SEARCHING DRUG TARGETS FOR MICROBES USING NITROGEN HETEROCYCLES

A THESIS
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FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN
THE FACULTY OF SCIENCE(CHEMISTRY)
BY

SHEETAL A. BHUVA

UNDER THE GUIDANCE
OF

Dr. (Mrs.) H. H. PAREKH

DEPARTMENT OF CHEMISTRY
SAURASHTRA UNIVERSITY
RAJKOT - 360 005
INDIA
2005

Gram : UNIVERSITY
Fax : 0281-2577633

Phone : (R) 2577392
(O) 2578512

SAURASHTRA UNIVERSITY
University Road,
Rajkot - 360 005.

Dr. (Mrs.) H. H. PAREKH
M.Sc., Ph.D.,F.I.C.
Professor and Head,
Department of Chemistry

Residence :
'RASDHARA',
32-B, University
Karmachari Co. Society,
University Road,
RAJKOT - 360 005.
GUJARAT (INDIA)

No.

Dt. : - 09 - 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.(Mrs.)*** **H. H. Parekh** and leads to some contribution in chemistry subsidised by a number of references.

Date : - 09 - 2005
Place : Rajkot.

(Sheetal A. Bhuva)

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

Date : - 09 - 2005
Place : Rajkot.

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


Dedicated to My
Family

ACKNOWLEDGEMENT

First and foremost, I pay all my homage and devote my emotions to God "Director of Life" to give a new direction to my study and without whose blessings this task would not have been accomplished. I bow my head in utter humility and complete dedication.

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From bottom of my heart, I thank my husband, Malay, whose support and constant inspiration made me complete my work successfully.

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SHEETAL A. BHUVA

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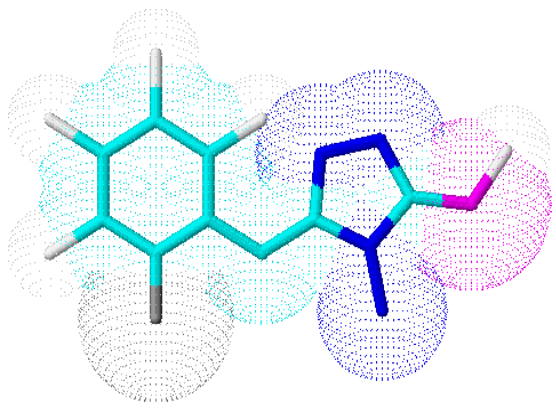


SYNOPSIS

The work incorporated in the thesis with the title "**SEARCHING DRUG TARGETS FOR MICROBES USING NITROGEN HETEROCYCLES**" has been described in three parts.

[A] STUDIES ON 1,2,4-TRIAZOLES

[B] STUDIES ON PYRAZOLES

[C] STUDIES ON MICROWAVE INDUCED SYNTHESIS OF 2,3-DIHYDRO-1,3,4-THIADIAZOLOTRIAZOLES

[A] STUDIES ON 1,2,4-TRIAZOLES

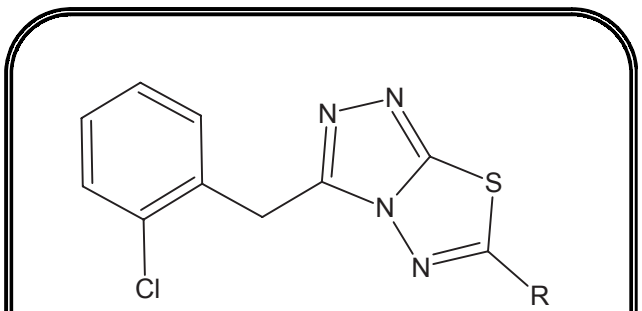
Compounds bearing 1,2,4-triazole nucleus shows variety of biological activities such as anti-tubercular, amoebicidal, hypnotic, fungicidal, anti-inflammatory, CNS depressant, anticonvulsant, antitumor etc.

Due to the wide range of biological activity, it was contemplated to synthesise some novel thiadiazoles, dihydrothiadiazoles, thiadiazepines, aryltriazoles, oxadiazoles and azomethines bearing triazole nucleus, which have been described as under.

PART - I : STUDIES ON 1,3,4-THIADIAZOLOTRIAZOLES

Thiadiazole derivatives have been found to be potent drug in pharmaceutical and possess a wide spectrum of biological activity such as antifungal, antibacterial, anticonvulsant, pesticidal, herbicidal and antithyroid. Some novel triazoles with 1,3,4-thiadiazole ring system have been prepared as under.

SECTION – I : **Synthesis and biological evaluation of 2-Aryl-4-o-cholorobenzyl–1,2,4-triazolo[3, 4–b]-1,3,4-thiadiazoles.**



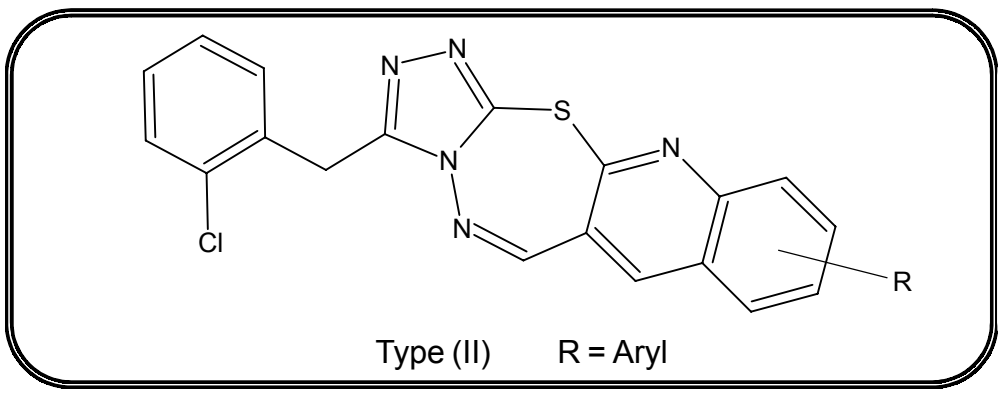
Type (I) R = Aryl

Substituted triazolo-1,3,4-thiadiazoles of type (I) have been prepared by condensation of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole with different aromatic acid in presence of phosphorous oxychloride.

PART - II : STUDIES ON 1,3,4-THIADIAZEPINES

Thiadiazepine derivative have attracted considerable attention in view of their great therapeutic importance as antifungal, antibacterial, antiamoebic, anti-HIV and anticancer agents. To approach these goal preparation of some novel thiadiazipines have been undertaken as under.

SECTION - I : **Synthesis and biological evaluation of 4-o-cholorobenzyl-1,2,4-triazolo[3,4-b] substituted quinolino [2,3-f]-1,3,4-thiadiazepines**



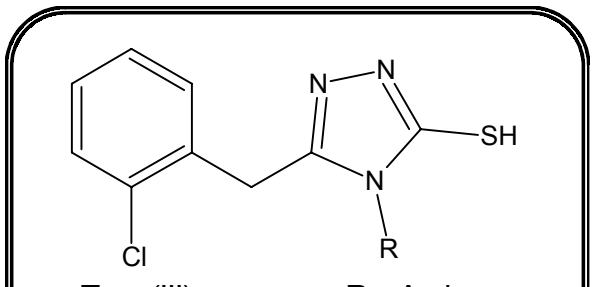
Type (II) R = Aryl

Thiadiazepine derivative of type (II) have been prepared by the condensation of 3-mercapto-4,N-amino-5-o-cholorobenzyl-1,2,4-triazole with substituted 2-chloro-3-formyl-quinolines.

PART - III : STUDIES ON 4-ARYLTRIAZOLES

4-Aryltriazole derivatives are important class of heterocycles having interesting pharmacological activities such as analgesic, CNS depressant, pesticidal, anti-inflammatory and antihypertensive. These valid observations led us to synthesize some new 1,2,4-triazole derivative which have been described as under.

SECTION – I : Synthesis and biological evaluation of 3-mercapto-4,N-aryl-5-o-cholorobenzyl-1,2,4-triazoles



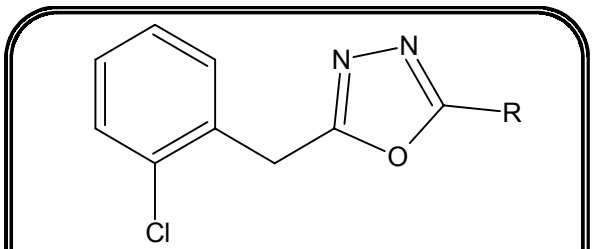
Type (III) R = Aryl

The synthesis of triazole derivatives of type (III) have been undertaken by heating of potassium o-chlorophenylaectamido dithiocarbamate with different aromatic amines.

PART - IV : STUDIES ON 1,3,4-OXADIAZOLES

Oxadiazole derivative are endowed with different therapeutic activities such as hypnotic, anaesthetic, antibacterial, antifungal, insecticidal and preservatives. In view of these facts, it was contemplated to synthesize some new oxadiazoles, which have been described as under.

SECTION - I : **Synthesis and biological evaluation of 2-Aryl-5-o-cholorobenzyl 1,3,4-oxadiazoles**



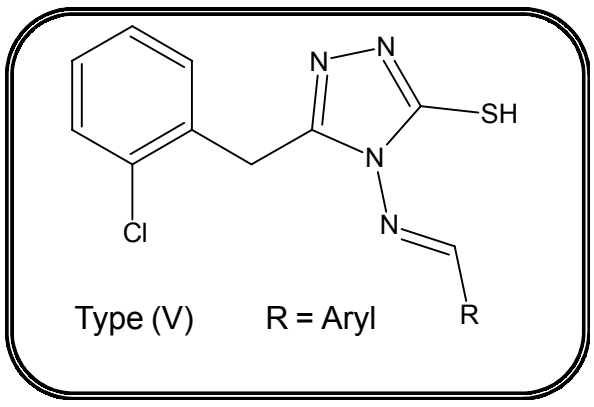
Type (IV) R = Aryl

The oxadiazole derivative of type (IV) have been prepared by the condensation of o-chlorophenylaceto hydrazide with different aromatic acid in presence of phosphorous oxychloride.

PART - V : STUDIES ON AZOMETHINES

Azomethine derivatives represent one of the modest class of compounds possessing wide range of therapeutic activities, such as antimicrobial, antibacterial, antibiotics and with a view to getting better therapeutic agent and to evaluate its pharmacological profile, different types of azomethine derivatives have been prepared, which have been described as under.

SECTION – I : **Synthesis and biological evaluation of 4,N-substituted benzalamino-3-mercapto-5-o-cholorobenzyl-1,2,4-triazoles**



Type (V) R = Aryl

The azomethine derivatives of type (V) have been prepared by the condensation of 3-mercapto-4,N-amino-5-o-cholorobenzyl-1,2,4-trizole with different aromatic aldehydes in presence of sulphuric acid.

[B] STUDIES ON PYRAZOLES

Pyrazole derivatives are known to exhibit wide number of biological and pharmacological activities such as antitubercular, antimicrobial, anti-inflammatory, antitumor, antiarthritic, antidepressant, plant growth regulator and also used as herbicidal and insecticidal.

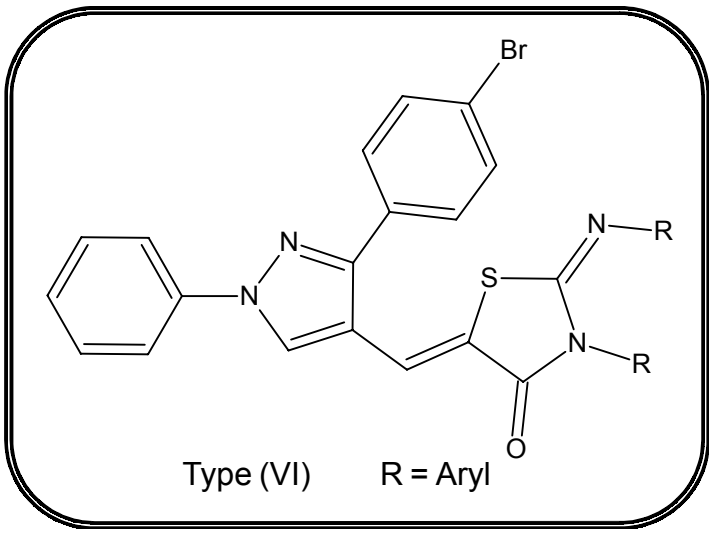
Considering the increasing importance of pyrazole nucleus we have undertaken the synthesis of some novel Thiazolidinones, Pyrimidinones, Thiopyrimidines, Cyanopyridones, Imidazolinones, and acetonitriles bearing pyrazole nucleus.

PART – I : STUDIES ON PYRIMIDINES

The emerging role of pyrimidines in pharmaceutical chemistry as well as in biochemistry stimulated tremendous interest in the synthesis of pyrimidines with therapeutic potential.

In order to achieving better therapeutic activity, we have synthesised some new pyrimidine derivatives bearing pyrazole nucleus which is described as under.

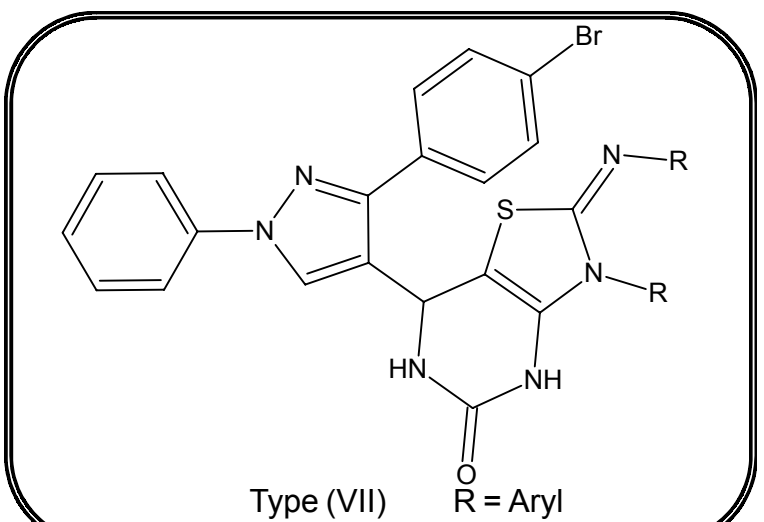
SECTION – I : Synthesis and biological evaluation of 2-arylimino-3,N-aryl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-4-Thiazolidinones



Type (VI) R = Aryl

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

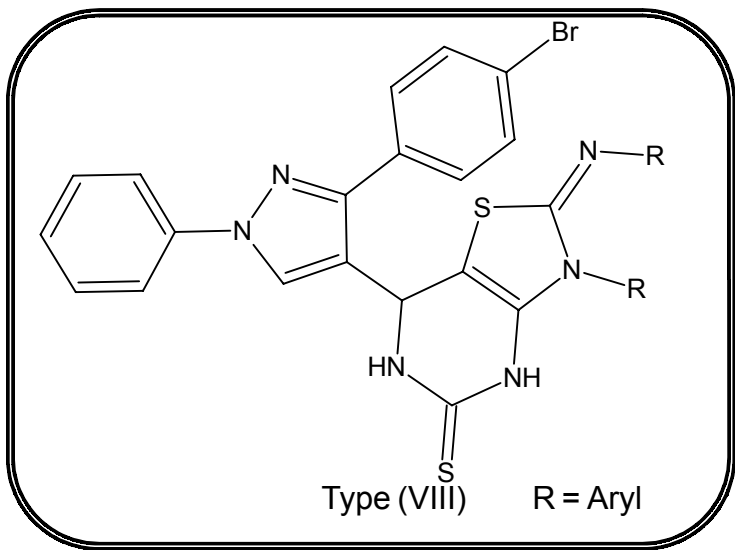
SECTION – II : Synthesis and biological evaluation of 6-arylimino-7,N-aryl-2- oxo-4-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)1,2,3,4–tetrahydro thiazolidino-[4, 5-d]-pyrimidines.



Type (VII) R = Aryl

Pyrimidinones of type (VII) have been prepared by the condensation of 2-arylimino-3,N-aryl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)4-thiazolidinones with urea in glacial acetic acid with fused sodium acetate.

SECTION – III : **Synthesis and biological evaluation of 6-arylimino-7, N-aryl-2-thio-4-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-1,2,3,4-tetrahydro-thiazolidino-[4, 5-d] pyrimidines**



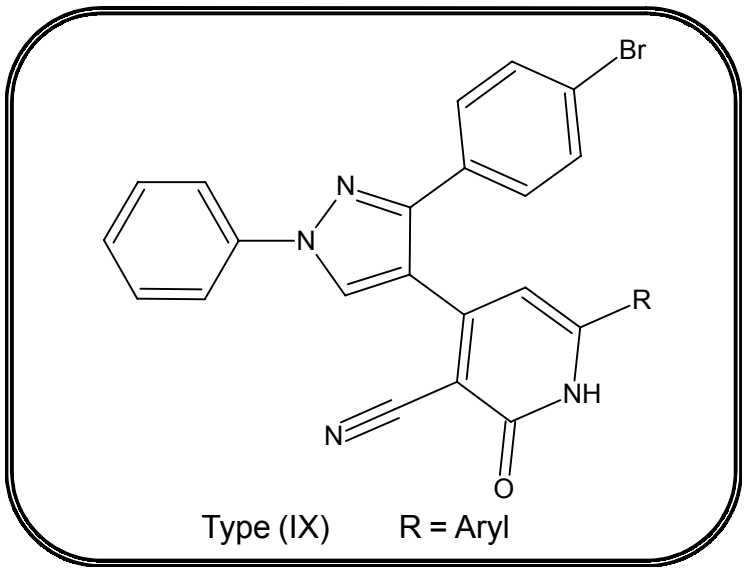
Type (VIII) R = Aryl

Thiopyrimidines of Type (VIII) have been synthesized by the condensation of 2-arylimino-3,N-aryl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)4-thiazolidinone with thiourea in glacial acetic acid with fused sodium acetate.

PART - II : STUDIES ON CYANOPYRIDONES

The group of compounds containing the cyanopyridone ring system have a prominent feature in medicinal chemistry and possess biological activities such as analgesic, antidiabetic, anticonvulsant, insecticidal and antibacterial etc. In view of these facts, it was contemplated to synthesise cyanopyridone derivatives which have been described as under.

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



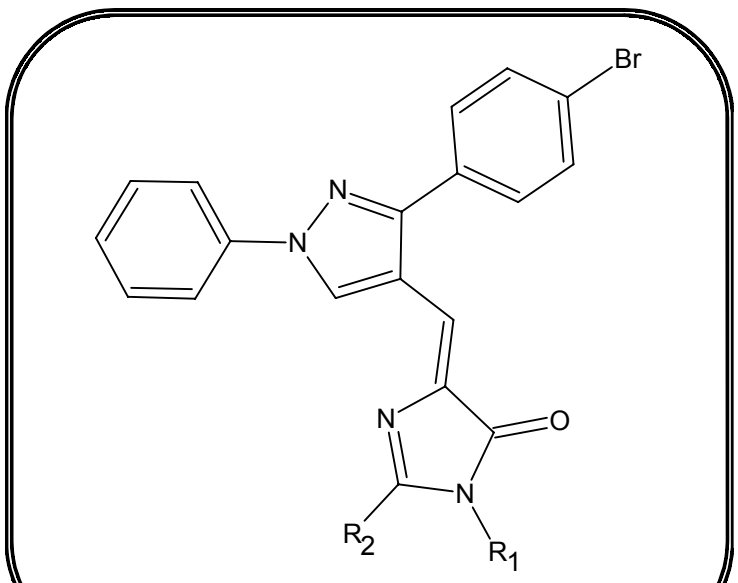
Type (IX) R = Aryl

The cyanopyridones of type (IX) have been prepared by condensation of 1-aryl-3-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-2-propene-1-ones with ethylcyanoacetate and ammonium acetate.

PART - III : STUDIES ON IMIDAZOLINONES

Imidazolinone derivatives plays a vital role owing to their wide range of biological activities such as anticonvulsant, sedative, hypnotic, anti-inflammatory, antihistamine and antithyoid. In order to develop medicinally important compounds, we have synthesised 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-bromophenyl-4'-pyrazolylmethino)-imidazolin-5-ones



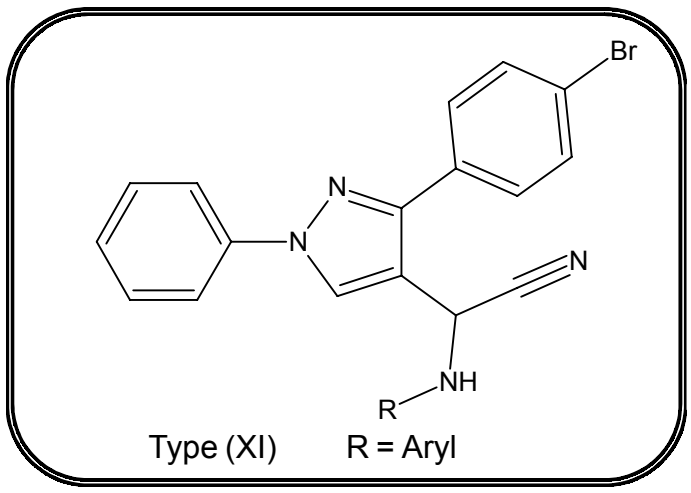
Type (X) R_1 = Aryl, R_2 = Alkyl/Aryl

The imidazolinone derivatives of Type (X) have been prepared by the condensation of 5-oxo-2-phenyl-4-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-oxazole with different aryl amines in pyridine.

PART - IV : STUDIES ON NITRILES

Recently substituted nitrile derivatives have been found to be biologically versatile compounds which possess a broad spectrum of pharmacological activities viz. cardiovascular, sedative, antifungal and antibacterial. By considering these valid observations, we have synthesised some new nitriles which have been described as under.

SECTION - I : Synthesis and biological evaluation of á-Arylamino-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolyl)-acetonitriles



Type (XI) R = Aryl

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

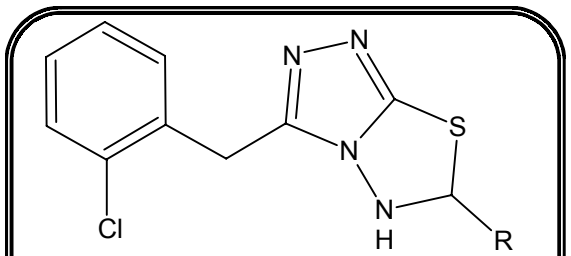
[C] STUDIES ON MICROWAVE INDUCED SYNTHESIS OF 2,3-DIHYDRO-1,3,4-THIADIAZOLOTRIAZOLES

In the recent year, MORE (Microwave Induced Organic Reaction Enhancement) technique has become very popular due to substantial reduction in reaction time, operational time, operational simplicity and formation of clear reaction products. Keeping this in view, we investigated the synthesis of the dihydrothiadiazoles using microwave irradiation and also by conventional method.

PART - I : STUDIES ON 2,3-DIHYDRO-1,3,4-THIADIAZOLOTRIAZOLES BY CONVENTIONAL AND MICROWAVE INDUCED SYNTHESIS

Dihydrothiadiazoles possess remarkable pharmacological importance and biological activities such as antifungal, antibacterials, pesticidal, herbicidal, and antithyroid. In view of these facts, it appeared of interest to design and synthesise thiadiazole derivatives which have been described as under.

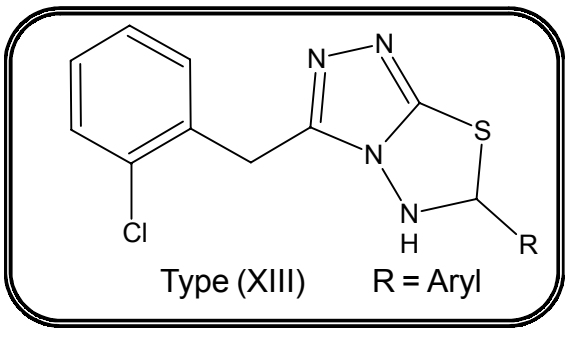
SECTION – I : **Synthesis and biological evaluation of 2-Aryl-4-o-cholorobenzyl-2,3-dihydro-1,2,4-triazolo[3,4–b]-1,3,4-thiadiazoles by conventional method.**



Type (XII) R = Aryl

The compounds of type (XII) have been prepared by the condensation of 3-mercapto-4,N-amino-5-o-cholorobenzyl-1,2,4-triazole with different aromatic aldehydes in presence p-toluenesulphonic acid.

SECTION - II : **Synthesis and biological evaluation of 2-Aryl-4-o-cholorobenzyl-2,3-dihydro-1,2,4-triazolo[3,4–b]-1,3,4-thiadiazoles by microwave method.**



Type (XIII) R = Aryl

The compounds of type (XIII) have been prepared by the condensation of 3-mercapto-4,N-amino-5-o-cholorobenzyl-1,2,4-triazol with different aromatic aldehydes in presence p-toluenesulphonic acid under microwave irradiation in few minutes. The advantages of microwave synthesis has been reported.

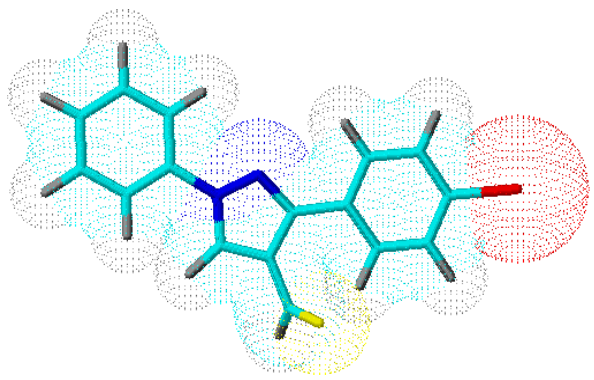
The constitution of newly synthesised products have been supported by using

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 :**

(i) All the compounds have been evaluated for their antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg. The biological activity of the synthesised compounds have been compared with standard drugs.

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



SEARCHING DRUG TARGETS FOR MICROBES USING NITROGEN HETEROCYCLES

"SEARCHING DRUG TARGETS FOR MICROBES USING NITROGEN HETEROCYCLES"

Heterocyclic chemistry has seen unparalled progress owing to their wide natural occurance, specific chemical reactivity and broad spectrum utility.

The known organic compounds have an enormous diversity of structure. Many of these structures contain ring systems. If the ring system is made up of atoms of carbon and atleast one other element, the compound can be classed as heterocyclic.

Most of the alkaloids which are nitrogeneous bases occuring in plants and many antibiotics including penicillin and strptomycin have also heterocyclic ring system. Many natural pigments such as indigo, haemoglobin and enthocyanin are heterocycles. Most of the sugars and their derivatives including vitamin-C for intance, exist largely in the form of five membered, vitamine B_6 (pyridoxine) is a derivatives of pyridine essential in amino acid metabolism. Important drugs, poisons and medicines (both natural and synthetic) such as sulphathiazole, pyrethrin, rotenmone, strychnine, reserpine, certain of the antihistaminics, the ergot alkaloids caeffine, cocaine, barbiturates etc. are heterocyclic compounds.

Medicinal chemistry concerns the discovery, the development, the identification of action of biologically active compound at the molecular level. Emphasis is 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.

AIMS AND OBJECTIVES

In the pharmaceutical field, there has always been and will continue to be a need for new and novel chemical entities with diverse biological activities. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesising pharmacologically interesting compounds of widely different composition.

During the course of research work, several entities have been designed, generated and characterised using spectral studies. The details are as under.

- ❖ To generate several derivatives like 1,3,4-thidiazolotriazoles, 1,3,4-thiadiazepines, 4-aryltriazoles, 1,3,4-oxadiazoles and azomethines bearing 1,2,4-triazole nucleus.

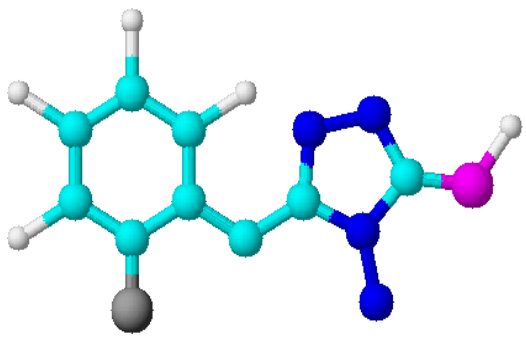
- ❖ To synthesise biologically active 2,3-dihydro-1,3,4-thiadiazolotriazoles bearing 1,2,4-triazole nucleus using microwave induced synthesis method.

- ❖ To generate several derivatives like thiazolidinones, pyrimidinones, thiopyrimidines, cyanopyridones, imidazolinones and nitriles bearing pyrazole nucleus.

- ❖ To check purity of all the compounds using thin layer chromatography.

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

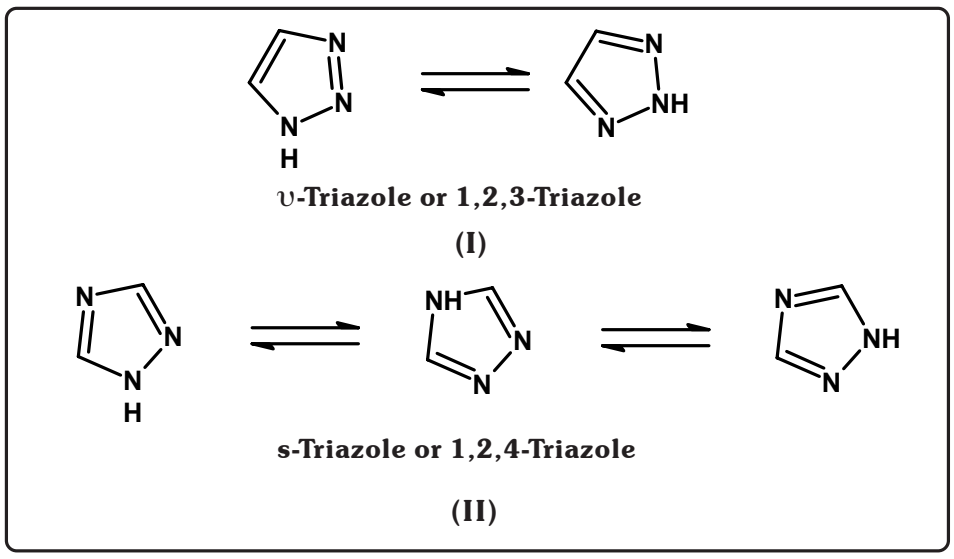
- ❖ To evaluate new product for better drug potential against different strains of bacteria, fungi and for antitubercular activity against *Mycobacterium Tuberculosis* H_{37} Rv.



[A] STUDIES ON 1,2,4-TRIAZOLES

INTRODUCTION

Triazole is one of the class of heterocyclic compounds with composition $C_2H_3N_3$ having five membered diunsaturated ring sytem containing three nitrogen and two carbon atoms. Triazole molecule is having following isomers viz υ-trizoles or 1,2,3-triazoles (I), s-triazoles or 1,2,4-triazoles (II).



υ-Triazole or 1,2,3-Triazole

(I)

s-Triazole or 1,2,4-Triazole

(II)

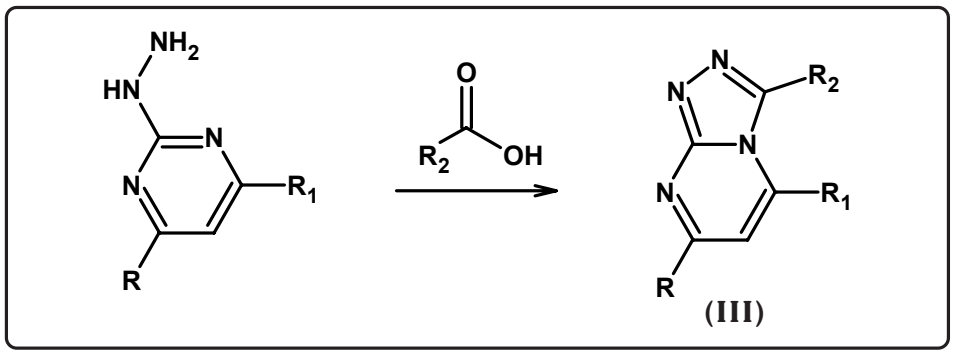
The chemistry of triazole derivatives have attained greater interest because of its useful application in medicine, agriculture and industrial chemistry. Bladin[1,2] is a pioneer worker in the filed of triazoles, synthesised the first derivatives in 1885.

1,2,4-Triazole derivatives are not only known for their medicinal applications, but also used as analytical reagents[3], photographic chemicals[4] and in polymer[5] synthesis.

SYNTHETIC ASPECTS

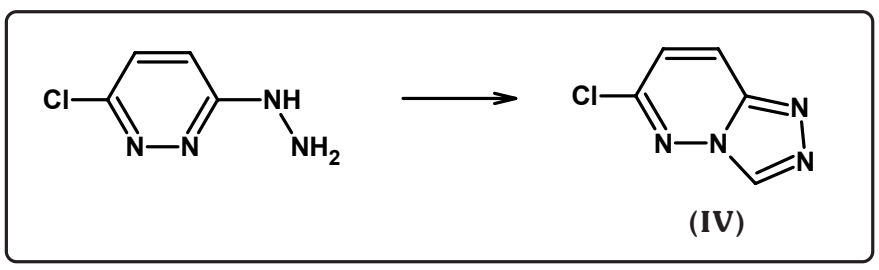
Several methods have been reported in the literature for the preparation of 1,2,4-triazoles. The procedure for synthesising 1,2,4-triazoles have been described as under.

1. C. S. Andotra and Sukhbinder Kaur[6] synthesised triazole pyrimidine by the reaction of aromatic acid with substituted hydrazino pyrimidine.



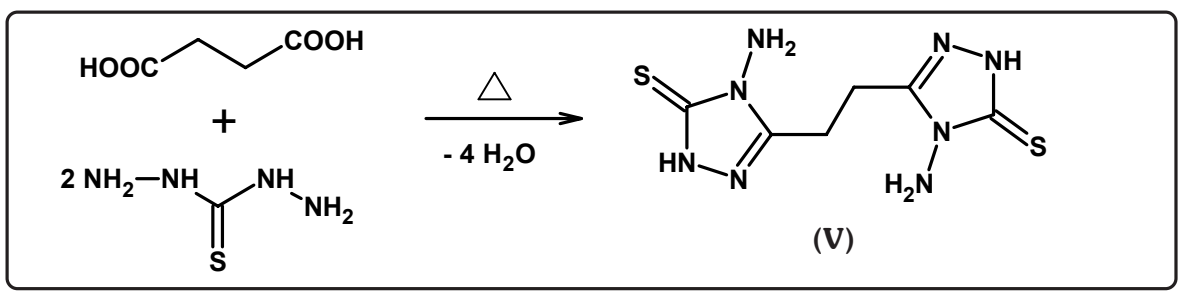
(III)

2. Ivanka Kolenc et. al.[7] synthesised 6-chloro-1,2,4-triazolo [4,3-b] pyridazin from 3-chloro-6-hydrazino pyridazin in presence of bis-o-(diethoxymethyl) dimethyl glyoxime.



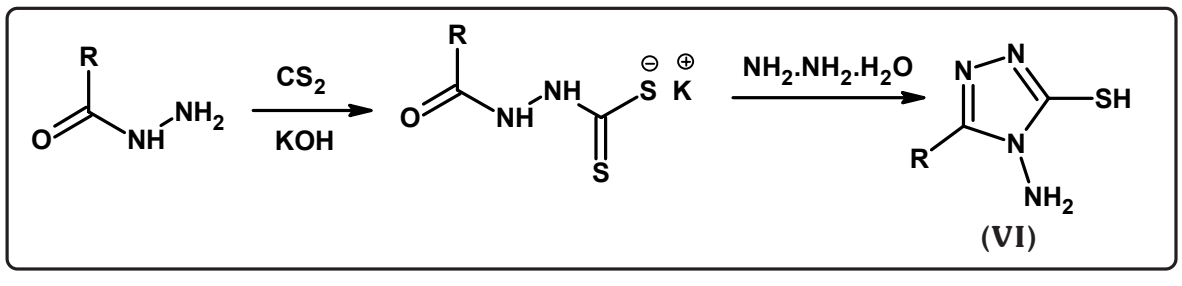
(IV)

3. A. Krutosikova and M. Dandarova[8] prepared 1,2,4-triazole by the reaction of hydrazone and triethyl orthopropionate in dry dimethyl sulfoxide at 170°C for 3 hrs.
4. Ahmad S. Shawali et. al.[9] synthesised 1,2-bis (4-amino-5-mercapto-4H-1,2,4-triazol-3-yl) ethane by heating succinic acid with two molar equivalents of carbonothioic dihydrazide in an oil bath at 170°C.



(V)

5. Reid and Heindel[10] reported that the reaction of aryl acid hydrazide with CS_2 / KOH and hydrazine hydrate furnished triazoles.

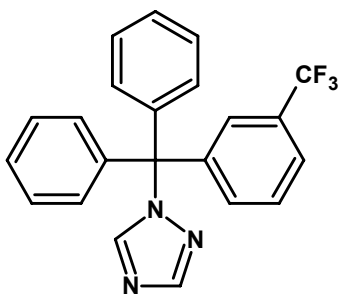


(VI)

THERAPEUTIC IMPORTANCE

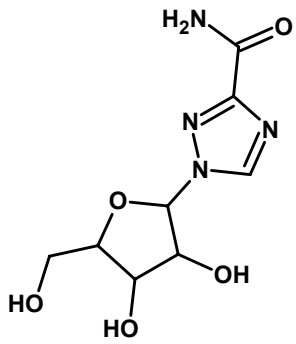
1,2,4-Triazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having 1,2,4-triazole nucleus with good activity are listed as under.

1. Fluotrimazole



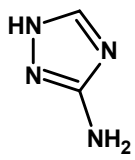
Fungicide

2. Rifavirin



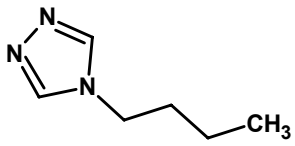
Antiviral, Antiinfections

3. Amitrole



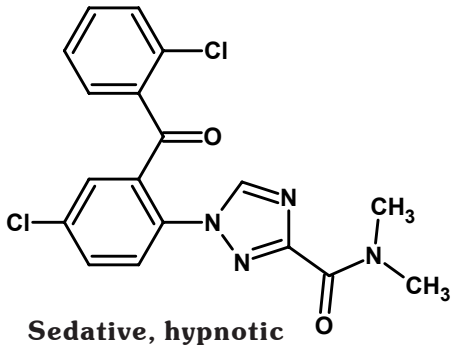
Antithyroid activity

4. Triazbutil



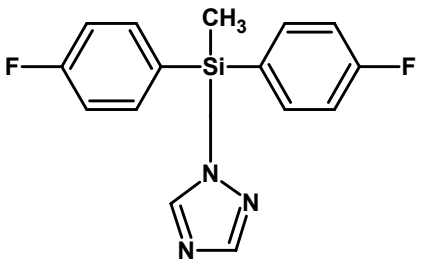
Fungicides

5. Rilmazafone



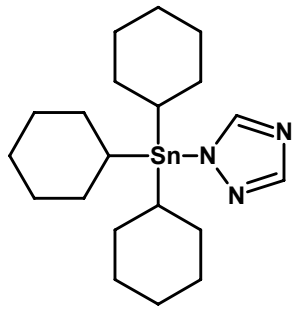
Sedative, hypnotic

6. Flusilazole



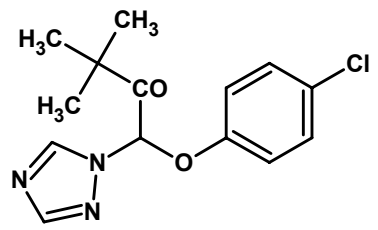
Antifungal

7. Azocyclotin



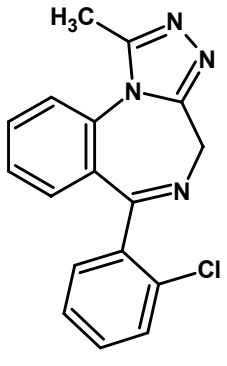
Pesticide

8. Triadimenol



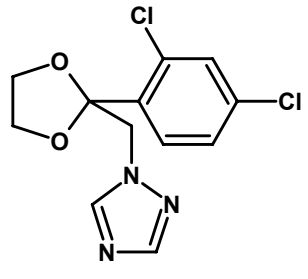
Fungicide

9. Triazolam



Plant growth regulator

10. Azaconazole



Antifungal

Literature survey reveals that various 1,2,4-triazole derivatives have resulted in many potential drugs and are known to exhibit a broad spectrum of biological activities.

3-Amino-1,2,4-triazole known as amitrole was the first triazole manufactured on large scale from aminogunidine formate, useful as herbicides[11] especially in wineyards and orchards and brain catalase activity[12].

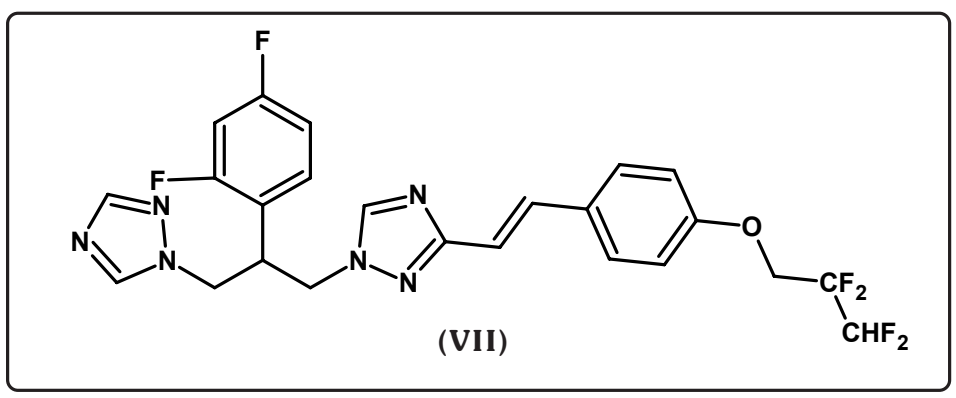
Therapeutic activity of 1,2,4-triazoles are listed as under.

1. Antimicrobial[13]
2. Antiviral[14]
3. Antiinflammatory[15]
4. Antihypertensive[16]
5. Anticonvulsant[17]
6. Anticancer & Anti-HIV[18]
7. Antileishmanial[19]

8. Antitumor[20]
9. Antidepressant & Anxiolytic[21]
10. Anthelmintics[22]
11. Bactericidal[23]
12. Diuretic[24]
13. Fungicidal[25]
14. Herbicidal[26]
15. Insecticidal & Acaricidal[27]
16. Plant growth regulator[28]

Synthesis of 1,2,4-triazole fused to another heterocyclic ring has focused attention due to their diverse applications as antibacterial, antidepressant, antiviral, antitumor and antiinflammatroy, pesticides, herbicides, lubricant and analytical reagent.[29,30]

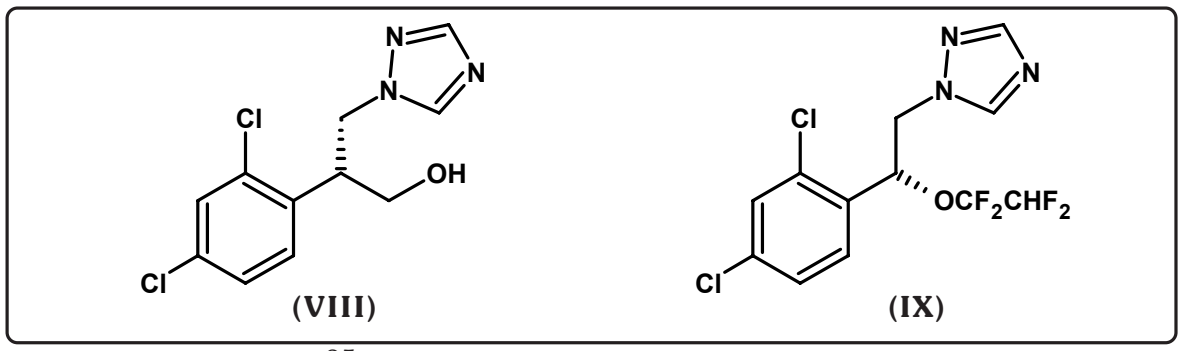
Andreina Liendo et. al.[31] have investigated both enantiomers of 2-(2,4-difluorophenyl)-1-(3-[(z)-4-(2,2,3,3-tetrafluoropropoxy)styryl]-1,2,4-triazol-1-yl)-3-(1,2,4-triazol-1-yl)-propan-2-ol. It has recently been shown that the R(+) enantiomer of bis triazole derivatives (VII) can induce radical parasitological cure in marine mouldes of the acute and chronic forms of the disease.



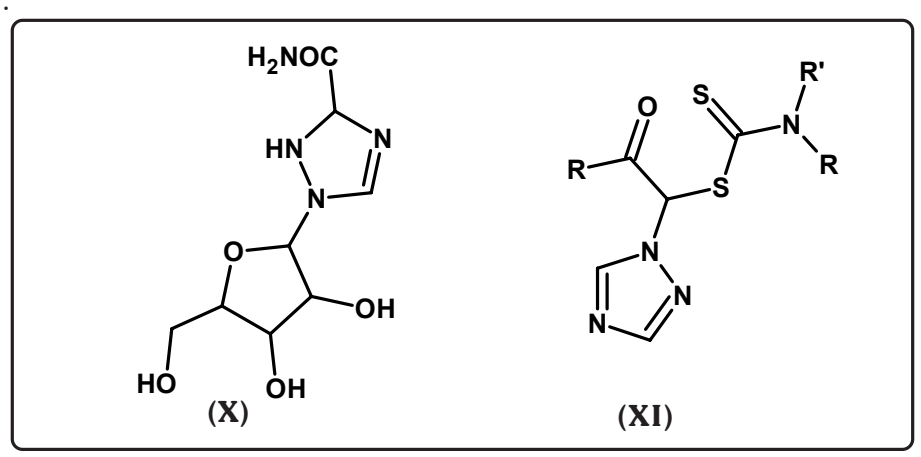
(VII)

Radwan M. and El-Zemity[32] have investigated a new series of 1,2,4-triazole derivatives and screened for their moluscicidal activity against two type of terrestrial Snail. Kalluraya B. et. al.[33] have formulated triazole derivatives possessing potential antimicrobial activity.

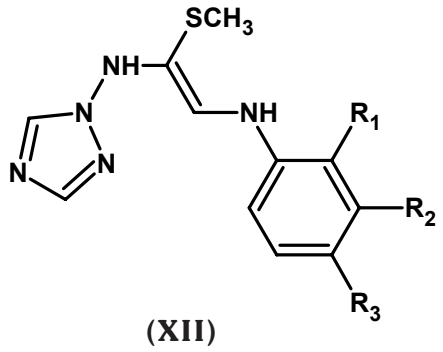
Daniele Binchi et. al.[34] have screened pure stereoisomer of two new triazole derivatives (VIII, IX) for their antifungal activity against variety of fungi showing an activity ratio R-form /S-form upto 400.



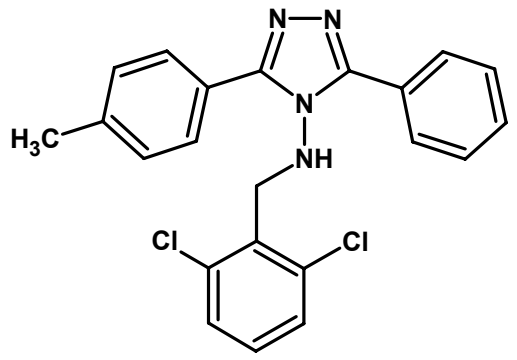
Yaseen A. et. al.[35] have prepared 1,5-dialkyl-3-(5-mercapto-4,N-aryl-1H-1,2,4-triazol-3-yl-methylene)-1H-1,2,4-triazole which exhibited remarkable activity against nine type of cancer and also antiviral activity. Bozena et. al.[36] have discovered triazole derivatives and tested their anticonvulsant and antinociceptive activity. Neslihan Demirbas and his co-workers[37] have documented antimicrobial activity of some newly synthesised 1,2,4-triazole derivatives. Sylvie Larrat et al.[38] investigated that ribavarin in combination with alpha-2-interferon is the consensus treatment for ehronic hipatitis C. and E. De Clercq. et. al.[39] screened ribavarin (X) for their antiviral and antimetabolic activities.



L. Z. Xu and co-workers[40] have synthesised an important class of triazole derivatives (XI) which are highly efficient low poisonous and inward absorbent[41-43] and studied their antifungal activity. Dawer Cui et. al.[44] have prepared some new triazoles (XII) and reported them as significant antifungal agent. M. Dincer et. al.[45] have synthesised triazole derivatives (XIII) as potential antimicrobial agent.

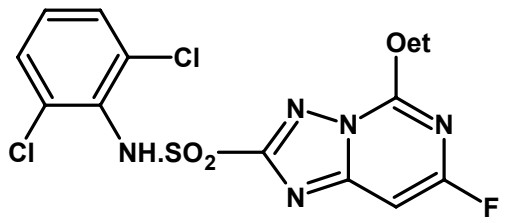


(XII)



(XIII)

L. Labanauskas et. al.[46] have documented antiinflammatory activity of some triazoles. Vera Klimesova et.al.[47] have reported 1,2,4-triazoles useful for tuberculosis inhibition. B. Shivarama Holla et al.[48] have investigated some triazole derivatives as anticancer agent. Damien Boeglin et. al.[49] have suggested 3,4,5-trisubstituted-1,2,4-triazole derivatives useful as antimicrobial agent. L. H. Mckendry and co-workers[50] have synthesised triazole derivatives (XIV) and reported them as broad spectrum broadleaf herbicides.



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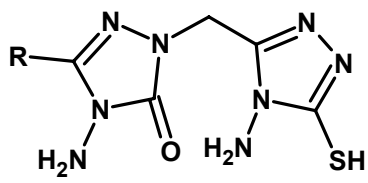


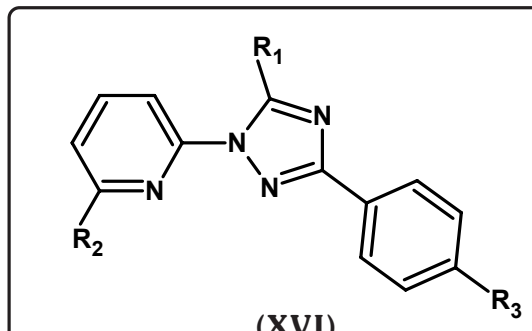
(XV)

Ilkay Kuaikguzel et. al.[51] have formulated some new triazole derivative possessing anticonvulsant activity B. Pirotte et. al.[52] have investigated triazoles as potential antibiotics. R. Pignatello et. al.[53] have documented analgesic, antipyretic, antimycotic and antiinflammatory activity of 1,2,4-triazoles. Neslihan Demirbas et. al.[54] have screened triazole derivatives (XV) for their antiinflammatory, anticancer, antituberculosis and antihypertensive acitivities.

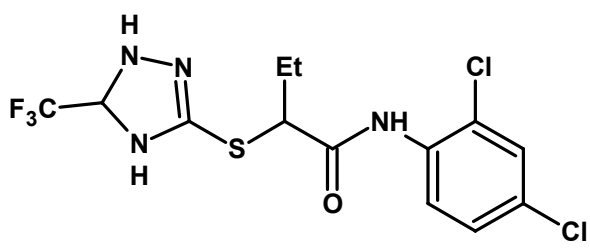
Yaseen A. Al-Soud et. al.[55] have documented antitumor activity of triazole derivatives. Chu, Chang-Hu et. al.[56] have investigated some new triazole derivatives and studied their antifungal activity. Neikamura, Hiroshi et. al.[57] have

investigated 1,2,4-triazole derivatives use for treatment of hyperuricemia. She, Dongmer et. al.[58] have reported plant growth regulatory activity of triazoles.

Recently, Krzysztof W. et. al.[59] have discovered 1,2,4-triazoles and reported their antimycobacterial activity. Balkovee et. al.[60] have formulated triazoles as antidiabetic agent. Maarouf et. al.[61] have documented analgesic and antiinflammatory activity of triazoles. Dae-Kee Kim et. al.[62] have been synthesised 1,2,4-triazole derivatives (XVI) and screened for their significant ALKS inhibitory activity. Fisher, Karl J. et. al.[63] have synthesised 1,2,4-triazole derivatives (XVII) to study their pesticidal and herbicidal activity.



(XVI)



(XVII)

In view of this and in continuation of our studies, it was thought judicious to investigate several derivatives like 1,3,4-thiadiazoles, 1,3,4-thiadiazepines, 4-aryl triazoles, azomethines and dihydrothiadiazoles bearing 1,2,4-triazole nucleus and other 1,3,4-oxadiazoles in order to achieving better therapeutic agents which have been described as under.

[A] STUDIES ON TRIAZOLES

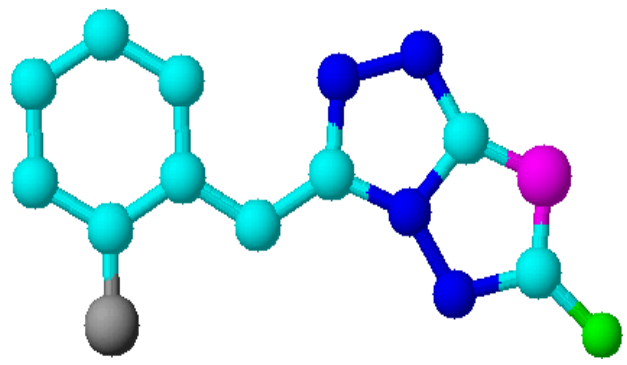
PART-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4-THIADIAZOLOTRIAZOLES

PART-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4-THIADIAZEPINES

PART-III : SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-ARYL TRIAZOLES

PART-IV : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4-OXADIAZOLES

PART-V : SYNTHESIS AND BIOLOGICAL EVALUATION OF AZOMETHINES

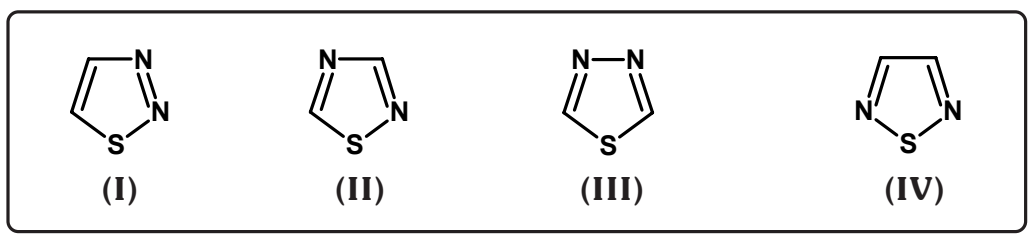


PART-I

STUDIES ON 1,3,4-THIADIAZOLO TRIAZOLES

INTRODUCTION

1,3,4-***T***hiadiazole derivatives have been found to be potent drug in pharmaceutical industries and exhibited various biological activities due to the presence of the –N=C–S group[29]. In thiadiazole ring system one sulphur and two nitrogen atoms are present in a five membered ring. According to their position, thiadiazole systems are classified as 1,2,3-thiadiazoles (I), 1,2,4-thiadiazoles (II), 1,3,4-thiadiazoles (III), and 1,2,5-thiadiazoles (IV).

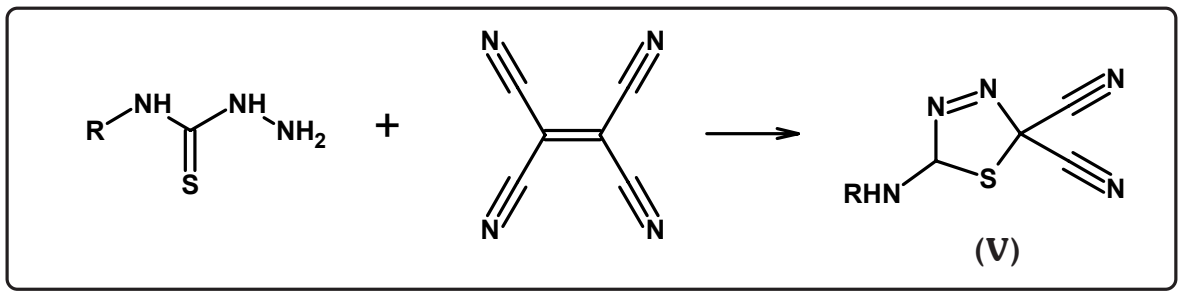


Fischer has described the first 1,3,4-thiadiazole in 1882 and further developed by Busch and co-workers. Due to the wide range of therapeutic activities, the compounds having thiadiazole nucleus have greatly accelerated the rate of progress in the field of pharmaceutical.

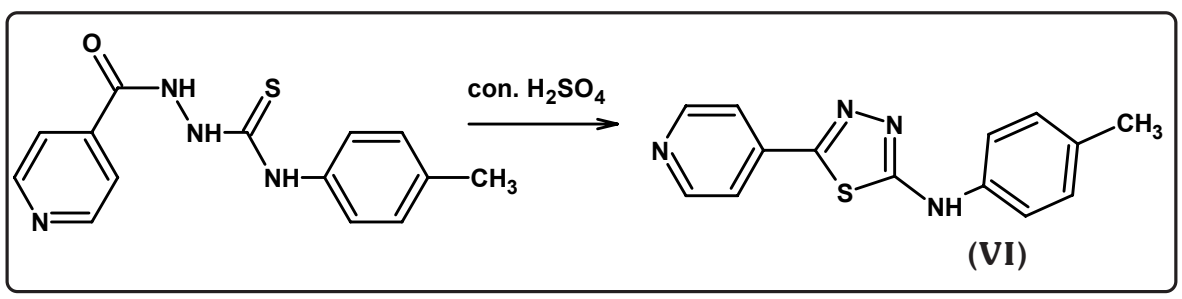
SYNTHETIC ASPECT

Literature survey reveals that several publications and patents[64] described the synthesis of 1,3,4-thiadiazoles as under.

1. Alaa Hassan et al.[65] synthesised 1,3,4-thiadiazoles by the cyclization of tetracyanoethene and 4-phenyl thiosemicarbazides.

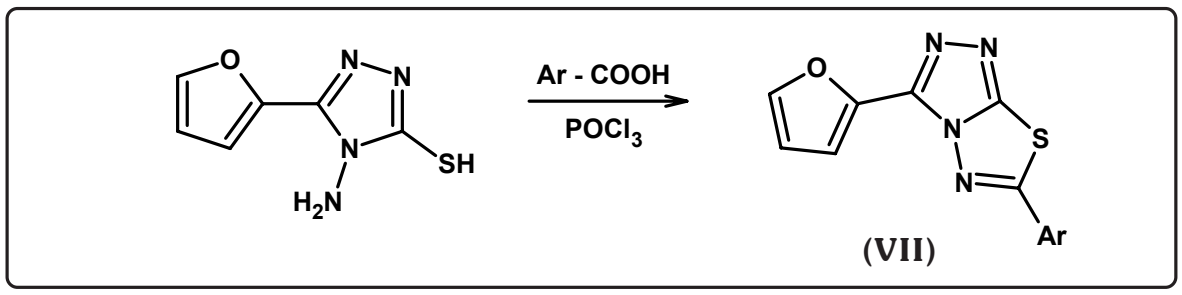


2. Khosrow Zamani et. al.[66] have prepared thiadiazole from the thiosemicarbazide by the cyclization in sulphuric acid.



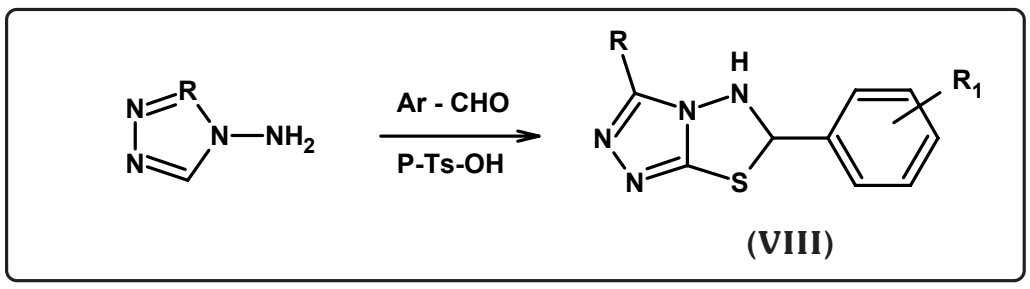
(VI)

3. Li-Xue Zhang et. al.[67] have synthesised 1,3,4-thiadiazoles by the cyclisation of aromatic acid with triazole in presence of catalyst like $POCl_3$.



(VII)

4. Jag Mohan et. al.[68] have prepared thiadiazole derivatives by the cyclisation of amino mercapto triazole and aryl aldehyde in presence of p-Ts-OH.



(VIII)

THERAPEUTIC IMPORTANCE

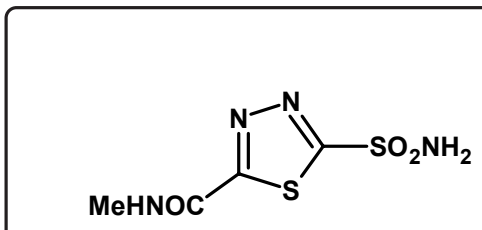
Extensive research has been carried out to enhance the activity and reduce toxicity of thiadiazole drugs. Various thiadiazole derivatives have resulted in many potential drugs and are known to exhibit numerous pharmacological activities like.

1. Amoebicidal[69]
2. Antiviral[70]
3. Antibacterial[71]
4. Antagonist agent[72]
5. Antiaflatoxigenic[73]
6. Antitumor[74]

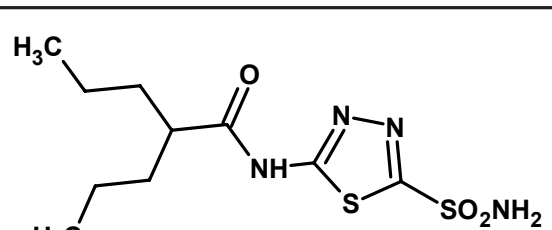
7. Algaecides and Antifouling[75]
8. Antitubercular[76]
9. Antipyretic[77]
10. Antinelmintic[78]
11. Antischistosomal[79]
12. CNS depressant[80]
13. Herbicidal[81]
14. Hypoglycemic[82]
15. Insecticidal[83]
16. Pesticidal[84]

Alireza Foroumadi and co-workers[85] have documented antituberculosis activity and cytotoxicity of 1,3,4-thiadiazoles. Hatice Dogan et. al.[86] have prepared 2,5-disubstituted-1,3,4-thiadiazolo derivatives as anticonvulsant and antimicrobial agent. Nalan Terzioglv and Aysel Gursoy[87] have discovered thiadiazoles and studied their anticancer activity.

Athansia Varvaresou et. al.[88] suggested thiadiazoles and reported them as antidepressant. Pradeep Mishra et. al.[89] have screened 1,3,4-thiadiazoles for their potent spasmolytic activity and anti-inflammatory activity. Acetazolamide (IX) was reported as diuretics and antiglaucoma by Celine Chazalete et. al.[90] and as Anticonvulsant by E. E. Chufan et. al.[91] Bernard Masercel et. al.[92] have synthesised 1,3,4-thiadiazoles possessing potent carbonic anhydrase inhibitor properties and also prepared 5-valproylamido 1,3,4-thiadiazole-2-sulfonamide (IX) useful as strong anticonvulsant.



(IX)

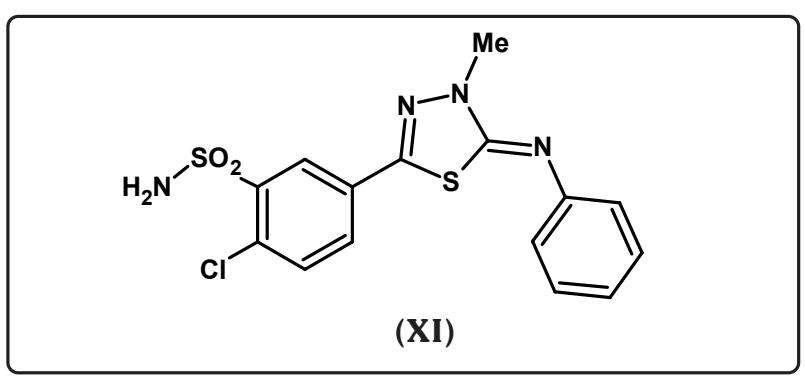


(X)

Metin Bulbul *et*. al.[93] have reported thiadiazoles as carbonic anhydrase inhibitor. Marina Kritsanida *et*. al.[94] have investigated thiadiazoles as antiviral activity. Fatemeh Soltani *et*. al.[95] synthesised thiadiazoles and studied their antibacterial activity. Andanappa K. Gadad *et*. al.[96] have prepared thiadiazoles possessing antituberculosis activity.

Erhan Palaska *et*. al.[97] synthesised thiadiazoles containing antiinflammatory activity. J. M. Colacino *et*. al.[98] have documented anti-influenza virus activity of thiadiazoles. Claudiu T. Supuran and Andrea Scozzafava[99] have reported 1,3,4-thiadiazole derivatives as carbonic anhydrase inhibitors and antitumor.

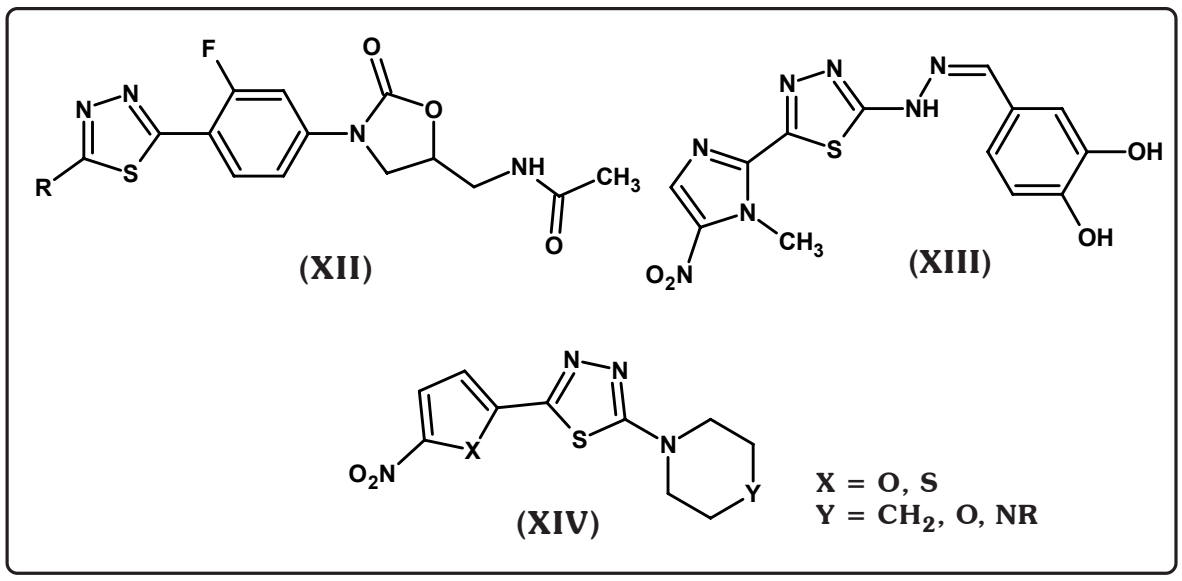
Laddi U. V. *et*. al.[100] have discovered thiadiazoles possessing antimicrobial and antituberculosis activity. Gamill Ronald B. *et*. al.[101] have reported thiadiazoles as antiinflammatory agents. Mobinikhaledi, A. *et*. al.[102] have investigated 1,3,4-thiadiazoles and tested for insecticidal activity. Che, Chao *et*. al.[103] have prepared thiadiazole derivatives showed antifungal and plant growth regulating effect, Vergne, Fabrice *et*. al.[104] have synthesised 1,3,4-thiadiazole derivatives (XI) and screened for their antiinflammatory anticacer and anti AIDS activity.



(XI)

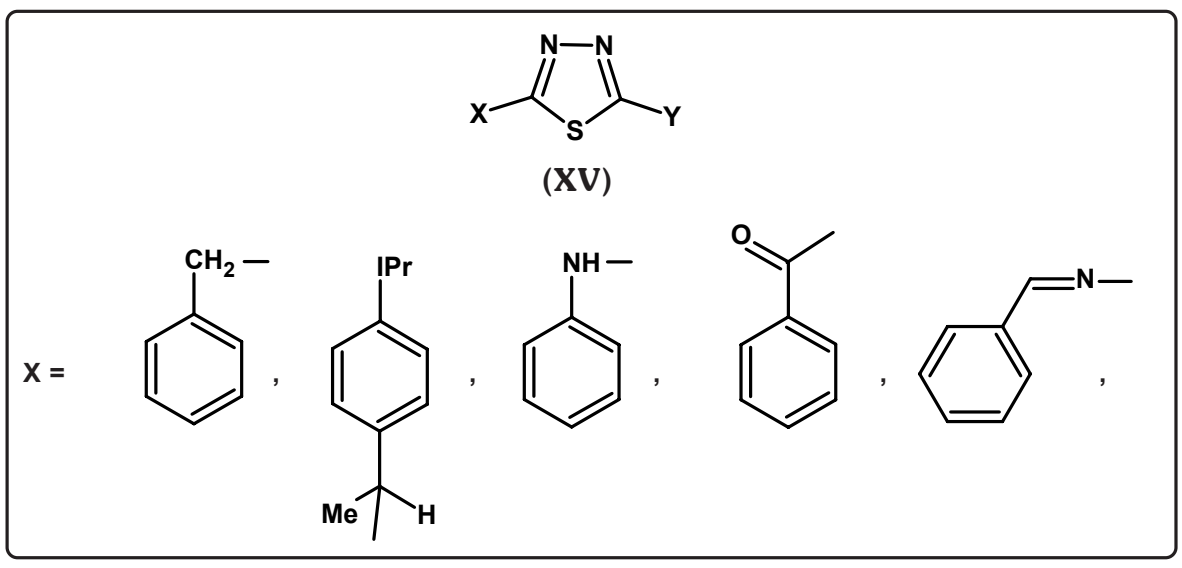
Recently, S. Karakus and S. Rollas[105] have screened thiadiazoles for their antituberculosis activity. Jui-Yi Chou *et*. al.[106] have synthesised thiadiazoles and reported them as anticancer. Zahra Kiani *et*. al.[107] have discovered thiadiazoles as antituberculosis agent. Lisa M. Thomasco *et*. al.[108] have prepared 1,3,4-thiadiazole (XII) possessing potent antibacterial activity against Gram positive and Gram negative organisms. Samir A. Carvalho and co workers[109] have

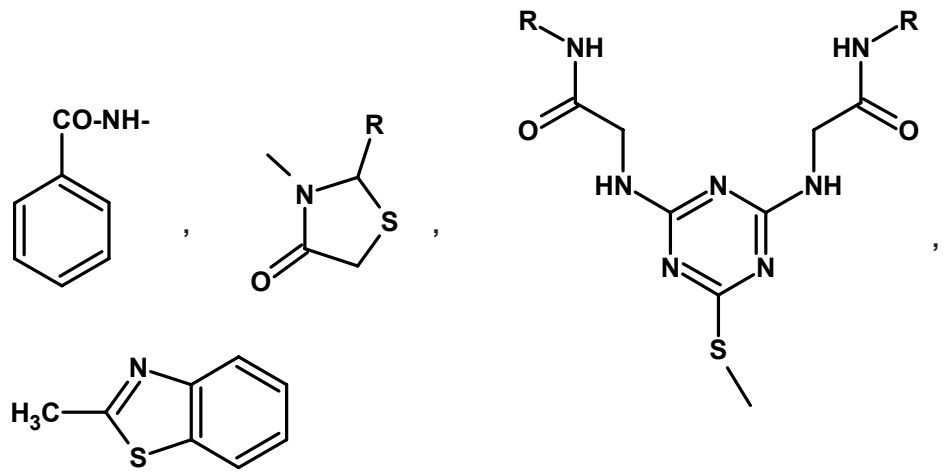
documented antitrypanosomal profile of 1,3,4-thiadiazole derivatives (XIII). Alireza faroumadi et. al.[110] have synthesised 1,3,4-thiadiazoles (XIV) and studied their leishmanicidal activity.



CONTRIBUTION FROM OUR LABORATORY

Parikh et. al. have used substituted thiadiazolinone[111], 4-pyridyl[112] moieties at 5-position (y) in 1,3,4-thiadiazole ring system and at 2-position (X) was substituted aryl, amino and s-triazine[113] H. H. Parekh et. al. have synthesised 1,3,4-thiadiazole having dapson[114,115] bis moiety at 5-position (y) and benzalamino, benzoylamino and sulphonamido[116], aryl[117] moiety substituted at 2-position (X). H. H. Parekh et. al.[118] have formulated some new thiadiazoles as biologically active agents. General structure for above references are as under.



Y = 

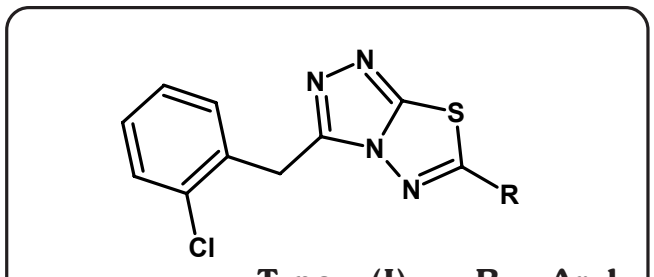
In view of the therapeutic activities of 1,3,4-thiadiazoles, it was contemplated to synthesise 1,3,4-thiadiazolo triazoles in search of agents possessing higher biological activity with least side effects, which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-o-CHLOROBENYL-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-1,3-4-THIADIAZOLES

The study of 1,3,4-thiadiazoles have revealed that thiadiazole derivatives are valuable drugs for various diseases. These valid observations led us to synthesise 1,3,4-thiadiazolo triazole of type (I) by the cyclisation of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole with different aromatic acids in presence of phosphorous oxychloride.

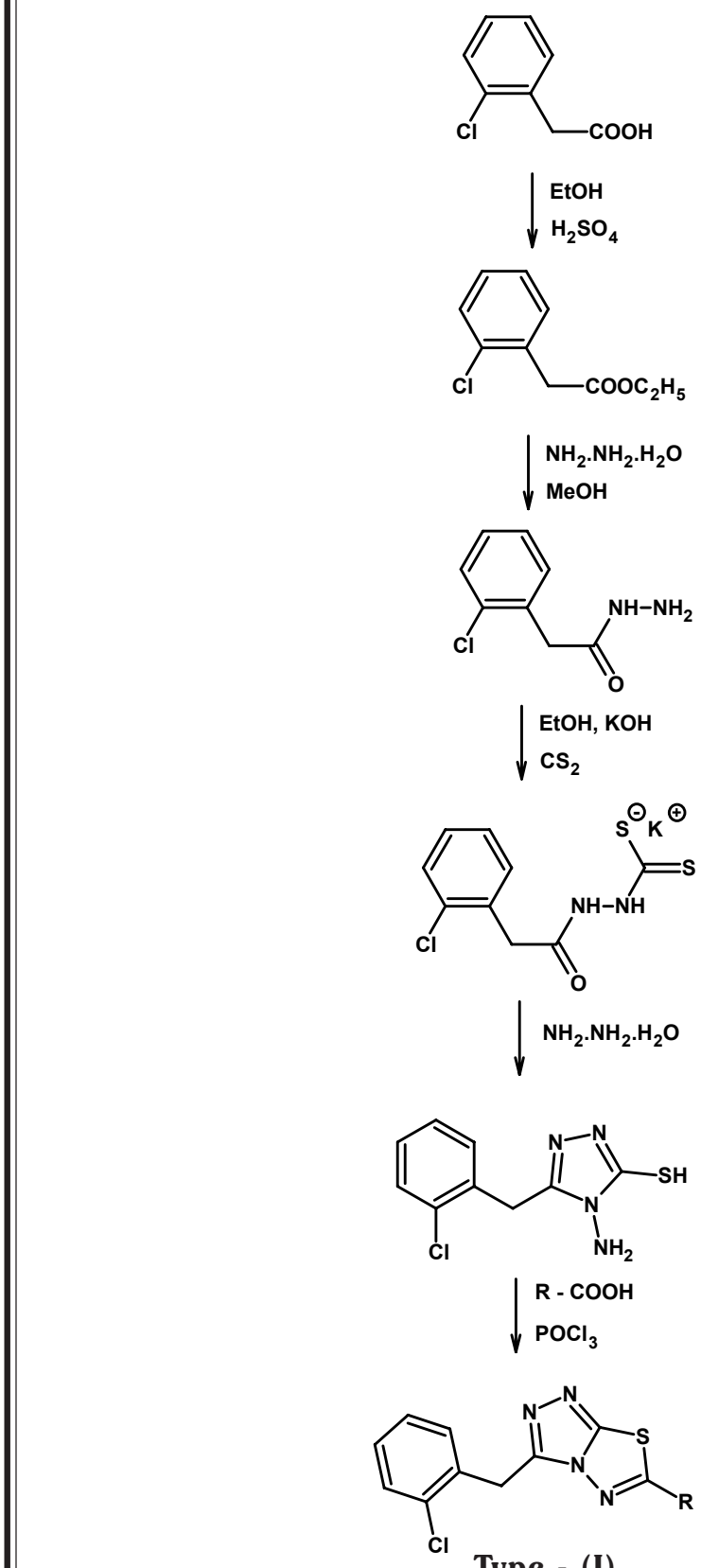


Type - (I) R = Aryl

The constitution of the synthesised compounds have been supported by 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.

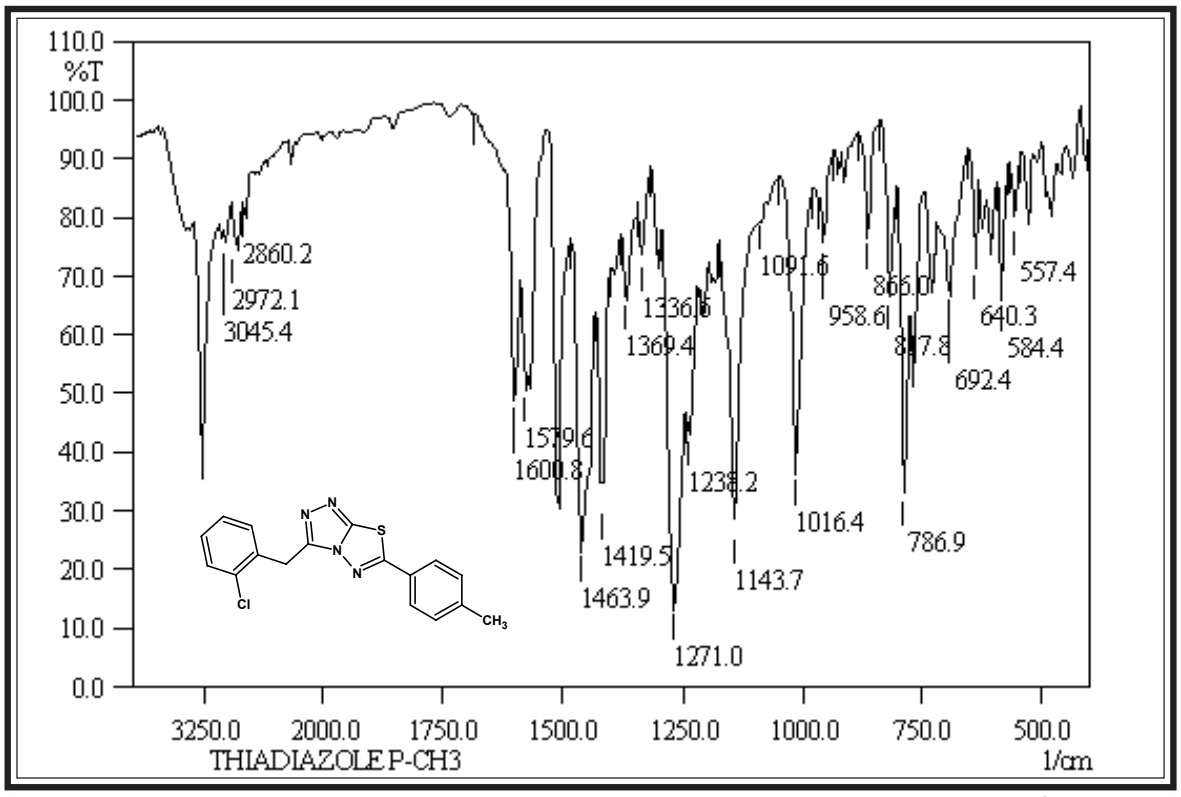
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 1.

REACTION SCHEME



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

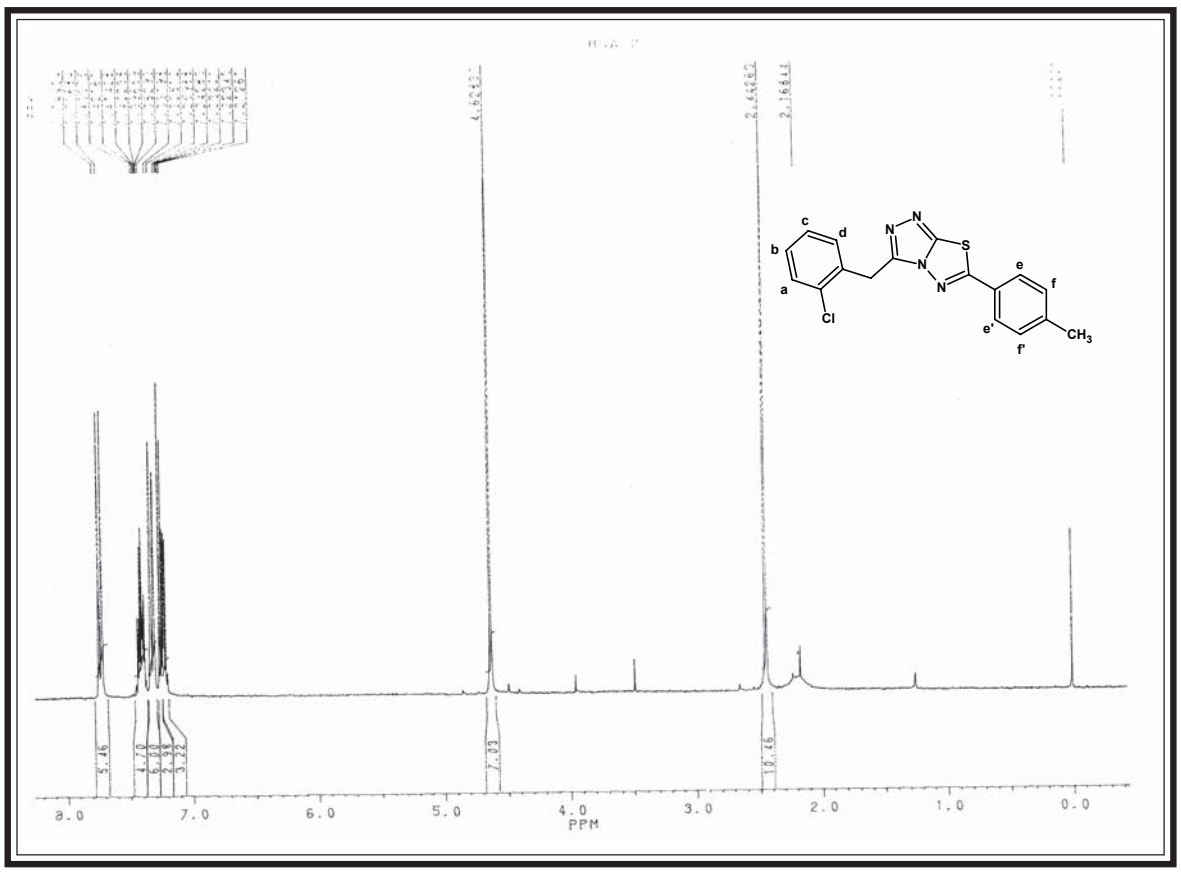
IR SPECTRAL STUDY OF 2-p-METHYLPHENYL-4-o-CHLOROBENZYL-1,2,4-TRIAZOLO-[3,4-b]-1,3,4-THIADIAZOLE



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.)	2972	2975–2950	545
$-CH_3$	C – H str. (sym.)	2860	2880–2860	"
	C – H def. (asym.)	1463	1470–1435	"
	C – H def. (sym.)	1369	1385–1370	"
Aromatic	C – H str.	3045	3080–3030	"
	C = C str.	1579	1585–1480	"
	C – H i.p. def.	1091	1125–1090	503
		1016	1070–1000	"
	C – H o.o.p.def.	817	835–810	"
Triazole	C = N str.	1600	1612–1593	498
	C – N str.	1336	1350–1200	503
	C – N – C str.	1143	1156–1132	498
	N – N str.	1016 overlapped	1050–1010	505
	C – Cl str.	786	800–600	498
Thiadiazole	C – S – C str.	692	720–570	"

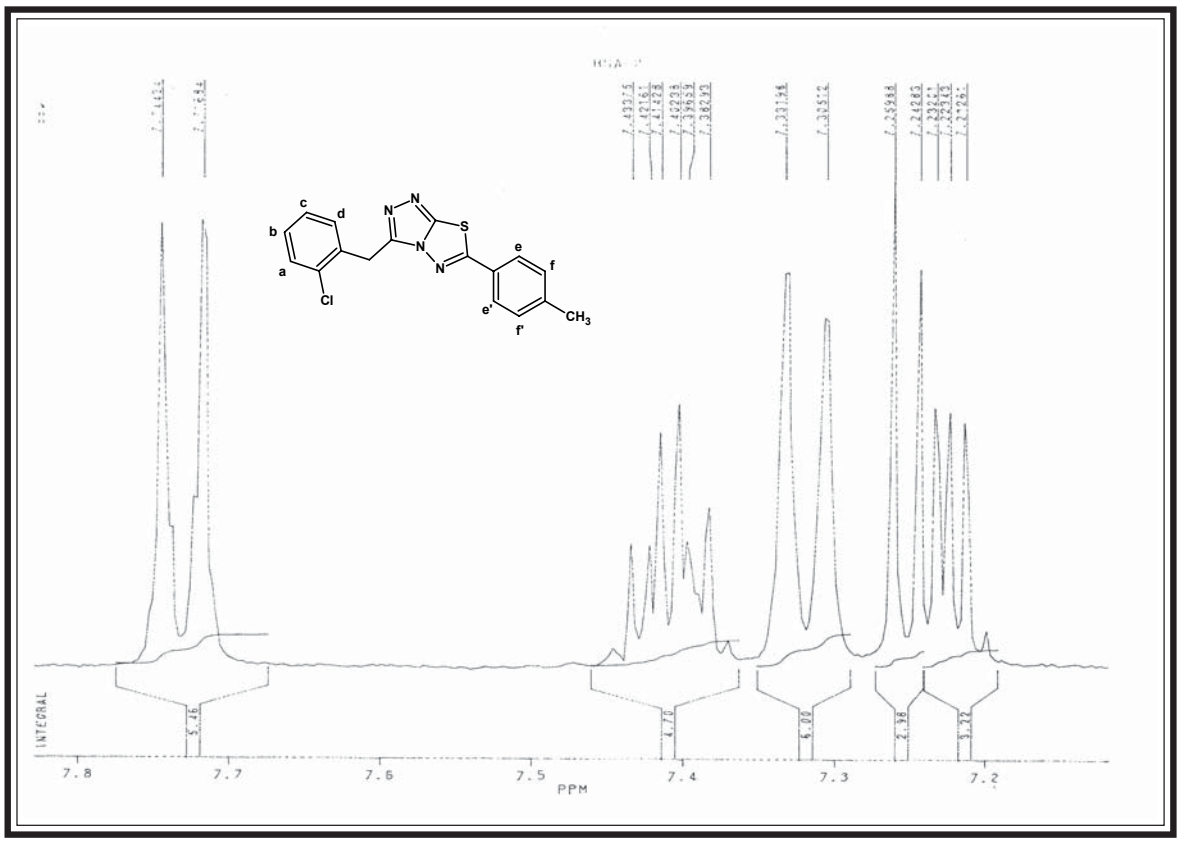
PMR SPECTRAL STUDY OF 2-p-METHYL-4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLES



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	2.44		3H	singlet	Ar-CH_3
2.	4.62		2H	singlet	-CH_2
3.	7.22-7.25		2H	multiplet	Ar-Hb,Ar-Hc
4.	7.32	Jef=9	2H	doublet	Ar-Hee'
5.	7.38-7.43		2H	multiplet	Ar-Ha, Ar-Hd
6.	7.72	Jfe=9	2H	doublet	Ar-Hff'

EXPANDED AROMATIC REGION



SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/7/2005 12:36:18 PM
Sample Name : RSB-1
Sample ID : RSB-1
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-1.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:8.7(Scan#:1003)
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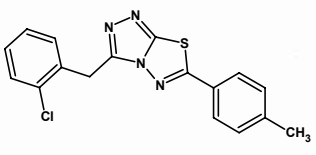
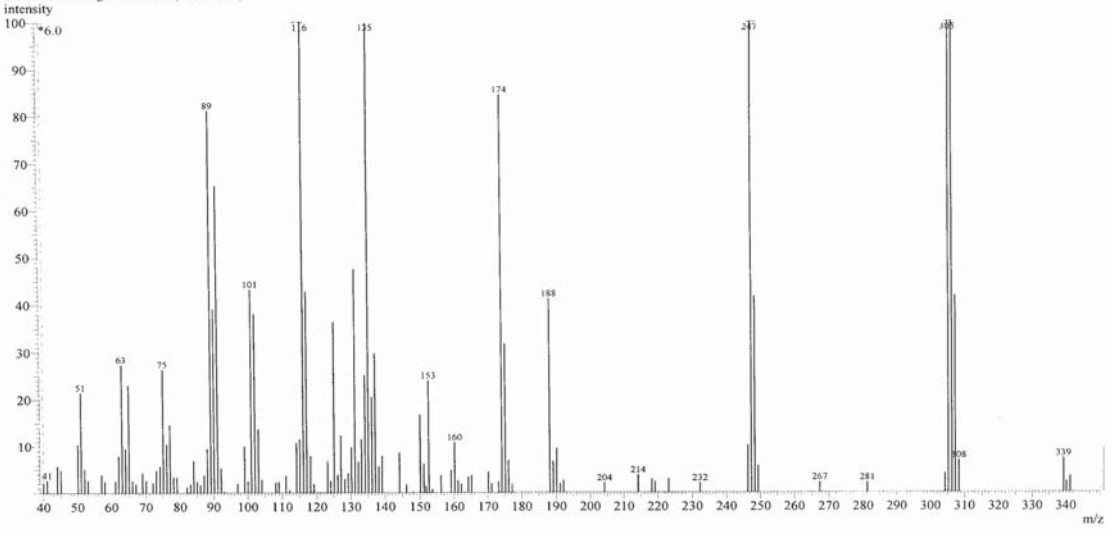
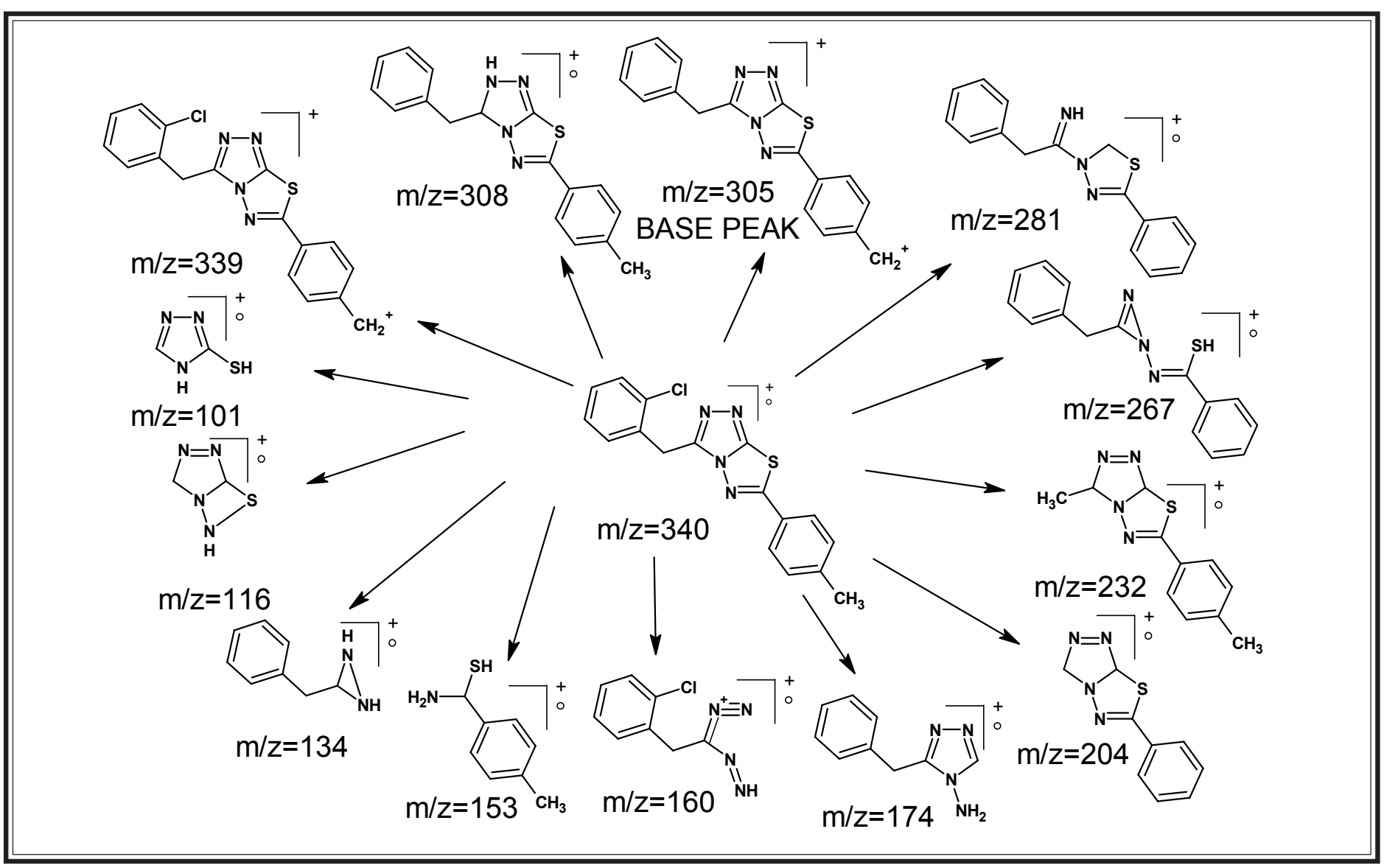
RawMode:Averaged 8.5-8.7(984-1004)
BG Mode:Averaged 12.5-13.5(1468-1587)
intensity



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m/z=174
m/z=204

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-1,3-4-THIADIAZOLES

[A] Synthesis of Ethyl-o-chlorophenylacetate[119]

A mixture of o-chlorophenylacetic acid (1.70g, 0.01M) in ethanol (20 ml) and con. H_2SO_4 (1 ml) was refluxed for 15 hrs. The reaction mixture was poured into ice cold water. The product was isolated and crystallised from ethanol. Yield 1.4g, 82%, m.p. 134°C.

[B] Synthesis of o-Chlorophenylacetohydrazide[120]

A mixture of ethyl-o-chlorophenylacetate (1.98g, 0.01M) in ethanol (20 ml) and hydrazine hydrate (0.5g, 0.01M) was refluxed for 7 hrs. The reaction mixture was poured into ice cold water. The product was isolated and crystallised from ethanol. Yield 1.7g, 85%, m.p. 158°C.

[C] Synthesis of Potassium o-chlorophenylacetamido dithiocarbamate

A mixture of potassium hydroxide (0.84g, 0.015M) in absolute ethanol (25 ml), o-chloro phenyl acetohydrazide (1.85g, 0.01M) and carbon disulfide (1.14ml, 0.015M) was stirred for 18 hrs. The product was precipitated by adding dry ether (150 ml). Yield 3.0g, 95%.

[D] Synthesis of 3-Mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole

A suspension of potassium o-chlorophenylacetamido dithiocarbamate (2.98g, 0.01M) hydrazine hydrate (95%, 1ml, 0.02M) and water (1 ml) was refluxed with stirring for 5 hrs. The content was dilute with water and acidified with acetic acid to get the product. It was crystllised from DMF/Ethanol. Yield 1.65g, 55%, m.p. 210°C, ($C_9H_9ClN_4S$: required : C, 44.91; H, 3.77; N, 23.28; found : C, 44.88; H, 3.73; N, 23.24%).

TLC solvent system : Acetone : Benzene (3 : 7).

[E] Synthesis of 2-p-Methylphenyl-4-o-chlorobenzyl-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazoles

A mixture of 3-mercapto-4,-N-amino-5-o-chlorobenzyl-1,2,4-triazole (2.40g, 0.01M) and p-methyl benzoic acid (1.36g, 0.01M) in phosphorous oxychloride (20 ml) was refluxed for 10 hrs. The resulting mixture was poured onto crushed ice and neutralised with sodium bicarbonate. The product was crystallised from ethanol. Yield, 1.9g, 79%, m.p. 218°C ($C_{17}H_{13}ClN_4S$: required : C, 59.91 ; H, 3.84 ; N, 16.44, found : C, 59.94 ; H, 3.88; N, 16.41%).

TLC solvent system Acetone : Benzene (3 : 7)

Similarly ohter 1,3,4-thiadiazolotrizole derivatives were synthesised. The physical data are recorded in Table No. 1.

[F] Antimicrobial activity of 2-Aryl-4-o-chlorobenzyl-1,2,4-triazolo [3,4,-b]-1,3,4-thiadiazoles

All the compounds have been evaluated for antimicrobial and antitubercular activity as described under.

(a) Antimicrobial activity

Antimicrobial activity was carried out by cup-plate agar diffusion method[121] 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. coccus, B. subtilis, P. vulgaris, E. coli* in seperate conical flasks at 40-50°C and mixed well by gently shaking. About 25 ml content of the flask were poured and evenly spreaded in a petridish (13 cm in diameter and allowed to set for 2 hrs. The cups 10 mm in diameter were formed by the help of borrer 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 0.04ml of DMF in a similar manner and zones of inhibition of the bacterial growth were measured in millimeter and are recorded in Graphical Chart No. 1.

The antibacterial activity data of the synthesised compounds have been compared with standard antibiotics like amoxycillin, benzoylpenicillin, ciprofloxacin and erythromycin.

(II) Antifungal activity

Aspergillus niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar slants. Sterilised Subouraud's agar medium was incoulated with 72 hrs old 0.5 ml suspension of fungal spores in separate flask. About 25 ml of the inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in diameter) were punched and filled with 0.04 ml (40 μg) solution of sample in DMF. The plates were incubated at 30°C for 48 hrs. After the completion of incubation period, the zones of inhibition of growth of fungi in the form of diameter in mm were measured. Along the test solution in each petridish one cup was filled up with solvent act as control. The zones of inhibition were compared with standard antifungal Greseofulvin. 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 towards *Mycobacterium Tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demostrating atleast > 90% inhibition in the primary screen have been retested at lower *Mycobacterium Tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibition concentration (MIC) in the BACTEC 460.

The antitubercular activity data have been compared with standard drug Rifampin at 6.25 μg/ml concentration and it showed 98% inhibition.

ANTIMICROBIAL ACTIVITY

Method	:	Cup-plate[121]
Gram positive bacteria	:	***Bacillus coccus***
		Bacillus subtilis
Gram negative bacteria	:	***Proteus vulgaris***
		Escherichia coli
Fungi	:	***Aspergillus niger***
Concentration	:	40 µg
Solvent	:	Dimethyl formamide
Standard drugs	:	Amoxicillin, Benzoylpenicillin, Ciprofloxacin,Erythromycin, Greseofulvin

The antibacterial activity was compared with standard drug viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin. The zones of inhibition measured in mm.

ANTITUBERCULAR ACTIVITY

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

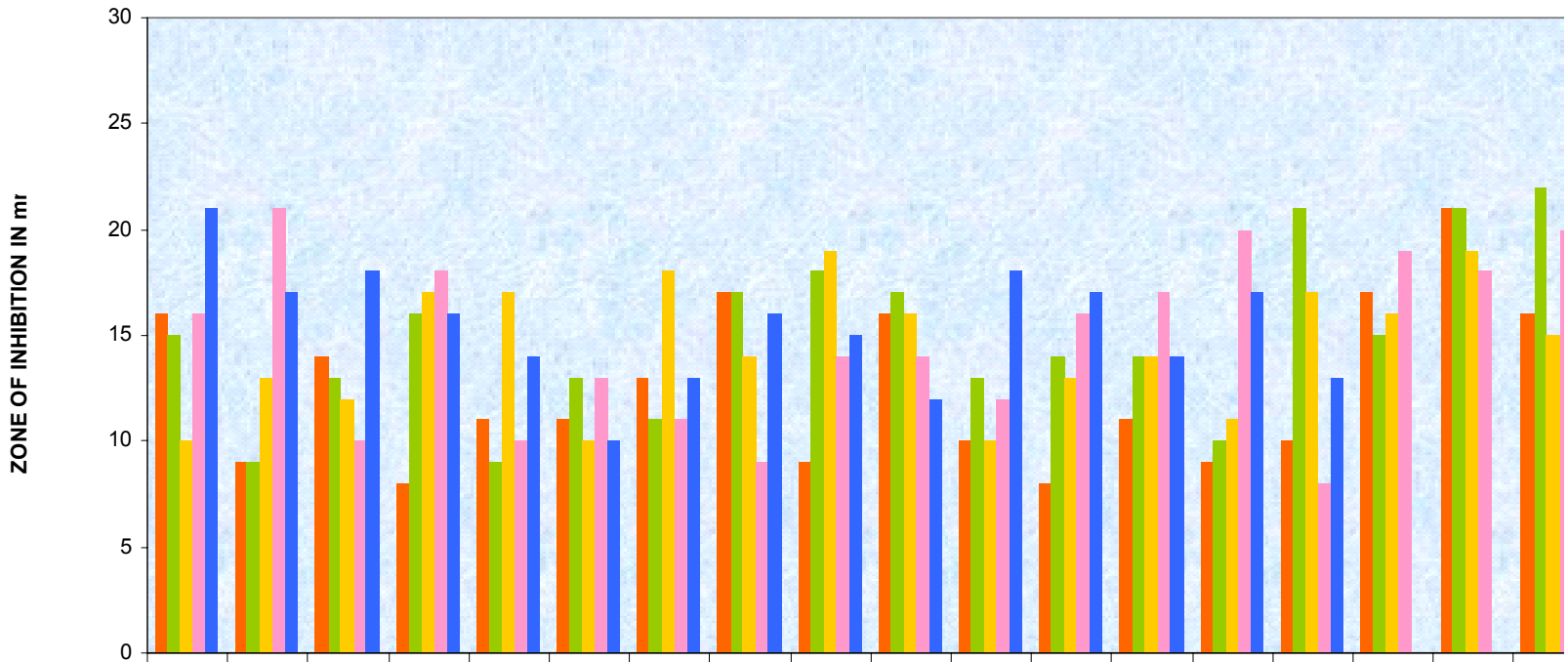
Method	:	BACTEC 460 Radiometric system
Bacteria	:	***Mycobacterium tuberculosis $H_{37}Rv$***
Concentration	:	6.25 µg
Standard drug	:	Rifampin

TABLE NO. 1 : PHYSICAL CONSTANTS OF 2-ARYL-4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLES

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	2-CH_3-C_6H_4-	$C_{17}H_{13}ClN_4S$	340.8	118	0.72	72	16.44	16.40
1b	4-CH_3-C_6H_4-	$C_{17}H_{13}ClN_4S$	340.8	218	0.81	79	16.44	16.41
1c	3-OCH_3-C_6H_4-	$C_{17}H_{13}ClN_4OS$	356.8	188	0.64	69	15.70	15.74
1d	4-OCH_3-C_6H_4-	$C_{17}H_{13}ClN_4OS$	356.8	166	0.62	76	15.70	15.68
1e	4-Cl-C_6H_4-	$C_{16}H_{10}Cl_2N_4S$	361.2	110	0.71	78	15.51	15.55
1f	4-F-C_6H_4-	$C_{16}H_{10}ClFN_4S$	344.7	136	0.80	65	16.25	16.21
1g	4-Br-C_6H_4-	$C_{16}H_{10}BrClN_4S$	405.7	158	0.58	59	13.81	13.85
1h	4- NO_2-C_6H_4-	$C_{16}H_{10}ClN_5O_2S$	371.8	180	0.77	67	18.84	18.80
1i	2-NH_2-C_6H_4-	$C_{16}H_{12}ClN_5S$	341.8	116	0.82	73	20.49	20.45
1j	2-OH-C_6H_4-	$C_{16}H_{11}ClN_4OS$	342.8	>200	0.79	61	16.34	16.38
1k	2-$OCOCH_3$-C_6H_4-	$C_{18}H_{13}ClN_4O_2S$	384.8	160	0.54	70	15.19	15.14
1l	2,4-$(OH)_2$-C_6H_3-	$C_{16}H_{11}ClN_4O_2S$	358.8	145	0.70	55	15.61	15.65
1m	-CH_2-C_6H_4	$C_{17}H_{13}ClN_4S$	340.8	182	0.66	80	16.14	16.18
1n	-CH=CH-C_6H_5	$C_{18}H_{13}ClN_4S$	352.8	152	0.51	84	15.88	15.84
1o	C_5H_4N-	$C_{15}H_{10}ClN_5S$	327.7	126	0.68	52	21.37	21.33

*TLC Solvent System : Acetone : Benzene (3 : 7)

GRAPHICAL CHART NO. 1 : 2-ARYL-4-o-CHLOROBENZYL-1,2,4-TRIAZOLO[3,4-b]-1,3,4-THIADIAZOLES



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m	1n	1o	Amoxycillin	Benzoylpenicillin	Ciproxac
B.coccus	16	9	14	8	11	11	13	17	9	16	10	8	11	9	10	17	21	16
B.subtilis	15	9	13	16	9	13	11	17	18	17	13	14	14	10	21	15	21	22
P.vulgaris	10	13	12	17	17	10	18	14	19	16	10	13	14	11	17	16	19	15
E.coli	16	21	10	18	10	13	11	9	14	14	12	16	17	20	8	19	18	20
A.niger	21	17	18	16	14	10	13	16	15	12	18	17	14	17	13	0	0	0

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

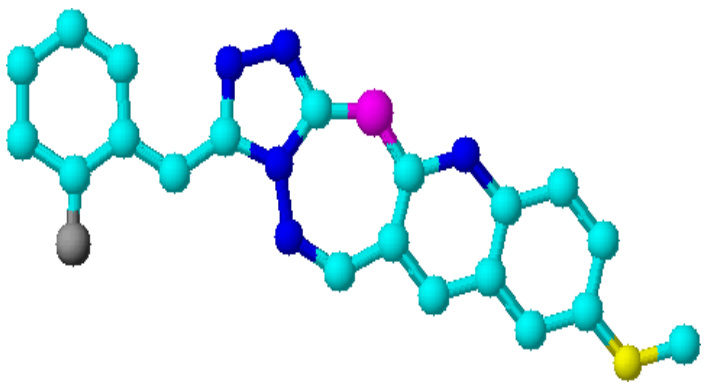
From the experimental data, it has been observed that the compounds bearing R=2-methylphenyl, 4-nitrophenyl, 2-hydroxy phenyl have displayed significant activity against ***B.coccus***. The compounds bearing R=4-methoxyphenyl, 4-nitrophenyl, 2-aminophenyl, 2-hydroxyphenyl have shown good activity against ***B.subtilis***.

In case of Gram negative bacterial strains, the maximum activity was displayed by the compounds bearing R=4-bromophenyl and 2-aminophenyl against ***P.vulgaris***. While the compounds with R=4-methylphenyl, 4-methoxyphenyl, benzyl and cinnamyl have shown considerable activity against ***E.coli***.

Antifungal activity :

All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=2-methylphenyl have displayed highest activity against ***A.niger***.

The antibacterial activity was compared with standard drug viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

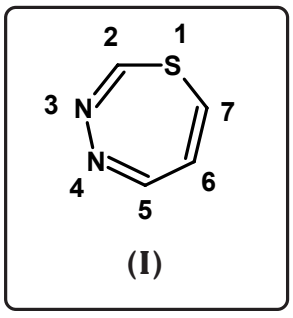


PART-II

STUDIES ON 1,3,4-THIADIAZEPINES

INTRODUCTION

1,3,4-***T***hiadiazepine derivatives are studied extensively because it represents one of the most active class of compounds possessing a wide spectrum of pharmacological activities. The thiadiazepine ring system have one sulphur atom and two nitrogen atoms at 1,3,4-position (I) in seven membered heterocyclic ring system.



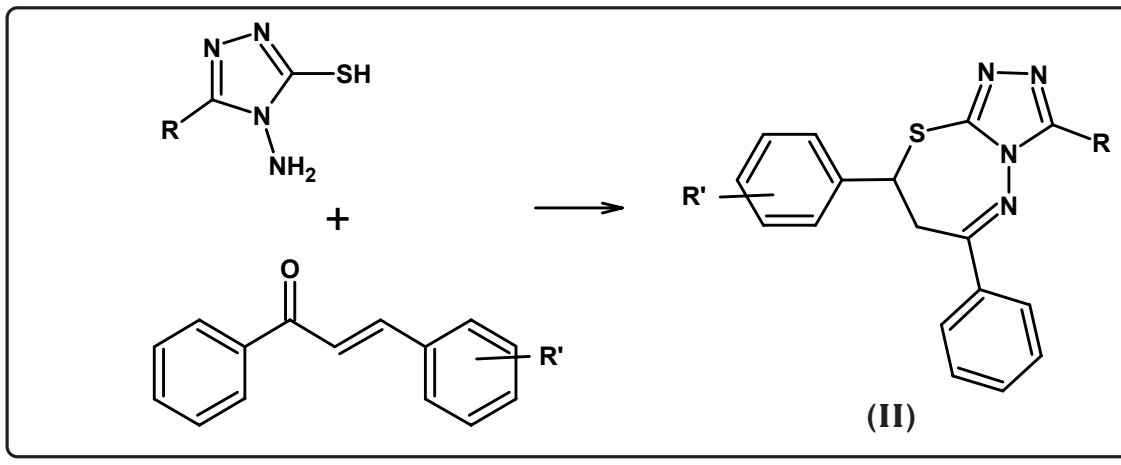
(I)

1,3,4-Thiadiazepines have attracted attention of chemists for both with regards to heterocyclic chemistry and the pharmacological activities associated with them.

SYNTHETIC ASPECT

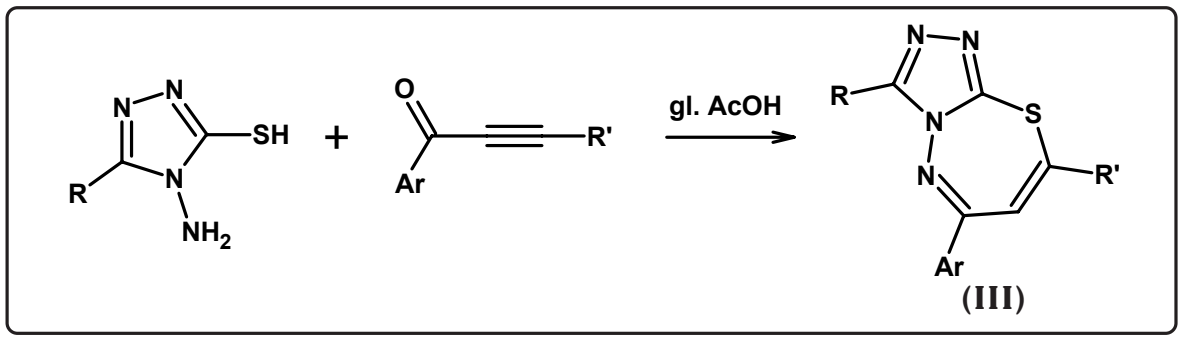
Different methods for the preparation of 1,3,4-thiadiazepine derivatives documented in literature are as follows.

1. Om Prakash et. al.[122] have synthesised thiadiazepine by Michael type addition of 4-amino-3-mercapto-1,2,4-triazole to α,β,-unsaturated carbonyl compounds.



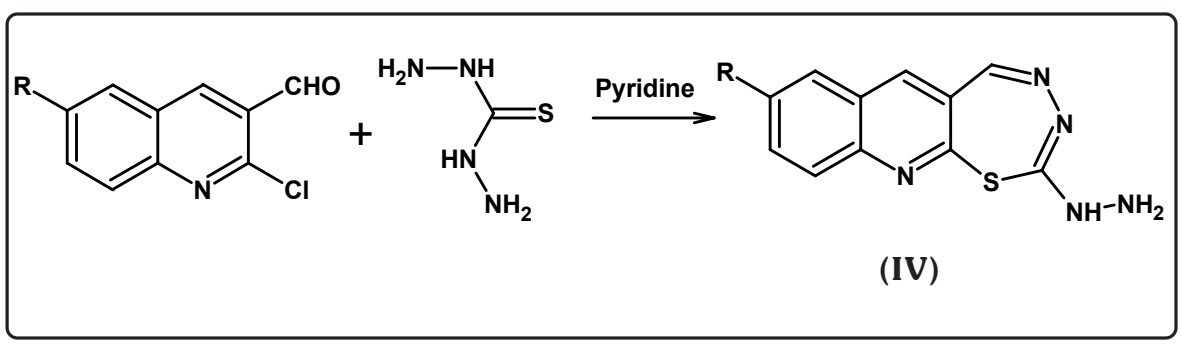
(II)

2. T. E. Glotova et. al.[123] have synthesised 1,3,4-thiadiazepine by treating α-acetylenic ketones with 4-amino-3-mercapto-1,2,4-triazole in glacial acetic acid.



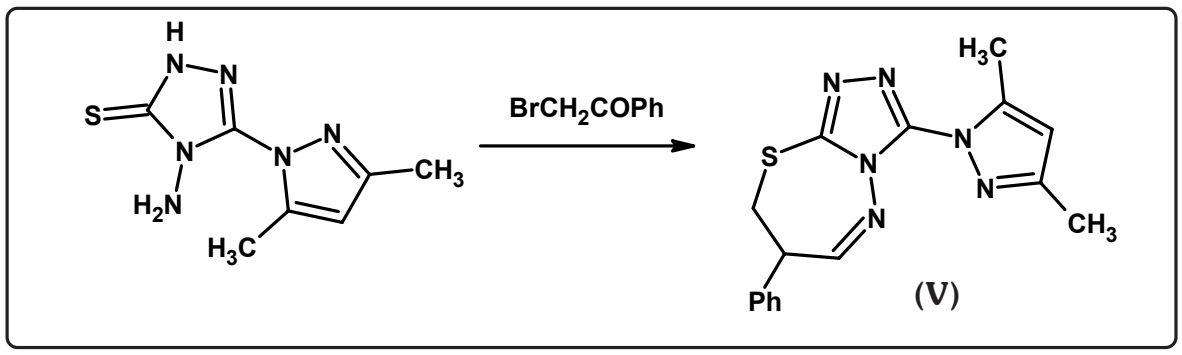
(III)

3. R. Gururaja et. al.[124] have synthesised quinolinethiadiazepine derivatives by condensation of 2-chloro-6-substituted quinoline-3-carboxaldehyde with thiocarbohydrazide in pyridine.



(IV)

4. Sinegibskaya A. D. et. al.[125] have synthesised thiadiazepine by reaction of 4-amino-3-hydrazino-1,2,4-triazoline-5-thione with α-and β-dicarbonyl compounds, then the treatment of Br-CH_2-CO-Ph.



(V)

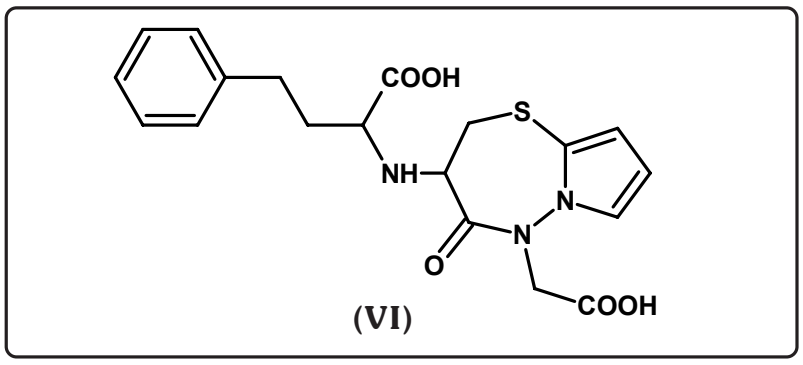
Several methods have also documented in literature[126-129].

THERAPEUTIC IMPORTANCE

Literature survey reveals that 1,3,4-thiadiazepine derivatives possess remarkable pharmacological importance. Biological activities described are as under.

1. Antitumor[130]
2. Antidepressant[131]
3. Antiviral[132]
4. Antiarrythmic[133]
5. Anti psychotic[134]
6. Anti HIV[135]
7. Anticonvulsant[136]
8. CCK antagonists[137]
9. Gastrin receptor antagonists[138]

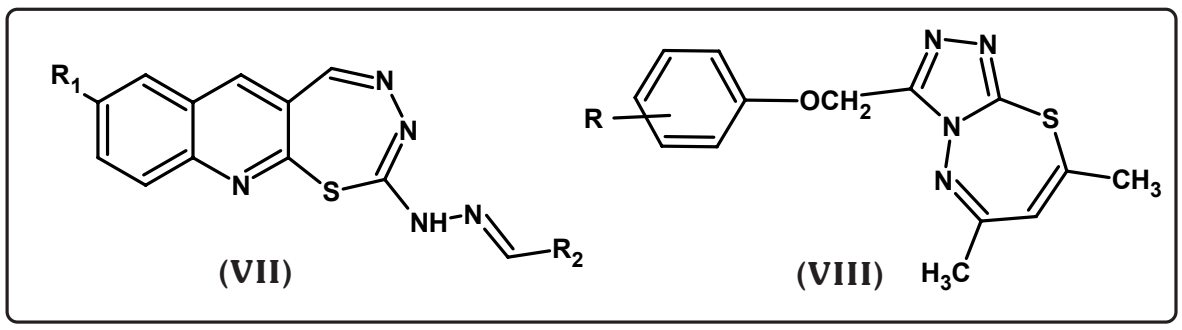
Borsini F. et. al.[139] have investigated thiadiazepines useful as potent antidepressant drugs. B. S. Holla and co-workers[140] have investigated some thiadiazepines as potent antimicrobial agents. Ammar Y. A. et. al.[141] have preared triazolo thiadiazepines as antifungal agents. Swati Sharma and co-workers[142] have discovered thiadiazepine derivatives as possible potential drug for cancer metastatics. Denis Pires di Lima[143] have synthesised thiadiazepines (VI) useful as angiotensin-converting enzyme (ACE) inhibitors and Bolos. J. et. al.[144] reported them as an important class of antihypertensive drugs.



(VI)

Giannotti D. and co-workers[145] have screened thiadiazepines for their antidepressant activity Khalil and Habib[146] have documented antimicrobial and anticancer activities of thiadiazepine derivatives. Marfe G. et. al.[147] have investigated thiadiazepines useful as anticancer agent.

Recently, M. Kidwai et. al.[148] have reported thiadiazepines as potential antimicrobial agent B. Shivarama Holla et. al.[149] have documented antibacterial and antiviral activity of thiadiazepines. Robert J. Cherney and co-workers[150] have demonstrated benzothiadiazepines as selective tumor necrosis factor α-converting enzyme inhibitors. Cherney R. J. et. al.[151] have synthesised thiadiazepines and reported them as selective tumor necrosis factor alpha converting enzyme inhibitor. R. Gururaja and co-workers[152] have synthesised 1,3,4-thiadiazepines (VII) and screened for their anthelmintic activity and antibacterial activity. Ashutosh Singh and Nizamuddin[153] have prepared thiadiazepines (VIII) and reported their molluscicidal activity.



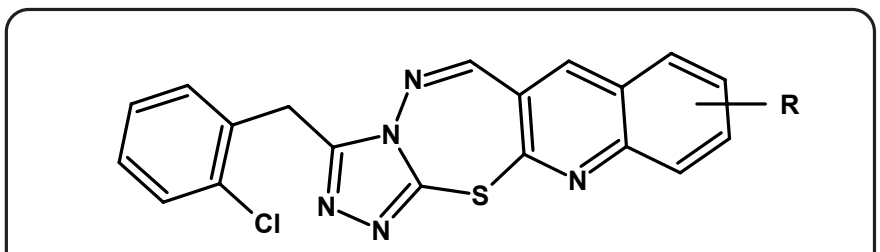
Thus the important role displayed by 1,3,4-thiadiazepine derivatives for various therapeutic and pharmaceutical activities prompted us to synthesise some new 1,3,4-thiadiazepines bearing triazole moiety in order to achieving compounds having better drug potential. This study is described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-SUBSTITUTED QUINOLINO [2,3-f] 1,3,4-THIADIAZEPINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-o-CHLOROBENZYL-1,24-TRIAZOLO [3,4,-b] SUBSTITUTED QUINOLINO [2,3-f] 1,3,4-THIADIAZEPINES

During the past years, considerable evidence has been accumulated to demonstrate the efficiency of thiadiazepines in including variety of therapeutic activity. To further assess the potential of such class of compounds as good therapeutic agents, a series of 1,3,4-thiadiazepines of type (II) have been synthesised by the condensation of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2-4-triazole with substituted 2-chloro-3-formyl-quinolines.

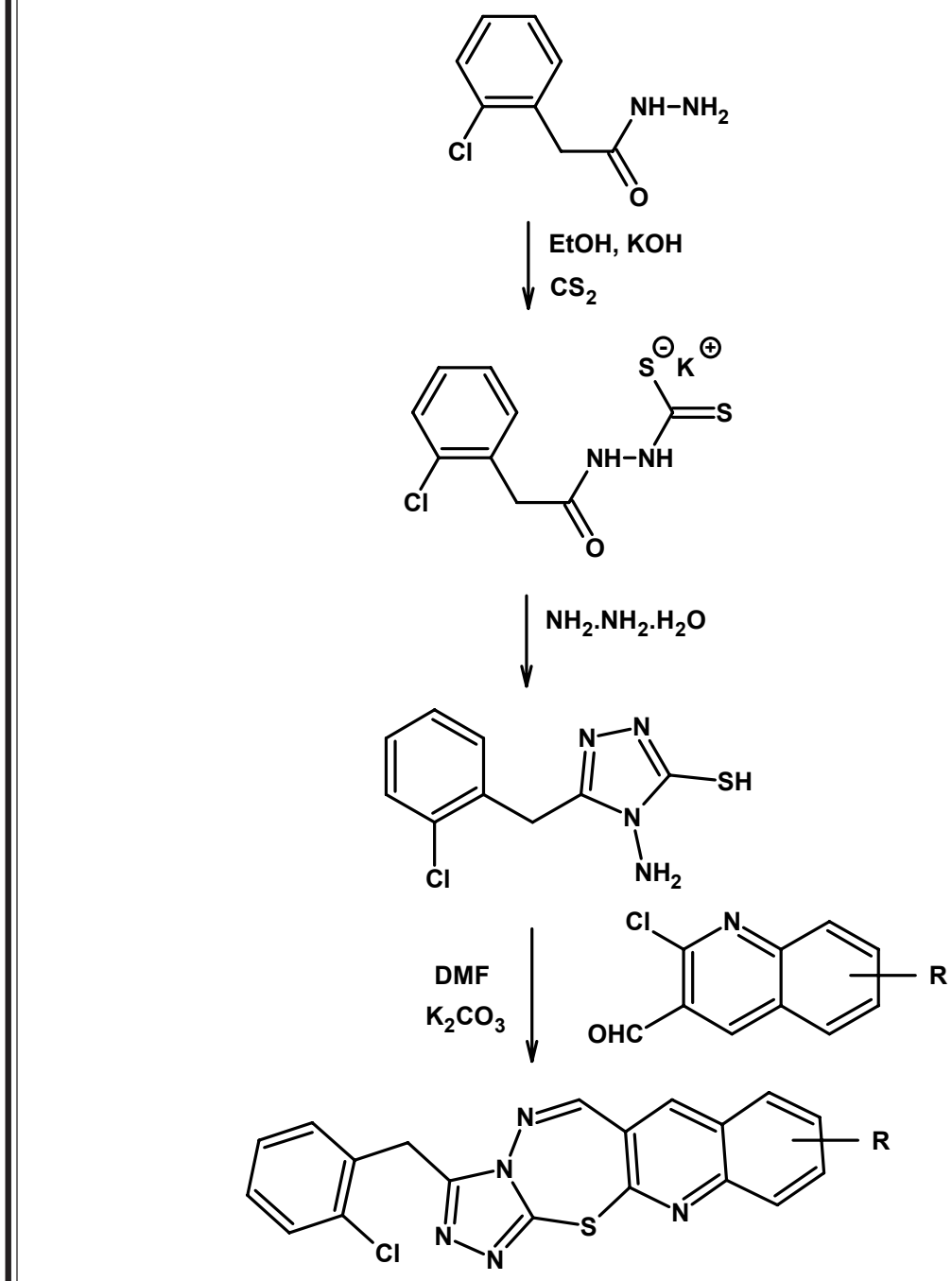


Type - (II) **R = Aryl**

The constitution of newly synthesised compounds have been supported by 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.

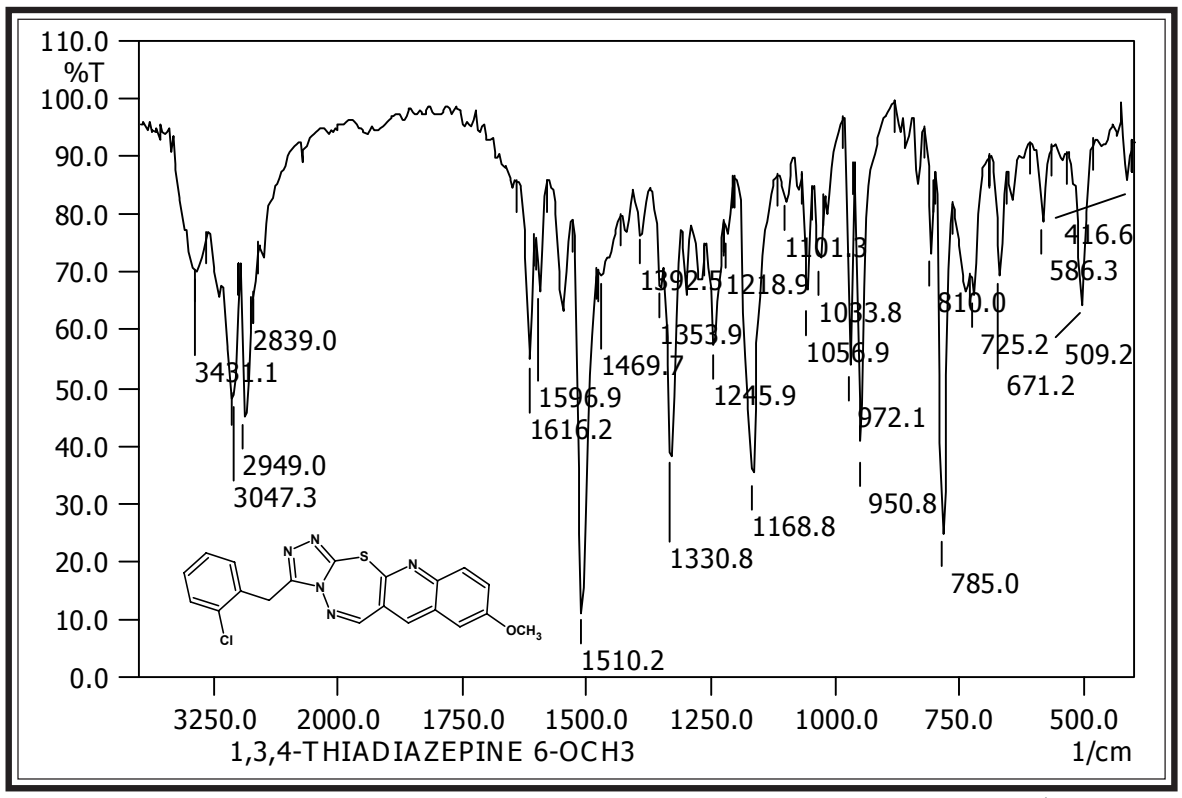
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 2.

REACTION SCHEME



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

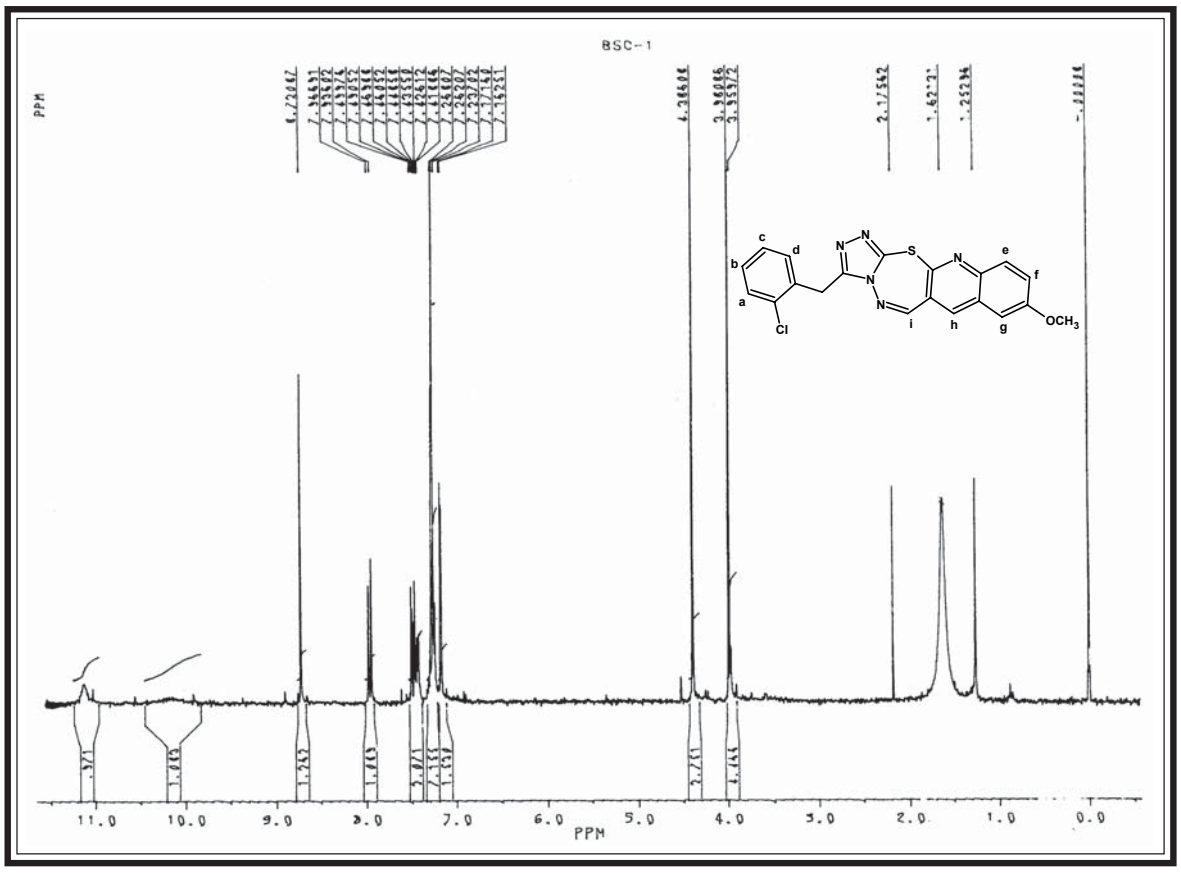
IR SPECTRAL STUDY OF 4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-6-METHOXY QUINOLINO [2,3-f]-1,3,4-THIADIAZEPINE



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.)	2949	2975–2950	498
$-CH_3$	C – H str (sym.)	2839	2880–2860	"
	C – H def. (asym.)	1469	1470–1435	"
	C – H def. (sym.)	1353	1385–1370	"
Aromatic	C – H str.	3047	3080–3030	"
	C = C str.	1510	1585–1480	"
	C – H i.p. def.	1101	1125–1090	503
	C – H o.o.p. def.	810	835–810	498
Triazole	C = N str.	1616 overlapped	1640–1500	"
	C – N str.	1330	1350–1200	504
	N – N str.	1033	1050–1010	503
	C – Cl str.	785	800–600	498
Ether	C – O – C str. (asym.)	1245	1275–1200	503
	C – O – C str. (sym.)	1056	1070–1020	"
Thiadiazepine	C – S – C str.	671	700–600	504
		1218	1250–1003	"
	C = N str.	1596	1640–1500	498

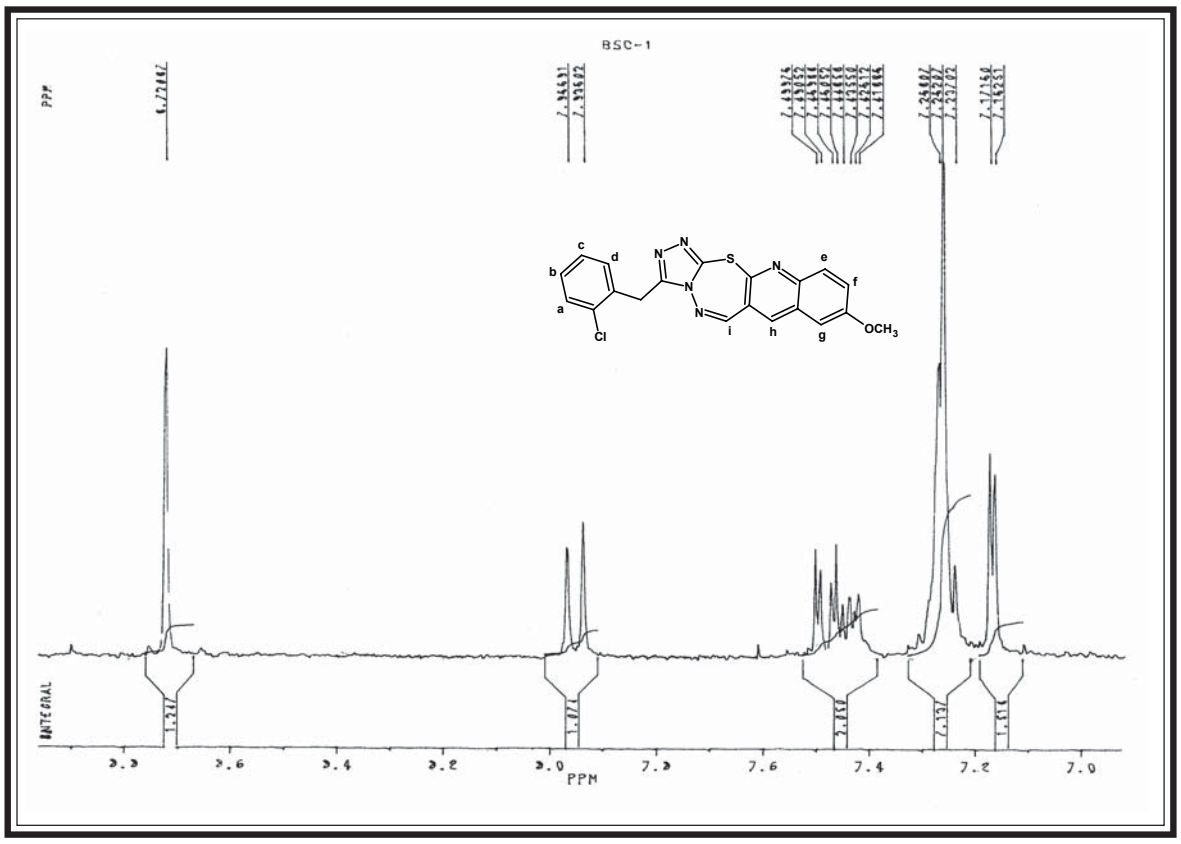
PMR SPECTRAL STUDY OF 4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b]-6-METHOXY QUINOLINO [2,3-f]-1,3,4-THIADIAZEPINE



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.98		3H	singlet	Ar-OCH_3
2.	4.38		2H	singlet	-CH_2
3.	7.16	Jgf=3	1H	doublet	Quinolin g
4.	7.23-7.26		4H	multiplet	Ar-Ha,Ar-Hb, Ar-Hc,Ar-Hd
5.	7.41-7.49		2H	multiplet	Quinoline f Ar-Hi
6.	7.94	Jef=9	1H	doublet	Quinoline e
7.	8.72		1H	singlet	Quinoline h

EXPANDED AROMATIC REGION

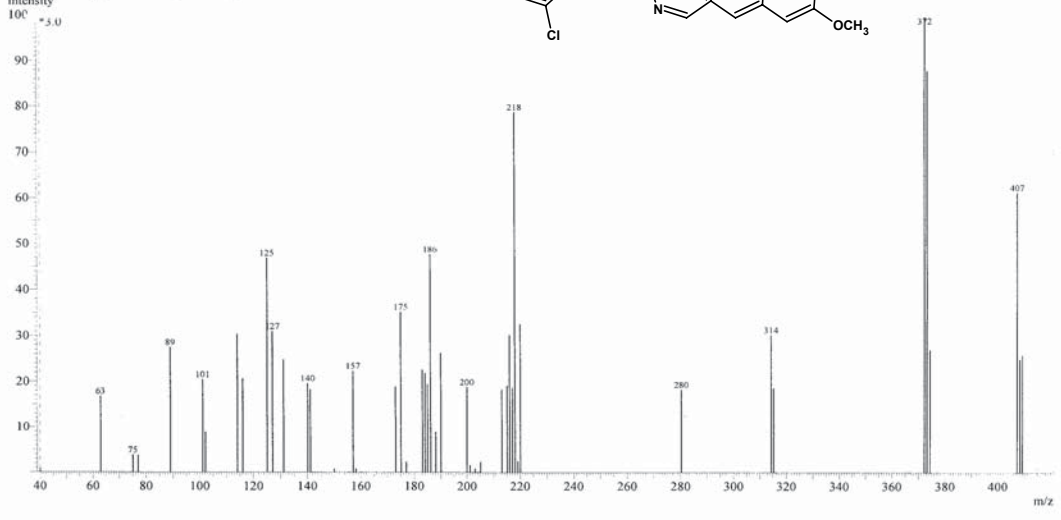


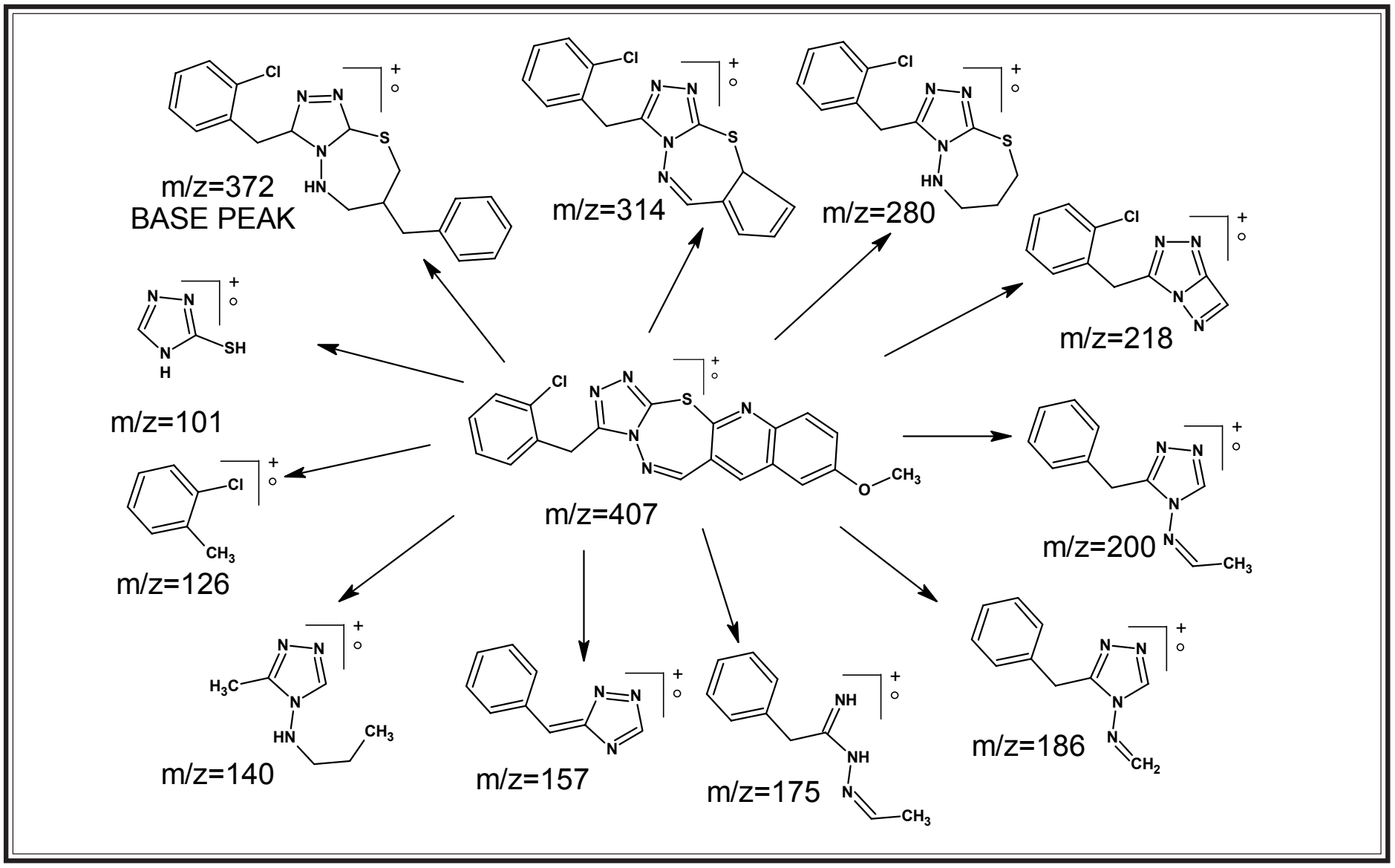
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/7/2005 1:56:28 PM
Sample Name : SB-3
Sample ID : SB-3
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-3.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:10.1(Scan#:1179)
MassPeaks:46 BasePeak:372(18362)
RawMode:Averaged 10.1-10.3(1177-1199)
BG Mode:Averaged 14.3-15.0(1685-1759)
intensity

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m/z=200
m/z=140
m/z=157
m/z=175
m/z=186

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b] SUBSTITUTED QUINOLINO [2,3-f] 1,3,4-THIADIAZEPINES

[A] Synthesis of Potassium o-chlorophenylacetamido dithiocarbamate

See [A] Part-I, Section-I (C).

[B] Synthesis of 3-Mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole

See [A] Part-I, Section-I (D).

[C] Synthesis of Substituted 2-chloro-quinoline-3-carboxaldehydes[154]

These were prepared by the reaction of substituted acetanilide with DMF and $POCl_3$ a well known vilsmeierhaack rearrangement.

[D] Synthesis of 4-o-Chlorobenzyl-1,2,4-triazolo [3,4-b]-6-methoxy quinolino [2,3-f]-1,3,4-thiadiazepines

A mixture of 3-mercapto-4, N-amino-5-o-chlorobenzyl-1,2,4-triazole (2.40g, 0.01M) 2-chloro-3-formyl-6-methoxy quinoline (2.20g, 0.01M) in dry DMF (20 ml) and anhydrous K_2CO_3 (2.09 g) was refluxed at 80°C for 4 hrs. It was cooled and poured onto crushed ice. The product was isolated and crystallised from ethanol. Yield 1.87g, 77%, m.p. 132°C ($C_{20}H_{14}ClN_5OS$; required : C, 58.89; H, 3.46; N, 17.17, found : C, 58.92; H, 3.42 ; N, 17.13%).

TLC solvent system : Acetone : Benzene (3 : 7).

Similarly other substituted 1,3,4-thiadiazepines were synthesised. The physical data are recorded in Table No. 2.

[E] Antimicrobial activity of 4-o-chlorobenzyl-1,2,4-triazolo [3,4-b] substituted quinolino [2,3-f] 1,3,4-thiadiazepines

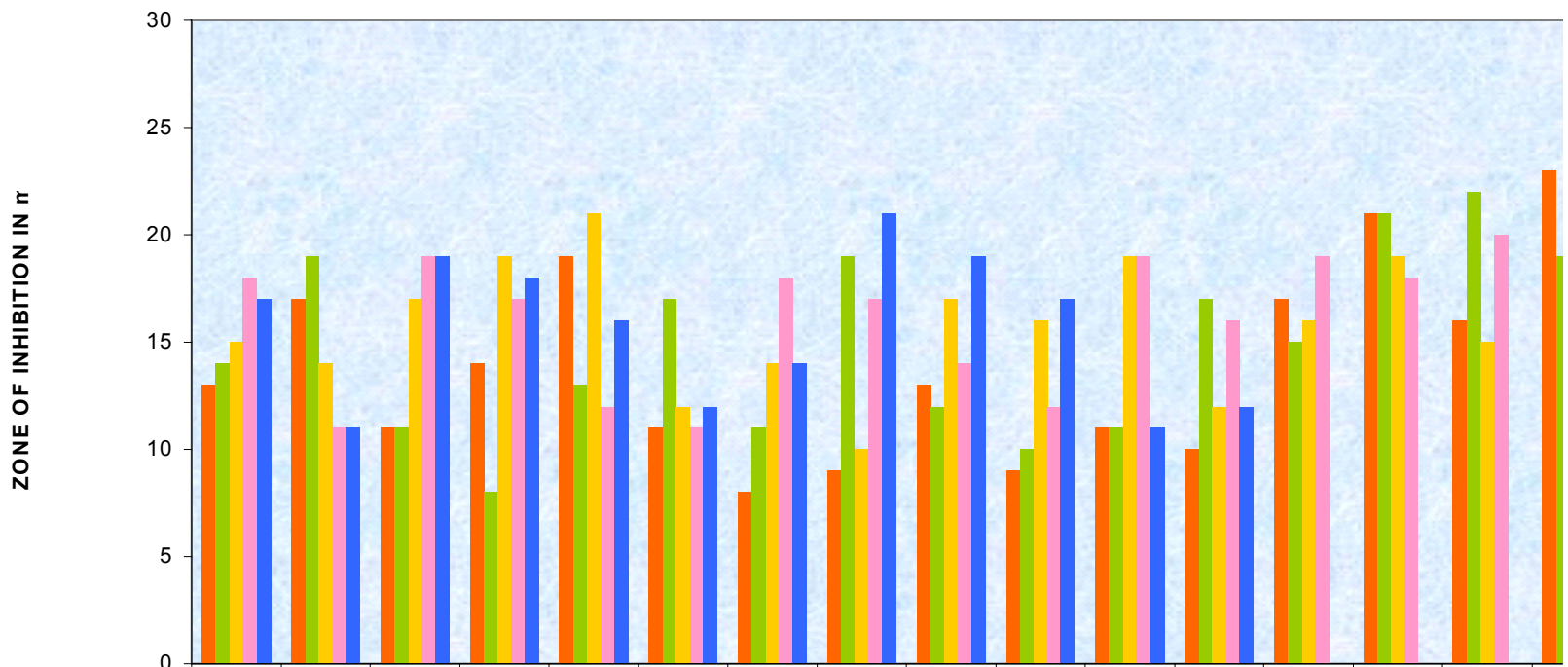
Antimicrobial testing was carried out as described in [A] Part-I, Section-I (F). The zone of inhibition of test solutions are recorded in Graphical Chart No. 2.

TABLE NO. 2 : PHYSICAL CONSTANTS OF 4-o-CHLOROBENYL-1,2,4-TRIAZOLO [3,4-b] SUBSTITUTED QUINOLINO [2,3,f] 1,3,4-THIADIAZEPINES

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	H	$C_{19}H_{12}ClN_5S$	377.8	250	0.80	59	18.53	18.50
2b	6-CH_3	$C_{20}H_{14}ClN_5S$	391.8	156	0.61	68	17.87	17.83
2c	8-CH_3	$C_{20}H_{14}ClN_5S$	391.8	124	0.57	64	17.87	17.90
2d	6-OCH_3	$C_{20}H_{14}ClN_5OS$	407.8	132	0.74	77	17.17	17.13
2e	8-OCH_3	$C_{20}H_{14}ClN_5OS$	407.8	146	0.73	56	17.17	17.20
2f	6-Cl	$C_{19}H_{11}Cl_2N_5S$	412.2	140	0.60	66	16.99	16.95
2g	7-Cl	$C_{19}H_{11}Cl_2N_5S$	412.2	164	0.65	70	16.99	16.98
2h	8-Cl	$C_{19}H_{11}Cl_2N_5S$	412.2	118	0.62	78	16.99	16.96
2i	8-F	$C_{19}H_{11}ClFN_5S$	395.8	128	0.59	57	17.69	17.65
2j	6,8-$(CH_3)_2$	$C_{21}H_{16}ClN_5S$	405.9	130	0.72	65	17.25	17.21
2k	6,7-$(Cl)_2$	$C_{19}H_{10}Cl_3N_5S$	446.7	152	0.63	55	15.68	15.64
2l	6-F,7-Cl	$C_{19}H_{10}Cl_2FN_5S$	430.2	132	0.68	73	16.28	16.32

*TLC Solvent System : Acetone : Benzene (3 : 7)

GRAPHICAL CHART NO. 2 : 4-o-CHLOROBENZYL-1,2,4-TRIAZOLO [3,4-b] SUBSTITUTED QUINOLINO[2,3-f]-1,3,4-THIADIAZEPINES



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Erm
B.coccus	13	17	11	14	19	11	8	9	13	9	11	10	17	21	16	
B.subtilis	14	19	11	8	13	17	11	19	12	10	11	17	15	21	22	
P.vulgaris	15	14	17	19	21	12	14	10	17	16	19	12	16	19	15	
E.coli	18	11	19	17	12	11	18	17	14	12	19	16	19	18	20	
A.niger	17	11	19	18	16	12	14	21	19	17	11	12	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

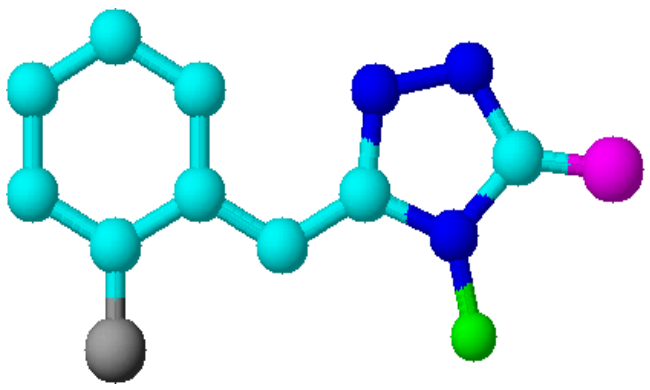
It has been concluded from the experimental data that the 1,3,4-thiadiazepine derivatives of type (II) were found to be moderately active against Gram positive bacteria like ***B.coccus*** and ***B.subtilis*** and show promising activity against Gram negative bacteria like ***P.vulgaris*** and ***E.coli***.

The maximum activity was observed in compounds bearing R=8-methoxy against ***B.coccus***. The significant activity was observed in compounds having R=6-methyl,8-chloro and 6-fluoro, 7-chloro substituents against ***B.subtilis***.

In case of ***P.vulgaris***, all the compounds were least active except R=6-methoxy, 8-methoxy, 6,7-dichloro. The compounds having R=8-methoxy, 6,7-dichloro have shown good activity against ***E.coli***.

Antifungal activity :

All the compounds exhibited mild activity against ***A.niger*** except compounds having R=8-chloro which showed highest activity against ***A. niger***.

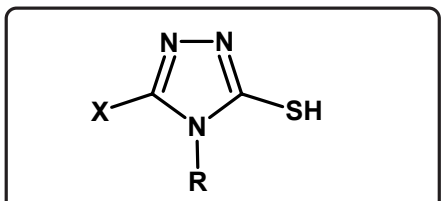


PART-III

STUDIES ON 4-ARYLTRIAZOLES

INTRODUCTION

Amongst nitrogen containing five membered heterocycles, 1,2,4-triazoles have proved to be the most useful framework for biological activities. The position of nitrogen atoms at 1,2 and 4 position activates the ring and proved to be most important pharmacological drugs. The medicinal chemists all over the world have focused their attention to evaluate 4-aryltriazole ring system (I).

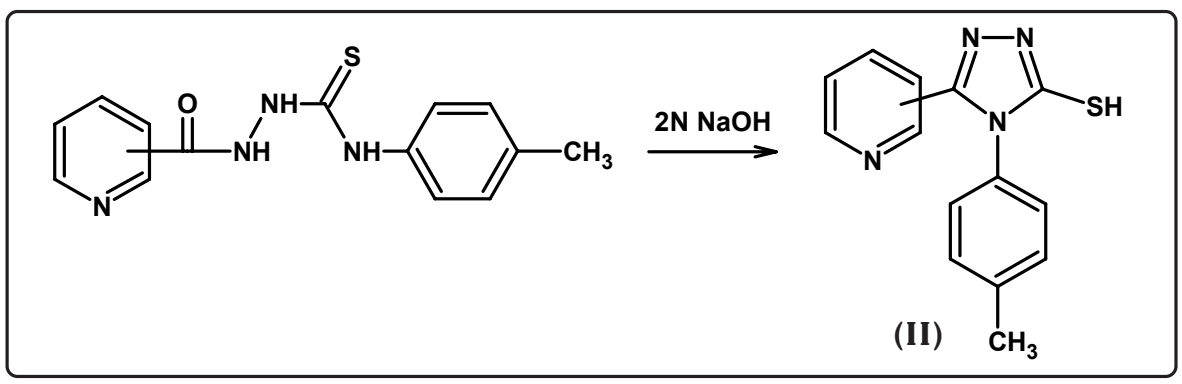


(I) R = Aryl

SYNTHETIC ASPECT

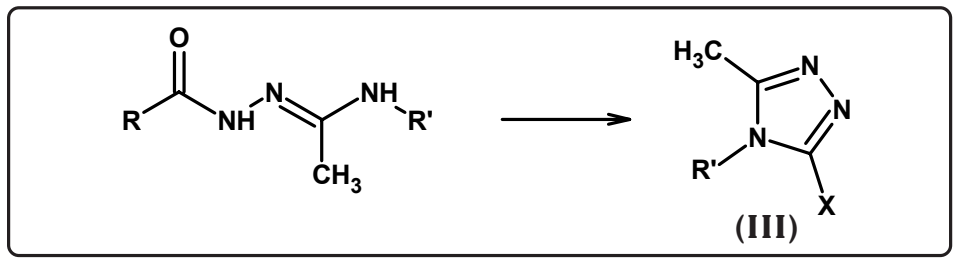
Several methods have been reported in the literatures for the preparation of 4-aryltriazoles.

1. Khosrow Zamani et al.[155] synthesised 4-aryltriazole from thiosemicarbazide by ring closure reaction with 2N NaOH.



(II)

2. Alan R. Katritzky et. al.[156] synthesised 4-aryltriazoles by the cyclization of semicarbazide.

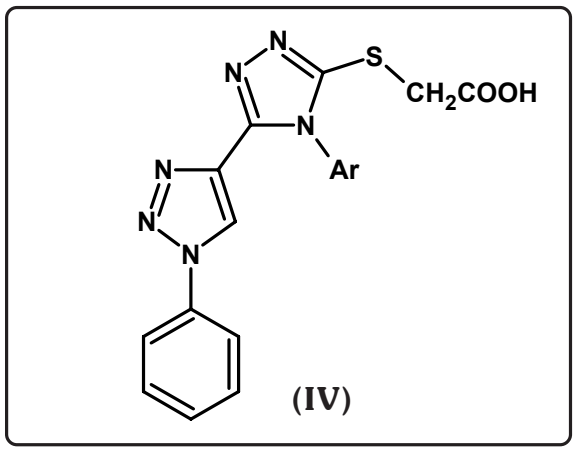


(III)

THERAPEUTIC IMPORTANCE

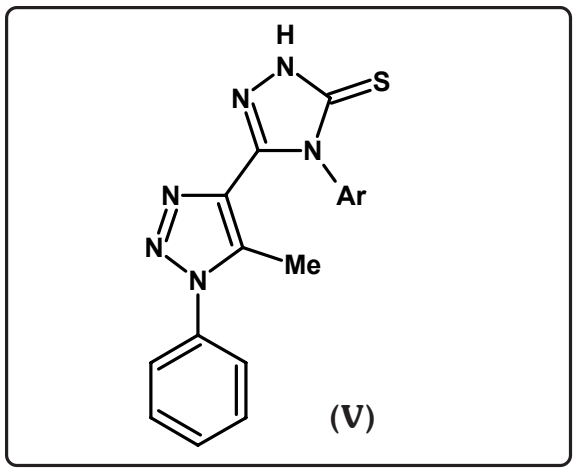
4-Aryltriazoles have attracted considerable attention as they appeared of interest to possess wide range of therapeutic activities. Different activity of 1,2,4-triazoles have been already discussed.

Athansia Varvaresou et. al.[157] have synthesised aryl triazoles possessing antidepressant activity. S. C. Bahel et. al.[158] have documented antifungal activity of aryltriazoles. Yasuda N. et. al.[159] have discovered aryltriazoles which have been extensively investigated for their antibacterial properties. Chu Changhu et. al.[160] have screened 4-aryl triazoles (IV) for their antifungal activity.



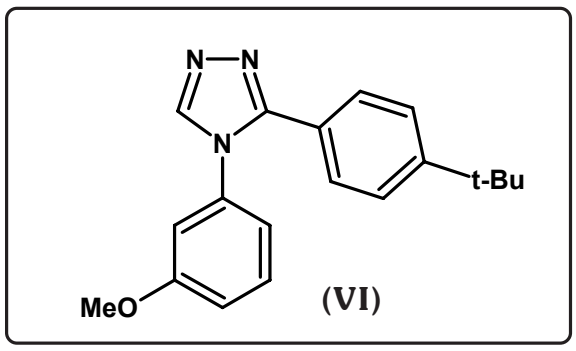
(IV)

Konosu T. and co-workers[161] have prepared aryltriazoles as fungicides. Varvaresou A. et al.[162] have synthesised triazoles and reported their antimicrobial potency and antidepressant activities. Papakonstantinou et. al.[163] have investigated some triazole derivatives possessing significant antiviral activity. Crisan O. et. al.[164] have screened antiinflammatory activity of triazoles. Chang et. al.[165] have synthesised aryl triazoles (V) and reported them as antifungal drugs.



(V)

Recently, Lowe R. F & co-workers[166] have reported aryltriazoles useful as antagonists. Holla B. et. al.[167] have documented anticancer activity of aryl triazoles. Wang Sheng et. al.[168] have reported triazoles as herbicidal agents. Some aryl triazoles possessing analgesic and diuretic activities have been synthesised by Shrivastava S. K.[169] Welsh et. al.[170] have discovered aryl triazoles (VI) & reported them as analgesic agents.



(VI)

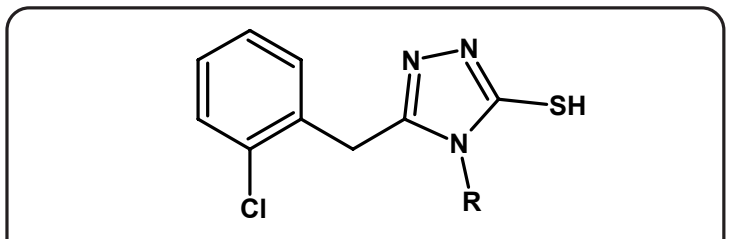
In view of above findings, it appeared of interest to design and synthesise 4-aryltriazole derivatives, which have been described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-MERCAPTO-4,N-ARYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-MERCAPTO-4,N-ARYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

4-Aryltriazole derivatives are associated with broad spectrum of pharmacological activity. In view of these findings, it appeared of interest to synthesise 3-mercapto-4,N-aryl-5-o-chlorobenzyl-1,2,4-triazoles. The synthesis of triazole derivatives of type (III) have been undertaken by heating of potassium-o-chlorophenyl acetamido dithiocarbamate with different aromatic amines.



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

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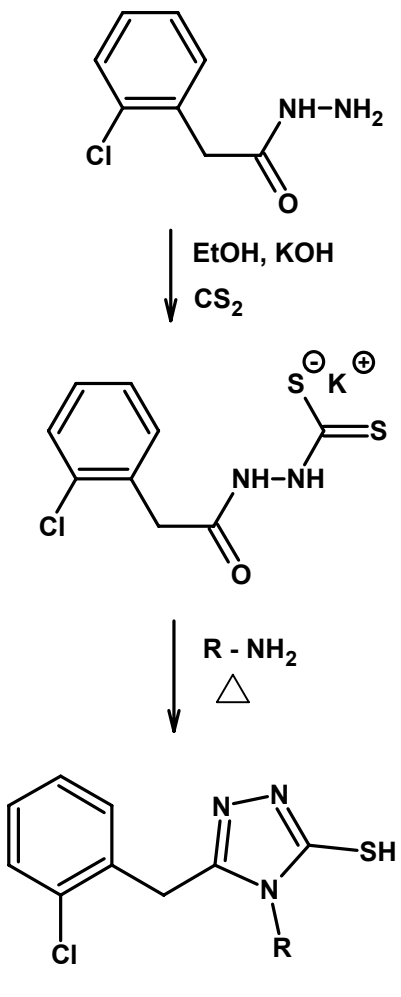
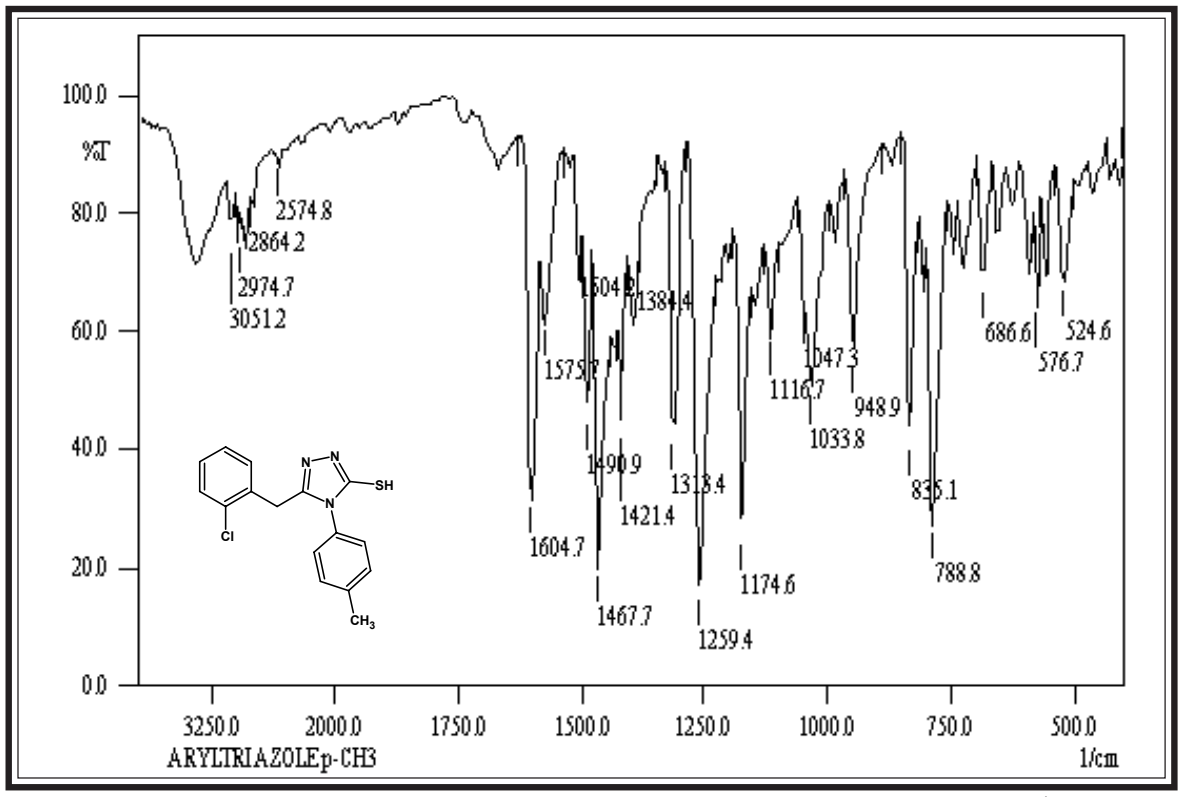
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 3.

REACTION SCHEME



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

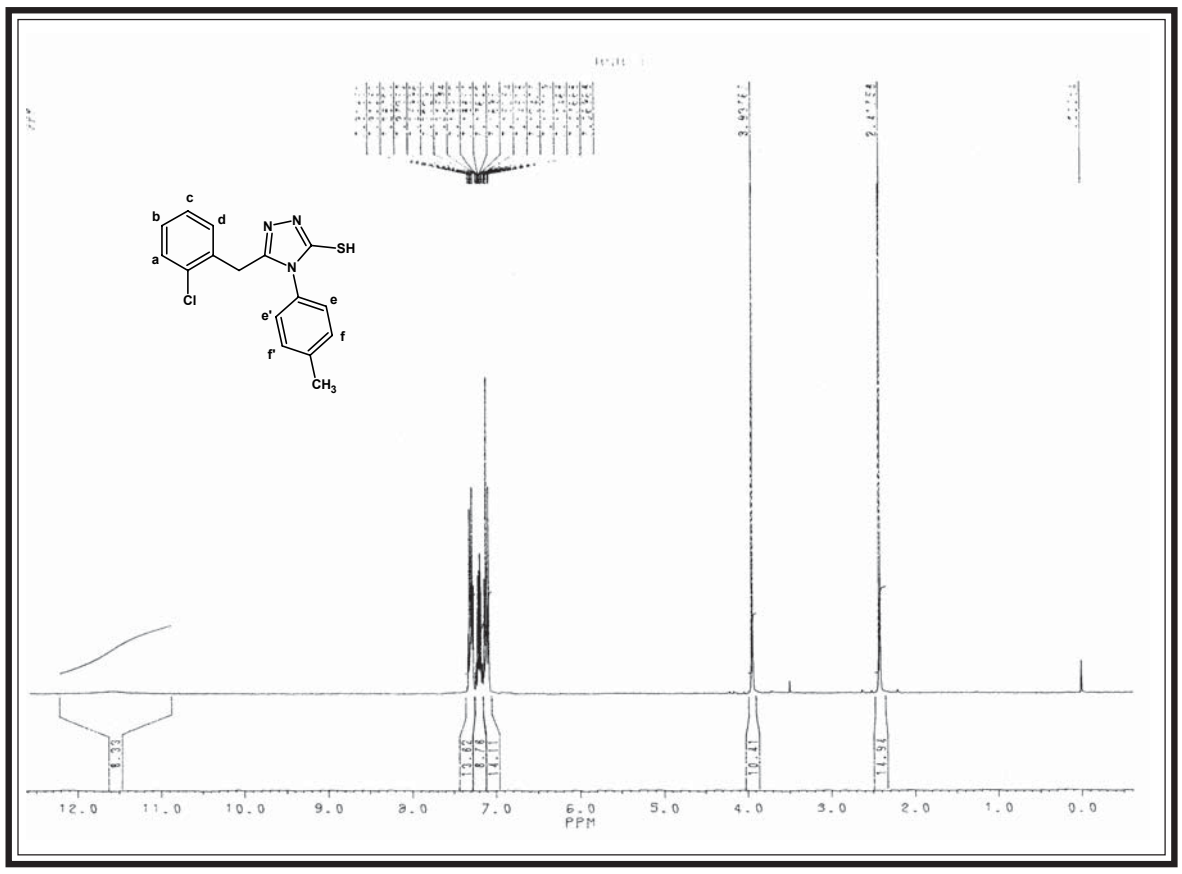
IR SPECTRAL STUDY OF 3-MERCAPTO-4,N-p-METHYLPHENYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLE



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.)	2974	2975–2950	498
$-CH_3$	C – H str (sym.)	2864	2880–2860	"
	C – H def. (asym.)	1467	1470–1435	"
	C – H def. (sym.)	1384	1385–1370	"
Aromatic	C – H str.	3051	3080–3030	503
	C = C str.	1575	1585–1570	"
		1490	1520–1480	"
	C – H i.p. def.	1116	1125–1090	"
		1047	1070–1000	"
	C – H o.o.p.def.	835	835–810	"
Triazole	C = N str.	1604	1612–1593	498
	N – Ph str.	1504	1504–1495	"
	N – N str.	1033	1050–1010	"
	C – N str.	1259	1350–1200	504
	C – S str.	686	700–600	"
	C – Cl str.	788	800–600	498
	S – H str.	2574	2600-2500	504

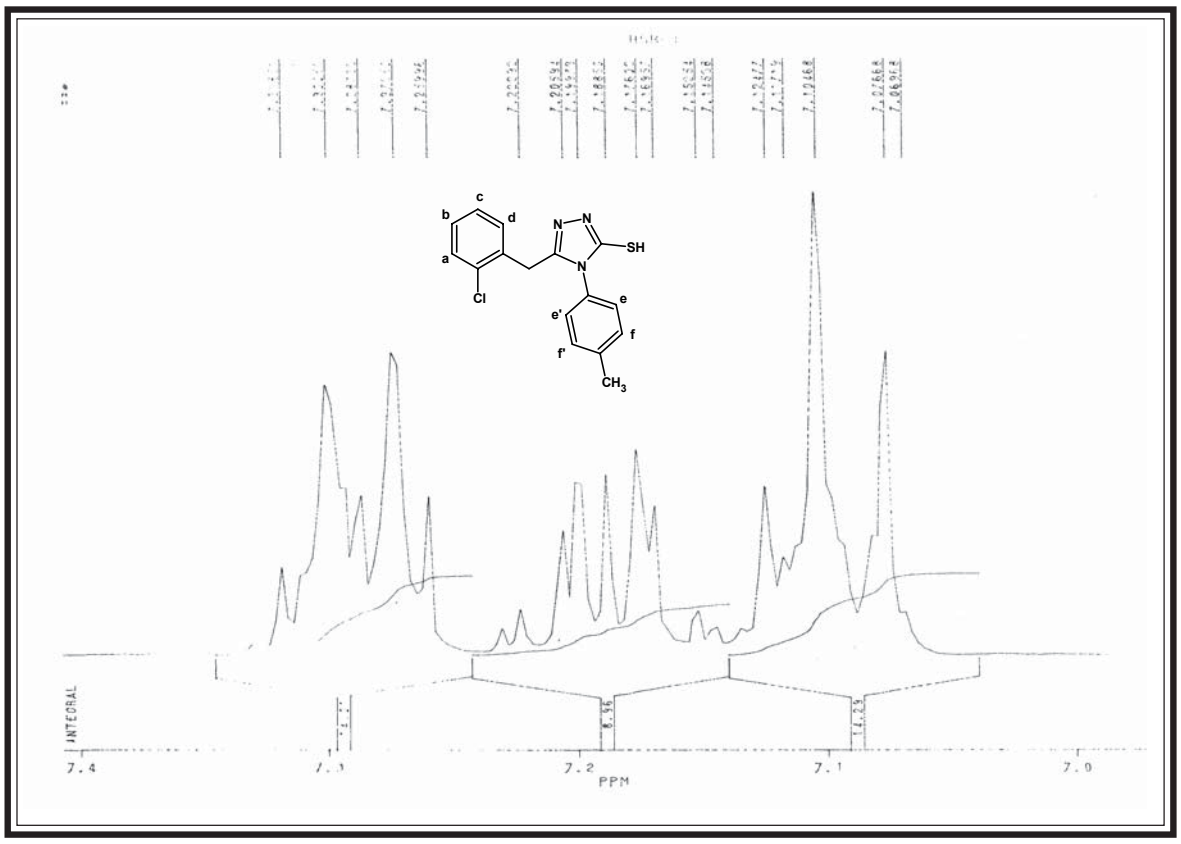
PMR SPECTRAL STUDY OF 3-MERCAPTO-4,-N-p-METHYLPHENYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLE



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	2.41		3H	singlet	Ar-CH_3
2.	3.93		2H	singlet	-CH_2
3.	7.07	Jef=9	2H	doublet	Ar-Hee'
4.	7.12		1H	multiplet	Ar-Hd
5.	7.14-7.22		2H	multiplet	Ar-Hb,Ar-Hc
6.	7.28	Jfe=9	2H	doublet	Ar-Hff'
7.	7.31		1H	multiplet	Ar-Ha
8.	11.52		1H	broad singlet	-SH

EXPANDED AROMATIC REGION

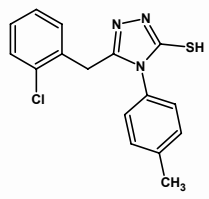


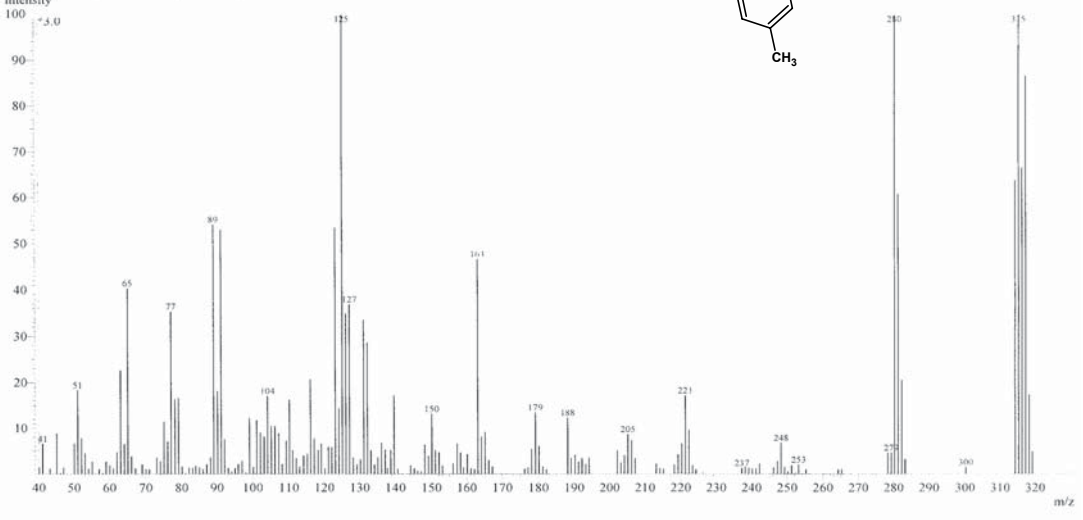
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

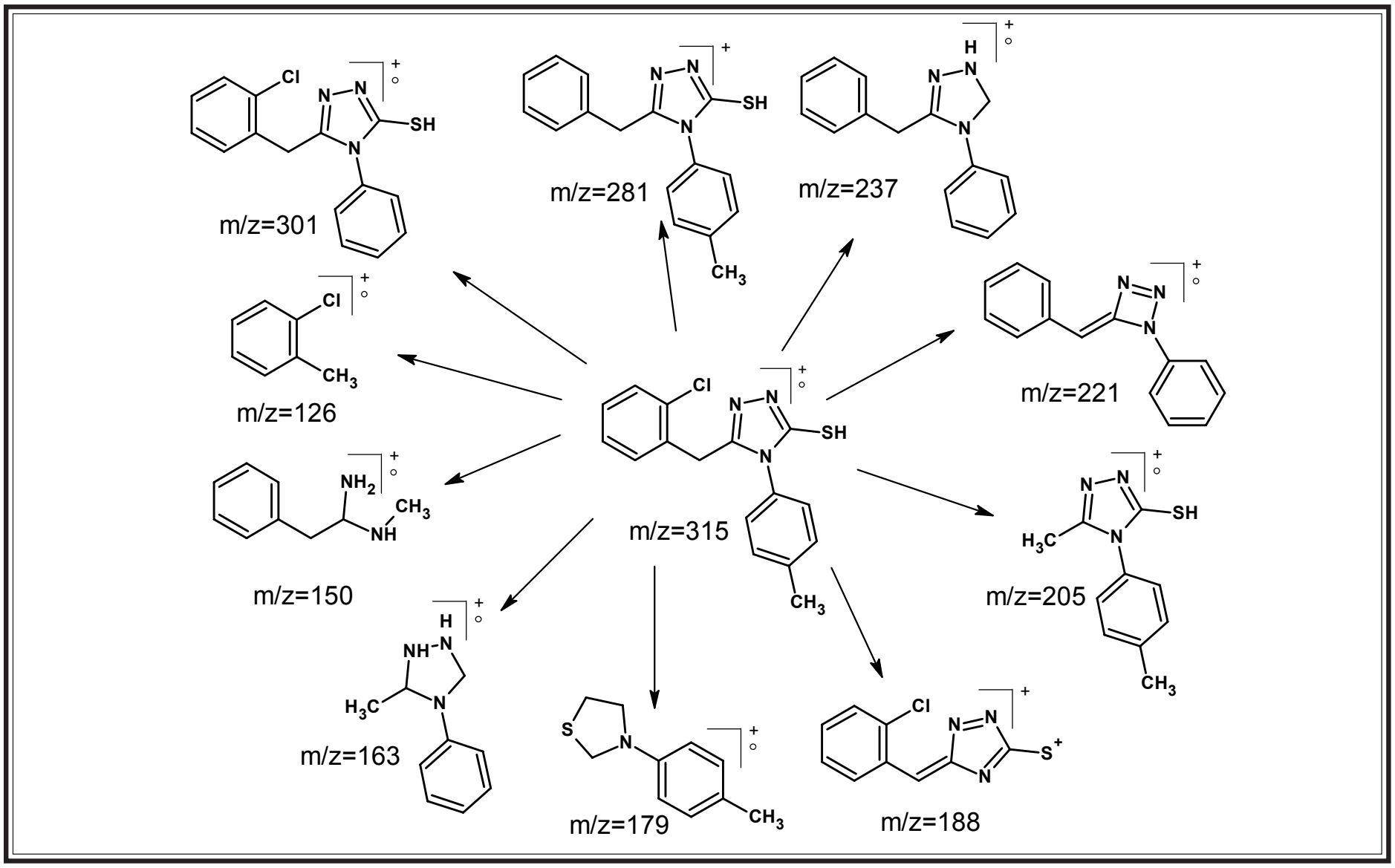
Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/7/2005 1:08:13 PM
Sample Name : SB-2
Sample ID : SB-2
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-2.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:8.5(Scan#:984)
MassPeaks:178 BasePeak:280(360476)
RawMode:Averaged 8.2-8.5(952-989)
BG Mode:Averaged 12.0-14.0(1403-1639)
intensity






m/z=301
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m/z=150
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m/z=205
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m/z=179
m/z=188

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-MERCAPTO-4,N-ARYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

[A] Synthesis of Potassium o-chlorophenylacetamido dithiocarbamate

See [A] Part-I, Section-I (C).

[B] Synthesis of 3-Mercapto-4,N-p-methylphenyl-5-o-chlorobenzyl-1,2,4-triazole

A mixture of potassium o-chlorophenylacetamido dithiocarbamate (2.98g, 0.01M) and p-toludine (1.07g, 0.01M) was heated till evalution of H_2S gas ceased. The product was dissolved in DMF (20 ml) and poured the reaction mixture onto crushed ice. The product was crystallised from ethanol. Yield 2.4g, 80%, m.p. 202°C ($C_{16}H_{14}ClN_3S$; required : C, 60.85 ; H, 4.47 ; N, 13.31, found : C, 60.81; H, 4.43; N, 13.35 %).

Similarly other 4-aryl triazoles were synthesised. The physical data are recorded in Table No. 3.

[C] Antimicrobial activity of 3-Mercapto-4,N-aryl-5-o-chlorobenzyl-1,2,4-triazoles

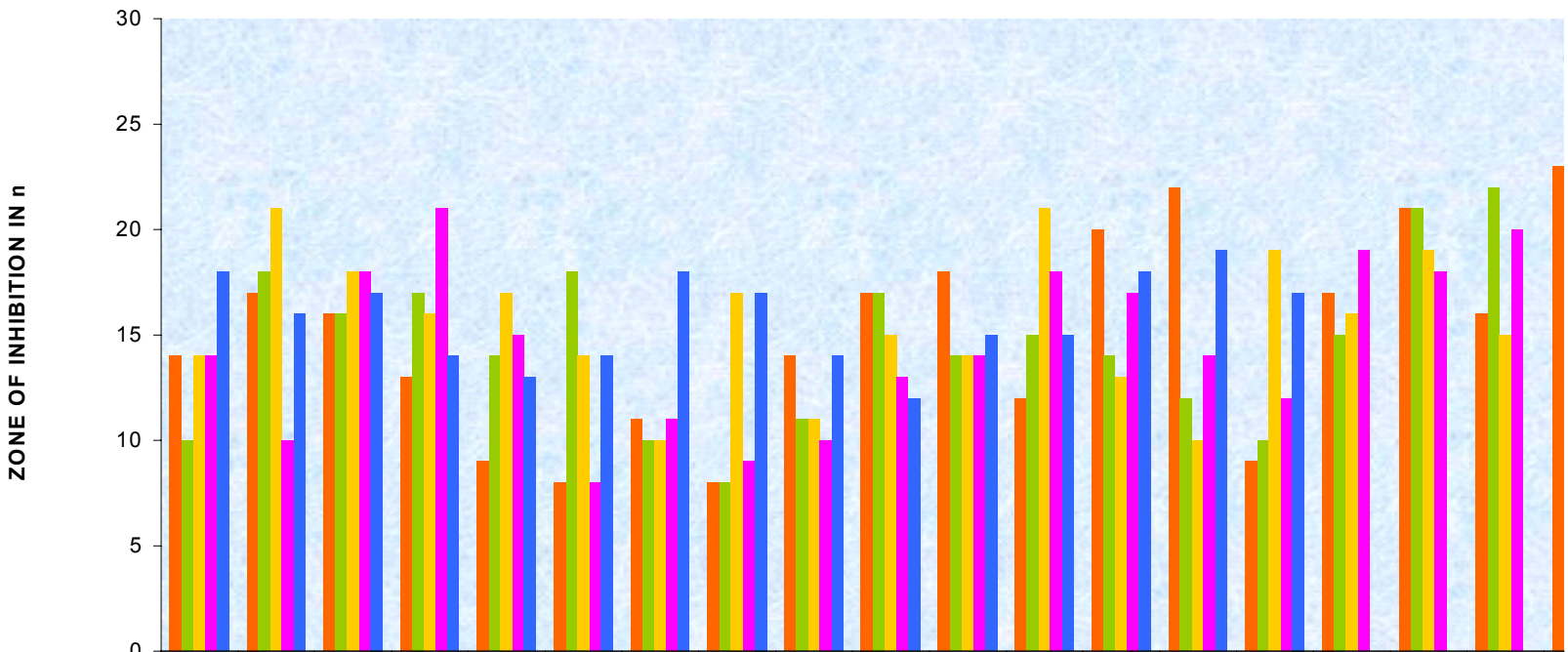
Antimicrobial testing was carried out as described in [A] Part-I, Section-I, (F). The zones of inhibition of test solution are recorded in Graphical Chart No. 3.

TABLE NO. 3 : PHYSICAL CONSTANTS OF 3-MERCAPTO-4,N-ARYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

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-	$C_{15}H_{12}ClN_3S$	301.7	182	0.65	64	13.92	13.88
3b	2-CH_3-C_6H_4-	$C_{16}H_{14}ClN_3S$	315.8	236	0.68	57	13.31	13.28
3c	4-CH_3-C_6H_4-	$C_{16}H_{14}ClN_3S$	315.8	202	0.71	80	13.31	13.35
3d	4-OCH_3-C_6H_4-	$C_{16}H_{14}ClN_3OS$	331.8	228	0.52	73	12.66	12.62
3e	2-Cl-C_6H_4-	$C_{15}H_{11}Cl_2N_3S$	336.2	139	0.63	82	12.50	12.46
3f	3-Cl-C_6H_4-	$C_{15}H_{11}Cl_2N_3S$	336.2	148	0.62	55	12.50	12.54
3g	4-Cl-C_6H_4-	$C_{15}H_{11}Cl_2N_3S$	336.2	150	0.54	67	12.50	12.52
3h	2-F-C_6H_4-	$C_{15}H_{11}ClFN_3S$	319.7	190	0.60	75	13.14	13.18
3i	4-F-C_6H_4-	$C_{15}H_{11}ClFN_3S$	319.7	131	0.53	52	13.14	13.10
3j	3-NO_2-C_6H_4-	$C_{15}H_{11}ClN_4O_2S$	346.7	284	0.58	58	16.16	16.12
3k	4-NO_2-C_6H_4-	$C_{15}H_{11}ClN_4O_2S$	346.7	250	0.59	69	16.16	16.20
3l	2,5-$(Cl)_2$-C_6H_3-	$C_{15}H_{10}Cl_3N_3S$	370.6	180	0.74	77	11.34	11.30
3m	3,4-$(Cl)_2$-C_6H_3-	$C_{15}H_{10}Cl_3N_3S$	370.6	176	0.56	68	11.34	11.38
3n	2,4-$(CH_3)_2$-C_6H_3-	$C_{17}H_{16}ClN_3S$	329.8	190	0.61	79	12.74	12.70
3o	3-Cl, 4-F-C_6H_3-	$C_{15}H_{10}Cl_2FN_3S$	354.2	188	0.64	83	11.86	11.84

*TLC Solvent System : Acetone : Benzene (4 : 6)

GRAPHICAL CHART NO. 3 : 3-MERCAPTO-4,N-ARYL-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	3m	3n	30	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Eo
B.coccus	14	17	16	13	9	8	11	8	14	17	18	12	20	22	9	17	21	16	
B.subtilis	10	18	16	17	14	18	10	8	11	17	14	15	14	12	10	15	21	22	
P.vulgaris	14	21	18	16	17	14	10	17	11	15	14	21	13	10	19	16	19	15	
E.coli	14	10	18	21	15	8	11	9	10	13	14	18	17	14	12	19	18	20	
A.niger	18	16	17	14	13	14	18	17	14	12	15	15	18	19	17	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

It has been observed from the experimental data that all compounds of type (III) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

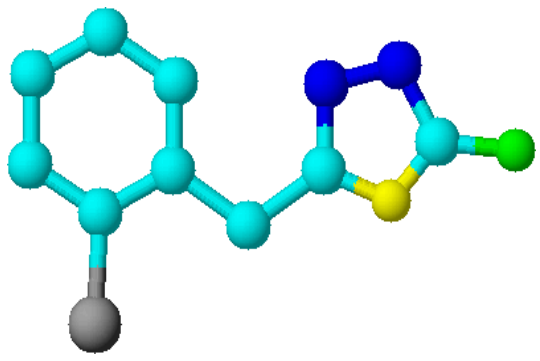
However, the maximum activity was observed in compounds bearing R=3,4-dichlorophenyl and 2,4-dimethylphenyl substituents against ***B.coccus***. The significant activity was observed in compounds bearing R=2-methylphenyl, 4-methoxyphenyl, 3-chlorophenyl and 4-nitrophenyl against ***B.subtilis***.

The maximum activity was displayed by the compounds bearing R=2-methylphenyl, 2,5-dichlorophenyl and 3-chloro,4-fluorophenyl against ***P.vulgaris***. In case of ***E.coli*** all the compounds were least active except R=4-methoxyphenyl.

Antifungal activity :

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds bearing R=2,4-dimethylphenyl against ***A.niger***.

The antibacterial activity was compared with standard drug viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

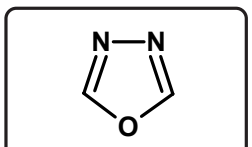


PART-IV

STUDIES ON 1,3,4-OXADIAZOLES

INTRODUCTION

1,3,4-***O***xadiazole is a thermally stable aromatic molecule[171]. They have been known for about 80 years, it is only in the last decade that investigations in this field have been intensified. This is because of large number of applications of 1,3,4-oxadiazoles in the most diverse areas viz. drug synthesis, dye stuff industry, heat resistant materials, heat resistant polymers and scintillators. Reviews of the relevant literature prior to 1965 are available[172].

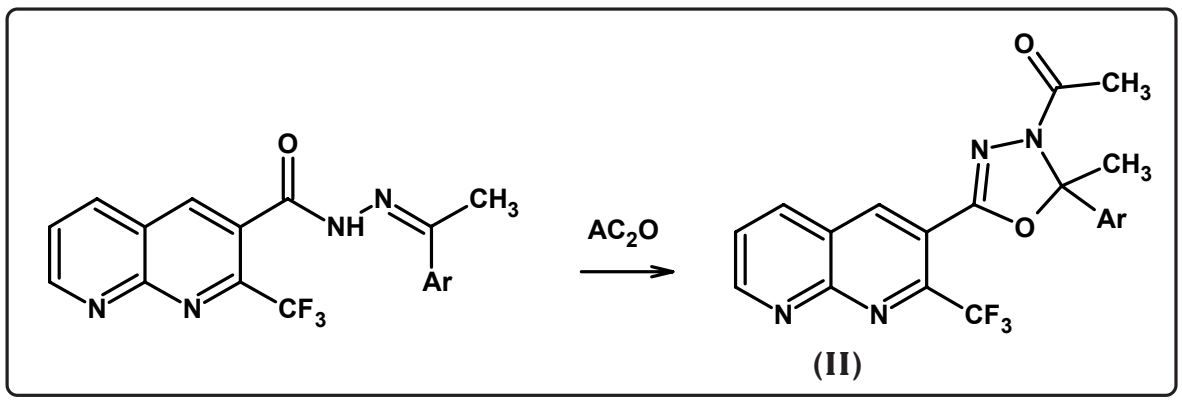


(I)

SYNTHETIC ASPECT

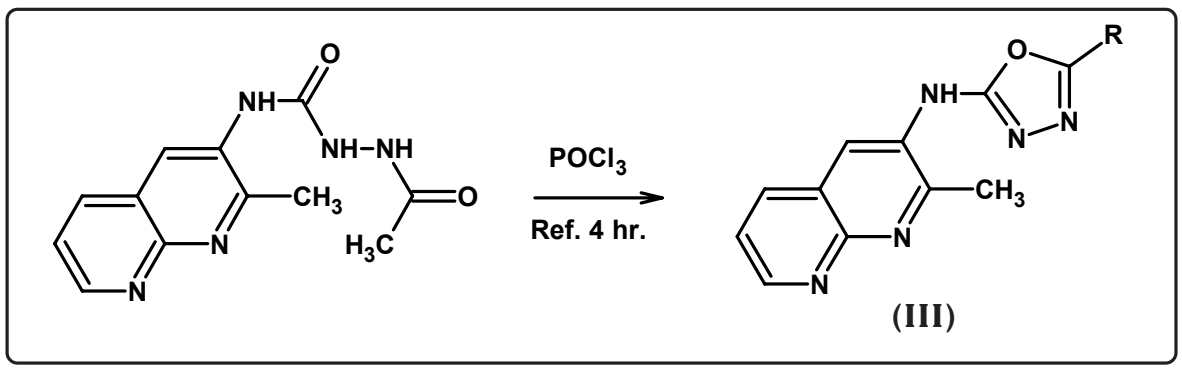
Most 1,3,4-oxadiazoles are best obtained by synthesis from acyclic precursors. Such reactions are 'one bond' or 'two-bond' cyclisation. Different methods for the synthesis have been cited in literature[173-180].

1. K. Mogilaiah and B. Sakram[181] have prepared 1,3,4-oxadiazole from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.

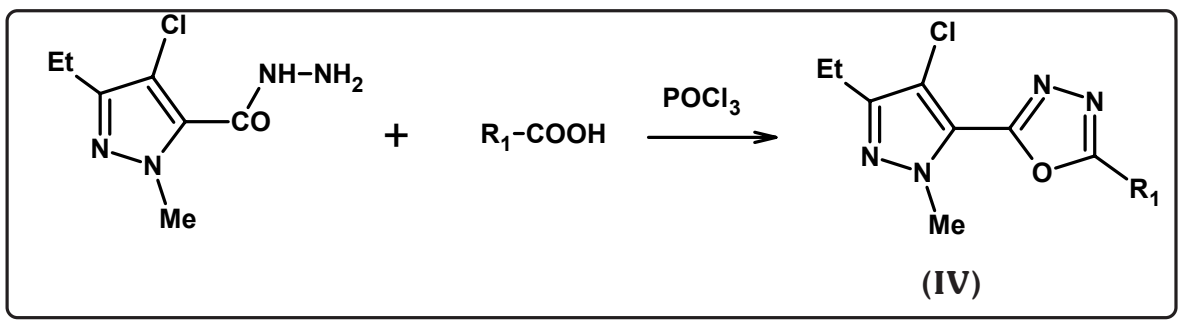


(II)

2. D. Ramesh and B. Sreenivasan[182] have synthesised 1,3,4-oxadiazoles from semicarbazide in presence of $POCl_3$.



5. Hansong Chen et. al.[183] have synthesised oxadiazoles by the reaction of hydrazide and aromatic acid in presence $POCl_3$.

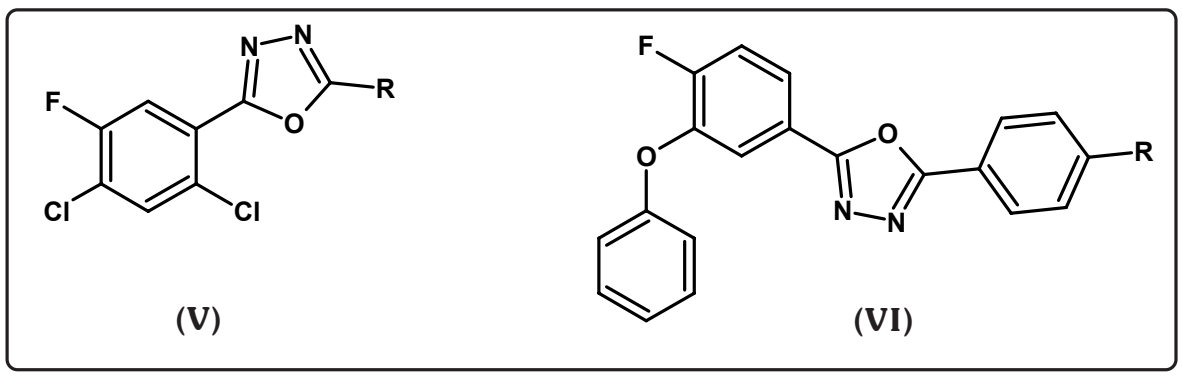


THERAPEUTIC IMPORTANCE

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

1. Antiproliferative[184]
2. Anticonvulsant[185]
3. Antihypertensive[186]
4. Antiviral & anticancer[187]
5. Analgesic[188]
6. Antiinflammatory[189]
7. Antibacterial[190]
8. Antifungal[191]
9. Cardiovascular[192]
10. Herbicidal[193]
11. Hypoglycemic[194]
12. Hypnotic and sedative[195]
13. MAO inhibitor[196]
14. Nematocidal and Insecticidal[197]

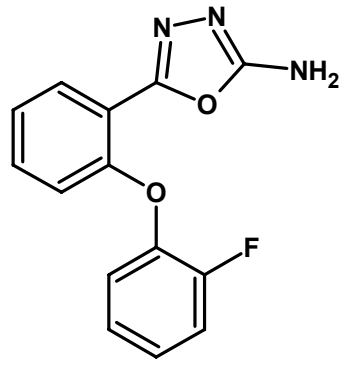
K. Subrahmanya Bhat *et.* al.[198] have prepared new fluorine containing 1,3,4-oxadiazoles (V) and reported them as potential antibacterial and anticancer agents. Sahin G. *et.* al.[199] have reported antimicrobial activity of oxadiazole derivatives. Maslat A.O. *et.* al.[200] have documented antibacterial, antifungal and genotixic activity of bis-1,3,4-oxadiazole derivatives. Mida Malvina Burbuliene *et.* al.[201] have investigated some oxadiazoles as anti-inflammatory agents. T.P. Mohan *et.* al.[202] have synthesied 2,5-disubstituted-1,3,4-oxadiazole derivatives (VI) and screened for their insecticidal activity.



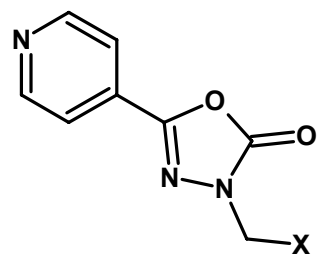
(V) **(VI)**

H. Liszkiewicz. *et.* al.[203] have screened oxadiazoles for their antimicrobial activity. A. El-Azzouny *et.* al.[204] have synthesied 1,3,4-oxadiazole derivatives and evaluated for their analgesic, antiinflammatory, ulcerogenic effects and inhibitory activity on plasma prostaglandin E_2 (PGE_2) Level. Some 1,3,4-oxadiazoles possessing insecticidal activity are synthesised by Xiumian Zheng *et.* al.[205] Takahiko Inoue *et.* al.[206] have reported oxadiazoles useful as prolyl aminopeptidase inhibitor.

Virginija Jakubkiene *et.* al.[207] have screened 1,3,4-oxadiazoles for their antiinflammatory activity. Song Cao *et.* al.[208] have investigated some oxadiazoles possessing insecticidal activity. S. Guniz Kucukguzel *et.* al.[209] have discovered oxadiazole derivatives and reported their antimycobacterial activity. Ali Almasired *et.* al.[210] have prepared 1,3,4-oxadiazoles of type (VII) as anticonvulsant agent. Maria Grazia Mamolo *et.* al.[211] have synthesised 3-substituted-5-(pyridin-4-yl)-3H-1,3,4-oxadiazole-2-one of type (VIII) and studied their antimycobacterial activity.

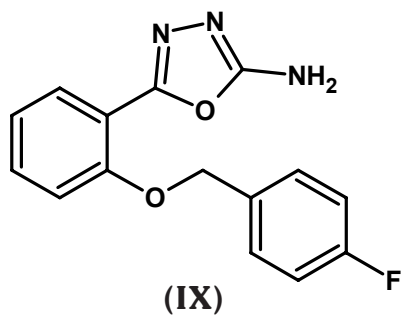


(VII)

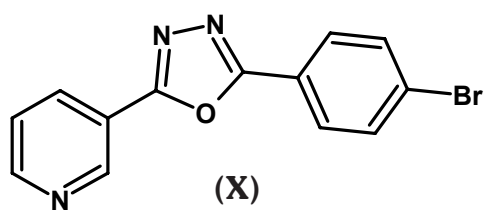


(VIII)

Recently, Ronald Kim et. al.[212] have discovered oxadiazole derivatives useful as protease inhibitors. Mohd Amir and Kumar Shikha[213] have documented antiinflammatory, analgesic and ulcerogenic activity of some newly synthesised oxadiazoles, Ali A. et. al.[214] have investigated some oxadiazole derivatives possessing antimicrobial and anti HIV-1- activity. Sherif A. et. al.[215] have reported oxadiazoles as potential antitumor and anti-HIV agents. Afshin Zarghi et. al.[216] have synthesised R-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles (IX) possessing anticonvulsant activity. Mahamud Tareq et. al.[217] have synthesised 2,5-disubstituted-1,3,4-oxadiazoles (X) useful as tyrosinase inhibitors.



(IX)

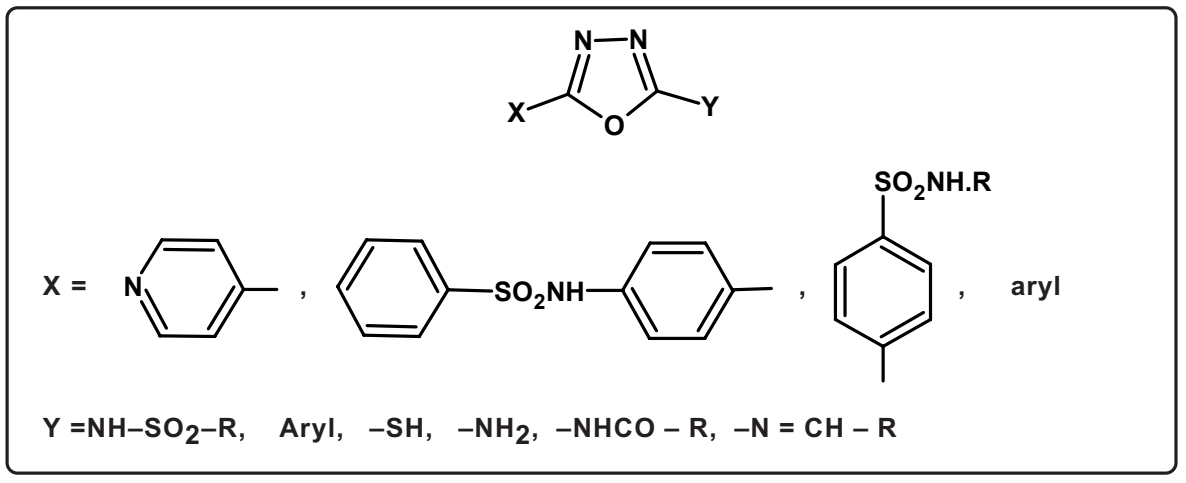


(X)

CONTRIBUTION FROM OUR LABORATORY

Parikh et. al. have synthesised 1,3,4-oxadizoles having substitution of aryl sulphonamido[218] and aryl[219] at 2-position (Y) and 4'-pyridyl, benzenesulphonamido phenyl, di-iodoquinolinoxy and aryl sulphonamido phenyl at 5-position (X) as antimicrobial agents. H. H. Parekh and co-workers have prepared 1,3,4-oxadiazoles having substituted triazine[220], phenyl sulphonyl[221], 2-isopropyl-5'-methylphenoxymethyl[222] moieties at 5-position (X)

and aryl, arylamino, arylsulphonamido, substituted benzalamino moeties at 2-position (Y) and screened their antimicrobial activity. General Structure for above references are as under.



H. H. Parekh et. al.[223-229] have formulated some new oxadiazole as biologically active agents. New 2,5-di substituted oxadiazoles were synthesised and assessed for antimicrobial activity by Parikh et. al.[230].

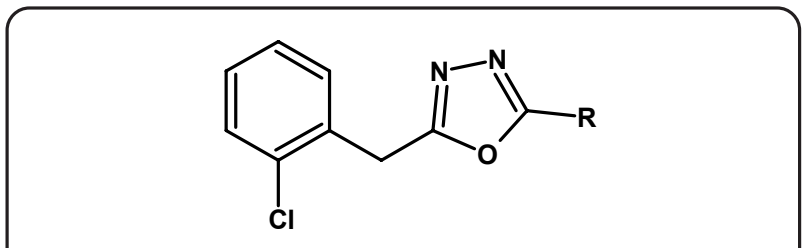
In view of the potential biological activities of 1,3,4-oxadiazole ring system, it was of interest to us to prepare some new derivatives of this family of heterocyclic ring, which have been described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLES

Oxadiazole derivatives have drawn the attention of chemists due to diversified biological activities associated with it. In view of these facts, it was contemplated to synthesise some newer oxadiazole derivatives with better potency. Oxadiazoles of type (IV) have been prepared by condensation of o-chlorophenyl acetohydrazide with different aromatic acid in presence of $POCl_3$.



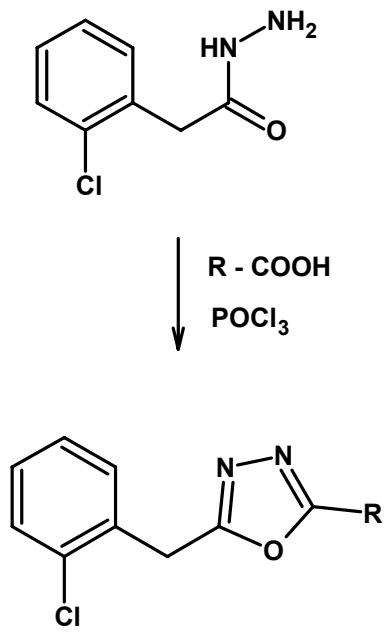
Type - (IV) **R = Aryl**

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

All the compounds 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. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 4.

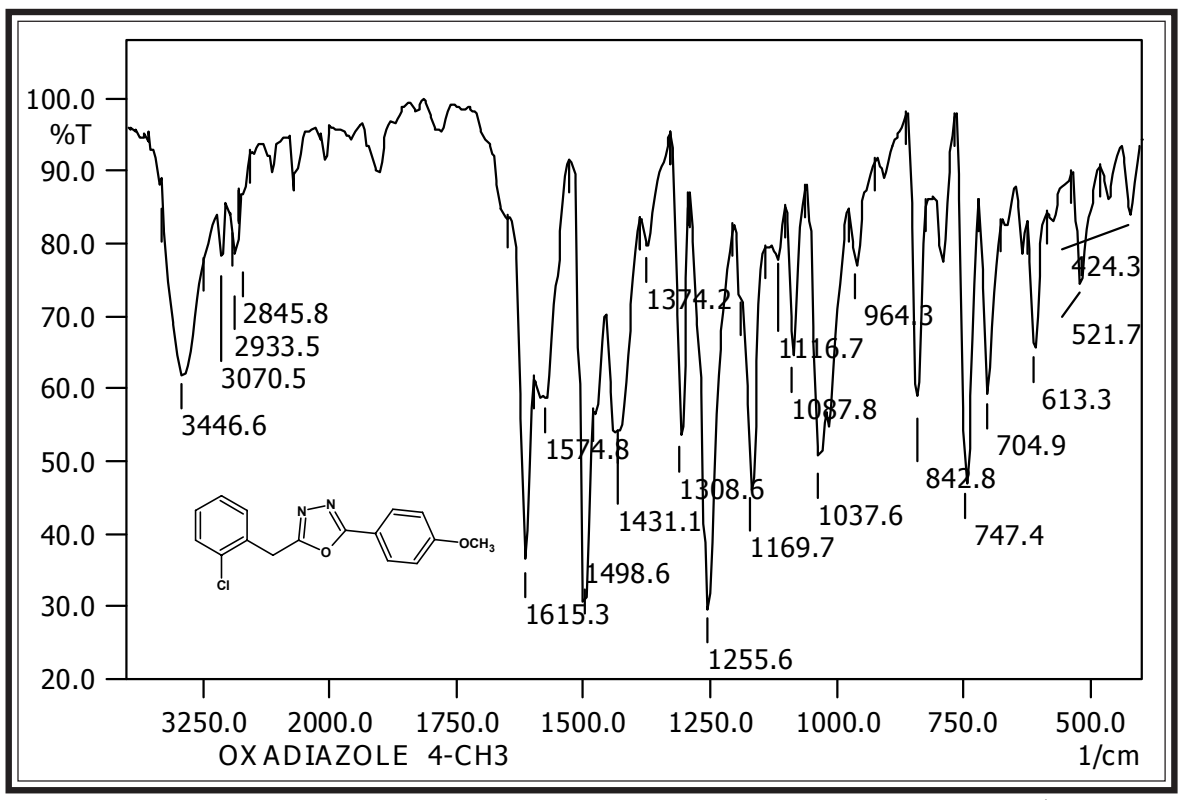
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** H_{37} ***Rv*** at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME



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

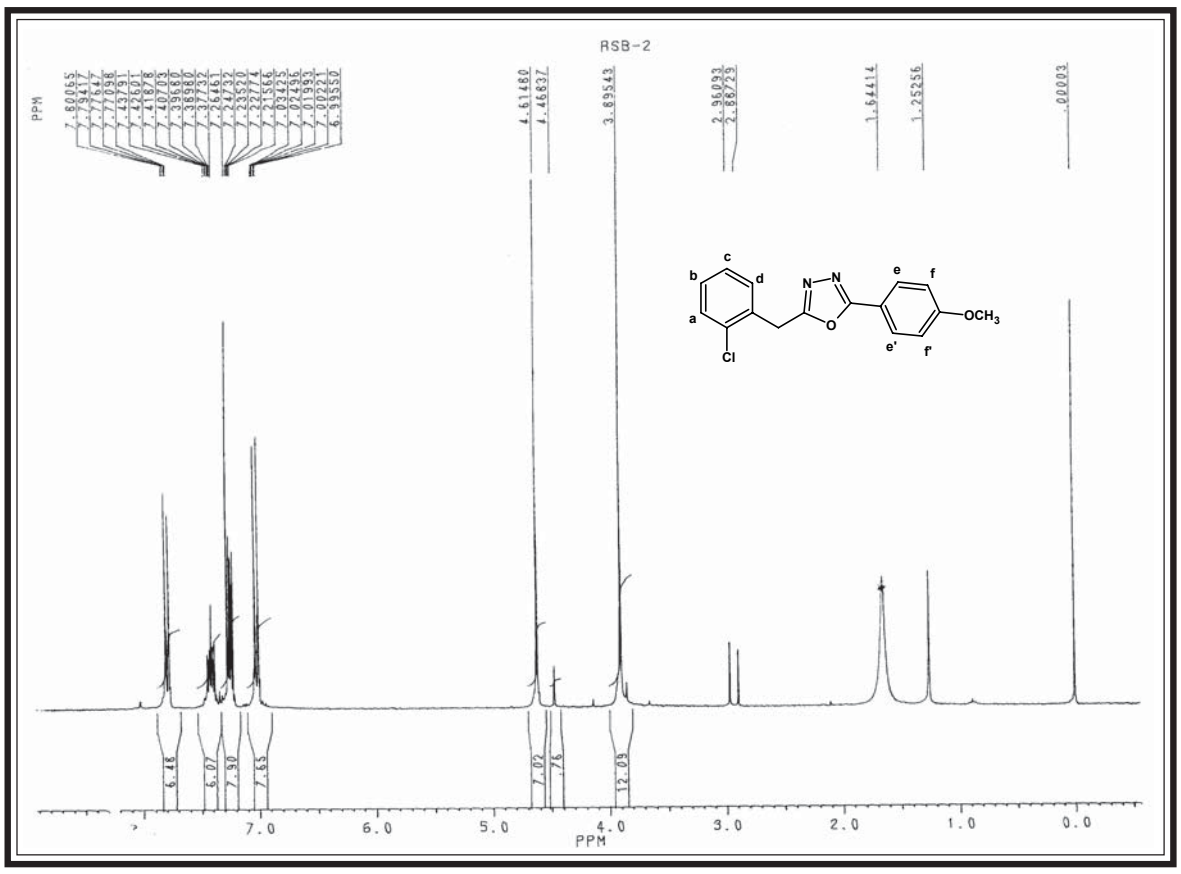
IR SPECTRAL STUDY OF 2-p-METHOXYPHENYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLE



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	498
$-CH_3$	C – H str (sym.)	2845	2880–2860	"
	C – H def. (asym.)	1431	1470–1435	"
	C – H def. (sym.)	1374	1385–1370	"
Aromatic	C – H str.	3070	3080–3030	503
	C = C str.	1498	1585–1480	"
	C – H i.p. def.	1116	1125–1000	"
	C – H o.o.p. def.	842	835–810	"
Oxadiazole	C = N str.	1615	1650–1580	498
	N – N str.	1037	1050–1010	503
	C – O – C str.	1087	1140–1070	"
	C – Cl str.	747	800–600	498
Ether	C – O – C str. (asym.)	1255	1275–1200	503
	C – O – C str. (sym.)	964	1075–1020	498

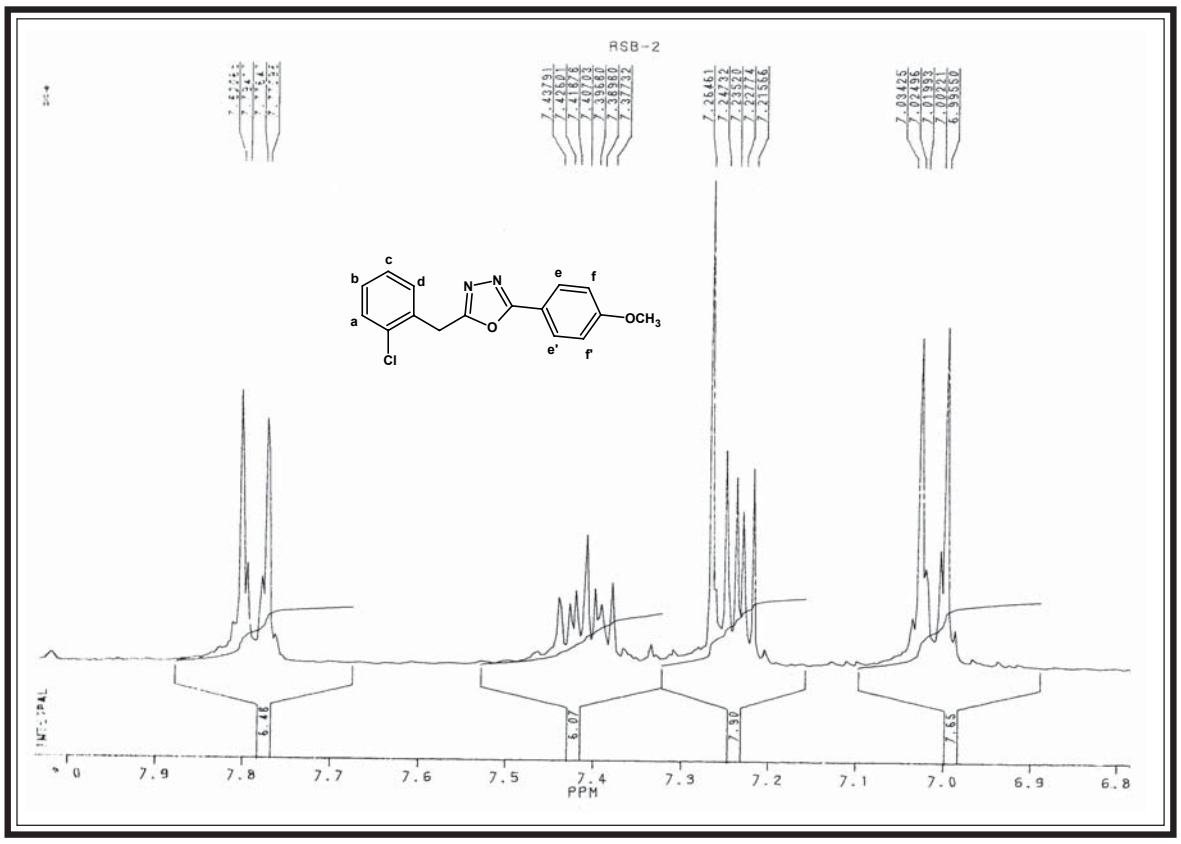
PMR SPECTRAL STUDY OF 2-p-METHOXYPHENYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLE

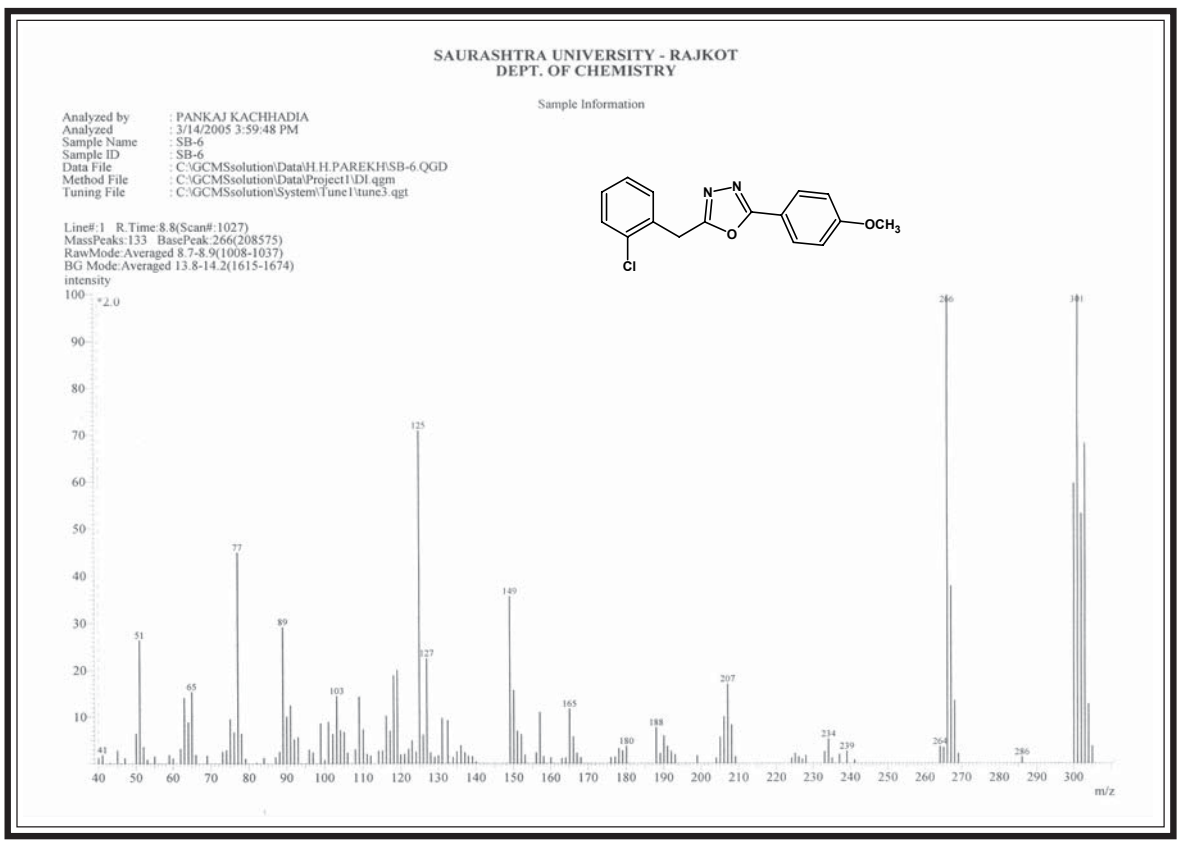


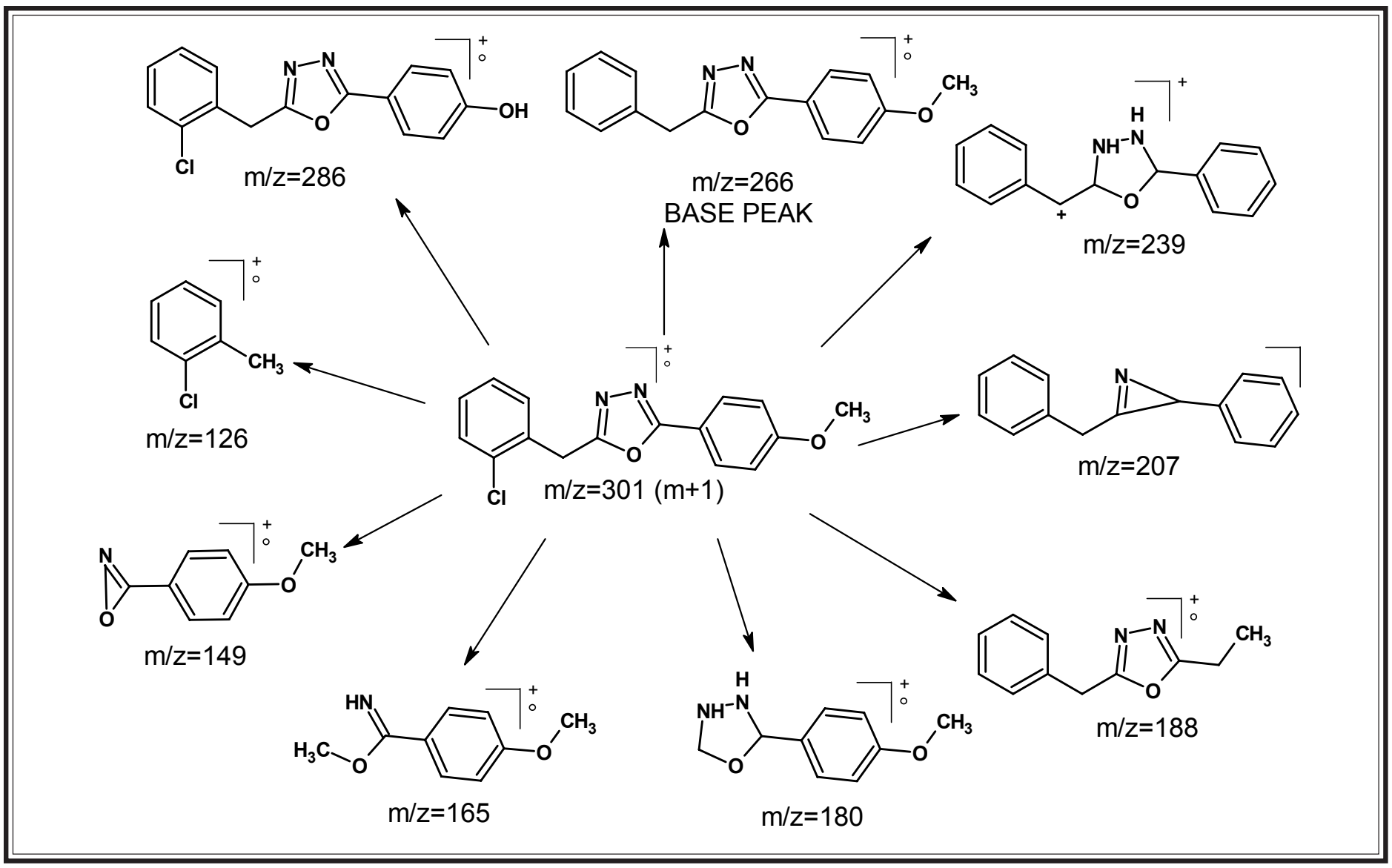
Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.89		3H	singlet	Ar-OCH_3
2.	4.61		2H	singlet	-CH_2
3.	7.00	Jfe=9	2H	doublet	Ar-Hff'
4.	7.21-7.25		2H	multiplet	Ar-Hb,Ar-Hc
5.	7.37-7.43		2H	multiplet	Ar-Ha,Ar-Hd
6.	7.78	Jef=9	2H	doublet	Ar-Hee'

EXPANDED AROMATIC REGION






m/z=286
m/z=266
BASE PEAK
m/z=239
m/z=126
m/z=301 (m+1)
m/z=207
m/z=149
m/z=165
m/z=180
m/z=188

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLES

[A] Synthesis of o-chlorophenylaceto hydrazide

See [A] Part-I, Section-I (B).

[B] Synthesis of 2-p-methoxyphenyl-5-o-chlorobenzyl-1,3,4-oxadiazole

A mixture of o- chlorophenylaceto hydrazide (1.85g, 0.01M) and 4-methoxy benzoic acid (1.52g, 0.01M) in phosphorous oxychloride (10 ml) was refluxed for 6 hrs. The content was cooled and poured onto crushed ice. It was neutralised with sodium bicarbonate solution. Product was isolated and crystallised from ethanol. Yield 1.2g, 64%, m.p. 179°C ($C_{16}H_{13}ClN_2O_2$: required : C, 63.90 ; H, 4.36 ; N, 9.31, found : C, 63.94; H, 4.32 ; N, 9.35%).

TLC solvent system : Acetone : Benzene (4 : 6).

Similarly other oxadiazoles were prepared. The physical data are recorded in Table No. 4.

[C] Antimicrobial activity of 2-Aryl-5-o-chlorobenzyl-1,3,4-oxadiazoles

Antimicrobial testing was carried out as described in [A] Part-I, Section-I, (F). The zones of inhibition of test solution are recorded in Graphical Chart No. 4.

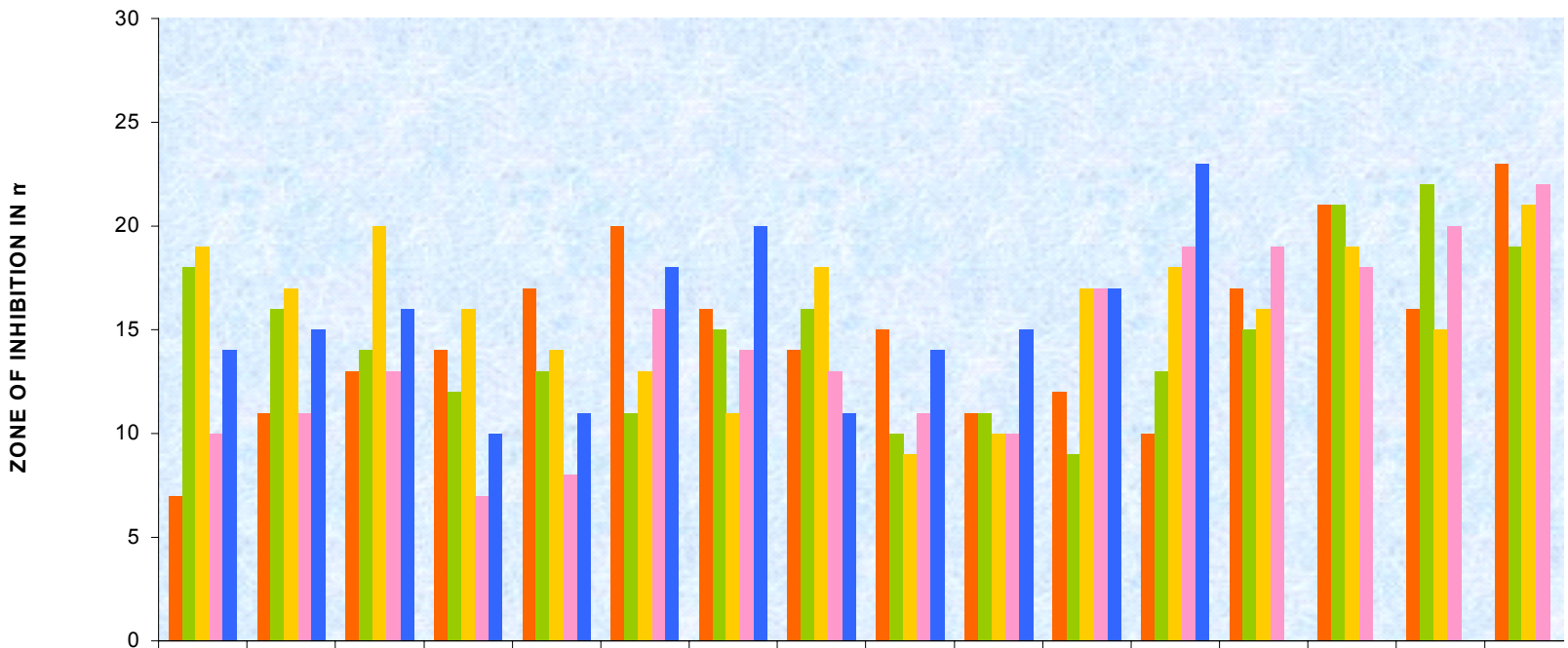
Antitubercular screening of the compounds of type (IV) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 4a.

TABLE NO. 4 : PHYSICAL CONSTANTS OF 2-ARYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLES

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	2-CH_3-C_6H_4-	$C_{16}H_{13}ClN_2O$	284.7	177	0.74	56	9.84	9.80
4b	4-CH_3-C_6H_4-	$C_{16}H_{13}ClN_2O$	284.7	172	0.85	61	9.84	9.88
4c	4-OCH_3-C_6H_4-	$C_{16}H_{13}ClN_2O_2$	300.7	179	0.93	64	9.31	9.35
4d	2-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_2O$	305.1	211	0.72	54	9.18	9.14
4e	4-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_2O$	305.1	160	0.82	72	9.18	9.22
4f	4-F-C_6H_4-	$C_{15}H_{10}ClFN_2O$	288.7	138	0.84	63	9.70	9.66
4g	4-Br-C_6H_4-	$C_{15}H_{10}BrClN_2O$	349.6	184	0.79	55	8.01	8.05
4h	2-OH-C_6H_4-	$C_{15}H_{11}ClN_2O_2$	286.7	170	0.92	60	9.77	9.73
4i	4-OH-C_6H_4-	$C_{15}H_{11}ClN_2O_2$	286.7	166	0.81	57	9.77	9.80
4j	2-$NH_2C_6H_4$-	$C_{15}H_{12}ClN_3O$	285.7	180	0.89	62	14.71	14.75
4k	4-NH_2-C_6H_4-	$C_{15}H_{12}ClN_3O$	285.7	136	0.76	66	14.71	14.68
4l	4-NO_2-C_6H_4-	$C_{15}H_{10}ClN_3O_3$	315.7	140	0.90	74	13.31	13.35

*TLC Solvent System : Acetone : Benzene (4 : 6)

GRAPHICAL CHART NO. 4 : 2-ARYL-5-o-CHLOROBENZYL-1,3,4-OXADIAZOLES



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

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

From the experimental data it has been concluded that the compounds bearing R=4-chlorophenyl and 4-bromophenyl have displayed considerable activity against ***B.coccus***. The compounds bearing R=2-methylphenyl, 4-methylphenyl and 2-hydroxyphenyl have shown maximum activity against ***B. subtilis***.

In case of Gram negative bacterial strains, the compounds bearing R=2-methylphenyl and 4-methoxyphenyl have fairly inhibited the growth of ***P.vulgaris***. All the compounds were inactive against ***E.coli*** except R=4-nitrophenyl.

Antifungal activity :

All the compounds were active against ***A.niger***. Maximum activity was shown by the compounds bearing R=4-bromophenyl and 4-nitrophenyl.

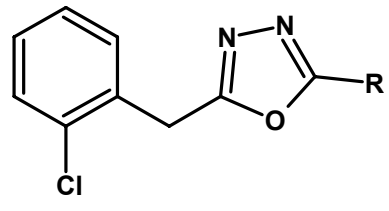
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

The compounds having R = 4-methylphenyl,4-methoxyphenyl and 4-fluorophenyl have displayed percentage inhibition in the range of 74-84% and compounds bearing R = 2-methylphenyl, 2-hydroxyphenyl and 4-nitrophenyl showed percentage inhibition in the range of 45-58% against ***Mycobacterium tuberculosis*** H_{37} ***Rv***.

The antitubercular activity data have been compared with standard drug Rifampin.

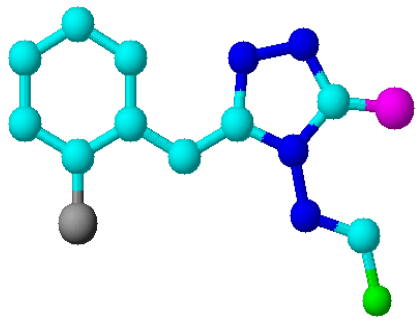
TABLE NO. 4a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



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*
295443	BSA-65	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	84	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295444	BSA-66	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	80	-	
295445	BSA-67	2-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	54	-	"
295446	BSA-68	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	48	-	"
295447	BSA-69	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	74	-	"
295448	BSA-70	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	82	-	"
295449	BSA-71	4-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	56	-	"
295450	BSA-72	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	45	-	"
295451	BSA-73	4-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295452	BSA-74	2-NH_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	76	-	"
295453	BSA-75	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	58	-	"
295454	BSA-76	C_5H_5N-	Alamar	$H_{37}Rv$	<6.25	68	-	"



PART-V

STUDIES ON AZOMETHINES

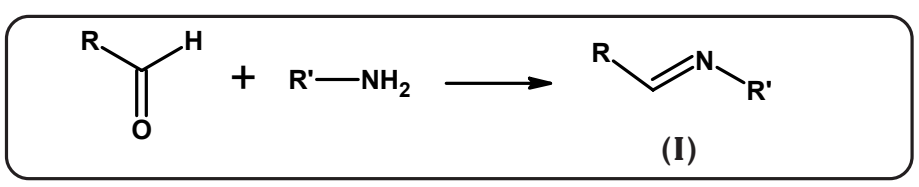
INTRODUCTION

Azomethine derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activity. Azomethines are also known as schiff bases and they are well known intermediates for the preparation of azetidinones, thiazolidinone, formazan, arylacetamide and many other entities of pharamaceutical potential. These are the compounds containing characteristic –HC=N– group.

SYNTHETIC ASPECT

Several methods[231-234] for the preparation of azomethine derivatives are documented in literature.

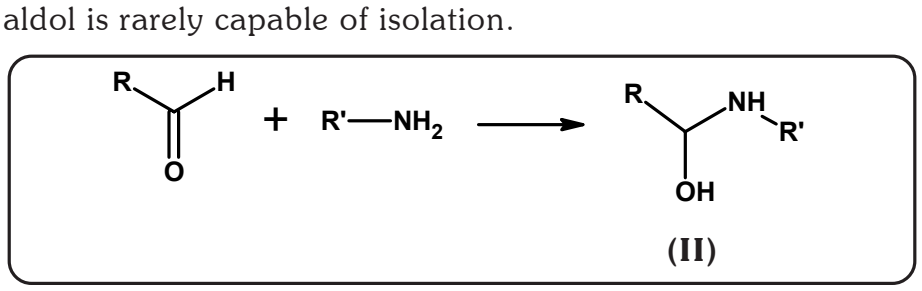
1. General account of the summary of reaction of aldehydes with amine.



(I)

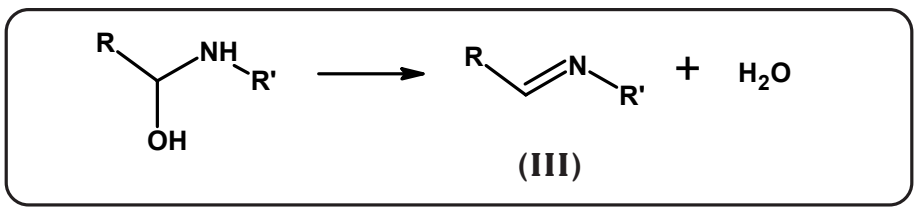
2. Imine formation involve two steps.

(a) Addition of the amine to the carbonyl group of the aldehyde gives aldol. The aldol is rarely capable of isolation.



(II)

(b) The loss of water to give an imine (azomethine). This corresponds to the "crotonaldehyde stage" of the aldol condensation.



(III)

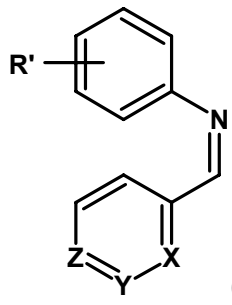
THERAPEUTIC IMPORTANCE

Azomethines have widely been used as pharmacologically useful entities because of their broad spectrum of biological activities which have been described as under.

1. Antibacterial[235]
2. Antischistosomal[236]
3. Antifungal[237]
4. Antiinflammatory[238]
5. Antiparasitic[239]
6. Plant harmone activity[240]
7. Antiviral[241]
8. Antipyretic[242]

Azomethines are characterized by -N=CH-(imine) gp which is important in elucidating the mechanism of transamination and recemisation reaction in biological systems[243,244]. Due to the great flexibility and diverse structural aspects, a wide range of azomethines have been synthesised and their complexation behaviour studied[245].

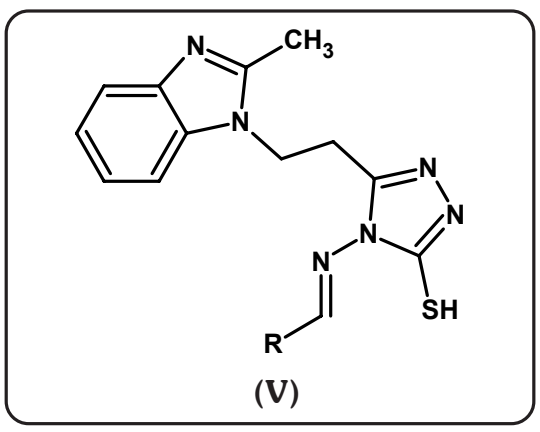
R. M. Metri et. al.[246] have synthesised and studied the biological activity of bis-triazole schiff bases. Komal Vashi and Naik[247] have investigated some azomethines as antibacterial agents. Some azomethines possessing antituberculosis activity has been reported by Hearn and Cynamon.[248] Iana Vazzana et. al.[249] have synthesised azomethine derivatives (IV) and reported them as antiinflammatory agents.



(IV)

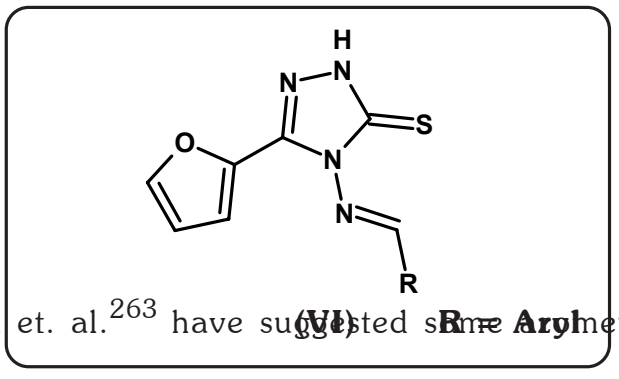
X = N; Y,Z = CH
Z = N, CF, OCH_3
X,Y = CH
R' = 3-CF_3, 4-SO_2NH_2, 4-SO_2CH_3

Pandeya S. N. and co-workers[250]have documented antibacterial, antifungal and anti HIV activity of some azomethine derivatives. Sabrina Castellano et. al.[251] have prepared azomethine derivatives and evaluated ***in vitro*** against several pathogenic fungi responsible for human disease. Hou and Xu [252] have investigated azomethine derivatives possessing bacteriostatic and fungistatic activity. Popescu et. al.[253] suggested some schiff bases useful as carbonic anhydrase inhibitors. B. S. Holla et. al.[254] have screened azomethines for their antibacterial activity. Sabrin C. et al.[255] have documented antifungal and antimycotic activity of azomethines. Afaf H. and co-workers[256] have prepared azomethines (V) possessing potential antimicrobial activity.



(V)

Ulusoy N et. al.[257] have discovered azomethine derivatives possessing antimicrobial and antituberculosis activities. Wang Y. and co-workers[258] have screened some azomethines having goods plant harmone activity. Pascal Rotheist et. al.[259] have reported some new azomethines as antiparasitic agents. B. Shivarama Holla et. al.[260] have documented antibacterial, antifungal and herbicidal activity of azomethine derivatives. C. T. Supuran et. al.[261] have reported azomethines useful as carbonic anhydrase inhibitors. Ergenc and co-workers[262] have synthesised azomethine derivatives (VI) showing antifungal activity.

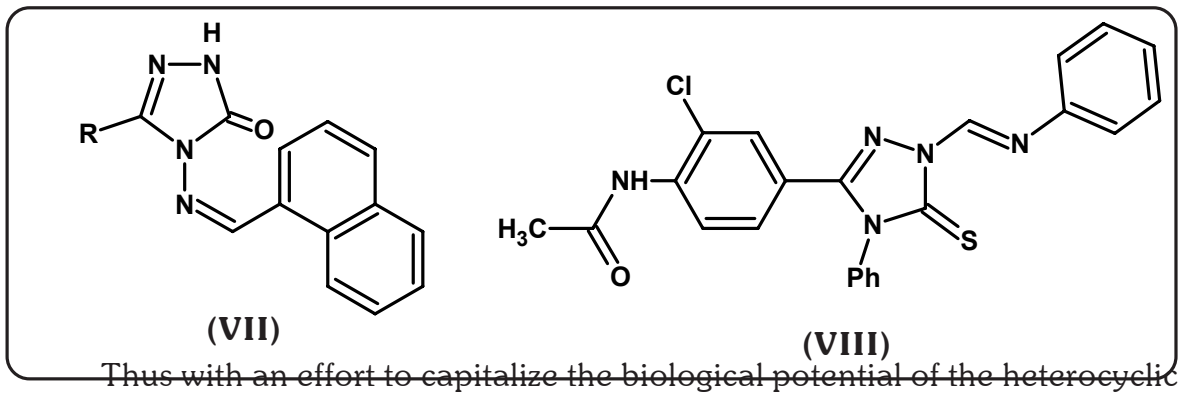


(VI) R = Aryl

A. Scozzafava et. al.[263] have suggested some azomethines useful as

carbonic anhydrase inhibitors.Das and co-workers[264] have prepared azomethines and were tested them for antiviral activity. Some Azomethine derivatives have been extensively investigated for their antiinflammatory activity by Adnan A. et. al.[265] De-Biplab et al.[266] have synthesised azomethines possessing significant antibacterial and antifungal activities.

Recently, Ilkay Kucukguzel et. al.[267] have screened azomethine derivatives for their anticonvulsant activity. B. S. Holla et. al.[268] have discovered azomethine derivatives and studied their anticancer activity. Hojatollah M. et. al.[269] have reported azomethines useful as anticonvulsant agent. Dimmoch J. et. al.[270] have reported azomethines as cytotoxic agents. Neslihan and Reyhan[271] have synthesised azomethines (VII) and studied their antitumor activity. R. S. Varma[272] has been synthesised a series of new azomethines (VIII) and evaluated them for antileishmanial activity.



(VII) (VIII)

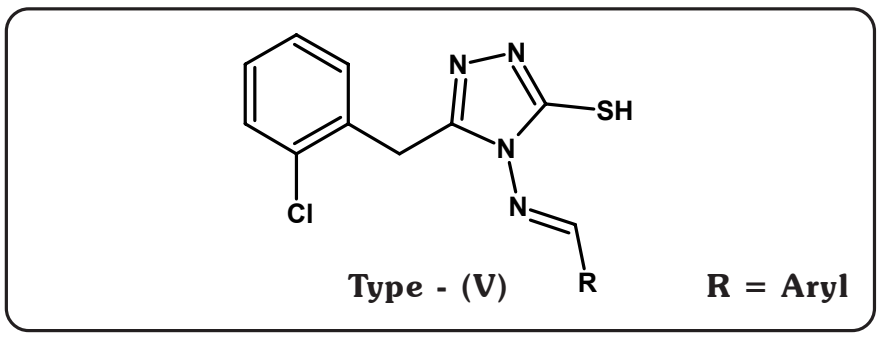
Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological study, we have undertaken the synthesis of azomethines bearing triazole moiety.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF 4-N-SUBSTITUTED BENZALAMINO-3-MERCAPTO-5-o-CHLOROBENZYL 1,2,4-TRIAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4,N-SUBSTITUTED BENZALAMINO-3-MERCAPTO-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

Much interest centres around azomethine derivatives because of their wide range of pharmacological properties. Hence, it was considered worthwhile to synthesise azomethine derivatives of the type (V) for the better drug potential. The azomethine derivatives were synthesised by the condensation of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazoles with different aromatic aldehydes in presence of sulphuric acid.

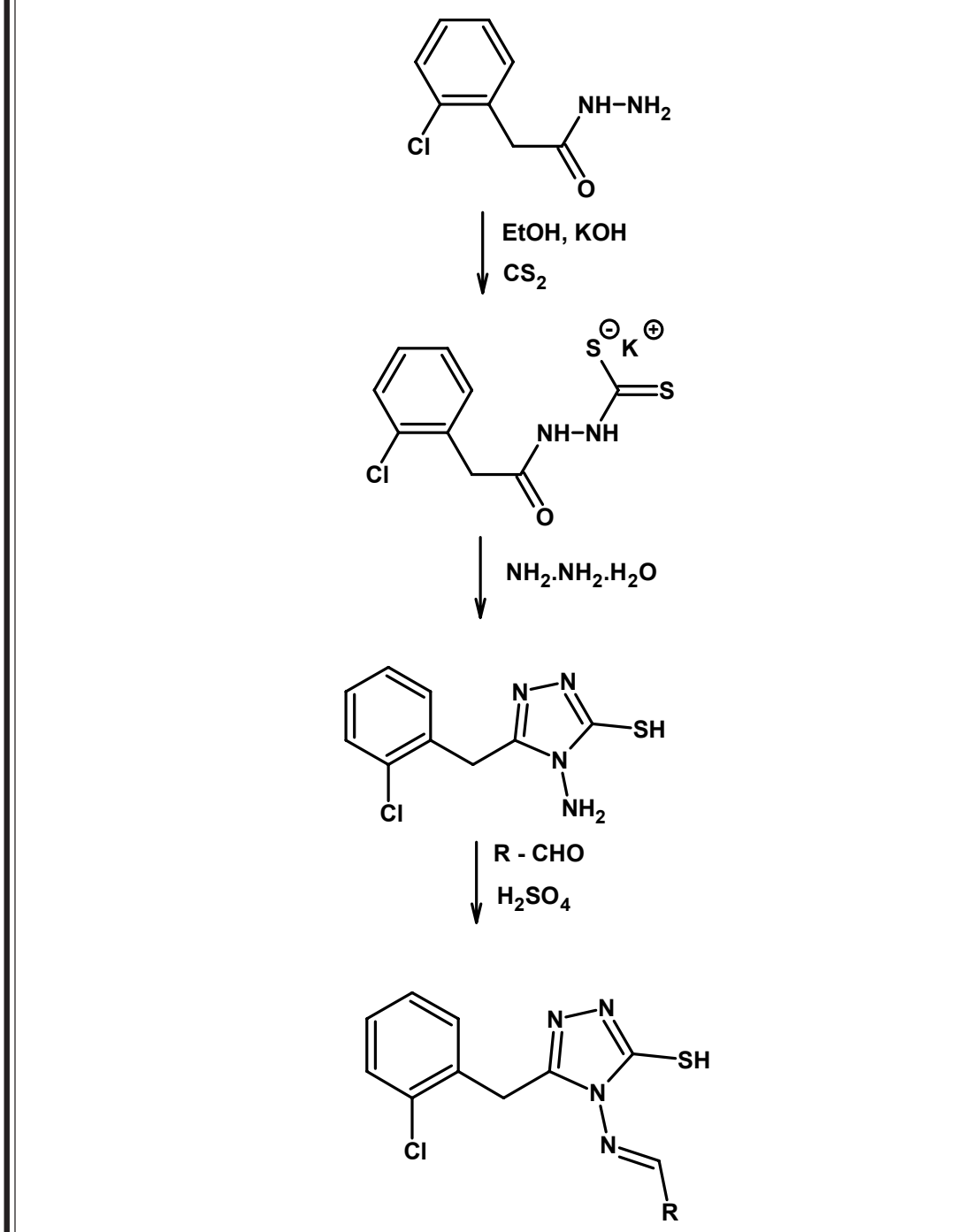


Type - (V) **R = Aryl**

The constitution of the synthesised compounds have been supported by 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.

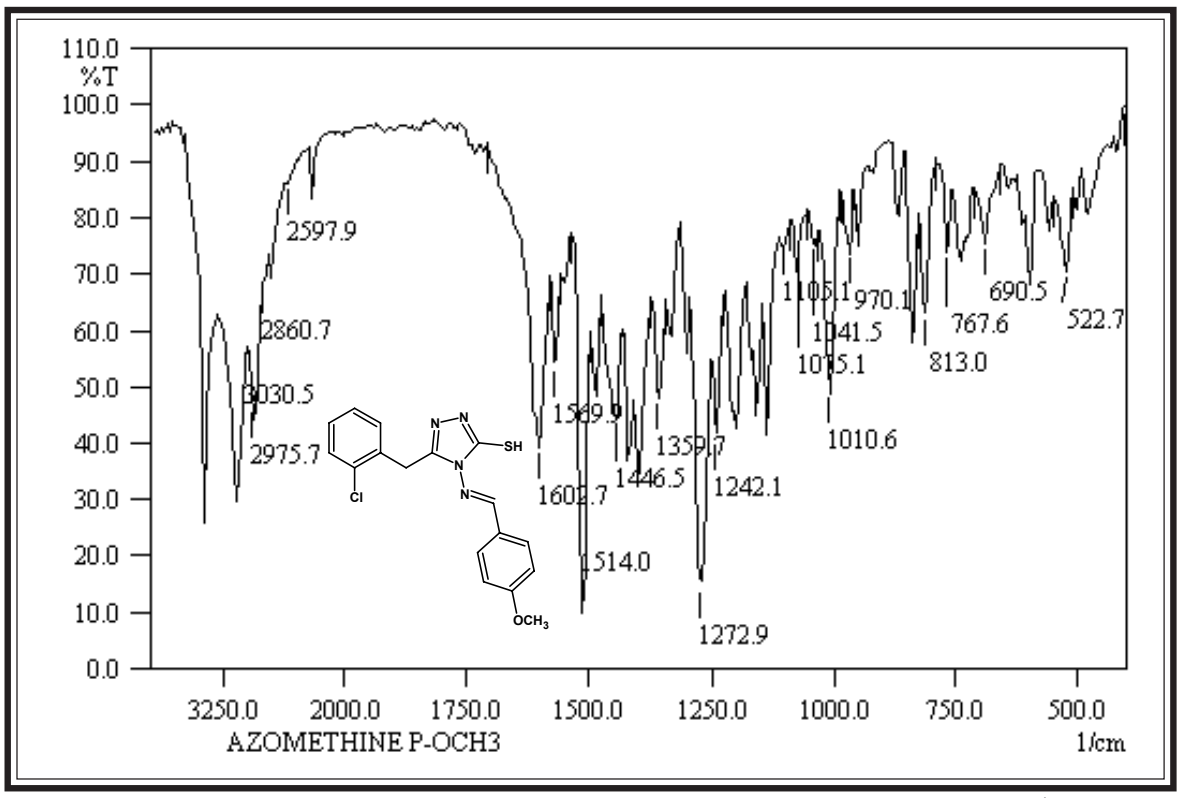
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 5.

REACTION SCHEME



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

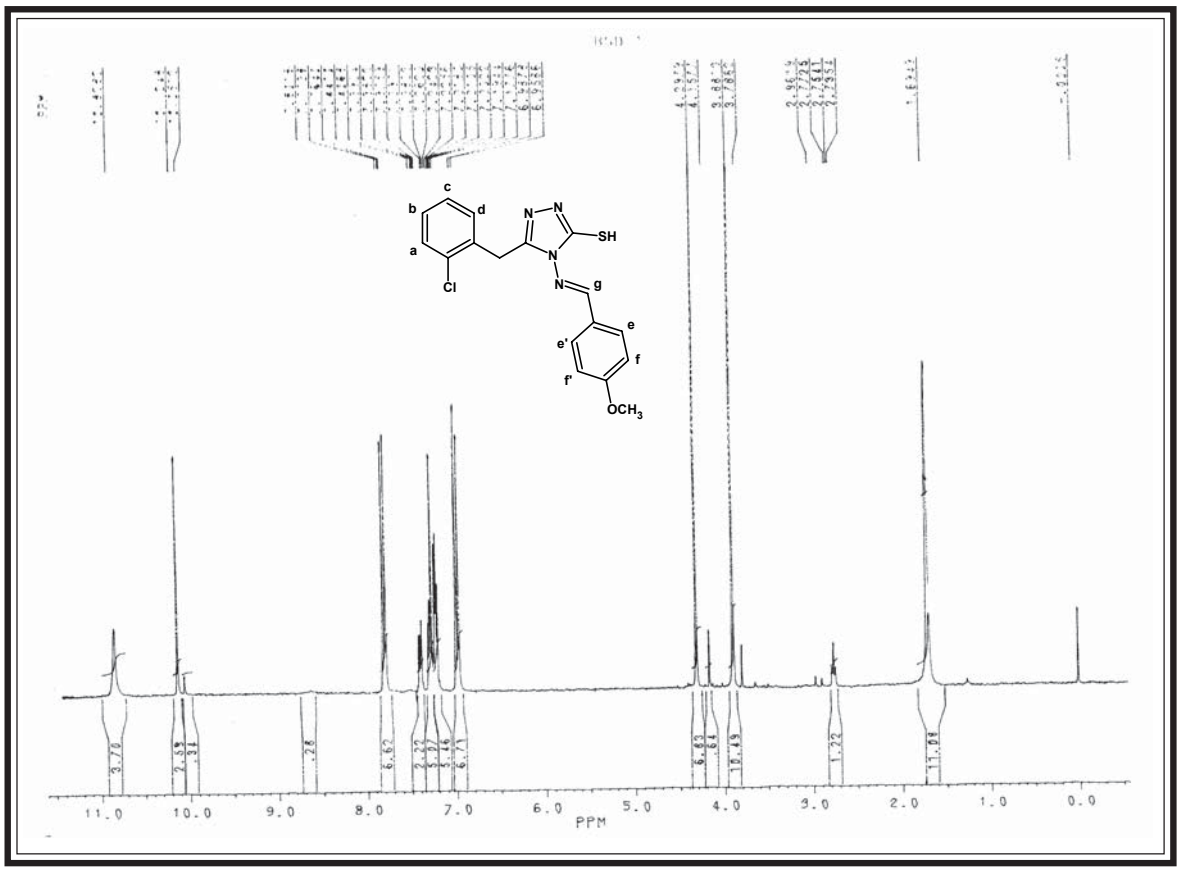
IR SPECTRAL STUDY OF 4,N-p-METHOXY BENZALAMINO-3-MERCAPTO-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES



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.)	2975	2975–2950	498
$-CH_3$	C – H str (sym.)	2860	2880–2860	"
	C – H def. (asym.)	1446	1470–1435	"
	C – H def. (sym.)	1359	1385–1370	"
Aromatic	C – H str.	3030	3080–3030	"
	C = C str.	1569	1585-1480	"
	C – H i.p. def.	1105	1125-1090	503
		1041	1070–1000	"
	C – H o.o.p def.	813	835–810	498
Triazole	C = N str.	1602	1612–1593	"
	C – N str.	1272	1350–1200	504
	N – N str.	1010	1050–1010	503
	C – S str.	690	700–600	504
	C – Cl str.	767	800–600	498
	S – H str.	2597	2600-2500	504
Ether	C – O – C str. (asym.)	1242	1275–1200	503
	C – O – C str. (sym.)	1075	1075–1020	"

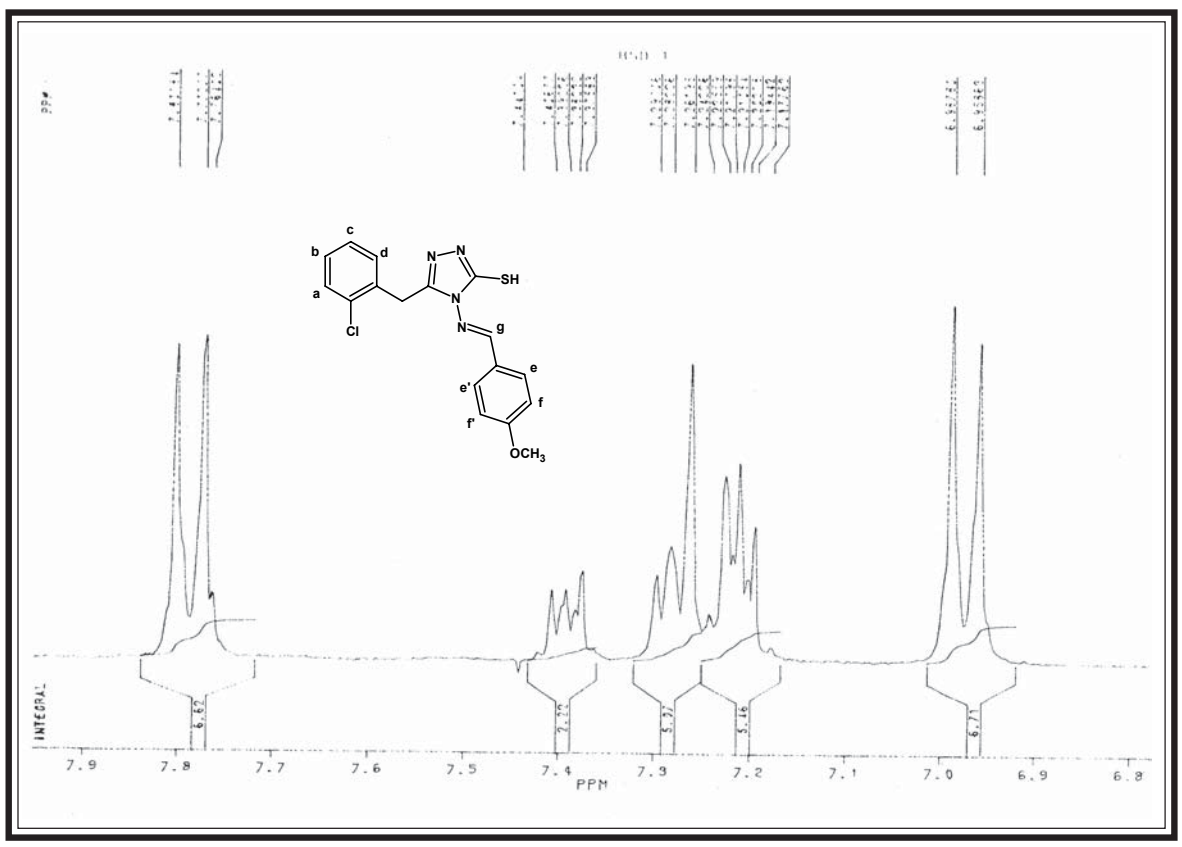
PMR SPECTRAL STUDY OF 4,N-p-METHOXY BENZALAMINO-3-MERCAPTO-5-o-CHLOROBENZYL-1,2,4-TRIAZOLE



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.88		3H	singlet	Ar-OCH_3
2.	4.29		2H	singlet	-CH_2
3.	6.96	Jfe=9	2H	doublet	Ar-Hff'
4.	7.19-7.29		3H	multiplet	Ar-Hb, Ar-Hc Ar-Hd
5.	7.39		1H	double doublet	Ar-Ha
6.	7.77	Jef=9	2H	doublet	Ar-Hee'
7.	10.12		1H	singlet	-CHg
8.	10.83	-	1H	broad singlet	-SH

EXPANDED AROMATIC REGION

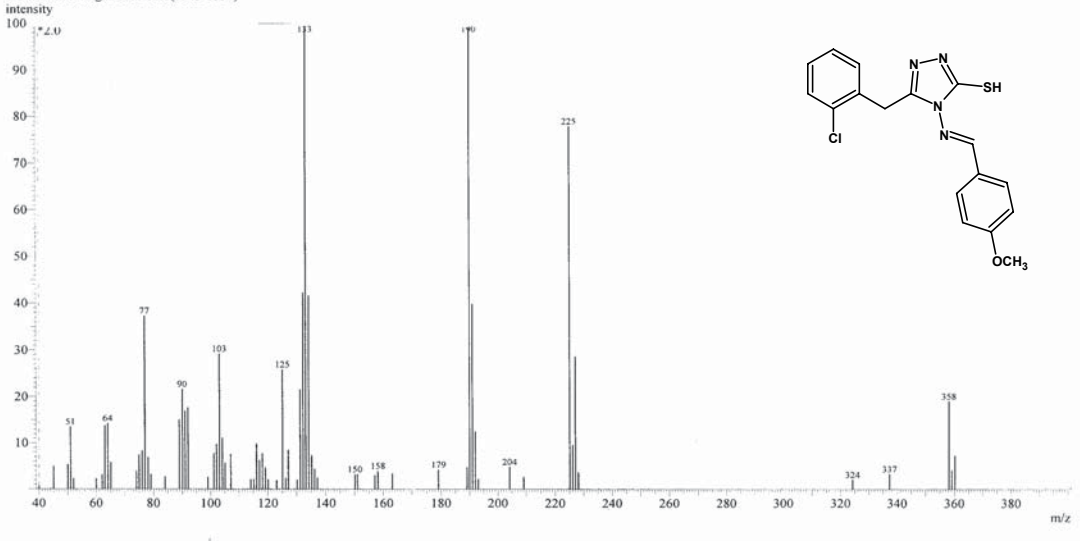


SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/14/2005 2:52:28 PM
Sample Name : SB-4
Sample ID : SB-4
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-4.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:8.3(Scan#:955)
MassPeaks:70 BasePeak:190(108040)
RawMode:Single 8.3(955)
BG Mode:Averaged 13.2-13.6(1543-1594)



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 4,N-SUBSTITUTED BENZALAMINO-3-MERCAPTO-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

[A] Synthesis of Potassium o-chlorophenylacetamido dithiocarbamate

See [A] Part-I, Section-I (C).

[B] Synthesis of 3-Mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole

See [A] Part-I, Section-I (D).

[C] Synthesis of 4,N-p-methoxybenzalamino-3-mercapto-5-o-chlorobenzyl-1,2,4-triazole

A mixture of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole (2.40g, 0.01M) and p-methoxybenzaldehyde (1.36g, 0.01M) in absolute alcohol (25 ml) in presence of sulphuric acid as a catalyst were refluxed for 8 hrs. The resulting mixture was poured onto crushed ice. The product was isolated and crystallised from ethanol. Yield 1.6g, 66%, m.p. 158°C ($C_{17}H_{15}ClN_4OS$: required : C, 56.90; H, 4.21 ; N, 15.61, found : C, 56.94 ; H, 4.18 ; N, 15.65%)

Similarly other derivatives have been synthesised. The physical data are recorded in Table No. 5.

[D] Antimicrobial activity of 4,N-substituted benzalamino-3-mercapto-5-o-chlorobenzyl-1,2,4-triazoles

Antimicrobial testing was carried out as described in [A] Part-I, Section-I, (F).

The zones of inhibition of test solution are recorded in Graphical Chart No. 5.

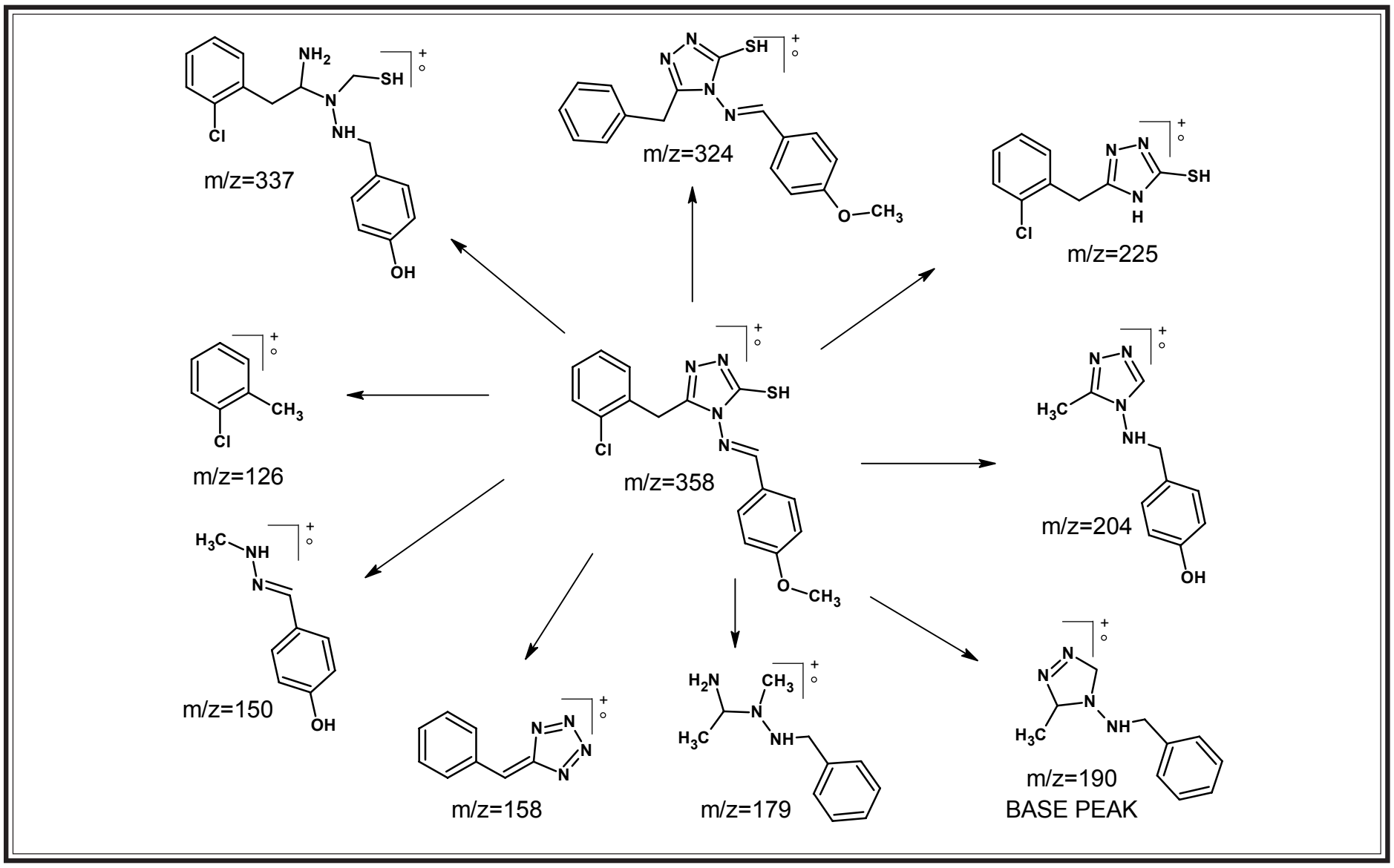
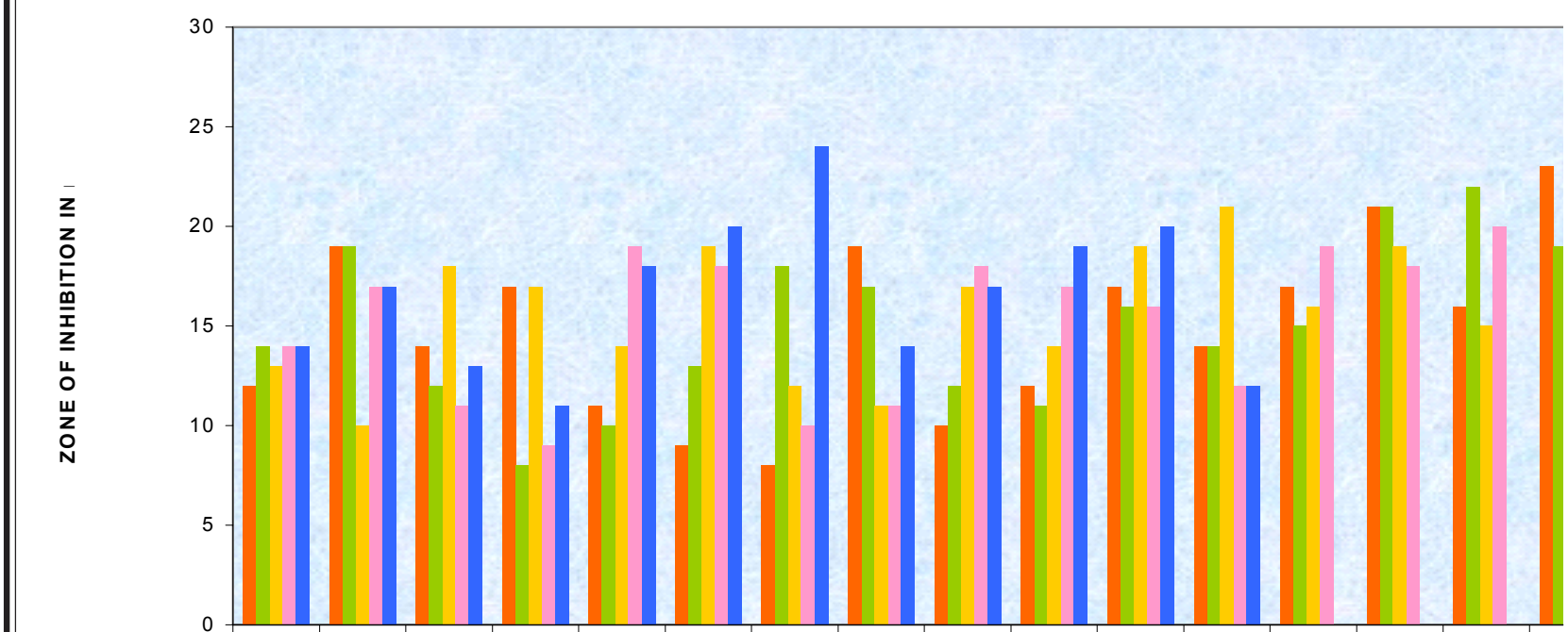

m/z=337
m/z=324
m/z=225
m/z=126
m/z=358
m/z=204
m/z=150
m/z=158
m/z=179
m/z=190
BASE PEAK

TABLE NO. 5 : PHYSICAL CONSTANTS OF 4,N-SUBSTITUTED BENZALAMINO-3-MERCAPTO-5-o-CHLOROBENZYL-1,2,4-TRIAZOLES

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
5a	C_6H_5-	$C_{16}H_{13}ClN_4S$	328.8	198	0.64	57	17.04	17.00
5b	4-OCH_3-C_6H_4-	$C_{17}H_{15}ClN_4OS$	358.8	158	0.52	66	15.61	15.65
5c	2-Cl-C_6H_4-	$C_{16}H_{12}Cl_2N_4S$	363.2	170	0.67	68	15.42	15.40
5d	4-Cl-C_6H_4-	$C_{16}H_{12}Cl_2N_4S$	363.2	200	0.57	55	15.42	15.46
5e	4-F-C_6H_4-	$C_{16}H_{12}ClFN_4S$	346.8	252	0.70	58	5.48	5.44
5f	2-NO_2-C_6H_4-	$C_{16}H_{12}ClN_5O_2S$	373.8	172	0.66	72	18.73	18.69
5g	3-NO_2-C_6H_4-	$C_{16}H_{12}ClN_5O_2S$	373.8	180	0.68	62	18.73	18.77
5h	2-OH-C_6H_4-	$C_{16}H_{13}ClN_4OS$	344.8	165	0.53	65	16.25	16.21
5i	4-OH-C_6H_4-	$C_{16}H_{13}ClN_4OS$	344.8	205	0.55	59	16.25	16.29
5j	9-$C_{14}H_9$-	$C_{24}H_{17}ClN_4S$	428.9	202	0.63	77	20.37	20.33
5k	3-OH,4-OCH_3-C_6H_3-	$C_{17}H_{15}ClN_4O_2S$	374.8	170	0.71	54	14.95	14.91
5l	3,4-$(OCH_3)_2$-C_6H_3-	$C_{18}H_{17}ClN_4O_2S$	388.8	132	0.59	56	14.41	14.37

*TLC Solvent System :Ethyl acetate : Hexane (2 : 8) (5a - 5l)
(3 : 7) (5c, 5k, 5l)

GRAPHICAL CHART NO. 5 : 4,N-SUBSTITUTED BENZALAMINO-3-MERCAPTO -5-o-CHLOROBENZYL-1,2,4-TRIAZOLES



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	Ery m
B.coccus	12	19	14	17	11	9	8	19	10	12	17	14	17	21	16	2
B.subtilis	14	19	12	8	10	13	18	17	12	11	16	14	15	21	22	1
P.vulgaris	13	10	18	17	14	19	12	11	17	14	19	21	16	19	15	2
E.coli	14	17	11	9	19	18	10	11	18	17	16	12	19	18	20	2
A.niger	14	17	13	11	18	20	24	14	17	19	20	12	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

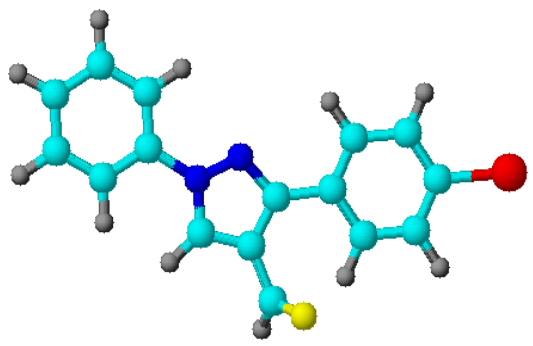
It was observed that most of the compounds were mild to moderately active against Gram positive and Gram negative bacterial strains.

Maximum activity was observed in compounds bearing R=4-methoxyphenyl and 2-hydroxyphenyl against ***B.coccus*** and ***B.subtilis***.

In case of ***P.vulgaris***, significant activity was displayed by compounds bearing R=2-chlorophenyl, 2-nitrophenyl and 3,4-dimethoxyphenyl. Compounds with R=4-fluorophenyl, 2-nitrophenyl and 4-hydroxyphenyl showed highest activity against ***E.coli***.

Antifungal activity :

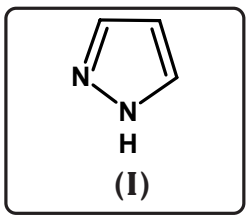
The compounds were tested against fungal species ***A.niger***. It has been concluded that all the compounds were active against ***A.niger***. Maximum activity was displayed by the compounds bearing R=2-nitrophenyl, 3-nitrophenyl and 3-hydroxy, 4-methoxyphenyl.



[B]
STUDIES ON PYRAZOLES

INTRODUCTION

Pyrazoles, which belong to an important class of heterocyclic compounds have been extensively explored for their applications in the field of medicine, agriculture and industrial chemistry. The pyrazole ring system (I) consists of a diunsaturated five memberd ring containing two adjecent Nitrogen atoms.



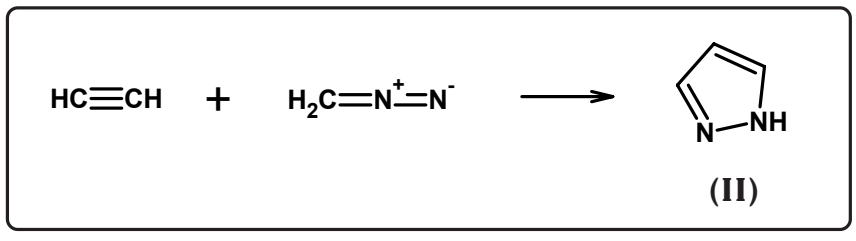
(I)

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

SYNTHETIC ASPECTS

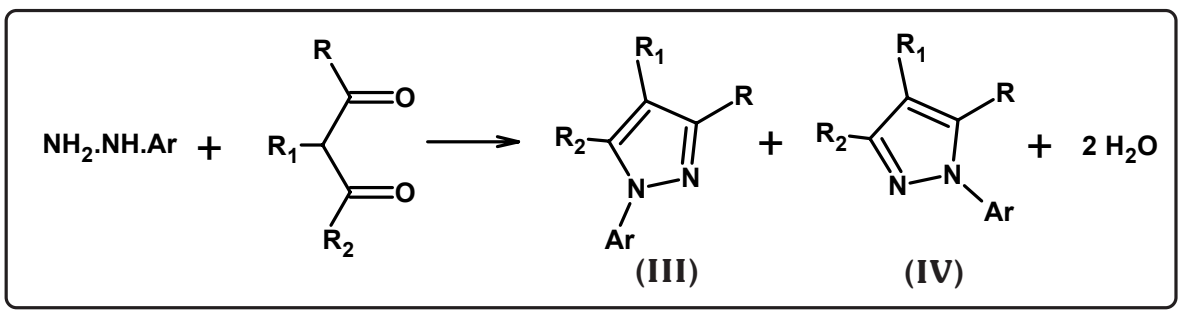
Different methods for the preparation of pyrazoles are available in literature which are as under.

1. H. V. Pechmann[273] has synthesised pyrazoles by the reaction of acetylenes and diazomethane.



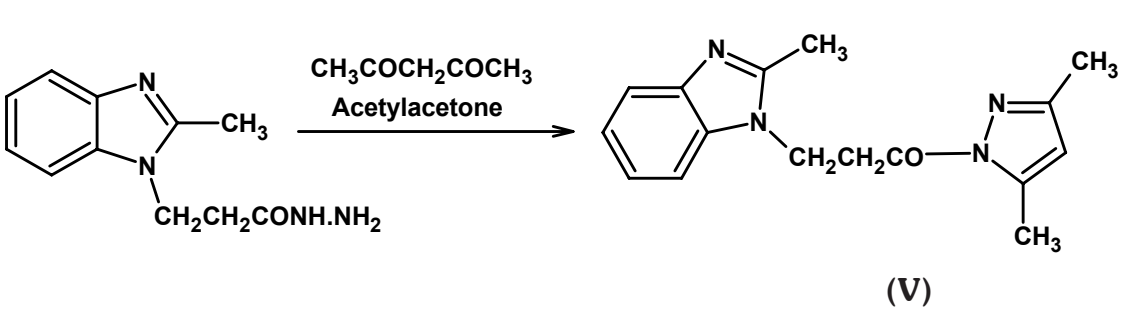
(II)

2. L. Knorr[274] has synthesised two structrually isomeric pyrazoles by the condensation of substituted hydrazines with 1,3-dicarbonyl compounds.



(III) (IV)

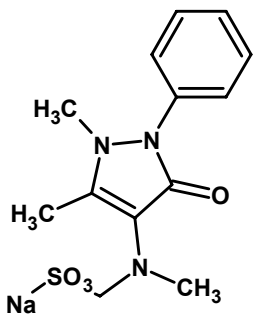
3. Afaf H. El-Masry et. al.[275] have synthesised 1-[3-(2-methylbenzimidazol-1-yl)propanoyl]-3,5-dimethyl pyrazole by the reaction of hydrazide with acetylacetone.



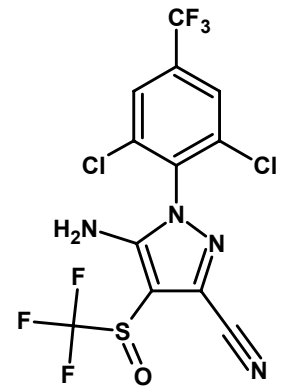
(V)

THERAPEUTIC IMPORTANCE

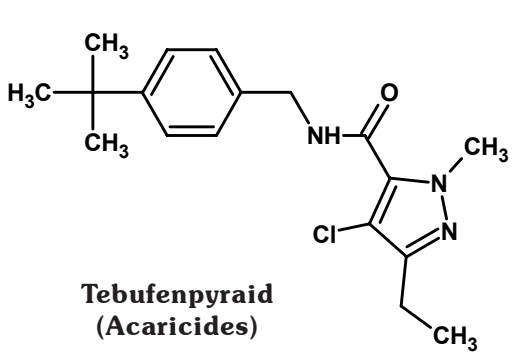
Pyrazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having pyrazole nulceus with good pharmacological activities are listed below.



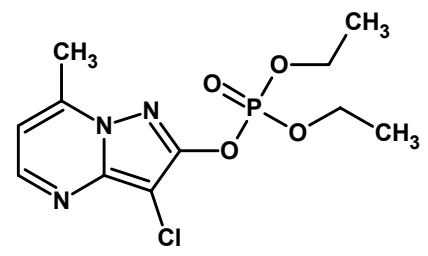
Sulpyrin
(Antipyretic)



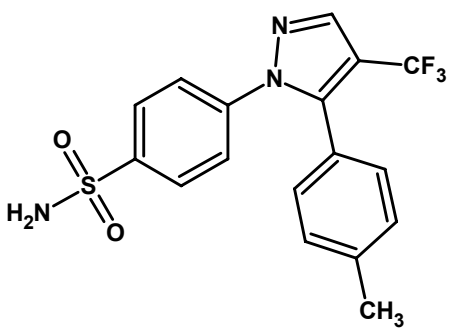
Fipronil
(Pesticide)



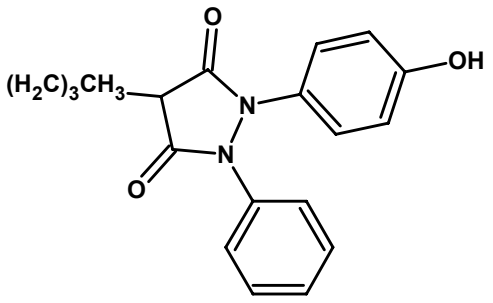
Tebufenpyraid
(Acaricides)



Chlorprazophos
(Insecticide)



Celecoxib
(Antiinflammatory)

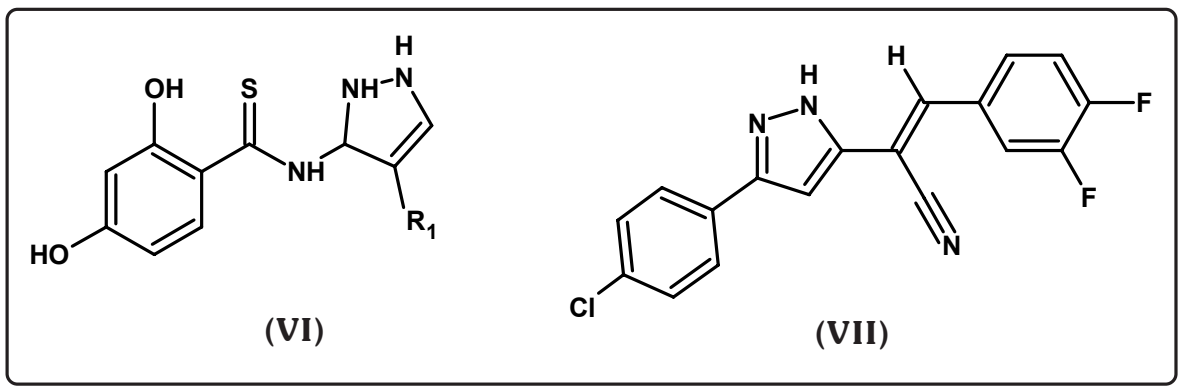


Oxyphenbutazone
(Antiarthritic)

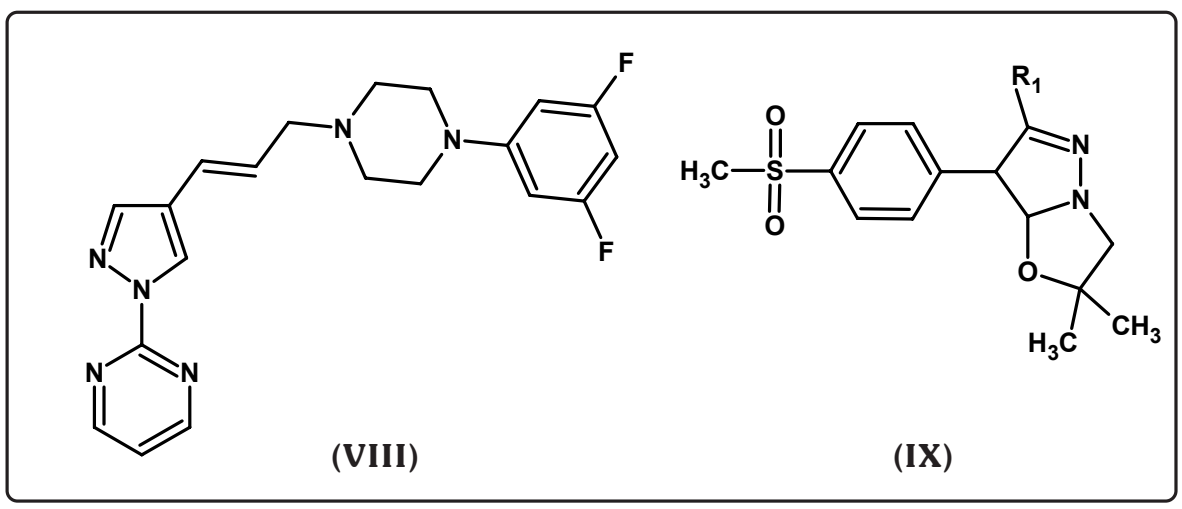
Pyrazole derivatives exhibit broad spectrum of therapeutic activity. Several biological activities associated with pyrazole derivatives have been described as under.

1. Anticancer[276]
2. Antitumar[277]
3. Antiulcer[278]
4. Antimicrobial[279]
5. Antiparasitic[280]
6. CNS depressant[281]
7. Herbicidal[282]
8. Immunosuppresants[283]
9. Lipoxygenase inhibitor[284]
10. Neurotonsin receptor[285]

Joanna M. et. al.[286] have prepared pyrazole derivatives (VI) and screened for their antimycotic activity. Gerard Pinnel et. al.[287] have discovered pyrazoles useful as antitumor agent. Carbau Romuald and co-workers[288] have reported pyrazole derivatives useful as reverse transcriptase inhibitors for the treatment of HIV infection. Bernard Banks et. al.[289] have reported antiparasitic activity of pyrazoles. Dange Visaykymar et. al.[290] have formulated pyrazoles as anticaner agent. Virinder S. Parmar et. al.[291] have synthesised pyrazole derivatives (VII) and studied their antiinvasive activity.

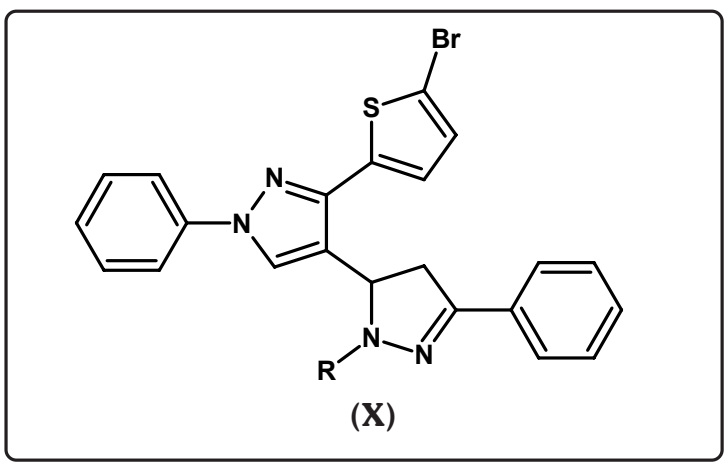


Aldo Balsamo and co-workers[292]have documented COX-2 inhibitory and antiinflammatory activity of pyrazoles. Grazid M. *et.* al.[293] have tested pyrazole derivatives for their antimicrobial activity. Florian P. *et.* al.[294] have discovered some pyrazole derivatives and studied their antitumor activity. Takehiro and Toshio[295] have reported antiinflammatory activity of pyrazoles. Baraldi *et.* al.[296] have discovered pyrazole derivatives and studied their antimicrobial and antitumor activity. Malisa J. *et.* al.[297] have formulated pyrazoles as anticonvulsant agent. Hitoshi O. *et.* al.[298] have synthesised pyrimidinyl pyrazole derivatives (VIII) and reported their antiproliferative activity against human lung cancer cell.



Maria M. *et.* al.[299] have investigated some pyrazole derivatives showing antimycobacterial activity S. Gupta *et.* al.[300] have documented antiinflammatory activity of pyrazoles. R. Ranatunge *et.* al.[301] have synthesised pyrazole derivatives (IX) and screened for their COX-2 inhibitory activity.

Recently, Giuseppe D. et. al.[302] have discovered pyrazole derivatives and studied their antileukemic activity. Junzo Kamei et. al.[303] have reported pyrazoles useful as cyclooxygenase-2-inhibitor. Zainaba D. et. al.[304] have investigated pyrazoles and screened for their antifungal activity. Giulia M. et. al.[305] have demonstrated antimicrobial activity of pyrazoles. Zhao Zhong et. al.[306] have documented anticoagulant activity of pyrazoles. Moyed and Evelin[307] have suggested pyrazole useful as antibacterial agent. Pier G. Baraldi et. al.[308] have formulated pyrazoles as antitumor agent. Adnan and Tarek[309] have synthesised pyrazole derivatives (X) and tested for their antiinflammatory, cyclooxygenase-2-inhibitory and antimicrobial activities.



(X)

Looking to the diversified biological activities, it appeared of interest to synthesise some pyrimidines,cyanopyridones, imidazolinones and nitriles bearing pyrazole moiety, in order to achieving compounds having better therapeutic importance. These study are described in following parts.

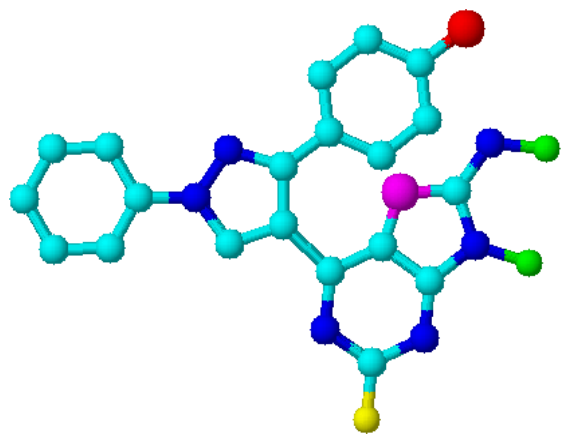
[B] STUDIES ON PYRAZOLES

PART-I : STUDIES ON PYRIMIDINES

PART-II : STUDIES ON CYANOPYRIDONES

PART-III : STUDIES ON IMIDAZOLINONES

PART-IV : STUDIES ON NITRILES

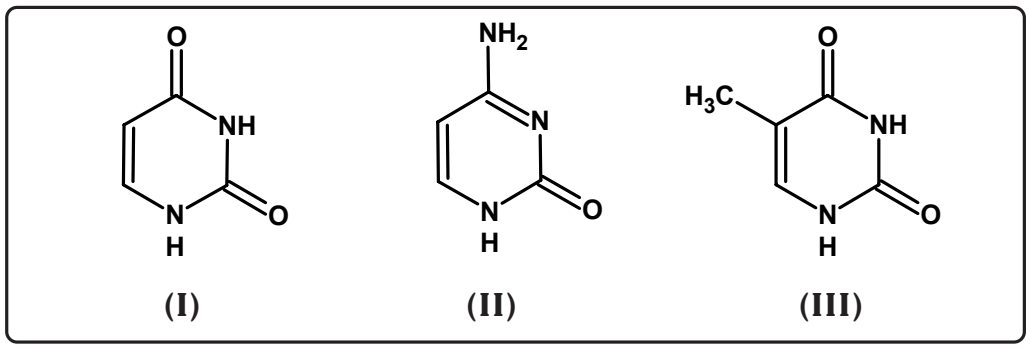


PART-I

STUDIES ON PYRIMIDINES

INTRODUCTION

Pyrimidine is a heterocylic aromatic organic compound, which contains two nitrogen atoms at position 1 and 3 of the six membered ring. They are occurring in nature in wide variety of forms. They include several nucleuic acid constituents like uracil (I), cytosine (II) and thymine (III) which have remarkable pharmaceutical importance because of their diverse biological activities. Pyrimidine is the parent compound of many drugs, including the barbiturates.

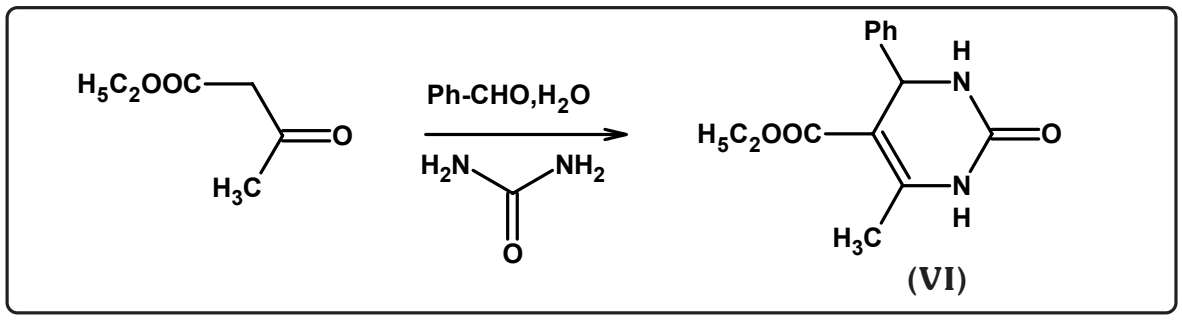


(I) **(II)** **(III)**

SYNTHETIC ASPECT

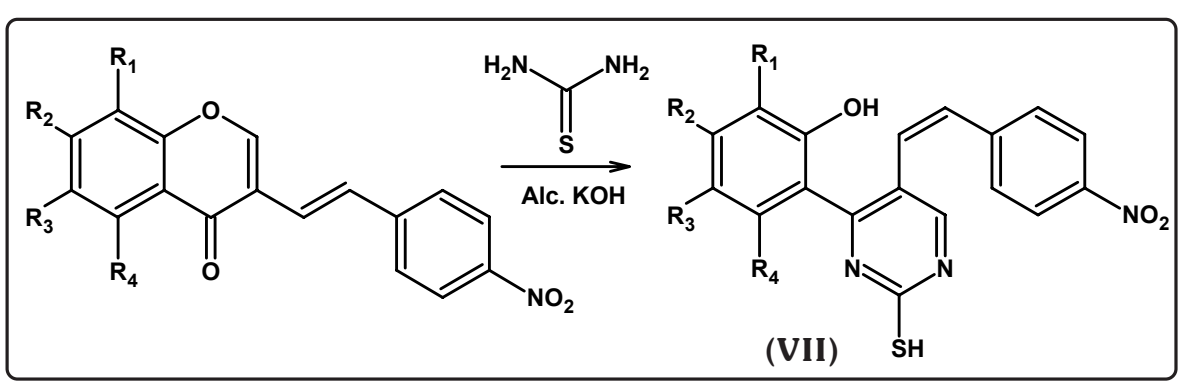
Different methods for ther synthesis of pyrimidines have been cited in the literature[310].

1. Bigi and co-workers[311] have synthesised pyrimidinones as shown under solvent free condition.



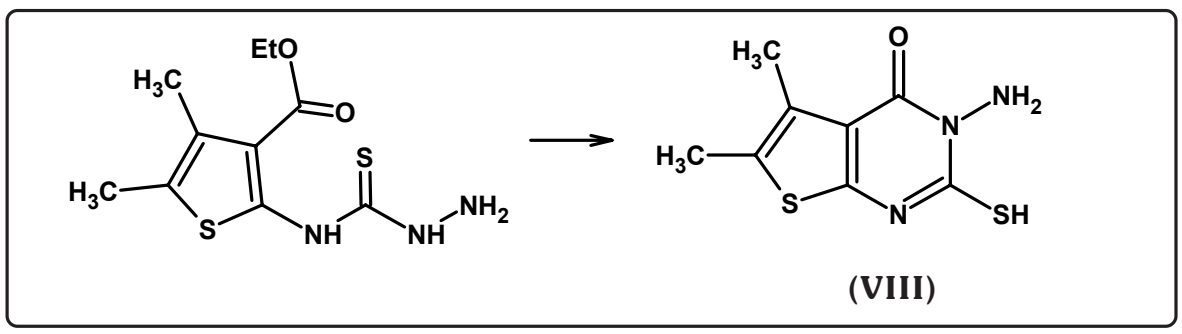
(VI)

2. B. K. Karale *et.* al.[312] have synthesised pyrimidine by the condensation of 1(4-nitrophenyl)-2-(chromon-3-yl) ethenes with thiourea in presence of alcoholic KOH.



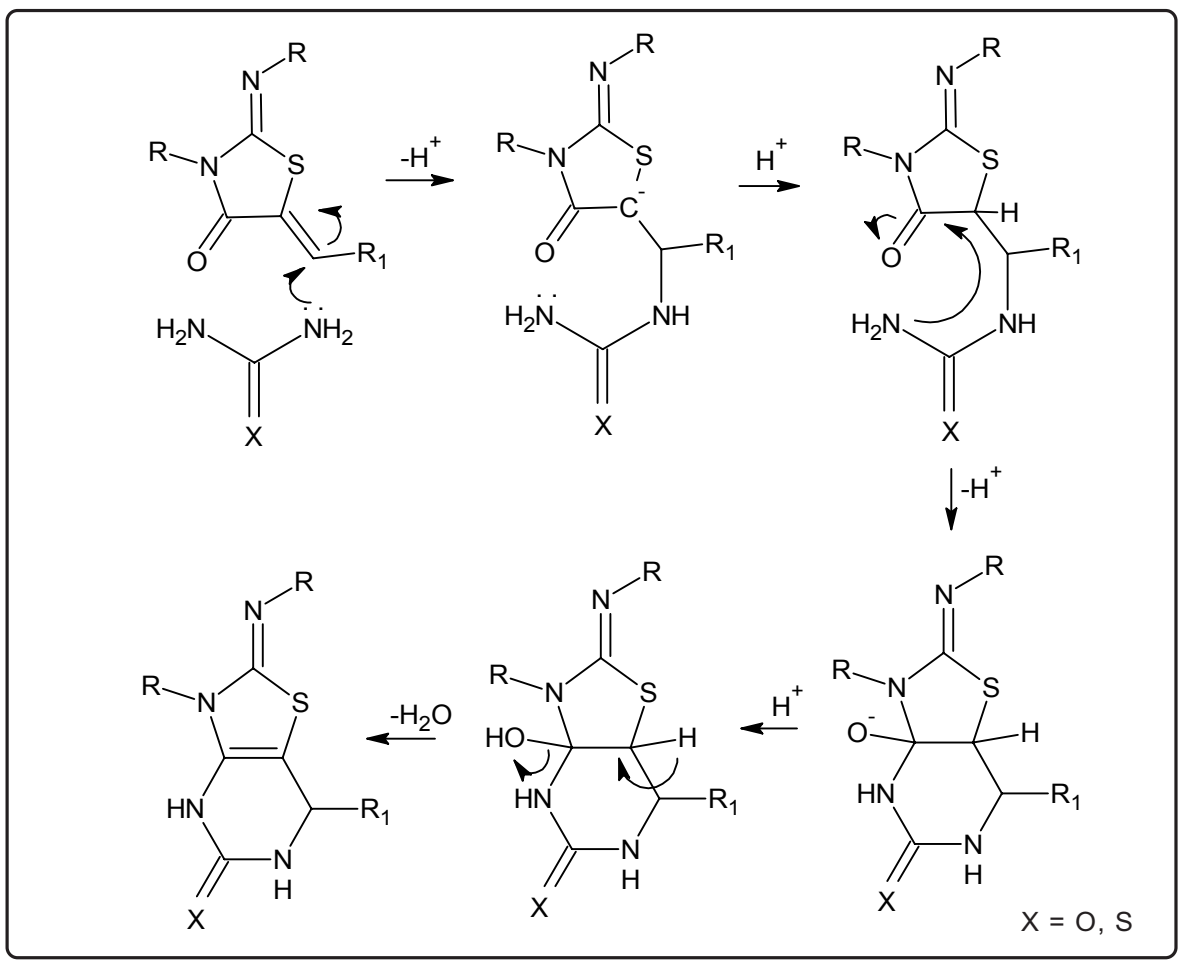
(VII)

3. V. Alagarsamy *et. al.*[313] have prepared pyrimidine from thiosemicarbazide.



(VIII)

MACHANISM

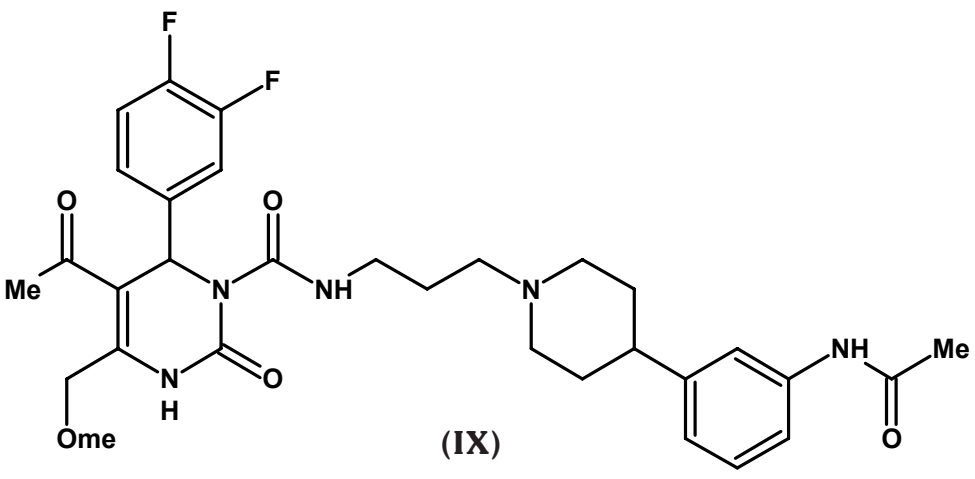


THERAPEUTIC IMPORTANCE

Pyrimidines are excellent reservoir of bioactive substances. In the past years, the literature is enriched with progressive findings about the synthesis and pharmacological action of pyrimidine derivatives. The important activities are as under.

1. Antibacterial[314]
2. Antiviral[315]
3. Antifilarial[316]
4. Antitumor[317]
5. Antiproliferative[318]
6. Antileishmanial[319]
7. Antimalarial[320]
8. Anticancer[321]
9. Antidepressant[322]
10. Herbicidal[323]

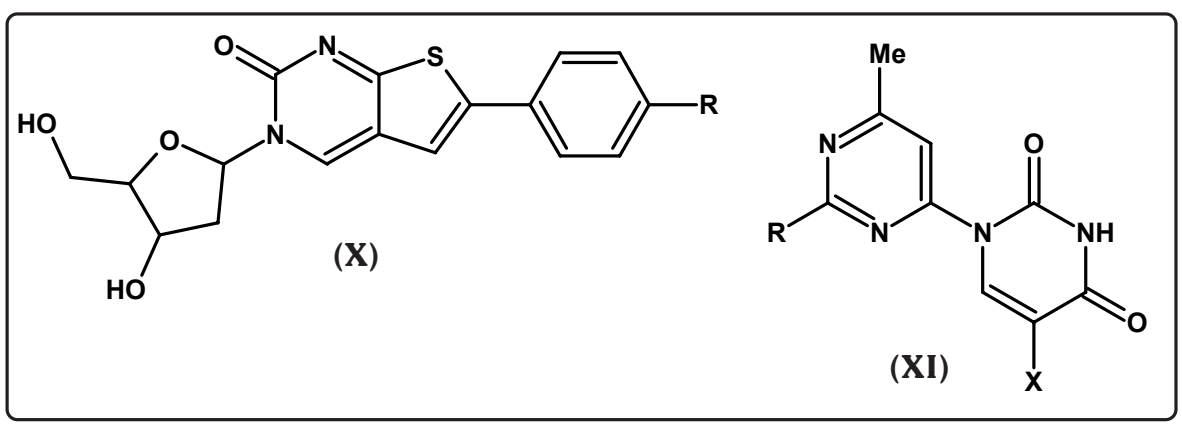
Hodgetts et. al.[324] have discovered pyrimidinone derivatives as selective modulators of CRF-1 receptors. Hamamoto Isami et. al.[325] have reported pyrimidines as pesticides. Drewes Mark Wilhelm et. al.[326] have tested pyrimidines as herbicides. Lagu Bharat et. al.[327] have investigated pyrimidine derivatives (IX) showing antagonist potency for melanine conc. hormone receptor.



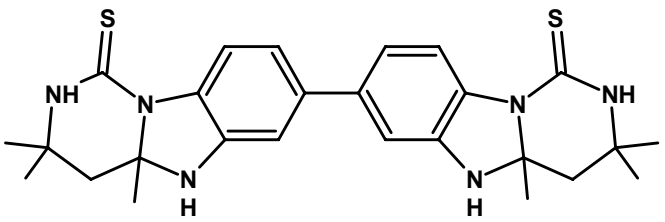
(IX)

Eberie M. *et*. al.[328] have formulated pyrimidines as pesticides. El-Agrody A. M. *et*. al.[329] have studied antimicrobial activity of pyrimidines. Gangjee Aleem *et*. al.[330] have tested pyrimidines for their antimycobacterium activity. Veerachamy A. *et*. al.[331] have reported pyrimidines as antihistaminic agent. Some pyrimidine derivatives possessing antiviral activity have been synthesised by Vadim A. M. *et*. al.[332], David L. Evers *et*. al.[333], Frank Staedtler *et*. al.[334], Nurolaini K. *et*. al.[335] and Dana H. *et*. al.[336] Jolanta *et*. al.[337] have discovered pyrimidine derivatives and studied their antitumor activity. Annette Angell *et*. al.[338] have synthesised pyrimidines (X) and tested them as antiviral agent.

Miroslav Otmar *et*. al.[339] have discovered pyrimidines possessing antiproliferative activity. Antonia Nikitenko *et*. al.[340] have prepared pyrimidine derivatives useful as respiratory syncytial virus (RSV) inhibitors. Gergely Keszler *et*. al.[341] have reported pyrimidines as Tyrosine Kinase inhibitors. James Kempson *et*. al.[342] have demonstrated pyrimidines as phosphodiesterase (PDE-7) inhibitors. Botta M. *et*. al.[343] have formulated pyrimidines as anti-HIV-1 agents. Khachatryan V. E. *et*. al.[344] have synthesised oxopyrimidines (XI) as antitumor agents.



Recently, S. K. Hadjikou *et*. al.[345] have discovered pyrimidines showing antitumor activity. Anu Agarwal *et*. al.[346] have prepared pyrimidines possessing antimalarial activity. Katsuhide Kamer *et*. al.[347] have documented remarkable neuroprotective activity of pyrimidines. Sham M. Sondhi *et*. al.[348] have synthesised thiopyrimidines (XII), (XIII), (XIV) and (XV) and reported their anti-inflammatory, analgesic and proten kinase inhibitory activities.



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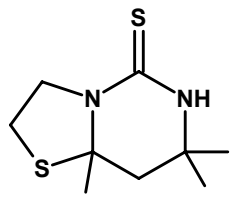
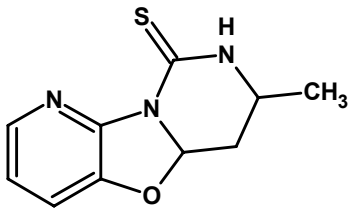
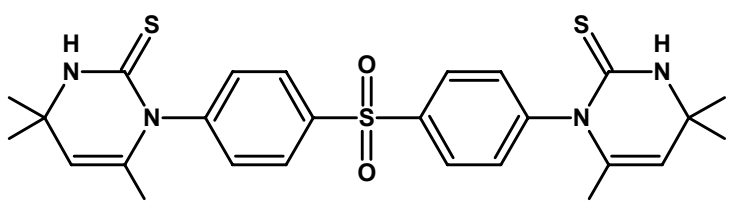


(XIII)

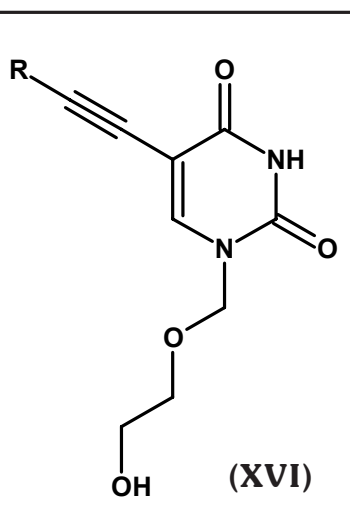


(XIV)

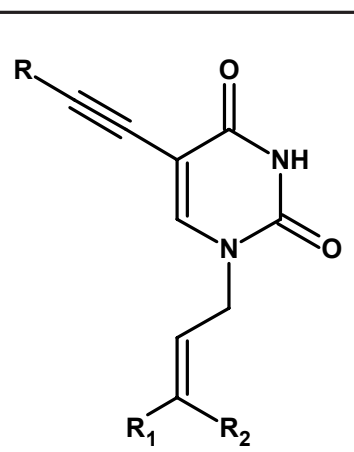


(XV)

Frank Biittner et. al.[349] have synthesised pyrimidines and evaluated for their antimicrobial and cytotoxic activities. Yasushi M. et. al.[350] have discovered some new pyrimidine derivatives and reported them as anticancer agents. Naveen Chandra et. al.[351] have screened pyrimidines for their antileishmanial activity. Richard J. et. al.[352] have prepared pyrimidines as adenosine kinase inhibitor. S.Chandrasekaran et. al.[353] have studied antibacterial activity of some newly synthesised pyrimidines. Brian A. Johus et. al.[354] have investigated pyrimidines as antiherpetics. Franck Amblard et. al.[355] have synthesised oxopyrimidines (XVI) and (XVII) possessing antiviral activity.



(XVI)



(XVII)

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

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

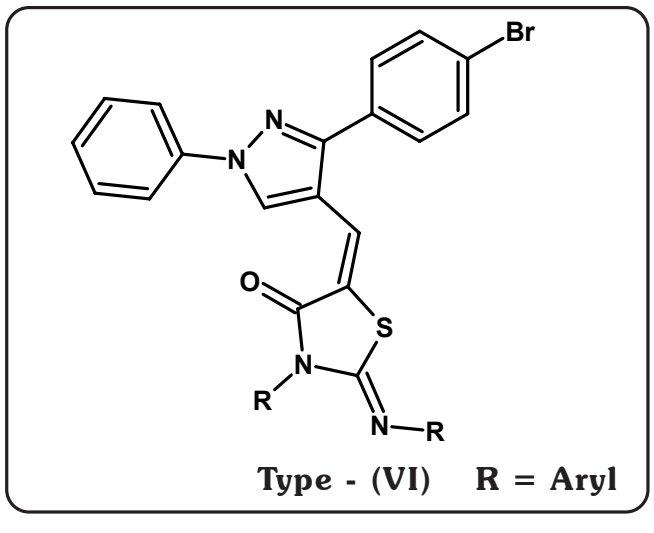
SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-(1',N-PHENYL-3'-p-BROMOPHENYL-PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5,-d]-PYRIMIDINES

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

SECTION-I

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

Arylidenes are associated with broad spectrum of pharmacological activity and it is a good synthon for various heterocyclic rings. With a view to obtaining compounds having better therapeutic activities, we have synthesied 2-arylamino-3-N-aryl-5-[1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino]-4-thiazolidinones by the condensation of 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole with various thiazolidinone derivatives.



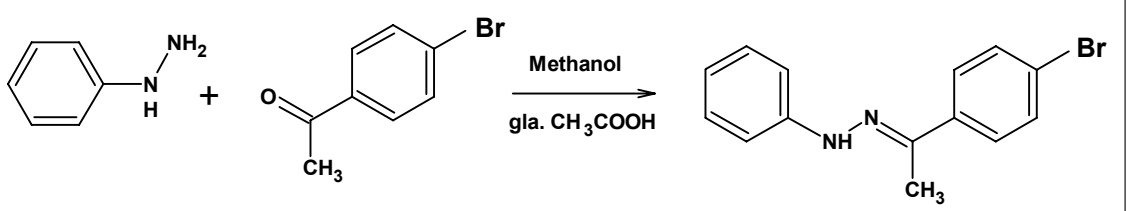
Type - (VI) R = Aryl

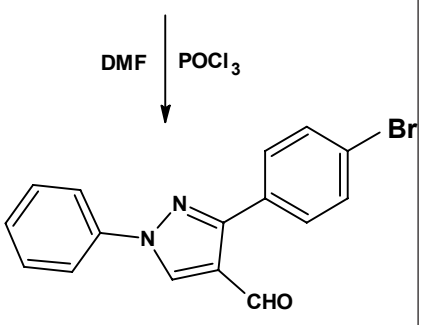
The constitution of the synthesised compounds have been supported by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

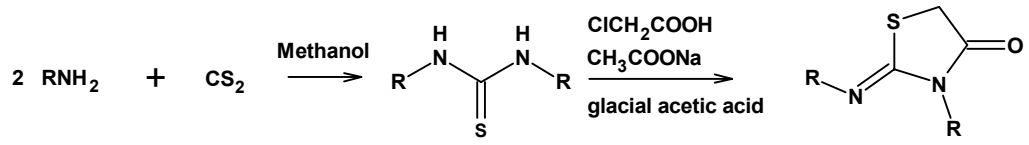
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 6.

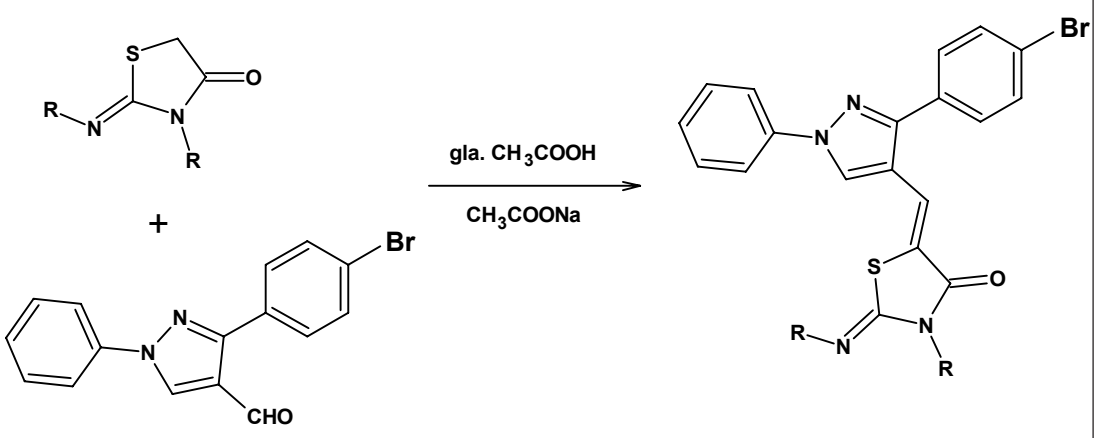
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** H_{37} ***Rv*** at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME





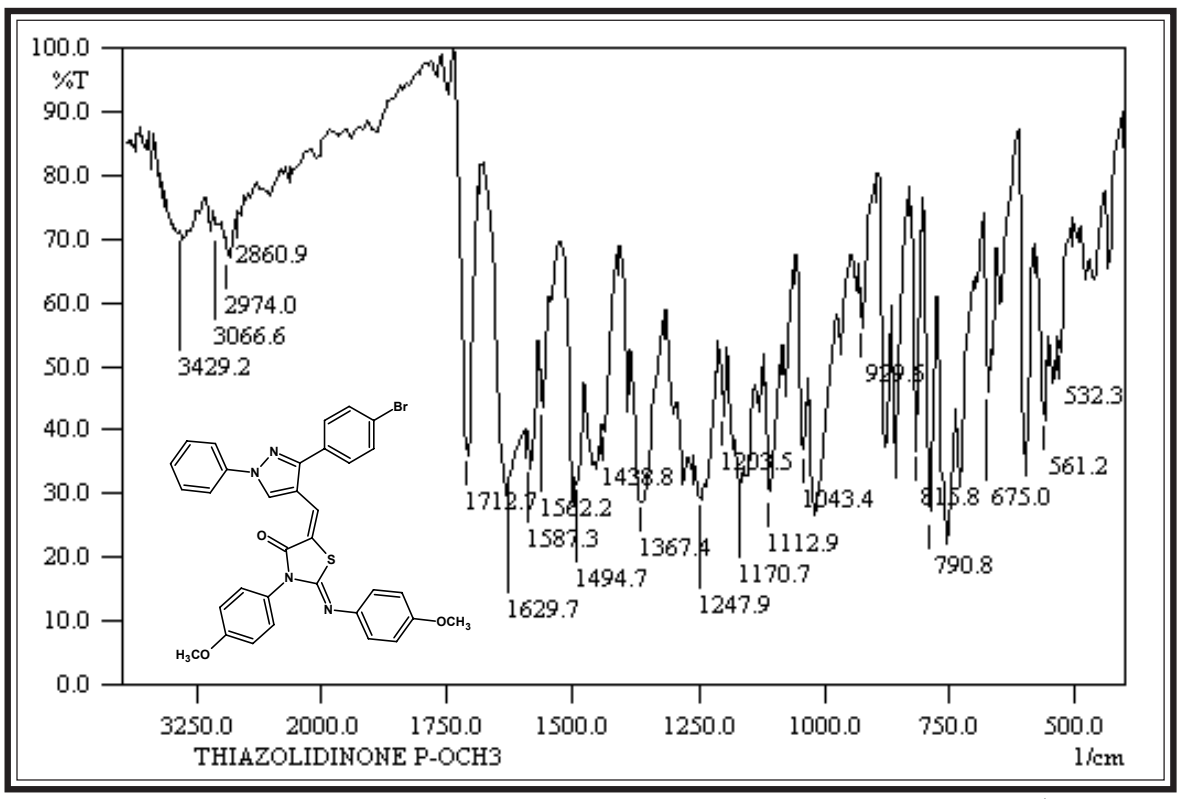




Type - (VI)

R = Aryl

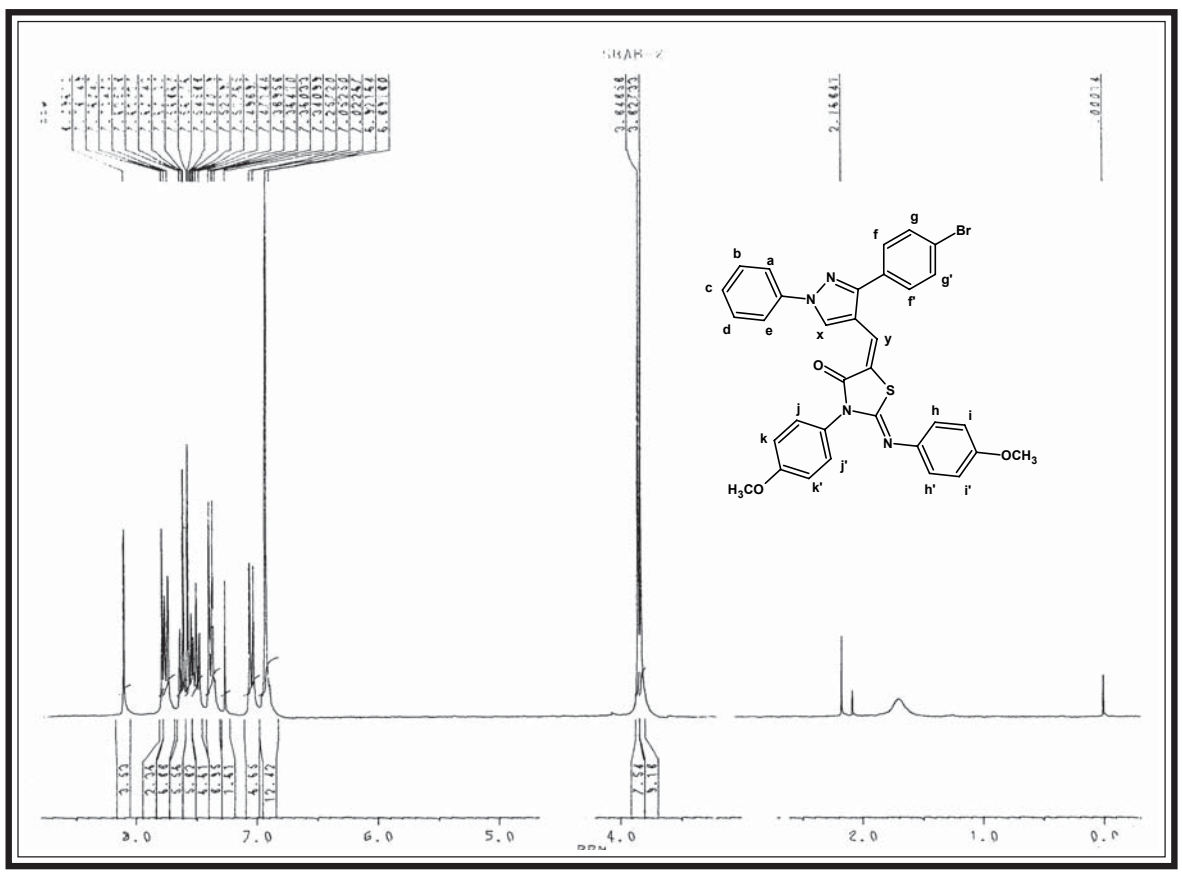
IR SPECTRAL STUDY OF 2-p-ANISYLIMINO-3,N-p-ANISYL-5-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONE



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.)	2974	2975–2950	498
$-CH_3$	C – H str (sym.)	2860	2880–2860	"
	C – H i.p. (def.)	1438	1470–1435	"
	C – H o.o.p (def.)	1367	1385–1370	"
Aromatic	C – H str.	3066	3080–3030	503
	C = C str.	1562	1585–1480	"
	C – H i.p. (def.)	1112	1125–1090	"
		1043	1070–1000	"
	C – H o.o.p (def.)	815	835–810	"
Pyrazole	C = N str.	1629	1630–1590	499
moiety	C – N str.	1203	1230–1020	"
	C – Br str.	561	600–500	498
Thiazolidinone	C = O str.	1712	1760–1655	502
ring	C – S – C str.	675	700–600	"
	C – N str.	1170	1220–1020	"
	C = N str.	1587	1640–1590	"
	N – H str.	3429	3500–3350	"

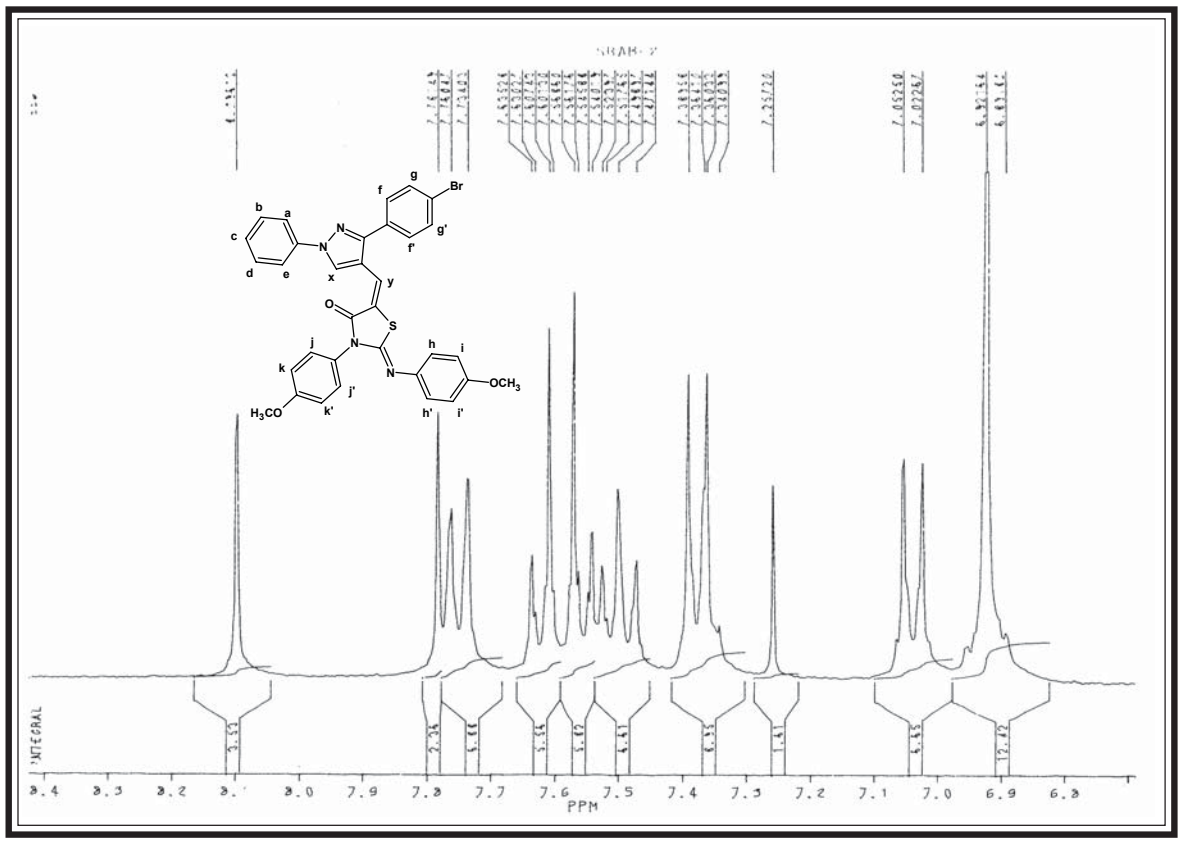
PMR SPECTRAL STUDY OF 2-(p-ANISYLIMINO)-3-N-p-ANISYL-5-(1'-N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL-METHINO)-4-THIAZOLIDINONE



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.82		3H	singlet	Ar-OCH_3
2.	3.84		3H	singlet	Ar-OCH_3
3.	6.92		4H	doublet	Ar-Hii', Ar-Hkk'
4.	7.03	Jhi=9	2H	doublet	Ar-Hhh'
5.	7.34-7.38		2H + 1H	doublet	Ar-Hff'+Ar-Hc
6.	7.47-7.51		2H	triplet	Ar-Hb,d
7.	7.54-7.56	Jgf=8.4	2H	doublet	Ar-Hgg'
8.	7.60-7.63	Jjk=8.4	2H	doublet	Ar-Hjj'
9.	7.73-7.76		2H	doublet	Ar-Ha,e
10.	7.76		1H	singlet	-CHy
11.	8.09		1H	singlet	Ar-Hx

EXPANDED AROMATIC REGION



SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 5/11/2005 1:54:28 PM
Sample Name : SB-14
Sample ID : SB-14
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-14.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune6.qgt

Line#:1 R.Time:11.9(Scan#:1392)
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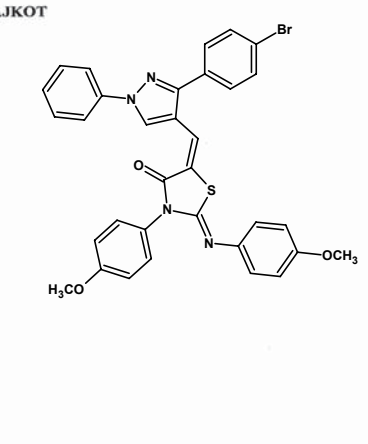
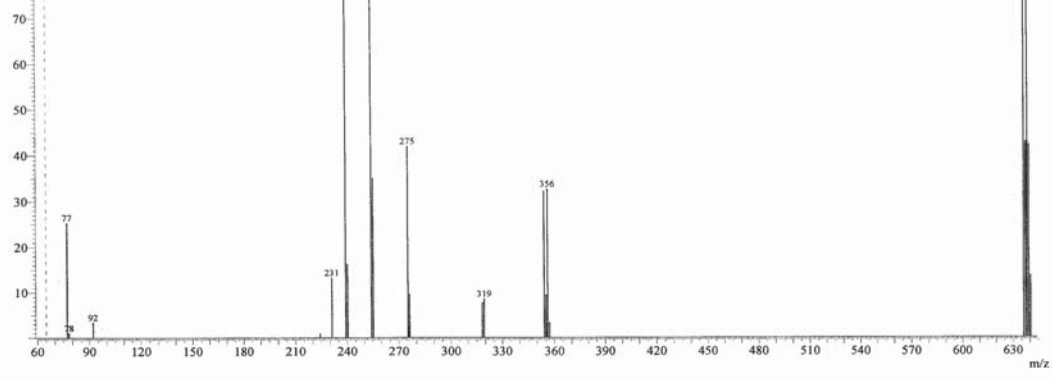
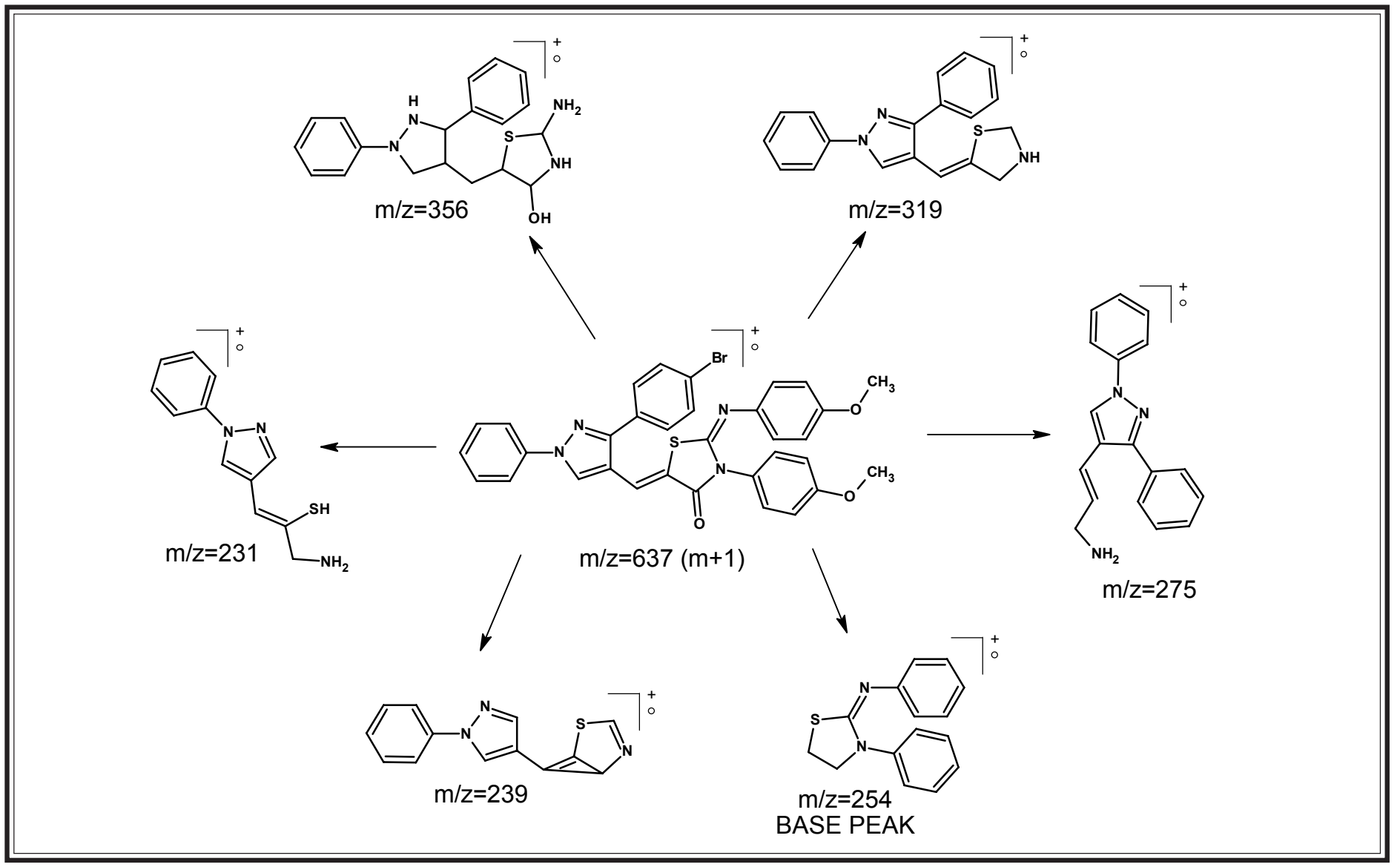
RawMode:Averaged 11.7-12.0(1370-1410)
BG Mode:Averaged 7.5-8.4(865-971)
intensity






m/z=356
m/z=319
m/z=231
m/z=637 (m+1)
m/z=275
m/z=239
m/z=254
BASE PEAK

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONES.

[A] Synthesis of N-Phenylamine-α-methyl-α-p-bromophenyl azomethine[356]

A mixture of phenylhydrazine (1.08, 0.01M) and 4-bromoacetophenone (1.99g, 0.01M) in absolute ethanol was refluxed in waterbath for 2 hrs. in presence of 1 ml glacial acetic acid. Product obtained after cooling was crystalized from absolute ethanol yield 2.43g, 99%; m.p. 39°C. ($C_{14}H_{13}BrN_2$ Required C : 58.15; H, 4.53; N, 9.69; Found C : 58.11; H, 4.57; N, 9.73%)

TLC solvent system : Acetone : Benzene (0.5 : 9.5).

[B] Synthesis of 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole

A compound N-phenylamine-α-methyl-α-p-bromophenyl-azomethine (2.88g, 0.01M) was added in a mixture to vilsmeier-Haack reagent (prepared by dropwise addition of 3 ml $POCl_3$ in ice cooled 25 ml DMF) and refluxed for 6 hrs. The reaction mixture was poured onto crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from methanol. Yield, 88%, 2.6g ; m.p. 126°C. ($C_{16}H_{11}BrN_2O$ Required C : 58.74; H: 3.39; N: 8.56 Found C: 58.71 ; H: 3.36; N: 8.52%).

TLC solvent system : Acetone : Benzene (2 : 8).

[C] Sythesis of N^1, N^3-Bis-p-anisyl thioura[357]

A mixture of p-anisidine (24.6g, 0.2M), carbon disulphide (7.6ml, 0.1M) and absolute alcohol (20 ml) was heated on waterbath for 5-6 hrs. On completion of reaction the excess of carbon disulphide and alcohol was removed by distilation. The product was treated with dilute hydrochloric acid to remove excess of amine present and crude product was isolated and crysallised in rectified spirit. Yield, 20.9g, 85%; m.p. 123°C. ($C_{15}H_{16}N_2O_2S$; Found : C, 62.48%; H, 5.59%; N, 9.71g Required : C, 62.46%; H, 5.54%; N, 9.73%).

TLC solvent system : Ethylacetate : Hexane (2 : 8).

[D] Synthesis of 2-p-Anisylimino-3-p-anisyl-5H-4-thiazolidinones[358]

A mixture of N^1,N^3-bis-p-anisyl thiourea (2.64, 0.01M) and chloroacetic acid (0.94, 0.01M) in glacial acetic acid (15 ml) was refluxed with fused sodium acetate (1.25g, 0.15M) for 8 hrs. The reaction product was poured onto crushed ice, kept overnight, crude product was isolated, crystallised from acetic acid. Yield 2.05g, 78%; m.p. 178°C ($C_{17}H_{16}N_2O_3S$: Found : C, 62.18%; H, 4.91%; N, 8.53%; Required : C, 62.17%; H, 4.47%; N, 8.52%).

TLC solvent system : Acetone : Benzene (0.5 : 9.5).

[E] Synthesis of 2-p-Methoxyphenylimino-3-p-methoxyphenyl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-4-thiazolidinone

A mixture of 2-p-methoxyphenylimino-3-p-methoxyphenyl-5H-4-thiazolidinone (3.28g, 0.01M) 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole (3.26g, 0.1M) and fused sodium acetate (1.25g, 0.015g) was refluxed in glacial acetic acid (15 ml) for 10 hrs. Cooled, poured onto crushed ice and treat with ammonia to remove excess of glacial acetic acid. The solid thus obtained was filtered, dried and crystallised from acetic acid. Yield, 2.3g, 71%, m.p. 222°C ($C_{33}H_{25}BrN_4O_3S$: Required C: 62.17; H: 3.95; N: 8.79; Found C: 62.20; H: 3.91; N: 8.83%).

TLC solvent system : Ethyl acetate : Hexane (1 : 9)

Similarly, other thiazolidinones were prepared. The physical data are recorded in Table No. 6.

[F] Antimicrobial activity of 2-Arylimino-3-aryl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-4-thiazolidinones

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

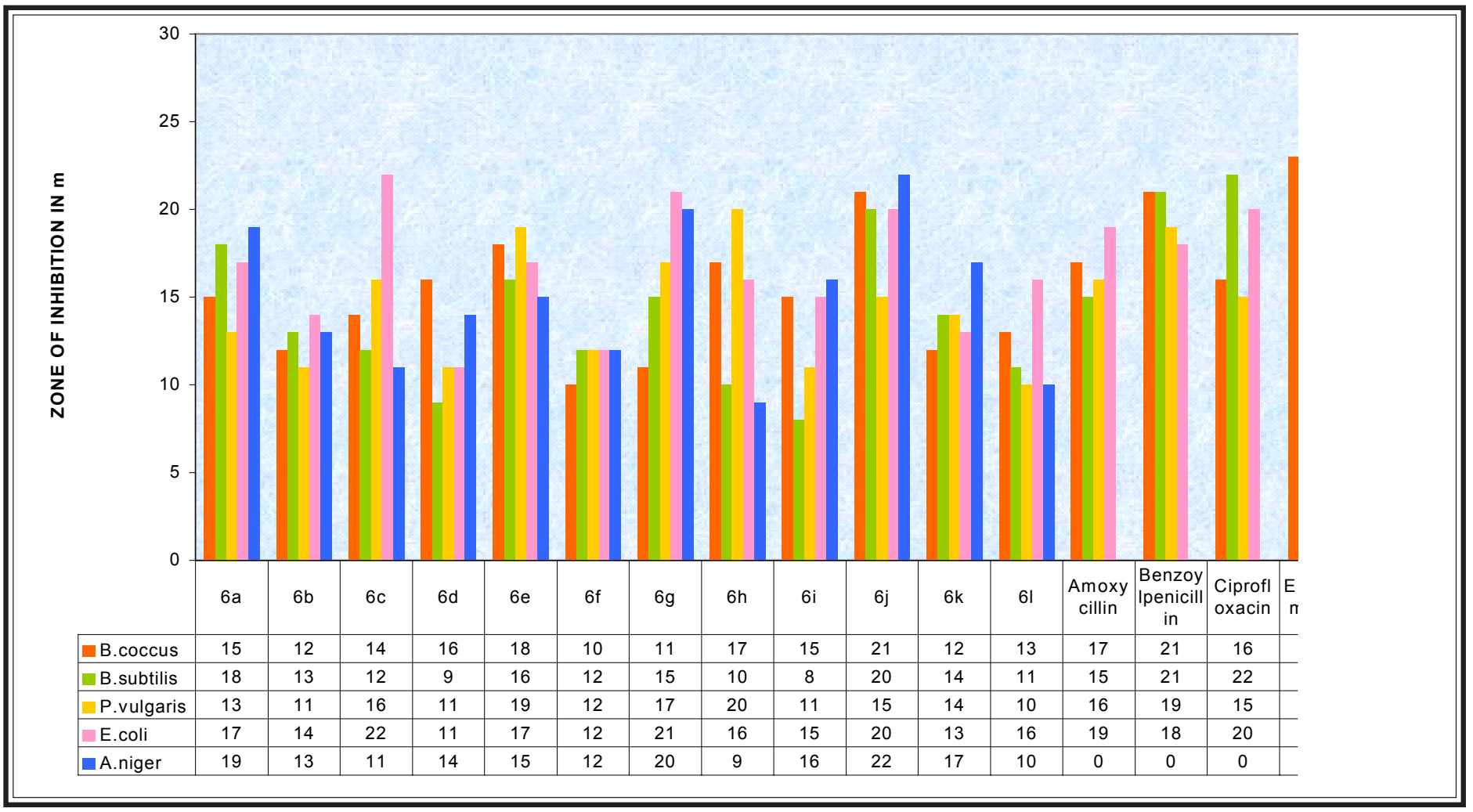
Antitubercular screening of the compounds of type (VI) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 6a.

TABLE NO. 6 : PHYSICAL CONSTANTS OF 2-ARYLIMINO-3,N-ARYL-5-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYLMETHINO)-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-	$C_{32}H_{21}BrN_4OS$	577.4	183	0.64	54	9.70	9.74
6b	2-CH_3-C_6H_4-	$C_{33}H_{25}BrN_4OS$	605.5	178	0.59	65	9.25	9.21
6c	4-CH_3-C_6H_4-	$C_{33}H_{25}BrN_4OS$	605.5	254	0.62	62	9.25	9.29
6d	4-OCH_3-C_6H_4-	$C_{33}H_{25}BrN_4O3S$	637.5	222	0.60	71	8.79	8.83
6e	4-Cl-C_6H_4-	$C_{31}H_{19}BrCl_2N_4OS$	646.3	180	0.58	56	8.67	8.63
6f	4-F-C_6H_4-	$C_{31}H_{19}BrF_2N_4OS$	613.4	152	0.63	79	6.19	6.15
6g	4-NO_2-C_6H_4-	$C_{31}H_{19}BrN_6O_5S$	667.4	130	0.71	72	12.59	12.63
6h	4-COOH-C_6H_4-	$C_{33}H_{21}BrN_4O_5S$	665.5	136	0.67	57	8.42	8.46
6i	3-Cl,4-F-C_6H_3-	$C_{31}H_{17}BrCl_2F_2N_4OS$	682.3	>280	0.66	82	8.21	8.20
6j	2,4-di-Cl-C_6H_3-	$C_{31}H_{17}BrCl_4N_4OS$	715.2	188	0.57	66	7.83	7.80
6k	2,5-di-Cl-C_6H_3-	$C_{31}H_{17}BrCl_4N_4OS$	715.2	190	0.59	59	7.83	7.87
6l	3,4-di-Cl-C_6H_3-	$C_{31}H_{17}BrCl_4N_4OS$	715.2	192	0.70	67	7.83	7.79

*TLC Solvent System :Ethyl acetate : Hexane (1 : 9)

GRAPHICAL CHART NO. 6 : 2-ARYLIMINO-3,N-ARYL-5-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONES



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	E m
B.coccus	15	12	14	16	18	10	11	17	15	21	12	13	17	21	16	
B.subtilis	18	13	12	9	16	12	15	10	8	20	14	11	15	21	22	
P.vulgaris	13	11	16	11	19	12	17	20	11	15	14	10	16	19	15	
E.coli	17	14	22	11	17	12	21	16	15	20	13	16	19	18	20	
A.niger	19	13	11	14	15	12	20	9	16	22	17	10	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

It has been observed from the experimental data that all the thiazolidinones of type (VI) markedly inhibited the growth of Gram positive and also Gram negative bacteria.

However, comparatively significant activity was observed in compounds with R=4-chlorophenyl and 2,4-dichlorophenyl against ***B.coccus*** and R=phenyl and 2,4-dichlorophenyl against ***B.subtilis***. Compounds bearing R=4-chlorophenyl, 2,5-dichlorophenyl showed good activity against ***P.vulgaris***. Maximum activity was observed in compounds bearing R=4-methylphenyl, 4-nitrophenyl and 2,4-dichlorophenyl against ***E.coli***.

Antifungal activity :

All the compounds were active against ***A.niger***. Maximum activity was shown by the compounds bearing R=4-nitrophenyl and 2,4-dichlorophenyl.

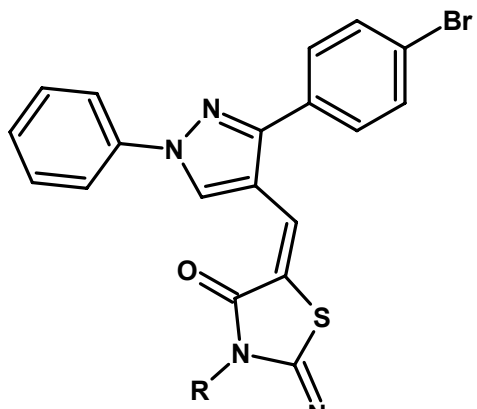
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

All the compounds of type (VI) displayed less activity against ***Mycobacterium tuberculosis $H_{37}Rv$.***

The antitubercular activity data have been compared with standard drug Rifampin.

TABLE NO. 6a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

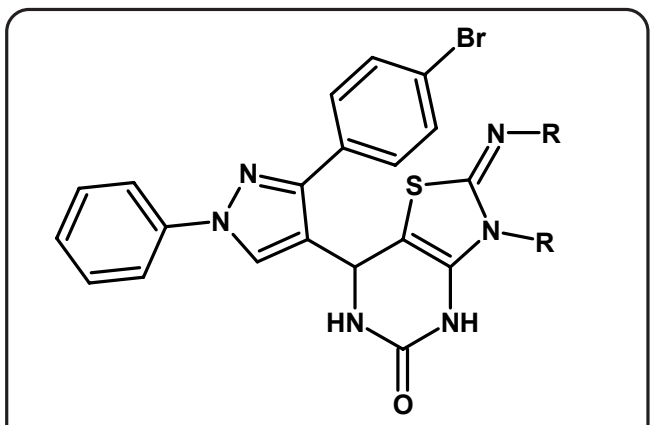
Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*Mtb Strain*	*Mic µg/ml*	*% Inhib*	*Activity*	*Comment*
295467	BSA-89	C_6H_4-	Alamar	$H_{37}Rv$	>6.25	26	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295468	BSA-90	2-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	23	-	
295469	BSA-91	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295470	BSA-92	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295471	BSA-93	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	28	-	"
295472	BSA-94	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	18	-	"
295473	BSA-95	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	5	-	"
295475	BSA-97	2,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295476	BSA-98	2,5-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295477	BSA-99	3,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	7	-	"
295478	BSA-100	4-COOH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12	-	"

SECTION-II

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

Many pyrimidinone derivatives are associated with diversified biological properties. It was thought of interest that a pyrimidinone ring couple to pyrazole nucleus and thioazolidinone nucleus, the resulting compounds may possess significant biological potency. Pyrimidinones of type (VII) have been prepared by the condensation of 2-arylimino-3-p-aryl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolyl methino)-4-thiazolidinone with urea in glacial acetic acid with fused sodium acetate.



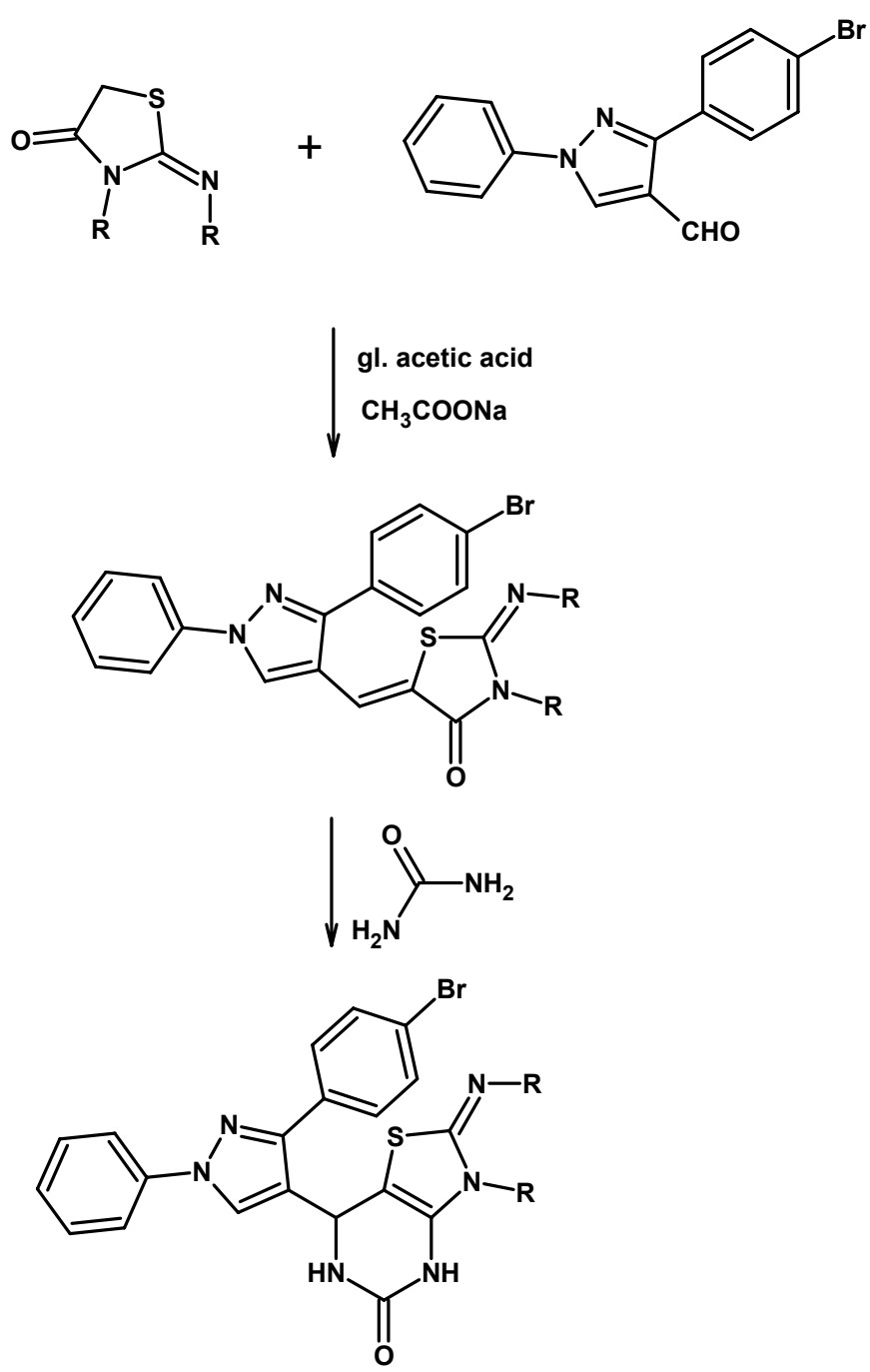
Type - (VII) R = Aryl

The constitution of the newly synthesised compounds have been supported by 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.

All the compounds 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. The biological activities of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 7.

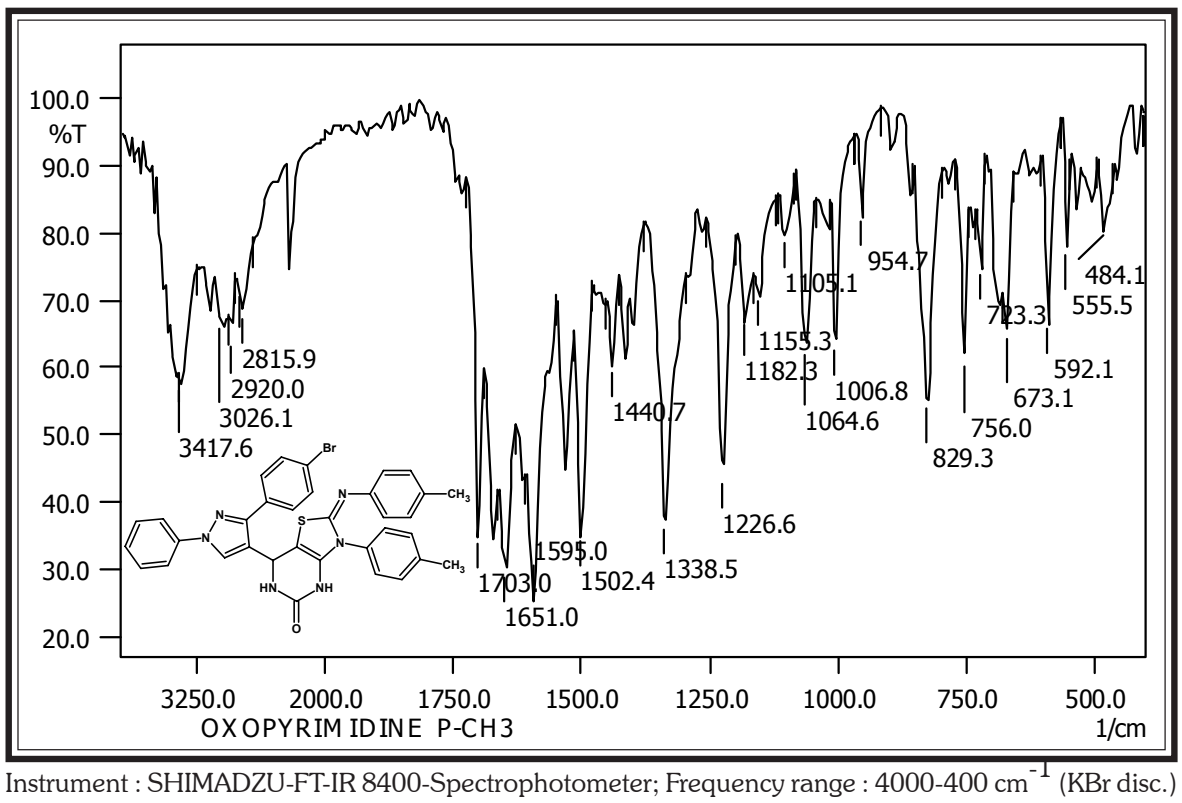
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** H_{37} ***Rv*** at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME



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

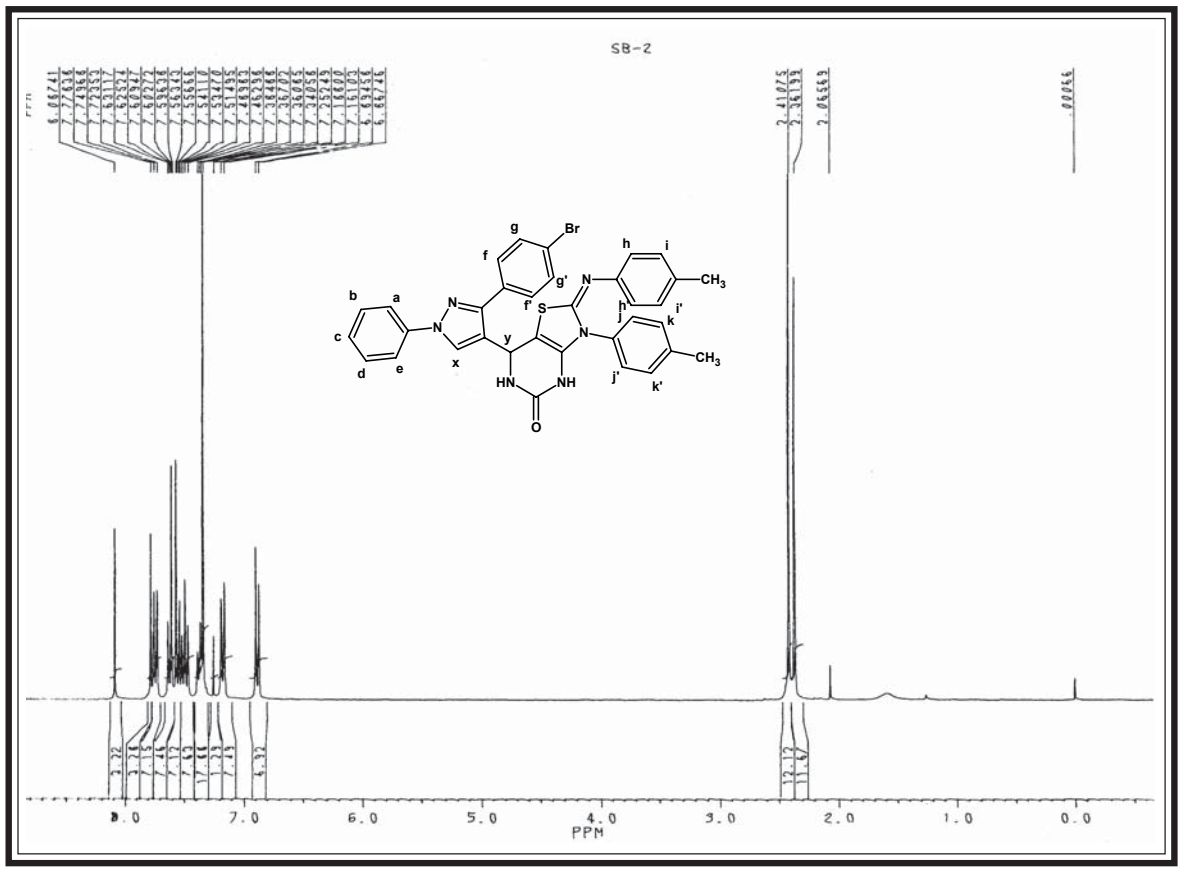
IR SPECTRAL STUDY OF 6-p-TOLYLIMINO-7,N-p-TOLYL-2-OXO-4-(1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINONE-(4,5-d) PYRIMIDINE



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.)	2920	2975–2950	498
$-CH_3$	C – H str (sym.)	2875	2880–2860	"
	C – H i.p. (def.)	1440	1470–1435	"
	C – H o.o.p (def.)	1338	1385–1370	"
Aromatic	C – H str.	3026	3080–3030	503
	C = C str.	1502	1585–1480	"
	C – H i.p. (def.)	1105	1125–1090	"
		1006	1070–1000	"
	C – H o.o.p (def.)	829	835–810	"
Pyrazole	C = N str.	1595	1610–1590	499
moiety	C – N str.	1182	1230–1020	"
	C – Br str.	592	600–500	498
Pyrimidinone	C = O str.	1703	1750–1600	506
ring	N – H str.	3417	3500–3350	"
	C – N str.	1651	1650–1550	"
	C – S – C str.	756	800–700	"
Ether	C – S – C str (asym.)	1226	1275–1200	"
	C – S – C str. (asym.)	1064	1075–1020	"

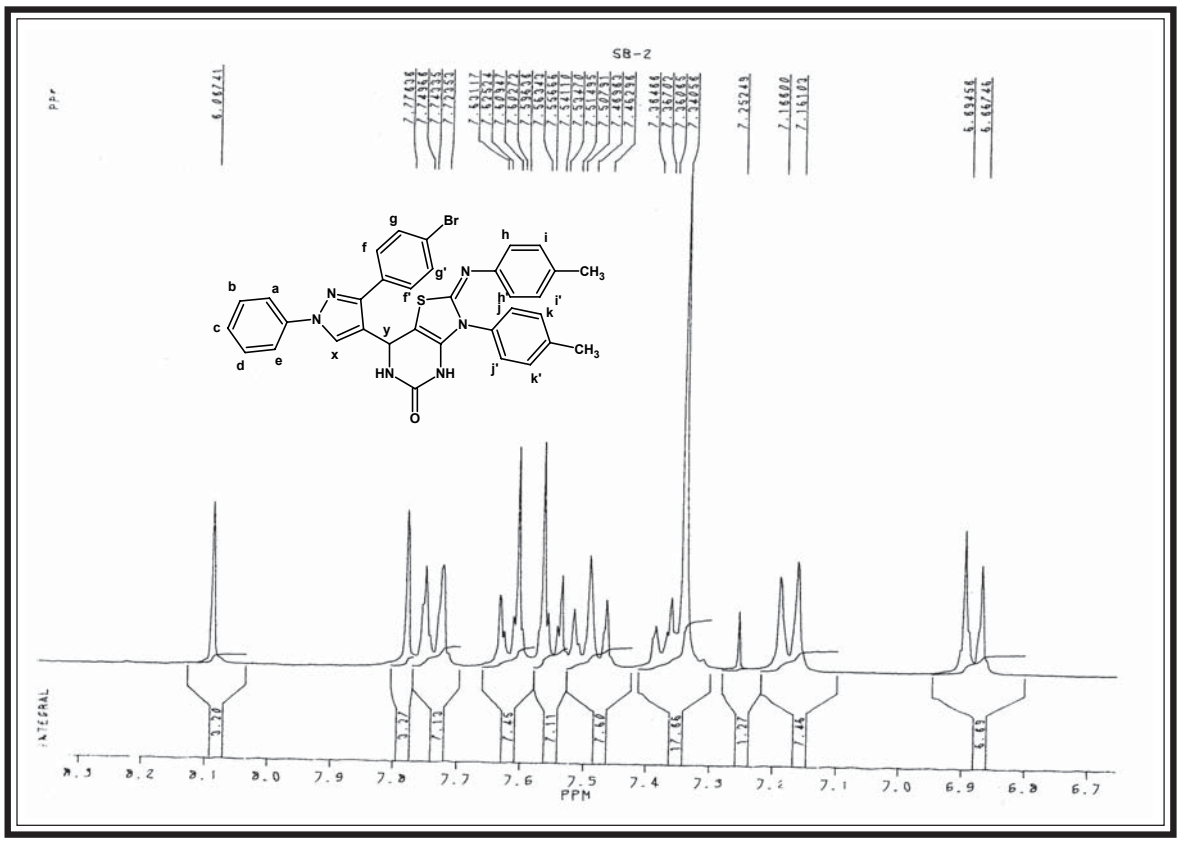
PMR SPECTRAL STUDY OF 6-p-TOLYLIMINO-7,N-p-TOLYL-2-OXO-4-(1',N-PHENYL-3'-BROMOPHENYL PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINO-[4,5-d]-PYRIMIDINE

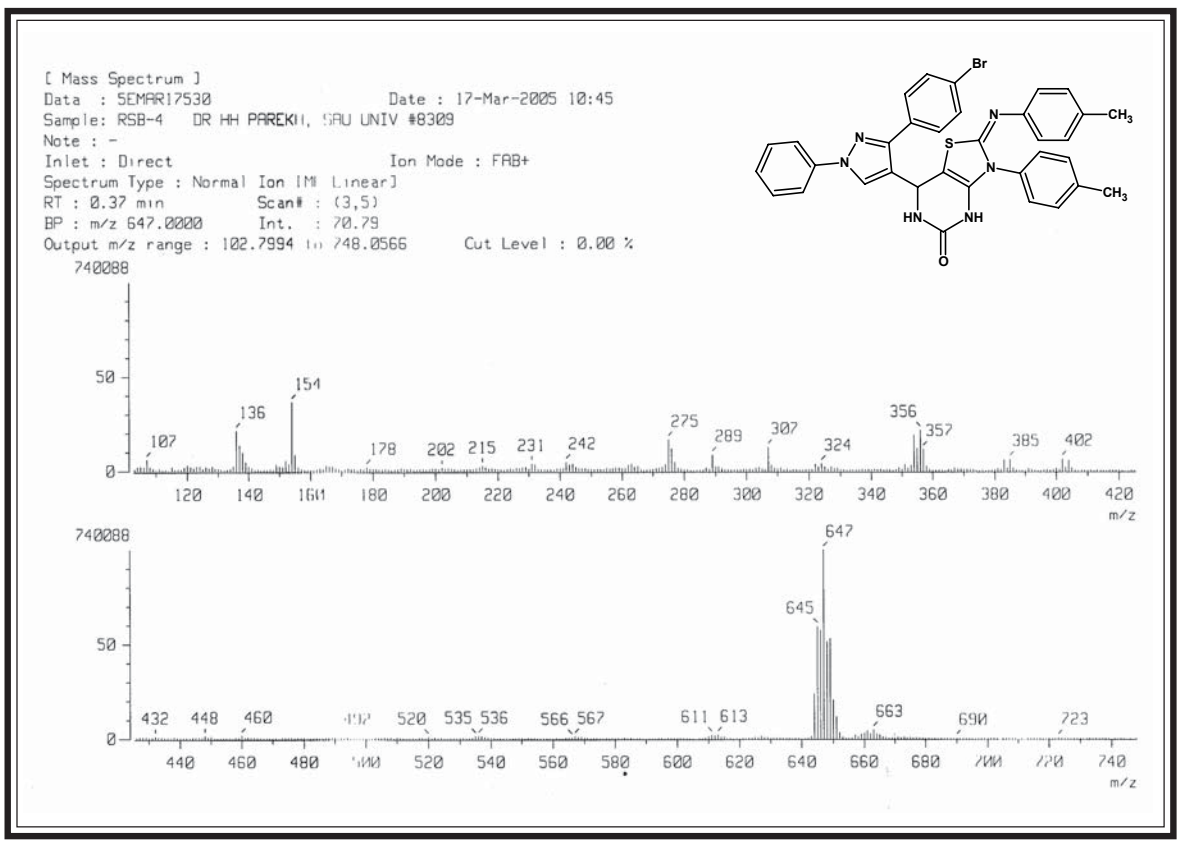


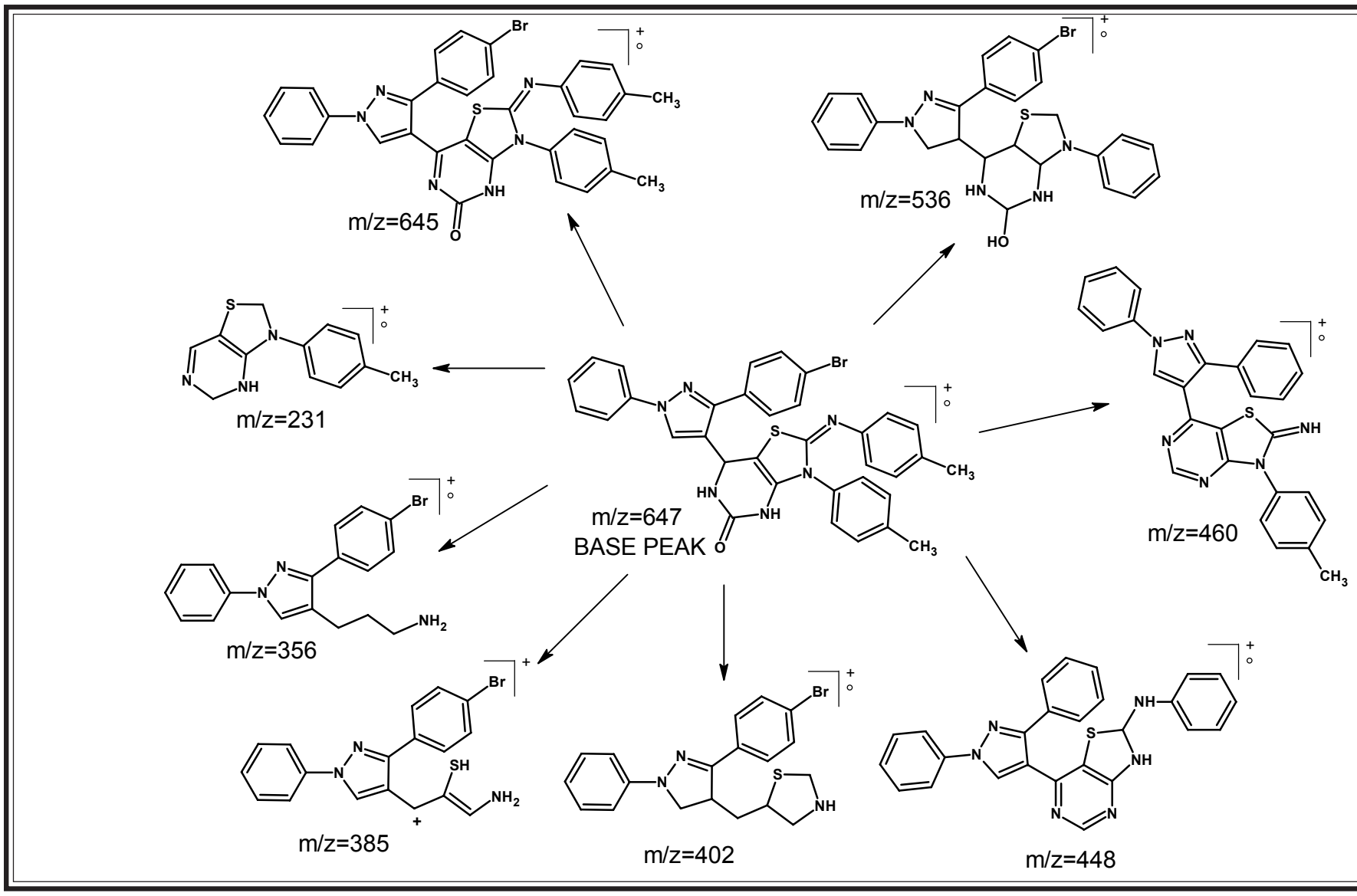
Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	2.36		3H	singlet	Ar-CH_3
2.	2.41		3H	singlet	Ar-CH_3
3.	6.86-6.89	Jkj=9	2H	doublet	Ar-Hkk'
4.	7.16-7.18	Jih=8.1	2H	doublet	Ar-Hii'
5.	7.34-7.38		5H	multiplet	Ar-Hc,Ar-Hhh' Ar-Hff'
6.	7.48		2H	triplet	Ar-Hb,d
7.	7.53-7.56	Jgf=8.7	2H	doublet	Ar-Hgg'
8.	7.60-7.63	Jjk=8.7	2H	doublet	Ar-Hjj'
9.	7.74		2H	doublet	Ar-Ha,e
10.	7.77		1H	singlet	-CHy
11	8.08		1H	singlet	Ar-Hx

EXPANDED AROMATIC REGION



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EXPERIMENTAL

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

[A] Sythesis of 2-p-Methylphenylimino-3-p-methylphenyl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)4-thiazolidinone

See, [B] Part-I, Section-I [E].

[B] Synthesis of 6-p-Methylphenylimino-7,N-p-methylphenyl-2-oxo-4-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-1,2,3,4-tetrahydro thiazolidino-[4,5-d] pyrimidine

A mixture of 2-p-methylphenylimino-3-p-methylphenyl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-4-thiazolidinone (6.05, 0.01M) and urea (0.60g, 0.01M) were taken in glacial acetic acid (20 ml) with fused sodium acetate (1.25g, 0.015g). The reaction mixture was refluxed for 12 hrs. Cooled and poured onto crushed ice. The solid thus obtained was filtered, dried and product was crystallised from methanol-DMF. Yield, 4.4g, 74% m.p. 248°C, ($C_{34}H_{27}BrN_6OS$: Required : C: 63.06; H: 4.20; N: 12.98; Found : C: 63.02; H: 4.24; N: 12.94%)

TLC solvent system : Acetone : Benzene (2 : 8).

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

[C] Antimicrobial activity of 5-Arylimino-7,N-aryl-2-oxo-4-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-1,2,3,4-tetrahydro-thiazolidinon-[4,5-d]-pyrimidines

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

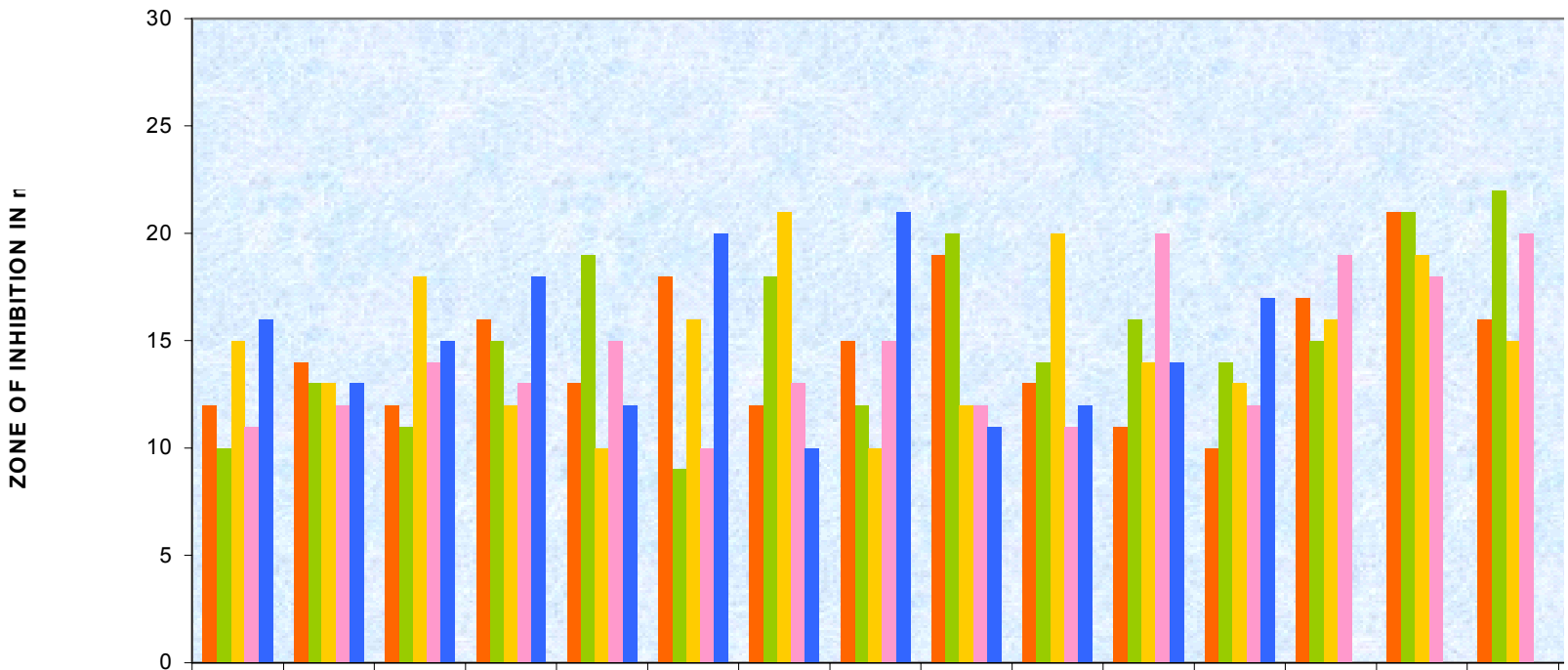
Antitubercular screening of the compounds of type (VII) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 7a.

TABLE NO. 7 : PHYSICAL CONSTANTS OF 6-ARYLIMINO-7,N-ARYL-2-OXO-4-[1',N-PHENYL-3'-p-BROMOPHENYL 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-	$C_{32}H_{23}BrN_6OS$	619.5	280	0.72	59	13.57	13.59
7b	2-CH_3-C_6H_4-	$C_{34}H_{27}BrN_6OS$	647.5	179	0.75	62	12.98	12.96
7c	4-CH_3-C_6H_4-	$C_{34}H_{27}BrN_6OS$	647.5	248	0.69	74	12.98	12.94
7d	4-OCH_3-C_6H_4-	$C_{34}H_{27}BrN_6O_3S$	679.5	226	0.73	55	12.37	12.33
7e	4-Cl-C_6H_4-	$C_{32}H_{21}BrCl_2N_6OS$	688.4	232	0.70	83	12.21	12.25
7f	4-F-C_6H_4-	$C_{32}H_{21}BrF_2N_6OS$	655.5	144	0.74	70	12.82	12.86
7g	4-NO_2-C_6H_4-	$C_{32}H_{21}BrN_8O_5S$	709.5	160	0.71	53	15.79	15.83
7h	4-COOH-C_6H_4-	$C_{34}H_{23}BrN_6O_5S$	707.5	140	0.68	69	11.88	11.84
7i	3-Cl,4-F-C_6H_3-	$C_{32}H_{19}BrCl_2F_2N_6OS$	724.4	196	0.77	72	11.60	11.64
7j	2,4-di-Cl-C_6H_3-	$C_{32}H_{19}BrCl_4N_6OS$	757.3	186	0.67	58	11.10	11.14
7k	2,5-di-Cl-C_6H_3-	$C_{32}H_{19}BrCl_4N_6OS$	757.3	126	0.60	55	11.10	11.8
7l	3,4-di-Cl-C_6H_3-	$C_{32}H_{19}BrCl_4N_6OS$	757.3	194	0.65	66	11.10	11.6

*TLC Solvent System : Acetone : Benzene (2 : 8)

GRAPHICAL CHART NO. 7 : 6-ARYLIMINO-7,N-ARYL-2-OXO-4-(1',N-PHENYL-3'-p-BROMOPHENYL 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	Benzoylpenicillin	Ciprofloxacin
B.coccus	12	14	12	16	13	18	12	15	19	13	11	10	17	21	16
B.subtilis	10	13	11	15	19	9	18	12	20	14	16	14	15	21	22
P.vulgaris	15	13	18	12	10	16	21	10	12	20	14	13	16	19	15
E.coli	11	12	14	13	15	10	13	15	12	11	20	12	19	18	20
A.niger	16	13	15	18	12	20	10	21	11	12	14	17	0	0	0

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

From the experimental data it has been observed that all the compounds of type (VII) were active against Gram positive and Gram negative bacterial species.

It was observed that the compounds showed good activity against Gram positive bacteria. Maximum activity was observed in compounds having R=4-methylphenyl, 4-nitrophenyl, 2,4-dichlorophenyl against ***B.coccus***. The compounds bearing R=4-fluorophenyl and 2,4-dichlorophenyl have fairly inhibited the growth of ***B.subtilis***. Compounds with R=4-carboxyphenyl and 2,5-dichlorophenyl showed highest activity against ***P.vulgaris***. Almost all compounds were found to be inactive against ***E.coli*** except R=3,4-dichlorophenyl.

Antifungal activity :

It has been found that all compounds were moderately active against ***A.niger***. The maximum activity was displayed by the compounds bearing R=3,4-dichlorophenyl against ***A.niger***.

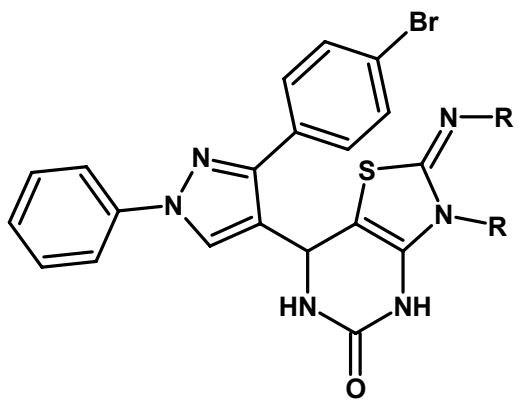
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

All the compounds of type (VII) were found to be less activite against ***Mycobacterium tuberculosis $H_{37}Rv$.***

The antitubercular activity data have been compared with standard drug Rifampin.

TABLE NO. 7a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

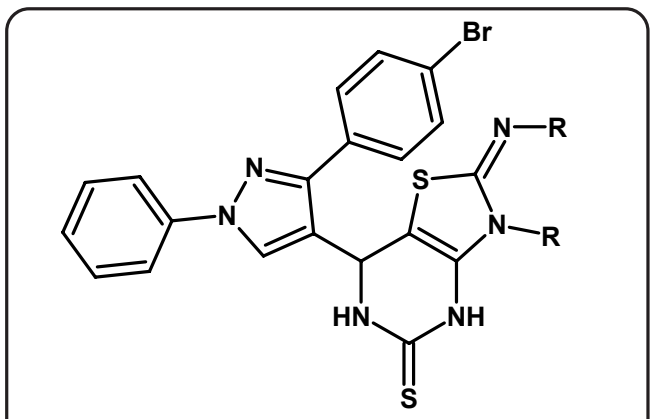
Dr. H. H. Parekh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Assay*	*Mtb Strain*	*Mic µg/ml*	*% Inhib*	*Activity*	*Comment*
295479	BSA-101	C_6H_4-	Alamar	$H_{37}Rv$	>6.25	14	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295480	BSA-102	2-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	28	-	
295481	BSA-103	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295482	BSA-104	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	3	-	"
295483	BSA-105	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	19	-	"
295484	BSA-106	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	25	-	"
295485	BSA-107	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	27	-	"
295486	BSA-108	3-Cl,4-F-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	26	-	"
295487	BSA-109	2,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	19	-	"
295488	BSA-110	2,5-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	8	-	"
295489	BSA-111	3,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	18	-	"
295490	BSA-112	4-COOH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	33	-	"

SECTION-III

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

Thiopyrimidines represent one of the most active classes of the compounds possessing a wide spectrum of biological activities such as significant ***in vitro*** activity against unrelated DNA and RNA viruses including polio and Herper viruses, diuretic, antitubercular spermidical etc. These valid observation led us to synthesise thiopyrimidines of type (VIII) by the condensation of 2-p-arylimino-3-p-aryl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-4-thiazolidinone with thiourea in glacial acetic acid with fused sodium acetate.



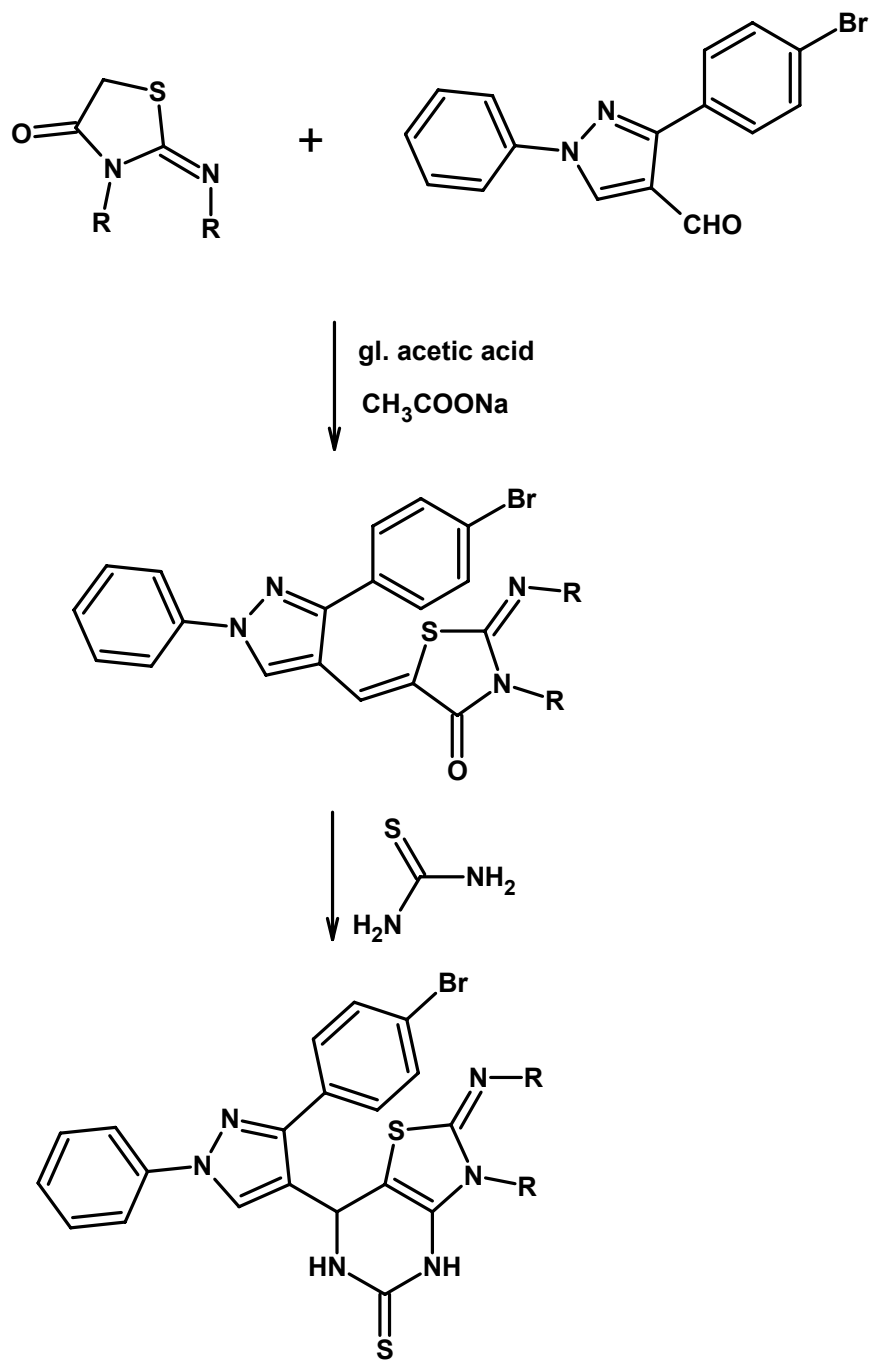
Type - (VIII) R = Aryl

The constitution of the newly synthesised compounds have been supported by 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.

All the compounds 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. The biological activities of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 8.

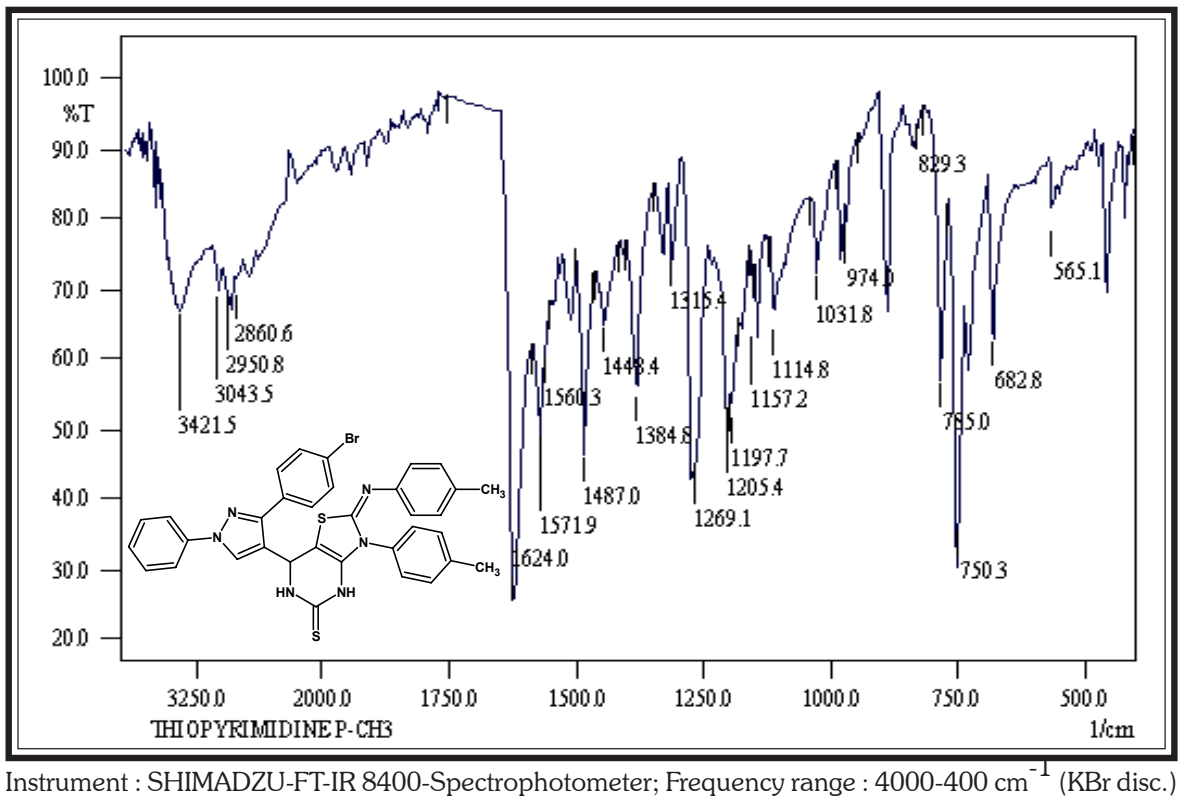
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** H_{37} ***Rv*** at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME



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

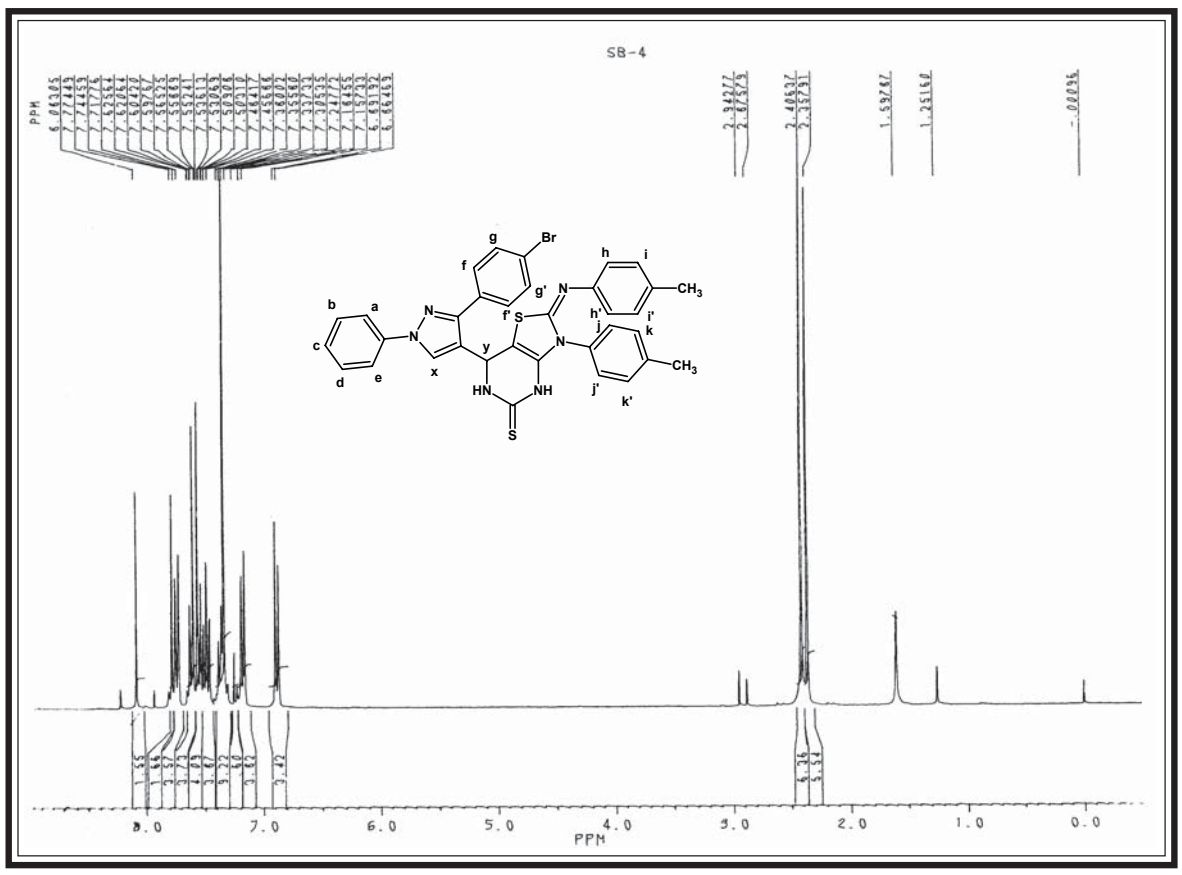
IR SPECTRAL STUDY OF 6-p-TOLYLIMINO-7,N-p-TOLYL-2-THIO-4-(1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINON-[4,5-d]-PYRIMIDINE



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.)	2950	2975–2950	498
$-CH_3$	C – H str (sym.)	2860	2880–2860	"
	C – H i.p. (def.)	1448	1470–1435	"
	C – H o.o.p (def.)	1384	1385–1370	"
Aromatic	C – H str.	3043	3080–3030	503
	C = C str.	1571	1585–1480	"
	C – H i.p. (def.)	1114	1125–1090	"
		1031	1070–1000	"
	C – H o.o.p (def.)	829	835–810	"
Pyrazole	C = N str.	1624	1630–1590	499
moiety	C – N str.	1205	1230–1020	"
	C – Br str.	565	600–500	498
Pyrimidine	C = S str.	750	750–700	502
ring	N – H str.	3421	3500–3350	"
	C – N str.	1560	1650–1550	"
	C – S – C str.	785	800–700	"
Ether	C – S – C str. (asym.)	1269	1275–1200	"
	C – S – C str. (sym.)	1031 overlapped	1075–1020	"

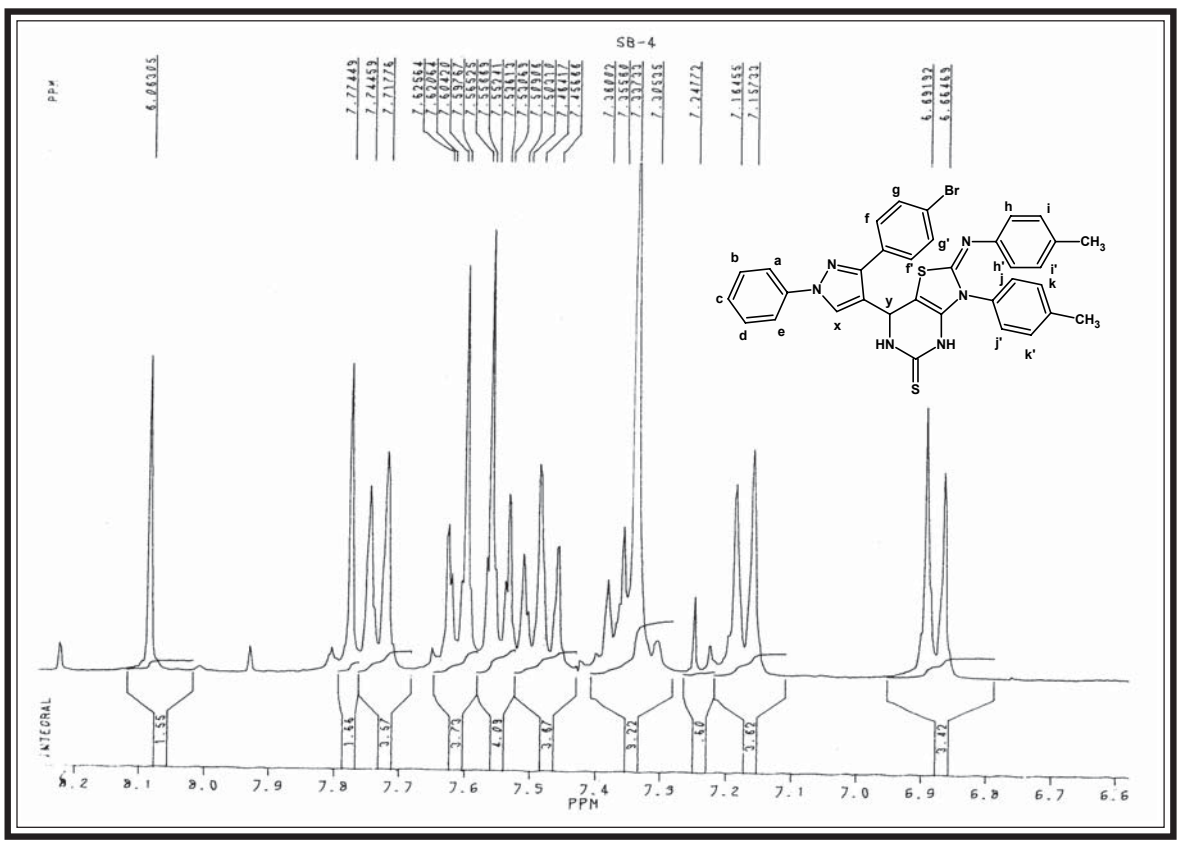
PMR SPECTRAL STUDY OF 6-p-TOLYLIMINO-7,N-p-TOLYL-2-THIO-4-(1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-4'-YL)-1,2,3,4-TETRAHYDRO-THIAZOLIDINO-[4,5-d]-PYRIMIDINE

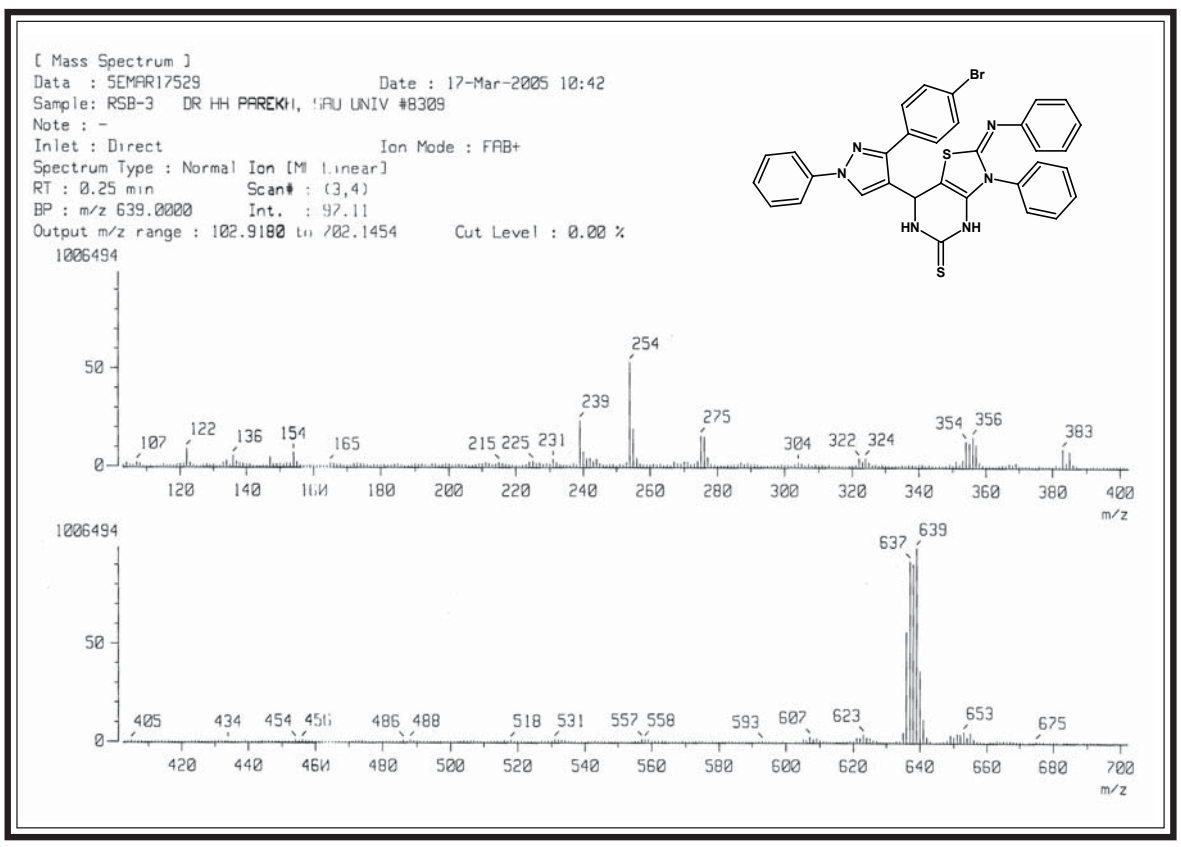


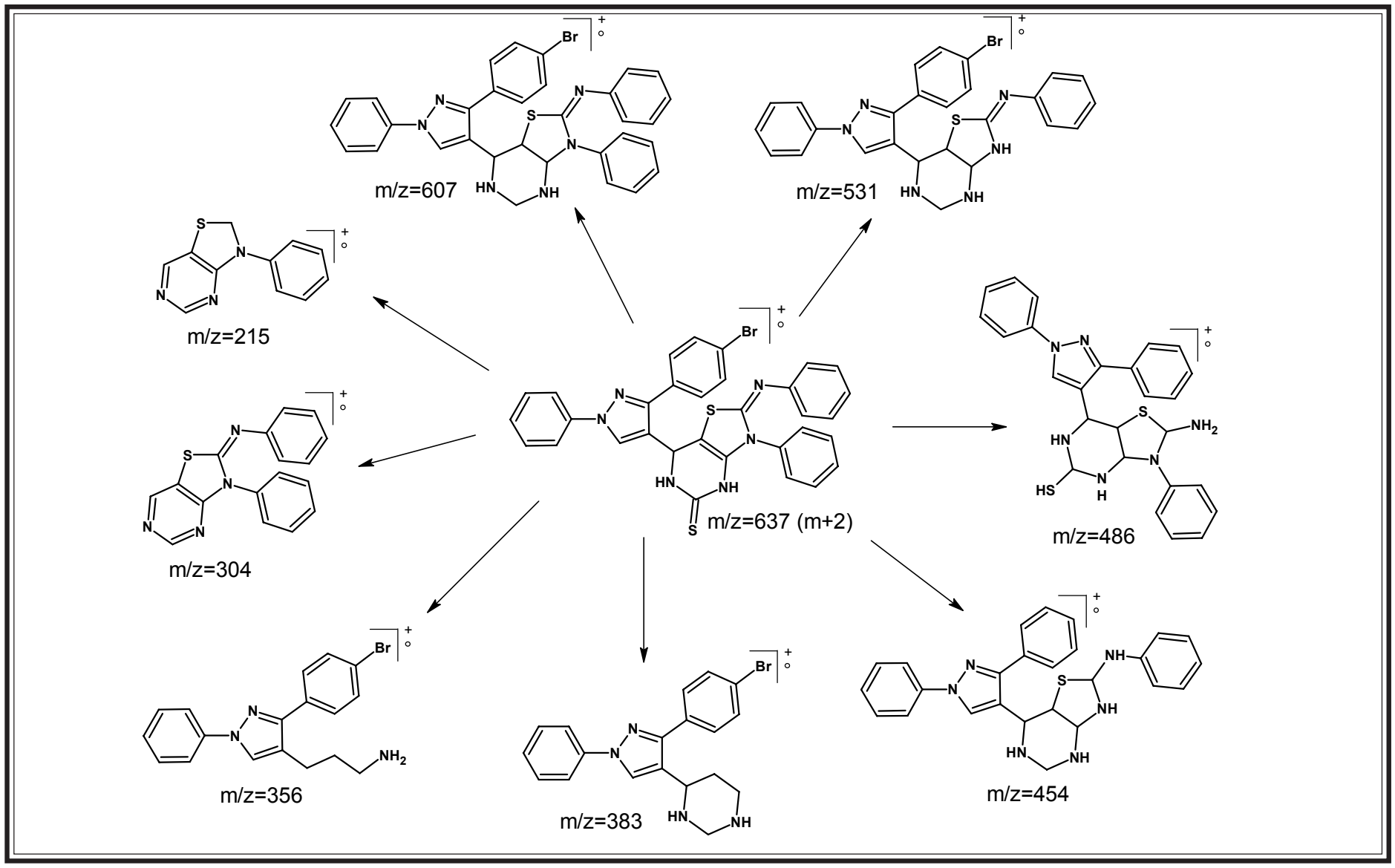
Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	2.36		3H	singlet	Ar-CH_3
2.	2.40		3H	singlet	Ar-CH_3
3.	6.87	Jkj=9	2H	doublet	Ar-Hkk'
4.	7.16	Jih=8.1	2H	doublet	Ar-Hii'
5.	7.33-7.38		5H	multiplet	Ar-Hc, Ar-Hhh' Ar-Hff'
6.	7.48		2H	triplet	Ar-Hb,d
7.	7.56	Jgf=8.4	2H	doublet	Ar-Hgg'
8.	7.60	Jjk=8.7	2H	doublet	Ar-Hjj'
9.	7.74		2H	doublet	Ar-Ha,e
10.	7.77		1H	singlet	-CHy
11	8.08		1H	singlet	Ar-Hx

EXPANDED AROMATIC REGION



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EXPERIMENTAL

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

[A] Synthesis of 2-p-Methylphenylimino-3-p-methylphenyl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)4-thiazolidinone

See, [B] Part-I, Section-I [E].

[B] Synthesis of 6-p-methylphenylimino-7,N-p-methylphenyl-2-thio-4-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-1,2,3,4-tetrahydro thiazolidino-[4,5-d] pyrimidine

A mixture of 2-p-methylphenylimino-3-p-methylphenyl-5-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-4-thiazolidinone (6.05, 0.01M) thiourea (0.76gm, 0.01M) were taken in glacial acetic acid (20 ml) with fused sodium acetate (1.25g, 0.015M). The reaction mixture was refulxed for 12 hrs. Cooled and poured onto crushed ice. The solid thus obtained was filtered, dried and crystallised from methanol-DMF. Yield, 4.3g, 72%, m.p. 186°C ($C_{34}H_{27}BrN_6S_2$: Required : C: 61.53; H: 4.10; N: 12.66; Found : C: 61.50; H: 4.14; N: 12.70%)

TLC solvent system : Acetone : Benzene (2.5 : 7.5).

Similarly, other thiopyrimidines were prepared. The physical data are recorded in Table No. 8.

[C] Antimicrobial activity of 6-Arylimino-7,N-aryl-2-thio-4-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-1,2,3,4-tetrahydro-thiazolidinon-[4,5-d]-pyrimidines

Antimicrobial testing was carried out as described in [A] Part-I, Section-I, (F). The zone of inhibition of the test solutions are recorded in Graphical Cahrt No.8.

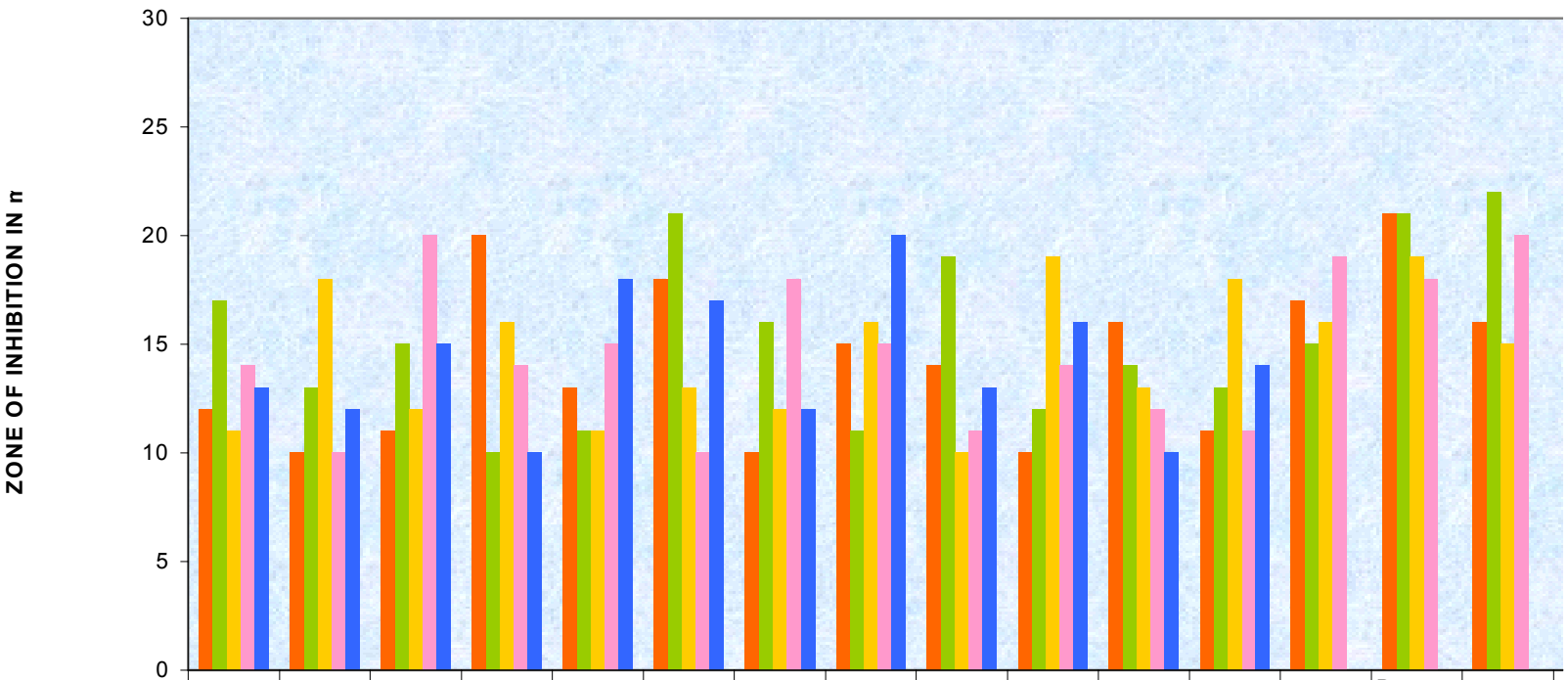
Antitubercular screening of the compounds of type (VIII) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 8a.

TABLE NO. 8 : PHYSICAL CONSTANTS OF 6-ARYLIMINO-7,N-ARYL-2-THIO-4-[1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-[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
8a	C_6H_5-	$C_{32}H_{23}BrN_6S_2$	635.6	194	0.56	74	13.22	13.26
8b	2-CH_3-C_6H_4-	$C_{34}H_{27}BrN_6S_2$	663.6	132	0.54	71	12.66	12.62
8c	4-CH_3-C_6H_4-	$C_{34}H_{27}BrN_6S_2$	663.6	186	0.63	72	12.66	12.70
8d	4-OCH_3-C_6H_4-	$C_{34}H_{27}BrN_6O_2S_2$	695.6	180	0.58	80	12.08	12.04
8e	4-Cl-C_6H_4-	$C_{32}H_{21}BrCl_2N_6S_2$	704.4	126	0.65	73	11.93	12.97
8f	4-F-C_6H_4-	$C_{32}H_{21}BrF_2N_6S_2$	671.5	134	0.55	70	5.66	12.70
8g	4-NO_2-C_6H_4-	$C_{32}H_{21}BrN_8O_4S_2$	725.5	190	0.60	82	15.44	15.40
8h	4-COOH-C_6H_4-	$C_{34}H_{23}BrN_6O_4S_2$	723.6	120	0.67	76	11.61	11.65
8i	3-Cl,4-F-C_6H_3-	$C_{33}H_{19}BrCl_2F_2N_6S_2$	740.4	193	0.57	68	11.35	11.31
8j	2,4-di-Cl-C_6H_3-	$C_{32}H_{19}BrCl_4N_6S_2$	773.3	182	0.59	84	10.87	10.83
8k	2,5-di-Cl-C_6H_3-	$C_{32}H_{19}BrCl_4N_6S_2$	773.3	174	0.61	72	10.87	10.90
8l	3,4-di-Cl-C_6H_3-	$C_{32}H_{19}BrCl_4N_6S_2$	773.3	196	0.56	66	10.87	10.85

*TLC Solvent System :Acetone : Benzene (2.5 : 7.5)

GRAPHICAL CHART NO. 8 : 6-ARYLIMINO-7,N-ARYL-2-THIO-4-(1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-4'-YL)1,2,3,4-TETRAHYDRO THIAZOLIDINO-[4,5-d]PYRIMIDINES



	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	I
B.coccus	12	10	11	20	13	18	10	15	14	10	16	11	17	21	16	
B.subtilis	17	13	15	10	11	21	16	11	19	12	14	13	15	21	22	
P.vulgaris	11	18	12	16	11	13	12	16	10	19	13	18	16	19	15	
E.coli	14	10	20	14	15	10	18	15	11	14	12	11	19	18	20	
A.niger	13	12	15	10	18	17	12	20	13	16	10	14	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

It has been observed from the experimental data that all compounds of type (VIII) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

However, comparatively good activity was observed in compounds with R=4-methoxyphenyl and 4-fluorophenyl against ***B.coccus***; R=4-fluorophenyl and 3-chloro,4-fluorophenyl against ***B.subtilis***.

In case of Gram negative bacterial strains, the maximum activity was displayed by the compounds bearing R=2-methylphenyl, 2,4-dichlorophenyl and 3,4-dichlorophenyl against ***P.vulgaris***. While the compounds bearing R=4-chlorophenyl and 4-nitrophenyl have shown considerable activity against ***E.coli***.

Antifungal activity :

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds bearing R=4-carboxyphenyl against ***A.niger***.

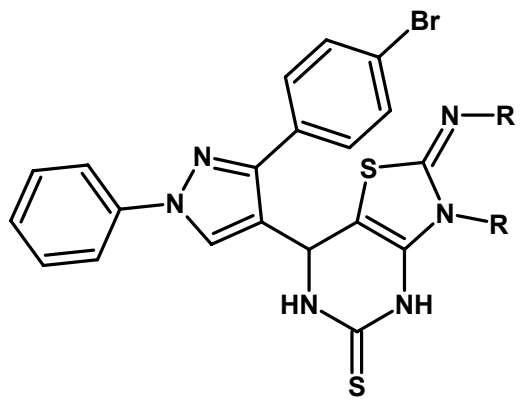
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

All the compounds of type (VIII) showed mild activity against ***Mycobacterium tuberculosis*** $H_{37}Rv$,

The antitubercular activity data have been compared with standard drug Rifampin.

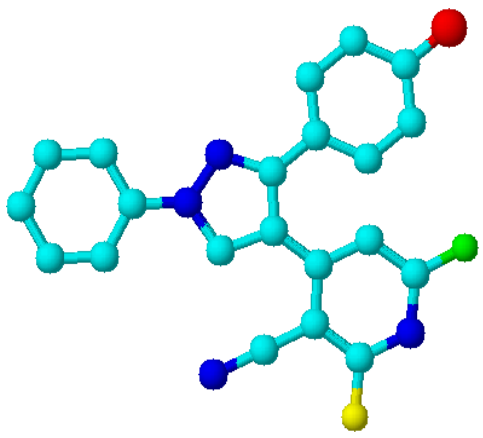
TABLE NO. 8a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



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*
295491	BSA-113	C_6H_4-	Alamar	$H_{37}Rv$	>6.25	5	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295492	BSA-114	2-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	21	-	
295493	BSA-115	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295494	BSA-116	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	4	-	"
295495	BSA-117	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	42	-	"
295496	BSA-118	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	37	-	"
295497	BSA-119	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	27	-	"
295498	BSA-120	3-Cl,4-F-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	28	-	"
295499	BSA-121	2,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295500	BSA-122	2,5-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	14	-	"
295501	BSA-123	3,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	16	-	"
295502	BSA-124	4-COOH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20	-	"

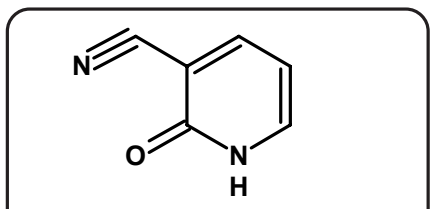


PART-II

STUDIES ON CYANOPYRIDONES

INTRODUCTION

Cyanopyridones, which belongs to an important group of heterocyclic compounds have been extensively explored for their applications in the field of medicine, cyanopyridones, with a carbonyl group at position-2 and cyano group at position-3 (I) have been subject of extensive study in recent past. Numerous reports have appeared in the literature which highlight their chemistry and use.

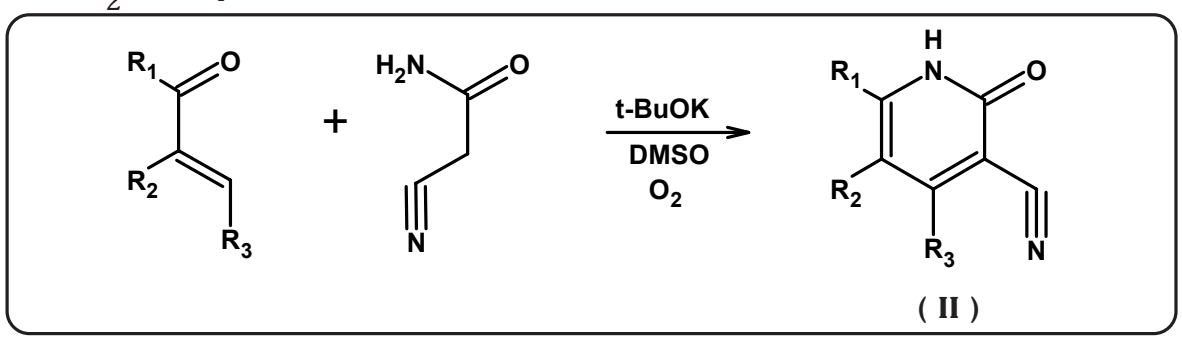


(I)

SYNTHETIC ASPECTS

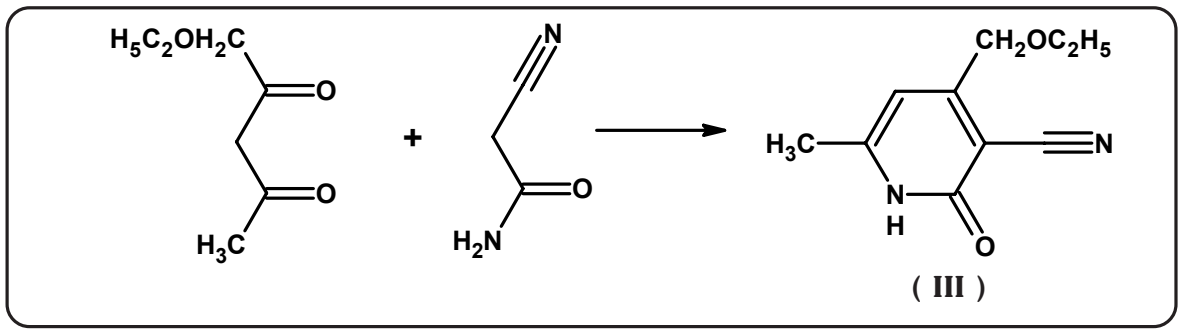
Different methods for preparation of cyanopyridones are as follows :

1. Rajul Jain et. al.[359] have synthesised 3-cyano-2-pyridone by the reaction of various enones with cyanoacetamide in presence of t-BuOK in DMSO under O_2 atmosphere.



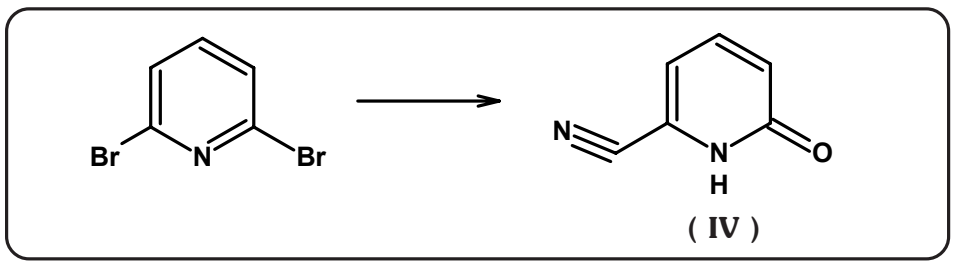
(II)

2. K. Follkers and S. A. Harris[360] have synthesised 3-cyano-2-pyridone by the condensation of cyanoacetamide with 1,3-diketone or 3-ketoester.



(III)

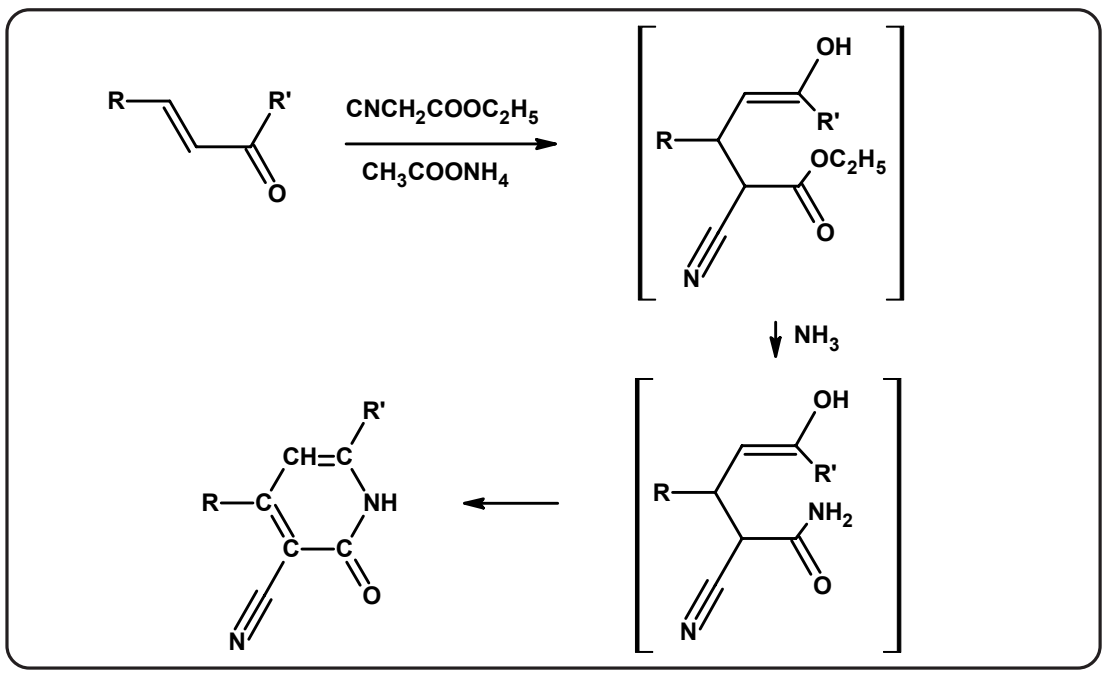
3. W. Russel Bowman et. al.[361] have synthesised cyanopyridone from 2,6-dibromopyridine in presence of chlorotrimethylsilane and sodium iodide in acetonitrile.



(IV)

MECHANISM

The addition reaction between ethylcyanoacetale and α,β-unsaturated ketone give cyanopyridone via Michael addition. Here, α,β–unsaturated compound is known as acceptor and active methylene group containing compound known as addender. It involves nucleophillic addition of carbanion to the C=C of the acceptor.



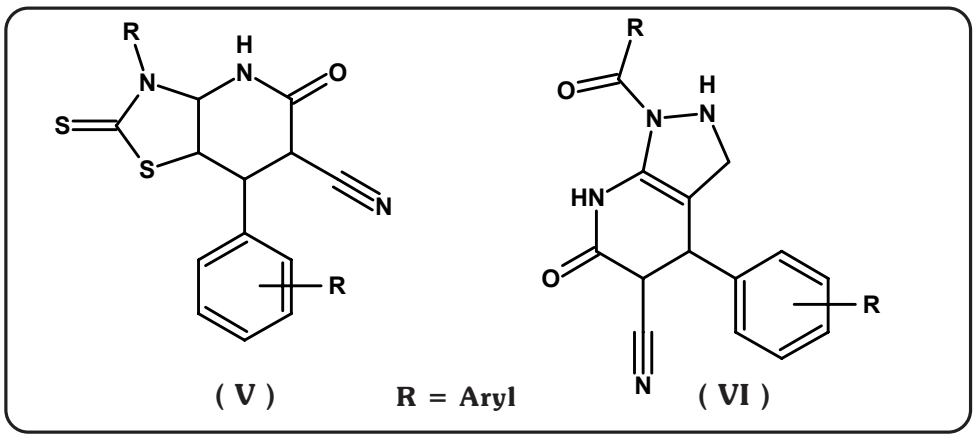
THERAPEUTIC IMPORTANCE

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

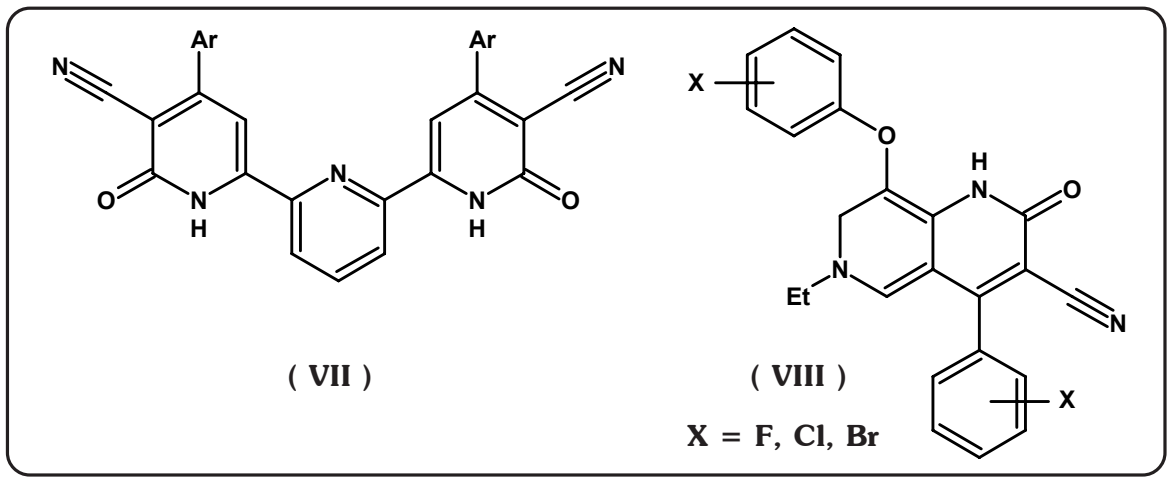
1. Anticancer[362]
2. Antimicrobial[363]
3. Angitensin II antagonist[364]

4. Antiviral[365]
5. Anti HIV[366]
6. Herbicidal[367]
7. Pesticidal[368]

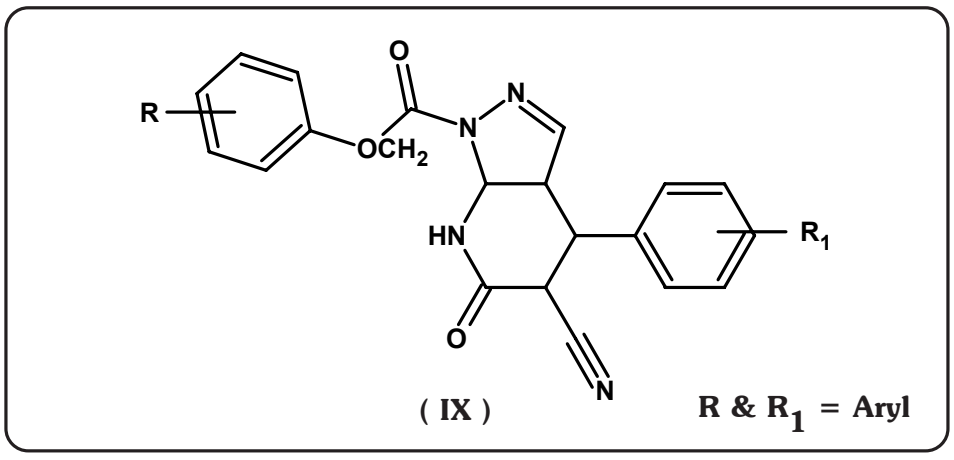
Salman A. S.[369] has investigated cyanopyridone derivatives showing interesting antifungal and antibacterial activities. Hussain Khan and co-workers[370,371] have prepared cyanopyridone derivatives (V) and (VI) and studied their insecticidal and pesticidal activities.



Pednekar[372] have documented antiviral, CNS depressant, bactericidal and ulcer inhibitor activities of cyanopyridones. Upadhyay and co-workers[373] have formulated cyanopyridone derivatives which showed antifungal and antileishmanial activities. E. Amer[374] prepared 3-cyano-2-pyridone derivatives (VII) displaying significant antimicrobial activity. Abou El-Fotooh and co-workers[375] have synthesised cyanopyridones (VIII) and reported them as anticancer agent.



Coburn Craig et. al.[376] have discovered some new pyridone derivatives as thrombin inhibitors. M. G. Nizamuddin et. al.[377] have prepared cynopyridone derivatives (IX) and screened for their antifungal activity.



(IX) R & R_1 = Aryl

Recently, Nersesyan K. et. al.[378] have investigated some new cyanopyridones possessing genotoxic activity in marine cells and antitumor activity. Xi Qi et. al.[379] have investigated cyanopyridones useful as phosphatase inhibitors and studied their biological activities. Darcq Michael. G. et. al.[380] have discovered some new cyanopyridone derivatives possessing antiviral activity, Isobe Y. et. al.[381] have prepared pyrimidine diones and evaluated them as antiallergic agents.

Smith Terence[382] has documented cyanopyridones useful as AMPA receptor antagonists for the treatment of dimyelinating disorders and neurodenerative disease. Devdas Balakudra et. al.[383] have demonstrated pyridones as modulators of P^{38} MAP kinase.

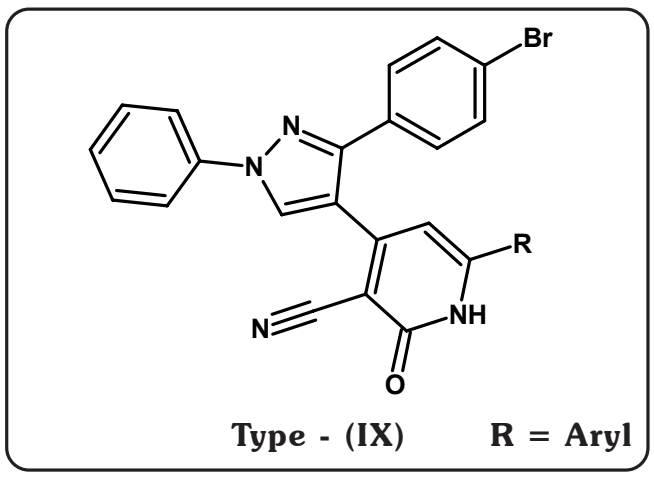
With an intension of preparing the compounds possessing better therapeutic activity, we have undertaken the prepareation of cyanopyridones which have been described as under.

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

The growing potent literature of recent years demonstrates that the cyanopyridone derivatives are used as better therapeutic agents. Prompted by these facts, the preparation of cyano pyridone derivatives of type (IX) by the condensation of 1-aryl-3-[1',N-phenyl-3'-p-bromophenyl-pyrazol-4'-yl]-2-propene-1-ones with ethylcyanoacetate in presence of ammonium acetate.

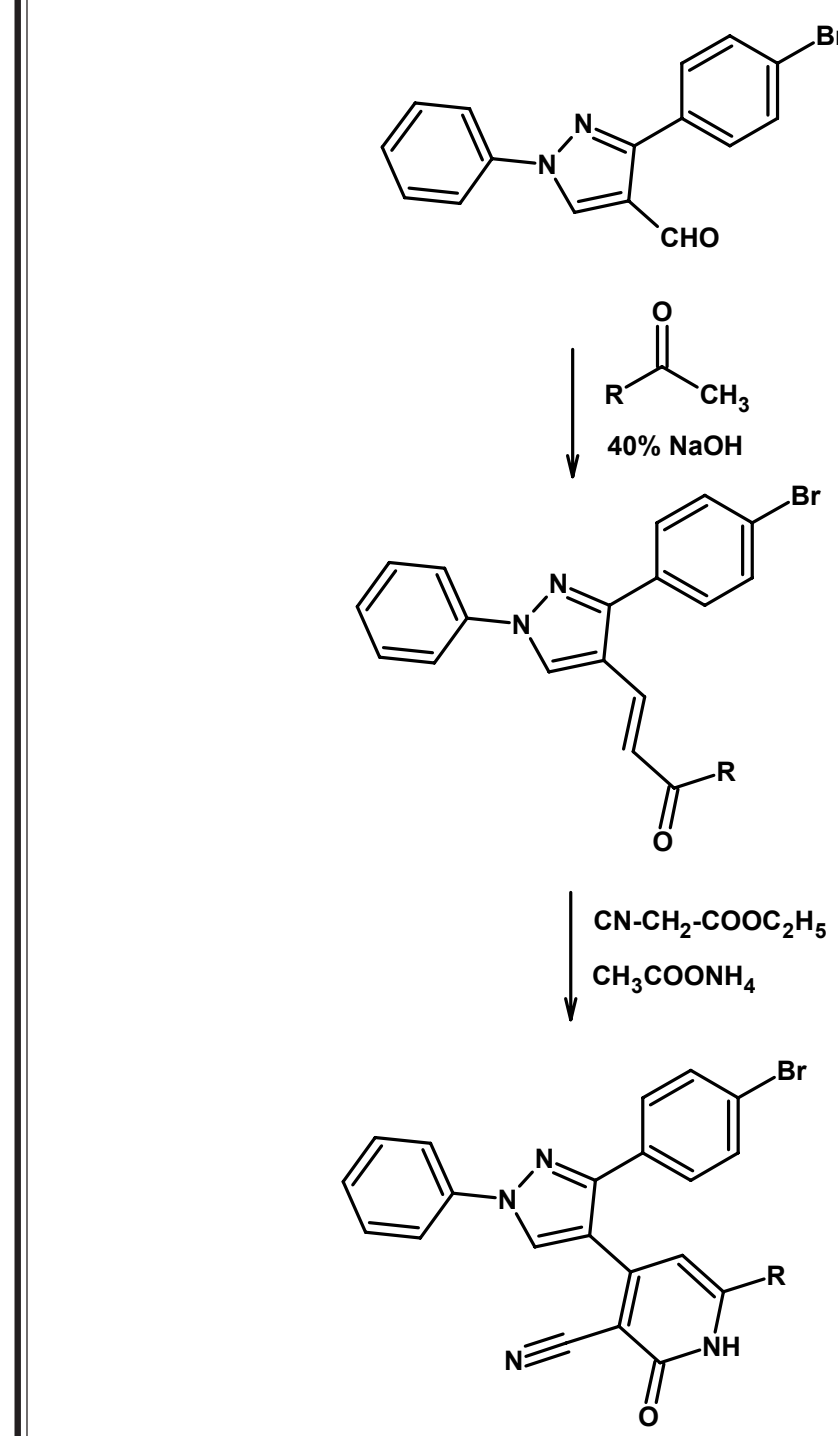


Type - (IX) **R = Aryl**

The constitution of the newly synthesised compounds have been supported by 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.

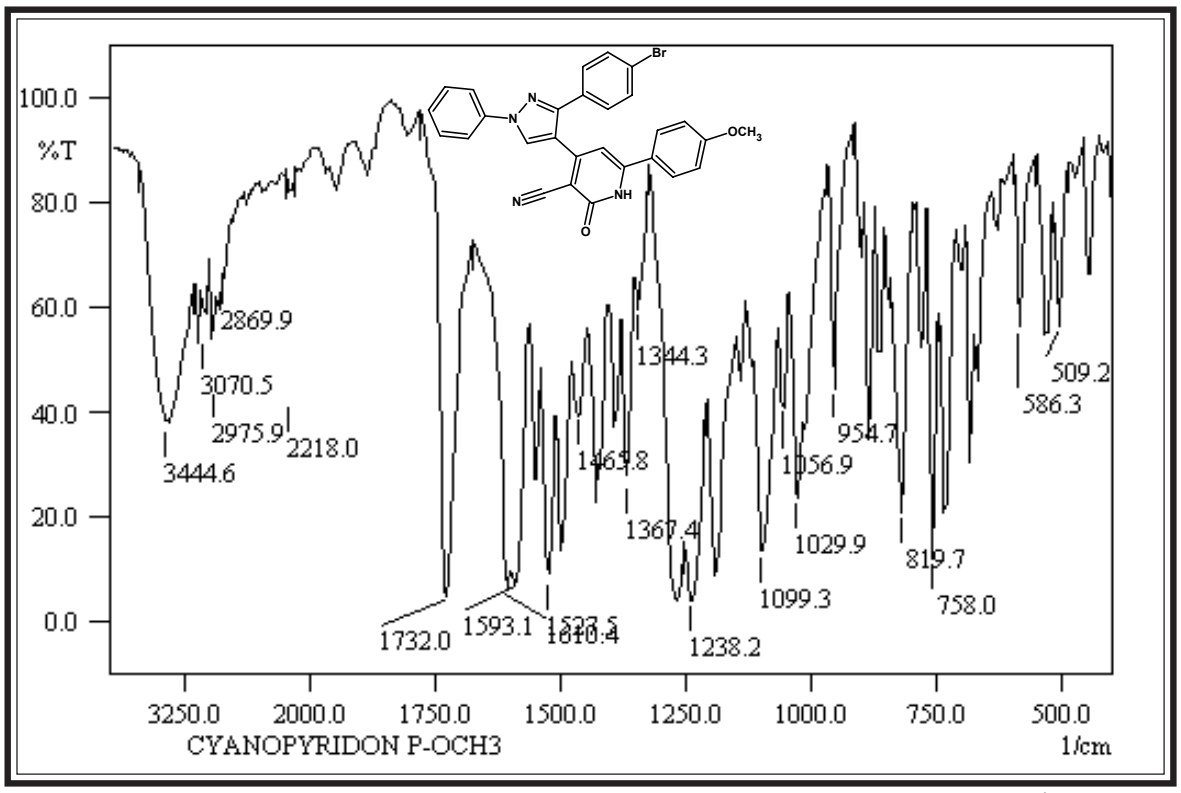
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 9.

REACTION SCHEME



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

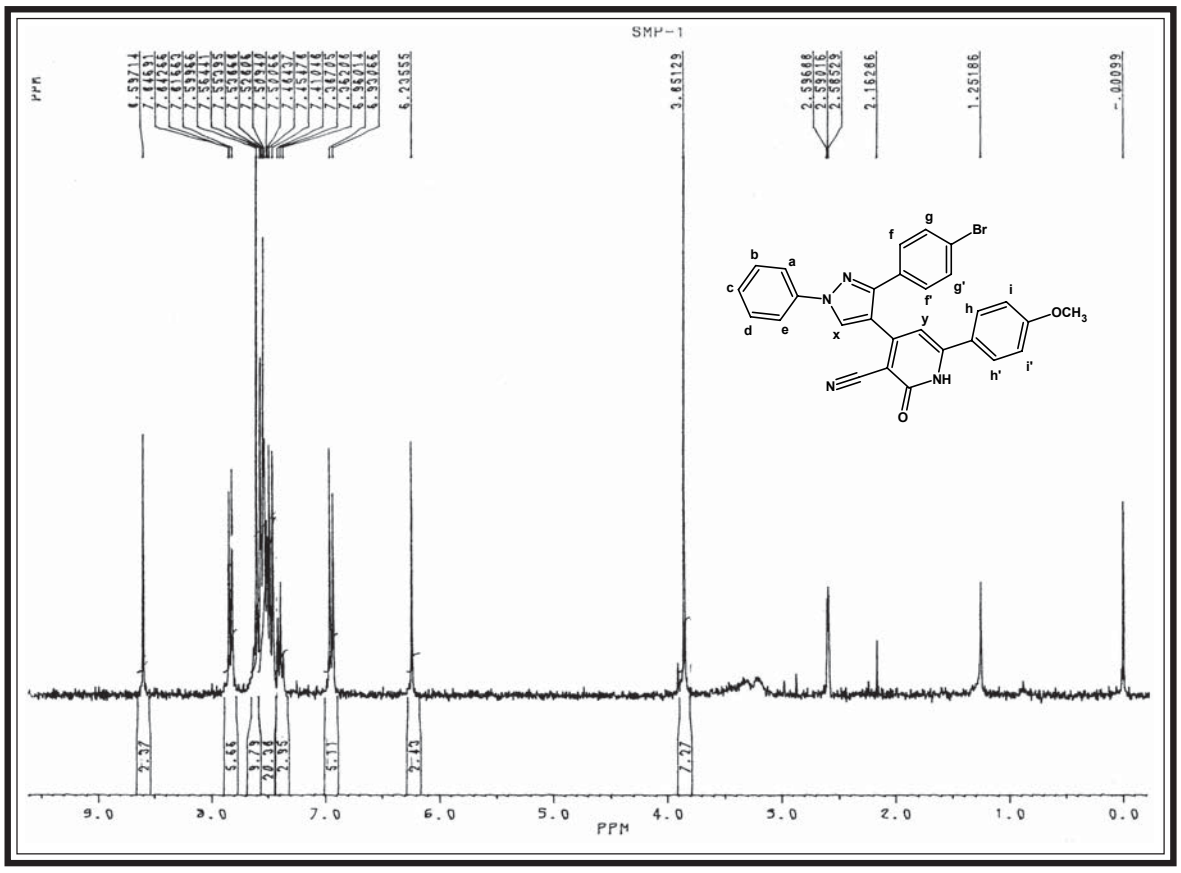
IR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-4'-YL)-6-p-ANISYL-1,2-DIHYDRO-2-PYRIDONE



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.)	2975	2975–2950	498
$-CH_3$	C – H str (sym.)	2869	2880–2860	"
	C – H def. (asym.)	1465	1470–1435	"
	C – H def. (sym.)	1367	1385–1350	"
Aromatic	C – H str.	3070	3080–3030	503
	C – H i.p. def.	1099	1125–1090	"
		1056	1070–1000	"
	C – H o.o.p def.	819	835–810	"
Pyrazole	C = N str.	1610	1610–1590	499
moiety	C = C str.	1527	1585–1480	"
	C – N str.	1344	1350–1200	"
	C – Br str.	586	600–500	498
Ether	C – O – C (asym.)	1238	1275–1200	503
	C – O – C (sym.)	1029	1075–1020	"
Pyridone	C ≡ N str.	2218	2240–2120	498
ring	C = O str.	1732	1760–1655	"
	N – H str.	3444	3450–3250	"
	N – H def.	1593	1650–1580	"

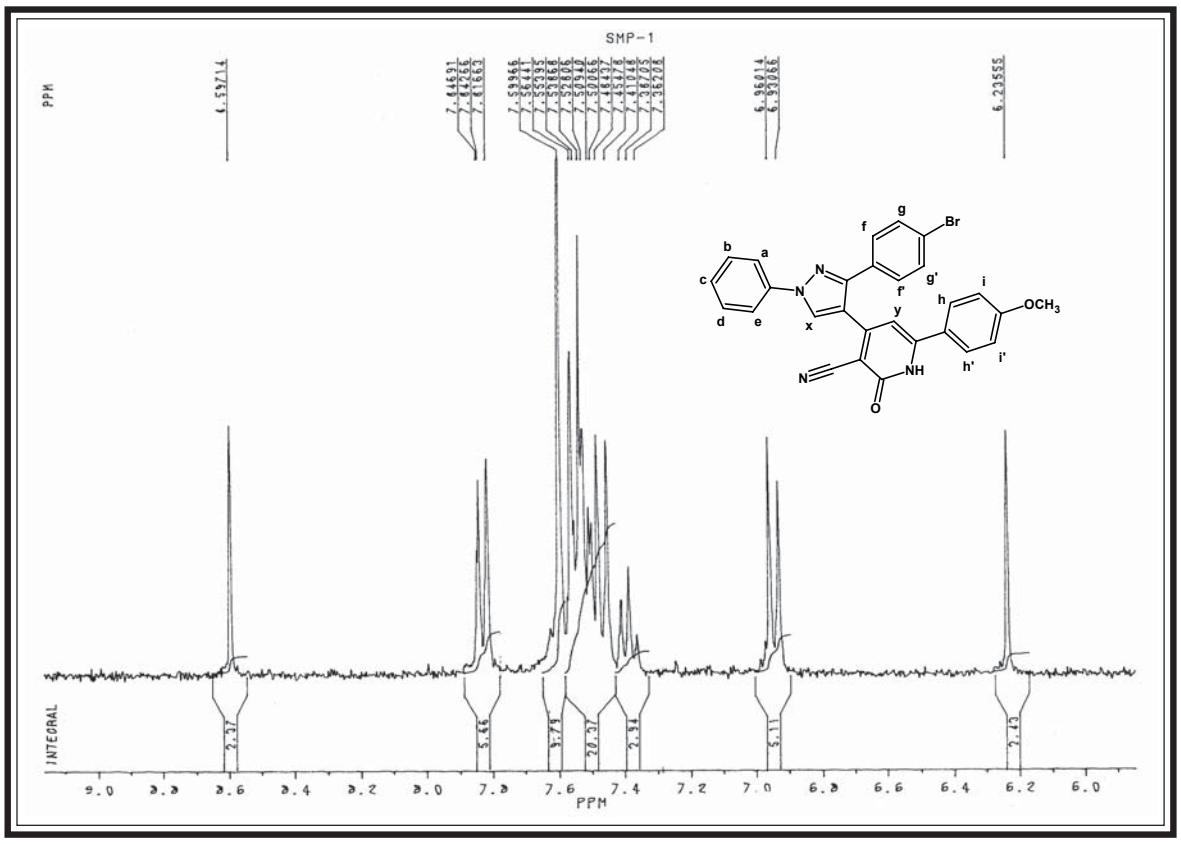
PMR SPECTRAL STUDY OF 3-CYANO-4-[1',N-PHENYL-3'-p-BROMOPHENYL PYRAZOL-4'-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.85		3H	singlet	Ar-OCH_3
2.	6.23		1H	singlet	CHy
3.	6.93-6.96	Jih=9	2H	doublet	Ar-Hii'
4.	7.38		1H	triplet	Ar-Hc
5.	7.45-7.53		4H	multiplet	Ar-Hhh' Ar-Hb,Ar-Hd
6.	7.55-7.59		4H	multiplet	Ar-Hgg' Ar-Ha,Ar-He
7.	7.81-7.84	Jfg=9	2H	doublet	Ar-Hff'
8.	8.59		1H	singlet	CHx

EXPANDED AROMATIC REGION



SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/21/2005 3:12:43 PM
Sample Name : SB-9
Sample ID : SB-9
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-9.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:15.5(Scan#:1822)
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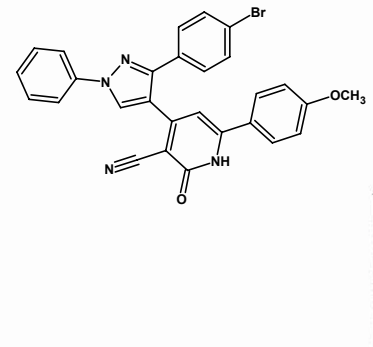
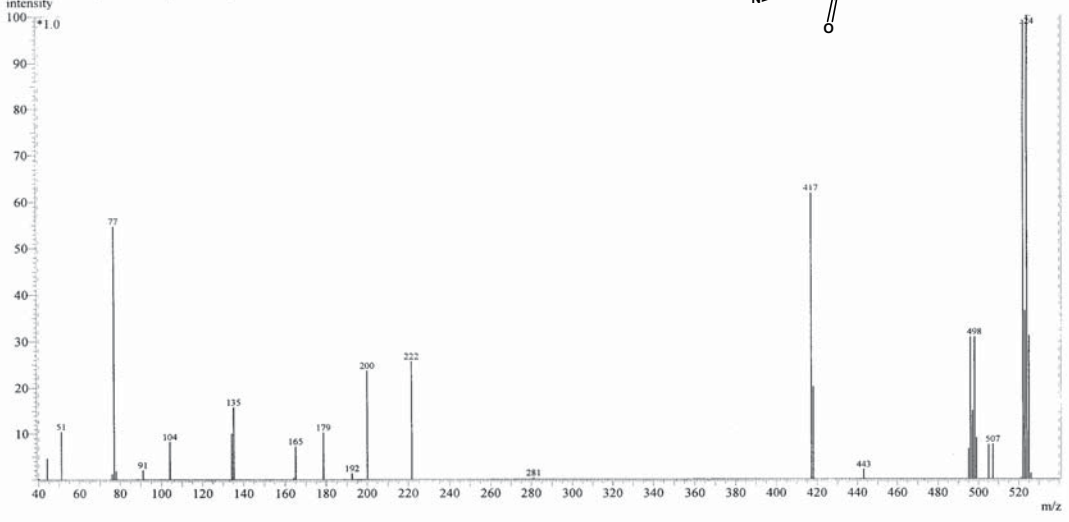
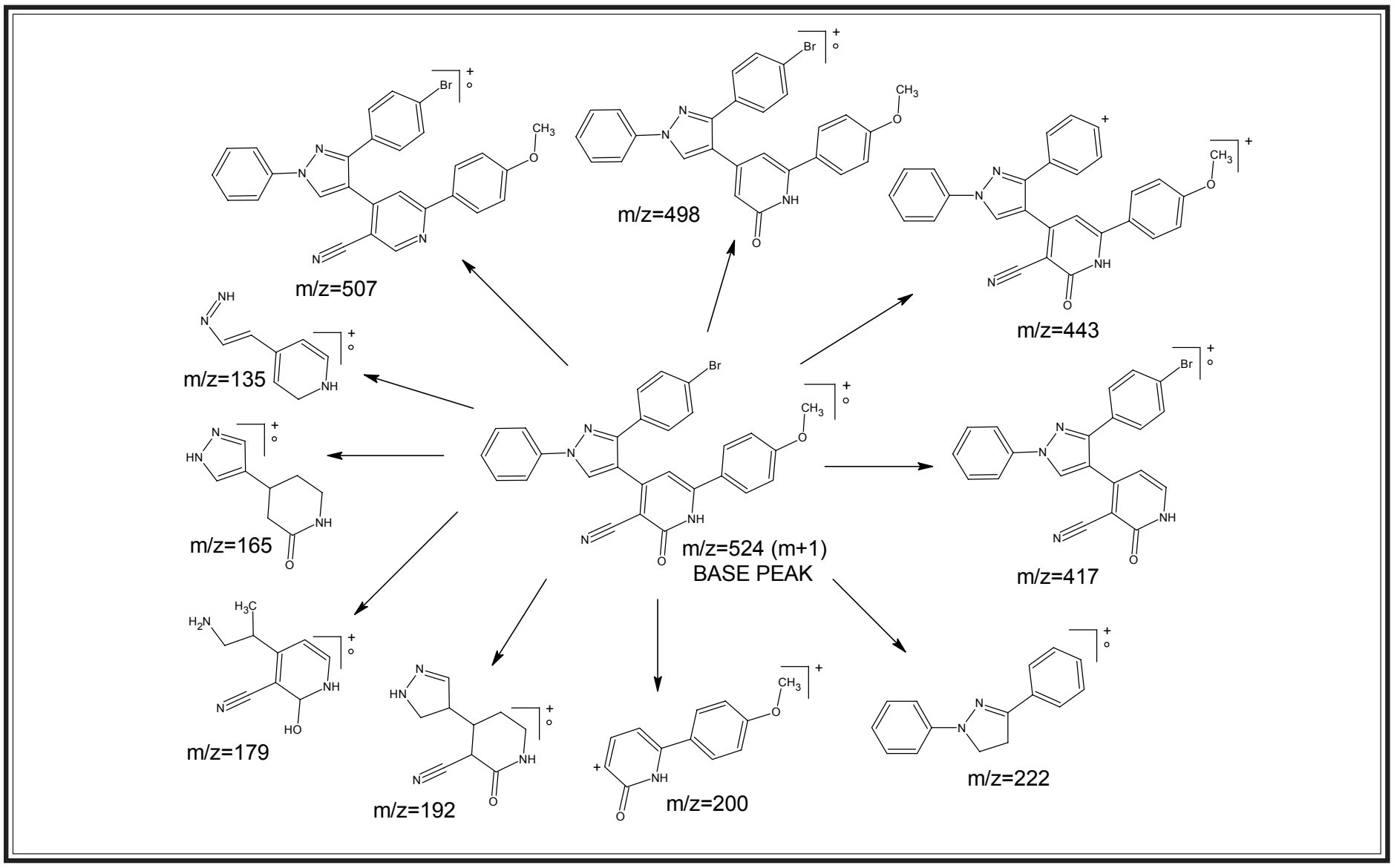
RawMode:Averaged 15.5-15.8(1819-1865)
BG Mode:Averaged 18.9-19.1(2235-2260)






m/z=507
m/z=498
m/z=443
m/z=135
m/z=165
m/z=524 (m+1)
BASE PEAK
m/z=417
m/z=179
m/z=192
m/z=200
m/z=222

EXPERIMENTAL

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

(A) Synthesis of N-phenylamine-α-methyl-α-p-bromophenyl azomethine

See [B], Part-I, Section-I (A).

(B) Synthesis of 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole

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

(C) Synthesis of 1-p-anisyl-3-(1',N-phenyl-3'-p-bromophenyl pyrazol-4'-yl)-2-propene-1-one

To a well stirred solution of 1,N-phenyl-3-p-bromophenyl-4-formylpyrazole (3.10g, 0.01M) and p-methoxyacetophenone (1.50g, 0.01M) in ethanol (25 ml), 40% NaOH added till the solution was basic. The reaction mixture was stirred for 24 hrs. The content was poured onto crushed ice, acidified, filtered and crystallised from ethanol. Yield 3.71g, 81% m.p. 129°C. ($C_{25}H_{19}BrN_2O_2$: required C, 65.37; H, 4.17; N, 7.36 found C, 65.38; H, 4.15; N, 7.31%).

TLC solvent system : Acetone : Benzene (2 : 8).

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

A mixture of 1-p-anisyl-3-(1',N-phenyl-3'-p-bromophenyl-pyrazol-4'-yl)-2-propene-1-one (4.59g, 0.01M) ethylcyanoacetate (1.13g, 0.01M) and ammonium acetate (5.92g, 0.08M) in absolute alcohol (20 ml) was refluxed for 18 hrs. The reaction mixture was poured onto crushed ice, filtered and crystallised from ethanol Yield 3.6g, 79% m.p.>300°C. ($C_{28}H_{19}N_4O_2Br$: Required : C, 64.26; H, 3.66; N, 10.70; Found : C, 64.21; H, 3.64; N, 10.65%).

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

(E) Antimicrobial activity of 3-Cyano-4-(1',N-phenyl-3'-p-bromophenyl pyrazole-4'-yl)-6-aryl-1,2-dihydro-pyridones

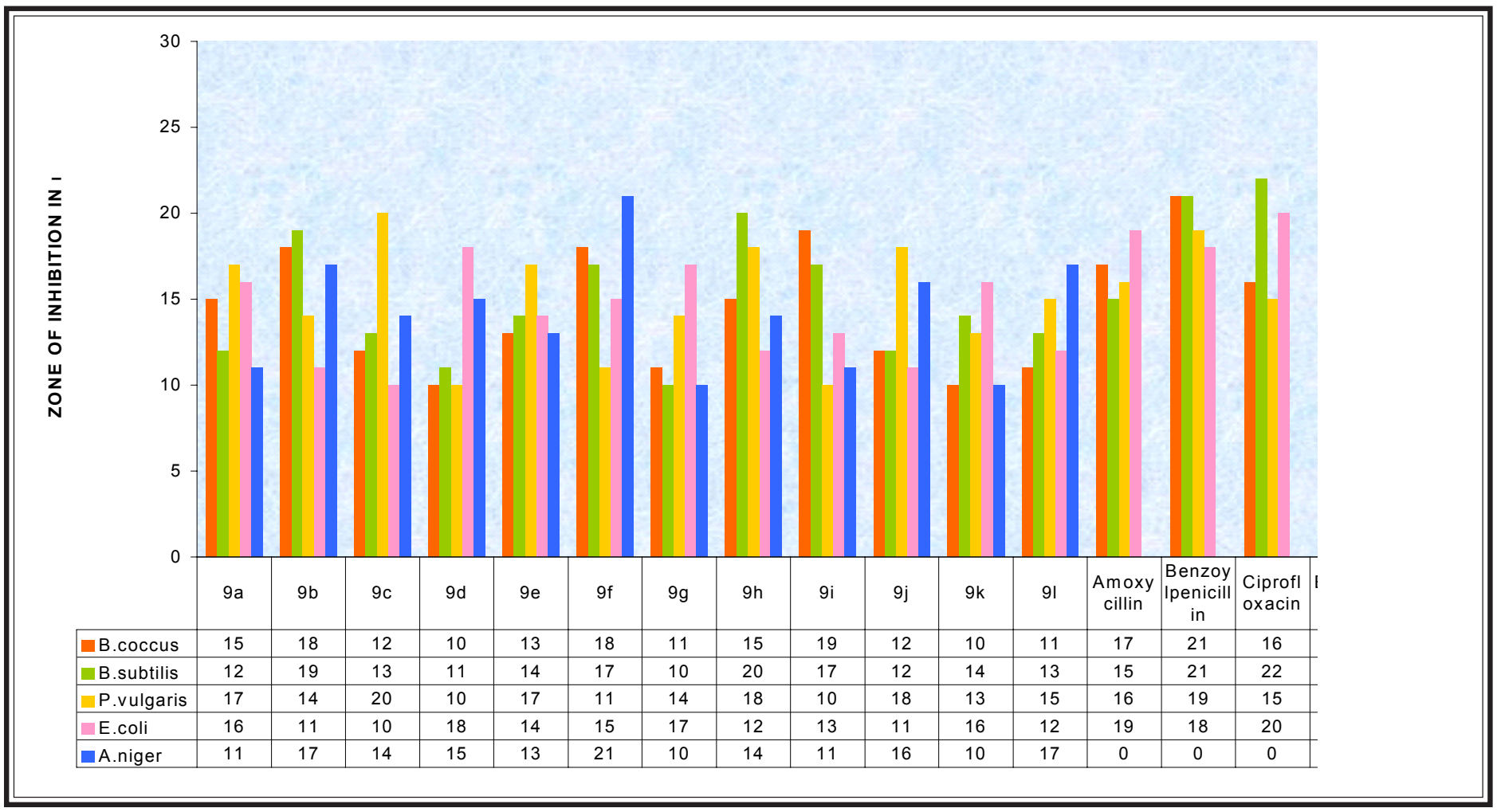
Antimicrobial testing was carried out as described in [A] Part-I, Section-I (F). The zone of inhibition of the test solution are recorded in Graphical Chart No. 9.

TABLE NO. 9 : PHYSICAL CONSTANTS OF 3-CYANO-4-[1',N-PHENYL-3'-p-BROMOPHENYL 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-	$C_{27}H_{17}BrN_4O$	493.3	164	0.82	76	11.36	11.32
9b	4-CH_3-C_6H_4-	$C_{28}H_{19}BrN_4O$	507.3	210	0.79	69	11.04	11.00
9c	4-OCH_3-C_6H_4-	$C_{28}H_{19}BrN_4O_2$	523.3	>300	0.86	79	10.70	10.65
9d	4-Cl-C_6H_4-	$C_{27}H_{16}BrClN_4O$	527.7	155	0.81	67	10.62	10.66
9e	4-F-C_6H_4-	$C_{27}H_{16}BrFN_4O$	511.3	138	0.75	72	10.96	10.94
9f	4-Br-C_6H_4-	$C_{27}H_{16}Br_2N_4O$	572.2	178	0.83	68	9.79	10.77
9g	3-NO_2-C_6H_4-	$C_{27}H_{16}BrN_5O_3$	538.3	140	0.84	74	13.01	13.03
9h	4-NO_2-C_6H_4-	$C_{27}H_{16}BrN_5O_3$	538.3	150	0.77	75	13.01	13.05
9i	4-NH_2-C_6H_4-	$C_{27}H_{18}BrN_5O$	508.3	148	0.76	58	13.78	13.74
9j	2-OH-C_6H_4-	$C_{27}H_{17}BrN_4O_2$	509.3	136	0.68	62	11.00	11.04
9k	4-OH-C_6H_4-	$C_{27}H_{17}BrN_4O_2$	509.3	160	0.78	73	11.00	11.03
9l	2,4-$(Cl)_2$-C_6H_3-	$C_{27}H_{15}BrCl_2N_4O$	562.2	180	0.74	59	9.96	9.92

*TLC Solvent System :Ethyl acetate : Hexane (1 : 8)

GRAPHICAL CHART NO. 9 : 3-CYANO-4-(1',N-PHENYL-3'-p-BROMOPHENYL-PYRAZOL-4'-YL)-6-ARYL-1,2-DIHYDRO-2-PYRIDONES



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin
B.coccus	15	18	12	10	13	18	11	15	19	12	10	11	17	21	16
B.subtilis	12	19	13	11	14	17	10	20	17	12	14	13	15	21	22
P.vulgaris	17	14	20	10	17	11	14	18	10	18	13	15	16	19	15
E.coli	16	11	10	18	14	15	17	12	13	11	16	12	19	18	20
A.niger	11	17	14	15	13	21	10	14	11	16	10	17	0	0	0

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

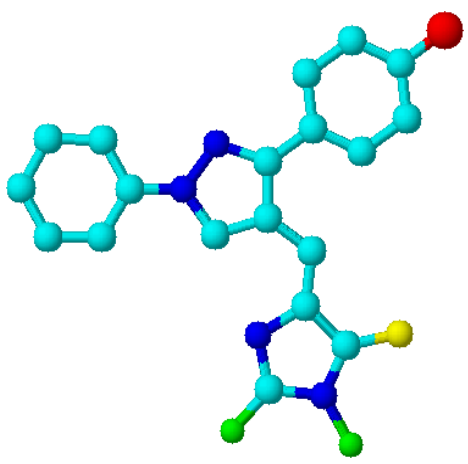
It has been concluded from the experimental data that all the cyanopyridones of type (IX) are active against different strains of Gram positive and Gram negative bacteria.

The significant activity was observed in compounds bearing R=4-methylphenyl, 4-bromophenyl and 4-aminophenyl against ***B.coccus*** and ***B.subtilis.***

The maximum activity was observed in compounds bearing R=4-methoxyphenyl, 4-nitrophenyl and 2-hydroxyphenyl against ***P.vulgaris*** and R=4-chlorophenyl against ***E.coli.***

Antifungal activity :

All the compounds exhibited mild activity against ***A.niger*** except compounds bearing R=4-bromophenyl which showed good activity against ***A.niger.***

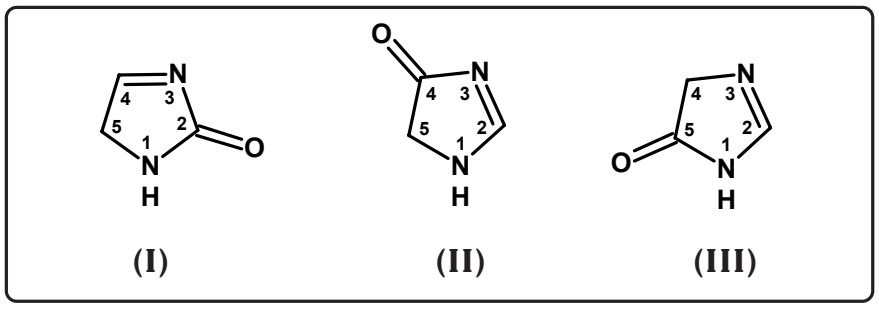


PART-III

STUDIES ON IMIDAZOLINONES

INTRODUCTION

*I*midazolinone is 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).

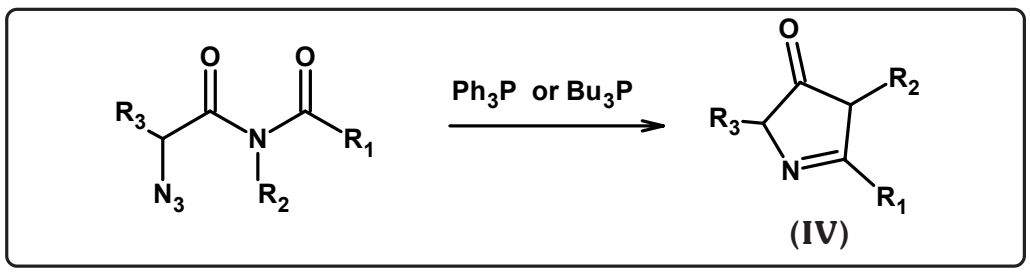


A. W. Hoffmann[384] for the first time discovered 5-oxo-imidazoline by heating N'-diacetylethylene diamine in a stream of dry hydrogen chloride. Moreover some compounds were prepared by A. Ladenburg[385] by the fusion of two equivalents of sodium acetate with one equivalent of ethylene diamine dihydrochloride.

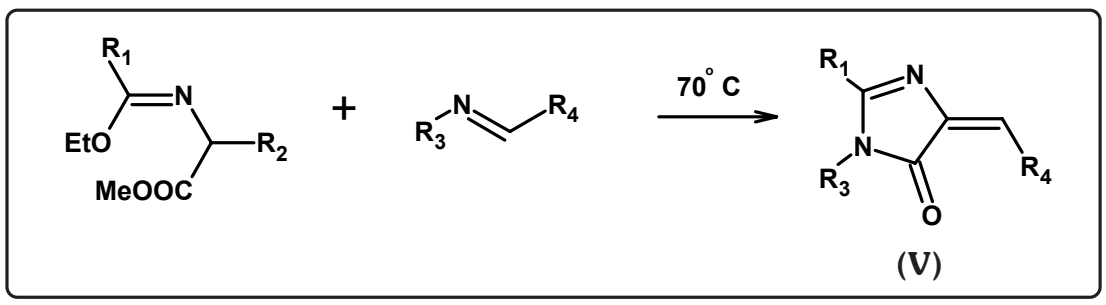
SYNTHETIC ASPECT

Various methods have been reported for the synthesis of imidazolinones in literature. Aminolysis of oxazolone with amine leads to the formation of imidazolinones which have been reported in literature[386].

1. Hisato Takeuchi et al.[387] have synthesised imidazolinones by the reaction of azido substituted imides with triphenylphosphine or tributylphosphine.

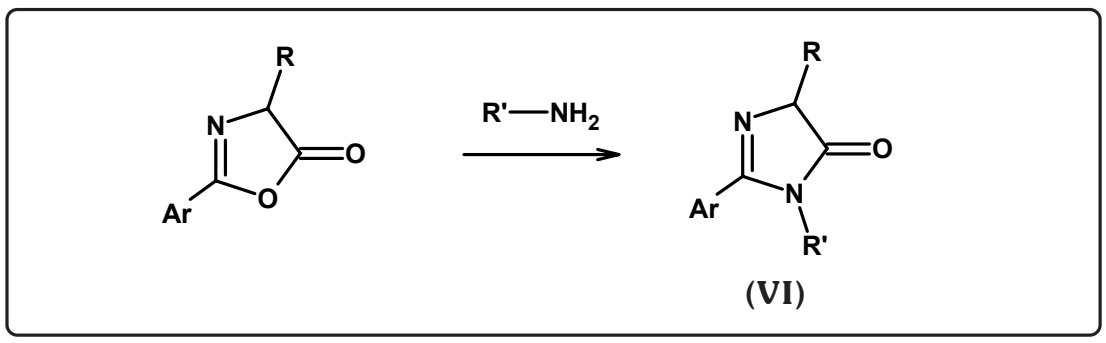


2. Jean Michel Lerestif et. al.[388] have synthesised imidazolinone from α-aminoester.



(V)

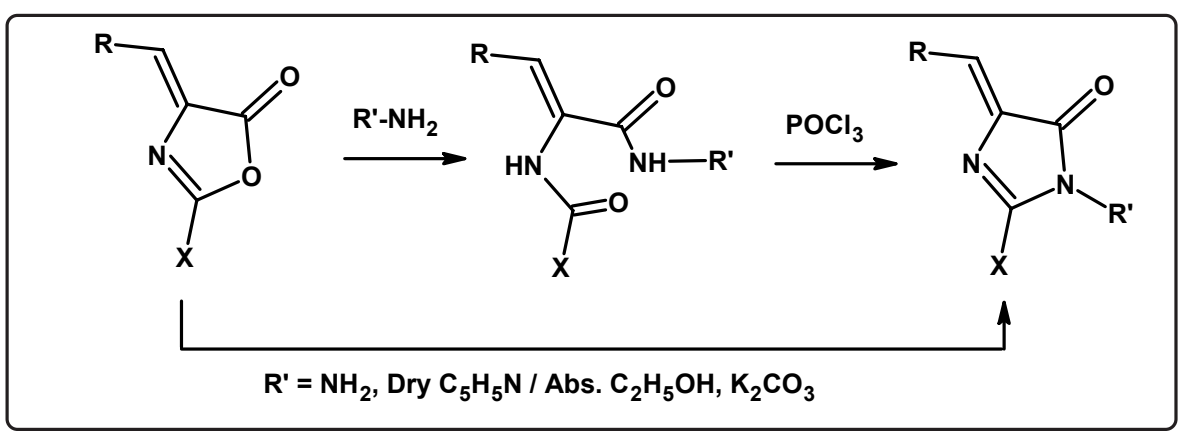
3. Rao Y. S. and Filler R[389] have prepared 2-arylimidazolin-5-ones by the treatment of an oxazolone intermediate with an aryl / alkylamine.



(VI)

MECHANISM

Azalactone reacts with variety of compounds such as water, alcohol, 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 closure can be effected under a variety of conditions. Substituted anilides have been converted to imidazolinone derivatives by the action of $POCl_3$.

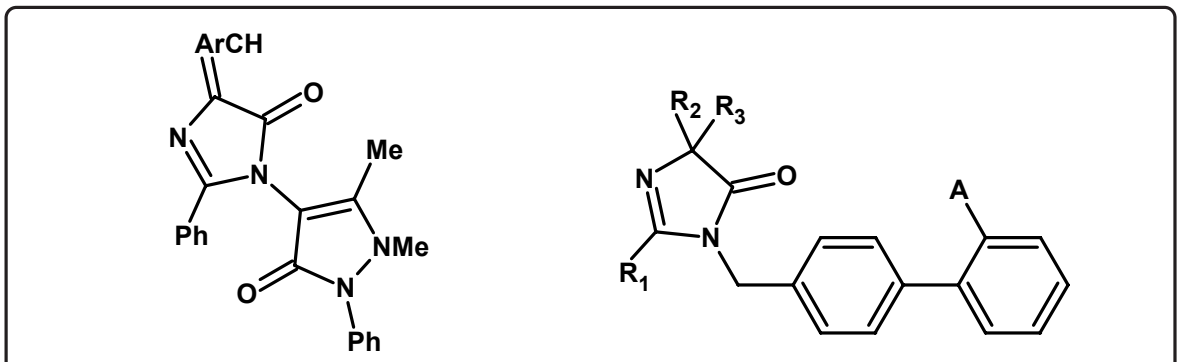
THERAPEUTIC IMPORTANCE

Imizapyr is a broad spectrum imidazolinone herbicide used to kill unwanted plants in industrial sites, coniferous forests, railroad rights of way, rubber plantations, oil palm plantation and sugarcane. Imazapyr kills plants by inhibiting the enzyme used when plant synthesise branched chain amino acids. The name of this enzyme is acetohydroxyacid syntheses.[390] Various imidazolinones are known to exhibit a broad spectrum of biological activities such as.

1. Antitubercular[391]
2. Antiviral[392]
3. Antiinflammatory[393-395]
4. Antimicrobial[396]
5. Anticonvulsant[397,398]
6. Antiparkinsonian[399,400]
7. Anthelmintic[401]
8. Antihistaminic[402]
9. Anticancer[403,404]
10. Antidiabetic[405]
11. Bactericidal[406,407]
12. Fungicidal[408,409]
13. Glucogon Antagonists[410]
14. Hypertensive[411]
15. Insecticidal[412]
16. Potent CNS depressant[413,414]
17. Sedative and hypnotics[415]
18. Thrombin inhibitor[416]

Siew Siew Pang et. al.[417] have discovered some new imidazolinone derivatives and reported their herbicidal activity. Imam Hidayat et. al.[418] have reported ALS-inhibitory activity of imidazolinones. Keun-Jin Oh et. al.[419] have investigated some imidazolinone derivatives abolished the enzymatic activity as

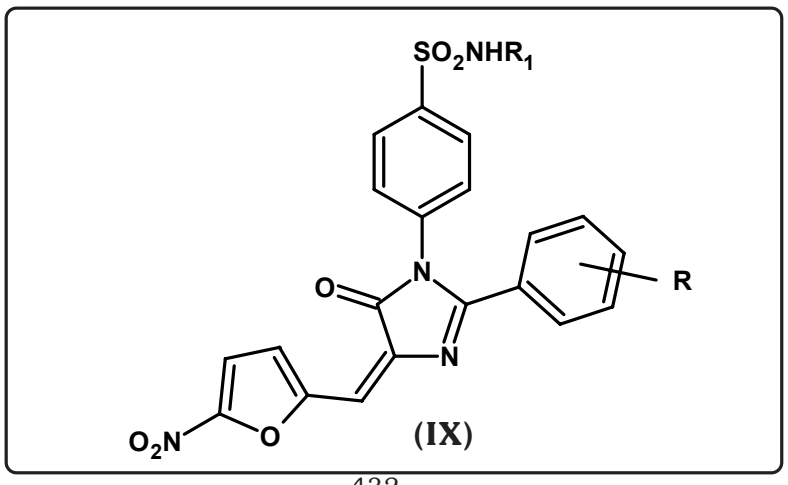
well as the binding affinity for the cofactor FAD (Flavin adenine dinucleotide). Rama Sharma and co-workers[420] have formulated 5-oxo-imidazolines possessing potential antimicrobial activity. Solankee A.[421] have synthesised some imidazolinone derivatives (VII) and screened for their anticancer activity.



(VII) (VIII)

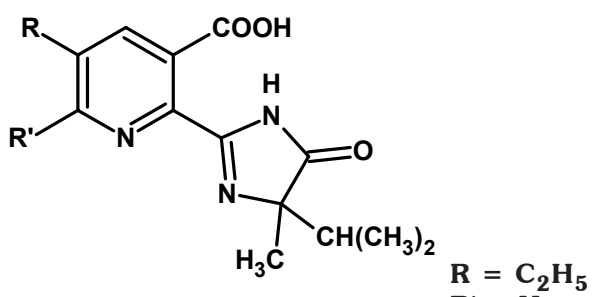
Yehudit Zohar et. al.[422] have discovered some imidazolinone derivatives and studied their antituberculosis activity. Armando Rossello et. al.[423] have found that imidazolinones are potential antifungal agent. Muchii Dalsuke et. al.[424] have synthesised new imidazolones as a telomerase inhibitors and antitumor agents. Mimi L. Quan et. al.[425] have synthesised imidazolinone derivatives (VIII) as nonpeptide angiotensin II receptor antagonists.

Jean M. R. et. al.[426] have discovered imidazolinones and tested as antileishmanial agents. Irene M. L. et. al.[427] have investigated some imidazolinone derivatives possessing antireteroviral activity. Lee Jin Ho et. al.[428] have formulated imidazolinones and tested for their anticancer activity. Ozaki Satoshi et. al.[429] have reported imidazolinones useful as analgesic and antagonists. Wepplo Peter John et. al.[430] have prepared imidazolinones showing herbicidal activity. El-Sayed A. S.[431] has synthesised imidazolinone derivatives (IX) and screened for their antibacterial and antifungal activities.



(IX)

Recently, Dung Tien Le et. al.[432] have reported imidazolinones as herbicide. Hashmukh Joshi and co-workers[433] have isolated imidazolinones and tested for their anticonvulsant and antimicrobial activity. Yong In Kuk et. al.[434] have investigated some imidazolinones and reported them an herbicides and Acetolactuse synthease (ALS) inhibitor. Declera et. al.[435] have documented anti HIV activity of some new imidazoline derivatives. Ding Ming-Wu et. al.[436] have discovered imidazolinones and studied their antifungal activity. C. Alister and co-workers[437] have documented herbicidal activity of imidazolinone derivatives. Aleksey N. Vasiliev et. al.[438] have synthesised imidazolinone derivatives (X) and reported their herbicidal activity.



R = C_2H_5
R' = H

(X)

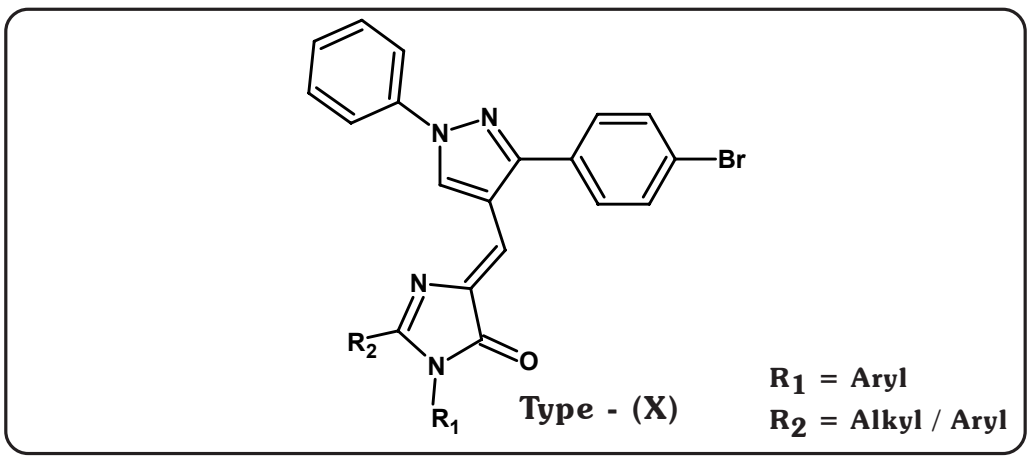
With a view to getting better therapeutic agents, it was contemplated to synthesise imidazolinones to enhance the overall activity of resulting compound which have been described as under.

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

SECTION-I

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

Imidazolinone derivatives occupy a unique place in field of medicinal chemistry due to wide range of biological activities exhibited by them. Looking at the interesting therapeutic activity of imidazolinones it was considered to synthesise a series of imidazolinones of type (X) for obtaining biologically potent agents which were prepared by the condensation of azalactone with different aromatic amines.



Type - (X)

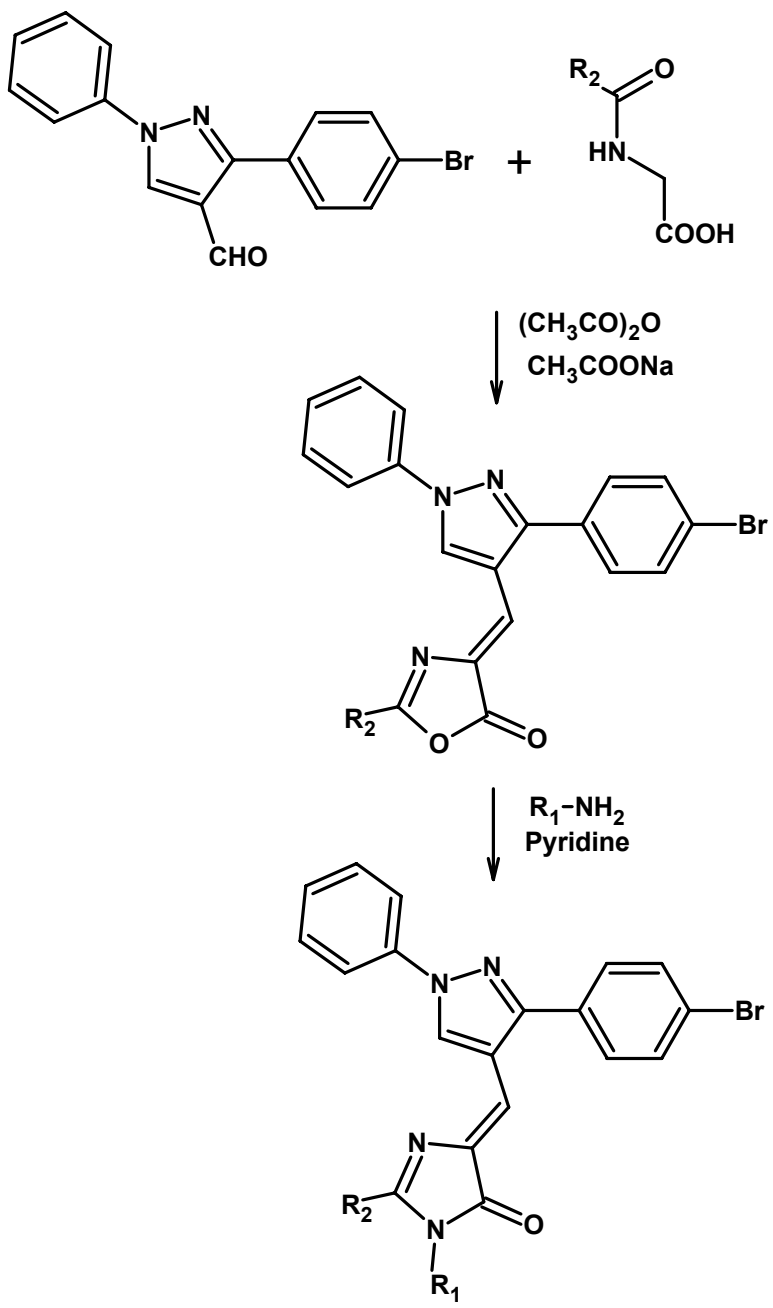
R_1 = Aryl
R_2 = Alkyl / Aryl

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

All the compounds 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. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 10.

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.

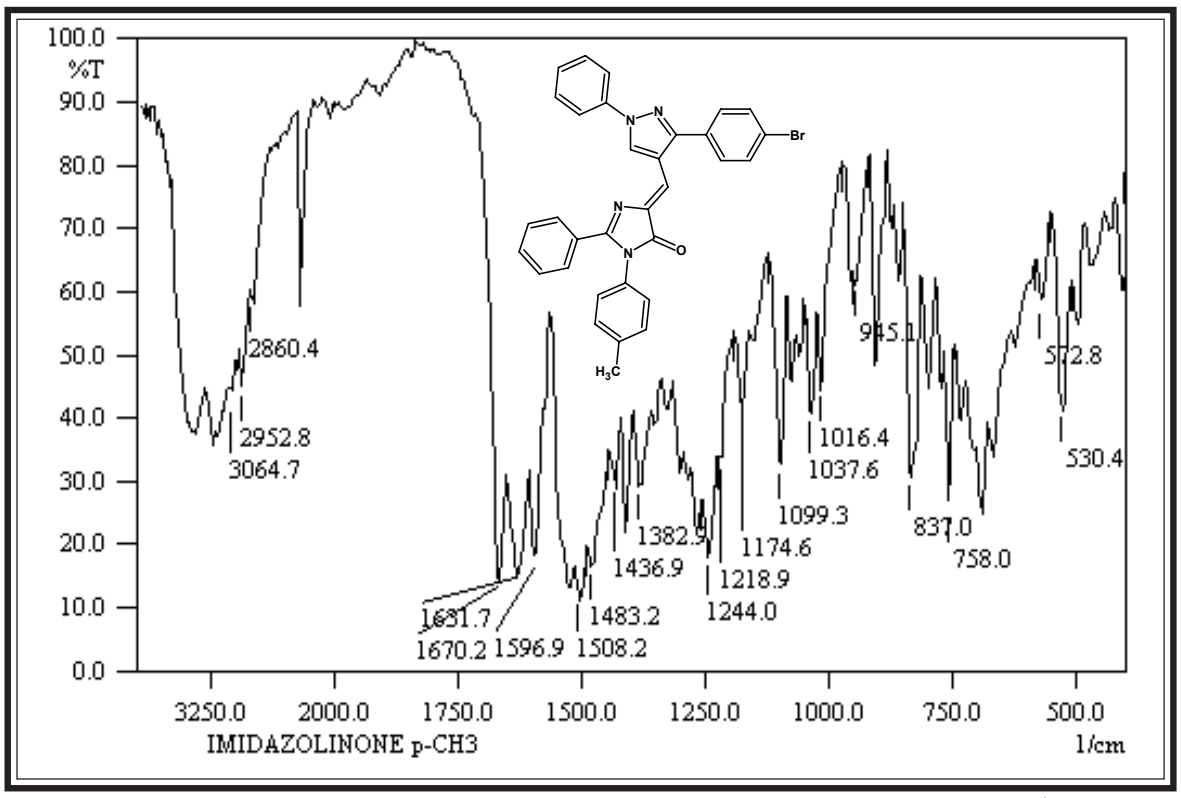
REACTION SCHEME



Type - (X)

R_1 = Aryl
R_2 = Alkyl / Aryl

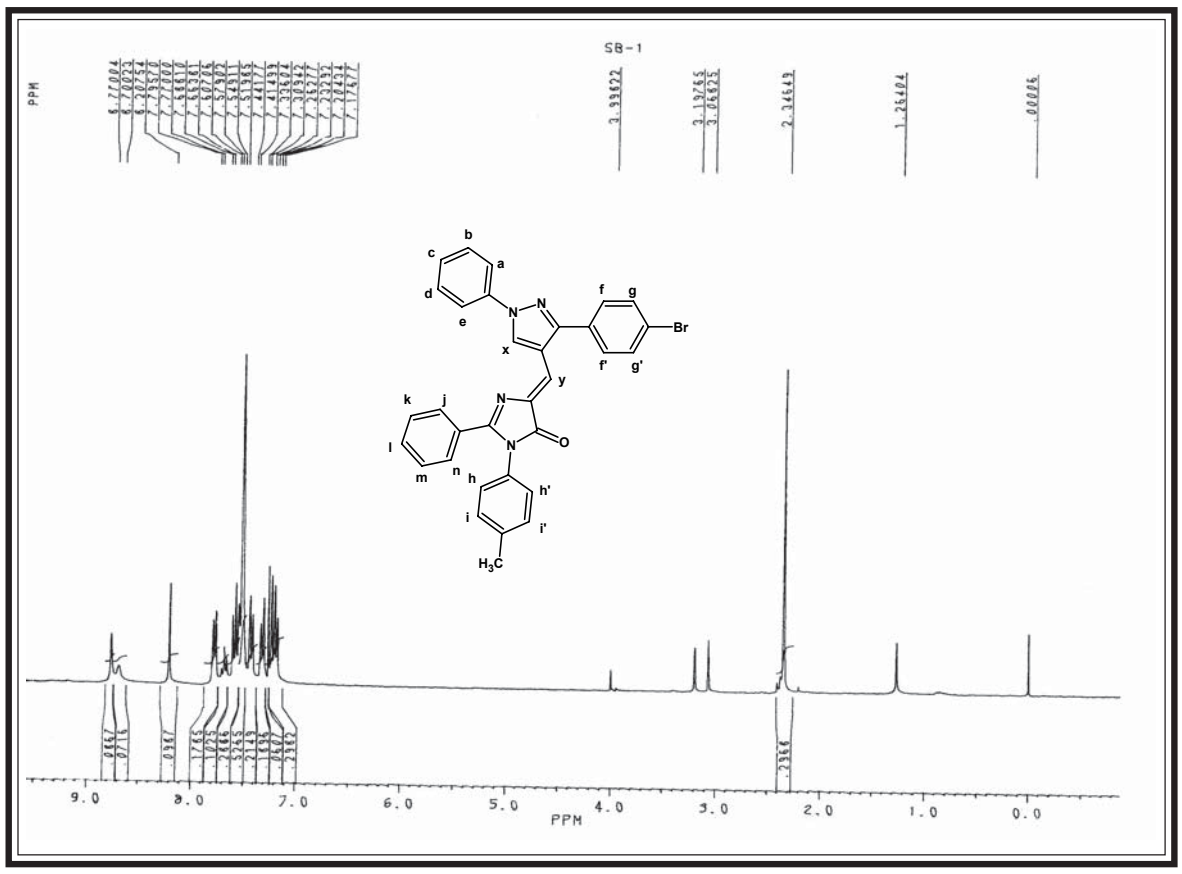
IR SPECTRAL STUDY OF 1,N-p-METHYLPHENYL-2-PHENYL-4-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL METHINO)-IMIDAZOLIN-5-ONE



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.)	2952	2975–2950	498
$-CH_3$	C – H str (sym.)	2860	2880–2860	"
	C – H i.p. (def.)	1436	1470–1435	"
	C – H o.o.p (def.)	1382	1385–1370	"
Aromatic	C – H str.	3064	3080–3030	503
	C = C str.	1508	1520–1480	"
	C – H i.p. (def.)	1098	1125–1090	"
		1038	1070–1000	"
	C – H o.o.p (def.)	837	835–810	"
Pyrazole	C = N str.	1596	1610–1590	499
moiety	C – N str.	1218	1230–1220	"
	C – Br str.	530	600–500	498
Imidazolinone	C = O str.	1670	1770–1655	"
ring	C = N str.	1631	1650–1550	"
	C – N str.	1244	1260–1220	"

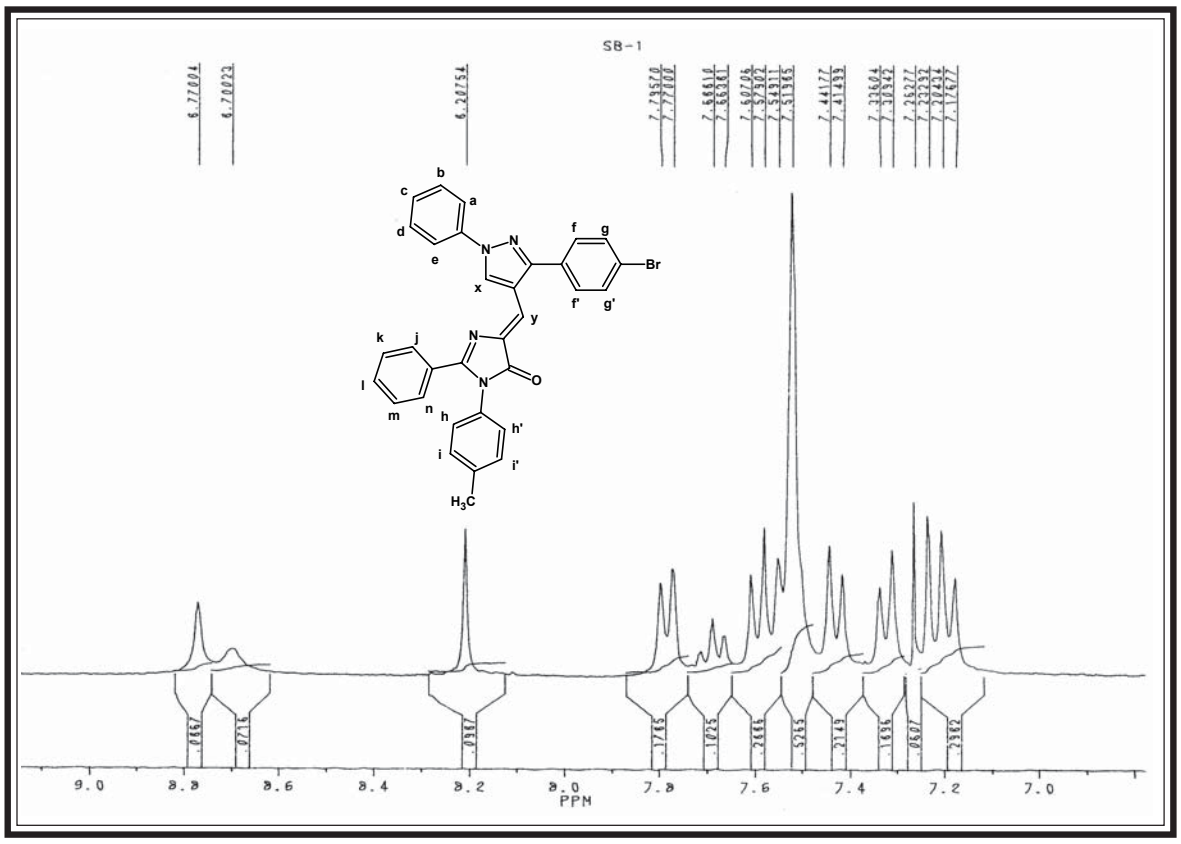
PMR SPECTRAL STUDY OF 1,N-METHYLPHENYL-2-PHENYL-4-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL METHINO)-IMIDAZOLIN-5-ONE

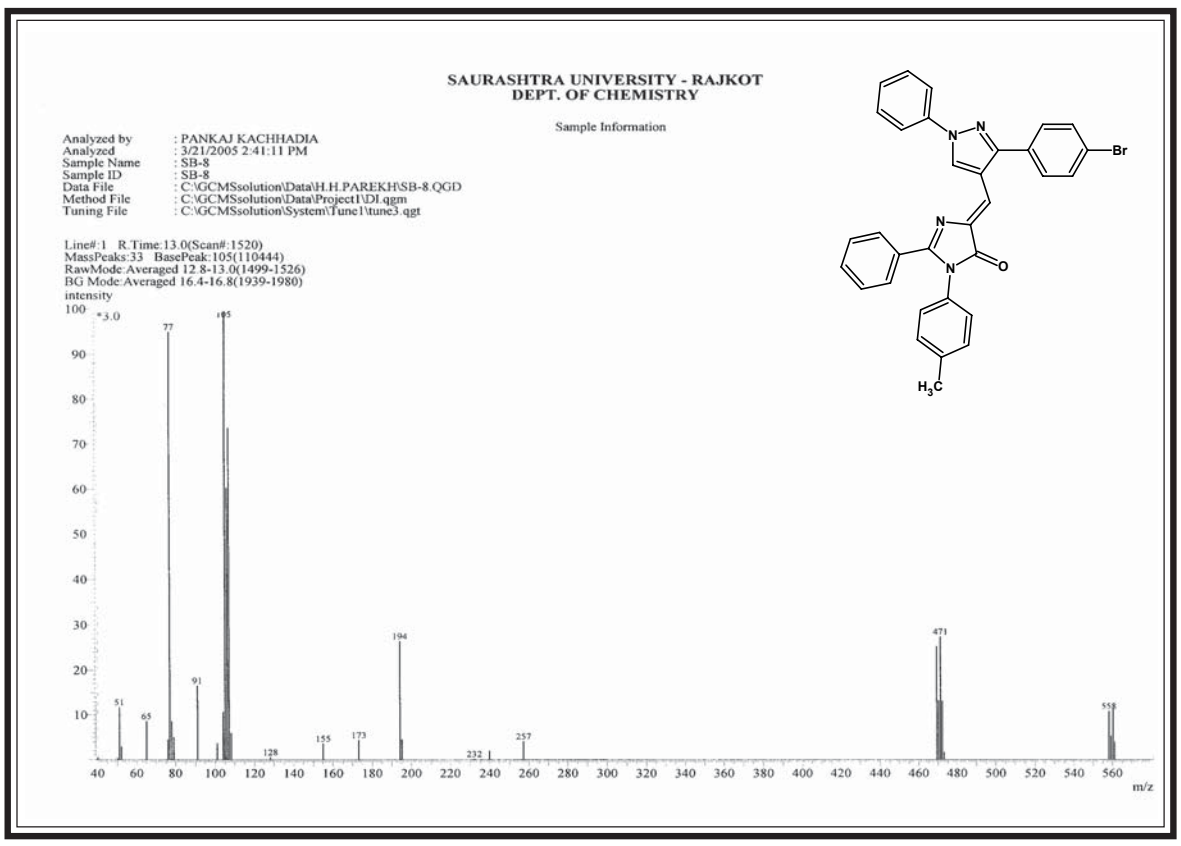


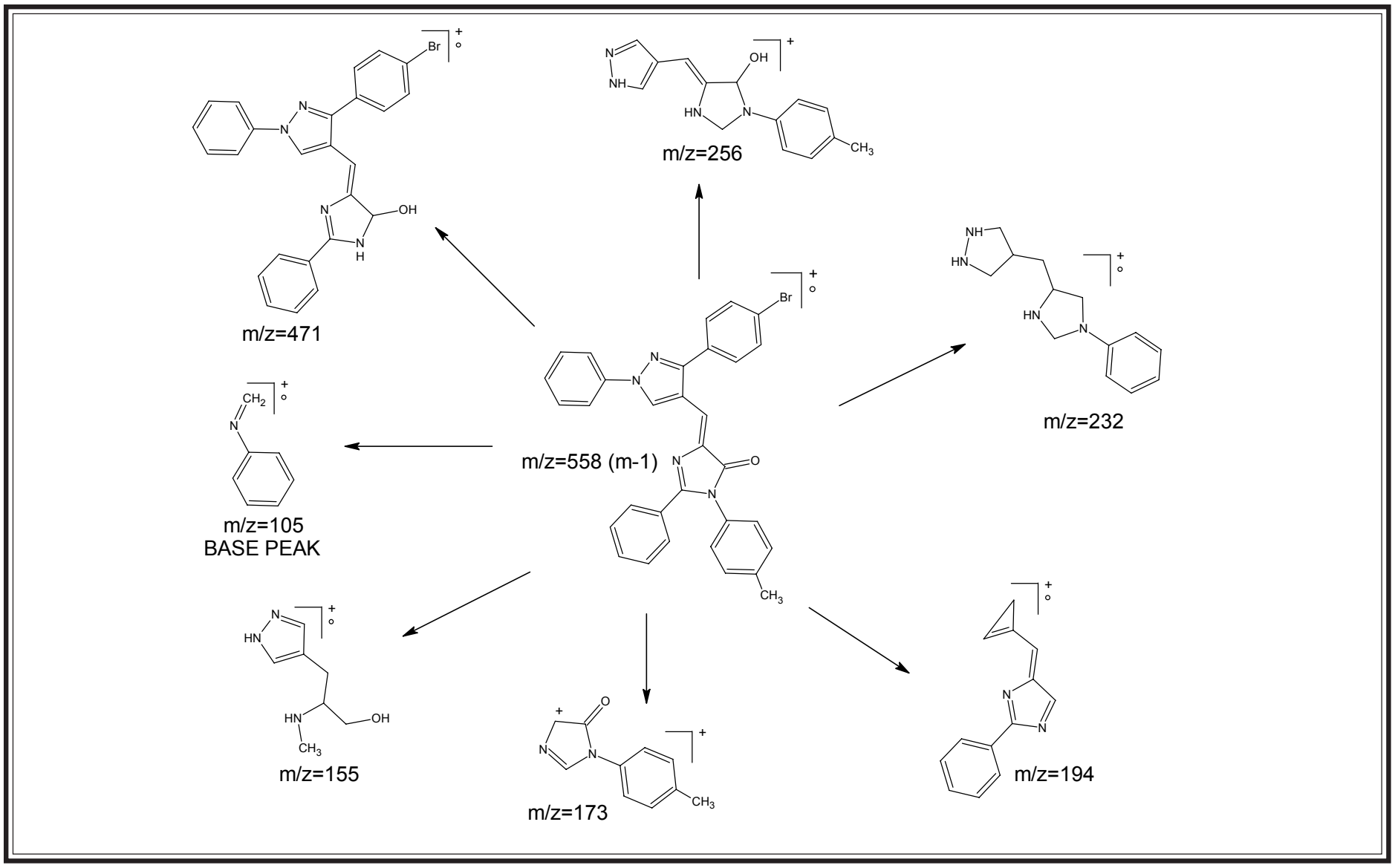
Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	2.34		3H	singlet	Ar-CH_3
2.	7.17-7.20	Jhi=9	2H	doublet	Ar-Hhh'
3.	7.23		1H	singlet	Ar-Hl
4.	7.30-7.33	Jih=9	2H	doublet	Ar-Hii'
5.	7.41-7.44	Jgf=9	2H	doublet	Ar-Hgg'
6.	7.51-7.60		8H	multiplet	ArHa,b,d,e Ar-Hj,k,m,n
7.	7.66		1H	triplet	Ar-Hc
8.	7.77-7.79	Jfg=7.5	2H	doublet	Ar-Hff'
9.	8.20		1H	singlet	Ar-Hx
10.	8.77		1H	singlet	Hy

EXPANDED AROMATIC REGION






m/z=471
m/z=256
m/z=232
m/z=558 (m-1)
m/z=105
BASE PEAK
m/z=155
m/z=173
m/z=194

EXPERIMENTAL

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

(A) Sythesis of 1,N-Phenyl-3-p-bromophenyl-4-formyl pyrazole

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

(B) Synthesis of 2-Phenyl-4-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-oxazolin-5-one

A mixture of 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole (3.26g, 0.01M), acetic anhydride (7.6ml, 0.075M), sodium acetate (2.0g, 0.025M) and hippuric acid (4.4g, 0.025M) was heated on waterbath for 4 hrs. Resulting mass was poured onto crushed ice, filtered, washed with hot water and crystallised from DMF. Yield, 2.31g, 71%, m.p. 152°C, ($C_{25}H_{16}BrN_3O_7$: Required C: 63.84; H: 3.43; N: 8.93; Found C : 63.80; H: 3.47; N: 8.97%).

TLC solvent system : Ethylacetate : Hexane (2 : 8)

(C) Synthesis of 1,N-Methylphenyl-2-phenyl-4-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolylmethino)-imidazolin-5-one

A mixture of 2-phenyl-4-(1',N-phenyl-3'-p-bromophenyl-4'-pyrazolyl methino)-oxazolin-5-one (4.70g, 0.01M) and p-toludine (1.07g, 0.01M) in dry pyridine (20 ml) was refluxed for 12 hrs. Resulting mass was poured onto crushed ice and neutralised with HCl, filtered and crystallised from DMF. Yield, 3.24g, 69%, m.p. 250°C ($C_{32}H_{23}BrN_4O$: Required C: 68.72; H: 4.14; N: 10.01; Found C: 68.76; H: 4.10; N: 10.05%).

TCL solvent system : Acetone : Benzene (1.5 : 8.5).

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

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

Antimicrobial testing was carried out as described in [A] Part-I, Section-I (F). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 10

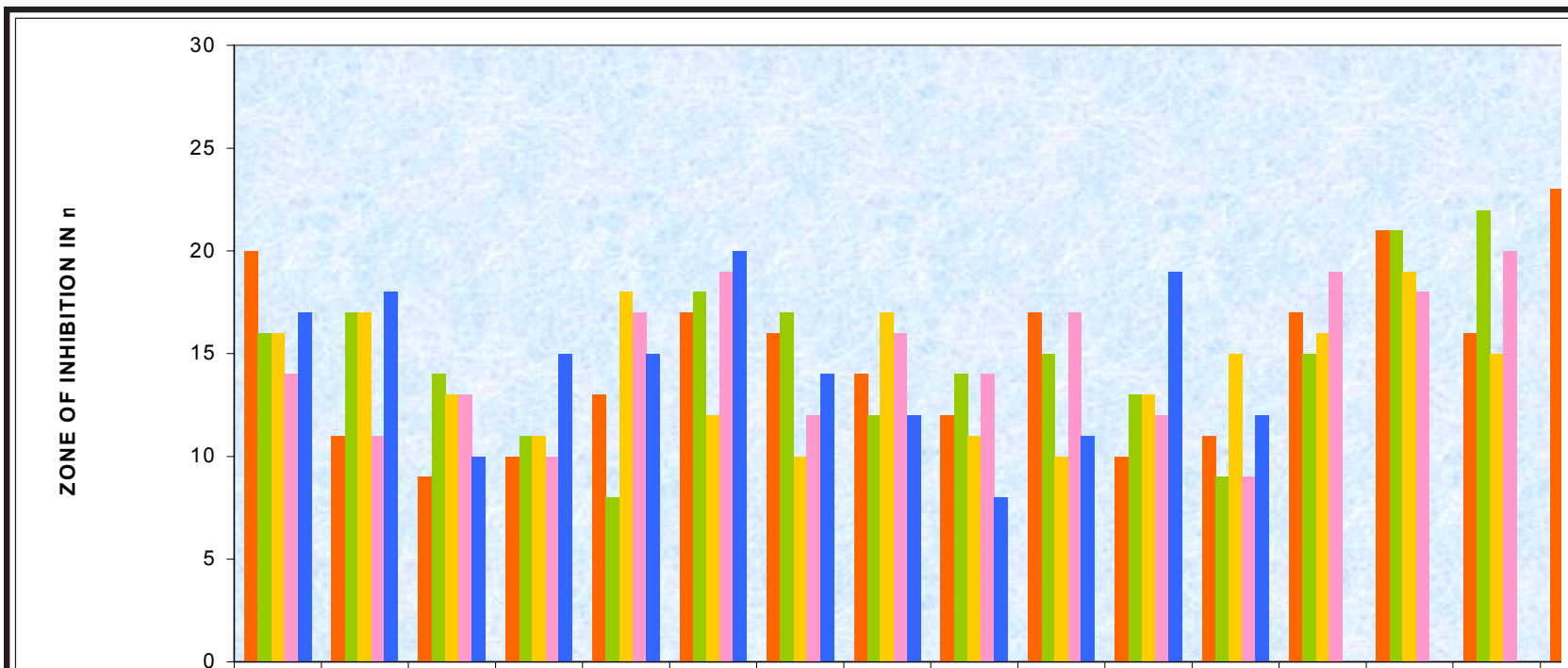
Antitubercular screening of the compounds of type (X) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 10a.

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

Sr. No. 1	R_1 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
10a	4-CH_3-C_6H_4-	$C_{32}H_{23}BrN_4O$	559.4	250	0.64	69	10.01	10.05
10b	2-OCH_3-C_6H_4-	$C_{32}H_{23}BrN_4O_2$	575.4	160	0.69	72	9.74	9.70
10c	4-OCH_3-C_6H_4-	$C_{32}H_{23}BrN_4O_2$	575.4	144	0.72	85	9.74	9.78
10d	3-Cl-C_6H_4-	$C_{31}H_{20}BrClN_4O$	579.8	150	0.80	63	9.66	9.62
10e	4-Cl-C_6H_4-	$C_{31}H_{20}BrClN_4O$	579.8	158	0.68	76	9.66	9.68
10f	4-F-C_6H_4-	$C_{31}H_{20}BrFN_4O$	563.4	194	0.75	65	9.94	9.98
10g	3-NO_2-C_6H_4-	$C_{31}H_{20}BrN_5O_3$	590.4	120	0.77	88	11.86	11.82
10h	4-NO_2-C_6H_4-	$C_{31}H_{20}BrN_5O_3$	590.4	155	0.74	74	11.86	11.88
10i	3-Cl,4-F-C_6H_3-	$C_{31}H_{19}BrClFN_4O$	597.8	130	0.67	66	9.37	9.33
10j	2,4-di-CH_3-C_6H_3-	$C_{33}H_{25}BrN_4O$	573.4	180	0.81	75	9.77	9.73
10k	2,4-di-Cl-C_6H_3-	$C_{31}H_{19}BrCl_2N_4O$	614.3	150	0.73	67	9.12	9.16
10l	3,4-di-Cl-C_6H_3-	$C_{31}H_{19}BrCl_2N_4O$	614.3	126	0.84	82	9.12	9.08

*TLC Solvent System : Acetone : Benzene (1.5 : 8.5)

GRAPHICAL CHART NO. 10 : 1,N-ARYL-2-ALKYL/ARYL-4-(1',N-PHENYL-3'-p-BROMOPHENYL -4'-PYRAZOLYLMETHINO)-IMIDAZOLIN-5-ONES



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	E n
B.coccus	20	11	9	10	13	17	16	14	12	17	10	11	17	21	16	
B.subtilis	16	17	14	11	8	18	17	12	14	15	13	9	15	21	22	
P.vulgaris	16	17	13	11	18	12	10	17	11	10	13	15	16	19	15	
E.coli	14	11	13	10	17	19	12	16	14	17	12	9	19	18	20	
A.niger	17	18	10	15	15	20	14	12	8	11	19	12	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

From the experimental data it has been concluded that the compounds bearing R=4-methylphenyl, 4-fluorophenyl and 2,4-dimethylphenyl have displayed considerable activity against ***B.coccus***. The compounds bearing R=2-methoxyphenyl, 4-fluorophenyl and 3-nitrophenyl have shown maximum activity against ***B.subtilis.***

In case of Gram negative bacterial strains, the significant activity was displayed by the compounds bearing R=2-methoxyphenyl, 4-chlorophenyl and 4-nitrophenyl against ***P.vulgaris*** and R=4-chlorophenyl, 4-fluorophenyl and 2,4-dimethylphenyl against ***E.coli.***

Antifungal activity :

All the compounds displayed mild activity except compound bearing R=4-fluorophenyl against ***A.niger.***

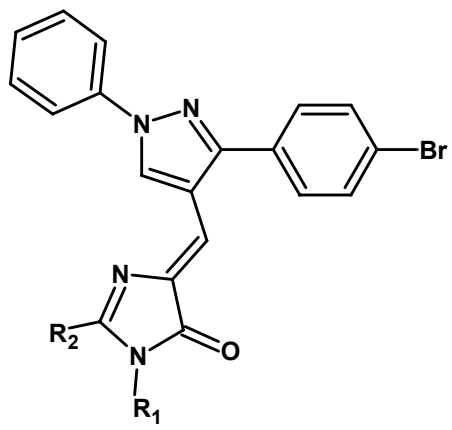
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

Almost all compounds were found to be less active against ***Mycobacterium tuberculosis*** $H_{37}Rv$ except 2-methoxyphenyl.

The antitubercular activity data have been compared with standard drug Rifampin.

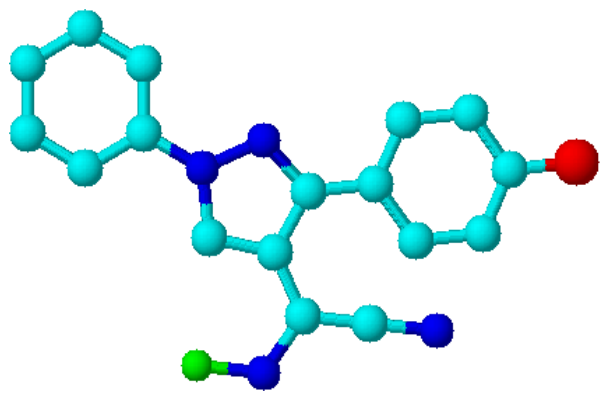
TABLE NO. 10a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



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*
295515	BSA-137	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	49	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295516	BSA-138	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	32	-	
295517	BSA-139	2-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	84	-	"
295518	BSA-140	2,4-$(CH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295519	BSA-141	2,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	37	-	"
295520	BSA-142	3,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	56	-	"
295521	BSA-143	3-Cl,4-F-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	34	-	"
295522	BSA-144	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	10	-	"
295523	BSA-145	4-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	10	-	"
295524	BSA-146	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295525	BSA-147	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	55	-	"
295526	BSA-148	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	50	-	"



PART-IV

STUDIES ON NITRILES

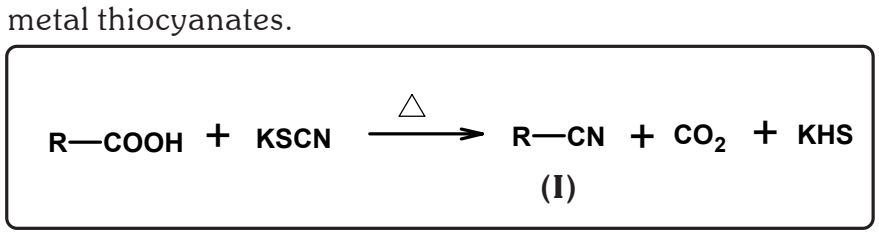
INTRODUCTION

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[439] in 1844. The first synthesis of nitrile has been reported by Wholer and Liebig[440] in 1832 and poleuze[441] in 1834. They are very much useful as intermediates for various products such as acrylonitrile for plastic synthetic rubber and fibers, phthalo nitrile for dye stuff. The simplest form of the organic nitriles is acetonitrile, often used as a solvent. Moreover nitrile gloves are also available which reduces pesticide and other hazardous chemicals exposure on your hands.

SYNTHETIC ASPECTS

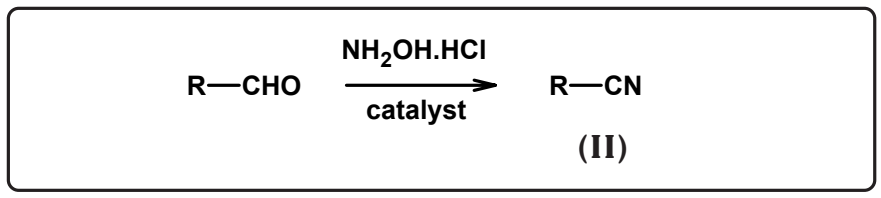
Few recent methods for the preparation of nitriles are as mentioned below.

1. E. A. Letts[442] has synthesised nitriles by the condensation of aromatic acids with metal thiocyanates.



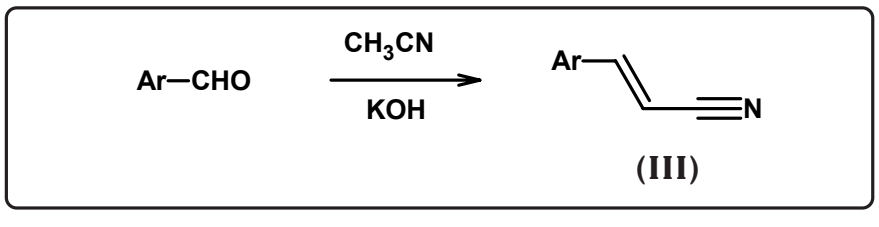
(I)

2. Biswanath Das et. al.[443] have prepared nitriles from aryl/alkyl aldehydes on treatment with $NH_2OH{\cdot}HCl$ under microwave irradiation in presence of $NaHSO_4$/ SiO_2 / HY-zeolite or silica chloride.



(II)

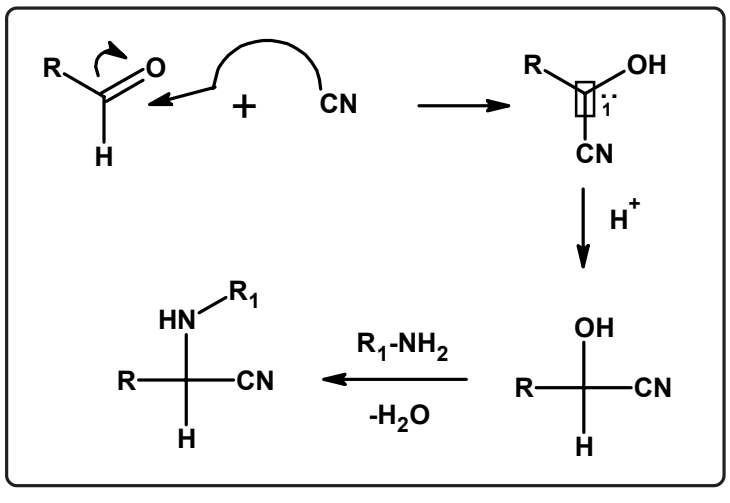
3. Stephen A. Dibiase et. al.[444] have synthesised E-& Z-cinnamonitrile from aryl aldehyde or ketones in presence of acetonitrile and potassium hydroxide.



(III)

MECHANISM

The mechanism of nitrile is shown as under.

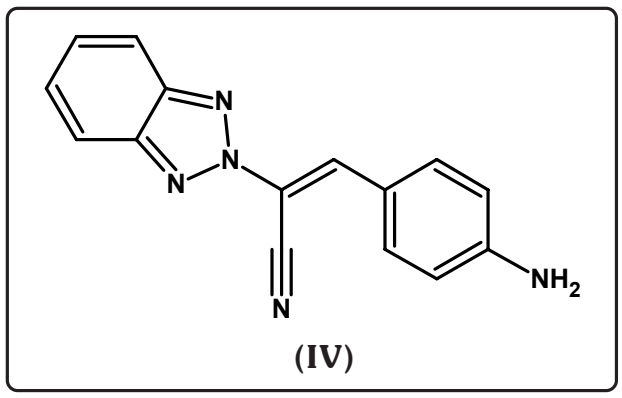


THERAPEUTIC IMPORTANCE

They shows various therapeutic activities which are described as under.

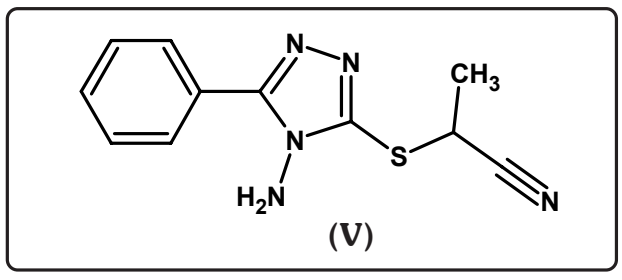
1. Antihypertensive[445]
2. Antimicrobial[446]
3. Antihypoxic[447]
4. Antiinflammatory[448]
5. Antiarrythemic[449]
6. Central nervous system agent[450]
7. Fungicidal[451]
8. Pesticidal[452]

Shibata yasushi and co-workers[453] have reported nitriles as insecticides. Parlo Sanna et. al.[454] have synthesised nitriles (IV) and screened for their antitubercular activity. Yogihara and co-workers[455] have documented antimicrobial and antiinflammatory activity of nitriles. Nosyrava et. al.[456] have formulated novel nitriles possessing muscle relaxant activity. Valmajer Juliya et. al.[457] have tested some new nitriles as anticonvulsant agent. Collin Xavier and co-workers[458] have synthesised nitriles and screened for their antifungal activity.



(IV)

Suzana Jovanovic *et*. al.[459] have suggested antiestrogenic activity of some nitrile derivatives. Bernard M. *et*. al.[460] have investigated nitriles as thromboxane receptor antagonists. Iwanowicz E. J. *et*. al.[461] have synthesised nitriles (V) and found preventing and treating IMPDH associated disorders, such as transplant rejection and autoimmune disease.



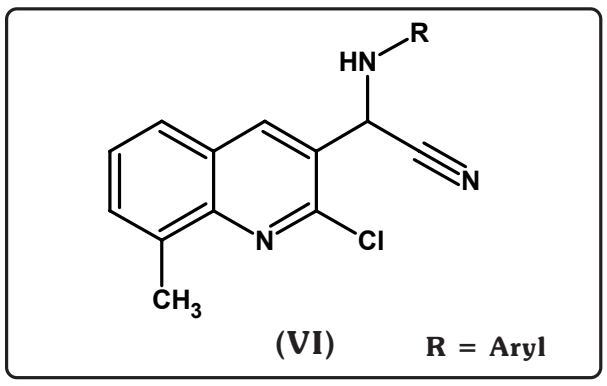
(V)

Recently, Olivier Nicolas and co-workers[462] have discovered nitrile derivatives possessing moderate antimalarial activity. S. Srinivasan *et*. al.[463] have investigated nitriles which showed antimicrobial activity. Ian J. S. Fairlamb *et*. al.[464] have prepared nitrile derivatives and tested for their antimicrobial activity. M. Hiroshi *et*. al.[465] have investigated some new nitriles and studied their pesticidal and marinantifouling activity.

Nurolaini Kifli *et*. al.[466] have discovered nitriles and reported their antiviral activity. Marion Nipper *et*. al.[467]have prepared nitriles useful as antimicrobial agent. Miroslav Otmar *et*. al.[468] have formulated nitriles possessing antiproliferative activity.

CONTRIBUTION FROM OUR LABORATORY

F. M. Bharmal and H. H. Parekh[469] have synthesised newer acetonitriles (VI) bearing quinoline moiety and tested them as antimicrobial agent.



(VI) **R = Aryl**

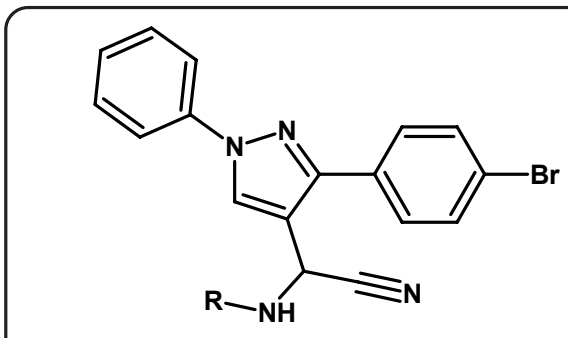
Looking to the interesting properties of nitriles, we have synthesised some new nitriles, which have been described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL EVALUATION OF α-ARYLAMINO-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-ACETONITRILES

SECTION-I

SYNTHESIS AND THERAPEUTIC EVALUATION OF α-ARYLAMINO-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-ACETONITRILES

Recently much interest has been focused on the synthesis and biodynamic activities of nitriles. With an intention for preparing agents with better therapeutic potency, the nitriles of type (XI) have been synthesised by the reaction of 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole with different aromatic amines in the presence of potassium cyanide and glacial acetic acid at 0-5°C.



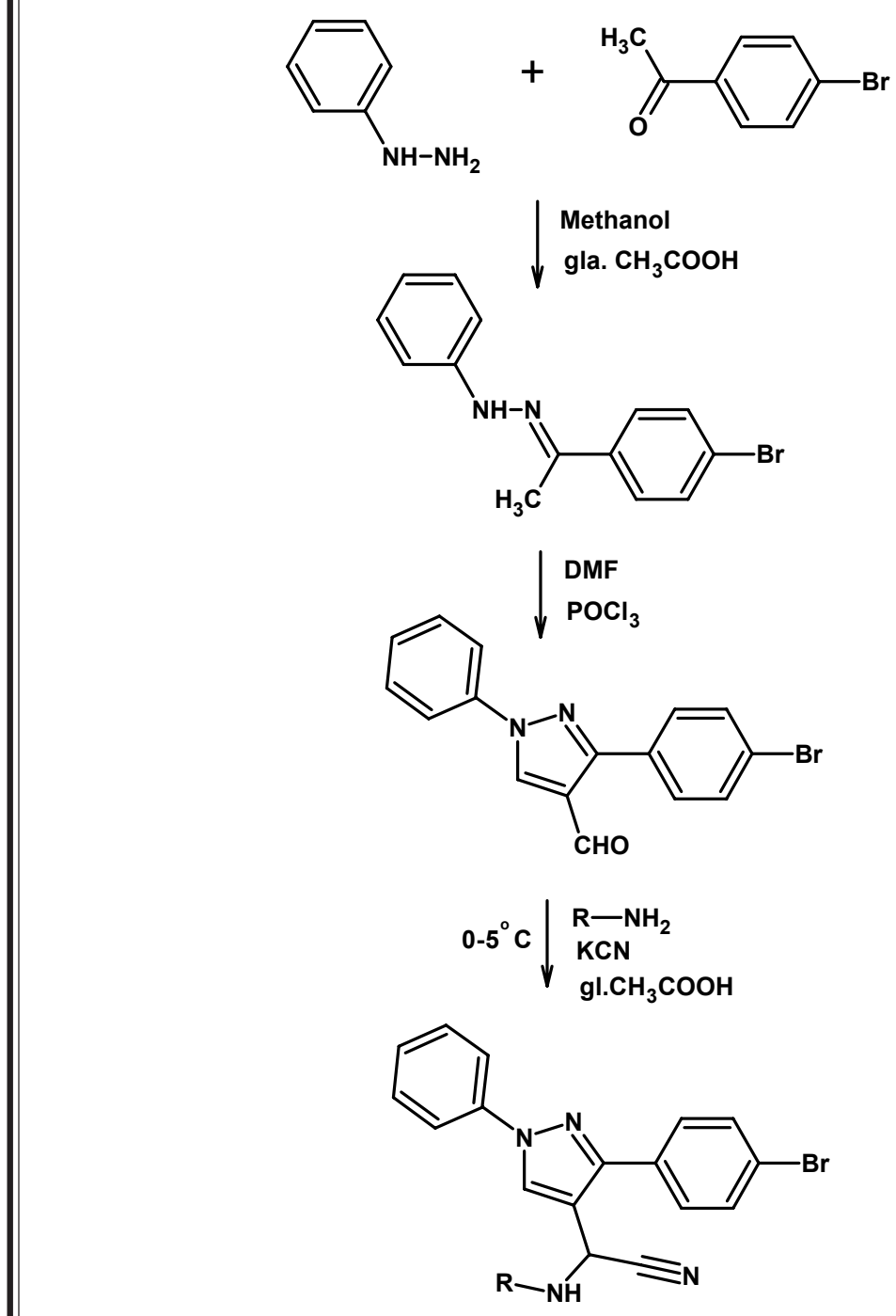
Type - (XI) R = Aryl

The constitution of the synthesised compounds have been supported by 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.

All the compounds 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. The biological activities of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 11.

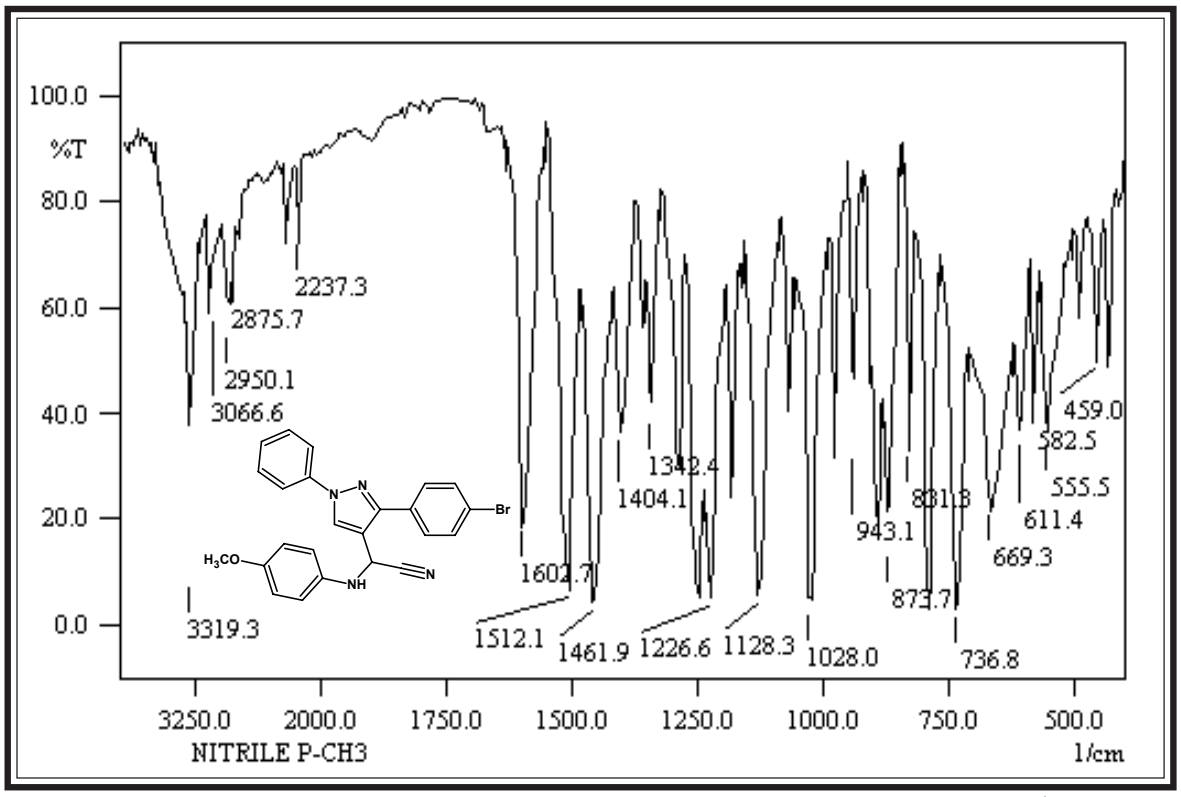
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** H_{37} ***Rv*** at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME



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

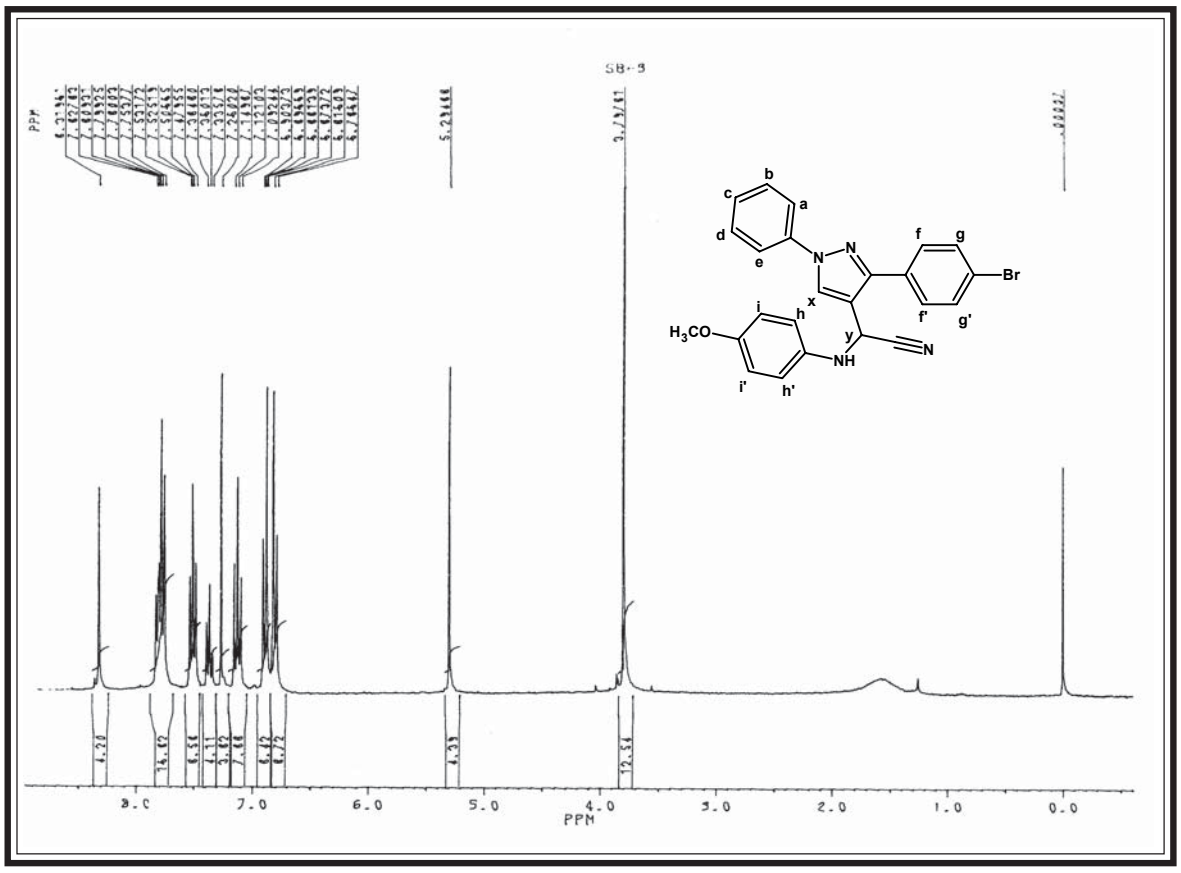
IR SPECTRAL STUDY OF α-p-ANISYLAMINO-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-ACETONITRILE



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.)	2950	2975–2950	498
$-CH_3$	C – H str (sym.)	2875	2880–2860	"
	C – H i.p. (def.)	1461	1470–1435	"
	C – H o.o.p (def)	1361	1385–1370	"
Aromatic	C – H str.	3066	3080–3030	503
	C = C str.	1512	1585–1480	"
	C – H i.p. (def.)	1128	1125–1090	"
		1028	1070–1000	"
	C – H o.o.p (def.)	831	835–810	"
Pyrazole	C = N str.	1602	1610–1590	499
moiety	C – N str.	1226	1230–1220	"
	C – Br str.	582	600–500	498
Nitrile	C ≡ N str.	2237	2240–2220	500
	N – H str. (sym.)	3319	3350–3200	"

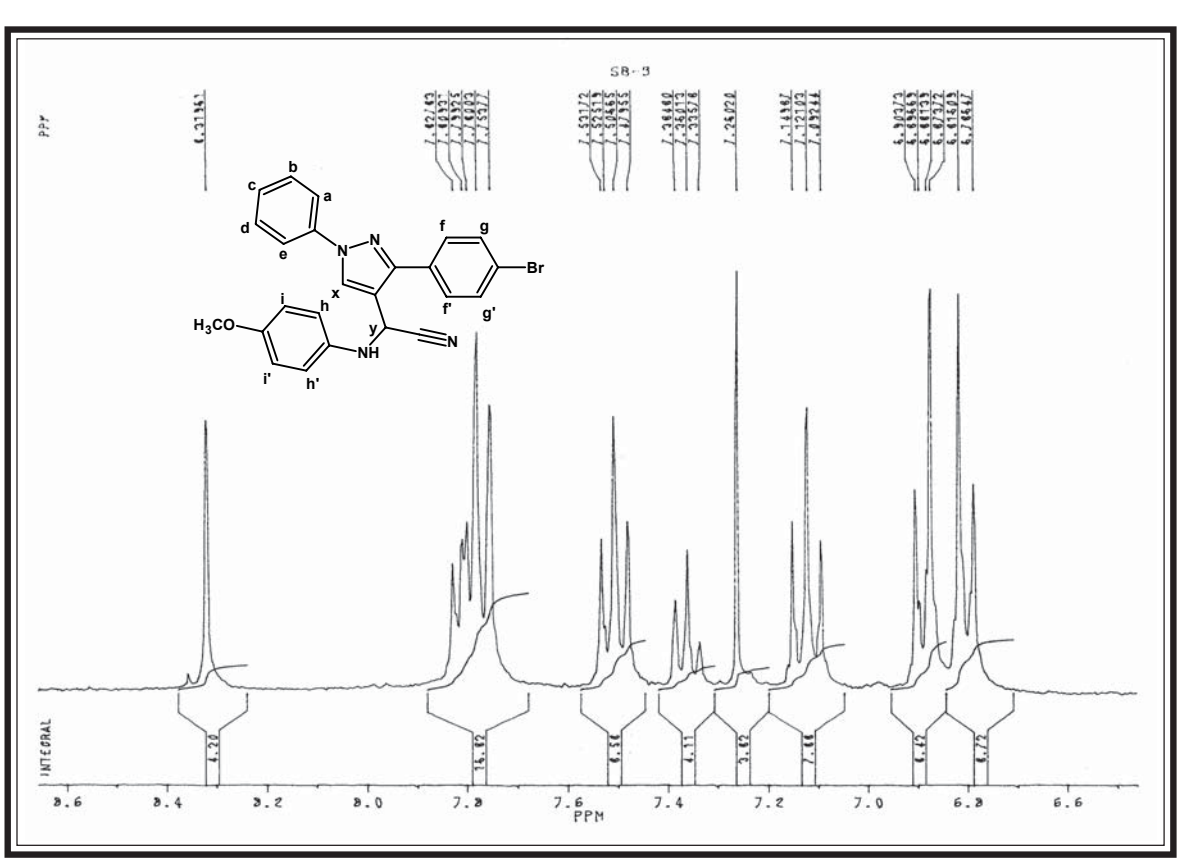
PMR SPECTRAL STUDY OF α-p-ANISYLAMINO-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-ACETONITRILE



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.79		3H	singlet	Ar-OCH_3
2.	5.29		1H	singlet	-CHy (nitrile)
3.	6.78-6.81	Jih=9	2H	doublet	Ar-Hii'
4.	6.87-6.90	Jhi=9	2H	doublet	Ar-Hhh'
5.	7.09-7.14		2H	triplet	Ar-Hb,Ar-Hd
6.	7.36		1H	triplet	Ar-Hc
7.	7.47-7.53		2H	triplet	Ar-Ha,Ar-He
8.	7.75-7.82		2H + 2H	multiplet	Ar-Hff',Ar-Hgg'
9.	8.31		1H	singlet	Ar-Hx

EXPANDED AROMATIC REGION

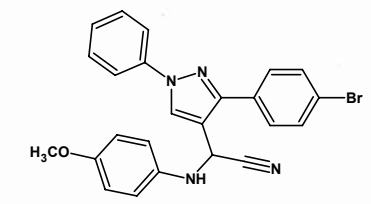


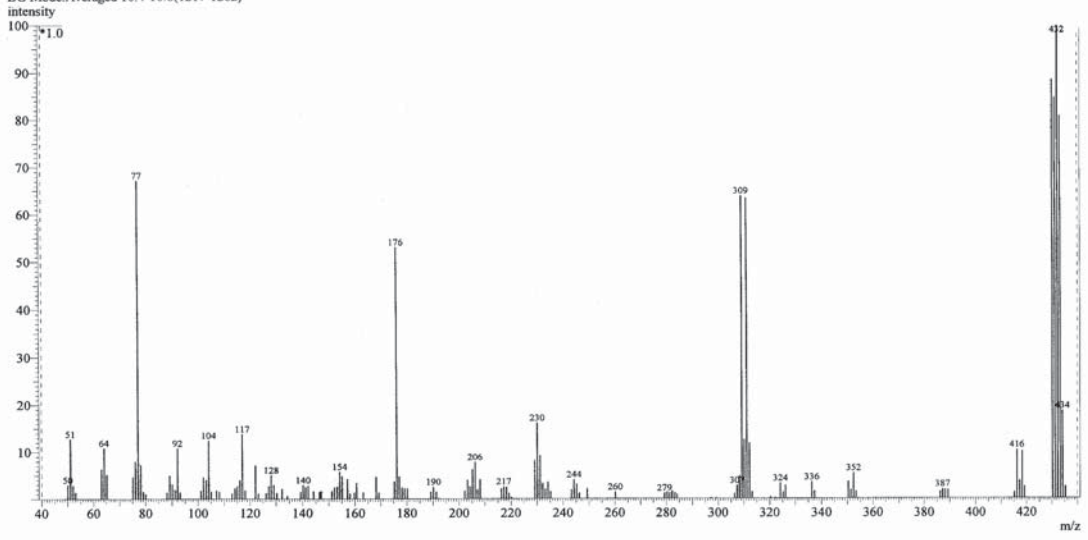
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

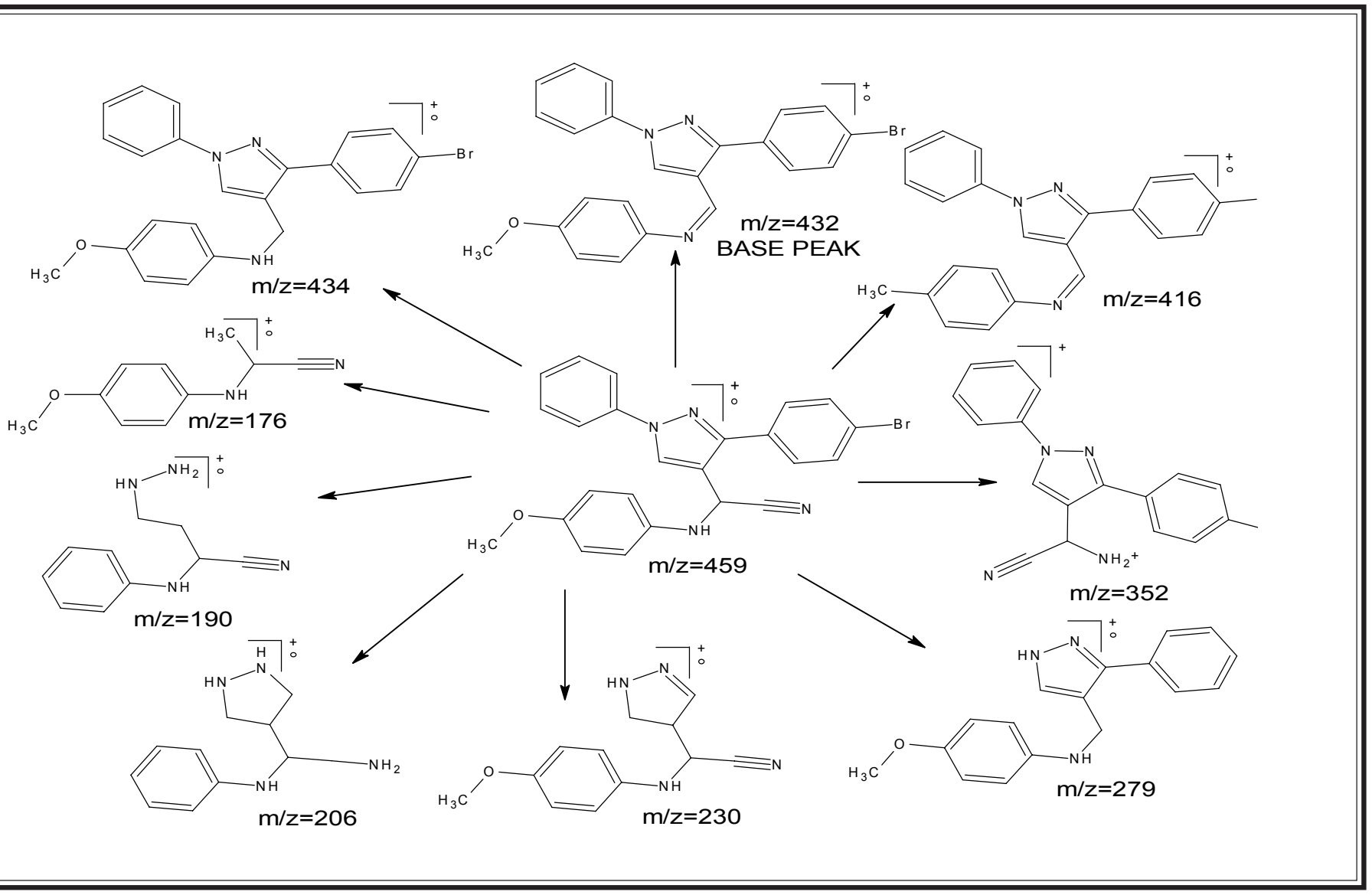
Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/28/2005 2:52:10 PM
Sample Name : SB-11
Sample ID : SB-11
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-11.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:8.2(Scan#:954)
MassPeaks:137 BasePeak:432(102016)
RawMode:Averaged 8.1-8.3(932-958)
BG Mode:Averaged 10.4-10.8(1217-1262)
intensity






m/z=434
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EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF α-ARYLAMINO-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-ACETONITRILES

(A) Sythesis of N-phenylamine-α-methyl-α-p-bromophenyl azomethine

See [B], Part-I, Section-I (A)

(B) Synthesis of 1,N-phenyl-3-p-bromophenyl-4-formyl pyrazole

See [B], Part-I, Section-I (B)

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

1,N-pheny-3-bromophenyl-4-formyl pyrazole (3.26g, 0.01M) dissolved in ethanol (25ml) was added to potassium cyanide (0.64g, 0.01M) dissolved in water (15 ml) followed by glacial acetic acid (12 ml). The contents were then stirred for 5 minutes to form cyanohydrine at 0°C. p-Anisidine (1.23g, 0.01M) dissolved in methanol was added to the reaction mixture, contents were stirred at room temperature for 24 hrs. The content was poured onto curshed ice. The solid product was filtered and crystallised from ethanol. Yield, 2.78g, 85%, m.p. 154°C, ($C_{24}H_{19}BrN_4O$: Required : C : 62.75; H, 4.17; N, 12.20; Found C, 62.71; H, 4.21; N, 12.24%).

TLC solvent system : Acetone : Benzene (1 : 9)

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

(D) Antimicrobial activity of α–Arylamino-1,N-phenyl-3-p-bromophenyl pyrazol-4-yl-acetonitriles

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

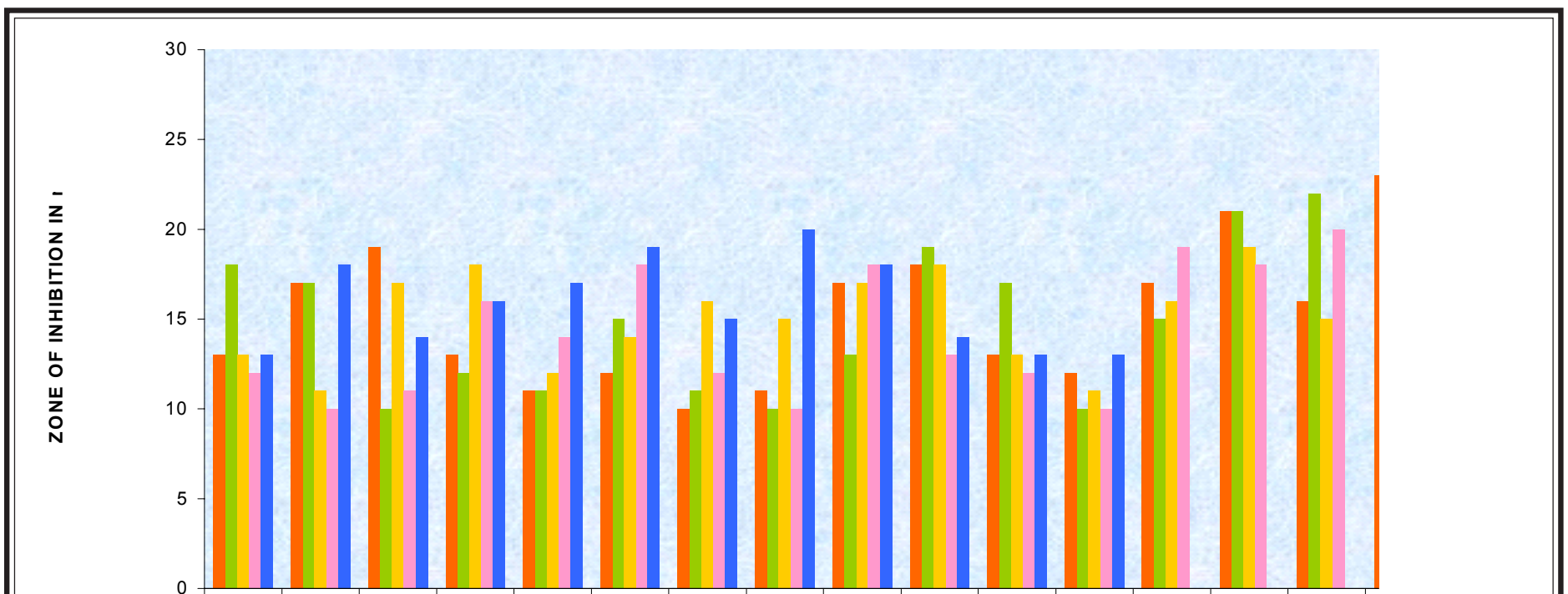
Antitubercular screening of the compounds of type (XI) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 11a.

TABLE NO. 11 : PHYSICAL CONSTANTS OF α-ARYLAMINO-(1'-N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-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	2-CH_3-C_6H_4-	$C_{24}H_{19}BrN_4$	443.3	164	0.82	72	12.64	12.61
11b	4-CH_3-C_6H_4-	$C_{24}H_{19}BrN_4$	443.3	184	0.85	77	12.64	12.68
11c	4-OCH_3-C_6H_4-	$C_{24}H_{19}BrN_4O$	459.3	154	0.77	85	12.20	12.24
11d	3-Cl-C_6H_4-	$C_{23}H_{16}BrClN_4$	463.7	172	0.69	62	12.08	12.12
11e	4-Cl-C_6H_4-	$C_{23}H_{16}BrClN_4$	463.7	169	0.84	66	12.08	12.04
11f	2-F-C_6H_4-	$C_{23}H_{16}BrFN_4$	447.3	127	0.85	79	12.53	12.57
11g	4-F-C_6H_4-	$C_{23}H_{16}BrFN_4$	447.3	172	0.67	80	12.53	12.49
11h	4-Br-C_6H_4-	$C_{23}H_{16}Br_2N_4$	508.2	178	0.83	73	11.02	11.06
11i	3-Cl,4-F-C_6H_3-	$C_{23}H_{15}BrClFN_4$	481.7	146	0.76	78	11.63	11.67
11j	2,4-di-CH_3-C_6H_3-	$C_{25}H_{21}BrN_4$	457.3	140	0.75	84	12.25	12.21
11k	3,4-di-Cl-C_6H_3-	$C_{23}H_{15}BrCl_2N_4$	498.2	155	0.74	69	11.25	11.21
11l	2,5-di-Cl-C_6H_3-	$C_{23}H_{15}BrCl_2N_4$	498.2	128	0.82	76	11.25	11.29

*TLC Solvent System :Acetone : Benzene (1 : 9) (11a - 11l)
(4 : 6) (11c, 11i, 11j, 11k)

GRAPHICAL CHART NO. 11 : á-ARYLAMINO-(1',N-PHENYL-3'-p-BROMOPHENYL-4'-PYRAZOLYL)-ACETONITRILES



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	Amoxycillin	Benzoylpenicillin	Ciprofloxacin	E
B.coccus	13	17	19	13	11	12	10	11	17	18	13	12	17	21	16	
B.subtilis	18	17	10	12	11	15	11	10	13	19	17	10	15	21	22	
P.vulgaris	13	11	17	18	12	14	16	15	17	18	13	11	16	19	15	
E.coli	12	10	11	16	14	18	12	10	18	13	12	10	19	18	20	
A.niger	13	18	14	16	17	19	15	20	18	14	13	13	0	0	0	

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

It has been observed from the experimental data that all compounds of type (XI) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

Almost all compounds were found to be inactive against ***B.coccus*** except R=2,4-dimethylphenyl. However, comparatively good activity was observed in compounds with R=2-methylphenyl and 2,4-dimethylphenyl against ***B.subtilis***.

The compounds bearing R=3-chlorophenyl and 2,4-dimethylphenyl have shown good activity against ***P.vulgaris***. The highest activity was observed in compounds bearing R=2-fluorophenyl and 2,5-dichlorophenyl against ***E.coli***.

Antifungal activity :

All the compounds exhibitied mild activity against ***A.niger*** except compound bearing R=4-bromophenyl which showed good activity against ***A.niger.***

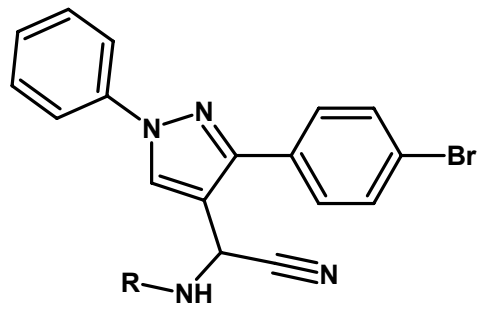
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

All the compounds displayed mild activity except compounds bearing R=3-chloro,4-fluorophenyl and 3,4-dichlorophenyl against ***Mycobacterium tuberculosis*** $H_{37}Rv$,

The antitubercular activity data have been compared with standard drug Rifampin.

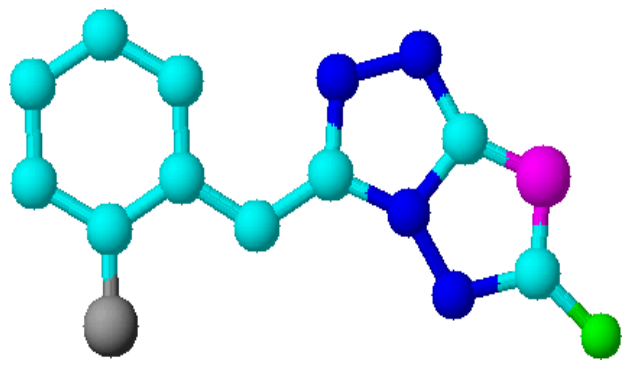
TABLE NO. 11a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



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*
295455	BSA-77	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	40	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295456	BSA-78	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	14	-	
295457	BSA-79	2-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	14	-	"
295458	BSA-80	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295459	BSA-81	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	18	-	"
295460	BSA-82	2-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	40	-	"
295461	BSA-83	4-F- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20	-	"
295462	BSA-84	4-Br- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	39	-	"
295463	BSA-85	3-Cl, 4-F-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	61	-	"
295464	BSA-86	2,4-$(CH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	22	-	"
295465	BSA-87	3,4-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	70	-	"
295466	BSA-88	2,5-$(Cl)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	28	-	"



[C]

STUDIES ON MICROWAVE INDUCED SYNTHESIS OF 2,3-DIHYDRO-1,3,4-THIADIAZOLOTRIAZOLES

INTRODUCTION

The term microwave was introduced just before World war-II. Microwave radiation is a descriptive term used to identity electromagnetic waves in frequency spectrum ranging from 1 Giga Hertz (10^9 Hz) to 30 Giga Hertz. These waves present several interesting and unusual features not found in other portions of the electromagnetic spectrum. These features make"microwaves" uniquely suitable for several useful applications like industrial, scintific, domestic and medicinal.

In recent years, the application of microwave heating in organic chemistry are of much interest. In the era of global warming, Microwave assisted reactions are of very much enviromently friendly as compared to conventional reactions. The advantages of microwave heating are decreased in rate of reaction and time, cleaner reactions, easier work up and better yields. It is also generally observed that the purity of products is improved due to shorter reaction period at high temperature and the absence of local overheating on the reaction walls which occurs under conventional heating.

Microwave heating is distinguished primarily by being a radiant process. Its relationship to ordinary heat is of much interest. Regular heat rays differ in frequency and properties. In the conventional method, heat is generated by molecular collisions which accomplish the energy transfer while microwaves cause heating through the absorption of energy quanta. Microwave generate instantaneous " incore" heating of materials, in a homogeneous and selective manner, especially those with poor heat conduction properties.

When molecules with permanent dipole are submitted to an electric field, they become aligned. If this field oscillates, the orientation changes at each alternation. The strong agitation provided by the reorientation of molecules, in phase with the electrical field excitation, caused an intense internal heating, upto 10^{o}C per second, when powerful waves are used.

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 product is heated and the ease of utilisation. Further more, as the depth of magnitude as the wavelength microwaves interact with substances of appreciable thickness (about 10 cm).

The interfacial polarisation, the Maxwell-Wagner effect, may also contribute to the heating effect when the conducting particles are in contact with a non conducting medium, e.g. in heterogenous reactions. It is particularly convenient that qualitatively the larger the dielecric constant, the greater the coupling with microwaves. Thus solvents such as water, methanol, DMF, ethyl acetate, chloroform, acetone acetic acid, dichloromethane and R-spirit are all heated when irradiated with microwaves. Non-polar solvents like carbon tetrachloride (CTC), toluene, xylene do not couple and therefore do not heat with microwave irradiation.

The rapid heating of food stuffs in microwave oven is routinely used by a significant proportion of mankind. However people have recognised other potential applications for this method of heating and scientists engaged in a number of disciplines have applied the rapid heating associated with microwave technology to a number of useful processes. These includes the preparation of samples for analysis[470], application to waste treatment[471], polymer technology[472], drug release/targeting[473] and ceramics. The technique has also found use in a range of decomposition[474] processes including hydrolysis of proteins and peptides.

In the recent years, MORE (Microwave induced Organic Reaction Enhancement) technique has become very popular. It has been reported that the rate of variety of organic reaction such as Diels Alder[475,476] Claisen reaction[477,478], Oxidation[479-481], Reduction[482], Diacetylation[483-485], Esterification[486] Hydrolysis of esters[487,488], Doenr Condensation[489], Konevenagel candensation[490] could be enhanced by microwave irradiation.

Generally, commercial microwave oven is being used in the chemical laboratory at a frequincy of 2450 MHz. The first application of microwave oven in organic synthesis began very recently. By the first experiments of Gedye and Giguere, the evidence for dramatic acceleration in some classical organic reactions established, and these were ascribed to temperature and pressure effects, when performed in closed Teflon vessels. The reaction can be carried out in teflon, polystyrene and glass vessels since these are transparent to microwaves. Microwave irradiation has also been applied for carrying out reactions in open vessels using organic solvents. The relatively low cost of modern domestic microwave oven makes them reasonably readily available to academic and industrial chemists.

Since solvents were used in these experiments, some problems with safe operation appeared and sometimes explosion resulted. Further development demonstrated the potential of solvent free reaction to solve these problems and to facilitate the scale-up of preparative runs. Recently, reactions under dry conditions using inorganic reagents are gaining more attention because of their enhance selectivity and milder conditions than those associated with conventional homogeneous reaction procedures. It should be noted that some of the inorganic additives reach temperatures in excess of 1000^{o}C very rapidly and decomposition of materials may be problematic, therefore some precautions regarding superheating and associated fire hazards or explosions are taken.

Detail review on "Microwave Assisted Reactions" by S. Caddick[491], involves variety of unusual chemical reactions like,

1. Aromatic Substitution Reactions
2. Alkane Functionalisation
3. Catalytic Transfer Hydrogenation
4. Oxime Synthesis
5. Radical Reactions
6. Peptide Synthesis

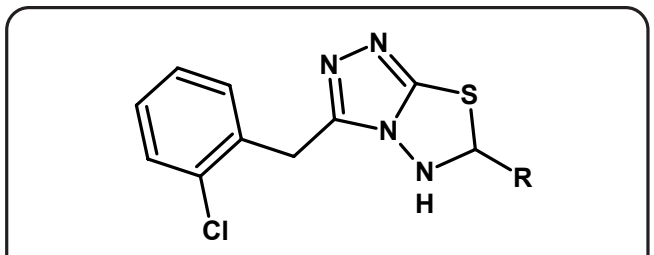
7. Rearrangements
8. Pericyclic Reactions

Dihydrothiadiazoles have attracted considerable attention as they appeared of interest to possess wide range of pharmacological activities. Synthetic aspect and therapeutic importance of 2,3-dihydro-1,3,4-thiadiazoles have been already discussed in [A], Part-I, studies on 1,3,4-thiadiazolotriazoles.

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLES BY CONVENTIONAL METHOD

Dihydrothiadiazoles play a vital role owing of their wide range of pharmacological activity. With a view to getting better therapeutic agents and to evaluate it's pharmacological profile, different type of dihydrothiadiazole derivatives of type (XII) have been prepared by the condensation of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazoles with different aromatic aldehydes in presence of p-toluenesulphonic acid.



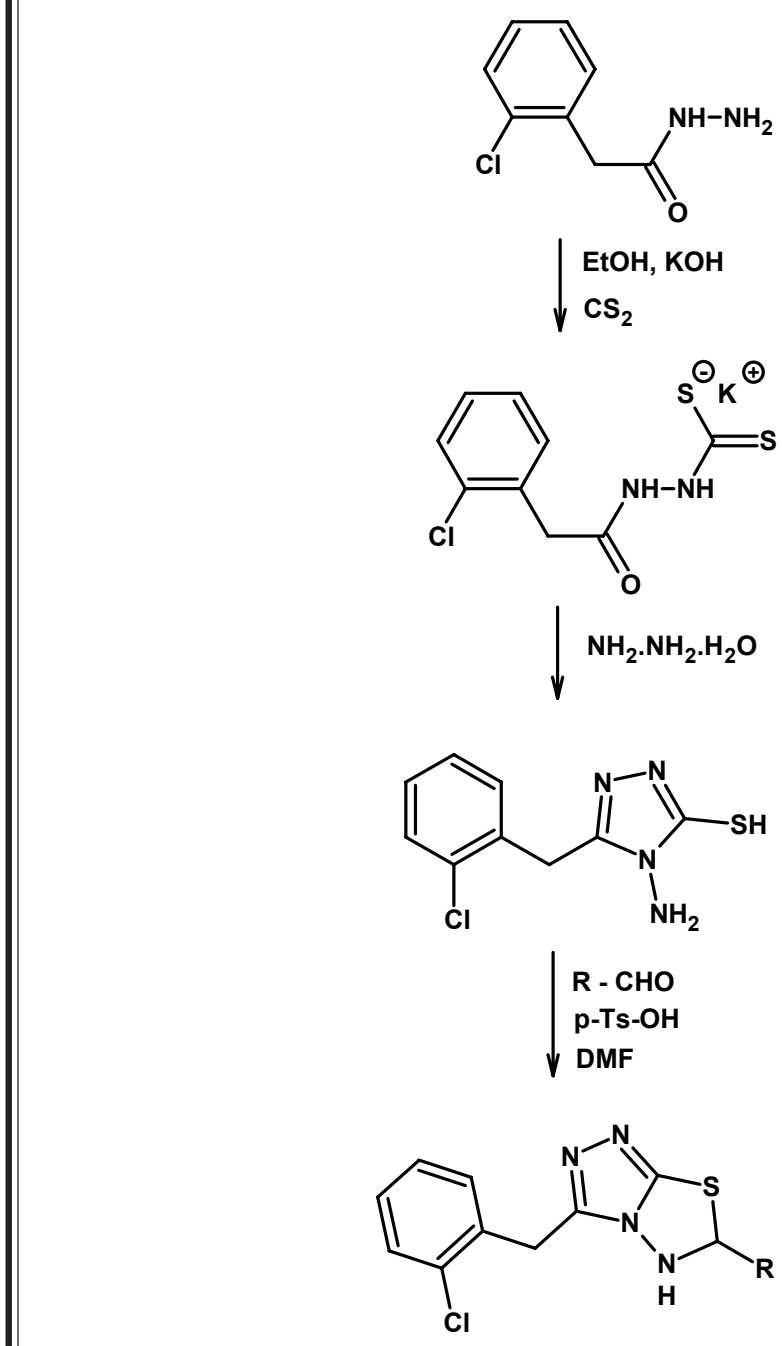
Type - (XII) R = Aryl

The constitution of newly synthesised compounds have been supported by 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.

All the compounds 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 40μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphicla Chart No. 12.

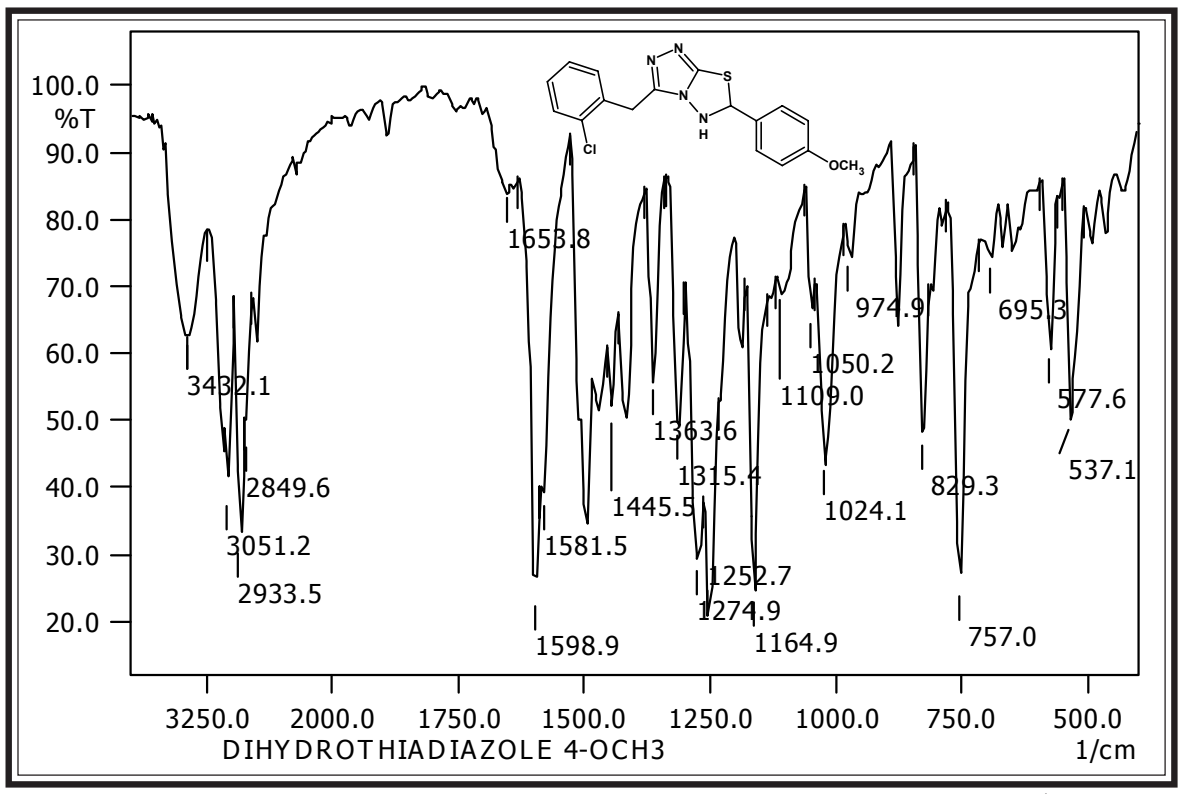
The synthesised compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** H_{37} ***Rv*** at concentration of 6.25 μg/ml using Rifampin as standard drug.

REACTION SCHEME



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

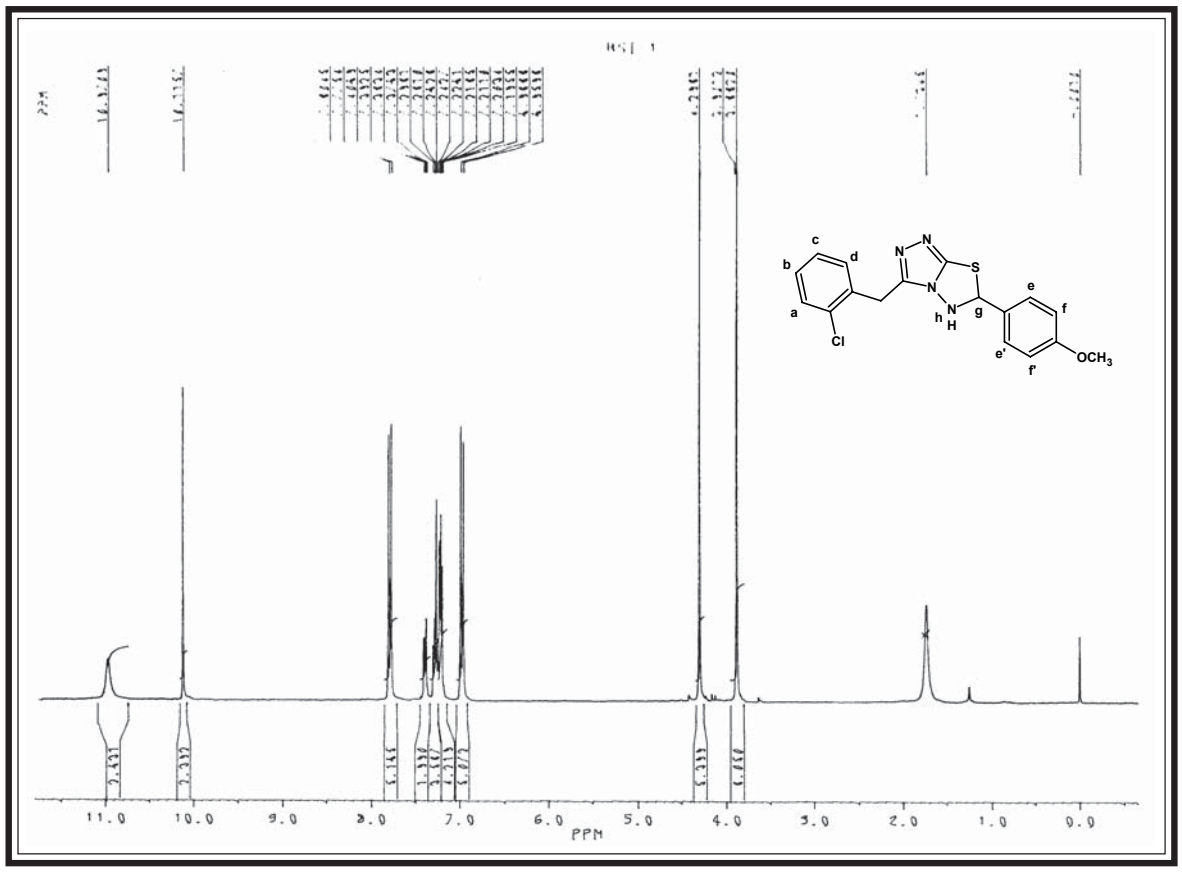
IR SPECTRAL STUDY OF 2-p-METHOXYPHENYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLE



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	498
$-CH_3$	C – H str (sym.)	2849	2880–1860	"
	C – H def. (asym.)	1445	1470–1435	"
	C – H def. (sym.)	1363	1385–1370	"
Aromatic	C – H str.	3051	3080–3030	503
	C = C str.	1581	1585–1480	"
	C – H i.p. def.	1109	1125–1090	"
		1050	1070–1000	"
	C – H o.o.p def.	829	835–810	"
Triazole	C = N str.	1598	1612–1593	504
	C – N str.	1164	1350-1200	498
	N – N str.	1024	1050–1010	"
	C – Cl sr.	757	800–600	503
Ether	C – O – C str. (asym.)	1252	1275–1200	498
	C – O – C str. (sym.)	974	1075–1020	"
Thiadiazole	N – H str.	3432	3450–3200	"
	N – N str.	1024	1050–1010	"
	C – S – C str.	695	720–570	503

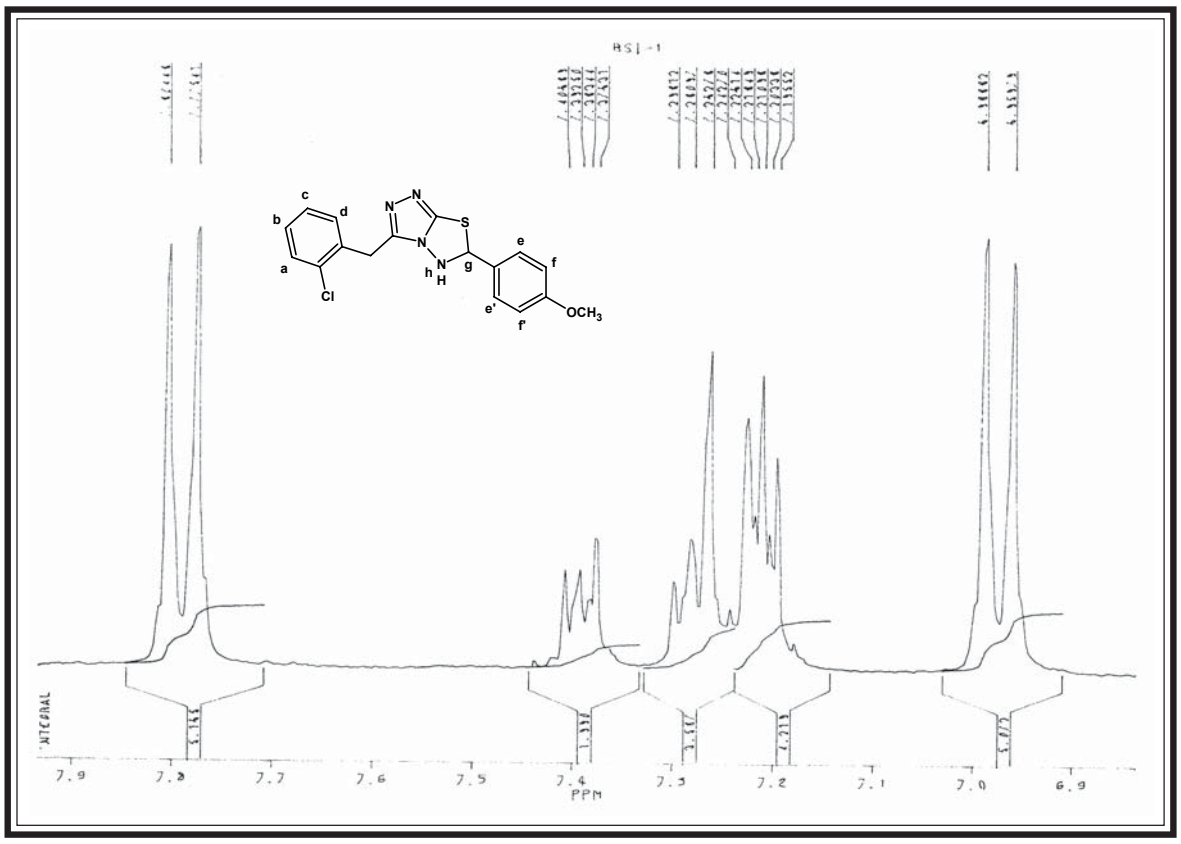
PMR SPECTRAL STUDY OF 2-p-METHOXYPHENYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO-[3,4-b]-1,3,4-THIADIAZOLE



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

Signal No.	Signal Position (δ ppm)	J Value In Hz	Relative No. of Protons	Multiplicity	Inference
1.	3.88		3H	singlet	Ar-OCH_3
2.	4.29		2H	singlet	-CH_2
3.	6.96	Jfe=9	2H	doublet	Ar-Hff'
4.	7.19-7.29		3H	multiplet	Ar-Hb, Ar-Hc Ar-Hd
5.	7.37-7.40		1H	triplet	Ar-Ha
6.	7.78	Jef=9	2H	doublet	Ar-Hee'
7.	10.11		1H	singlet	-CHg-
8.	10.97		1H	singlet	-NHh-

EXPANDED AROMATIC REGION

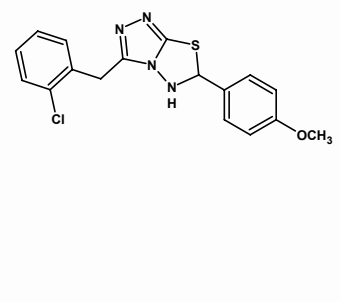


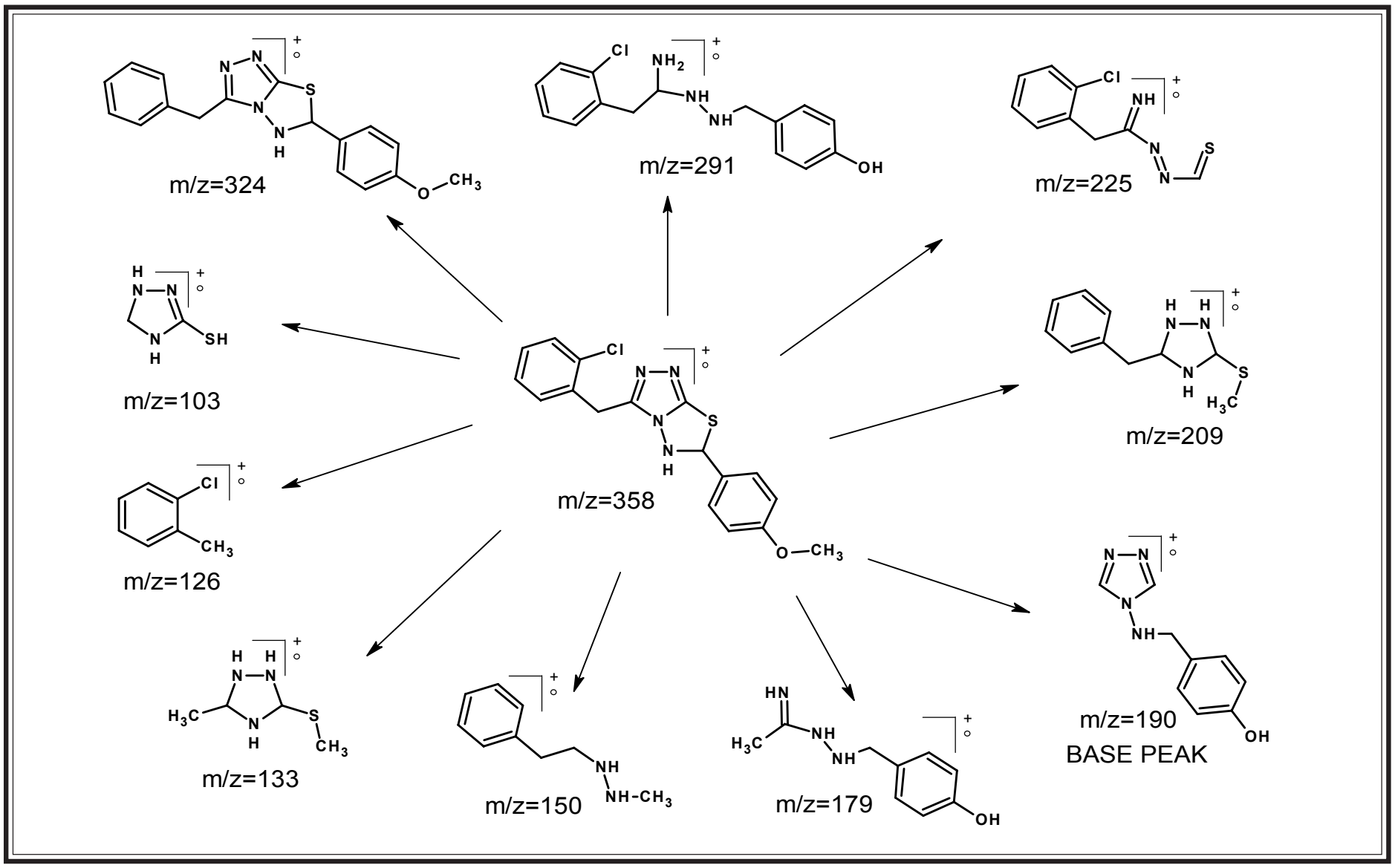
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Analyzed : 3/14/2005 3:23:42 PM
Sample Name : SB-5
Sample ID : SB-5
Data File : C:\GCMSsolution\Data\H.H.PAREKH\SB-5.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune3.qgt

Line#:1 R.Time:9.0(Scan#:1043)
MassPeaks:119 BasePeak:190(418486)
RawMode:Averaged 8.9-9.1(1038-1052)
BG Mode:Averaged 12.3-13.1(1443-1542)
intensity




m/z=324
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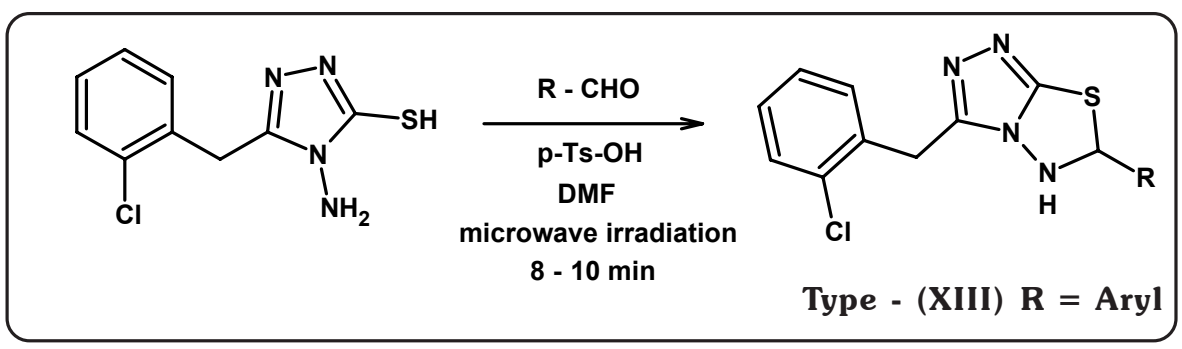
m/z=133
m/z=150
m/z=179
m/z=190
BASE PEAK

SECTION-II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLES BY MICROWAVE METHOD

As a part of our research program towards the non traditinal approach to the experimental set up of organic reactions, the concept of "Microwave induced Organic Reaction Enhancement" (MORE) chemistry has been utilised for rapid and efficient synthesis of some dihydrothiadiazoles which is described as under. The synthesis was carried out by irradiating condensation of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazol with different aromatic aldehydes in presence of p-toluenesulphonic acid.

Various preparations of the dihydro thiadiazoles by microwave irradiations are available in literature.[492-497]



The constitution of the synthesised compounds have been supported by using elemental analysis, 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 mass spectromatry m/z value indicates the molecular weight, i.e. when R=4-methoxy phenyl, molecular weight=358 m/z.

Q. Pro-M Microwave Oven, Questron Technologies corporation-CANADA, sample preparation system : 220 VAC, 60 Hz is used as a microwave irradiation source and data are compared in terms of yield and reaction period have been cited in Table No. 12a.

TABLE NO. 12a : COMPARISION OF CONVENTIONAL METHOD AND MICROWAVE INDUCED SYNTHESIS OF 2-ARYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [3,4-b]-1,3,4-THIADIAZOLES

Comp. No.	R	Thermal		Microwave		M.P. °C
		Reaction Period (hr.)	Yield %	Reaction Period (min.)	Yield %	
12a	C_6H_5-	10	54	8	79	190
12b	4-CH_3-C_6H_4-	14	66	9	76	202
12c	4-OCH_3-C_6H_4-	12	72	12	89	198
12d	2-Cl-C_6H_4-	12	56	6	77	160
12e	4-Cl-C_6H_4-	12	58	10	80	192
12f	4-F-C_6H_4-	12	62	8	74	196
12g	3-OH-C_6H_4-	11	49	8	68	165
12h	2-NO_2-C_6H_4-	13	64	8	78	180
12i	3-NO_2-C_6H_4-	13	68	8	72	> 300
12j	3-OCH_3,4-OH-C_6H_3-	12	59	10	81	208
12k	3,4-$(OCH_3)_2$-C_6H_3-	12	69	10	85	170
12l	9-$C_{14}H_9$-	10	75	6	84	142

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO[3,4,-b]-1,3,4-THIADIAZOLES

[A] Synthesis of potassium o-chlorophenylacetamido dithiocarbamate

See [A], Part-I, Section-I (C).

[B] Synthesis of 3-Mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole

See [A] Part-I, Section-I (D).

SECTION-I :

[A] Synthesis of 2-p-methoxyphenyl-4-o-chlorobenzyl-2,3-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles by conventional method.

A mixture of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole (2.40g, 0.01M), p-anisaldehyde (1.36g, 0.01M) in dry DMF (20 ml) and p-toluene sulphonic acid (50 mg) was refluxed for 12 hrs. The reaction mixture was poured onto crushed ice. The product was isolated and crystallised from ethanol. Yield 1.72g, 72%, m.p. 198°C, ($C_{17}H_{15}ClN_4OS$: Required : C, 56.90; H, 4.21; N, 15.61; Found : C, 56.86; H, 4.25; N, 15.57%).

TLC solvent system : Acetone : Benzene (4 : 6).

Similarly, other derivatives were synthesised. The physical data are recorded in Table No. 12.

(B) Antimicrobial activity of 2-Aryl-4-o-chlorobenzyl-2,3-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles.

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

Antitubercular screening of the compounds of type (XII) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (F) and the percentage of inhibition data of the compounds are recorded in Table No. 12a.

SECTION - II

(A) Synthesis of 2-p-methoxyphenyl-4-o-chlorobenzyl-2,3-dihydro-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles by microwave method.

A mixture of 3-mercapto-4,N-amino-5-o-chlorobenzyl-1,2,4-triazole (2.40g, 0.01M) p-anisaldehyde (1.36g, 0.01M) in dry DMF (20 ml) and p-toluene sulphonic acid (50 mg) was irradiated in a microwave oven for 8-10 min at 280 watts. The contents were cooled and poured onto crushed ice. The product was isolated and crystallised from ethanol. Yield 2.14g, 89%, m.p. 198°C.

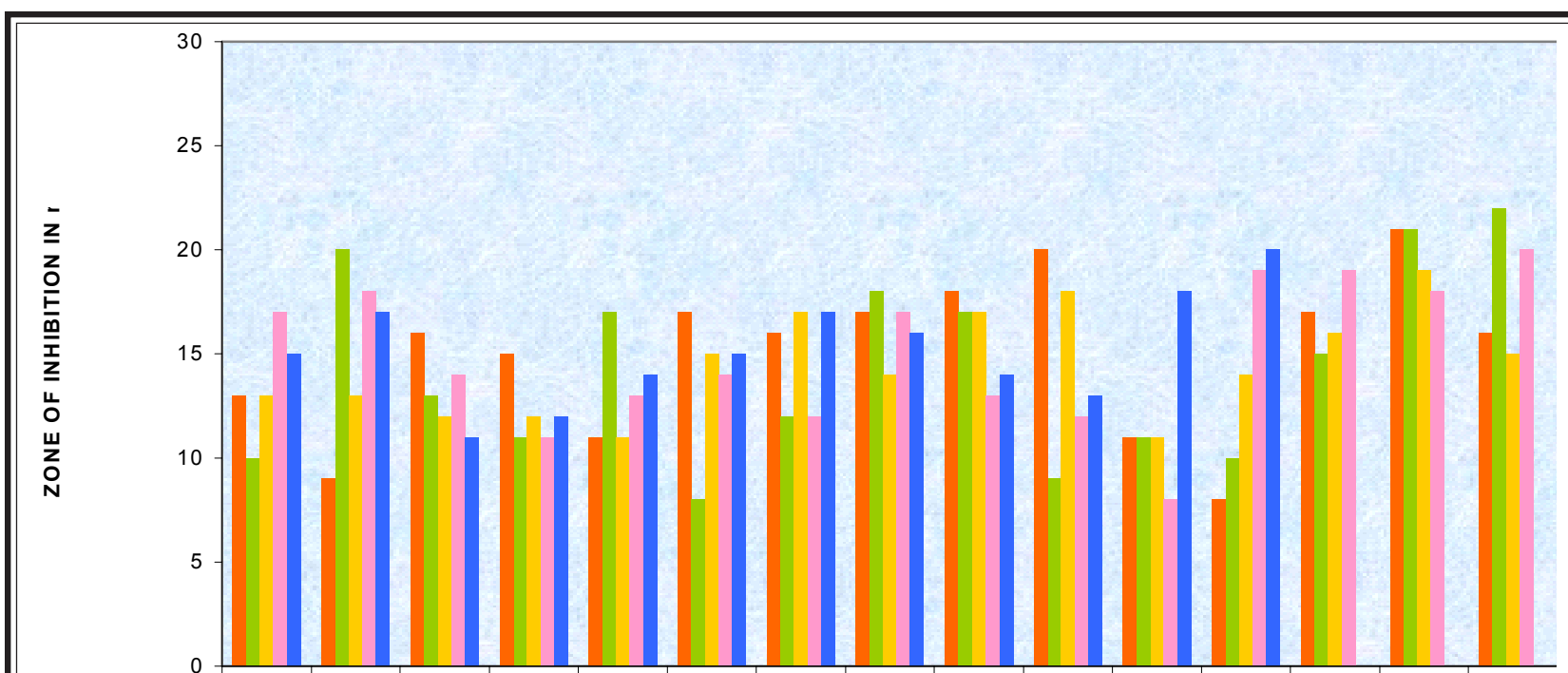
Similarly other derivatives have been synthesised.

TABLE NO. 12 : PHYSICAL CONSTANTS OF 2-ARYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO[3,4,-b]-1,3,4-THIADIAZOLES

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-	$C_{16}H_{13}ClN_4S$	328.8	190	0.80	54	17.04	17.08
12b	4-CH_3-C_6H_4-	$C_{17}H_{15}ClN_4S$	342.8	202	0.74	66	16.34	16.30
12c	4-OCH_3-C_6H_4-	$C_{17}H_{15}ClN_4OS$	358.8	198	0.78	72	15.61	15.57
12d	2-Cl-C_6H_4-	$C_{16}H_{12}Cl_2N_4S$	363.2	160	0.79	56	15.42	15.38
12e	4-Cl-C_6H_4-	$C_{16}H_{12}Cl_2N_4S$	362.2	192	0.81	58	15.42	15.46
12f	4-F-C_6H_4-	$C_{16}H_{12}ClFN_4S$	346.8	196	0.76	62	5.48	5.44
12g	3-OH-C_6H_4-	$C_{16}H_{13}ClN_4OS$	344.8	165	0.75	49	16.25	16.27
12h	2-NO_2-C_6H_4-	$C_{16}H_{12}ClN_5O_2S$	373.8	180	0.64	64	18.73	18.77
12i	3-NO_2-C_6H_4-	$C_{16}H_{12}ClN_5O_2S$	372.8	>300	0.70	68	18.73	18.70
12j	3-OH,4-OCH_3-C_6H_3-	$C_{16}H_{15}ClN_4O_2S$	374.8	208	0.80	59	14.95	14.92
12k	3,4-$(OCH_3)_2$-C_6H_3-	$C_{18}H_{17}ClN_4O_2S$	388.8	170	0.66	69	14.41	14.37
12l	9-$C_{14}H_9$	$C_{23}H_{16}ClN_4S$	429.9	142	0.68	75	16.29	16.26

*TLC Solvent System :Ethyl acetate : Hexane (1 : 9) (12a - 12l)
(4 : 6) (12c, 12i, 12j, 12k)

GRAPHICAL CHART NO. 12 : 2-ARYL-4-o-CHLOROBENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO[3,4-b]-1,3,4-THIADIAZOLES



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Amoxy cillin	Benzoy lpenicill in	Ciprofl oxacin
B.coccus	13	9	16	15	11	17	16	17	18	20	11	8	17	21	16
B.subtilis	10	20	13	11	17	8	12	18	17	9	11	10	15	21	22
P.vulgaris	13	13	12	12	11	15	17	14	17	18	11	14	16	19	15
E.coli	17	18	14	11	13	14	12	17	13	12	8	19	19	18	20
A.niger	15	17	11	12	14	15	17	16	14	13	18	20	0	0	0

RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY :

Antibacterial activity :

It has been concluded from the experimental data that all the dihydrothiadiazole derivatives (XII) markedly inhibit the growth of Gram positive bacteria and also Gram negative bacteria.

All compounds show moderate activity against Gram positive bacteria. However, maximum activity was observed in compounds bearing R=2-fluorophenyl, 4-nitrophenyl, 3-nitrophenyl and 3-hydroxy,4-methoxyphenyl against ***B.coccus*** whereas R=4-methylphenyl, 4-chlorophenyl, 2-nitrophenyl and 3-nitrophenyl against ***B.subtilis.***

In case of Gram negative bacterial strains, the maximum activity was displayed by the compounds bearing R=3-hydroxyphenyl, 3-nitrophenyl and 3-hydroxy,4-methoxyphenyl against ***P.vulgaris***. While the compounds with R=phenyl,4-methylphenyl and 9-anthryl have shown considerable activity against ***E.coli.***

Antifungal activity :

The antifungal data revealed that compounds were least toxic to the fungal strain. However, mild activity was shown by the compound bearing R=9-anthryl against ***A.niger***.

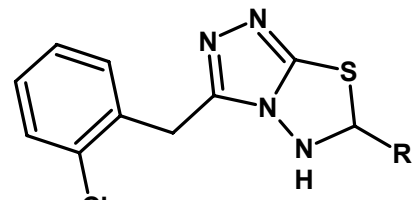
The antibacterial activity was compared with standard drugs viz. Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Greseofulvin.

Antitubercular activity :

Almost all compounds were found to be inactive against ***Mycobacterium tuberculosis*** $H_{37}Rv$ except 4-chlorophenyl and 9-anthryl.

The antitubercular activity data have been compared with standard drug Rifampin.

TABLE NO. 12a : 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*
295431	BSA-53	C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	Mic Rifampin = 0.25 µg/ml @ 98% Inhibition
295432	BSA-54	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	
295433	BSA-55	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295434	BSA-56	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	15	-	"
295435	BSA-57	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295436	BSA-58	3-OH- C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295437	BSA-59	4-CH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295438	BSA-60	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295439	BSA-61	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295440	BSA-62	3-OCH_3,4-OCH_3-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295441	BSA-63	3,4-$(OCH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	0	-	"
295442	BSA-64	9-$C_{14}H_9$-	Alamar	$H_{37}Rv$	>6.25	38	-	"

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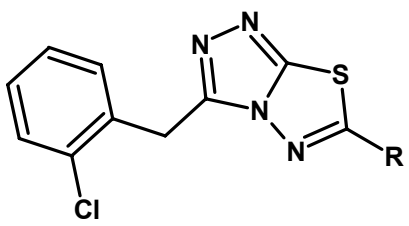
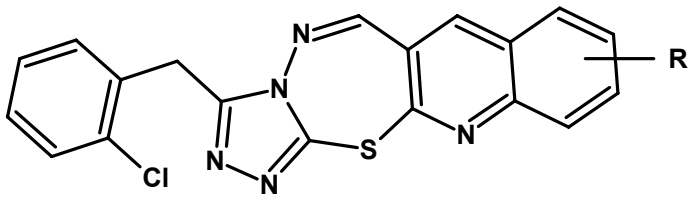
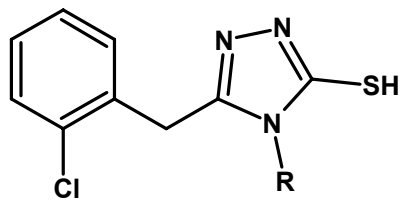
LIST OF NEW COMPOUNDS







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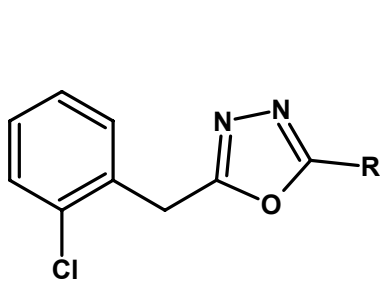
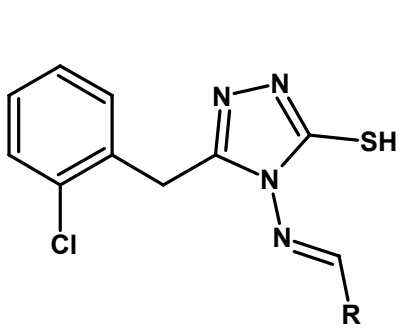
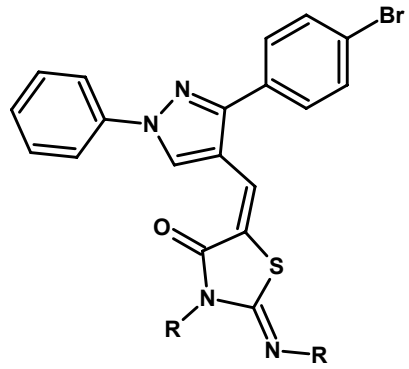
3-OCH_3-C_6H_4-	8-CH_3	4-CH_3-C_6H_4-
4-OCH_3-C_6H_4-	6-OCH_3	4-OCH_3-C_6H_4-
4-Cl-C_6H_4-	8-OCH_3	2-Cl-C_6H_4-
4-F-C_6H_4-	6-Cl	3-Cl-C_6H_4-
4-Br-C_6H_4-	7-Cl	4-Cl-C_6H_4-
4-NO_2-C_6H_4-	8-Cl	2-F-C_6H_4-
2-NH_2-C_6H_4-	8-F	4-F-C_6H_4-
2-OH-C_6H_4-	6,8-$(CH_3)_2$	3-NO_2-C_6H_4-
2-$OCOCH_3$-C_6H_4-	6,7-$(Cl)_2$	4-NO_2-C_6H_4-
2,4-$(OH)_2$-C_6H_3-	6-F, 7-Cl	2,5-$(Cl)_2$-C_6H_3-
-CH_2-C_6H_4		3,4-$(Cl)_2$-C_6H_3-
-CH=CH-C_6H_5		2,4-$(CH_3)_2$-C_6H_3-
C_5H_4N-		3-Cl,4-F-C_6H_3-







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4-OCH_3-C_6H_4-	2-Cl-C_6H_4-	4-CH_3-C_6H_4-
2-Cl-C_6H_4-	4-Cl-C_6H_4-	4-OCH_3-C_6H_4-
4-Cl-C_6H_4-	4-F-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	2-NO_2-C_6H_4-	4-F-C_6H_4-
4-Br-C_6H_4-	3-NO_2-C_6H_4-	4-NO_2-C_6H_4-
2-OH-C_6H_4-	2-OH-C_6H_4-	4-COOH
4-OH-C_6H_4-	4-OH-C_6H_4-	3-Cl, 4-F-C_6H_3-
2-NH_2-C_6H_4-	9-$C_{14}H_9$-	2,4-di-Cl-C_6H_3-
4-NH_2-C_6H_4-	3-OH, 4-OCH_3-C_6H_3-	2,5-di-Cl-C_6H_3-
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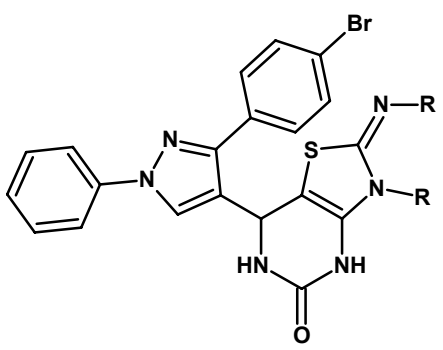

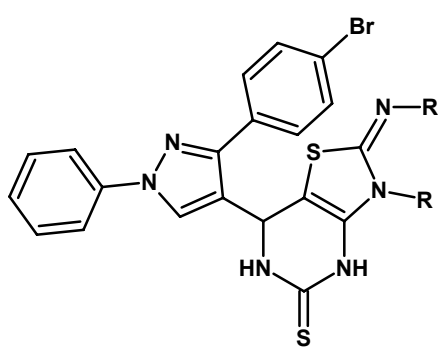

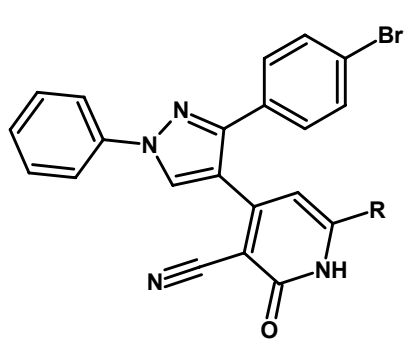

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4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-OCH_3-C_6H_4-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-Cl-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-F-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-Br-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-COOH-C_6H_4-	4-COOH-C_6H_4-	4-NO_2-C_6H_4-
3-Cl, 4-F-C_6H_3-	3-Cl, 4-F-C_6H_3-	4-NH_2-C_6H_4-
2,4-di-Cl-C_6H_3-	2,4-di-Cl-C_6H_3-	2-OH-C_6H_4-
2,5-di-Cl-C_6H_3-	2,5-di-Cl-C_6H_3-	4-OH-C_6H_4-
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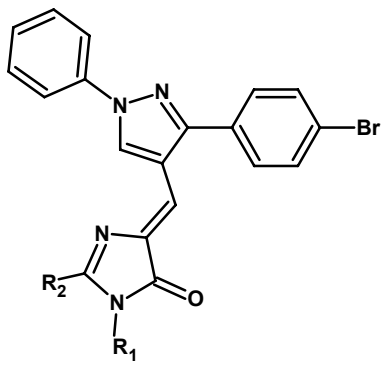

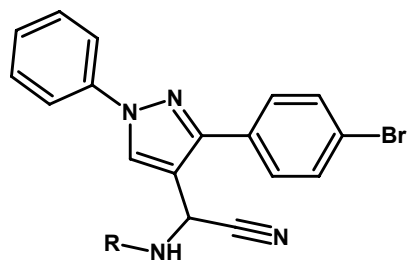

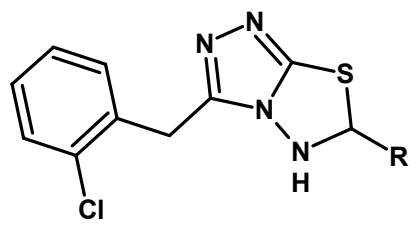

R	R	R
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2-OCH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
3-Cl-C_6H_4-	3-Cl-C_6H_4-	2-Cl-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	2-F-C_6H_4-	4-F-C_6H_4-
3-NO_2-C_6H_4-	4-F-C_6H_4-	3-OH-C_6H_4-
4-NO_2-C_6H_4-	4-Br-C_6H_4-	2-NO_2-C_6H_4-
3-Cl, 4-F-C_6H_3-	3-Cl, 4-F-C_6H_3-	3-NO_2-C_6H_4-
2,4-di-CH_3-C_6H_3-	2,4-di-CH_3-C_6H_3-	3-OCH_3,4-OH-C_6H_3-
2,4-di-Cl-C_6H_3-	3,4-di-Cl-C_6H_3-	3,4-$(OCH_3)_2$-C_6H_3-
3,4-di-Cl-C_6H_3-	2,5-di-Cl-C_6H_3-	9-$C_{14}H_9$-