DISCOVERING THE NEW CHEMICAL ENTITIES OF THERAPEUTIC INTEREST

A THESIS
SUBMITTED TO THE
SAURASHTRA UNIVERSITY
FOR THE DEGREE OF

Doctor of Philosophy

IN
THE FACULTY OF SCIENCE (CHEMSITRY)

BY

Harsha C. Vagadia

UNDER THE GUIDANCE

OF

Dr. (Mrs.) H. H. Parekh

Department of Chemistry
Saurashtra University
Rajkot- 360 005
Gujarat - (INDIA)

2005

Gram : UNIVERSITY
Fax : 0281-2577633

Phone : (R) 2584221
(O) 2578512

SAURASHTRA UNIVERSITY
University Road.
Rajkot - 360 005.

Dr. H.H.PAREKH
M.Sc., Ph.D.
Professor and Head
Department of Chemistry

Residence :
B-1,Amidhara Appartment
2-Jalaram plot,
University Road,
Rajkot - 360 005.
GUJARAT (INDIA)

No.

Dt. - -2005

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

The work included in the thesis is my own work under the supervision of ***Dr. H. H. Parekh*** and leads to some contribution in chemistry subsidised by a number of references.

Dt. : - -2005
Place : Rajkot.

(Harsha C. Vagadia)

This is to certify that the present work submitted for the Ph. D. Degree of Saurashtra University by ***Harsha C. Vagadia*** is her own work and leads to advancement in the knowledge of chemistry. The thesis has been prepared under my supervision.

Date : - -2005
Place : Rajkot.

Dr. H. H. PAREKH
Professor and Head,
Department of Chemistry,
Saurashtra University
Rajkot - 360 005.

DEDICATED TO
MY BELOVED FAMILY

acknowledgement

First & foremost, I Pay all my homage and devote, my emotions to "Almightly God" without whose blessing this task would not have been accomplished. I bow my head in utter humility and complete dedication.

I deem it to be my proud previlage to express my deep sense of gratitude and acknowledge my sincere indebtedness to my respected guide, Dr.(Mrs.)H.H.Parekh, Professor & Head, Department of Chemistry, for her unceasing interest, uncessant encouragment, constructive suggestions and gifted guidence through out the progress of this research work. I consider my self fortunates in having a guide like her & my gratefulness to her cannot be expressed in printed words.

I owe a great deal to great Legend Dr. A. R. Parikh, retired Professor & Head, Department of Chemistry, who is a Gem of a institute & always showed deep concern & was always approachable in time to show the silver lining in every dark cloud. I will never forget his constant inspiration with keen interest & ever vigilant guidance without which this task could not have been achieved.

I feel great pleasure to acknowledge my deepest sense of indebtedness to Dr. N. A. Chauhan, retired Professor, Department of Chemistry for his invaluable inspiration and moral support throughout the course of my research work.

Above all, I bow my head with utter respect to my beloved grandfather late Shri Amubhai & grandmother late Smt.Jeevuben who formed part of my vision and taught me the good thing that really matter in life. The happy memory of my grand parents still provide a persistent inspiration for my journey in this life. I bow my head with utter respect to my beloved mother Smt. Kantaben for her continuous source of inspiration, motivation & devotion to the family and my father Shri Chandubhai for the uncopromising principles that guided my life.Through the stress & strain of this study my sister Hetal has encouraged me to reach my destination.

I am also grateful to Asif for the inspiration and moral support through out my research work. I am thankful to my beloved kanchanmasi and Bhupatmama, my brothers Sunilbhai & Anilbhai, bhabhis Rashmi & Bharti,sisters Shobhana & Poonam and jijaji Shaileshbhai for their faith in me.I am thankful to my nephews Depency, Aemil & Dishin whose unstoping flow of love helped me to reach the goal.

Aove all, needless to say "Thanks" to express my deep indebtedness to my seniors Dr. Ranjan, Dr. Nila, Dr. Fatema and all my seniors and juniors who ever stood beside me with their helping hands and moral support.

I feel lucky and very proud to have intimate friends like Lata, Hemlata, Arti Thaker, Sheetal, Krishna, Meera,Arti Padnya and Nikunj who have been always participating with my problems & disappointment and rebuilt my confidance at an appropriate stages. I gratfully thanks for the help & co-ordination extended by my colleagues Ronak&Viral.

I am thankful to Mr. Harshad Joshi & Mrs. Namrata for their kind support and providing chemicals & glasswares in time. I am thankful to Mr. Devendra Goswami to magnifying the presentation of my work in the form of thesis.

I am thankful to the authorities of CIL-Chandhigarh, CDRI-Lucknow and Professor and Head, Department of Chemistry for providing facilities for spectral studies.

I gratfully acknowledge the most willing help and co-operation extended by TAACF, Southern Research Institute, Alabama U.S.A.

Finally, I express my grateful acknowledgement to the authorities of Saurashtra University for providing the research facilities.

Harsha C. Vagadia

CONTENTS

SYNOPSIS

A brief summary of the work incorporated in the thesis with the title **"DISCOVERING THE NEW CHEMICAL ENTITIES OF THERAPEUTIC INTEREST "**has been described as under.

[A] STUDIES ON PYRAZOLES

[B] STUDIES ON MICROWAVE INDUCED SYNTHESIS OF PYRAZOLINES

[A] STUDIES ON PYRAZOLES

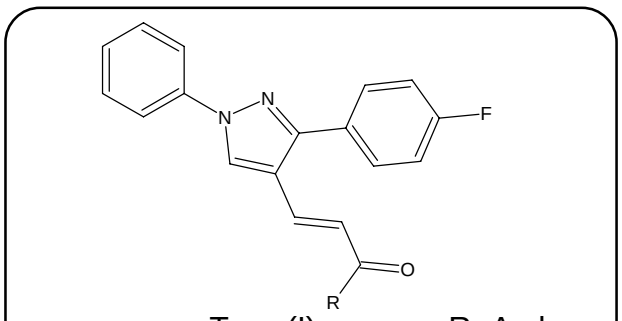
The research on the chemistry of pyrazoles has been a focus of attention for chemists for a long time, due to their wide spread diversified biological activities like antitubercular, antimicrobial, hypnotics, anti-inflammatory, antitumor, plant growth regulators and are also used as herbicidal and fungicidal.

Considering the increasing importance of pyrazole nucleus, the synthesis of some new chalcones, pyrazolines, cyanopyridines, thiazolidinones, pyrimidinones, isoxazoles, cyanopyridones, imidazolinones and nitriles has been undertaken in order study their pharmacological profile .

PART-I: STUDIES ON PYRAZOLYLPYRAZOLINES

Pyrazoline derivatives represent one of the modest class of compounds possessing wide range of pharmacological activities like anticancer, anthalmentic, antitubercular and anti-inflammatory etc. With a view to evaluate pharmacological profile, some new pyrazolines bearing 1-phenyl-3-fluorophenyl-4-formyl pyrazole moiety have been prepared which have been describes as under.

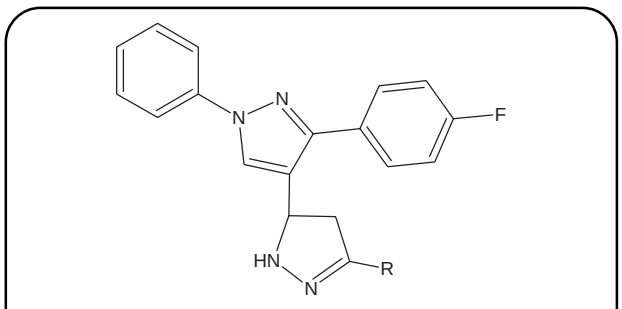
SECTION – I : Synthesis and biological evaluation of 1-Aryl-3-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-2-propene-1-ones.



Type (I) R=Aryl

The chalcones of type (I) have been prepared by the condensation of 1-phenyl-3-p-fluorophenyl-4-formyl pyrazole with different aryl ketones in presence of 40% KOH.

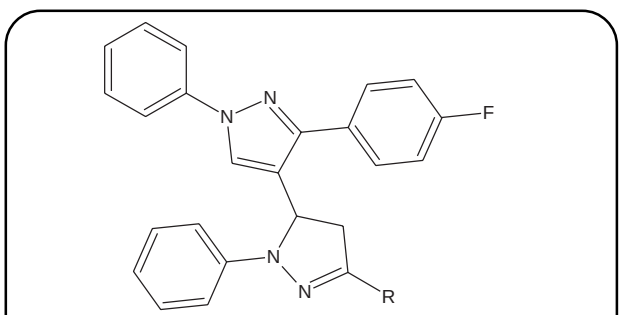
SECTION – II : Synthesis and biological evaluation of 3-Aryl-5-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-pyrazolines.



Type (II) R= Aryl

The pyrazoline derivatives of type (II) have been prepared by the reaction of chalcones of type (I) with hydrazine hydrate.

SECTION – III : Synthesis and biological evaluation of 1,N-phenyl-3-aryl-5-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-pyrazolines.



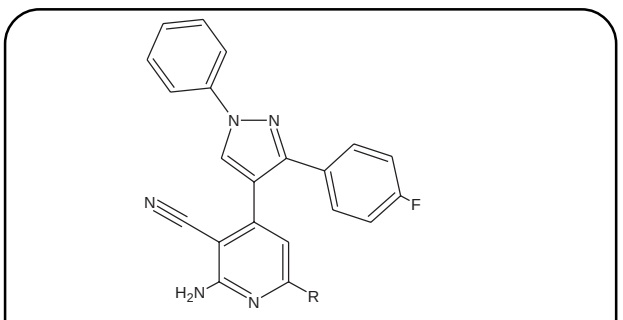
Type (III) R=Aryl

The pyrazolines of type (III) have been prepared by the reaction of chalcones of type (I) with phenyl hydrazine in presence of basic catalyst like piperidine.

PART-II : STUDIES ON CYANOPYRIDINES

The compounds containing the cyanopyridine ring system have a prominent feature in medicinal chemistry and possess biological activities such as antihypertansive, antibacterial, antidiabetic and anticholestemic. They have been also used as dyes for cotton and polyester fabrics. In view of these facts, it was contemplated to synthesize cyanopyridine derivatives, which have been described as under.

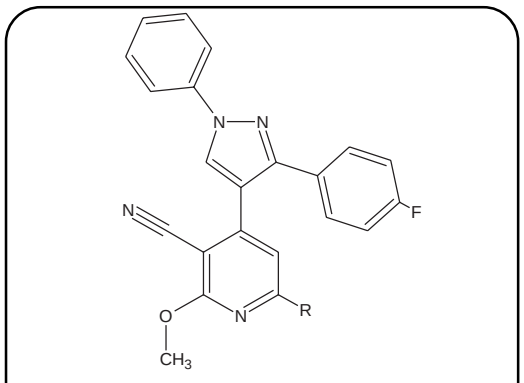
SECTION - I : Synthesis and biological evaluation of 2-Amino–3-cyano – 4 –[1',N-phenyl-3'-p– fluorophenyl– pyrazol– 4'-yl]–6-aryl–pyridines.



Type (IV) R=Aryl

2- Amino –3- cyano pyridines of type (IV) have been prepared by the condensation of chalcones of type (I) with ammonium acetate and malononitrile.

SECTION- II : Synthesis and biological evaluation of 2- Methoxy –3-cyano-4-[1', N- phenyl-3'- p-fluorophenyl –pyrazol –4'- yl] –6-aryl- pyridines.



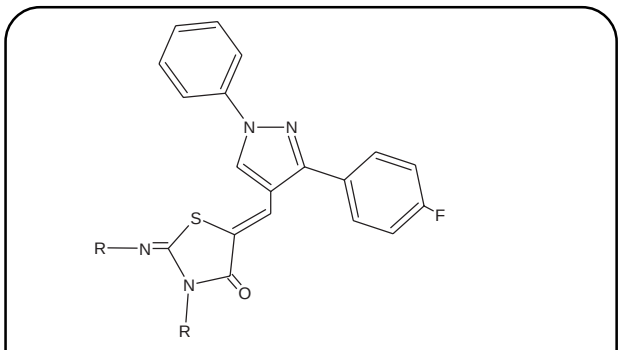
Type (V) R = Aryl

2- Methoxy-3-cyanopyridines of type (V) have been prepared by the condensation of chalcones of type (I) with malononitrile and sodium methoxide.

PART-III : STUDIES ON THIAZOLIDINONES

It has been reported that compounds bearing thiazolidinones nucleus show wide range of biological activities such as antitumor, antileprosy, antitubercular and antibacterial etc. By considering these valid observations, we have synthesized some new 5-arylidine-4-thiazolidinones shown as under.

SECTION – I : Synthesis and biological evaluation of 2-Arylimino–3,N-aryl –5 – [1',N- phenyl-3'-p– fluorophenyl– 4'-pyrazolyl methino]–4'-thiazolidinones.



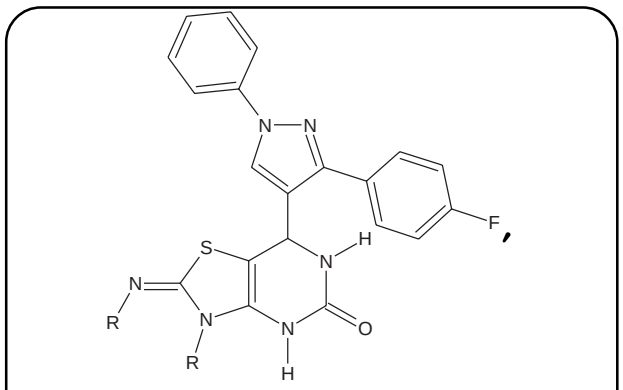
Type (VI) R = Aryl

The thiazolidinones of type (VI) have been prepared by condensation of 1, N-phenyl-3-p-fluorophenyl-4-formyl-pyrazole with different thiazolidinones in glacial acetic acid.

PART-IV: STUDIES ON PYRIMIDINONES

Pyrimidinones possess remarkable pharmaceutical importance and biological activity. Some of the pyrimidinones, which occurs as natural products like nucleic acid and vitamin-B can be used as therapeutic agents for treatment of AIDS and antitumor agent. Keeping in association of pyrimidinones with varied biological activity, it was thought worthwhile to synthesize new pyrimidinones as under.

SECTION –I : Synthesis and biological evaluation of 6-Arylimino–7,N-aryl –2-oxo –4-[1',N- phenyl-3'-p– fluorophenyl–pyrazol- 4'-yl]-1,2,3,4-tetrahydro thiazolidino-[4,5-d]-pyrimidines.



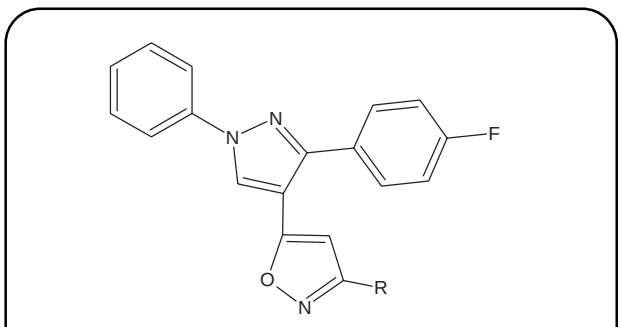
Type (VII) R=Aryl

The compounds of type (VII) have been synthesized by the condensation of type (VI) with urea in presence of hydrochloric acid as catalyst.

PART-V: STUDIES ON ISOXAZOLES

It has been reported that isoxazole derivatives possess remarkable pharmacological importance and biological activities such as antifungal, antibacterial, sedative and hypnotics etc. In order to develop medicinally important compounds, we have synthesized some new isoxazole derivatives shown as under.

SECTION – I : Synthesis and biological evaluation of 3-Aryl-5-[1',N- phenyl-3'-p–fluorophenyl– pyrazol– 4'-yl]–isoxazoles.



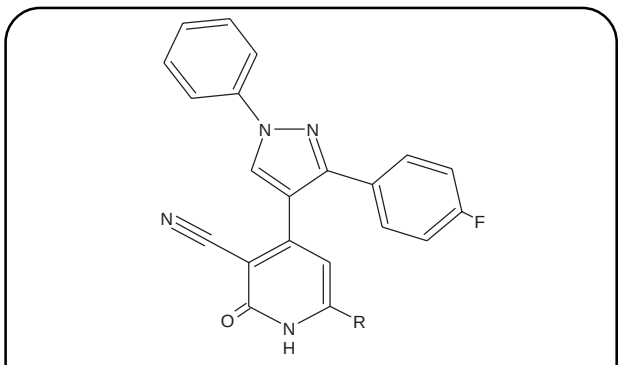
Type (VIII) R = Aryl

The isoxazole derivatives of type (VIII) have been prepared by the reaction of chalcones of type (I) with anhydrous sodium acetate and hydroxylamine hydrochloride in glacial acetic acid.

PART-VI: STUDIES ON CYANOPYRIDONES

Cyanopyridones play an important role owing to their wide range of biological activities such as analgesic, antidiabatic, anticonvulsant, insecticidal and antibacterial etc. It appeared of interest to design and synthesize cyanopyridone derivatives, which have been described as under.

SECTION – I : Synthesis and biological evaluation of 3-Cyano – 4 – [1', N- phenyl-3'-p– fluorophenyl– pyrazol– 4'-yl]–6-aryl–1, 2-dihydro-2-pyridones.



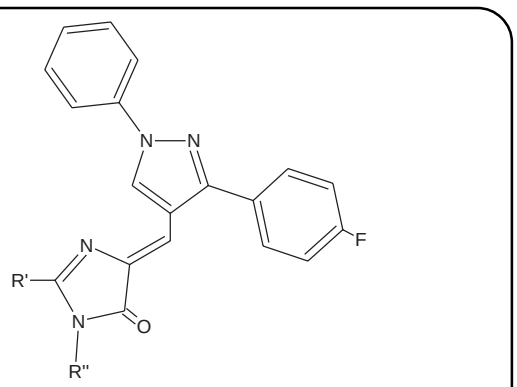
Type (IX) R = Aryl

The cyanopyridones of type (IX) have been prepared by the condensation of chalcones of type (I) with ethylcyanoacetate and ammonium acetate.

PART- VII: STUDIES ON IMIDAZOLINONES

Imidazolinone derivatives have been found to be potent drug in pharmaceutical and possess a wide range of biological activities such as anticonvulsant, sedative, hypnotic, anti-inflammatory, antihistamine and antithyroid etc. In order to develop medicinally important compounds, we have synthesized some new imidazolinones shown as under.

SECTION – I : Synthesis and biological evaluation of 1, N-Aryl-2-alkyl/aryl-4-[1',N- phenyl-3'-p– fluorophenyl– pyrazol– 4'-yl]–imidazolin-5-ones.



Type (X) R' =Alkyl/Aryl

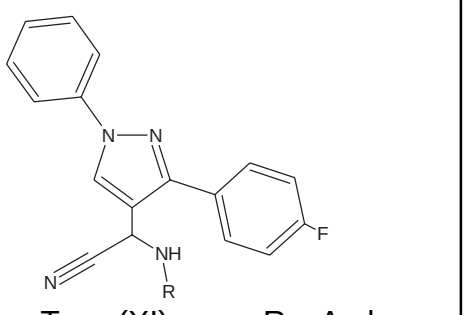
R" =Aryl

The imidazolinone derivatives of type (X) have been prepared by the condensation of azalactone with different aryl amines in pyridine.

PART-VIII: STUDIES ON NITRILES

Recently nitrile derivatives have drawn considerable attention due to their good pharmacological activities like cardiovascular, sedative, antifungal and antibacterial etc. Led by these considerations, we have synthesized some new nitriles, which have been described as under.

SECTION – I : Synthesis and biological evaluation of á–Arylamino-[1',N- phenyl-3'-p– fluorophenyl– pyrazol– 4'-yl]–acetonitriles



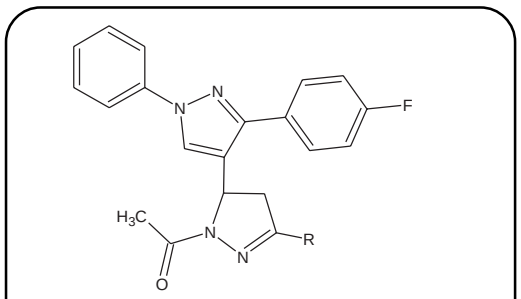
Type (XI) R = Aryl

The nitriles of type (XI) have been prepared by the condensation of 1,N-phenyl-3-p-fluorophenyl-4-formyl-pyrazole with different aromatic amines in the presence of sodium cyanide and glacial acetic acid at 0-5 ^{0} C.

[B] STUDIES ON MICROWAVE INDUCED SYNTHESIS OF PYRAZOLINES

In recent years **MORE** (Microwave Induced Organic Reaction Enhancement) technique has become very popular due to substantial reduction in reaction time, operational simplicity and formation of cleaner reaction products. Keeping these facts in view, we have synthesised acetyl pyrazoline derivatives using microwave irradiation and also by conventional method.

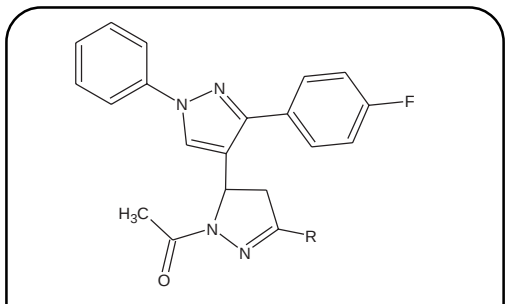
SECTION – I : Synthesis and biological evaluation of 1,N-Acetyl- 3-aryl-5-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-pyrazolines using conventional method.



Type (XII) R=Aryl

The pyrazoline derivatives of type (XII) have been investigated by the reaction of chalcones of type (I) with hydrazine hydrate in glacial acetic acid.

SECTION – II : Synthesis and biological evaluation of 1,N-Acetyl- 3-aryl-5-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-pyrazolines by Microwave induced synthesis.



Type (XIII) R=Aryl

The pyrazoline derivatives of type (XIII) have been synthesized by the reaction of chalcones of type (I) with hydrazine hydrate in glacial acetic acid under microwave irradiation in few minutes.Benefits of microwave irradiation have been discussed.

The constitution of newly synthesised compounds have been characterized using elemental analyses, Infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

***In Vitro* study on multiple biological activities:**

(1) All the compounds have been evaluated for their antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus Niger*** at a concentration of 40 ìg. The biological activity of the synthesized compounds has been compared with standard drugs.

(2) Selected compounds have been evaluated for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}R_V$ at a concentration of 6.25 ìg/ml using Rifampin as standard drug, which have been tested at Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), Alabama, U.S.A...

DISCOVERING THE NEW CHEMICAL ENTITIES OF THERAPEUTIC INTEREST

Medicinal chemistry concerns the discovery, the development, the identification of action of biologically active compound at the molecular level. Emphasis it put on drugs, but the interest of the medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of drugs and related compounds.

Medicinal chemistry is a part of pharmacology, this latter taken in its etymological sense 'pharmakon' + 'logs' : study of drugs. The activity of a given drug depends on a sequence of physio-chemical events that begin when the active molecule penetrates into the living organism and which culminates when the active molecule reaches its target and elicits the appropriate biological response. Classically it is addmitted that three characteristic phases govern the biological activity of a drug in a living organism. They are as under.

(I) The pharmaceutical phase

Sometimes it is also called biopharmaceutical phase, deals with the choice of the appropriate route of administration and with the choice of the pharmaceutical formulation most suited to the desired medical treatment.

(II) The pharmacokinetic phase

It controls the different parameters that govern the random walk of the drug between its application point and its final site of action and which ensure the destruction and/or the elimination once the effect is produced.

(III) The pharmacodynamic phase

It is the phase of the greatest interest to the medicinal chemist as it deals with the nature and the quality of the interaction of the drug with its biological target.

Modern medicinal chemistry began in the 1950s when organic chemists began to apply newly developed steric & electronic structure active relactionship of the steroids. During the second half of the twentieth century, chemistry and biology made possible the discovery of a steady stream of important new medicines. Chemistry contributed to these discoveries through impactful advantaces in both theory & practice of this art/science. Notable examples include invaluable advances in physical measurements, computational techniques, inorganic catalysis, stereochemical control of synthesis & the application of physical organic chemical concepts, typified by the transition state analog principle, to enzyme inhibitor design. At the same time biology continued to contribute through the discoveries of new concepts and understanding at a rate that may well be termed explosive.

During the 1970s, target validation became an important consideration in the selection of therapeutic programs explored by the pharmaceutical industry. In the strictest sense this strategy holds that intervention in any particular biochemical or pharmacological pathway has been fully validated only if it has been shown to work in human subjects. Any research program that does not pass this definitive test is there for thought to be a 'long shot'. In practise, this leads to the conclusion that a conservation porfolio of an organization's programs should strike some appropriate balance between' validated' and 'long shot' targets. In recent years succesful use of antibodies in neutralizing a target protein or other substance has come to the accepted as adequate validation; this is also the case for another validated technology, the use of 'knock-out' or 'knock-in' mice.

Inspite of all the qualified successes of synthetic drug research achieved in the last four decades to combat infectious disease of the more than 80,000 different ailments, unfortunately only about one third can be treated with drugs, most of them only symptomatically. The discovery of better, effective and safey drugs is needed to fight the cause of dreadful disease like cancer, acquired-immuno-deficiency-syndrome (AIDS), arthritis, cardiovascular diseases, disorders of the central nervous system (CNS) such as Alzheimer's disease and other vital infectious and metabolic disease like rheumatoid arthritis.

In order to meet these challenges one needs to adopt novel approaches in pharmaceutical research. Both molecular biology and genetic engineering will be exploited duly in opening up new routes.

It is earnestly believed that towards the begining of new century (2001 AD) keeping in view the tremendous global technological competition, one is left with no other choice than to internationalize research and development of pharmaceutical drugs to achieve the common objective "better drugs for a better word".

AIMS AND OBJECTIVES

Taking in view of the applicability of heterocylic compounds, we have undertaken the preparation of heterocycles bearing pyrazole nucleus. The placement of a wide variety of substituents of these nuclei have been designed in order to evaluate the synthesised products for their pharmacological profile against several strains of bacteria and fungi.

- ❖ To generate several derivatives like chalcones, pyrazolines, cyanopyridones, thiazolidinones, oxo-pyrimidines, isoxazoles, cyanopyridones, imidazolinones, nitriles bearing pyrazole moiety.

- To synthesise biologically active pyrazolines bearing pyrazole moiety using microwave induce synthesis method.

- In a programmed research directed towards the construction of medicinally active new heterocycles bearing pyrazole has been investigated in following parts.

- To characterise these products for stucture elucidation using spectroscopic technique like IR, PMR and Mass spectral studies.

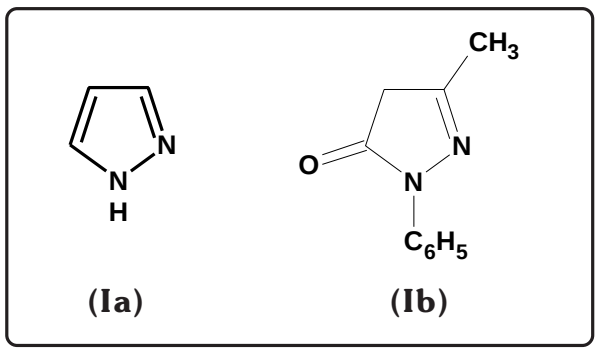
- Purity of all compounds have been checked by thin layer chromatography.

- To evaluate new product for better drug potential against different strains of bacteria, fungi and for antitubercular activity against *Mycobacterium Tuberculosis* H_{37} Rv.

[A]
STUDIES ON PYRAZOLE

INTRODUCTION

The pyrazole ring system (Ia) is consisting of three carbon atoms and two adjacent nitrogen atoms. The ring system does not occur naturally. Knorr[1,2] first syntehsised a compound (Ib) containing this system in 1833 by a reaction of ethylacetoacetate with phenylhydrazine. Pyrazoles have been extensively explored for their applications in the field of medicine, agriculture and industrial chemistry.

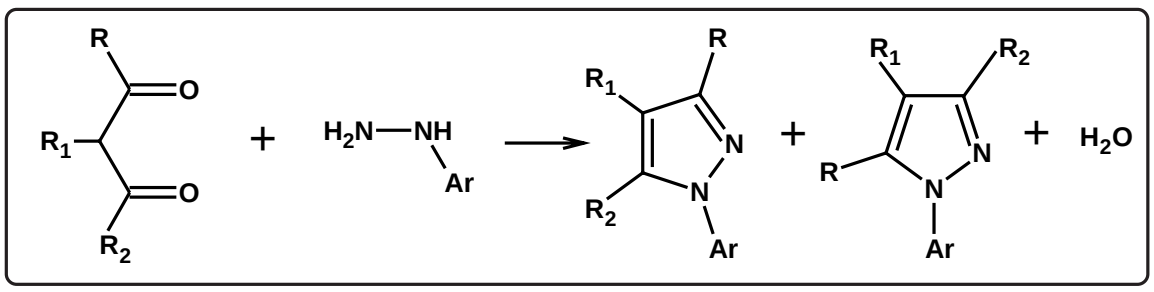


(Ia) **(Ib)**

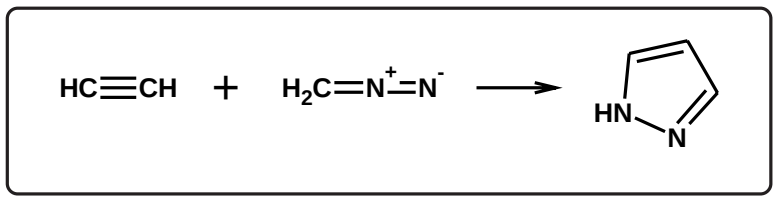
SYNTHETIC ASPECTS

Different methods of preparation are available in literature which are as under.

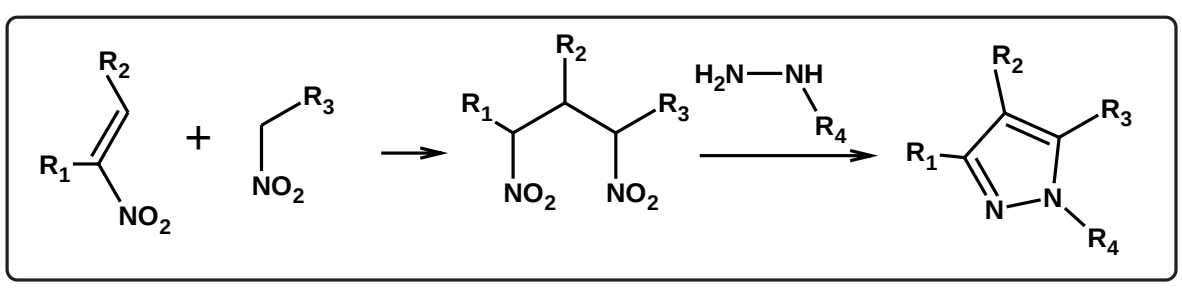
1. By the reaction of the substituted hydrazines, with 1,3-dicarbonyl compounds yielded two structurally isomeric pyrazole[3].



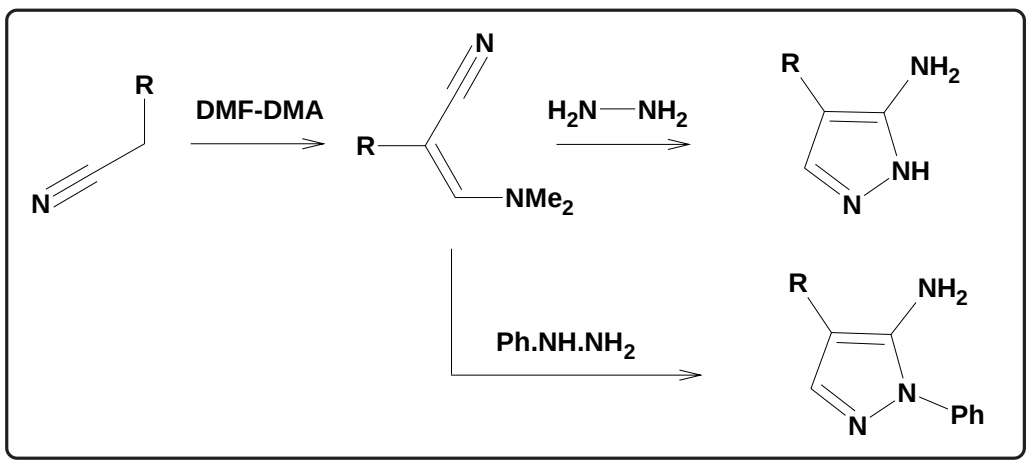
2. By the reaction of acetylene with diazomethane[4].



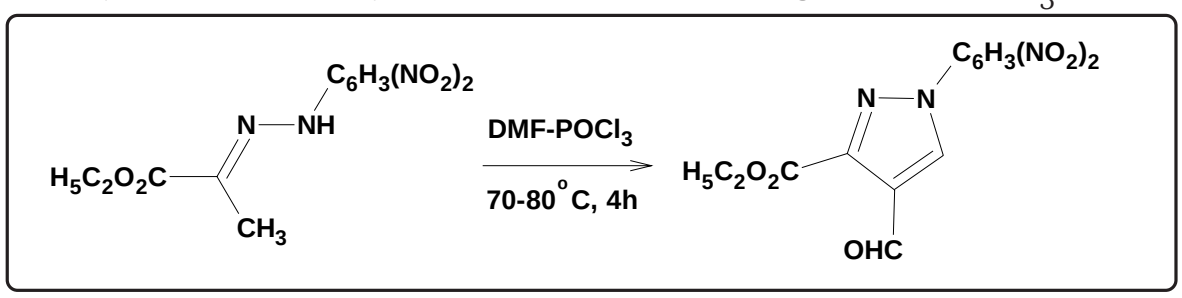
3. By the reaction of 1,3-dinitro alkanes with hydrazines[5].



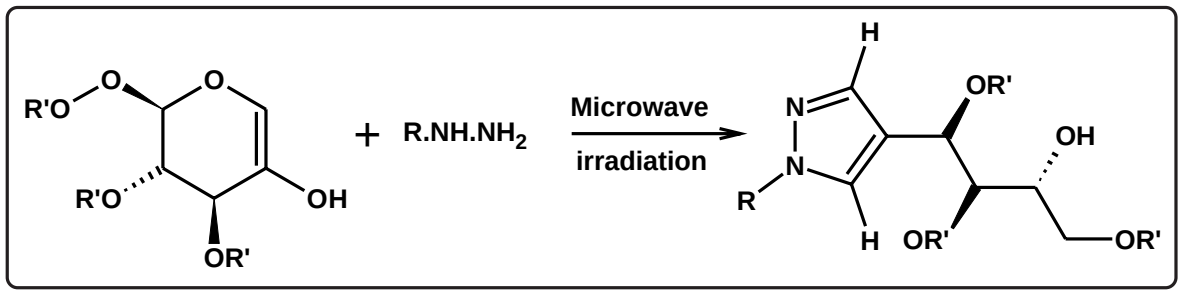
4. By the reaction of acetonitrile derivatives with dimethylformamide & diethyl acetal (DMF-DMA) in xylene gives an intermediate which on reaction with hydrazine hydrate or phenyl hydrazine in presence of HCl as catalyst yields pyrazole[6].



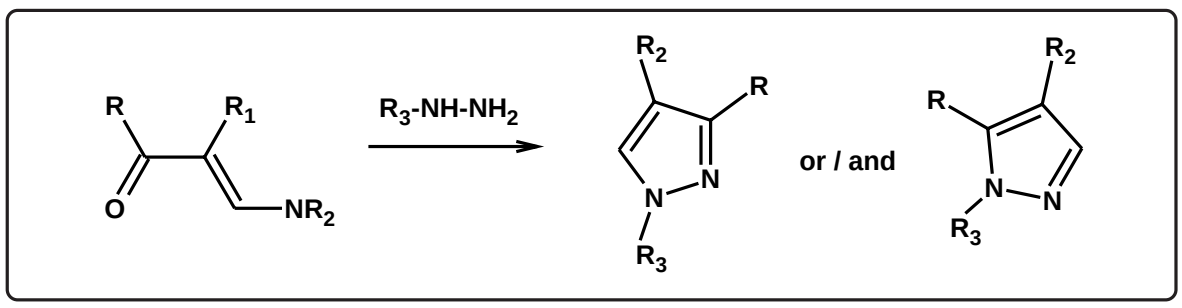
5. By the reaction of hydrazones with Vilsmeier reagent (DMF-$POCl_3$)[7].



6. By the reaction of 2-formyl glycals with aryl hydrazines under solvent free conditions give optically pure 4-substituted pyrazoles[8].

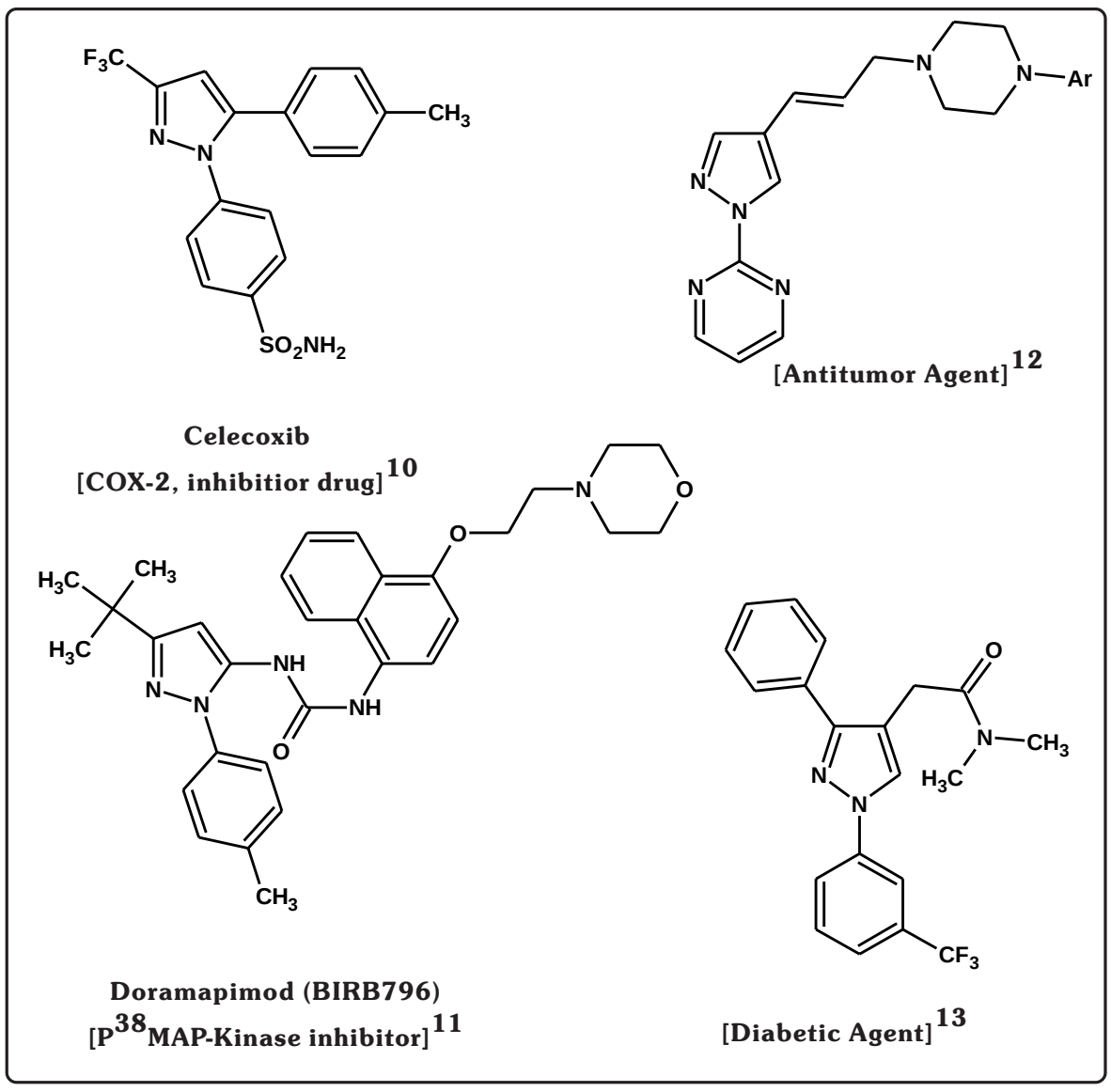


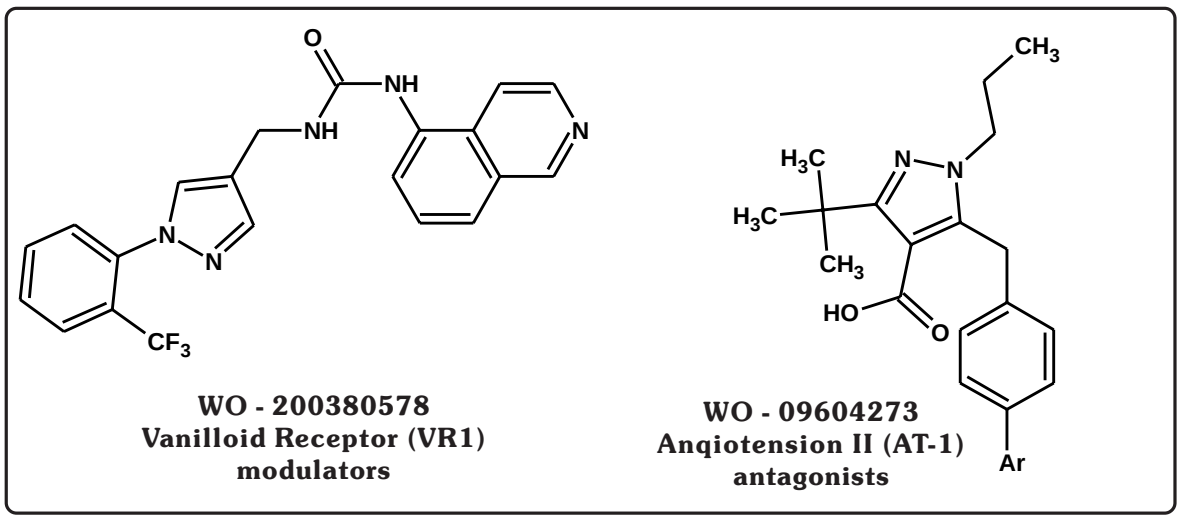
7. By the cyclocondensation of mono substituted hydrazines with enaminones afforded pyrazoles[9].



THERAPEUTIC IMPORTANCE

Pyrazole and its derivatives are shown to possess important biological and pharmaceutical activities. Pyrazole motifs in drug candidates with good pharmacological activities are listed below.





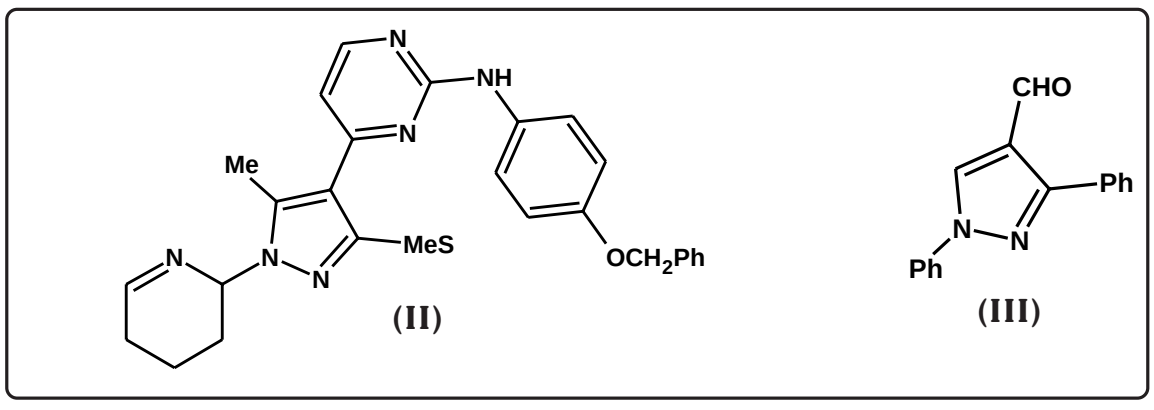
Several biological activities associated with pyrazole derivatives have been described as under.

1. Antitumor[14]
2. Herbicidal[15]
3. CNS depressant[16]
4. Antiulcer[17]
5. Anticancer[18]
6. Antimicrobial[19]
7. Neurotonsin receptor[20]
8. AntiHIV[21]
9. Antiviral[22]
10. Immuno suppresants[23]

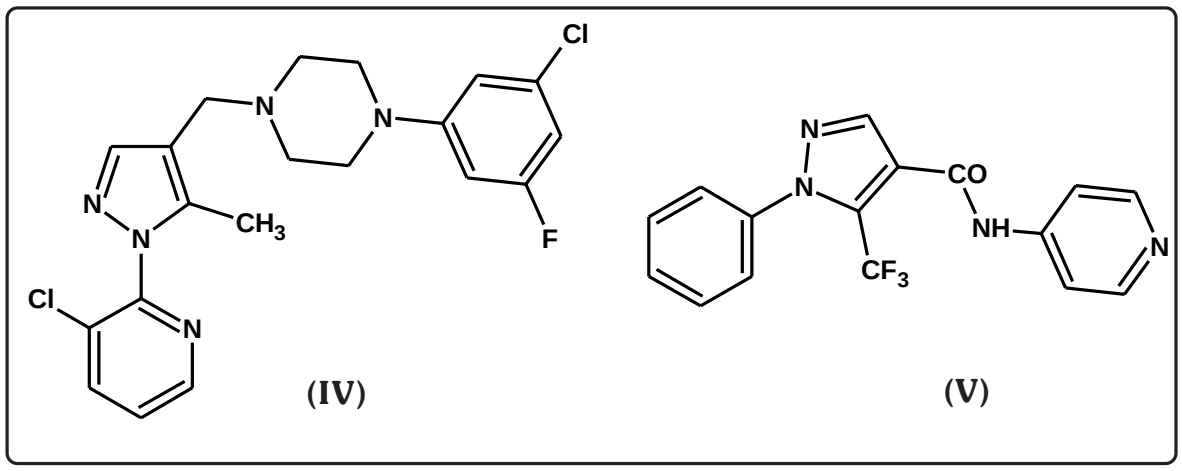
Jonh M. et. al.[24] have synthesised pyrazole as neoplasm inhibitors. Antonio Bellotti[25] has reported pyrazole derivatives as antitubercular & bacteriostatic agents. L. Villa & co-workers[26] have screened pyrazoles which are used in the rhematic disease & related syndromes. Yoshiro Usui & co-workers[27] have screened pyrazoles as fungicidal.

Bruderer-Hans & co-workers[28] have synthesised pyrazole & reported their tranquilizing activity. M. M. El-Kerdawy & co-workers[29] have prepared pyrazoles as herbicidal.

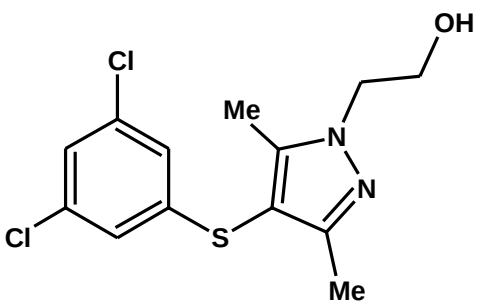
Young Choon Moon[30] has reported pyrazole derivatives (II) as protein kinase inibitors. El-Emery et. al.[31] have synthesised 1,3-diphenyl pyrazole derivatives (III) and reported their variety of biological activities.



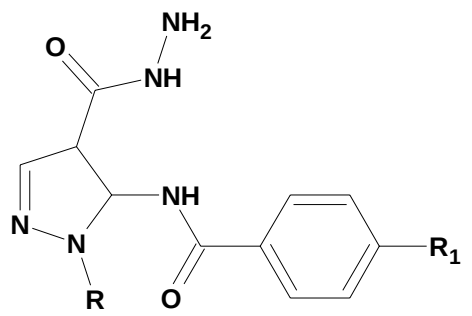
Feid-Allah Hassan[32] have prepared pyrazoles and reported their antidiabetic and antibacterial activity. Ejima Akio et. al.[33] have synthesised pyrazole derivatives as antitumor agent (IV). Recently, Atkinson R. N. et. al.[34] have synthesised pyrazoles as sodium channel blocker (V). Murakani Hirani et. al.[35] have synthesised pyrazole as antifoulling agent.



Graid Mamalo et. al.[36] have newly synthesised pyrazole derivatives tested for antimicrobial activity. Carbau Rouald and co-worker[37] have prepared pyrazole derivatives (VI) useful as reverse transcriptase inhibitors for the treatment of HIV infection. Giuseppe Daidone et. al. have studied pyrazole derivative with hydrazide as side of type (VII) used as to inhibit fibrosis and to treat fibrosis disorder[38,39].

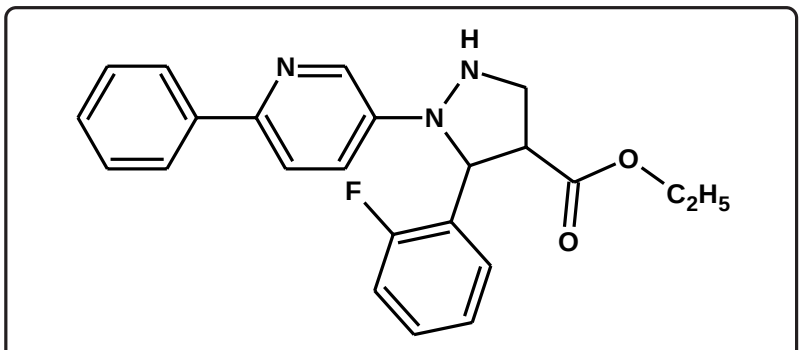


(VI)



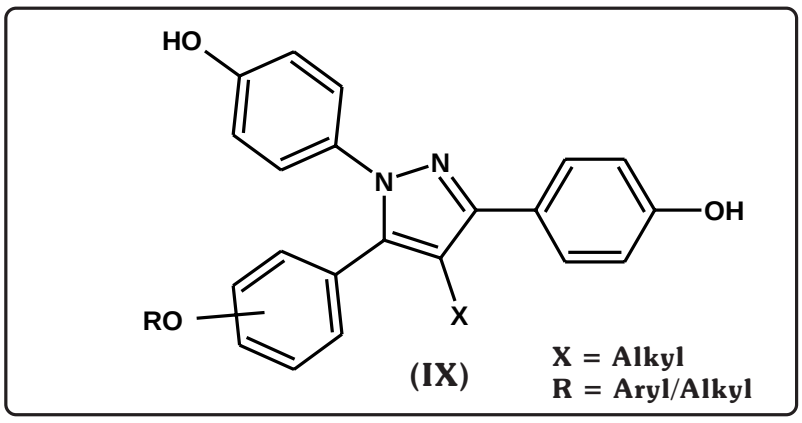
(VII) R, R' = Alkyl/Aryl

Laborde Edgardo *et.* al.[402] have found that pyrazole possess glycine transport-2-inhibitors activity. Andrew-Thurkaub *et.* al.[41] have synthesised high affinity C5a receptor modulator pyrazoles. Nagaaki Sato *et.* al.[42] have prepared pyrazole as neuropeptide T5 receptor antagonists. G. Yamanouch Pharma. Co[43] has suggested pyrazoles as glycine transporter protein inhibitors (VIII).



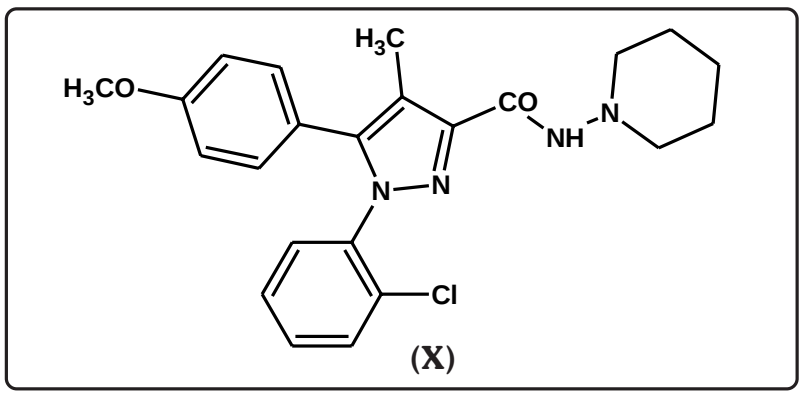
(VIII)

Ohki H. *et.* al.[44] have synthesised novel pyrimidinyl pyrazole derivatives possessing antiproliferature activity. Jun Sun *et.* al.[45] have studied pyrazole derivative of type (IX) used as antagonists for Estrogen receptor - α.



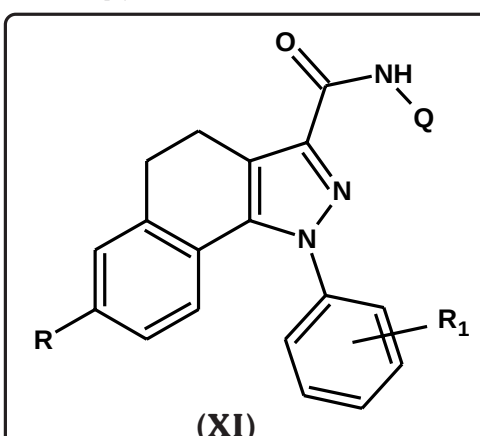
(IX) X = Alkyl
R = Aryl/Alkyl

Recently, some pyrazole derivatives (X) have been synthesised as a potential PET ligand for CB1 receptors by J. S. Dileep *et.* al.[46]



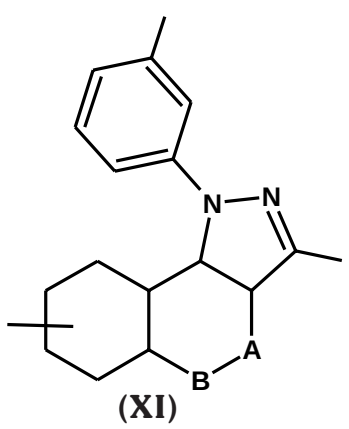
(X)

Gabriele Murineddu *et.* al.[47] have reported pyrazole derivatives (XI) as cannabinoid CB_1 & CB_2 receptor. Recently S. Prasanna & co-workers[48] have found pyrazole (XII) as COX-2 inhibitors.



(XI)

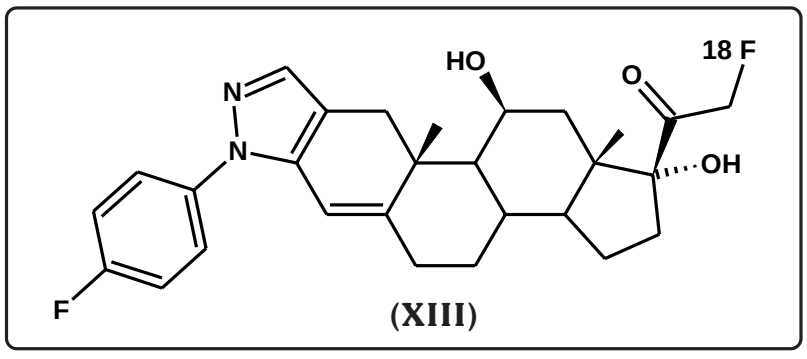
R,R' = Alkyl
Q = Heteroaryl



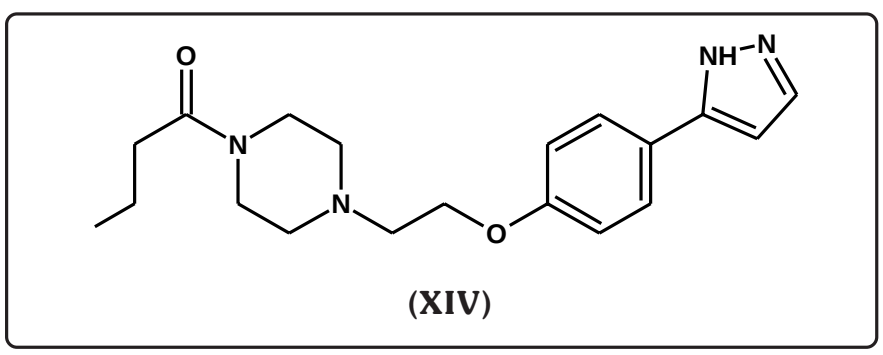
(XI)

A,B = hetero atom

Pyrazole(XIII) has found as potential glucocorticoid receptor ligand for position emission tomography (PET) by Frank Wiist *et.* al.[49]. Toshio Nakaura *et.* al.[50] have discovered pyrazole (XIV) as potent inhibitory activity toward 20-HETE synthase.

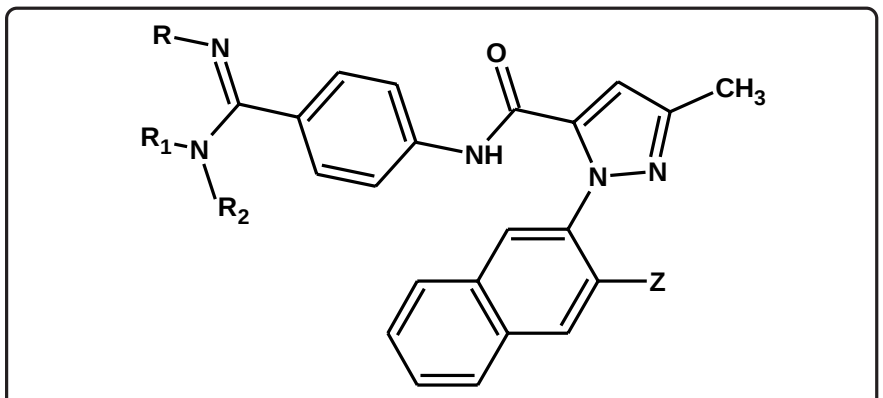


(XIII)



(XIV)

Zhaozhony J. Jia et. al.[51] have synthesised pyrazoles (XV) as potent and selective factor Xa inhiitors with desired *in vitro* anticoagulant activity.



(XV) **Z = F & SO_2Me**

Looking to the diversified biological activity, it appeared of interest to synthesise some chalcones, pyrazolines, cyanopyridines, thiazolidinones, pyrimidinones, isoxazoles, cyanopyridones, nitriles bearing pyrazole moiety, in order to achieving compounds having better therapeutic importance. These study are described in the following parts.

[A] STUDIES ON PYRAZOLES

PART - I : STUDIES ON PYRAZOLYLPYRAZOLINES

PART - II : STUDIES ON CYANOPYRIDINES

PART - III : STUDIES ON THIAZOLIDINONES

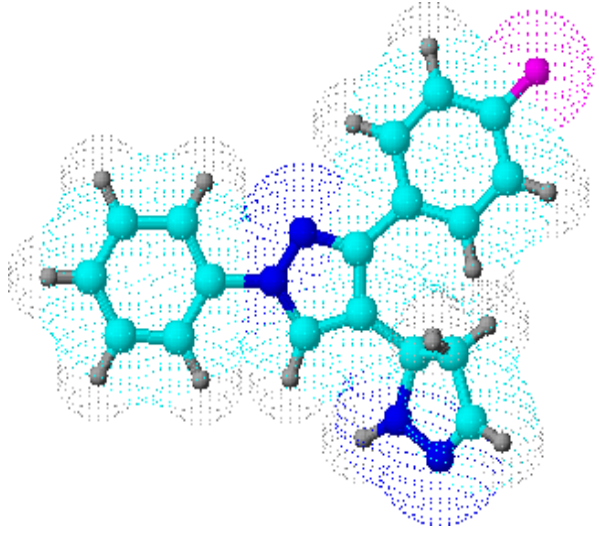
PART - IV : STUDIES ON PYRIMIDINONES

PART - V : STUDIES ON ISOXAZOLES

PART - VI : STUDIES ON CYANOPYRIDONES

PART - VII : STUDIES ON IMIDAZOLINONES

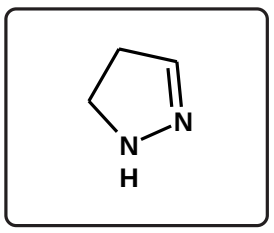
PART - VIII : STUDIES ON NITRILES



PART-I
STUDIES ON PYRAZOLINES

INTRODUCTION

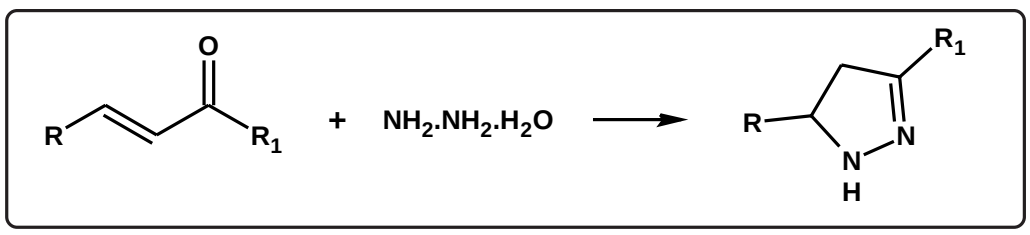
Amongst nitrogen containing five membered heterocycles, pyrazolines have been proved to be the most useful skeleton for biological activities. Pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemisry and the pharmacological activities associated with them. In 1967 Jakobe, reviewed the chemistry of pyrazolines, which have been studied extensively for their biodynamic behaviour[52] and industrial applications[53].



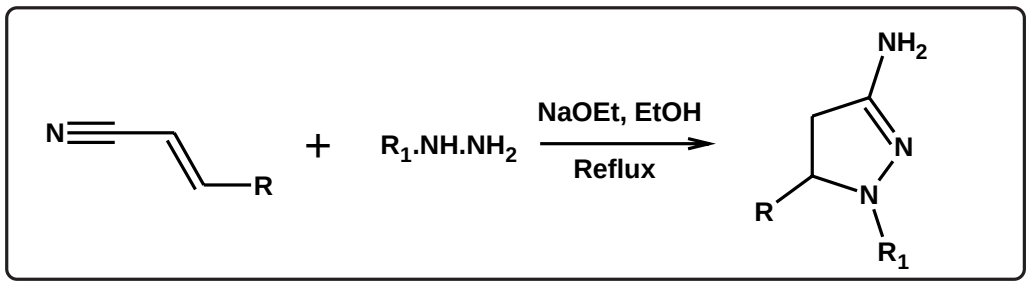
SYNTHETIC ASPECTS

Different methods for the preparation of 2-pyrazoline derivatives documented in literature are as follows.

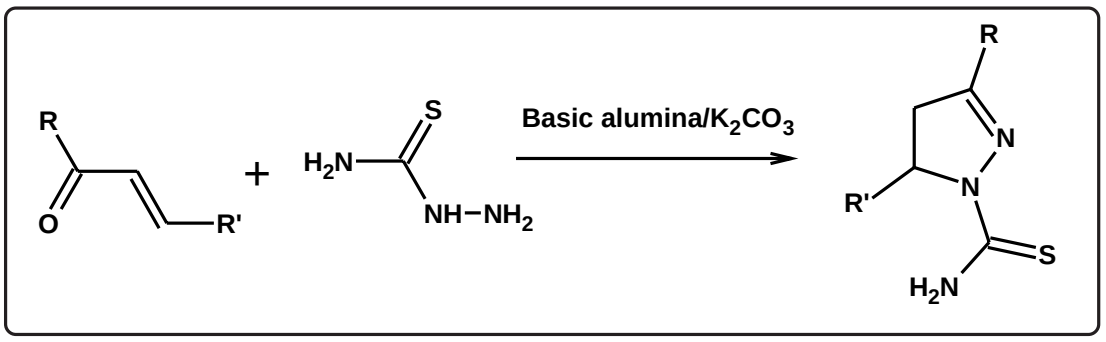
1. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate[54].



2. 2-Pyrazoline can also be prepared by the conjugate addition of hydrazines to α,β-unsaturated nitrile followed by cyclisation[55].



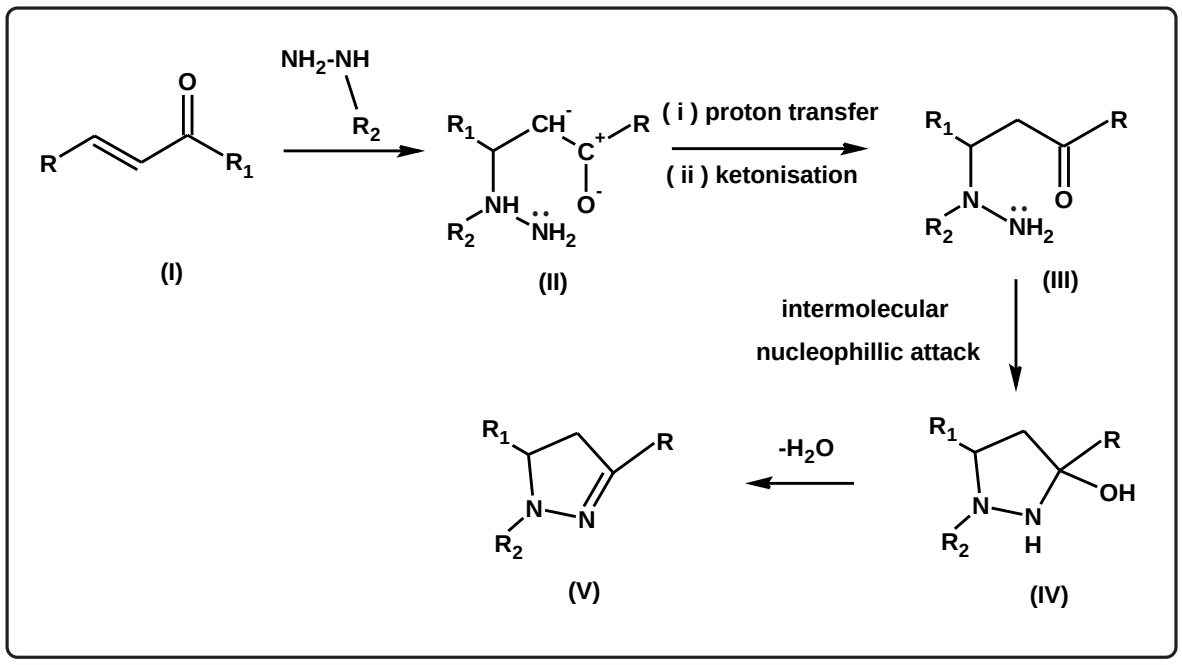
3. 2-Pyrazoline can be prepared by the condensation of α,β-unsaturated ketone and thiosemicarbazide in presence of basic alumina & K_2CO_3.[56]



4. Dipolar cycloaddition of nitriles of dimethyl fumarate, fumaronitrile and the N-aryl maleimides yields the corresponding pyrazolines[57].
5. Epoxidation of chalcones have epoxy ketones which reacted with hydrazine and phenyl hydrazine to give pyrazolines[58].

MECHANISM

The following mechanism seems to be operable for the condensation of chalcones with hydrazine hydrate[59].



Nucleophillic attack by hydrazine at the β-position of the α,β-unsaturated carbonyl system forms species (II), in which the -ve charge is mainly accomodated by the electronegative oxygen atom.

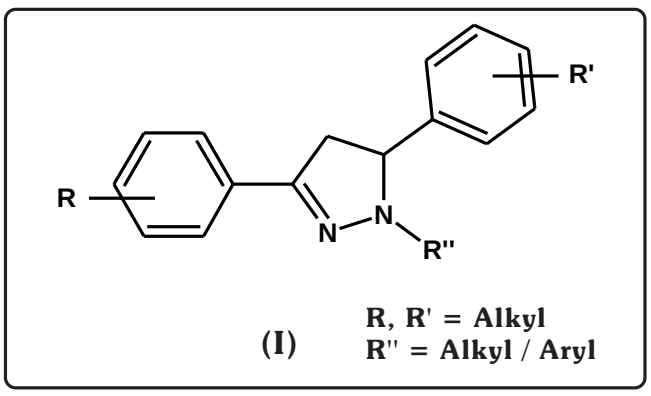
Proton transfer from the nitrogen to -ve oxygen produces an intermediate enol which simultaneously ketonises to ketoamine (III). Another intermolecular nucleophillic attack by the primary amino group to ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to carbonyl amine (IV). The later with a hydroxy group and amino group on the same carbon lose water molecule to yield the pyrazolines (V).

THERAPEUTIC IMPORTANT

From the literature survey, it was revealed that 2-pyrazoline derivatives shows following activities.

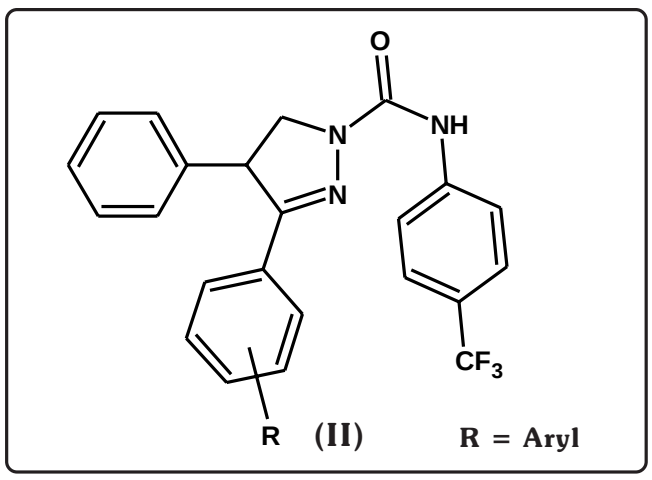
1. Analgesic[60]
2. Bactericidal[61]
3. Cardiovascular[62]
4. Diuretic[63]
5. Fungicidal[64]
6. Hypoglycemic[65]
7. Herbicidal[66]
8. Insecticidal[67]
9. Tranquilizing[68]
10. Antiallergic[69]
11. Anticonvulsant[70]
12. Antidiabetic[71]
13. Antiimplantation[72]
14. Antiinflammatory[73]
15. Antitumor[74]
16. Antineoplastic[75]

Ekta Bansal and co-workers[76] have synthesised 1-acetyl-5-substituted ary-3-(b-aminoaphthyl)-2-pyrazolines which acts as antiinflamnmatory agent. F. Chimenti et. al.[77] have discovered series of N.1-substituted 3-5-diphenyl pyrazolines (I) and reported their antiHelicobacter pyroli activity.



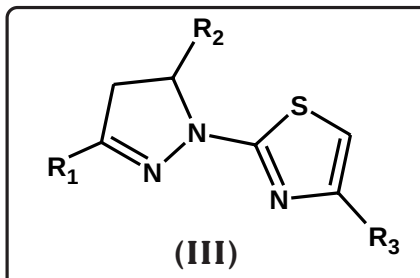
(I) **R, R' = Alkyl**
R'' = Alkyl / Aryl

Nugent Richard[78] investigated pyrazoines bis phosphanate ester as novel antiinflammatory and antiarthritic agents. Furthermore, Tsuboi et. al.[79] have synthesised some new (phenylcarbonyl) pyrazoline (II) as an insecticides and at 40% concentration show 100% mortality of spodopetra litura larve after seven drops.

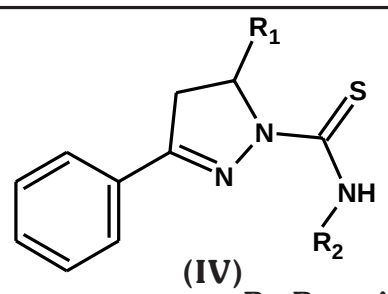


(II) **R = Aryl**

Gulhan Taran-Zitouni et. al.[80] have demonstrated 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazolines (III) as antihypertensive agents. S. P. Hiremath et. al.[81] have reported substituted pyrazolines as analgesic, antiinflammatory and antimicrobial agents. Malhotra et. al.[82] have prepared 1-thiocarbamoyl-2-pyrazolines derivatives (IV) as anticardiovascular agents.

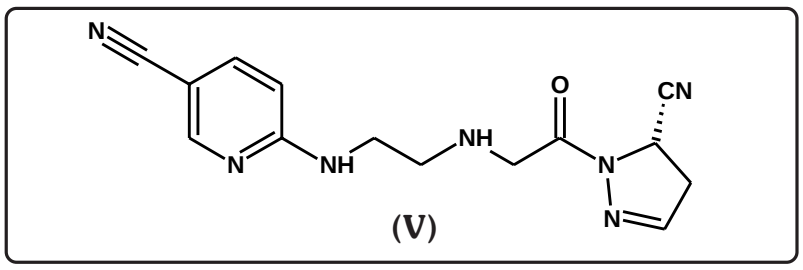


(III) **R_1,R_2,R_3 = Aryl**



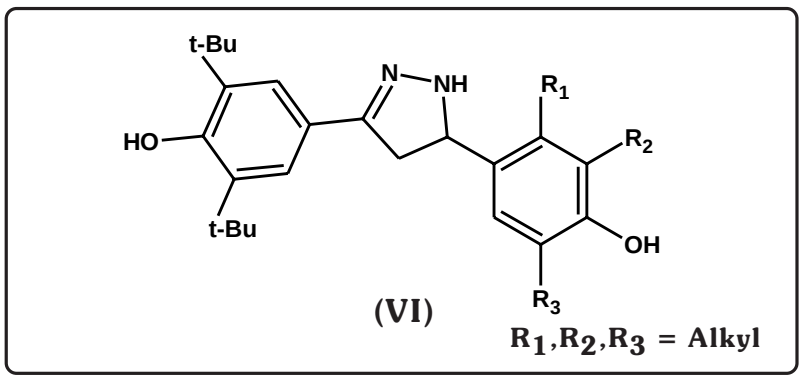
(IV) **R_1,R_2 = Aryl**

Nesrin Gokhan et. al.[83] have synthesised new 1,N-substituted thiocarbomoyl-3-phenyl-5-thienyl-2-pyrazoline derivatives and evaluated theirs for antidepressant, antiogenic and mammalianmonoamine oxidase (MAO)- A & B inhibitory activities. jin Hee Ahn et. al.[84] have synthesised new series of cyano pyrazoline derivatives (V) through achiral and chiral synthetic methods and evaluated for their ability to inhibite dipeptidyl peptidase IV (DP-IV) as potent antidiabetic agents.



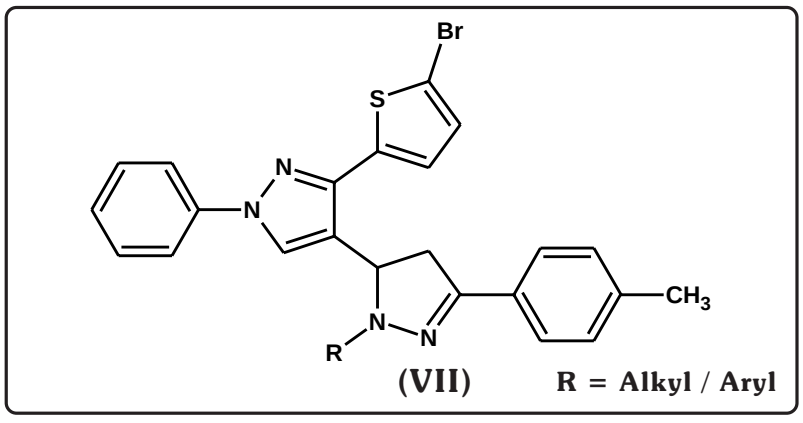
(V)

Maria Celoni et. al.[85] have discovered some new pyrazoline derivatives and reported as α_2-adrenoceptors and 5-HT receptors mediate, the antinociceptive effect. Novel 3,5-diaryl pyrazolines (VI) have been discovered as low density lipoprotein (LDL) oxidation inhibitor by Tae-Sock et. al.[86]



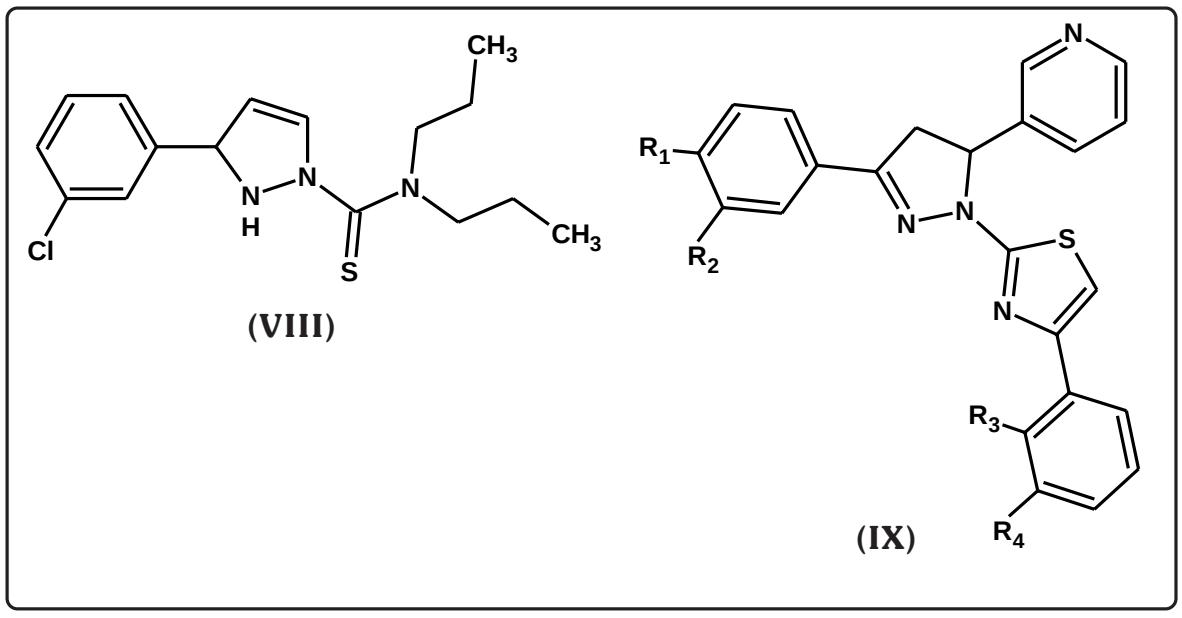
(VI) **R_1,R_2,R_3 = Alkyl**

Adnan and Tarek[87] have synthesised pyrazoline derivatives (VII) as antiinflammatory antimicrobial agents.



(VII) **R = Alkyl / Aryl**

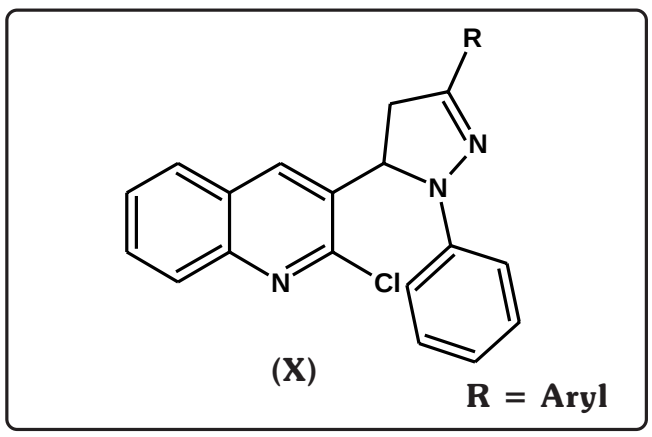
A series of new 1,N-substituted pyrazoline analogues (VIII) of thiosemicarbazones were synthesised by Mohammad Abid and Amir Azam[88] as antiamoebic agent. Abbas Sdhafiee et. al.[89] have demonstrated 1-(4-aryl-2-thiazolyl)-3,5-disubstituted-2-pyrazolines (IX) which acts as antinociceptive agents.



CONTRIBUTION FROM OUR LABORATORY

Parekh et. al.[90] have prepared 1-acetyl-5-aryl-3-[3-(3,4-dihydro-2-methyl-4-one-3-quinazolinyl)-phenyl]-2-pyrazolines which possess antimicrobial activity. Tejas Upadhyay et. al.[91] and sohit Rajvaidya et. al.[92] have prepared pyrzolines as antimicrobial agent.

A. V. Dobaria & Co-workers[93] has discoverd pyrazolines bearing chloroquinoline nucleus which used as antimicrobial agents. Jatin Upadhyay et. al.[94] have described pyrazoline derivatives as antimicrobial agents. Akhil Bhatt and co-workers[95] have reported pyrazoline derivatives showing antimicrobial activity.



(X)

R = Aryl

With an aim to synthesise better therapeutic agents, we have investigated some new pyrazolines to enhance the overall drug potential of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ARYL-3-[1'-N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-2PROPENE-1-ONES

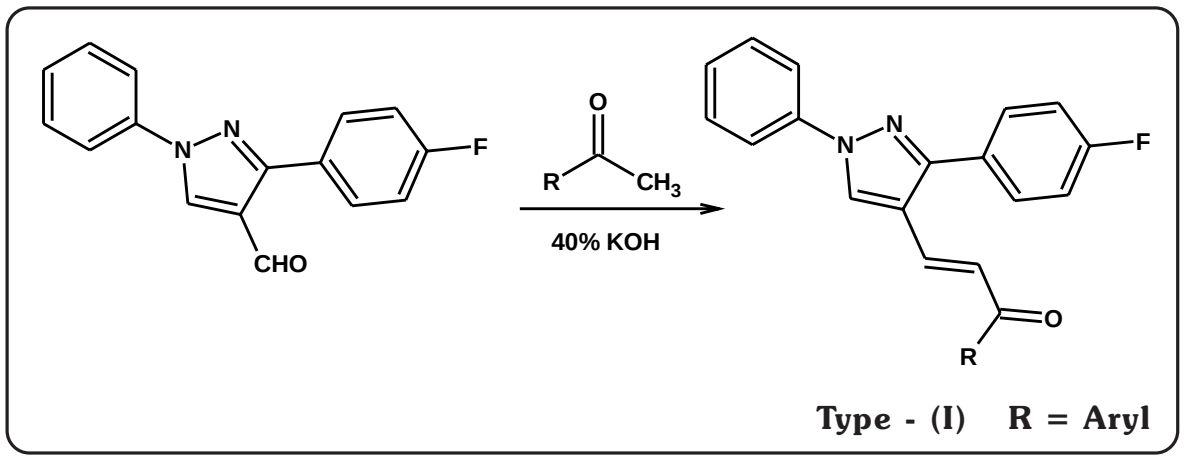
SECTION - II: SYNTHESIS AND THERAPEUTIC EVALUATION OF 3-ARYL-5-[1'-N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-PYRAZOLINES

SECTION - III : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1,N-PHENYL-3-ARYL-5-[1'N,-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-PYRAZOLINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-[1'-N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-2-PROPENE-1-ONES

Recently, much interest has been focused on the synthesis and biodynamic activities of chalcones and it is a good synthon for verious heterocyclic rings. With a view to obtainng compounds having better therapeutic activity, we have synthesised 1-aryl-3-(1',N-phenyl-3'-p-flurophenyl-pyrazol-4'-yl)-2-propene-1-ones by the condensation of 1-phenyl-3-p-fluorophenyl-4-formyl-pyrazole with various aromatic ketones in alkaline solution.

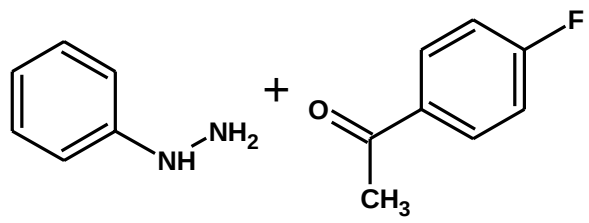


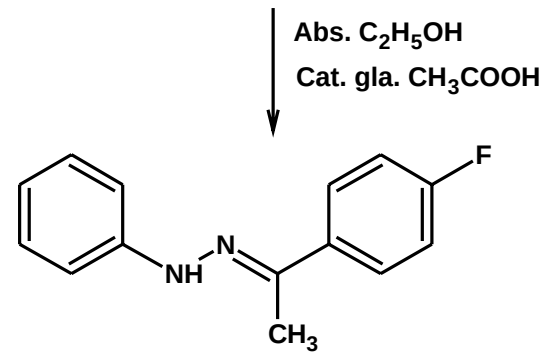
Type - (I) R = Aryl

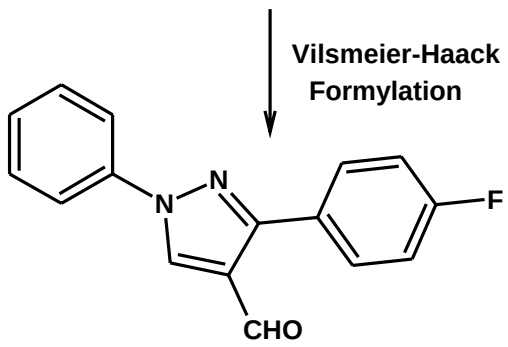
The constitution of the synthesised compounds have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

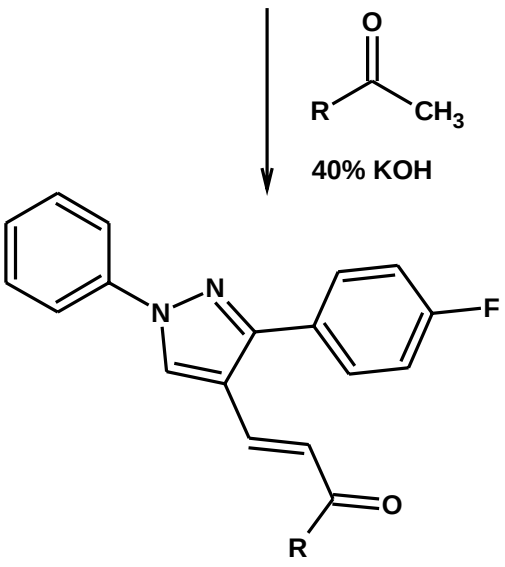
The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

REACTION SCHEME



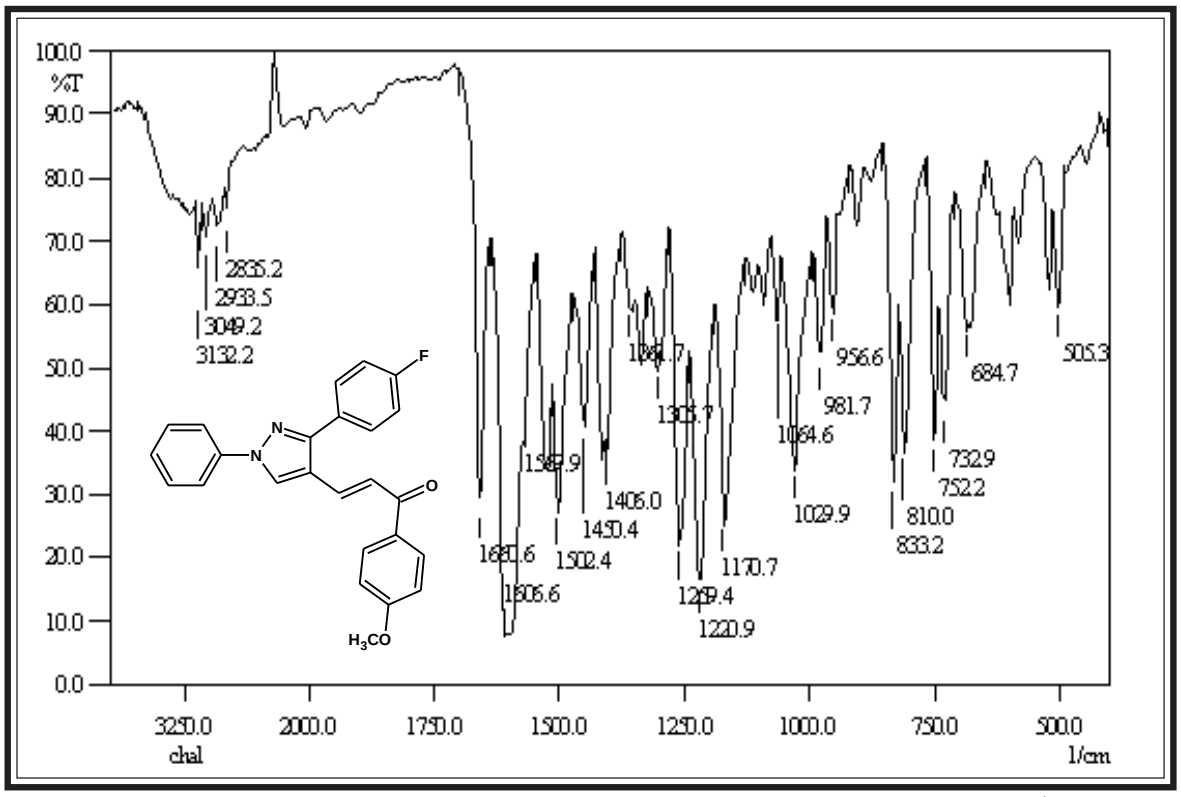






Type - (I) **R = Aryl**

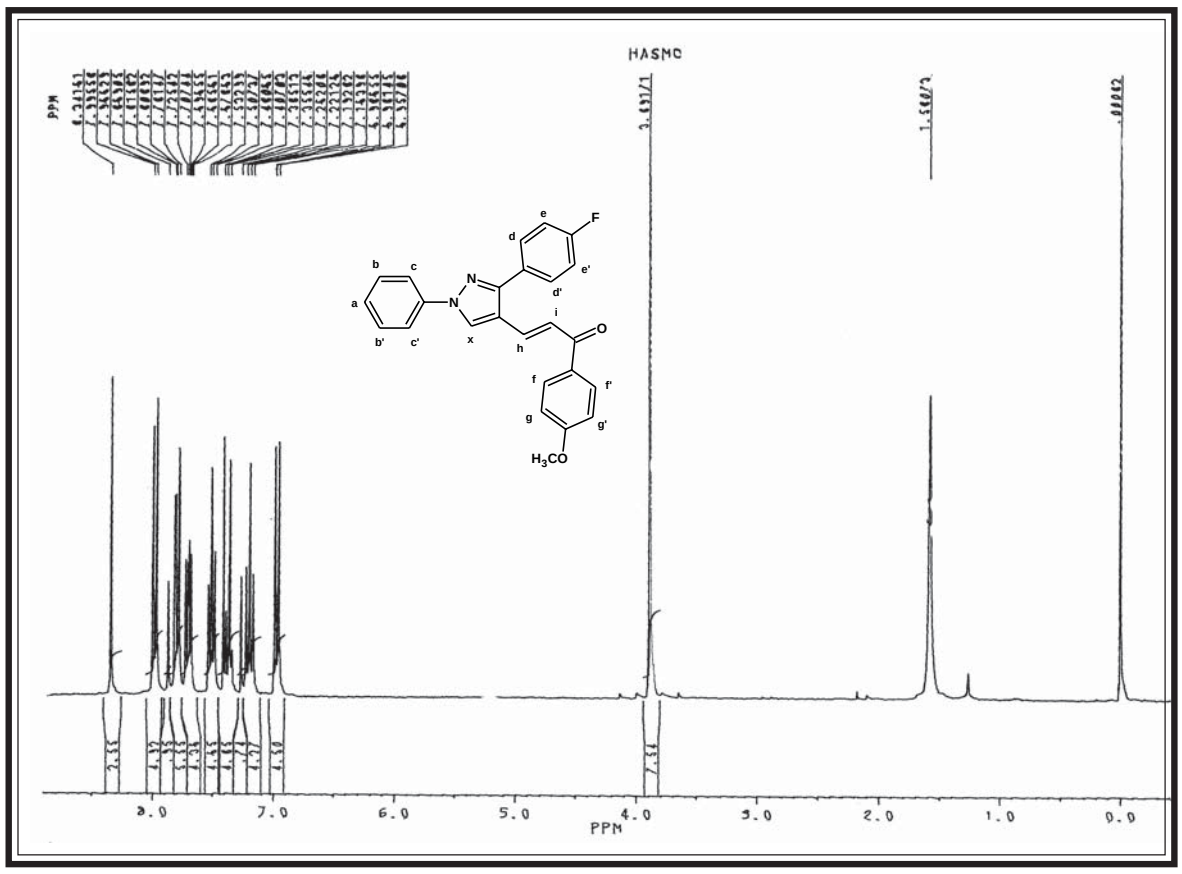
IR SPECTRAL STUDY OF 1-(p-ANISYL)-3-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-2-PROPENE-1-ONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2933	2975–2950	426
$-CH_3$	C – H str. (sym.)	2835	2880–2860	"
	C – H i.p. (def.)	1450	1470–1435	"
	C – H o.o.p. (def.)	1361	1385–1350	"
Aromatic	C – H str.	3049	3130–3030	427
	C = C str.	1502	1585–1480	"
	C – H i.p. (def.)	1064	1125–1090	"
	C – H o.o.p. (def.)	833	835-810	"
Pyrazole	C = N str.	1606	1650–1580	428
moiety	C – N str.	1259	1350–1200	"
	C – F	752	760-710	"
Ether	C – O – C str. (asym).	1220	1275–1200	"
	C – O – C str. (sym).	1029	1075–1020	"
Chalcone	C = O str.	1660	1760–1655	429

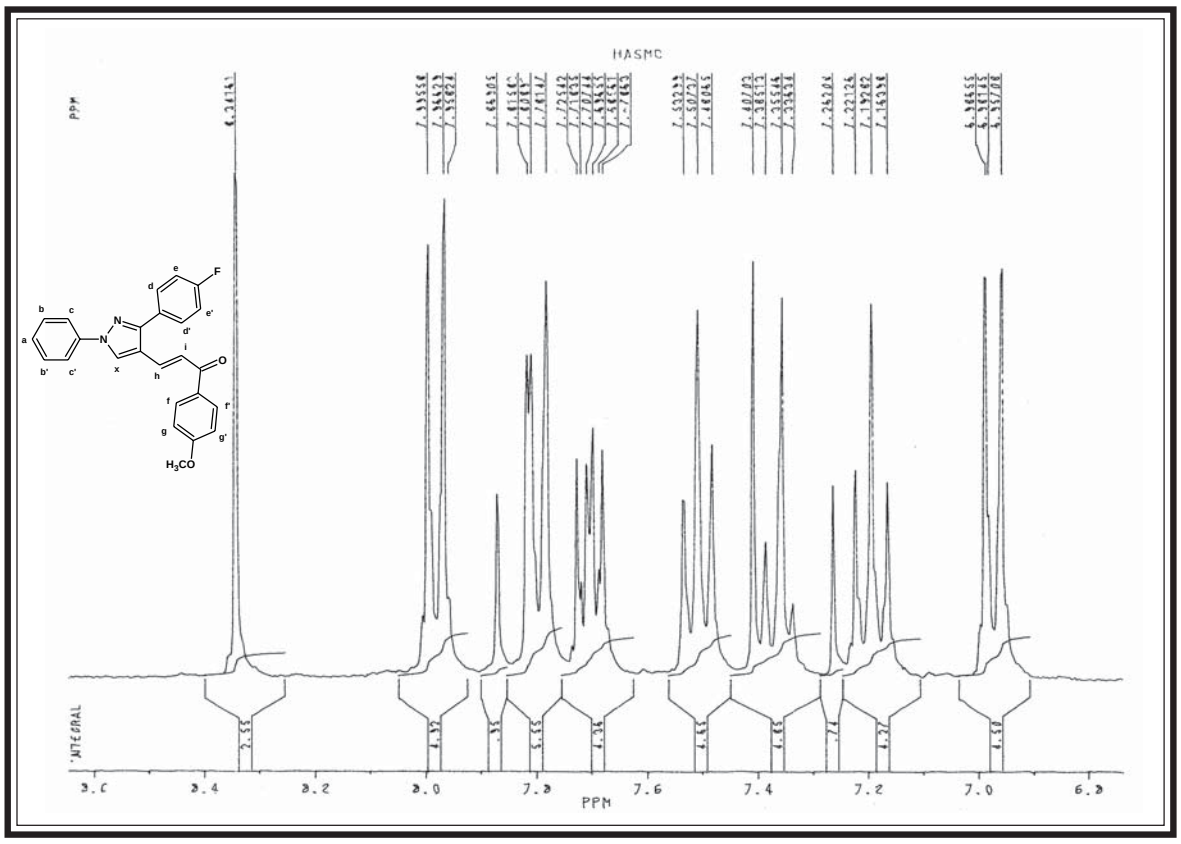
PMR SPECTRAL STUDY OF 1,p-ANISYL-3-[1',N-PHENYL-3'-p-FLOROPHENYL-PYRAZOL-4'-YL]-PROPENE-1-ONE

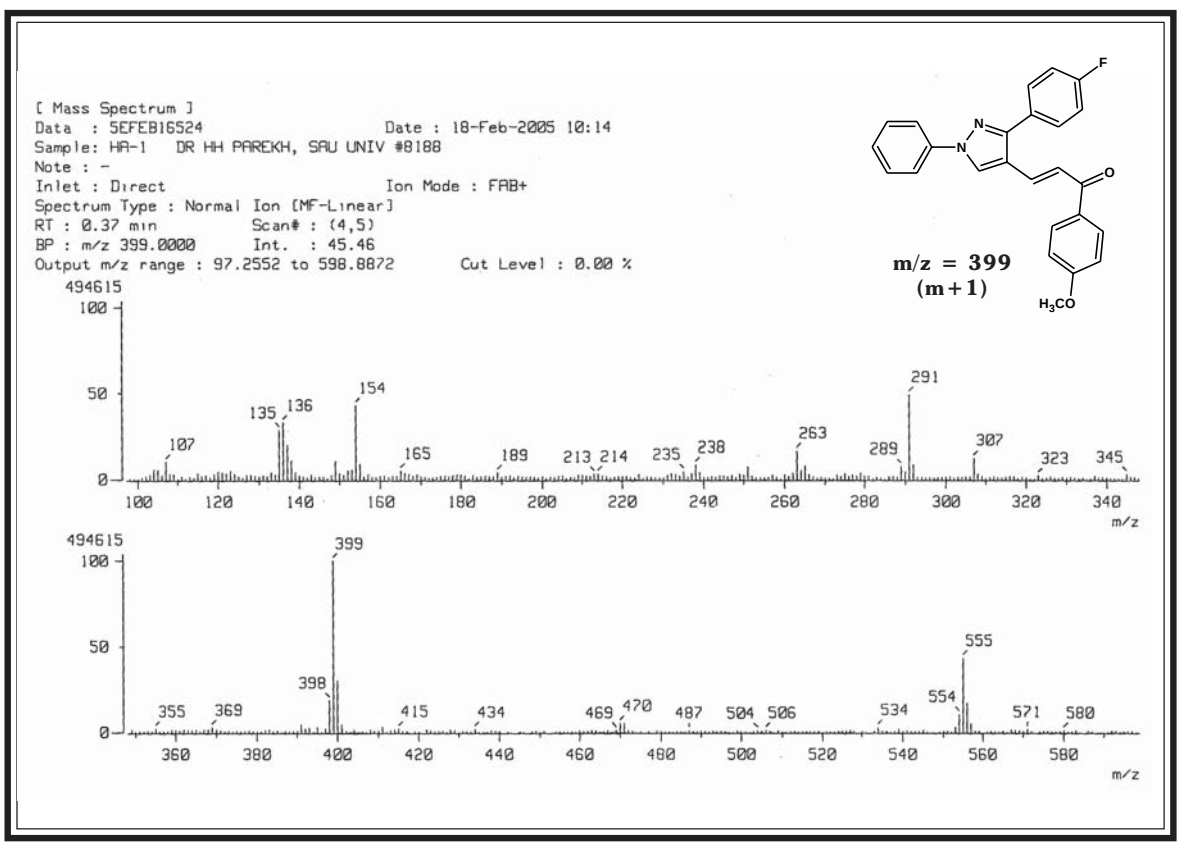


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.89	1H	singlet	Ar-OCH_3	-
2.	6.95-6.98	2H	doublet	Ar-Hgg'	Jgf=8.7
3.	7.16-7.22	2H	triplet	Ar-Hdd'	-
4.	7.33-7.40	2H	quartet	-CH(h&i)	-
5.	7.48-7.53	2H	triplet	Ar-Hee'	-
6.	7.67-7.72	2H	multiplet	Ar-Hbb'	-
7.	7.98-7.81	3H	triplet	Ar-Hcc'+Ha	-
8.	7.96-7.99	2H	doublet	Ar-Hff'	Jfg=8.7
9.	8.34	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





ANTIMICROBIAL ACTIVITY

Method	:	Cup-Plate[96]
Gran positive bacteria	:	***B. cocous and B. subtillus***
Gram negative bacteria	:	***Proteus vulgaris***
		Escherichia coli
Fungi	:	***Aspergillus niger***
Concentration	:	40 µg
Solvent	:	Dimethyl formamide
Standard drug	:	Amoxycillin, Benzoylpenicillin,
		Ciprofloxacin, Erythromycin, Greseofulvin.

The antimicrobial activity was compared with standard drugs viz. Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin, and antifungal activity was compared with viz Greseofulvin. The zone of inhibition measured in mm.

ANTITUBERCULAR ACTIVITY

The antitubercular activity was carried out at Tubrerculosis Antimicrobial Acquisition and Co-ordinating Facility (TAACF) U.S.A.

Method	:	BACTEC 460 Radiometric system.
Bacteria	:	***Mycobacterium tuberculosis*** $H_{37}Rv$
Concentrtion	:	6.25 µg/ml.
Standard drug	:	Rifampin

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-2-PROPENE-1-ONES

[A] Synthesis of N-Aminophenyl-α-methyl-p-flurophenyl azomethine

A mixture of phenylhydrazine (1.08 g, 0.01M) and p-flurophenyl aceto phenone (1.38 g, 0.01M) in absolute ethanol was refluxed in water bath for 2 hrs. in presence of 1 ml glacial acetic acid. The crude product was isolated and crystallised from absolute alcohol. yield. 90%, m.p. 38°C; ($C_{14}H_{13}FN_2$; Found : C, 72.63%, H, 5.70%; N, 12.21%; Required : C, 73.66%; H, 5.74%; N, 12.27%)

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

N-Aminophenyl-α-methyl-p-fluorophenyl azomethine (2.27g, 0.01M) was added in mixture of Vilsmeir-Haack reagent (prepared by dropwise addition of 3 ml $POCl_3$ in ice cooled 25 ml DMF). and refluxed for 5 hrs. The reaction mixture was poured into ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallised from ethanol yield 75%, m.p. 155°C; ($C_{16}H_{11}FN_2O$; Found C, 72.11%; H, 4.12%; N, 10.48%; Required ; C, 72.11%; H, 4.16%; N, 10.52%).

[C] Synthesis of 1-(p-Anisyl)-3-(1'-N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-2-propene-1-one

To a well stirred solution of 1,N-phenyl-3-p-fluorophenyl-4-formyl-pyrazole (2.65gm, 0.01M) and p-methoxy-acetophenone (1.5 g, 0.01M) in ethanol (25 ml), 40% KOH added till the solution become basic. The reaction mixture was stirred for 24 hrs. The contents were poured into ice, acidified, filtered and crystallised from ethanol. Yield,78%, m.p.180°C. ($C_{25}H_{19}FN_2O_2$; Found : C,75.33%; H, 4.77%; N, 6.94%; Requires : C, 75.36%; H, 4.81%; N, 7.03%).

Similarly, other substituted chalcones have prepared. The physical data are recorded in Table No. 1.

[D] Antimicrobial activity of 1-Aryl-3-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-2-propene-1-ones

All the products have been evaluated by antimicrobial activity as described under.

(a) Antimicrobial activity

It was carried out by cup-plate diffusion method which has been described as under.

(I) Antibacterial activity

The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of ***B. cocous, B. subtillus, E. coli, P. vulgaris*** in separate conical flasks at 40-50°C and mixed well by gentle shaking. About 25 ml content of the flast were poured and evenly spread in a pertidish (13 cm in diameter) and allowed to set for 2 hrs. The cup (10 mm in diameter) were formed by the help of borar in agar medium and filled with 0.04 ml (40 µg) solution of sample in DMF.

The plates were incubated at 37°C for 24 hrs. and the control was also maintained with 0.04 ml of DMF in a similar manner and the zones of inhibition of the bacterial growth were measured in millimeter and are recorded in graphical chart no.1.

(II) Antifungal activity

A. Niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar slants. Sterilised Sabouraud's agar medium was inoculated with 72 hrs. old 0.5 ml of suspension of fungal spores in a separate flask. About 25 ml of the inculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm

in diameter) were punched. The plates were incubated at 30°C for 48 hrs. After the completion of incubation period, the zones of inhibition of growth in the form of diameter in mm was measured Along the test solution, in each petridish one cup was filled up with solvent which acts as control. The zones of inhibition are recorded in graphical chart no.1.

(b) Antitubercular Activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition and Co-ordinating Facility (TAACF), U.S.A. Primary screening of the compounds for antitubercular activity have been conducted at 6.25 μg/ml towards ***Mycobacterium Tuberculosis*** $H_{37}Rv$ in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demonstrating atleast > 90%. inhibition in the primary screen have been retested at lower concentration towards ***Mycobacterium Tuberculosis*** $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in the BACTEC 460.

The antitubercular activity data have been compared with standard drug Rifampin at 0.25 μg/ml concentration and it showed 98% inhibition. The work is under progress.

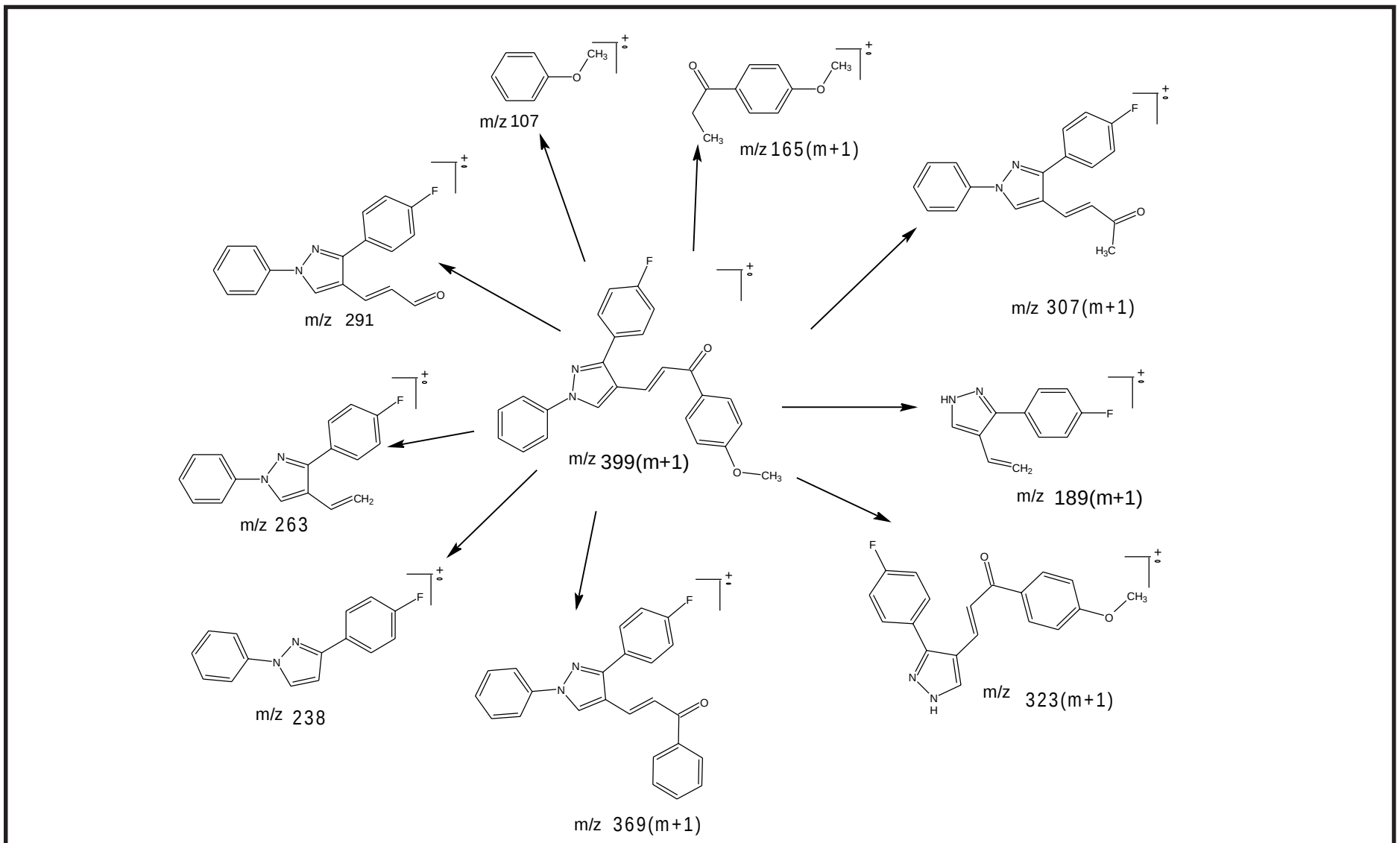
TABLE NO. 1 : PHYSICAL CONSTANTS OF 1-ARYL-3-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-2-PROPENE-1-ONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
1a	C_6H_5-	$C_{24}H_{17}FN_2O$	368	140	0.41	81	7.60	7.53
1b	4-OCH_3-C_6H_4-	$C_{25}H_{19}FN_2O_2$	398	180	0.59	78	7.03	6.94
1c	4-CH_3-C_6H_4-	$C_{25}H_{19}FN_2O$	382	193	0.47	70	7.33	7.26
1d	4-Cl-C_6H_4-	$C_{24}H_{16}ClFN_2O$	402	210	0.52	73	6.95	6.87
1e	4-F-C_6H_4-	$C_{24}H_{16}F_2N_2O$	386	189	0.61	86	7.25	7.16
1f	4-OH-C_6H_4-	$C_{24}H_{11}FN_2O_2$	384	240	0.73	84	7.29	7.22
1g	2-OH-C_6H_4-	$C_{24}H_{17}FN_2O_2$	384	178	0.44	74	7.29	7.20
1h	4-NO_2-C_6H_4-	$C_{24}H_{16}FN_3O_3$	413	191	0.56	82	10.16	10.09
1i	3-NO_2-C_6H_4-	$C_{24}H_{16}FN_3O_3$	413	188	0.64	72	10.16	10.10
1j	4-Br-C_6H_4-	$C_{24}H_{16}BrFN_2O$	447	218	0.57	77	6.26	6.21
1k	4-NH_4-C_6H_4	$C_{24}H_{18}FN_2O$	383	206	0.71	79	10.96	10.88
1l	C_4H_3S-	$C_{22}H_{15}FSN_2O$	374	174	0.58	76	7.48	7.42

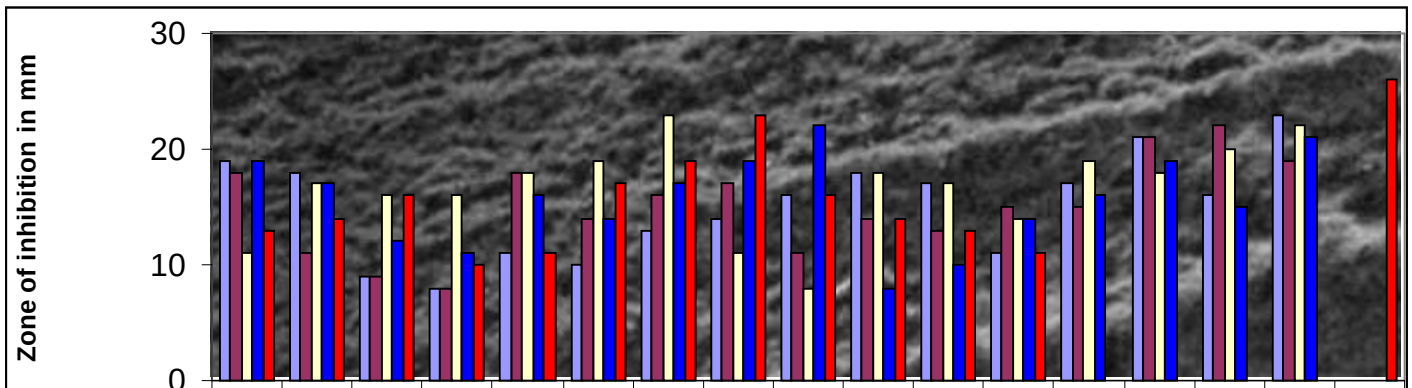
*TLC Solvent System : Acetone : Benzene

2 : 8 (1a-1e, 1g-1j, 1l)

3 : 7 (1f, 1k)


m/z 107
m/z 165(m+1)
m/z 291
m/z 307(m+1)
m/z 399(m+1)
m/z 263
m/z 189(m+1)
m/z 238
m/z 323(m+1)
m/z 369(m+1)

GRAPHYCAL CHART NO.1: ANTIMICROBIAL ACTIVITY OF 1-ARYL-3-[1'N-PHENYL-3'-p-FLOROPHENYL PYRAZOL-4'-YL]-2-PROPENE-1-ONES.



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Amoxycillin	Benzoyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	19	18	9	8	11	10	13	14	16	18	17	11	17	21	16	23	0
B. subtillus	18	11	9	8	18	14	16	17	11	14	13	15	15	21	22	19	0
E. coli	11	17	16	16	18	19	23	11	8	18	17	14	19	18	20	22	0
P. vulgaris	19	17	12	11	16	14	17	19	22	8	10	14	16	19	15	21	0
A. niger	13	14	16	10	11	17	19	23	16	14	13	11	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of chalcones (type-I) revealed that all the compounds were able to inhibit the growth of Gram positive & Gram negative bacterial strains.

Maximum activity was observed in compounds bearing R = phenyl and 4-fluorophenyl which was compared to standard drugs against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus***. Significant activity was displayed by compounds bearing R=4-methylphenyl, 4-nitrophenyl, 4-bromophenyl, thiopene except 4-chlorophenyl.

In case of Gram negative bacterial species, maximum activity was observed in compound bearing R=2-hydroxyphenyl and 3-nitrophenyl against Gram negative bacterial species ***P. vulgaris*** & ***E. coli*** singificant activity was displayed by compound bearing R=phenyl, 4-methoxyphenyl, 4-nitrophenyl, 4-bromophenyl and 4-hydroxyphenyl.

ANTIFUNGAL ACTIVITY

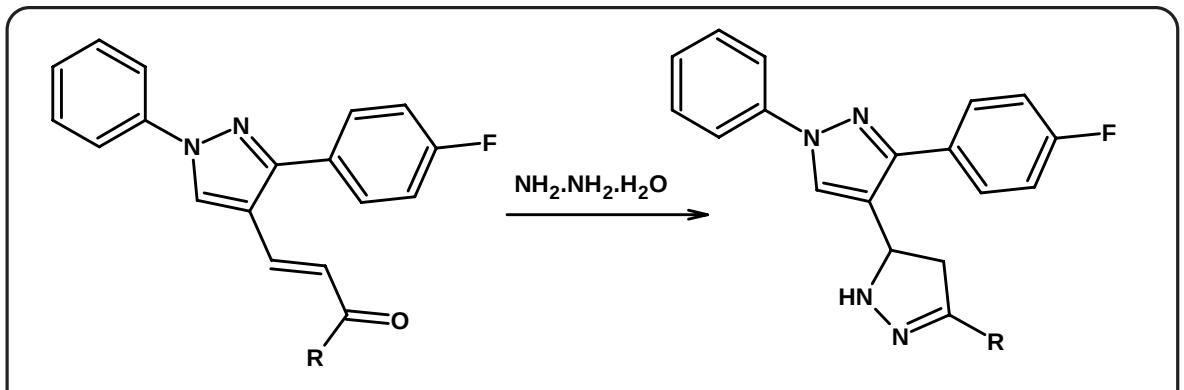
Most of the compound were mild to moderately active against fungal strain ***A. niger***. Maximum activity was observed in compound bearing R=4-nitrophenyl which was compared to standard drug.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1'-N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-PYRAZOLINES

Looking at versatile therapeutic importance and with an aim to getting better drug, it was considered worthwhile to synthesise some new pyrazolines. The preparation of 3-aryl-5-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-pyrazolines (II) has been undertaken by cyclocondensation of chalcones of type (I) with hydrazine hydrate.

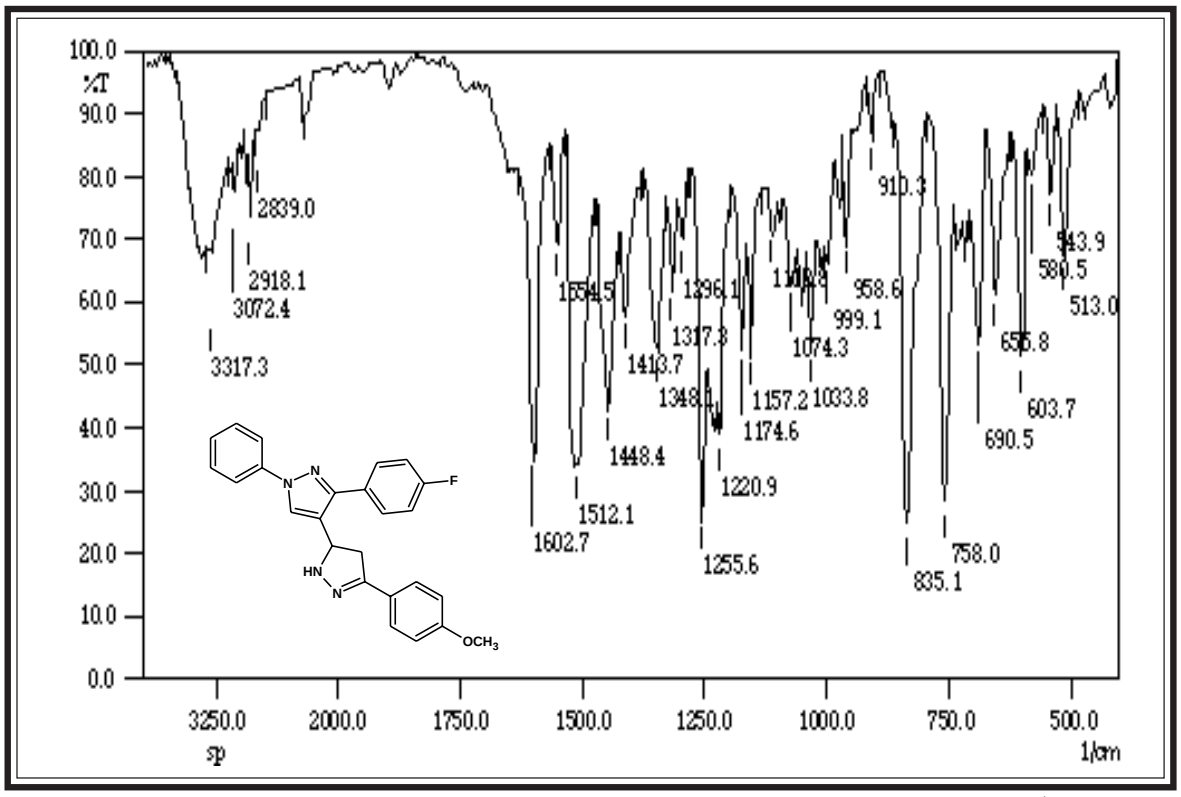


Type - (II) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

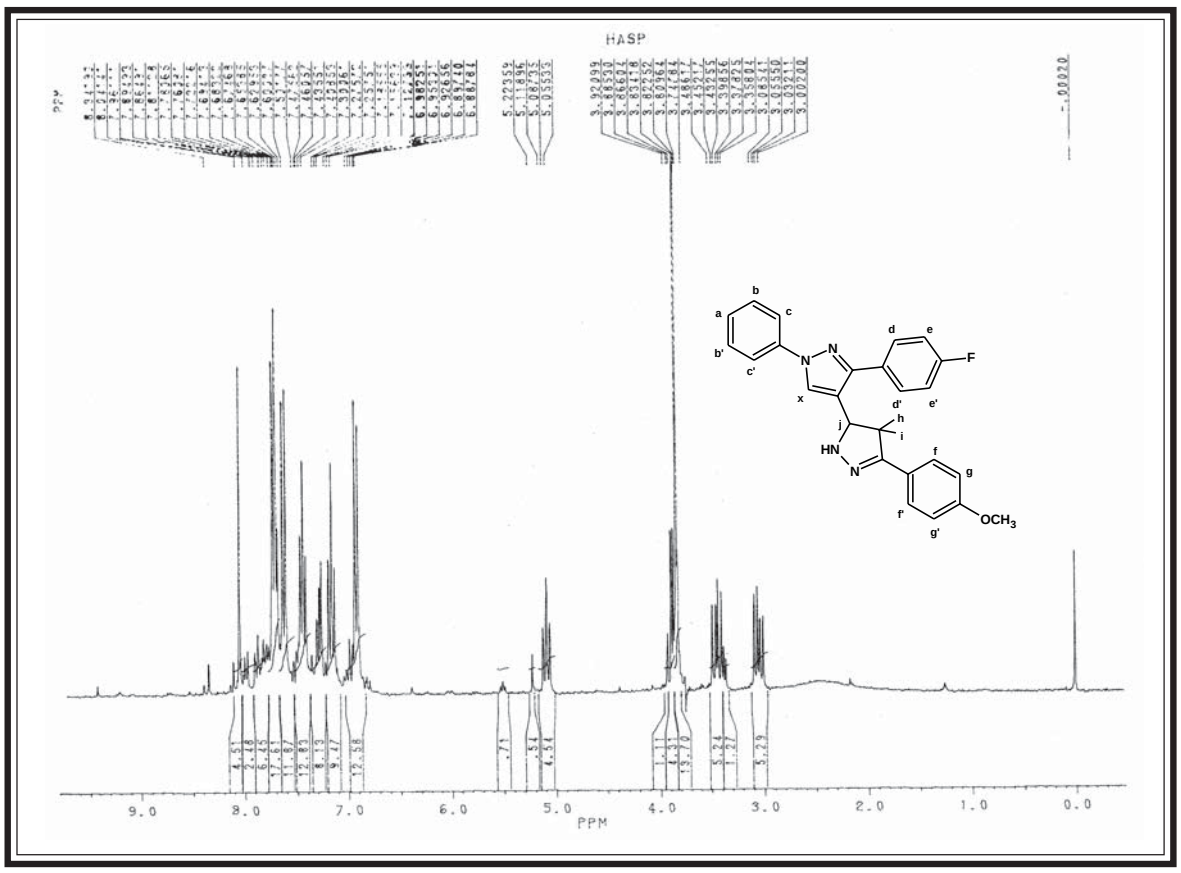
IR SPECTRAL STUDY OF 3-(p-ANISYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2918	2975–2920	426
$-CH_3$	C – H str. (sym.)	2839	2880–2820	"
	C – H i.p. (def.)	1448	1470–1435	"
	C – H o.o.p. (def.)	1348	1385–1350	"
Aromatic	C – H str.	3072	3080–3030	427
	C – H i.p. (def.)	1157	1160–1090	"
		1033	1070-1000	"
	C – H o.o.p (def.)	835	835–810	"
Pyrazole	C = N str.	1602	1650–1600	428
moiety	C = C str.	1512	1585–1480	"
	C – N str.	1317	1350–1200	"
	C – F str.	756	760–710	"
Ether	C – O – C (asym.)	1255	1275–1200	"
	C – O – C (sym.)	1074	1075–1020	"
Pyrazoline	C = N str.	1550	1627–1550	429
	N – H str.	3317	3450–3250	"

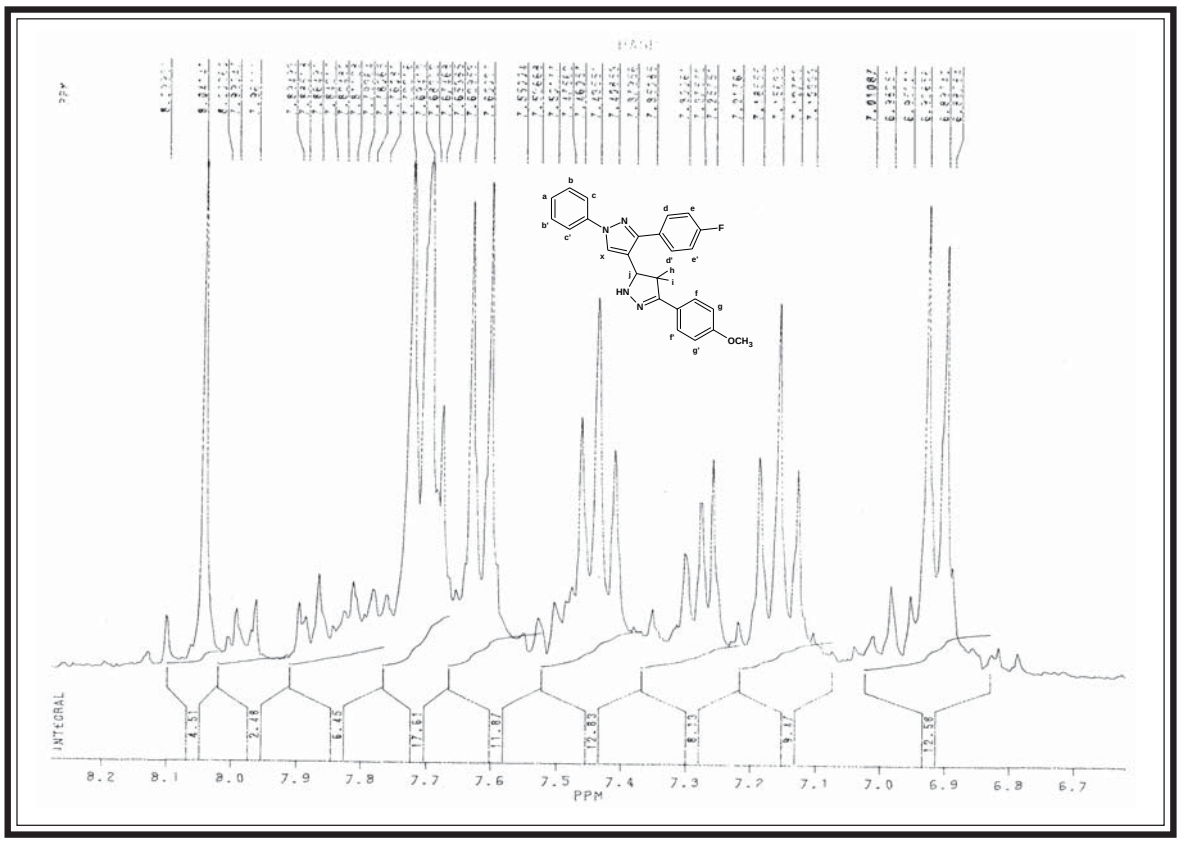
PMR SPECTRAL STUDY OF 3-(p-ANISYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE

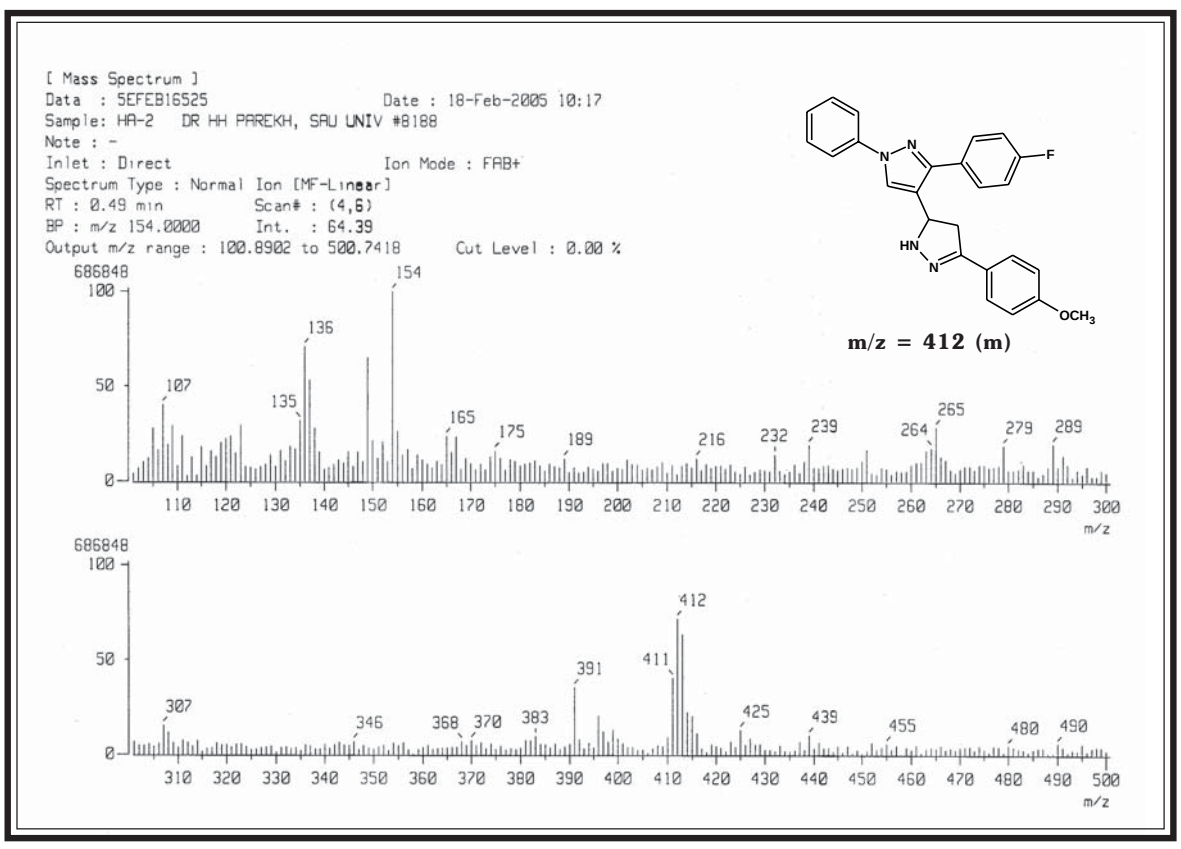


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.00-3.08	1H	d. doublet	CHh	Jhi = Jhj =
2.	3.35-3.48	1H	d. doublet	CHi	Jih = Jij =
3.	3.83	3H	singlet	Ar-OCH_3	-
4.	5.05-5.22	1H	d. doublet	CHj	Jih = Jji =
5.	6.88-6.92	2H	doublet	Ar-Hgg'	Jgf=8.7
6.	7.10-7.21	2H	triplet	Ar-Hdd'	-
7.	7.25-7.30	2H	triplet	Ar-Hbb'	-
8.	7.35-7.46	2H	triplet	Ar-Hcc'	-
9.	7.60-7.62	2H	doublet	Ar-Hee'	Jed=8.7
10.	7.67-7.72	3H	triplet	Ar-Hff'+Ha	Jfg=8.4
11.	8.04	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





m/z = 412 (m)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-PYRAZOLINES

[A] Synthesis of N-Aminophenyl-α-methyl-2-p-anisyl-azomethine

See Part-I, Section-I (A).

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See Part-I, Section-I (B).

[C] Synthesis of 1-(p-Anisyl)-3-(1'-N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-I (C).

[D] Synthesis of 3-(p-Anisyl)-5-(1'-N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-pyrazoline

A mixture of 1-(p-anisyl)-3-(1',N-phenyl-3'-p-flurophenyl-pyrazol-4'-yl)-2-propene-1-one (3.98 g, 0.01M) in 25 ml of absolute alcohol, add hydrazine hydrate (0.5g, 0.01M) was refluxed in water bath at temp. 80-90°C for 8 hrs. The reaction mixture was poured into ice. The product was isolated and crystallised from ethanol, yield 59%, m.p. 140°C; ($C_{25}H_{21}FN_4O$; Found : C, 7272%; H, 5.09%; N, 13.52% ; Requires : C, 72.80%; H, 5.13%; N, 13.58%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 2.

[E] Antimicrobial activity of 3-Aryl-5-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl-)pyrazolines

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No.2.

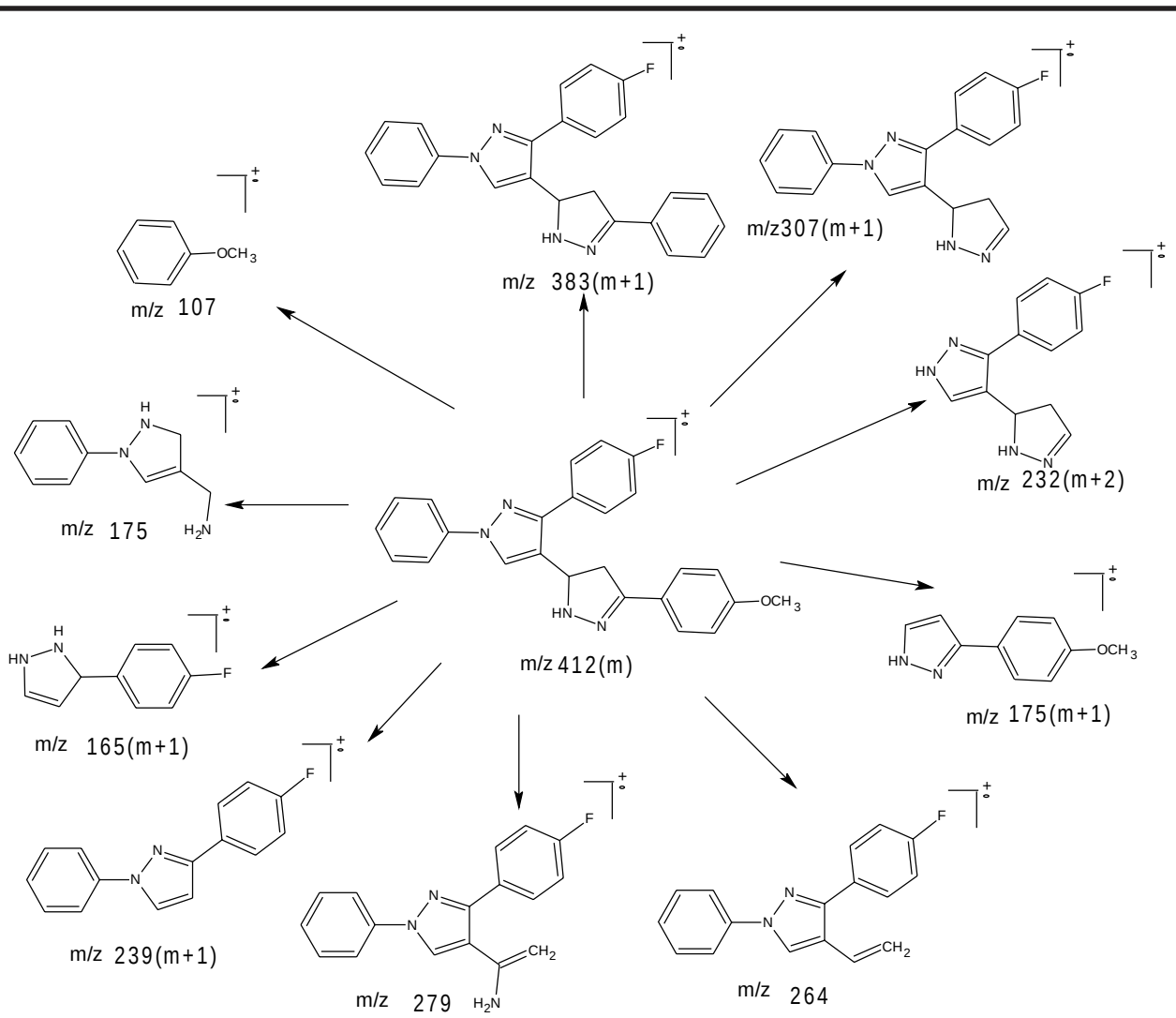
TABLE NO. 2 : PHYSICAL CONSTANTS OF 3-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
2a	C_6H_5-	$C_{24}H_{19}FN_4$	382	246	0.51	61	14.65	14.61
2b	4-OCH_3-C_6H_4-	$C_{25}H_{21}FN_4O$	412	140	0.38	59	13.58	13.52
2c	4-CH_3-C_6H_4-	$C_{25}H_{21}FN_4$	396	164	0.43	65	14.13	14.08
2d	4-Cl-C_6H_4-	$C_{24}H_{18}ClFN_4$	416	142	0.44	66	13.44	13.39
2e	4-F-C_6H_4-	$C_{24}H_{18}F_2N_4$	400	146	0.60	63	13.99	13.91
2f	4-OH-C_6H_4-	$C_{24}H_{19}FN_4O$	398	150	0.54	70	14.06	14.00
2g	2-OH-C_6H_4-	$C_{24}H_{19}FN_4O$	398	255	0.67	62	14.06	13.98
2h	4-NO_2-C_6H_4-	$C_{24}H_{18}FN_5O_2$	427	275	0.75	65	16.38	16.31
2i	3-NO_2-C_6H_4-	$C_{24}H_{18}FN_5O_2$	427	128	0.36	71	16.38	16.32
2j	4-Br-C_6H_4-	$C_{24}H_{18}BrFN_4$	461	160	0.49	64	12.14	12.07
2k	4-NH_2-C_6H_4	$C_{24}H_{20}FN_5$	397	157	0.39	68	17.62	17.56
2l	C_4H_3S-	$C_{22}H_{17}FSN_4$	388	184	0.52	67	14.42	14.37

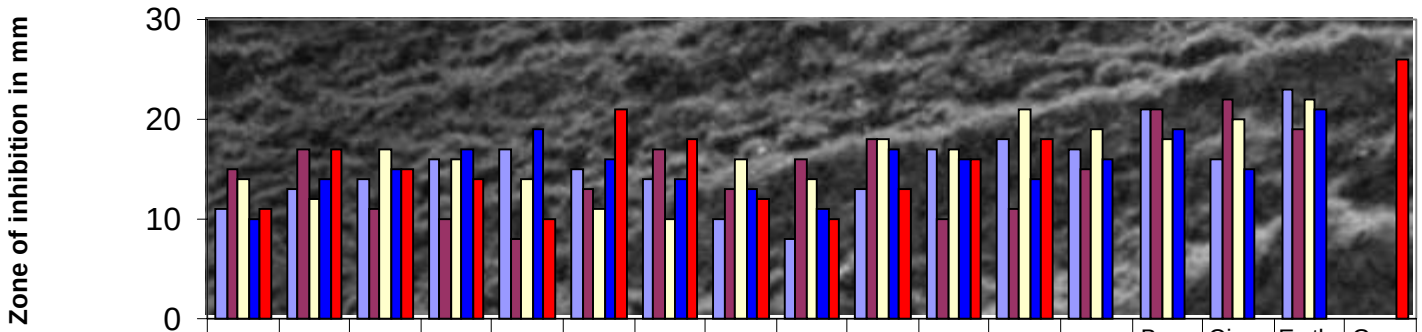
*TLC Solvent System : Ethyl acetate : Hexane

2 : 8 (3a-3f, 3i-3l)

2.5 : 7.5 (3g, 3h)


m/z 383(m+1)
m/z307(m+1)
m/z 107
m/z 232(m+2)
m/z 175
m/z 412(m)
m/z 175(m+1)
m/z 165(m+1)
m/z 239(m+1)
m/z 279
m/z 264

GRAPHYCAL CHART NO.2: **ANTIMICROBIAL ACTIVITY OF 3-ARYL-5-[1'N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-PYRAZOLINES.**



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Amoxycillin	Benzoyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	11	13	14	16	17	15	14	10	8	13	17	18	17	21	16	23	0
B. subtillus	15	17	11	10	8	13	17	13	16	18	10	11	15	21	22	19	0
E. coli	14	12	17	16	14	11	10	16	14	18	17	21	19	18	20	22	0
P. vulgaris	10	14	15	17	19	16	14	13	11	17	16	14	16	19	15	21	0
A. niger	11	17	15	14	10	21	18	12	10	13	16	18	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been concluded from the experimental data that pyrazoline derivatives (type-II) were able to inhibit the growth of Gram positive and Gram negative bacterial strains.

Maximum activity was observed in compounds bearing R=4-bromophenyl & phenyl against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus***. Significant activity was observed in compounds bearing R=4-methoxyphenyl, 4-aminophenyl against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus***.

While in case of Gram negative bacterial stains, maximum activity was observed in compound bearing R=4-fluorophenyl & 3-nitrophenyl & significant activity was observed in compound bearing R=4-bromophenyl & 4-aminophenyl against ***P. vulgaris*** & ***E. coli***. Other compounds were mild to moderately active.

ANTIFUNGAL ACTIVITY

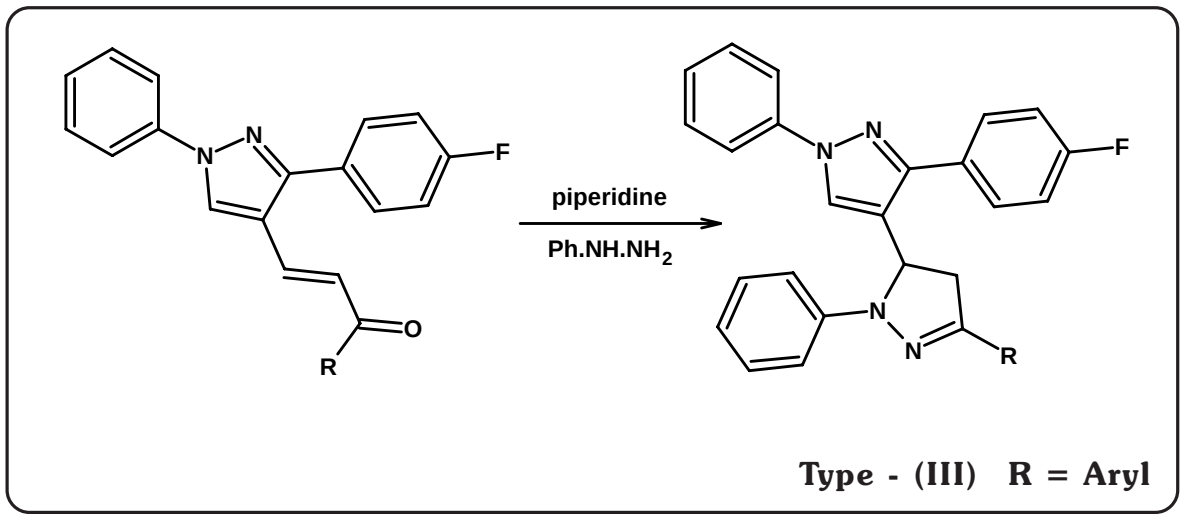
All the compound were mild to moderately active against fungal strain ***A. niger*** with comparable to standard drugs, while maximum activity was observed in compound bearing R=4-hydroxyphenyl.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

SECTION - III

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-PYRAZOLINES

Looking to the interesting therapeutic activities of pyrazolines, it was considered worthwhile to synthesise compounds bearing 1-N-phenyl-3-p-fluorophenyl-4-formyl-pyrazole moiety linked to the pyrazoline of type- (III) which have been prepared by the action of 1-aryl-3-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-2-propen-1-ones with phenyl hydrazine in presence of piperidine.

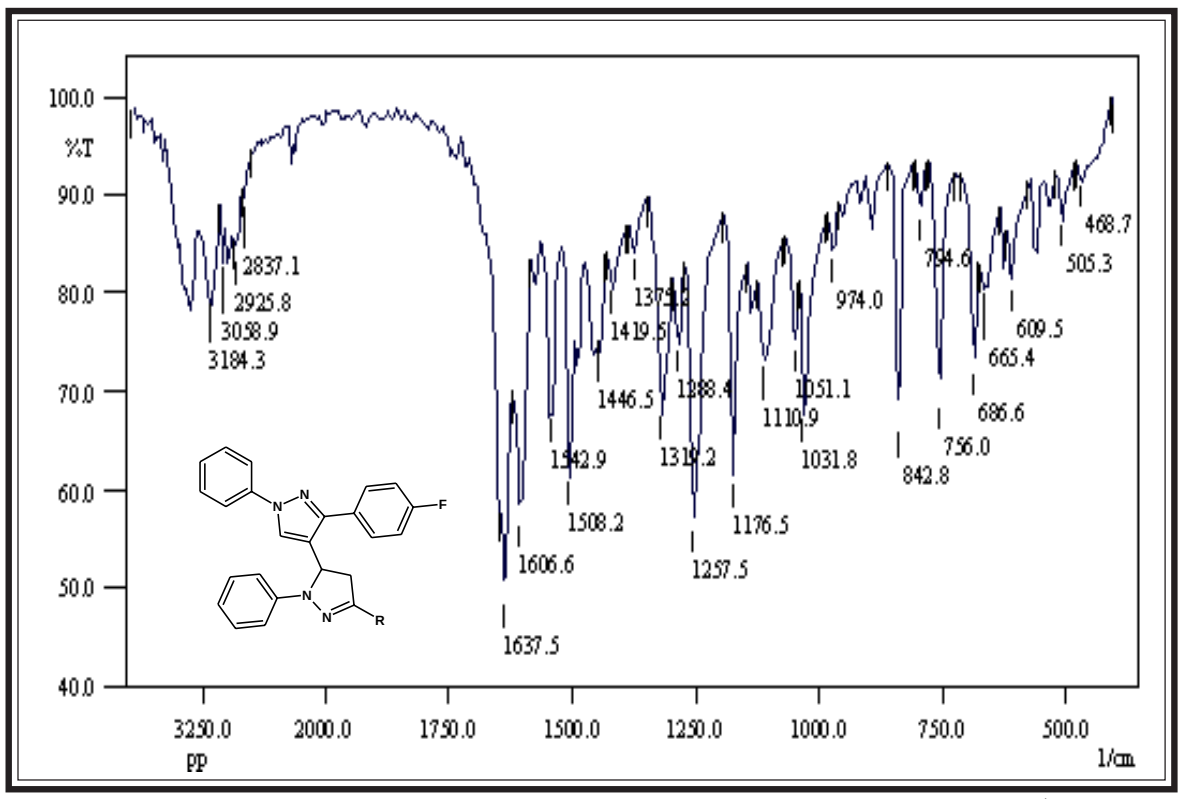


Type - (III) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

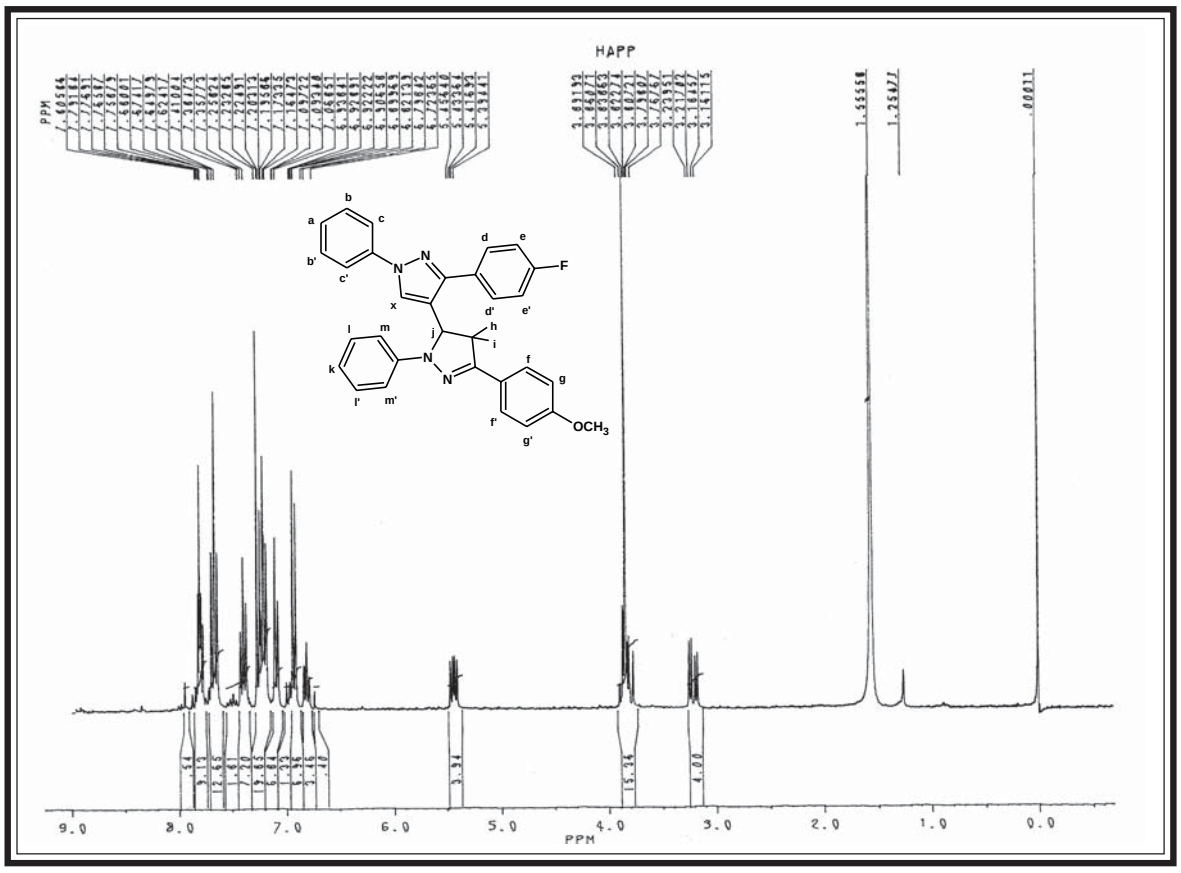
IR SPECTRAL STUDY OF 1,N-PHENYL-3-(p-ANISYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2925	2975–1920	426
$-CH_3$	C – H str. (sym.)	2837	2880–2850	"
	C – H i.p. (def.)	1446	1470–1435	"
	C – H o.o.p. (def.)	1375	1385–1350	"
Aromatic	C – H str.	3068	3080–3030	427
	C – H i.p. (def.)	1110	1125–1090	"
		1031	1070–1000	"
	C – H o.o.p (def.)	842	845–810	"
Pyrazole	C = N str.	1637	1650–1600	428
moiety	C = C str.	1506	1585–1480	"
	C – N str.	1286	1350–1200	"
	C – F str.	756	760–720	"
Ether	C – O – C str. (asym.)	1257	1275–1200	"
	C – O – C str. (sym.)	1061	1075–1020	"
Pyrazoline	C = N str.	1606	1627–1580	429
	C – H def.	686	698–680	"

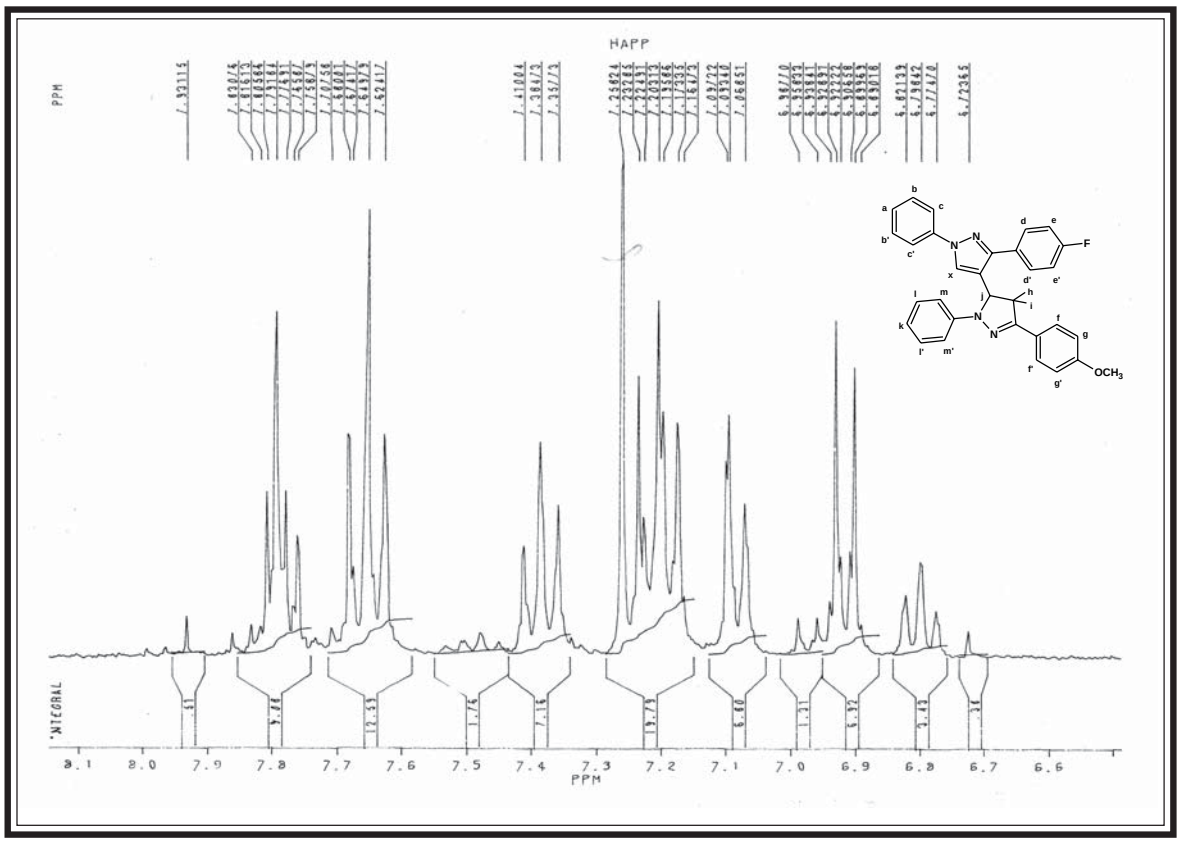
PMR SPECTRAL STUDY OF 1,N-PHENYL-3-(P-ANISYL)-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-PYRAZOLINE

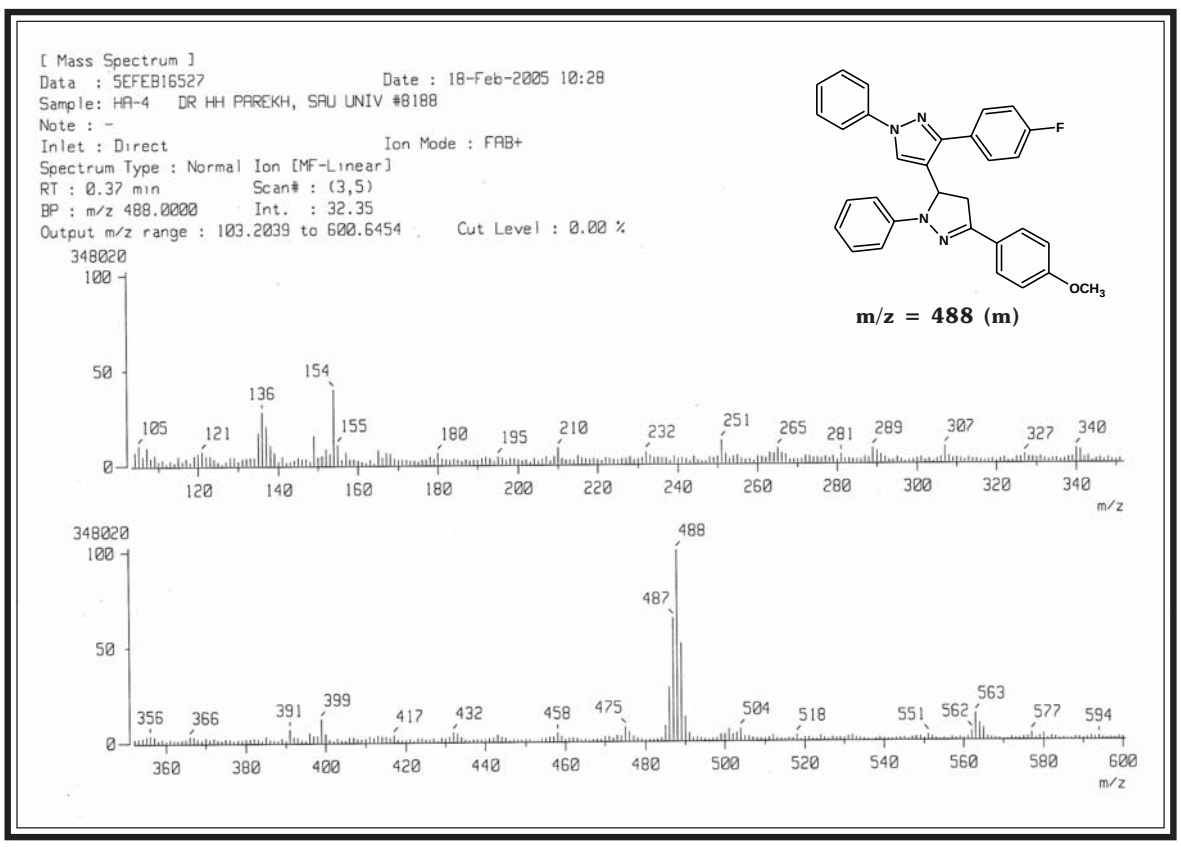


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.16-3.23	1H	d. doublet	CHh	-
2.	3.76-3.82	1H	d. doublet	CHi	-
3.	3.83	3H	singlet	Ar-OCH_3	-
4.	5.39-5.45	1H	d. doublet	CHj	-
5.	6.77-6.82	1H	triplet	Ar-Ha	-
6.	6.89-6.92	2H	doublet	Ar-Hgg	Jgf=6.96
7.	7.06-7.09	2H	doublet	Ar-Hdd'	Jde=8.7
8.	7.16-7.23	5H	multiplet	Ar-Hbb'+Hii+Hk	-
9.	7.35-7.41	2H	triplet	Ar-Hee'	-
10.	7.62-7.70	4H	triplet	Ar-Hmm'+Hcc'	-
11.	7.75-7.83	3H	quartet	Ar-Hff'+CHx	-

EXPANDED AROMATIC REGION





m/z = 488 (m)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-PYRAZOLINES

[A] Synthesis of N-Aminophenyl-α-methyl-α-p-fluorophenyl-azomethine

See Part-I, Section-I (A).

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See Part-I, Section-I (B).

[C] Synthesis of 1-(p-Anisyl)-3-(1'-N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-I (C).

[D] Synthesis of 1,N-Phenyl-3-(p-anisyl)-5-(1',-N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-pyrazoline

To a mixture of 1-(p-Anisyl)-3-(1',N-phenyl)-3'-p-fluorophenyl-pyrazol-4'-yl)-2-porpene-1-one (3.98g, 0.01M) in 25 ml of absolute alcohol add phenyl hydrazine (1.08g, 0.01M) was added in presence of basic catalyst like piperidine and refluxed for 12 hrs. at temp 70°C The reaction product was poured into ice. The product was isolated and crystallised from ethanol Yield 68%, m.p. 84°C ($C_{31}H_{25}FN_4O$; Found : C, 76.16%; H, 5.11%; N, 11.42%; Requires : C, 76.21%; H, 5.16%; N, 11.47%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 2.

[E] Antimicrobial activity of 1,N-phenyl-3-aryl-5-(1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-pyrazolines

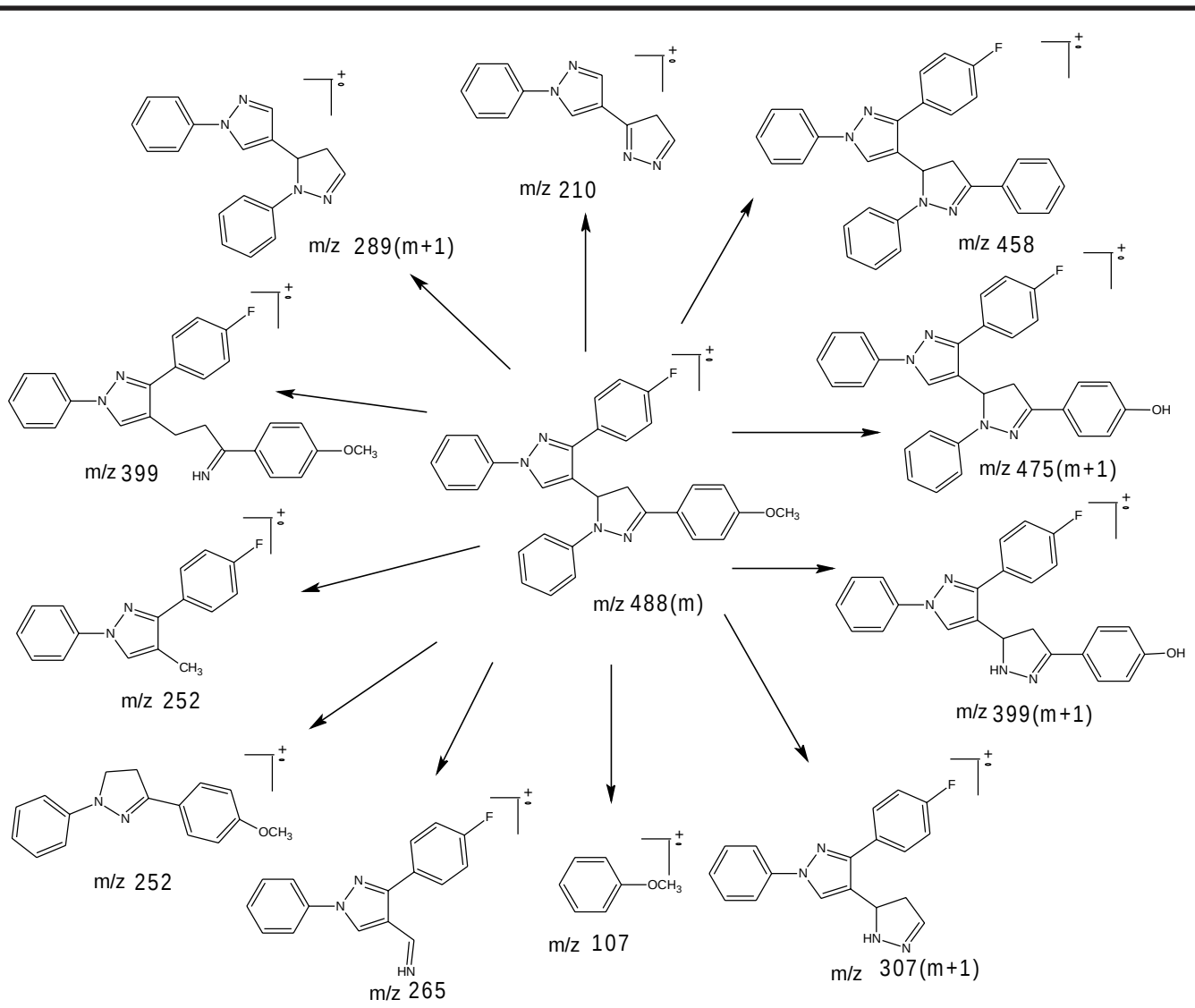
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No.3.

TABLE NO. 3 : PHYSICAL CONSTANTS OF 1,N-PHENYL-3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-PYRAZOLINES

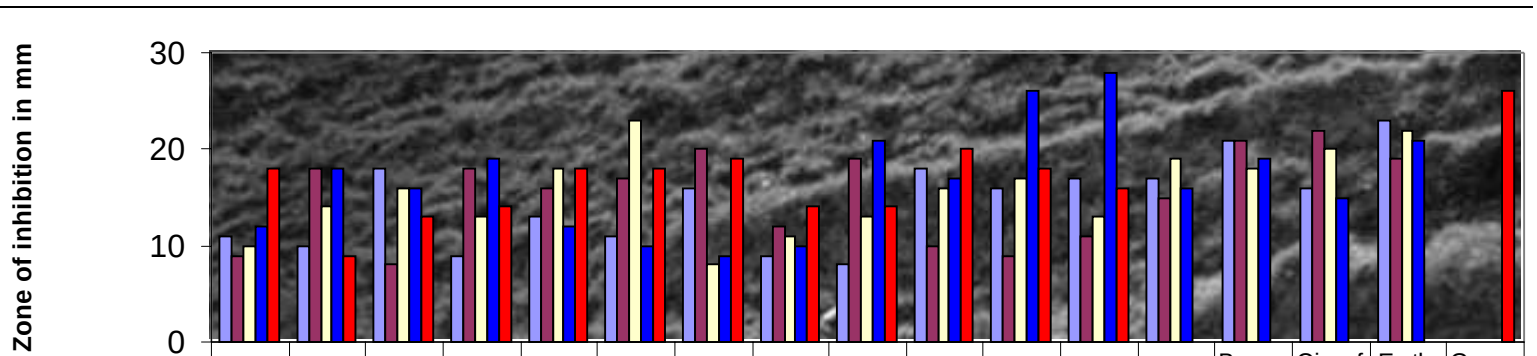
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
3a	C_6H_5-	$C_{30}H_{23}FN_4$	458	94	0.62	63	12.12	12.17
3b	4-OCH_3-C_6H_4-	$C_{31}H_{25}FN_4O$	488	84	0.53	68	11.47	11.42
3c	4-CH_3-C_6H_4-	$C_{31}H_{25}FN_4$	472	88	0.54	66	11.86	11.82
3d	4-Cl-C_6H_4-	$C_{30}H_{22}ClFN_4$	492	98	0.48	70	11.37	11.33
3e	4-F-C_6H_4-	$C_{30}H_{22}F_2N_4$	476	76	0.42	63	11.76	11.71
3f	4-OH-C_6H_4-	$C_{30}H_{23}FN_4O$	474	78	0.49	65	11.81	11.75
3g	2-OH-C_6H_4-	$C_{30}H_{23}FN_4O$	474	82	0.74	64	11.81	11.73
3h	4-NO_2-C_6H_4-	$C_{30}H_{22}FN_5O_2$	503	100	0.65	67	13.91	11.86
3i	3-NO_2-C_6H_4-	$C_{30}H_{22}FN_5O_2$	503	110	0.45	70	13.91	11.84
3j	4-Br-C_6H_4-	$C_{30}H_{22}BrFN_4$	537	80	0.69	61	10.43	10.36
3k	4-NH_2-C_6H_4	$C_{30}H_{24}FN_5$	473	94	0.44	71	14.79	14.72
3l	C_4H_3S-	$C_{28}H_{21}FN_4S$	464	91	0.54	60	12.06	12.01

*TLC Solvent System : Acetone : Benzene

2 : 8


m/z 488(m)
m/z 289(m+1)
m/z 210
m/z 458
m/z 399
m/z 475(m+1)
m/z 252
m/z 399(m+1)
m/z 252
m/z 265
m/z 107
m/z 307(m+1)

GRAPHYCAL CHART NO.3: **ANTIMICROBIAL ACTIVITY OF1,N-PHENYL 3-ARYL-5-[1'N-PHE NYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-PYRAZOLINES.**



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	Amoxycillin	Benzoyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	11	10	18	9	13	11	16	9	8	18	16	17	17	21	16	23	0
B. subtillus	9	18	8	18	16	17	20	12	19	10	9	11	15	21	22	19	0
E. coli	10	14	16	13	18	23	8	11	13	16	17	13	19	18	20	22	0
P. vulgaris	12	18	16	19	12	10	9	10	21	17	26	28	16	19	15	21	0
A. niger	18	9	13	14	18	18	19	14	14	20	18	16	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

It has been observed from the experimental data that pyrazolines (type-III) show maximum activity against Gram positive bacterial strains and moderately active against Gram negative bacterial strain.

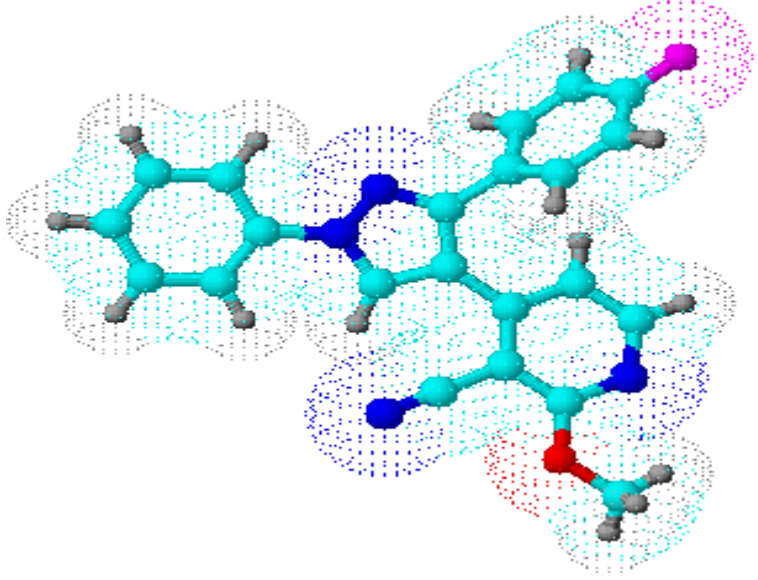
It has been observed that compounds bearing R=4-methylphenyl, 3-nitrophenyl & 2-hydroxyphenyl shows promising activity and compounds bearing R=4-methoxyphenyl, 4-chlorophenyl, 4-hydroxyphenyl, 4-aminophenyl & thiophene shows significant activity against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus***.

While in case of Gram negative bacterial strains, compounds were moderately active. Maximum activity was observed in compounds bearing R=4-nitrophenyl, 3-nitrophenyl & 4-fluorophenyl against Gram negative bacterial strains ***E. coli*** and ***P. vulgaris***.

ANTIFUNGAL ACTIVITY

All the compound were mild to moderately active against fungal strain ***A. niger***. Maximum activiy was observed in compound bearing R=4-bromophenyl.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.



PART-II
STUDIES ON CYANOPYRIDINES

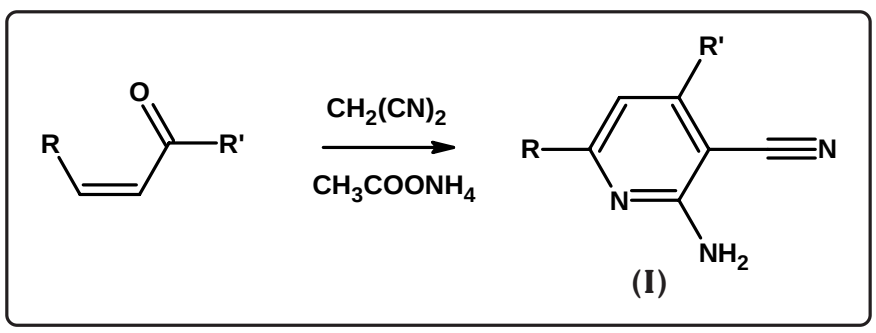
INTRODUCTION

Pyridine and its derivatives are very important in pharmaceutical, agriculture and industrial chemistry. Some pyridine system is active in the metabolism in the body certain nitrogenous plant products also have pyridine class compounds. They can be parent component of many drugs. Pyridine is also used as a denaturant for antifreeze mixtures, as a dyeing assistant in textiles and fungicides. Cyanopyridines, nicotinonitriles, nicotanamide and nicotinic acid are intermediates for the preparation of pharmaceuticals and agrochemicals.

SYNTHETIC ASPECTS

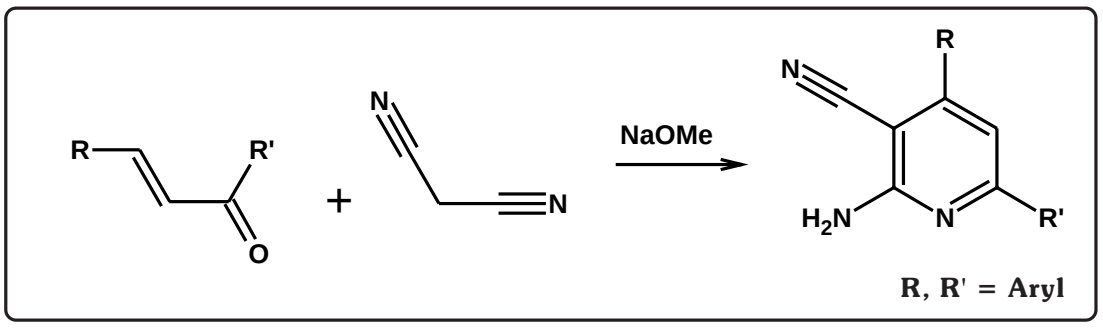
Preparation of 3-cyanopyridines is available in the literature[97-101] with different methods.

1. Samour and co-workers[102] have prepared substituted cyanopyridines(I) by the condensation of chalcones with malononitriles in presence of ammonium acetate.



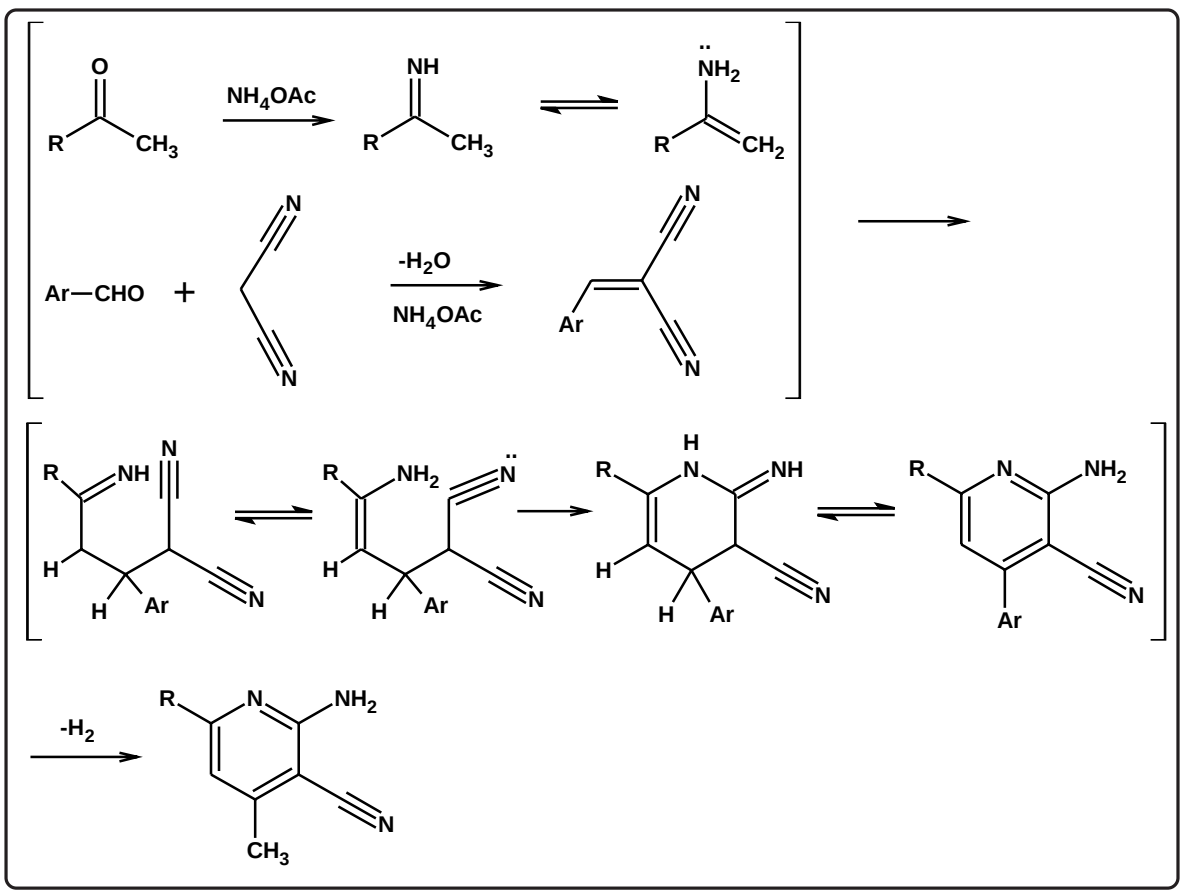
(I)

2. Feng Shi and co-workers[103] have prepared 2-amino-3-cyanopyridine derivative by the reaction of aromatic aldehyde, ketone, malono nitriles and ammonium acetate under microwave irradiation without solvent.
3. Dao-Lin & Kimiaki[104] have prepared 2-methoxy-3-cyano pyridine derivatives by the condensation of chalcones with malanonitrile in sodium methoxide.



MECHANISM

The reaction proceeds through conjugated addition of active methylene compounds to the α,β-unsaturated system as shown below[105].



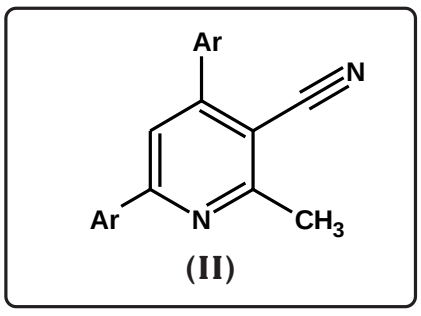
THERAPEUTIC IMPORTANCE

The extensive use of cyanopyridine derivatives have been established in medicine due to its variety of therapeutic activity shown as under.

1. Analgesic[106]
2. Insecticidal[107]

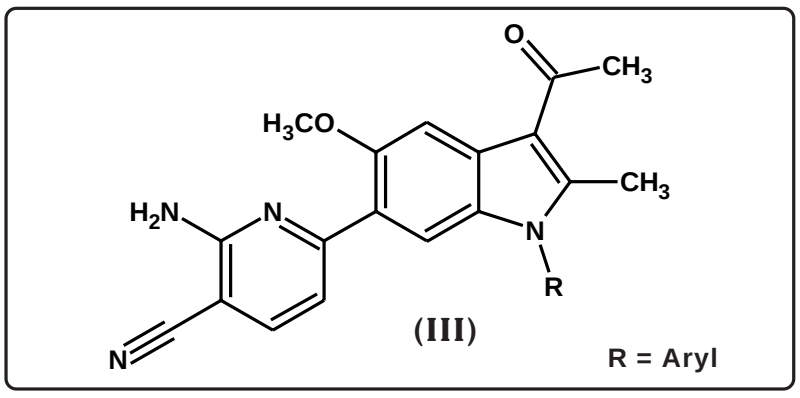
3. Antisoriasis[108]
4. Antihypertensive[109]
5. Antifungal[110]
6. Antiepileptic[111]
7. Antibacterial[112]
8. Anticonvulsant[113]

F. Manna et. al.[114] have prepared 3-cyano-pyridine derivatives as antiinflammatory, analgesic and antipyretic agents. Aivars Krauze et. al.[115] have synthesised 3-cyanopyridine derivatives & shown their neurotropic activity. Fatma Goda & co-workers[116] have synthesised 2-alkoxy pyridines (II) and studied their antimicrobial activity.



(II)

H. Yoshida et. al.[117] have studied the antihistamic & antiallergic activity of 3-cyanopyridine derivatives. Gadaginamath and co-workers[118] have synthesised various cyanopyridyl derivatives (III) and documented their variety of biological activities.

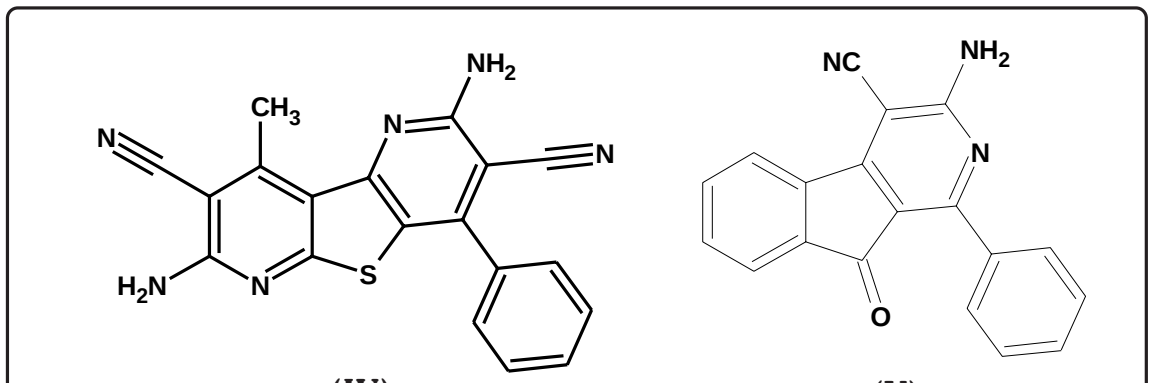


(III)

R = Aryl

Hammana Abou and co-workers[119] have studied the anticancer and anti-HIV activity of 3-cyanopyridines. Abdallah Navine et. al.[120] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity.

Abu and co-workers[121] have described novel fused cyanopyridines (IV) for the treatment and preparation of systemic fungal infection.

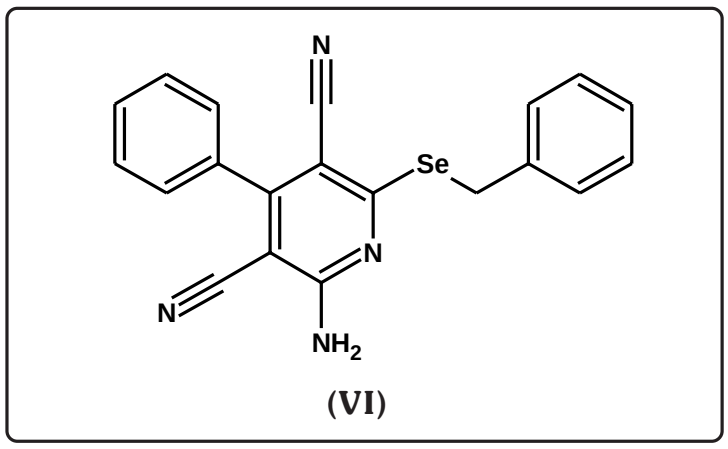


(IV) **(V)**

S. V. Roman et. al.[122] have investigated 2-amino-3-cyanopyridine derivatives and reported their biological activity. El-Taweel and co-workers[123] have described cyanopyridine derivatives (V) and showed their significant biological activity.

Francis and co-workers[124] have studied the effect of some substituted pyridines on the growth of the walker carcinosarcome-256 in tissue culture. H. W. Hoefling and co-workers[125] have documented 3- and 4-cyanopyridines as tuberculosis arresting agents.

Hironori et. al.[126] have prepared cyanopyridines and screened for their large conductance calcium activiated potassium channel opener activity. Pyachenko V. D. and co-workers[127] have shown some cyanopyridines (VI) which are useful in treatment of retroviral disease.

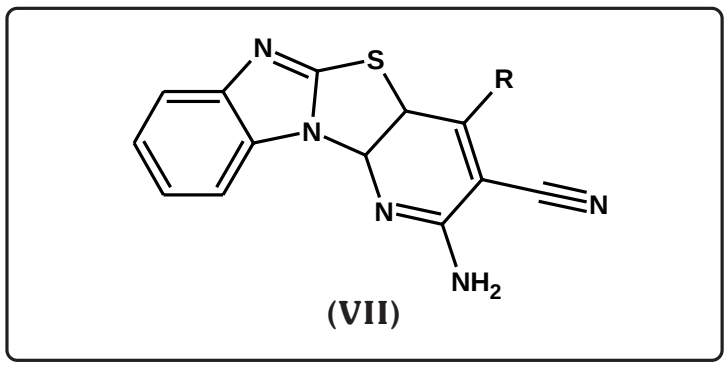


(VI)

CONTRIBUTION FROM OUR LABORATORY

Akhil Bhatt and co-workers[128] have synthesised cyanopyridines as potential antimicrobial agents. R. C. Khunt et. al.[129] have screened cyanopyridine derivatives used as biologically active agents. Synthesis and antimicrobial activity of cyanopyridines is shown by B. P. Kansagara et. al.[130] J. R. Patel & co-workers[131] have prepared cyanopyridines bearing 2-chloro-6-bromoquinoline nucleus as potential anticancer agents.

Synthesis and biological evaluation of cyanopyridines is screened by Pankaj Patel & co-workers[132]. Rajeev Doshi and co-workers[133] have described some novel cyanopyridines as a new class of potential antitubercular agents. Cyanopyridines have been screened by A. V. Dobaria et. al.[134] and showed their significant biological activity. Ketan Hirpara & co-workers[135] have discovered cyanopyridines as antitubercular agents (VII).



(VII)

Thus, diverse biological activities have been encountered in compounds containing cyanopyridine ring system. To further assess the potential of such a type of compounds, study of cyanopyridines have been carried out as under.

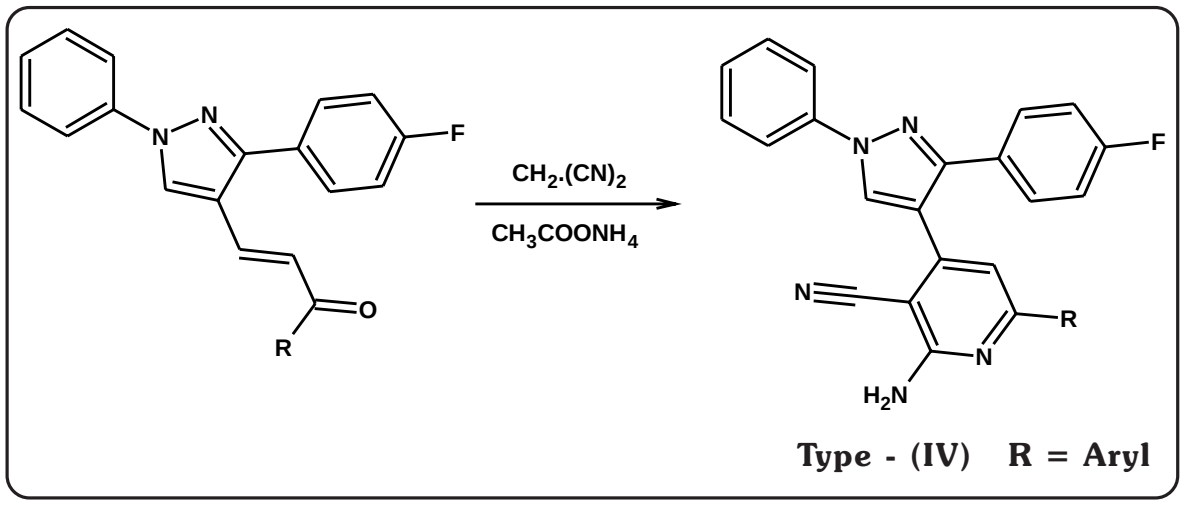
SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1,'N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL-PYRIDINES

SECTION - II: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1,'N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL-PYRIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'YL]-6-ARYL-PYRIDINES

In the past years, considerable evidence has been accumulated to demonstrate the efficiency of cyanopyridines. To further assess the potential of such a class of compounds cyanopyridine derivatives of type (IV) have been synthesised by condensation of malononitrile and ammonium acetate with 1-aryl-3-[1',N-phenyl-3'-p-flourophenyl pyrazole-4'-yl]-2-propene-1-ones.

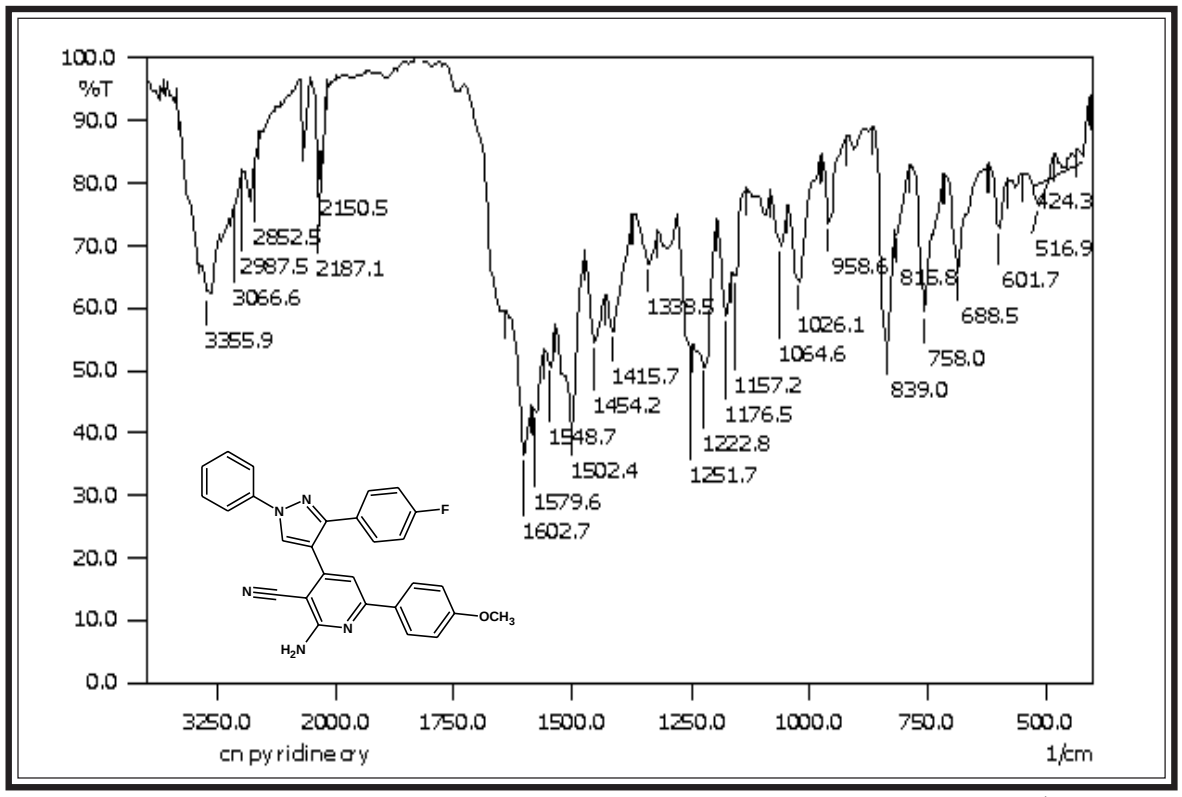


Type - (IV) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of synthesised compounds were compared with standard drugs.

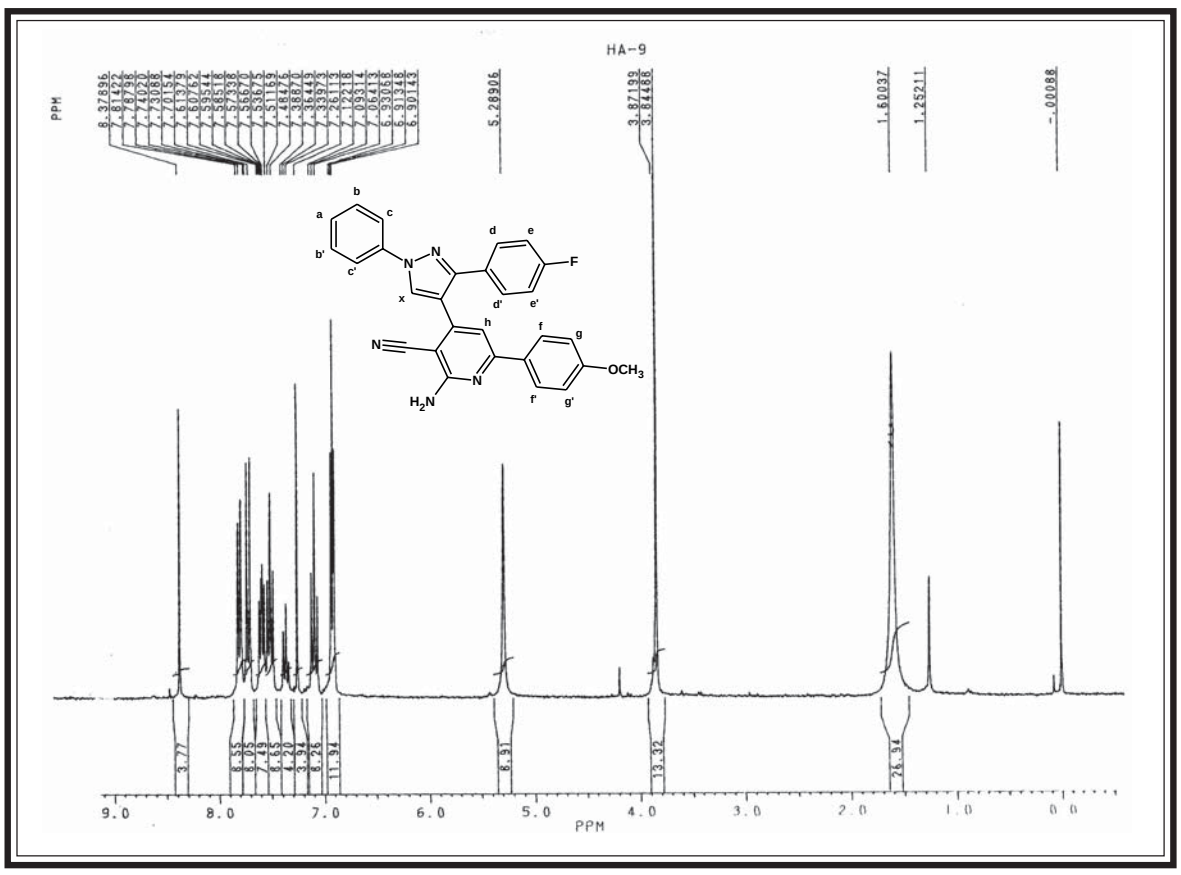
IR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-6-(p-ANISYL) PYRIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2987	2995–2920	429
$-CH_3$	C – H str. (sym.)	2852	2880–2850	"
	C – H i.p. (def.)	1454	1470–1435	"
	C – H o.o.p. (def.)	1338	1385–1330	"
Aromatic	C – H str.	3066	3080–3010	427
	C – H i.p. (def.)	1026	1110–1000	"
	C – H o.o.p (def.)	839	835–810	"
Pyrazole	C = N str.	1602	1650–1600	428
moiety	C = C str.	1546	1585–1480	"
	C – N str.	1222	1350–1200	"
	C – F str.	758	760–710	"
Ether	C – O – C str. (asym.)	1251	1275–1200	"
	C – O – C str. (sym.)	1064	1075–1020	"
Pyridine	C ≡ N str.	2187	2240–2120	429
ring	C = N str.	1579	1650–1600	"
	N – H str. ($-NH_2$)	3355	3400–3250	"

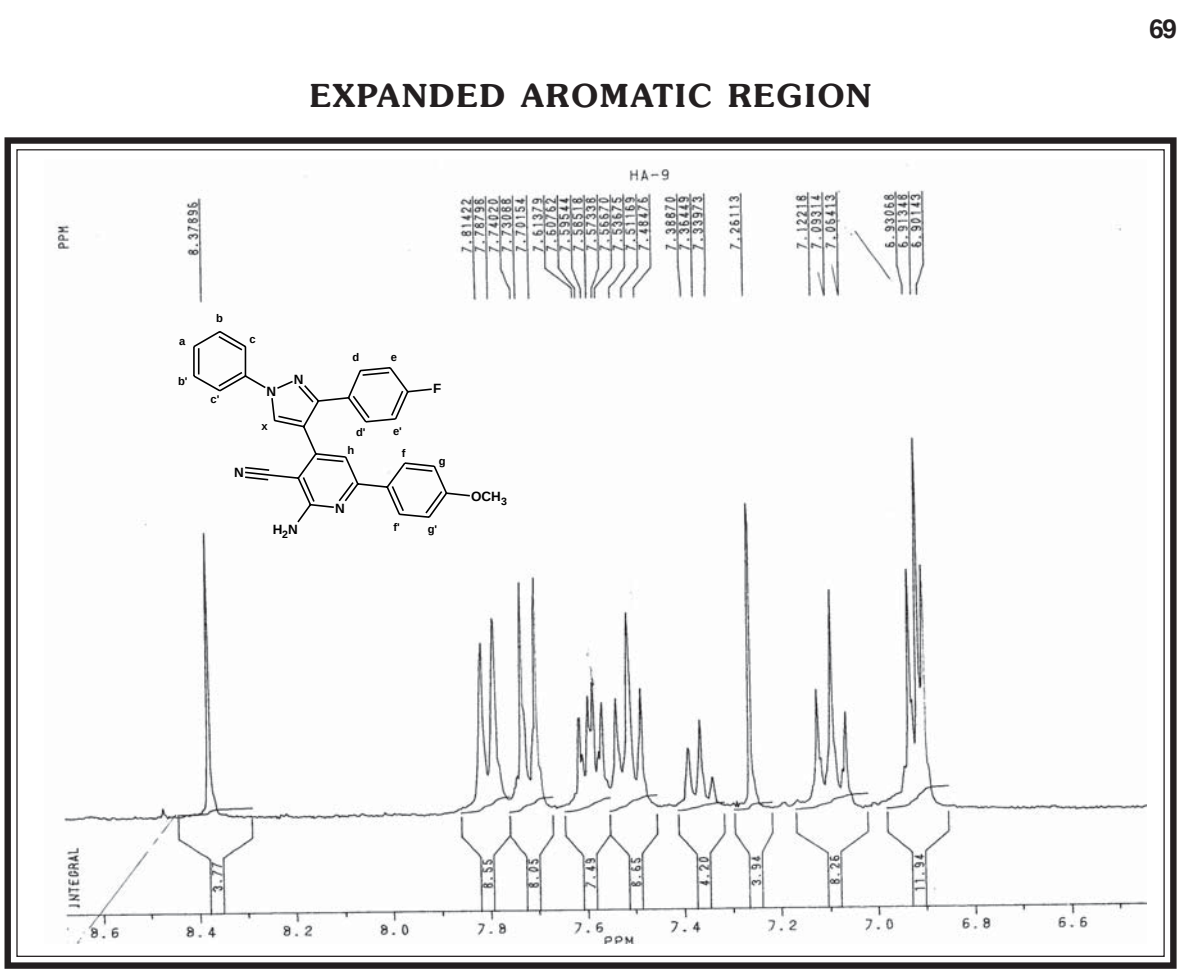
PMR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-p-FLUORO PHENYL PYRAZOL-4'-YL]-6-(p-ANISYL)-PYRIDINE

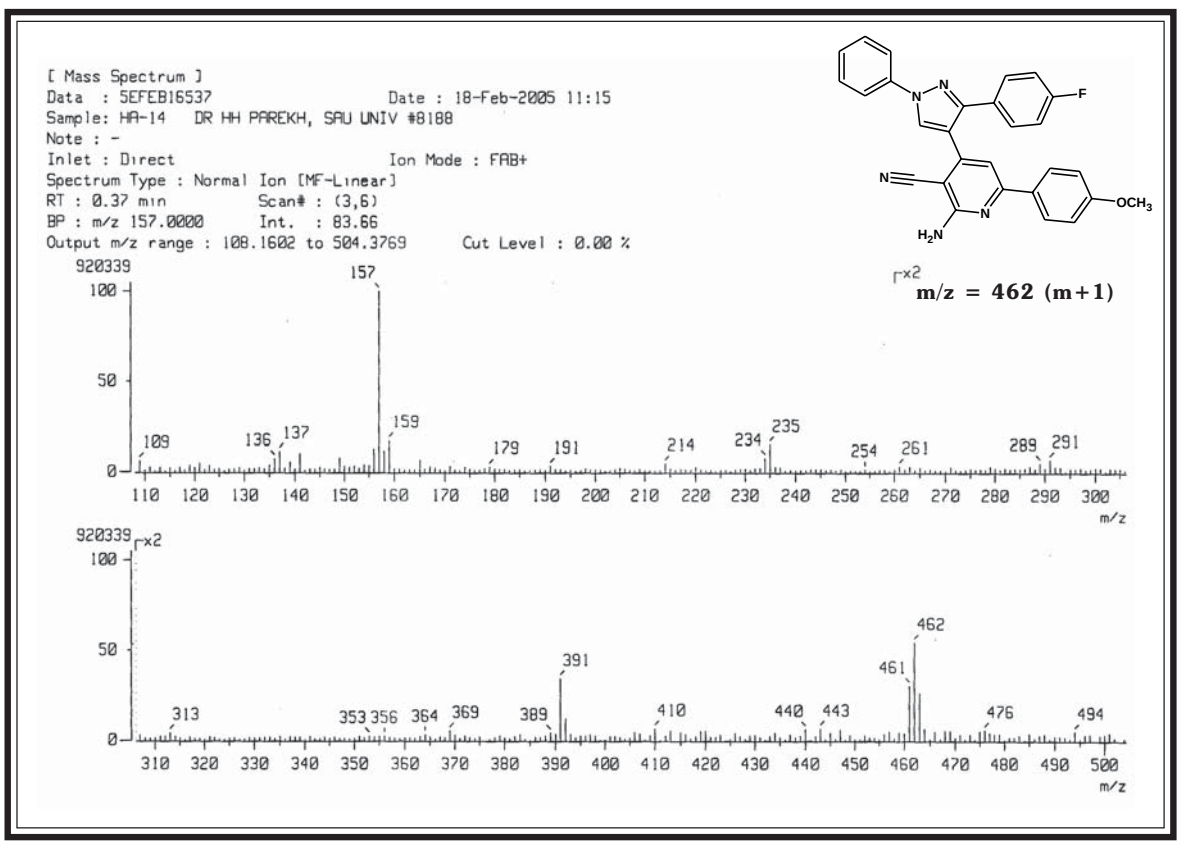


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.84	3H	singlet	Ar-OCH_3	-
2.	5.28	2H	singlet	-NH_2	-
3.	6.90-6.93	3H	triplet	Ar-Hgg' + Hh	Jgf=8.7
4.	7.06-7.12	2H	triplet	Ar-Hdd'	-
5.	7.33-7.38	1H	triplet	Ar-Ha	-
6.	7.48-7.53	2H	triplet	Ar-Hbb'	-
7.	7.56-7.61	2H	multiplet	Ar-Hcc'	-
8.	7.70-7.74	2H	doublet	Ar-Hee'	Jed=8.7
9.	7.78-7.81	2H	doublet	Ar-Hff'	Jfg=8.1
10.	8.37	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL PYRIDINES

[A] Synthesis of N-Aminophenyl-α-methyl-p-fluorophenyl azomethine

See Part-I, Section-I (A).

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See Part-I, Section-I (B).

[C] Synthesis of 1-phenyl-3-(1'-N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-I (C).

[D] Synthesis of 2-Amino-3-cyano-4-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-6-(p-anisyl)-pyridine

A mixture of 1-Anisyl-3-(1',N-phenyl)-3'-p-fluorophenyl-pyrazol-4'-yl)-2-porpene-1-one (3.98 g, 0.01M), malononitrile (0.66 g, 0.01 M) and ammonium acetate (6.61g, 0.08M) dissolved in absoulte alcohol was refluxed for 10 hrs. at to mp 60-70°C The reaction product was poured into ice, crude product was isolated, crystallised from ethanol. Yield 65%, m.p. 234°C ($C_{28}H_{20}FN_5O$; Found : C, 72.72%; H, 4.30%; N, 15.11%; Requires : C, 72.81%; H, 4.37%; N, 15.18%).

Similarly other cyanopyridines have been obtained. The physical data are recorded in Table No. 4.

[E] Antimicrobial activity of 2-Amino-3-cyano-4-[1',N-phenyl-3'-p-fluorophenyl pyrazole-4'-yl]-6-aryl-pyridines

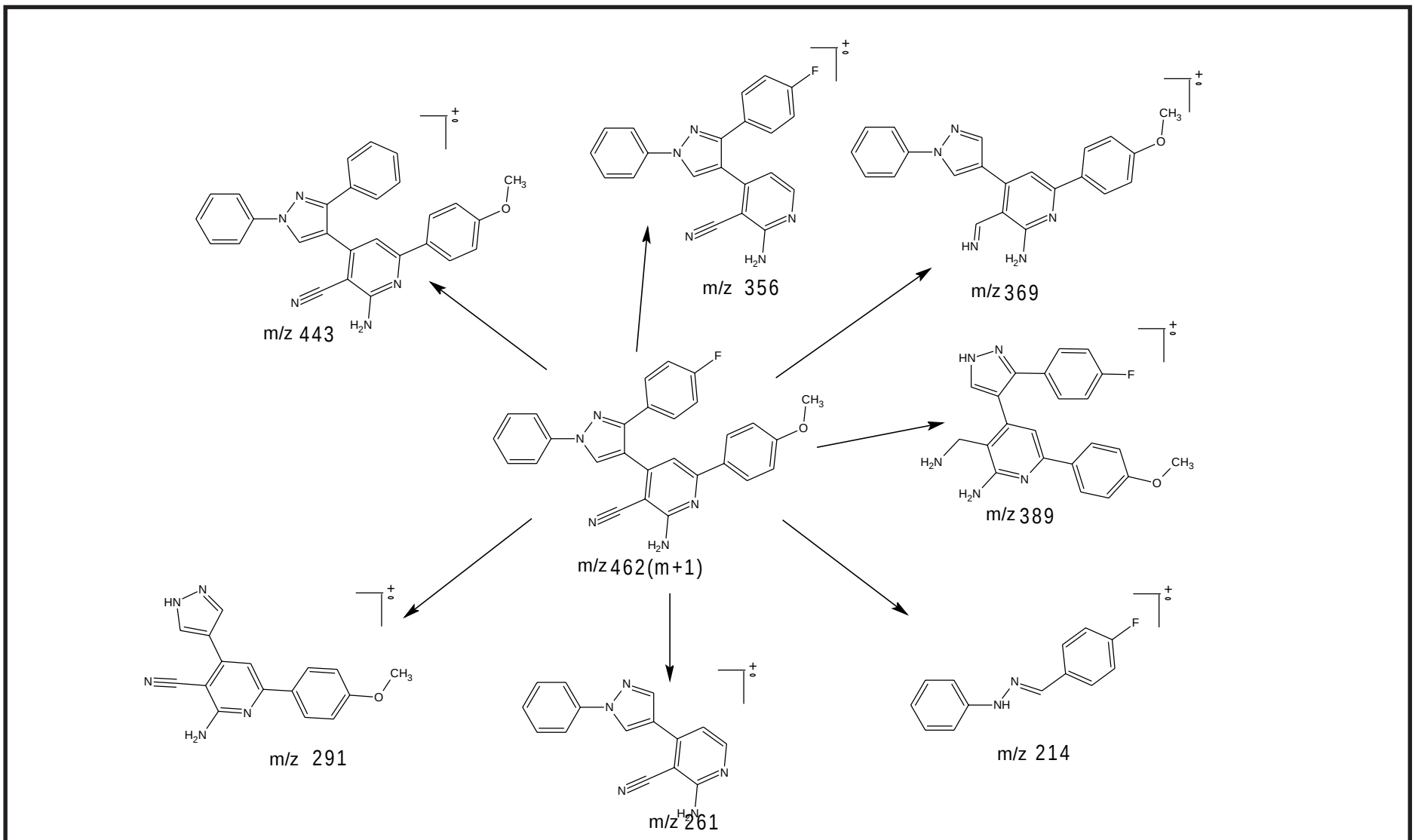
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No.4.

TABLE NO. 4 : PHYSICAL CONSTANTS OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL PYRIDINE

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
4a	C_6H_5-	$C_{27}H_{18}FN_5$	431	164	0.51	67	16.23	16.16
4b	4-OCH_3-C_6H_4-	$C_{28}H_{20}FN_5O$	461	234	0.61	65	15.18	15.11
4c	4-CH_3-C_6H_4-	$C_{28}H_{20}FN_5$	445	157	0.49	57	15.27	15.19
4d	4-Cl-C_6H_4-	$C_{27}H_{17}ClFN_5$	465	142	0.53	63	15.03	14.96
4e	4-F-C_6H_4-	$C_{27}H_{17}F_2N_5$	449	191	0.57	59	15.58	15.52
4f	4-OH-C_6H_4-	$C_{27}H_{18}FN_5O$	447	189	0.47	72	15.65	15.57
4g	2-OH-C_6H_4-	$C_{27}H_{18}FN_5O$	447	171	0.53	67	15.65	15.58
4h	4-NO_2-C_6H_4-	$C_{27}H_{17}FN_6O_2$	476	162	0.69	68	17.64	17.58
4i	3-NO_2-C_6H_4-	$C_{27}H_{17}FN_6O_2$	476	180	0.71	64	17.64	17.56
4j	4-Br-C_6H_4-	$C_{27}H_{17}BrFN_5$	510	174	0.50	66	17.72	17.65
4k	4-NH_2-C_6H_4	$C_{27}H_{19}FN_6$	446	194	0.64	60	18.82	18.75
4l	C_4H_3S-	$C_{25}H_{16}FN_5S$	437	205	0.58	69	16.01	15.94

*TLC Solvent System : Ethyl acetate : Hexane

2 : 8


m/z 443
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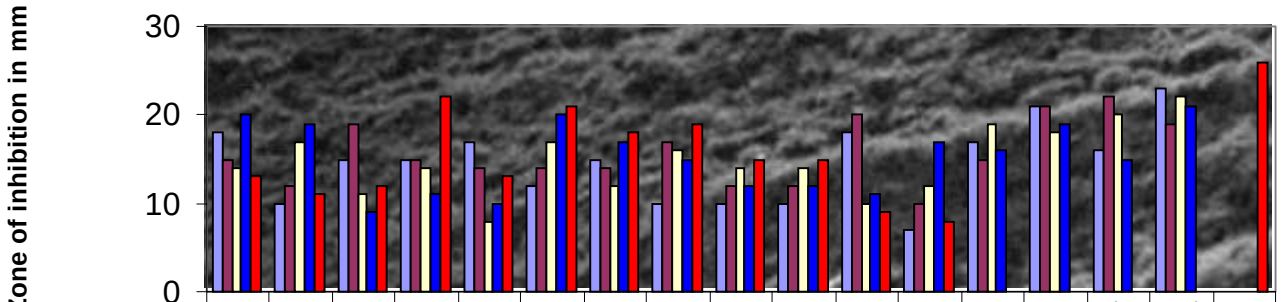
m/z 369
m/z 462(m+1)
m/z 389
m/z 291
m/z 261
m/z 214

GRAPHYCAL CHART NO.4: **ANTIMICROBIAL ACTIVITY OF 2-AMINO-3-CYANO- 4-[1'N-PHE NYL-3'-p-FLUOROPHENYL PYRAZOL-4'--6-ARYL-PYRIDINES.**



	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Amoxycillin	Benzoyl Peni	Ciprofloxacin	Erythromycin	Greseofulvi
B. cocous	18	10	15	15	17	12	15	10	10	10	18	7	17	21	16	23	0
B. subtillus	15	12	19	15	14	14	14	17	12	12	20	10	15	21	22	19	0
E. coli	14	17	11	14	8	17	12	16	14	14	10	12	19	18	20	22	0
P. vulgaris	20	19	9	11	10	20	17	15	12	12	11	17	16	19	15	21	0
A. niger	13	11	12	22	13	21	18	19	15	15	9	8	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of cyanopyridines (type-IV) revealed that most of the compounds were able to inhibit the growth of Gram positive and Gram negative bacterial strains.

Maximum activity was observed in compounds bearing R=4-aminophenyl, 4-methylphenyl & thienyl and significant activity was displayed by compounds bearing R=phenyl, 4-fluorophenyl and 4-bromophenyl against Gram positive bacterial strains ***B. cocous*** and ***B. subtillus***

While in case of Gram negative bacterial strains ***E. coli*** & ***P. vulgaris***, highest activity was observed in compounds bearing R=phenyl and 4-methoxyphenyl and significant activity was displayed by compounds bearing 4-hydroxyphenyl & thienyl.

ANTIFUNGAL ACTIVITY

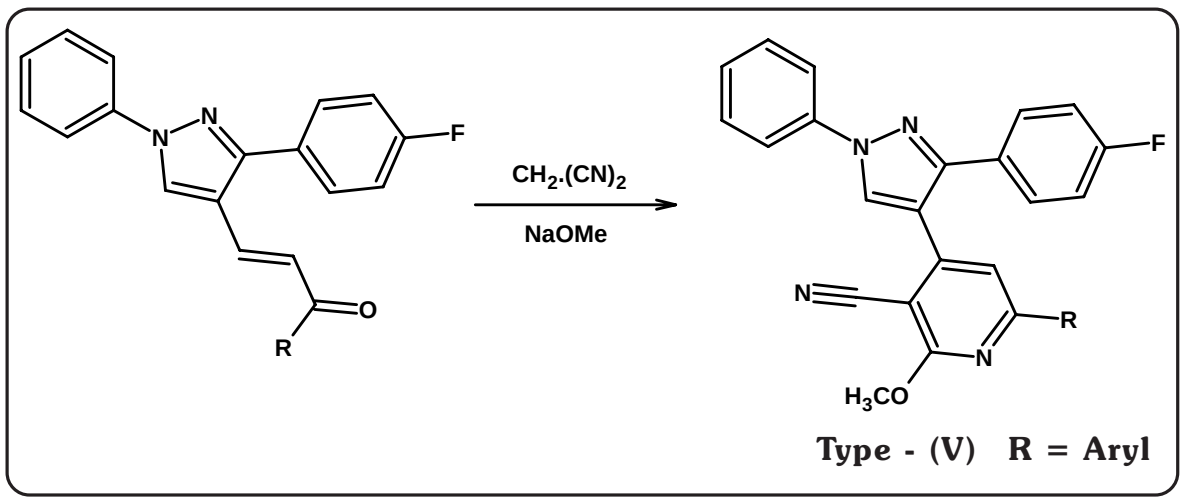
Most of the cyanopyridines were mildly active against fungal strain ***A. niger***. The maximum activity was displayed by compound bearing R=4-chlorophenyl.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL PYRIDINES

The pyridine nucleus is found in a large number of commonly used drugs which have diverse pharmacological activities. To achieving better drug potency cyano pyridine derivatives of type (V) have been prepared by the condensation of chalcones of type (I) with malononitrile in presence of sodium methoxide.



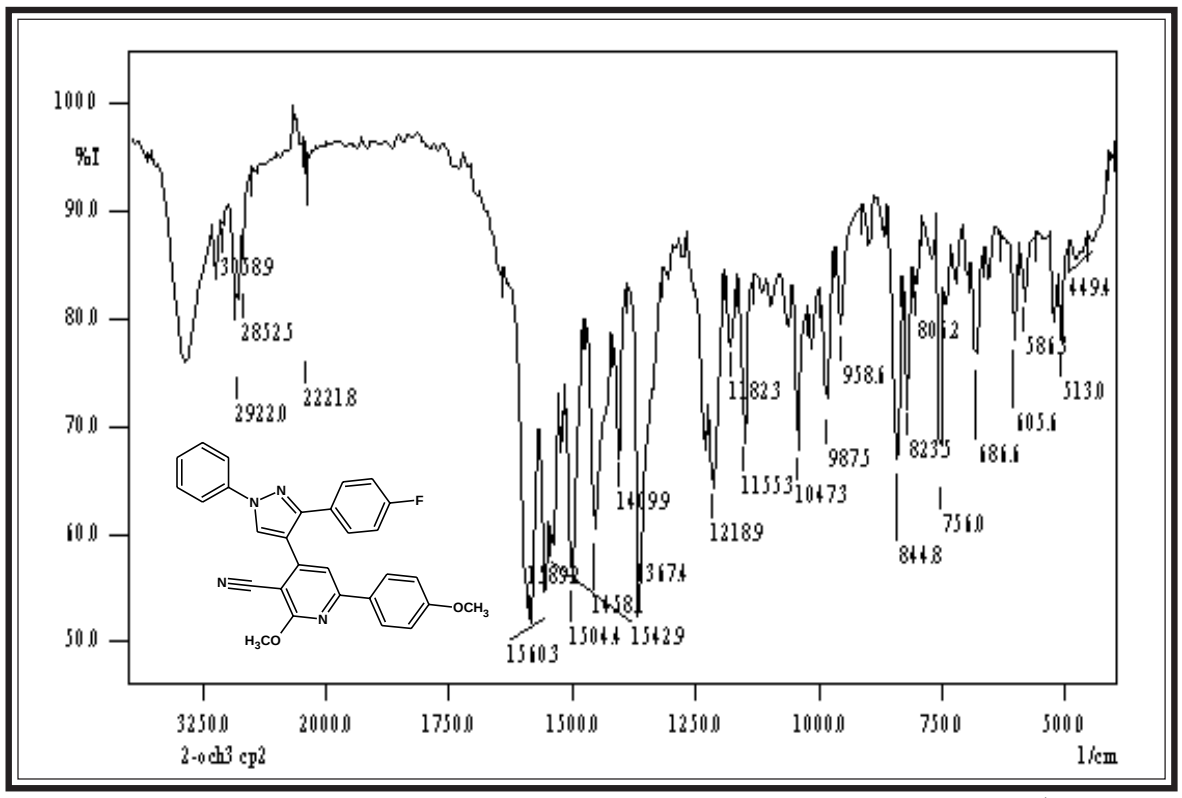
Type - (V) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at concentration of 6.25 μg/ml using Rifampin as standard drug.

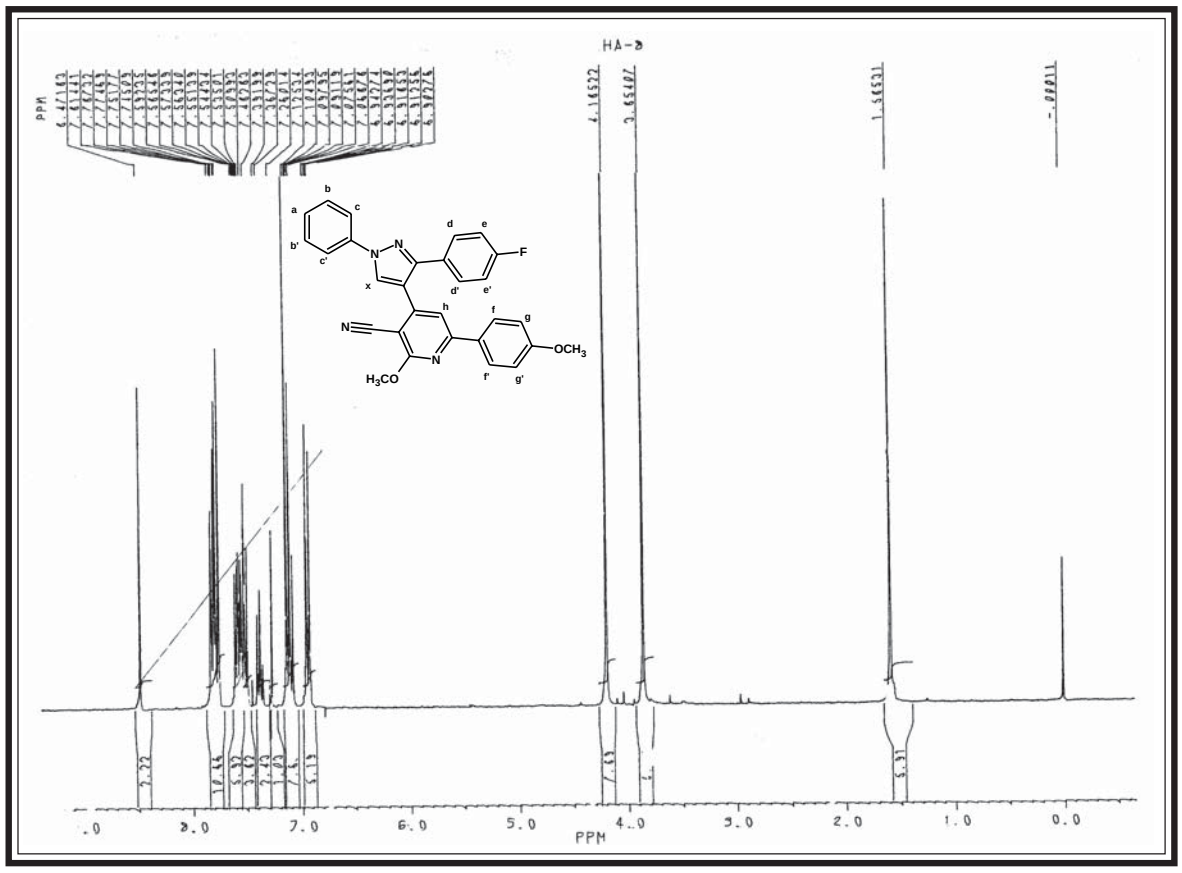
IR SPECTRAL STUDY OF 2-METHOXY-3-CYANO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-6-ANISYL PYRIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2922	2975–2920	426
$-CH_3$	C – H str. (sym.)	2852	2880–2840	"
	C – H def.(asym.)	1458	1470–1435	"
	C – H def.(sym.)	1367	1385–1350	"
Aromatic	C – H str.	3058	3080–3030	427
	C – H i.p. (def.)	1047	1070–1000	"
	C – H o.o.p (def.)	823	835–810	"
Pyrazole	C = N str.	1589	1650–1585	428
ring	C = C str.	1542	1585–1480	"
	C – N str.	1222	1350-1200	"
	C – F str.	756	750–700	"
Ether	C – O – C str. (asym.)	1218	1275–1200	"
Pyridine	C ≡ N str.	2221	2240–2120	429
ring	C = N str.	1560	1650–1550	"
	C = C str.	1504	1585-1480	"

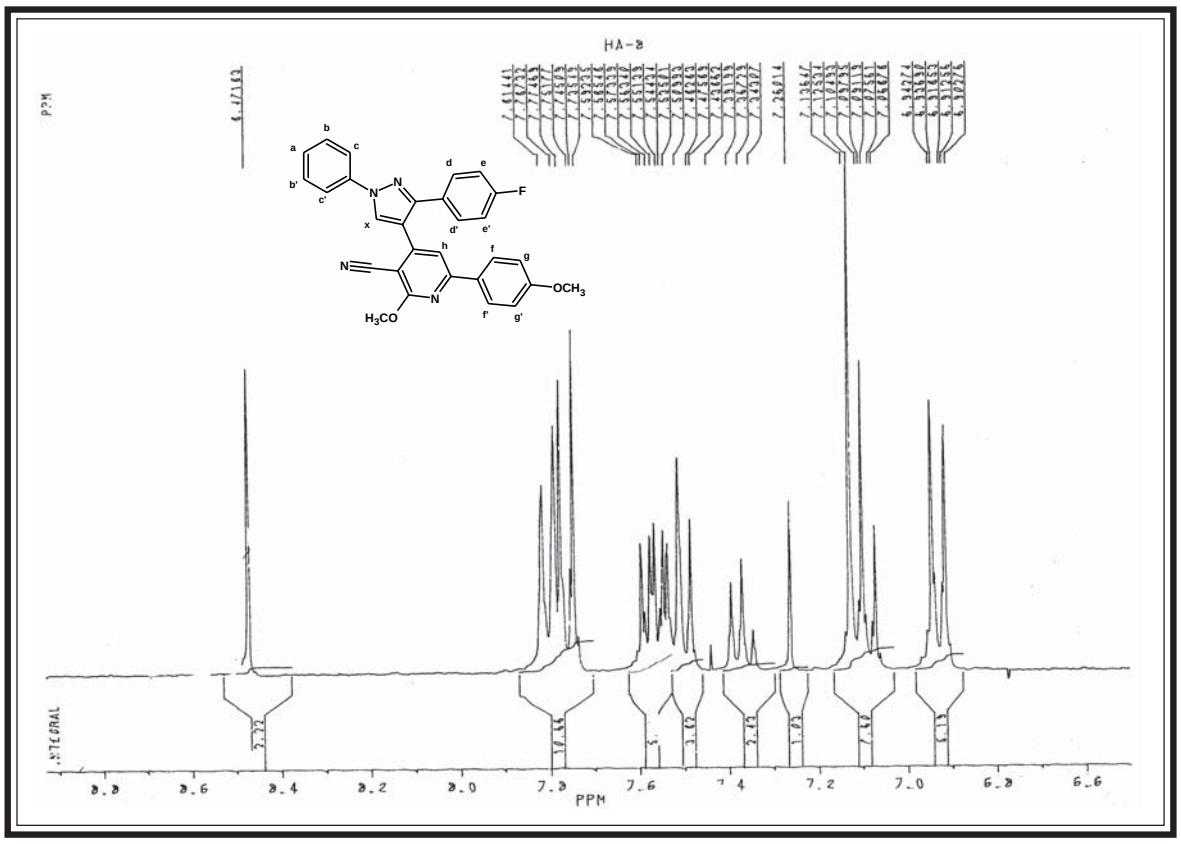
PMR SPECTRAL STUDY OF 2-METHOXY-3-CYANO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-YL)-6-(p-ANISYL)-PYRIDINE

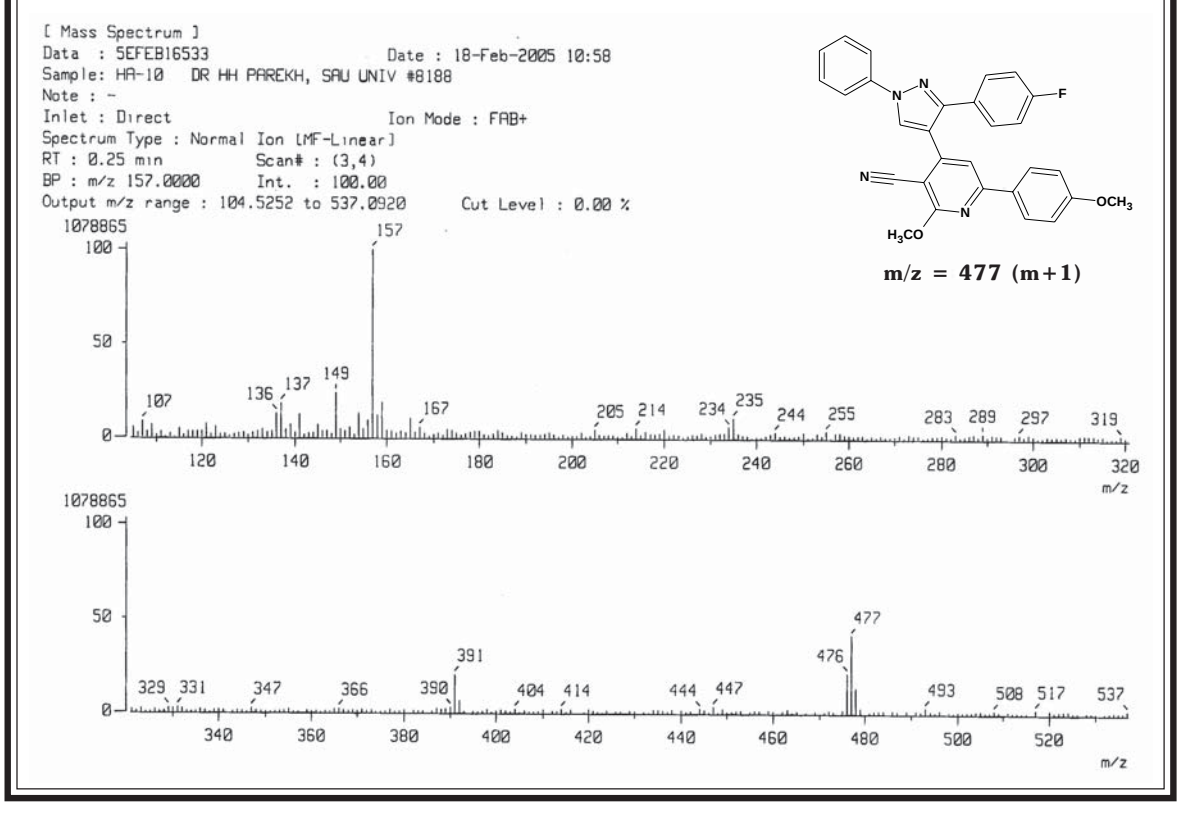


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.85	3H	singlet	Ar-$OCH_{3(1)}$	-
2.	4.18	3H	singlet	$OCH_{3(2)}$	-
3.	6.90-6.94	2H	doublet	Ar-Hgg'	Jgf=10.2
4.	7.06-7.13	3H	triplet	Ar-Hdd'+Hh	Jde = 6.9
5.	7.34-7.39	1H	triplet	Ar-Ha	-
6.	7.47-7.50	2H	doublet	Ar-Hbb'	Jbc=10.2
7.	7.53-7.58	2H	multiplet	Ar-Hcc'	-
8.	7.73-7.81	4H	d.doublet	Ar-Hff' + Hee'	Jfg=8.1 Jed=8.7
9.	8.47	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





m/z = 477 (m+1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-METHOXY-3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL PYRIDINES

[A] Synthesis of N-Aminophenyl-α-methyl-p-fluorophenyl-azomethine

See Part-I, Section-I (A).

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See Part-I, Section-I (B).

[C] Synthesis of 1-phenyl-3-(1'-N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-I (C).

[D] Synthesis of 2-Methoxy-3-cyano-4-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-6-anisyl-pyridine

A mixture of 1-anisyl-3-(1',N-phenyl)-3'-p-fluorophenyl pyrazol-4'-yl)-2-porpene-1-one (3.98 g, 0.01M), malononitrile (0.66 g, 0.01 M) and sodium methoxide (10 ml) (6.61g, 0.08M) dissolved in absoulte alcohol was refluxed for 10 hrs. in water bath at temp 70°C. The reaction product was poured into ice, crude product was isolated, crystallised from ethanol. Yield 70%, m.p. 270°C ($C_{29}H_{21}FN_4O_2$; Found : C, 73.04%; H, 4.36%; N, 11.68%; Requires : C, 73.10%; H, 4.44%; N, 11.76%).

Similarly other cyanopyridines have been obtained. The physical data are recorded in Table No. 5.

[E] Therapeutic activity of 2-Methoxy-3-cyano-4-[1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl]-6-aryl-pyridines

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No.5.

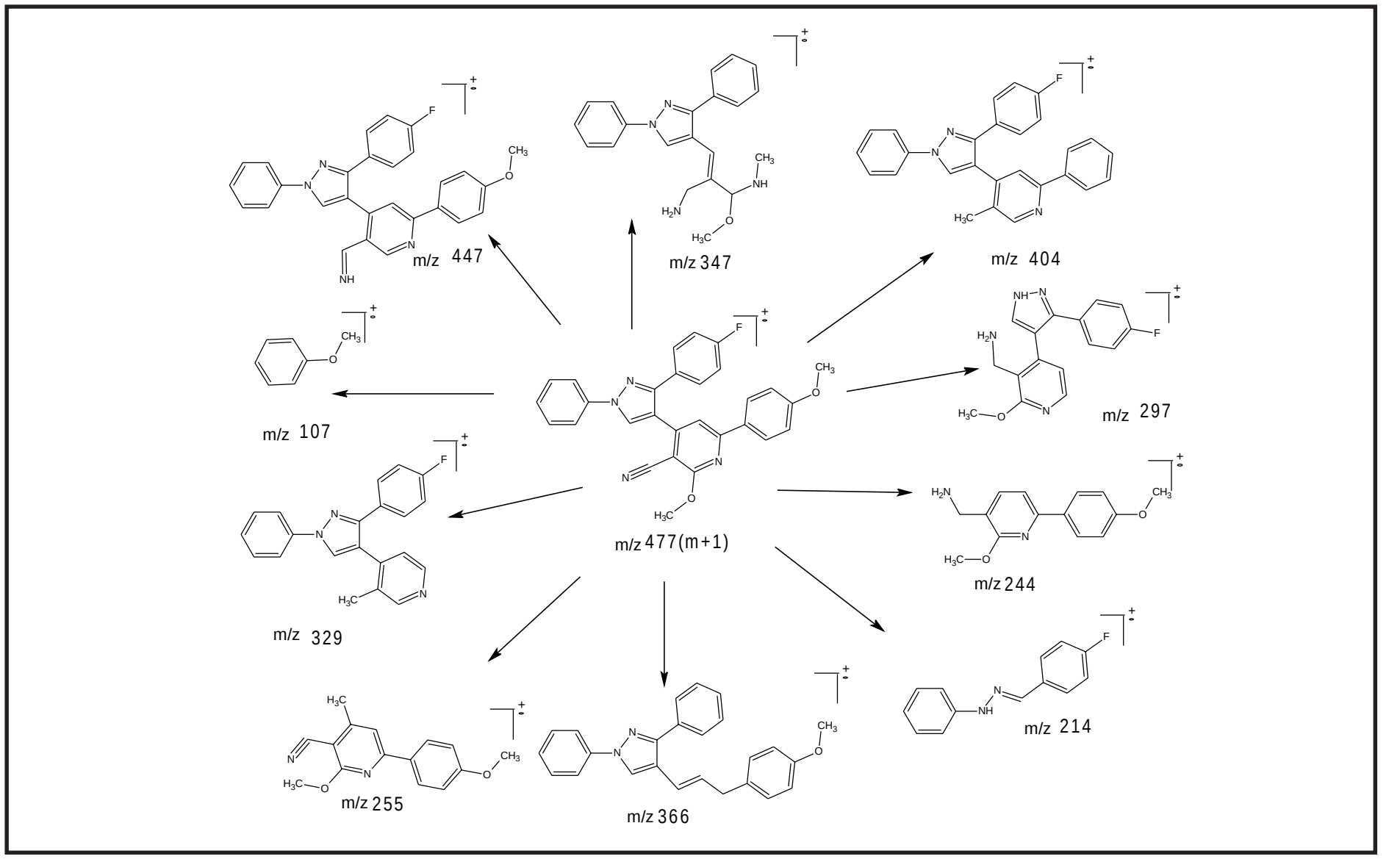
Antitubercular screening of the compounds of type(V) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 5a.

TABLE NO. 5 : PHYSICAL CONSTANTS OF 2-METHOXY-3-CYANO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-6-ARYL PYRIDINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
5a	C_6H_5-	$C_{28}H_{19}FN_4O$	446	240	0.42	61	12.55	12.49
5b	4-OCH_3-C_6H_4-	$C_{29}H_{21}FN_4O_2$	476	270	0.65	70	11.76	11.68
5c	4-CH_3-C_6H_4-	$C_{29}H_{21}FN_4O$	460	237	0.67	60	12.17	12.10
5d	4-Cl-C_6H_4-	$C_{28}H_{18}ClFN_4O$	480	231	0.57	63	11.65	10.58
5e	4-F-C_6H_4-	$C_{28}H_{18}F_2N_4O$	464	128	0.60	64	12.06	12.00
5f	4-OH-C_6H_4-	$C_{28}H_{19}FN_4O_2$	462	148	0.47	59	12.11	12.07
5g	2-OH-C_6H_4-	$C_{28}H_{19}FN_4O_2$	462	177	0.51	65	12.11	12.05
5h	4-NO_2-C_6H_4-	$C_{28}H_{18}FN_5O_3$	491	201	0.53	69	14.25	14.16
5i	3-NO_2-C_6H_4-	$C_{28}H_{18}FN_5O_3$	491	211	0.49	63	14.25	14.17
5j	4-Br-C_6H_4-	$C_{28}H_{18}BrFN_4O$	525	266	0.50	64	10.66	10.59
5k	4-NH_2-C_6H_4	$C_{28}H_{20}FN_5O$	461	166	0.59	68	15.18	15.11
5l	C_4H_3S-	$C_{26}H_{17}FN_4OS$	452	243	0.67	65	12.38	12.32

*TLC Solvent System : Ethyl acetate : Hexane

2 : 8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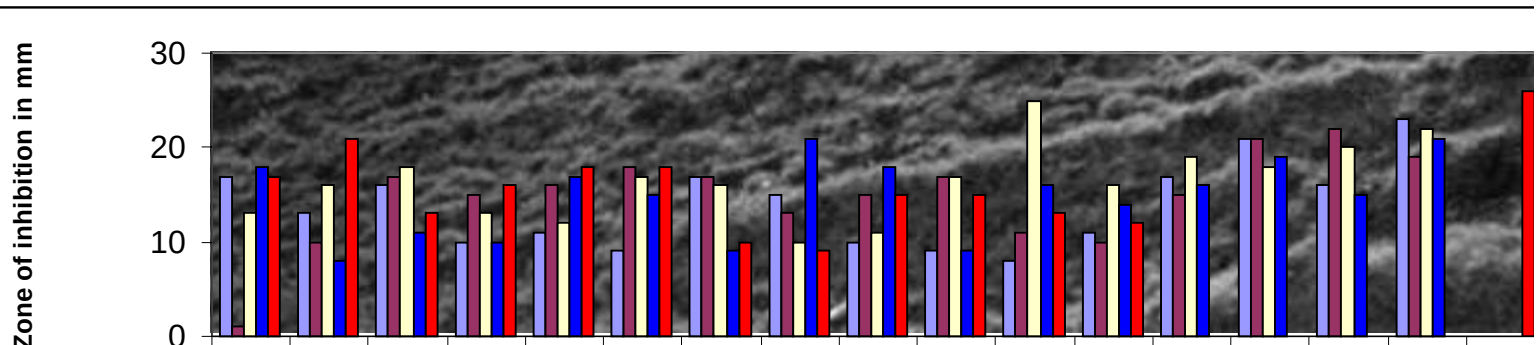
m/z 347
m/z 404
m/z 107
m/z 297
m/z 477(m+1)
m/z 329
m/z 244
m/z 255
m/z 366
m/z 214

GRAPHYCAL CHART NO.5: **ANTIMICROBIAL ACTIVITY OF 2-METHOXY-3-CYANO -4-[1'N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL] -6-ARYL-PYRIDINES.**



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Amoxycillin	Benzoyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	17	13	16	10	11	9	17	15	10	9	8	11	17	21	16	23	0
B. subtillus	1	10	17	15	16	18	17	13	15	17	11	10	15	21	22	19	0
E. coli	13	16	18	13	12	17	16	10	11	17	25	16	19	18	20	22	0
P. vulgaris	18	8	11	10	17	15	9	21	18	9	16	14	16	19	15	21	0
A. niger	17	21	13	16	18	18	10	9	15	15	13	12	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of 2-methoxy-3-cyanopyridines (type-V) revealed that most of the compounds were able to inhibit the growth of Gram positive & Gram negative bacterial strains.

Maximum activity was displayed by compounds bearing R=phenyl & 4-hydroxyphenyl and significant activity was displayed by compounds bearing R=4-methylphenyl & 4-chlorophenyl against Gram positive bacterial strains ***B. cocous*** and ***B. subtillus***

While in case of Gram negative bacterial strains, maximum activity was observed in compound containing R=4-methylphenyl and 4-nitrophenyl & significant activity was displayed by compounds bearing R=phenyl, 4-methylphenyl, 4-hydroxyphenyl and 3-nitrophenyl against ***E. coli*** & ***P. vulgaris***.

ANTIFUNGAL ACTIVITY

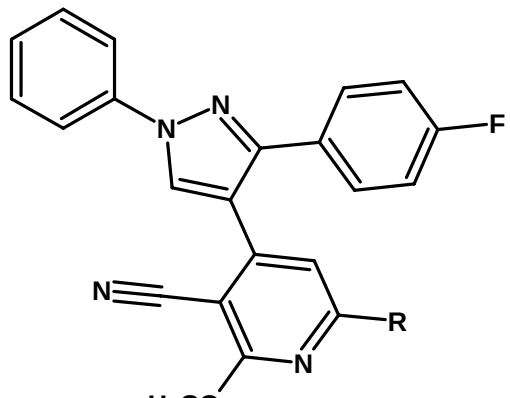
All the compound are mild to moderately active against fungal strain ***A. niger***. Maximum activity was displayed by compound bearing R=4-methoxyphenyl.

The antimicrobial activity shown by compounds was comparable with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds displayed activity, ranging from 2 to 95% inhibition against ***Mycobacterium tuberculosis $H_{37}Rv$***. Compounds with R = 4-methoxyphenyl, 4-fluorophenyl and thienyl exhibited maximum activity upto 95% inhibition.

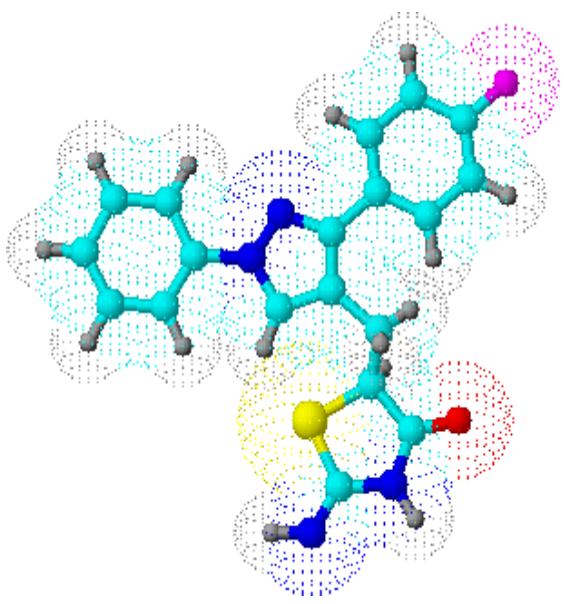
TABLE NO. 5a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

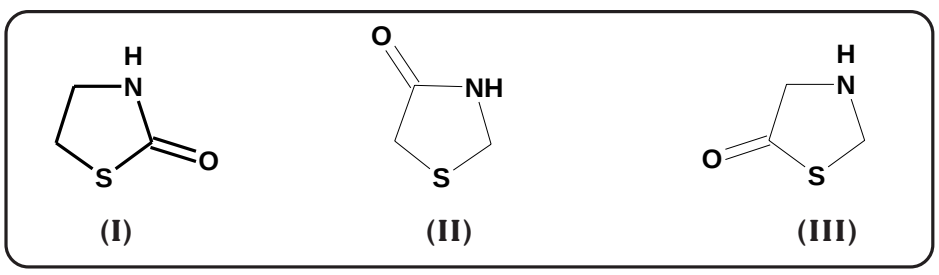
Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC µg/ml*	*% Inhib*	*Activity*	*Comment*
295634	HCV-128	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	67	-	MIC Rifampin = 0.25 µg/ml @ 98% Inhibition
295635	HCV-129	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	<6.25	95	+	"
295636	HCV-130	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	2	-	"
295637	HCV-131	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	5	-	"
295638	HCV-132	4-F- C_6H_4-	Alamar	$H_{37}Rv$	<6.25	92	+	"
295639	HCV-133	4-OH- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	73	-	"
295640	HCV-134	2-OH- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	88	-	"
295641	HCV-135	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295642	HCV-136	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	16	-	"
295643	HCV-137	4-Br--C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12	-	"
295644	HCV-138	4-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	76	-	"
295645	HCV-139	C_4H_3S-	Alamar	$H_{37}Rv$	<6.25	94	+	"



PART-III
STUDIES ON
THIAZOLIDINONES

INTRODUCTION

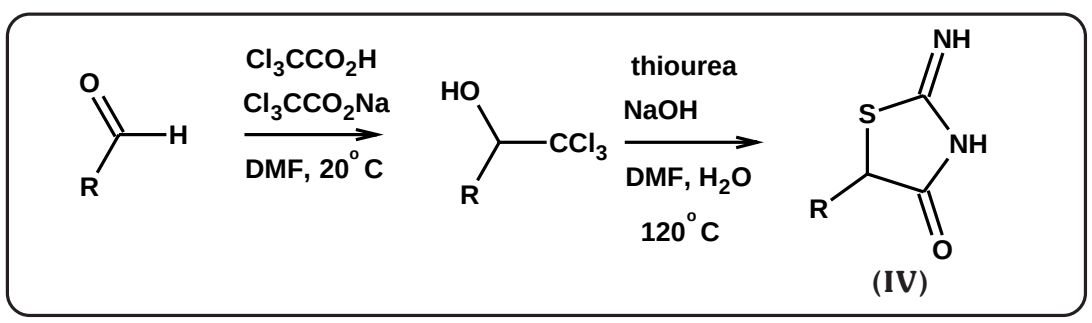
*T*hiazolidinones are derivatives of thiazolidines with carbonyl gp at position 2(I), 4(II) or 5(III) have been a great success in the field of chemistry and pharmacology. They are an integral part of pharmaceutically important compounds like penicillins. Substituted thiazolidinone derivatives represent important key intermediates for the synthesis of pharmacologically active drugs.



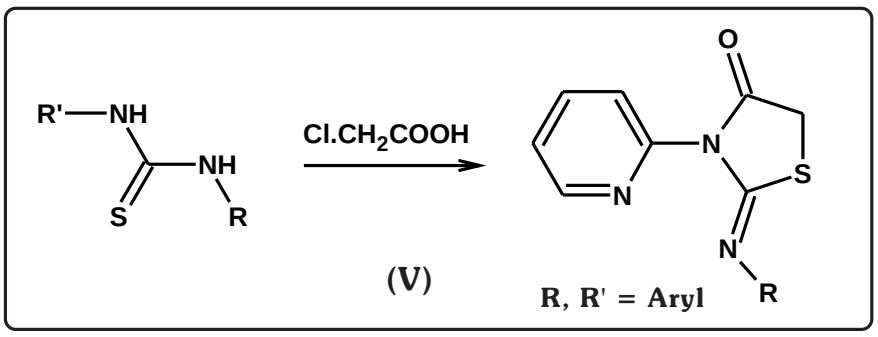
SYNTHETIC ASPECTS

Several methods for the preparation of 4-thiazolidinones are narrated in literature[136-143].

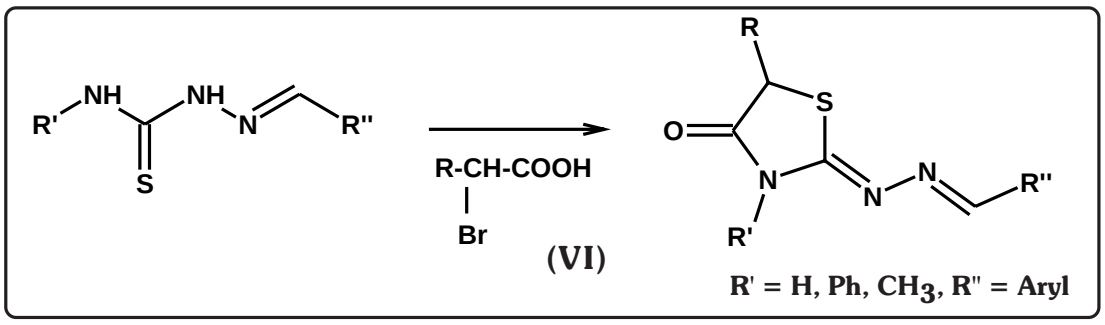
1. Jerome Blanchet & Jieping-Zhu[144] have synthesised 2-imino-4-thiazolidinones (IV) derivatives by the condensation of aldehyde, chloroform and thiourea.



2. R. Nath and K. Shankar[145] have prepared 4-thiazolidinones (V) by cyclisation of N-aryl-N'-(2'-pyridyl) thiocarbamide with chloroacetic acid.



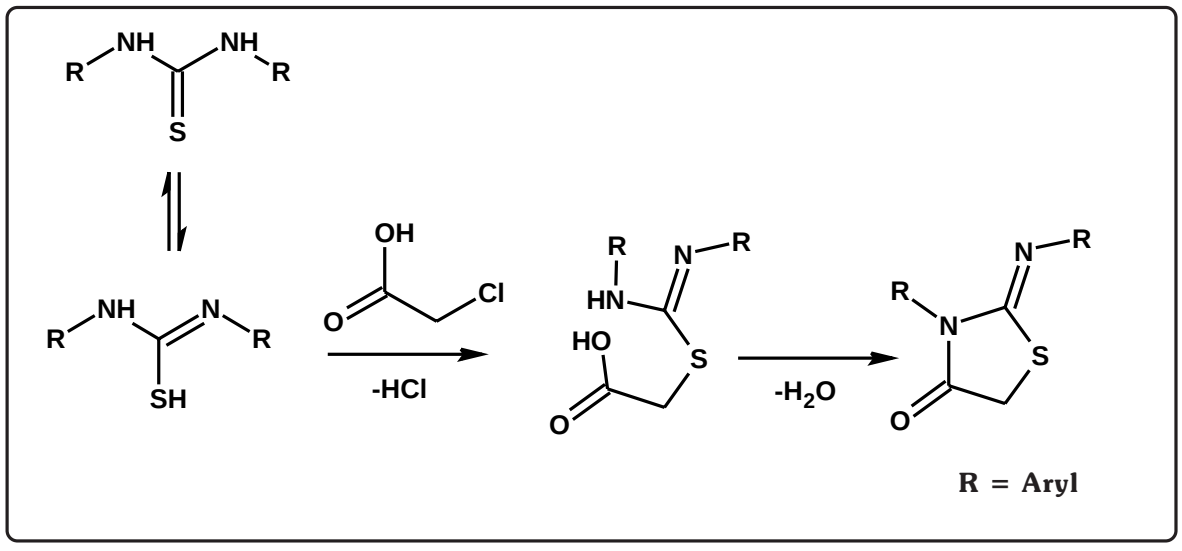
3. I. D. Shah and J. P. Trivedi[146] have synthesised thiazolidinones (VI) from 4-aryl-thiosemicarbazones by condensed them with chloroacetic acid, α-bromopropionic acid and α-bromophenyl acetic acids.



4. M. Saeda et. al.[147] have synthesised some new thiazolidinones.

MECHANISM

The reaction of 4-thiazolidinones proceeds by the attacks of the chloroacetic acid upon the C=S group. The tautomerism takes place with removal of HCl followed by removal of water and subsequent cyclisation.

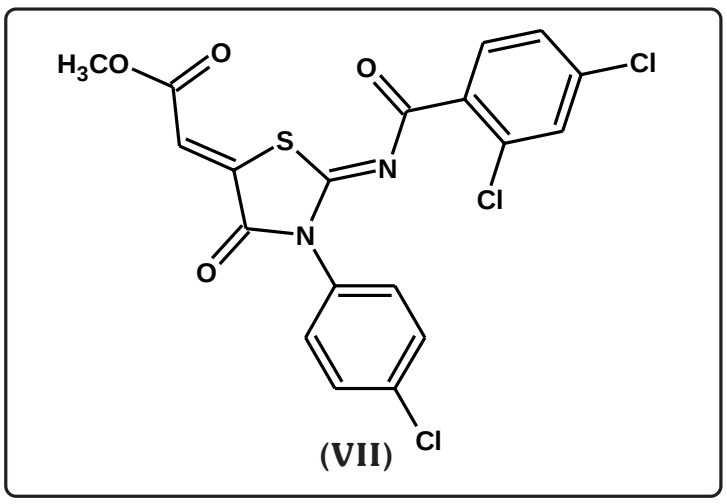


THERAPEUTIC IMPORTANCE

Much research has been carried out with an aim to finding therapeutic values of thiazolidinone skeleton since their discovery. The thiazolidinones, substituted at 2- and 3-positions are reported to exhibit a wide variety of biological activity.

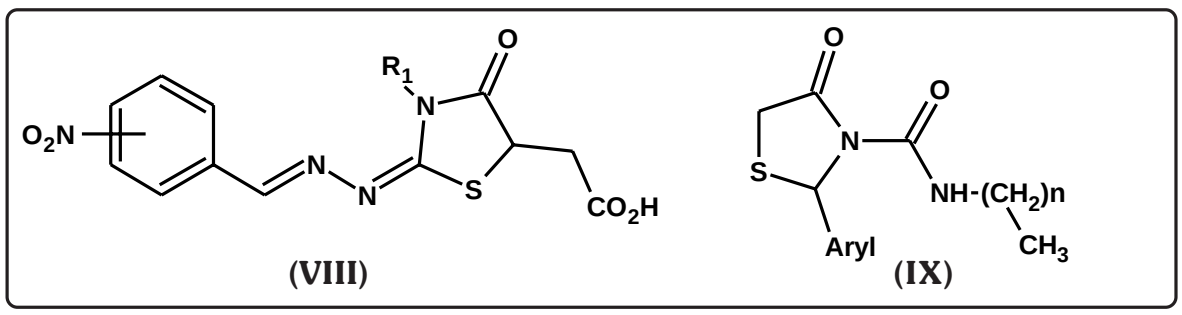
1. Anthelmintics[148,149]
2. Cardiovascular[150]
3. Mosquito repellant[151]
4. Antiviral[152]
5. Local anaesthetic[153]
6. Antitumor[154]
7. Antitubercular[155,156]
8. Anti HIV & anticancer[157]
9. Antimicrobial[158]
10. Herbicidal[159]

Kato Y. & co-workers[160] have discovered thiazolidinones (VII) as a novel non-peptide thrombin receptor anatagonist. Abbas S. F. & co-workers[161] have synthesised thiazolidinone derivatives which have been found to possess antimicrobial activity.

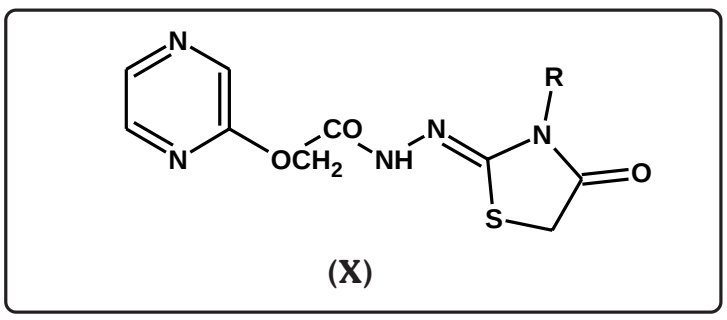


(VII)

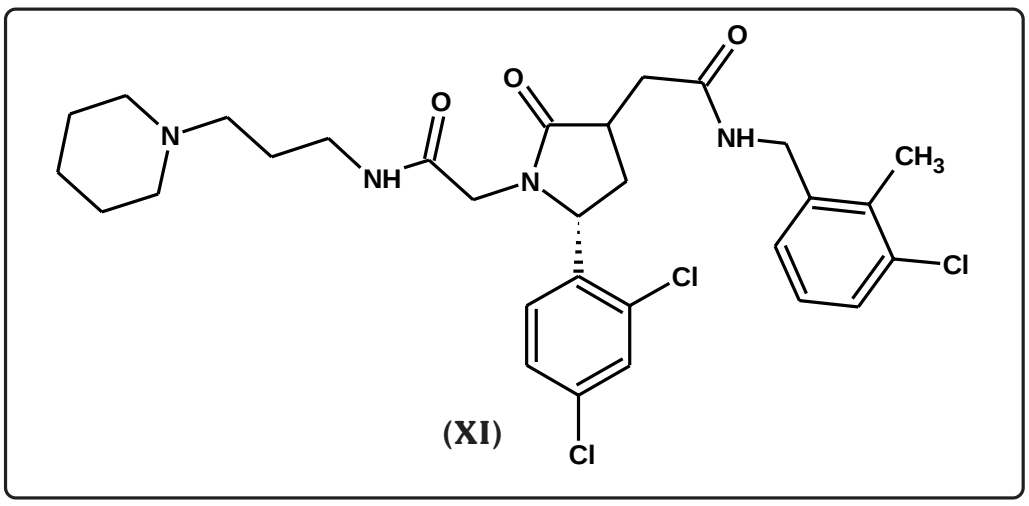
Romulo P. Tenorio et. al.[162] have prepared & shown anti-toxoplasma gondii activity of thiazolidinones derivatives (VII). Veeresa Gududuru & co-workers[163] have synthesised thiazolidinones (IX) to study their antiproliferative activity for prostate cancer.



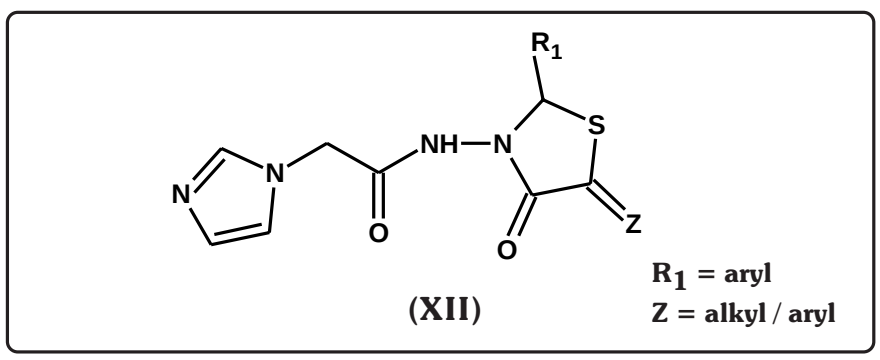
C. Bonde & co-workers[164] have synthesised pyrazine containing thiazolidinones (X) as antimicrobial agents. A. Rao & co-workers[165] have discovered thiazolidinones derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors.



Some antioxidant activity of thiazolidinones have been studied by Mei-Hsiu Shih & Fang-Ying Ke[166]. Aaron S. Anderson et. al.[167] have prepared thiazolidinones (XI) as CCR4 antagonists.

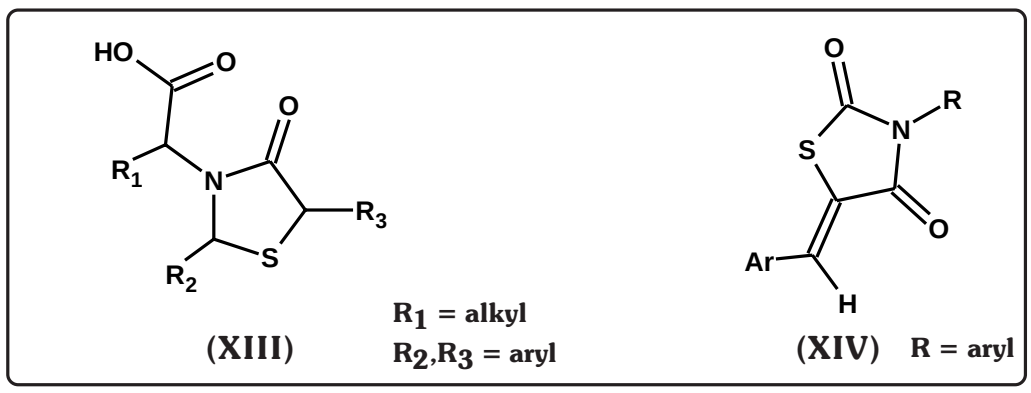


G. S. Gadaginamath et. al.[168] have prepared thiazolidinones as antimicrobial agent. R. S. Lodhi and co-workers[169] have synthesised and studied antimicrobial, antiinflammatory and analgesic property of 4-thiazolidinones and aryledene derivatives (XII)



(XII)

Pawar and co-workers[170] have reported synthesis and *in vitro* antibacterial activity of some 4-thiazolidinone derivatives. Richard E. Lee. et. al.[171] have synthesised & shown thiazolidinones (XIII) as inhibitors of *Mycobacterium tuberculosis.* 5-Arylidene-4-thiazolidinediones (XIV) have been found as aldose reductase inhibitors by Rosanna Maccari et. al.[172].



(XIII) (XIV)

CONTRIBUTION FROM OUR LABORATORY

Parikh et. al. have synthesised variety of 4-thiazolidinone derivatives bearing s-triazine[173], sulphonamido benzylamino[174], aryl substituted hydroxy and β,β-dichloro ethylamino phenyl moieties of 4-thiazolidinone ring system and have reported as potent antimicrobial agent.

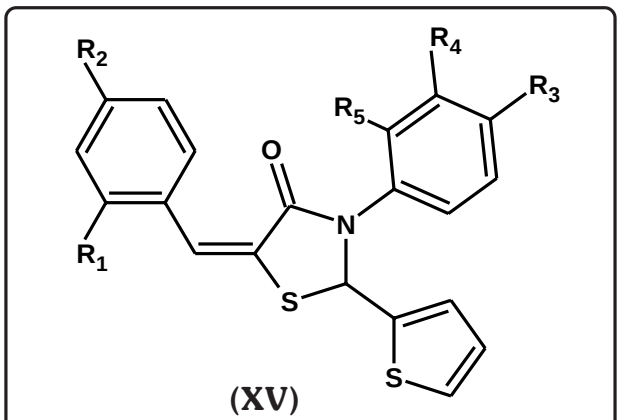
H. H. Parekh and co-workers have synthesised 4-thiazolidinones bearing acridine-9-yl[175], 6-hydroxy pyrimidine[176], 9-thiazolidinone ring system having antimicrobial activity.

D. G. Joshi & co-workers[177] have synthesised novel thiazolidinone derivatives as antitubercular agents. N. J. Datta & co-workers[178] have demonstated thiazolidinones as biologically active agent. A. H. Bapodara & co-workers[179] have prepared 4-thiazolidinones & showing their biological activity.

Multiple biological activities of 4-thiazolidinones have been discovered by S. B. Hirpara & co-workers[180].

Moreover, A. J. Baxi et. al.[181] have synthesised some new 4-thiazolidinones which shows anti-HIV, antitumor and antihypertensive activities. Recently, A. R. Parikh and co-workers[182] have assessed thiazolidinone derivatives bearing 7-methoxyquinoline nucleus for antimicrobial activity.

Siddique, Mohammad et. al.[183] have prepared substituted thiazolidinones and reported their antibacterial, antifungal, antithyroid and amoebicidal properties (XV).



(XV)

R_1 = OH, R_2, R_4, R_5 = H, R_3 = Me

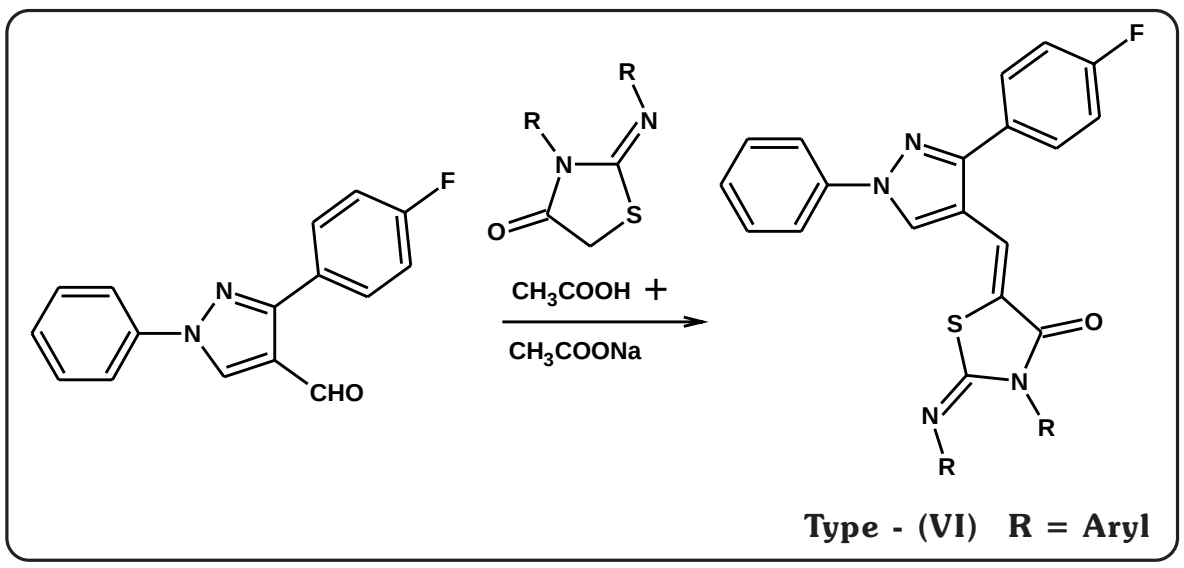
Considerable evidence has been accumulated to demonstrate the wide applications of thiazolidinone derivatives. In view of these findings, it appeared of interest to synthesise newer thiazolidinone derivatives with better potency.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-[1,'N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYL-METHINO]-4-THIAZOLIDINONES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYL METHINO]-4-THIAZOLIDINONES

Recently much interest has been foucused on the synthesis and biodynamic activities of arylidene and it is a good synthon for various heterocyclic rings. With a view to obtaining compounds having better therapeutic activities, we have synthesised 2-arylimino-3-N-aryl-5-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazol methino)-4-thiazolidinones by the condensation of pyrazole aldehyde with various thiazolidinone derivatives.

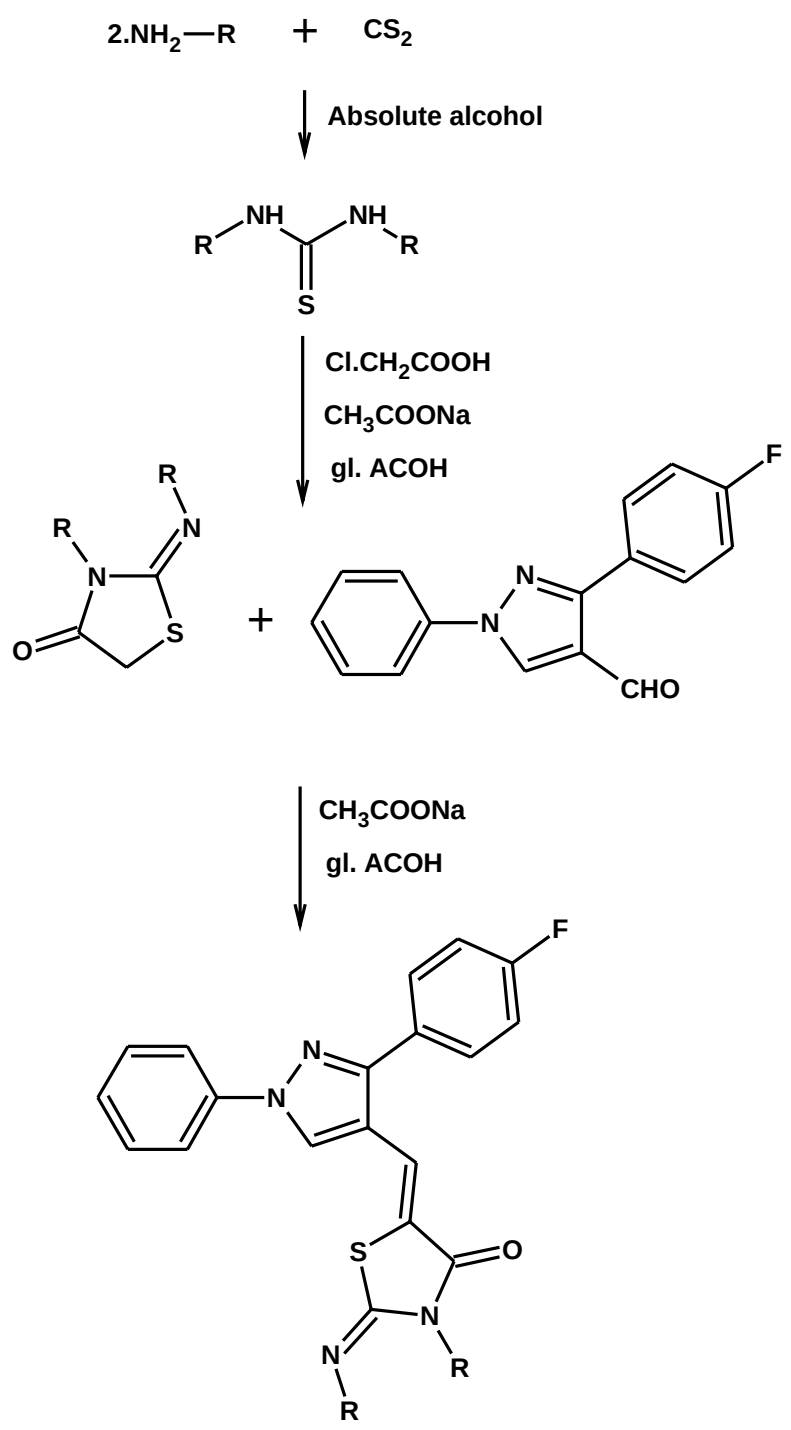


The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

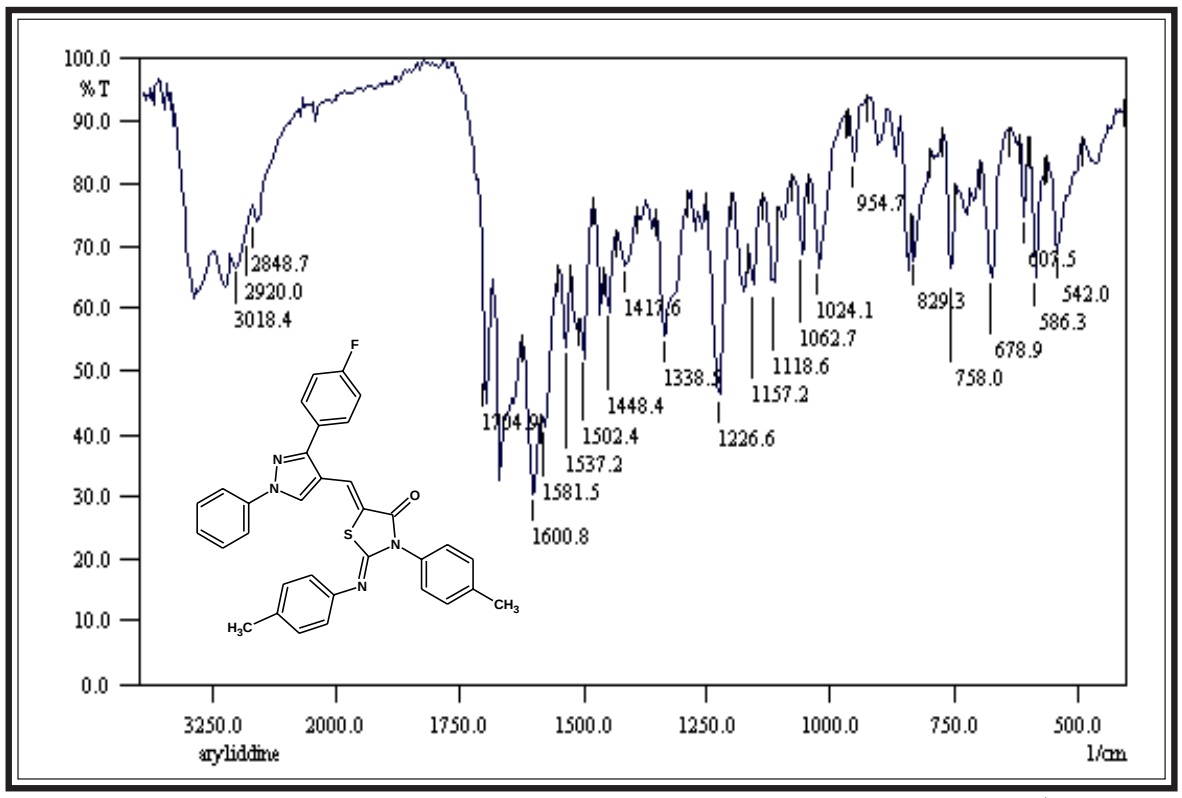
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME



Type - (VI) **R = Aryl**

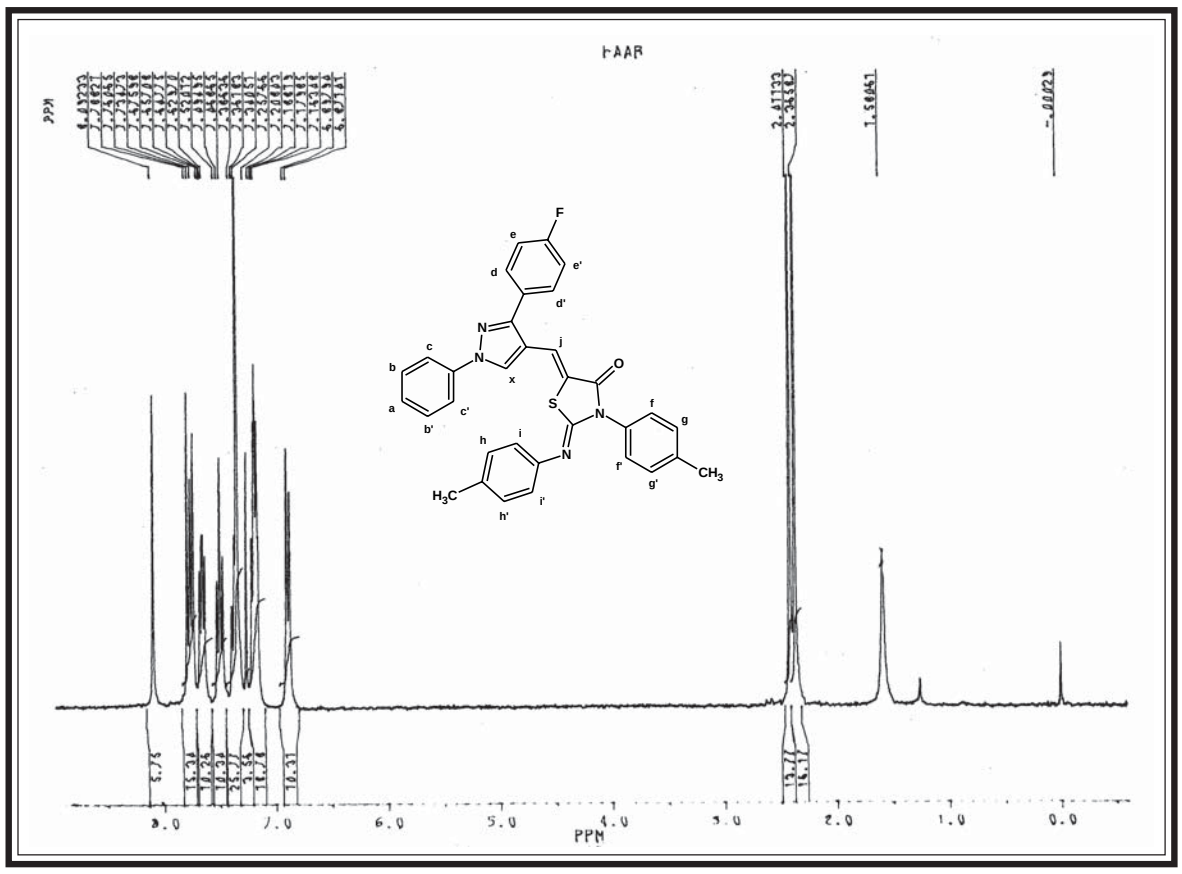
IR SPECTRAL STUDY OF 2-(p-TOLYLIMINO)-3,N-(p-TOLYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYL METHINO)-4-THIAZOLIDINONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2920	2975–2920	426
$-CH_3$	C – H str. (sym.)	2848	2880–2830	"
	C – H def. (asym.)	1446	1470–1435	"
	C – H def. (sym.)	1338	1385–1330	"
Aromatic	C – H str.	3018	3080–3050	427
	C – H i.p. (def.)	1118	1125–1090	"
		1062	1070–1000	"
	C – H o.o.p (def.)	829	835–810	"
Pyrazole	C = N str.	1600	1650–1600	428
ring	C = C str.	1537	1585–1480	"
	C – N str.	1226	1350–1200	"
	C – F str.	758	750–700	"
Thiazolidinone	C = O str.	1104	1760–1655	430
ring	C = N str.	1581	1650–1590	"
	C – S – C str.	678	700–600	"

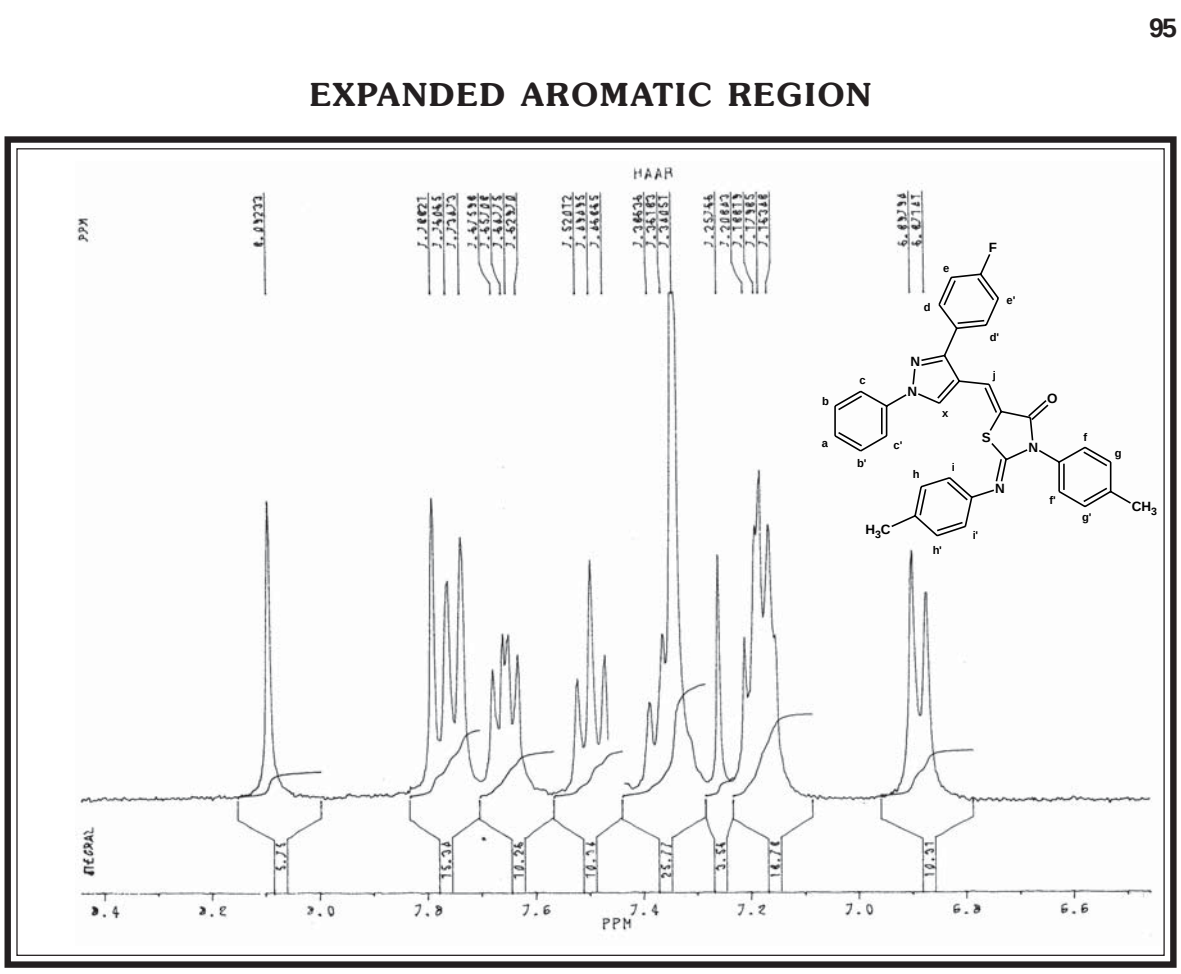
PMR SPECTRAL STUDY OF 2-(p-TOLYL) IMINO-3,-N-(p-TOLYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONES

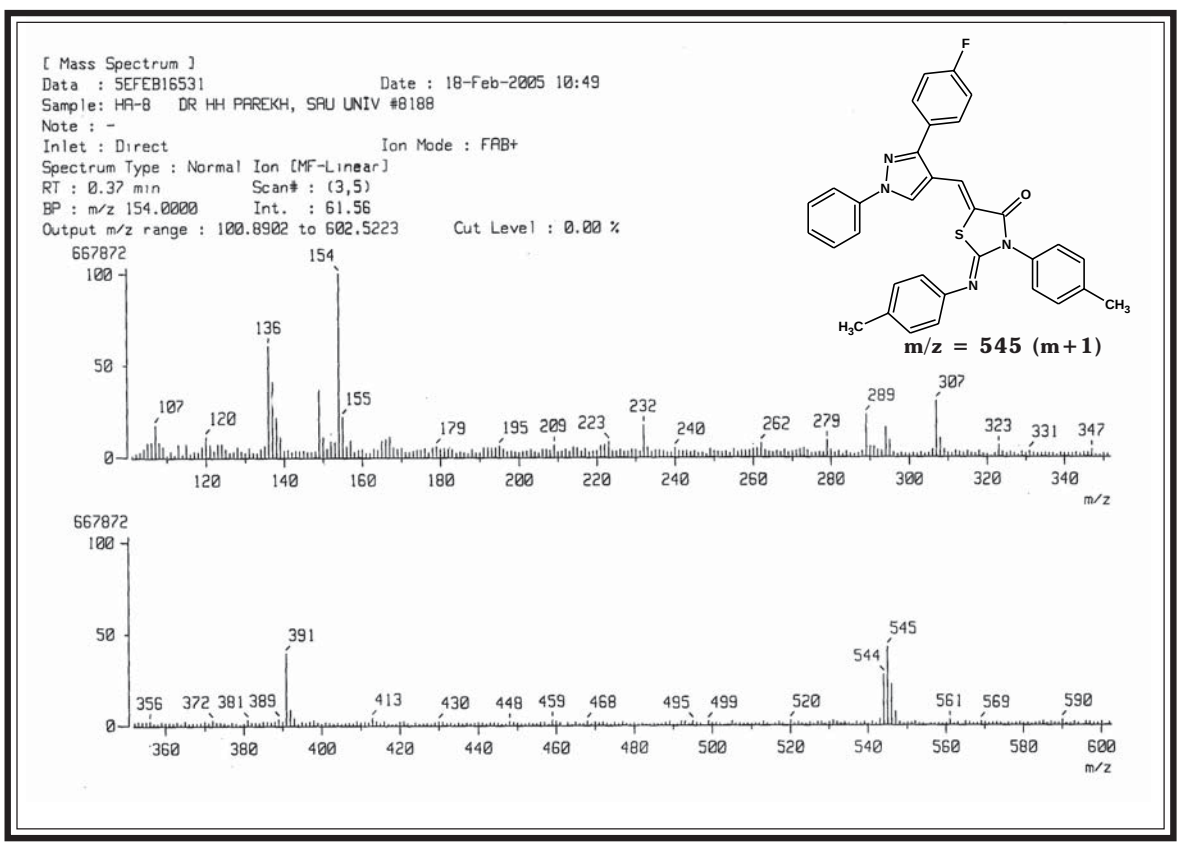


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	2.36	3H	singlet	Ar-CH_3	-
2.	2.47	3H	singlet	Ar-CH_3	-
3.	6.87-6.89	2H	doublet	Ar-Hgg'	Jgf=7.8
4.	7.76-7.20	4H	quartet	Ar-Hii' + Hdd'	-
5.	7.34-7.36	5H	triplet	Ar-Hff'+Hhh'+Ha	-
6.	7.46-7.52	2H	triplet	Ar-Hbb'	-
7.	7.62-7.67	2H	quartet	Ar-Hcc'	-
8.	7.73-7.78	3H	triplet	Ar-Hee'+CHj	Jed=7.8
9.	8.09	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYL METHINO)-4-THIAZOLIDINONES

[A] Preparation of N^1, N^3-Bis-p-tolyl thiourea[184]

In a round bottom flask, a mixture of p. toludine (0.2M), carbon disulphide (7ml, 0.01M) and absolute alcohol for 5-6 hrs. at temp 40°C. On completion of reaction, the excess of carbon disulphide and alcohol was removed by distillation. The product was treated with hydrochloric acid to remove excess of amine present and crude product was isolated and crystallised from ethanol. m.p. 193°C.

[B] Preparation of 2-Tolylimino-3-tolyl-5H-4-thiazolidinones[185]

A solution of N^1, N^3-bis-p-tolyl thiourea (0.01M) and chloroacetic acid (0.94g, 0.01M) in glacial acetic acid (15 ml) was refluxed with fused sodium acetate (1.25g, 0.015M) for 5 hrs. The reaction product was poured in water, kept overnight, crude product was isolated and crystallised from ethanol. m.p. 164°C.

[C] Preparation of 2-(p-Tolylimino)-3-(p-tolyl)-5-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolyl methino)-4-thiazolidinone

A mixture of 2-(p-tolylimino)-3-(p-tolyl)-5H-4-thiazolidinone (2.69g, 0.01M) 1,N-phenyl-3-p-fluorophenyl-4-formyl pyrazole (2.65g, 0.01M) and fused sodium acetate (1.25g, 0.015M) was refluxed in glacial acetic acid (15 ml) for 4-5hrs. at temp 120°C. cooled, poured into water and treated with ammonia to remove excess of glacial acetic acid. The product was isolated and crystallised from ethanol. yield 75% m.p. 230°C ($C_{33}H_{25}FN_4OS$: Found : C, 72.72%; H, 4.58%; N, 10.25% Requires : C, 72.77%; H, 4.63%; N, 10.29%).

Similarly other substituted thiazolidinones have been prepared. The physical data are recorded in Table No. 6.

[D] Therapeutic activity of 2-Arylimino-3,N-aryl-5-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolylmethino)-4-thiazolidinones

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No.6.

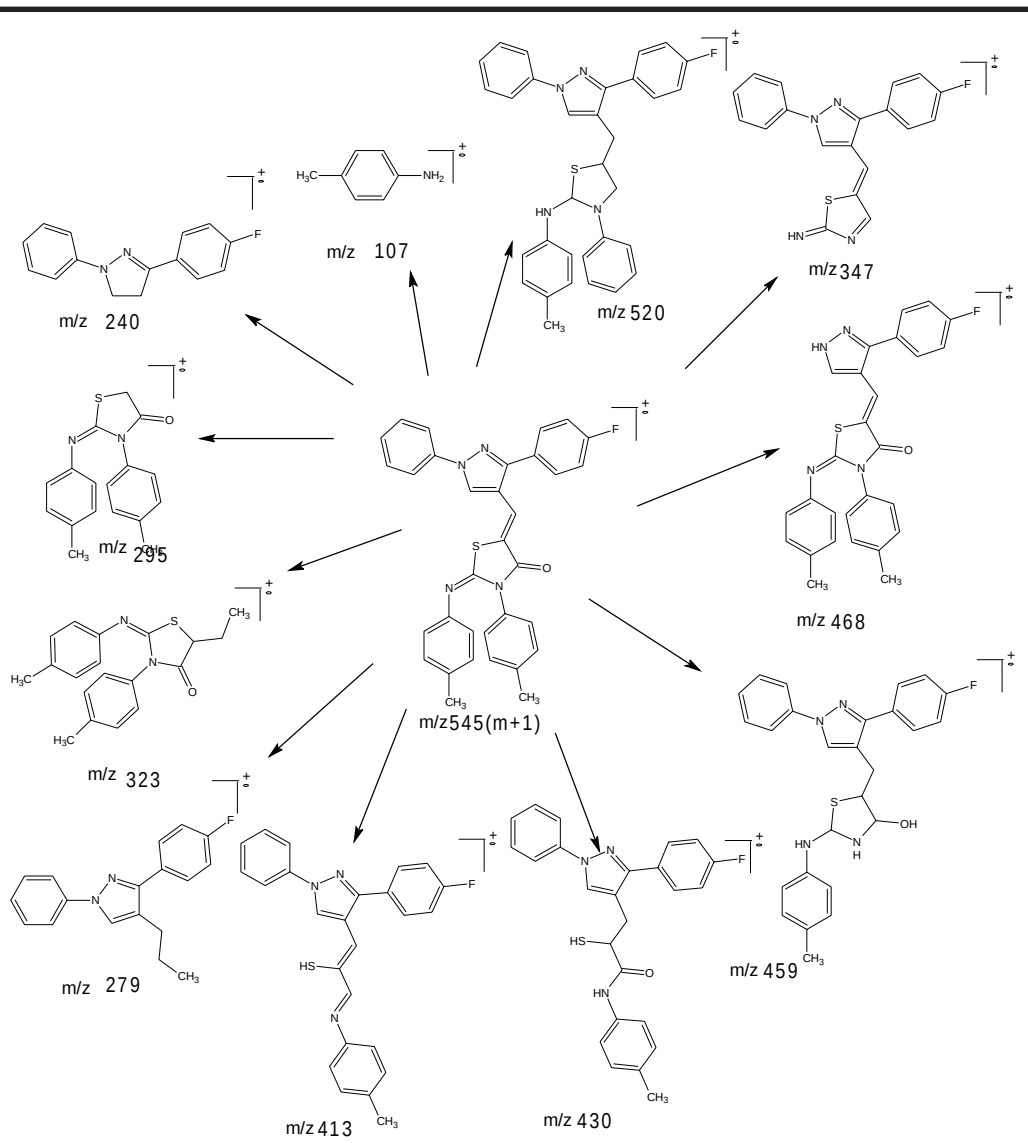
The antitubercular screening of the compounds of type(VI) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 6a.

TABLE NO. 6 : PHYSICAL CONSTANTS OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYL METHINO]-4-THIAZOLIDINONES

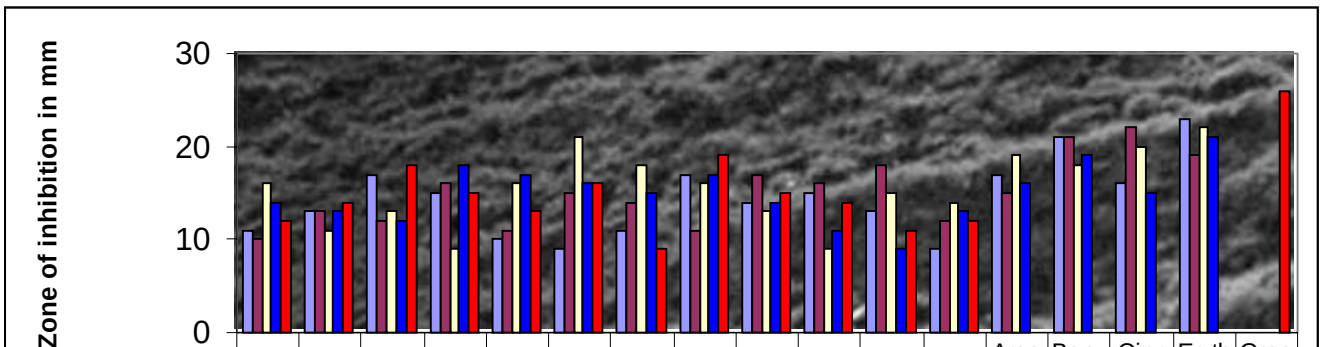
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
6a	C_6H_5-	$C_{32}H_{21}FN_4OS$	516	238	0.56	68	10.85	10.79
6b	4-OCH_3-C_6H_4-	$C_{33}H_{25}FN_4O_3S$	576	208	0.51	69	9.72	9.66
6c	4-CH_3-C_6H_4-	$C_{33}H_{25}FN_4OS$	544	230	0.53	75	10.29	10.25
6d	4-Cl-C_6H_4-	$C_{31}H_{19}Cl_2FN_4OS$	585	211	0.64	71	9.57	9.51
6e	4-F-C_6H_4-	$C_{31}H_{19}F_3N_4OS$	552	220	0.58	70	10.14	10.09
6f	3-Cl,4-F-C_6H_3-	$C_{31}H_{17}Cl_2F_3N_4OS$	621	218	0.41	75	9.02	8.97
6g	3-NO_2-C_6H_4-	$C_{31}H_{19}FN_6O_5S$	606	214	0.72	66	13.83	13.78
6h	2-NO_2-C_6H_4-	$C_{31}H_{19}FN_6O_5S$	606	216	0.75	64	13.83	13.76
6i	3,4-$(Cl)_2$-C_6H_3-	$C_{31}H_{17}Cl_4FN_4OS$	654	201	0.65	74	8.86	8.80
6j	4-Br-C_6H_4-	$C_{31}H_{19}Br_2FN_4OS$	674	225	0.60	67	8.31	8.26
6k	2,4-$(CH_3)_2$-C_6H_3-	$C_{35}H_{29}FN_4OS$	572	208	0.71	69	9.78	9.71
6l	2,5-$(Cl)_2$-C_6H_3	$C_{31}H_{17}Cl_4FN_4OS$	654	234	0.42	71	8.56	8.49

*TLC Solvent System : Acetone : Benzene

2.5 : 7.5


m/z 545(m+1)
m/z 520
m/z 347
m/z 468
m/z 459
m/z 430
m/z 413
m/z 279
m/z 323
m/z 295
m/z 240
m/z 107

GRAPHYCAL CHART NO.6: **ANTIMICROBIAL ACTIVITY OF 2-ARYLIMINO-3,N-ARYL-5-[1'N-PHENYL-3'-p-FLUOROPHENYL-4'-AZOLYLMETHINO]-4-THIAZOLIDINONES**



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Amoxycillin	Benzoyl Peni	Ciprofloxacin	Erythromycin	Greseofulvi
B. cocous	11	13	17	15	10	9	11	17	14	15	13	9	17	21	16	23	0
B. subtillus	10	13	12	16	11	15	14	11	17	16	18	12	15	21	22	19	0
E. coli	16	11	13	9	16	21	18	16	13	9	15	14	19	18	20	22	0
P. vulgaris	14	13	12	18	17	16	15	17	14	11	9	13	16	19	15	21	0
A. niger	12	14	18	15	13	16	9	19	15	14	11	12	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of thiazolidinones (type-VI) revealed that compounds were mild to moderately active against Gram positive and Gram negative bacterial strains.

Maximum activity was displayed by compounds bearing R=4-methylphenyl and 2-nitrophenyl and 2,4-dimethyl phenyl against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus***. Other compounds were less active against these bacterial strains.

In case of Gram negative bacterail strains ***E. coli*** & ***P. vulgaris***, maximum activity was observed in compounds bearing R=3-chloro,4-fluorophenyl and significant activity was displayed by compounds bearing R=4-chlorophenyl and 3-nitrophenyl against these bacterial strains.

ANTIFUNGAL ACTIVITY

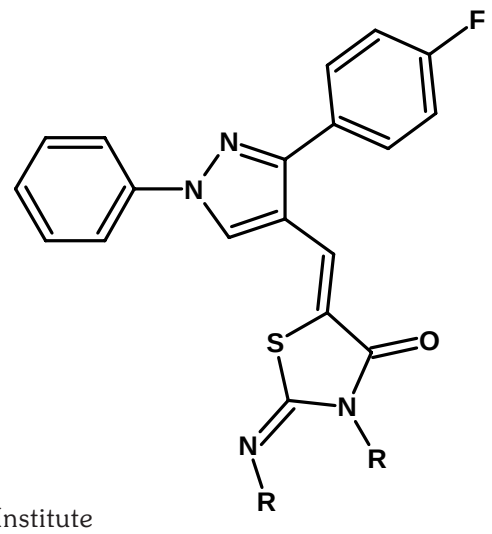
All the compounds are less active against fungal strain ***A. niger***.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds displayed antitubercular activity, ranging from 8 to 95% inhibition against ***Mycobacterium tuberculosis $H_{37}Rv$***. Compound with R = phenyl substituent exhibited maximum activity i.e. 95% inhibition.

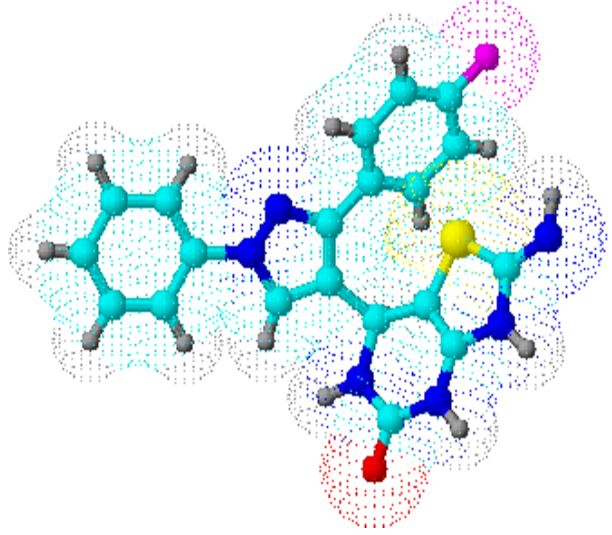
TABLE NO. 6a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC µg/ml*	*% Inhib*	*Activity*	*Comment*
295610	HCV-104	C_6H_5-	Alamar	$H_{37}Rv$	<6.25	95	+	MIC Rifampin = 0.25 µg/ml @ 98% Inhibition
295611	HCV-105	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	11	-	"
295612	HCV-106	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	14	-	"
295613	HCV-107	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	8	-	"
295614	HCV-108	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	16	-	"
295615	HCV-109	3-Cl,4-F-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	23	-	"
295616	HCV-110	3-NO_2- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20	-	"
295617	HCV-111	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295618	HCV-112	3/4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	9	-	"
295619	HCV-113	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295620	HCV-114	2/4-$(CH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	22	-	"
295621	HCV-115	2/5-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"

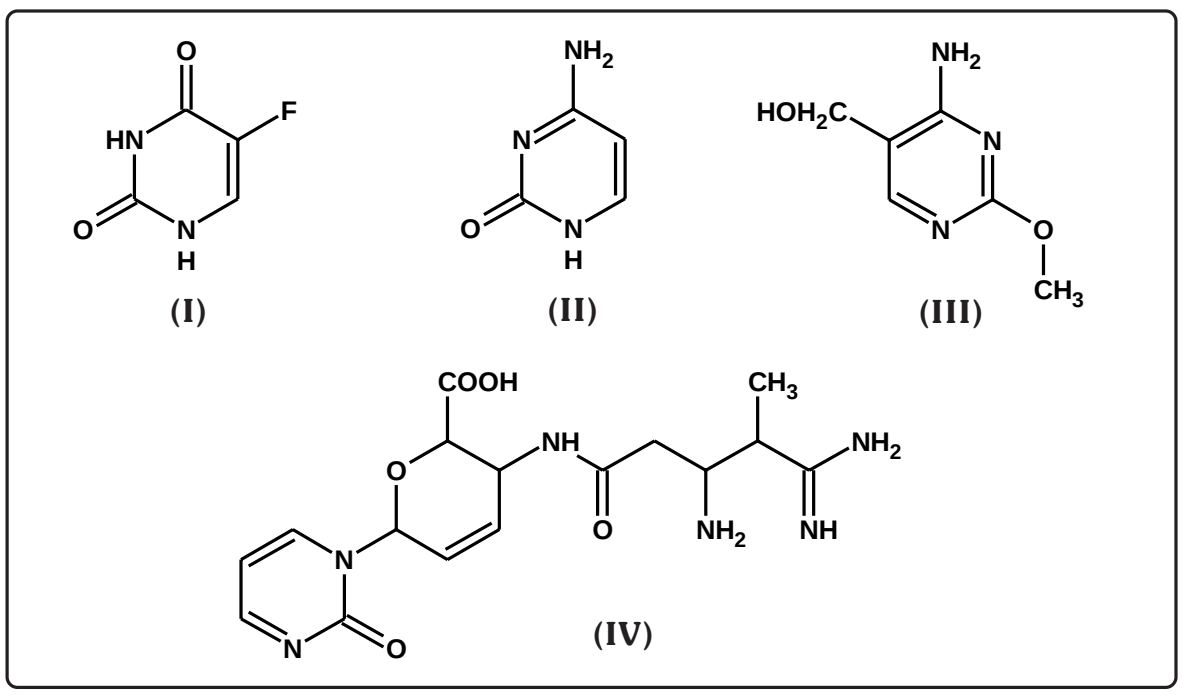


PART-IV
STUDIES ON PYRIMIDINONES

INTRODUCTION

Pyrimidine a heterocycle, containing nitrogen atoms at position 1 & 3 in six membered ring have been subject of substantial attention by synthetic & medicinal chemists because of the role of this heteroaromatic ring sustain in many biological system like nucleic acid (DNA, RNA) and co-enzymes. e.g. fluorouracil[186,187](I) which has been used in cancer treatment.

Some pyrimidines physiologically as well as pharmacologically important are as under. eg. cytosine (II), bedmethrin (III), blasticidine (IV).

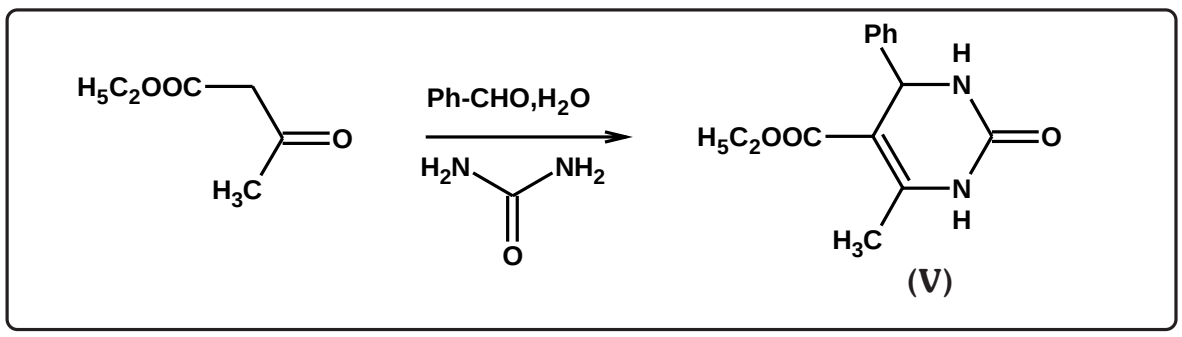


Synthetic pyrimidinone derivatives contribute much to the searchable literature of pyrimidinone derivatives in huge libraries owing to their wide applicability in different fields.

SYNTHESIS ASPECTS

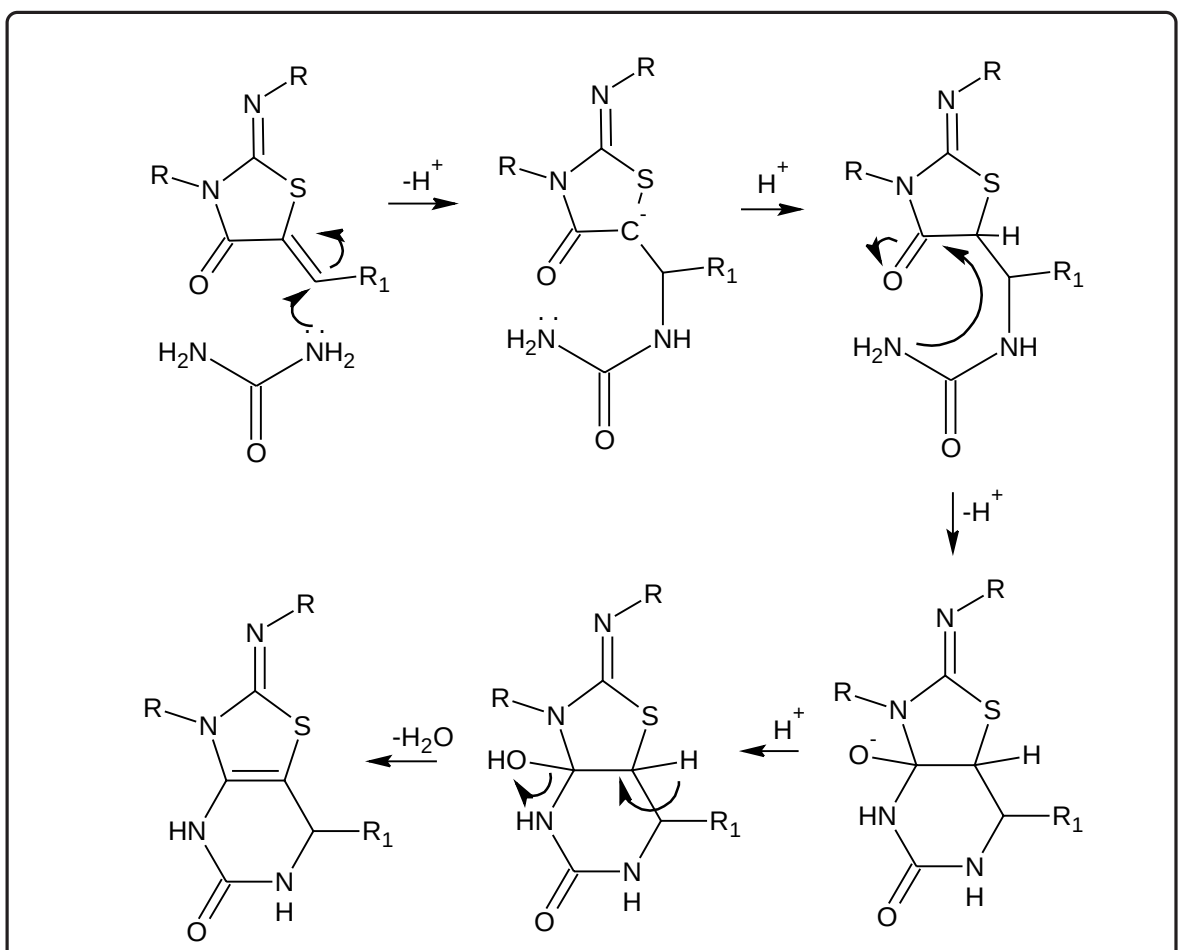
Different methods for the synthesis of pyrimidinones have been cited in the literature[188] are as under.

1. Bigi and co-worker[189] have synthesised pyrimidinones as shown below under solvent free condition.



(V)

MECHANISM



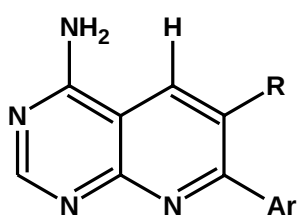
THERAPEUTIC IMPORTANCE

Pyrimidine derivatives have been proved to be of great importance in exhibiting and enhancing the biological activities such as

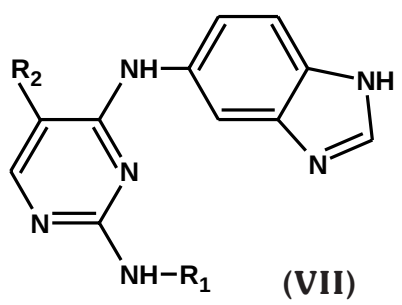
1. Antitumor[190]

2. Carcinostatic[191]
3. Antiinflammatory and anticonvulsant[192,193]
4. Antimalarial[194]
5. Antithyroid[195]
6. Anthelmintic[196]
7. AntiHIV[197,198]
8. Antilishmential[199]
9. Antiviral[200]
10. Antimicrobial[201]
11. Herbicidal[202]
12. Antagonists[203-205]

Moreover Norman M. H. *et.* al.[206] have synthesised pyrimidine derivatives as neuropeptide Y5 receptor antagonists. Azaryan *et.* al.[207] have synthesised pyrimidine diones as antitumor agent. Krivongov and co-workers[208] have synthesised pyrimidinone derivatives possessing immunotropic and antiinflammatory activity. Richard J. Perneu *et.* al.[209] have discovered pyrimidine derivatives (VI) as adenosine kinase inhibitors. Sharad Verma *et.* al.[210] have prepared pyrimidines (VII) as cyclin-dependent kinase inhibitors.

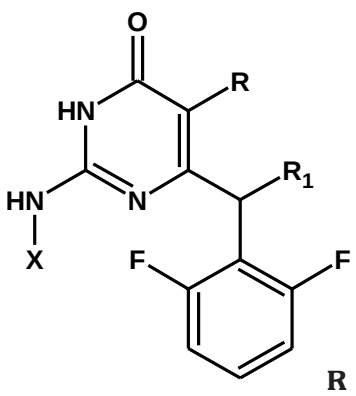


(VI) **R = Aryl / Alkyl**



(VII)

Timothy and co-workers[211] have suggested imidazolyl pyrimidinones as antiviral. Amjad Ali *et.* al.[212] have synthesised new fused pyrimidinones as antimicrobial agents. Antonello Mai *et.* al.[213] have synthesised pyrimidine derivative (VIII) as non-nucleoside reverse transcriptase inhibitors. Yari M. M. and co-workers[214] have investigated the pyrimidinone derivatives which possess calcium antagonist activity.

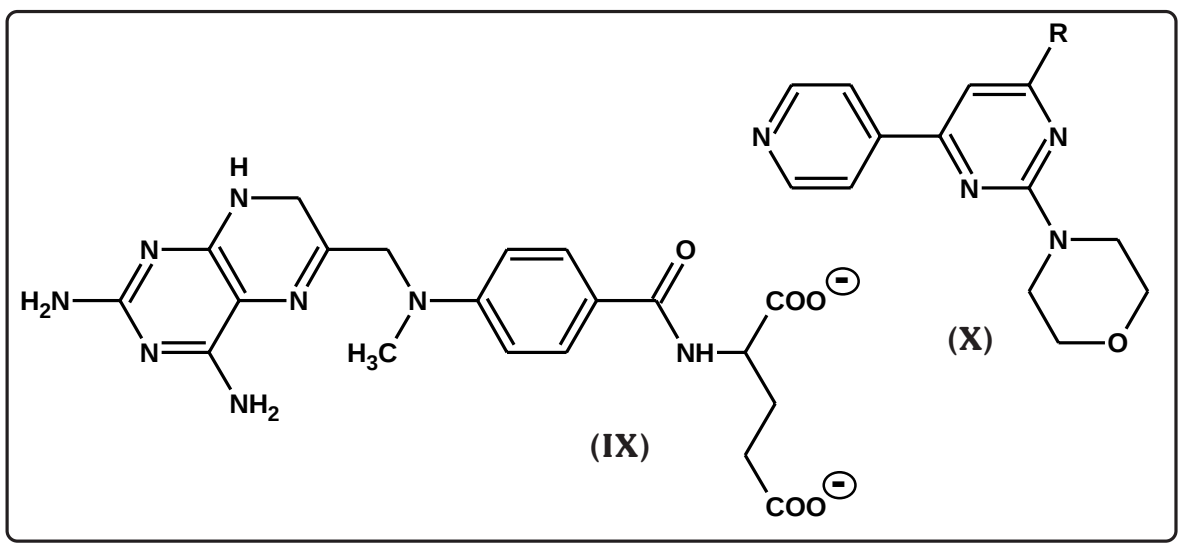


(VIII)

R = R_1 = H, Me

X = Alkyl / Aryl/ Aryl alkyl

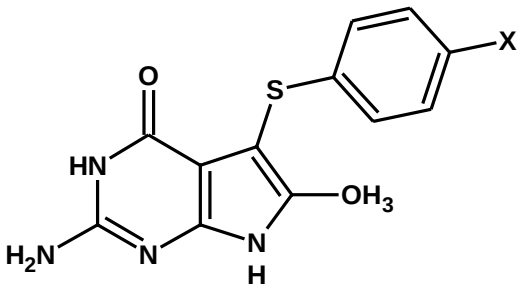
Baraldi P. G. et. al.[215] have discovered triazolo [1,5-c] pyrimidine derivatives as a new class of A_2A adenosine receptor antagonists. Balis F. M. et. al.[216] has investigated pyrimidines (IX) used in the treatment of leukamia in childhood. Amuti Kofies et. al.[217] have suggested pyrimidinones as herbicidal and plant growth regulators. K. Mogilaiah et. al.[218] have prepared spiropyrimidinones as antibacterial. Anu Agarwal co-workers[219] have discovered pyrimidines (X) as antimalarial agent.



(IX)

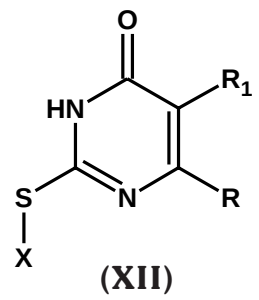
(X)

Aleem Gangiee & co-workers[220] have prepared pyrimidinone derivatives (XI) as non classical antitolate inhibitors of thymidylate synthase. Bruce M. A & co-workers[221] have prepared the dihydro pyrimidinones as NPY antagonist. Mona Mahran and co-workers[222] have reported pyrimidine derivatives as potent antimicrobial and antitumor agent. Viney Hather & A. K. Madan[223] have prepared pyrimidinones(XII) as anti-HIV agents.



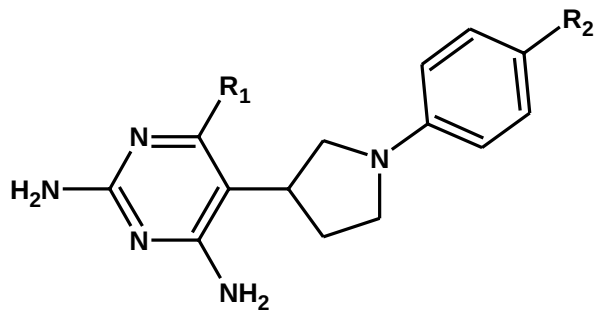
X = C, Cl, Br, CN, NO_2, CF_3, OCF_3

(XI)



(XII)

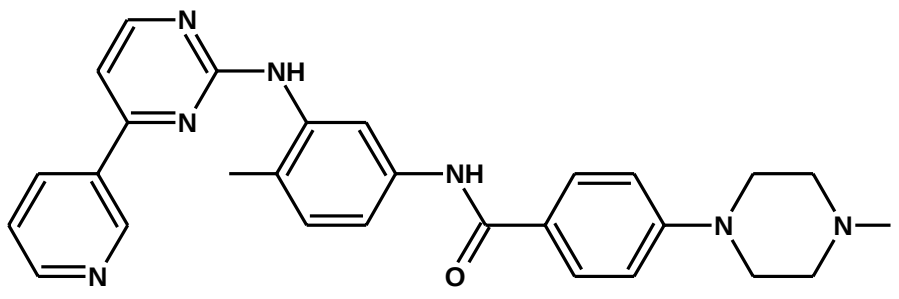
Tsann-Long Su et. al.[224] have reported pyrimidines (XIII) as antitumor agents. Recently, Michael Deininger & co-workers[225] have discovered pyrimidines (XIV) named (imatinib) as a therapeutic agent for chronic myloid leukemia. Saxena A. K. & co-workers[226] have prepared 2,6-disubstituted pyrimidinones as CNS agent. Barbuliene M. M. et. al.[227] have synthesised pyrimidinones as antiinflammatory agent.



(XIII)

R_1 = NH_2, OH

R_2 = H, Me, NO_2, CN, F, Cl, Br



(XIV)

Antitumor activity of new pyrimidinone of sesquiterpene lactones has been found by Angelina Quintero et. al.[228]. Patricia F. F. et. al.[229] have synthesised and screened for their leukocyte functions inhibitor activity. Dumas Jacques et. al.[230] have synthesised pyrimidinones and tested their hyperproliferative disorder activity.

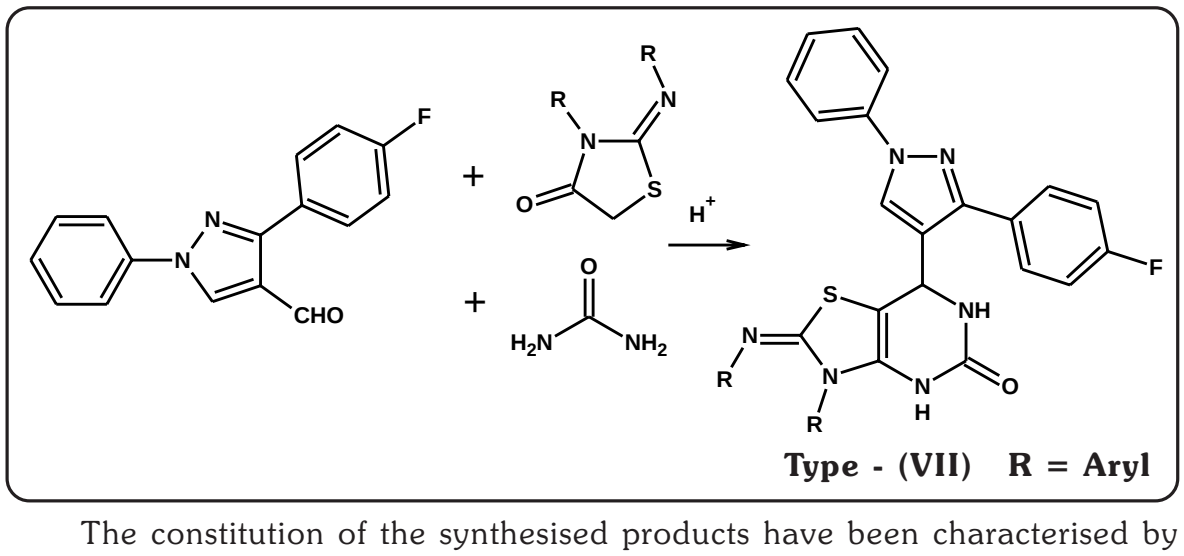
Thus, diverse biological activities have been encountered in compounds containing pyrimidinone ring system. To further assess the potential of such type of compounds, study of pyrimidinones have been undertaken as under.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDROTHIAZOLIDINO-[4,5-d]-PYRIMIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL),1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-d]-PYRIMIDINES

In the past years considerable evidence has been accumulated to demonstrate the efficiency of pyrimidinones. It was considered worthwhile to synthesise compounds bearing 2-arylimino-3-aryl-5-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolylmethino)-4-thiazolidinones of type (VII) which have been prepared by the condensation of 2-arylimino-3-aryl-5H-4-thiazolidinone, 1,N-phenyl-3-p-fluoro-phenyl-4-formyl-pyrazole and urea in presence of catalytic amount of conc. HCl as shown under.



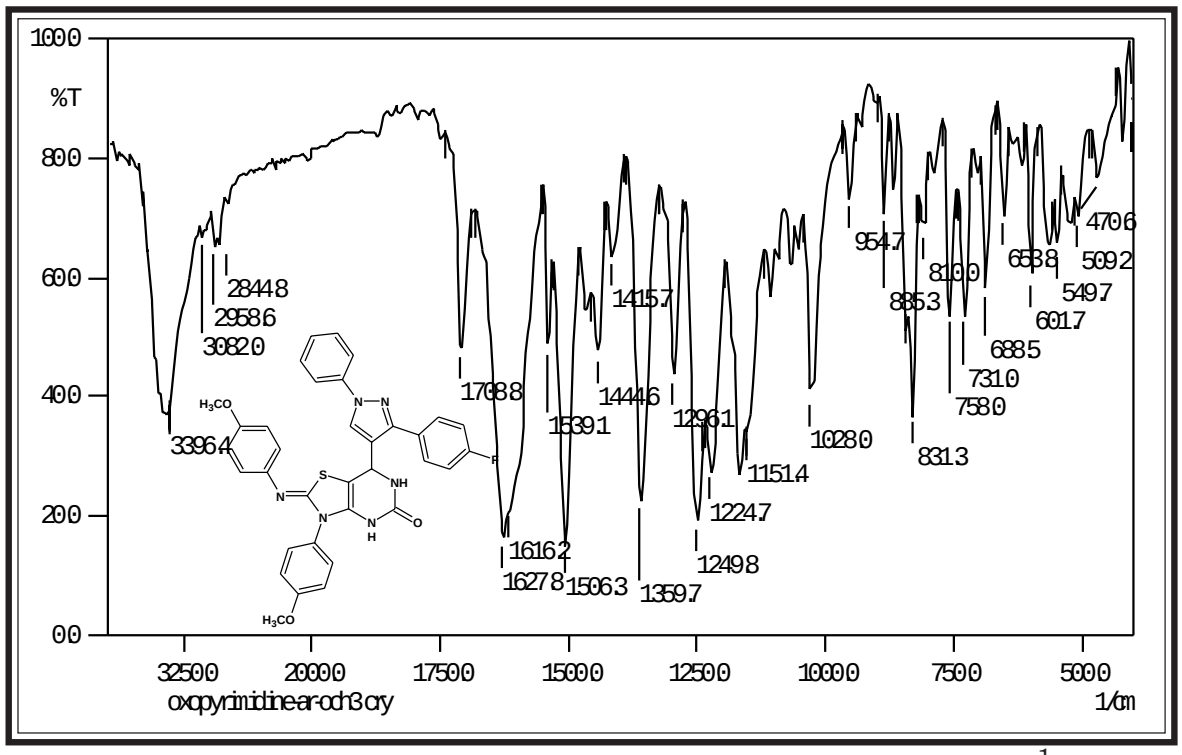
Type - (VII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at concentration of 6.25 μg/ml using Rifampin as standard drug.

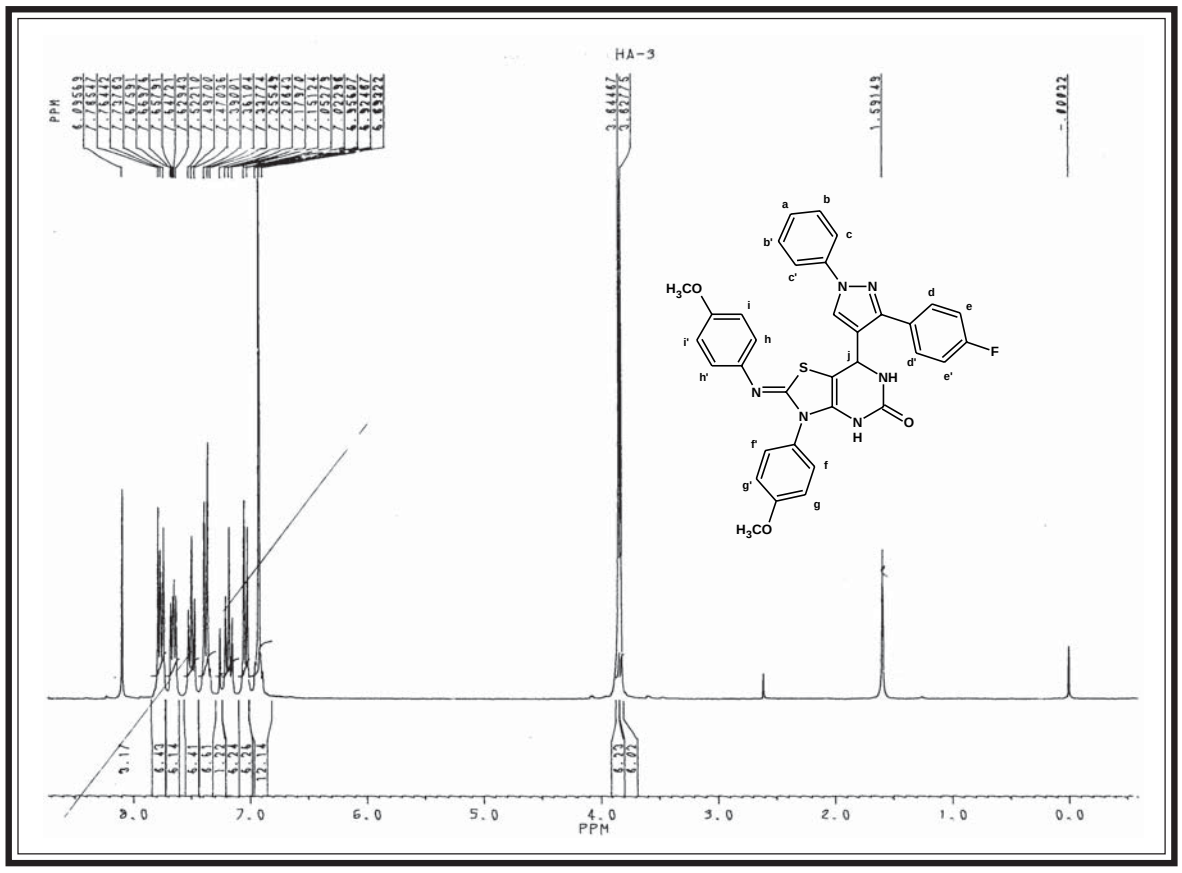
IR SPECTRAL STUDY OF 6-(p-ANISYLIMINO)-7,N-(p-ANISYL)-2-OXO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINON-[4,5-d]-PYRIMIDINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2958	2975–2950	426
$-CH_3$	C – H str. (sym.)	2844	2880–2840	"
	C – H def. (asym.)	1444	1470–1435	"
	C – H def. (sym.)	1359	1395–1370	"
Aromatic	C – H str.	3082	3090–3030	427
	C – H str.	1444	1520–1440	"
	C – H i.p. (def.)	1151	1125–1090	"
		1028	1070–1000	"
	C – H o.o.p (def.)	831	835–810	"
Pyrazole	C = N str.	1616	1610–1590	428
ring	C – N str.	1224	1230–1020	"
	C = C str.	1444	1585-1450	"
	C – F str.	758	760-710	"
Ether	C – O – C str. (asym.)	1249	1275–1200	"
Pyrimidine	C = O str.	1708	1750–1600	431
ring	N – H str.	3396	3500–3350	"
	C = N str.	1627	1650–1550	"
	C – S – C str.	758	800–700	"

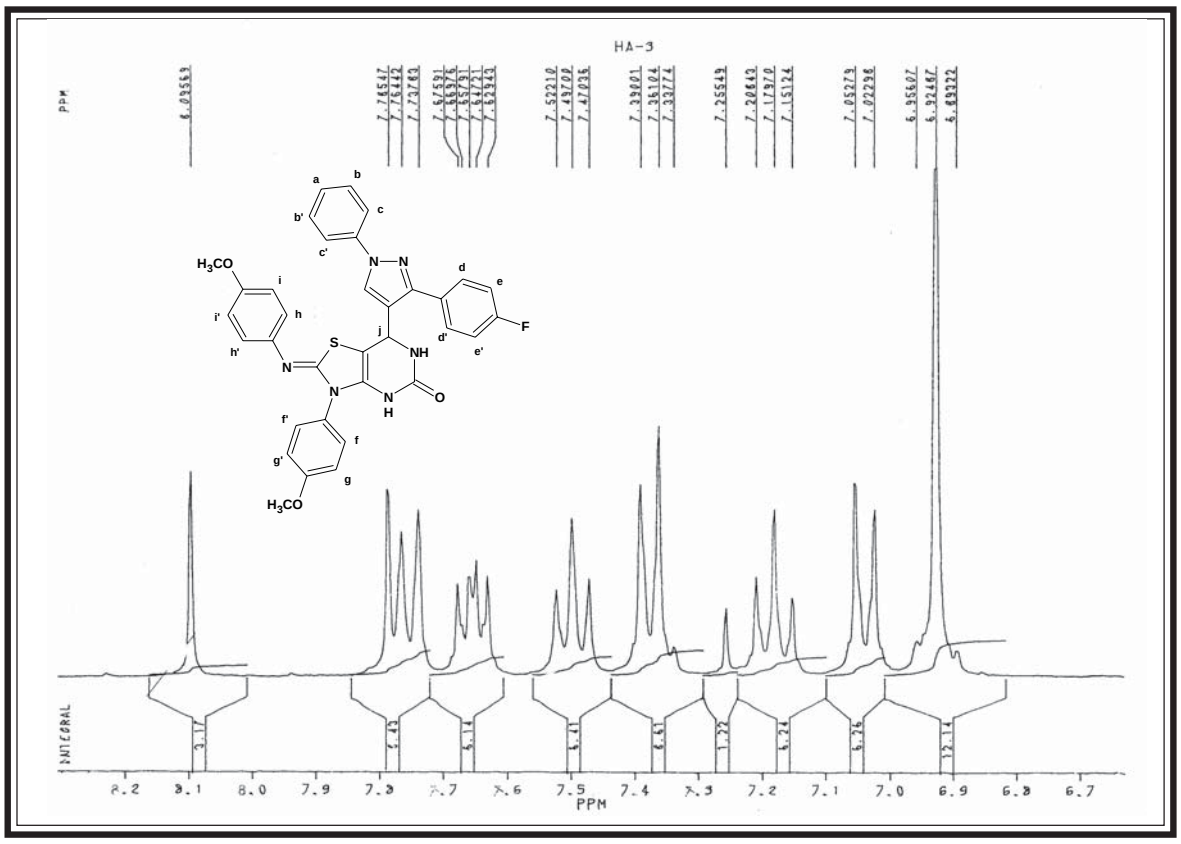
PMR SPECTRAL STUDY OF 6-(p-ANISYLIMINO)-7,N-(p-ANISYL)-2-OXO-4-[1',N-PHENYL-3'-P-FLUOROPHENYL PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5,d]-PYRIMIDINE

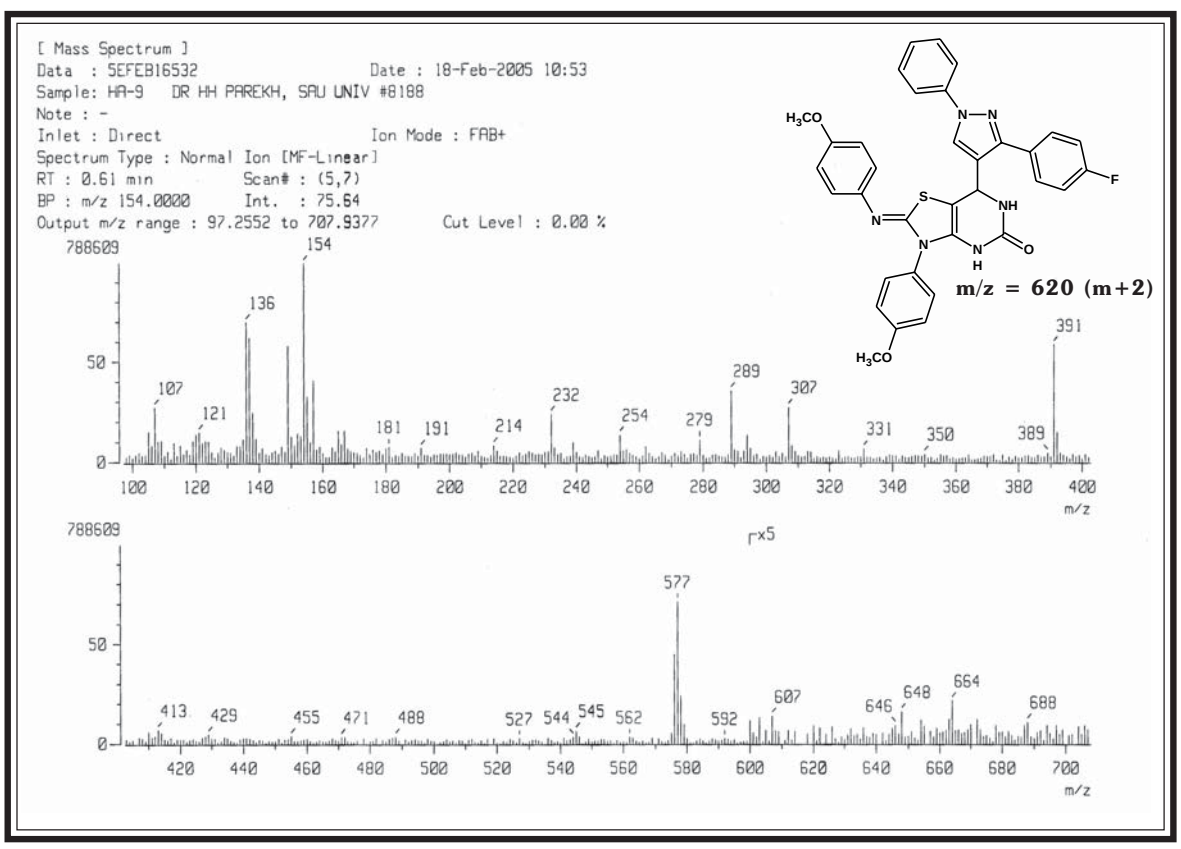


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1	3.82	3H	singlet	Ar-OCH_3	-
2.	3.84	3H	singlet	Ar-OCH_3	-
3.	6.89-6.95	4H	singlet	Ar-Hgg' + Hjj'	-
4.	7.02-7.05	2H	doublet	Ar-Hdd'	Jde=8.9
5.	7.15-7.20	2H	triplet	Ar-Hbb'	-
6.	7.33-7.39	3H	doublet	Ar-Hhh' + Ha	Jhi=8.7
7.	7.47-7.52	2H	triplet	Ar-Hff'	-
8.	7.62-7.67	2H	quartet	Ar-Hcc'	-
9.	7.73-7.78	3H	triplet	Ar-Hee' + CHj	Jed=8.1
10.	8.09	1H	singlet	CHx	

EXPANDED AROMATIC REGION





EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDRO-THIAZOLIDINO-[4,5-d]-PYRIMIDINES

[A] Preparation of 2-p-anisylimino-3-anisyl-5H-4-thiazolidinone

See, Part-III, Section-I (A)

[B] Preparation of 6-(p-anisylimino)-7,N-(p-anisyl)-2-oxo-4-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-1,2,3,4 tetrahydro thiazolidino-[4,5-d]-pyrimidine

A mixture of 2-(p-anisylimino)-3-(p-anisyl)-5H-4-thiazolidinone (3.28g, 0.01M) 1,N-phenyl-3-p-fluorophenyl-4-formyl-pyrazole (2.65g, 0.01M) and urea (0.60g, 0.01M) were taken in methanol (30 ml) and a catalytic amount of con. HCl (0.5 ml) was added. The reaction mixture was refluxed for 5 hrs, at temp 60°-70°C cooled, poured into water. The product was isolated and crystallised from methanol-DMF. Yield 70%, m.p. 222°C ($C_{34}H_{27}FN_6O_3S$, Found : C, 65.92%; H, 4.33%; N, 13.50% Requires : C, 66.01%; H,4.40%; N, 13.58%;).

Similarly other pyrimidines were prepared. The physical data are recorded in Table No. 7.

[C] Therapeutical activity of 6-Arylimino-7,N-aryl-2-oxo-4-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-1,2,3,4-tetrahydro-thiazolidino-(4,5-d)-pyrimidines

Antimicrobial testing was carried out as described in Part-I, Section-I(D). The zone of inhibition of the test solution are recorded in Graphical Chart No.7.

Antitubercular screening of the compounds of type(VII) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 7a.

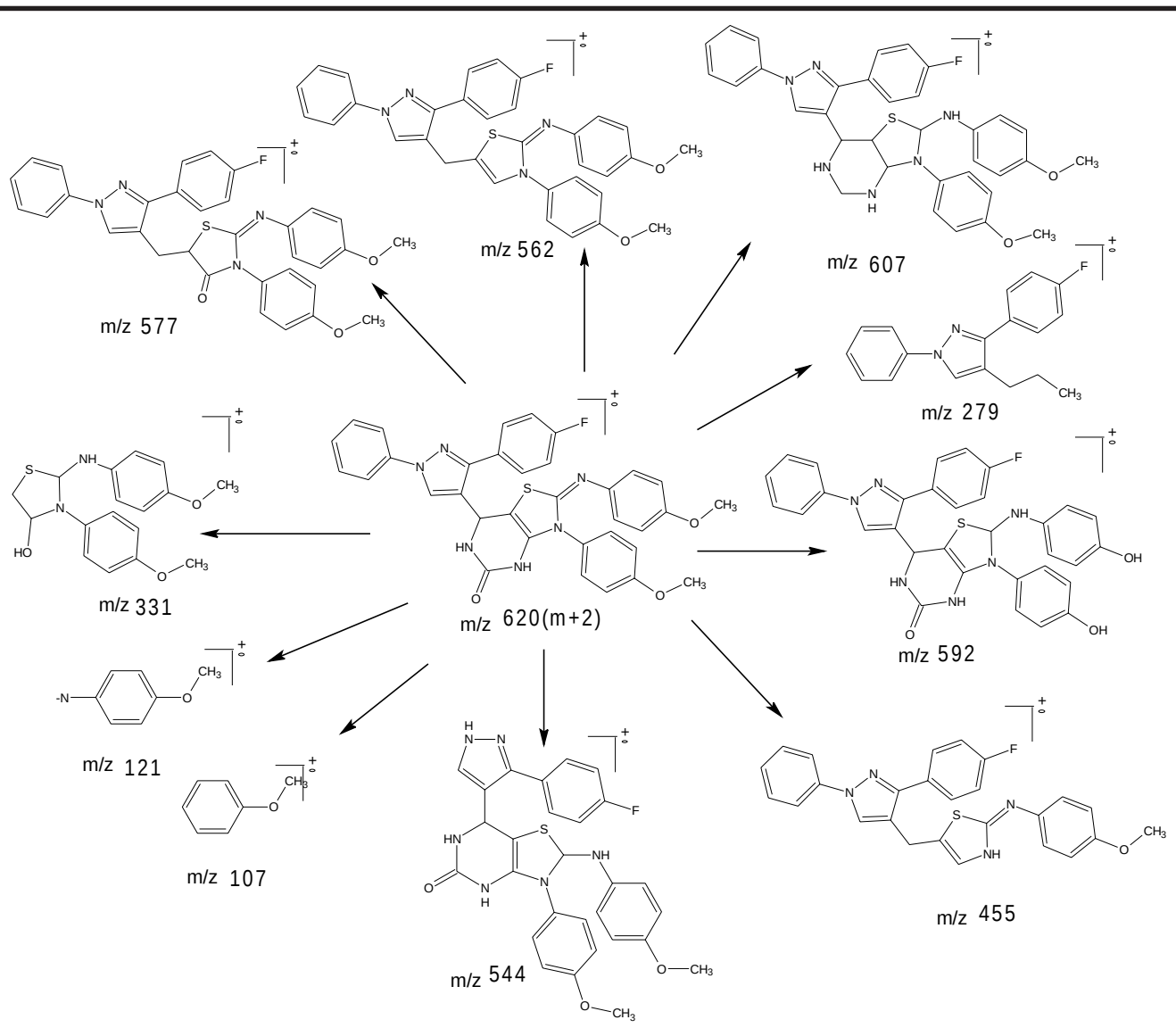
TABLE NO. 7 : PHYSICAL CONSTANTS OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1'-N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-1,2,3,4-TETRAHYDRO-THIAZOLIDINO [4,5,-d]-PYRIMIDINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
7a	C_6H_5-	$C_{32}H_{23}FN_6OS$	558	194	0.57	60	15.04	14.91
7b	4-OCH_3-C_6H_4-	$C_{34}H_{27}FN_6O_3S$	618	222	0.67	70	13.58	13.50
7c	4-CH_3-C_6H_4-	$C_{34}H_{27}FN_6OS$	576	207	0.49	64	14.32	14.21
7d	4-Cl-C_6H_4-	$C_{32}H_{21}Cl_2FN_6OS$	627	186	0.52	65	13.39	13.26
7e	4-F-C_6H_4-	$C_{32}H_{21}F_3N_6OS$	594	178	0.53	69	14.13	14.03
7f	3-Cl,4-F-C_6H_3-	$C_{32}H_{19}Cl_2F_3N_6OS$	663	167	0.51	59	12.67	12.53
7g	3-NO_2-C_6H_4-	$C_{32}H_{21}FN_8O_5S$	648	201	0.59	60	17.28	17.10
7h	2-NO_2-C_6H_4-	$C_{32}H_{21}FN_8O_5S$	648	236	0.60	62	17.28	17.13
7i	3,4-$(Cl)_2$-C_6H_3-	$C_{33}H_{19}Cl_4FN_6OS$	696	190	0.56	67	12.07	11.97
7j	4-Br-C_6H_4-	$C_{32}H_{21}Br_2FN_6OS$	716	229	0.61	63	11.73	11.64
7k	2,4-$(CH_3)_2$-C_6H_3-	$C_{36}H_{31}FN_6OS$	614	163	0.64	60	13.67	13.57
7l	2,5-$(Cl)_2$-C_6H_3-	$C_{32}H_{19}Cl_4FN_6OS$	696	172	0.66	71	12.07	11.94

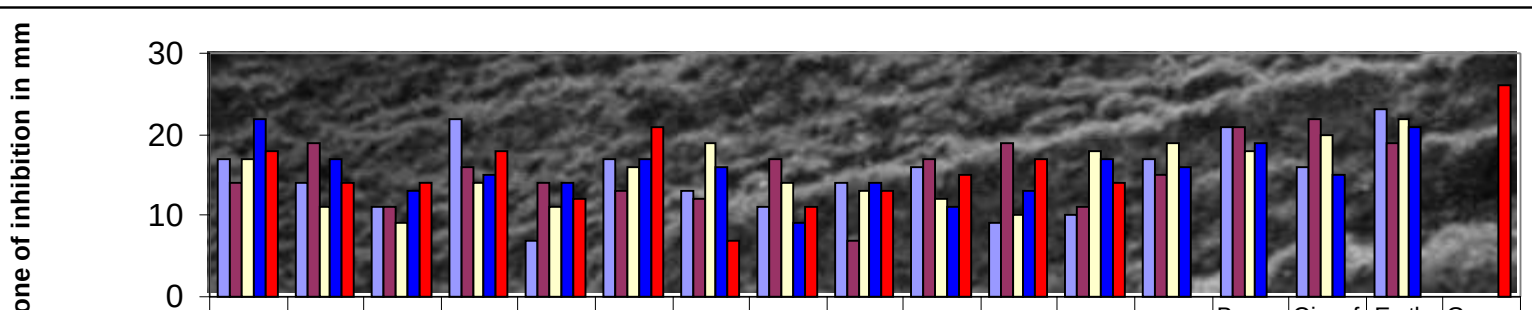
*TLC Solvent System : Acetone : Benzene

2 : 8 (7a-7d, 7i-7k)

3 : 7 (7e-7h, 7l)


m/z 577
m/z 562
m/z 607
m/z 279
m/z 331
m/z 620(m+2)
m/z 592
m/z 121
m/z 107
m/z 544
m/z 455

GRAPHYCAL CHART NO.7: **ANTIMICROBIAL ACTIVITY OF 6-ARYLIMINO-7,N- ARYL-2-OXO-4- [1'N-PHE NYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL] 1,2,3,4-TETRAHYDRO-THIAZOLIDINO(4,5-d)-PYRIMIDINES.**



	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	7k	7l	Amoxycillin	Benzoyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	17	14	11	22	7	17	13	11	14	16	9	10	17	21	16	23	0
B. subtillus	14	19	11	16	14	13	12	17	7	17	19	11	15	21	22	19	0
E. coli	17	11	9	14	11	16	19	14	13	12	10	18	19	18	20	22	0
P. vulgaris	22	17	13	15	14	17	16	9	14	11	13	17	16	19	15	21	0
A. niger	18	14	14	18	12	21	7	11	13	15	17	14	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of pyrimidinones (type-VII) revealed that most of the compounds were able to inhibit the growth of Gram positive and Gram negative bacterial strains.

Maximum activity was observed in compound bearing R=4-chlorophenyl and significant activity was displayed by compounds bearing R=phenyl, 4-methoxyphenyl, 4-bromophenyl & 2,4-dimethylphenyl against Gram positive bacterial strains ***B. cocous*** and ***B. subtillus***. Other compounds were less active against these bacterial strains.

In case of Gram negative bacterial strains highest activity was displayed by compounds bearing R=phenyl and 3-nitrophenyl and significant activity was observed in compounds bearing R=4-chlorophenyl and 2,5-dichlorophenyl against ***E.coli*** & ***P. vulgaris***.

ANTIFUNGAL ACTIVITY

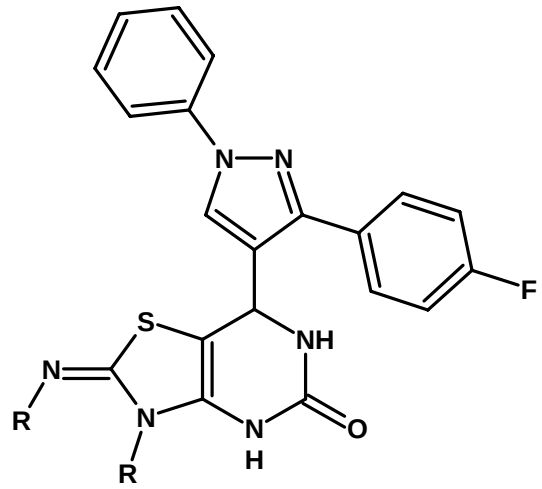
Most of the compounds were inactive against fungal strain ***A. niger***. Maximum activity was observed in compounds bearing R=3-chloro, 4-fluorophenyl.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds displayed mild antitubercular activity against ***Mycobacterium tuberculosis $H_{37}Rv$*** i.e. 1 to 39% inhibition.

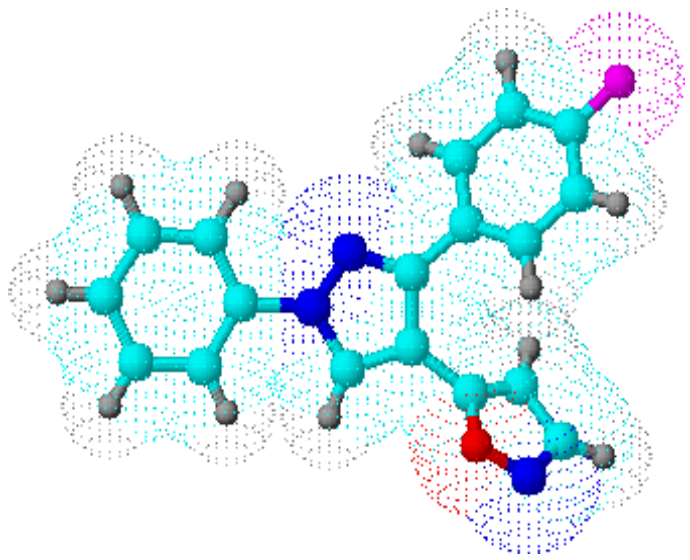
TABLE NO. 7a : PRIMARY ASSAY *OF* ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC µg/ml*	*% Inhib*	*Activity*	*Comment*
295622	HCV-116	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	13	-	MIC Rifampin = 0.25 µg/ml @ 98% Inhibition
295623	HCV-117	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	26	-	"
295624	HCV-118	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20	-	"
295625	HCV-119	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12	-	"
295626	HCV-120	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	18	-	"
295627	HCV-121	3-Cl,4-F-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	39	-	"
295628	HCV-122	3-NO_2- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295629	HCV-123	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295630	HCV-124	3/4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	1	-	"
295631	HCV-125	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20	-	"
295632	HCV-126	2/4-$(CH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	33	-	"
295633	HCV-127	2/5-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	22	-	"

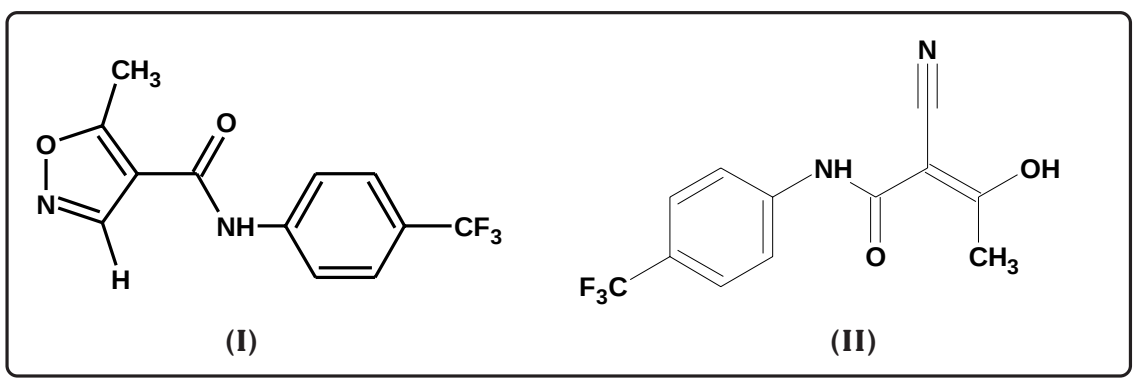


PART-V
STUDIES ON ISOXAZOLES

INTRODUCTION

Isoxazole derivatives have recently been intensively investigated. They are interesting objects from the synthetic, as well as physiochemical, biological and theoretical points of view.

Leflunomide (I) is an isoxazole derivative with antiinflammatory and immunomodulating activity. It is also considered a prodrug, it is rapidlly metabolized ***in vitro*** to its active metabolite A771726(II) via opening the isoxazole ring. Most of the immunomodulating activity appears to be related to A771726. It is also used for the management of the signs and symptoms of rheumatoid arthritis and to retard structural damage associated with the disease in adults with moderate to active rheumatoid arthritis[231-235].

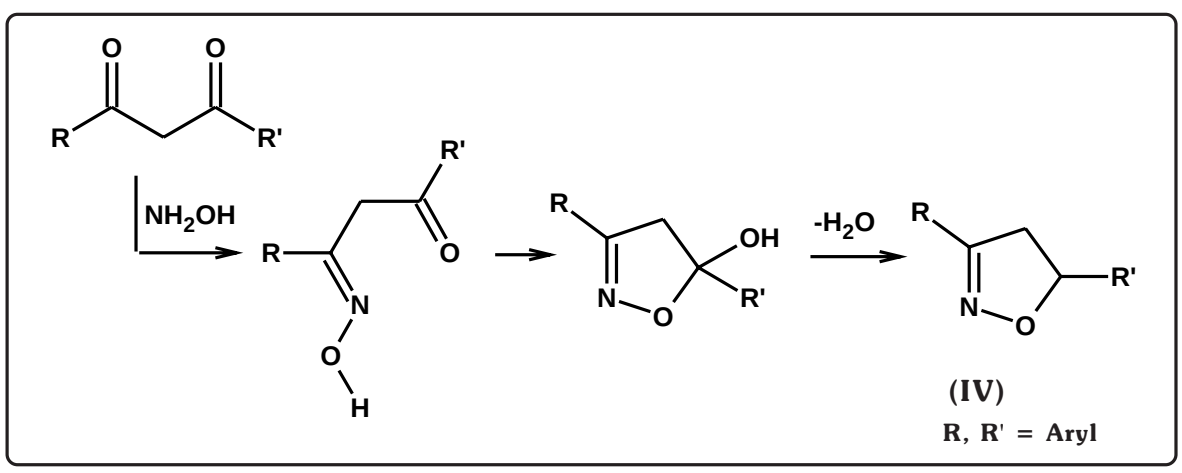


SYNTHETIC ASPECTS

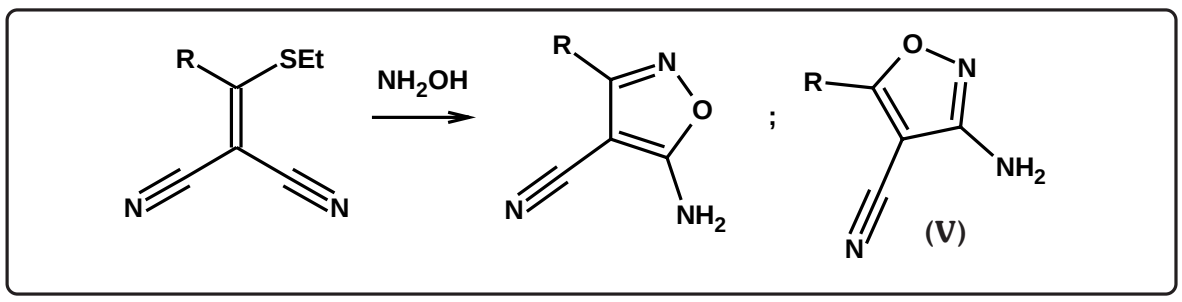
Isoxazoles may be prepared by the reaction between hydroxylamine and α,β-dicarbonyl compounds. The reaction proceeds via the formation of oxime, which possibly undergoes cyclization.

Isoxazoles can be prepared by various methods. They are described as under.

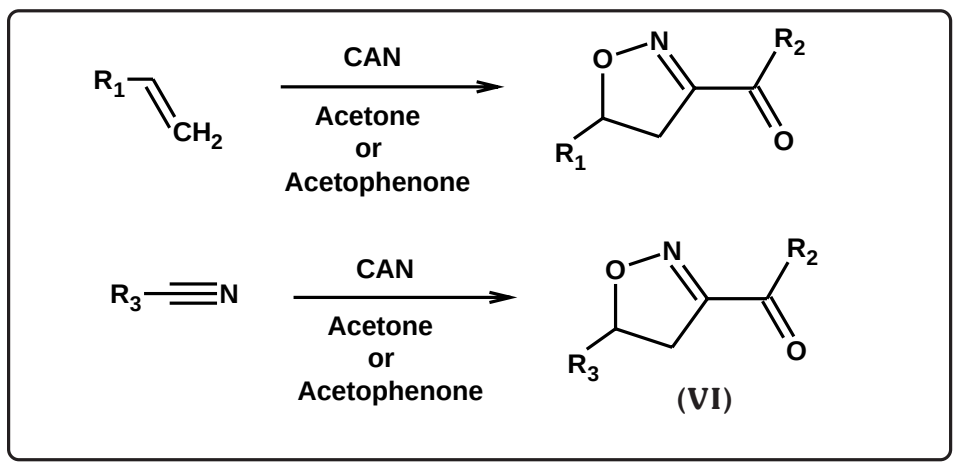
1. Fanshawe and Crawley[236] prepared isoxazoles (IV) from chalcones, hydroxylamine hydrochloride and KOH in methanol.



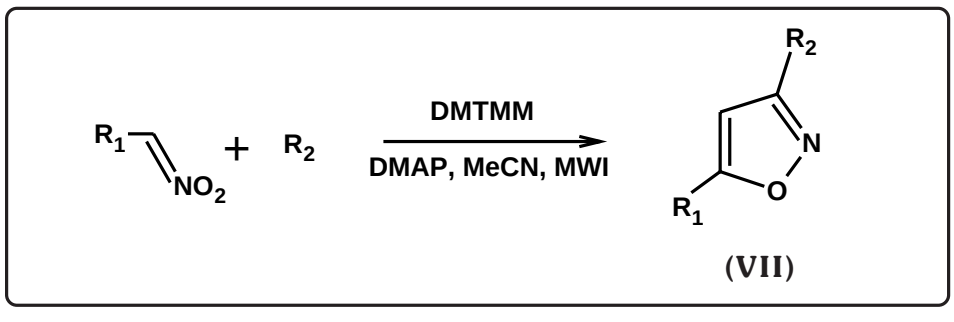
2. Lyubov N. Sobenina et. al.[237] have synthsised isoxazole (V) by the reaction of 2,2-dicyano-1-ethylthioethyl derivatives with hydroxylamine in methanol.



3. By the reaction of alkenes or alkynes with ammonium cerium (IV) nitrate in acetone or acetophenone under reflux gave corresponding isoxazole derivative[238].



4. By the reaction of nitroalkanes with alkynes using microwave irradiation, using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) and DMAP as catalyst[239].



(VII)

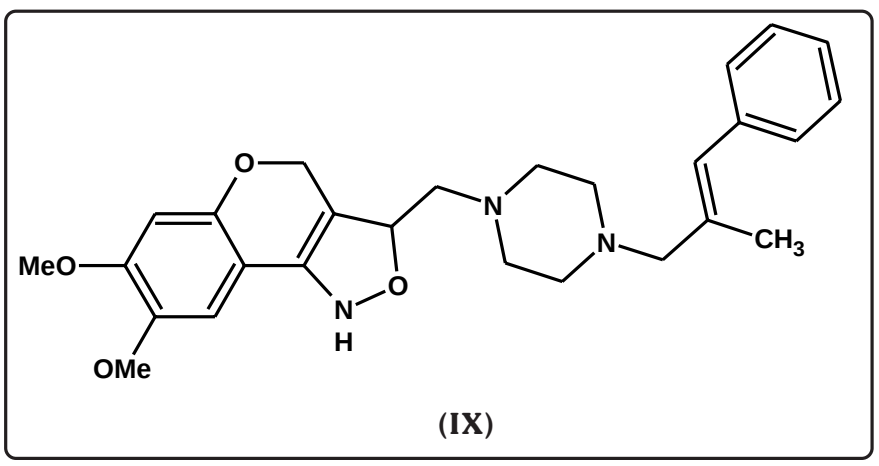
THERAPEUTIC IMPORTANCE

Isoxazoles possess wide therapeutic activities.

1. Antiinflammatory[240-242]
2. Anticonvulsant[243,244]
3. Muscle relaxant[245,246]
4. Antipyretic[247]
5. Antibacterial[248,249]
6. Antiviral[250]
7. Anticholestermic[251]
8. Diabetic[252]
9. Herbicidal[253]
10. Antitumor[254]
11. Antileukemiac[255]
12. Nematocidal[256]

Masui et. al.[257] have prepared isoxazoles having pesticidal activity. Some excellent herbicidal results are obtained by Reddy et. al.[258]. Moreover isoxazoles found to possess remarkable anxiolytic and antihypertensive effect, reported by Nyitrai et. al.[259]. Aicher et. al.[260] cited some isoxazole derivatives possessing hypoglycemic agents. R. Ulrich et. al.[261] have synthesised isoxazole derivatives and reported their adrenergic antagonist activity.

Andres J I et. al.[262] have discovered a new series of centrally active tricyclic isoxazoles (IX) combining serotinin (5-HT)-reuptake inhibition with alpha(2)-adreno-ceptor blocking activity which is described as potential antidepressant.

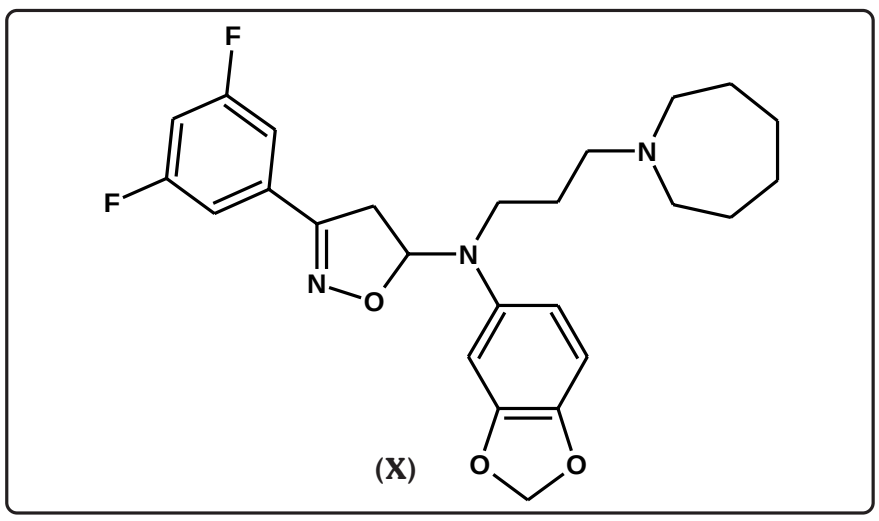


(IX)

Hongwu He et. al.[263] have prepared Methyl-1-(5-methyl-isoxazole-3-oxy-acetoxy)alkyl-methyl phosphinates and tested for their plant growth regulatory activity.

Chaumin, Wang, Yunfeng et. al.[264] have discovered isoxazoles as herbicidal. Wu, ahengde et. al.[265] have synthesised isoxazole derivatives as endothelin activity modulators. Corolin and co-workers[266] have studied isoxazoles, which have been used for the clinical trials of asthama.

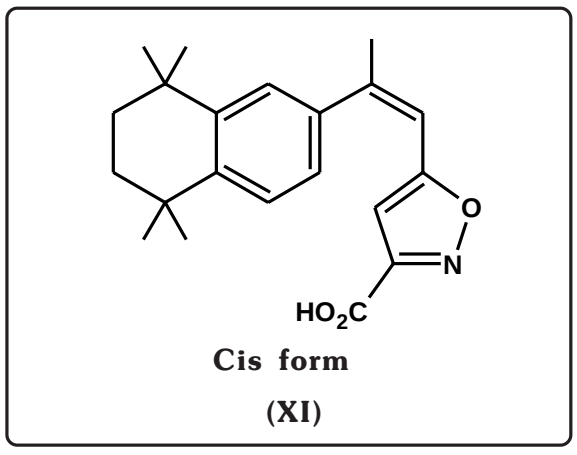
Nanterment P G et. al.[267] have discovered a non peptidic isoxazole derivative (X) reported as antagonist of the human platelet thrombin receptor (PAR_1).



(X)

Romero J. R.[268] has discovered a isoxazole derivative named pleconaril as a antipicornaviral agent and promising drug for the treatment of enteroviral and rhinoviral infections.

Daniele Simoni and Manlio Tolomeo[269] have designed a novel g1 phase targetting isoxazole derivative (XI) which is structurally related to arotinoids, was found to possess interesting apoptotic activity.



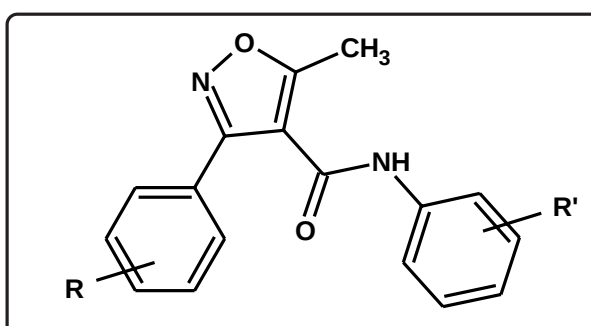
Cis form

(XI)

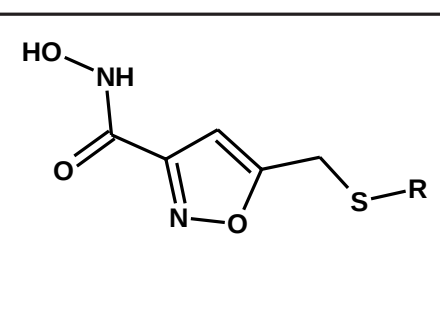
CONTRIBUTION FROM OUR LABORATORY

R. C. Khunt, A. R. Parikh and co-workers[270] have prepared isoxazole derivatives which possess antimicrobial activity. Rajeev Doshi & co-workers[271] have discovered isoxazoles as a new class of potential antitubercular agents. Ketan Hirpara et. al.[272] have synthesised isoxazoles as antitubercular agents. A. V. Dobaria et. al.[273] have described the isoxazole derivatives and their use as antimicrobial agents. B. P. Kansagar et. al.[274] have demonstrated various isoxazole and testd their antimicrobial activity.

Recently, Bo Lui et. al.[275] have discovered novel isoxazole carboxamides (XII) as growth hormone secretagogue receptor (GHS-R) antagonists. Patrizia Cali et. al.[276] have synthesised & reported isoxazoles (XIII) as peptide deformylase inhibitors and potential antibacterial agent.

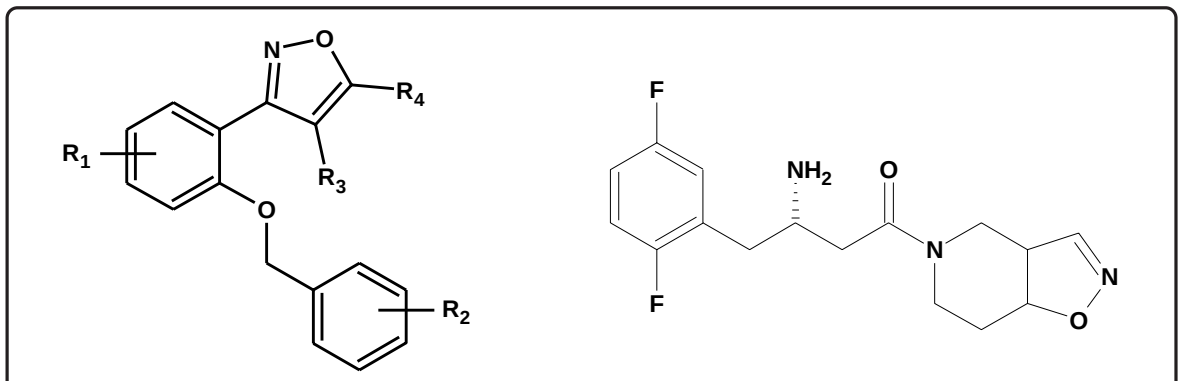


(XII) **R, R' = Aryl/Alkyl**



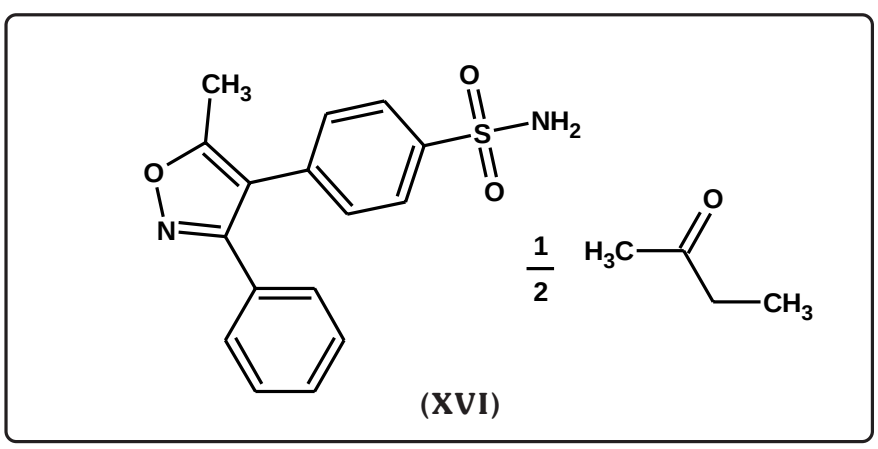
(XIII) **R= Alkyl/Aryl**

Isoxazole derivatives (XIV) as a novel class of activators for chloride conductance in the cystic fibrosis transmembrane conductance regulatorn protein has been identified by Robert Sammelson et. al.[277]. Wallace T. Ashton et. al.[278] have found isoxazole (XV) as dipeptidyl peptidase IV inhibitors.



(XIV) R_1, R_2 = Alkyl; R_3, R_4 = Alkyl/Aryl **(XV)**

H. S. Yathirajan et. al.[279] have synthesised novel 4-(5-methyl-3-phenylisoxazole-4-yl) benzene-sulfonamide ethylmethyl ketone (XVI) used as non-sterodial intiinflammatory drug. Makarov V. A. and co-workers[280] have discovered the novel [(biphenyloxy)propyl]isoxazole derivatives for inhibition of human rhinovirus-2 and coxsackievirus B_3 replication.



(XVI)

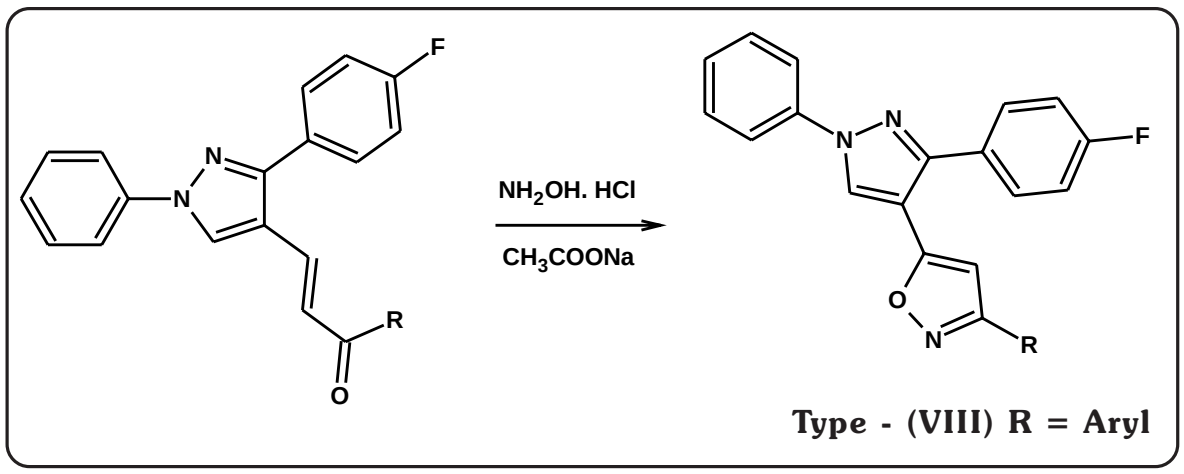
With an intension of preparing the compounds possessing better therapeutic activity, we have undertaken the preparation of isoxazoles bearing pyrazole moiety which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1'N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-ISOXAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-ISOXAZOLES

With a view to getting better drug potency, isoxazole derivatives of type (VIII) have been prepared by the condensation of chalcones of type (I) with hydroxylamine hydrochloride in presence of sodium acetate in glacial acetic acid. The chalcones were synthesised by the condensation of 1,N-phenyl-3-p-fluorophenyl-4-formyl pyrazole with different aromatic ketones.



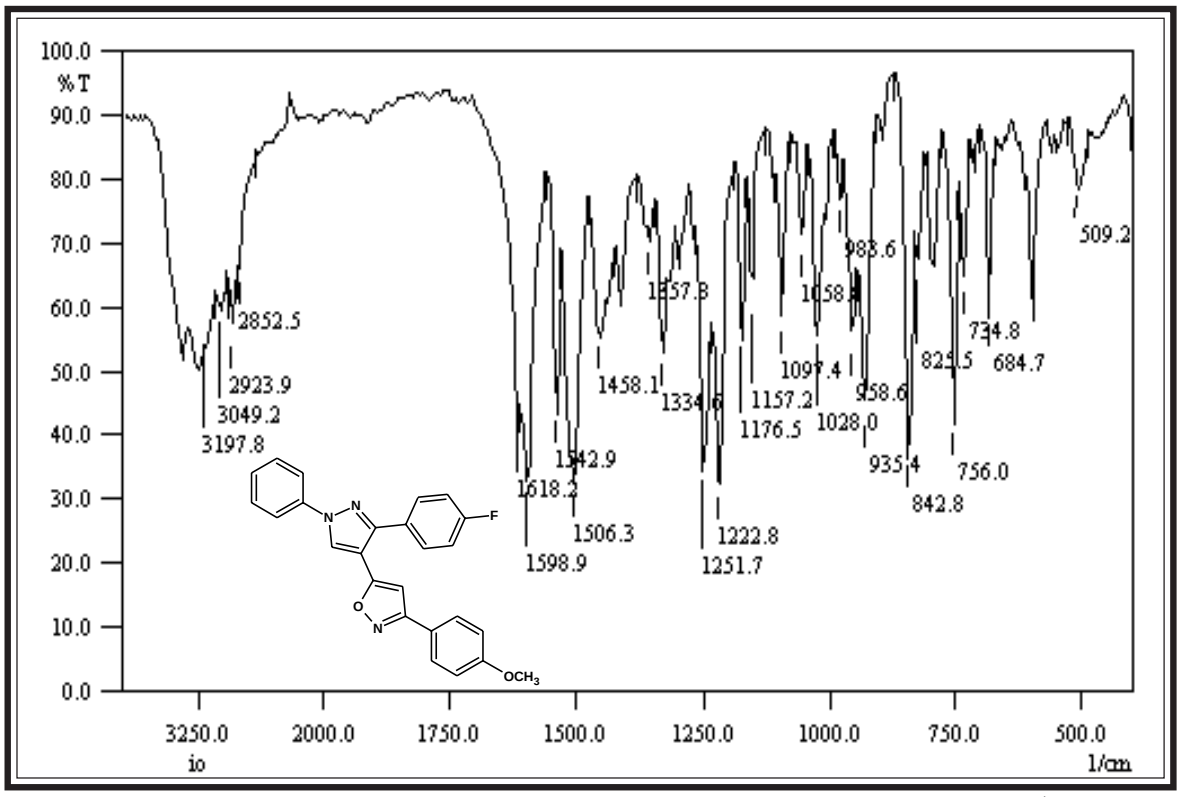
Type - (VIII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at concentration of 6.25 μg/ml using Rifampin as standard drug.

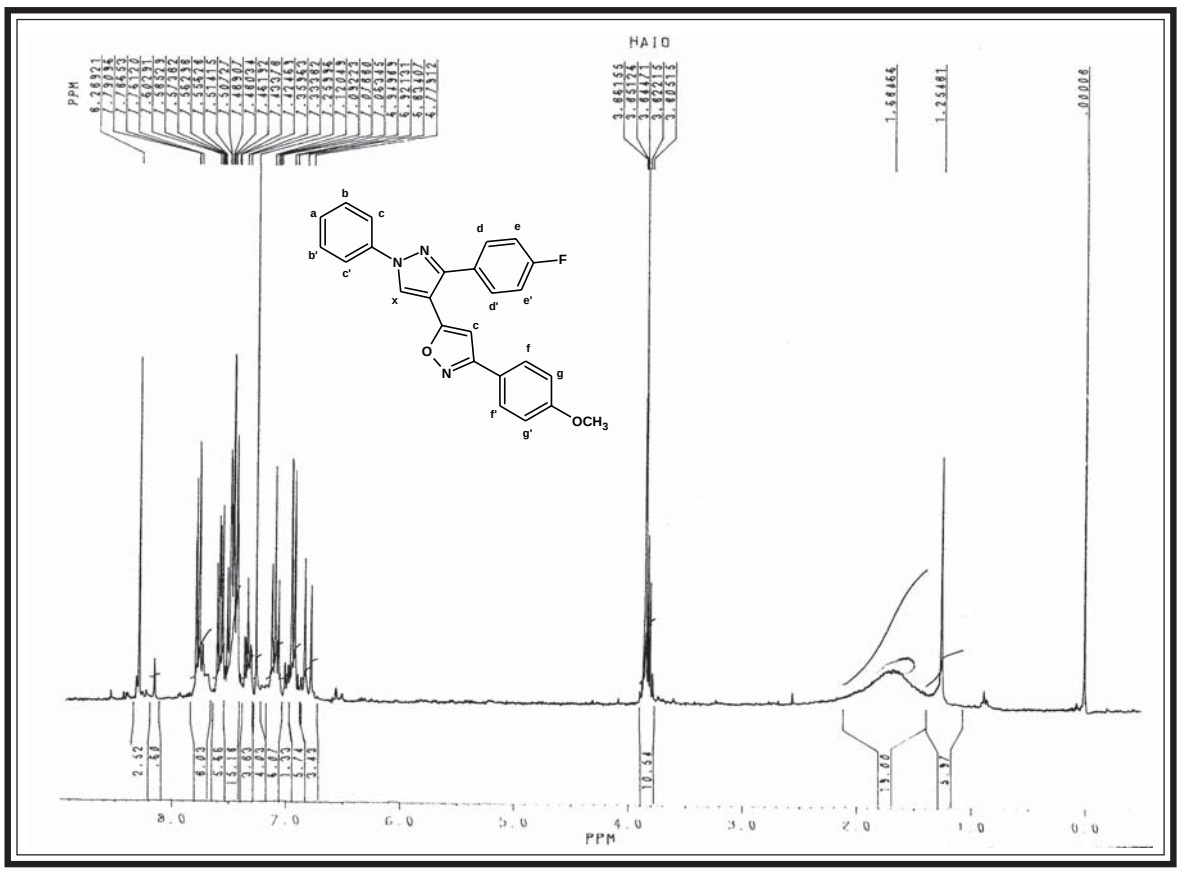
IR SPECTRAL STUDY OF 3-(p-ANISYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-ISOXAZOLE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2923	2975–2920	426
$-CH_3$	C – H str. (sym.)	2852	2880–2840	"
	C – H i.p. (def.)	1458	1470–1435	"
	C – H o.o.p. (def.)	1357	1385–1350	"
Aromatic	C – H str. (asym.)	3049	3080–3030	427
	C = C str.	1542	1585–1450	"
	C – H i.p. (def.)	1097	1125–1090	"
		1028	1070–1000	"
	C – H o.o.p. (def)	825	835–810	"
Pyrazole	C = N str.	1618	1650–1600	428
moiety	C – N str.	1334	1350–1200	"
	C – F str.	756	760–710	"
Ether	C – O – C str. (asym)	1222	1275–1200	"
	C – O – C str. (sym.)	1068	1075–1020	"
Isoxazole	C = C str.	1506	1585–1450	426
	C = N str.	1598	1650–1600	"
	N – O str.	842	850–800	"

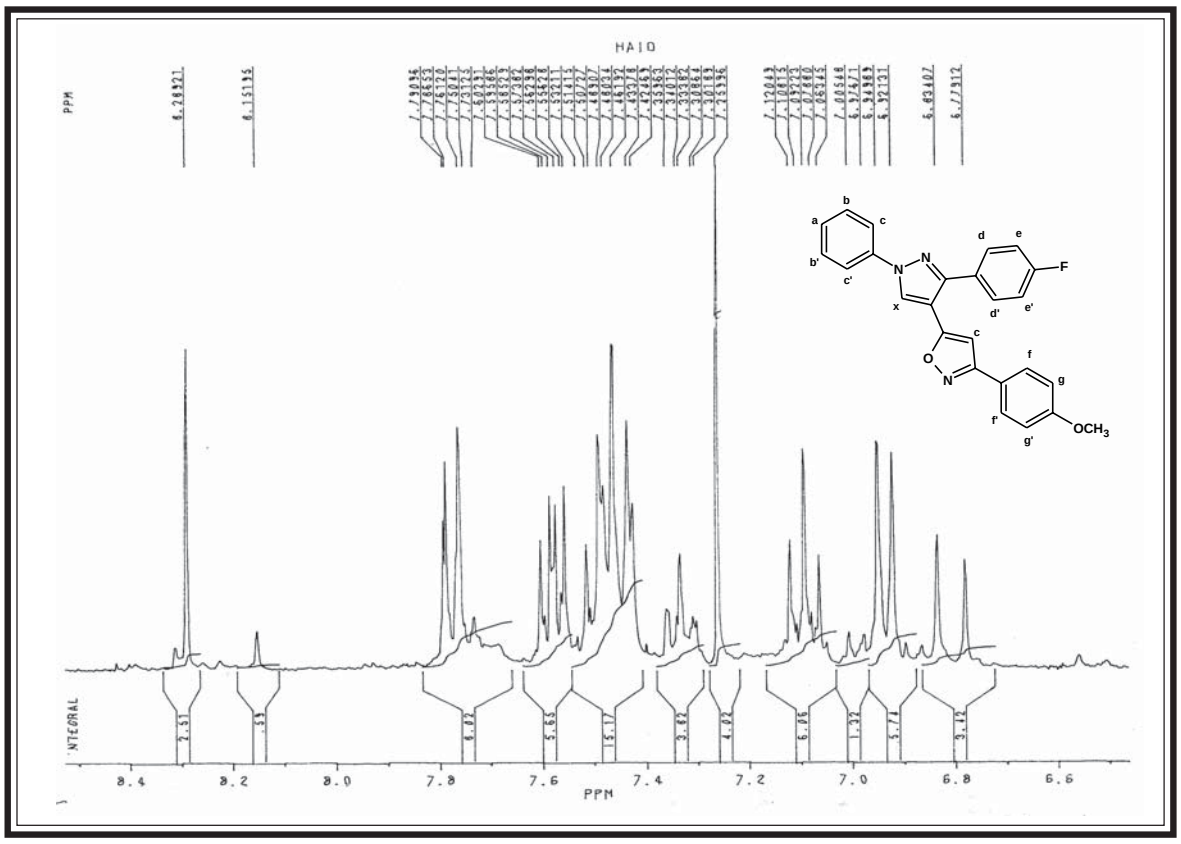
PMR SPECTRAL STUDY OF 3-(p-ANISYL)-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-ISOXAZOLES

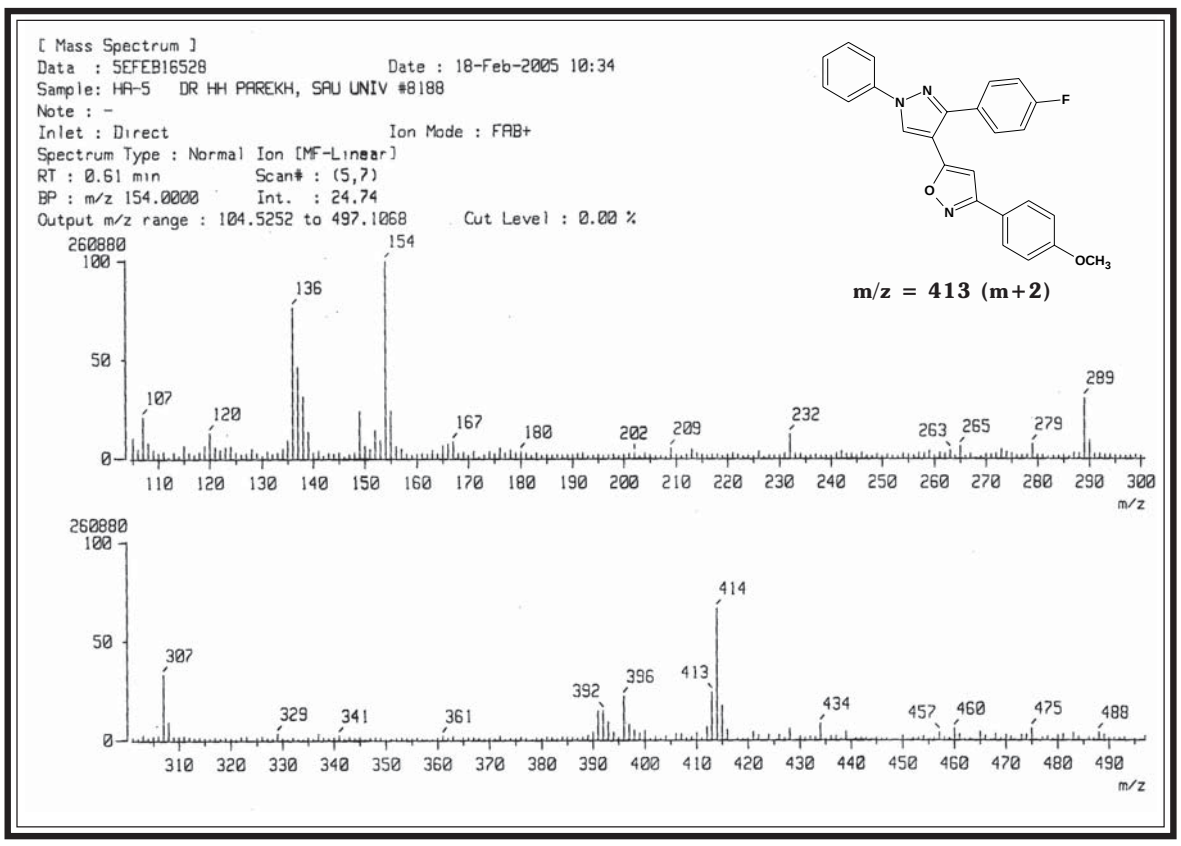


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.84	3H	singlet	Ar-OCH_3	-
2.	6.92-6.94	2H	doublet	Ar-Hgg'	Jgf=8.4
3.	7.06-7.12	2H	triplet	Ar-Hdd'	-
4.	7.30-7.35	1H	triplet	Ar-Ha	-
5.	7.42-7.50	4H	multiplet	Ar-Hbb'+Hee'	-
6.	7.55-7.60	2H	multiplet	Ar-Hcc'	-
7.	7.75-7.79	3H	triplet	Ar-Hff'+Hh	Jfg = 10.6
8.	8.28	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





m/z = 413 (m+2)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-ISOXAZOLES

[A] Synthesis of N-Aminophenyl-α-methyl-α-p-fluorophenyl-azomethine

See, Part-I, Section-I (A)

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See, Part- I, Section-I (B).

[C] Synthsis of 1-(p-Anisyl)-3-(1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-2-propene-1-one

See, Part-I, Section-I (C).

[D] Synthesis of 3-(p-Anisyl)-5-[1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl]-isoxazoles

To a mixture of hydroxy amine hydrochloride (0.79, 0.01M) in ethanol and anhydrous sodium acetate (0.82g, 0.01M) dissolved in minimum amount of hot acetic acid was added a solution of 1-(p-anisyl)-3-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-2-propene-1-one (3.98g, 0.01M) in ethanol (15 ml). The contents were refluxed on waterbath for 8 hrs. at temp 80°-90°C. The reaction product was poured into ice and crystallised from ethanol. Yield 73%, m.p. 183°C; ($C_{25}H_{18}FN_3O_2$; Found : C, 72.93%; H, 4.36%; N, 10.16%; Requires : C, 72.98%; H, 4.41%; N, 10.21%).

Similarly other substituted isoxazoles have been prepared. The physical data are recorded in Table No. 8.

[E] Therapeutic activity of 3-Aryl-5-[1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl]-isoxazoles

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 8.

Antitubercular screening of the compounds of type(VIII) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 8a.

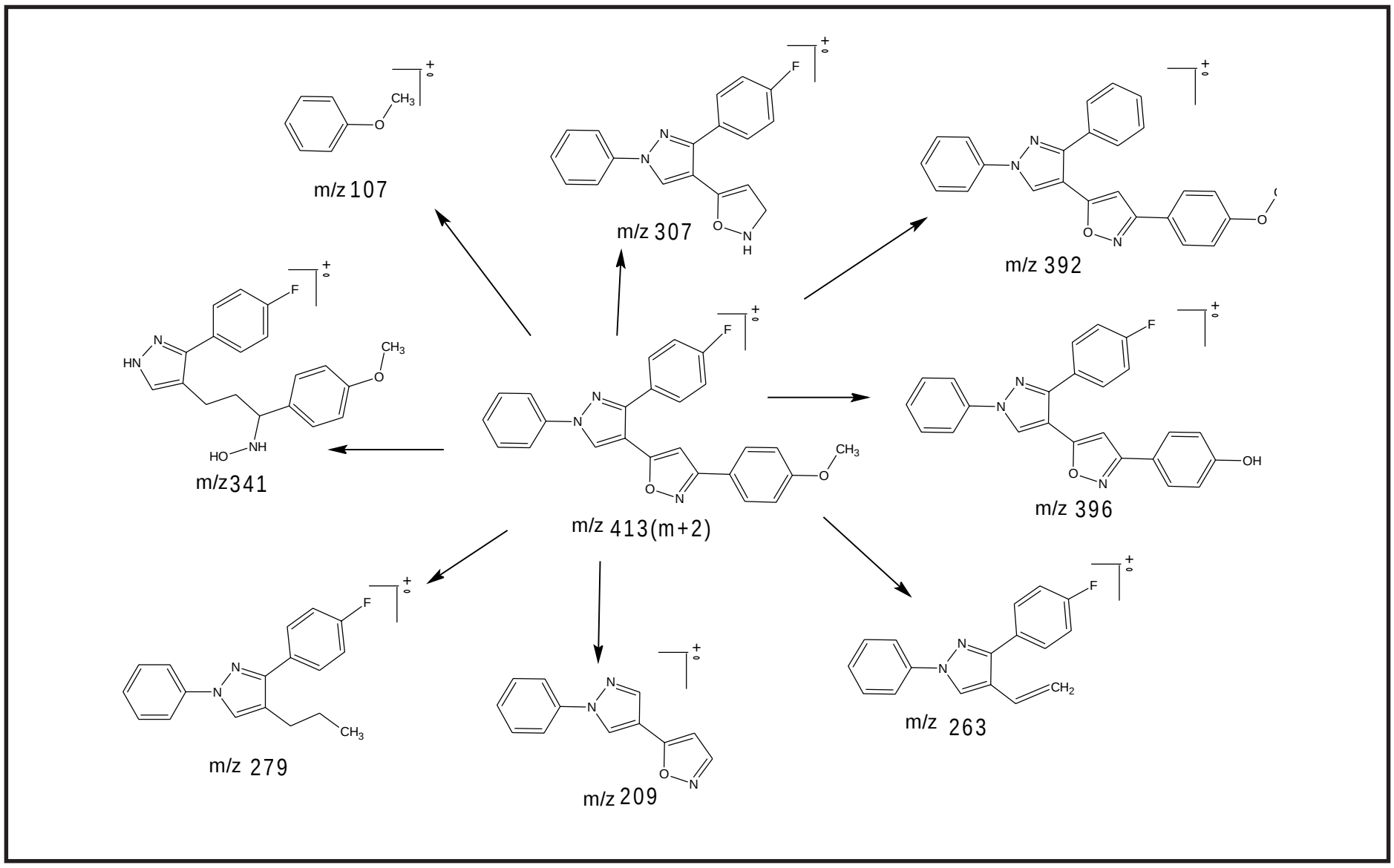
TABLE NO. 8 : PHYSICAL CONSTANTS OF 3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-ISOXAZOLES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
8a	C_6H_5-	$C_{24}H_{16}FN_3O$	381	98	0.56	70	11.02	10.96
8b	4-OCH_3-C_6H_4-	$C_{25}H_{18}FN_3O_2$	411	183	0.62	73	10.21	10.16
8c	4-CH_3-C_6H_4-	$C_{25}H_{18}FN_3O$	395	105	0.55	69	10.63	10.56
8d	4-Cl-C_6H_4-	$C_{24}H_{15}ClFN_3O$	415	119	0.61	72	10.10	10.05
8e	4-F-C_6H_4-	$C_{24}H_{15}F_2N_3O$	399	165	0.49	75	10.52	10.47
8f	4-OH-C_6H_4-	$C_{24}H_{16}FN_3O_2$	397	147	0.58	62	10.57	10.51
8g	2-OH-C_6H_4-	$C_{24}H_{16}FN_3O_2$	397	127	0.71	68	10.57	10.52
8h	4-NO_2-C_6H_4-	$C_{24}H_{15}FN_4O_3$	426	150	0.68	71	13.14	13.09
8i	3-NO_2-C_6H_4-	$C_{24}H_{15}FN_4O_3$	426	198	0.48	64	13.14	13.08
8j	4-Br-C_6H_4-	$C_{24}H_{15}BrFN_3O$	460	114	0.60	71	9.13	9.08
8k	4-NH_2-C_6H_4-	$C_{24}H_{17}FN_4O$	396	162	0.74	64	14.13	14.07
8l	C_4H_3S-	$C_{22}H_{14}FN_3OS$	387	159	0.46	67	10.85	10.81

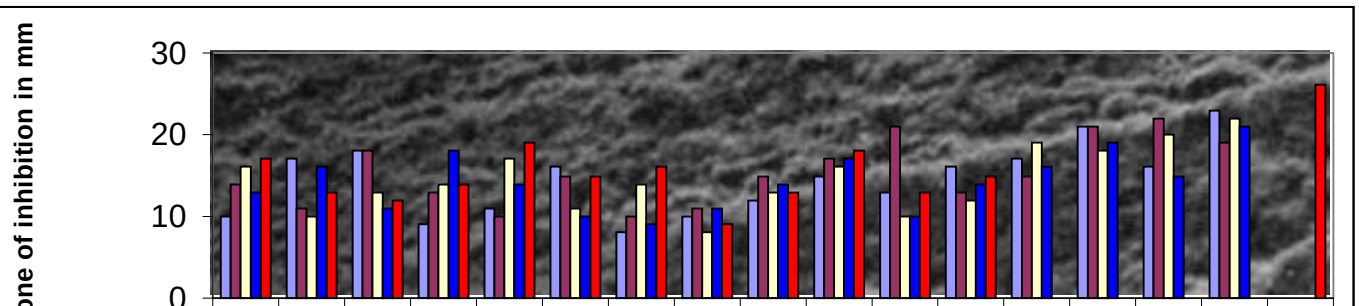
*TLC Solvent System : Ethyl acetate : Hexane

2 : 8 (2a-2f, 2h-2j, 2l)

3 : 7 (2g, 2k)


m/z 107
m/z 307
m/z 392
m/z 341
m/z 413(m+2)
m/z 396
m/z 279
m/z 209
m/z 263

GRAPHYCAL CHART NO.8: **ANTIMICROBIAL ACTIVITY OF 3-ARYL-5-[1'N-PHENYL-3'-p- FLUOROPHENYL PYRAZOL-4'-YL]-ISOXAZOLES.**



	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	Amoxycillin	Benzoyl Peni	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	10	17	18	9	11	16	8	10	12	15	13	16	17	21	16	23	0
B. subtillus	14	11	18	13	10	15	10	11	15	17	21	13	15	21	22	19	0
E. coli	16	10	13	14	17	11	14	8	13	16	10	12	19	18	20	22	0
P. vulgaris	13	16	11	18	14	10	9	11	14	17	10	14	16	19	15	21	0
A. niger	17	13	12	14	19	15	16	9	13	18	13	15	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The activity data shows that isoxazoles (type-VIII) were able to inhibit the growth of Gram positive & Gram negative bacterial strains.

Compounds bearing R=4-aminophenyl and 4-methylphenyl were observed to give maximum activity against Gram positive bacterial strains ***B. subtillus*** and ***B. cocous*** respectively as compared to standard drugs. Significant activity was displayed by compounds containing R=4-methoxyphenyl, 4-hydroxyphenyl, 3-nitrophenyl and thienyl.

In case of Gram negative bacterial strains, maximum activity was observed in compounds bearing 4-chlorophenyl and 4-fluorophenyl against ***P. vulgaris*** and ***E. coli***, significant activity was displayed by compounds bearing R=4-methoxyphenyl and 4-bromophenyl.

ANTIFUNGAL ACTIVITY

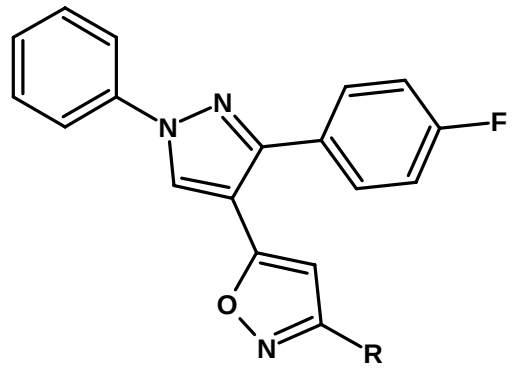
Most of the compound were mild to moderately active against fungal strain ***A. niger***.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds displayed antitubercular activity against ***Mycobacterium tuberculosis $H_{37}Rv$*** ranging from 16 to 99% inhibition. Compounds with R = 4-hydroxyphenyl, 2-hydroxyphenyl and 2-aminophenyl exhibited maximum activity upto 99% inhibition.

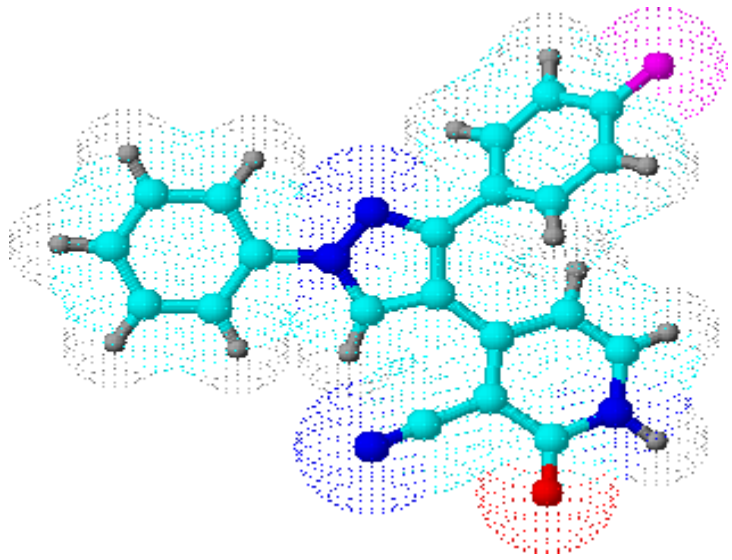
TABLE NO. 8a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

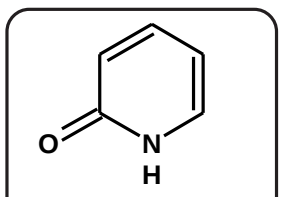
Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC µg/ml*	*% Inhib*	*Activity*	*Comment*
295574	HCV-68	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	82	-	MIC Rifampin = 0.25 µg/ml @ 98% Inhibition
295575	HCV-69	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	78	-	"
295576	HCV-70	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	69	-	"
295577	HCV-71	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	70	-	"
295578	HCV-72	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	75	-	"
295579	HCV-73	4-OH- C_6H_4-	Alamar	$H_{37}Rv$	<6.25	99	+	"
295580	HCV-74	2-OH- C_6H_4-	Alamar	$H_{37}Rv$	<6.25	90	+	"
295581	HCV-75	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	58	-	"
295582	HCV-76	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	16	-	"
295583	HCV-77	4-Br--C_6H_4-	Alamar	$H_{37}Rv$	>6.25	75	-	"
295584	HCV-78	4-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	<6.25	99	+	"
295585	HCV-79	C_4H_3S-	Alamar	$H_{37}Rv$	>6.25	70	-	"



PART-VI
STUDIES ON CYANOPYRIDONES

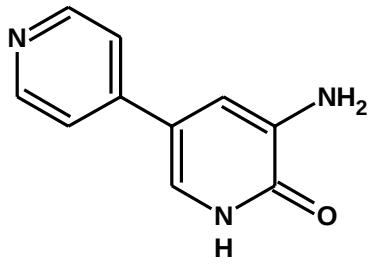
INTRODUCTION

Pyridones, which belongs to an important group of heterocyclic compounds have been extensively explored for their applications in the field of medicine. Pyridones, with a carbonyl group at position 2(I) have been subject of extensive study in recent past. Numerous reports have appeared in the literature which highlight their chemistry and use.

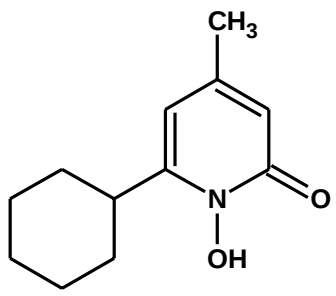


(I)

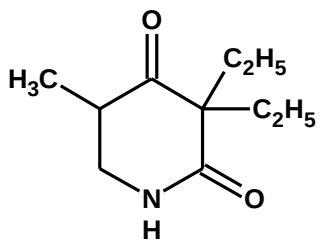
2-Pyridones are derivatives of pyridine with carbonyl group at 2-position (I). Someof the 2-pyridones are physiologically as well as pharmacologically important which are as under. eg. amrinone (II), ciclopirox (III)and methylprylon (IV).



(II)



(III)

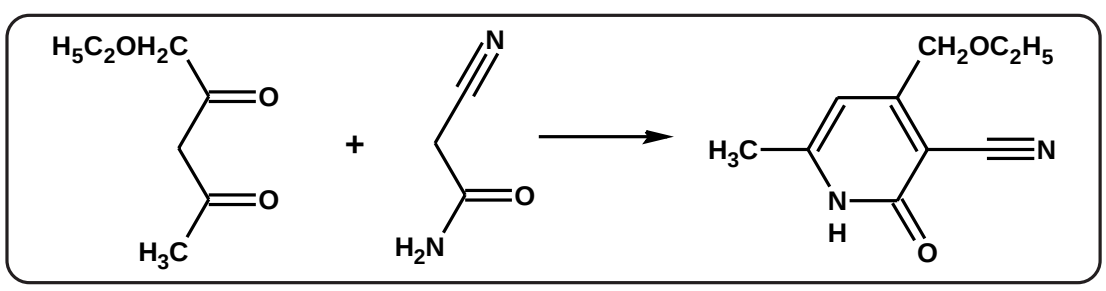


(IV)

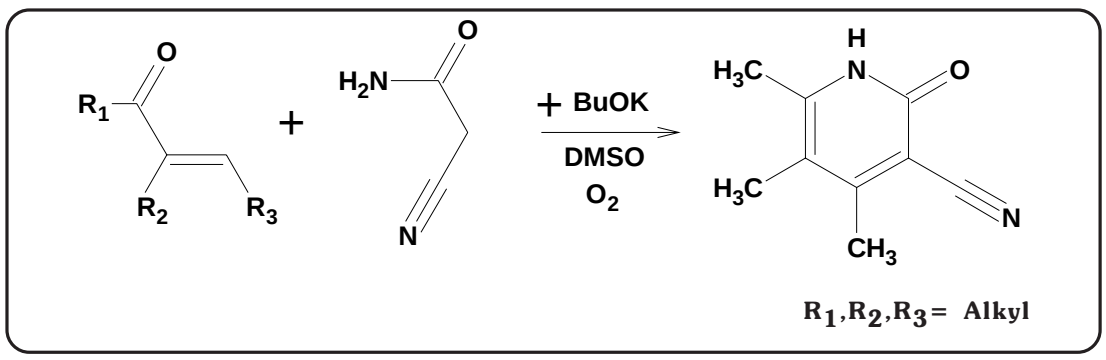
SYNTHETIC ASPECTS

Different methods for preparation of 2-pyridones are as follows :

1. K. Folkers and S. A. Harris[281] have synthsised 3-cyano-2-pyridones by the condensation of cyanoacetamide with 1,3-diketone or 3-ketoester.



2. Rajul Jain & co-workers[282] have prepared 3-cyano-2-pyridones by reaction of enones or enals with cyanoacetamide/BuOK in DMSO under O_2 atmosphere.



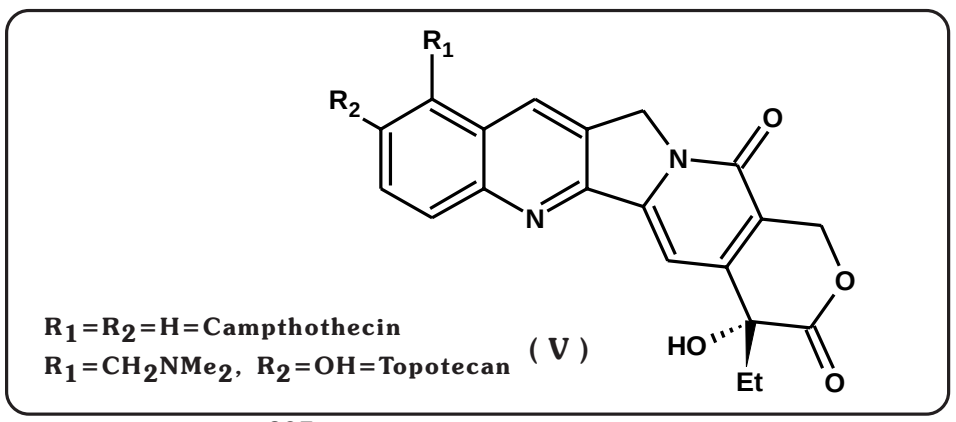
3. M. A. Sluyter and co-workers[283] have prepared fused 2-pyridones.
4. G. Simchen and G. Entemman[284] have synthesised 2-pyridones in which the ring nitrogen comes from a nitrile group in acyclic precursor.

THERAPEUTIC IMPORTANCE

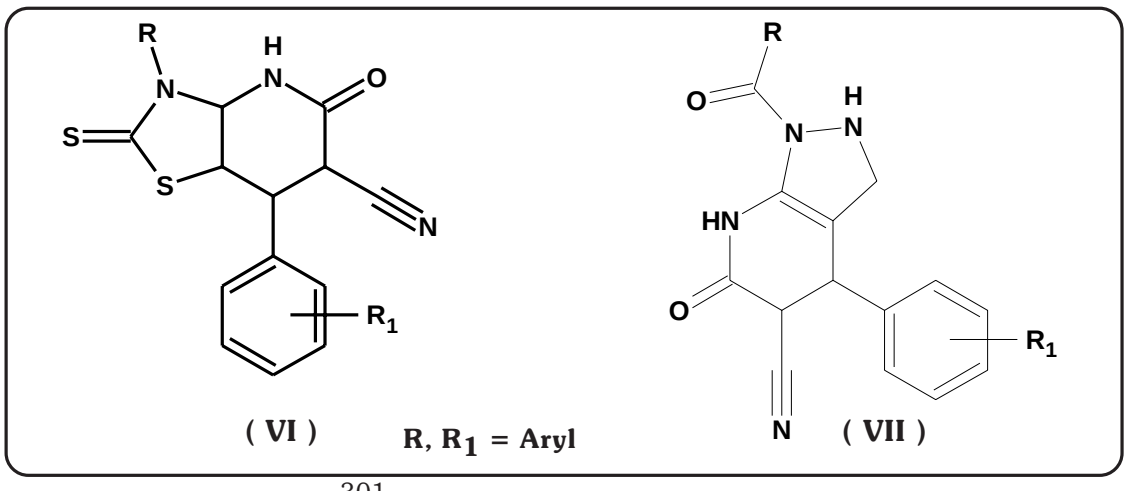
Pyridone derivatives have been found to possess variety of therapeutic activities as shown below.

1. Anticancer[285]
2. Herbicidal[286]
3. Pesticidal[287,288]
4. Antimicrobial[289]
5. Angitensin II antagonist[290,291]
6. Antiviral[292]
7. AntiHIV[293]

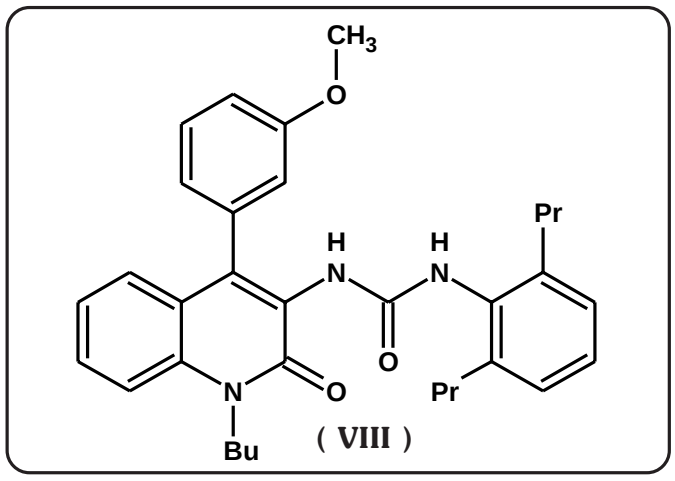
Salman A S [294] has prepared cyano pyridone derivatives as antibacterial & antifungal agent. Thomas C J et. al.[295] and M. Potmesil & H. Pinedo[296] have prepared 2-pyridone derivatives (V) as antineoplastics, antitumor & antiviral agent.



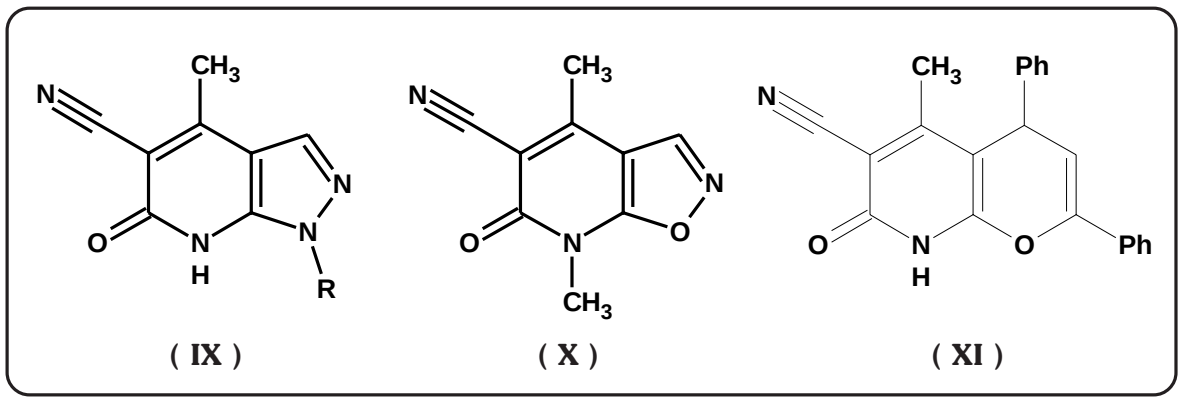
Peter and co-workers[297] have prepared pyridinylmethyl substituted pyridines and pyridones as angitensin II antagonist. H. Posnes[298] has synthesised 2-pyridones and 2-pyrones as physiologically active compounds. Mukhtar Hussain Khan and co-workers[299,300] have prepared 2-pyridone derivatives (VI) and (VII) which possess insecticidal and pesticidal activity.



Morishita Koji et. al.[301] have synthesised m-(2-oxo-1,2-dihydropyridyl) urea derivatives (VIII) possessing cholesterol acyltransterase (ACAT) inhibitory activity and are useful for the treatment of hyperlipidemia and arteriosclerosis.

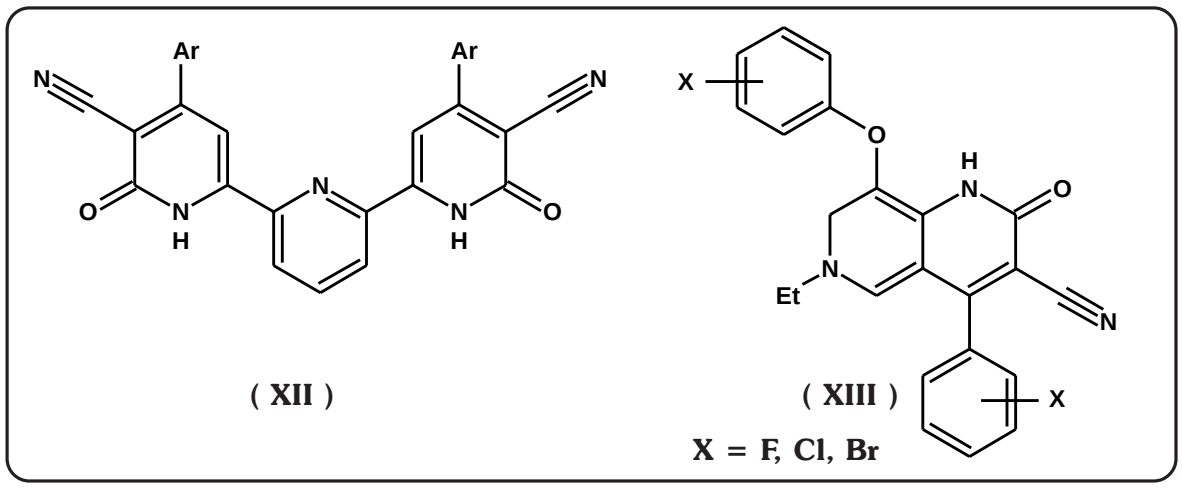


Collins et. al.[302] have prepared heteroaryl pyridones as GABA α_2/α_3 ligands. Pednekar[303] synthesised fused 2-pyridone derivatives (IX), (X) and (XI) as useful heterocyclic moieties as they possess broad spectrum of biological activities such as antiviral, CNS depressant, bactericidal and ulcer inhibitor.

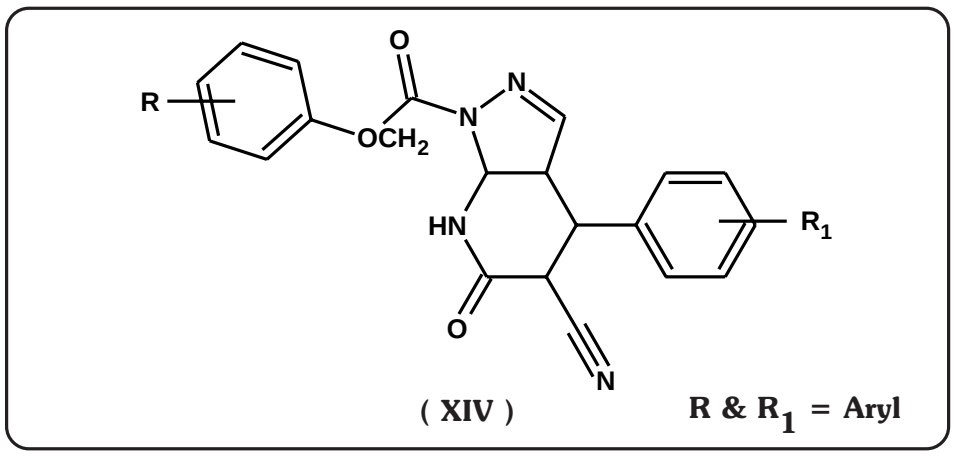


Moreover, several co-workers have prepared 2-pyridones as S_3 site of thrombin inhibitor[304], herbicidal[305], SH2 domain inhibitor[306], antimicrobial[307], GABA-A receptor[308] and antiinflammatory[309].

Upadhyay and co-workers[310] have synthesised cyanopyridone derivatives which showed antifungal and antileishmanial activities. E. Amer[311] has prepared 3-cyano-2-pyridone derivatives (XII) displaying high antimicrobial activity. Abou El-Fotooh and co-workers[312] have demonstrated pyridones (XIII) as anticancer agent.

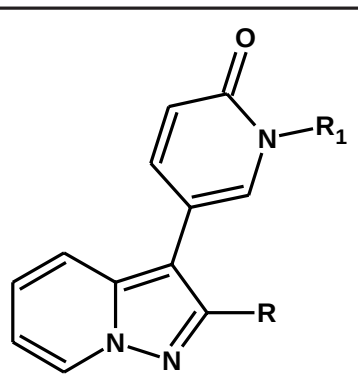


M. G. Nizamuddin *et.* al.[313] have prepared cyanopyridone derivatives (XIV) and documented their antifungal activity.

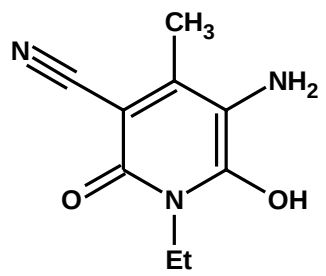


(XIV) R & R_1 = Aryl

Recently, Tanaka Akira *et.* al.[314] have prepared pyrazolo pyridone derivatives (XV). Haifeng Song & co-workers[315] have synthsised 3-cyano pyridones (XVI) which are used as dyes and pigment.

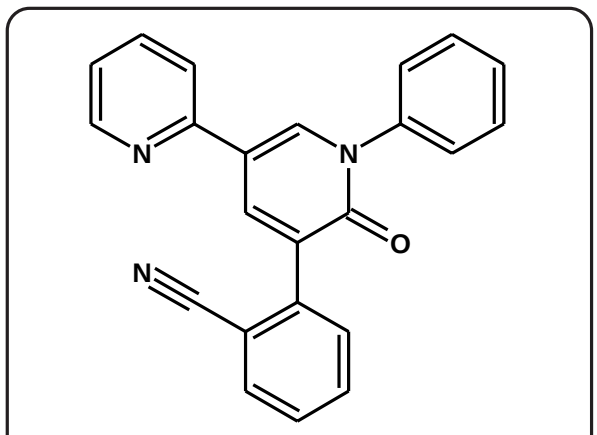


(XV) R & R_1 = Alkyl/Aryl



(XVI)

Darcy Michael G. *et.* al.[316] have discovered pyridones as antiviral agents. Smith Terence[317] has synthesised and reported pyridones (XVII) as AMPA receptor antagonists for the treatment of demyelinating disorders and neurodenerative diseases. Recently, it is found that pyridones possess antiallergic[318], p38 MAP Kinase[319] & modulating, thrombin inhibitor[320] activities.



(XVII)

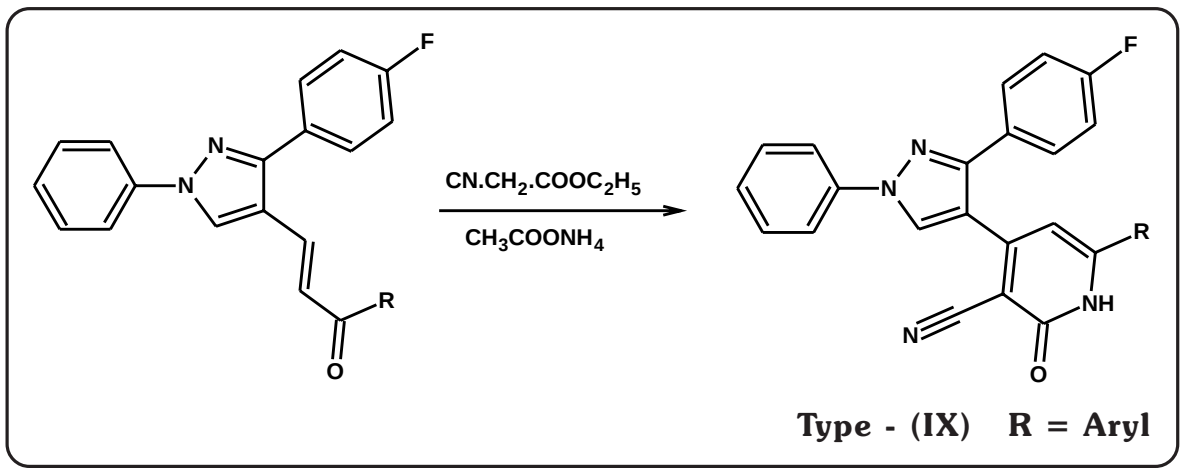
With an intension of preparing the compounds possessing better therapeutic activity, we have undertaken the preparation of cyanopyridones which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

Pyridone derivatives possess interesting therapeutic activity. Taking this into consideration, we have undertaken the preparation of pyridone derivatives by the condensation of chalcones of type (I) with ethyl cyanoacetate in presence of ammonium acetate as shown under.



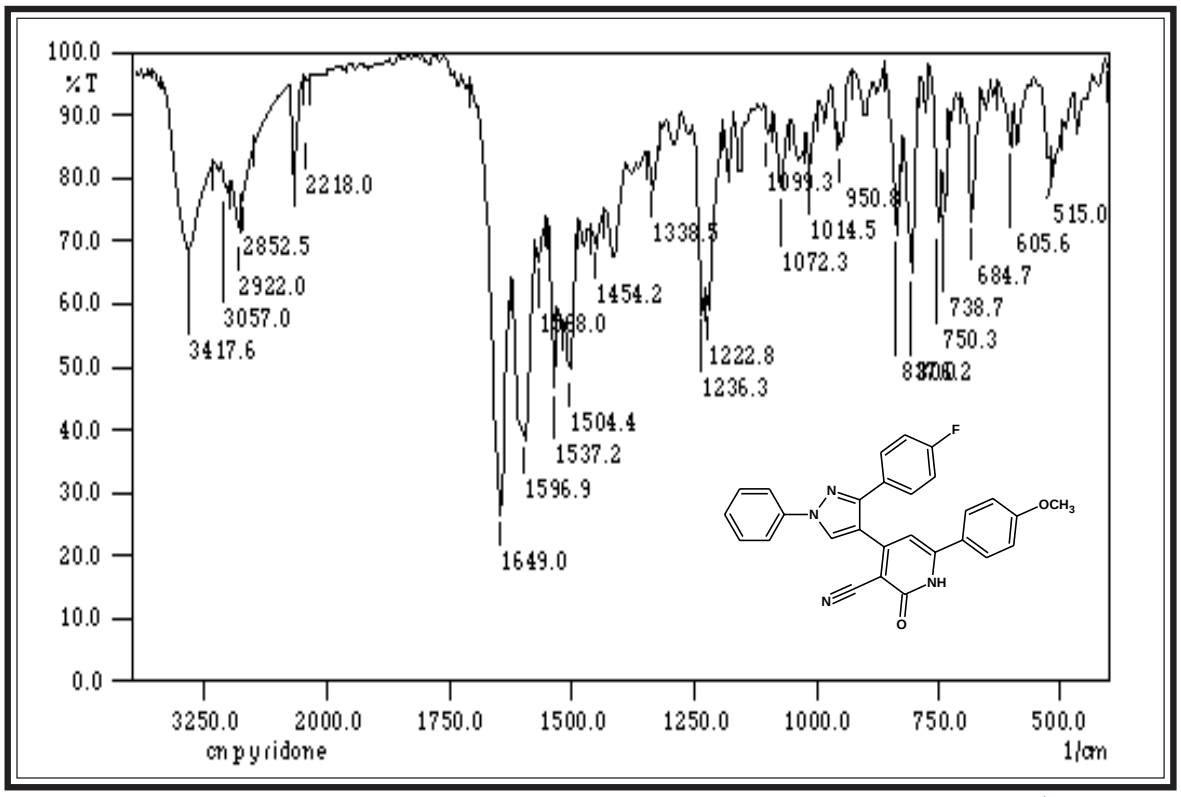
Type - (IX) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at concentration of 6.25 µg/ml using Rifampin as standard drug.

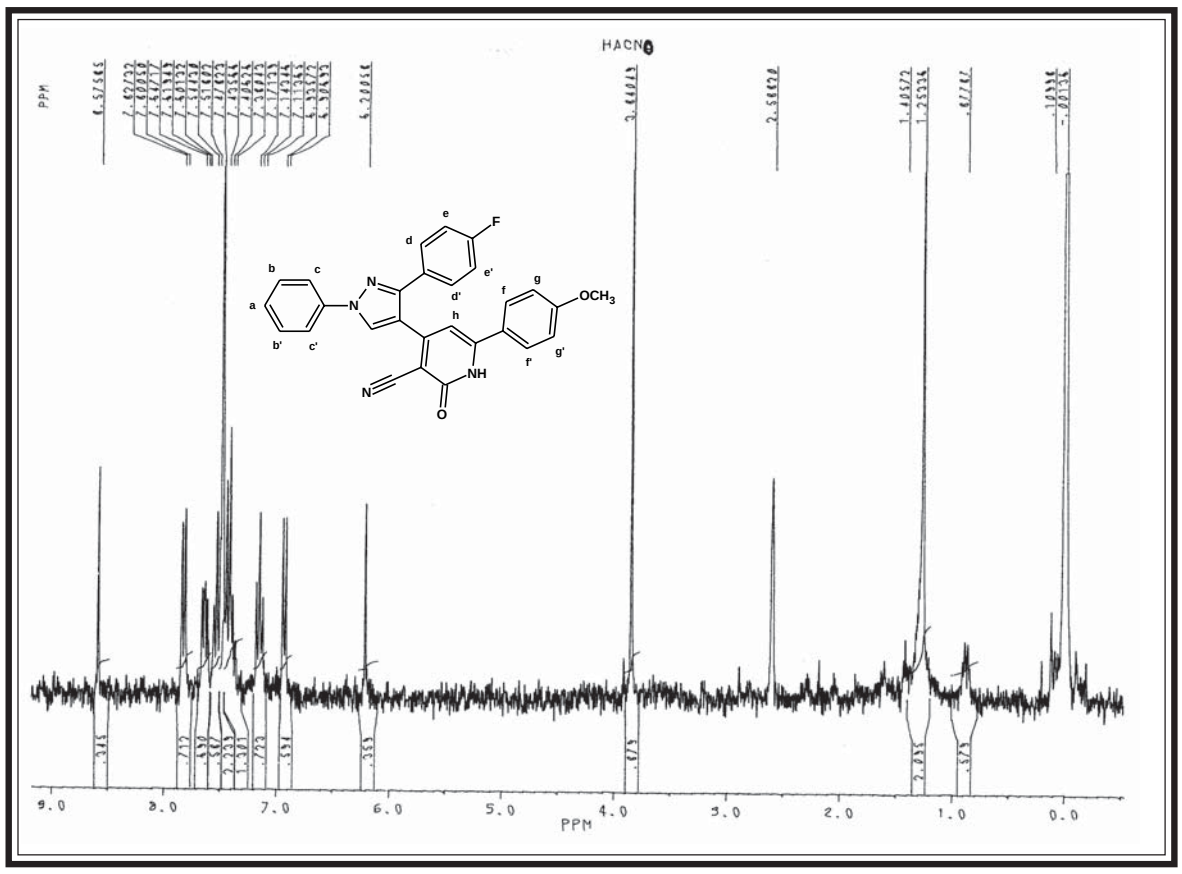
IR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-6-(p-ANISYL)-1,2-DIHYDRO-2-PYRIDONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2922	2975–2920	426
$-CH_3$	C – H str. (sym.)	2852	2880–2820	"
	C – H i.p. (def.)	1454	1470–1435	"
	C – H o.o.p. (def.)	1338	1385–1350	"
Aromatic	C – H str.	3057	3080–3030	427
	C – H i.p. (def.)	1099	1125–1090	"
		1014	1070–1000	"
	C – H o.o.p. (def.)	837	835–810	"
Pyrazole	C = N str.	1596	1650–1590	428
moety	C = C str.	1504	1585–1480	"
	C – N str.	1236	1350–1200	"
	C – F str.	750	760–700	"
Ether	C – O – C str. (asym)	1236	1275–1200	"
	C – O – C str. (sym.)	1072	1075–1020	"
Pyridone	C ≡ N str.	2218	2240–2120	432
ring	C = O str.	1649	1760–1655	"
	N – H str.	3417	3450–3250	"

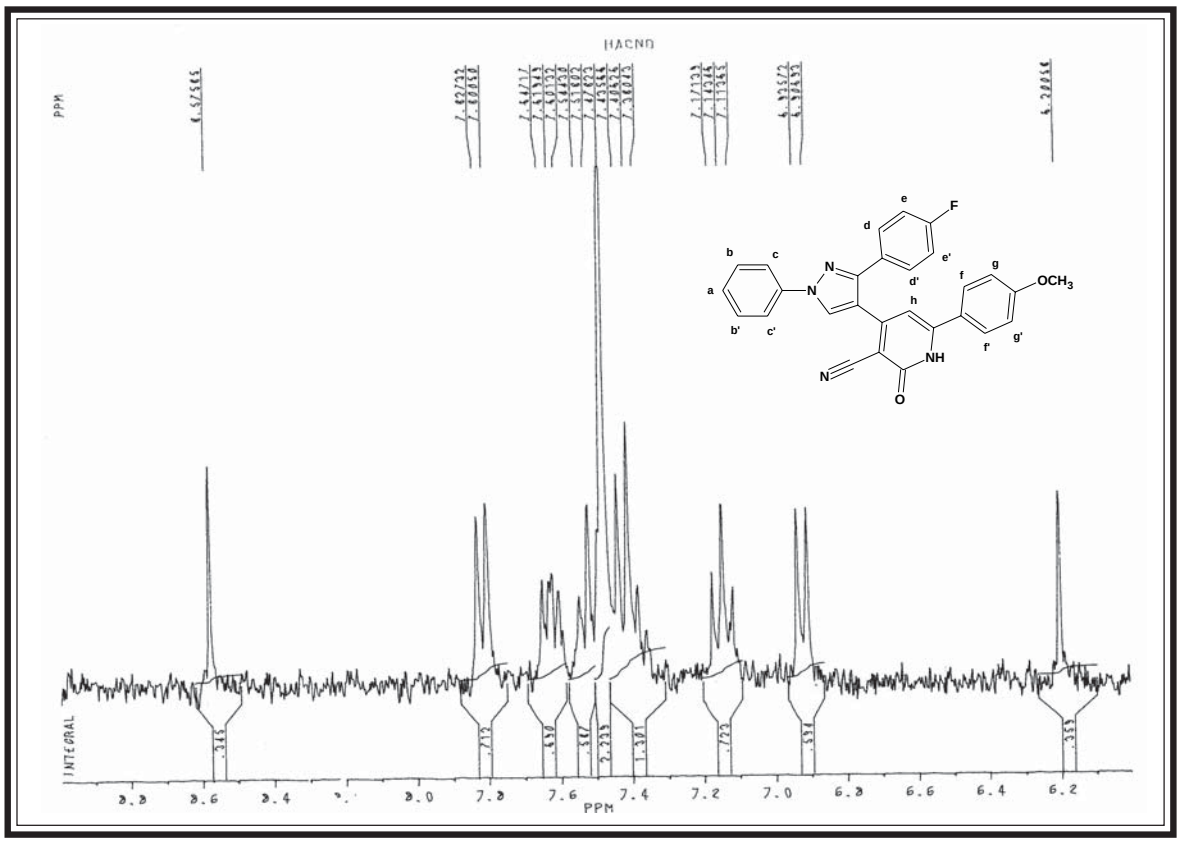
PMR SPECTRAL STUDY OF 3-CYANO-4-[1'N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-6-(p-ANISYL)1,2-DIHYDRO-2-PYRIDONE

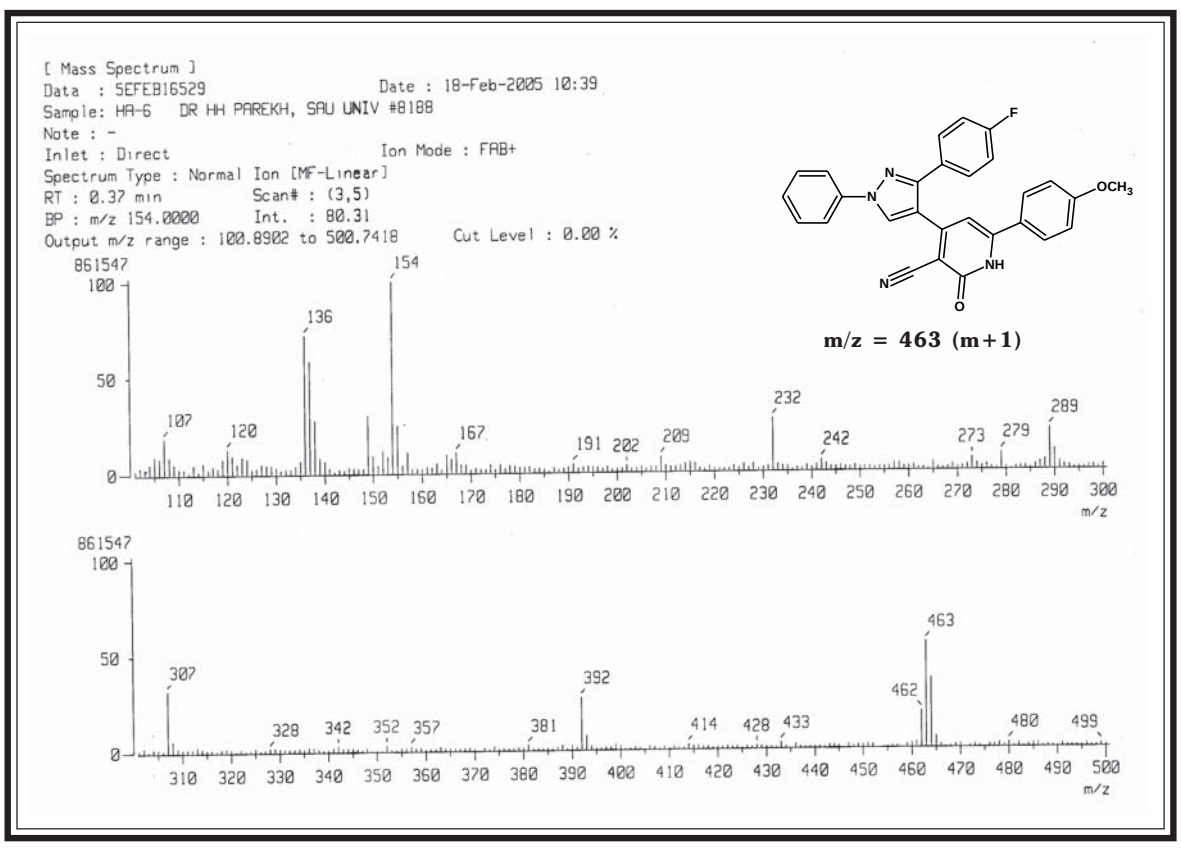


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.84	3H	singlet	Ar-OCH_3	-
2.	6.20	1H	singlet	Ar-Hh	-
3.	6.90-6.93	2H	doublet	Ar-Hgg'	Jgf=8.7
4.	7.11-7.17	2H	triplet	Ar-Hdd'	-
5.	7.38-7.43	3H	triplet	Ar-Hbb' + Ha	-
6.	7.51-7.54	2H	doublet	Ar-Hee'	Jed= 7.8
7.	7.60-7.64	2H	multiplet	Ar-Hcc'	-
8.	7.80-7.82	2H	doublet	Ar-Hff'	Jig=8.1
9.	8.57	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





m/z = 463 (m+1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-CYANO-4-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-6-ARYL 1,2-DIHYDRO-2-PYRIDONES

[A] Synthesis of N-Aminophenyl-α-methyl-2-p-fluorophenyl-azomethine

See, Part-I, Section-I (A)

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See, Part- I, Section-I (B).

[C] Synthesis of 1-(p-Anisyl)-3-(1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-2-propene-1-one

See, Part-I, Section-I (C).

[D] Synthesis of 3-cyano-4-(1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-6-(p-anisyl)-2-pyridone

A mixture of 1-(p-anisyl)-3-(1',N-phenyl-3'-p-flurophenyl-pyrazol-4'-yl)-2-propene-1-one (3.98g, 0.01M) ethyl cyano acetate (1.13g, 0.01M) and ammonium acetate (5.92g, 0.08M) in absolute alcohol was refluxed for 10 hrs. at temp 70°-80°C. The reaction product was poured into ice, filtered and crystallised from ethanol. Yield 68% m.p.> 300°C ($C_{28}H_{19}FN_4O_2$: Found : C, 72.63%; H, 4.07%; N, 12.02%; Requires : C, 72.72%; H, 4.14%; N, 12.11%).

Similarly other substituted pyridones have been prepared. The physical data are recorded in Table No. 9.

[E] Therapeutic activity of 3-Cyano-4-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-6-aryl-pyridones

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 9.

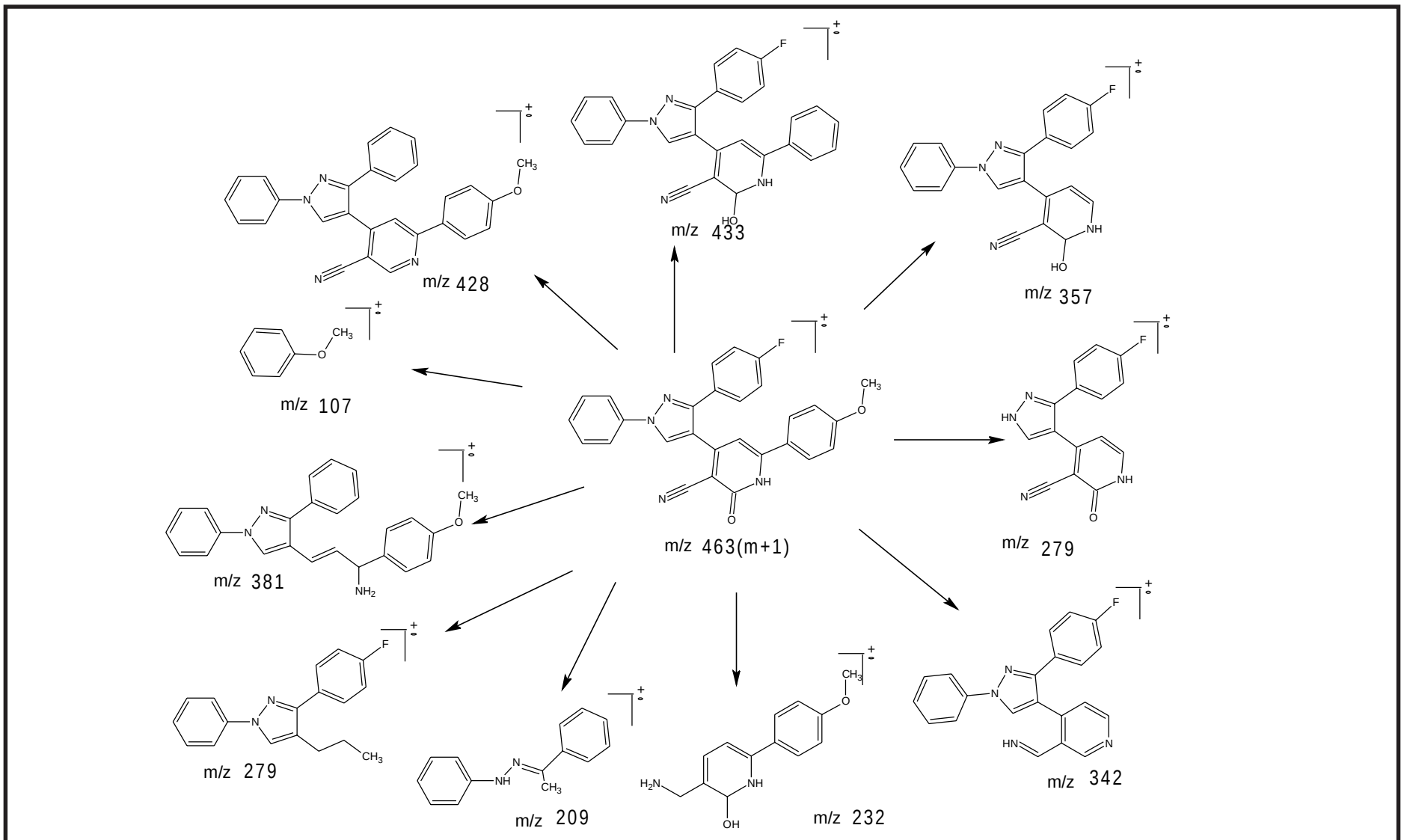
Antitubercular screening of the compounds of type(IX) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 9a.

TABLE NO. 9 : PHYSICAL CONSTANTS OF 3-CYANO-4-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

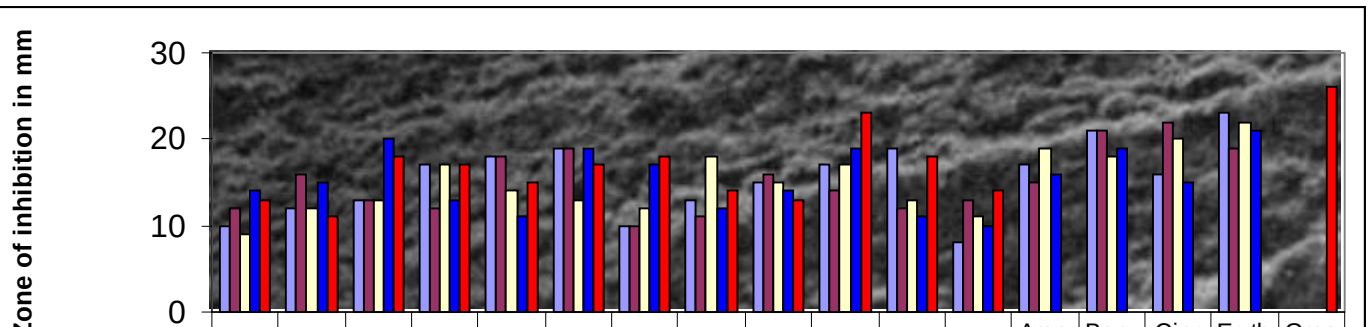
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
9a	C_6H_5-	$C_{27}H_{17}FN_4O$	432	117	0.41	61	12.96	12.86
9b	4-OCH_3-C_6H_4-	$C_{28}H_{19}FN_4O_2$	462	>300	0.52	68	12.11	12.02
9c	4-CH_3-C_6H_4-	$C_{28}H_{19}FN_4O$	446	102	0.63	60	12.55	12.47
9d	4-Cl-C_6H_4-	$C_{27}H_{16}ClFN_4O$	466	202	0.47	68	12.00	11.94
9e	4-F-C_6H_4-	$C_{27}H_{16}F_2N_4O$	450	122	0.46	64	12.44	12.38
9f	4-OH-C_6H_4-	$C_{27}H_{17}FN_4O_2$	448	192	0.72	72	12.49	12.40
9g	2-OH-C_6H_4-	$C_{27}H_{17}FN_4O_2$	448	162	0.60	65	12.49	12.38
9h	4-NO_2-C_6H_4-	$C_{27}H_{16}FN_5O_3$	477	138	0.56	62	14.67	14.61
9i	3-NO_2-C_6H_4-	$C_{27}H_{16}FN_5O_3$	477	182	0.75	74	16.67	14.59
9j	4-Br-C_6H_4-	$C_{27}H_{16}BrFN_4O$	511	232	0.48	71	10.96	10.88
9k	4-NH_2-C_6H_4-	$C_{27}H_{18}FN_5O$	447	131	0.51	64	15.65	15.57
9l	C_4H_3S-	$C_{25}H_{15}FN_4O_5$	438	112	0.66	67	12.78	12.70

*TLC Solvent System : Acetone : Benzene

2 : 8


m/z 428
m/z 433
m/z 357
m/z 107
m/z 463(m+1)
m/z 279
m/z 381
m/z 279
m/z 209
m/z 232
m/z 342

GRAPHYCAL CHART NO.9: **ANTIMICROBIAL ACTIVITY OF 3-CYANO-4-[1'N-PHENYL-3'-p- FLUOROPHENYL PYRAZOL-4'-YL] -6-ARYL-1,2-DIHYDRO-2-PYRIDONES.**



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Amoxycilli	Benzoyl	Ciproflox	Erythromy	Greseo
B. cocous	10	12	13	17	18	19	10	13	15	17	19	8	17	21	16	23	0
B. subtillus	12	16	13	12	18	19	10	11	16	14	12	13	15	21	22	19	0
E. coli	9	12	13	17	14	13	12	18	15	17	13	11	19	18	20	22	0
P. vulgaris	14	15	20	13	11	19	17	12	14	19	11	10	16	19	15	21	0
A. niger	13	11	18	17	15	17	18	14	13	23	18	14	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

From the activity data, it has been concluded that the pyridone (type-IX) derivatives were able to inhibit the growth of Gram positive and Gram negative bacterial strians.

Maximum activity was observed in compounds bearing R=4-hydroxyphenyl & 4-aminophenyl against Gram positive bacterial strains, ***B. cocous*** & ***B. subtillus***. Significant activity was observed in compounds bearing R=4-chlorophenyl, 4-bromophenyl, 4-fluorophenyl, 4-methoxyphenyl and 3-nitrophenyl against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus***.

In case of Gram negative bacterial strains, maximum activity was observed in compounds bearing R=4-methoxyphenyl and 4-nitrophenyl, while other compounds were mild to moderately activity.

ANTIFUNGAL ACTIVITY

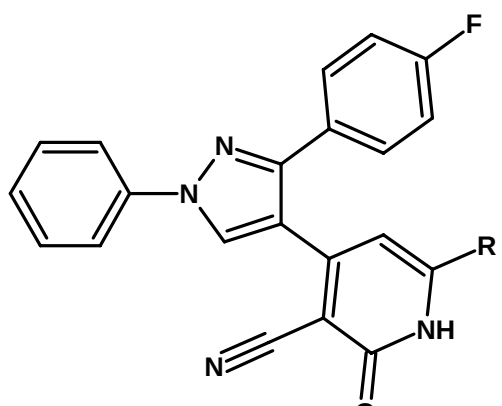
In case of fungal strain ***A. niger***, maximum activity was observed in compound bearing R=4-bromophenyl. All the others compounds were mild to moderately active.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds displayed antitubercular activity against ***Mycobacterium tuberculosis $H_{37}Rv$*** ranging from 5 to 83% inhibition. Compounds with R = thienyl showed maximum activity i.e. 83% inhibition.

TABLE NO. 9a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY

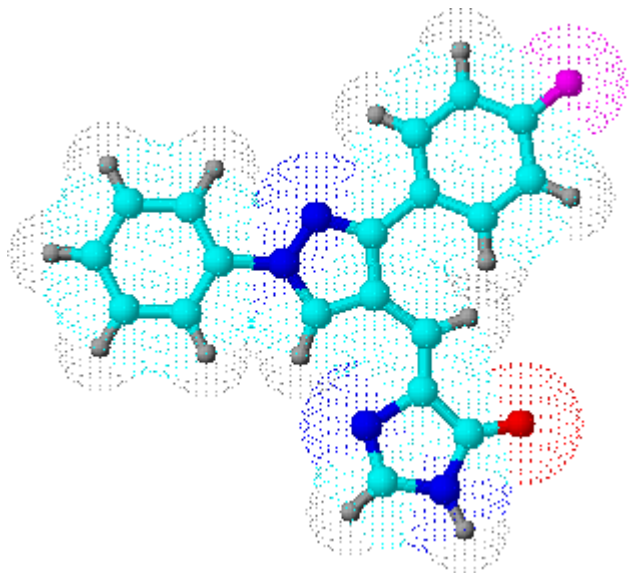


O

TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

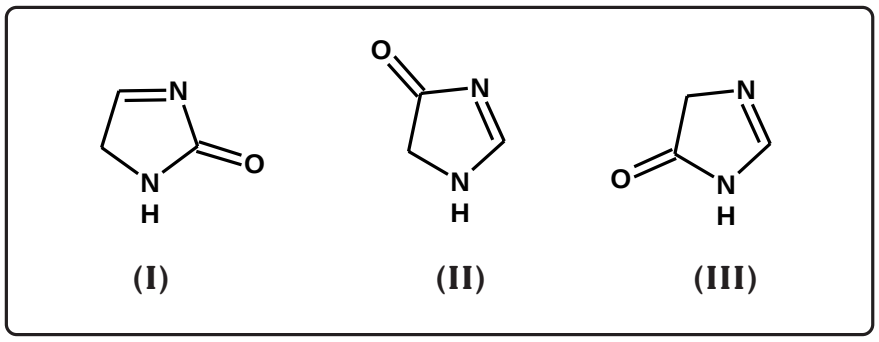
Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC µg/ml*	*% Inhib*	*Activity*	*Comment*
295562	HCV-56	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	60	-	MIC Rifampin = 0.25 µg/ml @ 98% Inhibition
295563	HCV-57	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	34	-	"
295564	HCV-58	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	41	-	"
295565	HCV-59	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	34	-	"
295566	HCV-60	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	34	-	"
295567	HCV-61	4-OH- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	37	-	"
295568	HCV-62	2-OH- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12	-	"
295569	HCV-63	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295570	HCV-64	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	5	-	"
295571	HCV-65	4-Br--C_6H_4-	Alamar	$H_{37}Rv$	>6.25	46	-	"
295572	HCV-66	4-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	53	-	"
295573	HCV-67	C_4H_3S-	Alamar	$H_{37}Rv$	>6.25	83	-	"



PART-VII
STUDIES ON
IMIDAZOLINONES

INTRODUCTION

Imidazolinone, a five membered heterocycle having 2-nitrogen atoms at the 1 and 3-positions and C=O group at following positions : 2-oxo-imidazoline (I), 4-oxo-imidazoline (II), 5-oxo-imidazoline (III).



(I) **(II)** **(III)**

The discovery of the 2-substituted-5-imidazolines dates back to the year 1888, when A. W. Hoffman[321] for the first time discovered 5-oxo-imidazoline by heating N'-diacetylethylene diamine in a stream of dry hydrogen chloride. Moreover the same compound was prepared by A. Ladenburg[322] by the fusion of two equivalents of sodium acetate with one equivalent of ethylene diamine dihydrochloride.

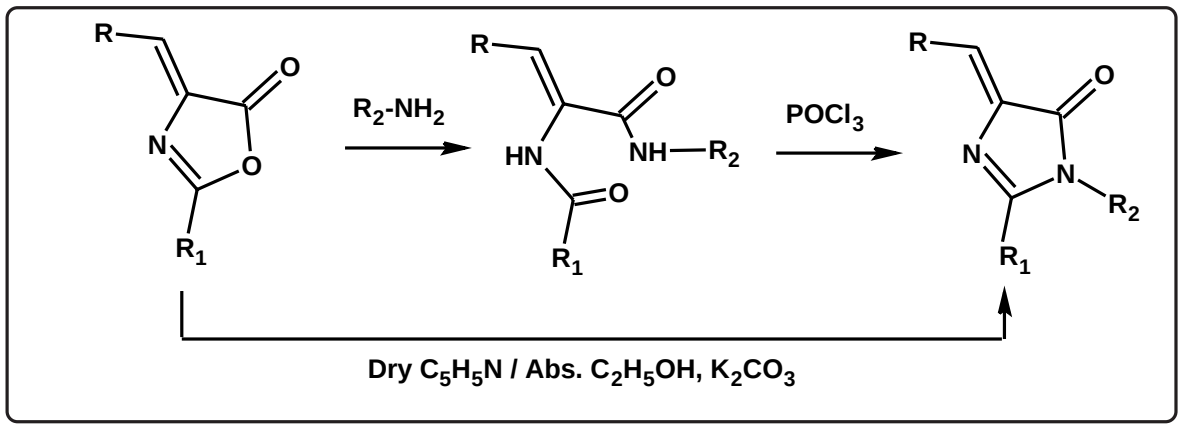
SYNTHETIC ASPECTS

Various methods have been reported for the synthesis of imidazolinones in literature[323] are as under.

1. Aminolysis of oxazolone with amine leads to the formation of imidazolinones[324].
2. A. Saxena et. al.[325] have synthesised new imidazolinones in pyridine.
3. Allimony et. al.[326] have synthesised new imidazolinone derivatives by conventional method.
4. Feng-Jun-Cai et. al.[327] have synthesised 5-imidazolinone derivatives by microwave irradiation.

MECHANISM

Azalactone reacts with variety of compounds such as water, alcohols, amines and hydrogen halides. Amides of α-acylamino acrylic acids obtained from the condensation of azalactone and primary amine can be converted to imidazolinones as shown under.



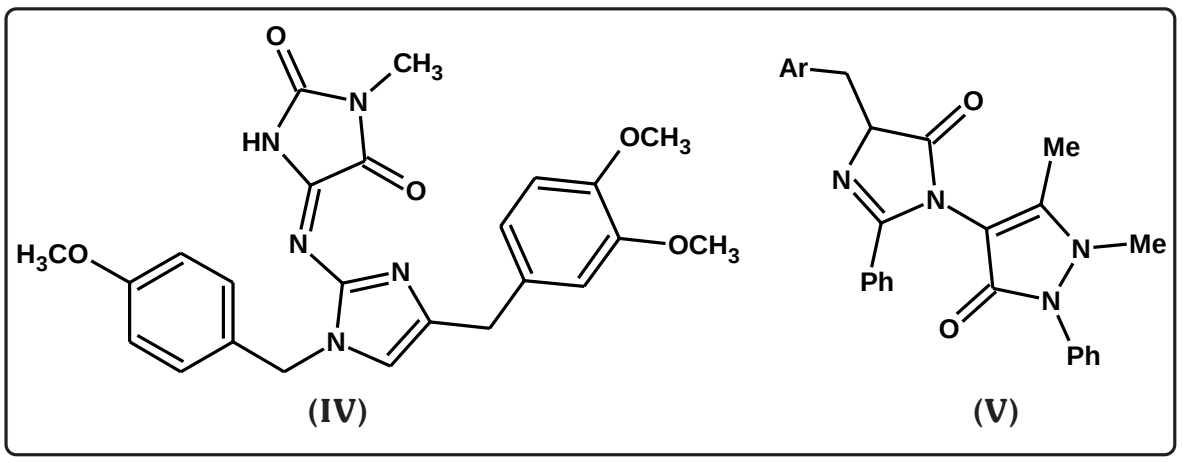
The ring closer can be effected under a variety of conditions. Substituted anilides have been converted to imidazolinone derivatives by the action of $POCl_3$.

THERAPEUTIC IMPORTANCE

Naphazoline hydrochloride, xylometazoline hydrochloride etc are various imidazolinone derivatives which have been used as adrenergic stimulants and tolazoline and phenotolamine as adrenergic blocking agents. Various imidazolinones are known to exhibit a broad spectrum of biological activities such as,

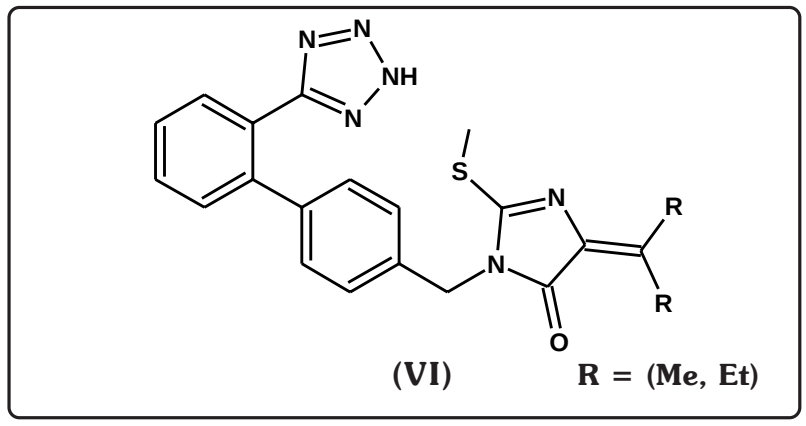
1. Antitubercular[328]
2. Potent CNS depressant[329]
3. Antiviral[330]
4. Antihypertensive[331]
5. Antiinflammatory[332]
6. Antimicrobial[333]
7. Anticonvulsant[334]
8. Fungicidal[335]
9. Anticancer[336]
10. Antidiabetic[337]

Prisinzano T. et. al.[338] have synthesised & reported imidazoline derivatives as human 5-HT(1D) serotonin receptor ligands. Zhong Jin[339] has found imizoline derivatives (IV) as cytoxic towards several tumor cell lines. Moutevelis-Minakakis P. et. al.[340] have synthesised imidazolines as antihypertensive agent. Katarzyna Kiee-Knonowicz et. al.[341] have discovered imidazolinones as antimicrobial agents. Solankee A. et. al.[342] have prepared imidazolinones (V) as anticancer agents.



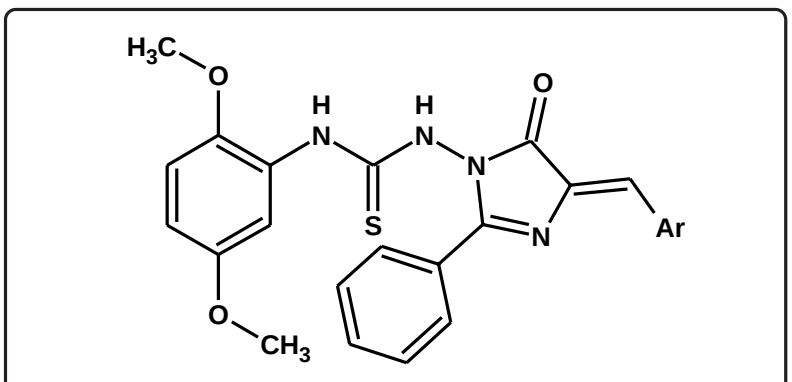
Havera Herbert J & co-workers[343] have synthesised imidazolinones as antiarrhythmic agents. Some androgenic inhibitor and estrogen activities of imidazoline derivatives have been found by Saad Samir F.[344].

Christopher Geoffrey et. al.[345] have synthesised imidazolinones and reported their antifungal activities. T. Okasaki et. al.[346] have discovered imidazolinone derivatives as angiotensine II receptor antagonist (VI). Kallurava B. et. al.[347] have reported antibacterial, antiinflammatory and analgesic activity of 5-oxo-imidazoline derivatives.



CONTRIBUTION FROM OUR LABORATORY

Dr. H. H. Parekh et. al.[348] have suggested imidazolinones as antitubercular and anticancer (VII) agents.

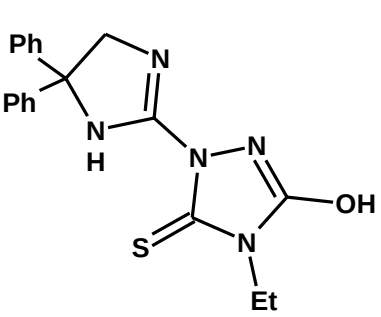


(VII)

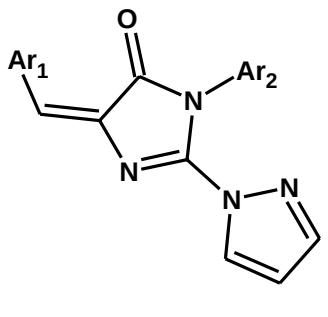
H. H. Parekh and co-workers[349] have synthesised 5-oxo-imidazolines as novel bioactive compounds derived from benzimidazole. P. H. Patel and co-workers[350] have discovered imidazolines bearing 2-amino-thiazole moiety as antimicrobial agents. R. C. Khunt, N. J. Datta and A. R. Parikh[351] have reported 5-oxo-imidazolines as biologically active agents. Hasmukh Kanjaria and co-workers[352] have described imidazolinones as potential antimicrobial agents. Satyan P. Patel and co-workers[353] have synthesis imidazolines as biologically active agents.

Joshi H. et. al.[354] have synthesised imidazolinones as potent anticonvulsant agents. Parikh et. al.[355] have reported 4-(4'-arylidene-2'-phenyl-5'-oxo-imidazolin-1'-yl)-benzophenone and screened for their antimicrobial activity.

Recently, it is found that imidazolinones possess anticancer[356] (VIII), antibacterial[357] (IX) and antimicrobial[358] activities. Coleman P. et. al.[359] have demonstrated imidazole derivatives as immune response modifiers. Essar Franz et. al.[360] have screened imidazolidines for treatment of urinary incontinence.



(VIII)



Ar_1, Ar_2 = Aryl

(IX)

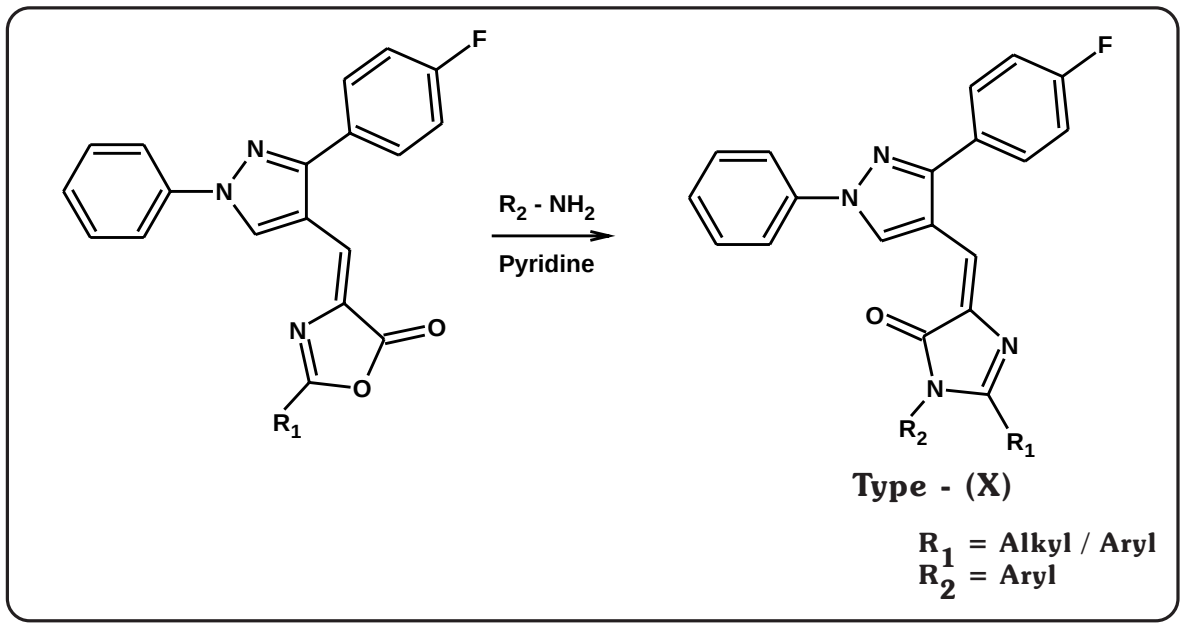
With a view to getting better therapeutic agent, it was contemplated to synthesise imidazolinones to enhance the overall drug potential of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ARYL-2-ALKYL/ARYL-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYLMETHINO)-IMIDAZOLIN-5-ONES.

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ARYL-2-ALKYL/ ARYL-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYL-METHINO)-IMIDAZOLIN-5-ONES

Imidazolinones represent one of the most active classes of compounds having a wide spectrum of biological activities with an aim to getting better therapeutic agent. The preparation of 5-oxo-imidazolines of type (X) have been undeartaken by the condensation of azalatone with different aromatic amines as shown in reaction scheme.



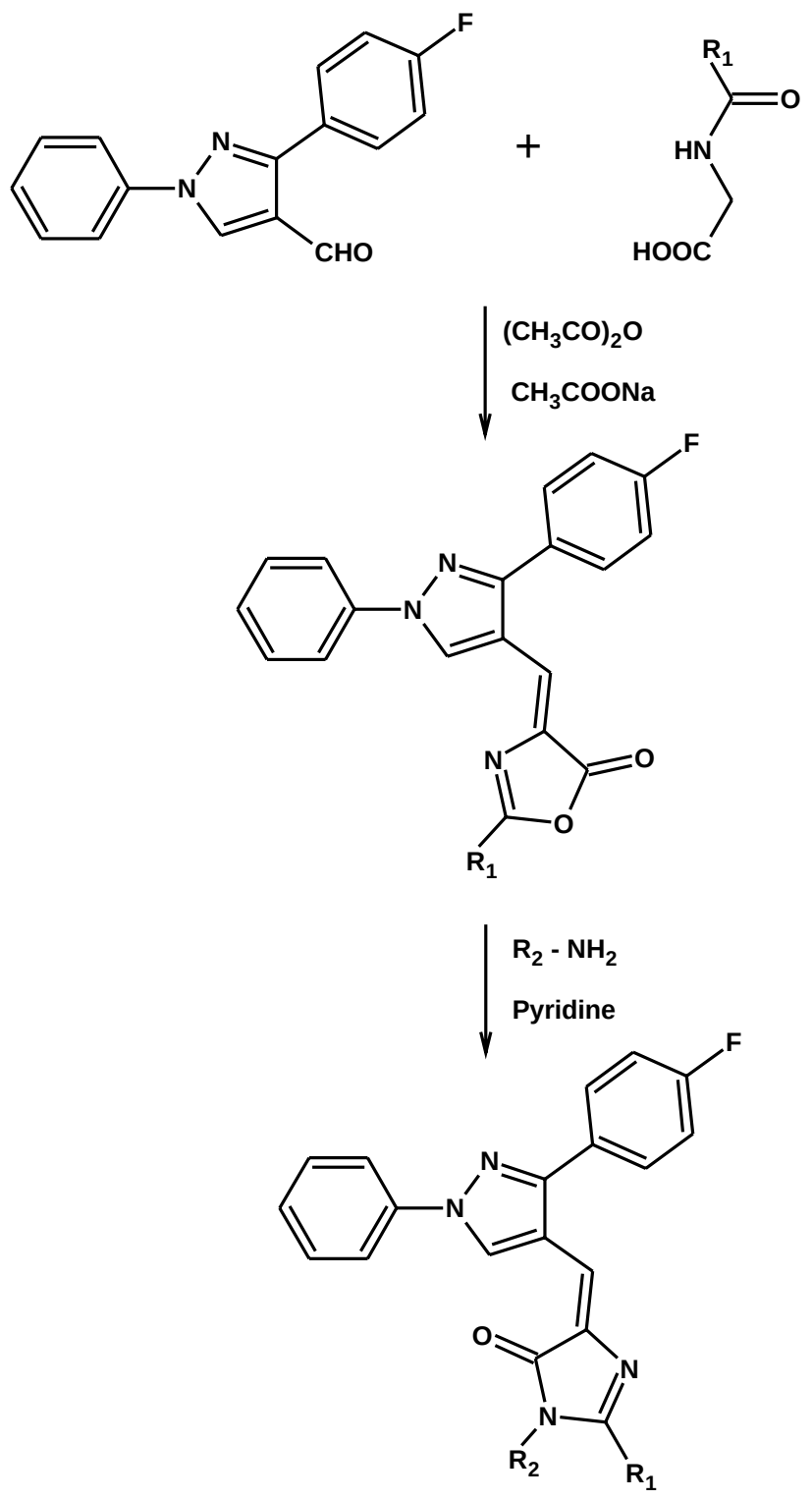
Type - (X)

R_1 = Alkyl / Aryl
R_2 = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

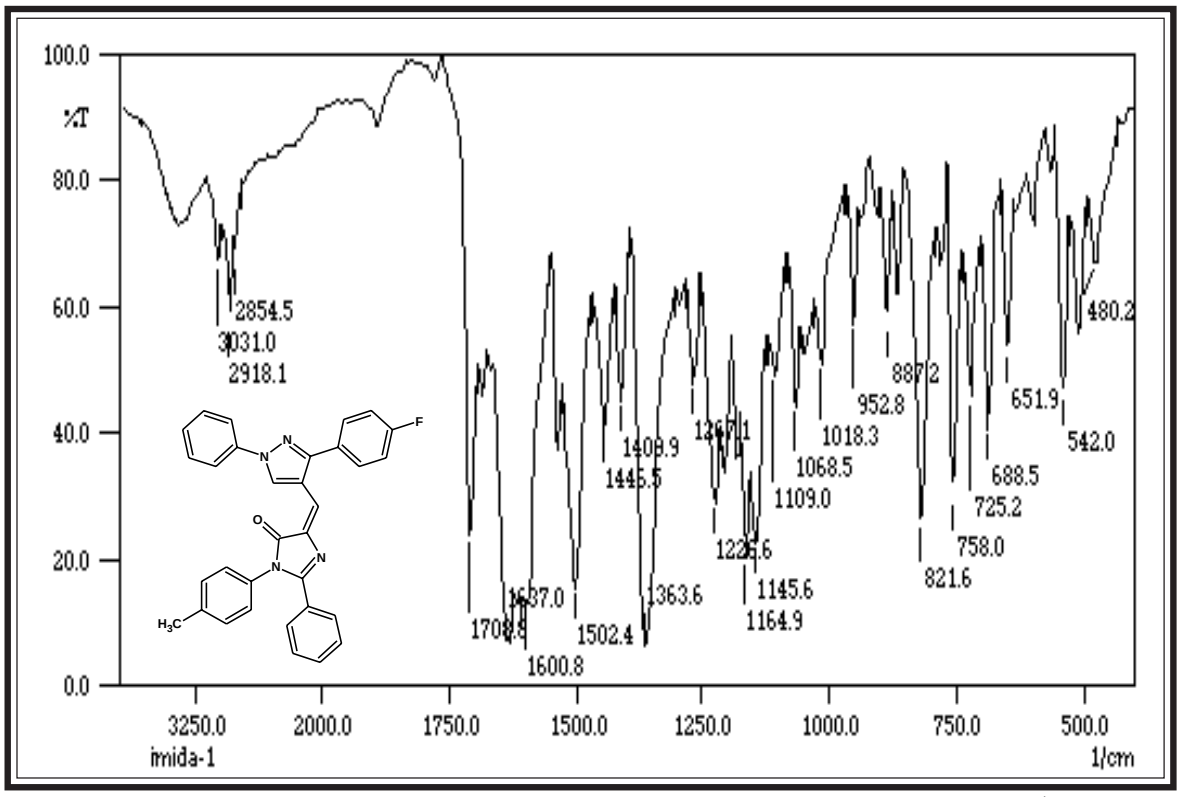
REACTION SCHEME



Type - (X)

R_1 = Alkyl / Aryl
R_2 = Aryl

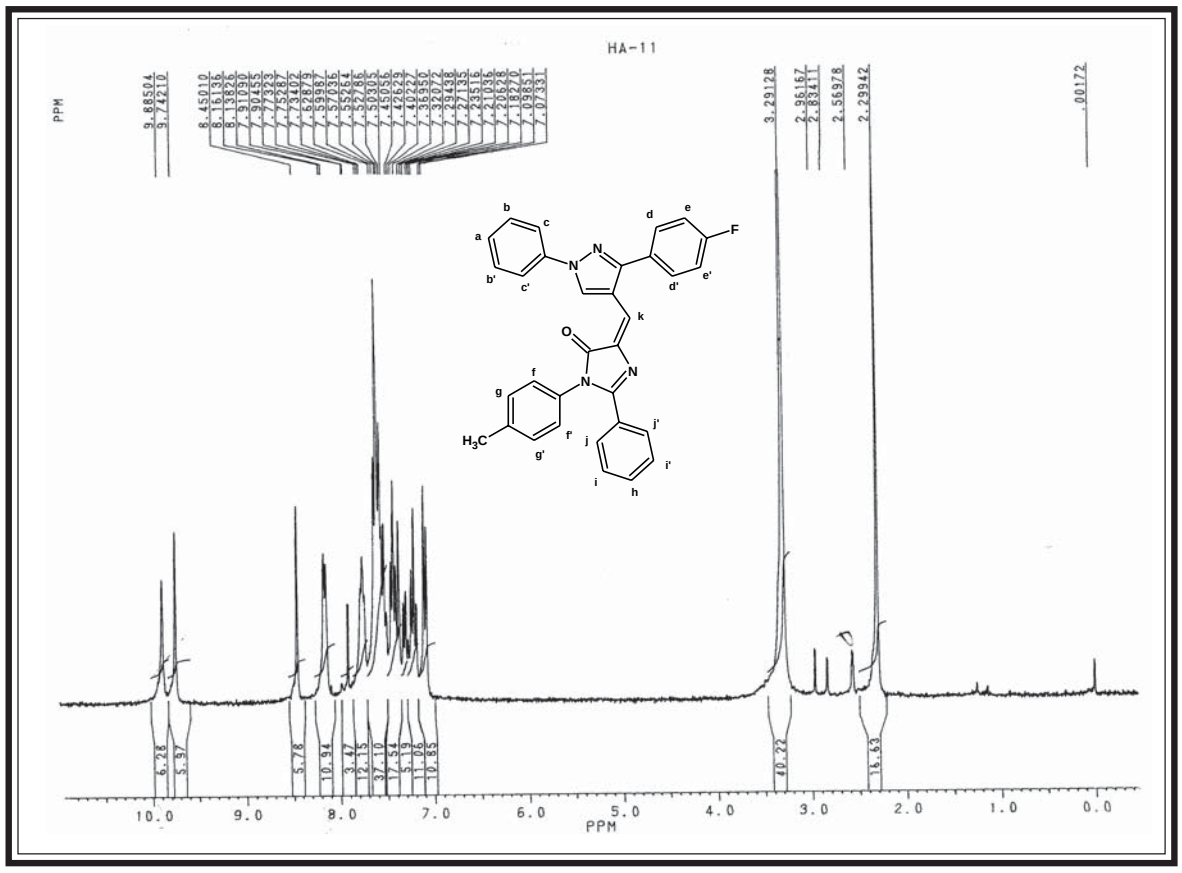
IR SPECTRAL STUDY OF 1,N-p-TOLYL-2-PHENYL-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOL METHINE)-IMIDAZOLIN-5-ONE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2918	2975–2920	426
$-CH_3$	C – H str. (sym.)	2854	2880–2860	"
	C – H i.p. (def.)	1446	1470–1435	"
	C – H o.o.p. (def.)	1363	1395–1370	"
Aromatic	C – H str.	3031	3090–3020	427
	C = C str.	1502	1585–1480	"
	C – H i.p. (def.)	1109	1125–1090	"
		1068	1070–1000	"
	C – H.o.o.p (def.)	821	840–810	"
Pyrazole	C = N str.	1600	1650–1590	428
moety	C = C str.	1502	1585–1480	"
	C – F	758	760–700	"
Imidazolinone	C = O str.	1708	1760–1655	426
ring	C = N str.	1637	1650–1580	"
	C – N – C str.	1145	1160–1130	"

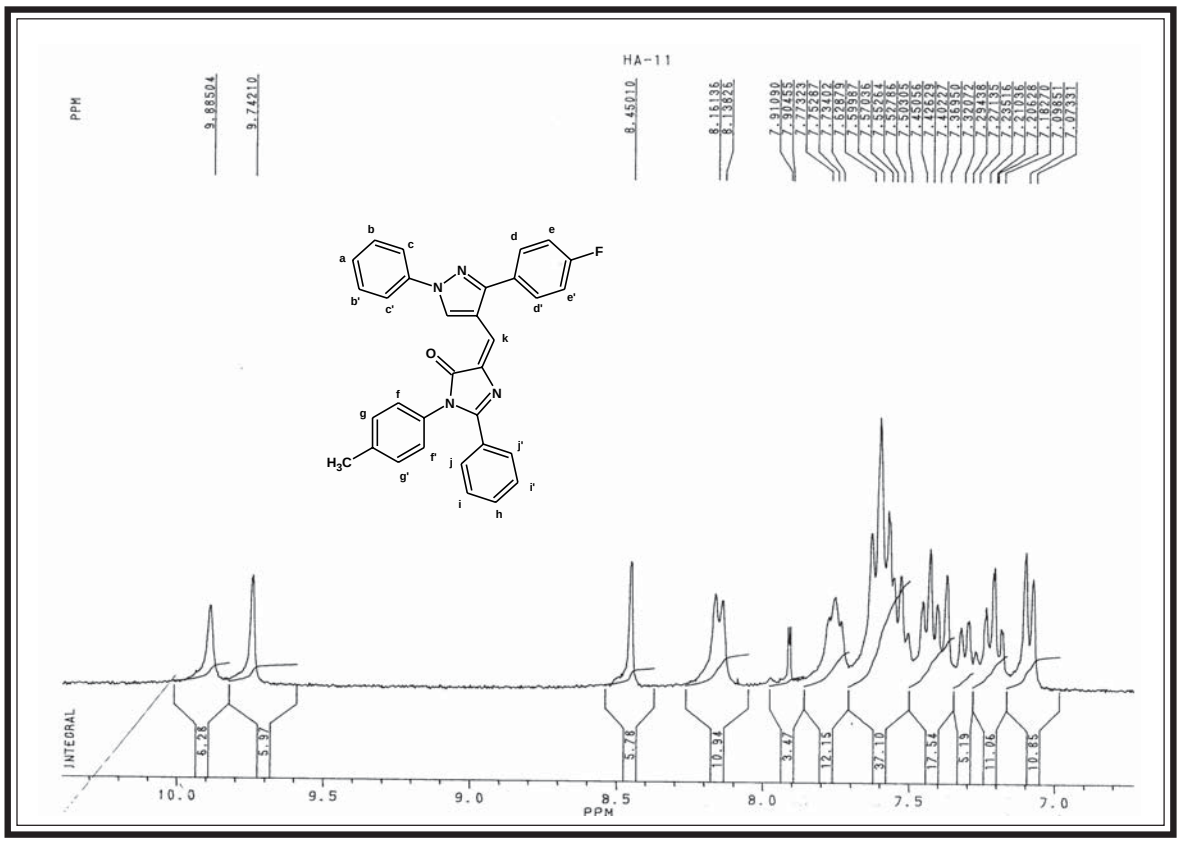
PMR SPECTRAL STUDY OF 1,N-TOLYL-2-PHENYL-4-[1',N-PHENYL,3'-p-FLUOROPHENYL-PYRAZOL-4'-YL-METHINO]-IMIDAZOLIN-5-ONES

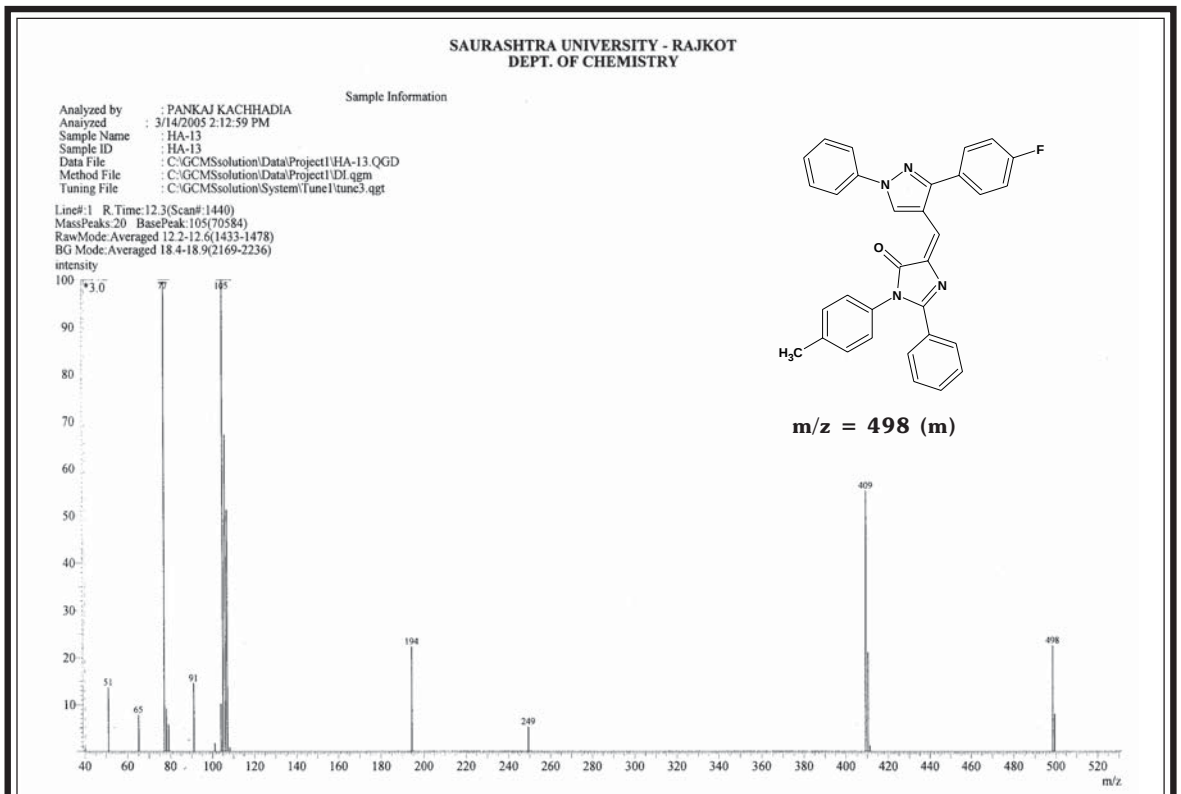


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1	2.29	3H	singlet	Ar-CH_3	-
2.	7.07-7.09	2H	doublet	Ar-Hgg'	
3.	7.18-7.21	2H	triplet	Ar-H*e*e'	Jef=7.6
4.	7.23-7.29	1H	triplet	Ar-Ha	-
5.	7.32-7.42	3H	quarlet	Ar-Hbb'+Hh	-
6.	7.50-7.62	6H	multiplet	Ar-Hii'+jj'+dd'	-
7.	7.73-7.77	2H	triplet	Ar-Hcc'	_-
8.	8.13-8.16	2H	doublet	Ar-Hff'	Jfe=6.9
9.	8.45	1H	singlet	CHx	-
10.	9.74	1H	singlet	CHk	-

EXPANDED AROMATIC REGION





EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ARYL-2-ALKYL/ ARYL-4-(1',N-PHENYL-3'-p-FLUOROPHENYLMETHINO)-IMIDAZOLIN-5-ONES

[A] Synthesis of 1,N-phenyl-3-p-fluorophenyl-4-formyl pyrazole

See, Part-I, Section-I (B).

[B] Synthesis of 2-phenyl-4-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolyl methino)-oxazolin-5-one

A mixture of 1,N-phenyl-3-p-fluorophenyl-4-formyl pyrazole (2.65gm, 0.01M), acetic anhydride (2.5 ml, 0.025 M) sodium acetate (1.2 gm 0.015M) and hippuric acid (2.59g, 0.015M) was heated on a water bath for 4 hrs. Resulting mass wass poured into ice cold water, filtered and crystallised from MeoH. Yield, 67%, m.p. 144°C, ($C_{25}H_{16}FN_3O_2$; Found : C, 73.26%; H, 3.88%; N, 10.17%; Requires : C, 73.34%; H, 3.94%; N, 10.26%).

[C] Synthesis of 1,N-Tolyl-2-phenyl-4-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolylmethino)-imidazoline-5-one

A mixture of 2-phenyl-4-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolylmethino)-oxazolin-5-one (4.08g, 0.01M) and toludine (1.07g, 0.01M) in dry pyridine (20 ml) was refluxed for 9 hrs. at temp. 140°C in oil bath. temp Resulting mass was poured into crushed ice and neutralised with HCl, filtered and crystallized from DMF. Yield, 67%; m.p. 244°C, ($C_{32}H_{23}FN_4O$: Found : C 78.96%; H, 6.57%; N, 11.14%; Required : C, 77.09%; H, 4.65%; N, 11.24%).

Similarly, other imidazolin-5-ones have been prepared. The physical constants are recorded in Table No. 10.

[D] Antimicrobial activity of 1,N-Aryl-2-alkyl/aryl-4-(1',N-phenyl-3'-p-fluorophenyl-4'-pyrazolylmethino)-imidazolin-5-ones

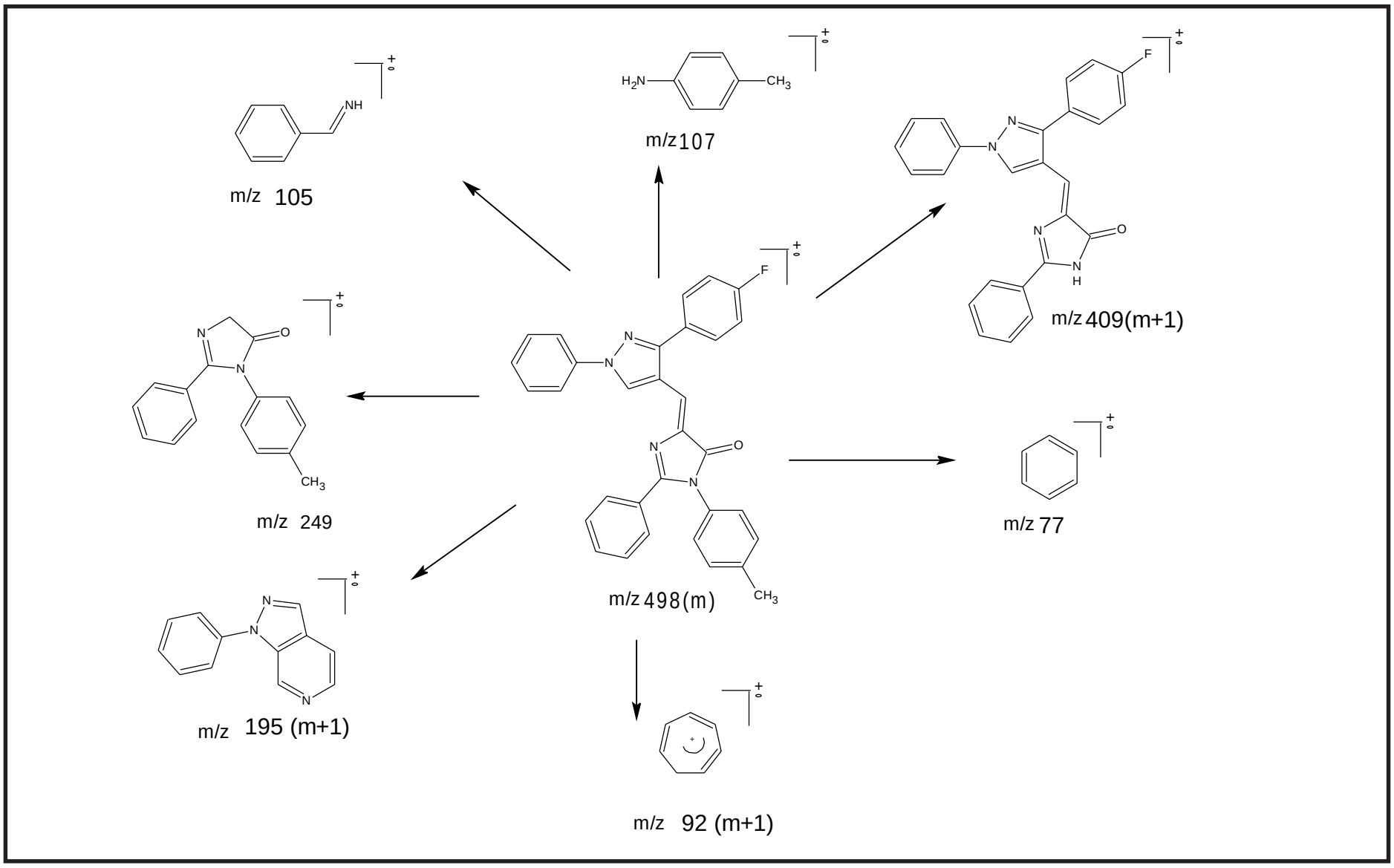
Antimicrobial activity was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No.10.

TABLE NO. 10 : PHYSICAL CONSTANTS OF 1,N-ARYL-2-ALKYL/ARYL-4-(1',N-PHENYL-3'-p-FLUOROPHENYL-4'-PYRAZOLYLMETHINO)-IMIDAZOLIN-5-ONES

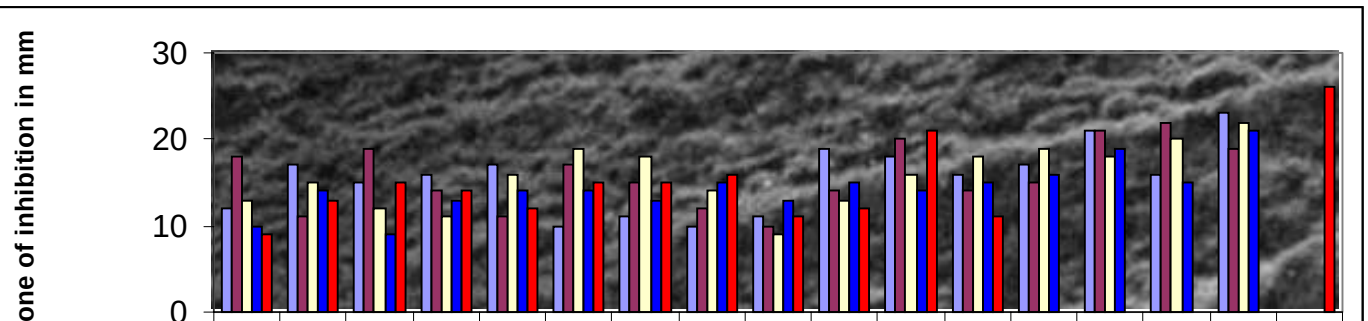
Sr. No. 1	R_1 2	R_2 3	Molecular Formula 4	Molecular Weight 5	M.P. °C 6	Rf* Value 7	Yield % 8	% of Nitrogen Calcd. 9	% of Nitrogen Found 10
10a	C_6H_5-	C_6H_5	$C_{31}H_{21}FN_4O$	484.5	232	0.62	68	11.56	11.48
10b	C_6H_5-	4-OCH_3-C_6H_4-	$C_{32}H_{23}FN_4O_2$	514.5	221	0.58	55	10.89	10.81
10c	C_6H_5-	4-CH_3-C_6H_4-	$C_{32}H_{23}FN_4O$	498.5	244	0.61	67	11.24	11.14
10d	C_6H_5-	4-Cl-C_6H_4-	$C_{31}H_{20}ClFN_4O$	518.9	205	0.57	63	10.80	10.72
10e	C_6H_5-	3-Cl-C_6H_4-	$C_{31}H_{20}ClFN_4O$	518.9	228	0.55	68	10.80	10.71
10f	C_6H_5-	4-F-C_6H_4-	$C_{31}H_{20}F_2N_4O$	502.5	195	0.51	57	11.15	11.07
10g	C_6H_5-	2-F-C_6H_4-	$C_{31}H_{20}F_2N_4O$	502.5	219	0.47	71	11.15	11.05
10h	C_6H_5-	3,4-$(Cl)_2$-C_6H_3-	$C_{31}H_{19}Cl_2FN_4O$	553.4	179	0.56	65	10.12	10.03
10i	C_6H_5-	3-Cl,4-F,C_6H_3-	$C_{31}H_{19}ClF_2N_4O$	536.9	188	0.49	58	10.43	10.32
10j	C_6H_5-	2,4-$(CH_3)_2$-C_6H_3-	$C_{33}H_{25}FN_4O$	512.5	213	0.59	66	10.93	10.83
10k	C_6H_5-	4-Br-C_6H_4-	$C_{31}H_{20}BrFN_4O$	563.4	209	0.64	59	9.94	9.87
10l	C_6H_5-	4-NO_2-C_6H_4-	$C_{31}H_{20}FN_5O_3$	529.5	237	0.50	60	13.23	13.15

*TLC Solvent System : Ethyl acetate : Hexane

1.5 : 8.5


m/z 105
m/z 107
m/z 409(m+1)
m/z 249
m/z 498(m)
m/z 77
m/z 195 (m+1)
m/z 92 (m+1)

GRAPHYCAL CHART NO.10: **ANTIMICROBIAL ACTIVITY OF 1,N-ARYL-2-ALKYL/ARYL-4-[1'N- PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL] -IMIDAZOLIN-5-ONES.**



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Amoxycillin	Benzoyl Peni	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	12	17	15	16	17	10	11	10	11	19	18	16	17	21	16	23	0
B. subtillus	18	11	19	14	11	17	15	12	10	14	20	14	15	21	22	19	0
E. coli	13	15	12	11	16	19	18	14	9	13	16	18	19	18	20	22	0
P. vulgaris	10	14	9	13	14	14	13	15	13	15	14	15	16	19	15	21	0
A. niger	9	13	15	14	12	15	15	16	11	12	21	11	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The activity data shows that all the imidazolinones (type-X) were able to inhibit the growth of Gram positive & Gram negative bacterial strains.

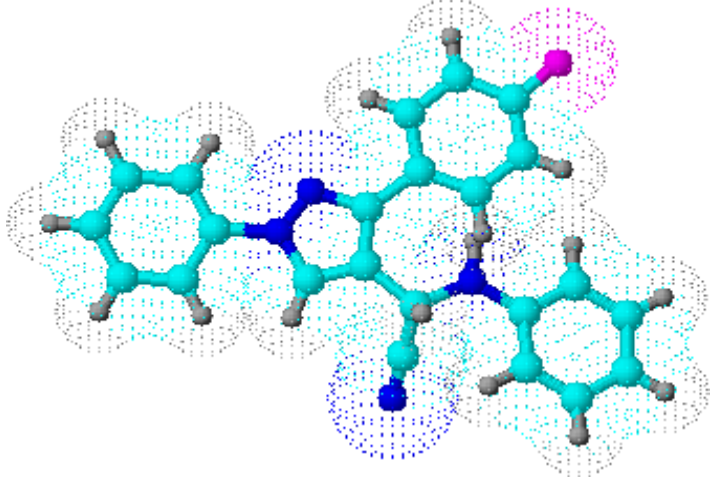
Compounds bearing R=4-methyphenyl 4-bromophenyl & 2,4-dimethylphenyl were observed to give the promising activity against Gram positive bacterial strains ***B. cocous*** & ***B. subtillus*** respectively, as compared to standard drugs. Significant activity was displayed by compounds bearing R=4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl and 4-nitrophenyl.

In case of Gram negative bacterial strains, maximum activity was observed in compounds bearing R=4-fluorophenyl and 3-nitrophenyl against ***E. coli*** and ***P. vulgaris***. Significant activity was displayed by compounds bearing R=2-fluorophenyl and 3,4-dichlorophenyl against these Gram negative bacterial strains.

ANTIFUNGAL ACTIVITY

All the compounds were mild to moderately active against fungal strain ***A. niger***. Maximum activty was observed in compound bearing R=4-bromophenyl.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.



PART-VIII
STUDIES ON NITRILES

INTRODUCTION

Nitriles are reported to possess various therapeutic activities, but due to their high toxicity, they have low therapeutic importance. The term "Nitrile" was first introduced by Febung[361] in 1844. The first synthesis of nitrile has been reported by Wohler and Liebig[362] in 1832 and Poleuze[363] in 1834. They are very much useful as intermediates for various products such as acrylonitrile for plastic, synthetic rubber and fibers, phthalonitrile for dye stuff.

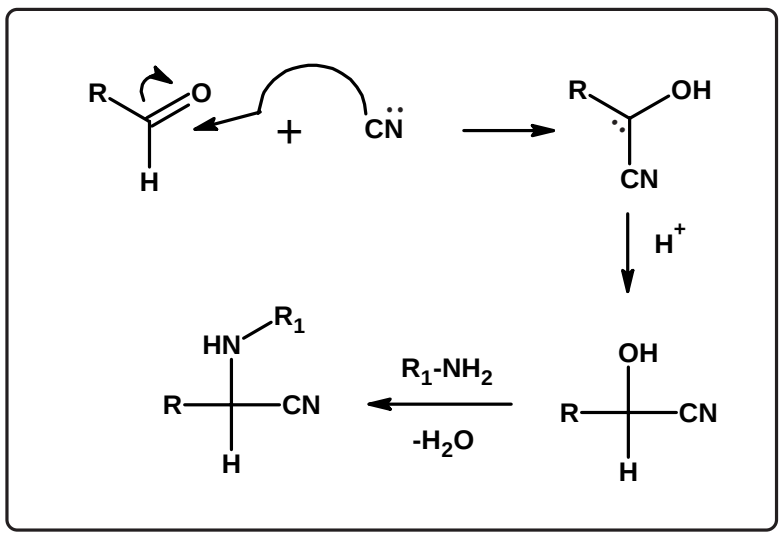
SYNTHETIC ASPECTS

D. Mowry[364] reviewed various methods of preparation of nitrile. Few recent methods are as mentioned below.

1. From alkylhalides using KCN tetraalkyl ammonium salt[365] and water in trace.
2. The pyrolysis of schiff's base[366]
3. MOhanakrishna A. K. and co-worker[367] have synthesised nitrile derivatives

MECHANISM

The mechanism of nitrle is shown as under.



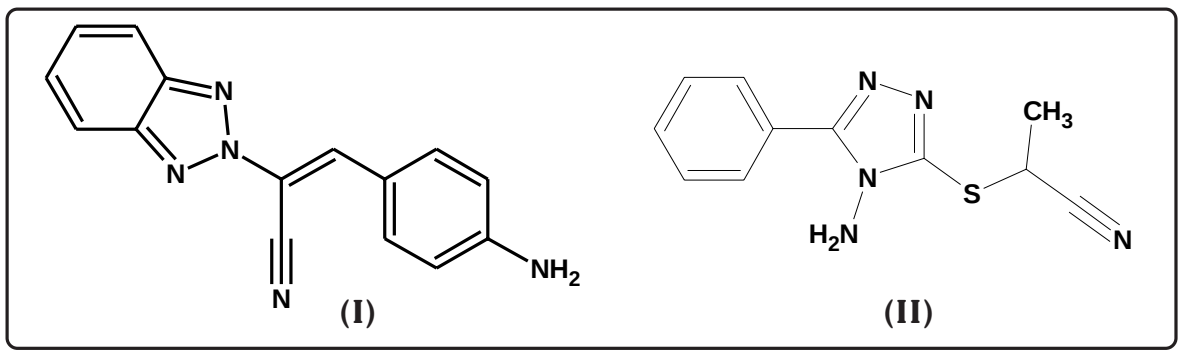
THERAPEUTIC EVALUATION

They shows various therapeutic activities, which are described as under.

1. Antihypertensive[368]
2. Central nervous system agent[369]
3. Antimicrobial[370]
4. Antihypoxic[371]
5. Antiinflammatory[372]
6. Antiarrytheymic[373]
7. Pesticidal[374]
8. Fungicidal[375]

Kobayashi Shigco et. al.[376] have synthesised new derivatives of nitriles. Nitriles with fused pyridine ring were reported as ulcer inhibitors[377]. Cardenalide nitrile showed moderate biological activity in rats[378]. M. C. Dougal[379] have synthesised nitriles and studied their pharmacological activities.

Parlo Sanna et. al.[380] have synthesised nitriles(I) and screened for their antitubercular activity. Iwanowicz E. J. et. al.[381] have prepared nitriles (II) and found to preventing and treating IMPDH associated disorders, such as transplant rejection and autoimmune disease.



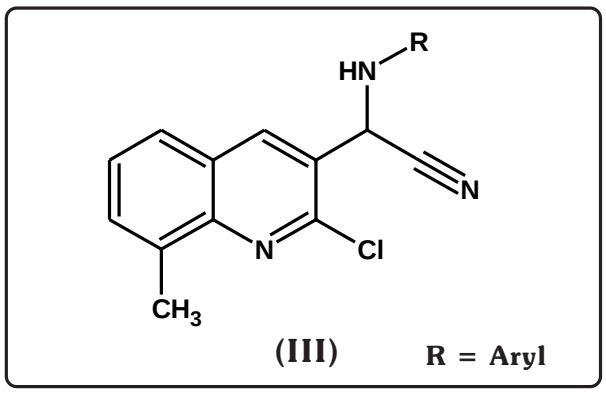
V. Juliya et. al.[382] synthesised some new nitriles and reported them as anticonvulsant agent. Shibata Yasushi and co-workers[383] have synthesised nitrile derivatives associated with insecticidal activity. Nosyrava et. al.[384] have prepared novel nitriles which have been shown to possess muscle relaxant activity. Yagihara and co-workers[385] have prepared nitrile which possess antimicrobial and antiinflammatory activity.

Altmann Eva et. al.[386] have discovered dipeptide nitriles as inhibitors of cysteine cathepsins. Shibata Yasushi et. al.[387] have synthesised and reported nitrile derivatives as insectisides and miticides.

Recently, Colin Xavier and co-workers[388] have synthesised antifungal acetonitriles. Bernard M. et. al.[389] have prepared nitriles as thromboxane receptor antagonists. Alwal K. S. et. al[390] have prepared nitriles as inhibitors of mitochondrial F_1F_{10} AT pase. Murakkami Hiroshi et. al.[391] have synthesised some new nitriles and screened for their pesticidal and marine antifouling activity.

CONTRIBUTION FROM OUR LABORATORY

F. M. Bharmal et. al.[392] have synthesised newer acetonitriles bearing quinoline moiety and tested as antimicrobial agents (III).



(III) **R = Aryl**

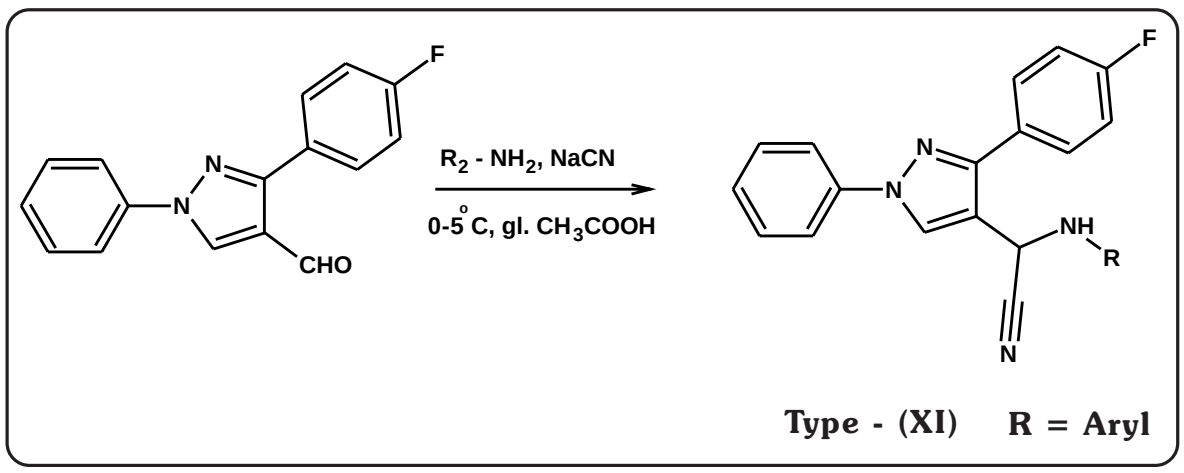
Looking to the interesting properties of nitriles, we have synthesised some new nitriles, which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF α-ARYLAMINO-1,N-PHENYL-3-p-FLUOROPHENYL-PYRAZOL-4-YL-ACETONITRILES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF α-ARYLAMINO-1,N-PHENYL-3-p-FLUOROPHENYL PYRAZOL-4-YL-ACETONITRILES

In view of the therapeutic activities of nitriles it was contemplated to synthesise some new nitriles in search of agents possessing higher biological activity. Nitrles of type (XI) have been synthesised by the reaction of 1,N-phenyl-3-p-fluorophenyl-4-formyl-pyrazole with different aromatic amines by the presence of sodium cyanide and glacial acetic acid at 0-5°C.



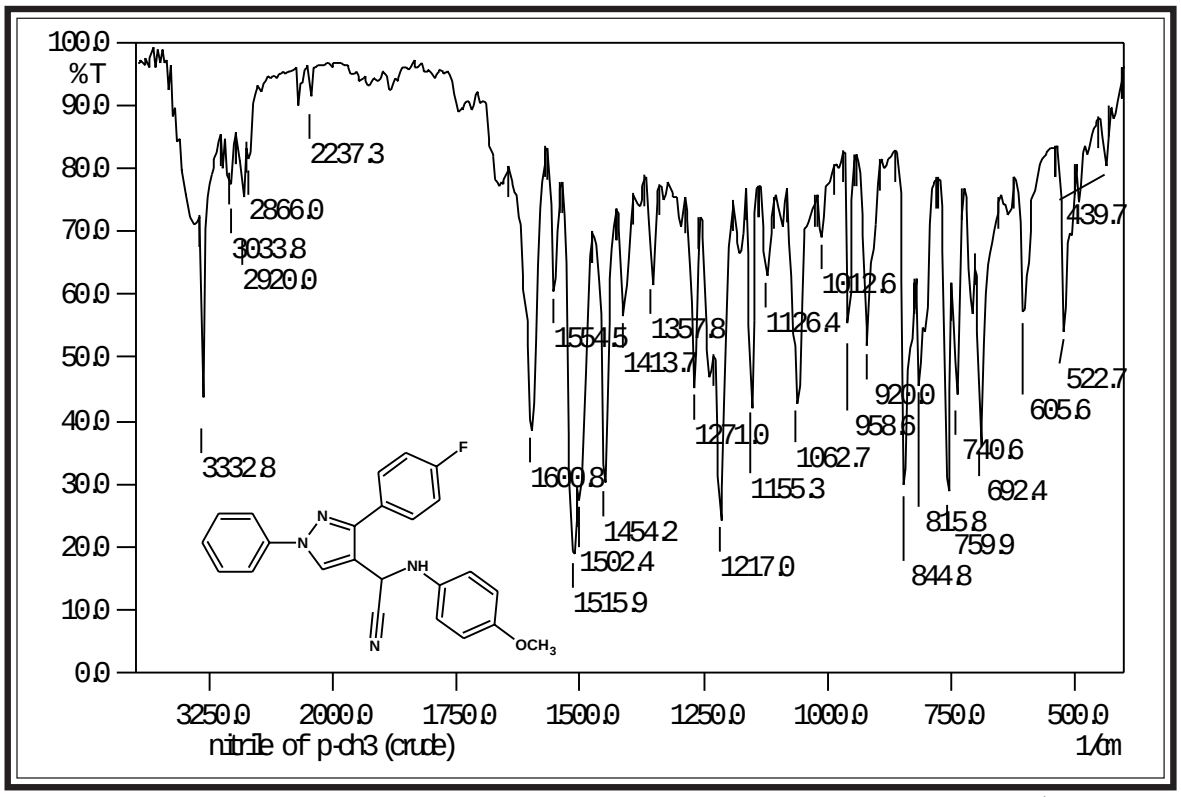
Type - (XI) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antimicrobial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at concentration of 6.25 μg/ml using Rifampin as standard drug.

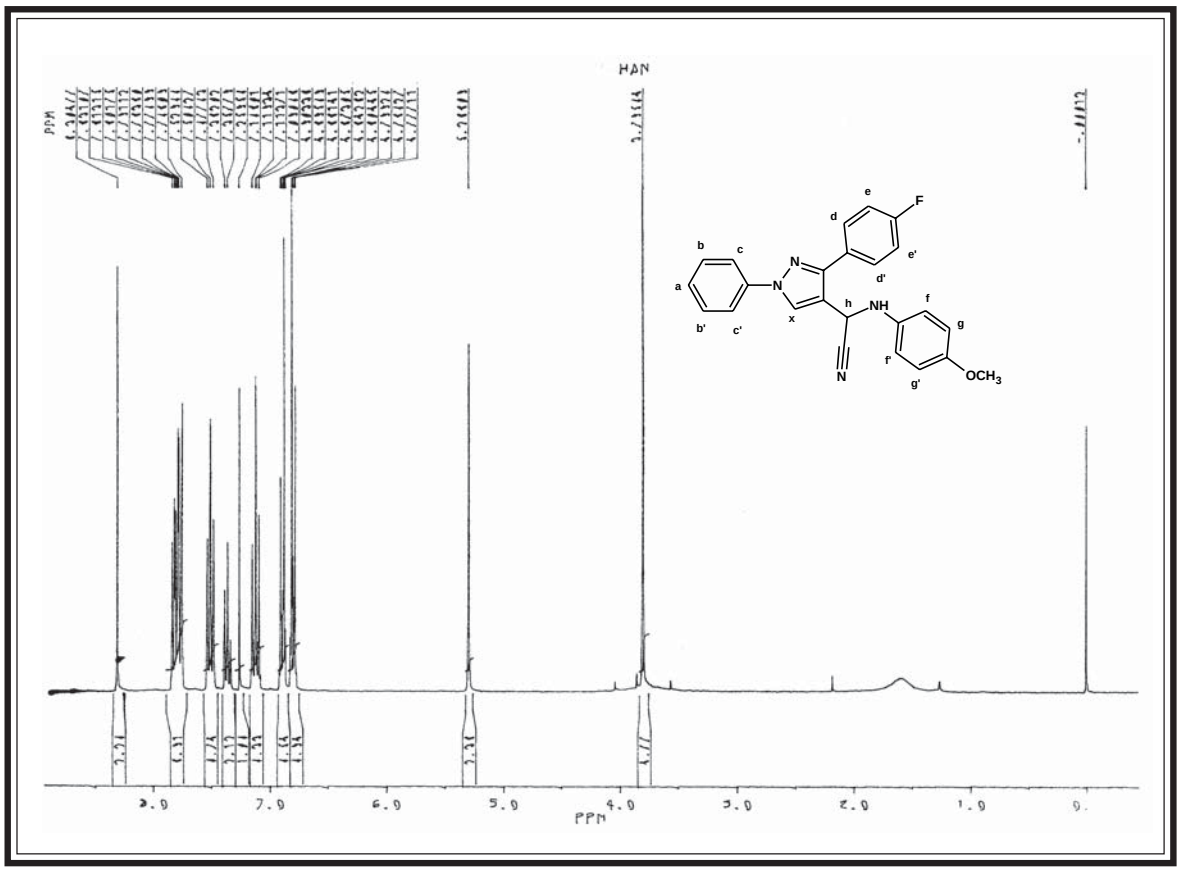
IR SPECTRAL STUDY OF α-(p-ANISYLAMINO)-1,N-PHENYL-3-p-FLUOROPHENYL-PYRAZOL-4-YL-ACETONITRILE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2920	2975–2920	426
$-CH_3$	C – H str. (sym.)	2866	2880–2860	"
	C – H i.p. (def.)	1454	1470–1435	"
	C – H o.o.p. (def.)	1357	1395–1370	"
Aromatic	C – H str.	3033	3090–3030	427
	C = C str.	1554	1520–1480	"
	C – H i.p. (def.)	1126	1125–1090	"
		1062	1070–1000	"
	C – H.o.o.p (def.)	815	835–810	"
Pyrazole	C = N str.	1600	1610–1590	428
moety	C – N str.	1217	1230–1220	"
	C = C str.	1515	1585–1480	"
	C – F	759	760–710	"
Nitrile	C ≡ N str.	2237	2240–2220	432
	N – H str. (sym.)	3332	3450–3200	"

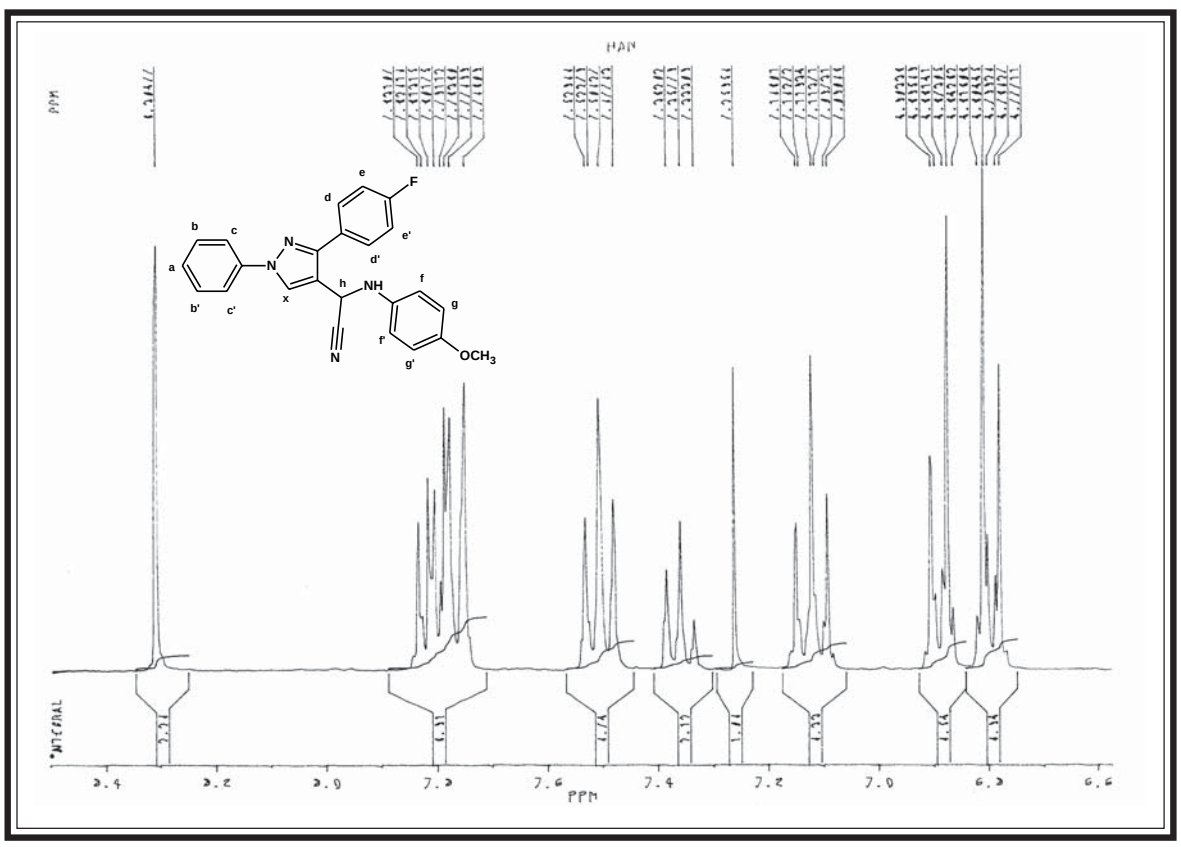
PMR SPECTRAL STUDY OF α-(p-ANISYLAMINO)-1,N-PHENYL-3-p-FLUOROPHENYL-PYRAZOL-4-YL ACETONITRILE

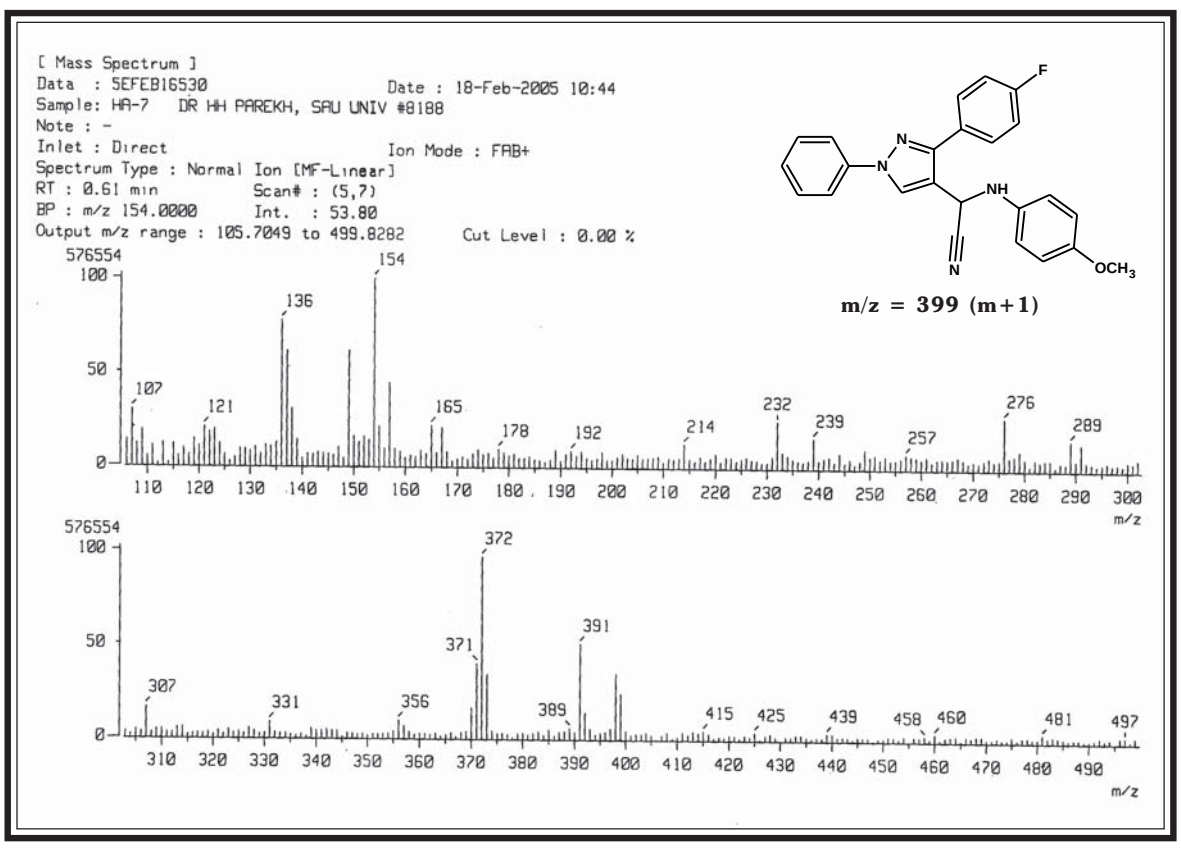


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	3.79	3H	singlet	Ar-OCH_3	-
2.	5.28	1H	singlet	CHh	-
3.	6.77-6.80	2H	doublet	Ar-Hgg'	Jgf=8.7
4.	6.87-6.90	2H	doublet	Ar-Hdd'	Jde=9
5.	7.09-7.14	2H	triplet	Ar-Hbb'	-
6.	7.33-7.36	1H	triplet	Ar-Ha	-
7.	7.47-7.52	2H	triplet	Ar-Hee'	-
8.	7.74-7.83	4H	multiplet	Ar-Hff' + Hcc'	-
9.	8.30	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





m/z = 399 (m+1)

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF α-ARYLAMINO-1,N-PHENYL-3-p-FLUOROPHENYL-PYRAZOL-4-YL-ACETONITRILES

[A] Synthesis of N-Phenylamino-α-methyl-α-p-fluorophenyl-azomethine

See, Part-I, Section-I (B).

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl-pyrazole

See, Part-I, Section-I (B).

[C] Synthesis of α-(p-Anisylamino)-1,N-phenyl-3-p-fluorophenyl-pyrazol-4-yl-acetonitrile

1,N-Phenyl-3-p-fluorophenyl-4-formyl-pyrazole (2.65g, 0.01M) dissolved in ethanol (20 ml) was added to sodium cyanide (0.48g, 0.01M) dissolved in water (5 ml) followed by glacial acetic acetic acid (5 ml). The contents were then stirred for 5 minutes to form cyanohydrin at 0°C. p-Anisidine (1.23g, 0.01M) dissolved in methanol was added to the reaction mixture, contents were kept at room temp. for 24 hrs. and poured into ice. The solid product was crystallized from DMF. Yield, 70%, m.p. 199°C ($C_{24}H_{19}FN_4O$; Found : C, 72.28%; H, 4.74%; N, 13.98%; Requires : C, 72.35%; H, 4.81%; N, 14.06%).

Similarly, other nitriles were prepared. The physical constants are recorded in Table No. 11.

[D] Therapeutic activity of α-Arylamino-1, N-phenyl-3-p-fluorophenyl-pyrazole-4-yl-acetonitriles

Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 11.

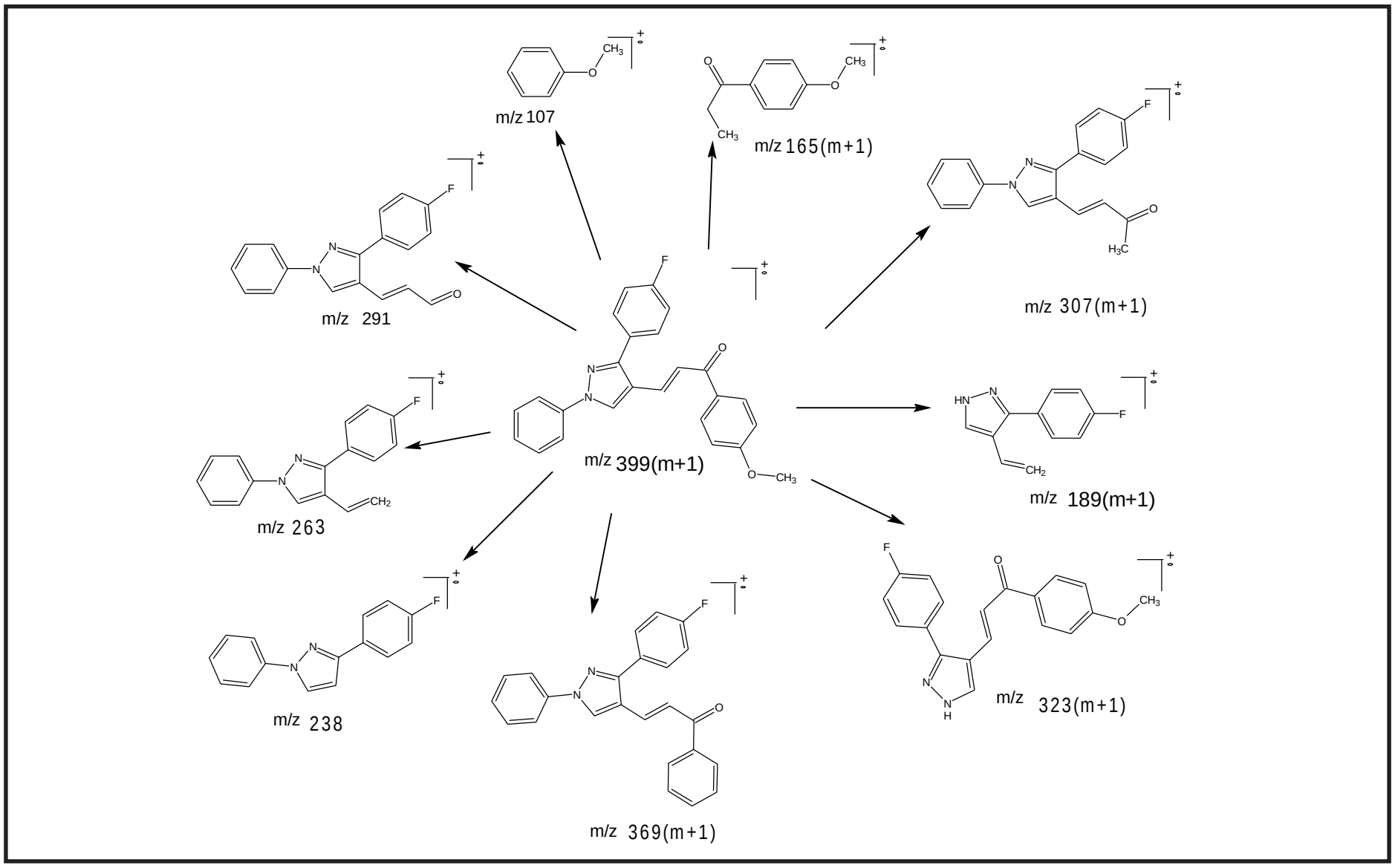
Antitubercular screening of the compounds of type(XI) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 11a.

TABLE NO.11 : PHYSICAL CONSTANTS OF α-ARYLAMINO-1,N-PHENYL-p-FLUOROPHENYL PYRAZOL-4-YL-ACETONITRILES

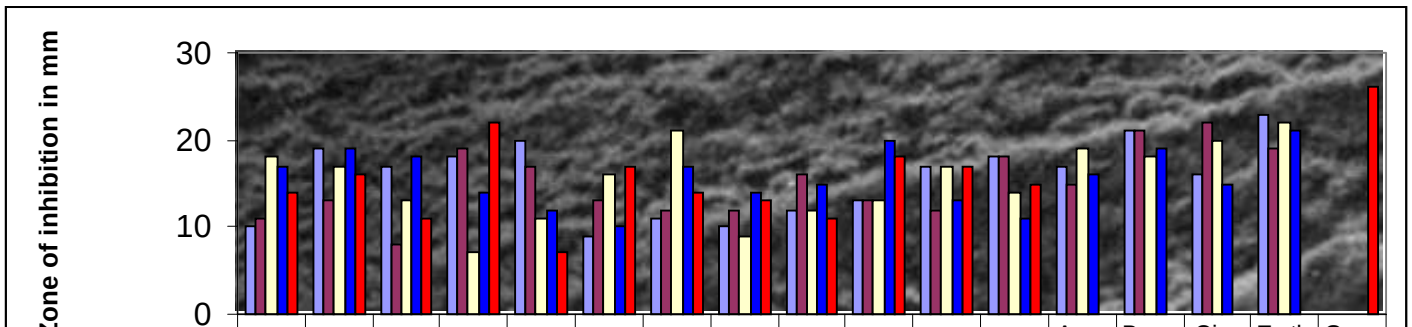
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
11a	C_6H_5-	$C_{23}H_{17}FN_4$	368.4	167	0.48	64	15.21	15.16
11b	4-OCH_3-C_6H_4-	$C_{24}H_{19}FN_4O$	398.4	199	0.47	70	14.06	13.98
11c	4-CH_3-C_6H_4-	$C_{24}H_{19}FN_4$	382.4	141	0.50	62	14.65	14.57
11d	2-CH_3-C_6H_4-	$C_{24}H_{19}FN_4$	382.4	172	0.52	58	16.65	16.56
11e	4-Cl-C_6H_4-	$C_{23}H_{16}ClFN_4$	402.8	189	0.57	71	13.91	13.85
11f	3-Cl-C_6H_4-	$C_{23}H_{26}ClFN_4$	402.8	177	0.60	67	13.91	13.83
11g	4-F-C_6H_4-	$C_{23}H_{16}F_2N_4$	386.3	154	0.63	61	14.50	14.42
11h	3,4-$(Cl)_2$-C_6H_3-	$C_{23}H_{15}Cl_2FN_4$	437.2	180	0.65	68	12.81	12.76
11i	2,3-$(Cl)_2$-C_6H_3-	$C_{23}H_{15}Cl_2FN_4$	437.2	193	0.53	63	12.81	12.73
11j	3-Cl,4-F-C_6H_3-	$C_{23}H_{15}ClF_2N_4$	420.8	202	0.56	59	13.31	13.24
11k	3-NO_2-C_6H_4-	$C_{23}H_{16}FN_5O_2$	413.4	162	0.55	69	16.94	16.87
11l	4-Br-C_6H_4-	$C_{23}H_{18}BrFN_4$	447.3	175	0.49	67	12.53	12.45

*TLC Solvent System : Acetone : Benzene

1.8 : 8.2


m/z 107
m/z 165(m+1)
m/z 307(m+1)
m/z 291
m/z 399(m+1)
m/z 263
m/z 189(m+1)
m/z 238
m/z 369(m+1)
m/z 323(m+1)

GRAPHYCAL CHART NO.11: **ANTIMICROBIAL ACTIVITY OF a-ARYLAMINO-1,N-PHENYL-3-p- FLUOROPHENYL PYRAZOL-4-YL -ACETONITRILES.**



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	Amoxycillin	Benzoyl Peni	Ciprofloxacin	Erythromycin	Greseofulvin
B. cocous	10	19	17	18	20	9	11	10	12	13	17	18	17	21	16	23	0
B. subtillus	11	13	8	19	17	13	12	12	16	13	12	18	15	21	22	19	0
E. coli	18	17	13	7	11	16	21	9	12	13	17	14	19	18	20	22	0
P. vulgaris	17	19	18	14	12	10	17	14	15	20	13	11	16	19	15	21	0
A. niger	14	16	11	22	7	17	14	13	11	18	17	15	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

The antibacterial activity of acetonitriles (type-XI) revealed that many compounds were able to inhibit the growth of Gram positive and Gram negative bacterial strains.

Maximum activity was observed in compounds bearing R=2-methylphenyl and 4-chlorophenyl against Gram positive bacterial strains ***B. cocous*** and ***B. subtillus***. Significant activity was displayed by compounds bearing R=4-methylphenyl, 4-methoxyphenyl 3-nitrophenyl and 4-bromophenyl.

While in case of Gram negative bacterial strains, highest activity was displayed by compounds bearing R=4-methoxyphenyl and 4-fluorophenyl against ***E. coli*** & ***P. vulgaris***. Significant activity was observed in compounds bearing R=phenyl, 2,3-dichlorophenyl and 3-chloro-4-fluorophenyl.

ANTIFUNGAL ACTIVITY

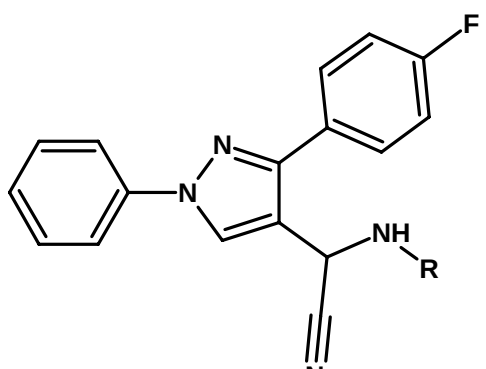
All the compounds were mild to moderately active against ***A. niger*** fungal strain. Maximum activity was displayed by compound bearing R=2-methylphenyl.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

ANTITUBERCULAR ACTIVITY

All the compounds were found to be less active against ***Mycobacterium tuberculosis*** $H_{37}Rv$ ranging from 3 to 41% inhibition.

TABLE NO. 11a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*MTb Strain*	*MIC µg/ml*	*% Inhib*	*Activity*	*Comment*
295598	HCV-92	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	0	-	MIC Rifampin = 0.25 µg/ml @ 98% Inhibition
295599	HCV-93	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295600	HCV-94	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12	-	"
295601	HCV-95	2-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	23	-	"
295602	HCV-96	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	3	-	"
295603	HCV-97	3-Cl-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	4	-	"
295604	HCV-98	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	4	-	"
295605	HCV-99	3/4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	41	-	"
295606	HCV-100	2/3-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295607	HCV-101	3-Cl,4-F--C_6H_3-	Alamar	$H_{37}Rv$	>6.25	8	-	"
295608	HCV-102	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	14	-	"
295609	HCV-103	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"

[B]

STUDIES ON MICROWAVE INDUCED SYNTHESIS

INTRODUCTION OF PYRAZOLINES

See Part-I

MICROWAVE INDUCED SYNTHESIS

INTRODUCTION

In the last few years Microwave induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis[393] & many researchers have described accelerated organic reaction and a large number of papers has appeared proving the synthetic utility of MORE chemistry in routing organic synthesis. It can be termed as "e-chemistry' because it is easy, effective, economical and eco-friendly and is believed to be a step to-wards green chemistry.

Microwave assisted synthesis in general is likely to have a large impact on synthetic organic chemistry in particular the medicinal/combinatorial chemistry communities compared to tradition processing of organic synthesis, microwave enhanced chemistry saves significant time and very offen improves yields.

GENERAL PRINCIPLES

The microwave region of the electromagnetic spectum lies between 1 cm and 1 m and in order to aviod interfering with radar and telecommunication activities which operate within this region, most domestic and commercial microwave instruments operate at 2.45 GHz. The heating effect utilised in microwave assisted organic transformations is due in the main, to dielectric polarisation, although conduction losses can be important particularly at higher temperatures. Whilst the polarisability of a molecule (determined by the Debye equation) is the sum of a number of contributions, only dipolar and interfacial

polarisation are important to heating effects associated with microwave irradiation. When a molecule is irradiated with microwaves it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation and consequently the molecule continually attempts to realign itself with the changing field and energy is absorbed. It is particularly convenient that qualitatively, the larger the dielectric constant the great the coupling with microwaves. Thus solvents such as water, methanol, DMF, ethyl acetate, acetone, chloroform, acetic acid and dichloromethane are all heated when irradiated with microwaves. Solvents such as hexane, toluene, diethyl ether, CCl_4, do not couple and therefore do not heat with microwave irradiation although it is of course possible to use mixtures comprising microwave active/microwave inactive solvents.

POWER SOURCES

The development of electron in tubes including those for the most microwave range, has been a mature field. Today it is feasible to generate almost any desired power level for microwave frequencies of practical interest limited only by cost.

Power sources in the millimeter wave range are mostly in the category of extended interaction Klystrons or narrow band backward wave oscillators. They are quite expensive and suffer from low life and efficiency. The most dramatic evolution of a microwave power is one of the cooker magnetron for microwave ovens. These tubes generate well over 700 Watt 2450 MHz into a matched load and exhibit a tube efficiency on the order of 70%. It is feasible to utilize a number of such tubes to generate large total power eq. 25 or 50 Kw.

APPLICATIONS IN ORGANIC SYNTHESIS

The first applications of microwave ovens in organic synthesis began very recently. In the first experiments, Gedye[394] and then Giguere[395], provided evidence for dramatic accelerations in some classical organic reactions and these were ascribed to temperature and pressure effects, when performed in closed teflon

vessels. Since solvents were used in these experiments, some problems with safe operation appeared, and explosions sometimes resulted. Further developments demonstrated the potential of solvent free reactions to solve these problems and to facilitate the scale up of preparative runs.

Three types of solvent free procedures can be coupled with microwave activation.

(i) reactions between heat reactants, needing at least one polar molecule, as liquid-liquid or liquid solid systems. In this later case, reactions presumably occur at the interface due to absoprtion of the liquid reactant at the surface of the solid one.

(ii) Reactions between supported reagents on solid mineral supports in dry media by impregnation of compounds on alumina, silicas or clays.

(iii) Phase Transfer Catalysis (PTC) conditions in the absence of organic solvent, i.e. when a liquid reagent acts both as a reactant and an organic phase. This last methodology can also be improved under sonochemical activation.

Microwaves constitutes very original procedure for heating materials, clearly different from the classical ways. Their main adavntages derive from the almost instantaneous "in core" heating of materials, in an homogeneous and selective manner. Especially those with poor neat conduction properties. This technique proves to be excellent in case where traditional heating has a low efficiency because of poor heat transmission and hence local overheating is a major inconvenience.

The main interests can thus be listed as the rapid transfer of energy into the bulk of the reaction mixture, without inertia since only the products is heated and the ease of utilization. Furthermore as the depth of penetration in materials in of the same order of magnitude as the wavelengh, microwaves interact with substance of appreciable thickness (about 10 cm).

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions.[396] Microwave reaction under solvent-free conditions are attractive in offering reduced pollution and offer low cost together with simplicity in processing and handling[397]. The recent introduction of microwave synthesis has gained acceptance and popularity among the synthetic chemist community & it includes virtually all types of chemical reactions such as Diels-Alder[398], Claisen[399], Vilsmeier[400], Oxidation[401], Substitution[402,403], Cyclisation[404,405], Catalytic transfer hydrogenation[406,407], Knoevenagel condensation[408], oxime synthesis[409], alkylation[410], decarboxylation[411], etc.

Malhotra V. et. al.[412] have demonstrated one-pot condensation of chalcones with thiosemicarbazide in ethanol under strogly basic condensation. Microwave enhanced esterification of α,β-unsaturated acids have been carried out by Kumar Mitra & co-workers[413]. Microwave assisted fungicidal 1,2,4-traizines, 1,2,4-tetrazoles, pyrazoles and triazoles have been synthesised by Mazahir Kidwai & co-workers[414].

Some other organic synthesis like 1,2-dihydropyridines[415], phthalimide[416], & quinazolinone[417] derivatives etc. also enhanced by the microwave irradiation.

Recently, microwave assisted some new organic reactions have been carried out which include synthesis of pyrazolines[418,419], isoxazoles[420], cyano-pyridines[421], quinoxalines and heterocyclic pyrazines[422], N-aryl phtalamic acids[423], substituted 2-pyridones[424] and sulfonylbenzimidazole-4,7-diones[425] with better biological activities.

As a part of ongoing research towards the non-traditional approach to the experimental setup of organic reaction, the concept of microwave enhanced

reaction has been utilised from rapid and efficient synthesis of 1,N-Acetyl-3-aryl-5-[1',N-phenyl-3'-p-flurophenyl-pyrazol-4'-yl]-pyrazolines. Microwave oven is used as a microwave irradiation source and compared in terms of yield and reaction period and have been cited in Talbe No. 12a.

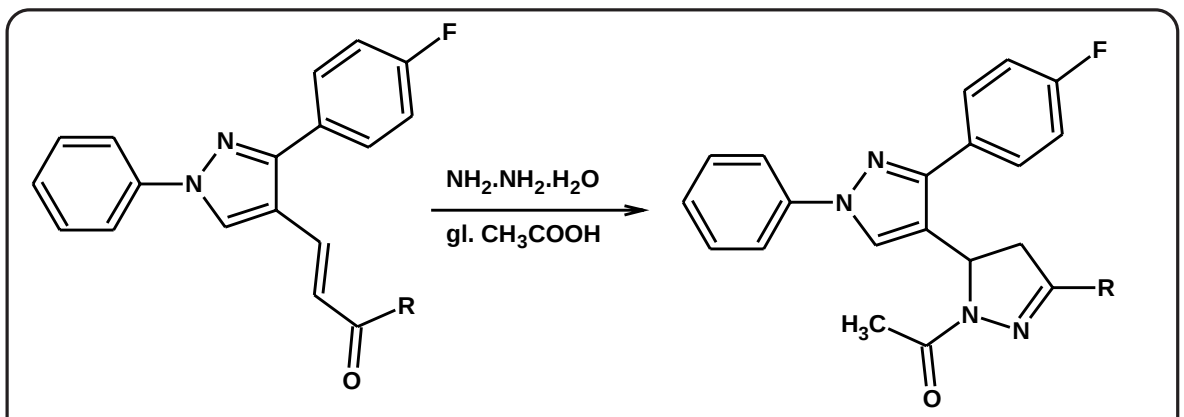
SECTION-I : SYNTHESIS OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL]-PYRAZOLINES USING CONVENTIONAL METHOD

SECTION-II : SYNTHESIS OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZO-4'-YL]-PYRAZOLINES USING MICROWAVE INDUCED SYNTHESIS

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-PYRAZOLINE USING CONVENTIONAL METHOD

Looking to the interesting properties of pyrazolines, it was considered worthwhile to synthesise a series of pyrazolines of type (IV) for obtaining biologically potent agents which were prepared by reacting chalcones with hydrazine hydrate in glacial acetic acid.

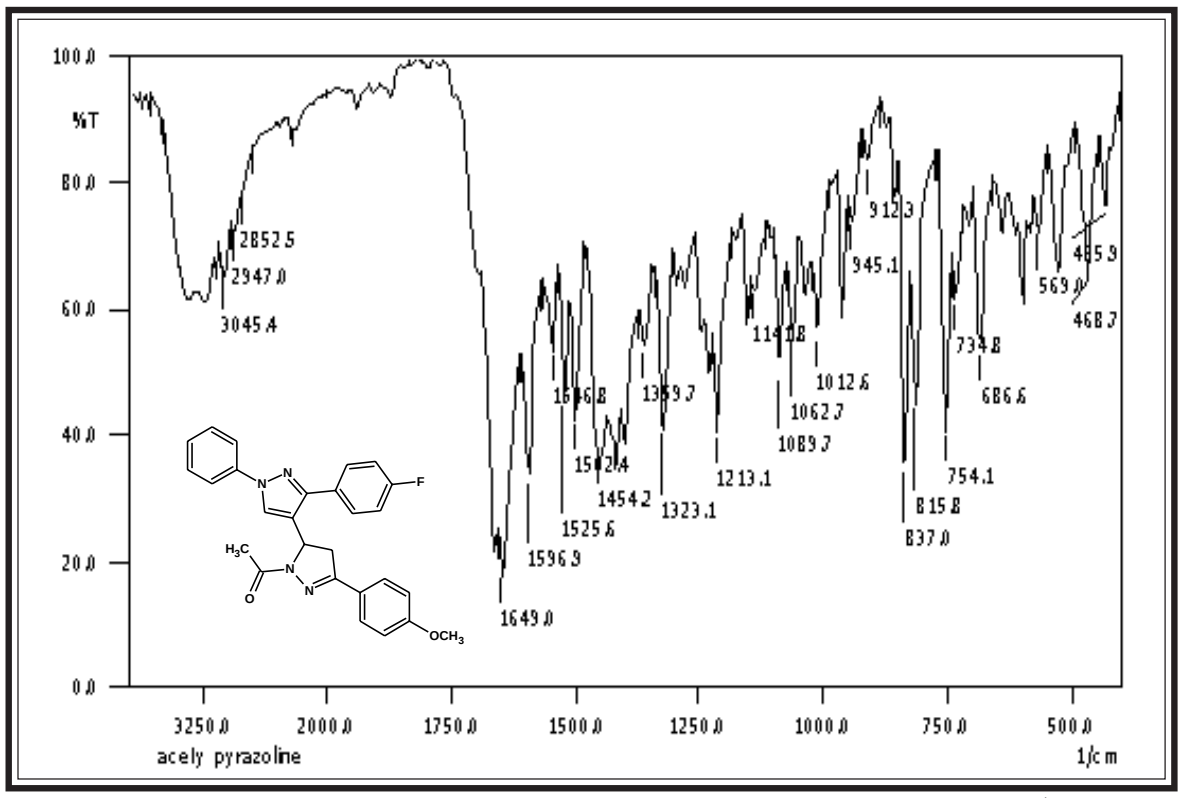


Type - (XII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesised compounds were compared with standard drugs.

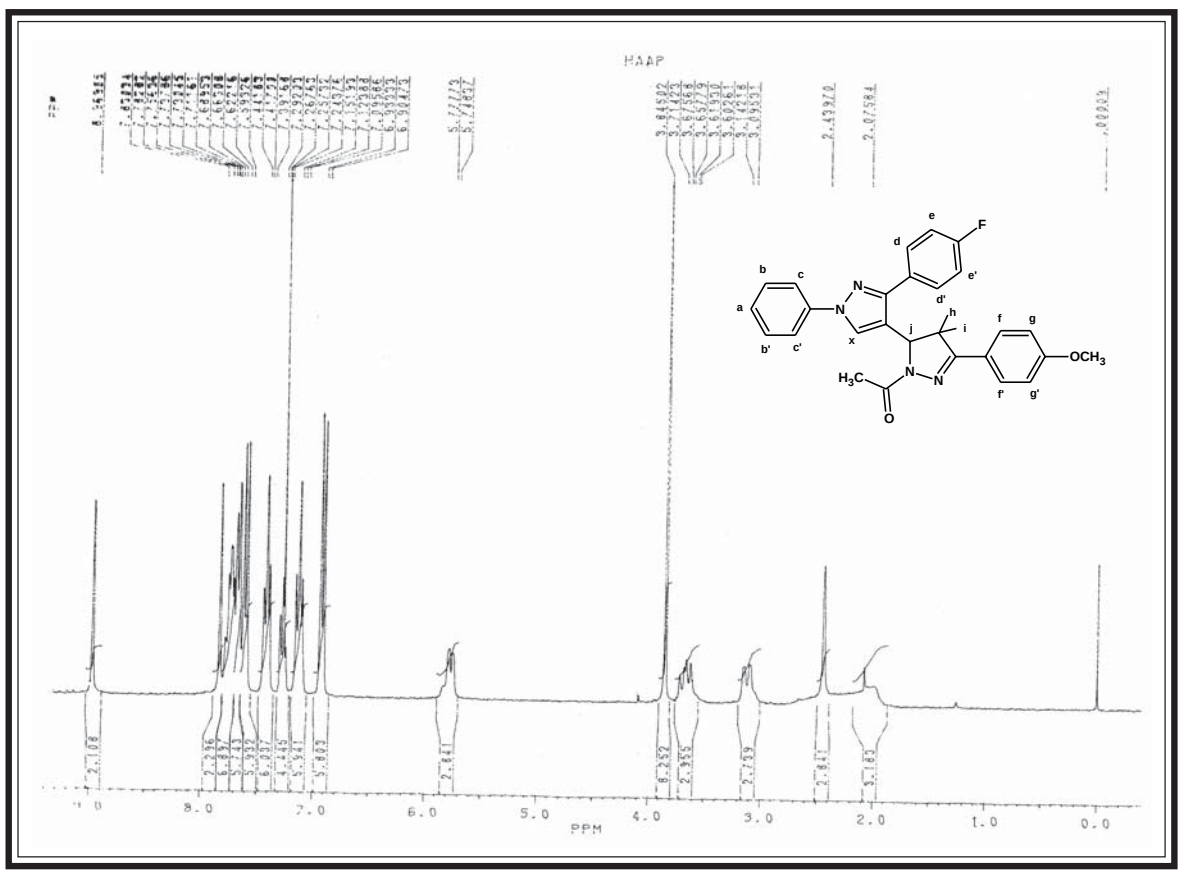
IR SPECTRAL STUDY OF 1,N-ACETYL-3-(p-ANISYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-PYRAZOLINE



Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.(asym.)	2947	2975–2920	426
$-CH_3$	C – H str. (sym.)	2852	2880–2860	"
	C – H i.p. (def.)	1454	1470–1435	"
	C – H o.o.p. (def.)	1359	1385–1350	"
Aromatic	C – H str.	3045	3080–3030	427
	C – H i.p. (def.)	1089	1125–1090	"
		1012	1070–1000	"
	C – H.o.o.p (def.)	837	840–810	"
Pyrazole	C = N str.	1596	1650–1585	428
moiety	C = C str.	1546	1585–1480	"
	C = N str.	1323	1350–1200	"
	C – F	754	760–710	"
Ether	C – O – C str. (asym.)	1213	1275–1200	"
	C – O – C str. (sym.)	1062	1075–1020	"
Pyrazoline	C = N str.	1596	1627–1580	429
	C – H def.	686	698–680	"
	C = O	1649	1760–1650	"

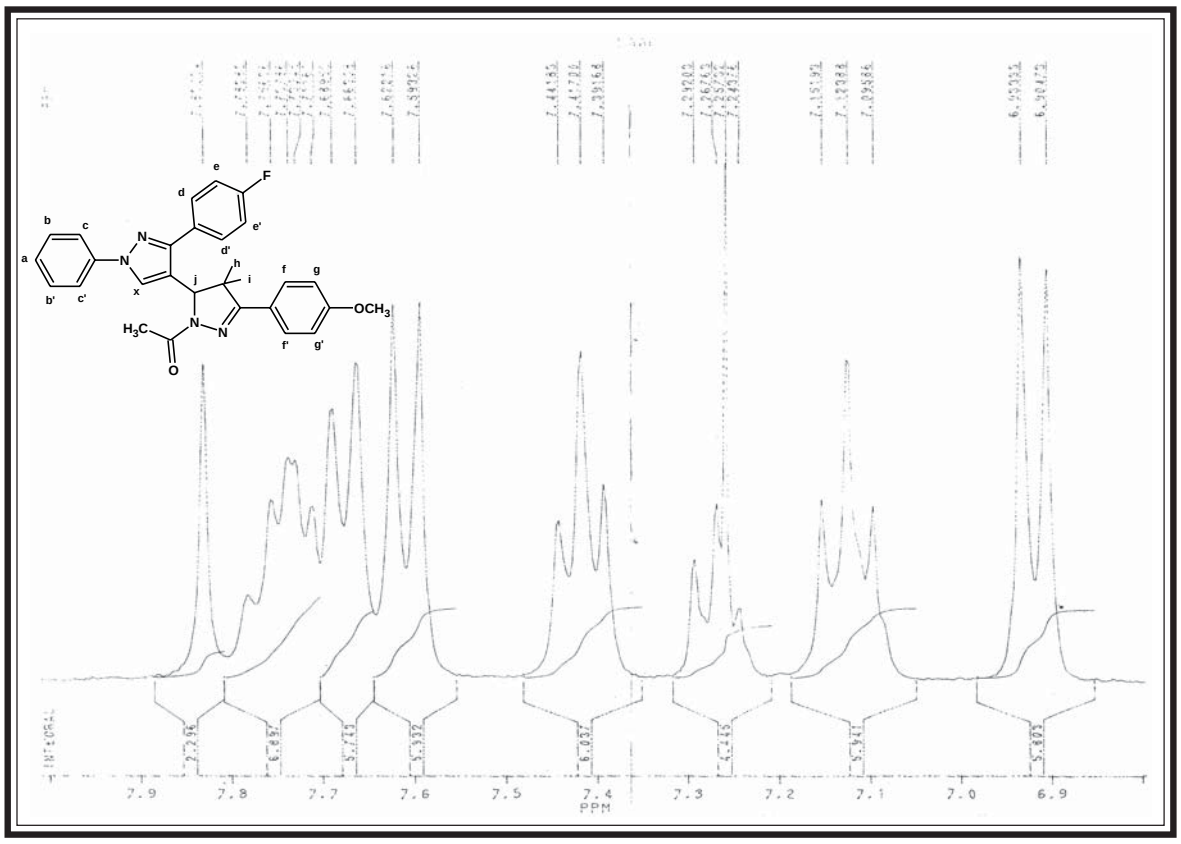
PMR SPECTRAL STUDY OF 1,N-ACETYL-3'-(p-ANISYL)-5-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-PYRAZOLINE

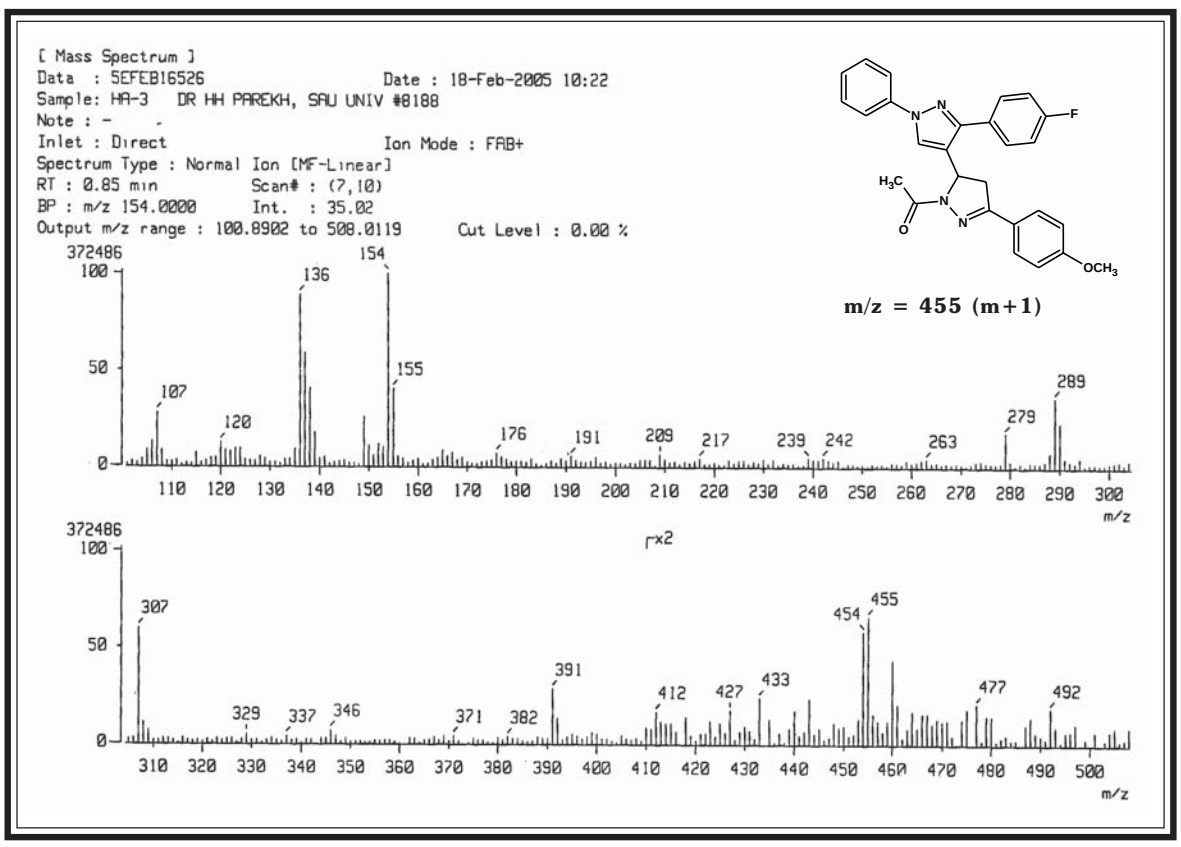


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J Value In Hz
1.	2.07	3H	singlet	$COCH_3$	-
2.	3.09-3.14	1H	d. doublet	CHh	-
3.	3.61-3.71	1H	d. doublet	CHi	-
4.	3.84	3H	singlet	Ar-OCH_3	-
5.	5.74-5.77	1H	d. doublet	CHj	-
6.	6.90-6.93	2H	doublet	Ar-Hgg'	Jgf=8.7
7.	7.09-7.15	2H	triplet	Ar-Hdd'	-
8.	7.39-7.44	2H	triplet	Ar-Hbb'	-
9.	7.59-7.62	2H	doublet	Ar-Hee'	Jef=8.7
10.	7.68-7.71	2H	doublet	Ar-Hff'	Jfg=7.9
11.	7.73-7.78	3H	multiplet	Ar-Hcc'+Ha	-
12.	7.83	1H	singlet	CHx	-

EXPANDED AROMATIC REGION





EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-(1',N-PHENYL-3'-p-FLUOROPHENYL PYRAZOL-4'-YL)-PYRAZOLINE

[A] Synthesis of N-Aminophenyl α-methyl-α-p-fluorophenyl azomethine

See, Part-I, Section-I (A).

[B] Synthesis of 1,N-Phenyl-3-p-fluorophenyl-4-formyl pyrazole

See, Part-I, Section-I (B).

[C] Synthesis of 1-(Anisyl)-3-(1'-N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl)-2-propene-1-one

See Part-I, Section-I (C).

[D] Synthesis of 1,N-Acetyl-3-(p-anisyl)-5-(1',N-phenyl-3'-p-fluorophenyl pyrazol-4'-yl) pyrazoline

To a mixture of 1-(p-Anisyl)-3-(1',N-phenyl-3'-p-fluorophenyl-pyrazole-4'-yl)-2-propene-1-one (3.98g, 0.01M) in 25 ml of absolute alcohol add hydrazine hydrate (0.5g, 0.01M) and glacial acetic acid 10 ml added, the contents were refluxed for 10 hrs. at temp 120°C. and poured into ice. The product was isolated and crystallised from ethanol. Yield 70% m.p. 200°C ($C_{27}H_{23}FN_4O_2$; Found : C, 71.31%; H, 5.06%; N, 12.28%; Requires : C, 71.35%; H, 5.10%; N, 12.33%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Total No. 12.

(E) Antimicrobial activity of 1,N-Acetyl-3-aryl-5-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-pyrazolines

Antimicrobial testing was carried out as described in Part-I, Section-I(D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 12.

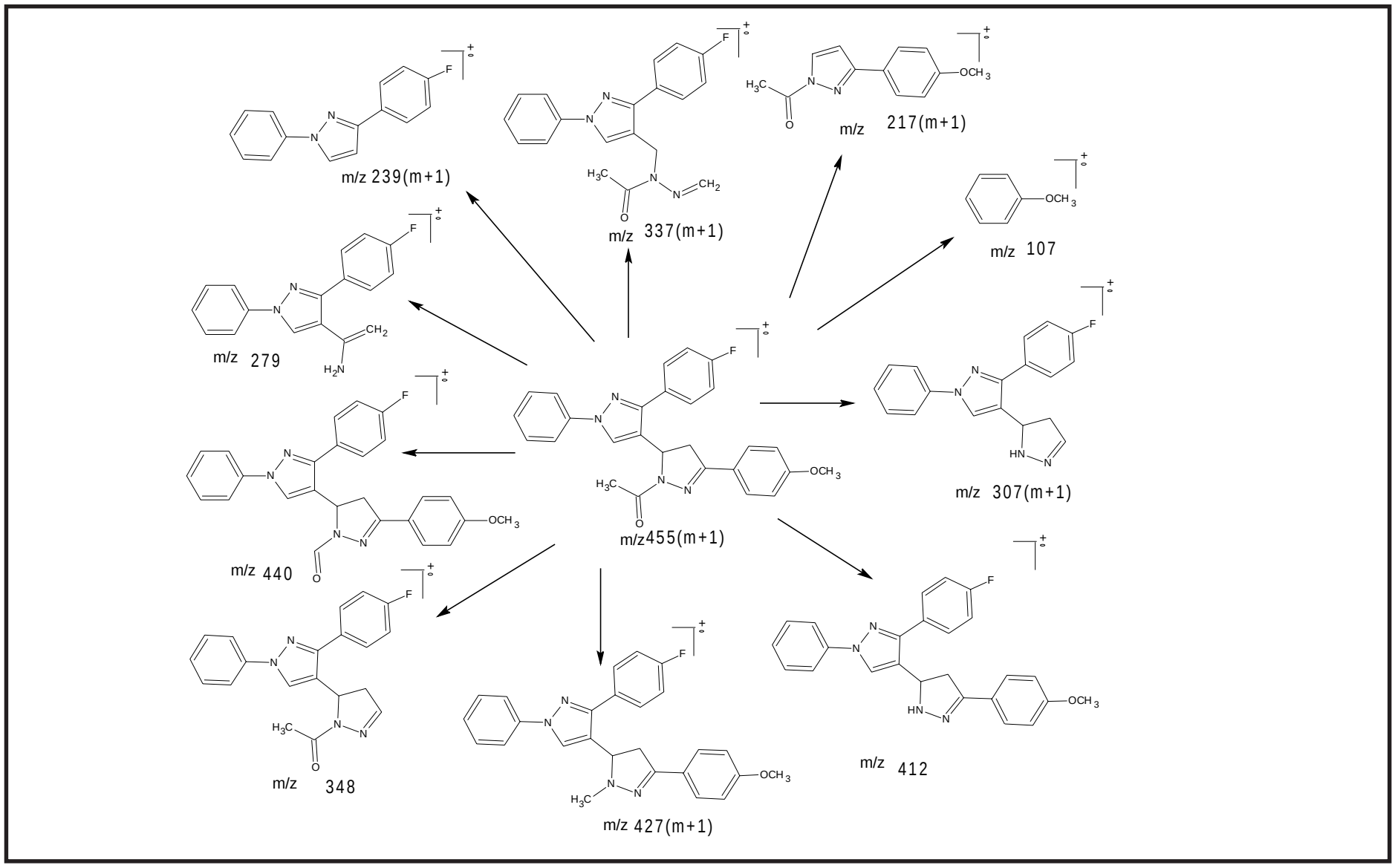
TABLE NO.12 : PHYSICAL CONSTANTS OF 1,N-ACETYL-5-ARYL-3-(1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL)-PYRAZOLINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
12a	C_6H_5-	$C_{26}H_{21}FN_4O$	424	220	0.49	60	13.20	13.14
12b	4-OCH_3-C_6H_4-	$C_{27}C_{23}FN_4O_2$	454	200	0.56	70	12.33	12.28
12c	4-CH_3-C_6H_4-	$C_{27}H_{20}FN_4O_2$	454	234	0.39	65	12.78	12.71
12d	4-Cl-C_6H_4-	$C_{26}H_{20}ClFN_4O$	458	240	0.47	71	12.21	12.15
12e	4-F-C_6H_4-	$C_{26}H_{20}F_2N_4O$	442	216	0.73	70	12.66	12.61
12f	4-OH-C_6H_4-	$C_{26}H_{21}FN_4O_2$	440	258	0.52	64	12.72	12.73
12g	2-OH-C_6H_4-	$C_{26}H_{21}FN_4O_2$	440	212	0.62	66	12.72	12.71
12h	4-NO_2-C_6H_4-	$C_{26}H_{20}FN_5O_3$	469	138	0.66	75	14.92	14.88
12i	3-NO_2-C_6H_4-	$C_{26}H_{20}FN_5O_3$	469	160	0.48	62	14.92	14.85
12j	4-Br-C_6H_4-	$C_{26}H_{20}BrFN_4O$	503	230	0.78	68	11.13	11.08
12k	4-NH_2-C_6H_4-	$C_{26}H_{22}FN_5O$	439	187	0.43	64	15.94	15.90
12l	C_4H_3S-	$C_{24}H_{19}FN_4SO$	430	207	0.59	72	13.01	12.95

*TLC Solvent System : Ethyl acetate : Hexane

1 : 9 (4c, 4k)

2 : 8 (4a-4b, 4d-4j, 4l)


m/z 239(m+1)
m/z 337(m+1)
m/z 217(m+1)
m/z 107
m/z 279
m/z 307(m+1)
m/z 440
m/z455(m+1)
m/z 348
m/z 427(m+1)
m/z 412

SECTION-II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-p-FLUOROPHENYL-PYRAZOL-4'-YL]-PYRAZOLINES USING MICROWAVE INDUCED SYNTHESIS

EXPERIMENTAL

A mix of 1-anisyl-3-(1',N-phenyl-3'-p-fluorophenyl-pyrazol-4'-yl)-2-propene-1-one (3.98g, 0.01M), hydrazine hydrate (0.5g, 0.01M) and glacial acetic acid (15 ml) was irradiated in a Q-Pro-M Microwave oven (220 VAC, 60Hz) [Questron Technologies Corporation-CANADA] at temp. 120°C for 9 min. under power level of 40% taking care not to heat the contents longer than 2 min at a time to avoid boiling off the reaction mixture. The contents were cooled and poured into ice cold. water. product was isolated & crystallised from ethanol, yield 74%, m.p. 201°C. ($C_{27}H_{23}FN_4O_2$ Found : C, 71.31%; H, 5.06%; N,12.28%; Requires : C, 71.35%; H, 5.10%; n, 12.33%)

Similarly other substituted pyrazolines have been prepared.

The constitution of the synthesised products have been characterised by using elements have been characterised by using elemental analyses, infrared and ^1H nuclear spectrometry.

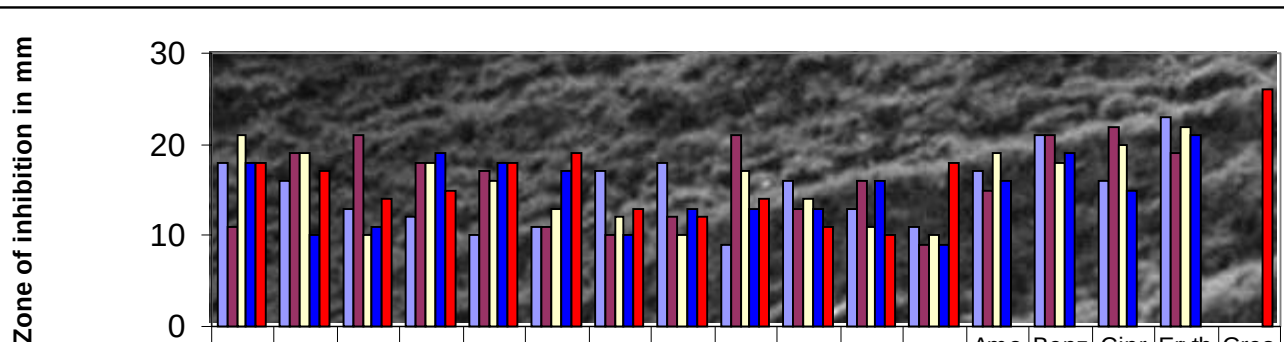
The synthesised products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive & Gram negative bacterial strians and antifungal activity to wards ***Aspergillus niger*** at a concentration of 40 mg/ml. The biological activities of synthesised compounds were compared with standard drugs.

Comparision of the convention and microwave induced synthesis of pyrazolines in terms of yield and reaction preiod have been eited in Table No. 12a.

TABLE NO. 12a : COMPARISION OF CONVENTIONAL AND MICROWAVE ENHANCED SYNTHESIS OF PYRAZOLINES

Comp. No.	R	Thermal		Microwave		M.P. ^{o}C
		Reaction Period (hr.)	Yield %	Reaction Period (min.)	Yield %	
12a	C_6H_5-	10	60	9	63	220
12b	4-OCH_3-C_6H_4-	10	70	10	72	200
12c	4-CH_3-C_6H_4-	10	65	9	68	234
12d	4-Cl-C_6H_4-	10	71	9	73	240
12e	4-F-C_6H_4-	10	70	8	72	216
12f	4-OH-C_6H_4-	10	64	9	66	258
12g	2-OH-C_6H_4-	10	66	10	69	212
12h	4-NO_2-C_6H_4-	10	75	7	77	138
12i	3-NO_2-C_6H_4-	10	62	9	64	160
12j	4-Br-C_6H_4-	10	68	9	70	230
12k	4-NH_2-C_6H_4-	10	64	8	67	187
12l	C_4H_3S-	10	72	7	74	207

GRAPHYCAL CHART NO.12: **ANTIMICROBIAL ACTIVITY OF1,N-ACETYL-3-ARYL-5-[1'N-PHE NYL- 3'-p-FLUOROPHENYL PYRAZOL-4'-YL] -PYRAZOLINES.**



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Amoxicillin	Benzoyl Peni	Ciprofloxacin	Erythromycin	Greseofulvi
B. cocous	18	16	13	12	10	11	17	18	9	16	13	11	17	21	16	23	0
B. subtillus	11	19	21	18	17	11	10	12	21	13	16	9	15	21	22	19	0
E. coli	21	19	10	18	16	13	12	10	17	14	11	10	19	18	20	22	0
P. vulgaris	18	10	11	19	18	17	10	13	13	13	16	9	16	19	15	21	0
A. niger	18	17	14	15	18	19	13	12	14	11	10	18	0	0	0	0	26

CONCLUSION

ANTIBACTERIAL ACTIVITY

From the experimental data, it was revealed that most of acetyl pyrazoline derivatives (type-XII), were able to inhibit the growth of Gram positive and Gram negative bacterial strains.

It has been observed that maximum activity was displayed by the compounds bearing R=phenyl, 4-methoxyphenyl and 3-nitrophenyl against Gram positive bacterial strains ***B. Cocous*** and ***B. Subtillus***. While significant activity was displayed by the compound bearing R=4-nitrophenyl, 2-hydroxyphenyl and thienyl against these Gram positive bacterial strains.

While in case of Gram negative bacterial strains, maximum activity was displayed by compounds bearing R=phenyl & 4-chlorophenyl against ***E. Coli*** & ***P. Vulgaris***. While significant activity was observed in compounds bearing R=4-methoxyphenyl, 4-fluorophenyl & 4-aminophenyl against these Gram positive bacterial strains.

ANTIFUNGAL ACTIVITY

All the compounds were less active against fungal strain ***A. niger***.

The antimicrobial activity shown by compounds was compared with known antibiotics like Amoxycillin, Benzoyl Penicillin, Ciprofloxacin, Erythromycin & Greseofulvin.

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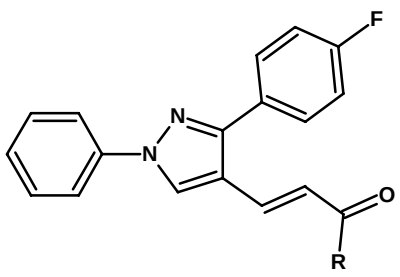
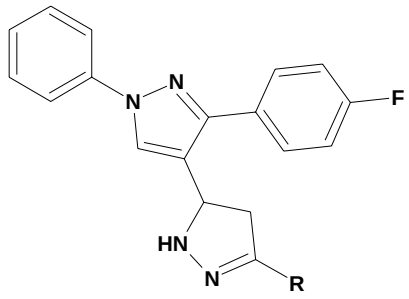
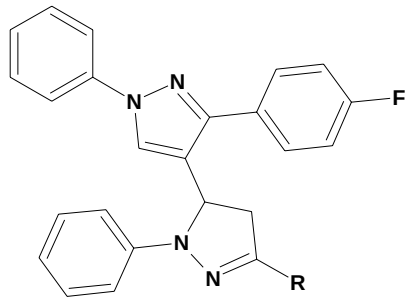
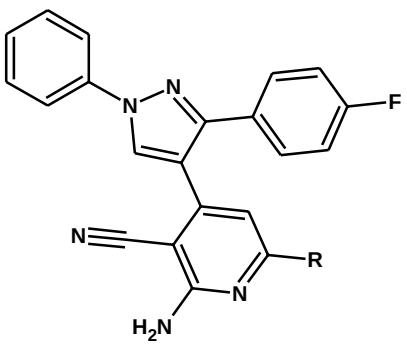
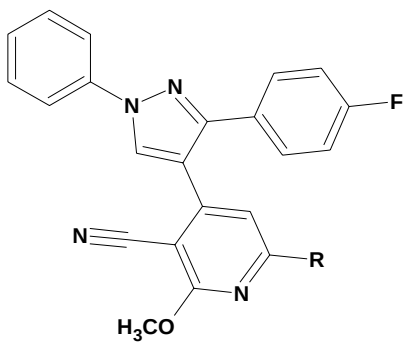


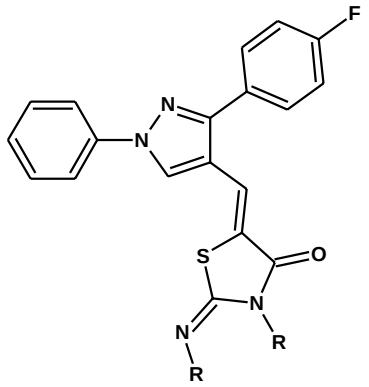




R	R	R
C_6H_5-	C_6H_5-	C_6H_5-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	4-OH-C_6H_4-
2-OH-C_6H_4-	2-OH-C_6H_4-	2-OH-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-C_6H_4-
4-NH_2-C_6H_4-	4-NH_2-C_6H_4-	4-NH_2-C_6H_4-
C_4H_3S-	C_4H_3S-	C_4H_3S-







R	R	R
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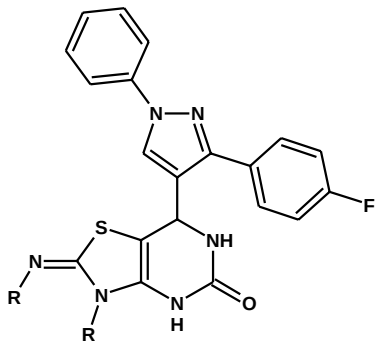
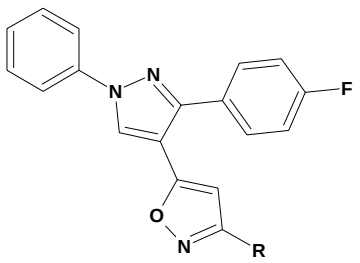
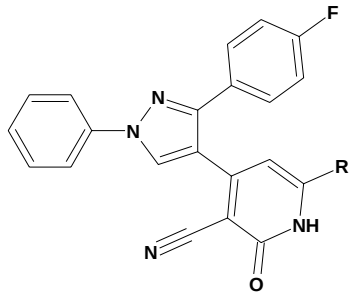
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	3-Cl, 4-F-C_6H_3-
2-OH-C_6H_4-	2-OH-C_6H_4-	3-NO_2-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	2-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	3,4-$(Cl)_2$-C_6H_3-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-C_6H_4-
4-NH_2-C_6H_4-	4-NH_2-C_6H_4-	2,4- $(CH_3)_2$-C_6H_3-
C_4H_3S-	C_4H_3S-	2,5- $(Cl)_2$-C_6H_3-







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C_6H_5-	C_6H_5-	C_6H_5-
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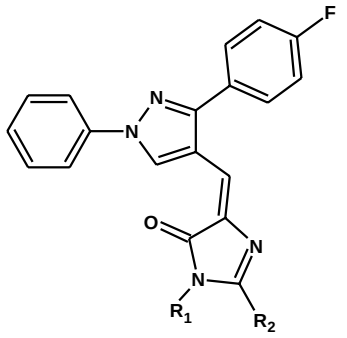
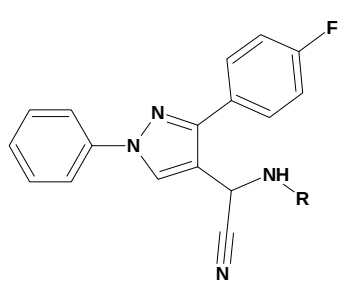
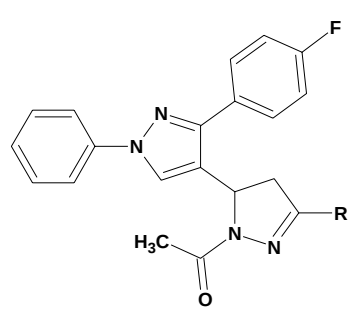
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
3-Cl, 4-F-C_6H_3-	4-OH-C_6H_4-	4-OH-C_6H_4
3-NO_2-C_6H_4-	2-OH-C_6H_4-	2-OH-C_6H_4-
2-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
3,4-$(Cl)_2$-C_6H_3-	3-NO_2-C_6H_4-	3-NO_2-C_6H_3-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-C_6H_4-
2,4-$(CH_3)_2$-C_6H_4-	4-NH_2-C_6H_4-	4-NH_2-C_6H_4-
2,5-$(Cl)_2$-C_6H_3-	C_4H_3S-	C_4H_3S-







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C_6H_5-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
C_6H_5-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
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C_6H_5-	3-Cl-C_6H_4-	4-Cl-C_6H_4-	4-F-C_6H_4-
C_6H_5-	4-F-C_6H_4-	3-Cl-C_6H_4-	4-OH-C_6H_4
C_6H_5-	2-F-C_6H_4-	4-F-C_6H_4-	2-OH-C_6H_4-
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C_6H_5-	3,4-$(Cl)_2$-C_6H_3-	3-Cl,4-F-C_6H_3-	4-Br-C_6H_4-
C_6H_5-	2,4-$(CH_3)_2$-C_6H_3-	3-NO_2-C_6H_4-	4-NH_2-C_6H_4-
C_6H_5-	3-Cl-4-F-C_6H_3-	4-Br-C_6H_4-	C_4H_3S-