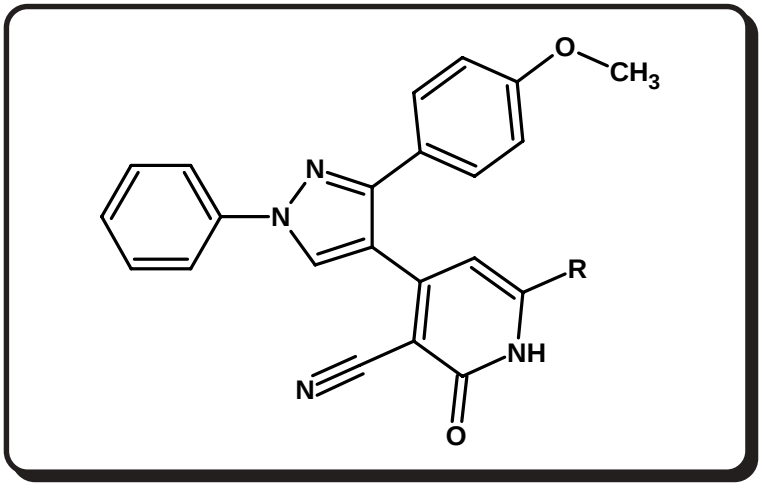
Ph. D.
Thesis
Chemistry

Ph. D. Thesis

DESIGN AND SYNTHESIS OF SOME HETEROCYCLES OF MEDICINAL INTEREST

Siddharth C. Patel



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

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

Date : - 04- 2004 ***(Siddharth C. Patel)***

Place : Rajkot

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

Date : - 04- 2004

Place : Rajkot

Dr. H. H. PAREKH

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Siddharth C. Patel

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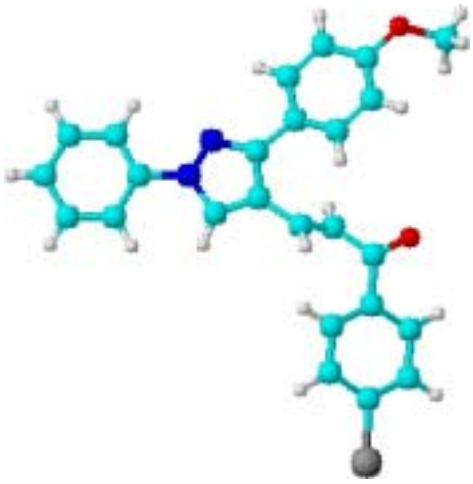


SYNOPSIS

The work is incorporated in the thesis with the title "**DESIGN AND SYNTHESIS OF SOME HETEROCYCLES OF MEDICINAL INTEREST**" has been described as under.

[A] STUDIES ON PYRAZOLES

[B] STUDIES ON TRIAZOLES

[A] STUDIES ON PYRAZOLES

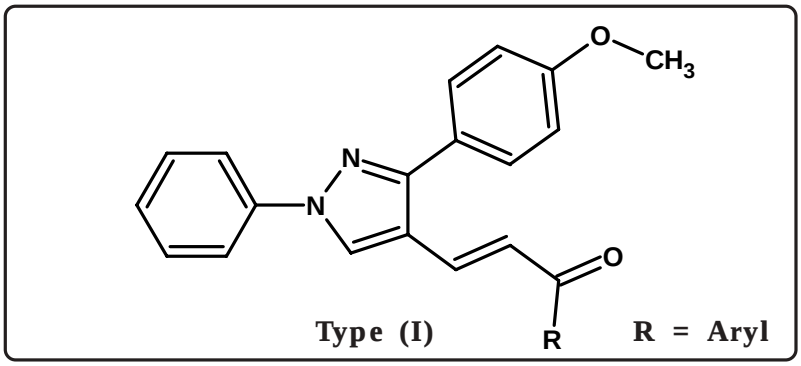
Pyrazole derivatives are associated with broad spectrum of pharmacological activities like antitubercular, antimicrobial, hypnotics, antiinflammatory, antitumor, plant growth regulators and are also used as herbicidal and insecticidal.

Considering the increasing importance of pyrazole nucleus, the synthesis of some new chalcones, pyrazolines, isoxazoles, cyanopyridines, cyanopyridones and arylidenes bearing 1,N-phenyl-3-p-anisyl-4-formyl pyrazole nucleus has been undertaken.

PART - I : STUDIES ON ISOXAZOLES

Isoxazoles possess remarkable pharmacological importance and biological activities such as antifungal, antibacterial, sedative and hypnotics etc. In view of there facts, it appeared of interest to design and synthesise isoxazole derivatives, which have been described as under.

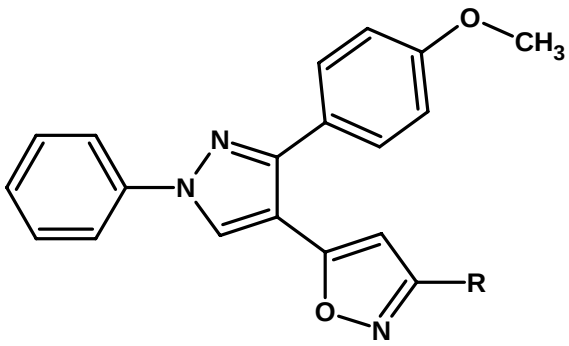
SECTION - I : Synthesis and biological evaluation of 1-Aryl-3-[1',N-phenyl-3'-p-anisyl-pyrazol-4'-yl]-2-propene-1-ones.



Type (I) **R = Aryl**

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

SECTION - II : Synthesis and biological evaluation of 3-Aryl-5-[1'-N-phenyl-3'-p-anisyl-pyrazol-4'-yl]-isoxazoles



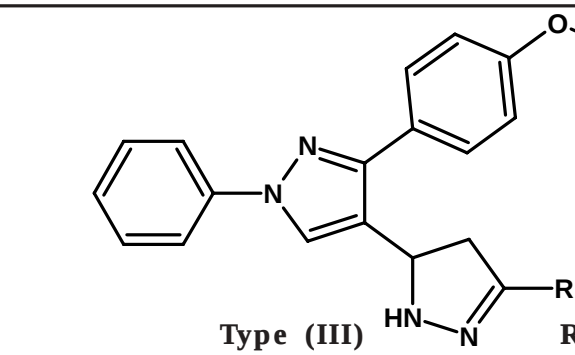
Type (II) **R = Aryl**

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

PART - II : STUDIES ON PYRAZOLYLPYRAZOLINES

Pyrazoline derivatives are associated with broad spectrum of pharmacological activities like anticancer, anthalmentic, antitubercular, antiinflammatory etc. In view of above findings, some new pyrazolines bearing 1-phenyl-3-p-anisyl-4-formyl pyrazole moiety have been prepared which have been described as under.

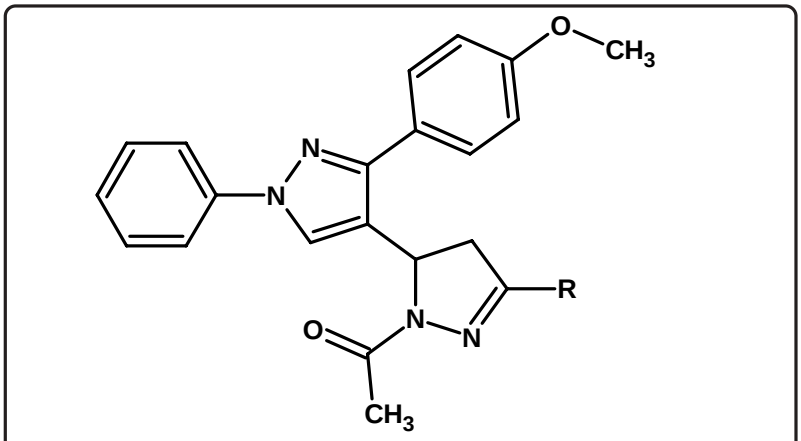
SECTION - I : Synthesis and biological evaluation of 3-Aryl-5-[1',N-phenyl-3'-p-anisyl-pyrazol-4'-yl]-pyrazolines



Type (III) **R = Aryl**

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

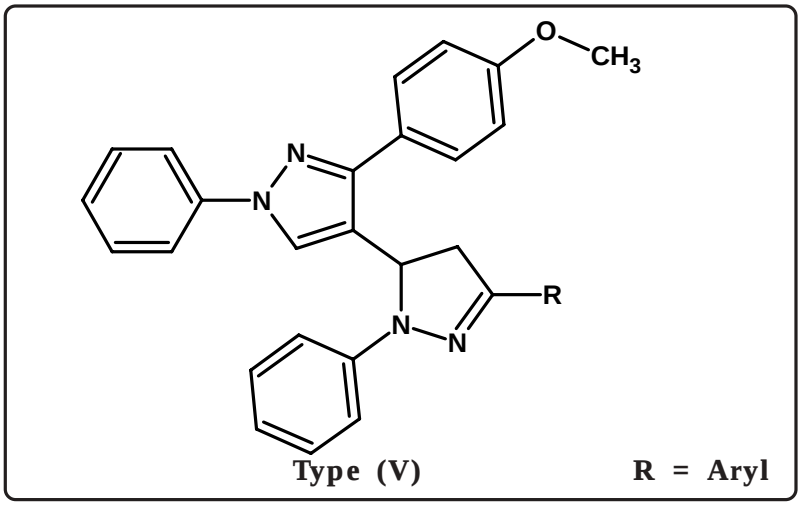
SECTION - II : Synthesis and biological evaluation of 1,N-Acetyl-3-aryl-5-[1',N-phenyl-3'-p-anisyl-pyrazol-4'-yl]-pyrazolines



Type (IV) **R = Aryl**

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

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



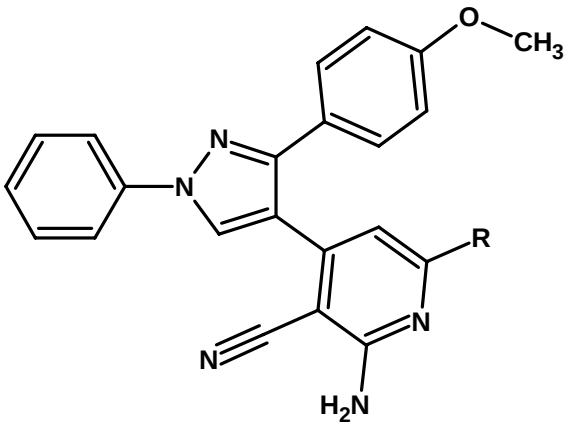
Type (V) **R = Aryl**

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

PART - III : STUDIES ON CYANOPYRIDINES

Cyanopyridine plays a vital role owing to their wide range of biological activities such as antihypertensive, antibacterial, antidiabetic and anticholestemic. They have been also used as dyes for cotton and polyester fabrics, it appeared of interest to design and synthesise cyanopyridine derivatives, which have been described as under.

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



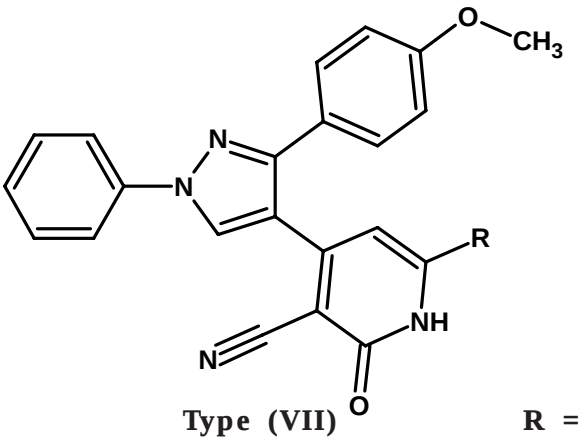
Type (VI) **R = Aryl**

2-Amino-3-cyanopyridines of type (VI) have been under taken by the condensation of chalcones of type (I) with ammonium acetate and malononitrile.

PART - IV : 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-Cyano-4-[1',N-phenyl-3'-p-anisyl-pyrazol-4'-yl]-6-aryl-1,2-dihydro-2-pyridones



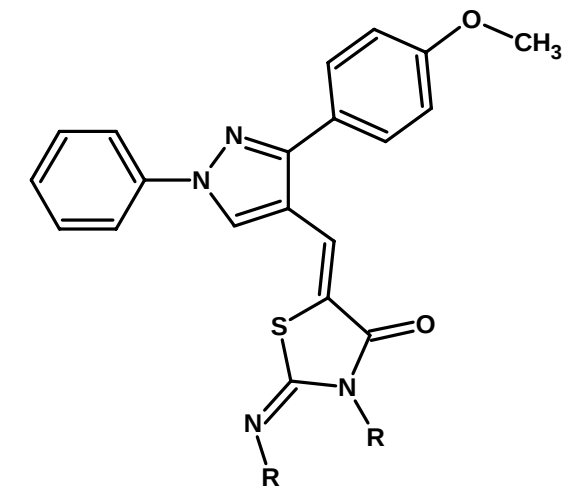
Type (VII) **R = Aryl**

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

PART - V : STUDIES ON THIAZOLIDINONES

It has been reported that 5-arylidene-4-thiazolidinone derivatives are associated with wide range of biological activities like antitumor, antileprosy, antitubercular, antibacterial etc. In order to develop medicinally important compounds, we have synthesised some new arylidenes shown as under.

SECTION - I : Synthesis and biological evaluation of 2-Aryl imino-3,N-aryl-5-[1',N-phenyl-3'-p-anisyl-4'-pyrazolylmethino]-4-thiazolidinones



Type (VIII) **R = Aryl**

The arylidenes of type (VIII) have been prepared by condensation of 1,N-phenyl-3-p-anisyl-4-formyl-pyrazol with different thiazolidinones in glacial acetic acid.

[B] STUDIES ON TRIAZOLES

We are engaged in a programme to explore some new heterocyclic entities in order to study their pharmacological profile. Our efforts are focused on introduction of chemical diversify in the molecular frame work in order to synthesizing active molecule of widely different composition.

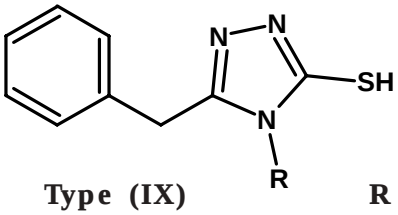
Compounds bearing 1,2,4-triazole moiety are endowed with a variety of biological activities such as antiinflammatory, CNS depressant, herbicidal, fungicidal etc.

Considering the increasing importance of triazole nucleus, it was contemplated to synthesise some new aryl triazoles, azomethines, and thiadiazoles bearing triazole nucleus, which have been described as under.

PART - I : STUDIES ON 4-ARYLTRIAZOLES

Different type of 1,2,4-triazole derivatives have drawn considerable attention due to their good pharmacological activities such as analgesic, CNS depressent, pesticidal, antiinflammatory and antihypertensive. By considering these valid observations, we have synthesised some new 1,2,4-triazoles which have been described as under.

SECTION - I : Synthesis and biological evaluation of 3-Mercapto-4,N-aryl-5-benzyl-1,2,4-triazoles



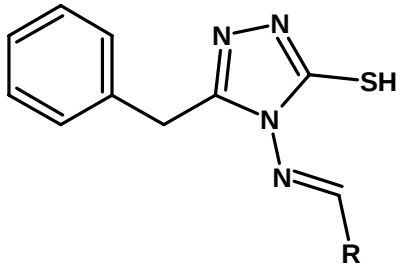
Type (IX) **R = Aryl**

The synthesis of triazole derivatives of type (IX) have been undertaken by heating of dithiocarbamate of phenyl acetic acid hydrazide with different aromatic amines.

PART - II : STUDIES ON AZOMETHINES

Azomethine derivatives represent one of the modest classes of compounds possessing wide range of therapeutic activities, such as antimicrobial, antibacterial, antibiotics etc. With a view to getting better therapeutic agents and to evaluate it's pharmacological profile, different type of azomethine derivatives have been prepared, which have been described as under.

SECTION - I : Synthesis and biological evaluation of 4-N-Substituted benzalamino-3-benzyl-5-mercapto-1,2,4-triazoles



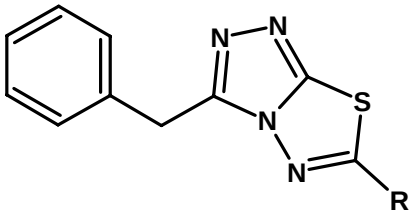
Type (X) **R = Aryl**

The synthesis of schiff's base derivatives of type (X) have been prepared by 3-mercapto-4-N-amino-5-benzyl-1,2,4-triazole with different aromatic aldehydes in presence of sulphuric acid.

PART - III : STUDIES ON 1,3,4-THIADIAZOLO TRIAZOLES

Thiadiazole derivatives represent one of the most active classes of compounds possessing wide spectrum of biological activities such as antithyroid, antibiotic, pesticidal, antifungal etc. Some new triazoles with 1,3,4-thiadiazole ring system have been prepared as under.

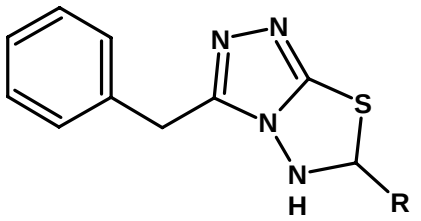
SECTION - I : Synthesis and biological evaluation of 2-Aryl-4-benzyl-1,2,4-triazolo[4,5-b]-1,3,4-thiadiazoles



Type (XI) R = Aryl

Substituted triazolo thiadiazoles (XI) have been prepared by condensation of 3-benzyl-4-N-amino-5-mercapto-1,2,4-triazole with different aromatic acids in presence of phosphorous oxychloride.

SECTION - II : Synthesis and biological evaluation of 2-Aryl-4-benzyl-2,3-dihydro-1,2,4-triazolo-[4,5-b]-1,3,4-thiadiazoles



Type (XII) R = Aryl

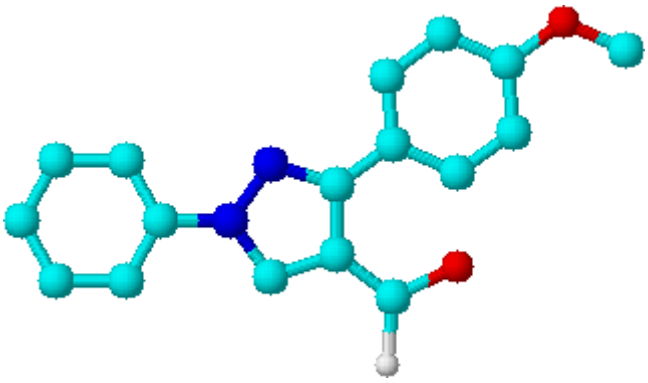
The compounds of type (XII) have been prepared by the condensation of 3-benzyl-4-N-amino-5-mercapto-1,2,4-triazole with different aromatic aldehydes in presence of p-toluenesulphonic acid.

The constitution of the newly synthesised products have been characterised 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 activites:

(i) All the compounds have been evaluated for their antibacterial activity towards Gram positive and Gram nagative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. 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 H37 Rv*** at a cocentration of 6.25 μg/ml using Rifampin as a standard drug, which have been tested by Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama U.S.A. The work is under progress.



DESIGN AND SYNTHESIS OF SOME HETEROCYCLES OF MEDICINAL INTEREST

INTRODUCTION

With the advent of modern civilization, human learned to cure themself by plant medicine. With the development of scientific knowledge, a more advance form of drug have been evaluated. The continuous progress of drug design ranging from single molecules to giant structure is extensively driven by the insticts, intution and experience of pharmaceutical research scientists. From ancient Aryuvedas people learn to use natural drugs as a curing tool. Thus many natural products by trial and error come in to practice for combating human ailments existant during early human observations. Such ancient plant medicines are the 'base' for shaping our current drugs.

Taking in view of the applicability of heterocyclic compounds, they are predominant among the types of compounds used as pharmaceuticals, as agrochemicals, as veterinary products, as optical brightening agents, as antioxidants, as corrosion inhibitors and as additives with a variety of other function. Heterocyclic compounds are also finding an increasing use as intermediates in organic synthesis. Heterocyclic compounds possess diversified applicability in pharmaceuticals because they have specific chemical reactivity and provides false synthon in biosynthetic process or block the normal functioning of biological receptors.

Heterocyclic compounds are found as a key component in biological processes. Nucleic acid bases, which are derivatives of the pyrimidine and purine ring systems, as being crucial to the mechanism of replication. Heterocyclic

compounds like ascorbic acid (vitamin C) and thiamine (vitamin B_1) are used as an essential diet ingredients.

In ancient "Aryuvedas" NEEM has been described as a antifungal and antibacterial medicine and till today it is being used against skin disease. Moreover NEEM has described as killer for "Sarkara" (blood-sugar) and acts as a antidiabetic drug in India. Similarly in China, Mauhang was in use for over 5000 years for the various types of fever & respiratory ailments.

In 1925 chemical investigations followed by pharmacological evaluation led this compound into modern medicine. Similarly during this period, urea stibamine was introduced as the first drug in 1920 for the treatment of Kala azar, in 1930 De Roywolfia prepration were first employed for sedative and hypotensive properties.

By serendipity, many such natural products have came into human observations for the treatment & curing human illness. An extraordinary chemotherapeutic properties of penicillin and it's dramatic time was developed for the treatment of wound made penicillin, almost commonly used as an inexpensive drug. The advent of sulphonamides draw attention to the different activity of various chemicals for bacterial and human cells, this important factors prompted the florey and chain in 1939 to investigate penicillins which was discovered ten years earlier by Alexander Fleming.

A large number of important drugs have been introduced during this period of 1940 to 1960. This period is known as 'Golden Period' of new drug discovery. Thus prontosil leading various sulpha drugs ; 1940 - Penicillin, antibiotics ; 1945 - Chloroquine, an antimalarial; 1950 - Methyldopa, antihypertensive; 1957 - chlorothiazide, diuretic; 1958 - adrenergic beta blockers, coronary vasodilatory; 1960 - semi synthetic penicillin, antibacterial; 1965 - trimethoprim, antimicrobial; 1967 - disodium chromoglycoate, antiallergic; 1972 - Cimetidine, H2 -

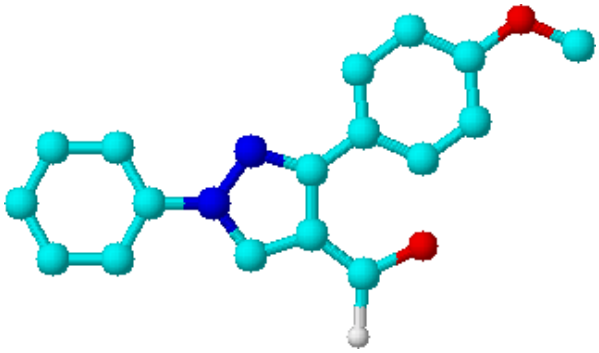
antagonist; 1975 - Verapamil, Calcium antagonist; 1981 - captopril, antihypertensive. These are some specific examples representing new therapeutics.

AIMS AND OBJECTIVES

With the consideration of the application of heterocyclic compounds, we have carried out the preparation of heterocycles bearing pyrazole and triazole nucleus. The placement of a wide variety of substituents of these nuclei have been designed in order to evaluate the synthesised products for their pharmacological profile against several strains of bacteria and fungi.

* To generate several derivatives like chalcones, isoxazoles, pyrazolines, cyanopyridines, cyanopyridones, thiazolidinones bearing pyrazole moiety.
* To synthesise therapeutically active moieties like aryl triazoles, azomethines, 1,3,4-thiadiazoles bearing triazole nucleus.
* To characterise these products for structure elucidation using spectroscopic techniques like IR, PMR and Mass spectral studies.
* Purity of all comopunds have been checked by thin layer chromatography.
* To evaluate these new products for better drug potential against different strains of bacteria and fungi.

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



A:
STUDIES ON PYRAZOLES

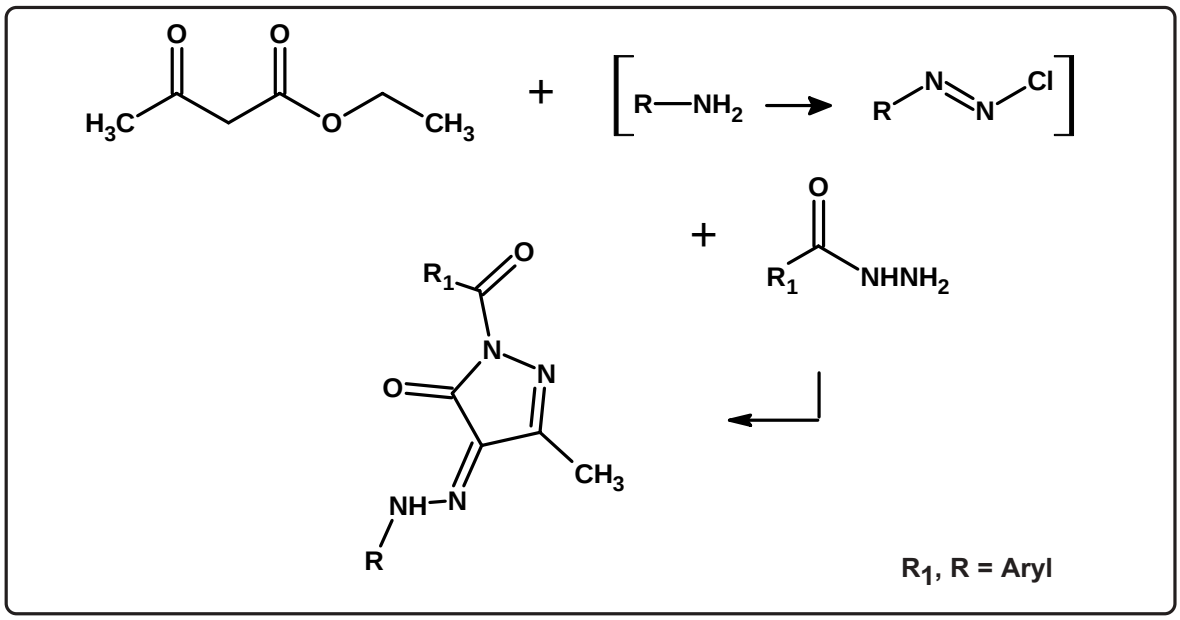
INTRODUCTION

Pyrazoles, which belong to an important group of heterocyclic compounds, have been extensively explored for their applications in the field of medicine, agriculture and industrial chemistry.

SYNTHETIC ASPECTS

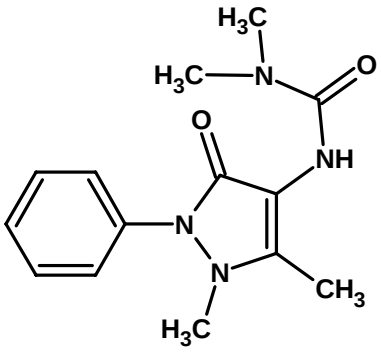
Different methods of preparation are available in literature which are as under ;

1. By the reaction of ethylacetoacetate with aryl hydrazines[1].
2. By the reaction of ethylacetoacetate with hydrazine hydrate[2].
3. By the reaction of ethylacetoacetate with aroyl hydrazines[3].
4. The ester group can be replaced by diazonium salt of amine and further it is condensed with hydrazine which on cyclization form pyrazolone[4].

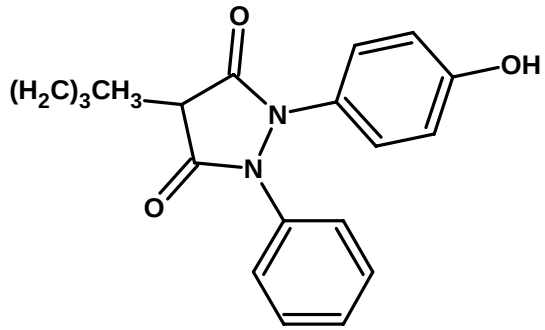


THERAPEUTIC IMPORTANCE

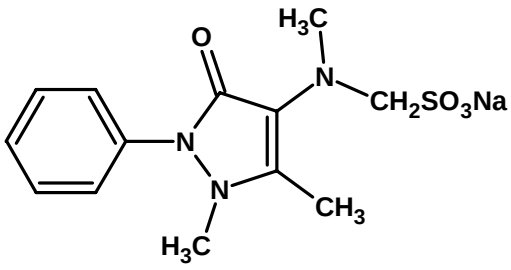
Pyrazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having pyrazole nucleus with good pharmacological activities are listed below.



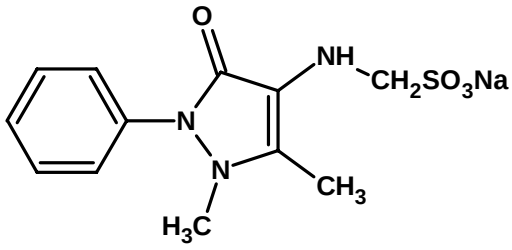
Aminopropylon
(Antipyratic, Analgesic)



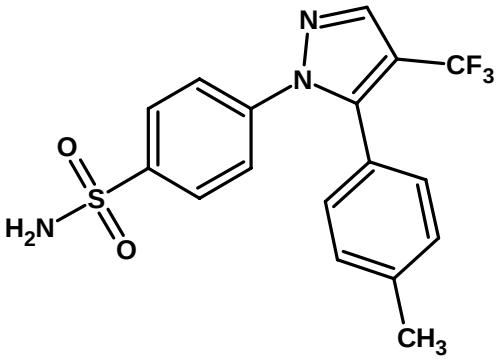
Oxyphenbutazone
(Antiarthritic)



Novalgin
(Antipyratic, Analgesic)



Melubrin
(Antipyratic, Analgesic)

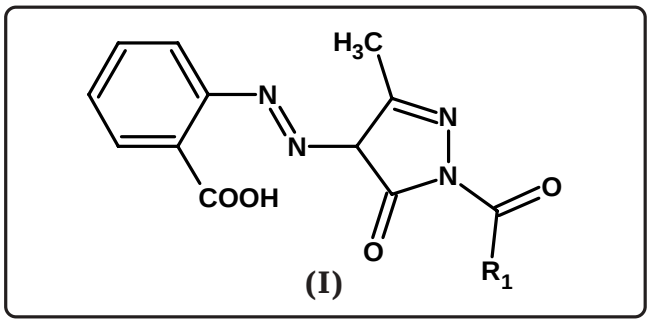


Celecoxib
(Antiinflammatory)

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

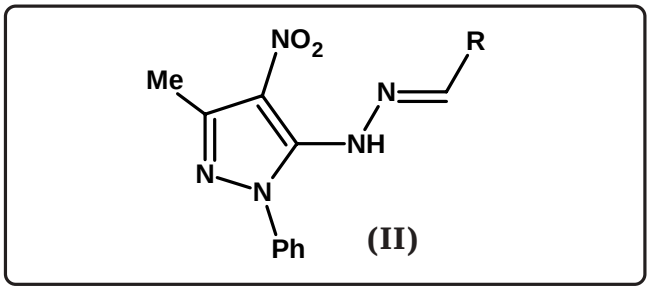
1. Anticancer[5]
2. CNS depressant[6]
3. Antiulcer[7]
4. Herbicidal[8,9]
5. Antitumor[10]
6. Immunosuppresants[11]
7. Antimicrobial[12]
8. Antiparasitic[13]
9. Neurotonsin receptor[14]
10. Lipoxygenase inhibitor[15]

Ashok Kumar and co-workers[16] have reported antibacterial activity of pyrazolones. M. Giula et. al.[17] have demonstrated pyrazolone derivatives as antiinflammatory, analgesic and platelet, antiaggregating agent. S. D. Bharadwaj and co-worker[18] have observed anticancer and anti-HIV activity, associated with some novel derivatives(I).



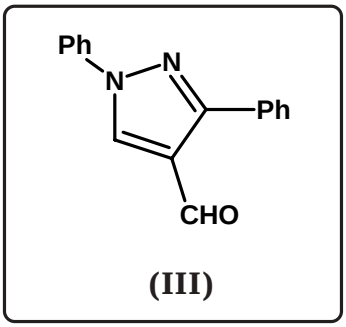
(I)

Barseiro et. al.[19] have prepared pyrazole derivatives and reported them as antiinflammatory and antiedematogenic agent (II).



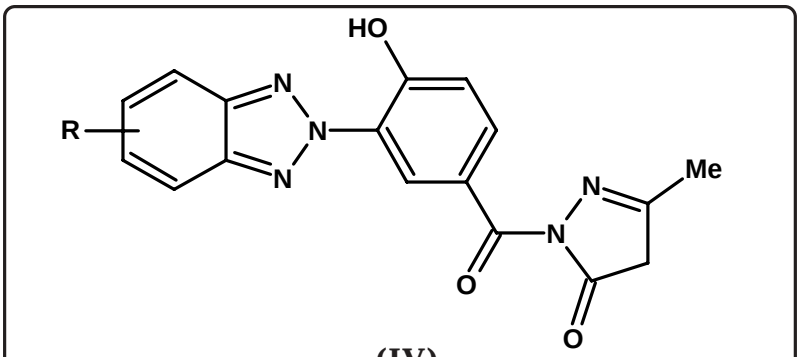
(II)

El-Emery et. al.[20] have synthesised 1,3-diphenyl pyrazole derivatives and documented their variety of bioloical activity (III).



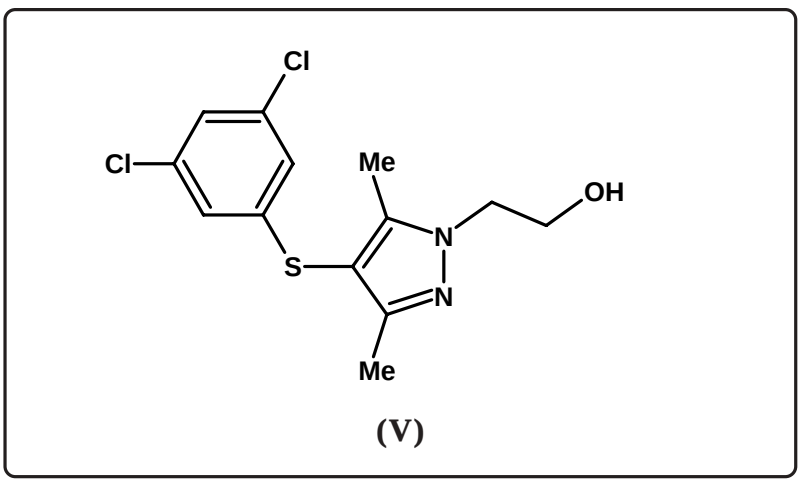
(III)

Rajeev Jain and co-worker[21] have prepared pyrazoline derivatives and reported as potent antimicrobial agent. X. X. Chun et. al.[22] have prepared substituted 3-methyl-5-pyrazoles (IV).



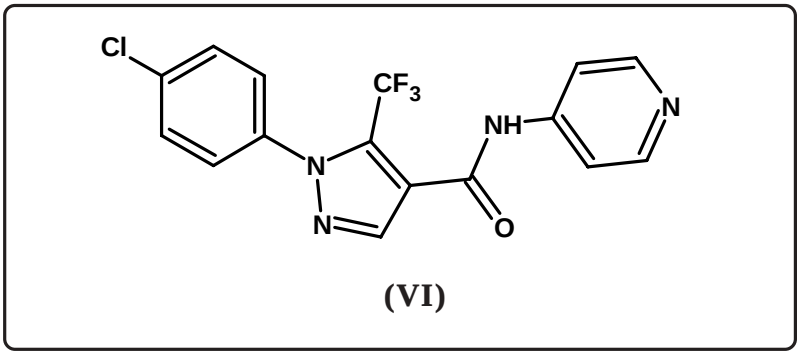
(IV)

Havaldar Freddy et al.[23] have synthesised 4,5-dihydro-3-phenyl-1H-pyrazole and reported their biological activity. Carbau Romuald and co-workers[24] have reported pyrazole derivatives (V) useful as reverse transcriptase inhibitors for the treatemet of HIV infection.



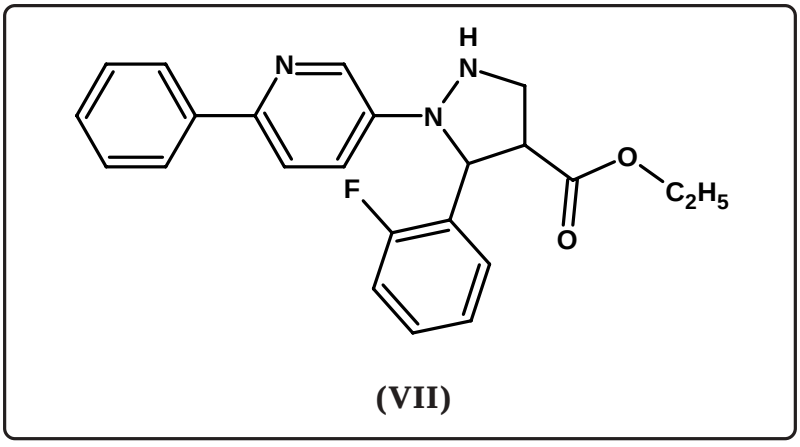
(V)

Recently, Atkinson R. N. et al.[25] have studied pyrazoles as sodium channel blocker (VI). Murakanii Hiroshi et al.[26] have documented pyrazoles as antifouling agents. Gellibeat Francoise et al.[27] have reported purasole derivatives as TGF-13 inhibitors.



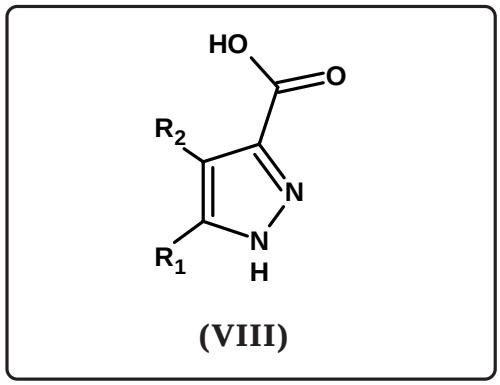
(VI)

Laborde Edgardo et al.[28] have found that pyrazoles possess glycine transporter2-inhibitors activity. Andrew Thurkaub et al.[29] have synthesised high affinity C_{5a} receptor modulator pyrazoles. Nagaaki Sato et al.[30] have prepared pyrazoles as neuropeptide T_5 receptor antagonists. G. M. B. Yamanouch Pharma. Co[31] has suggested pyrazoles as glycine trnsporter protein inhibitors (VII).



(VII)

Jacques Dumas and co-workers[32] have shown pyrazole derivatives as rafkinase and angiogenesis inhibitor agents. David L. S. et al.[33] have synthesied pyrazoles as activators of the nitrile oxide receptor and soluble guanglute cyclase agent. T. Van Herk et al.[34] have studied pyrazoles as nicotinic acid receptor (VIII). Barber Christopher et al.[35] have represented pyrazole derivatives as phosphidiesterase inhibitors.



(VIII)

Nishimura Tsoshihiro et al.[36] have synthesised pyrazole as inhibitors of human $SGLT_2$ (Sodium dependent glucose transporter-2).

Now a days, it is found that pyrazole derivatives possesses a number of biological activities. Such as fungicidal[37,38] ,herbicidal[39,40],Cardiovascular[41], antiinflammatory[42,43], anticancer[44-46], antiviral[47] and protein kinase inhibitors[48].

Loking to the diversified biological activity, it appeared of interest to synthesise some Chalcones, Isoxazoles, Pyrazolines, Cyanopyridines, Cyanopyridones and Thiazolidinones bearing pyrazole moiety, in order to achieving compounds having better therapeutic importance. These study are described in following parts.

[A] STUDIES ON PYRAZOLES

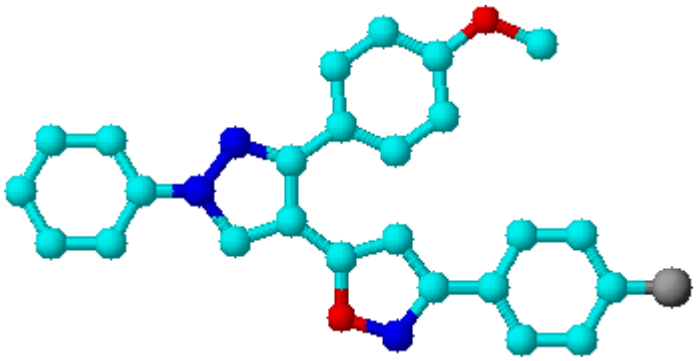
PART-I : STUDIES ON ISOXAZOLES

PART-II : STUDIES ON PYRAZOLYLPYRAZOLINES

PART-III : STUDIES ON CYANOPYRIDINES

PART-IV : STUDIES ON CYANOPYRIDONES

PART-V : STUDIES ON THIAZOLIDINONES

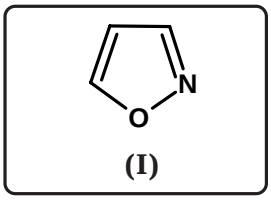


PART - I

STUDIES ON ISOXAZOLES

INTRODUCTION

Isoxazoles are a group of heterocyclic compounds containing two hetero atoms : Oxygen and Nitrogen.

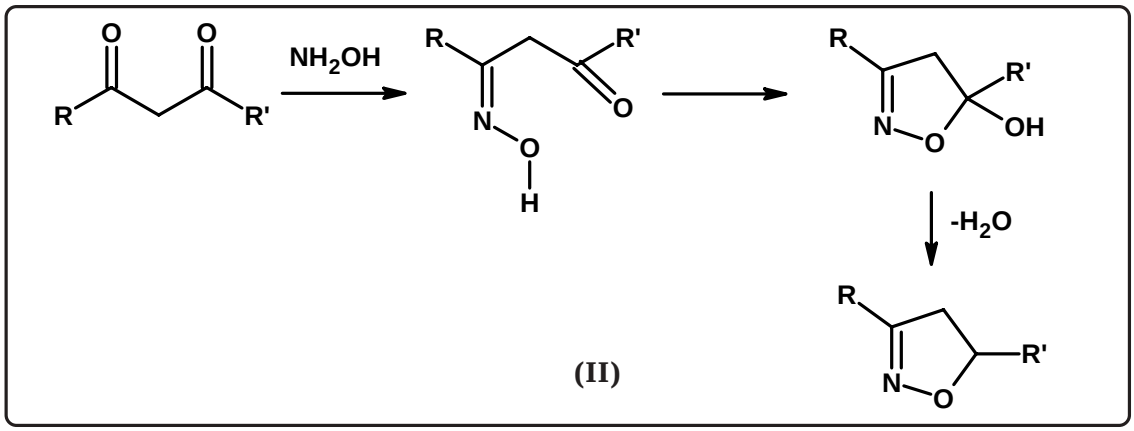


(I)

In 1888, Claisen first suggested an Isoxazole (I) for a product from the reaction of 1,3-diketone with hydroxylamine[49]. Subsequently a solid foundation for the chemistry of isoxazoles was laid down by Claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions, particularly in reducing or basic media, it becomes highly labile. The next important contribution to the chemistry of isoxazole was made by Quilico in 1946, when he began to study the formation of isoxazoles from nitrile N-oxides and unsaturated compounds[50].

SYNTHETIC ASPECTS

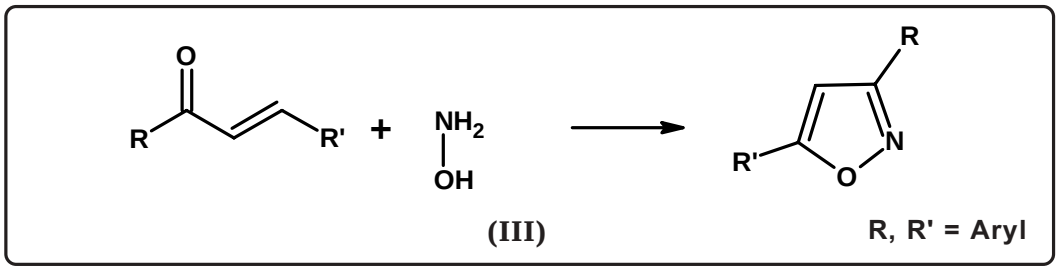
Isoxazoles may be prepared by the reaction between hydroxylamine and α,β-dicarbonyl compounds. The reaction proceeds via the formation of an oxime, which possibly undergoes cyclization.



(II)

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

1. Fanshawe and Crawley[51] prepared isoxazoles (III) from chalcones, hydroxylamine hydrochloride and KOH in methanol.



THERAPEUTIC IMPORTANCE

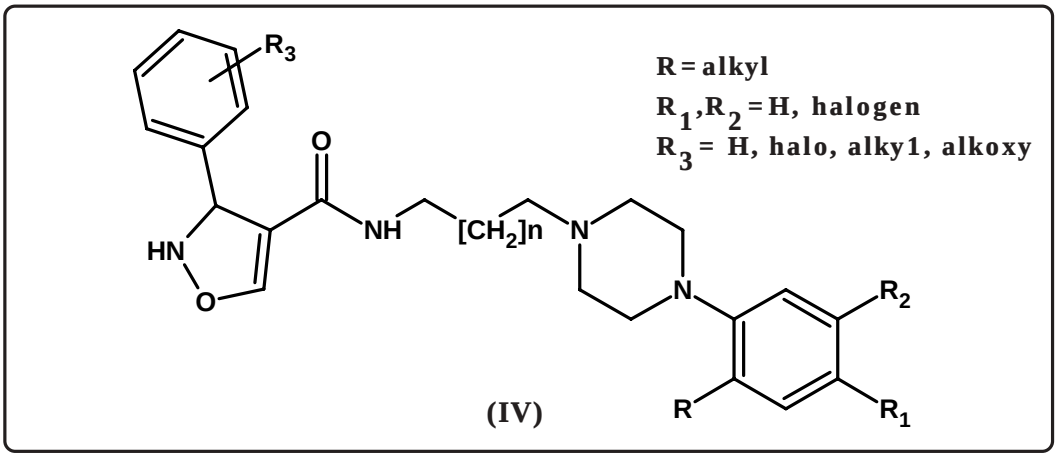
Isoxazoles possess wide therapeutic activities.

1. Antiinflammatory[52-54]
2. Anticonvulsant[55,56]
3. Muscle relaxant[57,58]
4. Antipyretic[59]
5. Anticholestermic[60]
6. Antibacterial[61,62]
7. Diabetic[63]
8. Nematocidal[64]
9. Antiviral[65]
10. Herbicidal[66]
11. Antileukemia[67]
12. Antitumor[68]

G. Daidone, Maggio et. al.[69] synthesised novel 3-(isoxazol-3-yl)-quinazolin-4(3H)-one derivatives and tested for their analgesic and antiinflammatory activities as well as for their acute toxicity and ulcerogenic effect. Some of them had a very low ulcerogenic effect.

C. B. Xue et. al.[70] reported that replacement of the benzamide in XUO57 (potent inhibitor) with an isoxazole carboxamide resulted in significant improvement *in vivo* potency. More importantly, the analogue XUO65 showed an excellent oral antiplatelet effect in dogs. Masui et. al.[71] have prepared isoxazoles having pesticidal activity. Some excellent herbicidal results are obtained by Reddy et. al.[72]. Moreover isoxazoles found to possess remarkable anxiolytic and antihypertesive effect, reported by Nyitrai et. al.[73]. Mishra et. al.[74] have synthesised and reported isoxazoles as useful agents for analgesic and antiinflammatory activities. Aicher et. al.[75] cited some isoxazole derivatives possessing hypoglycemic agents.

R. Ulrich et. al.[76] have synthesised isoxazole derivatives (IV) and reported their adrenergic antagonist activity.



(IV)

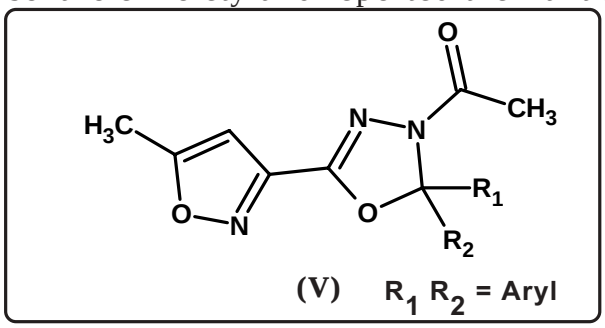
M. Dauria[77] studied photochemical behaviour of isoxazole derivatives. Manohara Y. N. et. al.[78] investigated thermal decomposition kinetics of Co(II) and Ni(II) complexes of substituted isoxazole and their antibacterial activity.

CONTRIBUTION FROM OUR LABORATORY

R. C. Khunt, A. R. Parikh and co-workers[79] have prepared isoxazole derivatives which possess antimicrobial activity. P. M. Patel and A. R. Parikh[80] have synthesised 3-(3'-bromo-4-acetamidophenyl)-5-aryl-isoxazoles showing antimicrobial activity. N. J. Datta et. al.[81] have described the isoxazole derivatives and their use as antimicrobial agents. B. P. Kansagara et. al.[82] have demonstrated various isoxazoles and tested their antimicrobial activity.

N. A. Vekariya, M. D. Khunt and co-workers[83] have reported isoxazole derivatives bearing quinoxaline moiety and described their anticancer activity. Sushil Korgaokar et. al.[84] have suggested 5-Aryl-3-(3'-ρ-chlorobenzene sulphonamidophenyl)-isoxazole derivatives as antimicrobial. A. H. Bhatt and co-workers[85] have synthesised isoxazole derivatives and described them as potential antimicrobial agents. Rajeev doshi et. al.[86] have prepared some novel isoxazole derivatives and reported as a new class of potential antitubercular agents. Manish Shah and co-workers[87] have demonstrated isoxazoles from 2-hydroxy-3,4-dichloroacetophenone as potential antimicrobial agents.

Xin-Ping Hui et. al.[88] have synthesised 1,3,4-oxadiazole derivatives (V) containing 5-methylisoxazole moiety and reported their antibacterial activity.



(V) R_1 R_2 = Aryl

Chaumin, Wang, Yunfeng et. al.[89] have synthesised isoxazoles as herbicidal. Archana et. al.[90] have prepared isoxazoles as anticonvulsant agents. Wu, Chengde et. al.[91] have synthesised isoxazole derivatives as endothelin activity modulators. Corolin C. and co-workers[92] have studied isoxazoles, which have been used for the clinical trials of asthama.

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

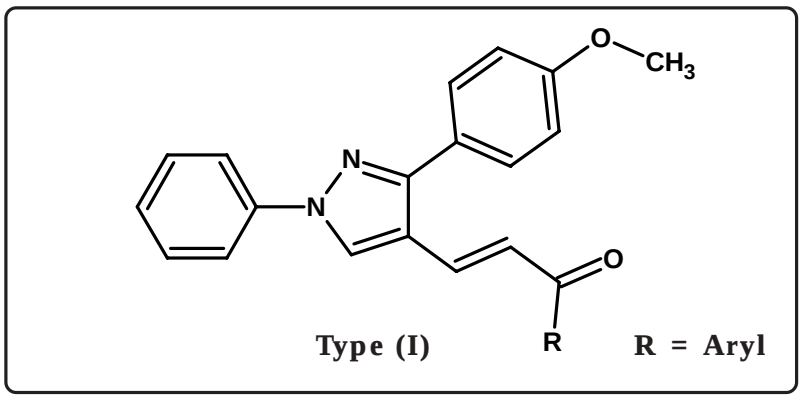
SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1-ARYL-3-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-2-PROPENE-1-ONES

SECTION - II: SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-ISOXAZOLES

SECTION - I

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

Recently, much interest has been focused on the synthesis and biodynamic activities of chalcones and it is a good synthon for various heterocycli rings. With a view to obtain compounds having better therapeutic activity, we have synthesised 1-aryl-3-[1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl]-2-propene-1-ones by the condensation of 1-phenyl-3-ρ-anisyl-4-formyl pyrazole with various aromatic ketones.

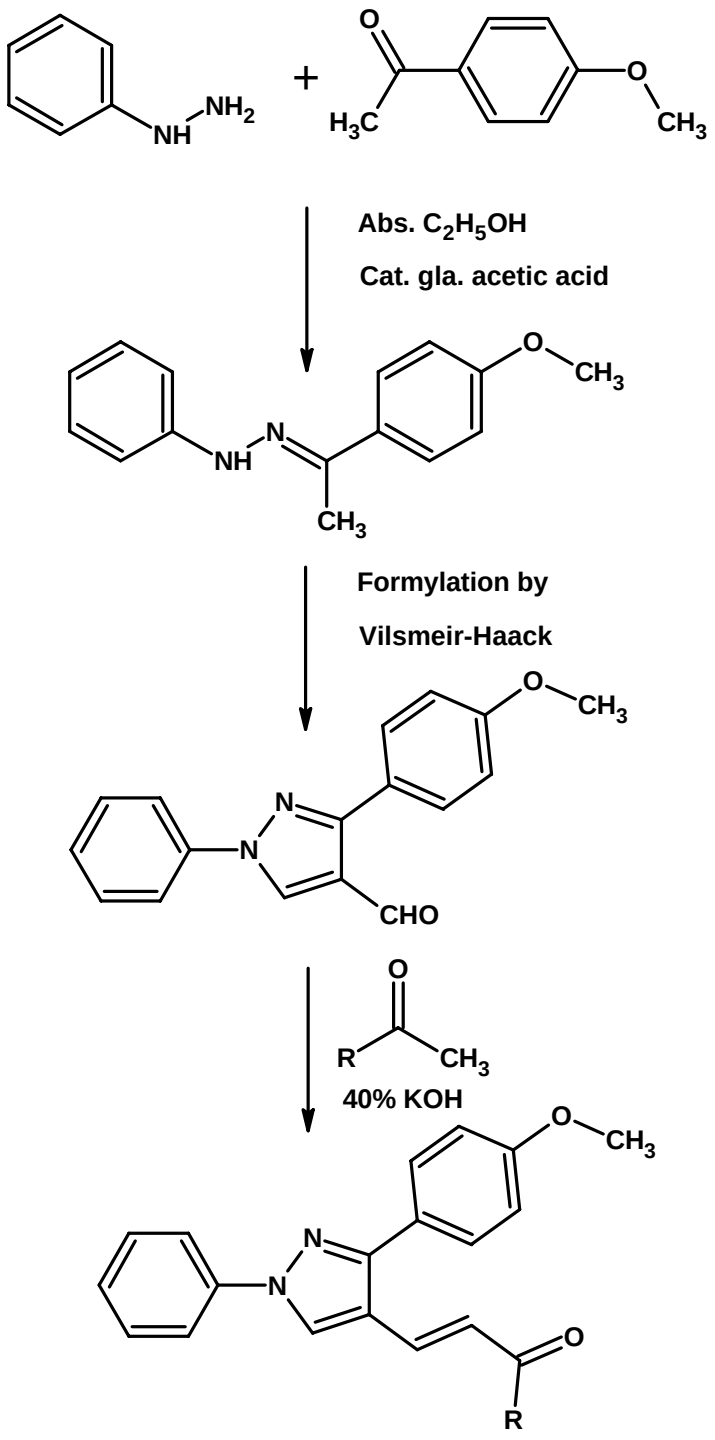


Type (I) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. wehen R = p-bromophenyl, molecular weight = 459, m/z = 461(m + 2).

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

REACTION SCHEME



Type (I) **R = Aryl**

ANTIMICROBIAL ACTIVITY

Method	:	Cup-plate[93]
Gram Positive bacteria	:	***Staphylococcus aureus***
		Bacillus megaterium
Gram negative bacterial	:	***Proteus vulgaris***
		Escherichia coli
Fungi	:	***Aspergillus niger***
Concentration	:	40μg
Solvent	:	Dimethyl formamide
Standard drugs	:	Ampicillin, Amoxicillin, Norfloxacin, Penicillin, Greseofulvin.

The antimicrobial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Penicillin and antifungal activity was compared with viz. Greseofulvin. The inhibition zones measured in mm.

EXPERIMENTAL

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

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

A mixture of phenylhydrazine (1.08 g, 0.01 M) and ρ-methoxy acetophenone (1.50 g, 0.01 M) in absolute ethanol was refluxed in water bath for 2 hrs. in presence of 1 ml glacial acetic acid. The crude product was isolated and crystallised from absolute alcohol. Yield 90%, m.p. 38°C; (Anal. Found : C, 74.91; H, 6.69; N, 11.62%; $C_{15}H_{16}N_2O$ Requires: C, 74.97; H, 6.71; N, 11.66%).

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

N-Aminophenyl-α-methyl-ρ-anisyl azomethine (2.4 g, 0.01 M) was added in mixture of Vilsmeier-Haack reagent (prepared dy dropwise addition of 3 ml $POCl_3$ in ice cooled 25 ml DMF) and refluxed for 5 hrs. The reaction mixture was poured into ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallised from ethanol. Yield 75%, m.p. 164°C; (Anal. Found : C, 73.33; H, 5.02; N, 10.01%; $C_{17}H_{14}N_2O_2$ Requires: C, 73.37; H, 5.07; N, 10.07%).

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

To a well stirred solution of 1-N-phenyl-3-ρ-anisyl-4-formyl pyrazol (2.78 g, 0.01 M) and ρ-bromoacetophenone (2 g, 0.01 M) in ethanol (25 ml), 40% KOH added till the solution was basic. The reaction mixture was stirred for 24 hrs. The contents were poured into ice, acidified, filtered and crystallised from ethanol. Yield 74%, m.p. 170°C; (Anal. Found : C, 65.32; H, 4.68; N, 6.03%; $C_{25}H_{19}N_2O_2Br$ Requires: C, 65.37; H, 4.71; N, 6.10%).

Similarly other substituted pyrazolone have been prepared. The physical data are recorded in Table No. 1.

(D) Antimicrobial activity of 1-Aryl-3-[1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl]-2-propene-1-ones

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

(a) Antimicrobial activity

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

(I) Antibacterial activity

The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of ***B. megaterium***, ***S. aureus***, ***E. coli***, ***P. vulgaris*** in separate conical flask at 40-50^{o}C and mixed well by gentle 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 borar in agar medium and filled with 0.04 ml (40 μg) solution of sample in DMF.

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

(II) Antifungal activity

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

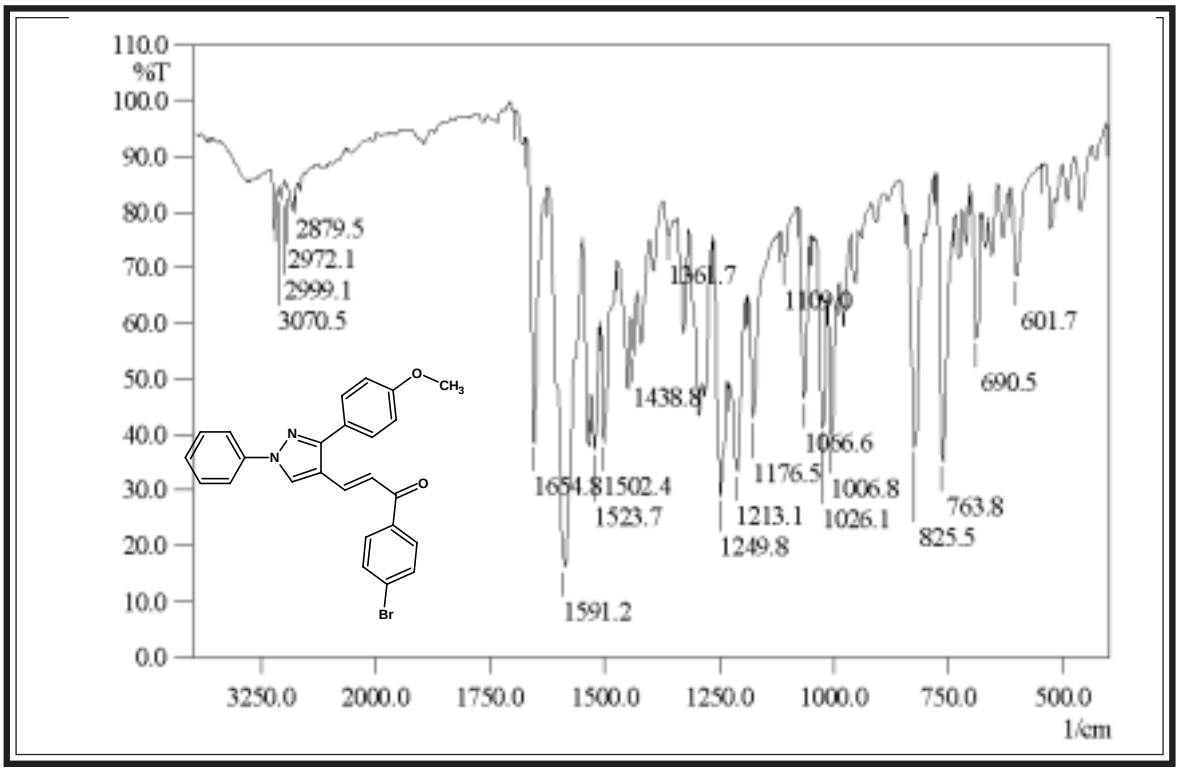
in diameter) were punched. The plates were incubated at 30^{o}C for 48 hrs. After the completion of incubation period, the zones of inhibition of growth in the form of diameter in mm was measured. Along the test solution, in each petridish one cup was filled up with solvent which acts as control. The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

(b) Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition and Co-ordinating Facility (TAACF), U.S.A. Primary screening of the compounds for antitubercular activity have been conducted at 6.25 μg/ml towards ***Mycobacterium Tuberculosis H37Rv*** in BACTEC 12B medium using the BACTEC 460 rediometric system. The compounds demonstrating atleast >90% inhibition in the primary screen have been retested at lower concentration towards ***Mycobacterium Tuberculosis H37Rv*** to determine the actual minimum inhibitory concentration (MIC) in the BACTEC 460.

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

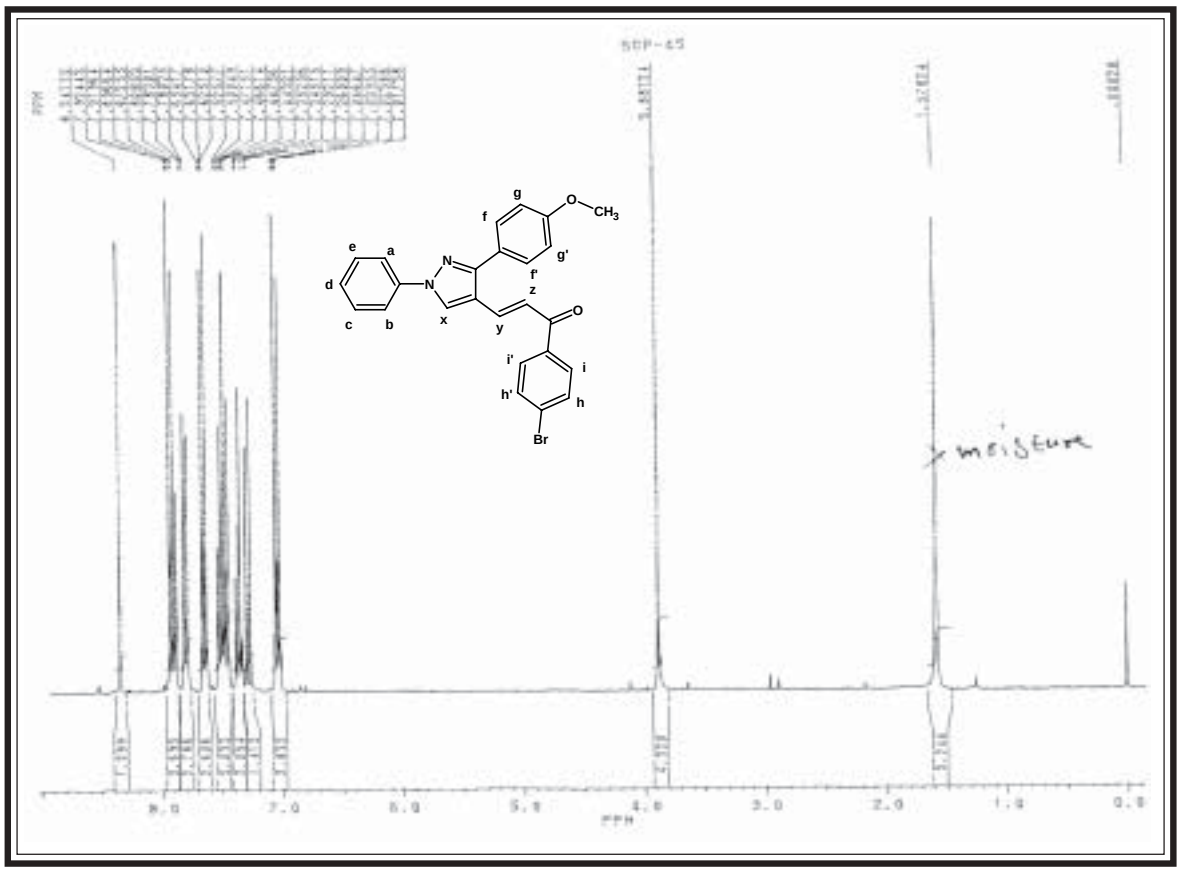
IR SPECTRAL STUDY OF 1-(ρ-BROMOPHENYL)-3-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-2-PROPENE-1-ONE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C–H str.(asym.)	2972.1	2975-2950	434
$-CH_3$	C-H str. (sym.)	2879.5	2880-2860	"
	C-H def. (asym.)	1438.8	1470-1435	"
	C-H def. (sym.)	1361.7	1385-1350	"
Aromatic	C-H str.	3070.5	3080-3030	435
	C=C str.	1502.4	1585-1480	"
	C-H i.p. def.	1109.0	1125-1090	"
		1066.6	1070-1000	"
	C-H o.o.p. def.	825.5	835-810	"
Pyrazole	C=N str	1502.4	1650-1600	434
moiety	C-N str.	1249.8	1350-1200	"
	C-Br		600-500	"
Ether	C-O-C str. (asym.)	1213.1	1275-1200	"
	C-O-C str. (sym.)	1026.1	1075-1020	"
Chalcone	C=O str.	1654.8	1760-1655	"
	CH=CH	2999.1	3050-3000	"

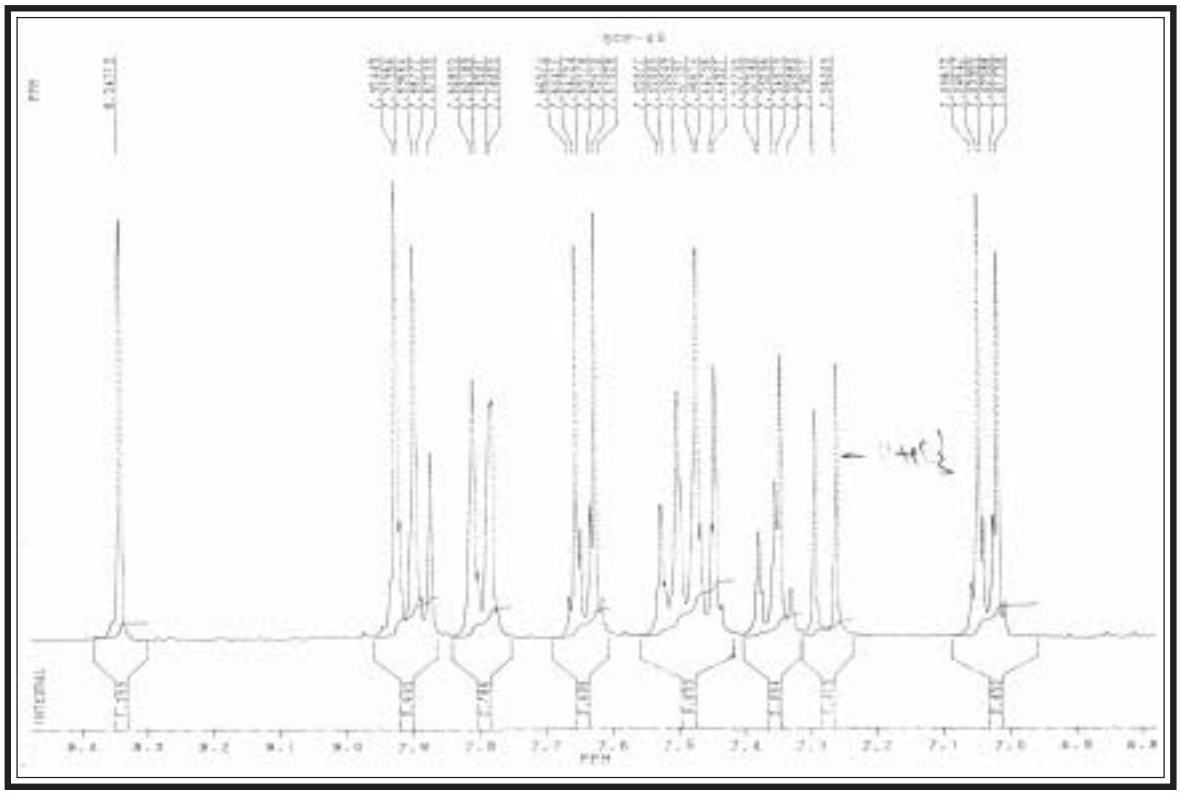
PMR SPECTRAL STUDY OF 1-(ρ-BROMOPHENYL)-3-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-2-PROPENE-1-ONE



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	3.88		3H	singlet	Ar-OCH_3
2	7.03	Jgf = 8.7	2H	doublet	Ar-Hgg'
3	7.34		2H	quartret	Ar-Hc, Ar-He
4	7.44	Jhi = 8.7	2H	doublet	Ar-Hhh'
5	7.46-7.50	Jzy = 12.0	1H	doublet	CHz(vinylic)
6	7.51		1H	doublet	Ar-Hd
7	7.63	Jfg = 8.7	2H	doublet	Ar-Hff'
8	7.79	Jih = 8.7	2H	doublet	Ar-Hii'
9	7.87-7.92		2H	multiplet	Ar-Ha, Ar-Hb
10	7.88-7.92	Jyz = 12.0	1H	doublet	CHy (vinylic)
11	8.34		1H	singlet	CHx

EXPANDED AROMATIC REGION

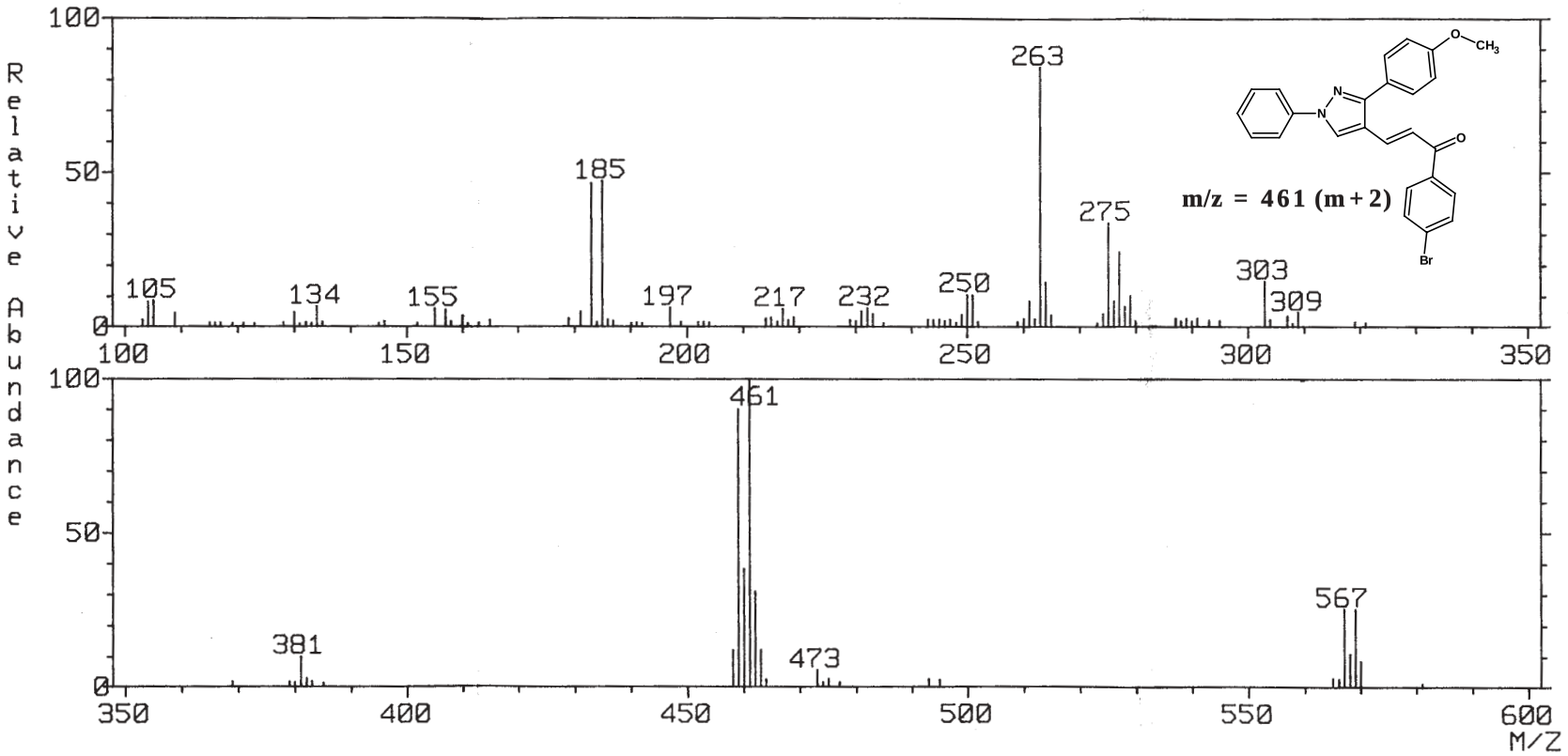


IR SPECTRAL DATA OF 1-ARYL-3-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-2-PROPENE-1-ONES

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

Sr. No.	R	C=O str. Chalcones
1a	C_6H_5-	1656
1b	4-NH_2-C_6H_4-	1658
1c	3-NH_2-C_6H_4-	1662
1d	4-Br-C_6H_4-	1654.8
1e	4-Cl-C_6H_4-	1658.7
1g	4-F-C_6H_4-	1654
1h	4-OCH_3-C_6H_4-	1656
1i	4-CH_3-C_6H_4-	1666.4
1j	4-NO_2-C_6H_4-	1658
1m	3-NO_2-C_6H_4-	1662
1n	4-OH-C_6H_4-	1666
1o	2-OH-C_6H_4-	1660

MASS SPECTRUM Data File: 3ESP30A 30-SEP- 3 9:30
SamPle: SCP-1 DR MRS H H PAREK SAU UNIV RAJKOT #6472
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 461.0000 Int. 5.2290 Lv 0.00
Scan# (1 to 2)



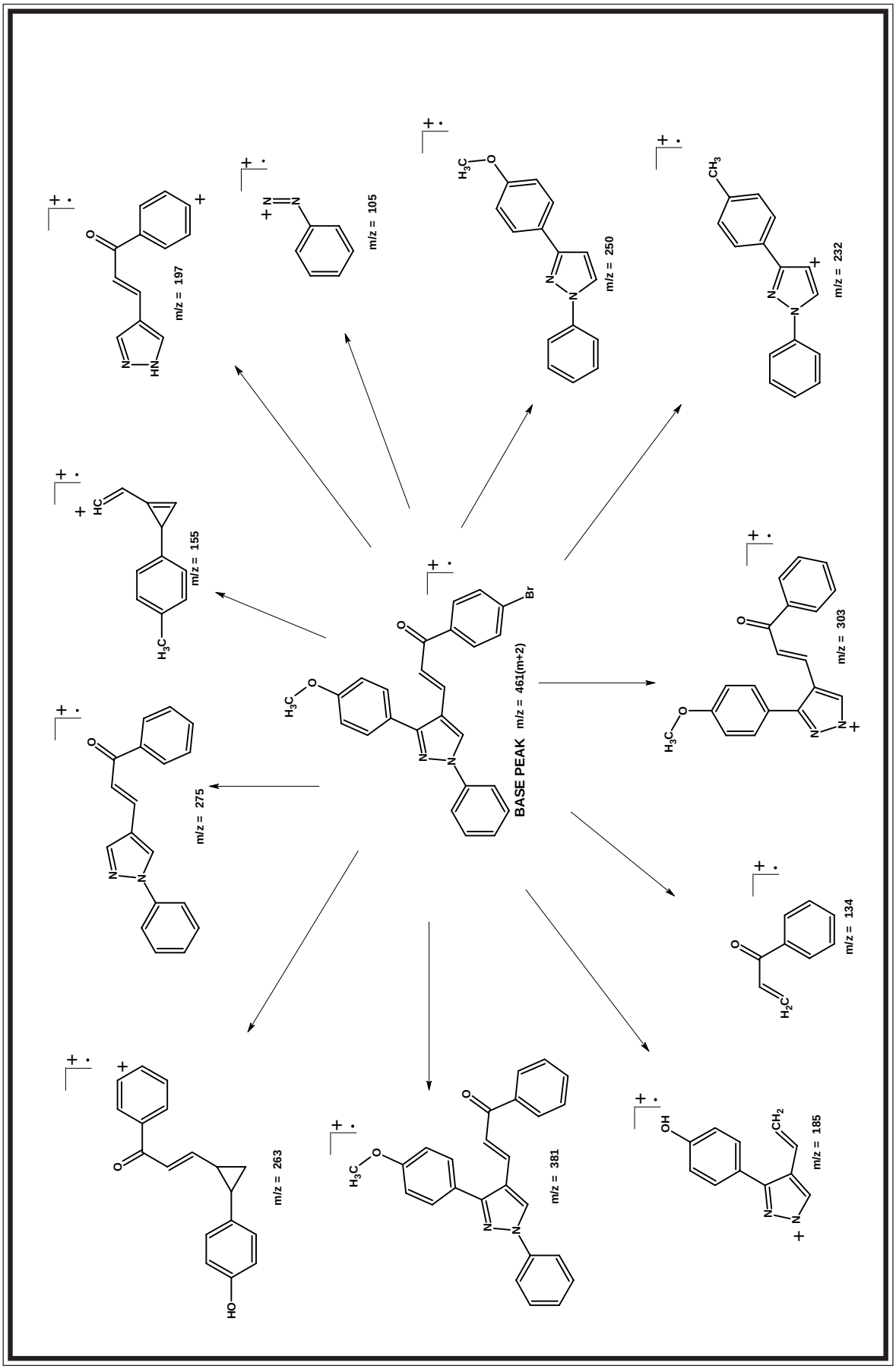

BASE PEAK m/z = 461(m+2)
m/z = 197
m/z = 105
m/z = 250
m/z = 232
m/z = 155
m/z = 303
m/z = 275
m/z = 134
m/z = 263
m/z = 381
m/z = 185

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

Comp. 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
1a	C_6H_5-	$C_{25}H_{20}N_2O_2$	380	190	0.42	82	7.36	7.32
1b	4-NH_2-C_6H_4-	$C_{25}H_{21}N_3O_2$	395	209	0.58	83	10.63	10.58
1c	3-NH_2-C_6H_4-	$C_{25}H_{21}N_3O_2$	395	214	0.48	71	10.36	10.56
1d	4-Br-C_6H_4-	$C_{25}H_{19}N_2O_2Br$	459	170	0.51	74	6.10	6.03
1e	4-Cl-C_6H_4-	$C_{25}H_{19}N_2O_2Cl$	415	152	0.62	87	6.75	6.71
1f	4-F-C_6H_4-	$C_{25}H_{19}N_2O_2F$	398	169	0.72	85	4.77	4.70
1g	4-OCH_3-C_6H_4-	$C_{26}H_{22}N_2O_3$	410	186	0.45	75	6.82	6.78
1h	4-CH_3-C_6H_4-	$C_{26}H_{22}N_2O_2$	394	158	0.55	83	7.10	7.05
1i	4-NO_2-C_6H_4-	$C_{25}H_{19}N_3O_4$	425	161	0.65	71	9.88	9.82
1j	3-NO_2-C_6H_4-	$C_{25}H_{19}N_3O_4$	425	181	0.56	78	9.88	9.81
1k	4-OH-C_6H_4-	$C_{25}H_{20}N_2O_3$	396	179	0.72	82	7.07	7.04
1l	2-OH-C_6H_4-	$C_{25}H_{20}N_2O_3$	396	166	0.57	78	7.07	7.01

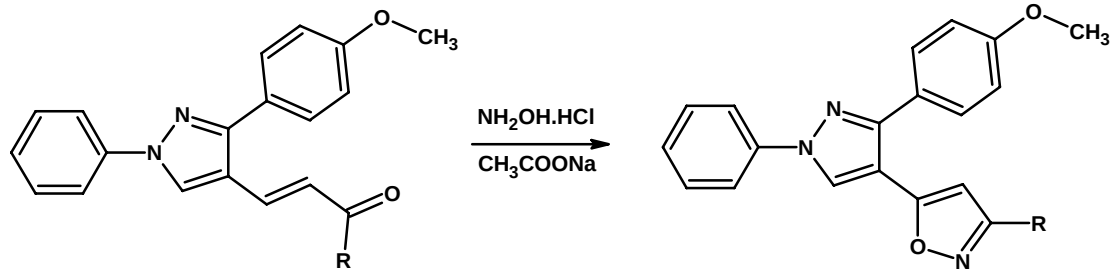
*TLC Solvent System : Ethylacetate : Hexane 2 : 8 (1a-1l)

3 :7 (1b, 1i)

SECTION - II

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

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



Type (II) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. when R = p-bromophenyl, molecular weight = 472, m/z = 473 (m + 1).

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

EXPERIMENTAL

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

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

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

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

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

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

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

(D) Synthesis of 3-(ρ-Bromophenyl)-5-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-isoxazole

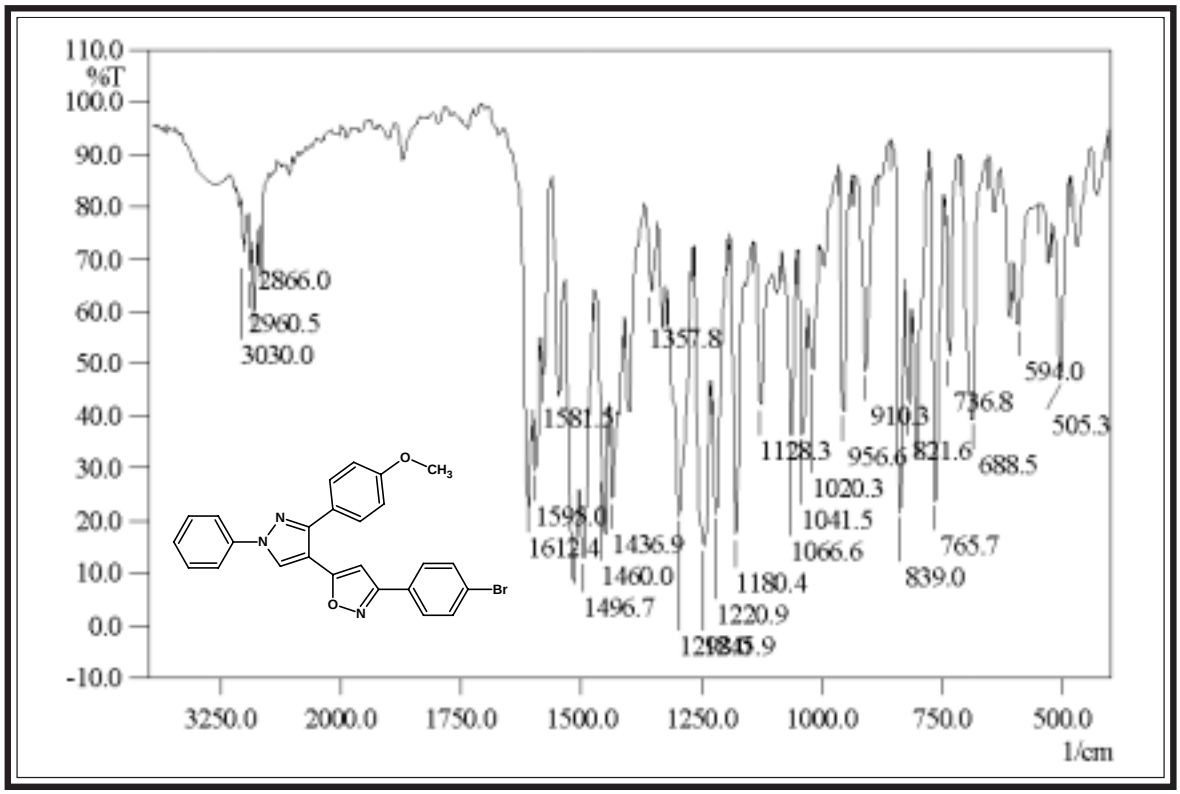
To a mixture of hydroxylamine hydrochloride (0.79, 0.01 M) in ethanol and anhydrous sodium acetate (0.82 g, 0.01 M) dissolved in minimum amount of hot acetic acid was added a solution of 1-(ρ-bromophenyl)-3-(1',N-phenyl)-3'-ρ-anisyl-pyrazol-4'-yl)-2-propene-1-one (4.59, 0.01 M) in ethanol (15 ml). The contents were refluxed on waterbath for 8 hrs. The reaction product was poured into ice and crystallised from ethanol. Yield 73%, m.p. 140^{o}C; (Anal. Found : C, 63.52; H, 3.80; N, 8.86%; $C_{25}H_{18}N_3O_2Br$ Requires: C, 63.57; H, 3.84; N, 8.90%).

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

(E) Antimicrobial activity of 3-Aryl-5-[1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl]-isoxazoles

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

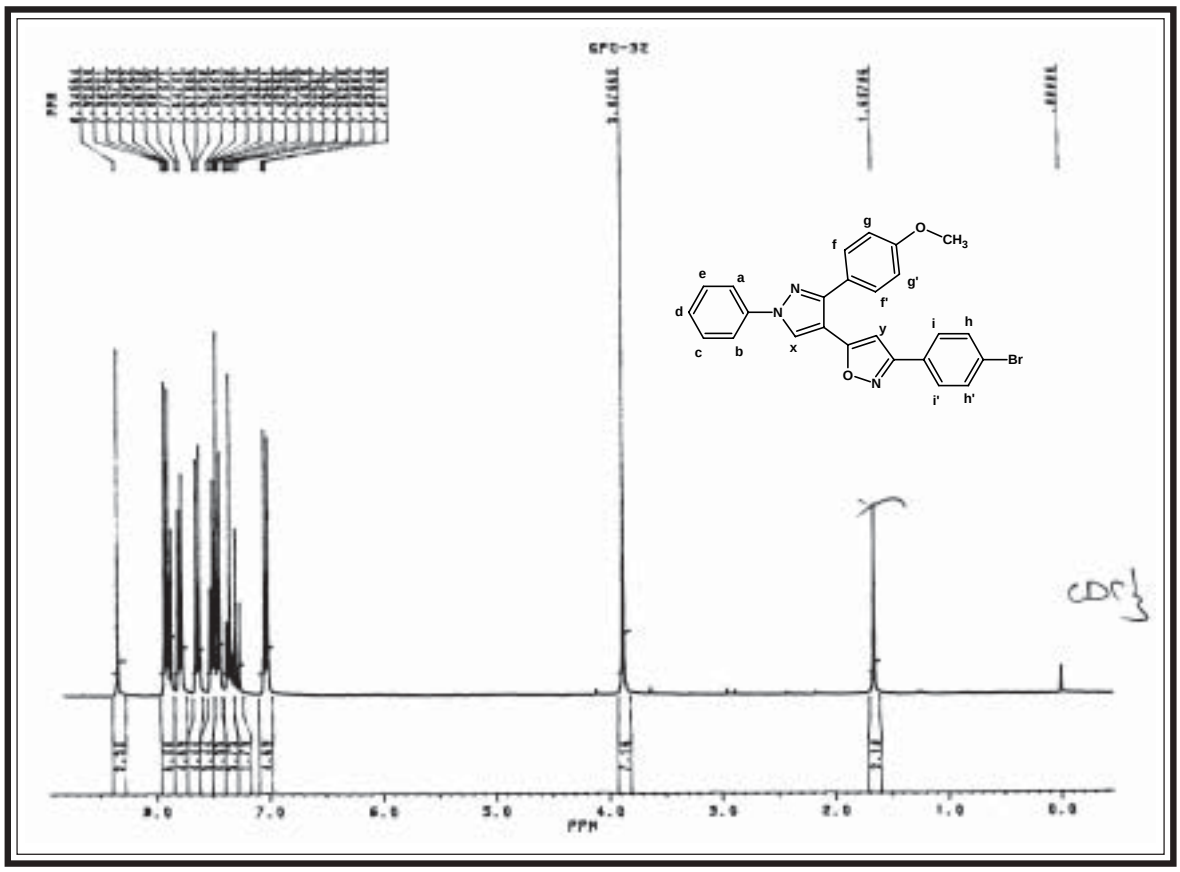
IR SPECTRAL STUDY OF 3-(ρ-BROMOPHENYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-ISOXAZOLE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C–H str.(asym.)	2960.5	2975-2950	434
-CH_3	C-H str. (sym.)	2866.0	2880-2860	"
	C-H def. (asym.)	1436.9	1470-1435	"
	C-H def. (sym.)	1357.8	1385-1350	"
Aromatic	C-H str.	3030.0	3080-3030	435
	C=C str.	1496.7	1585-1480	"
	C-H i.p. def.	1128.3	1125-1090	"
		1066.6	1070-1000	"
	C-H o.o.p. def.	821.6	835-810	"
Pyrazole	C=N str.	1612.4	1650-1600	434
moiety	C-N str.	1245.9	1350-1200	"
	C-Br str.	505.0	600-500	"
Ether	C-O-C str. (asym.)	1220.9	1275-1200	"
	C-O-C str. (sym.)	1020.3	1075-1020	"
Isoxazole	C=C str.	1581.5	1585-1570	"
	C=N str.	1460.0	1470-1460	"
	N-O str.	839.0	850-800	"

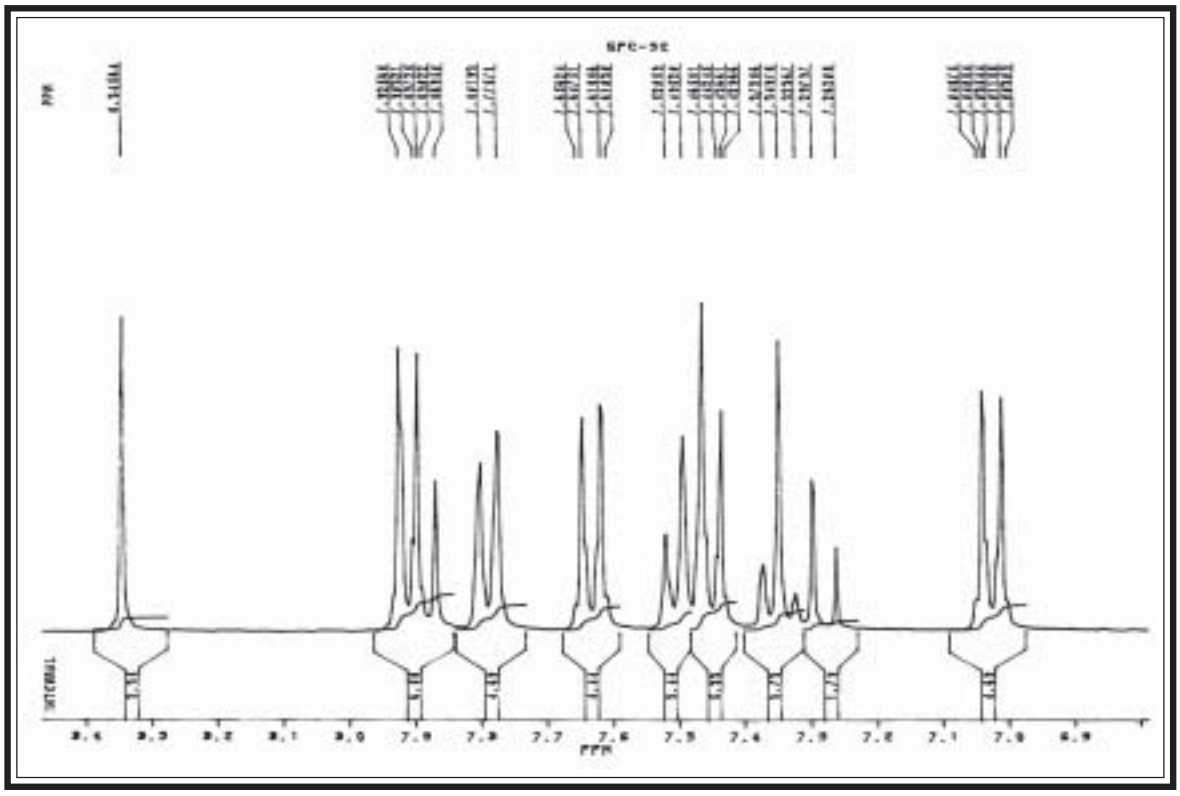
PMR SPECTRAL STUDY OF 3-(ρ-BROMOPHEYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-ISOXAZOLE



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	3.87		3H	singlet	Ar-OCH_3
2	7.23	Jgf = 8.7	2H	doublet	Ar-Hgg'
3	7.34		2H	triplet	Ar-Hc, Ar-He
4	7.44	Jhi = 8.7	2H	doublet	Ar-Hhh'
5	7.50		2H	doublet	Ar-Hd, CHy(isoxazole)
6	7.63	Jfg = 8.7	2H	doublet	Ar-Hff'
7	7.78	Jih = 8.7	2H	doublet	Ar-Hii'
8	7.86-7.92		2H	multiplet	Ar-Ha, Ar-Hb
9	8.34		1H	singlet	CHx

EXPANDED AROMATIC REGION



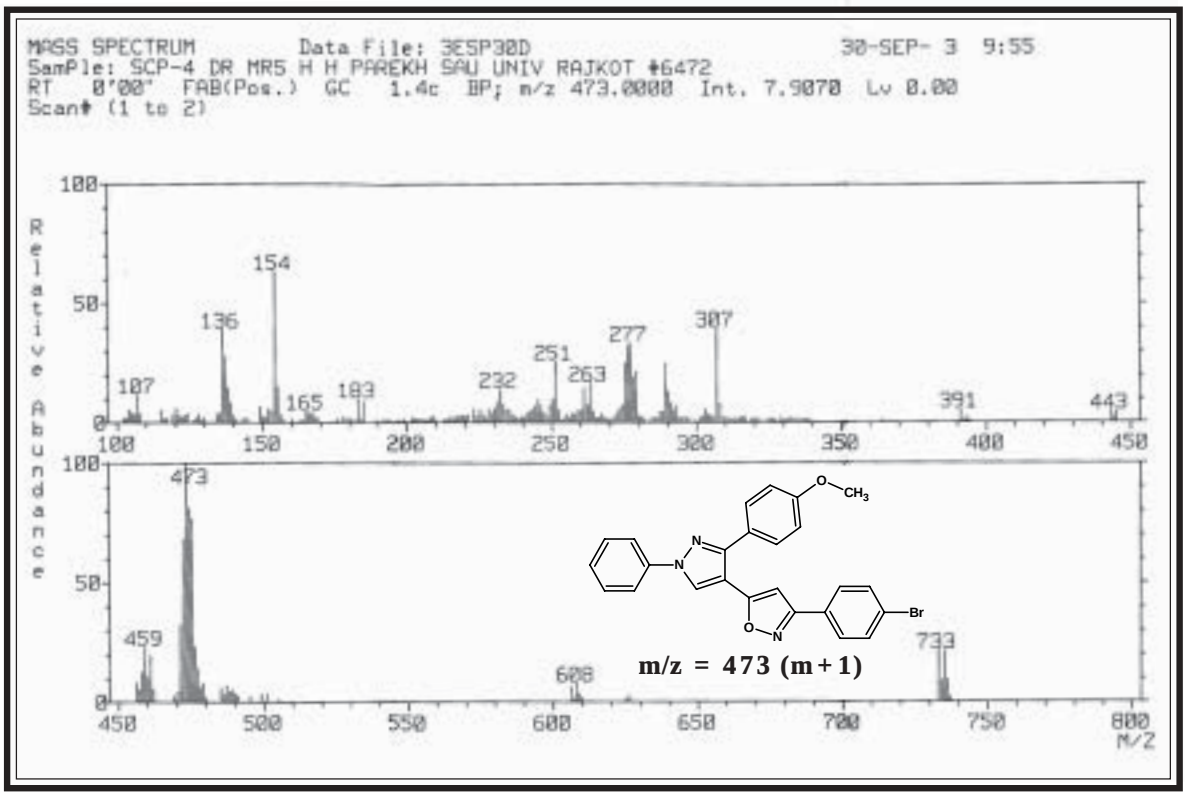
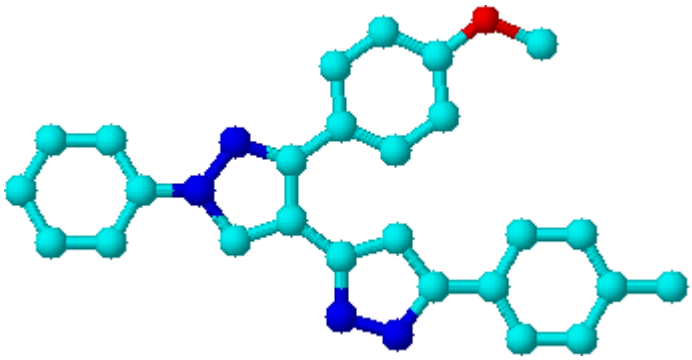


TABLE NO. 2 : PHYSICAL CONSTANTS OF 3-ARYL-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-ISOXAZOLE

Comp. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
2a	C_6H_5-	$C_{25}H_{19}N_3O_2$	393	155	0.61	69	10.68	10.62
2b	4-NH_2-C_6H_4-	$C_{25}H_{20}N_4O_2$	408	178	0.57	70	13.72	13.69
2c	3-NH_2-C_6H_4-	$C_{25}H_{20}N_4O_2$	408	162	0.60	72	13.72	13.65
2d	4-Br-C_6H_4-	$C_{25}H_{18}N_3O_2Br$	472	140	0.56	73	8.90	8.86
2e	4-Cl-C_6H_4-	$C_{25}H_{18}N_3O_2Cl$	426.5	156	0.55	75	9.82	9.77
2f	4-F-C_6H_4-	$C_{25}H_{18}N_3O_2F$	411	188	0.48	62	10.21	10.15
2g	4-OCH_3-C_6H_4-	$C_{26}H_{21}N_3O_3$	423	159	0.69	75	9.92	9.89
2h	4-CH_3-C_6H_4-	$C_{26}H_{21}N_3O_2$	407	148	0.72	68	10.31	10.28
2i	4-NO_2-C_6H_4-	$C_{25}H_{18}N_4O_4$	438	210	0.47	71	12.78	12.71
2j	3-NO_2-C_6H_4-	$C_{25}H_{18}N_4O_4$	438	181	0.60	64	12.78	12.73
2k	4-OH-C_6H_4-	$C_{25}H_{19}N_3O_3$	409	165	0.75	71	10.26	10.22
2l	2-OH-C_6H_4-	$C_{25}H_{19}N_3O_3$	409	146	0.45	64	10.26	10.20

*TLC Solvent System : Ethylacetate : Hexane (3 : 7)

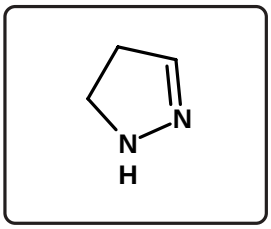


PART - II

STUDIES ON PYRAZOLYL PYRAZOLINES

INTRODUCTION

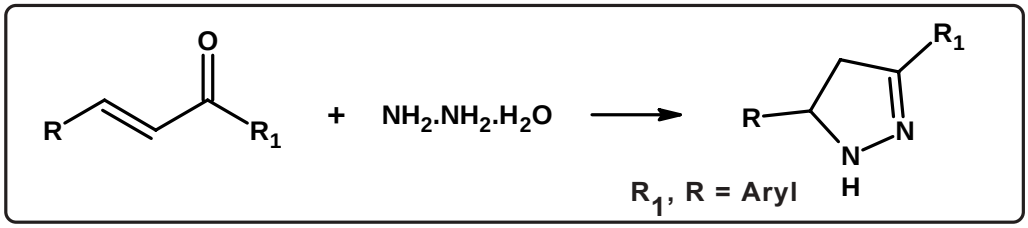
A pharmacological study of nitrogen containing five membered heterocyle, pyrazolines have proved them to be the most important molecule for the pharmacists. A dual feature like heterocylic & pharmacologically active pyrazolines attracted attention of medicinal chemists for their biological evalution as a drug. In 1967 Jarobe, reviewed the chemistry of pyrazolines, which have been studied extensively for their biodynamic behaviour[94] and industrial applications[95].



SYNTHETIC ASPECTS

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

1. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate[96].

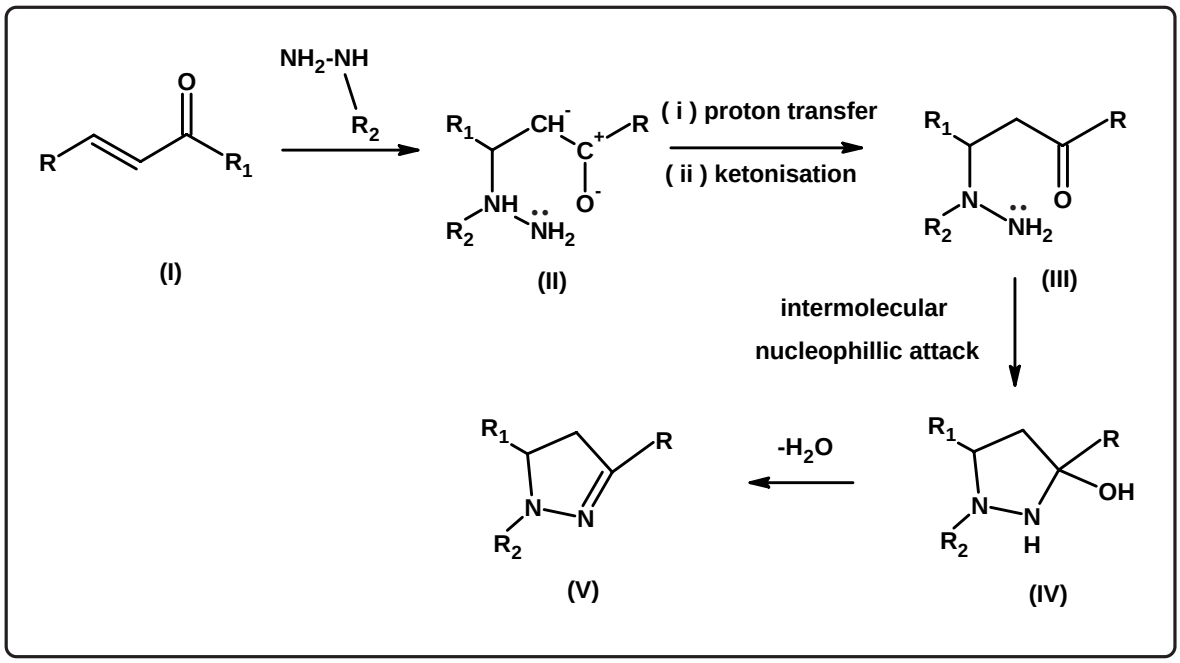


2. 2-Pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazines[97].
3. 2-Pyrazolines can be synthesised by the cycloaddition of diazomethane to substituted chalcones[98].

4. Dipolar cycloaddition of nitrilimines of dimethyl fumerate, fumaronitrile and the N-aryl maleimides yields the corresponding pyrazolines[99].
5. Epoxidation of chalcones have epoxy ketones which reacted with hydrazine and phenyl hydrazine to give pyrazoline[100].

REACTION MECHANISM

The following mechanism seems to be operable for the condensation of chalcones with hydrazine hydrate[101].



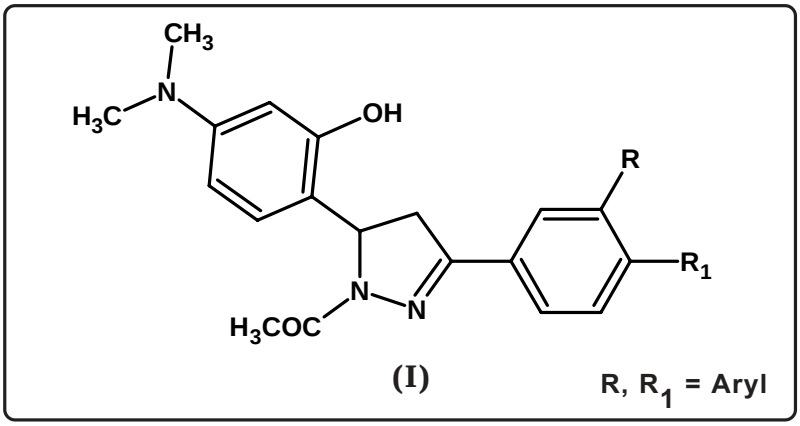
Nucleophilic attack by hydrazine at the β-carbon of the α,β-unsaturated carbonyl system forms species (II), in which the -ve charge is mainly accomodated by the electronegative oxygen atom. Proton transfer from the nitrogen to -ve oxygen produces an intermediate enol which simultaneously ketonises to ketoamine (III). Another intermolecular nucleophilic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to carbonyl amine (IV). The later with a hydroxy group and amino group on the same carbon lose water easily to yield the pyrazolines (V).

THERAPEUTIC IMPORTANCE

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

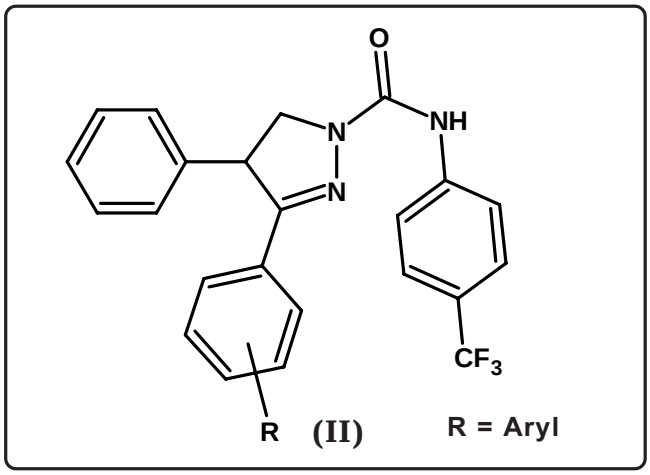
1. Analgesic[102]
2. Bactericidal[103]
3. Cardiovascular[104]
4. Diuretic[105]
5. Fungicidal[106]
6. Herbicidal[107]
7. Hypoglycemic[108]
8. Insecticidal[109]
9. Tranquilizing[110]
10. Antiallergic[111]
11. Anticonvulsant[112]
12. Antidiabetic[113]
13. Antiimplantation[114]
14. Antiinflammatory[115]
15. Antitumor[116]
16. Antineoplastic[117]

F. Manna and co-workers[118] have described 1-acetyl-5-(2'-bromophenyl)-4,5-dihydro-3-(2'-hydroxyphenyl)-1H-pyrazoline (I) and its derivatives which acts as potent antiinflammatory, analgesic and antipyretic agents.

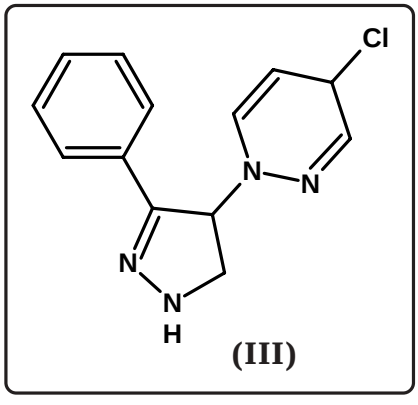


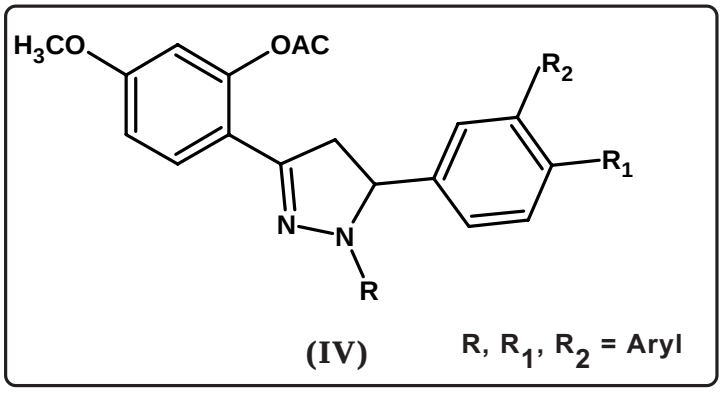
(I) R, R_1 = Aryl

Nugent Richard[119] investigated pyrazolines bis phosphonate ester as novel antiinflammatory and antiarthritic agents. Furthermore, Tsuboi et. al.[120] have synthesised some new (phenylcarbonyl) pyrazoline (II) as an insecticides and at 40% concentration shows 100% mortality of spodopetra litura larve after seven drops.

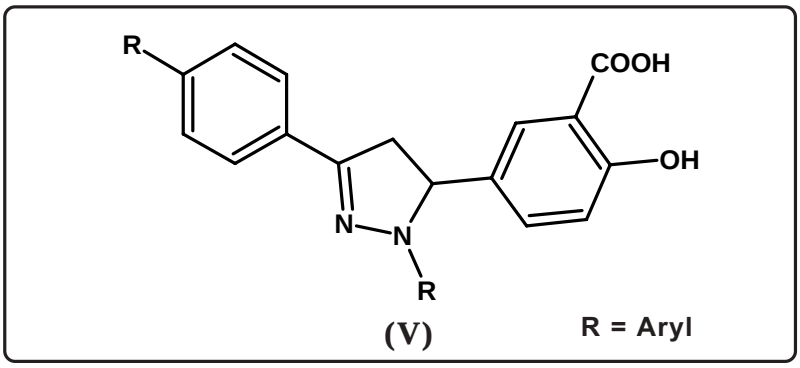


Tuntaway, Atif and co-workers[121] have patented 3-methyl-4'-(substituted phenylazo)-pyrazol-5-ones as antibacterial agents. Fuche Rainer et. al.[122] have prepared some 1H-pyrazoline (III) derivatives and reported them as pesticides. Johannes et. al.[123] have patented pyrazoline derivatives as insecticides. S. S. Sonarc et. al.[124] have synthesised 3-(2-acetoxy-4-methoxyphenyl)-5-(substitutedphenyl)-pyrazolines (IV) and tested their antimicrobial activity.





G. N. Mishirika et. al.[125] have also prepared 2-Pyrazoline derivatives of salicyclic acid (V) possessing antimicrobial properties.



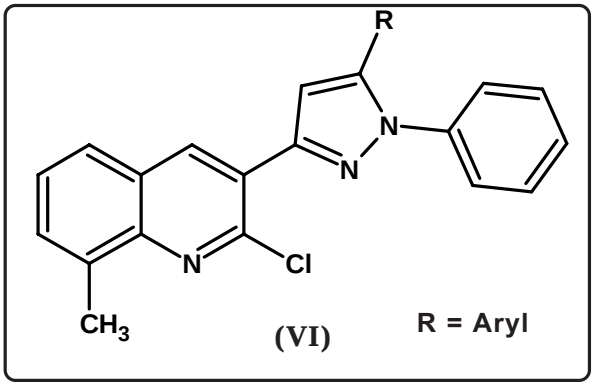
(V)

Udupi R. H. and Bhat A. R.[126] have reported the synthesis and biological activity of Mannich bases of certain 1,2-pyrazolines. Moreover, T. M. Stivenson et. al.[127] have also investigated N-Substituted pyrazoline type insecticide. Tanka Katsushori[128] et. al. have patented pyrazoline derivatives as herbicides. Moritaz Z. and Hadol[129] have demonstrated a semi emperial molecular orbital study on the reaction of amino-pyrazolinyl azo dye with singlet molecular oxygen. Shivananda M. K. and co-workers[130] have prepared pyrazolines and reported their antibacterial activity.

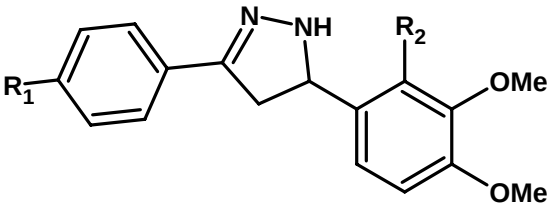
CONTRIBUTION FROM OUR LABORATORY

Parekh et. al.[131] have prepared 1-acetyl-5-aryl-3-[3-(3,4-dihydro-2-methyl-4-one-3-quinazolinyl)-phenyl]-2-pyrazolines which possess antimicrobial activity. Several pyrazolines bearing thymol moiety were evaluated for their ability as potent antimicrobial by K. P. Roda[132]. Vikani and co-workers[133] have prepared pyrazoline derivatives from arsanilic acid for their antimicrobial activity. Parekh et. al.[134] have synthesised and reported the antimicrobial activity of pyrazoline derivatives.

Jatin Upadhyay et. al.[135] have described by the pyrazoline derivatives and their use as antimicrobial agents. Akhil Bhatt and co-workers[136] have reported pyrazoline derivatives showing antimicrobial activity. Parekh et. al.[137] have synthesised phenyl pyrazoline derivatives bearing quinoline (VI) moiety and described their antimicrobial activity.



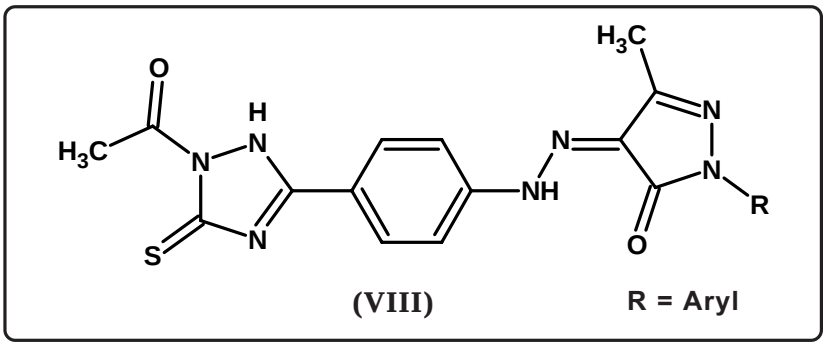
(VI) R = Aryl



R_1 = H, Cl, Br, Me, MeO
R_2 = H, Cl

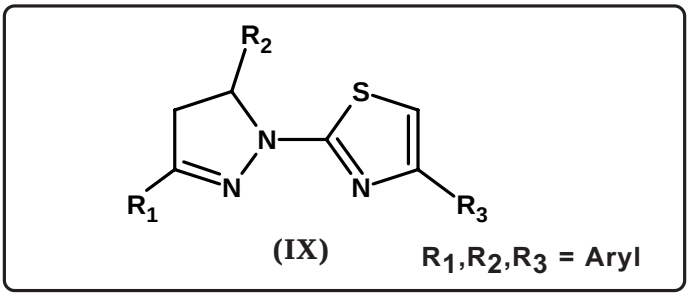
(VII)

E. Palska et. al.[138] have prepared 3,5-diphenyl-2-pyrazoline derivatives (VII) and studied their antidepressant activity. B. Shivarama Holla et. al.[139] have prepared some fluorine containing pyrazolines and N-acetyl pyrazolines as antibacterial agents. Guinizkucukguzel et. al.[140] have synthesised pyrazolines (VIII) as antimicrobial and anticonvulsant agents.

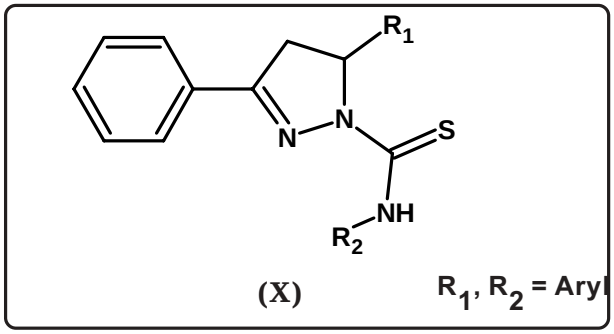


(VIII) R = Aryl

Gulhan Taran-Zitouni et. al.[141] have demonstrated 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazolines (IX) as antihypertensive agents. S. P Hiremath et. al.[142] have reported substituted pyrazolines as analgesic, antiinflammatory and antimicrobial agents. Malhotra et. al.[143] have prepared 1-thiocarbamoyl-2-pyrazolines derivatives (X) as anticardiovascular agents.



(IX) R_1,R_2,R_3 = Aryl



(X) R_1, R_2 = Aryl

Archana and V. K. Shrivastava et. al.[144] have synthesised quinazolinoyl pyrazoline as anticonvulsant agents. Almastead et. al.[145] have reported pyrazoline derivatives to increase erythropdietin and vascularization.

With an aim to synthesise better therapeutic agents, we have investigated some new pyrazolines, which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

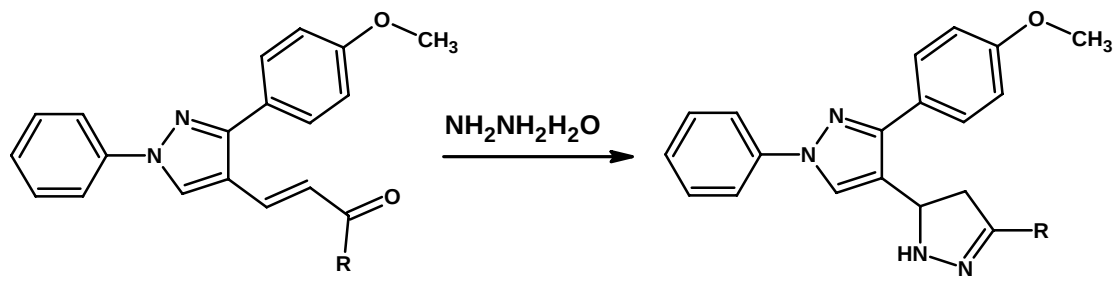
SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

SECTION-III : SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

Pyrazoline derivatives are endowed with valid antimicrobial activities. Looking at their versatile therapeutic importance and with an aim to getting better drug, it was considered worthwhile to synthesise some new pyrazolines. The preparation of 3-Aryl-5-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl) pyrazolines (III) has been undertaken by cyclocondensation of chalcones of type (II) with hydrazine hydrate.



Type (III) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. when R = p-chlorophenyl, molecular weight = 429, m/z = 430 (m + 1).

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

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

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

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

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

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

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

(D) Synthesis of 3-(ρ-Tolyl)-5-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-pyrazoline

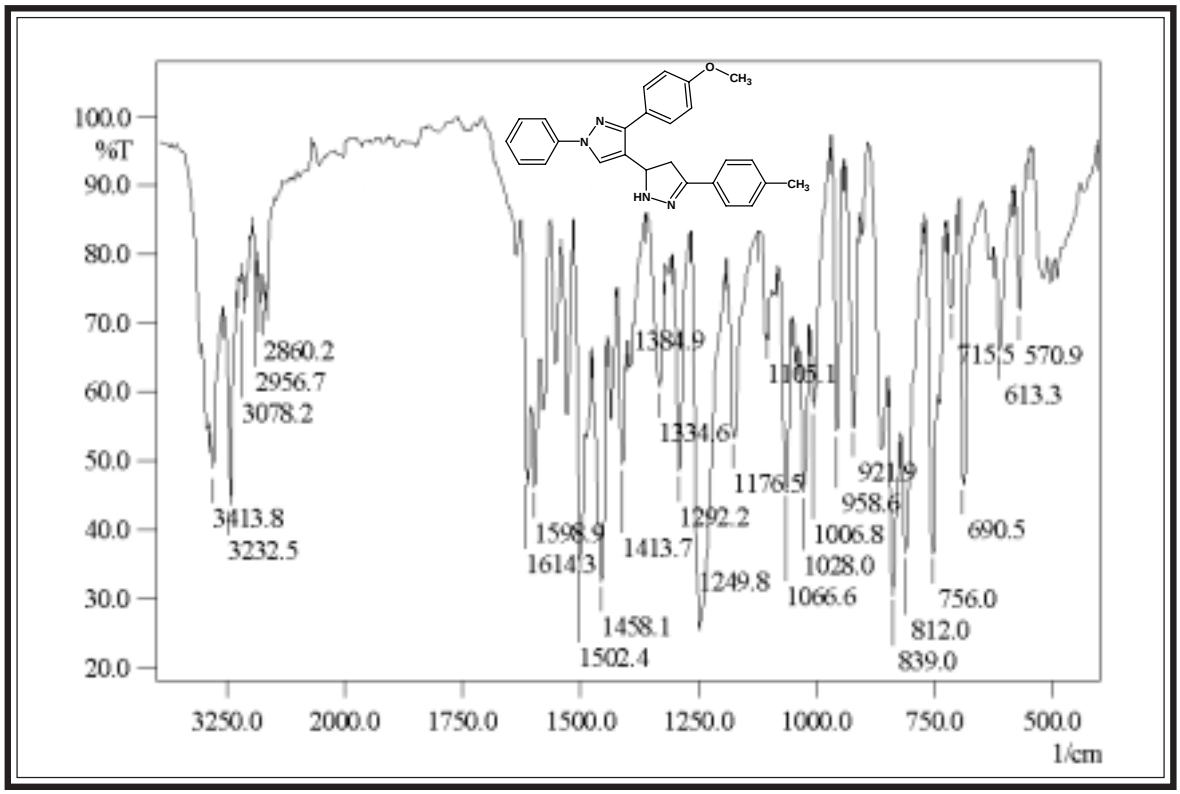
A mixture of 1-(ρ-tolyl)-3-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-2-propene-1-one (3.94 g, 0.01 M) in 25 ml of absolute alcohol, add hydrazine hydrate (0.5 g, 0.01 M) was refluxed for 8 hrs. The reaction mixture was poured into ice. The product was isolated and crystallised from ethanol. Yield 62%, m.p. 181^{o}C; (Anal. Found : C, 69.94 H, 4.87; N, 13.68%; $C_{26}H_{24}N_4O$ Requires: C, 70.01; H, 4.93; N, 13.72%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 3

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

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

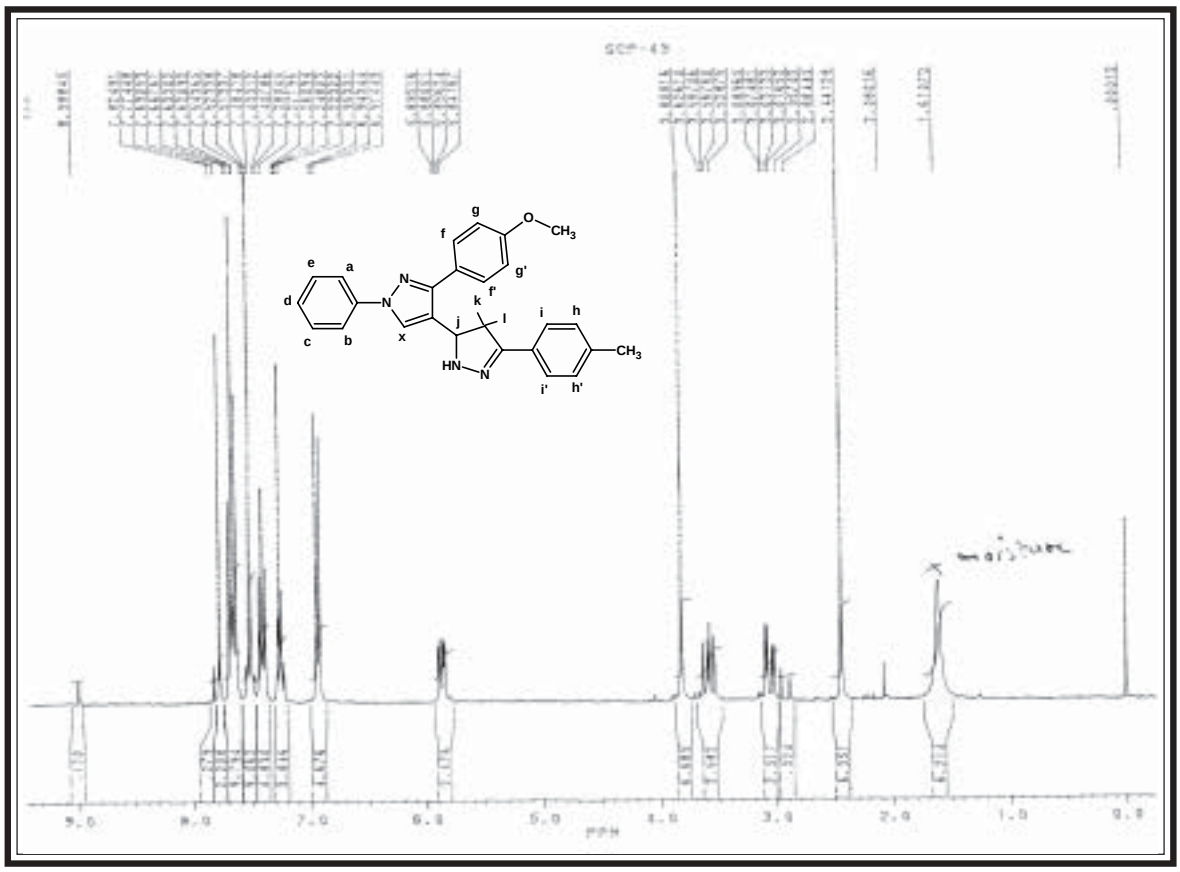
IR SPECTRAL STUDY OF 3-(ρ-TOLYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C–H str.(asym.)	2956.7	2975-2950	434
$-CH_3$	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1458.1	1470-1435	"
	C-H def. (sym.)	1384.9	1385-1350	"
Aromatic	C-H str.	3078.2	3080-3030	435
	C-H i.p. def.	1105.1	1125-1090	"
		1066.6	1070-1000	"
	C-H o.o.p. def.	812.0	835-810	"
Pyrazole	C=N str.	1598.9	1650-1600	434
moiety	C=C str.	1502.4	1585-1480	"
	C-N str.	1292.2	1350-1200	"
Ether	C-O-C (asym.)	1249.8	1275-1200	"
	C-O-C (sym.)	1028.0	1075-1020	"
Pyrazoline	C=N str.	1614.3	1627-1580	437
	C-H def.	690.5	698-690	"
	N-H str.	3413.8	3450-3250	434
	N-H def.	1598.0 (overlapped)	1650-1580	"

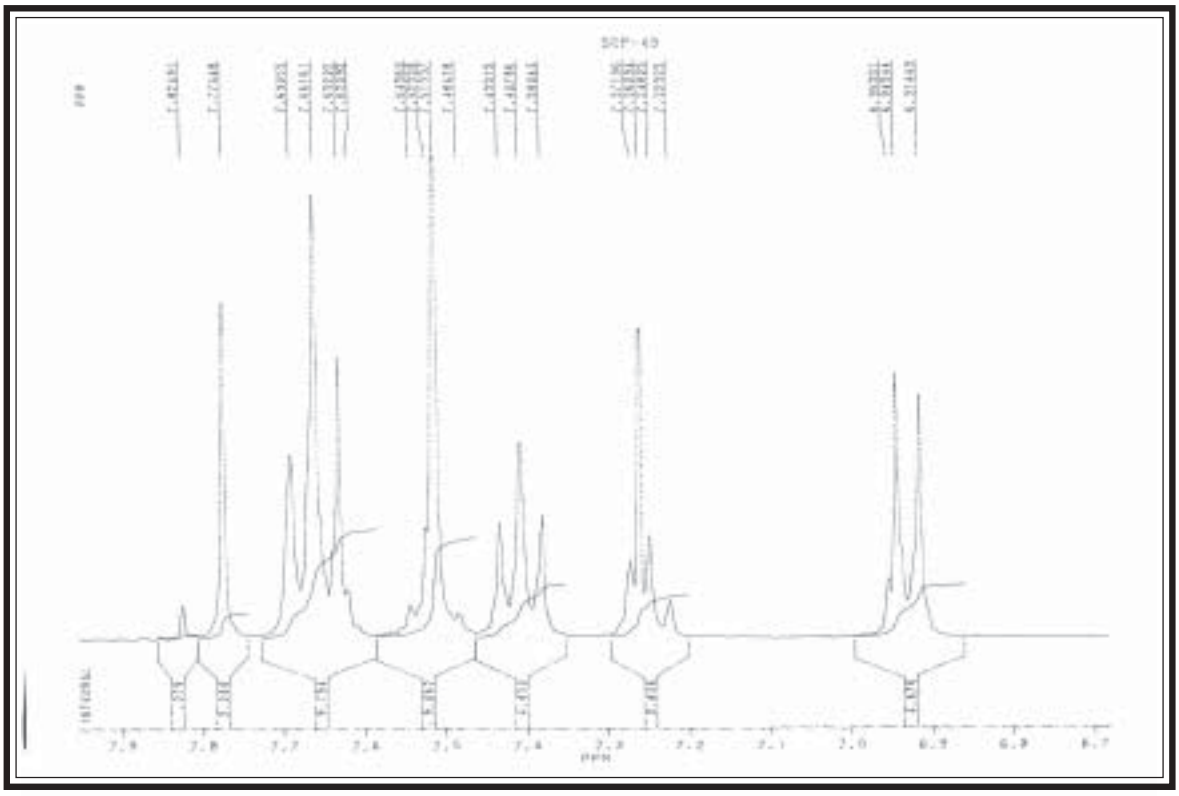
PMR SPECTRAL STUDY OF 3-(ρ-TOLYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINE

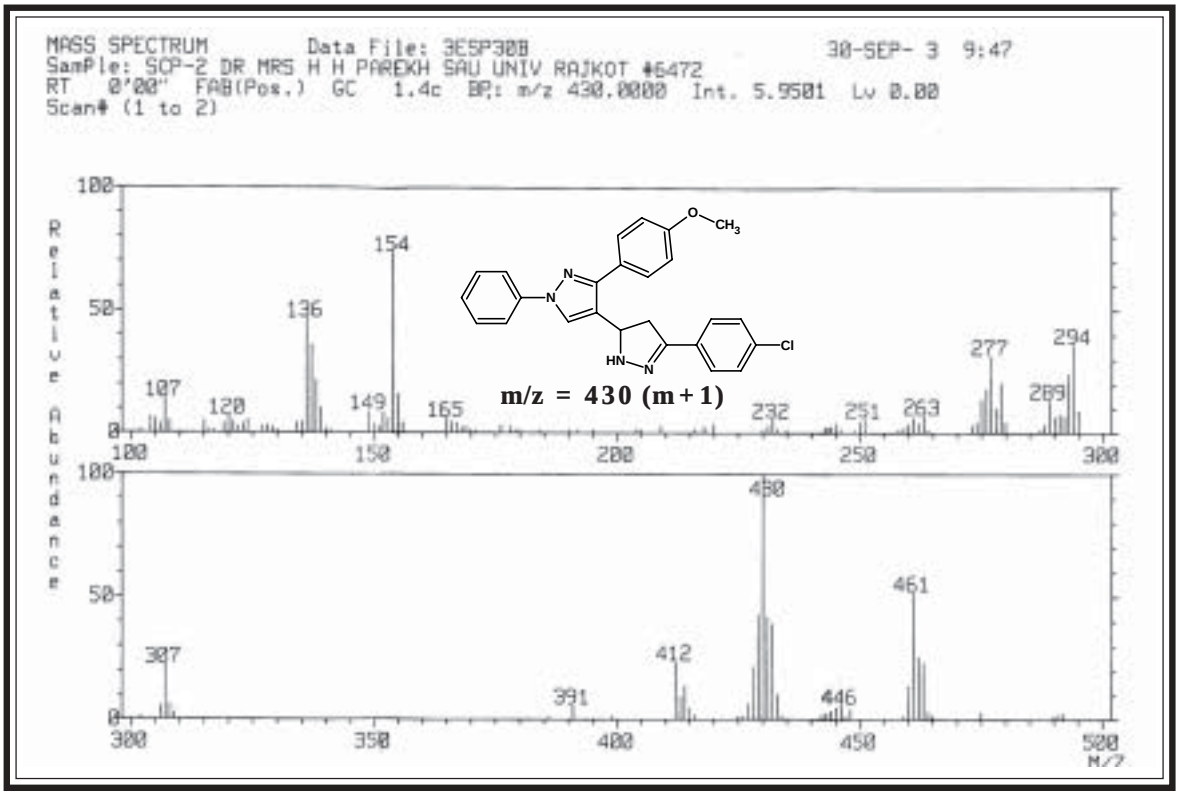


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

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	3.04	Jlk = 17.4, Jlj = 4.4	1H	d. doublet	CHl
3	3.57	Jkl = 17.4, Jkj = 11.6	1H	d. doublet	CHk
4	3.80		3H	singlet	Ar-OCH_3
5	5.86	Jjk = 11.6, Jjl = 4.4	1H	d. doublet	CHj
6	6.92	Jgf = 8.7	2H	doublet	Ar-Hgg'
7	7.26		1H	triplet	Ar-Hd
8	7.40		2H	triplet	Ar-Hc, Ar-He
9	7.48-7.54		4H	multiplet	Ar-Hhh' Ar-Ha, Ar-Hb
10	7.64	Jih = 8.7	2H	doublet	Ar-Hii'
11	7.67	Jfg = 8.7	2H	doublet	Ar-Hff'
12	7.77		1H	singlet	CHx

EXPANDED AROMATIC REGION





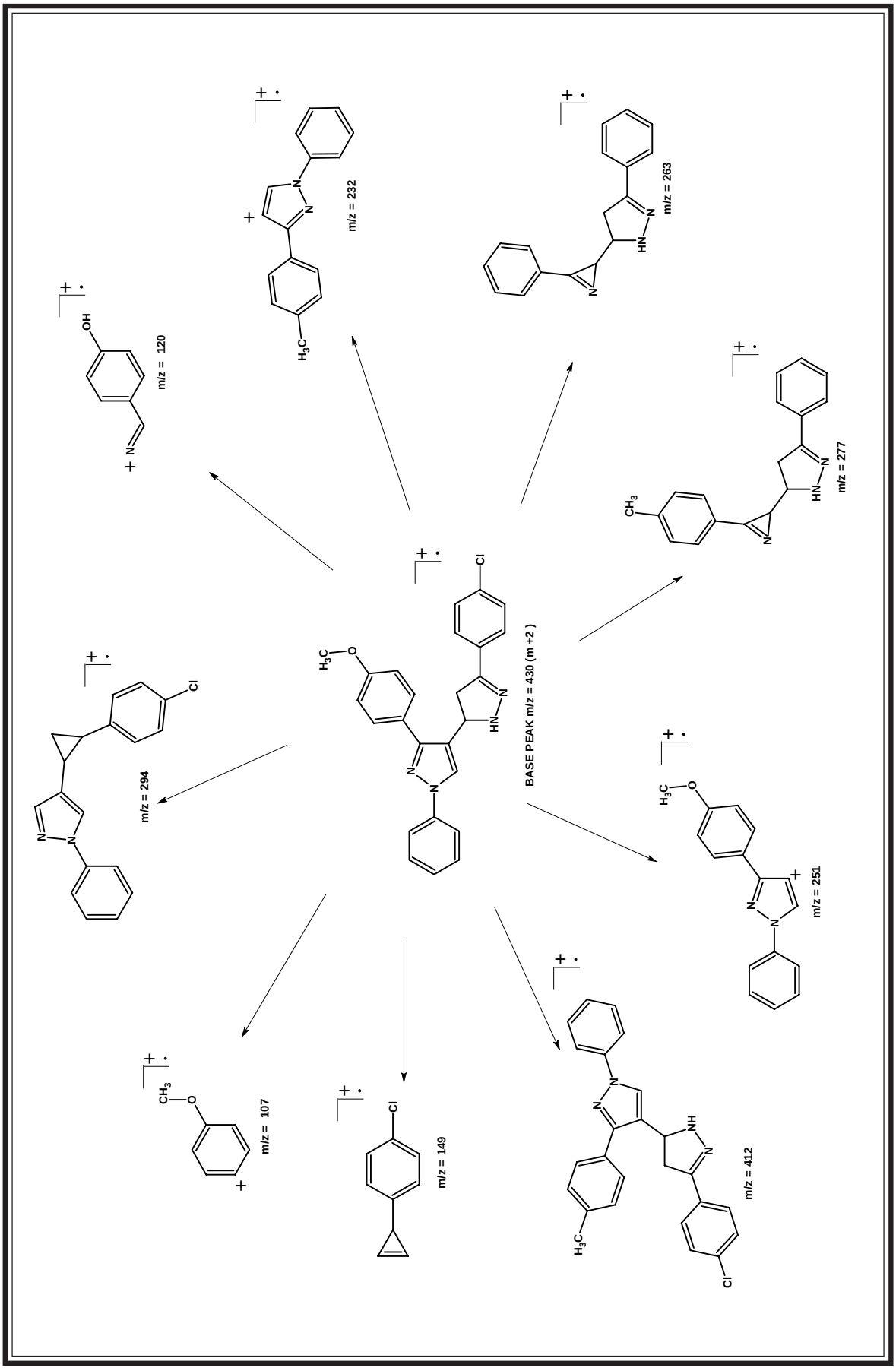

BASE PEAK m/z = 430 (m +2)
m/z = 120
m/z = 232
m/z = 263
m/z = 277
m/z = 294
m/z = 251
m/z = 107
m/z = 149
m/z = 412

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

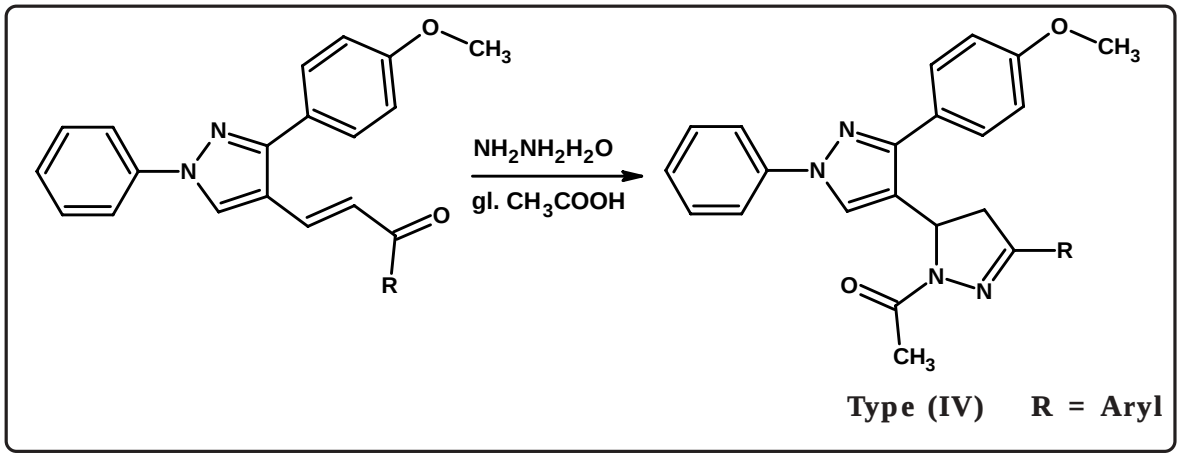
Comp. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
3a	C_6H_5-	$C_{25}H_{22}N_4O$	394	131	0.52	58	14.20	14.15
3b	4-NH_2-C_6H_4-	$C_{25}H_{23}N_5O$	409	159	0.42	61	17.10	17.06
3c	3-NH_2-C_6H_4-	$C_{25}H_{23}N_5O$	409	170	0.37	65	17.10	17.04
3d	4-Br-C_6H_4-	$C_{25}H_{21}N_4OBr$	473	144	0.43	64	11.84	11.78
3e	4-Cl-C_6H_4-	$C_{25}H_{21}N_4OCl$	429	155	0.50	66	13.06	13.01
3f	4-F-C_6H_4-	$C_{25}H_{21}N_4OF$	412	141	0.61	62	13.58	13.54
3g	4-OCH_3-C_6H_4-	$C_{26}H_{24}N_4O_2$	424	164	0.74	60	13.20	13.17
3h	4-CH_3-C_6H_4-	$C_{26}H_{24}N_4O$	408	181	0.66	62	13.72	13.68
3i	4-NO_2-C_6H_4-	$C_{25}H_{21}N_5O_3$	439	149	0.48	70	15.94	15.90
3j	3-NO_2-C_6H_4-	$C_{25}H_{21}N_5O_3$	439	160	0.34	72	15.94	15.89
3k	4-OH-C_6H_4-	$C_{25}H_{22}N_4O_2$	410	178	0.39	64	13.65	13.62
3l	2-OH-C_6H_4-	$C_{25}H_{22}N_4O_2$	410	165	0.51	68	13.65	13.59

*TLC Solvent System : Ethylacetate : Hexane (2 : 8)

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

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



Type (IV) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. wehen R = p-bromophenyl, molecular weight = 516, m/z = 517(m + 1).

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

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

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

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

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

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

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

(D) Synthesis of 1,N-Acetyl-3-(ρ-bromophenyl)-5-(1'-N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-pyrazoline

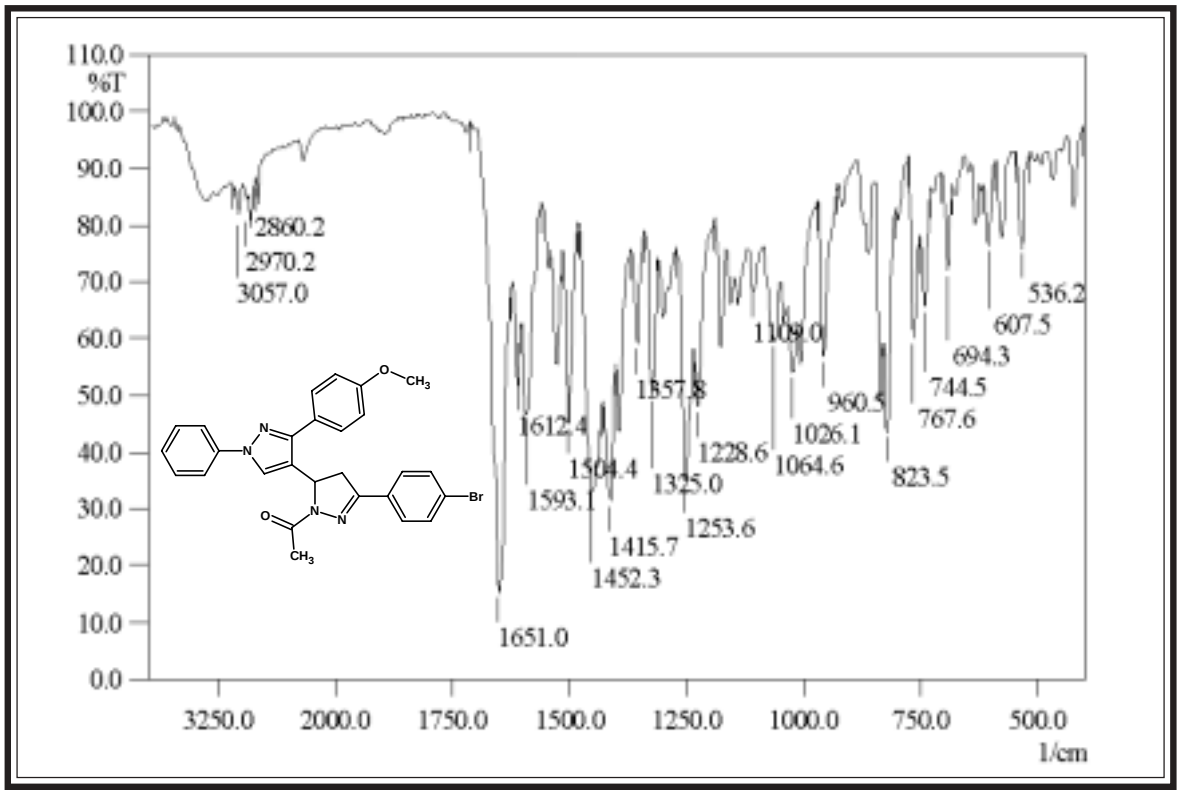
To a mixture of 1-(ρ-bromophenyl)-3-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-2-propene-1-one (4.59 g, 0.01 M) in 25 ml of absolute alcohol, add hydrazine hydrate (0.5 g, 0.01 M) and glacial acetic acid 10 ml added, the contents were refluxed for 10 hrs., and poured into ice. The product was isolated and crystallised from ethanol. Yield 70%, m.p. 180^{o}C; (Anal. Found : C, 62.88 H, 4.45; N, 10.83%; $C_{27}H_{23}N_4O_2Br$ Requires: C, 62.92; H, 4.50; N, 10.81%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No. 4

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

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

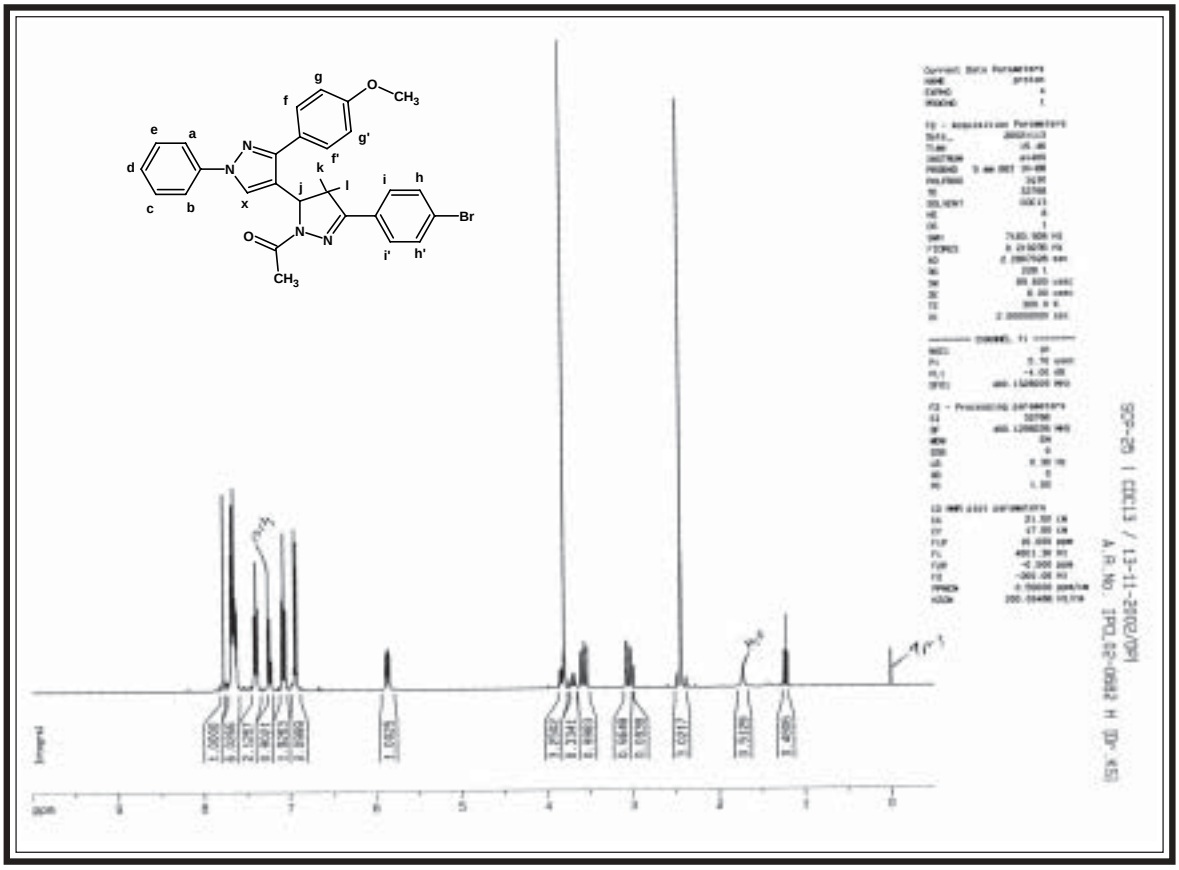
IR SPECTRAL STUDY OF 1,N-ACETYL-3-(ρ-BROMOPHENYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C–H str. (asym.)	2970.1	2975-2950	434
-CH_3	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1452.3	1470-1435	"
	C-H def. (sym.)	1357.8	1385-1350	"
Aromatic	C-H str.	3057.0	3080-3030	435
	C-H i.p. def.	1108.9	1125-1090	"
		1064.6	1070-1000	"
	C-H o.o.p. def.	823.5	835-810	"
Pyrazole	C=N str.	1612.4	1650-1600	434
moiety	C=C str.	1504.4	1585-1480	"
	C-N str.	1253.6	1350-1200	"
	C-Br str.	536.2	600-550	"
Ether	C-O-C (asym.)	1228.6	1275-1200	"
	C-O-C (sym.)	1026.1	1075-1020	"
Pyrazoline	C=N str.	1593.7	1627-1580	437
	C-H def.	694.5	698-690	"
	C=O	1651.0	1760-1655	434

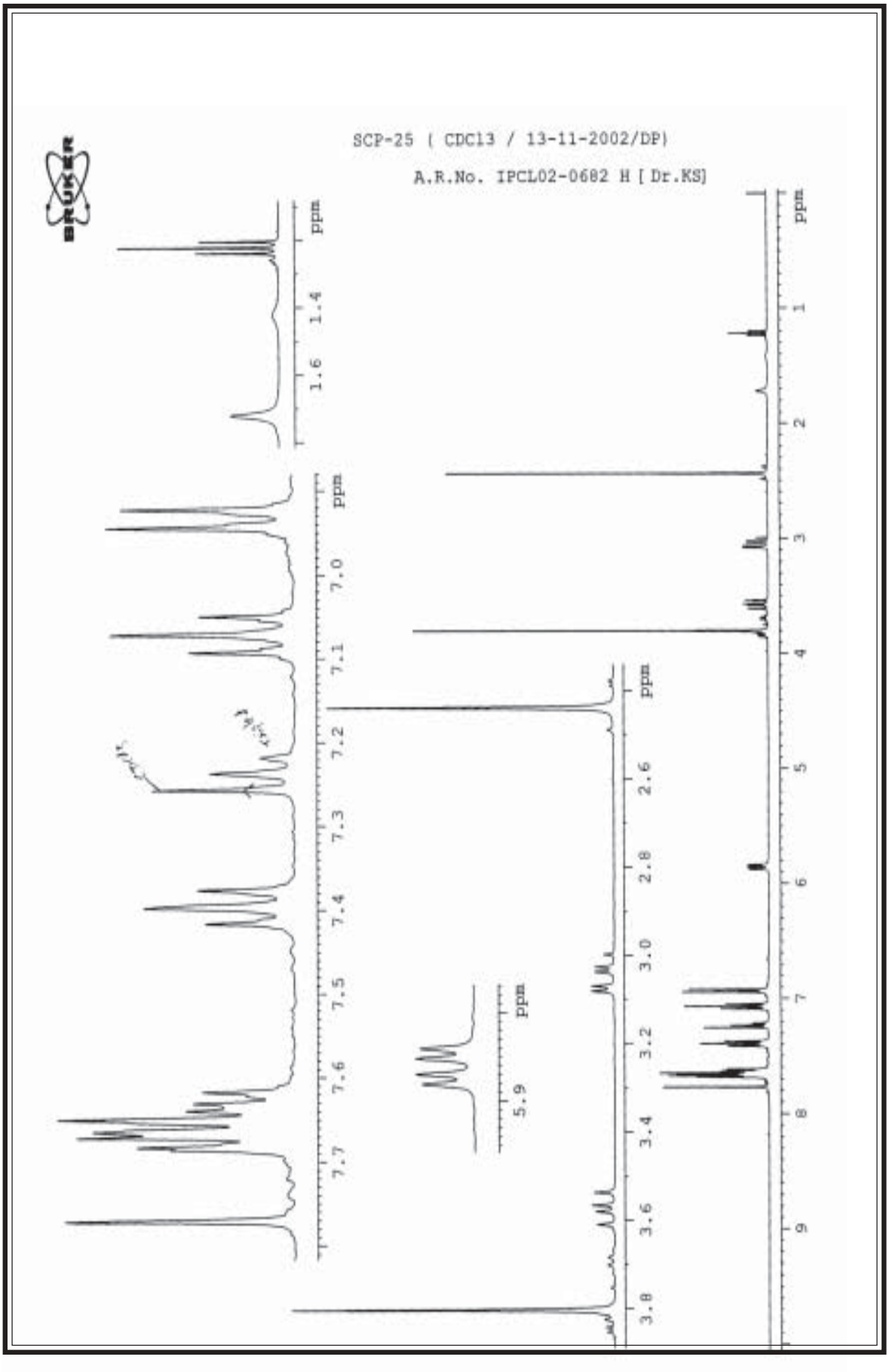
PMR SPECTRAL STUDY OF 1,N-ACETYL-3-(ρ-BROMOPHENYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINE

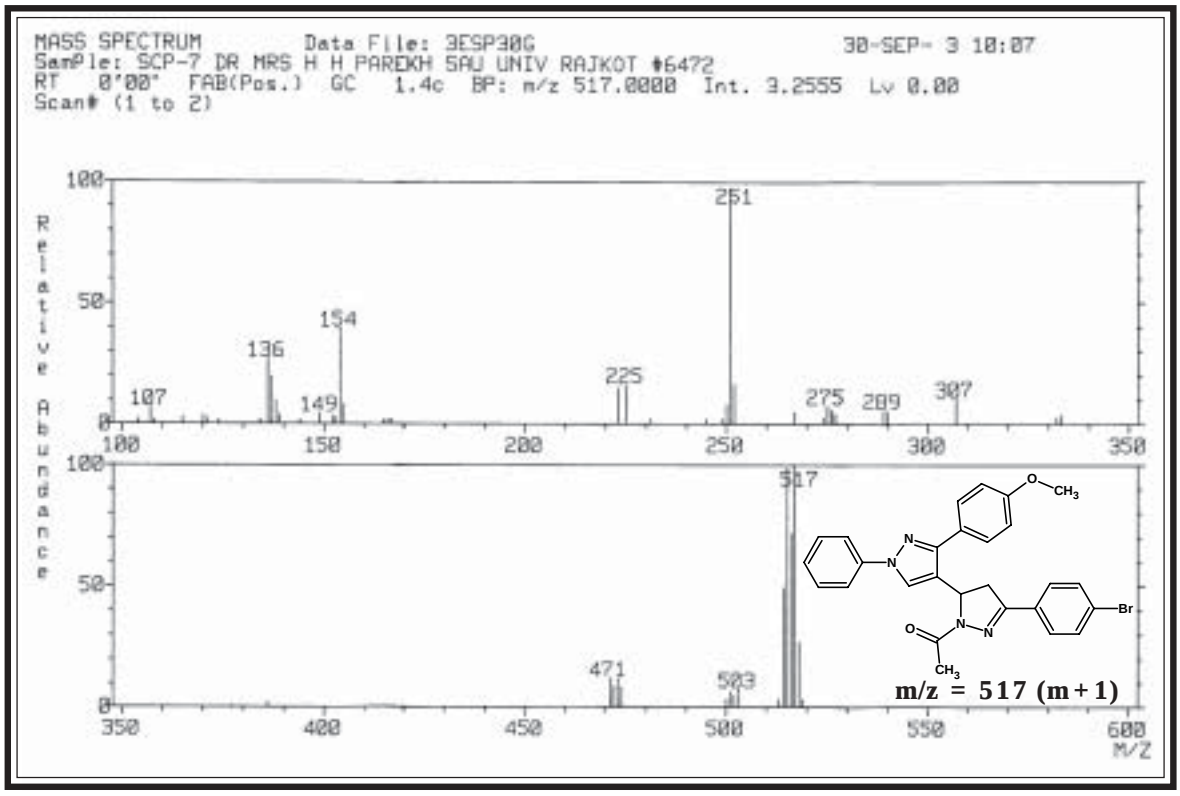


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J. Value in Hz	Relative No. of Protons	Multiplicity	Inference
1	2.43		3H	singlet	$-COCH_3$
2	3.05	Jlk = 13.0, Jlj = 3.4	1H	d. doublet	CHl
3	3.55	Jkl = 13.0, Jkj = 8.7	1H	d. doublet	CHk
4	3.80		3H	singlet	$Ar-OCH_3$
5	5.85	Jjk = 8.7, Jjl = 3.4	1H	d. doublet	CHj
6	6.93	Jgf = 6.6	2H	doublet	Ar-Hgg'
7	7.07		2H	triplet	Ar-Hc, Ar-He
8	7.25		1H	triplet	Ar-Hd
9	7.41		2H	triplet	Ar-Ha, Ar-Hb
10	7.61-7.68		6H	multiplet	Ar-Hhh'
					Ar-Hii'
					Ar-Hff'
11	7.77		1H	singlet	CHx

EXPANDED AROMATIC REGION





IR SPECTRAL DATA OF 1,N-ACETYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

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

Sr. No.	R	C=O str. Acetylpyrazolines
4a	C_6H_5-	1660
4b	4-NH_2-C_6H_4-	1654
4c	3-NH_2-C_6H_4-	1662
4d	4-Br-C_6H_4-	1651
4e	4-Cl-C_6H_4-	1658.7
4g	4-F-C_6H_4-	1666
4h	4-OCH_3-C_6H_4-	1650
4i	4-CH_3-C_6H_4-	1656.8
4j	4-NO_2-C_6H_4-	1654
4m	3-NO_2-C_6H_4-	1660
4n	4-OH-C_6H_4-	1655
4o	2-OH-C_6H_4-	1654

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

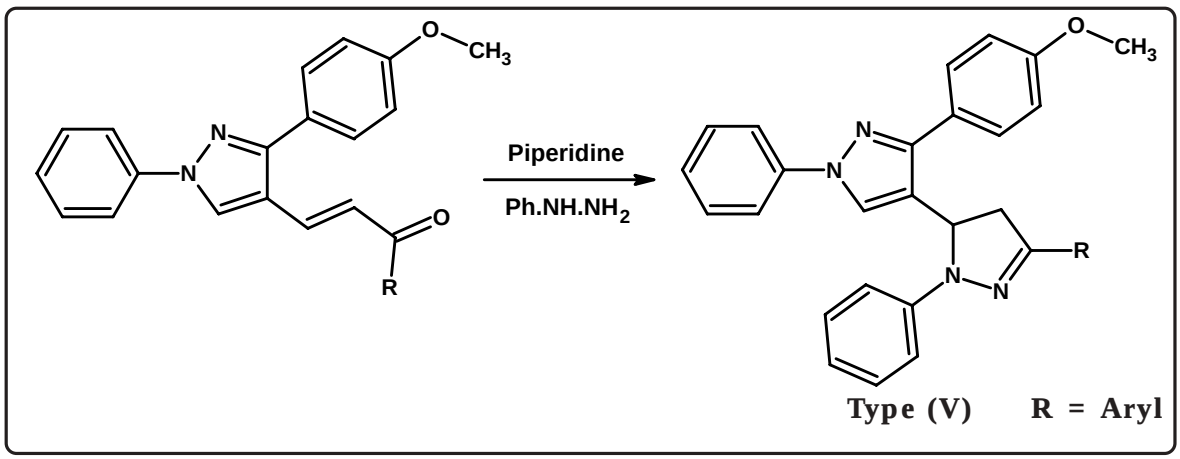
Comp. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
4a	C_6H_5-	$C_{27}H_{24}N_4O_2$	436.5	220	0.48	73	12.84	12.79
4b	4-NH_2-C_6H_4-	$C_{27}H_{25}N_5O_2$	451.5	212	0.55	60	15.51	15.47
4c	3-NH_2-C_6H_4-	$C_{27}H_{25}N_5O_2$	451.5	185	0.39	65	15.51	15.49
4d	4-Br-C_6H_4-	$C_{27}H_{23}N_4O_2Br$	516	180	0.46	70	10.87	10.81
4e	4-Cl-C_6H_4-	$C_{27}H_{23}N_4O_2Cl$	471	155	0.74	71	11.90	11.86
4f	4-F-C_6H_4-	$C_{27}H_{23}N_4O_2F$	454	178	0.51	66	12.33	12.28
4g	4-OCH_3-C_6H_4-	$C_{28}H_{26}N_4O_3$	466.5	175	0.61	71	12.01	11.96
4h	4-CH_3-C_6H_4-	$C_{28}H_{26}N_4O_2$	450.5	202	0.66	64	12.44	12.40
4i	4-NO_2-C_6H_4-	$C_{27}H_{23}N_5O_4$	481.5	181	0.47	75	14.54	14.49
4j	3-NO_2-C_6H_4-	$C_{27}H_{23}N_5O_4$	481.5	190	0.78	62	14.54	14.51
4k	4-OH-C_6H_4-	$C_{27}H_{24}N_4O_3$	452.5	179	0.42	68	12.38	12.35
4l	2-OH-C_6H_4-	$C_{27}H_{24}N_4O_3$	452.5	168	0.58	64	12.38	12.32

*TLC Solvent System : Ethylacetate : Hexane (2 : 8)

SECTION - III

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

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



Type (V) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. wehen R = p-bromophenyl, molecular weight = 549, m/z = 550 (m + 1).

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

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,N-PHENYL-3-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-PYRAZOLINES

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

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

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

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

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

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

(D) Synthesis of 1,N-Phenyl-3-(ρ-bromophenyl)-5-(1'-N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-pyrazoline

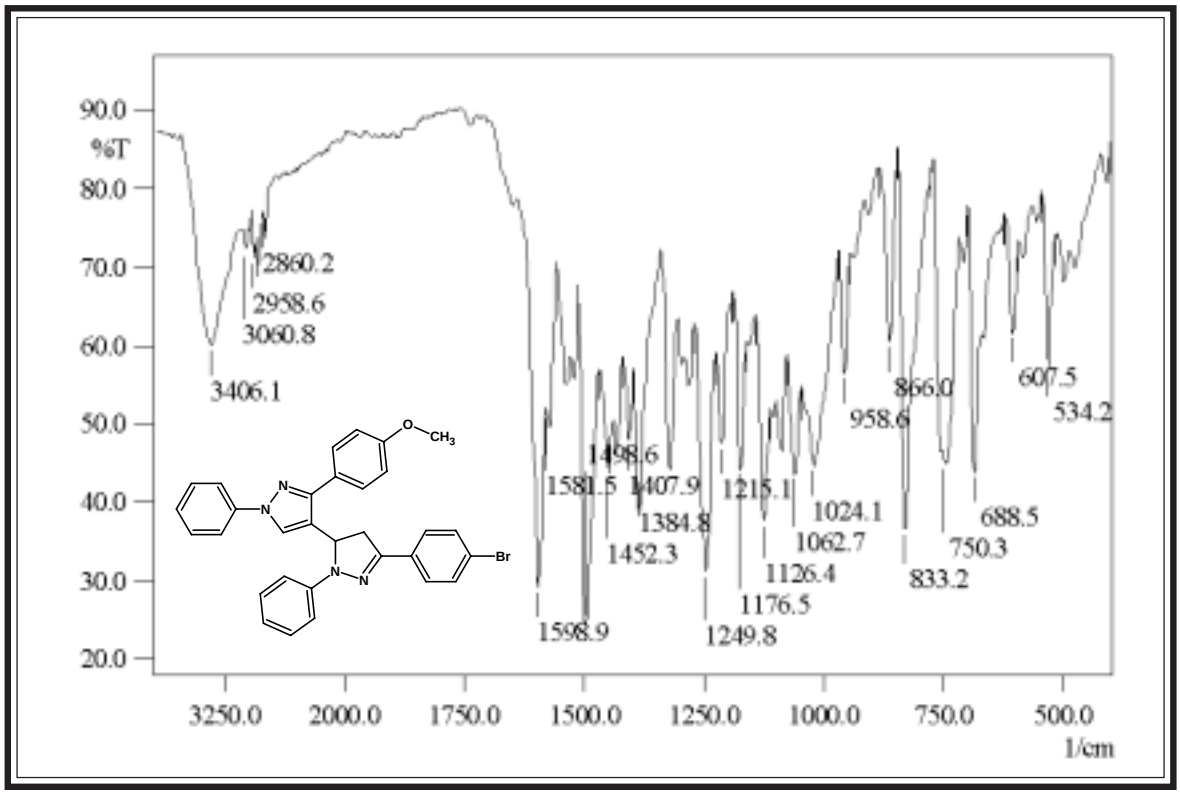
To a mixture of 1-(ρ-bromophenyl)-3-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-2-propene-1-one (4.59 g, 0.01 M) in 25 ml of absolute alcohol, add phenyl hydrazine (1.08 g, 0.01 M) was added in presence of basic catalyst like piperidine and refluxed for 12 hrs. The reaction product was poured into ice. The product was isolated and crystallised from ethanol. Yield 68%, m.p. 160^{o}C. (Anal. Found : C, 67.71 H, 4.53; N, 10.16%; $C_{31}H_{25}N_4OBr$ Requires: C, 67.76; H, 4.59; N, 10.20%).

Similarly other substituted pyrazolines have been prepared. The physical data are recorded in Table No.5

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

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

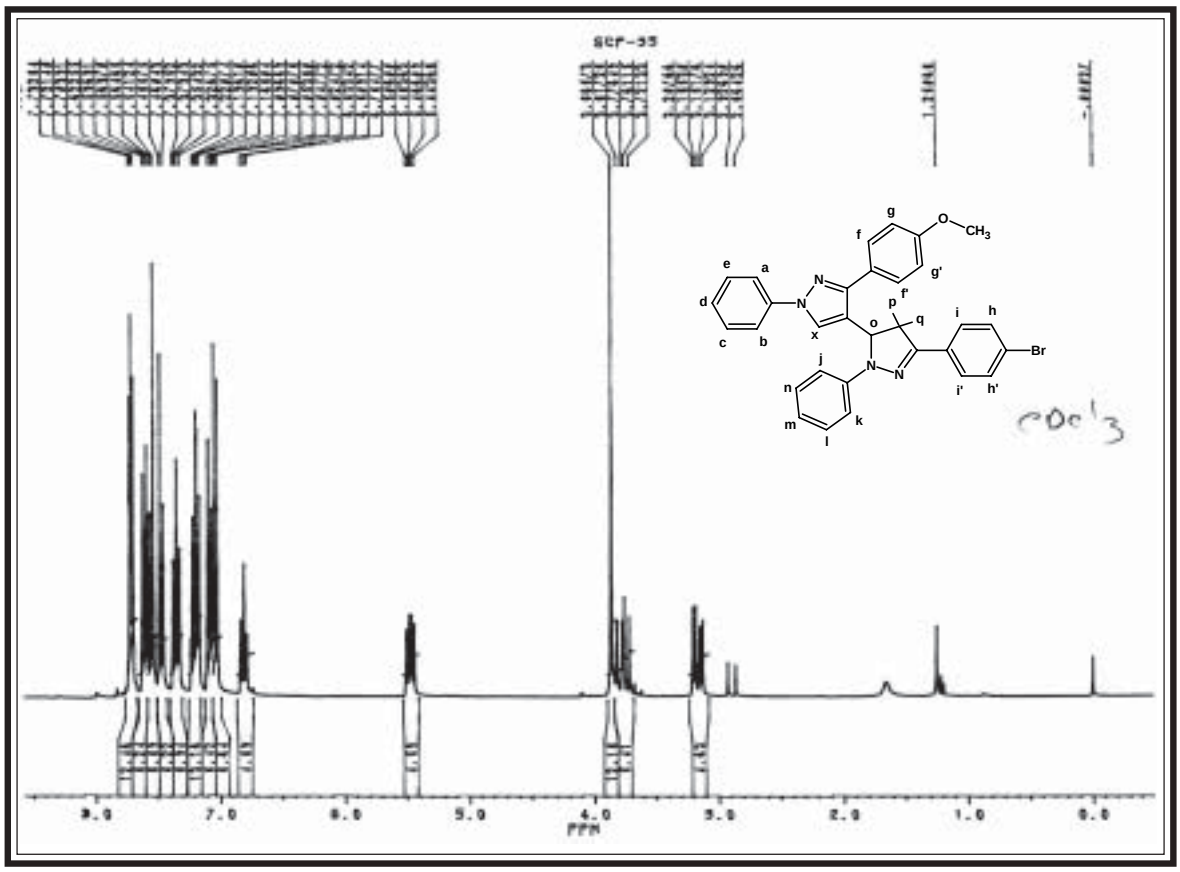
IR SPECTRAL STUDY OF 1,N-PHENYL-3-(ρ-BROMOPHENYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C–H str. (asym.)	2958.6	2975-2950	434
$-CH_3$	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1452.3	1470-1435	"
	C-H def. (sym.)	1384.8	1385-1350	"
Aromatic	C-H str.	3060.8	3080-3030	435
	C-H i.p. def.	1126.4	1125-1090	"
		1062.7	1070-1000	"
	C-H o.o.p. def.	833.2	835-810	"
Pyrazole	C=N str.	1598.9	1650-1600	434
moiety	C=C str.	1498.6	1585-1480	"
	C-N str.	1249.8	1350-1200	"
	C-Br	534	600-500	"
Ether	C-O-C (asym.)	1216.1	1275-1200	"
	C-O-C (sym.)	1024.1	1075-1020	"
Pyrazoline	C=N str.	1581.5	1627-1580	437
	C-H def.	688.5	698-690	"

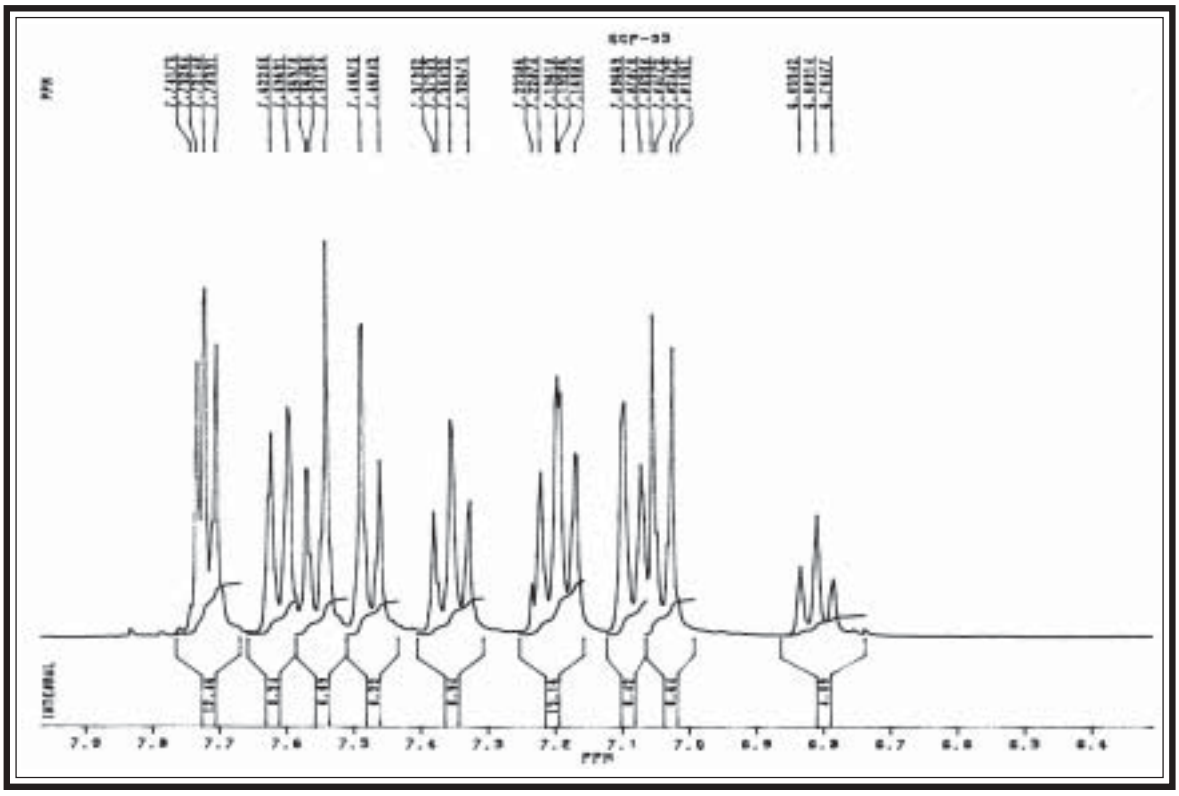
PMR SPECTRAL STUDY OF 1,N-PHENYL-3-(ρ-BROMOPHENYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINE



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	3.16	Jqp=16.8, Jqo=6.7	1H	d. doublet	CHq
2	3.75	Jpq=16.8, Jpo=12.0	1H	d. doublet	CHp
3	3.86		3H	singlet	Ar-OCH_3
4	5.47	Jop=12.0, Joq=6.7	1H	d. doublet	CHo
5	6.80		1H	triplet	Ar-Hm
6	7.03	Jgf=8.4	2H	doublet	Ar-Hgg'
7	7.08	Jhi=8.4	2H	doublet	Ar-Hhh'
8	7.16-7.23		3H	multiplet	Ar-Hj Ar-Hk, Ar-Hd
9	7.35		2H	triplet	Ar-Hc, Ar-He
10	7.47	Jfg=8.4	2H	doublet	Ar-Hff'
11	7.55	Jih=8.4	2H	doublet	Ar-Hii'
12	7.60		2H	doublet	Ar-Hl, Ar-Hn
13	7.70-7.74		3H	multiplet	Ar-Ha, Ar-Hb, CHx

EXPANDED AROMATIC REGION



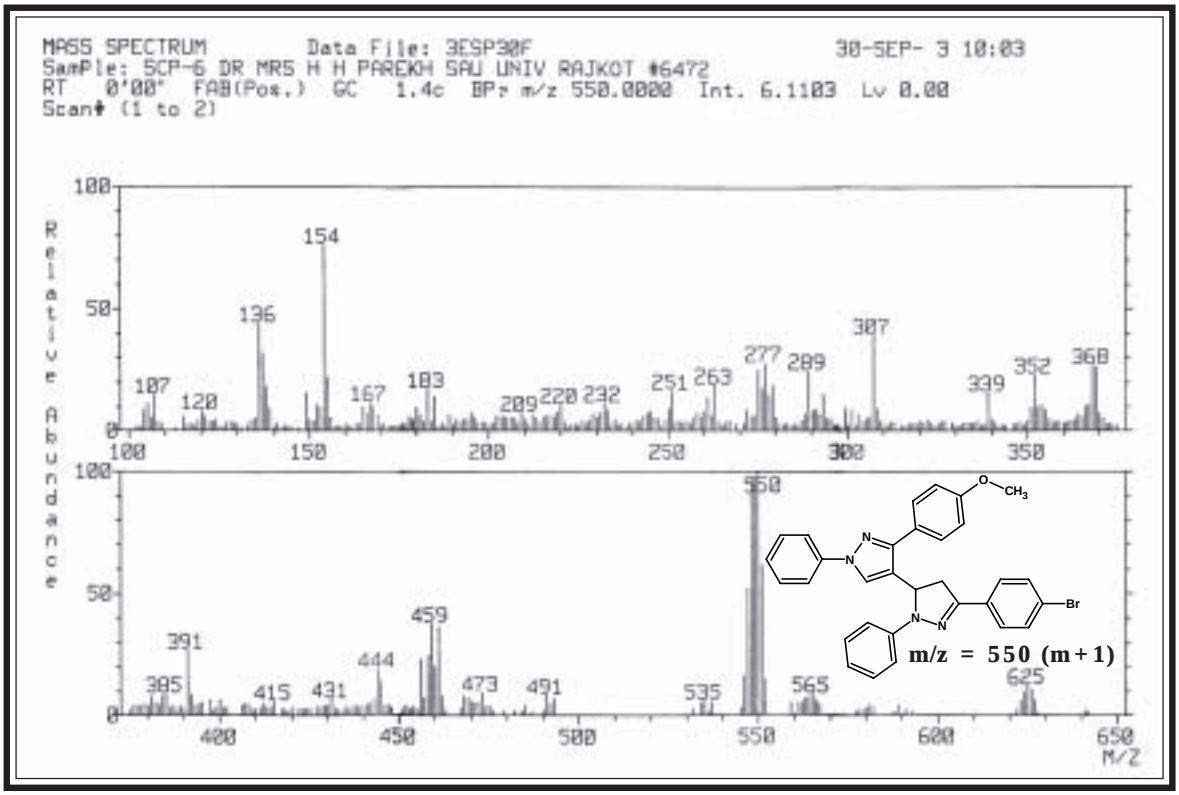
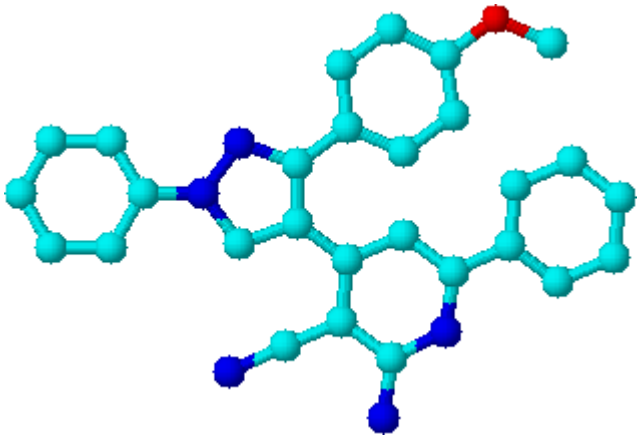


TABLE NO. 5 : PHYSICAL CONSTANTS OF 1,N-PHENYL-3-ARYL-5-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-PYRAZOLINES

Comp. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf* Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
5a	C_6H_5-	$C_{31}H_{26}N_4O$	470.5	154	0.61	62	11.91	11.88
5b	4-NH_2-C_6H_4-	$C_{31}H_{27}N_5O$	485	145	0.52	66	14.42	14.37
5c	3-NH_2-C_6H_4-	$C_{31}H_{27}N_5O$	485	133	0.48	62	14.42	14.36
5d	4-Br-C_6H_4-	$C_{31}H_{25}N_4OBr$	549	160	0.55	68	10.20	10.15
5e	4-Cl-C_6H_4-	$C_{31}H_{25}N_4OCl$	505	148	0.42	70	11.09	11.03
5f	4-F-C_6H_4-	$C_{31}H_{25}N_4OF$	488	155	0.49	65	11.47	11.42
5g	4-OCH_3-C_6H_4-	$C_{32}H_{28}N_4O_2$	500	164	0.65	64	11.19	11.16
5h	4-CH_3-C_6H_4-	$C_{32}H_{28}N_4O$	484	158	0.74	65	11.56	11.51
5i	4-NO_2-C_6H_4-	$C_{31}H_{25}N_5O_3$	515	175	0.69	70	13.58	13.52
5j	3-NO_2-C_6H_4-	$C_{31}H_{25}N_5O_3$	515	184	0.45	61	13.58	13.54
5k	4-OH-C_6H_4-	$C_{31}H_{26}N_4O_2$	486	150	0.44	71	11.51	11.47
5l	2-OH-C_6H_4-	$C_{31}H_{26}N_4O_2$	486	170	0.54	60	11.51	11.49

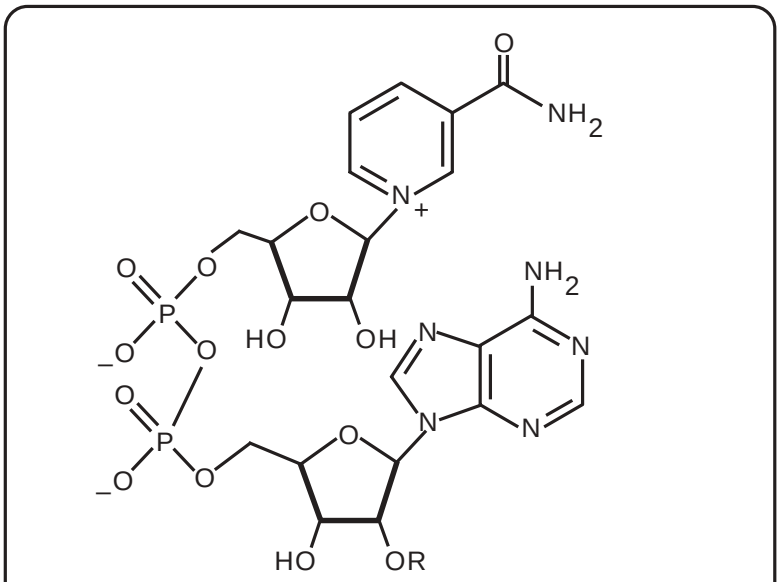
*TLC Solvent System : Ethylacetate : Hexane (2 : 8)



PART - III
STUDIES ON CYANOPYRIDINES

INTRODUCTION

Pyridine, which belongs to an important group of heterocyclic compounds has been extensively explored for its applications in the field of medicine, agriculture and industrial chemistry. Pyridine 3-carboxamide occurs as a component of the structure of the important coenzymes NADP + (I). One of the B_2 complex of vitamins, occurs in red blood carpuscles and participates in biochemical redox reaction.



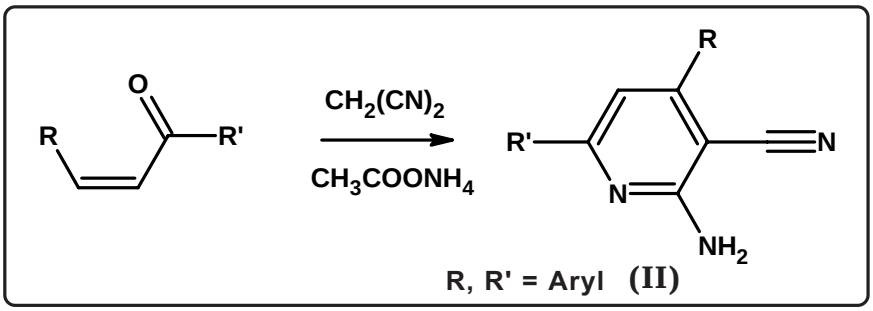
(I) R = $PO(OH)_2$

The availability of 3-cyanopyridine, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

SYNTHETIC ASPECT :

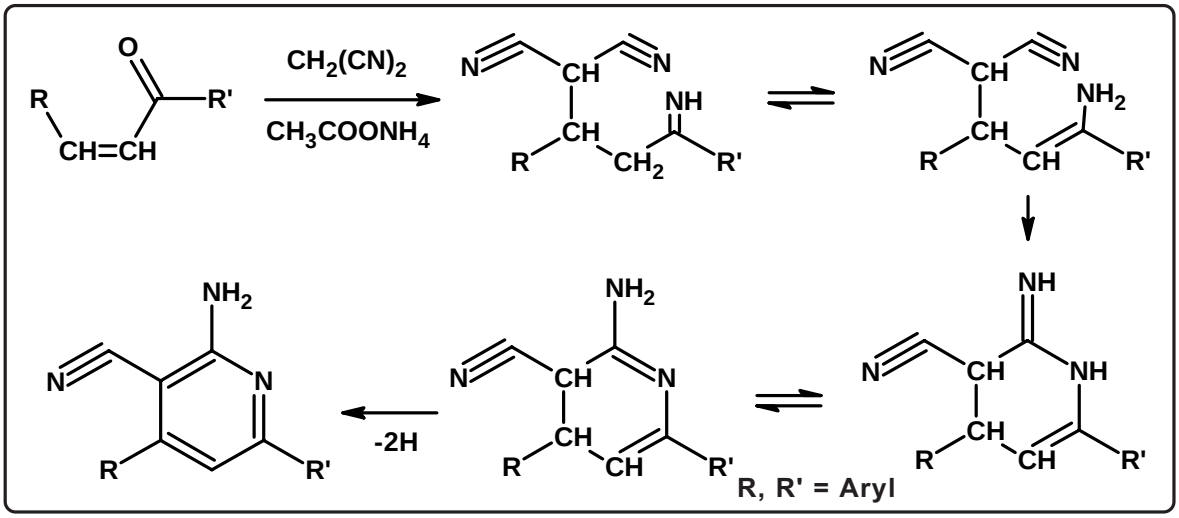
Different methods for preparation of 3-cyanopyridines are available in literature[146-152]. The well known method is

1. Sakurai and Midorikwa[153,154] have reported that malononitrile reacts with α,β-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines (II).



MECHANISM

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

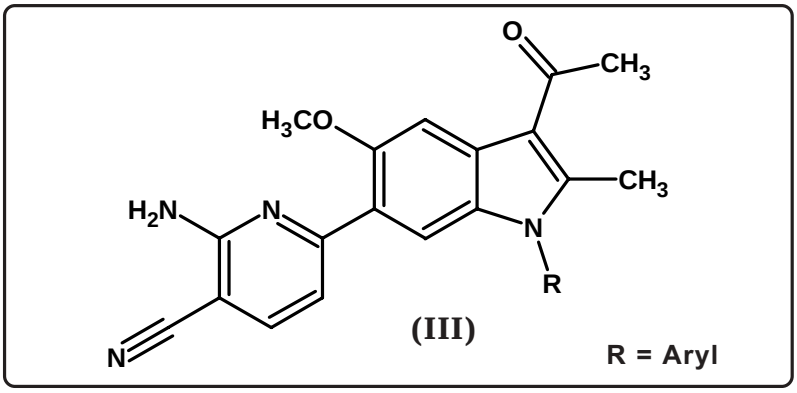


THERAPEUTIC IMPORTANCE

Cyanopyridines have attracted considerable attention as they appeared of interest to possess antibacterial, anticholestermic, antifungal, antihypertensive and antidiabetic activities. Kurt et. al.[155] have studied the analgesic activity of substituted 3-cyanopyridines. Hironori et al.[156] have prepared cyanopyridines and screened for their large conductance calcium acetivated potassium channel opener activity.

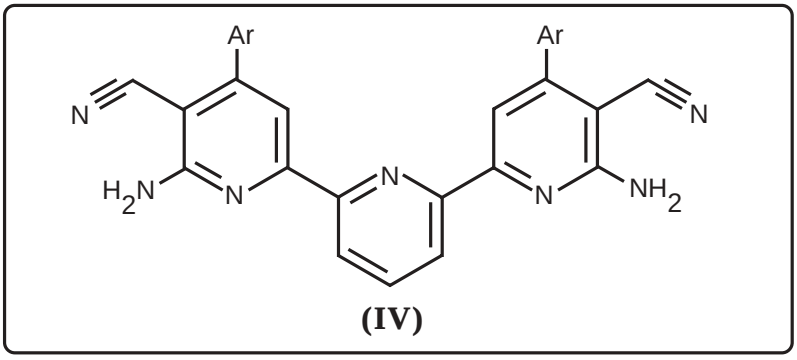
N. Latif and co-workers[157] have reported the antibacterial and antifungal activity of 2-amino-3-cyano-4,6-disubstituted pyridines. U. Teu and co-workers[158] have shown cyanopyridine as agrochemical fungicidies. M. Bernard and co-workers[159] reported the anticonvulsant properties of 3-cyanopyridines. Bhatt et. al.[160] have prepared 3-cyanopyridines as an immunosuppressive agent.

H. Yoshida et. al.[161] have studied the antihistamic and antiallergic activity of 3-cyanopyridine derivatives. Gadaginamath and co-workers[162] have synthesised various cyanopyridyl derivatives (III) and documented their variety of biological activities.



(III) R = Aryl

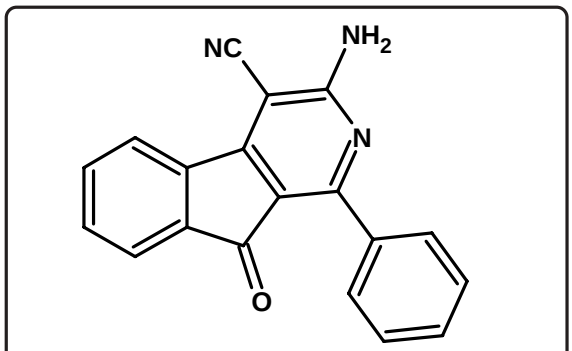
Manna Fedele and co-workers[163] have reported the antiinflammatory activity of 3-cyanopyridines. Abd El-Galil and co-workers[164] have prepared 3-cyanopyridines (IV) and studied their pharmacological activity.



(IV)

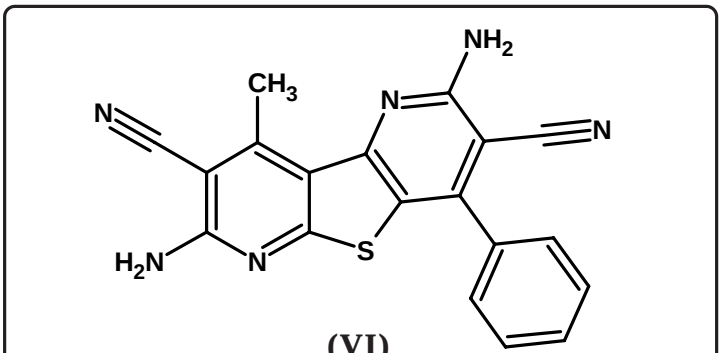
Hammana Abou and co-workers[165] have studied the anticancer and antiHIV activity of 3-cyanopyridines. Abdallah Navine et. al.[166] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity.

S. V. Roman et. al.[167] have investigated 2-amino-3-cyanopyridine derivatives and reported their biological activity. El-Taweel and co-workers[168] have described cyanopyridine derivatives (V) and showed their significant biological activity.



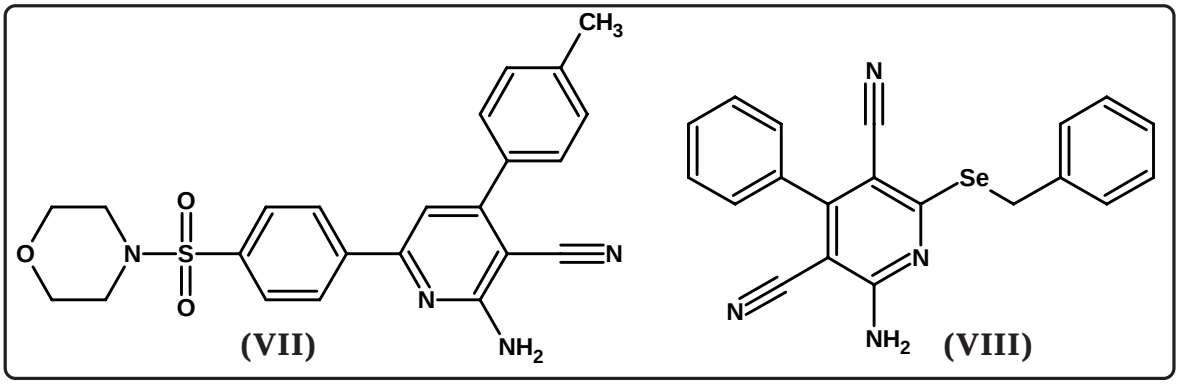
(V)

Abu and co-workers[169] have determined novel fused cyanopyridines (VI) for the treatment and preparation of systemic fungal infection.



(VI)

Hussan M. and co-workers[170] have prepared 3-cyanopyridines (VII) and reported their pharmacological activity. Pyachenko U. D. and co-workers[171] have shown some cyanopyridines (VIII) which are useful in treatment of retroviral disease.



(VII) **(VIII)**

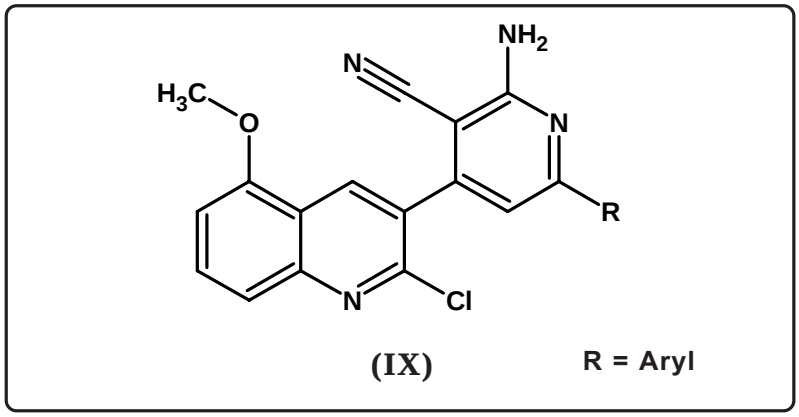
Streightoff[172] and seydal[173] have studied the bacteriostatic effect of some substituted 3-cyanopyridines. Francis and co-workers[174] have studied the effect of some substituted pyridines on the growth of the walker carcinosarcome-256 in tissue culture. Barton et al.[175] have reported fungicidal and insecticidal properties. W. Hoefling and co-workers[176] have documented 3-and 4-cyanopyridineds as tuberculosis arresting agents.

K. Kadlec and Hanslian[177] showed that 2-methyl-3-nitro-4-methoxyethyl-5-cyano-6-chloro pyridines caused occupational eczema in vitamin B_6 factory workers. Rigterink and Raymond[178] have suggested the pesticidal activity of 3-cyanopyridines. N-substituted 2-aminopyridines which possess anticonvulsant property have prepared by M. R. Pavia and co-workers.[179] 3-cyanopyridines reported by L. Castedo et al.[180] showed a minimum inhibitory concentration of 1.56 μg/ml against S. aureus. W. Von Benbenburg and co-workers[181] have synthesised 2-amino-3,6-disubstituted pyridines as antiepileptic agents.

CONTRIBUTION FROM OUR LABORATORY

Akhil Bhatt and co-workers[182] have synthesised cyanopyridines as potential antimicrobial agents. R. C. Khunt et al.[183] have screened cyanopyridine derivatives used as biologically active agents. Synthesis and antimicrobial activity of cyanopyridines showed by B. P. kansagara et al.[184] J. R. Patel and co-workers[185] have prepared cyanopyridines bearing 2-chloro-6-bromoquinoline nucleus as potential anticancer agents.

Synthesis and biological evaluation of cyanopyridines suggestd by Pankaj Patel and co-workers[186]. Rajeev Doshi and co-workers[187] have described some novel cyanopyridines as a new class of potential antitubercular agents. Cyanopyridines have screened by A. V. Dobariya et al.[188] and showed their significant biological activity. B. P. Kansagara and co-workers[189] have reported cyanopyridines having a quinoline nucleus and compounds found to be an antimicrobial (IX).



(IX) **R = Aryl**

Adriano Afouso et al.[190] have suggested that cyanopyridines are Fernesyl Protein transferase inhibitors. Hussain and co-workers[190] have prepared cyanopyridines as a antimicrobial agents. Wu Wenxue et al.[192] have reported cyanopyridines as histamine H_3 antagonists. Saudi Manal N. S. et al.[193] have found that cyanopyridines have fasciolicidal property.

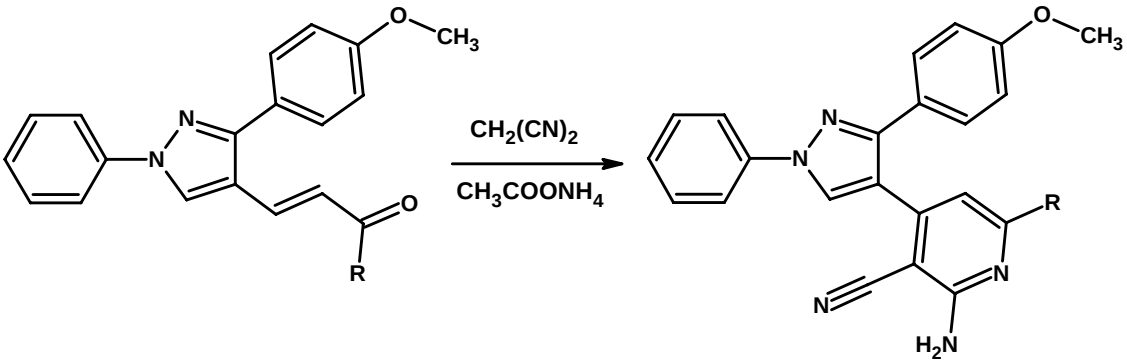
Thus, diverse biological activities have been encountered in compounds containing cyanopyridine ring system. To further assess the potential of such type of compounds, study of cyanopyridines have been carried out as under.

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

SECTION - I

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

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



Type (VI) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. wehen R = ρ-hydroxyphenyl, molecular weight = 459, m/z = 460 (m + 1).

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

EXPERIMENTAL

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

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

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

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

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

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

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

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

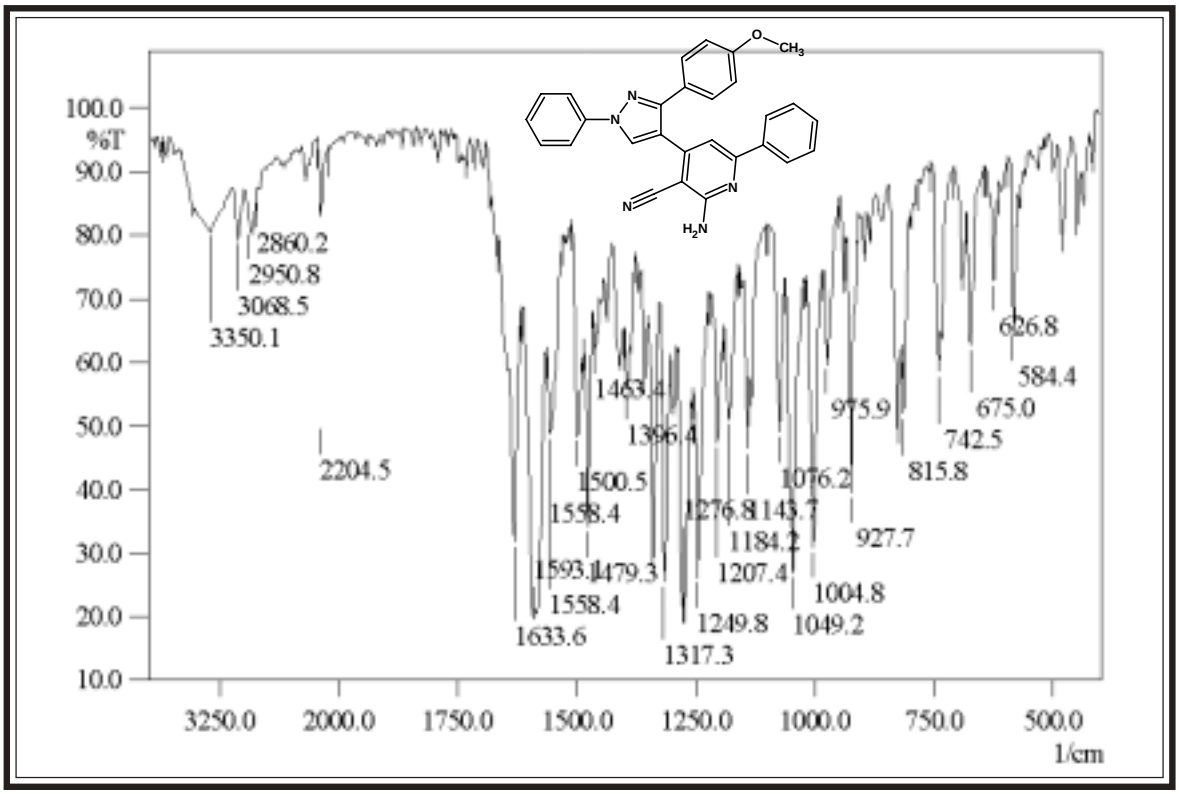
A mixture of 1-Phenyl-3-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-2-propene-1-one (3.80 g, 0.01 M), malanonitrile (0.66 g, 0.01 M) and ammonium acetate (6.61 g, 0.08 M) dissolved in absolute alcohol was refluxed for 10 hrs. The reaction product was poured into ice, crude product was isolated, crystallised from ethanol. Yield 65%, m.p. 178^{o}C. (Anal. Found : C, 75.78 H, 4.70; N, 15.73%; $C_{28}H_{21}N_5O$ Requires: C, 75.83; H, 4.77; N, 15.79%).

Similarly other cyanopyridines have been obtained. The physical data are recorded in Table No. 6

(E) Antimicrobial activity of 2-Amino-3-cyano-4-[1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl]-6-aryl-pyridines

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

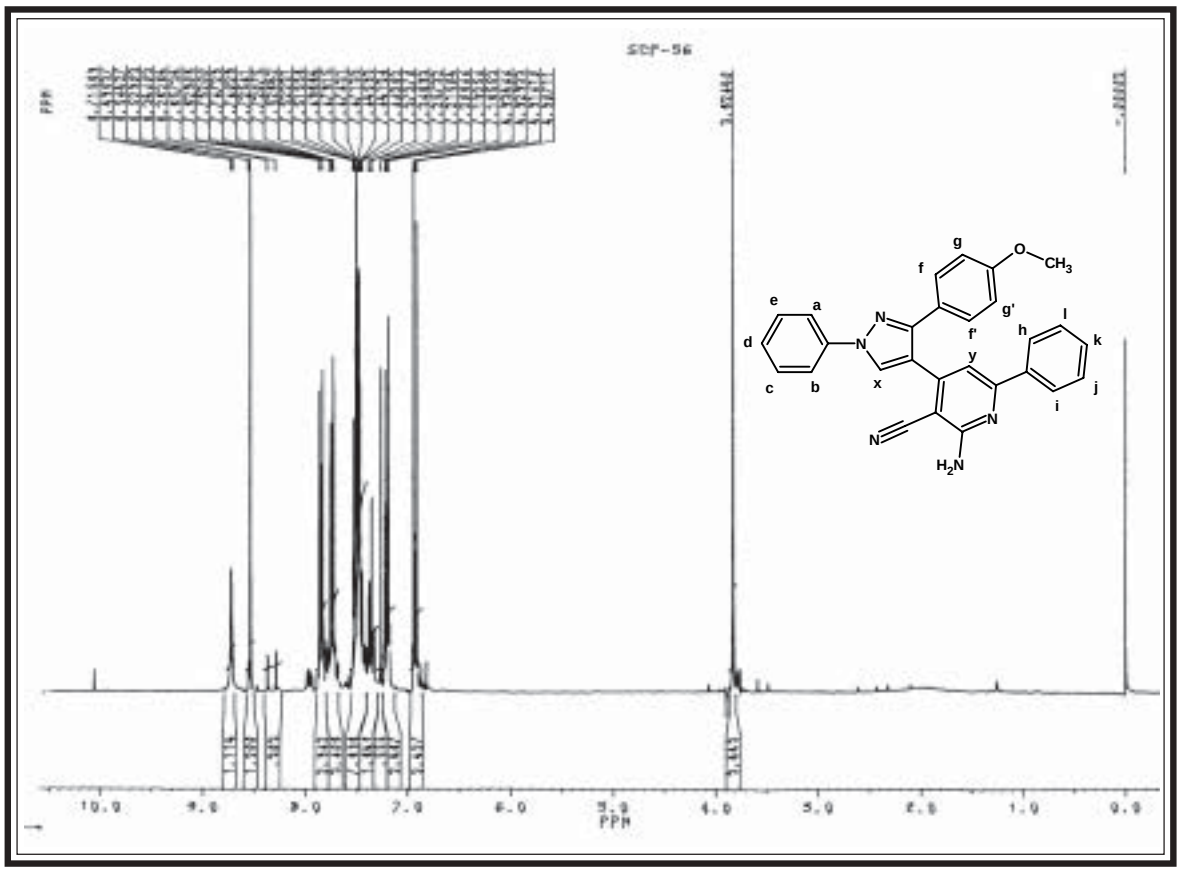
IR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-6-PHENYL PYRIDINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C–H str. (asym.)	2950.8	2975-2950	434
$-CH_3$	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1463.9	1470-1435	"
	C-H def. (sym.)	1342.4	1385-1350	"
Aromatic	C-H str.	3068.5	3080-3030	435
	C-H i.p. def.	1004.8	1070-1000	"
	C-H o.o.p. def.	815.8	835-810	"
Pyrazole	C=N str.	1593.1	1650-1600	434
moiety	C=C str.	1558.4	1585-1480	"
	C-N str.	1317.3	1350-1200	"
Ether	C-O-C (asym.)	1276.8	1275-1200	"
	C-O-C (sym.)	1049.2	1075-1020	"
Pyridine ring	C≡N str.	2204.5	2240-2120	"
	C=N str.	1633.6	1680-1600	"
	C=C str.	1076.2	1075-1020	"
	N-H str. ($-NH_2$)	3350.1	3350-3250	"

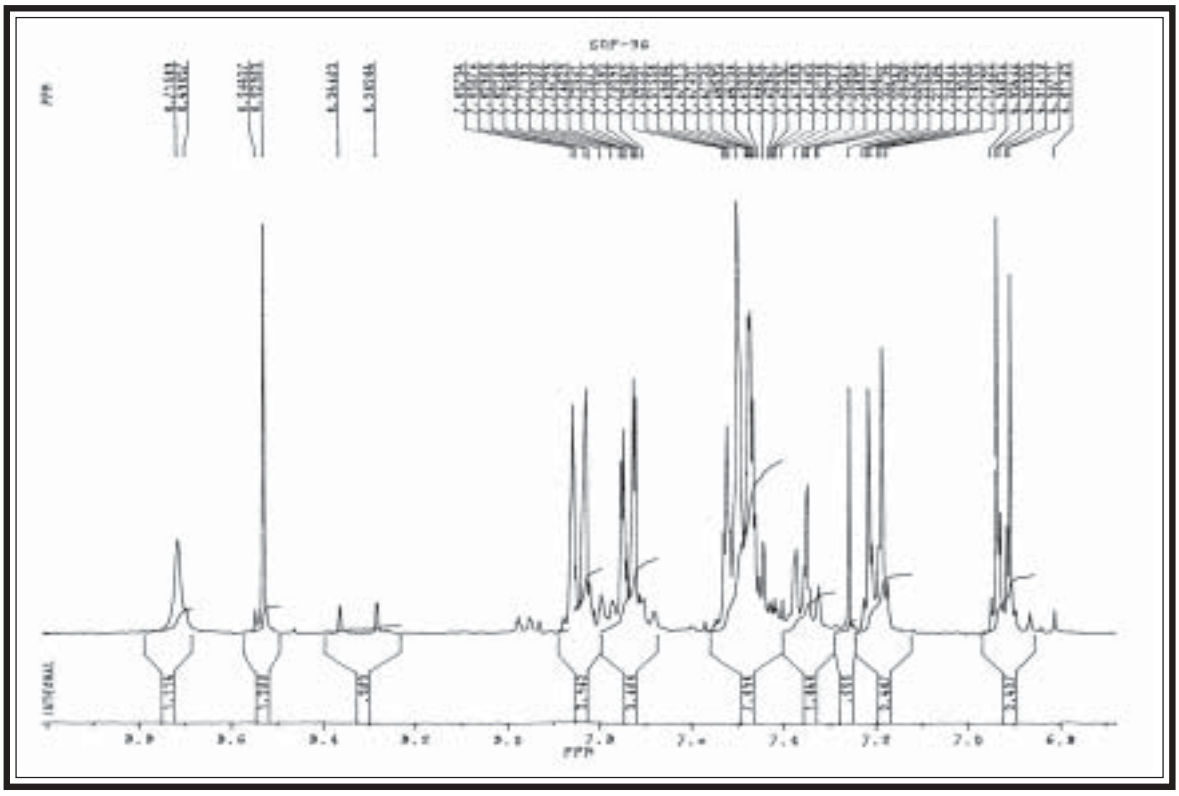
PMR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-6-PHENYL PYRIDINE



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	6.93	Jgf = 9.0	2H	doublet	Ar-Hgg'
3	7.17	Jfg = 9.0	2H	doublet	Ar-Hff'
4	7.34		1H	triplet	Ar-Hd
5	7.44-7.52		6H	multiplet	Ar-Hj-l,Ar-Hc, Ar-He, CHy
6	7.73		2H	doublet	Ar-Hh, Ar-Hi
7	7.83		2H	doublet	Ar-Ha, Ar-Hb
8	8.52		1H	singlet	CHx

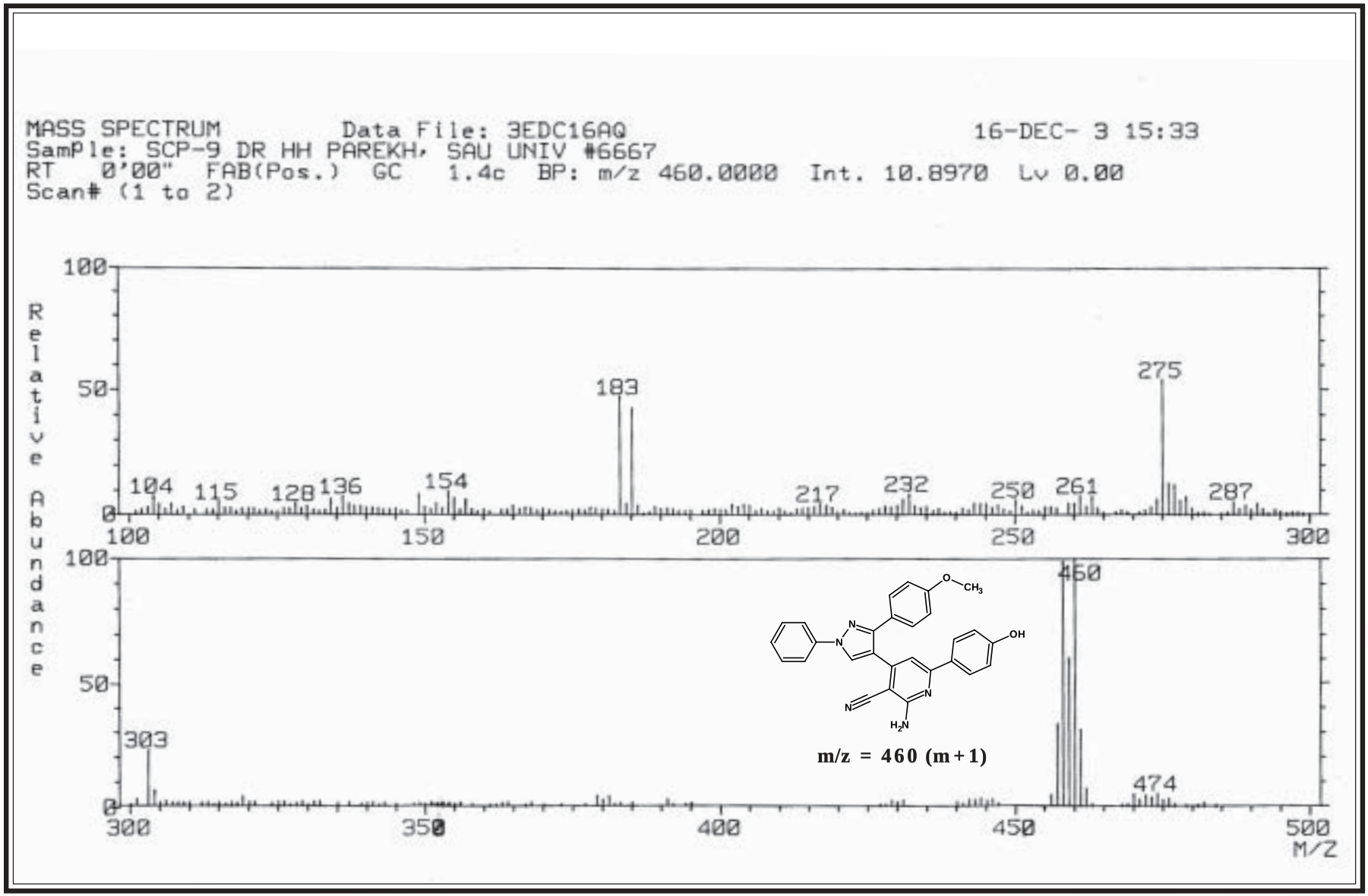
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 2-AMINO-3-CYANO-4-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-6-ARYL-PYRIDINES

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

Sr. No.	R	C≡N str. Cyanopyridines
6a	C_6H_5-	2204.5
6b	4-NH_2-C_6H_4-	2206
6c	3-NH_2-C_6H_4-	2212
6d	4-Br-C_6H_4-	2202.6
6e	4-Cl-C_6H_4-	2200.4
6g	4-F-C_6H_4-	2216
6h	4-OCH_3-C-$_6H_4$-	2204
6i	4-CH_3-C_6H_4-	2208
6j	4-NO_2-C_6H_4-	2206
6m	3-NO_2-C_6H_4-	2210
6n	4-OH-C_6H_4-	2202
6o	2-OH-C_6H_4-	2212


MASS SPECTRUM Data File: 3EDC16AQ 16-DEC- 3 15:33
SamPle: SCP-9 DR HH PAREKH, SAU UNIV #6667
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 460.0000 Int. 10.8970 Lv 0.00
Scan# (1 to 2)
Relative Abundance
100
50
0
104
115
128
136
154
183
217
232
250
261
275
287
100
150
200
250
300
303
460
474
350
400
450
500
M/Z
m/z = 460 (m+1)

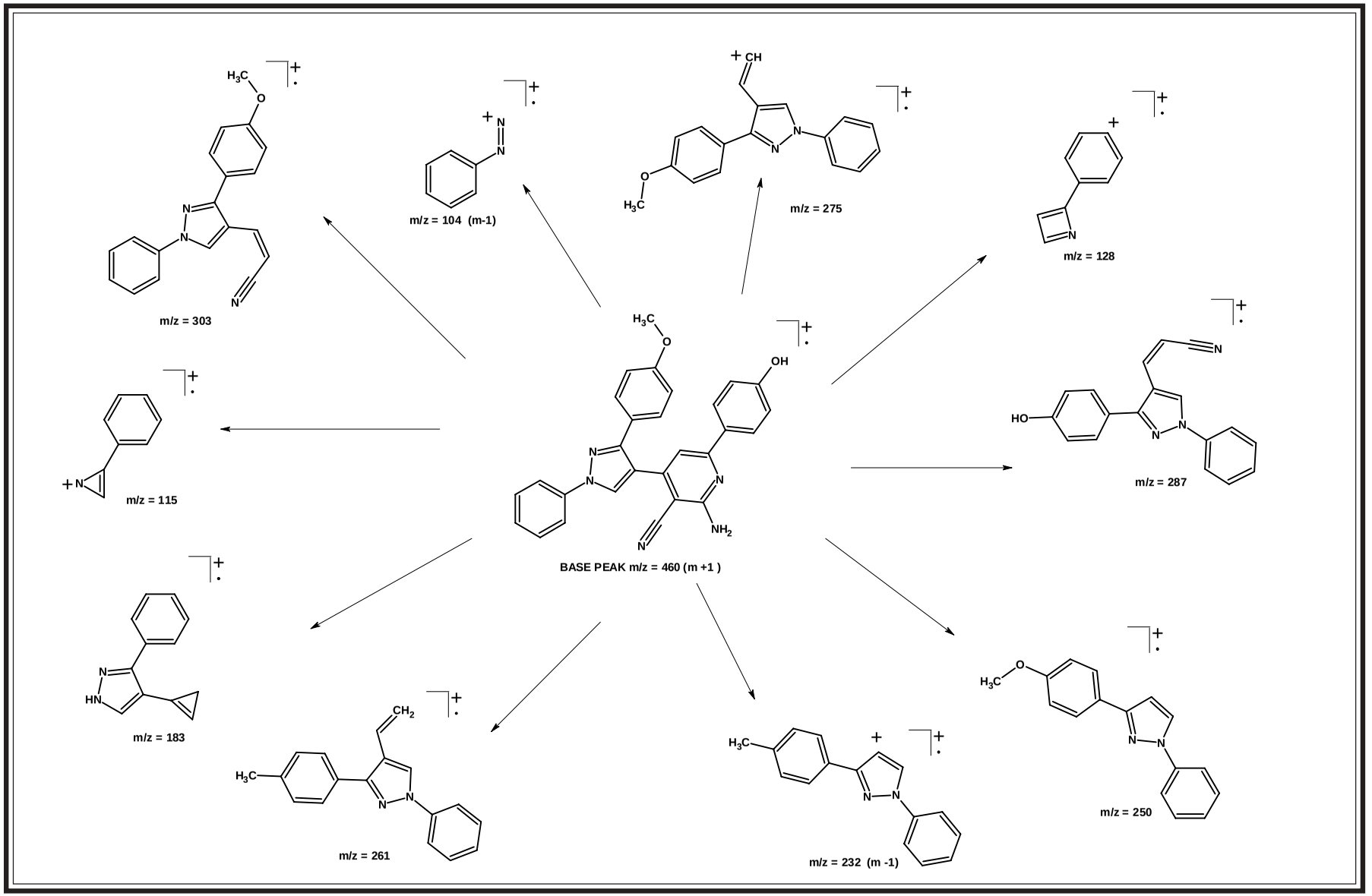
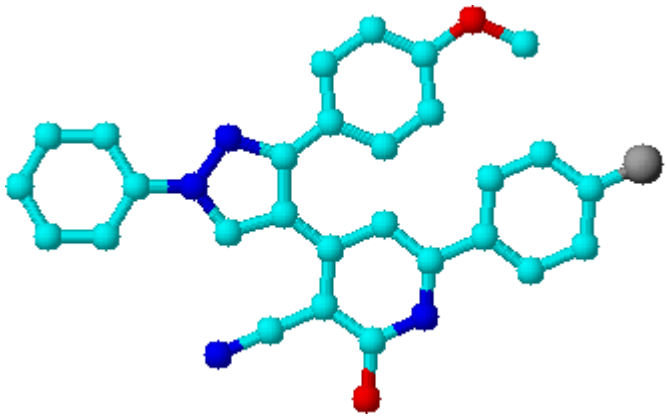

m/z = 303
m/z = 104 (m-1)
m/z = 275
m/z = 128
m/z = 115
m/z = 287
BASE PEAK m/z = 460 (m +1)
m/z = 183
m/z = 261
m/z = 232 (m -1)
m/z = 250

TABLE NO. 6 : PHYSICAL CONSTANTS OF 2-AMINO-3-CYANO-4-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-6-ARYL-PYRIDINES

Comp. 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-	$C_{28}H_{21}N_5O$	443	178	0.46	65	15.79	15.76
6b	4-NH_2-C_6H_4-	$C_{28}H_{22}N_6O$	458.5	184	0.54	62	18.33	18.28
6c	3-NH_2-C_6H_4-	$C_{28}H_{22}N_6O$	458.5	180	0.42	70	18.33	18.27
6d	4-Br-C_6H_4-	$C_{28}H_{20}N_5OBr$	522	181	0.49	69	13.41	13.38
6e	4-Cl-C_6H_4-	$C_{28}H_{20}N_5OCl$	478	220	0.64	74	14.65	14.60
6f	4-F-C_6H_4-	$C_{28}H_{20}N_5OF$	461	202	0.71	71	15.18	15.14
6g	4-OCH_3-C_6H_4-	$C_{29}H_{23}N_5O_2$	473.5	173	0.54	71	14.79	14.73
6h	4-CH_3-C_6H_4-	$C_{29}H_{23}N_5O$	457.5	188	0.59	68	15.31	15.29
6i	4-NO_2-C_6H_4-	$C_{28}H_{20}N_6O_3$	488	190	0.45	75	17.20	17.17
6j	3-NO_2-C_6H_4-	$C_{28}H_{20}N_6O_3$	488	185	0.76	64	17.20	17.15
6k	4-OH-C_6H_4-	$C_{28}H_{21}N_5O_2$	459	222	0.55	64	15.24	15.20
6l	2-OH-C_6H_4-	$C_{28}H_{21}N_5O_2$	459	195	0.41	66	15.24	15.18

*TLC Solvent System : Ethylacetate : Hexane (2 : 8) (6a-6l)

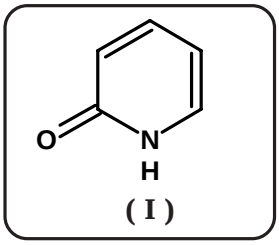
(3 : 7) (6e, 6g)



PART - IV
STUDIES ON CYANOPYRIDONES

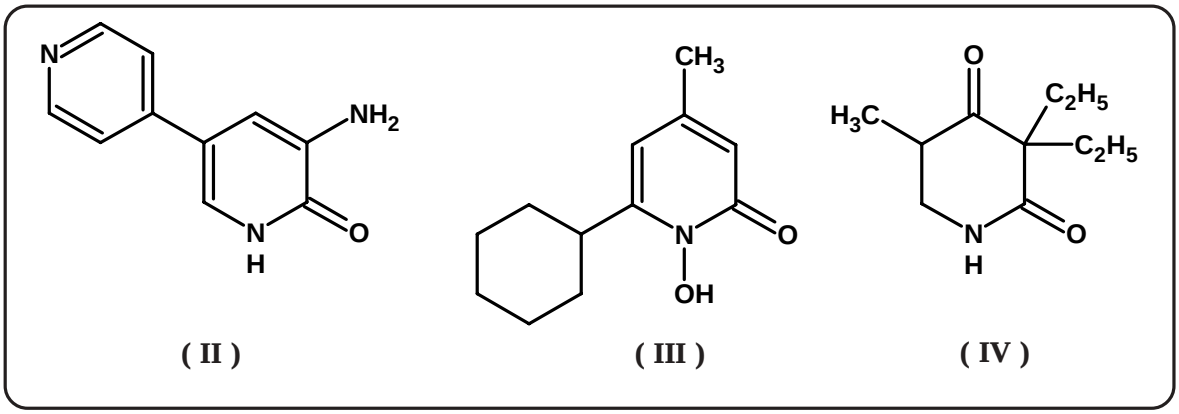
INTRODUCTION

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



(I)

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

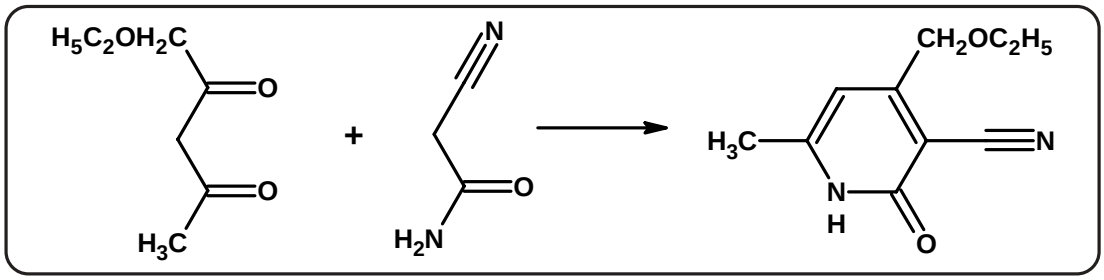


(II) **(III)** **(IV)**

SYNTHETIC ASPECTS

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

1. K. Folkers and S. A. Harris[194] have synthesised 3-cyano-2-pyridone by the condensation of cyanoacetamide with 1,3-diketone or 3-ketoester.



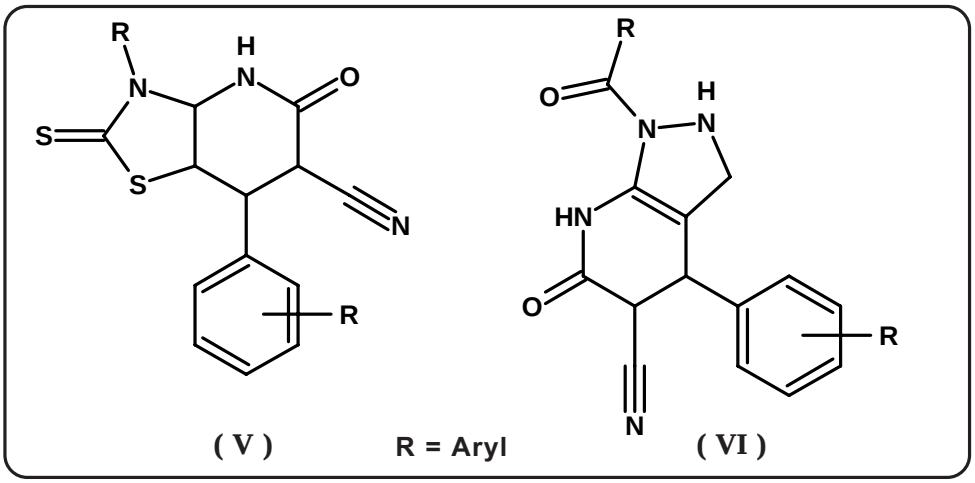
2. M. A. Sluyter and co-workers[195] have prepared fused 2-pyridones.
3. G. Simchen and G. Entemman[196] have synthesised 2-pyridone in which the ring nitrogen comes from a nitrile group in acyclic precursor.

THERAPEUTIC IMPORTANCE

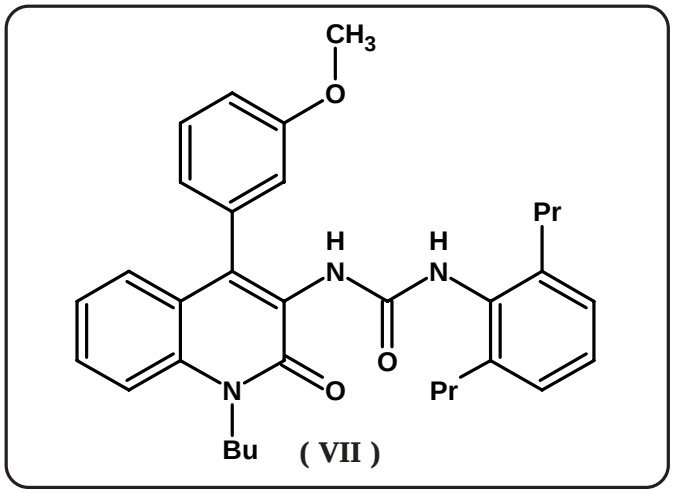
Pyridone derivatives have been found to possess variety of therapeutic activities as shown below.

1. Anticancer[197]
2. Herbicidal[198]
3. Pesticidal[199,200]
4. Antimicrobial[201]
5. Angitensin II antagonist[202-204]
6. Antiviral[205]
7. AntiHIV[206]

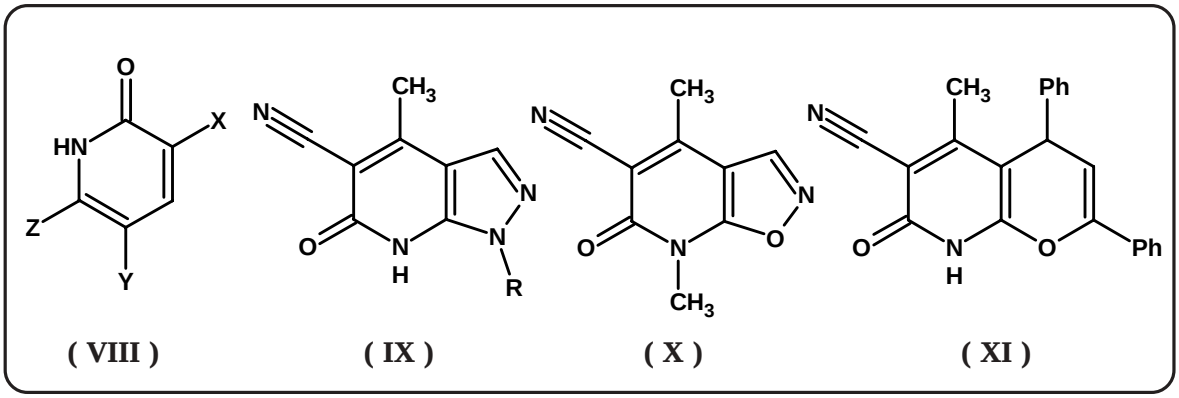
Peter and co-workers[207] have prepared pyridinylmethyl substituted pyridines and pyridones as angitensin II antagonist. H. Posnes[208] synthesised 2-pyridones and 2-pyrones as physiologically active compounds. Mukhtar Hussain Khan and co-workers[209,210] have prepared 2-pyridone derivatives (V) and (VI) which possess insecticidal and pesticidal activity.



Morishita Koji et. al.[211] have synthesised m-(2-oxo-1,2-dihydropyridyl) urea derivatives (VII) possessing cholesterol acyltransterase (ACAT) inhibitory activity and are useful for the treatment of hyperlipidemia and arteriosclerosis.

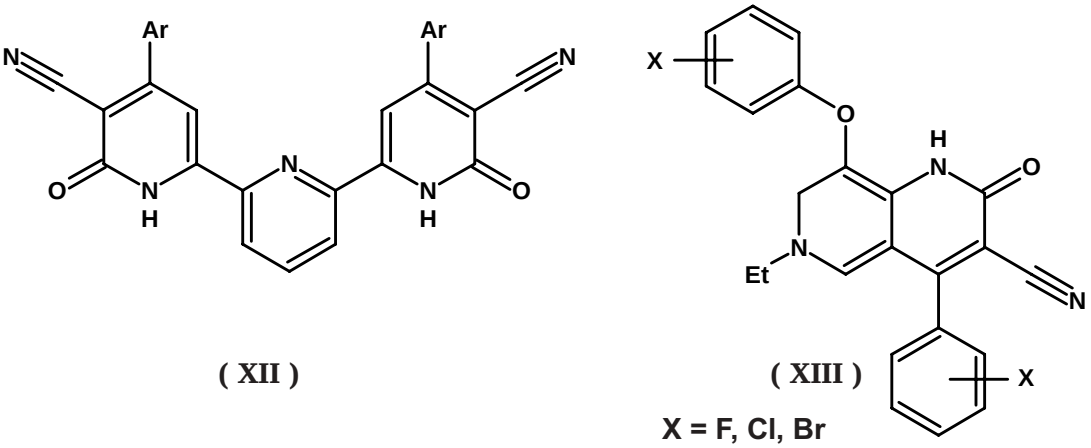


Collins et. al.[212] prepared heteroaryl pyridones as GABA α_2/α_3 ligands (VIII). Pednekar[213] synthesised fused 2-pyridone derivatives (IX), (X) and (XI) as useful heterocyclic moieties as they possess broad spectrum of biological activities such as antiviral, CNS depressant, bactericidel and ulcer inhibitor.

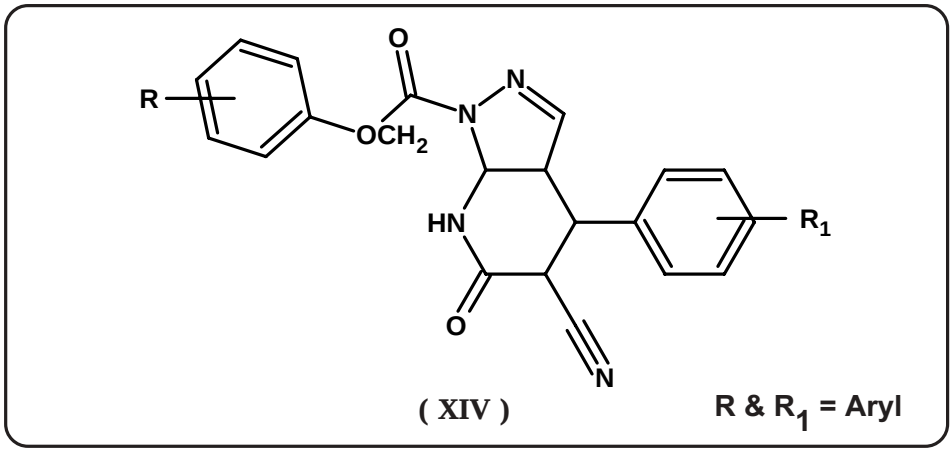


Moreover, several co-workers have prepared 2-pyridones as S_3 site of thrombin inhibitor[214], herbicidal[215], SH_2 domain inhibitor[216], antimicrobial[217], GABA-A receptor[218] and antiinflammatory[219].

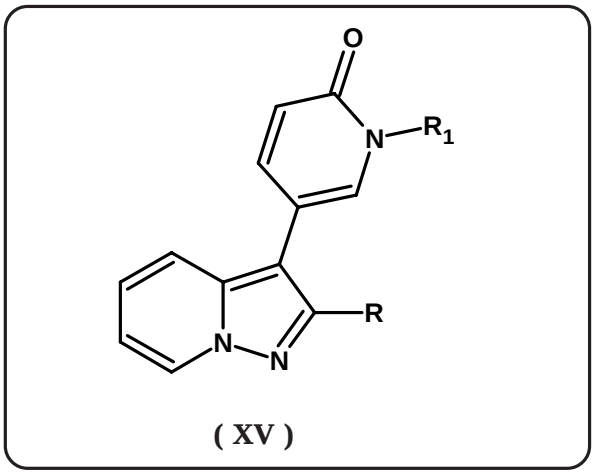
Upadhyay and co-workers[220] have synthesised cyanopyridone derivatives which showed antifungal and antileishmanial activities. E. Amer[221] prepared 3-cyano-2-pyridone derivatives (XII) displaying high antimicrobial activity. Abou El-Fotooh and co-workers[222] have demonstrated pyridones (XIII) as anticancer agent.



M. G. Nizamuddin et. al.[223] have prepared cyanopyridone derivatives (XIV) and documented their antifungal activity.



Tanaka Akira et. al.[224] have prepared pyrazolo pyridone derivatives (XV).



(XV)

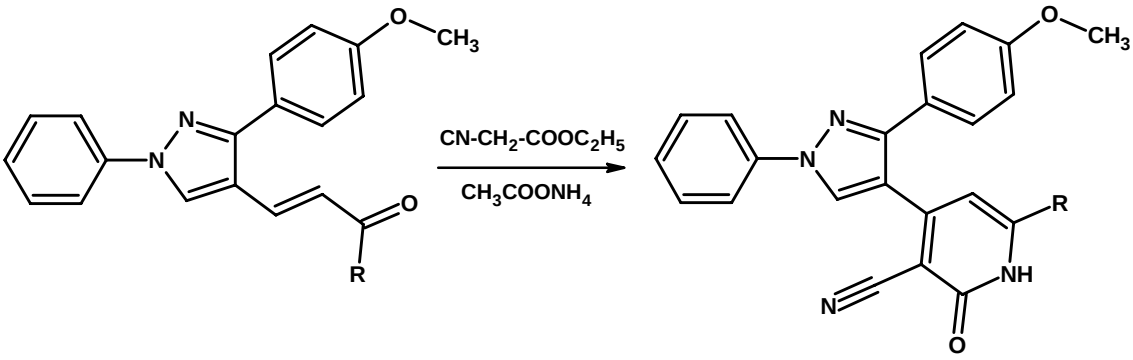
With an intension of preparing the compounds possessing better therapeutic activity, we have undertaken the preparation of cyanopyridones which have been described as under.

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

SECTION - I

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

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



Type (VII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry. In mass spectrometry the m/z value indicate the molecular weight, i.e. when R = ρ-bromophenyl molecular weight = 523, m/z = 523 (m).

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

EXPERIMENTAL

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

(A) Synthesis of N-Aminophenyl-α-methyl-ρ-anisyl azomethine

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

(B) Synthesis of 1,N-Phenyl-3-ρ-anisyl-4-formyl pyrazole

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

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

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

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

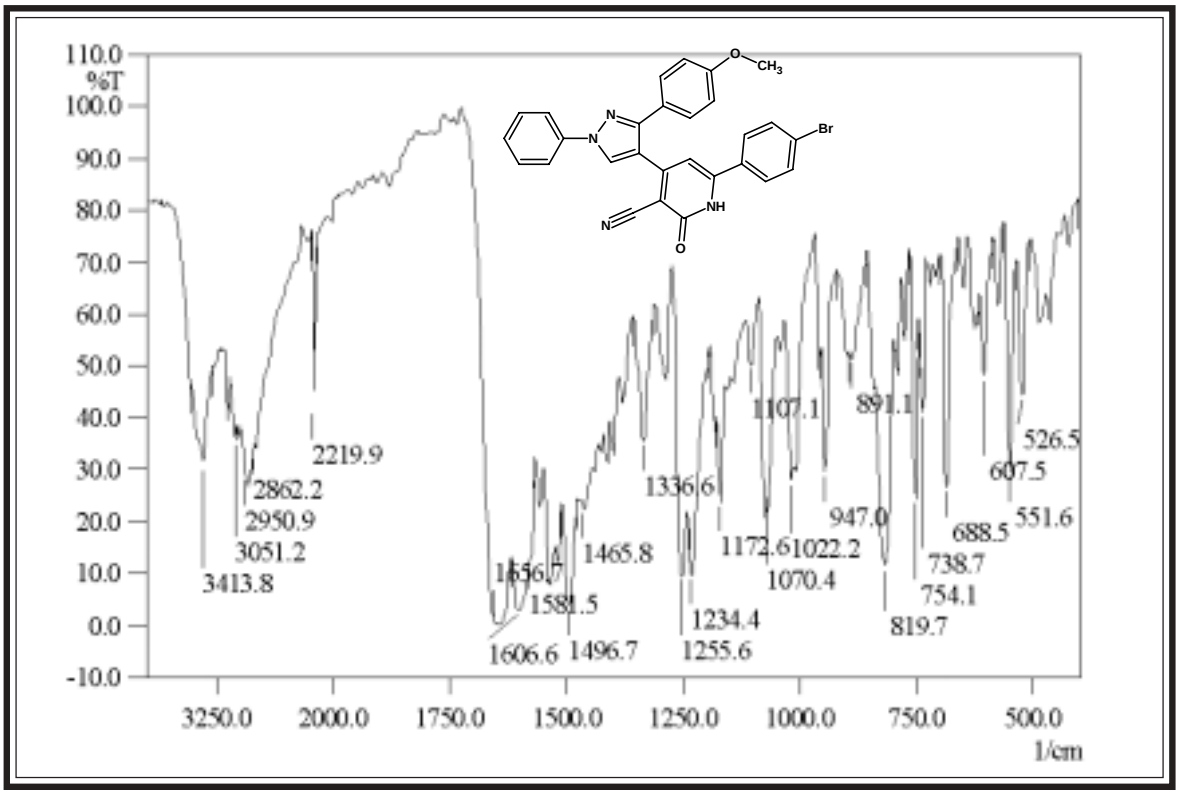
A mixture of 1-(ρ-bromophenyl)-3-(1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl)-2-propene-1-one (4.59 g, 0.01 M), ethylcyanoacetate (1.13 g, 0.01 M) and ammonium acetate (5.92 g, 0.08 M) in absolute alcohol was refluxed for 10 hrs. The reaction product was poured into ice, filtered and crystallised from ethanol. Yield 68%, m.p. 135°C. (Anal. Found : C, 64.21 H, 3.64; N, 10.65%; $C_{28}H_{19}N_4O_2Br$ Requires: C, 64.26; H, 3.66; N, 10.70%).

Similarly other substituted pyridones have been prepared. The physical data are recorded in Table No. 7

(E) Antimicrobial activity of 3-Cyano-4-[1',N-phenyl-3'-ρ-anisyl-pyrazol-4'-yl]-6-aryl-2-pyridones

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

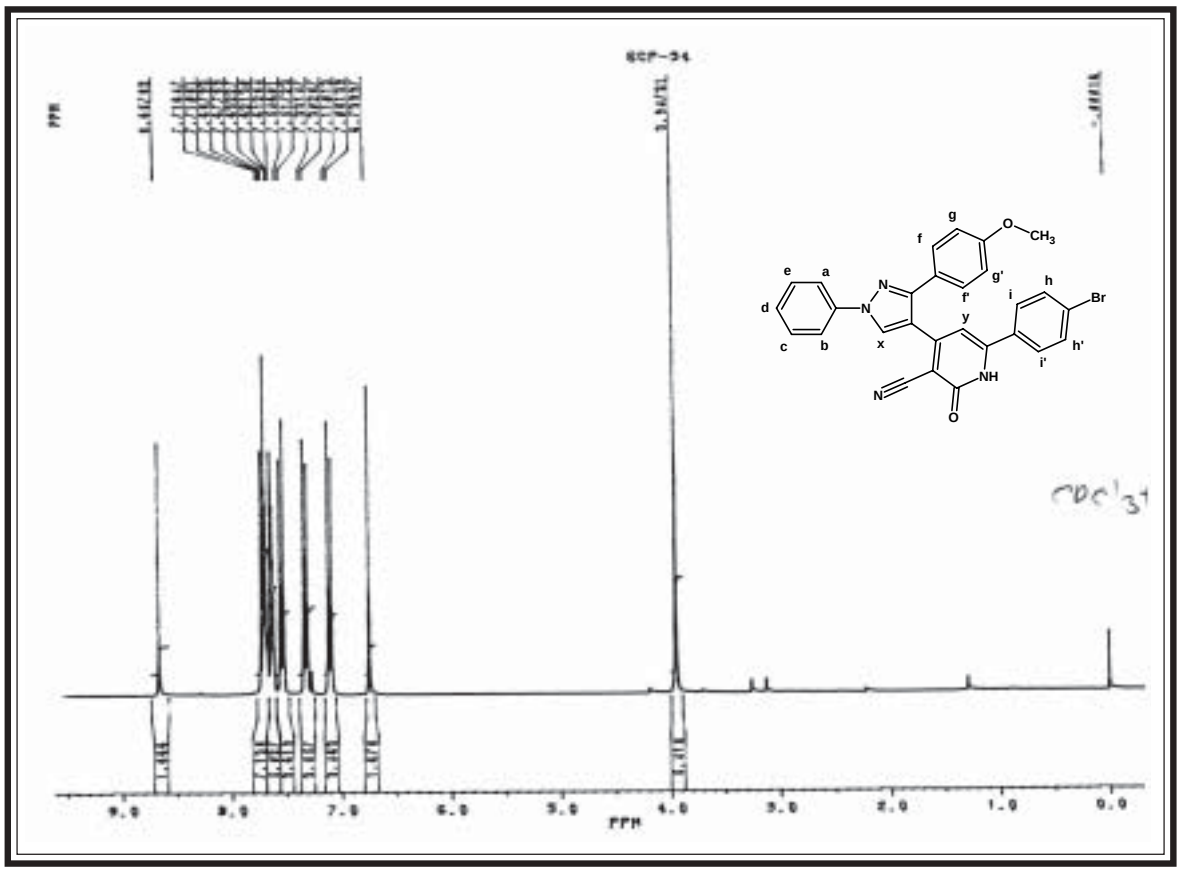
IR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-6-(ρ-BROMOPHENYL)-1,2-DIHYDRO-2-PYRIDONE



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.)	2950.9	2975-2950	434
-CH_3	C-H str. (sym.)	2862.2	2880-2860	"
	C-H def. (asym.)	1465.8	1470-1435	"
	C-H def. (sym.)	1380.9	1385-1350	"
Aromatic	C-H str.	3051.2	3080-3030	435
	C-H i.p. def.	1107.1	1125-1090	"
		1070.4	1070-1000	"
	C-H o.o.p. def.	819.7	835-810	"
Pyrazole	C=N str.	1606.6	1650-1600	434
moiety	C=C str.	1496.7	1585-1480	"
	C-N str.	1256.6	1350-1200	"
	C-Br str.	526.5	600-500	"
Ether	C-O-C (asym.)	1234.4	1275-1200	"
	C-O-C (sym.)	1022.2	1075-1020	"
Pyridone ring	C≡N str.	2219.9	2240-2120	"
	C=O str.	1656.7	1760-1655	"
	N-H str.	3413.8	3450-3250	"
	N-H def.	1581.5	1650-1580	"

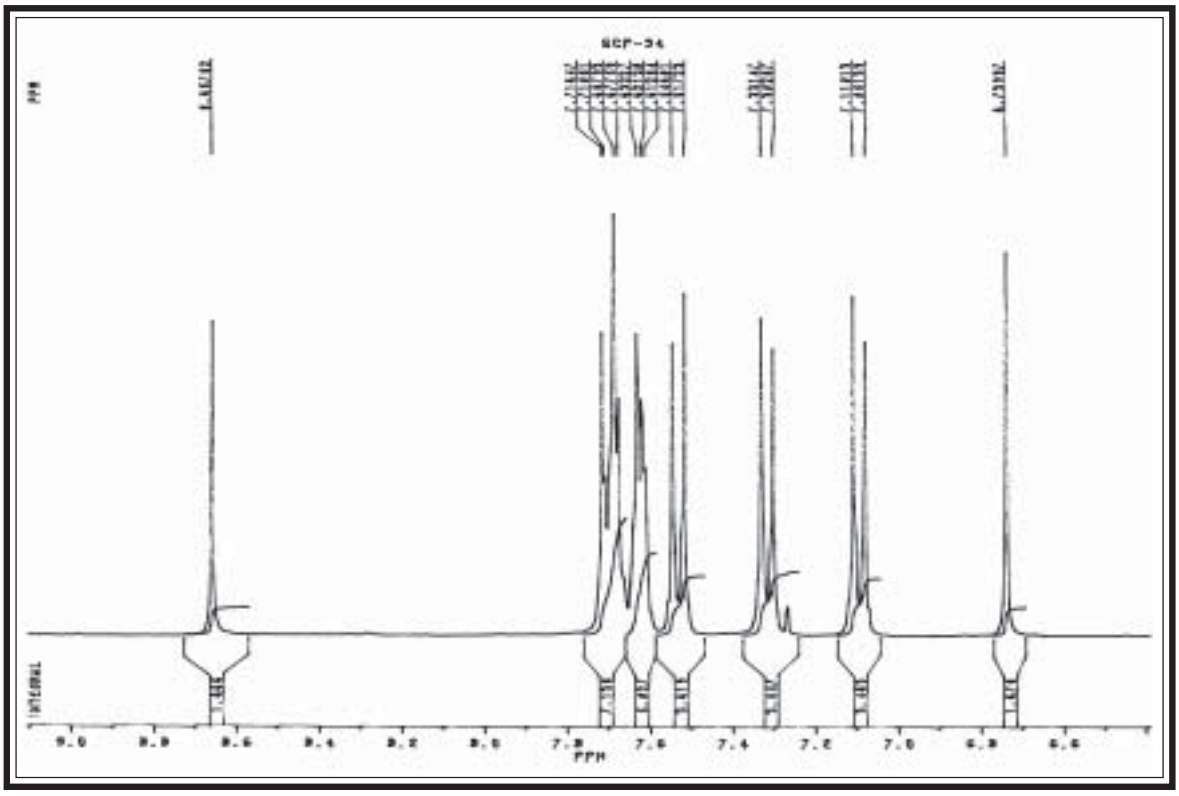
PMR SPECTRAL STUDY OF 3-CYANO-4-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-6-(ρ-BROMOPHENYL)-1,2-DIHYDRO-2-PYRIDONE



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	3.94		3H	singlet	Ar-OCH_3
2	6.73		1H	singlet	CHy
3	7.09	Jgf = 8.7	2H	doublet	Ar-Hgg'
4	7.31	Jhi = 8.7	2H	doublet	Ar-Hhh'
5	7.52	Jfg = 8.7	2H	doublet	Ar-Hff'
6	7.62		3H	doublet	Ar-Hc-e
7	7.69	Jih = 8.7	2H	doublet	Ar-Hii',Ar-Ha, Ar-Hb
7	8.65		1H	singlet	CHx

EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 3-CYANO-4-[1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

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

Sr. No.	R	C≡N str. Cyanopyridones	C=O str. Cyanopyridones
7a	C_6H_5-	2204	1658
7b	4-NH_2-C_6H_4-	2202	1654
7c	3-NH_2-C_6H_4-	2233	1649
7d	4-Br-C_6H_4-	2219.9	1656.7
7e	4-Cl-C_6H_4-	2218	1652
7g	4-F-C_6H_4-	2222	1660
7h	4-OCH_3-C_6H_4-	2210	1658
7i	4-CH_3-C_6H_4-	2216	1649
7j	4-NO_2-C_6H_4-	2212	1650
7m	3-NO_2-C_6H_4-	2218	1652
7n	4-OH-C_6H_4-	2214	1656
7o	2-OH-C_6H_4-	2212	1651

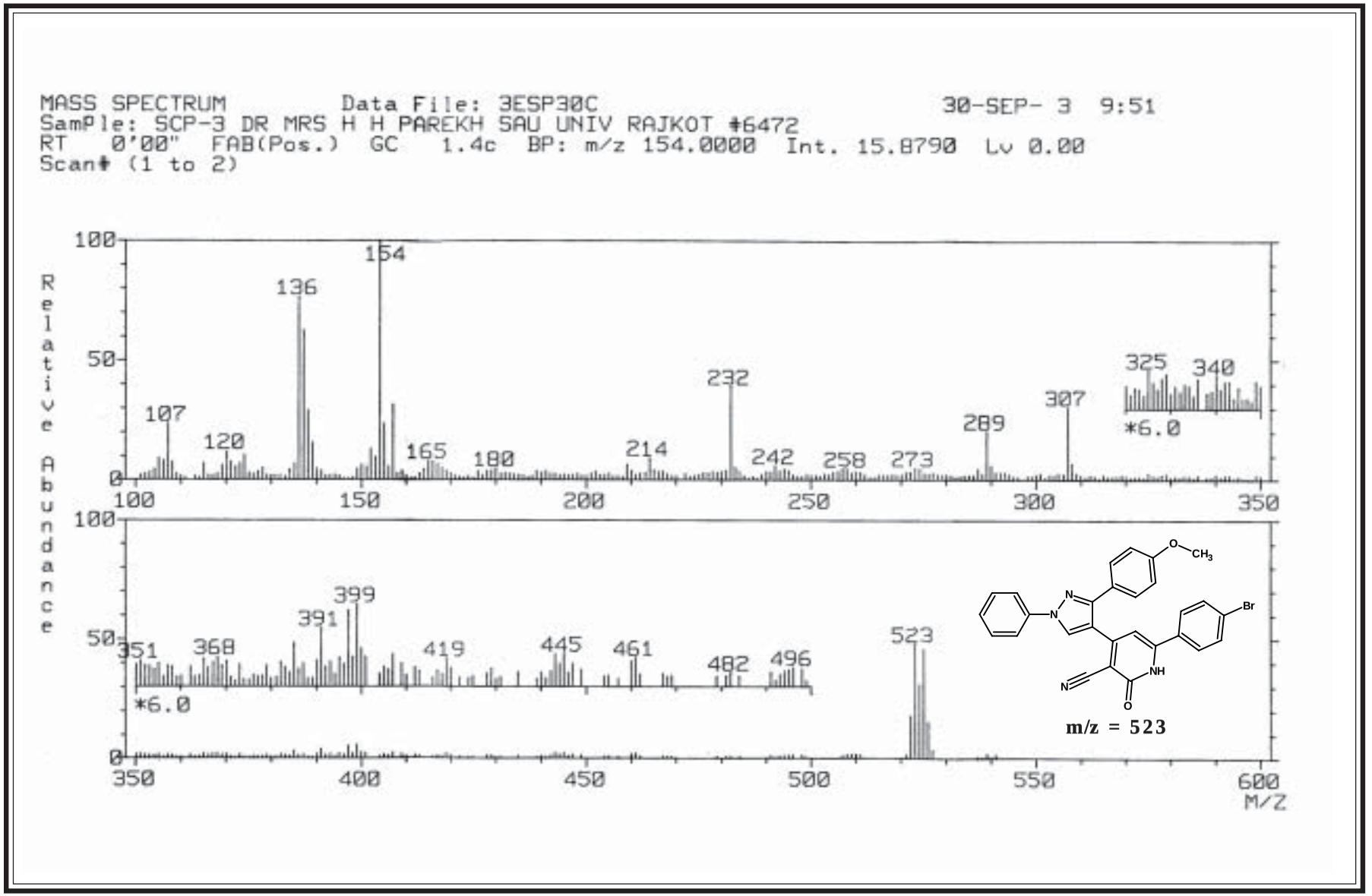
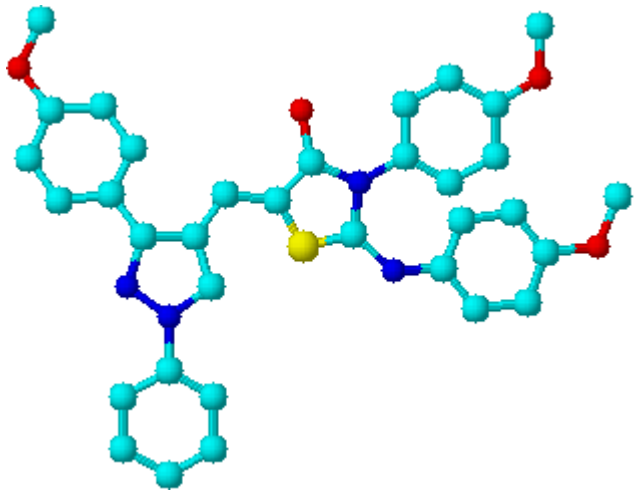

MASS SPECTRUM Data File: 3ESP30C 30-SEP- 3 9:51
Sample: SCP-3 DR MRS H H PAREKH SAU UNIV RAJKOT #6472
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 15.8790 Lv 0.00
Scan# (1 to 2)
Relative Abundance
M/Z
m/z = 523

TABLE NO. 7 : PHYSICAL CONSTANTS OF 3-CYANO-4-(1',N-PHENYL-3'-ρ-ANISYL-PYRAZOL-4'-YL)-6-ARYL-1,2,DIHYDRO-2-PYRIDONES

Comp. 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-	$C_{28}H_{20}N_4O_2$	444	158	0.51	60	12.60	12.57
7b	4-NH_2-C_6H_4-	$C_{28}H_{21}N_4O_2$	459	150	0.39	61	15.24	15.20
7c	3-NH_2-C_6H_4-	$C_{28}H_{21}N_4O_2$	459	152	0.46	68	15.24	15.21
7d	4-Br-C_6H_4-	$C_{28}H_{19}N_4O_2Br$	523	135	0.62	68	10.70	10.65
7e	4-Cl-C_6H_4-	$C_{28}H_{19}N_4O_2Cl$	479	165	0.71	64	11.70	11.67
7f	4-F-C_6H_4-	$C_{28}H_{19}N_4O_2F$	462	206	0.45	72	12.11	12.07
7g	4-OCH_3-C_6H_4-	$C_{29}H_{22}N_4O_3$	474	159	0.55	68	11.81	11.77
7h	4-CH_3-C_6H_4-	$C_{29}H_{22}N_4O_2$	458	161	0.59	65	12.22	12.20
7i	4-NO_2-C_6H_4-	$C_{28}H_{19}N_5O_4$	484	181	0.47	62	14.31	14.28
7j	3-NO_2-C_6H_4-	$C_{28}H_{19}N_5O_4$	484	155	0.74	71	14.31	14.29
7k	4-OH-C_6H_4-	$C_{28}H_{20}N_4O_3$	460	168	0.65	64	12.17	12.13
7l	2-OH-C_6H_4-	$C_{28}H_{20}N_4O_3$	460	170	0.50	74	12.17	12.11

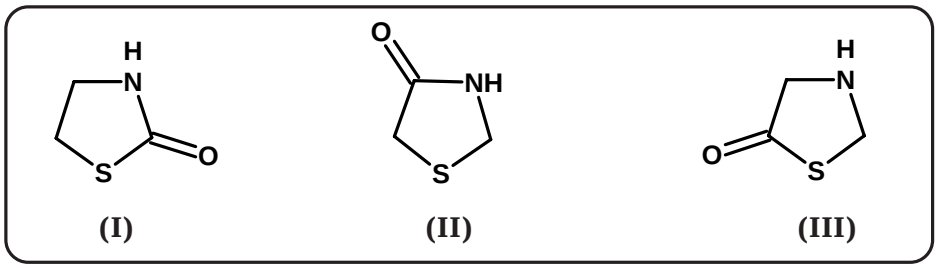
*TLC Solvent System : Ethylacetate : Hexane (2 : 8)



PART - V
STUDIES ON THIAZOLIDINONES

INTRODUCTION

*T*hiazolidinones, which belong to an important group of heterocyclic compounds have been extensively explored for their applications in the field of medicine. Thiazolidinones, with a carbonyl group at position 2(I), 4(II) or 5(III) have been subject of extensive study in recently.



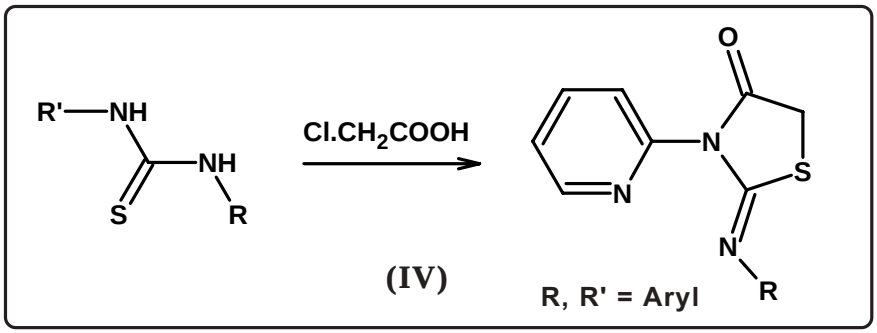
(I) **(II)** **(III)**

Substitutent in the 2,3 and 5 position may be varied, but the greatest difference in structure and properties is exerted by the groups attached to carbon atom at the 2-position and to nitrogen atom at the 3-position. The cyclic structure was assigned after recognisation of mercaptoacetic acid as a primary product of hydrolysis of 3-phenyl-2-phenylamino-4-thiazolidinones[225].

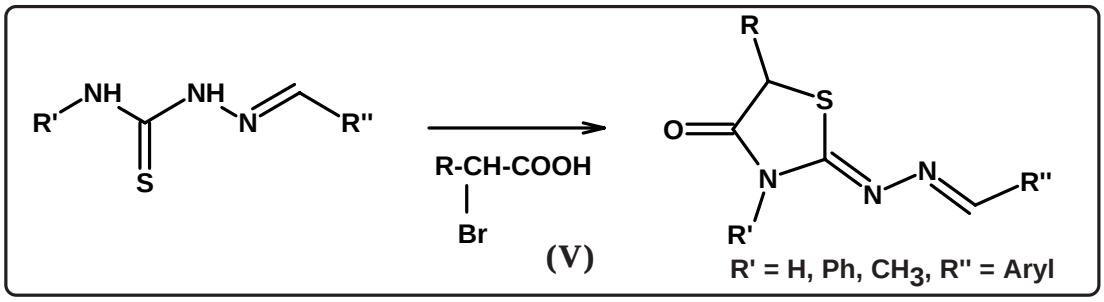
SYNTHETIC ASPECTS

Several methods for the preparation of 4-thiazolidinones are narrated in literature[226-234].

1. R. Nath and K. Shankar[235] have prepared 4-thiazolidinone by cyclisation of N-aryl-N'-(2'-pyridyl) thiocarbamide with chloroacetic acid.



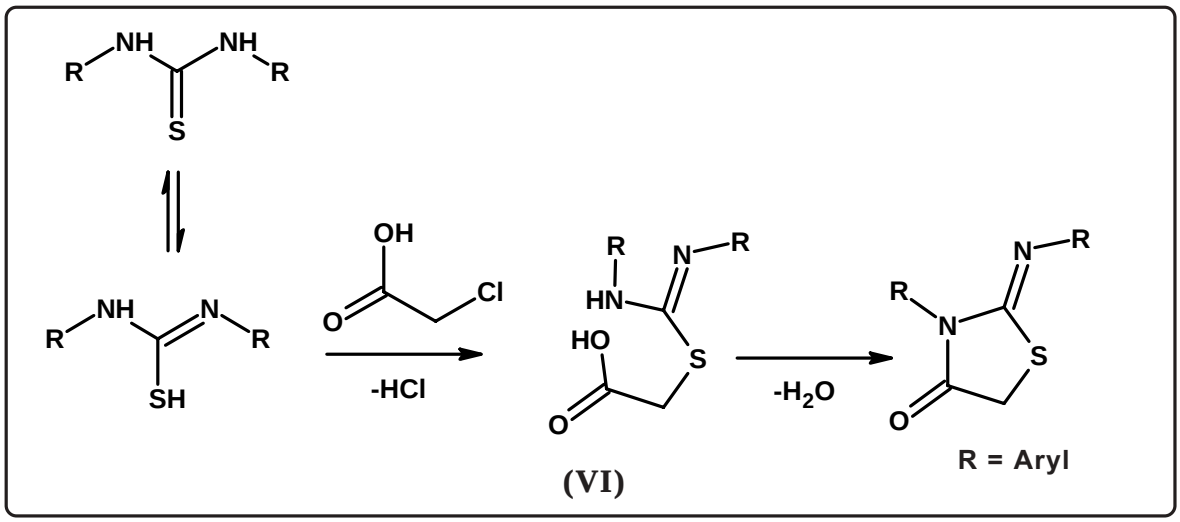
2. I. D. Shah and J. P. Trivedi[236] synthesised thiazolidinones from 4-arylthiosemicarbazones by condensed them with chloroacetic acid, α-bromopropionic acid and α-bromophenyl acetic acids.



3. M. Saeda et. al.[237] synthesised some new thiazolidinones.

MECHANISM

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

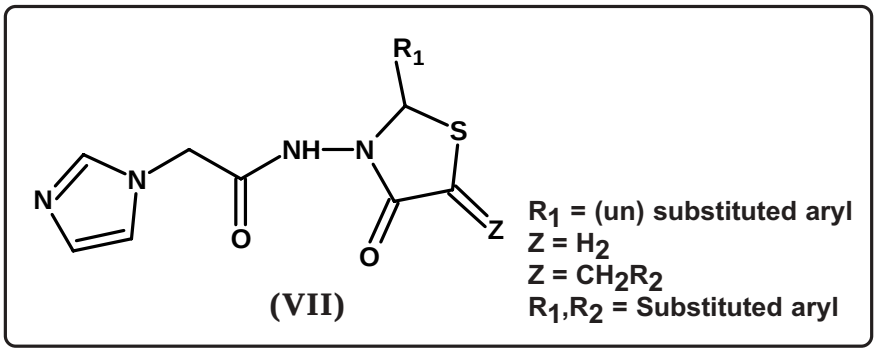


THERAPEUTIC IMPORTANCE

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

1. Anthelmintics[238,239]
2. Cardiovascular[240]
3. Mosquito repellant[241]
4. Antiviral[242]
5. Antitumor[243]
6. Local anaesthetic[244]
7. Antimicrobial[245]
8. Antitubercular[246,247]
9. Anti HIV and anticancer[248]
10. Insecticidal[249]
11. Herbicidal[250]

Hassan et. al.[251] have prepared 2-imino-4-thiazolidinones which have been found to possess antimicrobial activity. K. Mogilaiah and co-workers[252,253] isolated some 4-thiazolidinone derivatives and tested their antibacterial activity. G. S. Gadaginamath et. al.[254] also prepared thiazolidinone derivatives as antimicrobial agent. R. S. Lodhi and co-workers[255] have synthesised and studied antimicrobial, antiinflammatory and analgesic property of 4-thiazolidinone and aryledene derivatives (VII).



(VII)

Pawar and co-workers[256] reported synthesis and *in vitro* antibacterial activity of some 4-thiazolidinone derivatives.

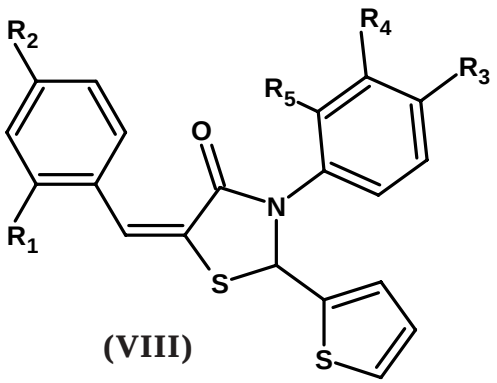
CONTRIBUTION FROM OUR LABORATORY

Parikh et. al. have synthesised variety of 4-thiazolidinone derivatives bearing S-triazine[257], benzoylamino acetamido[258], sulphonamido benzylamino[259], phthalazine-1-yl-amino[260], aryl substituted hydroxy and β,β-dichloro ethylamino phenyl moieties of 4-thiazolidinone ring system and have reported as potent antimicrobial agents. H. H. Parekh and co-workers have synthesised 4-thiazolidinones bearing dapson[261], s-triazine[262], acridine-9-yl[263], thymoloxyacetamido[264], 6-hydroxy pyrimidine[265], 9-thiazolidinone ring system having antimicrobial activity.

Moreover, A. J. Baxi et. al.[266] have synthesised some new 4-thiazolidinones which shows antiHIV, antitumor and antihypertensive activities. H. H. Parekh and co-workers[267,268] have synthesised new bis 4-thiazolidinones and studied their biological activity. Recently, A. R. Parikh and co-workers[269] have assessed thiazolidinone derivatives bearing 7-methoxyquinoline nucleus for antimicrobial activity.

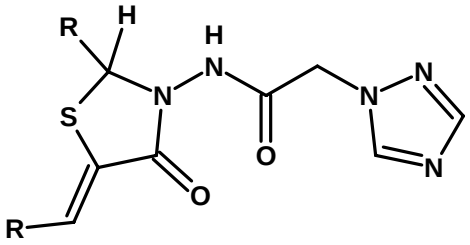
G. Bhawna et. al.[270] have synthesised thiazolidinone derivatives and compared their antiinflammation potency, ulcerogenic liability, cardiovascular and CNS effect. In other study, some thiazolidinone derivatives have been found to be promising antibacterial agent[271,272].

Siddique, Mohammad et. al.[273] have prepared substituted thiazolidinones and reported their antibacterial, antifungal, antithyroid and amoebicidal properties (VIII). S. K. Srivastava and co-workers[274] have suggested new thiazolidinones (IX) and reported their diuretic, analgesic and antimicrobial activities.



(VIII)

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



(IX)

R = Aryl

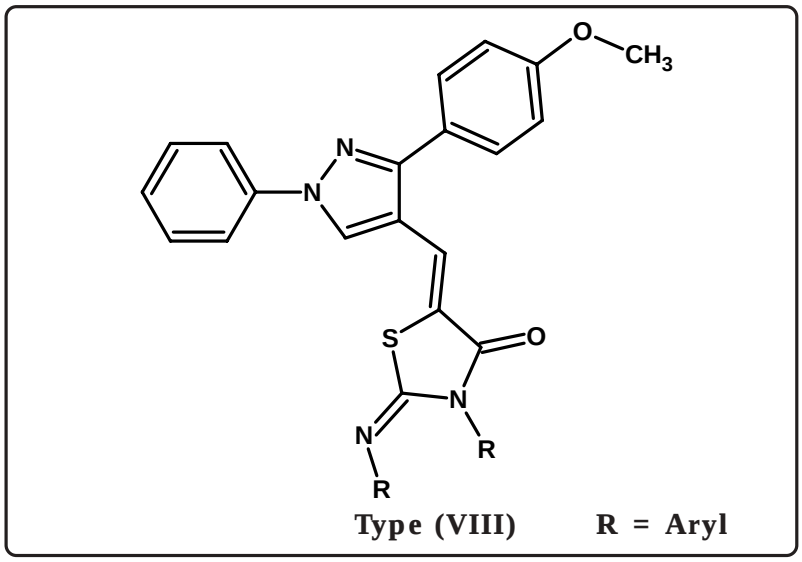
Considerable evidence has been accumulated to demonstrate the wide applications of thiazolidinone derivatives. In view of these findings,it appeared of interest to synthesise newer thiazolidinone derivatives with better potency.

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

SECTION - I

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

Recently, much interest has been focused on the synthesis and biodynamic activities of arylidene and it is a good synthon for constructing various heterocyclic rings. With a view of obtaining compounds having better therapeutic activities, we have synthesised 2-arylimino-3,N-aryl-5-[1',N-phenyl-3'-ρ-anisyl-4'-pyrazolylmethino]-4-thiazolidinones by the condensation of 1,N-phenyl-3-ρ-anisyl-4-formyl-pyrazole with various thiazolidinone compounds.

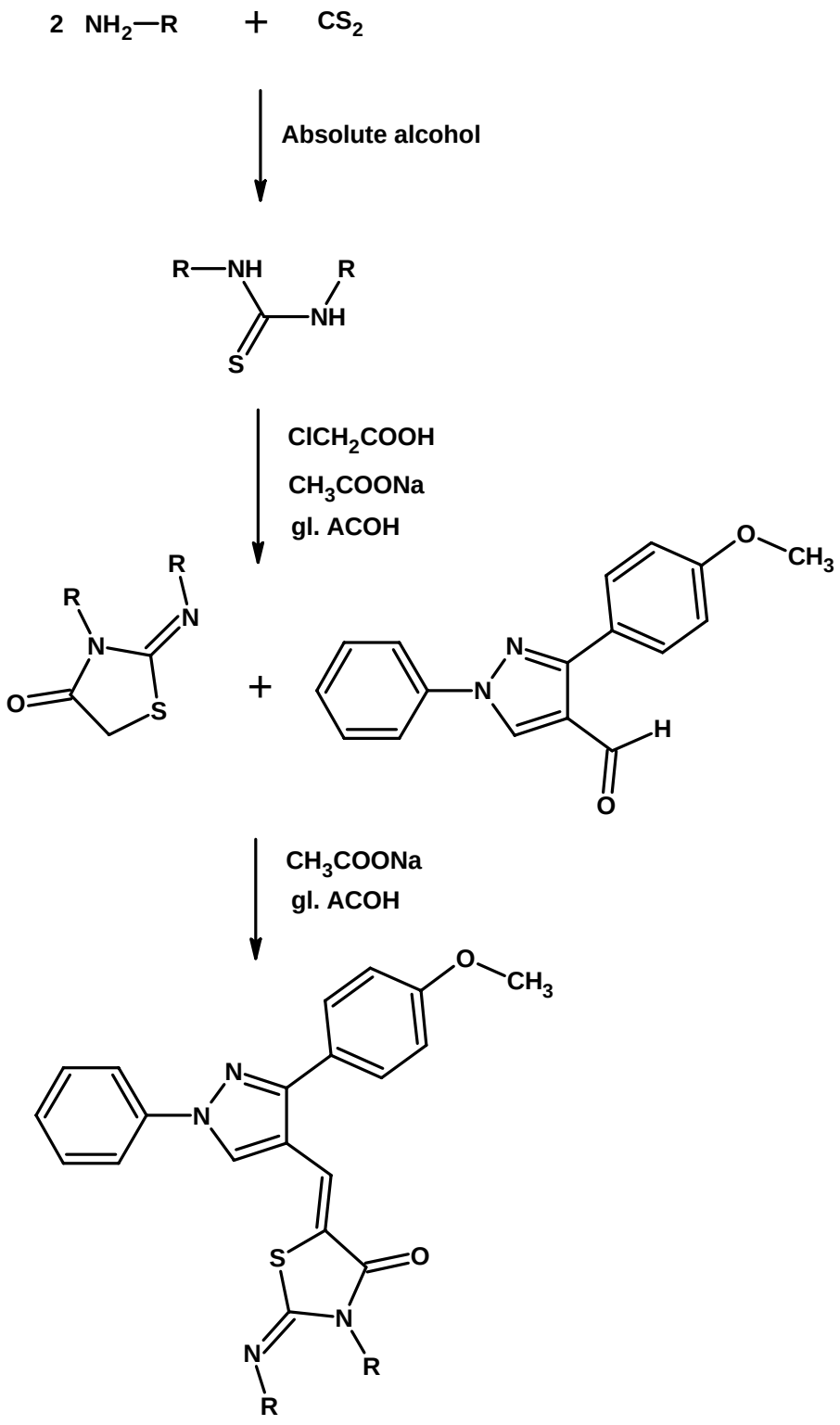


Type (VIII) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. when R = ρ-anisyl, molecular weight = 588, m/z = 589 (m + 1).

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

REACTION SCHEME



Type (VIII) **R = Aryl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-4'-PYRAZOLYLMETHINO]-4-THIAZOLIDINONES

(A) Preparation of N^1,N^3-Bisaryl thiourea[275]

In a round bottom flask, a mixture of arylamine (0.2 M), carbon disulphide (7 ml, 0.1 M) 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 distillation. The product was treated with dilute hydrochloric acid to remove excess of amine present and crude product was isolated and crystallised from ethanol.

(B) Preparation of 2-Arylimino-3-aryl-5H-4-thiazolidinones[276]

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

(C) Preparation of 2-(ρ-Anisylimino)-3,N-(ρ-anisyl)-5-(1',N-phenyl-3'-ρ-anisyl-4'-pyrazolylmethino)-4-thiazolidinones

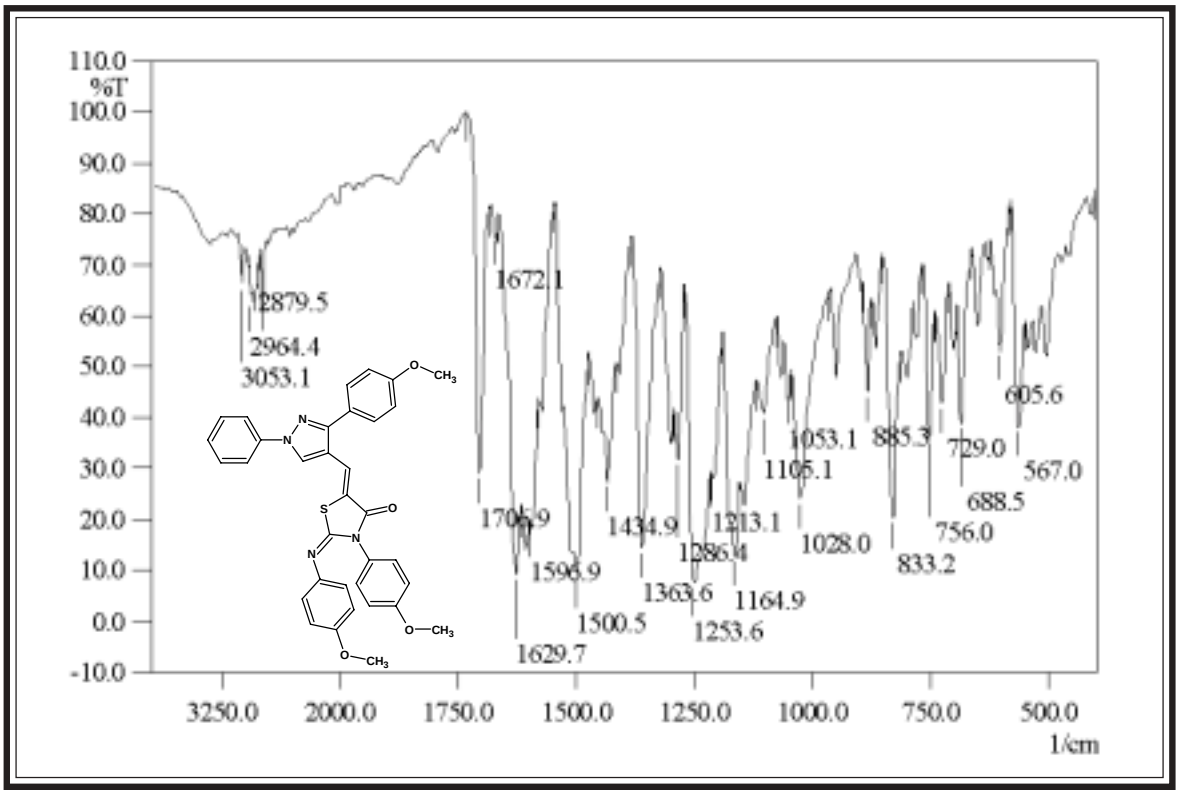
A mixture of 2-(ρ-anisylimino)-3-(ρ-anisyl)-5H-4-thiazolidinone (3.28 g, 0.01 M), 1,N-phenyl-3-ρ-anisyl-4-formyl-pyrazole (2.78 g, 0.01 M) and fused sodium acetate (1.25 g, 0.015 M) was refluxed in glacial acetic acid (15 ml) for 4-5 hrs., cooled, poured into water and treated with ammonia to remove excess of glacial acetic acid. The product was isolated and crystallised from ethanol. Yield 75%, m.p. 190°C. (Anal. Found : C, 66.33 H, 4.73; N, 9.49%; $C_{34}H_{28}N_4O_4S$ Requires: C, 66.37; H, 4.79; N, 9.52%).

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

(D) Antimicrobial activity of 2-Arylimino-3,N-aryl-5-(1',N-phenyl-3'-ρ-anisyl-4'-pyrazolylmethino)-4-thiazolidinones

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

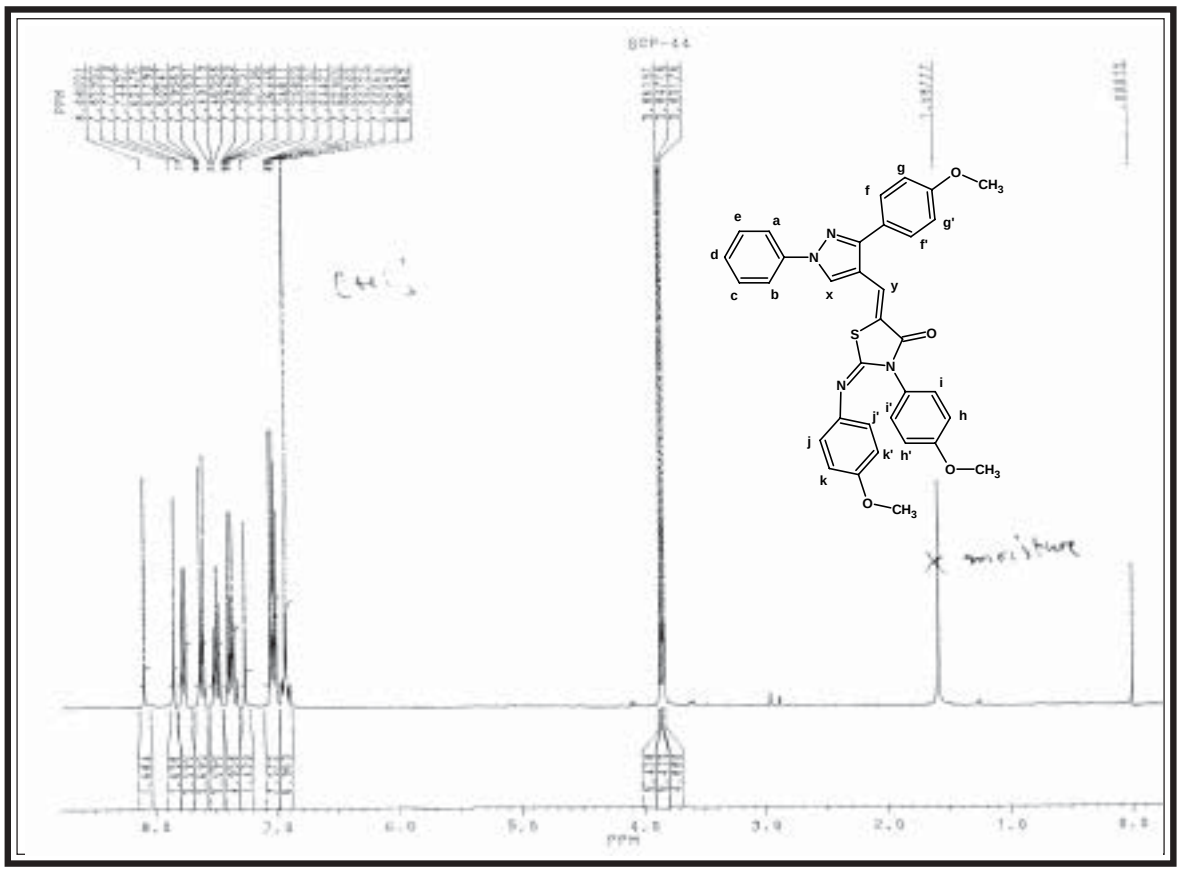
IR SPECTRAL STUDY OF 2-(ρ-ANISYLIMINO)-3,N-(ρ-ANISYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONE



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.)	2964.0	2975-2950	434
$-CH_3$	C-H str. (sym.)	2879.5	2880-2860	"
	C-H def. (asym.)	1434.9	1470-1435	"
	C-H def. (sym.)	1363.6	1385-1350	"
Aromatic	C-H str.	3053.1	3080-3030	435
	C-H i.p. def.	1105.1	1125-1090	"
		1053.1	1070-1000	"
	C-H o.o.p. def.	833.2	835-810	"
Pyrazole	C=N str.	1596.9	1650-1600	434
moiety	C=C str.	1500.5	1585-1480	"
	C-N str.	1253.6	1350-1200	"
Ether	C-O-C (asym.)	1213.1	1275-1200	"
	C-O-C (sym.)	1028.0	1075-1020	"
Thiazolidinone	C=O str.	1706.9	1760-1655	434
	S-C=N str.	1629.7	1640-1605	436
	C-S-C str.	688	700-600	"
Arylidene	=CH i.p.	1363.6 (overlapped)	1420-1290	"
		1672	1690-1600	"

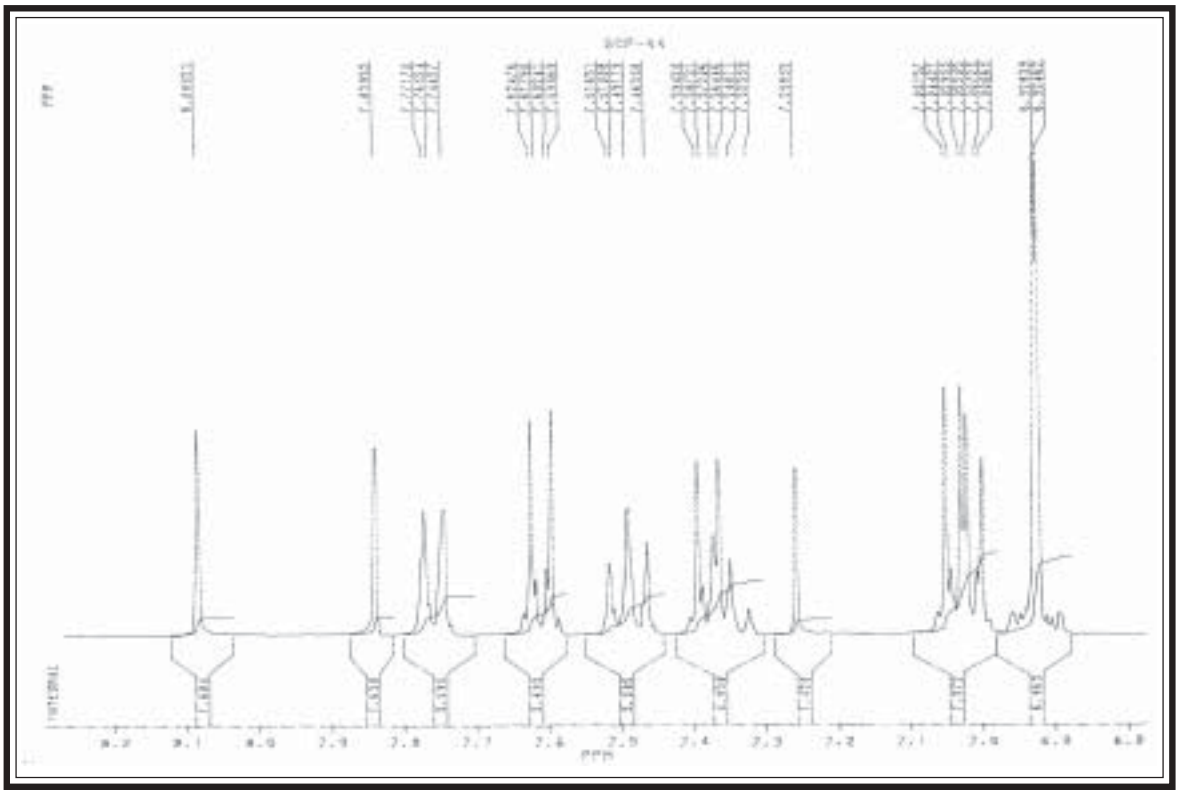
PMR SPECTRAL STUDY OF 2-(ρ-ANISYLIMINO)-3,N-(ρ-ANISYL)-5-(1',N-PHENYL-3'-ρ-ANISYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONE



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	3.83		3H	singlet	Ar-OCH_3
2	3.84		3H	singlet	Ar-OCH_3
3	3.86		3H	singlet	Ar-OCH_3
4	6.92		4H	doublet	Ar-Hhh'
					Ar-Hkk'
5	7.01	Jjk = 6.6	2H	doublet	Ar-Hjj'
6	7.04	Jih = 6.6	2H	doublet	Ar-Hii,
7	7.34		1H	doublet	Ar-Hd
8	7.37	Jgf = 8.7	2H	doublet	Ar-Hgg'
9	7.48		1H	triplet	Ar-Hc, Ar-He
10	7.61	Jfg = 8.7	2H	doublet	Ar-Hff'
11	7.75		2H	doublet	Ar-Ha, Ar-Hb
12	7.83		1H	singlet	CHy
13	8.08		1H	singlet	CHx

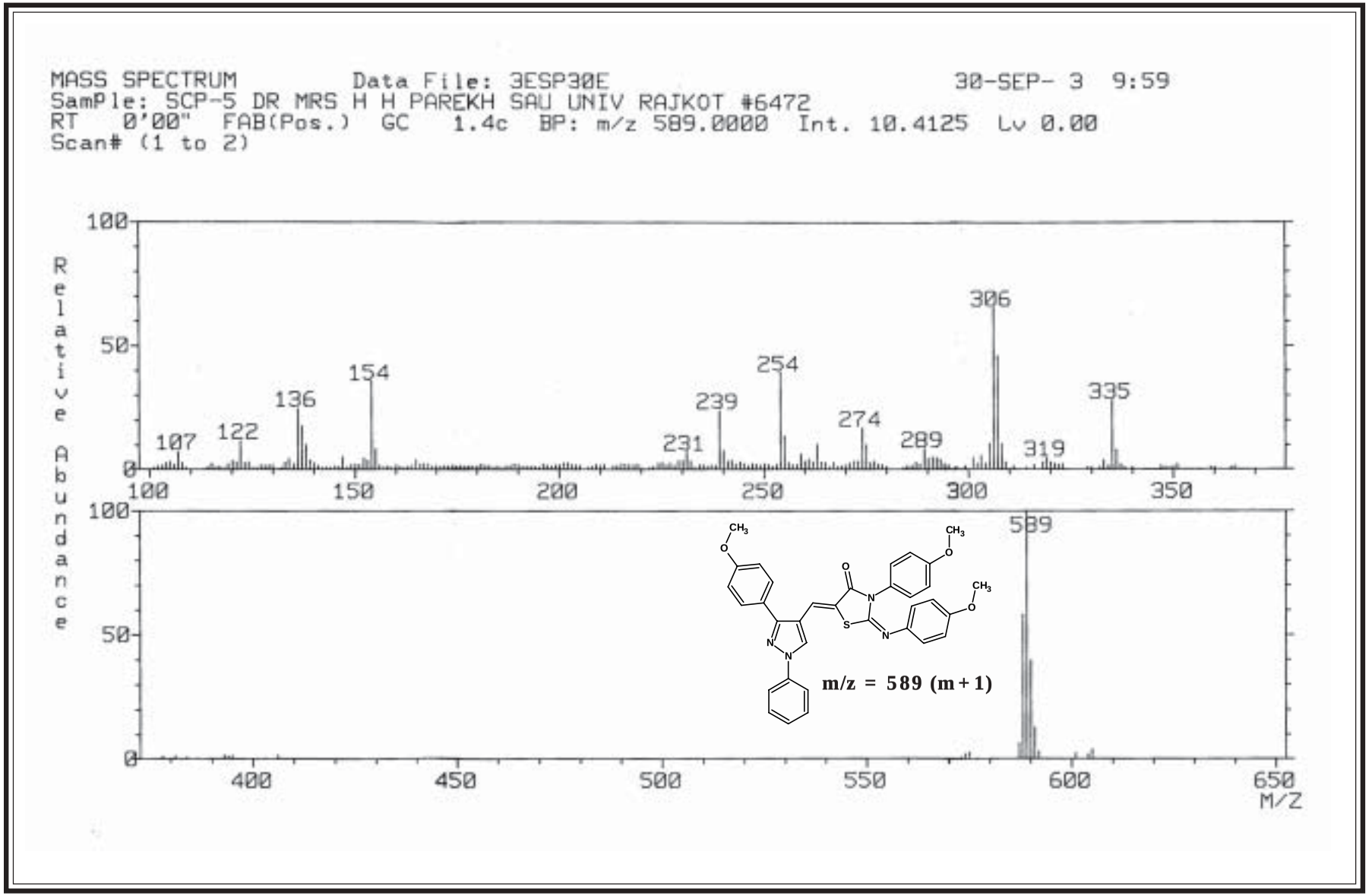
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 2-ARYLIMINO-3,N-ARYL-5-[1',N-PHENYL-3'-ρ-ANISYL-4'-PYRAZOLYLMETHINO]-4-THIAZOLIDINONES

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

Sr. No.	R	C=O str. Thiazolidinones
8a	C_6H_5-	1714
8b	4-COOH-C_6H_4-	1708
8c	4-Cl-C_6H_4-	1712
8d	3,4-$(Cl)_2$-C_6H_3-	1716
8e	4-F-C_6H_4-	1710
8f	4-OCH_3-C_6H_4-	1706
8g	4-CH_3-C_6H_4-	1703
8h	3-CH_3-C_6H_4-	1708
8i	2-CH_3-C_6H_4-	1706
8j	4-NO_2-C_6H_4-	1700
8k	3-NO_2-C_6H_4-	1708
8l	2-NO_2-C_6H_4-	1716


MASS SPECTRUM Data File: 3ESP30E 30-SEP- 3 9:59
SamPle: SCP-5 DR MRS H H PAREKH SAU UNIV RAJKOT #6472
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 589.0000 Int. 10.4125 Lv 0.00
Scan# (1 to 2)
Relative Abundance
M/Z
107
122
136
154
231
239
254
274
289
306
319
335
589
m/z = 589 (m+1)

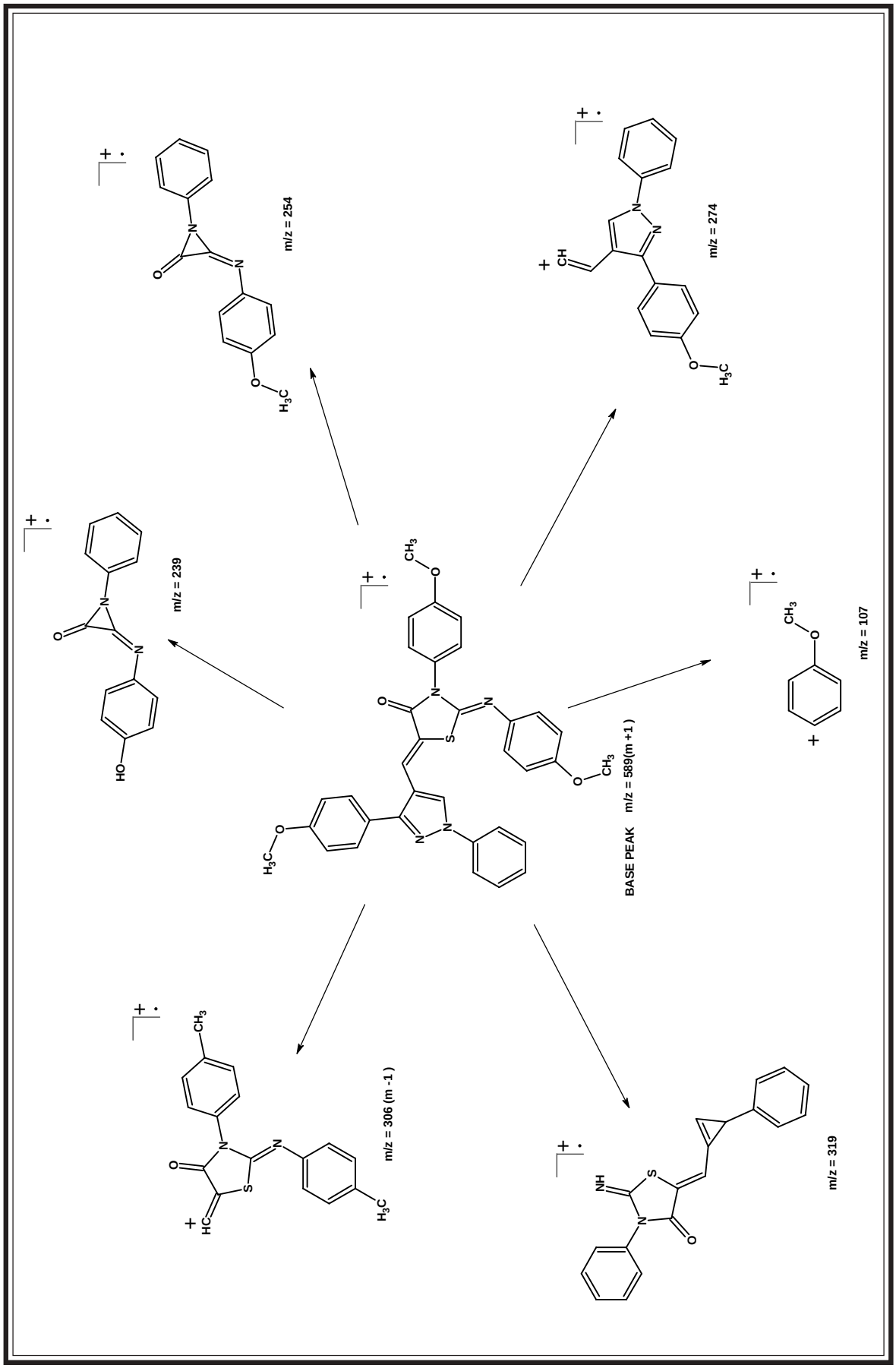
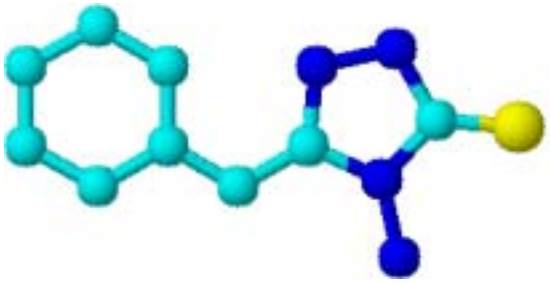

m/z = 254
m/z = 274
m/z = 239
m/z = 107
BASE PEAK m/z = 589(m +1)
m/z = 306 (m -1)
m/z = 319

TABLE NO. 8 : PHYSICAL CONSTANTS OF 2-ARYLIMINO-3,N-ARYL-5-(1',N-PHENYL-3'-ρ-ANISYL-4'-PYRAZOLYLMETHINO)-4-THIAZOLIDINONES

Comp. 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-	$C_{32}H_{24}N_4O_2S$	529	180	0.45	75	10.60	10.55
8b	4-COOH-C_6H_4-	$C_{34}H_{24}N_4O_6S$	617	185	0.61	68	9.09	9.04
8c	4-Cl-C_6H_4-	$C_{32}H_{22}N_4O_2S(Cl)_2$	597.5	214	0.42	69	9.38	9.34
8d	3,4-$(Cl)_2$-C_6H_3-	$C_{32}H_{20}N_4O_2SCl_4$	666	202	0.56	71	8.41	8.38
8e	4-F-C_6H_4-	$C_{32}H_{22}N_4O_2SF_2$	565	235	0.51	71	9.92	9.88
8f	4-OCH_3-C_6H_4-	$C_{34}H_{28}N_4O_4S$	589	190	0.42	75	9.52	9.47
8g	4-CH_3-C_6H_4-	$C_{34}H_{28}N_4OS$	557	188	0.59	70	10.06	10.01
8h	3-CH_3-C_6H_4-	$C_{34}H_{28}N_4O_2S$	557	195	0.74	66	10.06	10.02
8i	2-CH_3-C_6H_4-	$C_{34}H_{28}N_4O_2S$	557	211	0.70	65	10.06	10.04
8j	4-NO_2-C_6H_4-	$C_{32}H_{22}N_6O_6S$	619	198	0.62	70	13.59	13.52
8k	3-NO_2-C_6H_4-	$C_{32}H_{22}N_6O_6S$	619	171	0.65	74	13.59	13.56
8l	2-NO_2-C_6H_4-	$C_{32}H_{22}N_6O_6S$	619	225	0.59	67	13.59	13.54

*TLC Solvent System : Ethylacetate : Hexane (2 : 8) (8a-8l)

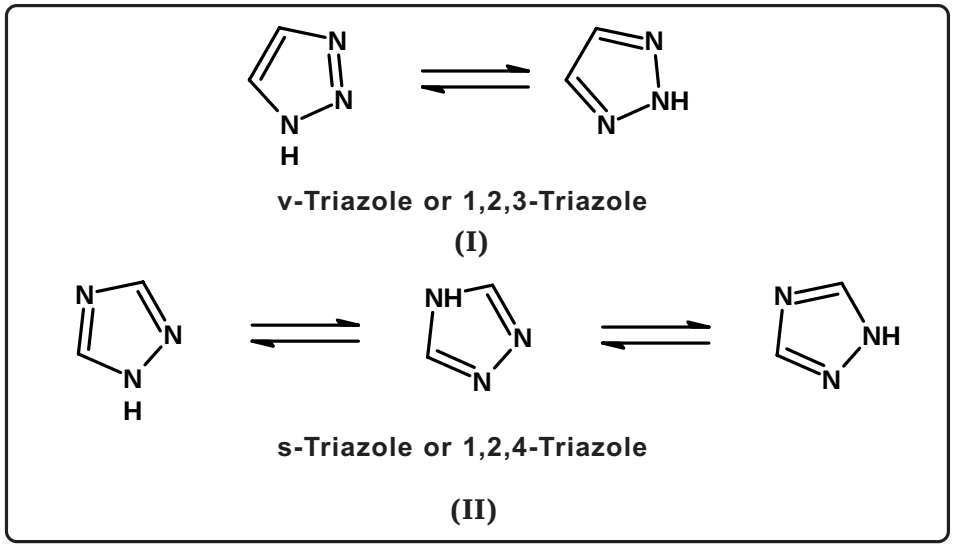
(3 : 7) 8e



B :
STUDIES ON TRIAZOLES

INTRODUCTION

Triazoles have occupied an important place in the pharmaceutical industry. Triazole molecule is having following isomers viz. v-triazoles or 1,2,3-triazoles (I), s-triazoles or 1,2,4-triazoles (II) and their benzo derivatives. Most of the work is reported on 1,2,4-triazoles or s-triazoles.



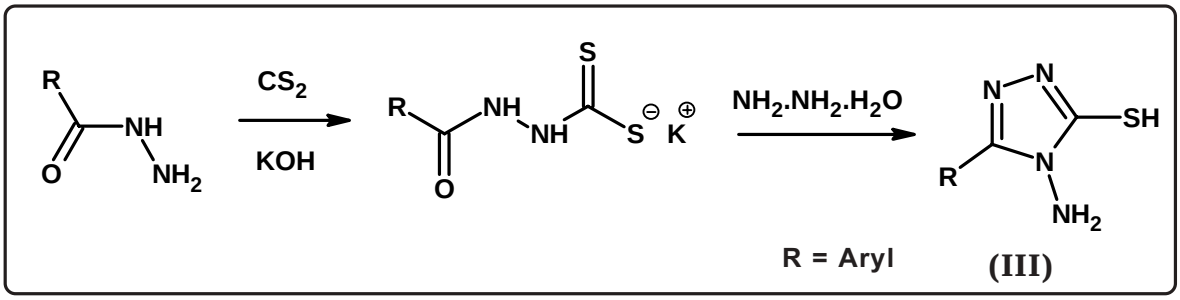
Bladin[277,278] a pioneer worker in the field of triazole synthesised the first derivative in 1885 and an alternative name for the ring system was coined by Andreocci[279] a 'pyrodiazole' which is regarded as a member of a class of compounds analogous to pyrrole.

1,2,4-Triazoles are not only known for their medicinal applications, but also used as an analytical reagents[280,281], dyes and photographic chemicals and in the preparation of polymers.

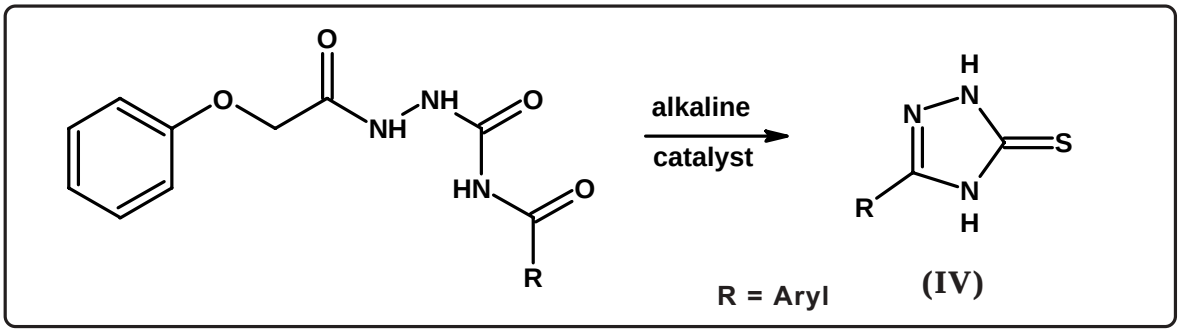
SYNTHETIC ASPECTS

Several methods have been reported in the literatures for the preparation of 1,2,4-triazoles shown as under.

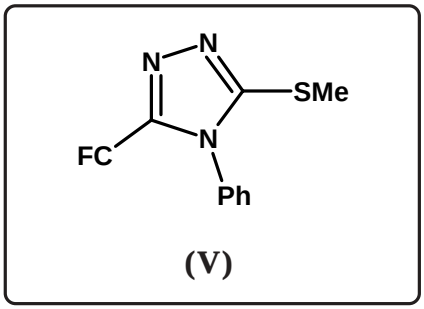
1. Reid and Heindel[282] reported that the reaction of aryl acid hydrazide with CS_2/KOH and hydrazine hydrate furnished triazoles.



2. Zhang Zivi et. al.[283] prepared 1,2,4-triazoles by the addition reaction of 2,4-dichlorophenoxyacetic acid hydrazide with R.CO.NCS gave aroylthiosemicarbazides. Cyclization of this in H_2O in the presence of alkaline catalyst gives triazoles.



3. Yan Shiquaing[284] prepared by the treatment of Ferrocenecarboxylic acid hydrazide with arylisothicyanate produced substituted thiosemicarbazides which on cyclisation gave 3,4-disubstituted-4H-1,2,4-triazole-5-thiol.

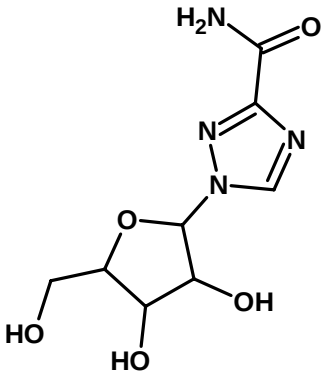


Different types of methods[285-287] for the preparation of 1,2,4-triazoles documented in literaturte.

THERAPEUTIC IMPORTANCE

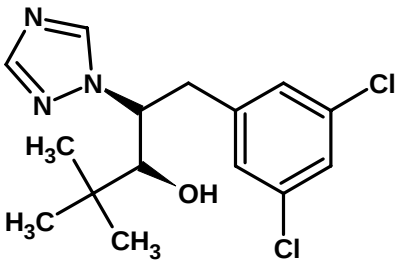
1,2,4-Triazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having 1,2,4-triazole nucleus with good activity are listed below.

1. Rifavirin



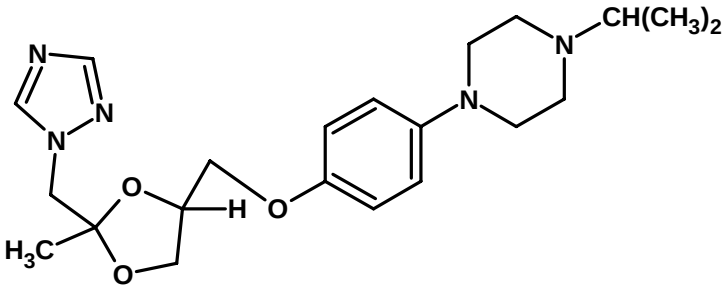
Antiviral, Antiinfectious

2. Diclobutrazole



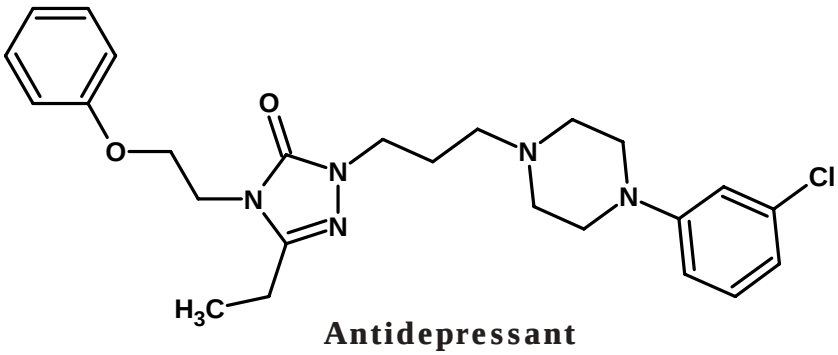
Plantgrowth regulator

3. Terconazole



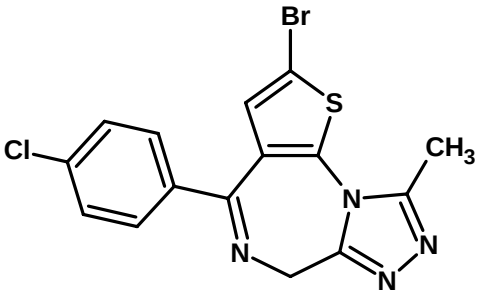
Antifungal

4. Nefazodone



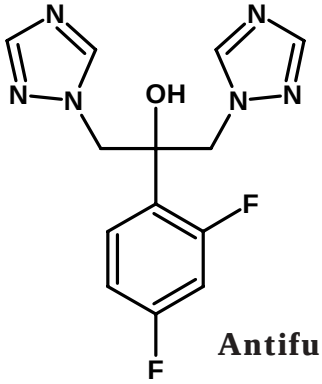
Antidepressant

5. Brotizolam



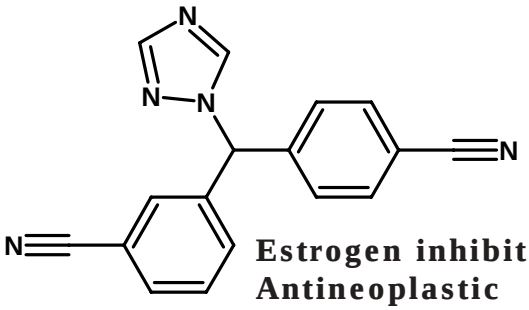
Sedative, Hypnotic

6. Fluconazole



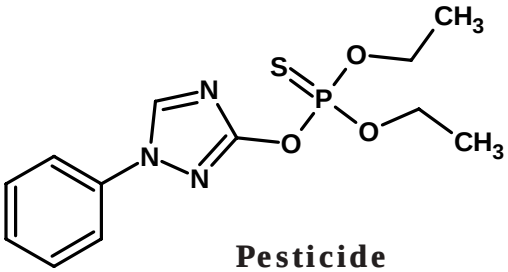
Antifungal

7. Letrozole



Estrogen inhibitor
Antineoplastic

8. Triazophose



Pesticide

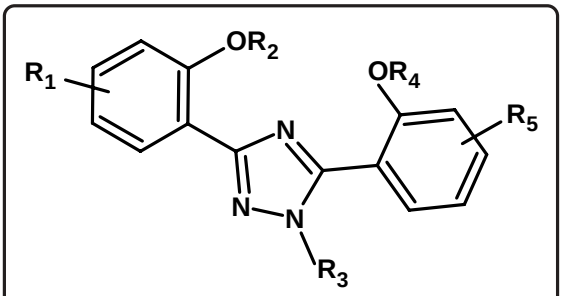
3-Amino-1,2,4-triazole was the first triazole manufactured on large scale from aminoguinidine formate useful as neutral herbicides[288]. Therapeutic activity of 1,2,4-triazoles are listed below.

1. Antihypertensive[289]
2. Bacteriocidal[290]
3. Antiviral[291]
4. Antiinflammatory[292]
5. Fungicidal[293]
6. Herbicidal[294]
7. Antitumor[295]
8. Insecticidal & Acaricidal[296]
9. Anticonvulsant[297]
10. Diuretic[298]
11. Anticancer & antiHIV[299]

12. Plant growth regulator[300]
13. Antimicrobial[301]
14. Antileishmanial[302]

1,2,4-Triazole derivatives have been used successfully in the control of fungal infection[303] and also as nematicidal[304], eosinophilla[305] inhibitors, hypoglycemic activity[306] and microbicides[307] for plant protection.

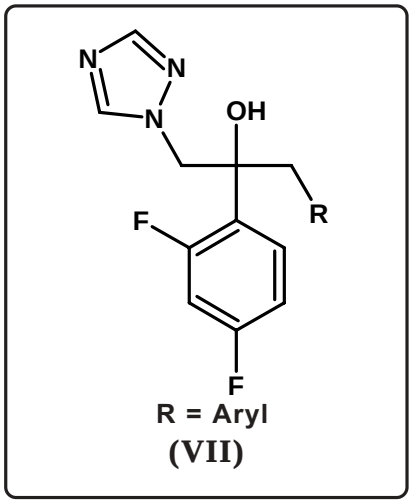
Amir Mohammad[308] have prepared 1,2,4-triazole derivatives as antiinflammatory agents. Shi Yan-Nian and co-workers[309] have 2H, pyrazolo, 1,2,4-triazole as plant growth regulator. Bignon Eric et. al.[310] have documented N-triazolyl-2-indol carboxamides useful as CCK - A agonists. Lattmann Rene et. al.[311] have reported 3,5-bis-hydroxylphenyl-1,2,4-triazoles (VI) useful as pharmaceutical chelators.



(VI)

Slawinski[312] have prepared triazole as potent cardiovascular agent. A number of 1H-1,2,4-triazole[313]derivatives have been synthesised for their broad spectrum of biological activities. Some of them were commerciallized as agrochemical, fungicides, insecticides, herbicides and plant growth regulators. Jautelat et. al.[314] have reported 1,2,4-triazoles as 100% inhibitor of Erisyphe graminis on barley. Sikorski[315] have determined triazoles useful for inhibiting cholesteryl ester transfer protein activity.

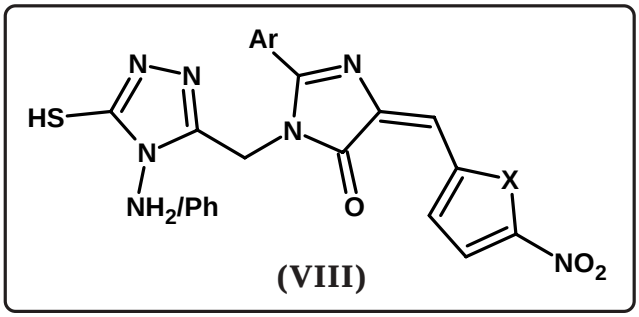
Varvaresou Athanasia and co-workers[316] have suggested indoyl-1,2,4-triazole and reported them as antidepressant and antimicrobial agents. Baba Alsuo et. al.[317] documented triazole useful as antiheumatic agents. Laddi U. V and co-workers[318] have prepared triazoles for antiinflammatory activity, ulcerogenic liability, antimicrobial and antitubercular agents. Sun-Qingyan et. al.[319] have determined triazoles (VII) and reported their antifungal activity.



(VII)

Some new 1H,1,2,4-triazoles possessing antiviral (antiinfluenza virus), antibacterial and antifungal agents synthesised by Sproula et. al.[320] Jag Mohan et. al.[321] have synthesised thiazolo-triazoles and studied for their antimicrobial activity.

Abdelal Ali et. al.[322] have investigated some 1,2,4-triazole derivatives as potential antitumor agents. Rollas Sevim et. al.[323] have screened 1,2,4-triazoles as antimicrobial and anticonvulsant agents. El.Sayed et. al.[324] have reported triazoles (IIX) as potent fungicides and bactericides.



(VIII)

MariMakoto et. al.[325] have synthesised water soluble triazoles as fungicides. Ladawahetty et. al.[326] have prepared triazoles as selective human GABA receptor for the treatment of anxiety and enhancing cognition. Giorgia Pastorin et. al.[327] have documented 1,2,4-triazoles as adenosine receptor antagonist and also as human A_3 and A_{2B} adenosine receptor. B. Shivarama Holla et. al.[328] have screened 1,2,4-triazoles as anticancer. Uesaka et. al.[329] documented triazoles as adrenergic α_2C receptor antagonists.

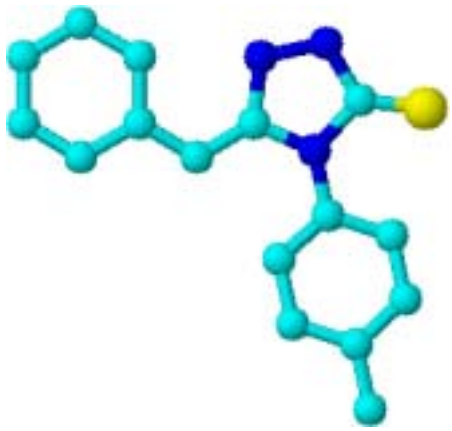
Looking to the diversified pharamacological activity, it appeared of interest to synthesise some 4-aryl triazoles, azomethines and 1,3,4-thiadiazolo triazoles bearing triazole moiety, in order to achieving compounds having better therapeutic importance. These study are described in following parts.

STUDIES ON TRIAZOLES

PART - I : STUDIES ON ARYLTRIAZOLE

PART - II : STUDIES ON AZOMETHINES

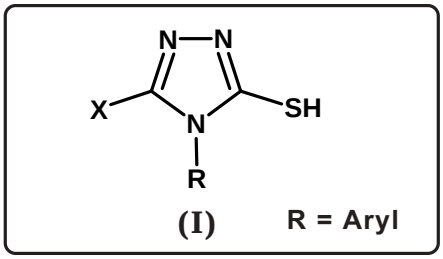
PART - III : STUDIES ON 1,3,4-THIADIAZOLO TRIAZOLES



PART - I
STUDIES ON 4-ARYLTRIAZOLES

INTRODUCTION

Amongst the five membered nitrogen containing heterocycles, the position of nitrogen atom on 1,2 and 4 position activates the ring and proved to be most important pharmacological drugs. The scientists all over the world have focused their attention to evaluate 4-Aryltriazole ring system (I).



(I) R = Aryl

SYNTHETIC ASPECTS

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

By the reaction of acid hydrazide with

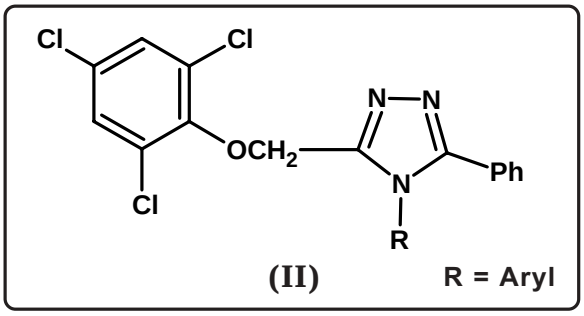
(a) Carbon disulphide, Al. KOH under cyclisation with different amine, hydrazine.

(b) Thiosemicarbazide derivatives followed by ring closure with NaOH.

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.

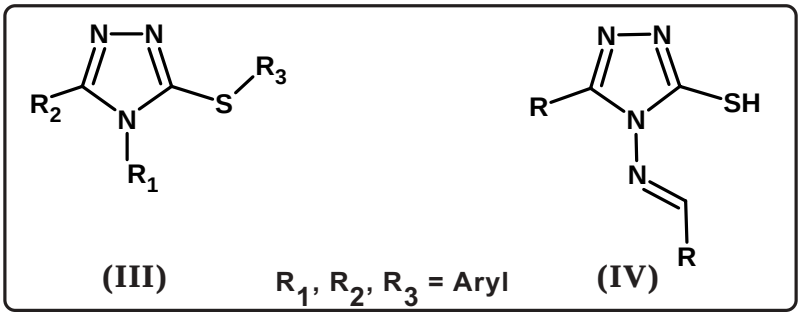
Furthermore Chambers et. al.[330] have investigated 4-aryl triazoles useful in the treatment of neurogenerative disease. Pier et. al.[331] reported as irreversible antagonist at the A_3, A_2A adenosine receptor[332]. Patel K. D. et. al.[333] have prepared triazoles (II) as antimicrobial agents.



(II) **R = Aryl**

Many co-workers have reported 4-aryl triazoles as aromatase-steroid sulfatase inhibitors[334], GSK-3 inhibitors[335], anticancer[336], fungicidal[337], antibacterial[338], antiinflammatory[339], PKB (Protein Kinase B) inhibitors[340], Herbicidal Agents[341-343].

Recently Galcera et. al.[344] have screened 4-aryltriazoles (III) as somatostatin receptors. Other co-workers have studied activity of triazoles like adenosine receptor antagonists[345,346], anticancer[347], analgesic and diuretics[348] and in the treatment of diseases caused due to excess of metal[349] in body. Heindel and co-workers[350] have synthesised 4-aryl triazoles (IV) useful as nitric oxide synthatase inhibitors.



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

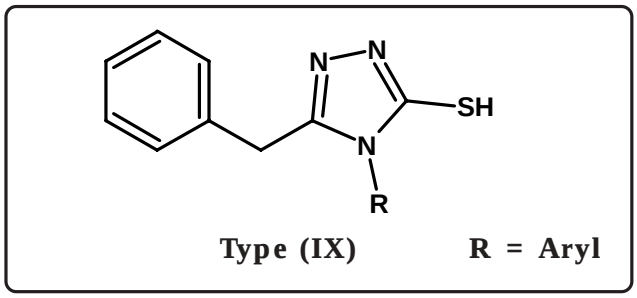
With an aim to synthesise better therapeutic agents, we have investigated some new 4-aryltriazole derivatives which have been described as under.

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

SECTION - I

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

The growing potent literature of recent years demonstrates that the triazole derivatives are useful as better therapeutic agents. These findings prompted us to synthesise 3-mercapto-4,N-aryl-5-benzyl-1,2,4-triazoles. The synthesis of triazole derivatives of type (IX) has been undertaken by heating potassium phenyl acetic acid hydrazide dithiocarbamate with different aromatic amines.

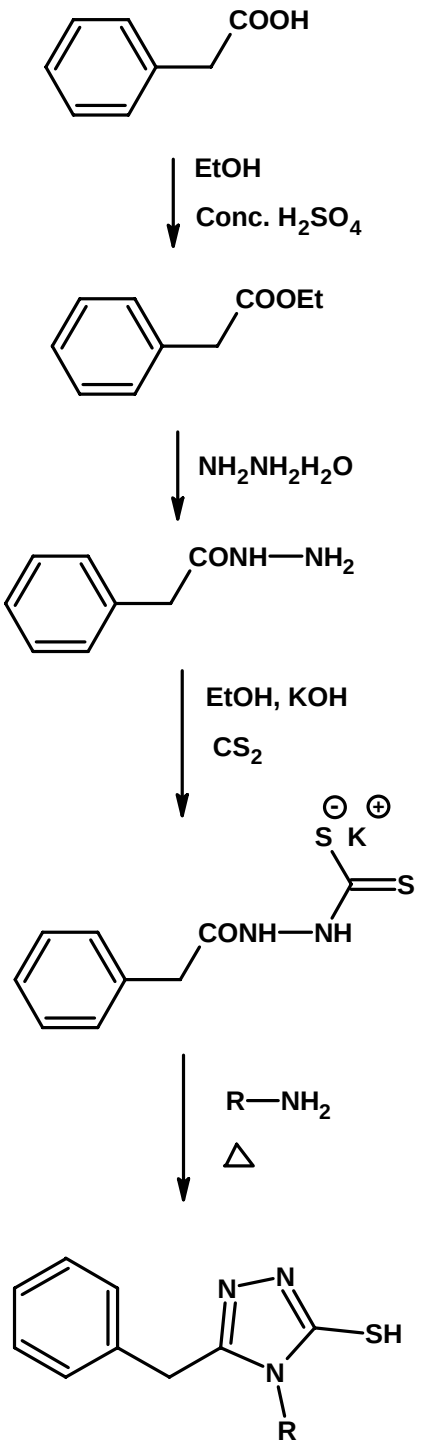


Type (IX) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry. In mass spectrometry m/z value indicates the molecular weight, i.e. when R = ρ-tolyl, molecular weight = 281, m/z = 282 (m + 1).

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

REACTION SCHEME



Type (IX) **R = Aryl**

EXPERIMENTAL

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

(A) Synthesis of Ethylphenyl acetate[351]

Phenyl acetic acid (1.36 g, 0.01 M) in 25 ml ethanol and 1 ml conc. sulfuric acid was refluxed for 15 hrs. and poured into ice. The product was isolated and treated with sat. sodium bicarbonate solution. Yield 85%, b.p. 229^{o}C.

(B) Synthesis of Phenylacetic acid hydrazide[351]

A mixture of Ethylphenylacetate (1.64 g, 0.01 M) and hydrazine hydrate (0.5 g, 0.01 M) was heated for 6 hrs. and poured into ice. The product was isolated and crystallised from water. Yield 80%, m.p. 184^{o}C.

(C) Synthesis of Potassium phenyl acetic acid hydrazide dithiocarbamate

A mixture of phenyl acetic acid hydrazide (1.5 g, 0.01 M), KOH (0.84 g, 0.015 M) and CS_2 1.5 ml in absolute alcohol was stirred for 24 hrs. and poured into ice. The product was isolated from diethyl ether.

(D) Synthesis of 3-Mercapto-4,N-(ρ-tolyl)-5-benzyl-1,2,4-triazole

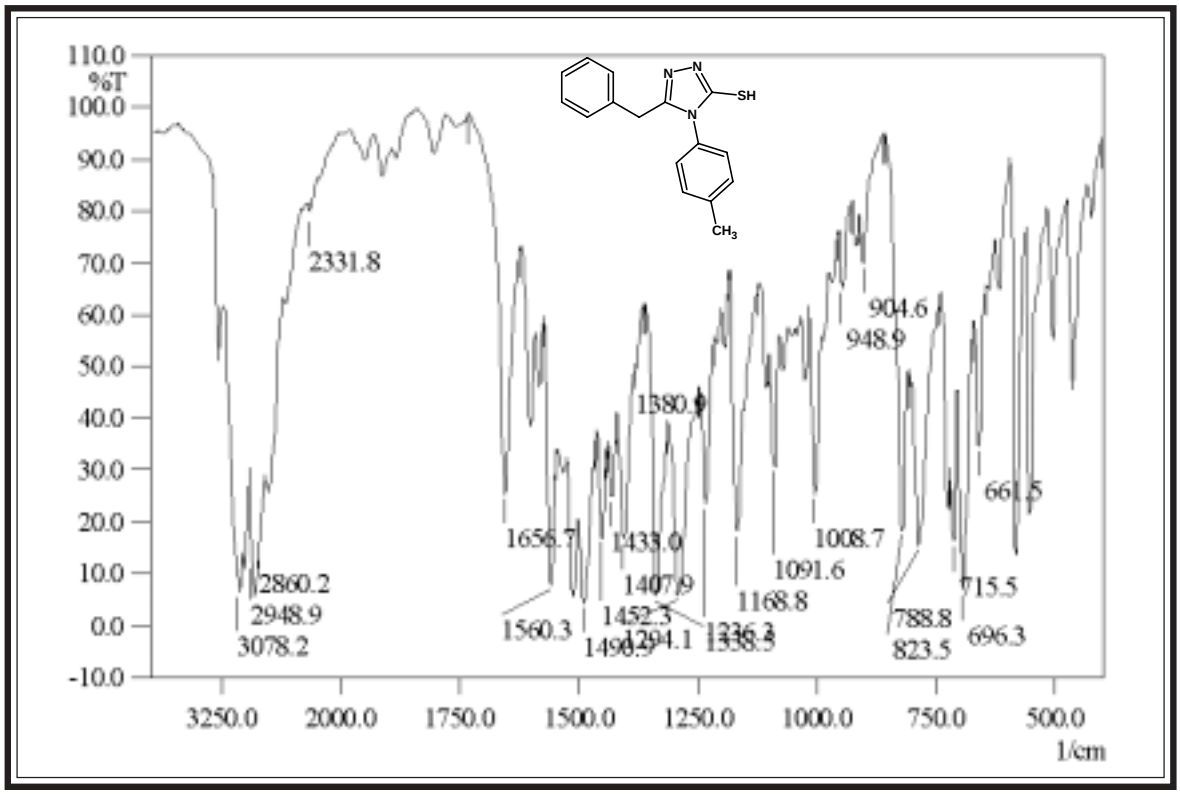
A mixture of (2.5 g, 0.01 M) potassium salt and ρ-toludine (1.07, 0.01 M) was heated upto evolution of H_2S gas caused nearly 10 hrs., DMF was added (20 ml) and contents were poured into ice. The crude product was filtered and crystallised from ethanol. Yield 64%, m.p. 180^{o}C. (Anal. Found : C, 68.26 H, 5.54; N, 14.86%; $C_{16}H_{15}N_3S$ Requires: C, 68.30; H, 5.57; N, 14.93%).

Similarly other 4-aryl triazoles were synthesised. The physical data are recorded in Table No. 9

(E) Antimicrobial activity of 3-Mercapto-4,N-aryl-5-benzyl-1,2,4-triazoles

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

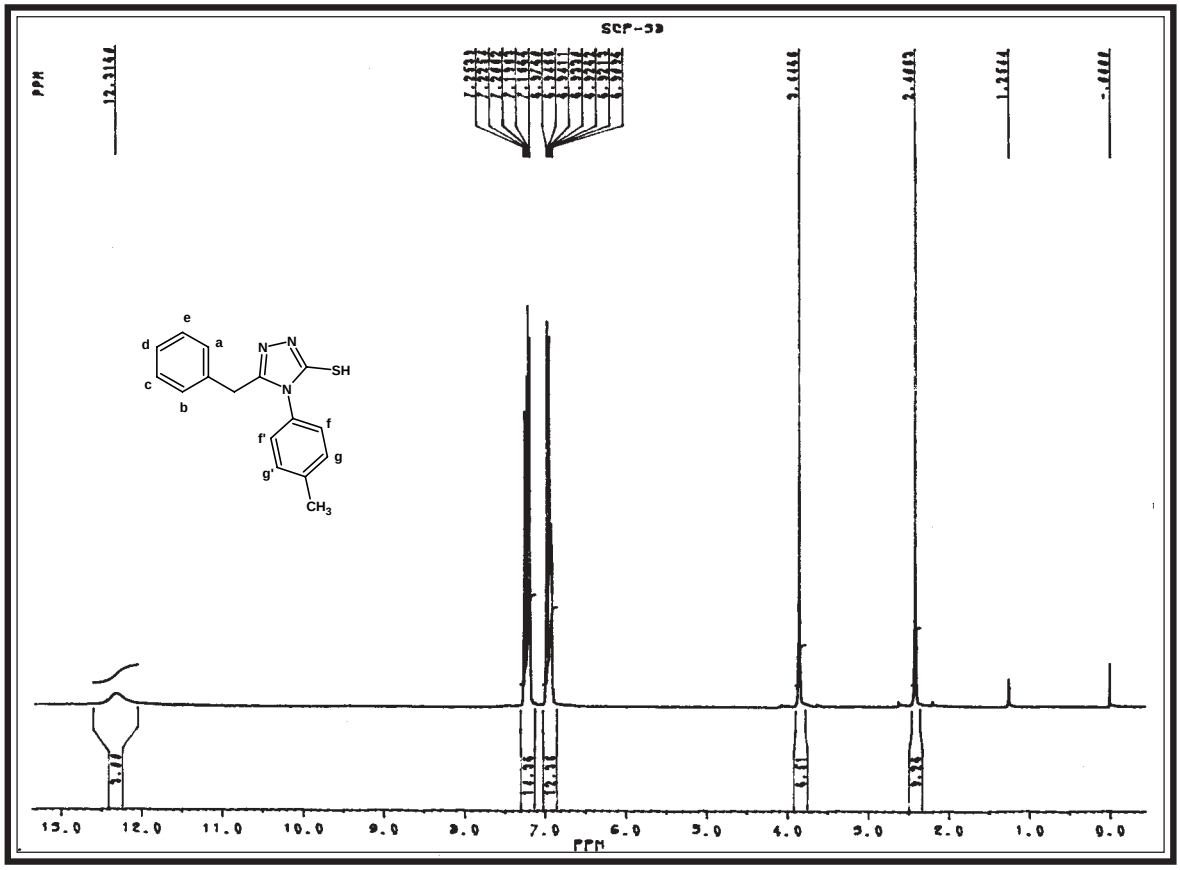
IR SPECTRAL STUDY OF 3-MERCAPTO-4,N-(ρ-TOLYL)-5-BENZYL-1,2,4-TRIAZOLE



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.)	2948.9	2975-2950	434
$-CH_3$	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1433.0	1470-1435	"
	C-H def. (sym.)	1380.9	1385-1350	"
Aromatic	C-H str.	3078.2	3080-3030	435
	C=C str.	1560.3	1585-1480	"
	C-H i.p. def.	1091.7	1125-1090	"
		1028.0	1070-1000	"
	C-H o.o.p. def.	823.5	835-810	"
Triazole	C=N str.	1656.7	1650-1600	434
	C-N str.	1168.8	1220-1020	"
	N-N str.	1008.7	1050-1010	"
	S-H str.	2331.8	2400-2300	438
	C-S str.	696.3	700-600	"

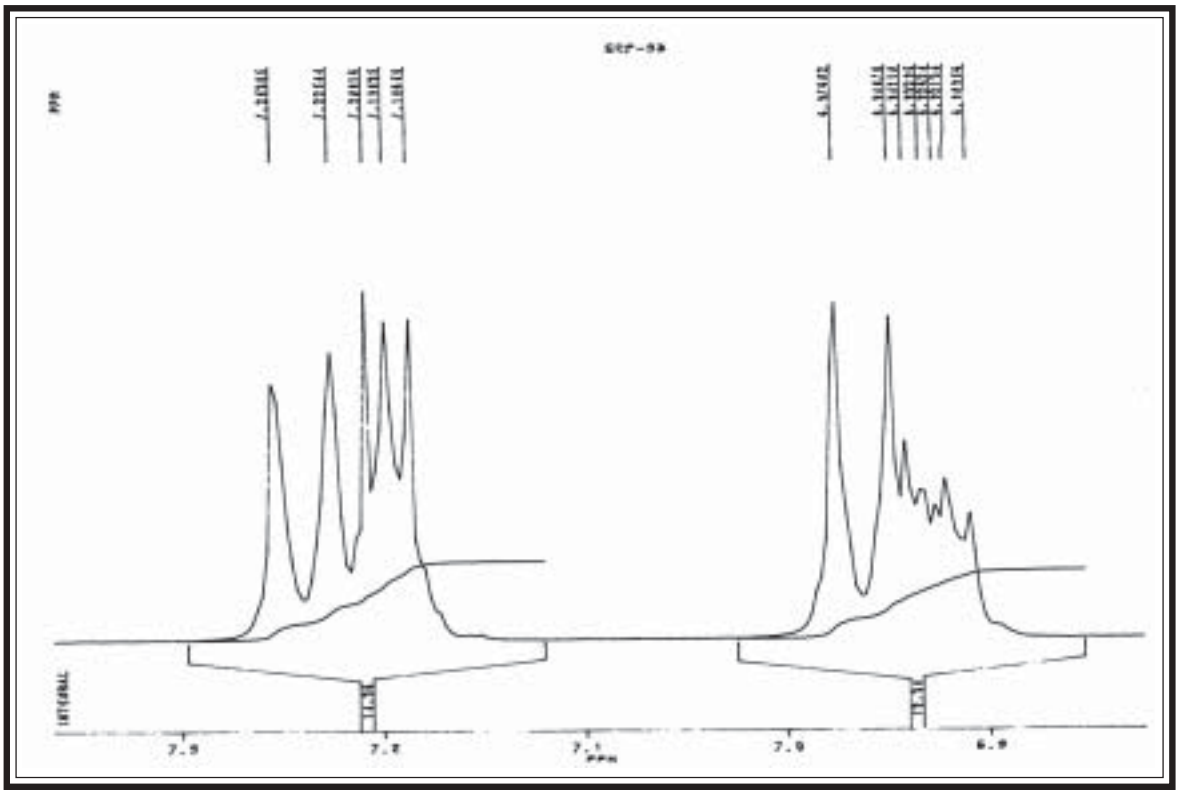
PMR SPECTRAL STUDY OF 3-MERCAPTO-4,N-(ρ-TOLYL)-5-BENZYL-1,2,4-TRIAZOLE



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	2.40		3H	singlet	Ar-CH_3
2	3.64		2H	singlet	-CH_2
3	6.90-6.94		2H	multiplet	Ar-Hc, Ar-He
4	6.95	Jgf = 8.4	2H	doublet	Ar-Hgg'
5	7.16-7.20		3H	multiplet	Ar-Ha, Ar-Hb, Ar-Hd
6	7.23	Jfg = 8.4	2H	doublet	Ar-Hff'

EXPANDED AROMATIC REGION



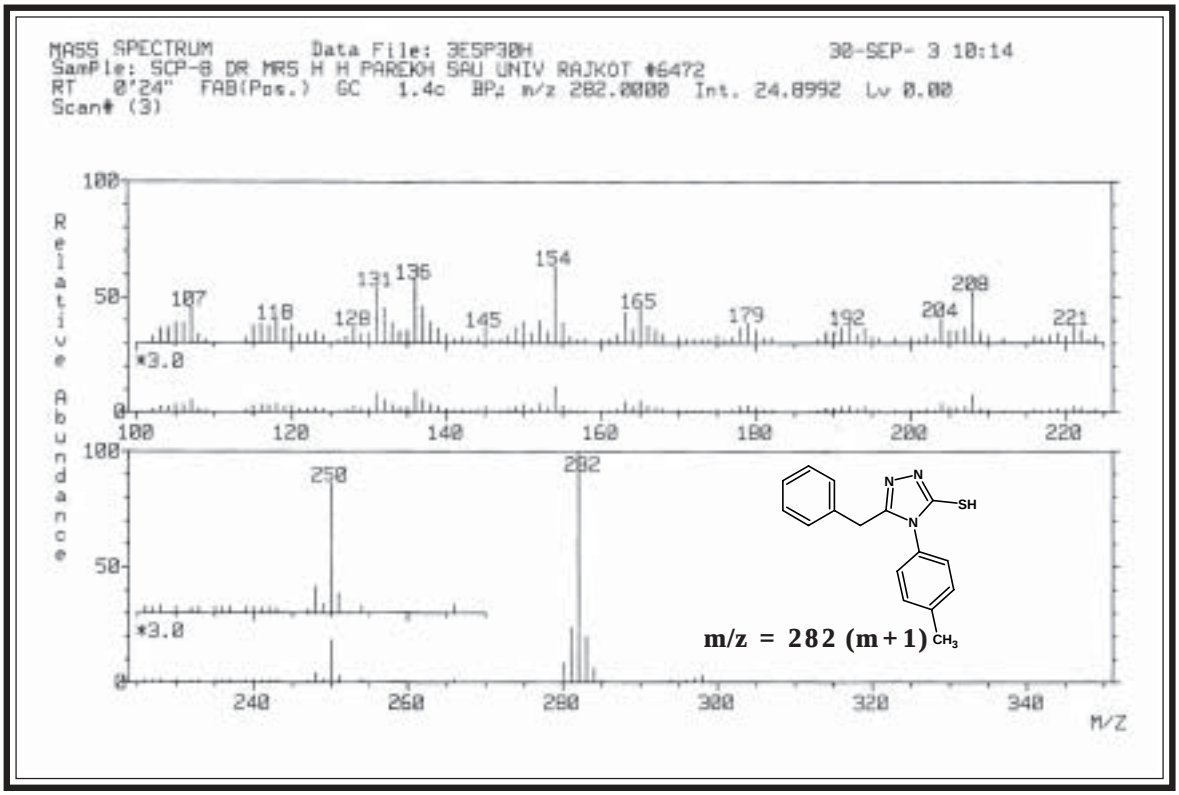
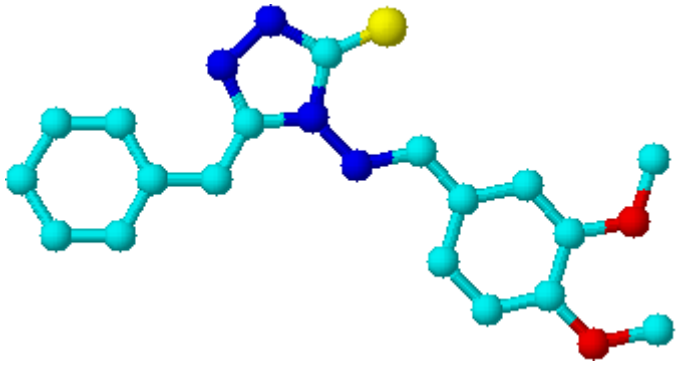


TABLE NO. 9 : PHYSICAL CONSTANTS OF 3-MERCAPTO-4,N-ARYL-5-BENZYL-1,2,4-TRIAZOLES

Comp. 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-	$C_{15}H_{13}N_3S$	267	188	0.49	55	15.72	15.65
9b	4-COOH-C_6H_4-	$C_{16}H_{13}N_3O_2S$	311	168	0.42	55	13.50	13.45
9c	4-Cl-C_6H_4-	$C_{15}H_{12}N_3SCl$	302	178	0.61	68	13.92	13.88
9d	3,4-$(Cl)_2$-C_6H_3-	$C_{15}H_{11}N_3SCl_2$	336	195	0.55	70	12.50	12.47
9e	4-F-C_6H_4-	$C_{15}H_{12}N_3SF$	285	191	0.56	60	14.41	14.36
9f	4-OCH_3-C_6H_4-	$C_{16}H_{15}N_3OS$	297	181	0.47	55	14.13	14.11
9g	4-CH_3-C_6H_4-	$C_{16}H_{15}N_3S$	281	180	0.75	64	14.93	14.89
9h	3-CH_3-C_6H_4-	$C_{16}H_{15}N_3S$	281	223	0.59	60	14.93	14.90
9i	2-CH_3-C_6H_4-	$C_{16}H_{15}N_3S$	281	170	0.45	54	14.93	14.87
9j	4-NO_2-C_6H_4-	$C_{15}H_{12}N_4O_2S$	312	198	0.67	58	17.94	17.90
9k	3-NO_2-C_6H_4-	$C_{15}H_{12}N_4O_2S$	312	207	0.61	64	17.94	17.88
9l	2-NO_2-C_6H_4-	$C_{15}H_{12}N_4O_2S$	312	164	0.58	63	17.94	17.91

*TLC Solvent System : Ethylacetate : Hexane (2 : 8)



PART - II
STUDIES ON AZOMETHINES

INTRODUCTION

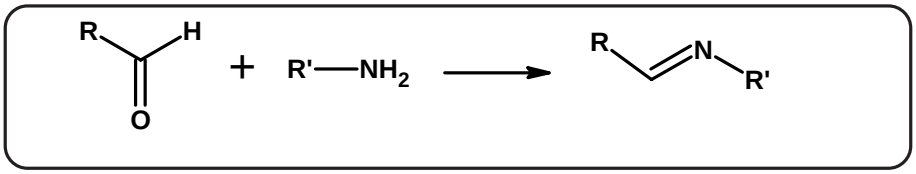
Azomethine derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activity. Azomethines are also known as schiff bases and they are well known intermediate for the preparation of azetidinone, thiazolidinone, formazan, arylacetamide and many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

Azomethines are obtained mainly by heating the aldehyde & aromatic amine together. However, it is sometimes more convenient to work in a solvent such as alcohol, dilute acetic acid or glacial acetic acid. Sometimes the reaction is aided by trace of acid; in other cases the hydrochloride of the amines can be used in the synthesis. In general schiff bases do not react further with either of the reagent used for their preparation, as do most of the other types of simple intermediates.

SYNTHETIC ASPECTS

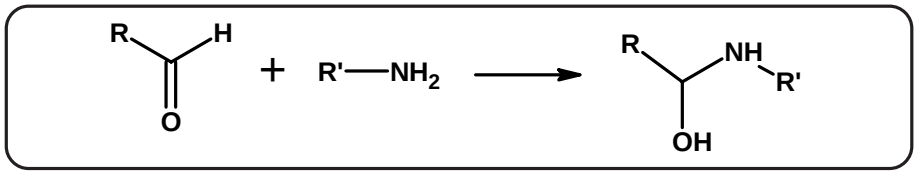
Several methods[352-355] for the preparation of azomethine derivatives are documented in literature.

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

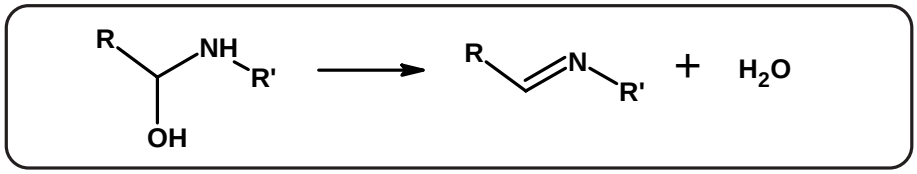


2. Imine formation involves two steps.

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

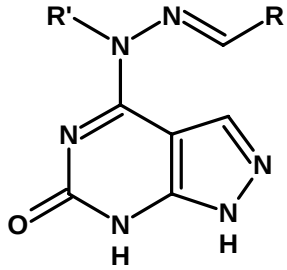


   (b) The loss of water to give an imine (azomethine), this corresponds to the "crotonaldehyde stage" of the aldol condensation.



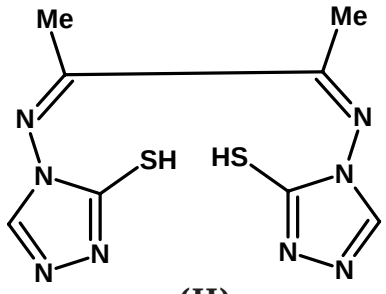
THERAPEUTIC IMPORTANCE

Smalders et. al.[356] documented some new azomethines like benzylidene naphthylamine which reacts with HP (O) $(OCH_2CH_2Cl)_2$ to give potential antitumor reagent phosphonates. Nagamatsu et. al.[357] have prepared some azomethines (I) by the condensation of 4-mercapto-1H-pyrazolo [3,4-d] pyrimidine-6(7H)-one with hydrazine hydrate to give (I), useful as xanthine oxidase inhibitors.



(I)

R = alkyl, aryl
R' = H, Me



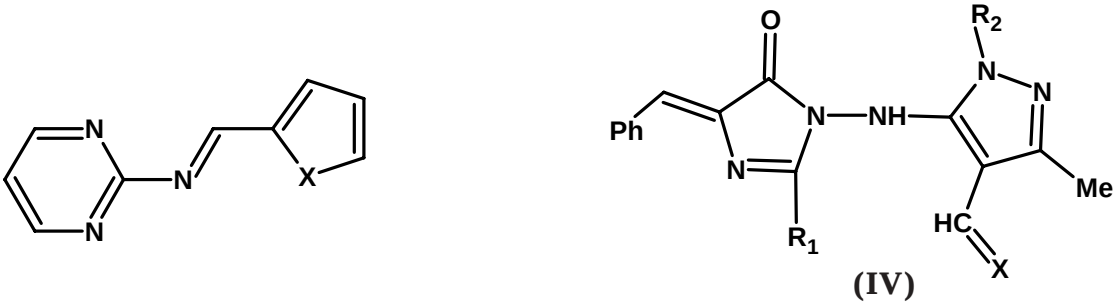
(II)

Yadawe M. S. and Patil S. A.[358] have prepared azomethines (II). which were screened for their antibacterial and antifungal activities.

A series of 4-[5-(halophenyl)-2-furfurylidene]-amino-3-mercapto-5-substituted-1,2,4-triazoles were synthesised by Holla B. et. al.[359] and reported their antibacterial activity.

Mehta R. H. et. al.[360] have synthesised coumarin azomethine derivatives and reported their antibacterial activity. Khalafallah A. and Hassan M. [361] have suggested some styryl schiff's bases as potential antibacterial and antifungal agents. Sharat El-Din and Nabaweya[362] have described compound having good antibacterial activity.

Chohan et. al.[363] have reported azomethines of type (III), which have been screened and compared for their antibacterial action against bacterial species.



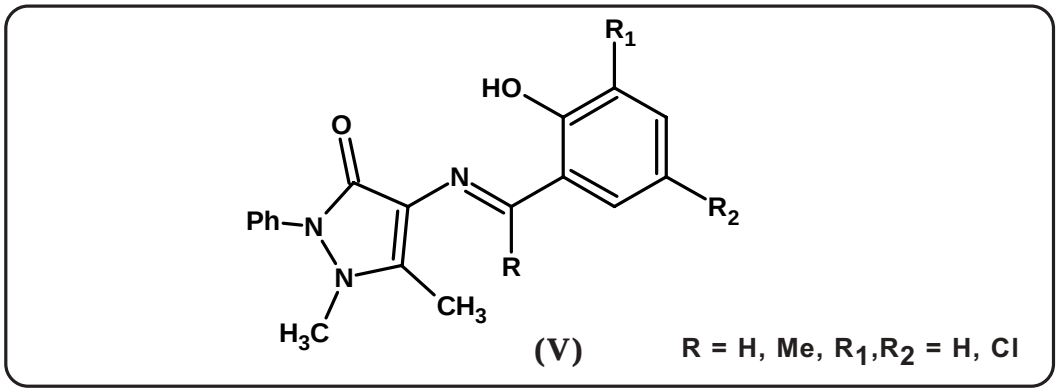
(III) X = O, S

(IV) R_1 = H, Me R_2 = H, Ph X = PhN,4-$MeOC_6H_4N$,4-$O_2NC_6H_4N$

De, Biplab and co-workers[364] have synthesised azomethines (IV) by the condensation of (imidazolinylamino) pyrazole carboxaldehydes with arylamines. Some of them were found to exhibit significant antibacterial and antifungal activities. Deshmukh M. and Doshi A. [365] have synthesised some new azomethines show good antimicrobial activity against test organism.

Wang, Yangang and co-workers[366] have screened some azomethines having good plant harmone activity. Das, and co-workers[367] have prepared schiff base of aminohydroxyguanidine (SB-ASHGS) & were tested for antiviral activity against herpes simplex virus type 1 (HSV-1) and adenovirus type 5 (Ad_5) alone with other heterocyclic SB-AHGS. Solankee Anjani et. al.[368] have suggested addition of 3,4,5-trimethoxybenzaldehyde to 4-thiazolidinones resulted in benzylidene derivatives having potential antibacterial activity.

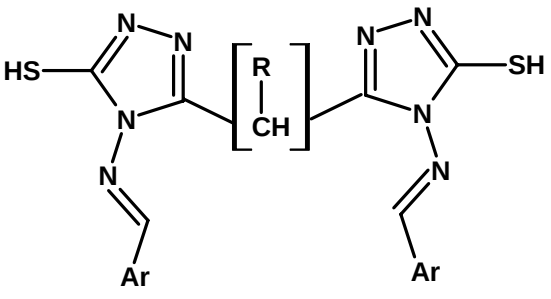
Ram Tilak et. al.[369] have synthesised some schiff bases, thiazolidinones Δ^2-triazolines and formazans bearing 2-chlorophenothiazines and screened against carrageenin induced edema in albino rats. The thiazolidinones showed promising antiinflammatory activity. Cascaval Alexandru; et. al.[370] have synthesised azomethine of type (V) which exhibited antipyretic properties.



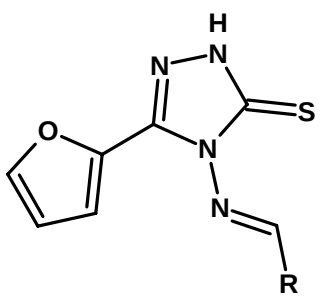
(V) **R = H, Me, R_1,R_2 = H, Cl**

Ali, Yousif et. al.[371] have reported some schiff's base derivatives of glucose contg. acetylenic bond were also prepared hydroxybenzaldehydes were first converted to o-prop-2-ynyl-benzaldehyde followed by their condensation with glucosamine. The compounds possess bactericidal activity. Pandeya V. et. al.[372] have prepared schiff bases showing good activity against vibrio cholerae.

Omar and et. al.[373] have described cyclocondensation of azomethines having good antischistosomal activity. Pawar R. P. et. al.[374] have synthesised azomethines by the condensation of iodovanillin with different substituted aromatic amines showing good antibacterial activity. A novel class of acetyl ferrocene derived from schiff bases possess antimicrobial activity by Chohan and co-workers[375]. Holla, B. S. et. al.[376] have documented azomethine (VI) bearing triazole moiety which possess good antibacterial activity. Ergenc and

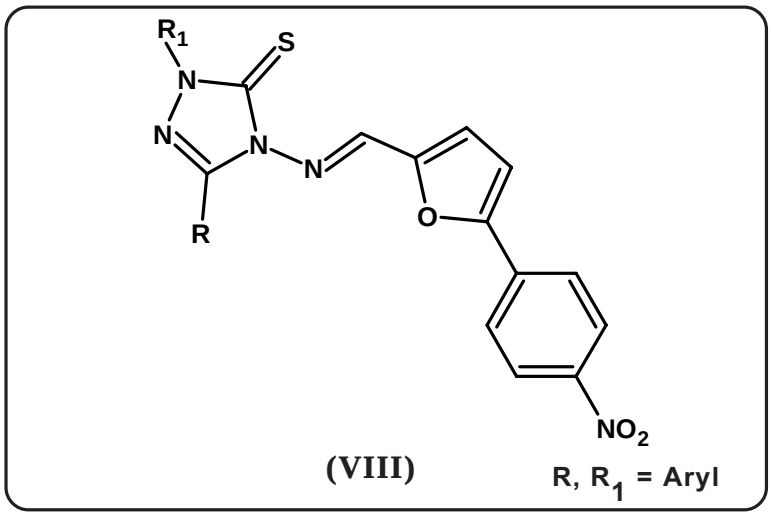


(VI)



(VII) **R = Aryl**

co-workers[377] have synthesised azomethine derivatives (VII) showing antifungal activity. Holla, B. S. et. al.[378] have prepared Mannich bases of type (VIII) as under.



(VIII) R, R_1 = Aryl

B. Shivarama et. al.[379] have synthesised azomethines which were found to possess antibacterial and antiinflammatory activity. Pascal Rotheist et. al.[380] have reported some new azomethines as antiparasitic agents. Adnan A. et. al.[381] studied the antiinflammatory activity of some azomethines. Dimmock J. et. al.[382] have suggested azomethines as cytotoxic agent.

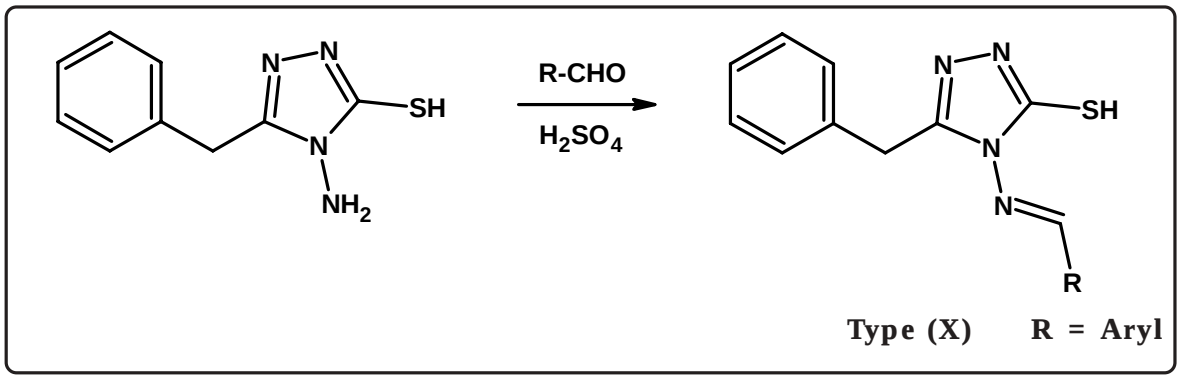
Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological study, we have undertaken the synthesis of azomethines bearing triazole moiety.

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

SECTION - I

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

Considerable evidence has been accumulated to demonstrate the wide applications of azomethines and also have drawn the attention of chemists due to diversified biological activities associated with it. In view of these findings, it appeared of interest to synthesise newer azomethines with better potency. Azomethines of type (X) have been prepared by the condensation of 3-mercapto-4-N-amino-5-benzyl-1,2,4-triazole with different aromatic aldehydes in presence of sulphuric acid.



Type (X) **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, i.e. When R = 1. 3,4-dimethoxyphenyl, molecular weight = 354, m/z = 355 (m+1).

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

EXPERIMENTAL

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

(A) Synthesis of Potassium phenylaceticacid hydrazide dithiocarbamate

Part - I, Section - I(C).

(B) Synthesis of 3-Mercapto-4,N-amino-5-benzyl-1,2,4-triazole

A mixture of (2.5 g, 0.01 M) potassium salt and hydrazine hydrate (0.75 g, 0.015 M) in 25 ml absolute alcohol was refluxed for 5 hrs. The reaction mixture was poured onto crushed ice and treated with gla. acetic acid. The product was filtered and crystallised from ethanol. Yield 65%, m.p. 140^{o}C. (Anal. Found : C, 52.38 H, 4.84; N, 27.12%; $C_9H_{10}N_4S$ Requires: C, 52.41; H, 4.89; N, 27.16%).

(C) Synthesis of 4,N-(3,4-Dimethoxybenzalamino)-3-benzyl-5-mercapto-1,2,4-triazole

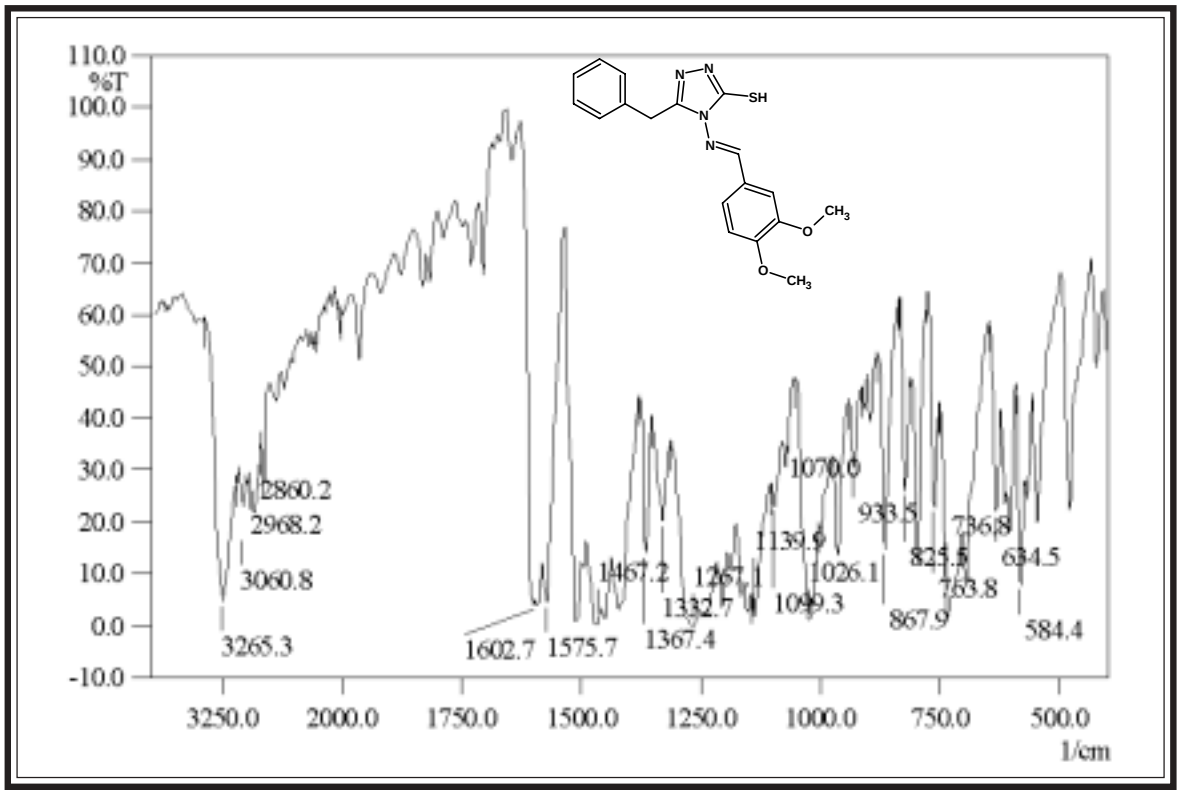
A mixture of 3-mercapto-4,N-amino-5-benzyl-1,2,4-triazole (2.06 g, 0.01 M) and veratraldehyde (1.66 g, 0.01 M) in 25 ml absolute alcohol in presence of sulphuric acid as a catalyst were refluxed for 10 hrs. The resulting mixture was poured into ice and the product was isolated and crystallised from ethanol. Yield 64%, m.p. 224^{o}C. (Anal. Found : C, 60.96 H, 5.09; N, 15.76%; $C_{18}H_{18}N_4O_2S$ Requires: C, 61.00; H, 5.12; N, 15.81%).

Similarly other azomethines have been synthesised. The physical data are recorded in Table No. 10

(D) Antimicrobial activity 4,N-Substituted benzalamino-3-benzyl-5-mercapto-1,2,4-triazoles

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

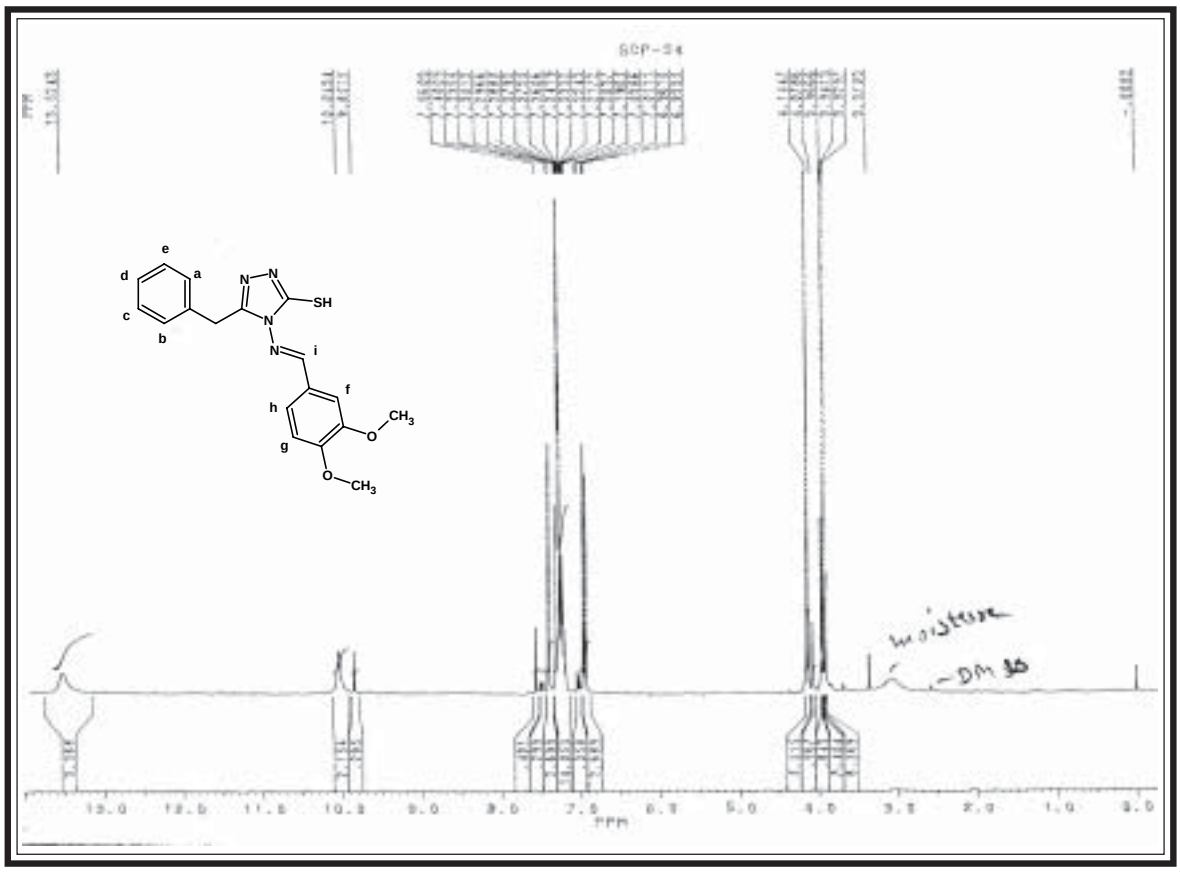
IR SPECTRAL STUDY OF 4,N-(3,4-DIMETHOXYPHENYLAMINO)-3-BENZYL-5-MERCAPTO-1,2,4-TRIAZOLE



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.)	2968.2	2975-2950	434
-CH_3	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1467.2	1470-1435	"
	C-H def. (sym.)	1365.5	1385-1350	"
Aromatic	C-H str.	3060.8	3080-3030	435
	C=C str.	1573.8	1585-1480	"
	C-H i.p. def.	1099.3	1125-1090	"
		1070.0	1070-1000	"
	C-H o.o.p. def.	825.5	835-810	"
Triazole	C=N str.	1602.7	1650-1600	434
	C-N str.	1332.7	1350-1200	"
	N-H str.	1026.1	1050-1010	"
	C-S str.	698.2	700-600	438

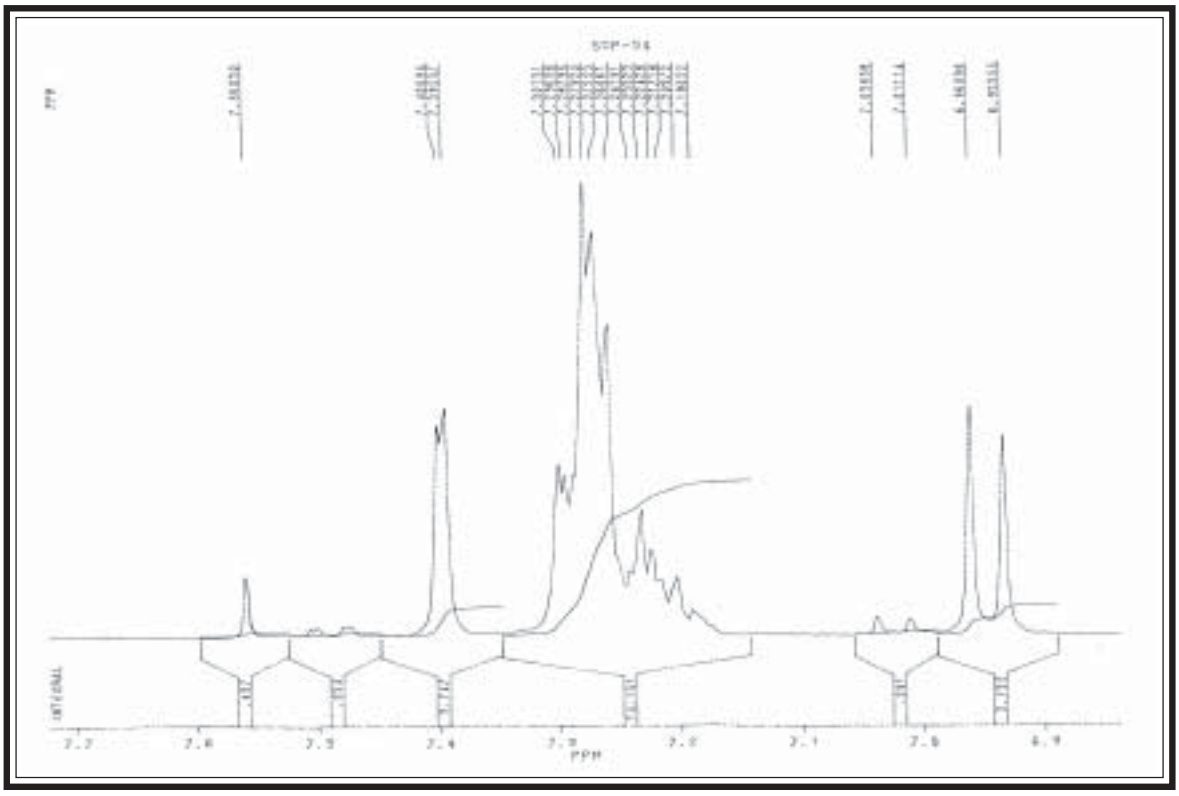
PMR SPECTRAL STUDY OF 4,N-(3,4-DIMETHOXYPHENYLAMINO)-3-BENZYL-5-MERCAPTO-1,2,4-TRIAZOLE



Internal Standard : TMS; Solvent : $CDCl_3 + DMSO_6$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J. Value in Hz	Relative No. of Protons	Multiplicity	Inference
1	3.92		3H	singlet	Ar-OCH_3
2	3.94		3H	singlet	Ar-OCH_3
3	4.14		2H	singlet	-CH_2
4	6.94	Jgh = 8.1	1H	doublet	Ar-Hg
5	7.19-7.30		6H	multiplet	Ar-Ha-e, Ar-Hh
6	7.39	Jfh = 1.5	1H	doublet	Ar-Hf
7	10.04		1H	singlet	CHi

EXPANDED AROMATIC REGION



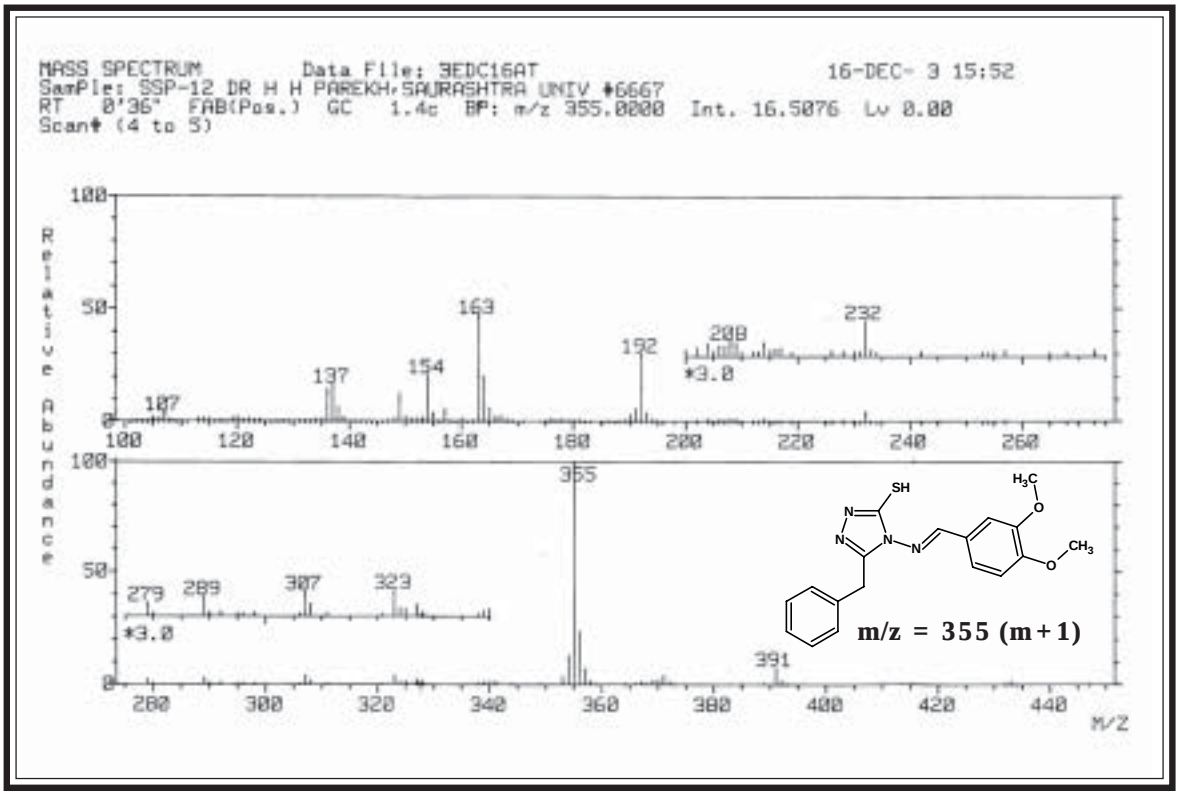
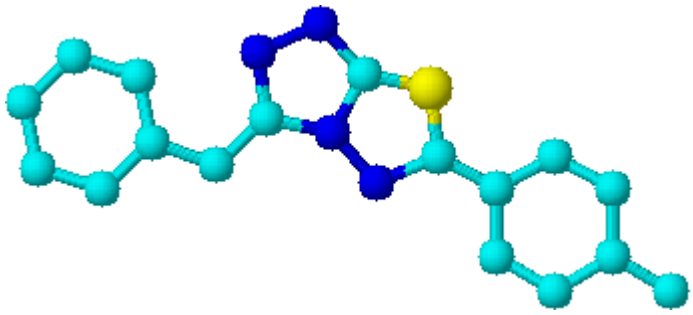


TABLE NO. 10 : PHYSICAL CONSTANTS OF 4-N-SUBSTITUTED BENZALAMINO-3-BENZYL-5-MERCAPTO-1,2,4-TRIAZOLES

Comp. 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
10a	C_6H_5-	$C_{16}H_{14}N_4S$	294	186	0.52	60	19.03	19.01
10b	-CH=CH-C_6H_5-	$C_{17}H_{14}N_4S$	306	181	0.63	61	18.29	18.24
10c	2-Cl-C_6H_4-	$C_{16}H_{13}N_4SCl$	329	191	0.50	74	17.04	17.00
10d	3,4-$(OCH_3)_2$-C_6H_3-	$C_{18}H_{18}N_4O_2S$	354	224	0.49	64	15.81	15.76
10e	4-OH,3-OCH_3-C_6H_3-	$C_{17}H_{16}N_4O_2S$	340	189	0.48	60	16.46	16.41
10f	4-OH-C_6H_4-	$C_{16}H_{14}N_4OS$	310	195	0.55	64	18.05	18.01
10g	3-OH-C_6H_4-	$C_{16}H_{14}N_4OS$	310	>250	0.59	58	18.05	18.02
10h	2-OH-C_6H_4-	$C_{16}H_{14}N_4OS$	310	211	0.62	55	18.05	17.98
10i	4-OCH_3-C_6H_4-	$C_{17}H_{16}N_4OS$	324	205	0.65	71	17.27	17.22
10j	2-OCH_3-C_6H_4-	$C_{17}H_{16}N_4OS$	324	178	0.73	54	17.27	17.21
10k	3-NO_2-C_6H_4-	$C_{16}H_{13}N_5O_2S$	339	177	0.60	66	20.64	20.61
10l	2-NO_2-C_6H_4-	$C_{16}H_{13}N_5O_2S$	339	170	0.64	65	20.64	20.59

*TLC Solvent System : Ethylacetate : Hexane (2 : 8) (10a-10l)

(3 : 7) (10c,10d,10e)

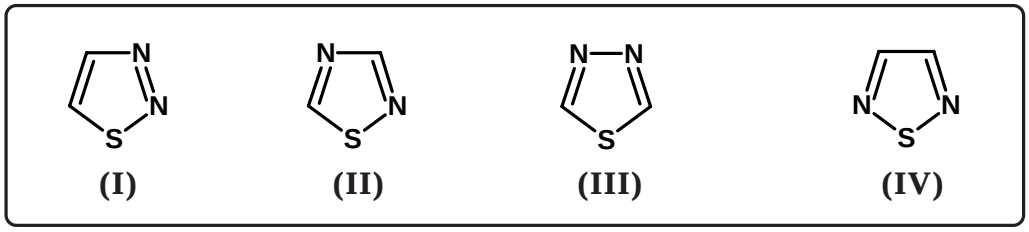


PART - III

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 possess a wide spectrum of biological activities. Thiadiazole ring system consists of one sulphur and two nitrogen atoms present in a five membered ring. According to their position, thiadiazole system can be classified as 1,2,3-thiadiazoles (I), 1,2,4-thiadiazoles (II), 1,3,4-thiadiazoles (III) and 1,2,5-thiadiazoles (IV).



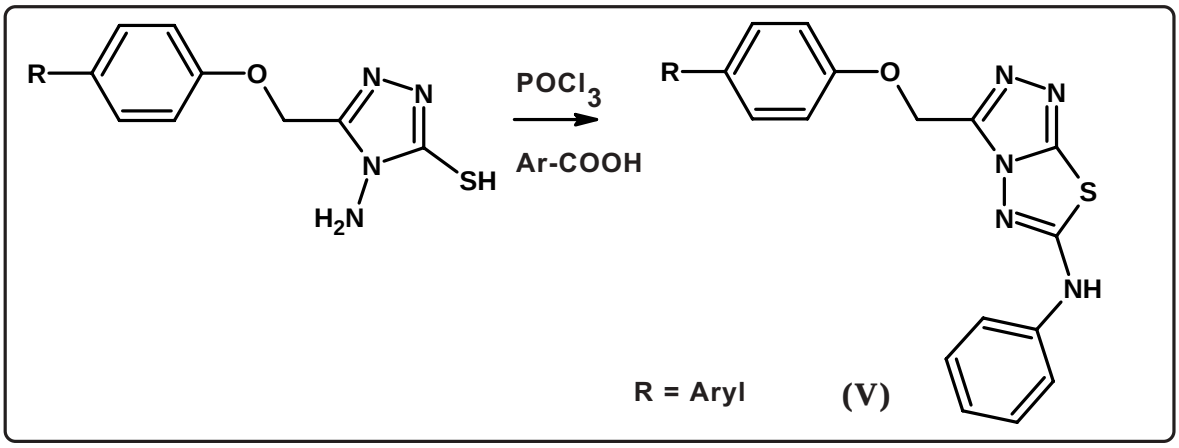
Fischer has described the 1,3,4-thiadiazoles in 1882, for the first time which was further developed by Bush & co-workers.Due to wide range of therapeutic activities,the compounds having thiadiazole nucleus have greatly accelerated the rate of progress in the field of pharmaceutical.

The literature of 1,3,4-thiadiazoles has been extensively reviewed by Sandstrom[383] 1947, Sherman[384] 1948, Bambas[385] 1952.

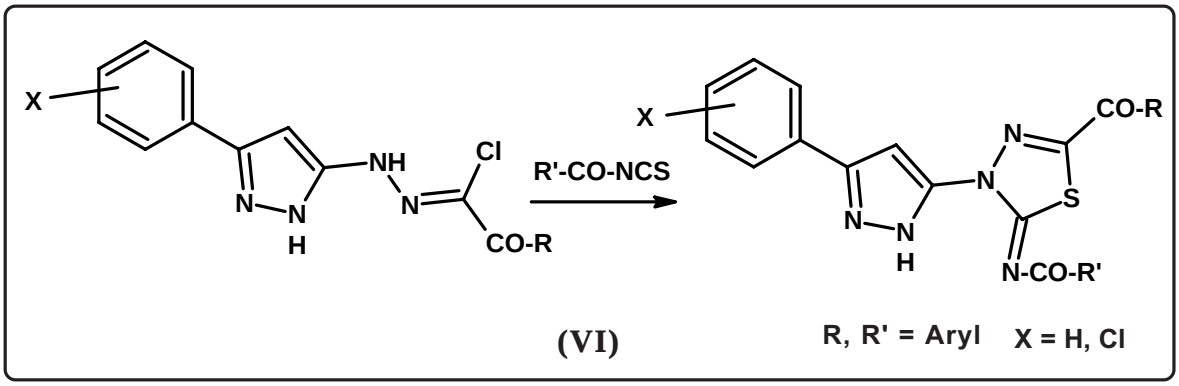
SYNTHETIC ASPECTS

Literature survey reveals that several publications and patents[386] described the synthesis of 1,3,4-thiadiazoles as under.

1. Q. Bano and co-workers[387] have synthesised 6-phenylamino 1,3,4-thiadiazoles.



2. M. K. Albrahim et. al.[388] have synthesised thiadiazoles from hydrazinyl chloride.

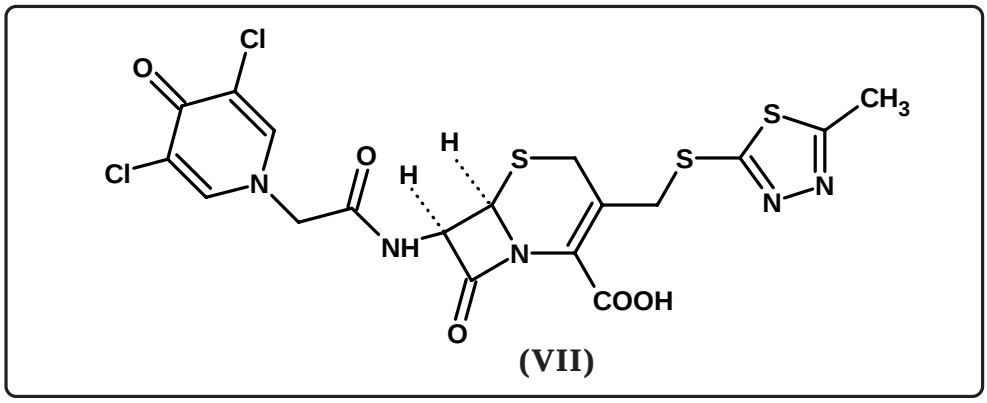


THERAPEUTIC IMPORTANCE

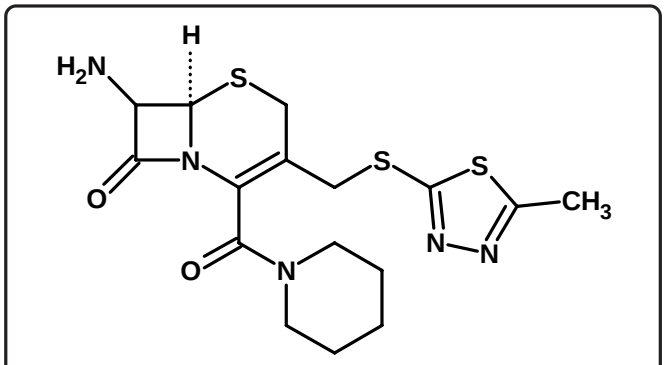
Extensive research has been carried out to enhance the activity and reduce toxicity of thiadiazole drugs. Various thiadiazole derivatives have resulted in many potential drugs and are known to exhibit a broad spectrum of biological activity.

Miller et. al.[389] have discovered 1,3,4-thiadiazole-2-sulphonamides and this compound has been extensively investigated for its effect on salt excretion, eye pressure and as anticonvulsant[390]. R. Gerike[391] have prepared Cefazedone (VII), a thiadiazole analog of cephalosporanic acid, useful as antibacterial agent. Recently Kidwai Mazaahir et. al.[392] have synthesised cephalosporin derivatives

(IIX) by microwave irradiation using solid support and reported them as antimicrobial agents.

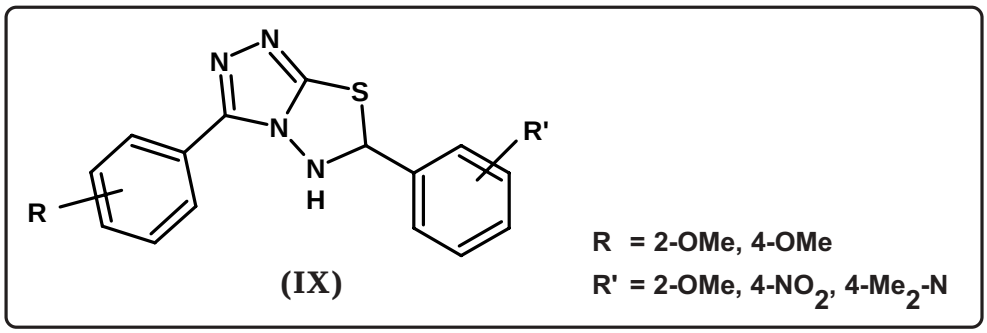


(VII)



(IIX)

Wang Zhong-Yi and co-workers[393] have synthesised some 3,6-diaryl-5,6-dihydro-triazolo [3,4-b]-1,3,4-thiadiazoles (IX) and documented thier *in vivo* antibacterial and antifungal properties.

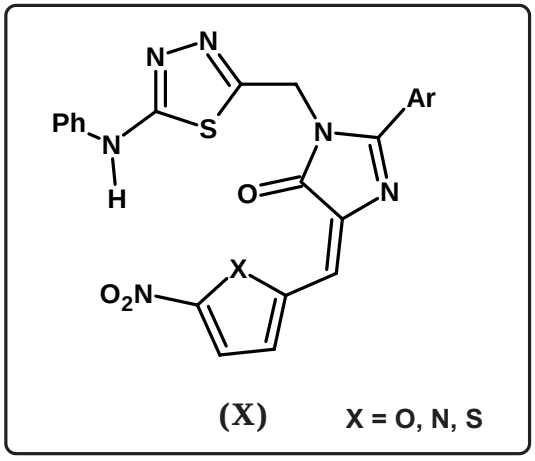


(IX)

The manifold implications of 1,3,4-thiadiazoles are well proved by a large number of patents available on it as therapeutic agents. Thiadiazole derivatives are having numerous pharmacological activities like,

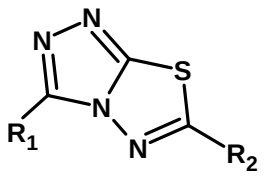
1. Insecticidal[394]
2. Antiviral[395]
3. CNS depressant[396]
4. Antibacterial[397]
5. Antifungal[398,399]
6. Hypoglycemic[400]
7. Antiinflammatory[401,402]
8. Antihypertensive[403,404]
9. Antitumor[405]
10. Antitubercular[406]
11. Antipyretic[407]
12. Anthalmentic[408]

El. Sayed et. al.[409] have reported thiadiazoles (X) as potent fungicides and bactericides.



(X) **X = O, N, S**

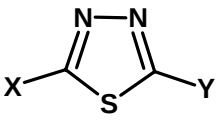
Several co-workers have reported thiadiazole derivatives having fungicidal[410], plant growth regulators[411], insecticidal[412], antibacterial[413] and metalloproteinase inhibitors[414] activity. Karimian et. al.[415] have prepared thiadiazole as inhibitors of cysteine activity dependant enzyme. Zhang et. al.[416] shown antimicrobial activity of thiadiazole derivatives where as Manjunath et. al.[417] reported antimicrobial and antiinflammatory activity (XI).



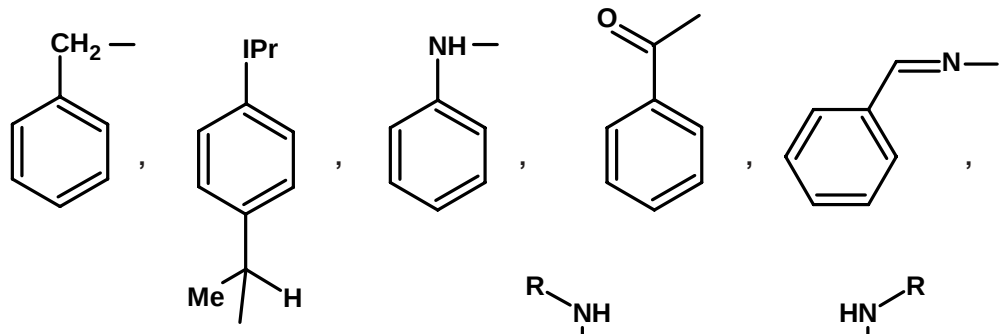
(XI) R_1, R_2 = Aryl

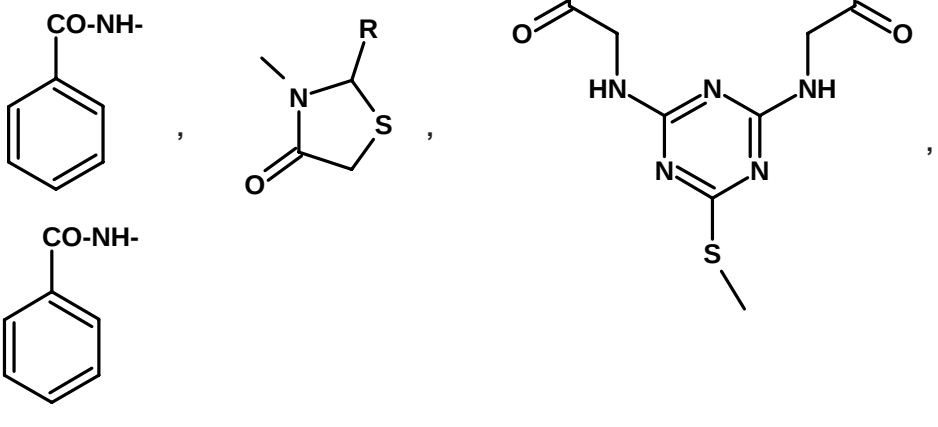
CONTRIBUTION FROM OUR LABORATORY

Parikh et. al. have used substituted thiadiazolinone[418], benzthiazole and s-triazine[419,420], 4-pyridyl[421] moieties at 5-position (Y) in 1,3,4-thiadiazole ring system and at 2-position (X) was substituted aryl, amino and s-triazine[422]. H. H. Parekh et. al. have synthesised 1,3,4-thiadiazole having dapson[423,424], bis moiety at 5-position (Y) and benzalamino, benzoylamino and sulphonamido[425], aryl[426] moiety substituted at 2-position (X). General structure for above references are as under.

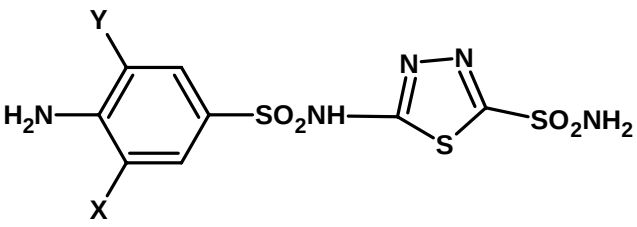


(XII)

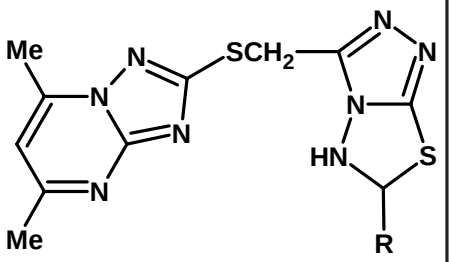
X = 

Y = 

Marc and co-workers[427] have investigated thiadiazoles (XIII) as antitumor agents. Nalan et. al.[428] have prepard some thiadiazoles and reported as anticancer. Some biological active thiadiazoles have synthesied by Pandey V. K. et al.[429]. Ma, Zhong et. al.[430] have screened thiadiazoles (XIV) as fungicides.



(XIII) X, Y = H, F, Cl, Br, I



(XIV) R = Aryl

Many co-workers have reported 1,3,4-thiadiazole derivatives as antitumor[431], nicotinic α_7 receptor[432] and antiinflammatory agents[433].

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.

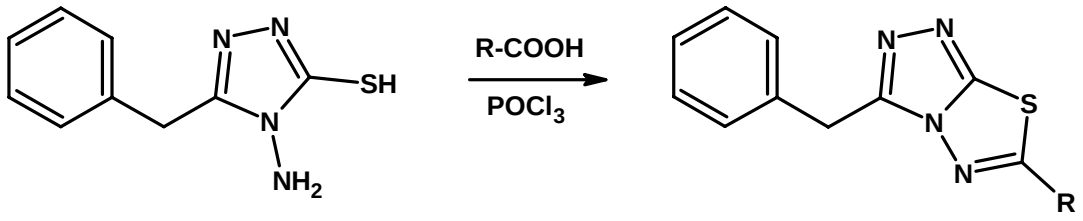
SECTION - I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-BENZYL-1,2,4-TRIAZOLO [4,5-b]-1,3,4-THIADIAZOLES

SECTION - II: SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-BENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [4,5-b]-1,3,4-THIADIAZOLES

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-BENZYL-1,2,4-TRIAZOLO [4,5-b]-1,3,4-THIADIAZOLES

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



Type (XI) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, When i.e. R = ρ-tolyl, molecular weight = 306, m/z = 307 (m+1).

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

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-BENZYL-1,2,4-TRIAZOLO [4,5-b]-1,3,4-THIADIAZOLES

(A) Synthesis of Potassium phenylacetic acid hydrazide dithiocarbamate

Part - I, Section - I(C).

(B) Synthesis of 3-Mercapto-4,N-amino-5-benzyl-1,2,4-triazole

Part - II, Section - I(B).

(C) Synthesis of 2-(ρ-Tolyl)-4-benzyl-1,2,4-triazolo [4,5-b]-1,3,4-thiadiazole

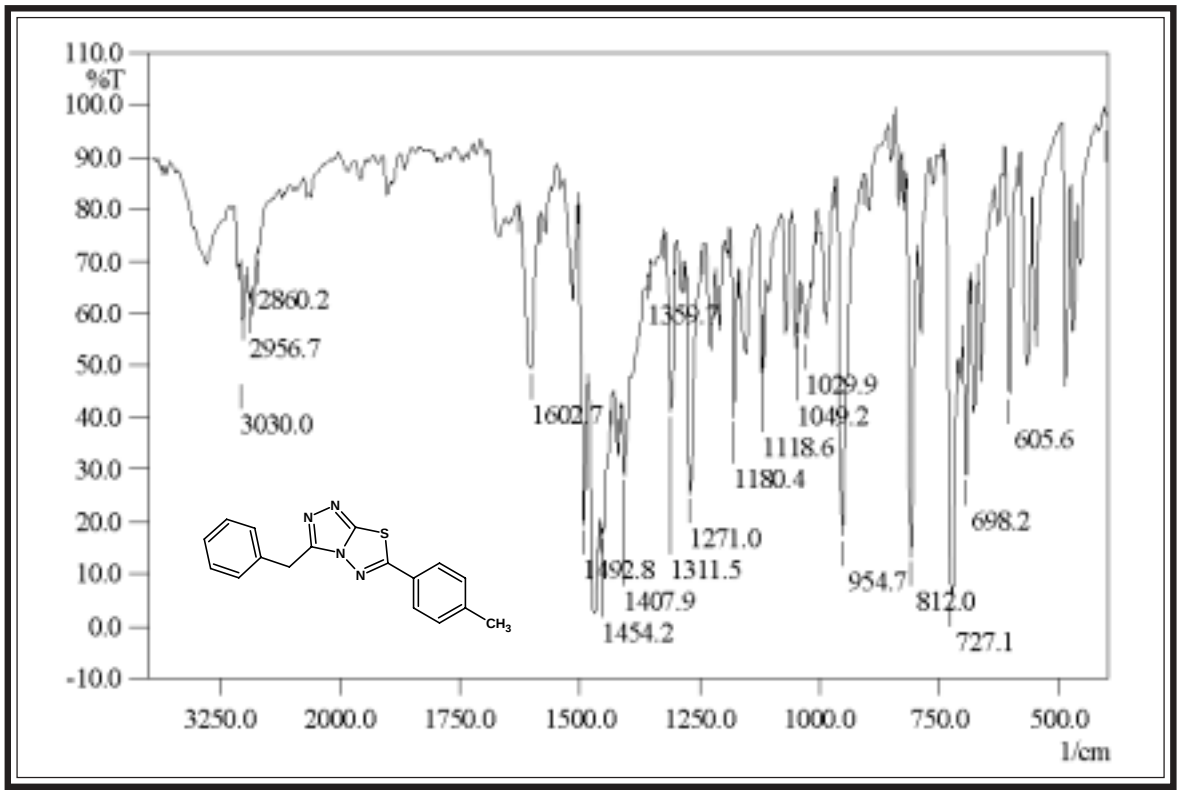
A mixture of 3-mercapto-4,N-amino-5-benzyl-1,2,4-triazole (2.06 g, 0.01 M) and ρ-toluic acid (1.36 g, 0.01 M) in 20 ml phosphorous oxychloride were refluxed for 10 hrs in oilbath. The resulting mixture was poured into ice and neutralised with sodium bicarbonate. The product was isolated and crystallised from ethanol. Yield 65%, m.p. 164^{o}C. (Anal. Found : C, 66.59 H, 4.56; N, 18.26%; $C_{17}H_{14}N_4S$ Requires: C, 66.64; H, 4.61; N, 18.29%).

Similarly other 1,3,4-thiadiazolo-triazole derivatives have been synthesised. The physical data are recorded in Table No. 11

(D) Antimicrobial activity 2-Aryl-4-benzyl-1,2,4-triazolo [4,5-b]-1,3,4-thiadiazoles

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

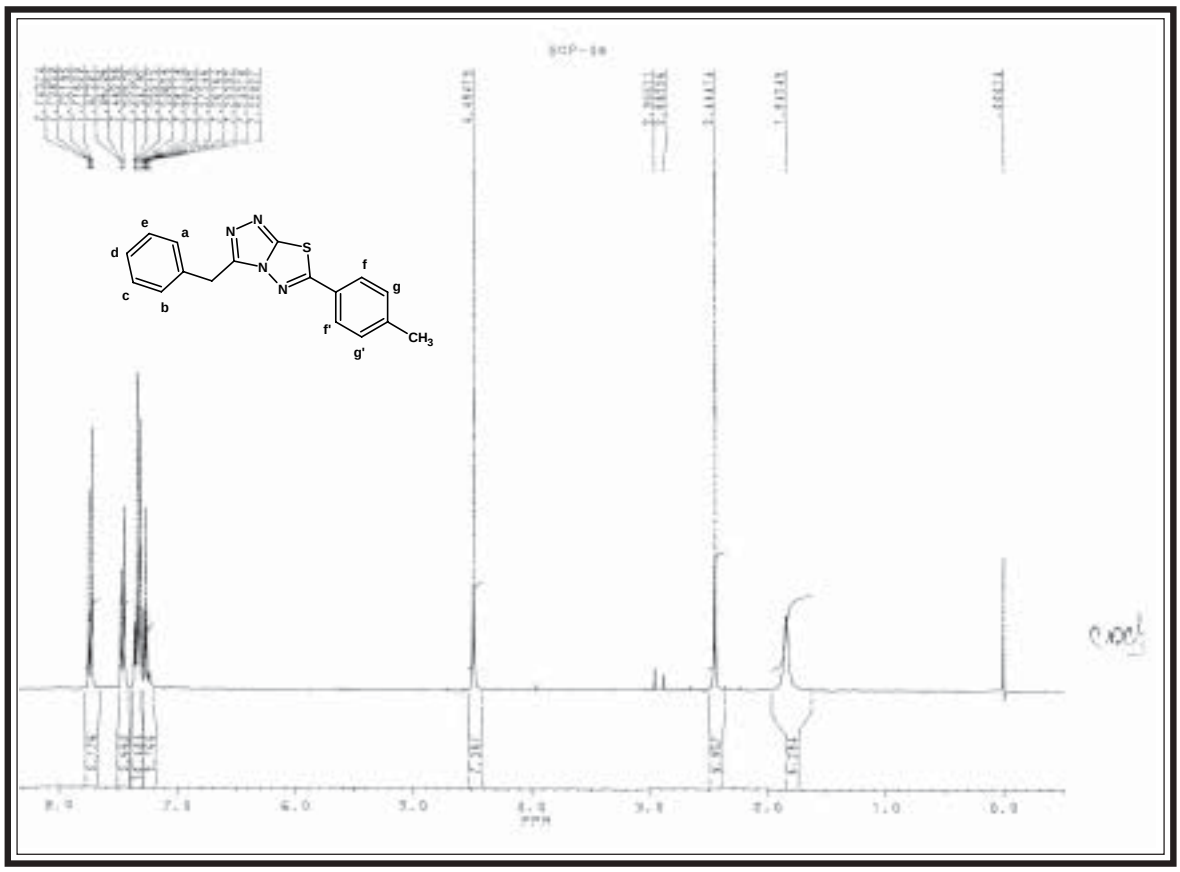
IR SPECTRAL STUDY OF 2-(ρ-TOLYL)-4-BENZYL-1,2,4-TRIAZOLO-[4,5-b]-1,3,4-THIADIAZOLE



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.)	2956.7	2975-2950	434
$-CH_3$	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1454.2	1470-1435	"
	C-H def. (sym.)	1359.7	1385-1350	"
Aromatic	C-H str.	3030.0	3080-3030	435
	C=C str.	1492.8	1585-1480	"
	C-H i.p. def.	1118.6	1125-1090	"
		1029.9	1070-1000	"
	C-H o.o.p. def.	812.0	835-810	"
Triazole	C=N str.	1602.7	1650-1600	434
	C-N str.	1311.5	1350-1200	"
	N-H str.	1029.0 (overlapped)	1050-1010	"
	C-N-C str.	1049.2	1070-1000	"
Thiadiazole	C-S-C str.	605.6	720-570	"

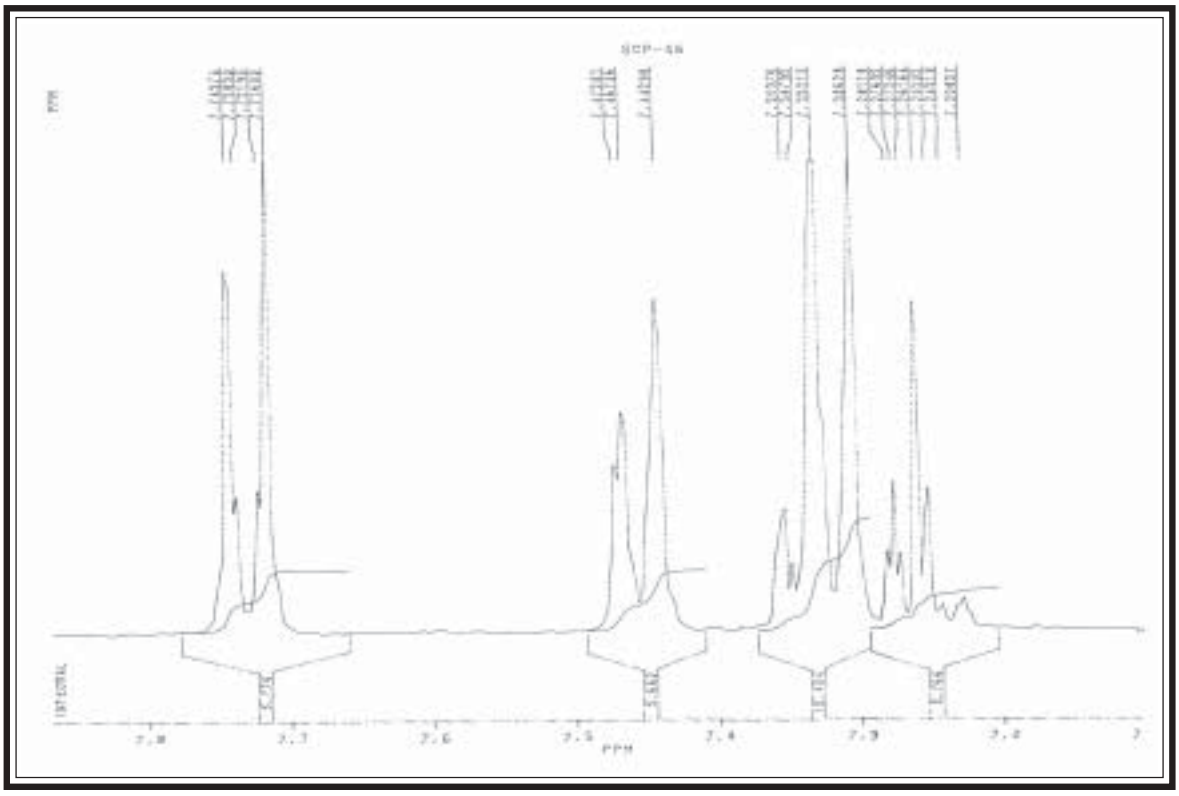
PMR SPECTRAL STUDY OF 2-(ρ-TOLYL)-4-BENZYL-1,2,4-TRIAZOLO-[4,5-b]-1,3,4-THIADIAZOLE

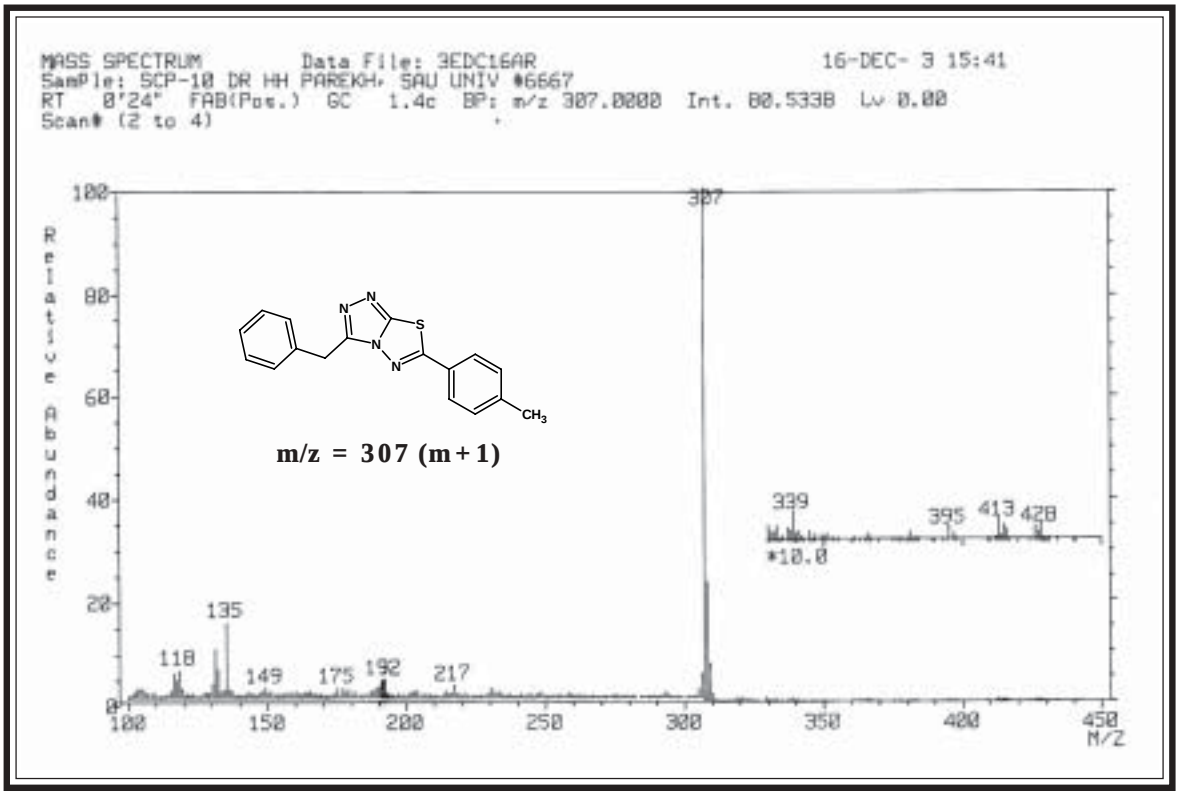


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	J. Value in Hz	Relative No. of Protons	Multiplicity	Inference
1	2.44		3H	singlet	Ar-CH_3
2	4.48		2H	singlet	-CH_2
3	7.27		2H	doublet	Ar-Hc, Ar-He
4	7.30-7.35		3H	multiplet	Ar-Ha, Ar-Hb, Ar-Hd
5	7.45	Jgf = 7.5	2H	doublet	Ar-Hgg'
6	7.73	Jfg = 8.1	2H	doublet	Ar-Hff'

EXPANDED AROMATIC REGION





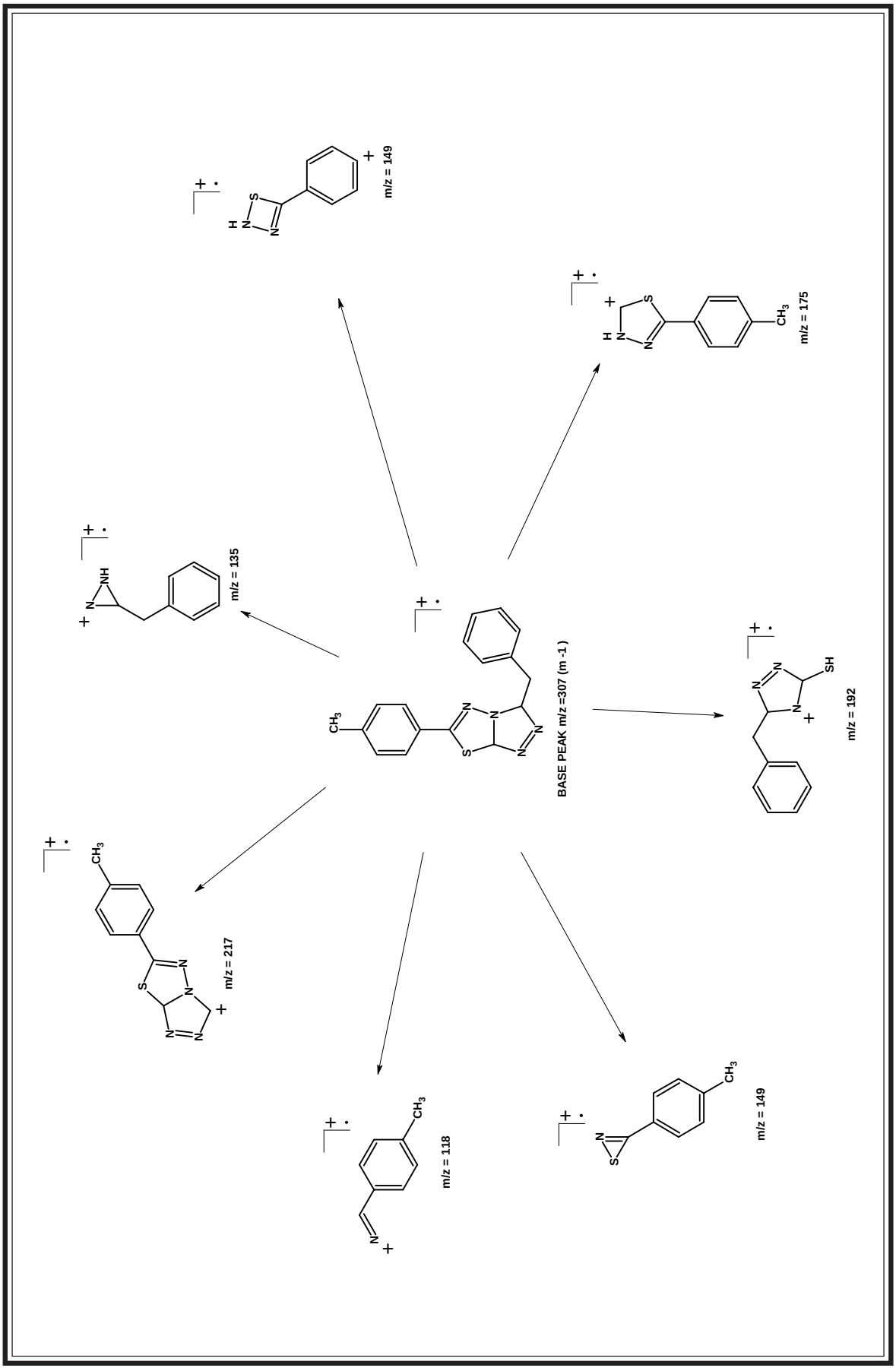

BASE PEAK m/z =307 (m -1)
m/z = 149
m/z = 175
m/z = 135
m/z = 192
m/z = 217
m/z = 118
m/z = 149

TABLE NO. 11 : PHYSICAL CONSTANTS OF 2-ARYL-4-BENZYL-1,2,4-TRIAZOLO (4,5-b)-1,3,4-THIADIAZOLES

Comp. 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	2-0AC-C_6H_5-	$C_{18}H_{14}N_4O_2S$	346	181	0.48	64	15.99	15.92
11b	4-NH_2-C_6H_4-	$C_{16}H_{13}N_5S$	307	170	0.69	72	22.78	22.72
11c	2-NH_2-C_6H_4-	$C_{16}H_{13}N_5S$	307	127	0.65	70	22.78	22.74
11d	-CH=CH-C_6H_5-	$C_{18}H_{14}N_4S$	318	158	0.58	58	17.60	17.56
11e	4-Cl-C_6H_4-	$C_{16}H_{11}N_4SCl$	327	151	0.42	70	17.14	17.11
11f	2-F-C_6H_4-	$C_{16}H_{11}N_4SF$	310	138	0.55	65	17.65	17.59
11g	2-OH-C_6H_4-	$C_{16}H_{12}N_4OS$	308	155	0.61	60	18.17	18.14
11h	4-OCH_3-C_6H_4-	$C_{17}H_{14}N_4OS$	322	166	0.54	54	17.38	17.32
11i	4-CH_3-C_6H_4-	$C_{17}H_{14}N_4S$	306	164	0.50	65	18.29	18.26
11j	2-CH_3-C_6H_4-	$C_{17}H_{14}N_4S$	306	178	0.52	61	18.29	18.23
11k	-CH_2-C_6H_5-	$C_{17}H_{14}N_4S$	306	145	0.58	72	18.29	18.25
11l	-C_5H_4N	$C_{15}H_{11}N_5S$	293	144	0.60	64	23.87	23.84

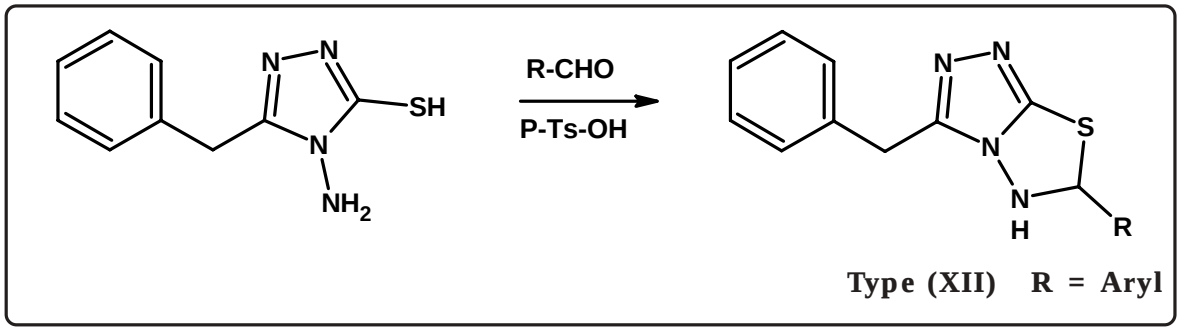
*TLC Solvent System : Ethylacetate : Hexane (2 : 8) (11a-11l)

(3 : 7) (11a,11k)

SECTION - II

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-BENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [4,5-b]-1,3,4-THIADIAZOLES

1,3,4-Thiadiazole derivatives are associated with broad spectrum of pharmacological activity. In view of these findings, it appeared of interest to synthesise newer 1,3,4-thiadiazole derivatives with better potency. 1,3,4-thiadiazoles of type (XII) have been prepared by the condensation of 3-mercapto-4,N-amino-5-benzyl-1,2,4-triazole with different aromatic aldehydes in presence of ρ-toluene sulphonic acid.



Type (XII) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also. In mass spectrometry the m/z value indicate the molecular weight, when i.e. R = 3,4-dimethoxyphenyl, molecular weight = 354, m/z = 355 (m + 1).

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

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL-4-BENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO [4,5-b]-1,3,4-THIADIAZOLES

(A) Synthesis of Potassum phenylacetic acid hydrazide dithiocarbamate

Part - I, Section - I(C).

(B) Synthesis of 3-Mercapto-4,N-amino-5-benzyl-1,2,4-triazole

Part - II, Section - I(B).

(C) Synthesis of 2-(3,4-Dimethoxyphenyl)-4-benzyl-2,3-dihydro-1,2,4-triazolo [4,5-b]-1,3,4-thiadiazole

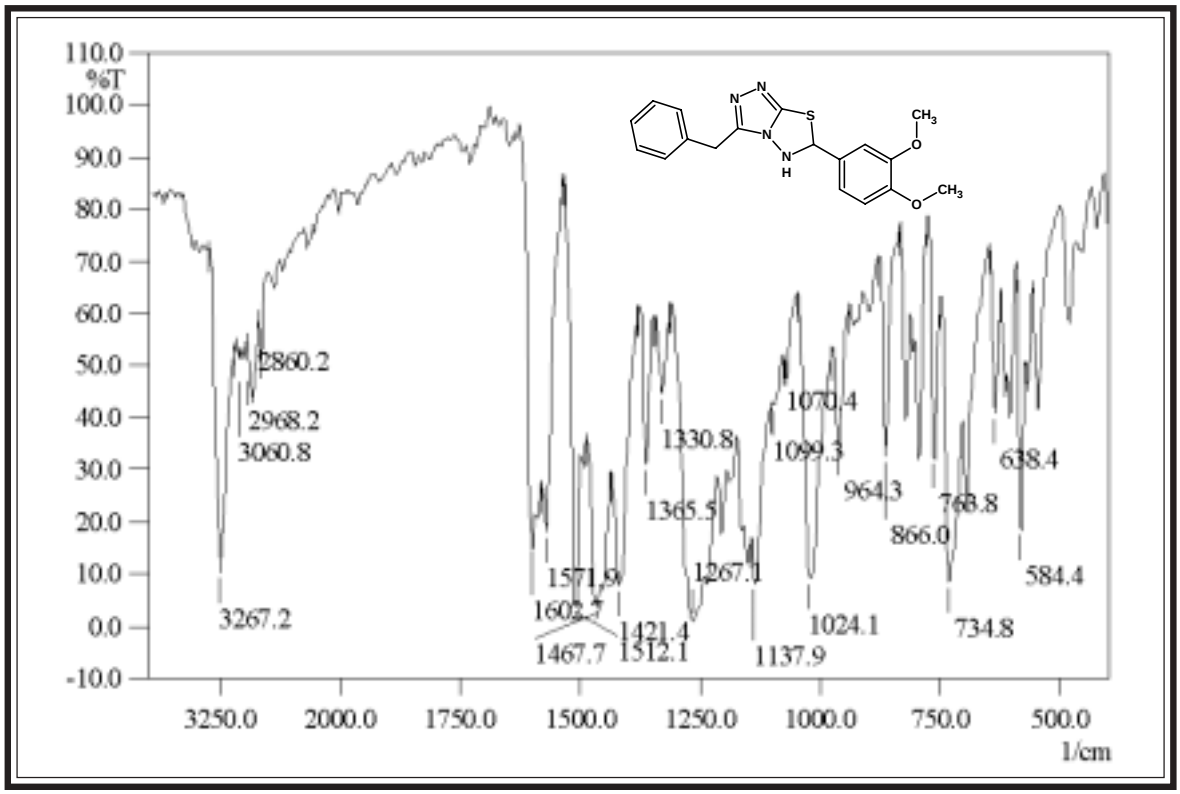
A mixture of 3-mercapto-4,N-amino-5-benzyl-1,2,4-triazole (2.06 g, 0.01 M) and veratraldehyde (1.66 g, 0.01 M) in 20 ml dry DMF and ρ–toluenesulphonic acid (50 mg) were refluxed for 12 hrs. The resulting mixture was poured into ice. The product was isolated and crystallised from ethanol. Yield 74%, m.p. 144°C. (Anal. Found : C, 60.94 H, 5.08; N, 15.78%; $C_{18}H_{18}N_4O_2S$ Requires: C, 61.00; H, 5.12; N, 15.81%).

Similarly other 1,3,4-thiadiazolo triazole derivatives have been synthesised. The physical data are recorded in Table No.12

(D) Antimicrobial activity 2-Aryl-4-benzyl-2,3-dihydro-1,2,4-triazolo [4,5-b]-1,3,4-thiadiazoles

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

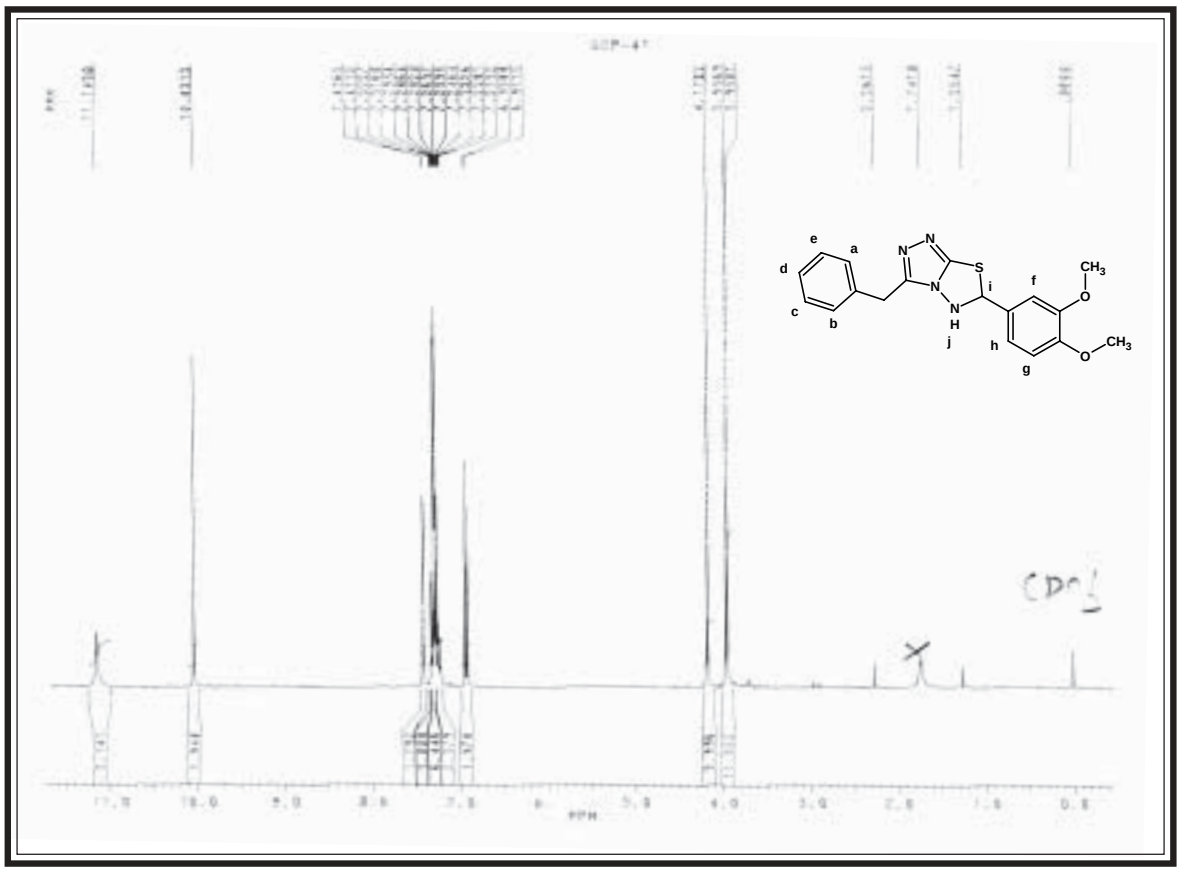
IR SPECTRAL STUDY OF 2-(3,4-DIMETHOXYPHENYL)-4-BENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO-[4,5-b]-1,3,4-THIADIAZOLE



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.)	2968.2	2975-2950	434
$-CH_3$	C-H str. (sym.)	2860.2	2880-2860	"
	C-H def. (asym.)	1467.7	1470-1435	"
	C-H def. (sym.)	1365.5	1385-1350	"
Aromatic	C-H str.	3060.8	3070-3030	435
	C=C str.	1512.1	1585-1480	"
	C-H i.p. def.	1099.3	1125-1090	"
		1070.4	1070-1000	"
Triazole	C=N str.	1602.7	1650-1600	434
	C-N str.	1330.8	1350-1200	"
	N-H str.	1024.1	1050-1010	"
Thiadiazole	C-S-C str.	584.4	720-570	"
	N-H str.	3267.2	3450-3250	"
	N-H def.	1571.9	1650-1580	"

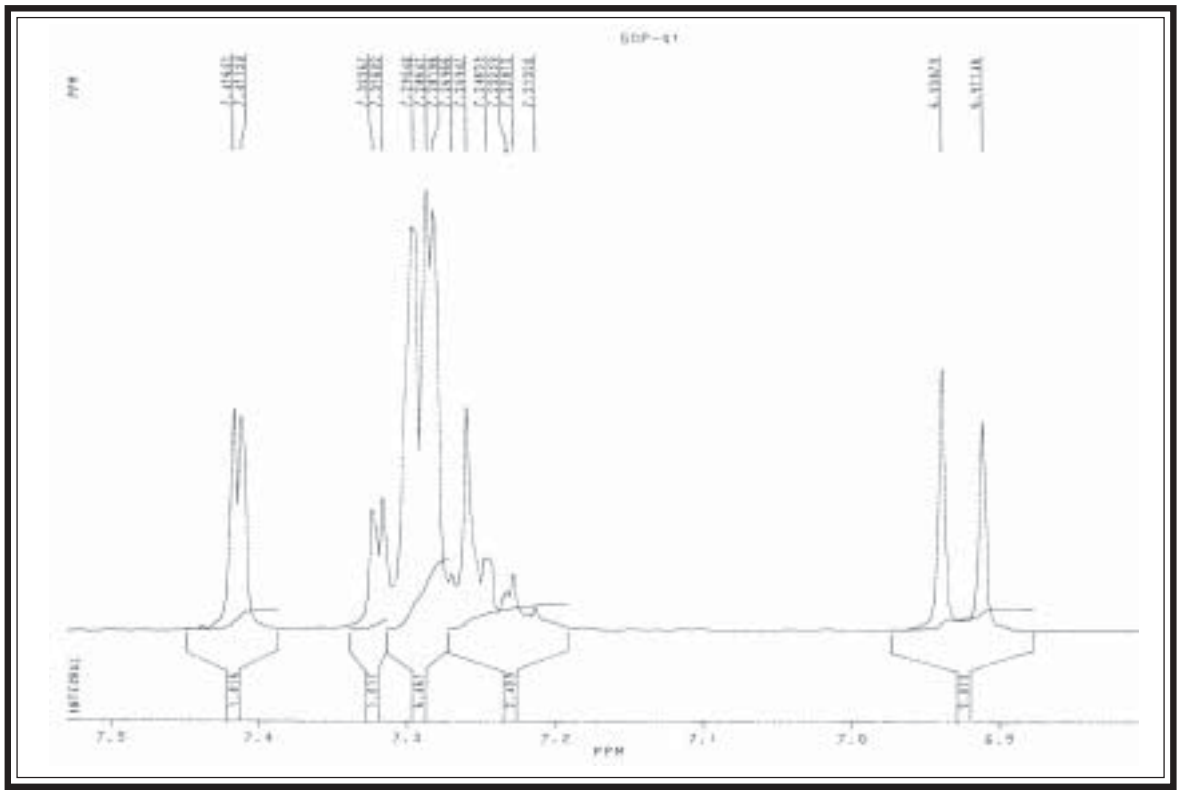
PMR SPECTRAL STUDY OF 2-(3,4-DIMETHOXYPHENYL)-4-BENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO-[4,5-b]-1,3,4-THIADIAZOLE



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	3.95		3H	singlet	Ar-OCH_3
2	3.95		3H	singlet	Ar-OCH_3
3	4.17		2H	singlet	-CH_2
4	6.92	Jgh = 8.1	1H	doublet	Ar-Hg
5	7.25		1H	singlet	Ar-Ha
6	7.28-7.29		4H	multiplet	Ar-Hc, Ar-Hd, Ar-e, Ar-Hh
7	7.31		1H	doublet	Ar-Hb
8	7.41	Jfh = 1.6	1H	doublet	Ar-Hf
9	10.03		1H	singlet	CHi
10	11.14		1H	singlet	CHj

EXPANDED AROMATIC REGION



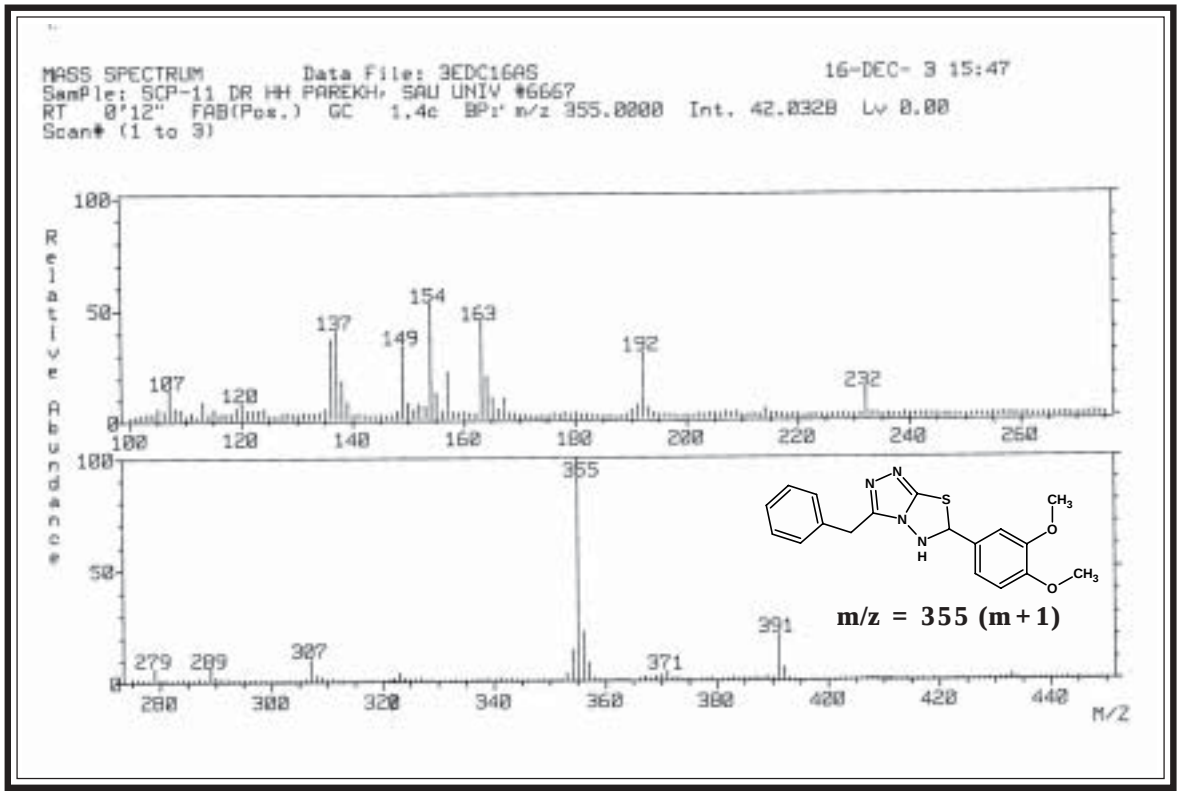


TABLE NO. 12 : PHYSICAL CONSTANTS OF 2-ARYL-4-BENZYL-2,3-DIHYDRO-1,2,4-TRIAZOLO (4,5-b)-1,3,4-THIADIAZOLES

Comp. 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-	$C_{16}H_{14}N_4S$	294	158	0.54	71	19.03	19.00
12b	-CH=CH-C_6H_5-	$C_{18}H_{16}N_4S$	320	132	0.59	73	17.49	17.43
12c	2-Cl-C_6H_4-	$C_{16}H_{13}N_4SCl$	329	128	0.65	65	17.04	17.01
12d	3,4-$(OCH_3)_2$-C_6H_3-	$C_{18}H_{18}N_4O_2S$	354	144	0.71	74	15.81	15.78
12e	4-OH,3-OCH_3-C_6H_3-	$C_{17}H_{16}N_4O_2S$	340	185	0.68	64	16.46	16.42
12f	4-OH-C_6H_4-	$C_{16}H_{16}N_4OS$	310	150	0.50	70	18.05	18.03
12g	3-OH-C_6H_4-	$C_{16}H_{16}N_4OS$	310	164	0.61	61	18.05	18.01
12h	2-OH-C_6H_4-	$C_{16}H_{16}N_4OS$	310	161	0.49	65	18.05	17.99
12i	4-OCH_3-C_6H_4-	$C_{17}H_{16}N_4OS$	324	178	0.62	69	17.27	17.22
12j	2-OCH_3-C_6H_4-	$C_{17}H_{16}N_4OS$	324	165	0.74	64	17.27	17.24
12k	3-NO_2-C_6H_4-	$C_{16}H_{13}N_5O_2S$	339	140	0.69	60	20.64	20.61
12l	2-NO_2-C_6H_4-	$C_{16}H_{13}N_5O_2S$	339	135	0.78	68	20.64	20.59

*TLC Solvent System : Ethylacetate : Hexane (2 : 8) (12a-12l)

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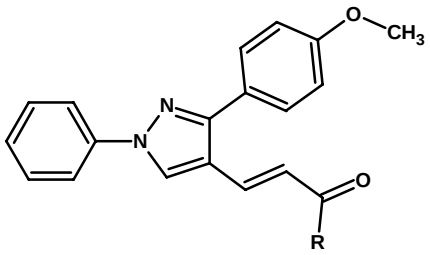
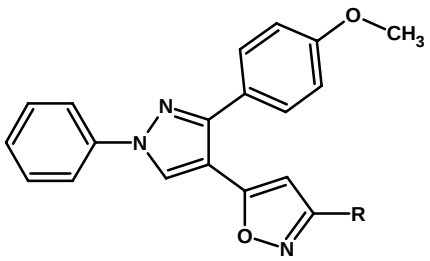
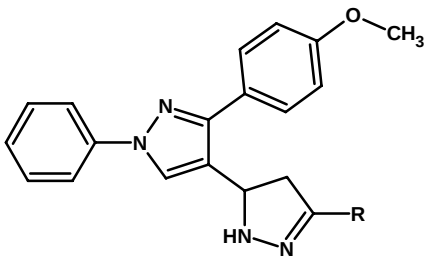
LIST OF NEW COMPOUNDS







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3-NH_2-C_6H_4-	3-NH_2-C_6H_4-	3-NH_2-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-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-
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4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	4-OH-C_6H_4-
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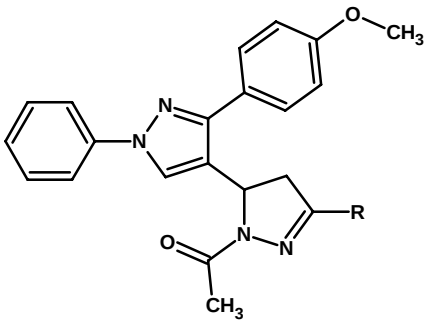

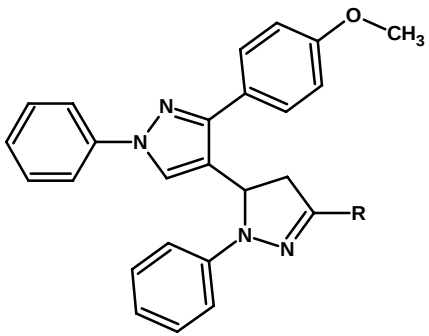

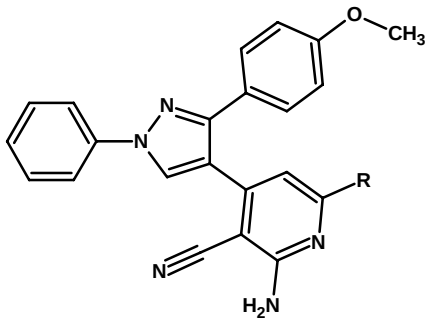

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3-NH_2-C_6H_4-	3-NH_2-C_6H_4-	3-NH_2-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-	4-Br-C_6H_4-
4-Cl-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-OH-C_6H_4-	4-OH-C_6H_4-	4-OH-C_6H_4-
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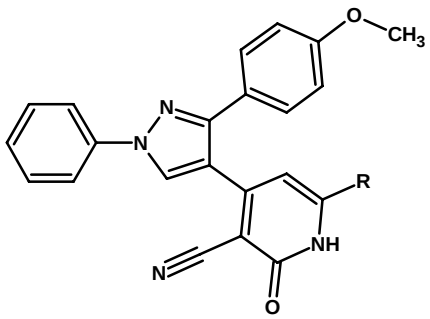

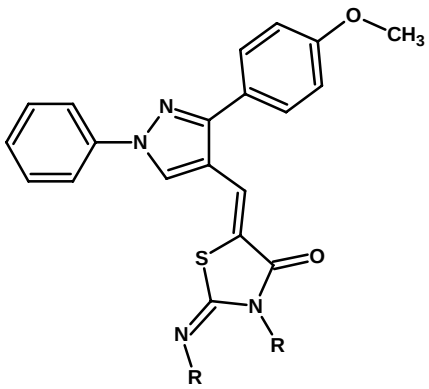

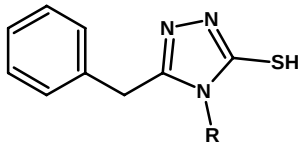

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3-NH_2-C_6H_4-	4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-Br-C_6H_4-	3,4-$(Cl)_2$-C_6H_3-	3,4-$(Cl)_2$-C_6H_3-
4-Cl-C_6H_4-	4-F-C_6H_4-	4-F-C_6H_4-
4-F-C_6H_4-	4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
4-OCH_3-C_6H_4-	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
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3-NO_2-C_6H_4-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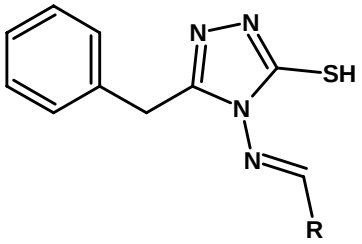

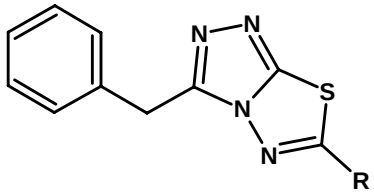

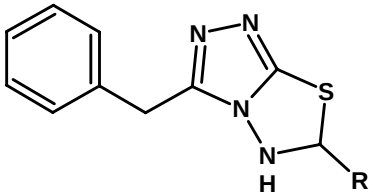

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2-Cl-C_6H_4-	2-NH_2-C_6H_4-	2-Cl-C_6H_4-
3,4-$(OCH_3)_2$-C_6H_3-	-CH=CH-C_6H_5-	3,4-$(OCH_3)_2$-C_6H_3-
4-OH,3-OCH_3-C_6H_3-	4-Cl-C_6H_4-	4-OH,3-OCH_3-C_6H_3-
4-OH-C_6H_4-	2-F-C_6H_4-	4-OH-C_6H_4-
3-OH-C_6H_4-	2-OH-C_6H_4-	3-OH-C_6H_4-
2-OH-C_6H_4-	4-OCH_3-C_6H_4-	2-OH-C_6H_4-
4-OCH_3-C_6H_4-	4-CH_3-C_6H_4-	4-OCH_3-C_6H_4-
2-OCH_3-C_6H_4-	2-CH_3-C_6H_4-	2-OCH_3-C_6H_4-
3-NO_2-C_6H_4-	-CH_2-C_6H_5-	3-NO_2-C_6H_4-
2-NO_2-C_6H_4-	-C_5H_4N	2-NO_2-C_6H_4-