-dicarbonyl compounds, and ammonium acetate in the presence of alumina sulfuric acid catalyst in minimum methanol at reflux temperature. This procedure offers several advantages including high yields, an environment friendly procedure, short reaction time, and a simple work-up procedure.

1,4-Dihydropyridines (DHPs) are class of nitrogen containing heterocycles having a 6-membered ring. 1,4-DHPs, which are the most potent calcium antagonists or calcium channel blockers, have received much attention due to their wide range of pharmaceutical and biological properties such as inhibition of human cytochrome P450 enzyme,[9] angiotensine-converting enzyme inhibition, and blood pressure control on chronic, nondiabetic nephropathies.[10] 1,4-DHP compounds play important roles in medicinal chemistry, for example nifedipine, amlodipine, felodipine, and nicardipine, which are the best selling drugs used in the treatment of cardiovascular diseases.[11]

Matloubi *et al.*[12] have synthesized one-pot four-component reaction of aldehydes, ethyl acetoacetate/5,5-dimethyl-1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate in the presence of 10 mol% of ZnO as a heterogeneous catalyst for the synthesis of corresponding 1,4- dihydropyridine and polyhydroquinoline derivatives *via* the Hantzsch condensation is described. The present methodology offers several advantages such as simple procedure, excellent yields, and short reaction time.



The usefulness of these calcium antagonists has led to the development of novel synthetic strategies to improve classical methods of preparation[13-15] and microwave activation stands among the alternative routes proposed the past decade.

Aromatization of 1,4-DHP has also attracted considerable attention in recent years as Böcker[16] has demonstrated that metabolism of drugs involves a cytochrome P-450 catalyzed oxidation in the liver. The so-obtained pyridines are devoid of the pharmacological activity of the parent heterocycles and are further transformed by additional chemical modifications. Due to the biological importance of the oxidation step of 1, 4-DHP, that reaction has been the subject of a large number of studies and a plethora of reagents has been utilized to mimic the *in vivo* transformation. In that field, surprising results have been collected when the reactions are performed under microwave irradiation.

The pioneering report on the use of microwave activation to obtain Hantzsch 1,4-DHP was published by Alajarin et al. in 1992.[17]This group prepared a series of 4-aryl derivatives in a domestic oven by the classical multicomponent method (aldehyde: 15 mmol; alkyl acetoacetate: 43 mmol; ammonia: 30 mmol; ethanol: 3 mL). Yields ranged from 15 to 52 % for a reaction time of 4 minutes. The authors claim that classical protocols for the formation of the same compounds require a reflux period of 12 hours but they did not notice any yield improvement when microwave irradiation was applied.

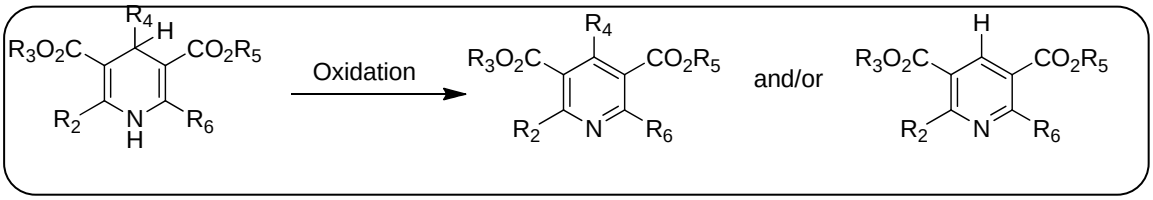
Three years later the same group extended its work[18] to the preparation of 3,5-unsymmetrically substituted 1,4-DHP starting from arylmethyleneacetoacetate (8 mmol) and 3-aminocrotonate (4 mmol) in ethanol (4.5 mL). This report again emphasizes that the rapidity of the microwave-assisted syntheses does not affect the isolated yields. The same year Zhang[19] obtained four 4-aryl 1,4-DHP from 3-aminocrotonate (20 mmol), methyl acetoacetate (20 mmol) and arylaldehydes (20 mmol) in a domestic oven. For the first time, the preparations were conducted in the absence of solvent. Yields ranging from 59 to 77 % are reported and optimized heating periods do not exceed 10 minutes. To avoid any loss of volatile material, the reaction flasks were fitted with a condenser containing xylene. Also in 1995, Khadilkar[20] used the same building blocks as Zhang but in the presence of a solvent (ethanol, volume not reported; 3-aminocrotonate: 10 mmol; methyl acetoacetate: 14 mmol; arylaldehyde: 10 mmol). The heterocycles were prepared in a domestic oven within 3 to 5 minutes in 32 to 80 % yield.

Interestingly, Khadilkar[21] also described the formation, in a domestic oven, of 1,4-DHP in an aqueous hydro trope solution (50% butylmonoglycolsulphate : 5 ml). The experiments were performed with 3-aminocrotonate (10 mmol), methyl acetoacetate (14 mmol) and aliphatic or aromatic aldehydes (10 mmol). The final products were obtained within 3 to 6 minutes in 35 to 97 % yield. All reactions described by Khadilkar [20,21] were carried out by exposing the reactants to microwaves in containers equipped with a condenser charged with precooled carbon tetrachloride. The coupling of microwave heating (in a domestic oven) with the use of a mineral solid support (alumina: 2 g) has later been exploited by Suarez [22] to synthesize, within 6 minutes and with a yield higher than 85 %, an unsymmetrical 1,4-DHP from methyl 3-aminocrotonate (3 mmol), ethyl acetoacetate (3 mmol) and benzaldehyde (3 mmol).

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

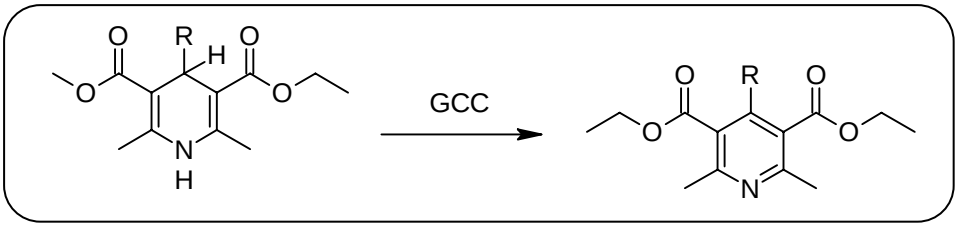
In 2001, a single-mode microwave reactor (SmithSyntheziser from Personal Chemistry, Uppsala, Sweden) was used for the first time to accelerate the preparation of series of 1,4-DHP from various alkyl acetoacetates (12.5 mmol), aldehydes (2.5 mmol) and 25 % aqueous ammonium hydroxide (10.0 mmol).[23] In comparison with experiments performed in domestic ovens, use of a laboratory synthesizer does not appear to provide improved results.

Oxidation of 1,4-DHP under microwave irradiation was reported for the first time in 1991 by Alvarez *et al.* [24,25] They oxidized a series of 1,4-DHP (0.5 g) in a domestic oven by treatment on a mixture of manganese dioxide and Mexican bentonite clay (5.0 g, prepared from 1:2 or 1:4 mixtures of potassium permanganate and clay) in the absence of solvent. The procedure is characterized by short reaction times (10 minutes) and fair to quantitative yields (47-100 %). The most noticeable results were observed when starting from 1,4-DHP bearing a methyl, ethyl, or propyl group in position 4. Indeed those reactions afforded, unexpectedly, mixtures of 4-alkylpyridines and 4-unsubstituted pyridine. In contrast, the same group related,[26] two years later, that those 4-alkyl 1,4-DHP (0.25 g) do not undergo the dealkylation process when they are treated for 1 minute in a domestic microwave oven in the presence of a HNO_3/Mexican bentonite clay system (2.5 g; prepared from a 1:1 mixture of the components). Aromatization of 1,4-DHP has also been studied by Varma.[27] He observed that solid state oxidation of 1, 4-DHP (1mmol) using elemental sulfur (1.3 mmol) and microwave activation in a domestic oven affords the dehydro derivatives, whichever the 4-substituent is.

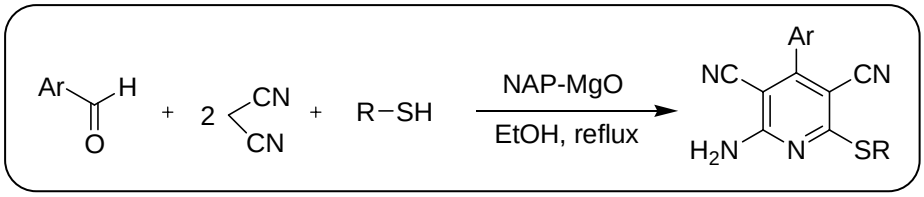


Glycinium chlorochromate[28] (GCC) supported onto silica gel was used as an effective oxidizing agent for the aromatization of 1,4-dihydropyridine.

Many of the reported reagents involve the use of strong oxidants such as $KMnO_4$,[29] CrO_3,[30] HNO_3,[31] Pyridinium chlorochromate (PCC),[32] Ceric ammonium nitrate (CAN),[33] bentonite clay-supported manganese dioxide,[34] Sulphar,[35] Palladium/Charcoal dehydrogenations[36] and bismuth nitrate.[37] However this aromatization reaction with most of these reagents leads to dealkylation at the 4-position or formation of side products.

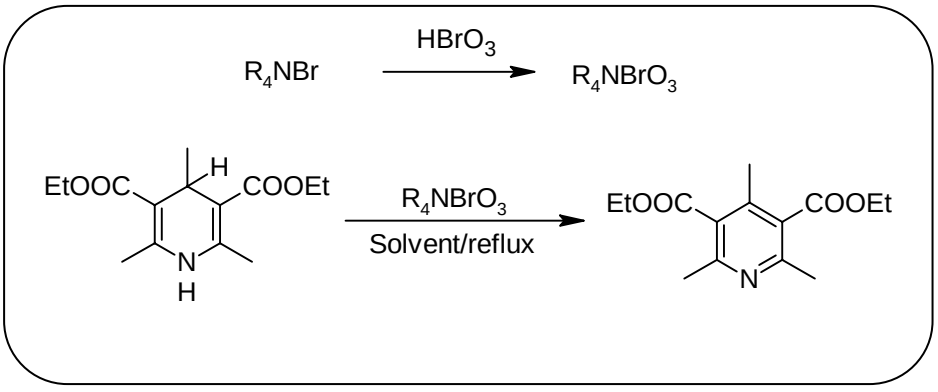


Lakshmi kantam *et al.*[38] have reported the one pot, three component synthesis of 2-amino-4-aryl-3,5-dicyano-6-sulfanylpyridines and the corresponding 1,4-dihydro-pyridines are from readily accessible starting materials. Heating of an ethanolic solution of structurally diverse aldehydes with various thiols and malononitrile in the presence of nanocrystalline magnesium oxide provides the highly substituted pyridine derivatives in moderate to high yields, each representing a privileged medicinal scaffold with their structural motif. After completion of the reaction, the catalyst can be recovered efficiently and reused with consistent activity.



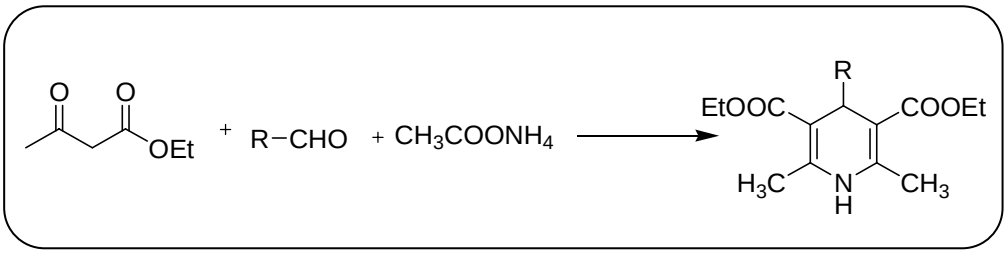
Gunaras *et al.*[39] investigated 1,4-dihydropyridine structure as a less harmful alternative to synthetic phenolic antioxidants in liposomes under conditions simulating food storage. The antioxidant activities (AOA) of 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines possessing various side chain length alkyls (CH_3 - $C_{16}H_{33}$) in ester moiety were tested in transition metalion catalyzed liposome peroxidation and compared with AOA of Trolox™ and Probucol™. The compounds with ethyl - butyl residues in the 3,5-position ester moieties exert the most pronounced AOA. The AOA of tested compounds is associated with their ability to incorporate into liposomes.

Quaternary ammonium bromate have been prepared from the corresponding bromide and used as a mild and efficient oxidizing agent for the aromatization of Hantzsch esters and related compounds to pyridine derivatives.[40]

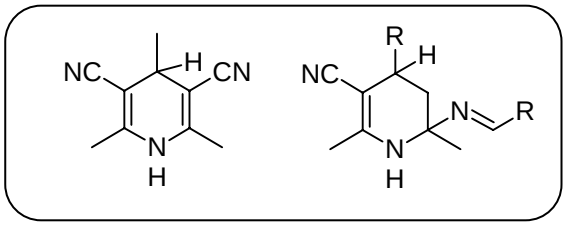


Mohammad *et al.*[41] had prepared 1,4-dihydropyridine under solvent free condition. Ethyl acetoacetate and a range of aldehydes in the presence of ammonium

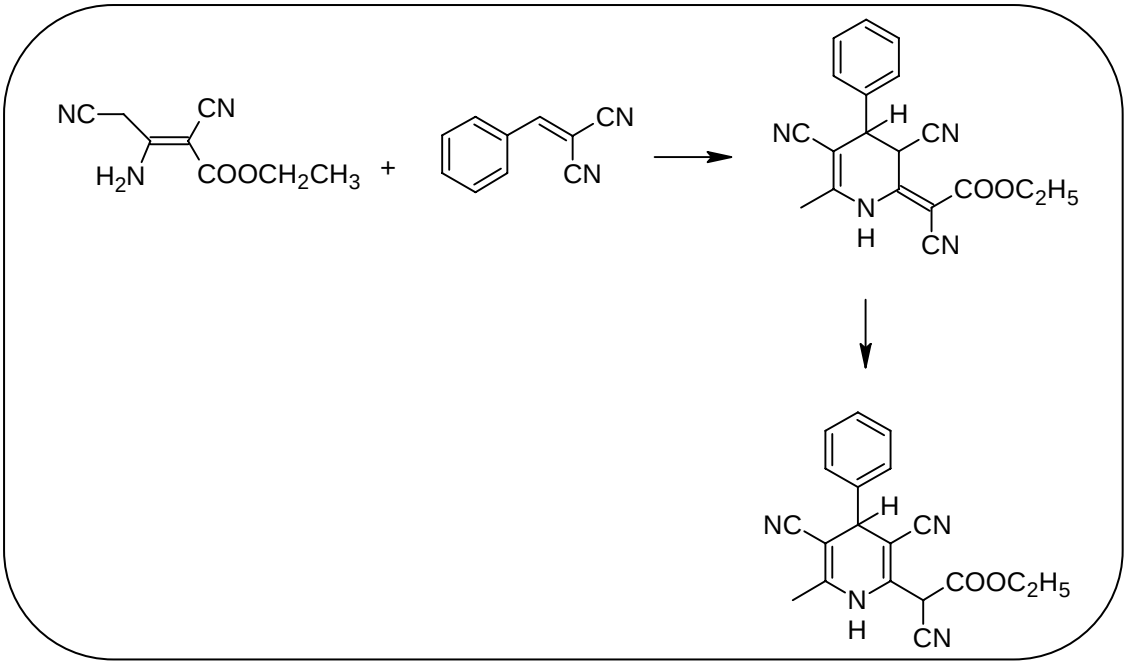
acetate were converted into 1,4-dihydropyridines under mild and solvent free conditions with good to excellent yields.



The preparation of Hantzch type 3,5-dicyano-1,4-dihydropyridine is sometime reported via formation of tetrahyropyridine, which are isolated at room temperature in the presence of ammonium acetate.[42]

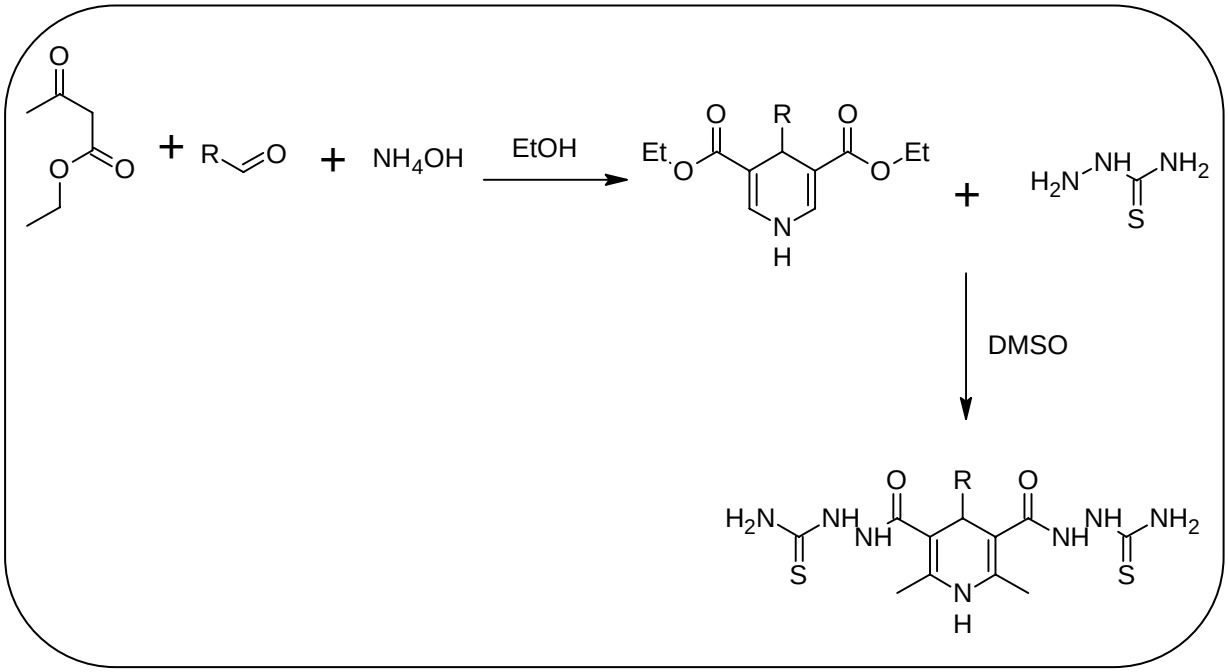


A novel synthesis of polyfunctionally-substituted pyridine was reported by Famhy *et al.*[43] During this reaction, sometimes the formation of tautomer was also reported.

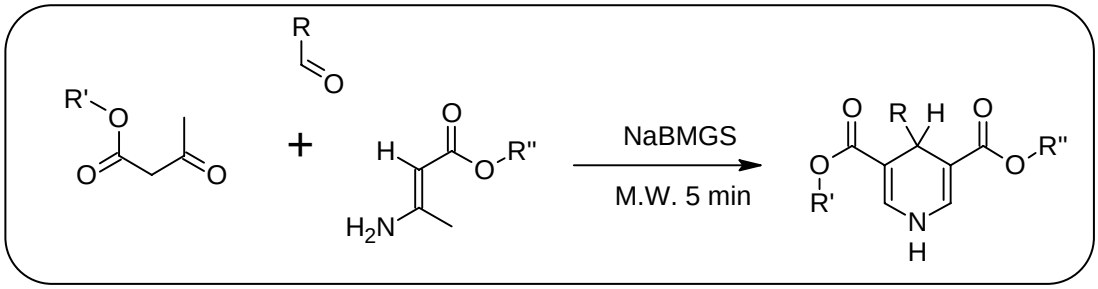


Radhakrishnan *et al.*[44] prepared 2,2'-(2,6-dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarbonyl)bis(hydrazinecarbothioamide) via thiosemicarbazide by the

hydrazinolysis method, it was the very good synthesis process for preparation of 1,4-dihydropyridine with DMSO solvent.



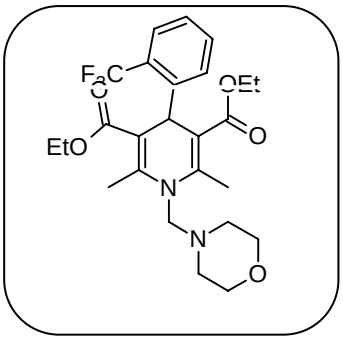
Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot reaction. Clearly, for multi-step synthetic procedures, the number of reactions and purification steps are among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Therefore, in the last decade, research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products. Khadilkar at el[45] prepared 4-Aryl-1,4-dihydropyridines(Hantzsch Esters) form an important class of calcium channel blokers. A number of such compounds have found clinical use. They report here, for the first time, the synthesis of different Hantzsch esters, including the drugs nifedipine and nitrendipine, carried out available sodium butylmono glycol sulphate (NaBMGS) 50% aqueous solution (Huls, Germany) as a solvent system, by reacting alkyl aminocrotonate with an aldehyde and alkyl acetoacetate.



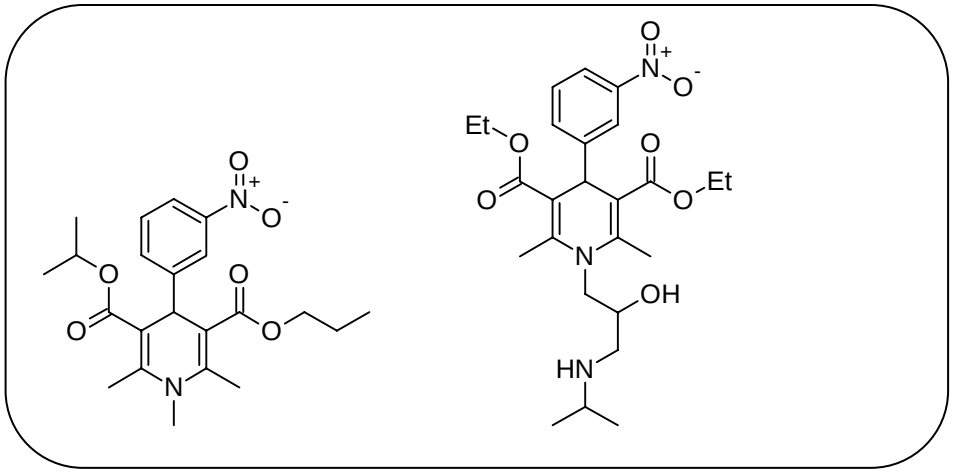
THERAPEUTIC IMPORTANCE

In 2001, Balalaie and Kowsari reported that microwave irradiation promoted the three-component reaction of an aromatic amine, an aromatic aldehyde, and ethyl propiolate to give N-substituted 1,4-dihydropyridine in a high yield.[46] This method may be useful for easily preparing 1,4-dihydropyridine but required expensive microwave apparatus and severe reaction conditions.[47]

Out of many 1,4-dihydropyridine drugs only Flordipine is N-substituted derivative that has proved to be very good calcium channel antagonist, contrary to be belief proposed by D.J.Triggle[48] that N-substituted 1,4-dihydropyridine did not show good antihypertensive activity, probably the concept of that time and -NH was believed to be essential for calcium channel antagonism.

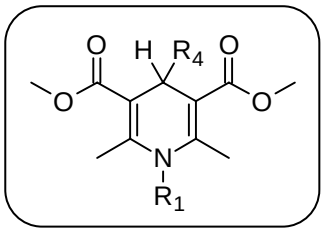


N-methylnimodipine was found to possess antidepressive[49] characteristics (20 mg. P.O reduce the immobile phase by approximately 22% comparison to control values), which provides excellent example of mechanism of action similar to that of Flordipine. V. Michael et.al.[50] prepared antihypertensive and coronary vasodilator N-substituted 1,4-dihydropyridine.

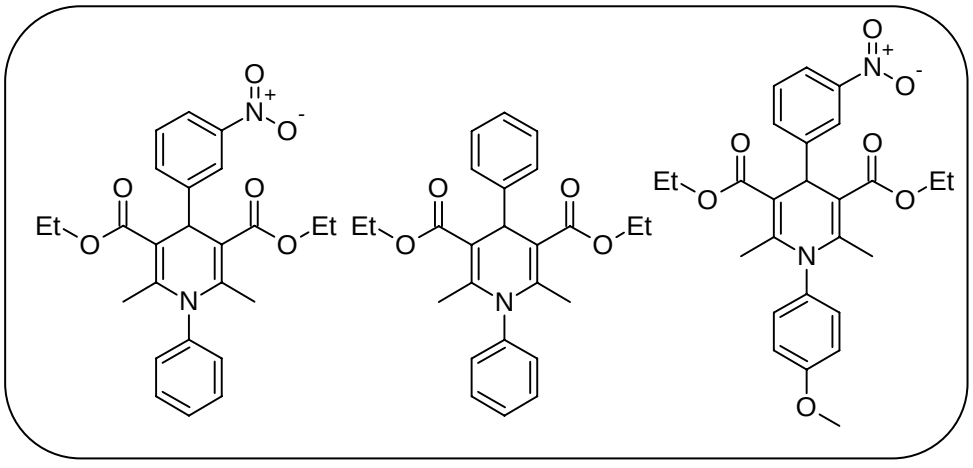


G. Guangyu and co-workers[51] have determined the expression of genes related to mitochondrial function in the substantia nigra of mice treated with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) using a cDNA array.

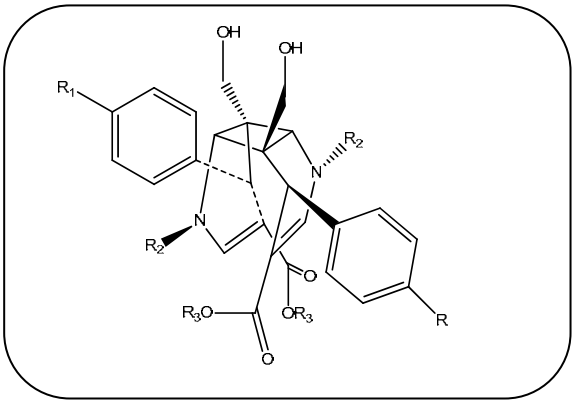
A detailed investigation on the electrochemical oxidation of some Hantzsch 1,4-dihydropyridine derivatives with the aim of study the influence of the hydrogen substituent on the N1 position of the heterocyclic ring have been carried out in protic and aprotic media by Lopez-Alarcon et al.[52]



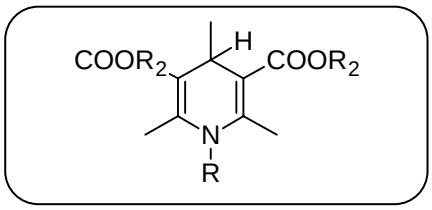
N-(Phenyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine as been synthesized and characterized by the X-ray diffraction method by A. Shah et al.[53] In 2005 same author[54] has been reported the synthesis of N-(Phenyl)-3,5-dicarbethoxy-2,6-dimethyl-4-(phenyl)-1,4-dihydropyridine and N-(4-methoxyphenyl)-3,5 dicarbethoxy-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine and characterized by the X-ray diffraction method.



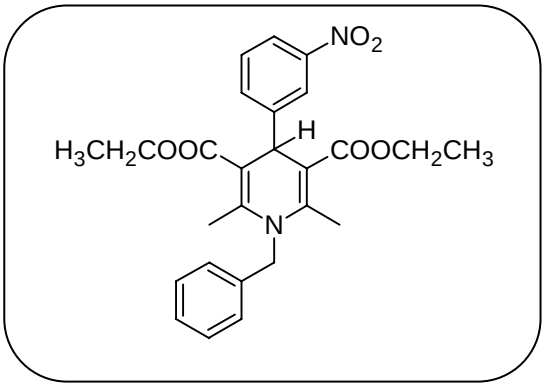
A first series of novel *N*-alkyl substituted *syn* dimeric 4-aryl-1,4-dihydropyridines have been synthesised and evaluated as *HIV-1* protease inhibitors in *in vitro* assays by A. Hilgerotha and co-workers.[55]



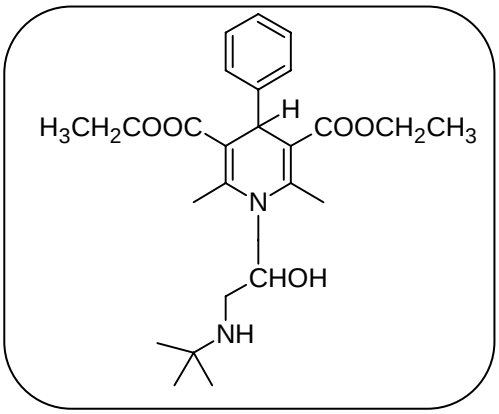
Bossert *et al.*[56-59] prepared many N-substituted 1,4-dihydropyridine derivative by Hantzsch reaction of an amine, acetoacetic ester and an aldehyde, where the condensation also proceeded in ethyl alcohol instead of pyridine.



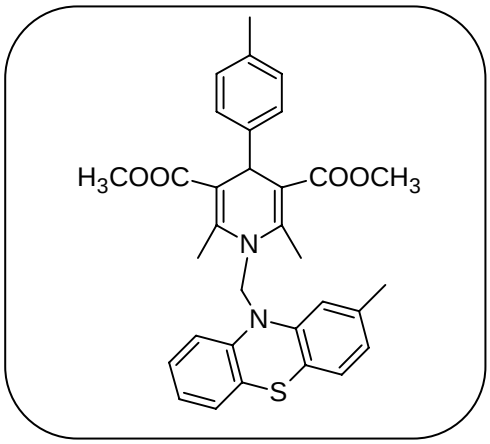
Duburs *et al.*[60] prepared N-benzyl-2,6-dimethyl-4-(3-nitro phenyl)- 3,5-dicarbethyoxy-1,4-dihydropyridine by the condensation of m-nitro benzaldehyde with ethyl acetoacetate and benzyl amine using pyridine as a solvent.



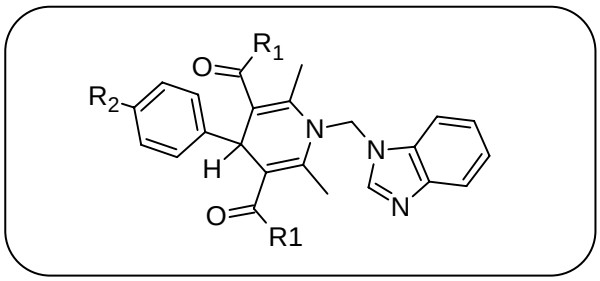
Michael *et al.*[61] prepared antihypertensive and coronary vasodilator N-substituted -1,4-dihydropyridine.



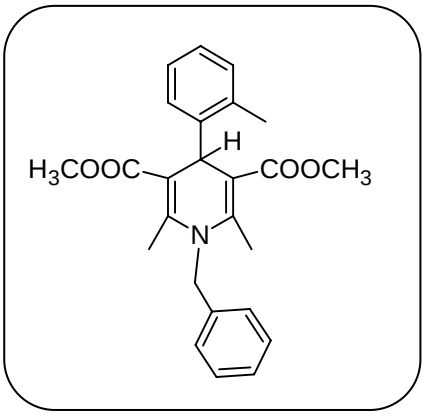
Shah *et al.*[62] also prepared some Mannich compounds and studied their antimicrobial profile.



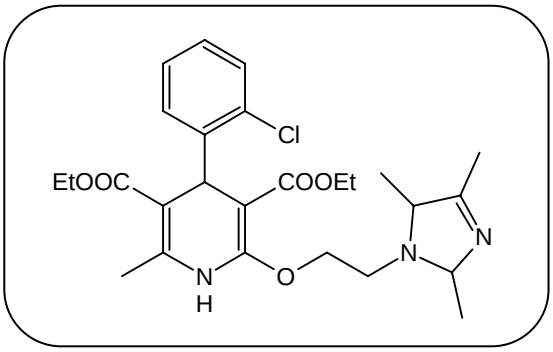
1,4-dihydropyridines were subjected to Mannich reaction to get new 2-alkyl-1-(1'-dihydropyridinyl methyl) benzimidazole as hybrid molecule and was expected to give promising biological active molecules. They were reported to have good antimicrobial activity[63] instead of usual cardiovascular profile.



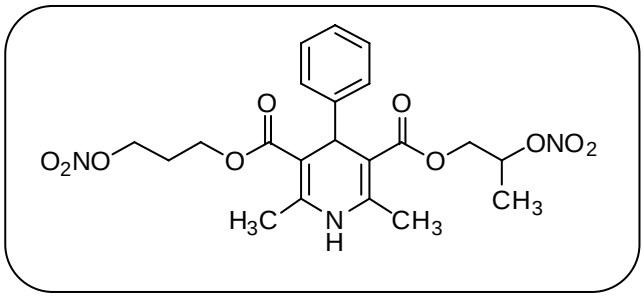
Pitzenberger *et al.*[64] investigated similar analogs in which benzyl amine reacted with acetoacetic ester via formation as titan amine complex, leading to usual Hantzsch synthesis.



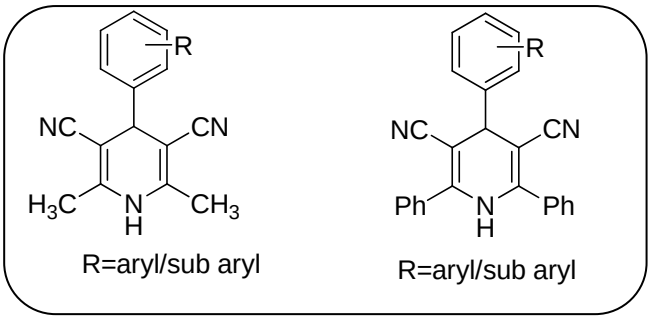
Alkaer *et al.*[65] converted Amlodipine into a derivative as potent vasodilator.



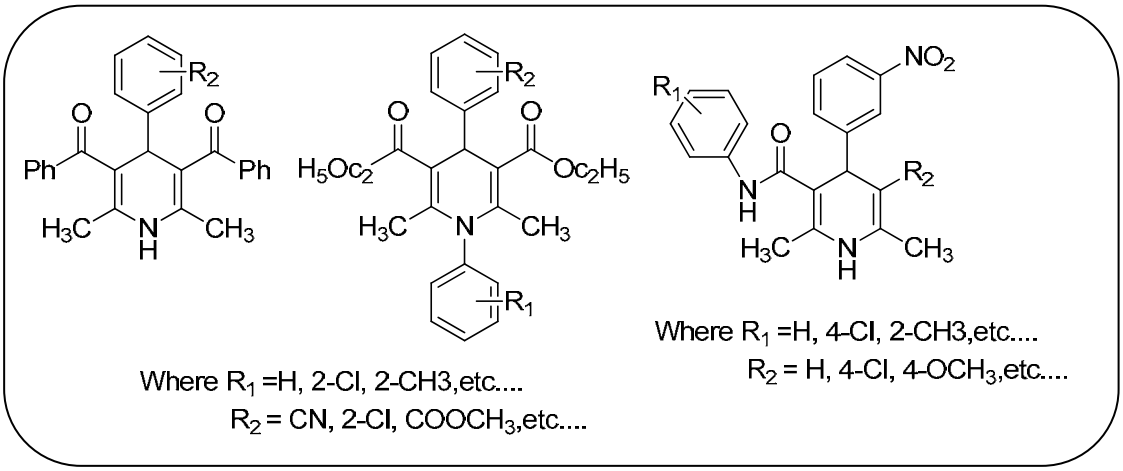
Tsuchida *et al.*[66] has shown that CD-349 can be appeared to be a potent cerebrovasodilator in dogs and could be useful in the treatment of cerebrovascular disorders in human.



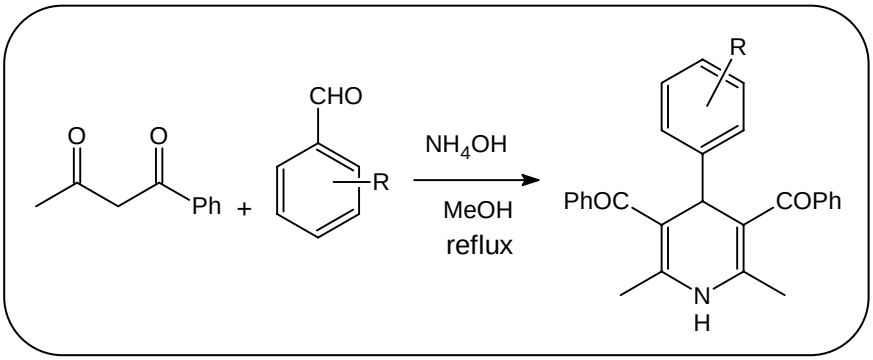
Another class of 1,4-DHPs having a cyano group at 3 and 5 position was prepared by Court *et al.*[67] in 1952. They have prepared 3,5-dicyano-2,6-diphenyl-4-(2-nitrophenyl)-1,4-dihydropyridine as well as 3,5-dicyano-2,6-dimethyl-4-(2-nitrophenyl) 1,4-dihydropyridine and other similar compounds.



At this laboratory, the researchers have reported the Tumor-specific Cytotoxicity and MDR-reversal activity of dihydropyridines.[68]



Gaveriya *et al.*[69] have reported the synthesis and MDR reversal activity in Tumor cells.



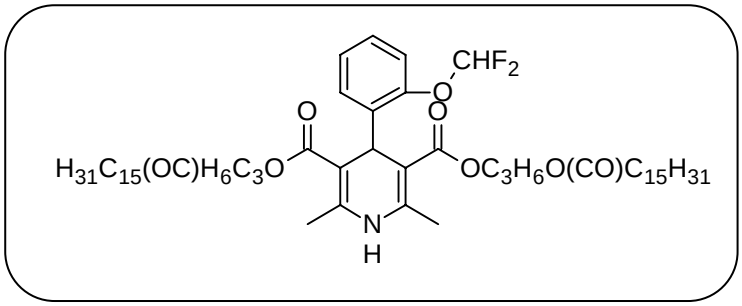
Dihydropyridine (DHP) chemistry began in 1882 when Hantzch published the synthesis. The DHP nucleus is common to numerous bioactive compounds which include various vasodilator, antihypertensive, bronchodilator, antiatheroschlerotic, hepatoprotective, antitumor, antimutagenic, eroprotective and antidiabetic agents.[68-73]

DHP have found commercial utility as calcium channel blockers, as exemplified by therapeutic agents such as Nifedipine,[74] Nitrendipine[75] and Nimodipine.[76] Second

generation calcium antagonists include DHP derivatives with improved bioavailability, tissue selectivity, and/or stability such as the antihypertensive, antianginal drugs like Elgodipine,[77] Furnidipine,[78-79] Darodipine,[80] Pranidipine,[81] Lemildipine,[82] Dexniguldipine,[83] Lacidipine[84] and Benidipine.[85] Number of DHP calcium agonists has been introduced as potential drug candidates for treatment of congestive heart failure.[86-87]

The key characteristic of calcium channel blockers is their inhibition of entry of calcium ions via a subset of channels, thereby leading to impairment of contraction. There are three main groups of calcium channel blockers, i.e. dihydropyridines, phenylalkylamines and benzothiazepines, typical examples of which are nifedipine, verapamil and diltiazem respectively.[88-91] Each has a specific receptor on the calcium channel and a different profile of pharmacological activity. Dihydropyridines have a less negative inotropic effect than phenylalkylamines and benzothiazepines but can sometimes cause reflex tachycardia.Dihydropyridines are able to reduce peripheral resistance, generally without clinically significant cardiodepression.

Among DHPs with other types of bioactivity, Cerebrocrast[92] has been recently introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered.[93] These recent examples highlights the level of ongoing interest toword new DHP derivatives and have prompted us to explore this pharmacophoric scaffold to develop a fertile source of bioactive molecules.



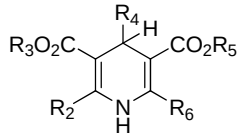
1,4-DHPs posses different pharmacological activities such as antitumor,[94] vasodilator,[95] coronary vasodilator and cardiopathic,[96] antimayocardiac ischemic, antiulcer,[97] antiallergic,[98] antiinflammatory[99] and antiarrhythmic,[100] PAF antagonist,[101] Adenosine A3 receptor antagonist[102] and MDR reversal activity.[103-104]

In particular, DHP-CA (calcium channel antagonist DHP) are extensively used for the treatment of hypertension,[105] subarachnoid hemorrhage,[106-107] myocardial infarction[108-111] and stable[112-113] and unstable angina[114-115] even though recently their therapeutic efficacy in myocardial infarction and angina has been questioned.[116] This class of compounds is also under clinical evaluation for the treatment of heart failure,[117] ischemic brain damage[118] nephropathies and atherosclerosis.[119]

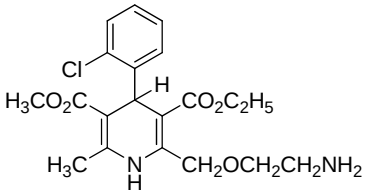
Catalysts such as Sc(OTf)3,[120] Silica gel/$NaHSO_4$,[121] heteropolyacid,[122] I_2,[123] CAN,[124] $Yb(OTf)_3$[125] and Baker's yeast [126] have also been used in this reaction.

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

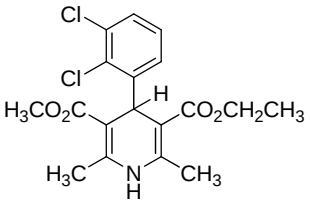
Described more than one century ago by Hantzsch,[127] dialkyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates (1,4-DHP) have now been recognized as vital drugs in the treatment of angina and hypertension. Some of them (Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine, Nifedipine, Nimodipine, Nitrendipine) have been commercialized and it has been proven that their therapeutic success is related to their efficacy to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart.[128-130]



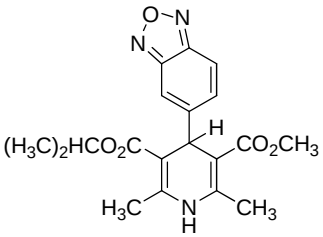
General Structure



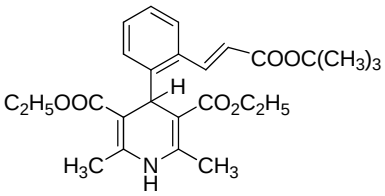
Amlodipine



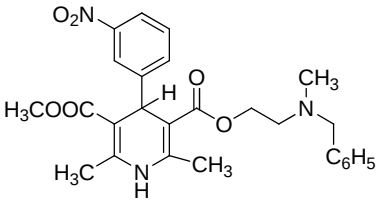
Felodipine



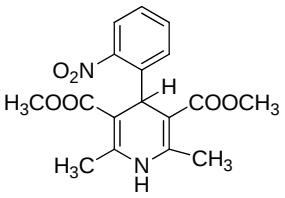
Isradipine



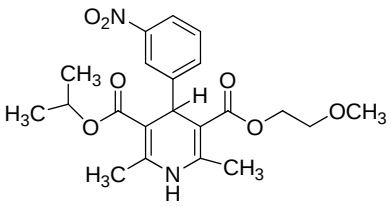
Lacidipine



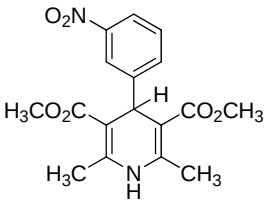
Nicardipine



Nifedipine



Nimodipine



Nitrendipine

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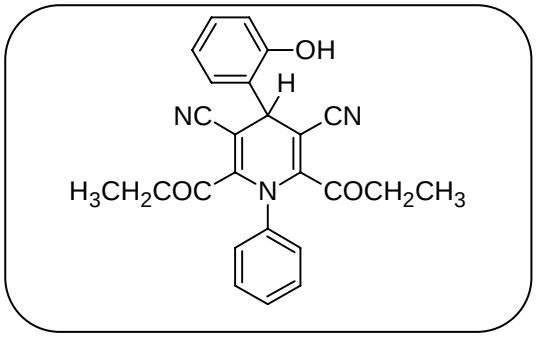
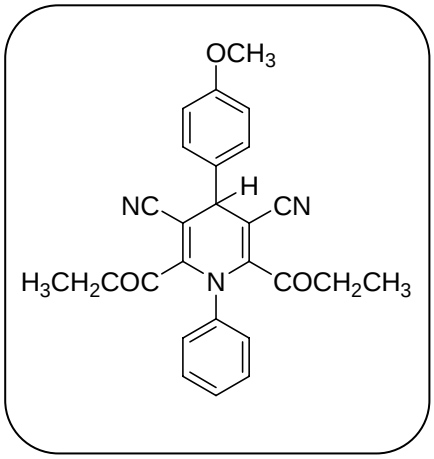
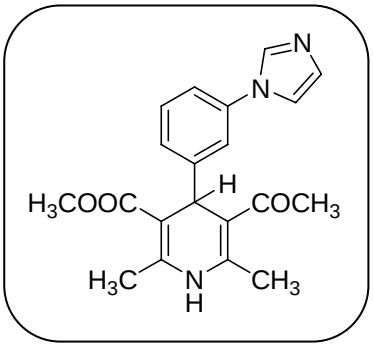
Shah *et al.*[131] prepared many cyano-1,4-dihydropyridines. Out of many compounds3,5-dicyano-2,6-diethoxy-4-(2-hydroxyphenyl)-N-(2-pyridyl)-1,4-dihydropyridine showed good anti-inflammatory activity and also showed moderated increase in blood pressure at 1mg/kg and 5 mg/kg.



Another compounds showed moderate hypotensive activity.



Cozzi *et al.*[132] prepared unsymmetric 4-[3-(1H-imidazol-1-yl-) Phenyl]-1,4-dihydropyridines and studied their antitumor activity. They correlated activity with Letrozole, Anastrozole and other aromatase inhibitors.



Work done from our laboratory

S. V. Rokad[133] have synthesized some new N-aryl-1,4-dihydropyridines containing furan nucleus as a antitubercular and antimicrobial activity. J. D. Akbari[134] reported molecular iodine –catalyzed one pot synthesis of some new Hantzsch 1,4-Dihydropyridine at ambient temperature this one was the very good iodine catalysed 1,4-dihydropyridine synthesis with excellent yields.

Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological screening, we have under taken the synthesis of several 1,4-dihydropyridines which has been described as under.

SECTION-1: MOLECULER IODINE CATALYZE AND CLASSICAL SYNTHESIS, CHARACTARIZATION AND X-RAY CRYSTAL LOGHRAPHIC STUDY OF DIISOPROPYL 1,4-DIHYDRO-1-(4-METHOXYPHENYL)-2,6-DIMETHYL-4-(3-NITROPHENYL) PYRIDINE-3,5-DICARBOXYLATE[DHP-02C].

Part – C

(Section-i)

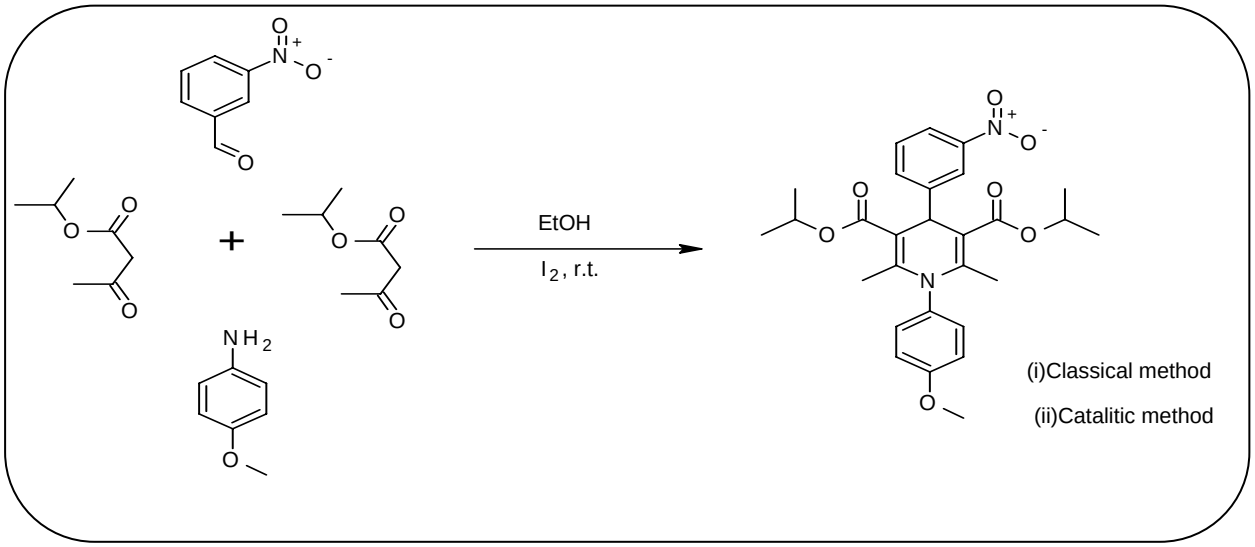
Molecular iodine catalyze and classical synthesis, characterization and X-ray crystallographic study of diisopropyl 1,4-dihydro-1-(4-methoxyphenyl)-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate.

SECTION-I

MOLECULER IODINE CATALYZE AND CLASSICAL SYNTHESIS, CHARACTARIZATION AND X-RAY CRYSTALLOGHRAPHIC STUDY OF DIISOPROPYL 1,4-DIHYDRO-1-(4-METHOXYPHENYL)-2,6-DIMETHYL-4-(3-NITRO PHENYL)PYRIDINE-3,5-DICARBOXYLATE[DHP-02C].

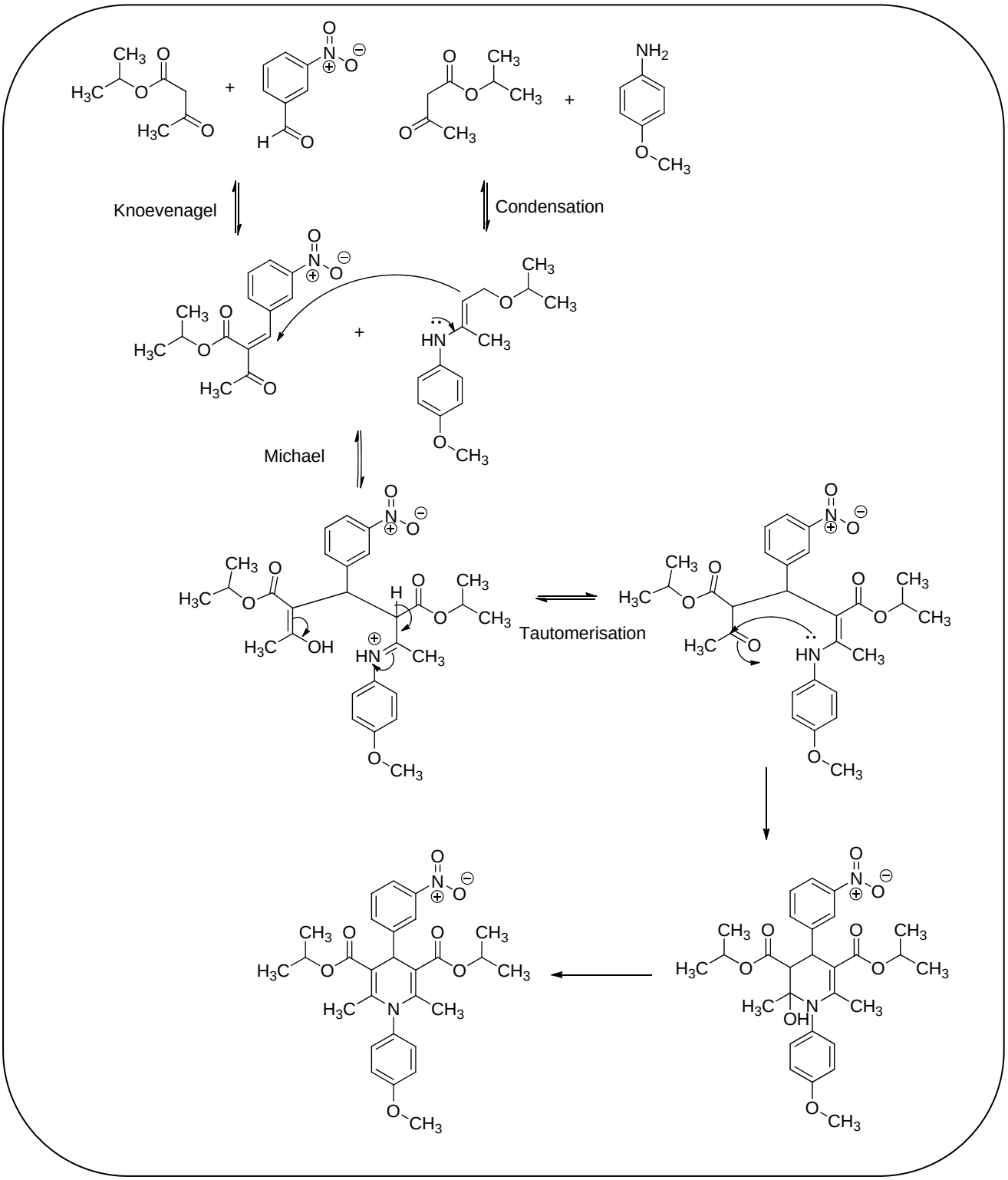
Molecular iodine and classical method are the very good synthesis method for the preparation of 1,4-dihydropyridine derivative Looking to this, the synthesis of 1,4-dihydropyridine derivative was undertaken by the condensation of isopropyl 3-oxobutanoate(isopropyl acetoacetate) with 3-nitro benzaldehyde and 4-methoxy aniline in the presence of ethanol solvent and iodine as a catalyst as shown in reaction scheme

REACTION SCHEME



The constitution of the synthesized compound have been characterized by using elemental analysis, FT-IR, ^{1}H NMR spectroscopy and further supported by mass spectroscopy. Purity of the compound have been checked on thin layer chromatographic plate.

REACTION MECHANISM



EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine and UV light. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR was determined in $CDCl_3$ solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Euro EA 3000 elemental analyzer and the results are in agreements with the structures assigned.

Classical method

[A] Synthesis of diisopropyl 1, 4-dihydro-1-(4- methoxyphenyl)-2, 6-dimethyl-4-(3-nitro phenyl) pyridine-3, 5-dicarboxylate[DHP-02C].

A mixture of 3-nitrobenzaldehyde (0.01 mol, 1.51 gm), isopropyl acetoacetate (0.02 mol, 2.88 gm) and 4-methoxyaniline (0.01 mol, 1.23 gm) was heated (without solvent) on steam bath for 2:30 hours. After elimination of water, methanol (25 ml) was added directly to the reaction mixture and refluxed further for 13 hours. The progress of the reaction was monitored continuously by TLC. After completion of reaction the solvent was removed at reduced pressure. The resulting product was crystallized from ethanol to give analytical grade pure products.

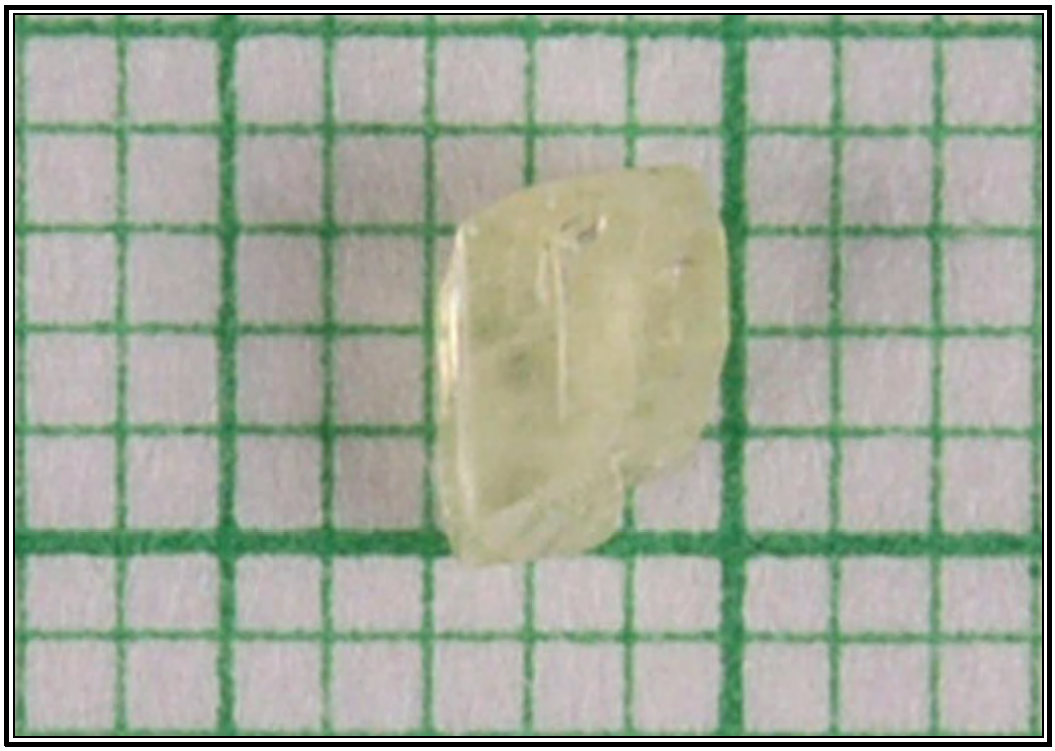
Catalytic method

[B] Synthesis of diisopropyl 1, 4-dihydro-1-(4- methoxyphenyl)-2, 6-dimethyl-4- (3-nitro phenyl) pyridine-3, 5-dicarboxylate [DHP-02C].

A mixture of benzaldehyde (5 mmol, 0.53 gm), isopropyl acetoacetate (10 mmol, 1.44 gm), 4-methoxy aniline (5 mmol, 0.615 gm) was heated (without solvent) on steam bath for 2:30 hours. After elimination of water, iodine (1.5 mmol, 0.38 gm) and ethanol (5 ml) directly charge to the reaction mixture. The reaction mixture was then stirred at room temperature until the reaction was completed (4 hours monitored by TLC). The reaction mixture was treated with aqueous $Na_2S_2O_3$ solution, extracted into ethyl acetate (2 × 20 ml).The solvent was removed *in vacuo* and the resulting crude product (94%) was recrystallized from the ethanol to give the analytical grade pure product. In catalytic method the overall yield of the product is higher than the conventional counterpart.

[C] Growth of diisopropyl 1, 4-dihydro-1-(4- methoxyphenyl)-2, 6-dimethyl-4-(3-nitro phenyl) pyridine-3, 5-dicarboxylate[DHP-02C] crystals:

In the present study, methanol were selected as solvent, however, methanol yielded good quality single crystals. The seed crystals were grown from controlled evaporation of saturated solution of diisopropyl 1, 4-dihydro-1-(4- methoxyphenyl)-2, 6-dimethyl-4-(3-nitro phenyl) pyridine-3, 5-dicarboxylate in methanol and good quality crystals were picked up for growth. A glass jar of 4 cm diameter and 7 cm length was selected as a crystallizer. This jar was kept in a water bath with temperature control of ± 0.1 °C. Water in the bath was stirred slowly. Supersaturated solution of diisopropyl 1, 4-dihydro-1-(4- methoxyphenyl)-2, 6-dimethyl-4-(3-nitro phenyl) pyridine-3, 5-dicarboxylate was poured into crystallizer and a seed crystal was hung by using very fine nylon thread. The temperature of the water bath was maintained at 40 °C and the evaporation rate was carefully controlled.



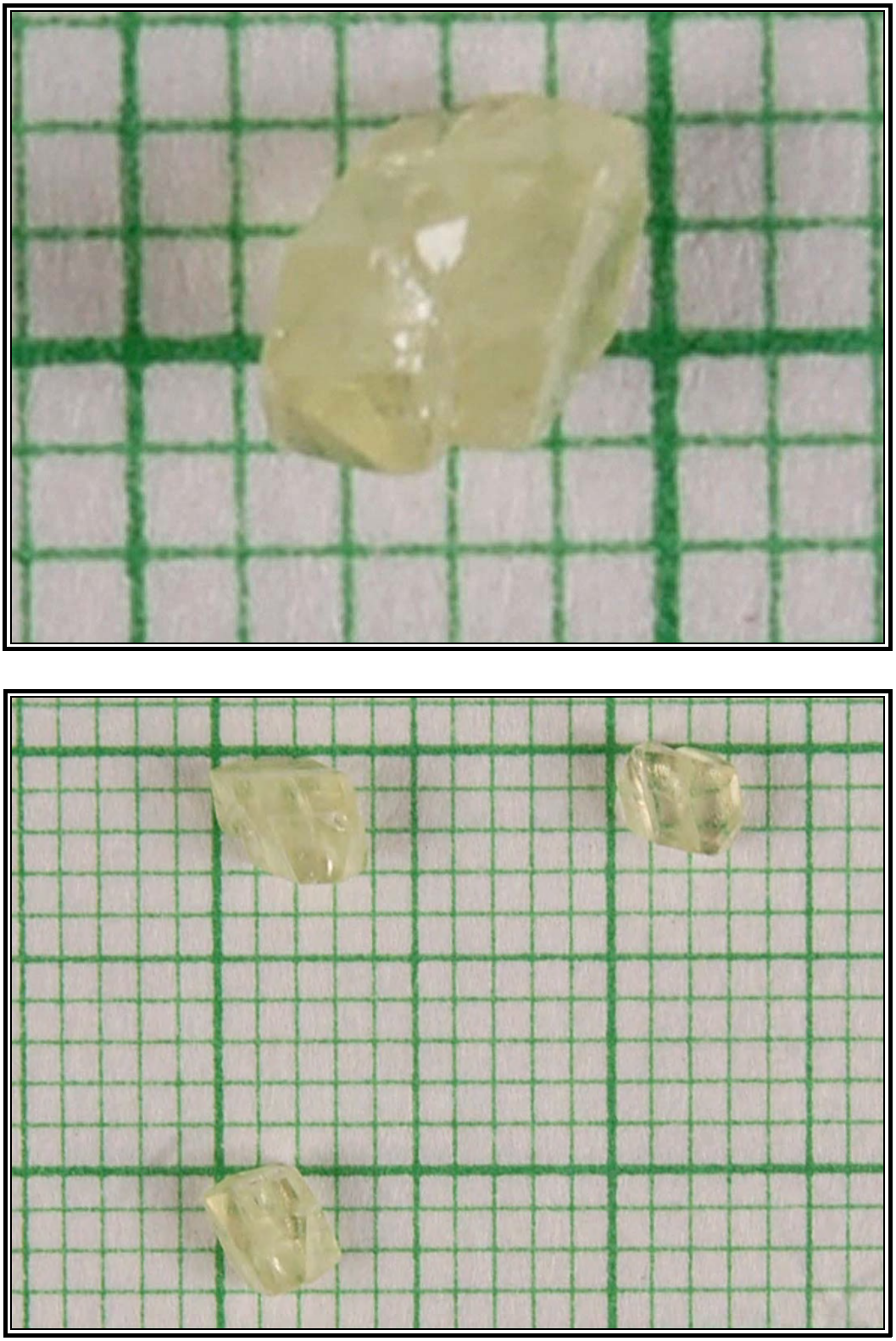
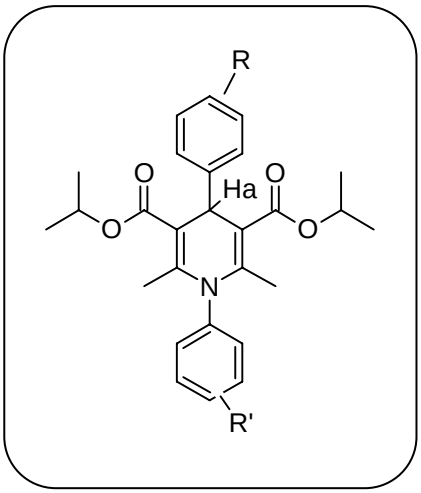


Figure [1]: Photograph of the grown DHP crystals

Good quality single crystals with maximum dimension 0.60 cm X 0.75 cm were obtained. Figure [1] show the types of crystals grown. The crystals were light-yellow in color.

Table-I[DHP-02C]: Physical constant of diisopropyl 1-substitutedphenyl 2,6dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylate[DHP-02C].



Sr. No.	Substitution R	R'	M.F.	M.W.	Conventional Method	Catalytic Method	R_f value
					Yield (%)	Yield (%)	
1.	3-Nitro	4-Methoxy	$C_{28}H_{32}N_2O_7$	508.56	22	81	0.51

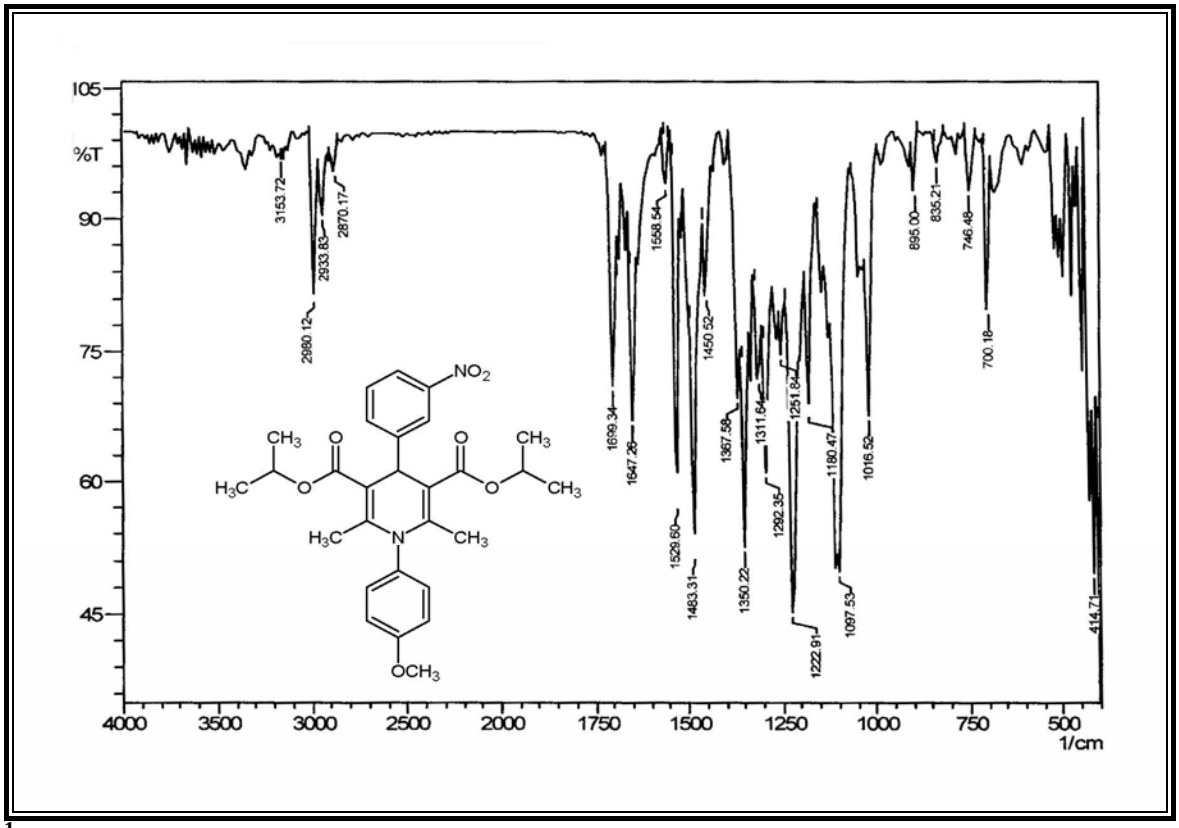
TLC solvent system:- E.A. : Hexane = 5 : 5

ANALYTICAL DATA

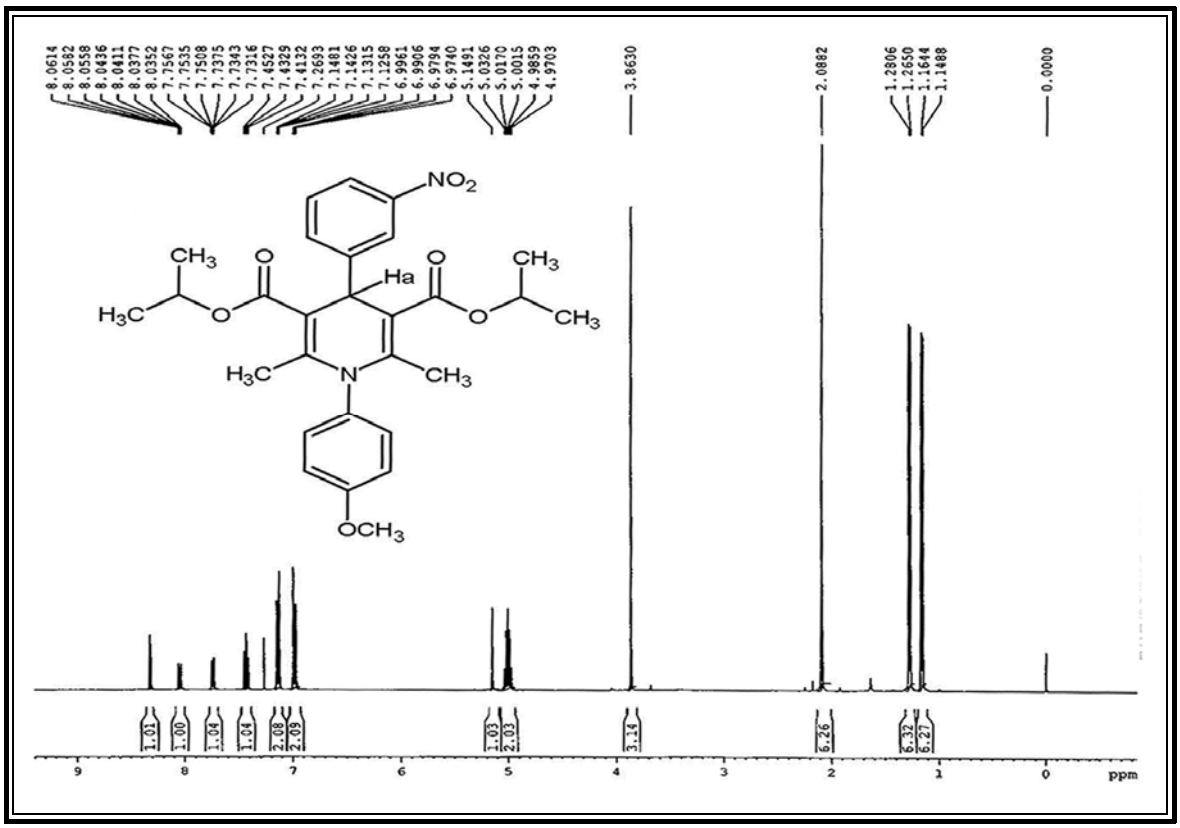
Diisopropyl 1, 4-dihydro-1-(4- methoxyphenyl)-2, 6-dimethyl-4-(3-nitro phenyl) pyridine-3, 5-dicarboxylate.(DHP-02C). mp 185-188°C; IR (DRS): 3142(C-H Str.), 2980(Asym., C-H str.), 2870(Asym.,C-H str.), 1699(-C=O, Str.), 1529(C=C Ar.), 1483 (i.p.d.asym., C-H str.), 1350(o.o.d.sym.C-H), 1016(C=H str., i.p. ben.), 835(C-H o.p.ben.) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.14-1.16(d, *J*=6.24 Hz, 6H, CH_3(isopropyle)),1.26-1.28(d, *J*=6.24 Hz, 6H, CH_3(isopropyle)), 2.08(s, 6H, CH_3), 3.86(s, 3H, OCH_3), 4.97-5.03(m, 2H, CH(isopropyle)), 5.14(m, 1H, Ha), 6.97-6.99(d,d, *J*=2.16 Hz, 2.2 Hz, 2H, Haa'), 7.12-7.14(d,d, *J*=2.28Hz, 2.2Hz, 2H, Hbb'), 7.41-8.32(m,4H, ArH). MS: *m/z* = 508 $[M]^+$; Anal. Calcd for $C_{18}H_{15}FN_2O_3$: C, 66.13; H, 6.34; N, 5.51. Found: C, 66.10; H, 6.26; N, 5.30%.

SPECTRAL STUDY OF SYNTHESIZED COMPOUND

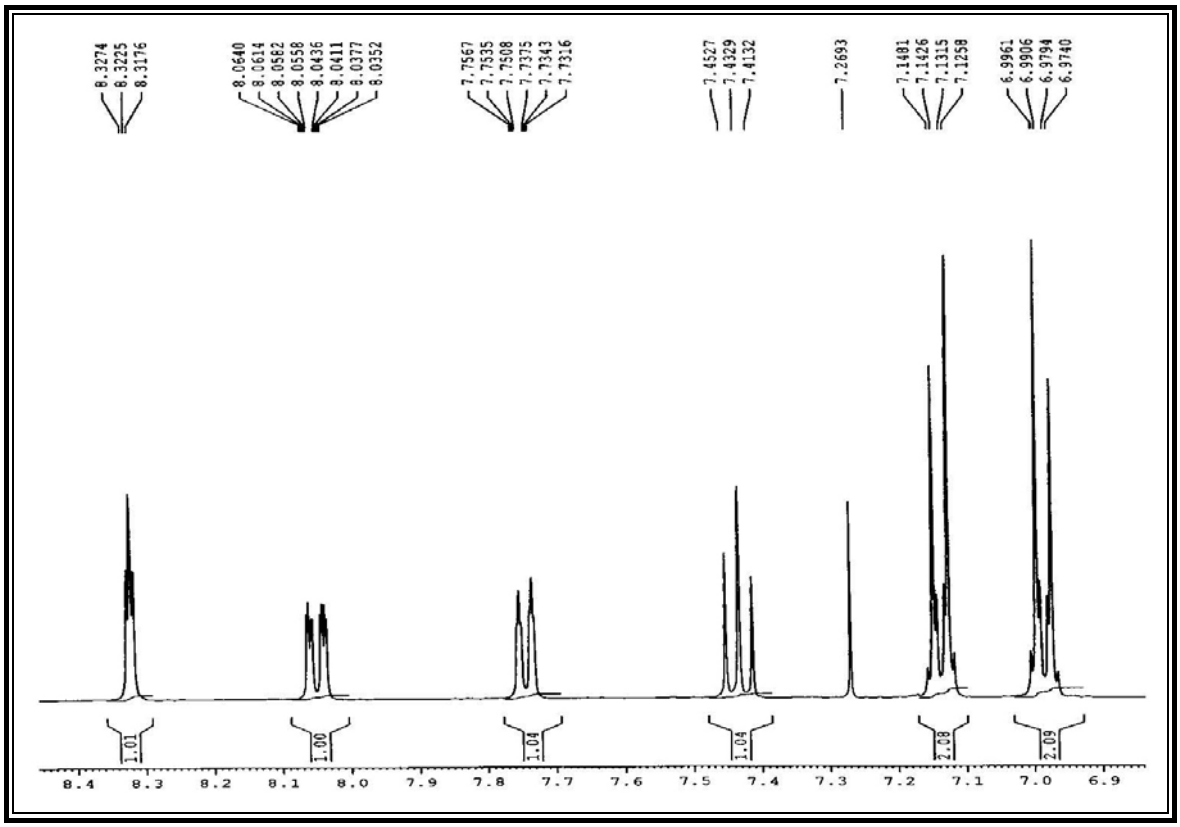
IR spectrum of compound DHP-02C.



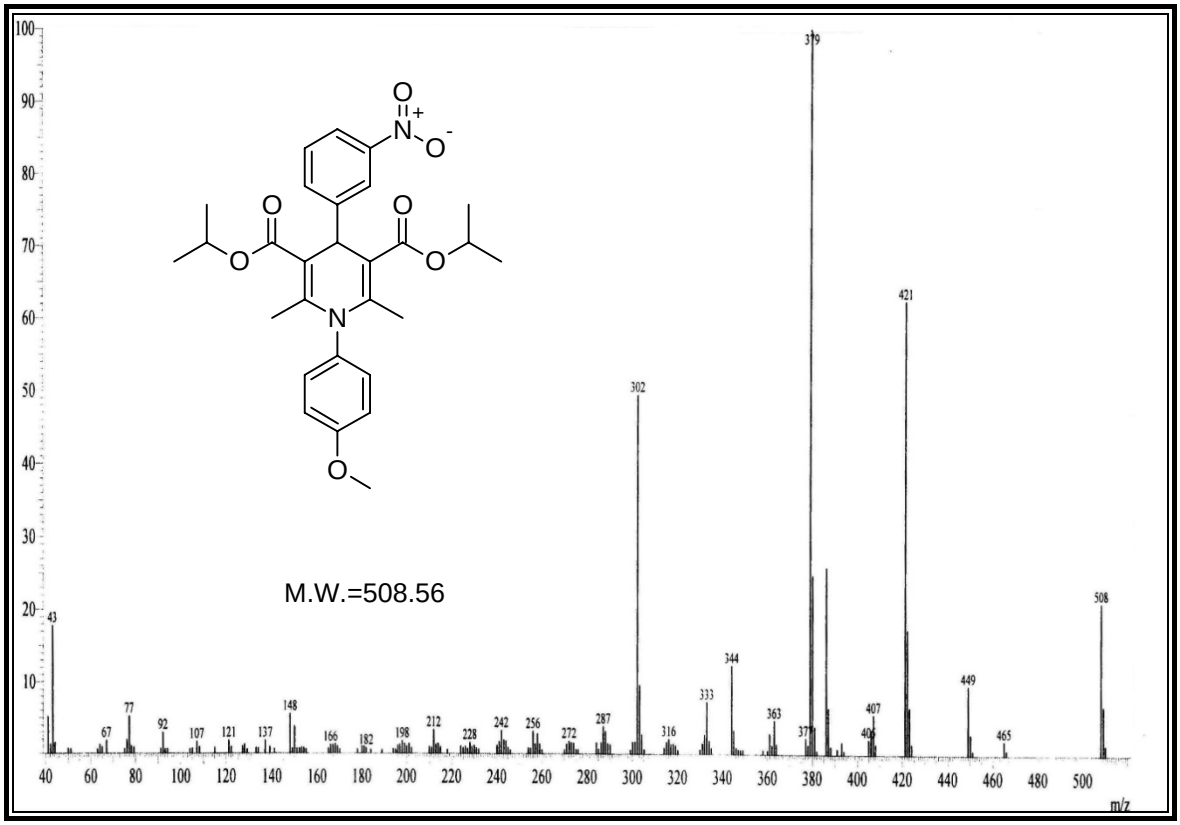
^{1}H NMR spectrum of compound DHP-02C.



Expanded ^{1}H spectrum of compound DHP-02C.



Mass spectrum of compound DHP-02C.



Single crystal X-ray Diffraction analysis

Single crystal X-ray diffraction is the most common experimental method of obtaining a detailed picture of a small molecule that allows resolution of individual atoms. It is performed by analyzing the diffraction of x-rays from an ordered array of many identical molecules. Many molecular substances, including proteins, polymers and other solidify in to crystals under the proper conditions. When solidifying in to the crystalline state, these individual molecules typically adapted as one of only a few possible orientations. A crystal is a three dimensional array of those molecules that are held together by Van der Waals and noncovalent bonding. The smallest representative unit of this crystal is referred to as the unit cell. Understanding the unit cell of these arrays simplifies the understanding of a crystal as a whole.

Characterization of DHP crystals

Single Crystal X-ray Diffraction and Structure Determination

The three dimensional intensity data were collected on an Enraf-Nonius CAD-4 diffractometer. The reflection data were collected at 293 K and ω/2θ scan mode was employed for data collection by using MoKα radiation (λ = 0.71073 Å). The structure has been elucidated by direct methods using SHELEX 97[135]. All non-hydrogen atoms of the molecule were located from the E-map. Isotropic refinement of the structure by least squares methods using SHELEX 97[136] was followed by anisotropic refinement of all the non-hydrogen atoms. All the hydrogen atoms were fixed stereo chemically. Atomic scattering factors were taken from International tables for crystallography (1992 Vol. C Tables 4.2.6.8 and 6.1.1.4). Geometrical and other structural calculations were performed by using PARST[137] programme. The experimental details and other measurement data are given in Table [II] Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (A^2) are given in Table [III]. Atomic displacement parameters (A^2) are given in Table [IV]. Geometric parameters (Å,°) of DHP-02C crystals are given in Table [V].An ORTEP diagram of the compound with atom numbering scheme is shown in figure [2], and figure [3] represents the packing diagram of DHPcrystals.[138]

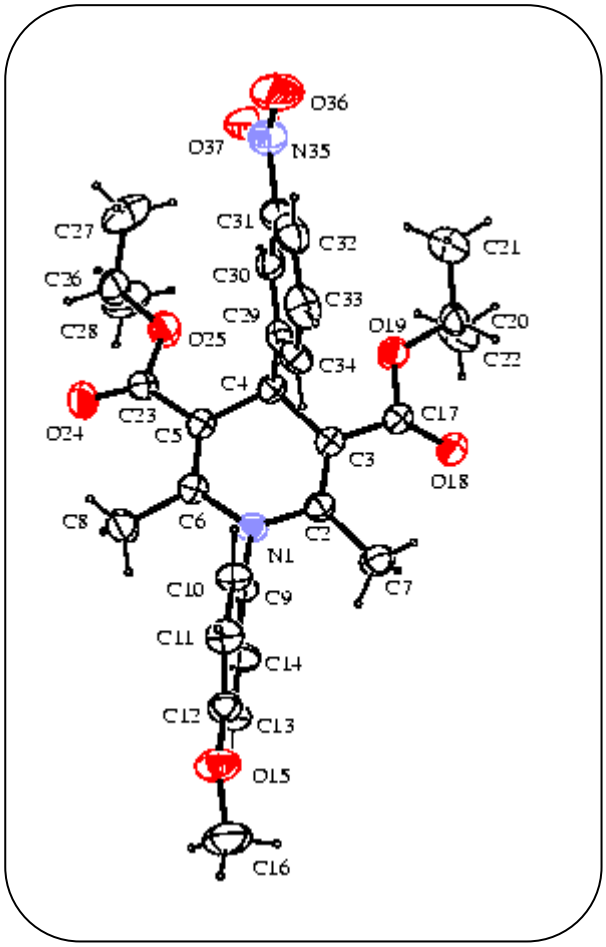


Figure [2]: ORTEP Diagram of DHP crystals

Table – II: Experimental details and other measurement data of DHP crystal

Crystal data and experimental data

Chemical formula	$C_{28}H_{32}N_2O_7$
Relative chemical formula weight	508.56
Symmetry cell setting	Triclinic
Symmetry space group	P-1
Cell dimensions	a=9.5043(8) Å b=10.7570(7) Å c=15.1279(12) Å
Cell angle α	90.501(6)°
Cell angle β	105.873(7)°
Cell angle γ	114.601(7)°
Cell volume *(V)*	1339.27(18) $Å^3$
Cell formula units Z	2
Cell measurement temperature T	293(2) K
Cell parameters from	3153 reflections
No. of recorded reflections	3153
Recording Range θ_{min}	3.3722°
Recording Range θ_{max}	29.0277°
Mo *K*α radiation	λ = 0.71073 Å
Crystal description	block
Crystal color	Light-Yellow
Crystal Size	0.30 X 20 X 20 mm
Crystal density measurements	
Crystal density(Dx)	1.261 mg/m^3
Crystal F (000)	540
μ	0.09 mm^{-1}
Absorpt process details	Crys Alis Red
Special details	
Computing data collection	CrysAlis Pro, Oxford Diffraction Ltd., Version: 1.171.34.40 (release 27-08-2010 CrysAlis171 .NET) (compiled Aug 27 2010,11:50:40)
Structure Determination	SHELXS-97 (Sheldrick, 2008)
Structure Drawing	ORTEP3 (Farrugia, 1997)
computing_publication_material	PLATON(Spek,1999)& PARST(Nardelli,1995)'

Table:III Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (A^2)				
N1N	0.5454(3)	0.3122(2)	0.46535(16)	0.0543(7)
C2 C	0.6907(4)	0.4335(3)	0.4872(2)	0.0506(8)
C3 C	0.7718(4)	0.4905(3)	0.5771(2)	0.0488(8)
C4 C	0.7183(3)	0.4147(3)	0.6544(2)	0.0473(7)
H4 H	0.7355	0.4837	0.7038	0.057
C5 C	0.5384(4)	0.3176(3)	0.6209(2)	0.0476(7)
C6 C	0.4637(4)	0.2640(3)	0.5308(2)	0.0505(8)
C7 C	0.7469(4)	0.4920(3)	0.4068(2)	0.0689(10)
H7A H	0.6708	0.4345	0.3500	0.103
H7B H	0.8518	0.4952	0.4134	0.103
H7C H	0.7541	0.5836	0.4054	0.103
C8C	0.2886(4)	0.1574(4)	0.4926(2)	0.0729(10)
H8A H	0.2620	0.1341	0.4269	0.109
H8B H	0.2187	0.1945	0.5048	0.109
H8C H	0.2742	0.0761	0.5220	0.109
C9 C	0.4847(4)	0.2280(3)	0.3756(2)	0.0514(8)
C10 C	0.5215(4)	0.1169(3)	0.3684(2)	0.0547(8)
H10 H	0.5830	0.0971	0.4205	0.066
C11 C	0.4672(4)	0.0366(3)	0.2846(2)	0.0628(9)
H11 H	0.4908	-0.0384	0.2800	0.075
C12 C	0.3773(4)	0.0671(3)	0.2067(2)	0.0572(8)
C13- C	0.3389(4)	0.1750(3)	0.2140(2)	0.0665(9)
H13 H	0.2775	0.1951	0.1619	0.080
C14 C	0.3912(4)	0.2535(4)	0.2984(2)	0.0674(10)
H14 H	0.3627	0.3256	0.3033	0.081

O15 O	0.3339(3)	-0.0171(2)	0.12593(16)	0.0828(8)
C16 C	0.2611(6)	0.0187(4)	0.0422(3)	0.1070(15)
H16A H	0.2367	-0.0487	-0.0085	0.161
H16B H	0.3344	0.1079	0.0333	0.161
H16C H	0.1626	0.0213	0.0448	0.161
C17 C	0.9226(4)	0.6192(3)	0.6040(2)	0.0523(8)
O18 O	0.9944(3)	0.6917(2)	0.55631(16)	0.0822(8)
O19 O	0.9781(3)	0.6499(2)	0.69719(15)	0.0682(7)
C20 C	1.1316(4)	0.7699(3)	0.7403(2)	0.0651(9)
H20 H	1.1983	0.7903	0.6983	0.078
C21 C	1.2148(5)	0.7310(5)	0.8269(3)	0.1041(14)
H21A H	1.2336	0.6538	0.8112	0.156
H21B H	1.1475	0.7064	0.8670	0.156
H21C H	1.3168	0.8079	0.8581	0.156
C22C	1.0989(5)	0.8909(4)	0.7570(4)	0.1150(17)
H22A H	1.0482	0.9118	0.6987	0.172
H22B H	1.1995	0.9693	0.7880	0.172
H22C H	1.0281	0.8694	0.7950	0.172
C23 C	0.4521(4)	0.2803(3)	0.6907(2)	0.0518(8)
O24O	0.3176(3)	0.1942(3)	0.68094(17)	0.0891(9)
O25 O	0.5433(3)	0.3580(3)	0.77256(16)	0.0820(8)
C26 C	0.4739(5)	0.3377(4)	0.8499(3)	0.0810(12)
H26 H	0.3717	0.2532	0.8336	0.097
C27C	0.5956(7)	0.3234(5)	0.9321(3)	0.1202(17)
H27A H	0.6084	0.2420	0.9185	0.180
H27B H	0.5577	0.3160	0.9854	0.180
H27C H	0.6982	0.4030	0.9447	0.180

C28 C	0.4423(6)	0.4586(5)	0.8653(3)	0.1123(16)
H28A H	0.3603	0.4595	0.8119	0.169
H28B H	0.5405	0.5418	0.8750	0.169
H28C H	0.4055	0.4528	0.9189	0.169
C29 C	0.8208(3)	0.3391(3)	0.6953(2)	0.0485(8)
C30 C	0.8803(4)	0.3461(3)	0.7905(2)	0.0568(8)
H30 H	0.8585	0.3974	0.8303	0.068
C31 C	0.9715(4)	0.2768(4)	0.8259(3)	0.0675(9)
C32 C	1.0054(4)	0.2001(4)	0.7710(3)	0.0778(11)
H32 H	1.0644	0.1518	0.7971	0.093
C33 C	0.9512(4)	0.1942(3)	0.6758(3)	0.0767(11)
H33 H	0.9768	0.1448	0.6371	0.092
C34 C	0.8584(4)	0.2629(3)	0.6389(2)	0.0584(9)
H34 H	0.8204	0.2578	0.5748	0.070
N35 N	1.0345(5)	0.2876(4)	0.9286(3)	0.0962(11)
O36-O	1.1211(4)	0.2294(4)	0.9581(3)	0.1430(14)
O37 O	0.9971(5)	0.3491(4)	0.9761(2)	0.1302(13)

Table: IV Atomic displacement parameters(A^2)						
N1	0.0572(17)	0.0623(16)	0.0429(16)	0.0017(13)	0.0145(13)	0.0260(15)
C2	0.056(2)	0.0542(18)	0.048(2)	0.0066(15)	0.0208(17)	0.0272(16)
C3	0.0532(19)	0.0475(16)	0.052(2)	0.0089(15)	0.0195(16)	0.0259(15)
C4	0.0547(19)	0.0484(16)	0.0477(18)	0.0089(14)	0.0224(15)	0.0263(15)
C5	0.0486(18)	0.0518(17)	0.054(2)	0.0088(15)	0.0228(16)	0.0284(15)
C6	0.0521(19)	0.0541(18)	0.052(2)	0.0042(15)	0.0183(17)	0.0278(16)
C7	0.080(2)	0.076(2)	0.052(2)	0.0109(17)	0.0221(19)	0.033(2)
C8	0.054(2)	0.086(2)	0.067(2)	-0.0025(19)	0.0183(19)	0.0203(19)
C9	0.0554(19)	0.0587(19)	0.0429(19)	0.0034(15)	0.0126(16)	0.0289(16)
C10	0.064(2)	0.0585(19)	0.0454(19)	0.0081(15)	0.0107(16)	0.0339(17)
C11	0.077(2)	0.0546(19)	0.061(2)	0.0045(17)	0.018(2)	0.0349(19)
C12	0.067(2)	0.0543(19)	0.047(2)	0.0020(16)	0.0171(17)	0.0239(17)
C13	0.072(2)	0.071(2)	0.052(2)	0.0044(17)	0.0041(18)	0.035(2)
C14	0.078(2)	0.074(2)	0.058(2)	0.0052(18)	0.0054(19)	0.050(2)
O15	0.112(2)	0.0769(16)	0.0501(16)	-0.0045(13)	0.0150(14)	0.0386(15)
C16	0.145(4)	0.098(3)	0.051(3)	0.002(2)	0.014(3)	0.038(3)
C17	0.057(2)	0.0531(18)	0.054(2)	0.0110(16)	0.0220(18)	0.0285(17)
O18	0.0751(17)	0.0845(17)	0.0591(15)	0.0159(13)	0.0230(14)	0.0070(14)
O19	0.0722(16)	0.0624(14)	0.0524(15)	-0.0007(11)	0.0222(12)	0.0109(12)
C20	0.056(2)	0.063(2)	0.060(2)	0.0001(17)	0.0172(18)	0.0106(18)
C21	0.086(3)	0.120(3)	0.085(3)	0.008(3)	0.006(3)	0.037(3)
C22	0.099(3)	0.063(2)	0.150(5)	-0.014(3)	0.000(3)	0.028(2)
C23	0.052(2)	0.0596(19)	0.053(2)	0.0084(17)	0.0172(18)	0.0315(17)

O24	0.0658(17)	0.1032(19)	0.0690(17)	0.0024(15)	0.0291(14)	0.0041(16)
O25	0.0675(16)	0.1061(19)	0.0551(15)	-0.0085(14)	0.0309(13)	0.0144(14)
C26	0.071(2)	0.099(3)	0.058(2)	-0.006(2)	0.035(2)	0.014(2)
C27	0.172(5)	0.161(5)	0.087(3)	0.053(3)	0.072(4)	0.105(4)
C28	0.152(4)	0.158(4)	0.080(3)	0.027(3)	0.058(3)	0.103(4)
C29	0.0398(17)	0.0478(17)	0.056(2)	0.0078(15)	0.0162(16)	0.0168(14)
C30	0.0509(19)	0.062(2)	0.064(2)	0.0153(17)	0.0235(17)	0.0265(17)
C31	0.057(2)	0.070(2)	0.074(3)	0.0243(19)	0.015(2)	0.029(2)
C32	0.053(2)	0.067(2)	0.115(4)	0.022(2)	0.015(2)	0.033(2)
C33	0.062(2)	0.065(2)	0.113(4)	0.003(2)	0.029(2)	0.035(2)
C34	0.0502(19)	0.0586(19)	0.064(2)	-0.0004(17)	0.0107(17)	0.0262(17)
N35	0.079(3)	0.105(3)	0.100(3)	0.044(2)	0.016(2)	0.043(2)
O36	0.127(3)	0.195(4)	0.128(3)	0.077(3)	0.019(2)	0.100(3)
O37	0.154(3)	0.177(4)	0.072(2)	0.025(2)	0.012(2)	0.098(3)

[Table: V]: Geometric parameters(Å, °) of DHP-02C crystals

Bond Lengths (Å)			
N1-C6	1.395(4)	O19 -C20	1.455(3)
N1 -C2	1.401(3)	C20- C22	1.492(5)
N1 -C9	1.453(4)	C20 -C21	1.495(5)
C2 -C3	1.356(4)	C20- H20	0.9800
C2 -C7	1.501(4)	C21- H21A	0.9600
C3 -C17	1.468(4)	C21- H21B	0.9600
C3- C4	1.511(4)	C21 -H21C	0.9600
C4- C5	1.517(4)	C22 -H22A	0.9600
C4 -C29	1.527(4)	C22- H22B	0.9600
C4- H4	0.9800	C22- H22C	0. 9600
C5 -C6	1.346(4)	C23- O24	1.193(3)
C5- C23	1.468(4)	C23-O25	1.332(4)
C6- C8	1.514(4)	O25- C26	1.470(4)
C7- H7A	0.9600	C26- C28	1.481(5)
C7- H7B	0.9600	C26- C27	1.507(6)
C7- H7C	0.9600	C26- H26	0.9800
C8 -H8A	0.9600	C27- H27A	0.9600
C8 -H8B	0.9600	C27 -H27B	0.9600
C8- H8C	0.9600	C27- H27C	0.9600
C9 -C14	1.368(4)	C28 -H28A	0.9600
C9 -C10	1.388(4)	C28- H28B	0.9600
C10- C11	1.368(4)	C28- H28C	0.9600
C10- H10	0.9300	C29- C30	1.385(4)
C11 -C12	1.384(4)	C29- C34	1.389(4)
C11- H11	0.9300	C30 -C31	1.373(5)
C12- C13	1.366(4)	C30- H30	0.9300
C12-O15	1.370(4)	C31 -C32	1.353(5)
C13- C14	1.370(4)	C31 -N35	1.488(5)
C13- H13	0.9300	C32 -C33	1.382(5)
C14 -H14	0.9300	C32- H32	0.9300
O15 -C16	1.408(5)	C33- C34	1.384(5)
C16 -H16A	0.9600	C33 -H33	0.9300
C16- H16B	0.9600	C34- H34	0.9300

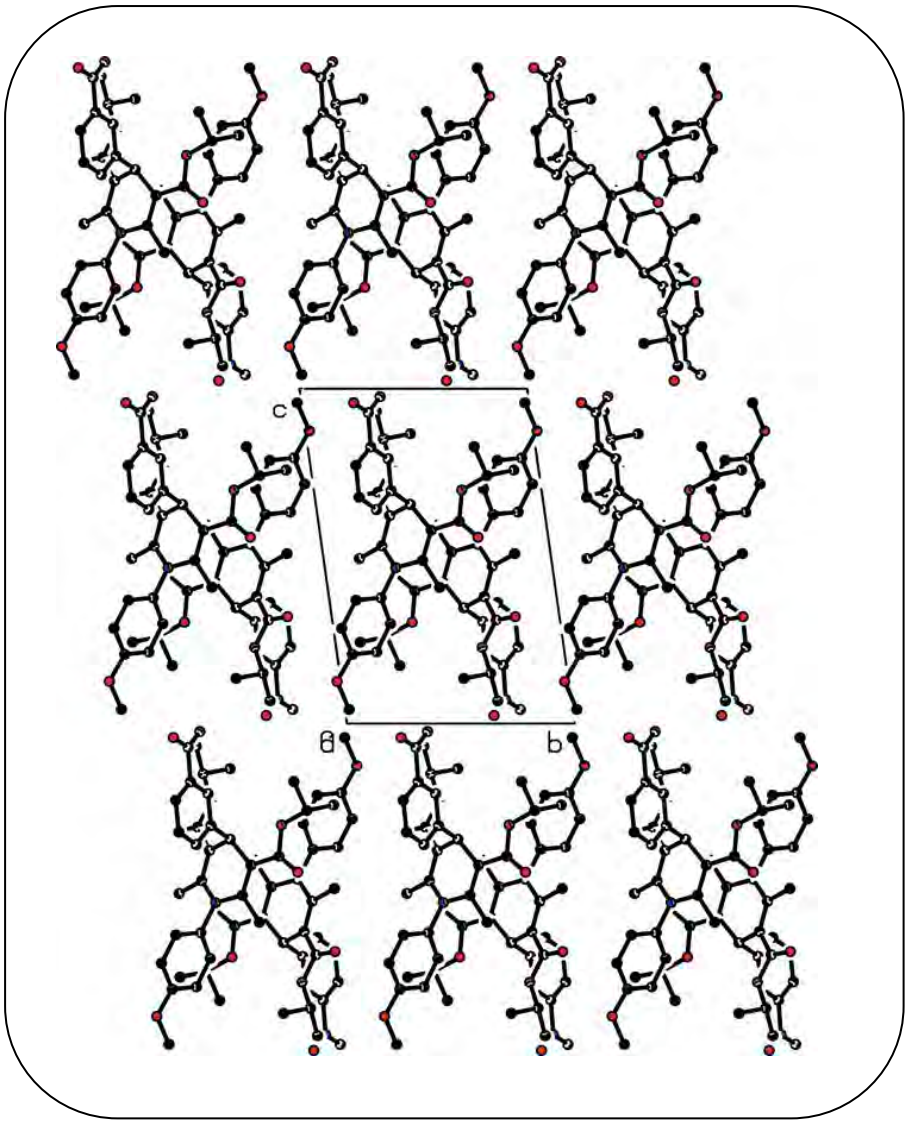
C16- H16C	0.9600	N35 -O37	1.187(4)
C17- O18	1.196(3)	N35 -O36	1.225(4)
C17 -O19	1.347(4)		

Bond Angles (°)			
C6 -N1- C2	121.3(2)	O19- C20- C22	109.1(3)
C6 -N1- C9	118.7(2)	O19 -C20- C21	106.6(3)
C2 -N1- C9	119.8(2)	C22- C20- C21	113.8(3)
C3- C2- N1	119.8(3)	O19 -C20- H20	109.1
C3 -C2 -C7	124.0(3)	C22- C20- H20	109.1
N1- C2 -C7	116.2(3)	C21- C20- H20	109.1
C2- C3- C17	122.2(3)	C20 -C21- H21A	109.5
C2 -C3 -C4	120.3(3)	C20-C21-H21B	109.5
C17- C3- C4	117.2(3)	H21A-C21-H21	109.5
C3 -C4 -C5	110.7(2)	C20-C21-H21C	109.5
C3- C4 -C29	111.3(2)	H21A-C21-H21	109.5
C5 -C4 -C29	111.7(2)	H21B-C21-H21	109.5
C3- C4 -H4	107.6	C20-C22-H22A	109.5
C5- C4 -H4	107.6	C20-C22-H22B	109.5
C29- C4 -H4	107.6	H22A-C22-H22B	109.5
C6- C5 -C23	121.8(3)	C20-C22-H22C	109.5
C6- C5- C4	120.5(3)	H22A-C22-H22C	109.5
C23- C5- C4	117.7(3)	H22B-C22-H22C	109.5
C5 -C6- N1	120.0(3)	O24 -C23- O25	120.5(3)
C5- C6 -C8	124.1(3)	O24- C23- C5	128.0(3)
N1- C6- C8	115.8(3)	O25- C23- C5	111.5(3)
C2- C7- H7A	109.5	C23- O25- C26	118.8(3)
C2- C7- H7B	109.5	O25- C26- C28	107.1(3)
H7A- C7- H7B	109.5	O25- C26- C27	106.9(3)
C2- C7 -H7C	109.5	C28- C26- C27	113.5(3)
H7A -C7 -H7C	109.5	O25- C26 -H26	109.7
H7B -C7- H7C	109.5	C28 -C26 -H26	109.7
C6- C8- H8A	109.5	C27- C26- H26	109.7
C6- C8 -H8B	109.5	C26-C27-H27A	109.5

H8A -C8- H8B	109.5	C26-C27-H27B	109.5
C6- C- H8C	109.5	H27A-C27-H27B	109.5
H8A -C8 -H8C	109.5	C26-C27-H27C	109.5
H8B -C8- H8C	109.5	H27A-C27-H27C	109.5
C14 -C9 -C10	119.0(3)	H27B-C27-H27C	109.5
C14-C9- N1	122.2(3)	C26-C28-H28A	109.5
C10- C9-N1	118.8(3)	C26-C28-H28B	109.5
C11- C10 -C9	120.1(3)	H28A-C28-H28B	109.5
C11 -C10- H10	120.0	C26-C28-H28C	109.5
C9 -C10- H10	120.0	H28A-C28-H28C	109.5
C10- C11- C12	120.0(3)	H28B-C28-H28	109.5
C10- C11- H11	120.0	C30 -C29- C34	118.1(3)
C12 -C11 -H11	120.0	C30- C29- C4	120.5(3)
C13 -C12 -O15	124.9(3)	C34- C29- C4	121.4(3)
C13- C12 -C11	120.0(3)	C31 -C30 -C29	119 .6(3)
O15 -C12 -C11	115.1(3)	C31- C30- H30	120.2
C12 -C13 -C14	119.7(3)	C29- C30 -H30	120.2
C12- C13-H13	120.1	C32 -C31- C30	122.4(4)
C14 -C13 -H13	120.1	C32- C31 -N35	119.5(4)
C9- C14- C13	121.2(3)	C30- C31- N35	118.1(4)
C9- C14 -H14	119.4	C31 -C32- C33	119.2(4)
C13 -C14 -H14	119.4	C31- C32- H32	120.4
C12 -O15- C16	118.1(3)	C33- C32- H32	120.4
O15-C16-H16A	109.5	C32 -C33 -C34	119.1(3)
O15-C16-H16B	109.5	C32 -C33- H33	120.5
H16A-C16-H16B	109.5	C34 -C33- H33	120.5
O15-C16-H16C	109.5	C33- C34- C29	121.5(3)
H16A-C16-H16C	109.5	C33- C34 -H34	119.2
H16B-C16-H16C	109.5	C29 -C34- H34	119.2
O18- C17- O19	121.0(3)	O37-N35-O36	124.4(5)
O18- C17- C3	129.6(3)	O37- N35- C31	119.0(4)
O19- C17- C3	109.4(3)	O36 -N35- C31	116.6(4)
C17 -O19 -C20	119.2(2)		

Torsion Angles (°)			
C6- N1 -C2-C3	13.7(4)	C12 -C13- C14 -C9	1.5(6)
C9- N1- C2-C3	-161.0(3)	C13- C12 -O15- C16	7.9(5)
C6- N1- C2-C7	-166.6(3)	C11- C12- O15- C16	-171.8(3)
C9 -N1- C2-C7	18.7(4)	C2 -C3- C17 –O1	0.8(5)
N1-C2-C3-C17	178.6(2)	C4- C3- C17- O1	174.6(3)
C7-C2-C3-C17	1.8(5)	C2 -C3 -C17 -O19	-178.8(3)
N1- C2- C3-C4	7.8(4)	C4- C3- C17- O19	-4.9(3)
C7- C2- C3-C4	-171.9(3)	O18- C17- O19-C20	-2.8(4)
C2- C3- C4-C5	-26.5(4)	C3 -C17 -O19 -C20	176.8(2)
C17-C3-C4-C5	159.5(2)	C17- O19- C20 -C22	94.3(4)
C2-C3-C4-C29	98.4(3)	C17 -O19 -C20- C21	-142.4(3)
C17-C3-C4-C29	-75.6(3)	C6 -C5- C23- O24	7.0(5)
C3-C4 -C5- C6	27.3(4)	C4 -C5- C23 -O24	-170.3(3)
C29- C4- C5 -C6	-97.4(3)	C6- C5- C23 -O25	-172.2(3)
C3-C4-C5-C23	-155.4(2)	C4- C5- C23- O25	10.5(4)
C29-C4-C5-C23	80.0(3)	O24- C23 -O25-C26	-1.3(5)
C23 -C5- C6- N1	173.7(3)	C5 -C23 -O25- C26	178.0(3)
C4- C5 -C6 -N1	-9.0(4)	C23- O25- C26- C28	-107.6(4)
C23- C5- C6- C8	-2.6(5)	C23- O25- C26 -C27	130.4(3)
C4- C5- C6- C8	174.7(3)	C3- C4 -C29- C30	134.9(3)
C2- N1- C6- C5	-13.1(4)	C5- C4- C29 -C30	-100.8(3)
C9- N1- C6- C5	161.7(3)	C3 -C4 -C29- C34	-44.5(4)
C2- N1- C6 -C8	163.5(3)	C5- C4- C29- C34	79.9(3)
C9 -N1- C6- C8	-21.7(4)	C34- C29- C30- C31	-0.9(4)
C6 -N1- C9- C14	99.7(4)	C4- C29- C30- C31	179.7(3)
C2- N1 -C9 -C14	-85.5(4)	C29- C30- C31 -C32	-0.5(5)
C6-N1-C9-C10	-79.6(3)	C29- C30- C31- N35	179.5(3)
C2-N1-C9-C10	95.3(3)	C30- C31- C32 -C33	2.2(5)
C14- C9- C10- C11	1.3(5)	N35- C31- C32 -C33	-177.8(3)
N1 -C9- C10 -C11	-179.4(3)	C31- C32- C33- C34	-2.4(5)
C9- C10 -C11- C12	0.8(5)	C32- C33- C34- C29	1.0(5)
C10- C11- C12- C13	-1.8(5)	C30- C29- C34- C33	0.6(4)
C10- C11- C12- O15	177.9(3)	C4- C29- C34- C33	-180.0(3)
O15 -C12- C13- C14	-179.0(3)	C32- C31- N35-O37	-176.1(4)

C11- C12- C13- C14	0.7(5)	C30- C31-N35- O37	3.9(6)
C10 -C9 -C14-C13	-2.5(5)	C32- C31- 35- O36	2.9(5)
N1- C9- C14- C13	178.3(3)	C30- C31-N35 -O36	-177.1(3)



[Figure-3]: Packing diagram of diisopropyl-1-(4-methoxyphenyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (DHP-02C) crystals

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