STUDIES ON SOME COMPOUNDS OF THERAPEUTIC INTEREST

A THESIS

SUBMITTED TO THE

SAURASHTRA UNIVERSITY

FOR THE DEGREE OF

Doctor of Philosophy

IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE

OF

Dr. V. R. Shah

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

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Place : Amreli

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

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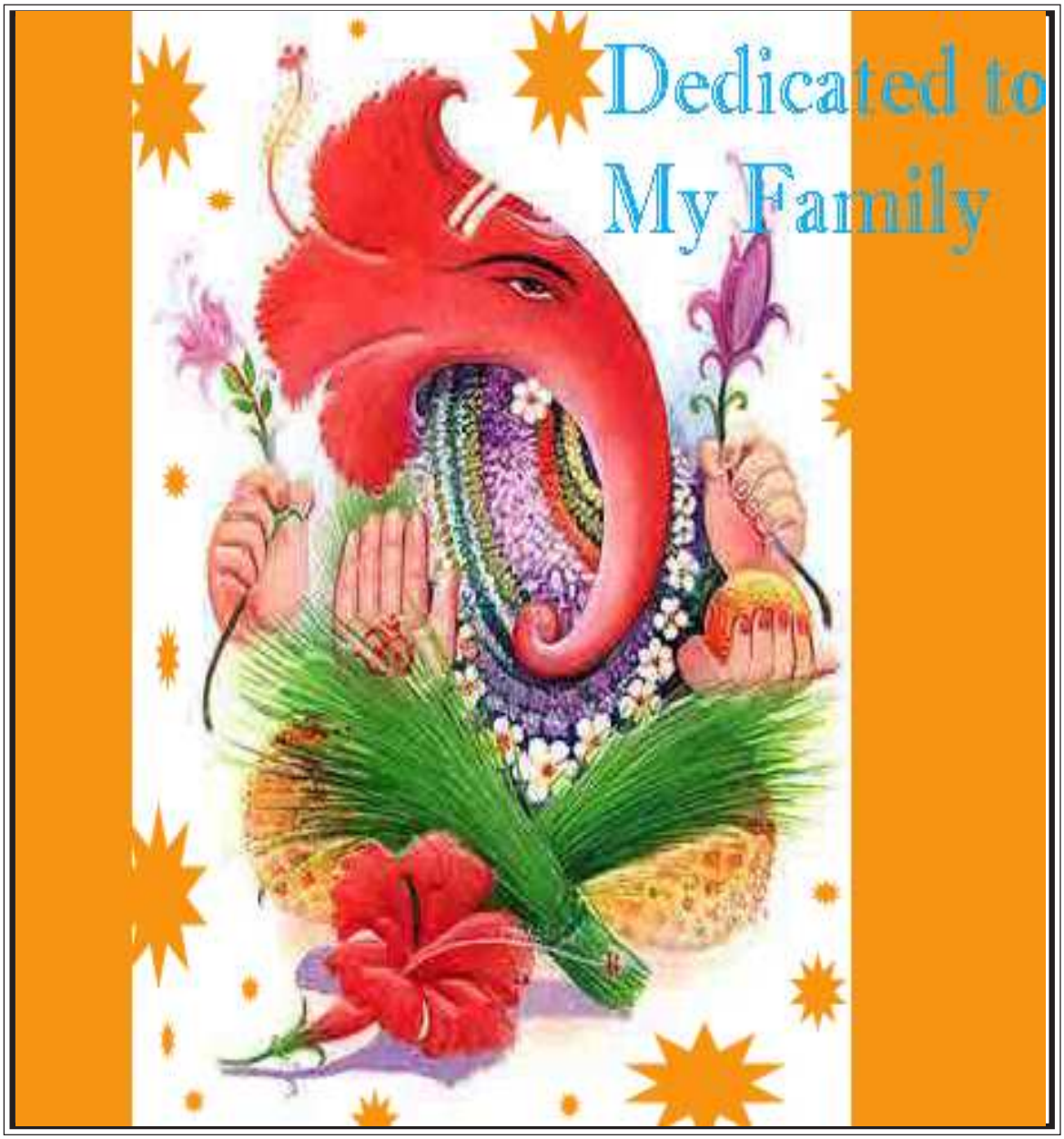
Dedicated to
My Family

ACKNOWLEDGMENTS

I wish to make devote supplication to THE ALMIGHTY without whose blessing this task would not have been accomplished. I bow my head in utter humility and complete dedication.

Words are insufficient to record my deep sense of gratitude to my esteemed teacher, Mentor and my research guide Dr. V. R. Shah, Lecturer, Department of Chemistry, Kamani Science College, Amreli as his constant inspiration with keen interest and ever vigilant guidance without which this task could not have been achieved. He has not only guided me but also acted as co-traveler too throughout my research work and ensured that I reach destination. The only way to thank him would be perhaps to strive to work similarly in years ahead and continue the chain succession.

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Its a moment of gratification and pride to look back with a sense of contentment at the long traveled path to be able to recapture some of the fine moments and to be able to thank to my seniors Dr. Sangani, Dr. Bhimani, Dr. Bhoot and words are not adequate to my feelings for my friends. I would like to thank my dear friends Jagdish, Mahesh, Kamlesh, Hitendra, Sameer, Janak, Mathukia, Chhantbar, Nayan, Atul, Niral, Thanki, Manoj, Jignesh, Ladani, Akbari, Trada, Rupesh, Manish, Vasoya, Vijay, Barival and Shukla for their tremendous support, encouragement and to share my frustrations in ups and downs during my research work.

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Nainesh N. Kansagara

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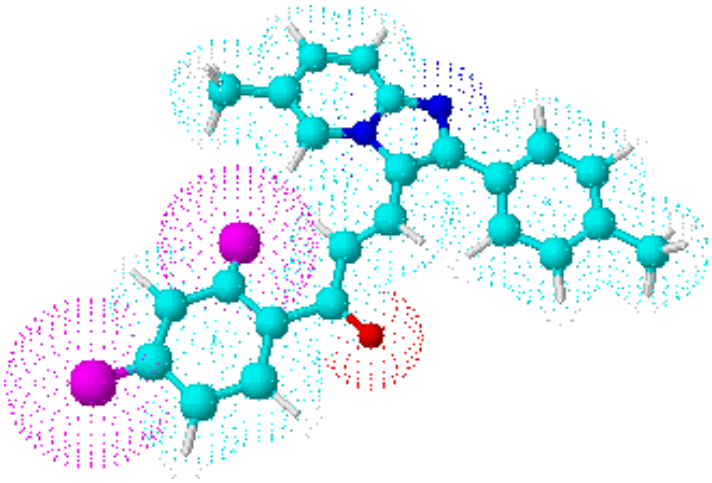

SYNOPSIS

SYNOPSIS

STUDIES ON SOME COMPOUNDS OF THERAPEUTIC INTEREST

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January - 2008

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SYNOPSIS of the thesis to be submitted to the Saurashtra University for the degree of **Doctor of Philosophy** in Chemistry

Faculty	:	Science
Subject	:	Chemistry
Title	:	**"STUDIES ON SOME COMPOUNDS OF THERAPEUTIC INTEREST"**
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The comprehensive summery of work incorporated in the thesis with the title **"STUDIES ON SOME COMPOUNDS OF THERAPEUTIC INTEREST "** has been described as under.

[A] STUDIES ON IMIDAZO[1,2-*a*]PYRIDINES

[B] STUDIES ON DIHYDROPYRIMIDINES

[C] STUDIES ON 1,4-DIHYDROPYRIDINES

[A] STUDIES ON IMIDAZO[1,2-*a*]PYRIDINES

We are engaged in a programme to explore novel heterocyclic entities in order to study their pharmacological profile our efforts are focused on introduction of chemical derivatives in the molecular frame work in order to synthesizing active molecules of different composition.

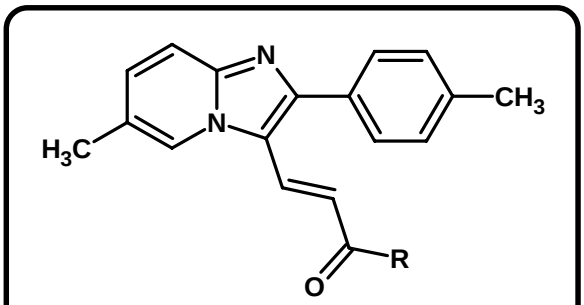
Heterocyclic compounds bearing imidazo[1,2-*a*]pyridine ring system are endowed with variety of biological activities. Our strategy is based on to develop new bioactive entities especially with pharmacological activities bearing heterocyclic ring system. Literature survey reveals that nitrogen containing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

Considering the increasing importance of [1,2-*a*] pyridine nucleus prompted us to design and synthesize some heterocycles with chalcones, pyrazolines, cyanopyridines, cyclohexenone, schiff's base, arylaminomethyl, thiazolidinone, etc bearing imidazo[1,2-*a*]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, antiviral and other pharmacological properties like anticonvulsant and anti-inflammatory. These valid observations led us to synthesize some new pyrazoline derivatives which have been described in following sections.

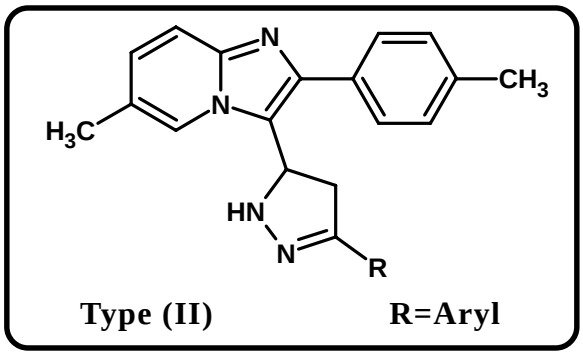
SECTION-I : Synthesis and biological screening of 1-Aryl 3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones



Type (I) **R = Aryl**

The chalcones of type (I) have been synthesized by the condensation of 6-Mehtyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde with different acetophenones in the presence of 40% Sodium hydroxide.

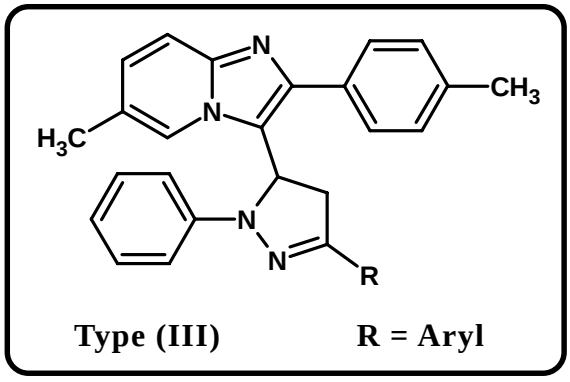
SECTION-II : Synthesis and biological screening of 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridines



Type (II) **R=Aryl**

Pyrazoline derivatives of type (II) have been synthesized by the cyclocondensation of the 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridin-3-yl]prop-2-ene-1-ones of type (I) with hydrazine hydrate.

SECTION-III : Synthesis and biological screening of 3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridines



Type (III) **R = Aryl**

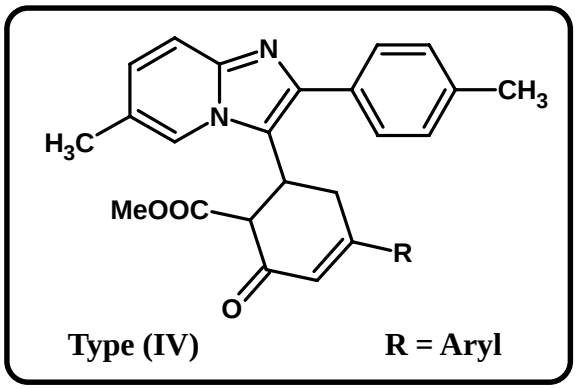
Pyrazoline derivatives of type (III) have been synthesized by the cyclocondensation of the 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridin-3-yl]prop-2-ene-1-ones of type (I) with phenyl hydrazine in methanol.

PART-II : STUDIES ON CYCLOHEXENONES

Cyclohexenone derivatives have drawn considerable attention due to their good pharmacological activities like antifungal, cardiovascular, sedative,

antibacterial, antiviral and other pharmacological properties. By considering these valid observations, we have synthesized some new cyclohexenone which have been described as under.

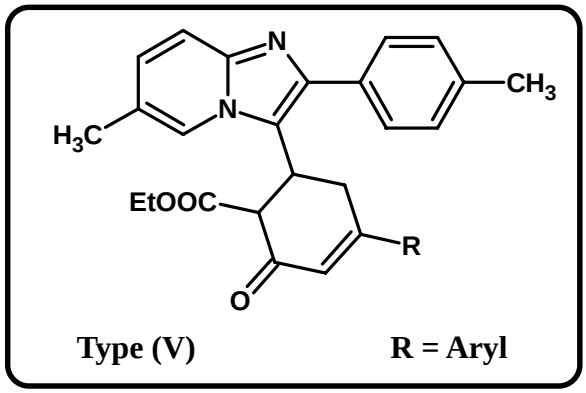
SECTION-I : Synthesis and biological screening of Methyl-4-aryl-6-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylates



Type (IV) **R = Aryl**

Cyclohexenones of type (IV) have been prepared by the condensation of chalcones of type (I) with methylacetoacetate in the presence of basic catalyst K_2CO_3.

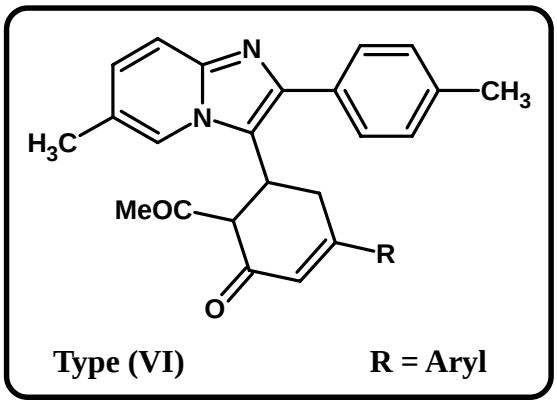
SECTION-II : Synthesis and biological screening of Ethyl-4-aryl-6-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylates



Type (V) **R = Aryl**

Cyclohexenones of type (V) have been prepared by the condensation of chalcones of type (I) with ethyl acetoacetate in the presence of basic catalyst K_2CO_3.

SECTION-III : Synthesis and biological screening of 1-Acetyl-4-aryl-6-[6-methyl-2-(4- methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-enes



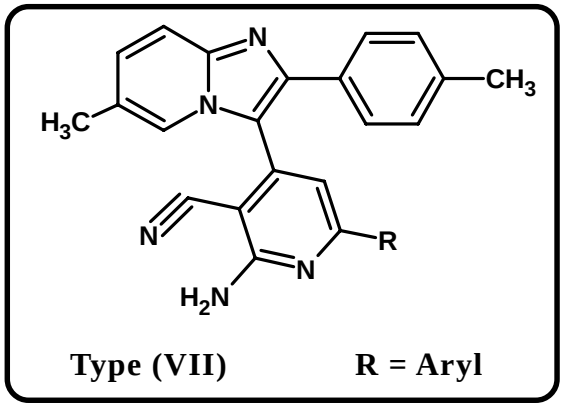
Type (VI) **R = Aryl**

Cyclohexenones of type (VI) have been prepared by the condensation of chalcones of type (I) with acetyl acetone in the presence of basic catalyst K_2CO_3.

PART-III : STUDIES ON CYANOPYRIDINES

Like other heterocyclic compounds, pyridines with different functional groups exhibit wide range of applications in the field of pharmaceutical and agriculture. Cyanopyridine derivatives have been reported to be active as anti-fungal, antidiabetic, anticholestemic, etc. On the basis of these results, we have synthesized some new derivatives which have been described as under.

SECTION-I : Synthesis and biological screening of 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles



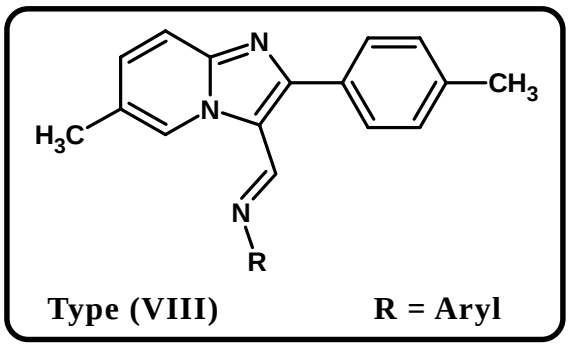
Type (VII) **R = Aryl**

Cyanopyridine derivatives of type (VII) have been prepared by the reaction of chalcones of type (I) with malononitrile and ammonium acetate.

PART-IV : STUDIES ON ARYLAMINOMETHYL DERIVATIVES

Arylaminomethyl derivative represents one of the modest classes of biological active agents which have been deeply studied as new potential agents. These have been reported to be active as antitubercular, anticancer, insecticidal, etc. In view of these valid observations, we have synthesized some new arylaminomethyl derivatives which have been described as under.

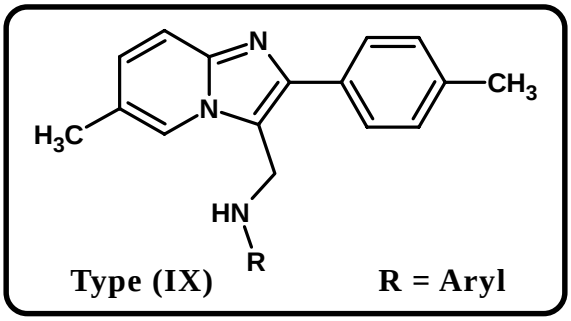
SECTION-I : Synthesis and biological screening of *N*-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines



Type (VIII) **R = Aryl**

The azomethines of type (VIII) have been prepared by the condensation of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde with different aromatic amines using acetic acid as a catalyst.

SECTION-II : Synthesis and biological screening of *N* -Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines



Type (IX) **R = Aryl**

The compounds of type (IX) have been synthesized by the reaction of arylamines of type (VIII) with $NaBH_4$.

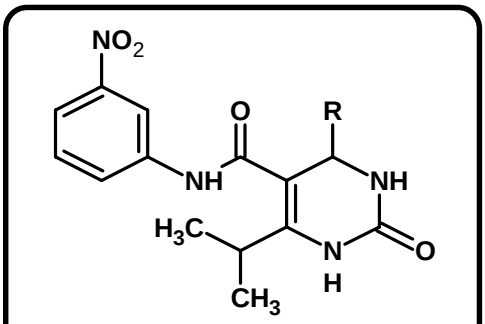
[B] STUDIES ON DIHYDROPYRIMIDINES

The synthesis of dihydropyrimidine derivatives is having important drug potential because of their pharmacological activities. Many of them are biologically important since they behave as calcium channel blockers, antihypertensive agents. This observation led us to synthesize some newer di hydropyrimidinones and dihydropyrimidinethiones derivatives shown as under.

PART-I : STUDIES ON DIHYDROPYRIMIDINONES

Dihydropyrimidinone and its derivatives have been important task for the research chemist. They possess biological activities such as significant *in vitro* activity against unrelated DNA and RNA virus, antimalarial, diuretic, antimicrobial and antineoplastic. That has been explored for developing biologically active molecules. The above observations created the interest for the synthesis of dihydropyrimidinones which have been described as under.

SECTION-I : Synthesis and biological screening of 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydro pyrimidine-2(1*H*)-ones



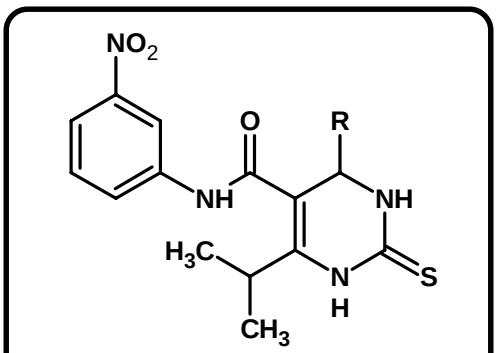
Type (X) **R = Aryl**

Dihydropyrimidinones of type (X) have been synthesized by the condensation of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide, urea and aryl aldehydes in the presence of HCl as a catalyst.

PART-II : STUDIES ON DIHYDROPYRIMIDINETHIONES

Thiopyrimidinone ring system have a prominent feature in medicinal chemistry and possess biological activities such as analgesic, insecticidal, antibacterial, antidiabetic, anticonvulsant, etc. In view of these facts, it was contemplated to synthesize thiopyrimidinone derivatives which have been described as under.

SECTION-I : Synthesis and biological screening of 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl)amino carbonyl]-3,4-dihydro pyrimidine-2(1*H*)-thiones



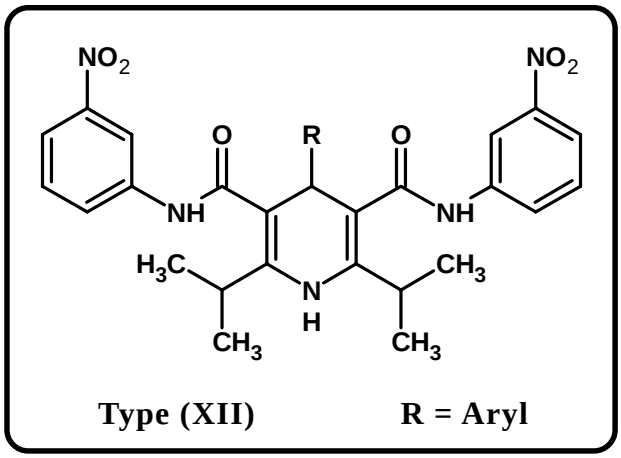
Type (XI) **R = Aryl**

Dihydropyrimidinethiones of type (XI) have been synthesized by the cyclization of 2-Arylidene-4-methyl-*N*-(3-nitrophenyl)-3-oxopentanamide with thiourea in presence of potassium bicarbonate.

[C] STUDIES ON 1,4-DIHYDROPYRIDINES

Recently 1,4-dihydropyridines have drawn considerable attention due to their good pharmacological activities like sedative, anticancer, antibacterial, cardiovascular, etc. By considering these valid observations, it was contemplated to synthesize some novel 1,4-dihydropyridines possessing higher biological activity that have been described as under.

SECTION-I : Synthesis and biological screening of 4-Aryl-2,6-diisopropyl -3,5-bis[*N*-(3-nitrophenyl)amino carbonyl]-1,4-dihydro pyridines



Type (XII) **R = Aryl**

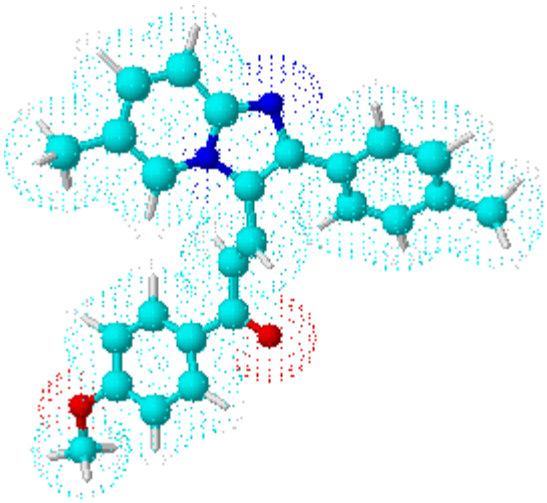
1,4-Dihydropyridines of type (XII) have been prepared by the cyclo condensation of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide with aryl aldehydes in ammonical methanol.

The constitution of the synthesized compounds has been characterized by elemental analyses, IR and ^{1}H NMR spectroscopy and further supported by MS spectra. Purity of all the compounds have been checked by TLC.

IN VITRO STUDIES ON BIOLOGICAL ACTIVITIES

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

DR. V. R. SHAH **NAINESH N. KANSAGARA**



STUDIES ON SOME COMPOUNDS OF THERAPEUTIC INTEREST

INTRODUCTION

The chemistry of therapeutic interested compounds had it's beginning when chemists, pharmacists and physicians isolated purified active principles of plant and animal tissues and later from micro organisms and their fermentation products. Some of these chemicals had been associated with therapeutic properties is often ill-defined disease condition.

The current interest in the creation of large, searchable libraries of organic compounds has captured an imagination of chemists and the drug discovery community. Efforts in numerous laboratories focused on the introduction of chemical diversity have been recently reviewed and pharmacologically interesting compounds have been identified from libraries of widely different composition.

The progress of drug design is extensively driven by the instincts, intuition and experience of pharmaceutical research scientists. It is often instructive to attempt to 'capture' these experiences by analyzing the historical record that is successful drug design projects to past. From this analysis the interference draw to play an important role in shaping our current and future projects. Towards this region, we would like to analyze the structures of a large number of drugs.

The word '**drug**' is derived from the French word '**drogue**' which means a dry herb. According to "WHO" a drug may be defined as "any substance or product which is used or intended to be used for modifying or exploring physiological system or pathological status for the benefit of recipient".

Drug's action is believed to be due to the interaction of the drug with enzymes, receptors and other molecules found in the biological system. The binding of a drug to the active or other sites of an enzyme usually has the effect of preventing the normal operation of that enzyme. The stronger the binding of the drug to the enzyme and greater

the number of sites occupied, the more effective the drug is likely to be in inhibiting the action of the enzyme.

The degree of drug activity is directly related to the concentration of the drug in the aqueous medium in contact with the active or receptor site. The factors affecting this concentration in a biological system can be classified in to two phase.

(I) The pharmacokinetic phase

It is concerned with the study of the parameters that control the journey of the drug from its point of administration to its point of action. It includes the absorption, distribution, metabolism and elimination of a drug.

(II) The pharmacodynamic phase

It is concerned with the result of the interaction of drug and body at the receptor site, that is, what the drug does to the body. This includes physiological and biochemical effects of drugs and their mechanism of action at macromolecular /sub cellular organ systems.

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 encounters a situation where a structure has adequate pharmacological 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 an 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 provide false synthons in biosynthetic process or block the normal functioning of biological receptors. The inhibition of amide resonance resulting into more susceptibility of β-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, haemoglobin and anthocyanin are heterocycles. Most of the sugars or 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.

The ultimate product of a successful drug design effort. Our goal for this is to begin to deconvolute this information in order to apply it to design the new drugs.

Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing Imidazo [1,2-a] pyridine, dihydropyridine and dihydropyrimidine nucleus.

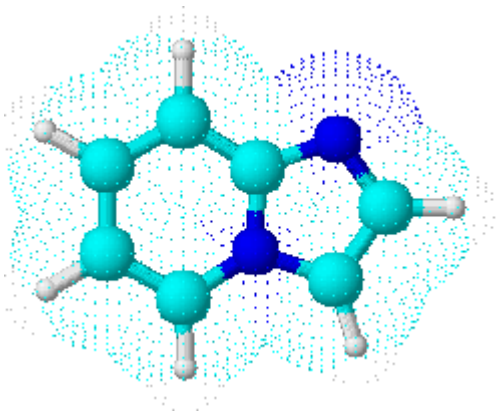
AIMS AND OBJECTIVES

In the pharmaceutical field, there is a need for new and novel chemical inhibitors of biological functions. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interested heter

ocyclic compounds of widely different composition. During the course of research work looking to the applications of heterocyclic compounds, several entities have been designed, generated and characterized using spectral studies. The aims and objectives of the work carried out are as under.

1. To synthesize pharmacologically active entities like chalcones, cyanopyridines, pyrazolines, pyrimidinones, dihydropyridines, methylamines, etc.
2. To characterise these products for structural elucidation using spectroscopic techniques like IR, NMR and Mass spectral studies.
3. To check the purity of all compounds using thin layer chromatography.
4. To evaluate these new products for better drug potential against different strains of bacteria and fungi.

In a programmed research directed towards the construction of therapeutically active new heterocycles bearing [A] Imidazo[1,2-*a*] pyridine, [B] Dihydropyrimidine and [C] Dihydropyridine nucleus has been investigated in following parts.



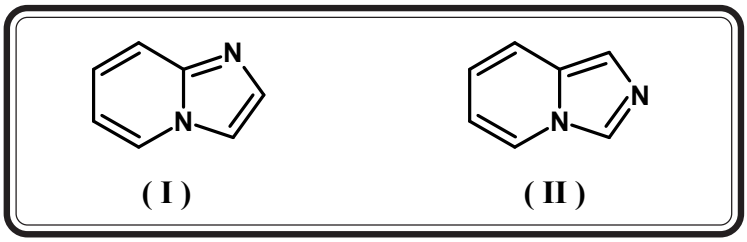
[A]

STUDIES ON

IMIDAZO[1,2-a]PYRIDINES

INTRODUCTION

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



(I) **(II)**

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-*a*]pyridine[2]. Many drugs contain imidazo[1,2-*a*] nucleus. Several procedures 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-*a*]pyridine was represented by W. L.Mosby[3]. Imidazo[1,2-*a*]pyridine derivatives not only known for their medicinal applications but they are also used in disperse dye[4].

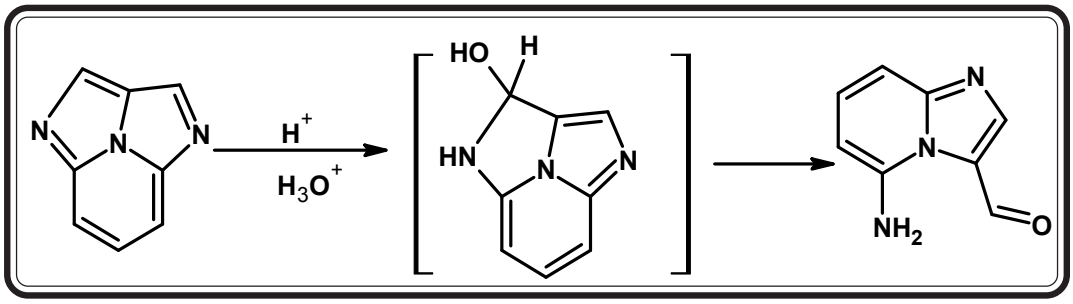
SYNTHETIC ASPECT

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

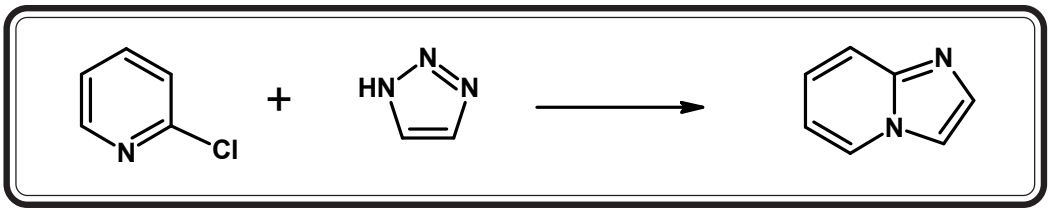
1. The Tschitschibabine[5] has synthesized imidazo[1,2-*a*]pyridine from 2-amino

pyridine with ω-bromoacetophenone.

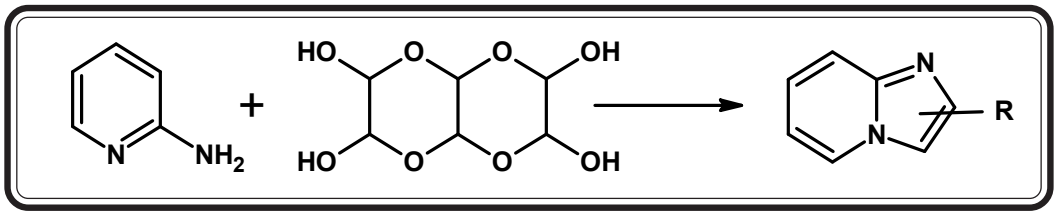
2. Paudler et al.[6] have synthesized 5-amino-3-formyl imidazo[1,2-a]pyridine from acid catalyzed hydrolysis of 1,4-diazatricyclo[3,2,2]azine.



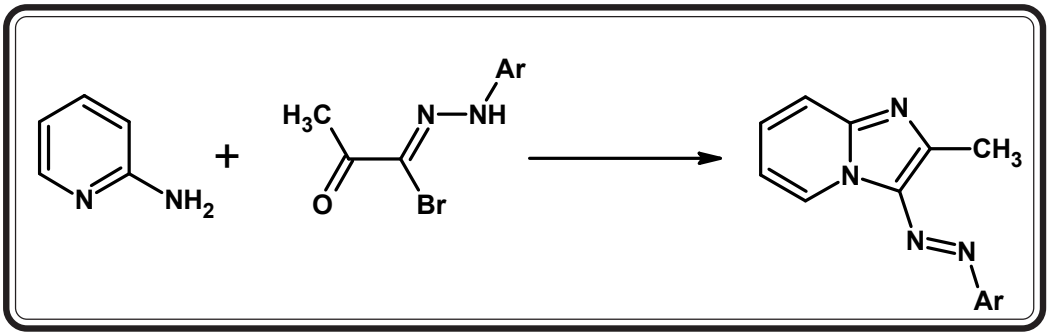
3. Reaction of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogens give imidazo[1,2-*a*]pyridine.[7]



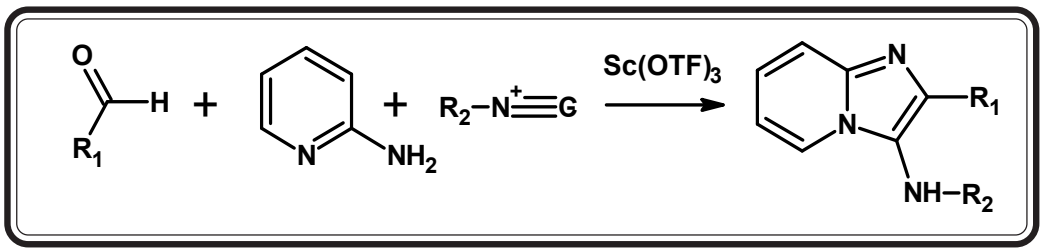
4. Groziak et al.[8] have synthesized imidazo[1,2-*a*]pyridine by the condensa-tion of 2-aminopyridine with glyoxal trimer dehydrate in aqueous $NaHSO_3$.



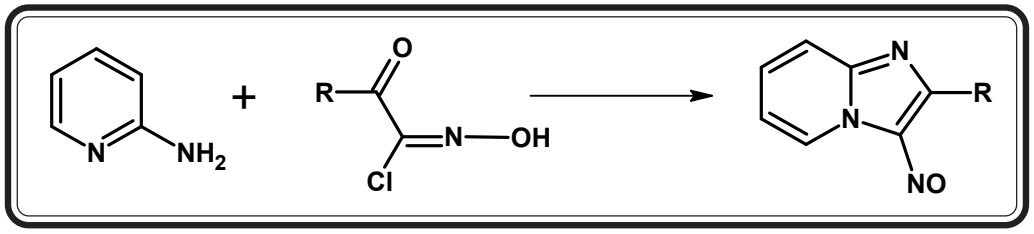
5. Imidazo[1,2-*a*]pyridine[9] nucleus can be also synthesized by the reaction of α-ketohydrazidoyl halide with heterocyclic amines.



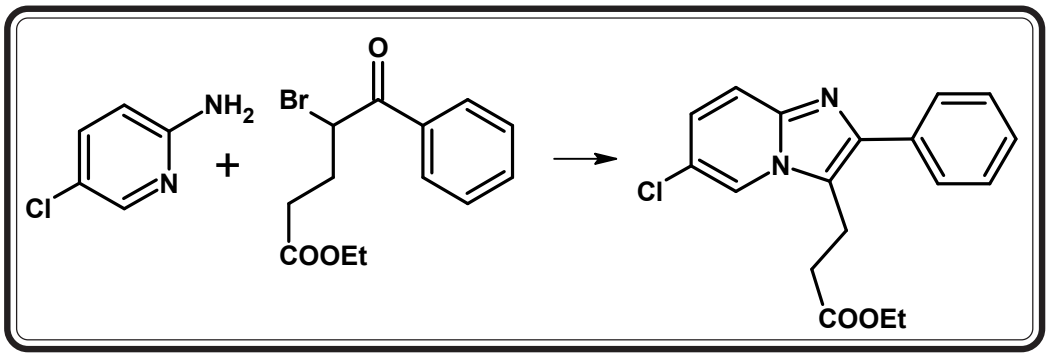
6. Tsai et al.[10] have been prepared 3-amino imidazo[1,2-*a*]pyridinederivatives by a three component condensation reaction between 2-aminopyridine, aldehyde and an isonitrile in the presence of scandium triflate as a catalyst.



7. Shawali et al.[11] have synthesized imidazo[1,2-*a*]pyridine nucleus by the reaction of α-ketohydroximoylchloride with 2-aminopyridine.

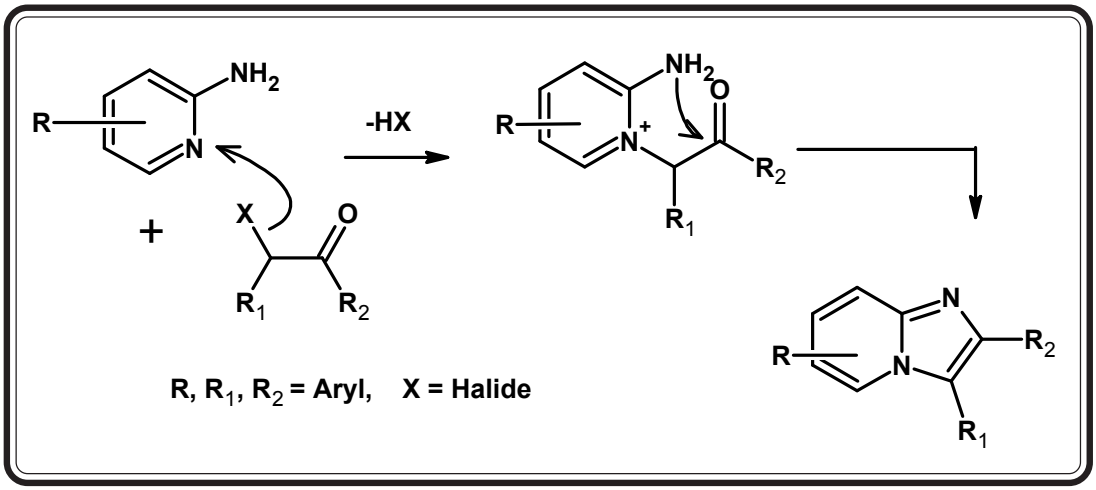


8. Ja´nos Gerencse´r [12] have direct Synthesis of Imidazo[1,2-*a*]pyridin-3-yl-carboxylic Acid Derivatives via the Condensation of 2-Amino-5-chloropyridine and Ethyl 4-Bromo-5-oxo-5-phenylpentanoate.



MECHANISM

The majority of imidazo[1,2-a]pyridine have been synthesized by 2-amino pyridine with a-halocarbonyl compound which cyclise at room temperature.



THERAPEUTIC IMPORTANT

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

1. Antiulcer[13]
2. Long-acting local anaesthetic[14]
3. Antiviral[15,16]
4. Hypnotic[17]
5. Antianxiety[18]
6. Antibacterials[19,20]
7. Antifungal agents[21]
8. Calcium channel blockers[22]
9. Antiherpetic activity[23,24]
10. Anti-inflammatory, analgesic, antipyretic[25,26]
11. Gastric antisecretory[27,28]
12. Hypnoselective and anxioselective activities[29]
13. β-Amyloid formation inhibitors[30]
14. Active nonpeptide bradykinin B_2 receptor antagonists[31]

15. Nonsedative anxiolytic[32]

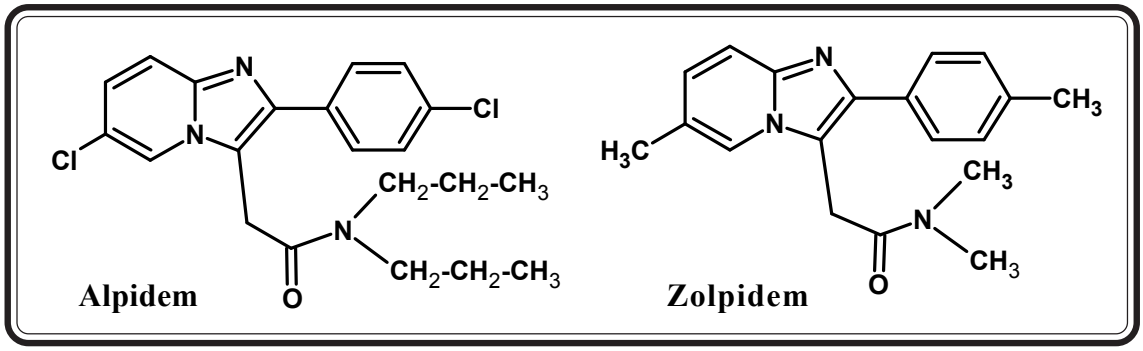
16. Benzodiazepine receptor agonists[33]

17. Anticytomegalo-zoster and antivaricellazoster virus[34-36]

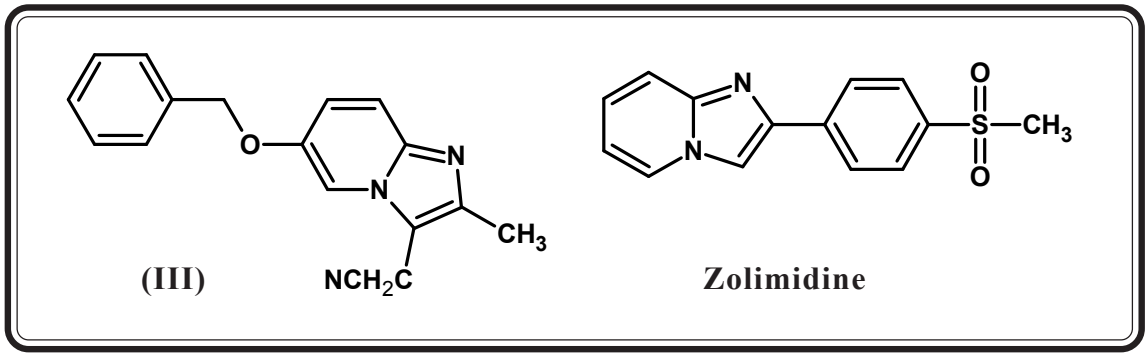
18. Cardiotonic agents[37]

19. Anthelmintic[38]

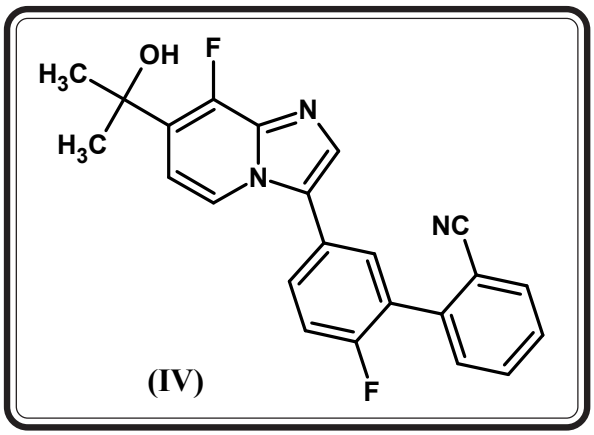
Some imidazo[1,2-a]pyridines are already in market include **alpidem**[39] [a ligand of both the central benzodiazepine receptors and the peripheral type benzodiazepine receptor] has sedative and anxiolytic properties and **zolpidem**[39] [a selective ligand for the central benzodiazepine receptor] is a hypnotic drug. Both **alpidem** and **zolpidem** have higher affinity for enzodiazpine-1 than for benzodiazepine-2 receptors[40] and their interaction with various receptor types has been reported[41].



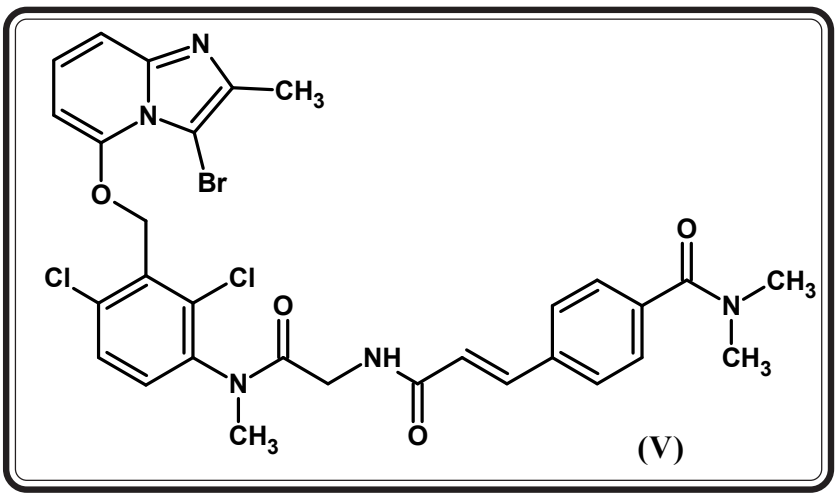
James J. Kaminski and co-workers[42] have investigated the imidazo[1,2-*a*]pyridine derivative 3-(cyanomethyl)-2-methyl-6-(phenylmethoxy)imidazo[1,2-*a*]pyridine (III) as an antiulcer agent. On the basis of the reported metabolism of zolimidine, they reported that the 3-cyanomethyl and 6-phenylmethoxy group have been established as metabolic sites.



Pharmaceutical research requires an increasing number of novel compounds to cover previously unexplored areas in the chemical space. There is also a need to increase the quality of the newly prepared molecules regarding their drug likeness and other pre-defined physicochemical parameters. Alexander C. Humphries and co-workers[43] have synthesized 8-fluoro imidazo[1,2-*a*]pyridine derivatives (IV).



(IV)

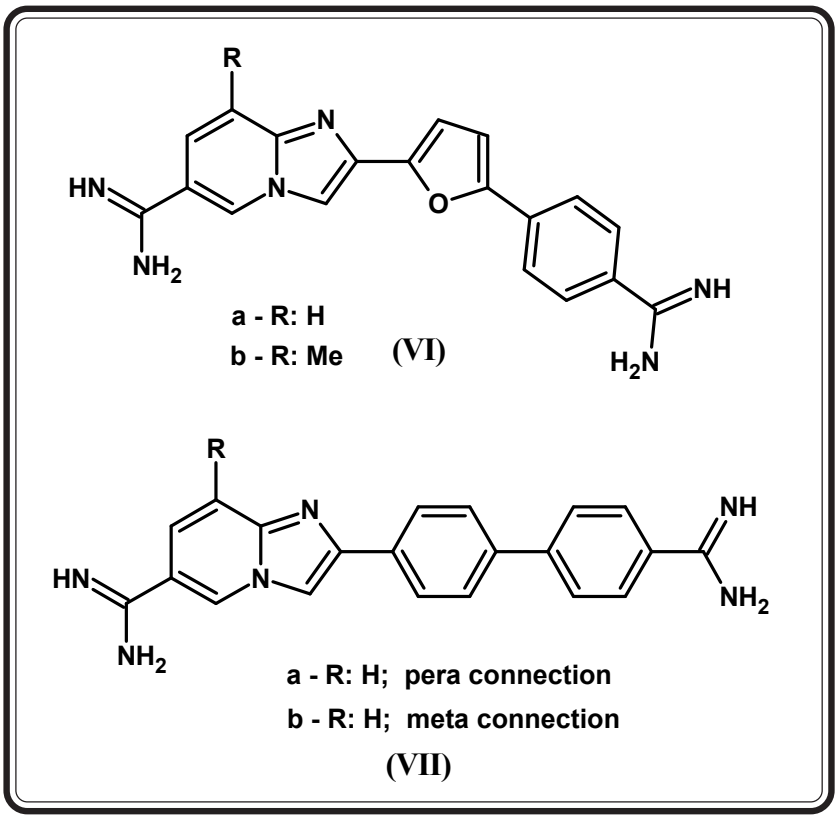


(V)

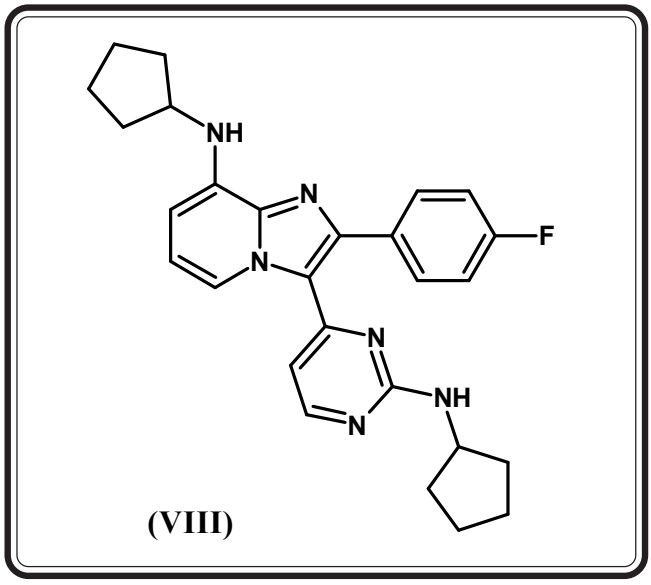
Evaluated as a bioisosteric replacement for imidazo[1,2-a]pyridine in an allosteric modulator ligand of the GABA receptor. Kristian S. Gudmundsson[44] have reported the synthesis and antiviral activities of newer Erythrofuranosyl imidazo[1,2-*a*]pyridine C-nucleosides. I. Aramori et al.[45] have been synthesized highly potent and selective non-peptide bradykinin receptor antagonist (V). A novel class of orally active non-peptide bradykinin B_2 receptor antagonist and discovering bioisosteres of the imidazo[1,2-*a*]pyridine moiety reported by Yoshito Abe.[46]Synthesis of acyclo-c-nucleosides in the

imidazo[1,2-*a*]pyridine and pyrimidine series as antiviral agents.[47] Dubinsky B and Vaidya AH [48] has defined like imidazo [1,2-*a*] pyridine derivatives is a new nonbenzodiazepine anxiolytic.

The imidazo[1,2-*a*]pyridine bearing a very good synthon variety of building blocks in both natural and synthetic bioactive compounds.[49-51] Mohamed A. Ismail [52] have recently synthesized some novel diamidine imidazo[1,2-*a*]pyridine like (VI) and (VII) and 5,6,7,8-tetrahydro imidazo[1,2-*a*]pyridines and their corresponding N-hydroxy and N-methoxy analogues which are potential for this series and their evaluation versus *trypanosoma b. rhodesiense* and *plasmodium falciparum*. Moreover synthesized aromatic diamidines exhibit broad spectrum antimicrobial activity including effectiveness against the protozoa[53] disease caused by *trypanosoma SP* and *plasmodium SP*. Novel substituted imidazo [1,2-*a*] pyridine compounds are disclosed which have a high degree of anthelmintic activity. Processes for the preparation of such compounds are also disclosed as well as active ingredients for the treatment of helminthiasis and anti ulsurative.



Kristjan S., Gudmundsson, Brian Johns A.[54] and Chaouni Bendallay A. et al.[55] have worked on synthesis of a novel imidazo[1,2-*a*] pyridine shown in (VIII) with potent activity against *herpes simplex* viruses.

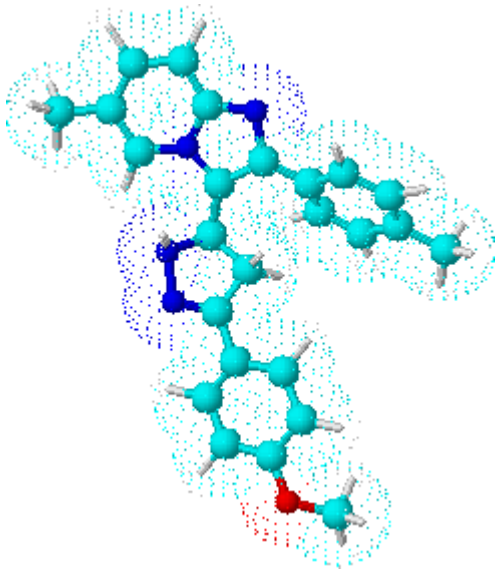


(VIII)

Thus the important role displayed by imidazo[1,2-*a*]pyridine and its derivatives for various therapeutic and biological activities prompted us to synthesise some chalcones, Phenylpyrazolines, cyanopyridines, thiozolidinones, cyclohexenone, schiff's base, aryl amino methyl derivatives bearing imidazo[1,2-*a*]pyridine moiety in order to get compounds having better biological activities as described in the following parts.

STUDIES ON IMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES

PART-I	**:**	**STUDIES ON PYRAZOLINES**
PART-II	**:**	**STUDIES ON CYCLOHEXENONES**
PART-III	**:**	**STUDIES ON CYANOPYRIDINES**
PART-IV	**:**	**STUDIES ON ARYLAMINOMETHYL DERIVATIVES**

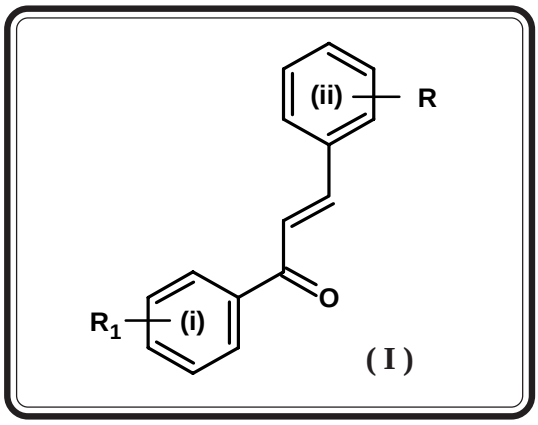


PART - I

STUDIES ON PYRAZOLINES

INTRODUCTION

The term "***chalcone***" was first coined by Kostanecki and Tambor[56]. The chemistry of chalcones has generated intensive scientific studies throughout the world. Chalcones are coloured compounds because of the presence of the chromophore and auxochrome. They are known as benzala cetophenones or benzylidene acetophenones. Chalcones are characterized by their possession of a structure (I) in which two aromatic rings (i) and (ii) are linked by an aliphatic three carbon chain.



(I)

The alternative names given to chalcones are phenyl styryl ketones, benzalacetophenone, β-phenyl acrylphenone, γ-oxo-α, γ-diphenyl-α-propylene and α-phenyl-β-benzoethylene.

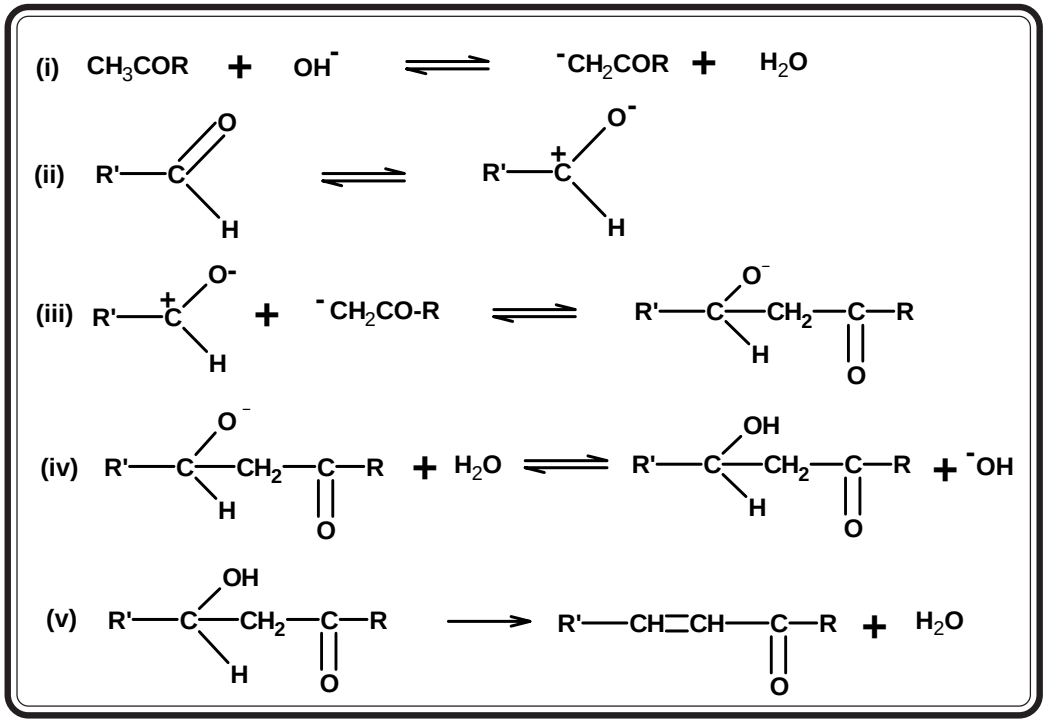
SYNTHETIC ASPECT

A considerable variety of methods are available for the synthesis of chalcones. The most convenient method is the one that involves the Claisen-Schmidth condensation of aryl methyl ketones with aryl aldehyde in the presence of alkali[57--58].

Several condensing agent used for the synthesis of chalcones are alkali of different strength[59-60], HCl[61-62], Phosphorous oxychloride[63], Piperidine[64], Anhydrous Aluminium Chloride[65], Boron trifluoride[66], Aminoacids[67], Perchloric acid[68] etc.

MECHANISM

The following mechanisms have been suggested for the synthesis of chalcone. Carbanion formation observes in presence of alkali media and the intermediate aldol type products formed readily undergoes dehydration even under mild condition and form unsaturated α-keto derivatives.



REACTIVITY OF CHALCONES

The chalcones have been found to be useful for the synthesis of many heterocyclic compounds.

1. Chalcones are intermediate compounds for the synthesis of some naturally occurring heterocyclic compounds like flavones, flavanones, flavanoid, dihydro flavanols, benzal coumarones, anthocyanine, etc.
2. Chalcone contain a Keto-Ethylenic group and therefore reactive towards a number of reagents yielding various heterocyclic compounds exhibiting significant biological activities viz. pyrazolines[69], cyanopyridines[70], cyanopyrans[71], cyanopyridones[72], pyrimidines[73-77], indazoles[78] etc.
3. They have been useful in providing structure of some natural products like

hemlocktanin[79], narighenin[80], plioretin[81] etc.

4. Chalcones are also useful for the detection of Fe(II)[82] and Ca(II)[83] ions in presence of Ba and Sr as it reacts with number of metal ions. Trihydroxy chalcones was used as an analytical reagent for amperometric estimation of copper[84] and for spectrophotomatric study of the germanium[85].
5. Chalcone and their derivatives are also found to be applicable as light stabilizing agent[86], sweetening agent[87], organic brightening agent, photo sensitive material, polymerisation catalyst, scintillators as well as fluorescent whitening agent.
6. The chalcones are natural biocides[88-89] and are well-known key intermediate in the synthesis of heterocyclic compounds possessing biodynamic behaviors.

THERAPEUTIC IMPORTANCE

Chalcone derivatives have been found to possess wide range of therapeutic activities as shown below

1. Antiallergic[90]
2. Antiinflammatory[91-92]
3. Antitumor[93-94]
4. Antispasmodic[95]
5. Antiulcer[96-97]
6. Anthelmintics[98-99]
7. Anticancer[100-101]
8. Antiviral and Antitubercular[102]
9. Anti HIV[103]
10. Bactericidal[104-105]
11. Cardiovascular[106]
12. Fungicidal[107-109]
13. Herbicidal[110]

14. Insecticidal[111-113]

Chalcones are potential biocides because some naturally occurring antibiotics[114] and showing their biological activity in the presence of the α,β-unsaturated carbonyl group. Nelson G. L.[115] has synthesized the analogues of prostaglandin (II).

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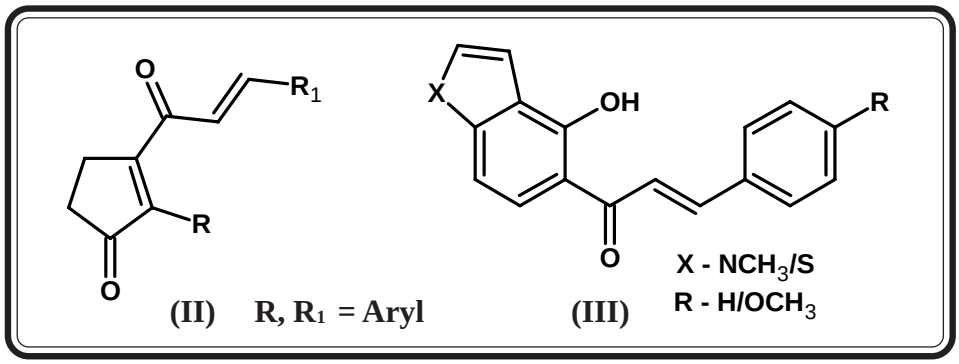
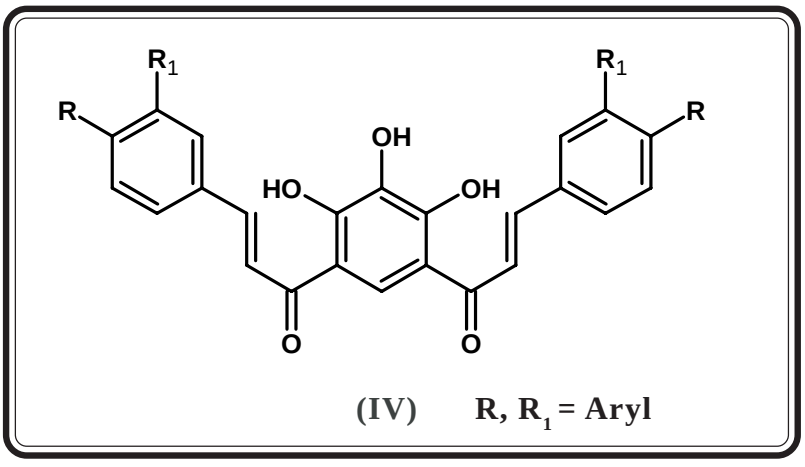


(II) R, R_1 = Aryl **(III)**

Prem P. Yadav and co-workers[116] have synthesized nitrogen and sulfur containing furanoflavonoids and thiophenylflavonoids (III), Which have been screened for antifungal and antibacterial activity. Meng C. Q. et al.[117] discovered some novel heteroaryl substituted chalcones as inhibitors of TNF-alpha-induced VCAM-1 expression.

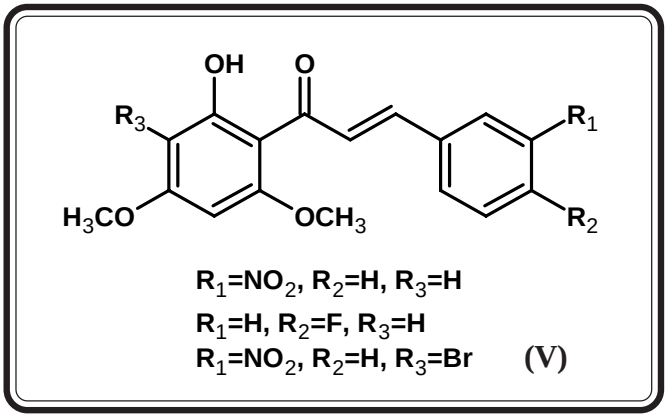
Some dihydrochalcones are well known for their sweetening property[118-119] and appear to be non-nutritive sweeteners. A dihydrochalcone **Uvaretin** from *Uvaria acuminata* has shown antitumor activity[120] in lymphocytic leukemia test. AhluwaliaV. K. et al.[121] have noted that 5-cinnamoylchalcones (IV) have shown good antibacterial activity.



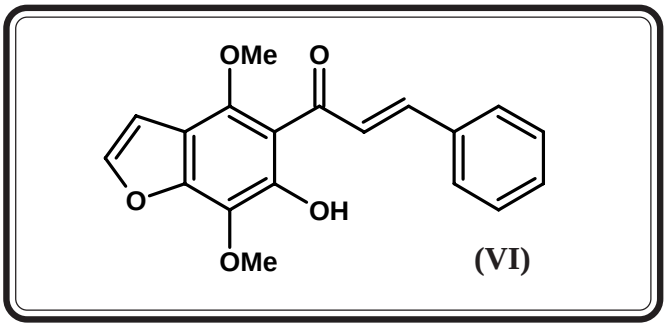
(IV) R, R_1 = Aryl

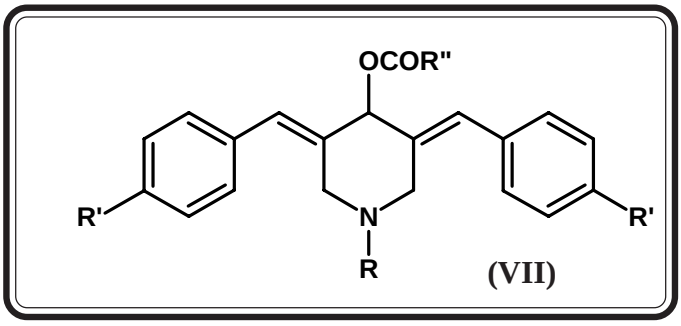
Paula Boeck et al.[122] have synthesized novel chalcone analogues (V) with

pharmacological activity. Analogues containing nitro, fluorine or bromine group respectively displayed increased activity against the parasites as compared with natural chalcone.



Furthermore, Alcaraz M. J. et al.[123] have described the role of nuclear factor-kappaB and heme oxygenase-1 in the mechanism of action of an antiinflammatory activity of chalcone derivative. Nerya O. et al.[124] have prepared chalcones as potent tyrosinase inhibitors. Sabzevari O. et al.[125] have constructed some new chalcone derivatives (VI) as molecular cytotoxic mechanisms for anticancer activity. Aneta Modzelewska et al.[126] have prepared novel chalcone and bis chalcone derivatives (VII) having anticancer activity.

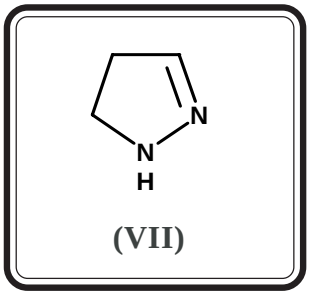




Chalcones have been proved to be an important intermediate for the synthesis of many heterocyclic compounds in organic chemistry. These facts prompted us to synthesize some new chalcone derivatives bearing imidazo[1,2-*a*]pyridine as a nucleus. We have prepare pyrazoline nucleus from chalcone, which are widely used in pharmaceutical field. The study of pyrazoline nucleus is as under.

INTRODUCTION

The chemistry of pyrazoline was reviewed by Jarobe in 1967, which have been studied extensively for their biodynamic behavior[127]. Pyrazoline have an important heterocyclic compounds have been extensively explored for their applications in the field of medicine.Pyrazoline has three possible tautomeric structures, but the structure (I) shown is the most stable. Amongst nitrogen containing five member heterocycles, pyrazolines have proved to be the most useful frame work for biological activities.



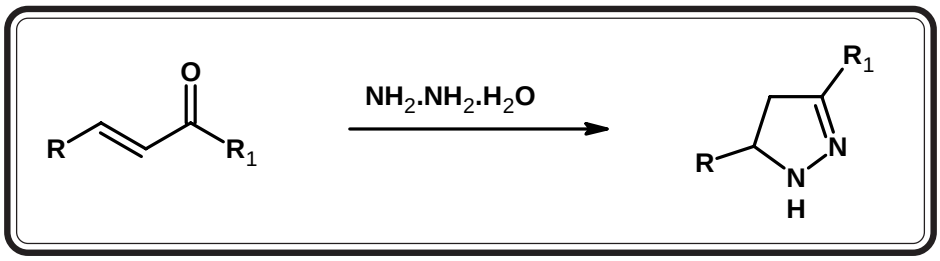
(VII)

SYNTHETIC ASPECT

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

1. 2-Pyrazolines can be synthesized by the cycloaddition of diazomethane to substituted chalcone[128].
2. Dipolar cycloaddition of nitrilimines of dimethyl fumarate, fumaronitrile and the N-aryl maleimides yielded the corresponding pyrazolines[129].
3. Epoxidation of chalcones with epoxy ketones on reaction with hydrazine hydrate and phenyl hydrazine to give pyrazolines[130].
4. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with

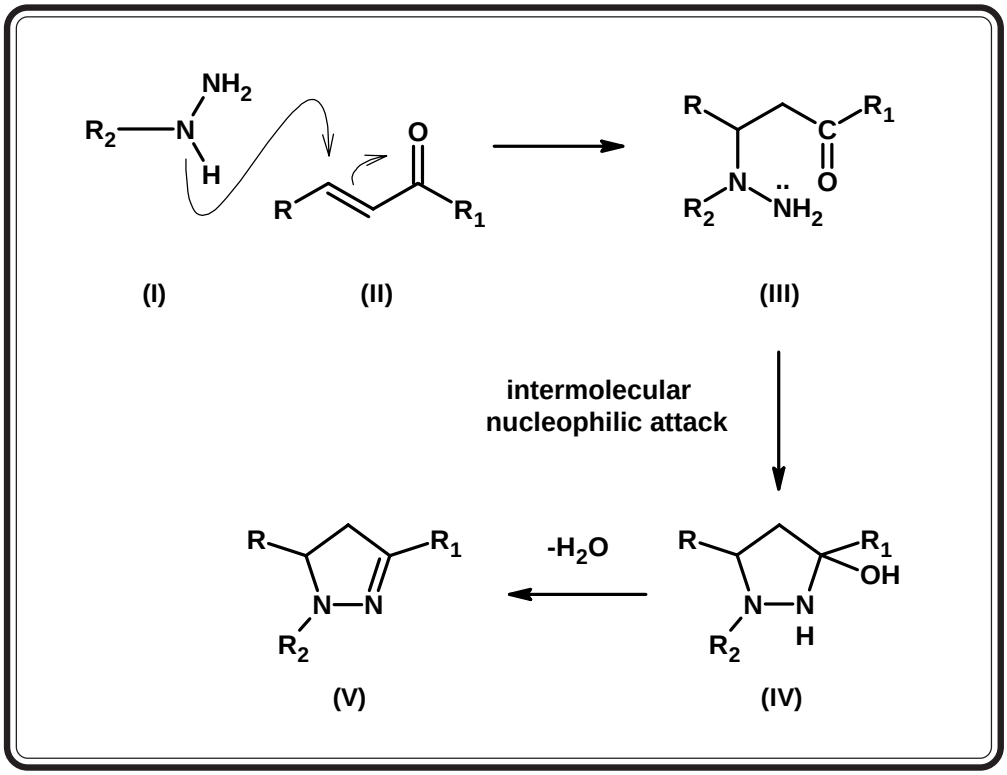
hydrazine hydrate[131].



5. 2-Pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazine[132]. Furthermore, Gyassi B. et al[133] have investigated the one pot synthesis of some pyrazolines in dry media under microwave irradiation. Paul S.et al[134] and Dandia Anshu et al[135] have also described the microwave synthesis of 2-pyrazolines.

MECHANISM

The following mechanism for pyrazoline by the condensation of chalcones with hydrazine hydrate[136].



Nucleophilic attack by hydrazine at the β-carbon of the α,β-unsaturated carbonyl system forms species (III). Another intramolecular nucleophilic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to carbonyl amine (IV). Later with a hydroxy group and amino group on the same carbon lose water molecule to yield the pyrazolines. The study of pyrazoline nucleus are as under.

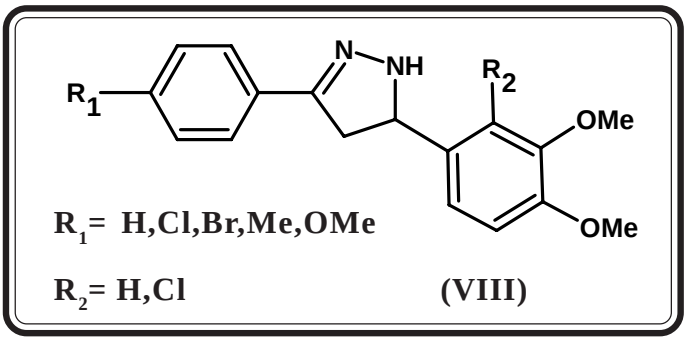
THERAPEUTIC IMPORTANCE

From the literature survey, it was revealed that pyrazolines are better therapeutic agents. Some of the activities are mentioned below.

1. Cardiovascular[137]
2. Diuretic[138]
3. Fungicidal[139]
4. Herbicidal[140]
5. Hypoglycemic[141]
6. Insecticidal[142]
7. Tranquilizer[143]
8. Antitumor[144]
9. Antineoplastic[145]
10. Antimicrobial[146]
11. Analgesic[147-148]
12. Bactericidal[149,150]
13. Antiallergic[151]
14. Anticonvulsant[152-153]
15. Antidiabetic[154]
17. Antiinflammatory[155]
18. Antiamoebic[156]

Abdalla M. M. et al.[157] have synthesized pyrazolines and tested their antiandrogenic activity. Berghot M. A. et al.[158] have prepared pyrazolines as antibacterial agents. Maurer Fritz et al.[159] have synthesized pyrazoles and screened for their pesticidal activity.

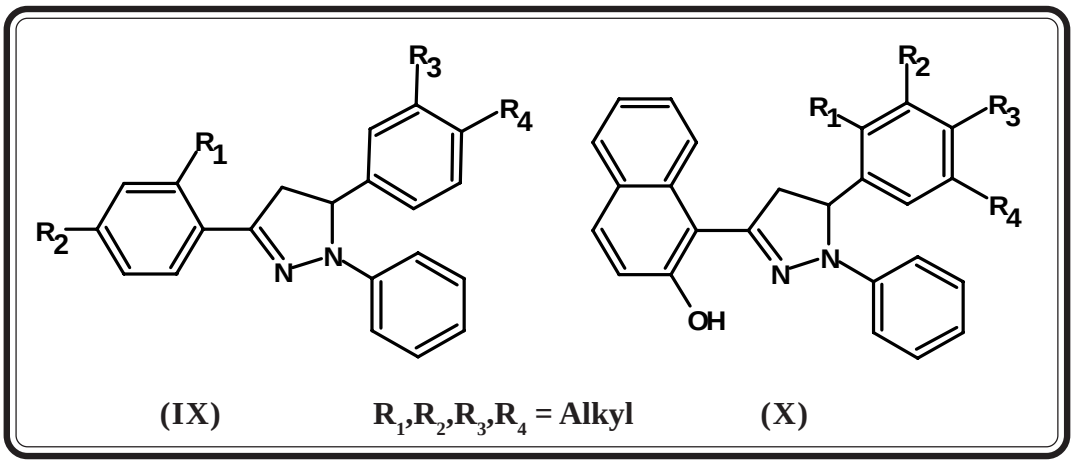
Palaska E. et al.[160] have prepared 3,5-diphenyl-2-pyrazolines (VIII) and cited their antidepressant activity. Gokhan N.et al.[161] reported pyrazolines as cholinstearase and selective monoamine oxidase β–inhibitiors Stavenson T.M.et al.[162] have also investigated N-substituted pyrazoline type insecticides. Katsushori T.[163] have patented pyrazoline derivatives as herbicides and Johannes et al.[164] have reported as insecticides.



R_1= H,Cl,Br,Me,OMe

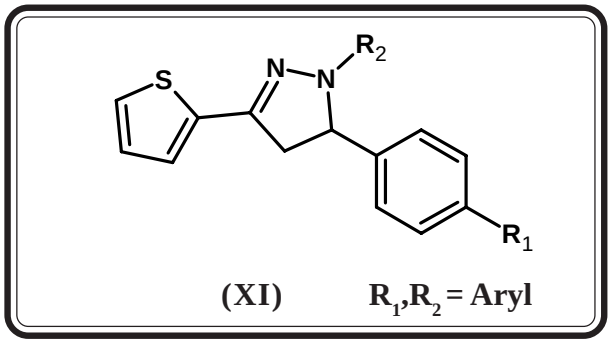
R_2= H,Cl **(VIII)**

Bhat and co-workers [165] synthesized pyrazoline derivatives, which have cytotoxic properties. Rajendra prasad Y. et.al.[166] have synthesized some 1,3,5-tryphenyl 2-pyrazoline and 3-[(2-hydroxy napthaline)-1-yl]-1,5-di phenyl 2-pyrazoline and reported as antidepresent(IX) & (X).

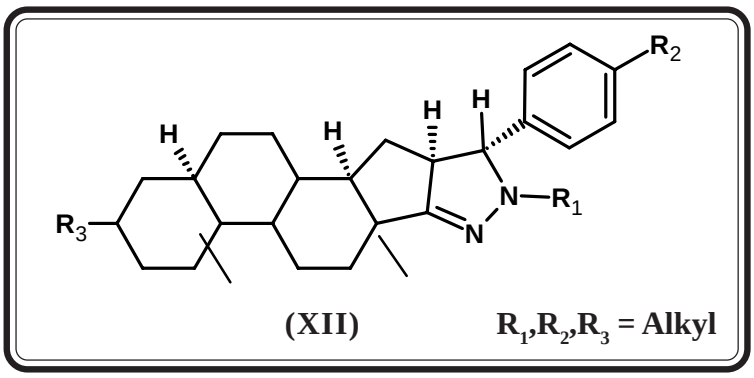


(IX) **R_1,R_2,R_3,R_4 = Alkyl** **(X)**

Mohmmad Abid and Amir Azam[167] have synthesized pyrazoline (XI) and reported as anti amoabic agent. Abd El.Galil E.Amr et.al [168] have screened some new 3-substituted pyrazolines (XII)and reported their antiandrogenic activity.

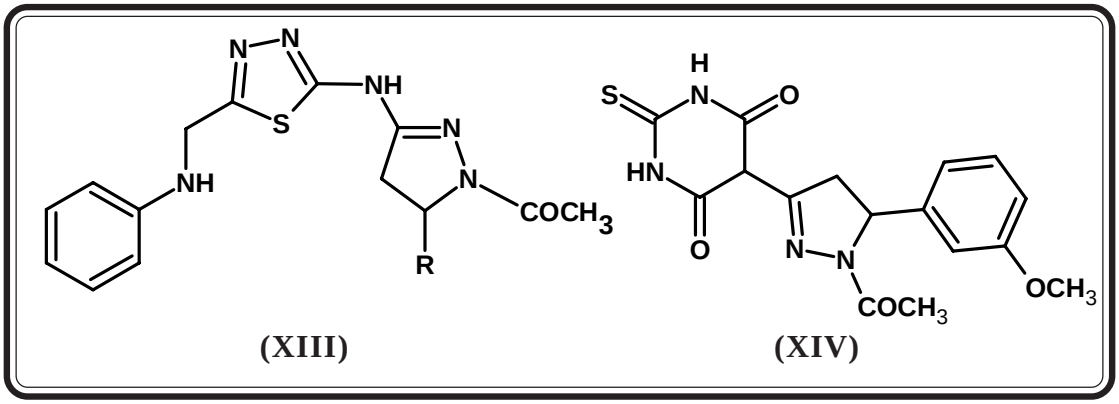


(XI) **R_1,R_2 = Aryl**



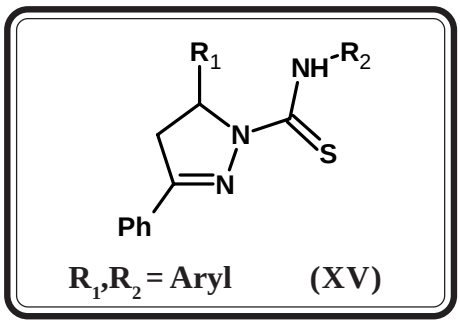
(XII) **R_1,R_2,R_3 = Alkyl**

Almstead J. et al.[169] have prepared pyrazolines as vascularization agent. Guniz Kucukguzel et al.[170] have synthesized pyrazolines as a anticonvulsant agents. Gulhan T.Z. and coworkers[171] have prepared pyrazolines as a hypotensive agent. Shalabh Sharma et al.[172] have synthesized pyrazolines and tested their anti-inflammatory activity (XIII). Ashok Kumar et al.[173] have synthesized pyrazolines as anticonvulsant agents (XIV). Maurer Fritz et al.[174] have synthesized pyrazoles and screened for their pesticidal activity.



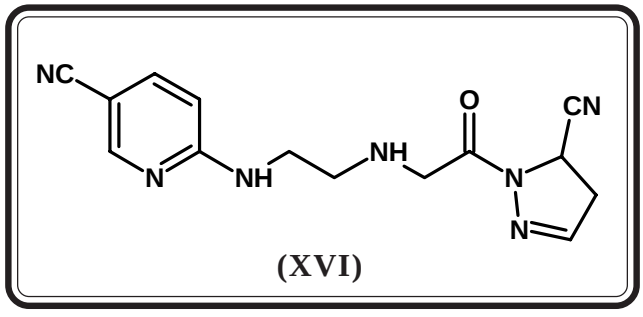
(XIII) **(XIV)**

Shivarama B. Holla et al.[175-176] have synthesized pyrazolines as antibacterial agent. Hiremath S. P. et al.[177] have synthesized pyrazolines as analgesic, anti-inflammatory and antimicrobial agent. Malhotra V. et al.[178] have synthesized new pyrazolines as a cardiovascular agent (XV).



R_1,R_2 = Aryl (XV)

Moreover, Ahn J. H. et al.[179] have described the synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent antidiabetic agents(XVI). Jeong T. S. et al.[180] have synthesized some novel 3,5-diaryl pyrazolines as cholesterol acyl transferase inhibitors. Nasr M. N. et al.[181] have reported the synthesis of Novel 3,3a,4,5,6,7-hexahydroindazole and aryl thiazolylpyrazoline derivatives as antiinflammatory agents. Berghot M. A. et al.[182] have prepared for antibacterial activity of pyrazole and pyrazoline derivatives of diazepam.

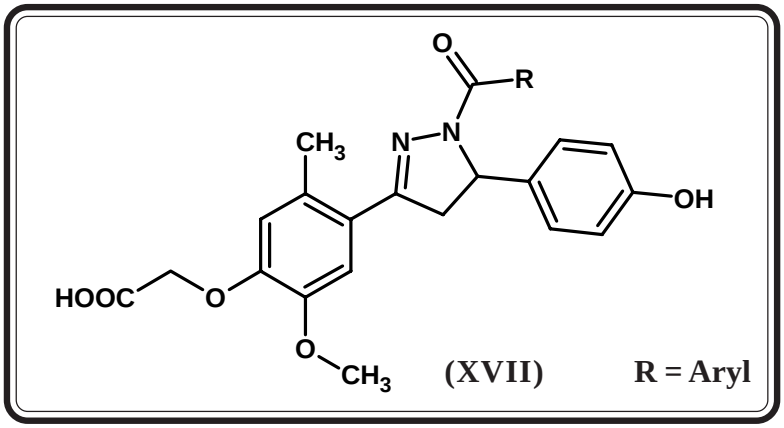


(XVI)

Recently, Gokhan N. et al.[183] have synthesized the pyrazoline derivatives of 1-N-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazolines as MAO inhibitors. Matysiak J. et al.[184] have reported some novel pyrazoline derivatives having antipsycotic activity. Tabarelli Z. et al.[185] have prepared some pyrazole derivative showed activity of antinociceptive effect of novel pyrazolines derivatives.

Novel bis(1-acyl-2-pyrazolines) are synthesized by Flora F. Barsoum[186] & co-

workers for potential anti-inflammatory and molluscicidal properties. Mohammad Shahar ya[187] & co-workers synthesized and evaluated of pyrazoline derivatives (XVII)as anti-bacterial agents.



(XVII) **R = Aryl**

With a view to get better therapeutic agent, it was contemplated to synthesize pyrazoline derivatives to enhance the overall activity of resulting compounds which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ARYL-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONES

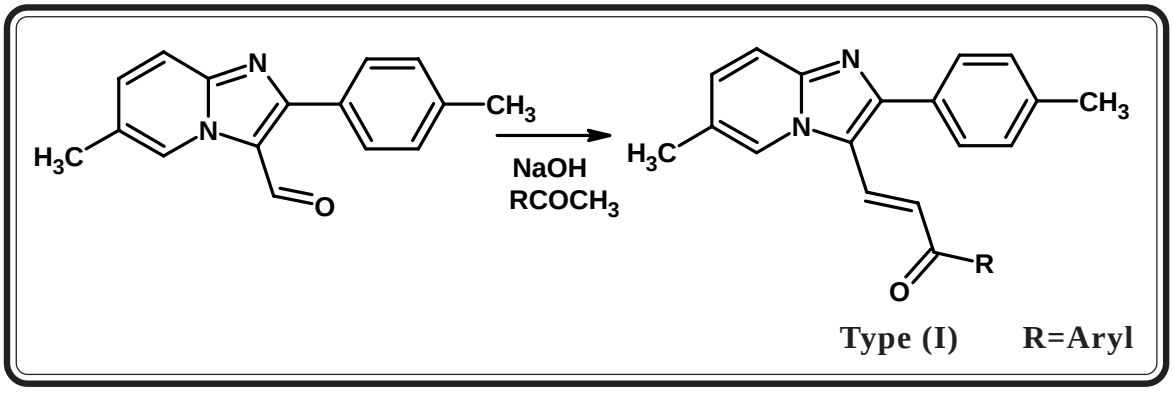
SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINES

SECTION-III : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-ARYL-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO [1,2-*a*]PYRIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ARYL-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONES

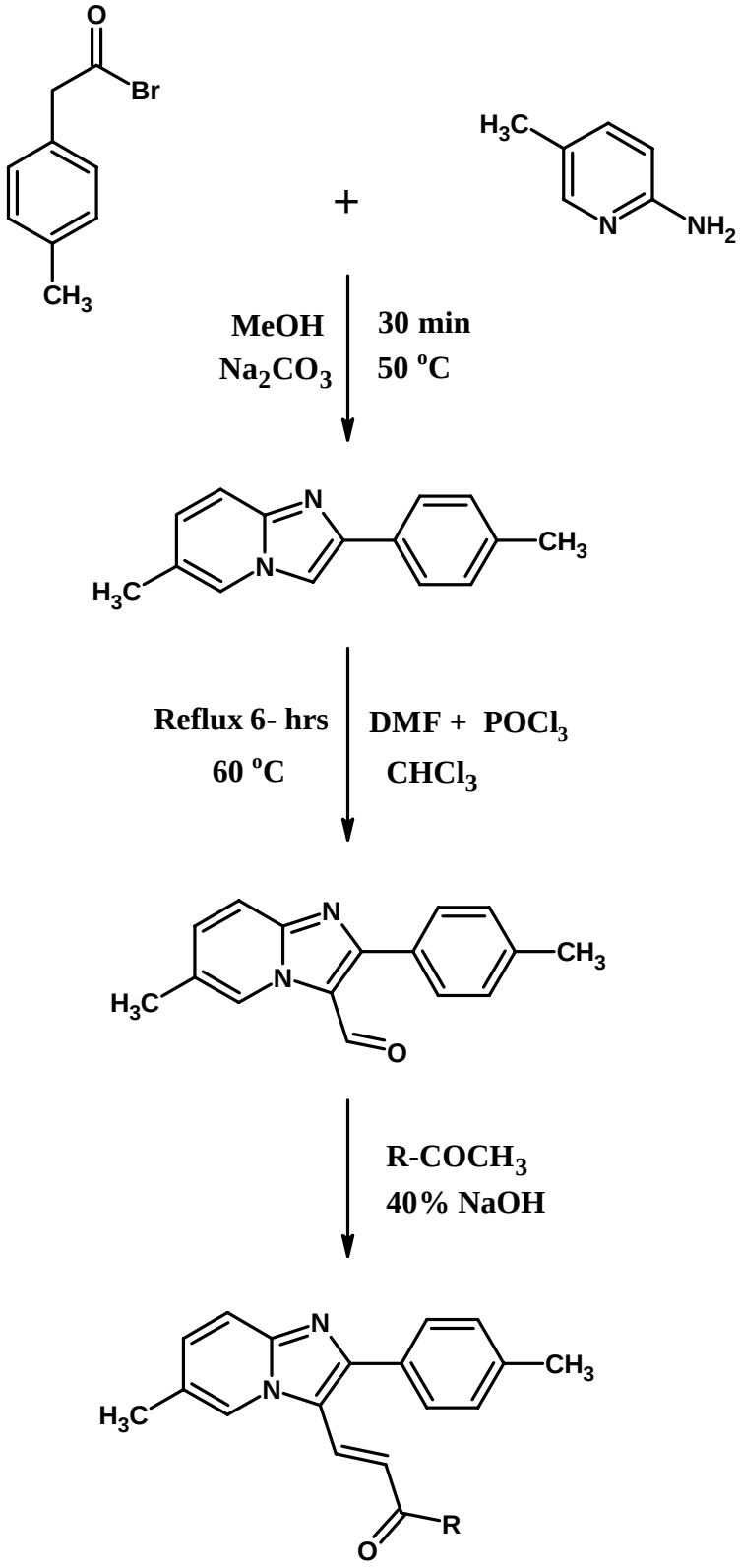
With the biodynamic activities of chalcones and it is a good synthon for various heterocyclic rings, the interest has been focussed on the synthesis of new chalcones. With a view to obtain compounds having better therapeutic activity, we have synthesized 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridin-3-yl]prop-2-ene-1-ones type-(I) by the condensation of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde with various aromatic ketones in the presence of NaOH.



The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR spectroscopy and further supported by Mass spectrometry.

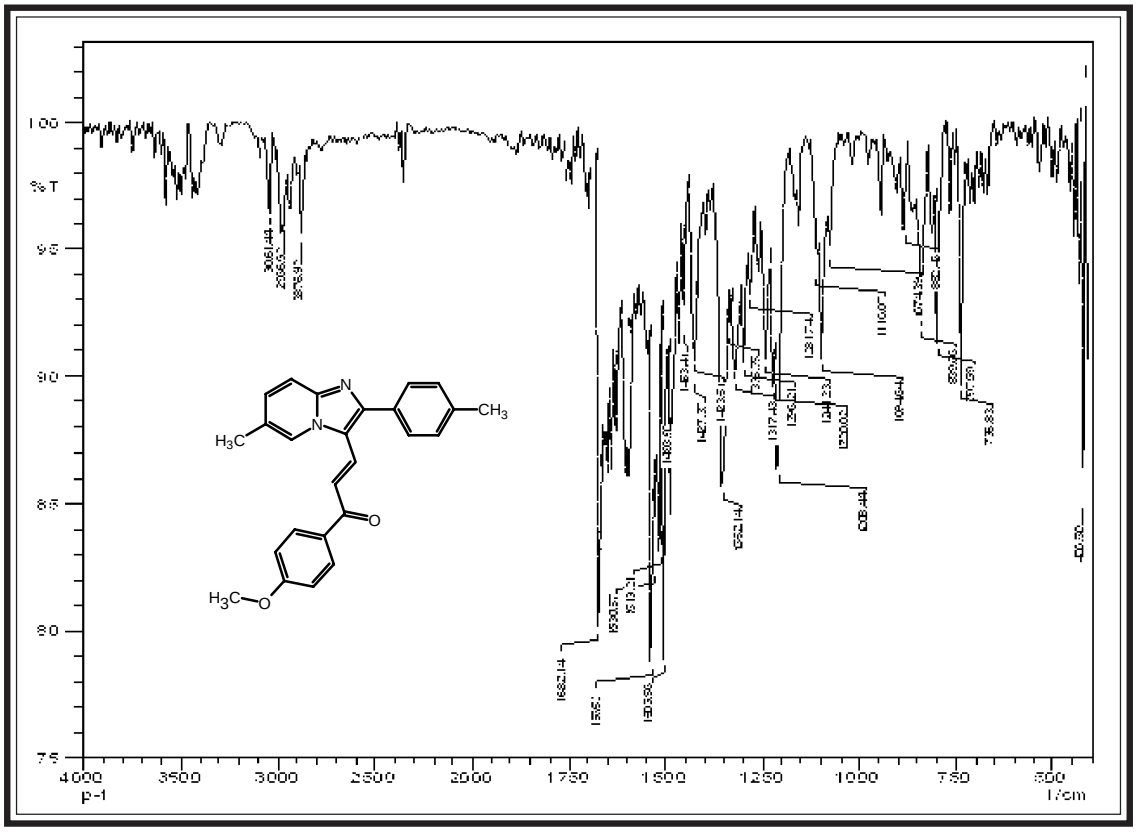
All the compounds have been screened for their *in vitro* biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

REACTION SCHEME



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

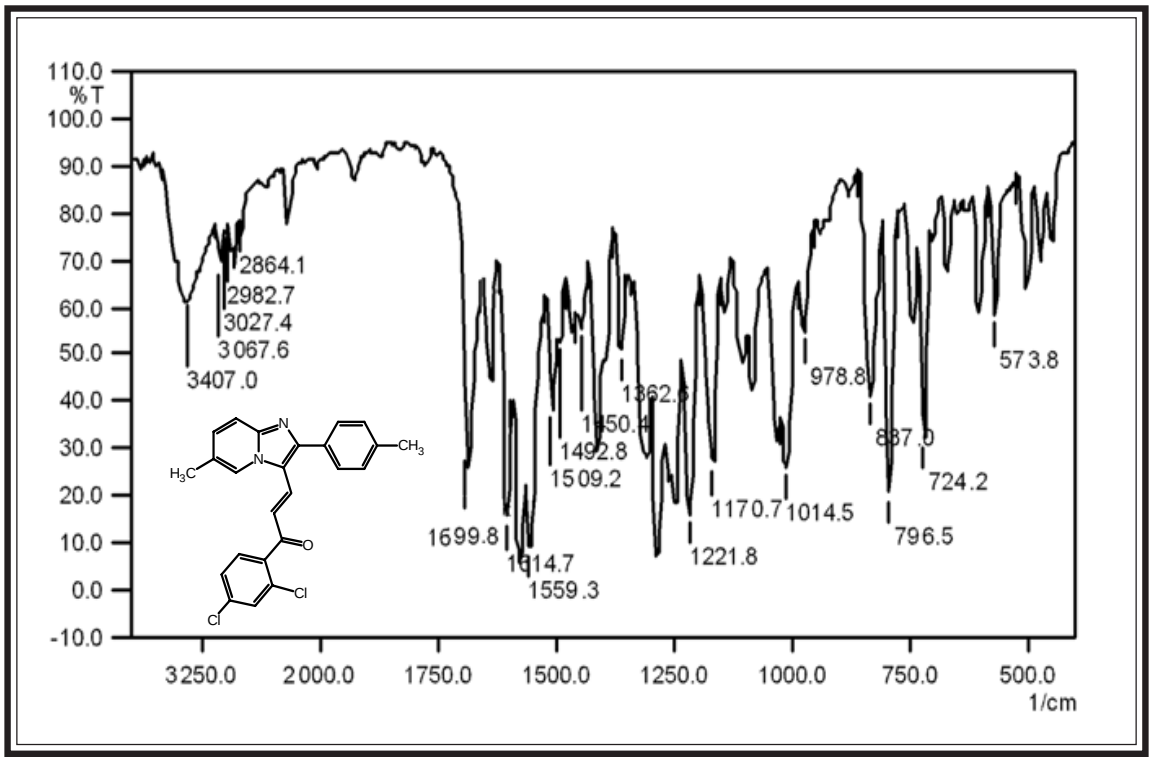
IR SPECTRAL STUDIES OF 1-(4-METHOXYPHENYL)-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym)	2966	2975-2950	189
$-CH_3$	C-H str. (sym)	2876	2880-2860	,,
	C-H i.p.def.(asym)	1453	1470-1435	,,
	C-H o.o.p.def(sym)	1352	1390-1370	,,
Aromatic	C-H str.	3061	3090-3030	190
	C=C str.	1503	1540-1480	,,
Imidazo[1,2-a]	C=N str.	1610	1612-1593	,,
pyridine	C-N str.	1110	1220-1020	,,
α,β-unsatur.	C=O str.	1682	1700-1640	189
ketone				
Vinyl	C=C str.	1536	1580-1550	,,

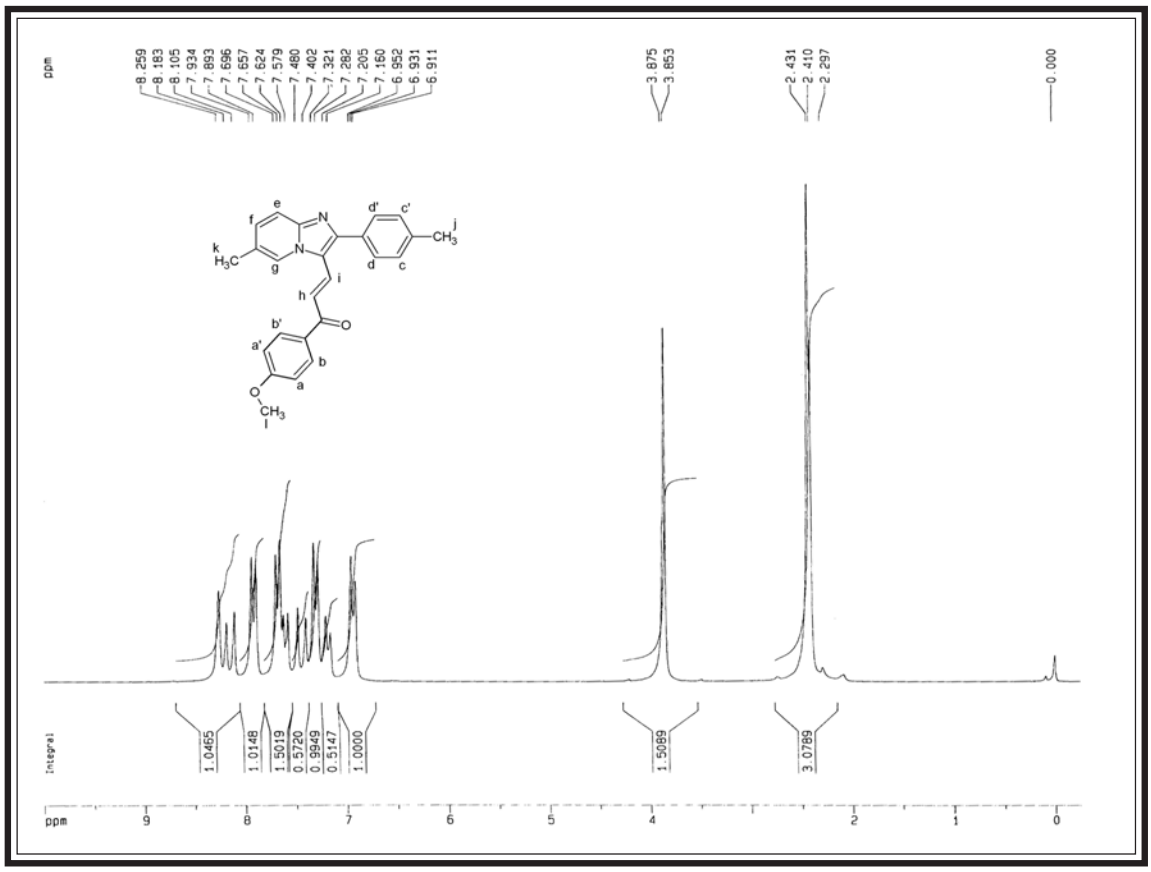
IR SPECTRAL STUDIES OF 1-(2,4-DICHLOROPHENYL)-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2982	2975-2950	189
$-CH_3$	C-H str. (sym.)	2864	2880-2860	,,
	C-H i.p.def. (asym.)	1450	1470-1435	,,
	C-H o.o.p. def. (sym.)	1362	1390-1370	,,
Aromatic	C-H str.	3067	3090-3030	190
	C=C str.	1509	1540-1480	,,
Imidazo[1,2-a]	C=N str.	1614	1612-1593	,,
pyridine	C-N str.	1170	1220-1020	,,
α,β-unsaturated	C=O str.	1699	1700-1640	189
ketone				
Vinyl	C=C str.	1559	1580-1550	,,
	C=C-H str.	3017	3050-3000	,,

NMR SPECTRAL STUDIES OF 1-(4-METHOXYPHENYL)-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONE

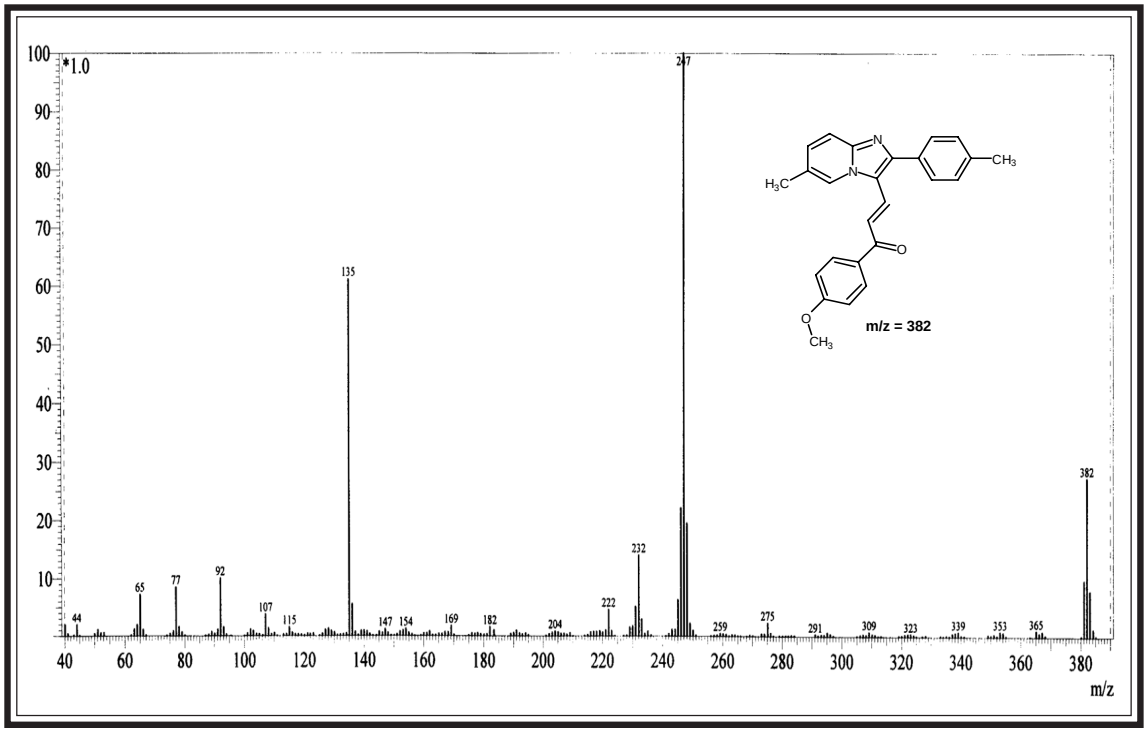


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

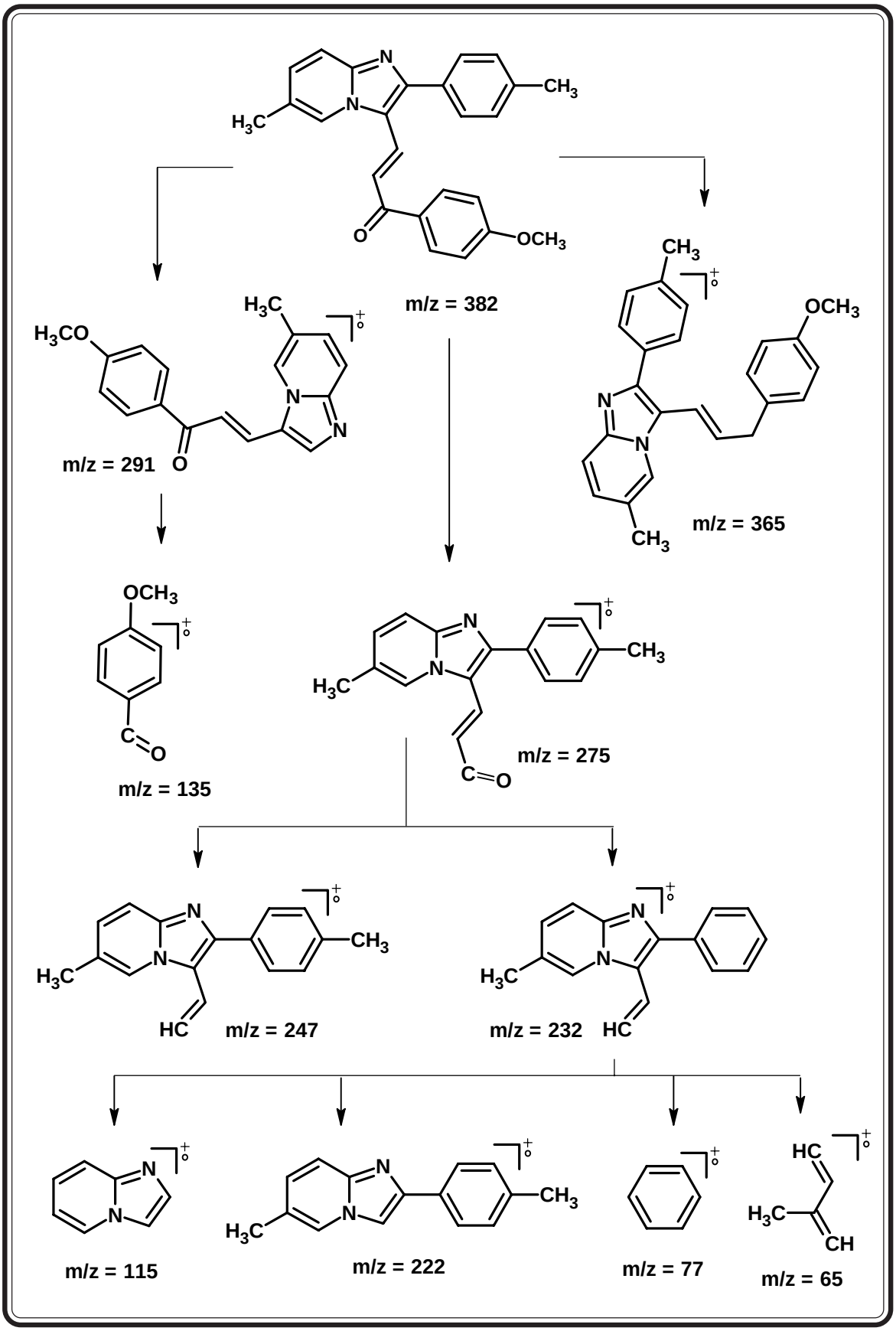
Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.41	3H	singlet	Ar-CH_3(j)	-
2	2.43	3H	singlet	Ar-CH_3(k)	-
3	3.85	3H	singlet	Ar-OCH_3(l)	-
4	6.91-6.95	2H	doublet	Ar-H(a-a')	8.2
5	7.16-7.20	1H	doublet	Ar-H(f)	9.0
6	7.28-7.32	2H	dd	Ar-H(c-c')	7.8
7	7.40-7.48	1H	doublet	CH=CH(h)	15.6
8	7.57-7.62	1H	doublet	Ar-H(e)	9.0
9	7.65-7.69	2H	doublet	Ar-H(d-d')	7.8
10	7.89-7.93	2H	doublet	Ar-H(b-b')	8.2
11	8.10-8.18	1H	doublet	CH=CH(i)	15.6
12	8.25	1H	singlet	Ar-H(g)	-

EXPANDED AROMATIC REGION

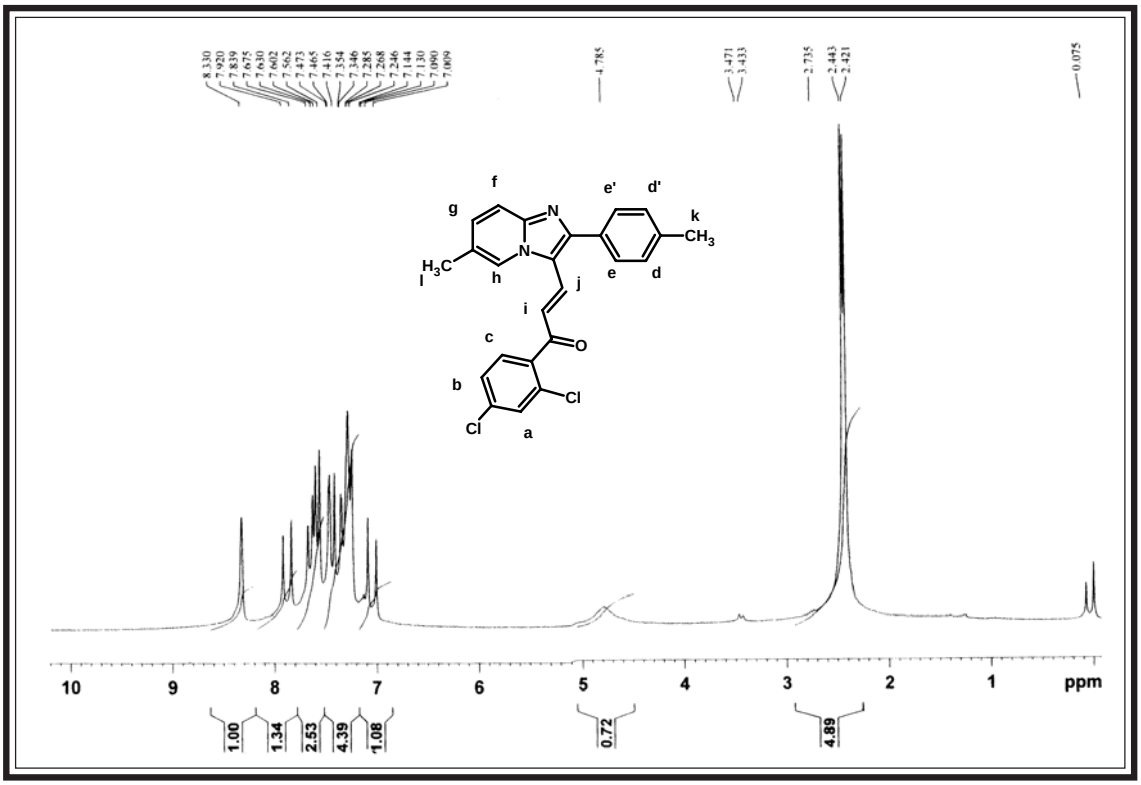
MASS SPECTRAL STUDIES OF 1-(4-METHOXYPHENYL)-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONE



MASS FRAGMENTATION



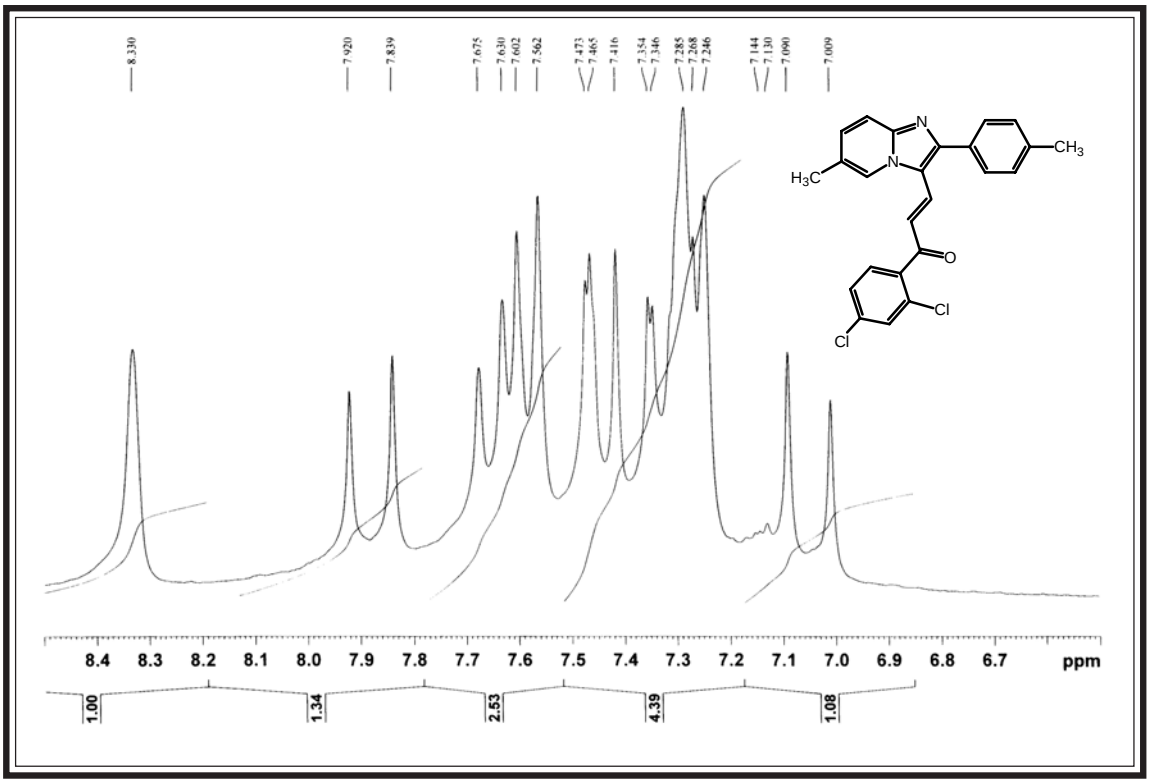
NMR SPECTRAL STUDIES OF 1-(2,4-DICHLOROPHENYL)-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONE



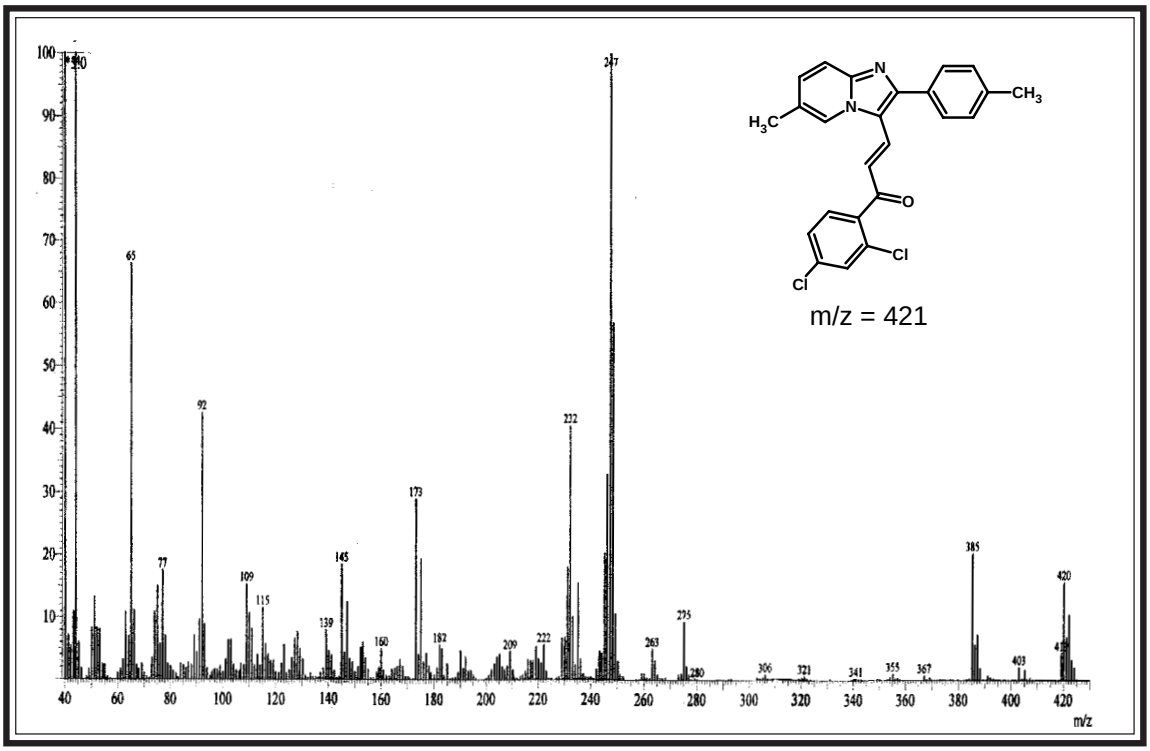
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.42	3H	singlet	Ar-CH_3(k)	-
2	2.44	3H	singlet	Ar-CH_3(l)	-
3	7.00-7.09	1H	doublet	CH=CH(i)	16.2
4	7.24-7.28	2H	doublet	Ar-H(d-d')	7.8
5	7.26-7.28	1H	doublet	Ar-H(g)	-
6	7.34-7.35	1H	doublet	Ar-H(c)	-
7	7.41-7.46	1H	doublet	Ar-H(f)	9.2
8	7.46-7.47	1H	doublet	Ar-H(b)	-
9	7.56-7.60	2H	doublet	Ar-H(e-e')	8.0
10	7.63-7.67	1H	doublet	Ar-H(a)	-
11	7.83-7.92	1H	doublet	CH=CH(j)	16.2
12	8.23	1H	singlet	Ar-H(h)	-

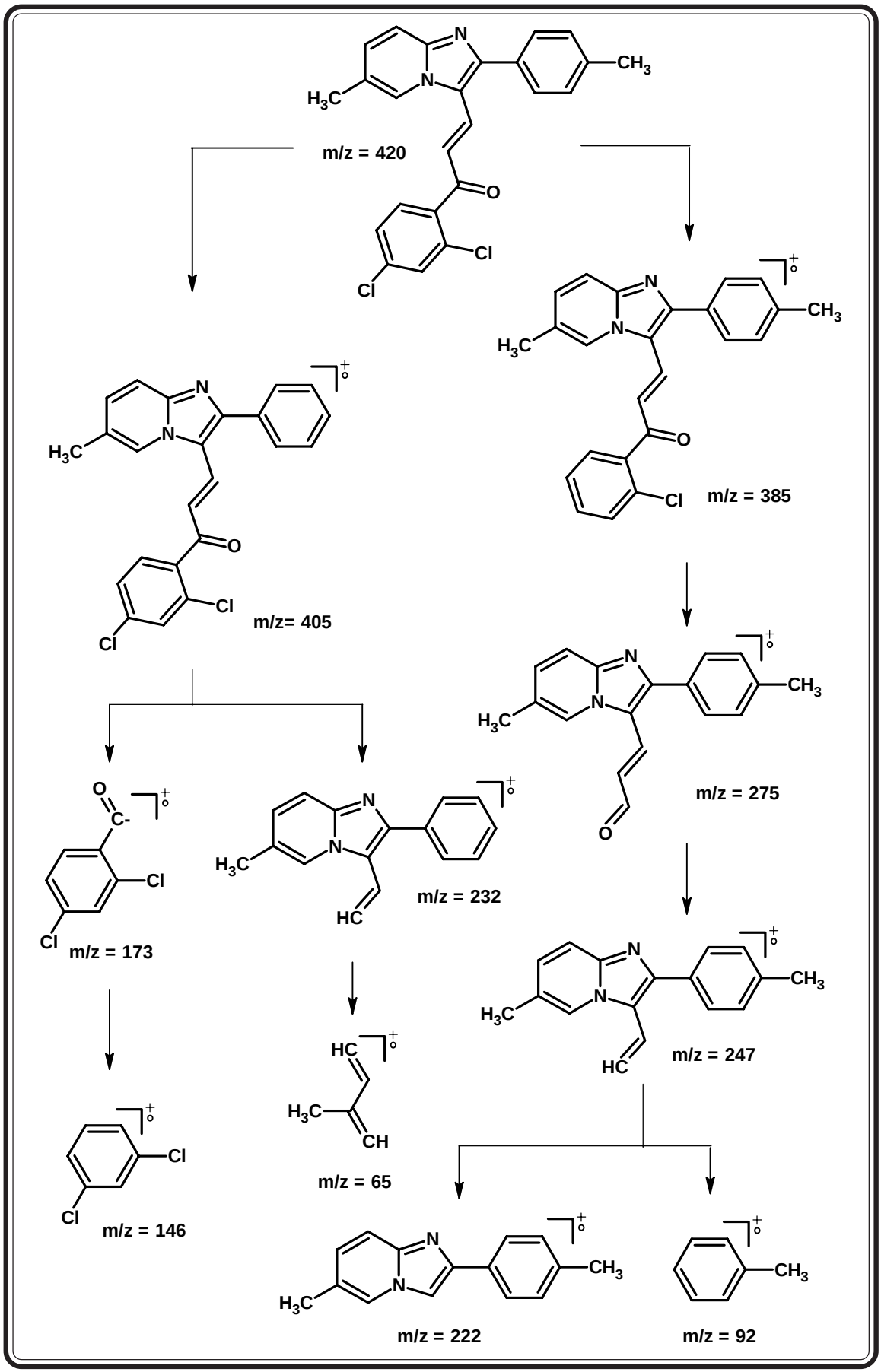
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF 1-(2,4-DICHLOROPHENYL)-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONE



MASS FRAGMENTATION



MICROBIOLOGICAL SCREENING

Method	:	Cup-Plate[188]
Gram positive bacteria	:	***Staphylococcus aureus & Bacillus subtilis***
Gram negative bacteria	:	***Pseudomonas aeruginosa & E. coli***
Fungi	:	***Aspergillus niger***
Concentration	:	40µg
Solvent	:	Dimethyl sulfoxide (DMSO)
Standard drugs	:	Amoxicillin, Benzoyl Penicillin,Ciprofloxacin, Erythromycin, Griseofulvin.

The antimicrobial activity was compared with standard drugs as mentioned above. The zone of inhibition was measured in millimeter.

ANTIMICROBIAL ACTIVITY

The purified products were screened for their antimicrobial activity using cup-plate[188] agar diffusion method. The control was with 0.04ml (40µg) of sample in DMSO. In cause of antibacterial activity, the plates were incubated at 37^{o}C for 24 hrs and for antifungal activity the plates were incubated at 30 ^{o}C for 48 hrs.

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ARYL-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

Align 1.0 lit 4/N RBF equiped with over head stirrer with condensor. Charged 100ml methanol and 21.3g (0.1 mol) 4-Methylphenyl acetyl bromide and then charged 11.9g (0.11mol) 5-Methyl-2-amino pyridine at room temperature stirr till clear solution obtained then lot wise 5.9g (0.055mol) Na_2CO_3 was added at room temperature. After complition of addition heated at 50 ^oC for 30 min then checked TLC. The reaction mixture was allowed to cool to room temperature and poured into 1.0 lit water. The formed solid was collected by filtration, washed with water, dried and crystallized from the isopropyl alcohol. Yield 86%, m.p. 209 ^oC.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde :

Align 2.0 lit 4/N RBF equiped with over head stirrer with condensor on water bath. Charged 84ml DMF and 1.0 lit $CHCl_3$ into RBF. It was cooled at 0 - 5 ^oC temperature. Slowly added 165ml $POCl_3$ within 1.0 h. During addition the exothermicity was controlled. Temperature raised at 10-15 ^oC and stirred for 30 minutes. 50g (0.225 mol) of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine was added slowly, temp raises, refluxed for 6 hrs. $CHCl_3$ was removed by vacuum distillation and reaction mass cooled at room temperature, poured into 2.0 lit ice cold water. Neutral pH adjusted bellow room temperature with the help of mild coustic solution. The solid mass was collected by filtration, washed with water, dried and crystallized from the methanol. Yield 80%, m.p. 152 ^oC.

[C] Synthesis of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde 2.5g (0.01mol) was dissolved in 25 ml methanol at room temperature. p-Methoxy acetophenone 1.40g (0.01mol) and 0.2 ml 40% sodium hydroxide solution was added. Stirred the content at room temperature for 24 hrs then filtered it and washed with chilled methanol. Yield 76 %, m. p. 200 ^{o}C, Elemental Analysis Calcd for $C_{25}H_{22}N_2O_2$ Requires : C-78.51%, H-5.80%, N-7.32%, Found : C-78.40%, H-5.72%, O-7.35%.

[D] Synthesis of 1-(2,4-Dichlorophenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde 2.5g (0.01mol) was dissolved in 25 ml methanol at room temperature and stirred till clear solution obtained. 2,4-Dichloro acetophenone 1.9 gm (0.01mol) and 0.2 ml 40% sodium hydroxide solution was added. Stirred the content at room temperature for 24 hrs then filtered it and washed with chilled methanol. Yield 68 %, m.p.205 ^{o}C, Elemental Analalysis Calcd for $C_{24}H_{18}Cl_2N_2O$ Requires : C-68.42%, H-4.31%, N-6.65%, Found : C-68.40%, H-4.12%, N-6.50 %.

Similarly, other 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones compounds were prepared. The physical data are recorded in table.01

[E] Biological screening of 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones :

(a) Antibacterial activity :

The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24hrs old subcultures of *Bacillus subtilis, Staphylococcus aureus, E.coli, Pseudomonas aeruginosa* in separate conical flasks at 35-40 ^{o}C and mixed well by gentle shaking. About 25 ml content of the flask was

poured and evenly spreaded in a sterilized petridish (13 cm diameter) and allowed to set for 2 hrs. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40µg) solution of sample in DMSO. The plates were incubated at 37°C for 24 hrs and the control was also maintained with 0.04ml of DMSO in a similar manner and the zone of inhibition of the bacterial growth were measured in millimeter and recorded in graphical chart no.1.

(b) Antifungal activity :

Aspergillus niger was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on sabouraud's agar medium. Sterilized sabouraud's agar medium was inoculated with 72 hrs old 0.5ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a sterilized petridish (13cm diameter) and allowed to set for 2 hrs. The cups (10mm diameter) were punched in petridish and loaded with 0.04ml (40µg) of solution of sample in DMSO. The plates were incubated at 30 °C for 48 hrs. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled up with solvent, which acts as control. The zones of inhibition of test solutions are recorded in graphical chart no.01.

Conclusion :

Antibacterial activity

The screening data indicated that among chalcone derivatives tested compounds **1b,1f,1j,1l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **1b,1c,1g,1k** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **1a,1e,1g,1h** and **1l** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

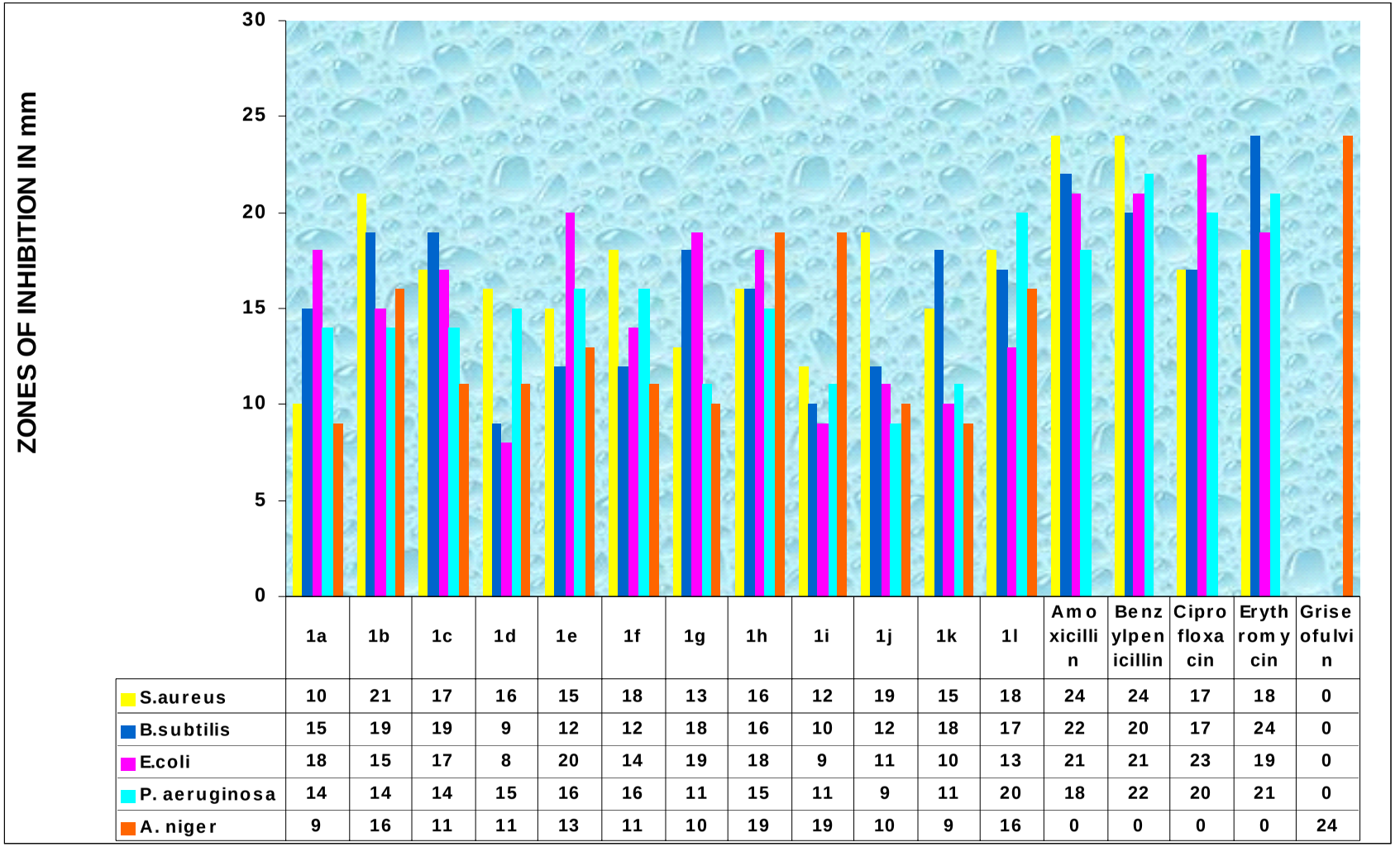
The screening data indicated that among chalcone derivatives tested compounds **1h,1i** showed greater degree of antifungal activity against *A.niger.*

TABLE-01 : PHYSICAL CONSTANTS OF 1-ARYL-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
1a	C_6H_5-	$C_{24}H_{20}N_2O$	352	178	75	7.75	7.71	0.48	S_1
1b	4-Cl-C_6H_4-	$C_{24}H_{19}ClN_2O$	386.5	172	72	7.24	7.28	0.50	S_1
1c	2,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{18}Cl_2N_2O$	421	205	68	6.65	6.54	0.54	S_2
1d	4-NO_2-C_6H_4-	$C_{24}H_{19}N_3O_3$	397	208	73	10.57	10.55	0.44	S_1
1e	4-OCH_3-C_6H_4-	$C_{25}H_{22}N_2O_2$	382	200	76	7.32	7.29	0.56	S_2
1f	4-CH_3-C_6H_4-	$C_{25}H_{22}N_2O$	366	196	78	7.65	7.60	0.55	S_2
1g	4-OH-3-OCH_3-C_6H_3-	$C_{25}H_{22}N_2O_3$	398	148	61	7.03	7.08	0.52	S_2
1h	4-Br-C_6H_4-	$C_{24}H_{19}BrN_2O$	431	175	82	6.49	6.42	0.46	S_1
1i	2-OH-C_6H_4-	$C_{24}H_{20}N_2O_2$	368	135	50	7.60	7.68	0.47	S_2
1j	4-OH-C_6H_4-	$C_{24}H_{20}N_2O_2$	368	145	78	7.60	7.58	0.49	S_1
1k	4-NH_2-C_6H_4-	$C_{24}H_{21}N_3O$	367	180	70	11.44	11.42	0.54	S_1
1l	2-C_4H_3S-	$C_{24}H_{18}N_2OS$	358	248	77	7.82	7.78	0.48	S_2

S_1 Toluene : Ethyl acetate (8 : 2), S_2 Toluene : Ethyl acetate (6 : 4)

Graphical Chart No. 01 : ANTIMICROBIAL ACTIVITY OF 1-ARYL-3-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*] PYRIDIN-3-YL]PROP-2-ENE-1-ONES

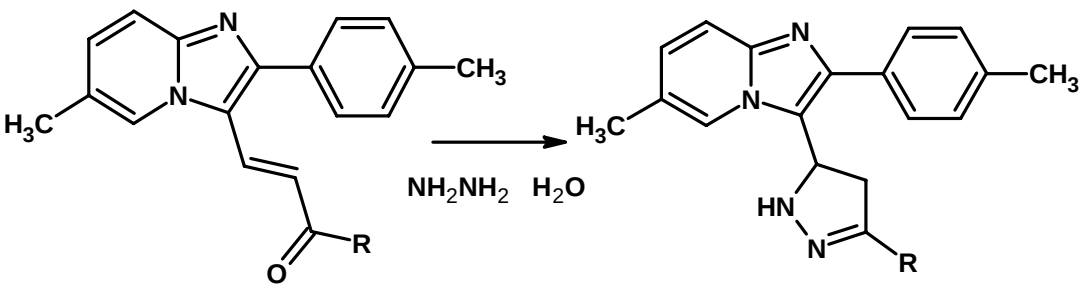


	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	10	21	17	16	15	18	13	16	12	19	15	18	24	24	17	18	0
B.subtilis	15	19	19	9	12	12	18	16	10	12	18	17	22	20	17	24	0
E.coli	18	15	17	8	20	14	19	18	9	11	10	13	21	21	23	19	0
P. aeruginosa	14	14	14	15	16	16	11	15	11	9	11	20	18	22	20	21	0
A. niger	9	16	11	11	13	11	10	19	19	10	9	16	0	0	0	0	24

SECTION - II

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINES

The broad spectrums of pharmacological properties have been demonstrated by the pyrazoline nucleus. Inspired by these facts, new pyrazoline derivatives of type (II) have been investigated. 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones type (I) treated with hydrazine hydrate in methanol to afford 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridines derivatives of type (II).

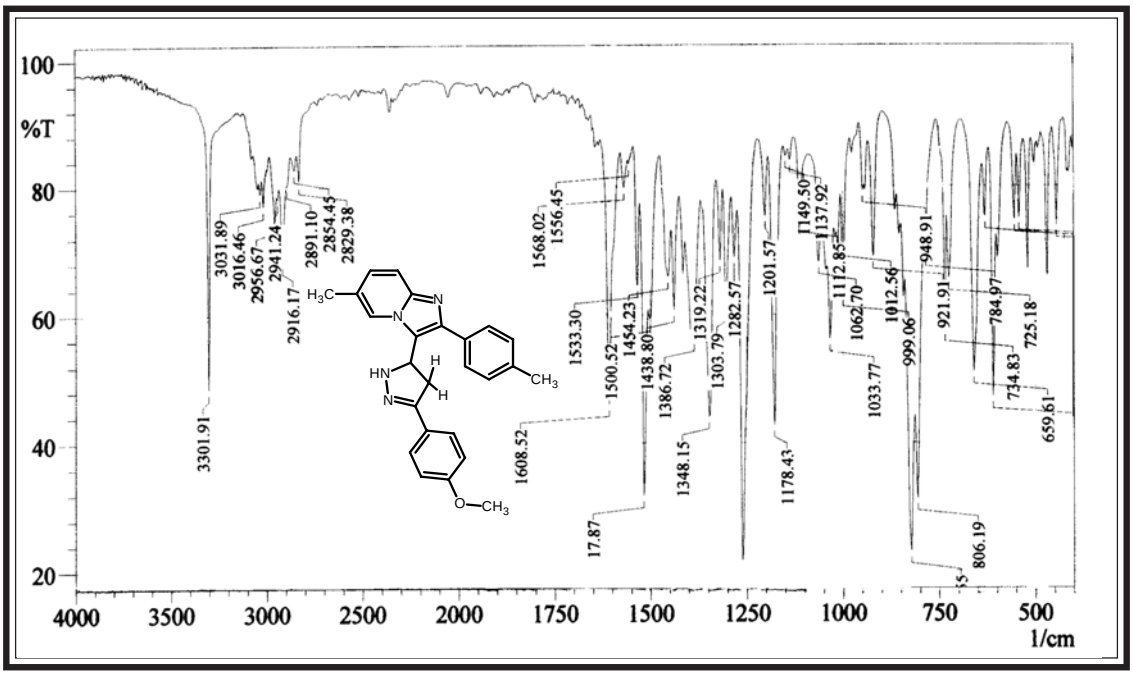


Type (I) **R = Aryl** **Type (II)**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

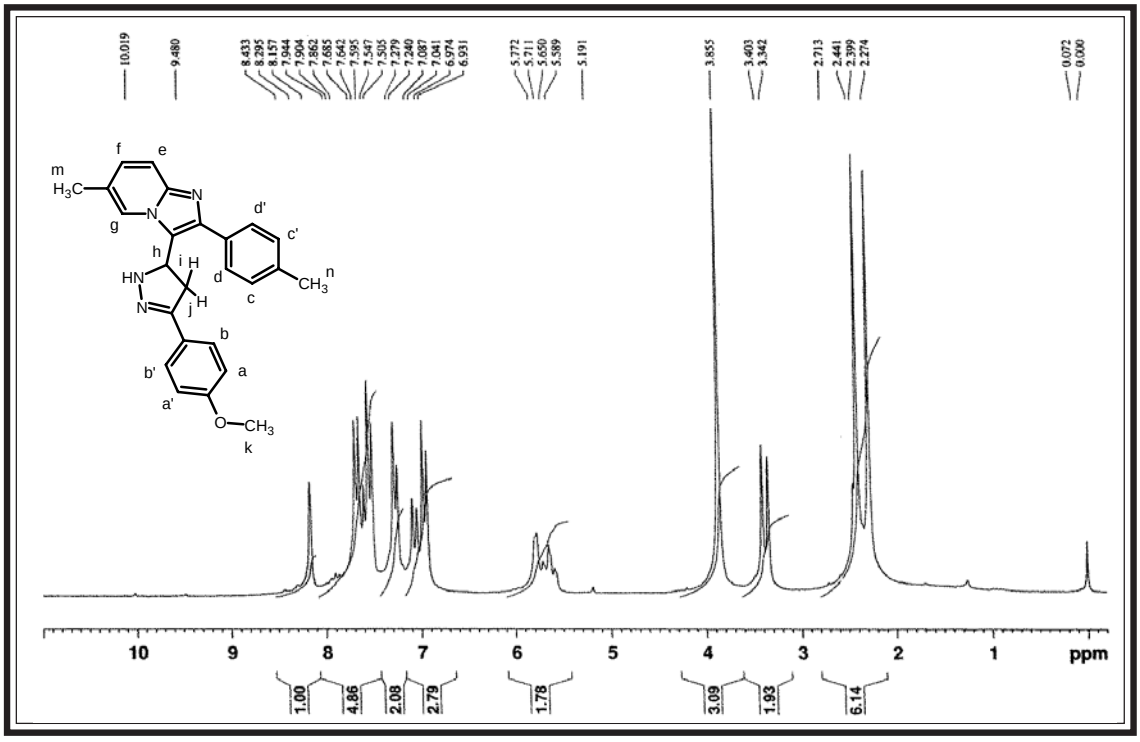
IR SPECTRAL STUDIES OF 3-[3-(4-METHOXYPHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2956	2975-2950	189
$-CH_3$	C-H str. (sym.)	2854	2880-2860	,,
	C-H def. (asym.)	1454	1470-1435	,,
Aromatic	C-H str.	3016	3090-3030	190
	C=C str.	1517	1540-1480	,,
	C-H i.p. (def.)	1062	1125-1090	,,
		820	835-810	,,
Methoxy	C-O str.	1260	1260-1200	,,
Pyrazoline	C=N str.	1608	1612-1593	,,
	N-H str.	3301	3400-3200	,,
Imidazo[1,2-a]	C=N str.	1568	1612-1593	,,
pyridine	C-N str.	1033	1220-1020	,,

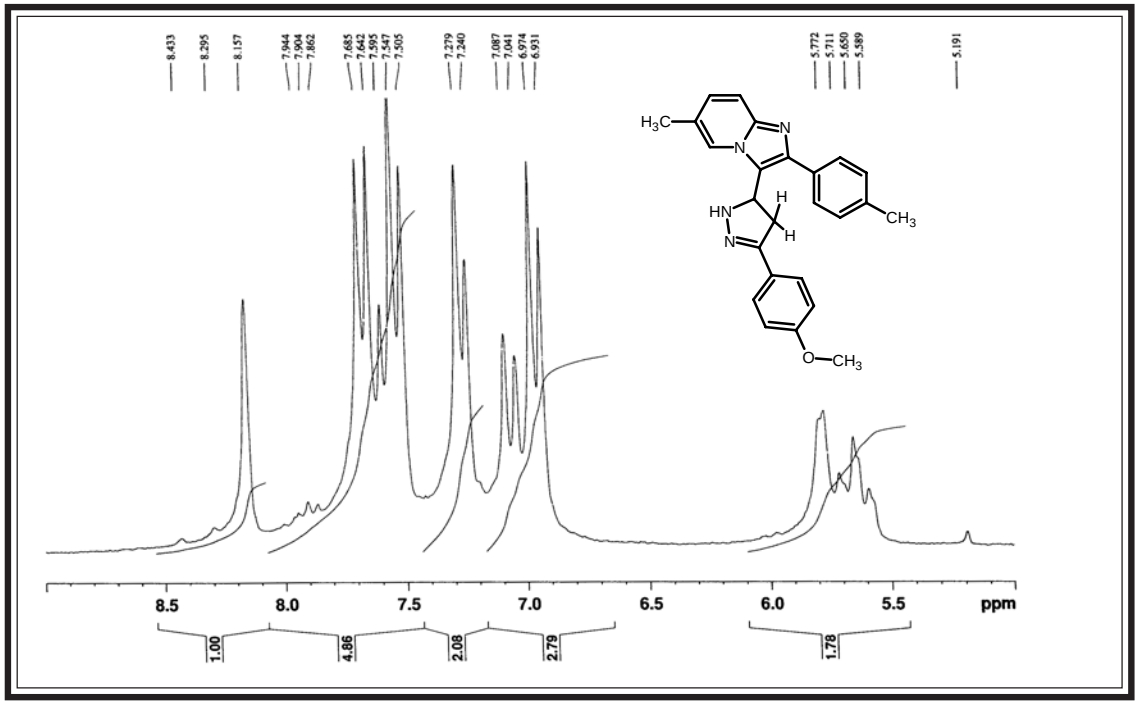
NMR SPECTRAL STUDIES OF 3-[3-(4-METHOXYPHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINE



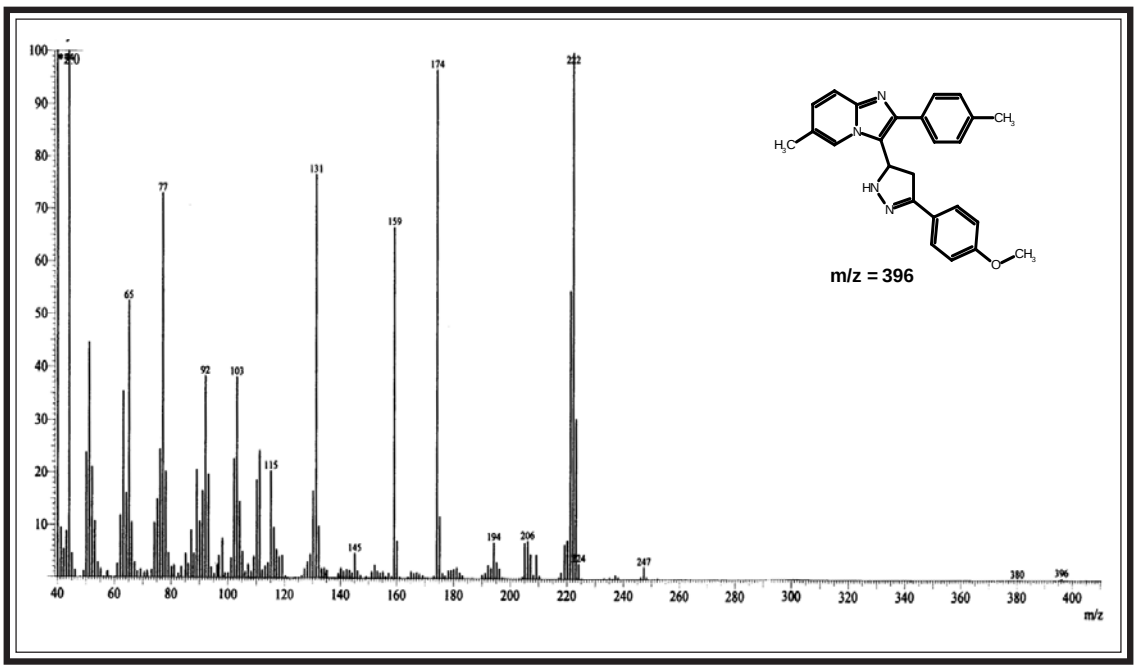
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	SignalPosition (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.27	3H	singlet	Ar-CH_3(n)	-
2	2.39	3H	singlet	Ar-CH_3(m)	-
3	3.34-3.40	2H	doublet	Ar-H(i-j)	12.2
4	3.85	3H	singlet	Ar-OCH_3(k)	-
5	5.58-5.77	1H	d.doublet	Ar-H(h)	12.2
6	6.93-6.97	2H	doublet	Ar-H(a-a')	8.6
7	7.04-7.08	1H	doublet	Ar-H(f)	9.2
8	7.24-7.27	2H	doublet	Ar-H(c-c')	7.8
9	7.50-7.54	2H	doublet	Ar-H(d-d')	8.4
10	7.54-7.59	1H	doublet	Ar-H(e)	9.6
11	7.64-7.68	2H	doublet	Ar-H(b-b')	8.6
12	8.29	1H	singlet	Ar-H(g)	-

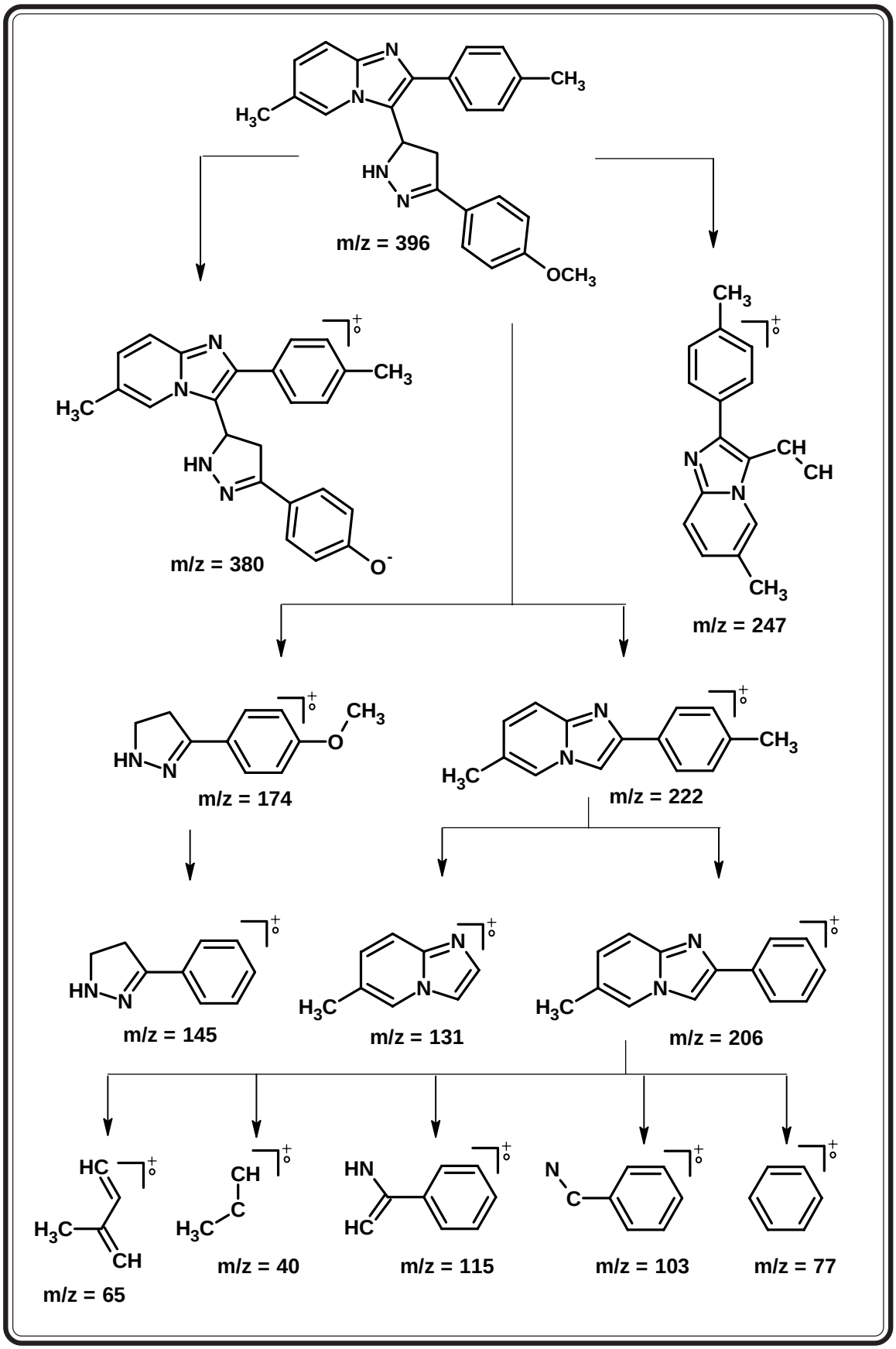
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF 3-[3-(4-METHOXYPHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-2-(4-METHYLEPHENYL)IMIDAZO[1,2-*a*]PYRIDINES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See(A), part-I, section-I (A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde:

See(A), part-I, section-I (B), page no.046.

[C] Synthesis of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

See(A), part-I, section-I (C), page no.047.

[D] Synthesis of 3-[3-(4-Methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]-6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

A mixture of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one 3.82 gm (0.01 mol) and hydrazine hydrate 1.0gm (0.02mol) in 25 ml methanol was stirred for 4hrs at room temperature. The reaction mass was kept overnight. Precipitated product was filtered out and recrystllized from ethanol. Yield 72 %, m.p. 204 ^{o}C, Elemental Analalysis Calculated for $C_{25}H_{24}N_4O$ Requires : C-75.73%, H-6.1%, N-14.14%, Found : C-75.64%, H-6.05%, N-14.12%.

Similarly, other 3-(3-Aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methyl phe nyl) imidazo[1,2- *a*]pyridines were prepared.The physical data are recorded in table no 02.

[E] Biological screening of 3-(3-Aryl-4,5-dihydro-1H-pyrazol-5-yl)-2-(4-methylphenyl)imidazo[1,2- a]pyridines :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.047. The zones of inhibition of test solutions are recorded in graphical chart no.02.

Conclusion :

Antibacterial activity

The screening data indicated that among simple pyrazoline derivatives tested compounds **2c**, **2f**, **2l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **2b, 2c, 2k** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **2a, 2e, 2g, 2k, 2l** and **2d, 2h** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

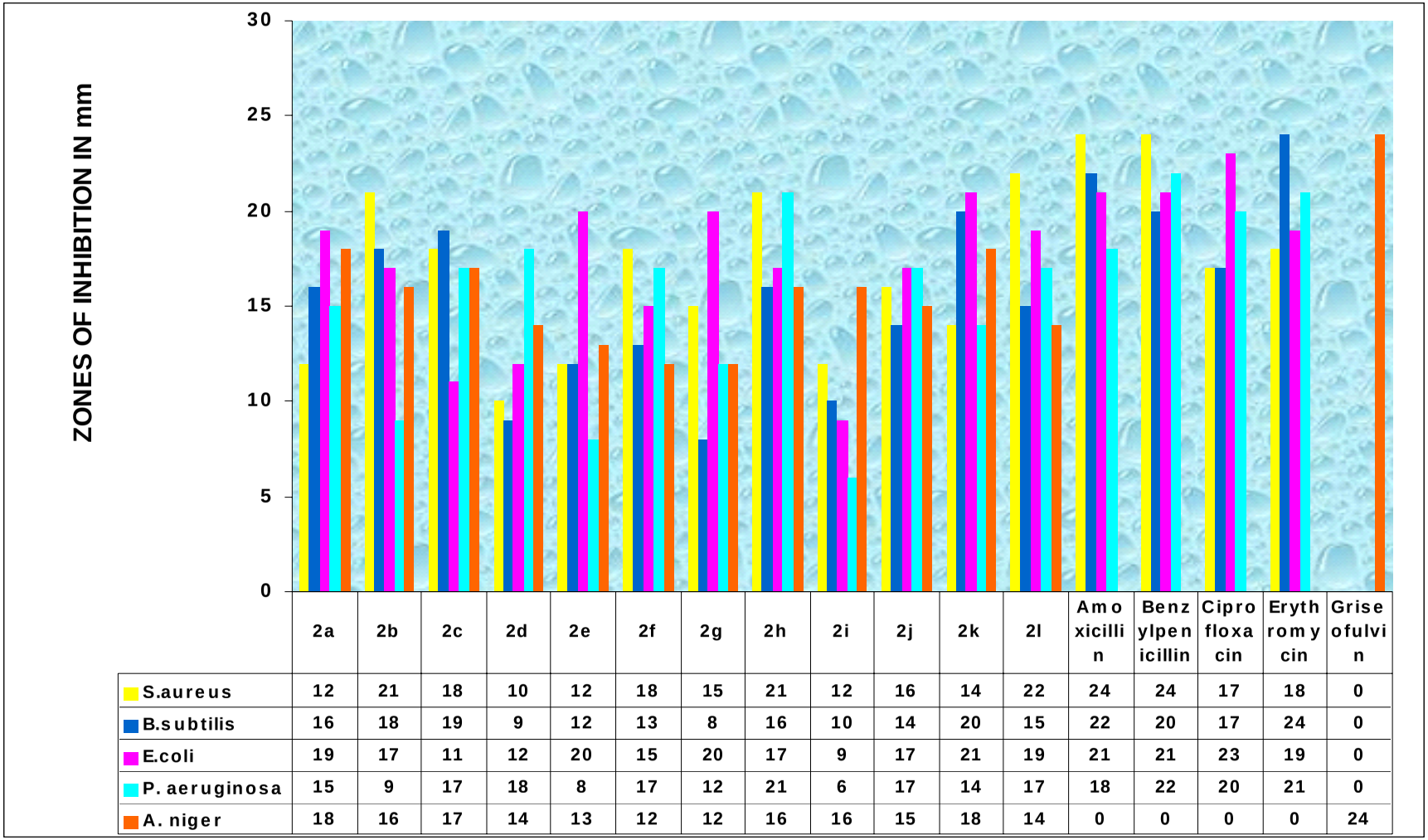
The screening data indicated that among simple pyrazoline derivatives tested compounds **2a, 2k** showed greater degree of antifungal activity against *A.niger.*

TABLE -02 : PHYSICAL CONSTANTS OF 3-(3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
2a	C_6H_5-	$C_{24}H_{22}N_4$	366	92	65	15.30	15.25	0.47	S_2
2b	4-Cl-C_6H_4-	$C_{24}H_{21}ClN_4$	400.5	194	75	13.98	13.80	0.49	S_2
2c	2,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{20}C_{l2}N_4$	435	196	72	12.87	12.96	0.57	S_1
2d	4-NO_2-C_6H_4-	$C_{24}H_{21}N_5O_2$	211	dec.200	65	17.03	17.08	0.55	S_2
2e	4-OCH_3-C_6H_4-	$C_{25}H_{24}N_4O$	396	204	72	14.14	14.12	0.60	S_2
2f	4-CH_3-C_6H_4-	$C_{25}H_{24}N_4$	380	147	68	14.73	14.68	0.50	S_1
2g	4-OH-3-OCH_3-C_6H_3-	$C_{25}H_{24}N_4O_2$	412	242	71	13.59	13.50	0.52	S_2
2h	4-Br-C_6H_4-	$C_{24}H_{21}BrN_4$	445	180	62	12.58	12.52	0.42	S_2
2i	2-OH-C_6H_4-	$C_{24}H_{22}N_4O$	382	202	75	14.65	14.62	0.49	S_1
2j	4-OH-C_6H_4-	$C_{24}H_{22}N_4O$	382	208	75	14.65	14.60	0.50	S_1
2k	4-NH_2-C_6H_4-	$C_{24}H_{23}N_5$	381	dec.186	78	16.94	16.90	0.55	S_2
2l	2-C_4H_3S-	$C_{22}H_{20}N_4S$	372	228	76	15.05	15.10	0.45	S_1

S_1 Toluene : Ethyl acetate (8 : 2), S_2 Ethyl acetate: Hexane (2 : 8)

Graphical Chart No. 02 : ANTIMICROBIAL ACTIVITY OF 3-(3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDINES

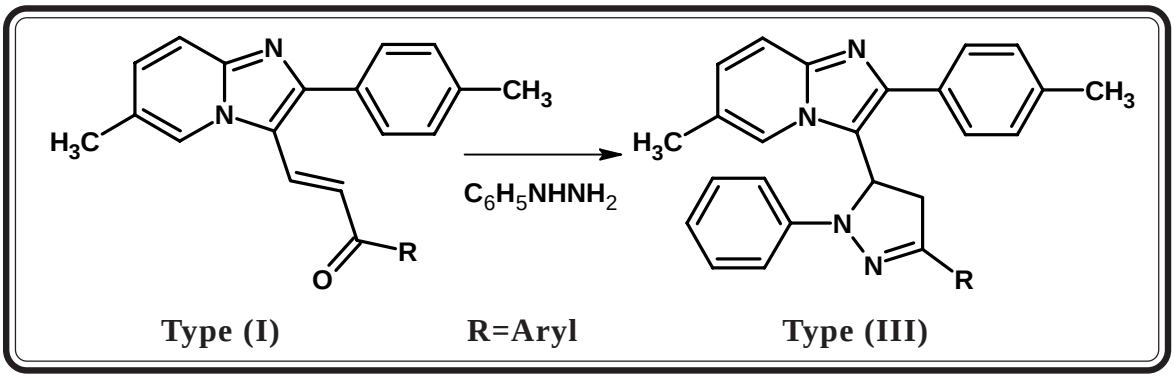


	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	12	21	18	10	12	18	15	21	12	16	14	22	24	24	17	18	0
B.subtilis	16	18	19	9	12	13	8	16	10	14	20	15	22	20	17	24	0
E.coli	19	17	11	12	20	15	20	17	9	17	21	19	21	21	23	19	0
P. aeruginosa	15	9	17	18	8	17	12	21	6	17	14	17	18	22	20	21	0
A. niger	18	16	17	14	13	12	12	16	16	15	18	14	0	0	0	0	24

SECTION - III

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-ARYL-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*]PYRIDINES

Various derivatives of phenyl pyrazoline exhibit interesting biological properties like anticancer, antiinflammatory, anticonvulsant, antipyretic, etc. With a view to prepare more potential drug value compounds, we have carried out the synthesis of phenyl pyrazoline derivatives of type-(III), which have been prepared by the condensation of chalcones of type-(I) with phenyl hydrazine in the presence of piperidine as a catalyst, which have been briefed as under.

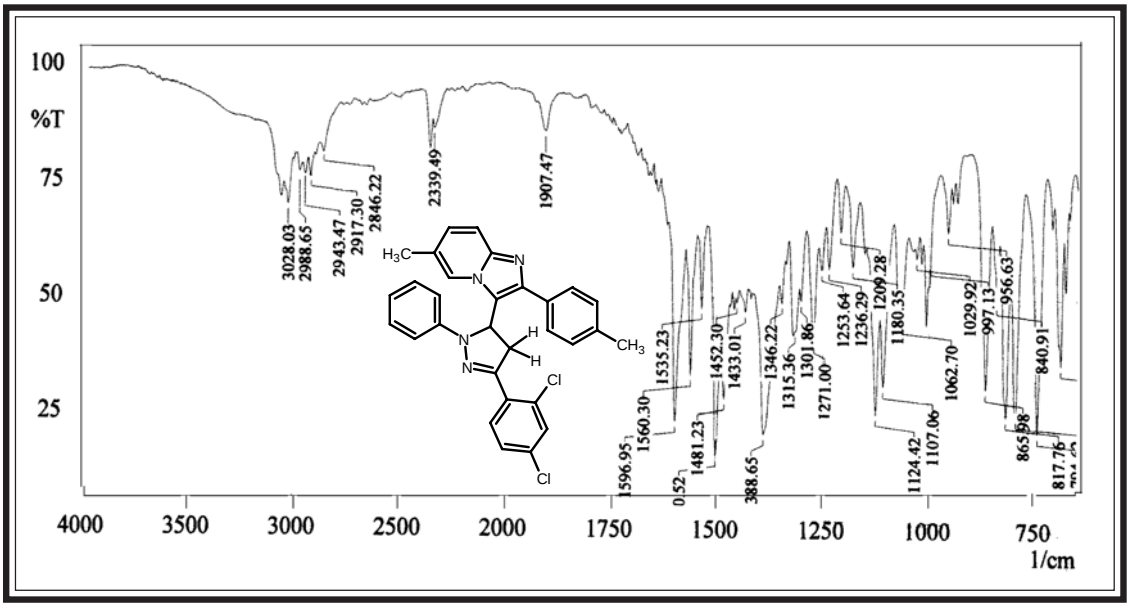


Type (I) **R=Aryl** **Type (III)**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

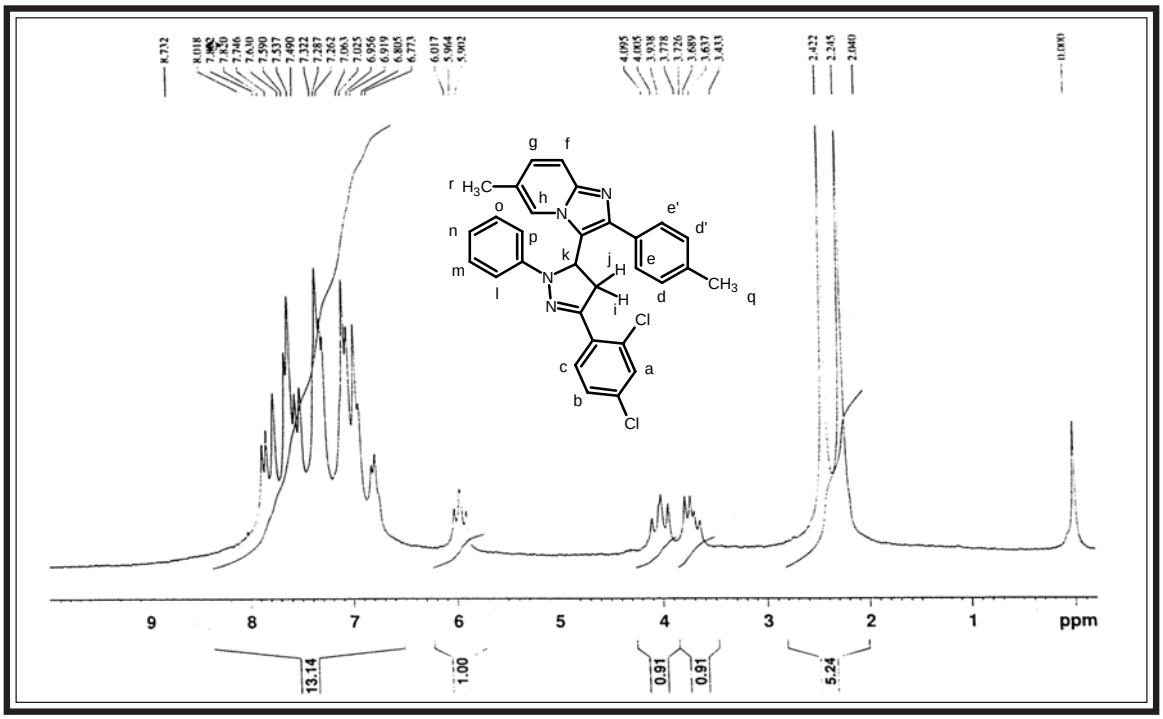
IR SPECTRAL STUDIES OF 3-[3-(2,4-DICHLOROPHENYL)-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]-6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*]PYRIDINE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2943	2975-2950	189
$-CH_3$	C-H str. (sym.)	2843	2880-2860	,,
	C-H def. (asym.)	1433	1470-1435	,,
	C-H def. (sym.)	1388	1390-1370	,,
Aromatic	C-H str.	3028	3090-3030	190
	C=C str.	1500	1540-1480	,,
	C-H i.p. (def.)	1062	1125-1090	,,
		817	835-810	,,
Halide	C-Cl str.	704	800-600	,,
Pyrazoline	C=N str.	1596	1612-1593	,,
Imidazo[1,2-a]	C=N str.	1560	1612-1593	,,
pyridine	C-N str.	1124	1220-1020	,,

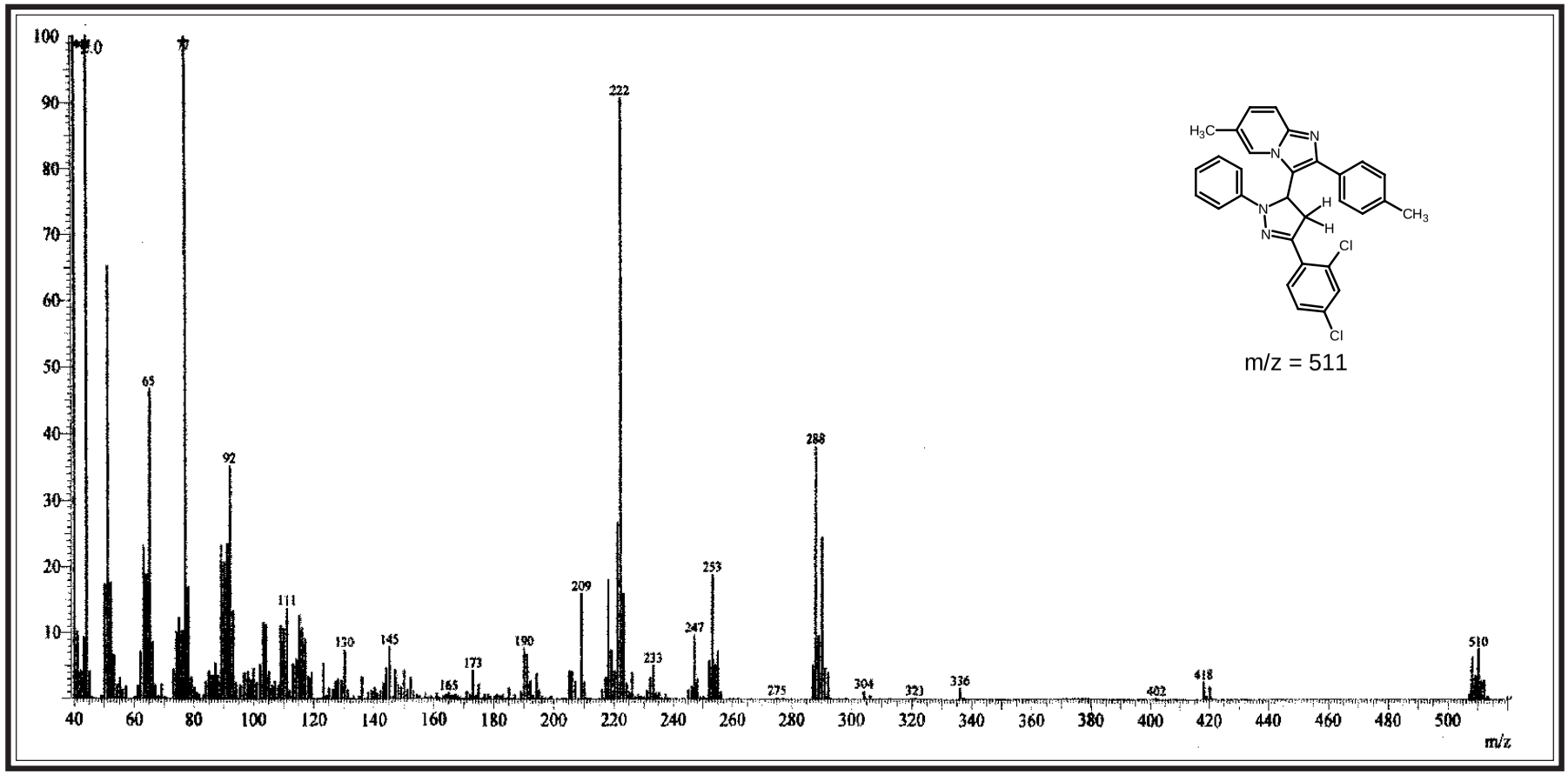
NMR SPECTRAL STUDIES OF 3-[3-(2,4-DICHLOROPHENYL)-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO [1,2-*a*]PYRIDINE



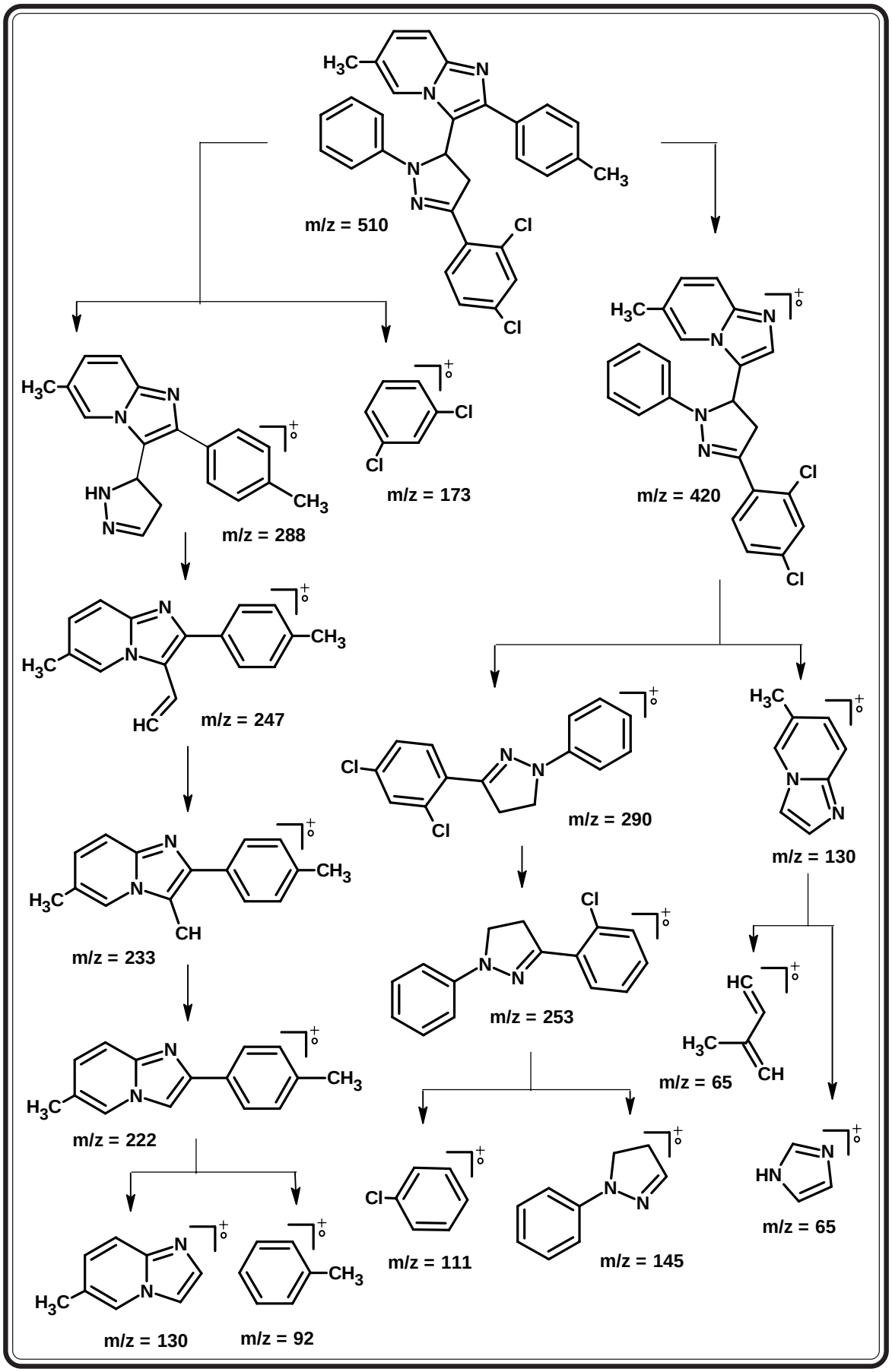
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.24	3H	singlet	Ar-CH_3(q)	-
2	2.42	3H	singlet	Ar-CH_3(r)	-
3	3.63-4.09	2H	d.doublet	Py-H(i-j)	10.4
4	5.90-5.96	1H	triplet	Ar-H(k)	-
5	6.77-6.80	1H	d.doublet	Ar-H(g)	6.4
6	6.91	1H	singlet	Ar-H(f)	-
7	6.95	1H	singlet	Ar-H(c)	-
8	7.02-7.06	2H	doublet	Ar-H(d-d')	7.6
9	7.26-7.28	1H	doublet	Ar-H(b)	5.0
10	7.32	3H	singlet	Ar-H(m,n,o)	7.0
11	7.49-7.53	1H	doublet	Ar-H(p-l)	9.4
12	7.59-7.63	2H	doublet	Ar-H(e-e')	8.0
13	7.74	1H	singlet	Ar-H(h)	-
14	7.82-7.86	1H	doublet	Ar-H(a)	8.4

MASS SPECTRAL STUDIES OF 3-[3-(2,4-DICHLOROPHENYL)-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL]-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO [1,2-*a*]PYRIDINE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3-ARYL-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL) IMIDAZO [1,2-*a*]PYRIDINES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See(A), part-I, section-I (A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde :

See(A), part-I, section-I (B), page no.046.

[C] Synthesis of 1-(2,4-Dichlorophenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

See(A), part-I, section-I (D), page no.047.

[D] Synthesis of 3-[3-(2,4-Dichlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl]-6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridine :

A mixture of 1-(2,4-Dichlorophenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one 4.21gm (0.01 mol), phenyl hydrazine 1.18gm (0.01 mol) and basic catalyst piperidine in 25ml methanol was refluxed for 28hrs. Rreaction mass was poured into chilled water. Product was filtered and dryed. it was recrystallized from ethanol. Yield 54 %, m.p.146 ^{o}C, Elemental Analysis Calculated for $C_{30}H_{24}Cl_2N_4$ Requires : C-70.45%, H-4.73%, N-10.95%, Found : C-70.34%, H-4.75%, N-10.93%.

Similarly other 3-(3-Aryl-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo [1,2-a]pyridines were prepared. The physical data are recorded in table no.03.

[E] Biological screening of 3-(3-Aryl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridines :

Antimicrobial testing was carried out as described in (A), part-I, Section-I(E), page no.047. The zones of inhibition of test solutions are recorded in graphical chart no.03.

Conclusion :

Antibacterial activity

The screening data indicated that among phenylpyrazoline derivatives tested compounds **3b**, **3h**, **3l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **3b, 3c, 3g, 3h, 3k** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **3k, 3l** and **3h** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

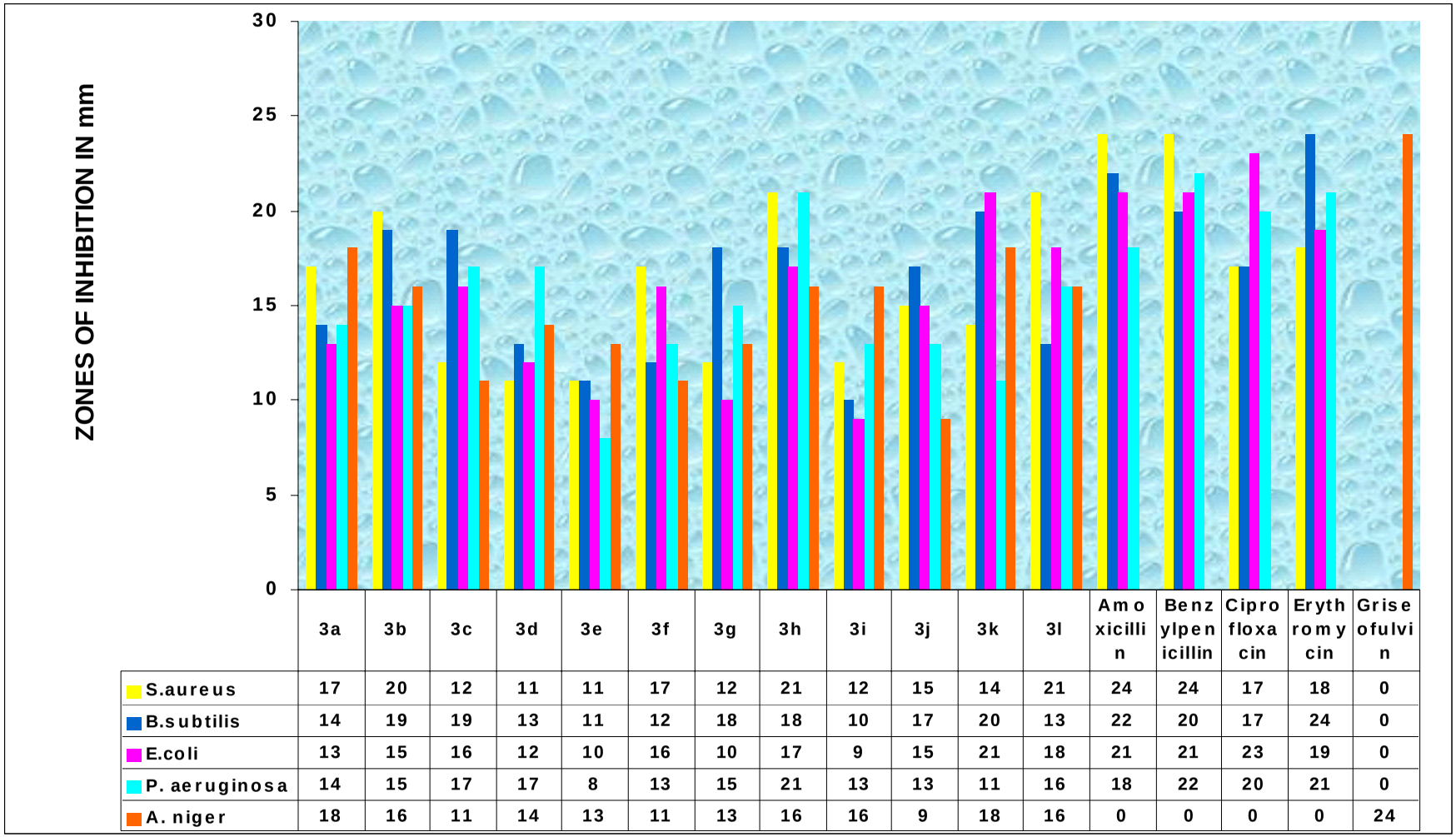
The screening data indicated that among phenylpyrazoline derivatives tested compounds **3a, 3k** showed greater degree of antifungal activity against *A.niger.*

TABLE -03 : PHYSICAL CONSTANTS OF 3-(3-ARYL-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO [1,2-*a*]PYRIDINES

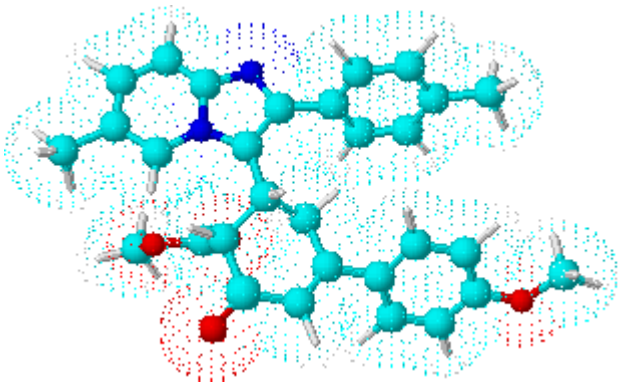
Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
3a	C_6H_5-	$C_{30}H_{26}N_4$	442	121	66	12.66	12.64	0.51	S_1
3b	4-Cl-C_6H_4-	$C_{30}H_{25}ClN_4$	476.5	151	74	11.75	11.73	0.47	S_1
3c	2,4-$(Cl)_2$-C_6H_3-	$C_{30}H_{24}C_{l2}N_4$	458	220	72	12.22	12.30	0.41	S_2
3d	4-NO_2-C_6H_4-	$C_{30}H_{25}N_5O_2$	487	225	50	14.37	14.30	0.52	S_2
3e	4-OCH_3-C_6H_4-	$C_{31}H_{28}N_4O$	472	146	54	11.86	11.79	0.54	S_1
3f	4-CH_3-C_6H_4-	$C_{31}H_{28}N_4$	456	dec.115	58	12.28	12.32	0.57	S_1
3g	4-OH-3-OCH_3-C_6H_3-	$C_{31}H_{28}N_4O_2$	488	132	62	11.47	11.44	0.51	S_2
3h	4-Br-C_6H_4-	$C_{30}H_{25}BrN_4$	521	dec.150	76	10.74	10.70	0.47	S_1
3i	2-OH-C_6H_4-	$C_{30}H_{26}N_4O$	458	90	52	12.22	12.20	0.49	S_1
3j	4-OH-C_6H_4-	$C_{30}H_{26}N_4O$	458	145	67	12.22	12.18	0.50	S_1
3k	4-NH_2-C_6H_4-	$C_{30}H_{27}N_5$	457	210	54	15.31	15.27	0.49	S_2
3l	2-C_4H_3S-	$C_{28}H_{24}N_4S$	448	140	62	12.50	12.41	0.47	S_1

S_1Ethyl acetate : Hexane (2 : 8), S_2 Toluene : Ethyl acetate (6 : 4)

Graphical Chart No. 03 : ANTIMICROBIAL ACTIVITY OF 3-(3-ARYL-1-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-5- YL)-6-METHYL-2-(4-METHYLPHENYL)IMIDAZO [1,2-*a*]PYRIDINES



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	17	20	12	11	11	17	12	21	12	15	14	21	24	24	17	18	0
B.subtilis	14	19	19	13	11	12	18	18	10	17	20	13	22	20	17	24	0
E.coli	13	15	16	12	10	16	10	17	9	15	21	18	21	21	23	19	0
P. aeruginosa	14	15	17	17	8	13	15	21	13	13	11	16	18	22	20	21	0
A. niger	18	16	11	14	13	11	13	16	16	9	18	16	0	0	0	0	24

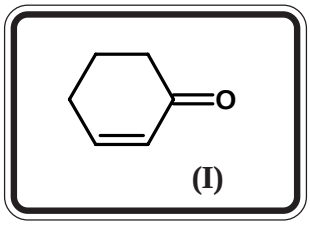


PART - II

STUDIES ON CYCLOHEXENONE

INTRODUCTION

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



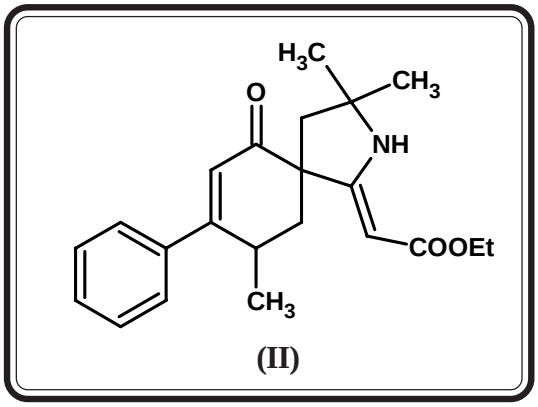
(I)

Cyclohexenone is the parent of a series of compounds which have an important role in agricultural and medicinal chemistry. Cyclohexenones can be synthesized by the treatment of α,β-unsaturated carbonyl compounds with ethyl acetoacetate in basic media. In recent years cyclohexenone derivatives have gained lot of interest because of its prominent pharmaceutical properties.

SYNTHETIC ASPECT

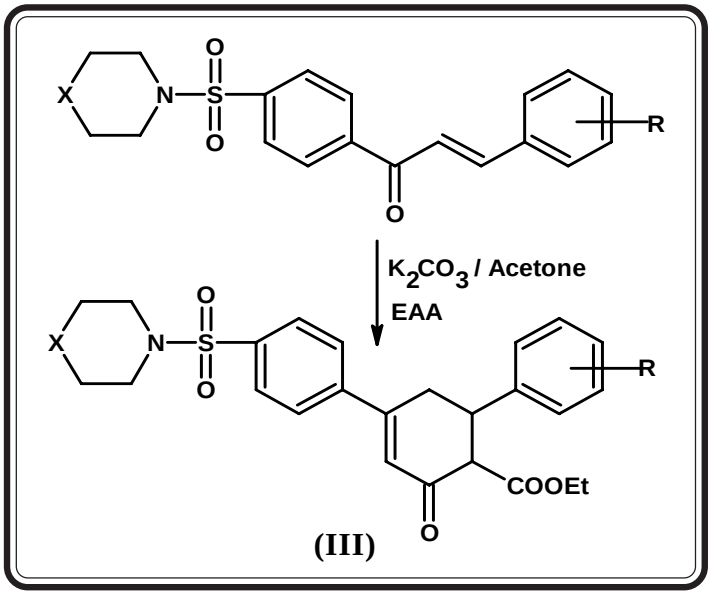
Different methods for the preparation of cyclohexenone derivatives have been described in literature.[191-204]

(I) Shklyaev et al.[205] have synthesized cyclo hexenone derivatives (II).



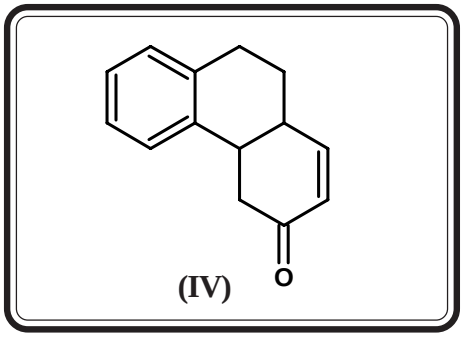
(II)

(II) Eman H. A. et al.[206] have been prepared cyclohexenone derivatives (III) from chalcones.



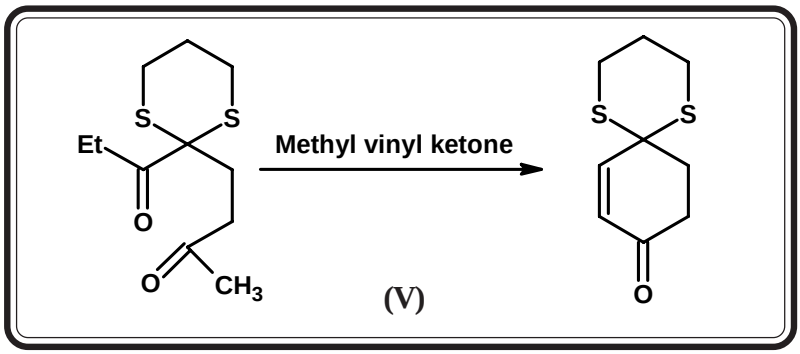
(III)

(III) In review of the earlier literature Gerald[207] et al.have described representative synthetic procedure of cyclohexenone derivatives (IV).



(IV)

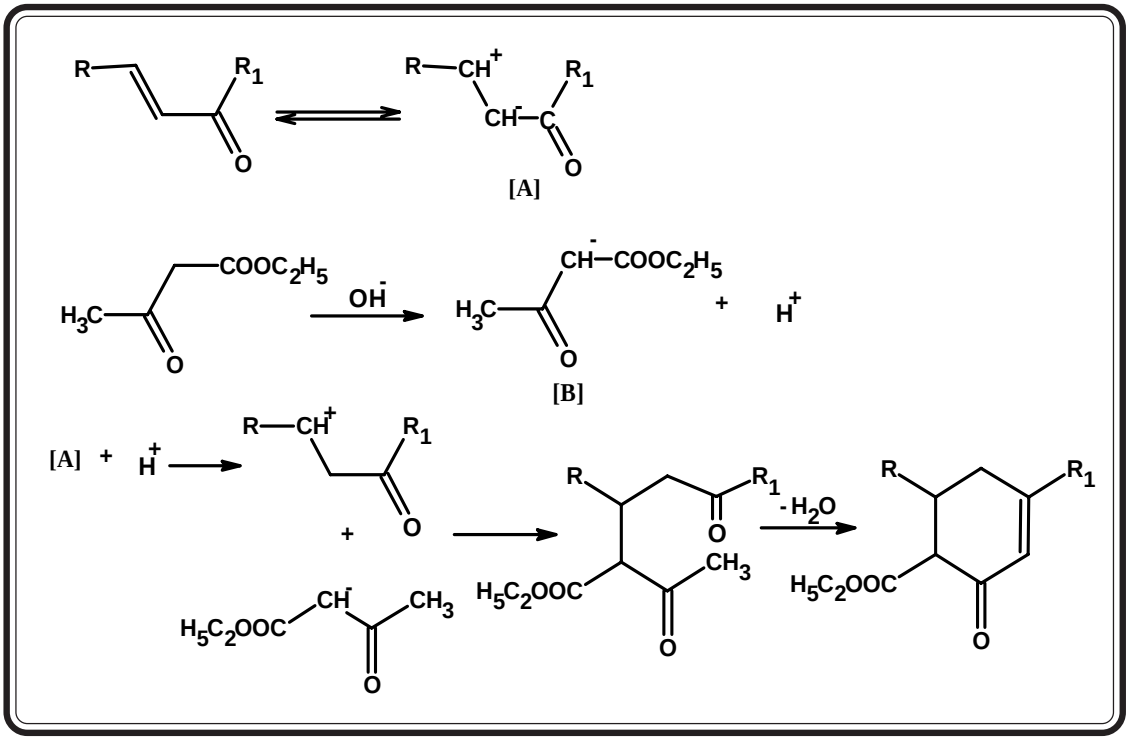
(IV) Page Philip C. and co-workers[208] have prepared substituted cyclohexenone derivative (V).



(V)

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, nucleophilic addition of carbanion takes place to the C=C of the acceptor. The α,β-unsaturated compound is known as acceptor and ethyl acetoacetate is known as donor.



THERAPEUTIC EVALUATION

Cyclohexenone and its derivatives are widely used in pharmaceutical industries. Considerable interest has been shown in the chemistry of cyclohexenones due to their wide spectrum of therapeutic activities which are listed as under.

1. Herbicidal[209]
2. Analgesic[210]
3. Anti-inflammatory[211]
4. Anticonvulsant[212]
5. Antibacterial[213]

6. Antagonist[214]

7. Antibiotic[215]

8. Cardiovascular[216]

Antimicrobial activity of cyclohexenones have been studied by Salama and Atshikh.[217] Cyclohexenone possess neutropeptide γ-receptor antagonist activity which was reported by Takehiro and co-workers[218].

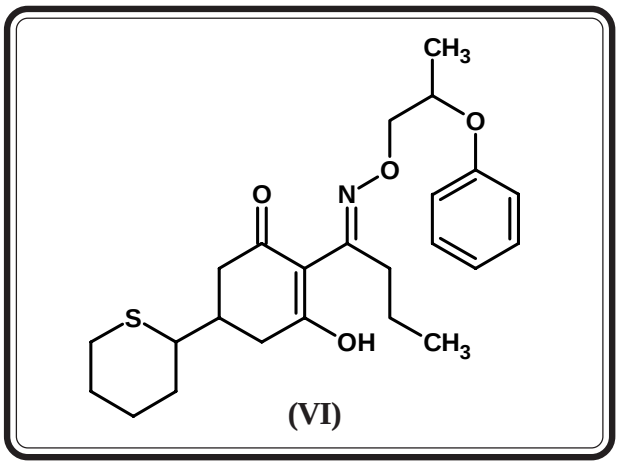
Broughton Howard[219] have demonstrated cyclohexenone as GABA A_5 receptor ligands for enhancing coagulating properties. Cyclohexenones possess inhibitory activity against the growth of lettuce seeding found by Kimura and co-workers.[220]

Cyclohexenones have various medicinal applications as an antiarrhythmic activity[221] of some cyclohexenone derivatives have been investigated. Cyclohexenone possess cardiovascular, osteoporosis, menpausal symptoms, estrogen dependent etc.

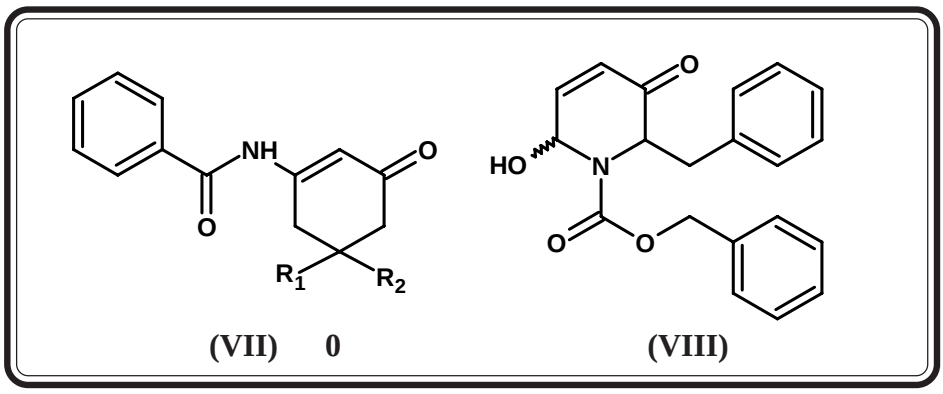
Cyclohexenone and its derivatives have been prepared and reported as broad spectrum of physiological properties viz., antibiotics,[222-223] herbicidal,[224] antimicrobial,[225] etc. Alekseeva L. M. and co-workers[226] have synthesized cyclohexenone derivatives which are useful as neurotropic activity. Toshiyuki et al.[227] have prepared some novel cyclohexenone and screened for their allergy inhibitor, antithrombotic platelet aggregation inhibitors and fibrinogen antagonist activity.

The presence of pesticidal activity among cyclohexenone derivatives is well documented. The compound 2-[(*E,Z*)-1-[(*2R,S*)-2-(4-chlorophenoxy) propoxyimino] butyl]-3-hydroxy-5-thian-3-yl)cyclohex-2-en)-one (VI) has been marketed under the name of ***'Profoxydine'*** as an herbicides.

Alan J. Anderson et al.[228] have synthesized cyclohexenone derivative and studied on the anticonvulsant activity and potential type (VII) phosphodiesterase inhibitor. Yasuko Takahashi et al.[229] have reported cyclohexenone derivatives and studied on novel g-secretase inhibitor (VIII).

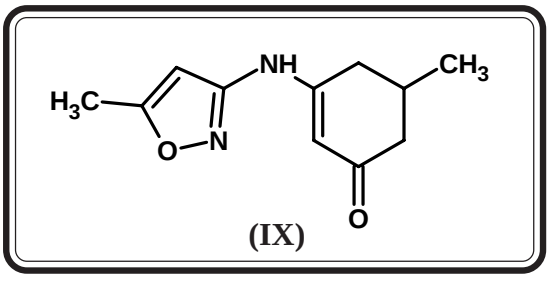


(VI)



(VII) 0 **(VIII)**

Eddington N. D. et al.[230] have synthesized ethyl 4-[(aryl)amino]-6-methyl-2-oxocyclohex-3-ene-1-carboxylates and screened their anticonvulsant activity. Cragoe, Edward J. et al.[231] have prepared 2,3-dihydro-5-(3-oxo-2-cyclohexen-1-yl)-2-benzofurancarboxylic acids and their salts which are used in the treatment of brain injury. K. R. Scott et al.[232] have synthesized cyclohexenone derivative (IX) and studied on the anticonvulsant activity.



(IX)

Vital contribution of Cyclohexenone ring system to the medicinal chemistry as an active constituent of antibiotics made chemists to explore for its derivatives as therapeutic agents. Accordingly, several derivatives of Cyclohexenone have been designed as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF METHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

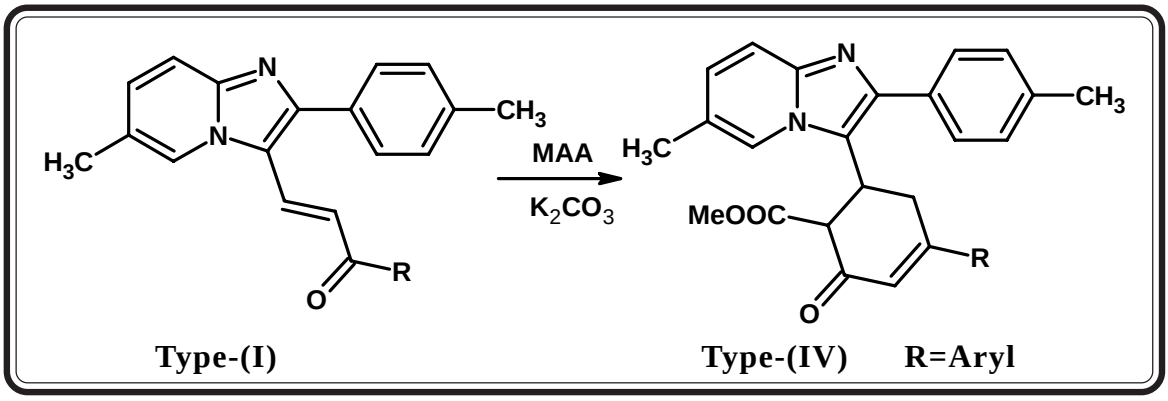
SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

SECTION-III : SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF METHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

Cyclohexenone derivatives have considerable attention in view of their potential pharmacological properties such as antimicrobial, anticonvulsant, anticancer, etc. led by these considerations, the preparation of cyclohexenone derivatives of type-(IV) has been undertaken. The synthesis was carried out by the condensation of 1-Aryl-3-[6-methyl -2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones of type-(I) with methyl acetoactate in the presence of basic catalyst like dry K_2CO_3 shown as under.

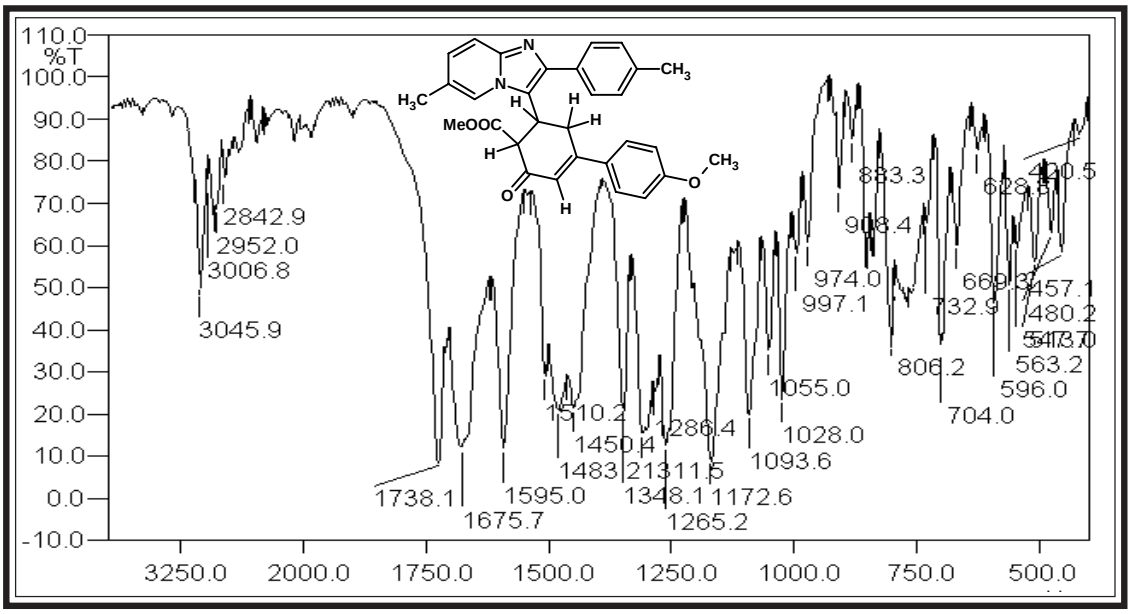


Type-(I) **Type-(IV)** **R=Aryl**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

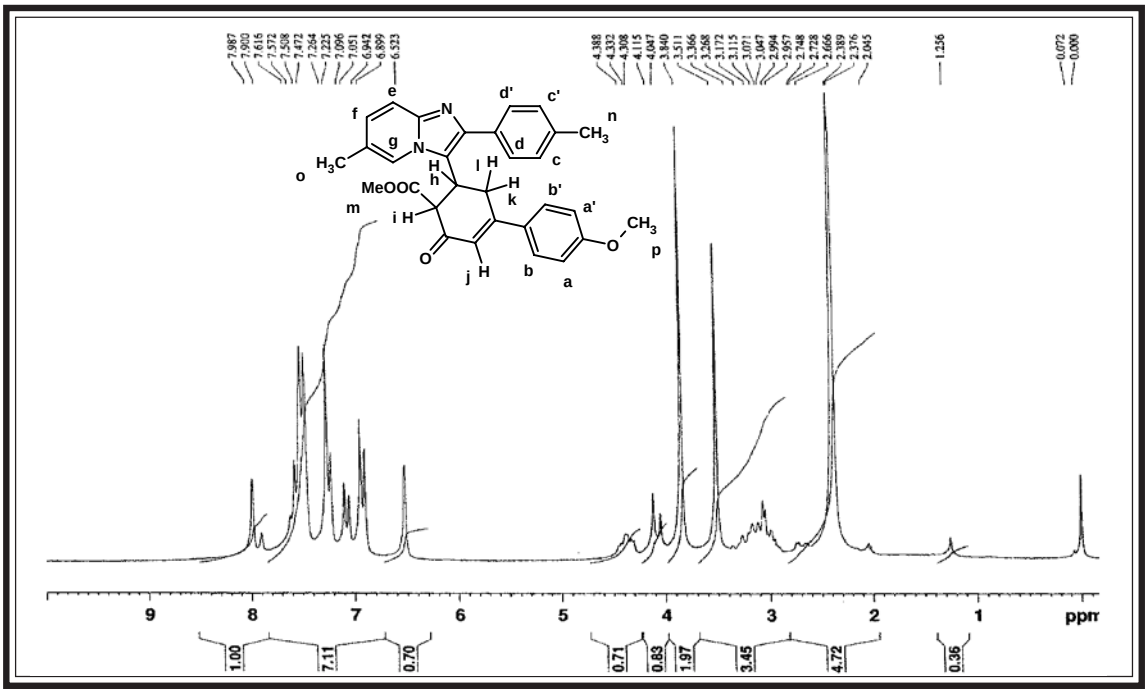
IR SPECTRAL STUDIES OF METHYL-4-(4-METHOXYPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2952	2975-2950	189
$-CH_3$	C-H str. (sym.)	2842	2880-2860	,,
	C-H def. (asym.)	1450	1470-1435	,,
	C-H def. (sym.)	1348	1390-1370	,,
Aromatic	C-H str.	3045	3090-3030	190
	C=C str.	1483	1540-1480	,,
	C-H i.p. (def.)	1093	1125-1090	,,
		806	835-810	,,
Methoxy	C-O str.	1265	1260-1200	,,
Cyclohex-	C=O str. of ester	1738	1750-1725	,,
enone	C=O str.of cyclo.	1675	1720-1690	,,
Imidazo[1,2-a]	C=N str.	1595	1612-1593	,,
pyridine	C-N str.	1172	1220-1020	,,

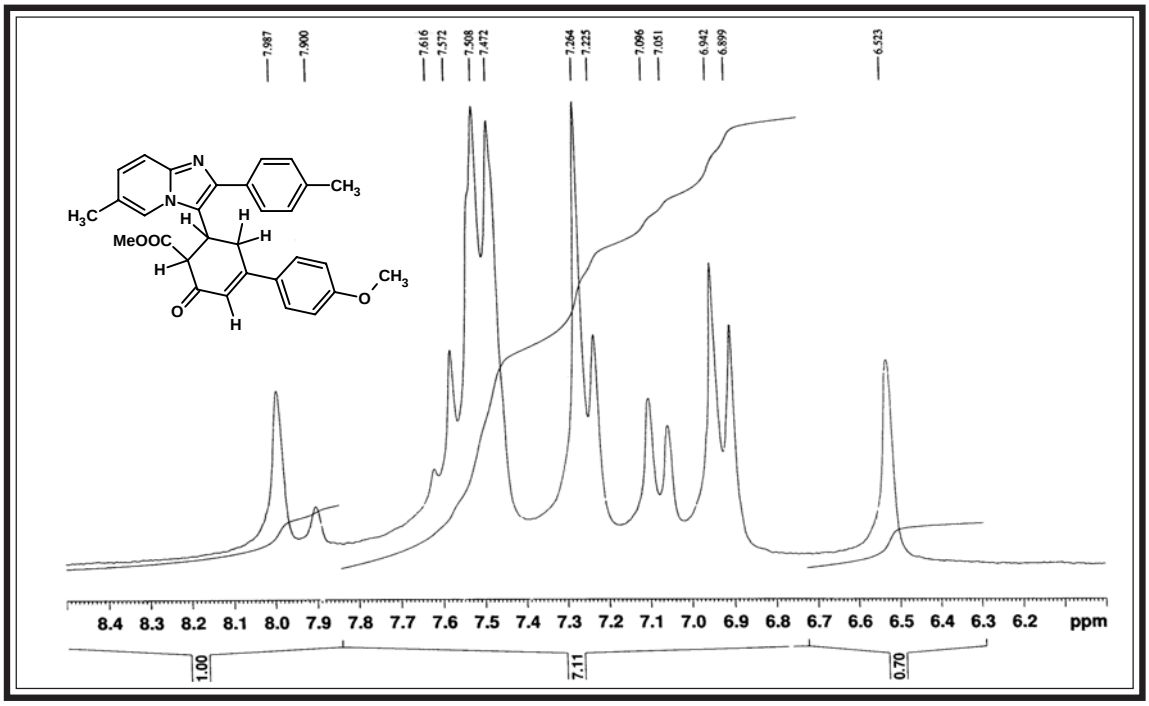
NMR SPECTRAL STUDIES OF METHYL-4-(4-METHOXYPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATE



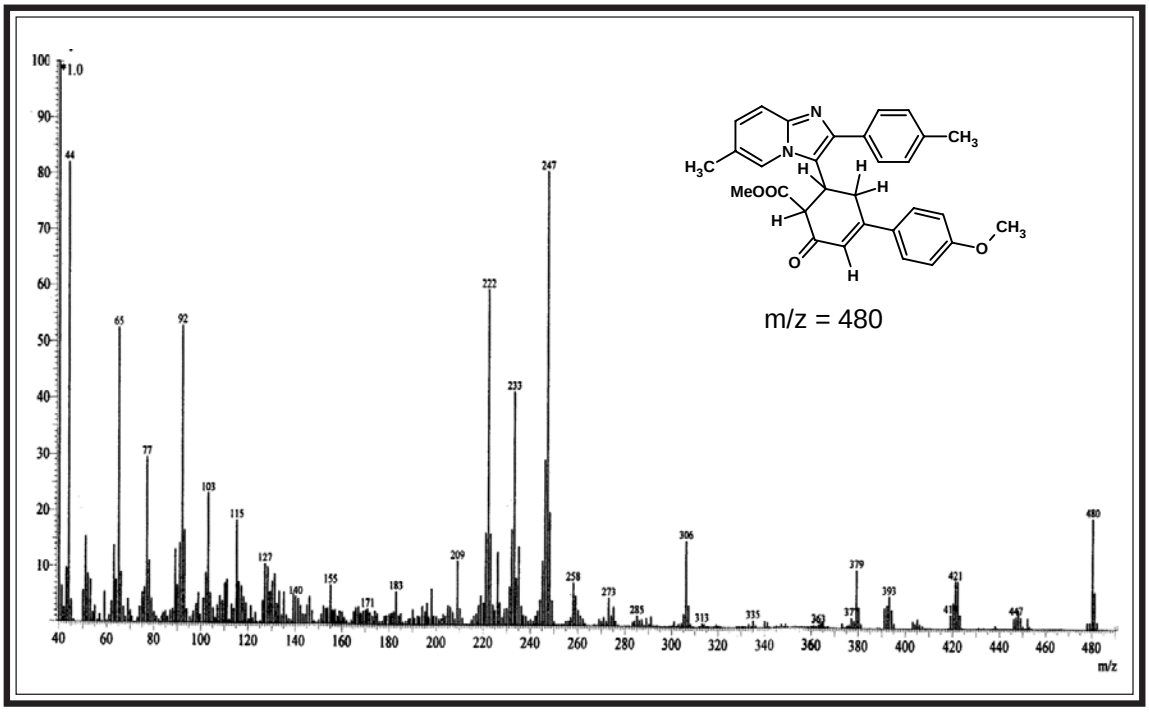
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.37	3H	singlet	Ar-CH_3 (o)	-
2	2.38	3H	singlet	Ar-CH_3 (n)	-
4	2.95-3.30	2H	doublet	Cyclo (l-k)	-
3	3.51	3H	singlet	O=C-O-CH_3	-
5	3.84	3H	singlet	Ar-OCH_3	-
6	4.07-4.11	1H	doublet	Cyclo(i)	13.6
7	4.30-4.38	1H	multiplet	Cyclo(h)	-
8	6.52	1H	singlet	Cyclo(j)	-
9	6.89-6.94	2H	doublet	Ar-(a-a')	8.6
10	7.05-7.096	1H	doublet	Ar-H (f)	9.0
11	7.22-7.26	2H	doublet	Ar- (c-c')	7.8
12	7.57-7.61	1H	doublet	Ar-(e)	8.8
13	7.47-7.50	4H	doublet	Ar-(b,b'-d,d')	7..2
14	7.98	1H	singlet	Ar-(g)	-

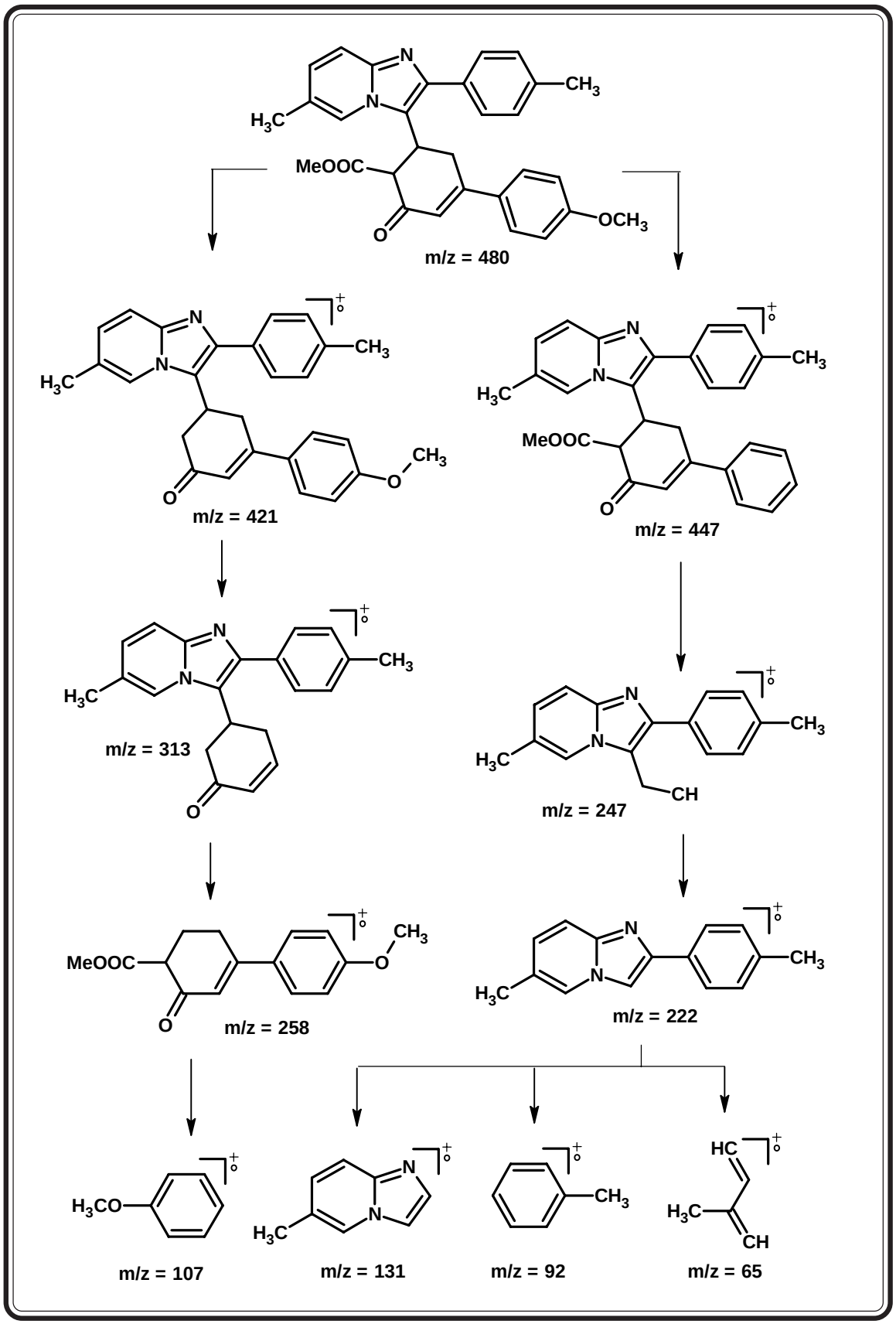
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF METHYL-4-(4-METHOXYPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF METHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See (A), part-I, section-I (A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde:

See (A), part-I, section-I (B), page no.046.

[C] Synthesis of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

See (A), part-I, section-I (C), page no.047.

[D] Synthesisof Methyl-4-(4-methoxyphenyl)-6-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylate :

A mixture of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one3.82gm (0.01mol), methyl acetoacetate 1.3 gm(0.01 mol) and dry K_2CO_3 2.76gm (0.02 mole) was taken in 40 ml dry acetone.The reaction mixture refluxed for 8 hrs. Allowed to stand for over night at room temperature and filtered it and washed with water. Dryed it and recrystallized from ethanol. Yield 65%, m.p.dec. 205 ^oC. Elemental Analysis Calcd. for $C_{30}H_{28}N_2O_4$ requires : C-74.98%, H-5.87%, N-5.83, found : C-75.08%, H-5.80%, N-5.67%.

Similarly, other Methyl-4-aryl-6-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylates were prepared. The physical data are recorded in table no.04.

[E] Biological screening of Methyl-4-aryl-6-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylates :

Antimicrobial testing was carried out as described in (A), part-I, section-I, (E), page no.047. The zones of inhibition of test solutions are reported in graphical chart no.04.

Conclusion :

Antibacterial activity

The screening data indicated that among cyclohexenone derivatives tested compounds **4b**, **4l** showed greater degree of antibacterial activity against *S.aureus*. However, the compounds **4b, 4c, 4e, 4h, 4j, 4k** showed greater degree of antibacterial activity against *B.subtilis*. The compounds **4d, 4k, 4l** showed greater degree of antibacterial activity against *E.coli* and no any compounds showed greater degree of antibacterial activity against *P. aeruginosa*.

Antifungal activity

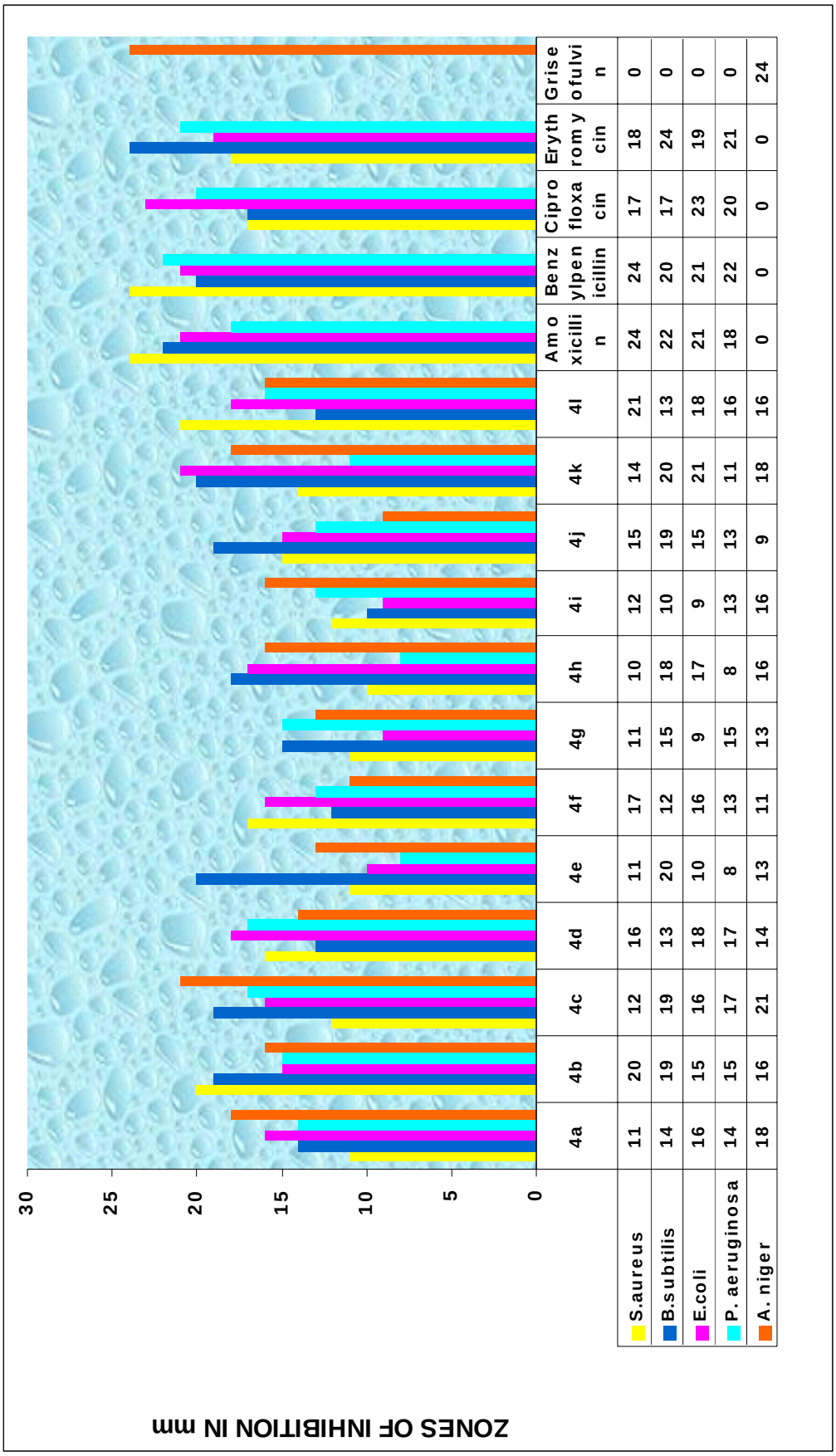
The screening data indicated that among cyclohexenone derivatives tested compounds **4a, 4c, 4k** showed greater degree of antifungal activity against *A.niger*.

TABLE - 04: PHYSICAL CONSTANTS OF METHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*] PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
4a	C_6H_5-	$C_{29}H_{26}N_2O_3$	450	dec.160	55	6.22	6.20	0.47	S_2
4b	4-Cl-C_6H_4-	$C_{29}H_{25}ClN_2O_3$	484.5	218	72	5.77	5.80	0.50	S_2
4c	2,4-$(Cl)_2$-C_6H_3-	$C_{29}H_{24}Cl_2N_2O_3$	519	dec.190	80	5.39	5.34	0.42	S_1
4d	4-NO_2-C_6H_4-	$C_{29}H_{25}N_3O_5$	495	196	75	8.48	8.30	0.49	S_2
4e	4-OCH_3-C_6H_4-	$C_{30}H_{28}N_2O_4$	480	dec.200	65	5.83	5.81	0.55	S_1
4f	4-CH_3-C_6H_4-	$C_{30}H_{28}N_2O_3$	464	184	78	6.03	6.11	0.52	S_2
4g	4-OH-3-OCH_3-C_6H_3-	$C_{30}H_{28}N_2O_5$	496	150	65	5.64	5.61	0.42	S_2
4h	4-Br-C_6H_4-	$C_{29}H_{25}BrN_2O_3$	529	dec.175	58	5.29	5.24	0.47	S_2
4i	2-OH-C_6H_4-	$C_{29}H_{26}N_2O_4$	466	dec.186	45	6.00	5.99	0.47	S_2
4j	4-OH-C_6H_4-	$C_{29}H_{26}N_2O_4$	466	dec.188	78	6.00	5.91	0.49	S_1
4k	4-NH_2-C_6H_4-	$C_{29}H_{27}N_3O_3$	465	148	69	9.03	9.04	0.52	S_2
4l	2-C_4H_3S-	$C_{27}H_{24}N_2O_3S$	456	dec.210	68	6.14	6.13	0.54	S_2

S_1 Ethyl acetate : Hexane (2 : 8), S_2 Ethyl acetate : Hexane (4 : 6)

Graphical Chart No.04 : ANTIMICROBIAL ACTIVITY OF METHYL-4-ARYL-6-[6-METHYL-2-(4-METHYL PHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

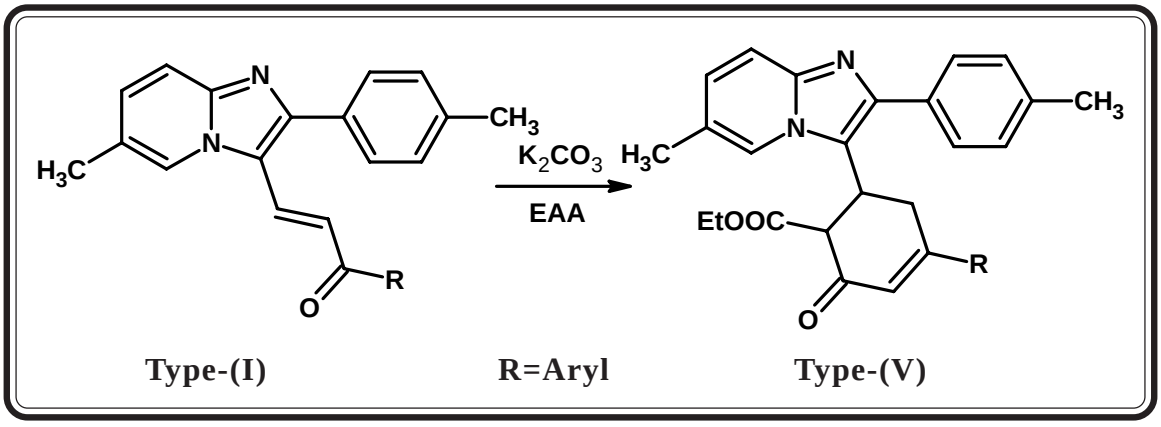


	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	11	20	12	16	11	17	11	10	12	15	14	21	24	24	17	18	0
B.subtilis	14	19	19	13	20	12	15	18	10	19	20	13	22	20	17	24	0
E.coli	16	15	16	18	10	16	9	17	9	15	21	18	21	21	23	19	0
P. aeruginosa	14	15	17	17	8	13	15	8	13	13	11	16	18	22	20	21	0
A. niger	18	16	21	14	13	11	13	16	16	9	18	16	0	0	0	0	24

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-4-(4-METHOXY PHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

Cyclohaxenone derivatives play important role to their wide range of biological activities. Looking to the interesting properties, we have synthesized a series of cyclohexenone of type-(V) for obtaining biologically potent agents, which were prepared by reacting 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones of type-(I) with ethyl acetoacetate in acetone media in presence of basic catalyst like dry K_2CO_3.

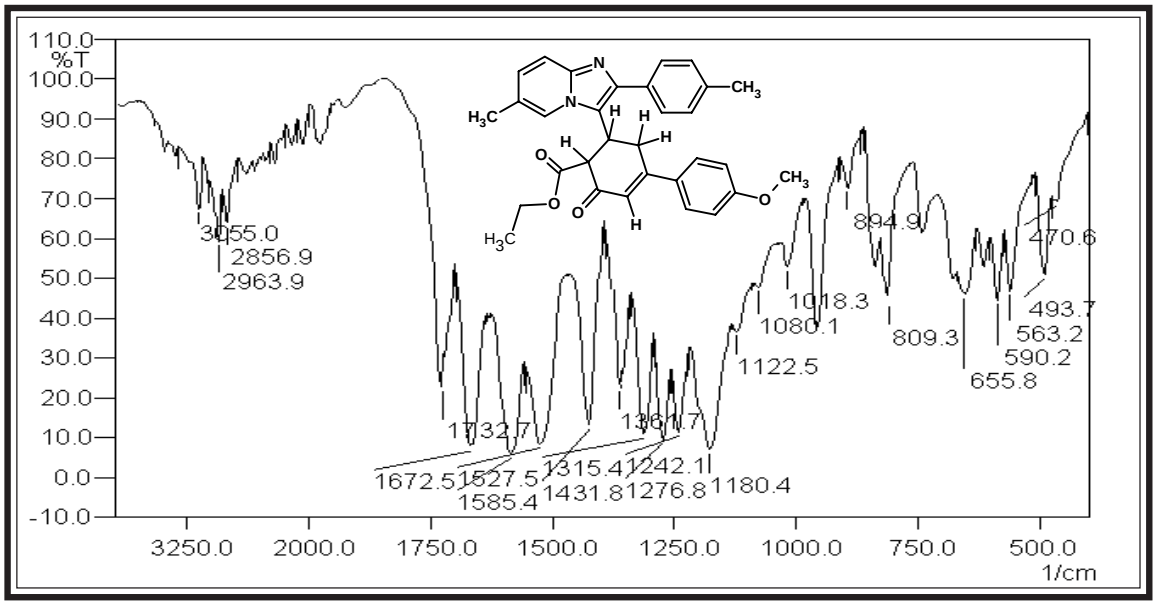


Type-(I) **R=Aryl** **Type-(V)**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

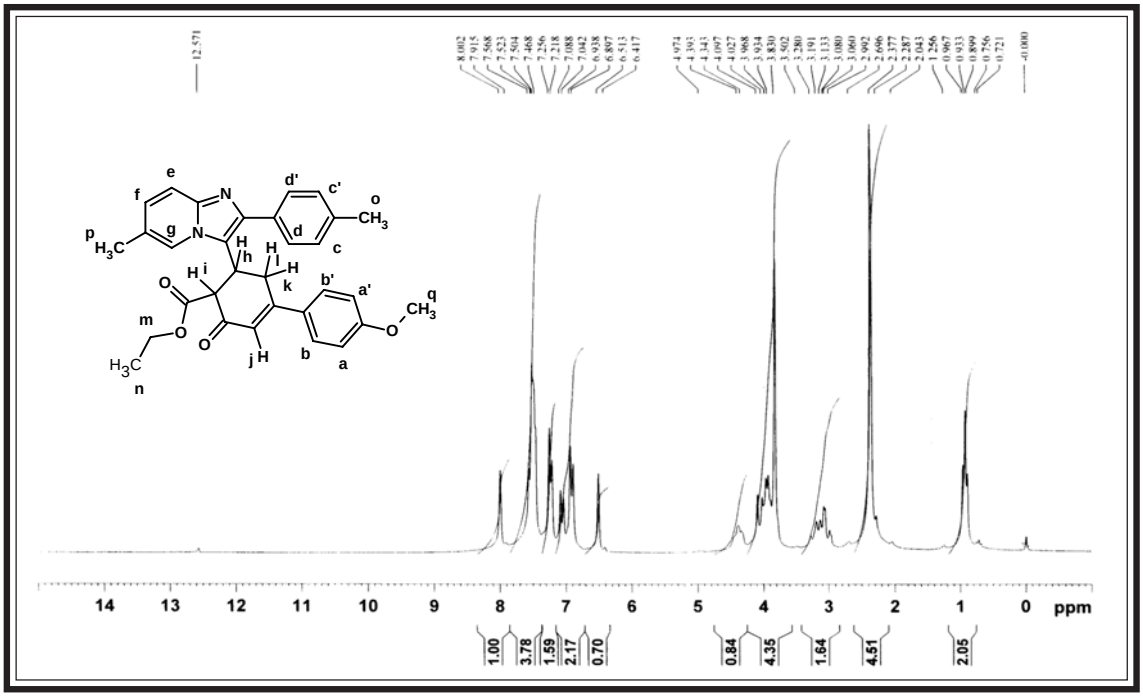
IR SPECTRAL STUDIES OF ETHYL-4-(4-METHOXYPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2963	2975-2950	189
$-CH_3$	C-H str. (sym.)	2856	2880-2860	,,
	C-H def. (asym.)	1431	1470-1435	,,
	C-H def. (sym.)	1361	1390-1370	,,
Aromatic	C-H str.	3055	3090-3030	190
	C=C str.	1527	1540-1480	,,
	C-H i.p. (def.)	1122	1125-1090	,,
		809	835-810	,,
Ethoxy	C-O str.	1242	1260-1200	,,
Cyclohexne	C=O str. of ester	1732	1750-1725	189
	C=O str.of cyclo.	1672	1720-1690	,,
Imidazo[1,2-a]	C=N str.	1585	1612-1593	,,
pyridine	C-N str.	1180	1220-1020	,,

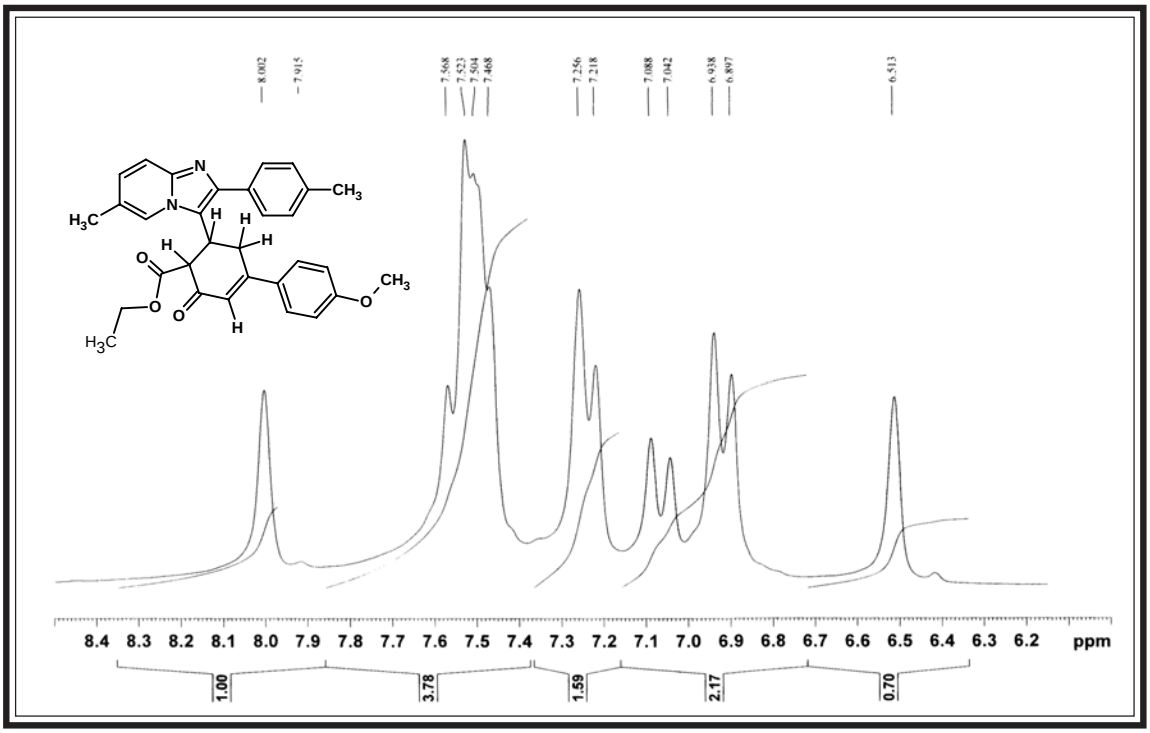
NMR SPECTRAL STUDIES OF ETHYL-4-(4-METHOXYPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATE



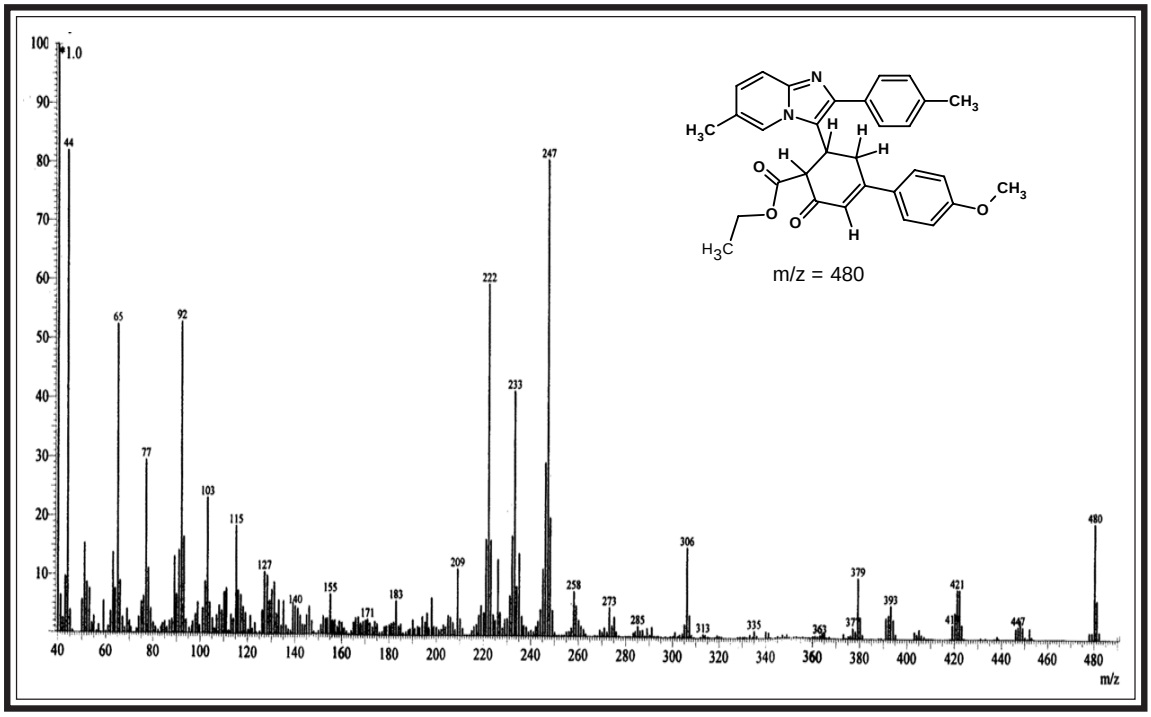
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	0.89-0.93	3H	triplet	Alkyl-CH_3(n)	-
2	2.37	6H	singlet	Ar-CH_3(o-p)	-
3	2.99-3.28	2H	doublet	Cyclo(k-l)	-
4	3.83	3H	singlet	Ar-OCH_3	-
5	3.93-3.96	2H	quartet	Alkyl-CH_2(m)	-
6	4.02-4.09	1H	doublet	Cyclo(i)	14.0
7	4.34-4.39	1H	multiplet	Cyclo(h)	-
8	6.51	1H	singlet	Cyclo(j)	-
9	6.89-6.93	2H	doublet	Cyclo(a-a')	8.2
10	7.04-7.08	1H	doublet	Ar-H (f)	9.2
11	7.21-7.25	2H	doublet	Ar- (c-c')	7.6
12	7.46-7.52	4H	doublet	Ar-(b,b'-d,d')	8.8
13	7.56	1H	doublet	Ar-(e)	-
14	8.00	1H	singlet	Ar-(g)	-

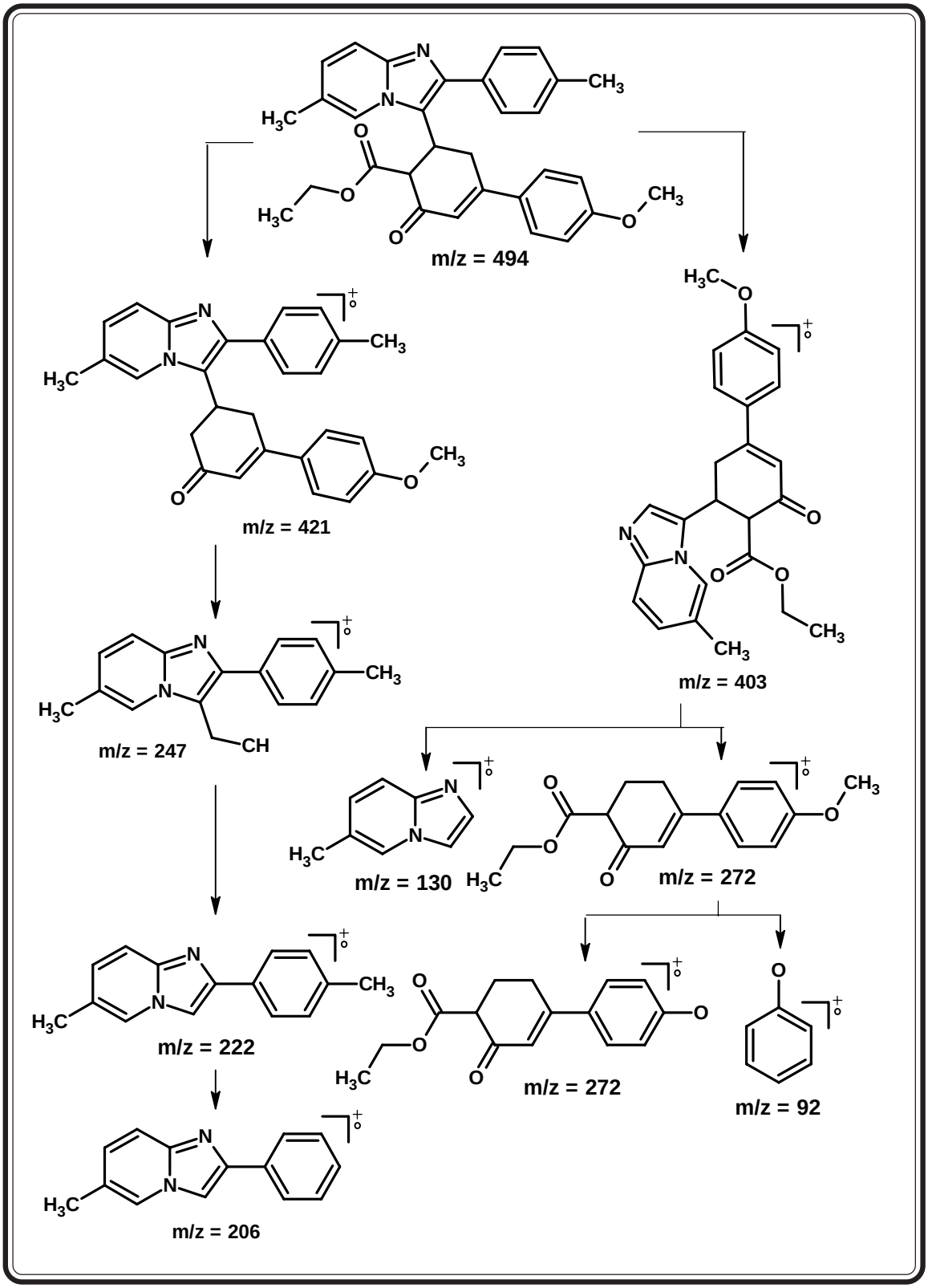
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF ETHYL-4-(4-METHOXYPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See (A), part-I, section-I(A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde:

See (A), part-I, section-I(B), page no.046.

[C] Synthesis of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

See (A), part-I, section-I(C), page no.047.

[D] Synthesis of Ethyl-4-(4-methoxyphenyl)-6-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylate :

1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one 3.82gm (0.01mol) was taken in 40 ml acetone and then ethyl acetoacetate 1.3 gm (0.01 mol) and dry K_2CO_3 2.76gm (0.02 mol) was added. The mixture was refluxed for 6.0 hrs and allowed to stand for over night at room temperature. Then it was filtered, washed with water, dried it and recrystallized from ethanol. Yield 55%, m.p.dec.220 ^oC. Elemental Analysis Calculated for $C_{31}H_{30}N_2O_4$ requires : C-74.98%, H-5.87%, N-5.83%, found : C-75.08%, H-5.80%, N-5.67%.

Similarly, other Ethyl-4-aryl-6-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylates were prepared. The physical data are recorded in table no.05.

[E] Biological screening of Ethyl-4-aryl-6-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene-1-carboxylates :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.047. The zones of inhibition of test solutions are reported in graphical chart no.05.

Conclusion :

Antibacterial activity

The screening data indicated that among cyclohexenone derivatives tested compounds **5h**, **5i**, **5l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **5b, 5k** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **5a, 5e, 5g, 5l** and **5f, 5i, 5j** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

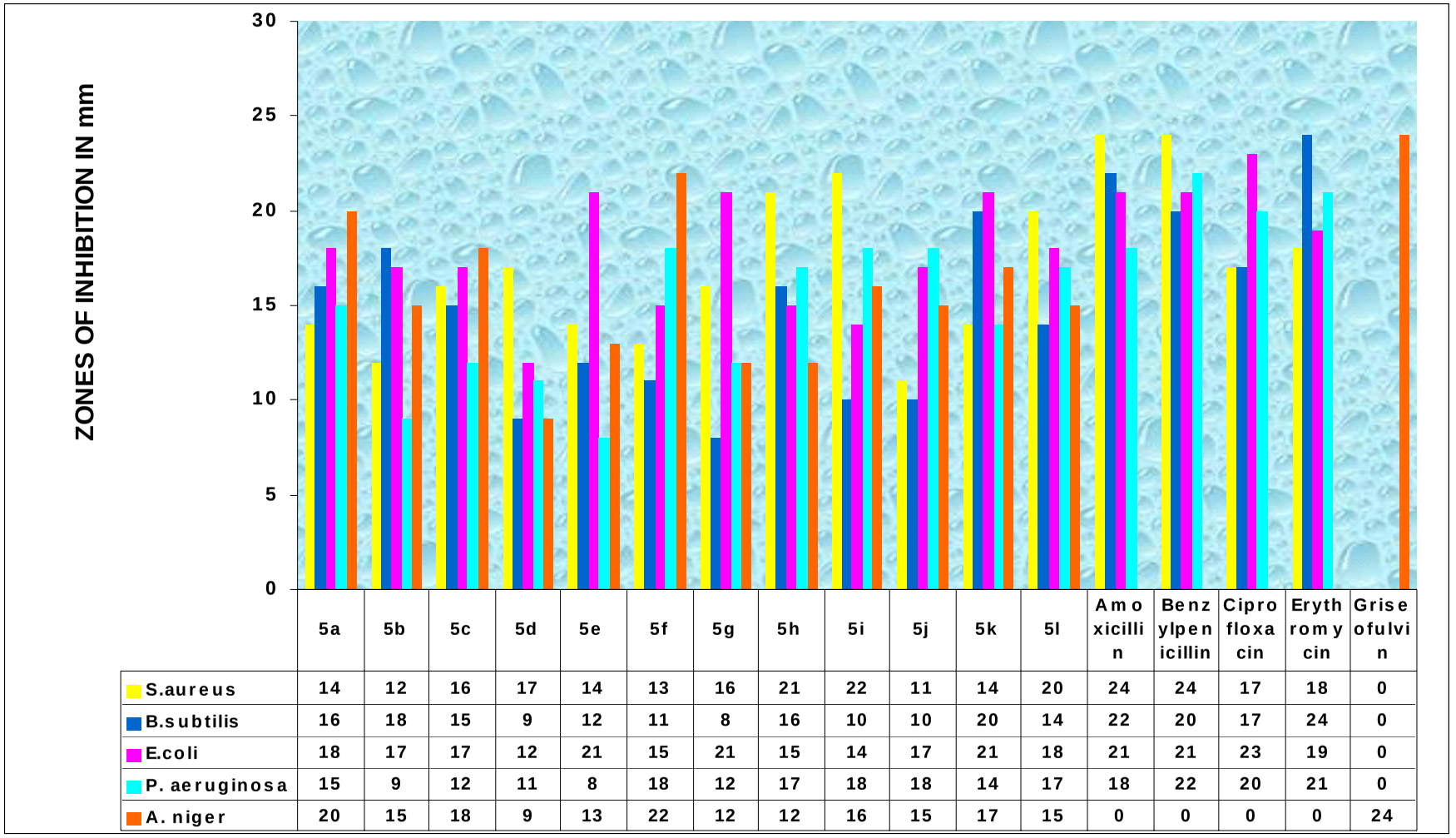
The screening data indicated that among cyclohexenone derivatives tested compounds **5c, 5f** showed greater degree of antifungal activity against *A.niger.*

TABLE - 05: PHYSICAL CONSTANTS OF ETHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
5a	C_6H_5-	$C_{30}H_{28}N_2O_3$	464	195	65	6.03	6.05	0.52	S_2
5b	4-Cl-C_6H_4-	$C_{30}H_{27}ClN_2O_3$	498.5	190	76	5.61	5.55	0.51	S_1
5c	2,4-$(Cl)_2$-C_6H_3-	$C_{30}H_{26}Cl_2N_2O_3$	533	134	78	5.25	5.31	0.49	S_1
5d	4-NO_2-C_6H_4-	$C_{30}H_{27}N_3O_5$	509	172	61	8.25	8.24	0.55	S_2
5e	4-OCH_3-C_6H_4-	$C_{31}H_{30}N_2O_4$	494	dec.220	55	5.66	5.61	0.60	S_2
5f	4-CH_3-C_6H_4-	$C_{31}H_{30}N_2O_3$	478	190	60	5.85	5.91	0.40	S_1
5g	4-OH-3-OCH_3-C_6H_3-	$C_{31}H_{30}N_2O_5$	510	135	71	5.49	5.48	0.55	S_1
5h	4-Br-C_6H_4-	$C_{30}H_{27}BrN_2O_3$	543	205	76	5.15	5.14	0.48	S_1
5i	2-OH-C_6H_4-	$C_{30}H_{28}N_2O_4$	480	192	45	5.83	5.80	0.46	S_2
5j	4-OH-C_6H_4-	$C_{30}H_{28}N_2O_4$	480	130	51	5.83	5.79	0.44	S_1
5k	4-NH_2-C_6H_4-	$C_{30}H_{29}N_3O_3$	479	170	56	8.76	8.77	0.44	S_2
5l	2-C_4H_3S-	$C_{28}H_{26}N_2O_3S$	470	200	54	5.95	5.96	0.50	S_2

S_1 Ethyl acetate : Hexane (2 : 8), S_2 Ethyl acetate : Hexane (4 : 6)

Graphical Chart No. 05 : ANTIMICROBIAL ACTIVITY OF ETHYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENE-1-CARBOXYLATES

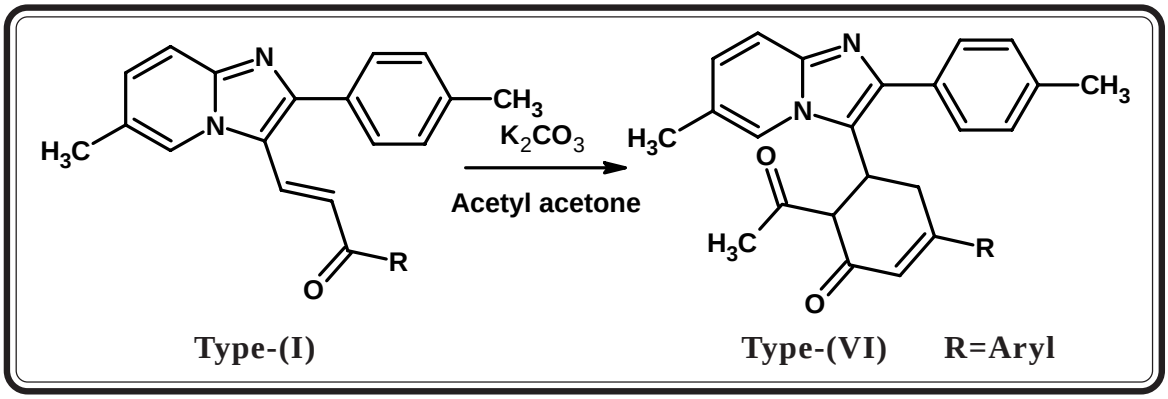


	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	14	12	16	17	14	13	16	21	22	11	14	20	24	24	17	18	0
B.subtilis	16	18	15	9	12	11	8	16	10	10	20	14	22	20	17	24	0
E.coli	18	17	17	12	21	15	21	15	14	17	21	18	21	21	23	19	0
P. aeruginosa	15	9	12	11	8	18	12	17	18	18	14	17	18	22	20	21	0
A. niger	20	15	18	9	13	22	12	12	16	15	17	15	0	0	0	0	24

SECTION-III

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENES

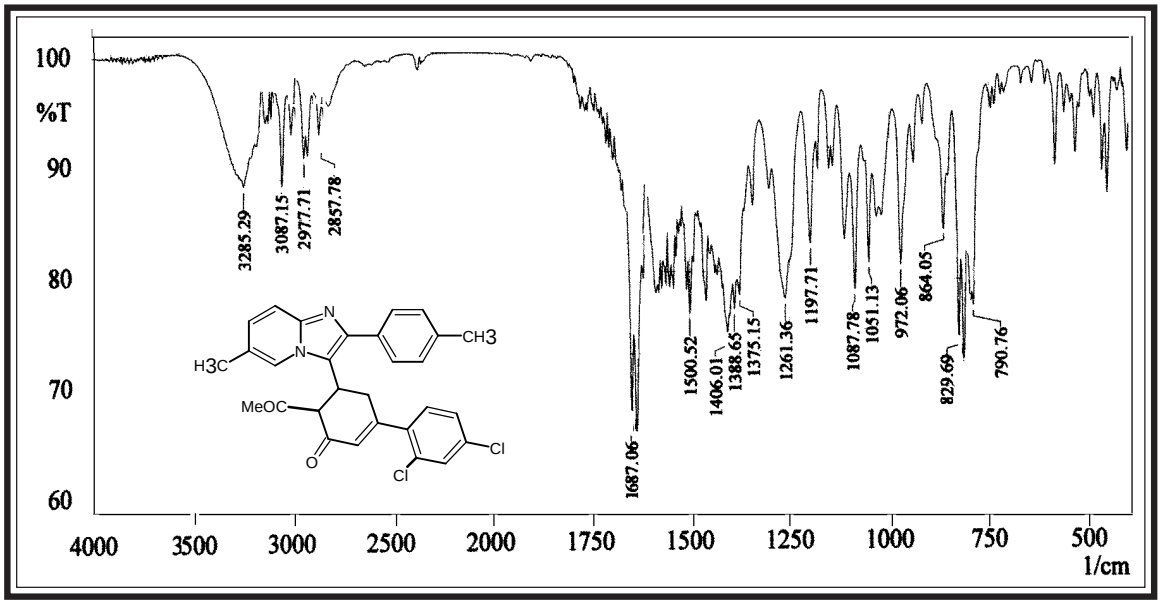
Cyclohexenone derivatives have considerable attention in view of their potential pharmacological properties such as antimicrobial, anticonvulsant, anticancer, etc. Led by these considerations, the preparation of cyclohexenone derivatives of type-(VI) has been undertaken. The synthesis was carried out by the condensation of 1-Aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones of type-(I) with acetyl acetone in the presence of basic catalyst like dry K_2CO_3 shown as under.



The structure elucidation of synthesized compounds has been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

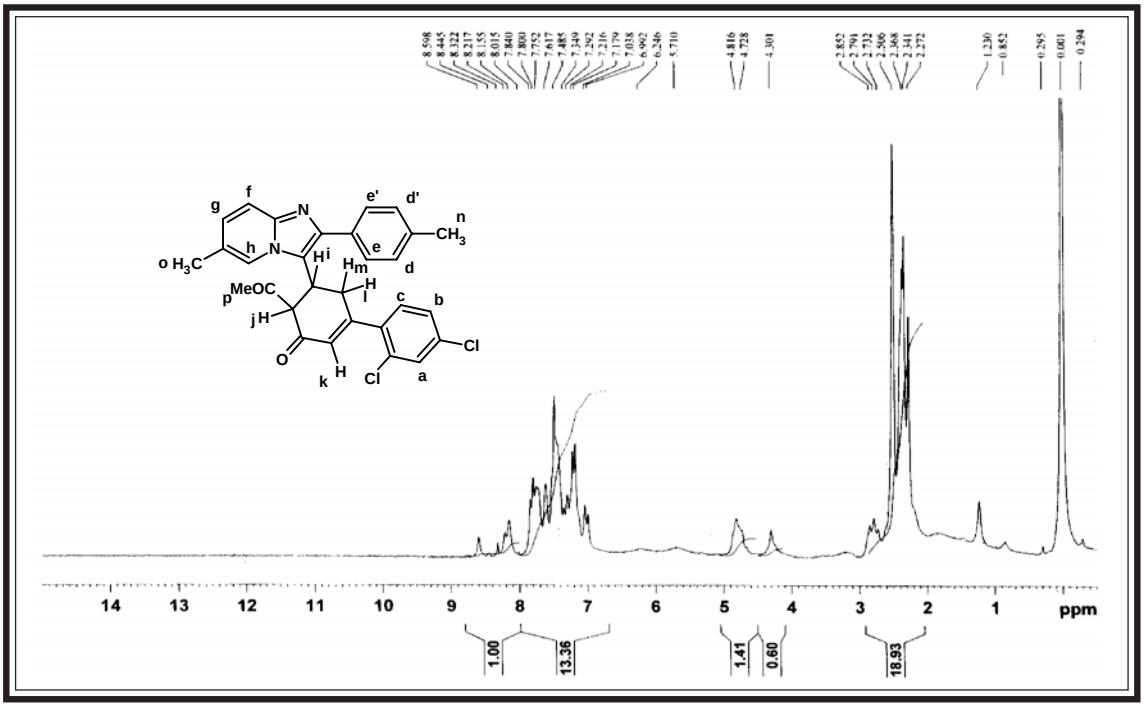
IR SPECTRAL STUDIES OF 1-ACETYL-4-(2,4-DICHLOROPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] CYCLOHEX-2-ONE-3-ENE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2977	2975-2950	189
$-CH_3$	C-H str. (sym.)	2857	2880-2860	,,
	C-H def. (asym.)	1406	1470-1435	,,
	C-H def. (sym.)	1388	1390-1370	,,
Aromatic	C-H str.	3085	3090-3030	190
	C=C str.	1500	1540-1480	,,
	C-H i.p. (def.)	1051	1125-1090	,,
		790	790-800	,,
Halide	C-Cl str.	605	800-600	,,
Cyclohex-	C=O str.	1687	1725-1690	,,
enone	C=O str.of cyclo.	1682	1720-1690	,,
Imidazo[1,2-a]	C=N str.	1583	1612-1593	,,
pyridine	C-N str.	1197	1220-1020	,,

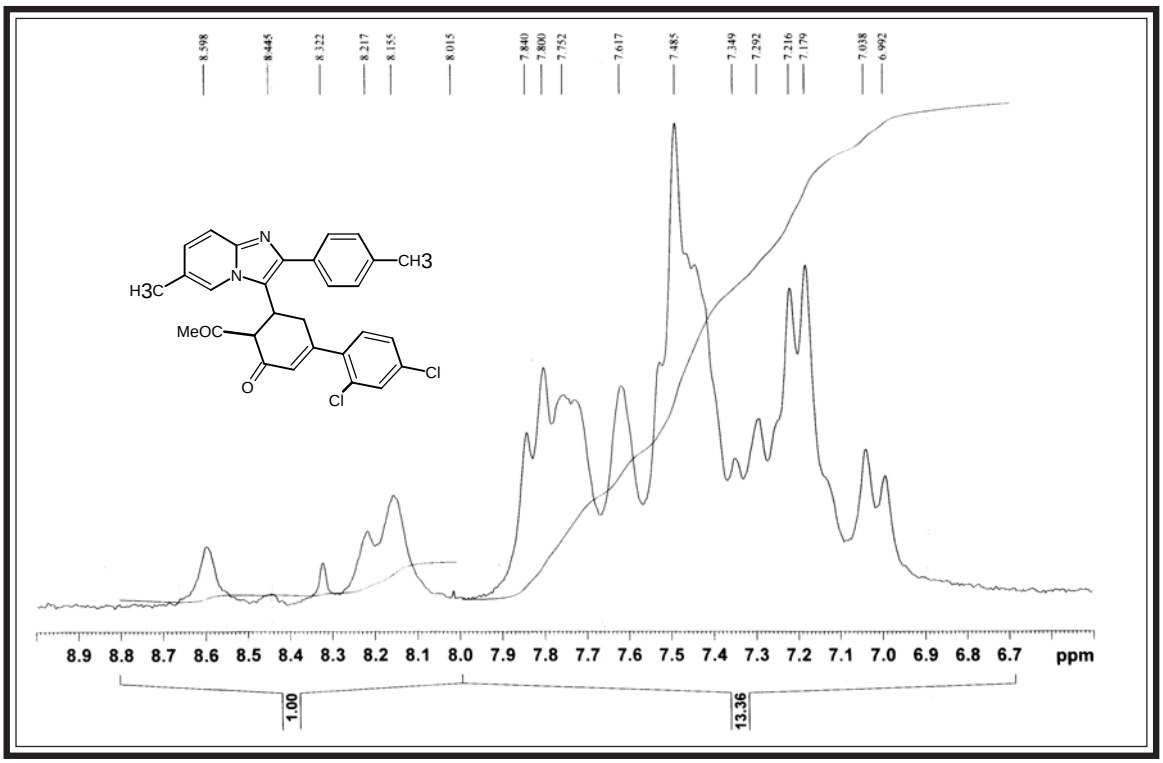
NMR SPECTRAL STUDIES OF 1-ACETYL-4-(2,4-DICHLOROPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] CYCLOHEX-2-ONE-3-ENE



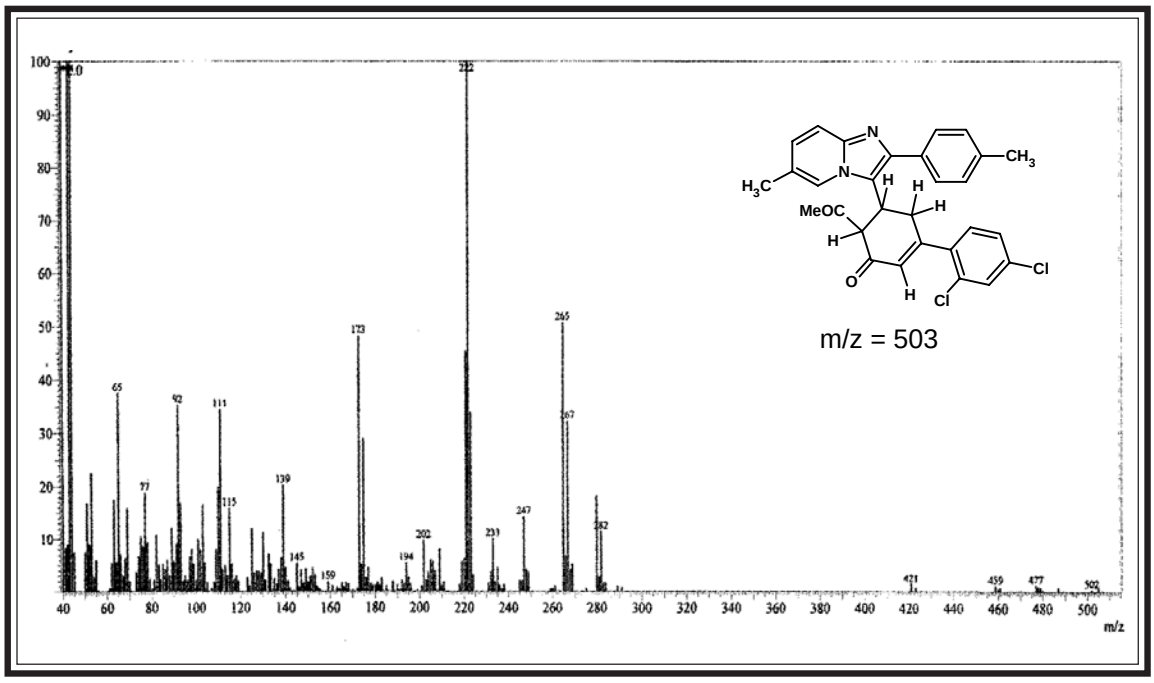
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.34	3H	singlet	Ar-CH_3(n)	-
2	2.36	3H	singlet	Ar-CH_3(o)	-
3	2.50	3H	singlet	O=C-CH_3(p)	-
4	2.73-2.85	2H	doublet	Cyclo(m-l)	-
5	4.30	1H	doublet	Cyclo(j)	-
6	4.72	1H	multiplet	Cyclo(i)	-
7	6.99-7.03	1H	singlet	Cyclo(k)	-
8	7.17-7.21	2H	doublet	Ar-H(d-d')	7.4
9	7.29-7.34	1H	doublet	Ar-H(g)	11.4
11	7.54	1H	doublet	Ar-H (f)	8.0
10	7.48	3H	multiplet	Ar-H(c,e-e')	-
12	7.61	1H	singlet	Ar-H (h)	-
13	7.75	2H	doublet	Ar-H (b)	8.8
14	7.80	1H	singlet	Ar-H (a)	8.0

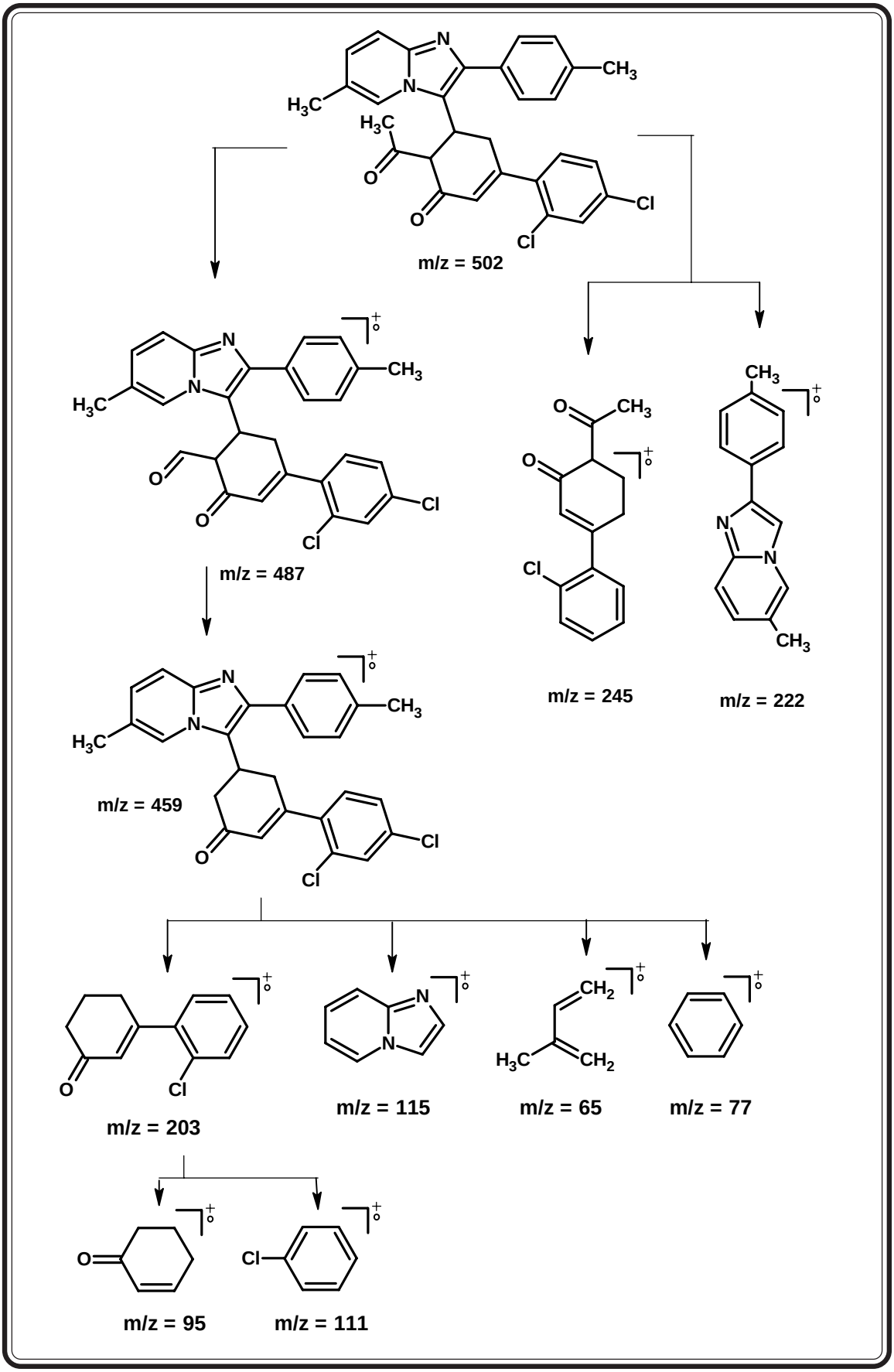
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF 1-ACETYL-4-(2,4-DICHLOROPHENYL)-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] CYCLOHEX-2-ONE-3-ENE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-4-ARYL-6-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See (A), part-I, section-I(A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde:

See (A), part-I, section-I(B), page no.046.

[C] Synthesis of 1-(2,4-Dichlorophenyl)3-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]prop-2-ene-1-one :

See (A), part-I, section-I(D), page no.047.

[D] Synthesis of 1-Acetyl-4-(2,4-dichlorophenyl)-6-[6-methyl-2-(4- methyl phenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-ene :

A mixture of 1-(2,4-Dichlorophenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*]pyridin-3-yl]prop-2-ene-1-one 4.21gm (0.01mol), acetylacetone 1.1gm (0.011 mol) and dry K_2CO_3 2.76gm (0.02 mol) was taken into 40 ml dry acetone. Reaction mass was refluxed for 10 hrs. Allowed to cool at room temperature for 6 hrs. Separated solid was filtred and washed with water. Dried it and recrystallized from ethanol. Yield 74%, m.p.dec 200 ^oC. Elemental Analysis Calculated for $C_{24}H_{18}Cl_2N_2O$ requires : C-68.42%, H-4.31%, N-6.65%, found : C-69.02%, H-4.50%, N-6.57%.

Similarly, other 1-Acetyl-4-aryl-6-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-enes were prepared. The physical data are recorded in table no.06 .

[F] Biological screening of 1-Acetyl-4-aryl-6-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]cyclohex-2-one-3-enes :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.047. The zones of inhibition of test solutions are reported in graphical chart no.06.

Conclusion :

Antibacterial activity

The screening data indicated that among cyclohexenone derivatives tested compounds **6a**, **6c**, **6d, 6i, 6l** showed greater degree of antibacterial activity against *S.aureus*. However, the compounds **6c, 6e, 6f, 6g, 6j** showed greater degree of antibacterial activity against *B.subtilis*. The compounds **6d, 6g, 6i, 6k** and **6h** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

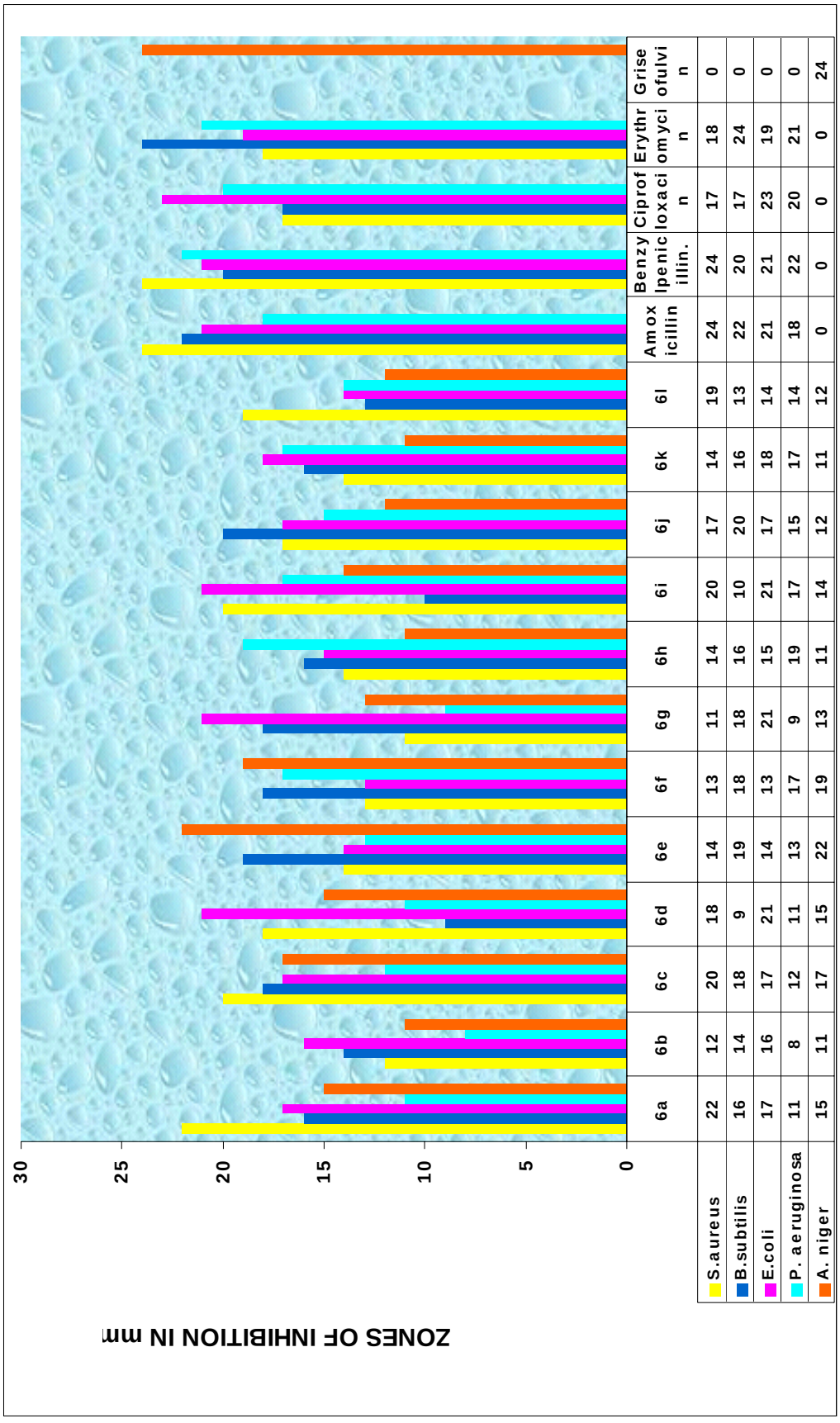
The screening data indicated that among cyclohexenone derivatives tested compounds **6e** showed greater degree of antifungal activity against *A.niger.*

TABLE -06 : PHYSICAL CONSTANTS OF 1-ACETYL-4-ARYL-6-[6-METHYL-2-(4- METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENES

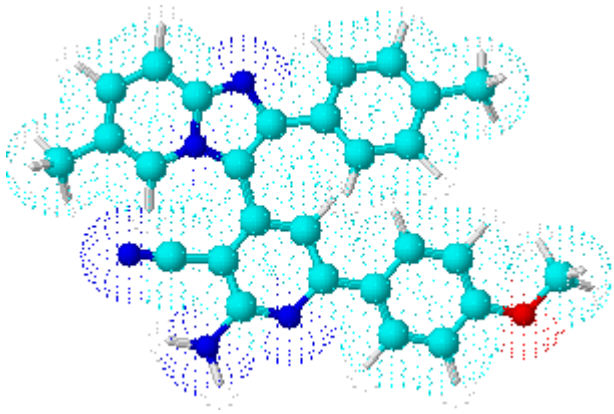
Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
6a	C_6H_5-	$C_{29}H_{26}N_2O_2$	434	116	71	6.45	6.43	0.51	S_1
6b	4-Cl-C_6H_4-	$C_{29}H_{25}ClN_2O_2$	468.5	240	65	5.97	5.89	0.48	S_1
6c	2,4-$(Cl)_2$-C_6H_3-	$C_{29}H_{24}Cl_2N_2O_2$	503	dec.200	74	5.56	5.54	0.50	S_2
6d	4-NO_2-C_6H_4-	$C_{29}H_{25}N_3O_4$	479	102	64	8.76	8.81	0.47	S_1
6e	4-OCH_3-C_6H_4-	$C_{30}H_{28}N_2O_3$	464	104	64	6.03	6.08	0.55	S_1
6f	4-CH_3-C_6H_4-	$C_{30}H_{28}N_2O_2$	448	167	68	6.25	6.27	0.41	S_2
6g	4-OH-3-OCH_3-C_6H_3-	$C_{30}H_{28}N_2O_4$	480	126	58	5.83	5.87	0.48	S_2
6h	4-Br-C_6H_4-	$C_{29}H_{25}BrN_2O_2$	513	96	72	5.45	5.41	0.50	S_1
6i	2-OH-C_6H_4-	$C_{29}H_{26}N_2O_3$	450	dec.190	59	6.22	6.28	0.55	S_2
6j	4-OH-C_6H_4-	$C_{29}H_{26}N_2O_3$	450	145	68	6.22	6.20	0.54	S_2
6k	4-NH_2-C_6H_4-	$C_{29}H_{27}N_3O_2$	449	dec.230	70	9.35	9.37	0.47	S_2
6l	2-C_4H_3S-	$C_{27}H_{24}N_2O_2S$	440	130	71	6.36	6.34	0.48	S_2

S_1 Ethyl acetate : Hexane (4 : 6), S_2 Ethyl acetate : Hexane (5 : 5)

Graphical Chart No.06 : ANTIMICROBIAL ACTIVITY OF 1-ACETYL-4-ARYL-6-[6-METHYL-2-(4-METHYL PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]CYCLOHEX-2-ONE-3-ENES



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Amoxicillin	Benzylpenicillin.	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	22	12	20	18	14	13	11	14	20	17	14	19	24	24	17	18	0
B.subtilis	16	14	18	9	19	18	18	16	10	20	16	13	22	20	17	24	0
E.coli	17	16	17	21	14	13	21	15	21	17	18	14	21	21	23	19	0
P. aeruginosa	11	8	12	11	13	17	9	19	17	15	17	14	18	22	20	21	0
A. niger	15	11	17	15	22	19	13	11	14	12	11	12	0	0	0	0	24



PART - III

STUDIES ON

CYANOPYRIDINES

INTRODUCTION

Pyridine with different functional groups, exhibit wide range of applications in the field of pharmaceutical, agriculture and dyes. Although many substituted pyridine compounds like other heterocyclic compounds are synthesized with their functional group present in cyclic compounds. The simple pyridine compounds are prepared by the cyclization of aliphatic raw material. The availability of 3-cyanopyridines, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

Most of pyridine derivatives are synthesized by manipulation of pyridine and its simple homologues in a manner similar to chemistry of the benzenoid chemistry. However the simple pyridine compounds are prepared by the cyclization of aliphatic raw materials. In our continuation work in the chemistry of pyridine nucleus, we have undertaken the synthesis of imidazo[1,2-*a*]pyridine derivatives.

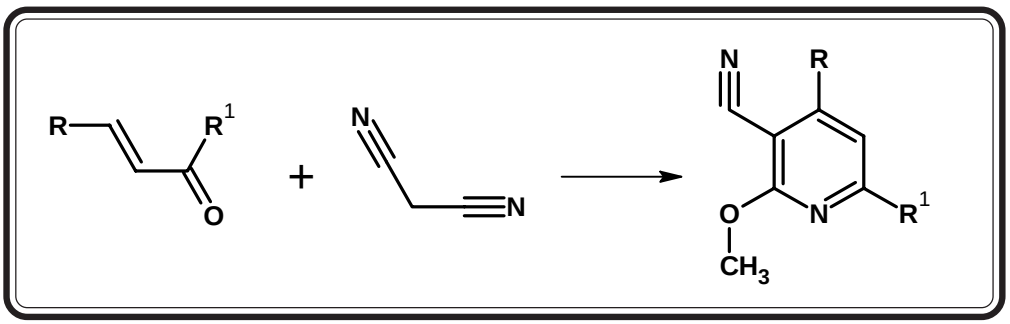
SYNTHETIC ASPECT

Different methods for the preparation of 3-cyanopyridines are available in literature.[233-239] The well known methods are:

1. Samour and co-workers prepared substituted cyanopyridines by the condensation of chalcones with ethyl acetoacetate and malanonitrile in presence of ammonium acetate.[240-241]
2. Tsutsumi et al.[242] have synthesized 3-cyano pyridines by cyclocondensation of cyanoacetamide with ethyl acetoacetate in the presence of base.
3. Substituted cyanopyridine derivatives were also prepared from 3-substituted phenyl pyrazolone derivatives with malononitrile.[243]

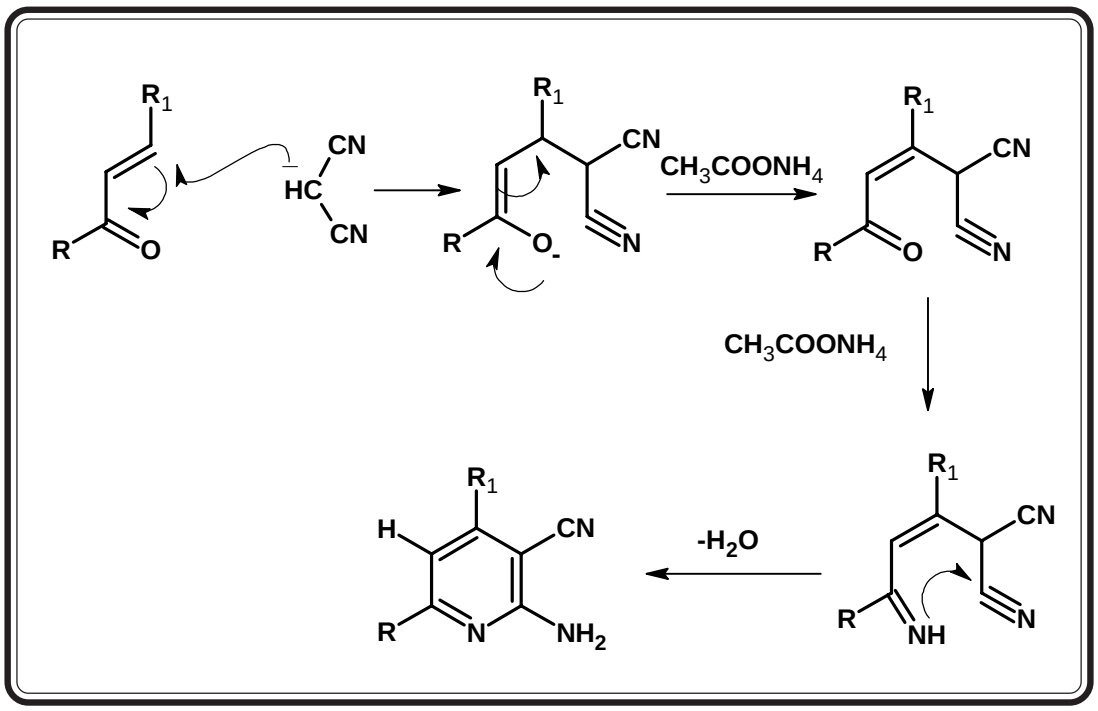
4. Sakuri and Midorikaw[244-245] have reported that malononitrile reacts with α,β-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines(III).

5. Dao-Lin& Kimiaki[246] have prepared 2-methoxy -3-cyano pyridine derivatives by the condensation of α,β- unsaturated ketones with malano nitrile in sodium methoxide.



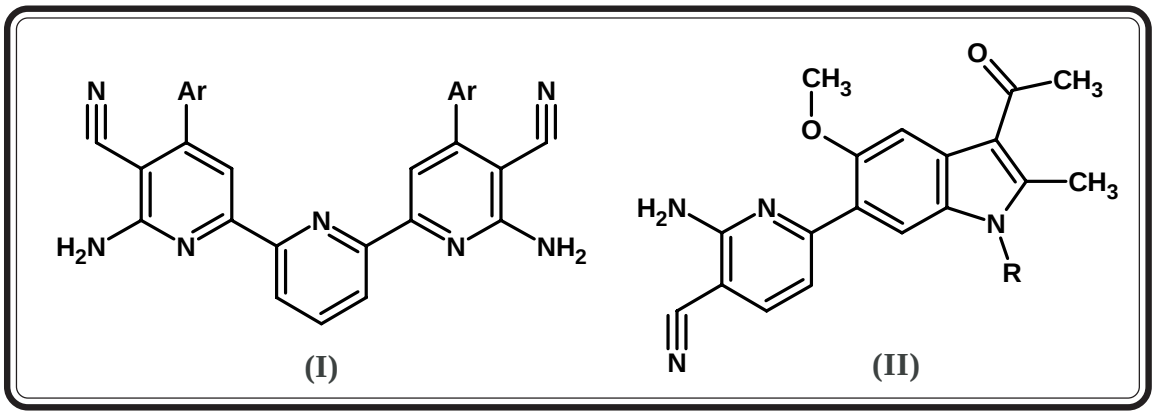
MECHANISM

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



THERAPEUTIC IMPORTANCE

Cyanopyridine have attracted considerable attention as they appeared of interest to possess antibacterial, anticholestemic, antifungal, antihypertensive and antidiabetic activities. Hammana Abou and co-workers[247] have studied anticancer and anti HIV activity of 3-cyanopyridines. Abdallah Navine et al.[248] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity. Manna Fedele and co-workers[249] have reported the antiinflammatory activity of 3-cyanopyridines. Yoshida H.et al.[250] have studied the antihistamic and antiallergic activity of 3-cyanopyridine derivatives. Abd El-Galil and co-workers[251] have prepared 3-cyanopyridines (I) and studied their pharmacological activity. Gadaginamath and co-workers[252] have synthesized various cyanopyridyl derivatives (II) and documented their variety of biological activities.



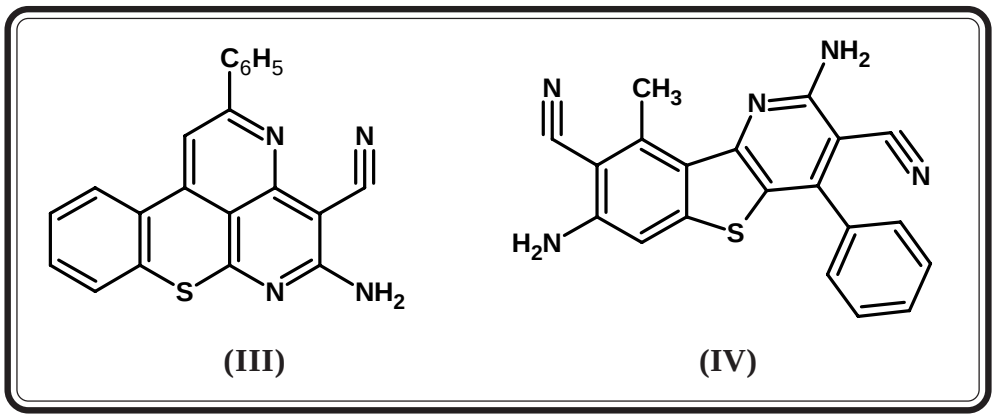
Roman S. V. et al.[253] have synthesized 2-amino-3-cyanopyridines and reported their biological activity. El-Taweel and co-workers[254] have prepared cyanopyridine derivatives and showed their significant biological activity. Parikh A.R.et al.[255] have synthesized 3-cyanopyridine derivatives as antimicrobial agent.

Hussan M. and co-workers[256] have prepared 3-cyanopyridines and reported their pharmacological activity. Pyachenko U. D. et al.[257] have synthesized some cyanopyridines which are useful in the treatment of retroviral disease.

Thiele Kurt et al.[258] have studied the analgesic activity of substituted 3-

cyanopyridines. N. Latif and co-workers[259] have reported the antibacterial and antifungal activity of 2-amino-3-cyano-4,6-disubstituted pyridines. M. Bernard et al.[260] have reported the anticonvulsant activity of 3-cyanopyridines. D.G. Bhatt et al.[261] have prepared 3-cyanopyridines as an immunosuppressive agent. U. Teu and co-workers[262] have shown cyanopyridine as agrochemical fungicides.

Van Allan J. A.et al.[263] have prepared fused heterocyclic 3-cyanopyridine (III). Abu and co-workers[264] have prepared novel fused cyanopyridines (IV) for the treatment and preparation of systemic fungal infection.



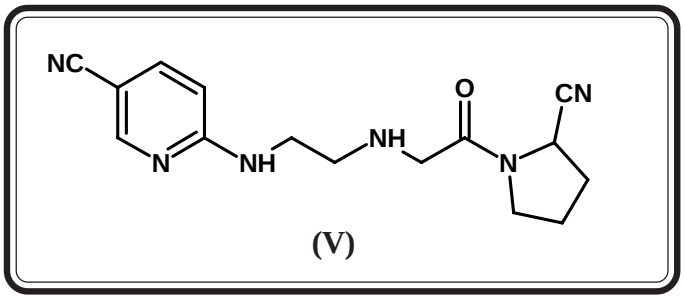
(III) **(IV)**

Kadlec K. and Hanslian[265] showed that 2-methyl-3-nitro-4-methoxyethyl-5-cyano-6-chloro pyridines caused occupational eczema in Vitamin B_6. Rigterink and Raymond[266] have studied the pesticidal activity of 3-cyanopyridines. Pavia M.R.et al.[267] have prepared N-substituted 2- aminopyridines which possess anticonvulsant property. 3-Cyanopyridines reported by L. Castedo et al.[268] showed a minimum inhibitory concentration of 1.56 μg/ml against *S.aureus*.

Baldwin J. J.[269-271] have prepared cyanopyridines exhibiting antihypertensive activity. Streightoff[272] and Seydel J.[273] have studied the bacteriostatic effect of some substituted 3-cyanopyridines. Francis and co-workers[274] have studied the effect of some substituted pyridines on the growth of the walker carcinosarcome-256 in tissue culture. Barton et al.[275] have reported fungicidal and insecticidal properties. W. Hoefling and co-workers[276] have studied 3 and 4-cyanopyridines as tuberculosis arresting agents.

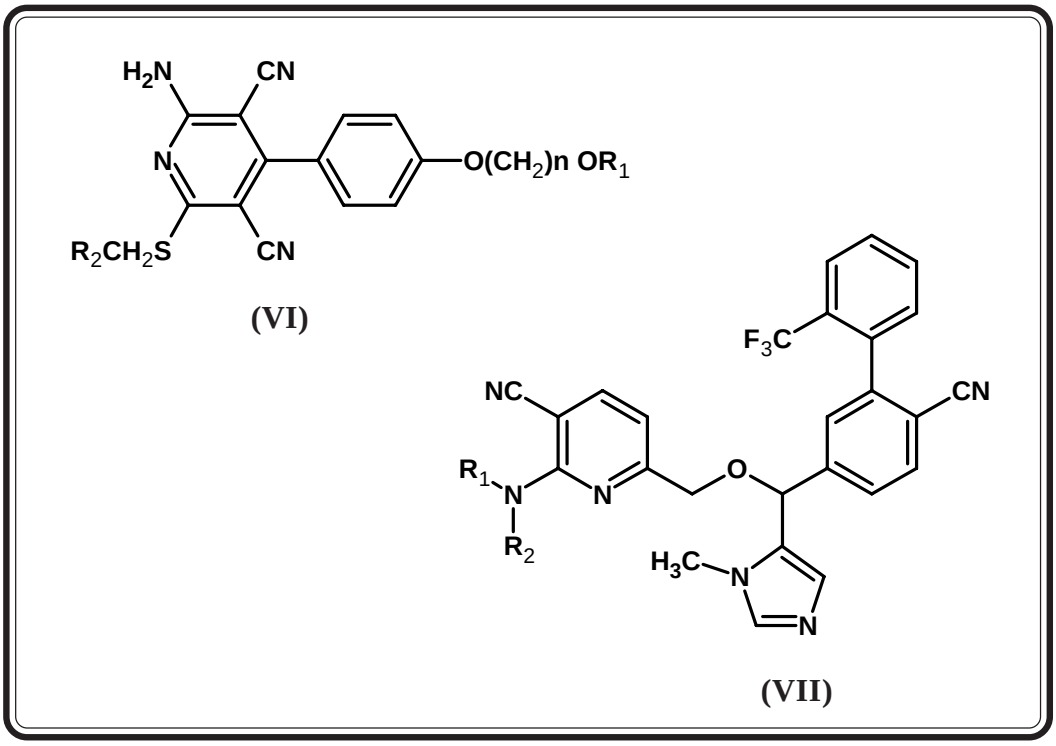
W.Von Behenburg and co-workers[277] have synthesized 2-amino-3,6- disubstituted pyridines as antiepileptic agents.

Dipeptidyl peptidase (DPP-IV) inhibition has the potential to become a valuable therapy for diabetes. Edwin B. Villhauer and co-workers[278] have reported the first use of solid-phase synthesis in the discovery of a new DPP-IV inhibitor class and a solution-phase synthesis that is practical up to the multikilogram scale. One compound, NVP-DPP728 (V), is profiled as a potent, selective and shortacting DPP-IV inhibitor that has excellent oral bioavailability and potent antihyperglycemic activity.

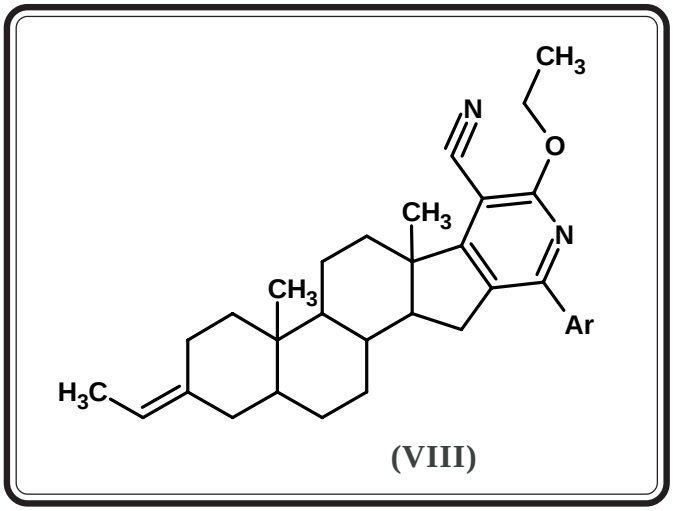


(V)

Marco J. L. et al.[279] have synthesized acetylcholinesterase inhibitors. Moustafa M. A. et al.[280] have prepared antibacterial agents. Eduardo H. S. Sousa et al.[281] documented thionicotinamide coordinated to a model system for the *in vitro* activation of thioamides antituberculosis drugs. Rosentreter Ulrich et al.[282] have synthesized a new cyanopyridine as receptor agonists in the treatment of cardiac or urogenital disease cancer, inflammation, neurodegenerative disease(VI). Gary T. Wang and co-workers[283] have synthesized o-trifluoromethylbiphenyl substituted 2-amino-nicotinonitriles as inhibitors of farnesyl transferase(VII). Abdel-Galil E. Amr and Mohamed M. Abdulla[284] have synthesized pyridine derivative (VIII) fused with steroidal structure.



(VI) **(VII)**



(VIII)

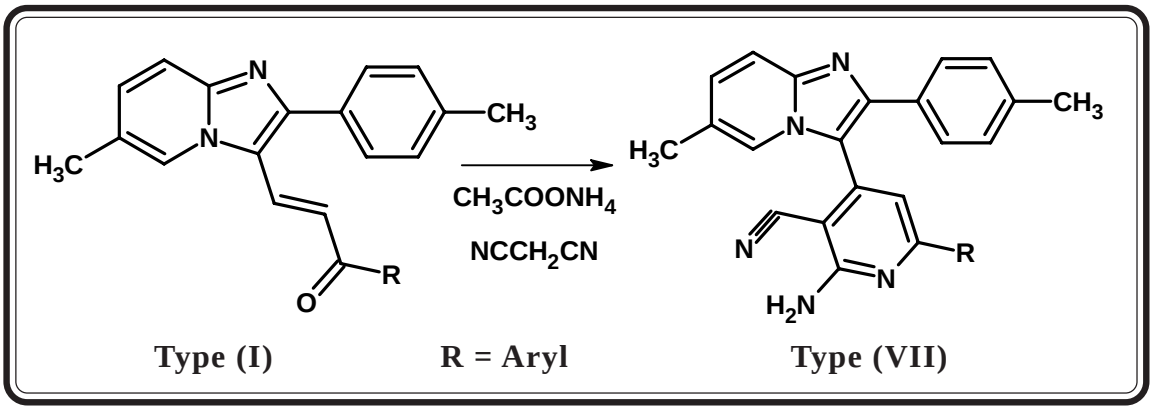
In view of therapeutic activities shown by cyanopyridines, it was contemplated to synthesise some new cyanopyridines in search of agents possessing higher biological activity with least side effect have been described as under.

SECTION-I :SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-6-ARYL-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]NICOTINONITRILES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-6-ARYL-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]NICOTINONITRILES

Cyanopyridines play a vital role owing to their range of biological and physiological activites. In the light of these biological activities and variety of industrial applications, some new 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles derivatives of type (VII) have been prepared by the cyclocondensation of 1-Aryl-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-ones with malononitrile in presence of ammonium acetate.

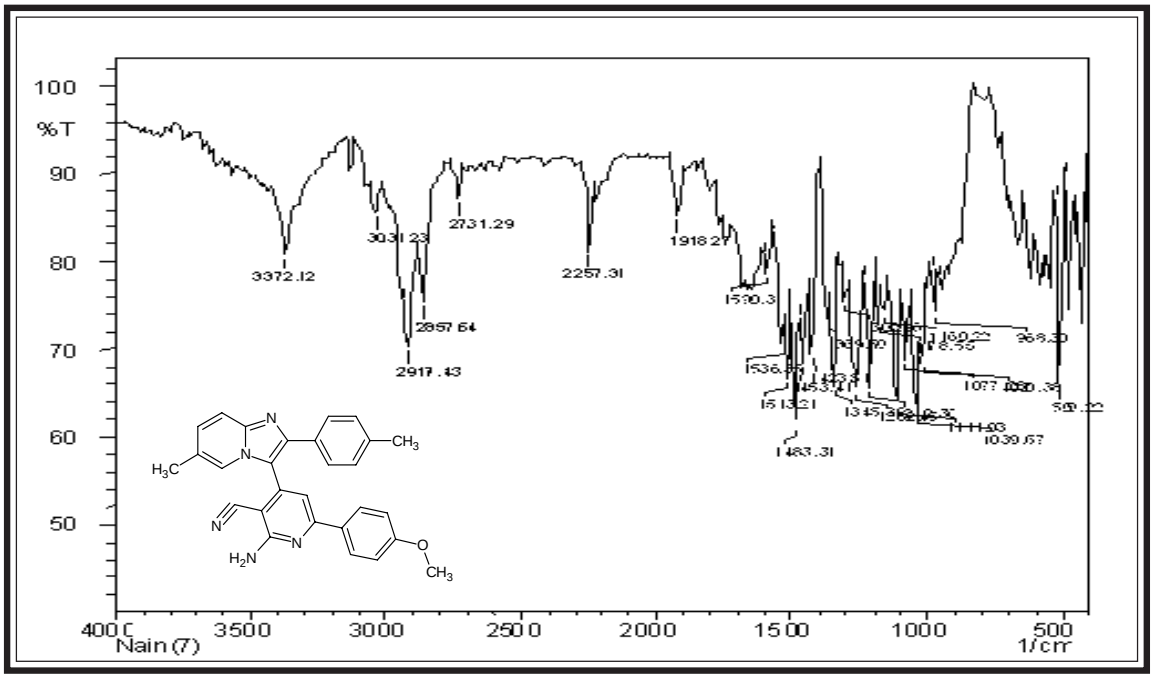


Type (I) **R = Aryl** **Type (VII)**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), pageno.047.

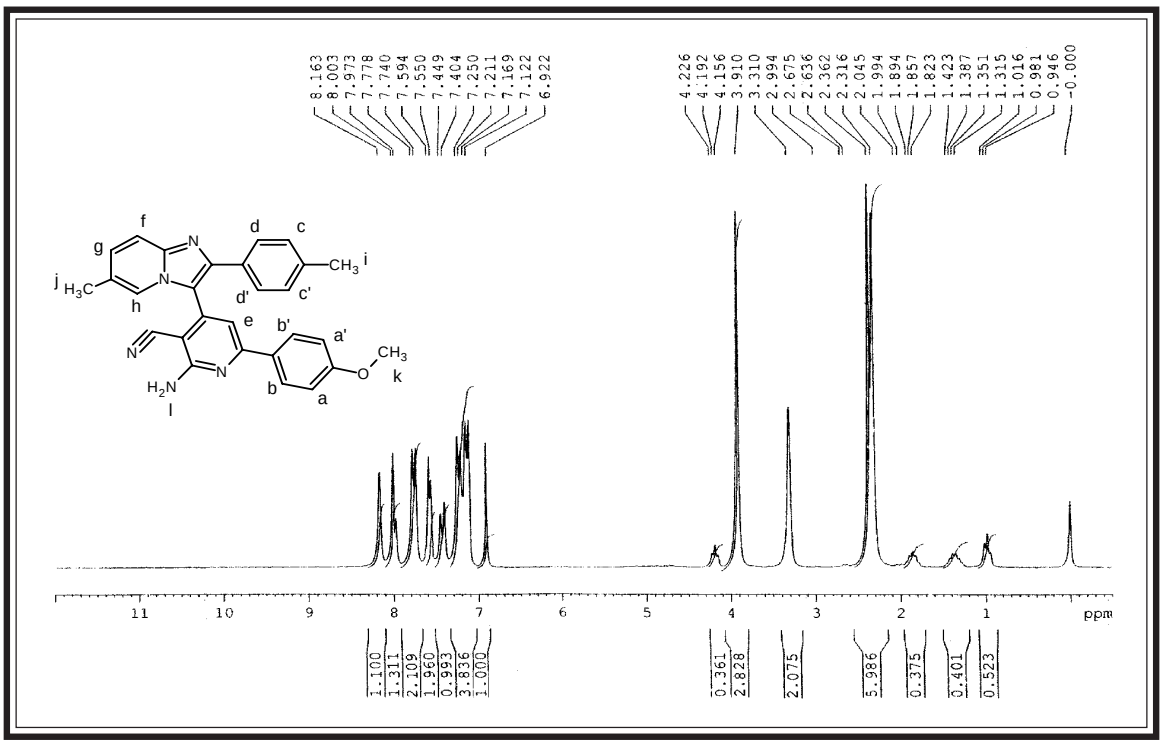
IR SPECTRAL STUDIES OF 2-AMINO-6-(4-METHOXYPHENYL)-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] NICOTINONITRILE



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

Type	Vibration	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2917	2975-2950	189
$-CH_3$	C-H str. (sym.)	2857	2880-2860	,,
	C-H def.(asym.)	1453	1470-1435	,,
	C-H def. (sym.)	1423	1390-1370	,,
Aromatic	C-Hstr.	3031	3090-3030	190
	C=C str.	1513	1540-1480	,,
	C-H o.o.p.(def)	800	800-850	,,
Amine	NH str.	3372	3400-3300	,,
Ether	C-O-C str.	1206	1260-1200	,,
Pyridine	C=C str.	1536	1650-1520	189
	C=N str.	1590	1580-1550	,,
Nitrile	C≡N str.	2257	2240-2120	,,
Imidazo[1,2-a]	C=N str.	1556	1580-1550	190
pyridine	C-N str.	1039	1220-1020	,,

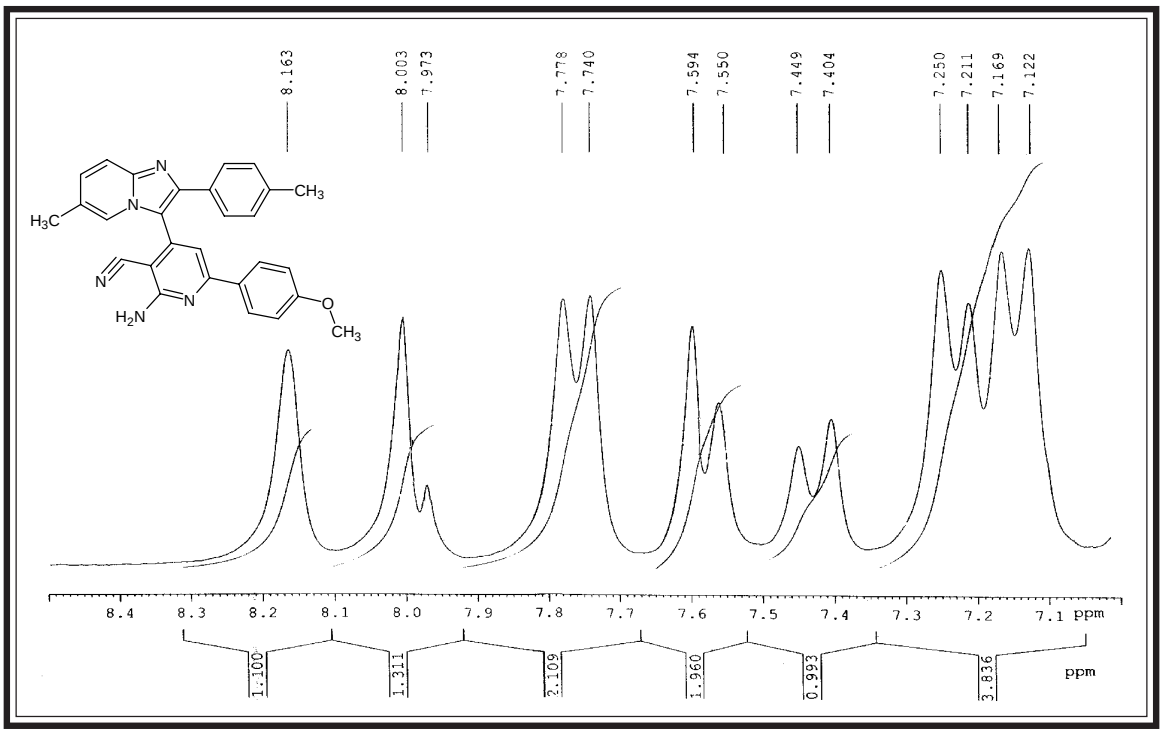
NMR SPECTRAL STUDIES OF 2-AMINO-6-(4-METHOXYPHENYL)-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] NICOTINONITRILE



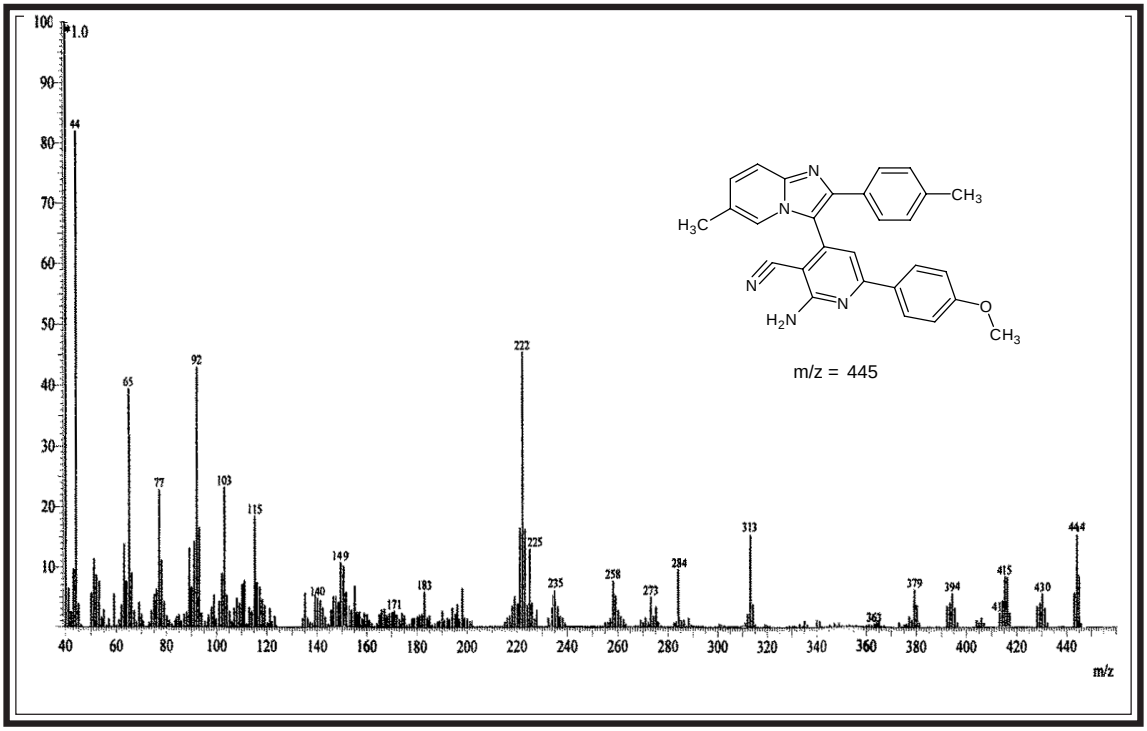
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.31	3H	singlet	Ar-CH_3(i)	-
2	2.34	3H	singlet	Ar-CH_3(j)	-
3	3.31	2H	singlet	NH_2(l)	-
4	3.91	3H	singlet	Ar-OCH_3(k)	-
5	6.92	1H	singlet	pyr- (e)	-
6	7.12-7.16	2H	doublet	Ar-H(a-a')	9.4
7	7.21-7.25	2H	doublet	Ar-H(c-c')	7.8
8	7.40-7.44	1H	doublet	Ar-H(g)	-
9	7.55-7.59	2H	doublet	Ar-H (d-d')	8.8
10	7.74-7.78	2H	doublet	Ar-H (b-b')	7.6
11	7.97-8.00	1H	doublet	Ar-(f)	-
12	8.16	1H	singlet	Ar-(h)	-

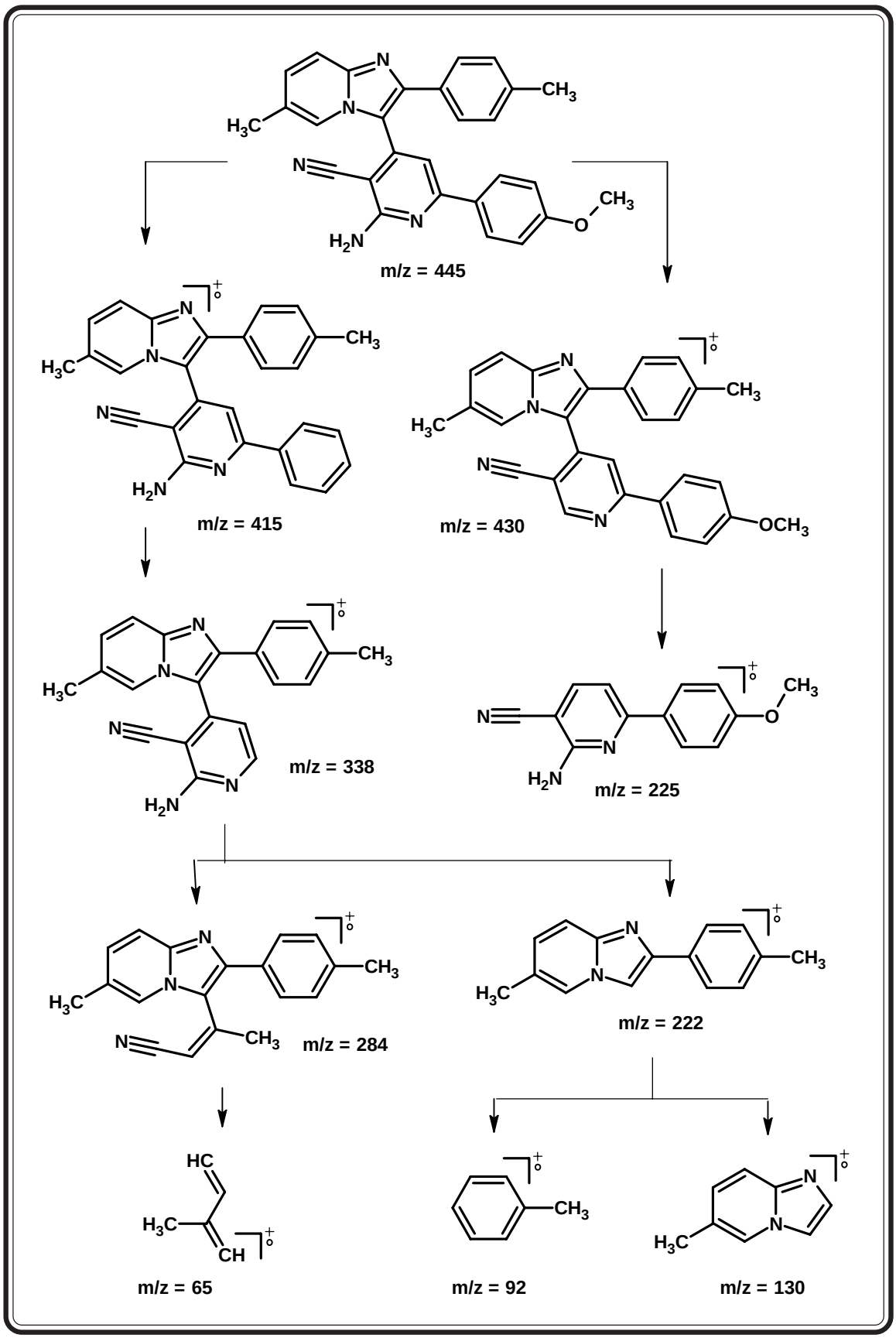
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF 2-AMINO-6-(4-METHOXYPHENYL)-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] NICOTINONITRILE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-6-ARYL-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]NICOTINONITRILES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See(A), part-I, section-I(A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde:

See(A), part-I, section-I(B), page no.046.

[C] Synthesis of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl) imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one :

See(A), part-I, section-I(C), page no.047.

[D] Synthesis of 2-Amino-6-(4-methoxyphenyl)-4-[6-methyl-2-(4-methyl phenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitrile :

A mixture of 1-(4-Methoxyphenyl)-3-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*] pyridin-3-yl]prop-2-ene-1-one 3.82gm (0.01mol), malononitrile 0.66 gm (0.01 mol) and ammonium acetate 6.16gm (0.08 mol) dissolved in methanol was refluxed for 12 hrs. The reaction mixture was poured into crushed ice and kept overnight. Solid separated was filtered and recrystallized from ethanol. Yield, 68%, m.p. 245^{o}C. Elemental Analysis Calculated for $C_{28}H_{23}N_5O$; Requires : C-75.49%, H-5.20%, N-15.72 %; Found : C-75.41%, H-5.15, N-15.73%.

Similarly, other 2-Amino-6-aryl-4-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles were synthesized. The physical data are recorded in table no.07.

[E] Antimicrobial activity of 2-Amino-6-aryl-4-[6-methyl-2-(4-methyl phenyl) imidazo[1,2-*a*]pyridin-3-yl]nicotinonitriles :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.047. The zones of inhibition of the test solutions are recorded in graphical chart no.07.

Conclusion :

Antibacterial activity

The screening data indicated that among cyanopyridine derivatives tested compounds **7f**, **7j**, **7l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **7k** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **7a, 7g** and **7c, 7h, 7j** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

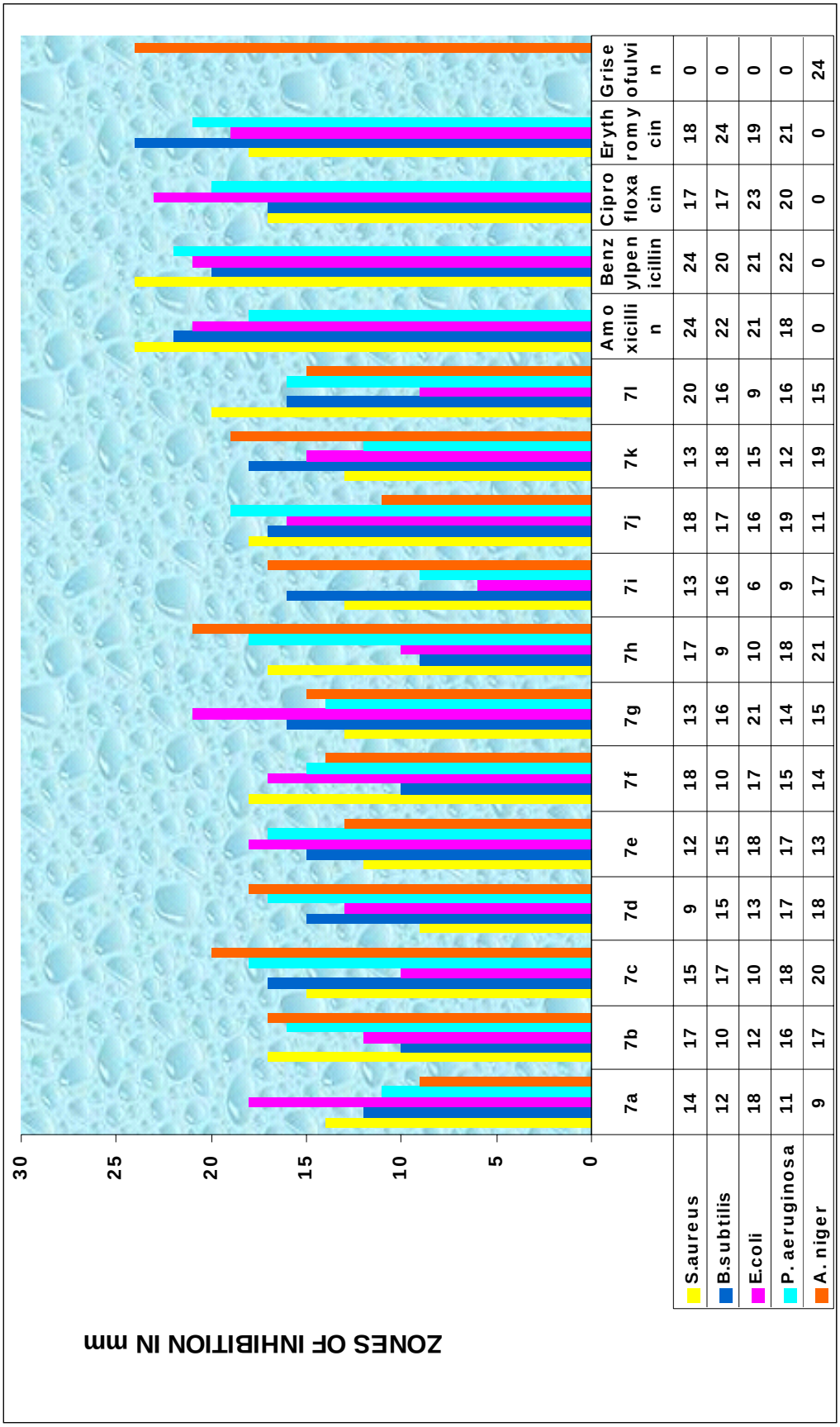
The screening data indicated that among cyanopyridine derivatives tested compounds **7c, 7d, 7k** showed greater degree of antifungal activity against *A.niger.*

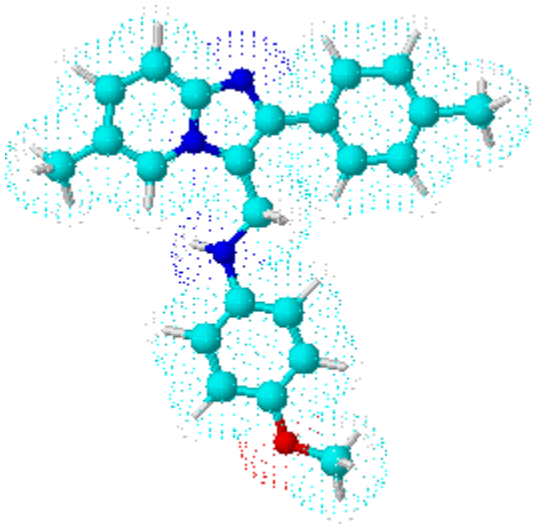
TABLE - 07: PHYSICAL CONSTANTS OF 2-AMINO-6-ARYL-4-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*] PYRIDIN-3-YL]NICOTINONITRILES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
7a	C_6H_5-	$C_{27}H_{21}N_5$	415	158	71	16.86	16.81	0.51	S_1
7b	4-Cl-C_6H_4-	$C_{27}H_{20}ClN_5$	449.5	240	65	15.57	15.59	0.48	S_1
7c	2,4-$(Cl)_2$-C_6H_3-	$C_{27}H_{19}Cl_2N_5$	484	dec.200	74	14.46	14.54	0.50	S_2
7d	4-NO_2-C_6H_4-	$C_{27}H_{20}N_6O_2$	460	144	64	18.25	18.31	0.47	S_1
7e	4-OCH_3-C_6H_4-	$C_{28}H_{23}N_5O$	445	245	68	15.72	15.79	0.55	S_1
7f	4-CH_3-C_6H_4-	$C_{28}H_{23}N_5$	429	189	65	16.31	16.27	0.41	S_2
7g	4-OH-3-OCH_3-C_6H	$C_{28}H_{23}N_5O_2$	461	226	58	15.17	15.27	0.48	S_2
7h	4-Br-C_6H_4-	$C_{27}H_{20}BrN_5$	494	196	72	14.17	14.12	0.50	S_1
7i	2-OH-C_6H_4-	$C_{27}H_{21}N_5O$	431	190	59	16.23	16.28	0.55	S_2
7j	4-OH-C_6H_4-	$C_{27}H_{21}N_5O$	431	145	68	16.23	16.31	0.54	S_2
7k	4-NH_2-C_6H_4-	$C_{27}H_{22}N_6$	430	230	70	19.52	19.47	0.47	S_2
71	2-C_4H_3S-	$C_{25}H_{19}N_5S$	421	110	71	16.61	16.54	0.48	S_2

S_1 Ethyl acetate : Hexane (5 : 5), S_2 Ethyl acetate : Toluene (4 : 6).

Graphical Chart No. 07 : ANTIMICROBIAL ACTIVITY OF 2-AMINO-6-ARYL-4-[6-METHYL-2-(4-METHYL PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]NICOTINONITRILES





PART - IV

STUDIES ON ARYL AMINOMETHYL DERIVATIVES

INTRODUCTION

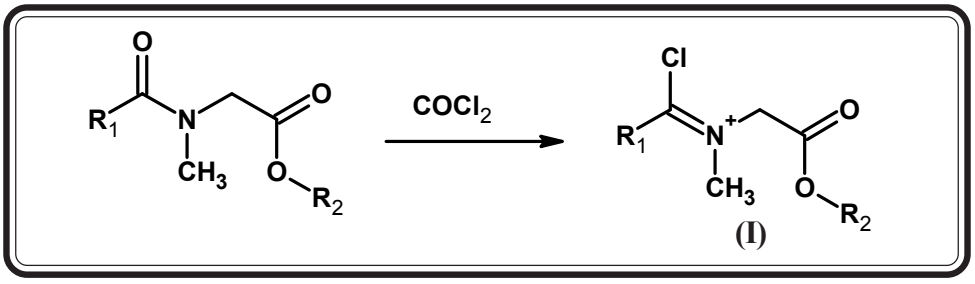
In recent years, interest has also focused on aza-analogs such as azomethine derivatives which show a very similar pharmacological profile. Over the past few years, several compounds have been developed. Azomethines are also known as schiff's bases and they are well known intermediates for the preparation of azetidinones, thiazolidinone, formazan, arylacetamide and many other entities of pharamaceutical potential. These are the compounds containing characteristic –HC=N– group.

Azomethines are obtained mainly by warming the aldehyde & aromatic amine togather. Howeve, 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. Synthetic Schiff's base derivatives contribute in huge libraries owing to their wide applicability in different fields.

SYNTHETIC ASPECT

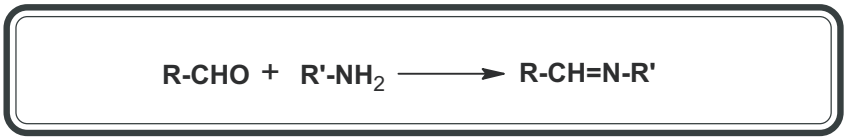
Different methods for the preparation of azomethine derivatives documented in literature are described as under.

1. A new one pot procedure for the generation of azomethine via chlorominium salt has been investigated by Rosaleen J. Anderson and co-workers.[285]



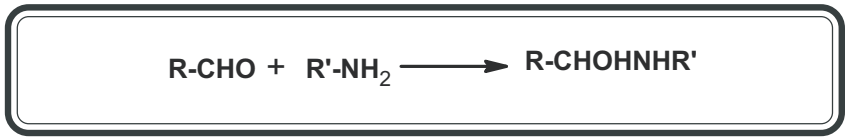
(I)

2. General account of the summary of reaction of aldehydes with amine (aromatic or aliphatic) has been reviewed by Murray. [286]

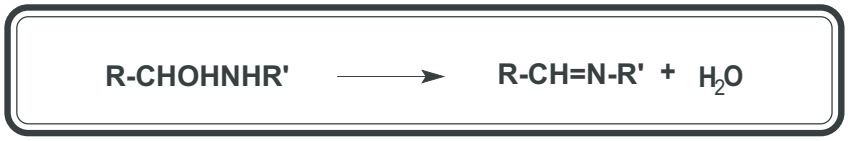


3. Strache[287] and Van Alphen [288] have prepared imine involves in two steps.

a. Reaction of amine and aldehyde gives aldol. Which is rarely capable of isolation.

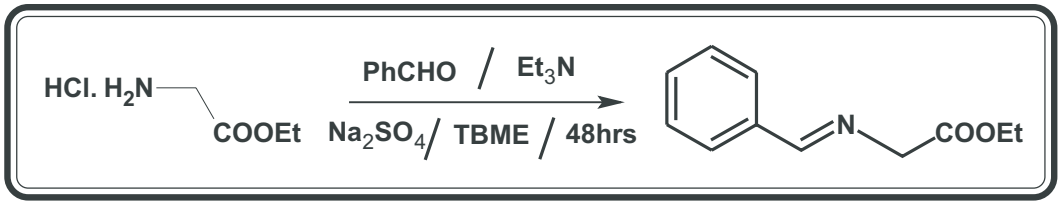


b. The loss of water to give an imine (azomethine), this corresponds to the "crotonaldehyde stage" of the aldol condensation.

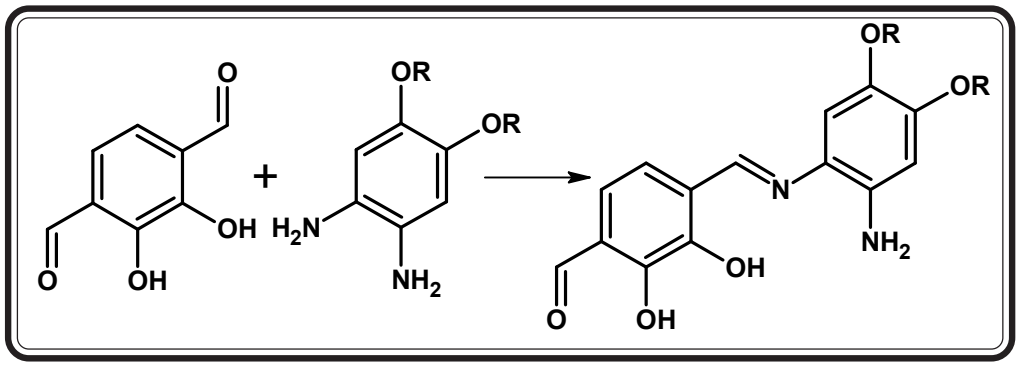


4. Oddo & Tognacchini [289] have introduced the comparative rates of formation of Schiff 's base from aromatic amine and aromatic aldehyde using a cryscopic method follow the course of reaction.

Pierre L. Beaulieu and co-workers [290] have synthesized (*E*)-*N*-phenyl methylene glycine ethyl ester by the cyclocondensation of glycine ethyl ester hydrochloride, *t*-butylmethyl ether (TBME), benzaldehyde was added followed by anhydrous Na_2SO_4 and triethylamine.



Amanda J. Gallant et al. [291] have prepared schiff 's bases by condensation of equimolar quantity of 3,6 diformyl catechol and substituted o-phenylenediamine.

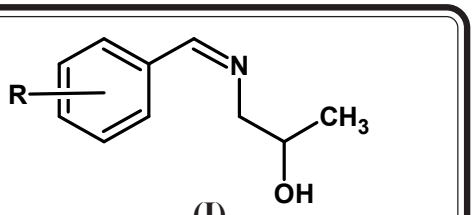


THERAPEUTIC IMPORTANCE

Literature survey reveals that various azomethines have resulted in many potential drugs and are known to possess broad spectrum of biological activites.

1. Antiviral[292]
2. Antifungal[293]
3. Antiparasitic[294]
4. Antibacterial[295]
5. Antipyretic[296]
6. Anti-inflammatory[297]
7. Plant hormone activity[298]
8. Antitubercular[299]

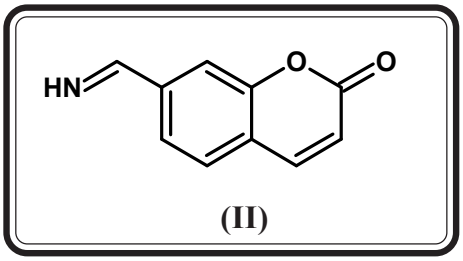
Smalders et al.[300] synthesized some new azomethine as potential antitumor agents. Sharaf El-Din and Nabaweya[301] have synthesized some azomethine derivatives (I) having good antibacterial activity. Chohan et al.[302] have synthesized azomethines, which have been screened and compared for their antibacterial action against bacterial species *Escherichia coli*, *Pesudomonas aeruginose* and *Klebisella pneumoniasa*.



(I)

R = 3,4 -OH, 3,4-NO_2

Schiff's bases exhibit a wide range of pharmacological activities like antifungal, antibacterial, antiviral, anti-inflammatory, etc. Mehta R. H. et al.[303] have synthesized coummarin schiff's base derivatives (II) and examined for their antibacterial activity. Khalafallah A. K. and Hassan M. E.[304] have prepared some styryl Schiff's bases spiro derivatives as potential antibacterial and antifungal activity.

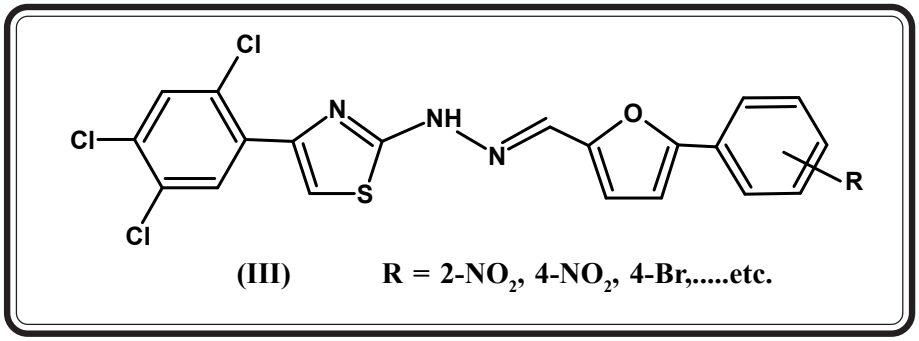


(II)

Deshmukh M. D. and Doshi A.G.[305] 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.[306] have synthesized diazomethines having good plant hormone activity. Das Arima et al.[307] 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).

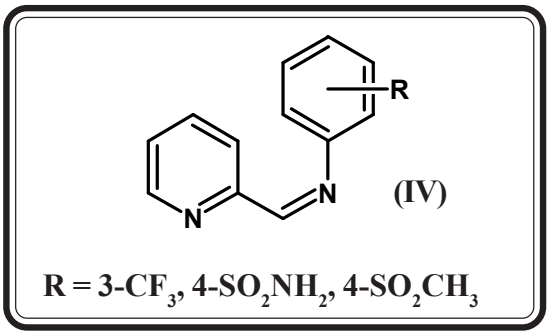
Sabrina Castellano et. al.[308] have prepared azomethine derivatives and evaluated *in vitro* against several pathogenic fungi responsible for human disease. B. Shivarama Holla et. al.[309] have documented antibacterial, antifungal and herbicidal activity of azomethine derivatives.Wang, Yangang and co-workers[310] have screened some azomethines having good plant homone activity. Pascal Rathelst et. al.[311]have reported some new azomethines as antiparasitic agents.

B.Shivarama Holla., et al.[312] have synthesized azomethines of type (III) having antibacterial and anti-inflammatory activity. Dimmock J. et. al.[313] have reported azomethines as cytotoxic agents.



(III) **R = 2-NO_2, 4-NO_2, 4-Br,.....etc.**

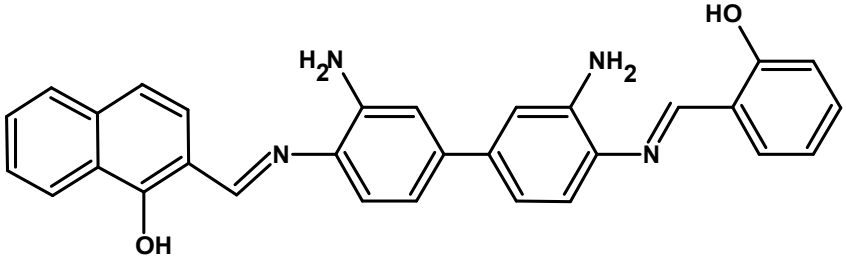
Iana Vazzana et. al.[314] have synthesised derivatives (IV) and reported them as anti-inflammatory agents. Neslihan and Reyhan[315] have synthesised azomethines and studied their antitumor activity. R. S. Varma[316] has been synthesised a series of new azomethines.



(IV)

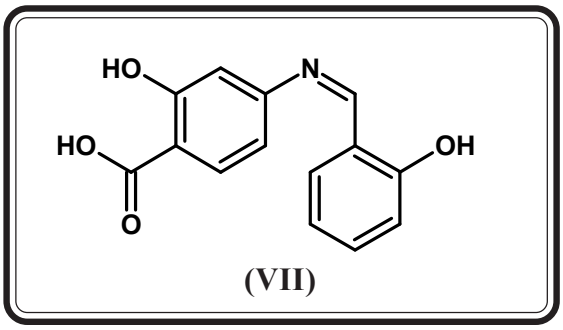
R = 3-CF_3, 4-SO_2NH_2, 4-SO_2CH_3

Recently, Parumal P. Selvam and co-workers[317] have synthesised azomethine derivatives and reported their antimicrobial activity. Zhanyong Guo et.al.[318-319] have synthesised schiff's base of carboxymethyl chitosan and reported their *in vitro* antifungal and antioxident activity. Sham M. Sondhi et. al.[320] have synthesised azomethine derivatives(IV) and documented their anti-inflammatory, analgesic and kinase (CDK-1, CDK-5, and GSK-3) inhibition activity.



(V)

Jayendra Patole et. al.[321] have reported schiff's base (VI) conjugates of p-Amino salicyclic acid containing hydroxyl-rich side chains show enhanced antimycobacterial activity against mycobacterium smegmatis and mycobaterium bovis BCG. Alaaddin Cukurovali et. al.[322] have designed and synthesized azomethine derivatives and investigated their antibacterial and antifungal activity. Anti-HIV ativity of schiff's base have reported by Dharmarajan and co-workers.[323]



(VII)

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

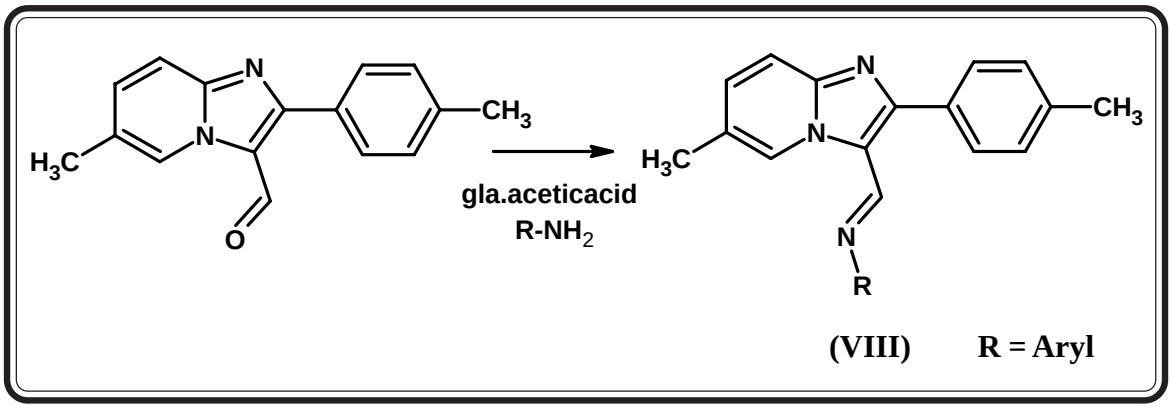
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*] PYRIDIN-3-YL]METHANIMINES

SECTION-II :SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINES

Looking to the interesting properties of azomethines, with an intension to synthesising better therapeutic agents, azomethine derivatives of type (VIII) have been synthesized by the condensation of 2-(4-Methylephenyl)imidazo[1,2-*a*]pyridin-3-carbaldehyde with different aromatic amines in order to study their biodynamic behaviour.

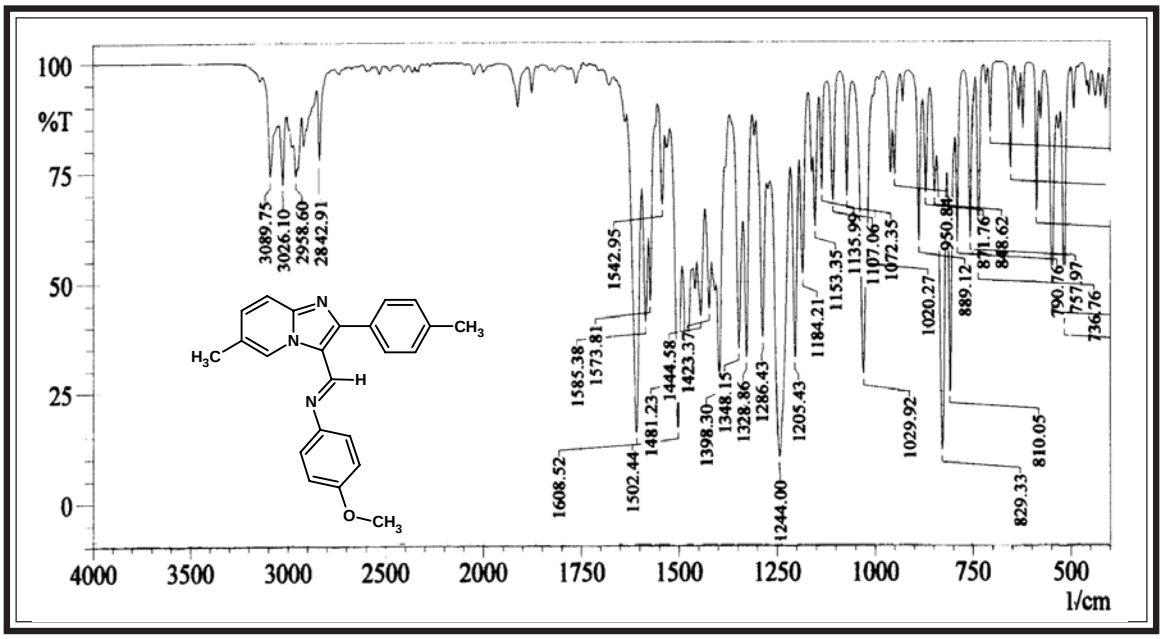


(VIII) **R = Aryl**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in(A), part-I, section-I(E), page no.047.

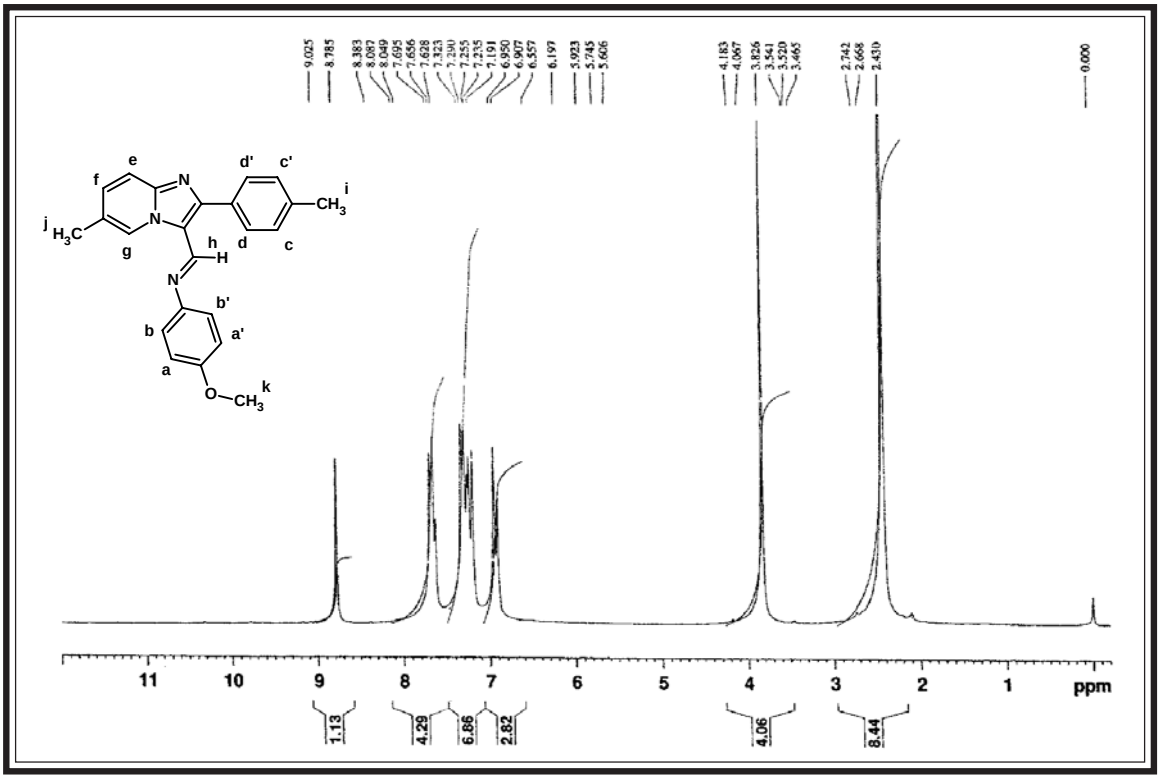
IR SPECTRAL STUDIES OF *N*-(4-METHOXYPHENYL)-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		observed	Reported	
Alkane	C-H str. (asym.)	2958	2975-2950	189
$-CH_3$	C-H str. (sym.)	2852	2880-2860	,,
	C-H def. (asym.)	1444	1470-1435	,,
	C-H def. (sym.)	1398	1390-1370	,,
Aromatic C-H str.	C-H str.	3026	3090-3030	190
	C=C str.	1481	1540-1480	,,
	C-H i.p. (def.)	1107	1125-1090	,,
		1029	1070-1000	,,
		829	835-810	,,
Imidazo[1,2-a]	C=N str.	1585	1612-1593	189
pyridine	C-N str.	1244	1220-1020	,,
Schiff's base	C=N str.	1608	1660-1580	,,

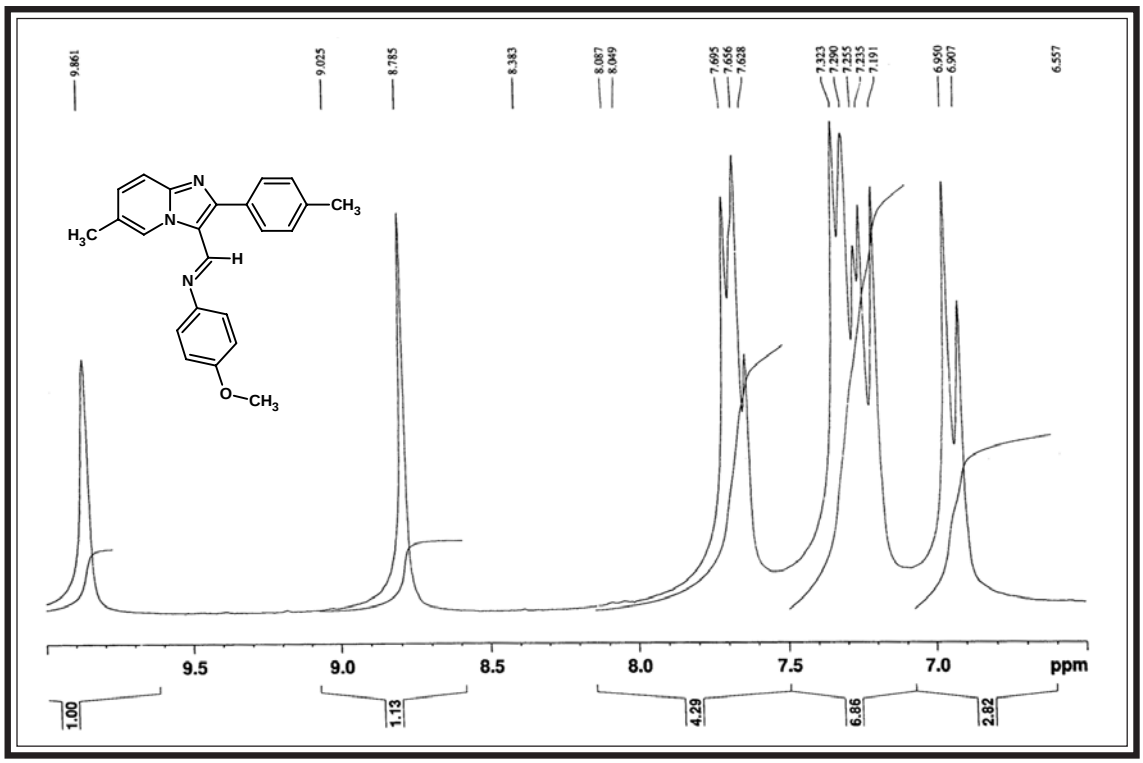
NMR SPECTRAL STUDIES OF *N*-(4-METHOXYPHENYL)-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINE



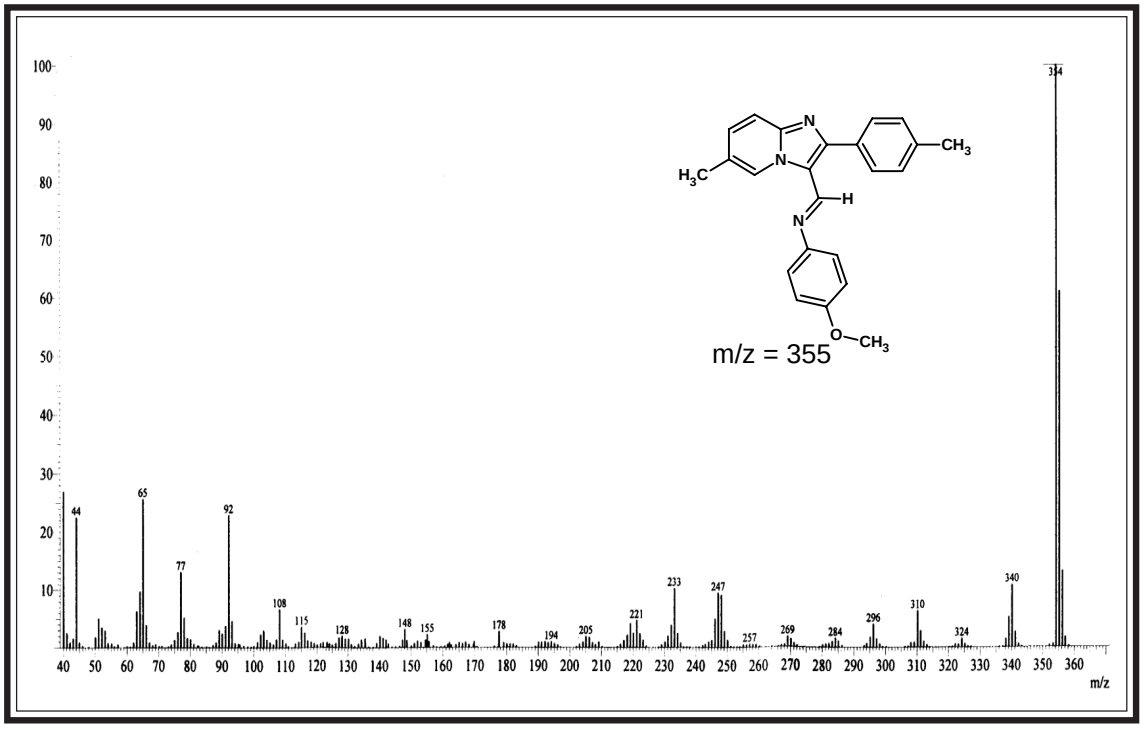
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.43	6H	singlet	Ar-CH_3(i-j)	-
2	3.82	3H	singlet	Ar-OCH_3(k)	-
3	6.90-6.95	2H	doublet	Ar-H(a-a')	8.6
4	7.19-7.23	2H	doublet	Ar-H(b-b')	8.8
5	7.25	2H	doublet	Ar-H(c-c')	7.0
6	7.29-7.32	2H	doublet	Ar-H(f-e)	6.6
7	7.62	1H	singlet	Ar-H(g)	-
8	7.65-7.69	2H	doublet	Ar-H(d-d')	7.8
9	8.78	1H	singlet	Ar-N=CH-(h)	-

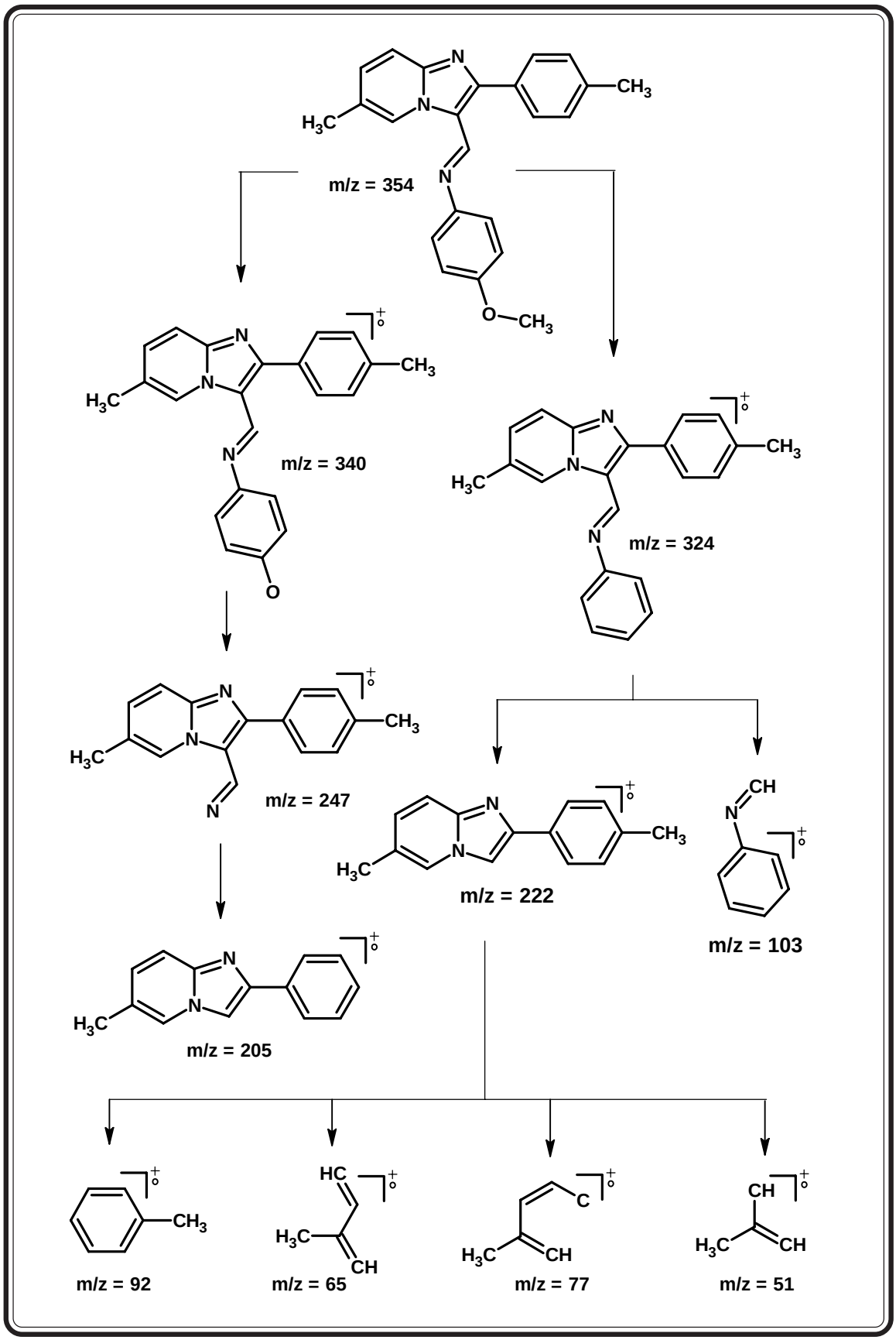
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF *N*-(4-METHOXYPHENYL)-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF (*E*)-*N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

See(A), part-I, section-I(A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde :

See(A), part-I, section-I(B), page no.046.

[C] Preparation of *N*-(4-Methoxyphenyl)-1-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]methanimine :

A mixture of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde 2.5g (0.01mol), p-anisidine 1.23g (0.01mol) and catalytic amount of glacial acetic acid in 20 ml methanol was refluxed for 16hrs. The contents was cooled and product isolated by filtration and dryed it. The crude product was recrystallized from methanol. Yield, 75%, m.p. 178 ^{o}C, Elemental Analysis Calculated for $C_{23}H_{21}N_3O$; Found : C-77.93%, H-5.66%, N-11.75%; Requires : C-77.72%, H-5.96%, N-11.82%.

Similarly, *N*-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines have been prepared. The physical data are recorded in table no.08.

[D] Biological screening of *N*-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridin-3-yl]methanimines :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), pageno.047. The zones of inhibition of test solutions are reported in graphical chart no.08.

Conclusion :

Antibacterial activity

The screening data indicated that among Schiff's base derivatives tested compounds **8d, 8k** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **8a, 8b, 8e, 8j, 8k** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **8i, 8k, 8l** and **8f, 8g, 8h, 8l** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

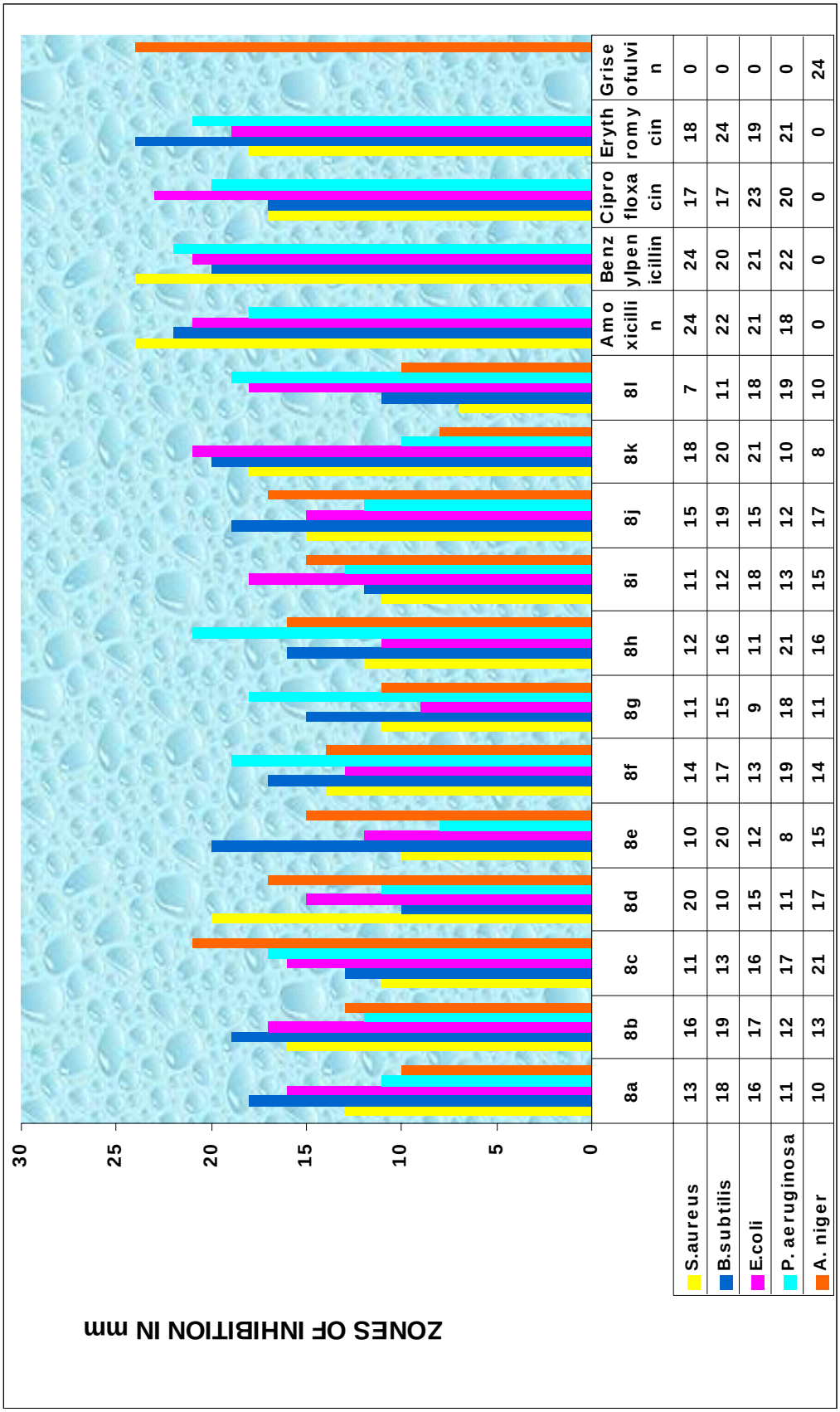
The screening data indicated that among Schiff's derivatives tested compounds **8c** showed greater degree of antifungal activity against *A.niger.*

TABLE -08 : PHYSICAL CONSTANTS OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
8a	4-OCH_3-C_6H_4-	$C_{23}H_{21}N_3O$	355	178	75	11.83	11.80	0.49	S_1
8b	4-OH-C_6H_4-	$C_{22}H_{19}N_3O$	341	186	62	12.31	12.25	0.47	S_1
8c	C_6H_5-	$C_{22}H_{19}N_3$	325	222	72	12.92	12.89	0.45	S_2
8d	4-Cl-C_6H_4-	$C_{22}H_{18}ClN_3$	359.5	236	65	11.68	11.75	0.47	S_2
8e	3-Cl-C_6H_4-	$C_{22}H_{18}ClN_3$	359.5	148	71	11.68	11.67	0.51	S_2
8f	2,5-$(Cl)_2$-C_6H_3-	$C_{22}H_{17}Cl_2N_3$	394	108	73	10.65	10.67	0.49	S_1
8g	3,4 -$(Cl)_2$-C_6H_3-	$C_{22}H_{17}Cl_2N_3$	394	225	65	10.65	10.59	0.55	S_2
8h	4-F-C_6H_4-	$C_{22}H_{18}FN_3$	343	184	70	12.24	12.27	0.54	S_1
8i	3-NO_2-C_6H_4-	$C_{22}H_{18}N_4O_2$	370	166	61	15.13	15.20	0.43	S_1
8j	4-NO_2-C_6H_4-	$C_{22}H_{18}N_4O_2$	370	120	78	15.13	15.10	0.42	S_2
8k	1-$C_{10}H_7$-	$C_{26}H_{21}N_3$	375	dec.176	64	11.2	11.19	0.45	S_1
8l	3-CH_3-C_6H_4-	$C_{23}H_{21}N_3$	339	118	62	12.38	12.41	0.47	S_2

S_1Ethyl acetate : Hexane (2 : 8), S_2 Toluene : Ethyl acetate (6 : 4)

Graphical Chart No. 08 : ANTIMICROBIAL ACTIVITY OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANIMINES

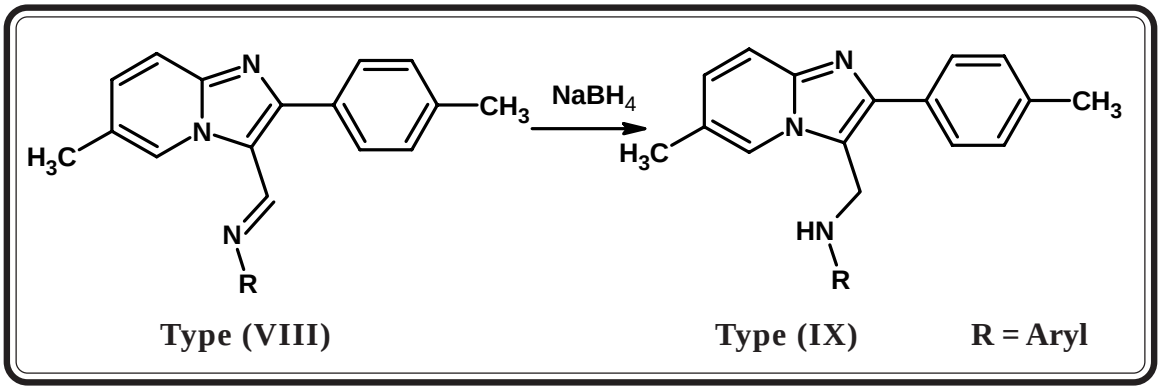


	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	13	16	11	20	10	14	11	12	11	15	18	7	24	24	17	18	0
B.subtilis	18	19	13	10	20	17	15	16	12	19	20	11	22	20	17	24	0
E.coli	16	17	16	15	12	13	9	11	18	15	21	18	21	21	23	19	0
P. aeruginosa	11	12	17	11	8	19	18	21	13	12	10	19	18	22	20	21	0
A. niger	10	13	21	17	15	14	11	16	15	17	8	10	0	0	0	0	24

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINES

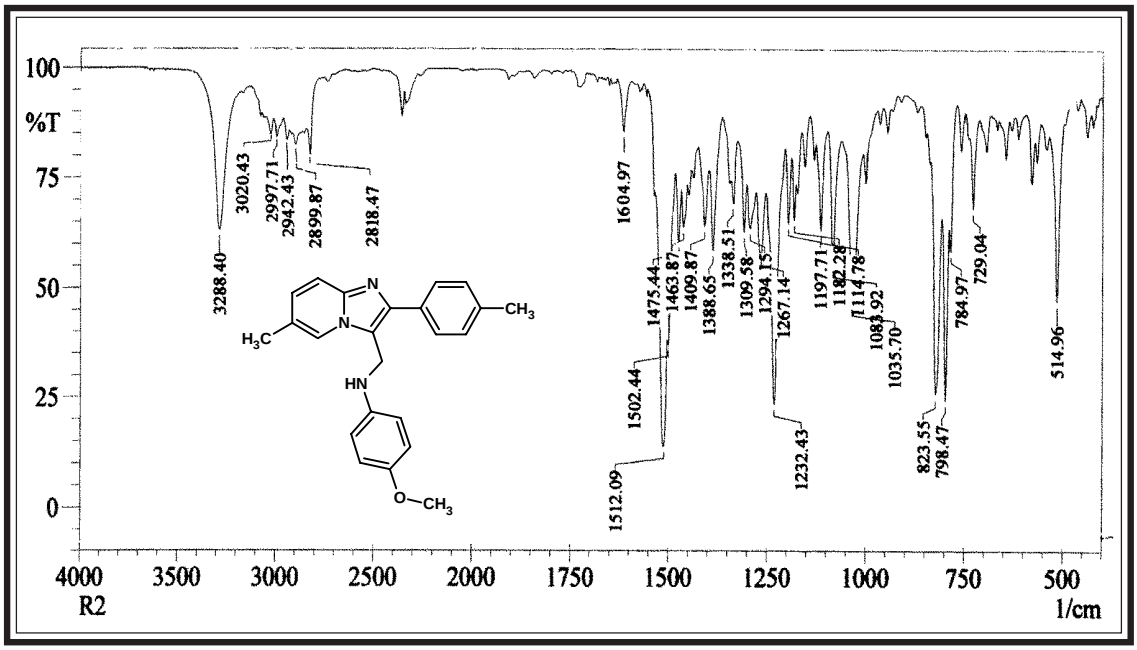
Aminomethyl derivatives of heterocyclic compounds are associated with diverse biological activities. These finding prompted us to synthesize some representative aminomethyl derivative of type (IX) bearing imidazo[1,2-*a*]pyridine moiety obtained by selective reduction of schiff's bases(imine group) of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



The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR 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* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in(A), part-I, section-I(E), page no.047.

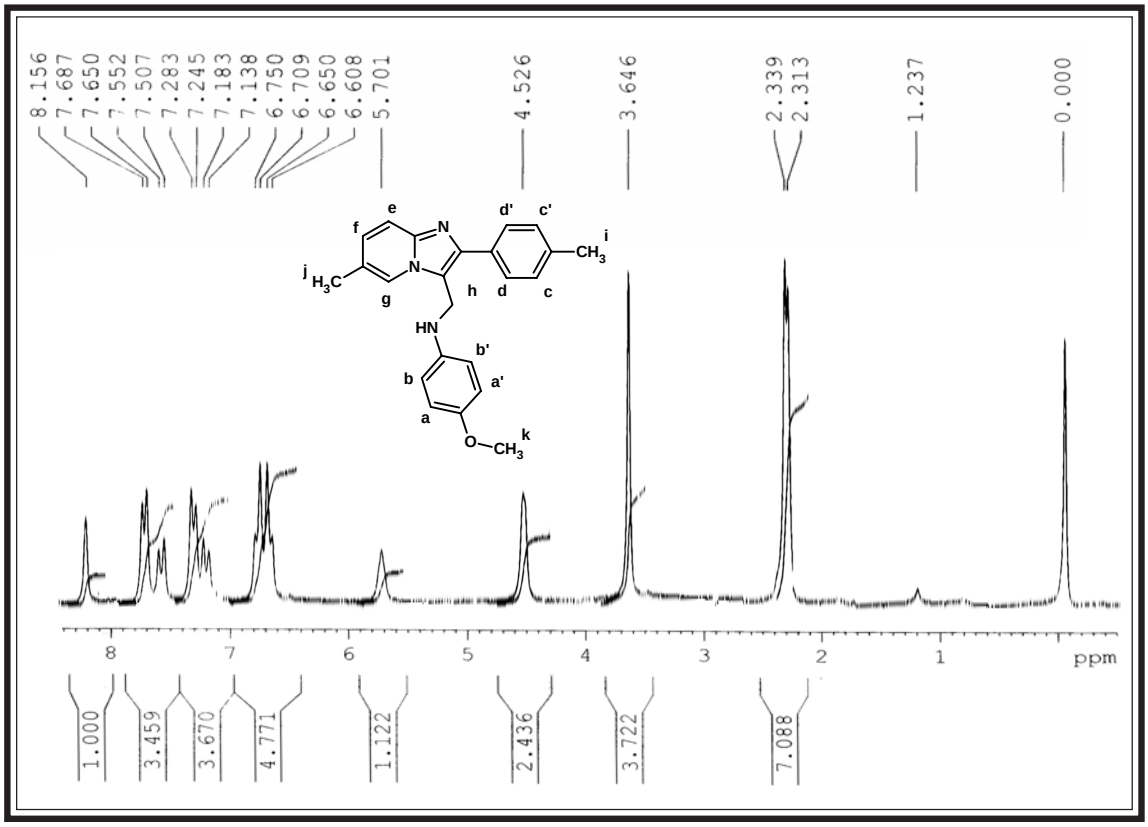
IR SPECTRAL STUDIES OF *N*-(4-METHOXYPHENYL)-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINE



Instrument : SHIMADZU FTIR 8400 Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		observed	Reported	
Alkane	C-H str. (asym.)	2942	2975-2950	189
-CH_3	C-H str. (sym.)	2899	2880-2860	,,
	C-H def. (asym.)	1463	1470-1435	,,
	C-H def. (sym.)	1388	1390-1370	,,
Aromatic C-H str.	C-H str.	3020	3090-3030	190
	C=C str.	1512	1540-1480	,,
	C-H i.p. (def.)	1114	1125-1090	,,
		1035	1070-1000	,,
		823	835-810	,,
Imidazo[1,2-a]	C=N str.	1604	1612-1593	190
pyridine	C-N str.	1232	1220-1020	,,
Amine	N-H str.	3288	3400-3200	,,

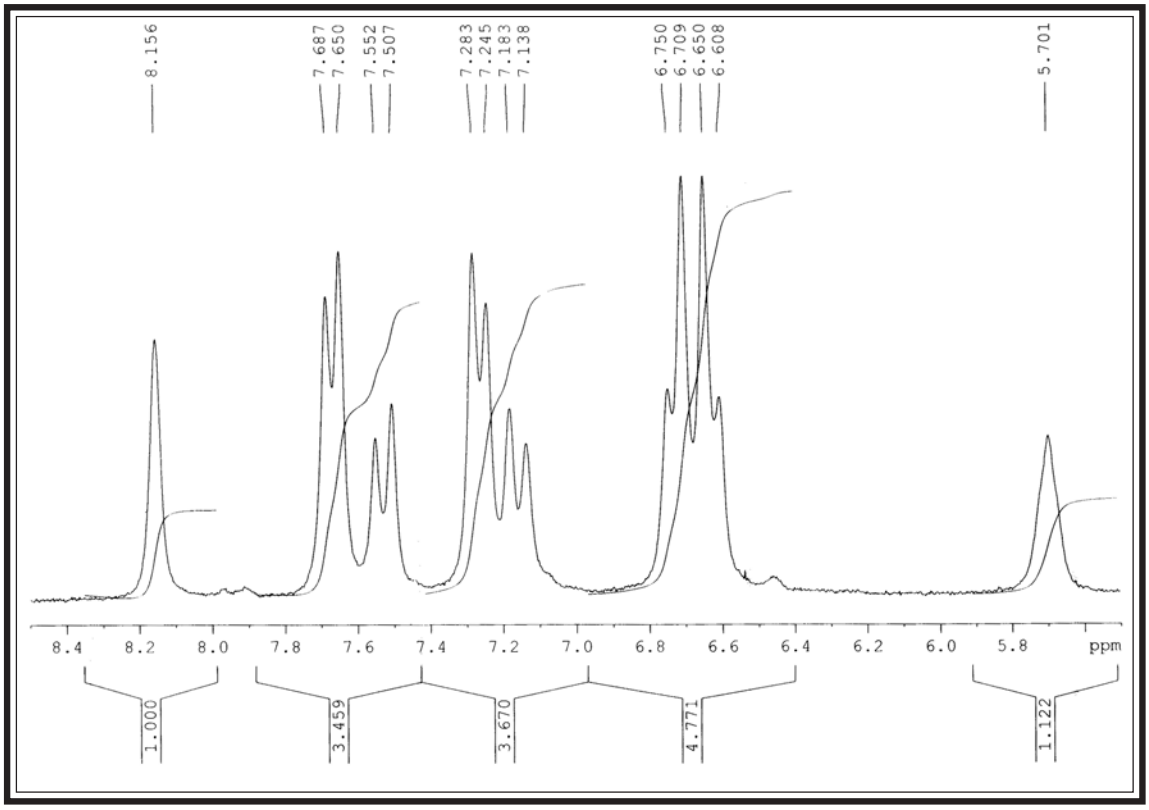
NMR SPECTRAL STUDIES OF *N*-(4-METHOXYPHENYL)-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINE



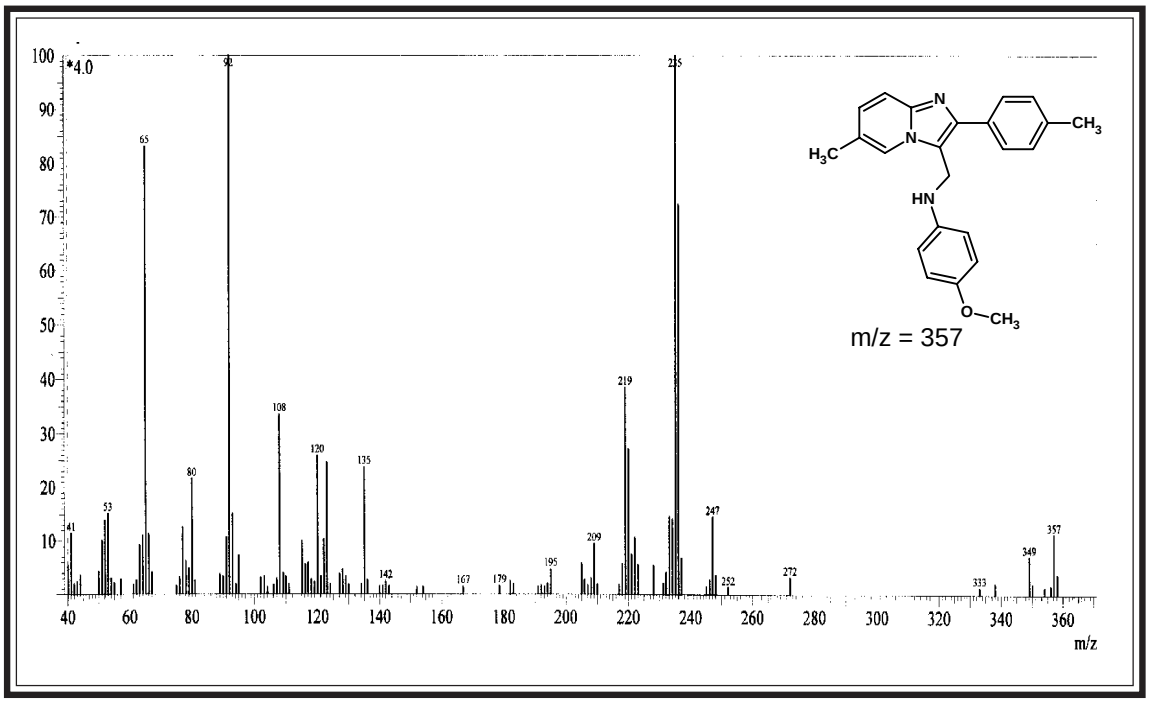
Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (200 MHz)

Signal No.	Signal Position (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	2.31	3H	singlet	Ar-CH_3(i)	-
2	2.33	3H	singlet	Ar-CH_3(j)	-
3	3.64	3H	singlet	Ar-OCH_3(k)	-
4	4.52	2H	singlet	Ar-N-CH_2-(h)	-
5	5.70	1H	singlet	Ar-NH	-
6	6.60-6.65	2H	doublet	Ar-H(b-b')	8.4
7	6.70-6.75	2H	doublet	Ar-H(a-a')	8.4
8	7.13-7.18	2H	doublet	Ar-H(f)	9.0
9	7.24-7.28	2H	doublet	Ar-H(c-c')	7.6
10	7.50-7.55	1H	doublet	Ar-H(e)	9.0
11	7.65-7.68	2H	doublet	Ar-H(d-d')	7.6
12	8.15	1H	singlet	Ar-(g)	-

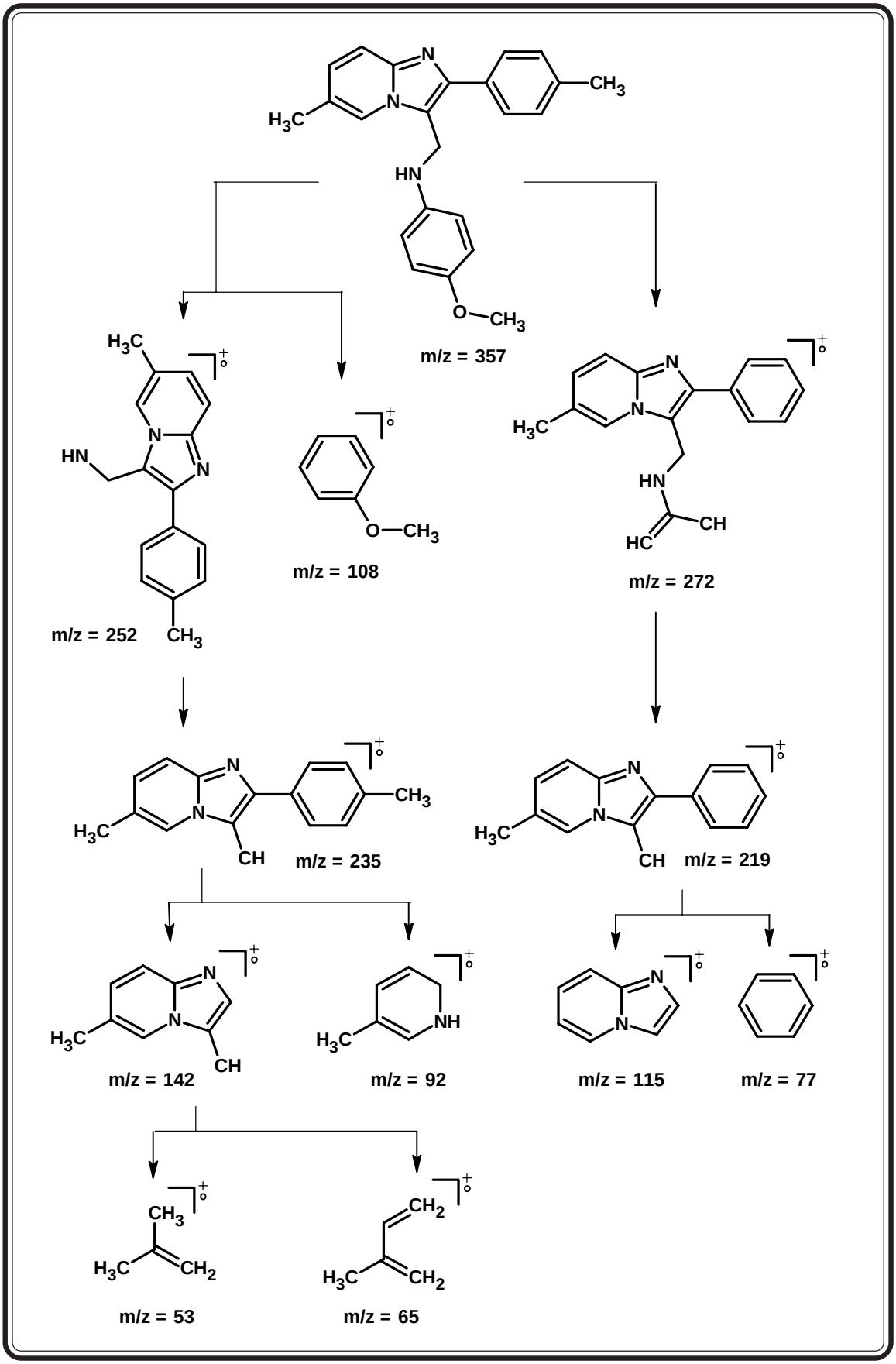
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF *N*-(4-METHOXYPHENYL)-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINES

[A] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine :

For preparation see(A), part-I, section-I(A), page no.046.

[B] Synthesis of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde :

For preparation see(A), part-I, section-I(B), page no.046.

[C] Preparation of *N*-(4-Methoxyphenyl)-1-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]methanimine :

For preparation see, part-IV, section-I(C), page no.128.

[C] Synthesis of *N*-(4-Methoxyphenyl)-1-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridin-3-yl]methanamine :

3.55g (0.01mol) *N*-(4-Methoxyphenyl)-1-[6-methyl-2-(4-methylphenyl)imidazo [1,2-*a*]pyridin-3-yl]methanimine was taken in 25ml methanol and cooled at 5-10 ^{o}C temperature. Sodium borohydride 0.57g (0.15mol) was added over a period of 30 min. The reaction mixture stirred over night at room temperature. Reaction mass was then poured in ice water and excess borohydride was neutralized by adding dil HCl. The product was extracted with ether and washed with water. Dried over anhydrous Na_2SO_4 and finally the ether was evaportated to give aminomethyl derivatives. Yield, 56%, m.p. 165 ^{o}C, Elemental analysis calculated for $C_{28}H_{23}N_5O$; Found : C- 77.98%; H-6.48%; N-11.99%; Requires : C-77.28%, H-6.49%, N-11.76%.

Similarly, other *N*-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines were prepared. The physical data are recorded in table no.09.

[E] Biological screening of *N*-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.047. The zones of inhibition of test solutions are reported in graphical chart no.09.

Conclusion :

Antibacterial activity

The screening data indicated that among arylaminomethyl derivatives tested compounds **9b**, **9d**, **9f** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **9e, 9i, 9j, 9l** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **9b, 9d, 9k** and **9a, 9f, 9h, 9l** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

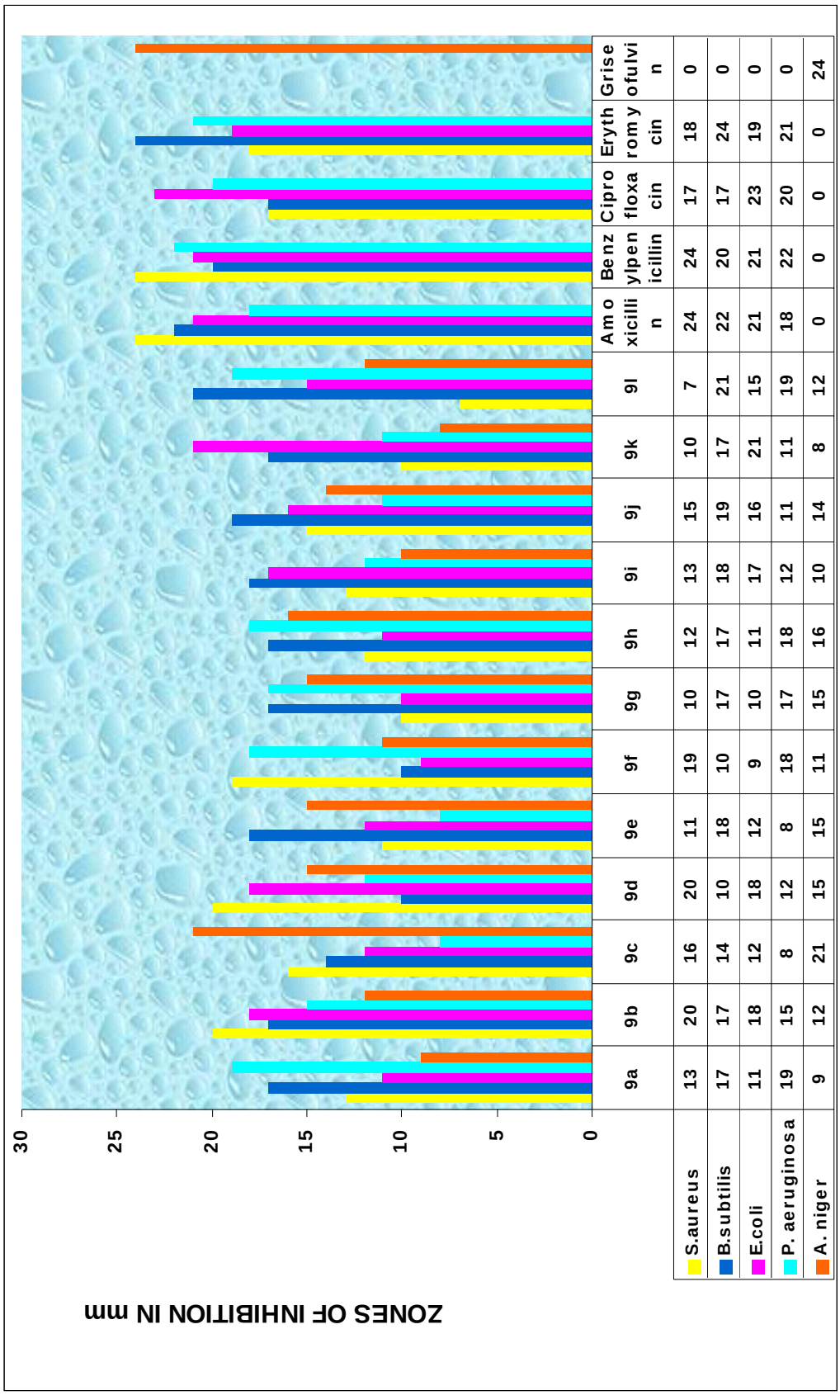
The screening data indicated that among arylaminomethyl derivatives tested compounds **9c** showed greater degree of antifungal activity against *A.niger.*

TABLE -09 : PHYSICAL CONSTANTS OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINES

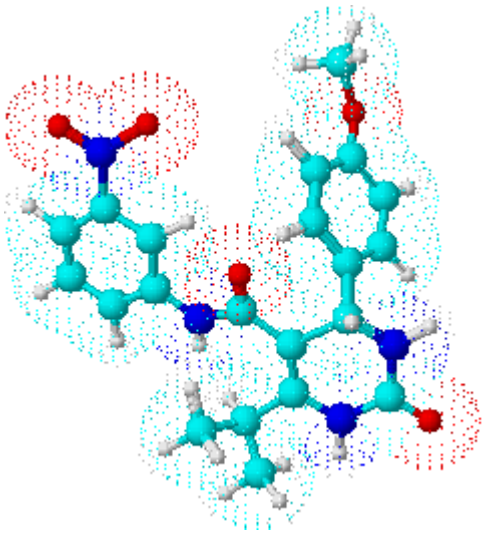
Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
9a	4-OCH_3-C_6H_4-	$C_{23}H_{23}N_3O$	357	165	56	11.76	11.72	0.49	S_1
9b	4-OH-C_6H_4-	$C_{22}H_{21}N_3O$	343	dec.195	61	12.24	12.22	0.47	S_1
9c	C_6H_5-	$C_{22}H_{21}N_3$	327	176	70	12.84	12.80	0.50	S_2
9d	4-Cl-C_6H_4-	$C_{22}H_{20}ClN_3$	361.5	dec.180	65	11.61	11.65	0.48	S_2
9e	3-Cl-C_6H_4-	$C_{22}H_{20}ClN_3$	361.5	178	61	11.61	11.68	0.42	S_2
9f	2,5-$(Cl)_2$-C_6H_3-	$C_{22}H_{19}Cl_2N_3$	396	194	72	10.60	10.56	0.55	S_2
9g	3,4 -$(Cl)_2$-C_6H_3-	$C_{22}H_{19}Cl_2N_3$	396	dec.260	75	10.60	10.61	0.48	S_1
9h	4-F-C_6H_4-	$C_{22}H_{20}FN_3$	345	138	63	12.17	12.15	0.51	S_2
9i	3-NO_2-C_6H_4-	$C_{22}H_{20}N_4O_2$	372	165	56	15.05	15.02	0.48	S_2
9j	4-NO_2-C_6H_4-	$C_{22}H_{20}N_4O_2$	372	136	64	15.05	15.06	0.55	S_2
9k	1-$C_{10}H_7$-	$C_{26}H_{23}N_3$	377	175	62	11.14	11.11	0.46	S_1
9l	3-CH_3-C_6H_4-	$C_{23}H_{23}N_3$	341	dec.204	51	12.41	12.40	048	S_2

S_1Ethyl acetate : Hexane (2 : 8), S_2 Hexane : Ethyl acetate (4 : 6)

Graphical Chart No. 09 : ANTIMICROBIAL ACTIVITY OF *N*-ARYL-1-[6-METHYL-2-(4-METHYLPHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHANAMINES



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	13	20	16	20	11	19	10	12	13	15	10	7	24	24	17	18	0
B.subtilis	17	17	14	10	18	10	17	17	18	19	17	21	22	20	17	24	0
E.coli	11	18	12	18	12	9	10	11	17	16	21	15	21	21	23	19	0
P. aeruginosa	19	15	8	12	8	18	17	18	12	11	11	19	18	22	20	21	0
A. niger	9	12	21	15	15	11	15	16	10	14	8	12	0	0	0	0	24



[B]

STUDIES ON

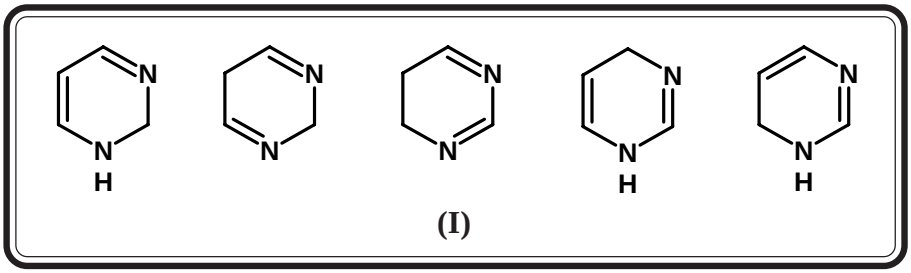
DIHYDROPYRIMIDINES

INTRODUCTION

Organic compounds containing six-membered aromatic heterocyclic rings are widely distributed in nature and often play an important role in various biochemical processes. Heteroaromatic rings also serve as bioisosters of several substituents including phenyl rings or carboxylic amide and often render greater pharmacological activity to the resulting compounds. As a result, they are commonly incorporated into new chemical entities by medicinal chemists. In some instances, however, these rings can serve as alternative sites for metabolic attack and at times may have the potential of undergoing unusual metabolic transformations that can result in toxic events.

Pyrimidine was first isolated by Gabriel and Colman in 1899. Despite the importance of dihydroazines (particularly those containing the 1,4-dihydropyrimidine and dihy dropyridine moiety[324]) for clarifying a wide range of theoretical, medicinal and biological problems, the chemistry of this group of compounds is still extremely spotty.[325-329] Structure-metabolism relationship (SMR) studies often reveal that incorporation of one or more heteroatoms in an aromatic ring influences the chemical and biochemical reactivity of these compounds and therefore alter their metabolism. Recently, the interest in the synthesis of these derivatives has increased tremendously because they exhibit promising activities as calcium-channel modulators, antihypertensive agents, *a*-1 receptor antagonists and neuropeptideY (NPY) antagonists[330-331] as an anticancer drug capable of inhibiting Kinesinmotor protein,[332] recently, interest has shifted from DHPM calcium channel modulators to other biologically active DHPM derivatives e.g. α–1 adreno ceptorselective antagonists, useful for the treatment of benign prostatic hyperplasia.[333]

Figure **(I)** depicts the five possible isomeric structures of dihydropyrimidines, exhibiting different dispositions of the double bonds.

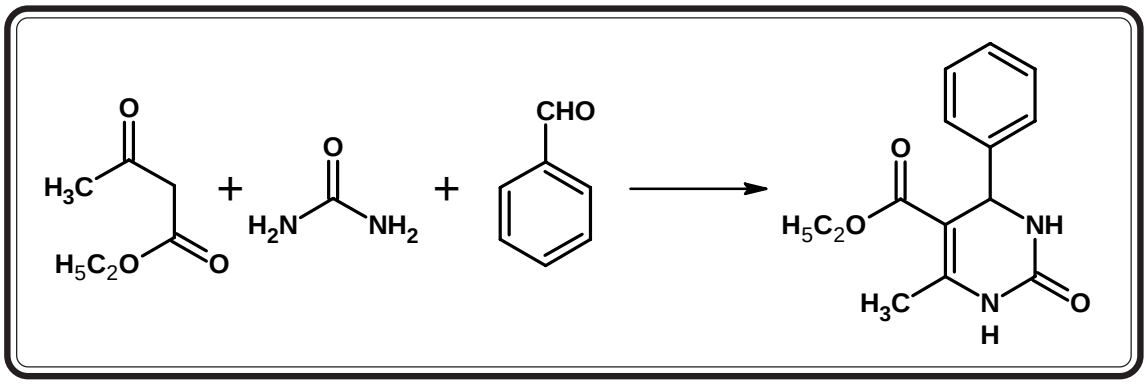


(I)

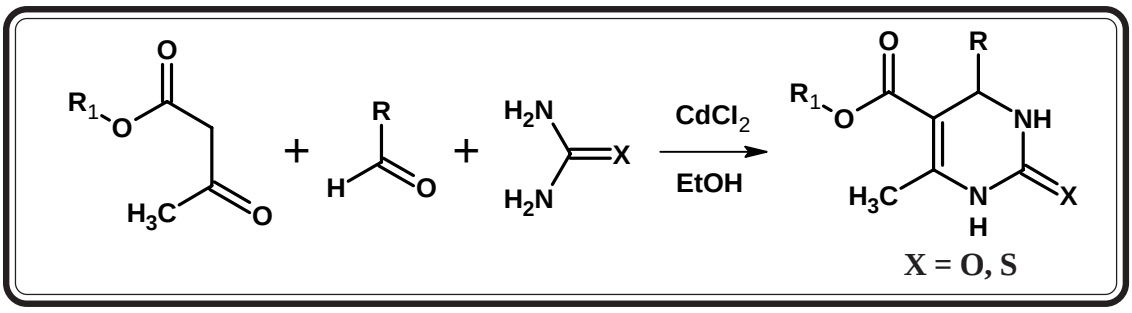
The synthetic strategies for the dihydropyrimidine nucleus involves one-pot to multi step approaches. In 1893, the Italian chemist Pietro Biginelli discovered a multicomponent reaction that produced these multifunctionalized dihydropyrimidinones. certainly ranks as one of the most recognized and often used MCR's for the generation of novel pyrimidine scaffolds.[334-336]

SYNTHETIC ASPECT

1. Biginelli reaction[337] (1893).



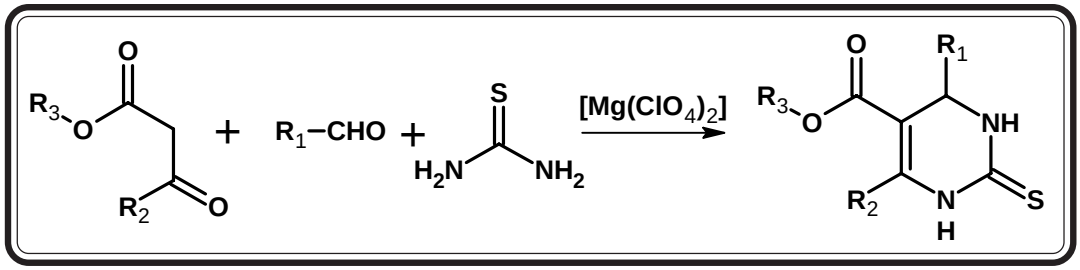
2. Shingare M. S. et al.[338] examined a simple but effective procedure for Biginelli condensation reaction of an aldehyde, β-ketoester and urea or thio urea using catalytic amount of cadmium chloride.



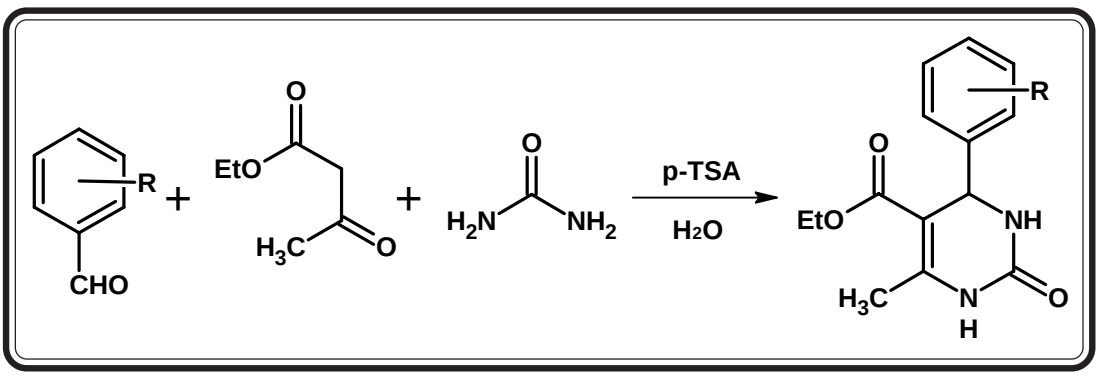
3. A novel one-pot condensation of an aldehyde,β-keto-ester and urea wasperformed using iodotrimethylsilane in acetonitrile for the first time at room temperature affording DHPMs.[339]

4. Reddy et al.[340] described practical route for the Biginelli reaction using zirconiumtetrachloride as a catalyst. Three component condensation reaction of an aromaticaldehyde, β-ketoester and urea or thiourea in ethanol afforded the cor responding DHPM-2-(1*H*)-ones in high yield.

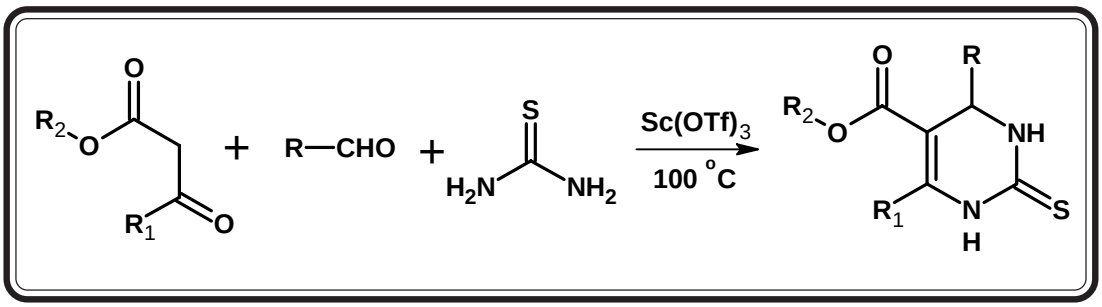
5. Zhang X et al.[341] developed a novel series of 4-substituted 3,4-dihydropyrimidine2(1H)-thiones employing magnesium perchlorate as an efficient catalyst under ultrasound irradiation.



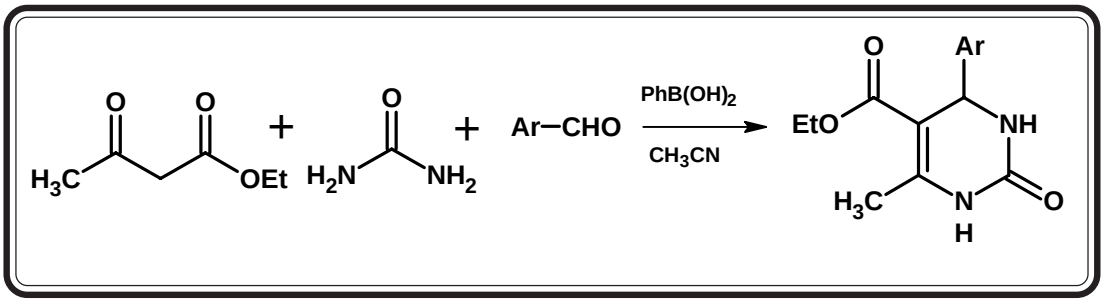
6. An important stage in process development is in pilot scale preparation of the target compound. A procedure involving water-based biphasic media has been developed for conducting some exothermic reactions on large scale. This protocol is rapid preparation of dihydropyrimidinones by a solvent-free, green chemistry procedure applied to the Biginelli reaction using *p*-toluensulfonic acid as catalyst.[342]



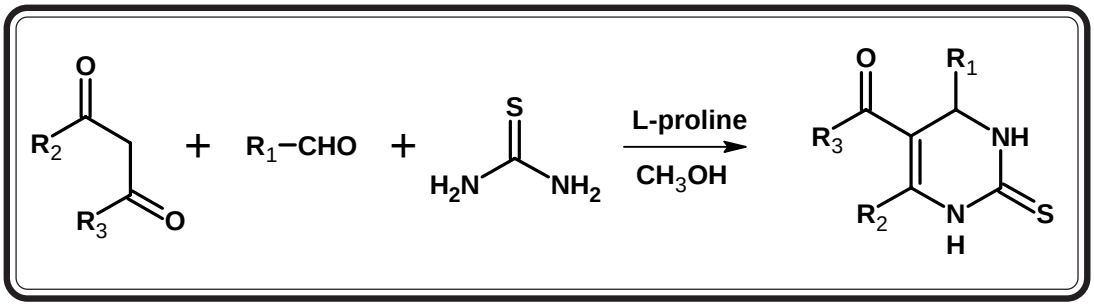
7. De. S. K. et al.[343] synthesized novel one pot Biginelli-type reaction. Aromatic aldehydes with β-dicarbonyl compound and thiourea in presence of catalytic amount of 5 % of $Sc(OTf)_3$ at 100 ^{o}C .



8. Abdelmadjid et. al.[344] synthesized 3,4-dihydropyrimidine derivative was achieved in good to excellent yields using phenylboronic acid as catalyst to promote the Biginelli three-component condensation.



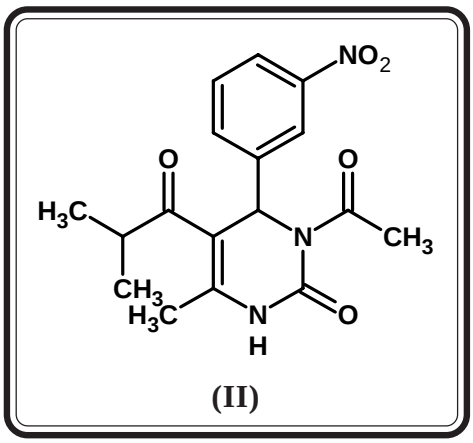
9. John Mabry et al.[345] synthesized different DHPMs via enamine intermediates using L-proline methyl ester hydrochloride found to be an effective catalyst for assembling dihydropyrimidine thiones under mild condition.



STEROGENIC CENTER

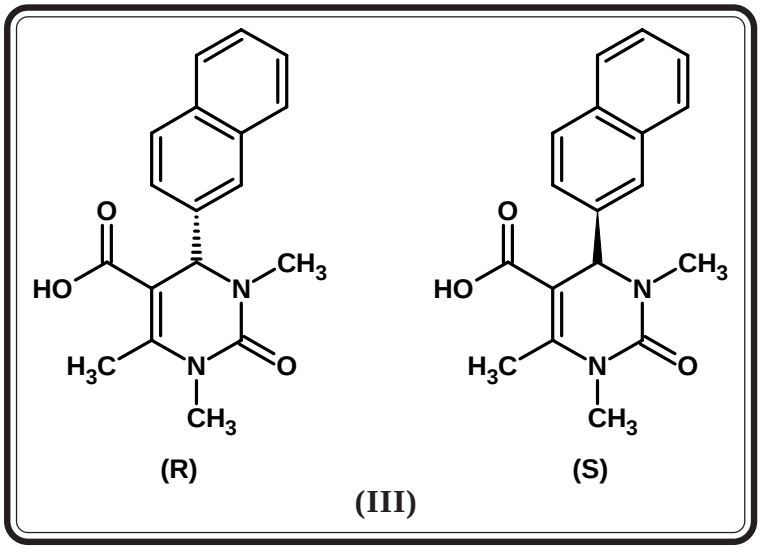
Dihydropyrimidines of the Biginelli type are inherently asymmetric molecules and the influence of the absolute configuration at the stereogenic center at C_4 on biological activity is well documented.[346]

For example, it is exclusively the (R)- enantiomer that carries the therapeutically desired antihypertensive effect. In other DHPM analogues, individual enantiomers were demonstrated to have opposing pharmacological activities.[347] Access to enatiomerically pure DHPMs it therefore of considerable interest and a prerequisite for the development of any drugs in this field (II).



(II)

In the absence of any known general asymmetric synthesis for this heterocyclic target system, resolution strategies have so far been the method of choice to obtain enantiomerically pure DHPMs. Optically pure DHPMs were obtained by resolution of the corresponding racemic-5-carboxylic acids via fractional crystallization of the corresponding diastereomeric R-methyl benzyl ammonium salts. The absolute configuration of acid (S) was proved by single crystal x-ray analysis of a suitable diastereomeric salt. This method may lead to both enantiomers (R) and (S) figer-(III) but unfortunately, it is not applicable in general to all DHPMs.



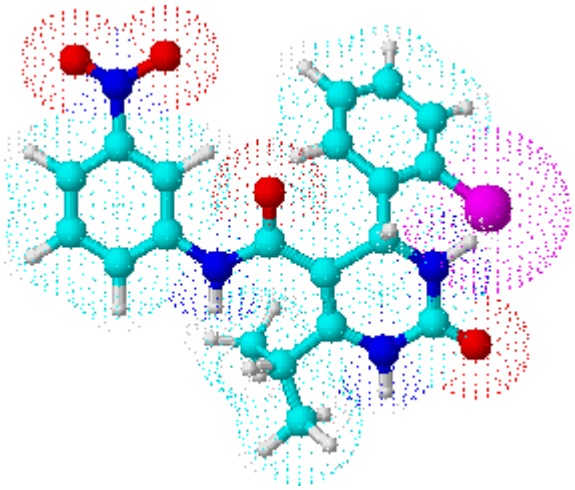
(III)

Due to recent advances in preparative chromatographic enantioseparation techniques, enantioselective HPLC and related methods have gained importance in the synthesis of single enantiomer drugs and intermediates. In a recent study, the chromatographic enantioseparation of DHPM derivatives accomplished by using a variety of commercially available chiral stationary phases (CSPs) in normal and reversed-phase analytical HPLC is reported.[348] Fre'chet and coworkers reported the separation of DHPMs on a standard Pirkle-type 3,5-dinitrobenzoylated CSP and the "reciprocal" preparation of DHPM-based CSP.[349-350]

Thus the important role displayed by DHPMs and its derivatives for various therapeutic and biological activities prompted us to synthesise some dihydropyrimidinones and dihydropyrimidinethiones in order to get compounds having better biological activities as described in the following parts.

PART-I : STUDIES ON DIHYDROPYRIMIDINONES

PART-II : STUDIES ON DIHYDROPYRIMIDINETHIONES



PART - I

STUDIES ON

DIHYDROPYRIMIDINONES

INTRODUCTION

In recent years, interest has also focused on aza-analogs such as dihydropyrimidines (DHPMs) which show a very similar pharmacological profile to classical dihydropyrimidine calcium channel modulators. [351-354] Over the past few years, several lead compounds have been developed[355] and claimed to be superior in potency and duration of antihypertensive activity to classical DHP drugs and compare favorably with second generation analogues such as amlodipine and nicardipine.[356]

Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Purines, uric acid, barbituric acid and anti-malarial and anti-bacterial agents also contain the pyrimidine ring. The chemistry of pyrimidine has been widely studied. Pyrimidine was first isolated by Gabriel and Colman in 1899.

These inherently asymmetric dihydropyrimidine (DHPM) derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure activity relationships and to get further insight into molecular interactions at the receptor level. Where as dihydropyridines of the nifedipine type (DHPs) are generally prepared by the well-known Hantzsch synthesis,[357] aza analogues of DHPMs are readily available through the so called Biginelli dihydropyrimidine synthesis .[358] This simple one-pot, acid catalyzed condensation reaction of ethyl acetoacetate, benzaldehyde and urea was first reported in 1893 by Pietro Biginelli.[359-360] In the following decades, the original cyclocondensation reaction has been extended widely to include variations in all three components, allowing access to a large number of multifunctionalized dihydropyrimidine derivatives.

DEFINITION OF MULTICOMPONENT REACTIONS (MCRs)

"In multicomponent reactions three or more reactants come togather in a single

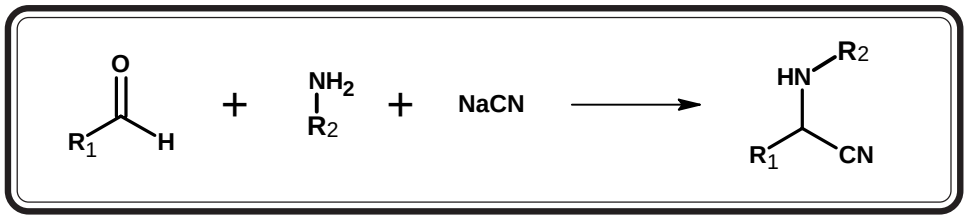
reaction vessel to form products that contain portions of all the components.[361]"

"MCRs converts more than two adducts directly in to their product by one-pot reactions.[362]"

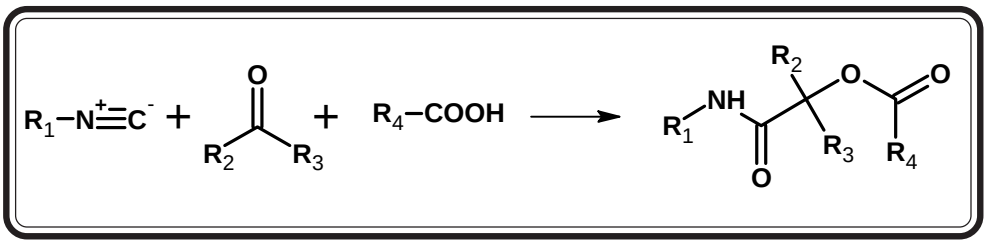
History and Types of Multicomponent Reactions (MCRs)

First officially reported MCR was by Strecker of α-amino nitrile in 1850.

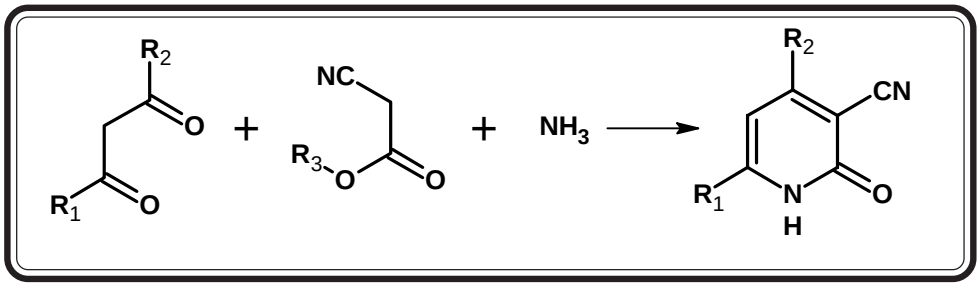
1. Strecker A. Synthesis[363]



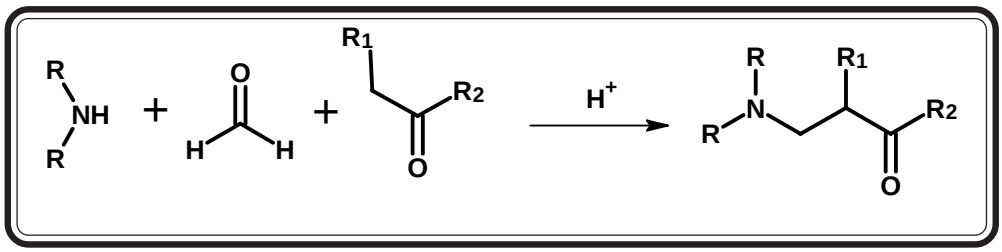
2. Passerini reaction.[364-365]



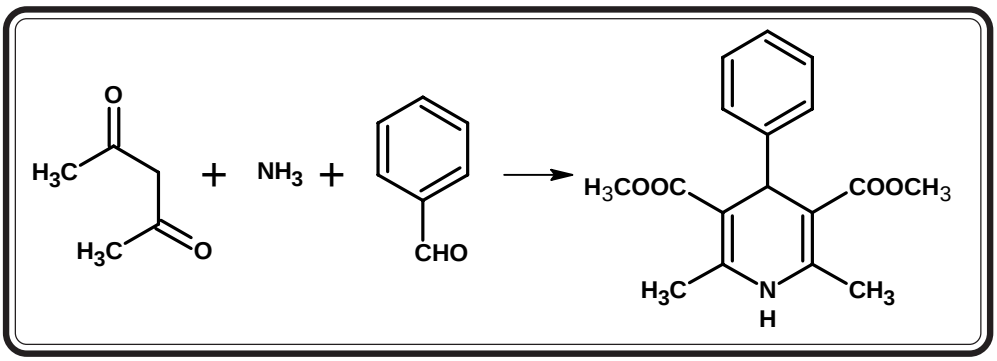
3. Guareschi-Thorpe condensation.[366-367]



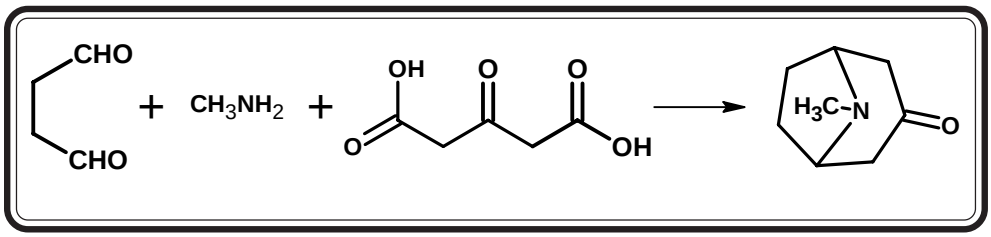
4. Mannich Reaction (1912).[368-370]



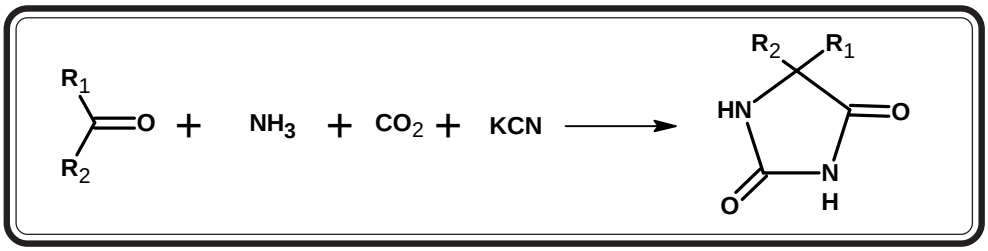
4. Hantzsch Dihydropyridine synthesis (1882).[371]



6. Robinsons synthesis of tropinone (1917).[372]

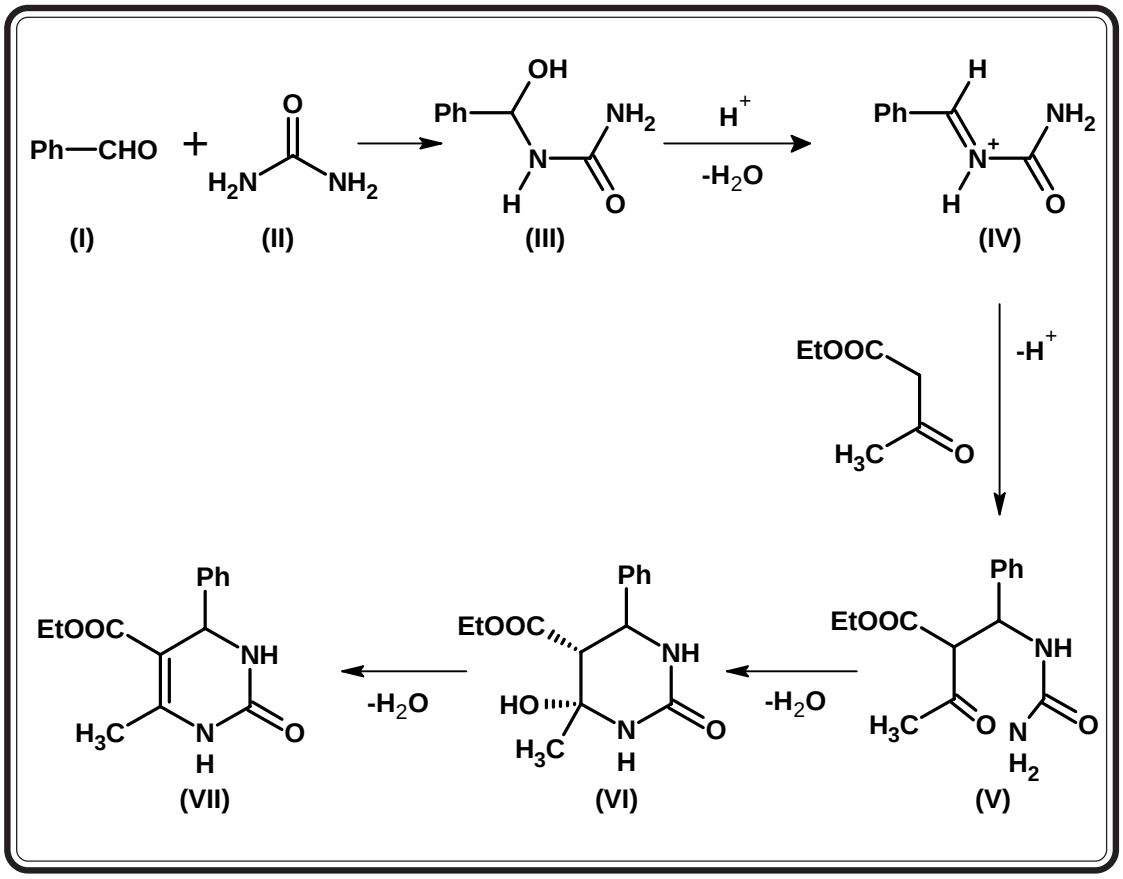


7. Bucherer-Bergs Hydantoin synthesis (1929).[373-374]



MECHANISM

Sweet and Fissekis Kappe[375] was reexamined the mechanism in 1997 using ^{1}H and ^{13}C spectroscopy to support the argument that the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type (III) from the aldehyde (I) and urea (II) precursors. Interception of the iminium ion (IV) by ethyl acetoacetate, presumably through its enol tautomer, produces an open chain ureide which subsequently cyclizes to hexahydropyrimidine(V). Acid-catalyzed elimination of water from (VI)ultimately leads to the final DHPM product (VII).



Finally the original mechanistic proposal put forward by Folkers and Johnson[376] in 1933 involving an aldehyde urea condensation product as key intermediate in the Biginelli condensation is essentially correct. The first step in this mechanism evidently involves the acid-catalyzed formation of an *N*-acyliminium ion precursor of type (IV) from an aldehyde and urea component. In the case of amides and carbamates, this reaction pathway is well-established,[377] and at least one example exists for ureas.[378] The second step can be regarded as an addition of a π-nucleophile, *i.e.* the enol tautomer of acetoacetate to the electrondeficient *N*-acyliminium species. Additions of π-nucleophiles to iminium species are very well-known and have proven to be valuable synthetic transformations in target oriented synthesis.[379] Importantly, several examples of this type of reaction involving 1,3-dicarbonyl compounds and urea derived *N*-acyliminium ions yielding dihydropyrimidines are reported in the literature,[380] providing additional support for this mechanism.

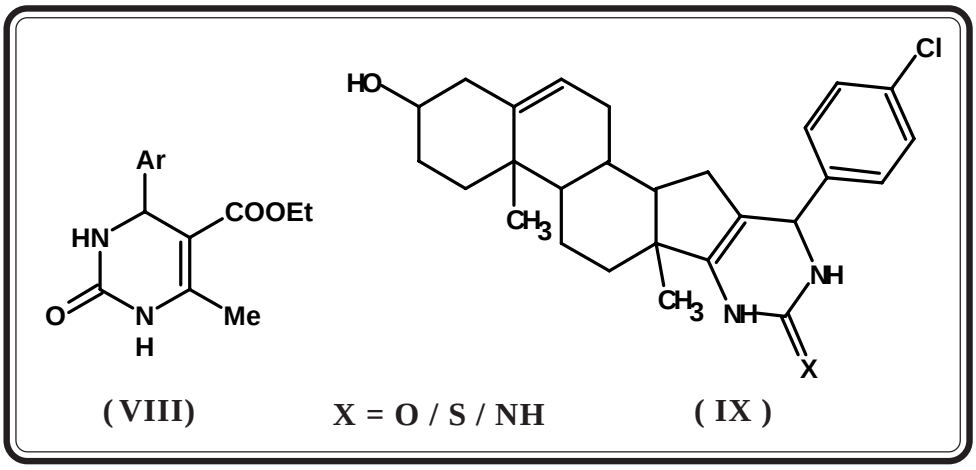
THERAPEUTIC IMPORTANCE

Dihydropyrimidines show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators. Over the past few years several lead-compounds were developed that are superior in potency and duration of antihypertensive activity to classical DHP drugs. These inherently asymmetric DHPM derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure activity relationships and to get further insight into molecular interactions at the receptor level.

Dihydropyrimidines have attracted considerable attention as they appeared of interest to possess wide range of therapeutic activities. Different activities are as under.

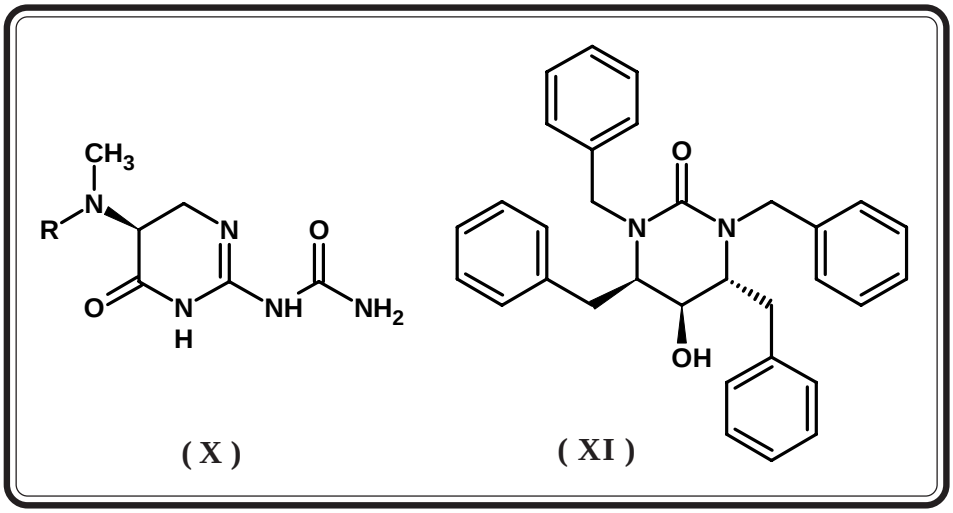
1. Anti-inflammatory[381]
2. Neuropeptide Y (NPY) antagonist[382]
3. Mitotic Kinesin inhibitor[383]
4. Metabotropic glutamate receptor antagonist[384]
5. Antiviral[385]
6. Anti-ichemic[386]
7. Blood platelet aggregation inhibitor[387]
8. Antitumor[388]
9. Coronary dilatory[389]
10. Cardiovascular activity[390-391]
11. Antihypertensive[392]
12. Calcium channel modulator[393-394]

Baldev Kumar et. al.[395] have prepared some new oxo-pyrimidine derivatives (VIII) and reported them as potent calcium channel blockers. Abd. El-Galil and M. Abdulla[396] have synthesized some fused steroidal oxo pyrimidine derivatives (IX) and reported them as androgenic anabolic agent as well as antiinflammatory agent.



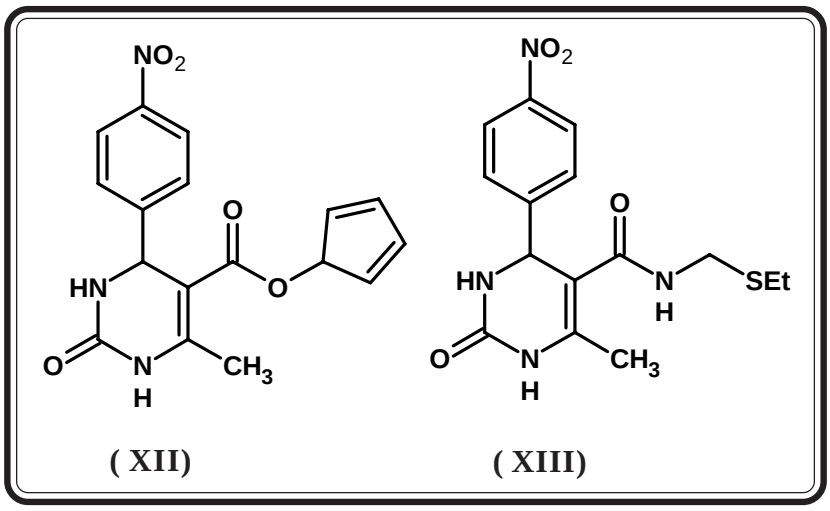
(VIII) **X = O / S / NH** **(IX)**

Recently, Vladimir N. Belov et. al.[397] have documented enantioselective synthesis of the novel antiinfective TAN-1057A via aminomethyl substituted dihydropyrimidinone heterocycle (X). Rajni Garg et. al.[398] suggest that the balance of hydrophobicity and a volume dependent polarizability plays a key role in the inhibition of the viral protease by these (XI) inhibitors.



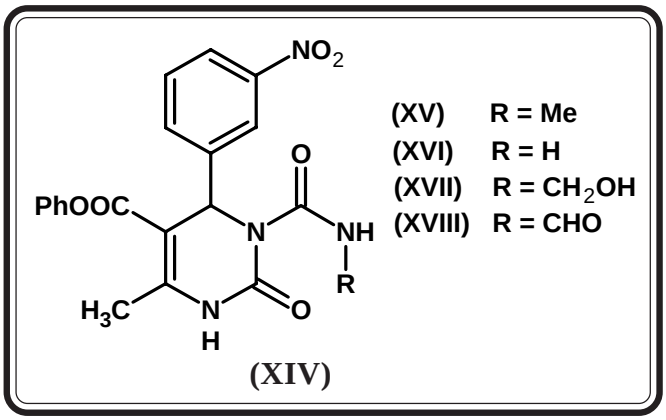
(X) **(XI)**

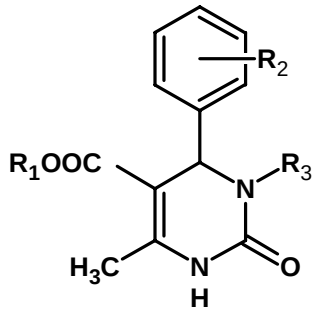
Several potent, cell permeable 4-aryl-dihydropyrimidones have been identified as inhibitors of fatty acid transporter FATP4. Christopher Blackburn et. al.[399] described that lipophilic ester substituents at the 5-position and substitution at the para-position (optimal group -NO_2 and CF_3) of the 4-aryl group led to active compounds (XII,XIII)



Atwal K. S. et al.[400] described that in order to explain the potent antihypertensive activity of the modestly active dihydropyrimidine calcium channel blocker (XIV), they carried out drug metabolism studies in the rat and found (XIV) is metabolized to compounds (XV-XVIII). Two of the metabolites, (XV) and (XVI) were found to be responsible for the antihypertensive activity of compound (XIV)**.** Potential metabolism of (XV) into (XVI) *in vivo*. Structure-activity studies aimed at identifying additional aryl-substituted analogues of (XIX) led to (XX,XXI,XXII) with comparable potential *in vivo*, though these compounds were less potent than (XXI) *in vitro*.

The results demonstrate that the active R-(-)-enantiomer (XXIII) of (XIX) is both more potent and longer acting than nifedipine as an antihypertensive agent in the SHR. The *in vivo* potency and duration of (XXIII) is comparable to the long acting dihydropyridine amlodipine.



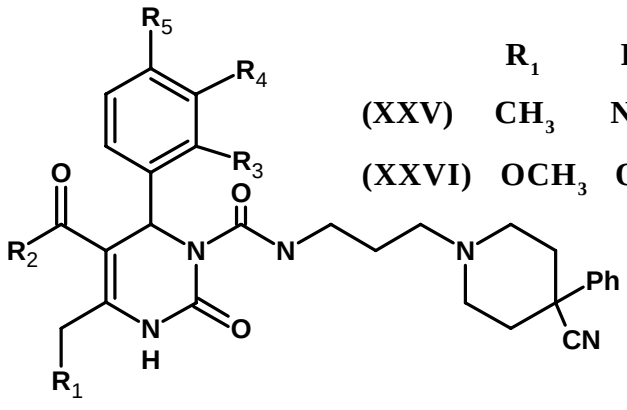


(XIX)

	R1	R2	R3
(XX)	i-pr	2-NO^2	$CONH_2$
(XXI)	i-pr	3-Cl	$CONH_2$
(XXII)	i-pr	2,3-oxadiazoyl	$CONH_2$
(XXIII)	i-pr	3-NO_2	$CONH_2$

Dennis Russowsky et al.[401] have reported manostrol was shown to be more active than its oxo analogue, except for HT-29 cell line, suggesting the importance of the sulfur atom for the antiproliferative activity. Manostrol and the thio derivatives displayed relevant antiproliferative properties with 3,4-methylenedioxy derivative being approximately more than 30 times potent against colon cencer (HT-29) cell line.

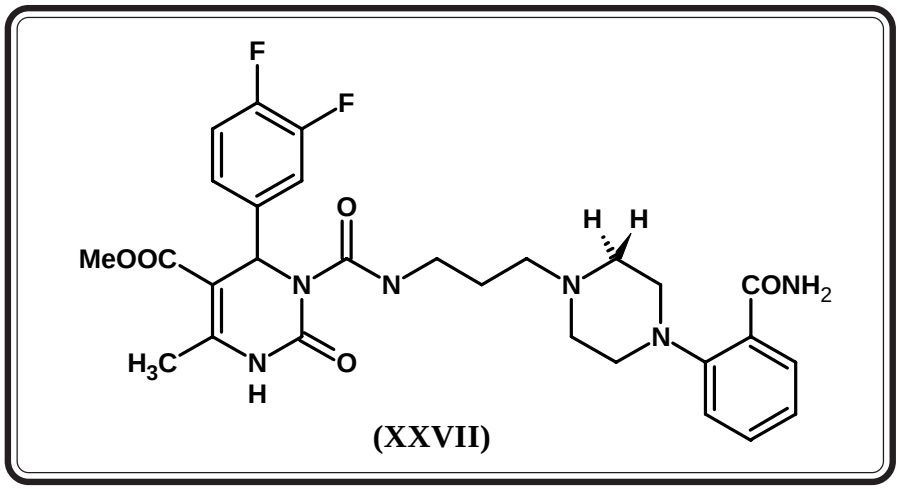
Murali T. G. et al.[402] have synthesized several DHPM one analogues(XXIV) among this (+)-(XXV) and (+)-(XXVI) give excellent selectivity (>880-fold) over α_{1b} and α_{1d} also showed good selectivity over several other recombinant human G-protein coupled receptors. These compounds showed good functional potency in isolated human prostate tissues, with Kbs comparable to their in vitro α_{1a} binding data. In addition, compound (+)-(XXV) also exhibited good uroselectivity (DBP Kb/ IUP Kb > 20-fold) in the in vivo experiments in dogs.



(XXIV)

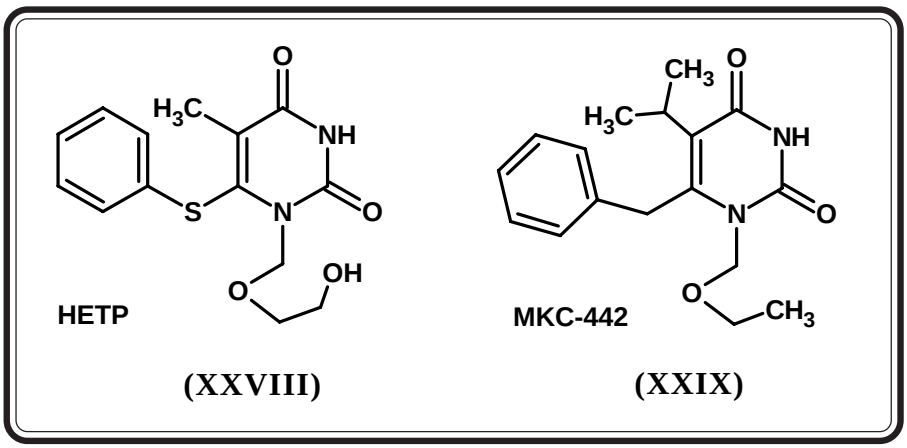
	R_1	R_2	R_3	R_4	R_5
(XXV)	CH_3	NH_2	F	H	F
(XXVI)	OCH_3	OMe	H	F	F

Bharat L. et al.[403] identify that compound **(+)-(XXVII)** was a lead compound with a binding and functional profile comparable to that of (+)-**(XXVI)**.



(XXVII)

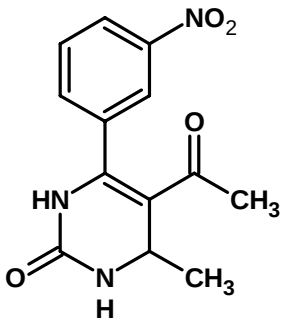
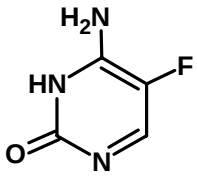
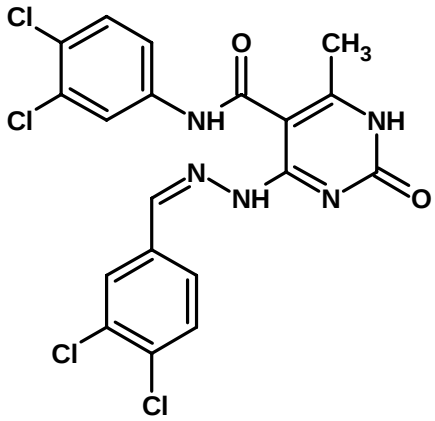
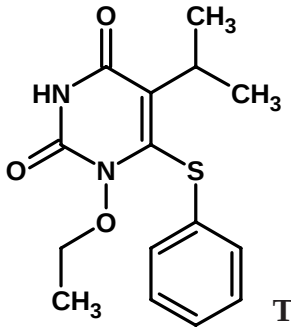
Andrew L. H. et al.[404] studied compounds belong to the HEPT (XXVIII) chemical series.[405-409] HEPT or 1-[(2-Hydroxyethoxy)-methyl]-6-(phenylthio)thymine was one of the earliest NNIs discovered but inhibits HIV-1 RT relatively weakly (IC50) 17 μM).[410] MKC-442 (XXIX) or 6-Benzyl-1-(ethoxymethyl)- 5-isopropyluracil (I-EBU) is a very potent inhibitor of HIV-1 RT (the IC_{50} being 2000-fold lower at 8 nM),[411-412] although only three relatively minor alterations have been made to the HEPT structure. The different spectrum of drug-resistance mutations between HEPT and MKC-442 parallels the variation in potency. A single mutation (Tyr188His) renders the virus effectively resistant to HEPT.[413]



(XXVIII) **(XXIX)**

NEW DRUG MOLECULES UNDER CLINICAL STUDY

Recently many new molecules which are under study from phase-I to phase-IV clinical trials for different pharmacological action have shown that the basic characteristic of morpholine to behave as hidden amine has attracted many medicinal chemists to incorporate this feature in drug design. Some interesting compounds are as under.

	Calcium Channel Blokers[414] Company Name: Merck & Co.
 **Flucytosine** (fluorocytosine)	Antifungal Agent.[415] *In vitro* susceptibility of Candida species isolated from cancer patients against some antifungal agents.
	Immunosuppressants Oncolytic Drug
 **TNK-6123**	Non-nucleoside HIV-1 reverse transcriptase inhibitor Compound was active not only against wild-type HIV-1 strains (IC50 = 3 nM against IIIB and NL4-3 HIV-1 strains) but also showed nanomolar

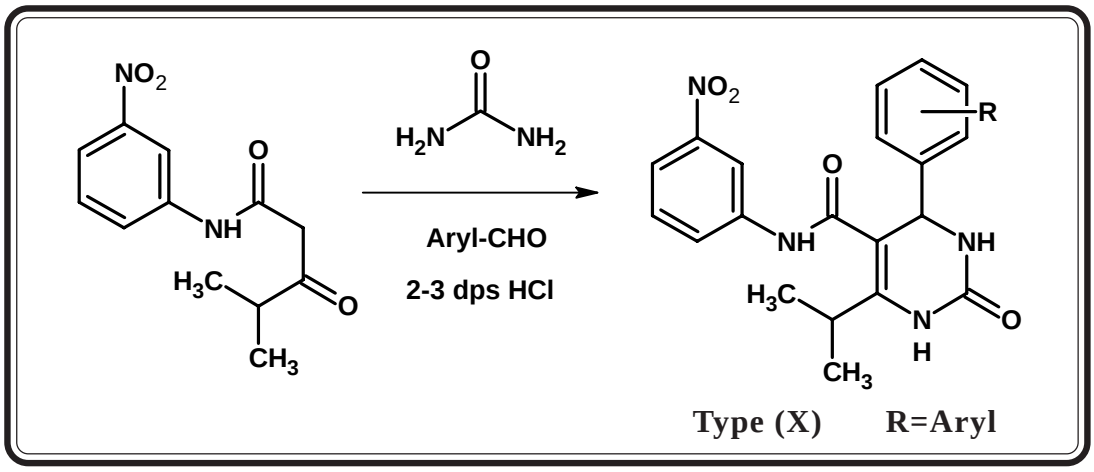
With an intention of preparing the compounds possessing better therapeutic activity, we have undertaken the synthesis of dihydropyrimidinones which have been described below.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBO NYL]-3,4-DIHYDROPYRIMIDINE-2-(1*H*)-ONES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONES

In the past years considerable evidence has been accumulated to demonstrate the efficiency of pyrimidinones. it was considered worthwhile to synthesize 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl)amino carbonyl]-3,4-dihydro pyrimidine-2(1*H*)-ones type-(X) by the condensation of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide nucleus, urea and various type of aromatic aldehyde in presence of con.HCl as shown under.

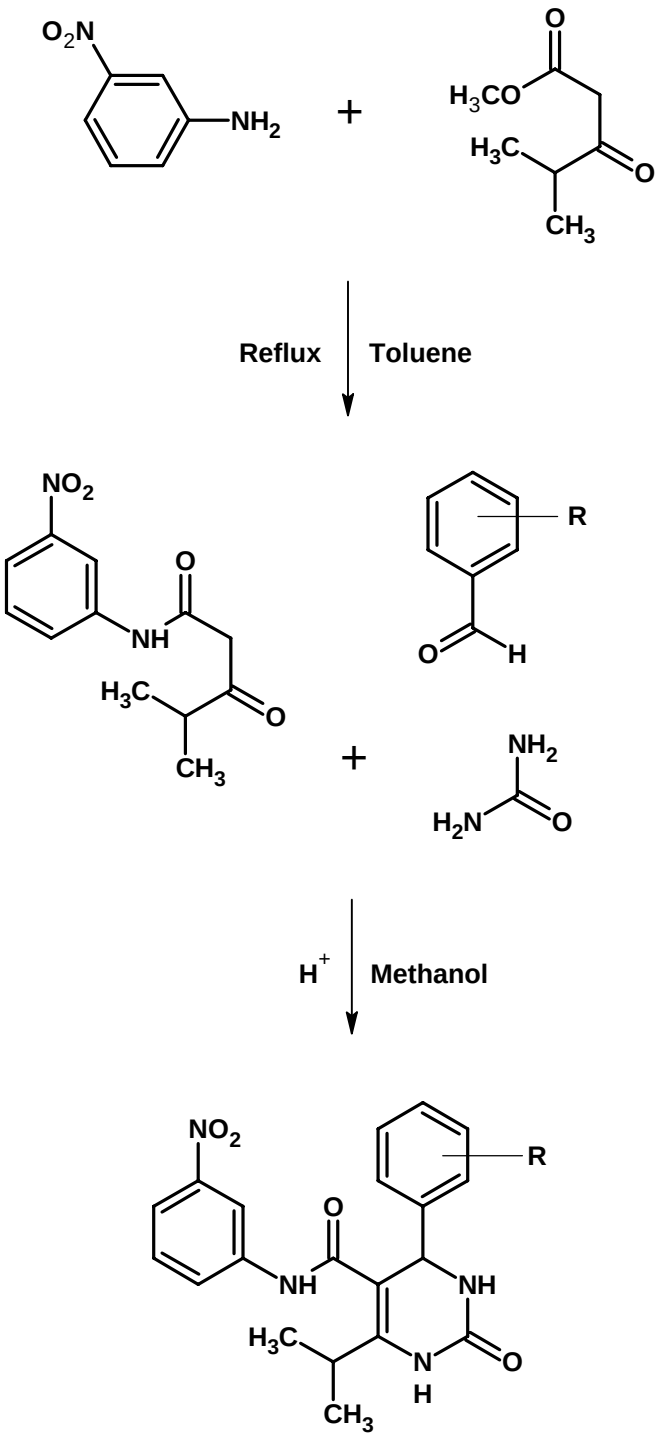


Type (X) R=Aryl

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR spectroscopy and further supported by Mass spectrometry.

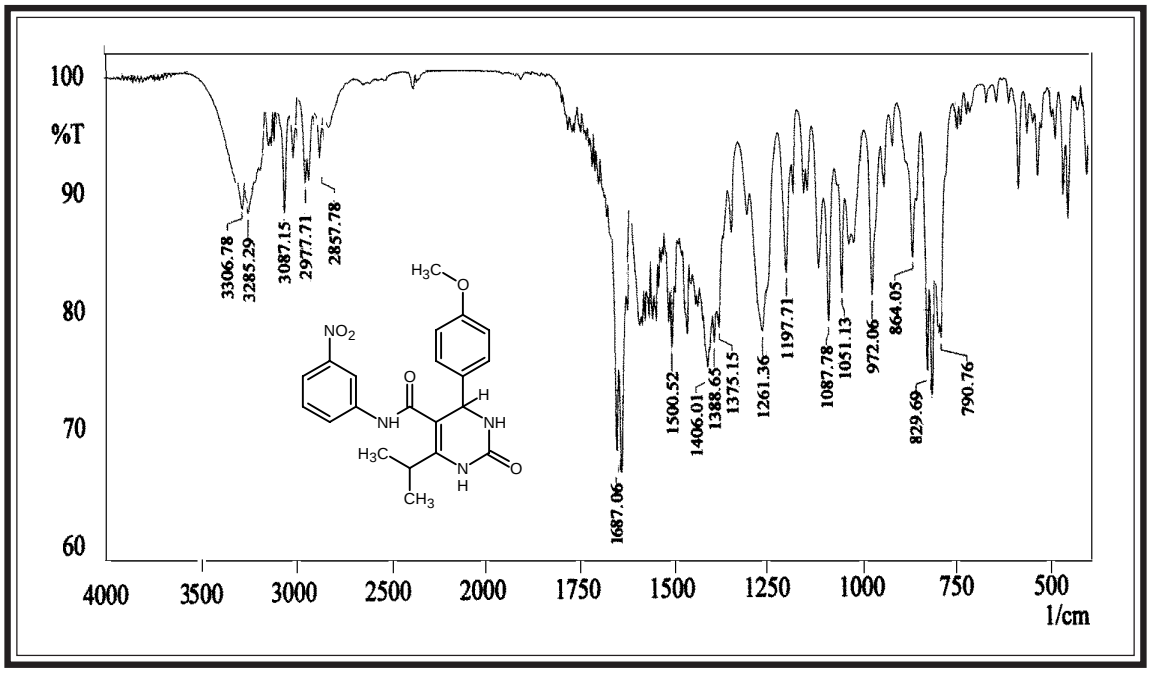
All the compounds have been screened for their *in vitro* biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

REACTION SCHEME



R = Aryl Type-(X)

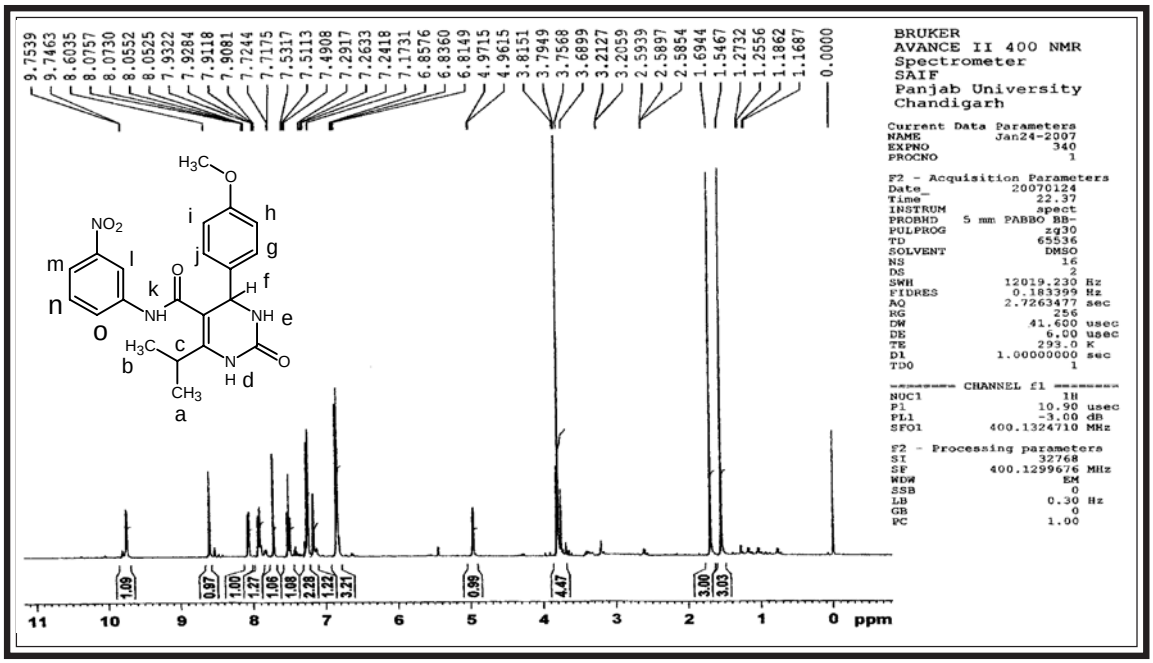
IR SPECTRAL STUDIES OF 4-(4-METHOXYPHENYL)-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2977	2975-2950	189
-CH_3	C-H str. (sym.)	2857	2880-2860	,,
	C-H i.p.def. (asym.)	1460	1470-1435	,,
	C-H o.o.p. def. (sym.)	1388	1390-1370	,,
Aromatic	C-H str.	3087	3090-3030	190
	C=C str.	1500	1540-1480	,,
	NO_2 str.	1360	1385-1365	,,
Pyrimidine	C=C str.	1580	1580-1520	,,
moity	C-H str.	3025	3080-3030	,,
	C-H i.p. def.	1087	1125-1090	,,
	C=O str.	1687	1700-1725	,,
	NH str.	3285	3300-3200	,,
Amide	NH str.	3306	3410-3380	189
	NH def.	1605	1635-1595	,,
	C=O str.	1677	1690-1660	,,

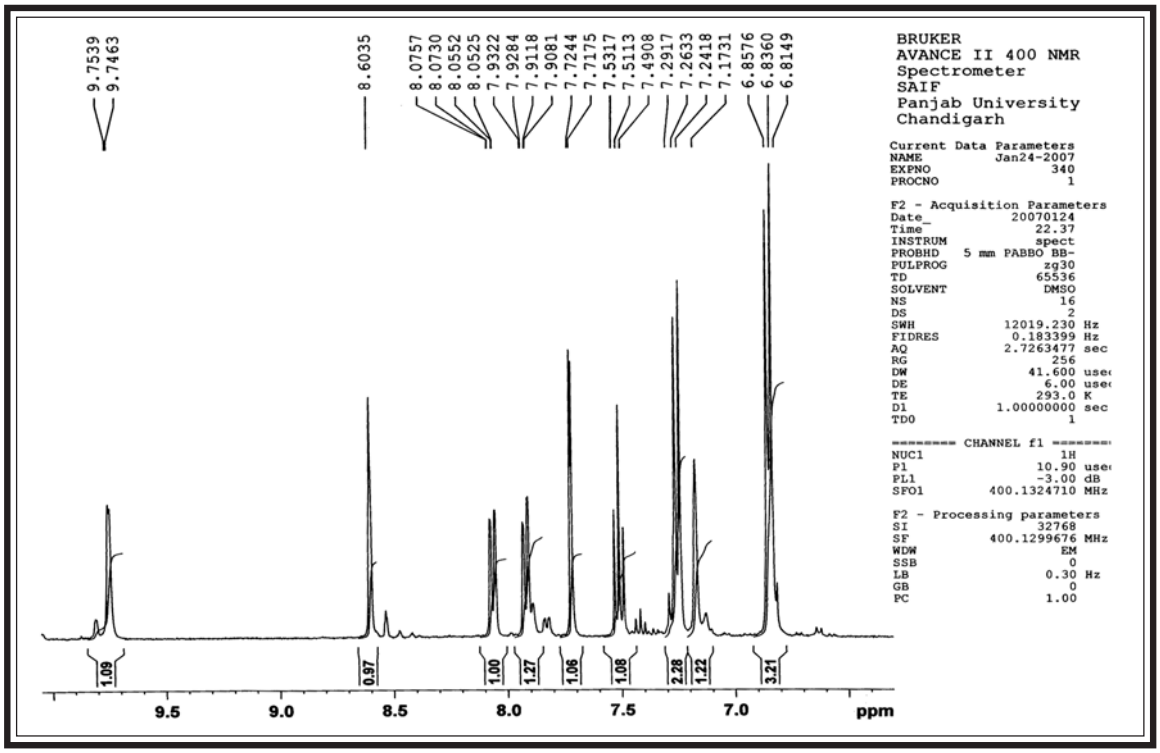
NMR SPECTRAL STUDIES OF 4-(4-METHOXYPHENYL)-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONE



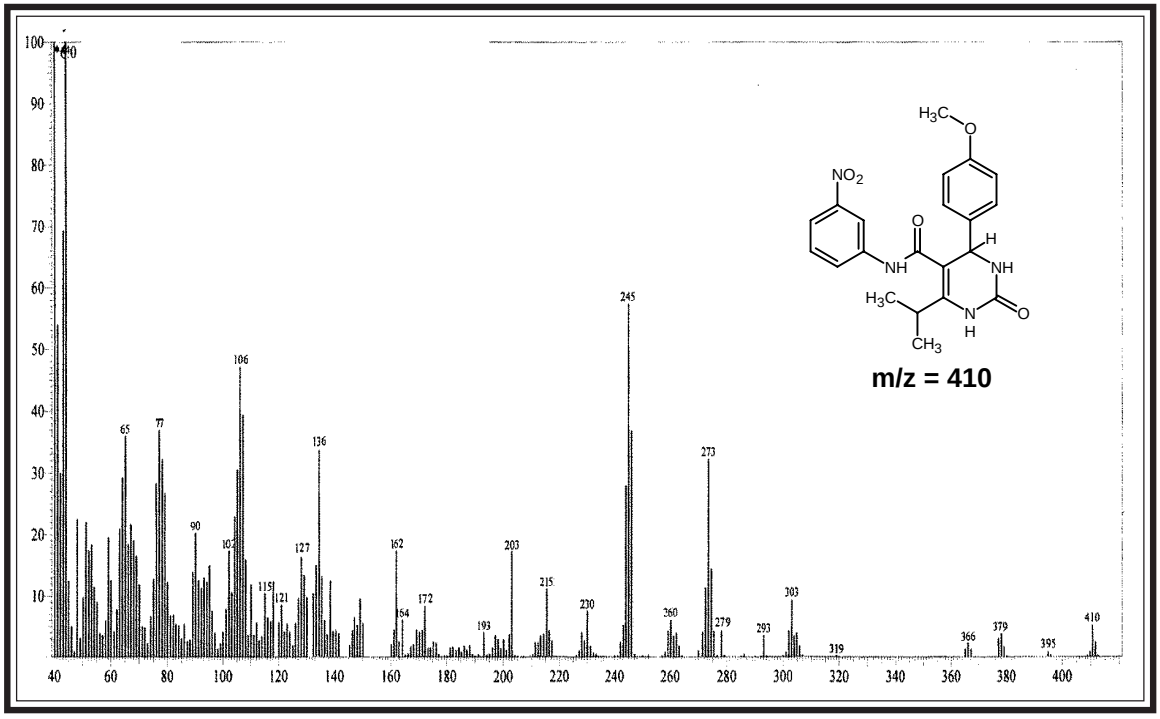
Internal Standard : TMS; Solvent : DMSO : Instrument : BRUKER Spectrometer (400 MHz)

Signal No.	SignalPosition (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	1.54	6H	doublet	CH-$(CH_3)_2$	-
				(a,b)	-
2	3.68-3.81	1H	multiplet	-CH(c)	-
3	3.79	3H	singlet	-OCH_3	-
4	4.96-4.97	1H	doublet	Ar-H(f)	4
5	6.83-6.85	2H	doublet	Ar-H(h-i)	8.64
8	7.173	1H	singlet	-NH(d)	-
9	7.24-7.26	2H	doublet	Ar-H(g-j)	8.6
10	7.49-7.53	1H	triplet	Ar-H(n)	-
11	7.71-7.72	1H	singlet	NH CO(k)	-
12	7.90-7.93	1H	doublet	Ar-H(o)	8.1,1.48
13	8.05-8.07	1H	doublet	Ar-H(m)	8.2,1.08
14	8.60	1H	singlet	Ar-H(l)	-
15	9.74-9.75	1H	doublet	-NH(e)	3.04

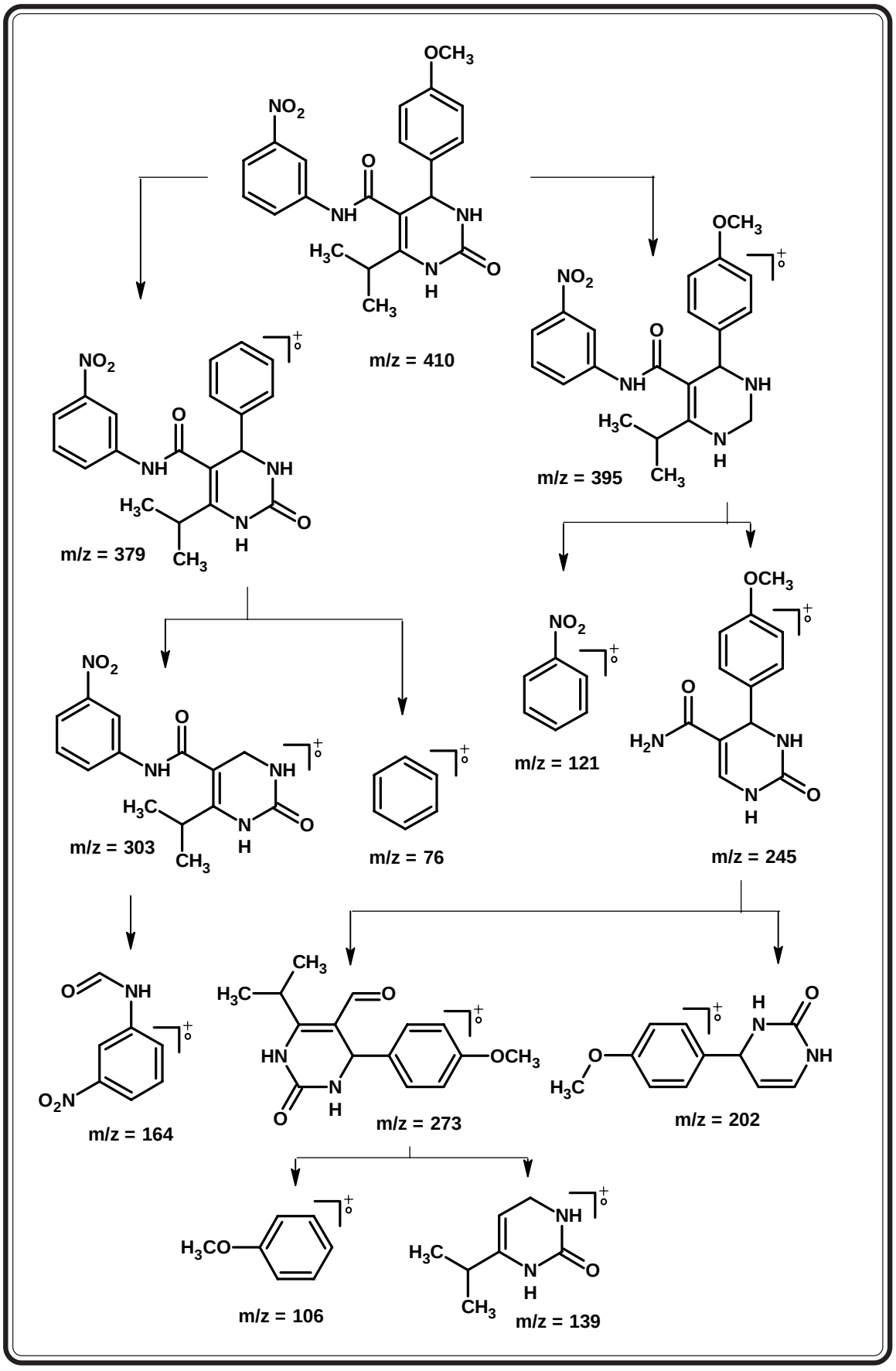
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF 4-(4-METHOXYPHENYL)-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONES

[A] Synthesis of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide :

A mixture of Methyl-4-methyl-3-oxopentanoate 1.44 gm (0.01 mol) and 3-Nitro aniline 1.38 gm (0.01 mol) was refluxed for 12 hrs in 30ml toluene. Methanol and toluene mixture was collected by azeotropic distilation. In residual reaction mass toluene was added toluene and washed with dilute HCl then with water. The resulting organic layer was kept over night at room temperature and filter it. Yield 71%, m.p.65 ^{o}C, Elemental analysis calculated for $C_{12}H_{14}N_2O_4$ Requires : C-57.59%, H-5.64%, N-11.19%, Found : C-57.56%, H-5.61% , N-11.06 %.

[B] Synthesis of 4-(4-Methoxyphenyl)-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydropyrimidine-2(1*H*)-one :

A mixture of urea 1.2 gm (0.02 mol), 4-Methoxy benzaldehyde 1.36g (0.01 mol) and 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide 2.50gm (0.01 mol) in 25 ml of methanol containing 2-3 drops of conc HCl was refluxed for 48hrs. The solution was allowed to stand for 1hr at room temperature. Filter it and the product was crystallized from methanol. Yield 41%, m.p.dec 250 ^{o}C, Elemental Anal.Cal. for $C_{21}H_{22}N_4O_5$ Requires : C-61.45%, H-5.40%, N-13.65%, Found : C-61.46%, H-5.31%, N-13.59 %.

Similarly, other 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydropyrimidine-2(1*H*)-ones were prepared. The physical data are recorded in table no.10.

[C] Biological screening of 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydropyrimidine-2(1*H*)-ones :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.047. The zones of inhibition of test solutions are recorded in graphical chart no.10.

Conclusion :

Antibacterial activity

The screening data indicated that among dihydropyrimidinone derivatives tested compounds **10f**, **10i**, **10l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **10c, 10d, 10i, 10j** showed greater degree of antibacterial activity against *B.subtilis.* The compounds **10a, 10c, 10g, 10k, 10l** and **10d, 10h, 10j** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

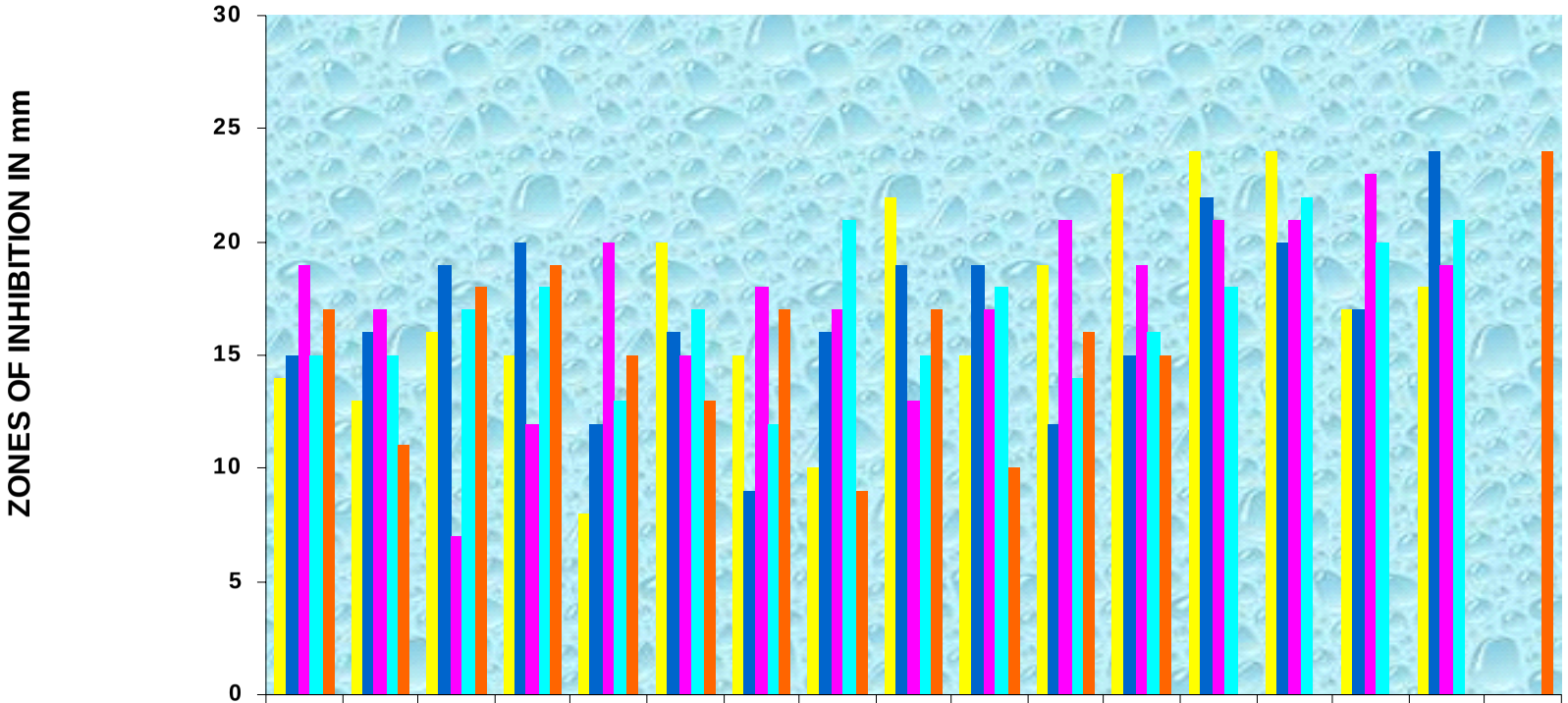
The screening data indicated that among dihydropyrimidinone derivatives tested compounds **10c, 10d** showed greater degree of antifungal activity against *A.niger.*

TABLE-10 : PHYSICAL CONSTANTS OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONES

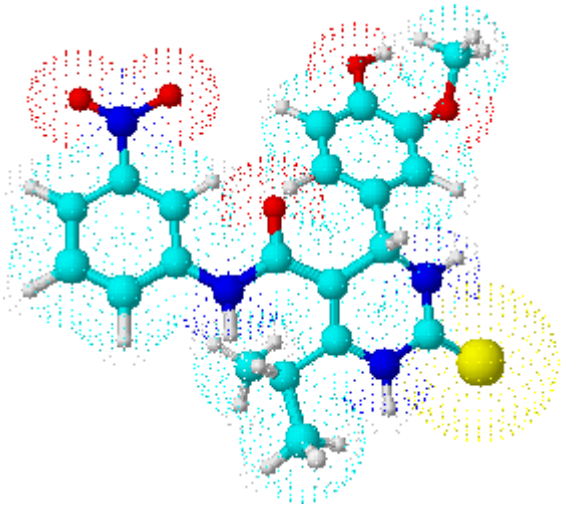
Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
10a	C_6H_5-	$C_{20}H_{20}N_4O_4$	380	dec.265	42	14.73	14.76	0.42	S_1
10b	4-OCH_3-C_6H_4-	$C_{21}H_{22}N_4O_5$	410	dec.250	44	13.65	13.62	0.55	S_2
10c	3,4- $(OCH_3)_2$-C_6H_3-	$C_{22}H_{24}N_4O_6$	440	231	51	13.52	13.55	0.57	S_2
10d	2,4,6-$(OCH_3)_3$-C_6H_2-	$C_{23}H_{26}N_4O_7$	470	180	40	11.91	11.87	0.47	S_1
10e	4-(OH)-3-(OCH_3)-C_6H_3-	$C_{21}H_{22}N_4O_6$	426	202	51	13.14	13.12	0.56	S_2
10f	4-OH-C_6H_4-	$C_{20}H_{20}N_4O_5$	396	220	54	14.14	14.20	0.47	S_2
10g	2-OH-C_6H_4-	$C_{20}H_{20}N_4O_5$	396	192	32	14.14	14.12	0.52	S_2
10h	4-F-C_6H_4-	$C_{20}H_{19}FN_4O_4$	398	dec.250	72	14.07	14.10	0.51	S_1
10i	4-Cl-C_6H_4-	$C_{20}H_{19}ClN_4O_4$	414.5	255	58	13.52	13.40	0.47	S_1
10j	2-Cl-C_6H_4-	$C_{20}H_{19}ClN_4O_4$	414.5	200	64	13.52	13.50	0.49	S_1
10k	3-Br-C_6H_4-	$C_{20}H_{19}BrN_4O_4$	459	102	56	12.20	12.18	0.41	S_2
10l	2-NO_2-C_6H_4-	$C_{20}H_{19}N_5O_6$	425	226	39	16.47	16.45	0.57	S_2

S_1 Toluene : Ethyl acetate (8 : 2), S_2 Ethyl acetate: Hexane (6 : 4)

Graphical Chart No. 10 : ANTIMICROBIAL ACTIVITY OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-ONES



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	14	13	16	15	8	20	15	10	22	15	19	23	24	24	17	18	0
B.subtilis	15	16	19	20	12	16	9	16	19	19	12	15	22	20	17	24	0
E.coli	19	17	7	12	20	15	18	17	13	17	21	19	21	21	23	19	0
P. aeruginosa	15	15	17	18	13	17	12	21	15	18	14	16	18	22	20	21	0
A. niger	17	11	18	19	15	13	17	9	17	10	16	15	0	0	0	0	24



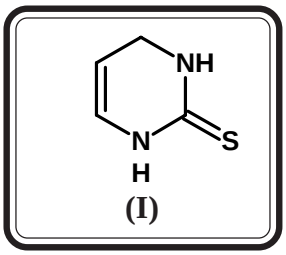
PART - II

STUDIES ON

DIHYDROPYRIMIDINETHIONES

INTRODUCTION

Generally pyrimidine derivatives such as 1,4 dihydro thiopyrimidinone(I) In the area of drug development, dihydroazines show great promise, particularly since the 4-aryldihydropyridines exhibit powerful vasodilation activity via modifying the calcium ion membrane channel.[416-420] Additionally, dihydropyridines have been found to be actively transport medication across biological membranes.[421]



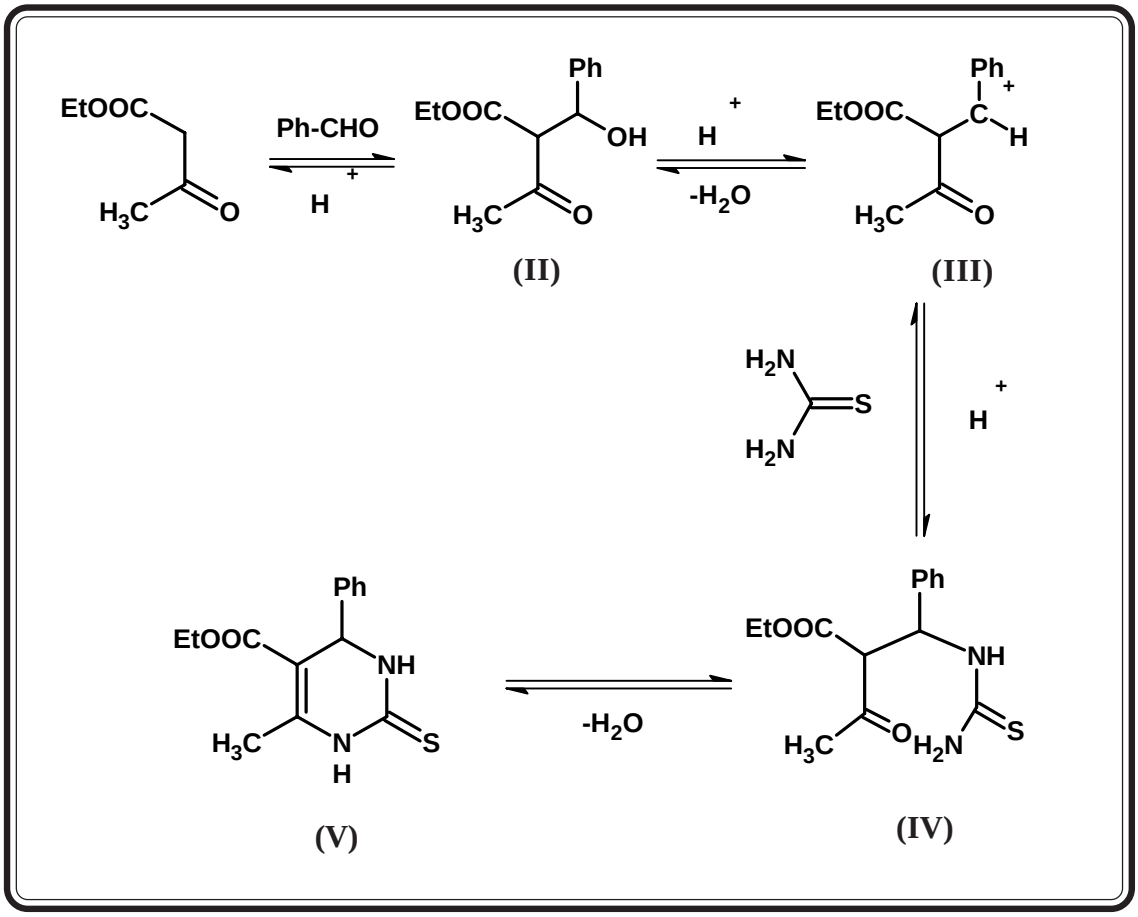
(I)

From the biochemical point of view, dihydroazines are of intense interest because of presence of this group at the active site of the "hydrogen transferring coenzyme" NADH (reduced nicotinamide adenine dinucleotide). This nucleotide is a central participant in metabolic processes in living organisms, participates in the reduction of various unsaturated functionalities.

MECHANISM

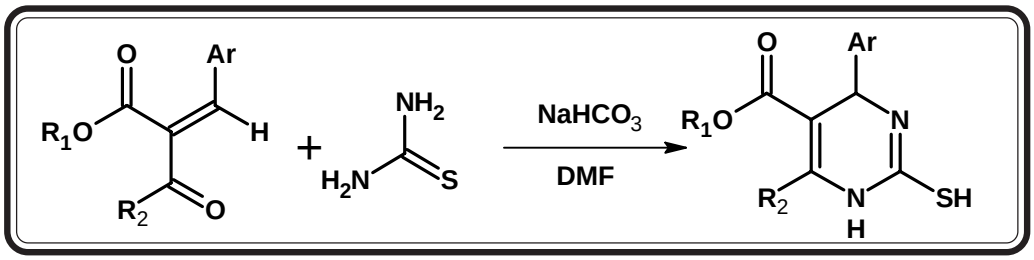
Despite the importance and current interest in dihydropyrimidines, the mechanism of the classical three-component Biginelli condensation[422] has not been elucidated with certainly and remains disputed. The "carbonium ion mechanism" was proposed by Sweet and Fissekis,[423] who investigated the reaction in 1973 and suggested that an acid-catalyzed aldol condensation is the first and limiting step of the Biginelli condensation. It was proposed that under acid catalysis benzaldehyde and ethyl acet oacetate would react in an aldol type fashion to produce the corresponding aldol (II), which dehydrates

in the presence of acid to the resonance stabilized carbonium ion[424-425](III)**.** Interception of cation (III) by urea or thiourea then produces ureides (IV)**,** which ultimately cyclize to the Biginelli products (V).



ATWAL MODIFICATION

Apart from the traditional Biginelli condensation, there are only a few other synthetic methods available that lead to DHPMs. Since most of these protocols lack the experimental and conceptual simplicity of the Biginelli one-pot, one-step procedure, none of these have any significance today or can complete with the original Biginelli MCR approach. One noticeable exception is the so called "Atwal modification" of the Biginelli reaction.[426-428] Here, an enone is first condensed with a suitable protected urea or thiourea derivative under almost neutral condition.



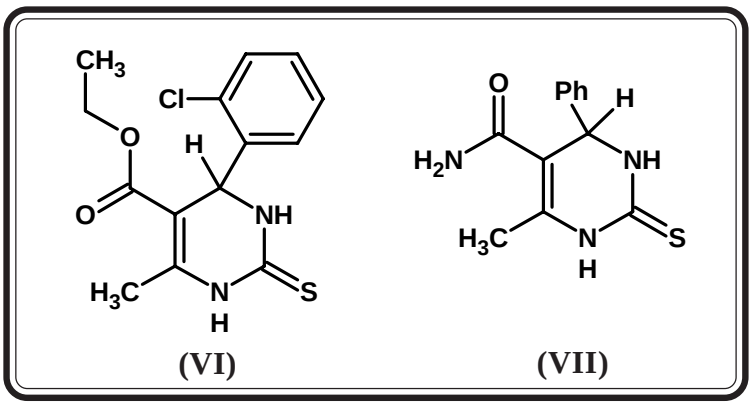
THERAPEUTIC IMPORTANCE

Since 1967, variety of dihydropyridine derivatives have been synthesized in search of more potent vasodilating compounds with longer duration of action. Recently, Bayer A.G.synthesized analogues of the dihydropyridine skeleton itself, for instance, dihydropyran, dihydrothiopyran, dihydropyridazine and dihydropyrazine. Due to the structural similarity between dihydro pyridine and dihydropyrimidine, we became interested in the synthesis and pharmacological activities of pyrimidine class.[429]

Dihydropyrimidinethiones have attracted considerable attention as they appeared of interest to possess wide range of therapeutic activities. Different activities shown by these derivatives are as under.

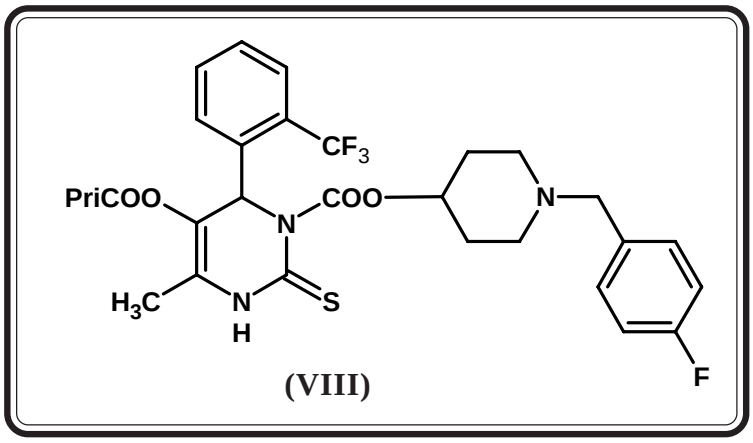
1. Antilukemic.[430]
2. α_{1a} Adrenergic receptor antagonist.[431-432]
3. Antitumor[433]
4. Cardiovascular[434-435]
5. Blood platelet aggregation inhibitor[436-437]
6. Antiinflammatory[438-439]
7. Anticarcinogenic[440]
8. Calcium channel modulator[441-443]
9. Autihypertensive[444-445]
10. Vasodialative[446]
11. anticarcinogenic activity[447]
12. analgesic [448]

Biginelli compound show a diverse range of biological activities. As early in 1930 simple derivative's**(VI)** interest focused on the antiviral activity of Biginelli compounds.[449]



Pyrimidine-5-carboxamides derivatives of type (VII) were reported to possess anticarcinogenic activity,[450] antiinflammatory,[451] analgesic[452] and blood platelet aggregation inhibitory activity.[453]

George C. et al.[454] prepared dihydropyrimidinethione (VIII) was equipotent to nifedipine and amlodipine *in vitro*. In the spontaneously hypertensive rat, dihydropyrimidinethione (VIII) is both more potent and longer acting than nifedipine and compares most favourably with the long acting dihydropyridine derivative amlodipine. Dihydropyrimidinethione (VIII) has the potential advantage of being a single enantiomer.

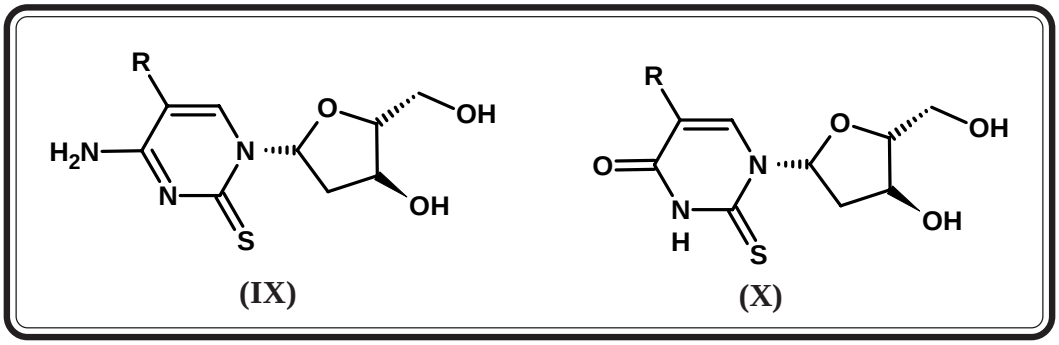


Salvatore B. et al.[455] studied the stopped flow fluorometry indicates that monastrol inhibits ADP release by forming an Eg5-ADP monastrol tertiory complex. Monastrol

reversibly inhibits the motility of human Eg5. Monastrol has no inhibitory effect on the following members of the kinesin superfamily: MC5 (Drosophila melanogaster Ncd), HK379 (H. sapiens conventional kinesin), DKH392 (D. melanogaster conventional kinesin), BimC1-428 (Aspergillus nidulans BimC), Klp15 (Caenorhabditis elegans C-terminal motor), or Nkin460GST (Neurospora crassa conventional kinesin).

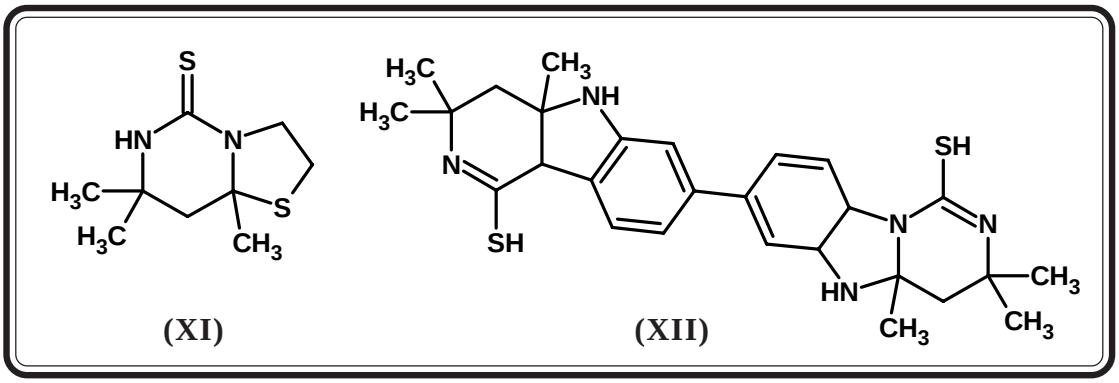
Massey A. et al.[456] report that growing human cells extensively incorporate the thiopyrimidine nucleoside 4-thiothymidine (S4TdR) into their DNA. The incorporated thiopyrimidine (S4T) can also undergo facile S-methylation to 4-thiomethylthymine (S4meT). The rate of methylation of S4TdR in model substrates is similar to that for the conversion of S6G to S6meG indicating that the DNA of cells grown in S4TdR will contain significant levels of S4meT.

Twenty 5-alkyl-2-thiopyrimidine nucleosides were newly synthesized by Shigeta S. et al.[457] and examined for antiviral activities against herpes simplex virus (HSV), varicella zoster virus (VZV) and human cytomegalovirus (HCMV). In this study, 2'-deoxy-5-alkyl-2-thiocytidine (IX) analogues had lower 50% effective concentration (EC50) values against HSV-1, and 2'-deoxy-5-alkyl-2-thiouridine (X) analogues showed lower activity.



Various 2-thiopyrimidine derivatives have been synthesized by Sondhi S.M. et al.[458] One of the compounds, Thiazolo[3,2-c]pyrimidine-5-thione derivatives (XI) showed good antiinflammatory (37.4% at 100mg/kg p.o.) and analgesic activity (75% at 100mg/kg p.o.). 7-(1-Mercapto-3,3,4a-trimethyl-4,4a,5,9b-tetrahydro-3H-pyrido[4,3-b]indol-

7-yl)-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-c]pyrimidine-1-thiol (XII) showed moderate activity against CDK-1 (IC(50)=5muM). The other compounds showed moderate antiinflammatory (5-20%), analgesic (25-75%) and protein kinase (CDK-5, GSK-3) inhibitory activities (IC(50)>10muM).



(XI) **(XII)**

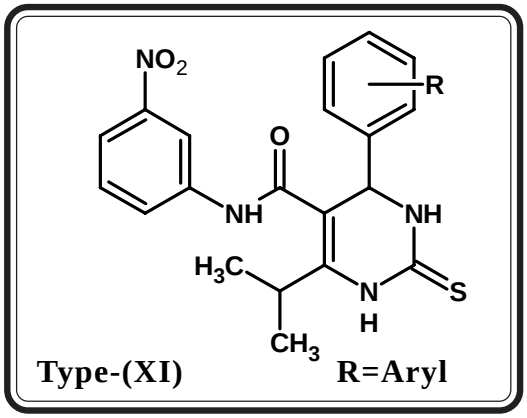
With an intention of preparing the compounds possessing better therapeutic activity, we have undertaken the synthesis of dihydropyrimidinethiones which have been described in following section.

SECTION-I : 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-ISOPROPYL-5-[N-(m-NITRO PHENYL)AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONES

Compounds containing pyrimidine ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these report, we have synthesized 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydro pyrimidine-2(1*H*)-thiones type-(XI) by the condensation of 2-Arylidene-4-methyl-*N*-(3-nitrophenyl)-3-oxopentanamide with thiourea in presence of potassium bicarbonate.

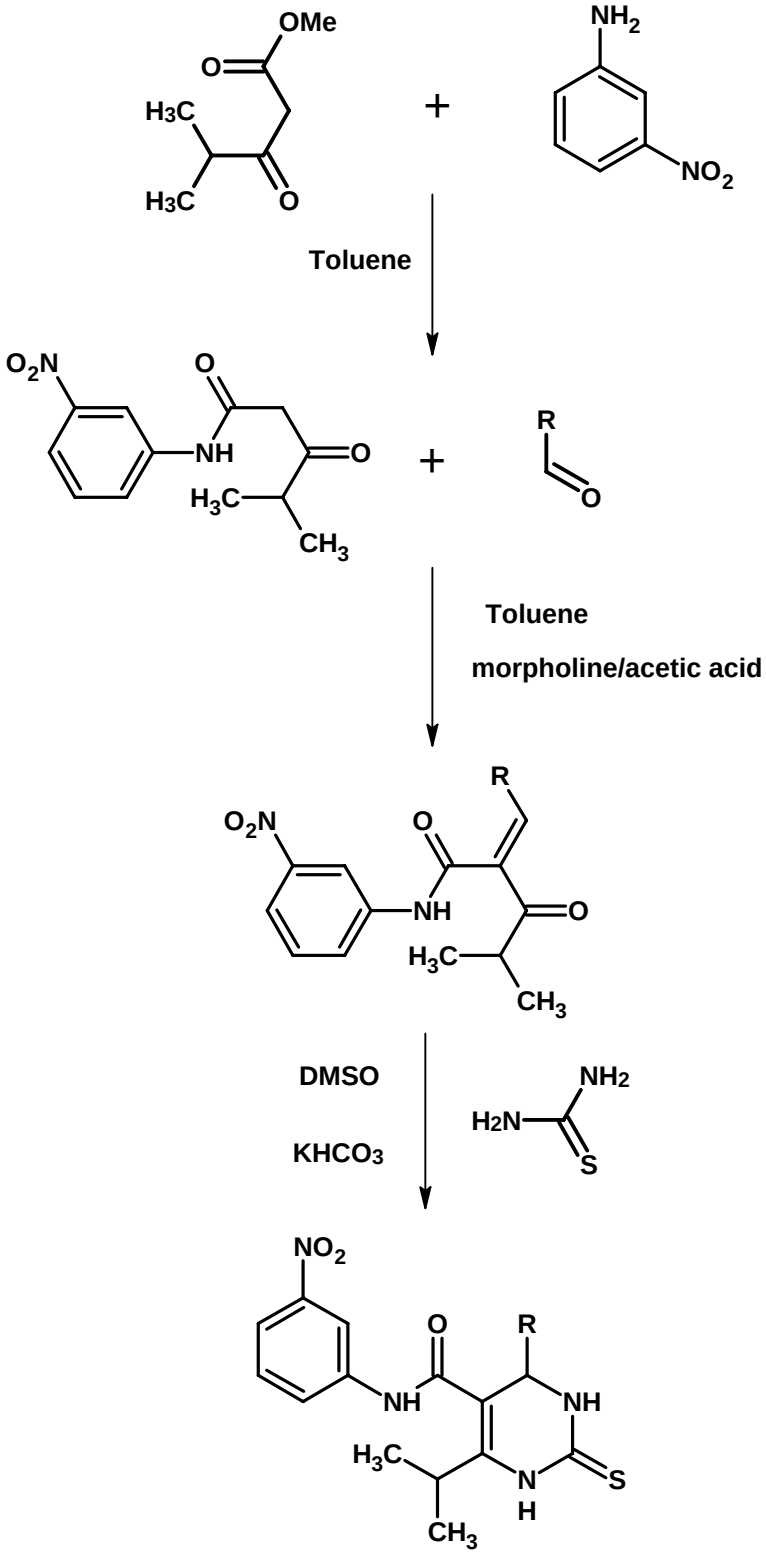


Type-(XI) **R=Aryl**

The structure elucidation of synthesized compounds have been characterized by using elemental analysis, IR spectra, ^{1}H NMR spectroscopy and further supported by Mass spectrometry.

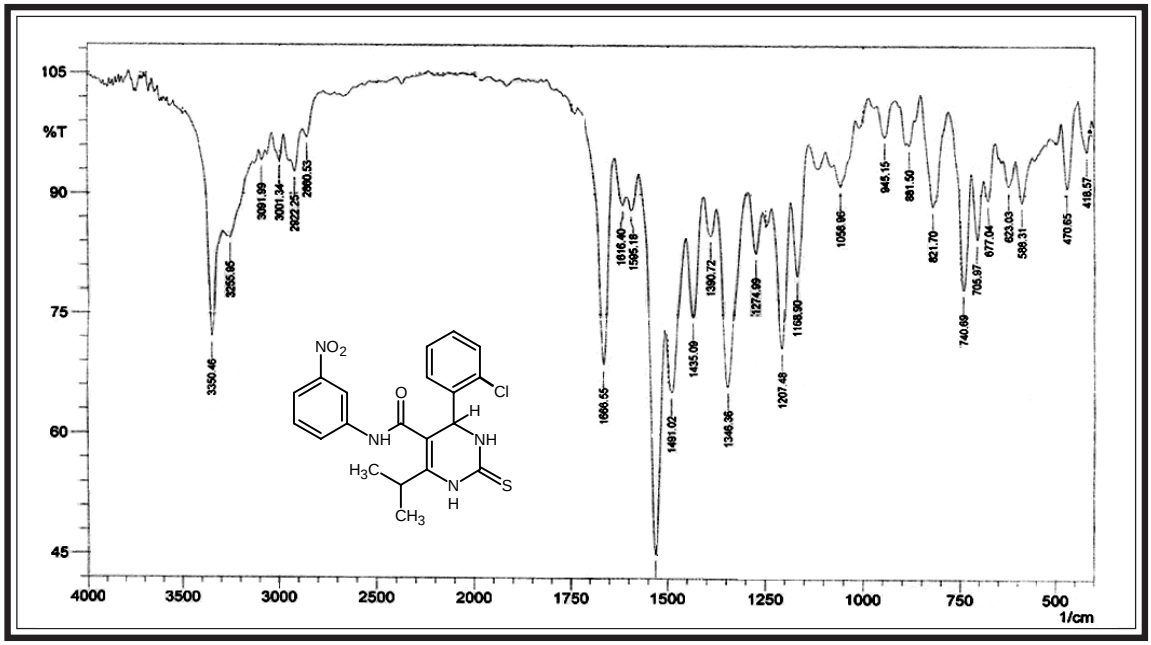
All the compounds have been screened for their *in vitro* biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

REACTION SCHEME



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

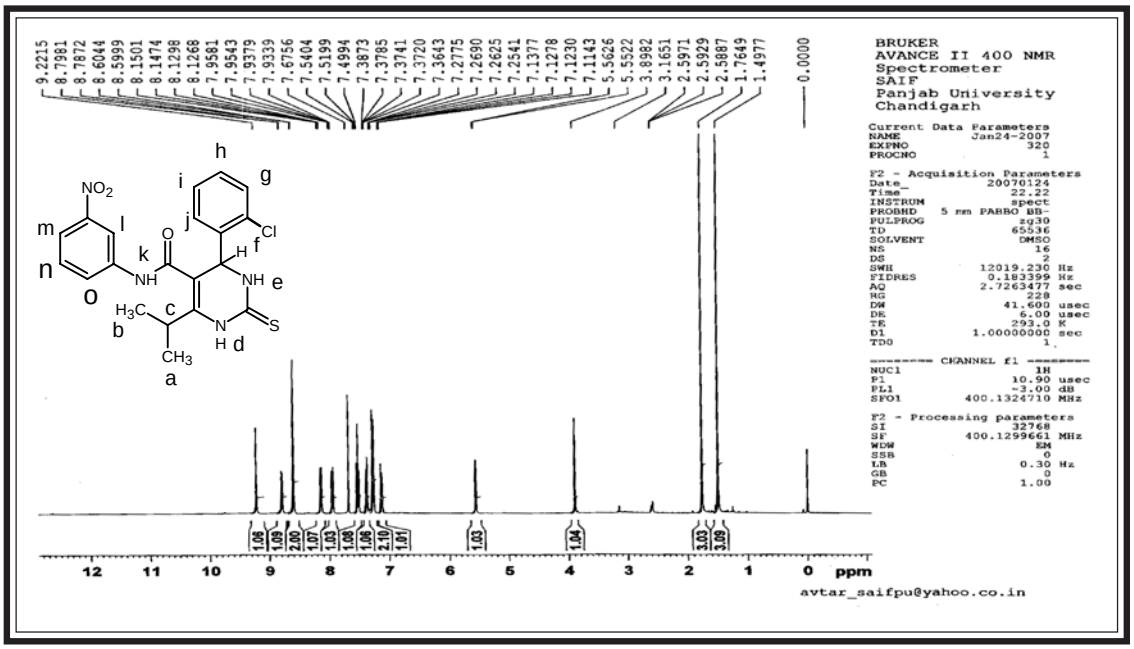
IR SPECTRAL STUDIES OF 4-(2-CHLOROPHENYL)-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL)AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2922	2975-2950	189
-CH_3	C-H str. (sym.)	2860	2880-2860	,,
	C-H i.p.def. (asym.)	1435	1470-1435	,,
	C-H o.o.p. def. (sym.)	1390	1390-1370	,,
Aromatic	C-H str.	3091	3090-3030	190
	C=C str.	1531	1540-1480	,,
	C-H o.o.p.(def)	821	832-802	,,
	NO_2 str.	1346	1385-1365	,,
Pyrimidine	C-H i.p. def.	1120	1125-1090	,,
	NH str.	3255	3300-3200	”
	C=S str.	1207	1270-1190	”
Amide	NH str.	3350	3410-3380	189
	NH def.	1616	1635-1595	,,
	C=O str.	1666	1690-1660	,,

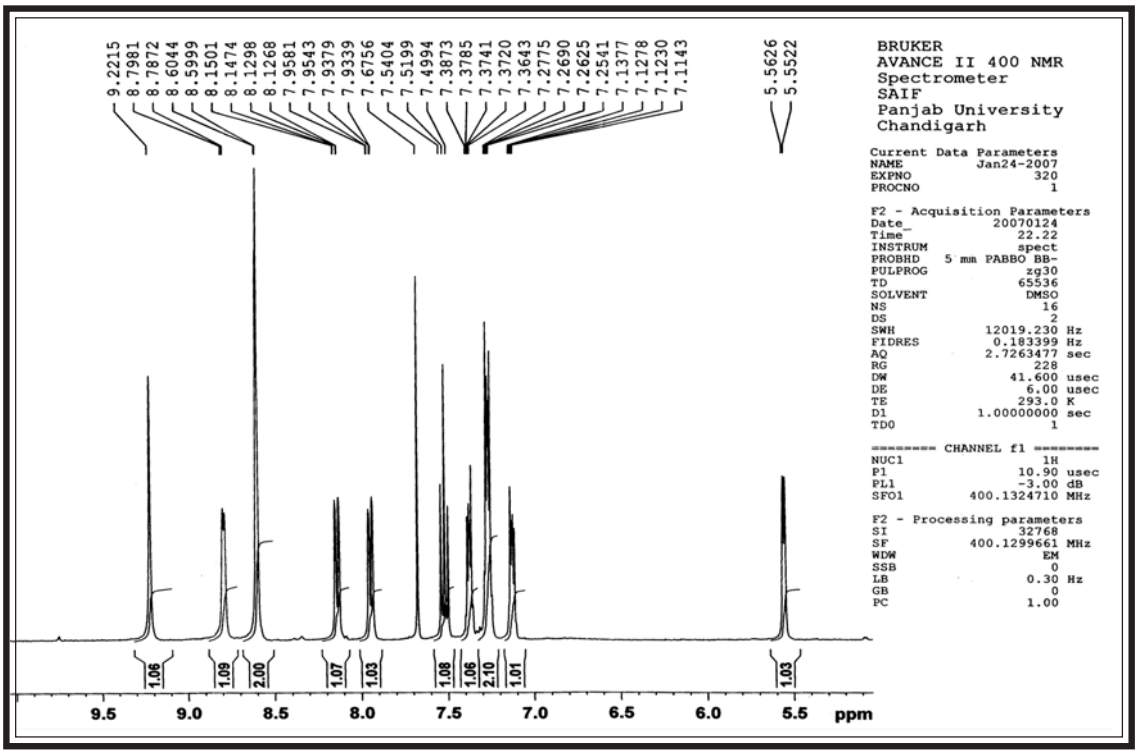
NMR SPECTRAL STUDIES OF 4-(2-CHLOROPHENYL)-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONE



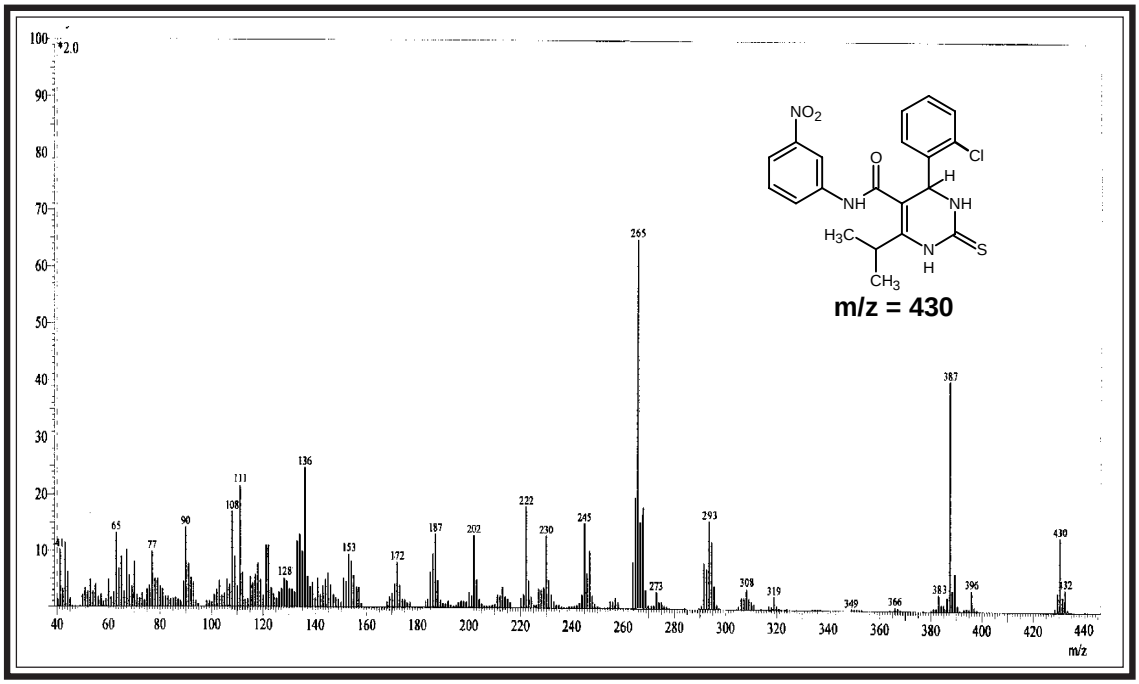
Internal Standard : TMS; Solvent : DMSO : Instrument : BRUKER Spectrometer (400 MHz)

Signal No.	SignalPosition (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	1.49	6H	doublet	-CH(CH_3)$_2$ (a,b)	-
2	3.89	1H	singlet	-CH(c)	-
3	5.55-5.56	1H	doublet	Ar-H(f)	4.16
4	7.11-7.13	1H	doublet	Ar-H(j)	5.64,3.4
5	7.25-7.27	2H	doublet	Ar-H(i-h)	5.98,3.4
6	7.36-7.38	1H	doublet	Ar-H(g)	-
7	7.49-7.54	1H	triplet	Ar-H(n)	-
8	7.93-7.95	1H	doublet	Ar-H(o)	8.08 ,1.6
9	8.12-8.15	1H	doublet	Ar-H(m)	8.12 ,1.2
10	8.59	1H	singlet	Ar-H(l)	-
11	8.60	1H	singlet	-NH CO(k)	-
12	8.78-8.79	1H	doublet	-NH(e)	4.36
13	9.22	1H	singlet	-NH(d)	-

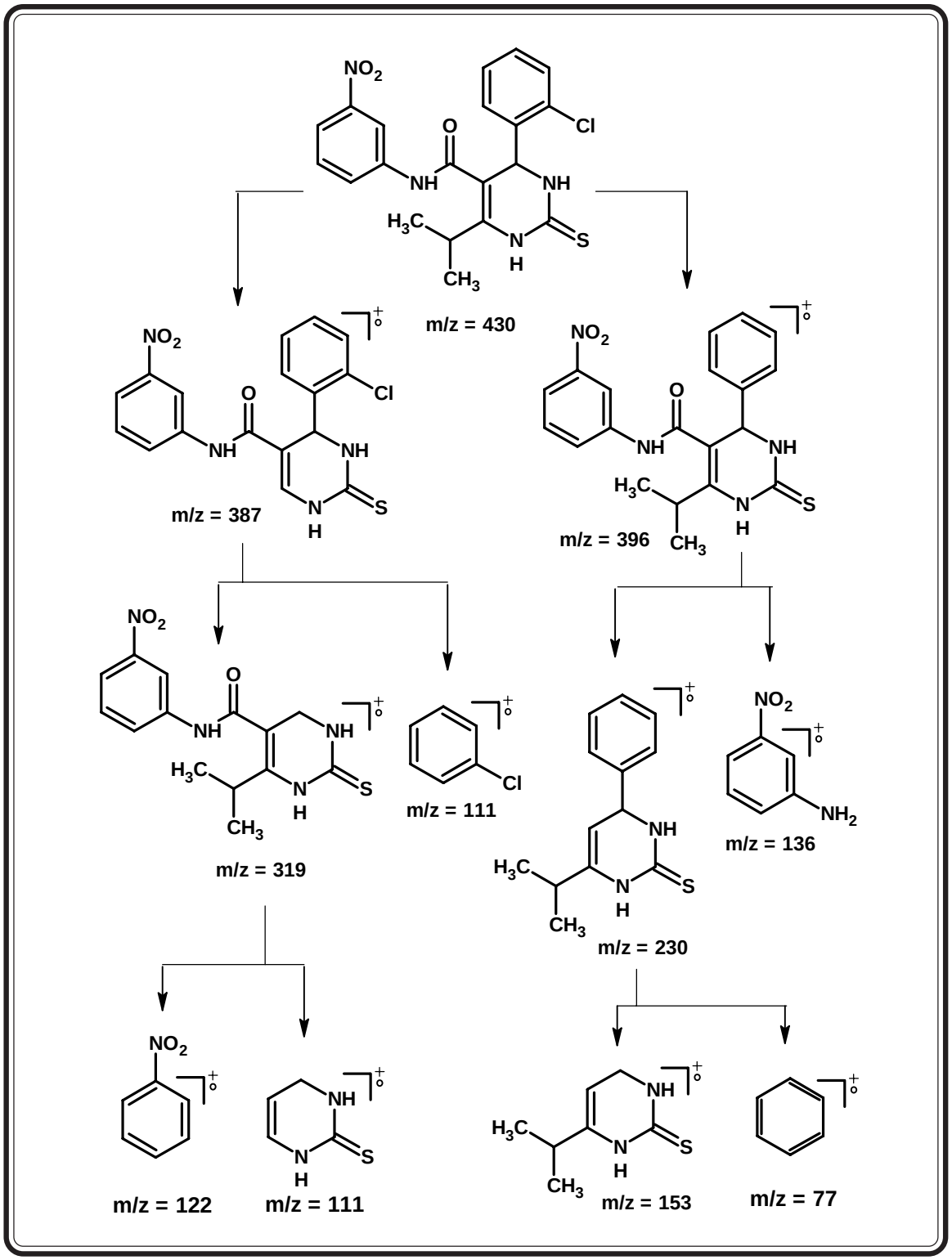
EXPANDED AROMATIC REGION



MAAS SPECTRAL STUDIES OF 4-(2-CHLOROPHENYL)-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONES

[A] Synthesis of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide :

See(B), part-I, section-I (A), page no.164.

[B] Synthesis of 2-(2-Chlorobenzylidene)-4-methyl-*N*-(3-nitrophenyl)-3-oxopentanamide :

To the mixture of 2-Chloro benzaldehyde 1.40gm (0.01mol) and 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide 2.50gm (0.01mol), morpholine, acetic acid and toluene were added and refluxed for 22 hrs with continuous removal of water by dean and stark apratus. After completion of the reaction, cooled it at room temperature, filtered the material and washed with toluene. Make a slurry of the material into the solution of sodium meta bisulphite and remove excess aryl aldehyde.

Similarly, other 2-(2-Arylidene)-4-methyl-*N*-(3-nitrophenyl)-3-oxopentanamide were prepared.

[C] Synthesis of 4-(2-Chlorophenyl)-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydropyrimidine-2(1*H*)-thione :

To the mixture of 2-(2-Chlorobenzylidene)-4-methyl-*N*-(3-nitrophenyl)-3-oxopentanamide 3.72gm (0.01mol) and thiourea 0.76gm (0.01mol) in DMSO, potassium bicarbonate was added and the mixture was stirred at 45-55 ^{o}C temperature for 20 hrs. After completion of the reaction, cool down the reaction mixture at room temperature. Slowly pour the reaction mixture into a mixture of crushed ice, dil. HCl and toluene.

Stir it for 1 hr then separate water layer and adjust pH 9-10 using liq NH_3. Filter the material and wash it with water. Recrystallized from isopropyl alcohol. Yield 56%, m.p.dec 250^{o}C ,Elemental analysis calculated for $C_{20}H_{19}ClN_4O_3S$ Requires : C-55.75%, H-4.44%, N-13.00%. Found : C-55.73%, H-4.45%, N-13.11%.

Similarly, other 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydropyrimidine-2(1*H*)-thiones were prepared. The physical data are recorded in table no.11.

[D] Biological screening of 4-Aryl-6-isopropyl-5-[*N*-(3-nitrophenyl) amino carbonyl]-3,4-dihydropyrimidine-2(1*H*)-thiones :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.47. The zones of inhibition of test solutions are recorded in graphical chart no.11.

Conclusion :

Antibacterial activity

The screening data indicated that among dihydropyrimidinethione derivatives tested compounds **11b**, **11f**, **11l** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **11k** showed greater degree of antibacterial activity against *B.subtilis*. The compounds **11c**, **11e**, **11g, 11l** and **11h**, **11j** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

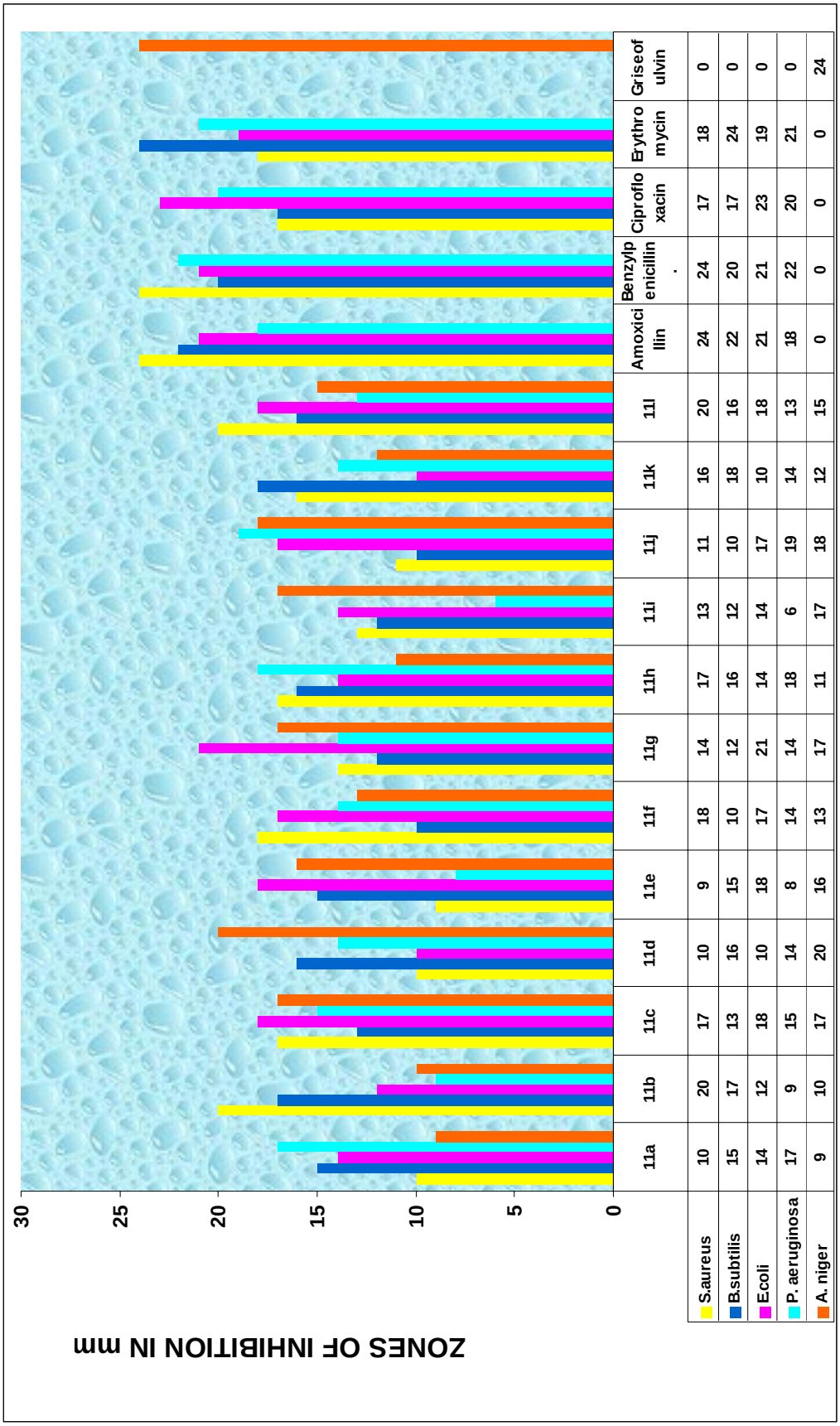
The screening data indicated that among dihydropyrimidinethione derivatives tested compounds **11d, 11j** showed greater degree of antifungal activity against *A.niger.*

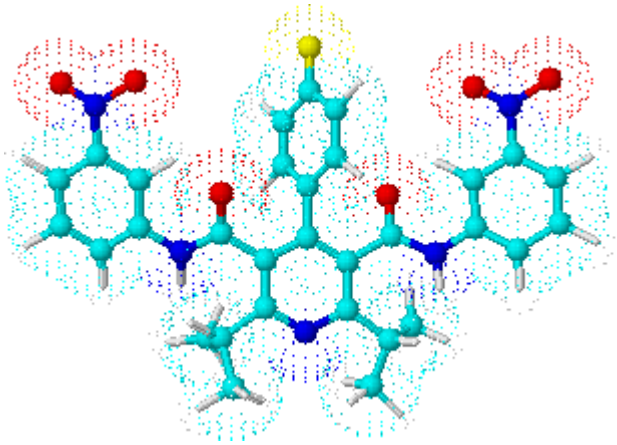
TABLE -11 : PHYSICAL CONSTANTS OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDROPYRIMIDINE-2(1*H*)-THIONES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
11a	C_6H_5-	$C_{20}H_{20}N_4O_3S$	396	122	42	14.14	14.12	0.43	S_1
11b	4-OCH_3-C_6H_4-	$C_{21}H_{22}N_4O_4S$	426	168	55	13.14	13.12	0.52	S_1
11c	3,4- $(OCH_3)_2$-C_6H_3-	$C_{22}H_{24}N_4O_5S$	456	135	47	12.28	12.19	0.47	S_1
11d	4-(OH)-3-(OCH_3)-C_6H_3-	$C_{21}H_{22}N_4O_5S$	442	239	47	12.66	12.72	0.49	S_1
11e	4-OH-C_6H_4-	$C_{20}H_{20}N_4O_4S$	412	174	61	13.59	13.57	0.51	S_2
11f	2-OH-C_6H_4-	$C_{20}H_{20}N_4O_4S$	412	178	51	13.59	13.61	0.57	S_2
11g	4-F-C_6H_4-	$C_{20}H_{19}FN_4O_3S$	414	244	55	13.52	13.57	0.45	S_2
11h	4-Cl-C_6H_4-	$C_{20}H_{19}ClN_4O_3S$	430.5	172	57	13.02	12.97	0.51	S_1
11i	2-Cl-C_6H_4-	$C_{20}H_{19}ClN_4O_3S$	430.5	dec.250	59	13.02	13.08	0.41	S_1
11j	3,4-$(Cl)_2$-C_6H_3-	$C_{20}H_{18}Cl_2N_4O_3S$	465	190	57	12.04	12.07	0.51	S_2
11k	3-Br-C_6H_4-	$C_{20}H_{19}BrN_4O_3S$	475	142	56	11.78	11.81	0.55	S_2
11l	3-NO_2-C_6H_4-	$C_{20}H_{19}N_5O_5S$	441	170	62	15.87	15.89	0.47	S_1

S_1 Toluene : Ethyl acetate (8 : 2), S_2 Ethyl acetate : Hexane (6 : 4)

Graphical Chart No. 11 : ANTIMICROBIAL ACTIVITY OF 4-ARYL-6-ISOPROPYL-5-[*N*-(3-NITROPHENYL) AMINO CARBONYL]-3,4-DIHYDRO PYRIMIDINE-2(1*H*)-THIONES





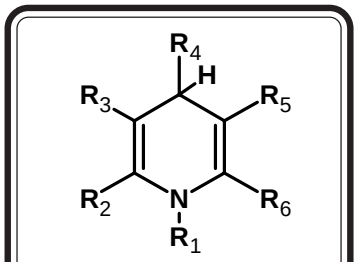
[C]

STUDIES ON

1,4-DIHYDROPYRIDINES

INTRODUCTION

In substituted 1,4-dihydro pyridine(I) either imino (NH) or substituted nitrogen atom is present at one position and hydrogen atom at four position of the six member hetrocyclic ring which can be represented as under.



(I)

Dihydropyridines are the largest and the most studied class of drugs having calcium channel blockers[459] activity. In addition to their proven clinical utilities in cardiovascular medicine, dihydropyridines are employed extensively as biological tools for the study of voltage-activated calcium channel.[460]

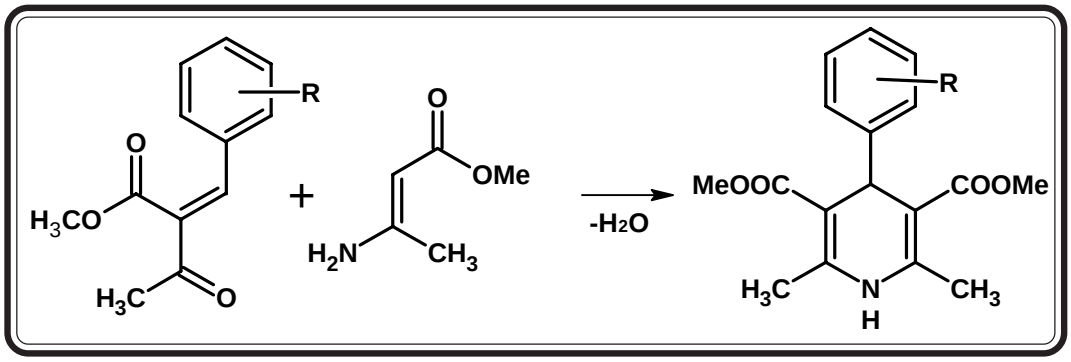
From study of DHP compounds, it is found that both the ester groups present at 3 and 5 position play an important role in cardiovascular activity, removal of these groups may led to reduction of the activity.[461] This conclusion has open up new scope for structural modifications at these positions. Very wide range of literature regarding the structure, synthesis, stereochemistry and hydrogen transfer mechanism of dihydropyridine is available.[462-467] As it is very pertinent to work on these issues, more than 10,000 articles, publications & patents are published in the literature on the 1,4-DHPs.

Lot's of 1,4-dihydropyridine derivatives have been synthesized and developed as calcium channel antagonists which inhibit smooth and cardiac muscle contractions by blocking the influx of Ca^{+2} through calcium channels and antihypertensive action.[468-170]

SYNTHETIC ASPECT

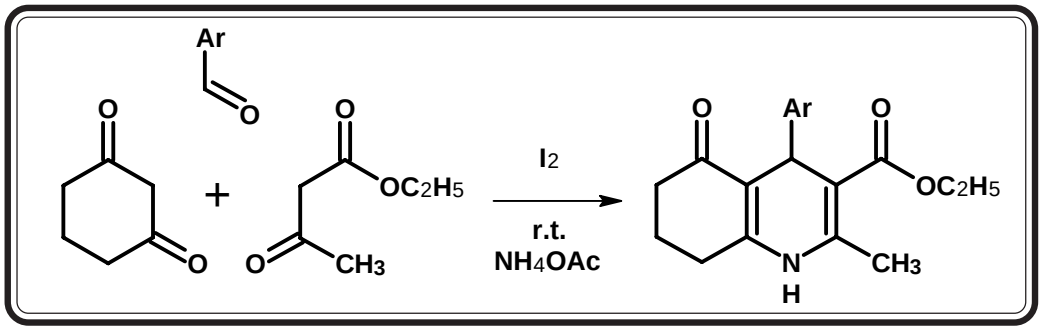
Different methods for the synthesis of 1,4-dihydropyridine are as follows.

1. By the knoevenagel condensation of benzaldehyde with acetoaceticester in pres ence of β-alanine as catalyst and subsequent cyclocondensation of the resulting benzylidene with 3-amino crotonate.[471]
2. By the regio and chemoselective addition of $Ph_2Cu(CN)Li_2$ to substituted N-alkyl pyridinium salts followed by acylation of the intermediate.[472]
3. By the condensation of 1,3-diketones, alkyl or aryl aldehydes with aqueous ammo nium hydroxide in the presence of piperidine or piperidyl acetate or potassium acetate or potassium carbonate or glacial acetic acid.[473-4775]
4. By the condensation of two moles of thiobarbituric acid, aromatic amines and aromatic aldehydes.[476-477]
5. By the condensation of aromatic or aliphatic aldehydes with acetoacetic ester and aromatic or aliphatic amine in presence of pyridine.[478-481]
6. By the condensation of arylidene with 3-aminocrotonate.[482]

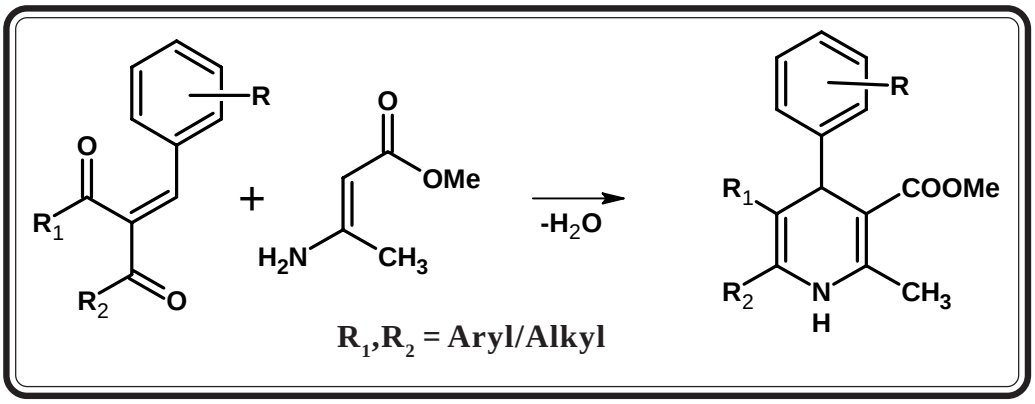


7. By the condensation of aliphatic or aromatic aldehydes with various 1,3-dike tones in presence of ammonia or ammonium carbonate.[483-485]
8. By the condensation of α,β-unsaturated ketones with malononitrile and cyanoac etamide.[486]
9. By the condensation of o-nitrobenzaldehyde, β-amino butaricacid and methyl propionate in glacial acetic acid.[487]

10. Shengkao Ko et al[488] have synthesized 1,4-dihydropyridine by one pot reaction, catalyzed by iodine at room temperature.



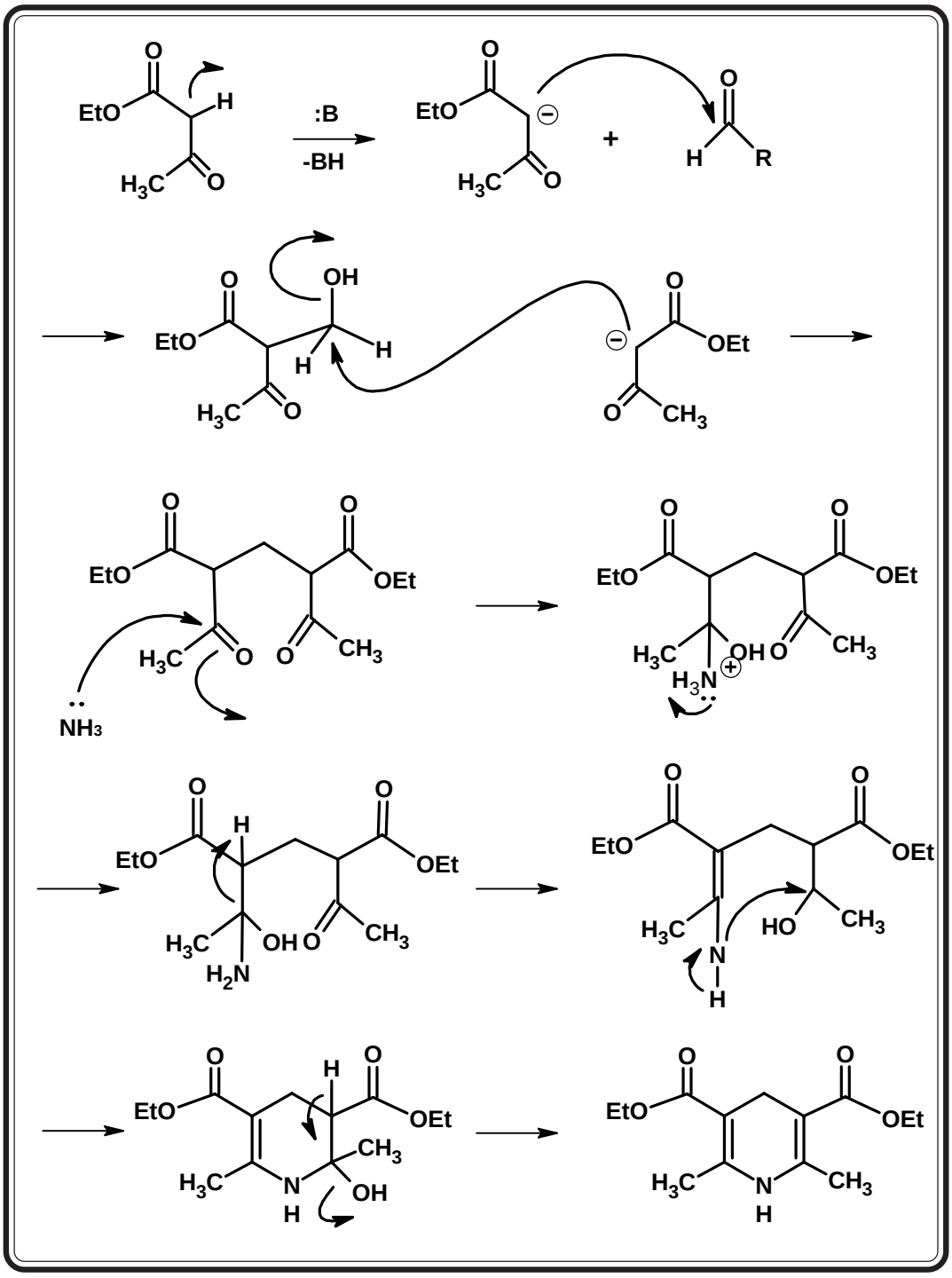
11. By the condensation of aliphatic or aromatic aldehydes with 3-amino croton ate and 1,3-diketone.[489-496]



MECHANISM

The first dihydropyridine was in fact isolated back in 1882 as a stable intermediate from this method.[497] In its simplest form of the synthesis involves heating an aldehyde, 1,3-diketone and ammonia.

The reaction almost certainly involves aldol condensation to form the benzylidene derivative as the first step. Conjugated addition of a second mole of 1,3-diketone would then afford the 1,5-diketone. Reaction of the carbonyl group with ammonia will lead to the formation of the dihydropyridine ring to give many drug molecules that has been used extensively for treatment of angina[498] and hypertension.[499]



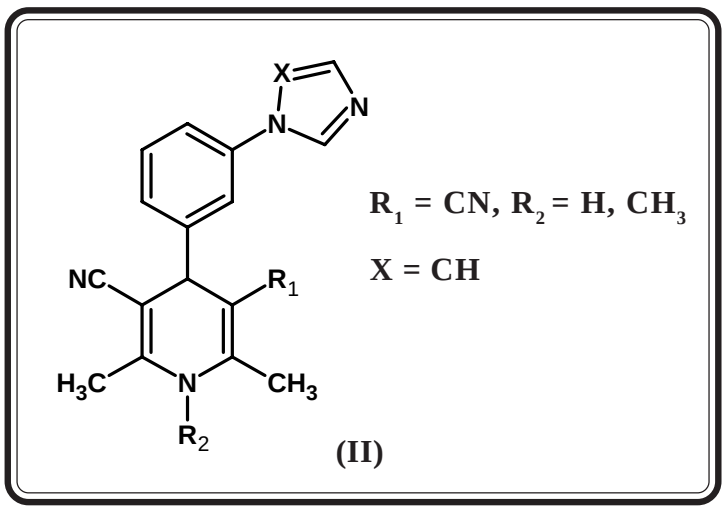
THERAPEUTIC INTEREST

The research on 1,4-dihydropyridine system is of current interest due to their valuable activities as calcium channel antagonist, vasodilator, cardiovascular, etc. Beside the currently established drugs Nifedipine[500-501] Nicardipine[502-503] many dihydropyridine de-

rivatives have been synthesized world wide[504] and have led to numerous second generation commercial products,[505-506] such as Nimodipine,[507-508] Nisodipine,[509] Nitrendipine,[510] Amlodopine,[511] Felodipine,[512] Isradipine,[513] Manidipine[514] and Nilvadipine.[515] Some of their compounds are characterized by longer bioactivity of greater tissue selectivity. 1,4-Dihydropyridine derivatives are associated with diverse biological activities viz.

1. Antiarythmic[516]
2. Antiinflammatory[517]
3. Antiallergic[518]
4. Antiulcer[519]
5. Vasodilator[520]
6. Enzymetic[521-522]
7. Antitubercular agents[523]

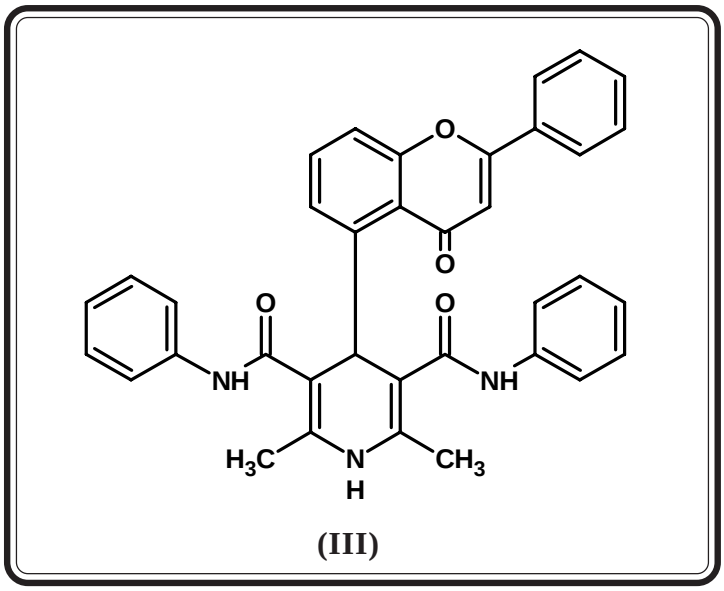
Cozzi et al.[524] studied anticancer activity especially as an aromatase inhibitory activity of dicyano and cyanoester derivatives of 1,4-DHP containing an imidazol-1-yl or 1,2,4-triazol-1-yl ring (II) at C4 position of phenyl ring. Aromatase inhibitory activity recorded *in vitro* near to 10^{-9}M concentration.



(II)

Kilcigil and coworkers[525] synthesized new type of symmetrical dicarbamoyl 1,4-dihydropyridines with some flavone derivatives at C_4 position of DHP ring by reacting 6-formylflavones with acetoacetanilide. Their aim was to investigate the calcium

antagonistic activity on this skeletal changes. Few newly synthesized compounds showed good calcium antagonistic activity with nifedipine as the reference compound.

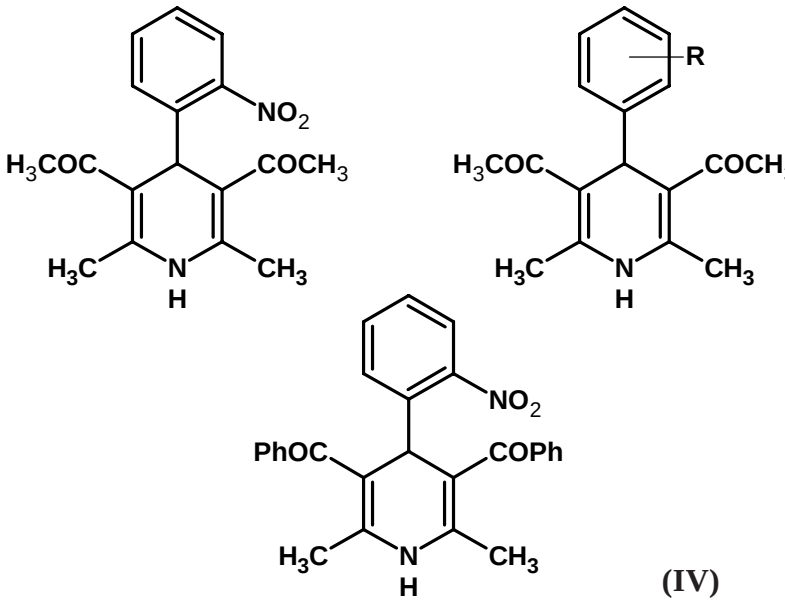


(III)

Shah et al[526] have synthesized many symmetrical DHPs with 3,5-diacetyl-1,4-dihydropyridine and they studied the interaction between ampicillin, erythromycin and synthesized molecules (IV) on different strains of *E.coli.*

They also studied and investigated the cytotoxic and *mdr* reversal activities against the mouse lymphoma cells transected with *mdr*[21].

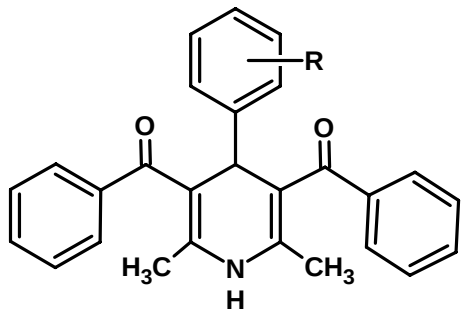
Moreover the same author group[527] synthesized many compounds with dibenzoyl functionality and concluded that new series of mdr modulators can be derived from the BzDHPs and they found that *mdr* reversal was dependant on the nature of substituents and their position at the C_4 phenyl ring of BzDHPs. Among them one compound has shown high mdr modulating potency and the tumor specific cytotoxicity including a new drug candidate for *mdr* cancer therapy.



(IV)

R= 3-CF_3, 3-NO_2, 3-Cl, 2-NO_2, 2-Cl, 3-Br, 3-OCH_3, 3-OPh etc...

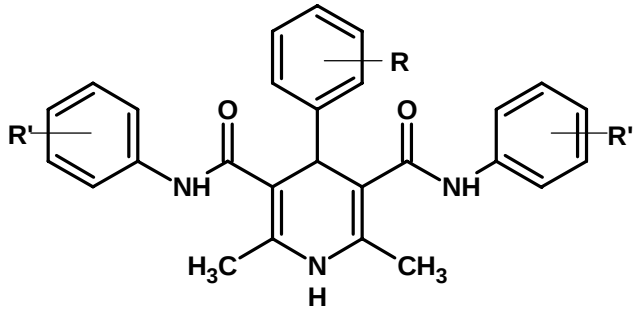
Shah et al[528] was pioneer in the investigation of the 3,5-diacetyl and 3,5-dibenzoyl-1,4-DHPs (DP1-11) (V)on vascular function *in vitro*, by comparing their mechanical and electrophysiological actions respectively, to quantify their multidrug resistance (*mdr*) reversing activity in L5178 Y mouse t-lymphoma cells transfacted with *mdr1* gene and they suggest that DP7 may represent a lead compound for the design of novel, safe and potent MDR chemosensitizers needed for the chemotherapy of the cancer and other diseases.



R= 3-CF_3, 3-NO_2, 3-Cl, 2-NO_2,

2-Cl, 3-Br, 3-OCH_3, 3-OPh etc... **(V)**

STRUCTURAL REQUIREMENT FOR ANTITUBERCULAR ACTIVITY IN 1,4-DHPS FROM QSAR STUDY



R= Cl, NO_2, Br, OC_6H_5 etc..

R'= NO_2, OCH_3, Cl etc.. **(VI)**

Many derivatives of the type (VI) were screened for their antitubercular activity against *M.tuberculosis* H_{37} RV out of which, among them some molecules showed >90% inhibition comparable to rifampicin.

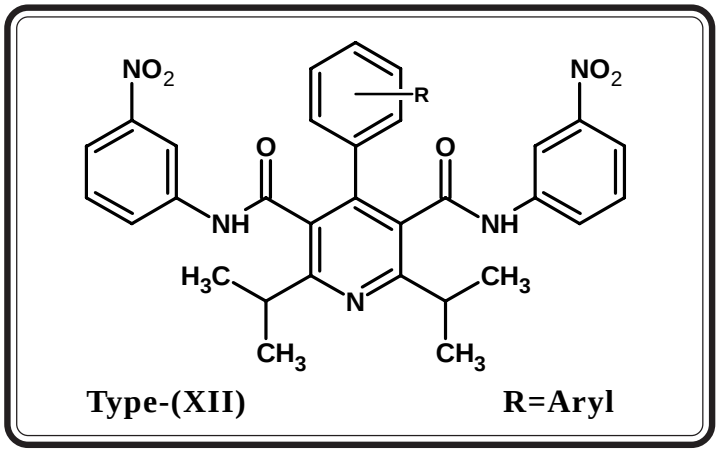
The QSAR study of all these derivatives indicates that the presence of bulkier substituents in the phenyl ring at C_4 position of the dihydropyridines positively contributes for the antitubercular activity[529]. The electronic influence of the substitutions at the carbamoyl phenyl ring present at 3 and 5 position of dihydropyridine are important for antitubercular activity. The presence of the electron withdrawing group(EWG) at meta and para position increases activity. This electronic influence the enzymatic hydrolysis of the amide bond present at 3 and 5 position of substituted dihydropyridines to corresponding acids inside the *M.tuberculosis*.

SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITRO PHENYL)AMINO CARBONYL]-1,4-DIHYDRO PYRIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITROPHENYL)AMINOCARBONYL]-1,4-DIHYDRO PYRIDINES

In view of getting better therapeutic agent and considering the association of various biological activity with pyrimidine nuclei, the synthesis of 4-Aryl-2,6-diisopropyl-3,5-bis[*N*-(3-nitrophenyl)aminocarbonyl]-1,4-dihydro pyridines of type-(XII) have been carried out by the condensation of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide, ammonical methanol and various type of aromatic aldehydes.

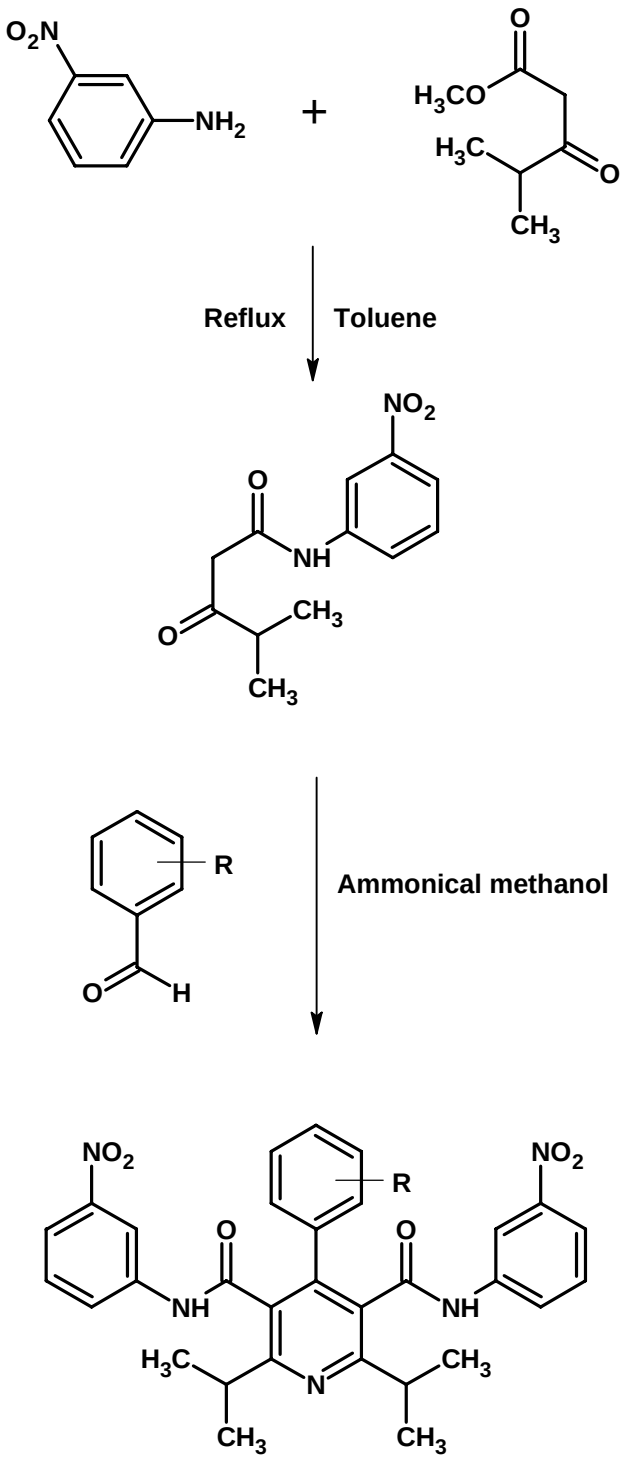


Type-(XII) **R=Aryl**

The structure elucidation of synthesized compounds has been characterized by using elemental analysis, IR spectra, ^{1}H NMR spectroscopy and further supported by Mass spectrometry.

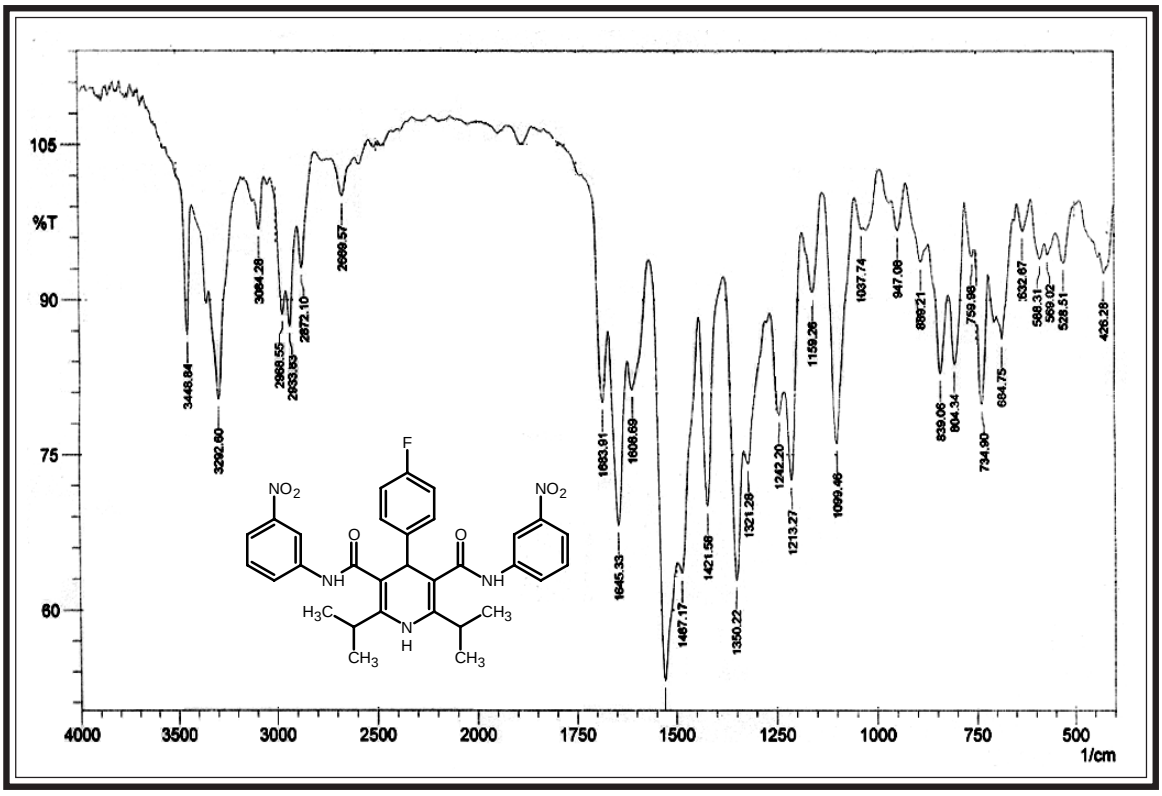
All the compounds have been screened for their *in vitro* biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40µg. The biological activities of synthesized compounds were compared with standard drugs. The details have been cited in (A), part-I, section-I(E), page no.047.

REACTION SCHEME



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

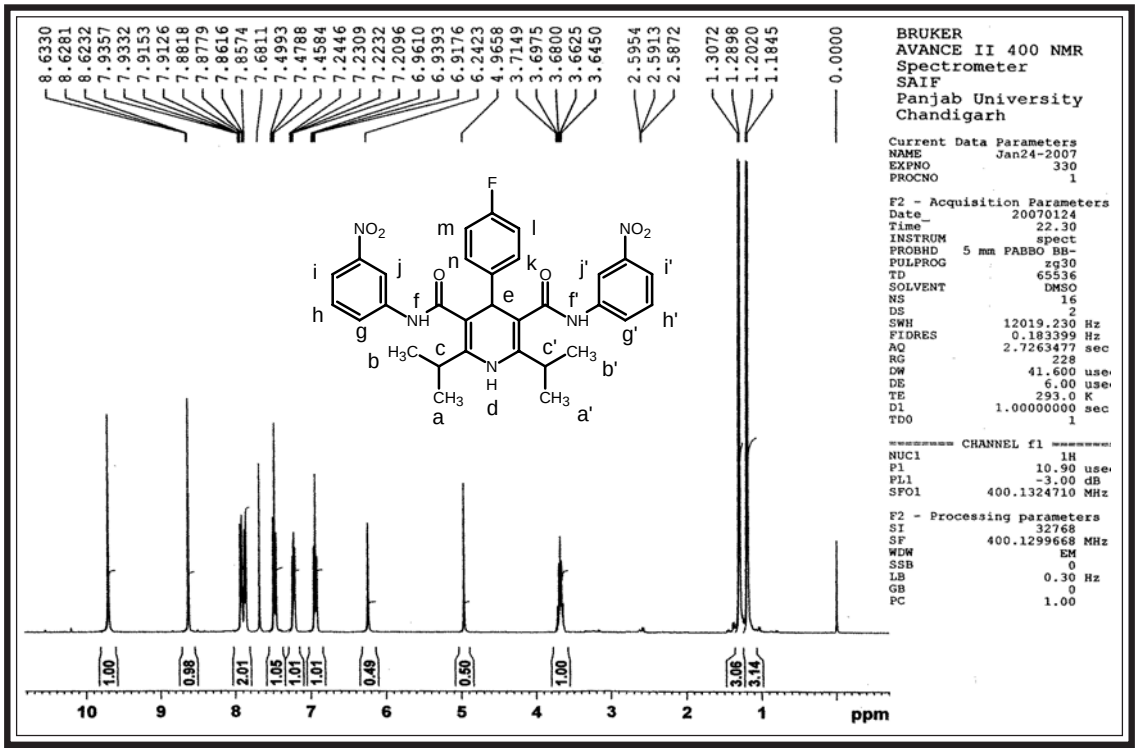
IR SPECTRAL STUDIES OF 4-(4-FLUOROPHENYL)-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITROPHENYL)AMINOCARBONYL]-1,4-DIHYDROPYRIDINE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref
		Observed	Reported	
Alkane	C-H str. (asym.)	2968	2975-2950	189
-CH_3	C-H str. (sym.)	2872	2880-2860	,,
	C-H i.p.def. (asym.)	1421	1470-1435	,,
	C-H o.o.p. def. (sym.)	1350	1390-1370	,,
Aromatic	C-H str.	3084	3090-3030	190
	C=C str.	1487	1540-1480	,,
	C-H i.p.(def)	1242	1269-1247	,,
	C-H o.o.p.(def)	804	832-802	,,
	NO_2 str.	1350	1385-1365	,,
Pyridine	C=C str.	1530	1580-1520	,,
moity	N-H str.	3448	3440-3400	,,
	C-N str.	1242	1300-1200	,,
Amide	NH str.	3292	3410-3380	189
	NH def.	1608	1635-1595	,,
	C=O str.	1645	1690-1660	,,

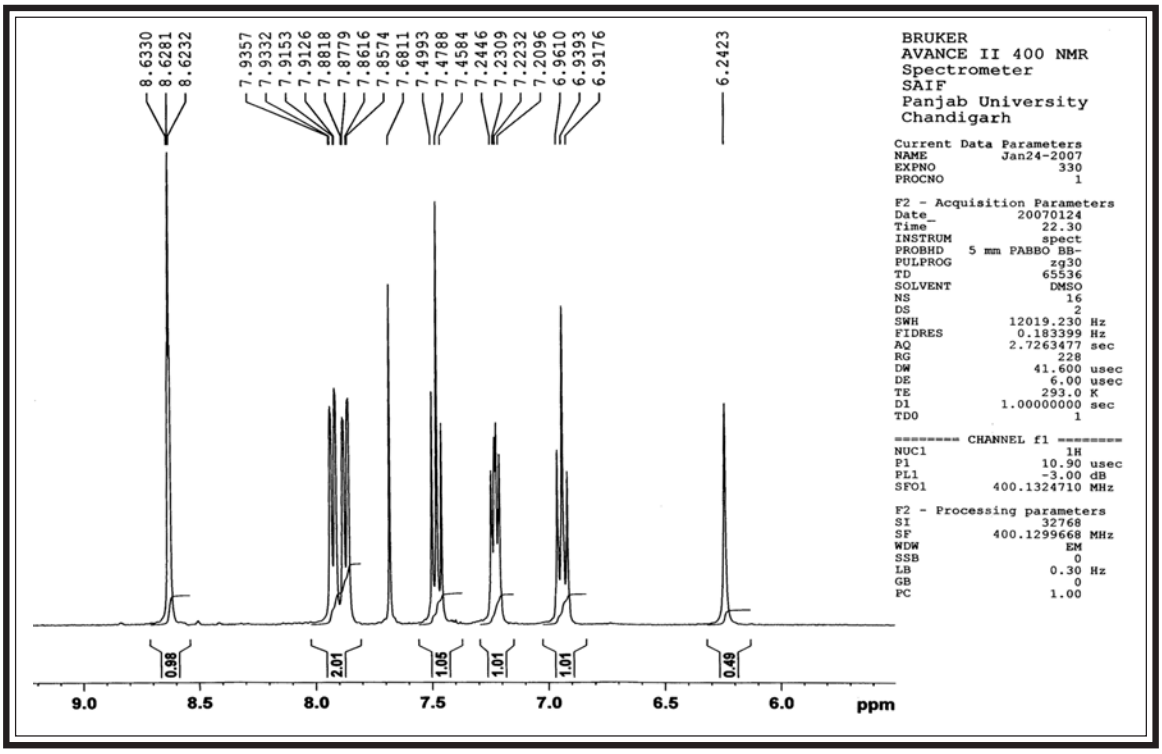
NMR SPECTRAL STUDIES OF 4-(4-FLUOROPHENYL)-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITROPHENYL)AMINOCARBONYL]-1,4-DIHYDRO PYRIDINE



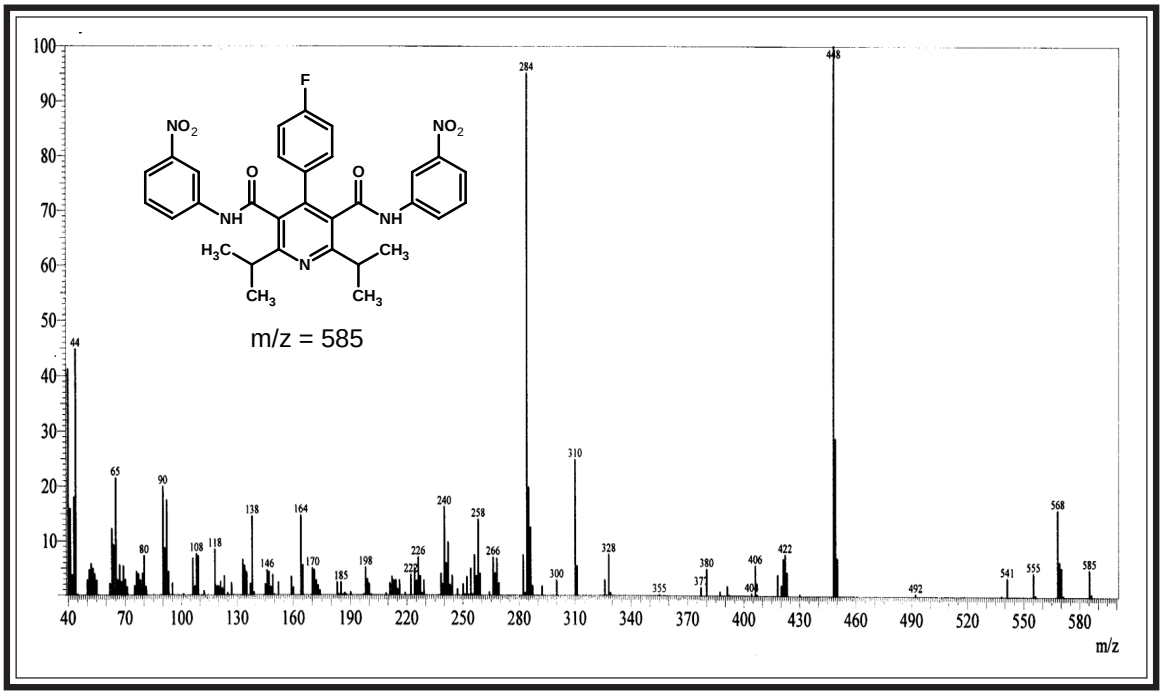
Internal Standard : TMS; Solvent : DMSO: Instrument : BRUKER Spectrometer (400 MHz)

Signal No.	SignalPosition (δppm)	Relative No of protons	Multiplicity	Inference	J Value In Hz
1	1.18-1.30	12H	doublet	-CH(CH_3)$_2$ (a-a',b-b')	7
2	3.64-3.71	2H	multiplate	-CH(c-c')	-
3	4.96	1H	singlet	Ar-H(e)	-
4	6.24	1H	singlet	-NH(d)	-
5	6.91-6.96	2H	triplet	Ar-H(n-k)	11
6	7.20-7.24	2H	doublet	Ar-H(l-m)	8.5
7	7.45-7.49	2H	triplet	Ar-H(h-h')	-
8	7.85-7.88	2H	doublet	Ar-H(g-g')	8.1 ,1.68
9	7.91-7.93	2H	doublet	Ar-H(i-i')	8.24,1.08
10	8.62-8.63	2H	triplet	Ar-H(j-j')	-
11	9.70	2H	singlet	-NH CO(f-f')	-

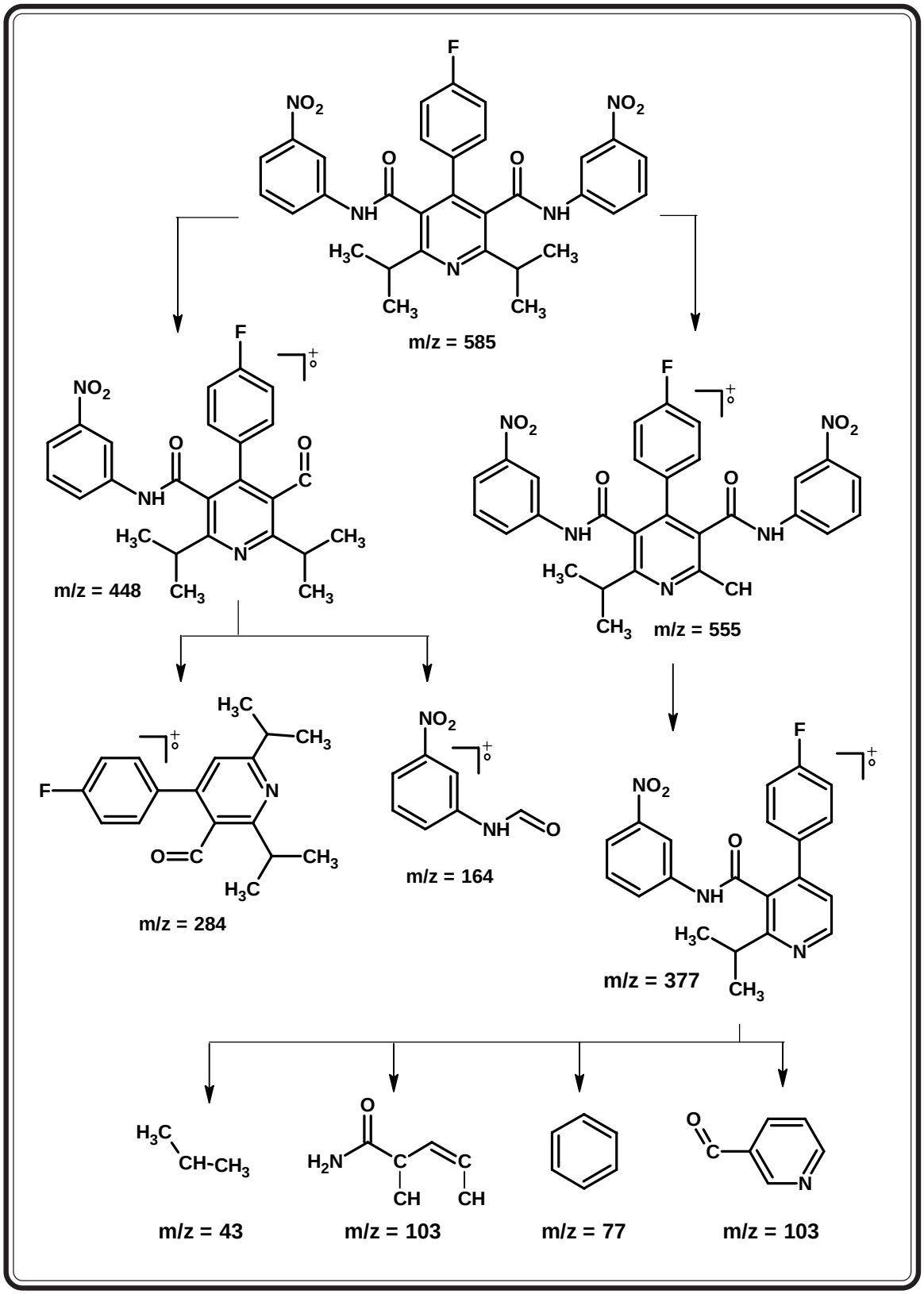
EXPANDED AROMATIC REGION



MASS SPECTRAL STUDIES OF 4-(4-FLUOROPHENYL)-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITROPHENYL)AMINOCARBONYL]-1,4-DIHYDRO PYRIDINE



MASS FRAGMENTATION



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITROPHENYL)AMINOCARBONYL]-1,4-DIHYDRO PYRIDINES

[A] Synthesis of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide :

See(B), part-I, section-I (A), page no.164.

[B] Synthesis of 4-(4-Fluorophenyl)-2,6-diisopropyl-3,5-bis[*N*-(3-nitrophenyl) aminocarbonyl]-1,4-dihydropyridine :

A mixture of 4-Methyl-*N*-(3-nitrophenyl)-3-oxopentanamide 2.50 gm (0.01 mol) and 4-Fluoro benzaldehyde 1.24gm (0.01mol) in ammonical methanol was refluxed for 8hrs. Cooled it at room temprature and kept over night. The resulting solid mass separated out was filtered and washed with methanol. Recrystallized the product from DMF and methanol. Yield 72%, m.p.dec.205^{o}C, Elemental analysis calculated for $C_{31}H_{28}FN_5O_6$ Requires : C-63.58%, H-4.82%, N-11.96%, Found : C-63.56, H-4.88, N-11.99%.

Similarly, other 4-Aryl-2,6-diisopropyl-3,5-bis[*N*-(3-nitrophenyl)amino carbonyl]-1,4-dihydropyridines. The physical data are recorded in table no.12.

[C] Biological screening of 4-Aryl-2,6-diisopropyl-3,5-bis[*N*-(3-nitrophenyl) aminocarbonyl]-1,4-dihydropyridines :

Antimicrobial testing was carried out as described in (A), part-I, section-I(E), page no.47. The zones of inhibition of test solutions are recorded in graphical chart no.12.

Conclusion :

Antibacterial activity

The screening data indicated that among dihydropyridine derivatives tested compounds **12b**, **12e, 12f**, **12l** showed greater degree of antibacterial activity against *S.aureus*. However, the compounds **12l** showed greater degree of antibacterial activity against *B.subtilis*. The compounds **12e**, **12g**, **12h** and **12b** showed greater degree of antibacterial activity against *E.coli* and *P. aeruginosa* respectively.

Antifungal activity

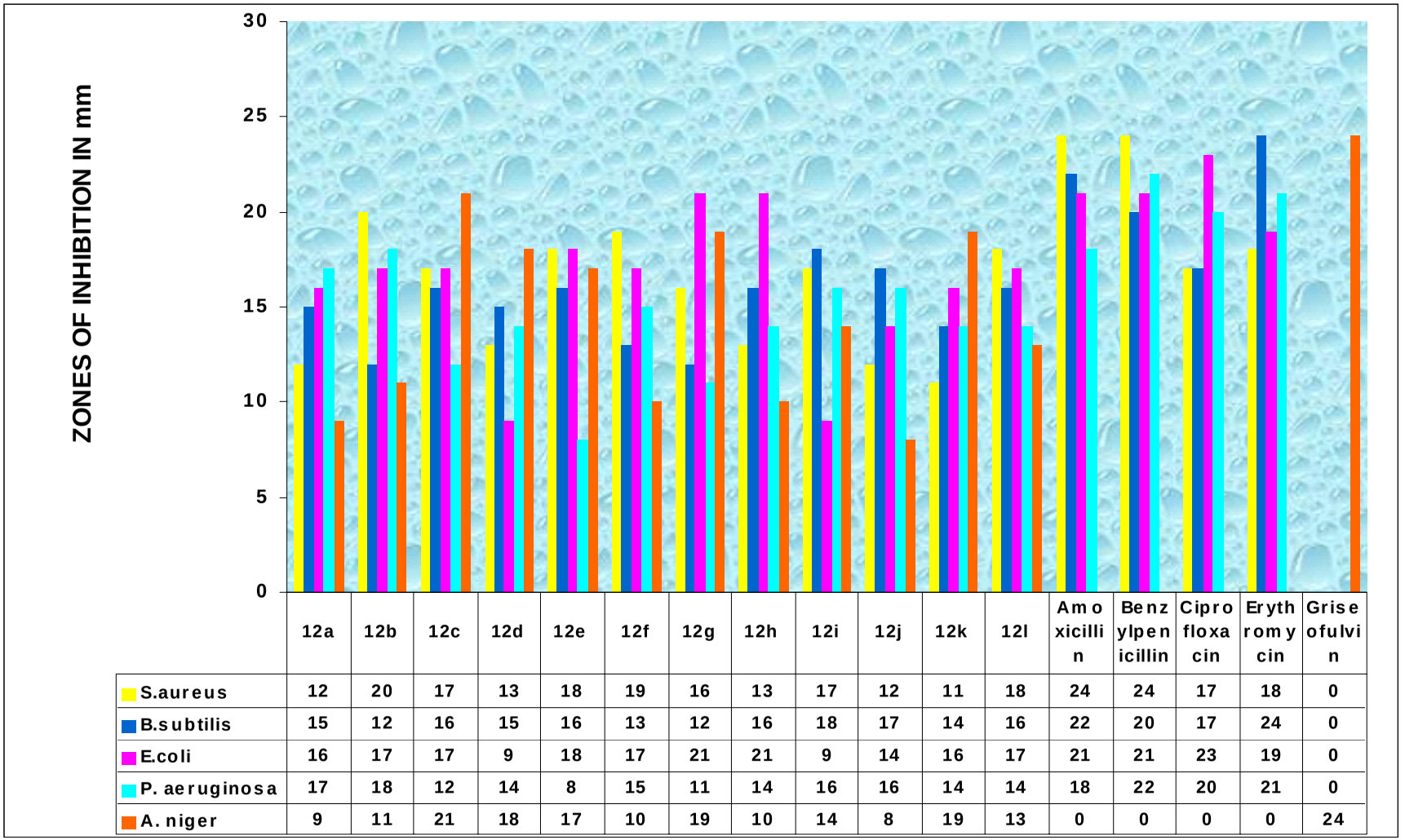
The screening data indicated that among dihydropyridine derivatives tested compounds **12c, 12d, 12g, 12k** showed greater degree of antifungal activity against *A.niger.*

TABLE-12 : PHYSICAL CONSTANTS OF 4-ARYL-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITROPHENYL)AMINOCARBONYL]-1,4-DIHYDROPYRIDINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	R_f Value	Solvent System
1	2	3	4	5	6	7	8	9	10
12a	C_6H_5-	$C_{31}H_{29}N_5O_6$	567	200	46	12.34	12.40	0.51	S_1
12b	4-OCH_3-C_6H_4-	$C_{32}H_{31}N_5O_7$	597	dec.240	56	11.75	11.70	0.52	S_2
12c	3,4- $(OCH_3)_2$-C_6H_3-	$C_{33}H_{33}N_5O_8$	627	146	44	11.16	11.14	0.43	S_2
12d	4-OH-C_6H_4-	$C_{31}H_{29}N_5O_7$	583	176	60	12.00	11.98	0.47	S_2
12e	4-(OH)-3-(OCH_3)-C_6H_3-	$C_{32}H_{31}N_5O_8$	613	186	50	11.41	11.39	0.53	S_2
12f	4-F-C_6H_4-	$C_{31}H_{28}FN_4O_5$	585	dec.205	72	11.96	11.90	0.55	S_1
12g	2-Cl-C_6H_4-	$C_{31}H_{28}ClN_5O_6$	601.5	105	70	11.63	11.64	0.57	S_1
12h	4-Cl-C_6H_4-	$C_{31}H_{28}ClN_5O_6$	601.5	195	75	11.63	11.61	0.42	S_1
12i	3,4-$(Cl)_2$-C_6H_3-	$C_{31}H_{27}Cl_2N_5O_6$	636	125	67	11.00	11.04	0.47	S_2
12j	5-Br-Vanilline	$C_{32}H_{30}BrN_5O_8$	692	112	46	10.11	10.08	0.48	S_1
12k	2-NO_2-C_6H_4-	$C_{31}H_{28}N_6O_8$	612	165	41	13.72	13.80	0.41	S_2
12l	3-NO_2-C_6H_4-	$C_{31}H_{28}N_6O_8$	612	188	49	13.72	13.68	0.47	S_1

S_1 Toluene : Ethyl acetate (5 : 5), S_2 Toluene : Ethyl acetate (4 : 6)

Graphical Chart No. 12 : ANTIMICROBIAL ACTIVITY OF 4-ARYL-2,6-DIISOPROPYL-3,5-BIS[*N*-(3-NITRO PHENYL) AMINOCARBONYL]-1,4-DIHYDROPYRIDINES



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Amoxicillin	Benzylpenicillin	Ciprofloxacin	Erythromycin	Griseofulvin
S.aureus	12	20	17	13	18	19	16	13	17	12	11	18	24	24	17	18	0
B.subtilis	15	12	16	15	16	13	12	16	18	17	14	16	22	20	17	24	0
E.coli	16	17	17	9	18	17	21	21	9	14	16	17	21	21	23	19	0
P. aeruginosa	17	18	12	14	8	15	11	14	16	16	14	14	18	22	20	21	0
A. niger	9	11	21	18	17	10	19	10	14	8	19	13	0	0	0	0	24

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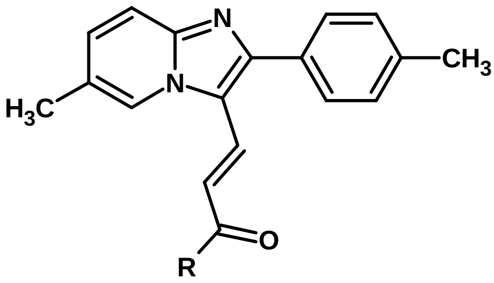
LIST OF NEW COMPOUNDS



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4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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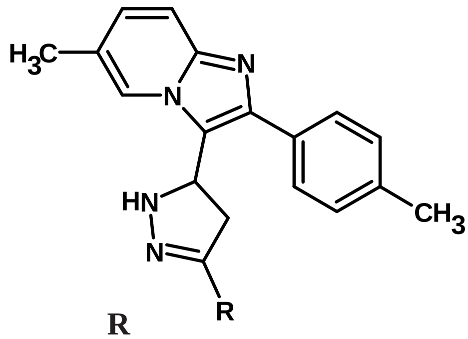
4-OH-C_6H_4-
4-NH_2-C_6H_4-
2-C_4H_3S-



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4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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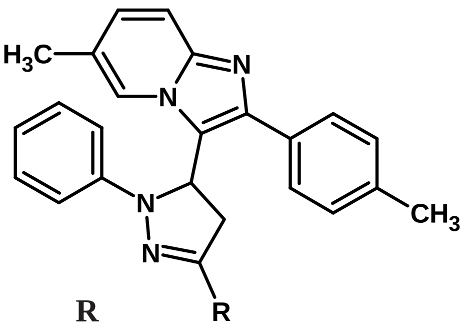
4-OH-C_6H_4-
4-NH_2-C_6H_4-
2-C_4H_3S-



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4-OCH_3-C_6H_4-
4-CH_3-C_6H_4-
4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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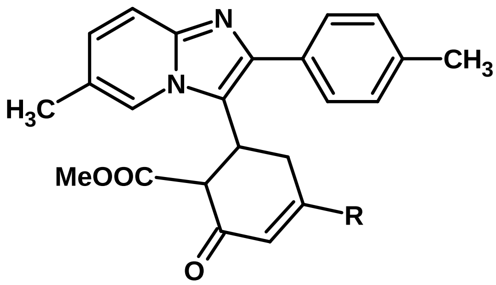

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4-CH_3-C_6H_4-
4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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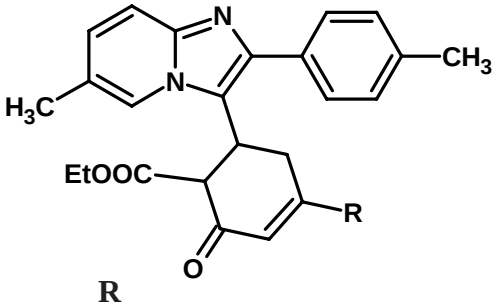

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4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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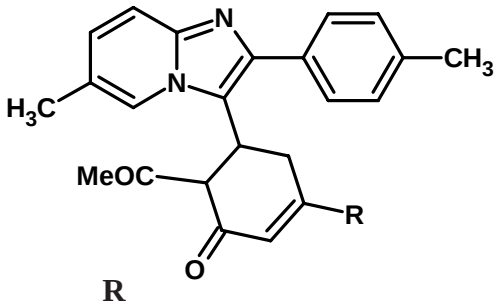
2-C_4H_3S-



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4-CH_3-C_6H_4-
4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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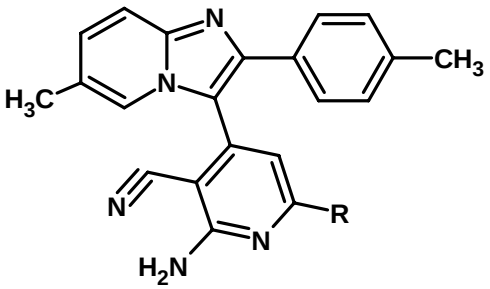
4-NH_2-C_6H_4-
2-C_4H_3S-



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4-CH_3-C_6H_4-
4-OH-3-OCH_3-C_6H_3-
4-Br-C_6H_4-
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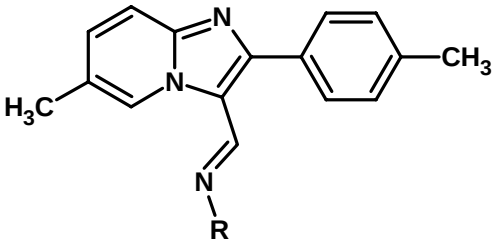

R

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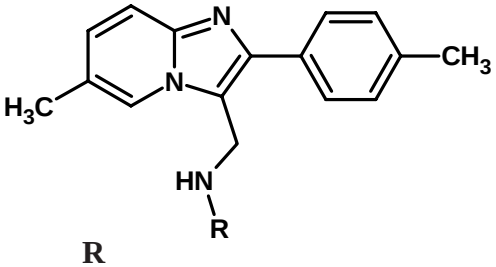
3-Cl-C_6H_4-
2,5-$(Cl)_2$-C_6H_3-
3,4 -$(Cl)_2$-C_6H_3-
4-F-C_6H_4-
3-NO_2-C_6H_4-
4-NO_2-C_6H_4-
1-$C_{10}H_7$-
3-CH_3-C_6H_4-



R

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2,5-$(Cl)_2$-C_6H_3-
3,4 -$(Cl)_2$-C_6H_3-
4-F-C_6H_4-
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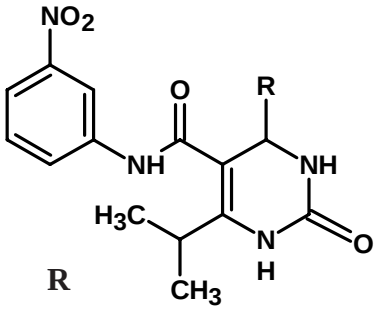

R

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2,4,6-$(OCH_3)_3$-C_6H_2-
4-(OH)-3-(OCH_3)-C_6H_3-
4-OH-C_6H_4-
2-OH-C_6H_4-
4-F-C_6H_4-
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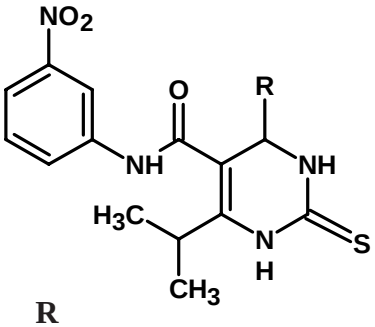

R

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4-(OH)-3-(OCH_3)-C_6H_3-
4-OH-C_6H_4-
2-OH-C_6H_4
4-F-C_6H_4--
4-Cl-C_6H_4-
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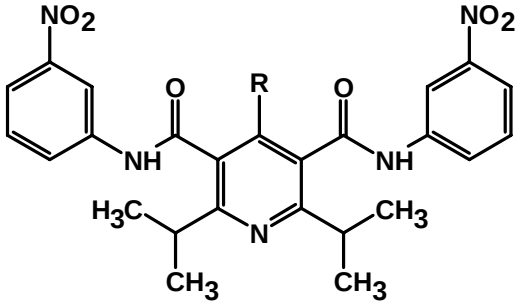
3-Br-C_6H_4-
3-NO_2-C_6H_4-



R

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4-(OH)-3-(OCH_3)-C_6H_3-
4-F-C_6H_4-
2-Cl-C_6H_4-
4-Cl-C_6H_4-
3,4-$(Cl)_2$-C_6H_3-
5-Br-Vanilline
2-NO_2-C_6H_4-
3-NO_2-C_6H_4-

Poster Presented in National / International Conferences

Oral presentation title is “Synthesis and antimicrobial screening of some novel dihydropyrimidinones” at national level conference on “**Frontiers of Research in Chemical Sciences**” by Department of Chemistry Govt Madhav Science College, Ujjain. 18-19th February 2007.