STUDIES ON MEDICINALLY INTERESTING CHEMICAL ENTITIES

A THESIS

SUBMITTED TO THE

SAURASHTRA UNIVERSITY

FOR THE DEGREE OF

Doctor of Philosophy

IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

Dushyant H. Purohit

UNDER THE GUIDANCE

OF

Dr. H. S. Joshi

DEPARTMENT OF CHEMISTRY

SAURASHTRA UNIVERSITY

RAJKOT - 360 005.

INDIA

2006

Gram : UNIVERSITY
Fax : 0281-2577633

Phone : (R) 0281-2584221
(O) 0281- 2578512

SAURASHTRA UNIVERSITY

University Road.
Rajkot - 360 005.

Dr. H. S. Joshi
M.Sc., Ph.D., F.I.C.S.
Associate Professor,
Department of Chemistry

No.

Residence :
B-1 Amidhara Apartment
2- Jalaram Plot,
University Road,
Rajkot - 360 005.
GUJARAT (INDIA)
Dt. 14 -02-2006.

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. S. Joshi*** and leads to some contribution in chemistry subsidized by a number of references.

Dt. : 14 -02-2006
Place : Rajkot.

(Dushyant H. Purohit)

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

Date : 14 -02-2006
Place : Rajkot.

Dr. H. S. Joshi
Associate Professor
Department of Chemistry
Saurashtra University
`Rajkot- 360 005


Dedicated
to
Lord Ganesha
&
My Family

ACKNOWLEDGEMENTS

First and foremost, I wish to pay my homage and devote my emotions to "Lord Ganesha", "The Wonderful Chemist" of this lovely world without whose blessings this task would not have been accomplished. I bow my head in utter humility and complete dedication.

For his faith in me, his encourage, his motivation & inspiration made me to reach these heights, He is one and only Dr. H. S. Joshi, Associate Professor, Department of Chemistry, Saurashtra University, Rajkot. My mentor, my guide reflects with his incredible personality and lightened up my life with indomitable determination. With his blessings, constant motivation and optimistic approach, I have achieved aims and objective of the present work.

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

I wish to thank Dr. R. C. Khunt, for her constant guidance and moral support during the course of my research work. I also wish thank to Dr. Mihir Joshi (Physics Department) for his constant guidance.

Above all, I bow my head with utter respect to my beloved mother Smt. Saralaben for her continuous source of inspiration, motivation and devotion to the family, and my father Shri Hareshbhai for the uncompromising principles that guided my life. Through the stress and strain of this study. I am gratefully appreciate the affection and co-operation extended to me by my sisters Purvi, Vidhatri and Bhavisha. I am thankful to my Jijaji Bhaveshkumar for their moral support during the course of my research work. I am thankful to my niece Rajvi, whose unstopping flow of love helped me to reach the goal. My thanks are also due to kind and affectionate inspiration

and amiability from my grandfather Shri Hematlal and grand mother Smt. Samrathben.

Above all, needless to say "Thanks" to express my deep indebtedness to my seniors Dr. Tapan, Dr. Dipen, Dr. Ashok, Dr. Siddharth, Dr. Paresh, Dr. Dinesh, Dr. Praful and all my Seniors who ever stood beside me with their helping hands and moral support.

I feel lucky and very proud to have intimate friends like Mayur, Pankaj, Mahesh, Jignesh, Manoj, Niral, Bhavin, Shukla, Sunil, Rupesh, Bharat Parekh, Kaushik, Shashi and Manish Maheta who have been always participating with my problems & disappointments and rebuilt my confidence at an appropriate stages. I cherish the affection and help rendered by my friends like Khushi, Chandni and Leena who had given her kind support during the course of my research work.

I am thankful to Mr. Harshad Joshi and Mrs. Namrata for their kind support and providing chemicals and glasswares on time. I am thankful to Mr. Murad Ganja and Mr. Rajendra Chavada to magnifying the presentation of my work in the form of thesis.

I Gratefully acknowledge the most willing help and co-operation for providing facilities for spectral studies by CIL, Chandigarh and Tuberculosis Antimicrobial Acquisition Co-ordinating Facility, Alabama, U. S. A. for kind co-operation extended by them for antitubercular activity and Department of Chemistry, Saurashtra University, Rajkot for providing facilities for Mass and IR spectral studies.

I am beholden to entire Chemistry farternity for their ungruding co-operation and I am also thankful to the Saurashtra University for providing me research facilities.

Dushyant H. Purohit

CONTENTS

SYNOPSIS

A comprehensive summary of the work to be incorporarated in the thesis entitled **"STUDIES ON MEDICINALLY INTERESTING CHEMICAL ENTITIES"** included investigation pertaining to 1,2,4-triazole and phenylamino derivatives, which have been described as under.

[A] STUDIES ON TRIAZOLE DERIVATIVES

[B] STUDIES ON PHENYLAMINO DERIVATIVES

[A] STUDIES ON TRIAZOLE DERIVATIVES

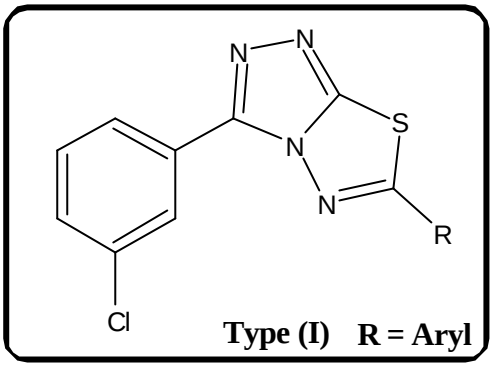
1,2,4-Ttiazole and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities. The synthesis of these heterocycles has received considerable attention in recent years. Five membered ring bearing three nitrogen atoms is known as triazole. The chemistry of 1,2,4-triazole has assumed importance because of their versatility in the synthesis of many heterocyclic compounds.

With a view to supplement of these valid observations and to evaluate its pharmacological profiles, it was thought worthwhile to synthesized some new heterocycles bearing 1,2,4-triazole nucleus, which have been described as under.

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

The synthesis of compounds incorporating 1,3,4-thiadiazole rings has been attracted widespread attention due to their diverse pharmacological properties like antibiotic, antifungal, herbicidal, antitubercular, etc. To approach this goal synthesis of some 1,3,4-thiadiazole have been undertaken, which have been described as under.

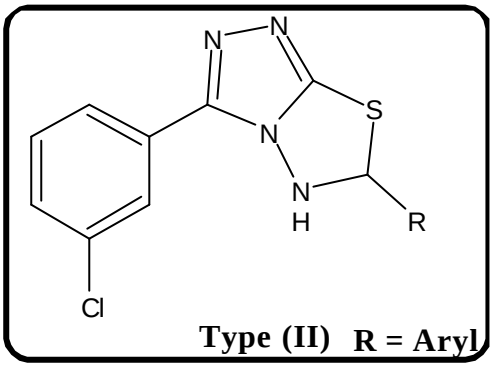
SECTION-I : Synthesis and biological evaluation of 3-(m-chlorophenyl)-6-aryl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles



Type (I) R = Aryl

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

SECTION-II : Synthesis and biological evaluation of 3-(m-chlorophenyl)-6-aryl-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles



Type (II) R = Aryl

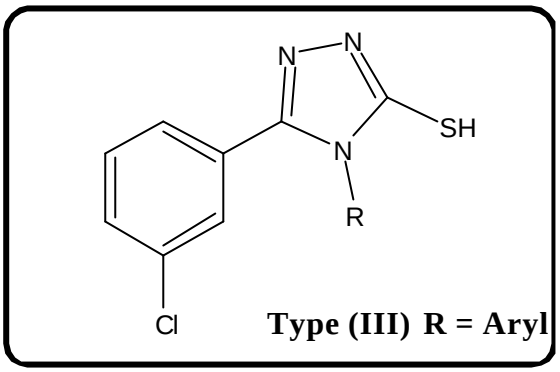
1,3,4-Thiadiazole derivatives of Type(II) have been synthesized by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic aldehydes in the presence of p-toluenesulphonic acid.

PART-II : STUDIES ON 4-ARYLTRIAZOLE DERIVATIVES

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

some new 1,2,4-triazole derivatives have been synthesized described as under.

SECTION-I : Synthesis and biological evaluation of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols



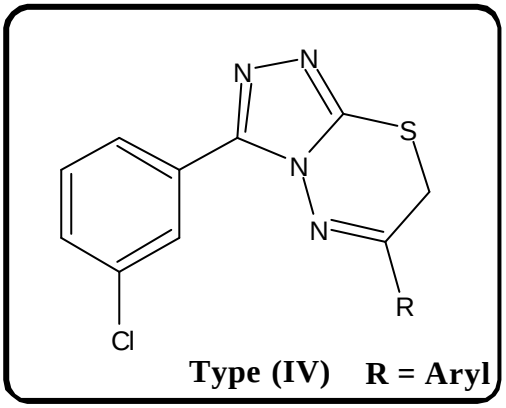
Type (III) R = Aryl

4-Aryltriazole derivatives of Type(III) have been synthesized by reaction of potassium-m-chlorobenzyl dithiocarbamate with different aromatic amines.

PART-III : STUDIES ON THIADIAZINES

Literature survey reveals that various 1,3,4-thiadiazines have resulted in many potential drugs and known to exhibit a broad spectrum of biological activities such as antibacterial, cardiovascular, antifungal, antitubercular, etc. Hence it was considered worthwhile to synthesized 1,3,4-thiadiazine derivatives for better drug potential, which have been described as under.

SECTION-I : Synthesis and biological evaluation of 3-(m-chlorophenyl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines



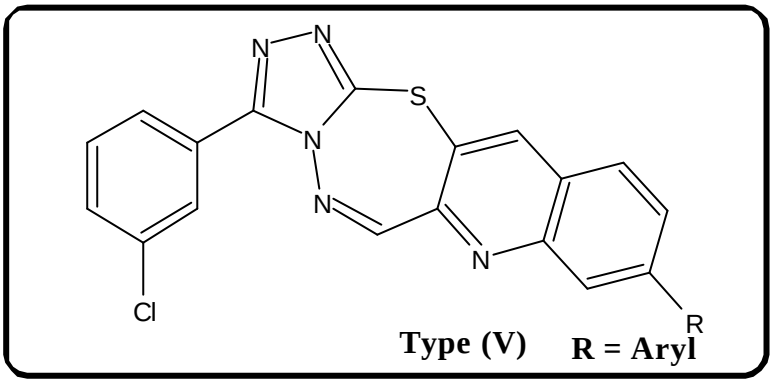
Type (IV) R = Aryl

Thiadiazines of Type (IV) have been synthesized by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different substituted phenacyl bromides.

PART-IV : STUDIES ON THIADIAZEPINES

Seven membered rings containing sulfur and two nitrogen atoms exhibit wide spectrum of biological activities such as anticancer, antibacterial, anti HIV, and antitubercular. In order to develop compounds with better drug potential, it was considered of interest to synthesize some new thiadiazepines, which have been described as under.

SECTION-I : Synthesis and biological evaluation of 3-(m-chlorophenyl)-9-alkyl[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[6,7-*b*]quinolines



Type (V) R = Aryl

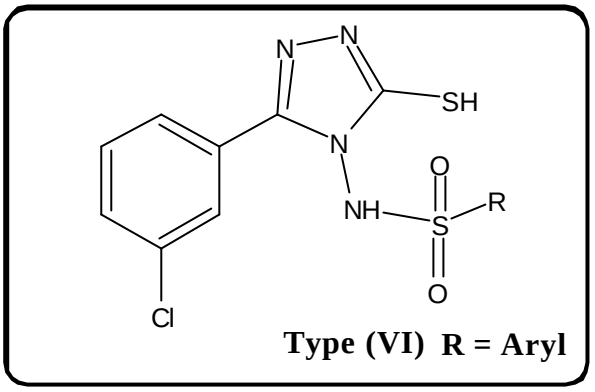
The compounds of Type (V) have been prepared by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with substituted 2-chloro-3-formylquinolines, which have been prepared by Wielsmayerhacck rearrangement.

PART-V : STUDIES ON SULPHONAMIDES

Sulphonamide derivatives have been reported to be associated with diverse biological activities such as herbicidal, antihypertensive, anticonvulsant, antiviral, antimalarial, anticancer and antimicrobial. With a view to getting better therapeutic

agent and to evaluate its pharmacological profile, different type of sulphonamides have been prepared, which have been described as under.

SECTION-I : Synthesis and biological evaluation of [3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl]arylsulfonamides



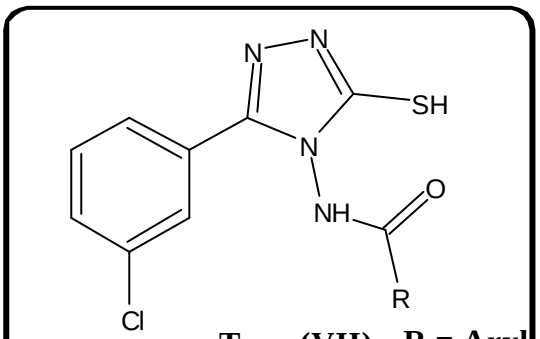
Type (VI) R = Aryl

Sulphonamide derivatives of Type (VI) have been synthesized by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different carboxyaryl sulphonyl chloride.

PART-VI : STUDIES ON ARYL AMIDES

Substituted aryl amide shows different biological activities like antipyretic, analgesic, antiseptic, antimoebic etc. To attempt to develop a potentially bioactive agents synthesis of some new aryl amides have been undertaken, which have been described as under.

SECTION-I : Synthesis and biological evaluation of [3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl]arylamides



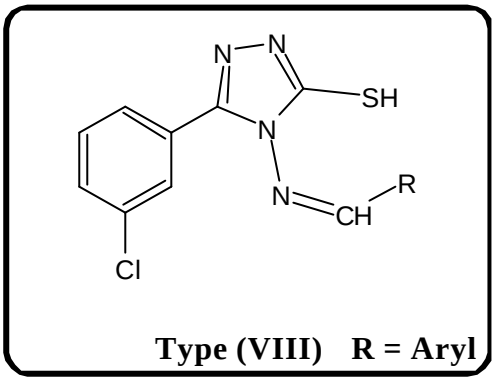
Type (VII) R = Aryl

Arylamide derivatives of type (VII) have been synthesized by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic acid chlorides.

PART-VII : STUDIES ON MANNICH BASES

Mannich bases containing bridged N-atom exhibit pronounced biological activities. They possess diverse pharmacological action like antibacterial, antimalarial and analgesic. Hence it is pertinent to synthesize some novel mannich bases, which have been described as under.

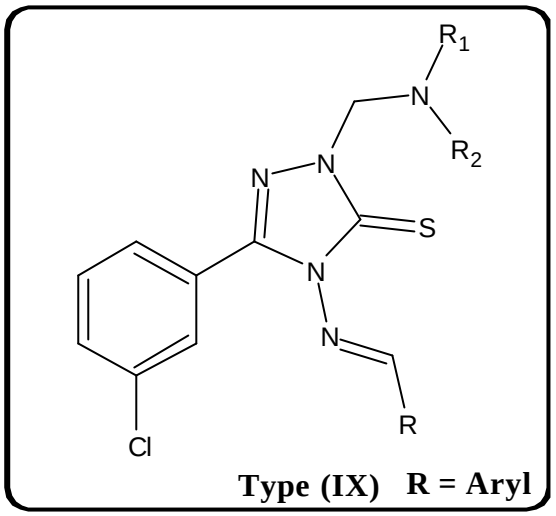
SECTION-I : Synthesis and biological evaluation of 5-(m-chlorophenyl)-4-{[(1*E*)-(4-aryl)methylene]amino}-4*H*-1,2,4-triazole-3-thiols



Type (VIII) R = Aryl

The synthesis of schiff's bases (VIII) have been undertaken by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic aldehyde in the presence of sulphuric acid.

SECTION-II : Synthesis and biological evaluation of 5-(m-chlorophenyl)-2-{[(4-substituted)amino]methyl}-4-{[(1-*E*)-(4-aryl)methylene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones



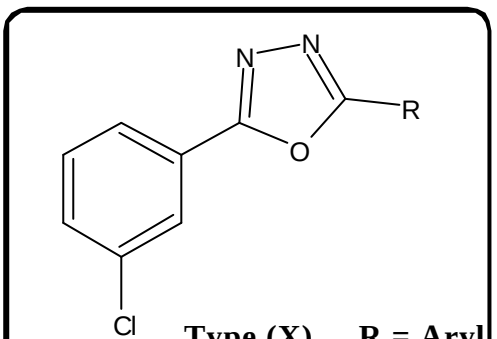
Type (IX) R = Aryl

Mannich bases of type (IX) have been synthesized by the condensation of Schiff bases of type (VIII) with different secondary amines and formaldehyde.

PART-VIII : STUDIES ON OXADIAZOLES

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

SECTION-I : Synthesis and biological evaluation of 2-(m-chlorophenyl)-5-aryl-1,3,4-oxadiazoles



Type (X) R = Aryl

Oxadiazoles of type (X) have been synthesized by the cyclo condensation of m-chlorobenzohydrazide with different aromatic acids in the presence of $POCl_3$.

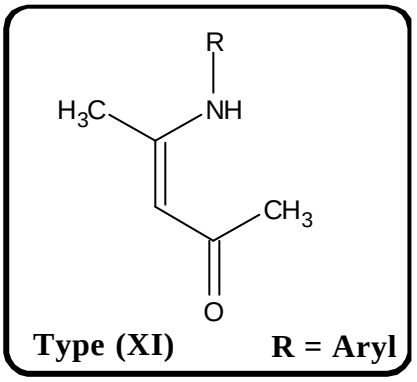
[B] STUDIES ON PHENYLAMINO DERIVATIVES

The 4-phenylamino derivatives are important class of organic compounds with diverse range of biological activities. Many examples of biologically active molecules are known which possessing 4-phenylamno nucleus.

In order to develop better medicinally interesting compounds, it was considered of interest to synthesize some new 4-phenyhlamino derivatives as described under.

SECTION-I : Synthesis and biological evaluation of 4-(aryl amino) pent-3-en-2-ones

Phenylamino derivatives represents one of the modest class of compounds possessing wide range of therapeutic activities such as antibiotic, antifungal, herbicidal, insecticidal, antitubercular etc. To approach this goal synthesis of some phenylamino derivatives have been undertaken, which described as under.



Type (XI) **R = Aryl**

Phenylamino derivatives of type (XI) have been synthesized by the condensation of acetyl acetone with different aromatic amines in the presence of pyridine.

SECTION-II : X-ray crystallographic study of 4-(2-hydroxy phenylamino)pent-3-en-2-one

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

Single crystal of 4-(2-hydroxy phenylamino)pent-3-en-2-one were grown by slow evaporation technique at constant temperature using methanol as a solvent. Good quality single crystals were harvested within 45days. The crystals are exhibiting photo conducting nature.

In vitro study on multiple biological activities:

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

Some of the selected compounds have been sent to Tuberculosis Antimicrobial Acqistion Coordinating Facility (TAACF) Alabama, USA, for antimicrobial data of synthesized compound. The compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 µg/ml using Rifampin as a standard drug.

STUDIES ON MEDICINALLY INTERESTING CHEMICAL ENTITIES

INTRODUCTION

The starting point for every medicinal chemistry project is a lead compound with a given pharmaceutical activity. However, the biological activity of a molecule must be complemented by other properties that make the molecule a good drug. It is estimated that a large proportion of molecules fails in late stage of drug development due to drug-drug interaction or poor ADME (adsorption, distribution, metabolism and excretion) features. Not detecting these liabilities early in the drug discovery process can be extremely costly and time consuming. The aim of medicinal chemistry has shifted from activity to selectivity. The more selective a compound is for a particular target the more effective it is likely to be and the fewer the side effects it will have. Medicinal chemistry concerns the discovery, the development and the identification of action of biologically active compound at the molecular level. Emphasis is put on drugs, but the interest of the medicinal chemistry is also concerned with the study, identification and synthesis of metabolic products of drugs and related compounds.

Drugs are chemicals of low molecular weight (~ 100-500) which interact with macromolecular targets to produce a biological response. The biological response may be therapeutically useful in the case of medicines or harmful in the case of poisons. Most drugs used in medicine are potential poisons if taken in higher doses than recommended.

Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity. The majority of synthetic heterocyclic compounds have found widespread use, for example as anticancer agents, antitubercular, analeptics, analgesic, hypnotics and as pesticides, insecticides and weed killers. Various synthetic procedures have been developed and considerable diversity in the ring is achieved. Heterocyclic compounds are enormous, their chemistry is complex and synthesizing them requires great skill.

Modern medicinal chemistry began in the 1950s when organic chemists began to apply newly developed steric and electronic structure active relationship of the steroids.

During the second half of the twentieth century, chemistry and biology made possible the discovery of a steady stream of important new medicines. Chemistry contributed these discoveries through impactful advantages in both theory and practice of this art/ science. Notable examples include in valuable advances in physical measurements, computational techniques, inorganic catalysis, stereochemical control of synthesis and the application of physical organic chemical concepts, typified by the transition state analog principle, to enzyme inhibitor design. At the same time biology continued to contribute through the discoveries at a rate that may well be termed explosive.

The interesting medicinal activities of heterocyclic compounds have stimulated considerable research work in recent years leading to the synthetic utility. Taking in a view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing triazole nucleus. The placement of a wide variety of substituents of these nuclei have been designed in order to evaluate the synthesized products for their pharmacological profile against several strains of bacteria and fungi.

AIMS AND OBJECTIVES

In the medicinal field, there has always been and will continue to be a need for new and novel chemical inhibition of biological fraction. Our efforts are focused on the molecular frame work in order to synthesizing medicinally interesting compounds of widely different composition.

During the course of research work, looking to the applications of the heterocyclic compounds, several entities have been designed, generated and characterized using spectral studies.

1. To generate several derivatives like thiadiazoles,thiadiazines, thiadiazepines, aryltriazoles, sulphonamides, arylamides bearing 1,2,4-triazole as a basic moiety.

2. To synthesize phenylamino derivatives and characterized by X-ray crystallography of that compounds.

3. To characterize these all products for structure elucidation using spectroscopic techniques like IR, NMR and Mass spectral studies.

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

5. To evaluate these new products for better drug potential against different strains of bacteria and fungi.

6. Selected compounds have been sent to " Tuberculosis Antimicrobial Acquisition and Co-ordinating Facility" (TAACF), Southern Research institute, U.S.A. for their in *vitro* antitubercular screening.

STUDIES ON

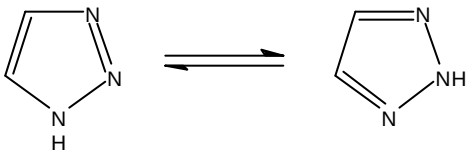
1,2,4-TRIAZOLES

INTRODUCTION

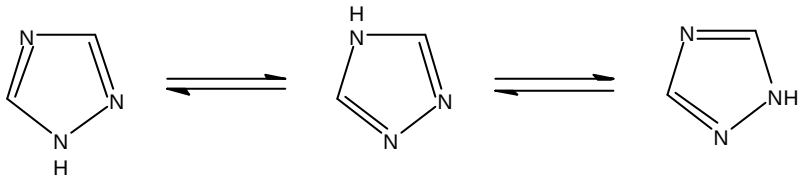
Triazoles are well known five membered heterocyclic compounds and several procedures for their synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of nitrogen containing heterocyclic entities. In fact, certain nitrogen containing heterocycles are used as pharmaceuticals e.g. analgesic, anti-inflammatory, antipyretic, agrochemicals where as some other is being studied for their medicinal interest.

The knowledge of such applications has pointed out that nitrogen containing heterocycles are important target to be prepared to our research on medicinally interesting chemical entities.

Triazoles have occupied an important place in the drug industry. Triazoles are of two types 1,2,3-triazole (I) and 1,2,4-triazole (II).



?-Triazole or 1,2,3-Triazole (I)



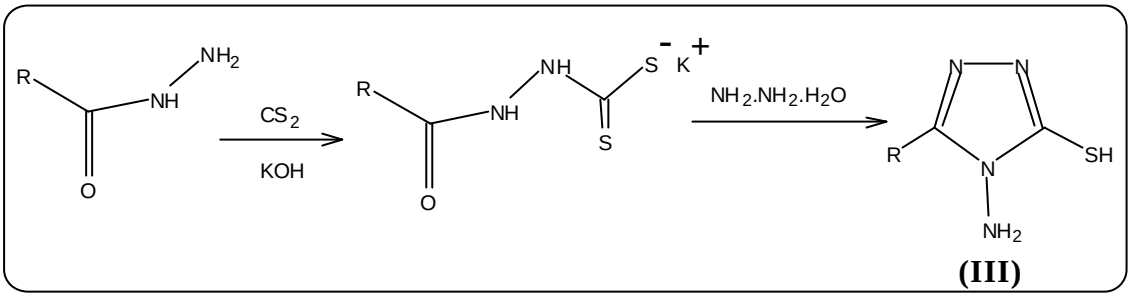
s-Triazole or 1,2,4-Triazole (II)

Hoggarth[1] and Meyer[2] have been studied briefly with the chemistry of 1,2,4-triazoles. Bladin[3,4] is a pioneer scientist in the field of triazole, who had synthesized the first derivative of 1,2,4-triazole in 1885. 1,2,4-triazole derivatives not only known for their medicinal applications, but they are also used as analytical reagents[5], dyes and photographic chemicals[6], corrosion inhibitors[7,8] and in the preparation of polymers[9].

SYNTHETIC ASPECT

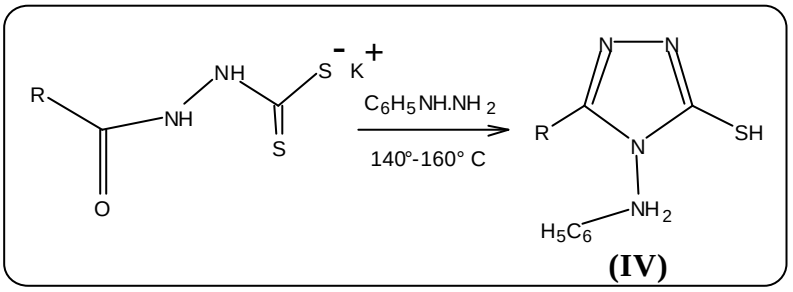
Several methods have been reported in the literature for the synthesis of 1,2,4-triazoles. The starting material for the synthesis of triazoles is thiosemicarbazide or dithiocarbamate derivatives having nitrogen containing functions. The procedures for synthesizing 1,2,4-triazoles have been described as under.

1. Reid and heindel[10] reported that the reaction of aryl acid hydrazide with CS_2/ KOH and hydrazine hydrate yields triazoles.



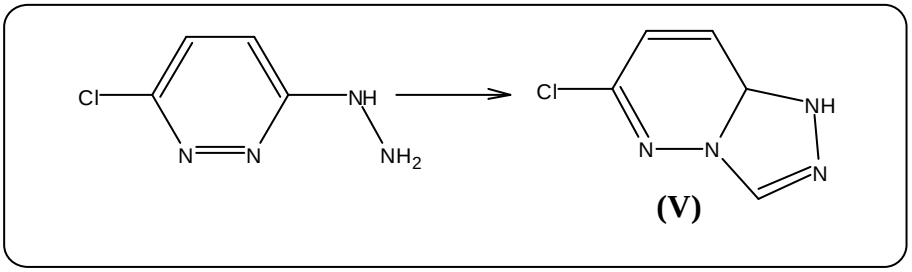
(III)

2. Chande et al.[11] have synthesized 4-amino 5-mercapto-s-triazoles from a *a*-acyldithio carbazinate and phenyl hydrazine at 140-160°C.



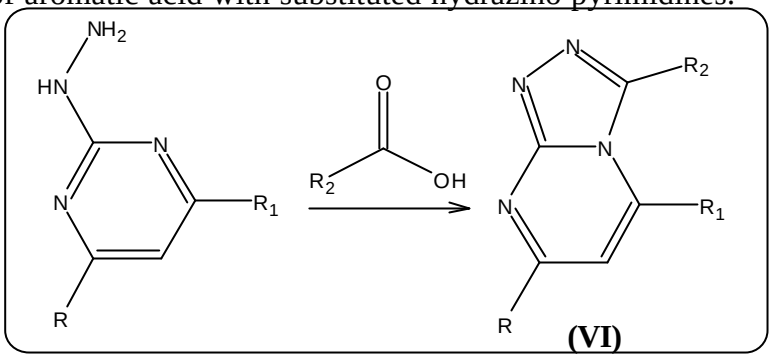
(IV)

3. Ivanka Kolenc et al.[12] synthesized 6-chloro-1,2,4-triazolo [4,3-b] pyridazin from 3-chloro-6-hydrazino pyridazin in the presence of bis-o-(diehoxymethyl) dimethyl glyoxime.



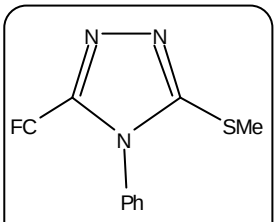
(V)

4. C. S. Andotra and Sukhbinder Kaur[13] synthesized triazole pyrimidine by the reaction of aromatic acid with substituted hydrazino pyrimidines.



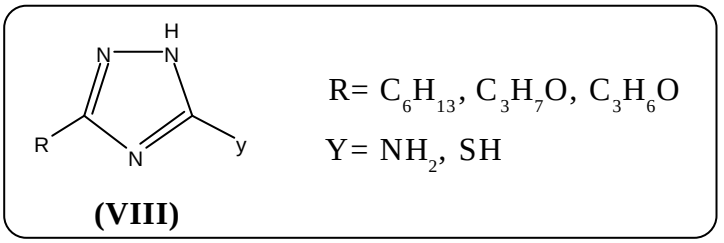
(VI)

5. Yan Shiquaing[14] reported 3,4-disubstituted-4H-1,2,4-triazole-5-thiol (VI) from the reaction of ferrocenecarboxylic acid hydrazide with aryl isothiocyanate.



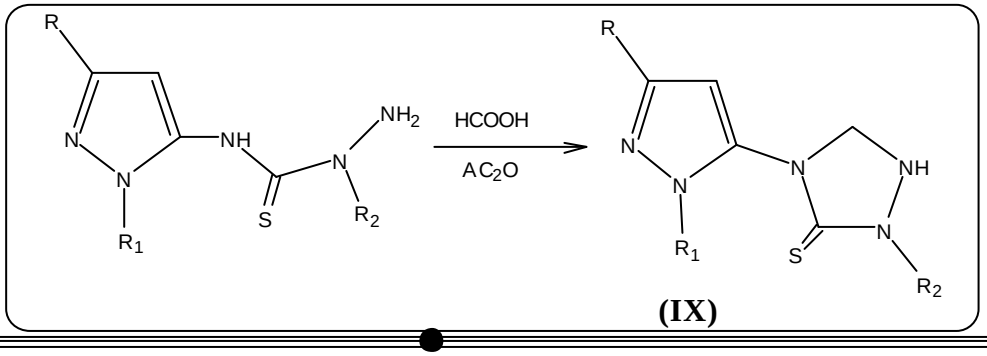
(VII)

6. Ver shilov and coworkers[15] have synthesized 3-perfluoro substituted 1,2,4-triazolyl-5-amines and 5-thiols by the reaction of RCOF with NH_2-NH-CX-NH_2 (X=NH,S) to give $RCONHNHCXNH_2$ followed by intramolecular cyclization.



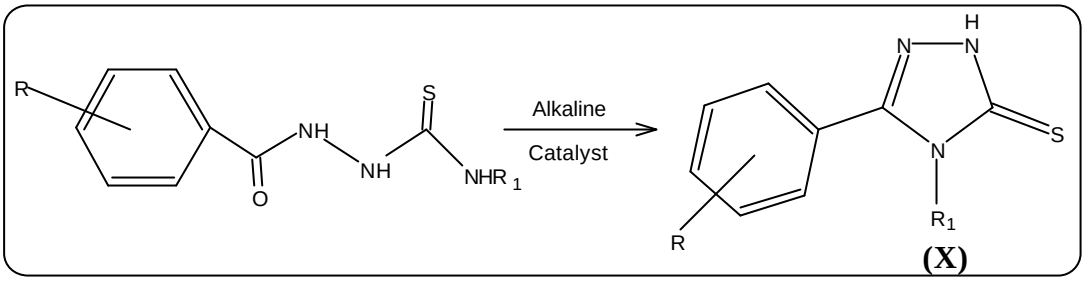
(VIII)

7. Triazole nucleus can be also synthesized by the reaction of thiosemi carbazide with formic acid in the presence of acetic anhydride[16].



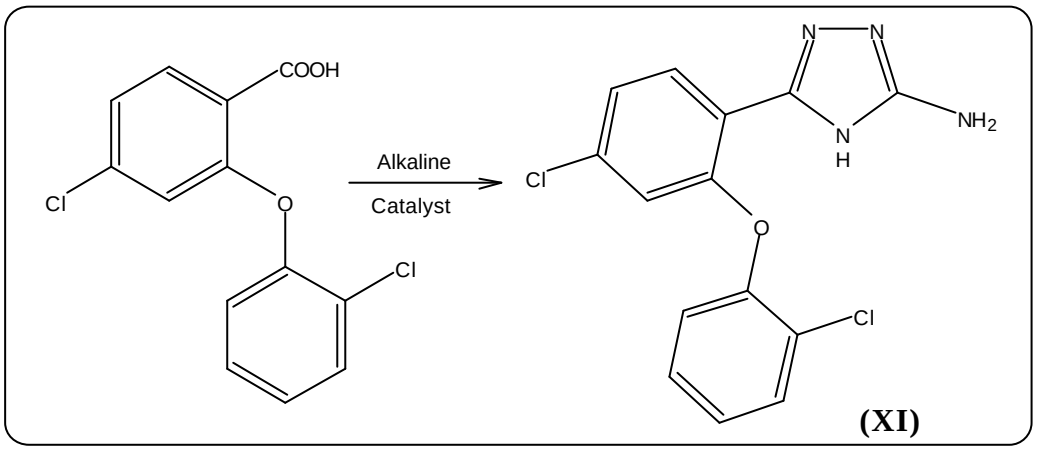
(IX)

8. L.Labanauskas et al.[17] have prepared triazoles by the addition reaction of thiosemicarbazide with substituted benzoyl chloride in the presence of pyridine. Then the substituted thiosemicarbazide cyclised in water in the presence of alkaline catalyst.



(X)

9. Abbas Shafiee et al.[18] have prepared 3-amino-5-[4-chloro -2-(2-chlorophenoxy) phenyl]-4H-1,2,4-triazole from 4-chloro -2-(2-chlorophenoxy) benzoic acid by reaction with $SOCl_2$ and amino guanidine hydrogen carbonate in the presence of alkaline catalyst.

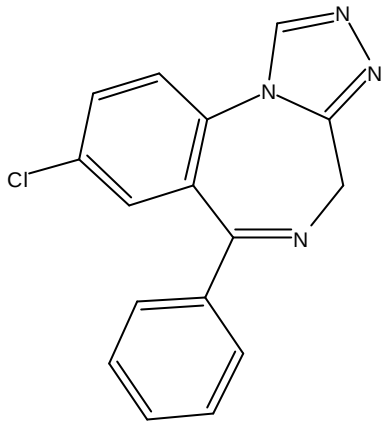


(XI)

BIOLOGICAL IMPORTANCE

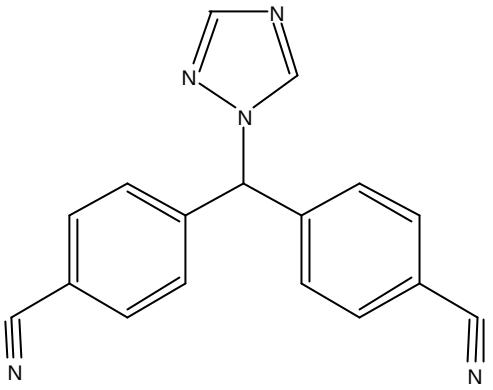
Triazoles are potential bioactive agents due to their wide spectrum of therapeutic importance. Drug molecules having 1,2,4-triazole nucleus with good activity are listed as under.

1. Estazolam



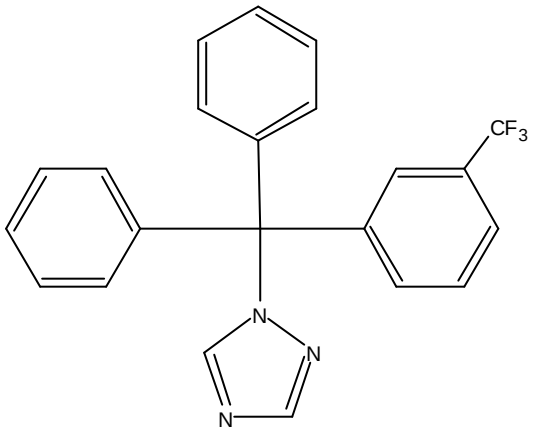
Receptor Agonist

2. Letrozole



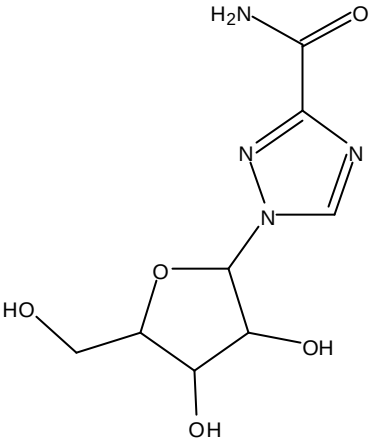
Antineoplastic

3. Fluotrimazole



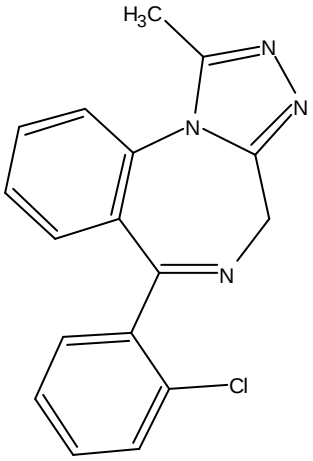
Fungicide

4. Rifavirin



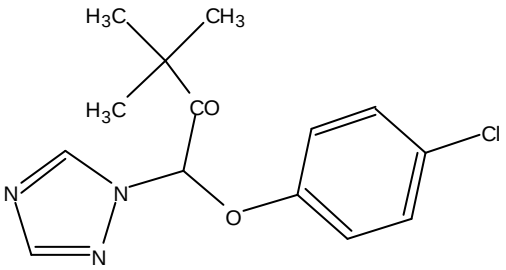
Antiviral, Antiinfection

5. Triazolam



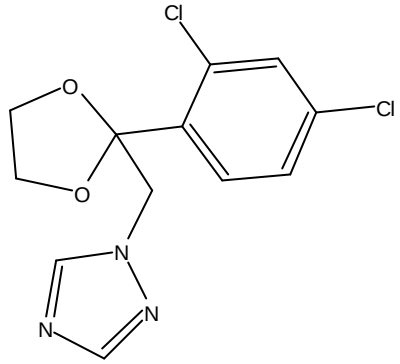
Plant growth regulator

6. Triadimenol



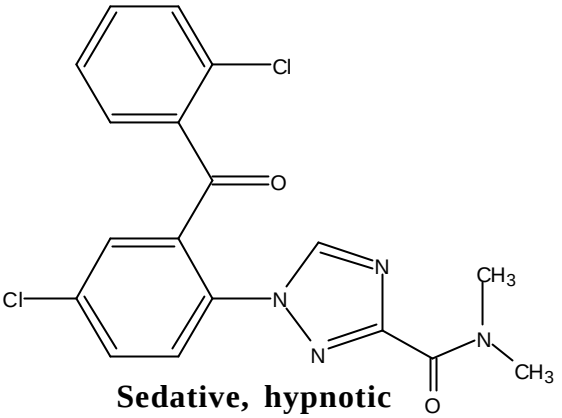
Fungicide

7. Azaconazole



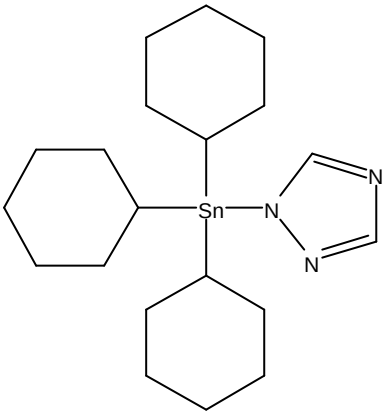
Antifungal

8. Rilmazafone



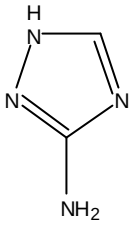
Sedative, hypnotic

9. Azocyclotin



Pesticide

10. Amitrole



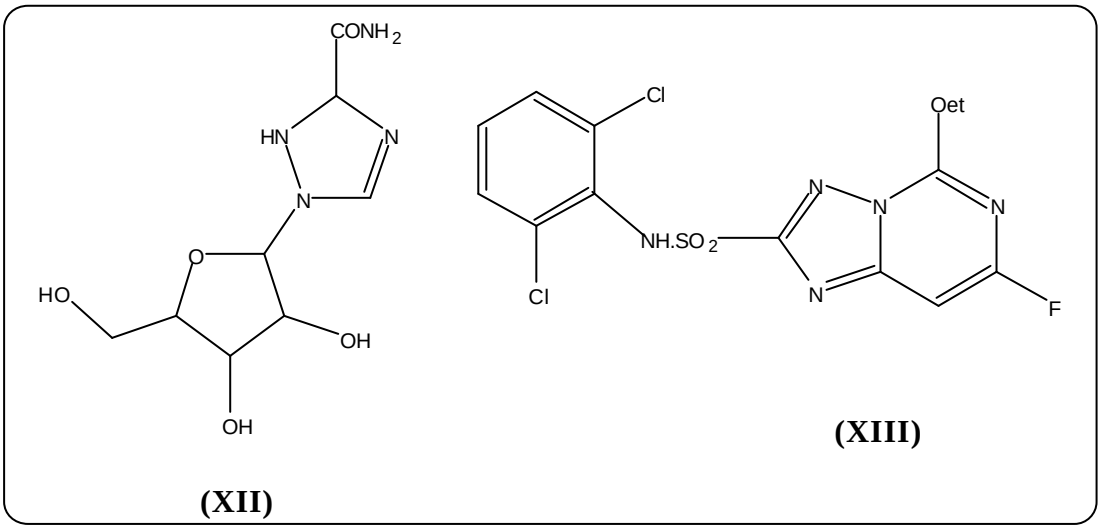
Antithyroid activity

Literature survey reveals that various 1,2,4-triazole derivatives display significant biological activities. 3-Amino-1,2,4-triazole was the first 1,2,4-triazole to be manufactured on large scale from aminoguanidine formate, useful as herbicides.[19] Therapeutic activity of 1,2,4-triazoles are as under.

1. Bactericidal[20]
2. Diuretic[21]
3. Fungicidal[22]
4. Herbicidal[23]
5. Insecticidal and acaricidal[24]

6. Plant growth regulator[25]
7. Anticancer and Anti-HIV[26]
8. Antileshmanial[27]
9. Antitumor[28]
10. Antidepressant and anxiolytic[29]
11. Anthelmintics[30]
12. Antimicrobial[31]
13. Antiviral[32]
14. Antiinflammatory[33]
15. Antihypertensive[34]
16. Anticonvulsant[35]

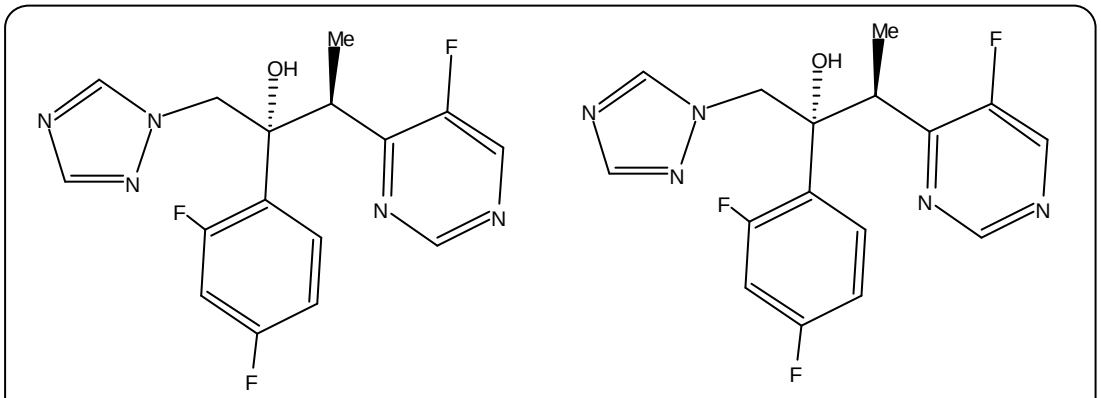
Yaseen A.et al.[36] have prepared 1,5-dialkyl-3-(5-mercapto-4-N-aryl-1H-1,2,4-triazol-3-yl-methylene)-1H-1,2,4-triazole which exhibited remarkable activity against nine type of cancer and also antiviral activity. Bozena et al.[37] have synthesized triazole derivatives and tested for their anticonvulsant and antinociceptive activity. Sylvie Larrat et al.[38] investigated that ribavarin in combination with alpha-2-interferon is the consensus treatment for chronic hepatitis C. and E. De Clercq et al.[39] screened ribavarin (XII) for their antiviral and antimetabolic activities.



(XII) **(XIII)**

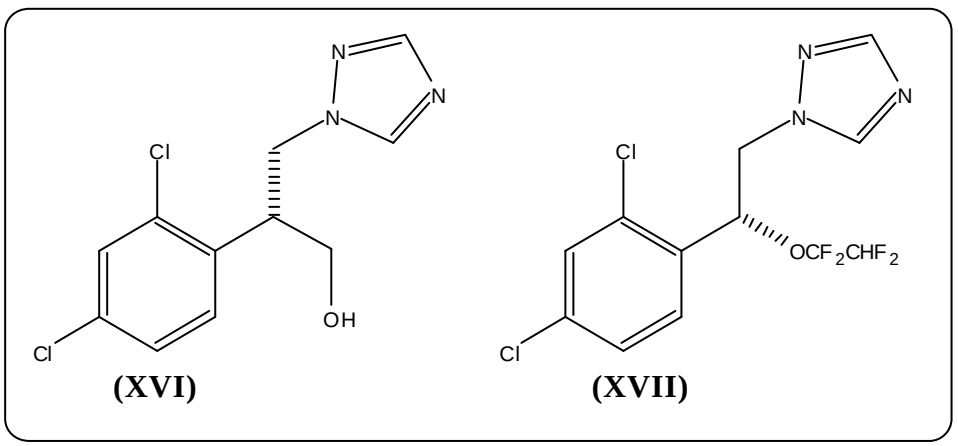
B. Shivarama Holla et al.[40] have investigated some triazole derivatives as anticancer agents. Damien Boeglin et al.[41] have suggested 3,4,5-trisubstituted 1,2,4-triazole derivatives useful as an antimicrobial agents. Mckendry and co-workers[42] have synthesized triazole derivatives (XIII) and reported them as broad spectrum broadleaf herbicides. L. Labanauskas et al.[43] have documented antiinflammatory activity of some triazoles. Vera Klimesova et al.[44] have reported 1,2,4-triazoles useful for tuberculosis inhibition.

Dickinson Roger P. and co-workers[45] have prepared Voriconazole (XIV) and found highly active against *Aspergillus fumigatus* and *a*-(hetero-arylmethyl)-1H-1,2,4-triazole-1-ethanol derivatives (XV) are active against *Candida albicans* and *Cryptococous neofermans*.



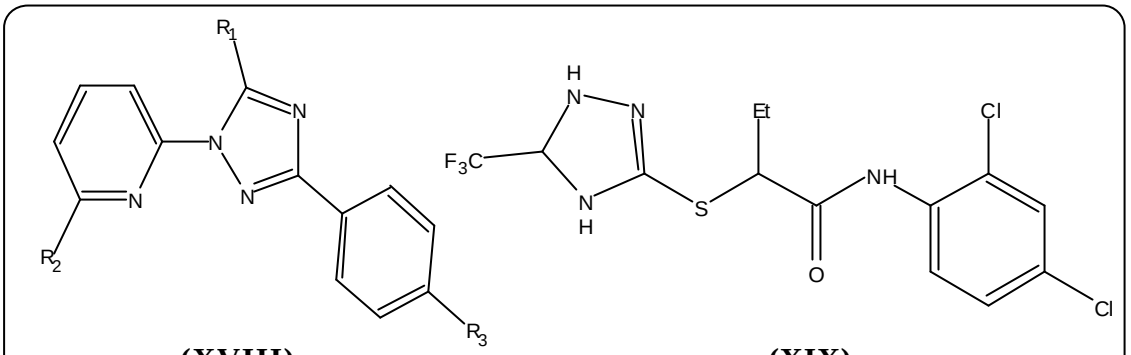
(XIV) **(XV)**

Daniele Binchi et al.[46] have screened pure stereoisomer of two new triazole derivatives (XVI , XVII) for their antifungal activity against variety of fungi showing an activity ratio R-form / S-form up to 400.



(XVI) **(XVII)**

Recently, Krzysztof W. et al[47] have discovered 1,2,4-triazole and reported their antimycobacterial activity. Dae-Kee Kim et al.[48] have been synthesized 1,2,4-triazole derivatives (XVIII) and screened for their significant ALKS inhibitory activity. Fisher Karl J. et al.[49] have synthesized 1,2,4-triazole derivatives (XIX) to study their pesticidal and herbicidal activity. Balkovee et al.[50] have formulated triazoles as antidiabetic agent. Maarouf et al.[51] have documented analgesic and antiinflammatory activity of 1,2,4-triazole derivatives.



(XVIII) **(XIX)**

Thus the important role displayed by triazole moiety for various therapeutic and medicinal activities promoted us to synthesize some thiadiazoles, thiadiazines, thiadiazepines, aryl triazoles, sulphonamides, aryl amides and mannich bases bearing triazole moiety, in order to achive compounds having better drug potential. This study is described in the following parts.

PART-I : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF THIADIAZOLES.

PART-II : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF 4-ARYL TRIAZOLES.

PART-III : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF THIADIAZINES.

PART-IV : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF THIADIAZEPINES.

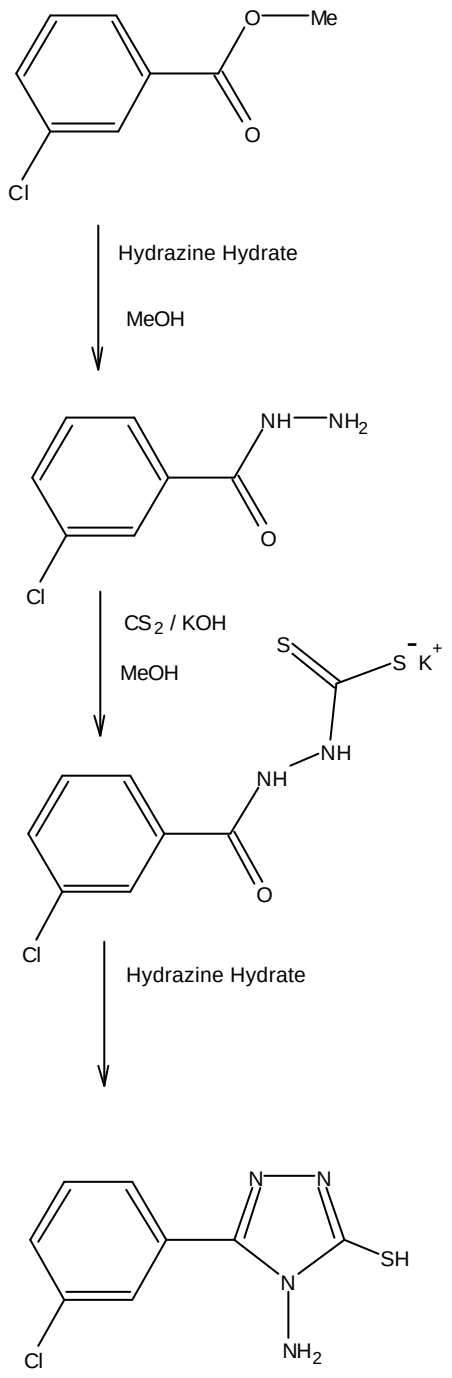
PART-V : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF SULPHONAMIDES.

PART-VI : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF ARYL AMIDES.

PART-VII : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF MANNICH BASES.

PART-VIII : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF OXADIAZOLES.

REACTION SCHEME



REFERENCES :

1. Hoggarth, E ;
   "Chemistry of Carbon Compd." Edited by E.H.Rodd.,IV A.P.452-63.
2. Meyer V. Jacopson P.;
   "Hand book of organic Chemistry", 2, Pt.3, Soc. **1-2**, 590,(1920).
3. Bladin J.A.;
   Ber., **18,** 1544 (1885).
4. Bladin J.A.;
   Ber., **19,** 2598 (1886).
5. M. Busch ;
   Ber., **38,**856 (1905).
6. T. Nakaic, S. meedu, T. Kurahashi ;
   Jpn.Pat., 7389932, (1973); *Chem.Abstr*., **81,** 65182 (1974).
7. M.A. Quraishi, Hariom K.Sharma ;
   Materials Chemistry and Physics, **78,** 18-21 (2002).
8. S. Ramesh, S. Rajeswari ;
   Electrochimica Acta., **49,** 811-820 (2004).
9. Colter R.J.,Matzner M.;
   'Ring terming polymerization', part **B-1,** 'heterocyclic Ring',
   Academic, New York, (1972).
10. Jack R. Reid and Ned D. Heidel ;
    J.Heterocyclic Chem., **13,** 925 (1976).
11. Madhukar S. Chande, Jayesh D.Bhandari and Vishwas R.Joshi ;
    Indian J. Chem., **32B,** 1218 (1993).
12. Ivanka Kolenc, Marijan Kocever, Slovenko Polanc ;
    Acta. Chim.Slov., **46(2),** 281-288 (1999).
13. C.S.Andotra and Sukhbinder Kaur ;
    Indian Journal of Chemistry, **43B,** March (2004).
14. Yan Shiquaing, Chem Ning and Wu Hui ;
    Hecheng Huaxue **4(3),** 220 (1996); *Chem.Abstr.*,**126,** 17168w (1997).
15. Vershilov S.V.,Popova L.M. and Mungalov V.E.,
    Zh.Prikl.Khim.(5-Peterburg) **67(7),** 1124 (1994);
    Chem.Abstr.,**122,**265316h (1995).

16. Shin-ichi Nagai, Taiser Weda, Mastoshi Takamura ;
J. Heterocyclic Chem., **35,** 293 (1998).
17. L. Labanauskas et al.;
IL Farmaco., **59,** 255-259 (2004).
18. Abbas Shafiee et al.;
Bioorganic and Medicinal Chemistry., **11,** 769-773 (2003).
19. K. T. Potta ;
J. Chem. Soc., 3461 (1954).
20. Pourmorad F., Shafiee A. ;
J. Sci. Islamic Repub. Iran, **9,** 30 (1998); *Chem.Abstr.,***129,** 175593e (1998).
21. Chekovskaya L. G., Khush E. G., Rogyllchenko G. K.;
Farm. 2h (kiev)., **5,** 67-68 (1989); Chem.Abstr., 112, 198233a (1990).
22. Itoh Katsumi, Kitazaki Tomoyuki, Matsushita Yoshihiro ;
Eur. Pat. Appl. EP 884311; *Chem.Abstr.,***130,** 66505c (1999).
23. Fusaka Takafumi, Ujikawa Osamu, Kajiwara Takeshi, Tanaka Yasushi
PCT Int. Appl. WO 97, **11,** 075 ; *Chem.Abstr.,* **126,** 29335p (1997).
24. Shibata Yasushi, Aoyagi Koichiro, Ichikawa Naomi ;
PCT Int. Appl. WO 99 02507 ; *Chem.Abstr.,* **130,** 95554y (1999).
25. Chu Chang Hu, Sun Xiao Wen, Zhang Zi Yi, Li Zhi Chun ;
Chin Chem. Lett., **10,** 361 (1999).
26. Mark D.Abel, Randy T. Hewgill, Katherine J. Malczylc, Ronald G. Micetich;
J. Heterocycl.Chem., **35,** 193 (1998).
27. R. S. Verma, Vinita Bajpai and A. Kapil ;
Indian J. Heterocycl. Chem., **10,** 117 (2000).
28. Ellis, Michael J., Stevens, Malcolm F.G. ;
J. Chem. Soc., **23,** 3180-3185 (Eng.) (2001); *Chem.Abstr.,***137,** 185433g (2002).
29. Turan-Zitouni G., Kaplancikli Z.A., Kilic F.S.;
Chem. Abstr., **138,** 271613t (2003).

30. Kudari S. M., Beede S. M., Munera Wahaja ;
Asian. J. Chem., **9,** 20 (1997); Chem.Abstr.,126 (1997).
31. Murthy Sreenivasa, nagappa V.A.N., Nargund L.V.G.;
Indian J. Heterocylc.Chem., **8,** 23 (1998); Chem.Abstr., 130, 6644m (1999).
32. Archana Jyoti S. Sanjay S.,Saxena V.K.;
J.Indian.Chem.Soc., **68,** 103 (1991).
33. Bozo Eva, Szilagyi Geza, Janky Judit ;
Arch. Pharm. (Weinheim. Ger.) **322,** 583 (1989); Chem.Abstr., 112, 55731a (1990).
34. Reigz D. B. ;
Sci. Pharm., **65,** 277 (1997); *Chem. Abstr.*, **123,** 167389g (1998).
35. Karali N., Capan G., Eegene N., Gursoy A. ;
Sci. Pharm., 65, 277 (1997); Chem. Abstr., 123, 167389g (1998).
36. Yaseen A. Al-Soud, Mohammed N. Al-Dweri, Najim A. Al-Masoudi ;
IL Farmaco, **59(10),** 775-783, Oct. (2004).
37. Bozena Modzelewska-Banachiewicz, Jacek Banachiewicz, Anna Codkowska, Ewa Jagiello-Wojtowicz and Liliana Mazur ;
Eur. Journal of Med.Chem., **39(10),** 873-877, Oct. (2004).
38. Sylvie Larrat Francoise Stanke Labesque,Agnes Plages,Jean-Pierre Zarski, et al.;
Antimicrob Agent Chemother., **47(1),**124-129, Jan-(2003).
39. E. De. Clercq, M. Cools, J. Balzarin ; R. Snoeck, G.Anderi, M. Hosoya, S. Shigeta, T. Ueda, N. Minakawa and A. Matsuda ;
Antimicrob Agent Chemother., **35(4),** 679-684, April (1991).
40. B. Shivarama Holla, B. Veerendra, M.K. Shivanda, Boja Poojary ;
Eur. J. Med. Chem., **38 (7-8),** 759-767, Jul-Aug. (2003).
41. Damien Boeglin, Sonia Cantel, Annie Heitz, Jean Martineiz and Jean-Alain Fehrentz ;
Organic Letters., **5,** 4465-4468 (2003).
42. L. H. Mckendry, M.K. Tomalia, N.H. Terando and F.H. White ;
International isotope Society Central us abstract, **13-14,** May (1997).
43. L. Labanauskas, E. Udrenate, P. Gaidelis, A. Bruktus ;
IL Farmaco, **59(4),** 255-259, April, (2004).

44. Vera Klimesova, Lenka Zahajska, karel Waisser, Jarmita Kaustova, Ute Mollmann ;
IL Farmaco, **59(4),** 279-288, April (2004).

45. Dickinson Roger P., Bell Andrew W., Hitehcock Christopher ;
Bio. Org. Med. Chem. Lett., **6,** 2031 (1996), U.K. 109,496 ;
Chem.Abstr., **125,** 275787g (1996).

46. Daniele Binchi, Pietro Cesti, Paolo Golini, Sandro Spezia, Carlo Garvaglia, Luigi Mirenna
Pure abd Appl. Chem., **64(8),** 1073-1078 (1992).

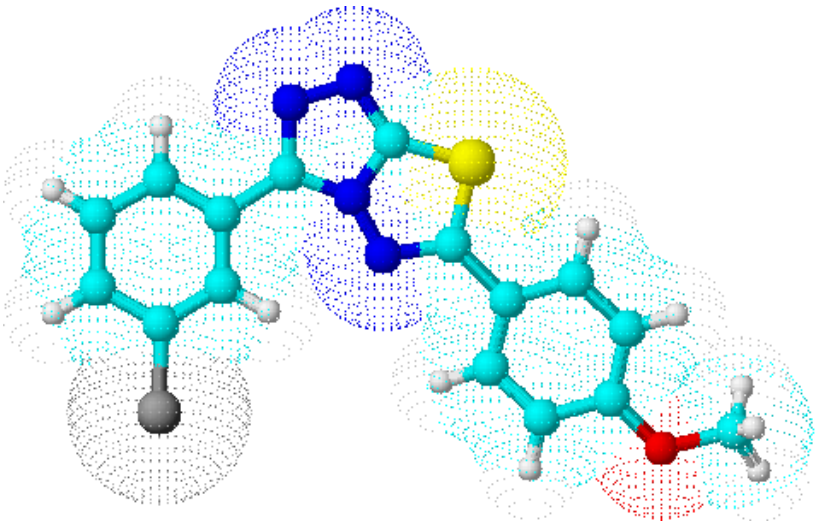
47. Krzysztof Walczok, Andrzej Gondela, Jerzy Suarnski ;
Eur. J. Med. Chem., **38(10),** 849-853. Oct., (2004).

48. Dae-Kee Kim, Joonseop Kim and Hyun-Ju-Park ;
Bioorg. And Med. Chem., **12(9),** 2013-2020. May (2004).

49. Fisher Karl J., Felix Ray A. ;
Oliver, Robert M. ACS Symposium Series, **800,** 9-15 (2002). *Chem. Abstr.,***136,** (13), 200148 (2002).

50. Balkovec, James M.; Thieringer, Rolf Nundt, Steven S.; Hermanowski-Vosatka.Anne:Graham.Donald W;Patel Gool F.et al.;
PCT Int. Appl. WO 03, 65983 (Cl.A61K) (2003). *Chem. Abstr.,* **139(12),** 180065v (2003).

51. Maarouf Azza R. ; Qato, Mazen K.; Boulatova. Nailia ; El-Naddat, Ahmed R.;
J. of Pharmaceutical Science., **15(1),** 77-81(2001) ; *Chem. Abstr.,* **136(12),** 183765x (2002).

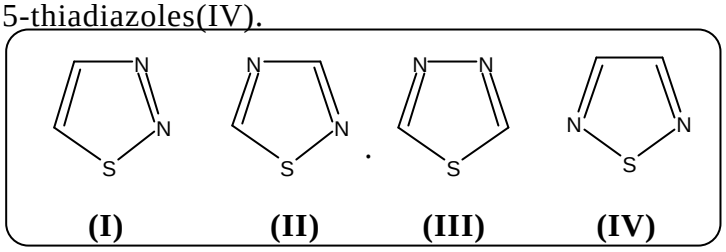


PART - I

STUDIES ON THIADIAZOLES

INTRODUCTION

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

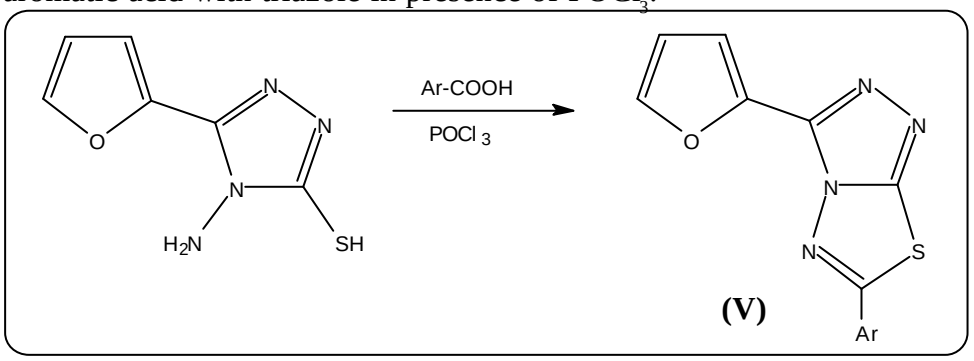


Among these four types of thiadiazoles, 1,3,4-thiadiazole is well known. Fischer has described the first 1,3,4-thiadiazole in 1882 and further developed by Buch and co-workers.

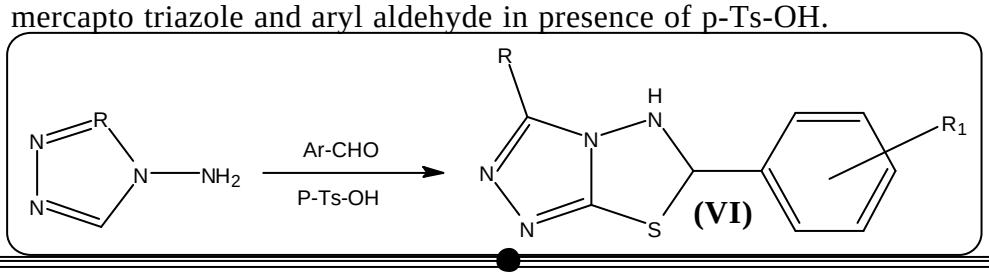
SYNTHETIC ASPECT

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

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

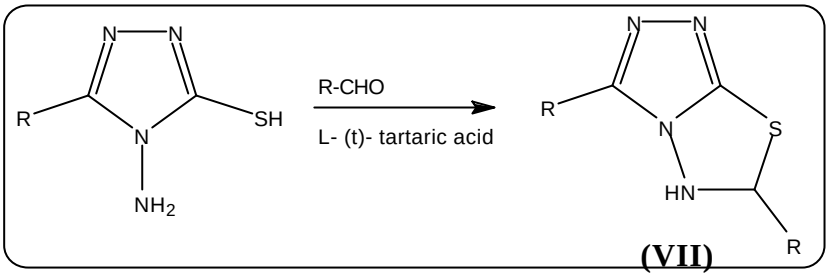


2. Jag Mohan et al.[4] have prepared thiadiazole derivatives by the cyclization of amino mercapto triazole and aryl aldehyde in presence of p-Ts-OH.



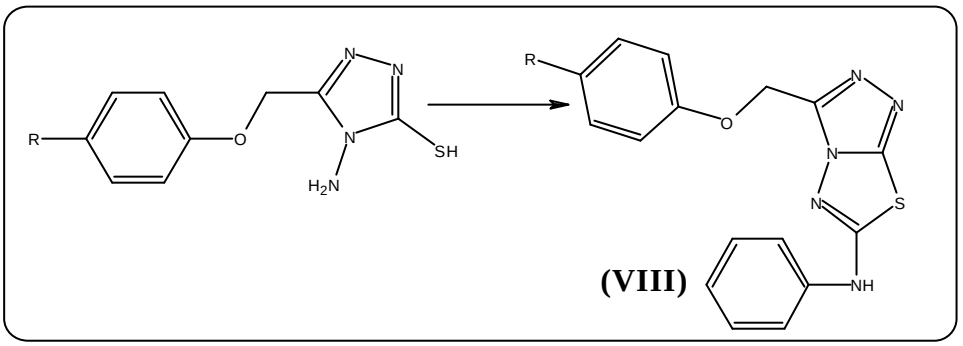
3. Microwave irradiation used for the preparation of thiadiazole using DMF as an energy transfer medium was reported by Kidwai Mazaahir et al.[5]

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



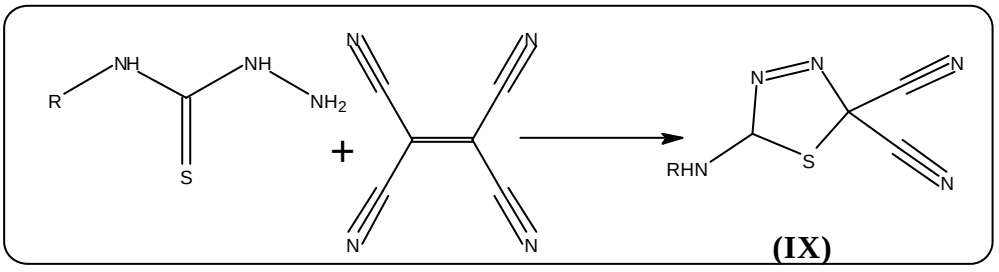
(VII)

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



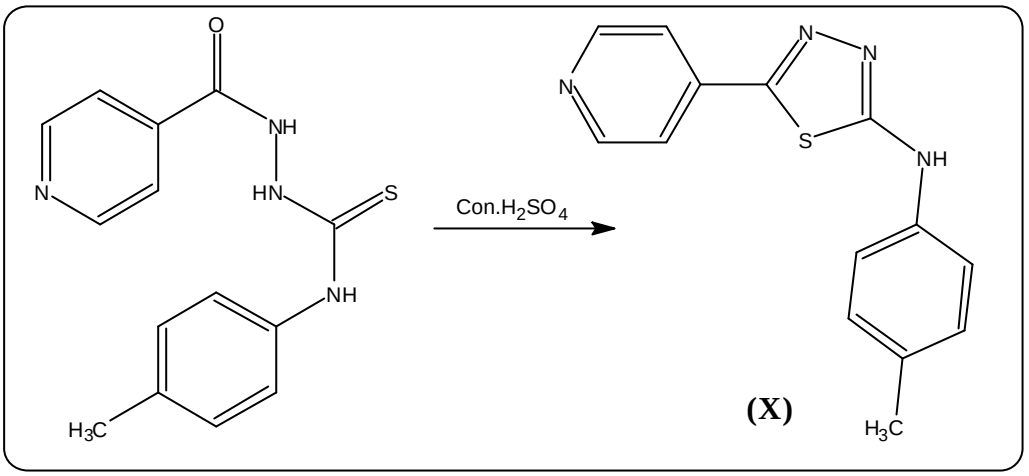
(VIII)

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



(IX)

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



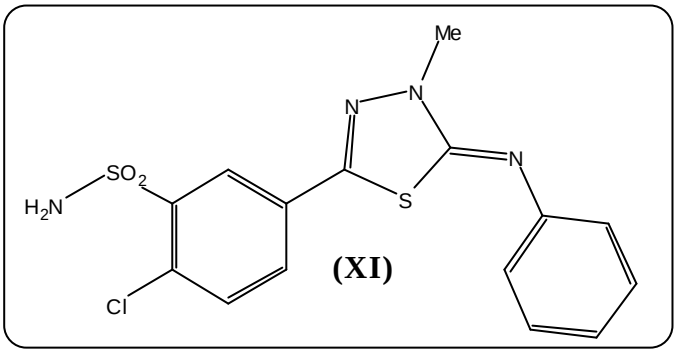
(X)

BIOLOGICAL IMPORTANCE

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

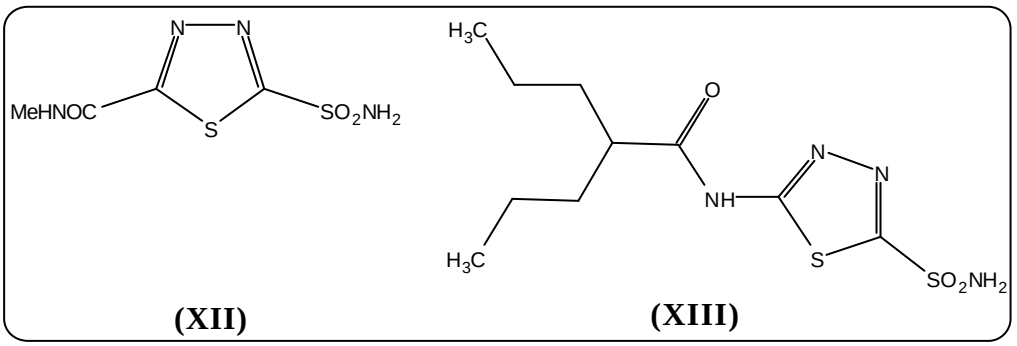
1. Antitumor[10]
2. Antiviral[11]
3. Antibacterial[12]
4. Amoebicidal[13]
5. Antagonist agent[14]
6. Antitubercular[15]
7. Antipyretic[16]
8. Antinelmintic[17]
9. CNS depressant[18]
10. Antischistosomal[19]
11. Herbicidal[20]
12. Insecticidal[21]
13. Pesticidal[22]
14. Hypoglycemic[23]

Vergne, Fabrice et al.[24] have synthesized 1,3,4-thiadiazole derivatives (XI) and screened for their antiinflammatory, anticancer and anti-HIV activity. Laddi U.V. et al.[25] have discovered thiadiazoles possessing antimicrobial and antituberculosis activity. Gamill Ronald B. et al.[26] have reported thiadiazoles as antiinflammatory agents. Mobinikhaledi, A. et al.[27] have investigated 1,3,4-thiadiazoles and tested for insecticidal activity. Che,Chao et al.[28] have prepared thiadiazole derivatives showed antifungal and plant growth regulating effect.



(XI)

Celine Chazalete et al.[29] have synthesized acetazolamide (XII) possessing diuretics and antiglaucoma activity. Athansia Varvaresou et al.[30] suggested thiadiazoles and reported them as antidepressant. Pradeep Mishra et al.[31] have screened 1,3,4-thiadiazoles for their potent spasmolytic activity and anti-inflammatory activity. Bernard Masercel et al.[32] have synthesized 1,3,4-thiadiazoles possessing potent carbonic anhydrase inhibitor properties and also prepared 5-valproyl amino 1,3,4-thiadiazole-2-sulphonamide (XIII) as strong anticonvulsant.

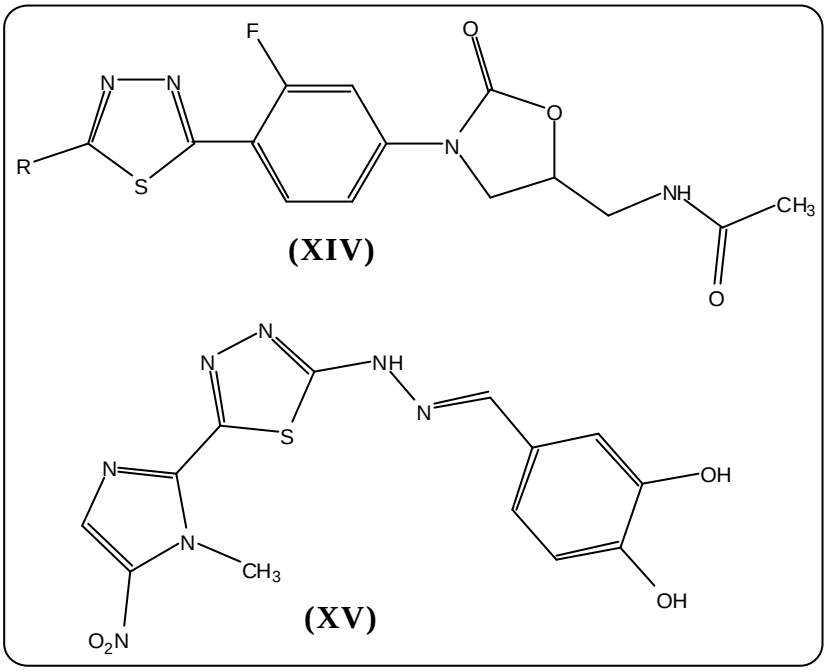


(XII) **(XIII)**

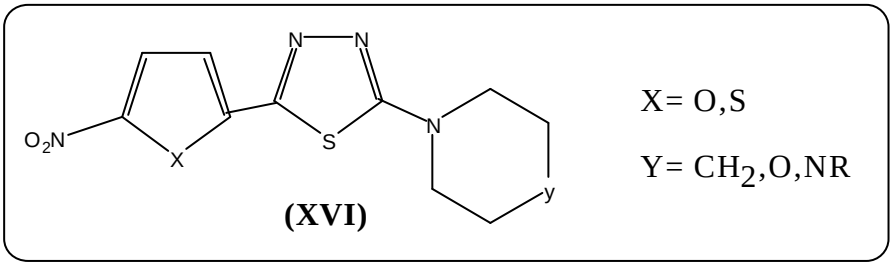
Claudiu T. Supuran and Andrea Scozzafava[33] have reported 1,3,4-thiadiazole derivatives as carbonic anhydrase inhibitors and antitumor. Erhan Palaska et al.[34]

synthesized thiadiazoles containing anti-inflammatory activity. J. M. Colacino et al.[35] have documented anti-influenza virus activity of thiadiazoles.

Lisa M. Thomasco et al.[36] have prepared 1,3,4-thiadiazole (XIV) possessing potent antibacterial activity against Gram positive and Gram negative organisms. Samir A. Carvalho and co-workers[37] have documented antitrypanosomal profile of 1,3,4-thiadiazole derivatives (XV). Zahra Kiani et al.[38] have discovered thiadiazoles as antituberculosis agent.



Alireza faroumadi et al.[39] have synthesized 1,3,4-thiadiazoles (XVI) and studied their leishmanicidal activity. Hatice Dogan et al.[40] have prepared 2,5-disubstituted-1,3,4-thiadiazolo derivatives as anticonvulsant and antimicrobial agent. Nalan Terzioglv and Aysel Gursoy[41] have discovered thiadiazoles and studied their anticancer activity. Alireza Foroumadi and co-workers[42] have documented antituberculosis activity and cytotoxicity of 1,3,4-thiadiazoles.



Recently S. Karakus and S. Rollas[43] have screened thiadiazoles for their antituberculosis activity. Jui-Yi Chou et al.[44] have synthesized thiadiazoles and reported them as anticancer agents.

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

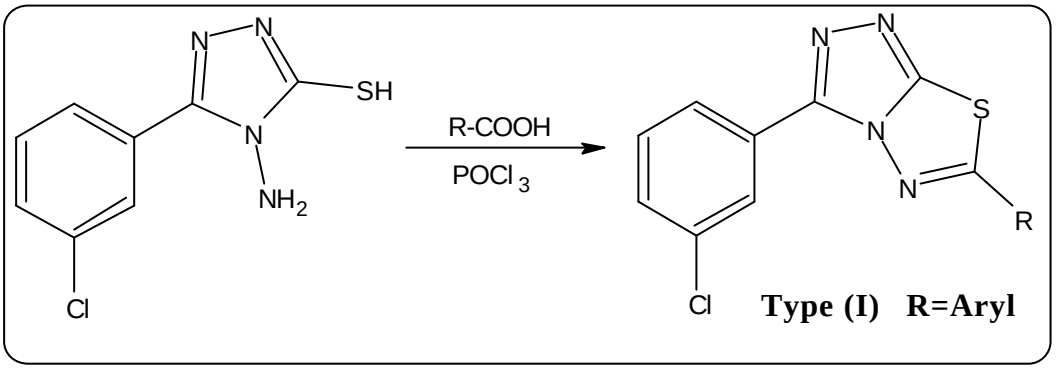
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREEINING OF 3-(m-CHLOROPHENYL)-6-ARYL[1,2,4]TRIAZOLO[3,4-b] [1,3,4]THIADIAZOLES.

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL-5,6-DIHYDRO[1,2,4] TRIAZOLO[1,3,4]THIADIAZOLES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLES.

Thiadiazole derivatives are associated with broad spectrum of biological activities. In view of these finding it appeared of interest to synthesize some newer thiadiazole derivatives, with better potency. Thiadiazoles of type (I) have been prepared by cyclocondensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic acids in presence of $POCl_3$, as shown in reaction scheme.



Type (I) R=Aryl

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

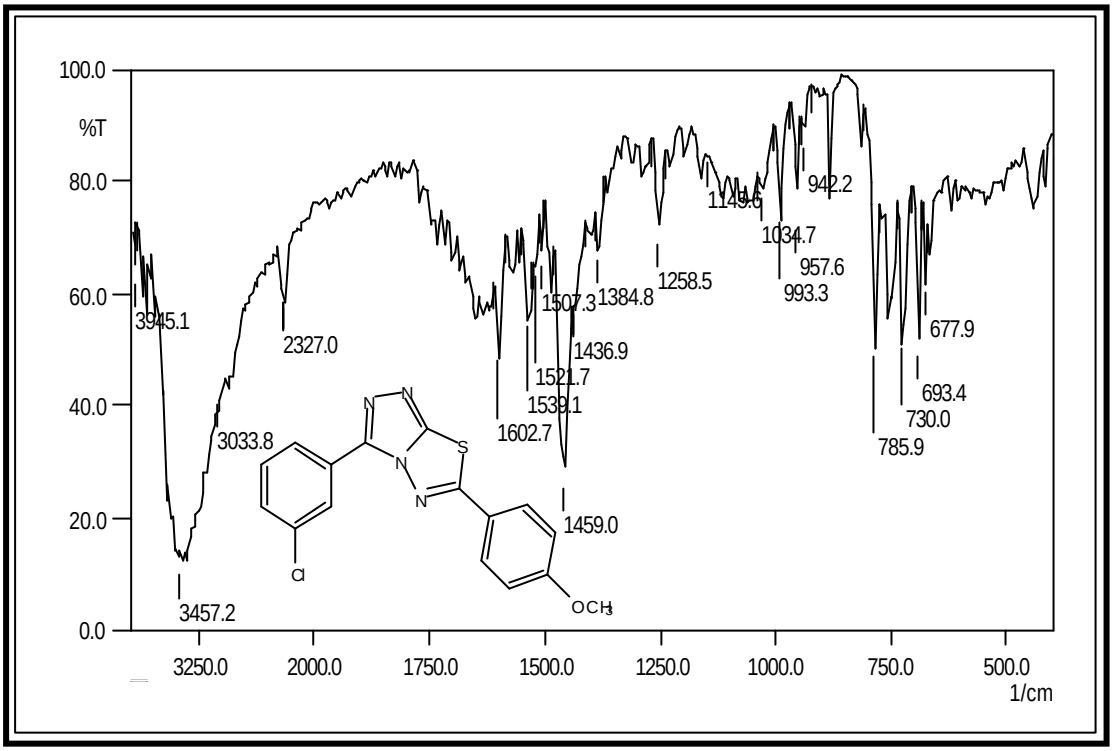
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of the synthesized compounds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

ANTIMICROBIAL ACTIVITY

Method	: Cup-plate[45,46]
Gram positive bacteria	: *Bacillus substillus*
	Bacillus megaterium
Gram negative bacteria	: *Proteus vulgaris*
	Escherichia coli
Fungi	: *Aspergillus niger*
Concentration	: 40 µg/ml
Solvent	: Dimethyl formamide
Standard drugs	: Ampicillin, Amoxycillin, Norfloxacin, Benzyl-penicillin, Greseofulvin

The antimicrobial activity was compared with standard drugs Viz., Ampicillin, Amoxycillin, Norfloxacin, Benzyl penicillin and antifungal activity was compared with Greseofulvin. The zones of inhibition have been measured in mm.

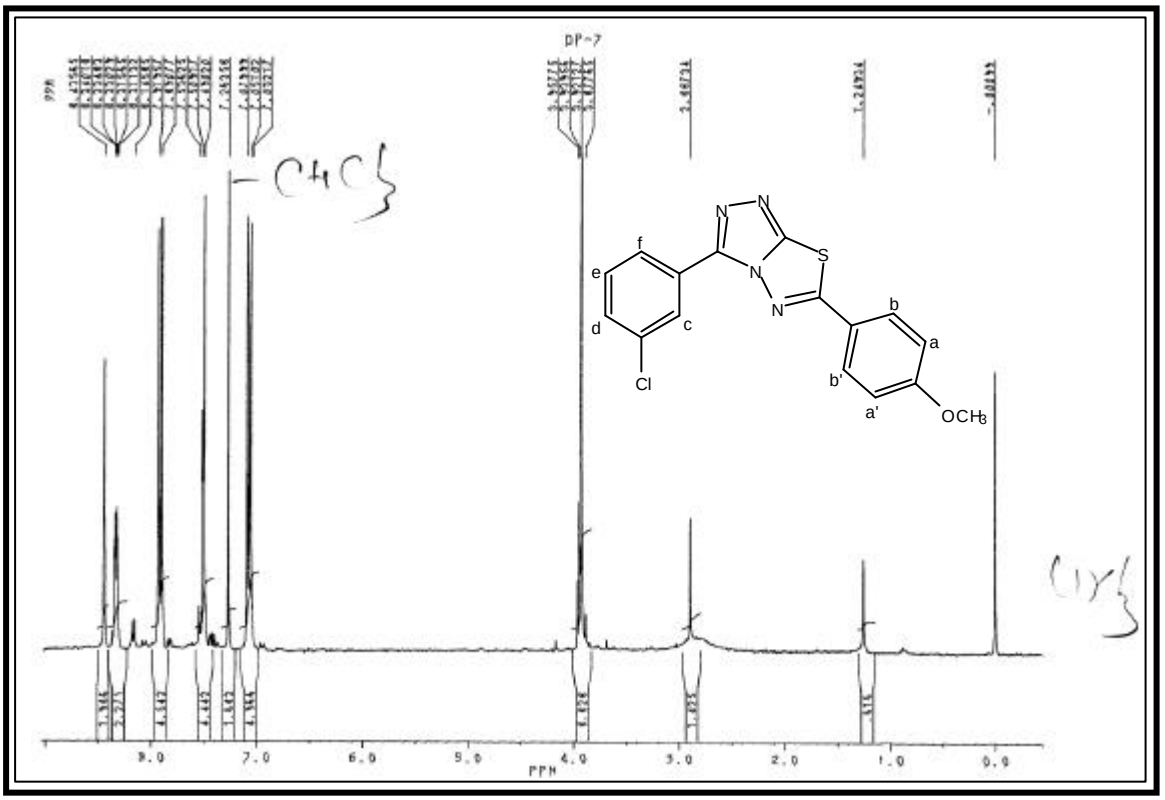
IR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-METHOXYPHENYL)[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIZOLE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3033	3080-3030	47
	C=C str.	1507	1585-1480	47
	C-H i.p. (def)	1145	1145-1090	47
		1034	1070-1000	47
Triazole	C=N str.	1602	1612-1593	47
	C-N str.	1384	1380-1310	48
	C-N-C str.	1145	1146-1132	47
	N-N str.	1034	1050-1010	49
Ether	C-O-C str.(asym.)	1258	1275-1200	48
(Ar-O-R)	C-O-C str.(sym.)	1034	1075-1020	47
Halide	C-Cl str.	758	800-600	47
Thiadizole	C-S-C str.	693	720-570	47

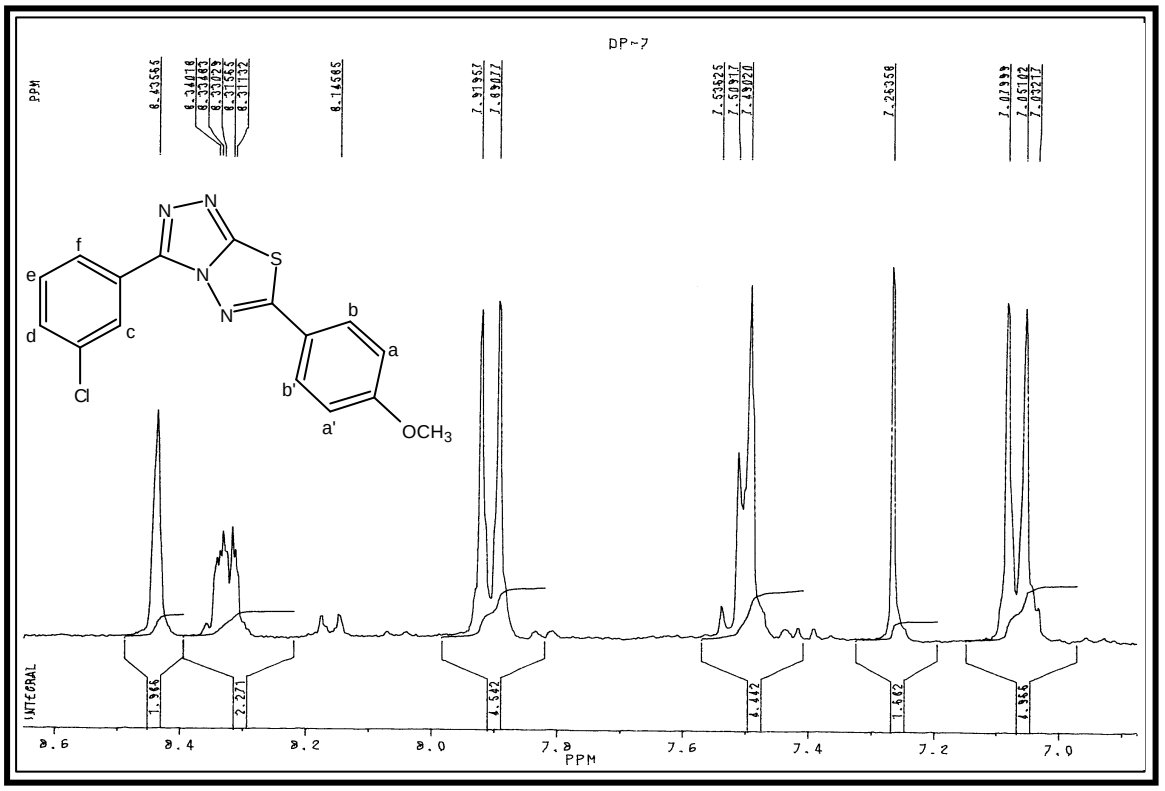
NMR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-METHOXYPHENYL)[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIZOLE



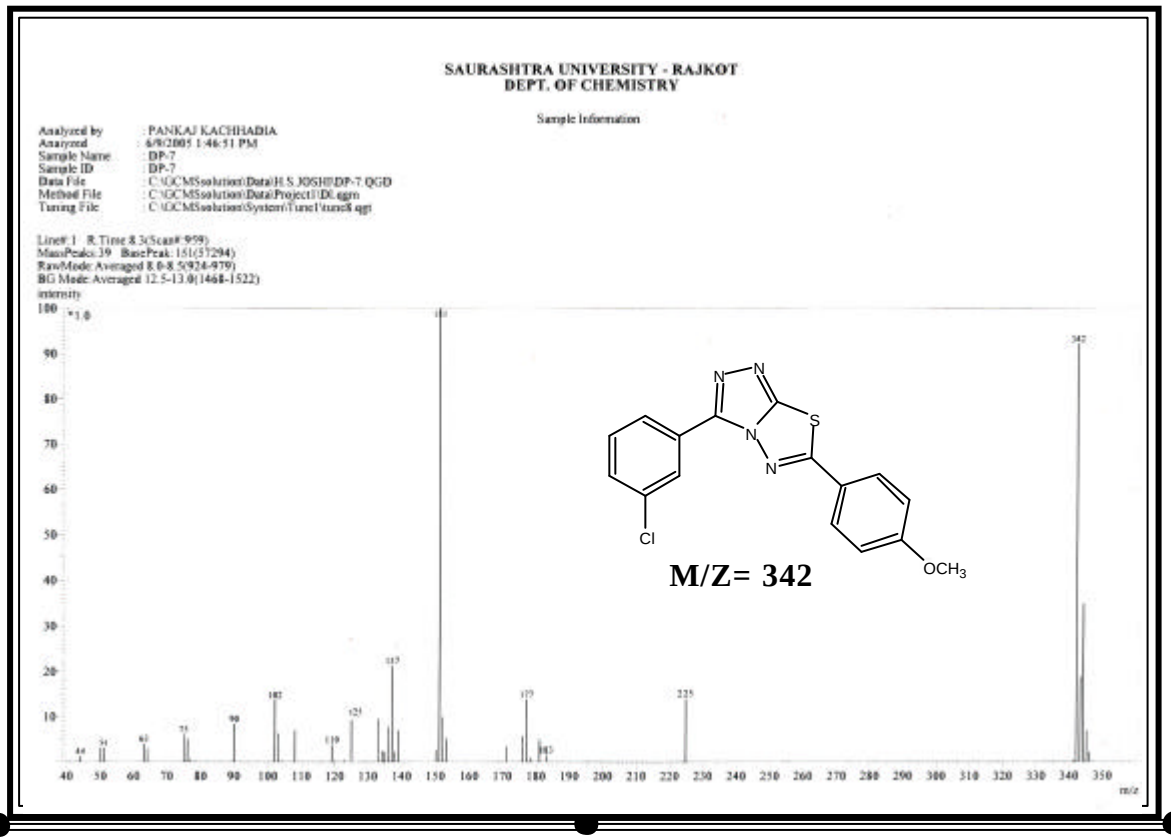
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.92	3H	singlet	Ar-OCH_3	-
2	7.06	2H	doublet	Ar-H(aa')	Jab=8.4
3	7.50	2H	doublet	Ar-H(ed)	Jed=8.1
4	7.90	2H	doublet	Ar-H(bb')	Jba=8.7
5	8.34-8.31	1H	double doublet	Ar-Hd	Jde=5.7
6	8.43	1H	singlet	Ar-Hc	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-METHOXYPHENYL)[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIZOLE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLES.

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

To a mixture of potassium hydroxide (8.40g, 0.15 mol) and 3-chlorobenzohydrazide (17.0g, 0.1mol) in methanol (25ml), carbon disulphide (11.4g, 0.15mol) was added. This mixture was stirred for 12-14 hours. It was then diluted with dry ether (200 ml) and thus the solid obtained was filtered and washed with ether and dried. There is no need to purify the salt for further reaction.

[B] Preparation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol.

A suspension of the potassium salt (24.5g, 0.1 mol), hydrazine hydrate (10 ml, 0.2 mol) and water (2 ml) was refluxed with stirring for 3 hours. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odour) and a homogeneous solution resulted. Dilute the solution with of cold water (100 ml)and neutralized with glacial acetic acid, precipitated a white solid. The product was filtered, washed with cold water and crystallized from dioxane yield 60%, m.p. 190^{o}C.

[C] Preparation of 3-(m-chlorophenyl)-6-(p-methoxyphenyl)[1,2,4]triazole [3,4-b][1,3,4]thiadiazole

A mixture of p-methoxy benzoic acid (1.52g, 0.01 mol) and 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (2.26g, 0.01 mol)in $POCl_3$ (25 ml) was refluxed for 10 hrs. The reaction mixture was poured onto crushed ice and thus solid separated out was filtered, washed with water and crystallized from methanol. Yield 64%, m.p. 210^{o}C. Anal, Calcd. For $C_{16}H_{11}ClN_4OS$: C, 56.06 ; H, 3.23 ; N, 16.34 %; Found : C, 56.02 ; H, 3.20 ; N, 16.30%.

Similarly other thiadiazoles were prepared and the physical constants are recorded in Table No. 1.

[D] Antimicrobial activity of 3-(m-chlorophenyl)-6-aryl-[1,2,4]triazole[3,4-b][1,3,4]thiadiazoles

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

(a) Antimicrobial activity

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

(I) Antibacterial activity

The purified products were screened for their antimicrobial activity. The nutrient agar broath prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of ***B. coccous, B. subtillis, E. Coli,*** **and** ***P. vulgaris*** in separate conical flasks at 40-50°C and mixed well by gentle shaking. About 25ml content of the flask were poured and evenly spreaded in a petridish (13cm in diameter) and allowed to set for 2 hrs. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40μg) solution of sample in DMF.

The plates were incubated at 37°C for 24 hrs. and the control was also maintained with 0.04 mole of DMF in a similar manner and the zones of inhibition of 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 subouraud's agar plants. Sterilized sabouraud's agar medium was inoculated with 72 hrs. old 0.5 ml suspension of fungal spores in a separate flask.

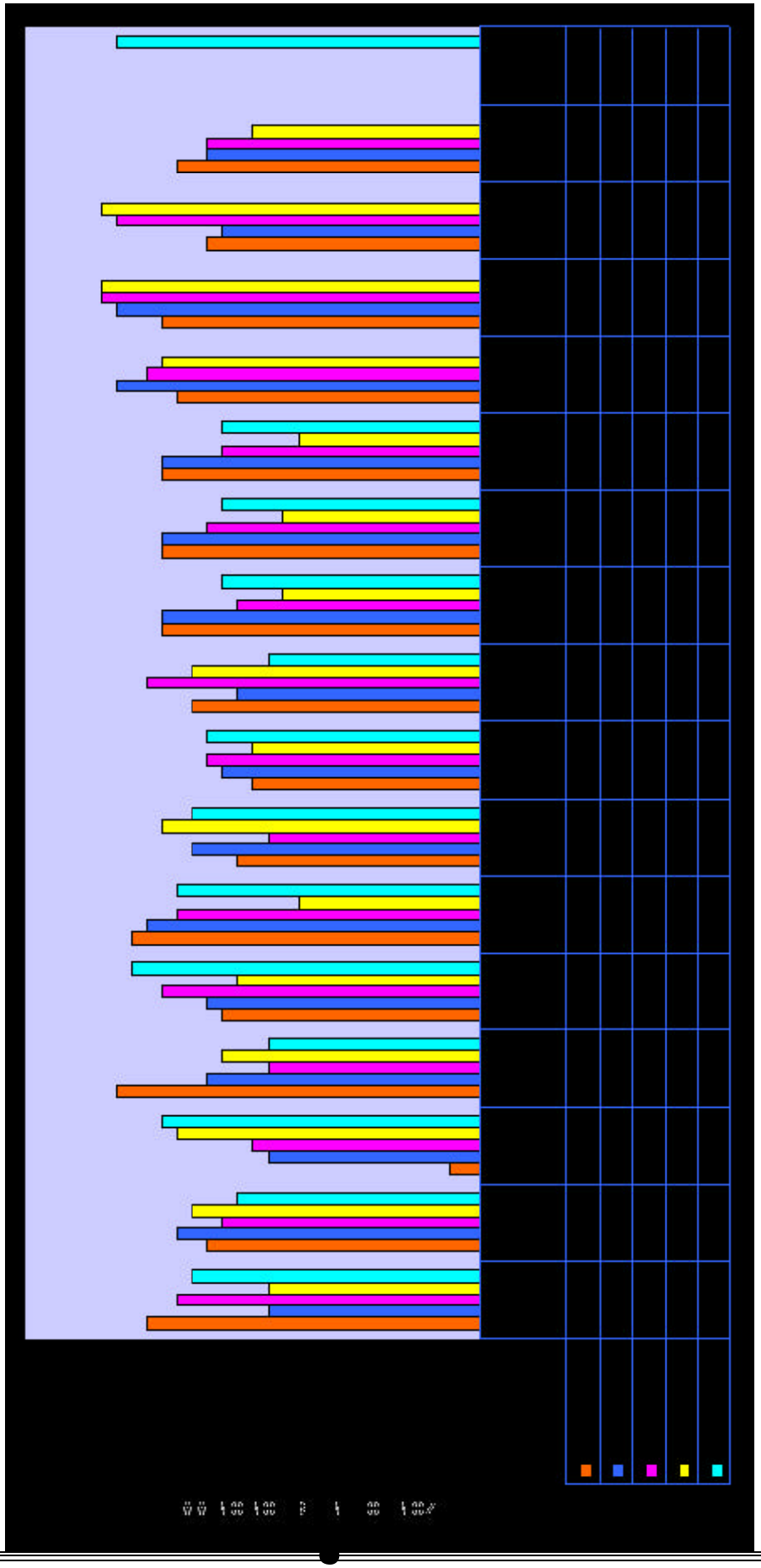
About 25 ml of inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The plates were incubated at 30°C for 48 hrs. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled with solvent which act as control. The zones of inhibition are recorded in Graphical Chart No. 1.

TABLE-1 : PHYSICAL CONSTANTS OF 3-(m-CHLOROPHENYL)-6-ARYL[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
1a	4-OCH_3-C_6H_4-	$C_{16}H_{11}ClN_4OS$	342	210	64	16.34	16.30	0.50	S2
1b	2,4-$(OH)_{2}$-C_6H_4-	$C_{15}H_9ClN_4O_2S$	344	165	68	16.25	16.27	0.41	S2
1c	2-CH_3-C_6H_4-	$C_{16}H_{11}ClN_4S$	326	190	79	17.14	17.10	0.44	S1
1d	3-OC_6H_5-C_6H_4-	$C_{15}H_9ClN_4OS$	328	185	58	17.04	17.00	0.52	S2
1e	4-Br-C_6H_4--	$C_{15}H_8BrClN_4S$	391	230	67	14.30	14.33	0.54	S2
1f	3-Cl-C_6H_4-	$C_{15}H_8Cl_2N_4S$	347	181	71	16.14	16.10	0.53	S1
1g	4-NO_2-C_6H_4-	$C_{15}H_8ClN_5O_2S$	357	190	79	19.57	19.60	0.49	S2
1h	3-NO_2-C_6H_4-	$C_{15}H_8ClN_5O_2S$	357	185	58	19.57	19.60	0.54	S1
1i	4-C_5H_4N-	$C_{13}H_8ClN_5S$	301	195	60	23.21	23.20	0.58	S1
1j	4-Cl-C_6H_4-	$C_{15}H_8Cl_2N_4S$	347	180	64	16.14	16.20	0.43	S2
1k	2-Cl-C_6H_4-	$C_{15}H_8Cl_2N_4S$	347	198	83	16.14	16.20	0.46	S2
1l	2-OH-C_6H_4-	$C_{15}H_9ClN_4OS$	328	250	79	17.04	17.00	0.48	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

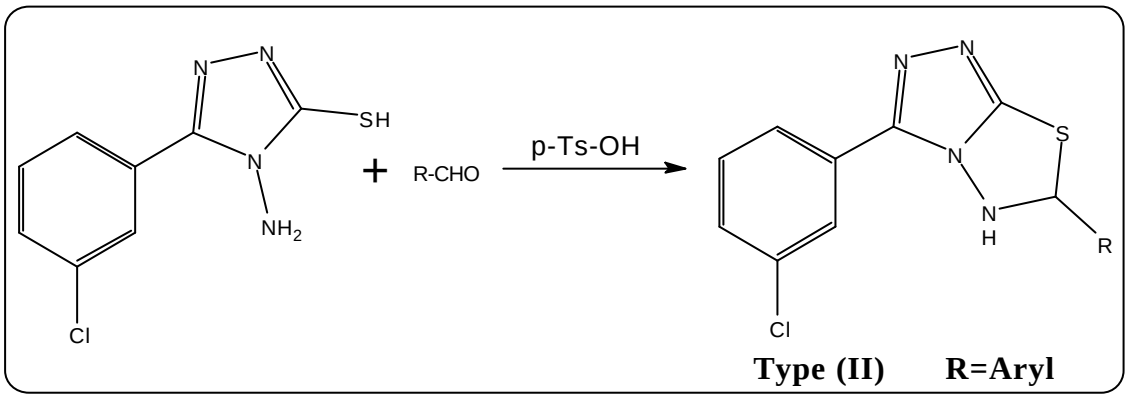
Graphical Chart No. 1 :Antimicrobial Activity of 3-(m-chlorophenyl)-6-aryl[1,2,4]triazolo [3,4-b][1,3,4]thiadiazoles



SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL-5,6-DIHYDRO[1,2,4]TRIAZOLO[1,3,4]THIADIAZOLES.

Thiadiazole derivatives are endowed with variety of biological activities. Looking to the interesting properties of thiadiazoles, it was considered worthwhile to synthesize a series of 3-(m-chlorophenyl)-6-aryl-5,6-dihydro[1,2,4]triazole[1,3,4]thiadiazoles of type (II) for obtaining biologically potent agents. Thiadiazoles of type (II) have been synthesized by cyclocondensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic aldehydes in presence of p-TsOH (p-toluene sulphonic acid) as a catalyst, as shown under.

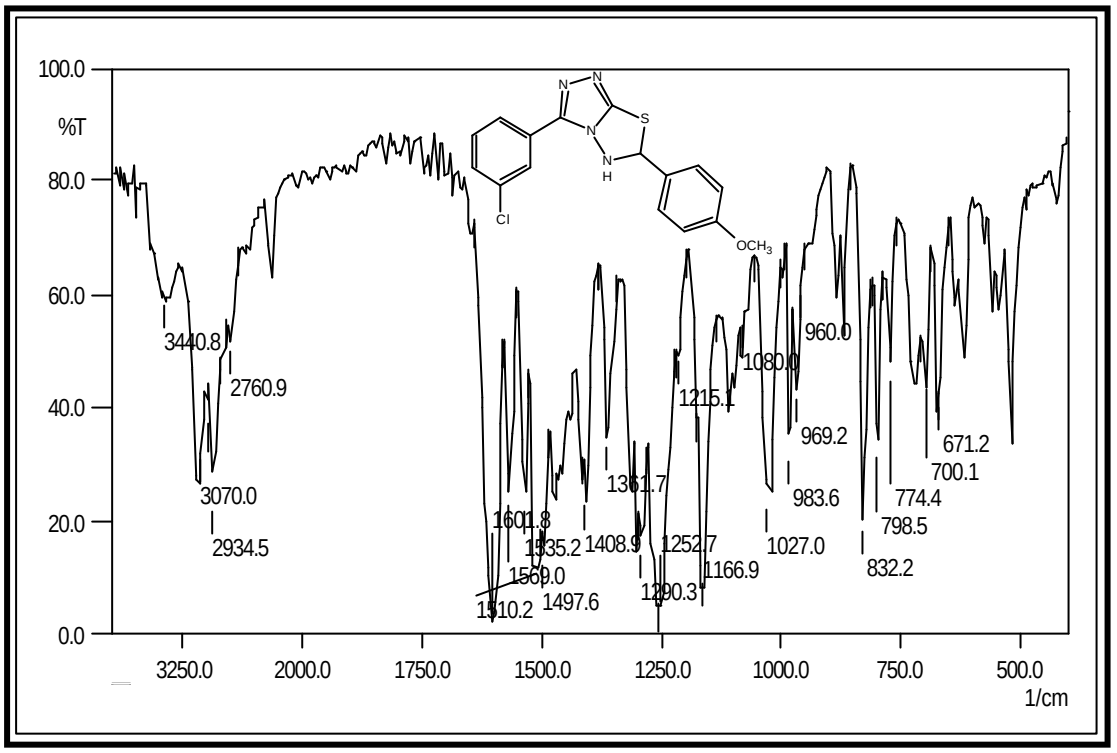


Type (II) R=Aryl

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

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

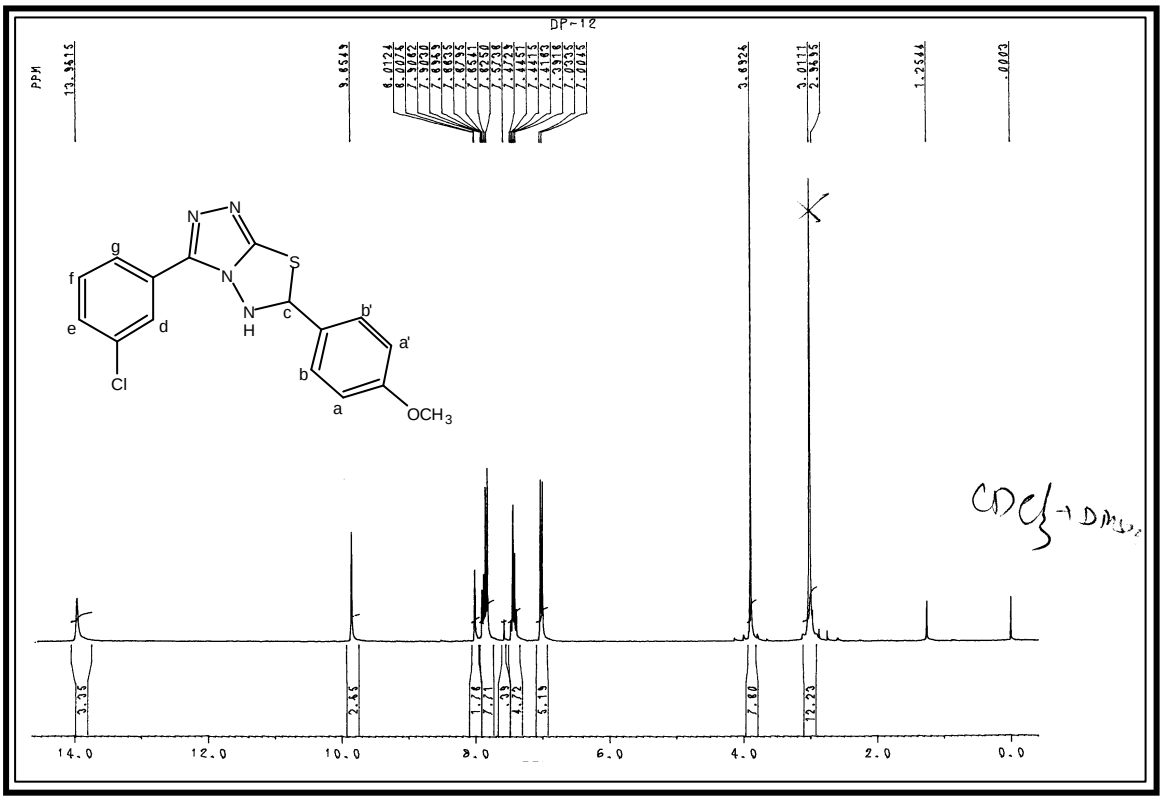
IR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-MEHOXYPHENYL)-5,6-DIHYDRO[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3070	3080-3030	47
	C=C str.	1535	1585-1480	47
	C-H i.p. (def)	1080	1125-1090	47
		1027	1070-1000	47
	C-H o.o.p. (def)	832	835-810	47
Triazole	C=N str.	1601	1612-1593	47
	C-N str.	1166	1220-1020	50
	N-N str.	1027	1050-1010	47
Ether	C-O-C str.(asym.)	1252	1275-1200	48
(Ar-O-R)	C-O-C str.(sym.)	1027	1075-1020	47
Halide	C-Cl str.	774	800-600	50
Thiadizole	N-H str.	3440	3450-3200	47
	N-H def.	1569	1650-1580	47
	C-S str.	700	720-570	48

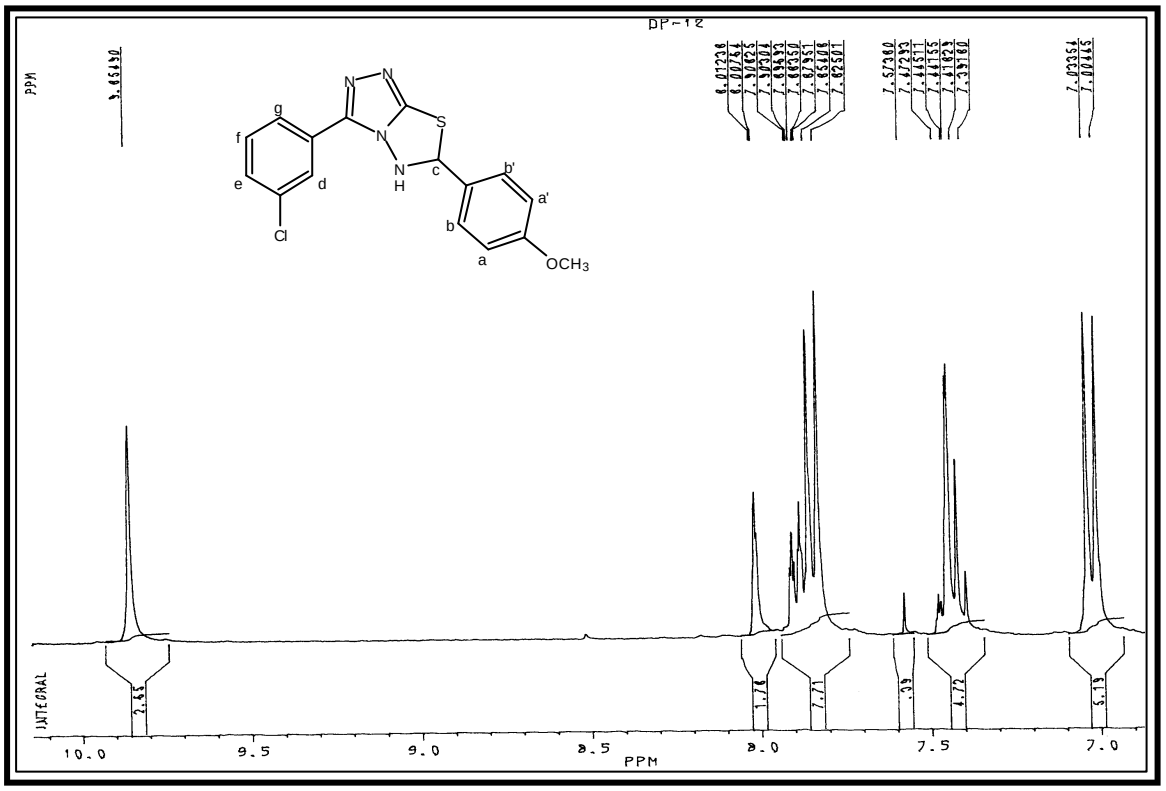
NMR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-MEHOXYPHENYL)-5,6-DIHYDRO[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLE



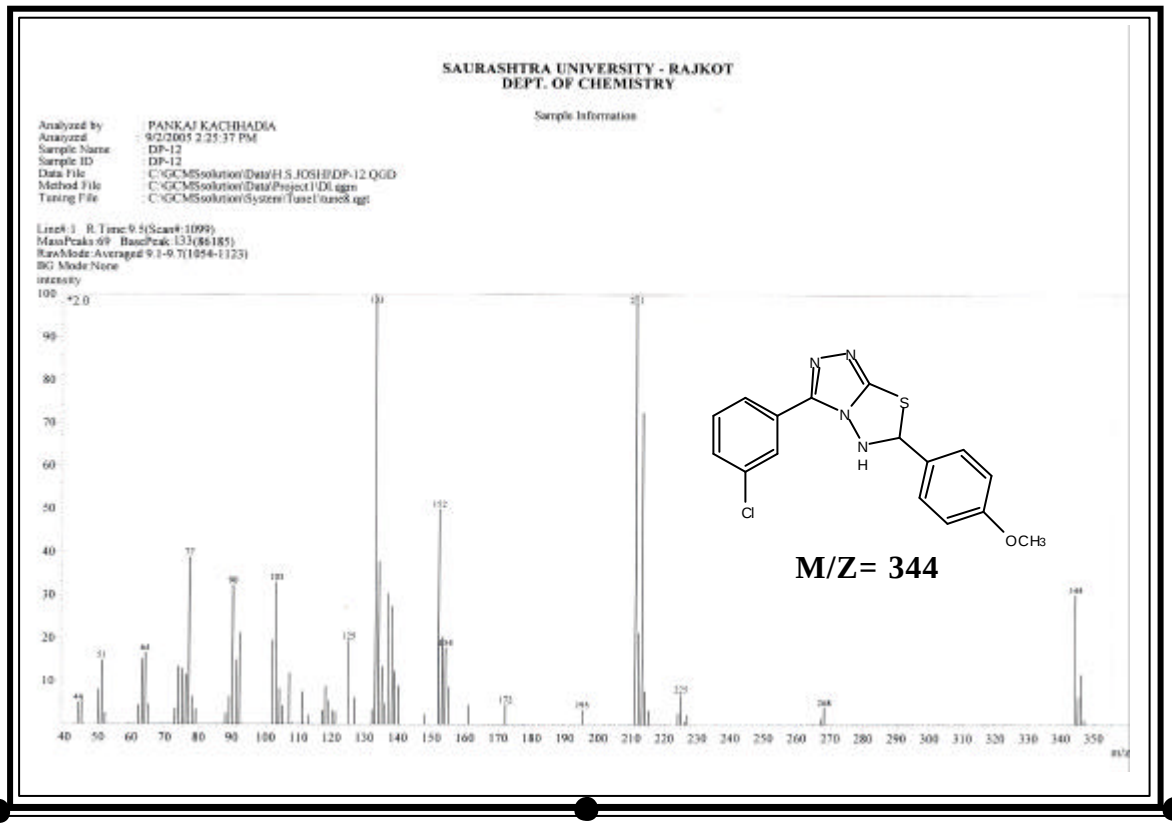
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.89	3H	singlet	Ar-OCH_3	-
2	7.01	2H	doublet	Ar-H(aa')	Jab=8.7
3	7.44	2H	doublet	Ar-H(fg)	Jfe=8.1
4	7.88	2H	doublet	Ar-H(bb')	Jba=8.7
5	7.90	1H	doublet	Ar-He	Jef=7.5
6	8.01	1H	singlet	Ar-Hd	-
7	9.85	1H	singlet	Ar-Hc	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-MEHOXYPHENYL)-5,6-DIHYDRO[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL-5,6-DIHYDRO[1,2,4]TRIAZOLO[1,3,4]THIADIAZOLES.

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

See Part-I, Section-I [A]

[B] Preparation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol.

See Part-II, Section-I [B]

[C] Preparation of 3-(m-chlorophenyl)-6-(p-methoxyphenyl)-5,6-dihydro[1,2,4]triazole[1,3,4]thiadiazole

A mixture of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (2.26g, 0.01mol), p-anisaldehyde (1.39g, 0.01 mol) and p-Ts-OH (50 mg) in dry DMF (50 ml) was refluxed with stirring for 10 hrs. The reaction mixture was poured on to crushed ice and thus solid separated was filtered, washed with water and crystallized from methanol yield 60%, m.p. 265°C, Anal. Calcd. For $C_{16}H_{13}ClN_4OS$: C, 55.73; H, 3.80; N, 16.25 %; Found: C, 55.70; H, 3.76; N, 16.21 %.

Similarly other aromatic aldehyde have been condensed. The physical constants are recorded in Table No.2.

[D] Antimicrobial activity of 3-(m-chlorophenyl)-6-aryl-5,6-dihydro[1,2,4]triazole[1,3,4]thiadiazoles

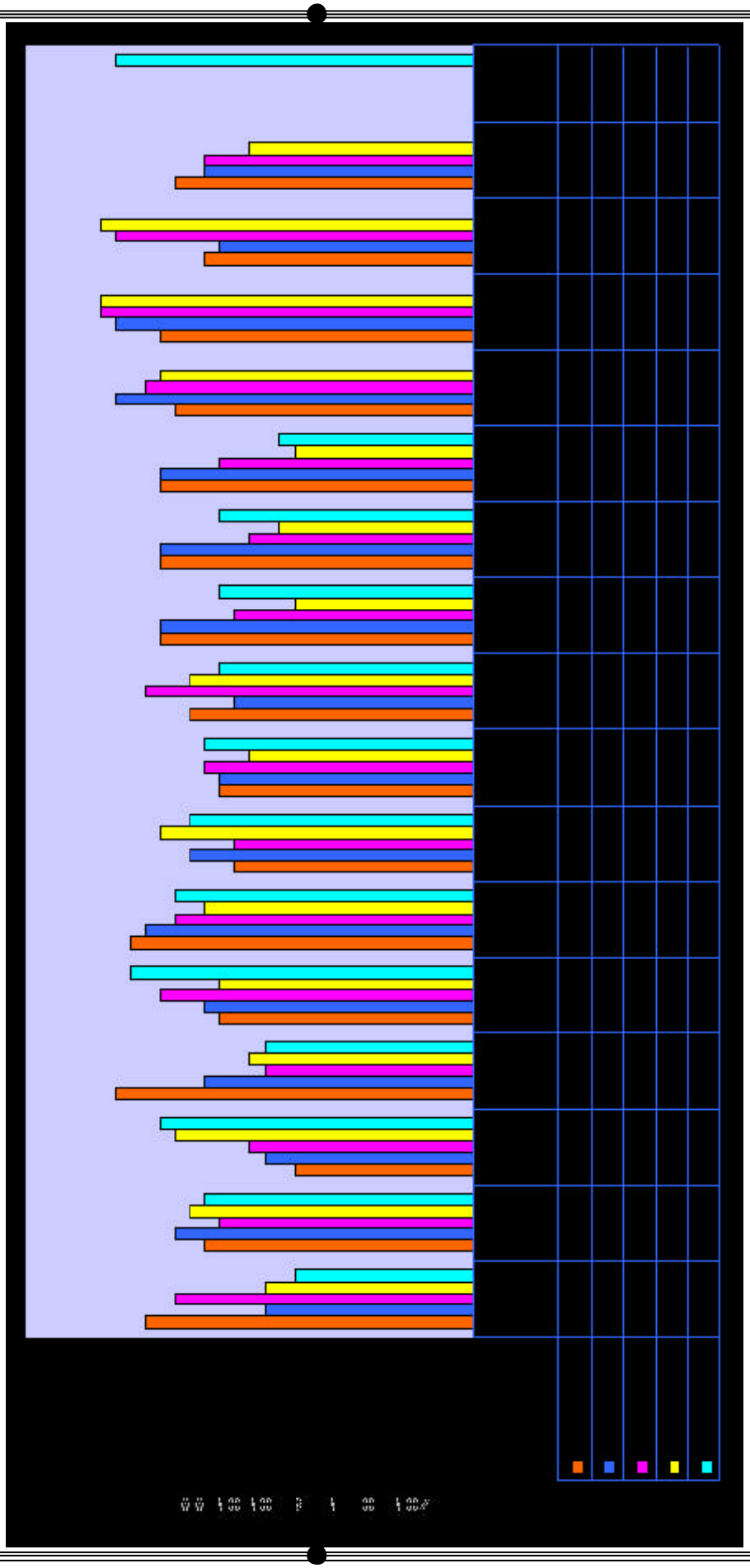
Antimicrobial testing was carried out as described in Part-(I), Section-I (D). The zones of inhibition of the test solution are recorded in Graphical Chart No.2.

TABLE-2 : PHYSICAL CONSTANTS OF 3-(m-CHLOROPHENYL)-6-ARYL-5,6-DIHYDRO[1,2,4]TRIAZOLO[3,4-b] [1,3,4]THIADIAZOLES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
2a	4-OCH_3-C_6H_4-	$C_{16}H_{13}ClN_4OS$	344	265	60	16.25	16.21	0.52	S2
2b	3,4-$(OCH_3)_2$-C_6H_3-	$C_{17}H_{15}ClN_4O_2S$	374	195	58	14.95	14.93	0.57	S2
2c	3-NO_2-C_6H_4-	$C_{15}H_{10}ClN_5O_2S$	359	230	69	19.47	19.44	0.47	S1
2d	2-NO_2-C_6H_4-	$C_{15}H_{10}ClN_5O_2S$	359	210	58	19.47	19.44	0.42	S2
2e	4-OH-C_6H_4-	$C_{15}H_{11}ClN_4OS$	330	180	47	16.94	16.90	0.57	S2
2f	-C_6H_5-	$C_{15}H_{11}ClN_4S$	314	181	61	17.80	17.79	0.52	S1
2g	3-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4S$	349	195	59	16.04	16.00	0.48	S2
2h	4--CH_3-C_6H_4-	$C_{16}H_{13}ClN_4S$	328	221	58	17.04	17.01	0.52	S1
2i	4-F-C_6H_4-	$C_{15}H_{10}ClFN_4S$	332	189	50	16.84	16.81	0.51	S1
2j	3-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4S$	349	178	64	16.04	16.00	0.49	S2
2k	2-OH-C_6H_4-	$C_{15}H_{11}ClN_4OS$	330	198	53	16.94	16.92	0.47	S2
2l	3-OC_6H_5-C_6H_4-	$C_{21}H_{15}ClN_4OS$	406	231	49	13.70	13.69	0.48	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

Graphical Chart No. 2 :Antimicrobial Activity of 3-(m-chlorophenyl)-6-aryl-5,6- dihydro [1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles



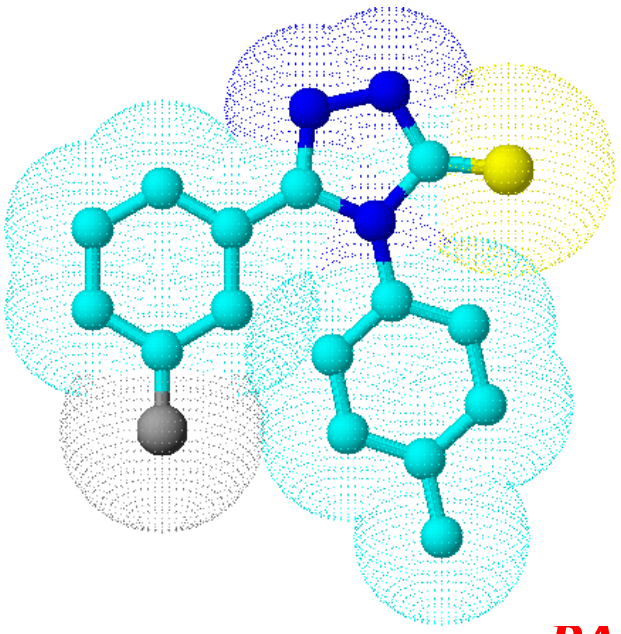
REFERENCES

1. Holla B.S., Poorjary N.K., Rao S.B., Shivananda M.K. ;
   Eur. J. Med. Chem., **37,** 511 (2002).
2. Howard Sard, Peter C. Meltzer and Raj K. Razdan ;
   J. Heterocycl. Chem., **22,**361 (1985).
3. Li-Xue Zhang, An-Jiang Zhang, Xian-Xan Chem, Xin-Xiang Lei, Xiang-Yung Nan., et al.;
   Molecules, **7,** 681-689 (2002).
4. Jag Mohan, Anupama, Anju Rathee. ;
   Indian J. Heterocycl. Chem., **10,** 01-04 (2000).
5. Kidwai Mazaahir, Kumar rajesh, Srivastava Anil, Gupta H.P. ;
   Bio. Org. Chem., **26(5),** 289-294 (1998) ; *Chem. Abstr.,* **131,** 237538x (1990).
6. Wang, Zhong- Yi, You, Tian-pa, You, Ling-Feng. ;
   Youji Huaxue, **19(3),** 288-92 (1999) ; *Chem. Abstr.,***131,** 199657w (1999).
7. Q. Bano, N Tiwari, S Giri and Nizammuddin. ;
   Indian J. Chem., **32B,** 399-403 (1993).
8. Alla A. Hassan, Nasr K. Mohamed, Ahmed M. Shawky and Dietrich Dopp;
   ARKIVOC, 118-128(i) (2003).
9. Khosrow Zamani, Khaht Faghini, M. Reza Sangi and Javed Zolghrenin. ;
   Turk J. Chem., **27,** 119-125 (2003).
10. Mahram Mond A., El-Sherbeny Magda, El-Obaid Abdul-Rahman M.A.; Badria Farid A. ;
    *Alexandria J. Pharm. Sci.,***12(1),**39-44 (1998);
    *Chem.Abstr.,***129**,67756b (1998).
11. F. Malinoski and V. Stoller ;
    Virology, **110,** 281(1981) ; *Chem. Abstr.,***94,** 186145v (1981).
12. Shi Hai-Jian, Shihao-Xin, Wang-Zhong Yi, Youji Huazue, 19(2), 119-199 (1999).
    *Chem.Abstr.,***131,** 447161k (1999).

13. J. Bourdais, D. Dauvillier, P. Gayral, M.C. Rigo Heir, T. Julien, M. Gasquest,T. C. Jamoulle, C.L.Lapiere. ;
Eur. J.Med.Chem., **16,** 233 (1981).
14. Allan Robin D., Apsotopoulos Christine, Richarson Jennider A. ;
Aust. J. Chem., **43(10),** 1767-72 (1990).
15. Kidwai Mazaahir, Kumar Rajesh, Shrivastava Anil, Gupta H. D. ;
Bio.Org.Chem., **26(5),** 289-294 (1998) ; *Chem.Abstr.,* **131,** 237538x (1999).
16. Schenone Silvia, Bruno Olga, Ranise Angelo, Bondvalli Francesco. ;
Farmaco, **53,** (8-9), 586-589 (1998) ; *Chem.Abstr.,* **130,** 296650q (1999).
17. Lee Byung H., Dutton Fred E., Clotheir Michael F., Bowman Jerry.;
Bio.Org.Med.Chem. Lett., **9(12),** 1727-1732 (1999).
18. M.R.Mody, A.R.Prasad, T.Ramlingam and P.B.Sattur. ;
Ibid., **59,** 769 (1982) ; *Chem.Abstr.,* **97,**2161310 (1982).
19. Omar Mohmoud T. ;
Egypt J. Pharm. Sci., 1997 (Pub 1998), **38 (4-6),** 271-280 (1997) ; *Chem.Abstr.* ,**131,** 257474x (1999).
21. K.Hoggarth, Paul Rathgab. ;
J. Indian Chem. Soc., **52,** 750 (1975); Chem.Abstr. 72, 127345 (1969).
22. C. Tony. ;
Gen. Offen., **2,** 050, 479 (1971) ; *J.Indian.Chem.Soc.,* **52,** 750, (1975).
23. Huebl Dieter, Pierob Ernst Albrecht, Jappien H., Baument D. ;
Ger. Chem. D.E., **3,** 821, 953 (Cl. CO7D285/72); *Chem.Abstr.,* **113,**6350n (1990).
24. Galad A.K., Khaji I. M. Mahajan Shetti C.S. ;
Indian J. Heterocycl.Chem. **2(1),** 207-56 (1992).
24. Vergne Febrice, Andrianjard Charles, Ducrot Pierre. ;
Eur. Pat. Appl. EP 1, **193,**261 (Cl. CO7D285/135) (2002); *Chem.Abstr.,***136(18),** 279460v, (2002).
25. Laddi U.V., Talawar M.B., Desai S.R., Bennur R.S., Bennur S.C. ;
Indian J. Chem. Section B : Organic Chemistry including Medicinal Chemistry, **40 B (9),** 828-833 (2001); *Chem.Abstr.* **136(5),** 69794f (2002).

26. Gamill Ronald B., Vander Velde Susan, Nugent Richard Allen. ;
PCT Int. Appl. WO 99, **20,** 618 (Cl.CO7D285/135) (1999).
*Chem.Abstr.,***130(23),** 311799z (1999).
27. Mobinikhaledi A.; Zamani Kh; Iqbal R., Tofight T. ;
J.of the Chemical Society of Pakistan, **24(4),** 269-274 (2002).
28. Che Chao, Mao Shu-Fen, Quin Zhao-Hai; Yingyong Hua-Xue. ;
Chem.Abstr. **137(23),** 3378162 (2003).
29. Celin Chazalette, Bernard Masereel, Stephanie Rolin, Anne Thiry, Andrea Scozzafava; et al.;
Bioorg. Med. Chem. Lett., **14,** 5781-5786 (2004).
30. Athansia Varvaresou, Theodora Siatrapapastailkoudi, Andrew Tsotinis, Anna Tsantili-Kakoulidene, Alexandre Vamvakides. ;
IL Farmaco, **53(5),** 320-326, (1998).
31. Pradeep Mishra, Shakva A.K. Agrawal R.K., Patniak G.K. ;
Short Communication, **22(2),** 113-116, (1990).
32. Bernard Masercel, Stephanie Robin, Francesco Abbate, Andrea Scozzafava, Claundiu T. Supuran.;
J.Med.Chem., **45,** 312-320, (2002).
33. Claudiu T. Supuran, Andred Scozzafava. ;
Eur.J.Med.Chem., **35(9),** 867-874 (2000).
34. Erhan Palaska, Gulay Sahin, Pelm Kelrcen N., Tugba Durla, Gulcan Altinok.;
IL Farmaco, **57(2),** 101-107 (2002).
35. J.M. Colacino, D.C.Delong, J.R.Nelson, W.A.Spitzer, J.Tang, F.Victar, C.Y.Wu. ;
Antimicrob. Agents Chemother, **34(11),** 2156-2163 (1990).
36. Lisa M. Thomasco, Robert C. Gadwood, Elizabeth A. Weaver, Jason M. Ochoada, Charles W. Ford. et al. ;
Biorg. Med. Chem. Lett. **13(23),** 4193-4196 (2003).
37. Samir A. Carvalho, Edson F. da Silva, Richardo M. Santa-Rita, Solange L.de Castro, Carlos A.M. Fragd ;
Bioorg. Med. Chem.Lett., **14(24),** 5976-5970 (2004).
38. Zahra Kiani, Fatemeh Sottani, Alireza Foroumadi. ;
IL Farmaco, **58(11),** 1073-1076, (2003).

39. Alireza Foroumadi, Shirin Pournourmmadi, Fatemch Soltani, Mitra Asgharian-Rezaee, et al. ;
Bioorg. Med. Chem. Lett. **15(8),** 1983-1985 (2005).
40. Hatice N. Dogan, Arzu Duran, Sevim Rollas, Goksel Sener, Meral K. Uysal and Dumrul Gulen. ;
Bioorg. andMed. Chem., **10(9),** 2893-2898, (2002).
41. Nalan Terzioglu, Aysel Gursoy. ;
Eur. J. Med. Chem., **38(7-8),** 781-786, (2003).
42. Alireza Foroumadi, Ali Asadipour, Maryam Mirzaci, Javad Karimi, Saeed Emami. ;
IL Farmaco, **57(9),** 765-769, (2002).
43. S. Karakus and S. Rollas. ;
IL Farmaco, **57(7),** 577-581, (2002).
44. Jui-Yi Chou, Shin-Yu Lai, Shiow-Lin Pan, Gucy-Mei Jow, Ji-Wang Chern, Jih-Hwa Guh. ;
Biochemical Pharmacology, **66(1),** 115-124, (2003).
45. A.L. Berry. ;
The antimicrobial Susceptibility test, Principle and Practice, illusled and *Febiger, Philadelphia,* 180-93 (1976).
46. F. Simoncina, R.Rangane and C. Calani. ;
Farmaco Ed. Part, **23(10),** 559-70 (1968). *Chem.Abstr.,* **69,** 019851d (1968).
47. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
48. C. N. R. Rao;
"Chemical application of Infrared spectroscopy" Academic press, New York (1963).
49. "Strukturaufklarang Organischer Verbindungen"
Mit Spektroskopischem methoden zweite, uberarbeiete and erganzte Auflage (Springer -verlag, Berlin Beidel -berg, New York- 1981).
50. Silverstein Bassler and Morrill.;
Spectroscopic identification of organic compounds fifth edition (1991) by John Wiley & Sons Inc.



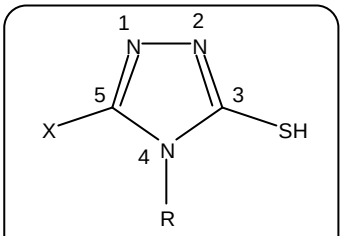
PART - II

STUDIES ON

4- ARYLTRIAZOLES

INTRODUCTION

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

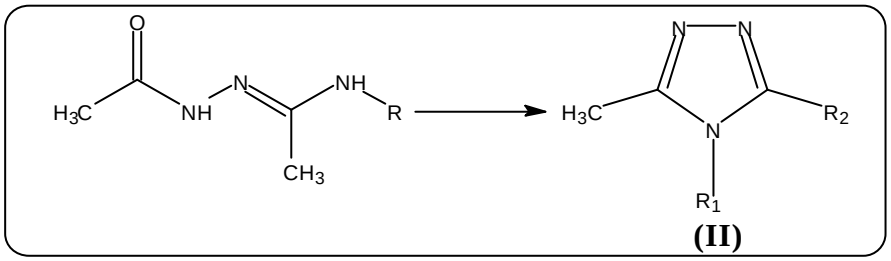


(I) R=Aryl

SYNTHETIC ASPECT

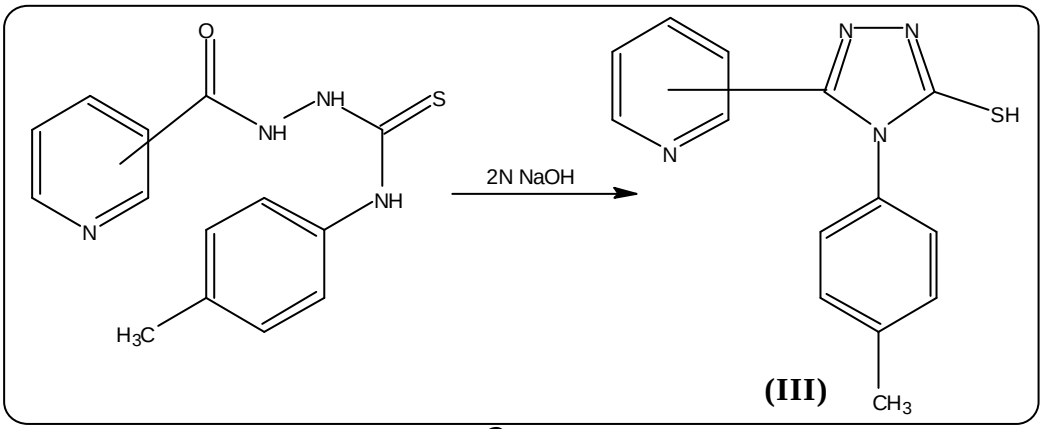
Several methods have been reported in the literature for the preparation of 4-aryltriazoles.

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



(II)

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



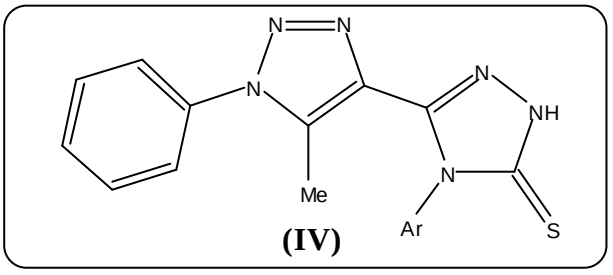
(III)

BIOLOGICAL IMPORTANCE

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

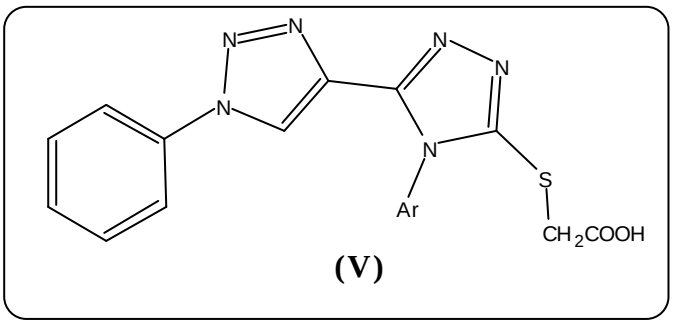
1. Antiinflammatory[3]
2. Biocides[4]
3. Cholesteryl ester transfer protein[5]
4. Antidepressant[6]

Chang et al.[7] have synthesized aryltriazoles (IV) and reported them as antifungal drugs. Crisan O. et al.[8] have screened antiinflammatory activity of triazoles. Varvaresou A. et al.[9] have synthesized triazoles and reported their antimicrobial potency and antidepressant activities. Papakonstantinou et al.[10] have investigated some triazole derivatives possessing significant antiviral activity. Konosu T. and co-workers[11] have prepared aryltriazoles as fungicides.



(IV)

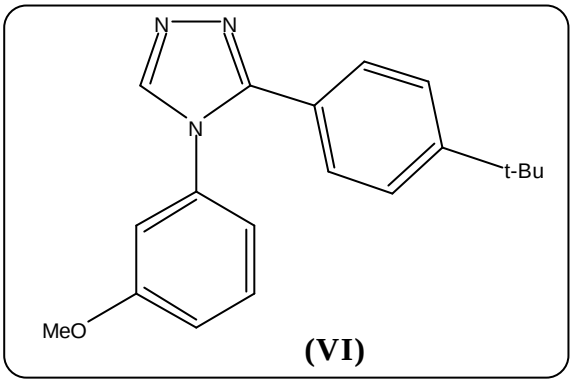
Yasuda N. et al.[12] have discovered aryltriazoles which have been extensively investigated for their antibacterial properties. S.C. Bahel et al.[13] have documented anti-fungal activity of aryl triazoles. Athansia varvaresou et al.[14] have synthesized aryltriazoles possessing antidepressant activity. Chu. Changhu et al.[15] have screened 4-aryltriazoles (V) for their antifungal activity.



(V)

Some aryltriazoles possessing analgesic and diuretic activities have been synthesized by Shrivastava S.K. et al.[16] Wang Sheng et al.[17] have reported triazoles as herbicidal agents.

Lowe R.F. and co-workers[18] have reported aryltriazoles as useful antagonists. Holla B. et al.[19] have documented anticancer activity of aryltriazoles. Welsh et al.[20] have discovered aryltriazoles (VI) and reported them as analgesic agents.



(VI)

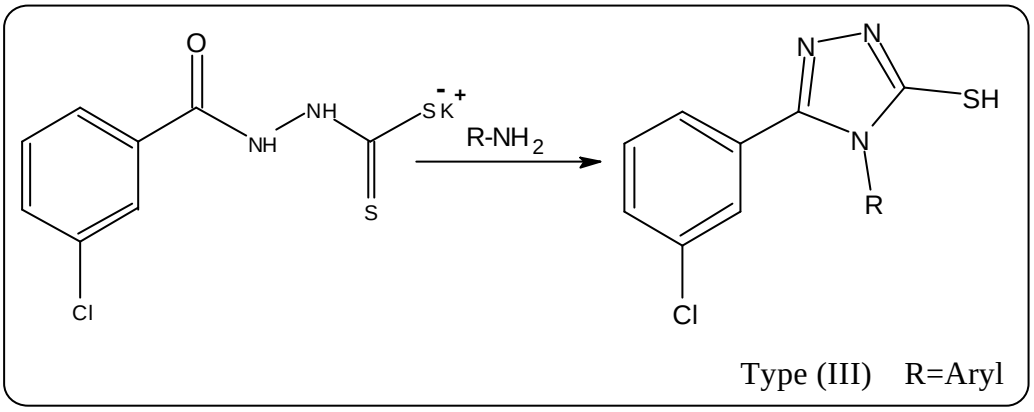
Looking to this significant biological activity of 4-aryltriazole derivatives, it was subject of interest to study some 4-aryltriazole derivatives which have been described as under.

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

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-4-ARYL-4*H*-1,2,4- TRIAZOLE-3-THIOLS.

4-Aryltriazole derivatives are associated with broad spectrum of pharmacological activity. In views of these findings, it appeared of interest to synthesize 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols. The synthesis of triazole derivatives of type(III) have been undertaken by heating dry potassium-m-chloro benzyl dithiocarbamate with different aromatic amines.

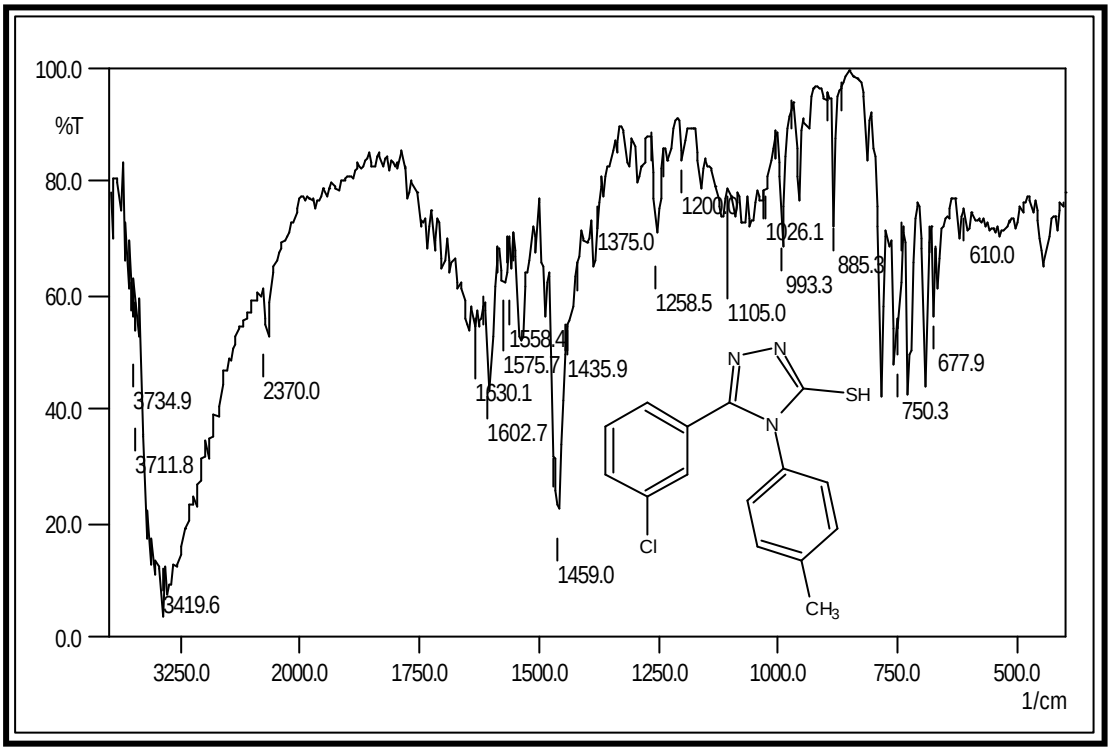


Type (III) R=Aryl

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

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

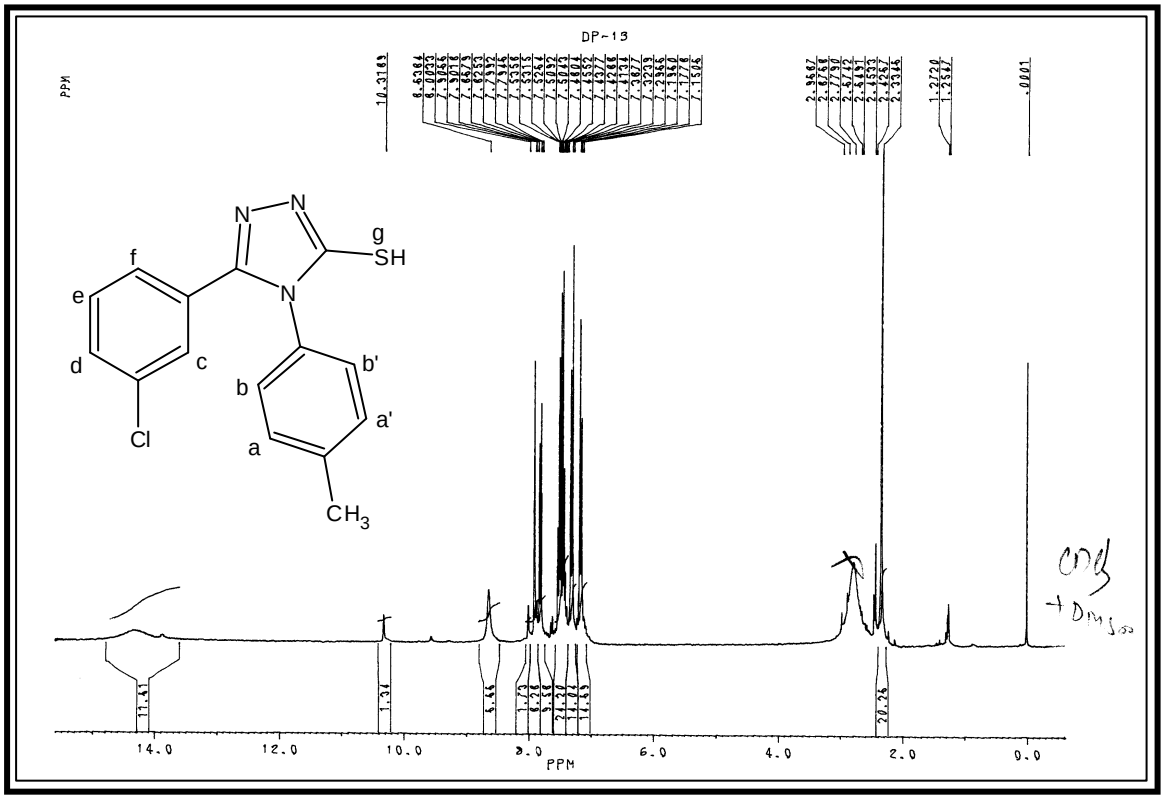
IR SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-4-(p-METHYLPHENYL)-4*H*-[1,2,4]TRIAZOLE-3-THIOL



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	2975-2950	21
-CH_3	C-H str. (sym.)	2850	2880-2860	21
	C-H def.(asym.)	1435	1470-1435	21
	C-H def.(sym.)	1375	1385-1370	21
Aromatic	C-H str.	3030	3080-3030	22
	C=C str.	1558	1585-1570	22
		1459	1520-1480	22
	C-H i.p. (def)	1105	1125-1090	22
	C-H o.o.p. (def)	815	835-810	22
Triazole	S-H str.	2370	2400-2300	23
	C=N str.	1630	1640-1500	21
	C-N str.	1200	1220-1020	21
	N-N str.	1026	1050-1010	23
	C-S str.	667	700-600	23
Halide	C-Cl str.	758	800-750	23

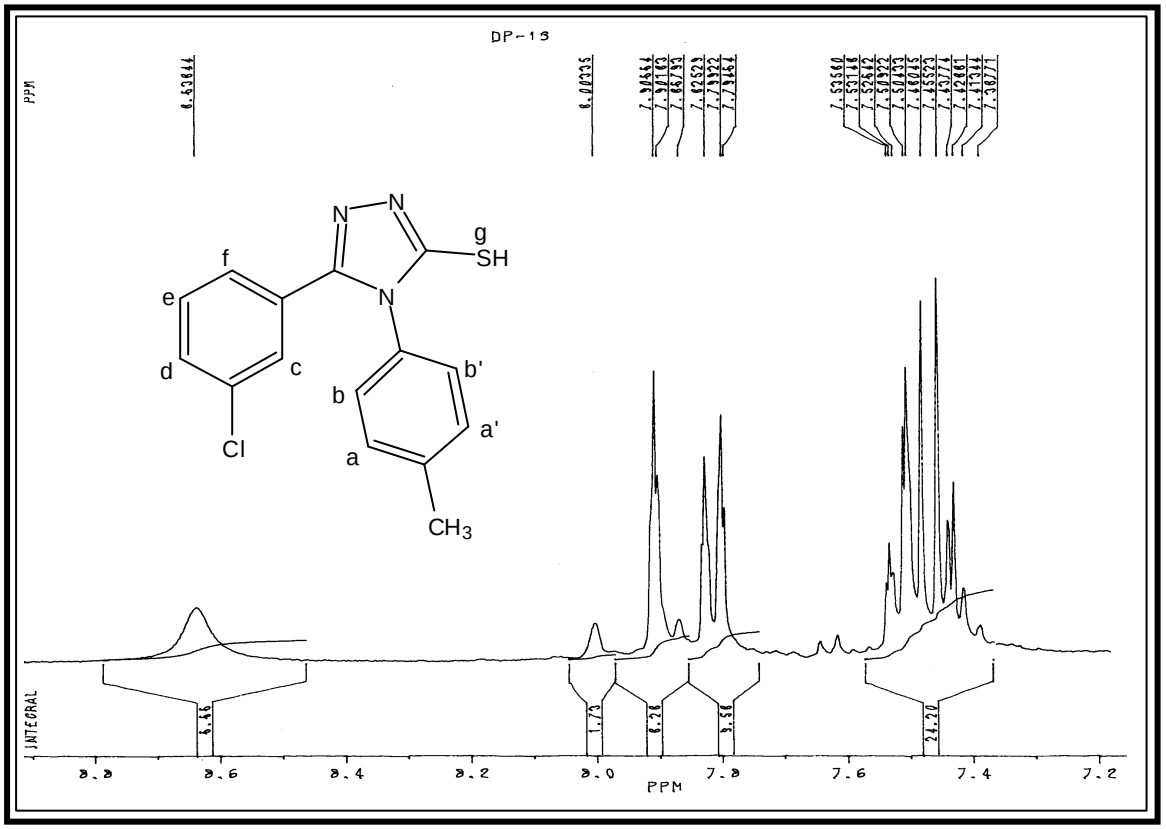
NMR SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-4-(p-METHYLPHENYL)-4*H*-[1,2,4]TRIAZOLE-3-THIOL



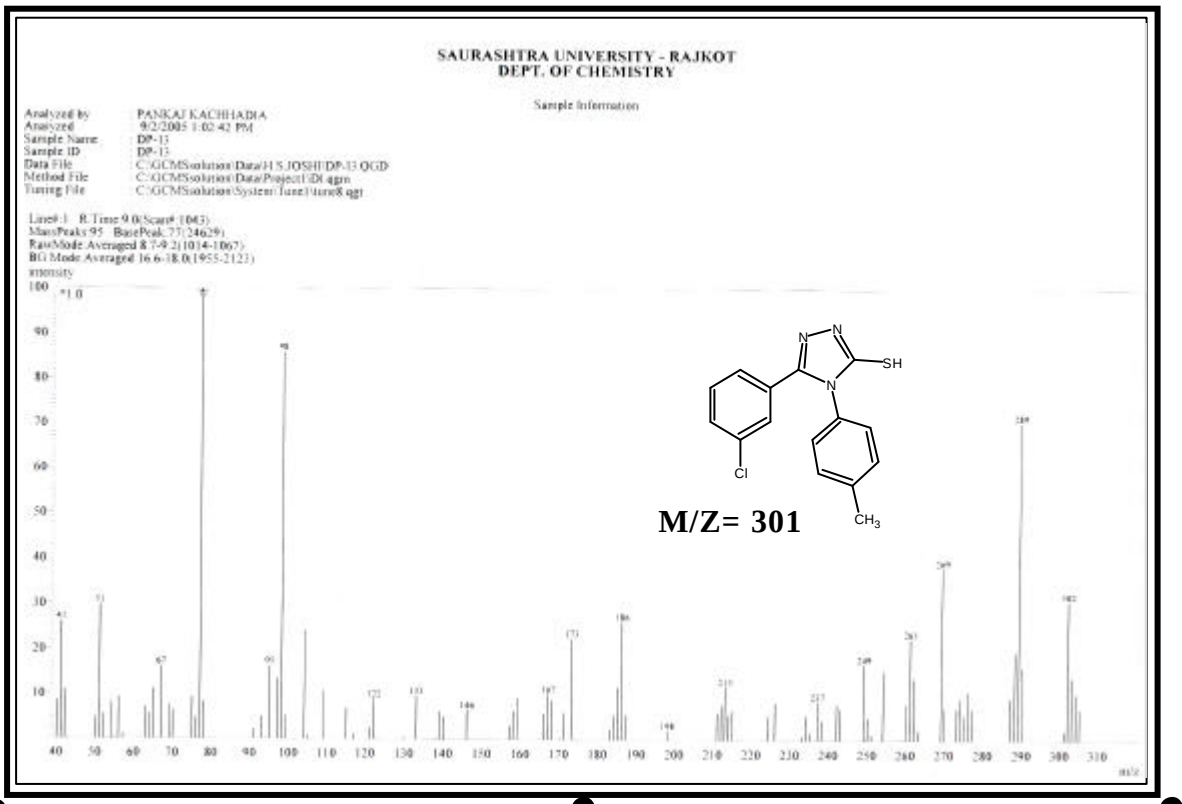
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.42	3H	singlet	Ar-CH_3	-
2	7.38-7.53	4H	multiplet	Ar-(Haa'+Hef)	-
3	7.79	2H	doublet	Ar-Hbb'	-
4	7.90	2H	doublet	Ar-Hde	-
5	8.63	1H	broad	-SH	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-4-(p-METHYLPHENYL)-4*H*-[1,2,4]TRIAZOLE-3-THIOL



EXEPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-4-ARYL-4*H*-1,2,4- TRIAZOLE-3-THIOLS.

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

See Part-I, Section-I (A)

[B] Preparation of 5-(m-chlorophenyl)-4-(p-methyl phenyl)-4*H*-1,2,4-triazole-3-thiols.

A mixture of potassium-m-chlorobenzyl dithiocarbamate (2.85g, 0.01M) and p-toludine (1.07g, 0.01M) was heated at 140°C until the evolution of H_2S gas ceased (10 hrs.). The product was dissolved in DMF (20ml), treated with dilute HCl and then poured on to crushed ice. The product was crystallized from ethanol. Yield 70%, m.p. 220°C. Anal: calcd. For $C_{15}H_{12}ClN_3S$: C,59.70; H,4.01; N,13.92 %; Found ; C,59.66; H,3.96; N,13.90 %.

Similarly other aromatic amines were condensed. The physical constants are recorded in Table No.3.

[C] Antimicrobial activity of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

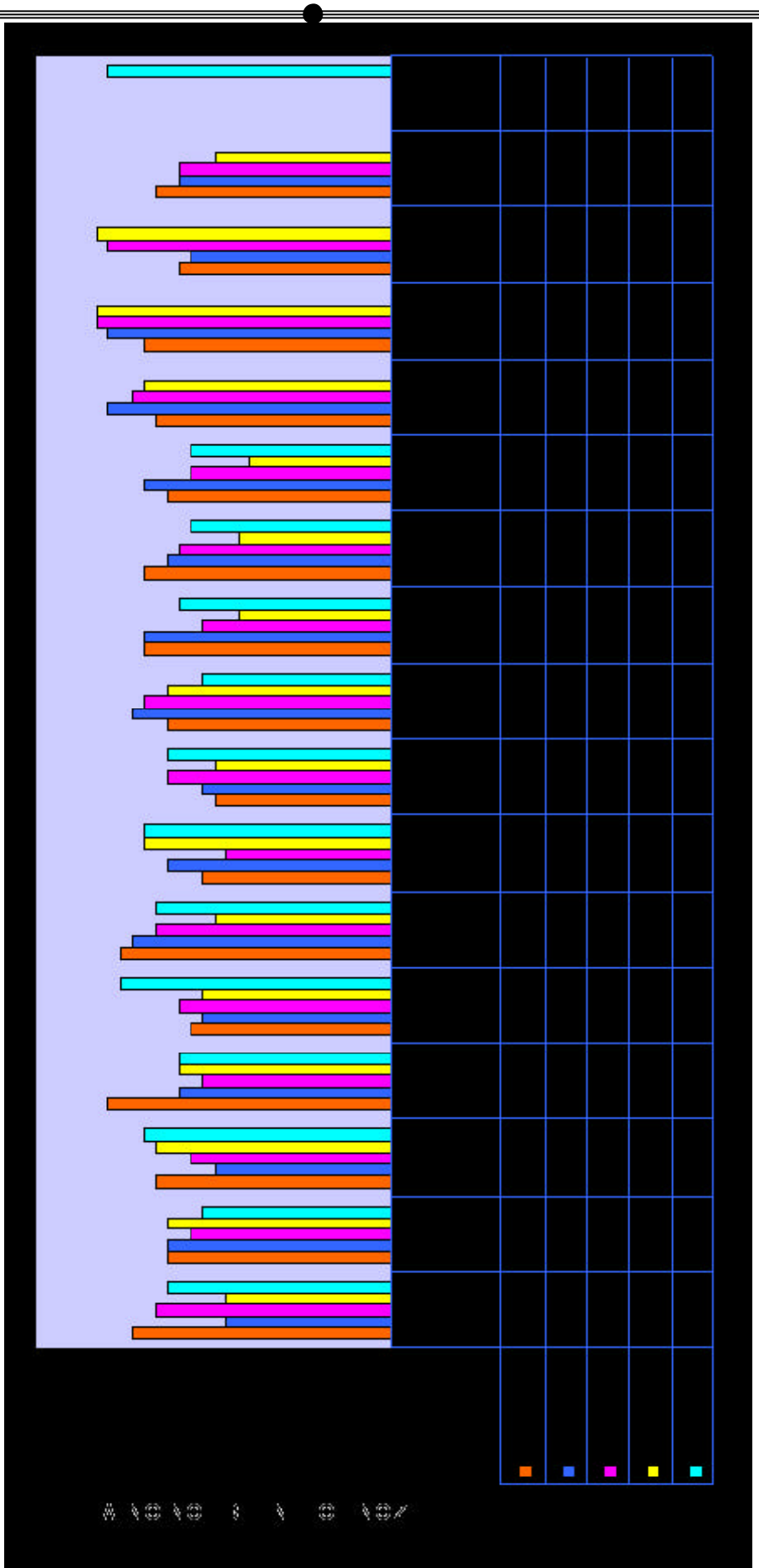
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of compounds are recorded in Graphical chart No.3.

TABLE-3 : PHYSICAL CONSTANTS OF 5-(m-CHLOROPHENYL)-4-ARYL-4*H*-1,2,4-TRIAZOLE-3-THIOLS

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
3a	2,5-$(Cl)_2$-C_6H_3-	$C_{14}H_8Cl_3N_3S$	356	220	70	11.78	11.76	0.42	S2
3b	3-NO_2-C_6H_4-	$C_{14}H_9ClN_4O_2S$	332	195	68	16.84	16.81	0.57	S2
3c	3-Cl-C_6H_4-	$C_{14}H_9Cl_2N_3S$	322	183	69	13.04	13.00	0.49	S1
3d	4--COOH-C_6H_4-	$C_{15}H_{10}ClN_3O_2S$	331	175	58	12.67	12.65	0.62	S2
3e	4-OCH_3-C_6H_4-	$C_{15}H_{12}ClN_3OS$	317	210	61	13.22	13.21	0.46	S2
3f	4-NO_2-C_6H_4-	$C_{14}H_9ClN_4O_2S$	332	191	71	16.84	16.81	0.51	S1
3g	3--COOH-C_6H_4-	$C_{15}H_{10}ClN_3O_2S$	331	170	68	12.67	12.65	0.55	S2
3h	2-NO_2-C_6H_4-	$C_{14}H_9ClN_4O_2S$	332	230	58	16.84	16.81	0.44	S1
3i	3-Cl-4-F-C_6H_3-	$C_{14}H_8Cl_2FN_3S$	340	189	60	12.35	12.31	0.57	S1
3j	2-COOH-C_6H_4-	$C_{15}H_{10}ClN_3O_2S$	331	188	64	13.22	13.21	0.45	S2
3k	4-CH_3-C_6H_4-	$C_{15}H_{12}ClN_3S$	301	220	70	13.92	13.90	0.52	S2
3l	4-CH_3-C_6H_4-	$C_{15}H_{12}ClN_3S$	301	240	70	13.92	13.90	0.48	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

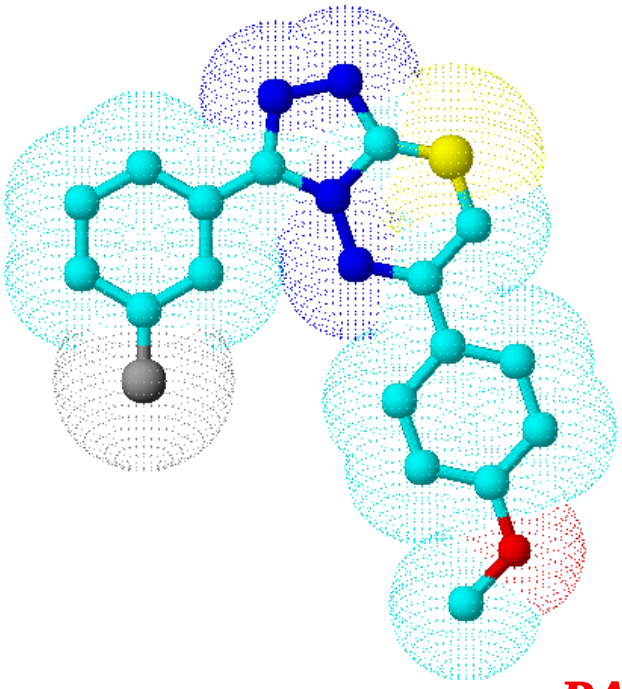
Graphical Chart No. 3 : Antimicrobial Activity of 5-(m-chlorophenyl)-4-aryl-4*H*-[1,2,4]triazole-3-thiols



REFERENCES

1. Alan R. Katrizky, Dmytro O. Tymoshenko, Ke Chem and Ashraf A. Fattah. ;
   ARKIVOC, **(ii),** 101-108 (2001).
2. Khosrow Zamani, Khalid Faghini, M. Reza Sangi, Javed Zologharnein.
   Turk J. Chem., **27,** 119-125 (2003).
3. Amir, Mohammed, Oberoi, antu, alam, Shah. ;
   Indian J. Chem., **38B,** 237-239 (1990) ; *Chem.Abstr.,***131,** 5225x (1999).
4. Jautelat, Manfred, Tiemann, Ralf, Dutzmann, Stefan, Stonzel, Klaus.
   Ger. Offen. DE **19,** 520,098 (1996); *Chem.Abstr.,* **126,** 89373q (1997).
5. Silkoski, James A. ;
   PCT Int. appl.wo 99, 14,204 (Cl. Co7D249/12) ; *Chem.Abstr.,* **130,** 237570b (1999).
6. Amir, Mohd., Srivastva, jagriti. ;
   Pharmakeutike, **9(2),** 79-83, (1996) ; *Chem. Abstr.,* **126,** 89317z (1997).
7. Chang-Hu Chu, Xin-Ping Hui, Yan Zhang, Zi-Yi Zhang, ZhiiChan Li, Ren-An Liao. ;
   J. of the Chinese Chem. Soc., **48,** 121-125 (2001).
8. Crisan O., Bojta M., Vsrea Manoz Teresa, Terencio Mari Carmen, Asensio Aguitas Gregorio, Ziahario V. ;
   Farmaco, **49(5),** 15-22 (2001).
9. Varvaresou A., Siatra-Papaskaikoudi T., Dalla Tsotinis A., Vamakides A. ;
   Framaco., **53(5),** 320-6 (1998).
10. Papakonstantinoy-Geroufalia S.S., Tani E. Todoulou O. Papadki-Viliraki A., Filippatos E., et al.;
    J. Pharm Pharmacol., **50(1),** 117-24 (1998).
11. Konosu T.,Tajima Y.,Takeda N,Miyaoka T.,Kasahara M, Yasuda H., Oida S. ;
    Chem. Pharm Bull (Tokyl), **39(10),** 2581-9 (1991).

12. Yasuda N., Iwagami H., Sasaki Y. ;
J. of Antibiol. (Tokyo), **36(11),** 1516-24 (1983).
13. S.C. Bahel, B.L. Dubey, N. Nath, Janmejai K. Shrivastava. ;
Inorganica Chimica Acta, **91(3),** L43-L45 (1984).
14. Athasia Varvaresou, Theodora Siatra Papastaikoudi, Andrew Tsotinis, Anna Tsantili Kakoulidon, Alexandre Vamvakides. ;
IL Farmaco, **53(5)**, 320-329, (1998).
15. Chu Changhu, Zhang Yan, Hui Xingping, Zhang Ziyi, Li Zhichun, Liao Renan, et al. ;
Kexueban, **37(2),**91-94(Ch.)(2001);Chem. Abstr., 136(18), 279394b (2002).
16. Shrivastava S.K. ; Shrivastava Soumya, Shrivastava S.D. ;
Indian J. Chem., **41B(9),** 1937-1945 (2002) ; Chem.Abstr., 138(11), 153485e (2003).
17. Wang Sheng, Liu Dan, Feng, Guj-Rong, Gong Yin-Xiang, Wang Yan Gang. ;
Chem. Abstr., **137 (19),** 279157x (2002).
18. Lowe R.F. Nelson J, Dang T.N. Crowe P.D, Pahuja A,Mc Carthy J.R. et al. ;
J. Med. Chem., **10,** 48(5), 1540-9 (2005).
19. B.Shivarama Holla, B. Veerendra, M.K. Shivananda, Boja Poojary.;
Eur. J. Med. Chem., **38,** 759-769 (2003).
20. Welsh Willum J., Yu Seong-jue, Nair Anil. ;
PCT. Int. App. WO 03, 66, 050 (Cl.A6lk31/41) (2003); *Chem.Abstr.*, **139(13),** 197487g (2003).
21. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
22. C. N. R. Rao;
"Chemical application of Infrared spectroscopy" Academic press, New York (1963).
23. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.

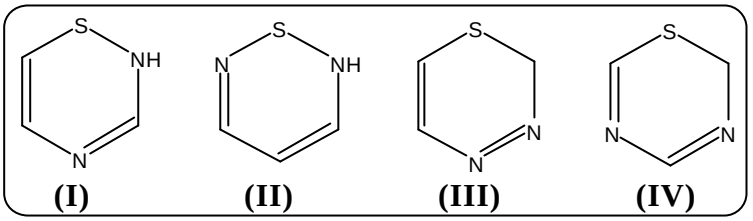


PART - III

STUDIES ON THIADIAZINES

INTRODUCTION

Thiadiazine is a six membered heterocyclic ring system having two nitrogen atoms and one sulphur atom. These may be of four types 2H-1,2,4-Thiadiazine (I); 2H-1,2,6-Thiadiazine (II); 2H-1,3,4-Thiadiazine (III) and 2H-1,3,5-Thiadiazine (IV).

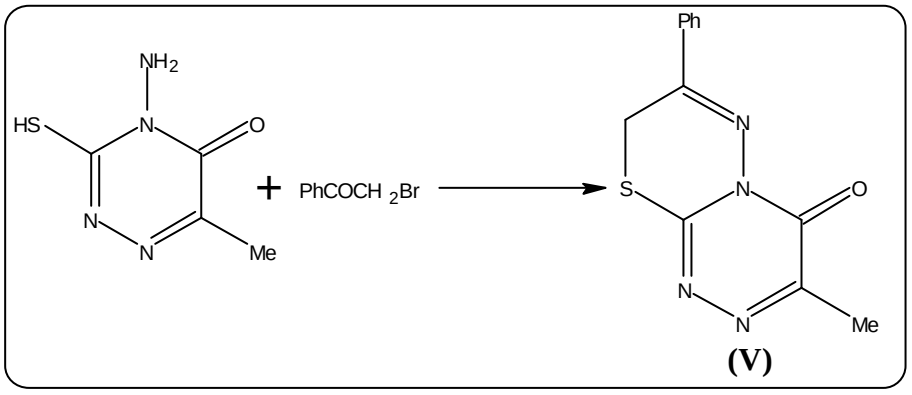


1,3,4-Thiadiazine derivatives are studied extensively because it represents one of the most active class of compounds possessing a wide spectrum of pharmacological activities.[1-3] Many 1,3,4-thiadiazine derivatives involve in many biological processes and serves as a medicinally interesting compounds.

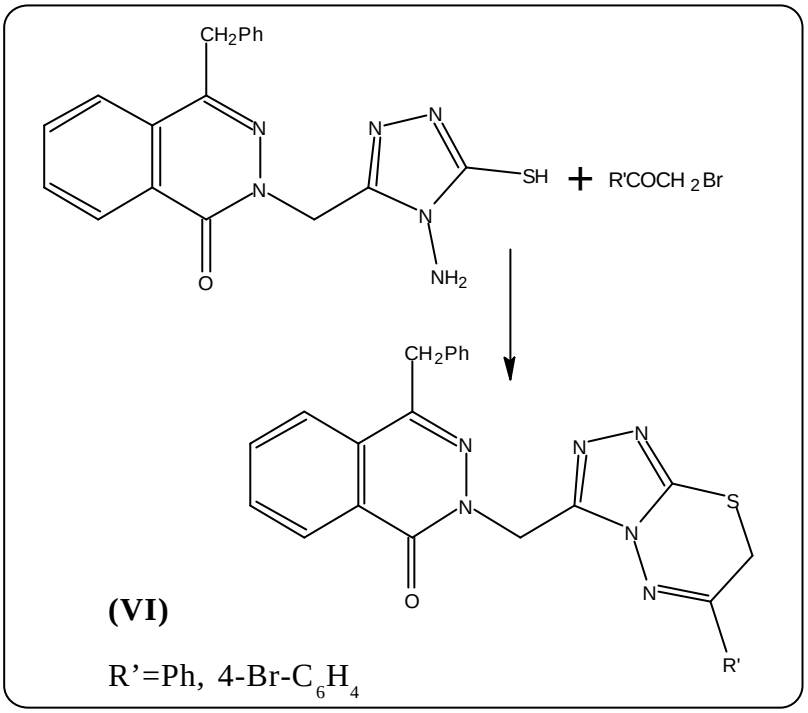
SYNTHETIC ASPECT

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

1. Heravi M.M. et al.[4] have reported that the cyclization of 4-amino-3-mercapto-6-methyl-[1,2,4]triazine-5-one with phenacyl bromide gives 1,3,4-thiadiazine derivatives (V).



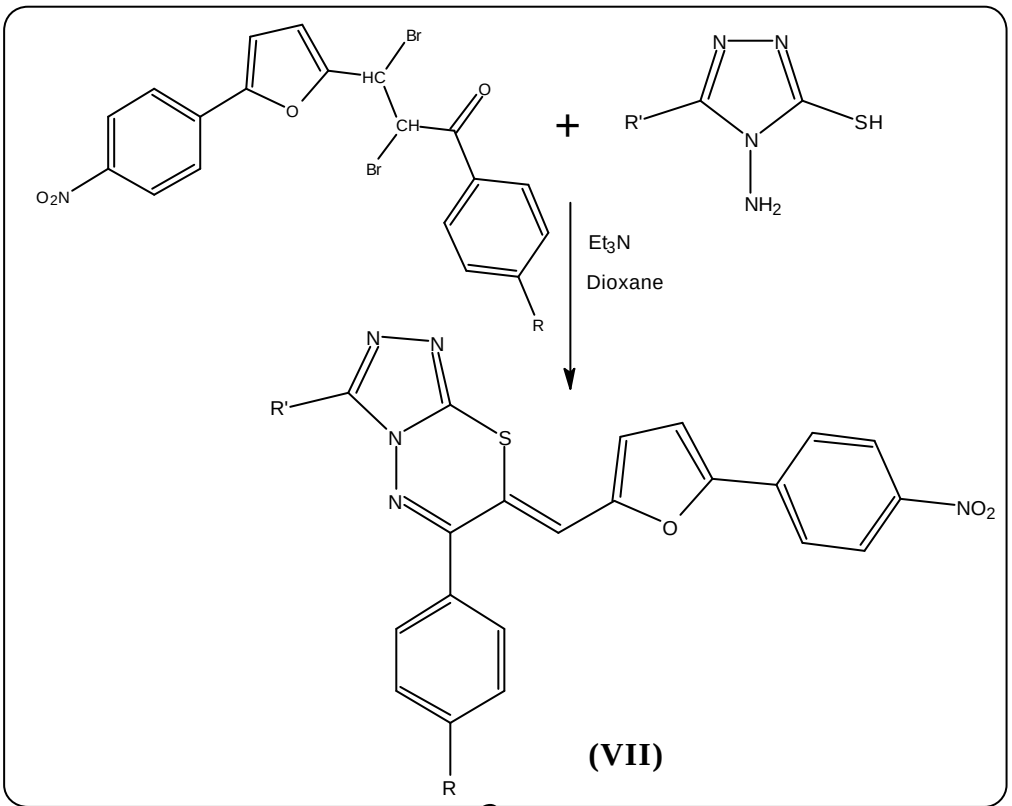
2. Bayoumy B.E. El-Feky S.A. et al.[5] have designed thiadiazine ring system (VI) by the reaction of phthalazinone triazole with phenacyl bromide.



(VI)

R'=Ph, 4-Br-C_6H_4

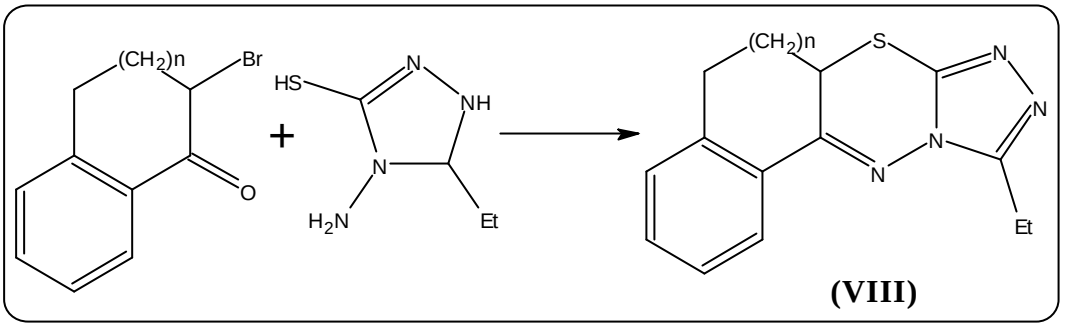
3. B.Shivarama Holla et al.[6] have synthesized triazole thiadiazines (VII) by the cyclization of 2,3-dibromo-1-aryl-3-[5-(p-nitrophenyl)-2-furyl]-2-propen-1-ones and substituted 1,2,4-triazole.



(VII)

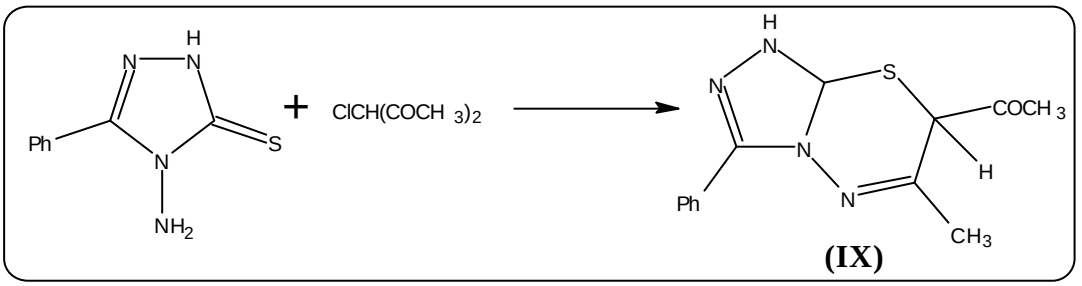
4. Campaigne E. and Selby T. P.[7] have prepared 1,3,4-thiadiazine by the condensation of ethyl-4-chloroacetoacetate with thiosemicarbazide.

5. Alberecht William L. et al.[8] have synthesized s-triazolocycloalkyl hydrothiadiazines (VIII) by the cyclization of *a*-haloketones with 5-substituted-4-amino-4H-1,2,4-triazole-3-thiols.



(VIII)

6. Ahmad S. Shawali et al.[9] have synthesized triazolothiadiazines (IX) by the cyclization of 4-amino-3-mercapto-5-phenyl-1,2,4-triazole and 3-chloro-2,4-pentaanedione.



(IX)

BIOLOGICAL IMPORTANCE

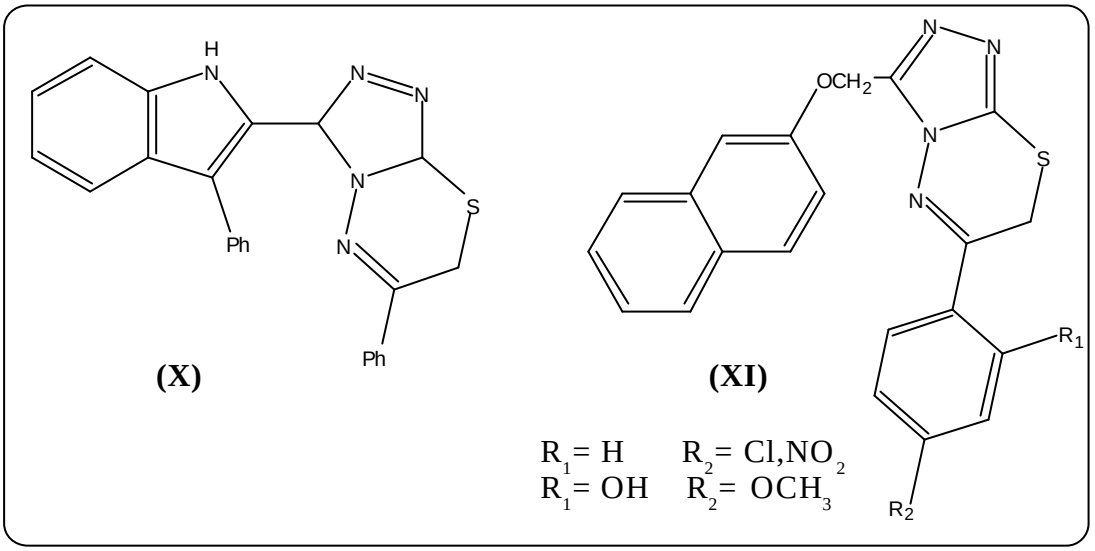
Literature survey reveals that various 1,3,4-thiadiazines have resulted in many potential drugs and are known to exhibit a broad spectrum of biological activities. 1,3,4-Thiadiazine derivatives possess wide range of therapeutic activities which are as under.

1. Antifungal[10]
2. Antibacterial[11]
3. Antimicrobial[12]
4. Antiinflammatory[13]
5. Cardiovascular[14-15]

6. Analgesic[16]

7. Antidepressant[17]

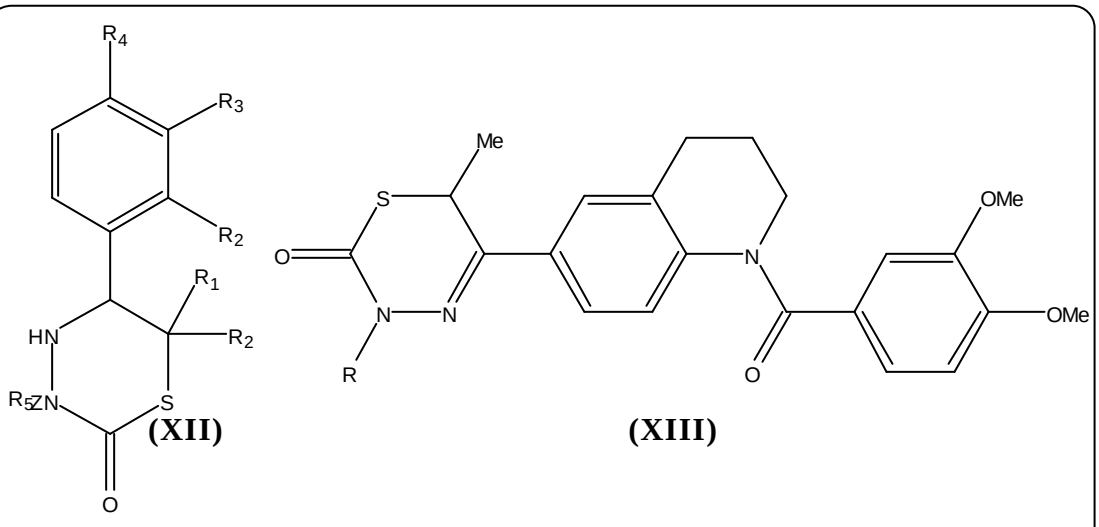
Renuka Devi Patil and J.S. Biradar[18] have reported triazolothiadiazine derivatives as anthelmintic, antiinflammatory and anticatatonic active agents (X). Turan-Zitouni G. et al.[19] have demonstrated analgesic activity of triazole thiadiazines (XI).



(X) **(XI)**

R_1= H R_2= Cl,NO_2
R_1= OH R_2= OCH_3

Mazzone G. et al.[20-21] reported 1,3,4-thiadiazine derivatives as weak antiinflammatory agent and also reported their analgesic activity. Jonas Rochus et al.[22-23] have prepared new thiadiazine derivatives useful as phosphodiesterase IV inhibitors (XII) and cardiovascular agents (XIII).

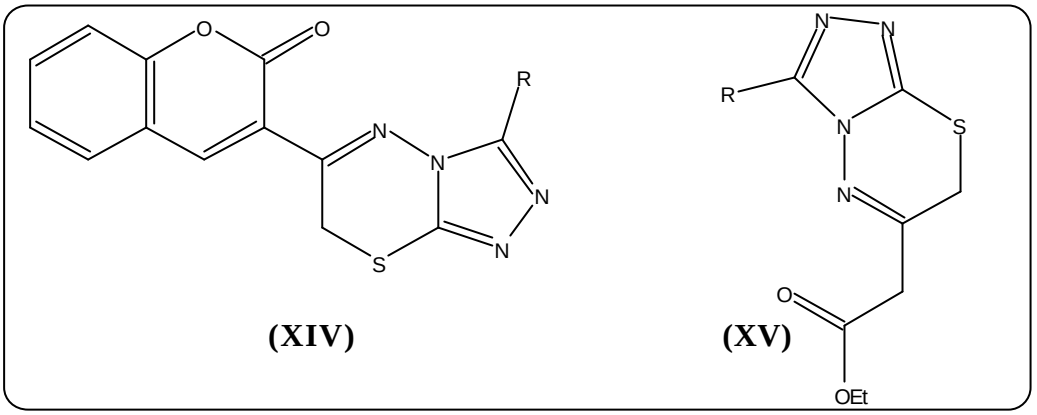


(XII) **(XIII)**

Z= bond OR alkylene R1,R2 = H OR Halo

R5= Substituted Phenyl R3,R4 = OH, alkoxy, halo

Aboul-Fadi T. et al.[24] reported antituberculous activity of thiadiazines. Pirotte B. et al.[25] have documented thiadiazine derivatives as ATP channel openers. Kalluraya B. et al.[26-27] have reported 3-substituted-7*H*-6-(6-bromo-3-coumarinyl)-s-triazolo [3,4,b] [1,3,4] thiadiazines and subjected to antibacterial activity (XIV). Lee, An Rong Taiwan have been reported and pentented triazolothiadiazines as antiinflammatory agents (XV).



(XIV) **(XV)**

Nadkarni B.A. et al.[28] have reported anthelmintic activity of 1,3,4-thiadiazines. El-Shorbagi A N. et al.[29] documented antimicrobial activity of thiadiazine derivatives. Holla B.S. et al.[30] have also reported antibacterial and anticancer activity of 1,3,4-thiadiazines. Vicentini C.B. et al.[31] have documented thiadiazines as fungicides.

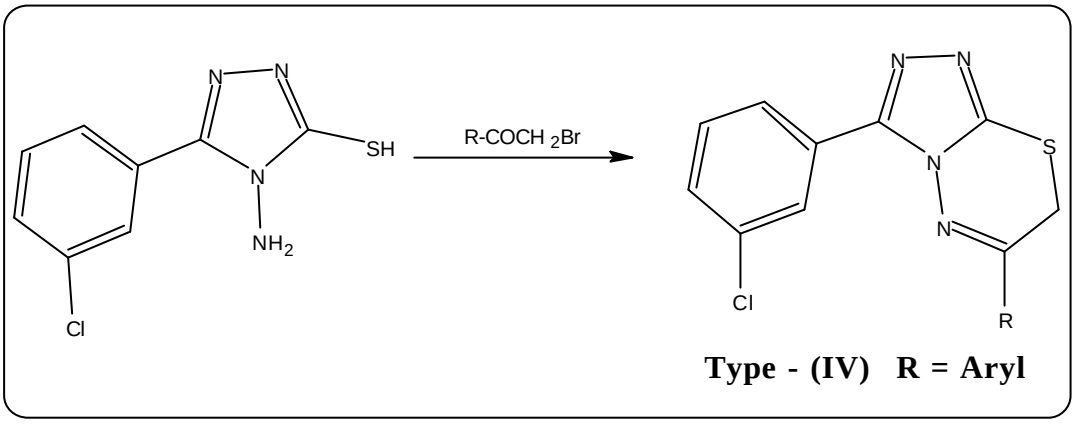
The diverse biological activities have been encountered in compounds containing triazolothiadiazine ring system. Therefore it was considered worthwhile to synthesize 1,3,4-thiadiazine derivatives which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL-7*H*-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL-7*H*-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINES.

Thiadiazine derivatives represent on of the most active class of compounds having a wide spectrum of biological activities. With an aim to getting better therapeutic agent, the preparation of 1,3,4-thiadiazine of type (IV) have been undertaken by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different substituted phenacyl bromides.

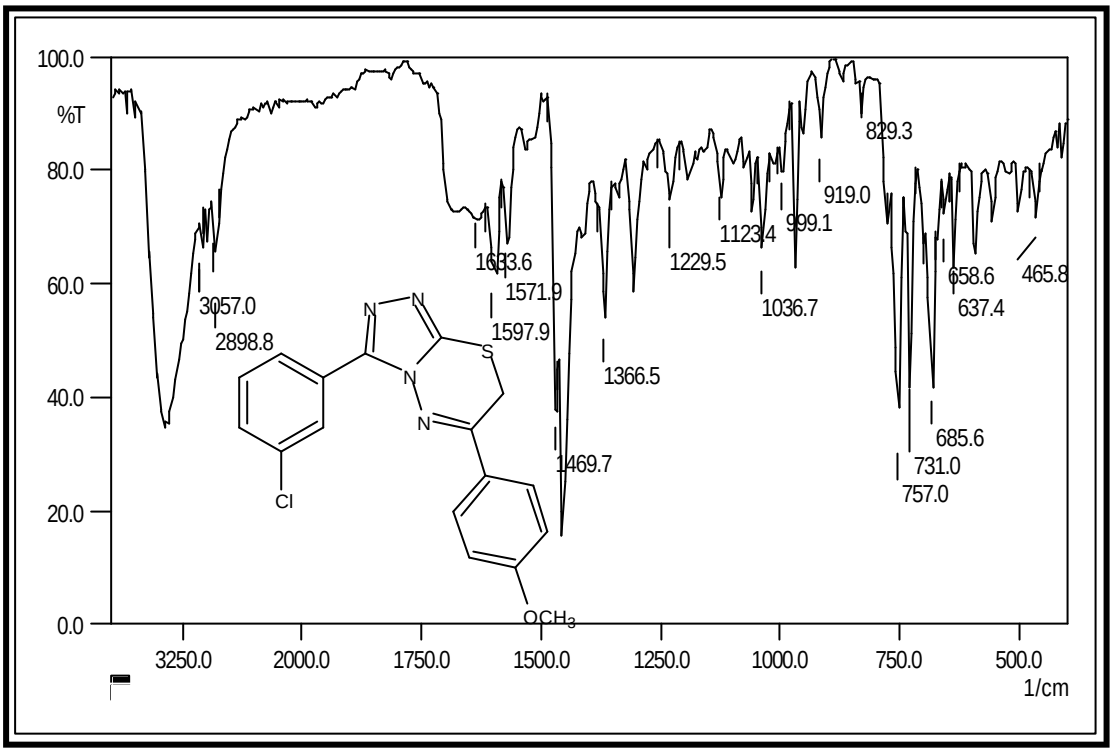


Type - (IV) R = Aryl

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

All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No.4.

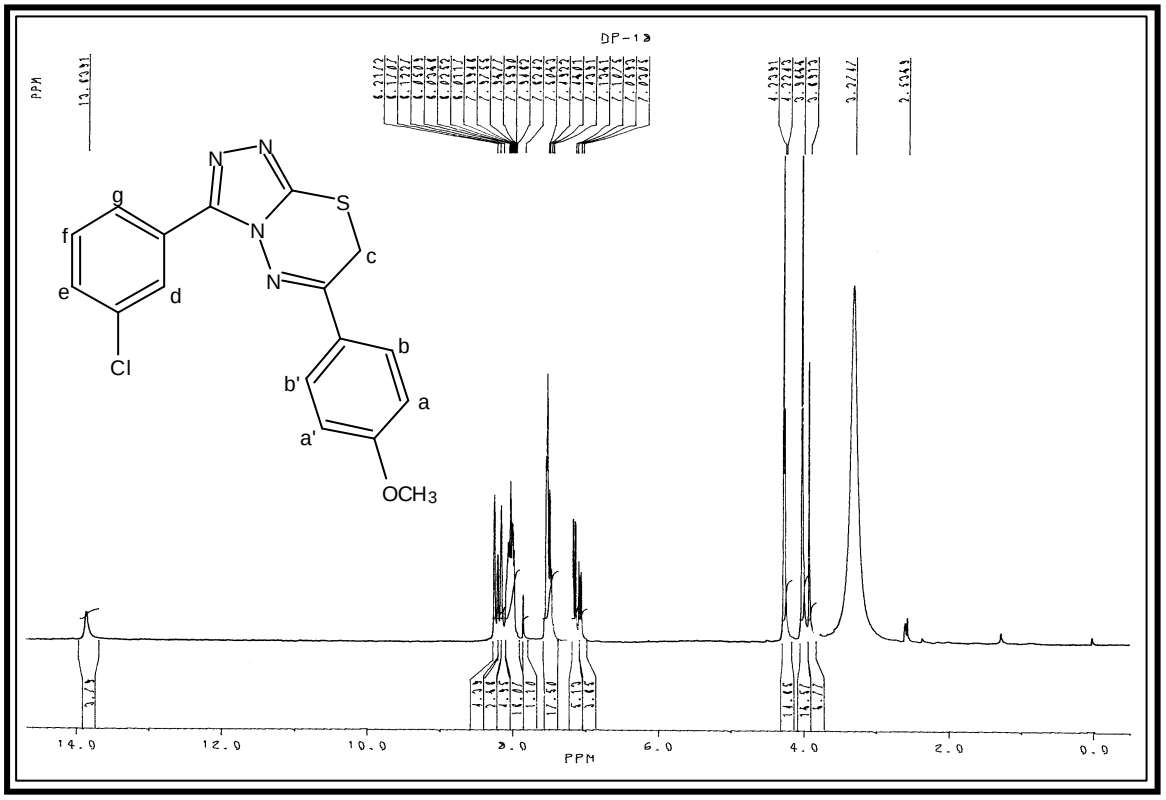
IR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-METHOXYPHENYL)-7*H*-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3057	3080-3030	35
	C=C str.	1571	1585-1480	35
	C-H i.p. (def)	1123	1125-1000	36
	C-H o.o.p. (def)	829	835-810	36
Triazole	C=N str.	1636	1650-1580	37
	C-N str.	1036	1050-1010	35
	N-N str.	1123	1220-1020	36
Ether	C-O-C str.(asym.)	1229	1275-1200	36
(Ar-O-R)	C-O-C str.(sym.)	1036	1075-1020	35
Halide	C-Cl str.	757	800-600	35

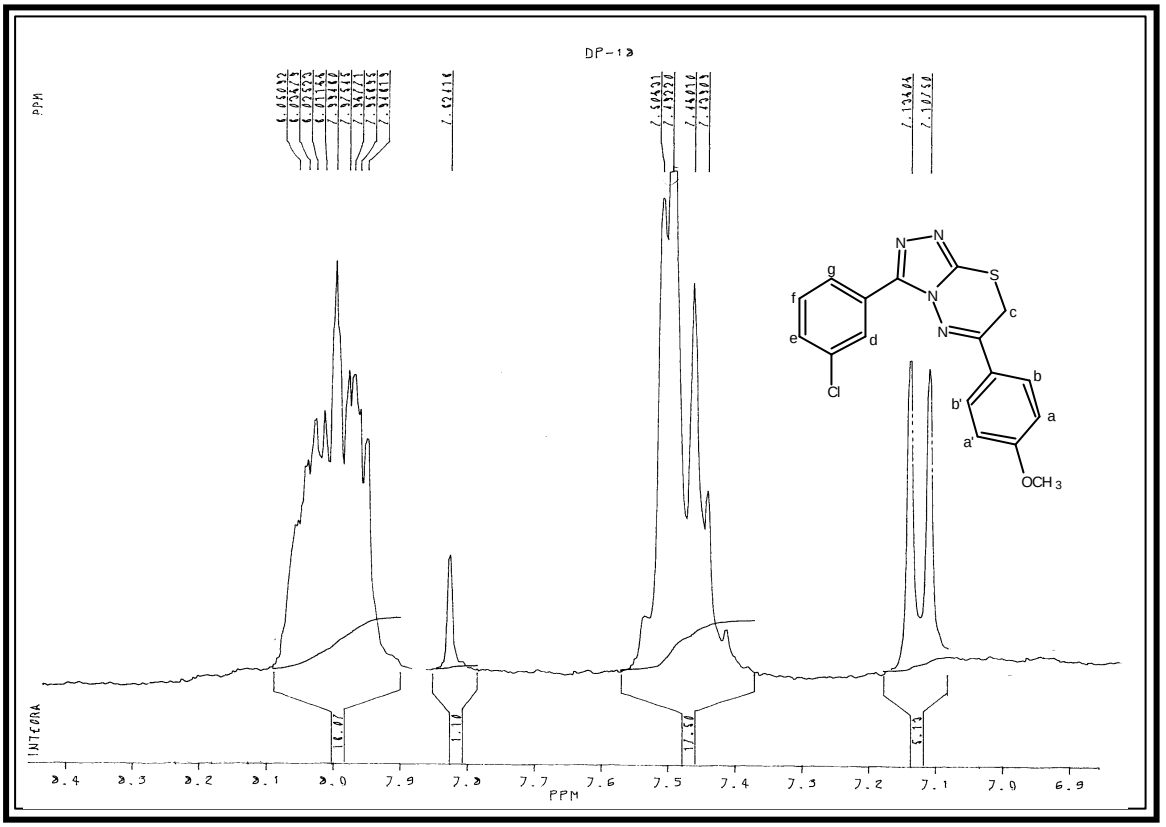
NMR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-METHOXYPHENYL)-7*H*-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINE



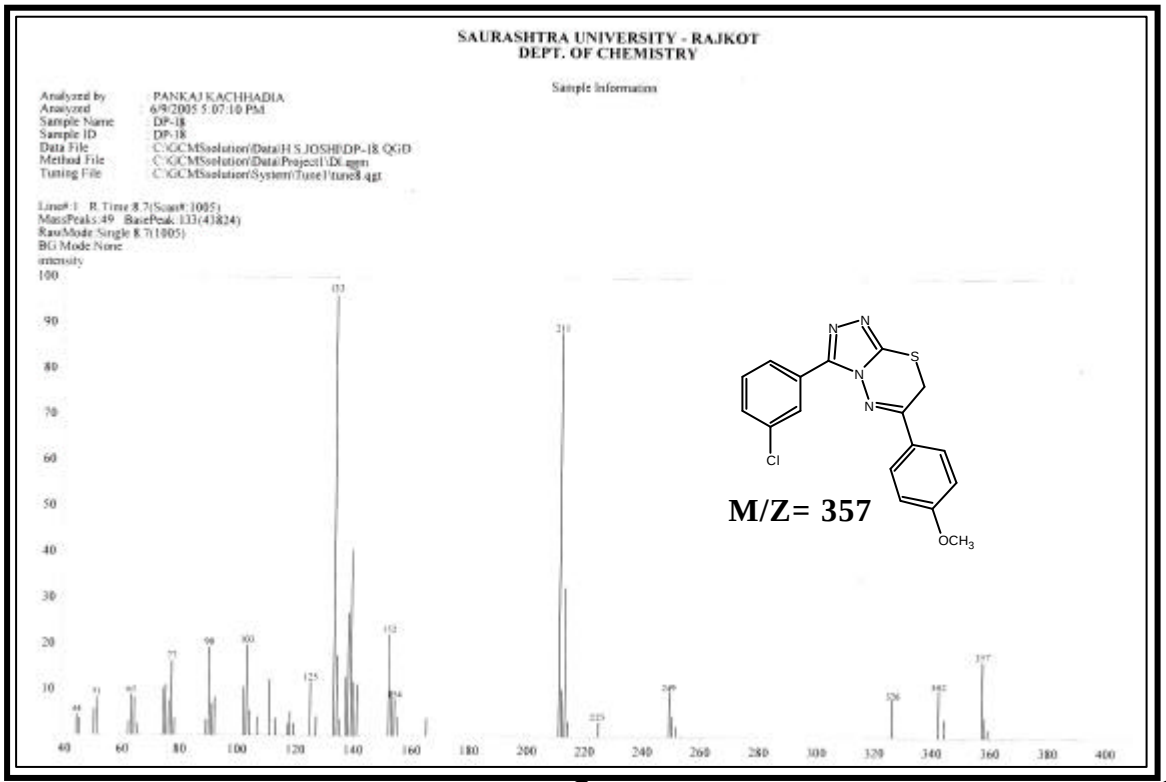
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.98	3H	singlet	Ar-OCH_3	-
2	4.22	2H	singlet	Ar-Hc	-
3	7.11	2H	doublet	Ar-Haa'	-
4	7.43-7.50	4H	multiplet	Ar-(Hbb'+Hfg)	-
5	7.94-8.05	2H	multiplet	Ar-Hed	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-6-(p-METHOXYPHENYL)-*7H*-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-6-ARYL-7*H*-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZINES.

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

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

[B] Preparation of 5-(m-chlorophenyl)-4-aryl-4*H*-12,4-triazole-3-thiols.

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

[C] Preparation of p-methoxyphenacyl bromide.

To a well stirred solution of p-methoxy acetophenone (1.50g, 0.01mol) in glacial acetic acid (20 ml) and hydrochloric acid (0.11 ml) at ambient temperature, bromine (0.8g, 0.01mol) in glacial acetic acid (10 ml) was added over a period of 1hr. The reaction mixture was diluted with water (500 ml) and extracted with chloroform. The combined extracts were dried (over $MgSO_4$) and concentrated to give 4-methoxy phenacyl bromide.

Similarly other substituted phenacyl bromides were prepared by using literature methods.[32-34]

[D] Preparation of 3-(m-chlorophenyl)-6-(p-methoxyphenyl)-7*H*-[1,24] triazolo[3,4-b][1,3,4]thiadiazine.

A mixture of 5-(m-chlorophenyl)-4-aryl-4*H*-12,4-triazole-3-thiol (2.26g, 0.01 mol) and p-methoxyphenacyl bromide (2.28g,0.01mol) in dry methanol (50ml) was heated under reflux for 5 hrs. The content was cooled and neutralized with aqueous potassium carbonate solution. The solid thus separated was filtered, washed with water and recrystallized from ethanol. Yield 60%, m.p. 210°C. Anal.Calcd. For $C_{17}H_{13}ClN_4OS$: C,57.22; H,3.63; N,15.70 %; Found: C,57.18; H,3.60; N,15.66 %.

Similarly other phenacyl bromides have been condensed. The physical constants are recorded in Table No.4.

[E] Antimicrobial activity of 3-(m-chlorophenyl)-6-aryl-7*H*- [1,2,4]triazole [3,4-b]thiadiazines.

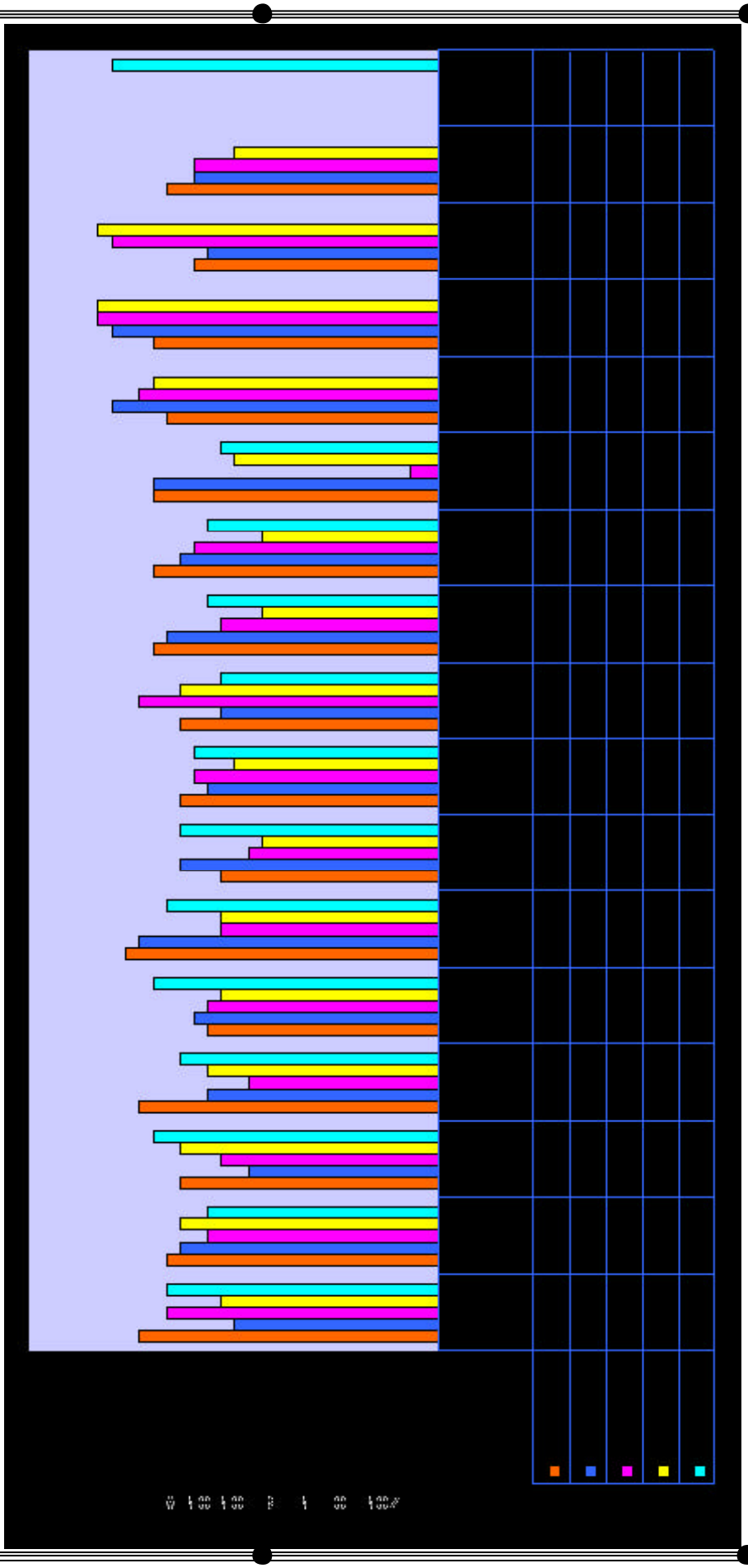
Antimicrobial testing was carried out as described in part-(I), section-I (D). The zones of inhibition of compounds are recorded in Graphical Chart No.4.

TABLE-4 : PHYSICAL CONSTANTS OF 3-(m-CHLOROPHENYL)-6-ARYL-7*H*-[1,2,4]-TRIAZOLO[3,4-b][1,3,4]-THIADIAZINES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
4a	4-Cl-C_6H_4-	$C_{17}H_{11}Cl_2N_3S$	360	210	60	11.66	11.64	0.32	S2
4b	4-OCH_3-C_6H_4-	$C_{18}H_{14}ClN_3OS$	355	210	60	15.70	15.66	0.47	S2
4c	-C_6H_5-	$C_{17}H_{12}ClN_3S$	325	180	69	12.90	13.87	0.59	S1
4d	4 -NO_2-C_6H_4-	$C_{17}H_{11}ClN_4O_2S$	370	175	58	15.11	15.09	0.62	S2
4e	2-OH-C_6H_4-	$C_{17}H_{12}ClN_3OS$	341	210	67	12.29	12.25	0.54	S2
4f	4-F-C_6H_4-	$C_{17}H_{11}ClFN_3S$	343	190	61	12.22	12.20	0.51	S1
4g	4-SCH_3-C_6H_4-	$C_{18}H_{14}ClN_3S_2$	371	180	69	11.30	11.27	0.45	S2
4h	4-SO_2CH_3-C_6H_4-	$C_{18}H_{14}ClN_3O_2S_2$	403	210	58	10.40	10.36	0.52	S1
4i	4-CH_3-C_6H_4-	$C_{18}H_{14}ClN_3S$	339	179	60	12.36	12.35	0.57	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

Graphical Chart No. 4 :Antimicrobial Activity of 3-(m-chlorophenyl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazines

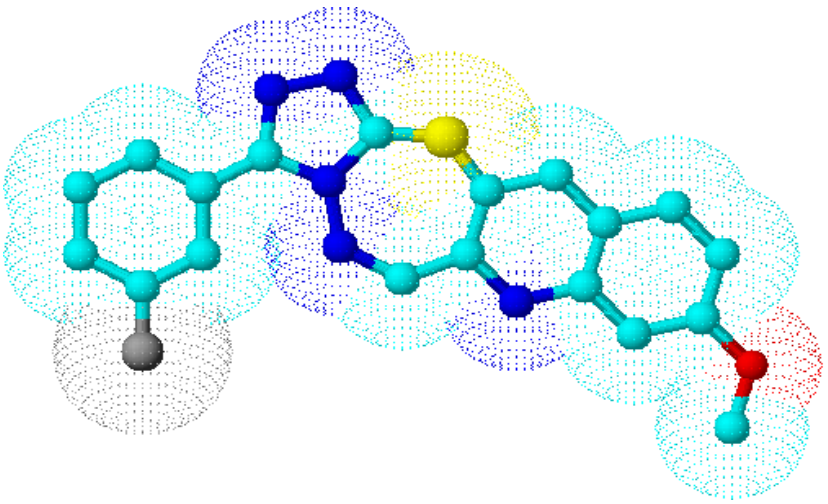


REFERENCES

1. Thiboult T.D. ;
   *U.S. Pat.*4436549 (1984) ; *Chem.Abstr.,* **101,** 23510g (1984).
2. Hargreaves R.B., Mc Loughlin B.J., Mills S.D. ;
   *Eur. Pat. Appl.*85227, (1983) ; *Chem.Abstr.,***100,**6561 (1984).
3. Edwards L.H. ;
   Canadian Pat. 1121349 (1982) ; *Chem.Abstr.,* **97,**144885 (1982).
4. Heravi M.M., Khosrofar P. ;
   *J.Sci.Islamic Repub.Iran.,***7(2),**86-88(1996);*Chem.Abstr.,***125,**195597e (1996).
5. Bayoumy B.E. El-Feky S.A., El-Mobayed M.;
   Egypt J. Chem., **33(3),** 267-751 (1990) ; *Chem.Abstr.,* **118,** 169038j (1993).
6. B.Shivarama Holla et al. ;
   IL Farmaco **56,** 919-927 (2001).
7. Campaigne E. and Selby T.P. ;
   J. Heterocycl. Chem., **15(3),** 401-11 (1978) ; *Chem.Abstr.,***89,** 24266e (1978).
8. Alberecht William L., Jones Winton D., Jr. Sweet F. William ;
   J. Heterocycl Chem., **15(2),** 209-15 (1978) ; *Chem.Abstr.,* **89,** 24265d (1978).
9. Ahmad S. Shawali et al.,
   Phosphorus, Sulfur and Silicon, **177,** 487-496 (2002).
10. Mohan Jag, Verma Pratime. ;
    *J. Indian.Chem.Soc.,***69(5),** 268-9 (1992); *Chem.Abstr.,* **118,** 124459f (1993).
11. Bayoumy B.E., Ei-Kafrawy A, ; El-Bahaie, Youssif Sh. ;
    Egypt. J. Pharm. Sci. **32(3-4),** 817-25 (1991).
12. Jag Mohan and Anupama ;
    Indian J. Chem., **40B,** 368-371 (2001).

13. Abd El-Samie Z.K., Al-Ashmawi M.I., Abd. El-Fattah;
Egypt J.Pharm. Sci.**29(1-4),** 251-8(1988);Chem.Abstr.,**110,** 231589e (1989).
14. Joans Rochus, Piulats Jaime, Lues Inge, Klockow Michael. ;
Eur. Pat. Appl.Ep. **294,** 647.; *Chem. Abstr.,***110,**192866w (1989).
15. Coates William Hohn, Kruse Lawrence Ivan. ;
Eur. Pat. Appl. Ep. 314400 ; *Chem.Abstr.,* **112,** 55918s (1990).
16. Turan-Zitouni G., Kaplancikli, Z.a., Erol, Kilik, F.S. ;
Farmaco, **54(4),** 218-223 (1999) ; *Chem.Abstr.,* **131,** 144579s (1999).
17. W.L.Albrecht., F.W.Sweet. ;
U.S.Pat. **3,**954,983 (1976) ; *Chem.Abstr.* **85,** 78172g, (1976).
18. Renuka Devi Patil and J.S. Biradar. ;
Indian J. Chem., **39B,** 929-935, (2000).
19. Turan-Zitouni G., Kaplancikli, Z.a., Erol, Kilik, F.S. ;
Farmaco, **54(4),** 218-223 (1999).
20. Mazzone G. et al. ;
Farmaco [Sci]. Jul; **42(7),** 525-39 (1978).
21. Mazzone G.et al.;
Farmaco. Oct; **44(10),** 933-44 (1989).
22. Jonas Rochus, Wolf Michael, Klockow Michael. ;
*Eur. Pat. Appl. Ep.***723,** 962; *Chem.Abstr.,***125,** 168032k (1996).
23. Jonas Rochus, Lues Inge, Beier Norbert, Minck KlauspOtto.;
Eur. Pat. Appl. Ep. **721,** 950.; *Chem.Abstr.,***125,** 168029a (1996).
24. Aboul Fadi T. et al. ;
Pharmazie, **54(4),** 244-7 Apr. (1999).
25. Pirotte B. et al. ;
J. Med. Chem., **43(8),** 1456-66 Apr (2000).
26. Kalluraya Balkrishna, Chimbalkar Ramesh. ;
Orient J. Chem., **11(3),** 242-245 (1995).; *Chem.Abstr.,***125,**16794r (1996).
27. Kalluraya B. et al. ;
Boll Chim Farm., **137(5),** 169-72 May (1998).
28. Nadkarni B.A. et al. ;
Arzneimittelforschung., **51(7),** 569-73 (2001).

29. El-Shorbagi A.N. et al. ;
Arch Pharm (Weinhein)., **333(9),**; 281-6 Sep (2000).
30. Holla B.S. et al. ;
Farmaco., **56(8),** 565-70 Aug (2001).
31. Vicentini C.B. et al. ;
J. Agric Food Chem., **50(17),** 4839-45 Aug (2002).
32. Ideam. ;
Bull. Soc. Chim France [3], **21,** 69, (1899).
33. Langley. ;
Org. Syn. Coll. Vol. I, 127 C 2nd ed. (1941).
34. Horng-Chih Huang, James J. Li, Danny J. Garland, Timothy S. Chamberlain, Davoid B. Reitz. ;
J. Med. Chem., **39(1),** 260, (1996).
35. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
36. C. N. R. Rao;
"Chemical application of Infrared spectroscopy" Academic press, New York (1963).
37. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.

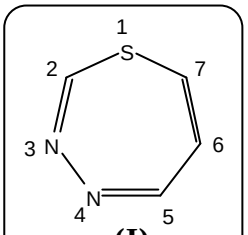


PART - IV

STUDIES ON THIADIAZEPINES

INTRODUCTION

In seven membered ring system, the presence of two nitrogen and one sulphur hetero atoms defines an interesting class of compounds, the thiadiazepines. 1,3,4-thiadiazepine derivatives are studied extensively because it represents one of the most active class of compounds possessing a wide spectrum of pharmacological activities. Keeping in association of thiadiazepine with varied activity, we have been studied 1,3,4-thiadiazepine (I).



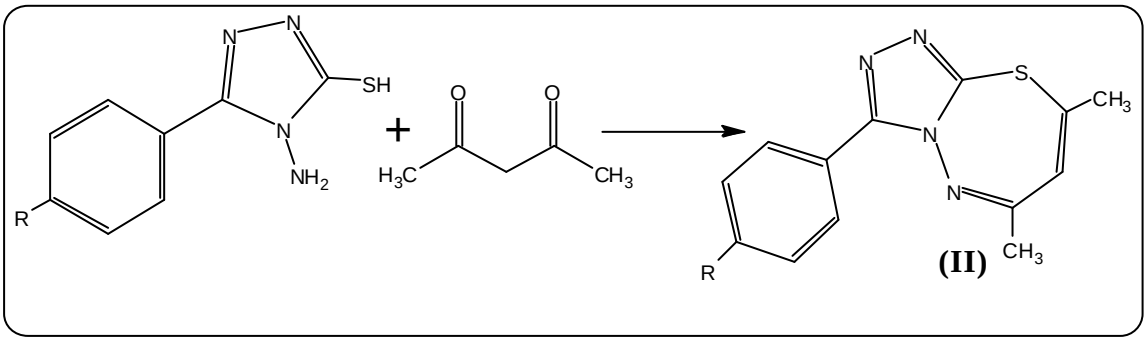
(I)

1,3,4-Thiadiazepine derivatives have been found to be potent drug in pharmaceutical industries.

SYNTHETIC ASPECT

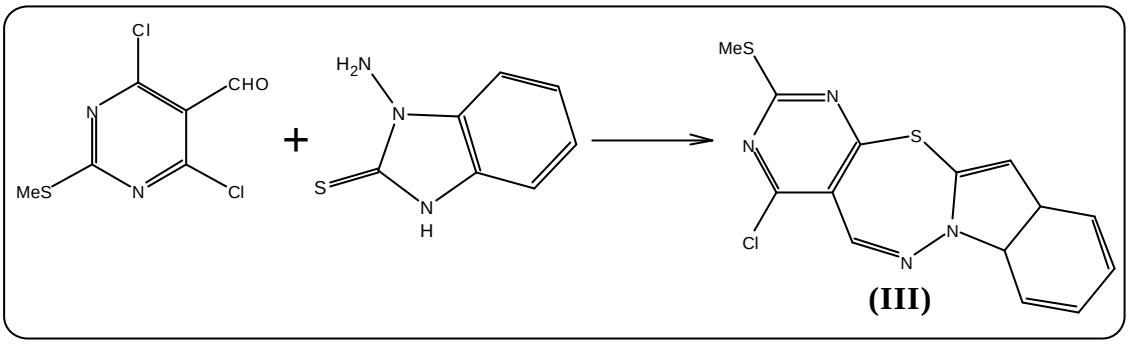
Different methods for the synthesis of thiadiazepine derivatives have been described in literature.[1-3]

1. 1,2,4-Triazolo [3,4-b][1,3,4] thiadiazepine (II) have synthesized by Tiwari Nirupama et al.[4] by cyclocondensation of 4-amino-5-mercapto-1,2,4-triazoles with 2,4-pentanedione.



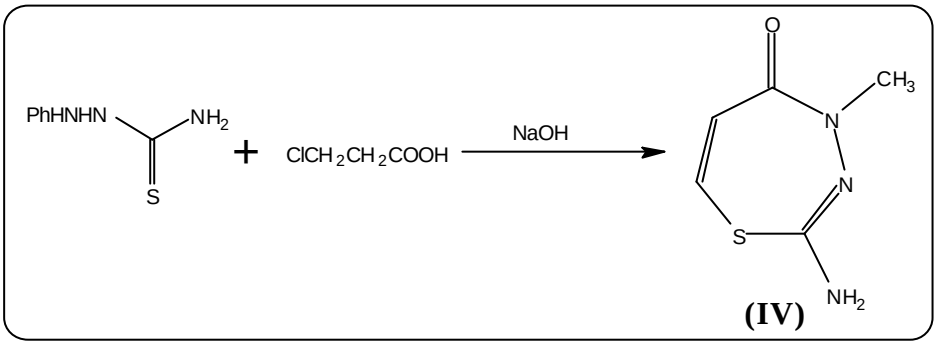
(II)

2. Brukstus A.[5] have been synthesized benzimidazo [2,1-b] pyrimido [5,4-f][1,34] thiadiazepine (III).



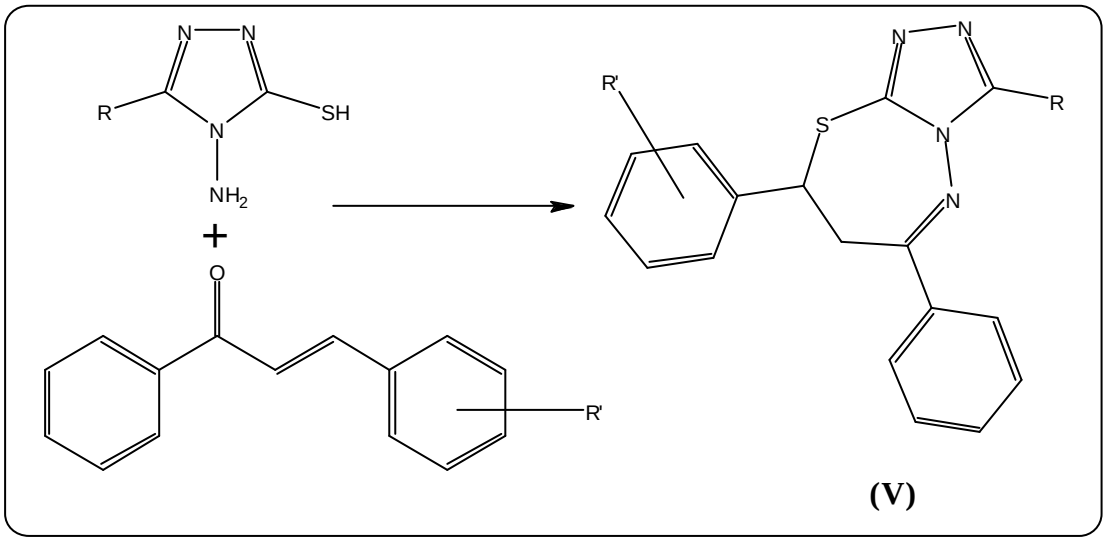
(III)

3. Cyclization of $ClCH_2CH_2COOH$ with $PhNHNHCSNH_2$ in presence of AcOH containing NaOH at reflux temperature to give 2-amino-4-phenyl-6H, 7H-1,3,4-thiadiazepin-5-one[6](IV).



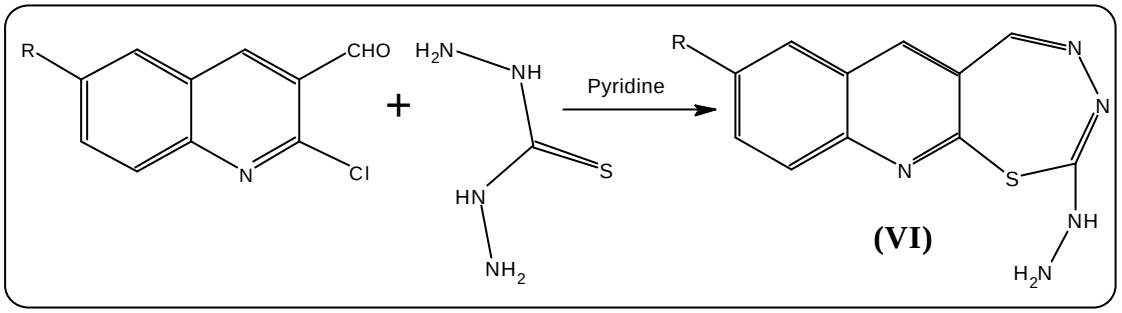
(IV)

4. Om Prakash et al.[7] have synthesized thiadiazepine by Michael type addition of 4-amino-3-mercapto-1,2,4-triazole to *a,a*-unsaturated carbonyl compounds.

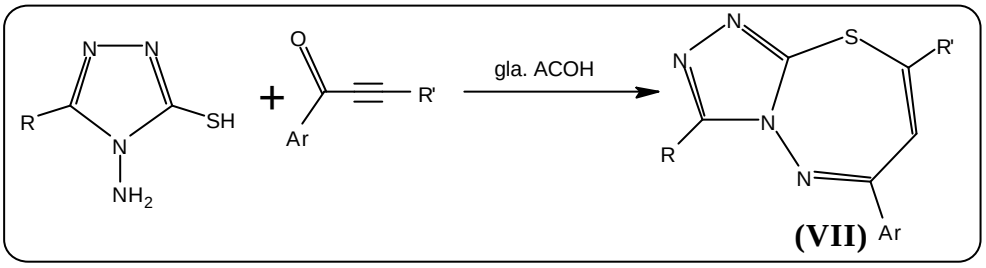


(V)

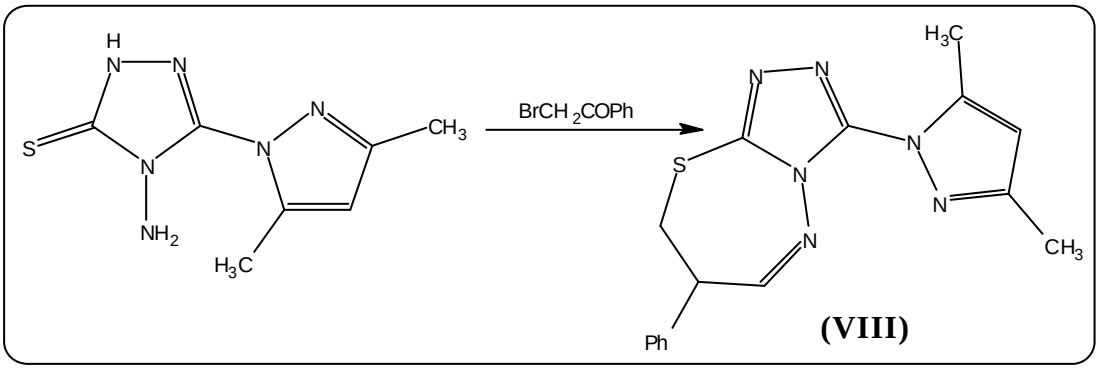
5. Quinoline thiadiazepine derivatives (VI) have synthesized by R.Gururaja et al.[8] by condensation of 2-chloro-6-substituted quinoline-3-carboxaldehyde with thiocarbohydrazide in pyridine.



6. T.E. Glotova et al.[9] have synthesized 1,3,4-thiadiazepine (VII) by treating *a*-acetylenic ketones with 4-amino-3-mercapto-1,2,4-triazole in glacial acetic acid.



7. Sinegibskaya A.D.et al.[10] have synthesized thiadiazepine (VIII) by reaction of 4-amino-3-hydrazino-1,2,4-triazoline-5-thione with *a* and *a*-dicarbonyl compounds then the treatment of Br-CH_2-CO-Ph.



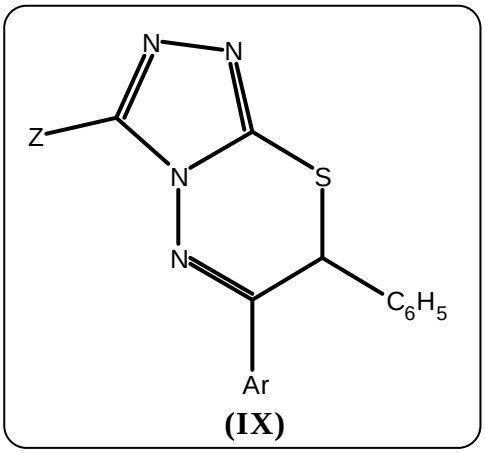
Several methods have also documented in literature.[11-14]

BIOLOGICAL EVALUATION

The various therapeutic activities of thiadiazepine derivatives have been reported as under.

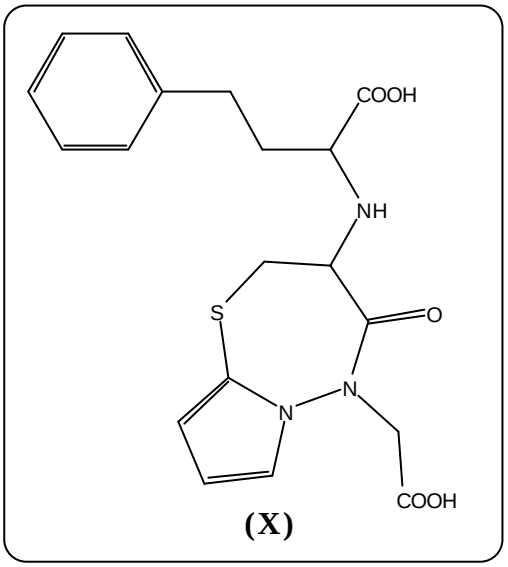
1. Anti-HIV[15]
2. Anticonvulsant[16]
3. CCK antagonists[17]
4. Gastrin receptor antagonists[18]
5. Antiviral[19]
6. Antiarrythmic[20]
7. Antipsychotic[21]
8. Antitumor[22]
9. Antidepressant[23]

Khalil and Habib[24] have documented antimicrobial and anticancer activities of thiadiazepine derivatives. Marfe G. et al.[25] have investigated thiadiazepines useful as anticancer agents. Giannotti D. and coworkers[26] have screened thiadiazepines for their antidepressant activity. U.V. Laddi and coworkers[27] have prepared thiadiazepines (IX) and tested for their antimicrobial and antituberculosis activities.



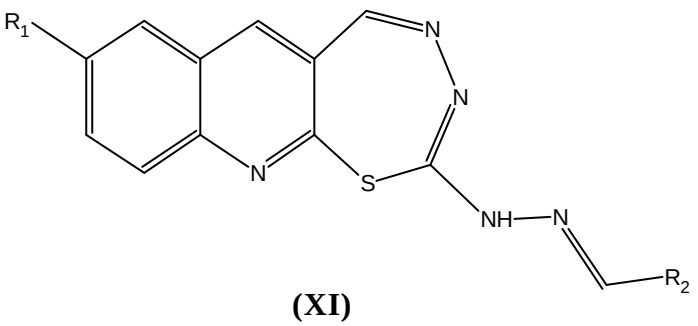
(IX)

B.S. Holla and coworkers[28] have investigated some thiadiazepines as potent antimicrobial agents. Ammar Y.A. et al.[29] have prepared triazole thiadiazepines as antifungal agents. Swati Sharma and coworkers[30] have discovered thiadiazepine derivatives as possible potential drug for cancer metastatics. Borsini F. et al.[31] have investigated thiadiazepines which is useful as potent antidepressant drugs. Denis Pires di Lima[32] have synthesized thiadiazepines (X) useful as an angiotensin-converting enzyme (ACE) inhibitors and Bolos I. et al.[33]reported them as an important class of antihypertensive drugs.



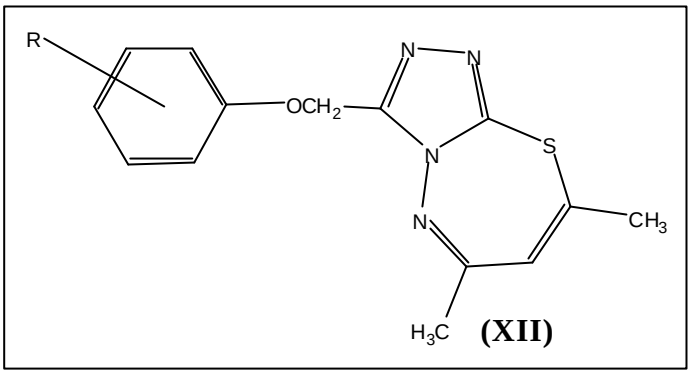
(X)

R. Gururaja and coworkers[34] have synthesized 1,3,4-thiadiazepines (XI) and screened for their anthelmintic activity and antibacterial activity. B. Shivarama Holla et al.[35] have documented antibacterial and antiviral activity of thiadiazepines. M. Kidwai et al.[36] have reported thiadiazepines as potential antimicrobial agent.



(XI)

Ashutosh Singh and Nizamuddin[37] have prepared thiadiazepines (XII) and reported their mulluscicidal activity. Robert J. Cherney and coworkers[38] have demonstrated benzothiadiazepines as selective tumor necrosis factor *a*-converting enzyme inhibitors. Cherney R.J. et al.[39] have synthesized thiadiazepines and reported them as selective tumor necrosis factor alpha converting enzyme inhibitor.



(XII)

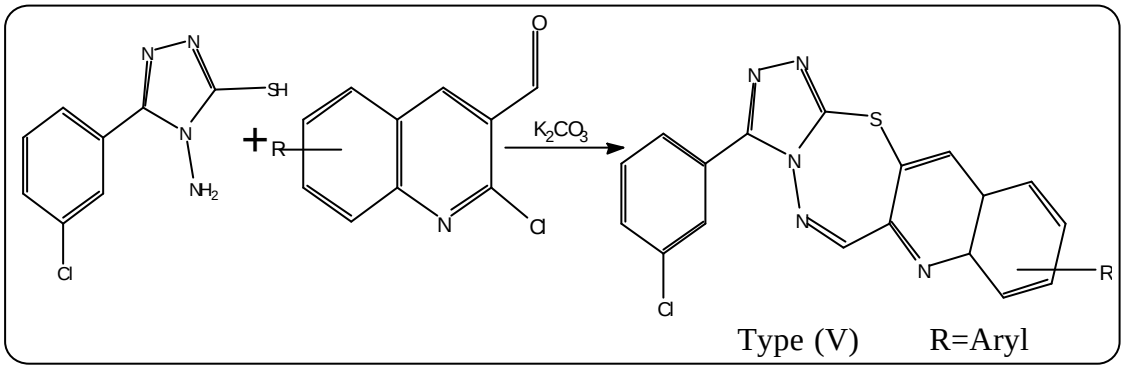
In view of vast therapeutic activities of 1,3,4-thiadiazepines, it was contemplated to synthesize some new thiadiazepine derivatives in search of agents possessing higher biological activities with least side effect, which have been described in following section.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-9-AlkYL[1,2,4]TRIAZOLO [3',4' : 2,3][1,3,4]THIADIAZEPINO[6,7-b] QUINOLINES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-9-ALKYL[1,2,4]TRIAZOLO[3',4':2,3][1,3,4]THIADIAZEPINO[6,7-b]QUINOLINES.

1,3,4-Thiadiazepine derivatives occupy a unique place in the field of medicinal chemistry due to wide range of biological activities exhibited by them. To further assess the potential of such class of compounds as good therapeutic agents, a series of 1,3,4-thiadiazepines of type (V) was carried out by one step reaction of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol 2-chloro-3-formylquinolines in presence of K_2CO_3.

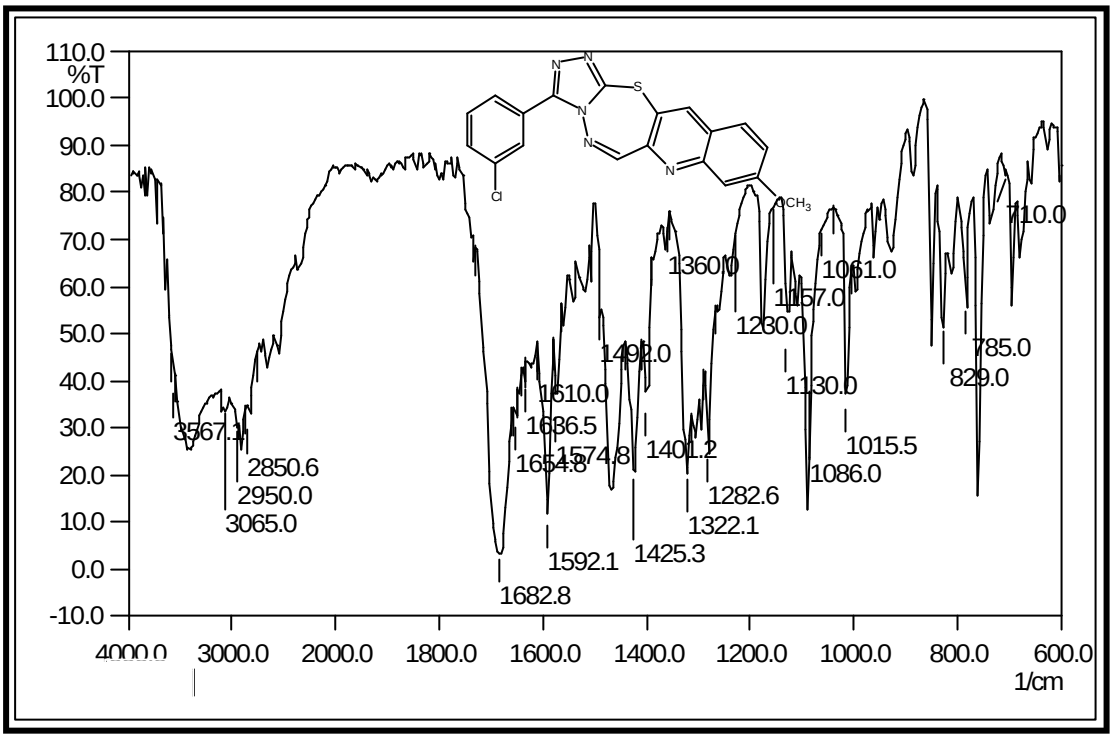


Type (V) R=Aryl

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

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

IR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-9-METHOXY[1,2,4]TRIAZOLO[3',4':2,3]THIADIAZEPINO[6,7-b]QUINOLINE

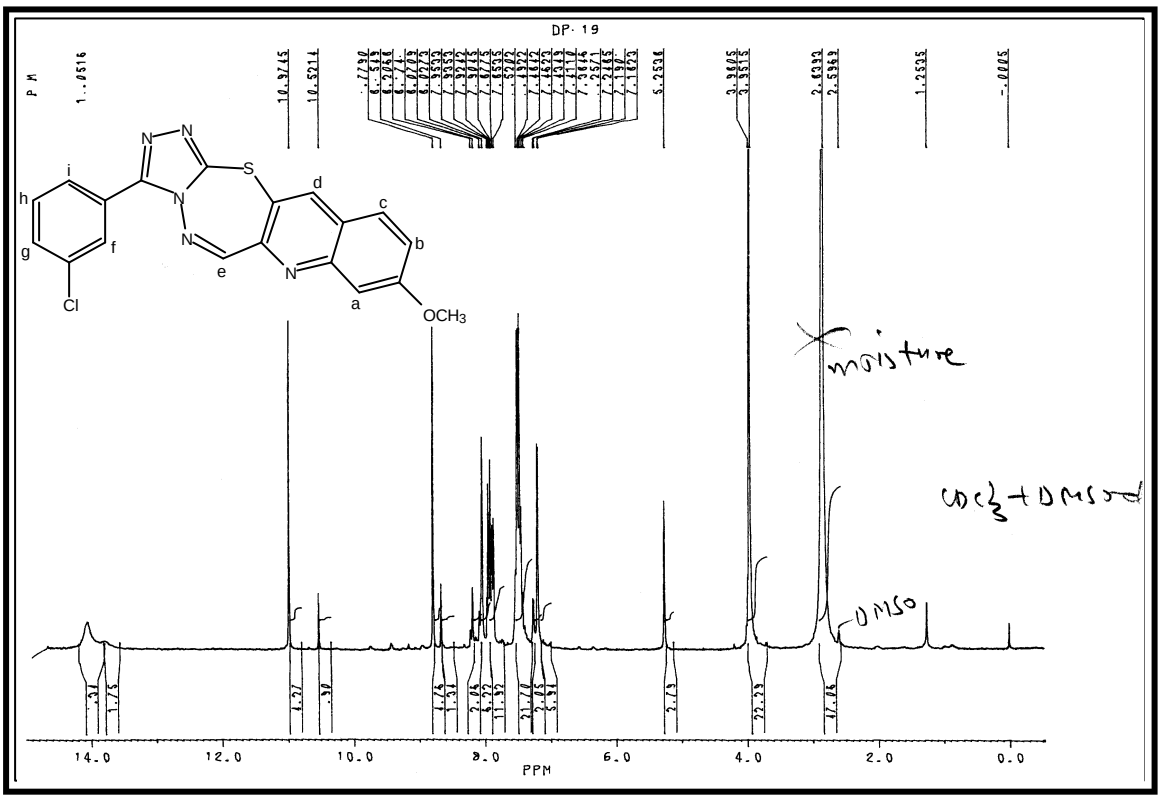


Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2950	2975-2950	40
-CH_3	C-H str. (sym.)	2850	2880-2860	40
	C-H def.(asym.)	1425	1470-1435	40
	C-H def.(sym.)	1360	1385-1370	40
Aromatic	C-H str.	3065	3080-3030	40
	C=C str.	1492	1520-1480	40
	C-H i.p. (def)	1130	1125-1090	41
	C-H o.o.p. (def)	829	835-810	40
Triazole	C=N str.	1636	1640-1500	40
	C-N str.	1157	1220-1020	42
	N-N str.	1015	1050-1010	41
Thiadiazepine	C-S-C str.	710	700-600	42
		1086	1250-1000	42
Ether	C-O-C str.(asym.)	1230	1275-1200	41
(Ar-O-R)	C-O-C str.(sym.)	1061	1070-1000	41
Halide	C-Cl str.	758	800-600	41

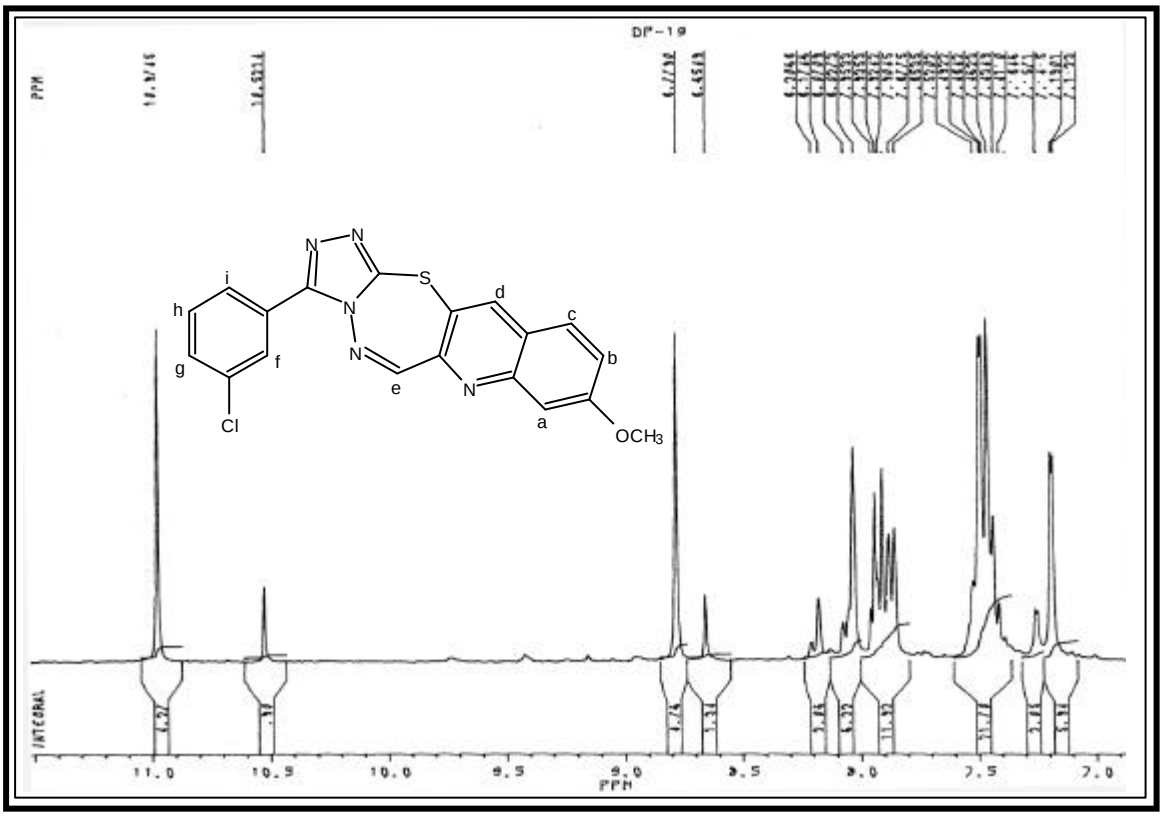
NMR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-9-METHOXY[1,2,4]TRIAZOLO[3',4':2,3]THIADIAZEPINO[6,7-b]QUINOLINE



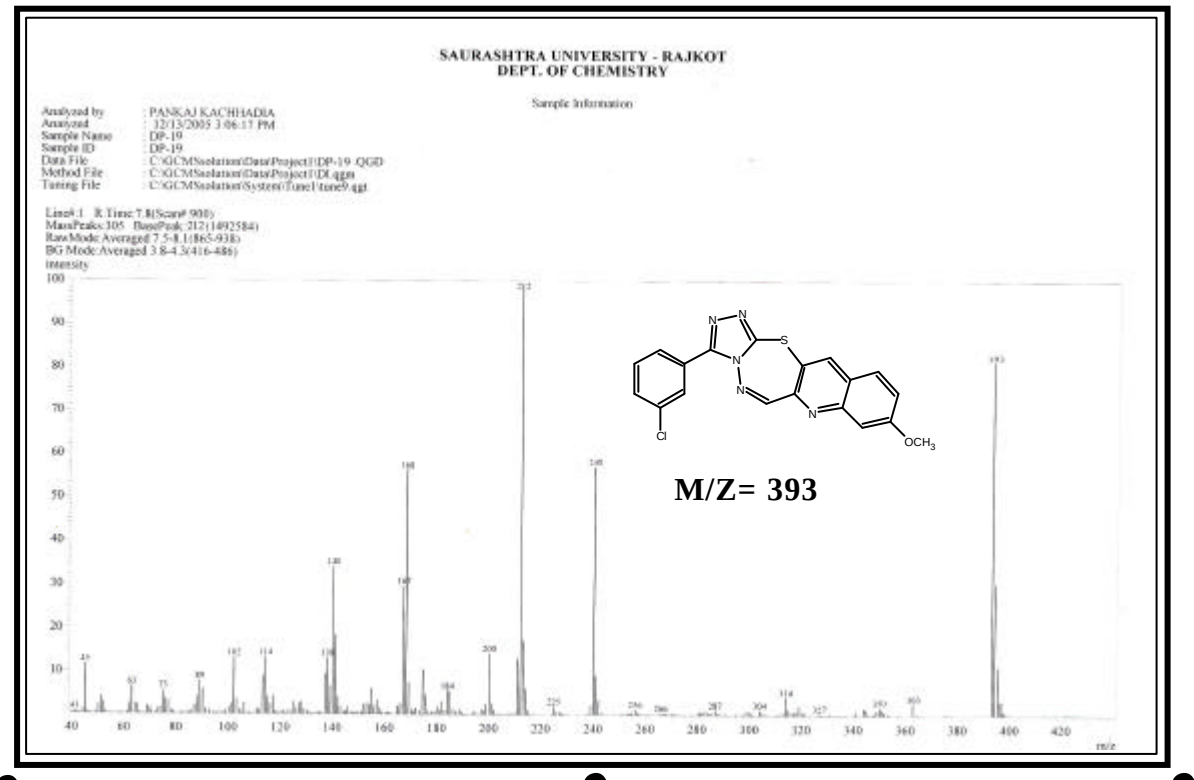
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.98	3H	singlet	Ar-OCH_3	-
2	7.19	1H	doublet	Ar-Hc	-
3	7.49-7.41	3H	multiplet	Ar-Hbhi	-
4	7.93-7.85	2H	multiplet	Ar-Hag	-
5	8.07	1H	singlet	Ar-Hf	-
6	8.77	1H	singlet	Ar-Hd	-
7	10.97	1H	singlet	Ar-He	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-9-METHOXY[1,2,4]TRIAZOLO[3',4':2,3]THIADIAZEPINO[6,7-b]QUINOLINE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-9-ALKYL[1,2,4]TRIAZOLO[3',4':2,3][1,3,4]THIADIAZEPINO[6,7-b]QUINOLINES

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

See Part-I, Section-I [A].

[B] Preparation of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

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

[C] Preparation of substituted 2-chloro-3-formylquinolines.

These were prepared by the condensation of substituted acetanilide with DMF / $POCl_3$ using well known Wielsmayerhacck rearrangement.

[D] Preparation of 3-(m-chlorophenyl)-9-methoxy[1,2,4]triazole[3',4':2,3] [1,3,4]thiadiazepine[6,7-b]quinoline.

To a mixture of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (2.26g, 0.01 mol) and 2-chloro-3-formyl-6-methoxyquinoloine (2.07g, 0.01 mol) in dry DMF (20 ml) anhydrous K_2CO_3 (2.0g) was added. Then the reaction mixture was stirred at 70-80^{o}C for 4 hrs. The content was cooled and poured onto crushed ice. The product was isolated and crystallized from methanol. Yield 54%, m.p. 274^{o}C. Anal.Calcd. for $C_{19}H_{12}ClN_5OS$: C, 57.94; H, 3.07; N, 17..78 %; Found: C, 57.90; H, 3.03; N, 17.75%.

Similarly other substituted thiadiazepines were prepared. The physical constants are recorded in Table No.5.

[E] Antimicrobial of 3-(m-chlorophenyl)-9-alkyl[1,2,4]triazole[3',4':2,3] [1,3,4]thiadiazepine[6,7-b]quinoline.

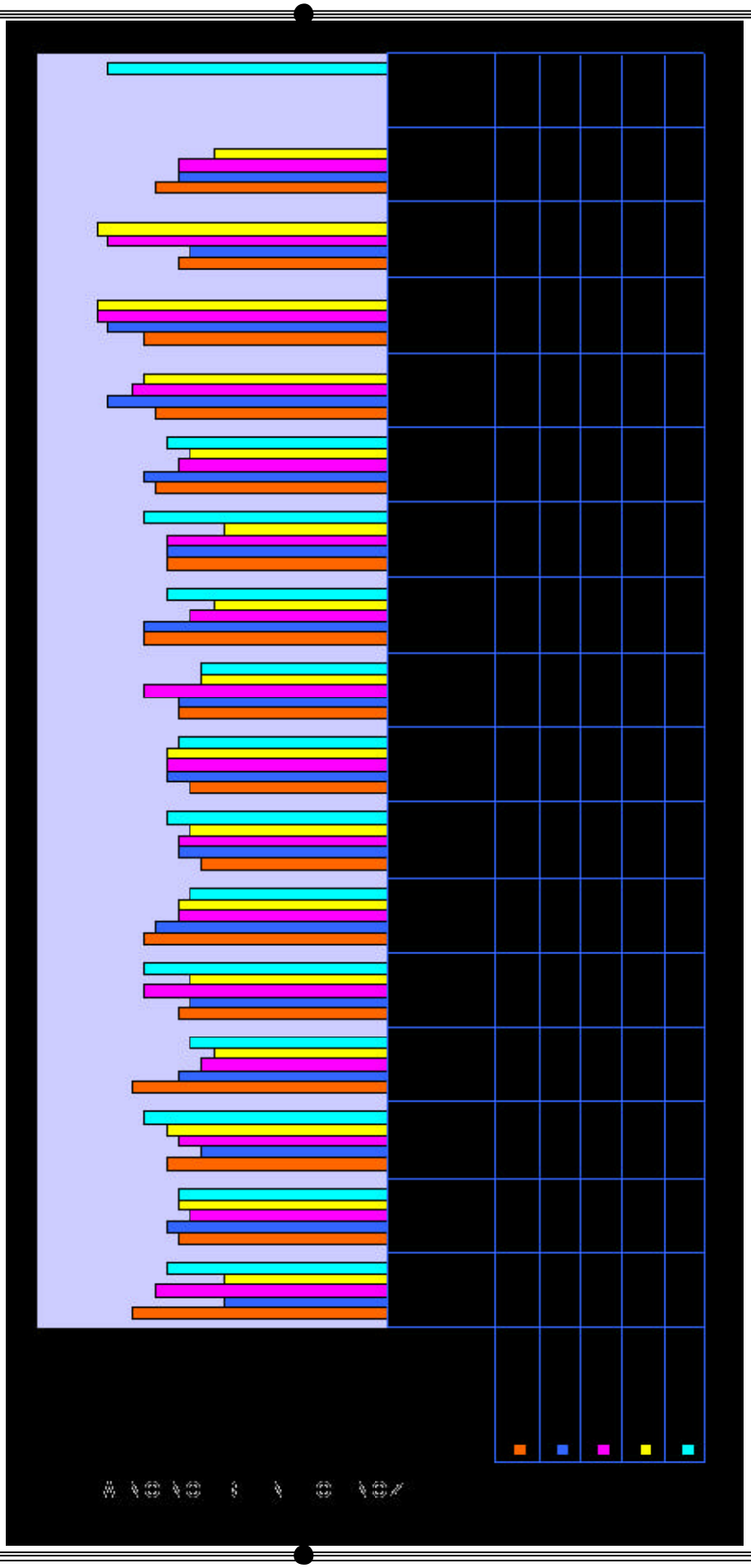
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of compounds are recorded in Graphical Chart No.5.

TABLE-5 : PHYSICAL CONSTANTS OF 3-(m-CHLOROPHENYL)-9-ALKYL[1,2,4]-TRIAZOLO[3',4':2,3][1,3,4]-THIADIAZEPINO[6,7-b]QUINOLINES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. °C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
5a	-H-	$C_{18}H_{12}ClN_5S$	365	274	54	19.14	19.10	0.42	S2
5b	-6-Cl-	$C_{18}H_{11}Cl_2N_5S$	400	165	68	17.50	17.49	0.46	S2
5c	-7-Cl-	$C_{18}H_{11}Cl_2N_5S$	400	183	59	17.50	17.49	0.44	S1
5d	-6,8-$(CH_3)_2$-	$C_{20}H_{16}ClN_5S$	393	165	58	17.78	17.75	0.48	S2
5e	-6-OCH_3-	$C_{19}H_{14}ClN_5OS$	393	274	54	17.78	17.75	0.51	S2
5f	-8-CH_3-	$C_{19}H_{14}ClN_5S$	379	181	61	18.44	18.40	0.53	S1
5g	-6,7-$(Cl)_2$-	$C_{18}H_{10}Cl_3N_5S$	434	190	59	16.11	16.10	0.47	S2
5h	-6-CH_3-	$C_{19}H_{14}ClN_5S$	379	280	48	18.44	18.40	0.52	S1
5i	-6-Br-	$C_{18}H_{11}BrClN_5S$	444	189	60	15.75	15.70	0.58	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

Graphical Chart No. 5 :Antimicrobial Activity of 3-(m-chlorophenyl)-9-alkyl[1,2,4]triazolo[3,4':2,3][1,3,4]thiadiazepino[6,7-b]quinolines

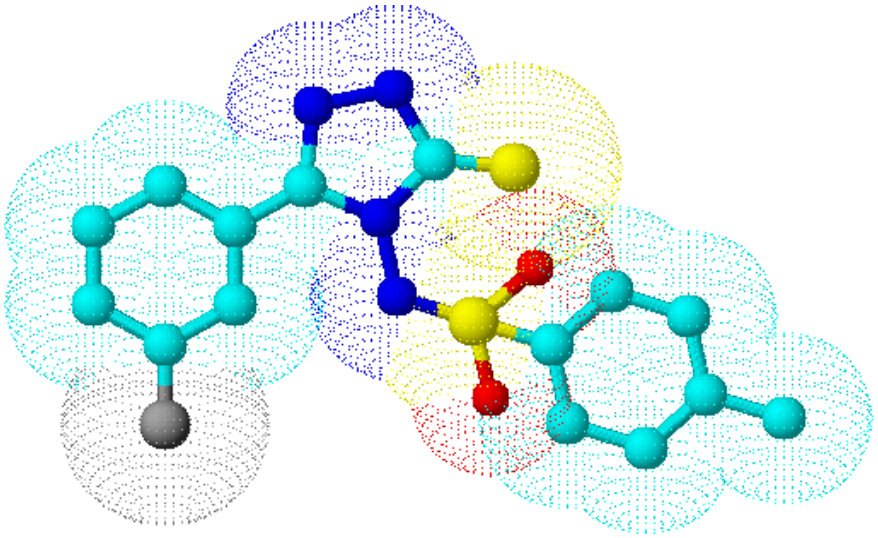


REFERENCES

1. Plescia S., Agozzino P., Fabra I. ;
   *J. Heterocycl. Chem.,***19(8),** 1431-2 (1997); *Chem.Abstr.,* **88,** 136581a (1978).
2. Mahajan Mohinder P., Sondhi Sham M., Ralhan Narender K. ;
   Aust. J. Chem. **30(9),** 2057-61 (1977); *Chem.Abstr.,* **90,** 50818k (1978).
3. Sondhi S.M., Mahajan M.P., Ganda A.K. Ralhan N.K. ;
   Indian J.Chem., **16B(5),** 433-5 (1978); *Chem.Abstr.,* **90,** 22999t (1979).
4. Tiwari Nirupama, Singh Kumud, Nizamuddin. ;
   *Indian J. Heterocycl. Chem.,***2(3),** 195-8 (1993);*Chem.Abstr.,* **119,**160252n (1993).
5. Brukstus A., Sadauskas T., Tumkewicius S. ;
   Khim. Geterotsikl. Soedin **(3),** 195-8 (1996); *Chem.Abstr.,* **119,** 167911j (1996).
6. Pleshnev V. I.;
   Farm. 2h. (Kiev) **(1),** 84-5 (1978); *Chem. Abstr.,* **89,** 109404y (1978).
7. Om Prakash, Deepak Sharma, Ravi Kumars. ;
   Indian J. Heterocycle, **14,** 111-114, Oct.Dec. (2004).
8. R. Gururaja, Jyoti C. Hegde, H.M. Vagdevi, Balakrishnan Kullaraya.
   Indian J. Heterocycl. Chem., **14,** 97-100, Oct-Dec. (2004).
9. T.E. Glotovq, A.S. Nakhmanovich, L.S. Romanenko, M.V. Sigalov. ;
   Chemistry of Heterocycl. Compounds, **27,** 7, 795-798, July (1991).
10. Sinegibskaya A.D., Pashkevich K.I., Saloutin V.I., Dank E. Kh. ;
    *Khim. Geterotaski Soedin,***4,**559-9 (1978); *Chem.Abstr.,***89,**109406a (1978).
11. Duong Vang Tue, Nguyen Dong Quang ; Dau Van Tuong. ;
    *Tap.Chi.Hoa.Hoc.,***30(2),** 34-6,41 (1992); *Chem.Abstr.,***119,** 249926h (1993).
12. Nakhmanovich A.S., Glotova T.E. ;
    Khim. Geterotsiki, Soedin, **1,**130-131 (1996); Chem.Abstr., 125, 167933t (1996).
13. Mohamed Nasir K. ;
    Pharmazie **53(8),** 529-533 (1998); *Chem.Abstr.,* **129,** 266439d (1998).
14. Song Choong Eui, Kim Ji-Sook, Choi Jung Hoon. Jin Byung Woo. ;
    Heterocycles, **51(1),** 161-168 (1999); *Chem.Abstr.,* **130,** 196635f (1999).

15. Moriwaki Minoru, Yamato Hirotake, Juchi Takayula. ;
Jpn. Kokoi Tokkyo Koho JP, **06,** 128, 257, [94, 128, 257]; *Chem.Abstr.,***121,** 157682o (1994).
16. Hodge Carl Nicholas, Fernandez Christina Howard. ;
PCT Int. Appl. WO 94, **08,** 977; Chem.Abstr., 121, 157681n (1994).
17. Showell Graham A., Bourrain Sylvie, Neduvelil Joseph G. ;
J. Med. Chem., **37(6),** 719-21 (1994); *Chem.Abstr.,* **120,** 323525r (1994).
18. Bright Robert, Coote Steven J., Freman Stephen. ;
Synth. Commun., **16(22),** 4195-4209 (1996); *Chem.Abstr.,* **126,** 171570k (1997).
19. Tantawy Atif, Abdelal A.M., Broom A.D. ;
Alexandria J. Pharm. Sic., **3(1),** 79-81 (1989); *Chem.Abstr.,* **112,** 5580y (1989).
20. Ogawa Kazuo, Malsushita Yohichi. ;
Chem.Pharm.Bull.**40(9),**2442-7 (1992); *Chem.Abstr.,***118,**169082u (1992).
21. Liegois Jean Francois F., Bruhwyler Jacques, Damas Jacques. ;
J. Med.Chem., **36(15),** 2167-74 (1993); *Chem.Abstr.,***119,** 139192h (1993).
22. F. Melani, L. Cecchi and G. Filacchioni. ;
J. Heterocyclic Chem., **21,** 813 (1984).
23. G. Stefancich and R. Silxestri. ;
J. Heterocyclic Chem., **26,** 745 (1989).
24. Khalil M.A., Habib N.S.;
Arch Pharm., (Weinheim) **323(8),** 471-4. Aug (1990).
25. Marfe G. Silvestri R, De Martino G, Sinibaldi Salimel P. Morgante E., Russo MA and Distefano C.;
www.med.miami.edu./MNBWS/Marfe llo.html.;
26. Giannootti D. Vitig, Sbraci P, Pestellini V. Volterra G. Borsini 31. Denis Pires de Lima. ;
Quimica Nova, **22(3),** June (1999).
27. U.V. Laddi, M.B. Ralawar, S.R. Desai, R.S. Bennur and S.C. Bennur.;
Indian J. Chem., **40B,** 828-833 (2001).

28. B.Shivarama Holla, P.M. Akberali, and M.K. Shivanada. ;
IL Farmaco, **56(12),** 919-927, Dec. (2001).
29. Ammar Y.A., Ghorab M.M., El-Sharief. et al.
Hetero atom Chem., **13(3),** 199-206 (Eng.) (2002); *Chem. Abstr.,* **137(14),** 201263j, (2002).
30. Swati Sharma, Anop K., Prakash Lalit.;
Indian J. Chem., **35(B),** 11, 1221-1224 (1996).
31. Borsini F., Volterra G., Lecci A., Evangelista S., et al.;
Arzneimittel forschang, **41(6),** 573-80, Jan. (1991).
32. Denis Pires de Lima. ;
Quimica Nova, **22(3),** June (1999).
33. Bolos J., Perez-Beroy A., Gubert S., Anglada L., Sacristan A., Ortiz J.A. ;
Tetrahedron Letters, **48,** 42, 9567-9576 (1992).
34. R. Gururaja, Jyoti C. Hegda, H.M. Vagdevi and Balakrishna Kulluraya.
Indian J. Heterocyclic Chem., **97-100,** Oct.-Dec. (2004).
35. B.Shivarama Holla, P.M. Akberali, and M.K. Shivanada. ;
IL Farmaco, **56(12),** 919-927, Dec. (2001).
36. M. Kidwai, P.Sapra, P. Misra, R.K. Saxena and M. Singh. ;
Bioorg. And Med. Chem.; **9,** (2), 217-220, Feb. (2004).
37. Ashutosh Singh and Nizamuddin. ;
Indian J. H. Chem., **14,** 131-134, Oct-Dec. (2004).
38. Robert J. Cherney, James J.W.Duan,matthew E. Voss, Lihua Chen, Li-Wang;
J. Med. Chem., **46(10),** 1811 (2003); *Chem.Abstr.,* **138(26),** 401710k (2003).
39. Cherney R.J., Duan J.J., Voss ME, Chem, L, Wang L, Meyer D.T., Wasserman Z.R., Hardman K.D., et al. ;
J. Med. Chem., **46(10),** 1811-23, May (2003).
40. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
41. C. N. R. Rao;
"Chemical application of Infrared spectroscopy" Academic press, New York (1963).
42. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.



PART - V

STUDIES ON SULPHONAMIDES

INTRODUCTION

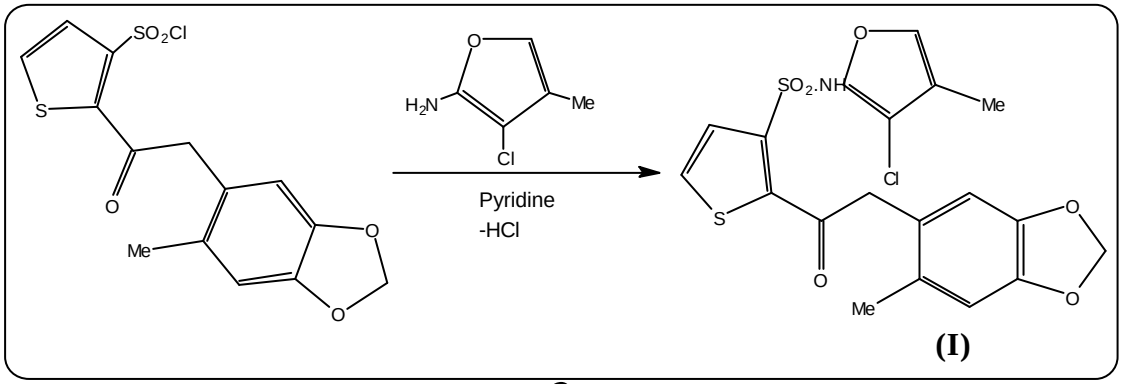
The invention of sulphonamides arouse from an early claim that sulphonamide group increased the chemotherapeutic era by making possible a direct attack on microbial infection.[1] Sulphonamide was first synthesized by Glemo in 1908. Gerhald Domagk in 1935 tested protonsil towards infection by hemolytic *streptococci* and found it very effective antibacterial which led to the synthesis of newer molecules by incorporating different nucleus.

Sulphonamides have the general formula of R-SO_2-N-R'-R'' where R=organic radical, R' and R''= hydrogen or organic radical. Depending upon the nature of R, the sulphonamides are classified as aliphatic, aromatic and heterocyclic. The aliphatic sulphonamides have not yet become important. Aromatic and heterocyclic sulphonamides have achieved great commercial significance. Sulphonamides continue to be used as an antibacterial because they are effective, inexpensive and free of super infection problems of the broad spectrum antibiotics.[2]

SYNTHETIC ASPECT

Various methods have been reported for the synthesis of sulphonamides in literature.[3-5]

1. Natesan Murugesan et al.[6] have prepared sulphonamide derivatives and studied their biological activity.
2. Some novel sulphonamide derivatives (1) have synthesized by Wa, Chengde and coworkers.[7]

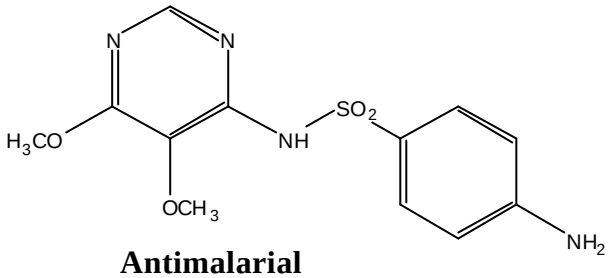


(I)

BIOLOGICAL EVALUATION

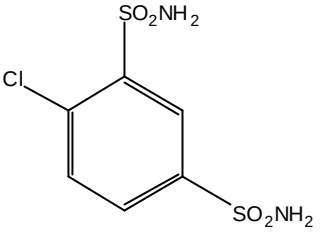
Some sulphonamide derivatives are recently in clinical use are listed below.

Suplhadoxine



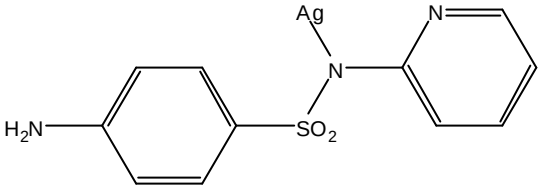
Antimalarial

Clofenamide



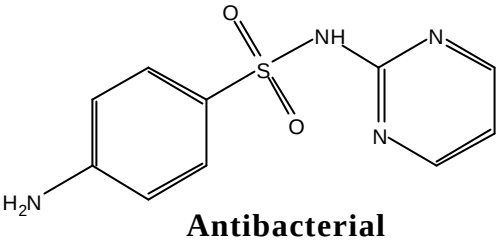
Diuretic

Silver Sulphadiazine



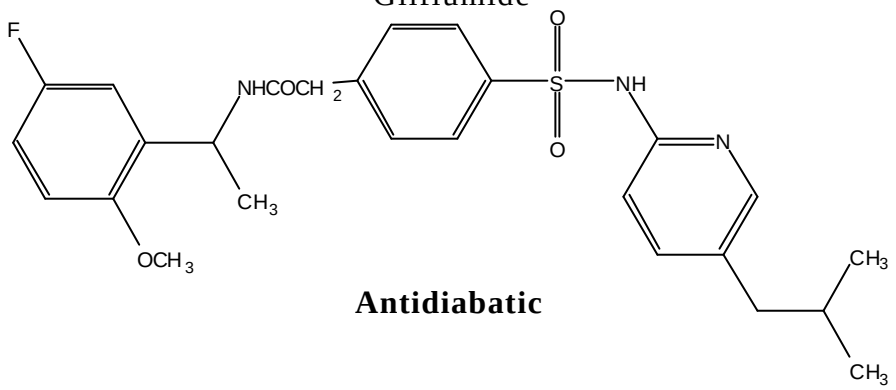
Antimicrobial in burns

Sulphadiazine



Antibacterial

Gliflumide



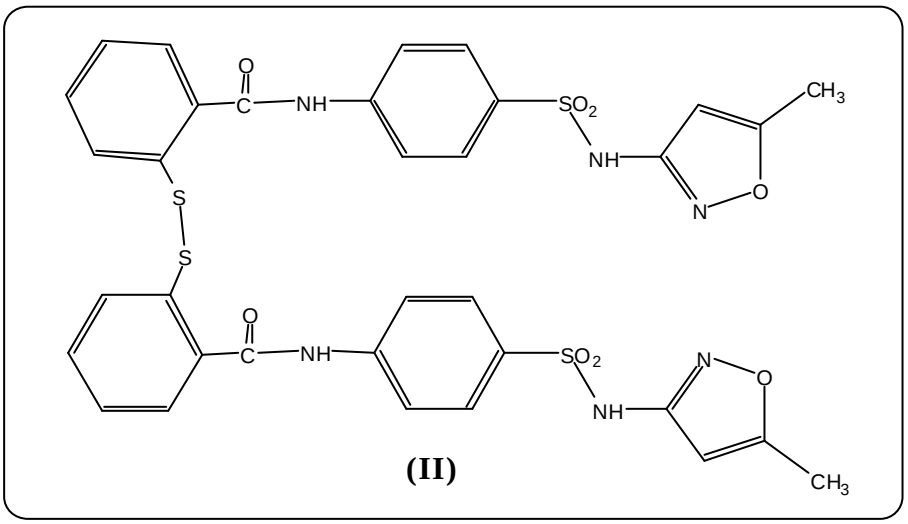
Antidiabatic

Monograms and review,[8,9] surveying various aspects of sulpha drugs have been published. Considerable research has been done to extend the activity and to reduce the toxicity of sulpha drugs.

Several sulphonamide derivatives have been reported to be associated with diverse biological activities are listed as under.

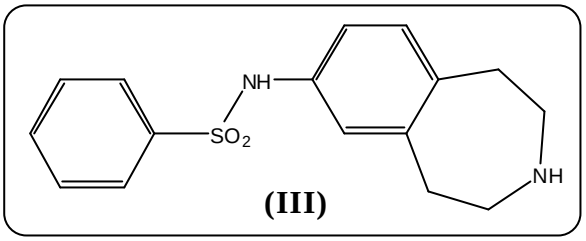
1. Diuretic[10]
2. Hypoglycemic[11]
3. Herbicidal[12,13]
4. Antihypertensive[14]
5. Anticonvulsant[15]
6. Antimalarial[16]
7. Antiviral[17]
8. Anti-HIV[18,19]
9. Antiinflammatory[20,21]
10. Antitumor[22,23]

Mengelers M. J. et al.[24] have synthesized some new sulphonamide derivatives and reported their *in vitro* antimicrobial activity. Some new sulphonamide derivatives (II) have discovered by Jim A.Turpin and coworkers[25] which are used as an anti-HIV agents.



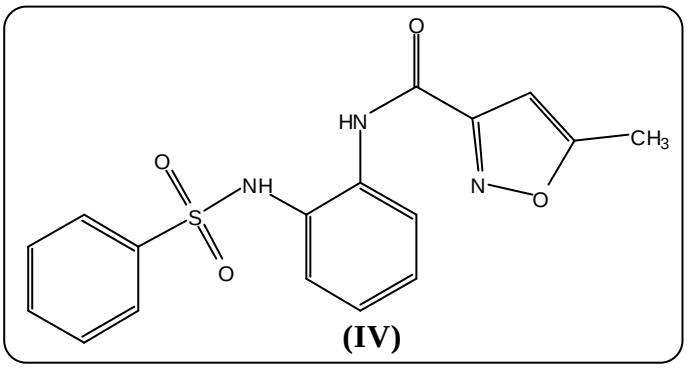
(II)

Thaisrivongs S. and coworkers[26] have synthesized sulphonamide derivatives and reported them as a novel HIV protease inhibitors. Cooper and coworkers[27] have prepared sulphonamide derivatives (III) and documented their antipsychotic activity.



(III)

Maillard J Y. et al.[28] have documented antimicrobial activity of sulphonamide derivatives. Casini A. and coworkers[29] have documented anticancer activity of sulphonamide derivatives. De Clercq E. et al.[30] have reported anti-HIV activity of sulphonamide derivatives. Some novel sulphonamides (IV) prepared by Morohashi, Hirohiso and coworkers[31] and studied their pharmacological activity and has been found as anticancer agent.



(IV)

Scozzafava A and coworkers [32] have reported sulphonamide derivatives as anticancer and antiviral agents. Supuran CT.et al.[33] have documented anticancer, antiinflammatory and antiviral activity of sulphonamide derivatives. Dieter B.and coworkers[34] have reported antibacterial activity of the sulphonamides. Supuran CT.et al.[35] documented antiviral activity of sulphonamide derivatives.

Dominguez J N et al.[36] have synthesized some novel sulphonamides and reported their antimicrobial activity. Bialk H M and coworkers[37] have documented antimicrobial activity of some sulphonamide derivatives.

Link J T, Sorensen B, Jacobson P B. and coworkers[38] have documented antidiabetic activity of sulphonamides. Tortorano A M. et al.[39] reported fungicidal activity of sulphonamide derivatives.

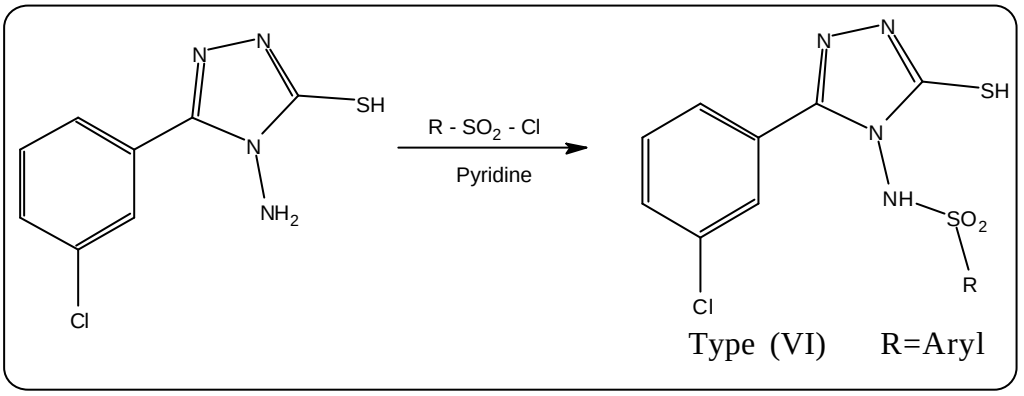
In the past years considerable evidence has been accumulated to demonstrate the pharmacodynamic and chemotherapeutic activities of sulphonamide derivatives. To further assess the potential of such type of compounds, study of sulphonamide derivatives have been carried out as described under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYL SULPHONAMIDES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYLSULPHONAMIDES.

Looking to the interesting properties of sulphonamides, it was considered worthwhile to synthesize a series of sulphonamide derivatives of type (VI) for obtaining biologically potent molecules by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different carboxy arylsulphonyl chloride in pyridine.

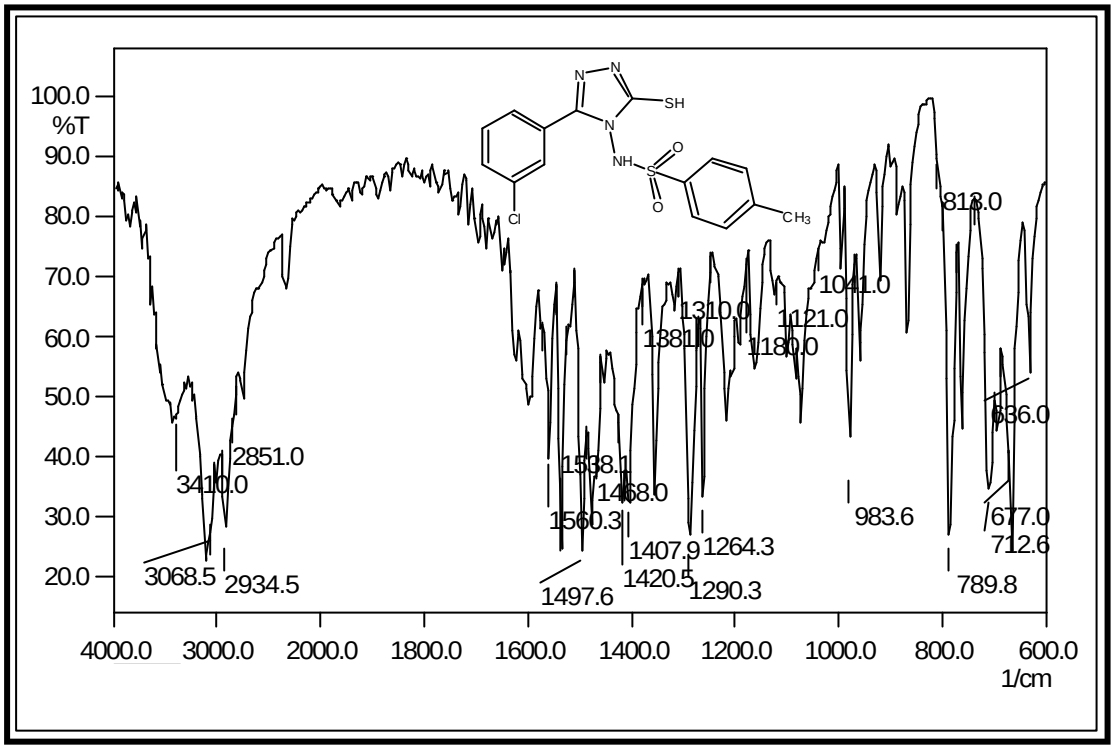


Type (VI) R=Aryl

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

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

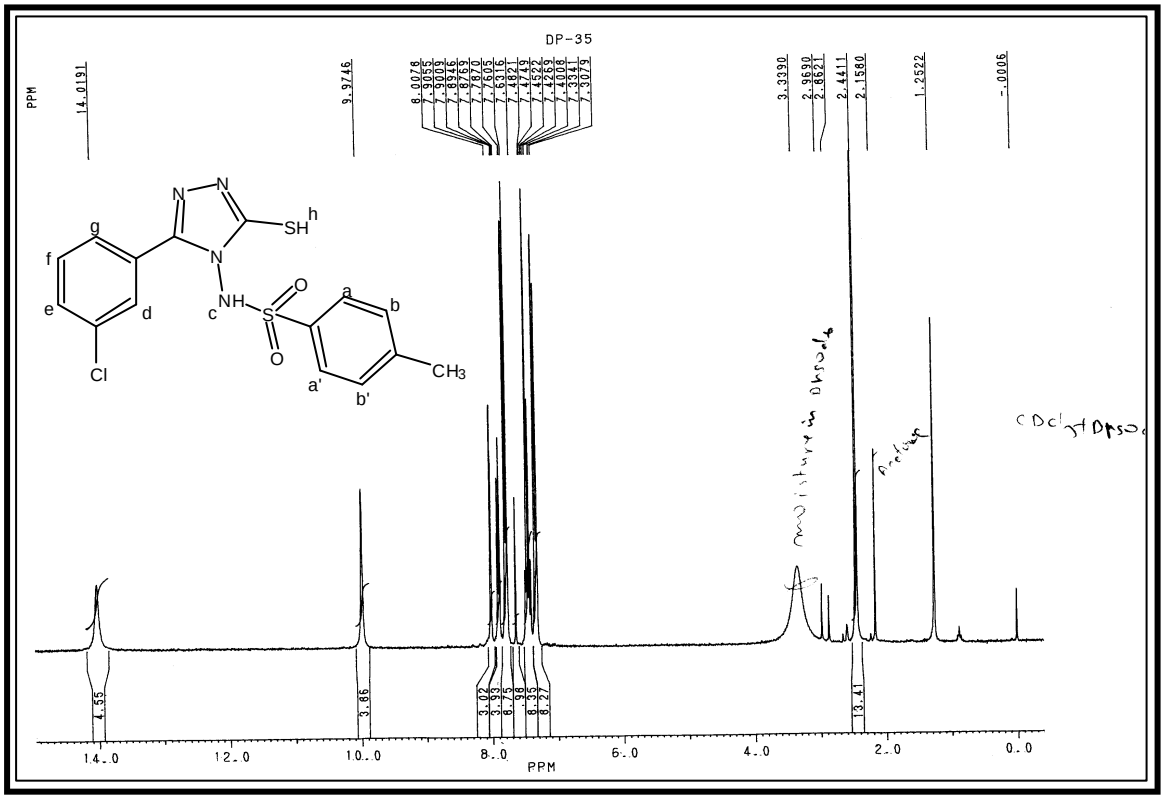
IR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL-(p-METHYLPHENYL)SULPHONAMIDE



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.)	2934	2975-2950	40
-CH_3	C-H str. (sym.)	2851	2880-2860	40
	C-H def.(asym.)	1468	1470-1435	40
	C-H def.(sym.)	1381	1385-1370	40
Aromatic	C-H str.	3068	3080-3030	40
	C=C str.	1497	1520-1480	40
	C-H i.p. (def)	1121	1125-1090	41
	C-H o.o.p. (def)	813	835-810	40
Triazole	C=N str.	1588	1640-1500	40
	C-N str.	1121	1220-1020	42
	N-N str.	1041	1050-1010	40
Sulphonamide	-NH str.	3410	3350-3000	40
	-SO_2	1310	1350-1300	40
Halide	C-Cl str.	78	800-600	40

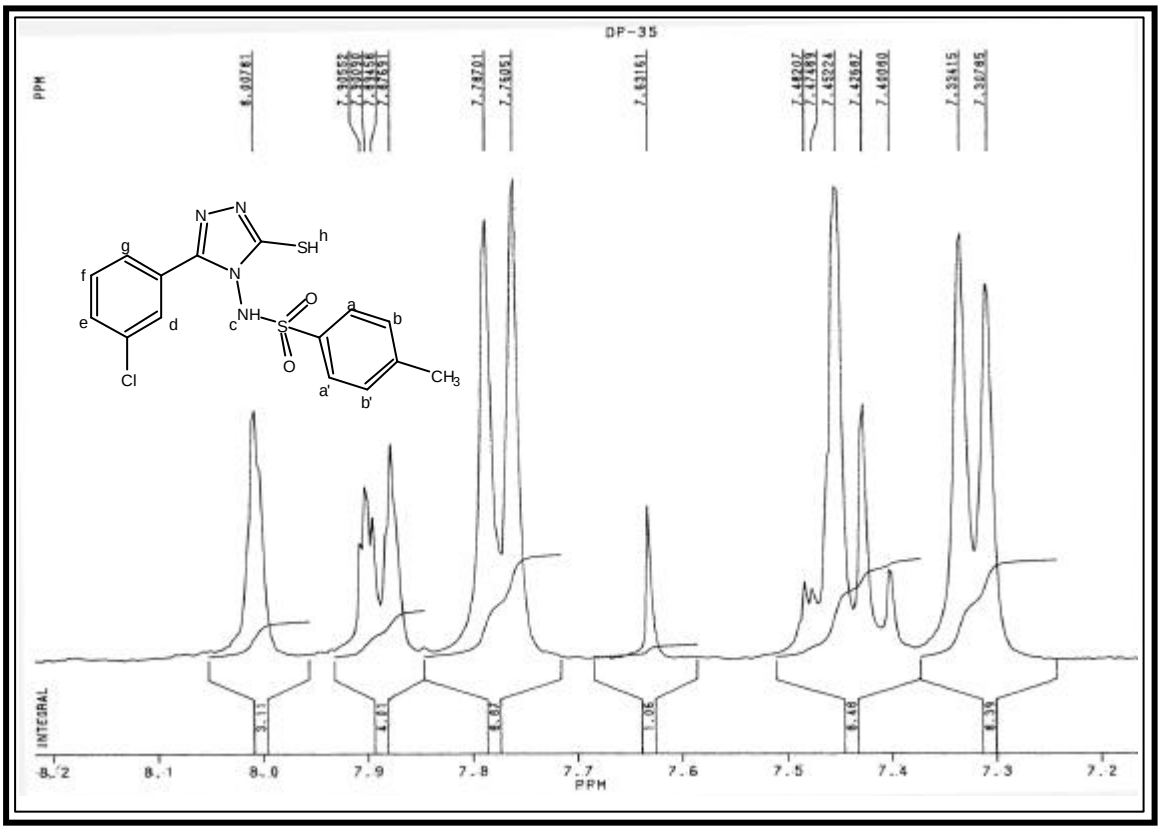
NMR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL-(p-METHYLPHENYL)SULPHONAMIDE



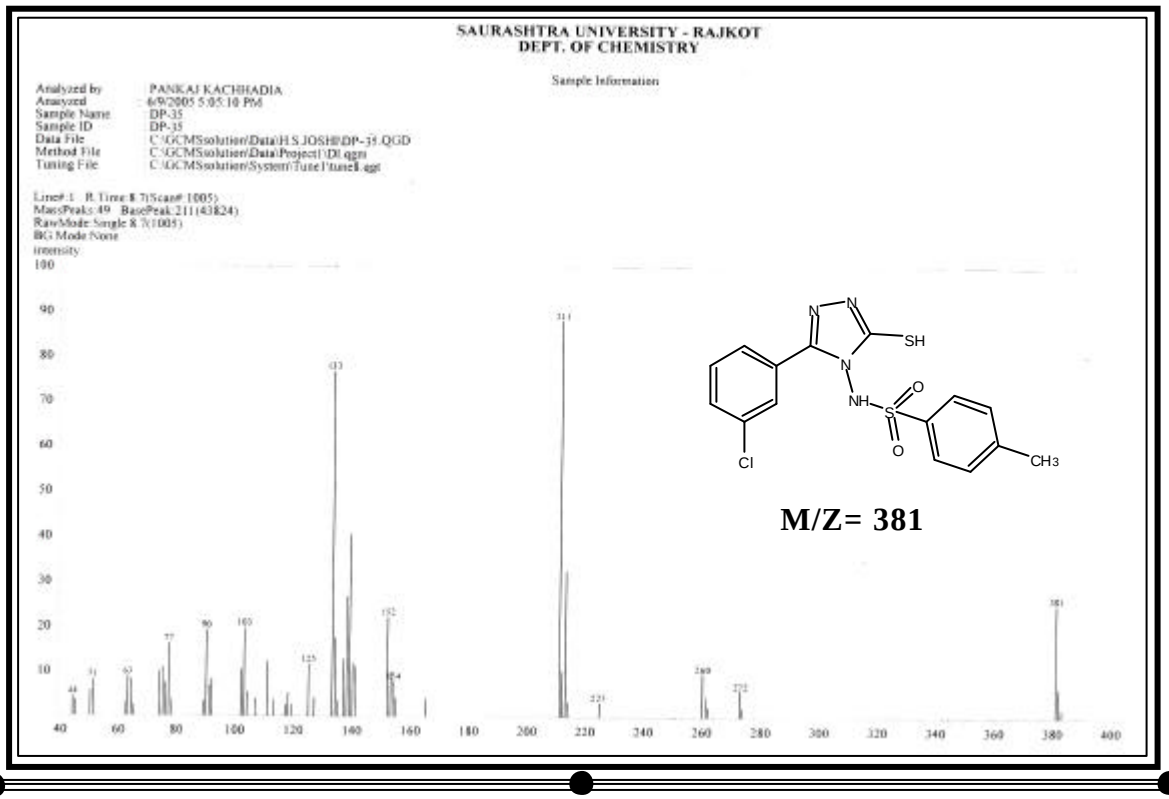
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.44	3H	singlet	Ar-CH_3	-
2	7.31	2H	doublet	Ar-Haa'	Jab=8.1
3	7.40-7.48	2H	doublet	Ar-Hfg	Jfe=7.8 Jfg=7.8
4	7.78-7.76	2H	doublet	Ar-Hbb'	Jba=8.1
5	7.90	1H	doublet	Ar-He	Jef=7.2
6	8.00	1H	singlet	Ar-Hd	-
7	9.97	1H	singlet	Ar-Hc	-
8	14.01	1H	broad	Ar-Hh	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL -(p-METHYLPHENYL)SULPHONAMIDE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYL SULPHONAMIDES.

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

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

[B] Preparation of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

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

[C] Preparation of 3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl-p-methylphenyl sulphonamide.

A mixture of p-tolylsulphonylchloride (1.90g, 0.01 mol) and 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols (2.26g, 0.01 mol) was refluxed in dry pyridine for 4-5 hrs. The product was isolated and recrystallised from ehanol. Yield 70 %, m.p. 240°C. Anal.Calcd. for $C_{15}H_{13}ClN_4S_2O_2$: C,47.30; H,3.44; N,14.71% ; Found: C,47.27; H,3.43; N,14.69 %.

Similarly other sulphonamides have synthesized and physical constants are recorded in Table No.6.

[D] Antimicrobial activity of 3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl aryl sulphonamides.

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

TABLE-6 : PHYSICAL CONSTANTS OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYLSULPHONAMIDES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
6a	4-CH_3-C_6H_4-	$C_{15}H_{13}ClN_4O_2S_2$	380	240	70	14.71	14.69	0.42	S2
6b	2,4-$(Cl)_2$-C_6H_3-	$C_{14}H_9Cl_3N_4O_2S_2$	435	175	58	12.86	12.84	0.47	S2
6c	3-CH=CH-COOH-C_6H_4-	$C_{17}H_{13}ClN_4O_4S_2$	436	180	59	12.82	12.80	0.42	S1
6d	4-F-C_6H_4-	$C_{14}H_{10}ClFN_4O_2S_2$	384	167	58	14.56	14.52	0.41	S2
6e	3-COOH-6-Cl-C_6H_3-	$C_{15}H_{10}Cl_2N_4O_4S_2$	445	210	60	12.58	12.55	0.50	S2
6f	3-COOH-4-CH_3-C_6H_3-	$C_{16}H_{13}ClN_4O_4S_2$	424	188	61	13.19	13.15	0.52	S1
6g	3-COOH-4-Cl-C_6H_3-	$C_{15}H_{10}Cl_2N_4O_4S_2$	445	190	56	12.58	12.55	0.44	S2
6h	3-COOH-4-NO_2-C_6H_3-	$C_{15}H_{10}ClN_5O_6S_2$	455	260	58	15.36	15.34	0.54	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

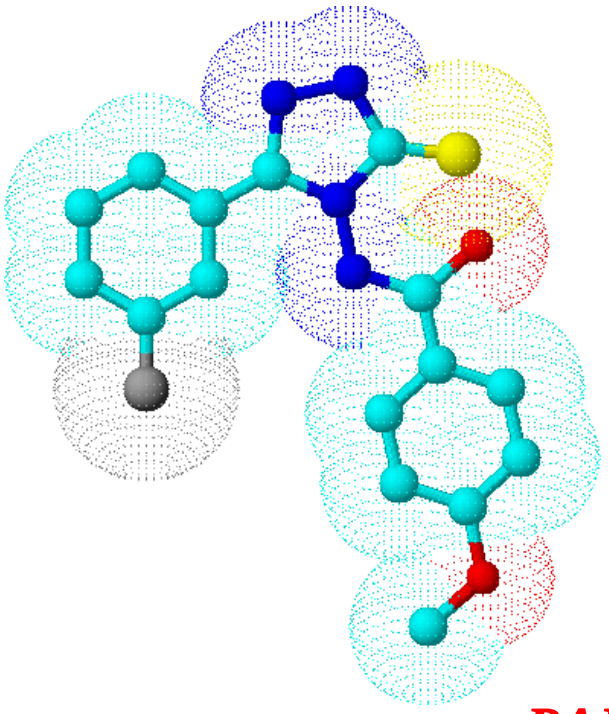
Graphical Chart No. 6 :Antimicrobial Activity of 3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl aryl sulphonamides.

REFERENCES

1. Shepherd R.G. ;
   Sulphonamides and other p-aminobenzoic acid antagonists in medicinal chemistry,1, **255,** (1949).
2. Krupp M.A. and Chalton M.J. ;
   Current Medicinal diagnoses and treatment, (1980).
3. C.M. Suter;
   "The organic chemistry of sulphur", John Wiley and Inc.Ny; **103-175,** 575-639 (1964).
4. E. Muller et al. ;
   Methoden der organischem chemie (houben Wely) 9. 4th Ed. Georg. Themie, Verlag Stuffgart, West Germany (1955).
5. P.R. Carter and D.H. Hey.;
   J.Chem.Soc., 147-9 (1948) ; *Chem.Abstr.,* **42,** 4968 (1948).
6. Wa.Chengde, Blok, Natalie, Patricia, Wood word, Timothy, Keller, Kasiu.;
   Chem. Abstr., No. 11 Vol. **137,** p-154844n (2002).
7. Natesan Murgesan, Zheng Xiang Guphilip, D. Stevin, Skren sperges, Arvind Mathur, Joel C. Barrish.
   J.M.C., Vol **43(16),** P 3111-3117, (2002).
8. F.L.Rose.;
   Chem.Ind. (London), **21,** 658-65 (1964); *Chem.Abstr.* ,**61,** 2901b (1964).
9. R.S. Mc Cutcheon. ;
   Pharm. Index., **7,** 4A, 4-8 (1984).
10. Feit P. Worner, O.B.T. Neilsen and H. Bruun. ;
    Brit., **1,** 523, 631 (1978); *Chem.Abstr.*, **91,** 56629h (1979).
11. Henquin J.C. ;
    Diabotologia **60(1),** 904-12 (1992); *Chem,Abstr.,* **118,** 87p (1993).
12. I.S. Cloudsdate, R.J. Anderson, H.R. Chinn, G.W. Craiq, P.N. Peng, P.L. Herberich and J.C. Pomes. ;
    Acs. Syme. Jer. 584, **37,** (1995) ; *Chem. Abstr.,* **122,** 125875h (1995).
13. Abe. Takuai, Akiyoshi Yuji, Shirashi, Hirashi, Ikas; Kojima. Mikio ; Hayama. Takashi. ;
    Eur. Pat. Appl. EP 567,014,27, Oct.(1993) ; *Chem.Abstr.,* **121,** 8335n (1994).

14. P. O. Wester. ;
Acta Med. Scand, **196(6),** 489-94 (1974); *Chem.Abstr.* ,**82,** 93324g (1975).
15. V. Hagen, e. Morgenstern and Georges. ;
Pharmazie, **35(3),** 183-5 (1980); *Chem.Abstr.,* **93,** 106817g (1980).
16. Joachim K. Seydel, Helmut Pieper and Albrecht Jung. ;
Ger. Offen. D.E. **3,** 919, 214; *Chem.Abstr.,* **114,** 185536t (1991).
17. Henry K. Soolewski and Dionizy Skwaski. ;
Ann. Acta. Pol. Pharm., **46(3),** 232-6 (1989); *Chem.Abstr.,* **114,** 6421 (1991).
18. M.L. Vazquez and co-workers. ;
Pat. Int. Appl. Wo **94,** 04, 493 (1994); *Chem.Abstr.,* **122,** 55727k (1995).
19. M.I. Reider, R. Krause, I.R. Bird and G.A. Debakan. ;
J. Acquived Immune Defic, Syndr., Hum. Rerovirol. **8(2),** 134 (1995); *Chem. Abstr.,* **122,** 230194n (1995).
20. K.H. Patel and K.R. Desai. ;
Proc. Nat. Acad. Sci., India, Sec. A **60(1),** 7 (1990); *Chem.Abstr.,* **114,** 164164e (1991).
21. Yoshikawa Yashinavi, Saito Hideji and Oochi Yutake. ;
Jpn. Kokkai Tokyo Jp. **04,** 174, 782 (1992); *Chem.Abstr.,* **118,** 38917 (1993).
22. J.J. Howbert. A.C. Thomas, E.K. Kenneth and V.T. eddie. ;
J. Mrd. Chem. **33(9),** 2393-407 (1990); *Chem.Abstr.,* **113,** 114771j (1990).
23. Hiroshi Yoshino, Nirihiri Ueda.;
PCT. Int. Appl. Wo 95, **03,** 279 (1995); *Chem.Abstr.,***122,** 314588c (1995).
24. Mengelers M.J. et al. ;
Am J Vet Res. Jul ; **50(7),** 1022-28 (1989).
25. Jim A. Turpin, Yong, Sheng, Song, John K. Inman, Ingium Huang, Ettore Appela;
J. Medicinal Chem. Vol **42(1),** p 69-73 (1999).
26. Thaisrivongs S. et al. ;
*J. Med. Chem.,*Jun 7, **39(12),** 2400-10 (1996).

27. Cooper, David Gwyn, Forbes, Ian Thomson et. al. ;
PCT. Int. Appl. Wo 03, **68,** 732 (Cl. CO7C3O7/10), (2003).
28. Maillard J.Y. et al.;
J. Hosp. Infect. Dec; **40(4),** 313-23 (1998).
29. Casini A. et al. ;
Curr Cancer Drug Targets., Mar; **2(1),** 55-75 (2002).
30. De Clercq E. et al. ;
Med.Res.Rev. Nov; **22(6),** 531-65 (2002).
31. Morohashi, Hirohiso, sutoltiroshi (Japan) ;
PCT Int. Appl.wo **98,** 5413 (Cl 07 C31,146), ., *J. Appl.*,**97,** 156.
30, Dec (1998); *Chem.Abstr.,* Vol. **130(4),** 694, 38382s (1999).
32. Scozzafava A. et al. ;
Curr. Med. Chem. Jun; **10(11),** 925-53, (2003).
33. Supuran C.T. et al. ;
Med. Res. Rev. Sep; **23(5),** 535-58 (2003).
34. Dieter B., Hein-Peter K., et al. ;
Antimicrobial agents and chemotherapy **48(2),** 525-532; C.A..
141(1);468p (2004).
35. Supuran C.T. et al. ;
Mini Rev Med. Chem., Feb; **4(2),** 189-200 (2004).
36. Dominguez J.N. et al. ;
Farmaco Apr; **60(4),** 307-11 (2005).
37. Bialk H.M. et al. ;
Environ Sci Technol., Jun 15; **39(12),** 4463-73 (2005).
38. Link J.T., Soensen B., et al. ;
J. Med.Chem., Aug,11; **48(16),** 5295-304 (2005).
39. Tortorano A.M. et al. ;
J.Med. Microbiol. Oct; **54** (Pt 10); 955-57 (2005).
40. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
41. C. N. R. Rao;
"Chemical application of Infrared spectroscopy" Academic press, New York (1963).
42. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.



PART - VI

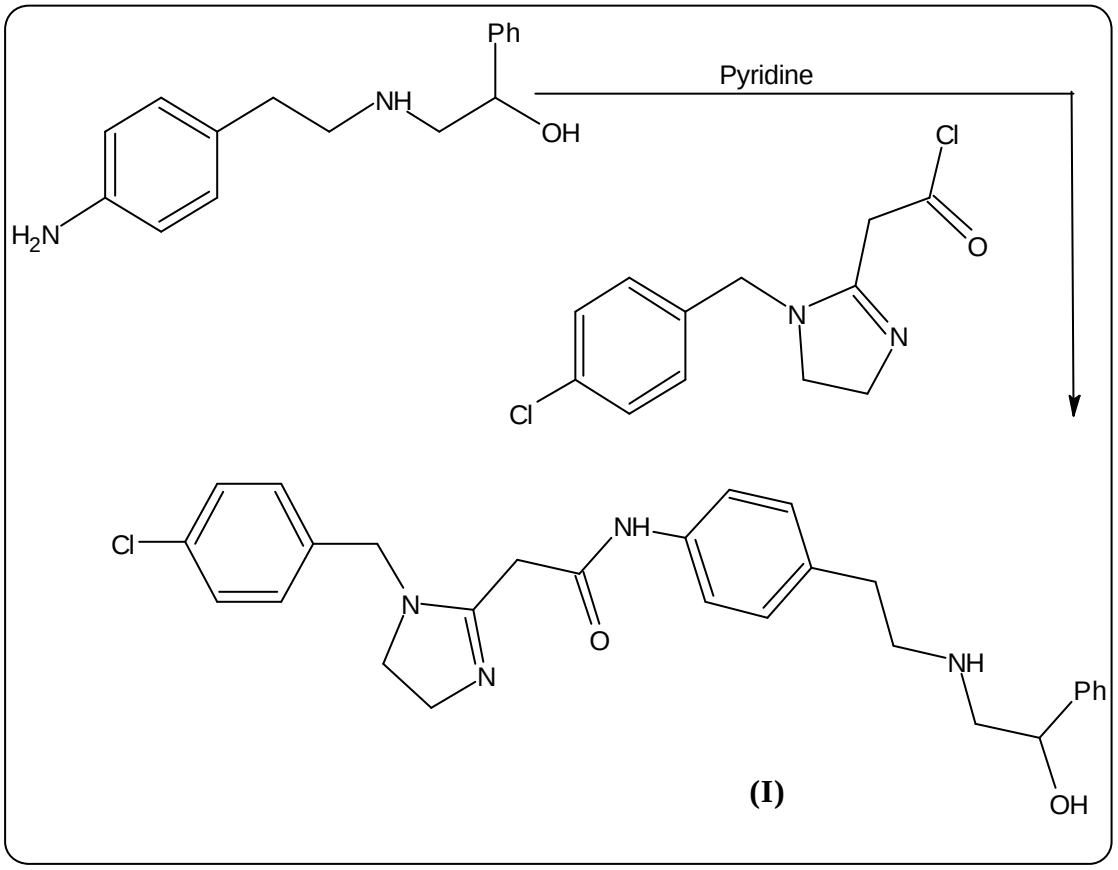
STUDIES ON ARYLAMIDES

INTRODUCTION

The Characteristic group present in the simple carboxylic amide is $–CONH_2$. They are the acyl substitution products of ammonia. Many natural products are amides, urea, diamides of carbonic acid. The peptides and proteins are linear structure of cyclic polyamides. The alkaloids of pepper, piperidine and chavicine are N-substituted amides of unsaturated acid. N-isobutyl amides of certain highly unsaturated aliphatic acids occur in plants, shows insecticidal activity[1]. Amides derived from polyacetylenic acid have been isolated from certain fungi[2].

SYNTHETIC ASPECT

Various methods for the synthesis of aryl acetamides are described in literature[3-8]. Marayama Tatsuya, Suzuki Onda[9] have synthesized arylamide (I) as under.



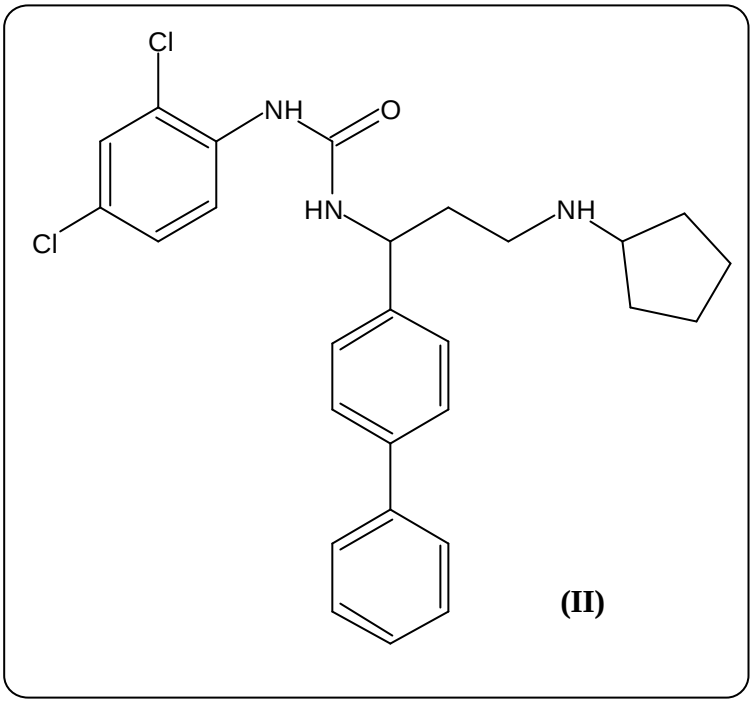
(I)

BIOLOGICAL EVALUATION

Amides and substituted amides have widely been used as pharmacologically useful entities. Some arsano organometallic compounds like tryparsamide and arsacetin having amide group have proved to be successful chemotherapeutic agents. The biological activities of aryl amide derivatives have been reported as under.

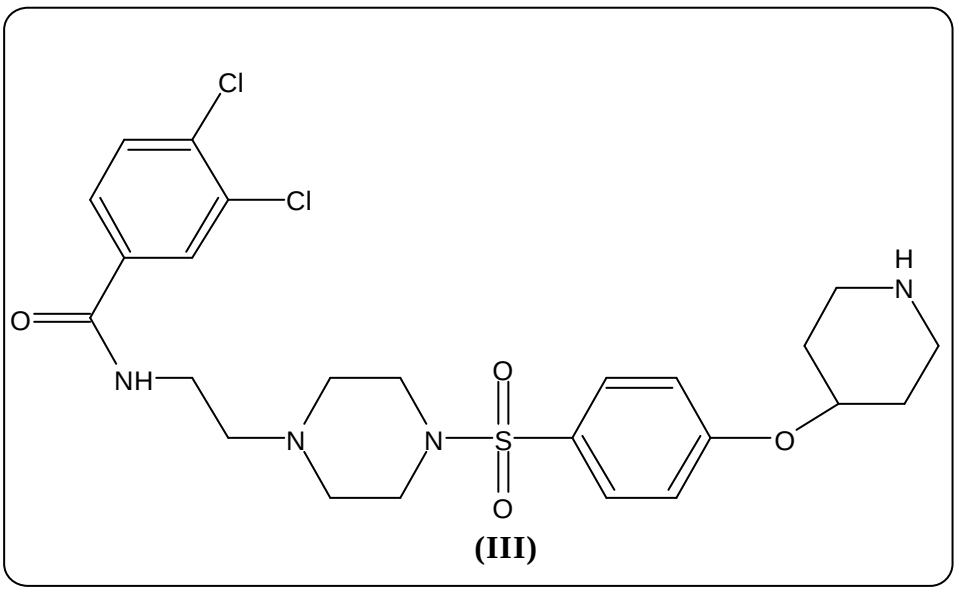
1. Anticonvulsant[10]
2. Antiallergic[11]
3. Herbicidal[12]
4. Cardiotonic[13]
5. Antimicrobial[14,15]
6. Analgesic[16]
7. Antiulcer[17]
8. MAO inhibitor[18]
9. Anticancer[19,20]
10. Antiinflammatory[21]
11. Anti-HIV[22]
12. Sodium channel blockers[23]

Sanderson Philip E.J. et al.[24] have synthesized aryl amides and studied their biological activity. Moloney et al.[25] have reported aryl amide derivatives as antiulcer agents. Foster James et al.[26] have synthesized some new amide derivatives as potent anticonvulsant. Mulik et al.[27] have studied some aryl amides shows antibiotic activity. Bridge Gory[28] et al. have screened arylamides as anti-HIV agent. Laura and co-workers[29] have prepared arylamides as antibacterial agents. Hobbs et al.[30] have designed some amides (II) and reported them as MCH-receptor antagonist.



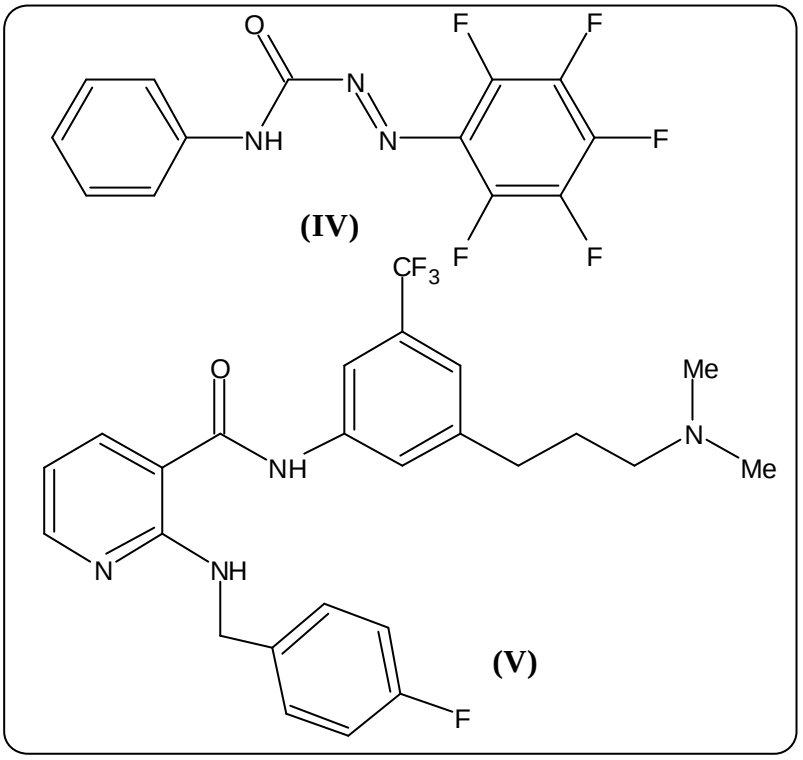
(II)

A.K. Mallams[31] has reported arylamide derivatives as antitumor agent. More over S. J. Laulloo et al.[32] and J. Hazarika[33] have prepared some novel biologically active arylamide derivatives and reported them as antimicrobial agents. Dhanak Dushyant et al.[34] have synthesized arylamide (III) useful as urotensin-II antagonist.



(III)

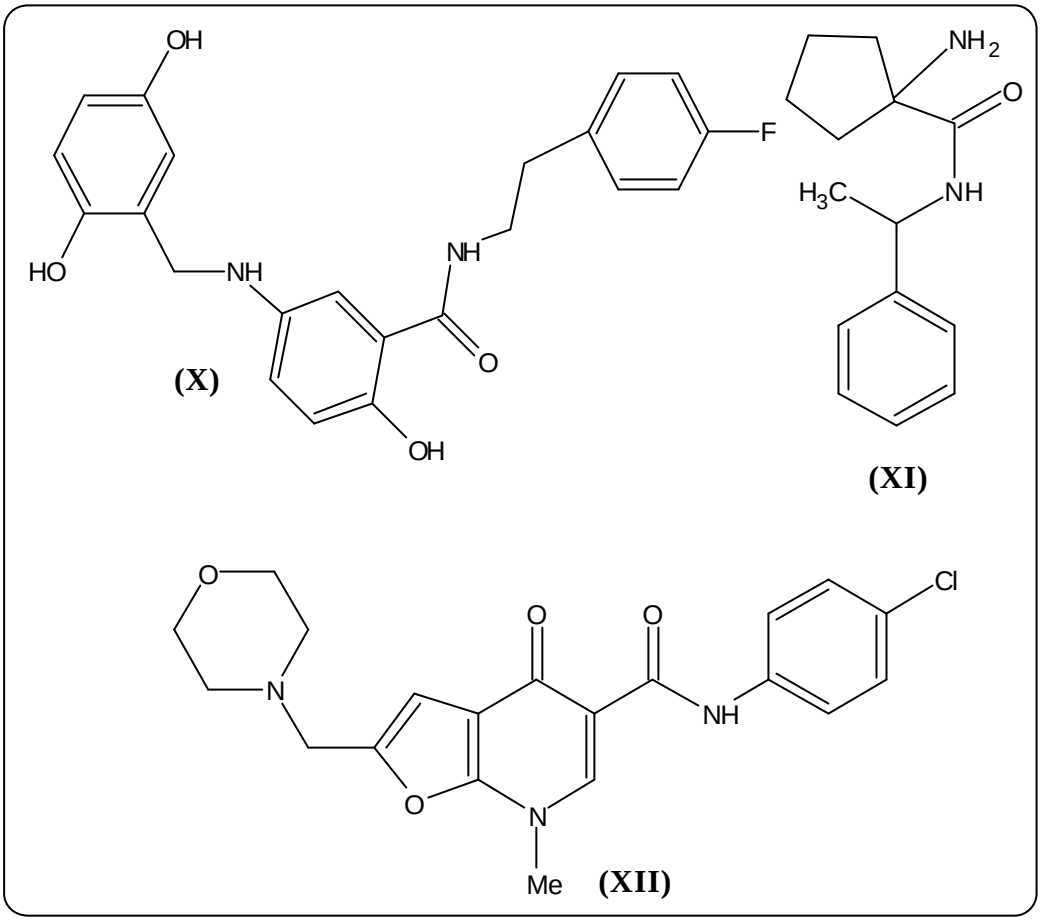
Tabuchi et al.[35] have screened arylamide derivatives as novel potent antagonist of human neuropeptide YY_5 receptor. Chan[36] have recorded substituted benzophenone arylamide derivatives as inhibitor reverse transcriptase. Pieters et al.[37] have synthesized new diazene carboxamides (IV) as anticancer agents. Anthony and co-workers[38] have investigated amides as anti-HIV. Chen et al.[39] have reported arylamides (V) as antitumor agents.



(IV)

(V)

James B. and co-workers[40] have screened arylamides as selective opioid-K receptor antagonist. Fanrong mu et al.[41] have demonstrate new arylamide (X) as anticancer. Bin Ho et al.[42] have investigated arylamide derivatives (XI) as anticonvalsant agent. Cudahy et al.[43] have prepared arylamide (XII) and reported them as antiviral agent.



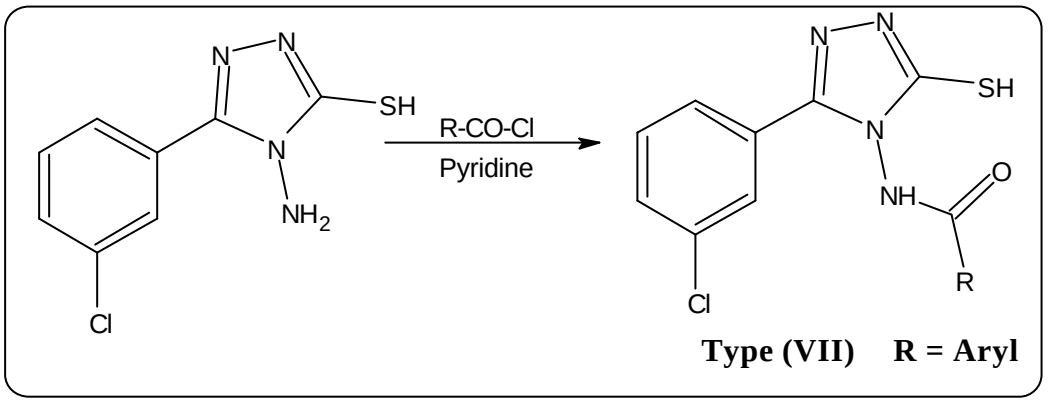
In the past years, considerable evidence have been accumulated to demonstrate the pharmacodynamic and chemotherapeutic activities of amide derivatives. To further assess the potential of such type of compounds, the synthesis have been carried out which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYLAMIDES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYLAMIDES

Arylamide derivatives are associated with broad spectrum of pharmacological activity. With an intension of preparing the compounds possesing better therapeutic activity,arylamides of type-(VII) have been synthesised by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic acid chlorides.

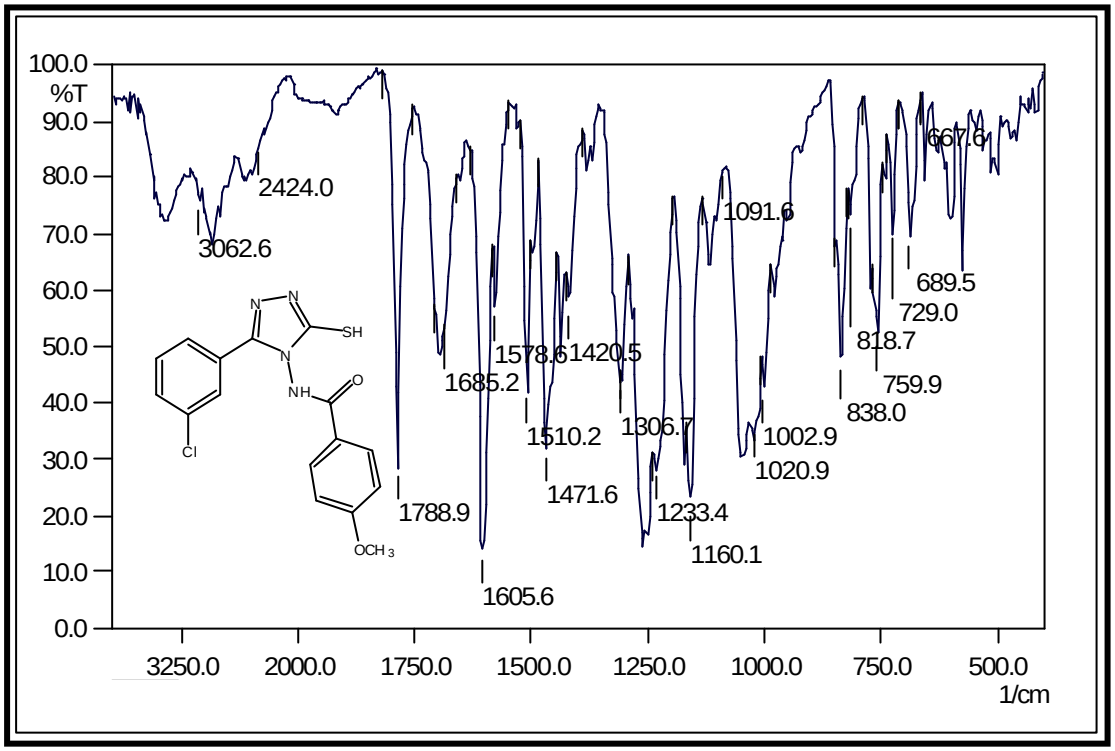


Type (VII) R = Aryl

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

All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No.7.

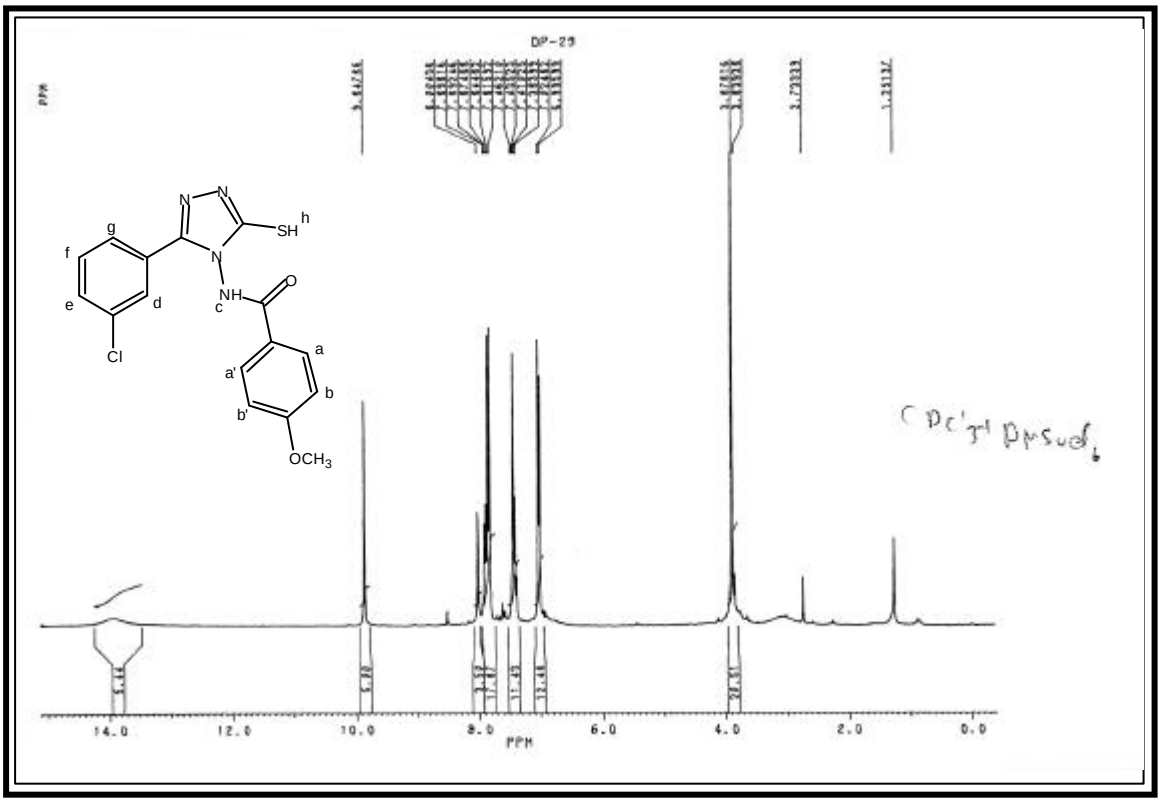
IR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL - (p-METHOXYPHENYL)AMIDE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3062	3080-3030	44
	C=C str.	1510	1585-1480	44
	C-H i.p. (def)	1091	1125-1090	45
	C-H o.o.p. (def)	818	835-810	45
Triazole	C=N str.	1605	1650-1580	46
	C-N str.	1233	1220-1020	46
	N-N str.	1020	1050-1010	45
Ether	C-O-C str.(asym.)	1233	1275-1200	46
(Ar-O-R)	C-O-C str.(sym.)	1002	1070-1000	46
Amide	-NH str.	3220	3300-3100	44
-CO-NH	-NH def	1578	1650-1580	44
	C=O str. (Amide)	1685	1690-1630	44
Halide	C-Cl str.	729	800-600	45

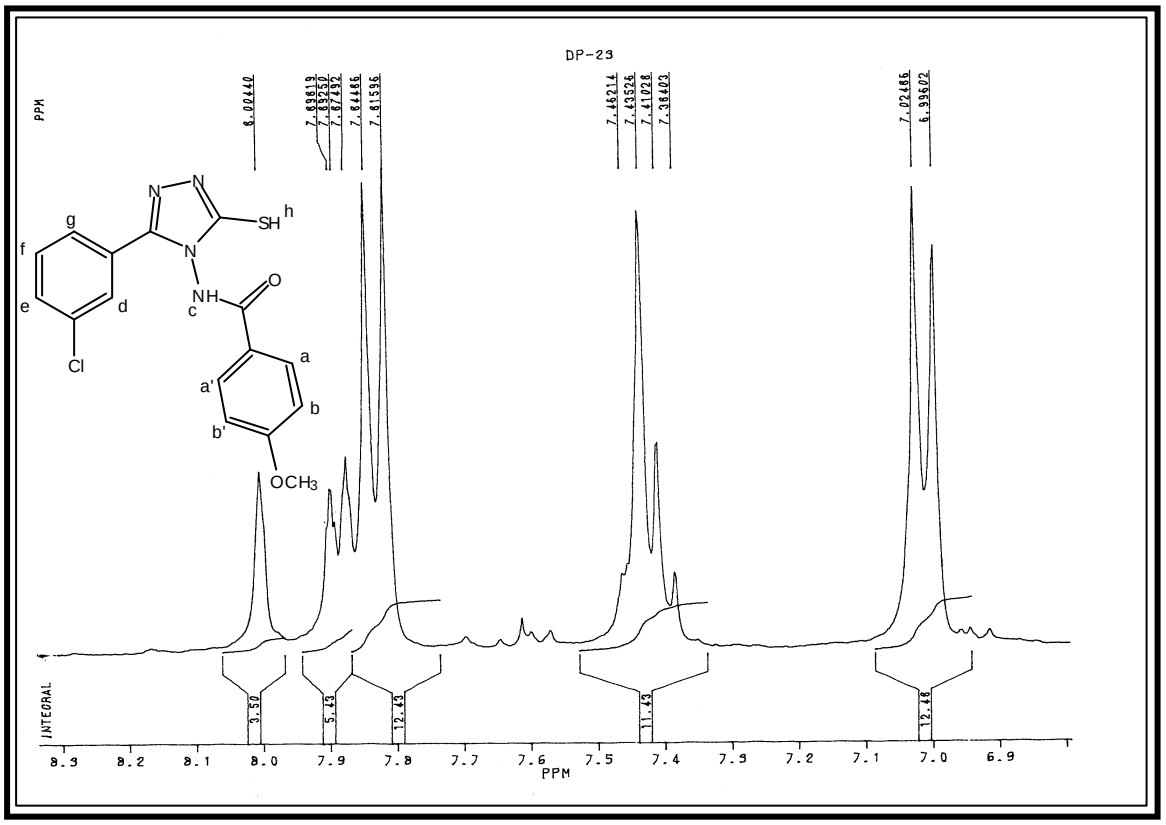
NMR SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL - (p-METHOXYPHENYL)AMIDE



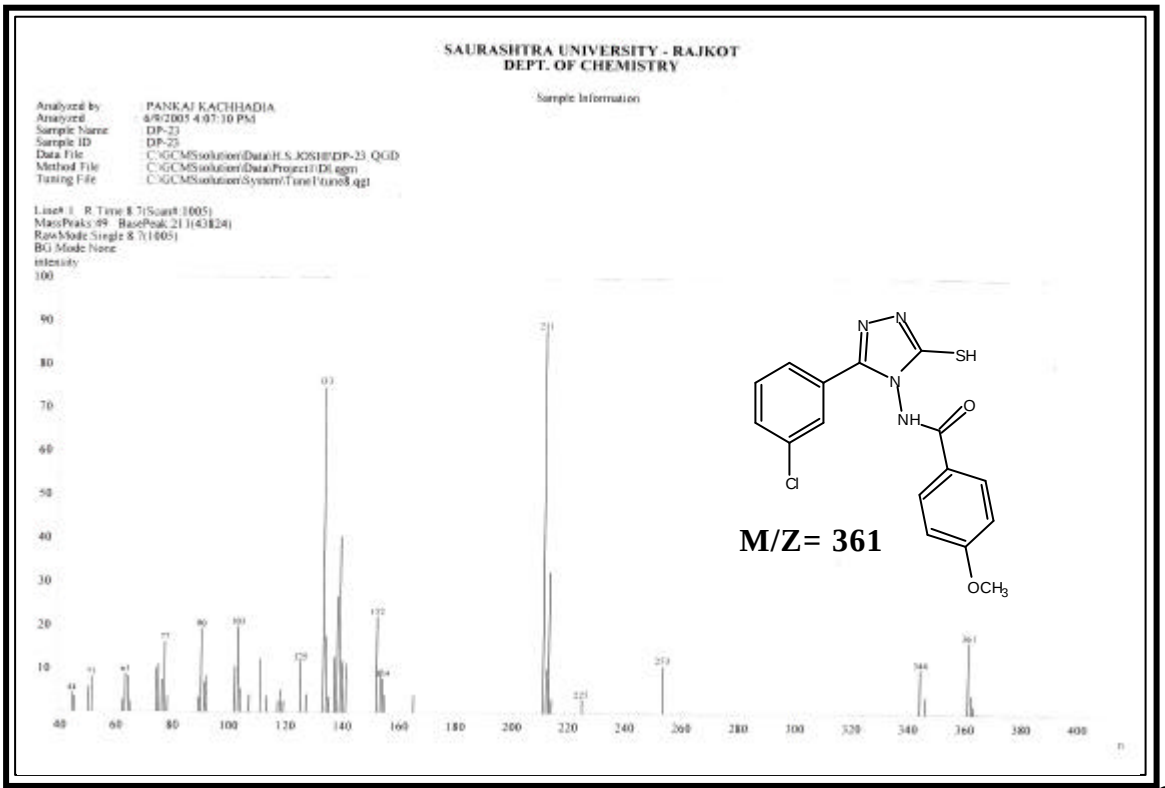
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.87	3H	singlet	Ar-OCH_3	-
2	6.95	2H	doublet	Ar-Hbb'	Jba=8.4
3	7.41-7.46	2H	doublet	Ar-Hfg	Jfe=7.5 Jfg=7.8
4	7.82	2H	doublet	Ar-Haa'	Jab=8.7
5	7.88	1H	doublet	Ar-He	Jef=7.2
6	8.00	1H	singlet	Ar-Hd	-
7	9.84	1H	singlet	-NH	-
8	13.90	1H	broad	-SH	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL (p-METHOXYPHENYL)AMIDE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYLAMIDES

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

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

[B] Preparation of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

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

[C] Preparation of 3-(m-Chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl-p-methoxy phenylamide.

A mixture of p-methoxybenzoylchloride (1.70g, 0.01 mol) and 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols (2.26g, 0.01 mol) was refluxed in dry pyridine for 8 hrs. The product was isolated and crystallised from ehanol. Yield 70 %, m.p. 180°C. Anal.Calcd. for $C_{16}H_{13}ClN_4SO_2$: C,53.26; H,3.63; N,15.53% ; Found: C,53.22; H,3.60; N,15.50 %.

Similarly other arylamides have synthesized and physical constants are recorded in Table No.7.

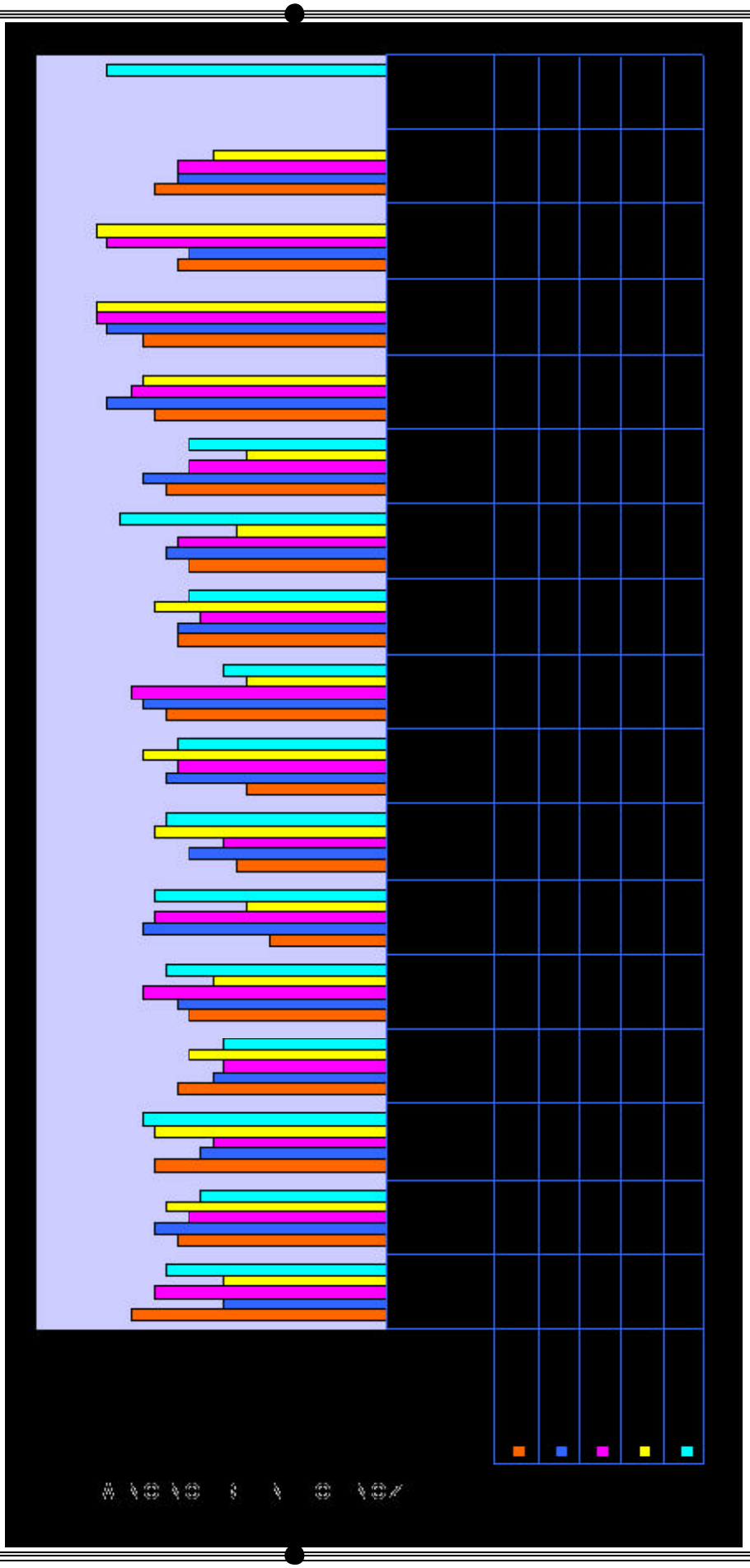
[D] Antimicrobial activity of 3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl arylamides.

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

TABLE-7 : PHYSICAL CONSTANTS OF 3-(m-CHLOROPHENYL)-5-MERCAPTO-4*H*-1,2,4-TRIAZOL-4-YL ARYLAMIDES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
7a	4-OCH_3-C_6H_4-	$C_{16}H_{13}ClN_4O_2S$	360	180	70	15.53	15.50	0.51	S2
7b	2-CH_3-C_6H_4-	$C_{16}H_{13}ClN_4OS$	344	165	68	16.25	16.21	0.47	S2
7c	4-Br-C_6H_4-	$C_{15}H_{10}BrClN_4OS$	409	183	61	13.68	13.65	0.43	S1
7d	4-NO_2-C_6H_4-	$C_{15}H_{10}ClN_5O_3S$	375	170	58	18.64	18.60	0.42	S2
7e	4-C_5H_4N	$C_{14}H_{10}ClN_5OS$	331	179	60	21.11	21.18	0.46	S1
7f	2-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4OS$	365	210	57	15.34	15.30	0.56	S2
7g	2,4$(OH)_2$-C_6H_3-	$C_{15}H_{11}ClN_4O_3S$	362	181	71	15.44	15.40	0.51	S1
7h	3-OC_6H_5-C_6H_4-	$C_{21}H_{15}ClN_4O_2S$	442	198	68	13.25	13.21	0.45	S2
7i	3-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4OS$	365	260	58	15.34	15.30	0.54	S1
7j	3-NO_2-C_6H_4-	$C_{15}H_{10}ClN_5O_3S$	375	210	53	18.64	18.60	0.48	S1
7k	4-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4OS$	365	156	58	15.34	15.30	0.42	S2
7l	2-OH-C_6H_4-	$C_{15}H_{11}ClN_4O_2S$	346	170	56	16.16	16.12	0.52	S2

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)



Graphical Chart No. 7 :Antimicrobial Activity of 3-(m-chlorophenyl)-5-mercapto-4*H*-1,2,4-triazol-4-yl arylamides.

REFERENCES

1. F.D. Gunstone;
   Progr. Org. Chem., **4,** 1-30 (1958); *Chem Abstr.,* **52,** 9940 (1958).
2. J.D. Bullock;
   "Acetylenic Compounds as Natural Products", Quart. Rev., **10,** 371 (1956).
3. J. Deinert;
   J. Pr. Chem., **52,** 433 (1985).
4. M-Carmack and M.A. Spienfman;
   The Willagerod Reaction; Org. Reaction, **3,** 83 (1946).
5. E. Cherbuliez and F. Landolt;
   Helv. Chim. Acta., **29,** 1436 (1946); *Chem. Abstr.,* **40,** 7158 (1946).
6. H. R.V. Arslein and R. Bentlex;
   J.Chem.Soc., **3509** (1951); *Chem.Abstr.,* **46,** 8010 (1951).
7. R. Radziszeiski;
   Ber., **18,** 355 (1985).
8. W. E. Burge;
   A. M. J. Physiol., **48,** 133 (1919); *Chem Abstr.,* **13,** 1869 (1920).
9. Maruyama, Tatsuya, Suzuki Onda;
   Chem. Abstr., **130(23),** 311793v (1999).
10. E. E. Beedle and D. W. Robertson;
    Eur. Pat. Appl. EP., **279,** 633 (1988); *Chem. Abstr.,* **110,**7875n (1989).
11. D. T. Connor and M. D. Mullican;
    U. S. US 4, **764,** 525 (1988); *Chem.Abstr.* , **109,** 211063e (1988).
12. Y. Itami, T. Harada, Noritsugu Yamasak, Fujishima Hiroshi;
    Jpn. Kokai; Tokyo Koho JP **62,** 252, 755 (1987); *Chem. Abstr.,* **109,** 12859m (1988).

13. K. Sakakibara, N. Yeneshima and T. Osawa;
Jpn. Kokai; Tokyo Koho JP **62,** 252, 785 (1987); *Chem. Abstr.,* **108,** 112238p (1988).

14. Tadashi Ohsumilnoue, Satory and co-workers;
Eur. Pat. Appl. EP **86,** 111 (1982); *Chem. Abstr.,* **100,** 85434a (1984).

15. Y. D. Kulkarni, Ali S. Mohd., S. Rowhana;
Indian Drugs; **25(12),** 505-7 (1988); *Chem. Abstr.,* **110,** 114786f (1989).

16. E. F. Lioma, C. Dacumpu and M. Capo;
J. Pharm. Pharmaco., **43(9),** 68 (1991); *Chem. Abstr.,* **114,** 1778 (1991).

17. Ikou Veda, Katsuyaki Ishi, Katsue Shinogaki, Masao Seiki and Hieha Chieo Akai;
Chem. Pharm. Bull., **38,** 3035 (1990); *Chem. Abstr.,* **114,** 135867 (1991).

18. Harfenist M., Joyner C.T., Harfenis Morton, Joyner Charlest, Mize Partic D., White Helen L;
J. Med. Chem., **37(13),** 2085-9 (1994); *Chem. Abstr.,* **121,** 57436t (1994).

19. Z. L. Yaan, S.P. Xu;
Yaoxure xue bao, **29(6),** 468 (1994); *Chem. Abstr.,* **122,** 105374r (1995).

20. T. Lida, T. Kaminuma, N. Koge et al.;
Jpn. Kokai Tokkyo Koho JP **06,** 361, 531 (1994); *Chem. Abstr.,* **122,** 151388w (1995).

21. M. Babizhyer and M. C. Seguin;
PCT Int. Appl. WO **9,** 419, 325 (1994); *Chem.Abstr.,* **122,** 1311862 (1995).

22. Mahmad M. Sheha, Nadia M. Mafouz, Hoda Y. Hassan;
Eur. Jou. Med. Chem., **35,** 887-894 (2000).

23. Atkinson, Robert Nelson; Gross, Michael, Francis;
PCT Int. Appl. WO **03** 37274 (Cl. A61K) (2003); *Chem.Abstr.,* **138(24),** 368888z (2003).

24. Sanderson Philip E.J., Cutronakellie J., Dyer Donal;
Chem.Abstr., **128(23),** 294675x (1999).
25. Moloney Brain Anthony, Har del David, Saville Stones;
Chem.Abstr., **131(13),** 170272f (1999).
26. Foster James E., Nicholson Jessam et al.;
Bio. Org. Med. Chem., **7(11),** 2415-2425 (1999); *Chem. Abstr.,* **132,** 165991f (2000).
27. Mulik A.R., Deshmukh M. B. ;
J. Indian. Chem. Soc., **78(3),** 150751 (2001); *Chem. Abstr.,* **135(6),** 76815w (2001).
28. Bridge Gory, Renato, Kaller Al; Zhoy Yuaxi;
PCT Int. Appl. WO **02,** 22599 (Cl. CO7D401/12)(2002);
Chem.Abstr., **136(17),** 263159t (2002).
29. Laura Bettineti., Karin Schlotter, Peter Mening;
J. Medicinal Chem., **Vol-45,** P. 4594 (2002).
30. Hobbs, Douglas W., Guo, Tao., Tuenter Rachaec C., Gu, Huizhong;
PCT Int. Appl. WO **02** 76929 (Cl. COC275/40) (2002); *Chem. Abstr.,* **137(18),** 263068h (2002).
31. Mallams Alan K. ;
U.S. US **5,** 925, 757; Chem. Abstr., 131(7), 878214 (1999).
32. S. Jhaumeer-Laulloo and M. Witvrouw;
Indian J. Chem., **39B (11),** 842 (2000).
33. J. Hazarika, J.C.S. Kataky;
Indian J. Chem., **40B(3),** 255 (2001).
34. Dhanak, Dushyant; Knight, Steven D., Jin Jian., Rivero Raiph A
PCT Int. Appl. WO **02,** 781888 (Cl. CO7D401/02) (2002);
Chem. Abstr., **137(20),** 294980d (2002).
35. Tabuchi, Sejichiro., Itani Hiromichi, Sakata Yoshihiko, Oohasi Hiroko, Satoh Yoshinari ;
Bio. Org. and Med. Chem. Lett., **12(8),** 1171-1175 (2002);
Chem. Abstr., **137(18),** 262978t (2002).
36. Chan, Joseph Howing;
PCT Int. Appl. WO **02** 70470 (Cl. CO7C311/51) (2002); *Chem. Abstr.,* **137(6),** 232453a (2002).

37. Pieters Luc, Kosmrji Janez, Lenarsic Roman, Kocever Marijan, Polano Slovenko ;
ARKIVOC, **2(3),** (Eng) (2001); *Chem. Abstr.,* **137(16),** 232366z (2002).

38. Anthony, Neville j., Gomez, Robert P., Bennett Jennifer J., Young Steven D. ;
PCT Int. Appl. WO **02,** 55079 (Cl. A61K31/44) (2002); *Chem. Abstr.,* **137(8),** 109214w (2002).

39. Chen, Guoqing, Booker Shen, Cai Gololin, Croghan Michael, Di Pietro Lucian;
PCT Int. Appl. WO **02,** 55501 (Cl. CO7D213/81) (2002);
Chem. Abstr., **137(8),** 10921s (2002).

40. James B. Thomas ,Robert N. Atkinson, N. Ariane Vinson.;
J. Med. Chem . **46(14)**, 1670 (2003)

41. Fanrong Mu, Ernest Hamel, Debbie J. Lee, Donaid E. ;
***J. Med. Chem.,* 46(9)** , 1670 (2003).

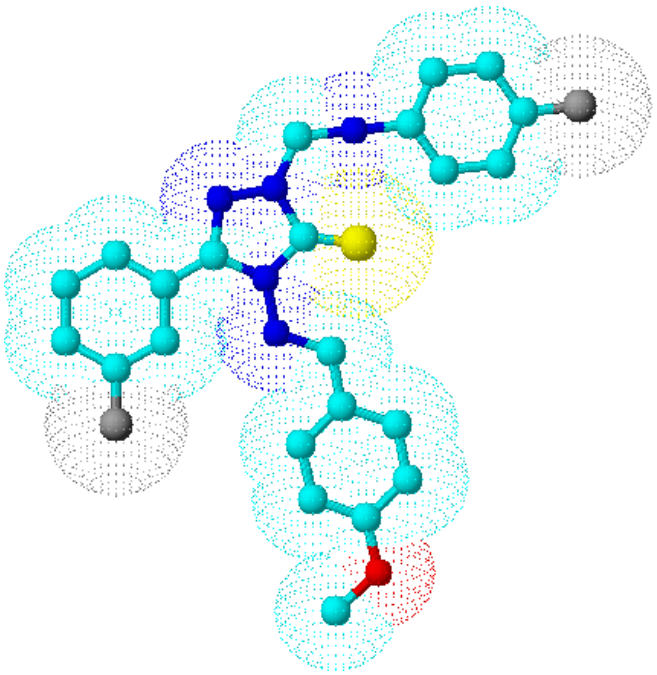
42. Bin Ho, A. Michele, Crider, James P. stables. ;
Euro. J. Med. Chem., **36** , 265-286 (2001).

43. Cudahy, Michele M. , ; Shnute, Mark E. ; Tanis, Steven P. ;
PCT Int. Appl. WO **03** 59911 (Cl. CO7D491/04) (2003) ; *Chem. Abstr.,* **139(8)** , 117477q (2003).

44. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).

45. C. N. R. Rao;
"*Chemical application of Infrared spectroscopy"* Academic press, New York (1963).

46. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.



PART - VII

STUDIES ON MANNICHBASES

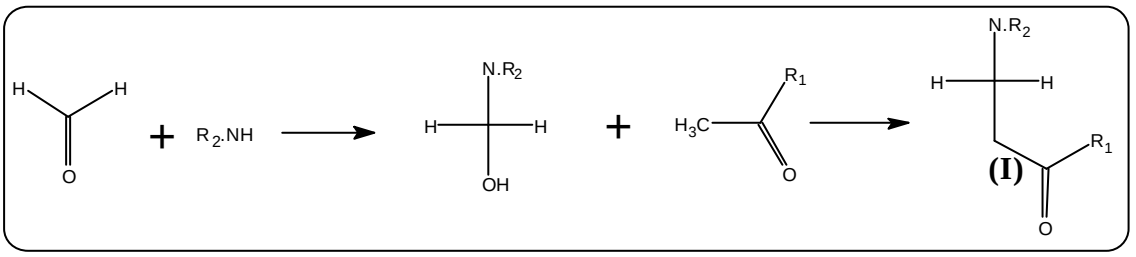
INTRODUCTION

Mannich bases containing bridged N-atom exhibit pronounced biological activities. The study of mannich reaction attracted a great deal of attention to the chemists because it plays a vital role owing to their wide range of industrial applications. Mannich bases are also employed as intermediate in chemical synthesis.[1-3]

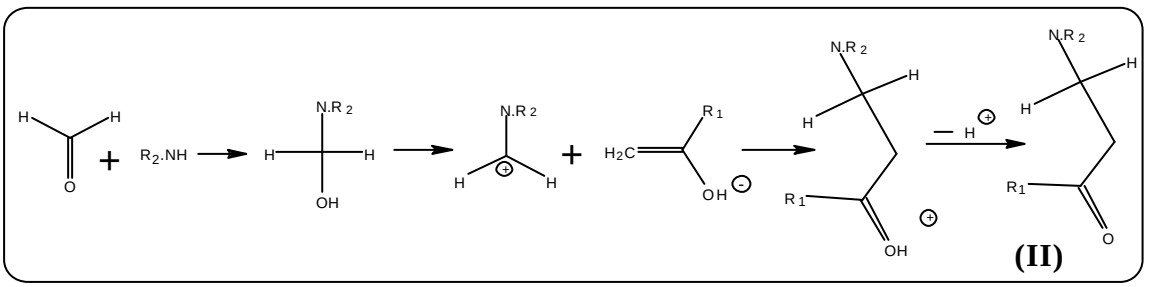
Mannich bases possess diverse pharmacological action like antibacterial, antimalarial and analgesic. Several therapeutic important molecules prepared through mannich reactions have received more attention in recent years.[4-6] Mannich bases have gained important because of their technological applications in polymer chemistry,[7] especially as paints and surface active agents and exhibits complexation characteristic with many transition metal ions.

Over the years there has been much controversy about the mechanism of the mannich reaction especially as to whether the aldehyde is first attacked by active hydrogen compound or by ammonia or amine. Studies of the reaction kinetics have led to the following mechanistic proposals.

The Base-Catalysed Reaction:



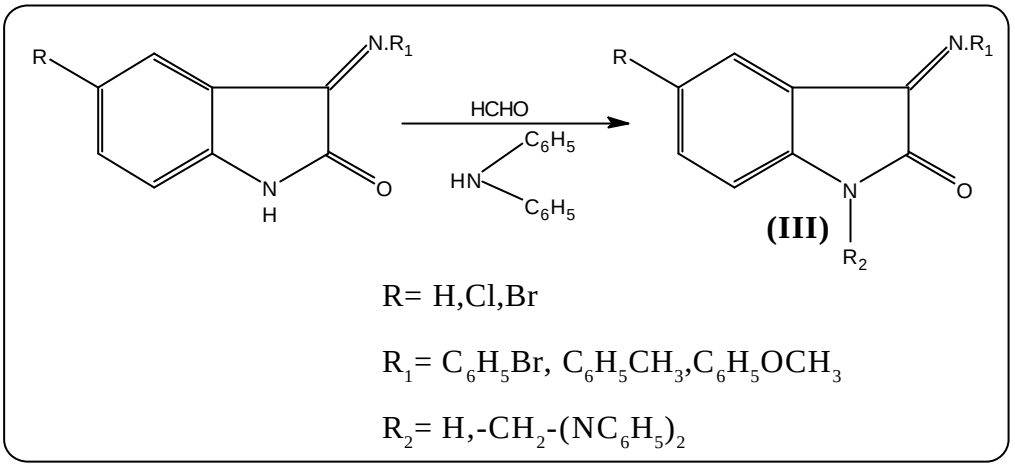
The Acid-Catalysed Reaction:



SYNTHETIC ASPECT

Different methods have cited in literature to synthesize mannich bases by several workers[8-9] using various interesting substractes.

1. Seshaiah Krishnan et al.[10] have synthesized mannich bases (III) from the schiff bases of isatin in presence of formaldehyde and diphenyl amine.

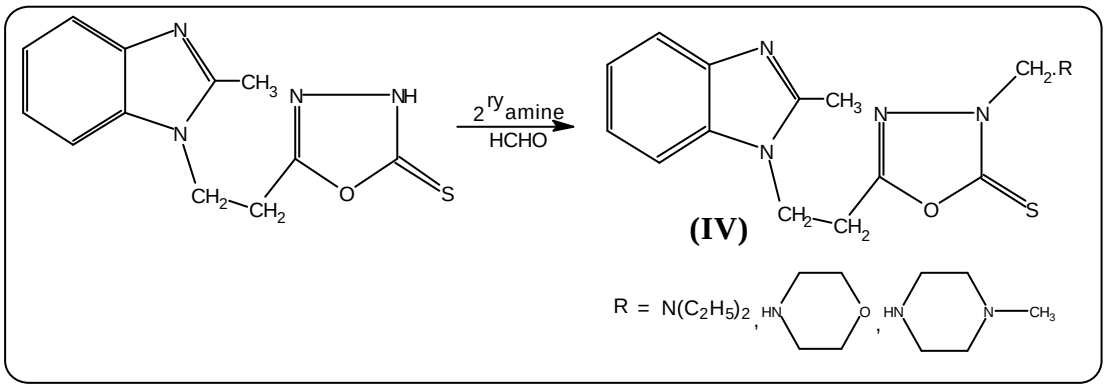


R= H,Cl,Br

R_1= C_6H_5Br, $C_6H_5CH_3$,$C_6H_5OCH_3$

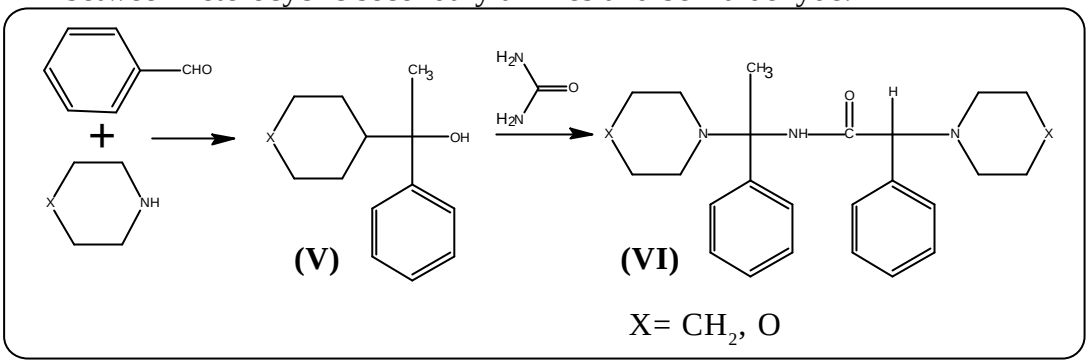
R_2= H,-CH_2-$(NC_6H_5)_2$

2. Afaf H. El-masry, H.H.Fahmy and coworkers[11] have synthesized mannich base derivatives (IV) by the condensation of 5-[2-(2-methylbenzimidazole-1-yl)ethyl][1,3,4]oxadiazole-2(3H)-thione with different secondary amine in the presence of formaldehyde and also reported their antimicrobial activity.



3. Pandeya and Sriram D.[12] have synthesized mannich bases by the condensation of the acidic group of isatin with formaldehyde and secondary amines.

4. Venkatesha Prabhu G. and Vankappayya D.[13] have synthesized aminobenzylated mannich bases (V) and (VI) by the condensation reaction between heterocyclic secondary amines and benzaldehyde.



5. Gadre J.N. and coworkers have synthesized mannich bases of 8-alkyl-7-hydroxy coumarin.
6. Fox, Raymond C. et al.[15] have reported the preparation of some novel metal selective mannich bases.

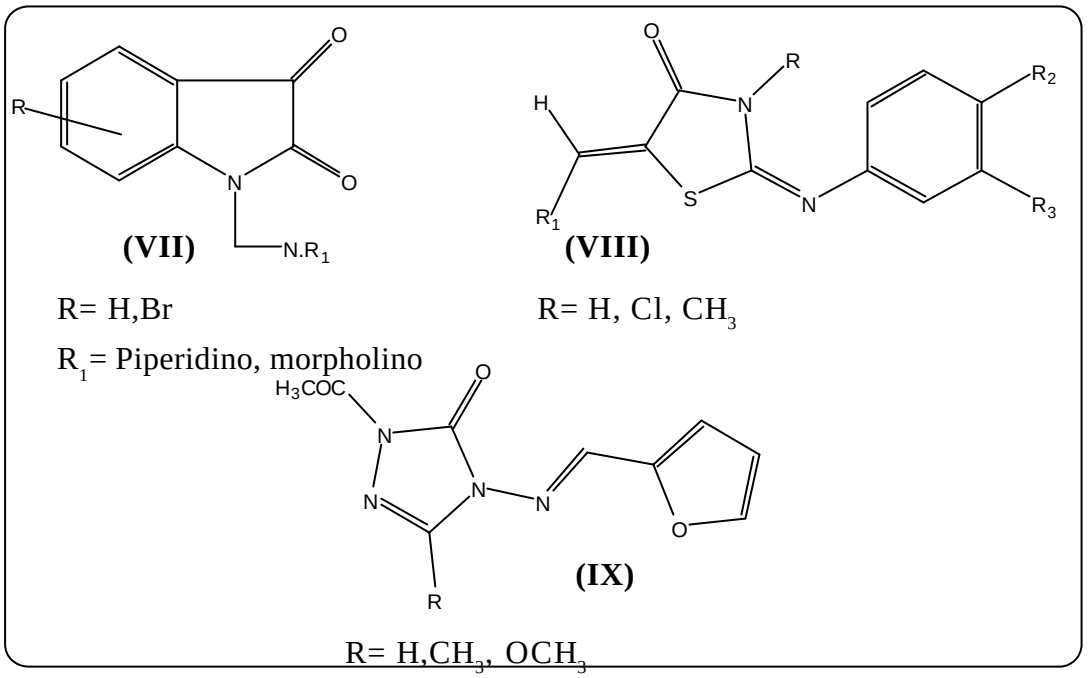
BIOLOGICAL IMPORTANCE

Mannich bases are associated with a wide varieties of biological activities and industrial applications such as,

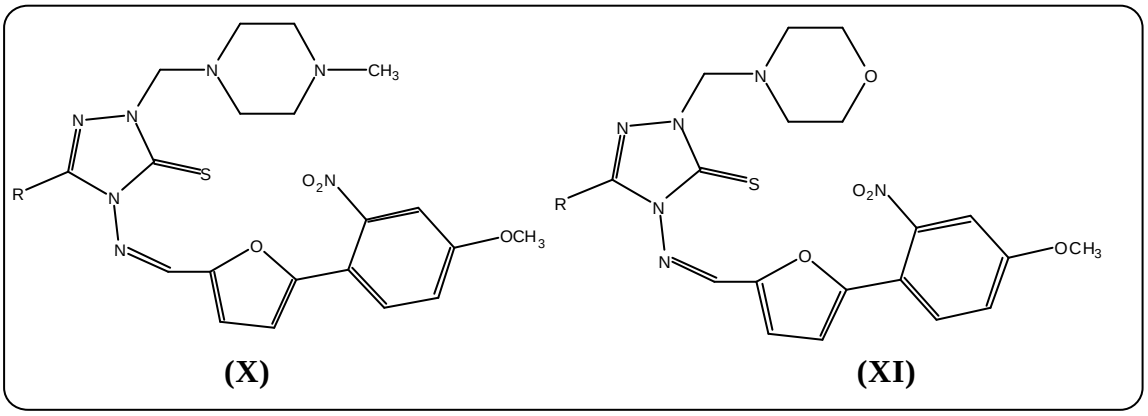
1. Antifungal[16]
2. Antitumor[17]
3. Antibacterial[18]
4. Antipsychotic[19]
5. Cytotoxic[20]
6. Anti-inflammatory[21]
7. Antileishmanial[22]

Recently Surendra Pandeya , Shivkumar Smitha et al.[23] have synthesized some new mannich base derivatives (VI) of isatin and reported their biological activities. N.J.Gaikwad and coworkers[24] have synthesized mannich bases of 4-thiazolidinone (VIII) anticonvulsant activity of all the synthesized compounds have

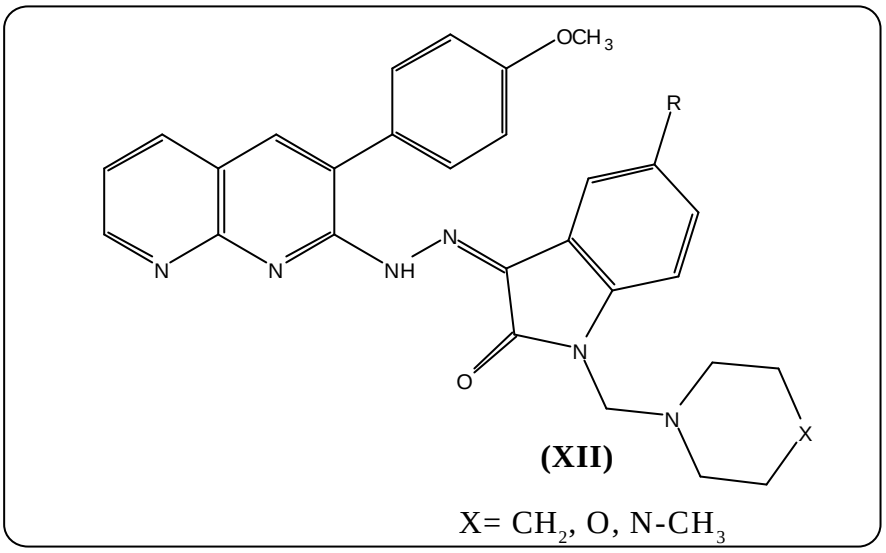
also been evaluated. Haydar Yuksek et al.[25] have also prepared novel mannich bases (IX).



B.Shivarama Holla et al.[26] have prepared mannich bases and tested them for anthelmintic activity (X) and all the newly synthesized compounds were tested for their antibacterial and antifungal activity (XI).



Movrin M, Maysinger D. and coworkers [27] have synthesized mannich bases from nitroxoline and reported them as biologically active agents. Erol D. D.et al.[28] have synthesize some novel mannich base derivatives from 6-acyl-3-(3,5-dimethylpiperidino methyl)-2(3H)-benzooxazolones and reported their biological activities. H.M.Hassan and S.A.M. Shedid[29] have synthesized some new mannich bases and reported antimicrobial activity of some novel mannich bases containing 1,8-napthyridine moiety (XII).



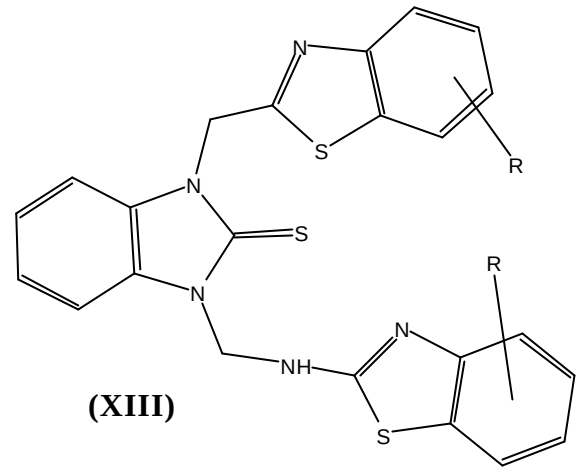
(XII)

X= CH_2, O, N-CH_3

Scott MK, Martin GE and coworkers[31] have reported some pyrrole mannich bases as potential antipsychotic agents. Gul HI, Ojanen T and coworkers[32] have reported antifungal activity of some mono, bis and quaternary mannich bases derived from actophenone. Li Y, Yang Z S et al.[33] have synthesized some mannich base derivatives and reported their antimalarial activity.

Lorand T, Kocsis B and coworkers[34] have synthesized some new mannich ketones and reported their antibacterial activity. Sriram D et al.[35] have reported synthesis, antibacterial, antifungal and anti-HIV evaluation of schiff and mannich bases of isatin and their derivatives with triazole. Seshaiah Krishnan, Sridhan and coworkers[36] have synthesized some new mannich base derivatives and reported that mannich bases exhibit higher antibacterial activity than the corresponding schiff base.

Gul H I, Ojanen T et al.[37] have documented antifungal activity of bis mannich bases derived from acetophenones. Gul H I, Calis U and coworkers[38] have synthesize some mono mannich bases and evaluate their anticonvulsant activity. Shingare M.S. et al.[39] have described the synthesis and the antiviral activity of mannich bases (XIII).



(XIII)

R= H,4-Me, 5-OMe, 5-Cl, 6-Br

H.S.Joshi et al.[40] have been synthesized some novel amino benzylated mannich bases and reported their antimicrobial activities.

In view of the importance of mannich bases as versatile synthetic intermediates and the availability of scanty literature on therapeutic properties, we have undertaken the preparation of mannich bases in following sections.

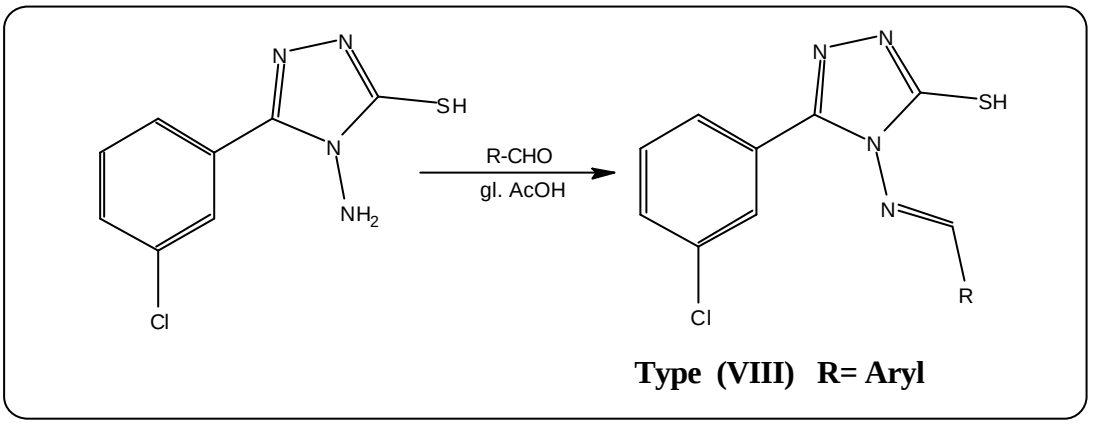
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-4-{[(1*E*)-(4-ARYL)METHYLENE] AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOLS

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-2-{[(BIS-ARYL/ ALKYL)AMINO] METHYL}-4-{[(1-*E*)-(4-ARYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-4-{[(1*E*)-(4-ARYL)METHYLENE]AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOLS

Schiff's bases possess a wide range of therapeutic activities and intermediate for many heterocyclic compounds, hence it appeared of interest to synthesize some new Schiff bases of type (VIII) in association with 1,2,4-triazole nucleus. It has been prepared by the condensation of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol with different aromatic aldehydes in the presence of glacial acetic acid.

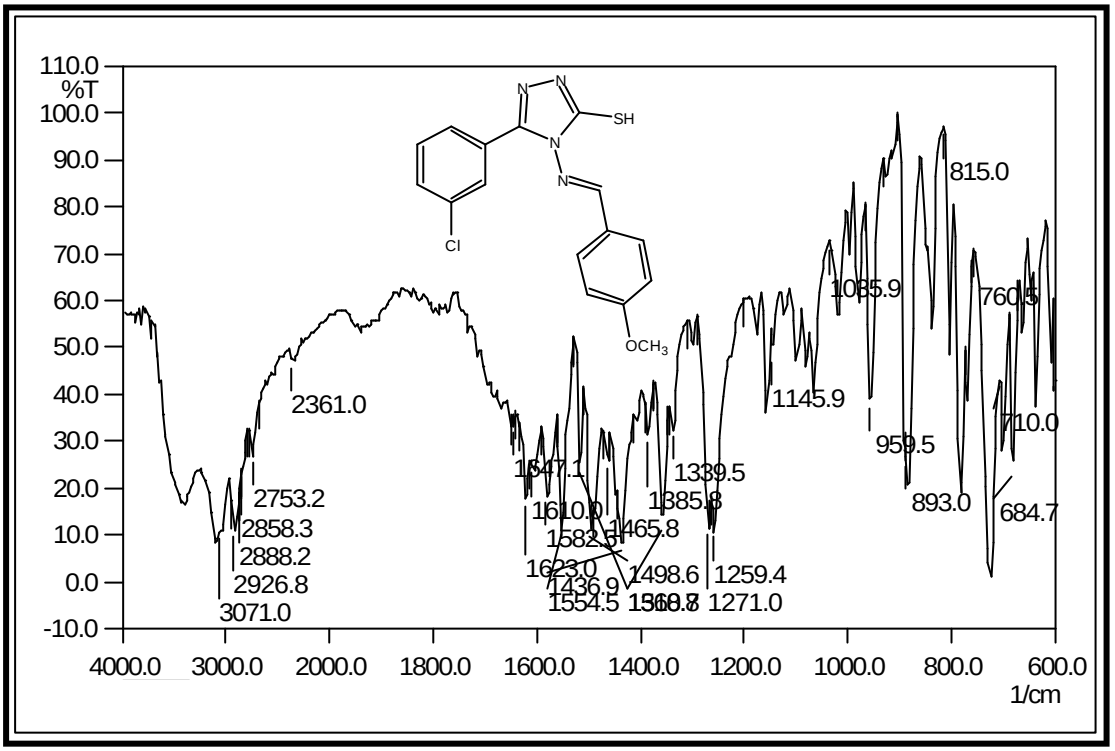


Type (VIII) R= Aryl

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

All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No.8.

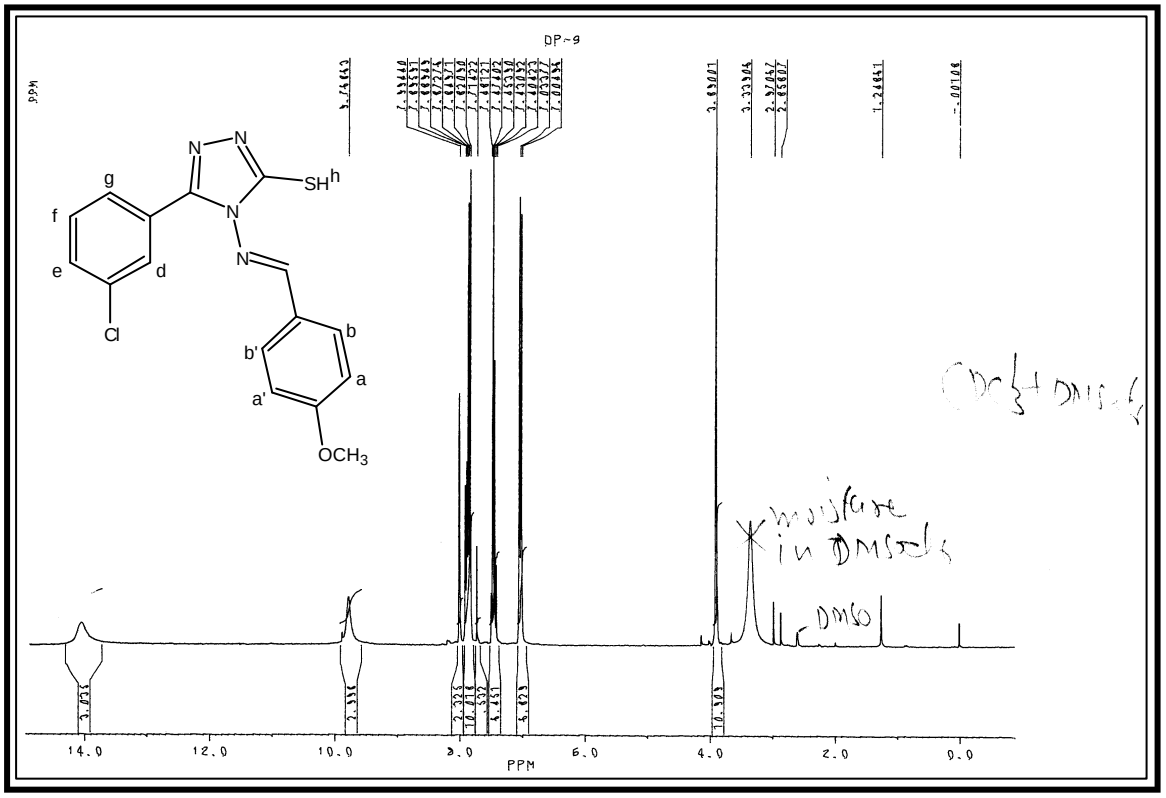
IR SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-4{[(1*E*)-4-(p-METHOXYPHENYL)METHYLENE]AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOL



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.)	2926	2975-2950	41
-CH_3	C-H str. (sym.)	2858	2880-2860	41
	C-H def.(asym.)	1465	1470-1435	41
	C-H def.(sym.)	1385	1385-1370	41
Aromatic	C-H str.	3071	3080-3030	42
	C=C str.	1560	1585-1480	42
	C-H i.p. (def)	1145	1125-1090	42
	C-H o.o.p. (def)	815	835-810	43
Triazole	C=N str.	1620	1640-1500	43
	C-N str.	1145	1220-1020	42
	N-N str.	1035	1050-1010	43
Ether	C-O-C str.(asym.)	1271	1275-1200	43
(Ar-O-R)	C-O-C str.(sym.)	1035	1075-1020	42
Schiff's base	-C=N str.	1610	1660-1580	41
Halide	C-Cl str.	760	800-600	42

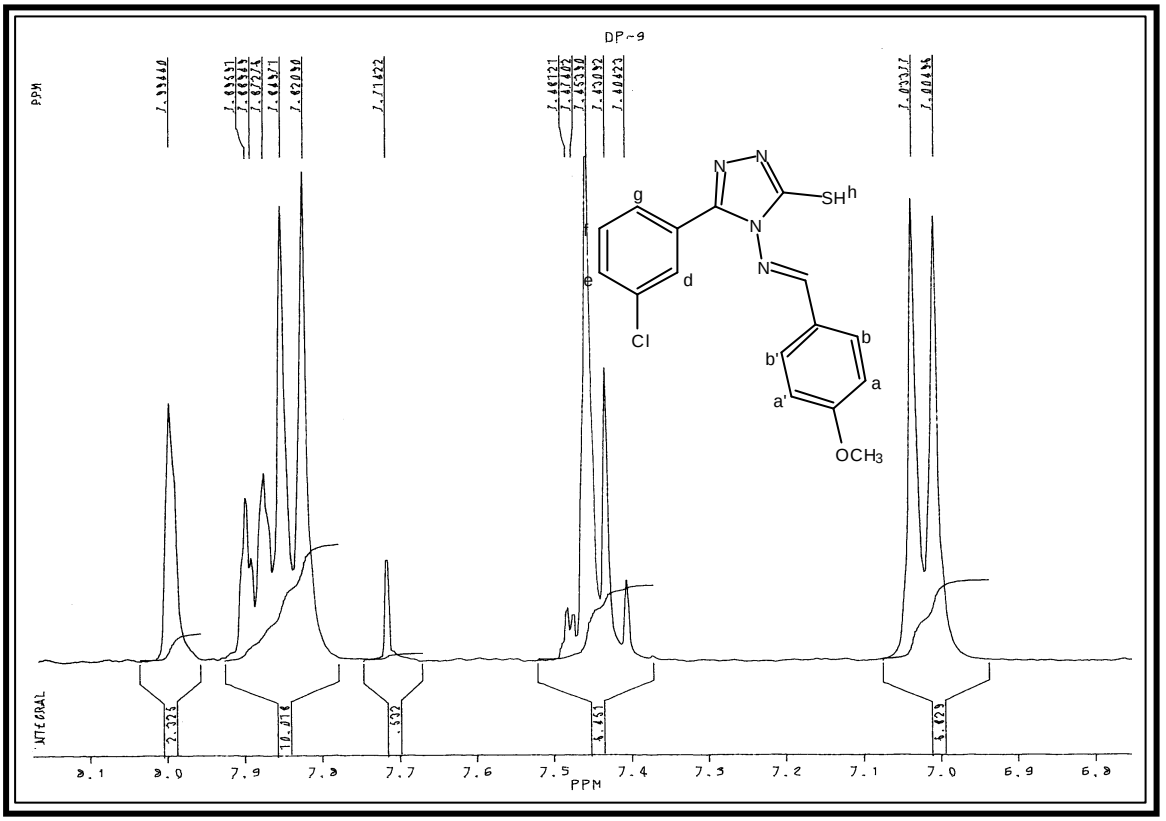
NMR SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-4{[(1*E*)-4-(p-METHOXYPHENYL)METHYLENE]AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOL



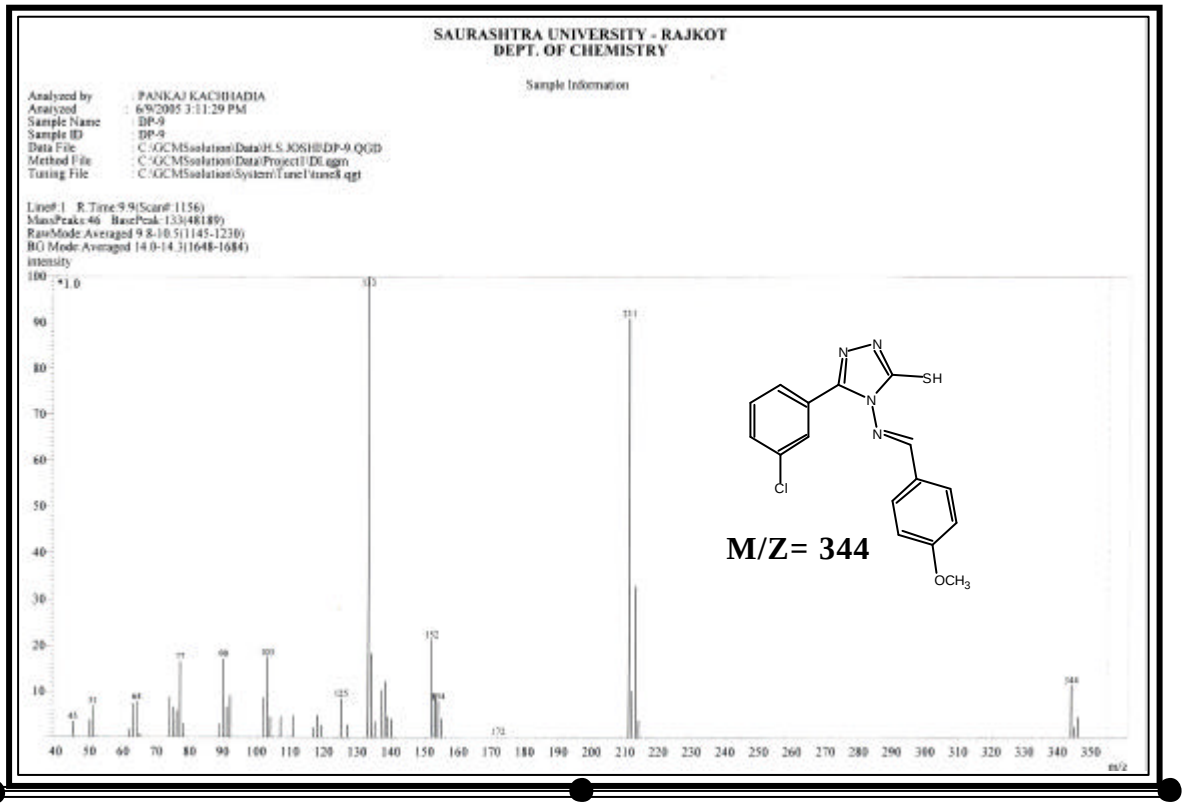
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.89	3H	singlet	Ar-OCH_3	-
2	7.01	2H	doublet	Ar-Haa'	Jab=8.7
3	7.45	2H	doublet	Ar-Hfg	Jfe=6.9
4	7.83	2H	doublet	Ar-Hbb'	Jba=8.7
5	7.88	1H	doublet	Ar-He	Jef=6.9
6	7.99	1H	singlet	Ar-Hd	-
7	9.76	1H	singlet	Ar-Hc	-
8	14.00	1H	broad	Ar-Hh	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-4{[(1*E*)-4-(p-METHOXYPHENYL)METHYLENE]AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOL



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-4-{[(1*E*)-(4-ARYL)METHYLENE]AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOLS

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

See Part-I, Section-I (A)

[B] Preparation of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

See Part-I, Section-I (B)

[C] Preparation of 5-(m-chlorophenyl)-4-{[(1*E*)-(p-methoxyphenyl) methylene]amino}-4*H*-1,2,4-triazole-3-thiol.

To a solution of 4-amino-5-(m-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (2.26g, 0.01 mol) in DMF (10 ml), p-anisaldehyde (1.36g, 0.01 mol) was added with constant stirring. To this mixture 1.0 ml glacial CH_3COOH (1.0 ml) was added as a catalyst. The reaction mixture was refluxed for 8 hrs. The content were cooled and poured onto crushed ice and triturated with sodium bisulphate solution. The product was isolated and crystallized from methanol. Yield 70%, m.p. 213°C, Anal. Calcd. For $C_{16}H_{13}ClN_4OS$: C, 55.73; H, 3.80; N, 16.25 %; Found: C, 55.70; H, 3.76; N, 16.21 %.

Similarly other aromatic aldehydes were condensed. The physical constants are recorded in Table No.8.

[D] Antimicrobial activity of 5-(m-chlorophenyl)-4-{[(1*E*)-(4-aryl) methylene]amino}-4*H*-1,2,4-triazole-3-thiols.

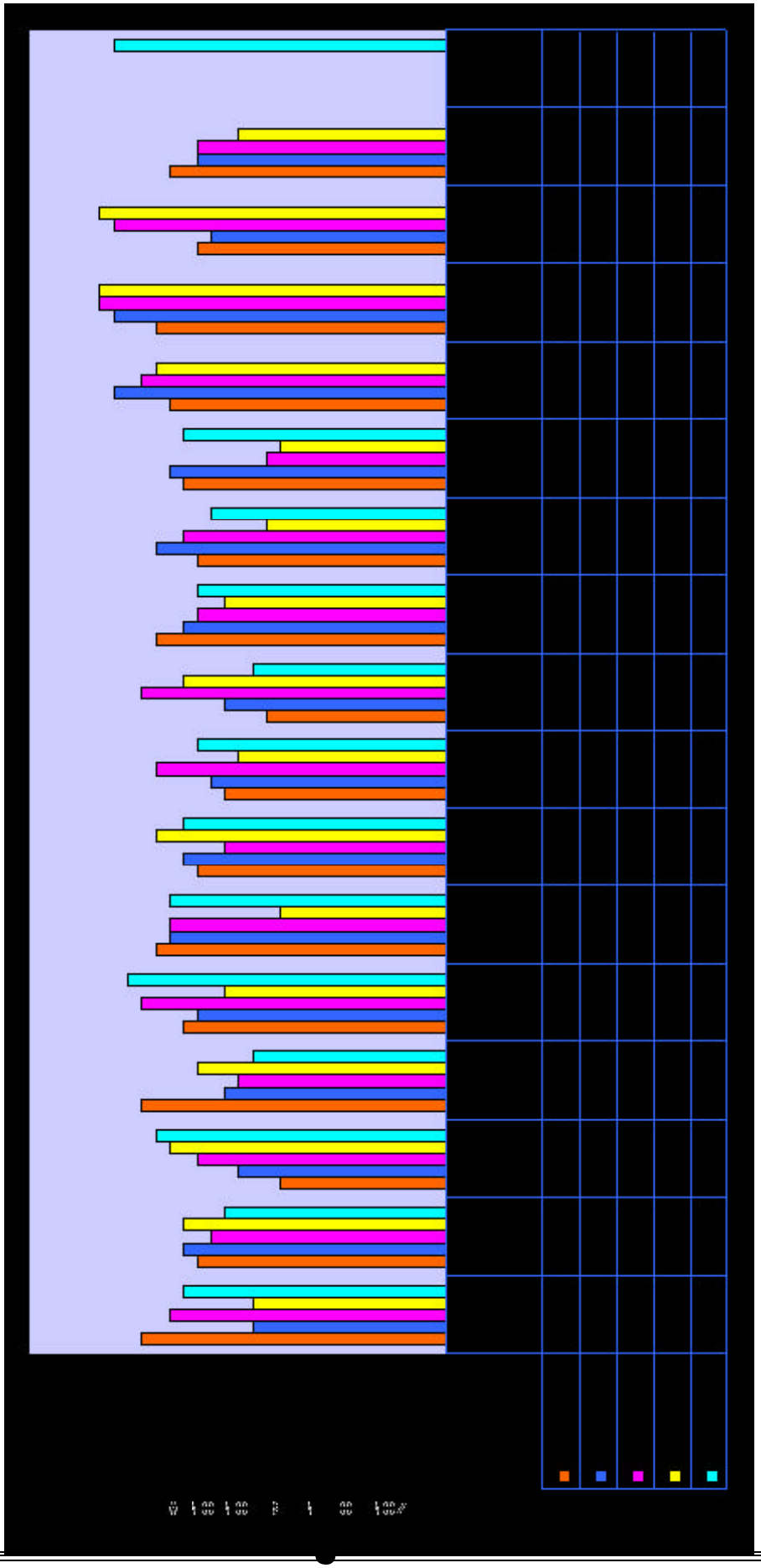
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of compounds are recorded in Graphical Chart No.8.

TABLE-8 : PHYSICAL CONSTANTS OF 5-(m-CHLOROPHENYL)-4-{[(1*E*)-(4ARYL)METHYLENE]AMINO}-4*H*-1,2,4-TRIAZOLE-3-THIOLS

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. °C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
8a	4-OCH_3-C_6H_4-	$C_{16}H_{13}ClN_4OS$	344	213	70	16.25	16.21	0.42	S2
8b	3-NO_2-C_6H_4-	$C_{15}H_{10}ClN_5O_2S$	359	160	68	19.47	19.45	0.47	S2
8c	4-OH-C_6H_4-	$C_{15}H_{11}ClN_4OS$	330	180	67	16.94	16.90	0.48	S1
8d	3-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4S$	349	175	58	16.04	16.00	0.43	S2
8e	4-F-C_6H_4-	$C_{15}H_{10}ClFN_4S$	332	170	60	16.84	16.80	0.51	S1
8f	2-OH-C_6H_4-	$C_{15}H_{11}ClN_4OS$	330	219	62	16.94	16.90	0.52	S2
8g	3,4-$(OCH_3)_2$-C_6H_3-	$C_{17}H_{15}ClN_4O_2S$	374	180	45	14.95	14.91	0.59	S1
8h	2-NO_2-C_6H_4-	$C_{15}H_{10}ClN_5O_2S$	359	165	56	19.47	19.45	0.45	S2
8i	C_6H_5-	$C_{15}H_{11}ClN_4S$	314	231	58	17.80	17.76	0.54	S1
8j	4-CH_3-C_6H_4-	$C_{16}H_{13}ClN_4S$	328	194	61	17.04	17.00	0.43	S1
8k	4-Cl-C_6H_4-	$C_{15}H_{10}Cl_2N_4S$	349	156	58	16.84	16.80	0.46	S2
8l	3-OC_6H_5-C_6H_4-	$C_{21}H_{15}ClN_4OS$	406	170	61	13.77	13.75	0.44	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

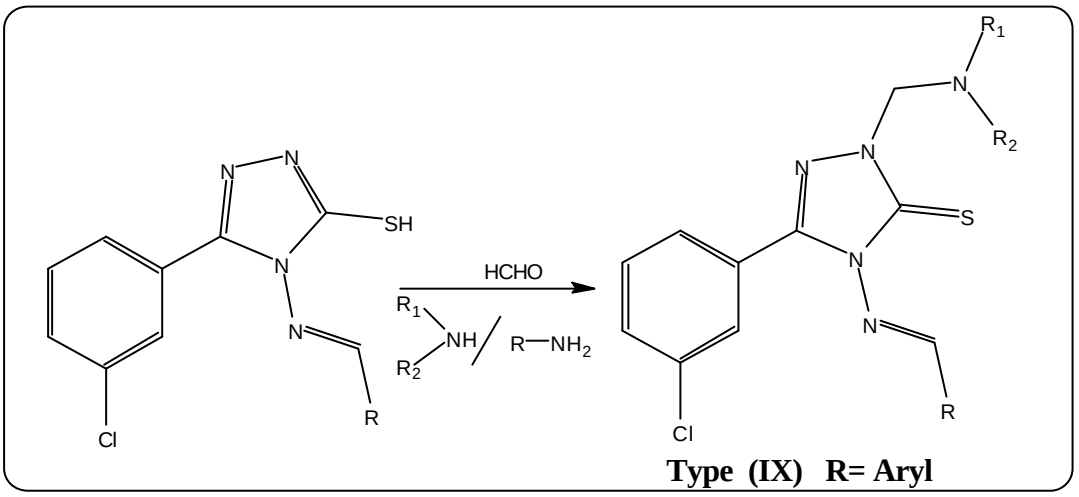
Graphical Chart No. 8 :Antimicrobial Activity of 5-(m-chlorophenyl)-4-{[(1*E*)-(4- aryl) methylene]amino}-4*H*-1,2,4-triazole-3-thiols.



SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-2-{[(4-SUBDTITUTED)AMINO]METHYL}-4-{[(1-*E*)-(4-ARYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONES

In view of getting better therapeutic agent and considering the association of various biological activity with triazole nuclei, the preparation of mannich bases of type (IX) have been undertaken from 5-(m-chlorophenyl)-4-{[(1*E*)-(4-aryl)methylene]amino}-4*H*-1,2,4-triazole-3-thiols with primary / secondary amines and formaldehyde in dioxane.

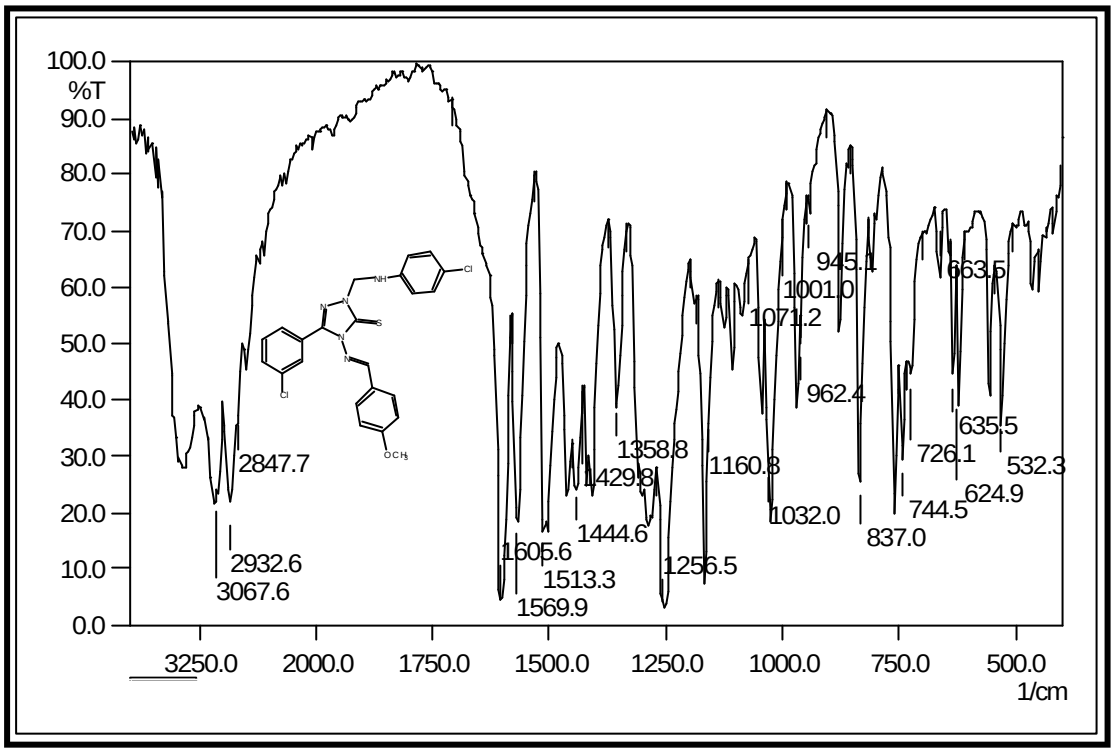


Type (IX) R= Aryl

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

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

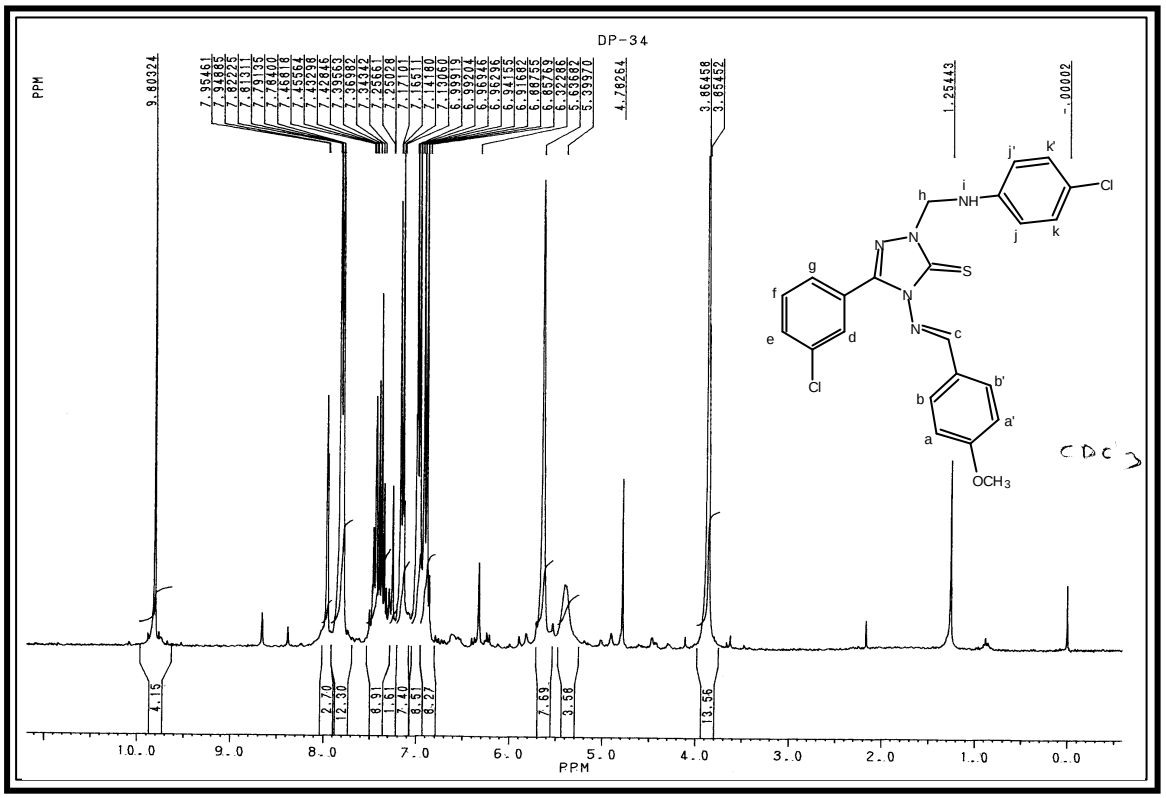
IR SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-2-[4-(p-CHLROANILINOMETHYL)]-4-{[(1-*E*)-[4-(p-METHOXYPHENYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONE



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.)	2932	2975-2950	41
-CH_3	C-H str. (sym.)	2847	2880-2860	41
	C-H def.(asym.)	1429	1470-1435	41
	C-H def.(sym.)	1358	1385-1370	41
Aromatic	C-H str.	3067	3080-3030	42
	C=C str.	1513	1585-1480	42
	C-H i.p. (def)	1071	1125-1090	43
	C-H o.o.p. (def)	837	835-810	43
Triazole	C=N str.	1605	1650-1500	42
	C=S str.	1256	1250-1050	41
		663	750-700	41
	C-N str.	1160	1220-1020	42
	N-N str.	1032	1050-1010	43
Ether	C-O-C str.(asym.)	1256	1275-1200	42
(Ar-O-R)	C-O-C str.(sym.)	1001	1075-1020	42
Halide	C-Cl str.	744	800-600	41

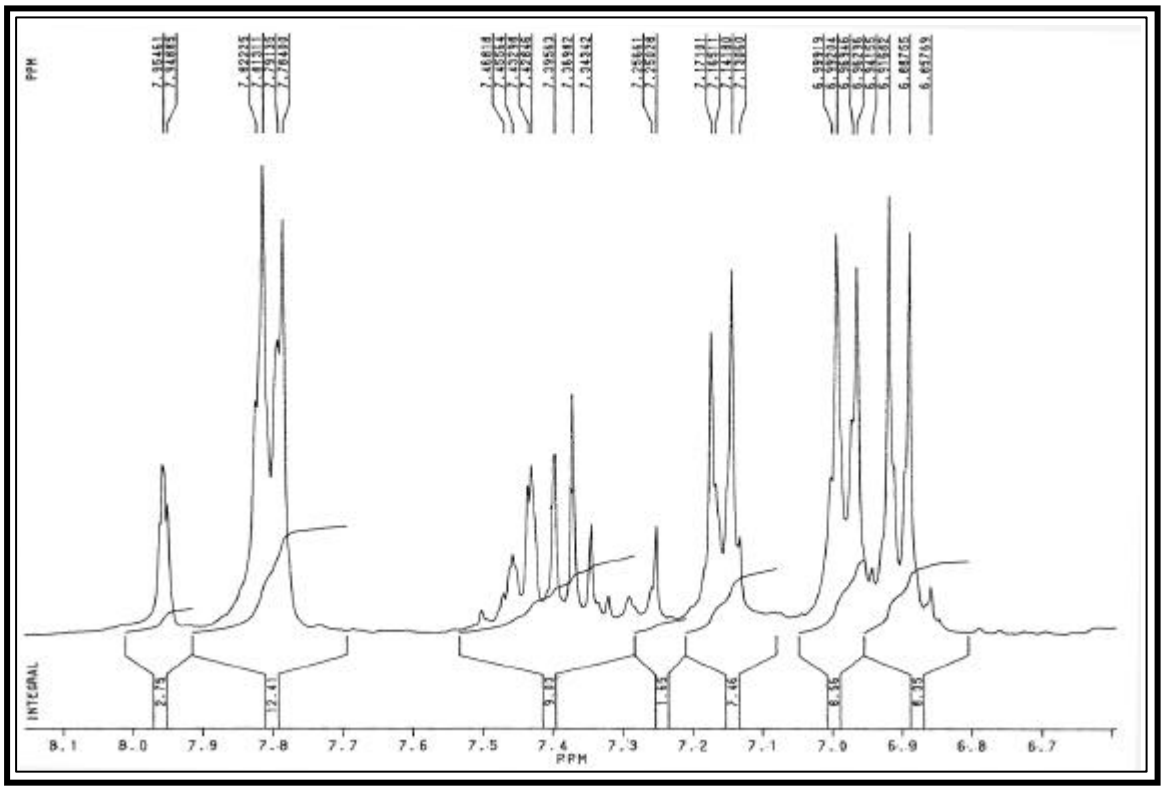
NMR SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-2-[4-(p-CHLOROPHENYL)AMINOMETHYL)]-4-{[(1-*E*)-[4-(p-METHOXYPHENYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONE



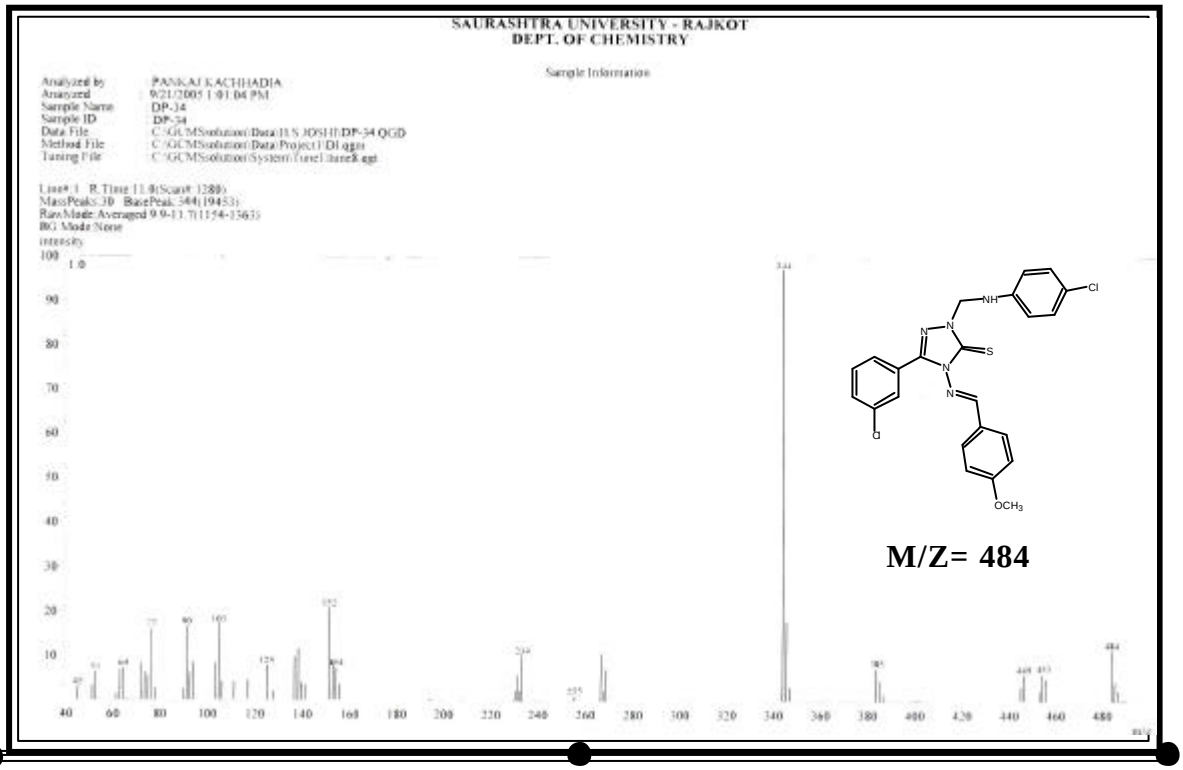
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.86	3H	singlet	Ar-OCH_3	-
2	5.63	2H	singlet	Ar_h	-
3	6.86	2H	doublet	Ar-Ha,a'	-
4	6.99	2H	doublet	Ar-Hj,k'	-
5	7.16	2H	doublet	Ar-Hb,b'	-
6	7.35-7.46	3H	multiplet	Ar-Hf,g,c	-
7.	7.78-7.81	2H	doublet	Ar-Hk,k'	-
8.	7.94	1H	doublet	Ar-Hd	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 5-(m-CHLOROPHENYL)-2-[4-(p-CHLOROPHENYL)AMINOMETHYL)]-4-{[(1-*E*)-[4-(p-METHOXYPHENYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 5-(m-CHLOROPHENYL)-2-{[(4-SUBDTITUTED)AMINO]METHYL}-4-{[(1-*E*)-(4-ARYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONES

[A] Preparation of potassium-m-chlorobenzyl dithiocarbamate.

See Part-I, Section-I (A)

[B] Preparation of 5-(m-chlorophenyl)-4-aryl-4*H*-1,2,4-triazole-3-thiols.

See Part-I, Section-I (B)

[C] Preparation of 5-(m-chlorophenyl)-4-{[(1*E*)-(4-aryl)methylene]amino}-4*H*-1,2,4-triazole-3-thiols

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

[D] Preparation of 5-(m-chlorophenyl)-2-[4-(p-chlorophenyl)aminomethyl-4-{[(1-*E*)-4-(p-methoxyphenyl)methylene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thione.

To a solution of 5-(m-chlorophenyl)-4-{[(1*E*)-4-(p-methoxyphenyl) methylene]amino}-4*H*-1,2,4-triazole-3-thiol (3.44g, 0.01 mol), formaldehyde (0.3g, 0.01 mol) and p-chloroaniline (1.28g, 0.01 mol) in dioxane (50 ml) was added. The mixture was stirred for 24 hrs. and left overnight in a freeze. The solution was poured onto crushed ice. The product was isolated, dried and recrystallised from dioxane Yield 50%, m.p. 220°C. Anal. Calcd. For $C_{23}H_{19}Cl_2N_5OS$: C, 57.03; H, 3.95; N, 14.46 %; Found: C, 57.00; H, 3.91; N, 14.42 %.

Similarly other amines condensed with 4-benzal-amino triazoles. The physical constants are recorded in Table No.9.

[E] Antimicrobial activity of 5-(m-chlorophenyl)-2{[(4-substituted) amino] methyl}-4-{[(1-*E*)-(4-aryl)methylene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

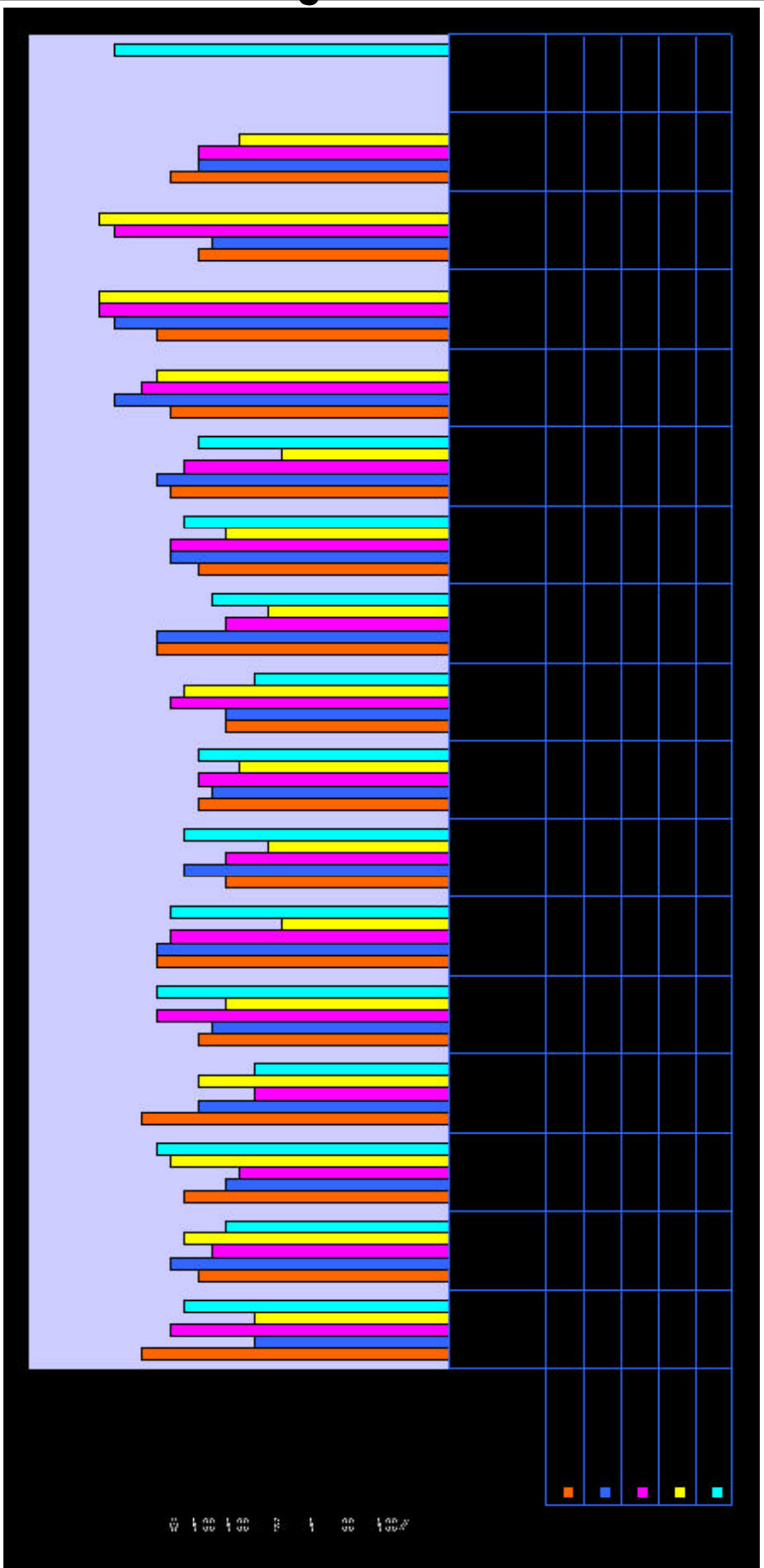
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of compounds are recorded in Graphical Chart No.9.

TABLE-9 : PHYSICAL CONSTANT OF 5-(m-CHLOROPHENYL)-2-(4-SUBSTITUTED)AMINO]METHYL}-4-{[(1-*E*)-(4-ARYL)METHYLENE]AMINO}-2,4-DIHYDRO-3*H*-1,2,4-TRIAZOLE-3-THIONES

Sr. No	R	R_1,R_2	Molecular Formula	Molecular Weight	M.P. ^{0}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10	11
9a	4-CH_3 -C_6H_4-	C_4H_8O-	$C_{21}H_{22}ClN_5OS$	428	220	50	16.36	16.32	0.52	S2
9b	2-CH_3 -C_6H_4-	C_4H_8O	$C_{21}H_{22}ClN_5OS$	428	180	47	16.36	16.32	0.43	S1
9c	3,4-$(OCH_3)_2$-C_6H_3-	C_4H_8O	$C_{22}H_{24}ClN_5O_3S$	474	270	42	14.78	14.74	0.47	S2
9d	4-OCH_3 -C_6H_4-	C_4H_8NH	$C_{21}H_{23}ClN_6OS$	443	220	40	8.97	18.93	0.51	S2
9e	2-OCH_3 -C_6H_4-	4-Cl-C_6H_4	$C_{23}H_{19}Cl_2N_5OS$	484	258	57	14.46	14.42	0.53	S1
9f	4-OCH_3 -C_6H_4-	4-Cl-C_6H_4	$C_{23}H_{19}Cl_2N_5OS$	484	220	50	14.46	14.42	0.46	S1
9g	4-CH_3 -C_6H_4-	4-Cl-C_6H_4	$C_{23}H_{19}Cl_2N_5S$	468	290	61	14.95	14.92	0.42	S1
9h	2-Cl-C_6H_4-	4-Cl-C_6H_4	$C_{22}H_{16}Cl_3N_5S$	489	214	46	14.33	14.33	0.43	S2
9i	2-OCH_3 -C_6H_4-	C_4H_8N-CH_3	$C_{22}H_{25}ClN_6OS$	457	287	54	18.39	18.35	0.41	S1
9j	4-OCH_3 -C_6H_4-	C_4H_8N-CH_3	$C_{22}H_{25}ClN_6OS$	457	245	48	18.39	18.35	0.47	S2
9k	4-CH_3 -C_6H_4-	C_4H_8N-CH_3	$C_{22}H_{25}ClN_6S$	441	234	51	19.06	19.02	0.43	S1
9l	2-Cl-C_6H_4-	C_4H_8N-CH_3	$C_{21}H_{22}Cl_2N_6S$	461	250	40	18.21	18.18	0.51	S2

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

Graphical Chart No. 9 :Antimicrobial Activity of 5-(m-chlorophenyl)-2{[(4-substituted) amino] methyl}-4-{[(1-*E*)-(4-aryl)methylene]amino}-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

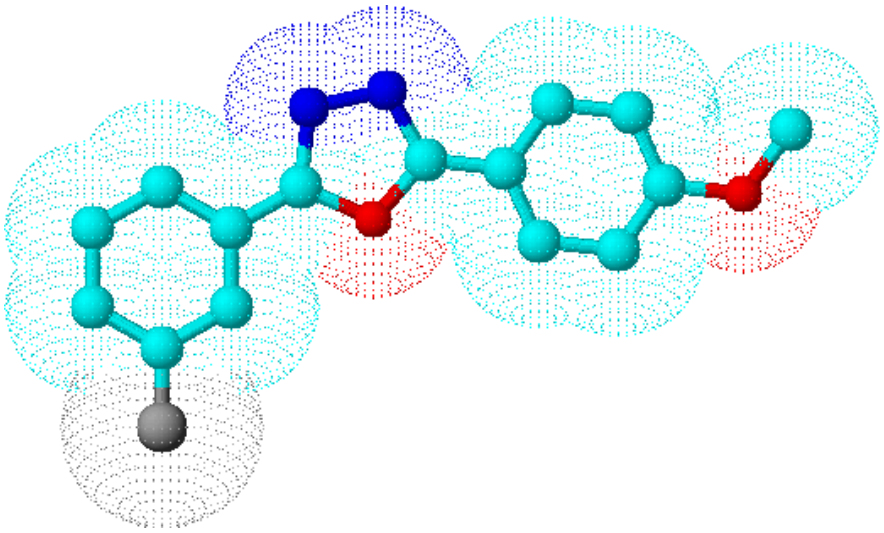


REFERENCES

1. R. Caganiat, G. Kirsch, M. Wierzbicki, K. Lepage et al.; *Eur. J. Med. Chem*., **15**, 439(1980).
2. J. R. Dimmock, S. K. Raghavan, B. M. Logan and G.E. Begam; *J. Med. Chem*., **18**, 249 (1083).
3. Maurilio Tramontini and Luigi Angiolini ; Mannich bases; *Chemistry and uses* (CRC Press, Ann Aror,-Londan) (1994).
4. Henry H. Eytey S. C., Papageovgiou G. and Wilkins K. F.; *Tetrahedron Lett*., **29**, 2997 (1978).
5. J. S. Flower; *J. org. Chem*., **42**, 237 (1977).
6. K. Masuda, T. Toga and N. Hayashi; *J. Labelled Compd*., **11**, 301 (1975).
7. M. Traimontini, L. Angolini and N. Ghedini; *Polymer*, **29**, 271 (1988).
8. Mannich and kathuer; *Arch. Pharm*., 257, 18 (1919).
9. Sabastiyan A. and Venkappyya D., *J. Indian chem. Soc*., **61**, 16(1984).
10. Seshaiah Krishnan, Sridhar, et al.; *Biol. Pharm. Bull*, **24**(10) 1149-1152 (2001).
11. Afaf H.El-masry, H.H.Fahmy, et al.; *Molecules*, **5**, 1429-1438 (2000).
12. Pandeya, S. N..; Sriram, D. *Acta Pharm. Turc*., **40**(1), (1998)33-38(Eng.) *Chem.Abstr*., **129**, 109060c,(1998).
13. Venkatesha Prabhu G. and Vanappayya D.; *J.Indian Chem.Soc*., **72**,511-514,681-684 (1995).
14. Gadre J. N., Thatle C. S.; Vele Pramod; *Indian J. Heterocyclic. Chem*., **8(1)**, 71-72 (1998); Chem.Abstr.,130,66360b (1999).
15. Fox, Raymond C. And Taylor Paul D.; *Synth. Commun*. **28(21)**, 3983-3989 (1998); *Chem.Abstr*., **130**,2488y (1999).

16. Pattanaik J. M., Pattanaik M., Bhatta D.;
Indian J. Heterocycl. Chem.,**8(1)**, 75-76(1998); Chem.Abstr., 130,66444g (1999).
17. Piao, Riyang; Liu, Baili; J. Zhizhong; et al Zhongguo Yaowu Huaxue Zazhi Bianjibu, **8(3)**, 157-162(ch) (1998).
18. J.N.Gadre, C.S. Thatte and Pramod Vele;
Indian J. heterocyclic Chem., **8**, 71-74 (1998).
19. Rae Ducan Robertson and Gibson Samuel George; PCT Int. Appl. Wo 98 21,206,EP Appl.96/203,175(1996);*Chem.Abstr*.,**129**,27899u (1998).
20. Gul, H. Inci; Ereiyas, Frcin; Denizci, Akin;
Adv. Mass. Spectrom, (1998), **14**,DO37790/1-Do37790/14(Eng)Elsevier Science, *Chem. Abstr*, **130**,15,196560c (1999).
21. Udapi, R. H.; Bhat, A.R.; Kumar Krishna.;
Indian J.Heterocycle. Chem. 1998,**8(2)**, 143-146(Eng), *Chem.Abstr*.,130, 19,252282c (1999).
22. V. J. Ram and N. Haque;
Indian J. Chem., **34**, 514 (1995).
23. Surendra Pandeya, Shivkumar et al.;
Acta Pharm. **55** 27-46 (2005).
24. N.J. Gaikwad, M. Yunus, H.A. Husain, D. B. Meshram;
Indian J. Heterocycl. Chem., **12(2)**, 165-166,(2002).
25. Haydar Yuksek, Zafer Ocak, Mustada Ozdemir et al.;
Indian j.heterocycl. Chem.,**13(1)**, 49-52, (2003).
26. B. Shivarama Holla, B. Veerendra, M. K. Shivananda, Boja Poojary, K. P. Latha, V.P. Vaidya; *Indian J.Heterocycl.Chem*.,**13(1)**,61-64, (2003).
27. Movrin M, Maysinger et al.;
Pharmazie, Aug; **35(8)**; 458-60 (1980).
28. Erol D D, Rosen A et al.;
Arzneimittelforschung., Aug; **39(8)** 851-3 (1989).
29. H. M. Hassan, S.A.M. Shedid.;
J. Serb.Chem. Soc. **63(2)** 125-130 (1996).
30. K.Mogilaiah and G. Kankaiah ;
Indian J. Heterocycl.Chem., **11(4)**, 283-286 (2002).

31. Scott M.K., Martin G.E., et al.;
*J.Med.Chem.*Feb 7;**35(3)**; 552-8 (1992).
32. Gul H.I., Ojanen et al.;
Arzneimittelforschung, ; **51(1)** ;72-5 (2001).
33. Li Y, Yang Z S, et al.;
Bioorg Med Chem.Oct **11(20)**; 4363-8 (2003).
34. Lorand T, Kocsis B, et al.;
Eur J Med Chem., Oct; **37(10)**; 803-12 (2002).
35. Pandeya S. N. Sriram D and et al.;
Arzneimittelforschung, Jan, **50(1)**, 55-9 (2000).
36. Seshaiah Krishnan, Shridhan et al.;
Eur. J. Med. Chem., Jul-Aug; **36(7-8)**; 615-25 (2001).
37. Gul H.I.,Ojanen et al.;
Biol Pharm Bull, Oct; **25(10)**; 1307-10 (2002).
38. Gul H.I., Calis U.,et al.;
Bioorg Med.Chem.Oct 1; **11(20)**;4363-8 (2003).
39. Shingare M.S., Mane D.V.; Shinde D.B., Thore S.N.;
Asian J.Chem., **8(2)**,225-8 (1996).
40. H.S.Joshi;
J.Ind.Chem.Soc., **80**, 711-713 (2003).
41. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
42. C. N. R. Rao;
"Chemical application of Infrared spectroscopy" Academic press, New York (1963).
43. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.

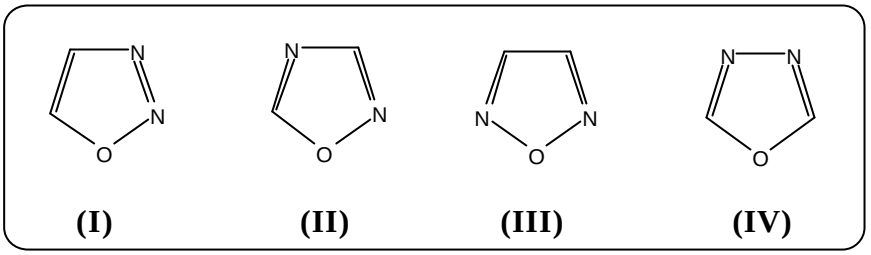


PART - VIII

STUDIES ON OXADIAZOLES

INTRODUCTION

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



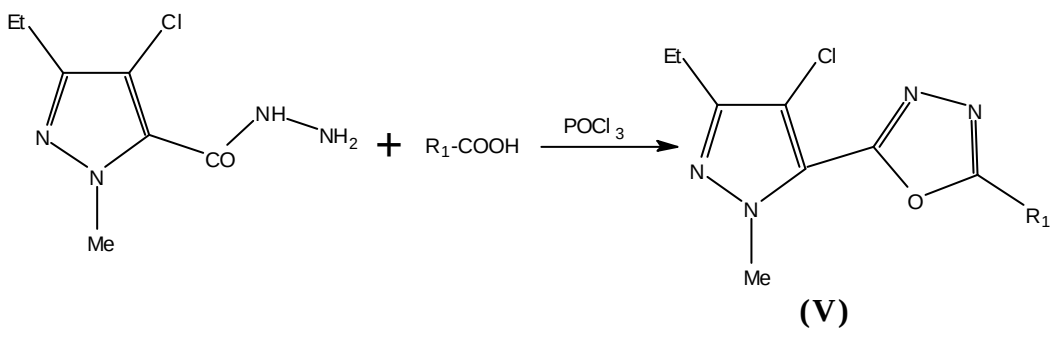
(I) **(II)** **(III)** **(IV)**

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

SYNTHETIC ASPECT

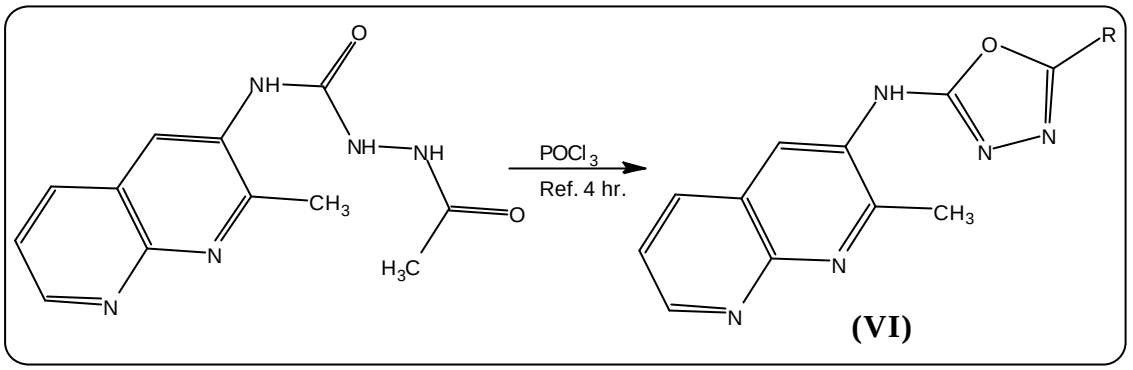
Most 1,3,4-oxadiazoles are best obtained by synthesis from acyclic precursors. Such reactions are 'one bond' or 'two bond' cyclization. Different methods for the synthesis have been cited in literature.[3-10]

1. Hansong Chen et al.[11] have synthesized oxadiazoles by the reaction of hydrazide and aromatic acid in presence of $POCl_3$.



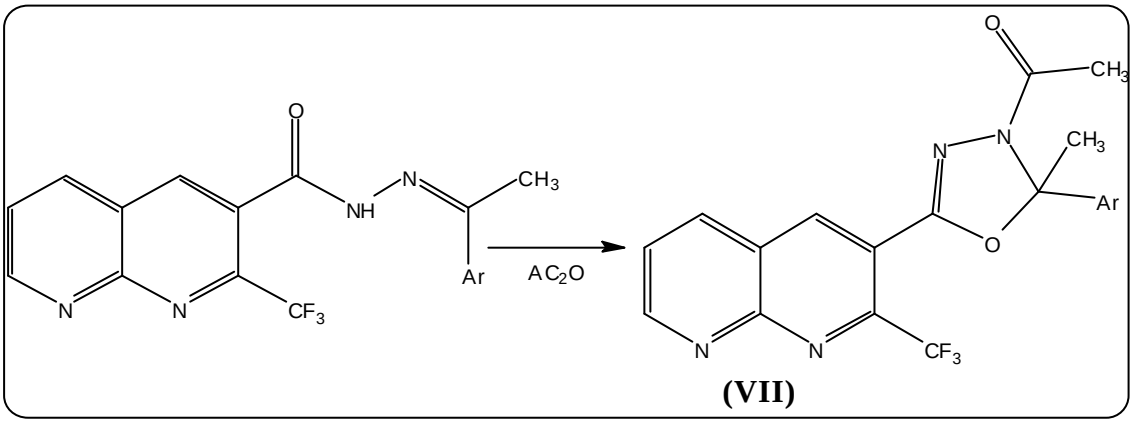
(V)

2. D.Ramesh and B.Sreenivasan[12] have synthesized 1,3,4-oxadiazoles from semicarbazide in presence of $POCl_3$.



(VI)

3. K.Mogilaiah and B.Sakram[13] have prepared 1,3,4-oxadiazole from acetophenone-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.



(VII)

BIOLOGICAL EVALUATION

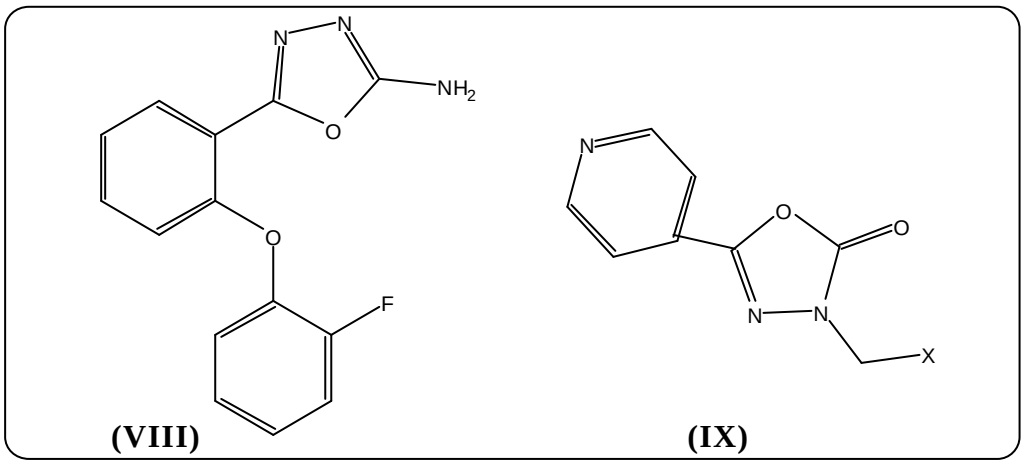
2,5-Disubstituted-1,3,4-oxadiazole derivatives have been tested for various pharmacological activities, which have been summerised as under.

1. Antibacterial[14]
2. Antiinflammatory[15]
3. Analgesic[16]
4. Antiviral and anticancer[17]
5. Antihypertensive[18]
6. Anticonvulsant[19]
7. Antiproliferative[20]

8. Antifungal[21]
9. Cardiovascular[22]
10. Herbicidal[23]
11. Hypoglycemic[24]
12. Hypnotic and Sedative[25]
13. MAO inhibitor[26]
14. Insecticidal[27]

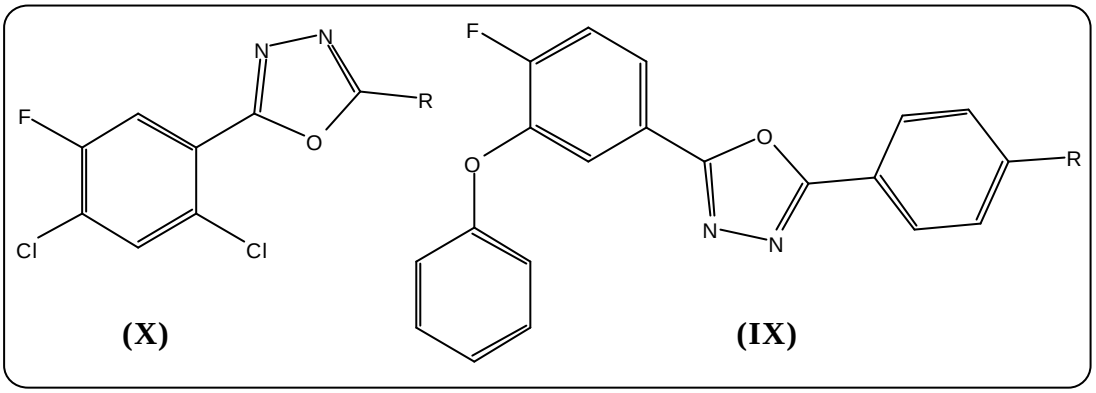
Some 1,3,4-oxadiazoles possessing insecticidal activity were synthesized by Xiumian Zheng et al.[28] Takahiko Inoue et al.[29] have reported oxadiazole useful as prolyl aminopeptidase inhibitor. H. Liszkiewicz. et al.[30] have screened oxadiazoles for their antimicrobial activity. A.El-Azzouny et al.[31] have synthesized 1,3,4-oxadiazole derivatives and evaluated for their analgesic, antiinflammatory, ulcerogenic effects and inhibitory activity on plasma prostaglandin E_2 (PGE_2) Level.

Virginija Jakubkiene et al.[32] have screened 1,3,4-oxadiazoles for their antiinflammatory activity. Song Cao et al.[33] have investigated some oxadiazoles possessing insecticidal activity. S. Guniz Kucukguzel et al.[34] have discovered oxadiazole derivatives and reported their antimycobacterial activity. Ali Almasired et al.[35] have prepared 1,3,4-oxadiazoles of type (VIII) as anticonvulsant agent. Meria Grazia Mamolo et al.[36] have synthesized 3-substituted-5-(pyridine-4-yl)-3H-1,3,4-oxadiazole-2-one of type (IX) and studied their antimycobacterial activity.



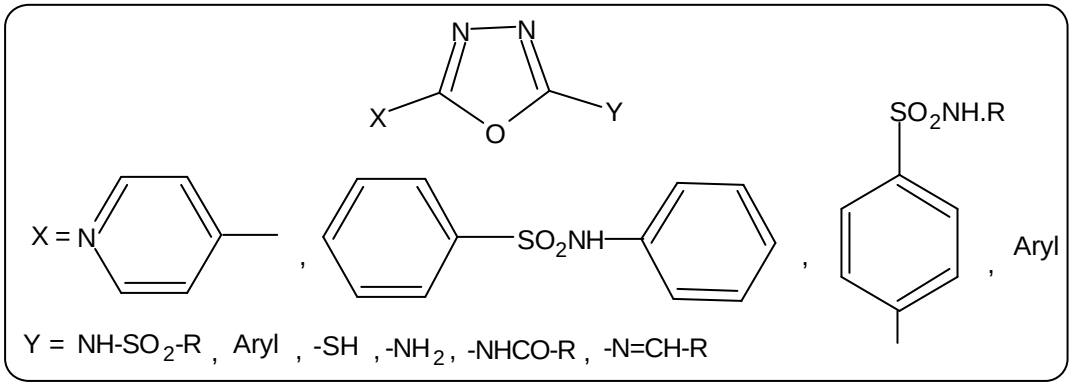
(VIII) **(IX)**

Sahin G. et al.[37] have reported antimicrobial activity of oxadiazole derivatives. Maslat A.O.et al.[38] have documented antibacterial, antifungal and genotixic activity of bis-1,3,4-oxadiazole derivatives. Mida Malvina Buruliene et al.[39] have investigated some oxadiazoles as anti-inflammatory agents. K.Subrahmanya Bhat et al.[40] have prepared new fluorine containing 1,3,4-oxadiazoles (X) and reported them as potential antibacterial and anticancer agents. T.P.Mohan et al.[41] have synthesized 2,5-disubstituted-1,3,4-oxadiazole derivatives (XI) and screened for their insecticidal activity.

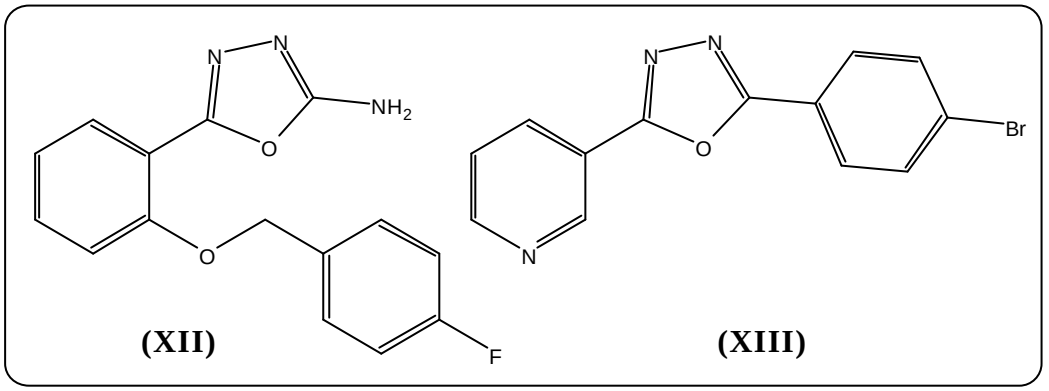


(X) **(IX)**

Joshi et.al. have synthesized 1,3,4-oxadiazoles having substitution of aryl sulphonamido[42] and aryl[43] at 2-position (Y) and 4'-pyridyl, benzenesulphonamido phenyl, di-iodoquinolinoxy and aryl sulphonamide phenyl at 5-position (X) as antimicrobial agents. H.H.Parekh and co-workers have prepared 1,3,4-oxadiazoles having substituted triazine[44] phenyl sulphonyl[45] 2-isopropyl-5'-methylphenoxymethyl[46] moieties at 5-position (X) and aryl, arylamino, arylsulphonamido, substituted banzalamino moieties at 2-position (Y) and screened for their antimicrobial activity. General structure for above references are as under.



Recently, Ronald Kim et al.[47] have discovered oxadiazole derivatives useful as protease inhibitors. Mohd Amir and Kumar Shikha[48] have documented antiinflammatory, analgesic and ulserogenic activity of some newly synthesized oxadiazoles. Ali A.et al.[49] have investigated some oxadiazole derivatives possessing antimicrobial and anti-HIV -1-activity. Sherif A. et al.[50] have reported oxadiazoles as potential antitumor and anti-HIV agents. Afshin Zarghi et al.[51] have synthesized R-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles (XII) possessing anticonvulsant activity. Mahamud Tareq et al.[52] have synthesized 2,5-disubstituted-1,3,4-oxadiazoles (XIII) useful as tyrosinase inhibitors.



(XII) **(XIII)**

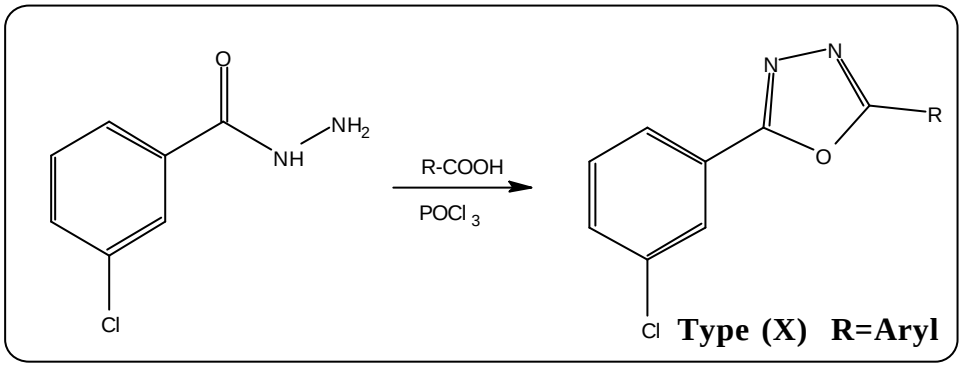
In view of the potential biological activities of 1,3,4-oxadiazole ring system, it was of interest to us to prepare some new derivatives of this family of heterocyclic ring which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(m-CHLOROPHENYL)-5-ARYL-1,3,4-OXADIAZOLES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(m-CHLOROPHENYL)-5-ARYL-1,3,4-OXADIAZOLES

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

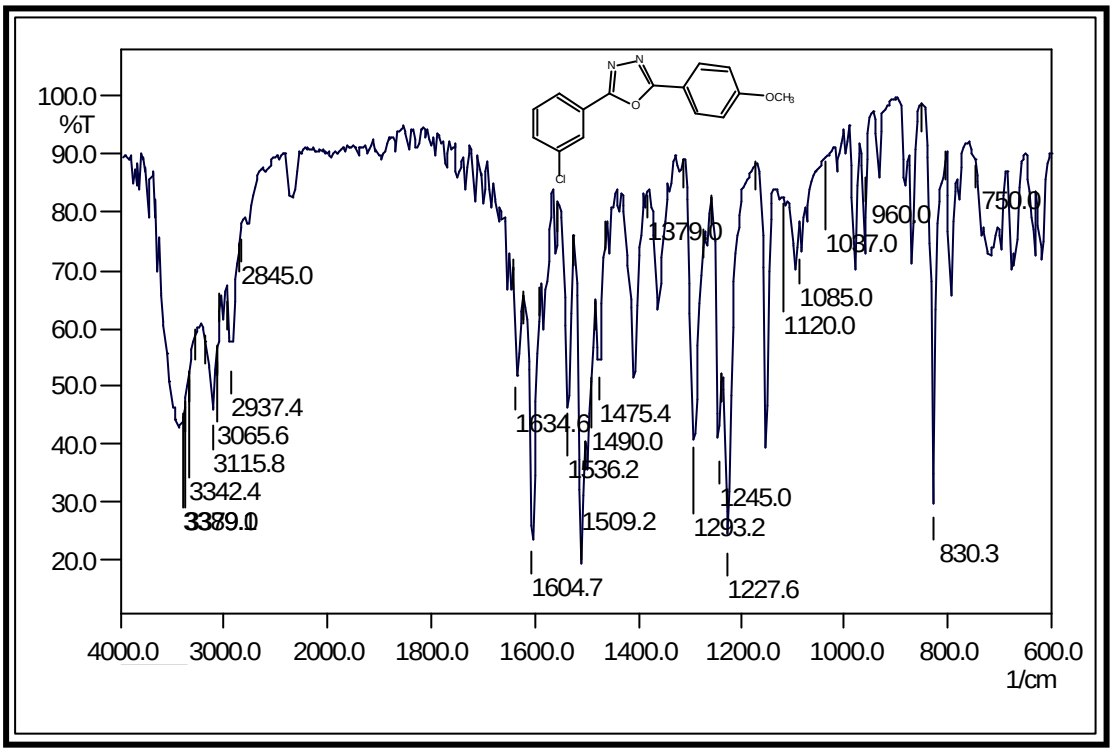


Type (X) R=Aryl

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

All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No.10.

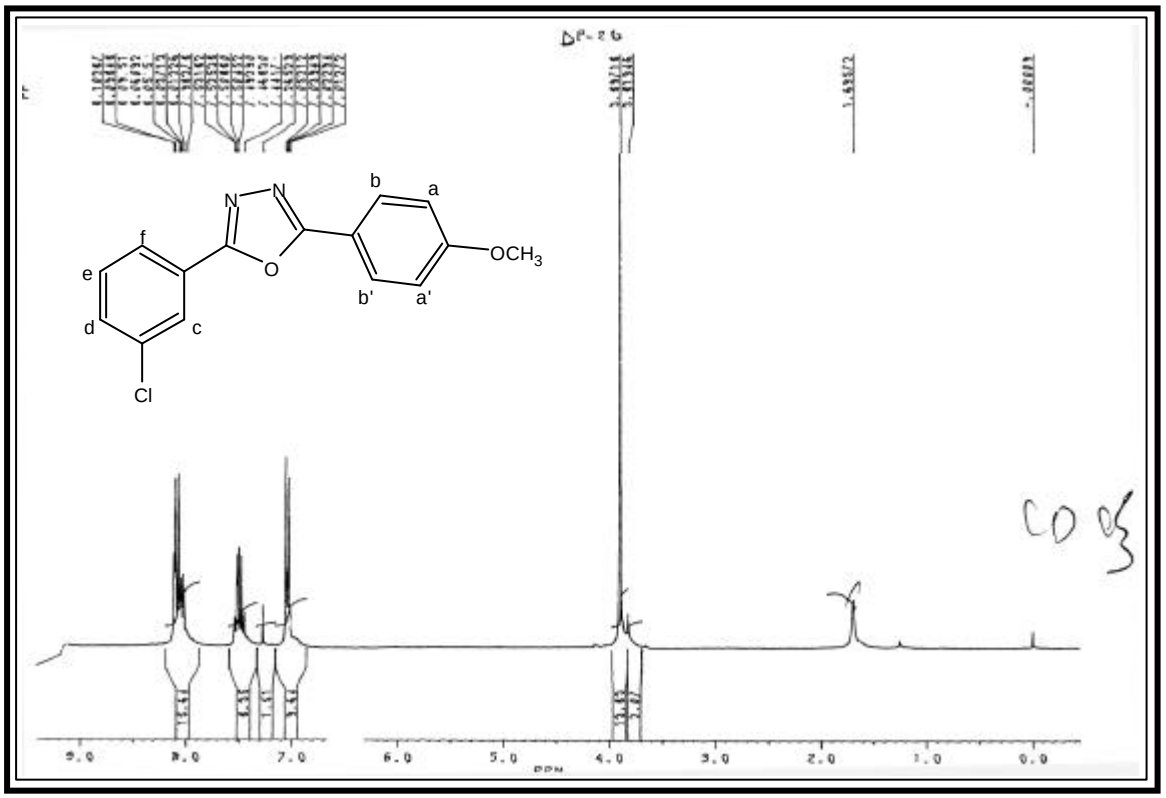
IR SPECTRAL STUDIES OF 2-(m-CHLOROPHENYL)-5-METHOXYPHENYL-1,3,4-OXADIAZOLE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2937	2975-2950	53
-CH_3	C-H str. (sym.)	2845	2880-2860	53
	C-H def.(asym.)	1475	1470-1435	53
	C-H def.(sym.)	1379	1385-1370	53
Aromatic	C-H str.	3065	3080-3030	54
	C=C str.	1509	1585-1480	54
	C-H i.p. (def)	1120	1125-1000	54
	C-H o.o.p. (def)	830	835-810	53
Triazole	C=N str.	1634	1650-1580	54
	C-N str.	1120	1220-1020	54
	N-N str.	1035	1050-1010	54
Ether	C-O-C str.(asym.)	1245	1275-1200	55
(Ar-O-R)	C-O-C str.(sym.)	1037	1075-1020	55
Halide	C-Cl str.	750	800-600	55

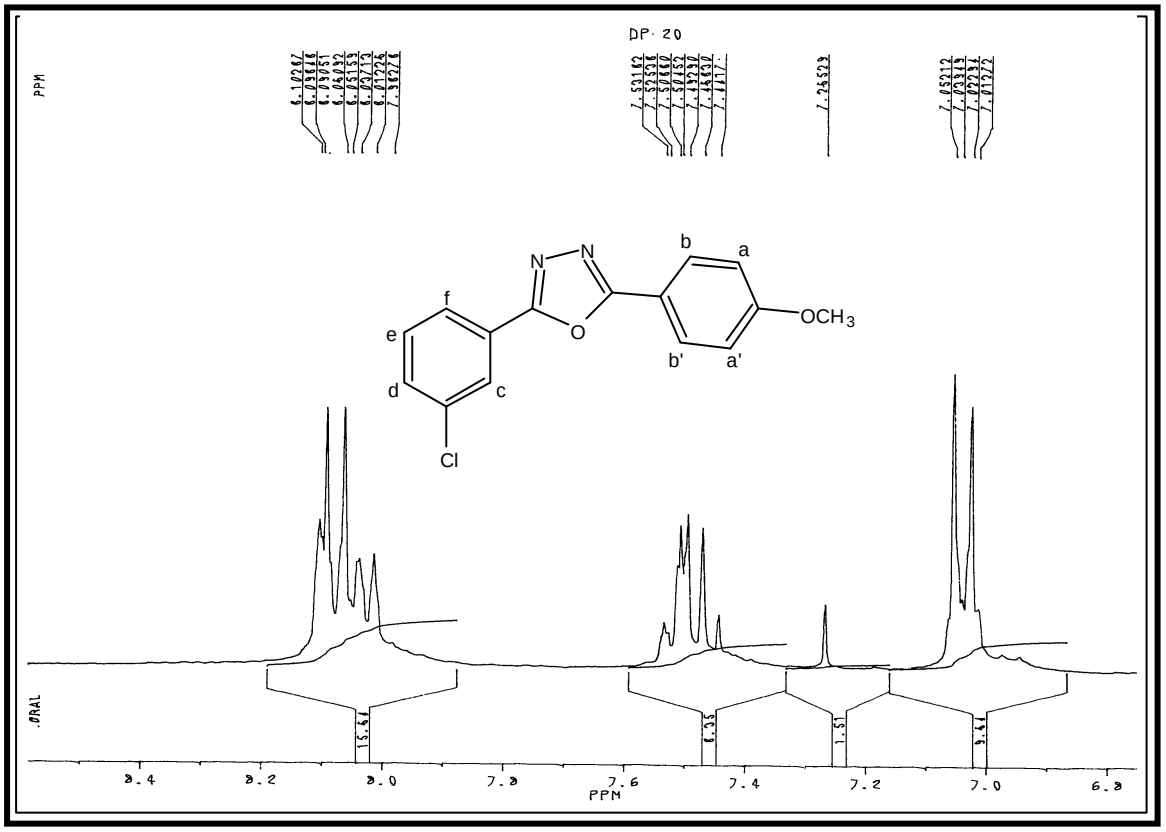
NMR SPECTRAL STUDIES OF 2-(m-CHLOROPHENYL)-5-METHOXYPHENYL-1,3,4-OXADIAZOLE



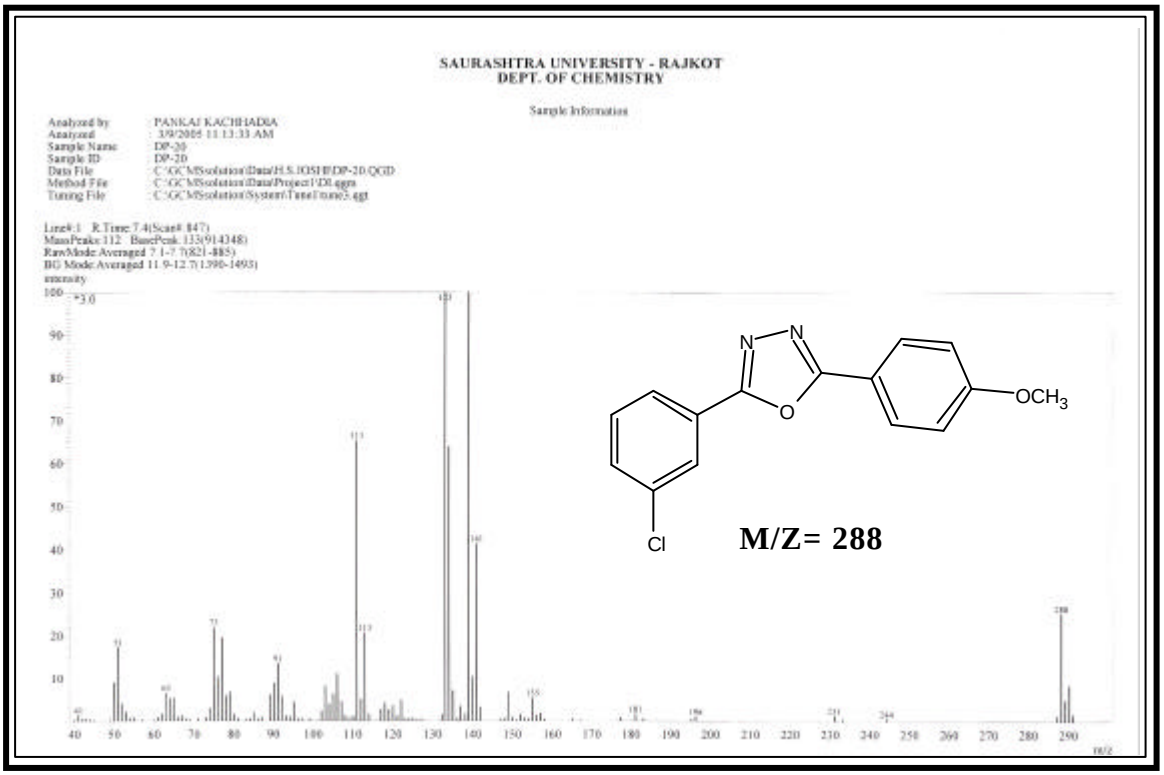
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.92	3H	singlet	Ar-OCH_3	-
2	3.8	3H	singlet	Ar-OCH_3	-
3	6.93-6.97	2H	doublet	Ar-Hj,j'	Jji=9.6
4	7.31-7.37	3H	multiplet	Ar-H(a,c,e)	-
5	7.34-7.46	1H	doublet	-CHk	Jkl=15.9
6	7.46-7.57	2H	triplet	Ar-H(b,d)	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 2-(m-CHLOROPHENYL)-5-METHOXYPHENYL-1,3,4-OXADIAZOLE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(m-CHLOROPHENYL)-5-ARYL-1,3,4-OXADIAZOLES

[A] Synthesis of m-chloro benzohydrazide.

A mixture of methyl 3-chlorobenzoate (1.70g, 0.01mol) and hydrazine hydrate (2.0 ml, 0.02 mol) in ethanol was refluxed in water bath for 2 hrs. The reaction mixture was poured onto crushed ice. Crude product was isolated and crystallized from ethanol.

[B] Synthesis of 2-(m-chlorophenyl)-5-(p-methoxyphenyl)-1,3,4-oxadiazole.

A mixture of m-chloro benzohydrazide (1.70g, 0.01mol) and p-methoxy benzoic acid (1.52g, 0.01mol) in phosphorous oxychloride (10 ml) was refluxed for 6 hrs. The content was cooled, poured onto crushed ice and neutralised with sodium bicarbonate solution. Crude product was isolated and crystallised from ethanol. Yield **64%, m.p. 180**^{0}C Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.43 ; H, 3.87 ; N, 9.77 % Found : C, 62.40 ; H, 3.85 ; N, 9.74 %.

Similarly other oxadiazoles have been prepared. The physical data are recorded in table No. 10.

[C] Antimicrobial activity of 2-(m-Chlorophenyl)-5-aryl-1,3,4-oxadiazoles.

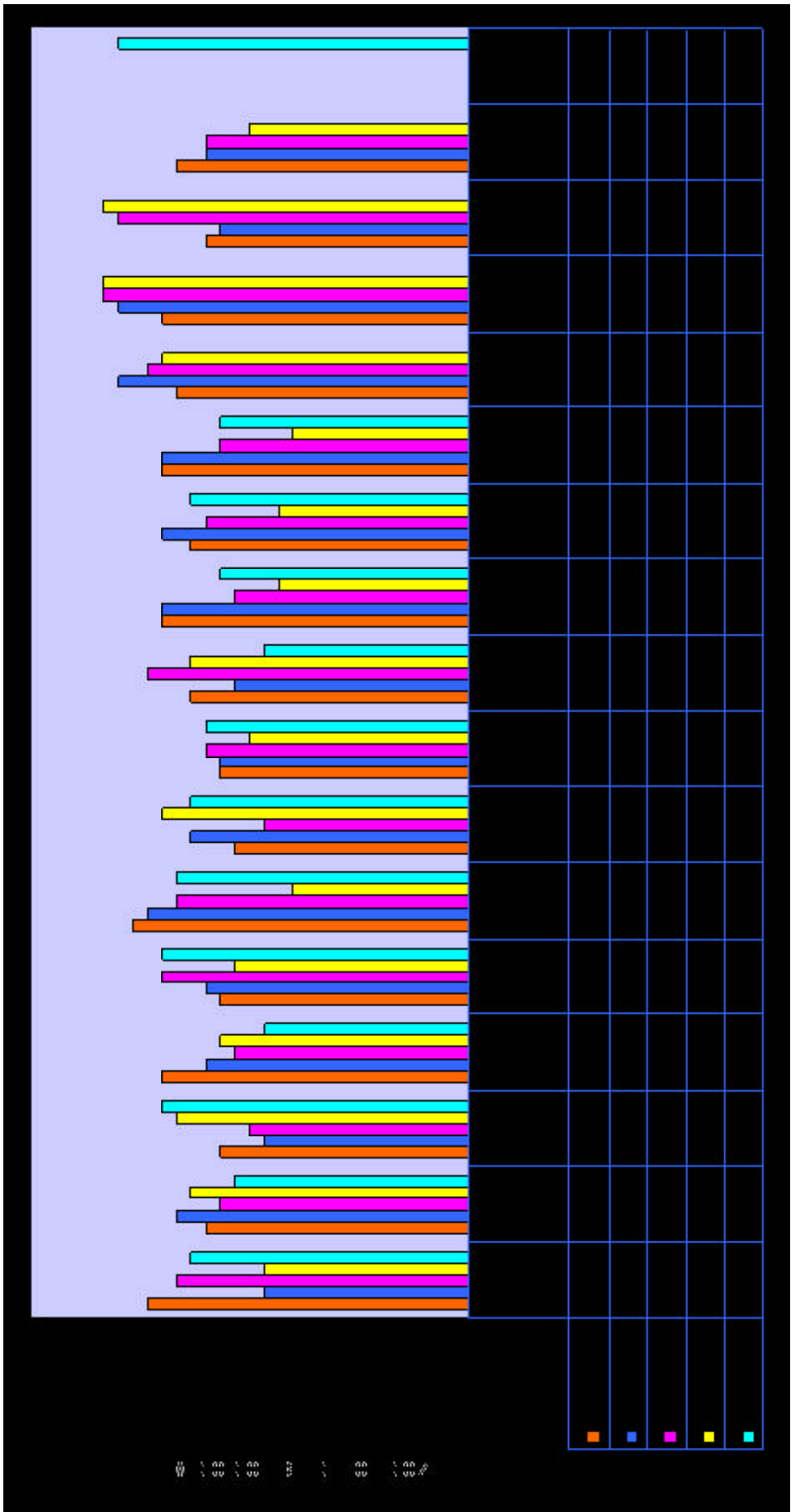
Antimicrobial testing was carried out as described in Part-I, Section (D). The zones inhibition of the compounds are recorded in Graphical Chart No.10.

TABLE-10 : PHYSICAL CONSTANTS OF 2-(m-CHLOROPHENYL)-5-ARYL-1,3,4-OXADIAZOLES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
10a	4-OCH_3-C_6H_4-	$C_{15}H_{11}ClN_2O_2$	287	180	64	9.77	9.74	0.42	S2
10b	2,4-$(OH)_2$-C_6H_3-	$C_{14}H_9ClN_2O_3$	289	165	58	9.70	9.66	0.47	S2
10c	2-CH_3-C_6H_4-	$C_{15}H_{11}ClN_2O$	271	190	65	10.35	10.31	0.49	S1
10d	3-OC_6H_5-C_6H_4-	$C_{20}H_{13}ClN_2O_2$	349	165	58	8.03	8.00	0.54	S2
10e	4-Br-C_6H_4-	$C_{14}H_8BrClN_2O$	336	197	45	8.35	8.31	0.51	S1
10f	3-Cl-C_6H_4-	$C_{14}H_8Cl_2N_2O$	291	210	67	9.62	9.58	0.39	S2
10g	4-NO_2-C_6H_4-	$C_{14}H_8ClN_3O_3$	302	186	54	13.93	13.90	0.51	S1
10h	3-NO_2-C_6H_4-	$C_{14}H_8ClN_3O_3$	302	190	65	13.93	13.90	0.47	S2
10i	4-C_5H_4N	$C_{13}H_8ClN_3O$	258	210	58	16.31	16.27	0.54	S1
10j	4-Cl-C_6H_4-	$C_{14}H_8Cl_2N_2O$	291	232	49	9.62	9.58	0.47	S1
10k	2-Cl-C_6H_4-	$C_{14}H_8Cl_2N_2O$	291	156	58	9.62	9.58	0.48	S2
10l	2-OH-C_6H_4-	$C_{14}H_9ClN_2O_2$	273	179	61	10.27	10.23	0.52	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

Graphical Chart No. 10 : Antimicrobial Activity of 2-(m-Chlorophenyl)-5-aryl-1,3,4-oxadiazoles.



REFERENCES

1. C. Aniswarth. ;
   J. American Chem. Soc., **87,** 5800 (1965).
2. A. Hetzheim and K. Mockel. ;
   Adv. Heterocyclic Chem., **7,** 183 (1966).
3. Cugureanu Constantin. ;
   Rev. Chim., **47(5),** (1996); *Chem.Abstr.,* **125,** 195512y (1996).
4. Holla B. Shivarama, Poojary K. Narayana, Kallaraya Balakrishna, et. al. ;
   Indian J. Heterocycl. Chem., (1996); *Chem.Abstr.,* **125,** 221742v (1996).
5. Brain Christoper T., Paul Jahen M., Loong Yuonne. ;
   Tetrahedron Lett., (1999); *Chem.Abstr.,* **130,** 352229i (1999).
6. Al-Talib Mahmohd, Orabi Sultan Able. ;
   Indian J. Heterocycycl.Chem., (1999); *Chem.Abstr.,* **131,** 129950n (1999).
7. Bentiss Fonad, Lagence Michel. ;
   J. Heterocycl. Chem., (1999); *Chem.Abstr.,* **132,** 35656j (2000).
8. Kovalenko S.N., Sytnik K.M., Nikit-Chenko V.M., Rasanova S.V.;
   Chem.Heterocycl. Compd (N.Y.) (1999); *Chem.Abstr.,* **132,** 35657r (2000).
9. Ziyaen A.A., Galustyan G.G. ;
   Chem.Heterocvcl.Compd. (N.Y.) (1999); *Chem.Abstr.,* **132,** 334416e (2000).
10. Yu Jian-Xin, Liu Fang-Ming, Lu Wen-Jie, Li Yan-Ping, Zao Xin-Min. ;
    Youji Xuaxue (2000); *Chem.Abstr.,* **132,** 194358k (2000).
11. Hansong Chen, Zhengming Li and Yufeng Han. ;
    J. Agric. Food. Chem., **48(11),** 5312-5315 (2002).
12. D. Ramesh, B. Sreenivasuhi. ;
    Indian J. Heterocycl. Chem., **13,** 163-164, Dec. (2003).
13. K. Mogilaiah and B. Sakram. ;
    Indian J. Heterocyclic Chem., **13,** 289-292, June (2004).
14. Kocabalkanli Ayse, Ates Oznur, Otuk Gulten. ;
    IL Farmaco, **56(12),** 978-979 (2001); *Chem. Abstr.,* **137(1),** 6127r (2002).
15. Weinder Wells, Michuc A., Henninger Todde, Hlasta Dennis. ;
    U.S. Pat. Appl. Publ. US 49, **213,** (Cl. 514-e52.051 eo7D413/02) (2002);
    Chem.Abstr., **136(22),** 340680k (2002).

16. Khan M.S.Y., Akhtar M. ;
Indian J. of Chem., Sec-B, Org, Chem. Ind. Med. Chem., **42B(4),** 900-904 (2003); *Chem.Abstr.,* **139(11),** 164749r (2003).

17. Shah H.P., Shah B.R., Bhatt J.J., Desai N.C., Trived P.B., Undavia N.K. ;
*Indian J.Chem.,Sec-B;Org.Chem.,Incl. Med.Chem.,***37B(2),**180-182 (1998).

18. Singh Amarika and Mishra Upama. ;
Proc. Indian Natt. Sci. acad., Part-A, **57(5)**, 573-8 (1991); *Chem.Abstr.,* **116,** 151711x (1992).

19. Khan M.S.Y., Khan R.M., Drabu Sushma. ;
Indian J. of Heterocyclic Chem., **11(2),** 119-122 (2001); *Chem.Abstr.,* **137(23),** 337829f (2002).

20. Cignarella Giorgio, Pinna Gerado, Murineddu Gabriele. ;
PCT Int. Appl. WO 03, **66,** 628 (Cl.CO7D413/04) (2003); *Chem.Abstr.,* **139(12),** 180069z (2003).

21. Grover, Gaurav; Kini, Suriarana G. ;
Indian J. heterocycl. Chem., **12(3),** 289-290 (2002); *Chem.Abstr.,* **139(13)** 197430h (2003).

22. Jegham Samir, Loched Alistair,Nedelec Alain, Galli Frederich ;
PCT Int. Appl. WO 98, 50383 (1998); *Chem.Abstr.,***129,** 343500t (1998).

23. Battarini France, La Porta Piero, Meazza Giovanni, Zanardi Giampaolo. ;
Eur. Pat EP 769, **845,** (1997); *Chem. Abstr.,* **127,** 318878y (1998).

24. Hussain M.I. and Jamali Mohd. Raghib. ;
Indian J. Chem., **27B(1),** 43-6 (1988); *Chem.Abstr.,* **109,**128913 (1988).

25. G.W. Adelstein, C.H. Yen, E.J. Dajani and R.G. Bainchi. ;
J. Med. Chem., **19,** 221 (1976).

26. Mazouz F., Lebroto L., Milcent R. and Burstein C. ;
Eur.J.Med.Chem., **25(81),**659-71(1990);*Chem.Abstr.* ,**114,**185388w (1991).

27. R. Nyfeler, W.Eckhardt, Ernst Benger and Odd Kristiansen. ;
Eur. Pat. Appl. EP 255, **565,**05 (1988); *Chem.Abstr.,* **110,** 114837y (1989).

28. Xiumian Zheng, Zhong Li, Yanli Wang, Weidong Chen, Qingchun Huang, Chuaziang Liu and Gonghua Song. ;
Journal of Fluorine Chemistry, **123(2),** 163-169, Oct. (2003).

29. Takahiko Inoue, Kiyosh; Ito, Tomohiro Tozaka, Susumi Hatakeyama, Nobutada Tanaka, Kazuo T., Nakamura and Tadashi Yoshimoto. ;
Archives of Biochemistry and Biophysics, **416(2),** 147-154, Aug. (2003).

30. H. Liszkiewicz, M.W. Kowalska, J.Wietrzyk and A. Opolski. ;
Indian J. of Chem., **42B(11),** 2846, Nov. (2003).

31. A.A. El-Azzouny, Y.A. Makiad, H. Bartsch, W.A. Zaghery, W.M. Ibrahim, M.S. Mohamed. ;
XVIIIth International Symposium on Med.Chem., Poster 316, Aug (2004).

32. Virginija Jakubkiene, Milda Malvina Burbuline, Giedrute Mekuskiene, Emikja Udrenaite. Povilas Gaidelis and Povilas Vainilavicius. ;
IL Farmaco, **58(4),** 323-328, April (2003).

33. Song Cao, Xuhong Qian, Gonghug Song, Qingchun Huang. ;
Journal of Fluoring Chemistry, **117(1),** 63-66, Sep. (2002).

34. S. Guniz Kucukguzel, F. Elcin Oruc, Sevim, Rollas, Fikrettin Sahin and Ahmet Ozbek. ;
Eur. J. Med. Chem., **37(3),** 197-206, March (2002).

35. Ali Almasirad, Sayyed A. Tabatabai, Mehrda Faizi, Abbas Kebriaeezadeh Nazila Mehrahi, Afshin Dalvadi and Abbas Shafiee. ;
Bioorganic and Med. Chem.Letters., **14(24),** 6057-6059, Dec. (2004).

36. Maria Grazia Mamolo, Daniele Zampieri, Luciano Vio, Maurizio Fermeglia, Marco Ferrene Elena Banfi. Et. al. ;
Bioorg. and Med. Chem., **13(11),** 3797-3809 June (2005).

37. Sahin G., Palaska E., Ekizogly M., Ozalp M. ;
IL Farmaco, **57(7),** 539-42, Jul (2002).

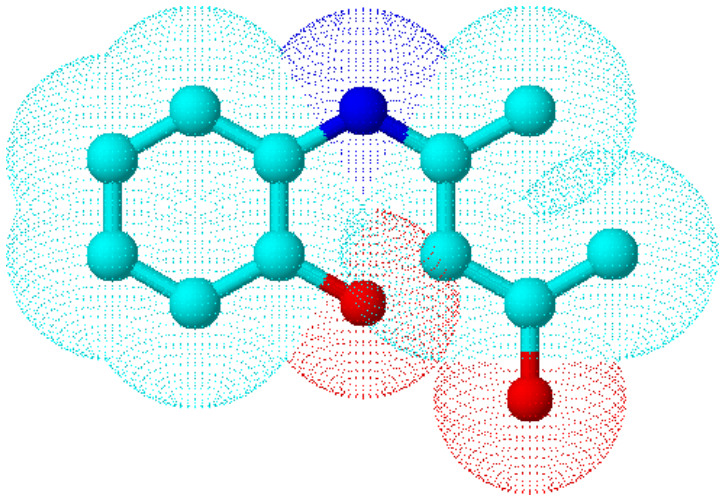
38. Maslat AO, Abussaud M., Tashtoush H, Al-Talib M. ;
Pol. J. Pharmacol., **54(1),** 55-59, Jan-Feb. (2002).

39. Milda Malvina Burbuliene,Virginija Jakubkiene,Giedrute Mekukiene.et. al.;
IL Farmaco, **59(10),** 767-774, Oct. (2004).

40. K.Subrahmanya Bhat, M.S. Karthikeyan, D. Shivarama Holla and N. Suchetha Shetty. ;
Indian J. Chem., **43B,** (8), 1765, Aug (2004).

41. T.P. Mohan, B.Vishalakshi, K.S. Bhat, K.S. Bhat, K.S. Rao and G.N. Kendappa. ;
Indian J. Chem., **43B(8),** 1798, Aug. (2004).

42. V.L. Pachhamia and A.R. Parikh. ;
J. Indian Chem. Soc., **65,** 357-61 (1988); *Chem.Abstr.,* **109,** 230899y (1988).
43. H.S. Joshi and A.R. Parikh. ;
J. Indian Chem. Soc., **67,** 858 (1990); *Chem.Abstr.,* **114,** 247210f (1991).
44. C.L. Patel and Hansa Parekh. ;
J. Indian Chem. Soc., **65,** 606-67 (1988).
45. R.N. Vansdadia, K.P. Roda and Hansa Parekh. ;
J. Indian Chem. Soc., **65,** 809-11 (1988).
46. R.N. Vansdadia, K.P. Roda and Hansa Parekh. ;
J. Indian Chem. Soc., **65,** 782-83 (1988).
47. Ronald M. Kim, Elizabeth A. Rouse, Kevin T. Chapman, William A. Schleif,David B. Olsen, Mark Stahlhut, Carrie A. et. al. ;
Bioorganic and Medicinal Chem. Letters, **14(18),** 4651-4654, Sep. (2004).
48. Mohd Amir and Kumar Shikha. ;
Europian J. Med. Chem., **39(6),** 535-545, June (2004).
49. Ali A. El-Emam. Omar A. Al-Deeb, Mohamed Al-Omar, Jochen Lehmann. ;
Bioorg and Med. Chem., **12(19),** 5107-5113, Oct. (2004).
50. Sherif A.F. Rostom, Manal A. Shalaby, Mahel A. El-Demellawy. ;
Eur. J. Med. Chem., **38 (11-12),** 959-974 Dec. (2003).
51. Afshin Zarghi, Sayyed A. Tabatabai, Mehrdad Faizi, Avideh Ahadian, Parisa Navabi, Vahideh Zanganeh, Abbas Shafiee. ;
Bioorg. and Med. Chem. Letters, **15(7),** 1863-1865, April (2005).
52. Mahmud Tareq Hussan Khan, Mahammud Iabal Choudhry, Khalid Mohammed Khan, Niubeen Rani and Atta-ur-Rahman. ;
Bioorg and Med. Chem., **13(10),** 3385-3395, May (2005).
53. V. M. Parikh;
"Absorption spectroscopy of organic molecule". Addition Wesley Pub. Co. London, 243-256 (1978).
54. C. N. R. Rao;
"*Chemical application of Infrared spectroscopy"* Academic press, New York (1963).
55. Silverstein Bassler and Morrill.;
Spectrometric identification of organic compounds fifth edition (1991) by John Wiely & Sons Inc.



[B]

STUDIES ON

PHENYLAMINO DERIVATIVES

INTRODUCTION

Phenyl amino derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activity. Different types of phenyl amino derivatives shows variety of pharmacological activities such as antibiotic, antifungal, herbicidal, insecticidal, antitubercular etc. Phenyl amino derivatives have a speciality is that aniline moiety is electron donor as compared to that of aliphatic amino group.

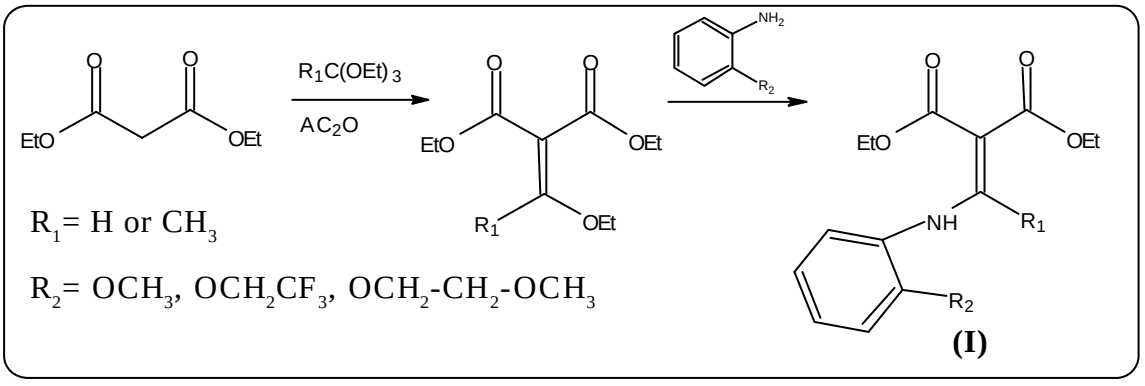
Aryl amino molecules are chromophore with characteristic of absorption and emission spectra, due to the conjugation between the nitrogen lone pair electrons and the phenyl π-electrons. N-Alkyl or N-phenyl substitution of aromatic amines leads to superior performance in material chemistry such as hyper polarizability[1], electroluminescence,[2-3] etc.

4-Phenyl amino derivatives are also model of the polyaniline polymer.[4] The remarkable properties and its dual fluorescent derivatives of this molecule have fascinated chemists and tremendous effeorts have been devoted to understand their behaviour.[5-13]

SYNTHETIC ASPECT

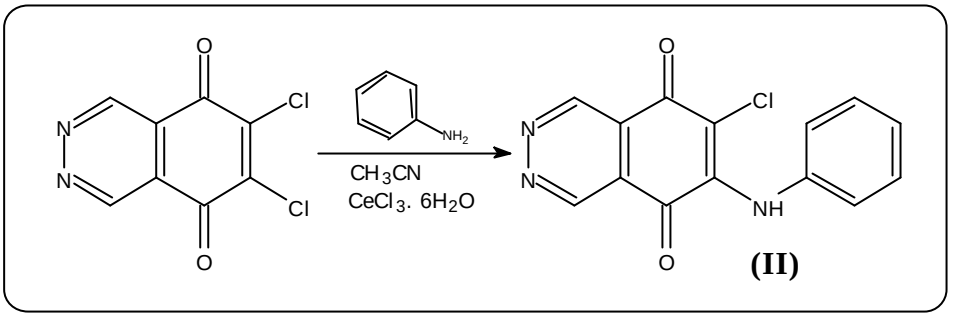
Different methods have been cited in literature to synthesize phenyl amino derivatives by several workers using various interesting substactes.

1. Eul Kgun Yum and co-workers[14] have synthesized phenyl amino derivatives (I) by the reaction of different anilines and the compound, which was obtained by the reaction of diethyl malonate and triethyl orthoformate or triethyl orthoacetate.



(I)

2. Jin Sung Kim and co-workers[15] have synthesized 6-chloro-7-phenyl amino-5,8-phthalazinedione derivatives (II) by the condensation of 6,7-dichloro-5,8-phthalazinedione with different aromatic amines in presence of CH_3CN and cerium (III) chloride hexahydrate.



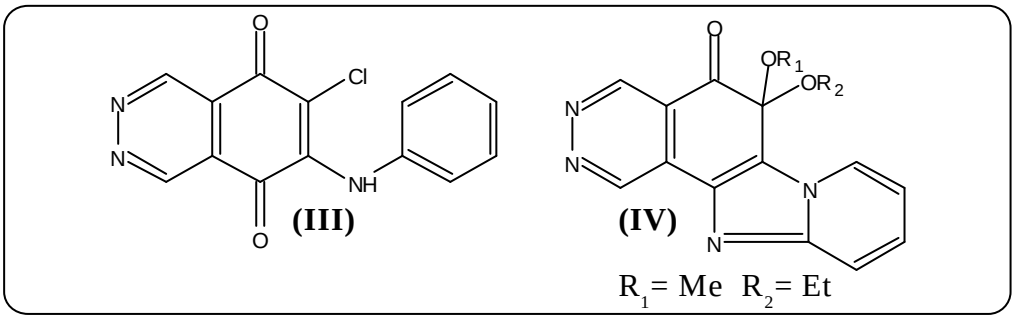
(II)

BIOLOGICAL EVALUATION

Phenyl amino derivatives have been tested for various pharmacological activities, which have been summerised as under.

1. Antitubercular[16]
2. Antifungal[17]
3. Anticancer[18]
4. Herbicidal[19-21]
5. Antibiotic[22-24]
6. Cardiovascular[25]

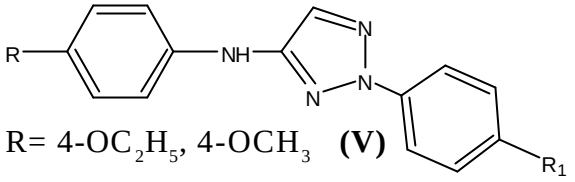
Jin Sung Kim, Kyung Ho Yoo and co-workers[26-28] have prepared phenyl amino phthalazine derivatives (III, IV) and reported them as biologically active heterocycles particularly as an anticancer agents.



(III) **(IV)**

R_1= Me R_2= Et

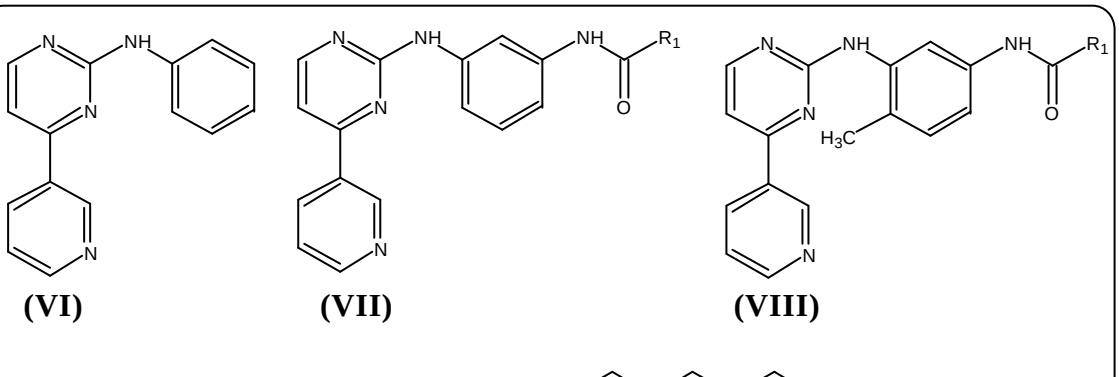
Mauleon D, Pujol M.D., Rosell G[29] have synthesized some new 4-aryl amino derivatives and reported their biological activity. Bakhite EA, et al[30] have synthesized phenyl amino derivatives and documented their antibacterial and antifungal activity. Wen-Fq Kuo and coworkers[31] have synthesized some new 4-aryl amino-1,2,3-triazoles (V) and reported their biological activity.



R= 4-OC_2H_5, 4-OCH_3 **(V)**

R_1= 4-CH_3, 4-Cl

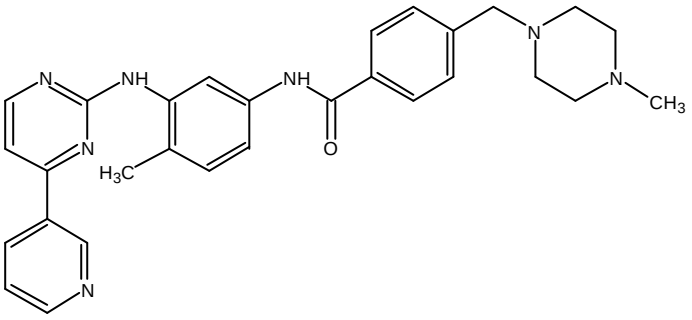
Satyanarayana D et al[32] have synthesized 4-phenyl amino derivatives and reported their antimicrobial and anti-inflammatory activity. Renaud Capdeville and Alex Matter[33] have developed some new phenyl amino derivatives (VI, VII, VIII,IX) and proved them as an anticancer agents.



(VI)

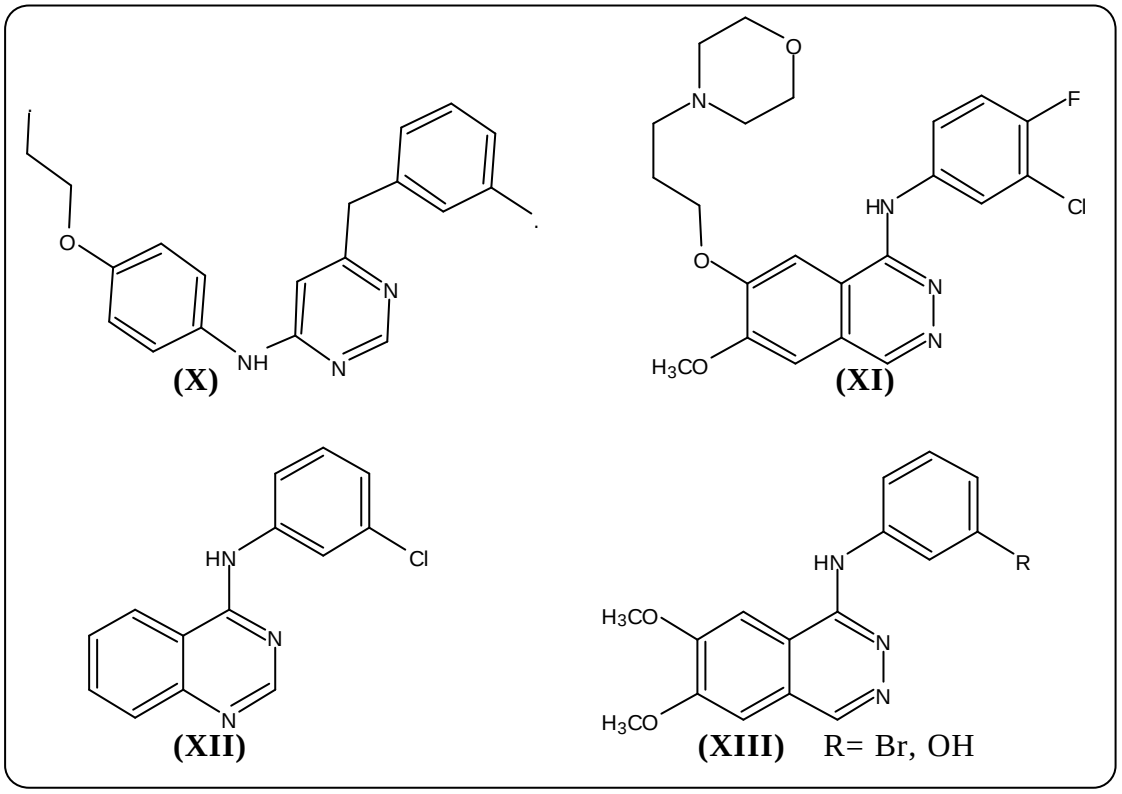
(VII)

(VIII)

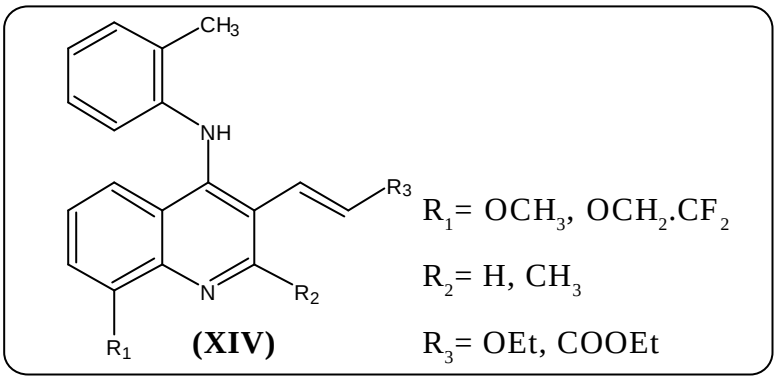


(IX)

Bucsh RA et al.[34] have synthesized some new aryl amino derivatives and tested for their antimicrobial activity. Hagen SE and co-workers[35] have synthesized aryl amino derivatives and reported their antibacterial activity. G.W. Rewcastle et al[36] have synthesized some new 4-(phenyl amino)pyrimidine derivatives (X,XI,XII,XIII) and reported them as ATP-Competitive Protein Kinase inhibitors with potential agents for cancer chemotherapy.



Hong CY and co-workers[37] have reported antibacterial activity of some aryl amino derivatives. Imamori K et al.[38] have documented antibacterial activity of aryl amino derivatives. Hyae Gyeng et al.[39] have synthesized some new phenyl amino derivatives (XIV) and documented them as Gastric H^+/K^+-ATPase inhibitors.



(XIV)

R_1= OCH_3, $OCH_2.CF_2$

R_2= H, CH_3

R_3= OEt, COOEt

Looking to this significant biological activity of 4-aryl amino derivatives, it was subject of interest to study some 4-aryl amino derivatives which have been described as under.

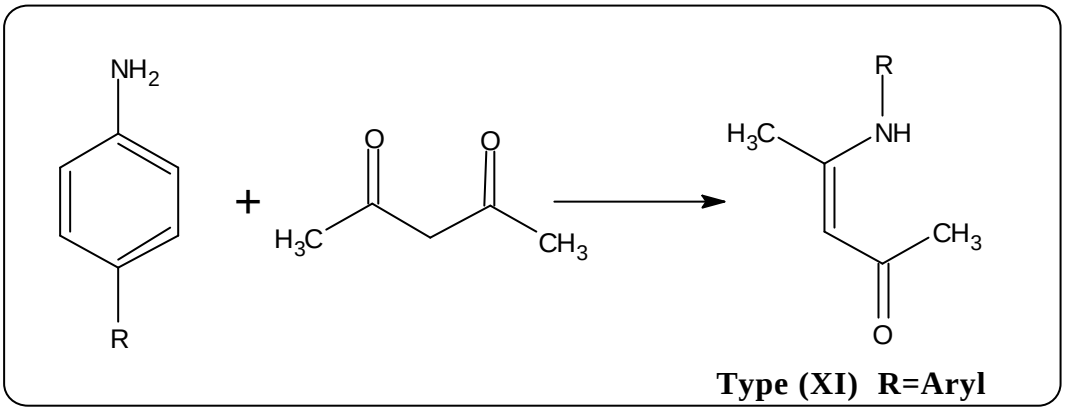
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 4-(ARYLAMINO)-PENT-3-EN-2-ONES.

SECTION-II : X-RAY CRYSTALLOGRAPHIC STUDY OF 4-(2-HYDROXY PHENYLAMINO)PENT-3-EN-2-ONE.

SECTION-I

SYNTHESI S AND BIOLOGICAL SCREENING OF 4-(ARYLAMINO)PENT-3-EN-2-ONES.

4-Aryl amino derivatives represents one of the modest class of compounds possessing wide range of therapeutic activities . In views of these findings, it appeared of interest to synthesize 4-(arylamino)pent-3-en-2-ones. The synthesis of phenyl amino derivatives of type (XI) have been undertaken by the condensation of acetyl acetone with different aromatic amines in the presence of pyridine.

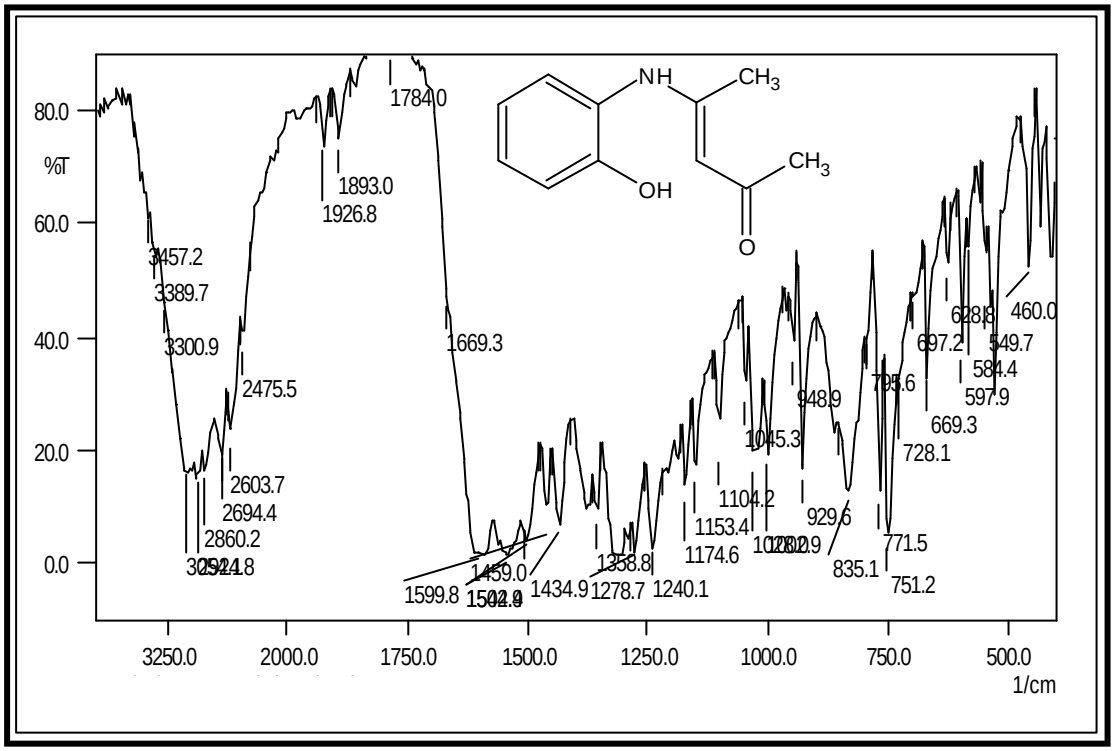


Type (XI) R=Aryl

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

All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No.11.

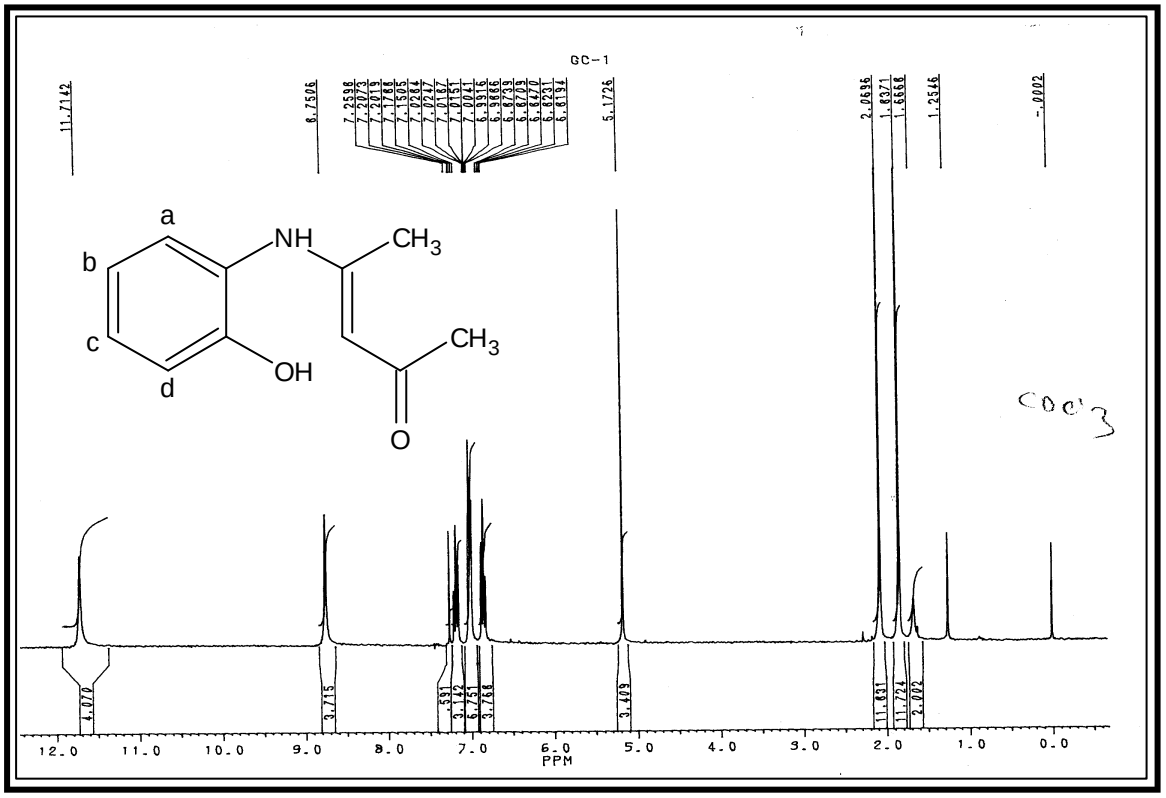
IR SPECTRAL STUDIES OF 4-(2-HYDROXY PHENYLAMINO)-PENT -3-EN-2-ONE



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.)	2924	2975-2950	76
-CH_3	C-H str. (sym.)	2860	2880-2860	76
	C-H def.(asym.)	1459	1470-1435	76
	C-H def.(sym.)	1358	1385-1370	76
Aromatic	C-H str.	3060	3080-3030	77
	C=C str.	1502	1585-1480	77
	C-H i.p. (def)	1045	1125-1090	77
	C-H o.o.p. (def)	835	835-810	77
Hydroxy	-OH str.	3389	3400-3200	76
Amine	-NH str.	3457	3500-3400	77
Carboxyl	-C=O str.	1669	1750-1665	78
	-C-O-C str.	1174	1200-1150	78

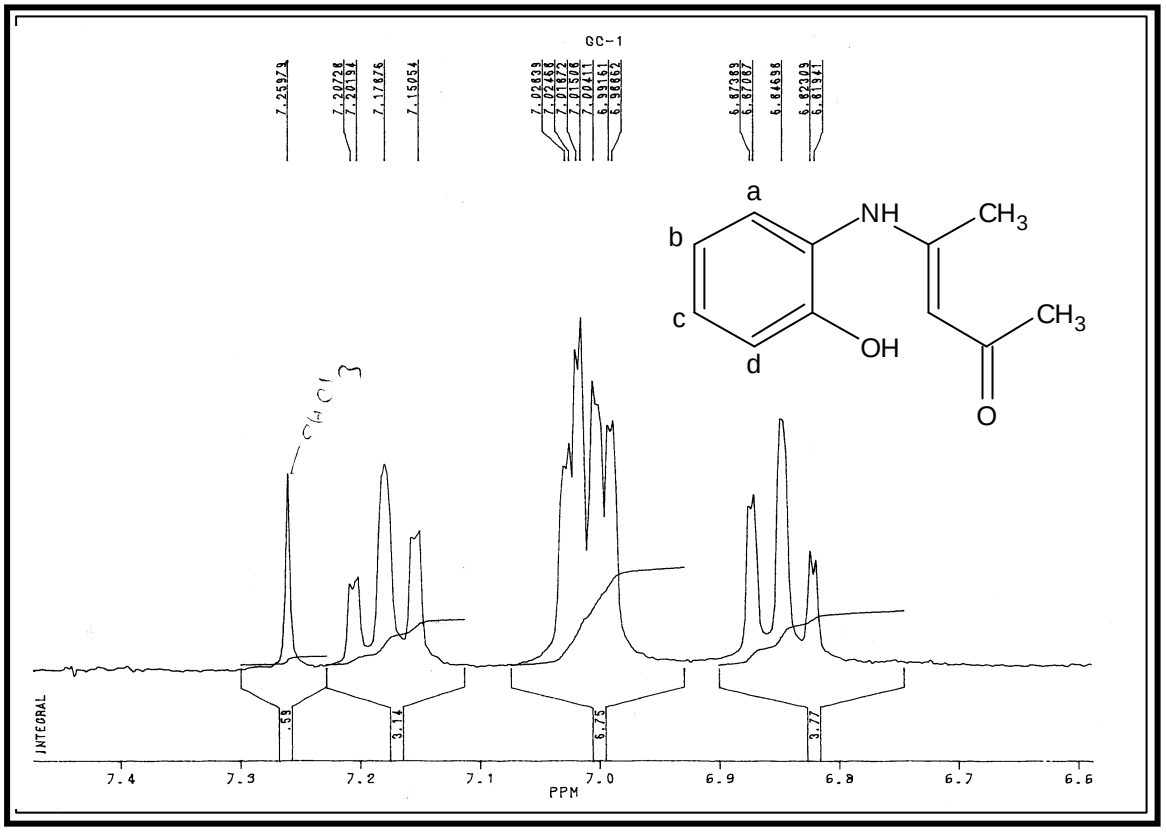
NMR SPECTRAL STUDIES OF 4-(2-HYDROXY PHENYLAMINO)-PENT -3-EN-2-ONE



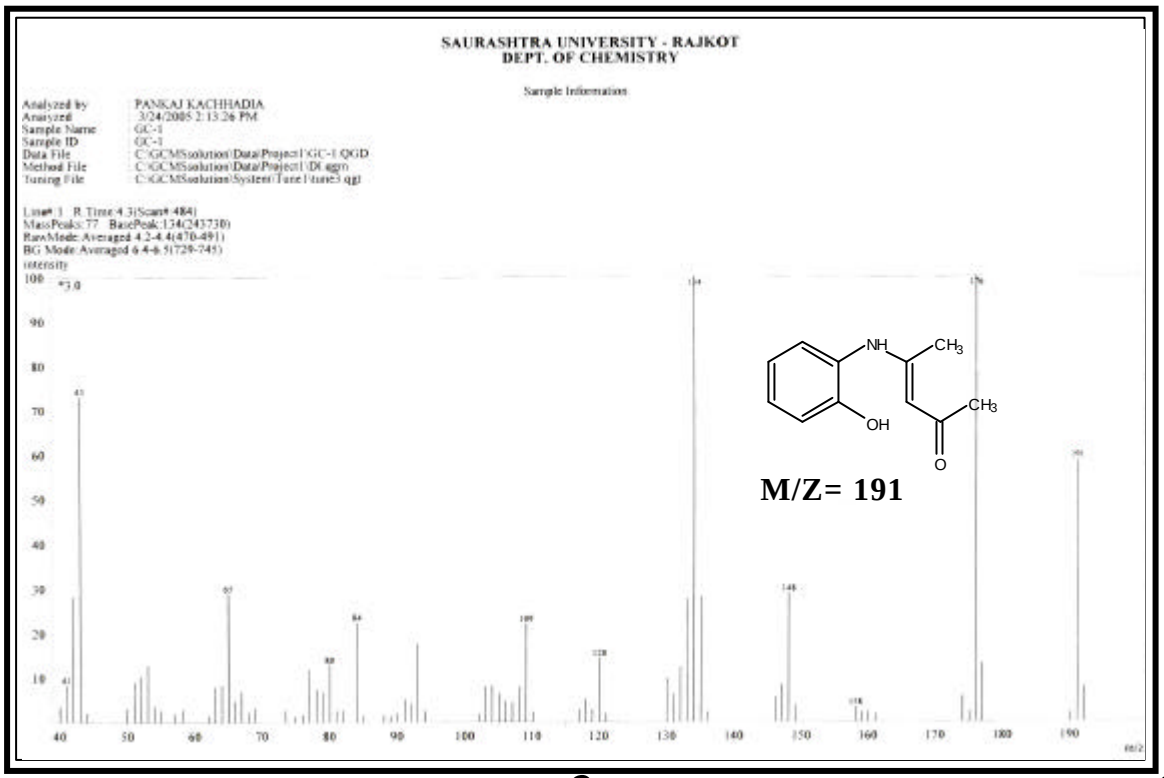
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)

Signal No.	Signal Position (d ppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.83	3H	singlet	-C-CH_3	-
2	2.06	3H	singlet	-$COCH_3$	-
3	5.17	1H	singlet	=CH	-
4	6.84	1H	triplet of doublet	-CHa	Jab=9.0 Jac=3.0
5	6.96-7.02	2H	multiplet	-CHb,c	-
6	7.17	1H	triplet of doublet	-CHd	Jdc=9.0 Jdb=3.0
7	8.75	1H	singlet	-NH	-
8	11.71	1H	broad singlet	-OH	-

Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 4-(2-HYDROXY PHENYLAMINO)-PENT -3-EN-2-ONE



EXPERIMENTAL

SYNTHESI AND BIOLOGICAL SCREENING OF 4-(ARYLAMINO)PENT-3-EN-2-ONES.

[A] Preparation of 4-(2-hydroxy phenylamino)pent -3-en-2-one.

A solution of 2-amino phenol (1.09 gm, 0.01 mole) and acetyl acetone (1.00 gm, 0.01 mole) in methanol (20 ml) was stirred for 12 hrs. in the presence of few drops of pyridine at room temperature. The reaction mixture was allowed to stand at room temperature for 24 hrs. The content was pour in to ice-cold water. The solid separated was filtered and washed with water and recrystallized from methanol. Yield 64%, m.p.170^{o}C. Calculated for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; found: C, 69.07; H, 6.87; N, 7.30%.

Similarly other aromatic amines were condensed. The physical constants are recorded in Table No.11.

[B] Antimicrobial activity of 4-(arylamino)pent-3-en-2-ones.

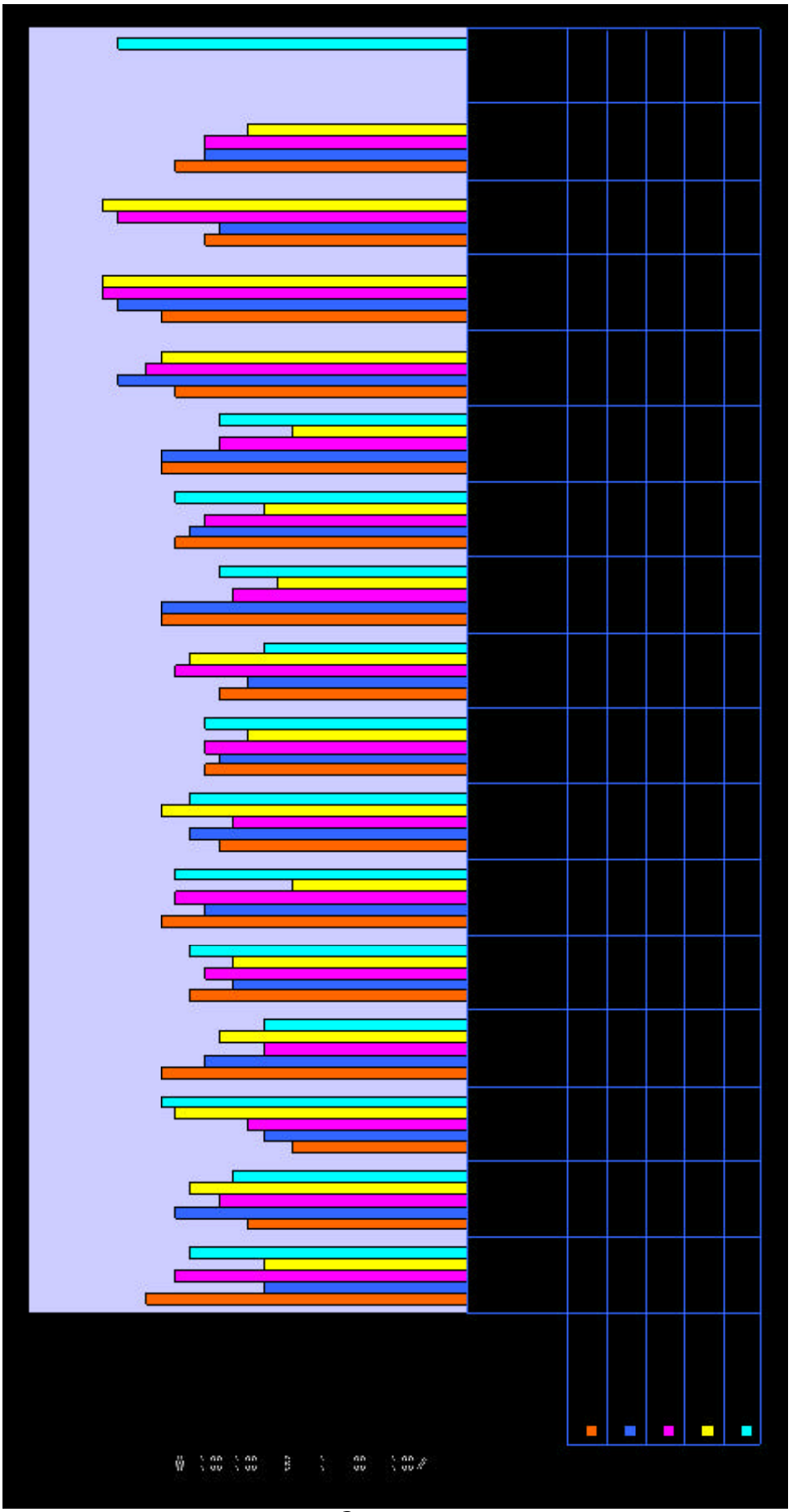
Antimicrobial testing was carried out as described in part-I, Section-I (D). The zones of inhibition of compounds are recorded in Graphical chart No.11.

TABLE-11 : PHYSICAL CONSTANTS OF 4-(ARYLAMINO)PENT-3-EN-2-ONES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
11a	2-OH-C_6H_4-	$C_{11}H_{13}NO_2$	191	170	64	7.32	7.30	0.49	S2
11b	4-OH-C_6H_4-	$C_{11}H_{13}NO_2$	191	165	61	7.32	7.30	0.47	S2
11c	4-Cl-C_6H_4-	$C_{11}H_{12}ClNO$	210	180	58	6.68	6.64	0.43	S1
11d	4-COOH-C_6H_4-	$C_{12}H_{13}NO_3$	219	160	49	6.39	6.35	0.42	S2
11e	4-OCH_3-C_6H_4-	$C_{12}H_{15}NO_2$	205	183	60	6.68	6.64	0.51	S1
11f	4-NO_2-C_6H_4-	$C_{11}H_{12}N_2O_3$	220	210	59	12.72	12.70	0.56	S2
11g	3-COOH-C_6H_4-	$C_{12}H_{13}NO_3$	219	197	44	6.39	6.35	0.55	S1
11h	2-NO_2-C_6H_4-	$C_{11}H_{12}N_2O_3$	220	190	56	12.72	12.70	0.45	S2
11i	3-Cl-4-F-C_6H_3-	$C_{11}H_{11}ClFNO$	227	240	58	6.15	6.11	0.47	S1
11j	3-OH-C_6H_4-	$C_{11}H_{13}NO_2$	191	210	59	7.32	7.30	0.47	S1
11k	4-CH_3-C_6H_4-	$C_{12}H_{15}NO$	189	310	58	7.40	7.36	0.49	S2
11l	2-CH_3-C_6H_4-	$C_{12}H_{15}NO$	189	170	61	7.40	7.36	0.52	S1

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

Graphical Chart No. 11 : Antimicrobial Activity of 4-(arylamino)pent-3-en-2-ones.



SECTION-II

Single crystal X-ray Diffraction analysis

Single crystal X-ray diffraction is the most common experimental method of obtaining a detailed picture of a small molecule that allows resolution of individual atoms. It is performed by analyzing the diffraction of x-rays from an ordered array of many identical molecules. Many molecular substances, including proteins, polymers and other solidify in to crystals under the proper conditions. When solidifying in to the crystalline state, these individual molecules typically adapted as one of only a few possible orientations. A crystal is a three dimensional array of those molecules that are held together by Van der Waals and noncovalent bonding. The smallest representative unit of this crystals is referred to as the unit cell. Understanding the unit cell of these arrays simplifies the understanding of a crystal as a whole.

Growth and Characterization of 4-(2-hydroxy-phenylamino)-pent-3-en-2-one (HPAP) Crystal:

N-Phenyl, especially N-Benzyl amino acids find applications in peptide synthesis and are valuable building blocks for the synthesis of chiral compounds[40]. The development of 4-(3', 5'-dibromo 4'-hydroxyphenyl) amino-6,7-dimethoxy quinazoline[41] has provided the basis for new treatment as well as prevention programs for allergic asthma. Owing to the medicinal properties of hydroxyl-phenyl amino derivatives, the crystal growth of organic material 4-(2-hydroxy-phenylamino)-pent-3-en-2-one (HPAP) has been carried out. A part from the crystal structure determination and different characterizations such as photoconductivity measurement and NLO test have also been carried out.

Growth of HPAP Crystals:

In the present study, acetone and methanol both were selected as solvents; however, methanol yielded good quality single crystals. The seed crystals were grown from controlled evaporation of saturated solution of HPAP in methanol and good quality crystals were picked up for growth. A glass jar of 4 cm diameter and 7 cm length was selected as a crystallizer. This jar was kept in a water bath with temperature control of $\pm$ 0.1 ^{0}C. Water in the bath was stirred slowly. Supersaturated solution of HPAP was poured into crystallizer and a seed crystal was hung by using very fine nylon thread. The temperature of the water bath was maintained at 40 ^{0}C and the evaporation rate was carefully controlled.

Figure [1]: Photograph of the grown HPAP crystals

Good quality single crystals with maximum dimension 1.5 cm X 0.75 cm were obtained. Figures [1] show the types of crystals grown. The crystals were yellowish brown in color.

Characterization of HPAP Crystals

Single Crystal X-ray Diffraction and Structure Determination

The three dimensional intensity data were collected on an Enraf-Nonius CAD-4 diffractometer. The reflection data were collected at 293 K and ? /2? scan mode was employed for data collection by using MoK_{α} radiation (λ = 0.71073 Å). The structure has been elucidated by direct methods using SHELEX 97[42]. All non-hydrogen atoms of the molecule were located from the E-map. Isotropic refinement of the structure by least squares methods using SHELEX 97[43] was followed by anisotropic refinement of all the non-hydrogen atoms. All the hydrogen atoms were fixed stereochemically. Atomic scattering factors were taken from International tables for crystallography (1992 Vol. C Tables 4.2.6.8 and 6.1.1.4). Geometrical and other structural calculations were performed by using PARST[44] programme. The experimental details and other measurement data are given in Table [I]. The atomic coordinates and anisotropic displacement parameters of the non-hydrogen atoms are given in Table [II] and geometry of intra and intermolecular hydrogen interactions are given in Table [III]. The bond lengths and bond angles are given in Table [IV]. An ORTEP diagram of the compound with atom numbering scheme is shown in figure [2] and figure [3] represents the packing diagram of HPAP crystals, which showing the hydrogen-bonding network[45].

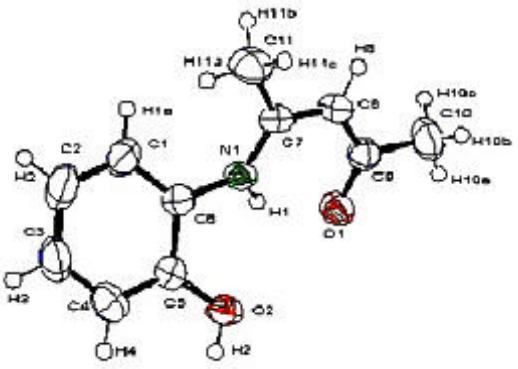


Figure [2] : ORTEP Diagram of HPAP Crystals

Table [I]

Crystal data from single crystal XRD	
Crystal data and experimental data.	
Formula	$C_{11}H_{13}NO_2$
Relative formula weight	192.23
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Cell dimensions	a = 8.839(3)Å
	b = 10.517(2)Å
	c = 11.223(3)Å
Z	4
V	1043.4(5)Å^3
T	293(2) K
Dx	1.224 Mg/m^3
μ	0.084 mm^{-1}
$?_{max}$	24.95^o
Radiation ($M_o K_a$)	λ=0.71073 Å
Crystal Size	0.3 x 0.2 x 0.3 mm
F (000)	412
Total no. of reflections	1095
No. of independent reflections	1078
No. of observed reflections	1079
No. of parameters	128
R-value	0.0425
Rw	0.1211
Refinement method	Full- matrix least- squares on F^2
Goodness-of-fit on F^2	1.043

$(?/s)_{max}$	0.005
$(??)_{max}$	0.204 e. Å^{-3}
$(??)_{min}$	–0.179 e. Å^{-3}
Measurement:	ENRAF-NONIUS DetectorProgram
Program system:	ENRAF-NONIUS Program
Structure determination:	SHELXS97
Structure drawing:	ORTEP III
Refinement:	SHELXL97

Table [II]

Atomic coordination of non-hydrogen atom of HPAP crystals

Atomic coordinates (x 10^4) and equivalent isotropic thermal parameters (Å^2 x 10^3) for non-hydrogen atoms

Atom	X	Y	Z	U_{eq}^*
O1	4531(2)	6847(2)	8517(2)	55(1)
O2	0807(2)	7068(2)	9604(2)	54(1)
N1	1977(3)	5782(2)	7819(2)	40(1)
C1	-0309(4)	4410(3)	7765(3)	57(1)
C2	-1712(4)	4127(3)	8227(4)	70(1)
C3	-2280(4)	4813(3)	9156(3)	65(1)
C4	-1468(3)	5800(3)	9641(3)	55(1)
C5	-0072(3)	6120(2)	9177(2)	41(1)
C6	0517(3)	5424(3)	8216(2)	41(1)
C7	2593(3)	5780(3)	6732(2)	42(1)
C8	4032(3)	6224(3)	6552(2)	46(1)
C9	4953(4)	6765(3)	7444(3)	44(1)
C10	6472(4)	7294(4)	7122(3)	68(1)
C11	1679(4)	5332(4)	5685(3)	66(1)

$\mathbf{U_{eq}^* = (1/3)} \sum_i \sum_j \mathbf{U_{ij}\, a_i^*\, a_j^*\, (a_i . a_j)}$

Table [III]

Geometry of intra and inter molecular hydrogen interactions

Geometry of intra and inter molecular hydrogen interactions.			
X-H...A	H...A(Å)	X...A(Å)	X-H...A(°)
O2-H2…O1	1.831(2)	2.650(1)	176.5(2)
N1-H1…O1(i)	1.934(1)	2.639(3)	138.4(1)
Equivalent position: (i) -x-1/2, -y+3/2, -z+2			

Table [IV]

Various bonds and bond length of HPAP crystals

Bond lengths (Å) and bond angles (°)			
Bond Lenghts (Å)			
O1-C9	1.263(3)	C3-C4	1.375(5)
O2-C5	1.352(3)	C4-C5	1.381(4)
N1-C7	1.336(3)	C5-C6	1.403(4)
N1-C6	1.416(4)	C7-C8	1.370(4)
C1-C2	1.377(5)	C7-C11	1.502(4)
C1-C6	1.389(4)	C8-C9	1.410(4)
C2-C3	1.363(5)	C9-C10	1.498(5)
Bond Angles (°)			
C7-N1-C6	131.2(2)	C1-C6-N1	124.7(3)
C2-C1-C6	120.1(3)	C5-C6-N1	116.2(2)
C3-C2-C1	120.4(3)	N1-C7-C8	120.9(2)
C2-C3-C4	120.7(3)	N1-C7-C11	119.7(3)
C3-C4-C5	120.1(3)	C8-C7-C11	119.4(3)
O2-C5-C4	124.0(3)	C7-C8-C9	124.6(3)

O2-C5-C6	116.4(2)	O1-C9-C8	122.3(3)
C4-C5-C6	119.6(3)	O1-C9-C10	118.0(3)
C1-C6-C5	119.1(3)	C8-C9-C10	119.7(3)

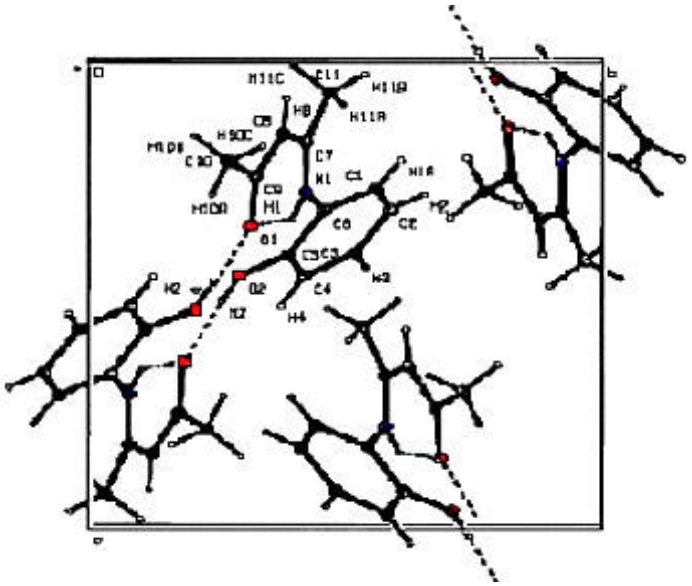


Figure [3] : Packing diagram 4-(2-hydroxyphenylamino)-pent-3-en-2-one showing the hydrogen-bonding network

Description of the Crystals:

The phenyl ring has geometry, which is more or less similar to its standard values [46-47]. The bonds distances, O1-C9 and N1-C7, are shorter than the normal expected values and the variation of this kind in the value of bond distances has been observed in case of some analogous structures[46-49]. The small value of N1-C7 [1.336(3) Å] in comparison to C6 [1.416(4) Å] results into significant variation in C7-N1-C6 bond angle [131.2 (2)^0]. The difference in C-N bond distances could be due to presence of carbonyl group located at C9 position. Shorting of C7-N1 bond length and a large value of the C-N-C bond angle leads to the existence of N1-H1…O1 intramolecular H- bond [50]. The magnitude of torsion along C6-N1 bond is 35. 3^0. The torsional deformation in other bonds of the side chain is insignificant. The oxygen atom O2 is deviated significantly below the plane of phenyl ring [deviation being -0.823 (2) Å] and it results in the formation of O2-H2…O1 intermolecular interaction. The crystal structure is stabilized by an intra molecular N1-(amino)-H1…O1 (one) and inter molecular O2-H2…O1 hydrogen

bond which falls in the range of 'intermediate hydrogen bonds' as proposed by Desiraju and Steiner[50]. Both kinds of interactions are depicted in the unit cell-packing diagram figure [3] in which the molecules are held together through a hydrogen-bonded network. The intramolecular bond results into a virtual six membered ring thus making the present molecule look like as two ring structure. The molecule exhibit typical orthorhombic symmetry. In both the interactions, O1 acts as a bifurcated acceptor atom whereas O2 and N1 act as donors. The details of hydrogen bonding is shown in Table [III].

Using compiled data for a large number of O-H…O and N-H…O contacts, Desiraju and Steiner[50] have found significant statistical directionality and concluded that these are legitimately viewed as 'intermediate' hydrogen bonds, with a greater contribution to packing forces than simple van der Waal interactions.

Photoconductivity and NLO Studies of HPAP Crystals:

Polished sample of the HPAP was attached to a microscope slide and two electrodes of thin copper wires were fixed by the use of silver paint. The distance (d) between the electrical contacts was 0.112 cm. The sample was connected in series to a d.c. power supply and a picoammeter (Keithley 480). The details of the experimental set-up used in the present study are reported elsewhere[51]. The applied voltage was increased from 0 to 300 V in the steps of 20 V and the corresponding dark current was recorded. The sample was then exposed to the radiation from a 100 W halogen lamp containing iodine vapour and tungsten filament. The emission spectrum of the halogen lamp was observed to be a continuous one with wavelengths ranging from 300 to 1000 nm. The photocurrent was recorded for the same range of the applied voltage. Figure [4] shows the field dependence of dark and photo currents of HPAP crystals and Table [V] gives the data of dark current and photocurrent for HPAP crystals.

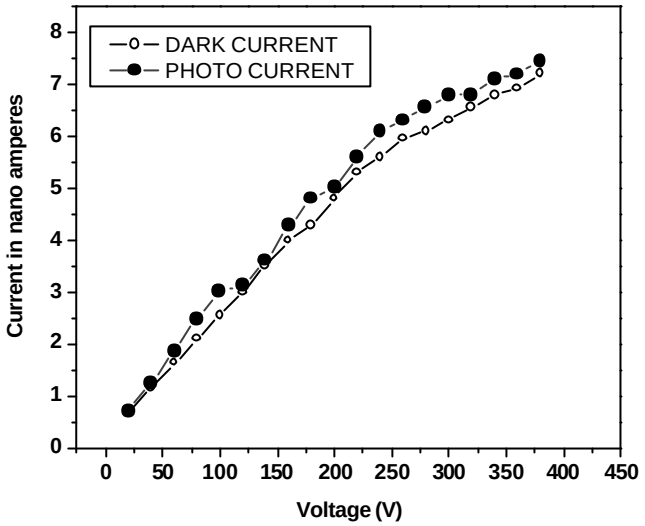


Figure [4] : Field dependent conductivity of the HPAP crystals

Table [V]

Photoconductivity Studies of HPAP Crystals

Voltage (V)	Dark Current (nA) I	Photo Current (nA) I_p
20	0.68	0.71
40	1.16	1.25
60	1.64	1.87
80	2.10	2.49
100	2.55	3.01
120	3.00	3.12
140	3.50	3.61
160	3.99	4.28
180	4.28	4.80
200	4.80	5.00
220	5.30	5.60
240	5.60	6.10
260	5.95	6.30
280	6.10	6.55
300	6.30	6.79
320	6.55	6.80
340	6.79	7.10
360	6.92	7.12
380	7.20	7.23

It can be noticed from figure [4] that both dark and photo currents increase almost linearly for HPAP crystals but the dark current is less than the photocurrent, which is known as *positive photoconductivity*. Photoconductivity is explained in detail by Joshi [52]. Photoconductivity was also reported in pure and doped L-argenin phosphate (LAP) crystals by Pragasam [53]. This type of behavior of photoconductivity is due to the increasing number of charge carriers or their life time.

Non-Linear Optics (NLO) is the experimental set-up or the apparatus in which the linear input results in *non-linear output*. Before the advent of lasers, transparent optical materials were assumed to be passive, that is, unaffected by light traveling through them. The high powers of Laser beams made it possible for the first time to observe that the presences of light can, in fact, affect the medium. Intense light can change the refractive index of absorption of the material. When this happens, the light itself is affected by the change, in a nonlinear way. This can convert Laser in to harmonics of higher orders, i.e. into different colors. This was first observed by Franken et al.[54] in 1961.

In the case of linear optical transitions an electron absorbs a photon from the incoming light and does a transition to the next higher unoccupied allowed state.

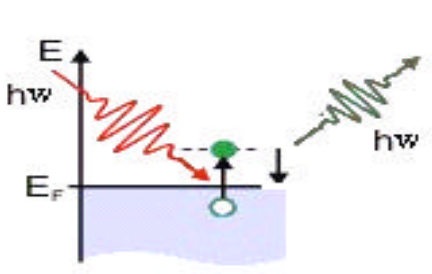


Figure [5-a]

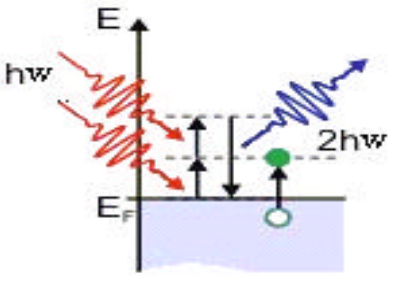


Figure [5-b]

Figure [5] : Formation of SHG from the crystals

When this electron relaxes it emits a photon of frequency less than or equal to the frequency of the incident light [Fig. 5-a]. Second harmonic generation (SHG), on the other hand, is a two photon process where this excited electron absorbs another photon of same frequency and does a transition to yet another allowed state at higher energy. This electron, on having transition back to its original state, emits a photon of a frequency which is two times that of the incident light [Fig. 5-b]. This results in the frequency doubling in the output [55].

The non-linear optics is traditionally introduced by considering that the dielectric susceptibility ? can be expanded in a Taylor series in terms of oscillating optical field. The term $?_1$ is the dielectric susceptibility measured at low powers. The term $?_2$, linear in the field, multiplies the incident optical field, generating second harmonic frequencies. The term $?_3$ is quadratic in the field, producing third harmonic frequencies or introducing a change in the index of refraction. There is a close relationship between $?_2$ and electro-optic effect. In that phenomenon, an applied electric field multiplied by the optical field creates an index change through the $?_2$ term, so that the index of refraction is controlled by an external applied field[56]. Chelma and Zyss[57] have compiled detailed information on this phenomenon and materials observing that.

Materials, which possess optical nonlinearities, have been studied extensively for their possible applications in various fields, for example, telecommunication, optical computing, optical data storage and optical information processing[58-60]. Organic NLO materials are, generally, more versatile than their inorganic counterparts due to their more favorable nonlinear response, but these substances are often formed by weak van der Waals and hydrogen bonds and hence possess a high degree of delocalization[61]. Many organic crystals are well known for their potential NLO applications, such as p-hydroxyacetophenone[62], benzoyl glycine[63], hippuric acid[64], etc. Recently, Dhanuskodi and Vasantha[65] and Dhanuskodi and Manikandan[66], have reported the growth of

semi-organic NLO materials, L-aluminium oxalate and methyl-p-hydroxy benzoate, respectively. However, these crystals have inherent limitations such as increased optical absorption, narrow transparency window and poor mechanical and thermal stability. On the other hand, the inorganic NLO crystals have excellent mechanical and thermal properties but possess relatively modest optical nonlinearties because of the lack of ð - electron localization. Potassium dihydrogen phosphate (KDP)[67], ammonium dihdrogen phosphate (ADP)[68], lithium niobate[69], potassium penta borate[70] etc., are well known inorganic NLO materials. Combining the high optical nonlinearity and chemical flexibility of organics with temporal and thermal stability as well as excellent transmittance of inorganics, a new class of semiorganic materials has been developed, which is attracting a great deal of attention in the nonlinear optical field[71-72]. L-Histidine tetrafluoroborate (L-HFB) is a semiorganic NLO material, having SHG efficiency five times greater than KDP[73]. There are many other semiorganic materials with potential SHG efficiency, for example, amino-acid salts; L-arginine phosphate monohydrate[74] and zinc cadmium thiyocynate (ZCTC)[75].

In the present study, NLO properties of the HPAP crystals were measured by measuring the second harmonic generation (SHG) efficiency. The crystal was evaluated by the Kurtz and Perry powder technique using a Q-switched, mode locked Nd:YAG laser. A microcrystalline material of KDP was used for the comparison purpose with HPAP sample in the SHG measurements. The fundamental laser beam of 1064 nm was used as a source. For a laser input pulse of 6.2 mJ, the second harmonic signal (532 nm) of 23 to 24 mV and 275 mV were obtained through HPAP and KDP crystal, respectively. Thus the SHG efficiency of HPAP crystal was nearly one tenth of KDP crystals. But the NLO properties can be increased either by proper doping of the suitable material or by making the proper inorganic salt of HPAP.

REFERENCES

1. C.M. Whitaker, E.V. Patterson, K.L. Kott. ;
   J. Am. Chem. Soc., **118,** 9966 (1996).
2. A. Yamamori, C. Adamovich, T. Koyama ;
   Appl. Phys., **86,** 4369 (1999).
3. D. Kolosov, V. Adamovich, P. Djurovich. ;
   J. Am. Chem. Soc., **124,** 9945 (2002).
4. S. Kapelle, W. Retting, R.Lapouyade. ;
   Chem. Phys. Lett., **348,** 416 (2001).
5. W. Retting, Angew., et al. ;
   Chem. Int. Ed. Engl., **25,** 971 (1986).
6. Y. Ilichew, W. Kuhnle, K.A. Zachariasse. et. al. ;
   J. Phys. Chem. A.., **102,** 5670 (1998).
7. C. Cornelissen, W. Retting. ;
   J. Phys. Chem., A **102,** 7754 (2000).
8. W. Retting, B. Zietz. ;
   Chem. Phys. Lett., **317,** 187 (2000).
9. C. Ma, W.M. Kwok, P. Matousek, A.W. Parker. ;
   J. Phys. Chem., A **106,** 3294 (2002).
10. S. Dorairaj, H.J. Kim. ;
    J. Phys. Chem., A **106,** 2322 (2002).
11. M.M. Martin, P. Plaza, P. Chagenet-Barret. ;
    J. Phys. Chem., A **106,** 2351 (2002).
12. A.B.J. Parusel, W. Retting. ;
    J. Phys. Chem., A. **106,** 804 (2002).
13. J. Dobkowski, J. Wojcik, J. Michl, et al. ;
    J. Am. Chem. Soc., **124,** 2406 (2002).
14. Eul Kgun Yum, Ok-Kyung Yang. et al. ;
    *Bull. Korean Chem. Soc.,*Vol.**25,** , No.7. 1091 (2004).
15. Jin Sung Kim, Kye Jung Shin, Dong Chan Kim, et al. ;
    Bull. Korean Chem. Soc., Vol.**23,** 1425-28 (2002).
16. Foks H, Pancechowska-Ksepko D. et al. ;
    Acta Pol. Pharm., **61(6)**, Nov-Dec., 473-6 (2004).

17. Emmer G., Grassberger M.A., et al. ;
J. Med. Chem., **37 (13)**, Jun., 1908-17 (1994).
18. Medina-Gundrum L., Cerna C, Gomez L, et al. ;
Invest New Drugs, **23(1)**, Jan.; 3-9 (2005).
19. Maczynski M, Zimecki M, Ryng S. et al. ;
Acta Pol. Pharm., **61,** Dec., 82-3 (2004).
20. McGuigan C, Thiery J.C, Daverio F, Jiang W.G., et al. ;
*Bioorg Med. Chem.***13(9),** May., 3219-27 (2005).
21. Asproni B, Talani G., Busonero F, et al. ;
*J. Med. Chem.***, 48(7),** 2638-45 (2005).
22. Kramer W., Durckheimer W., Girbig F., Gutjahr U. ;
Biochim Biophys Acta. **1028 (2)**, Oct., 174-82 (1990).
23. Ciucci A., Manzini S., Lombardi P., Arcamone F. ;
*Nucleic Acids Res.,***24(2),** Jan; 311-5 (1996) .
24. Umekawa K., Hasegawa H., et al.;
Jpn. J. Pharmacol., **84(1)**, Sep., 7-15 (2000).
25. Randle J.C., Peglion J.L., Renaud J.F. ;
J. Cardiovasc Pharmacol. **17(2),** Feb. 348-50 (1991).
26. Jin Sung Kim., Kyung Ho Yoo. et al. ;
*Bull Korean Chem. Soc.,***Vol.23,** , 1425-1428 (2002).
27. Morton R. A. ;
Biochemistry of Quinones; Academic Press., ; New York, 1965.
28. Efimove G.A., Efros L.S. et al. ;
Zh. Org. Khim., **3,** 162 (1967).
29. Mauleon D, Pujol MD, Rosell G;
J.Med.Chem., **31(11)**, Nov; 2122-6 (1988).
30. Bakhite EA, Abdel-Rahman, Mohmed OS ;
Phamazie., **55(8),** Aug, 577-83 (2000).
31. Wen-Fq Kuo, I-Tzu Lin, Shiaw-Wen Sun, Mou-Yung.
J.Chin.Chem.Soc., **48,** 769-782 (2001).
32. Satyanarayana D, Gorge S, Subrahmanyam EV, Kalluraya B.
Boll.Chim.Farm., **140(4),** Jul-Aug; 228-32 (2001).
33. Renaud Capdeville, Elisabeth Buchdunger,et al. ;
Novartis Oncology, Novartis Pharma AG, **S-272,** 033.

34. Bucsh RA, Domagala JM, Laborde E, et al. ;
J.Med.Chem. **36(26)**, Dec., 4139-51(1993).

35. Hagen SE, Domagala JM, Gracheck SJ, et al. ;
J.Med.Chem., **37(6)**, Mar., 732-8 (1994).

36. G.W.Rewcastle, W.A.Denny, H.D.H. Showalter ;
*Current Organic Chemistry.,***4,** 679-706 (2000).

37. Hong CY, Kim YK, Chang JH, Kim SH, ;
J.Med.Chem., **40(22)**, Oct, 3584-93 (1997).

38. Imamori K, Asaoka T, MatsumotoM.
Jpn.J.Antibiot., **48(12)**, Dec., 1891-8 (1995).

39. Hyae Gyeong Cheon, Sung Soo Kim, et al. ;
Bull.Korean.Chem.Soc.,**Vol.25,** No.7,1091-1094 (2004).

40. G. M. Coppola and H. F. Schuster; *'In Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids',* Wiley; New York, (1987).

41. R. S. Coleman and W. Chem;
Org. Lett., **3** (2001) 1141.

42. G. M. Sheldrick, SHELX97,
'*Program for Crystal Structure Determination'*,
University of Gottingen, Germany, (1997)a.

43. G. M. Sheldrick, SHELX97,
'*Program for Refinement of Crystal Structure'*,
University of Gottingen, Germany, (1997)b.

44. M. J. Nardelli;
Appl. Cryst., **28** (1995) 659.

45. L. J. Farrugia, Molecular Graphics-ORTEP-3 for windows.;
J. Appl. Cryst. **30** (1997) 565.

46. J. Jean-Claude Bertrand, F. B. James and J. George;
Acta Cryst., **C49,** (1993) 1070.

47. Q. Yang, Y. Tang, W. Yang and H. Chen;
A*cta Cryst.,* **C54** (1998) 1532.

48. K. Chinnakali, Hoong-Kun Fun, K. Sriraghavan and Vaylakkavoor and T. Ramkrishnan.;
A cta Cryst., **C54** (1998) 955.

49. C. C. Ersanli C. Albayrak, M. Odabasoglu and A. Erdonmez.;
Acta Cryst., **C59** (2003) 6012.

50. G. J. Desiraju and T. Steiner.;
'*The Weak Hydrogen Bond',* IUCr, New York (1999).

51. F. P. Xavier, A. R. Inigo and G. J. Goldsmith;
J. Prophyrins Phthalocyanines, **3** (1999) 679.

52. V. N. Joshi.;
'*Photoconductivity',* Marcel Dekker, New York, 1990.

53. A. Joseph Arul Pragasam.;
Ph. D. Thesis, University of Madras, Chennai, India (2004).

54. P. A. Franken, A. E. Hill, C. W. Peters, and G. Weinreich.;
Phys. Rev. Lett., **17** (1961) 118.

55. http://physik.uni-graz.at/~sas/NLO/node1.html

56. E. Garmire.;
Physics Today, (1994) 23.

57. D. S. Chelma and J. Zyss.;
"Non-linear Optical Properties of Organic Molecules and Crystals', **Vol. 1-2.** Academic Press, Orlando.

58. S. Chenthamarai, D. Jayaraman, P. M. Ushasree, K. Meera, C. Subramanian and P. Ramasamy.;
Mat. Chem. Phys., **64** (2000) 179.

59. M. S. Wong, C. Bosshard, F. Pan and P. Gunter.;
Adv. Mater., **8**, (1996) 677.

60. V. G. Dmitriev, G. G.Gurzadyan and D. N. Nicogosyan.;
'*Handbook of Nonlinear Optical Crystals',* Springer- Verlag, New York, (1999).

61. M. N. Bhat, and S. M. Dharmaprakash;
J. Cryst. Growth, **236** (2002) 376.

62. N. Vijayan,, R. Ramesh Babu, M. Gunasekaran, K. Gopalkrishnan,et al; *J. Cryst. Growth,* **249** (2003) 315.

63. H. S. Nagaraja, V. Upadhyaya, P. Mohan Rao, A. P. Sreeramana.; *J. Cryst. Growth,* **193** (1998) 674.

64. M. Narayan Bhat and S. M. Dharmaprakash; *J. Cryst. Growth,* **243** (2002) 526.

65. S. Dhanuskodi and K. Vasantha; *Cryst. Res. Technol.*, **39 (3)** (2004) 259.

66. S. Dhanuskodi and S. Manikandan; *Cryst. Res. Technol.*, **39 (7)** (2004) 586.

67. F. Zernike, and J. E. Midwinter; '*Applied Nonlinear Optics,'* John Wiley and Sons, New York (1973).

68. P. D. Maker, R. W. Terhune, M. Nynenoff and C.M. Savage; *Phys. Rev. Lett.,* **8** (1962) 21.

69. R. C. Miller G. D. Boyd and A. Savage; *Appl. Phys. Lett.* **6** (1965) 77.

70. S. A. Rajasekar, K. Thamizharasan, A. Joseph, Arul Pragasam; *J. Cryst. Growth,* **247** (2003) 199.

71. Y. J. Ding and X. D. Mu, and X. Gu; *J. Nonlinear Opt. Phys.& Mater.,* **9** (2000) 21 .

72. X. W. Wang, D. Xu, M. K. Lu, D. R. Yuan, and S. X. Xu, *Mater. Res. Bull.,* **36** (2001) 879.

73. M. D. Aggarwal, J. Choi, W. S. Wang, K. Bhat, R. B. Lal, A. D. Shields,; *J. Cryst.Growth,* **204** (1999) 179.

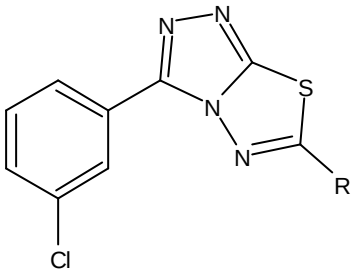
74. D. Eimerl, S. Velsko, L. Davis, F. Wang, G. Loiacono and G. Kennedy; *IEEE J. Quan. Electron.* **25** (1989) 179.

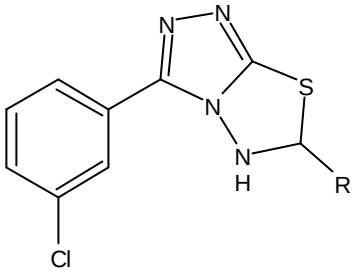
75. K. V. Rajendran, D. Jayaraman, R. Jayavel, and P. Ramasamy; *9th National Seminar on Crystal Growth',* Chennai, (2003).

76. V. M. Parikh; *"Absorption spectroscopy of organic molecule".* Addition Wesley Pub. Co. London, 243-256 (1978).

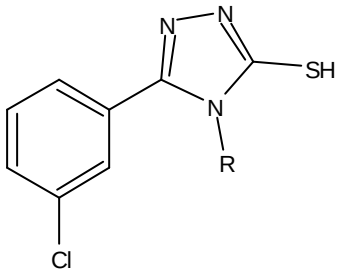
77. C. N. R. Rao; "*Chemical application of Infrared spectroscopy"* Academic ress, New York (1963).

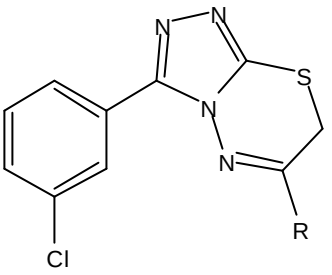
78. Silverstein Bassler and Morrill.; *Spectrometric identification of organic compounds* fifth edition (1991) by John Wiely & Sons Inc.



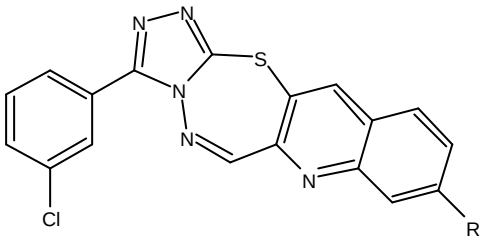


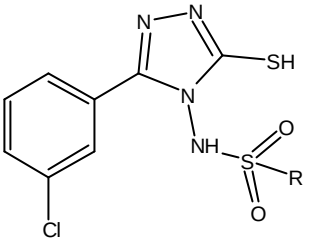
	R		R
T	4-OCH_3-C_6H_4-	**T**	4-OCH_3-C_6H_4-
T	2,4-$(OH)_{2-C6}H_4$-	**T**	3,4-$(OCH_3)_2$-C_6H_3-
T	2-CH_3-C_6H_4-	**T**	3-NO_2-C_6H_4-
T	3-OC_6H_5-C_6H_4-	**T**	2-NO_2-C_6H_4-
T	4-Br-C_6H_4--	**T**	4-OH-C_6H_4-
T	3-Cl-C_6H_4-	**T**	C_6H_5-
T	4-NO_2-C_6H_4-	**T**	3-Cl-C_6H_4-
T	3-NO_2-C_6H_4-	**T**	4--CH_3-C_6H_4-
T	4-C_5H_4N-	**T**	4-F-C_6H_4-
T	4-Cl-C_6H_4-	**T**	3-Cl-C_6H_4-
T	2-Cl-C_6H_4-	**T**	2-OH-C_6H_4-
T	2-Cl-C_6H_4-	**T**	3-OC_6H_5-C_6H_4-



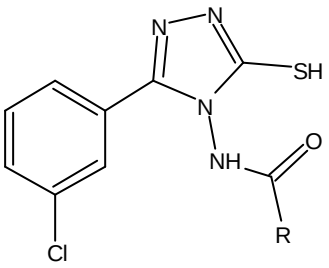


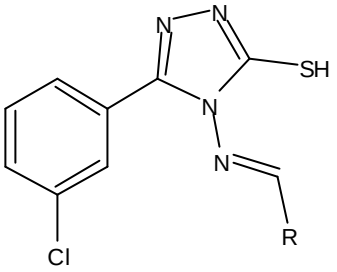
	R		R
T	2,5-$(Cl)_2$-C_6H_3-	**T**	4-Cl-C_6H_4-
T	3-NO_2-C_6H_4-	**T**	4-OCH_3-C_6H_4-
T	3-Cl-C_6H_4-	**T**	C_6H_5-
T	4--COOH-C_6H_4-	**T**	4 -NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-	**T**	2-OH-C_6H_4-
T	4-NO_2-C_6H_4-	**T**	4-F-C_6H_4-
T	3--COOH-C_6H_4-	**T**	4-SCH_3-C_6H_4-
T	2-NO_2-C_6H_4-	**T**	4-SO_2CH_3-C_6H_4-
T	3-Cl-4-F-C_6H_3-	**T**	4-CH_3-C_6H_4-
T	2-COOH-C_6H_4-		
T	4-CH_3-C_6H_4-		
T	4-CH_3-C_6H_4-		
T	4-NH_2-C_6H_4-		



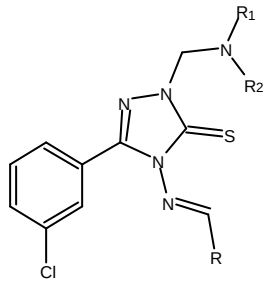


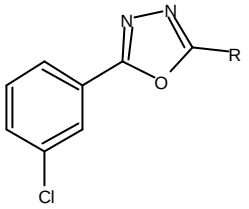
	R		R
T	H-	**T**	4-CH_3-C_6H_4-
T	6-Cl-	**T**	2,4-$(Cl)_2$-C_6H_3-
T	7-Cl-	**T**	3-CH=CH-COOH-C_6H_4-
T	6,8-$(CH_3)_2$-	**T**	4-F-C_6H_4-
T	6-OCH_3-	**T**	3-COOH-6-Cl-C_6H_3-
T	8-CH_3-	**T**	3-COOH-4-CH_3-C_6H_3-
T	6,7-$(Cl)_2$-	**T**	3-COOH-4-Cl-C_6H_3-
T	6-CH_3-	**T**	3-COOH-4-NO_2-C_6H_3-
T	6-Br-		



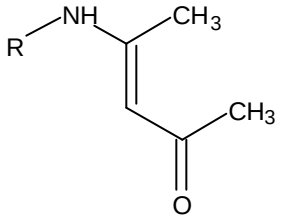


	R		R
T	4-OCH_3-C_6H_4-	**T**	4-OCH_3-C_6H_4-
T	2-CH_3-C_6H_4-	**T**	3-NO_2-C_6H_4-
T	4-Br-C_6H_4-	**T**	4-OH-C_6H_4-
T	4-NO_2-C_6H_4-	**T**	3-Cl-C_6H_4-
T	4-C_5H_4N-	**T**	4-F-C_6H_4-
T	2-Cl-C_6H_4-	**T**	2-OH-C_6H_4-
T	2,4$(OH)_2$-C_6H_3-	**T**	3,4-$(OCH_3)_2$-C_6H_3-
T	3-OC_6H_5-C_6H_4-	**T**	2-NO_2-C_6H_4-
T	3-Cl-C_6H_4-	**T**	C_6H_5-
T	3-NO_2-C_6H_4-	**T**	4-CH_3-C_6H_4-
T	4-Cl-C_6H_4-	**T**	4-NO_2-C_6H_4-
T	2-OH-C_6H_4-	**T**	3-OC_6H_5-C_6H_4-





	R	R_1, R_2		R
T	4-CH_3 -C_6H_4-	C_4H_8O-	**T**	4-OCH_3-C_6H_4-
T	2-CH_3 -C_6H_4-	C_4H_8O-	**T**	2,4-$(OH)_2$-C_6H_3-
T	3,4-$(OCH_3)_2$-C_6H_3-	C_4H_8O-	**T**	2-CH_3-C_6H_4-
T	4-OCH_3 -C_6H_4-	C_4H_8NH	**T**	3-OC_6H_5-C_6H_4-
T	2-OCH_3 -C_6H_4-	4-Cl-C_6H_4	**T**	4-Br-C_6H_4-
T	4-OCH_3 -C_6H_4-	4-Cl-C_6H_4	**T**	3-Cl-C_6H_4-
T	4-CH_3 -C_6H_4-	4-Cl-C_6H_4	**T**	4-NO_2-C_6H_4-
T	2-Cl-C_6H_4-	4-Cl-C_6H_4	**T**	3-NO_2-C_6H_4-
T	2-OCH_3 -C_6H_4-	C_4H_8N-CH_3	**T**	4-C_5H_4N
T	4-OCH_3 -C_6H_4-	C_4H_8N-CH_3	**T**	4-Cl-C_6H_4-
T	4-CH_3 -C_6H_4-	C_4H_8N-CH_3	**T**	2-Cl-C_6H_4-
T	2-Cl-C_6H_4-	C_4H_8N-CH_3	**T**	2-OH-C_6H_4-



	R
T	2-OH-C_6H_4-
T	4-OH-C_6H_4-
T	4-Cl-C_6H_4-
T	4-COOH-C_6H_4-
T	4-OCH_3-C_6H_4-
T	4-NO_2-C_6H_4-
T	3-COOH-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-Cl-4-F-C_6H_3-
T	3-OH-C_6H_4-
T	4-CH_3-C_6H_4-
T	2-CH_3-C_6H_4-