STUDIES ON CHEMICAL ENTITIES OF MEDICINAL INTEREST

A THESIS

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IN

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BY

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UNDER THE GUIDANCE

OF

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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.

Date: - -2010 ***(Kaushik A. Joshi)***
Place: Rajkot

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

Date: - -2010
Place: Rajkot

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Dedicated
To my beloved
parents

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(KAUSHIK A. JOSHI)

CONTENTS

[C] STUDIES ON IMIDAZO[1,2-α] PYRIDINES

Synopsis

The research work incorporated in the thesis with the title "**STUDIES ON CHEMICAL ENTITIES OF MEDICINAL INTEREST**" has been described as under the following parts.

PART[A] : STUDIES ON ISOPROPYL BENZOIC ACID DERIVATIVES

PART[B] : STUDIES ON THIOPHENE-2-CARBALDEHYDE DERIVATIVES

PART[C] : STUDIES ON IMIDAZO [1,2-α]PYRIDINE DERIVATIVES

PART [A] : STUDIES ON ISOPROPYL BENZOIC ACID DERIVATIVES

Isopropyl benzoic acid and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities. The synthesis of this moiety has received considerable attention in recent years. Isopropyl benzoic acid is also known as ***Cumic acid***.

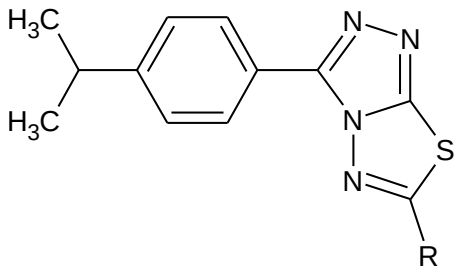
The chemistry of 1,2,4-triazole has assumed importance because of their versatility in the synthesis of many heterocyclic compounds. The synthesis of these heterocycles has received considerable attention in recent years.

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.

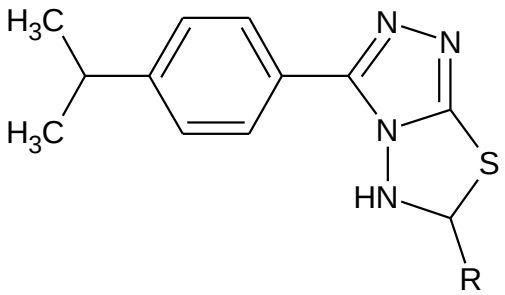
SECTION-I : Synthesis and biological screening of 6-Aryl-3-(4-isopropylphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles



Type (I) R= Aryl

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

SECTION-II : Synthesis and biological screening of 5,6 Dihydro-6-aryl-3-(4-isopropylphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles



Type (II) R= Aryl

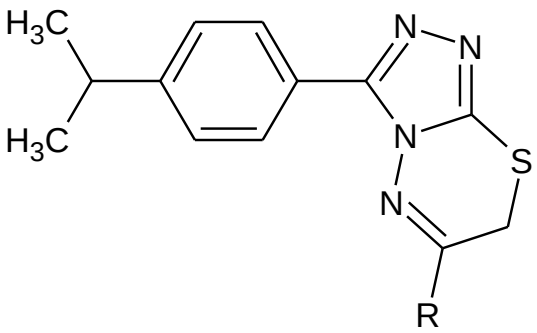
1,3,4-Thiadiazole derivatives of Type(II) have been synthesized by the condensation of 1-amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol with different aromatic aldehydes in the presence of p-toluenesulphonic acid.

PART-II : 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 screening of 6-Aryl-3-(4-isopropylphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines



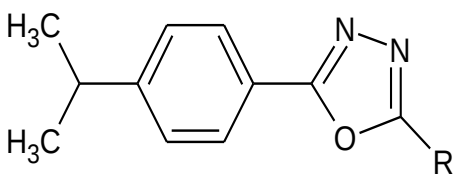
Type (III) R=Aryl

Thiadiazines of Type (III) have been synthesized by the condensation of 1-amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol with different substituted phenacyl bromides.

PART-III : 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 screening of 2-(4-Isopropylphenyl)-5-aryl-1,3,4-oxadiazoles



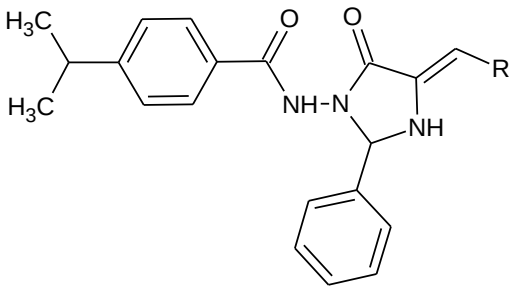
Type (IV) R=Aryl

Oxadiazoles of type (IV) have been synthesized by the cyclo condensation of isopropylbenzohydrazide with different aromatic acids in the presence of $POCl_3$.

PART-IV: STUDIES ON IMIDAZOLONES

The discovery of imidazolones as potent biologically active agent has led to the exploration of large number of structural variants, containing imidazolones moiety as an invariable ingredient. Its derivative have shown various biologically activities such as anathematic, antimicrobial, antihistamine, anti-inflammatory, antibacterial etc. in order to develop therapeutically important compounds, it was consider of interest to synthesize some imidazolones shown as under.

SECTION-I : Synthesis and biological screening of *N*-((*E*)-4-(Arylidene)-5-oxo-2-phenylimidazolidin-1-yl)-4-isopropylbenzamides



Type (V) R=Aryl

The synthesis of imidazolones of type–(V) have been under taken by the reaction of 4- isopropylbenzohydrazide with substituted azalactones which in turn have been prepared by well known Erlenmeyer azalactone synthesis.

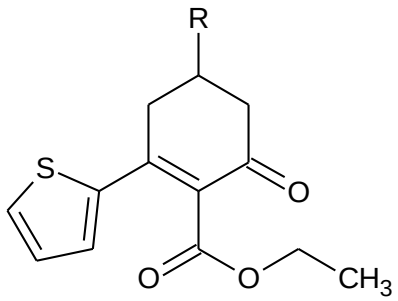
PART [B] : STUDIES ON THIOPHENE-2-CARBALDEHYDE DERIVATIVES

Heterocyclic compounds bearing thiophene-2-carbaldehyde ring system and their derivatives are demonstrates various biological and pharmacological activities. Our works are paying attention on introduction of chemical multiplicity in the molecular frame work, in order to synthesizing active molecules of widely different composition. Literature assessment reveals that sulfur containing heterocyclic compounds have acknowledged considerable attention in remedial science due to their biological and pharmacological activities such as anti-HIV, antitubercular, antimicrobial, anticonvulsant, anticancer, antiviral etc. Considering the increasing importance of thiophene-2-carbaldehyde nucleus, we have undertaken the synthesis of some new arylaminomethyl and oxadiazole derivatives bearing thiophene-2-carbaldehyde nucleus, which have been described as under.

PART - I : STUDIES ON INDAZOLES

Cyclohexenone and indazole derivatives have been found to be associated with various pharmacological activities such as antifungal, antibacterial, anticoagulant, antipyretic, anti-inflammatory etc., led by these considerations some new indazole have been synthesized which have been described as under.

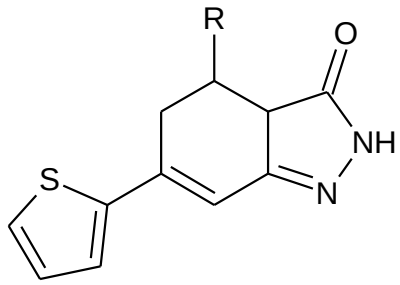
SECTION - I : Synthesis and biological screening of Ethyl 6-oxo-4-aryl-2-(thiophen-2-yl)cyclohex-1-enecarboxylates



Type (VII) R=Aryl

Cyclohexenone derivatives of Type-(VII) have been synthesized by the cyclocondensation of the chalcones of ethyl acetoacetate in presence of sodium ethoxide.

SECTION -II : Synthesis and biological screening of 4,Dihydro-4-aryl-6-(thiophen-2-yl)-2*H*-indazole-3(3a*H*)-ones



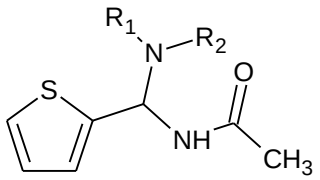
Type (VII) R=Aryl

Indazole derivatives of Type-(VIII) have been prepared by the condensation of cyclohexenone derivatives of Type-(VII) with hydrazine hydrate.

PART- II : STUDIES ON AMINOBENZYLATED MANNICH BASES

Mannich bases containing bridged head *N*-atom exhibit pronounced biological activities. It play an important role as intermediate in synthesis of various organic compounds.Mannich base also exhibit complexation characteristics with many transition metal atoms. Hence, it is pertient to synthesize some novel mannich base with a hope that these compound may have biological activies.

SECTION-I : Synthesis and biological screening of *N,N*-((Dialkyl/aryl amino)(thiophen-2-yl)methyl)acetamides



Type (VIII) R_1,R_2 =Aryl

The preparation of mannich bases of type (IX) has been under taken by the undertaken by the condensation of acetamide with secondary amine and thiophene-2-carbaldehyde.

PART [C] : STUDIES ON IMIDAZO[1,2-α] PYRIDINES

Heterocyclic compounds bearing imidazo[1,2-α]pyridine ring system are endowed with variety of biological activities. Our strategy is based on to develop new bioactive entities especially with pharmacological activities bearing heterocyclic ring system. Literature survey reveals that nitrogen containing heterocyclic compounds like imidazo[1,2-α]pyridines have received considerable attention in medicinal science due to their biological and pharmacological activities like anti-inflammatory, herbicidal, hypnotic, sedative, antimicrobial, antitubercular, CNS depressant, antithyroid and many other therapeutic activities.

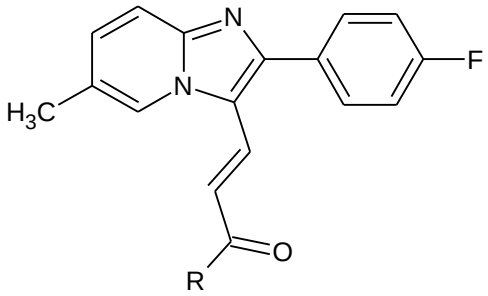
These valid observations prompted us to design and synthesize some heterocycles like chalcones, pyrazolines, cyanopyridines, mannich bases, pyrimidines, isoxazoles, imidazolinones etc., bearing imidazo[1,2-α]pyridine nucleus, which have been described as under.

PART-I : STUDIES ON PYRAZOLINES

Among a wide variety of heterocycles that have been explored for developing biologically active molecules like pyrazolines have played important role in medicinal

chemistry. Pyrazolines have been found to posses bactericidal, fungicidal, antiviral and other pharmacological properties like anticonvulsant, antidepressant and anti-inflammatory. These valid observations led us to synthesize some new pyrazoline derivatives for better drug potential which have been described in following sections.

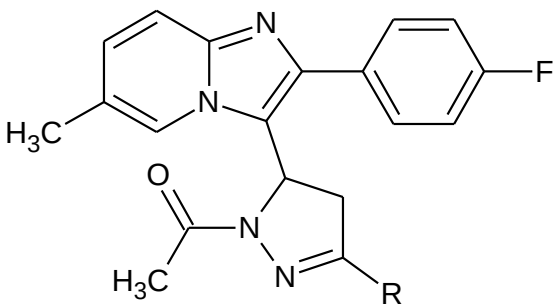
SECTION-I : Synthesis and biological screening of (2*E*)-3-(2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-1-arylprop-2-en-1-ones



Type (X) R= Aryl

The chalcones of Type(X) have been synthesized by the condensation of 2-(4-Fluoro phenyl)imidazo[1,2-α]pyridin-3-carbaldehyde with different aryl ketones in the presence of 40% NaOH.

SECTION-II : Synthesis and biological screening of 1-(5-(2-(4-fluorophenyl)-6-methyl-*H*-imidazo[1,2-α]pyridin-3-yl)-4,5-dihydro-3-arylpyrazol-1-yl)ethanones.



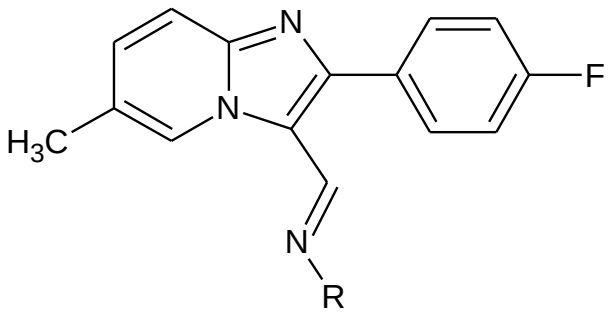
Type (XI) R= Aryl

Pyrazoline derivatives of Type(XI) have been synthesized by the cyclocondensation of the chalcones of Type (X) with hydrazine hydrate in glacial acetic acid.

PART-II : STUDIES ON ARYLAMINOMETHYL DERIVATIVES

Arylaminomethyl derivatives represents one of the modest class of biological active agents which have been deeply studies during search on new potential agents. These have been reported to be active as antimicrobial, antitubercular, anticancer, insecticidal etc. In view of these valid observations, it was contemplated to synthesis some new arylaminomethyl derivatives possessing higher biological activity which have been described as under.

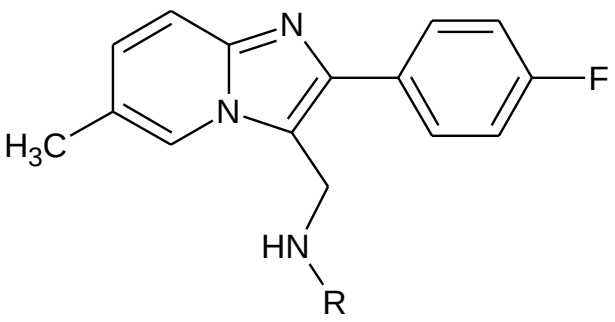
SECTION-I :Synthesis and biological screening of (*17E*)-*N*-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-arylamines.



Type (XII) R= Aryl

The azomethines of Type (XII) have been prepared by the condensation of 2-(4-Fluorophenyl)imidazo[1,2-α]pyridin-3-carbaldehyde with different aromatic amines.

SECTION-II :Synthesis and biological screening of *N*-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)methyl)-4-arylamines.



Type (XIII) R= Aryl

The compound of Type (XIII) have been synthesized by the reaction of arylamines of Type (XII) with an. $NaBH_4$.

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

All the compounds have been evaluated for their antibacterial activity towards *Gram +ve* and *Gram -ve* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration 2000/1000/500 µg/ml. The biological activities of the synthesized compounds have been compared with standard drugs.

Studies on Chemical Entities of Medicinal Interest

INTRODUCTION

Research programs for the discovery of new drugs and for improving the evolution criteria are under way in many laboratories. In addition knowledge of specific constituents of the mycobacterium cell and their biochemical roles have advanced considerably in the recent years and may permit a more rational approach to the design of new drug action on specific targets. Also, recent improvements in the knowledge of the mechanism of action of available drugs and the biochemical mechanism of resistance to them may be used as a basis for design new and better weapons to fight the mycobacterium diseases.

The last few decades have witnessed massive advances in biochemistry, physiology, pharmacology and genetics. This has to a better understanding of working the body at the molecular level. This in turn has resulted a much better understanding of the structure and function of important drug targets e.g. enzymes and receptors and that how drugs can be designed for these targets. Advances in organic chemistry have made possible the synthesis of complexes molecules. Enantiometry is an important process in medicinal chemistry since life is inherently chiral and the drug targets within the body are chiral. As such, they can distinguish between the enantiomers of a chiral drug, so the use of recemic drug is inherently wasteful, since only one enantiomer is ideally designed to interact with its target. Moreover, the existences of the “wrong” enantiomer could create problems if it interacted with a different receptor, resulting inside effects.

A prerequisite for the design of safe drugs is knowledge about the various metabolic reactions that xenobiotics and endogenous compounds undergo in the organism. Because pharmacological activity depends on molecular structure, the medicinal chemist is restricted in the choice of functional groups for the design of new drugs. Often he finds or she encounters a situation where a structure has adequate pharmacologic activity but has an inadequate

pharmacokinetic profile (i.e., absorption, distribution, metabolism and excretion). This is because pharmacology and pharmacokinetic departments in the pharmaceutical industry often do not collaborate at the early stage of drug development. It is only later, when the new compound is tested in animals or in humans, that pharmacokinetic disadvantages become obvious.

Modern drug discovery starts with the identification of a pharmacologic target that is hypothetically the primary cause of disease. Potential targets include host cell genes, receptors, signaling systems, organelles and biochemical such as enzymes. Additionally, an element of a disease modifying process, such as anti-inflammatory mediator, may be a target. Biological processes required for propagation of infectious agents have also proven to be therapeutically useful targets; examples include protease and reverse transcriptase of the human immuno deficiency virus (HIV). Common to all targets selected as therapeutic opportunities is the hypothesis that some type of pathogenetic linkage exists to the disease causing process, rather than to specific signs, symptoms, or effects.

Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity and provides false synthons in biosynthetic process or block the normal functioning of biological receptors. The inhibition of amide resonance resulting into more susceptibility of ß-lactam to nucleophile is considered at least in part responsible for antibacterial property, apparently by acetylating transpeptidase and thus inhibiting bacterial cell wall biosynthesis.

Most of the alkaloids which are nitrogenous bases occurring in plants and many antibiotics including penicillin and streptomycin have also heterocyclic ring system. Many natural pigments such as indigo, hemoglobin and anthocyanin are heterocycles. Most of the sugars are their derivatives including Vitamin C for instance, exist largely in the form of five

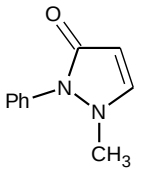
membered. Vitamin B_6 (Pyridoxine) is a derivative of pyrimidine essential in amino acid metabolism.

Important drugs, poisons and medicines (both natural and synthetic) such as sulphathiazole, pyrenthrin, rotenmone, alpidem, zolpidem, fluconazole, strychnine, reserpine, certain of the antihistamines, the ergot alkaloids caffeine, cocaine, barbiturates, etc. are heterocyclic compounds.

Research in the field of pharmaceutical has its most important task in the development of new and better drugs and their successful introduction into clinical practice. Central to these efforts, accordingly stand the search for pharmaceutical substances and preparation which are new and original. In addition to these objectives the searching for drug which exhibit a clear advantage over a drug already known. Such advantages may be qualitative or quantitative improvement in activity, the absence of undesirable side effect, a lower toxicity, improved stability or decreased cost. It is important at the outset to note that drug discovery is not an unambiguous term in the pharmaceutical Research and Development world. For example, it can be defined using either programmatic or organizational approaches (or both), with several options on each category. Hence, it is important first to understand this variability and to adopt a specific definition for the purpose of this discussion.

During the period of 1930-1950 there was an urgent need for new drug to treat disease which had a high mortality rate, there was only limited appreciation of the hazard such drugs might present, and toxicological studies before clinical trials were fairly rudimentary. Proving the proverb ***Necessity is the mother of invention***, during the decade of 30 and 40s a large number of drugs introduced. Therefore this period is regarded as ***Golden Period*** of new drug discovery.

The contribution of organic chemistry to be development of scientific medicine in the 19th century mainly from acyclic and carbocyclic compounds, although the pyrazoline antipyrin (1) was introduced as an antipyretic and analgesic in 1984 and the first barbiturate baritone (veranol) (2) in 1903. Guttmann treated, malaria with methylene blue in 1891, with slight success, and in 1912 he introduced acriflavine as trypancide, it has proved to be more valuable as an antiseptic. Phenazopyridini (pyridium) (3) was introduced for the same purpose in 1926, and although it is relatively ineffective it has continued to be used since it has some analgesic action.



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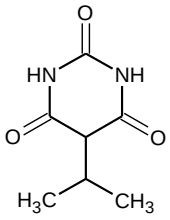

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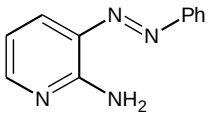


(3)

AIM AND OBJECTIVES

Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing isopropylbenzoic acid, thiophene-2-carbaldehyde and imidazo[1,2-α]pyridine nucleus. The placements of a wide variety of substituents on these nuclei have been designed in order to evaluate the synthesized products for their pharmacological profile against selected strains of bacteria and fungi. During the course of our work, looking to the application of heterocyclic compounds, several entities have been designed, generated and characterized using spectral studies. The details are as under.

[1] To generate several derivatives of Isopropyl benzoic acid and their fused derivatives such as Thiadiazoles, Thiadiazines, Oxadiazoles, Imidazolones.

[2] To generate Chalcones, Indazoles and Mannich base derivatives.

[3] To generate Acetyl pyrazoline and Arylaminomethyl derivatives like Schiff's base and it's reduction.

[4] To check purity of all synthesized compounds using thin layer chromatography.

[5] To characterize these synthesized products for structure elucidation using various spectroscopic techniques like IR, ^{1}H NMR, mass spectral studies and C, H, N analysis.

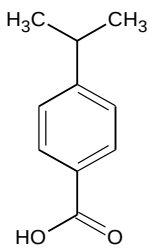
[6] To evaluate these new synthesized products for better drug potential against different strains of bacteria (*Staphylococcus aureus, Bacillus substilis, Escherichia coli, Salmonella Paratyphi*) and fungi (*Aspergillus niger, Candida albicans*).

Part- A

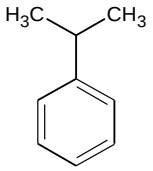
Studies on Isopropyl Benzoic Acid Derivatives

INTRODUCTION

Isopropyl benzoic acid (1) and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities. The synthesis of this moiety has received considerable attention in recent years. Isopropyl benzoic acid is also known as cumic acid or cuminic acid and cumin (2) has also known as Jeera.



(1)



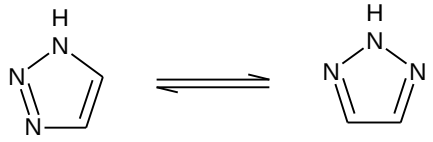
(2)

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. Triazoles have occupied an important place in the drug industry. 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.

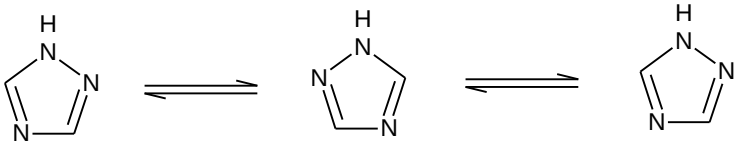
During our prior art studies we observed research carried on the triazoles of isopropyl benzoic acid. We found that triazoles of isopropyl benzoic acid have not been synthesized yet. Thus taking into the consideration that probably the synthesized compounds may prove to be very potent analgesic, anticoagulant, anti-inflammatory, antipyretic agents. For the same purpose we carried out some microbial studies which

are showing some positive results.

Triazoles are of two types 1,2,3-triazole (3) and 1,2,4-triazole (4).



1,2,3-Triazole (3)



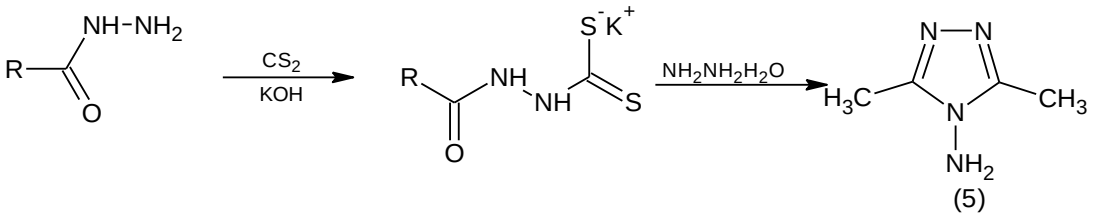
1,2,4-Triazole (4)

Hao Z[1] and Staben Steven[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

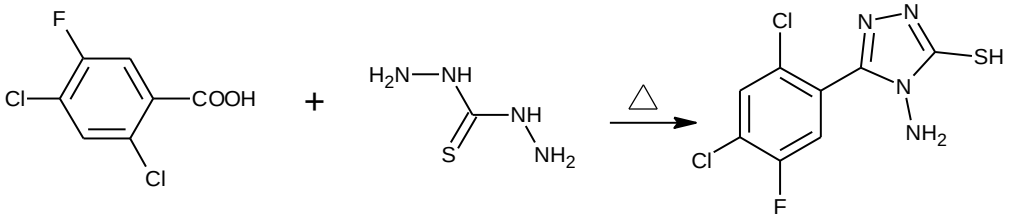
Several methods have been reported in the literature for the synthesis of 1,2,4-triazoles. The starting material for the synthesis of triazoles is thiosemicarbazide or dithiocarbamate derivatives having nitrogen containing functions. The procedures for synthesizing 1,2,4-triazoles have been described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

1. Reid and heindel[10] reported that the reaction of aryl acid hydrazide with CS_2/ KOH and hydrazine hydrate yields triazoles (5).



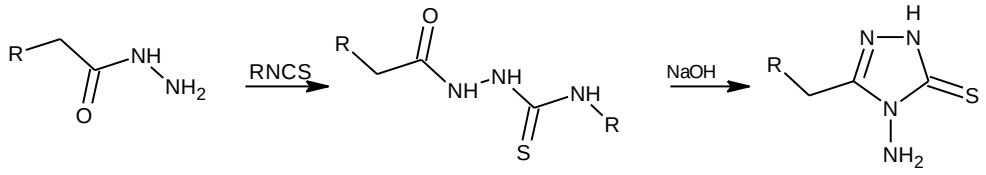
(5)

2. K. S. Bhat et al.[11] have synthesized 4-amino-3-(2,4-dichloro-5-fluorophenyl) 1,2,4-triazol-5-thiol (6) with the help of thiocarbohydrazide and 2,4 dichloro-5 fluoro benzoic acid.



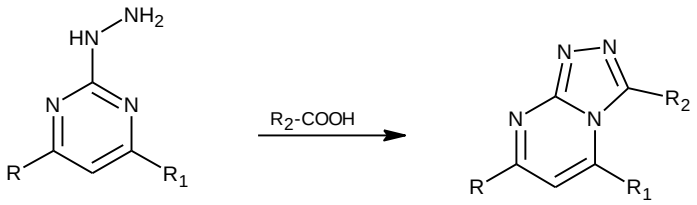
(6)

3. N. U. Guzeldemirci et al.[12] have prepared 1,2,4 triazole (7) in the presence of NaOH from aryl acid hydrazide.



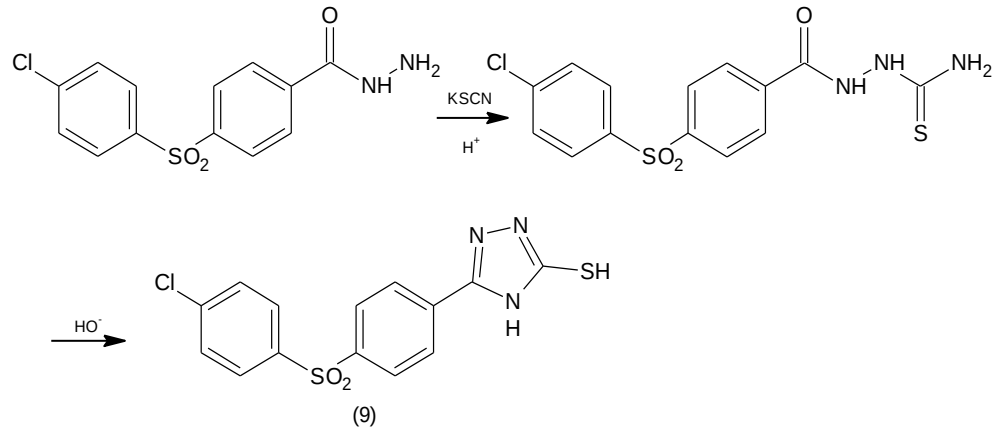
(7)

4. C. S. Andotra and Sukhbinder Kaur[13] synthesized triazole pyrimidine (8) by the reaction of aromatic acid with substituted hydrazino pyrimidines.



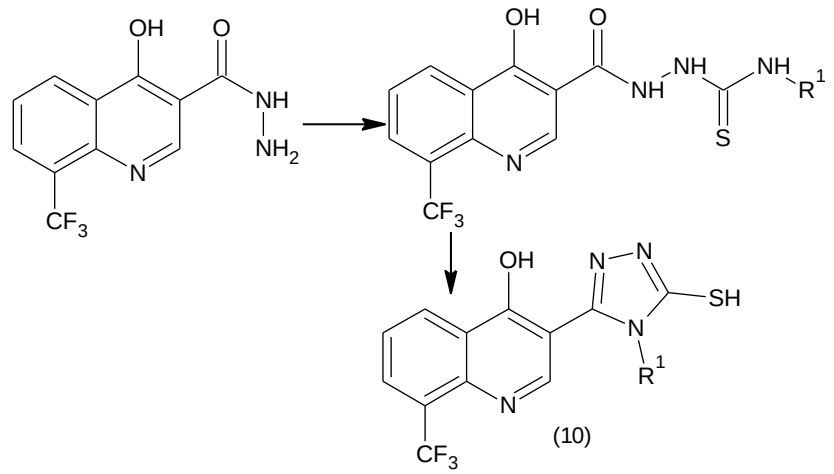
(8)

5. S. F. Barbuceanu et al.[14] have reported 5-[4-(4-chlorophenylsulfonyl)phenyl]-4*H*-1,2,4-triazole-3-thioles (9) and It is prepared from 4-(4-chlorophenylsulfonyl)-benzoic acid hydrazides.



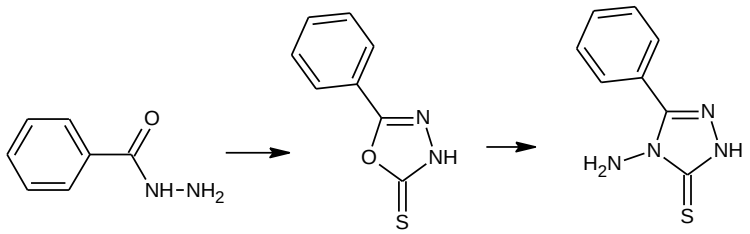
(9)

6. Sumesh eswaran et al.[15] also synthesized 1,2,4 triazole (10) from 4-hydroxy-8-(trifluoromethyl)quinoline-3- carbohydrazide.



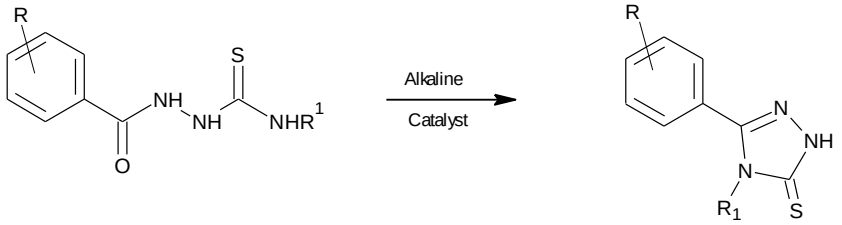
(10)

7. Zhizhang Li[16] prepared the sulphhydryl derivative (11) of 1,2,4-triazole by the reaction of 4-amino-5-phenyl-2*H*-1,2,4-triazole-3(4*H*)-thione.



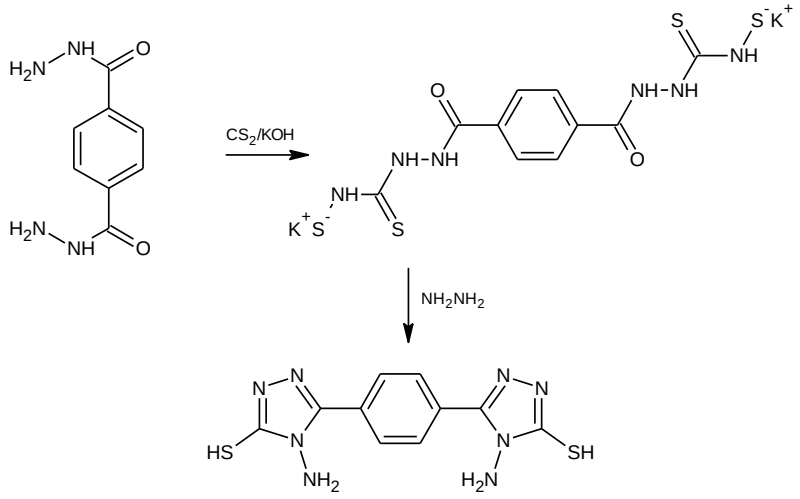
(11)

8. L. Labanauskas et al.[17] have prepared triazoles (12) 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.



(12)

9. Vikrant S. Palekar et al.[18] have prepared 1,4-phenylenebis(4-amino-4*H*-1,2,4-triazole-3-thiol) (13) from bis-dithiocarbazinate in the presence of potassium hydroxide, carbon disulphide and hydrazine hydrate.

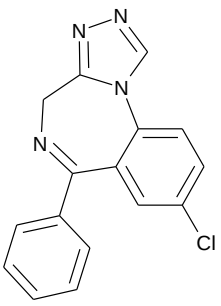


(13)

BIOLOGICAL EVALUATION

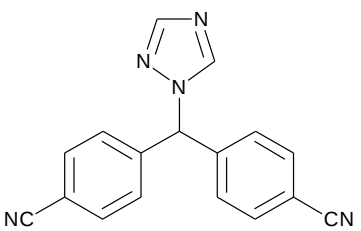
Triazoles are potential bioactive agents due to their wide spectrum of therapeutic importance. Drug molecules having 1,2,4-triazole nucleus with good activity are listed as under.

1. Estazoalm



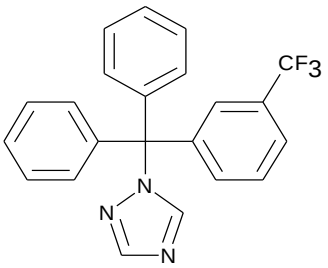
Receptor Agonist

2. Letrozole



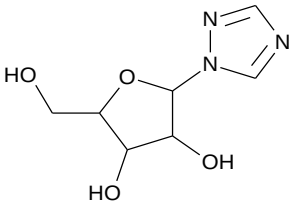
Antineoplastic

3. Fluotrimazole



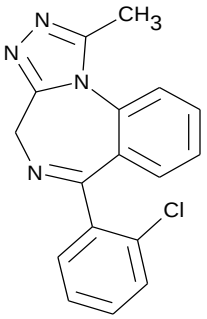
Fungicide

4. Rifavirin



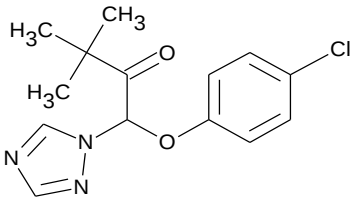
Antiviral, Antiinfection

5. Triazolam



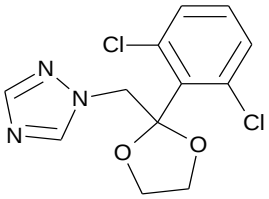
Plant growth regulator

6. Triadimenol



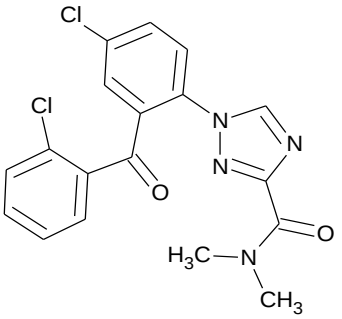
Fungicide

7. Azaconazole



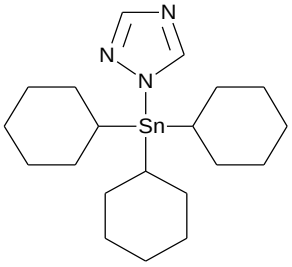
Antifungal

8. Rilmazafone



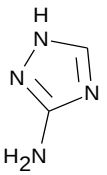
Sedative,hypnotic

9. Azocyclotin



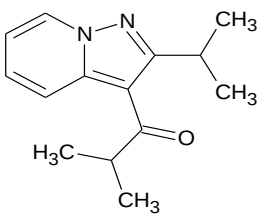
Pesticide

10. Amitrole



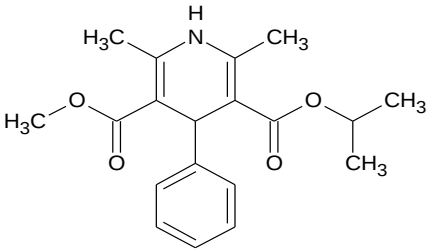
Antithyroid activity

11. Ibudilast



Antiallergic

12. Isradipine

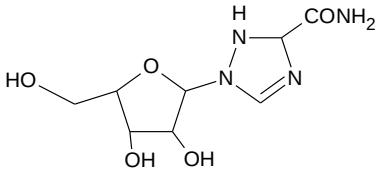


Antagonist

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 amino guanidine format, 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[28,29]
10. Antidepressant and anxiolytic[30]
11. Antimicrobial[31]
12. Antiviral[32]
13. Antiinflammatory[33]
14. Antihypertensive[34]
15. Anticonvulsant[35]

B. Kahveci et al.[36] have prepared 4-arylmethylideneamino-3-(R- benzyl) -4,5-dihydro-1*H*-1,2,4-triazol-5-ones via microwave assisted which exhibited remarkable anti fungal activity. Ram Janam Singh et al.[37] have synthesized 4-aryl-5-(isomeric pyridoyl)-3*H*-1,2,4-triazoles as potent bacteriocidal agents which active against *S. aureus, E. coli, B. subtilis* and *P. aeruginosa*. Najim A. Al-Masoudi et al.[38] have suggested 5-amino-4-phenyl-4*H*-1,2,4-triazole-3-thiol and their metal complexes which posses *vitro* anti-HIV activity. E. De Clercq et al.[39] screened ribavarin (14) for their antiviral and antimetabolic activities.



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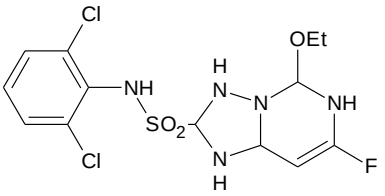
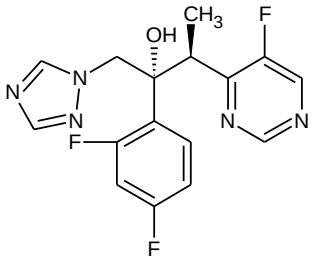


(15)

Hoong-Kun Fun et al.[40] have investigated 4-Amino-3-(1-naphthyloxymethyl)-1*H*-1,2,4-triazole-5(4*H*)-thione. B. Kahveci et al.[41] have suggested 3-aryl-4-arylmethylideneamino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones derivatives useful as an antifungal agents. Mckendry and co-workers[42] have synthesized triazole derivatives (15) and reported them as broad spectrum broadleaf herbicides. H. A. Abdel-Aziz et al.[43] have synthesized some piperidine-based 1,3-thiazole, 1,3,4-thiadiazole, and 1,3-thiazolo[2,3-*c*]-1,2,4-triazole derivatives which posses anti-arrhythmic activity. B. F. Abdel-Wahab et al.[44] have reported 1,2,4-triazoles useful for antimicrobial agent.

R. P. Dickinson and co-workers[45] have prepared Voriconazole (16) and found highly active against *Aspergillus fumigatus* and *a*-(hetero-arylmethyl)-1*H*-1,2,4-triazole-1-ethanol derivatives (17) are active against *Candida albicans* and *Cryptococous neofermans*.



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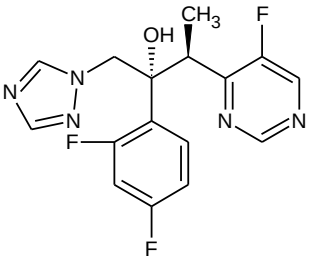
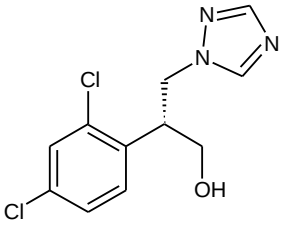


(17)

Daniele Binchi et al.[46] have screened pure stereoisomer of two new triazole derivatives (18,19) for their antifungal activity against variety of fungi showing an activity ratio R-form / S-form up to 400.



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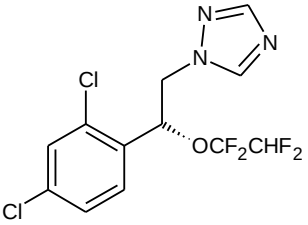
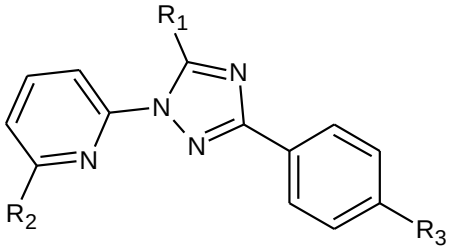


(19)

M. A. Kaldrikyan et al.[47] have discovered some benzofuryl-substituted 1,2,4-triazoles and reported their antitumor activity. Dae-Kee Kim et al.[48] have been synthesized 1,2,4-triazole derivatives (20) and screened for their significant ALKS inhibitory activity. K. J. Fisher et al.[49] have synthesized 1,2,4-triazole derivatives (21) to study their pesticidal and herbicidal activity. Xiang-Shu Cui et al.[50] have formulated 3-substituted-4-(4-hexyloxyphenyl)-4*H*-1,2,4-triazoles as anticonvulsa-nt agent. Maarouf et al.[51] have documented analgesic and anti-inflammatory activity of 1,2,4-triazole derivatives.



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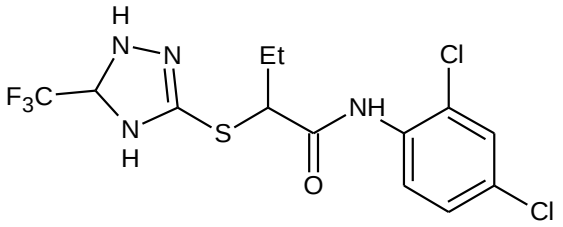


(21)

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

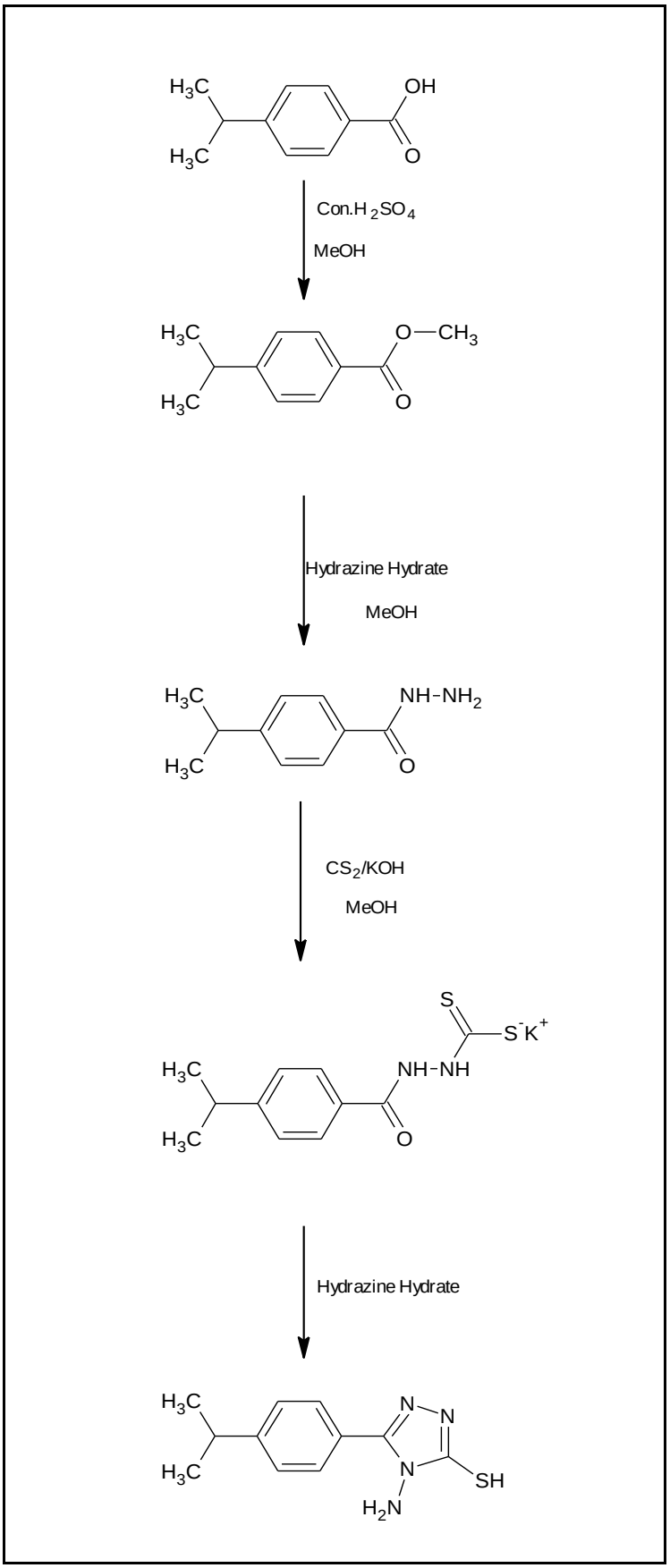
PART-I : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF THIADIAZOLES.

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

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

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

REACTION SCHEME



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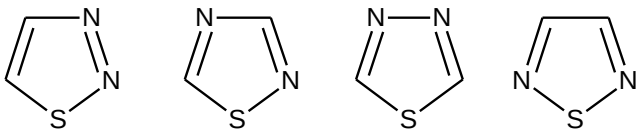
Part- A

(Part-I)

Studies on 1,3,4-Thiadiazole Derivatives

INTRODUCTION

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



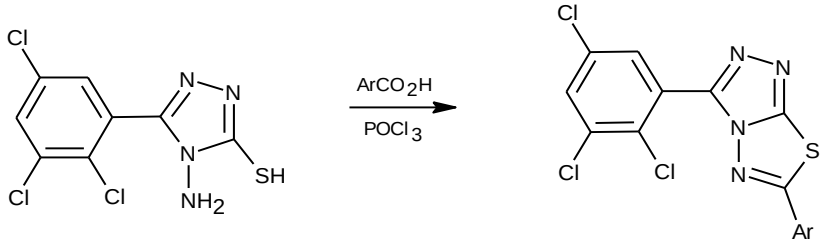
(1) (2) (3) (4)

Among these four types of thiadiazole, 1, 3, 4-thiadiazole is well known. 1,3,4-Thiadiazole is used to formulate finished greases, lubricating oils, gear, automatic transmission. It is used as an ash less copper corrosion inhibitor and extreme pressure (EP) agent.

SYNTHETIC ASPECT

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

1. Prakash Karegoudar et al.[3] have prepared thiadiazole derivatives (5) by the cyclization of aromatic acid with triazole in presence of $POCl_3$



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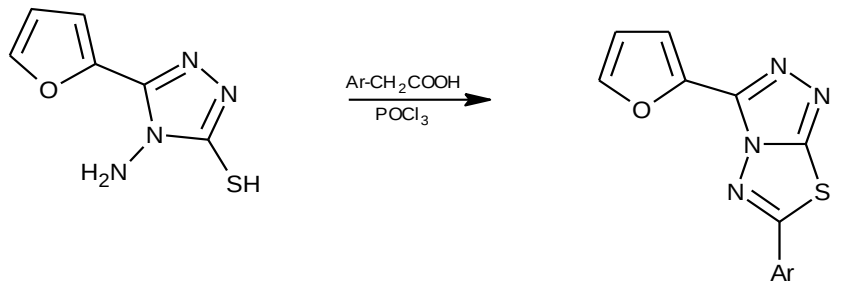
2. Li-xue Zhang et al.[4] have synthesized 1,3,4-thiadiazoles (6) by the cyclization of aromatic acid with triazole in presence of $POCl_3$.



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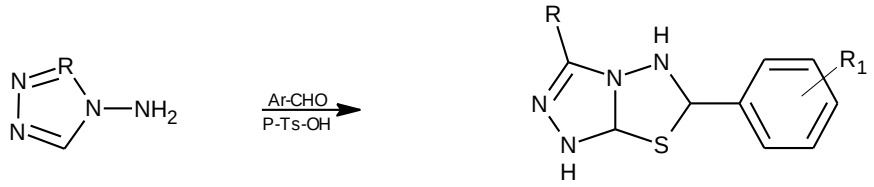
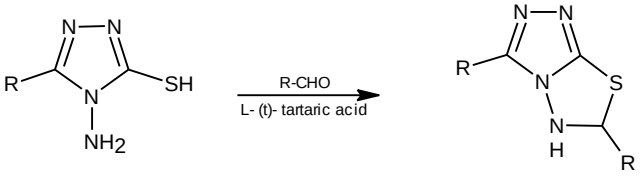
3. Jag Mohan et al.[5] have prepared thiadiazole derivatives (7) by the cyclization of amino mercapto triazole and aryl aldehydes in presence of p-Ts-OH.



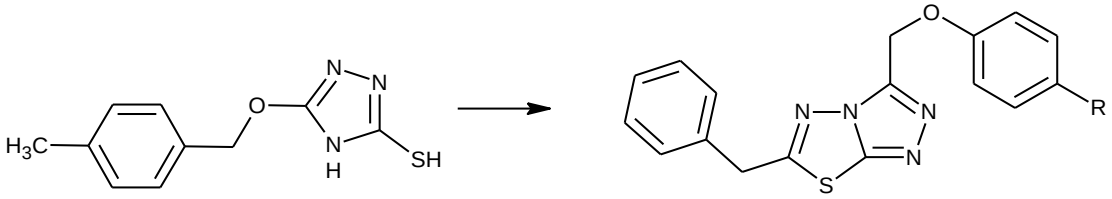
(7)

4. Zhong-Yi et al.[6] have been prepared thiadiazole derivatives (8) from amino mercapto triazole and aryl aldehydes in presence of L-(+)-tartaric acid.

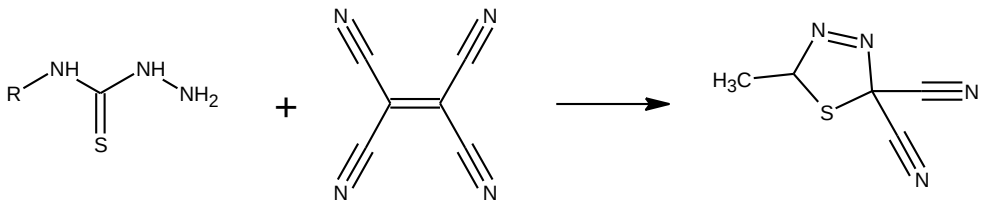


(8)

5. Q. Bano and co-workers[7] have been prepared 6-phenyl amino-1,3,4-thiadiazole (9) by reacting triazole with amino acid.



6. Alaa Hassan et al.[8] have prepared 1,3,4-thiadiazoles (10) by the cyclization of tetracyanoethene and 4-phenyl thiosemicarbazides.



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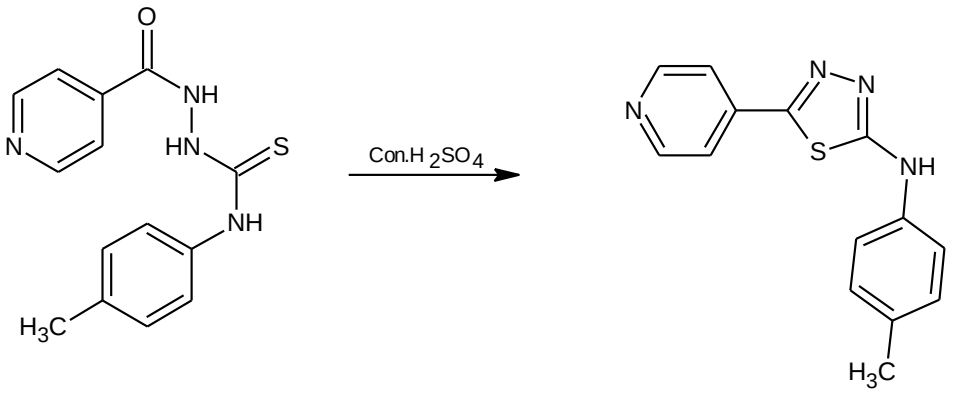
7. Khosrow Zamani et al.[9] have prepared thiadiazoles (11) from the thiosemicarbazide by the cyclization in sulphuric acid.



(11)

BIOLOGICAL EVALUATION

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. Antiinflammatory[14]
6. Antitubercular[15]
7. Antipyretic[16]
8. Anticancer[17]
9. CNS depressant[18]

10. Antischistosomal[19]

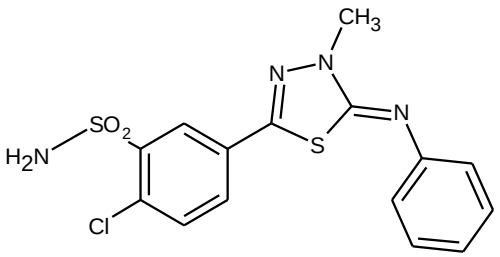
11. Herbicidal[20]

12. Insecticidal[21]

13. Pesticidal[22]

14. Hypoglycemic[23]

Vergne Fabrice et al.[24] have synthesized 1,3,4-thiadiazole derivatives (12) and screened for their anti-inflammatory, anticancer and anti-HIV activity. Laddi U.V. et al.[25] have discovered thiadiazoles possessing antimicrobial and antituberculosis activity. D.A. Ibrahim[26] has reported thiadiazoles as anti-tumor agents. Mohd. Amir et al.[27] have investigated 1,3,4-thiadiazoles and tested for analgesic activity. Vinod Mathew et al.[28] have prepared thiadiazole derivatives showed antifungal and antibacterial activity.



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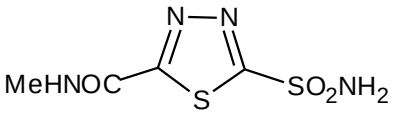
Celine Chazalete et al.[29] have synthesized acetazolamide (13) possessing diuretics and antiglaucoma activity. V S. Palekar et al.[30] have synthesized 1,3,4-thiadiazole derivatives and screened for their anti-inflammatory, antibacterial activity. C. X. Tan et al.[31] have investigated 1,3,4-thiadiazoles and tested for electrochemical properties. 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 (14) as strong anticonvulsant.



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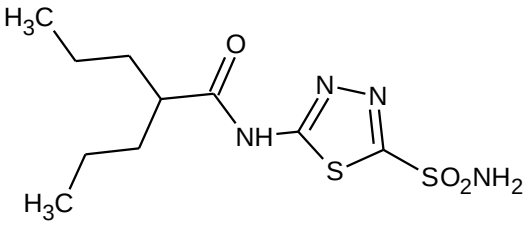

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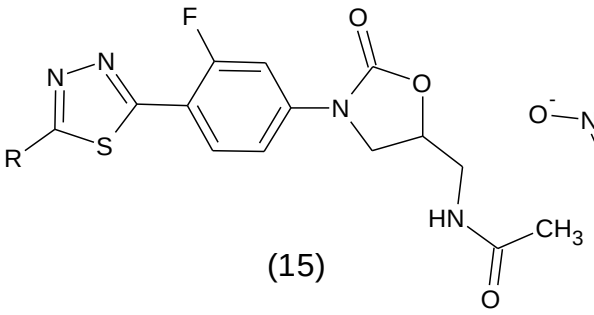
T M. Abdel-Rahman[33] has prepared 1,3,4-thiadiazole derivatives and possessing anticancer activity. A. M. Taha[34] synthesized thiadiazoles containing anti-microbial activity. J. M. Colacino et al.[35] have documented anti-influenza virus activity of thiadiazoles. L. M. Thomasco et al.[36] have prepared 1,3,4-thiadiazole (15) possessing potent antibacterial activity against Gram positive and Gram negative organisms. S. A. Carvalho and co-workers[37] have documented antitrypanosomal profile of 1,3,4-thiadiazole derivatives (16). Zahra Kiani et al.[38] have discovered thiadiazoles as antituberculosis agent.



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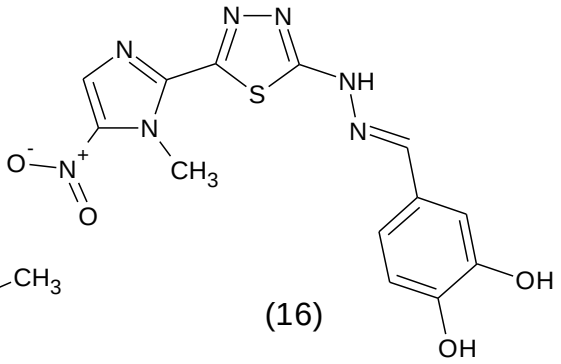
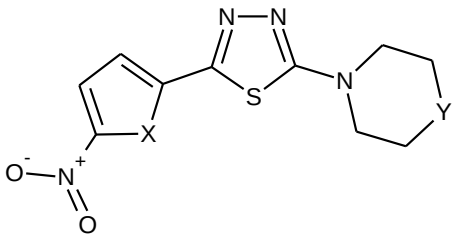


(16)

Alireza faroumadi et al.[39] have synthesized 1,3,4-thiadiazoles (17) 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.



(17)

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.

Work done from our laboratory

K. M. Thaker[45] have synthesized 2-(3',5'-dichlorobenzo[*b*]thiophen-2'-yl)-5-arylamino-1,3,4-thiadiazoles from triazole. S. L. Vasoya[46] have synthesized some new thiosemicarbazide and 1,3,4-thiadiazole heterocycles bearing the benzo[*b*]thiophene nucleus as potent antitubercular and antimicrobial agents.

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

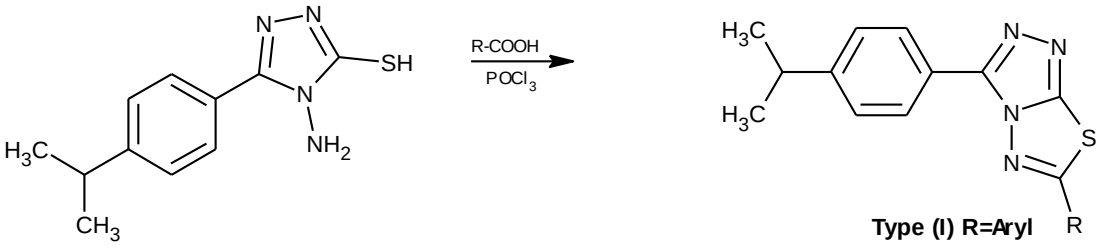
SECTION-I: SYNTHESIS AND BIOLOGICAL SCREEINING OF 6-ARYL-3-(4-ISOPROPYLPHENYL)-[1,2,4]TRIAZOLO[3,4-*b*] [1,3,4] THIADIAZOLES.

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

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ARYL-3-(4-ISOPROPYL-PHENYL)-[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 1-amino-3-[4-(propan-2-yl) phenyl]-1*H*-1,2,4-triazole-5-thiol with different aromatic acids in the presence of $POCl_3$ as shown in reaction scheme.



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, Candida albicans*** at a concentration of 2000/1000/500 µg/ml. The biological activities 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 Table No.1b.

ANTIMICROBIAL ACTIVITY

Method : Mueller Hinton Agar Medium Method[51]

Gram Positive Cocci : *Staphylococcus aureus*

Gram positive Rods : *Bacillus subtilis*

Gram Negative Rods : *Escherichia coli, Salmonella Paratyphi*

Multicellular Fungi : *Aspergillus niger*

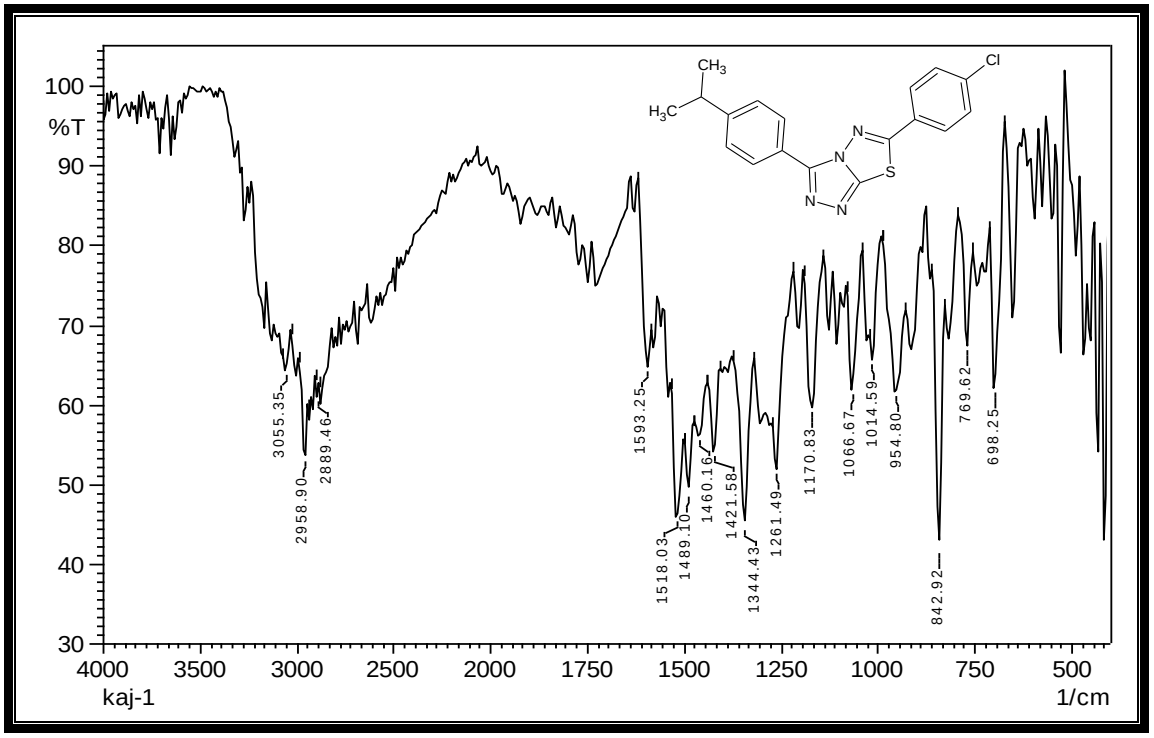
Unicellular Fungi : *Candida albicans*

Concentration : 2000 µg / ml, 1000 µg / ml, 500 µg /ml

Solvent : DMSO

Standard drugs : Ciprofloxacin

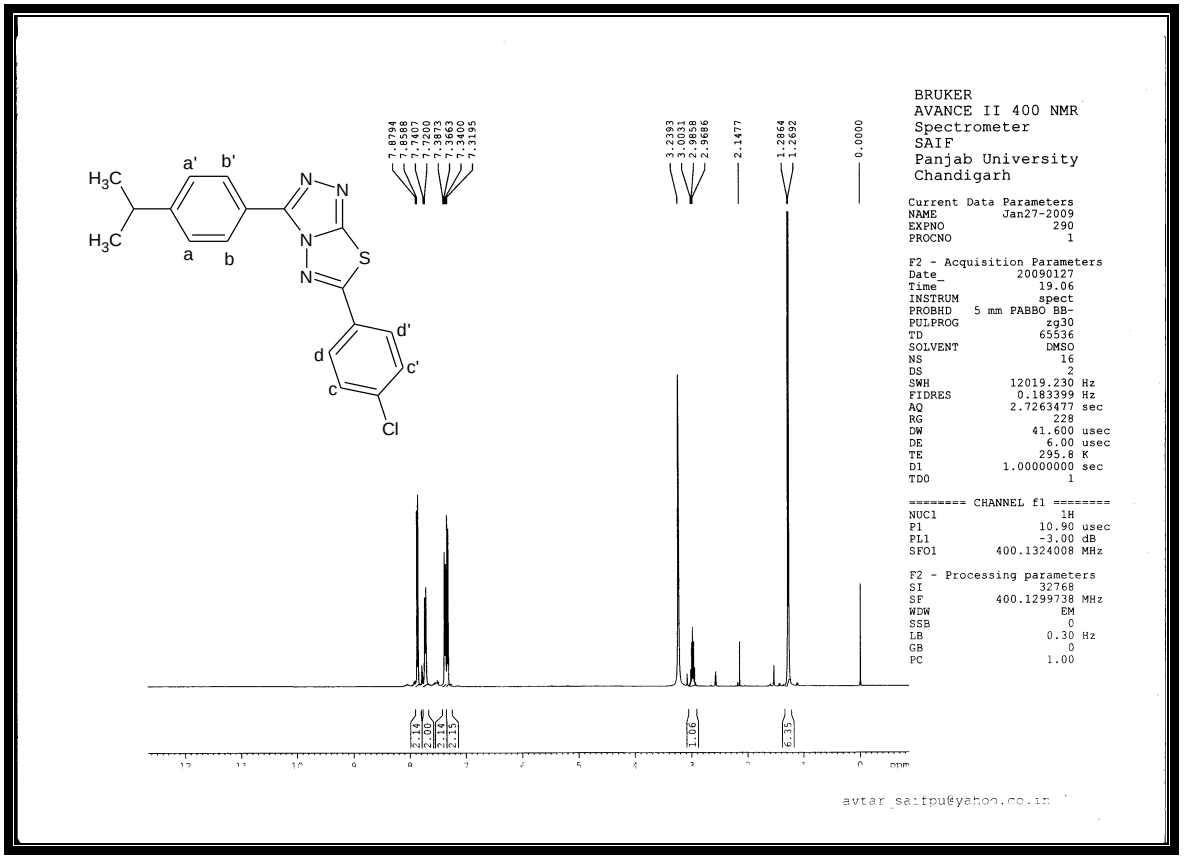
IR SPECTRAL STUDIES OF 6-(4-CHLOROPHENYL)-3-(4-ISOPRO PYLPHENYL)- [1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2958	2975-2950	47
	C-H str.	2889	2880-2860	49
	C-H def.	1460	1470-1435	47
	C-H def.	1344	1385-1370	50
Aromatic	C-H str.	3055	3080-3030	47
	C=C str.	1518	1585-1480	47
	C-H i.p. (def)	1066	1145-1090	50
	C-H def. (sym.)	1014	1070-1000	50
Isopropyl	$-CH(CH_3)_2$	2889	2800-2900	48
Triazole	C=N str.	1593	1612-1593	47
	C-N str.	1344	1380-1310	48
	C-N-C str.	1170	1146-1132	47
	N-N str.	1014	1050-1010	49
Thiadiazole	C-S-C str.	698	720-570	47
Halide	C-Cl str.	769	800-600	49

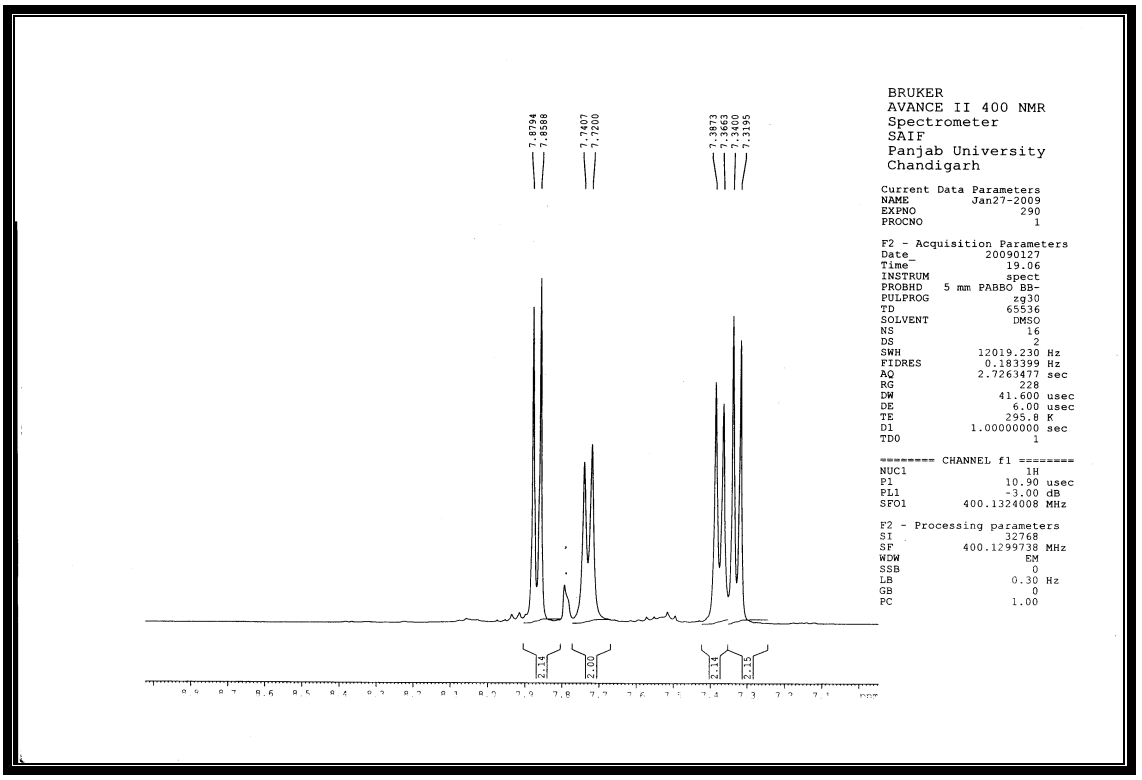
NMR SPECTRAL STUDIES OF 6-(4-CHLOROPHENYL)-3-(4-ISOPRO-PYLPHENYL)-[1,2,4]TRIAZOLO[3,4-b][1,3,4]THIADIAZOLE



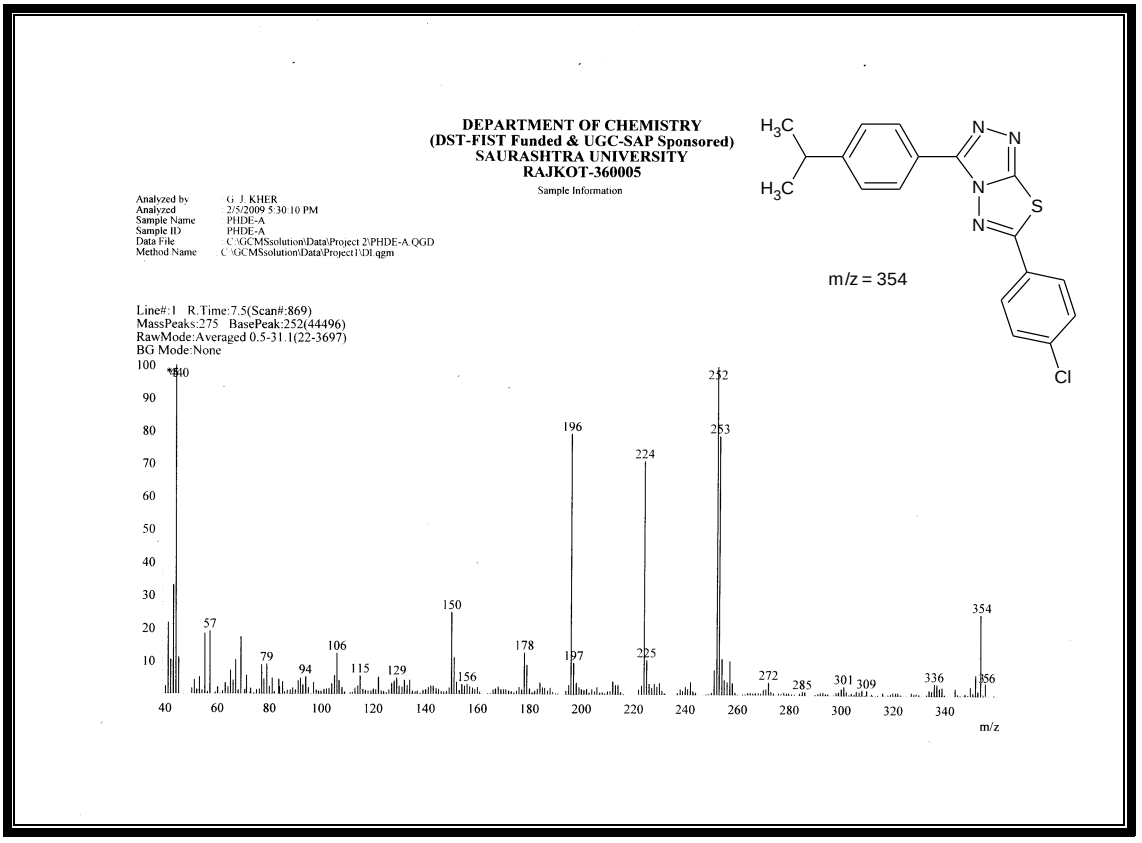
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (400MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	1.26-1.28	6H	doublet	$-CH_3$	6.88
2	2.96-3.00	1H	multiplet	-CH	-
3	7.31-7.34	2H	doublet	-Ar-Ha-a'	8.2
4	7.36-7.38	2H	doublet	-Ar-Hb, b'	8.4
5	7.72-7.74	2H	doublet	-Ar-Hc,c'	8.28
6	7.85-7.87	2H	doublet	-Ar-Hd,d'	8.24

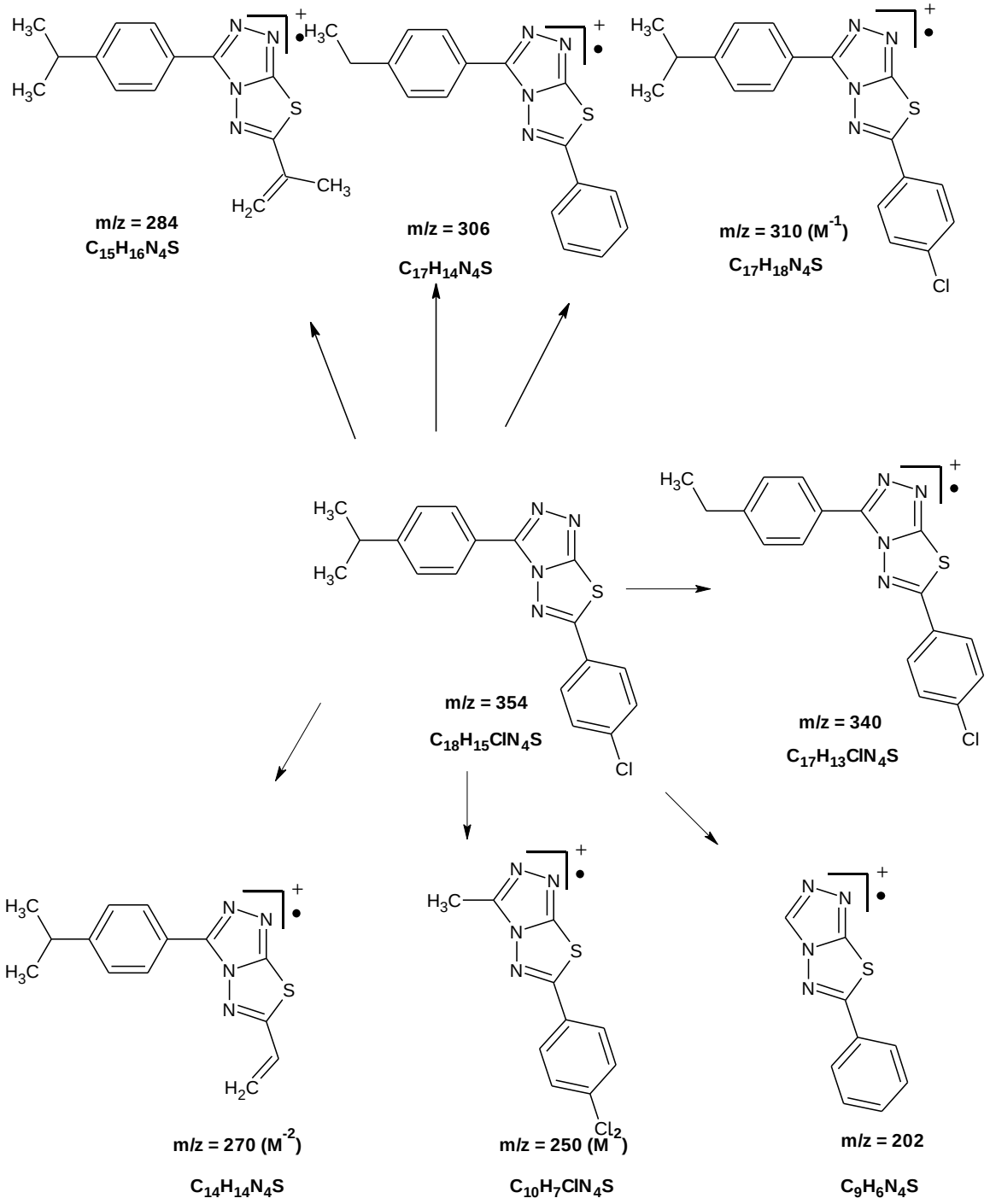
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 6-(4-CHLOROPHENYL)-3-(4-ISOPRO PYLPHENYL)-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE



PROPOSED MASS FRAGMENTATION OF 6-(4-CHLOROPHENYL)-3-(4-ISOPROPYLPHENYL)-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLE



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Preparation of Potassium 4-isopropylbenzyl dithiocarbamate.

To a mixture of potassium hydroxide (8.40g, 0.15mol) and 4-isopropyl benzohydrazide (17.8g, 0.1mol) in methanol (25 ml), carbon disulphide (11.4g, 0.15mol) was added. This mixture was stirred for 12-14 hrs. 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 1-Amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol.

A suspension of the potassium salt (29.2g, 0.1mol), hydrazine hydrate (10 ml, 0.2mol) and water (2 ml) was refluxed with stirring for 3 hrs. The color of the reaction mixture changed to green, hydrogen sulfide was evolved (lead acetate paper and odor) and a homogeneous solution resulted. Dilute the solution with 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 °C.

[C] Preparation of 6 -(4-Chlorophenyl) -3-(4-isopropylphenyl)-[1,2,4] triazolo [3,4-*b*][1,3,4]thiadiazole.

A mixture of p-chloro benzoic acid (1.56g, 0.01mol) and 1-amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol (2.34g, 0.01mol) 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 °C Anal.Calcd. For $C_{18}H_{15}ClN_4S$; C, 60.92; H,4.26; N,15.79 %; Found: C,61.33; H,4.39; N,15.93 %

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

[D] Antimicrobial activity of 6-Aryl-3-(4-isopropylphenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

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

- **Preparation of Agar dilution plates**

(1) Appropriate dilutions i.e. 1 ml quantity of antimicrobial solution are added to mueller hinton agar (19 ml quantity) that have been allowed to equilibrate in a water bath to 45 to 50 °C. One part of antimicrobial solution is added to nine parts of liquid agar.

(2) The agar and antimicrobial solution were mixed thoroughly and the mixture was poured into borosil glass petri dishes having 9 cm diameter on a level surface to result in an agar depth of 3 to 4 mm.

(3) The plates should be poured as quickly after mixing as possible to prevent cooling and partial solidification in the mixing container, avoiding bubbles.

(4) The agar was allowed to solidify at room temperature, and the plates were either used immediately or stored in sealed plastic bags at 2 to 8 °C for up to five days for reference work, or longer for routine tests.

(5) Plates stored at 2-8 °C were allowed to equilibrate at room temperature before use, assuring that the agar surface was dry before inoculating the plates. If necessary, plates were placed in an incubator or laminar flow hood for approximately 30 minutes with their lids. It helps agar to hasten drying of the agar surface.

Preparation of solutions of antimicrobial agents to be incorporated into the agar based medium:

10 mg of the antimicrobial agent was dissolved in 5 ml of DMSO to prepare the main stock of the compound to be tested. 1 ml of this main stock was added to 19 ml of mueller hinton agar medium to take the final concentration of 500 µg / ml in the agar medium. The main stock solution was further diluted in demineralized water by two fold dilution procedure to obtain the desired concentration in the agar medium, i.e. 2000 µg /ml, 1000 µg / ml, 500 µg/ml.

- **Preparation of inoculum of the test cultures:**

One loopful of culture from the slant was inoculated into 5 ml mueller hinton broth in a test tube. The tube was incubated at 32 °C for 4 to 6 hours till the absorbance at 625 nm, equals that of 0.5 mac farland standards. (Section 5, NCCL guidelines). The absorbance readings were taken against a sterile mueller hinton broth media blank. The density of the suspension was adjusted to 10^8 colony forming units (CFU) per milliliter by comparing its turbidity to a mac farland 0.5 $BaSO_4$ standard.

- **Preparation of 0.5 Mac Farland standard:**

It was used as a reference for turbidity measurement for bacterial cultures before they were used as inoculum for spot inoculate the mueller hinton agar media containing antimicrobial agents. Briefly, 0.5 ml of 1.175% w/v $BaCl_2$ solution was added to 99.5 ml of 1 % v/v H_2SO_4 solution with constant stirring, the absorbance of the solution was measured 625nm against demineralized water blank by UV spectrophotometer. The absorbance was in the range of 0.08 to 0.1 optical densities.

- **Interpretation of Results:**

(1) In case of positive control, plate due to complete absence of antimicrobial agent and its solvent bacterial / fungal cultures gave luxuriant growth.

(2) In the solvent control plate inhibition of growth of microbes due to presence of

organic solvent DMSO.

(3) The microbial cultures, if shown 1-5 colonies per spot inoculated instead of confluent growth as in the control plate, it was considered to be inhibited by test antimicrobial compounds.

(4) The microorganisms that were sensitive to the concentration of antimicrobial in mueller hinton agar plate did not produce a circle of growth at the inoculum site.

(5) The microbes that were resistant to it appeared as circular colonies. The agar plates were marked with a grid so that each microorganism could be identified by a number.

- **Antibacterial Activity Determination:**

Organic compounds may be bacteriostatic or bacteriocidal for microbial cultures. To check this, from the mueller hinton agar plates (showing no visible growth of bacteria), sub culturing was carried out on nutrient agar plates (Collins, 1967). After streaking, nutrient agar plates were incubated for 24 hrs at 37°C. Then after observation was made to see the colonies formed. If colonies were found, the dilution was considered as bacteriostatic and if no colonies observed, it was considered as bactericidal. Bacteriocidal dilutions of the organic compounds were considered as exact minimum inhibitory concentration (MIC) for a particular organic compound.

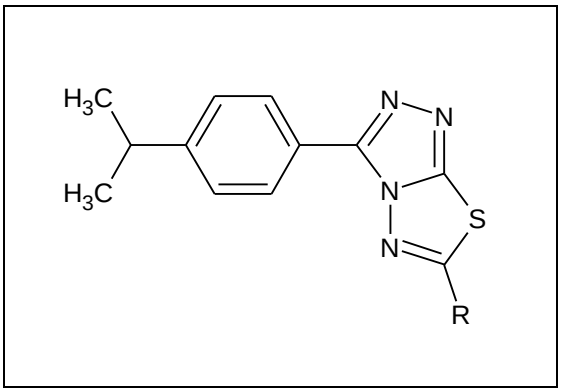
- **Antifungal Activity Determination:**

For fungal cultures the fungal media yeast nitrogen base agar plate (YNBG) 6.7 g and glucose 10 g, dissolved in 100 ml of distilled water and filter sterilized was used. The inoculum was prepared from 3-4 days old sabouraud's dextrose agar slants. The growth was uniformly mixed with distilled water. The Size of inoculum prepared for inoculating YNBG agar plates was 10^2–10^3 cfu/ml, adjusted with mac farland

solution. After inoculation of properly diluted fungal solution, the plates were incubated at 37 °C for 48 hrs.

Antimicrobial testing were carried out as described in part - I, Section - I (D). The zones of inhibition of test solutions are recorded in Table No. 1b.

Table-1a: Physical constants of 6-Aryl-3-(4-isopropylphenyl)-[1,2,4]triazole [3,4-*b*][1,3,4]thiadiazoles.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
1a	4-OCH_3-C_6H_4-	$C_{19}H_{18}N_4OS$ 350.43	250	68	65.12 (65.02)	5.18 (5.08)	15.99 (15.86)
1b	2,4-$(OH)_2$-C_6H_3-	$C_{18}H_{16}N_4O_2S$ 352.41	195	62	61.35 (61.12)	4.58 (4.22)	15.90 (15.84)
1c	2-CH_3-C_6H_4-	$C_{19}H_{18}N_4S$ 334.43	180	56	68.23 (68.01)	5.42 (5.21)	16.75 (16.44)
1d	3-OC_6H_5-C_6H_4-	$C_{24}H_{20}N_4OS$ 412.50	190	62	69.88 (69.34)	4.89 (4.87)	13.58 (13.33)
1e	4-Br-C_6H_4-	$C_{18}H_{15}BrN_4S$ 399.30	230	65	54.14 (54.02)	3.79 (3.61)	14.03 (13.85)
1f	4-Cl-C_6H_4-	$C_{18}H_{15}ClN_4S$ 354.85	245	54	60.92 (60.86)	4.26 (4.08)	15.79 (15.66)
1g	4-NO_2-C_6H_4-	$C_{18}H_{15}N_5O_2S$ 365.40	240	45	59.16 (59.09)	4.14 (4.10)	19.17 (19.06)
1h	3-NO_2-C_6H_4-	$C_{18}H_{15}N_5O_2S$ 365.40	210	53	59.16 (59.01)	4.14 (4.03)	19.17 (19.01)
1i	2-OH-C_6H_4-	$C_{18}H_{16}N_4OS$ 336.41	190	59	64.26 (64.08)	4.79 (4.20)	16.65 (16.08)
1j	2-Cl-C_6H_4-	$C_{18}H_{15}ClN_4S$ 354.85	165	65	60.92 (61.35)	4.26 (4.09)	15.79 (15.30)

TABLE 1A: ANTIMICROBIAL ACTIVITY OF 6-ARYL-3-(4- ISOPROPYLPHENYL)-[1,2,4] TRIAZOLO [3,4-*b*] [1,3,4] THIADIAZOLES.(in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	1a	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-
2.	1b	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+	-	-	-
3.	1c	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
4.	1d	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
5.	1e	-	-	-	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-
6.	1f	-	-	-	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-
7.	1g	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+	-	-	-
8.	1h	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
9.	1i	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	-	-
10.	1j	+	+	-	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-

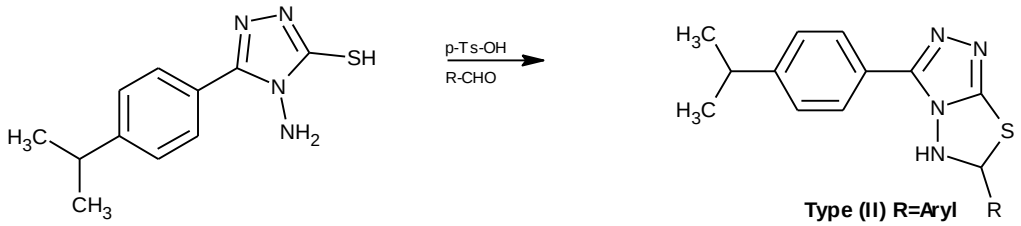
Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 5,6-DIHYDRO-6-ARYL-3-(4-ISOPROPYLPHENYL)-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLES

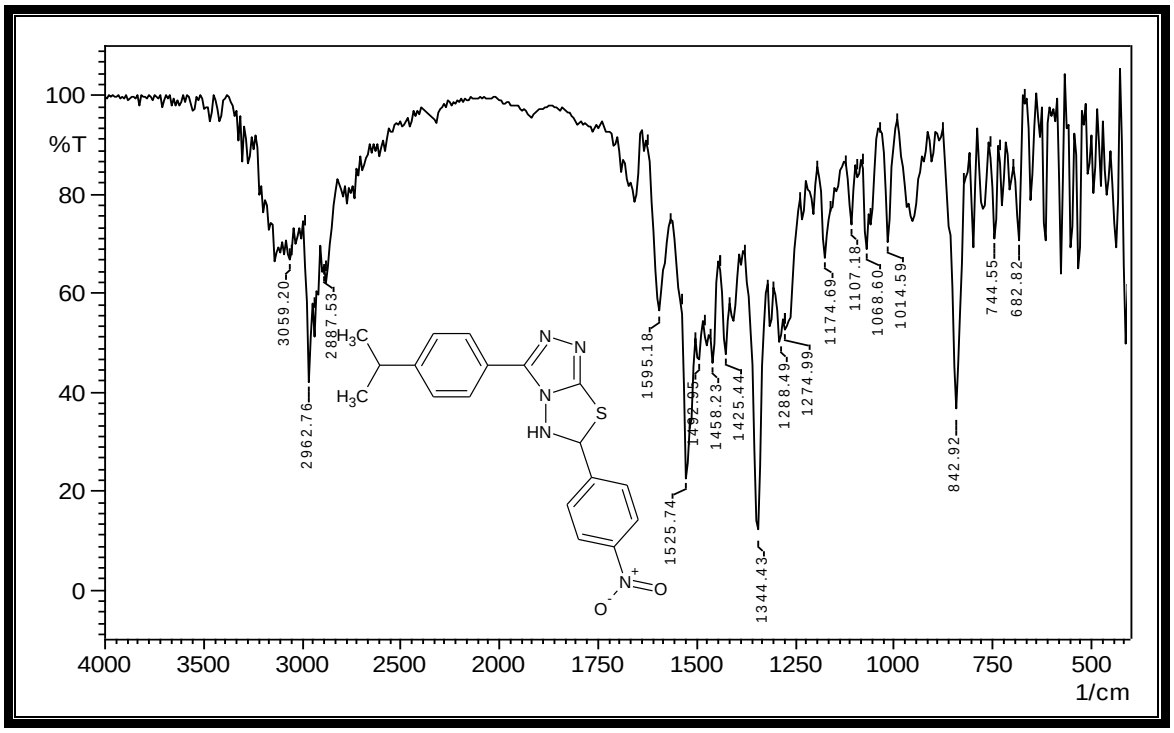
Thiadiazole derivatives are endowed with variety of biological activities. Looking to the interesting properties of thiadiazoles, it was considered worthwhile to synthesize a series of 5,6-dihydro-6-aryl-3-(4-isopropylphenyl)-[1,2,4]triazoles[3,4-*b*][1,3,4] thiadiazoles of type (II) for obtaining biologically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



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, Candida albicans*** at a concentration of 2000/1000/500 µg/ml. The biological activity of the synthesized compounds has been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Table No.2b.

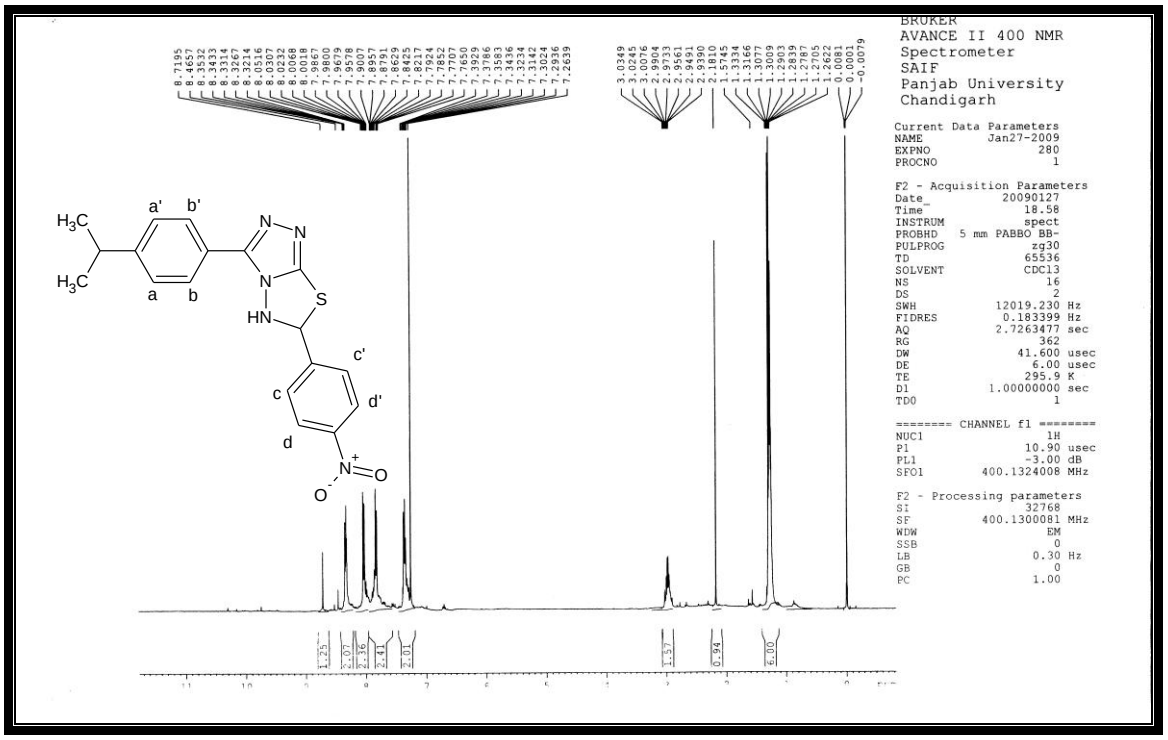
IR SPECTRUM OF 5,6-DIHYDRO-3-(4-ISOPROPYLPHENYL)-6-(4-NITRO-PHENYL)-[1,2,4]TRIZOLO[3,4-*b*][1,3,4]THIADIAZOLE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2962	2975-2950	47
	C-H str.	2887	2880-2860	49
	C-H def.	1458	1470-1435	47
	C-H def.	1344	1385-1370	50
Aromatic	C-H str.	3059	3080-3030	47
	C=C str.	1525	1585-1480	47
	C-H i.p. (def)	1068	1145-1090	50
	C-H def. (sym.)	1014	1070-1000	50
Isopropyl	$-CH(CH_3)_2$	2887	2800-2900	48
Triazole	C=N str.	1595	1612-1593	47
	C-N str.	1344	1380-1310	48
	C-N-C str.	1174	1176-1132	47
	N-N str.	1014	1050-1010	49
Thiadiazole	C-S-C str.	682	720-570	47
Nitro	N=O str	1525	1560-1515	49

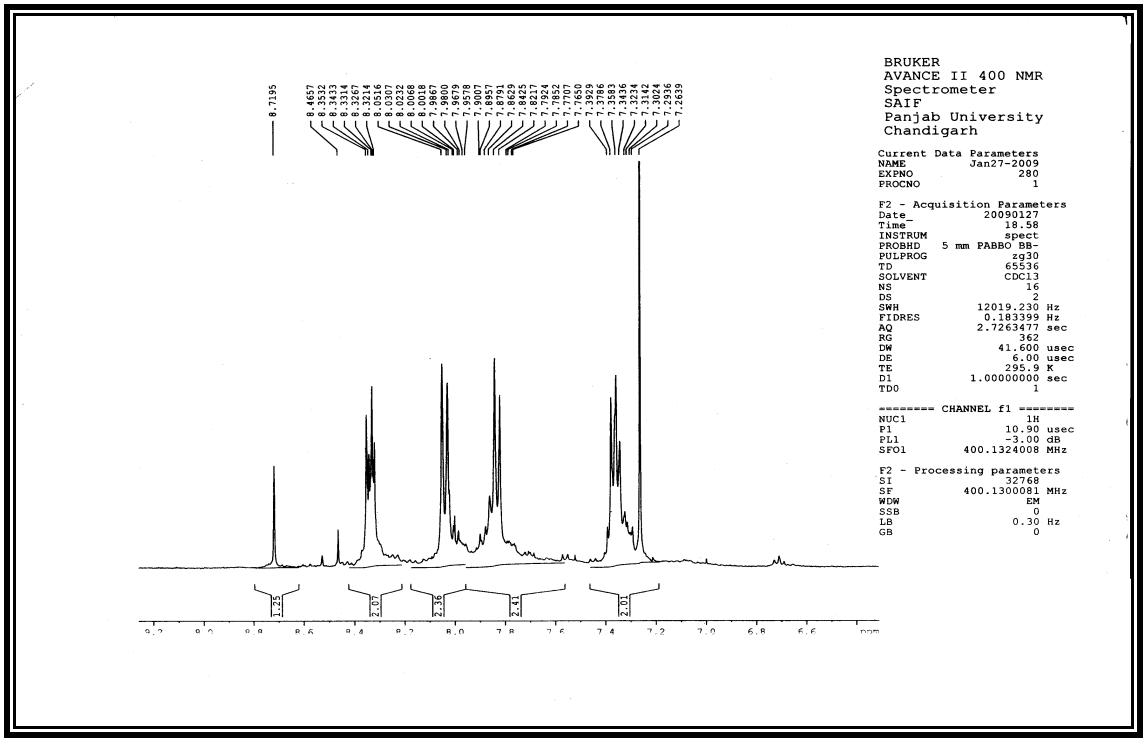
NMR SPECTRAL STUDIES OF 5,6-DIHYDRO-3-(4-ISOPROPYLPHEN YL)-6-(4-NITROPHENYL)-[1,2,4]TRIZOLO[3,4-*b*][1,3,4]THIADIAZOLE



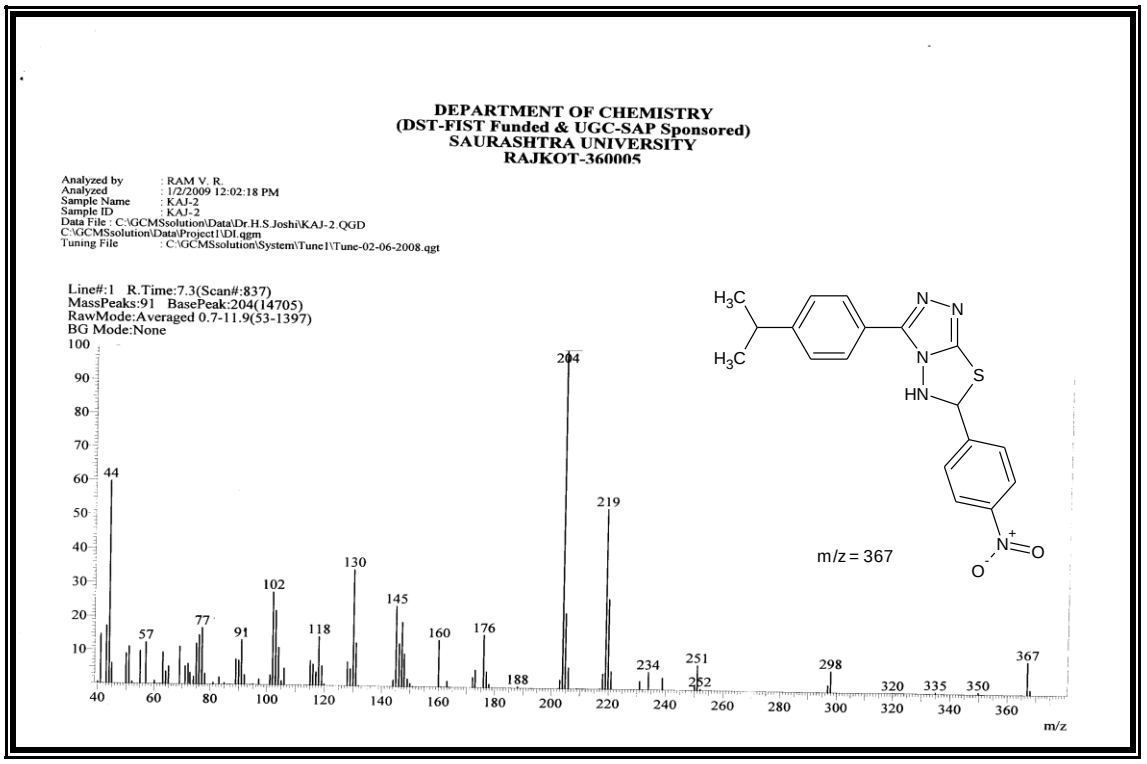
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (400MHz)

Sr.	Chemical shift in	Relative No. of	Multiplicity	Inference	J value in
1.	1.26-1.33	6H	doublet	$-CH_3$	-
2.	2.18	1H	singlet	-CH	
3.	2.93-3.03	1H	multiplet	-CH	-
4.	7.29-7.39	2H	multiplet	-Ar-Ha-a'	-
5.	7.76-7.90	2H	multiplet	-Ar-Hb,b'	-
6.	7.95-8.05	2H	multiplet	-Ar-Hc,c'	-
7.	8.32-8.35	2H	multiplet	-Ar-Hd,d'	-
8.	8.71	1H	singlet	-NH	-

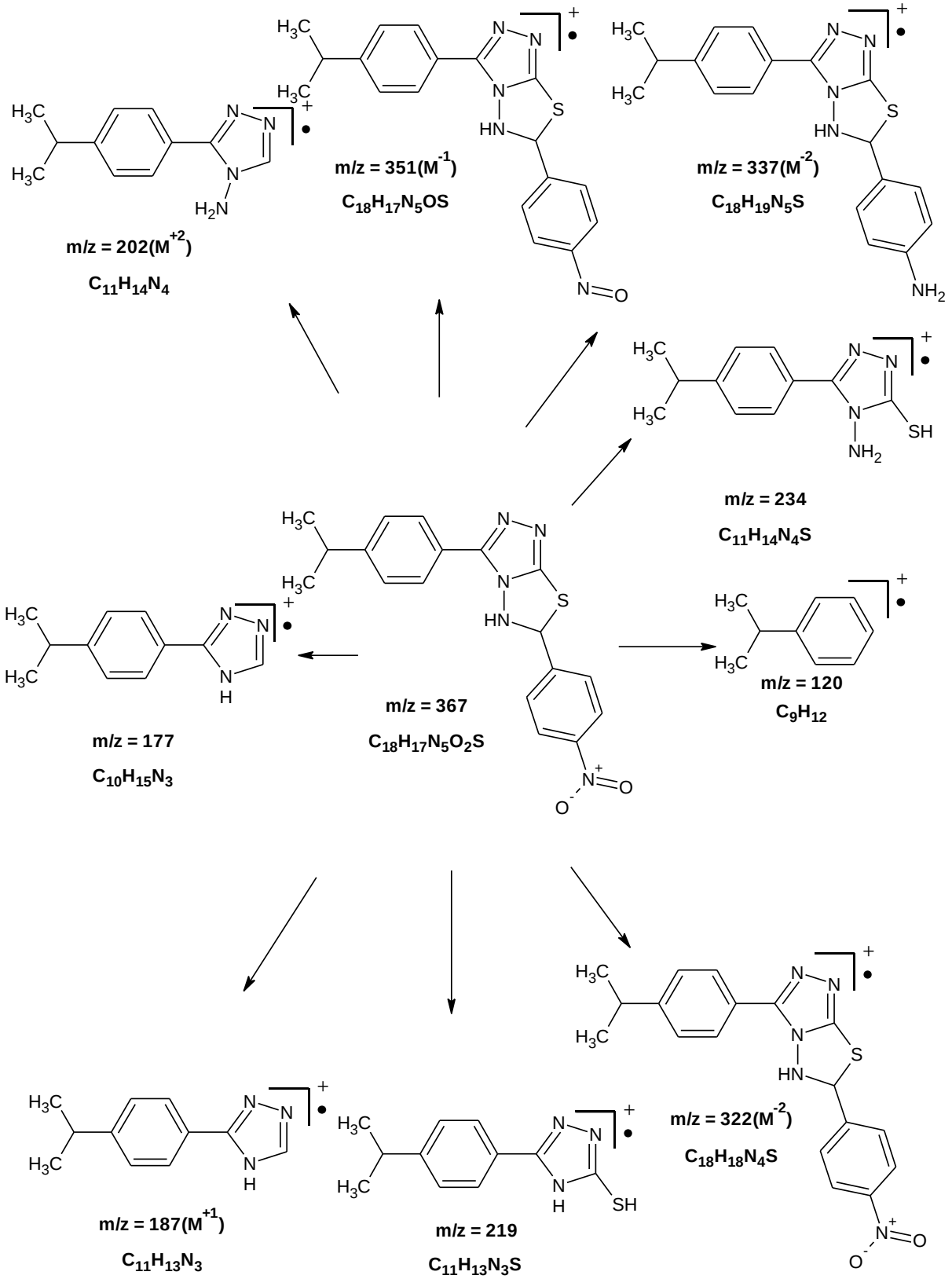
Expanded region of Aromatic region



MASS SPECTRAL STUDIES OF 5,6-DIHYDRO-3-(4-ISOPROPYLPHENYL)-6-(4-NITROPHENYL)-[1,2,4]TRIZOLO[3,4- *b*][1,3,4]THIADIAZOLE



PROPOSED MASS FRAGMENTATION OF 5,6-DIHYDRO -3-(4-ISOPRO-PYLPHENYL)-6-(4-NITROPHENYL)-[1,2,4]TRIZOLO[3,4-*b*][1,3,4]THIADI-AZOLE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Preparation of Potassium 4-isopropylbenzyl dithiocarbamate

See Part-I, Section-I [A]

[B] Preparation of 1-Amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol.

See Part-I, Section-I [B]

[C] Preparation of 5,6-Dihydro-3-(4-isopropylphenyl)-6(4-Nitrophenyl)-[1,2,4] triazole [3,4-*b*][1,3,4]thiadiazole

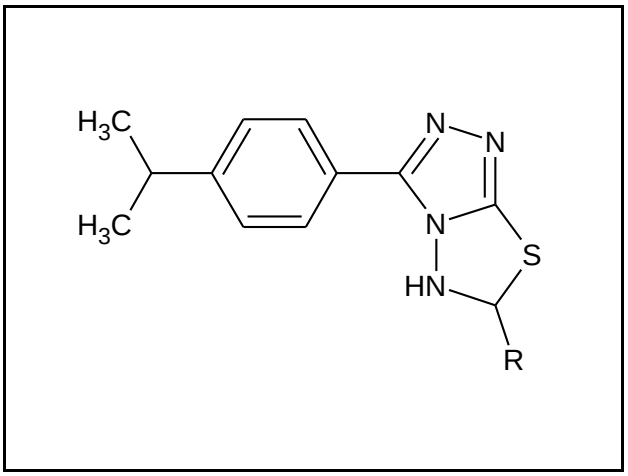
A mixture of 1-amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol (2.34g, 0.01mol), p-nitrobenzaldehyde (1.65g, 0.01mol) and p-Ts-OH (50 mg) in dry DMF (50 ml) was refluxed with stirring for 10 hrs. The reaction mixture was poured on to crushed ice and thus solid separated was filtered, washed with water and crystallized from methanol yield 60%, m.p. 265°C Anal. Calcd. For $C_{18}H_{17}N_5O_2S$; C, 58.84; H,4.66; N,19.06 %; Found: C,58.53; H,4.93; N,19.32 %.

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

[D] Antimicrobial activity of 5,6-Dihydro-6-aryl-3-(4-isopropylphenyl)-[1,2,4] triazole [3,4-*b*][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 Table No. 2b.

Table-2a: Physical constants of 5,6-Dihydro-6-aryl-3-(4-isopropylphenyl)-[1,2,4] triazole [3,4-*b*][1,3,4]thiadiazoles



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
2a	4-OCH_3-C_6H_4-	$C_{19}H_{20}N_4OS$ 352.45	231	58	64.75 (65.19)	5.72 (5.36)	15.90 (16.26)
2b	3,4-$(OCH_3)_2$-C_6H_3-	$C_{20}H_{22}N_4O_2S$ 382.47	196	54	62.80 (62.16)	5.80 (5.46)	14.65 (14.32)
2c	4-NO_2-C_6H_4-	$C_{18}H_{17}N_5O_2S$ 367.42	180	60	58.84 (58.79)	4.66 (4.23)	19.06 (18.85)
2d	2-NO_2-C_6H_4-	$C_{18}H_{17}N_5O_2S$ 367.42	185	61	58.84 (58.53)	4.66 (4.17)	19.06 (19.02)
2e	4-OH-C_6H_4-	$C_{18}H_{18}N_4OS$ 338.42	221	64	63.88 (63.75)	5.36 (5.09)	16.56 (16.03)
2f	C_6H_5-	$C_{18}H_{18}N_4S$ 322.42	195	53	67.05 (66.94)	5.63 (5.34)	17.38 (17.09)
2g	3-Cl-C_6H_4-	$C_{18}H_{17}ClN_4S$ 356.87	180	49	60.58 (60.36)	4.80 (4.68)	15.70 (15.43)
2h	4-CH_3-C_6H_4-	$C_{19}H_{20}N_4S$ 336.45	154	45	67.83 (67.64)	5.99 (5.45)	16.65 (16.41)
2i	4-F-C_6H_4-	$C_{18}H_{17}FN_4S$ 340.41	184	58	63.51 (63.27)	5.03 (4.82)	16.46 (16.29)
2j	2-OH-C_6H_4-	$C_{18}H_{18}N_4OS$ 338.42	193	45	63.88 (63.68)	5.36 (5.11)	16.56 (16.23)

TABLE 2A: ANTIMICROBIAL ACTIVITY OF 5,6-DIHYDRO-6-ARYL-3-(4-ISOPROPYLPHENYL)-[1,2,4] TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLES.(in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	2a	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-
2.	2b	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+	-	-	-
3.	2c	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
4.	2d	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
5.	2e	-	-	-	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-
6.	2f	+	+	-	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-
7.	2g	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
8.	2h	+	+	+	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-
9.	2i	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-
10.	2j	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+	-	-	-

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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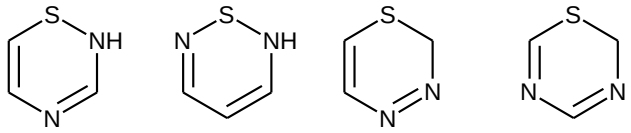
Part- A

(Part-II)

Studies on 1,3,4-Thiadiazine Derivatives

INTRODUCTION

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



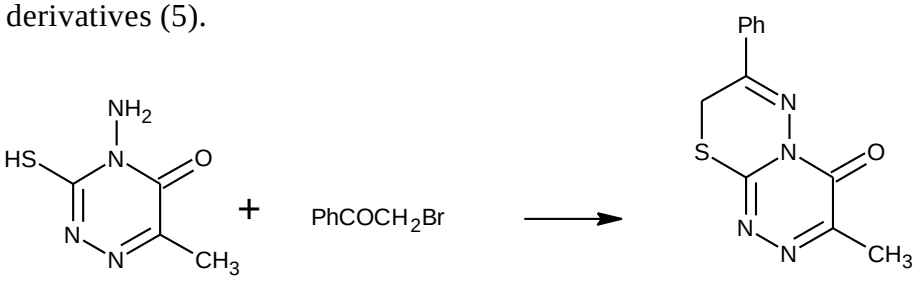
(1) (2) (3) (4)

The literature survey reveals that there are not many examples of triazoles fused with thiadiazines. Those incorporating the N-C-S linkage as in the skeleton of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine exhibit a broad spectrum of antimicrobial activity.[1-3] Many 1,3,4-thiadiazine derivatives involve in many biological processes and serves as a medicinally interesting compounds.

SYNTHETIC ASPECT

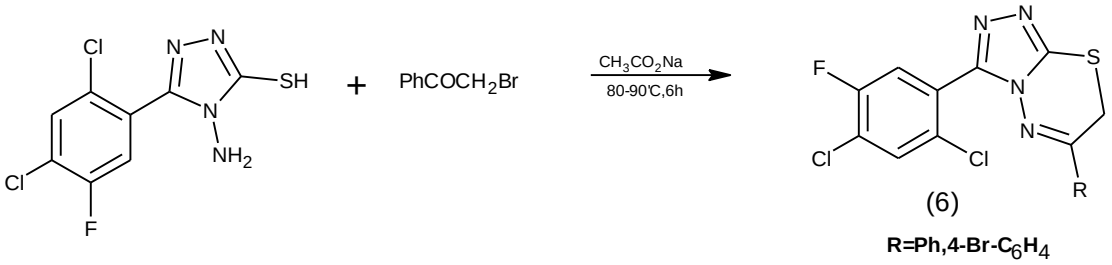
Different methods for the preparation of 1,3,4-thidiazine derivatives described in literature are as follows.

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



(5)

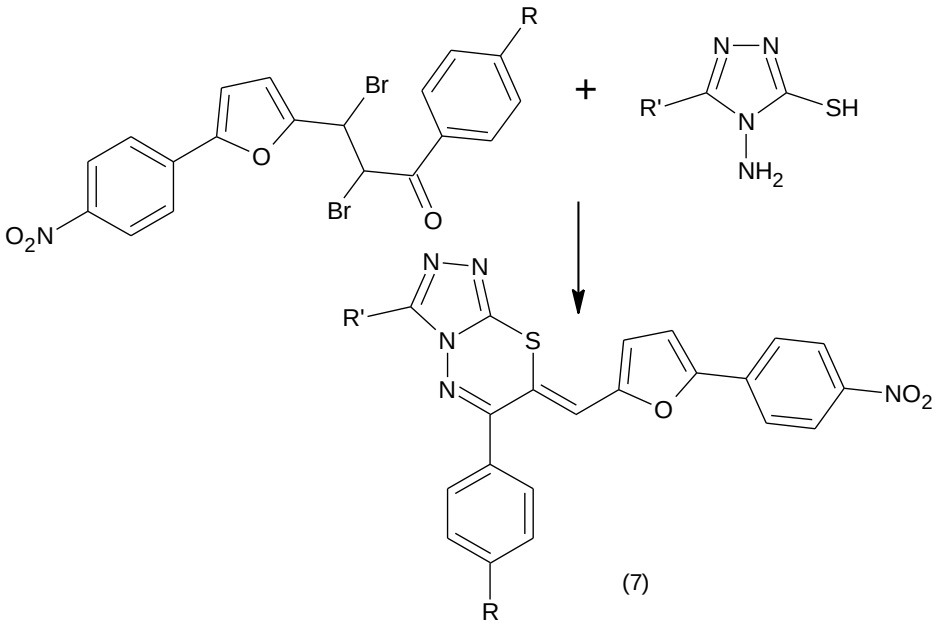
2. K. S. Bhat et al.[5] have designed thiadiazine ring system (6) by the reaction of triazole with phenacyl bromide.



(6)

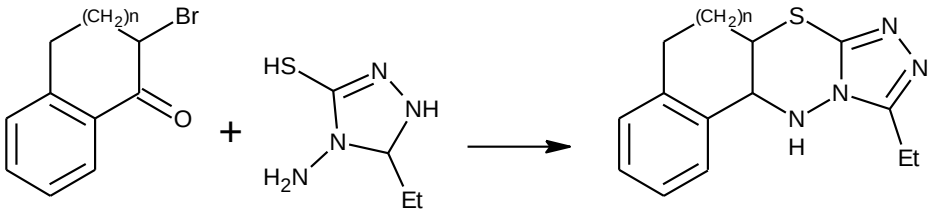
R=Ph,4-Br-C_6H_4

3. B. Shivarama Holla et al.[6] have synthesized triazole thiadiazines (7) 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.



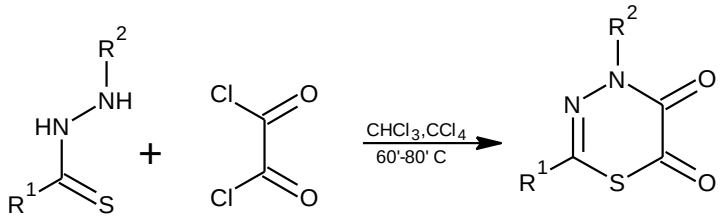
(7)

4. S. Peri Aytaç et al.[7] have prepared 1,3,4-thiadiazine by the condensation of 4-amino-3-substituted-1,2,4-triazole-5-thiones with phenacyl bromides.
5. W. L. Alberecht et al.[8] have synthesized s-triazolocycloalkyl hydro-thiadiazines (8) by the cyclization of *a*-haloketones with 5-substituted-4-amino-4*H*-1,2,4-triazole-3-thiols.



(8)

6. N. N. Kuzmich et al.[9] have synthesized triazolothiadiazines (9) by the reaction of thiobenzohydrazide with oxalyl chloride.



(9)

R_1,R_2=H or Ph

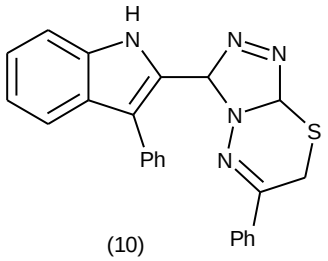
BIOLOGICAL EVALUATION

Literature survey shows that various 1,3,4-thiadiazines have resulted in many potential drugs and are known to exhibit a broad spectrum of biological activities.

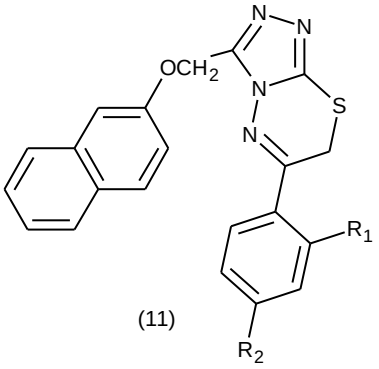
1,3,4-Thiadiazine derivatives possess wide range of therapeutic activities which are as under.

1. Antifungal[10]
2. Antibacterial[11]
3. Antimicrobial[12]
4. Antiinflammatory[13]
5. Cardiovascular[14]
6. AntiHIV[15]
7. Antidiabetic[16]
8. Antidepressant[17]

R. D. Patil and J. S. Biradar[18] have reported triazole thiadiazine derivatives as anthelmintic, anti-inflammatory and anticatatonic active agents (10). G. Turan-Zitouni et al.[19] have demonstrated analgesic activity of triazole thiadiazines (11).



(10)

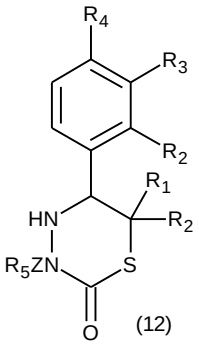


(11)

R_1=H, R_2=Cl,NO_2

R_1=OH, R_2=OCH_3

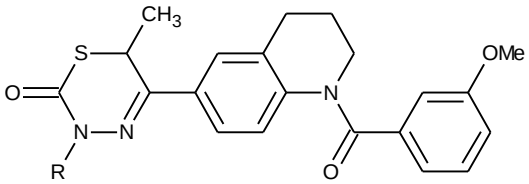
G. Mazzone et al.[20-21] reported 1,3,4-thiadiazine derivatives as weak anti-inflammatory agent and also reported their analgesic activity. Jonas Rochus et al.[22-23] have prepared new thiadiazine derivatives useful as phosphodiesterase IV inhibitors (12) and cardiovascular agents (13).



(12)

Z= bond OR alkylene

R_5= Substituted Phenyl

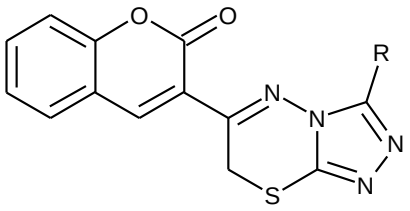


(13)

R_1,R_2 = H OR Halo

R_3,R_4 = OH, alkoxy, halo

Z. A. Kaplancıklı et al.[24] have reported antimicrobial activity of thiadiazines. Prakash Karegoudar et al.[25] have documented thiadiazine derivatives as anti-inflammatory agent. B. Kalluraya 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 (14).



(14)

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

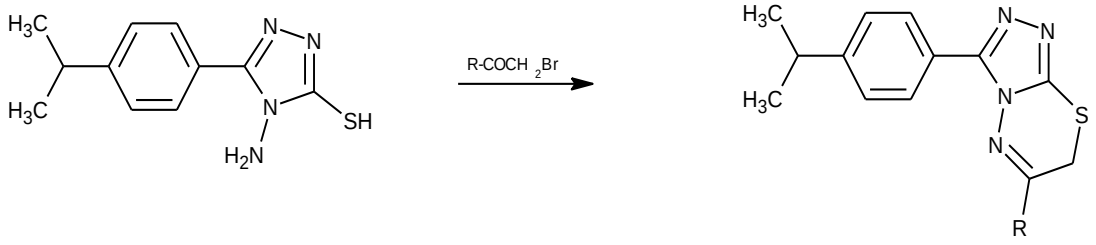
The diverse biological activities have been encountered in compounds containing triazolothiadiazine ring system. Therefore it was considered worthwhile to synthesize 1,3,4-thiadiazine derivatives which have been described as under.

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

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ARYL-3-(4-ISOPROPYLPHENYL)-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 1-amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol with different substituted phenacyl bromides.

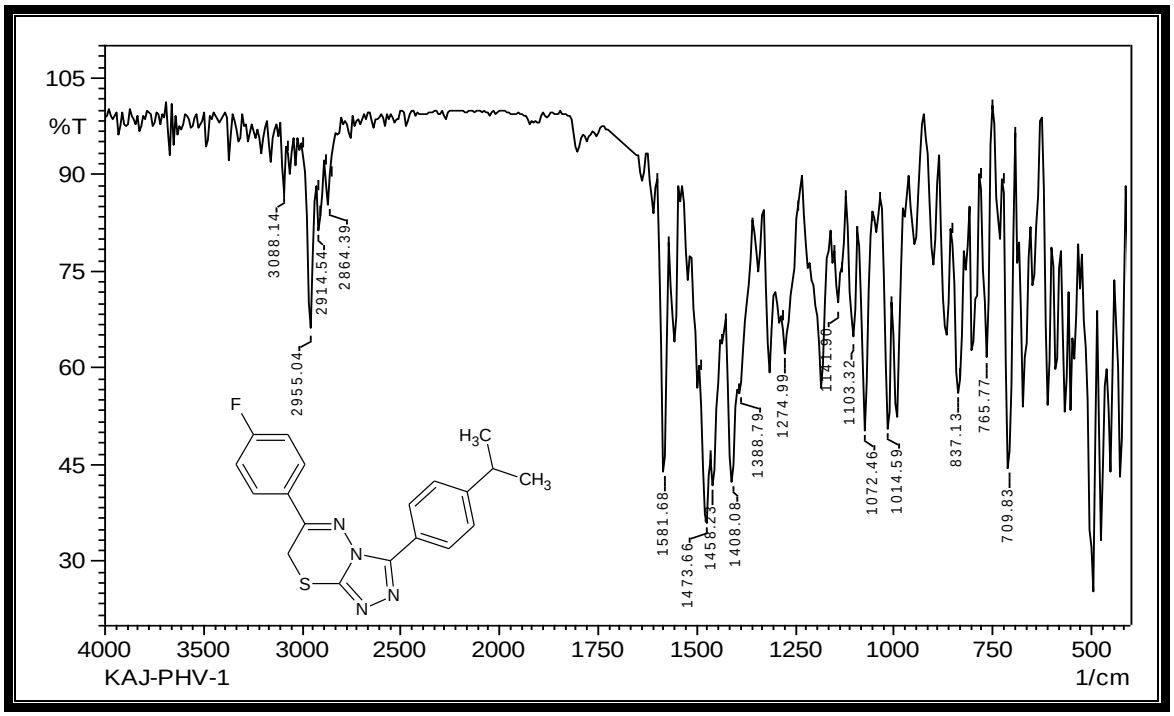


Type -(IV) R = Aryl

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.3b.

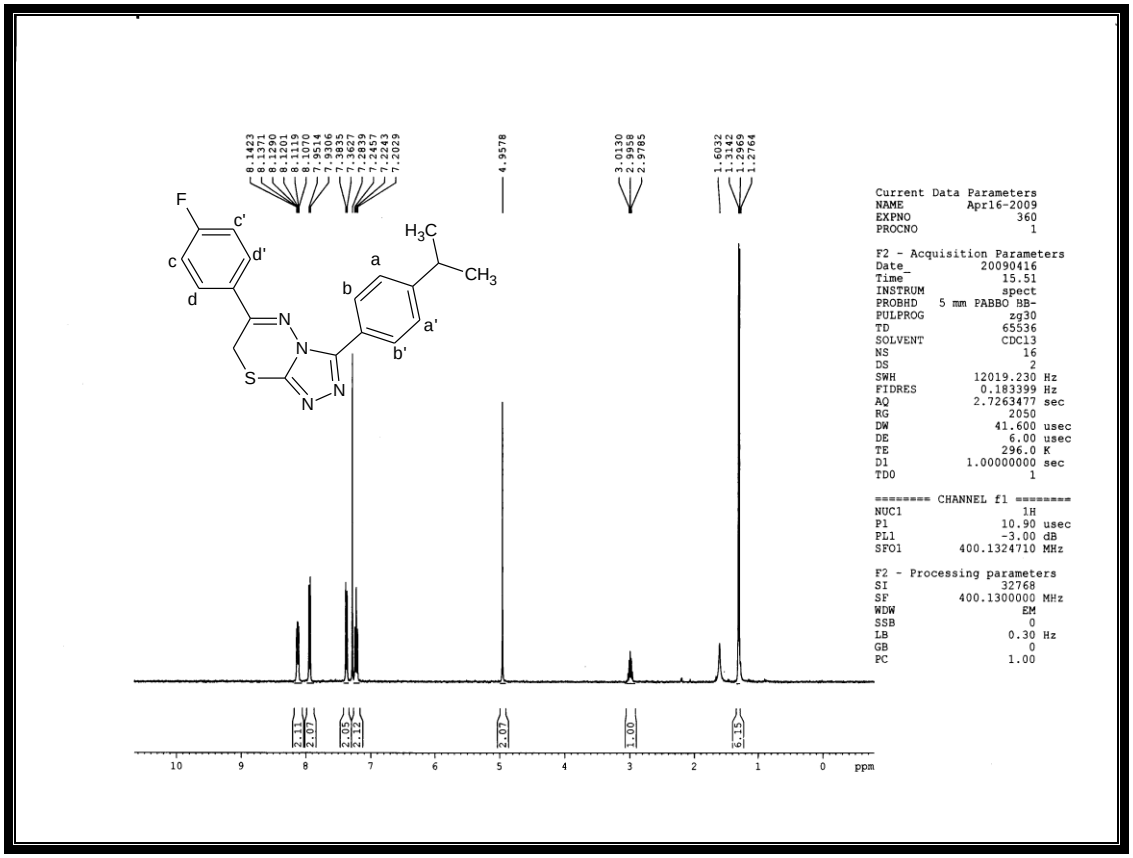
IR SPECTRAL STUDIES OF 6-(4-FLUOROPHENYL)-3-(4-ISOPROPYL-PHENYL)-7*H*-[1,2,4]TRIAZOLO[3,4-*b*][1,3,4]THIADIAZINE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2955	2975-2950	36
	C-H str. (sym.)	2864	2880-2860	37
	C-H def. (asym.)	1458	1470-1435	35
	C-H def. (sym.)	1388	1385-1370	36
Aromatic	C-H str.	3088	3095-3050	35
	C=C str.	1581	1585-1480	35
	C-H i.p. (def)	1103	1125-1000	36
	C-H o.o.p. (def)	765	835-810	36
Isopropyl	$-CH(CH_3)_2$	2955	2800-2900	36
Triazole	C=N str.	1581	1650-1580	37
	C-N str.	1014	1050-1010	35
	N-N str.	1141	1220-1020	36
Thiadiazine	C-S-C str.	765	720-570	37
Halide	C-F str.	1141	1200-1000	37

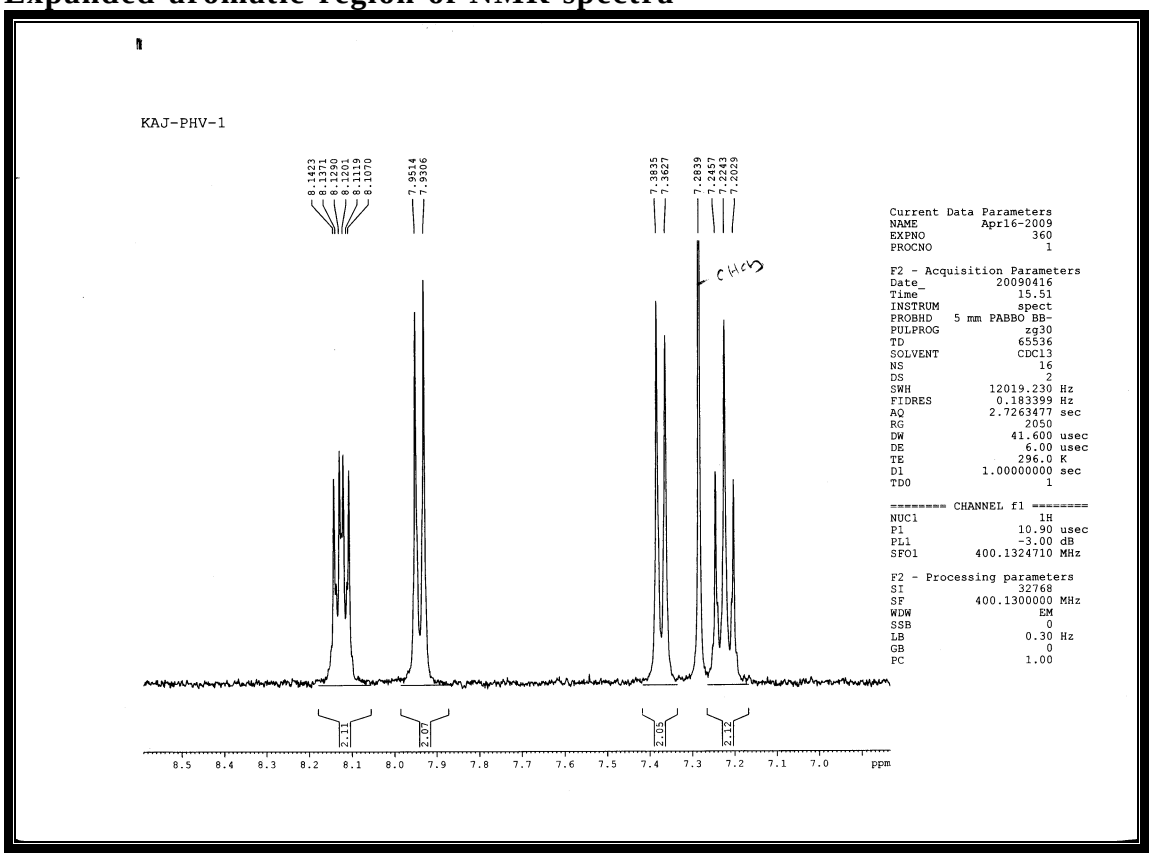
NMR SPECTRAL STUDIES OF 6-(4-FLUOROPHENYL)-3-(4-ISOPRO PYLPHENYL)-7*H*-[1,2,4]TRIAZOLO[3,4 *b*][1,3,4]THIADIAZINE.



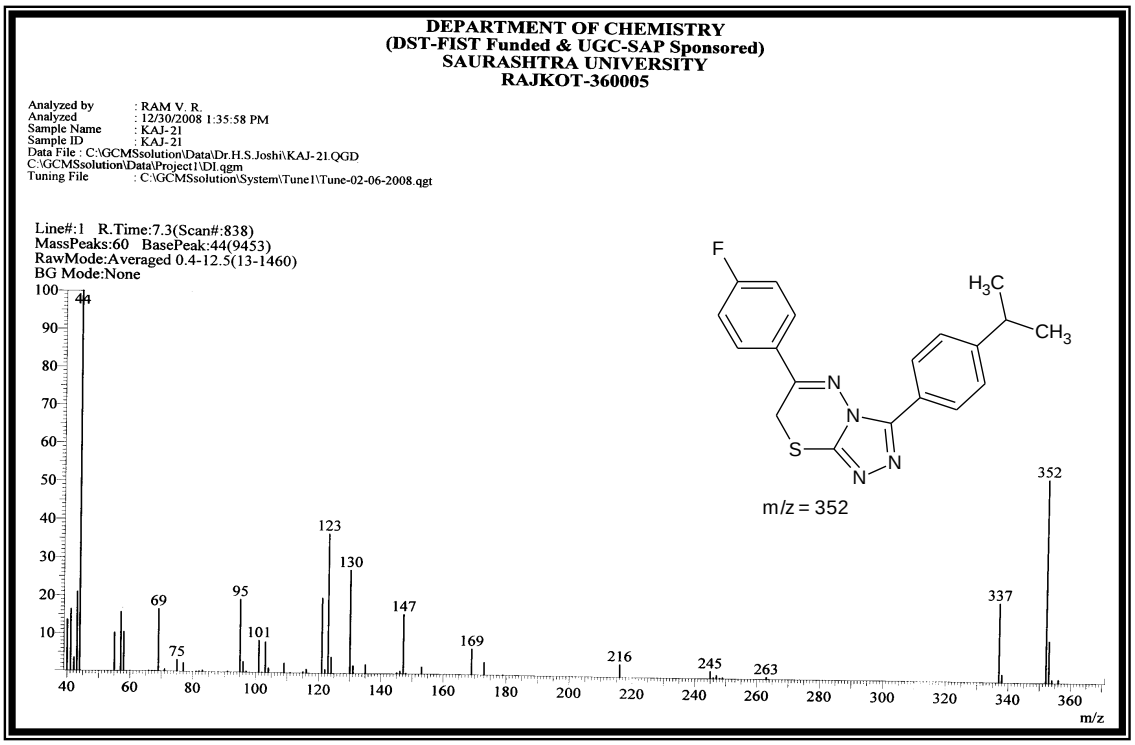
Instrumental Standard : TMS; Solvent: CDCl3 ; Instrument : BRUKER Spectrometer (400MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	1.27-1.31	6H	doublet	$-CH_3$	6.92
2	2.97-3.01	1H	multiplet	-CH	
3	4.95	2H	singlet	$-CH_2$	
4	7.20-7.24	2H	triplet	-Ar-Ha,a'	8.56
5	7.36-7.38	2H	doublet	-Ar-Hb,b'	8.32
6	7.93-7.95	2H	doublet	-Ar-Hc,c'	8.32
7	8.10-8.14	2H	multiplet	-Ar-Hd,d'	

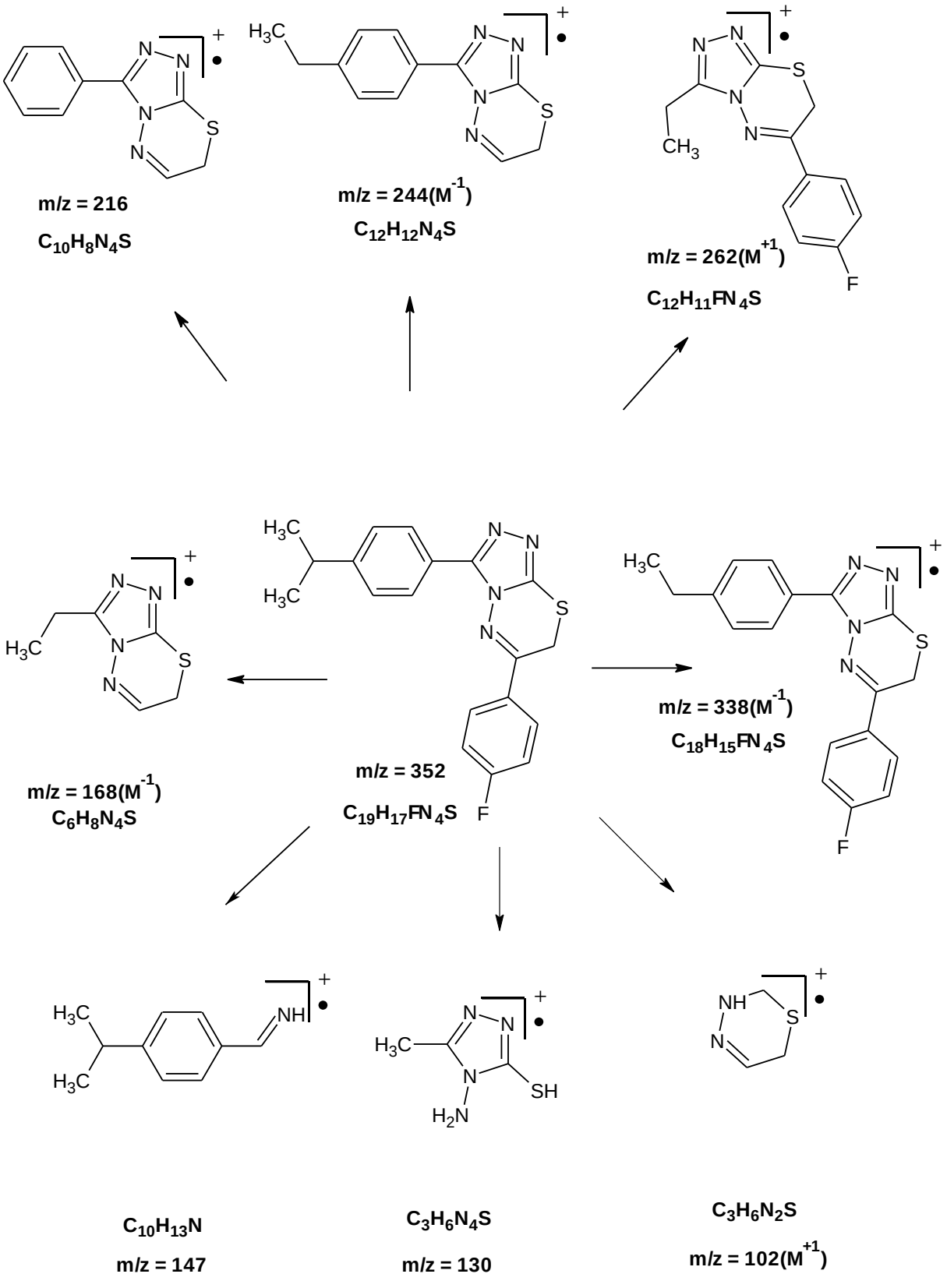
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 6-(4-FLUOROPHENYL)- 3-(4- ISOPROPYL PHENYL)-7*H*-[1,2,4] TRIAZOLO[3,4-*b*][1,3,4]THIADIAZINE.



PROPOSED MASS FRAGMENTATION OF 6-(4-FLUOROPHENYL)- 3-(4-ISO PROPYLPHENYL)-7*H*-[1,2,4] TRIAZOLO[3,4-*b*][1,3,4]THIADIAZINE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Preparation of Potassium 4-isopropylbenzyl dithiocarbamate

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

[B] Preparation of 1-Amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazole-5-thiol

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

[C] Preparation of 4-Fluorophenacyl bromide.

To a well stirred solution of 4-fluoro acetophenone (1.38g, 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-fluoro phenacyl bromide.

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

[D] Preparation of 6-(4-Fluorophenyl)-3-(4-isopropylphenyl)-7*H*-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazine.

A mixture of 1-amino-3-[4-(propan-2-yl)phenyl]-1*H*-1,2,4-triazolo-5-thiol (2.34g, 0.01mol) and p-fluoro phenacyl bromide (2.17g, 0.01mol) in dry methanol (50 ml) was heated under reflux for 5 hrs. The content was cooled and neutralized with

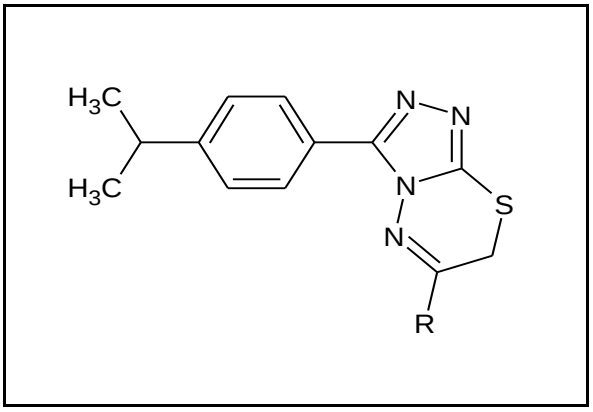
aqueous potassium carbonate solution. The solid separated was filtered out and washed with water. The product was crystallized from ethanol. Yield 57%, m.p. 210 °C. Anal. Calcd. For $C_{19}H_{17}FN_4S$; C, 64.75; H,4.86; N,15.90 %; Found: C,64.68; H,4.67; N,15.79%

Similarly other phenacyl bromides have been condensed. The physical constants are recorded in Table No.3a.

[E] Antimicrobial activity of 6-Aryl-3-(4-isopropylphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines.

Antimicrobial testing was carried out as described in part-(I), section-I(D). The zones of inhibition of compounds are recorded in Table No.3b.

Table-3a: Physical constants of 3-(4-Isopropylphenyl)-6-aryl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazines.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
3a	4-F-C_6H_4-	$C_{19}H_{17}FN_4S$ 352.42	205	57	64.75 (64.68)	4.86 (4.67)	15.90 (15.79)
3b	4-Cl-C_6H_4-	$C_{19}H_{17}ClN_4S$ 368.88	180	45	61.86 (61.48)	4.65 (4.31)	15.19 (15.02)
3c	4-Br-C_6H_4-	$C_{19}H_{17}BrN_4S$ 413.33	205	40	55.21 (54.03)	4.15 (3.98)	13.55 (13.23)
3d	C_6H_4-	$C_{19}H_{18}N_4S$ 334.43	178	46	68.23 (68.08)	5.42 (5.16)	16.75 (16.49)
3e	4-NO_2-C_6H_4-	$C_{19}H_{17}N_5O_2S$ 379.43	169	56	60.14 (60.06)	4.52 (4.16)	18.46 (18.23)
3f	2-OH-C_6H_4-	$C_{19}H_{18}N_4OS$ 350.43	175	58	65.12 (65.09)	5.18 (4.86)	15.99 (15.71)
3g	4-OCH_3-C_6H_4-	$C_{20}H_{20}N_4OS$ 364.46	159	51	65.91 (65.48)	5.53 (5.37)	15.37 (15.22)
3h	4-CH_3-C_6H_4-	$C_{20}H_{20}N_4S$ 348.46	180	50	68.93 (68.74)	5.79 (5.47)	16.08 (16.01)

TABLE 3A : ANTIMICROBIAL ACTIVITY OF 6-ARYL-3-(4-ISOPROPYLPHENYL)-7*H*-[1,2,4] TRIAZOLO[3,4-*b*][1,3,4]THIADIAZINES. (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	3a	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	-
2.	3b	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	-
3.	3c	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4.	3d	-	-	+	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+
5.	3e	+	+	+	+	+	+	+	-	-	+	-	-	+	+	-	+	+	-
6.	3f	+	+	-	+	+	+	+	+	-	+	+	-	+	-	-	+	-	-
7.	3g	+	+	-	+	+	+	+	+	-	+	+	-	-	-	-	-	-	-
8.	3h	+	-	+	+	+	+	+	-	+	+	-	+	+	-	+	-	+	+

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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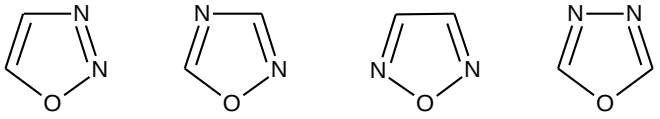
Part- A

(Part-III)

Studies on 1,3,4- Oxadiazole Derivatives

INTRODUCTION

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



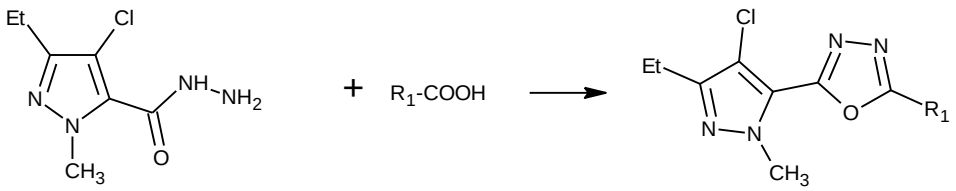
(1) (2) (3) (4)

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

SYNTHETIC ASPECT

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

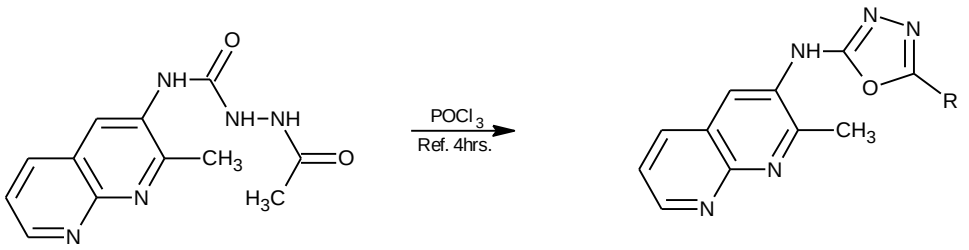
1. Hansong Chen et al.[9] have synthesized oxadiazoles (5) by the reaction of hydrazide and aromatic acid in presence of $POCl_3$.



(5)

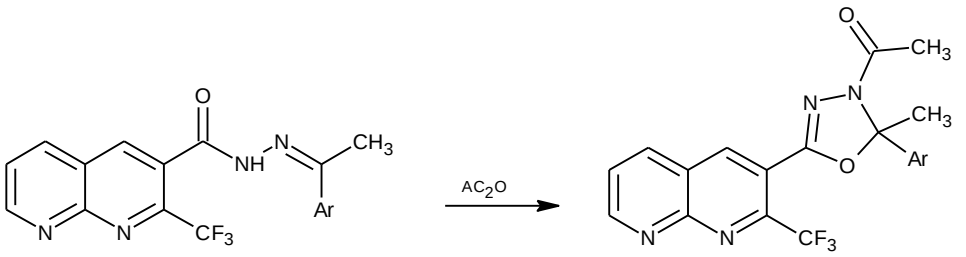
2. D. Ramesh and B. Sreenivasan[10] have synthesized 1,3,4-oxadiazoles (6) from

semicarbazide in presense of $POCl_3$.



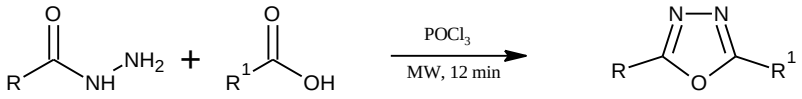
(6)

3. K. Mogilaiah and B. Sakram[11] have prepared 1,3,4-oxadiazole (7) from aceto-phenone-2-trifluoromethyl- 1,8-naphthyridine-3-carbonyl hydrazone in presence of acetic anhydride.



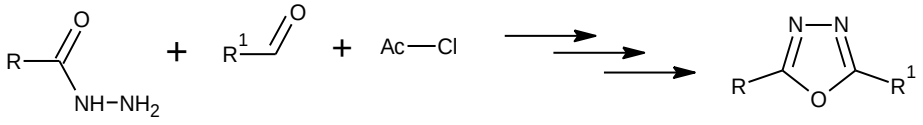
(7)

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



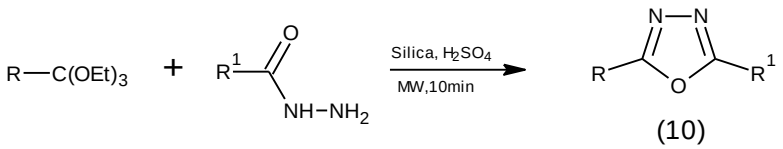
(8)

5. L. Somogyi[13] synthesized 1,3,4-oxadiazole (9) from several steps, from aryl hydrazide and aryl aldehyde.



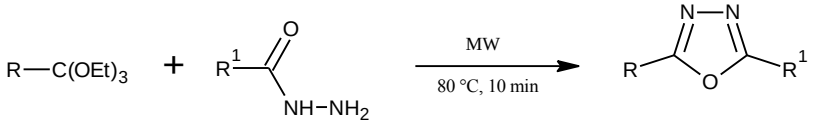
(9)

6. Silica sulfuric acid catalyst used for the rapid and ecofriendly synthesis of 1,3,4-oxadiazoles (10) at ambient temperature by M. Dabiri et al[14].



(10)

7. Green chemistry and one-pot, solvent-free using microwave radiated synthesis of 1,3,4-oxadiazoles (11) were reported by V. Polshettiwar[15]



(11)

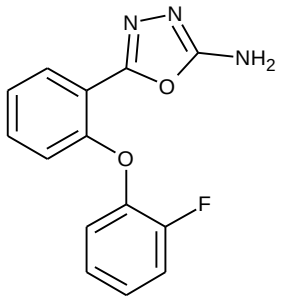
BIOLOGICAL EVALUATION

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

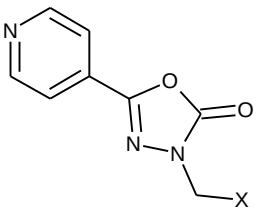
1. Antibacterial[16]
2. Antiinflammatory[17]
3. Analgesic[18]
4. Antiviral and anticancer[19]
5. Antihypertensive[20]
6. Anticonvulsant[21]
7. Antiproliferative[22]
8. Antifungal[23]
9. Cardiovascular[24]
10. Herbicidal[25]
11. Hypoglycemic[26]
12. Hypnotic and Sedative[27]
13. MAO inhibitor[28]
14. Insecticidal[29]

Bhardwaj Niti 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, anti-inflammatory, ulcerogenic effects and inhibitory activity on plasma prostaglandin E_2 (PGE_2) Level.

Santos Filho et al.[32] have reported 1,3,4-oxadiazoles for their anti-inflammatory activity. Song Cao et al.[33] have investigated some oxadiazoles possessing insecticidal activity. Krishna Kant Jha 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 (12) as anticonvulsant agent. Meria Grazia Mamolo et al.[36] have synthesized 3-substituted-5-(pyridine-4-yl)-3*H*-1,3,4-oxadiazole-2-one of type (13) and studied their antimycobacterial activity.

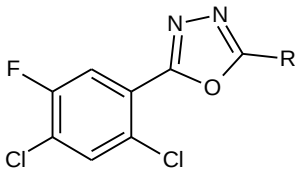


(12)

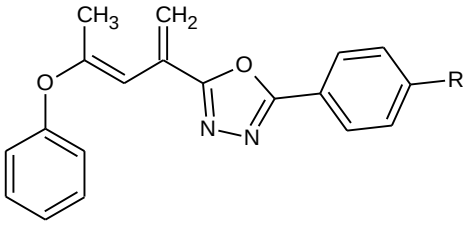


(13)

H. Rajak. et al.[37] have reported antimicrobial activity of oxadiazole derivatives. J. A. Christopher. et al.[38] have documented human immunodeficiency virus infection of 1,3,4-oxadiazole derivatives. B. Jayashankar et al.[39] have synthesized some oxadiazoles as anti-inflammatory and analgesic agents. K. Subrahmanya Bhat et al.[40] have prepared new fluorine containing 1,3,4-oxadiazoles (14) 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 (15) and screened for their insecticidal activity.

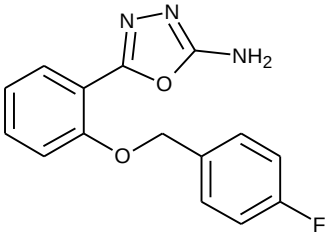


(14)



(15)

Ronald Kim et al.[42] have discovered oxadiazole derivatives useful as protease inhibitors. Mohd Amir and Kumar Shikha[43] have documentedanti-inflammatory, analgesic and ulserogenic activity of some newly synthesized oxadiazoles. Ali A.et al.[44] have investigated some oxadiazole derivatives possessing antimicrobial and anti-HIV-1 activity. Sherif A. et al.[45] have reported oxadiazoles as potential antitumor and anti-HIV agents. Afshin Zarghi et al.[46] have synthesized R-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles (16) possessing anticonvulsant activity. Mahamud Tareq et al.[47] have synthesized 2,5-disubstituted-1,3,4-oxadiazoles (17) useful as tyrosinase inhibitors.



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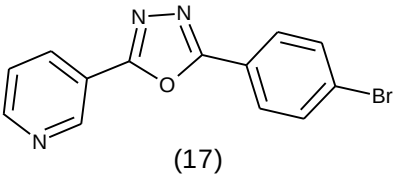


(17)

Work done from our laboratory

K. M. Thaker[48] have synthesized 2-(3',5'-dichlorobenzo[*b*]thiophen-2'-yl)-5-aryl-1,3,4-oxadiazoles in the presence of aromatic acid. S. L. Vasoya[49] reported facile synthesis of some new azetidinones and acetyl oxadiazoles bearing benzo[*b*]thiophene nucleus as a potent biological active agent. Synthesis and antimicrobial activity of 2-aryl-5-(5',7'-diiodo-8'-quinolinoxy)-1,3,4-oxadiazoles have been reported by H. S. Joshi[50].

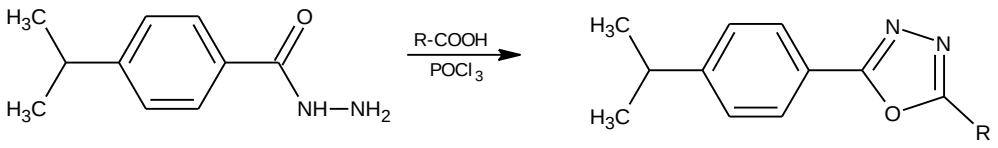
Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological screening, we have under taken the synthesis of several oxadiazoles which has been described as under.

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

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4-ISOPROPYLPHENYL)-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 (IV) have been prepared by condensation of 4-isopropylbenzohydrazide with different aromatic acid in presence of $POCl_3$.

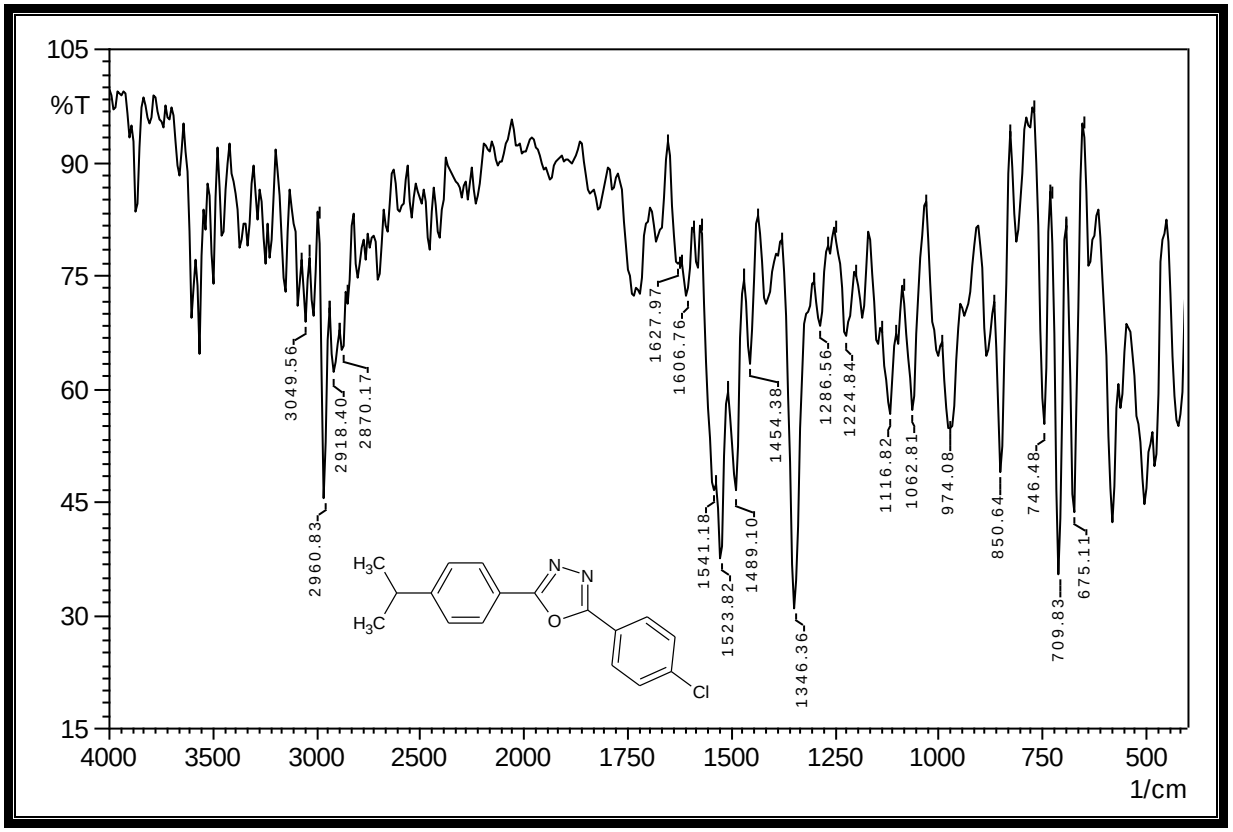


Type (IV) R=Aryl

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.4b.

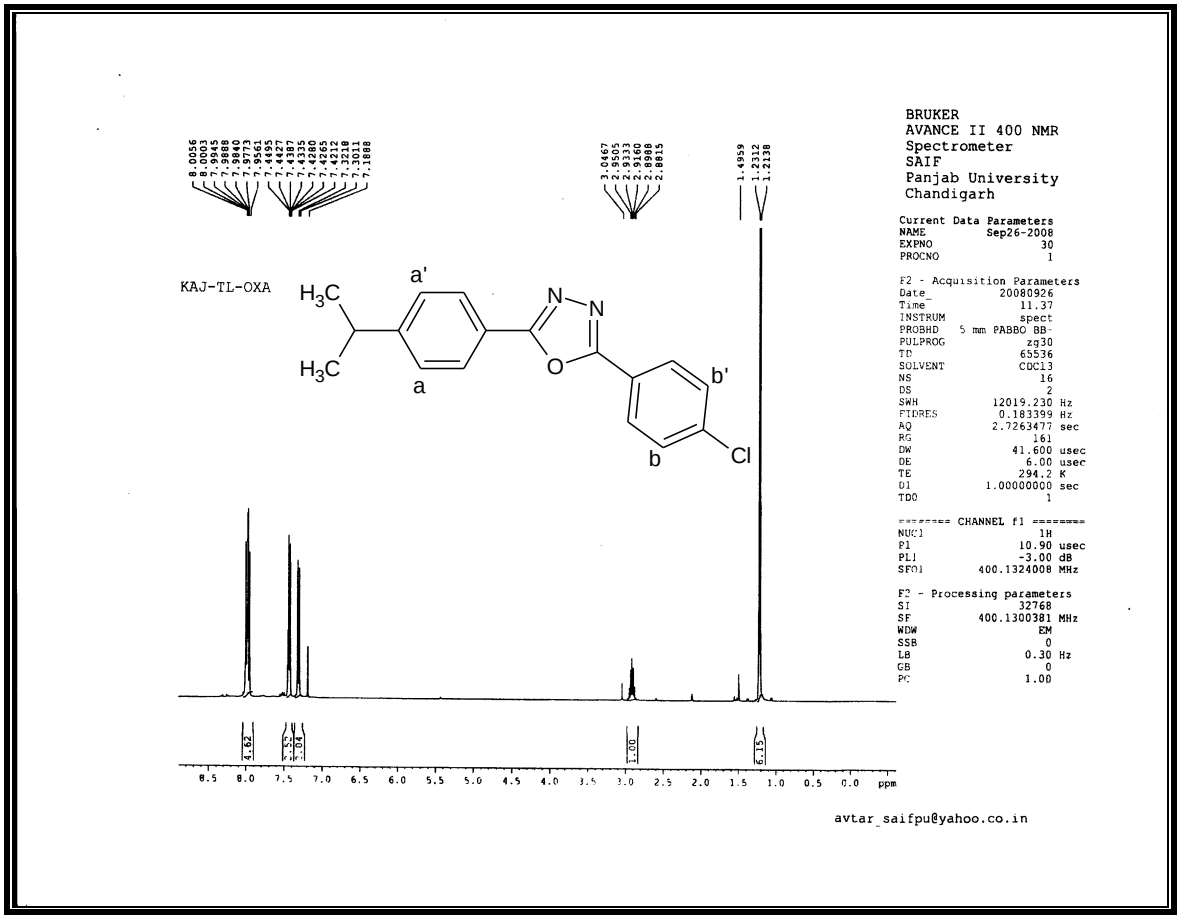
IR SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-5-(4-ISOPROPYL-PHENYL)-1,3,4-OXADIAZOLE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2960	2975-2950	51
	C-H str. (sym.)	2870	2880-2860	51
	C-H def. (asym.)	1454	1470-1435	51
	C-H def. (sym.)	1346	1385-1370	51
Aromatic	C-H str.	3049	3080-3030	52
	C=C str.	1523	1585-1480	52
	C-H i.p.(def)	1062	1125-1000	52
	C-H o.o.p. (def)	850	835-810	51
Isopropyl	$CH(CH_3)_2$	2870	2800-2900	36
Oxadiazole	C=N str.	1606	1650-1580	52
	-N-N- str.	1116	1220-1020	52
	-C-O-C- str.	1062	1075-1020	52
Halide	C-Cl str.(asym.)	746	800-600	53

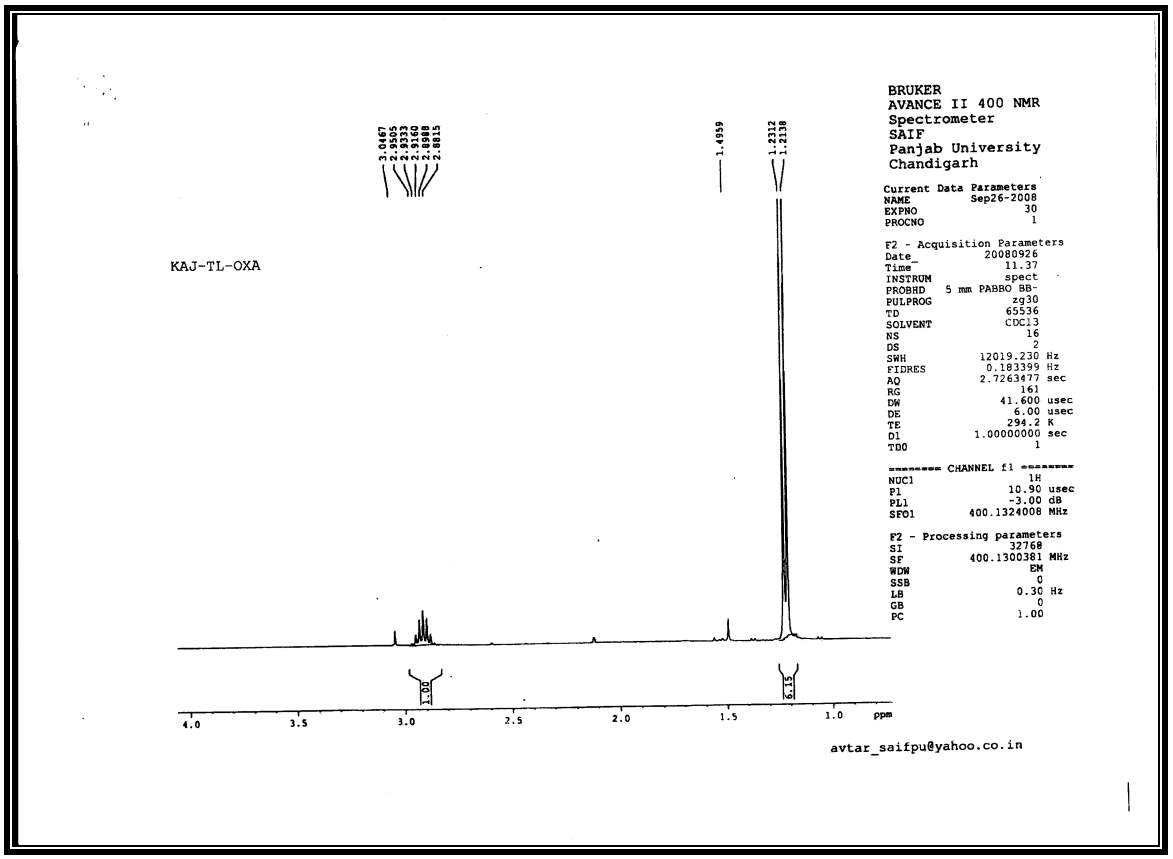
NMR SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-5-(4-ISOPROPYL-PHENYL)-1,3,4-OXADIAZOLE.



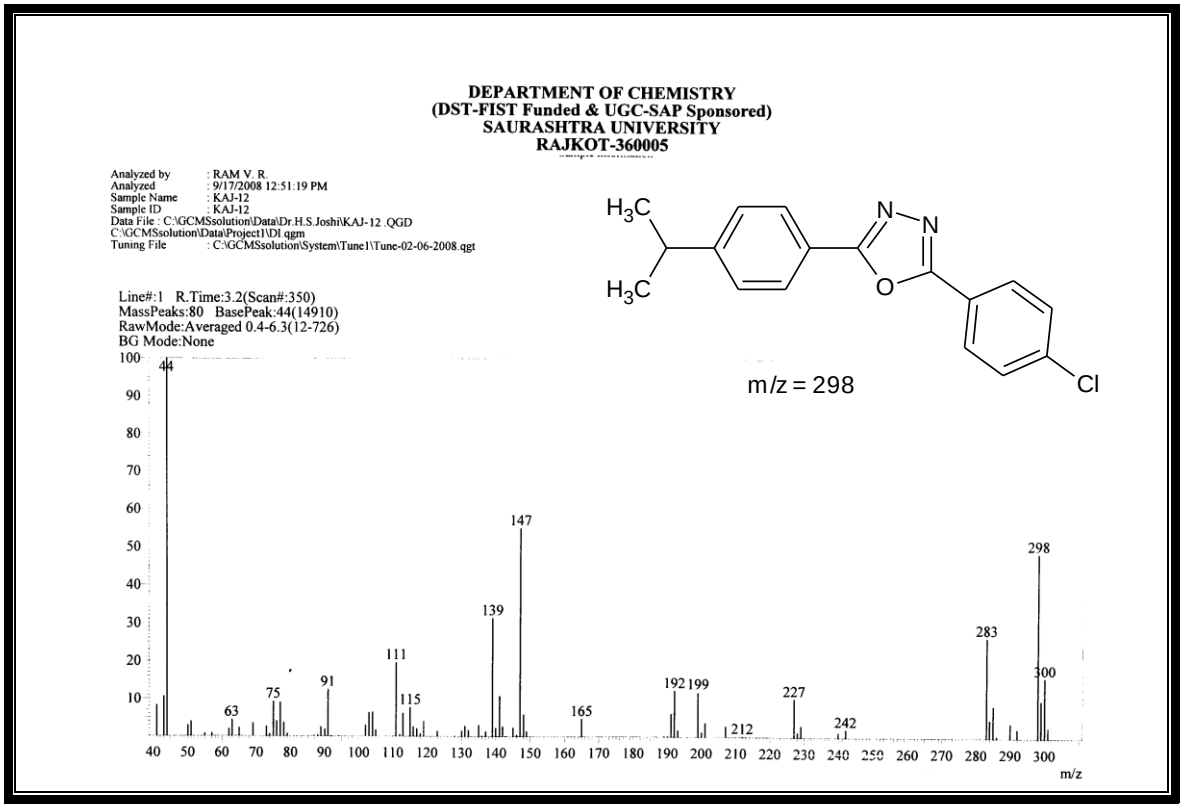
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (400MHz)

Sr.No.	Chemical shift in ppm	Relative No. of protons	Multiplicity	Inference	J value in Hz
1	1.21-1.23	6H	doublet	$-CH_3$	6.96
2	2.88-2.95	1H	multiplet	-CH	-
3	7.30-7.32	2H	doublet	Ar-Ha,a'	8.28
4	7.42-7.44	2H	doublet	Ar-Hb,b'	11.32
5	7.97-8.0	4H	multiplet	Ar-H	

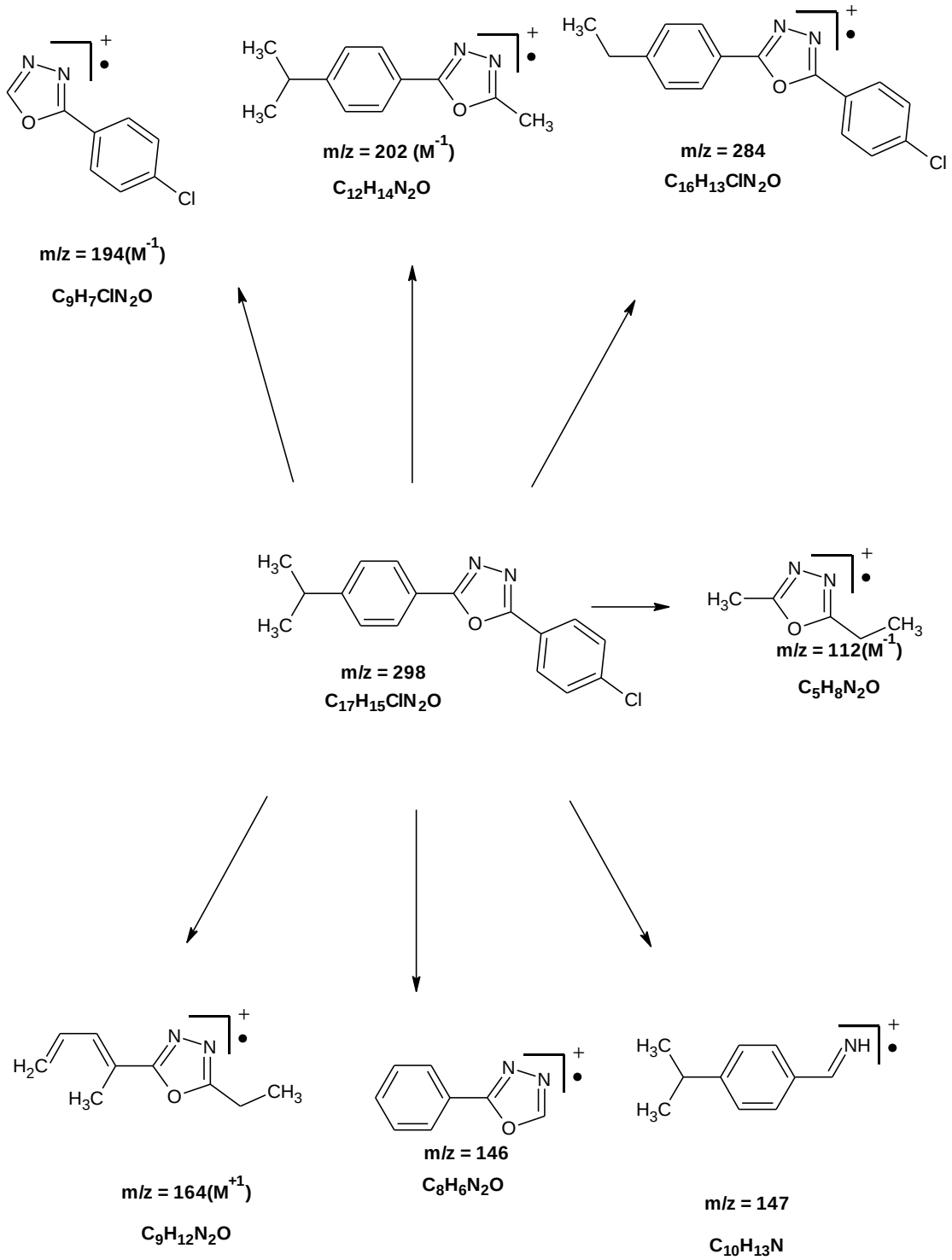
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-5-(4-ISOPROPYL-PHENYL)-1,3,4-OXADIAZOLE.



PROPOSED MASS FRAGMENTATION OF 2-(4-CHLOROPHENYL)-5-(4-ISOPROPYLPHENYL)-1,3,4- OXADIAZOLE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Preparation of 4-Isopropylbenzohydrazide.

A mixture of methyl 4-isopropylbenzoate (1.78g, 0.01mol) and hydrazine hydrate (2.0 ml, 0.02mol) 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] Preparation of 2-(4-Chlorophenyl)-5-(4-isopropylphenyl)-1,3,4-oxadiazole

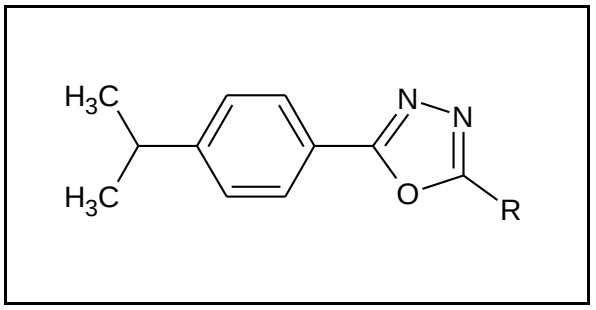
A mixture of 4-Isopropylbenzohydrazide (1.78g, 0.01mol) and 4-chloro benzoic acid (1.56g, 0.01mol) in phosphorous oxychloride (10 ml) was refluxed for 6 hrs. The content was cooled, poured onto crushed ice and neutralized with sodium bicarbonate solution. Crude product was isolated and crystallized from ethanol. Yield 60%, m.p 78 °C Anal. Calcd $C_{17}H_{15}ClN_2O$; C,68.34; H,5.06; N,9.38 %; Found: C,68.70; H,4.83; N,9.49 %.

Similarly other oxadiazoles have been prepared. The physical data are recorded in table No. 4a.

[C] Antimicrobial activity of 2-(4-Isopropylphenyl)-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 Table No.4b.

Table-4a: Physical constants of 2-(4-Isopropylphenyl)-5-aryl-1,3,4-oxadiazoles



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
4a	4-OCH_3-C_6H_4-	$C_{18}H_{18}N_2O_2$ 294.34	240	68	73.45 (73.09)	6.16 (6.13)	9.52 (9.21)
4b	C_6H_5-	$C_{17}H_{16}N_2O$ 264.32	210	54	77.25 (77.03)	6.10 (6.05)	10.60 (10.22)
4c	2-CH_3-C_6H_4-	$C_{18}H_{18}N_2O$ 278.34	200	56	77.67 (77.61)	6.52 (6.26)	10.06 (10.01)
4d	4-Br-C_6H_4-	$C_{17}H_{15}BrN_2O$ 343.21	250	62	59.49 (59.32)	4.41 (4.13)	8.16 (8.09)
4e	3-Cl-C_6H_4-	$C_{17}H_{15}ClN_2O$ 298.76	265	69	68.34 (68.13)	5.06 (4.86)	9.38 (9.27)
4f	4-NO_2-C_6H_5-	$C_{17}H_{15}N_3O$ 309.31	190	58	66.01 (65.86)	4.89 (4.65)	13.58 (13.42)
4g	3-NO_2-C_6H_4-	$C_{17}H_{15}N_3O$ 309.31	160	66	66.01 (65.83)	4.89 (4.61)	13.58 (13.19)
4h	4-Cl-C_6H_4-	$C_{17}H_{15}ClN_2O$ 298.76	251	64	68.34 (68.19)	5.06 (5.00)	9.38 (9.19)
4i	4-NH_2-C_6H_4-	$C_{17}H_{17}N_3O$ 279.33	240	68	73.10 (73.04)	6.13 (6.08)	15.04 (15.00)
4j	2-OH-C_6H_4-	$C_{17}H_{16}N_2O_2$ 280.32	220	50	72.84 (72.79)	5.75 (5.59)	9.99 (9.84)

TABLE 4B : ANTIMICROBIAL ACTIVITY OF 2-(4-ISOPROPYLPHENYL)-5-ARYL-1,3,4-OXADIAZOLES

(in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	4a	+	+	-	+	+	+	+	+	-	-	-	-	+	+	-	+	+	+
2.	4b	+	+	-	+	-	+	+	-	+	-	+	+	-	+	-	+	+	-
3.	4c	-	-	-	+	+	-	-	-	-	+	+	-	+	+	+	+	+	-
4.	4d	-	-	-	+	+	-	-	-	-	-	-	-	+	+	-	+	+	-
5.	4e	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
6.	4f	+	+	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-
7.	4g	+	+	-	+	+	+	+	+	-	-	-	-	+	+	-	+	+	+
8.	4h	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	-
9.	4i	+	+	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+
10.	4j	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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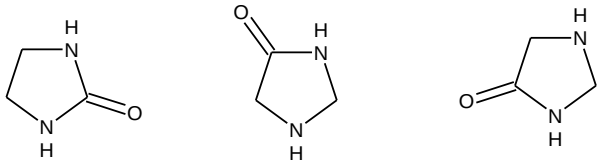
Part- A

(Part-IV)

Studies on Imidazolones Derivatives

INTRODUCTION

Imidazolinone, a five membered heterocycle having 2-nitrogen atoms at the 1 and 3-positions and C=O group at following positions: 2-oxo-imidazoline (1), 4-oxo-imidazoline (2), 5-oxo-imidazoline (3). Imidazolines are structurally related to guanidines and amidines.



(1) (2) (3)

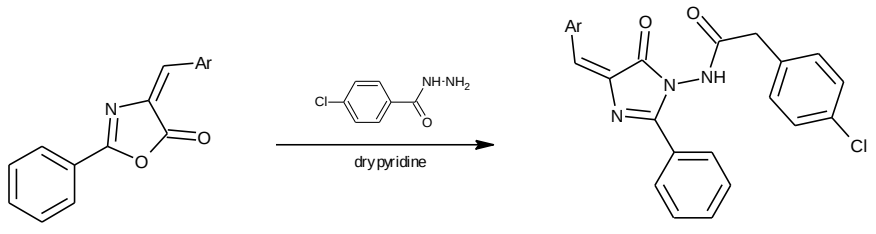
The discovery of the 2-substituted-5-imidazolines dates back to the year 1888, when A. W. Hoffmann[1] for the first time discovered 5-oxo-imidazoline by heating N^1-diacetyl ethylene diamine in a stream of dry hydrogen chloride and moreover the same compound was prepared by A. Ladenburg[2] by the fusion of two equivalents of sodium acetate with one equivalent of ethylene diamine dihydrochloride.

Imidazolinone has been used extensively as a corrosion inhibitor on certain transition metals, such as copper. Preventing copper corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion.

SYNTHETIC ASPECT

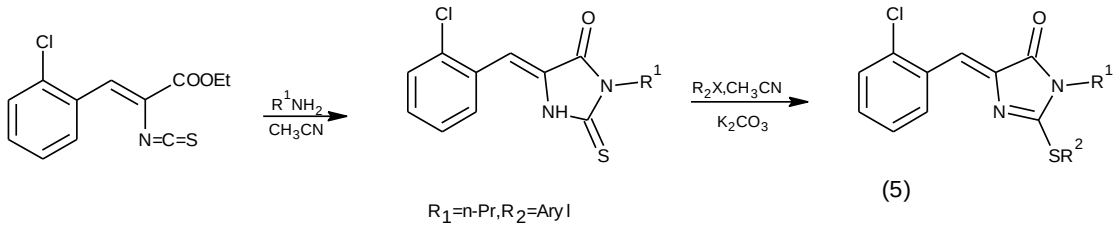
Various methods have been reported for the synthesis of imidazolinones in literature[3]. Aminolysis of oxazolone with amines led to the formation of imidazolinones which has been reported in literature[4].

1. A. Saxena et al.[5] have synthesized new imidazolinone derivatives (4).



(4)

2. X. Huang[6] et al. have synthesized some new imidazolinone derivatives (5).



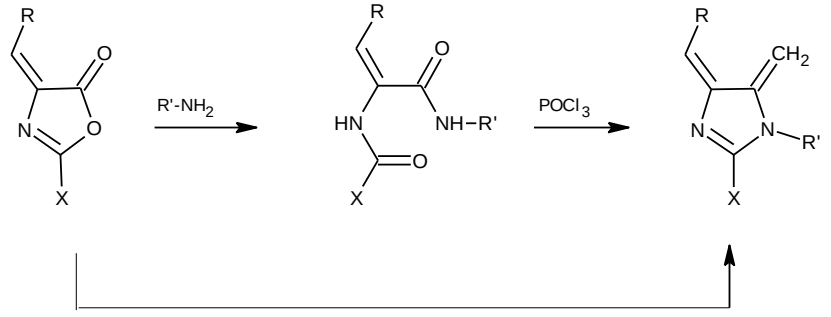
(5)

R_1=n-Pr,R_2=Aryl

3. A. V. Patel et al.[7] have synthesized new Imidazolinone derivatives by conventional method.
4. Zeng, Han et al.[8] have synthesized 5-imidazolinone derivatives with 2-bromoacetic acid as a starting material.

MECHANISM

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



R' = NH_2,Dry C_5H_5N/Abs.C_2H_5OH,K_2CO_3

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

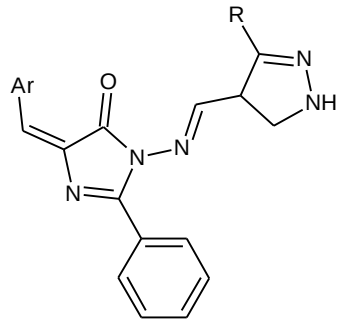
BIOLOGICAL EVALUATION

Naphazoline hydrochloride, xylometazoline hydrochloride etc. are various imidazolinone derivatives which have been used as adrenergic stimulants and tolazoline

and phentolamine as adrenergic blocking agents. Various imidazolinones are known to exhibit a broad spectrum of biological activities such as:

1. Antitubercular[9]
2. Anti cancer[10]
3. Insecticidal[11]
4. Antiviral[12]
5. Hypertensive[13]
6. Antiinflammatory[14]
7. Glucagon antagonists[15]
8. Antimicrobial[16]
9. Antihistaminic[17]
10. Antidiabetic[18]

Bascou and co-workers[19] have prepared some new imidazolinones and reported their agrochemical activity. Kolhe Vishnu et al.[20] have reported anti AIDS, antibacterial and fungicidal activity of 5-oxo-imidazolines. Herbicidal activity of imidazolinone derivatives have been reported by U. Akyoshi et al.[21] Ding M. et al.[22] and Pilkington B. et al.[23] have reported a new series of biologically active analogues of 5-oxo-imidazolines. Imidazolinone derivatives[24] which possess antifungal activity have been reported. Some new 5-oxoimidazolines[25] as antimicrobial agents have been investigated. L. Joseph Patel and co-workers[26] have prepared substituted imidazolinones which inhibited the abnormal cell growth in human body. B. Kalluraya et al.[27] (IV) have reported antibacterial, antifungal, anti-inflammatory and analgesic activity of 5- oxo-imidazolines.



(6)

Work done from our laboratory

A. M. Vyas[28] have synthesized some new imidazolones. Synthesis of some new imidazolones and 1,2,4-triazoles bearing benzo[*b*]thiophene nucleus as antimicrobial agents have been reported by K. M. Thakar[29]. 1-*N*-substituted benzalaminothiocarbonyl-2-methyl-4-(8'-hydroxyquinolin-7'-yl)methine-5-imidazolones have been reported by A. M. Vyas[30].

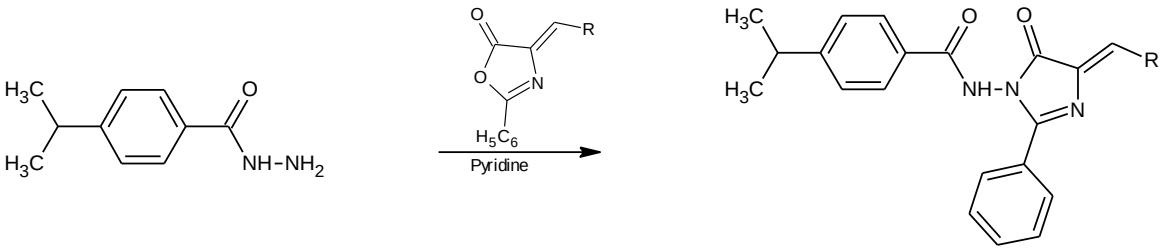
Literature survey reveals that the compounds bearing imidazolones moiety possess potential drug activity. Looking to the diversified biological activities we have synthesized some pyrazole derivatives in order to achieving better therapeutic agents. These studies are described in following section.

SECTION - I : **SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-(4-(ARYLIDENE)-4,5-DIHYDRO-5-OXO-2-PHENYLIMIDAZOL-1-YL)-4- ISOPROPYLBENZAMIDES**

SECTION – I

SYNTHESIS AND BIOLOGICAL SCREENING OF N-(4-(ARYLIDENE)-4,5-DIHYDRO-5-OXO-2-PHENYLIMIDAZOL-1-YL)-4-ISOPROPYLBENZAMIDES.

Various imidazolinones have resulted in many potential drugs and are known to possess a broad biological spectrum. In view of getting better therapeutic agents and considering the association of various biological activities with 4-isopropylbenzohydrazide nucleus, the preparation of 5-imidazolones of type-(V) have been undertaken by the condensation of 4-isopropylbenzohydrazide with substituted azalactones which in turn have been prepared by well known Ertenmeyer azalactone synthesis.

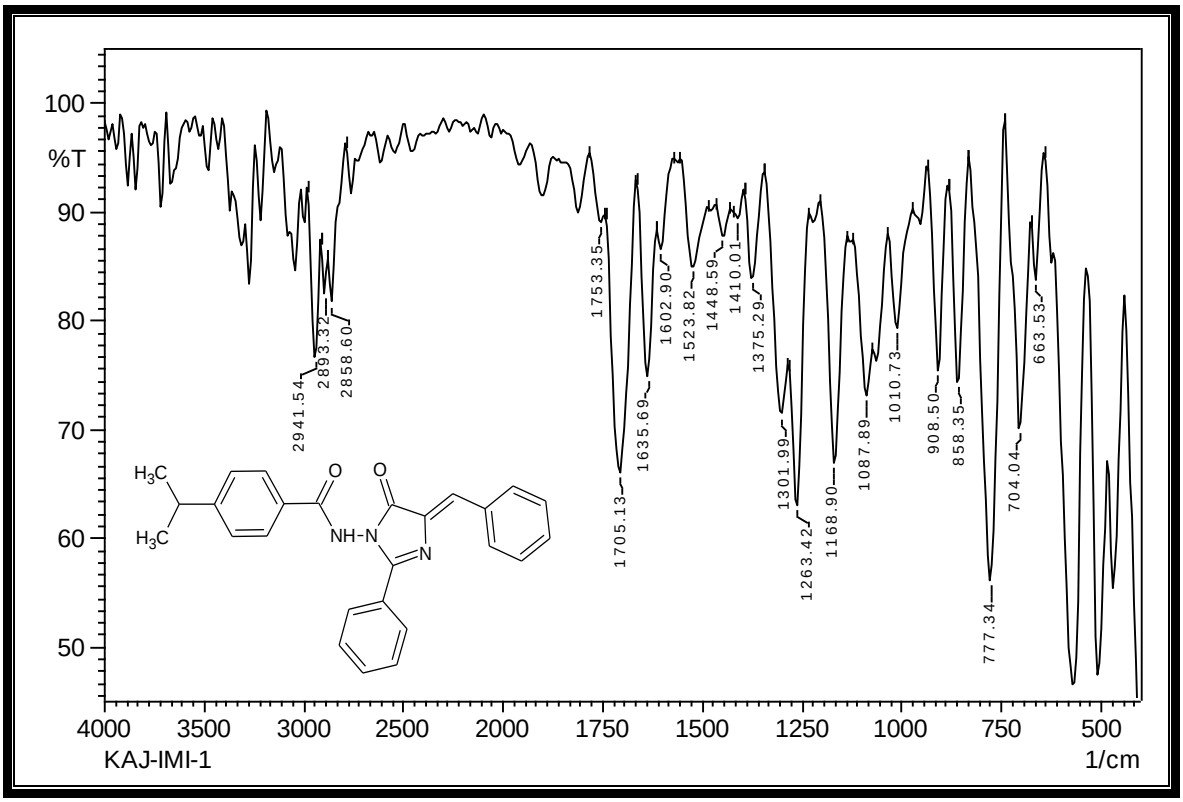


Type (V) R= Aryl

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.5b.

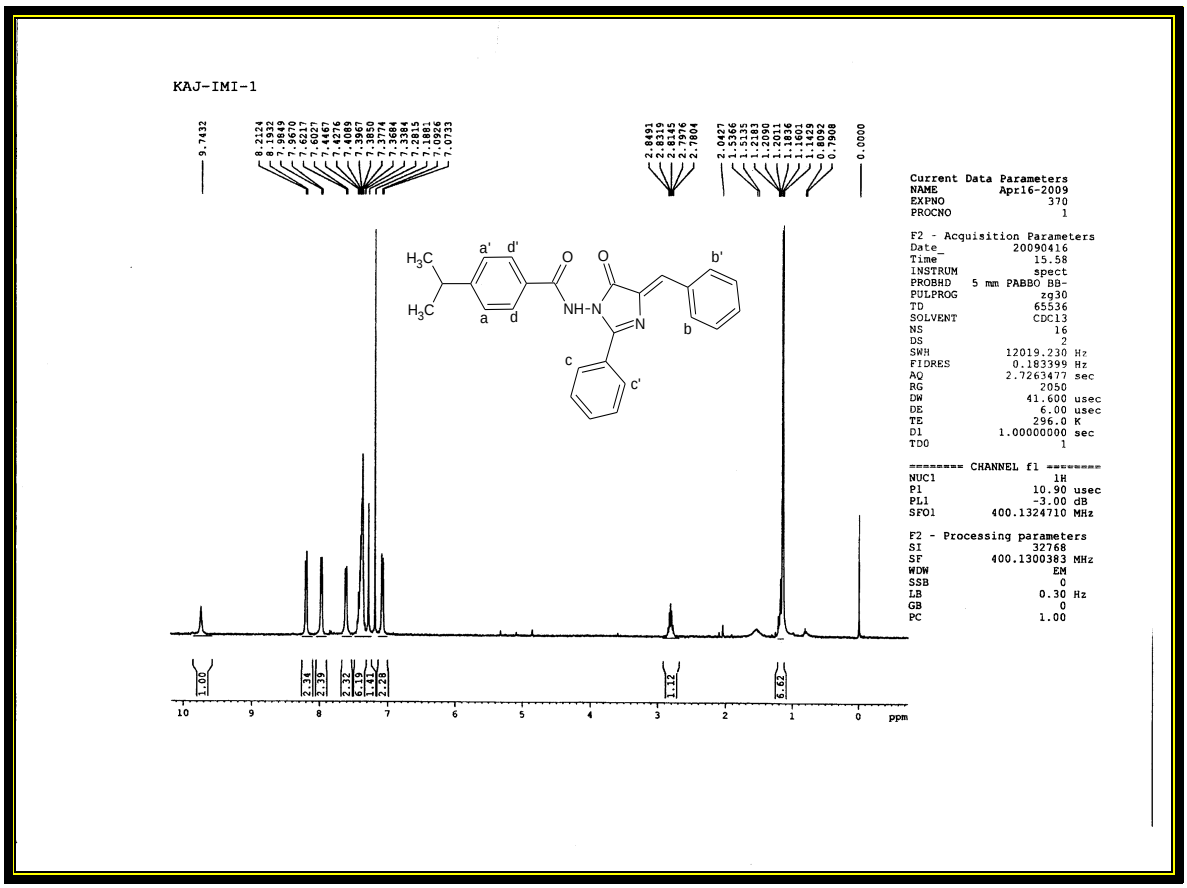
IR SPECTRAL STUDIES OF N-(4-BENZYLIDENE-4,5-DIHYDRO-5-OXO-2-PHENYLIMIDAZOL-1-YL)-4-ISOPROPYLBENZAMIDE



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane-CH_3	C-H str.	2941	2975-2940	31
	C-H str. (sym.)	2858	2880-2860	31
	C-H def.	1448	1470-1435	31
	C-H def. (sym.)	1375	1395-1370	31
Aromatic	C-H str.	2941	2980-2930	32
	C=C str.	1523	1585-1480	32
	C-H I.p.(def)	1067	1125-1000	32
	C-H o.o.p.	663	700-600	31
Isopropyl	-$CH(CH_3)_2$	2893	2800-2900	36
Imidazoline	C=N str.	1635	1650-1580	32
	C=O str.	1753	1760-1700	32
	C-N str.	1010	1050-1010	33
Amide	N-H bend.	1635	1630-1550	33

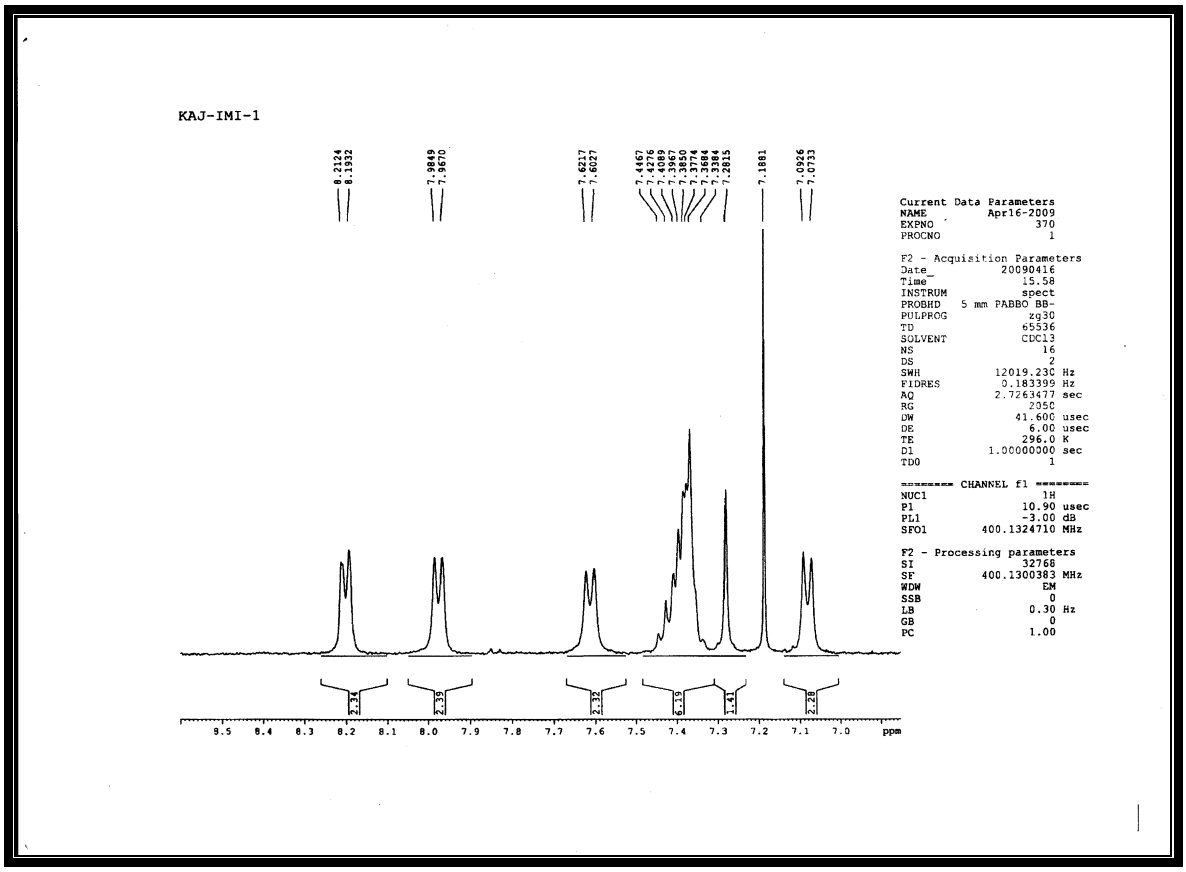
NMR SPECTRAL STUDIES OF *N*-(4-BENZYLIDENE-4,5-DIHYDRO-5-OXO-2-PHENYLIMIDAZOL-1-YL)-4-ISOPROPYLBENZAMIDE



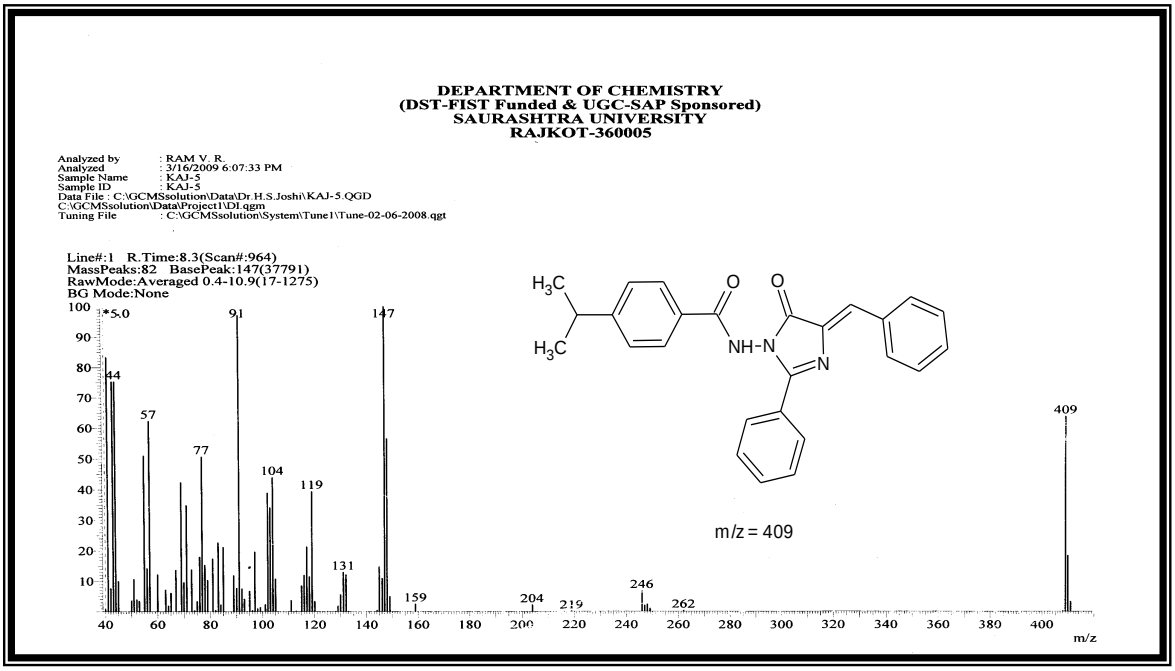
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (400MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	1.42-1.46	6H	doublet	$-CH_3$	6.88
2	2.78-2.84	1H	multiplet	-CH	---
3	7.07-7.09	2H	doublet	-Ar-Ha,a'	7.72
4	7.28	1H	singlet	-CH	---
5	7.36-7.44	6H	multiplet	-Ar-H	---
6	7.60-7.62	2H	doublet	-Ar-Hb,b'	7.60
7	7.96-7.98	2H	doublet	-Ar-Hc,c'	7.16
8	8.19-8.21	2H	doublet	-Ar-Hd,d'	7.68
9	9.74	1H	singlet	-NH	---

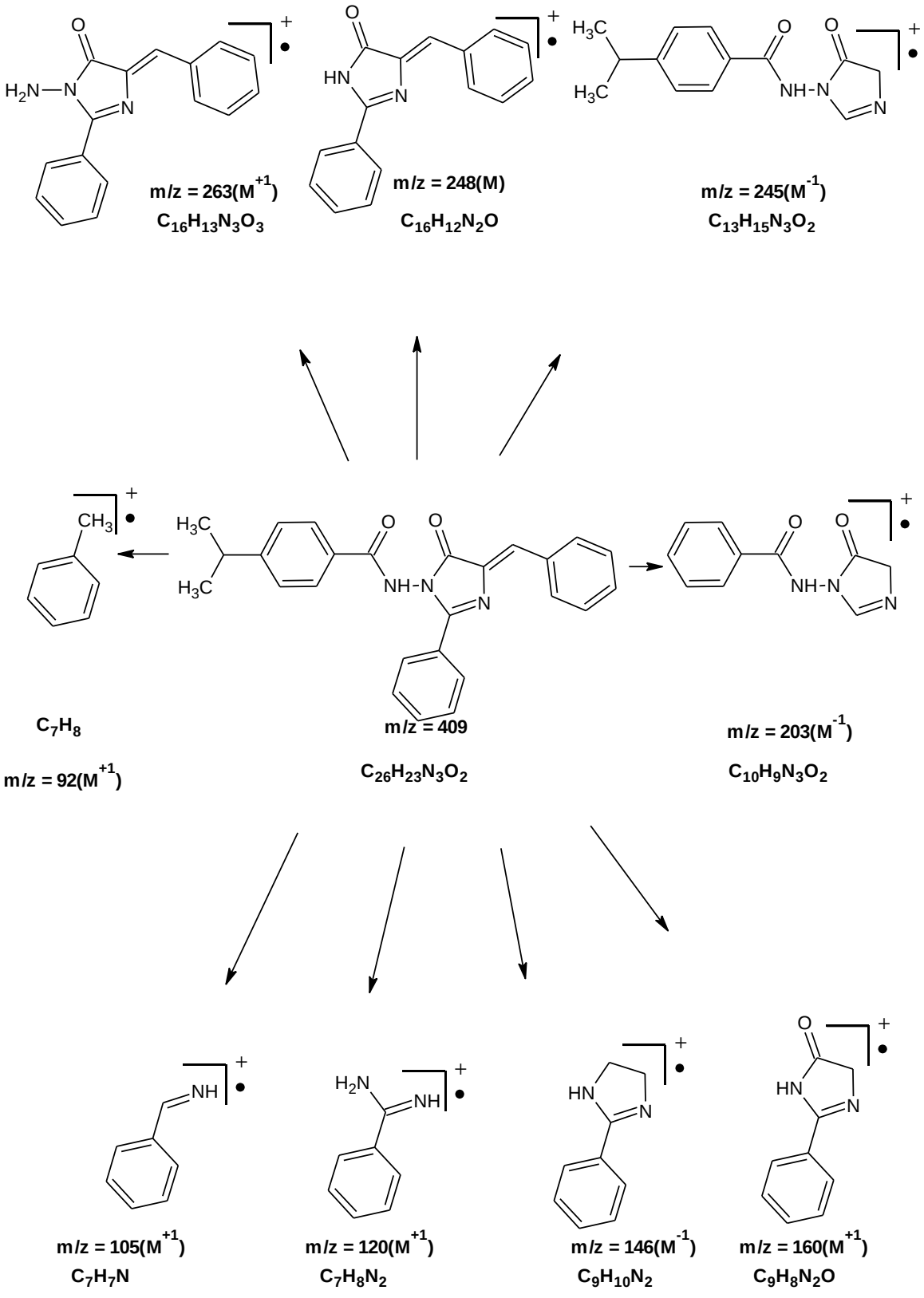
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF *N*-(4-BENZYLIDENE-4,5-DIHYDRO-5 OXO-2-PHENYLIMIDAZOL-1-YL)-4-ISOPROPYLBENZAMIDE



PROPOSED MASS FRAGMENTATION OF *N*-(4-BENZYLIDENE-4,5-DIHYDRO-5-OXO-2-PHENYLIMIDAZOL-1-YL)-4-ISOPROPYLBENZAMIDE



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of 4-Isopropylbenzohydrazide.

A mixture of methyl 4-isopropylbenzoate (1.78g, 0.01mol) and hydrazine hydrate (2.0 ml, 0.02mol) 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 4-Arylidene-2-phenyl-5-oxazolinones.

These were prepared by the condensation of substituted benzaldehyde with benzoyl glycine in presence of sodium acetate and acetic anhydride as described by Vogel[34].

[C] Synthesis of *N*-(4-Benzylidene-4,5-dihydro-5oxo-2-phenylimidazol-1-yl)-4-iso propylbenzamide isopropyl benzamide.

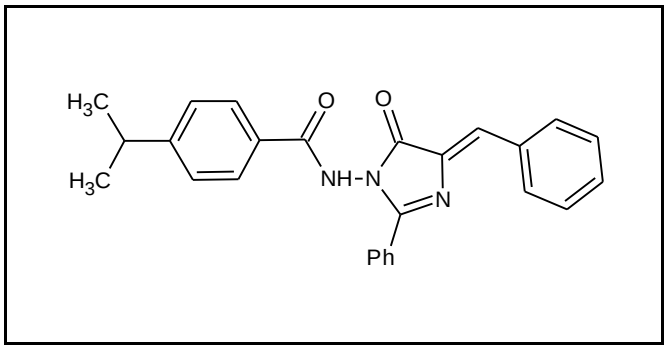
To a mixture of (4*Z*)-4-benzylidene-2-phenyloxazol-5(4*H*)-one(2.49g 0.01mol) and 4-isopropylbenzohydrazide (1.78g, 0.01mol) in 20ml of pyridine were refluxed for 6-8 hrs. The excess of solvent was removed under reduced pressure and reaction mixture was poured in crushed ice. The product was isolated and crystallized from benzene. Yield 64%, m.p 130 °C Anal. cald. for $C_{26}H_{23}N_3O_2$; C, 76.26; H,5.66; N,10.26 %; Found: C,76.23; H,5.88; N,10.65 %

Similarly other substituted imidazolones have been prepared. The physical constants are recorded in Table No.5a.

[D] Antimicrobial activity of *N*-(4-(Arylidene)-4,5dihydro-5-oxo-2-phenylimidazol-1-yl)-4-isopropylbenzamides.

Antimicrobial testing was carried out as described in Part-I, Section (D). The zones inhibitions of the compounds are recorded in Table No.5b.

Table-5a: Physical constants of *N*-(4-Arylidene-4,5-dihydro-5oxo-2-phenyl imidazol-1-yl)-4-isopropylbenzamides



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
5a	C_6H_5-	$C_{26}H_{23}N_3O_2$ 409.47	240	65	76.26 (76.13)	5.66 (5.38)	10.26 (10.03)
5b	3-NO_2-C_6H_4-	$C_{26}H_{22}N_4O_4$ 454.47	205	58	68.71 (68.45)	4.88 (4.47)	12.33 (12.18)
5c	4-NO_2-C_6H_4-	$C_{26}H_{22}N_4O_4$ 454.47	190	42	68.71 (68.36)	4.88 (4.58)	12.33 (12.06)
5d	4-OH -C_6H_4-	$C_{26}H_{23}N_3O_3$ 425.47	240	55	73.39 (73.05)	5.45 (5.28)	9.88 (9.61)
5e	2-NO_2-C_6H_4-	$C_{26}H_{22}N_4O_4$ 454.47	195	49	68.71 (68.36)	4.88 (4.76)	12.33 (12.06)
5f	2-OCH_3-C_6H_5-	$C_{27}H_{25}N_3O_3$ 439.50	220	53	73.78 (73.33)	5.73 (5.61)	9.56 (9.33)
5g	4-F-C_6H_4-	$C_{26}H_{22}FN_3O_2$ 427.47	228	65	73.05 (72.00)	5.19 (4.93)	9.83 (9.75)
5h	4-Cl-C_6H_4-	$C_{26}H_{22}ClN_3O_2$ 443.92	198	45	70.34 (70.13)	5.00 (4.95)	9.47 (9.40)
5i	4-OCH_3-C_6H_4-	$C_{27}H_{25}N_3O_3$ 439.50	208	66	73.78 (73.35)	5.73 (5.44)	9.56 (9.26)

TABLE 5B: ANTIMICROBIAL ACTIVITY OF *N*-4-(ARYLIDENE)-4,5DIHYDRO-5-OXO-2-PHENYL-IMIDAZOL-1-YL)-4-ISOPROPYLBENZAMIDES. (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	**5a**	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2.	**5b**	+	+	-	+	+	-	+	+	-	-	-	-	+	+	-	-	-	-
3.	**5c**	+	+	-	+	+	-	-	-	-	-	-	-	+	+	+	+	+	+
4.	**5d**	+	+	+	+	+	+	+	+	-	-	-	-	+	+	-	-	-	-
5.	**5e**	+	+	-	+	+	-	+	+	-	+	+	+	-	-	-	+	+	-
6.	**5f**	-	-	-	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+
7.	**5g**	+	-	+	+	-	-	-	+	-	+	+	-	-	-	+	-	+	+
8.	**5h**	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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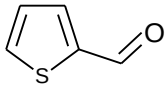
Part- B

Studies on Thiophene-2-Carbaldehyde Derivatives

INTRODUCTION

Thiophene-2-carbaldehyde (1) is an aromatic heterocyclic compound consisting of four carbon atoms and one sulfur atom in a five-membered ring. Thiophene was discovered by Viktor Meyer in 1883 as a contaminant in benzene[1]. Related to thiophene are benzothiophene and dibenzothiophene, containing the thiophene ring fused with one and two benzene rings.

It was observed that isatin forms a blue dye if, it is mixed with sulfuric acid and crude benzene. Victor Meyer was able to isolate the substance responsible for this reaction from benzene. This new heterocyclic compound was thiophene[2].



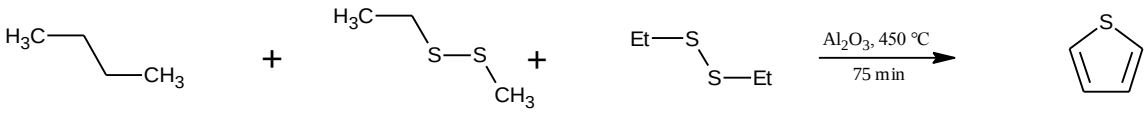
(1)

Thiophenes are important class of heterocyclic compounds and are recurring building blocks in organic chemistry with applications in pharmaceuticals. The benzene ring of a biologically active compound may often be replaced by a thiophene without loss of activity[3]. Thiophene and its derivatives occur in petroleum, sometimes in concentrations up to 1-3%. The thiophenic content of liquids from oil and coal is removed via the hydrodesulfurization (HDS) process.

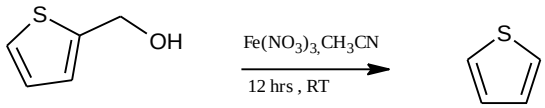
SYNTHETIC ASPECT

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

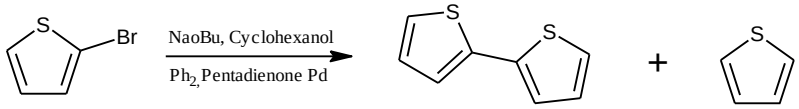
1. A. Y. Kopylov and co-workers[4] synthesized thiophene via butane, (methyldi-sulfanyl)ethane and (ethyldisulfanyl)ethane, using alluminium oxide as a catalyst.



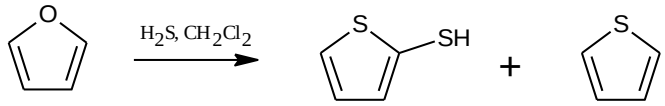
2. Liang, Xinmiao and workers[5] synthesized thiophene using ferrous nitrate and cyno methane.



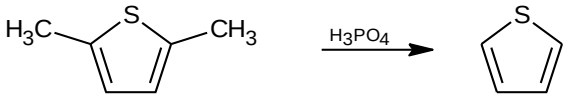
3. Moon, Jeongju and workers[6] synthesized thiophenes and 2,2'-bithiophene using Sodium butoxide and cyclohexenone, palladium as catalyst.



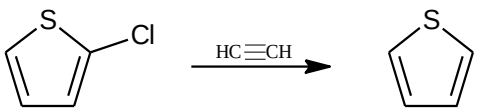
4. N. T. Berberova et al.[7] synthesized thiophenes and thiophene-2-thiol via dichloro methane and hydrogen sulphide at 20-25 °C.



5. A. R. Katritzky et al.[8] synthesized thiophenes from 2,5-dimethylthiophene using hydrophosphoric acid.



6. E. N. Deryagina and worker[9] synthesized thiophenes from 2-chlorothiophene and ethyne.

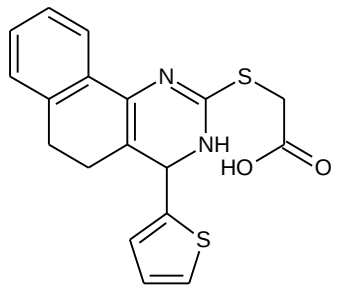


BIOLOGICAL EVALUATION

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

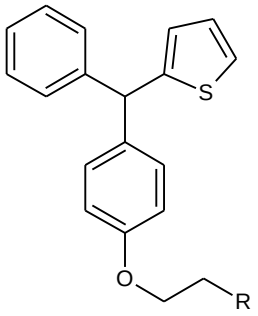
1. Analgesic[10-12]
2. Antimicrobial[13-15]
3. Anticonvulsant[16,17]
5. Antifungal[18,19]
6. Antihistaminic[20,21]
7. Antiinflammatory[22-25]
8. Antitumor[26-28]
9. Antiviral[29-31]
10. β-Adrenergic[32]
11. Diuretic[33]
12. Insecticidal[34-36]
13. antipsychotic[37,38]
14. Anticancer[39-42]

S. F. Mohmad[43] have prepared {[4-(thiophen-2-yl)-3,4,5,6-tetrahydrobenzo [*H*]quinazolin-2-yl]sulfanyl} acid (2) as a anti viral and anti cancer agent.



(2)

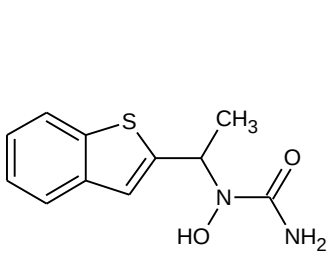
Gautam Panda[44] have prepared 2-{phenyl[4-(2-phenylethoxy)phenyl] methyl} thiophene (3) and tested for its antitubercular activity.



(3)

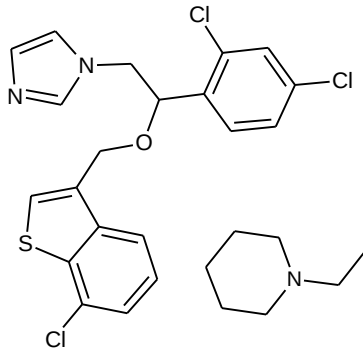
M. S. Malamas and coworkers[45] have synthesized novel thiophene derivatives inhibitors of protein tyrosine phosphatase 1B with antihyperglycemic properties. S. S. Perez et al.[46] developed 5-substituted thiophene derivatives with dual action at 5-HT_1A serotonin receptors and serotonin transporter as a new class of antidepressants. Synthesis and serotonergic activity of thiophene-4-piperazine derivatives as novel antagonists for the vascular 5-HT_1B receptor has been achieved by G. P. Moloney and group[47].

Derivatives of benzo[b]thiophene are also available as drug, some of them are shown as under:



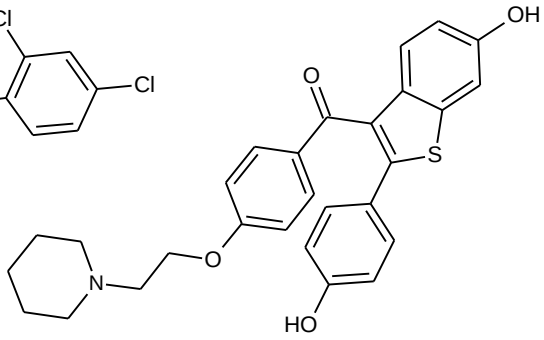
Zileuton (ZYFLOTM)

Antiashthamatic



Sertaconazole

Antifungal



Raloxifene

Anticancer/Osteroporosis

Work done from our laboratory

V. V. Kachhadia[48,49] have synthesized cyclohexenones, thiohydantoins and thiazolidinones derivatives bearing benzo[*b*]thiophene nucleus and reported their antitubercular and antimicrobial activity.

S. L. Vasoya[50,51,52] reported facile synthesis of some new azetidinones, acetyl oxadiazoles, thiosemicarbazides, 1,3,4-thiadiazoles, thiosemicarbazide as a potent antitubercular and antimicrobial agents bearing benzo[*b*]thiophene nucleus.

In view of procuring highly potent biodynamic agents after this literature survey and on continuation of our on going work on thiophenes derivatives for their various methods of synthesis and different biological activities, synthesis of thiophene have been undertaken in order to achieving superior therapeutic agents. This can be summarized in the following sections as under.

PART-I:

SECTION:I SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF CYCLOHEXENONES.

SECTION:II SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF INDAZOLES.

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

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Part- B

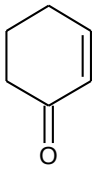
(Part-I)

Studies on Indazole Derivatives

INTRODUCTION

Cyclohexenones are derivatives of cyclohexane with carbonyl group at position-1 and double bond at position-2. There are different types of cyclohexenone derivatives but the greatest difference in structure and properties is exerted by the groups attached to carbon atom.

Cyclohexenones is the parent of a series of compounds that is important in agricultural and medicinal chemistry. Cyclohexenones can be conveniently synthesized by the treatment of α, β-unsaturated carbonyl compounds with ethyl acetoacetate in basic media.



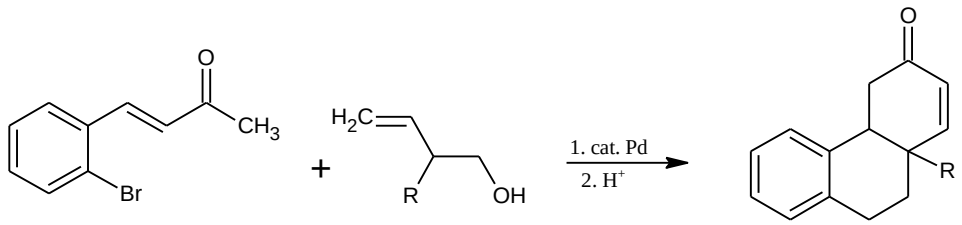
(1)

Cyclohexenone derivatives have gained lot of interest because of their prominent pharmaceutical properties.

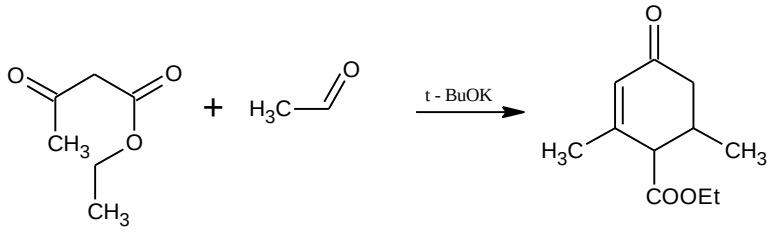
SYNTHETIC ASPECT

Various method for the synthesis of cyclohexenone derivatives have been described in literature[1-9].

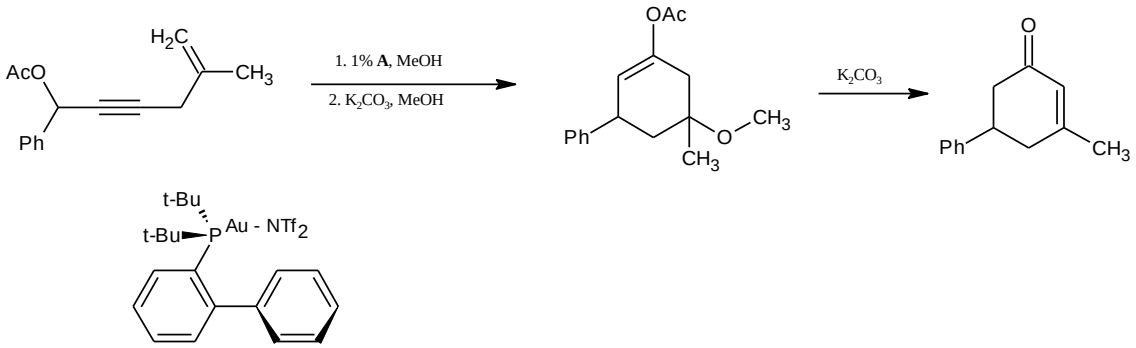
1. A review of the earlier literature by Gerald et al.[10] described representative synthetic procedure of cyclohexenone derivatives.



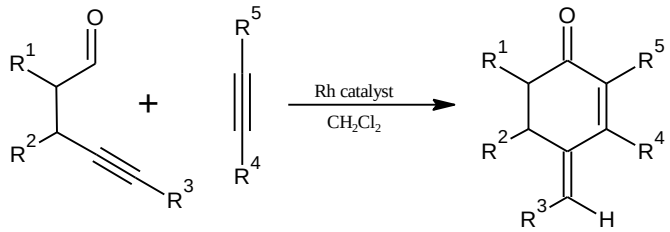
2. Byong-Don Chong et al.[11] have been prepared cyclohexenone derivatives by tandem michael addition-aldol condensation of β-keto esters to conjugate enones (or enals) in t-BuOH.



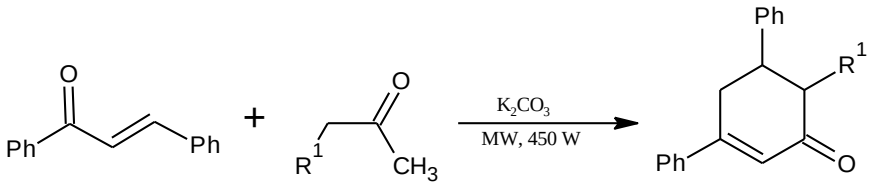
3. Andrea Buzas et al.[12] have been prepared cyclohexenone by reaction of various substituted 5-en-2-yn-1-yl acetates with using biphenyl phosphine as catalyst in methanol in basic media.



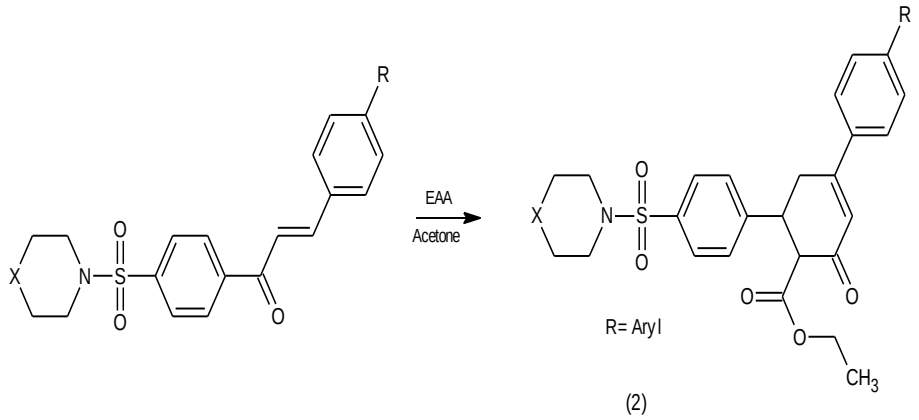
4. Ken Tanaka et al.[13] have synthesized cyclohexenone from 4-alkynals and alkynes in presence of Rh catalyst via novel [4+2] annulations.



5. Surya Prakash Rao and co workers[14] reported solvent-free microwave mediated Michael addition reactions to form cyclohexenones with 98 % yield.



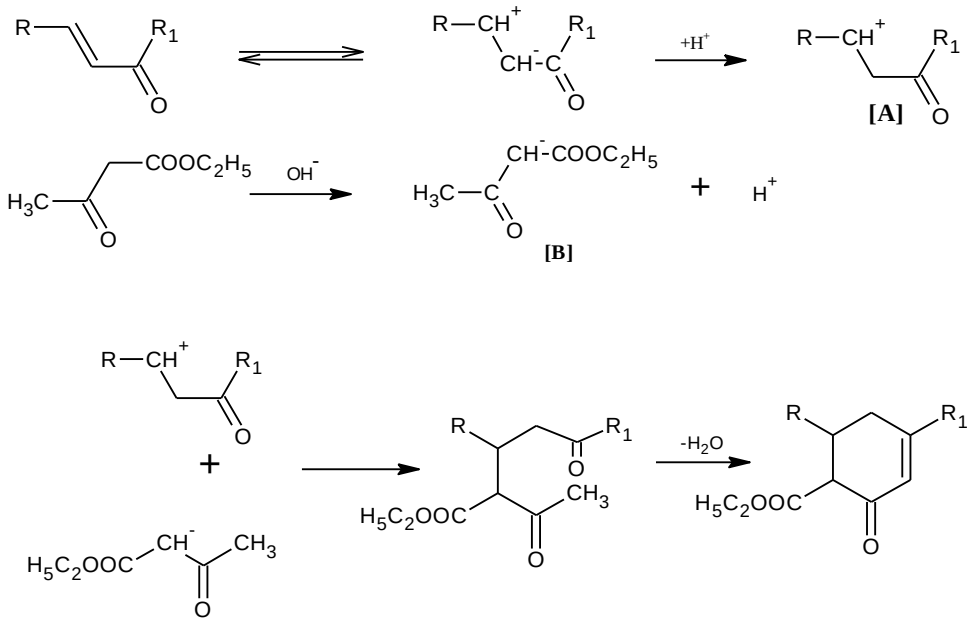
6. H. A. Eman et al.[15] have synthesized cyclohexenone derivatives from chalcone.



7. Page Philip C. and co-workers[16] have prepared ethyl substitute cyclohexenone derivatives.

8. S. S. Lokanatha Rai et al.[17] have reported synthesis of 6-methoxy-7-methyl-3-aryl-cyclohexyl-4-oxo-2-napthoate derivatives.

MECHANISM



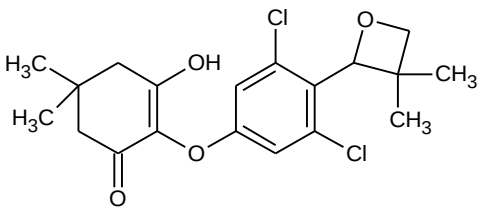
The addition reaction between ethyl acetoacetate and α,β-unsaturated ketone give cyclohexenone via michael addition. This reaction has been carried out in basic media by using sodium ethoxide or anhydrous K_2CO_3 in acetone. During the reaction, nucleophillic addition of carbanion take place to the C=C of the acceptor. The α,β-unsaturated compounds is known as acceptor and ethyl aceto acetate is known as donor.

BIOLOGICAL EVALUATION

Cyclohexenone and its derivatives are widely used in pharmaceutical industries some of them are as under.

1. Analgesic[18]
2. Antibiotic[19]
3. Anticancer[20]
4. Anticonvulsant[21]
5. Antitumor[22]
6. Cardiovascular[23]
7. Neurotropic activity[24]
8. Antiplatelet[25]
9. Antifungal[26]

Zhang Guo-Liang et al.[27] have reported some new cyclohexenones as anti-HIV-1 agents. Felix et al.[28], Nippon[29] and Engel Stephan et al.[30] (3) and (4) have been synthesized cyclohexenone derivatives as herbicidal agent.



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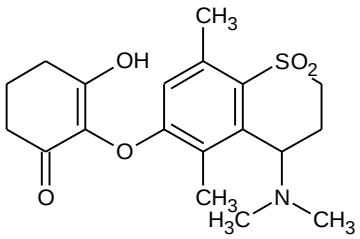
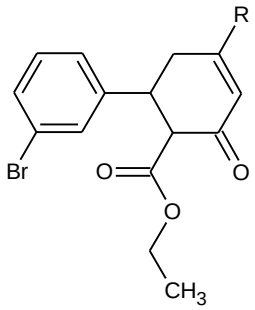


(4)

R. Joachim et al.[31] and Yoshida Shigeo et al.[32] have reported cyclohexenone derivatives having plant growth regulators which proved more effective than chlormequat chloride.

Moreover K. Reiner et al.[33] have reported cyclohexenone (5) derivatives having herbicidal agent. Gonzalez de Aguilar et al.[34] have reported some new cyclohexenones as

Neurotropic agents which have useful in cultured central nervous system neurons. Cyclohexenones possess inhibitory activity against the growth of lettuce seedling found by Kimara et al.[35] H. S. Joshi et al.[36] have synthesized and reported their antitubercular and antimicrobial activity.



(5) **R=Aryl**

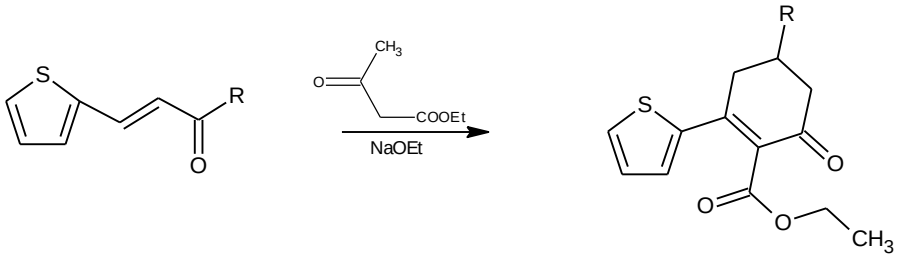
Thus, with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological screening, we have undertaken the synthesis of several cyclohexenone derivatives which has been described as under.

SECTION - I :SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL 6-OXO-4-ARYL-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL 6-OXO-4-ARYL-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATES.

Cyclohexenone possess a various pharmaceutical activities such as anticonvulsant, antidiabetic etc. Looking to the interesting properties of cyclohexenones, it was considered worthwhile to synthesize a series of cyclohexenones of type (VII) by the cyclocondensation of chalcones with ethyl cyano acetate in sodium ethoxide.

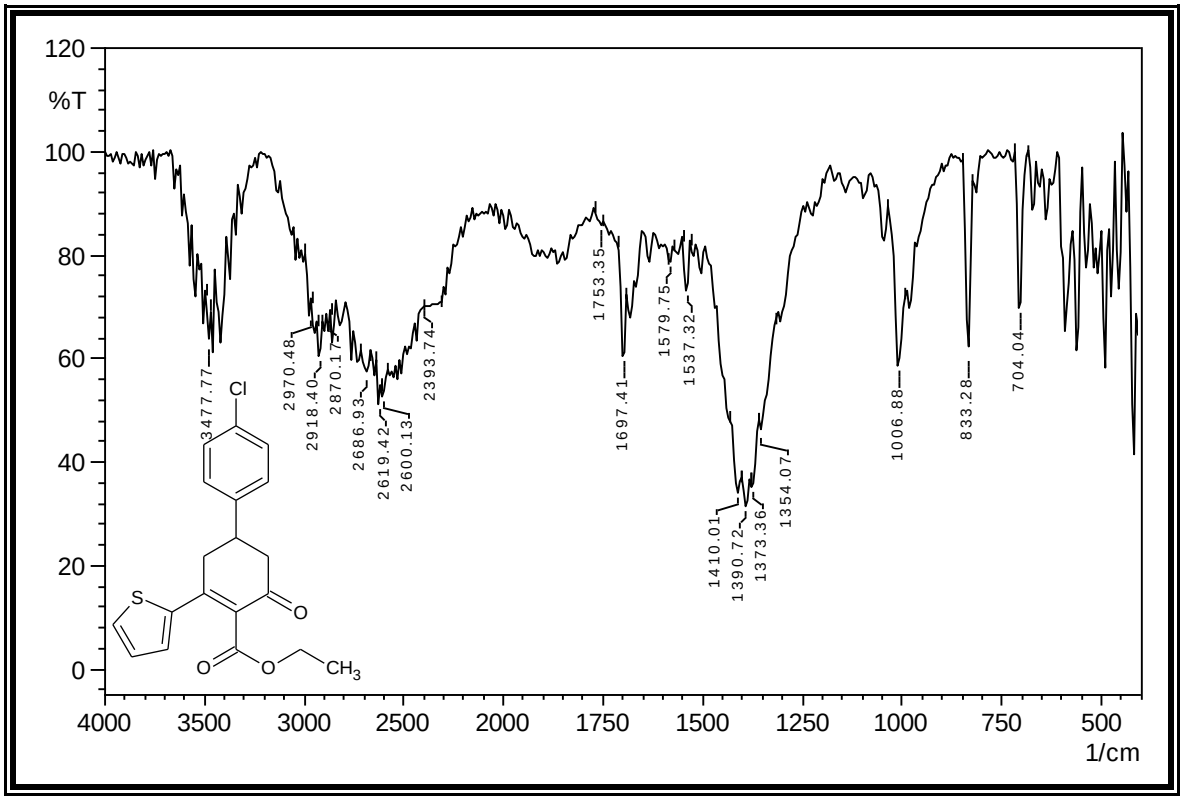


Type (VII) R = Aryl

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.7b.

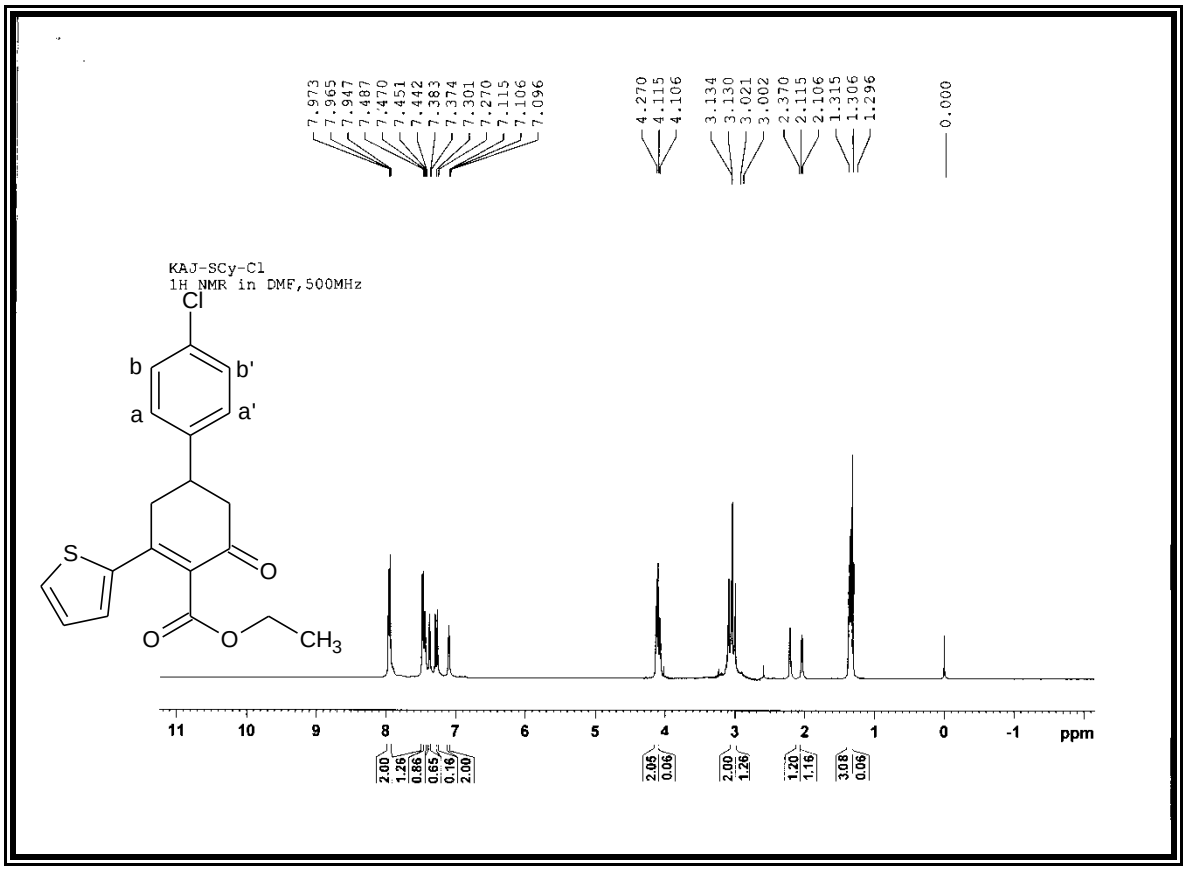
IR SPECTRAL STUDIES OF ETHYL 4-(4-CHLOROPHENYL)-6-OXO-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2970	2975-2940	79
	C-H str. (sym.)	2870	2880-2860	78
	C-H def.	1410	1470-1435	78
	C-H def. (sym.)	1373	1395-1370	78
Aromatic	C-H str.	2970	2980-2940	77
	C=C str.	1537	1585-1480	80
	C-H I.p.(def)	1006	1125-1000	80
	C-H o.o.p.	704	700-600	77
Thiophene	>C=S str.	1579	1590-1550	79
Cyclohexenone	>C=O str.	1697	1700-1675	79
Ester	>C=O str.	1753	1735-1750	81
Ether	C-O-C str.	1006	1075-1020	80
Halide	-C-Cl str.	704	800-600	77

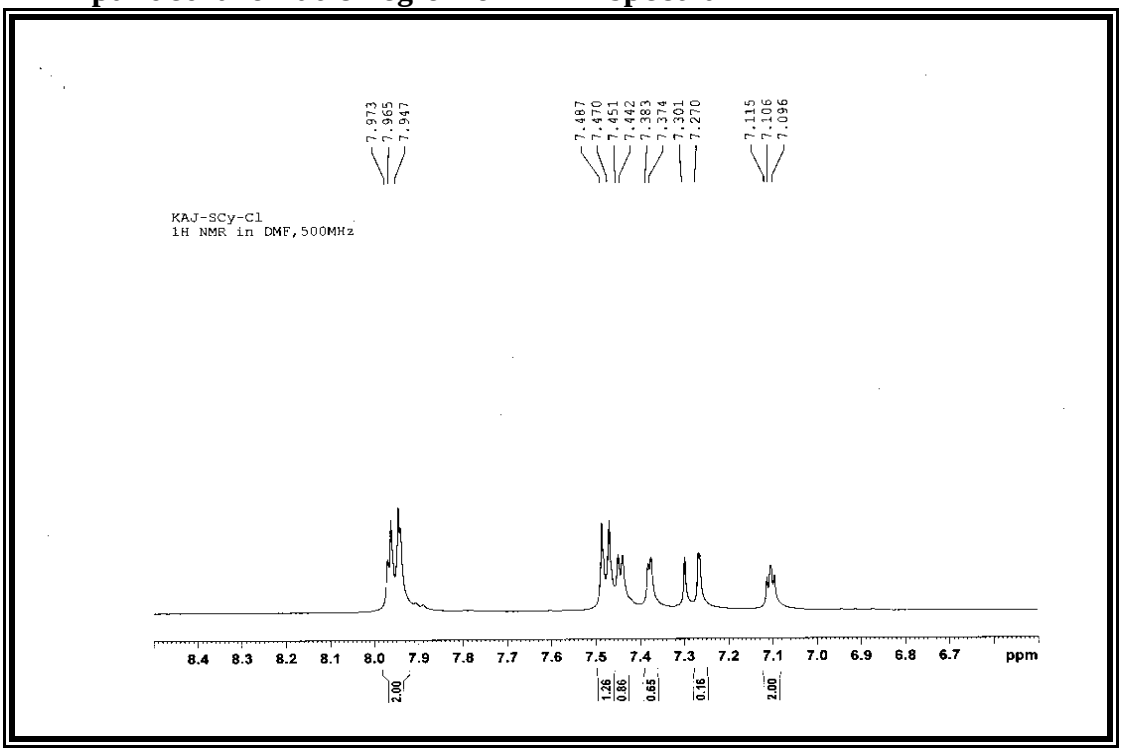
NMR SPECTRAL STUDIES OF ETHYL 4-(4-CHLOROPHENYL)-6-OXO-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATE.



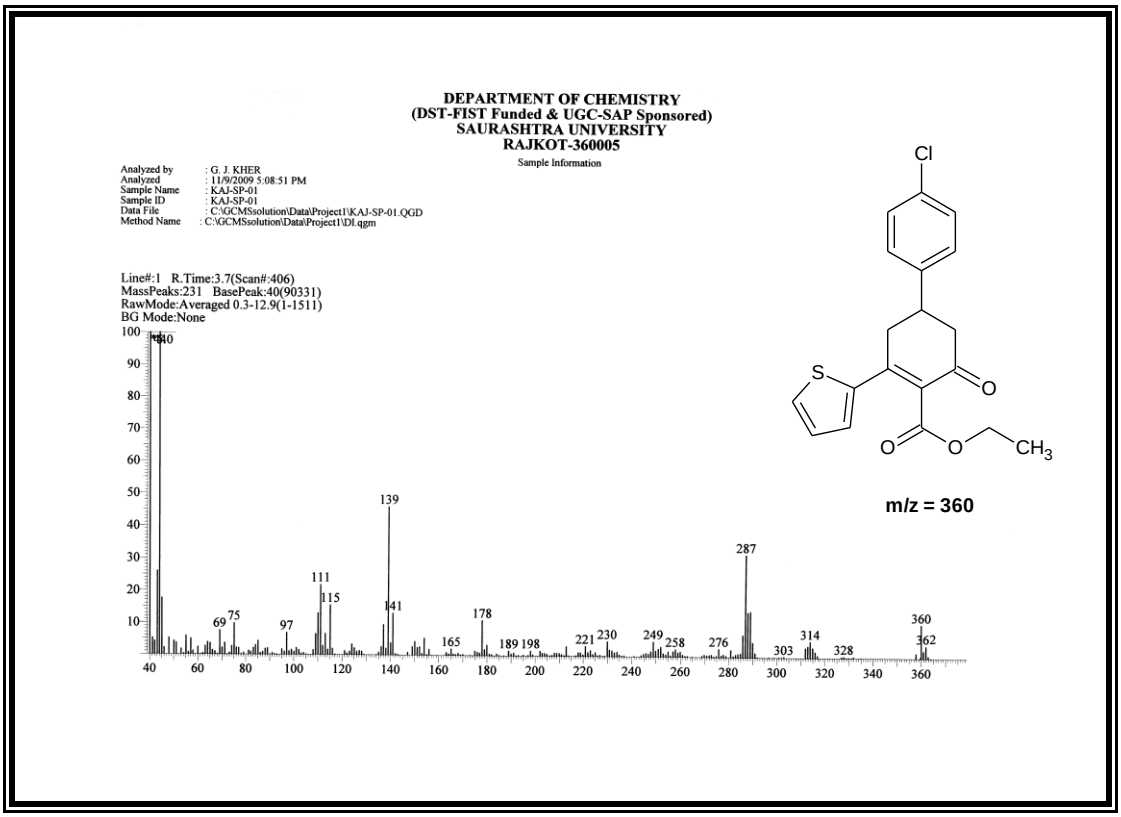
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1.	1.29-1.31	3H	triplet	$-CH_3$	4.5
2.	2.10-2.37	2H	doublet	$-CH_2$	4.5
3.	3.00-3.02	1H	multiplet	-CH	-
4.	3.13-3.23	2H	doublet	$-CH_2$	2.0
5.	4.10-4.27	2H	doublet	$-CH_2$	4.5
6.	7.09-7.11	2H	triplet	$Ar-H_{a,a'}$	5.0
7.	7.27-7.30	1H	multiplet	Ar-H	-
8.	7.44-7.48	2H	multiplet	$Ar-H_{b,b'}$	-
9.	7.94-7.97	2H	multiplet	Ar-H	-

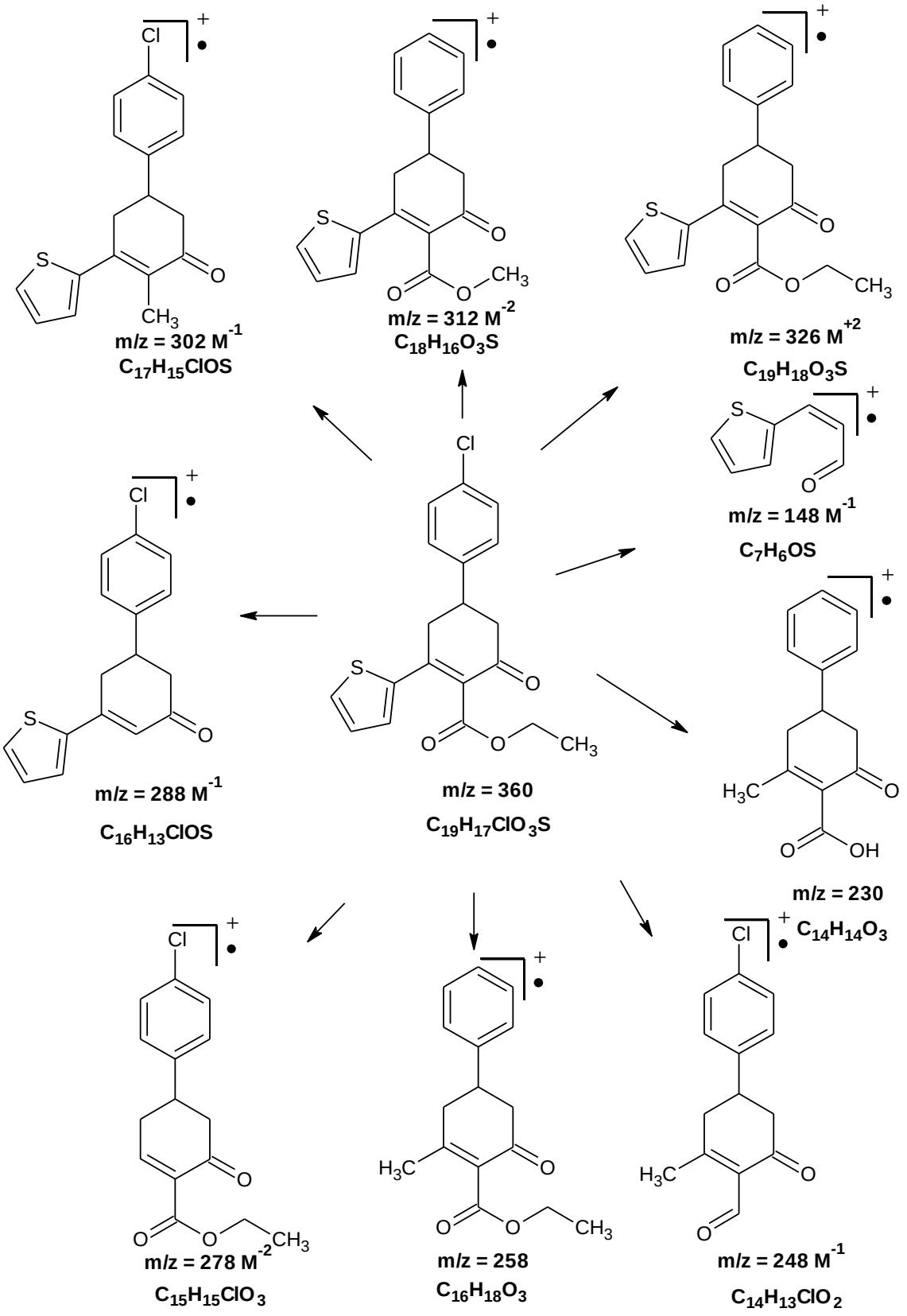
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF ETHYL 4-(4-CHLOROPHENYL)-6-OXO-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATE.



PROPOSED MASS FRAGMENTATION OF ETHYL 6-OXO-4-ARYL-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Preparation of (*E*)-1-Phenyl-3-(thiophen-2-yl)prop-2-en-1-ones

These were prepared by condensation of thiophen-2-carbaldehyde and substituted acetophenone in the presence of sodium hydroxide as described by N. M. Rateb[82] and Dalla Via[83], M. M. Hania[84]

[B] Preparation of Ethyl 4-(4-chlorophenyl)-6-oxo-2-(thiophen-2-yl)cyclohex-1-enecarboxylate

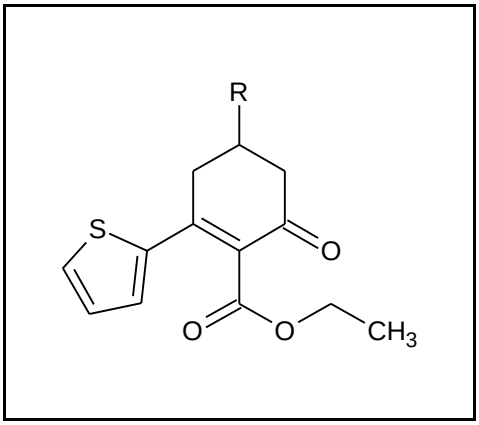
A mixture of (*E)*-1-(4-chlorophenyl)-3-(thiophen-2-yl)prop-2-en-1-one (2.48gm, 0.01mol) and ethyl acetoacetate (1.3 ml, 0.01mol) in solid sodium ethoxide (25 gm) was refluxed for 8 hrs. The crude product was isolated by pouring the mixture into ice-cold water followed by neutralization with conc. HCl and crystallized from ethanol. Yield 68%, M. P. 140 °C, Anal. Calcd. for $C_{19}H_{17}ClO_3S$ requires: C, 63.24; H, 4.75; O, 13.30%, Found: C, 63.28; H, 4.71; O, 13.33%.

Similarly other Ethyl 6-oxo-4-aryl-2-(thiophen-2-yl)cyclohex-1-enecarboxylate were prepared. The physical data are recorded in Table No. 7a.

[C] Antimicrobial activity of Ethyl 6-oxo-4-aryl-2-(thiophen-2-yl)cyclohex-1-enecarboxylates

Antimicrobial testing were carried out as described in part - I, Section - I (D). The zones of inhibition of test solutions are recorded in Table No. 7b.

Table-7a: Physical constants of Ethyl 6-oxo-4-aryl-2-(thiophen-2-yl)cyclohex-1-enecarboxylates



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
7a	C_6H_5	$C_{19}H_{18}O_3S$ 326.40	110	66	69.91 (69.74)	5.56 (5.30)	-
7b	2-Cl-C_6H_4-	$C_{19}H_{17}ClO_3S$ 360.85	95	58	63.24 (63.06)	4.75 (4.55)	-
7c	4-Cl-C_6H_4-	$C_{19}H_{17}ClO_3S$ 360.85	120	54	63.24 (63.07)	4.75 (4.68)	-
7d	3-Cl-C_6H_4-	$C_{19}H_{17}ClO_3S$ 360.85	115	63	63.24 (63.04)	4.75 (4.61)	-
7e	4-NO_2-C_6H_4-	$C_{19}H_{17}NO_5S$ 371.40	114	55	61.44 (61.23)	4.61 (4.11)	3.77 (3.59)
7g	4-NH_2-C_6H_4-	$C_{19}H_{17}NO_3S$ 341.42	119	52	66.84 (66.57)	5.61 (5.54)	4.10 (4.05)
7h	2-OH-C_6H_4-	$C_{19}H_{18}O_4S$ 342.40	124	45	66.65 (66.38)	5.30 (5.04)	-
7i	4-OH-C_6H_4-	$C_{19}H_{18}O_4S$ 342.40	109	49	66.65 (66.48)	5.30 (5.24)	-

TABLE 7B : ANTIMICROBIAL ACTIVITY OF ETHYL 6-OXO-4-ARYL-2-(THIOPHEN-2-YL)CYCLOHEX-1-ENECARBOXYLATES (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	7a	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+
2.	7b	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
3.	7c	+	+	+	+	+	+	-	-	-	+	+	-	+	+	-	+	+	-
4.	7d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
5.	7e	+	+	-	+	+	+	+	+	-	-	-	-	+	+	-	+	+	-
6.	7g	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
7.	7h	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+
8.	7i	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-

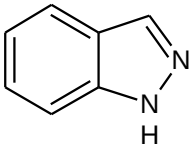
Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

SECTION-II

INTRODUCTION

Indazole was first described in 1869, by Buchner that the benzo derivatives of pyrazole is called benzopyrazole or indazole (6). Indazoles can be considered as either azaindazoles or azaisoindazoles. The compounds of medicinal interest in this group so far have been non-steroidal anti-inflammatory agents or analgesic.

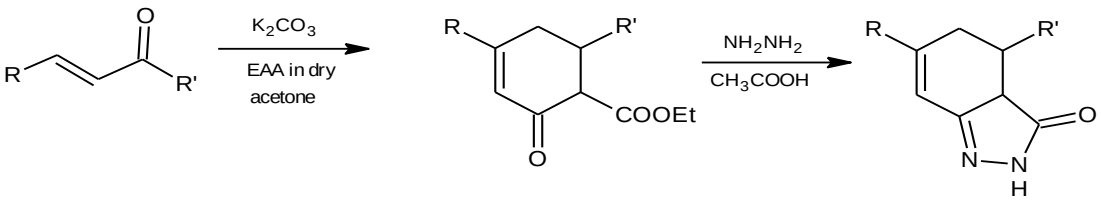


(6)

SYNTHETIC ASPECT

Literature[37-39] survey different methods are available for the preparation of indazoles. Some of them are as under.

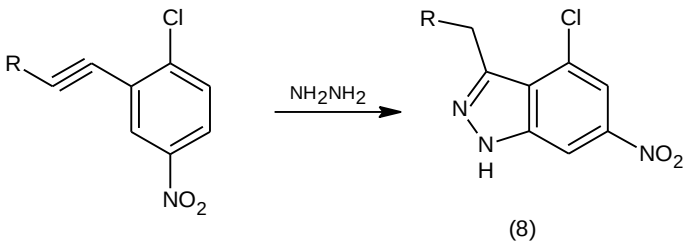
1. Indazoles can be synthesized from chalcone derivatives via cyclohexenone derivatives[40,41].



(7)

2. Indazoles[42] can prepared by the cyclization of 2,3-dialkoxy or hydroxyl acetophenones hydrazones in presence of PPA.

3. Cyclocondensation of activated acetylene with hydrazine afforded indazole derivatives[43]



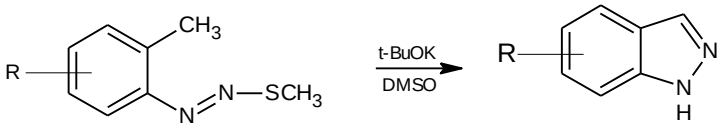
(8)

4. Reaction of substituted azo sulfides with potassium-t-butoxide in DMSO led to the corresponding 1-H indazole derivatives[44].

5. Okhim L-Yu et al.[45] synthesized some indazole derivatives by heating benzylidene aniline derivatives in DMF.

6. Indazole ring system[46] can also be designed by the diazotization of substituted anilines eg. o-toludine.

7. Caron Stephane and co-workers[47] have described that the condensation of 2-acyl aryl mesylates with hydrazines affords corresponding indazole derivatives.



(9)

BIOLOGICAL EVALUATION

Indazole derivatives are biologically interesting class of compounds. They are associated with various pharmacological properties such as.

1 Antiallergic[48]

2 Antihypertensive[49]

3 Antiinflammatory[50]

4 Antineoplastic[51]

5 Antipyretic[52]

6 Antipsychotics[53]

7 Antitumor[54]

8 Antiviral[55]

9 Cytotoxic[56]

10 Enzyme inhibitors[57]

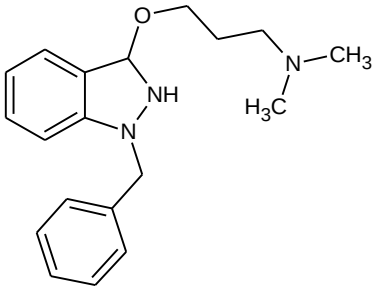
11 Fungicidal[58]

12 Herbicidal[59]

13 Pesticidal[60]

14 Sedative[61]

Indazoles are non-steroidal anti-inflammatory agents or analgesic. The prototype is Benzydamine[62] (10), a fairly potent nonsteroidal anti-inflammatory agent with significant antipyretic and analgesic properties. The other example are Bendazue[63] (11) and Tetrydamine[64] (12).



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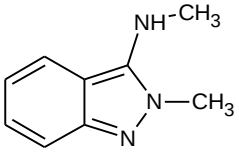

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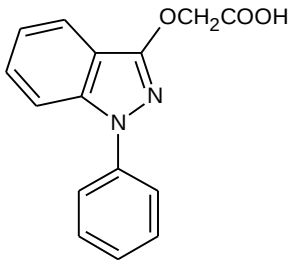
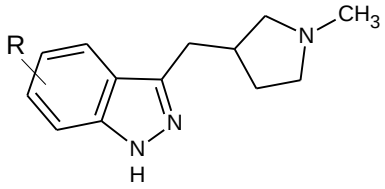


(12)

Ooe Taka nori et al.[65] reported some indazoles as hematinics, immuno stimulants and antitumor agents. Some indazole derivatives[66] showed activity for enhancing macrophage phagocytosis, improving immunity and antitumor activity. Yamaguchi Masahisa et al.[67] prepared some indazole derivatives as novel antiasthamatic agents with dual activities of thromboxane-α_2 synthetic inhibitor and bronchodialations.

Lavielle Gilbert et al.[68] documented the [(pyrrolidinyl) methyl]-indazoles (13) as 5-HT_3 like antagonist and remedy for the treatments of migrains and Schizoprenia[69]. Meshaw Richard Eric et al.[70] have synthesized 4-amino ethoxy indazoles useful as dopamine D_2 agonists. Allan David and co-workers[71] have synthesized some indazole derivatives (14) and postulated them as fibrinogen antagonist.



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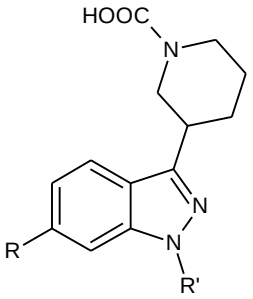
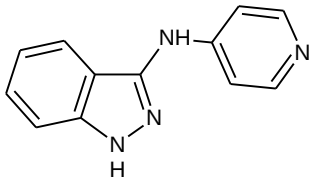


(14)

Effland Richard Charles et al.[72]synthesised 3-(pyridyl amino)-indazoles (15) and reported their use as antidepressants and anxiolytics. Some sulfonyl indazoles (16) synthesized by Duzinska-usareulicz et al.[73] have been found to possess anti-inflammatory activity.



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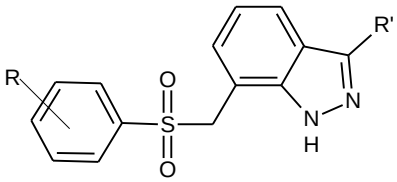


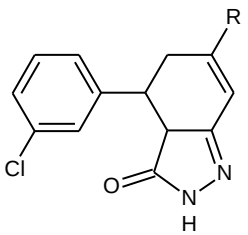
(16)

Several co-workers have patented indazole derivatives useful as hypolipidemic or hypocholersterolemic[74] and cardiovascular[75] agents.

Among variety of pharmacological properties have been encountered with indazole systems. Keeping the above in mind some novel indazole derivatives have been synthesized which have been described as under.

Work done from our laboratory

H. S. Joshi et al[76] have synthesized some indazoles (17) and reported their antitubercular and antimicrobial activity.



(17)

K. H. Popat[76] have synthesized 6-carbethoxy-5-(3'-chlorophenyl)-3-aryl-2-cyclohexenones as a anticancer, antitubercular and antimicrobial agent. 6-Aryl-4-(3'-chlorophenyl)-3-oxo-2,3a,4,5-tetrahydro-1*H*-indazoles have been reported by V. V. Kachhadiya.[77] D. H. Vyas[1] have synthesized some cyclohexenones and indazoles derivatives as an antimicrobial and antitubercular agent.

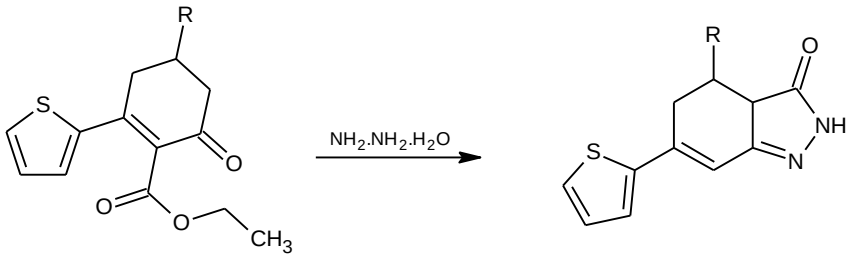
Thus with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological screening, we have under taken the synthesis of several indazoles which has been described as under.

SECTION - II: SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDAZOLE3(3a*H*)-ONES.

SECTION - II

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDAZOLE-3(3a*H*)-ONES.

The synthesis of indazole has attracted the attention of chemists because of their potential pharmacodynamic properties. Looking to the interesting properties of indazoles, it appeared to synthesize a series of 4-aryl-4,5dihydro-6-(thiophen-2-yl)-2*H*-indazole-3(3a*H*)-one of type (VIII) for obtaining biologically potents molecules by reacting ethyl 6-oxo-4-aryl-2-(thiophen-2-yl)cyclohex-1-enecarboxylate of type (VII) with hydrazine hydrate in presence of glacial acetic acid.

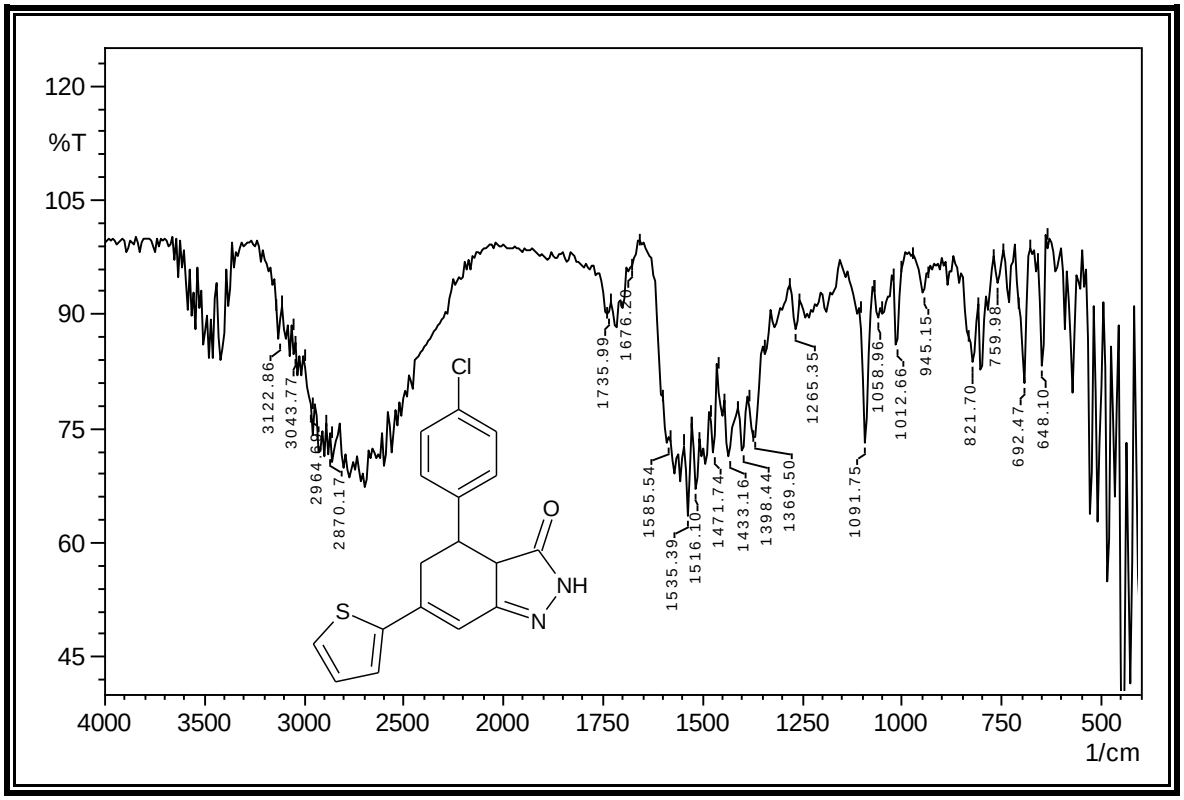


Type (VII) **Type (VIII) R=Aryl**

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.8b.

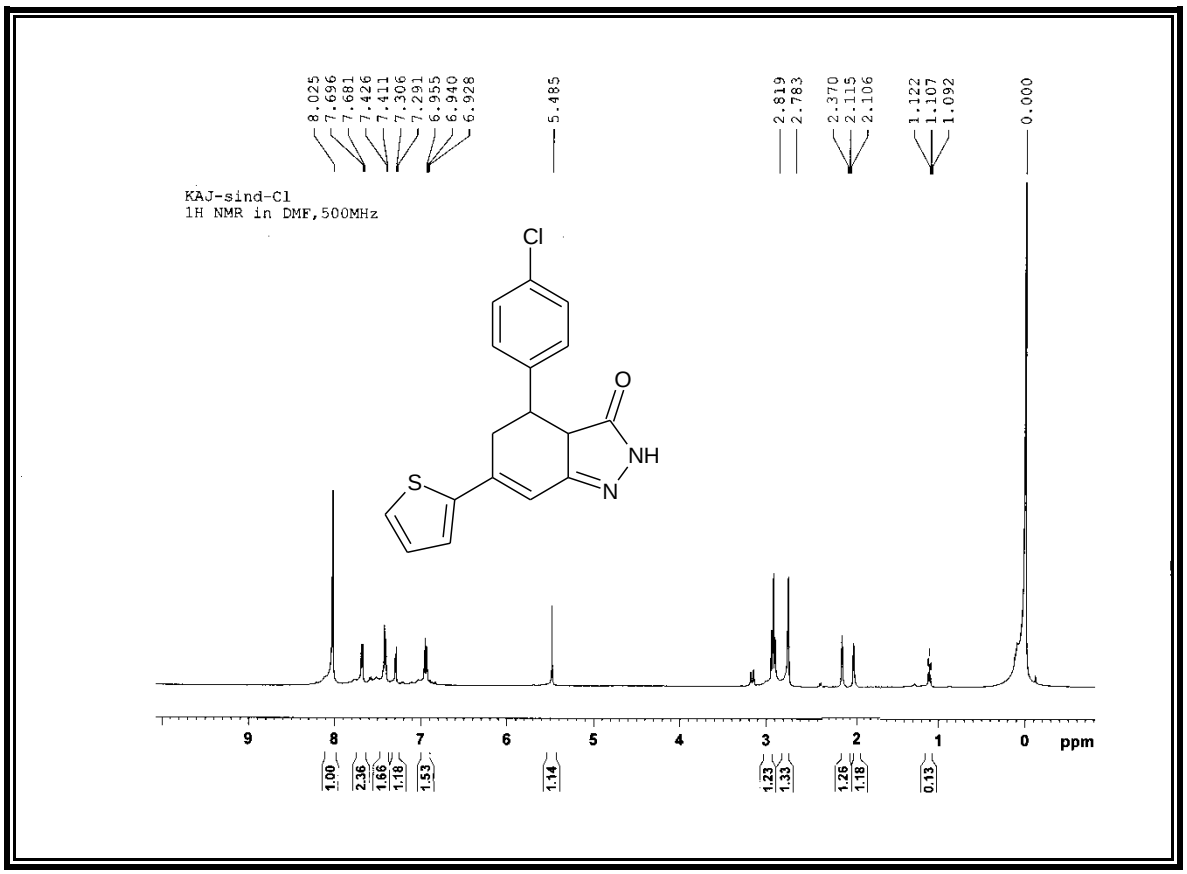
IR SPECTRAL STUDIES OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDA ZOLE-3(3a*H*)-ONE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2964	2975-2940	79
	C-H str. (sym.)	2870	2880-2860	78
	C-H def.	1471	1470-1435	78
	C-H def. (sym.)	1369	1395-1370	78
Aromatic	C-H str.	2964	2980-2930	77
	C=C str.	1535	1585-1480	80
	C-H I.p.(def)	1058	1125-1000	80
	C-H o.o.p.	648	700-600	77
Thiophene	>C=S str.	1585	1590-1550	79
Indazole	>C=N str.	1735	1735-1717	79
Amide	>C=O str.	1735	1735-1717	81
Amine	-NH- str.	3122	3350-3000	77
Halide	C-Cl str.	648	800-600	80

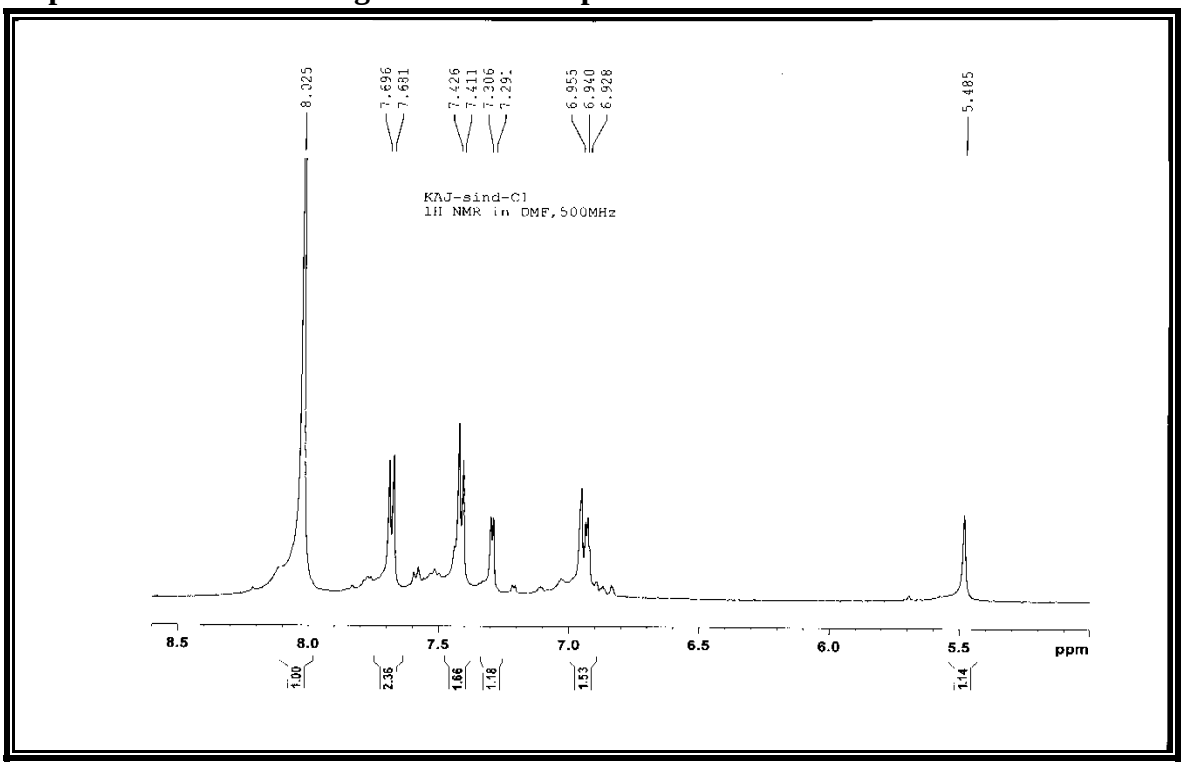
NMR SPECTRAL STUDIES OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDAZOLE-3(3a*H*)-ONE.



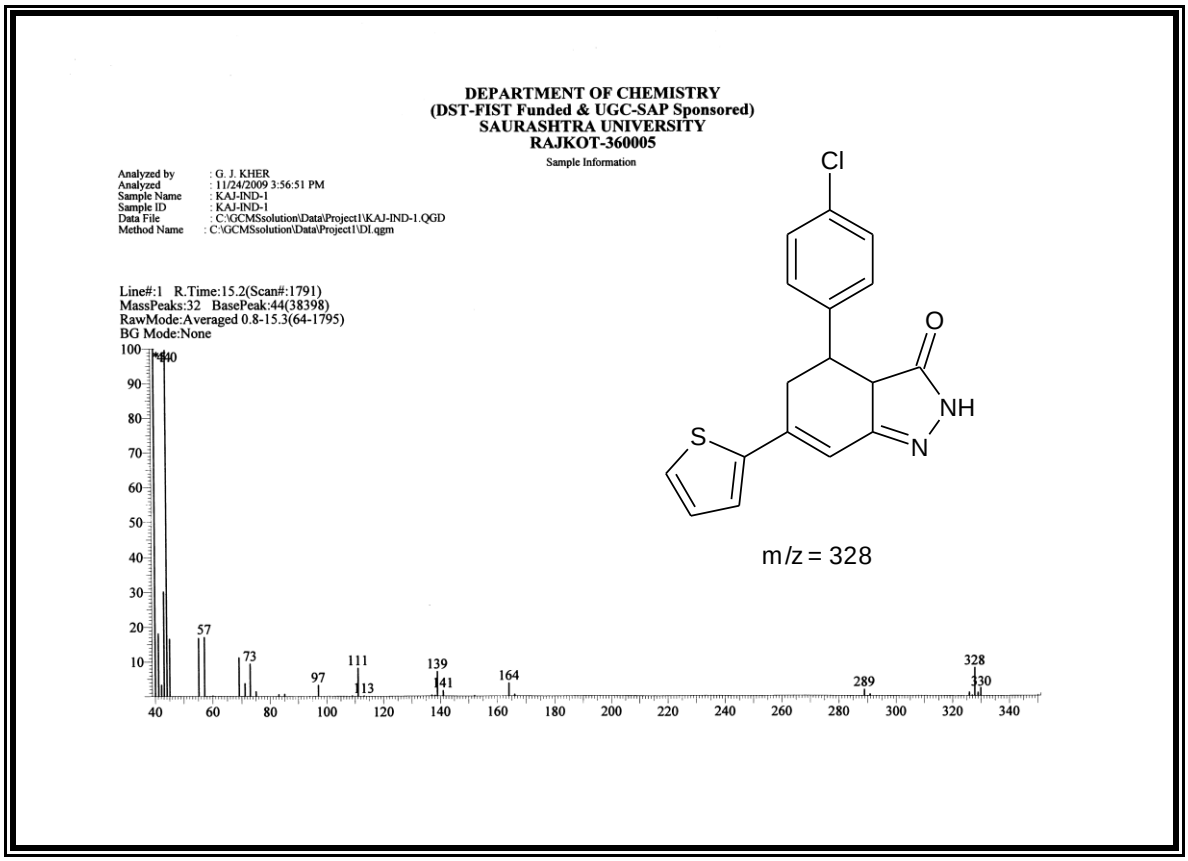
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	2.10-2.37	2H	doublet	$-CH_2$	4.5
2	2.78	1H	singlet	-CH	-
3	2.81	1H	multiplet	-CH	-
4	5.48	1H	singlet	-CH	-
5	6.92-6.95	2H	multiplet	Ar-Ha,a'	-
6	7.29-7.30	1H	doublet	Ar-H	7.5
7	7.41-7.42	2H	doublet	Ar-Hb,b'	7.5
8	7.68-7.69	2H	doublet	Ar-2H	7.5
9	8.02	1H	singlet	-NH	-

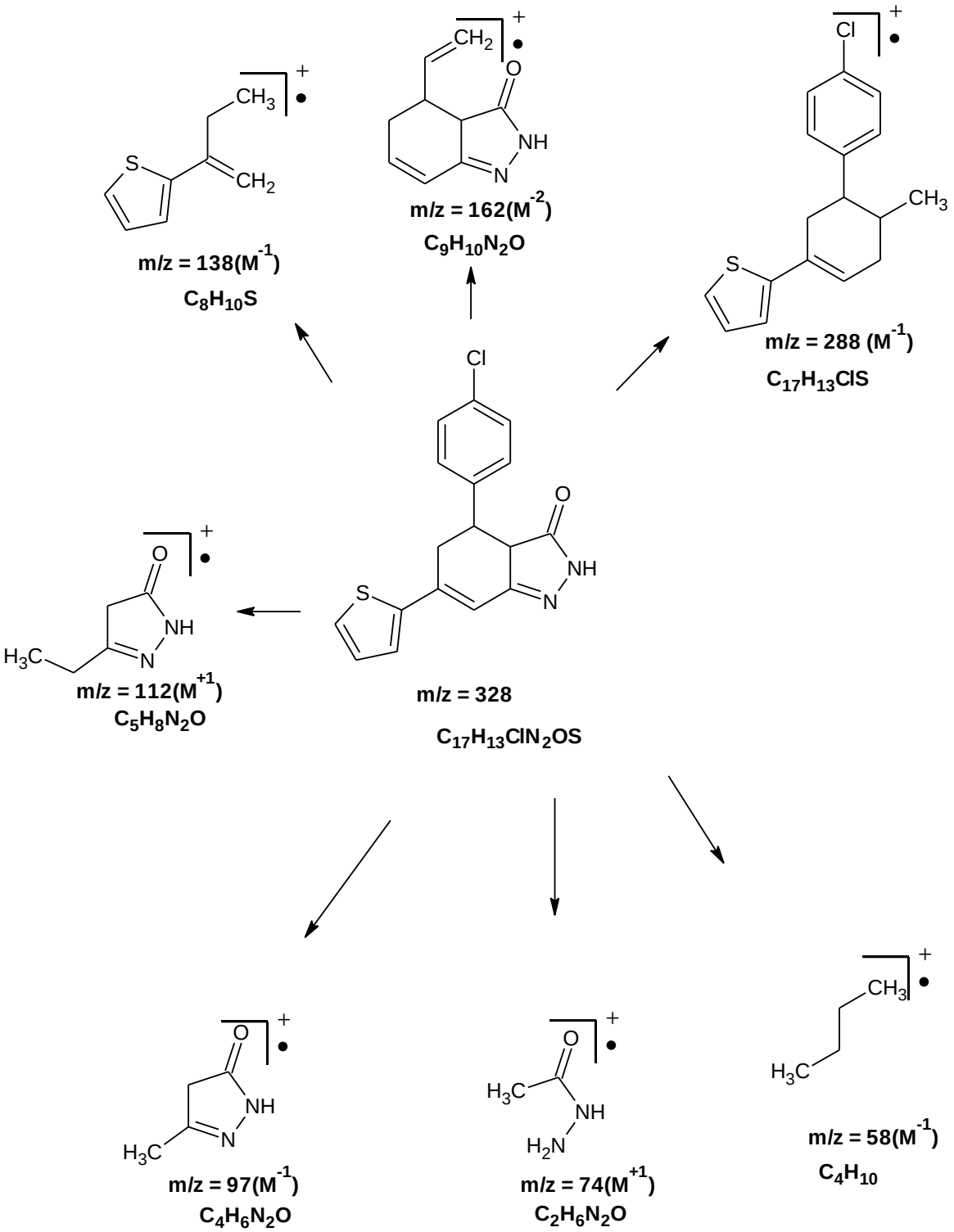
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDAZOLE-3(3a*H*)-ONE



PROPOSED MASS FRAGMENTATION OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDAZOLE-3(3a*H*)-ONE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of (*E*)-1-Phenyl-3-(thiophen-2-yl)prop-2-en-1-ones

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

[B] Synthesis of Ethyl-4-(4-chlorophenyl)-6-oxo-2-(thiophen-2-yl)cyclohex-1-enecarboxylate

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

[C] Synthesis of 4-(4-Chlorophenyl)-4,5-dihydro-6-(thiophen-2-yl)-2*H*-indazole-3(3a*H*)one

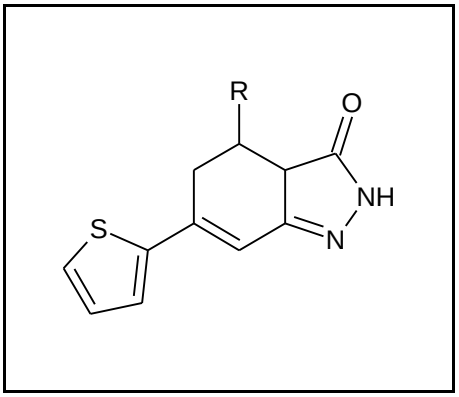
To a solution of Ethyl-4-(4-chlorophenyl)-6-oxo-2-(thiophen-2-yl)cyclohex-1-enecarboxylate(3.60gm, 0.01mol) in ethanol hydrazine hydrate (0.76gm, 0.01mol) was added and mixture was refluxed at 90 °C for 6 hrs on waterbath. The solid obtained upon cooling was filtered and crystallized from methanol. Yield 72%, M.P. 220 °C, Anal Calcd. for $C_{17}H_{13}ClN_2OS$ Cald.: C, 62.10; H, 3.98 N, 8.52%, Found: C, 62.05; H, 3.95; N, 8.56%.

Similarly other 4-aryl-4,5dihydro-6-(thiophen-2-yl)-2*H*-indazole-3(3a*H*)-ones were prepared. The physical data are recorded in Table No. 8a.

[D] Antimicrobial activity of 4-Aryl-4,5dihydro-6-(thiophen-2-yl)-2*H*-indazole-3(3a*H*)-ones.

Antimicrobial testing were carried out as described in Part-I, Section-I (D). The zones of inhibition of test solutions are recorded in Table No. 8b

Table-8a: Physical constants of 4-Aryl-4,5dihydro-6-(thiophen-2-yl)-2*H*-indazole-3(3a*H*)-ones



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
8a	C_6H_5	$C_{17}H_{14}N_2OS$ 294.37	135	52	69.36 (69.19)	4.79 (4.54)	9.52 (9.36)
8b	2-Cl-C_6H_4-	$C_{17}H_{13}ClN_2OS$ 328.81	124	59	62.10 (62.04)	3.98 (3.90)	8.52 (8.37)
8c	4-Cl-C_6H_4-	$C_{17}H_{13}ClN_2OS$ 328.81	156	62	62.10 (62.00)	3.98 (3.69)	8.52 (8.28)
8d	3-Cl-C_6H_4-	$C_{17}H_{13}ClN_2OS$ 328.81	142	58	62.10 (62.01)	3.98 (3.86)	8.52 (8.49)
8e	4-NO2-C_6H_4-	$C_{17}H_{13}N_3O_3S$ 339.36	149	51	60.17 (60.02)	3.86 (3.79)	12.38 (12.29)
8g	4-NH_2-C_6H_4-	$C_{17}H_{15}N_3OS$ 309.38	154	44	66.00 (65.88)	4.89 (4.73)	13.58 (13.32)
8h	2-OH-C_6H_4-	$C_{17}H_{14}N_2O_2S$ 310.37	162	38	65.79 (65.61)	4.55 (4.46)	9.03 (8.97)
8i	4-OH-C_6H_4-	$C_{17}H_{14}N_2O_2S$ 310.37	148	64	65.79 (65.64)	4.55 (4.48)	9.03 (8.91)

TABLE 8B : ANTIMICROBIAL ACTIVITY OF 4-ARYL-4,5DIHYDRO-6-(THIOPHEN-2-YL)-2*H*-INDAZOLE-3(3a*H*)-ONES (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			Bacillus subtilis			Escherichia coli			Salmonella paratyphi B			Aspergillus niger			Candida albicans		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	8a	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-
2.	8b	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
3.	8c	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4.	8d	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-
5.	8e	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
6.	8g	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-
7.	8h	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-
8.	8i	+	+	-	+	+	-	+	+	+	+	+	-	-	-	-	-	-	-

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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Part- B

(Part-II)

Studies on Mannich base Derivatives

INTRODUCTION

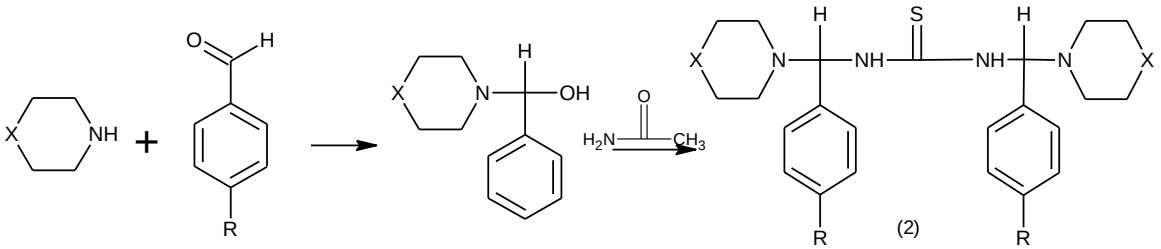
The study of mannich reaction attracted a great deal of attention to the chemists because it plays a vital role due to their wide range of biological and industrial applications. Mannich bases are also employed as intermediate in chemical synthesis.[1-3]

Much interest has been focused on the synthesis of mannich bases due to its wide variety of pharmacological activities. Mostly, they are found to be antineoplastic, analgesic and antibiotic drugs. Several therapeutic important molecules prepared through mannich reaction have received more attention in recent years.[4-6] Mannich bases have gained important because of their technological application in polymer chemistry[7], especially as paints and surface active agent and it also exhibits complexation characteristic with many transition metal ions.

SYNTHETIC ASPECT

Different methods have been cited to synthesized some new mannich bases by several co-workers using various interesting substrates.

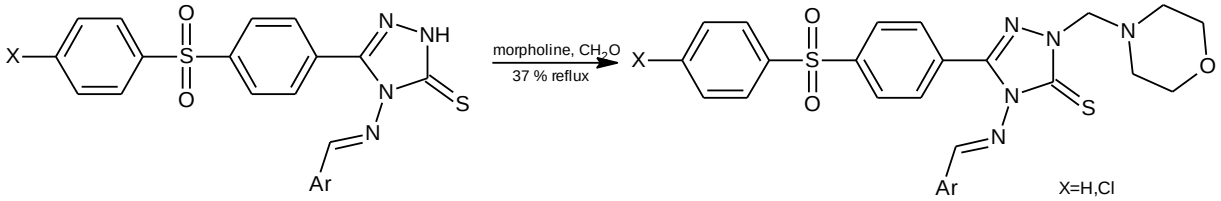
1. Several new aminobenzylated mannich bases (2) have been prepared by condensing reaction between heterocyclic secondary amines, aldehydes and acetamide, urea and thiourea.[11]



2. B. Anil Reddy[9] have synthesized benzimidazole using mannich base.

3. E. Philip Jesudason[10] have prepared mannich bases of benzimidazoles.

4. Gabriela Laura Almajan et al.[8] synthesized mannich bases (1) from some triazole moiety.



(1)

BIOLOGICAL EVALUATION

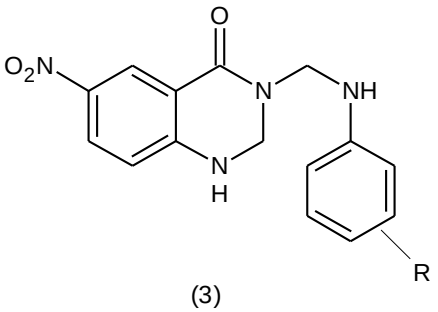
A wide variety of pharmacological properties and industrial applications have been encountered with several mannich bases such as,

1. Antibacterial[12]
2. Antitumor[13]
3. Antiinflammatory[14]
4. Cytotoxic Activity[15]
5. AntiHIV[16]
6. Antimalarial[17]
7. Antiproliferation[18]
8. Antiparasitic[19]
9. Antitubercular[20]
10. Antifungal[21]
11. Anticancer[22]

Several therapeutic important molecules containing heterocyclic secondary amines are well known. For example, Manafflazineis a famous antiarthritic agent and minorine is used as antidepressant.

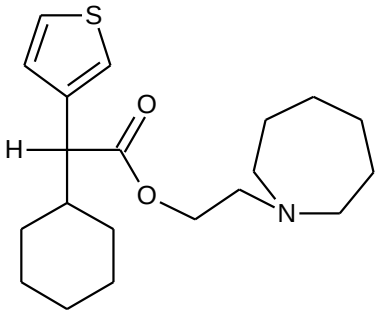
S. K. Sridhar[23] have synthesized some new mannich bases and screened for anti-inflammatory activity. A. R. Bhat et al.[24] have reported mannich bases of quinoxaline and evaluated for their antibacterial, antifungal and antitubercular activities.

P. Y. Shirodkar and M. M. Vartak[25] have studied the antitubercular activity of mannich bases of 6-nitro-3-*N*-arylamino methyl-1,2,3,4-tetrahydro-4-oxo-2-thioquinoxalines (3).



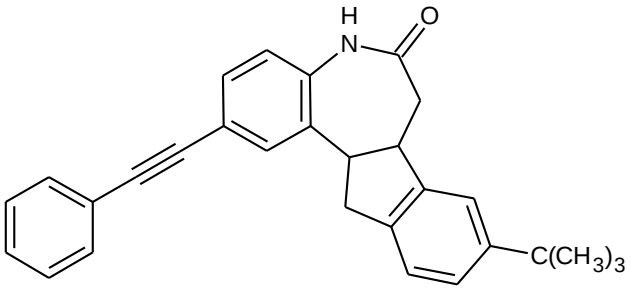
(3)

Craig J. Roxburgh[26] et al have reported mannich bases and tested them for local anesthetic activity (4).



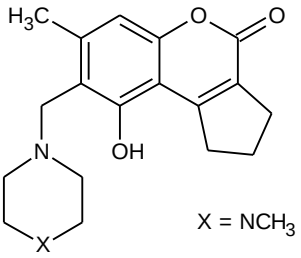
(4)

Christina Reichwald et al.[27] have synthesized mannich bases of 9-tert-Butyl-2-phenylethinylpaullone from 1,3-diarylpropenones using aromatic aldehydes and acetophenone derivatives as starting materials and studied their antileishmanial activity.



(5)

Yan Huang, et al.[28] have synthesized some mannich bases and reported as anticancer agent. Ya. L. Garazd et al.[29] have prepared mannich bases of hydroxyl-coumarines (6) which posses various biological activities.



(6)

Work done from our laboratory

K. S. Nimavat[30] have synthesized some new aminobenzylated mannich bases from 3-bromobenzaldehyde and reported as an antimicrobial agent. Mannich bases of 4-amino-3-mercapto-5-pyridin-3'-yl-[1,2,4]-triazole reported by T. K. Dave[31]. Green chemistry approach to potentially bioactive aminobenzylated mannich bases through active hydrogen compounds reported by S. L. Vasoya[32].

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

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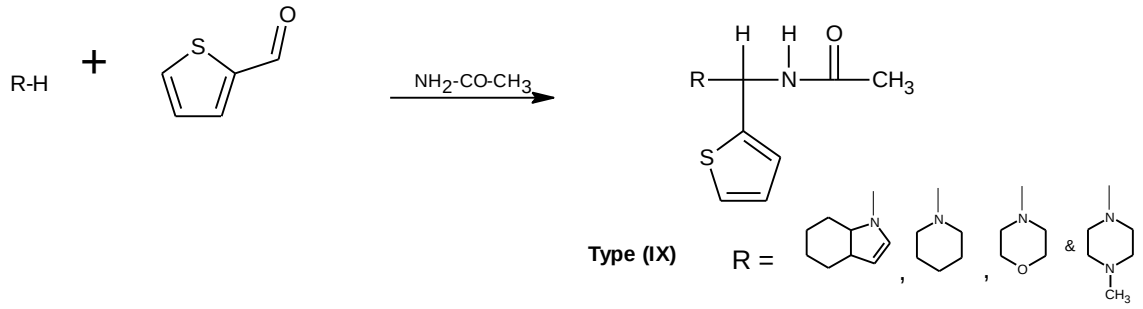
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF *N,N*-((DIALKYL/ARYLAMINO)(THIOPHEN-2- YL)METHYL) ACETAMIDES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF *N,N*-((DIALKYL/ARYL AMINO)(THIOPHEN-2-YL)METHYL)ACETAMIDES

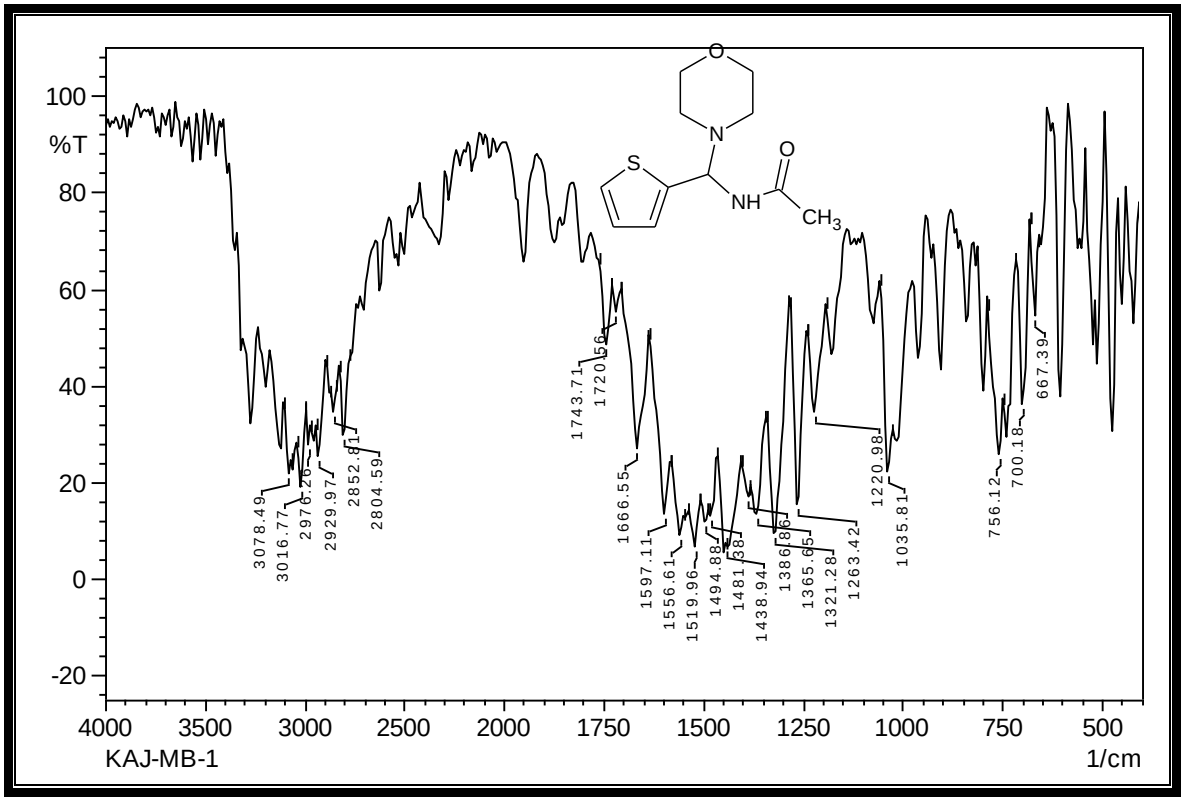
Mannich bases compounds have gained interest in last several year due to their biological, physiological and therapeutic activity. With an intention to synthesizing better therapeutic drugs, we have synthesized some new amino benzylated mannich bases of type (IX) by condensation of acetamide with secondary amine and thiophene-2-carbaldehyde.



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, Candida albicans*** at a concentration of 2000/1000/500 µg/ml. The biological activity of the synthesized compounds has been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Table No.9b.

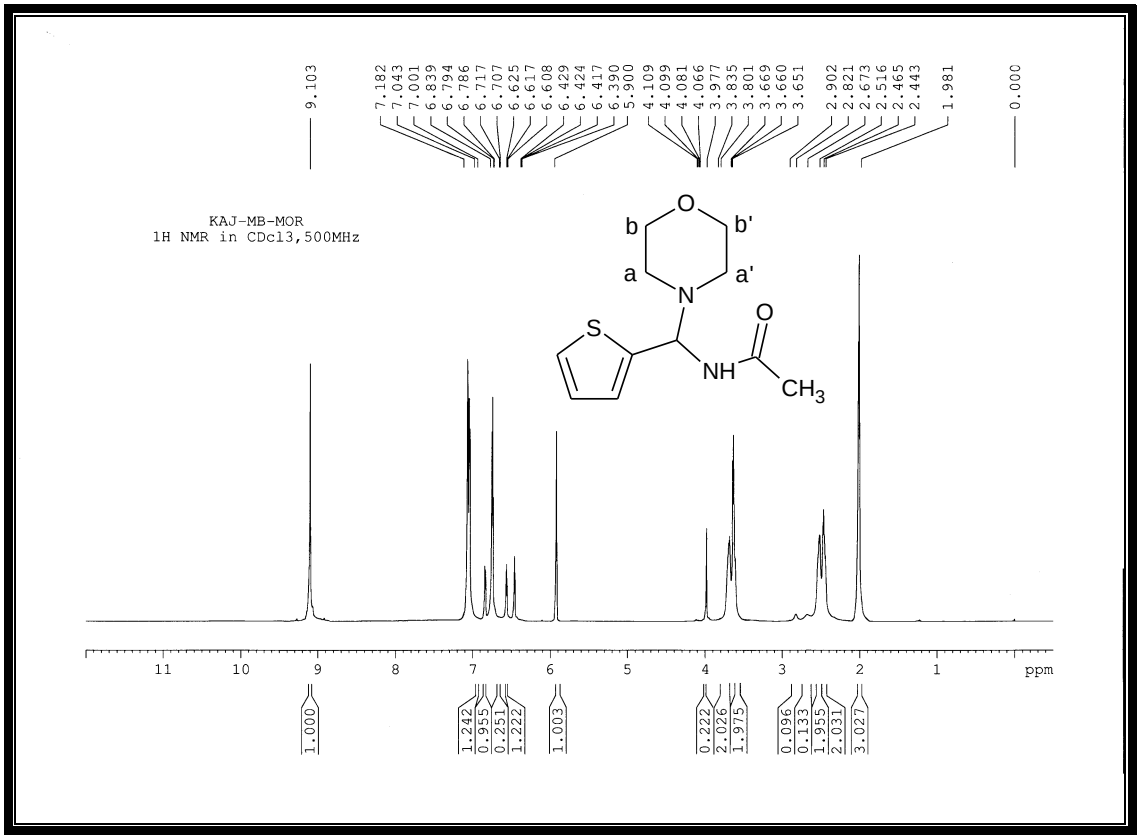
IR SPECTRAL STUDIES OF *N*-(MORPHOLINO(THIOPHEN-2-YL) METH-YL)ACETAMIDE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2929	2975-2940	33
	C-H str. (sym.)	2852	2880-2860	34
	C-H def.	1438	1470-1435	33
	C-H def. (sym.)	1365	1395-1370	33
Aromatic	C-H str.	2929	2980-2940	34
	C=C str.	1519	1585-1480	33
	C-H I.p.(def)	1072	1125-1000	34
	C-H o.o.p.	667	700-600	33
Thiophene	>C=S str.	1556	1590-1550	35
Mannich base	C-N str.	1365	1380-1310	48
	C-O-C str.	1035	1075-1020	34
Amide	>C=O str.	1666	1695-1660	33
Amine	-NH-str	3271	3350-3000	35

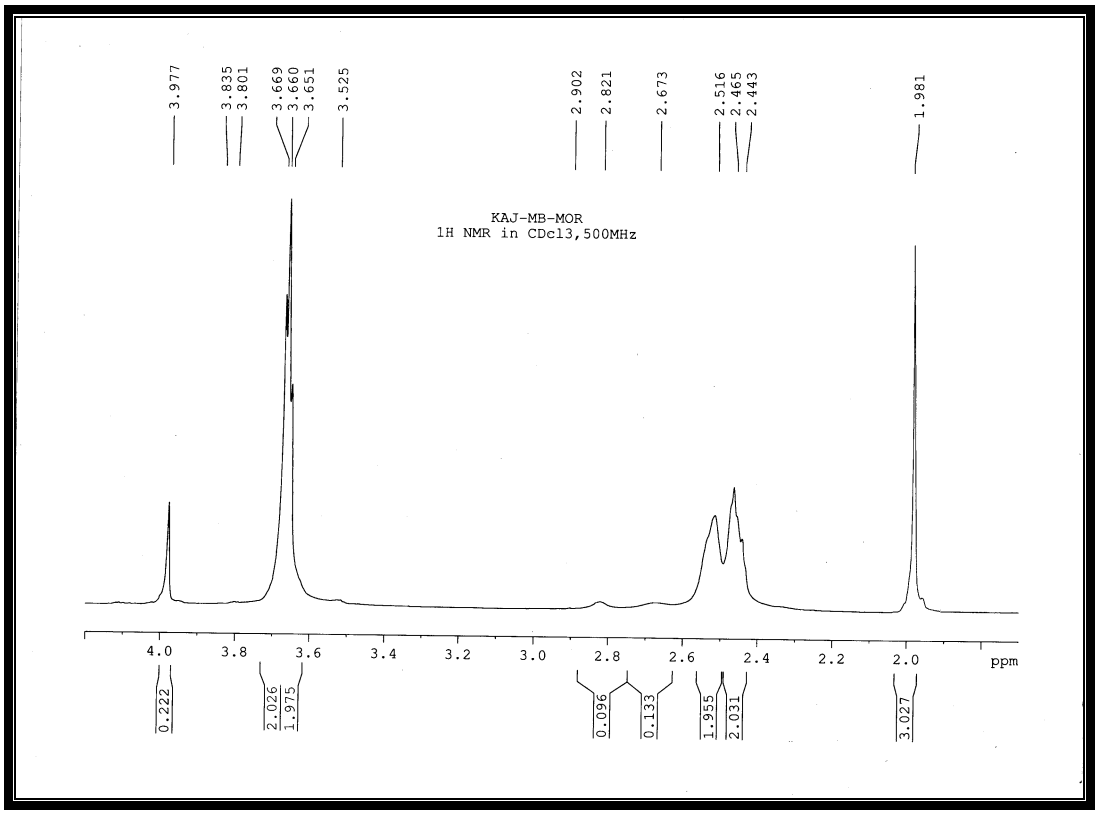
NMR SPECTRAL STUDIES OF *N*-(MORPHOLINO(THIOPHEN2-YL) METHYL)ACETAMIDE



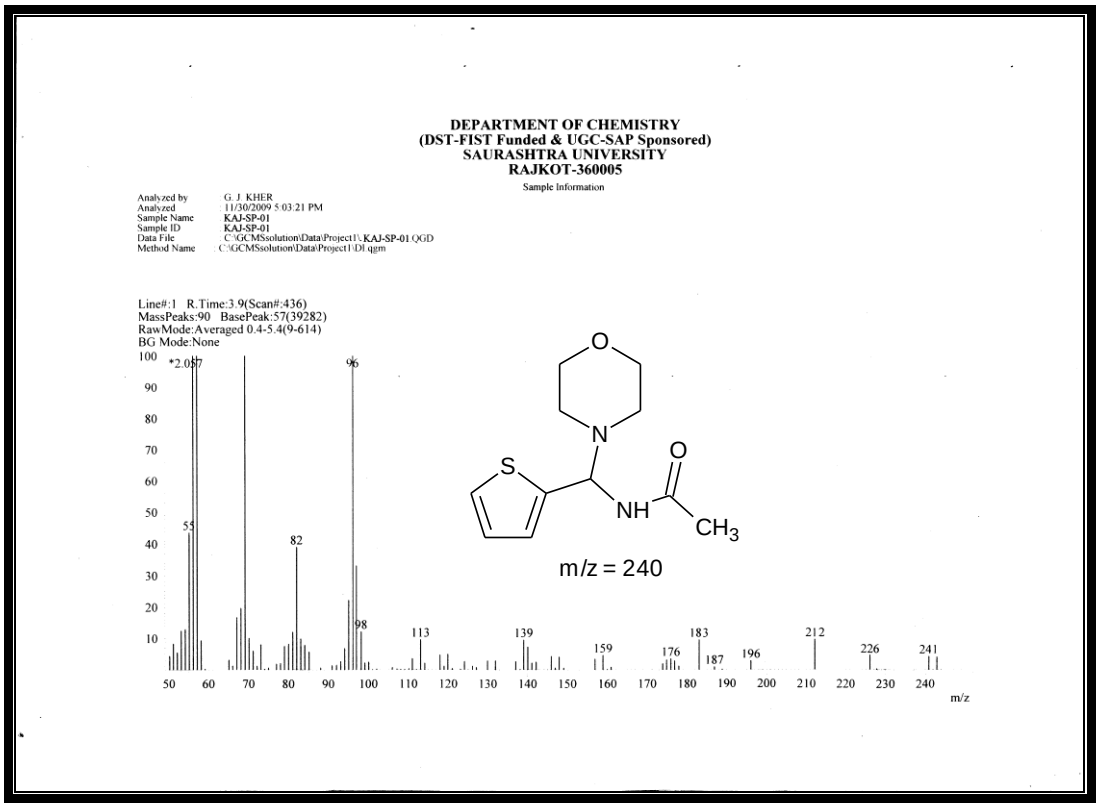
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference
1	1.98-2.0	3H	singlet	$-CH_3$
2	2.44-2.46	4H	multiplet	$-2CH_2$
3	3.65-3.66	4H	multiplet	$-2CH_2$
4	5.90	1H	singlet	-CH
5	6.99-7.00	1H	multiplet	-Ar-H
6	7.17-7.19	1H	multiplet	-Ar-H
7	7.57-7.75	1H	multiplet	-Ar-H
8	9.10	1H	singlet	-NH

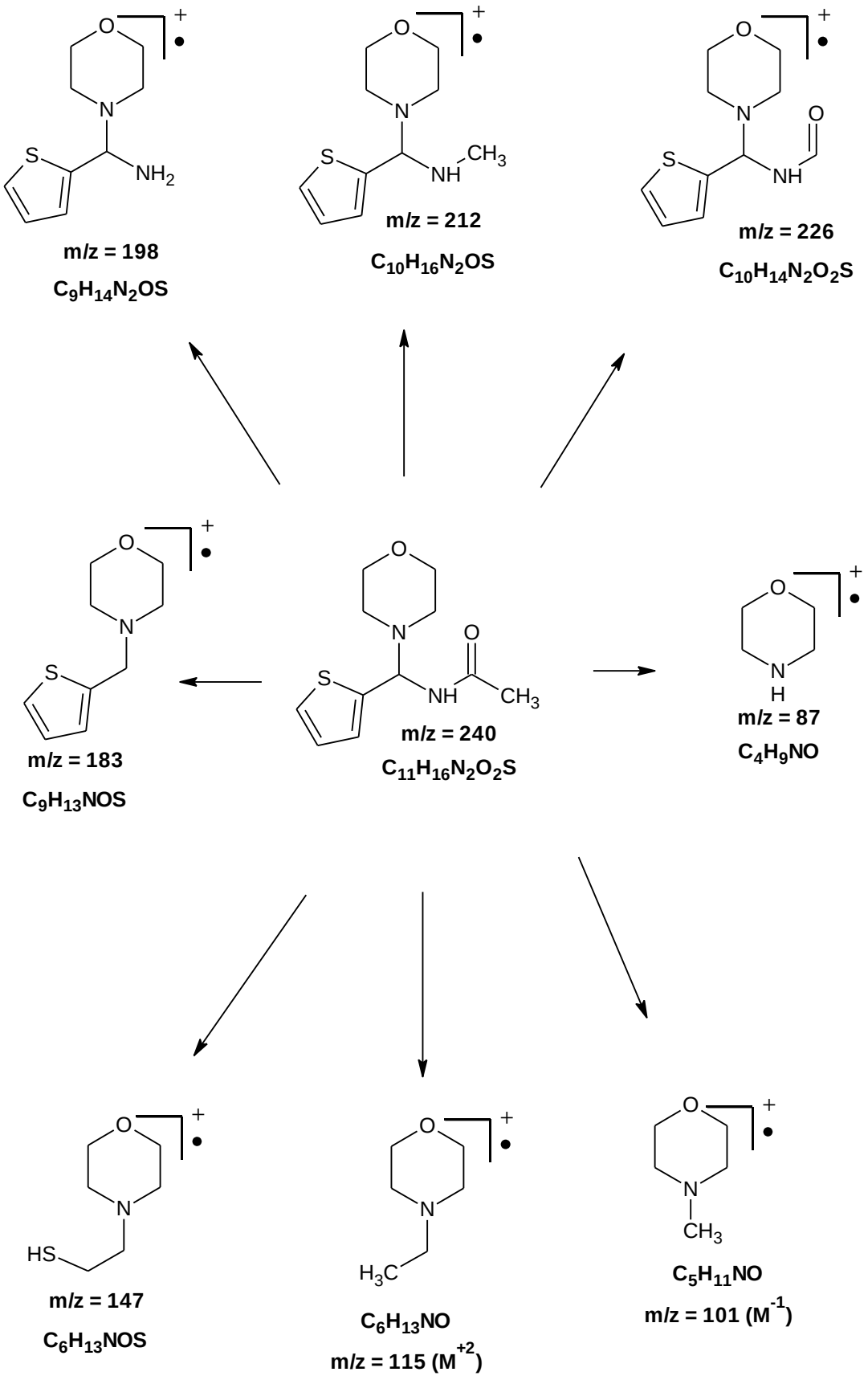
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF *N*-(MORPHOLINO(THIOPHEN-2-YL)METHYL)ACETAMIDE.



PROPOSED MASS FRAGMENTATION OF *N,N*-((DIALKYL /ARYL AMINO) (THIOPHEN-2-YL)METHYL)ACETAMIDES



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of *N*-(Morpholino(thiophen-2-yl)methyl)acetamide.

A mixture of acetamide (4.40gm, 0.075mol) and morpholin (4.35ml, 0.05mol) was stirred to get a clear solution and it was cooled in ice bath. Thiophene 2-carbaldehyde (5.6 gm, 0.05mol) was added to the cold solution and the reaction mixture was stirred for 3 hrs. at 5 °C in ice bath. A white semi solid was observed and stirred rarely. The crude product was washed with water and crystallized from methanol. Yield 57% m.p. 154 °C Anal. Cald. For $C_{11}H_{16}N_2O_2S$, : C, 54.98 ; H, 6.71 ; N, 11.66 % Found : C, 54.92 ; H, 6.74 ; N, 11.64 %.

[B] Synthesis of *N*-((Piperidin-1-yl)(thiophen-2-yl)methyl)acetamide

A mixture of acetamide (4.40gm, 0.075mol) and piperidine (4.3ml, 0.05mol) was stirred to get a clear solution and it was cooled in ice bath. Thiophene 2-carbaldehyde (5.6 gm, 0.05mol) was added to the cold solution and the reaction mixture was stirred for 2hrs.at 5 °C in ice bath. The resulting solution was kept at room temperature for a week and stirred intermittently. The crude product was washed with water and CCl_4, dried and crystallized from methanol. Yield 65% m.p. 123 °C Anal. Cald. For $C_{12}H_{18}N_2OS$, : C, 60.47 ; H, 7.61 ; N, 11.75 % Found : C, 60.48 ; H, 7.58 ; N, 11.71 %.

[C] Synthesis of *N*-((1*H*-Indol-1-yl)(thiophen-2-yl)methyl)acetamide

A mixture of acetamide (4.40gm, 0.075mol) and indole (11.7gm, 0.1mol) was stirred to get a clear solution and it was cooled in ice bath. Thiophene 2-carbaldehyde (5.6

gm, 0.05mol) was added to the cold solution and the reaction mixture was stirred for 1hrs.at 5 °C in ice bath. The solution was kept at room temperature for 3 days and stirred irregularly. The product was washed with water and CCl_4, dried and crystallized from methanol. Yield 58% m.p. 131 °C Anal. Cald. For $C_{15}H_{14}N_2OS$, : C, 66.64 ; H, 5.22 ; N, 10.36 % Found : C, 66.61 ; H, 5.19 ; N, 10.31 %.

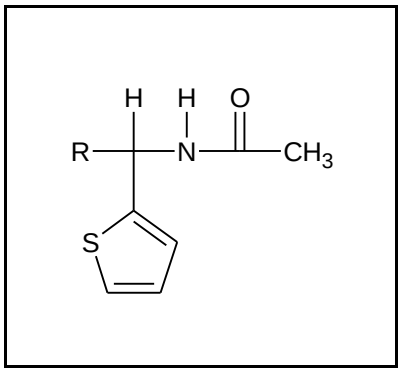
[D] Synthesis of *N*-((Diethyl amino)(thiophen-2-yl)methyl)acetamide

A mixture of acetamide (4.40gm, 0.075mol) and diethyl amine (0.73gm, 0.1mol) was stirred to get a clear solution and it was cooled in ice bath. Thiophene 2-carbaldehyde (5.6 gm, 0.05mol) was added to the cold solution and the reaction mixture was stirred for 6 hrs. at 5 °C in ice bath. The resulting solution was kept at room temperature for 5 days and stirred occasionally. The crude product was crystallized from methanol. Yield 71% m.p. 156 °C Anal. Cald. For $C_{11}H_{18}N_2OS$, : C, 58.37 ; H, 8.02 ; N, 12.38 % Found : C, 58.35 ; H, 8.01; N, 12.31 %.

[E] Antimicrobial activity of *N,N*-((Dialkyl/Arylamino)(thiophen-2-yl) methyl)acetamides.

Antimicrobial testing was carried out as described in Part-I, Section (D). The zones inhibitions of the compounds are recorded in Table No.9b.

Table-9a: Physical constants of *N,N*-((Dialkyl/arylamino)(thiophen-2-yl)methyl) acetamides.



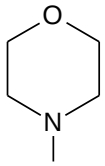
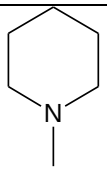
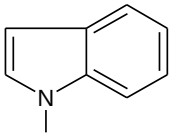
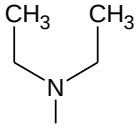
Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
9a		$C_{11}H_{16}N_2O_2S$ 240.32	154	57	54.98 (54.82)	6.71 (6.54)	11.66 (11.44)
9b		$C_{12}H_{18}N_2OS$ 238.34	123	65	60.47 (61.36)	7.61 (7.58)	11.75 (11.61)
9c		$C_{15}H_{14}N_2OS$ 270.34	131	58	66.64 (66.51)	5.22 (5.19)	10.36 (10.21)
9d		$C_{11}H_{18}N_2OS$ 226.33	156	71	58.37 (58.15)	8.02 (7.91)	12.38 (12.11)

TABLE 9B : ANTIMICROBIAL ACTIVITY OF *N,N*-((DIALKYL/ARYLAMINO)(THIOPHEN-2-YL) METHYL)ACETAMIDES (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	9a	-	-	-	-	-	-	+	+	-	+	+	-	+	+	+	+	+	+
2.	9b	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	+	+	-
3.	9c	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
4.	9d	+	+	+	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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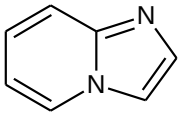
Part- C

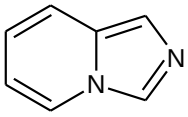
Studies on Imidazo[1,2-α] pyridine Derivatives

INTRODUCTION

Bridge nitrogen containing fused heterocycles represents important building blocks in both natural and synthetic bioactive compounds which have been shown to possess diverse therapeutic activities[1]. Hence they are interesting target to be prepared to our research on medicinally interesting heterocyclic entities. Aza-indolizine are of two types, imidazo[1,2-α]pyridine (1) and imidazo[1,5-α]pyridine (2).



(1)



(2)

The aza-indolizine contains a phenyl ring fused to a imidazole ring is indicated in the structure, hence it is also known as imidazo[1,2-α]pyridine[2]. Several procedure for their synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of bridgehead nitrogen containing fused heterocyclic entities.

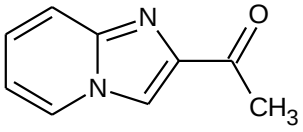
The constitution of imidazo[1,2-α]pyridine was reviewed by W. L. Mosby[3] in 1961. Imidazo[1,2-α]pyridine derivatives not only known for their pharmacological applications, they are also used in disperse dyes[4].

SYNTHETIC ASPECT

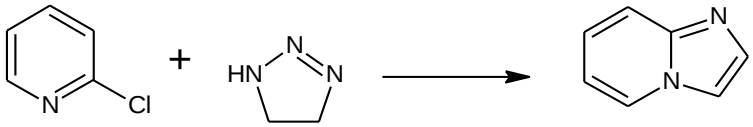
Classical methods have been reported in the literature for the synthesis of imidazo[1,2-α]pyridines. The procedure for synthesizing imidazo[1,2-α]pyridines have been described as under.

1. The synthesis of imidazo[1,2-α]pyridine from 2-aminopyridine with ω-bromoacetophenone was reported by Tschitschibabine[5].

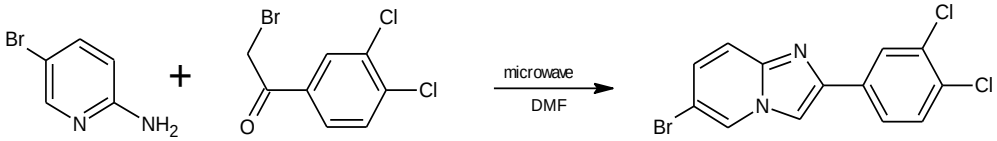
2. 2-Acetylimidazo[1,2-α]pyridine[6] can be constructed by the cyclocondensation of 2-aminopyridine with bromo butanedione.



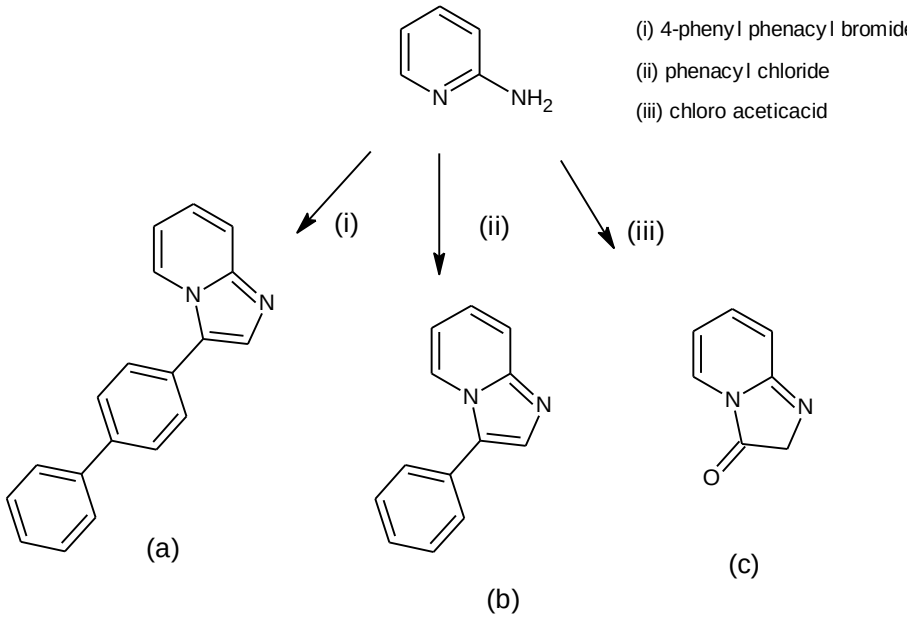
3. Reaction of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogen's give the imidazo[1,2-α]pyridine[7].



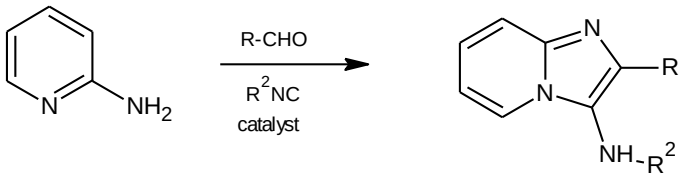
4. Shankarappa A Biradar[8] have synthesized 6-bromo-2-(3,4-dichlorophenyl) imidazo[1,2-α]pyridine using microwave irradiation from 5-bromo-2-aminopyridine And 2-bromo-1-(3,4-dichlorophenyl)ethanone.



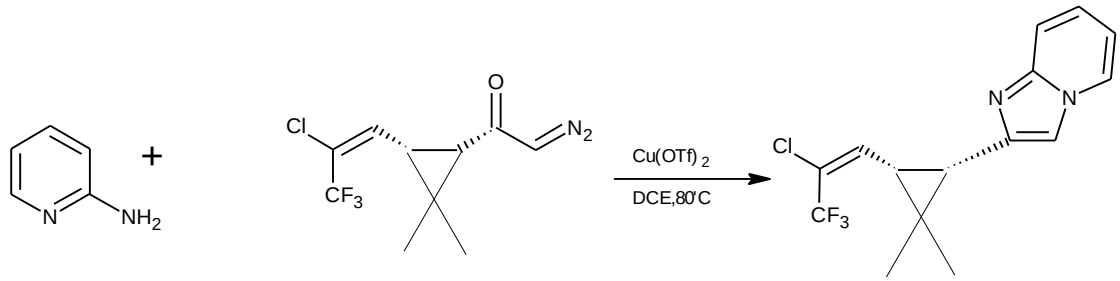
5. Jumat Salimon[9] et al. synthesized imidazo[1,2-α]pyridine-3(2*H*)-one & 3-Substituted-4-yl imidazo[1,2-α] pyridine from 2-aminopyridine.



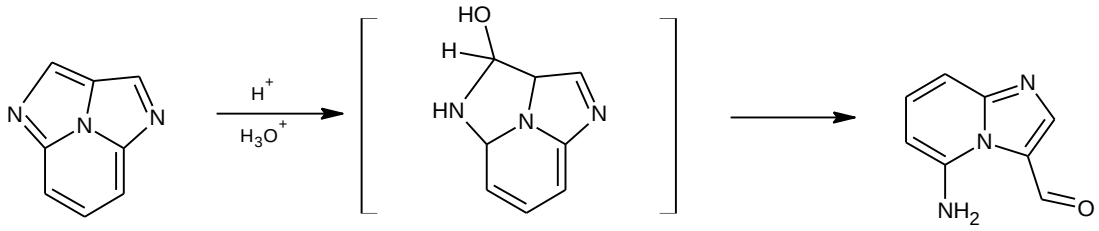
6. Synthesis of imidazo[1,2-α]pyridines using catalytic zinc chloride microwave irradiation from 2-aminopyridine and aryl aldehyde by Amanda L. Rousseau[10].



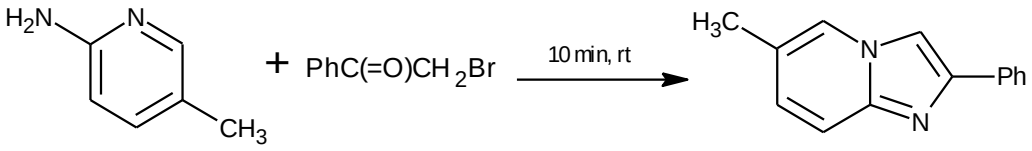
7. Synthesis of Cu(OTf)2-catalyzed imidazo[1,2-α]pyridines from a-diazoketones and 2-aminopyridines by J. S. Yadav[11]



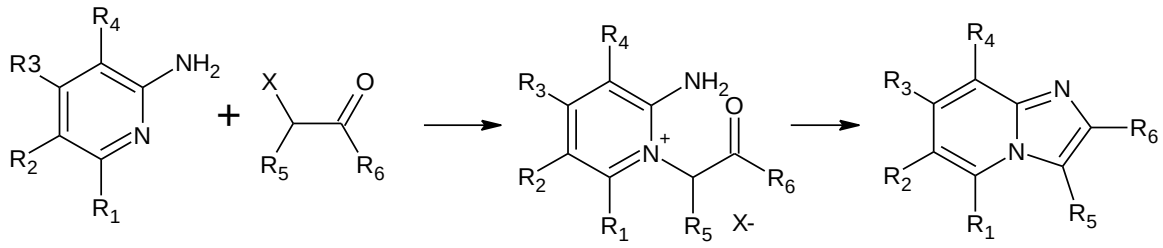
8. Paudler et al.[12] have synthesized 5-amino-3-formylimidazo[1,2-α]pyridine from acid catalyzed hydrolysis of 1,4-diazacycl[3,2,2]azine.



9. Zhu Dongjian et al.[13] have synthesized imidazo[1,2-α]pyridines from 2-aminopyridine and phenasyl bromide at R.T.



MECHANISM



(3) (4) (5) (6)

The majority of imidazo[1,2-α]pyridine have been synthesized by the reaction of 2- aminopyridine with a α-halocarbonyl compound which form oniumhalide which is further cyclize at room temperature to gives imidazo[1,2-α]pyridine.

BIOLOGICAL EVALUATION

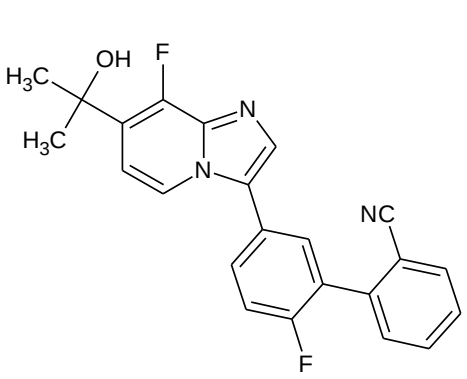
Imidazo[1,2-α]pyridines are potential bioactive agents due to their wide spectrum of therapeutic importance. A large number of substituted imidazo[1,2-α]pyridine derivatives are prepared and tested for varieties of biological activities such as,

1. Anti-inflammatory, anti cancer[14]

2. Antiviral[15,16]
3. Antianxiety[17]
4. Antiulcer[18,19]
5. Antifungal agents[20]
6. Anthelmintic[21]
7. Antibacterials[22,23]
8. Hypnotic[24]
9. Antiherpetie[25,26]
10. Gastric antisecretory[27,28]
11. Hypnoselective and anxioselective[29]
12. b-Amyloid formation inhibitors[30]
13. Benzodiazepine receptor agonists[31]
14. Nonsedative anxiolytic[32]
15. Active nonpeptide bradykinin B_2 receptor antagonists[33]
16. Cardiotonic agents[34]
17. Anticytomegalo-zoster and antivaricellazoster virus[35-37]
18. Long-acting local anesthetic[38]
19. Calcium channel blockers[39]

Alexander C. Humphries and co-workers[40] have synthesized 8-fluoro imidazo[1,2-α]pyridine derivatives (7) and evaluated as a bioisosteric replacement for imidazo[1,2-α]pyridine in an allosteric modulator ligand of the GABAA receptor. Carlos Jaramillo, and co-workers[41] reported Stereo dynamics of Ar–CO rotation and conformational preferences of 2-amino-3-(2,4-difluorobenzoyl)-imidazo[1,2-α]pyridine. I. Aramori et

al.[42] have been synthesized imidazo[1,2-α]pyridine derivatives which are highly potent and selective non-peptide bradykinin receptor antagonist (8).



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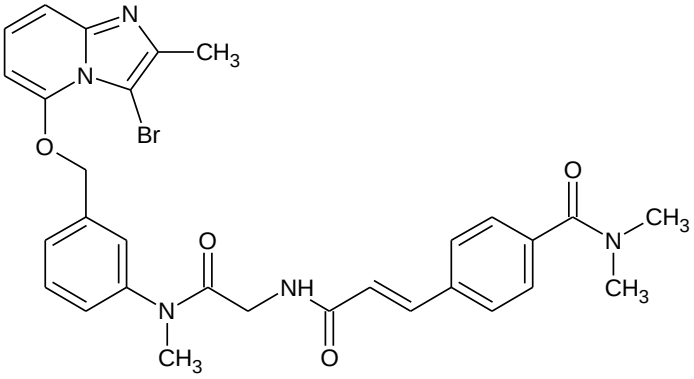
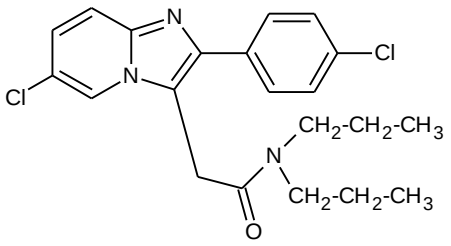
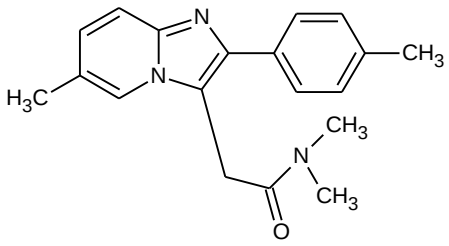


(8)

Several imidazo[1,2-α]pyridine nucleus already in market which include alpidem[43] [a ligand of both the central benzodiazepine receptors and the peripheral type (Mitochondrial) benzodiazepine receptor] has sedative and anxiolytic properties and zolpidem[43] [a selective ligand for the central benzodiazepine receptor] is a hypnotic drug. Both alpidem and zolpidem have higher affinity for benzodiazepine-1 than for benzodiazepine-2 receptors[44] and their interaction with various receptor has been reported[45].



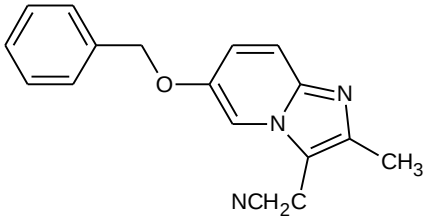
Alpidem



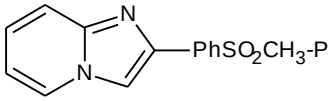
Zolpidem

James J. Kaminski and co-workers[46] have investigated imidazo[1,2-α]pyridine derivative 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-α]pyridine (9) for an antiulcer activity. On the basis of the reported metabolism of zolimidine, they reported

that the 3-cyanomethyl and 8-phenylmethoxy group have been established as metabolic sites.

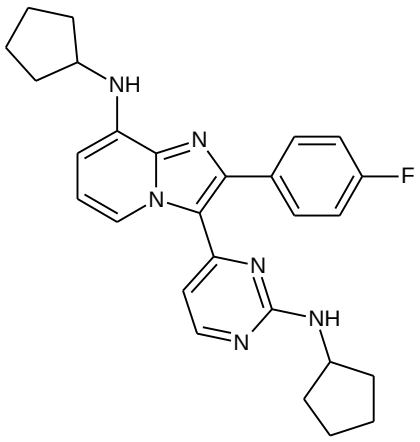


(9)

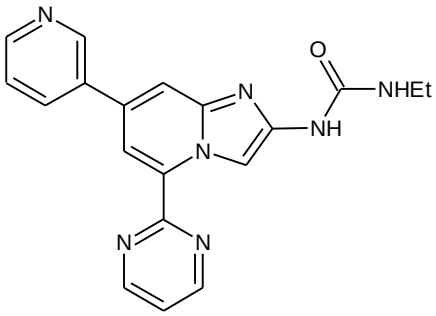


Zolmidine

Brian A. Johns et al.[47] and Chaouni-Bendallah A. et al.[48] synthesized a novel imidazo[1,2-α]pyridines (10) with potent activity against Herpes Simplex viruses. J. T. Starr et al.[49] have synthesized 5-(2-Pyrimidinyl)-imidazo[1,2-α]pyridines (11) from 2-amino-4-bromo-6-ethoxycarbonylpyridine and evaluated as a anti bacterial agent.

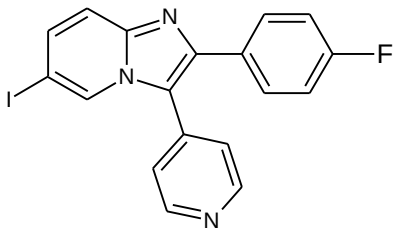


(10)



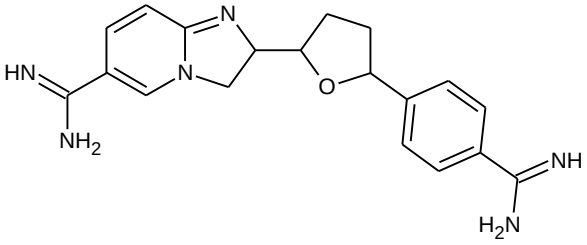
(11)

Sebastien Follot et al.[50] have synthesized 2-(4-Fluorophenyl)-6-iodo-3-pyridin-4-limidazo[1,2-α]pyridine (12) from 6-iodo-2-(4-fluorophenyl)imidazo[1,2-α]pyridine and evaluated as anti-apoptosis agents. Imidazo[1,2-α]pyridine units appear as important building blocks in both natural and synthetic bioactive compounds[51-53] and recognition on DNA binding and to yield different pharmacokinetic profile.



(12)

Mohamed A. Ismail and co-workers[54] have synthesized some newer diamine imidazo[1,2-α]pyridine (13), 5,6,7,8-tetrahydo imidazo[1,2-α]pyridines and their corresponding N-hydroxy and N-methoxy analogues and evaluated against Trypanosoma b. rhodesiense (T. B. rhodesiense) and Plasmodium falciparum (P. falciparum). Luke R. Odell and co-workers[55] have synthesized 6-substituted 3-amino-imidazo[1,2-α]pyridines (14) which has active against Mycobacterium tuberculosis glutamine synthetase inhibitors. R. B. Lacerda and co-workers[56] have find out a novel analgesic and anti-inflammatory 3-arylamine- imidazo [1,2-α] pyridine.



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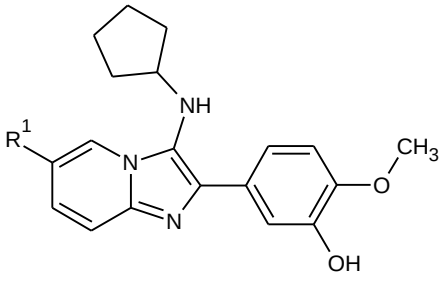

(14)

Thus the important role displayed by imidazo[1,2-α]pyridine and its derivatives for various therapeutic and biological activities prompted us to synthesize some Chalcones, Acetyl pyrazolines, Cyano pyridines, Thiopyrimidines, Oxopyrimidines, Mannich bases Isoxazoles, Schiff bases, Imidazolinone derivatives bearing Imidazo[1,2-α]pyridine moiety in order to achieve compounds having better therapeutic activities described as in the following parts.

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

PART-II : SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF ARYLAMINOMETHYL MANNICH BASE DERIVATIVES.

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Part- C

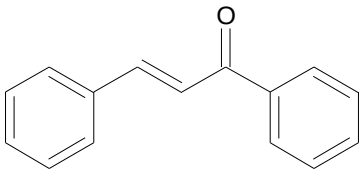
(Part-I)

Studies on Chalcone Derivatives

INTRODUCTION

The term ***Chalcone*** was first coined by Kostanecki and Tambor[1], who did pioneering work in the synthesis of natural coloring compounds. The chemistry of chalcones has generated intensive precise studies all over the world, especially interesting for their biological and industrial applications. Chalcones are colored compounds because of the presence of the chromophore and auxochromes. They are known as benzalacetophenones or benzylidene acetophenones.

Chalcones (1) are characterized by their possession of a structure in which two aromatic rings are linked by an aliphatic three carbon chain.



(1)

The chalcones were known from different names like phenyl styryl ketones, beanzalacetophenone, α-phenyl acrylphenone, γ-oxo-α,γ-diphenyl-α-propylene and α-phenyl-α-benzoethylene.

SYNTHETIC ASPECT

Claisen-Schmidt condensation

A significant variety of methods are existing in literature for the synthesis of chalcones. The most convenient way is the Claisen-Schimidt condensation which involves aryl methyl ketones with aryl aldehyde in presence of alcoholic alkali[2].

Various modifications have been applied to Claisen-Schimidt condensation to get better yield and to synthesize biologically active analogs. Different catalysts have been reported to increase the yield of the reaction. Microwave synthesis strategies have also

applied to shorten the reaction time. Solid phase synthesis and combinatorial chemistry has made possible to generate library of chalcone derivatives.

Solid-Phase Synthesis

During the past two decades, combinatorial chemistry has appeared as one of the most valuable tools used to accelerate drug discovery and lead optimization processes. The emergence of this new field has promoted the transfer of solution-phase functional group transformations to the solid phase.

A. R. Katritzky and coworker have synthesized chalcone derivatives by using sodium methoxide as a catalyst and Wang resin as a solid support[3]. Jian Cao and group reported polymer-supported selenium-induced solid–phase synthesis[4]. Recently Kamal Ahmed et al demonstrated solid-phase synthetic protocol for the chalcone and its derivatives[5].

Liquid-Phase Synthesis

In the solid phase synthesis there are some disadvantages of this methodology compared to standard solution-phase synthesis, such as difficulties to monitor reaction progress, the large excess of reagents typically used in solid-phase supported synthesis, low loading capacity and limited solubility during the reaction progress and the heterogeneous reaction condition with solid phase[6].

Recently S. Yongjia et al reported soluble polymer-supported synthesis of chalcone derivatives[7]. Saravanamurugan and coworker used ZSM-5 catalyst and Liquid phase synthesis strategy for the derivative preparation[8]. E. V. Stoyanov and group demonstrated liquid phase synthesis of 2'-hydroxychalcone derivatives[9].

Microwave Assisted Synthesis

Microwave irradiation (MWI) has become an established tool in organic synthesis, because of the rate enhancements, higher yields and often, improved selectivity with respect to conventional reaction conditions[10].

In recent years, solvent free reactions using either organic or inorganic solid supports have received increasing attention. K. Mogilaiah and coworker describe synthesis of chalcones with p-toluene sulphonic acid (PTSA) as a catalyst under microwave irradiation and solvent free conditions[11], S. Katade et al. reported recently the synthesis of chalcones with microwave irradiation and reported the reaction time decreases and overall yield of the product was increases[12].

Catalysts

The other catalysts employed in synthesis and some time with advantages are alkali of different strength[13,14], hydrochloric acid[15,16], phosphorous oxychloride[17], piperidine[18], anhydrous aluminium chloride[19], boron trifluoride[20], amino acids[21], perchloric acid[22] etc. recently S. Ryo and group reported synthesis using Ruthenium as a catalyst and get better yield[23].

Chalcones can also be synthesized by condensing several other reagents instead of an aldehyde and ketone.

1. Nencki reaction with cinnamic acid on an aromatic compounds[24].
2. Diazo coupling of phenyl diazonium chloride with benzoyl acrylic acid[25].
3. Friedel craft's cinnamoylation[26].
4. Fries rearrangement of aryl cinnamates[27].

REACTION MECHANISM

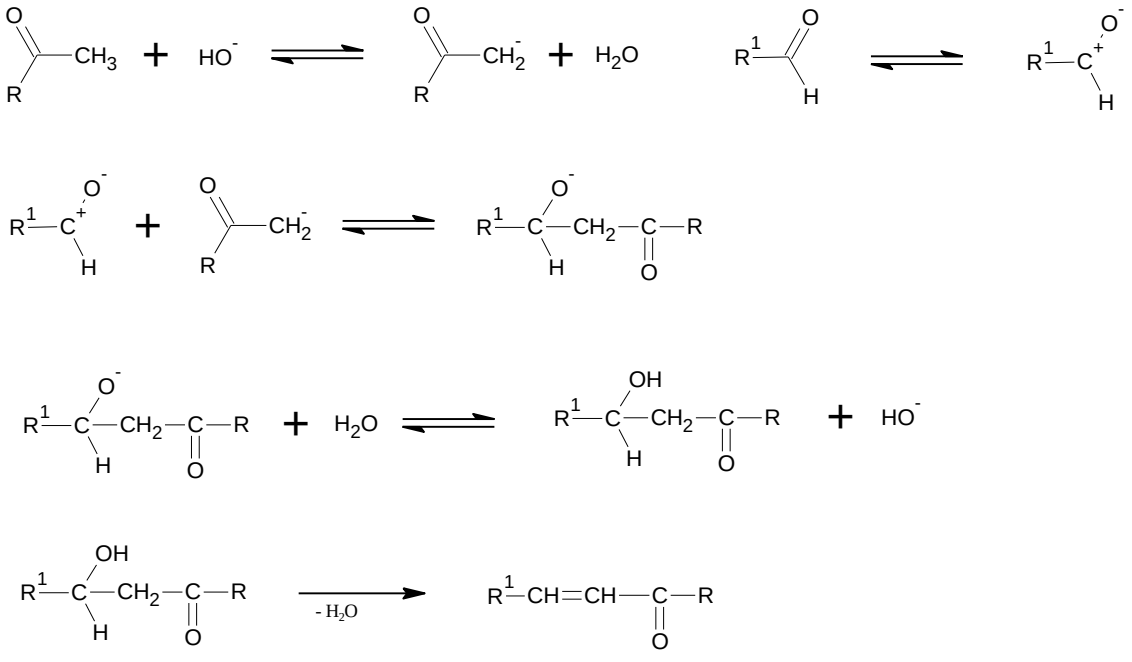
The following two mechanisms have been suggested for the synthesis of chalcones.

(A) Base catalyzed

(B) Acid catalyzed

(A) Base catalyzed:

Two alternative mechanisms were advanced for the reaction of benzaldehyde with acetophenone in the presence of a basic catalyst[28].

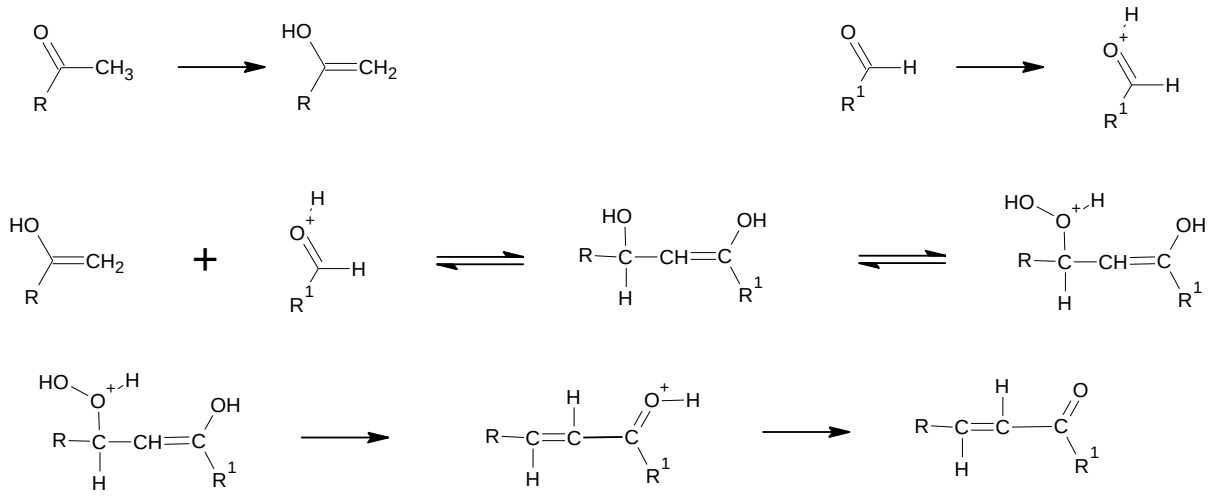


The intermediate aldol type products formed readily undergoes dehydration even under mild condition, particularly when R and R' are aryl groups.

(B) Acid catalyzed:

The formation of chalcones by the acid catalyzed condensation of acetophenones and aldehydes has been studied.[29] The rate of reaction depends on the first power of the

concentration of aldehyde and the Hammet acidity function. Also the condensation step has been shown to be the rate determining step in this reaction. The following mechanism seems to be operable.



REACTIVITY OF CHALCONES

The chalcones have been initiated to be useful for the syntheses of multiplicity of heterocyclic compounds are as under.

1. Chalcones with alkaline hydrogen peroxide in methylene dichloride gives oxirane.[30]
2. Chalcones with tertiary amine and N-methylmorpholinium salt in acetonitrile by using o-(diphenyl phosphinyl)hydroxylamine produces aziridines.[31]
3. Chalcones on reaction with benzamidine hydrochloride under microwave assisted condition in DMF affords dihydropyrimidines.[32]
4. Chalcones on reaction with 2-aminopyridine in glacial acetic acid affords pyridopyrimidines.[33]
5. Chalcone gives imine derivatives with amine in presence of sulfuric acid as catalyst.[34]

6. Chalcones on condensation with malononitrile in pyridine forms 2-amino-3-cyanopyrans.[35]
7. Chalcones on reaction with thiourea in presence of alkali/acid yields 2-thienopyrimidines.[36]
8. Chalcones react with P_2S_5 yielded 2-isothiazolidines.[37]
9. Chalcones react with sodium nitrile in presence of glacial acetic acid in ethanol produces 2-1*H*-pyrimidines.[38]
10. Isoxazoles[39] can be prepared by the treatment of chalcones with hydroxylamine hydrochloride and sodium acetate.
11. Chalcones on condensation with 2-aminobenzothiazole in ethanol forms 2,3-dihydro-1,5-benzothiazepine.[40]
12. Pyrazoline[41] and its derivatives can be prepared by the condensation of chalcones with hydrazine hydrate and acetic acid.
13. Chalcones on treatment with guanidine hydrochloride in presence of alkali affords 2-amino pyrimidines.[42]
14. Cyanopyridone derivatives[43] can be prepared by the condensation of chalcones with ethyl cyanoacetate.

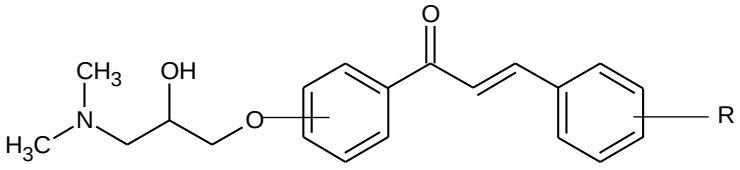
BIOLOGICAL EVALUATION

Chalcones are potential biocides, some naturally occurring antibiotics and amino chalcones probably own their genetic activity due to the presence of α,β-unsaturated carbonyl group. Few of them are as below.

1. Antibecterial[44]
2. Antifeedant[45]

3. Antitubercular[46]
4. Antimalarial[47,48]
5. Antioxidant[49]
6. Antifilarial[50,51]
7. Anti-oedematogenic[52]
8. Antimicrobial[53-55]
9. Antihistaminic[56,57]
10. Anticancer[58,59]
11. Anti-Leishmania[60]
12. Anti-inflammatory[61]

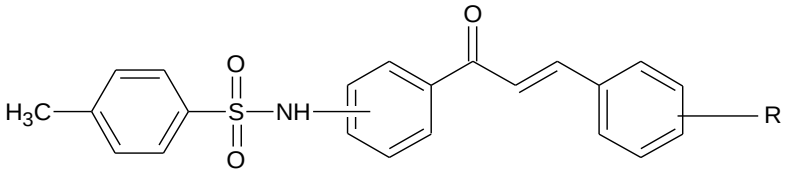
Nakahara Kazuhiko et al.[62] have synthesized chalcones as carcinogen inhibitors. Antitubercular agents of chalcone derivatives have been prepared by Lin Yuh-Meei et al.[63] Ko Horng-Huey et al.[64] have reported chalcones as anti-inflammatory agents. Some of the chalcones have been reported for their use for treatment of glaucoma[65] and showed antifungal,[66] aldose reductase inhibitors,[67] anticancer[68] activities. Satyanarayana M. et al.[69] have synthesized chalcone (2) derivatives as anti hyperglycemic activity.



(2)

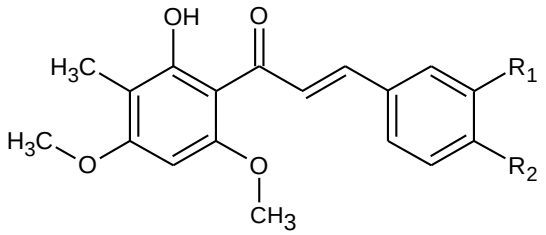
Hollosy F. et al.[70] have prepared some new chalcones as plant derived protein tyrosine kinase inhibitors as anticancer agents. Meng C. Q. et al.[71] have discovered some novel heteroaryl substituted chalcones as inhibitors of TNF-alpha-induced VCAM-1 expression. V. K. Ahluwalia et al.[72] have noted that 5-cinnamoylchalcones have exposed

good as antibacterial agents. Woo Duck Seo et al.[73] have synthesized chalcone derivatives (3) reported as α-glucosidase inhibitors.



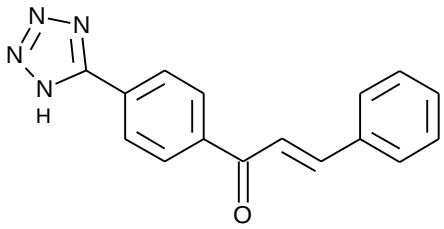
(3)

A. Araico and co-workers[74] have synthesized chalcone derivatives as inhibitor of cyclo-oxygenase-2 and 5-lipoxygenase. Alcaraz M. J. et al.[75] have described the role of nuclear factor-kappa-B and hemeoxygenase-1 in the action of an anti-inflammatory chalcone derivatives in RAW 264.7 cells. Xue C. X. et al.[76] documented chalcones as antimalarial agents. Prem P. Yadav and co-workers[77] have synthesized nitrogen and sulfur containing furanoflavonoids and thiophenylflavonoids which have been screened for antifungal and antibacterial activity. Opletalova Veronika et al.[78] have synthesized chalcones and screened for their cardiovascular agents. H. H. Ko et al.[79] have prepared some new chalcones for potent inhibition of platelet aggregation. S. Khatib et al.[80] synthesized some novel chalcones as potent tyrosinase inhibitors. Fu Y. et al.[81] have demonstrated chalcones as licochalcone-A. O. Nerya et al.[82] have prepared some new chalcones as potent tyrosinase inhibitors. Sung Hee Lee and co-workers[83] have designed and synthesized chalcones and reported their anti-inflammatory activity. Paula Boeck, Camila Alves and Bartira Rossi-Bergmann[84] have synthesized some newer chalcone analogues (4) which shows antileishmanial activity.



(4)

Xiang Wu et al.[85] have synthesized ferrrocenyl chalcones and reported their antiplasmodial activity. Ban H. S. et al.[86] have synthesized some newer chalcones as inhibition of lipopolysaccharide-induced expression of inducible nitric oxide syntheses and tumor necrosis factor-alpha by 2'-hydroxychalcone derivatives in RAW 264.7 cells. Simon Feldbaek Nielsen et al.[87] have described some chalcone derivatives (5) as antibacterial agents.

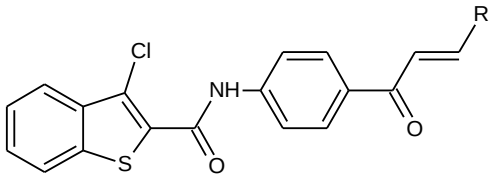


(5)

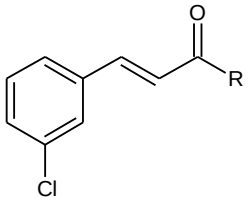
Morever, Aneta Modzelewska et al.[88] have prepared novel chalcone and bis chalcone derivatives having anticancer activity. Seo et al.[89] reported the chalcones as a glucosidase inhibitors.

Work done from our laboratory

V. V. Kachhadia[90] have synthesized some chalcone derivatives (6) as antimicrobial and antitubercular agent. K. H. Popat[91,92] have synthesized some chalcone derivatives(7) as antitubercular agents from 3-chlorobenzaldehyde.

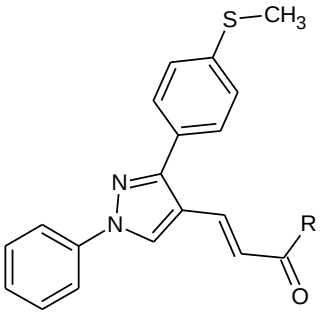


(6)

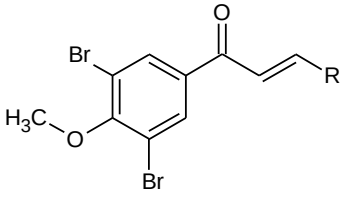


(7)

Synthesis of some chalcone derivatives from aromatic aldehyde have been reported by P. T. Chovatia.[93] D. H. Vyas[94] reported some new pyrazoline (8) and isoxazole derivatives as antitubercular and antimicrobial agent and he also synthesized some new cyanopiperidinones (9) and cyanopyridones[95], pyrazoline derivatives[96] as a antimicrobial agent.

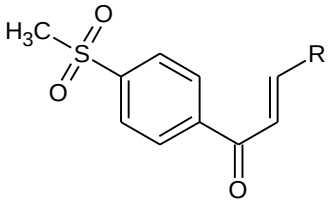


(8)

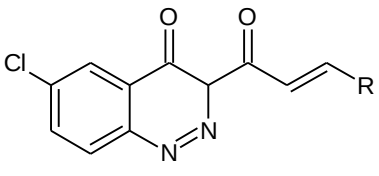


(9)

D. J. Paghdar[97] have reported chalcone derivatives bearing 4-(methylsulfonyl) phenyl nucleus (10) as potent antitubercular and antimicrobial agents Synthesis and evaluation of pharmacological activity of chalcone derivatives (11) have been reported by M. R. Patel.[98] Synthesis of some new pyrazolo[3,4-*d*]pyrimidines and thiazolo[4,5-*d*]pyrimidines from arylidine and reported their antimicrobial activities by J. D. Akbari.[99]



(10)



(11)

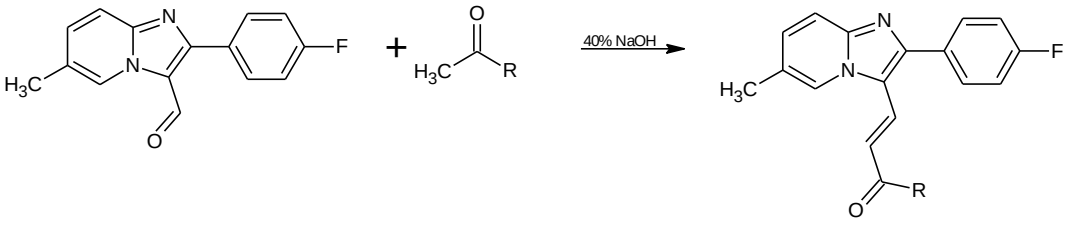
Chalcones have been proved to be an important intermediate for the synthesis of many heterocyclic compounds in organic chemistry. These facts pormpted us to synthesize some new chalcone derivatives bearing imidazo[1,2-a]pyridine nucleus, in order to achiving better therapeutic agents described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-1-ARYLPROP-2-EN-1-ONES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-1-ARYLPROP-2-EN-1-ONES.

With the biodynamic activities of chalcones and as a fine synthon for different heterocyclic rings, the awareness has been paying attention on the creation of new chalcones. With a observation to obtained compounds having better therapeutic activity, we have synthesized (2*E*)-3-(2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-*a*]pyridin-3-yl)-1-arylprop-2-en-1-ones. by the condensation of 2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine-3-carbaldehyde. with various aromatic ketones by using alkali as catalyst.

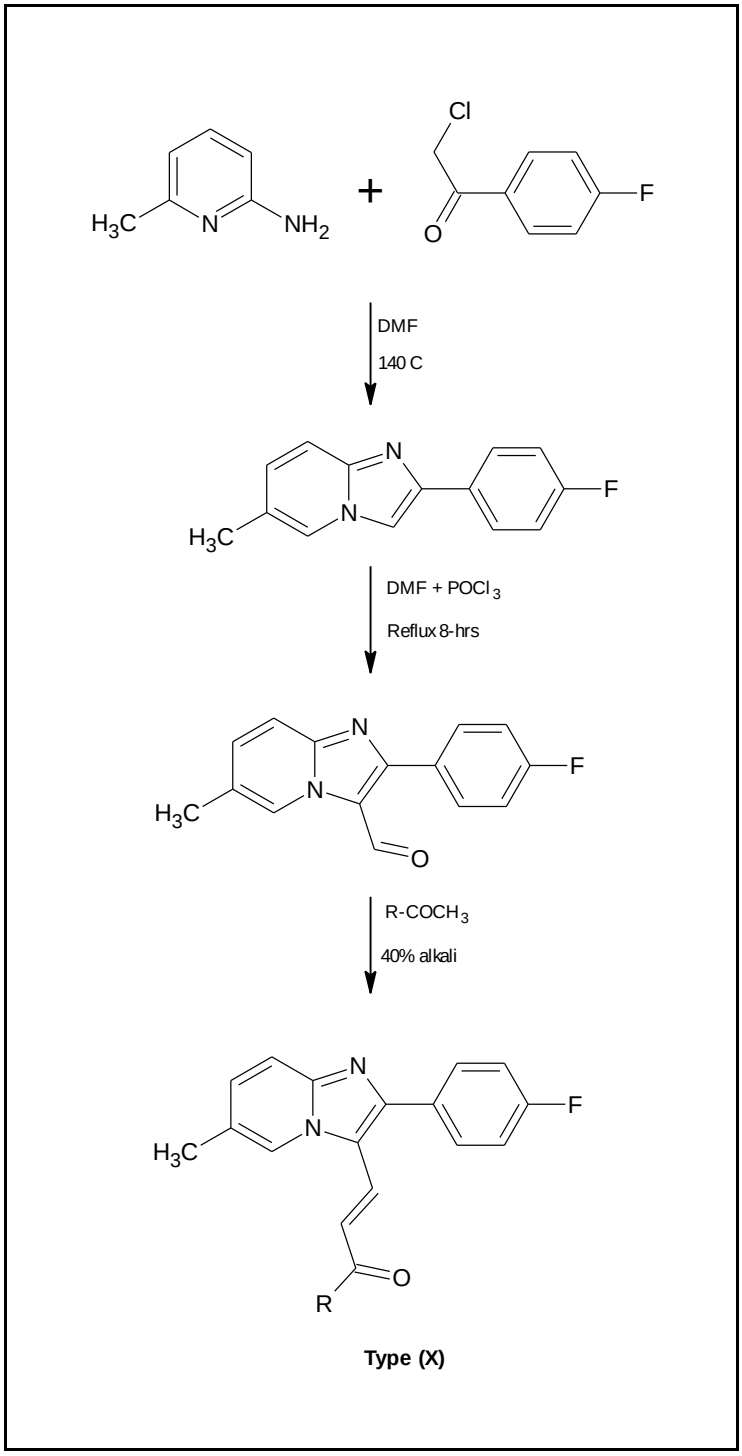


Type (X) R= Aryl

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.

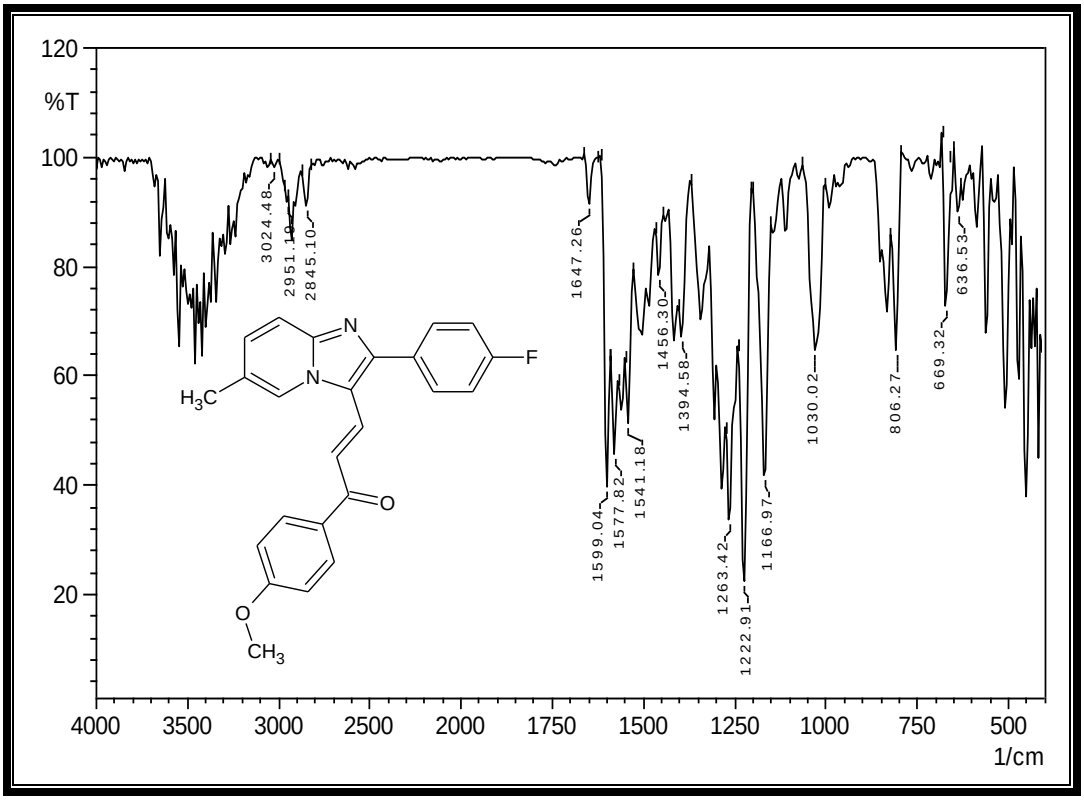
All the compounds have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger, Candida albicans*** at a concentration of 2000/1000/500 µg/ml. The biological activity 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 Table No10b.

REACTION SCHEME



Type (X)

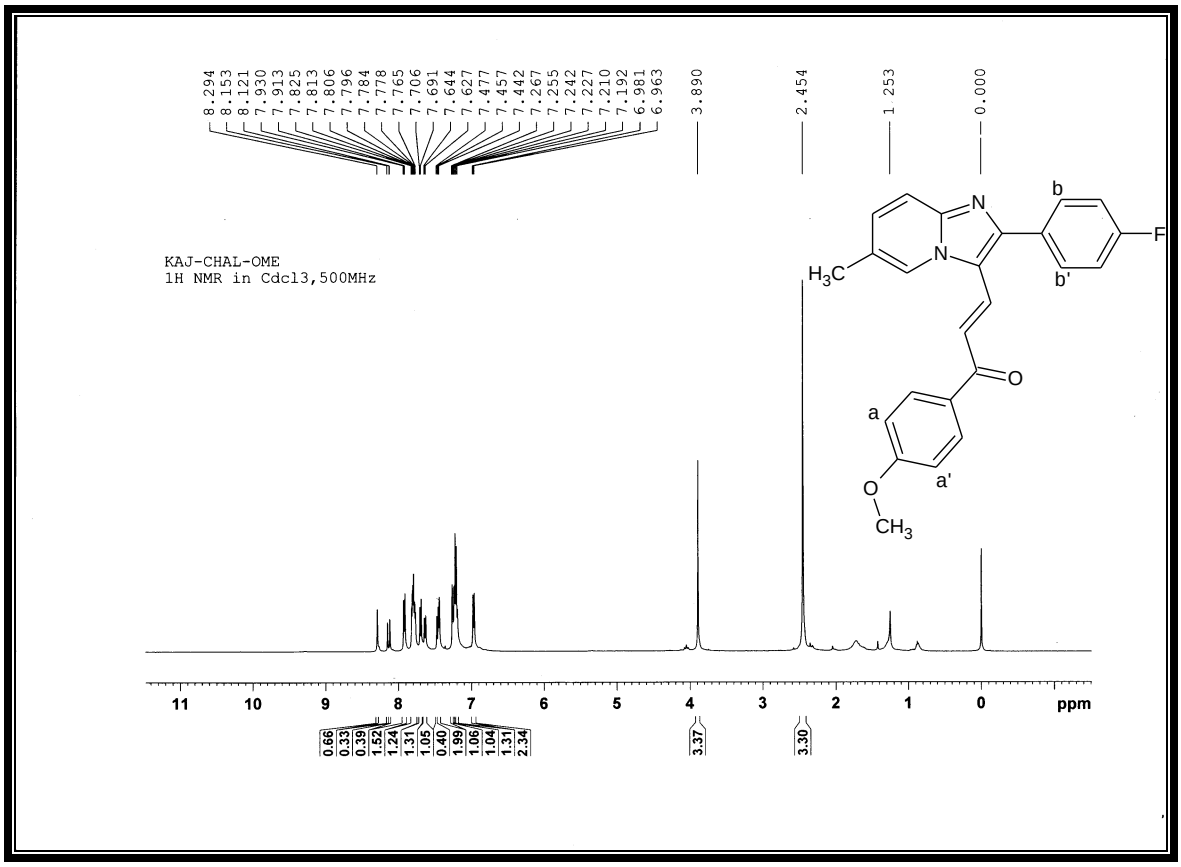
IR SPECTRAL STUDIES OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2951	2975-2940	101
	C-H str. (sym.)	2845	2880-2860	101
	C-H def.	1456	1470-1435	102
	C-H def. (sym.)	1394	1395-1370	100
Aromatic	C-H str.	2951	2980-2930	100
	C=C str.	1541	1585-1480	101
	C-H I.p.(def)	1030	1125-1000	101
	C-H o. o. p.	669	700-600	100
Imidazo[1,2-*a*]pyridine	C=N	1599	1612-1593	100
	C-N	1166	1220-1020	100
Chalcone	C=C str.	1577	1580-1550	101
	C=O str.	1647	1640-1700	102
Vinyl	CH=CH str	3024	3050-3000	102
Ether	C-O-C str	1222	1260-1200	102
Halide	C-F str.	1166	1200-1000	101

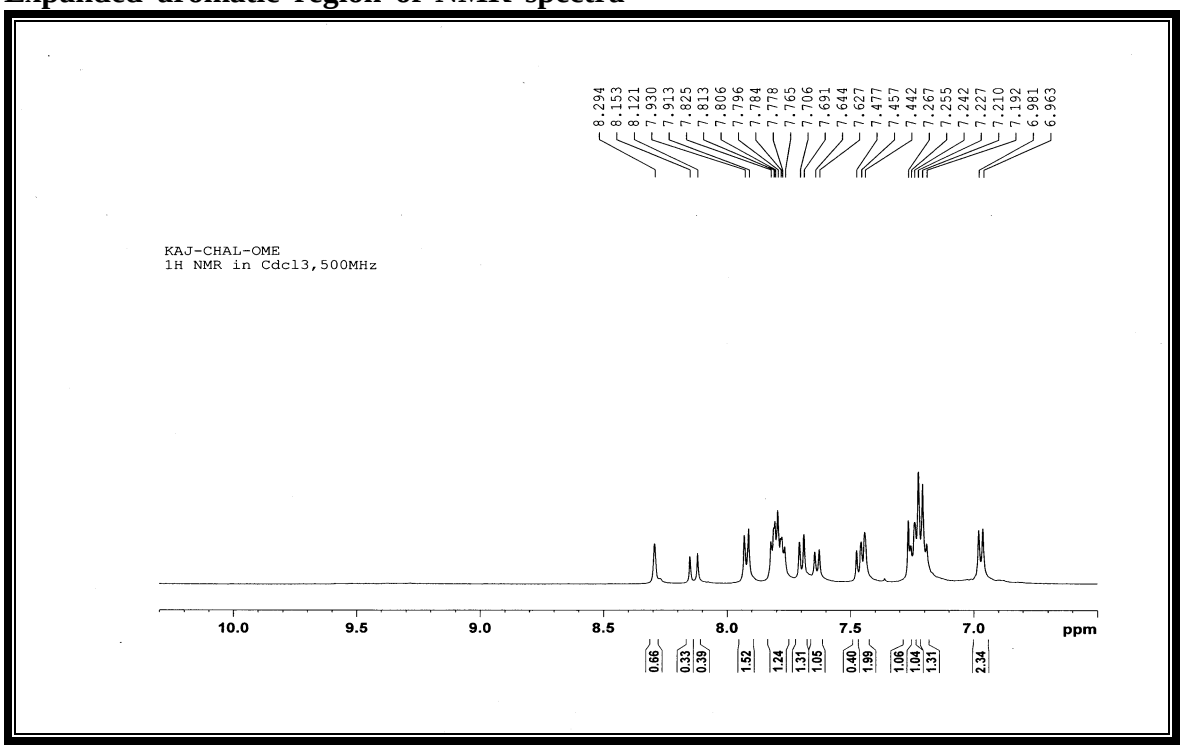
NMR SPECTRAL STUDIES OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6- METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.



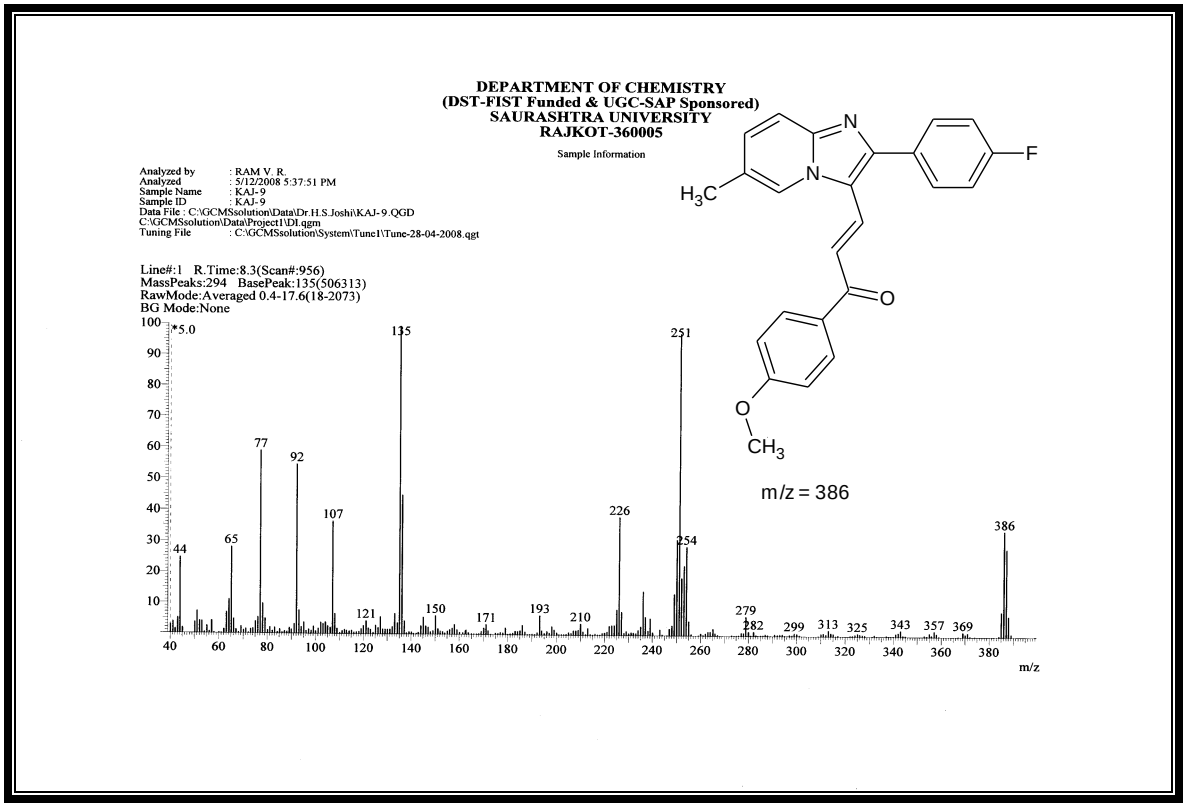
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	2.45	3H	singlet	$-CH_3$	-
2	3.89	3H	singlet	$-OCH_3$	-
3	6.96-6.98	2H	doublet	-Ar-Ha-a'	9.0
4	7.19-7.26	3H	multiplet	-Ar-H	-
5	7.44-7.47	2H	multiplet	-Ar-H	-
6	7.62-7.64	1H	doublet	-CH=CH	8.5
7	7.69-7.70	1H	doublet	-CH=CH	7.5
8	7.76-7.82	1H	multiplet	-Ar-H	-
9	7.91-7.93	2H	doublet	-Ar-Hb,b'	8.5
10	8.29	1H	singlet	-Ar-H	-

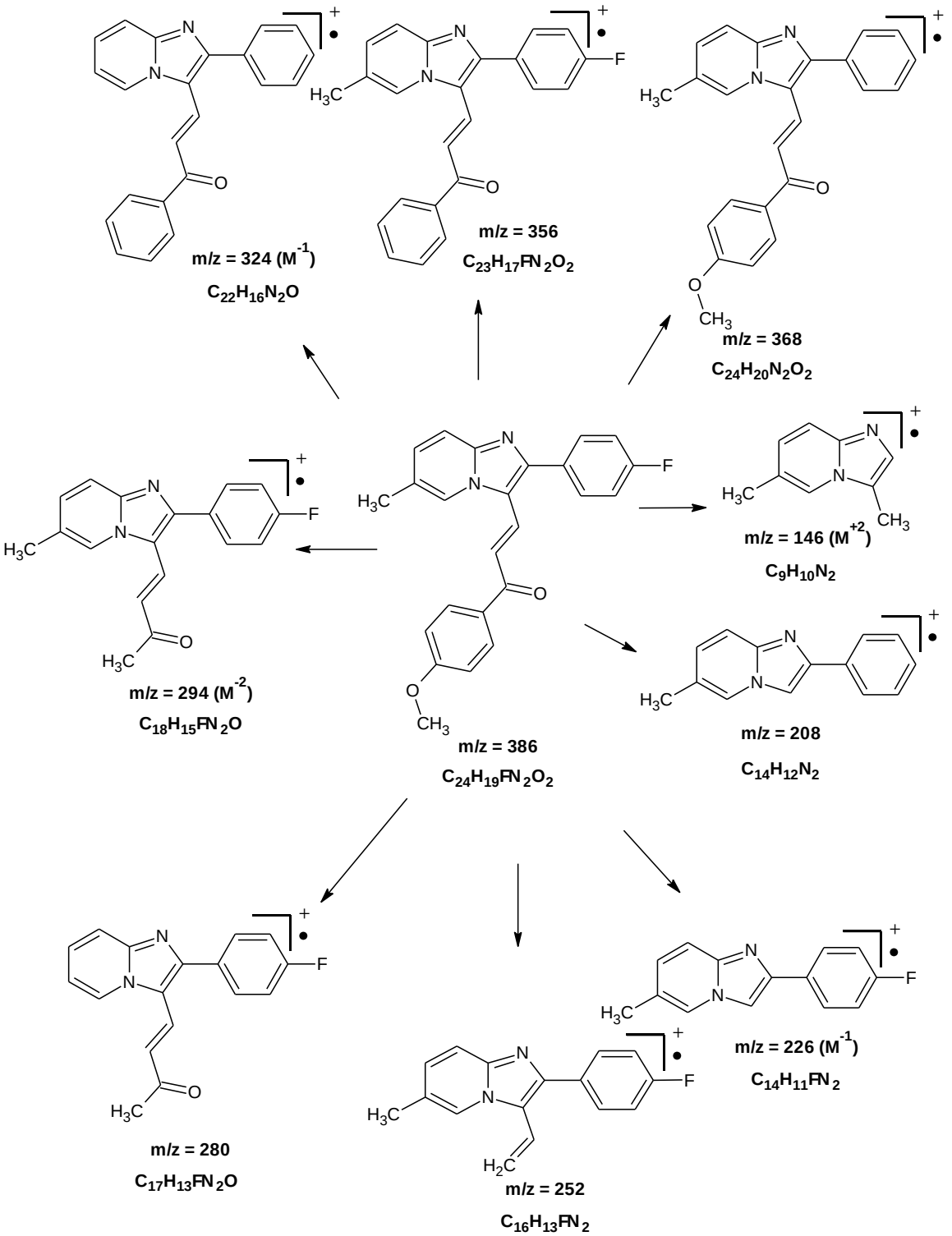
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6- METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.



PROPOSED MASS FRAGMENTATION OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6- METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine.

A solution of 6-methylpyridin-2-amine (27.0gm, 0.25mol) in DMF(100 ml) was added to 2-chloro-1-(4-fluorophenyl)ethanone (15.4gm, 0.1mol) and the reaction mixture was refluxed with stirring for 6 hrs. Cool the content, the solid separated was filtered and dried in vacuo. Yield 68%, m.p192 °C, Anal. Calcd. for $C_{11}H_{14}FN_2$: Require: C, 74.32, H, 4.90, N, 12.38 % ; Found: C, 74.30, H, 4.96, N, 12.35 %.

[B] Synthesis of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo [1,2-α]pyridine-3-carbal-dehyde.

To a well stirred solution of phosphorus oxychloride (11 ml), chloroform (32 ml) and DMF (8 ml) maintained at 0-10 °C. was added slowly to a solution of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine. (4.52gm, 0.02mol) in chloroform (140 ml). The mixture so obtained was refluxed for 8 hrs., the solution was evaporated to dryness in vacuo. the residue was treated with cold water and filtered and crystallized from methanol. Yield 59%, m. p. 186 °C , Anal. Calcd. for $C_{15}H_{11}FN_2O$ Require: C, 70.86, H, 4.36, N, 11.02 %; Found: C, 70.81, H, 4.29, N, 11.01 %.

[C] Synthesis of (2*E*)-3-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo [1,2-α]pyridin-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one.

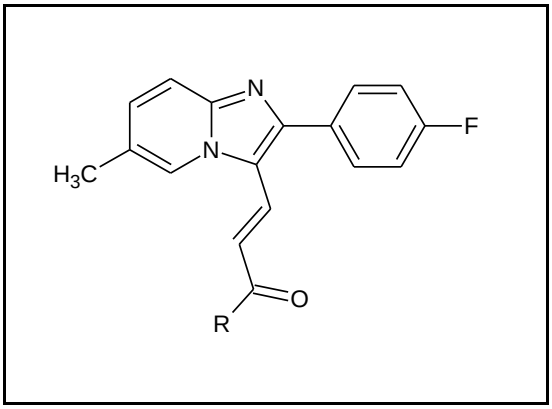
To a solution of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine-3-carbaldehyde (2.54gm, 0.01mol), p-methoxyacetophenone (1.5gm, 0.01mol) in ethanol (25 ml) and 40% NaOH solution was added till the solution become basic. The reaction mixture was stirred for 24 hrs. The content was poured on to crushed ice. Upon neutralization the solid separated was crystallized from ethanol. Yield 61%; m.p.209 °C. Anal. Calcd. For $C_{24}H_{19}FN_2O_2$; Required : C, 74.60; H, 4.96; N, 7.25%; Found: C, 74.55; H, 4.91; N, 7.19%.

Similarly other (2*E*)-3-(2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-1-arylprop-2-en-1-ones. have been prepared. The physical constants are recorded in Table No.10a.

[E] Antimicrobial activity of (2*E*)-3-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo [1,2-α]pyridin-3-yl)-1-arylprop-2-en-1-one.

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.10b.

Table-10a: Physical constants of (2*E*)-3-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo [1,2-α]pyridin-3-yl)-1-arylprop-2-en-1-ones.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd. (Found)		
					C	H	N
10a	C_6H_5-	$C_{23}H_{17}FN_2O$ 356.39	166	65	77.51 (77.39)	4.81 (4.64)	7.86 (7.79)
10b	4-CH_3-C_6H_4-	$C_{24}H_{19}FN_2O$ 370.41	147	62	77.82 (77.64)	5.17 (5.01)	7.56 (7.44)
10c	2-CH_3-C_6H_4-	$C_{24}H_{19}FN_2O$ 372.43	158	58	77.82 (77.69)	5.17 (5.00)	7.56 (7.31)
10d	2,5-$(CH_3)_2$-C_6H_3-	$C_{25}H_{21}FN_2O$ 384.44	152	59	78.10 (78.04)	5.51 (5.34)	7.29 (7.17)
10e	4-OCH_3-C_6H_4-	$C_{24}H_{19}FN_2O_2$ 386.41	209	61	74.60 (74.45)	4.96 (4.81)	7.25 (7.19)
10f	2,4-$(Cl)_2$-C_6H_3-	$C_{23}H_{15}Cl_2FN_2O$ 425.28	176	47	64.96 (64.11)	3.56 (3.48)	6.59 (6.38)
10g	4-Cl-C_6H_4-	$C_{23}H_{16}ClFN_2O$ 390.83	165	69	70.68 (70.44)	4.13 (4.04)	7.17 (7.01)
10h	3-Cl-C_6H_4-	$C_{23}H_{16}ClFN_2O$ 390.83	158	68	70.68 (70.41)	4.13 (4.07)	7.17 (7.06)
10i	4-NO_2-C_6H_4-	$C_{23}H_{16}FN_3O_3$ 401.38	189	55	68.82 (68.79)	4.02 (3.93)	10.47 (10.39)
10j	4-F-C_6H_4-	$C_{23}H_{16}F_2N_2O$ 374.38	197	49	73.79 (73.66)	4.31 (4.19)	7.48 (7.38)

TABLE 10B : ANTIMICROBIAL ACTIVITY OF (2*E*)-3-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO [1,2-*a*]PYRIDIN-3-YL)-1-ARYLPROP-2-EN-1-ONES. (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1	10a	-	-	-	+	+	-	-	-	-	-	-	-	+	+	-	+	+	-
2	10b	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
3	10c	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
4	10d	-	-	-	+	+	-	-	-	-	-	-	-	+	+	-	+	+	-
5	10e	-	-	-	+	+	-	-	-	-	-	-	-	+	+	-	+	+	-
6	10f	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+
7	10g	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
8	10h	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	-
9	10i	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
10	10j	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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Part- C

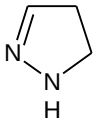
(Part-I)

Studies on Pyrazole Derivatives

INTRODUCTION

The chemistry of pyrazoles has been reviewed by C. H. Jarobe in 1967. Pyrazoles have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. Pyrazole have been studied extensively because of ready accessibility, diverse chemical reactivity, broad spectrum of biological activity[1] and varieties of industrial applications[2].

Pyrazole has three possible tautomeric structures, but 2-pyrazole (1) consist a unique class of nitrogen containing five member heterocycles.

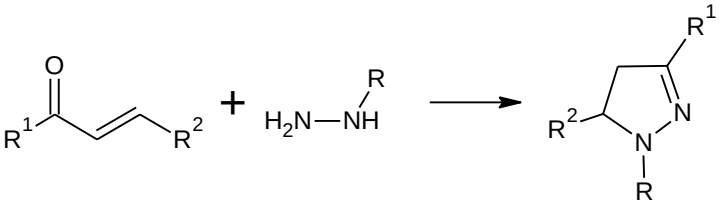


(1)

As evident from the literature in recent years a significant portion of research work in heterocyclic chemistry has been devoted to pyrazoles containing different alkyl, aryl and heteroaryl groups as substituents.

SYNTHETIC ASPECT

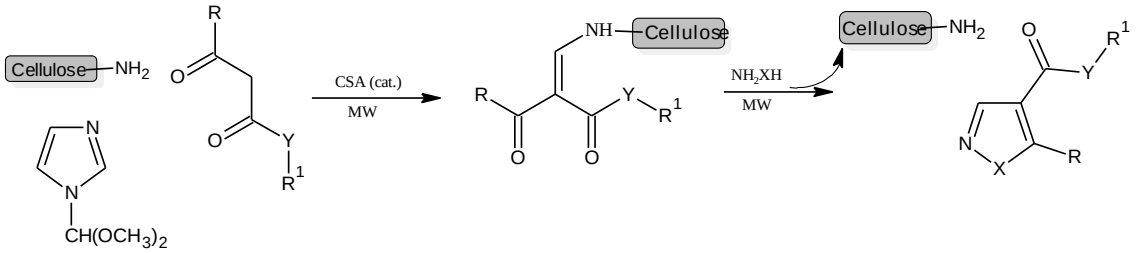
Different methods are available from the literature for the preparation of 2-pyrazole derivatives. The most common procedure for the synthesis of 2-pyrazoles is the reaction of an aliphatic or aromatic hydrazine with α,β-unsaturated carbonyl compounds.



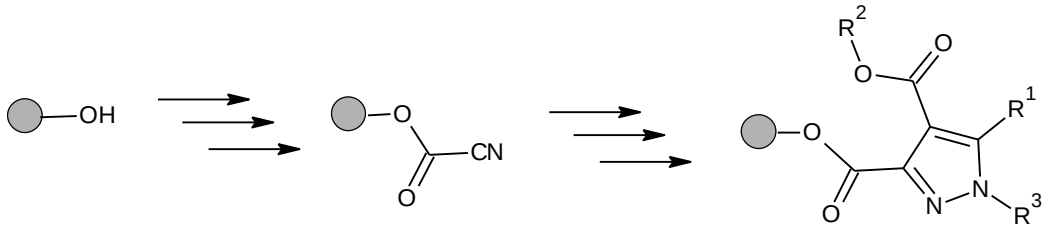
Alternative synthetic routes for improved yield, shorter reaction time and milder conditions to synthesize new analogs

Solid-Phase Synthesis

L. L. De[3] reported cellulose beads as a new versatile solid support for Microwave-assisted synthesis of pyrazole and isoxazole libraries.



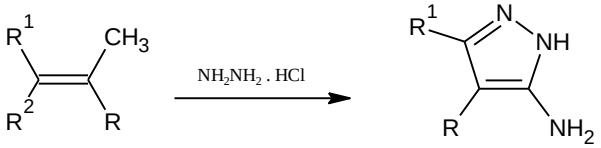
Wang resin supported solid - phase synthesis of pyrazoledicarboxylic acid derivatives by functionalization of cyanoformate was reported by C. F. Morelli et al.[4]



Similarly many other solid phase synthesis of pyrazole motif were reported using different solid support such as (4-formyl-3-methyoxyphenoxy)methylpolystyrene (FMP) resin[5], polymer-supported vinylsulfone[6], Kenner 'safety catch' resin[7], KOH powder[8].

Liquid-Phase Synthesis

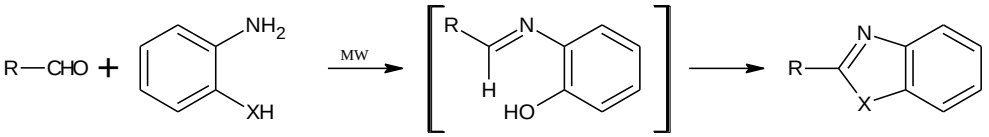
X. L. Ren and coworkers[9] have synthesized pyrazole derivatives using liquid phase synthesis strategy.



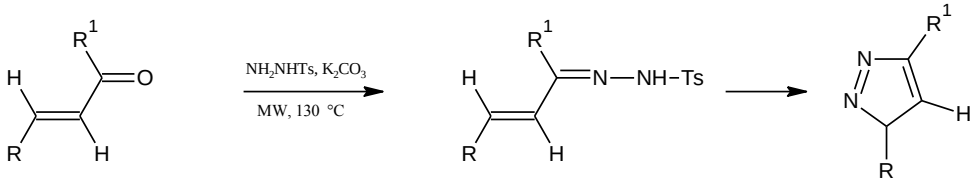
V. N. Pathak and group reported 3,5-diarylpyrazole synthesis using phase transfer catalyst[10,11], heterocyclic pyrazole was synthesized by the W. C. Shen and coworkers[12].

Microwave Assisted Synthesis

Microwave irradiation and solvent-free conditions was reported for the rapid and efficient synthesis by M. A. H. Zahran[13].



New "Green" approaches to the synthesis of pyrazole derivatives were reported by A. Corradi et al.[14]



Similarly in literature there are number of the report that uses the microwave irradiation for the rapid synthesis, high yield or towards the green approach of the reaction under solvent free conditions some of them are reported as below.

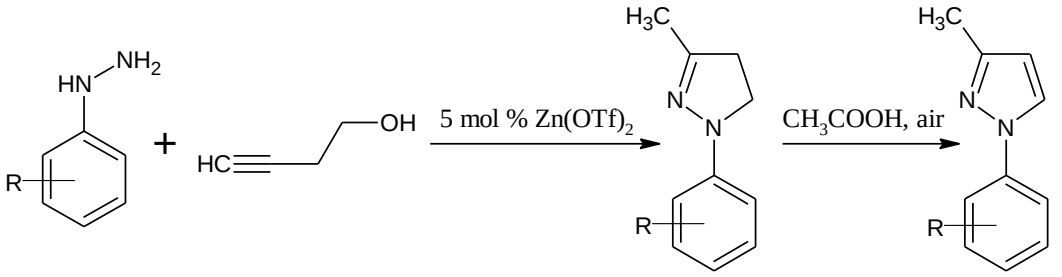
S. S. Chauhan derives pyrazoles from diaryl 1,3-diketones[15] and also several author documented pyrazoles from 1,3-dipolar cycloaddition of diazo compounds to acetylene derivatives[16], regiospecific synthesis of 5-trifluoromethyl-4,5-dihydropyrazoles[17], micro wave mediated combinatorial synthesis[18], under dry media[19], synthesis of trichlorometh- ylpyrazolines[20], catalyzed by p-toluenesulphonic acid[21], microwave studies on synthesis[22].

P. D. Sauzem[23] reported deign and microwave-assisted synthesis of 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles, and one step synthesis of 3,5-disubstituted pyrazoles were carried out by M. Outirite[24].

Catalysts

Many of the organic chemists prefer to use catalyst to get the desire product with high yield and within sort reaction time and to convert the reaction condition from drastic to easily operational with some specific catalyst.

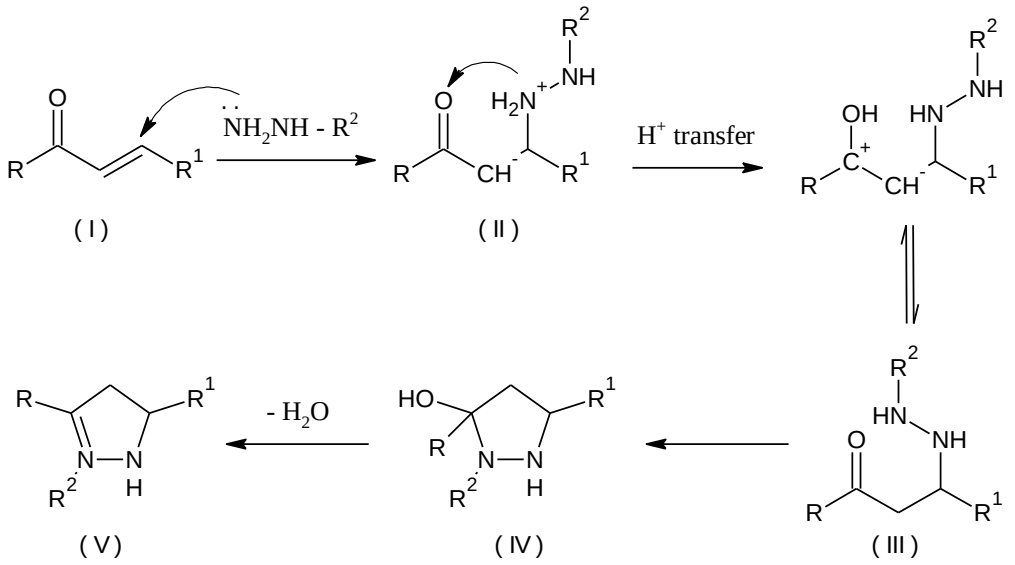
R. Ali reported stereoselective synthesis of *N*-vinyl pyrazoles in solvent-free conditions using dipotassium hydrogen phosphate powder[25], Zinc-catalyzed synthesis of pyrazolines and pyrazoles via Hydrohydrazination were reported by K. Alex.[26]



In literature there are number of the catalysts are used for the synthesis of pyrazole system like Conjugate base[27], Iodine(III)[28], Hafnium chloride[29], Tungstophosphoric acid[30], p-toluenesulphonic acid[31], Sulfamic acid[32], Ytterbium(III)perfluorooctanoate[33], Silver(I)[34], organocatalysts[35].

REACTION MECHANISM

The following mechanism seems to be operable for pyrazoline by the condensation of chalcones with hydrazine hydrate[36].



Nucleophillic attack by hydrazine at the β-carbon of the α,β-unsaturated carbonyl system I forms species II, in which the negative charge is mainly accommodated by the electronegative oxygen atom.

Proton transfer from the nitrogen to oxygen produces an intermediate and which simultaneously ketonises to ketoamine III. Another intramolecular nucleophillic attack by

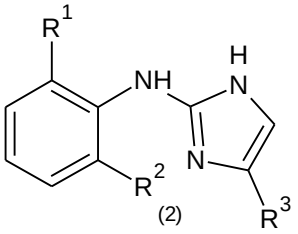
the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to hydroxyl amine IV. The later with a hydroxy group and amine group on the same carbon loses water easily to yield the pyrazolines V.

BIOLOGICAL EVALUATION

From the literature survey, it was revealed that 2-pyrazolines are better therapeutic agents. They possess valuable bioactivities like

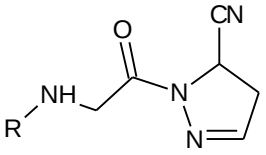
1. Antiinflammatory[37,38]
2. Analgesic[39,40]
3. Bactericidal[41]
4. Fungicidal[42,43]
5. Anticonvulsant[44]
6. Pesticidal[45,46]
7. Antidepressant[47]
8. Antiamoebic[48]
9. Insecticidal[49]
10. Antineoplastic[50,51]
11. Herbicidal[52]

M. K. Shivnanda and co-workers[53] have prepared pyrazolines and reported their antibacterial activity. Antimycotic activity of pyrazoline derivatives (2) have been reported by Joanna Matysiak and Andrzej Niewiadomy[54]. J. Almstead et al.[55] have prepared pyrazolines as vascularization agent. T. Z. Gulhan and coworkers[56] have prepared pyrazolines as a hypotensive agent.



(2)

S. Sharma et al.[57] have synthesized pyrazolines and tested their anti-inflammatory activity. Antiamoebic activity of pyrazoline derivatives have been reported by Asha Budakoti and co-workers[58]. J. H. Ahn et al.[59] have reported as inhibition of cyano-pyrazoline (3) derivatives as potent antidiabetic agents. T. S. Jeong et al.[60] have synthesized some novel 3,5-diaryl pyrazolines (4) as human acyl-Co A: cholesterol acyltransferase inhibitors. G. Ucar et al.[61] reported pyrazolines as cholinstearase andselective monoamine oxidase-B inhibitiors for the treatment of parkinson and alzheimer's diseases. M. N. Nasr et al.[62] have reported the synthesis of newer arylthiazolylpyrazoline derivatives as anti-inflammatory agents. M. A. Berghot et al.[63] have prepared for convergent synthesis and antibacterial activity of pyrazole and pyrazoline derivatives of diazepam.



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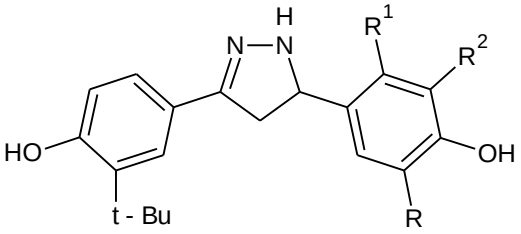
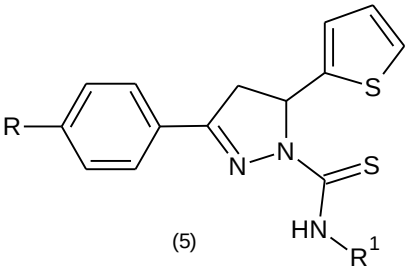


(4)

N. Gokhan et al.[64] have synthesized the pyrazoline derivatives of 1-*N*-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazolines (5) as MAO inhibitors. Mohammad Abid and Amir Azam[65] have synthesized 1-*N*-substituted cyclized pyrazoline of thiosemicarbazones (6) and reported as antiamoebic agents. V. Malhotra et al.[66] have documented new pyrazolines as a cardiovascular agents. Antidepressant activity of pyrazoline derivatives have been reported by Y. R. Prasad and co-worker[67].



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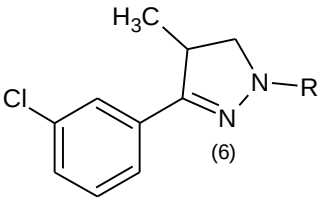
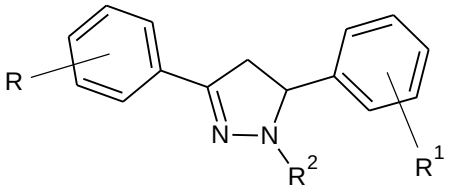


(6)

Abd El-Galil E. Amr et al.[68] have synthesized some new 3-substituted androstano[17,16-*c*]-5,2-aryl-pyrazolines and reported their antiandrogenic activity. B. Bizzarri et al.[69] have reported in vitro selective anti-helicobacter pylori activity (7) of pyrazoline derivatives. Bhat and co-workers[70] reported cytotoxic properties of pyrazoline derivatives. Antibacterial activity of pyrazoline derivatives have been reported by A. M. Gandhi and co-workers[71]. B. S. Holla et al.[72] have synthesized pyrazolines as antibacterial agents. S. P. Hiremath et al.[73] have synthesized pyrazolines as analgesic, anti-inflammatory and antimicrobial agents. Rajendra Prasad et al.[74] have synthesized some 1,3,5-triphenyl-2-pyrazolines (8) and 3-(2"-hydroxynaphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines and reported as antidepressant agents. J. H. M. Lange et al.[75] synthesized and reported 3,4-diaryl pyrazoline analogues as potent and selective CB_1 cannabinoid receptor antagonists. N. T. Ha- Duong et al.[76] have been synthesized some pyrazole derivatives as inhibitors for the active sites of human liver cytochromes P450 of the 2C subfamily.



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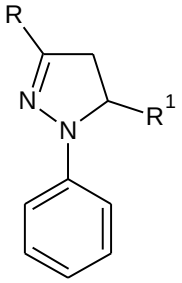
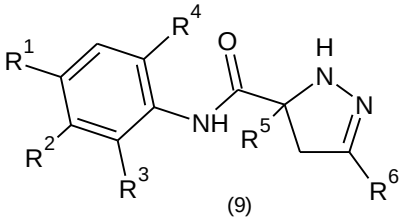


(8)

X. Zhang and co-workers[77] have been prepared pyrazoline derivatives (9) as potent selective androgen receptor modulators. M. E. Camacho and co-workers[78] have been reported 4,5-dihydro pyrazoles (10) as Inhibitory nNOS activity in rat brain.



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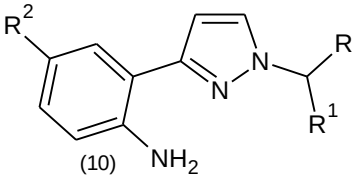
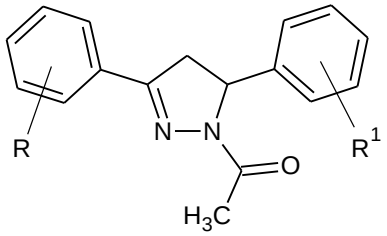
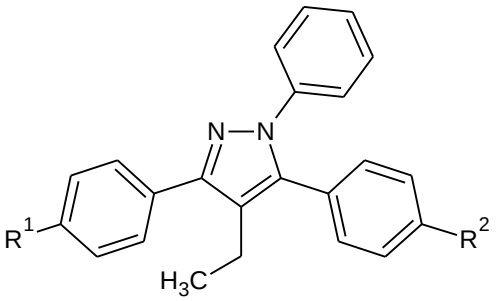


(10)

F. Chimenti and co-workers[79] have been demonstrated a novel series of 1-acetyl-3-(4-hydroxy-and 2,4-dihydroxyphenyl)-5-phenyl-4,5-dihydro-(1*H*)-pyrazole derivatives (11) and investigated for the ability to selectively inhibit the activity of monoamine oxidase (MAO). Y. R. Huang et al.[80] have been prepared a series of 4-alkyl-1,3,5-triarylpyrazoles (12) as ligands for the estrogen receptor. C. D. Cox et al.[81] and J. R. Goodell et al.[82] have been reported separately some pyrazoline derivatives as anti-obesity agents by antagonizing CB_1 receptors and therapeutic candidates for parkinson's disease. A series of 3-(4-fluorophenyl)-4,5-dihydro-*N*-[4-(trifluoromethyl)-phenyl]-4-[5-(trifluoromethyl)-2-pyridyl]-1*H*-pyrazole-1-carboxamide has been synthesized and studied for their potent foliar activity against both lepidoptera and orthoptera insects by P. K. Leonard et al.[83] Bruce G. Szczepankiewicz et al.[84] have been prepared some pyrazole derivatives as ant mitotic agents with activity in multi-drug resistant cell lines.



(11)



(12)

Guniz Kuchkguzel et al.[85] have synthesized pyrazolines as a antimicrobial and anticonvulsant agents. Gulhan T. Z. and co-workers[86] have prepared pyrazolines as a hypotensive agent.

Work done from our laboratory

K. S. Nimavat[87] have synthesized 1-substituted 3-aryl-5-(3'-bromophenyl)-pyrazolines and studied anticancer, antitubercular and antimicrobial activity. D. H. Vyas[88] reported synthesis and biological activity of some pyrazoline derivatives bearing 3,5-dibromo-4-methoxybenzaldehyde nucleus.

P. T. Chovatia[89] have been reported 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives as a antitubercular and antimicrobial agent. T. K. Dave[90] reported synthesis, antitubercular and antimicrobial evaluation of pyrazole derivatives bearing nicotinic acid nucleus. Synthesis of some pyrazolo[3,4-*d*]pyrimidines and thiazolo[4,5-*d*]pyrimidines and evaluation of their antimicrobial activities with derivatives of urea and thiourea was reported by J. D. Akbari[91,92].

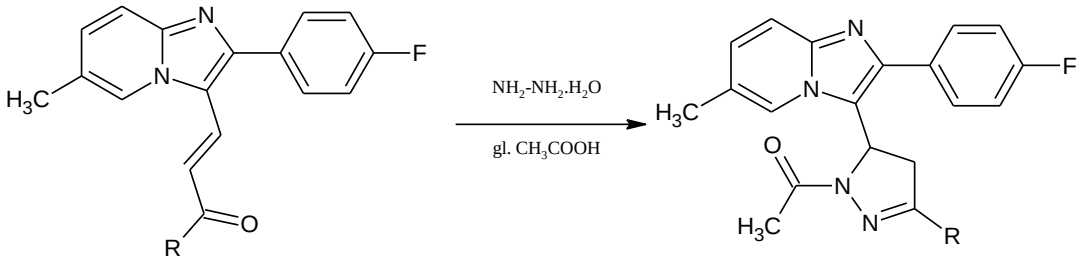
Literature survey reveals that the compounds bearing pyrazole moiety possess potential drug activity. Looking to the diversified biological activities we have synthesized some pyrazole derivatives in order to achieving better therapeutic agents. These studies are described in following section.

SECTION-II :- SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(5-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-4,5-DIHYDRO-3-ARYLPYRAZOL-1-Yl)ETHANONES.

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(5-(2-(4-FLUOROPHEN-YL)-6-METHYL*H*-IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-4,5-DIHYDRO-3-ARYL PYRAZOL-1-Yl)ETHANONES.

Pyrazolines play a vital role owing of their wide range of biological activity and with an aim to getting better drug, it was considered worthwhile to synthesize some new acetyl pyrazolines. The preparation of 1-(5-(2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-4,5-dihydro-3-arylpyrazol-1-yl)ethanones. Type(XI) have been under taken by cyclocondensation of chalcones of Type (X) with hydrazine hydrate in glacial acetic acid.

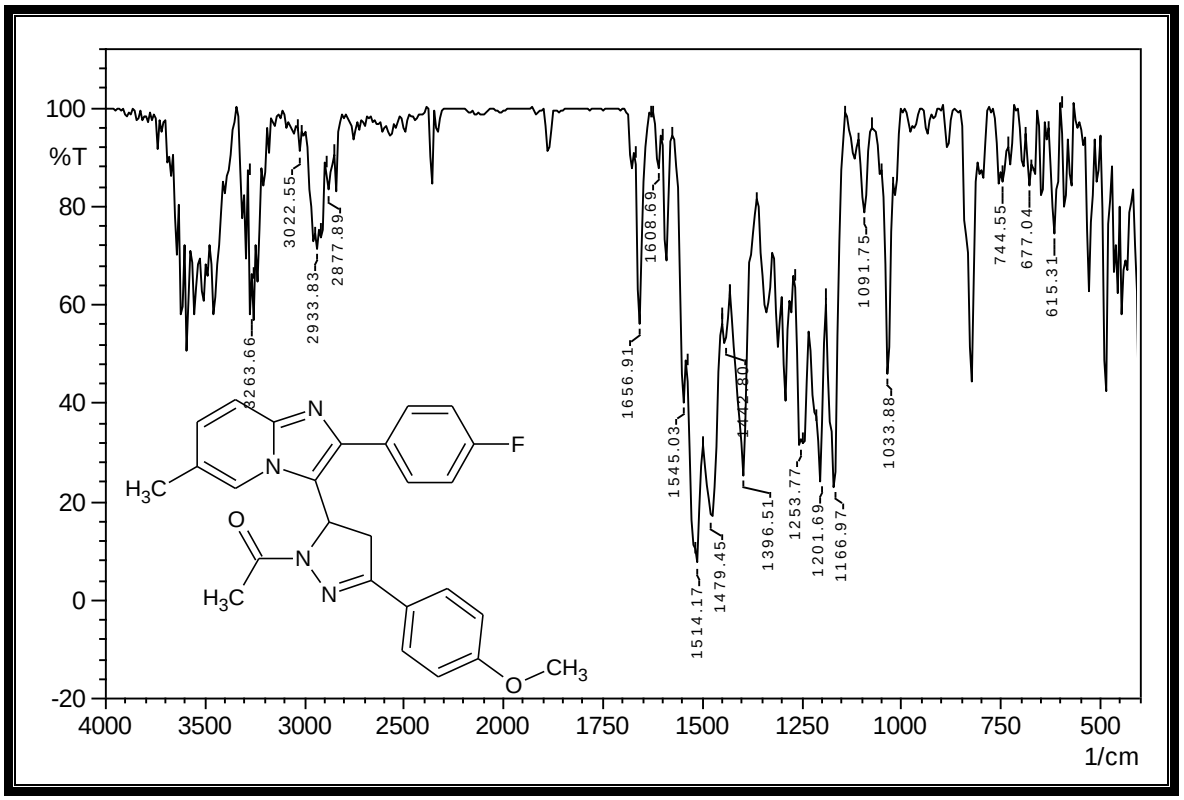


Type (X) R= Aryl **Type (XI) R= Aryl**

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, Candida albicans*** at a concentration of 2000/1000/500 µg/ml. The biological activity of the synthesized compounds has been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Table No.11b.

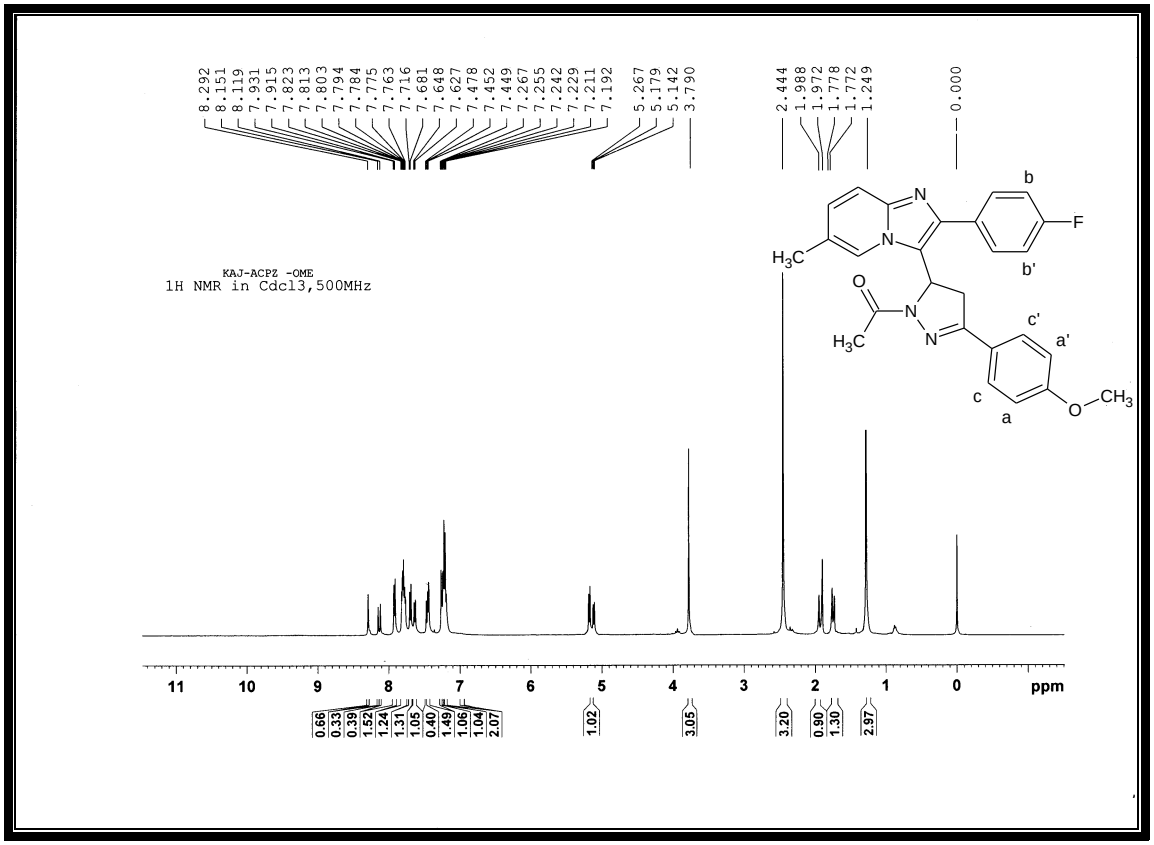
IR SPECTRAL STUDIES OF 1-(5-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL)-4,5-DIHYDRO-3-(4-METHOXYPHENYL) PYRAZOL-1-Yl)ETHANONE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.	2933	2975-2930	93
	C-H str. (sym.)	2877	2880-2860	93
	C-H def.	1442	1470-1435	95
	C-H def. (sym.)	1396	1395-1370	95
Aromatic	C-H str.	2933	2980-2930	94
	C=C str.	1545	1585-1480	94
	C-H I.p.(def)	1033	1125-1000	96
	C-H o.o.p.	615	700-600	96
Imidazo[1,2-α]pyridine	C=N str.	1589	1612-1593	94
	C-N str.	1033	1220-1020	95
Acetyl Pyrazoline	C=O str.	1577	1700-1612	94
	C=N str.	1656	1612-1593	95
Ether	C-O-C str	1240	1260-1200	96
Halide	C-F str.	1091	1200-1000	96

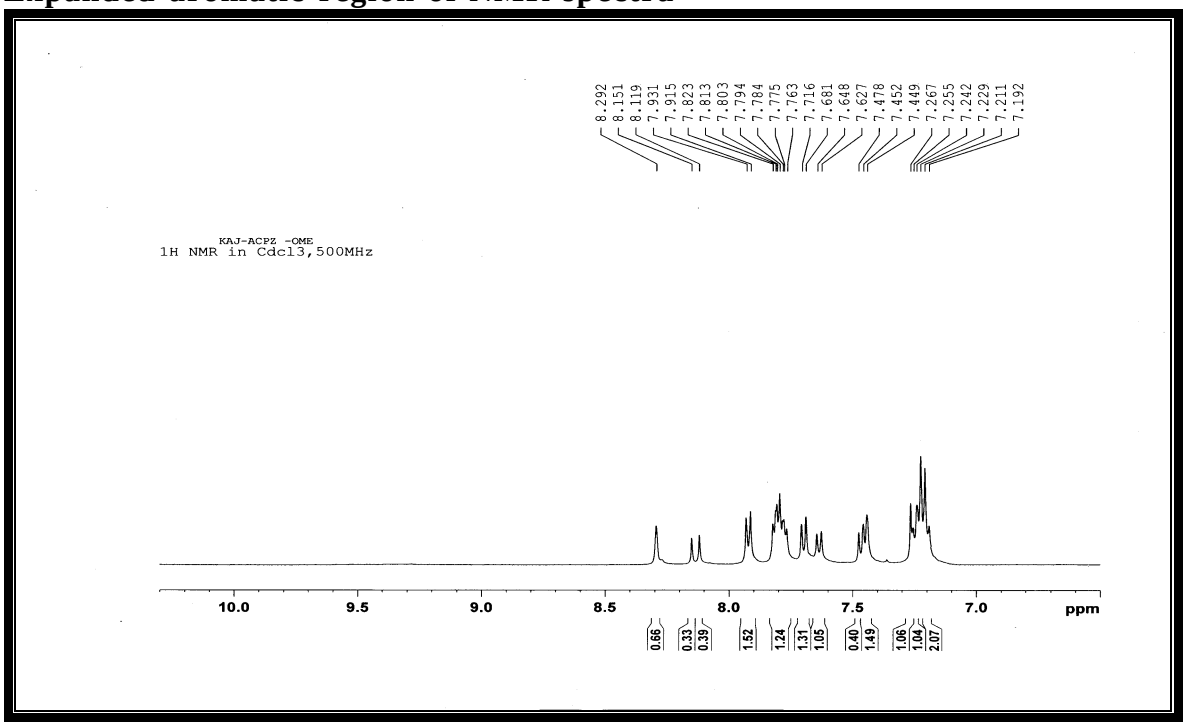
NMR SPECTRAL STUDIES OF 1-(5-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL)-4,5-DIHYDRO-3-(4-METHOXYPHENYL) PYRAZOL-1-YI)ETHANONE.



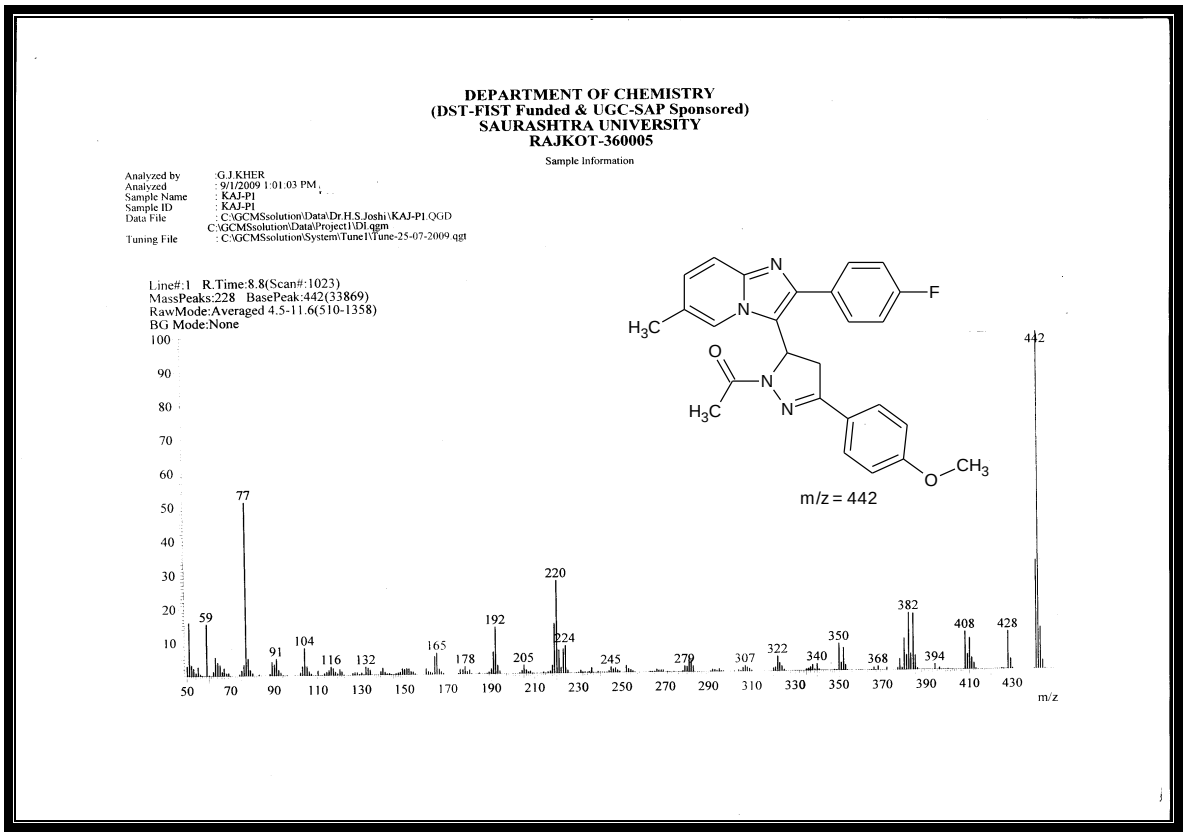
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument: BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	1.24	3H	singlet	$-CH_3$	-
2	1.77-1.78	1H	doublet	-CH	8.0
3	1.97-1.98	1H	doublet	-CH	8.0
4	2.44	3H	singlet	$-COCH_3$	-
5	3.79	3H	singlet	$-OCH_3$	-
6	5.14-5.26	1H	multiplet	-CH	-
7	7.19-7.26	4H	multiplet	-Ar-4Ha,a'&b,b'	-
8	7.44-7.45	1H	multiplet	-Ar-H	-
9	7.62-7.64	1H	doublet	-Ar-H	10.5
10	7.68-7.71	1H	multiplet	-Ar-H	-
11	7.77-7.82	1H	multiplet	-Ar-H	-
12	7.91-7.93	2H	doublet	-Ar-Hc,c'	8.0
13	8.29	1H	singlet	-Ar-H	-

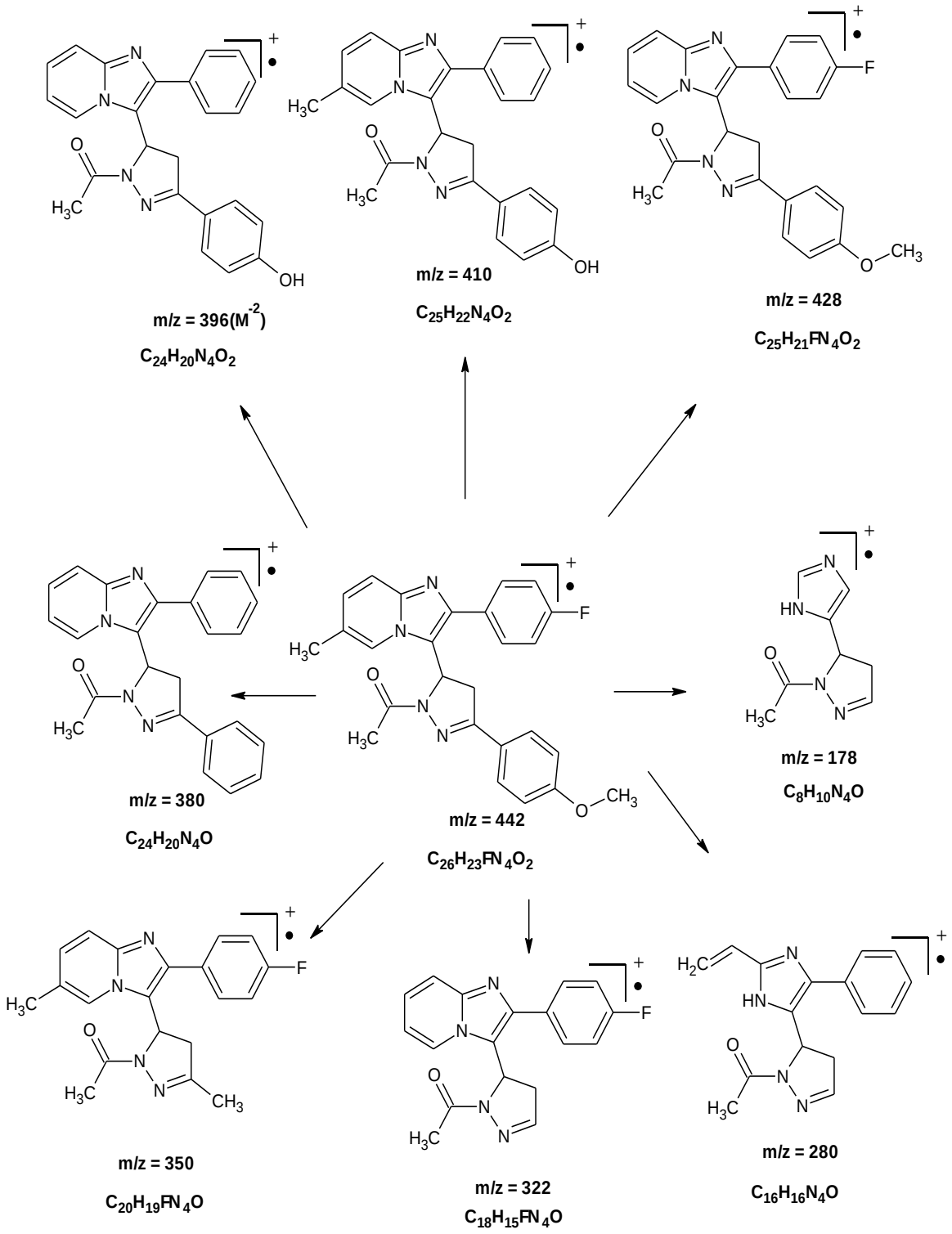
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF 1-(5-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO [1,2-α]PYRIDIN-3-YL)-4,5-DIHYDRO-3-(4-METHOXYPHENYL)PYRAZOL-1-Yl)ETHANONE.



PROPOSED MASS FRAGMENTATION OF 1-(5-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL)-4,5-DIHYDRO-3-(4-METHOXYPHENYL)PYRAZOL-1-Yl)ETHANONE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of (2*E*)-3-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-1-arylprop-2-en-1-ones.

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

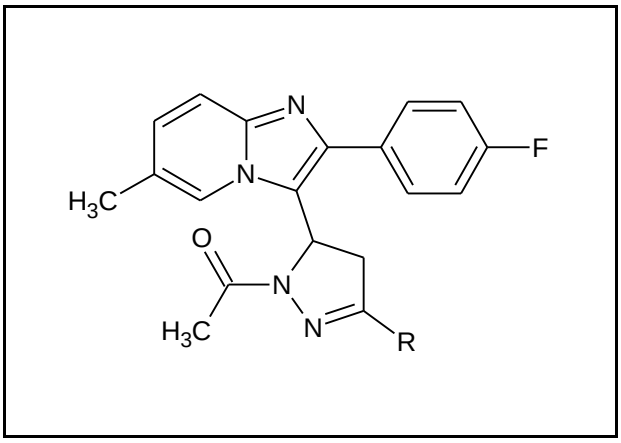
[B] Synthesis of 1-(5-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-4,5-dihydro-3-(4-methoxyphenyl)pyrazol-1-yl)ethanone.

A mixture of (2*E*)-3-(2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-1-arylprop-2-en-1-ones. (3.86gm, 0.01mol) and hydrazine hydrate (0.04mol, 99 %) in 20 ml acetic acid was refluxed on an oil-bath for 10-11 hrs. The solution was poured on crushed ice. The product was isolated and crystallized from dioxane. Yield 65%, m. p. 186 °C , Anal. Calcd. for $C_{26}H_{23}FN_4O_2$ Require: C, 70.57, H, 5.24, N, 12.66 %; Found: C, 70.59, H, 5.28, N, 12.69 %.

[E] Antimicrobial activity of 1-(5-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)-4,5-dihydro-3-(4-methoxyphenyl)pyrazol-1-yl)ethanone.

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

Table-11a: Physical constants of 1-(5-(2-(4-Fluorophenyl)-6-methyl*H*imidazo[1,2-*a*]pyridin-3-yl)-4,5-dihydro-3-arylpyrazol-1-yl)ethanones.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
11a	C_6H_5-	$C_{25}H_{21}FN_4O$ 412.15	197	61	72.80 (72.68)	5.13 (5.01)	13.58 (13.25)
11b	4-CH_3-C_6H_4-	$C_{26}H_{23}FN_4O$ 426.48	167	58	73.22 (73.04)	5.44 (5.23)	13.14 (13.01)
11c	2-CH_3-C_6H_4-	$C_{26}H_{23}FN_4O$ 426.48	174	49	73.22 (73.05)	5.44 (5.39)	13.14 (13.03)
11d	2,5-$(CH_3)_2$-C_6H_3-	$C_{27}H_{25}FN_4O$ 440.51	152	66	73.62 (73.49)	5.72 (5.66)	12.72 (12.49)
11e	4-OCH_3-C_6H_4-	$C_{26}H_{23}FN_4O_2$ 442.48	186	65	70.57 (70.39)	5.24 (5.18)	12.66 (12.49)
11f	2,4-$(Cl)_2$-C_6H_3-	$C_{25}H_{19}ClFN_4O$ 481.90	157	61	62.38 (62.26)	3.98 (3.86)	11.64 (11.54)
11g	4-Cl-C_6H_4-	$C_{25}H_{20}ClFN_4O$ 446.34	165	51	67.19 (67.01)	4.51 (4.26)	12.54 (12.36)
11h	3-Cl-C_6H_4-	$C_{25}H_{20}ClFN_4O$ 446.34	154	45	67.19 (66.04)	4.51 (4.22)	12.54 (12.31)
11i	4-NO_2-C_6H_4-	$C_{25}H_{20}FN_5O_3$ 457.45	163	53	65.64 (65.39)	4.41 (4.22)	15.31 (15.16)
11j	4-F-C_6H_4-	$C_{25}H_{20}F_2N_4O$ 430.44	210	46	69.76 (69.36)	4.68 (4.47)	13.02 (12.92)

TABLE 11B : ANTIMICROBIAL ACTIVITY OF 1-(5-(2-(4-FLUOROPHENYL)-6-METHYL*H*IMIDAZO[1,2-*a*]PYRIDIN-3-YL)-4,5-DIHYDRO-3-ARYLPYRAZOL-1-Yl(ETHANONES). (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	**11a**	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
2.	**11b**	+	+	-	+	+	+	+	+	+	+	+	-	+	+	-	-	-	-
3.	**11c**	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+
4.	**11d**	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-
5.	**11e**	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
6.	**11f**	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7.	**11g**	+	+	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-
8.	**11h**	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
9.	**11i**	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	-	-
10.	**11j**	+	+	-	-	-	-	+	+	+	-	-	-	+	+	-	+	+	-

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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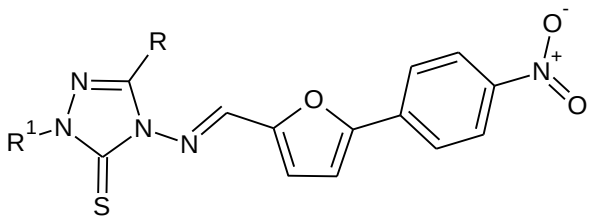
Part- C

(Part-II)

Studies on Arylaminomethyl Derivatives

INTRODUCTION

Azomethine derivatives have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activity. Azomethines are also known as schiff's base named after Hugo schiff, and they are well known intermediate for the preparation of azetidinone, thiazolidinone, formazone, aryl acetamide and many other derivatives. These are the compounds contain characteristic -C=N group. B. S. Holla et al.[1] have documented azomethine (1) having triazole moiety and possess good antibacterial activity.



(1)

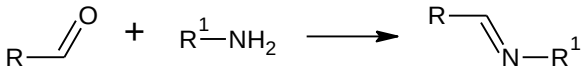
Azomethines are obtained mainly by warming the aldehyde and aromatic amine together. However, it is more convenient to work in a solvent such as alcohol, dilute acetic acid or glacial acetic acid. Some time the reaction is aided by trace of acid in other cases the hydrochloride of the amines can be used in the synthesis.

In general schiff's bases do not react further with either of the reagents used in their preparation as do most of the other types of simple intermediates.

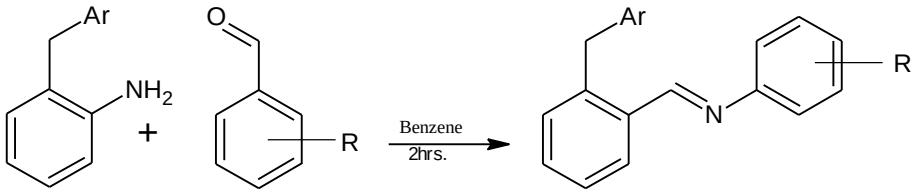
SYNTHETIC ASPECT

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

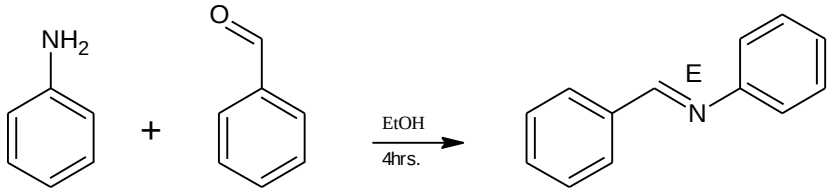
1. General account of the summary of reaction of aldehydes with amine (aromatic or aliphatic) has been reviewed by Murray.[2]



2. E. C. Creencia and group[3] reported synthesis from ortho substituted aniline with 55 % yield in 2 hrs. in benzene.

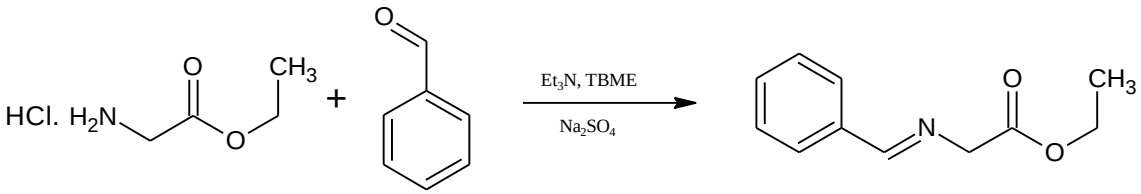


3. D. Bleger et al.[4] have synthesized schiff's base of aniline and benzaldehyde in ethanol with short reaction time of 4 hrs. and reported E isomer as major product.

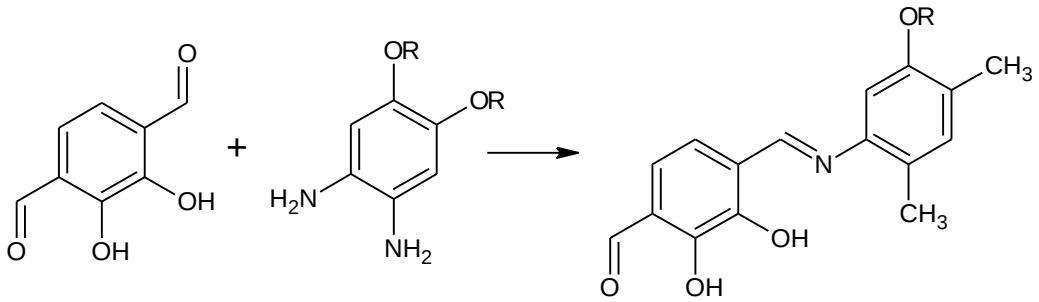


4. U. K. Roy and coworkers[5] have reported preparation of schiff's base with 100 % of yield with toluene as a solvent.

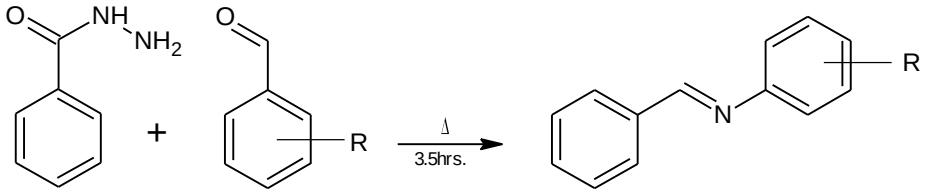
5. L. B. Pierre and coworkers[6] have synthesized (*E*)-*N*-phenyl methylene glycineethyl ester by the cyclocondensation of glycine ethyl ester hydrochloride, *t*-butylmethyl ether (TBME), benzaldehyde was added followed by anhydrous Na_2SO_4 and triethylamine.



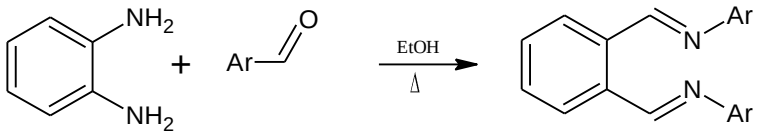
6. J. G. Amanda et al.[7] have prepared schiff bases by condensation of equimolar quantity of 3,6-diformylcatechol and substituted o-phenylenediamine.



7. L. Somogyi[8] reported some azomethine derivatives of phenylhydrazide in 99 % yield and with short reaction time of 3.5 hours in polar solvent.



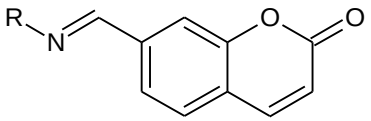
8. Schieff's base of o-phenelene diamine with substituted benzaldehyde was reported by M. Zintl and coworkers[9].



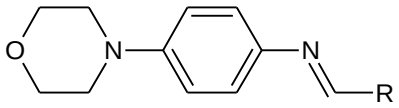
BIOLOGICAL EVALUATION

Schiff bases exhibit a wide range of pharmacological activities like antifungal, antibacterial, antiviral, anti-inflammatory etc. R. H. Mehta et al.[10] have synthesized

coummarin schiff's base derivatives (2) and examined for their antibacterial activity. A. K. Khalafallah and M. E. Hassan[11] have prepared some styryl schiff's bases spiro derivatives as potential antibacterial and antifungal activity. P. Perumal[12] have synthesized some azomethine derivatives (3) having good antibacterial activity.



(2)



(3)

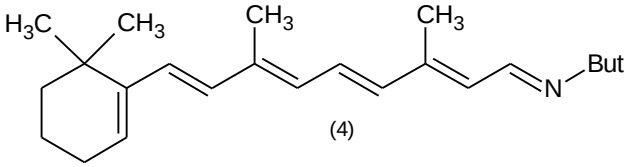
M. D. Deshmukh and A. G. Doshi[13] prepared some new schiff's bases show good antimicrobial activity against test organism *S. aureus, E. coli, Saigella dysenteridse* and *Salmonella typhi*. Wang et al.[14] have synthesized diazomethines having good plant hormone activity. Das Arima et al.[15] have prepared schiff's bases of aminohydroxy guanidine (SB-AHG5) and tested for antiviral activity against Herpes Simplex virus Type I (HSV-1) and adenovirus Type-5 (Ad-5).

Ali, yusuf et al.[16] have synthesized some schiff's base derivatives of glucose containing acetylenic bond. The prepared schiff bases were tested for their bactericidal activity against *E. coli* and *S. aureus*.

B. S. Holla et al.[17] have prepared schiff's bases and reported them as antimicrobial agents. Pandey Taruna et al.[18] prepared azomethines and their boron complexes and screened for their antifungal and antibacterial properties. It is evident that azomethines along with quite toxic but their activity increased after complexation. Omar et al.[19] have determined cyclocondensation of azomethines having good antischistosomal activity. Chohan and coworkers[20,21] have synthesized a novel class of acetyl ferrocene

derived from schiff bases possess antimicrobial activity. Some azomethine derivative screened for various antibacterial strains.

Das Joydip et al.[22] have synthesized trans-*N*-refinylidene-n-butylamine (4) which found stabilized in liposome's of phophatidylcholine. The rate of formation of the schiff's base is found to decrease with increasing cholesterol concentration in the membrane. V. M. Patel[23] has synthesized some new schiff's bases having good antibacterial activity.

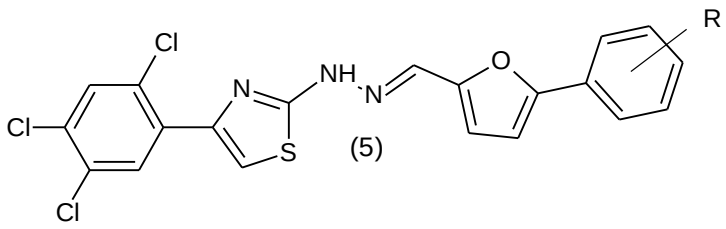


(4)

Ram Tilak et al.[24] have synthesized some schiff's bases, of 2-chloro phenothiazines and screened against carrageenin-induced edema in albino rats. A. Cascaval et al.[25] have synthesized azomethines, which have good analgesic and antipyretic properties. S. N. Pandeya et al.[26] have synthesized schiff bases showed good activity against *Vibrio cholerae non-o., Shigella boydii, Enterococcus faecalis* and *Edwaredsiella torla* with MIC in the rang of 10-25 μg/ml. Some compounds were found to be active against *Salmonellal typhi* and *Vibro cholerae-0,* (MIC 25-150 μg/ml).

K. N. Venugopal et al.[27] have synthesized schiff base of 4-hydroxy-6-carboxyhaydrazino benzothiophene analog with different substituted aldehydes and determined pharmacological study. Ergenc and coworkers[28] have synthesized azomethine derivatives having antifungal activity. B. Yadav and S. S. Sangapure[29] have synthesized some azomethines and tested for their biological activity. B. S. Holla et al.[30] have prepared some new schiff's bases having anticancer activity.

R. V. Chambhare et al.[31] have prepared some azomethines and tested for their antimicrobial activity. M. S. Karthikeyan et al.[32] have synthesized azomethines (5) having antibacterial and anti-inflammatory activity.



(5)

Work done from our laboratory

K. M. Thaker et al.[33] have prepared some schiff bases bearing benzo[*b*]thiophene nucleus and tested for their antitubercular and antimicrobial activity. S. L. Vasoya[34] reported facile synthesis of some new azomethines bearing benzo[*b*]thiophene nucleus as a potent biological active agent.T. K. Dave[35,36] have been reported synthesis and pharmacological study of Mannich bases of 4-amino-3-mercapto-5-pyridin-3'-yl-[1,2,4]-triazole and schiff base bearing nicotinic acid nucleus with antitubercular and antimicrobial evaluation.

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

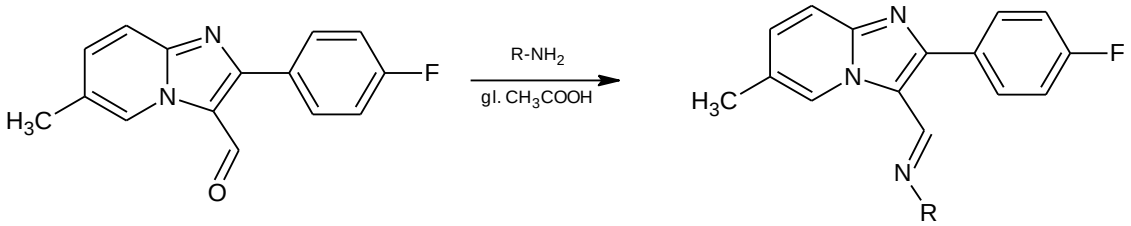
SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO [1,2-α]PYRIDIN-3-YL]METHYLENE)-4-ARYLAMINES.

SECTION-II: SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO [1,2-α]PYRIDIN-3-YL)METHYL)-4-ARYLAMINES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO [1,2-α]PYRIDIN-3-YL]METHYLENE)-4-ARYLAMINES.

Looking to the interesting properties of azomethines, with an intension to synthesizing better therapeutic agents, azomethine derivatives of Type (XII) have been synthesized by the condensation of 2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine-3-carbaldehyde with different aromatic amines in order to study their biodynamic behavior.

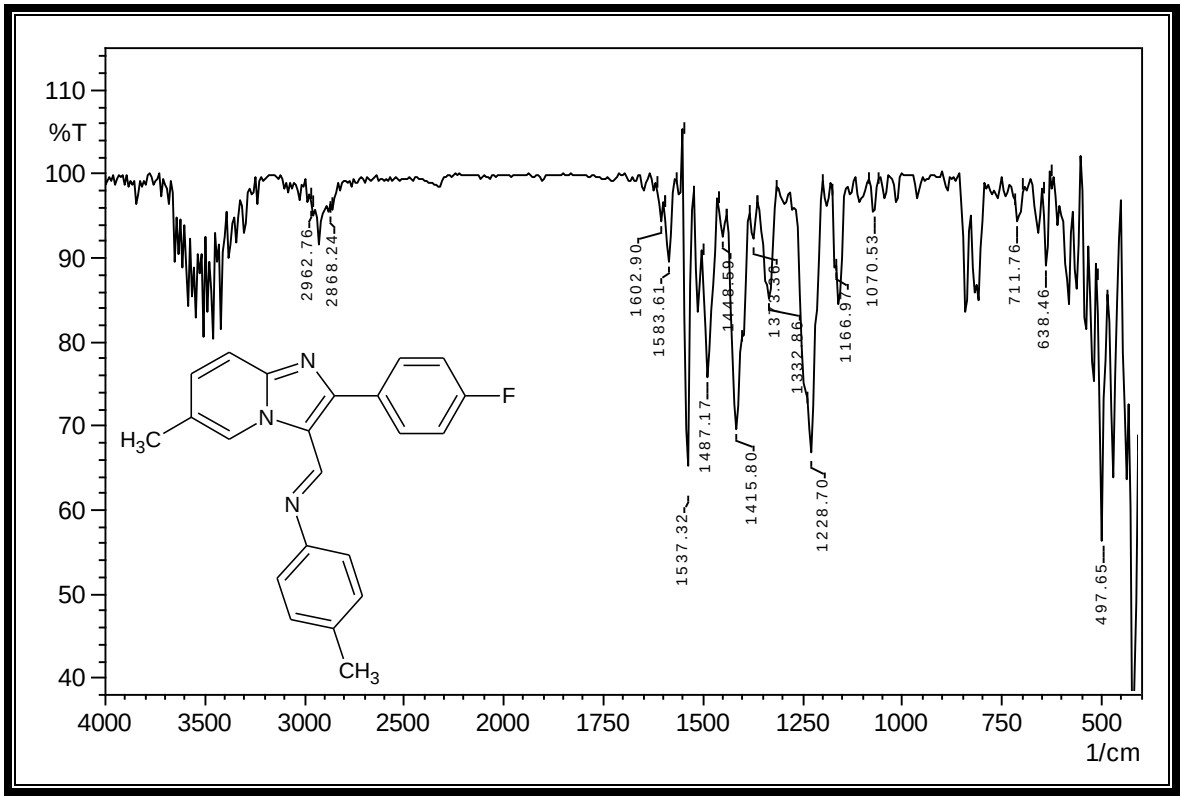


Type (XII) R= Aryl

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.12b.

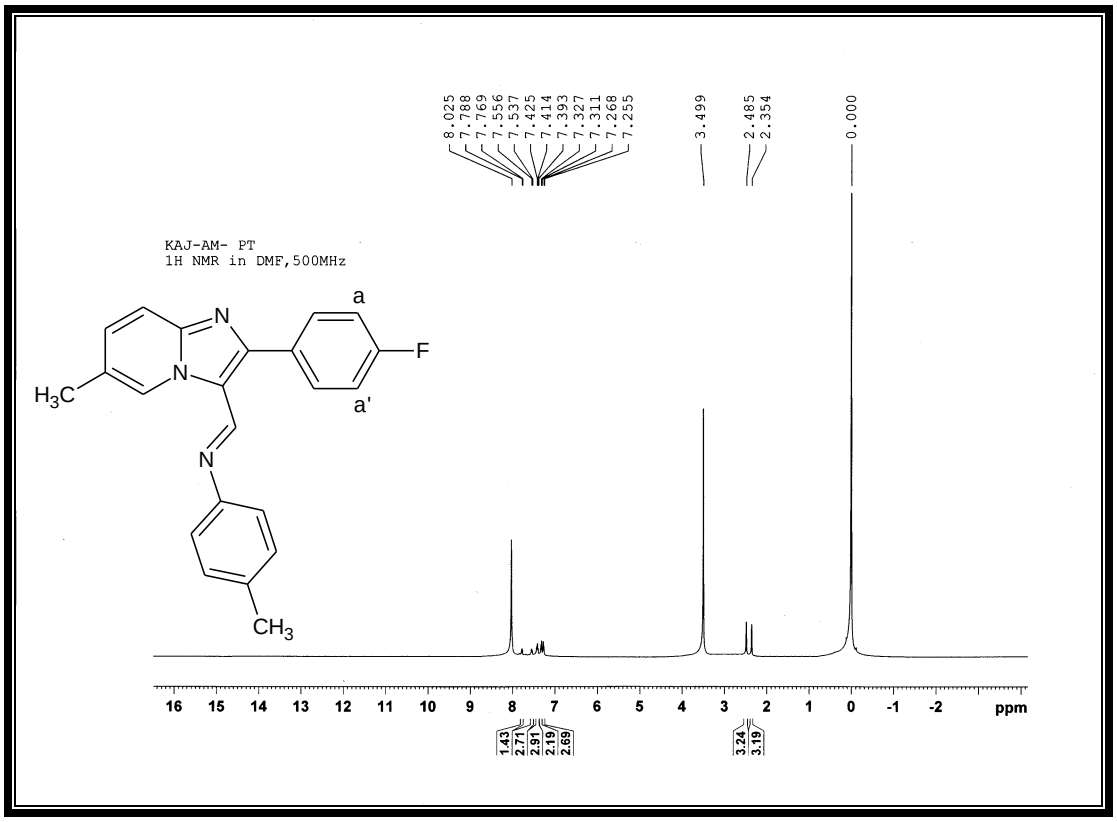
IR SPECTRAL STUDIES OF *N*(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDINE-3-YL)METHYLENE)-4-METHYLBENZENAMINE.



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str.	2962	2975-2940	37
	C-H str. (sym.)	2868	2880-2860	38
	C-H def.	1448	1470-1435	37
	C-H def. (sym.)	1373	1395-1370	38
Aromatic	C-H str.	2962	2980-2930	40
	C=C str.	1487	1585-1480	40
	C-H I.p.(def)	1070	1125-1000	39
	C-H o.o.p.	638	700-600	39
Imidazo[1,2-α]pyridine	C=N str.	1602	1615-1593	37
	C-N str.	1070	1220-1020	38
Schiff base	C=N str.	1583	1660-1580	37
Halide	C-F str.	1070	1200-1000	39

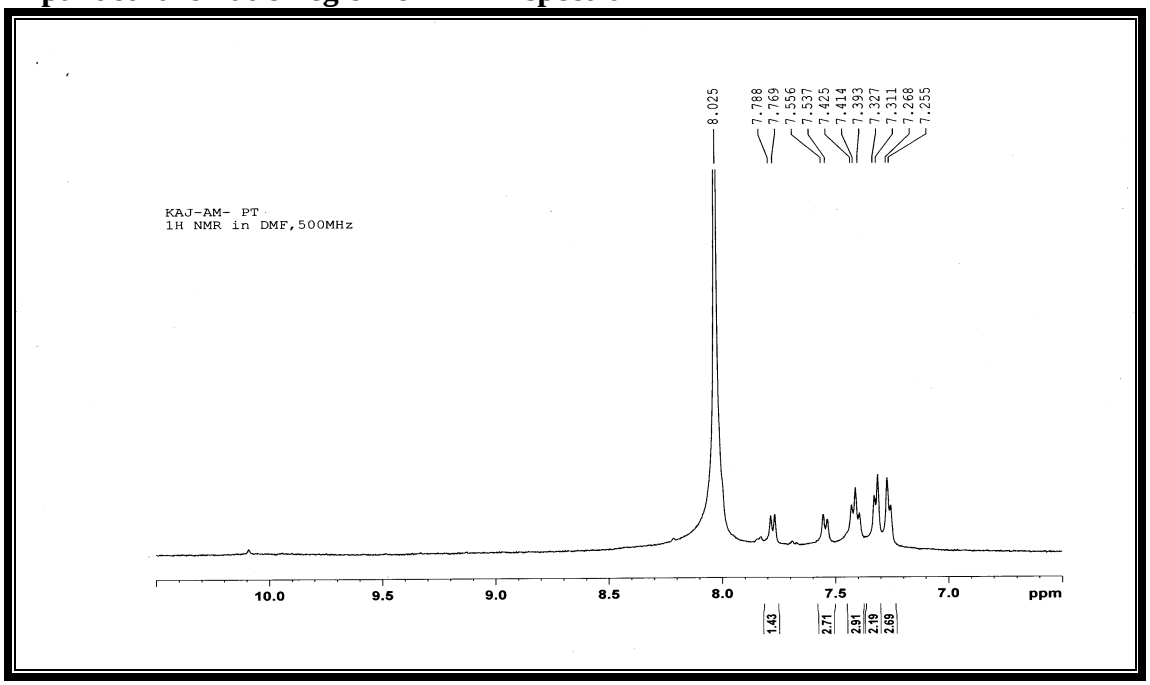
NMR SPECTRAL STUDIES OF *N*(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDINE-3-YL)METHYLENE)-4-METHYLBENZENAMINE.



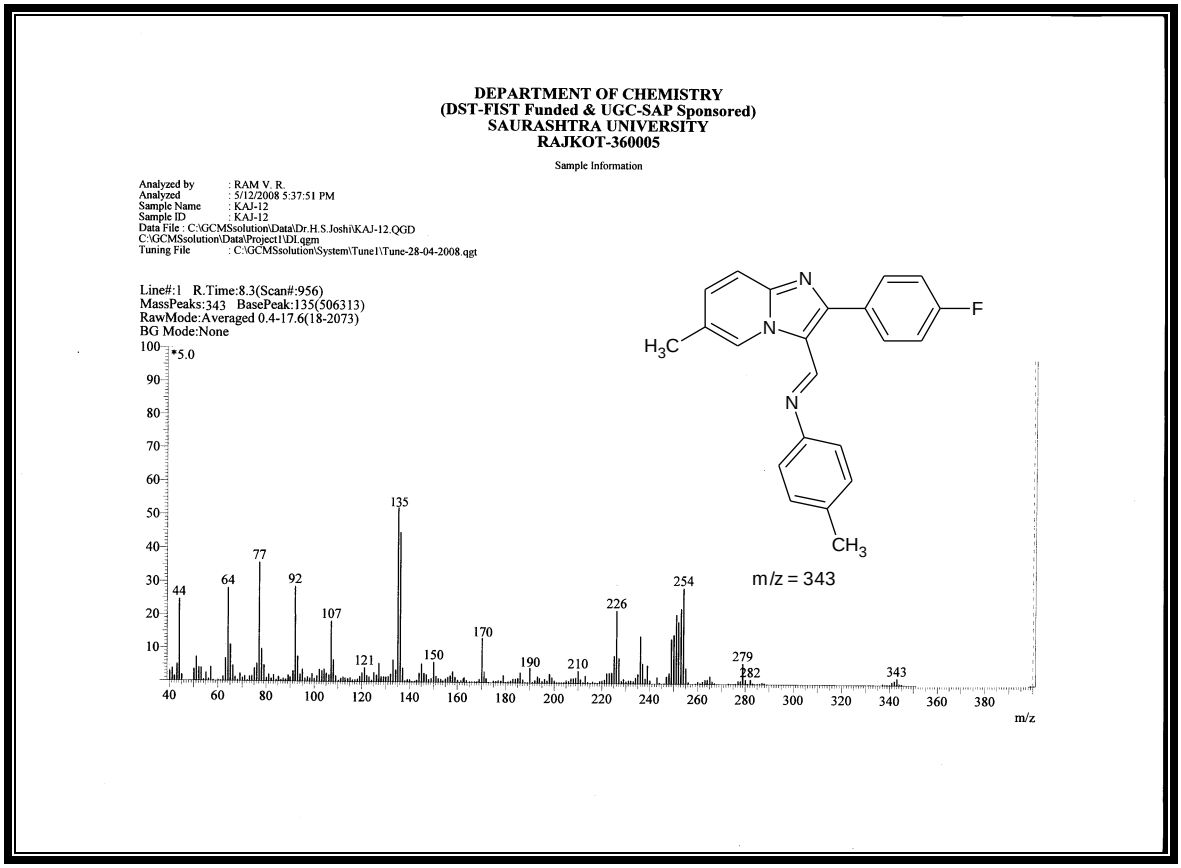
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1.	2.35	3H	singlet	$-CH_3$-Ar	-
2.	2.48	3H	singlet	$-CH_3$	-
3.	7.25-7.26	3H	doublet	-Ar-H	6.5
4.	7.31-7.32	2H	doublet	-Ar-Ha,a’	8.0
5.	7.39-7.42	3H	triplet	-Ar-H	5.0
6.	7.53-7.55	3H	doublet	-Ar-H	9.5
7.	7.76-7.78	1H	doublet	-Ar-H	10.0

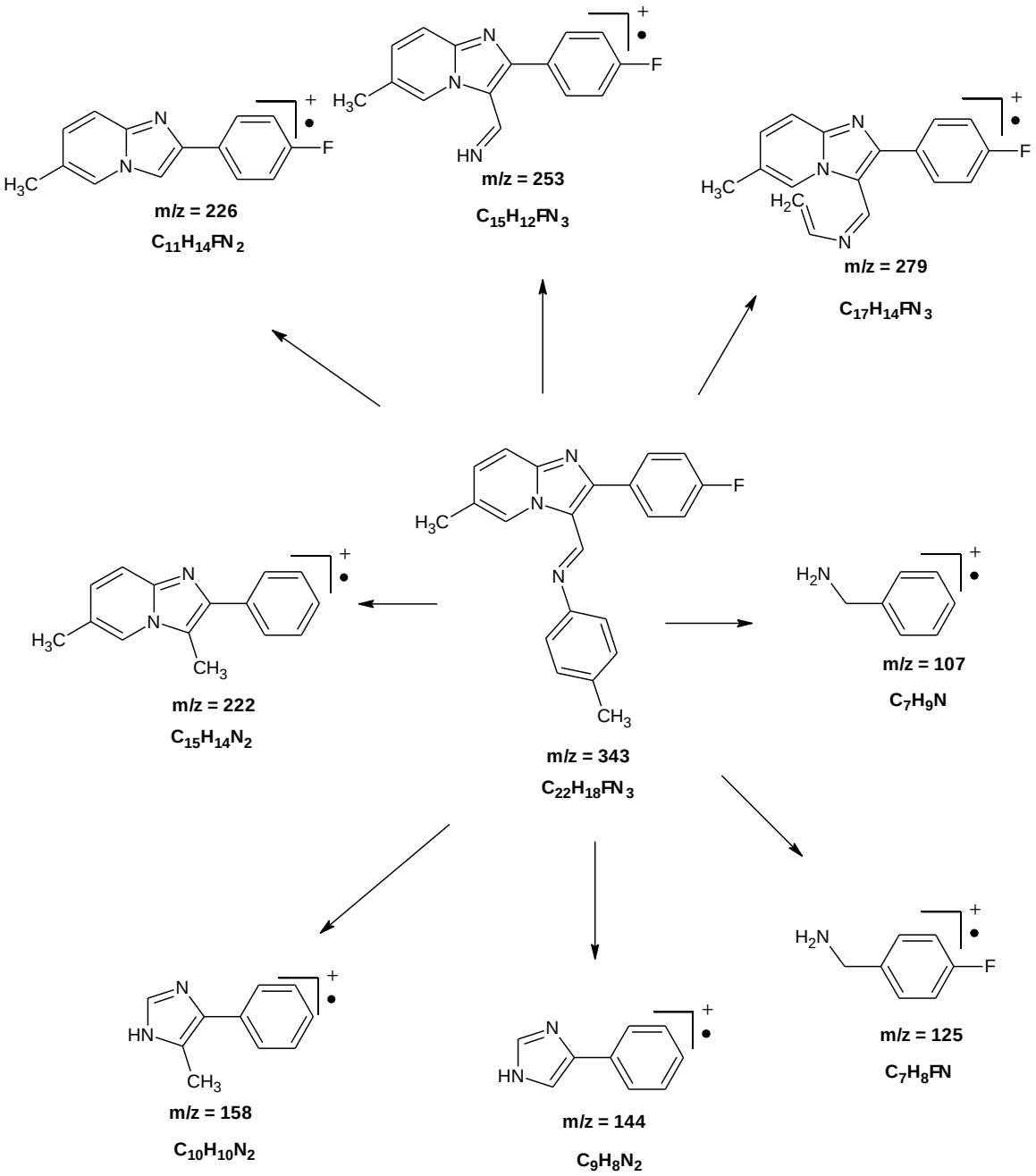
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF *N*(2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDINE-3-YL)METHYLENE)-4-METHYLBENZENAMINE.



PROPOSED MASS FRAGMENTATION OF *N*(2-(4-FLUOROPHENYL)-6-METH- YL*H*-IMIDAZO[1,2-α]PYRIDINE-3-YL)METHYLENE)-4-METHYLBENZENAMINE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. Various proportion of Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of 2-(4-Fluorophenyl)-6-methyl-*H*-imidazo[1,2-α] pyridine-3-carbal dehyde.

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

[B] Synthesis of *N*-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl] methylene)-4-methylbenzenamine.

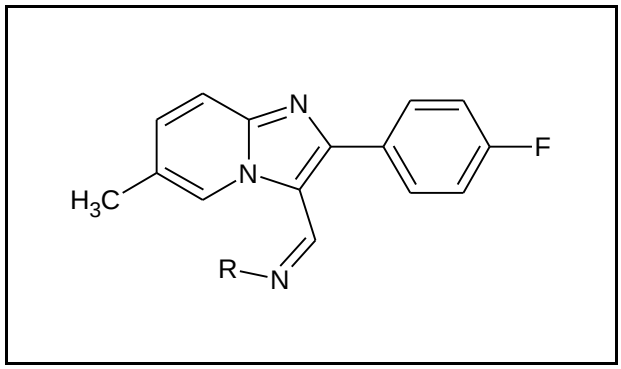
A mixture of 2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridine-3-carbal-dehyde (2.54gm, 0.01mol) and p-toludine (1.08gm, 0.01mol) in methanol (20 ml) in presence of catalytic amount of glacial acetic acid was refluxed for 6 hrs. The contents were cooled and product isolated was crystallized from methanol. Yield, 52%, m.p. 188 °C, $C_{18}H_{22}FN_3$; Found : C, 76.98%; H, 5.33%; N,12.29%; Requires : C, 76.95%; H, 5.28%; N, 12.24%.

Similarly, other *N*-(2-(4-fluorophenyl)-6-methyl*H*-imidazo [1,2-α]pyridin-3-yl]methylene)-4-arylamines were prepared. The physical constants are recorded in Table No. 12a.

[A] Antimicrobial activity of *N*-(2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α] pyridin-3-yl]methylene)-4-arylamines.

Antimicrobial testing was carried out as described in part-(I), section-I(D). The zones of inhibition of compounds are recorded in Table No.12b.

Table-12a: Physical constants of *N*-(2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α] pyridin-3-yl]methylene)-4-arylamines.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
12a	C_6H_5-	$C_{21}H_{16}FN_3$ 329.37	163	81	76.58 (76.49)	4.90 (4.78)	12.76 (12.69)
12b	4-CH_3-C_6H_4-	$C_{22}H_{18}FN_3$ 343.39	154	72	76.95 (76.80)	5.28 (5.18)	12.24 (12.13)
12c	2-CH_3-C_6H_4-	$C_{22}H_{18}FN_3$ 343.39	147	86	76.95 (76.84)	5.28 (5.16)	12.24 (12.19)
12d	2,5-$(CH_3)_2$-C_6H_3-	$C_{23}H_{20}FN_3$ 357.42	158	78	77.29 (77.16)	5.64 (5.44)	11.76 (11.59)
12e	4-OCH_3-C_6H_4-	$C_{22}H_{18}FN_3O$ 359.39	110	73	73.52 (73.39)	5.05 (5.91)	11.69 (11.55)
12f	2,5-$(Cl)_2$-C_6H_3-	$C_{21}H_{14}Cl_2FN_3$ 398.26	159	66	63.33 (63.21)	3.54 (3.39)	10.55 (10.39)
12g	4-Cl-C_6H_4-	$C_{21}H_{15}ClFN_3$ 363.81	168	70	69.33 (69.28)	4.16 (4.09)	11.55 (11.34)
12h	4-F-C_6H_4-	$C_{21}H_{15}F_2N_3$ 347.36	113	67	72.61 (72.49)	4.35 (4.18)	12.10 (12.06)

TABLE 12B: ANTIMICROBIAL ACTIVITY OF (17*E*)-N-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO [1,2-α]PYRIDIN-3-YL]METHYLENE)-4-ARYLAMINES. (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1.	12a	+	+	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	-
2.	12b	+	+	-	+	+	+	-	-	-	+	+	-	+	+	+	-	-	-
3.	12c	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
4.	12d	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
5.	12e	-	-	-	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-
6.	12f	+	+	-	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-
7.	12g	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
8.	12h	+	+	+	+	+	+	-	-	-	-	-	-	+	+	-	+	+	-

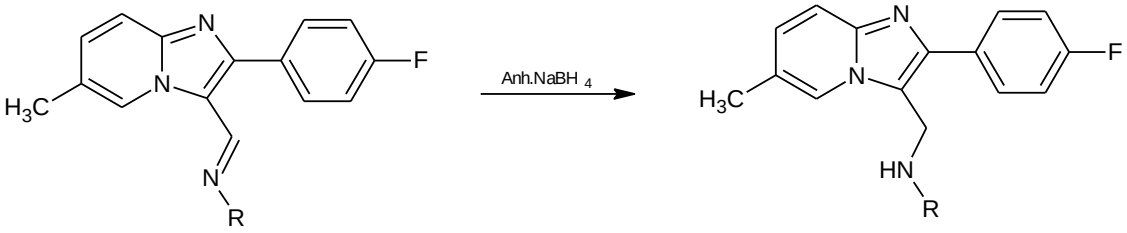
Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL]METHYL)-4-ARYLAMINES.

Aminomethyl derivatives of heterocyclic compounds are associated with diverse therapeutical activities. These finding prompted us to synthesize some representative aminomethyl derivative of Type (XIII) bearing imidazo[1,2-α]pyridine moiety obtained by selective reduction of (imine group) schiff's bases of Type (XII) with sodium borohydride in controlled experimental condition as shown in the reaction scheme.

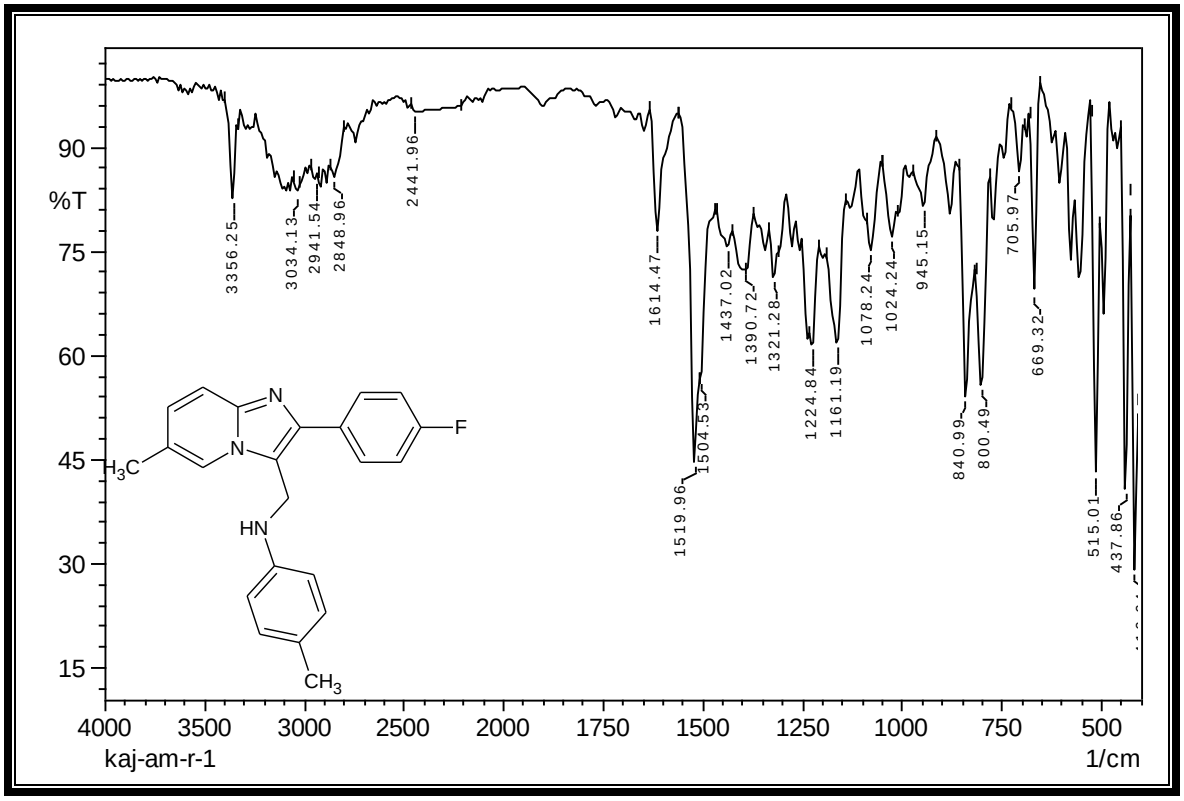


Type (XII) R= Aryl **Type (XIII) R= Aryl**

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, Candida albicans*** at a concentration of 2000/1000/500 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 Table No.13b.

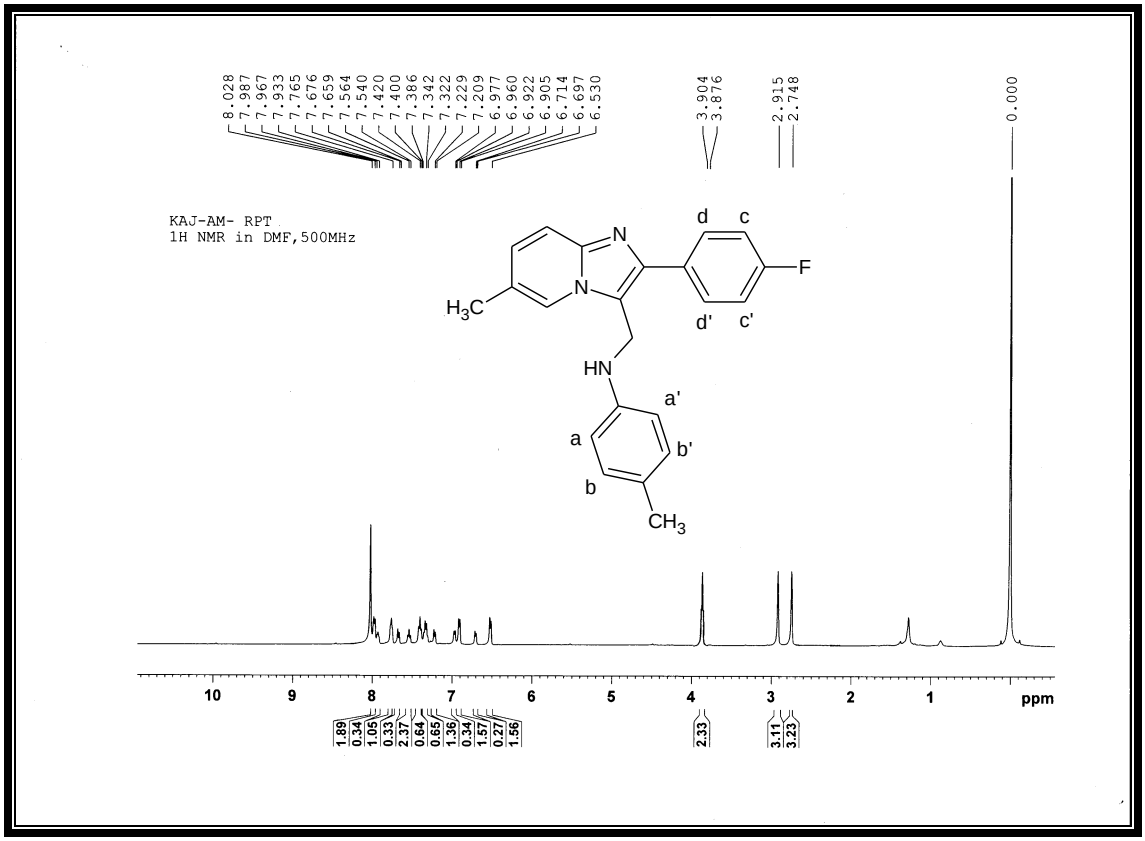
IR SPECTRAL STUDIES OF *N*-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL)METHYL)-4-METHYLBENZENAMINE.



Instrument: SHIMADZU-FT-IR 8400-Spectrophotometer; Frequency range : 4000-400 cm-1 (KBr pallet method)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str.	2941	2975-2940	37
	C-H str. (sym.)	2848	2880-2860	38
	C-H def.	1437	1470-1435	37
	C-H def. (sym.)	1390	1395-1370	38
Aromatic	C-H str.	2941	2980-2930	40
	C=C str.	1504	1585-1480	40
	C-H I.p.(def)	1078	1125-1000	39
	C-H o.o.p.	669	700-600	39
Imidazo[1,2-α]pyridine	C=N str.	1614	1615-1593	37
	C-N str.	1024	1220-1020	38
Amine	-NH str.	3356	3400-3200	37
Halide	C-F str.	1161	1200-1000	39

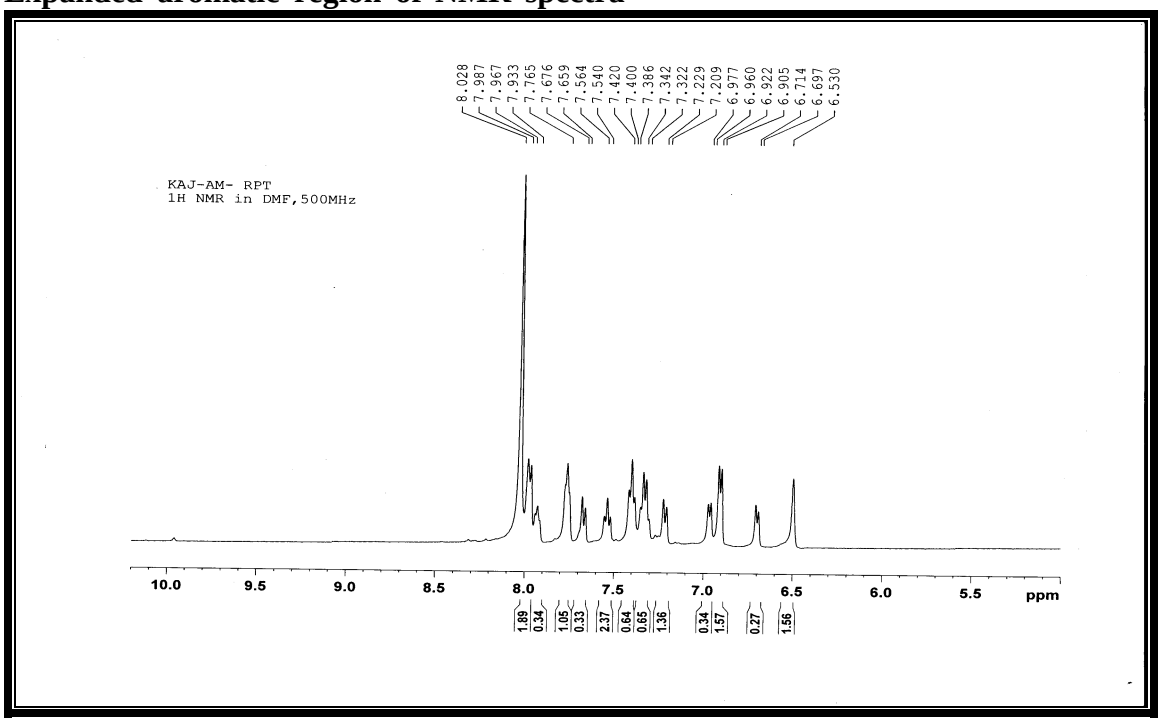
NMR SPECTRAL STUDIES OF *N*-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL)METHYL)-4-METHYLBENZENAMINE.



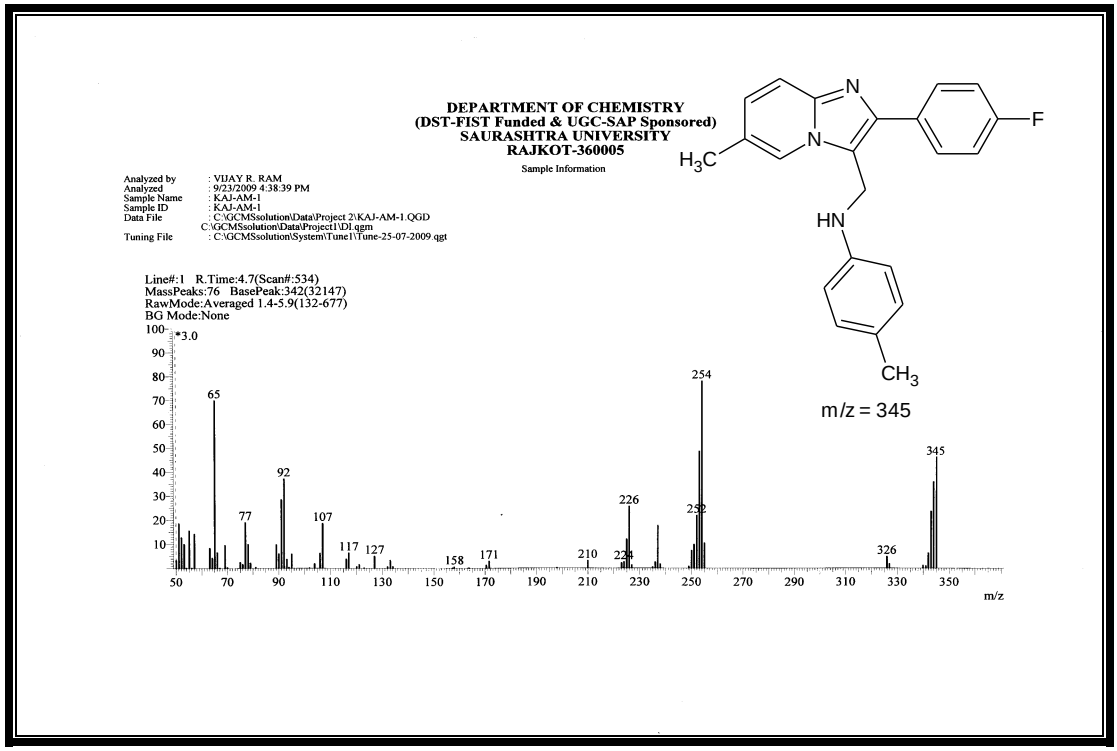
Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (500MHz)

Sr. No.	Chemical shift in ppm	Relative No. of proton	Multiplicity	Inference	J value in Hz
1	2.74	3H	singlet	Ar-CH_3	-
2	2.91	3H	singlet	-CH_3	-
3	3.87-3.90	2H	singlet	-CH_2	-
4	6.530	2H	doublet	-Ar-Ha-a'	-
5	6.30-6.92	2H	doublet	-Ar-Hb,b'	8.5
6	7.20-7.22	1H	doublet	-Ar-H	10.0
7	7.32-7.34	1H	doublet	-Ar-H	10.0
8	7.38-7.42	1H	triplet	-Ar-H	10.0
9	7.54-7.56	2H	triplet	-Ar-Hc,c'	12.0
10	7.67-7.64	1H	singlet	-NH	-
11	7.93-7.96	2H	multiplet	-Ar-Hd,d'	-

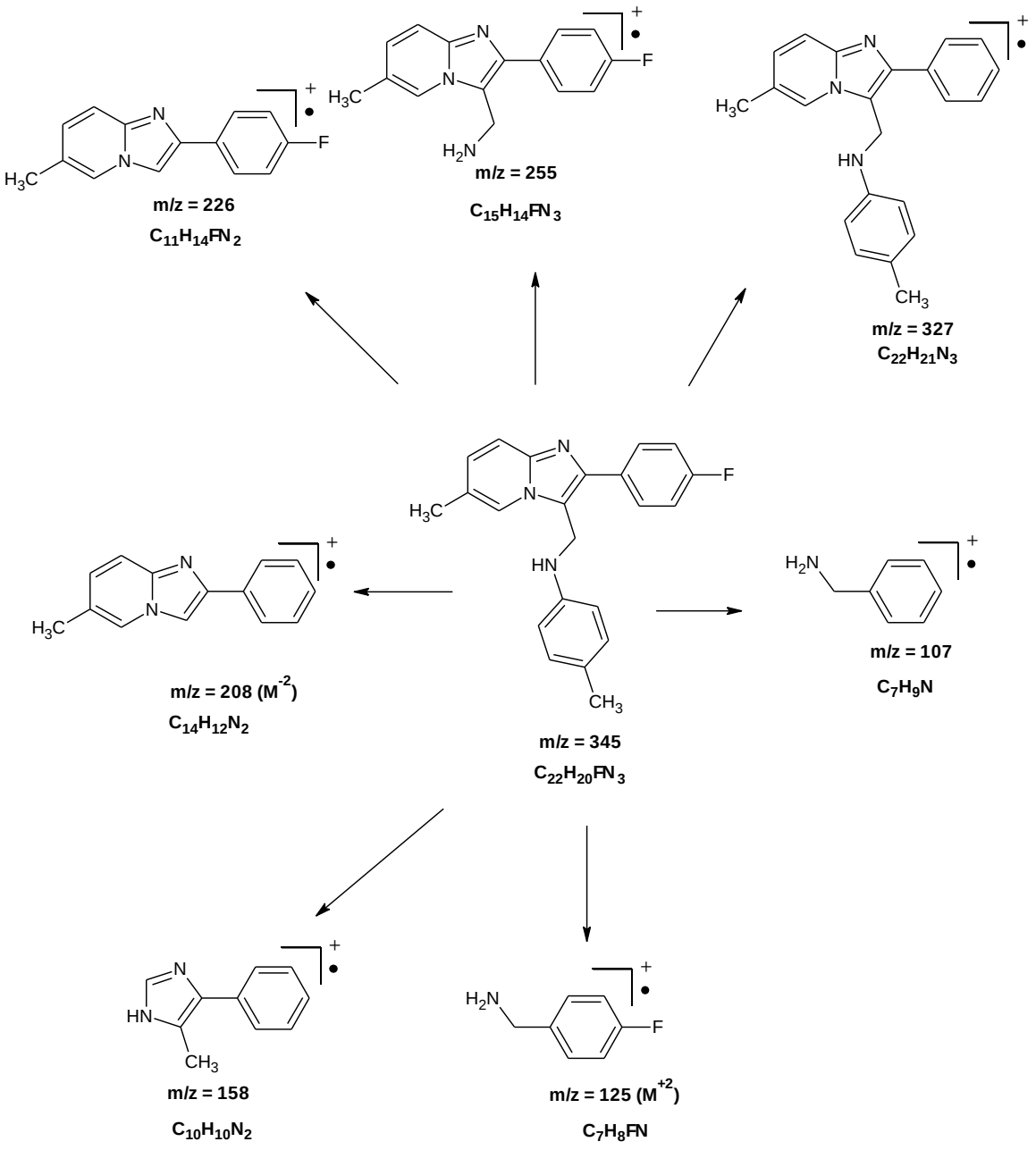
Expanded aromatic region of NMR spectra



MASS SPECTRAL STUDIES OF *N*-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL)METHYL)-4-METHYLBENZENAMINE.



PROPOSED MASS FRAGMENTATION OF *N*((2-(4-FLUOROPHENYL)-6-METHYL *H*-IMIDAZO[1,2-α]PYRIDINE-3-YL)METHYLENE)-4-METHYLBENZENAMINE.



EXPERIMENTAL SECTION

Melting points of all the synthesized compounds were taken in open capillary bath on controlled temperature heating mental. The crystallization of all the compounds was carried out in appropriate solvents. TLC was carried out on silica coated aluminum sheet (Merck prepared plates) as stationary phase. 55 % Ethyl acetate in hexane was used as a mobile phase.

[A] Synthesis of *N*-((2-(4-Fluorophenyl)-6-methylh-imidazo[1,2-α]pyridin-3-yl)methylene)-4-methylbenzenamines.

See, Part-III **[A]**, Section-I [B].

[B] Synthesis of *N*-((2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)methyl)-4-methylbenzenamine.

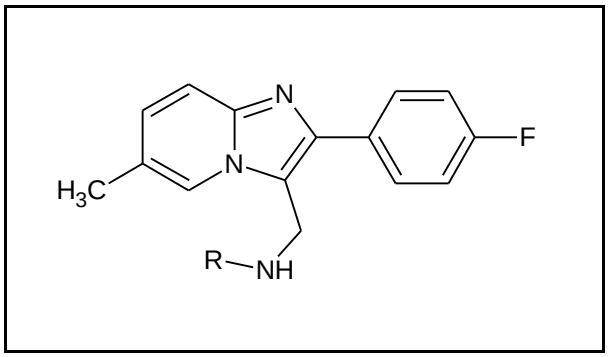
Sodium borohydride (0.15mol, 0.57gm) was added to a methanolic solution of *N*-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl]methylene)-4-methylbenzenamines. (0.01mol, 3.43gm) over a period of 30 minutes at temperature 5-10 ^{o}C with constant stirring. The reaction mixture was kept over night at room temp. The excess sodium borohydride was neutralized by adding water and the product was extracted with ether. The ether extract was washed with water untill become neutral, then dried over anhydrous Na_2SO_4 and finally the ether was evaporated to give aminomethyl derivatives. Crystallized from ethanol. Yield, 65%, m.p. 163 °C, $C_{22}H_{20}FN_3$; Found : C, 76.34; H, 5.71; N, 12.02 %; Requires : C, 76.50; H, 5.84; N, 12.17 %.

Similarly, other (17*Z*)-*N*-((2-(4-fluorophenyl)-6-methyl*H*-imidazo[1,2-α]pyridin-3-yl)methylene)-4-arylamines were prepared. The physical constants are recorded in Table No. 13a.

[C] Antimicrobial activity of *N*-((2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α] pyridin-3-yl)methyl)-4-arylamines.

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.13b.

Table-13a: Physical constants of *N*-((2-(4-Fluorophenyl)-6-methyl*H*-imidazo[1,2-α] pyridin-3-yl)methyl)-4-arylamines.



Sr. No.	Substitution R	Molecular Formula/ Molecular Weight	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
13a	C_6H_5-	$C_{21}H_{16}FN_3$ 331.38	185	58	76.11 (76.02)	5.47 (5.29)	12.68 (12.43)
13b	4-CH_3-C_6H_4-	$C_{22}H_{20}FN_3$ 345.41	163	65	76.50 (76.34)	5.84 (5.71)	12.17 (12.02)
13c	2-CH_3-C_6H_4-	$C_{22}H_{20}FN_3$ 345.41	174	75	76.50 (76.39)	5.84 (5.74)	12.17 (12.09)
13d	2,5-$(CH_3)_2$-C_6H_3-	$C_{23}H_{22}FN_3$ 359.43	160	63	76.85 (76.64)	6.17 (6.01)	11.69 (11.61)
13e	4-OCH_3-C_6H_4-	$C_{22}H_{20}FN_3O$ 361.41	198	55	73.11 (73.04)	5.58 (5.29)	11.63 (11.41)
13f	2,5-$(Cl)_2$-C_6H_3-	$C_{21}H_{14}Cl_2FN_3$ 398.26	188	45	63.01 (62.72)	4.03 (3.89)	10.50 (10.19)
13g	4-Cl-C_6H_4-	$C_{21}H_{17}ClFN_3$ 365.83	176	63	68.95 (68.65)	4.68 (4.52)	11.49 (11.32)
13h	4-F-C_6H_4-	$C_{21}H_{17}F_2N_3$ 349.37	186	49	72.19 (72.03)	4.90 (4.62)	12.10 (11.83)

TABLE 13B : ANTIMICROBIAL ACTIVITY OF *N*-((2-(4-FLUOROPHENYL)-6-METHYL*H*-IMIDAZO[1,2-α]PYRIDIN-3-YL]METHYL)-4-ARYLAMINES. (in µg/ml)

No.	Code No.	Antibacterial activity												Antifungal activity					
		Gram +*ve* Bacteria						Gram -*ve* Bacteria						Uni/Multicellular Fungi					
		Staphylococcus aureus			*Bacillus subtilis*			*Escherichia coli*			*Salmonella paratyphi B*			*Aspergillus niger*			*Candida albicans*		
		2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500	2000	1000	500
1	13a	+	+	-	+	+	-	+	+	-	+	+	-	+	+	+	+	+	-
2	13b	-	-	-	+	+	-	-	-	-	+	+	-	+	+	+	-	-	-
3	13c	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
4	13d	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-
5	13e	-	-	-	+	+	-	+	+	-	+	+	-	-	-	-	-	-	-
6	13f	+	+	-	-	-	-	-	-	-	-	-	-	+	+	-	+	+	-
7	13g	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8	13h	+	+	-	-	-	-	-	-	-	-	-	-	+	+	-	+	+	-

Where (+) = New synthesized compounds were active against microorganism

(-) = New synthesized compounds were inactive against microorganism

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