STUDIES ON HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST

A THESIS

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SAURASHTRA UNIVERSITY

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IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE

OF

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

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

Dt. : .08.2006 ***(Mahesh J. Ladani)***
Place : Rajkot.

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

Date : -08-2006
Place : Rajkot.

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DEDICATED
TO MY
BELOVED FAMILY

ACKNOWLEDGEMENTS

" Shree Ganeshay Namah "

Hats off to the Omnipresent, Omniscient and Almighty God, the glorious fountain and continuous source of inspirations! I offer salutations to him and my head bows with rapturous dedication from within my heart, to the Omnipotent Lord "Shree Krishna".

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Who in this world can entirely and adequately thank the parents who have given us everything that we possess in this life? The life it self is

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As with the completion of this task, I find myself in difficult position on attempting to express my deep indebtedness to Mayur Joshi .

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Mahesh J. Ladani

SYNOPSIS

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

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

[B] STUDIES ON DIHYDROPYRIMIDINES

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

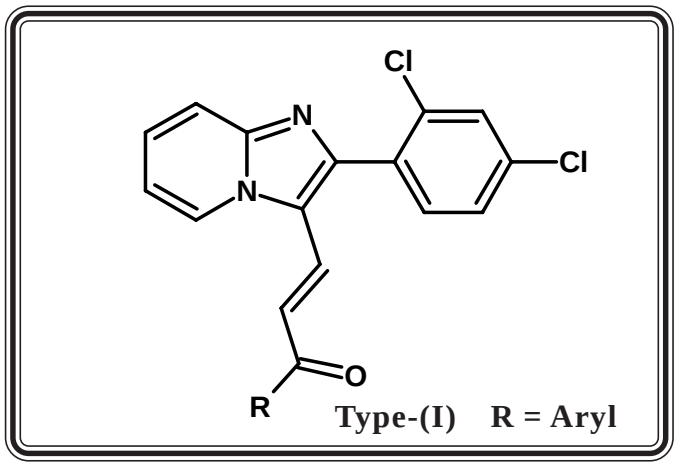
Heterocyclic compounds bearing imidazo[1,2-a]pyridine ring system are endowed with variety of biological activities. Our strategy is based on to develop a new bioactive entities especially with pharmacological activities bearing heterocyclic ring system. Literature survey reveals that nitrogen containing 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 depressant, antithyroid and many other therapeutic activities.

These valid observations prompted us to design and synthesize some heterocycles like chalcones, pyrazolines, cyanopyridines,mannich bases, pyrimidines, isoxazoles, imidazolinones etc., bearing imidazo[1,2-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, fungicidal, antiviral and other pharmacological properties like anticonvulsant,antidepressant and anti-inflammatory. These valid observations led us to synthesize some new pyrazoline derivatives for better drug potential which have been described in following sections.

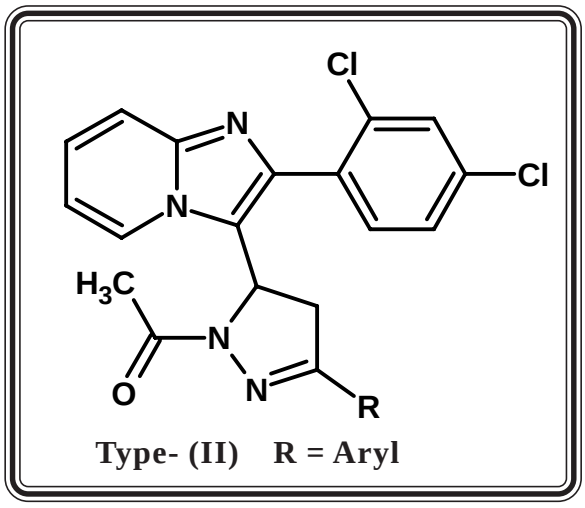
SECTION-I : Synthesis and biological screening of (2E)-3-[2-(2,4-dichloro phenyl)imidazo[1,2-a]pyridin-3-yl]-1-arylprop-2-en-1-ones



Type-(I) R = Aryl

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

SECTION-II : Synthesis and biological screening of 3-(1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenyl)imidazo[1,2-a] pyridines



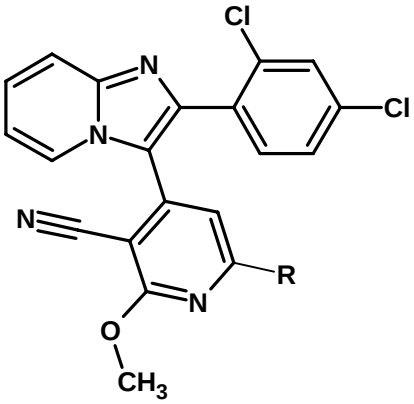
Type- (II) R = Aryl

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

PART-II : STUDIES ON CYNOPYRIDINES

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 antifungal, antidiabetic, anticholestemic and antihypertensive. On the basis of these results, we have synthesized some new dervatives which have been described as under.

SECTION-I : Synthesis and biological screening of 4-[2-(2,4-dichlorophenyl) imidazo[1,2-*a*]pyridin-3-yl]-2-methoxy-6-arylnicotinonitriles



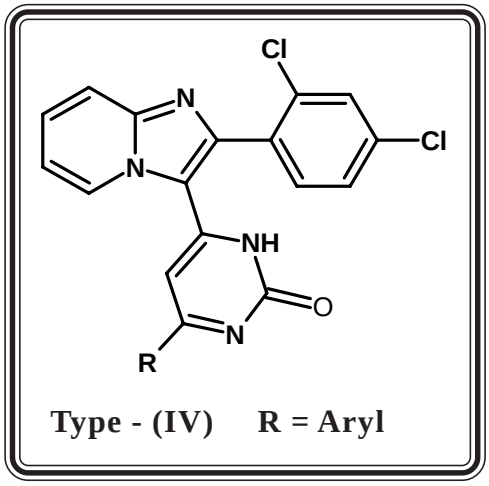
Type-(III) R = Aryl

Cyanopyridines of Type (III) have been synthesized by the condensation of the chalcones of Type (I) with malononitrile and sodium methoxide.

PART-III : STUDIES ON PYRIMIDINES

Pyrimidine nucleus possess remarkable pharmaceutical importance and biological activities, some of their derivatives occur as natural products, like nucleic acids and vitamin B. Many pyrimidine derivatives have displayed diverse pharmacological activities like antitumor etc. In view of our on going interest in the synthesis of substituted pyrimidines, the synthesis of some new potentially bioactive pyrimidine derivatives have been undertaken which have been described as under.

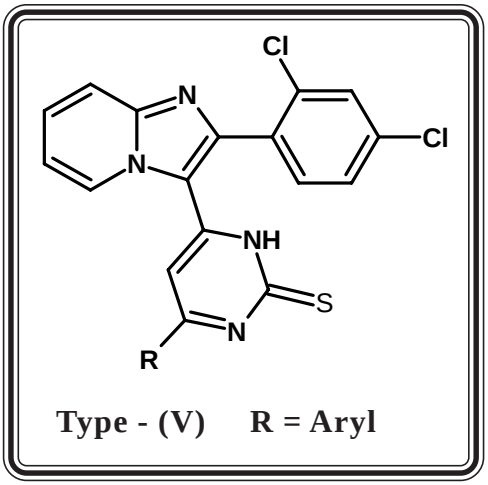
SECTION-I : Synthesis and biological screening of 6-[2-(2,4-dichlorophenyl) imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-ones



Type - (IV) R = Aryl

Pyrimidine derivatives of Type (IV) have been prepared by the cyclization of chalcones of Type (I) with urea in presence of basic catalyst like KOH.

SECTION-II : Synthesis and biological screening of 6-[2-(2,4-dichlorophenyl) imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-thiones



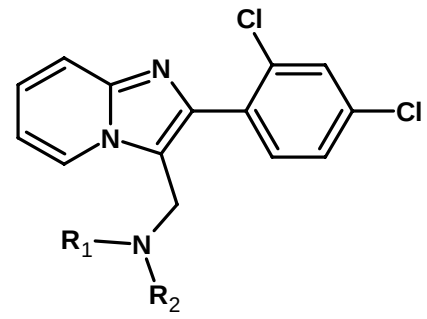
Type - (V) R = Aryl

Pyrimidinethione derivatives of Type (V) have been prepared by the cyclocondensation of chalcones of Type (I) with thiourea in presence of basic catalyst like KOH.

PART-IV : STUDIES ON MANNICH BASES

Mannich base containing bridge N-atom exhibit diverse pharmacological activities like antibacterial, antimalarial, antineoplastic, analgesic and anticonvulsant. Mannich bases are also found as intermedate in organic synthesis and good chelating agents. Hence it is pertinent to synthesize some new mannich bases, which have been described as under.

SECTION-I :Synthesis and biological screening of *N*-{[2-(2,4-dichlorophenyl) imidazo[1,2-*a*]pyridin-3-yl]methyl}-*N*,*N*-diaryl/alkyl amines



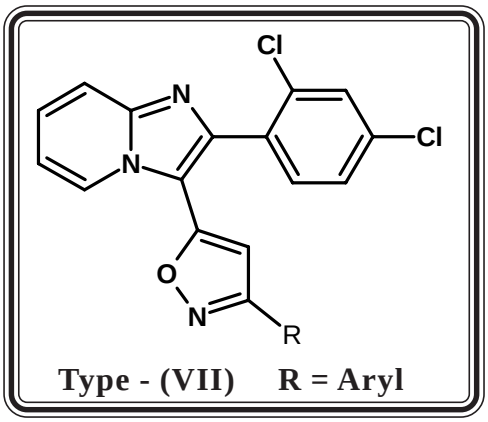
Type - (VI) R_1, R_2 = Aryl

Mannich bases of Type (VI) have been synthesized by the condensation of 2-(2,4-dichlorophenyl)imidazo[1,2-a]pyridine with different secondary amines and formaldehyde in the presence of acidic catalyst like HCl.

PART-V : STUDIES ON ISOXAZOLES

Isoxazole derivatives represent one of the modest class of compound possessing broad range of biological activities such as antidepressants, skeleton muscle relaxant, antidiabetic,anti-inflammatory, analgesic etc. In order to developing medicinally important compounds we have synthesized some isoxazole derivatives shown as under.

SECTION-I :Synthesis and biological screening of 2-(2,4-dichlorophenyl)-3-(3-arylisoxazol-5-yl)imidazo[1,2-*a*]pyridines



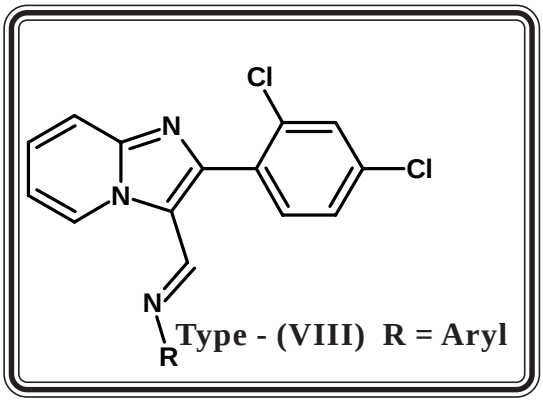
Type - (VII) R = Aryl

Isoxazole derivatives of Type (VII) have been prepared by the reaction of chalcones of Type (I) with hydroxylamine hydrochloride in the presence of sodium acetate in acetic acid.

PART-VI : STUDIES ON ARYLAMINOMETHYL DERIVATIVES

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

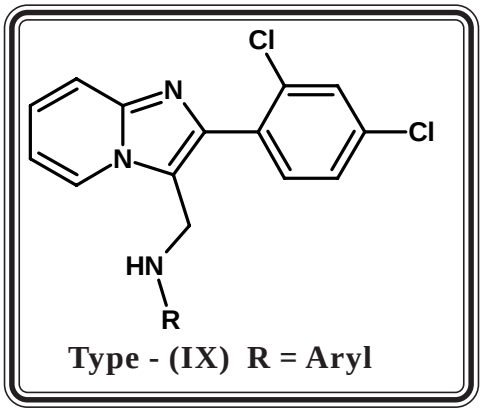
SECTION-I :Synthesis and biological screening of *N*-{(1*E*)-[2-(2,4-dichloro phenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-*N*-arylamines



Type - (VIII) R = Aryl

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

SECTION-II :Synthesis and biological screening of *N*-{[2-(2,4-dichloro phenyl)imidazo[1,2-a]pyridin-3-yl]methyl}-*N*-arylamines



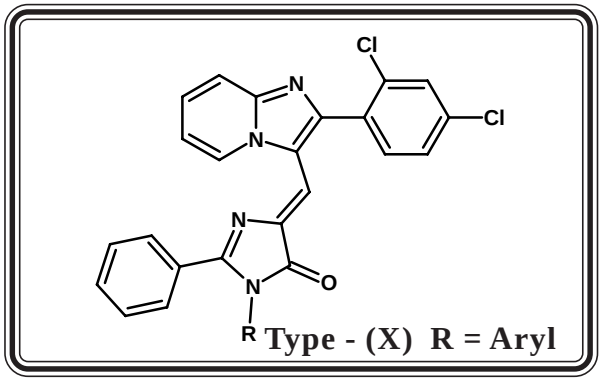
Type - (IX) R = Aryl

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

PART-VII : STUDIES ON IMIDAZOLINONES

The group of compounds containing the imidazolinone ring system have a prominent feature in medicinal chemistry. 5-Oxoimidazoline derivatives have been reported to be active as anticonvulsant, potent CNS depressant, anticancer, sedative, hypnotics and as mono amino oxidase (MAO) inhibitor. In view of the above finding some new imidazolinone derivatives bearing imidazo[1,2-a]pyridine nucleus, which have been described as under.

SECTION-I : Synthesis and biological screening of (5*Z*)-5-{[2-(2,4-dichloro phenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-3-aryl-2-phenyl-3,5-dihydro-4*H*-imidazol-4-ones



Type - (X) R = Aryl

The imidazolinone derivatives of Type (X) have been synthesized by the reaction of azalactone with different arylamine in pyridine.

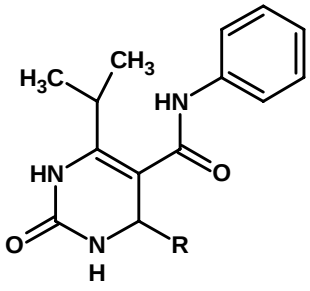
[B] STUDIES ON DIHYDROPYRIMIDINES

The synthesis of dihydropyrimidine derivatives is important drug potential because of their pharmacological activities such as antiviral, antitumor, antibacterial and anti-inflammatory. Many of them are biologically important since they behave as calcium channel blockers, antihypertensive agents. This observation led us to synthesise of some newer dihydropyrimidinones and dihydropyrimidinethiones derivatives shown as under.

PART-I : STUDIES ON DIHYDROPYRIMIDINONES

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

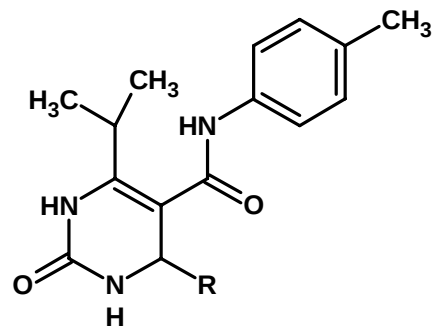
SECTION-I : Synthesis and biological screening of 6-isopropyl-4-aryl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides



Type - (XI) R = Aryl

Dihydropyrimidinones of Type (XI) have been synthesized by the condensation of 4-methyl-3-oxo-N-phenylpentanamide, urea and aryl aldehydes.

SECTION-II : Synthesis and biological screening of 6-isopropyl-4-aryl-*N*-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides



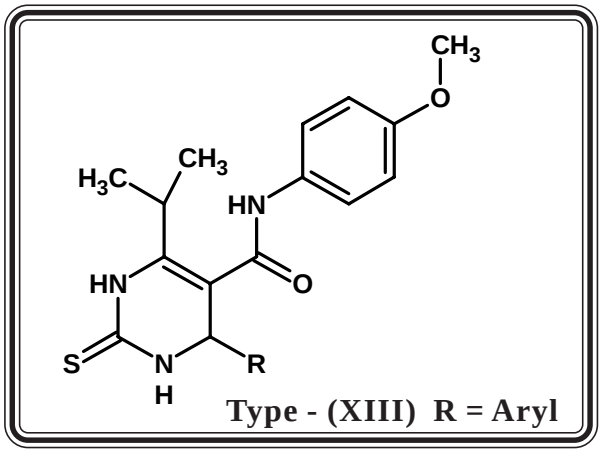
Type - (XII) R = Aryl

Dihydropyrimidinones of Type (XII) have been synthesized by the cyclocondensation of 4-methyl--N-(4-methylphenyl)-3-oxo-pentanamide, urea and aryl aldehydes.

PART-II : STUDIES ON DIHYDROPYRIMIDINTHIONES

Dihydropyrimidinthione and its derivatives represents one of the most active class of compounds possessing a broad spectrum of pharmacologically activities like anti-inflammatory, antibacterial, calcium channel blockers, antihypertensive agent and anticancer. In view of these facts, we have undertaken the synthesis of compounds as shown as under.

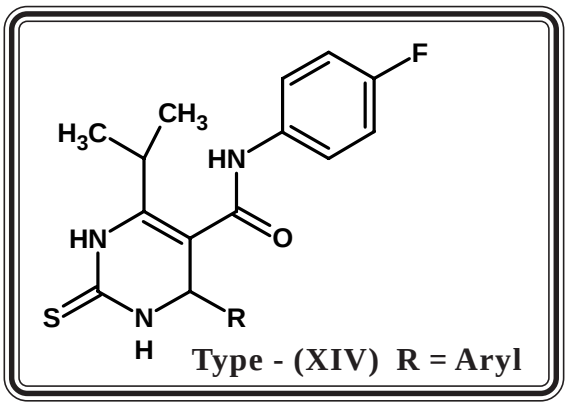
SECTION-I : Synthesis and biological screening of 6-isopropyl-*N*-(4-methoxy phenyl)-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides



Type - (XIII) R = Aryl

Dihydropyrimidinthiones of Type (XIII) have been synthesized by the cyclization of 4-methyl--N-(4-methoxyphenyl)-3-oxo-pentanamide with thiourea and aryl aldehydes.

SECTION-I : Synthesis and biological screening of *N*-(4-fluorophenyl)-6-isopropyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides



Type - (XIV) R = Aryl

Dihydropyrimidinthiones of Type (XIV) have been prepared by the condensation of 4-methyl--N-(4-fluorophenyl)-3-oxo-pentanamide, thiourea and aryl aldehydes.

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

In vitro studies on multiple biological activities.

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

(II) All the compounds have been also evaluated for their antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards **Aspergillus niger** at a concentration of 40 mg/ml. The biological activity of the synthesized compounds have been compared with standard drugs.

INTRODUCTION

STUDIES ON HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST

INTRODUCTION

With the advancement in science and technology, remarkable progress has been made in the field of medicine including diagnosis, treatments and pharmaceutics. Recent drug discovery techniques based on Structure Activity Relationships, High Throughput Screening and Spectroscopy have triggered and spearheaded the discoveries of many natural and synthetic drugs.

Despite these developments, of the known 30,000 Human diseases or disorders, only one third can be treated symptomatically with drugs (either in part or fully) and that to a great economic and social cost. This is because of the fact that the drug available today are still not very effeetive perticularly with respect to the fight against drug resistant pathogens and newly emerging infections. This include infectious diseases such as AIDS, influenza, tuberculosis and malaria as well as other chronic disorders like cancer, central nervous system disabilities (e. g. Alzheimer's disease). These infectious diseases (microbial) will continue to be the leading causes of permature death in human beings of both developed and developing nations as their resistance to many conventional drugs is increasing. Therefore, microbial resistance especially by bacteria and protozoa to drugs is of special concern to communities worldwide and to researchers.

The discovery of bacteria in 1683 by van Leuwenhoek helped mankind to understand the infectious pathogens and appropriately develop antiseptic and antibiotic protocol in the following years. By the beginnning of 20th century, Paul Ehrlich proposed the principle of chemotherapy and his work including Structure Activity Relationships significantly contributed to shaping synthetic protocols and helped in the later discoveries of antibacterial drugs. Antibiotics were designed either to kill bacteria (bactericidal) or to nullify growth (bacteriostatic) and three groups of antibacterial agents, which included bacterial cell wall inhibitors, protein synthesis inhibitors and DNA inhibitors, were developed to fight the bacterial infections. The sulphonamides were the

first group of effective antibacterials to be developed following a chance discovery in 1932 by Domagk of antibacterial activity in the synthetic azo dye, **prontosil**.

In 1928, Alexander Fleming observed that colonies of *Staphylococcus* bacteria were dissolved by penicillium mould. This discovery was then further developed by Florey and Chain when in 1939 they demonstrated that the active component from the mould, penicillin, could cure a human bacterial infection. This key finding lead to the industrialisation of the production of **penicillin** as an antibiotic in 1943. Four years later the first penicillin resistant bacteria were observed.

Many antibacterial drugs were developed in the late 1940s following the first report of resistance in *Staphylococcus aureus* (1941) and in *Mycobacterium tuberculosis* (1940s), a mycobacterium which also developed resistance later to the drugs **isoniazid** and **rifamycin** in the 1950s and 1960s. However, by the 1980s most major infectious diseases in the developed world were almost eradicated and half the major pharmaceutical companies in Japan and the USA stopped their antibacterial drug development programs. As a result drug resistant pathogens were on the rise worldwide. *Streptococci* that causes nosocomial infections showed innate resistance to drugs including **cephalosporins**, **clindamycin** and **aminoglycoside**. The bacterium (*Staphylococcus aureus*) has now developed multi drug resistant strains and threatens to put an end to successful chemotherapy.

Bioactive natural products are mainly secondary metabolites which are used by the host as defensive and protective mechanisms against their enemies and predators. Generally, screening of these secondary metabolites and development of drugs is a very hard task requiring much effort starting from botanical identification, collection, extraction, isolation, purification and compound identification to pharmacological and clinical testing. However, the enormous chemical diversity and highly unusual structures provided by natural products is greater than that provided by most available combinatorial approaches based on heterocyclic compounds.

Today the chief source of agents for the cure, the mitigation or prevention of disease are organic, natural or synthetic, together with so called organometallics. Such agents have their origin in a number of ways (a) From naturally occuring materials of both plant and animal origin and (b) From the isolation of organic compounds synthesized in laboratory whose structures are closely related to those of naturally occuring compounds for e.g. atropine, steroids, morphine, cocaine etc.

Heterocyclic compounds are used as pharmaceuticals, as agrochemicals and as vaterinary products. They are used as optical brightening agnets, as antioxidants, as corrosion inhibitors, and as additives with a variety of other functions. Heterocyclic comopounds are also finding an increasing use as intermediates in organic synthesis.

AIMS AND OBJECTIVES:

In the pharmaceutical field, these had always been and will continue to be need for new and novel chemical inhibitors of biological function. Our efforts are focused on biological function of chemical diversity in the molecular frame work in order to synthesising pharmacologically interesting compounds of widely different composition.

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

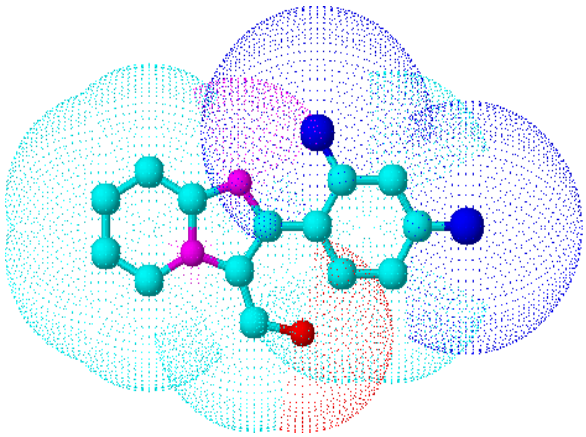
(I) To generate several derivatives like chalcones, pyrazolines, cyanopyridines, pyrimidines, isoxazoles, mannich bases, arylaminomethyl derivatives, imidazolinones bearing imidazo[1,2-a]pyridine moiety.

(II) To generate several derivatives like dihydropyrimidinones and dihydropyrimidinthiones.

(III) To characterize these products for structure elucidation using spectroscopic technique like IR, ^{1}H NMR and Mass spectral studies.

(IV) Purity of all compounds have been checked by thin layer chromatography.

(V) To evaluate these new product for better drug potential against different strain of bacteria, fungi and for antitubercular activity.



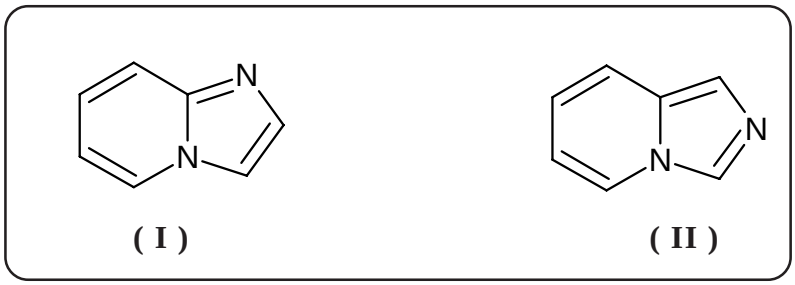
[A]

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 to possess diverse therapeutic activities[1]. Hence they are interesting target to be prepared to our research on medicinally interesting heterocyclic entities. Aza-indolizine are of two types, imidazo[1,2-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]. Several procedure for their synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of bridgehead nitrogen containing fused heterocyclic entities.

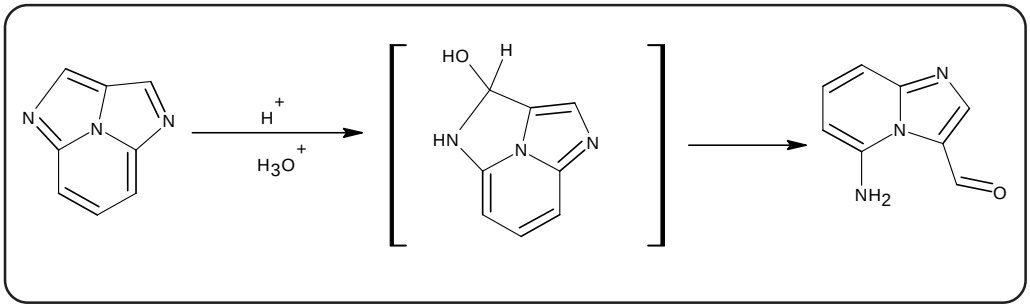
The constitution of imidazo[1,2-a]pyridine was represented by W. L. Mosby[3]. Imidazo[1,2-a]pyridine derivatives not only known for their medicinal applications, but they are also used in disperse dye[4].

SYNTHETIC ASPECT

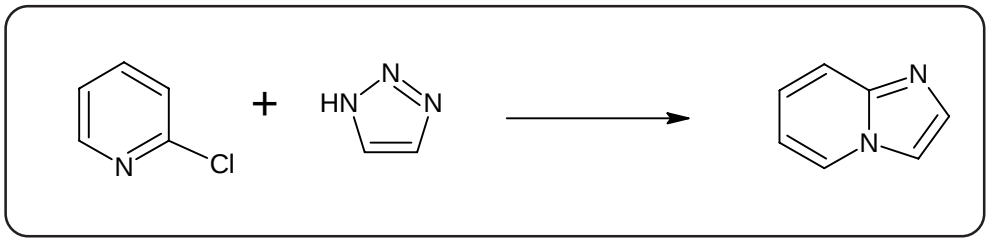
Several methods have been reported in the literature for the synthesis of imidazo[1,2-a]pyridines. The procedure for synthesizing imidazo[1,2-a]pyridines have been described as under.

1. The Tschitschibabine[5] has synthesize imidazo[1,2-a]pyridine from 2-aminopyridine with ω-bromoacetophenone.

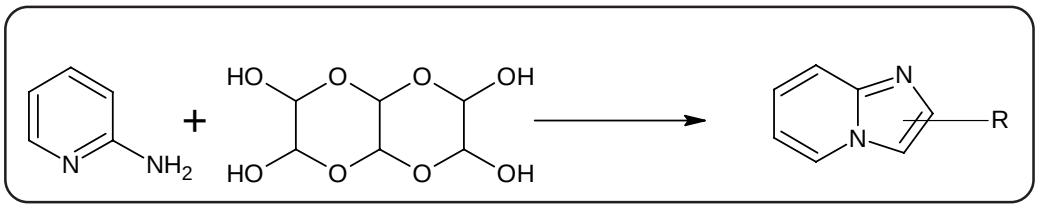
2. Paudler et al.[6] have synthesized 5-amino-3-formyl imidazo[1,2-a]pyridine from acid catalyzed hydrolysis of 1,4-diazacycl[3,2,2]azine.



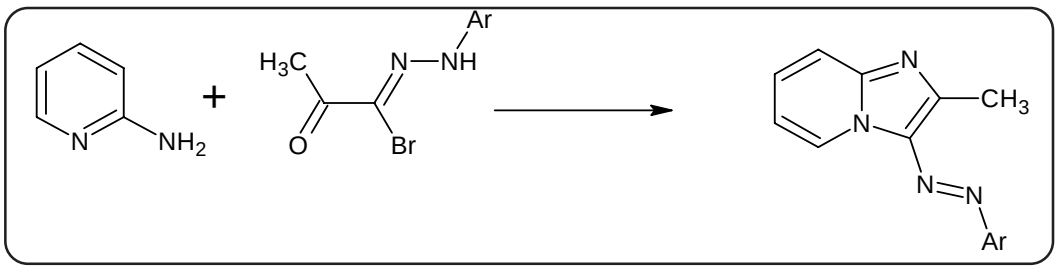
3. Reaction of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogens give imidazo[1,2-a]pyridine[7]



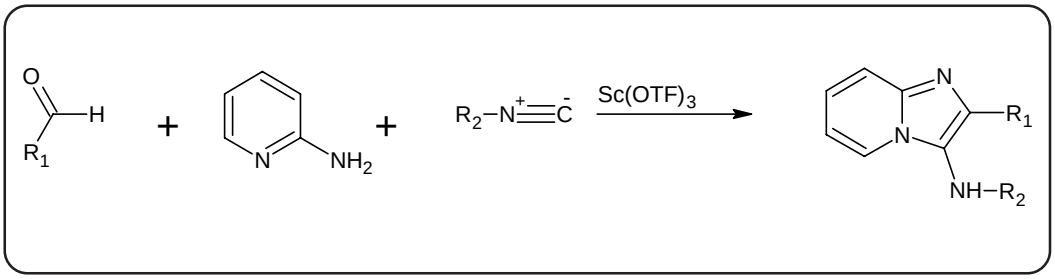
4. Groziak et al.[8] have synthesized imidazo[1,2-a]pyridine by the condensation of 2-aminopyridine with glyoxal trimer dehydrate in aqueous $NaHSO_3$.



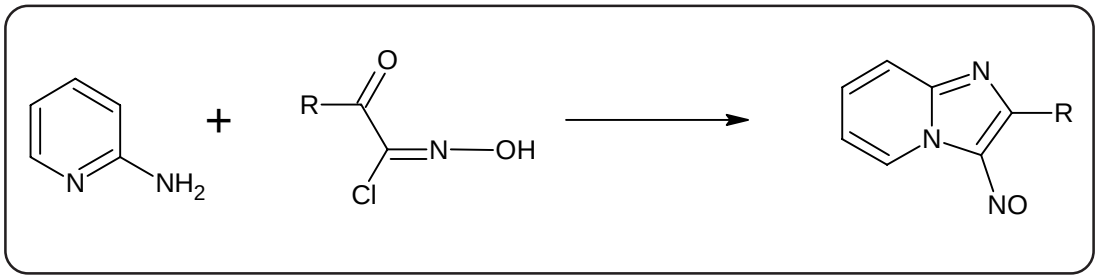
5. Imidazo[1,2-a]pyridine[9] nucleus can be also synthesized by the reaction of α-ketohydrazidoyl halide with heterocyclic amines.



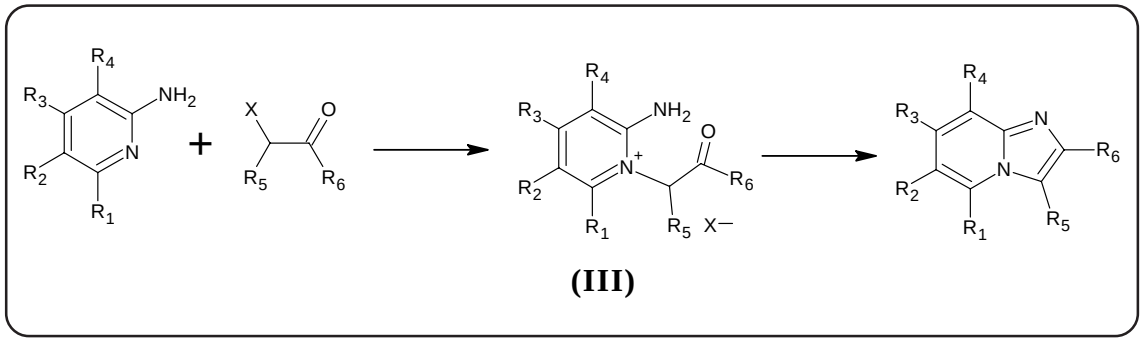
6. Tsai et al.[10] have been prepared 3-amino imidazo[1,2-a]pyridine derivatives by a three component condensation reaction between 2-aminopyridine, aldehyde and an isonitrile in the presence of scandium triflate as a catalyst.



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



MECHANISM



(III)

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

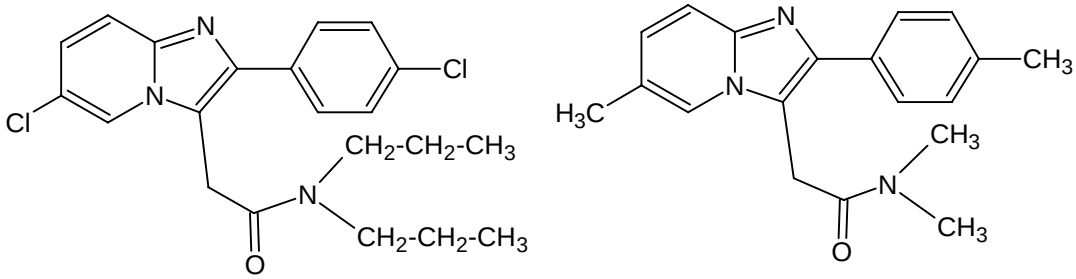
THERAPEUTIC IMPORTANT

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[12,13]
2. Long-acting local anesthetic[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. Antiinflammatory, 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]

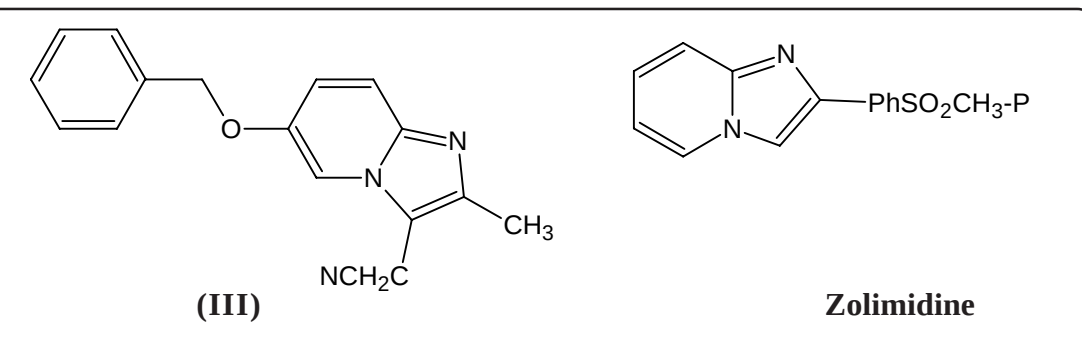
Several imidazo[1,2-a]pyridines already in market include **alpidem**[39] [a ligand of both the central benzodiazepine receptors and the peripheral type (Mitochondrial) benzodiazepine receptor] has sedative and anxiolytic properties and **zolpidem**[39] [a selective ligand for the central benzodiazepine receptor] is a hypnotic drug. Both

alpidem and **zolpidem** have higher affinity for benzodiazepine-1 than for benzodiazepine-2 receptors[40] and their interaction with various receptor types has been reported[41].



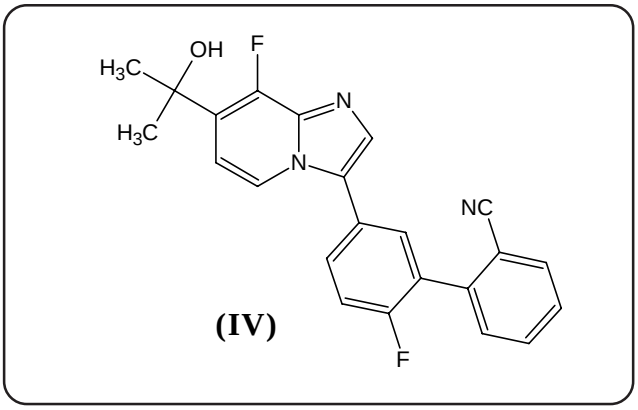
Alpidem **Zolpidem**

James J. Kaminski and co-workers[42] have investegated the imidazo[1,2-a]pyridine derivative 3-(cyanomethyl)-2-methyl-8-(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 8-phenylmethoxy group have been established as metabolic sites in.

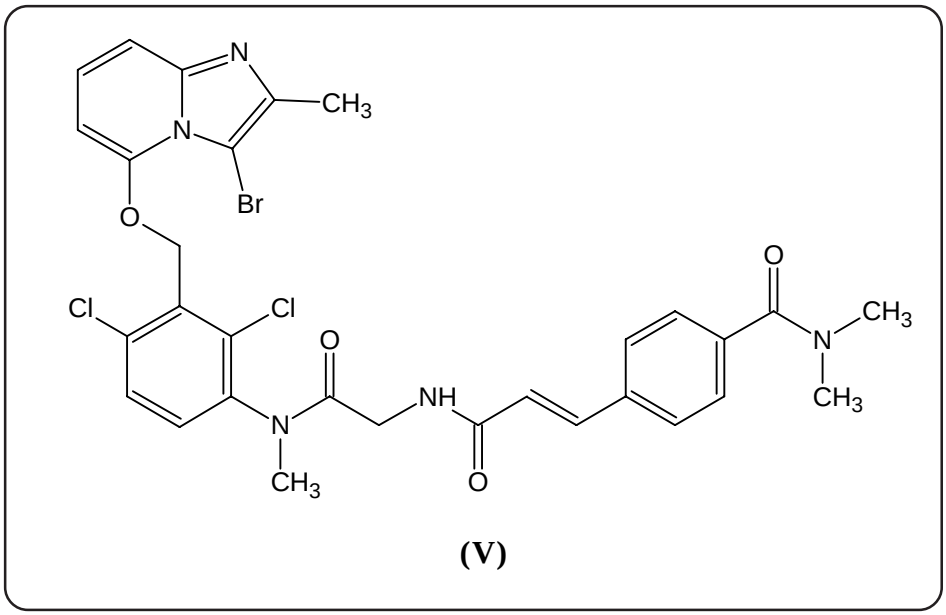


(III) **Zolimidine**

Alexander C. Humphries and co-workers[43] have synthesized 8-fluoro imidazo[1,2-a]pyridine derivatives (IV) and evaluated as a bioisosteric replacement for imidazo[1,2-a]pyridine in an allosteric modulator ligand of the $GABA_A$ 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).

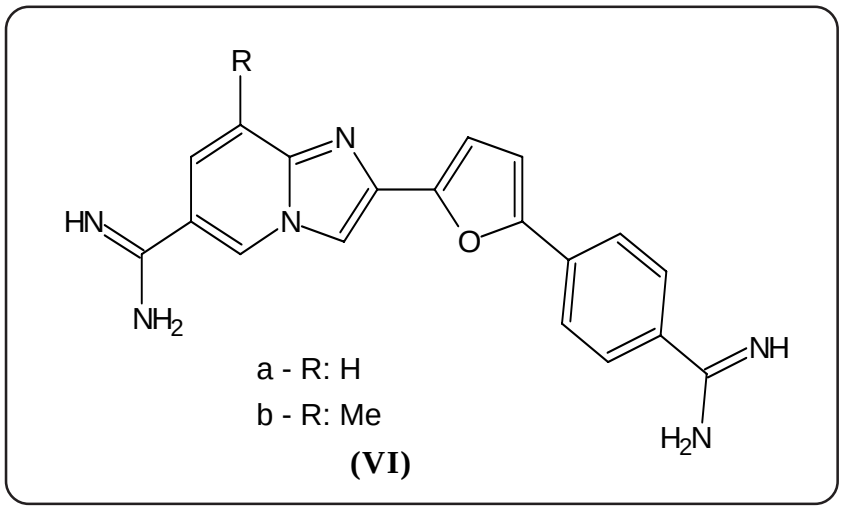


(IV)



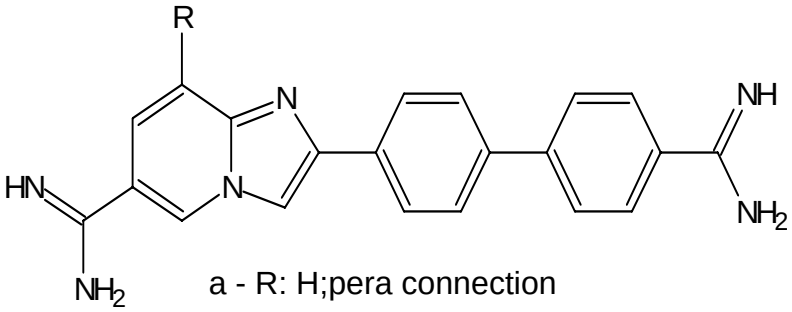
(V)

The imidazo[1,2-a]pyridine units appear as important building blocks in both natural and synthetic bioactive compounds.[46-48] Mohamed A. Ismail[49] have synthesized some novel diamidine imidazo[1,2-a]pyridine like (VI) and (VII) and 5,6,7,8-tetrahydo 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 (T. B. rhodesiense) and plasmodium falciparum (P. falciparum). Aromatic diamidines exhibit broad spectrum antimicrobial activity including effectiveness againts the protozoan disease caused by Trypanosoma SP and Plasmodium SP[50].



a - R: H
b - R: Me

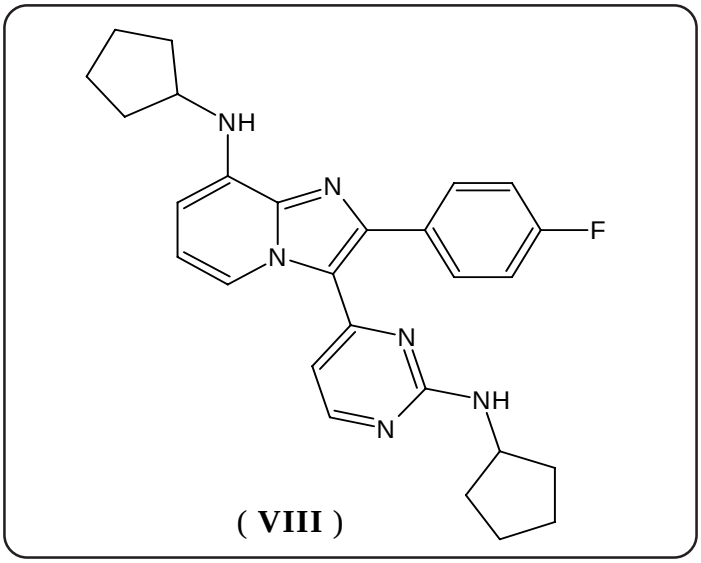
(VI)



a - R: H;pera connection
b - R: H;meta connection

(VI)

S. Kristjan, Gudmundsson, A. Brian Johns[51] and A. Chaouni Bendallay et al.[52] 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 synthesize some Chalcones, Acetyl pyrazolines, Cyano pyridines, Thiopyrimidines, Oxopyrimidines, Mannich bases, Isoxazoles, Schiff bases, Imidazolinone derivatives bearing imidazo[1,2-a]pyridine moiety in order to achive 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 CYANOPYRIDINES

PART-III : STUDIES ON PYRIMIDINES

PART-IV : STUDIES ON MANNICH BASES

PART-V : STUDIES ON ISOXAZOLES

PART-VI : STUDIES ON ARYLAMINO METHYL DERIVATIVES

PART-VII: STUDIES ON IMIDAZOLINONES

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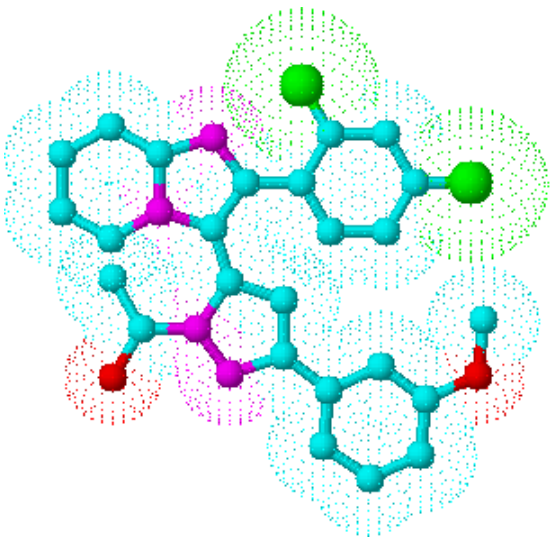


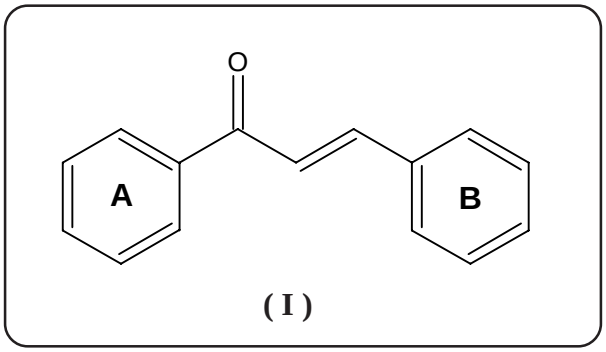
PART - I

STUDIES ON

PYRAZOLINES

INTRODUCTION

The term "***chalcone***" was first coined by Kotanecki and Tambor[1]. The chemistry of chalcones have generated intensive scientific studies throughout the world, specially interesting for their biological and industrial applications. Chalcones are coloured compounds because of the presence of the chromophore and auxochromes. They are known as *benzalacetophenones* or *benzylidene acetophenones*. Chalcones (I) are characterized by their possession of a structure in which two aromatic rings A and B are linked by an aliphatic three carbon chain.



(I)

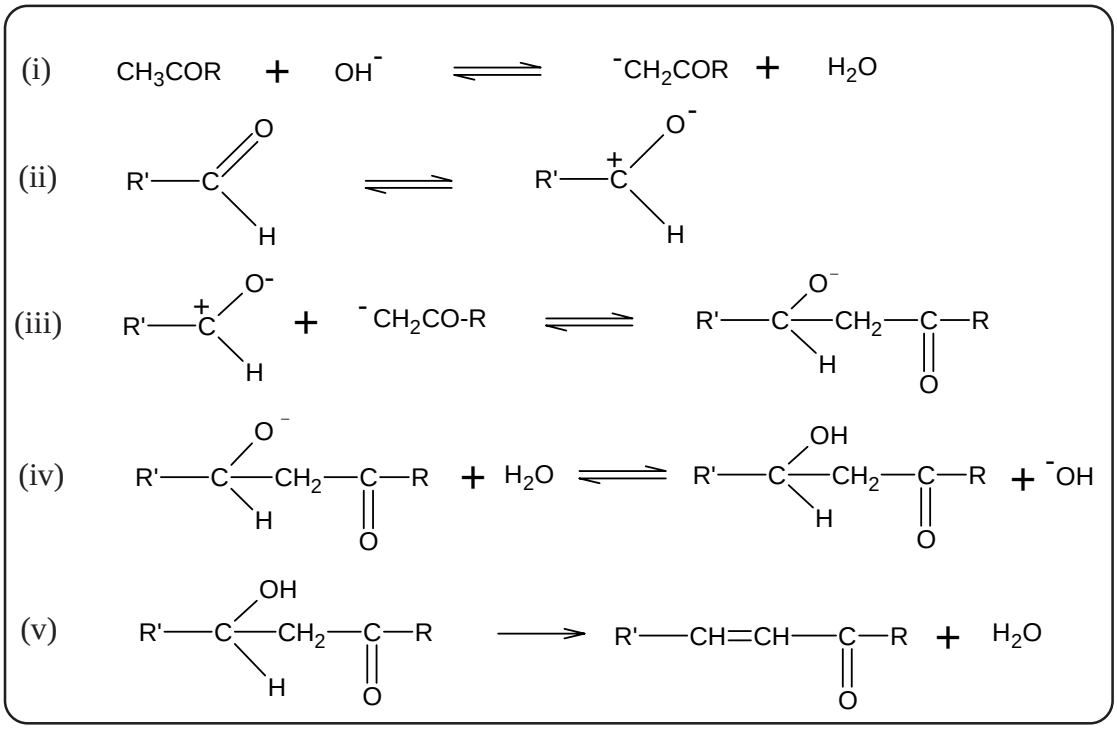
The alternative names given to chalcones are phenyl styryl ketones, beanzalacetophenone, β-phenyl acrylphenone, γ-oxo-α,γ-diphenyl-α-propylene and α-phenyl-β-benzoethylene.

SYNTHETIC ASPECT

A variety of a methods are available for the synthesis of chalcones. The most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of a aryl methyl ketones with aryl aldehyde in the presence of alcoholic alkali.[2-3] Various condensing agent used for the synthesis of chalcones are alkali of different strength.[4,5], Hydrogen chloride[6,7], Phosphorous oxychloride[8], Piperidine[9], Anhydrous Aluminium Chloride[10], Boron trifluoride[11], Borax[12], Aminoacids[13], Perchloric acid[14] etc.

MECHANISM

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



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

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 occuring heterocyclic compounds like flavones, flavanones, flavanoid, dihydro flavanols, benzal coumarinones, anthocyanins, 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[15], cyanopyridines[16], cyanopyrans[17], cyanopyridones[18], pyrimidines[19-21], isoxazoles[22], indazoles[23] etc.
3. They have been useful in providing structure of some natural products like cyanomulcurin[24], eviodictoyl[25], hemlocktanin[26], narighenin[27], plioretin[28] etc.
4. Chalcones are also useful for the detection of Fe(II)[29] and Ca(II)[30] 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[31] and for spectrophotomatric study of the germanium.[32]

5. Chalcone and their derivatives are also found to be applicable as light stabilizing agent[33], sweetening agent[34], organic brightening agent, photo sensitive material, polymerisation catalyst, scintillators as well as fluorescent whitening agent.

6. The chalcones are natural biocides[35,36] and are well-known key intermidiate in the synthesis of heterocyclic compounds possessing biodynamic behaviour.[37-38]

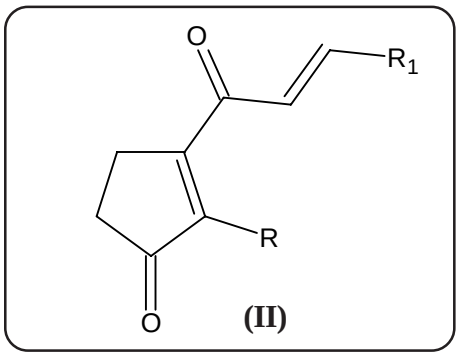
THERAPEUTIC IMPORTANCE

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

1. Antiallergic[39]
2. Antiinflammatory[40,41]
3. Antitumor[42,43]
4. Antispasmodic[44]
5. Antiulcer[45,46]
6. Anthelmintics[47,48]
7. Anticancer[49,50]
8. Antiviral and Antitubercular[51]
9. Anti HIV[52]
10. Bactericidal[53,54]
11. Cardiovascular[55]
12. Fungicidal[56-58]
13. Herbicidal[59]
14. Insecticidal[60-62]

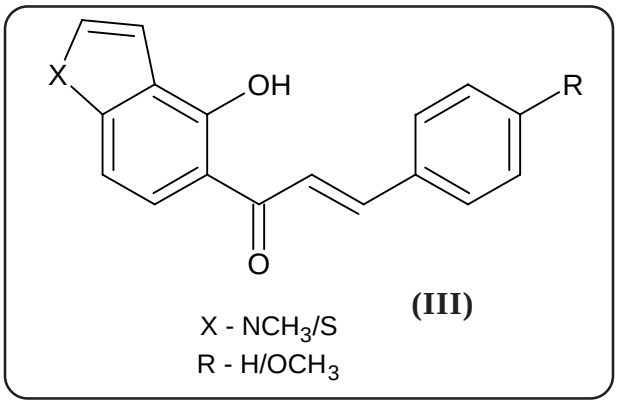
Chalcones are potential biocides, because some naturally occurring antibiotics[63] and aminochalcones[64,65] probably own their biological activity in the presence of the α,β-unsaturated carbonyl group. Nelson G. L.[66] has synthesized the analogues of

prostaglandin (II).



(II)

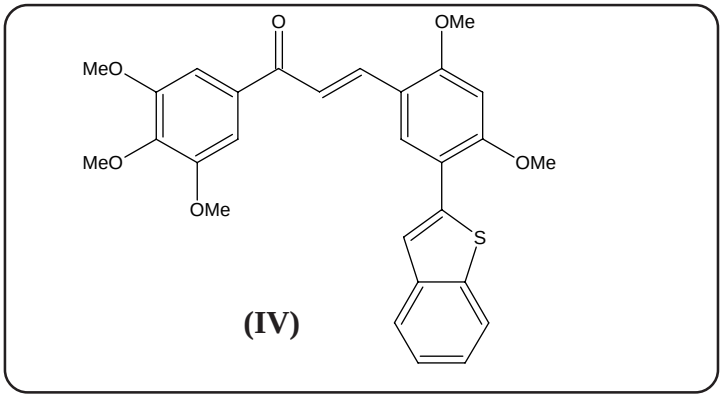
Prem P. Yadav and co-workers[67] have synthesized nitrogen and sulfur containing furanoflavonoids and thiophenylflavonoids (III), Which have been screened for antifungal and antibacterial activity. Meng C. Q. et al.[68] discovered some novel heteroaryl substituted chalcones (IV) as inhibitors of TNF-alpha-induced VCAM-1 expression.



(III)

X - NCH_3/S

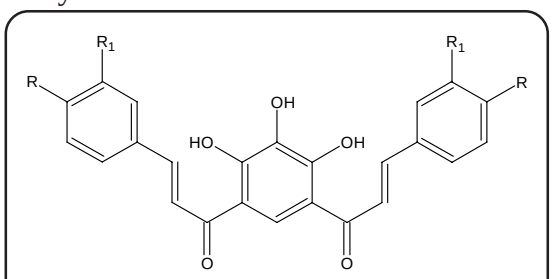
R - H/OCH_3



(IV)

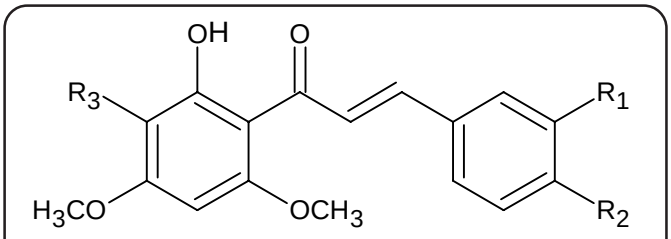
Some dihydrochalcones are well known for their sweetening property[69,70] and appear to be non-nutritive sweeteners. A dihydrochalcone **Uvaretin** from *Uvaria acuminata* has shown antitumor activity[71] in lymphocytic leukemia test.

V. K. Ahluwalia et al.[72] have noted that 5-cinnamoylchalcones (V) have shown good as antibacterial activity.



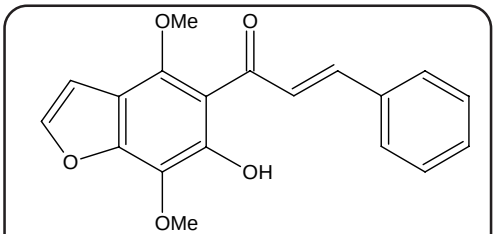
(V)

Paula Boeck et al.[73] have synthesized novel chalcone analougs (VI) with antileishmanial activity. Analougs containing nitro, fluorine or bromine group respectively displayed increased selectivity against the parasites as compared with natural chalcone.

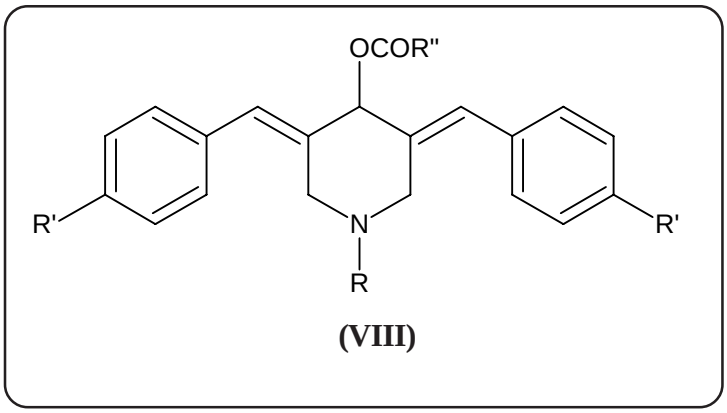


R_1=NO_2, R_2=H, R_3=H
R_1=H, R_2=F, R_3=H
R_1=NO_2, R_2=H, R_3=Br **(VI)**

Furthermore, Alcaraz M. J. et al.[74] 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.[75] have prepared chalcones as potent tyrosinase inhibitors. Sabzevari O. et al.[76] have constructed some new chalcone derivatives (VII) as molecular cytotoxic mechanisms for anticancer activity. Aneta Modzelewska et al.[77] have prepared novel chalcone and bis chalcone derivatives (VIII) having anticancer activity.



(VII)

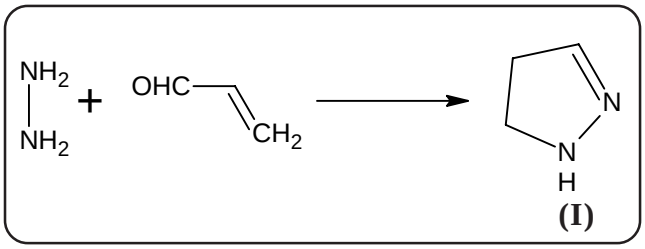


(VIII)

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

INTRODUCTION

The chemistry of pyrazoline was reviewed by Jarobe in 1967. Pyrazoline has three possible tautomeric structures, but the structure (I) shown is the most stable which can be prepared by the action of hydrazine hydrate with acrolein.



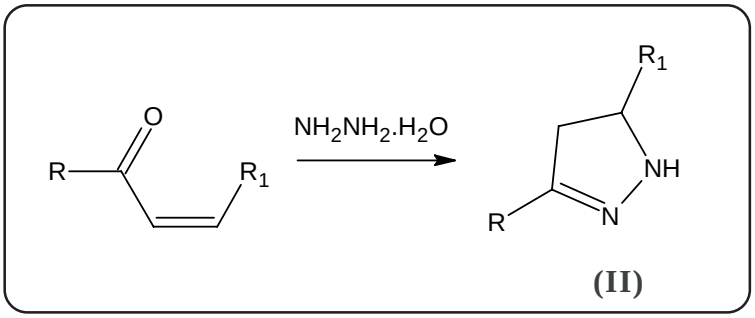
(I)

2-Pyrazoline consist a unique class of five member nitrogen heterocycle. During the past year considerable evidance has been accumulated to demostrate the importance of 2-pyrazoline derivatives. There has been considerable interest in the pyrazoline ring system both with regard to heterocyclic chemistry and the pharmacological activities of several of its derivatives.

SYNTHETIC ASPECT :

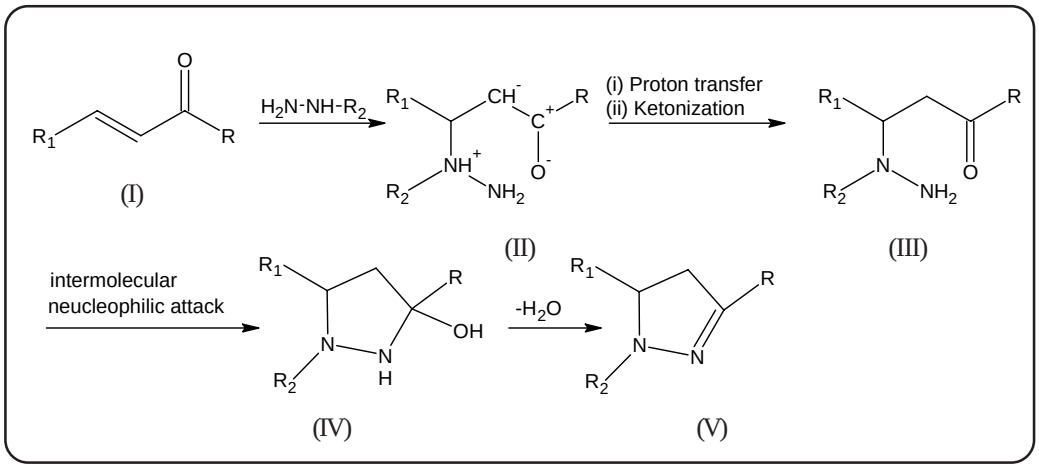
Different methods for the preparation of 2-pyrazoline derivatives documented in literature are as follows.

1. 2-Pyrazolines can be synthesized by the cycloaddition of diazomethane to substituted chalcones[78]
2. Epoxy ketone reacts with hydrazine and phenyl hydrazine to give pyrazolines[79]. Furthermore, B. Gyassi et al.[80] investigated the one pot synthesis of some pyrazolines in dry media under microwave irradiation S. Paul et al.[81] and Dandia Anshu et al.[82] have alsodescribed the microwave assisted synthesis of 2-pyrazolines.
3. 2-Pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazines.[83]
4. 2-Pyrazolines (II) can be constructed by the cyclocondensation of chalcones with hydrazine hydrate.[84]



MACHANISIM

The following mechanism seems to be operable for pyrazoline by the condensation of chalcones with hydrazine hydrate.[85]



Nucleophilic attack by hydrazine at the β-carbon of the α,β-unsaturated carbonyl system (I) forms species (II), in which the negative charge is mainly accomodated by the electronegative oxygen attom.

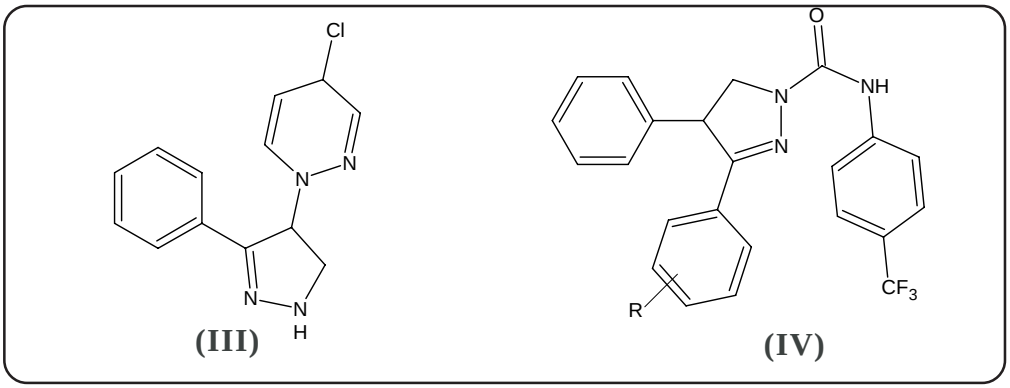
Proton transfer from the nitrogen to negative oxygen produces an intermediate enol which simultaneously ketonises to ketoamine (III). Another intramolecular nucleophilic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to carbonyl amine (IV). The later with a hydroxy group and amino group on the same carbon lose water molecule to yield the pyrazoline (V).

THERAPEUTIC IMPORTANCE

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

1. Antimicrobial[86]
2. Anticonvulsant and Antidepressant[87]
3. Antiallergic[88]
4. Fungicidal[89,90]
5. Antidiabetic[91]
6. Antiimplantation[92]
5. Antiinflammatory[93, 94]
6. Antitumor[95]
7. Antineoplastic[96]
9. Analgesic[97,98]
10. Bactericidal[99,100]
14. Herbicidal[101]
11. Cardiovascular[102]
12. Diuretic[103]
15. Antiamoebic[104]
16. Tranquilizer[105]

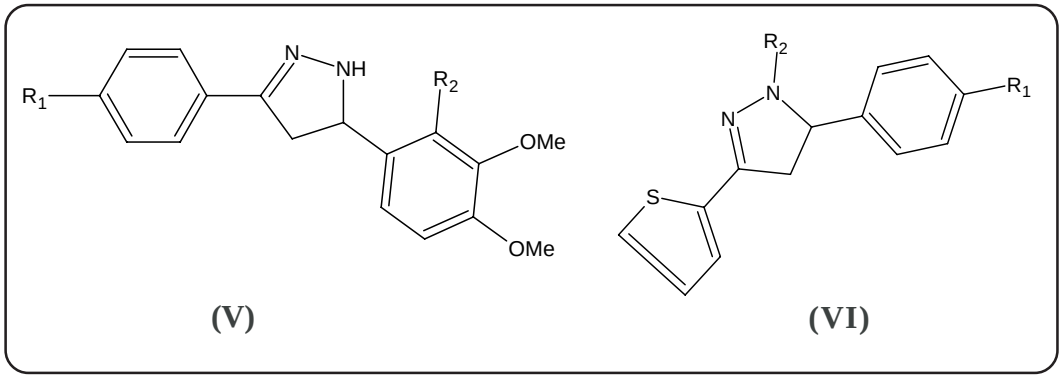
Moreover F. Manna et al.[106] have described 1-acetyl-5-(2'-bromophenyl)-4,5-dihydro-3-(2'-hydroxyphenyl)-1H-pyrazoline and its derivatives act as potent antiinflammatory, analgesic and antipyretic agents. Udupi R. H. and Bhatt A. R.[107] have reported the synthesis and biological activity of Mannich bases of certain 1,2-pyrazolines. Nugent Richard[108] investigated pyrazolines bis phosphonate ester as novel antiinflammatory and antiarthritic agent. Fuche Rainer et al.[109] have prepared some new 1H-pyrazoline derivatives (III) and reported them as pesticides. Furthermore, Tsubai et al.[110] have synthesized some new(phenylcarbamoyl) pyrazolines (IV) as an insecticides and at 40% concentration shows 100% mortality of spodopetra litura larve after seven drops.



(III) **(IV)**

Abdalla M. M. et al.[111] have synthesized pyrazolines and tested their antiandrogenic activity. Berghot M. A. et al.[112] have prepared pyrazolines as antibacterial agents. Maurer Fritz et al.[113] have synthesized pyrazoles and screened for their pesticidal activity.

E. Palska et al.[114] have prepared 3,5-diphenyl-2-pyrazolines (V) and cited their antidepressant activity. B. Shivrama et al.[115,116] have synthesized pyrazolines as antibacterial agents. Hiremath S. P. et al.[117] have reported pyrazolines as analgesics, antiinflammatory and antimicrobial agents. Goodell et al.[118] have synthesized some newer 1,3,5-trisubstituted pyrazoline derivatives (VI) which shows anti west nile virus activity.



(V) **(VI)**

Almstead J. et al.[119] have prepared pyrazolines as vascularization agents. Guniz Kuchkguzel et al.[120] have synthesized pyrazolines as a antimicrobial and anticonvulsant agents. Gulhan T. Z. and co-workers[121] have prepared pyrazolines as a hypotensive agent.

Moreover, T. M. Stivensen et al.[122] have also investigated N-substituted pyrazoline type insecticides. Tanka Katsohori[123] have patented pyrazoline derivatives as herbicides and Johannes et al.[124] as insecticides. Moritaz Z. and Hadol[125] investigated a semi emperial molecular orbital study on the reaction of aminopyrazolinyl azodye with singlet molecular oxygen. Shivnanda M. K. and co-workers[126] have prepared substituted pyrazolines and reported their antibacterial activity.

S. S. Sonarc et al.[127] have synthesized-3-(2-acetoxy-4-methoxyphenyl)-5-(substituted phenyl)-pyrazolines and tested their antimicrobial activity. H. H. Parekh[128] et al. have also synthesized some new pyrazolines as an antimicrobial agent. G. N. Mishirika et al.[129] have also prepared 2-pyrazolines of salicyclic acid possessing antimicrobial properties. Tunfawy, Atif and co-workers[130] have patented 3-methyl-4'-(substituted phenylazo)-pyrazol-5-ones as antibacterial agents.

Thus, significant biological properties associated with pyrazoline derivatives have aroused considerable interest to design the compounds with better drug potential and to study their pharmacological profile, which have been described as under.

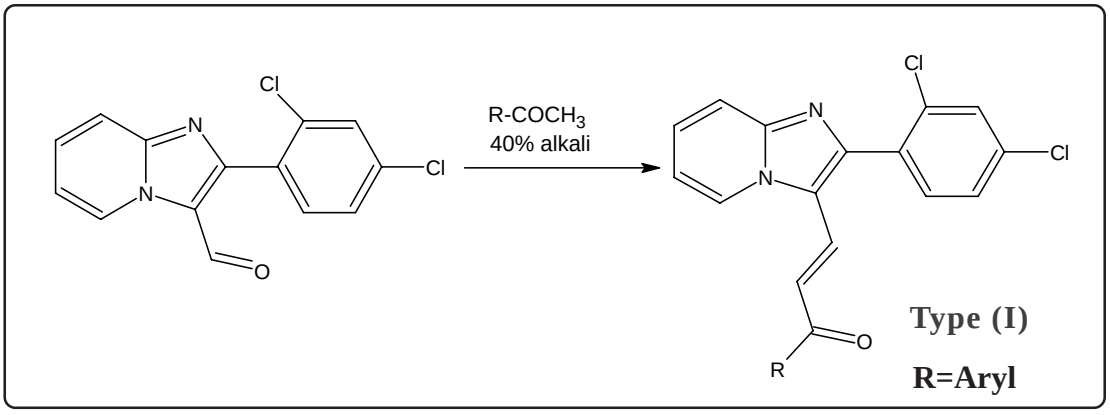
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF (2*E*)-3-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-1-ARYLPROP-2-EN-1-ONES

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

SECTION - I

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

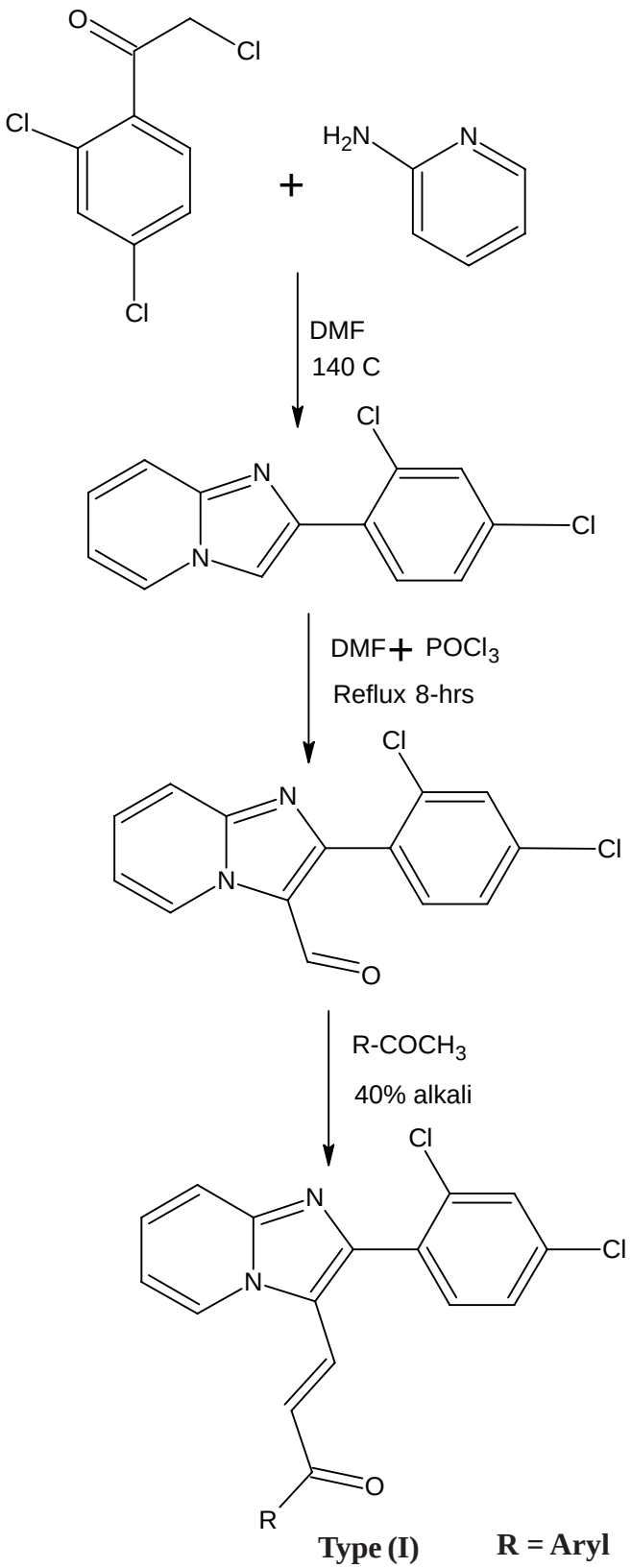
Chalcone derivatives occupy a unique place in the field of medicinal chemistry due to wide range of biological activities exhibited by them, prompted by these facts, the preparation of chalcones of Type (I) have been carried out by condensation of 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde with different ketones.



The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

REACTION SCHEME



Type (I) **R = Aryl**

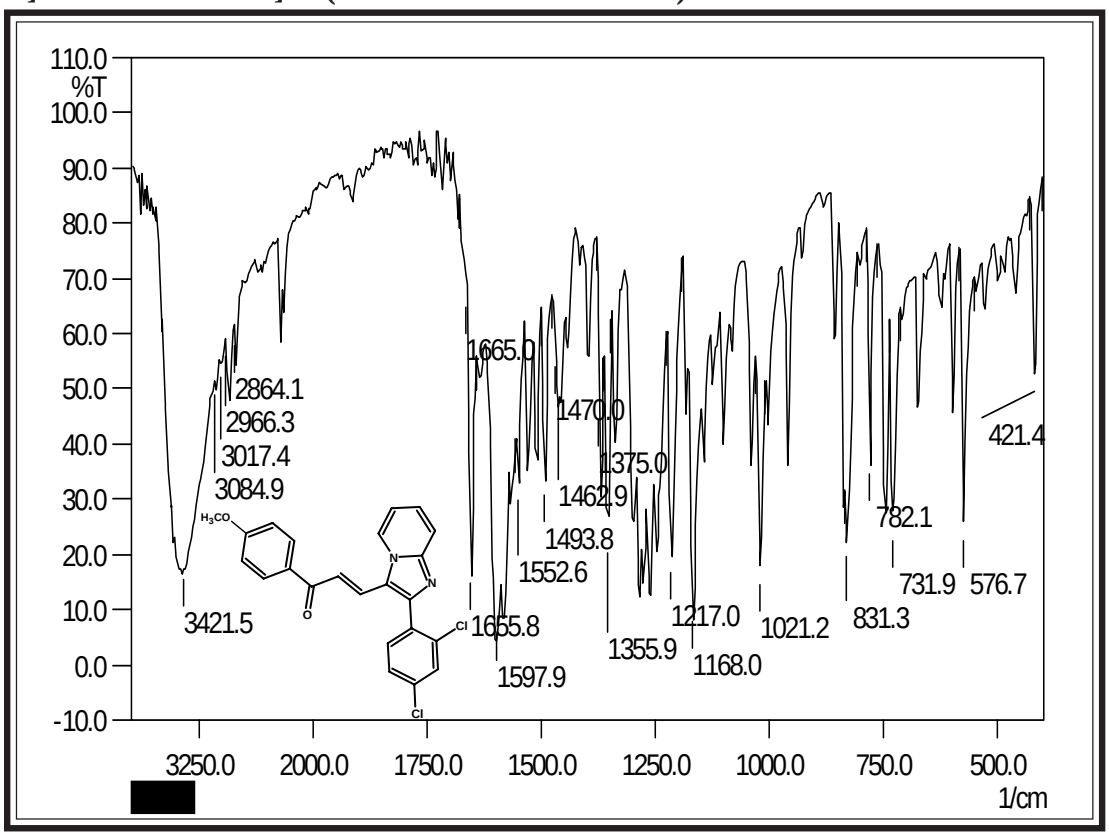
MICROBIOLOGICAL EVALUATION

ANTIMICROBIAL ACTIVITY

Method	:	Cup-Plate[133]
Gram positive bacteria	:	***Staphylococcus aureus***
		Bacillus Coccus
Gram negative bacteria	:	***Pseudomonas aeruginosa***
		Aerogenes
Fungi	:	***Aspergillus niger***
Concentration	:	40μg/ml
Solvent	:	Dimethyl formamide
Standard drugs	:	Amoxicillin, Benzyl Penicillin, Ciprofloxacin, Erythromycin, Greseofulvin

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

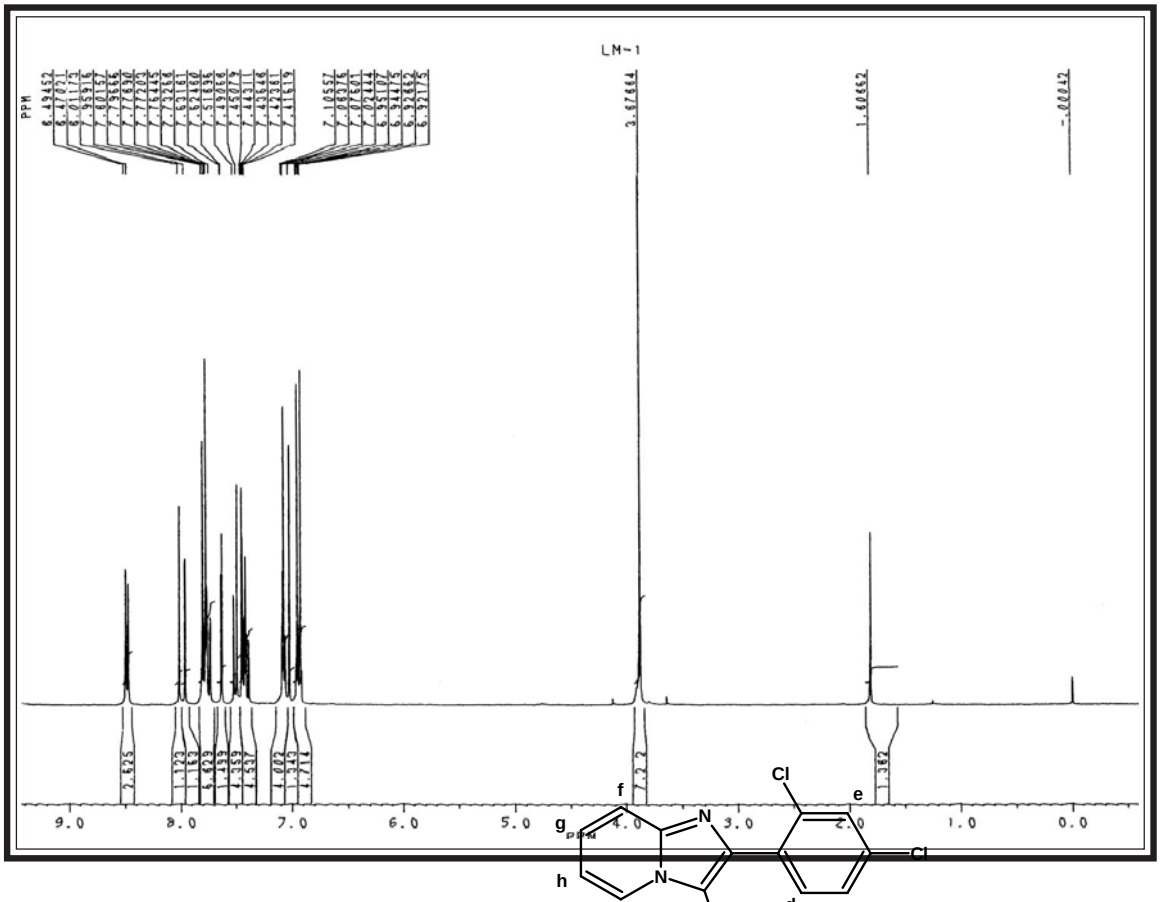
IR SPECTRAL STUDIES OF (2*E*)-3-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE



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	131
$-CH_3$	C-H str. (sym.)	2864	2880-2860	,,
	C-H def. (asym.)	1462	1470-1435	,,
	C-H def. (sym.)	1375	1390-1370	,,
Aromatic	C-H str.	3084	3090-3030	132
	C=C str.	1493	1540-1480	,,
Halide	C-Cl str.	731	800-600	131
Vinyl	CH=CH str.	3017	3050-3000	,,
Chalcone	C=C str.	1552	1580-1550	,,
	C=O str.	1665	1672-1652	,,
Imidazo[1,2-a]	C=N Str.	1597	1612-1593	,,
pyridine	C-N Str.	1168	1220-1020	132
	C=CStr.	1470	1540-1480	,,
Ether	C-O-C Str.	1217	1260-1200	,,

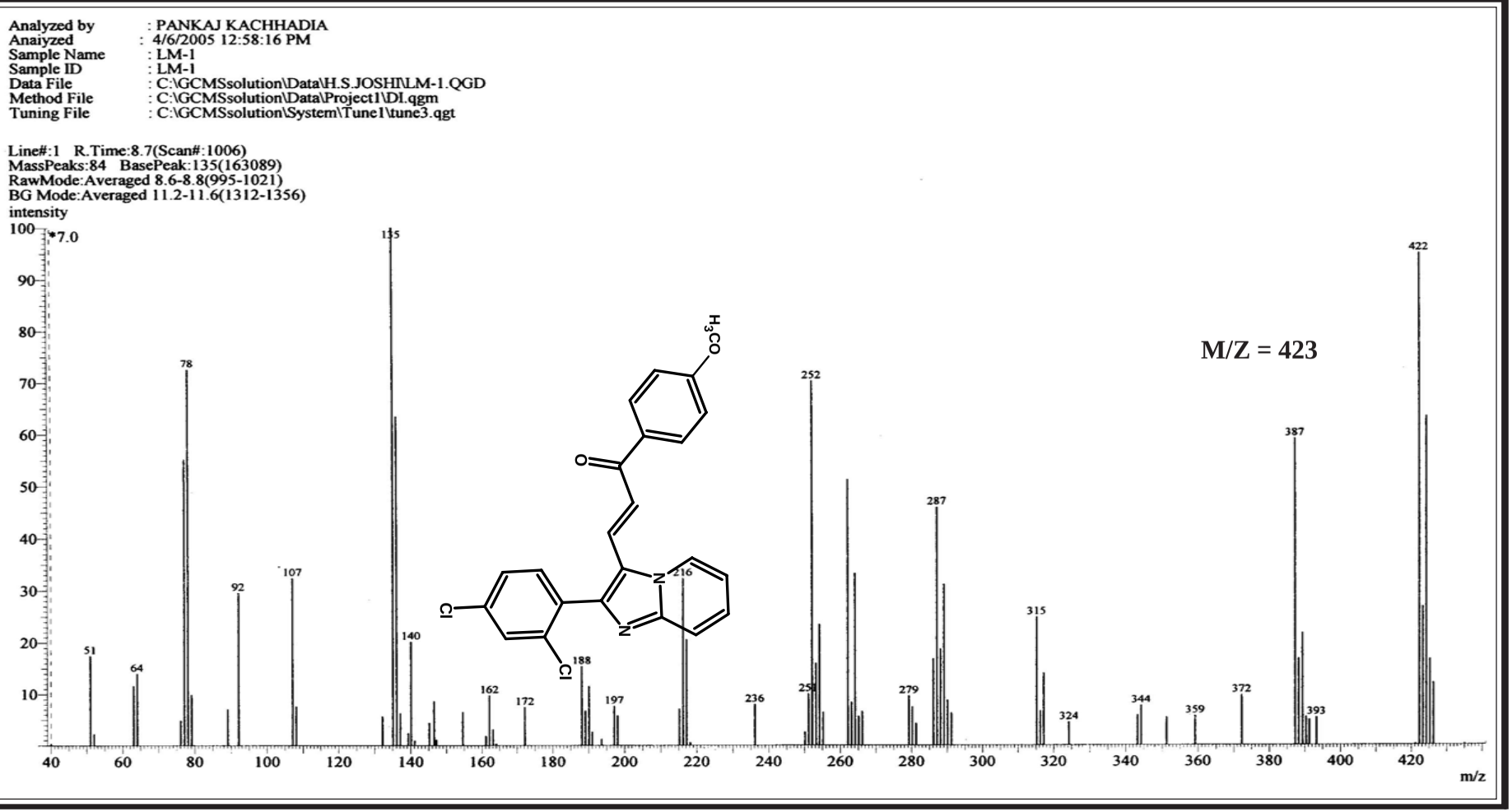
NMR SPECTRAL STUDIES OF (2*E*)-3-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.5	3H	singlet	Ar-OCH_3	-
2	6.92-6.95	2H	doublet	Ar-H(a,a')	J=9
3	7.10-7.02	1H	doublet	Ar-H(x)	J=15
4	7.30-7.50	4H	multiplet	Ar-H(g,h,i,j)	-
5	7.62	1H	doublet	Ar-H(e)	J=2.1
6	7.70	1H	dd	Ar-H(c)	J=9.0,J=3.0
7	7.82	2H	doublet	Ar-H(b,b')	J=9.0
8	7.95	1H	doublet	Ar-H(y)	J=18.0
9	8.47	1H	doublet	Ar-H(d)	J=9.0

TABLE-1 : MASS SPECTRAL STUDIES OF (2*E*)-3-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE



EXPERIMENTAL

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

(A) Synthesis of 2-(2,4-Dichlorophenyl)imidazo[1,2-a]pyridine

To the solution of 2-amino pyridine (23.5 gm, 0.25 mol), 2-chloro-1-(2,4-dichlorophenyl)ethanone (22.4 gm, 0.1 mol) in DMF (250 ml) was added. The reaction mixture was stirred and reflux for 4 hour. After cooling, the crystallized product was filtered and dried in vacuum. Yield 72%, m.p172^{o}C, Anal. Calcd. for $C_{13}H_8CL_2N_2$: Require: C, 59.34, H, 3.06, N, 10.65 % ; Found: C, 59.12, H, 3.02, N, 10.67 %.

(B) Synthesis of 2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridine-3 carbaldehyde

To a well mixed solution of phosphorus oxychloride (11 ml), chloroform (32 ml) and DMF (8 ml) maintained at 0-10^{o}C, was added slowly to a solution of 2-(2,4-dichlorophenyl)imidazo[1,2-a]pyridine (5.26 gm, 0.02 mol) in 140 ml chloroform. The mixture so obtined was refluxed for 8 hour. Cool the solution and evaporated to dry in vaccum. The residue was treated with cold water, filter and crystallized from methanol. Yield 90%, m. p. 212^{o}C , Anal. Calcd. for $C_{14}H_8Cl_2N_2O$ Require : C, 57.76, H, 2.77, N, 9.62 % ; Found: C, 57.70, H, 2.80, N, 9.60 %.

(C) Synthesis of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-(4-methoxyphenyl)prop-2-en-1-one

Dissolve 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine-3 carbaldehyde (2.91gm, 0.01mol)in a mixture of methanol (25 ml) + DMF (25 ml). To this add p-methoxyacetophenone (1.40gm, 0.01mol) and methanol (25 ml). Stirr the content at room temperature for 24 hr. in presence of catalytical amount of 40% KOH. The resulting solution was poured on to crushed ice, thus the solid seprated was filterated and crystallized from ethanol, Yield 56 %, m. p. 180^{o}C , Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O_2$ Require : C, 65.26, H, 3.81, N, 6.62 % ; Found: C, 65.24, H, 3.80, N, 6.60 %.

Similarly, other compounds were prepared. The physical data are recorded in Table No. 1

(D) Biological screening of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-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 24 hr. old subcultures of **Bacillus coccus, Staphylococcus aureus, Aerogenes, Pseudomonas aeruginosa** in separate conical flasks at 40-50^{0}C and mixed well by gentle shaking. About25 ml content of the flask was poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hr. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40mg) solution of sample in DMF.The plates were incubated at 37^{0}C for 24 hr. and the control was also maintained with 0.04ml of DMF 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

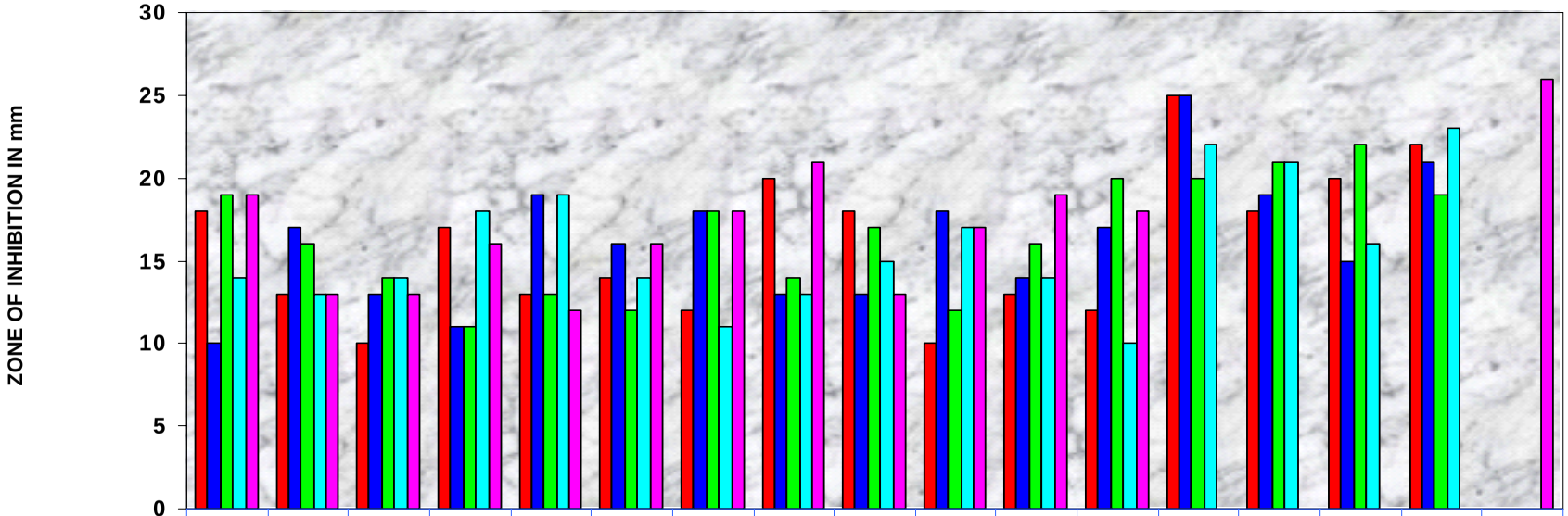
***Aspergillus* niger** was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on sabourauds agar slants sterilized sabourauds agar medium was inoculated with 72 hr. old 0.5ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a petridish (13cm diameter) and allowed to set for 2 hr. the cups (10mm diameter) were punched. The plates were incubated at 30 ^{0}C for 48 hr. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measure. Along the test solution in each petridish one cup was filled up with solvent, which acts as control. The zone of inhibition of test solution are recorded in Graphical Chart No. 1

TABLE : 1 PHYSICAL CONSTANTS OF (2*E*)-3-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-1-ARYLPROP-2-EN-1-ONES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
1a	C_6H_5-	$C_{22}H_{14}Cl_2N_2O$	393.26	186	60	7.12	7.11	0.51	S_1
1b	4-CH_3-C_6H_4-	$C_{23}H_{16}Cl_2N_2O$	407.29	175	58	6.88	6.87	0.49	S_2
1c	2-CH_3-C_6H_4-	$C_{23}H_{16}Cl_2N_2O$	407.29	167	65	6.88	6.86	0.50	S_1
1d	2,5-$(CH_3)_2$-C_6H_3-	$C_{24}H_{18}Cl_2N_2O$	421.31	192	62	6.65	6.64	0.41	S_1
1e	4-OCH_3-C_6H_4-	$C_{23}H_{16}Cl_2N_2O_2$	423.29	180	56	6.62	6.60	0.48	S_2
1f	2,4-$(Cl)_2$-C_6H_3-	$C_{22}H_{12}Cl_4N_2O$	462.15	235	58	6.06	6.08	0.55	S_2
1g	4-Cl-C_6H_4-	$C_{22}H_{13}Cl_3N_2O$	427.71	220	55	6.65	6.64	0.53	S_2
1h	4-Br-C_6H_4-	$C_{22}H_{13}BrCl_2N_2O$	472.16	183	65	5.93	5.91	0.57	S_2
1i	4-S-CH_3-C_6H_4-	$C_{23}H_{16}Cl_2N_2OS$	439.35	190	62	7.14	7.12	0.46	S_1
1j	4-F-C_6H_4-	$C_{22}H_{13}Cl_2FN_2O$	411.25	182	60	6.81	6.80	0.44	S_1
1k	3-NO_2-C_6H_4-	$C_{22}H_{13}Cl_2N_3O_3$	438.26	250	57	9.59	9.58	0.54	S_2
1l	4-NO_2-C_6H_4-	$C_{22}H_{13}Cl_2N_3O_3$	438.26	282	56	9.59	9.56	0.45	S_2

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

GRAPHICAL CHART NO. 1 : (2*E*)-3-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-1-ARYLPROP-2-EN-1-ONES

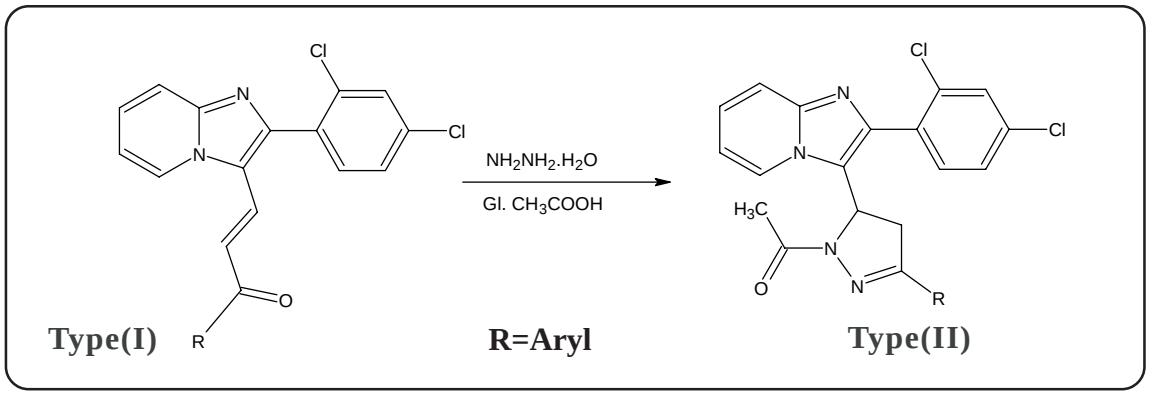


	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Amoxycillin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	18	13	10	17	13	14	12	20	18	10	13	12	25	18	20	22	0
S.aureus	10	17	13	11	19	16	18	13	13	18	14	17	25	19	15	21	0
Aerogenes	19	16	14	11	13	12	18	14	17	12	16	20	20	21	22	19	0
Pseudomonas	14	13	14	18	19	14	11	13	15	17	14	10	22	21	16	23	0
A.niger	19	13	13	16	12	16	18	21	13	17	19	18	0	0	0	0	26

SECTION - II

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

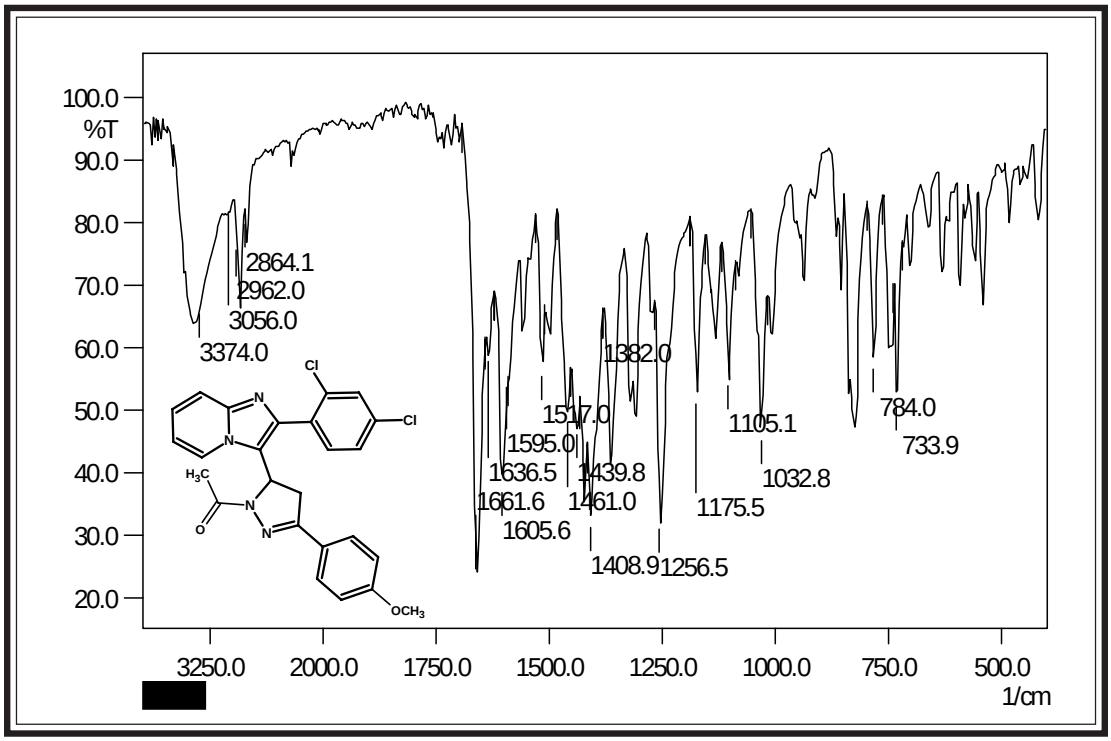
The broad spectrums of pharmacological properties have been demonstrated by the pyrazoline nucleus. Inspired by these facts, new pyrazoline derivatives of Type (II) have been investigated. The (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones of Type (I) on treatment with hydrazine hydrate in acetic acid yielded 3-(1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridines derivatives of Type (II).



The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

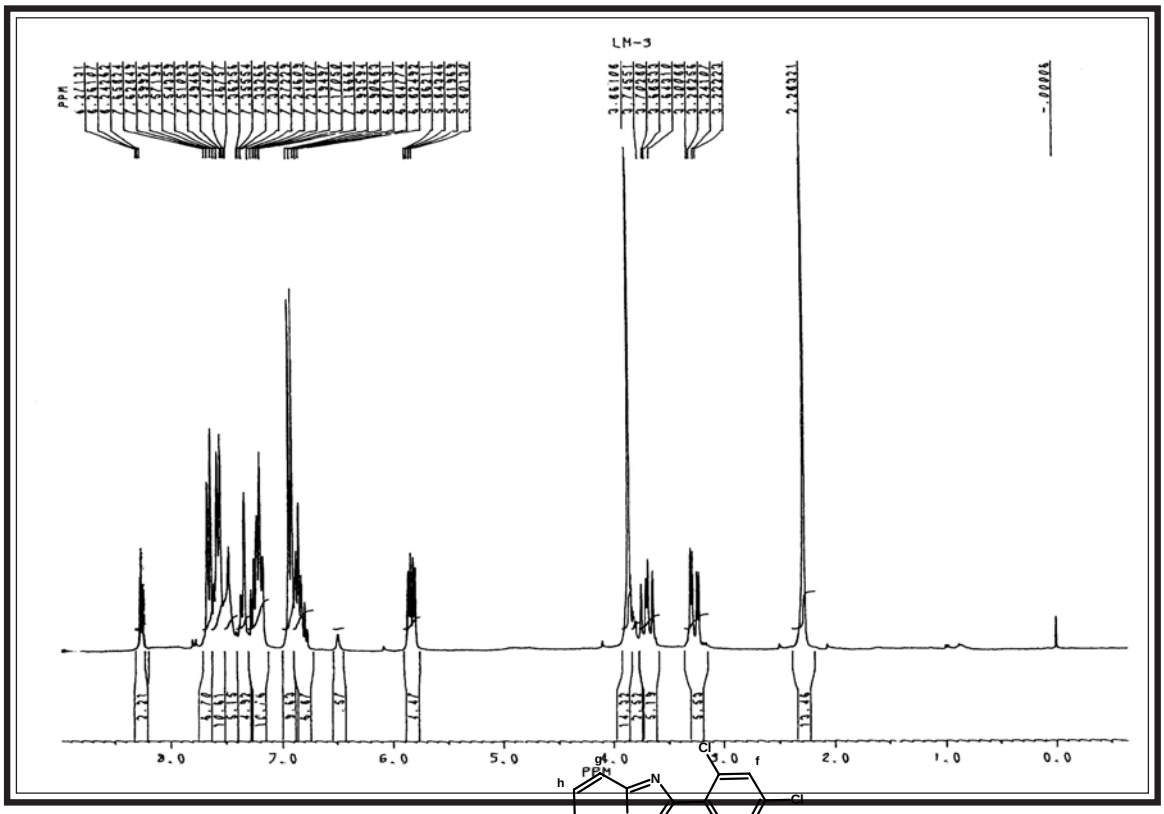
IR SPECTRAL STUDIES OF 3-(1-ACETYL-3-(4-METHOXYPHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDINE

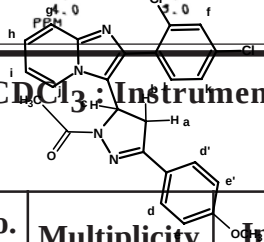


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2962	2975-2950	131
-CH_3	C-H str. (sym.)	2864	2880-2860	,,
	C-H def. (asym.)	1460	1470-1435	,,
	C-H def. (sym.)	1382	1390-1370	,,
Aromatic	C-H str.	3056	3090-3030	132
	C=C str.	1517	1540-1480	,,
Ether	C-O-C str.	1256	1260-1200	,,
Pyrazoline	C=O str.	1661	1612-1593	131
	C=N str.	1605	1612-1593	,,
	N-H str.	3374	3400-3200	,,
Imidazo[1,2-a]	C=N str.	1595	1612-1593	,,
pyridine	C-N str.	1032	1220-1020	,,
Halide	C-Cl str.	784	800-600	132

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

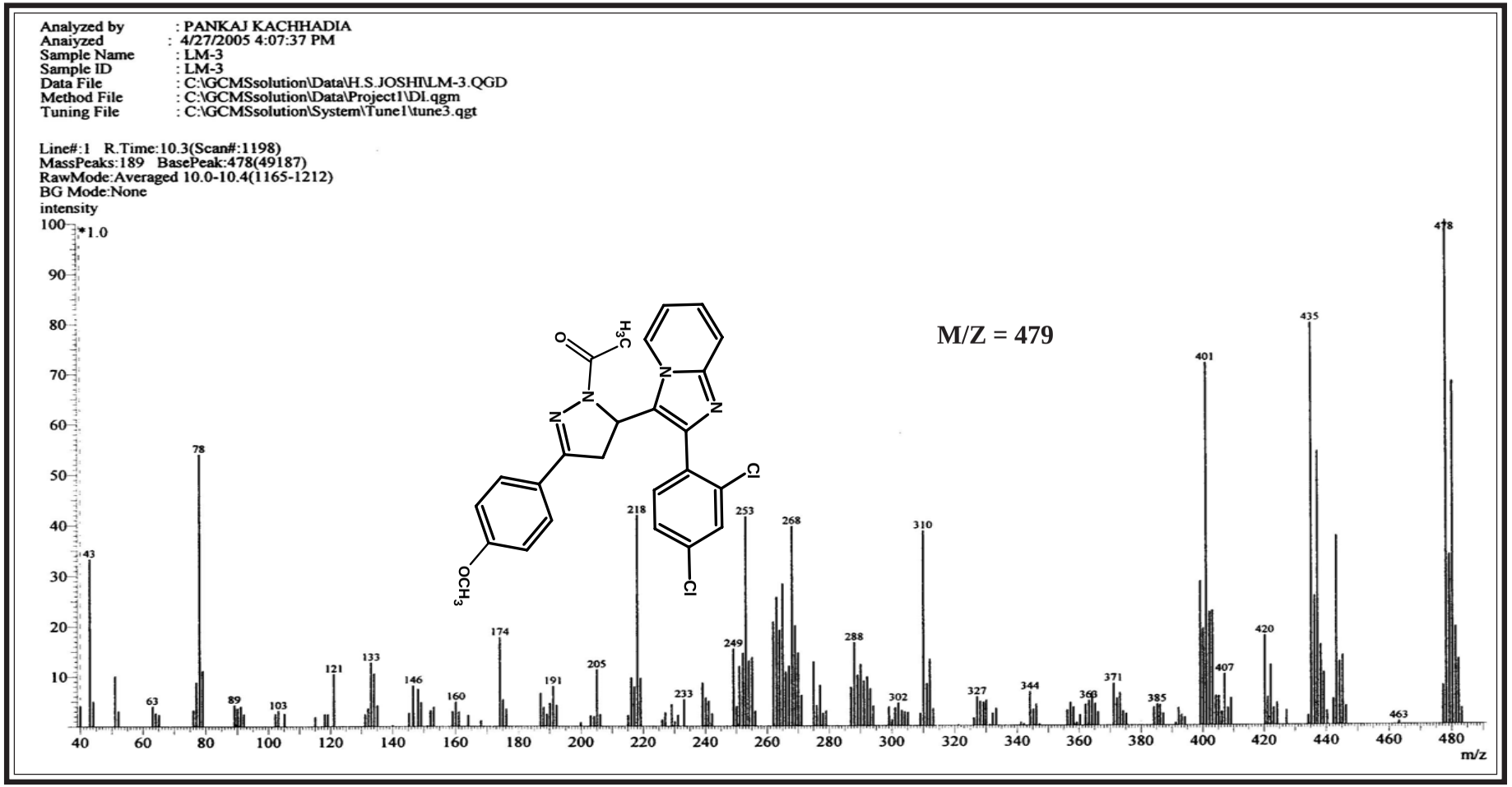




Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.26	3H	singlet	Ar-CO-CH_3	-
2	3.25	1H	dd	C-H(a)	-
3	3.68	1H	dd	C-H(b)	-
4	3.85	3H	singlet	Ar-OCH_3	-
5	5.81	1H	dd	C-Hc	-
6	6.80	1H	doublet	Ar-H(l)	J=6.2
7	6.91	2H	doublet	Ar-H(e,e')	J=9.0
8	7.15-7.40	4H	multiplet	Ar-H(g,h,i,j)	-
9	7.57	1H	dd	Ar-H(k)	J=9.0,J=2.1
10	7.63	2H	doublet	Ar-H(d,d')	J=9.0
11	8.26	1H	doublet	Ar-H(f)	J=3.0

TABLE-2 : MASS SPECTRAL STUDIES OF 3-(1-ACETYL-3-(4-METHOXYPHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDINE



EXPERIMENTAL

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

(A) Synthesis of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones

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

(B) Synthesis of 3-(1-Acetyl-3-(4-methoxphenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine

A mixture of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-(4-methoxyphenyl)prop-2-en-1-one (4.23 gm, 0.01 mol) and hydrazine hydrate (0.5gm, 0.01 mol) in glacial acetic acid (25 ml) was refluxed for 8 hr. The product was isolated and crystallized from ethanol. Yield 64 %, m.p. 200 ^{O}C, Anal. Calcd. for $C_{25}H_{20}Cl_2N_4O_2$; Requires: C, 62.64; H, 4.21; N, 11.69 %; Found: C, 62.63; H, 4.20; N, 11.68 %.

Similarly, other 3-(1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridines were prepared. The physical data are recorded in Table No.2

(C) Biological screening of 3-(1-Acetyl-3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridines

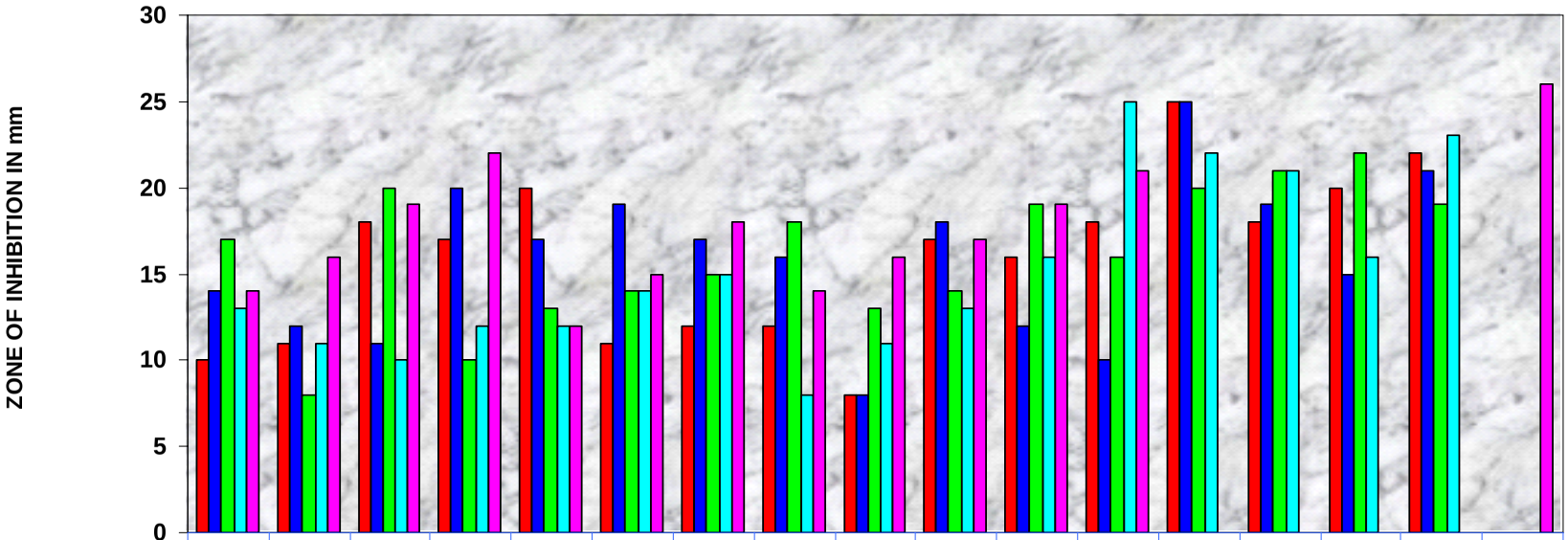
Antimicrobial testing were carried out as described in **(A)** Part-I Section-I(D). The zones of inhibition of test solutions are recorded in Graphical Chart No.2

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

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
2a	C_6H_5-	$C_{24}H_{18}Cl_2N_4O$	449.33	180	68	12.47	12.46	0.47	S_2
2b	4-CH_3-C_6H_4-	$C_{25}H_{20}Cl_2N_4O$	463.35	165	62	12.09	12.00	0.53	S_2
2c	2-CH_3-C_6H_4-	$C_{25}H_{20}Cl_2N_4O$	463.35	185	58	12.09	11.98	0.49	S_1
2d	2,5-$(CH_3)_2$-C_6H_3-	$C_{26}H_{22}Cl_2N_4O$	477.38	173	53	11.74	11.73	0.52	S_2
2e	4-OCH_3-C_6H_4-	$C_{25}H_{20}Cl_2N_4O_2$	479.35	200	64	11.69	11.68	0.57	S_2
2f	2,4-$(Cl)_2$-C_6H_3-	$C_{24}H_{16}Cl_4N_4O$	518.22	130	69	10.81	10.80	0.50	S_1
2g	4-Cl-C_6H_4-	$C_{24}H_{17}Cl_3N_4O$	483.77	170	61	11.58	11.56	0.58	S_1
2h	4-Br-C_6H_4-	$C_{24}H_{17}BrCl_2N_4O$	528.22	160	63	10.61	10.60	0.54	S_2
2i	4-S-CH_3-C_6H_4-	$C_{25}H_{20}Cl_2N_4OS$	495.24	200	50	11.31	11.29	0.59	S_1
2j	4-F-C_6H_4-	$C_{24}H_{17}Cl_2FN_4O$	467.32	180	66	11.99	11.98	0.60	S_1
2k	3-NO_2-C_6H_4-	$C_{24}H_{17}Cl_2N_5O_3$	494.32	210(d)	57	14.17	14.16	0.55	S_2
2l	4-NO_2-C_6H_4-	$C_{24}H_{17}Cl_2N_5O_3$	494.32	120	55	14.17	14.14	0.45	S_1

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

GRAPHICAL CHART NO. 2 : 3-(1-ACETYL-3-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-5-YL)-2-(2,4-DICHLOROPHENYL) IMIDAZO[1,2-*a*]PYRIDINES



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Amoxycillin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	10	11	18	17	20	11	12	12	8	17	16	18	25	18	20	22	0
S.aureus	14	12	11	20	17	19	17	16	8	18	12	10	25	19	15	21	0
Aerogenes	17	8	20	10	13	14	15	18	13	14	19	16	20	21	22	19	0
Pseudomonas	13	11	10	12	12	14	15	8	11	13	16	25	22	21	16	23	0
A.niger	14	16	19	22	12	15	18	14	16	17	19	21	0	0	0	0	26

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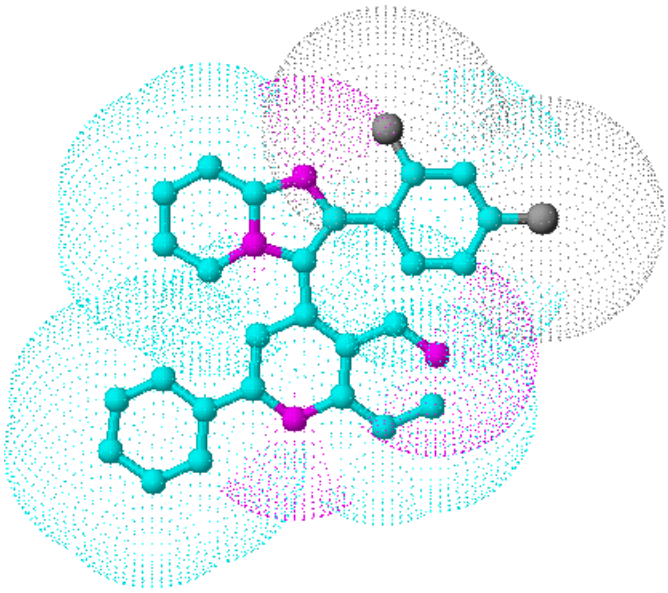


PART - II

STUDIES ON

CYNOPYRIDINES

INTRODUCTION

Pyridine with different functional groups, exhibit wide range of applications in the field of medicine, agriculture and dyes. Although many substituted pyridine compounds like other heterocyclic compounds are synthesized with their functional group present from a 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 undrtaken the synthesis of imidazo[1,2-a]pyridine derivatives such as 4-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-2-methoxy-6-aryl nicotinonitriles via chlacones.

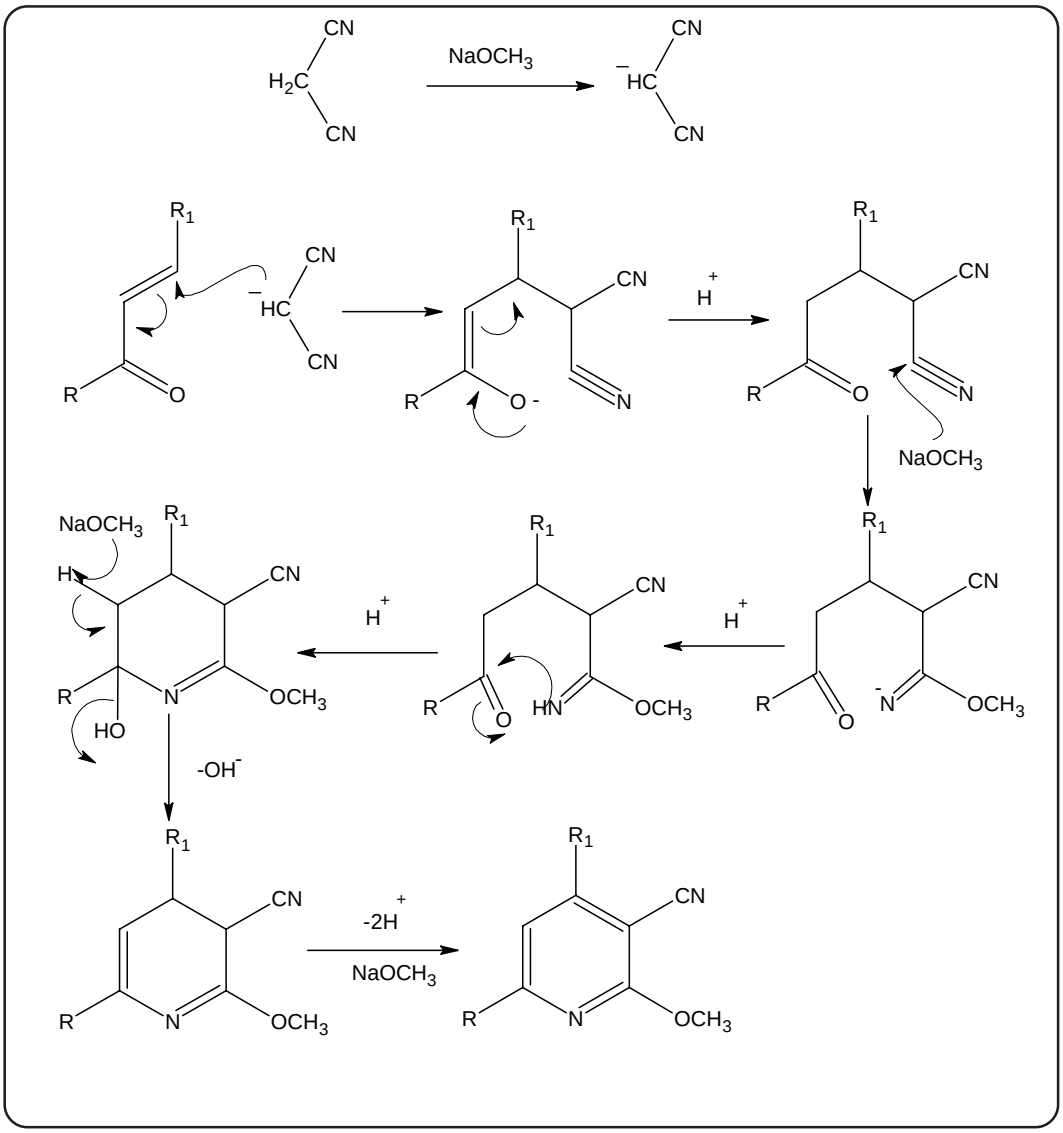
SYNTHETIC ASPECT :

Different methods for the preparation of 3-cyanopyridines are available in literature.[1-7] The well known methods are:

1. Substituted cyanopyridine derivatives were prepared from 3-substituted phenyl pyrazolone derivatives with malononitrile.[8]
2. Samour and co-workers[9] have prepared substituted cyanopyridines by the condensation of chalcones with malononitrile in presence of ammonium acetate.
3. Sakurai and Midorikaw[10,11] have reported that malononitrile reacts with α,β-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines.
4. Matthew D. Bowman et al.[12] have synthesized fluorescent cyanopyridine and deazalumazine dyes using small molecule macroarrays.

MECHANISM

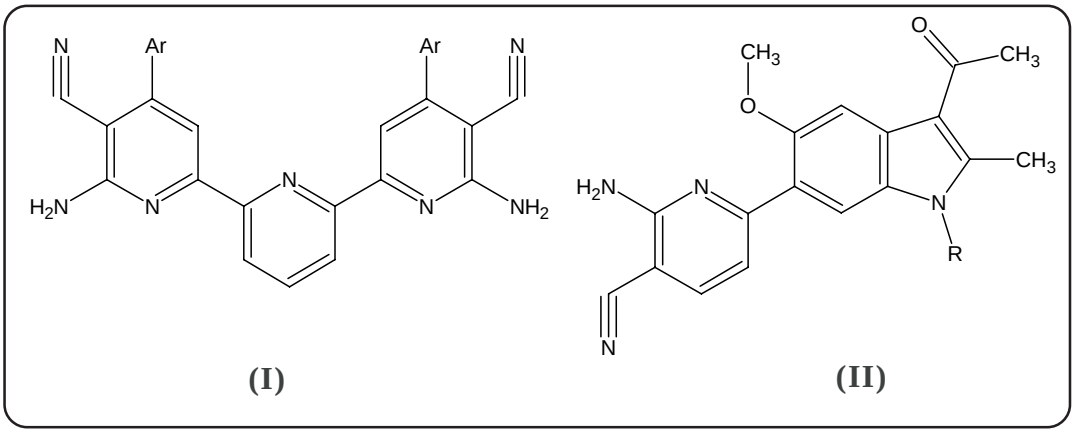
The reaction proceeds through conjugate addition of active methylene compounds to the α,β-unsaturated system as shown below.



THERAPEUTIC IMPORTANCE

Cyanopyridines have attracted considerable attention as they appeared of interest to possess antibacterial, anticholestemic, antifungal, antihypertensive and antidiabetic activities. E. G. Hammana Abou and co-workers[13] have studied anticancer and anti HIV activity of 3-cyanopyridines. Abdallah Navine et al.[14] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity. Manna Fedele and co-workers[15] have reported the antiinflammatory activity of 3-cyanopyridines. H. Yoshida et al.[16] have studied the antihistaminic and antiallergic activity of 3-cyanopyridine

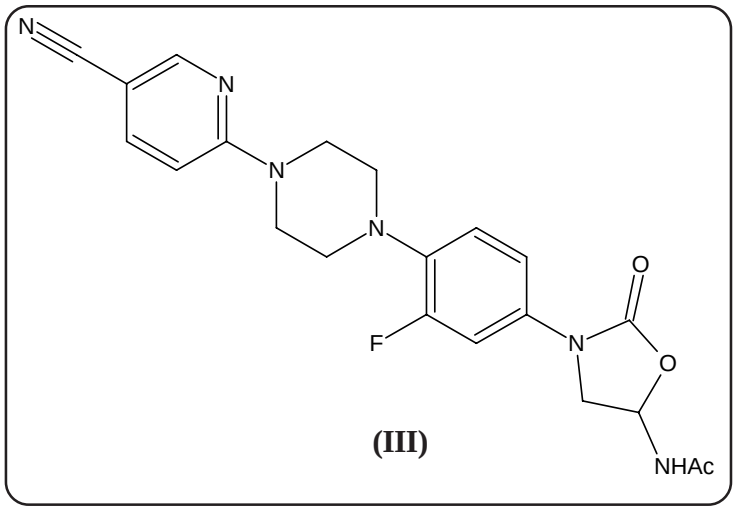
derivatives. Abd El-Galil and co-workers[17] have prepared 3-cyanopyridines (I) and studied their pharmacological activity. Gadaginamath et al.[18] have synthesized various cyanopyridyl derivatives (II) and documented their variety of biological activities.



(I) **(II)**

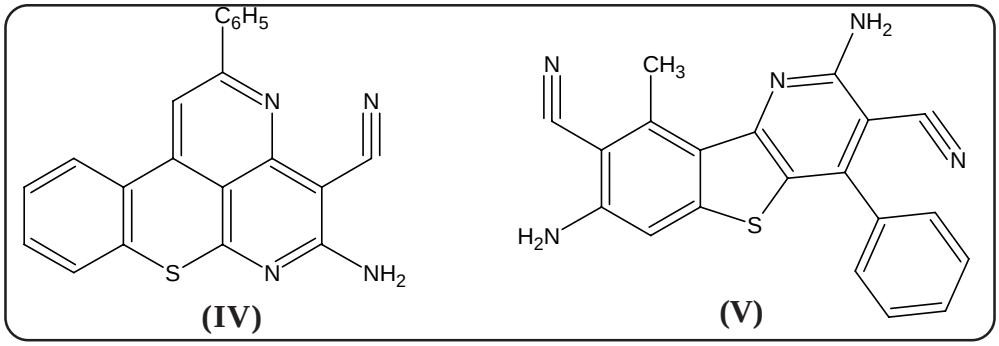
Many naturally occurring and synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties[19]. Among them, 2-amino-3-cyanopyridines have been identified as IKK-2 inhibitors[20].

J. J. Baldwin[21-23] have prepared cyanopyridines exhibiting antihypertensive activity. Streightoff[24] and Seydal[25] have studied the bacteriostatic effect of some substituted 3-cyanopyridines. Francis and co-workers[26] have studied the effect of some substituted pyridines on the growth of the walker carcinosarcome-256 in tissue culture. Barton et al.[27] have reported fungicidal and insecticidal properties. John A. Tucker et al.[28] have synthesized novel piperazinyl oxazolidinone containing cyanopyridine (III) as an antibacterial agents.

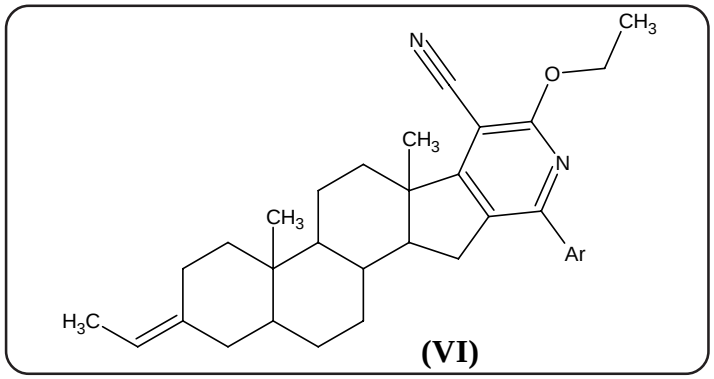


(III)

W. Von Behenburg et al.[29] have synthesized 2-amino-3,6-disubstituted pyridines as antiepileptic agents. V.Scott and E. Joseph[30,31] have prepared 2-amino-3-cyanopyridine derivatives which were found to be useful as antipsoriasis pharmaceuticals. J. A. Vann Allan et al.[32] have prepared fused heterocyclic 3-cyanopyridine (IV). Abu and co-workers[33] have prepared novel fused cyanopyridines (V) for the treatment and preparation of systemic fungal infection.

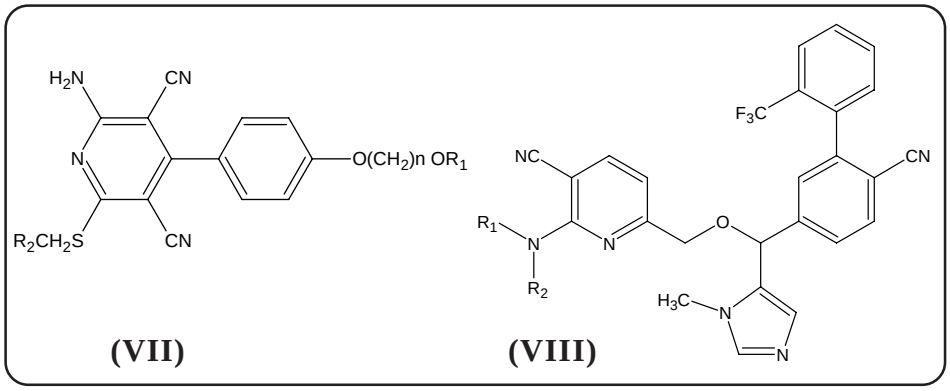


Abdel Galil E. Amr et al.[34] have synthesized heterocyclic pyridine derivatives (VI) fused with steroidal structure. Initially the acute toxicity of the compounds was assayed via the determination of their LD_{50}. Heterocyclic pyridine fused with steroid structure are active as antiinflammatory agents. Henryk foks et al.[35] investigated new 3-cyanopyridine derivatives show an antibacterial activity.



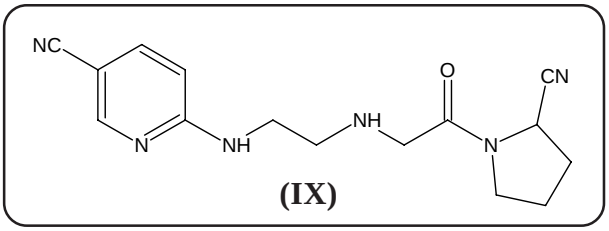
Marco J. L. et al.[36] have synthesized acetylcholinesterase inhibitors. Moustafa M. A. et al.[37] have prepared antibacterial agents. Eduardo H. S. Sousa et al.[38] documented thionicotinamide coordinated to the a model system for the *in vitro* activation of thioamides antituberculosis drugs. Rosentreter Ulrich et al.[39] have synthesized a new cyanopyridine as receptor agonists in the treatment of cardiac or urogenital disease cancer, inflammation, neurodegenerative disease (VII). Gary T. Wang

and co-workers[40] have synthesized of o-trifluoromethylbiphenyl substituted 2-amino-nicotinonitriles (VIII) as inhibitors of farnesyl transferase.



(VII) **(VIII)**

Dipeptidyl peptidase (DPP-IV) inhibition has the potential to become a valuable therapy for diabetes. Edwin B. Villhauer and co-workers[41] 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 (IX), is profiled as a potent, selective and shortacting DPP-IV inhibitor that has excellent oral bioavailability and potent antihyperglycemic activity.



(IX)

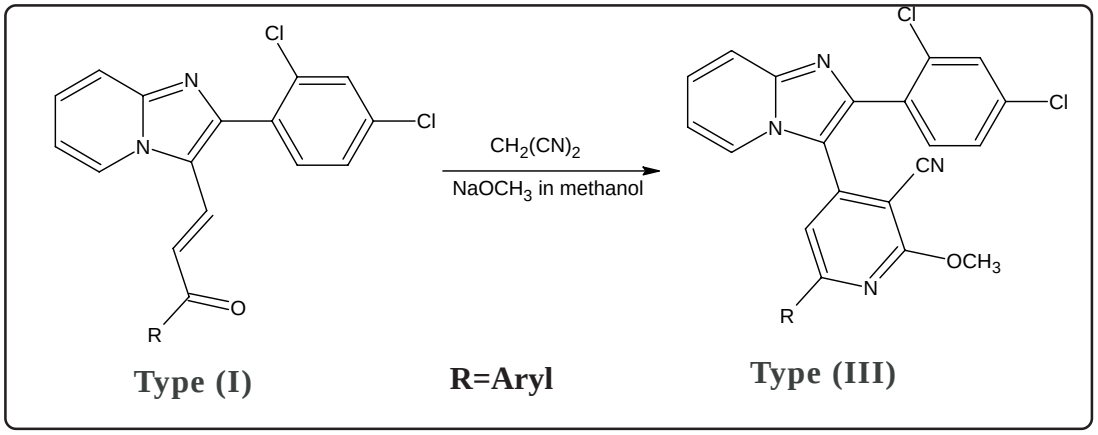
In view of therapeutic activities shown by cyanopyridines, it was contemplated to synthesize some new cyanopyridines in search of agents possessing higher biological activity with least side effect have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 4-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] -2-METHOXY-6-ARYLNICOTINONITRILES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-2-METHOXY-6-ARYL 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 4-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*] pyridin-3-yl]-2-methoxy-6-arylnicotinonitriles derivatives of Type (III) have been prepared, by the cyclocondensation of (2*E*)-3-[2-(2,4-dichlorophenyl) imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones of Type (I) with malononitrile in presence of sodium methoxide.

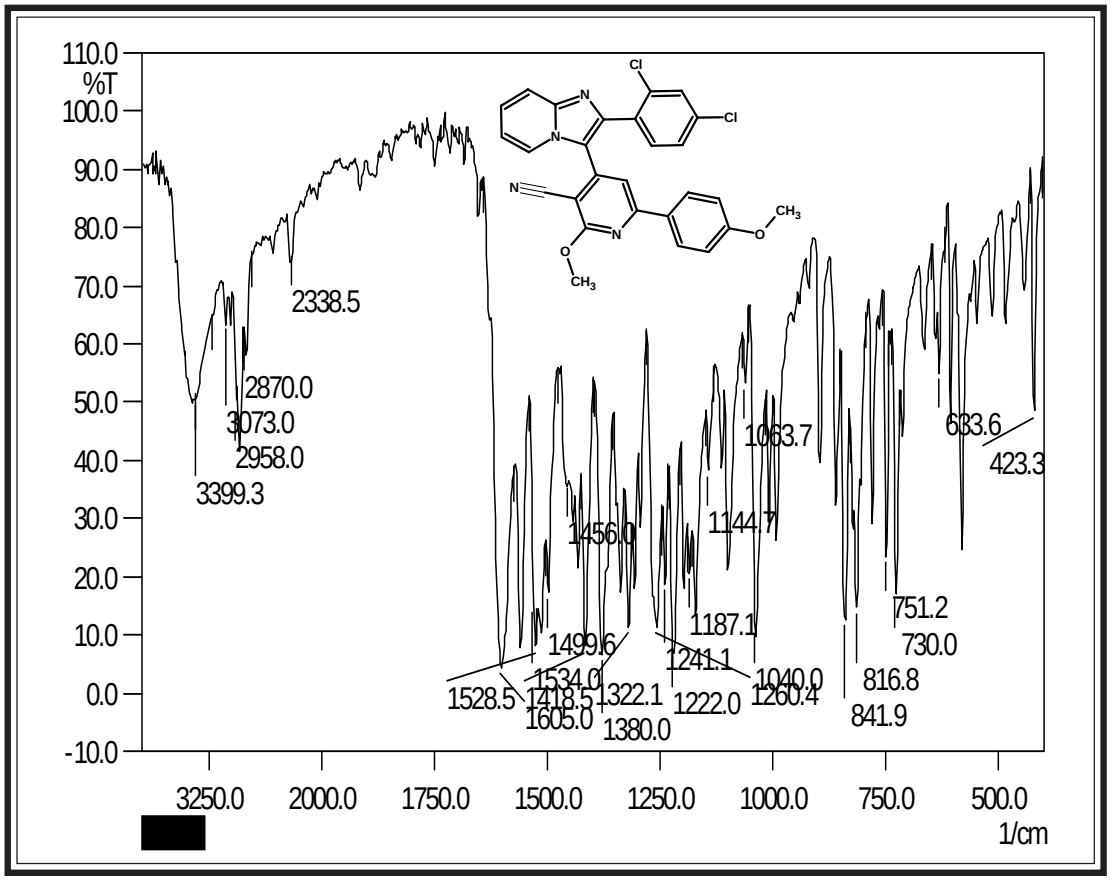


Type (I) **R=Aryl** **Type (III)**

The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^1H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

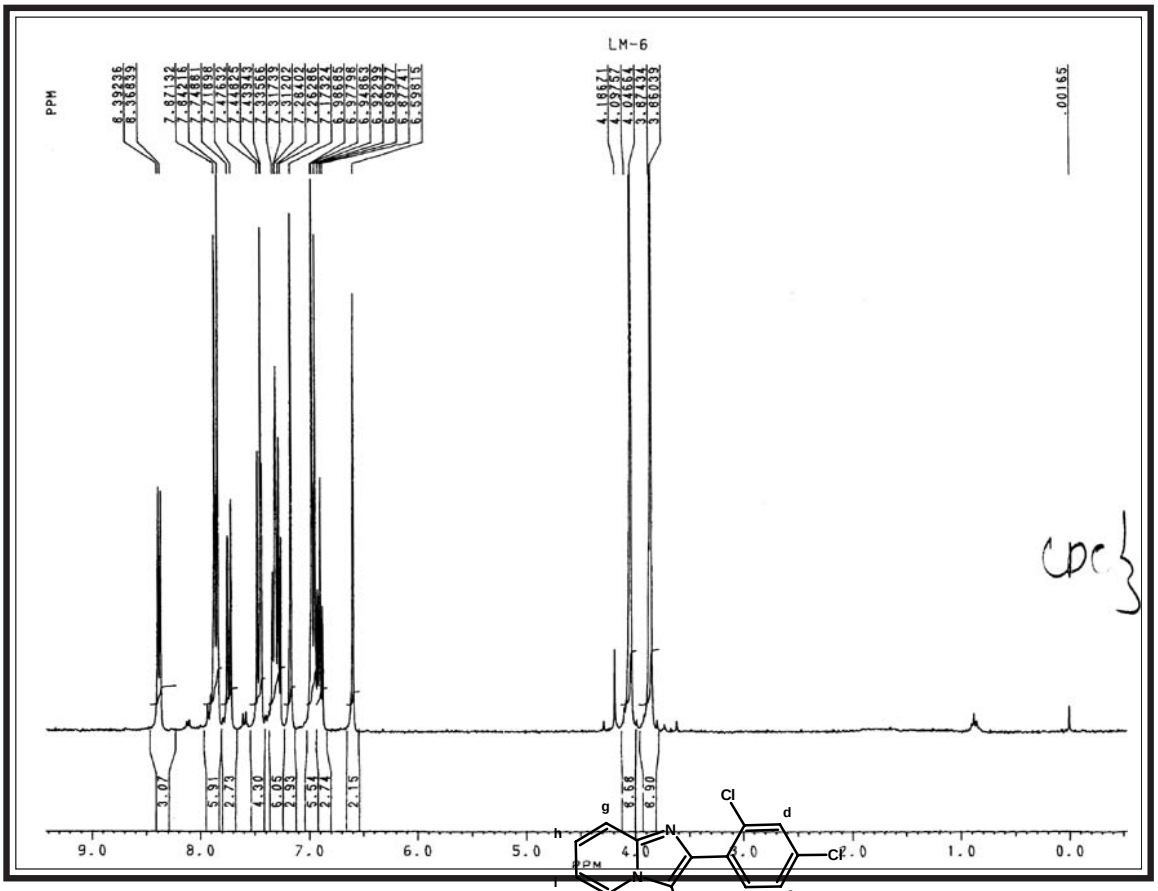
IR SPECTRAL STUDIES OF 4-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a] PYRIDIN-3-YL]-2-METHOXY-6-(METHOXYPHENYL)NICOTINONITRILE



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	42
-CH_3	C-H str. (sym.)	2870	2880-2860	,,
	C-H def. (asym.)	1456	1470-1435	,,
	C-H def. (sym.)	1380	1390-1370	,,
Aromatic	C-H str.	3073	3090-3030	43
	C=C str.	1534	1540-1480	,,
Halide	C-Cl str.	729	800-600	42
Ether	C-O-C str.	1222	1260-1200	,,
Pyridine	C=C str.	1499	1650-1520	43
	C=N str.	1605	1580-1550	,,
Nitrile	C=N str.	2338	2240-2120	,,
Imidazo[1,2-a]	C=N str.	1556	1580-1550	42
pyridine	C-N str.	1040	1220-1020	,,

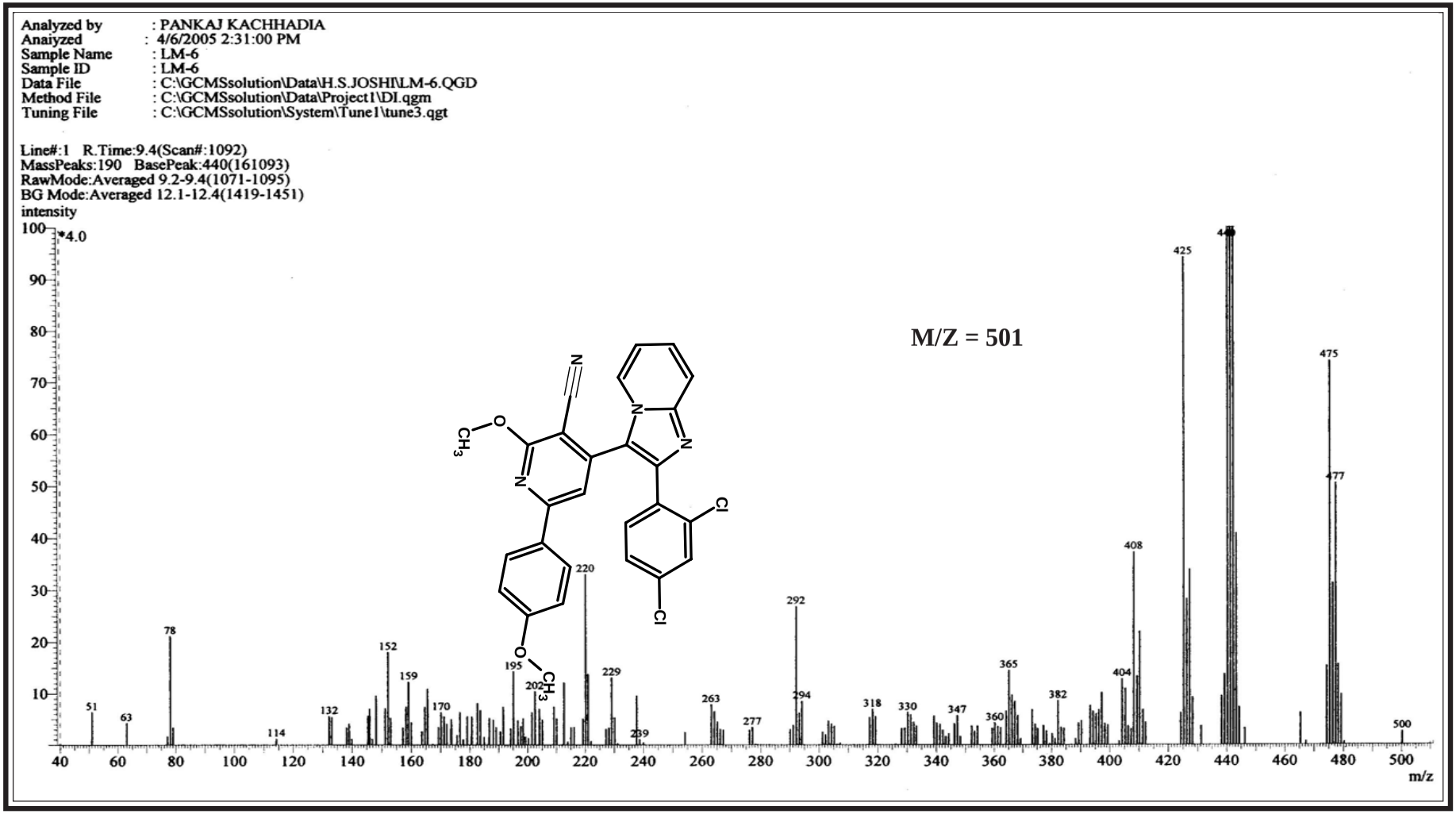
NMR SPECTRAL STUDIES OF 4-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-2-METHOXY-6-(4-METHOXYPHENYL)NICOTINONITRILE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.86	3H	singlet	Ar-OCH_3(a)	-
2	4.04	3H	singlet	Ar-OCH_3(b)	-
3	6.59	1H	singlet	Ar-H(c)	-
4	6.87-6.98	4H	multiplet	Ar-H(g,h,i,j)	-
5	7.33-7.26	1H	dd	Ar-H(e)	J=6.0,J=1.5
6	7.43-7.33	1H	doublet	Ar-H(d)	J=2.7
7	7.74-7.71	2H	doublet	Ar-H(k,k')	J=9.0
8	7.90-7.84	2H	doublet	Ar-H(l,l')	J=9.0
9	8.39-8.36	1H	doublet	Ar-H(f)	J=9.0

TABLE-3 : MASS SPECTRAL STUDIES OF 4-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]-2-METHOXY-6-(METHOXYPHENYL)NICOTINONITRILE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-2-METHOXY-6-ARYL NICOTINONITRILES

(A) Synthesis of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones

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

(B) Synthesis of 4-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-2-methoxy-6-(4-methoxyphenyl)nicotinonitrile

To a solution of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-(4-methoxyphenyl)prop-2-en-1-one(4.23 gm, 0.01 mol), malononitrile (0.60gm, 0.01 mol) in methanol (10ml) and sodium methoxide, which prepared from sodium metal (46mg) and absolute methanol (20ml) was added. The content was heated under reflux with stirring for 12 hr. The reaction mixture was cooled and poured on to crushed ice, the seperated solid was filtered out and crystallized from ethanol. Yield 62%, m.p. 175^{O}C, Anal. Calcd. for $C_{27}H_{18}Cl_2N_4O_2$; Requires: C,64.68; H, 3.62; N, 11.17; Found: C, 64.66 ; H, 3.60; N,11.16%.

Similarly, other 4-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-2-methoxy-6-arylnicotinonitriles were prepared. The physical data are recorded in Table No.3

(C) Biological screening of 4-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-2-methoxy-6-arylnicotinonitriles

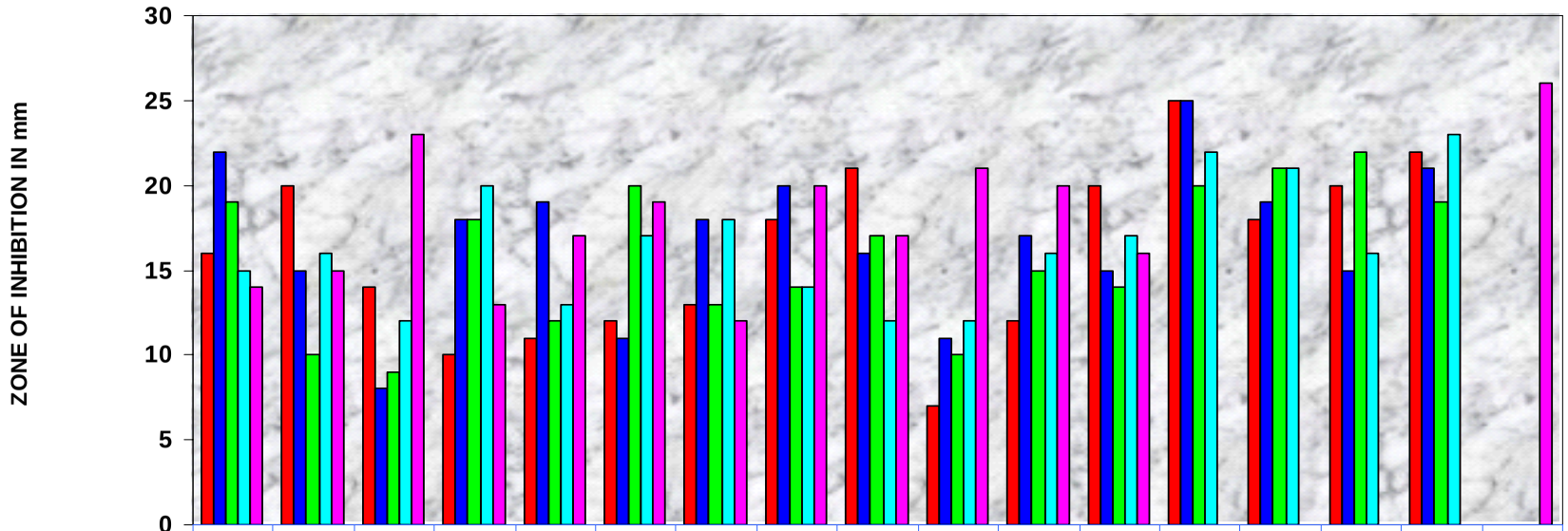
Antimicrobial testing were carried out as described in **(A)** Part-I Section-1 (D). The zones of inhabition of test solution are recorded in Graphical Chart No 3.

TABLE : 3 PHYSICAL CONSTANTS OF 4-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-2-METHOXY-6-ARYLNICOTINONITRILES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
3a	C_6H_5-	$C_{26}H_{16}Cl_2N_4O$	471.33	190	54	11.89	11.87	0.52	S_1
3b	4-CH_3-C_6H_4-	$C_{27}H_{18}Cl_2N_4O$	485.36	187	64	11.54	11.52	0.58	S_2
3c	2-CH_3-C_6H_4-	$C_{27}H_{18}Cl_2N_4O$	485.36	165	53	11.54	11.53	0.44	S_2
3d	2,5-$(CH_3)_2$-C_6H_3-	$C_{28}H_{20}Cl_2N_4O$	499.39	193	68	11.22	11.21	0.46	S_1
3e	4-OCH_3-C_6H_4-	$C_{27}H_{18}Cl_2N_4O_2$	501.36	175	62	11.17	11.16	0.56	S_1
3f	2,4-$(Cl)_2$-C_6H_3-	$C_{26}H_{14}Cl_4N_4O$	540.22	250	57	10.37	10.35	0.52	S_2
3g	4-Cl-C_6H_4-	$C_{26}H_{15}Cl_3N_4O$	505.78	240	66	11.08	11.00	0.50	S_2
3h	4-Br-C_6H_4-	$C_{26}H_{15}BrCl_2N_4O$	550.23	200	61	10.18	10.00	0.53	S_2
3i	4-S-CH_3-C_6H_4-	$C_{27}H_{18}Cl_2N_4OS$	517.43	206	50	10.83	10.81	0.48	S_1
3j	4-F-C_6H_4-	$C_{26}H_{15}Cl_2FN_4O$	489.32	290	58	11.45	11.44	0.56	S_2
3k	3-NO_2-C_6H_4-	$C_{26}H_{15}Cl_2N_5O_3$	516.33	220(d)	62	13.56	13.52	0.53	S_2
3l	4-NO_2-C_6H_4-	$C_{26}H_{15}Cl_2N_5O_3$	516.33	200(d)	64	13.56	13.54	0.49	S_1

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

GRAPHICAL CHART NO. 3 : 4-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-2-METHOXY-6-ARYLNICOTINONITRILES



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	Amoxicilllin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	16	20	14	10	11	12	13	18	21	7	12	20	25	18	20	22	0
S. aureus	22	15	8	18	19	11	18	20	16	11	17	15	25	19	15	21	0
Aerogenes	19	10	9	18	12	20	13	14	17	10	15	14	20	21	22	19	0
Pseudomonas	15	16	12	20	13	17	18	14	12	12	16	17	22	21	16	23	0
A.niger	14	15	23	13	17	19	12	20	17	21	20	16	0	0	0	0	26

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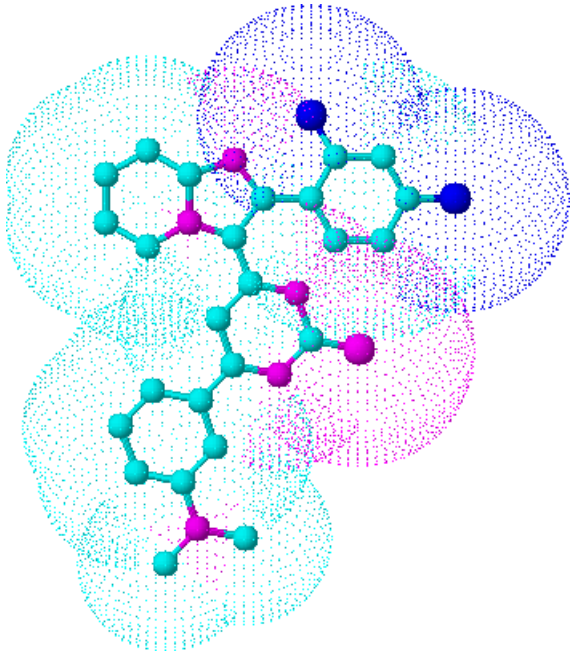
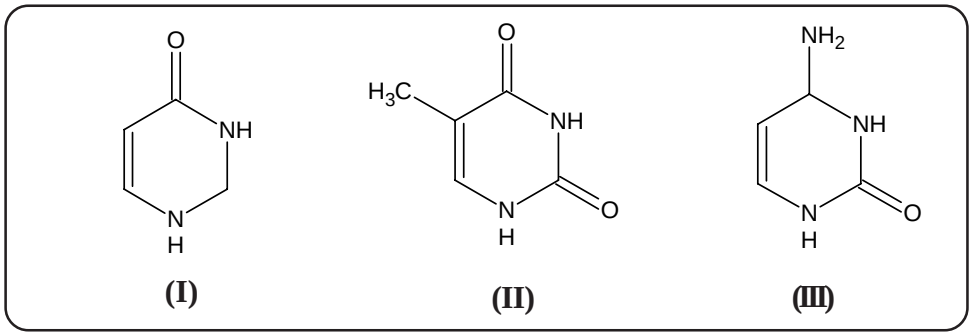


PART - III

STUDIES ON PYRIMIDINES

INTRODUCTION

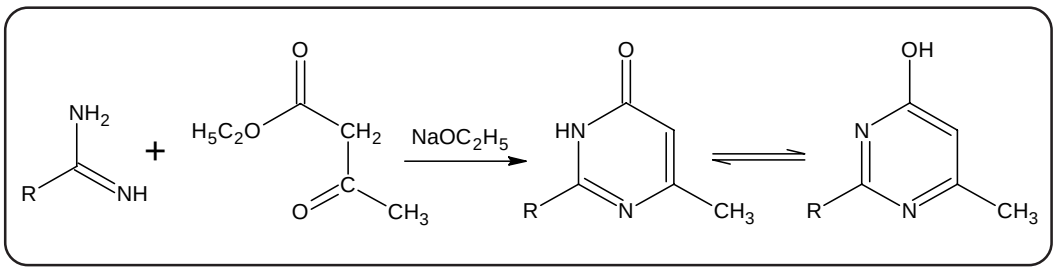
Pyrimidine derivatives like **uracil** (I), **thymine** (II) and **cytosine** (III) occur widely in nature showing remarkable pharmaceutical importance because of their diverse pharmacological activities. Several analogues of nucleic acid have been used as a compound that interfere with the synthesis and function of nucleic acids, an example is fluorouracil which has been used in cancer treatment.



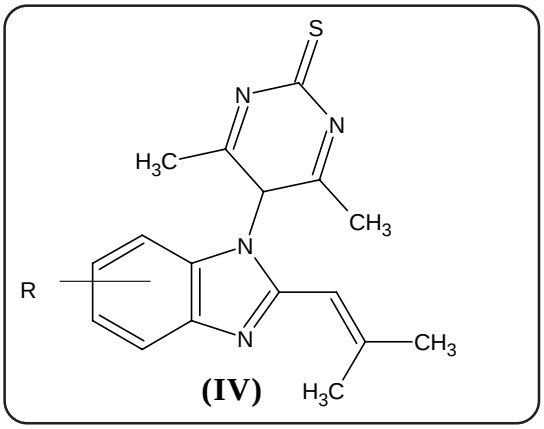
Pyrimidine is considered to be a resonance hybrid of the charged and uncharged cannonical structures, its resonance energy has been found to be less than benzene or pyridine. The naturally occuring pyrimidine derivatives was first isolated by Gabrial and Colman in 1870, and its structure was confirmed in 1953 as 5-β-D-gluco-pyranoside of divicine.

SYNTHETIC ASPECT

A very important general method for preparing pyrimidines is the condensation between a three carbon compounds of the type YCH_2Z, where Y and Z = COR, CO_2R, CN, and compounds having the amidine structure $R(C=NH)NH_2$, where R = OH (urea), SH or SR (thiourea or its s-derivative). The condensation is carried out in the presence of sodium hydroxide or sodium ethoxide. This general reaction may be illustrate by the condensation of acetamidine with ethylacetoacetate to form 4-hydroxy-2,6-dimethylpyrimidine.

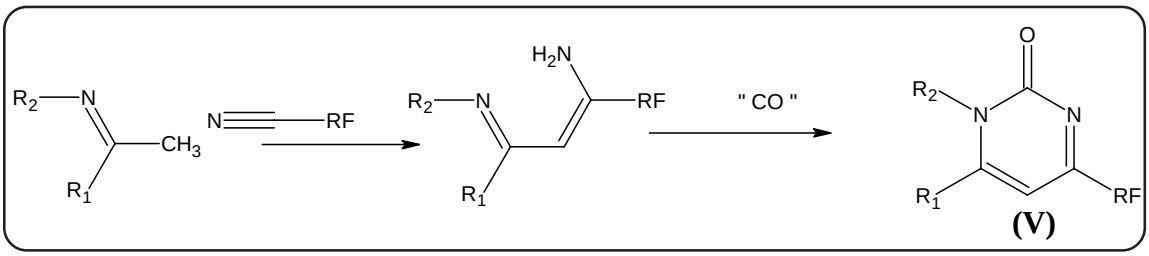


The reaction of chalcone with guanidine hydrochloride in presence of potassium t-butoxide in t-butanol yielded corresponding 2-amino pyrimidine derivatives.[1] Pratibha Sharma and co-workers[2] have investigated 4,6-dimethyl-5-[2-(2-methylprop-1-enyl)-1*H*-benzimidazol-1-yl]pyrimidine-2(5*H*)-thiones (IV) under kinetically controlled phase transfer catalysis conditions.



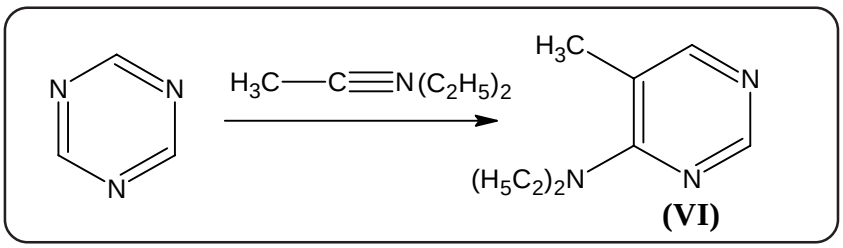
(IV)

The condensation of the azaenolates derived from readily available ketimines with fluorinated nitriles offers an efficient and straightforward entry to new fluorinated 1,3-vinylogous amides. These versatile compounds in turn react with triphosgene to yield new fluorinated pyrimidin-2(1H)-ones (V) in high yields[3].



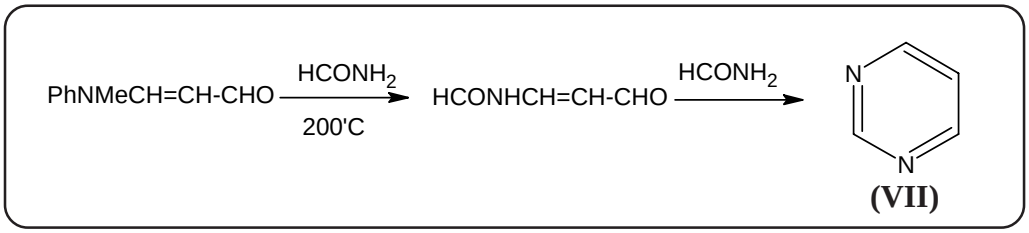
(V)

Fikret karci et al.[4] have synthesized 4-amino-1H-benzo[4,5]imidazo[1,2-a] pyrimidin-2-one by the reaction of 2-aminobenzimidazole with ethylcyanoacetate. Pyrimidines (VI) can also be prepared by cycloaddition reaction of 1,3,5-triazines,which act as electron deficient dienes.



(VI)

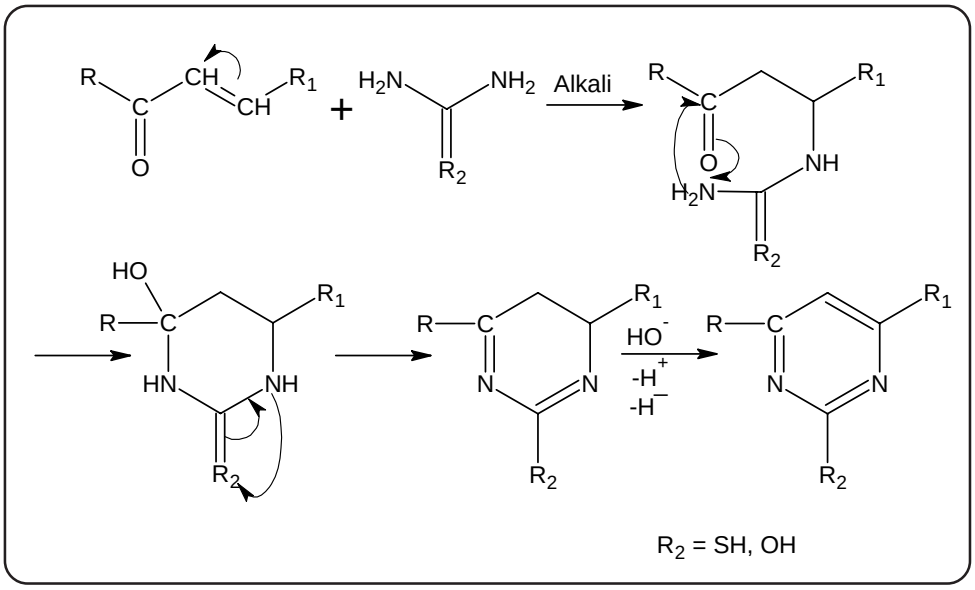
There are many other methods of pyrimidine ring synthesis which are of more limited scope. The reaction of 1,3-dicarbonyl compound or an equivalent reagent with formamide provides a route of several pyrimidine which are unsubstituted at the 2-position.



(VII)

REACTION MECHANISM

The reaction mechanism for the formation of pyrimidine derivatives described as under.

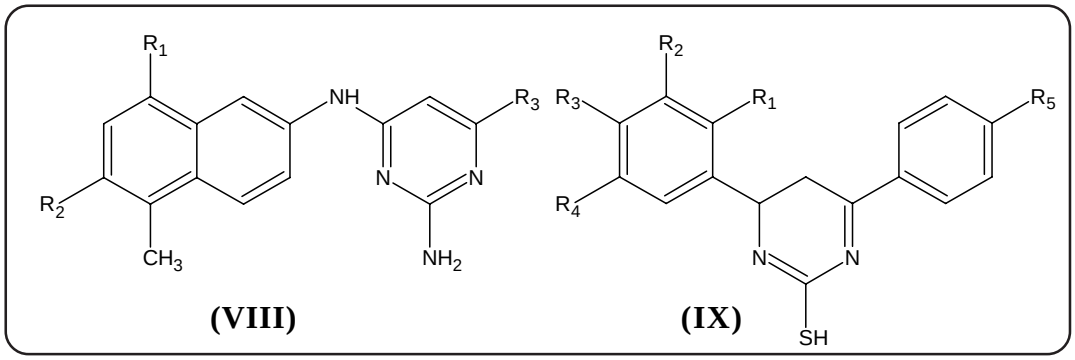


THERAPEUTIC IMPORTANCE

It is revealed from the literature survey that pyrimidine derivatives have been found possessing biological activities reported as under.

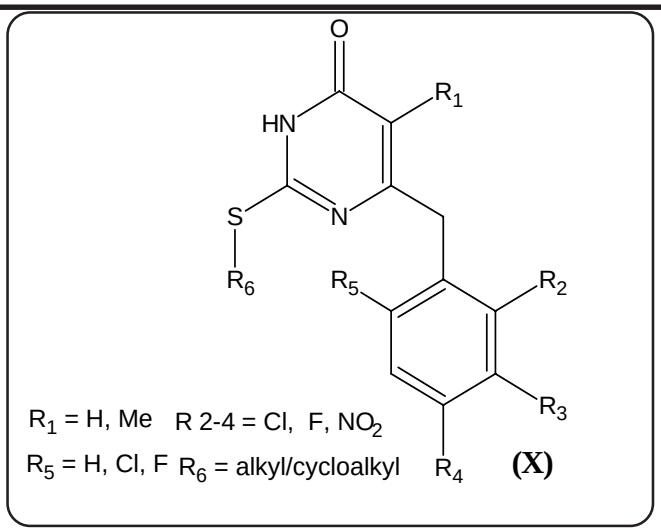
1. Anticonvulsant[5]
2. Antidiabetic[6]
3. Fungicidal[7]
4. Insecticidal[8]
5. Antitubercular[9]
6. Tranquilizing[10]
7. Antibacterial[11]
8. Antihypertensive[12]
9. Analgesic[13]
10. Diuretic[14]

Patil L. R. et al.[15] have synthesized some new pyrimidines bearing paracetamol and imidazolyl moieties. B. J. Ghiya et al.[16] synthesized some mercapto pyrimidine derivatives (VIII) and screened for their anticancer, antitubercular and anti HIV activities.Kaplina N. V. and co-workers[17]have shown herpes inhibiting activity of some mercapto pyrimidine derivatives (IX).



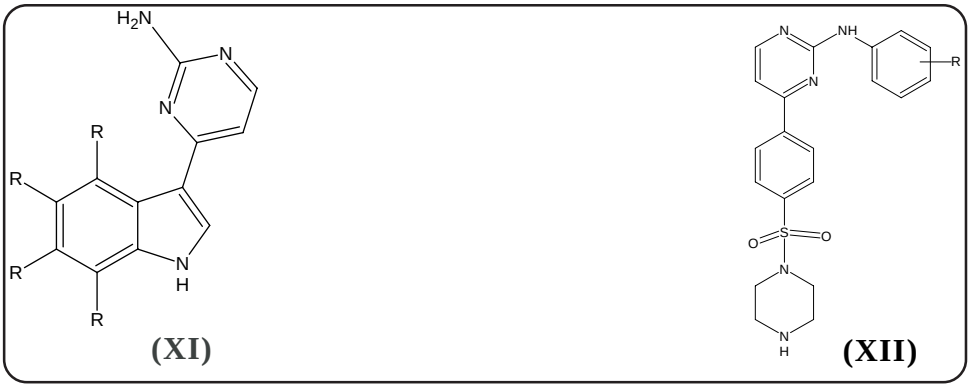
(VIII) **(IX)**

Paolo La Colla et al.[18] have synthesized various 5-alkyl-2-(alkyl/cycloalkkyl thio)-6-(2,6-dichloro/2,6-difluoro phenylmethyl)-3,4-dihydropyrimidin-4(3H)-ones (X) and tested as anti-HIV-1 agents in both cell-based and enzyme (recombinant reverse transcriptase, rRT)assay.



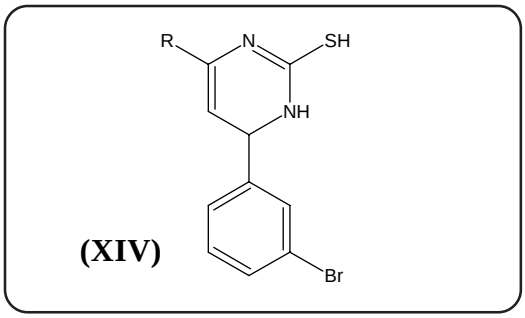
(X)

Marie Gompel and co-workers[19] showed that pyrimidine derivatives (XI) inhibit various protein kinases such as cyclin-dependent kinases, glycogen synthase kinase-3, cyclic nucleotide-dependent kinases and casein kinase. Alistair H et al.[20] have synthesized a novel series of aminopyrimidine IKK-2 inhibitors which shows excellent *in vitro* inhibition of this enzyme and good selectivity over the IKK1 isoform. The relative potency and selectivity of these compounds has been rationalized using QSAR and structure-based modelling (XII).



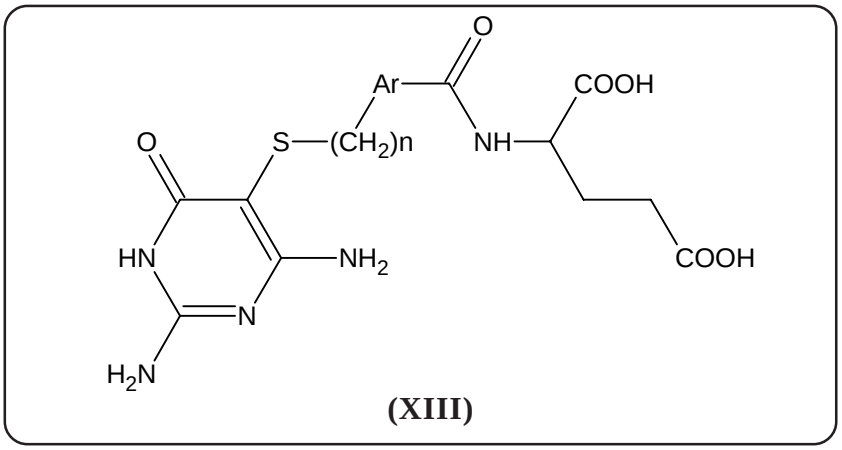
(XI) **(XII)**

H. S. Joshi et al.[21] have sythesized some new pyrimidines (XIV) as antitubercular and antimicrobial agents.



(XIV)

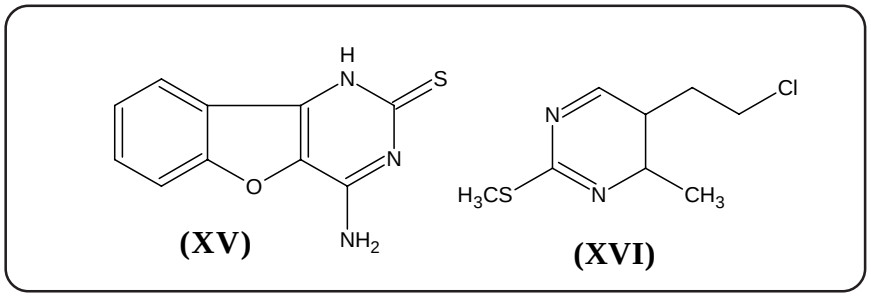
Michael D. Varney and co-workers[22] have synthesized and evaluated 5-thia-2,6-diamino-4 (3H)-oxopyrimidines (XIII) as potent inhibitors of Glycinamide Ribonucleotide Transformylase with potent cell growth inhibition.



(XIII)

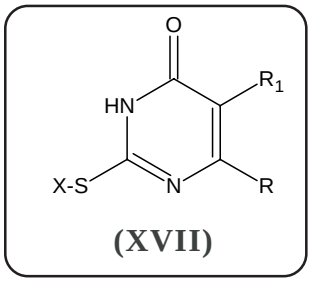
Moreover, Chaudhari Bipinchandra et al.[23] prepared N6-(2-aminopyrimidin-4-yl)-quinoline-4,6-diamine as N-type calcium channel antagonists for the treatment of pain. Devi E. Sree and co-workers[24] have prepared pyrimidine derivatives and tested for antimicrobial activity. Kovalenko A. L.[25] synthesized and reported antifungal activity of pyrimidine derivatives. Shiv P. Singh and co-workers[26] synthesized 4-(4-pyrazolyl)-2-aminopyrimidines and tested them for their antimicrobial activity.

S. S. Sangapure and A. M. Mulagi[27] have tested the antimicrobial activity of benzofuro[3,2-d]pyrimidine derivatives (XV). El Sayed[28] and A. M. Badaway have synthesized alkylated substituted mercapto pyrimidine derivatives (XVI) and studied their anticancer and antineoplastic activity. H. Y. Moustafa[29] have reported some pyrimidine derivatives and studied their biological activities.



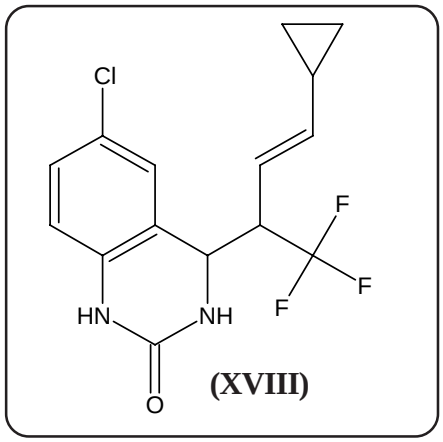
(XV) **(XVI)**

Viney Lather and co-workers[30] have been proposed to predict the anti-HIV activity of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines (XVII). These models are capable of providing lead structures for development of potent but safe anti-HIV agents.



(XVII)

Whittingham J. L. et al.[31] have described pyrimidine ring as a platform for antimalarial drug. Han G. Z. et al.[32] documented the pyrimidine derivatives as anticancer actions of 2-methoxyestradiol and microtubule-disrupting agents in human breast cancer. Tack D. K. et al.[33] reported anthracycline *vs* nonanthracycline therapy for breast cancer. Cano-Soldado P. et al.[34] have described pyrimidine nucleus as an inhibitors of HIV-1 reverse transcriptase. Gompel M. et al.[35] have isolated pyrimidine derivatives,a new family of protein kinase inhibitors from the ascidian aplidium meridianum. Junmei Wang et al.[36] have prepared pyrimidine (XVIII) as HIV-1 Reverse Transcriptase.



(XVIII)

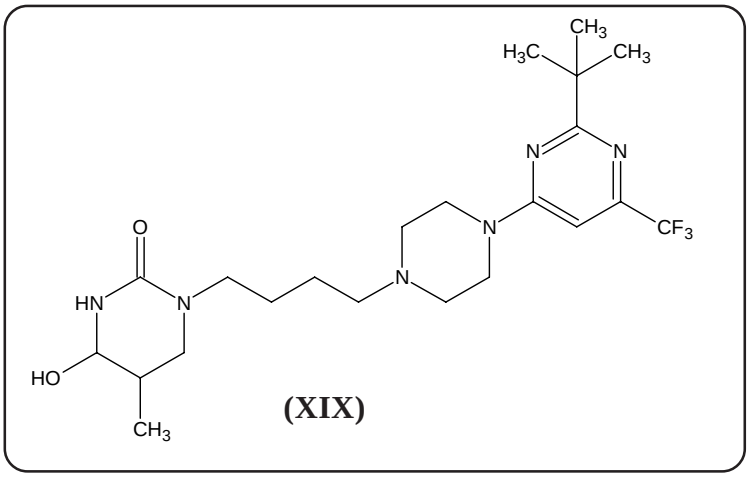
Shimizu T. co-workers[37] have described N3-substituted pyridine and related pyrimidine nucleosides as antinociceptive effects in mice. Sanmartin C. et al.[38] have prepared new symmetrical derivatives as cytotoxic agents and apoptosis inducers. Agarwal A. et al.[39] have synthesized 2,4,6-trisubstituted pyrimidine derivatives as

pregnancy interceptive agents.

Mai A. et al.[40] have synthesized 5-alkyl-2-alkylamino-6-(2,6-difluorophenylalkyl)-3,4-dihydropyrimidin-4(3H)-ones, a new series of potent, broad-spectrum non-nucleoside reverse transcriptase inhibitors belonging to the DABO family. Yamamoto I. et al.[41] have reported some oxopyrimidines searching for the novel antagonist or agonist of barbiturates to the sleep mechanism based on the uridine receptor. Huang Y.L. et al.[42] have synthesized non classical antifolates, 5-(N-phenylpyrrolidin-3-yl)-2,4,6-triaminopyrimidines and 2,4-diamino-6(5H)-oxopyrimidines as antitumor activity.

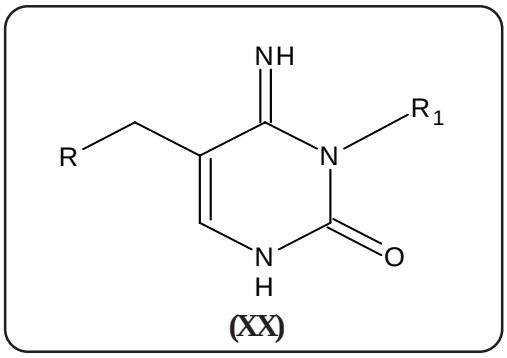
Shigeta S. et al.[43] have been synthesized 5-alkyl-2-thiopyrimidine nucleoside analogues and examined for antiviral activities against Herps Simplex virus (HSV), Varicella-Zoster virus (SZV) and Human Cytomegalo virus (HCMV).

Herve Ganeste and co-workers[44] synthesized substituted 1H-pyrimidin-2-one (XIX) with selective dopamine D_3-receptor antagonists activity.



(XIX)

Sanjay batra et al.[45] have synthesized several 1-(2-cyano-3-aryl-allyl)-3-urea by the reaction between allylamines generated from Baylis-Hilman acetates and substituted isocyanates and isothiocyanate. Further, their cyclization in the presence of a base led to the formation of 5-arylmethyl-4-imino-3-aryl-3,4-dihydro-1H-pyrimidin-2-ones (XX). All the compounds were tested for their antibacterial activity.



(XX)

2-(Arylcarbonylmethyl)thio-6-alpha-naphthylmethyl derivatives of dihydro alkoxy benzyl oxopyrimidines[46] (DABO) were newly found to exhibit activity against both HIV-1 and HIV-2. The compounds were evaluated for their *in vitro* anti-HIV activity in MT-4 cells.

Looking to the diversified activities exhibited and in continuation of our work on the synthesis of biologically active heterocycles, the synthesis and biological screening of pyrimidine derivatives have been described as under.

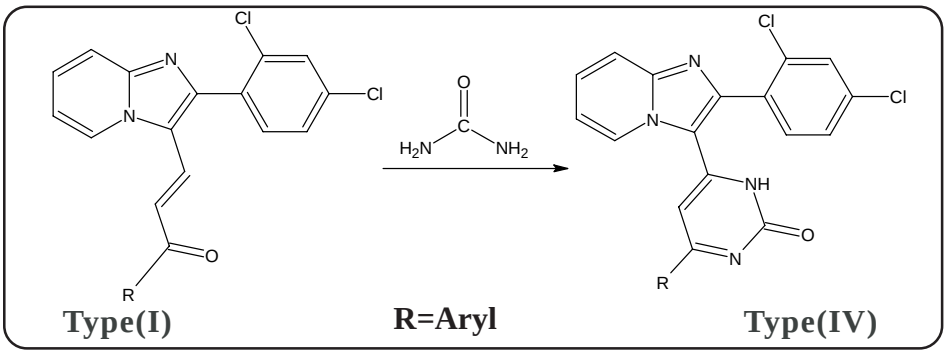
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-ONES

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-THIONES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-ONES

In the past years considerable evidence has been accumulated to demonstrate the efficiency of pyrimidinones. 6-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-ones of Type (VII) have been prepared by the condensation of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones of Type (I) with urea in presence of catalytic amount of conc. HCl as shown under.

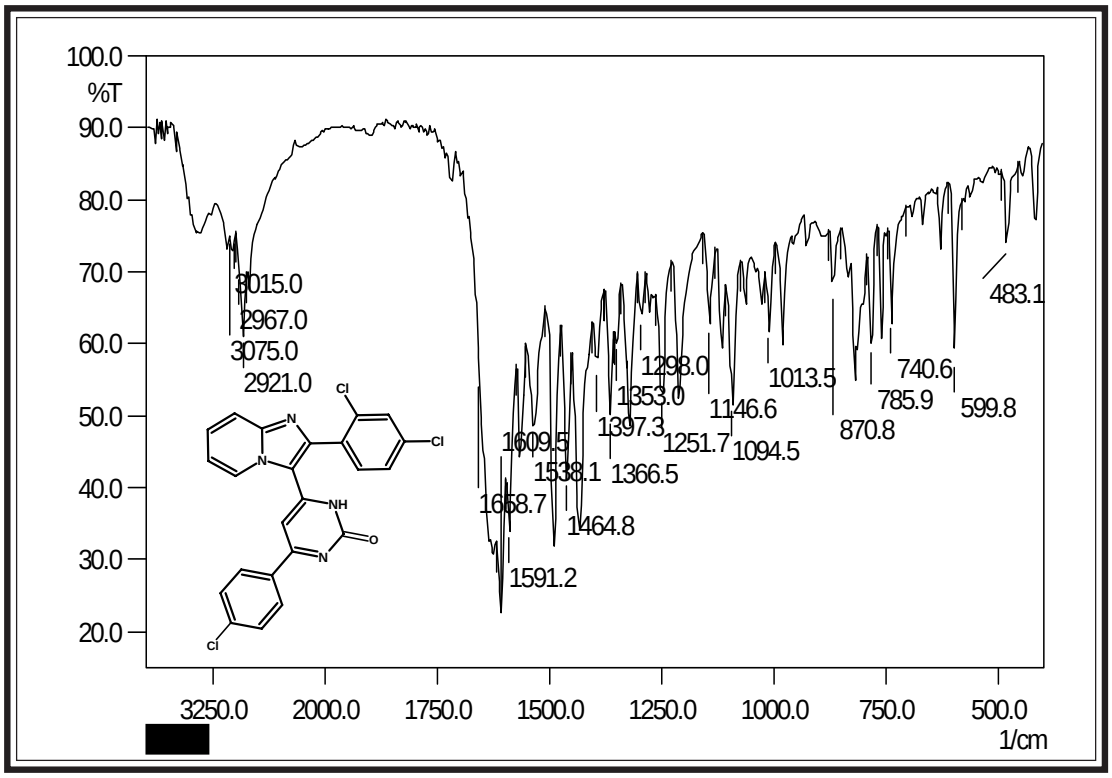


Type(I) **R=Aryl** **Type(IV)**

The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

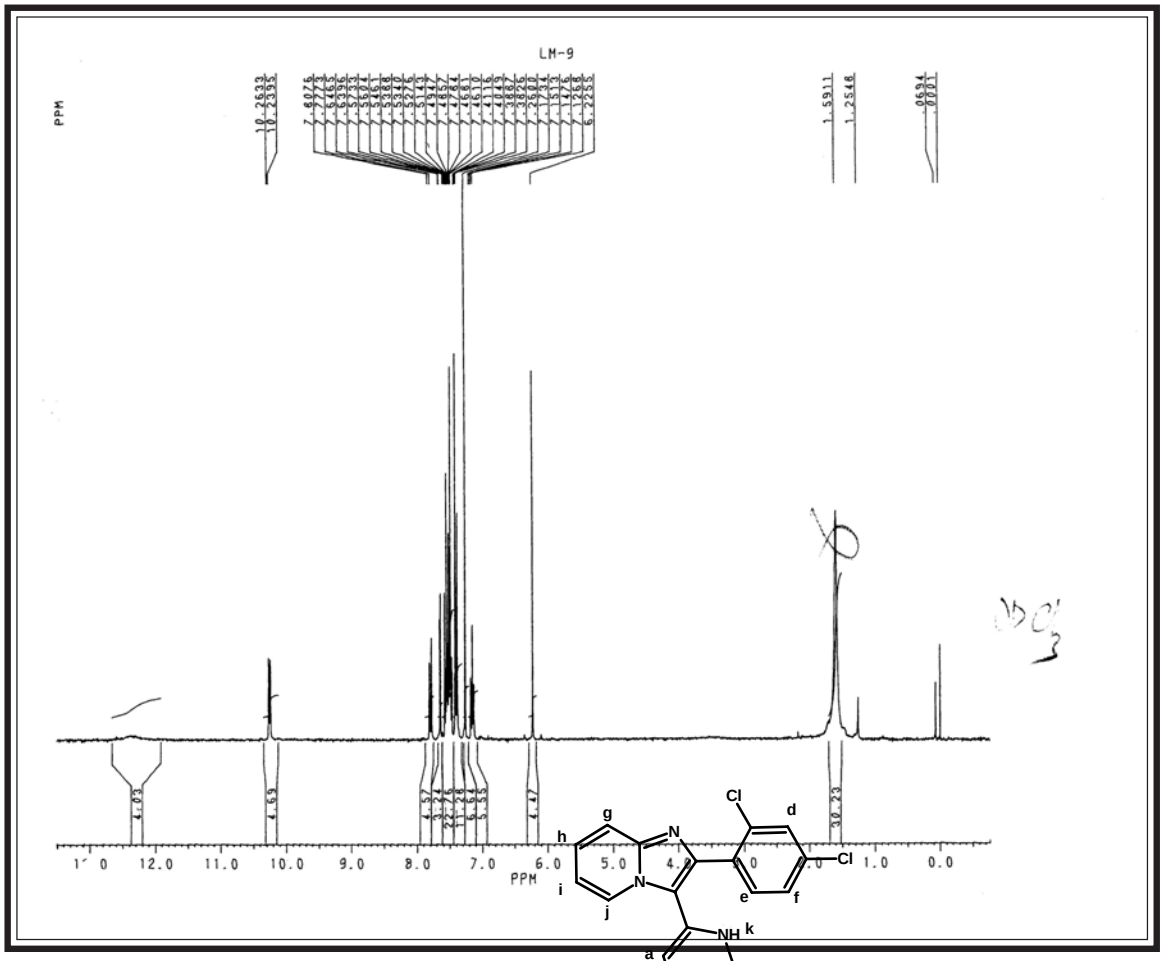
IR SPECTRAL STUDIES OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-(4-CHLOROPHENYL)PYRIMIDIN-2(1H)-ONE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3075	3090-3030	48
	C=C str.	1464	1540-1480	,,
		1094	1125-1090	,,
		1013	1070-1000	,,
Halide	C-Cl str.	785	800-600	47
Vinyl	CH=CH str.	3015	3050-3000	48
oxopyri.	C=O str.	1658	1672-1652	,,
imidazo[1,2-a]	C=N str.	1591	1612-1593	47
pyridine	C-N str.	1146	1220-1020	,,

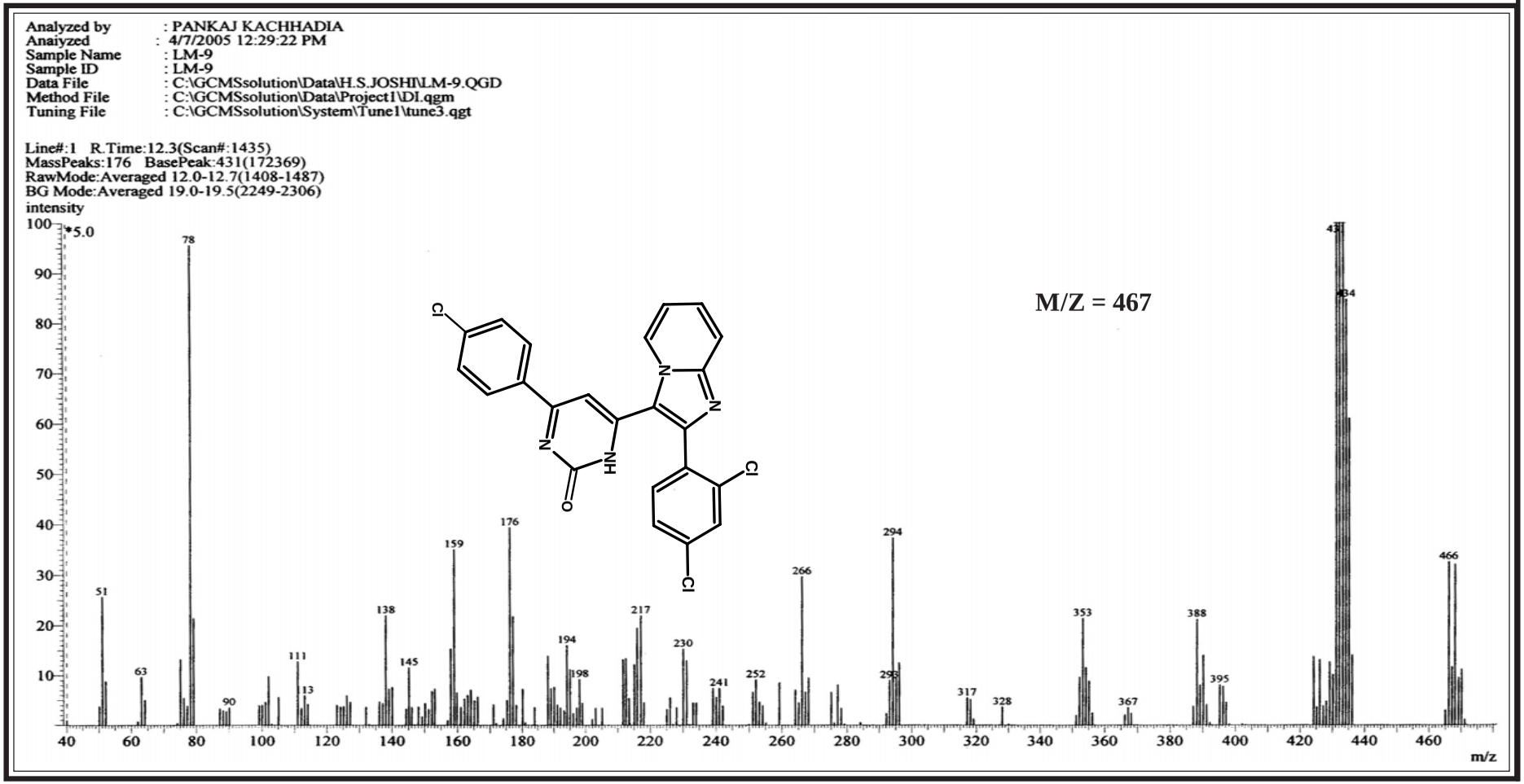
NMR SPECTRAL STUDIES OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-(4-CHLOROPHENYL)PYRIMIDIN-2(1H)-ONE



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

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	6.2	1H	singlet	Ar-CH(a)	-
2	7.14	1H	dd	Ar-H(f)	J=6.0,J=1.2
3	7.35	4H	dd	Ar-H(b,b',c,c')	J=9.0
4	7.52	4H	multiplet	Ar-H(g,h,i,j)	-
5	7.65	1H	doublet	Ar-H(d)	J=3.0
6	7.80	1H	doublet	Ar-H(e)	J=9.0
7	10.3	1H	singlet	Ar-NH(k)	-

TABLE-4 : MASS SPECTRAL STUDIES OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-(4-CHLOROPHENYL)PYRIMIDIN-2(1H)-ONE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-ONES

(A) Synthesis of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones

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

(B) Synthesis of 6-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-(4-chlorophenyl)pyrimidin-2(1H)-one

To a solution of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-(4-chlorophenyl)prop-2-en-1-one (4.27gm, 0.01 mol) and urea (0.60gm, 0.01 mol) in ethanol (15 ml) was refluxed in presence of alcoholic KOH for 12 hr. The excess solvent was distilled off and the residue was neutralized with dilute HCl,thus the separated solid was filtered out and crystallized from ethanol. Yield 67 %, m.p. 260^{o}C Anal. Calcd. for $C_{23}H_{13}Cl_3N_4O$ Requires: C, 59.06; H, 2.80; N, 11.98 % Found: C, 59.00; H, 2.79, N, 11.97 %.

Similarly, other 6-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-ones were prepared.The physical data are recorded in Table No. 4.

(C) Biological screening of 6-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-ones

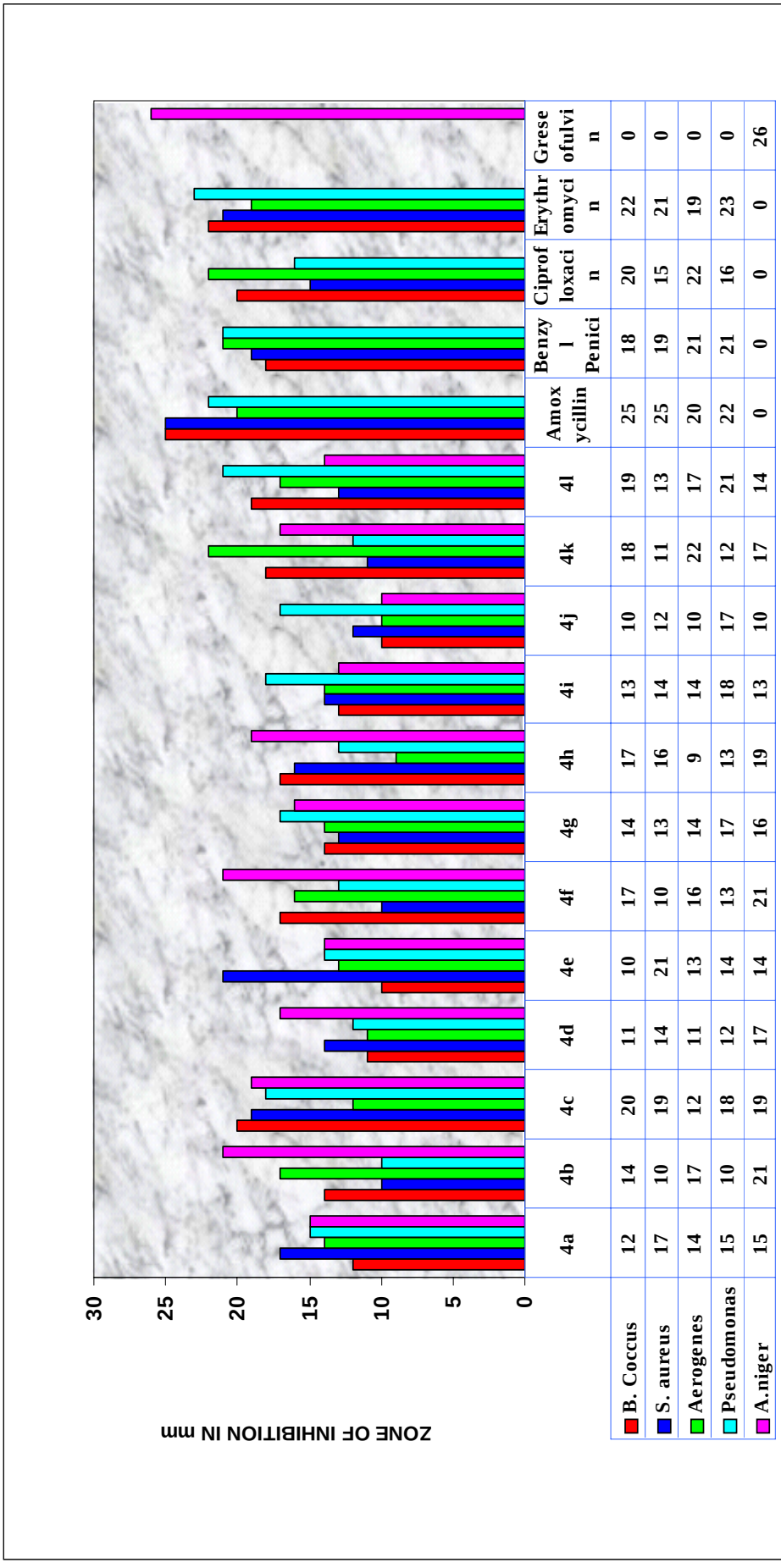
Antimicrobial testing were carried out as described in **(A)** Part-I, Section-I (D). The zones of inhibition of test solution are reported in Graphical Chart No. 4.

TABLE : 4 PHYSICAL CONSTANTS OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYL PYRIMIDIN-2(1H)-ONES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
4a	C_6H_5-	$C_{23}H_{14}Cl_2N_4O$	433.29	180	68	12.93	12.92	0.58	S_2
4b	4-CH_3-C_6H_4-	$C_{24}H_{14}Cl_2N_4O$	447.31	165	52	12.53	1252	0.50	S_1
4c	2-CH_3-C_6H_4-	$C_{24}H_{14}Cl_2N_4O$	447.31	169	58	12.53	12.51	0.54	S1
4d	2,5-$(CH_3)_2$-C_6H_3-	$C_{25}H_{18}Cl_2N_4O$	461.34	155	60	12.14	12.13	0.44	S_2
4e	4-OCH_3-C_6H_4-	$C_{24}H_{16}Cl_2N_4O_2$	463.31	195	64	12.09	12.00	0.55	S_2
4f	2,4-$(Cl)_2$-C_6H_3-	$C_{23}H_{12}Cl_4N_4O$	502.17	272	72	11.16	11.15	0.53	S_1
4g	4-Cl-C_6H_4-	$C_{23}H_{13}Cl_3N_4O$	467.73	260	67	11.98	11.97	0.48	S_2
4h	4-Br-C_6H_4-	$C_{23}H_{13}BrCl_2N_4O$	512.18	220	48	10.94	10.93	0.52	S_1
4i	4-S-CH_3-C_6H_4-	$C_{24}H_{16}Cl_2N_4OS$	479.38	160	66	11.69	11.67	0.46	S_1
4j	4-F-C_6H_4-	$C_{23}H_{13}Cl_2FN_4O$	451.27	245	64	12.42	12.40	0.49	S_2
4k	3-NO_2-C_6H_4-	$C_{23}H_{13}Cl_2N_5O_3$	478.28	280	59	14.64	14.62	0.57	S_2
4l	4-NO_2-C_6H_4-	$C_{23}H_{13}Cl_2N_5O_3$	478.28	285	61	14.64	14.63	0.42	S_1

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

GRAPHICAL CHART NO. 4 : 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-ONES

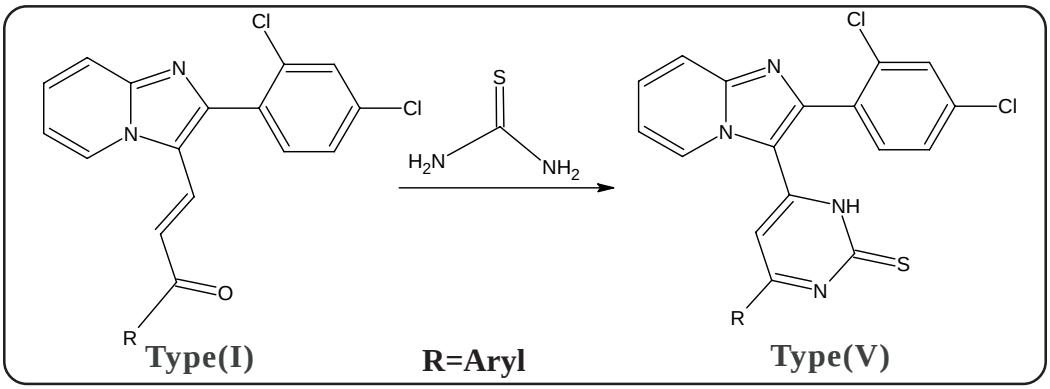


	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Amoxycillin	Benzyl Penici	Ciprofloxacin	Erythromycin	Griseofulvin
B. Coccus	12	14	20	11	10	17	14	17	13	10	18	19	25	18	20	22	0
S. aureus	17	10	19	14	21	10	13	16	14	12	11	13	25	19	15	21	0
Aerogenes	14	17	12	11	13	16	14	9	14	10	22	17	20	21	22	19	0
Pseudomonas	15	10	18	12	14	13	17	13	18	17	12	21	22	21	16	23	0
A.niger	15	21	19	17	14	21	16	19	13	10	17	14	0	0	0	0	26

SECTION - II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-THIONES

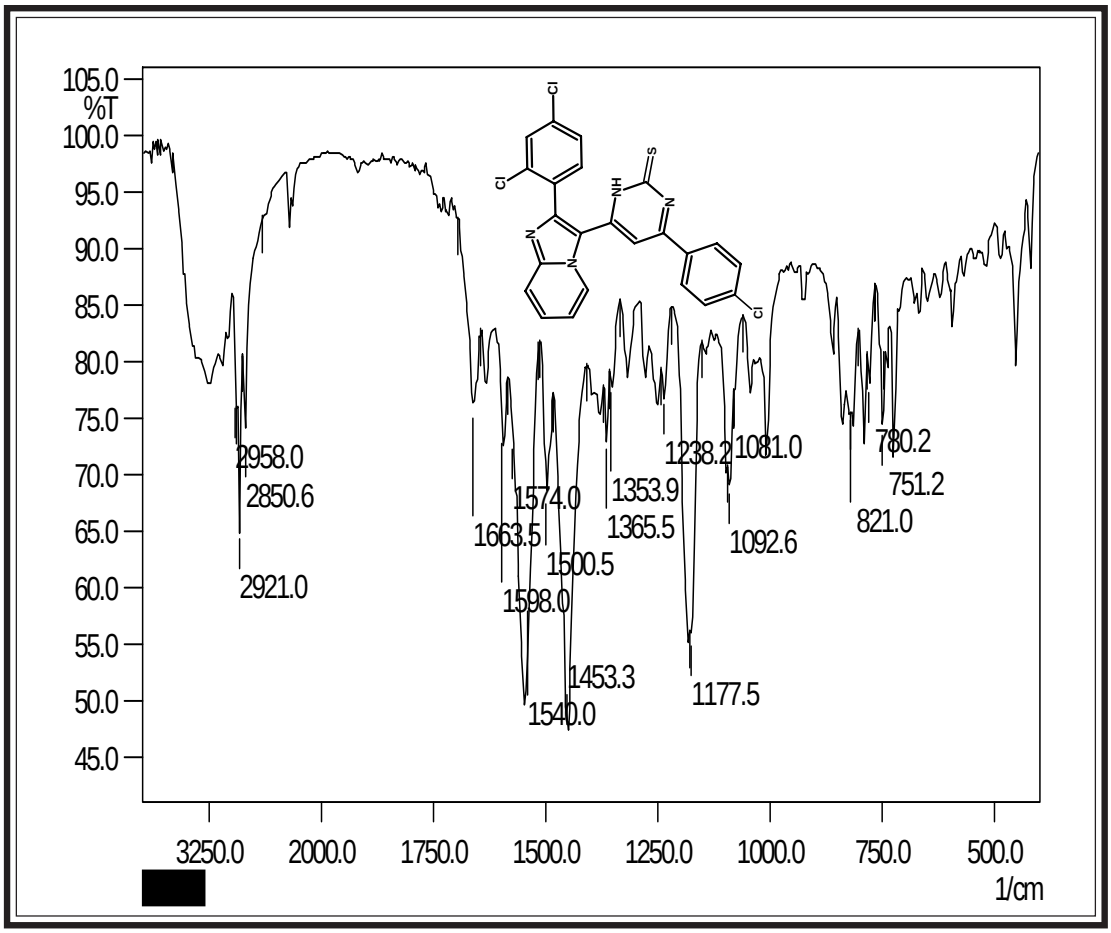
Thiopyrimidines represent one of the most active classes of compounds possessing a wide spectrum of biological activities, such as significant *in vitro* activity against unrelated DNA and RNA viruses including polio viruses, diuretic, antitubercular etc. These valid observations led us to synthesize 6-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-thiones of Type (VIII) by cyclocondensation of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones of Type (I) and thiourea in presence of HCl as catalyst.



The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

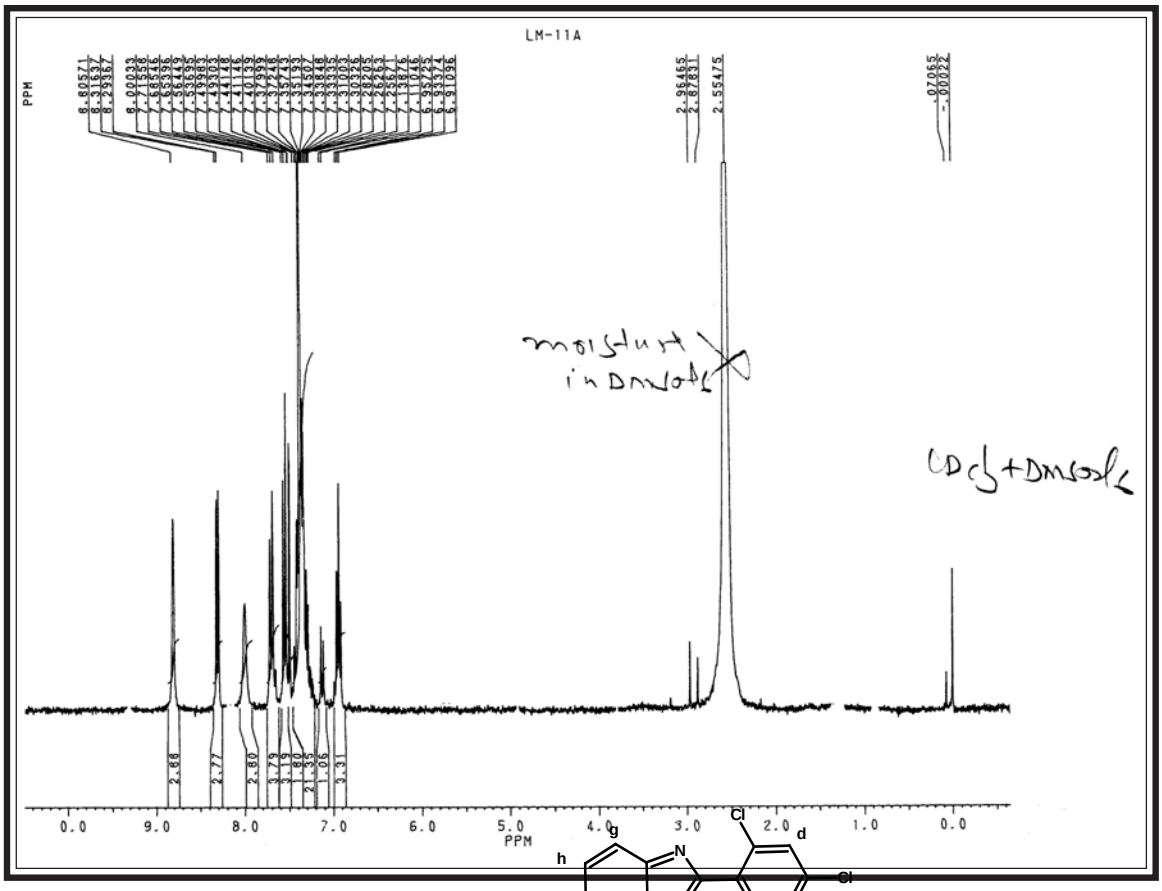
IR SPECTRAL STUDIES OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO [1,2-a]PYRIDIN-3-YL]-4-(4-CHLOROPHENYL)PYRIMIDIN-2(1H)-THIONE

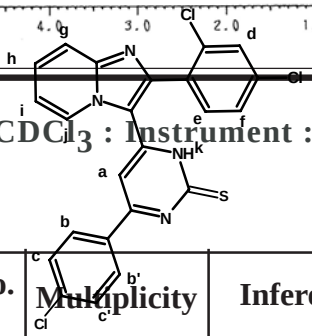


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3045	3090-3030	47
	C=C str.	1500	1540-1480	,,
	C-H i.p. def..	1081	1125-1090	,,
	C-H o.o.p. def..	821	835-810	,,
Thiopyrimidine	C=S str.	1574	1590-1550	48
Imidazo[1,2,-a]	C=N str.	1598	1612-1593	,,
pyrimidine	C=C str.	1540	1590-1550	,,
	C-N str.	1092	1220-1020	,,
	C-Cl str.	780	800-600	47

NMR SPECTRAL STUDIES OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO [1,2-a]PYRIDIN-3-YL]-4-(4-CHLOROPHENYL)PYRIMIDIN-2(1H)-THIONE

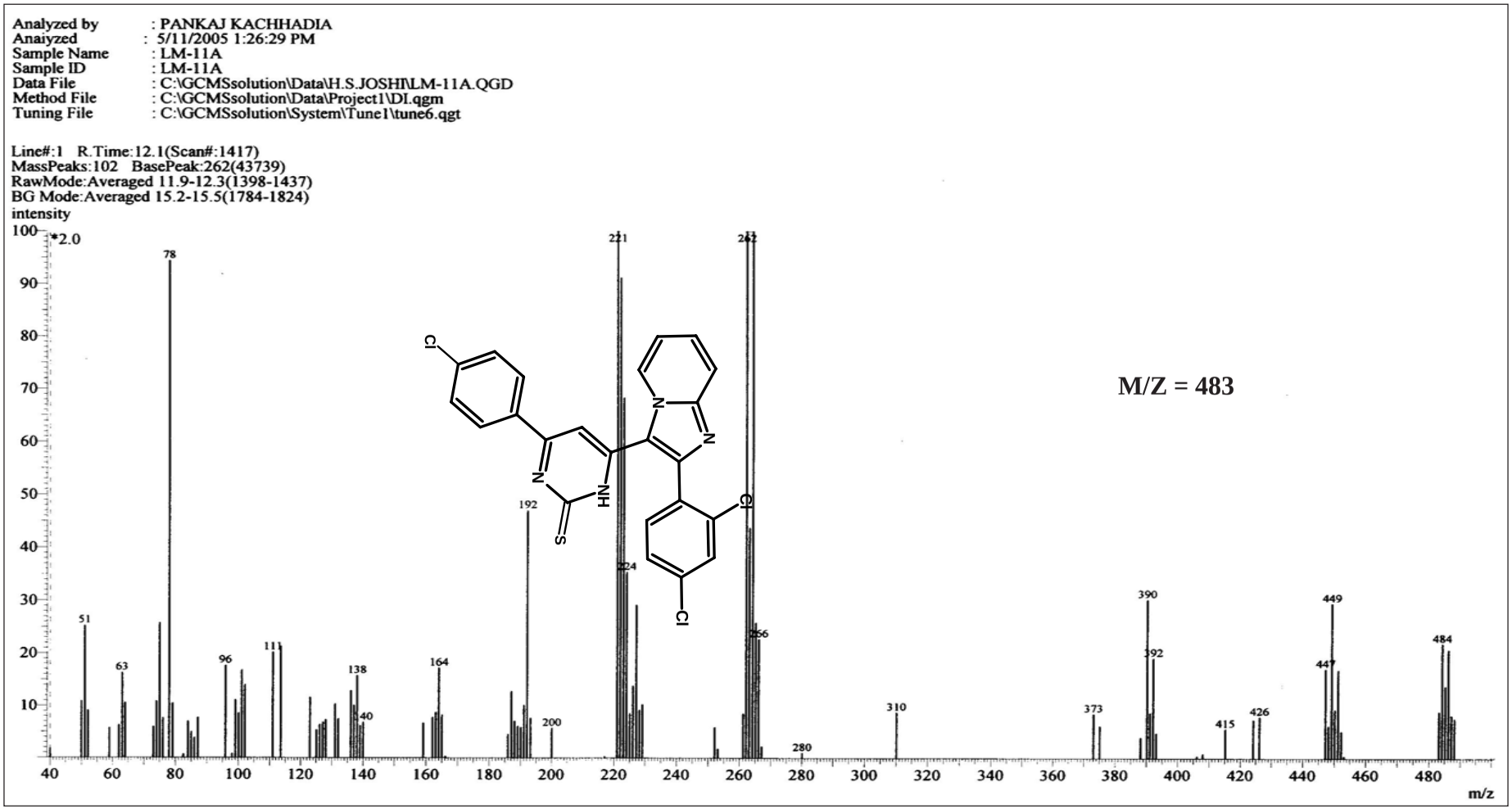




Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	6.90	2H	doublet	Ar-CH(b,b')	J=8.1
2	7.12	2H	doublet	Ar-H(c,c')	J=7.5
3	7.32	4H	multiplet	Ar-H(g,h,i,j)	-
4	7.50	1H	dd	Ar-H(f)	J=9.0,J=1.8
5	7.70	1H	doublet	Ar-H(e)	J=9.0
6	8.00	1H	singlet	Ar-H(a)	-
7	8.3	1H	doublet	Ar-CH(d)	J=6.0
8	8.8	1H	singlet	Ar-NH(k)	-

TABLE-5 : MASS SPECTRAL STUDIES OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]-4-(4-CHLOROPHENYL)PYRIMIDIN-2(1H)-THIONE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-THIONES

(A) Synthesis of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones

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

(B) Synthesis of 6-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-(4-chlorophenyl)pyrimidin-2(1H)-thione

A mixture of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-(4-chlorophenyl)prop-2-en-1-one (4.27gm, 0.01 mole) and thiourea (0.78gm, 0.01 mol) in methanol (15 ml) was refluxed on oil-bath in presence of alcoholic KOH for 10 hr. The solvent was distilled off and the residue was neutralized with dilute HCl, the separated solid was filtered out and crystallized from ethanol. Yield 71 %, m.p. 200°C Anal. Calcd. for $C_{23}H_{13}Cl_3N_4S$ Requires: C, 57.10; H, 2.71; N, 11.58 % Found: C, 57.00; H, 2.70, N, 11.57 %.

Similarly, other 6-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-thiones were prepared. The physical data are recorded in Table No. 5.

(C) Biological screening of 6-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-4-arylpyrimidin-2(1H)-thiones

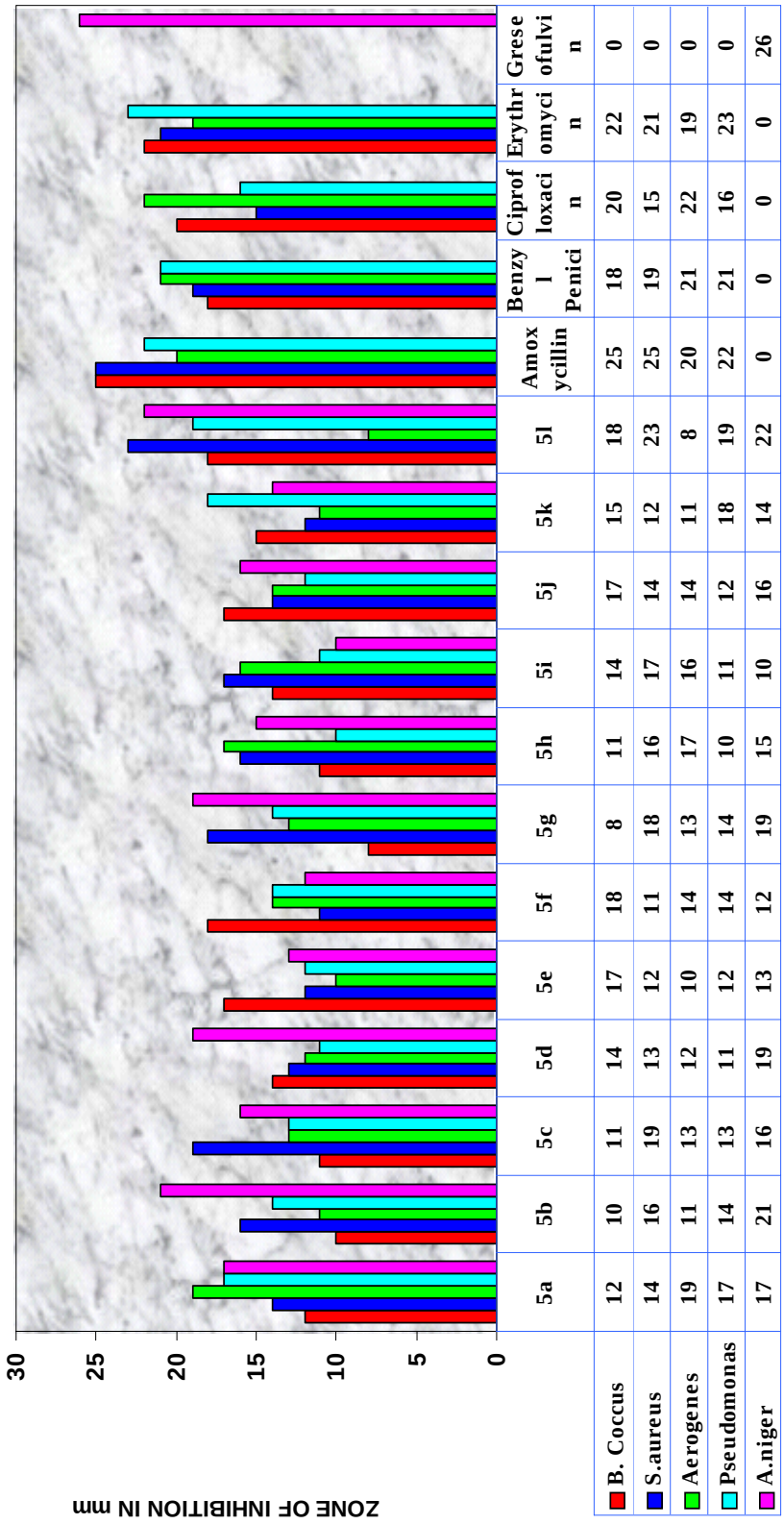
Antimicrobial testing were carried out as described in **(A)**Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 5.

TABLE : 5 PHYSICAL CONSTANTS OF 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYL PYRIMIDIN-2(1H)-THIONES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
5a	C_6H_5-	$C_{23}H_{14}Cl_2N_4S$	449.35	160	68	12.47	12.46	0.62	S_2
5b	4-CH_3-C_6H_4-	$C_{24}H_{16}Cl_2N_4S$	463.38	165	54	12.09	12.00	0.42	S_1
5c	2-CH_3-C_6H_4-	$C_{24}H_{16}Cl_2N_4S$	463.38	162	60	12.09	11.99	0.54	S_1
5d	2,5-$(CH_3)_2$-C_6H_3-	$C_{25}H_{18}Cl_2N_4S$	477.40	155	63	11.74	11.73	0.48	S_1
5e	4-OCH_3-C_6H_4-	$C_{24}H_{16}Cl_2N_4OS$	479.38	160	46	11.69	11.68	0.56	S_2
5f	2,4-$(Cl)_2$-C_6H_3-	$C_{23}H_{12}Cl_4N_4S$	518.24	225	52	10.81	10.80	0.54	S_1
5g	4-Cl-C_6H_4-	$C_{23}H_{13}Cl_3N_4S$	483.80	200	71	11.58	11.57	0.48	S_2
5h	4-Br-C_6H_4-	$C_{23}H_{13}BrCl_2N_4S$	528.05	240	69	10.61	10.60	0.51	S_1
5i	4-S-CH_3-C_6H_4-	$C_{24}H_{16}Cl_2N_4S_2$	495.44	105(d)	59	11.31	11.29	0.47	S_1
5j	4-F-C_6H_4-	$C_{23}H_{13}Cl_2FN_4S$	467.34	260	66	11.99	11.98	0.49	S_2
5k	3-NO_2-C_6H_4-	$C_{23}H_{13}Cl_2N_5O_2S$	494.35	120(d)	70	14.17	14.15	0.54	S_1
5l	4-NO_2-C_6H_4-	$C_{23}H_{13}Cl_2N_5O_2S$	494.35	130	58	14.17	14.16	0.61	S_2

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

GRAPHICAL CHART NO. 5 : 6-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]-4-ARYLPYRIMIDIN-2(1H)-THIONES



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Amoxycillin	Benzyl Penicil	Ciprofloxacin	Erythromycin	Griseofulvin
B. Coccus	12	10	11	14	17	18	8	11	14	17	15	18	25	18	20	22	0
S.aureus	14	16	19	13	12	11	18	16	17	14	12	23	25	19	15	21	0
Aerogenes	19	11	13	12	10	14	13	17	16	14	11	8	20	21	22	19	0
Pseudomonas	17	14	13	11	12	14	14	10	11	12	18	19	22	21	16	23	0
A.niger	17	21	16	19	13	12	19	15	10	16	14	22	0	0	0	0	26

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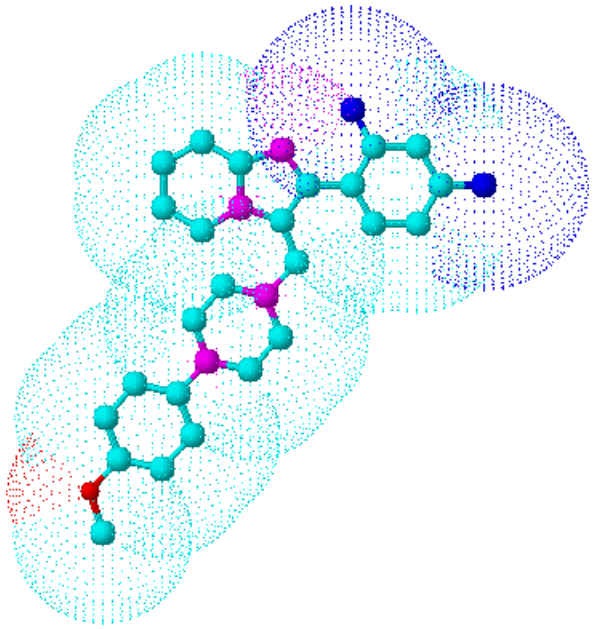


PART - IV

STUDIES ON

MANNICH BASES

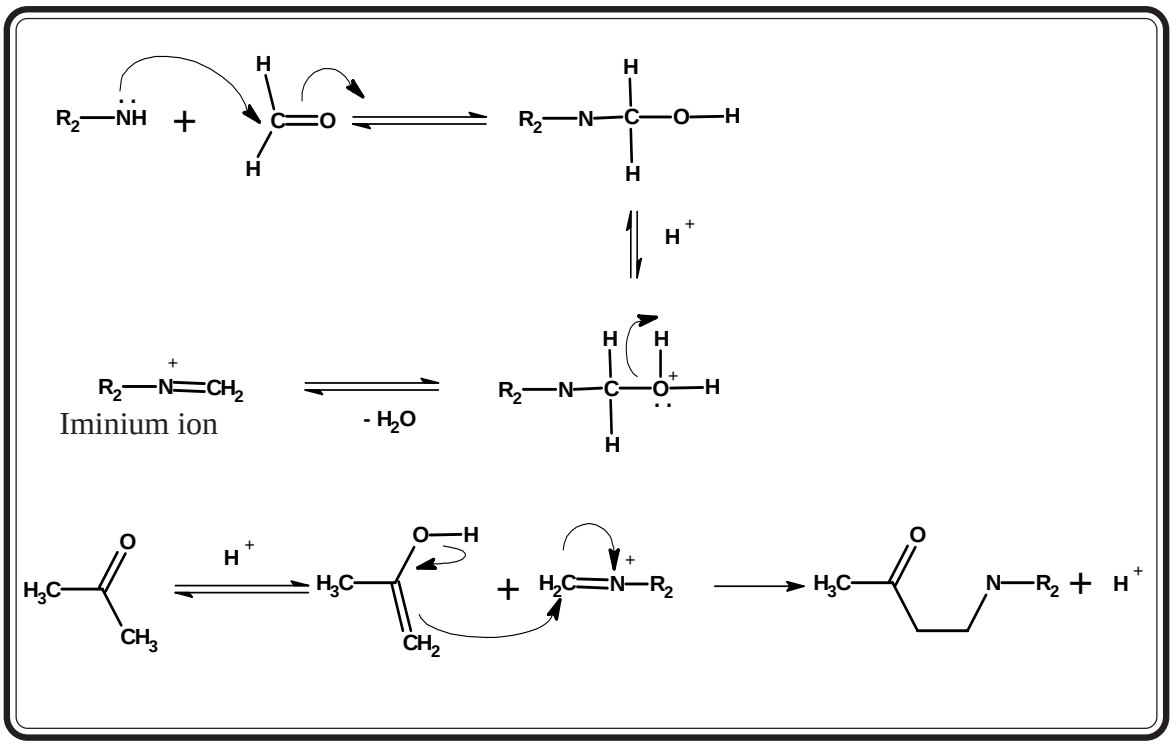
INTRODUCTION

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

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

Over the years there has been much controversy about the mechanism of the mannich reaction. Studies of the reaction kinetics have led to the following mechanistic proposals.

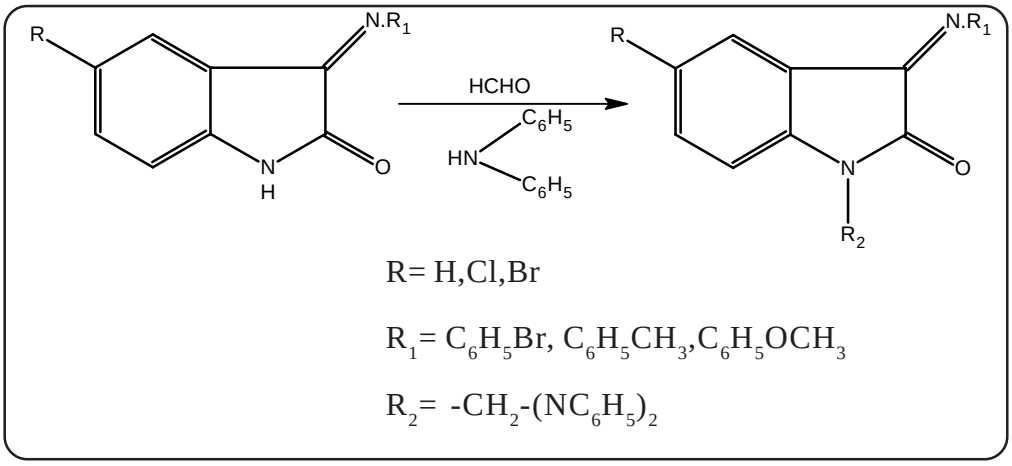
MECHANISM



SYNTHETIC ASPECT

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

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

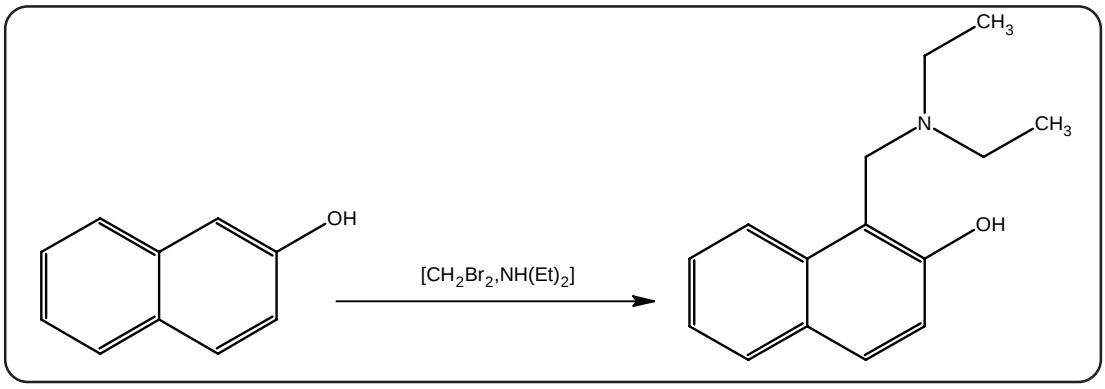


R= H,Cl,Br

R_1= C_6H_5Br, $C_6H_5CH_3$,$C_6H_5OCH_3$

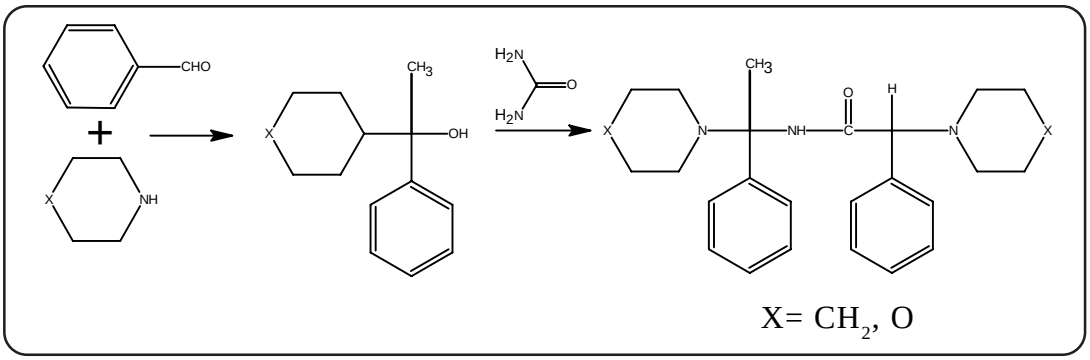
R_2= $-CH_2-(NC_6H_5)_2$

2. Yung-son Hon et al.[11] have prepared mannich bases from the reaction of phenolic compounds with a preheated mixture of dibromomethane and diethylamine.



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

4. Venkatesha Prabhu G. et al.[13] have synthesized aminobenzylated mannich bases by the condensation reaction between heterocyclicsecondary amines and benzaldehyde.



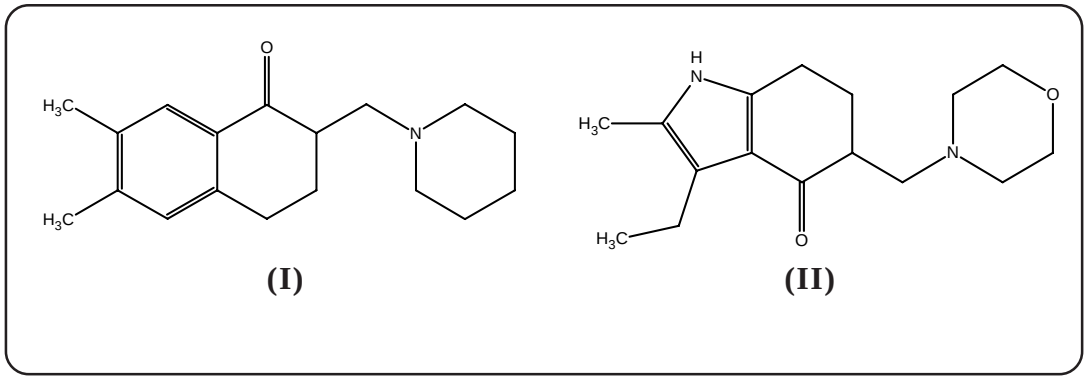
5. Chi and co-workers[14] have synthesized mannich base using 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane, formaldehyde and phenolic derivatives in benzene.
6. Christos A. Kontogiorgis et al.[15] have synthesized mannich base of coumarine.

BIOLOGICAL IMPORTANCE

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

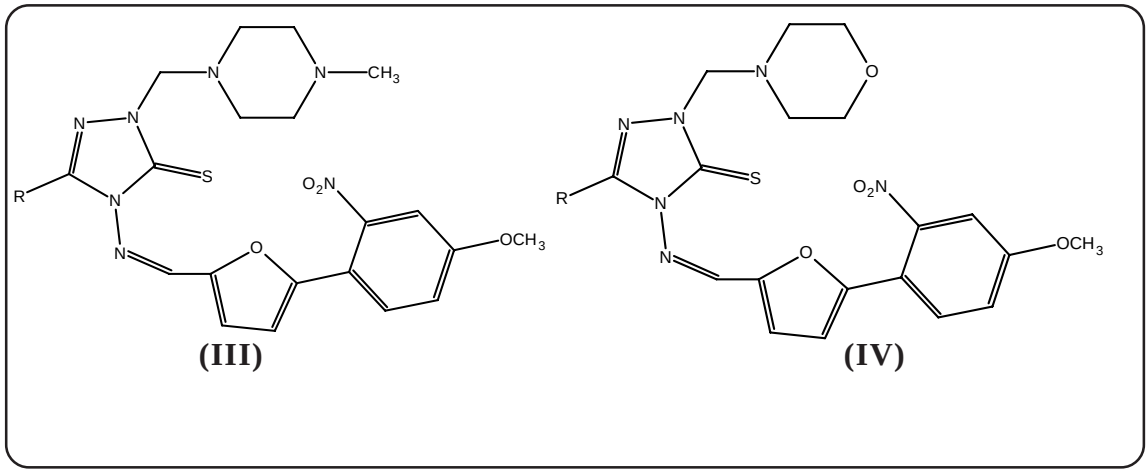
1. Antiinflammatory[16-18]
2. Cytotoxic and anticancer[19]
3. Tranquilizing[20,21]
4. Analgesic[22]
5. Antifungal[23]
6. Antibacterial[24]
7. Antipsychotic[25]
8. Antitumor[26]
9. Antileishmanial[27]
10. Antimalarial[28]

J. Knoll et al.[29] have prepared the mannich base (I) which was the most potent neuroleptic compound of a series of aryl substituted analogues. Molindone[30] (II) which has been reported to demostrate potent neuroleptic activity. Jan Balzarini and co-workers[31] have prepared the mannich base of chalcone shows cytotoxic activities.



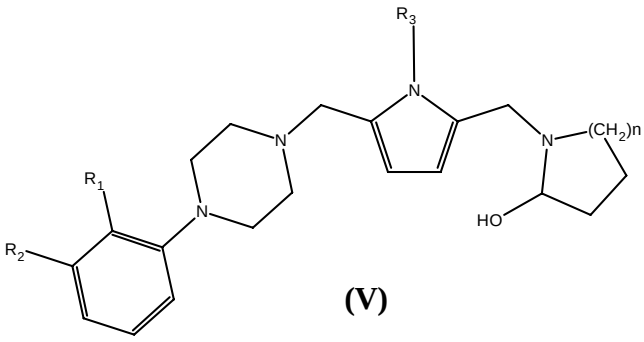
(I) **(II)**

B.Shivarama Holla et al.[32] have prepared mannich bases (III) and tested them for anthelmintic activity and all the newly synthesized compounds (IV) were tested for their antibacterial and antifungal activity.

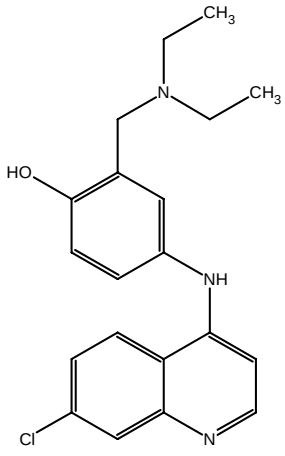


(III) **(IV)**

Amodiaquine[33,34], a mannich base derivative (V), which shown an antimalarial activity superior than chloroquine in areas of high chloroquine resistance. M. L. Edwards et al.[35] have prepared the mannich base of 4-phenyl-3-buten-2-one as an antiherps agent. Malcolm K. Scott and co-workers[36] have prepared the pyrrole mannich base (VI) as a potent antipsychotic agents.



(V)

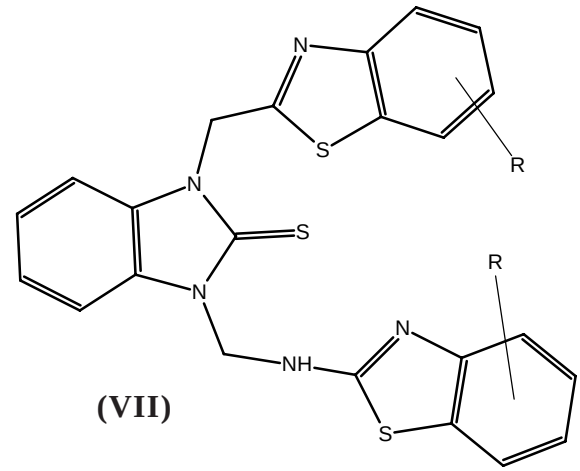


(VI)

Movrin M., Maysinger D. et al.[37] have synthesized mannich bases from nitroxoline and reported them as biologically active agents. Gul H. I. et al.[38] have reported antifungal activity of some mono, bis and quaternary mannich bases derived from acetophenone. Li Y, Yang Z. S. et al.[39] have synthesized some mannich base derivatives and reported their antimalarial activity.

Lorand T. and Kocsis B.[40] have synthesized some new mannich ketones and reported their antibacterial activity. Erol D. D. et al.[41] have synthesized some novel mannich base derivatives from 6-acyl-3-(3,5-dimethylpiperidino methyl)-2(3H)-benzooxazolones and reported their biological activities. H.M.Hassan and S.A.M. Shedid[42] have synthesized some new mannich bases and reported antimicrobial activity of some novel mannich bases containing 1,8-napthpyridine moiety.

Ojanen T. et al.[43] have documented antifungal activity of bis mannich bases derived from acetophenones. Calis U. et al.[44] have synthesized some mono mannich bases and evaluate their anticonvulsant activity. Shingare M. S. et al.[45] have described the synthesis and the antiviral activity of mannich bases (VII).



(VII)

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

H.S.Joshi et al.[46] have been synthesized some novel amino benzylated mannich bases and reported their antimicrobial activities.

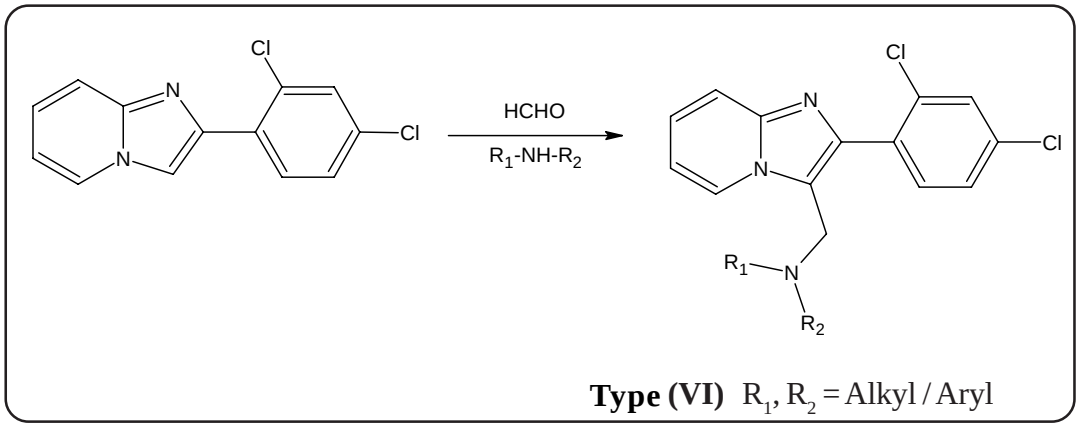
In view of the importance of mannich bases as versatile synthetic intermediates and the availability of scanty literature on therapeutic properties, we have undertaken the preparation of mannich bases in following sections.

SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYL}-*N*,*N*-DIARYL/ALKYLAMINES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYL}-*N*,*N*-DIARYL/ALKYLAMINES

In view of getting better therapeutic agent and considering the association of various biological activity with imidazo[1,2-a]pyridine nucleus, the preparation of mannich bases of Type(VI) have been undertaken from 2-(2,4-dichlorophenyl) imidazo[1,2-*a*]pyridine with primary /secondary amines and formaldehyde in methanol.

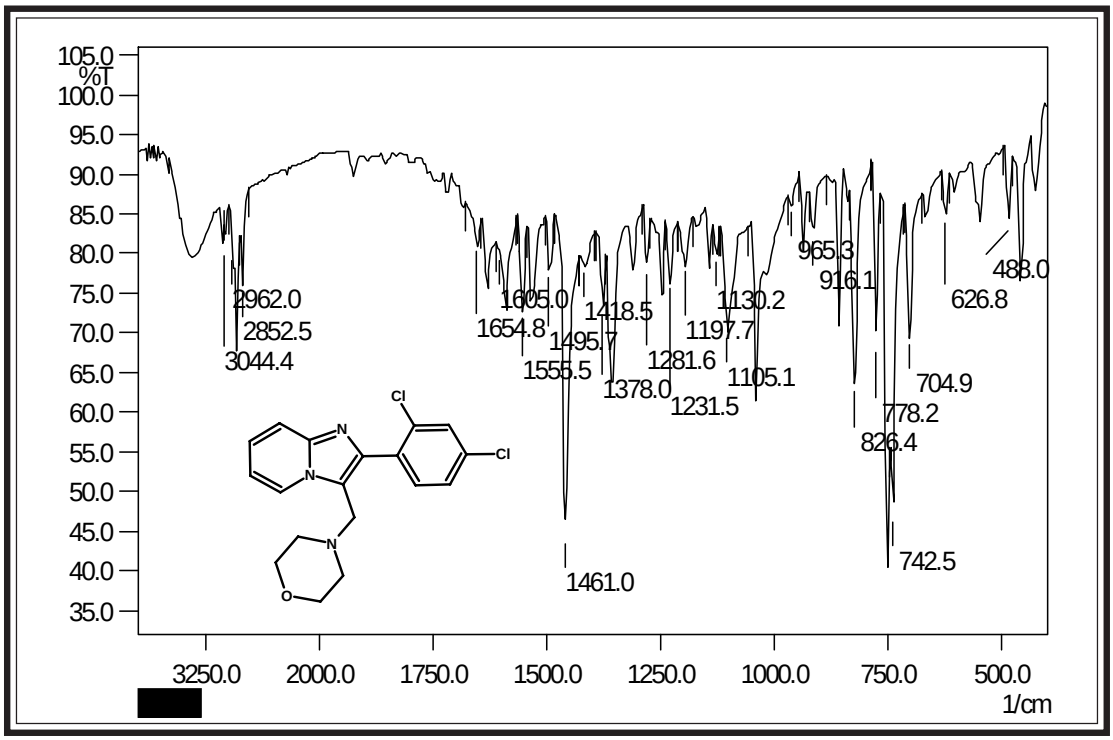


Type (VI) R_1, R_2 = Alkyl / Aryl

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

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

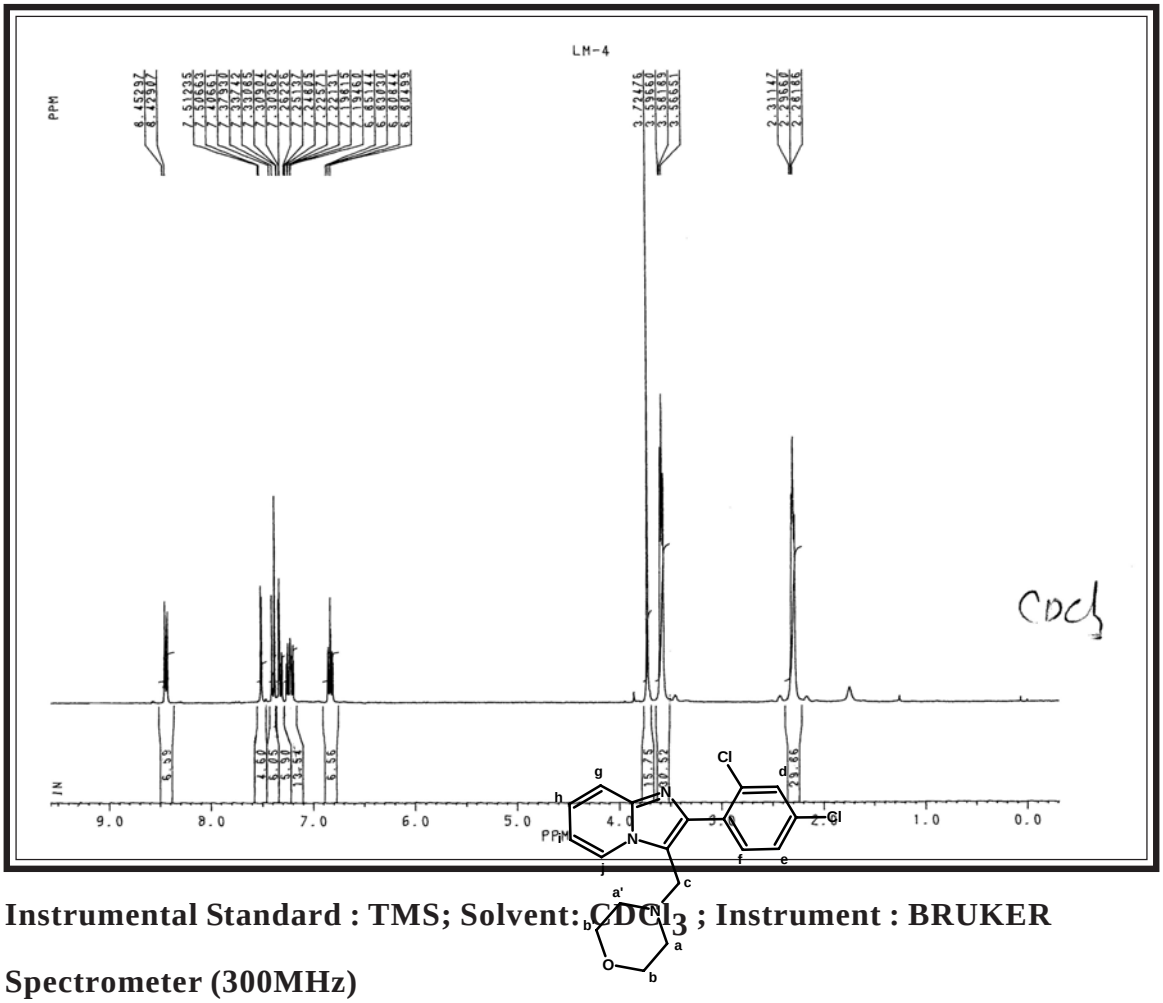
IR SPECTRAL STUDIES OF 2-(2,4-DICHLOROPHENYL)-3-(MORPHOLIN-4-YLMETHYL)IMIDAZO[1,2-*a*]PYRIDINE



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

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2962	2975-2950	47
-CH_2	C-H str. (sym.)	2852	2880-2860	,,
	C-H i.p.def. (asym.)	1460	1470-1435	,,
	C-H o.o.p.def.	1378	1395-1370	,,
Aromatic	C-H str.	3044	3090-3030	48
	C=C str.	1555	1540-1480	,,
	C-H i.p.def.	1105	1125-1000	,,
	C-H o.o.p. (def)	826	835-810	,,
Imidazo[1,2-a]	C=N str.	1605	1612-1593	47
pyridine	C-N str.	1197	1220-1020	,,
	C=C str.	1495	1540-1480	,,
	C-Cl str.	778	800-600	,,
Ether	C-O-C str.	1231	1260-1200	48

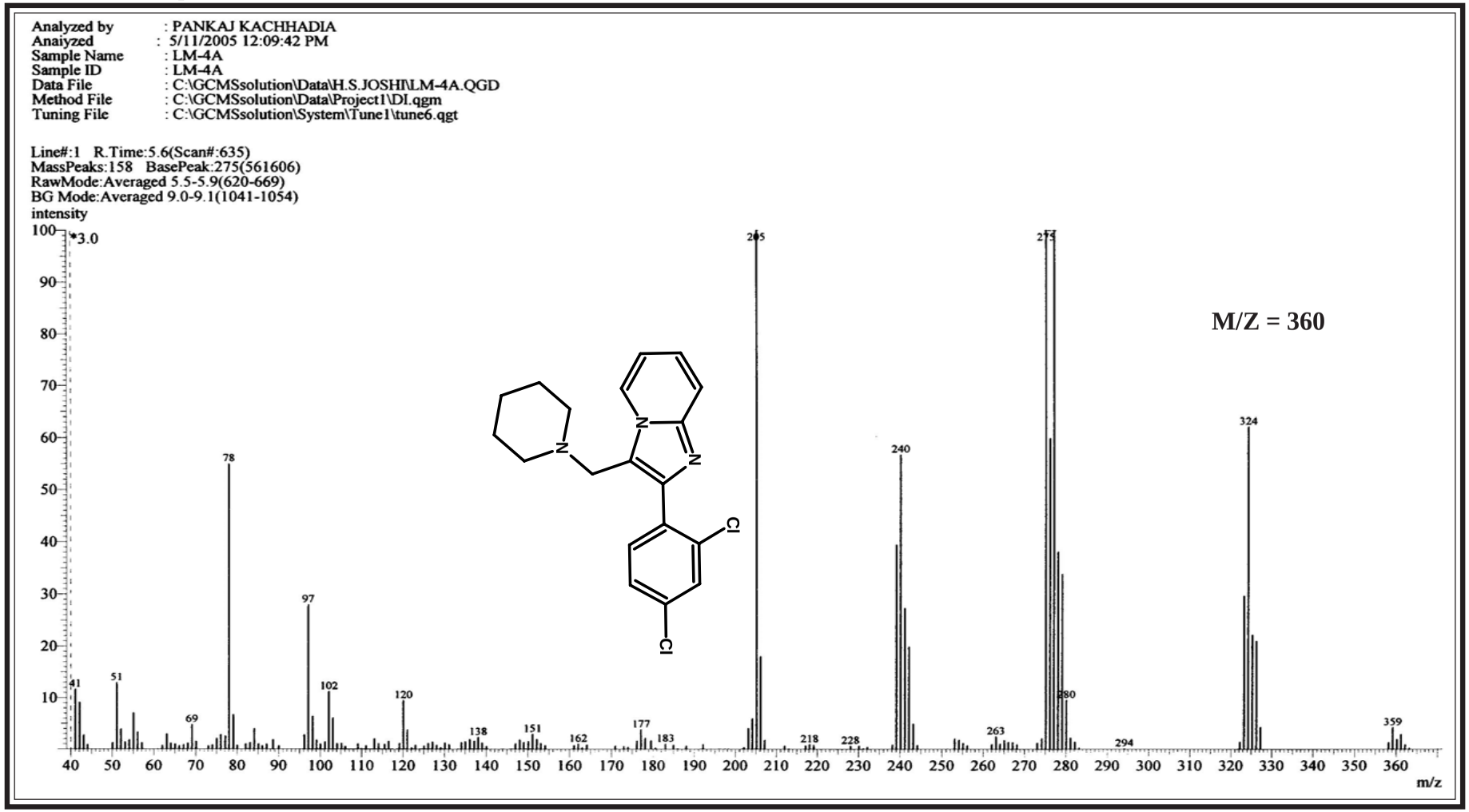
NMR SPECTRAL STUDIES OF 2-(2,4-DICHLOROPHENYL)-3-(MORPHOLIN-4-YLMETHYL)IMIDAZO[1,2-*a*]PYRIDINE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1.	2.29	4H	triplet	C -H(b,b')	-
2.	3.60	4H	triplet	C-H(a,a')	-
3.	3.70	2H	singlet	C-H(c)	-
4.	7.50	1H	doublet	Ar-H(d)	J=3
5.	8.43	1H	doublet	Ar-H(f)	J=9
6.	6.82	1H	dd	Ar-H(e)	J=6, J=1.6
7.	7.40-7.19	4H	multiplate	Ar-H (g,h,i,j)	-

TABLE-6 : MASS SPECTRAL STUDIES OF 2-(2,4-DICHLOROPHENYL)-3-(PIPERIDIN-1-YLMETHYL)IMIDAZO[1,2-*a*]PYRIDINE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYL}-*N*,*N*-DIARYL/ALKYL AMINES

[A] Preparation of 2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridine

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

[B] Preparation of 2-(2,4-Dichlorophenyl)-3-(morpholin-4-ylmethyl)imidazo[1,2-*a*]pyridine

To a solution of 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine (2.63g, 0.01 mol), formaldehyde (0.3g, 0.01 mol) and morpholine (0.88g, 0.01 mol) in methanol (50 ml) was added and stirred for 8 hr. and left overnight in a freeze. The content was poured on to crushed ice. The product was isolated, dried and crystallised from hexane Yield 60%, m.p. 140°C. Anal. Calcd. For $C_{18}H_{17}Cl_2N_3O$: C, 59.68; H, 4.73; N, 11.60 %; Found: C, 59.65; H, 4.70; N, 11.61 %.

Similarly other amines condensed with 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine. The physical constants are recorded in Table No.6.

[C] Biological screening of *N*-{[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methyl}-*N*,*N*-diaryl/alkylamines

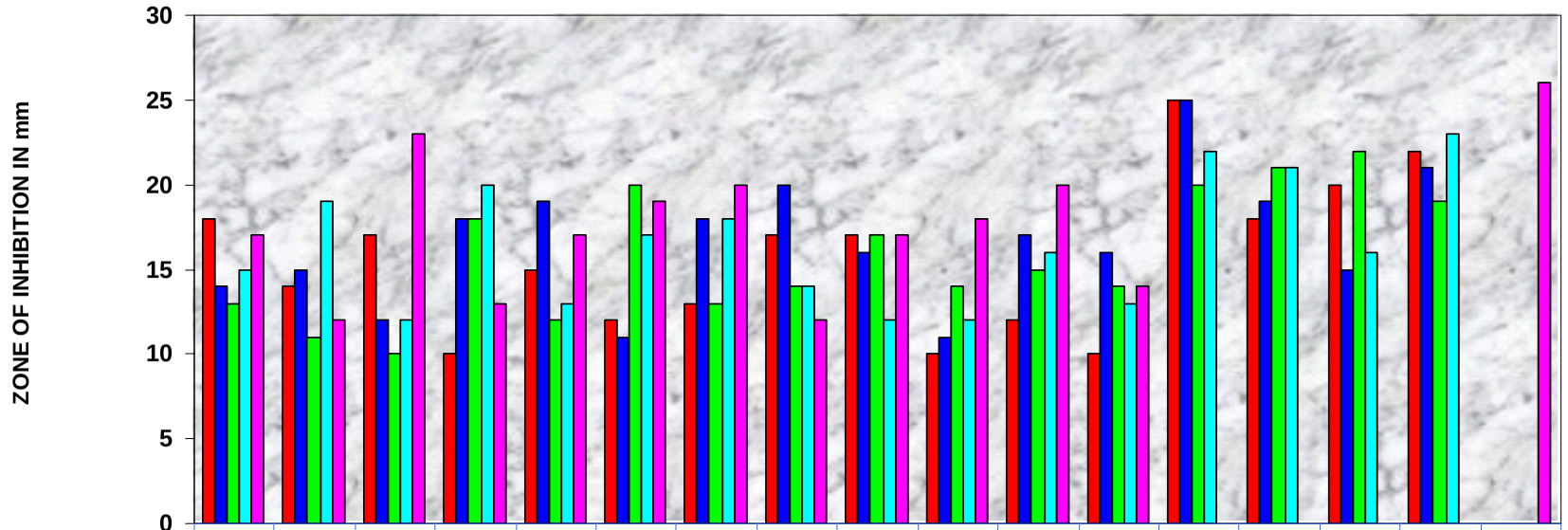
Antimicrobial testing was carried out as described in **(A)** Part-I, Section-I (D). The zones of inhibition of compounds are recorded in Graphical Chart No.6.

TABLE : 6 PHYSICAL CONSTANTS OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYL}-*N*,*N*-DIARYL/ALKYLAMINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
6a	C_4H_8O-	$C_{18}H_{17}Cl_2N_3O$	362.25	140	60	11.60	11.61	0.55	S1
6b	C_5H_{10}-	$C_{19}H_{19}Cl_2N_3$	360.28	160	58	11.66	11.64	0.48	S2
6c	$C_{11}H_{15}NO$-	$C_{25}H_{24}Cl_2N_4O$	467.39	170	62	11.99	12.00	0.50	S1
6d	$C_6H_{13}NO$-	$C_{20}H_{22}Cl_2N_4O$	405.32	145	55	13.82	13.81	0.45	S1
6e	$C_6H_{13}N$-	$C_{20}H_{22}Cl_2N_4$	389.32	176	76	14.39	14.37	0.52	S2
6f	$C_{10}H_{13}N$-	$C_{24}H_{22}Cl_2N_4$	437.36	162	58	12.81	12.79	0.56	S2
6g	$C_5H_{11}N$-	$C_{19}H_{20}Cl_2N_4$	375.29	178	60	14.93	14.92	0.49	S2
6h	$C_{11}H_{15}N$-	$C_{25}H_{24}Cl_2N_4$	451.39	165	69	12.41	12.44	0.59	S2
6i	C_4H_8-	$C_{18}H_{17}Cl_2N_3$	346.25	189	62	12.14	12.12	0.47	S1
6j	C_2H_6-	$C_{16}H_{15}Cl_2N_3$	320.21	178	60	13.12	13.10	0.44	S1
6k	C_4H_{10}-	$C_{18}H_{19}Cl_2N_3$	348.26	135	87	12.07	12.06	0.54	S2
6l	$C_{12}H_{10}$-	$C_{26}H_{19}Cl_2N_3$	444.35	142	56	09.46	09.44	0.43	S2

S1 Hexane : Ethyl acetate (3 : 7), S2 Hexane : Ethyl acetate (6 : 4)

GRAPHICAL CHART NO. 6 : ***N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYL}-*N*,*N*-DIARYL/ALKYLAMINES**



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Amoxicilllin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	18	14	17	10	15	12	13	17	17	10	12	10	25	18	20	22	0
S. aureus	14	15	12	18	19	11	18	20	16	11	17	16	25	19	15	21	0
Aerogenes	13	11	10	18	12	20	13	14	17	14	15	14	20	21	22	19	0
Pseudomonas	15	19	12	20	13	17	18	14	12	12	16	13	22	21	16	23	0
A.niger	17	12	23	13	17	19	20	12	17	18	20	14	0	0	0	0	26

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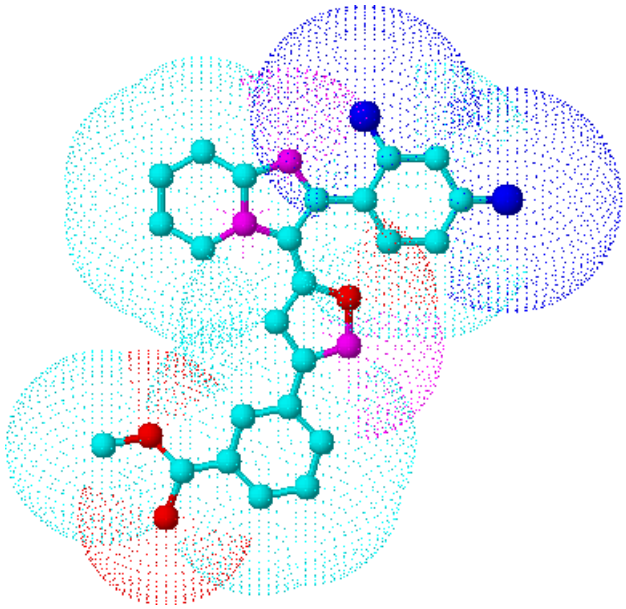
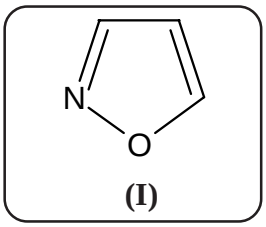


PART - V

STUDIES ON ISOXAZOLES

INTRODUCTION

***I*soxazole** is a five membered heterocyclic compound having two hetero atom: oxygen at position 1 and nitrogen at position 2. In 1888, Claisen first reported an isoxazole (I) for a product from the reaction of 1,3 diketone with hydroxylamine.[1] Subsequently a solid foundation for the chemistry of isoxazole was laid down by Claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions. Particularly in reducing or basic media, it becomes very highly labile.



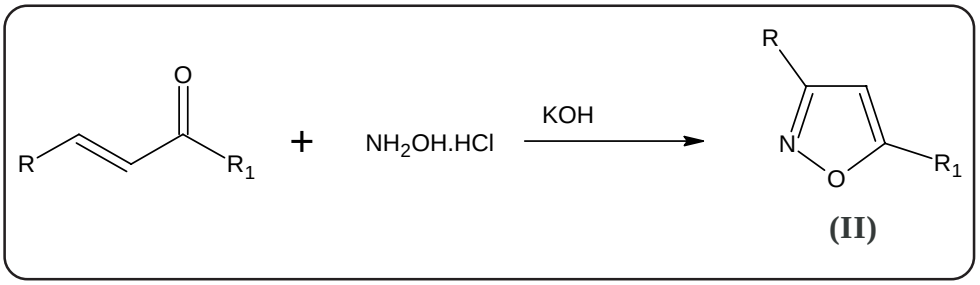
(I)

The next important contribution to the chemistry of isoxazoles was made by Quelico[2] in 1945, when he begain to study the formation of isoxazoles from nitrile N-oxide and unsaturated compounds.

SYNTHETIC ASPECT

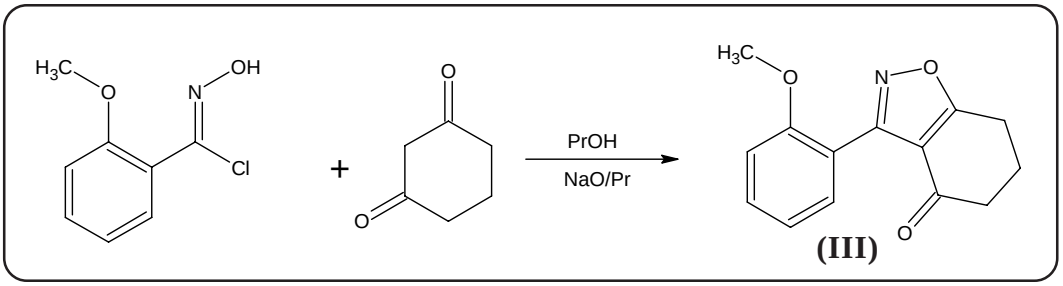
Isoxazoles can be prepared by various method, which are described as under.

1. Dawood Kamal et al.[3] have prepared isoxazole derivatives from enamino nitriles.
2. Tayade V. B. et al.[4] synthesized some new 3,5-diarylisoxazoles from the reaction of 2-aryl acetophenones with hydroxyl amine hydrochloride in presence of alkali.
3. Crawley L. S. and Fanshawe W. J.[5] were prepared isoxazole(II) from α,β-unsaturated carbonyl compounds, hydroxyl amine hydrochloride and KOH in methanol.



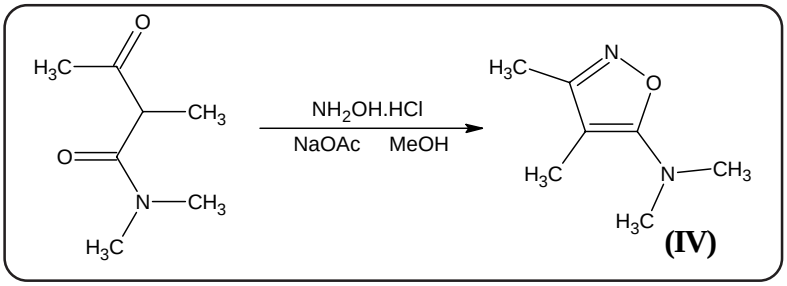
(II)

4. Keisuke Suzuki et al.[6] have synthesized functionalized isoxazole (III) derivatives by cyclocondensation of C-chlorooximes with cyclic 1,3-diketones.



(III)

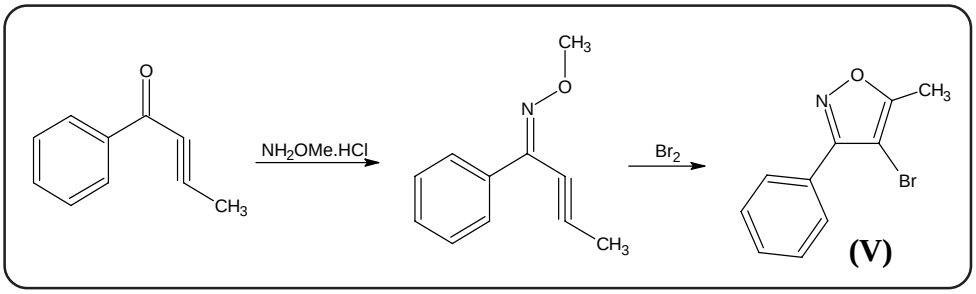
5. Mark Lautens and Ame´lie Roy[7] have constructed isoxazoles (IV), were achieved in good yields in a rapid and simple way by using *N*-acetoacetyl derivatives.



(IV)

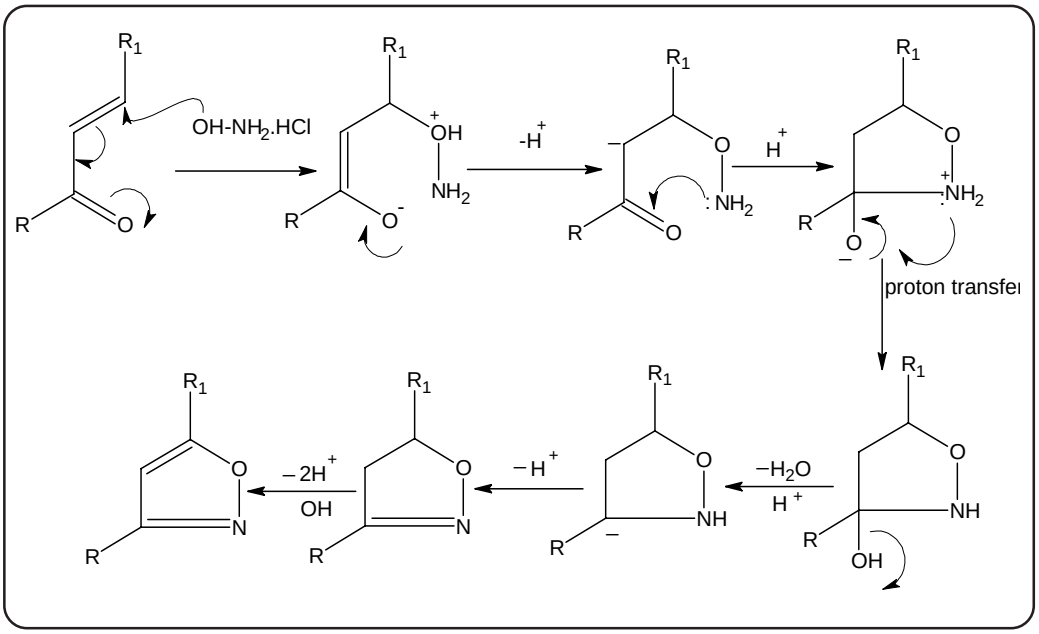
6. Solid phase synthesis of isoxazole derivatives based on aminoacids was reported by Lidia De Luca and co-workers[8] in the presence of basic catalyst and dichloro methane used as a solvent. One-Pot synthesis of polyfunctionalized isoxazoles[9] have been prepared by the reaction of dipyrrolidinium 3,3-dimethylpentanedinitrile -2,4-dinitronate and acetyl chloride in benzene.

7. A variety of 3,5-disubstituted 4-bromoisoxazoles (IV)[10] were prepared in good to excellent yields under mild reaction conditions as under.



(V)

REACTION MECHANISM

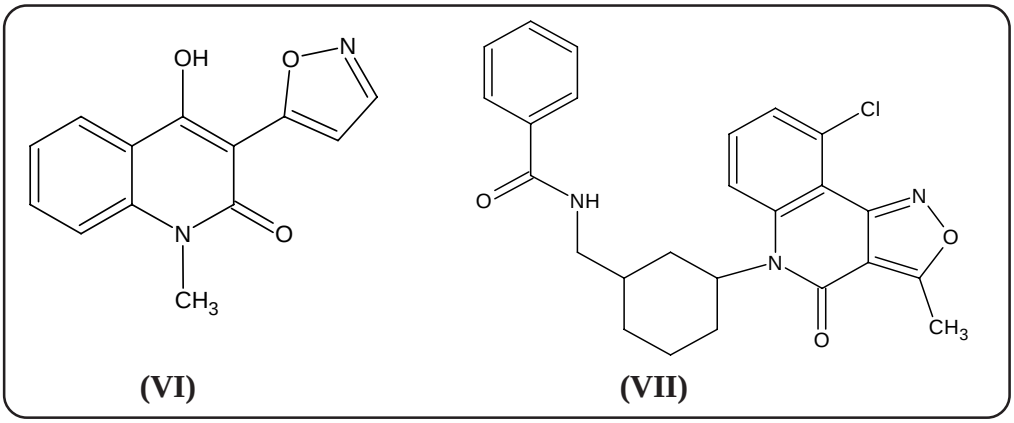


THERAPEUTIC IMPORTANCE

Isoxazole derivatives exhibit various biological activities such as,

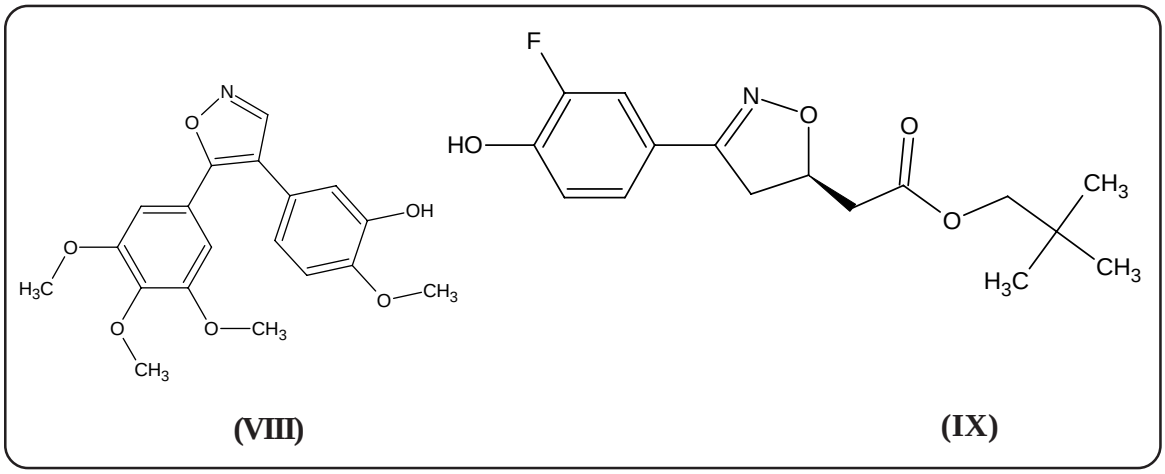
1. Anticonvulsant[11,12]
2. Anticholestermic[13]
3. Antibacterial[14-16]
4. Anthelmintics[17]
5. Anticancer[18]
6. Adenosine antagonist[19]
7. Fungicidal[20-22]
8. Herbicidal[23,24]
9. Hypoglycemic[25]
10. Muscle relaxant[26,27]
11. Nematocidal[28]
12. Insecticidal[29]
13. Antiinflammatory[30-33]
14. Antimicrobial[34]
15. Antiviral[35]

Stefano Chimichi and co-workers[36] have investigated cytotoxic activity of 3-quinolinoyl isoxazoles (VI) against leukemia and adenocarcinoma derived cell lines in comparison to the normal human keratinocytes. Novel cyclohexyl drug resistance modulators[37] (VII) were synthesized and evaluated for *in vitro* inhibition of the drug resistance transporter, MRP1.



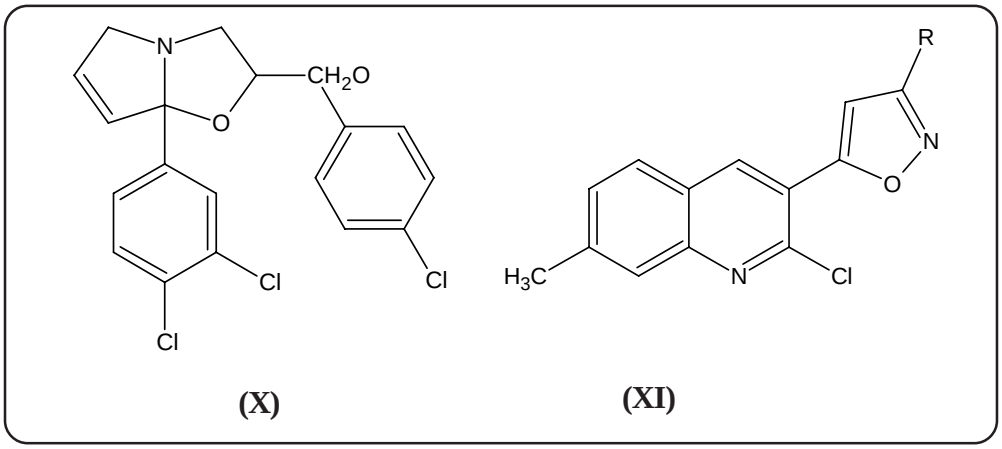
(VI) **(VII)**

Julia Kaffy et al.[38] have been synthesized various five membered heterocycles with oxygen and nitrogen atoms. The 4,5 diarylisoxazole (VIII) exhibited greater antitubulin activity, but modest antiproliferative activity. Kaifan Cheng and Yousef Al-Abed[39] have reported isoxazole derivatives (IX) have found 20-Fold more potent than 3-(4-hydroxyphenyl)-4,5-dihydro-5-acetic acid methyl ester isoxazole inhibits MIF tautomerase with an IC_{50} of 550 nM.



(VIII) **(IX)**

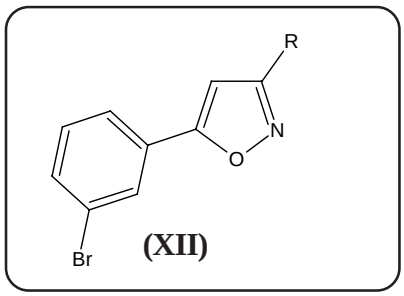
Aicher Thomas D. et al.[40] reported isoxazoles (X) as hypoglycemic agents. H. H. Parekh et al.[41] have synthesized 3-(p-methoxyphenyl)-5-(2'-chloro-7'-methylquinolin-3'-yl)-isoxazole (XI) and studied thier biologcal activity.



(X) **(XI)**

Moreover, S. Rung and D. Dus[42] have synthesized some new isoxazoles as remedy for leukemia. M. Scobie and co-workers[43] have prepared isoxazole derivatives and studied their antitumor activity. G. Daidone et al.[44] synthesized novel 3-(isoxazol-3-yl)-quinazolin-4-(3H)-one derivatives and tested for their analgesic and antiinflammatory activities as well as for their acute toxicity and ulcerogenic effect. Salter M. W. et al.[45] have prepared some novel isoxazoles as cellular neuroplasticity mechanisms mediating pain persistence. Matringe M. et al.[46] have reported some new p-hydroxyphenylpyruvates dioxygenase inhibitor-resistant plants. Mehlisch D. R. et al.[47] have synthesized isoxazole derivatives as analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. Ray W. A. et al.[48] have reported isoxazole derivatives as cardiovascular toxicity of valdecoxib.

H. S. Joshi et al.[49] have synthesized isoxazole derivatives (XII) and reported their antitubercular and antimicrobial activity.



(XII)

Welsing P. M. et al.[50] have documented the isoxazoles as tumornecrosis factor blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands. Bingham S. J. et al.[51] have synthesized isoxazole derivatives as an antiuclear agents. Barbachyn M. R. et al.[52] have described the phenylisoxazolines as novel and viable antibacterial agents active against *Gram-positive* pathogens.

Masui et al.[53] have prepared isoxazoles having pesticidal activity. Some excellent herbicidal results obtained by Reddy et al.[54] C. B. Xue et al.[55] have reported an oral antiplatelet effect in dogs.

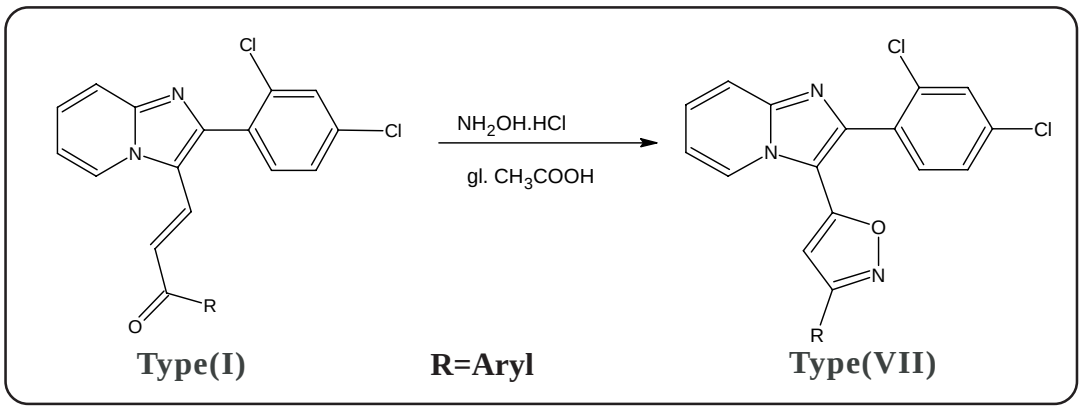
With an intension of preparing the compounds possessing better therapeutic activity, we have under taken the preparation of isoxazoles bearing imidazo[1,2-a]pyridine derivatives which have been described as follows.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(2,4-DICHLOROPHENYL)-3-(3-ARYLISOXAZOL-5-YL) IMIDAZO[1,2-*a*]PYRIDINES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(2,4-DICHLORO PHENYL)-3-(3-ARYLISOXAZOL-5-YL)IMIDAZO[1,2-*a*]PYRIDINES

Isoxazoles have been reported to have various pharmacological activities like antibacterial, antifungal, insecticidal etc. In order to achieving better drug potency, we have prepared isoxazole derivatives of Type (VII) by the cyclocondensation of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones of Type (I) with hydroxylamine hydrochloride in presence of sodium acetate in glacial aletic acid.

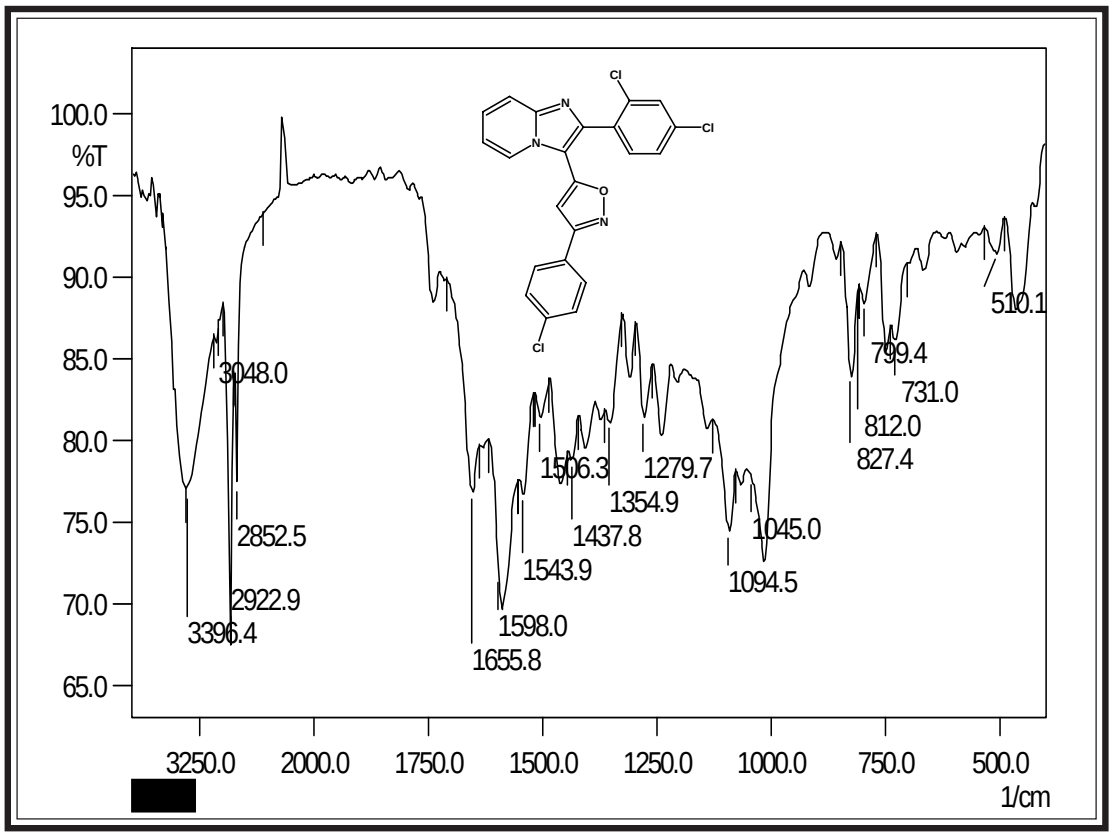


Type(I) **R=Aryl** **Type(VII)**

The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

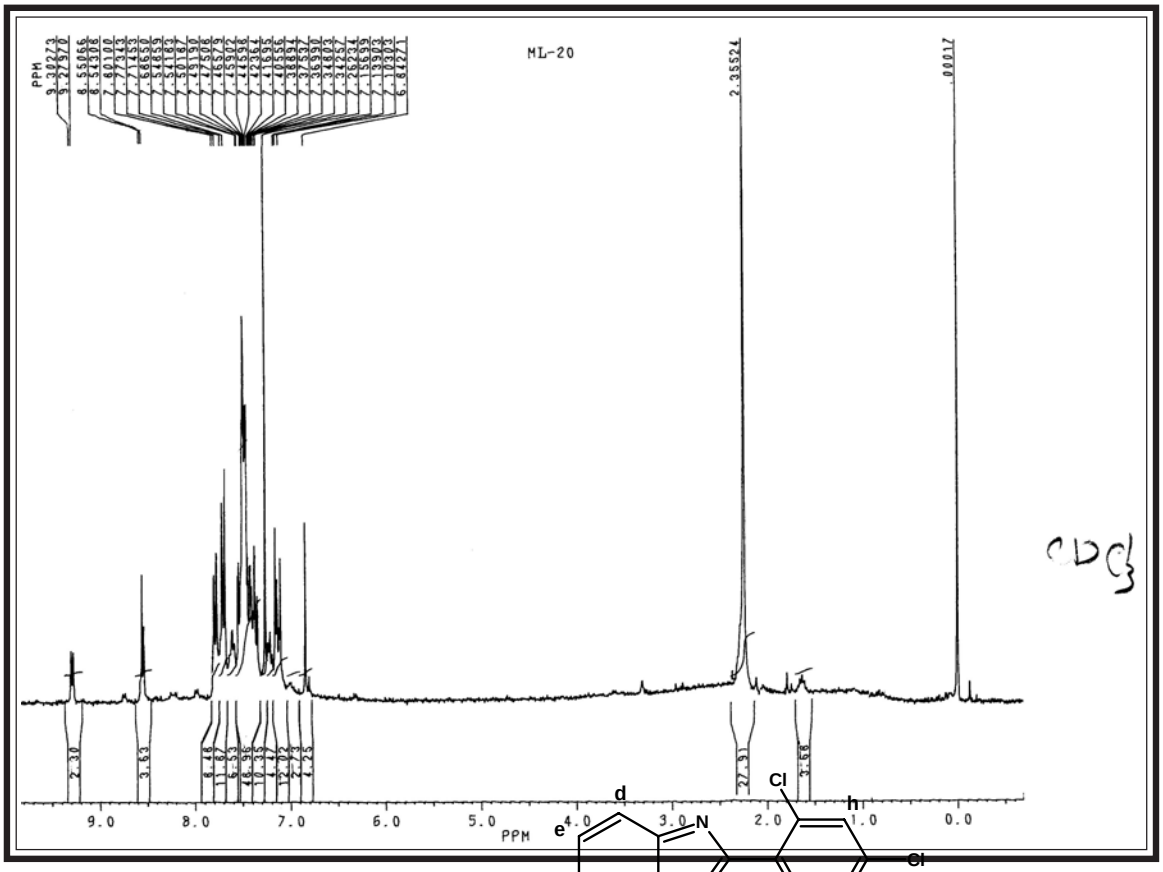
IR SPECTRAL STUDIES OF 2-(2,4-DICHLOROPHENYL)-3-[3-(4-CHLOROPHENYL)ISOXAZOL-5-YL]IMIDAZO[1,2-*a*]PYRIDINE

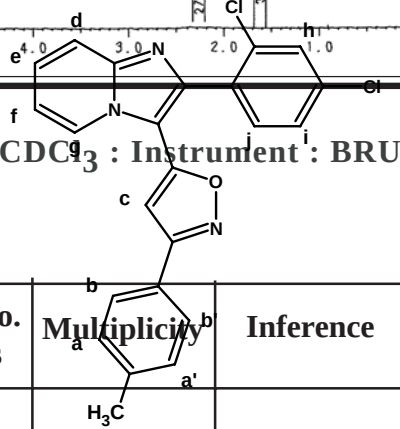


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Aromatic	C-H str.	3048	3090-3030	57
	C=C str.	1506	1540-1480	,,
	C-H o.o.p. def.	812	835-810	,,
Halide	C-Cl str.	799	800-600	56
	C-O str.	1045	1050-1040	,,
Isoxazole	C=C str.	1655	1680-1550	57
	C=N str.	1543	1690-1460	,,
	N-O str.	827	850-810	,,
Imidazo[1,2-a]	C=N str.	1598	1612-1593	56
pyridine	C-N str.	1094	1220-1020	,,

NMR SPECTRAL STUDIES OF 2-(2,4-DICHLOROPHENYL)-3-[3-(4-METHYLPHENYL)ISOXAZOL-5-YL]IMIDAZO[1,2-*a*]PYRIDINE

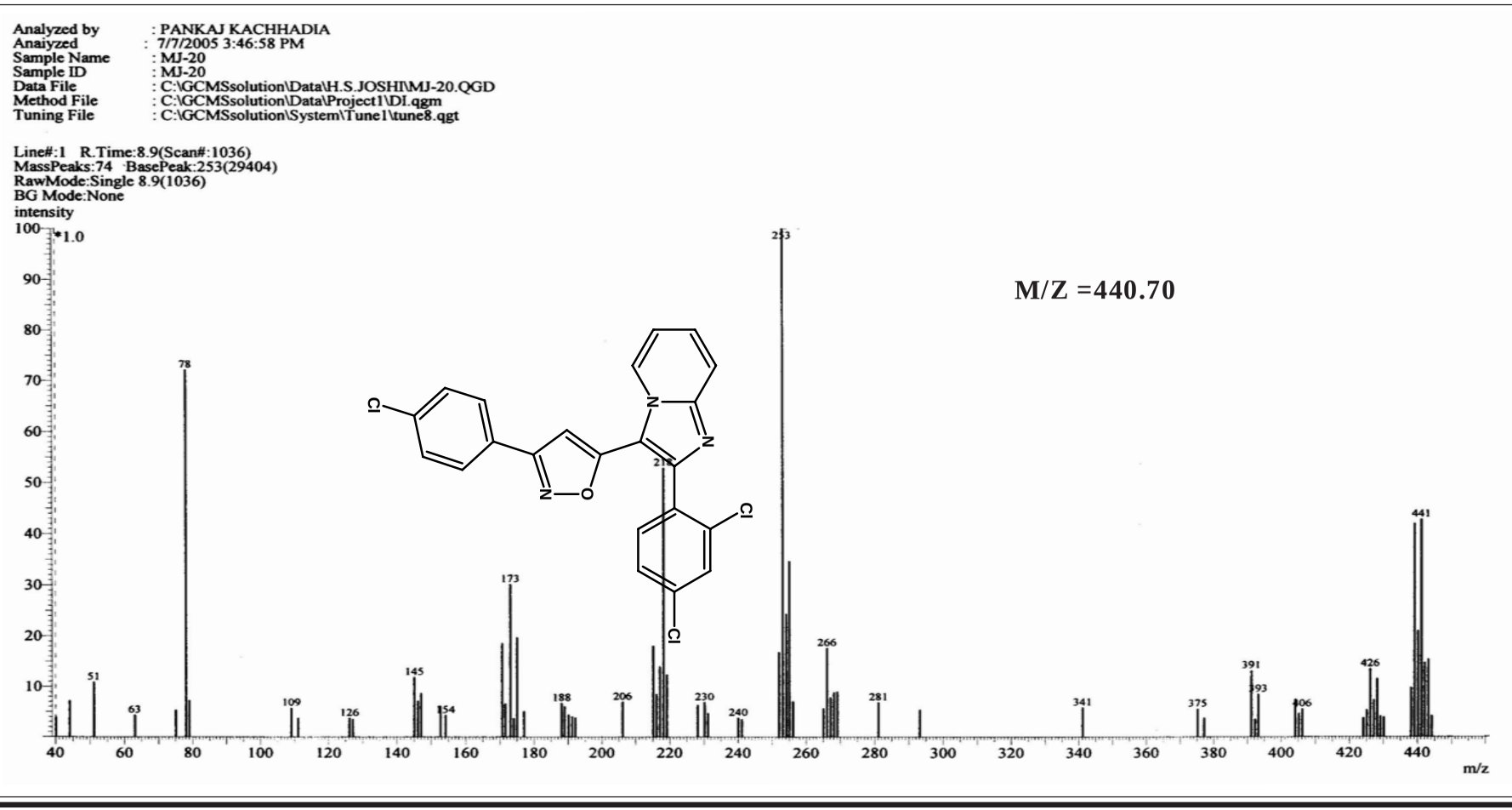




Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.35	3H	singlet	Ar-CH_3	-
2	6.84	1H	singlet	Ar-H(c)	-
3	7.10-7.13	1H	dd	Ar-H(i)	J=6.2,J=2.5
4	7.34-7.54	4H	multiplet	Ar-H(d,e,f,g)	-
5	7.68-7.71	2H	doublet	Ar-H(a,a')	J=9.0
6	7.77-7.80	1H	doublet	Ar-H(j)	J=9.0
7	8.54-8.55	1H	doublet	Ar-H(h)	J=2.1
8	9.27-9.30	2H	doublet	Ar-H(b,b')	J=9.0

TABLE-7 : MASS SPECTRAL STUDIES OF 2-(2,4-DICHLOROPHENYL)-3-[3-(4-CHLOROPHENYL)ISOXAZOL-5-YL]IMIDAZO[1,2-*a*]PYRIDINE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(2,4-DICHLOROPHENYL)-3-(3-ARYLISOXAZOL-5-YL) IMIDAZO[1,2-*a*]PYRIDINES

(A) Synthesis of (2*E*)-3-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-arylprop-2-en-1-ones

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

(B) Synthesis of 2-(2,4-Dichlorophenyl)-3-[3-(4-chlorophenyl)isoxazol-5-yl]imidazo[1,2-*a*]pyridine

To a solution of (2*E*)-3-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]-1-(4-chlorophenyl)prop-2-en-1-ones (4.27 gm, 0.01 mol) in ethanol (25 ml), anhydrous sodium acetate (0.739gm, 0.01 mol) and hydroxylamine hydrochloride (0.59 gm, 0.01 mol) in acetic acid were added. The reaction mixture was refluxed on oil bath for 7-8 hr. The product was isolated and crystallized from ethanol. Yield 54 %, m.p. 160^{O}C Anal. Calcd. For $C_{22}H_{12}Cl_3N_3O$ Requires ; C, 59.96; H, 2.74; N, 9.53; Found C, 59.94, H, 2.73; N, 9.52%.

Similarly, other 2-(2,4-dichlorophenyl)-3-(3-arylisoxazol-5-yl)imidazo [1,2-*a*]pyridines were prepared. The physical data are recorded in Table No.7.

(C) Biological screening of 2-(2,4-Dichlorophenyl)-3-(3-arylisoxazol-5-yl) imidazo[1,2-*a*]pyridines

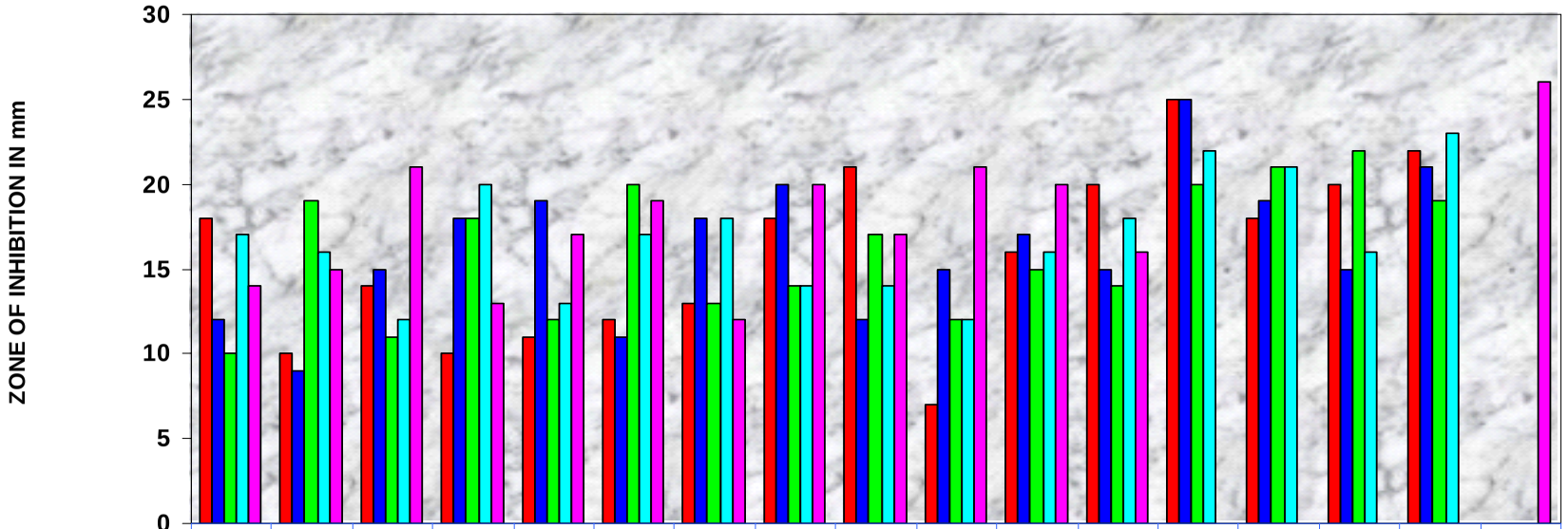
Antimicrobial testing were carried out as described in **(A)** Part-I Section-1 (D). The zones of inhibition of test solution are reported in Graphical Chart No 7.

TABLE : 7 PHYSICAL CONSTANTS OF 2-(2,4-DICHLOROPHENYL)-3-(3-ARYLISOXAZOL-5-YL)IMIDAZO [1,2-*a*]PYRIDINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
7a	C_6H_5-	$C_{22}H_{13}Cl_2N_3O$	406.26	162	42	10.34	10.32	0.58	S_2
7b	4-CH_3-C_6H_4-	$C_{23}H_{15}Cl_2N_3O$	420.29	154	56	10.00	9.99	0.44	S_2
7c	2-CH_3-C_6H_4-	$C_{23}H_{15}Cl_2N_3O$	420.29	148	64	10.00	9.98	0.50	S_1
7d	2,5-$(CH_3)_2$-C_6H_3-	$C_{24}H_{17}Cl_2N_3O$	434.31	193	57	9.67	9.68	0.41	S_1
7e	4-OCH_3-C_6H_4-	$C_{23}H_{15}Cl_2N_3O_2$	436.29	174	61	9.63	9.62	0.52	S_2
7f	2,4-$(Cl)_2$-C_6H_3-	$C_{22}H_{11}Cl_4N_3O$	475.15	163	68	8.84	8.83	0.56	S_1
7g	4-Cl-C_6H_4-	$C_{22}H_{12}Cl_3N_3O$	440.70	160	54	9.53	9.52	0.43	S_2
7h	4-Br-C_6H_4-	$C_{22}H_{12}BrCl_2N_3O$	485.16	170	48	8.66	8.65	0.57	S_1
7i	4-SCH_3-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.25	146	58	9.29	9.28	0.41	S_1
7j	4-F-C_6H_4-	$C_{22}H_{12}Cl_2FN_3O$	424.25	162	66	9.90	9.89	0.46	S_2
7k	3-NO_2-C_6H_4-	$C_{22}H_{12}Cl_2N_4O_3$	451.26	170	45	12.42	12.41	0.53	S_1
7l	4-NO_2-C_6H_4-	$C_{22}H_{12}Cl_2N_4O_3$	451.26	161	56	12.42	12.40	0.51	S_1

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

GRAPHICAL CHART NO. 7 : 2-(2,4-DICHLOROPHENYL)-3-(3-ARYLISOXAZOL-5-YL) IMIDAZO[1,2-*a*] PYRIDINES



	7a	7b	7c	7d	7e	7f	7g	7h	7j	7j	7k	7l	Amoxicilllin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Griseofulvin
B. Coccus	18	10	14	10	11	12	13	18	21	7	16	20	25	18	20	22	0
S. aureus	12	9	15	18	19	11	18	20	12	15	17	15	25	19	15	21	0
Aerogenes	10	19	11	18	12	20	13	14	17	12	15	14	20	21	22	19	0
Pseudomonas	17	16	12	20	13	17	18	14	14	12	16	18	22	21	16	23	0
A.niger	14	15	21	13	17	19	12	20	17	21	20	16	0	0	0	0	26

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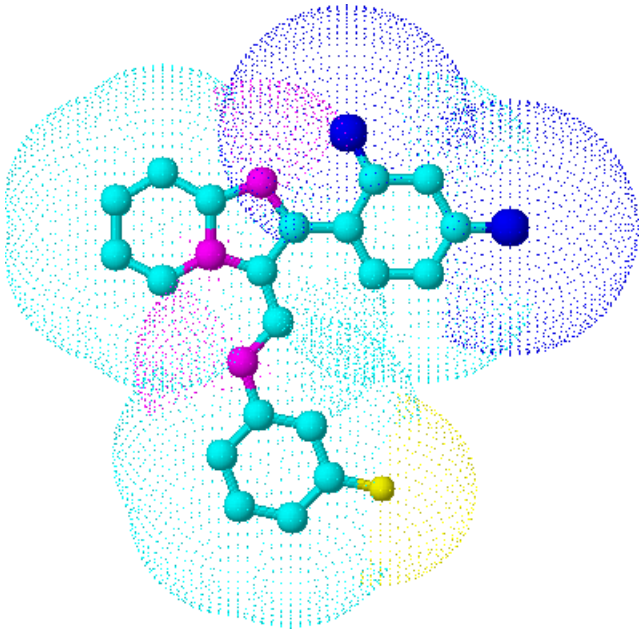
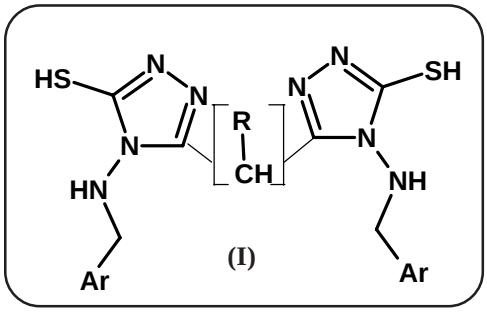


PART - VI

STUDIES ON ARYLAMINOMETHYL DERIVATIVES

INTRODUCTION

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



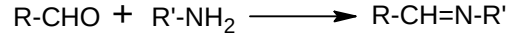
(I)

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

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

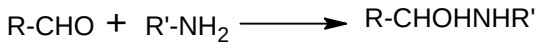
SYNTHETIC ASPECT :

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



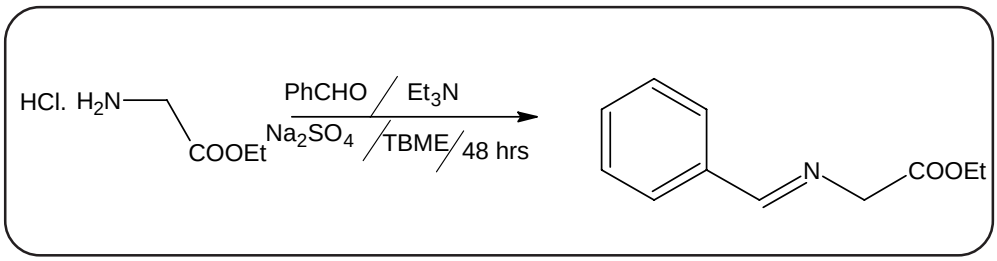
2. Oddo and Tognacchini[3] have introduced the comparative rates of formation of Schiff's base from aniline and substituted aniline and aromatic aldehyde.
3. Strache[4] and Van Alphen[5] have prepared imine involves in two steps.

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

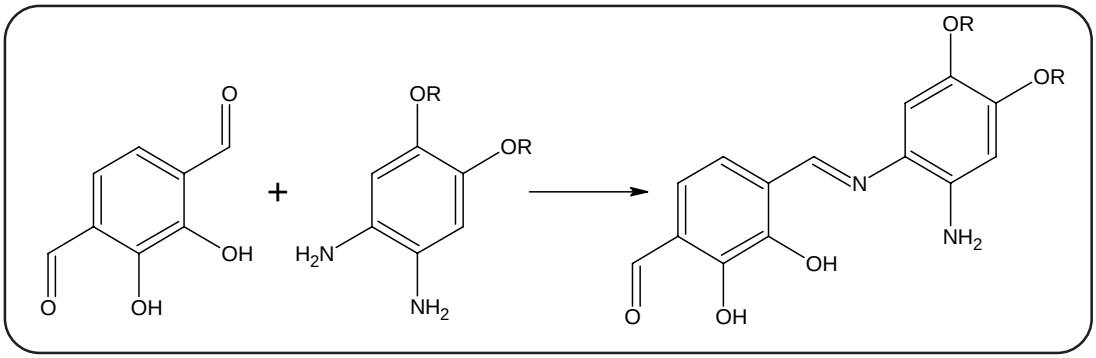


b. The loss of water to give an imine (azomethine), this corresponds to the "crotonaldehyde stage" of the aldol condensation.

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



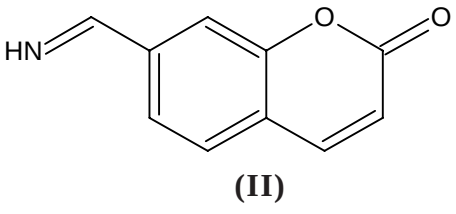
Amanda J. Gallant et al.[7] have prepared schiff bases by condensation of equimolar quantity of 3,6 diformyl catechol and substituted o-phenylenediamine.



THERAPEUTIC IMPORTANCE

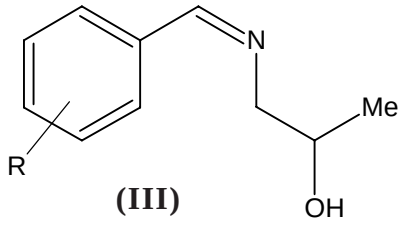
Schiff bases exhibit a wide range of pharmacological activities like antifungual, antibacterial, antiviral, antiinflammatory etc. Mehta R. H. et al.[8] have synthesized coummarin schiff's base derivatives (II) and examined for their antibacterial activity. Khalafallah A. K. and Hassan M. E.[9] have prepared some styryl Schiff's bases spiro derivatives as potential antibacterial and antifungal activity. Sharaf El-Din, and

Nabaweyal[10] have synthesized some azomethine derivatives (III) having good antibacterial activity.



(II)

R = Ph, 4-Br-C_6H_4, 4-NO_2-C_6H_4, 2-Cl-C_6H_4CONH



(III)

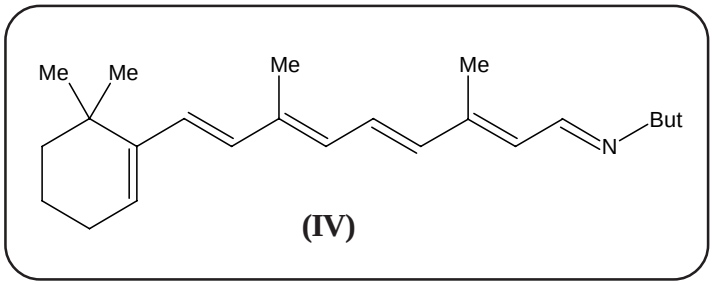
R = 3,4 -OH, 3, 4-NO_2 3,4-$(OMe)_2$

Deshmukh M. D. and Doshi A. G.[11] 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.[12] have synthesized diazomethines having good plant hormone activity. Das Arima et al.[13] have prepared Schiff's bases of aminohydroxy guanidine (SB-AHG5) and tested for antiviral activity against Herpes Simplex virus Type I (HSV-1) and adenovirus Type-5 (Ad-5).

Ali, yousif et al.[14] have synthesized some Schiff's base derivatives of glucose containing acetylenic bond. The prepared Schiff base were tested for their bactericidal activity against E. coli and Staphylococcus aureus.

Holla B. S. et al.[15] have prepared mannich bases. Pandey Taruna et al.[16] prepared azomethines and their boron complexes and screened for their antifungal and antibacterial properties. It is evident that azomethines along with quite toxic but their activity increased after complexation. Omar et al.[17] have determined cyclocondensation of azomethines having good antischistosomal activity. Chohan and co-workers[18,19] have synthesized a novel class of acetyl ferrocene derived from schiff bases possess antimicrobial activity. some azomethine derivative screened for various antibacterial strains.

Das Joydip et al.[20] have synthesized trans-N-refinylidene-n-butylamine (IV) which found stabillized in liposomes of phophatidylcholine. The rate of formation of the Schiff's base is found to decrease with increasing cholesteral concentration in the membrane. Patel V. M.[21] have synthesized some new Schiff's bases having good antibacterial activity.

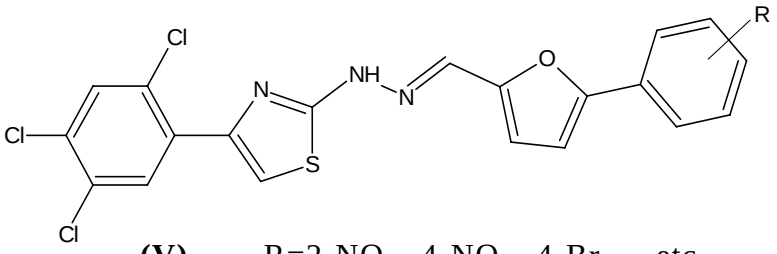


(IV)

Ram Tilak et al.[22] have synthesized some Schiff's bases, of 2-chloro phenothiazines and screened against carrageenin-induced edema in albino rats. Cascaval Alexandru et al.[23] have synthesized azomethines, which have good analgesic and antipyretic properties. Pandeya S. N. et al.[24] have synthesized Schiff bases showed good activity against Vibrio cholerae non-o., Shigella boydii, Enterococcus faecalis and Edwaredsiella torla with MIC in the rang of 10-25 µg/ml. Some compounds were found to be active against Salmonellal typhi and Vibro cholerae-0, (MIC 25-150 µg/ml).

Pawar et al.[25] have synthesized azomethines by the condensation of iodovanillin with different substituted aromatic amines, and determined antibacterial activity. Ergenc and co-workers[26] have synthesised azomethine derivatives having antifungal activity. Yadav Bodke and S. S. Sangapure[27] have synthesised some azomethines and tested for their biological activity. B. Shivarama Holla et al.[28] have prepared some new Schiff's bases having anticancer activity.

Ravindra V. Chambhare et al.[29] have prepared some azomethines and tested for their antimicrobial activity. B. Shivarama Holla et al.[30] have synthesized azomethines (V) having antibacterial and antiinflammatory activity.



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

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

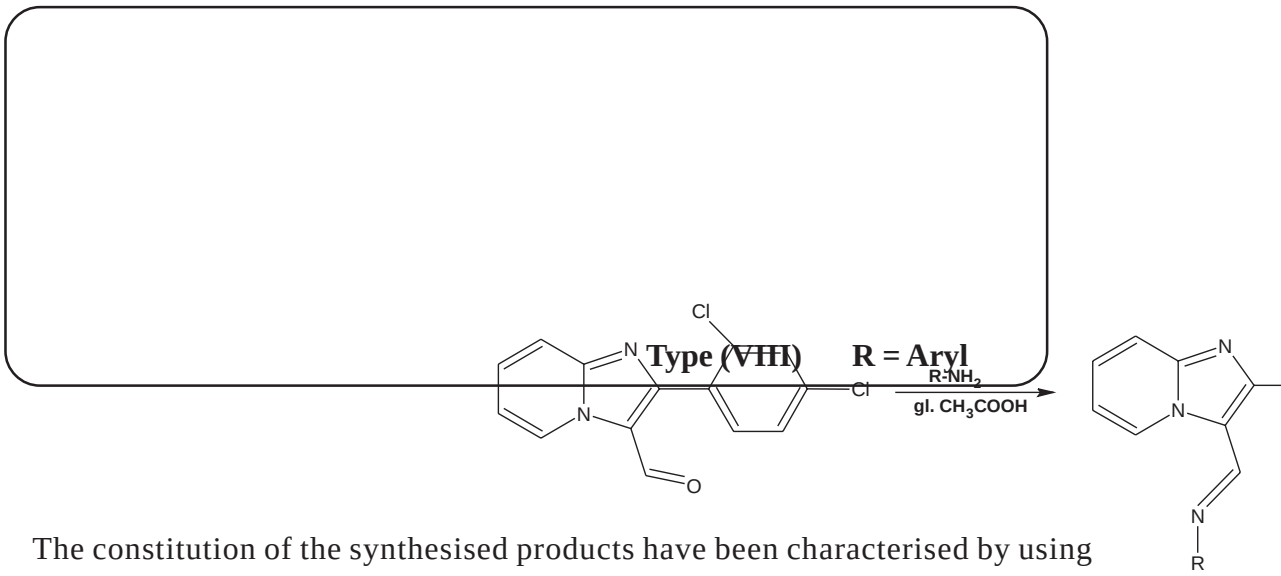
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{(1*E*)-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-ARYLAMINES

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*-ARYLAMINES

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{(1*E*)-[2-(2,4-DI CHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-ARYLAMINES

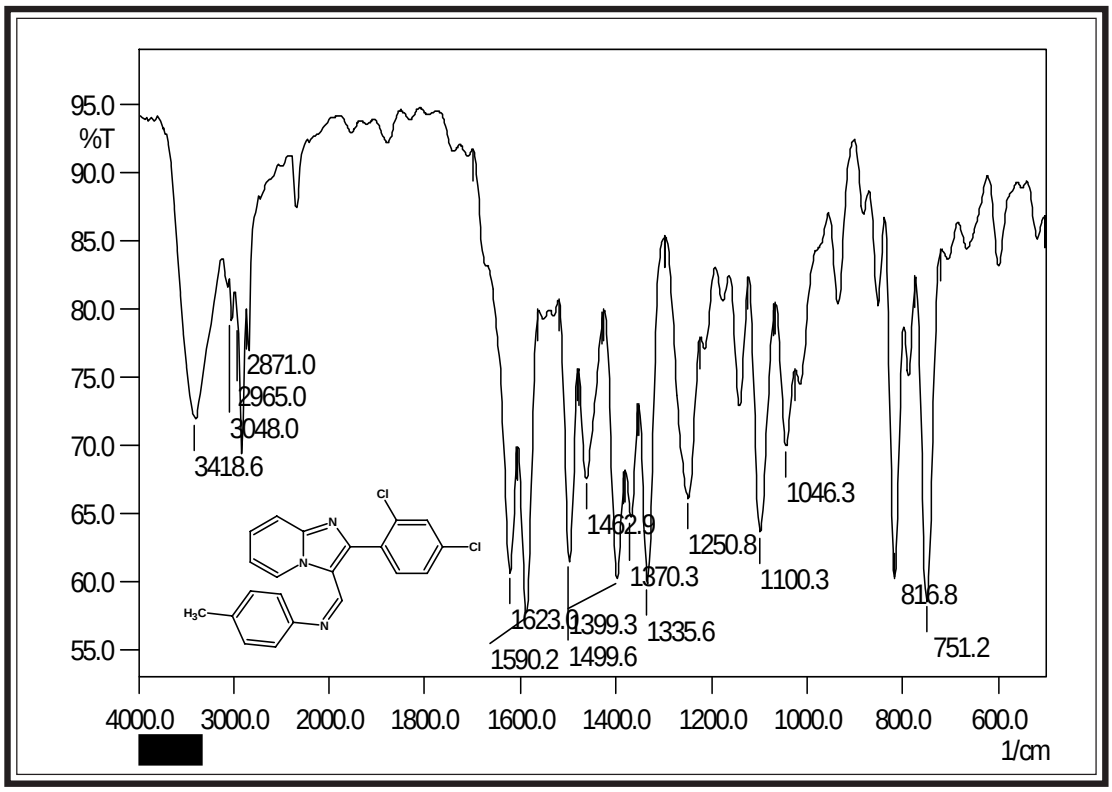
The growing patent literature of recent years demonstrates that the azomethine derivatives are used as better therapeutic agents. In view of these findings, it appeared of interest to synthesize Schiff's base of the Type (VIII) by the condensation of 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde with various aromatic amines in order to study their biodynamic behavior.



The constitution of the synthesised products have been characterised by using elemental analysis, infra red and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

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

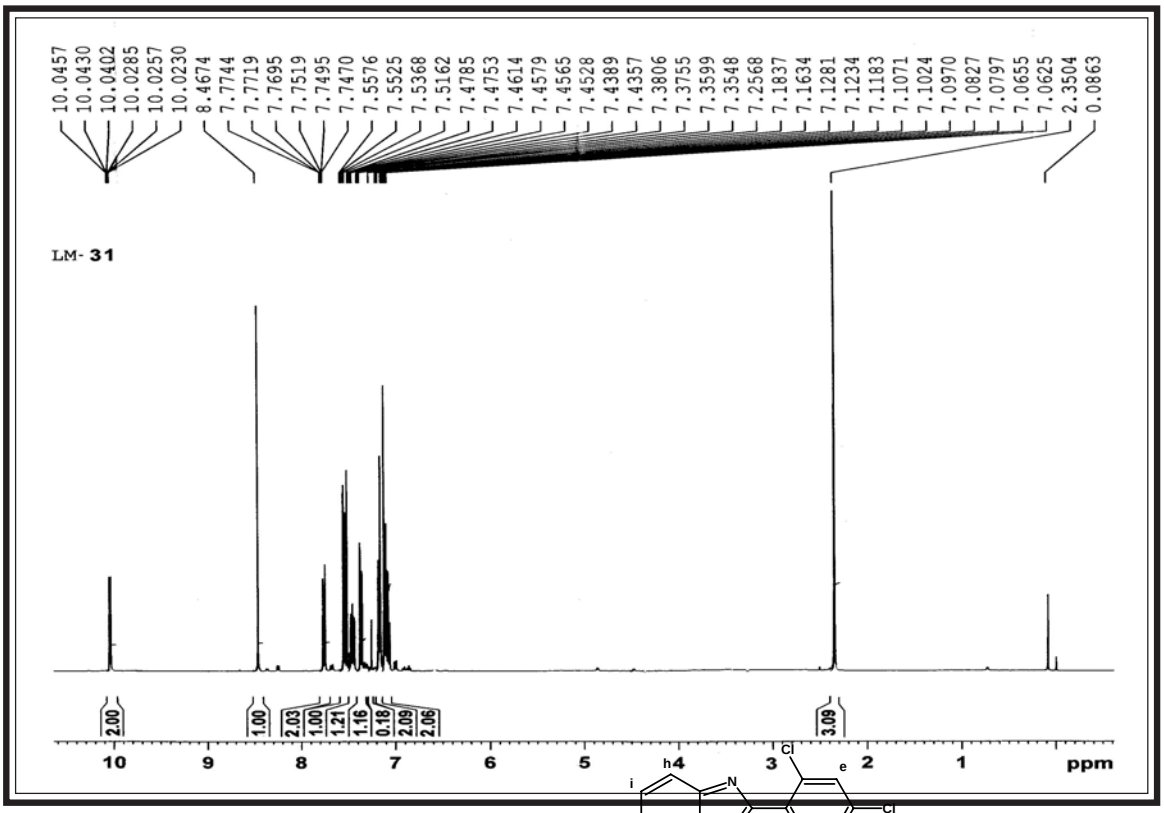
IR SPECTRAL STUDIES OF *N*-{(1*E*)-[2-(2,4-DICHLOROPHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-(4-METHYL PHENYL)AMINE



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.)	2965	2975-2950	31
$-CH_3$	C-H str. (sym.)	2871	2880-2860	,,
	C-H def. (asym.)	1462	1470-1435	,,
	C-H def. (sym.)	1370	1390-1370	,,
Aromatic	C-H str.	3048	3090-3030	32
	C=C str.	1499	1540-1480	,,
Halide	C-Cl str.	751	800-600	31
Schiff base	C=N str.	1622	1660-1580	32
Imidazo[1,2-a]	C=N str.	1590	1612-1593	31
pyridine	C-N str.	1100	1220-1020	,,

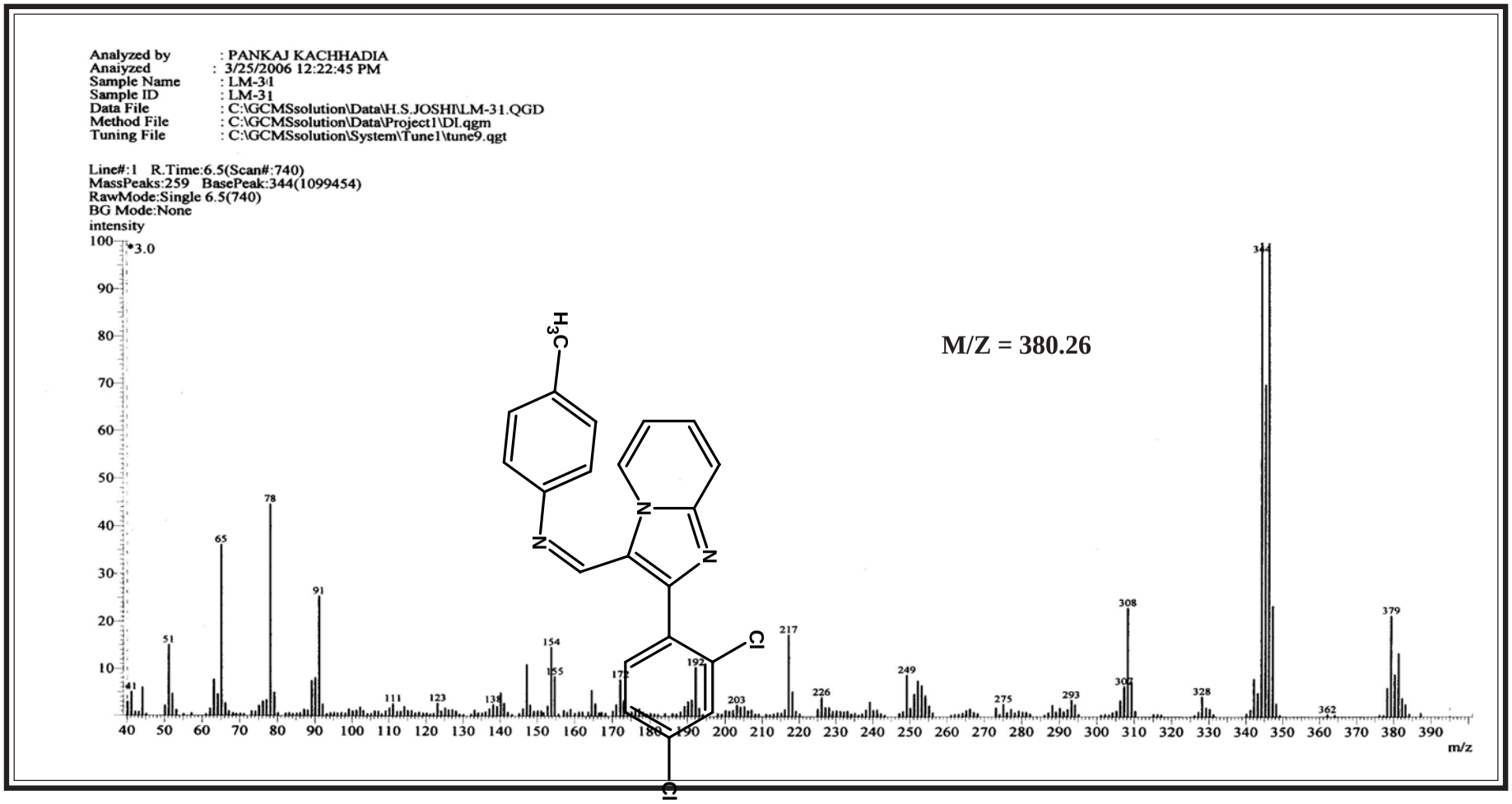
NMR SPECTRAL STUDIES OF *N*-{(1*E*)-[2-(2,4-DICHLOROPHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-(4-METHYL PHENYL)AMINE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1.	2.35	3H	singlet	Ar-CH_3	-
2.	8.46	1H	singlet	Ar-CH (d)	-
3.	7.06-7.12	4H	multiplet	Ar-CH (h, i, j, k)	-
4.	7.34-7.38	1H	doublet	Ar-CH (e)	J=1.5
5.	7.43-7.55	2H	multiplet	Ar-CH (g,f)	-
6.	7.74-7.77	2H	doublet	Ar-CH (b,b')	J=9
7.	10.02-10.04	2H	doublet	Ar-CH (c,c')	J=6.2

TABLE-8 : MASS SPECTRAL STUDIES OF *N*-{(1*E*)-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-(4-METHYLPHENYL)AMINE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{(1*E*)-[2-(2,4-DI CHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-ARYLAMINES

[A] Synthesis of 2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridine-3 carbaldehyde

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

[B] Synthesis of *N*-{(1*E*)-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-*N*-(4-methylphenyl)amine

A mixture of 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine-3 carbaldehyde (2.91g, 0.01M) and p-toludine(1.07g, 0.01M) in ethanol (20 ml) was refluxed in presence of glacial aceticacid in catalytic amount for 6 hr. The content was cooled and product isolated was crystallised from ethanol. Yield, 65%, m.p. 190°C, $C_{21}H_{15}Cl_2N_3$; Found : C, 66.33%; H, 3.98%; N,11.05%; Requires : C, 66.31%; H, 3.97%; N, 11.00%).

Similarly, other *N*-{(1*E*)-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-*N*-arylamines were prepared. The physical constants are recorded in Table No. 8.

[D] Biological screening of *N*-{(1*E*)-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-*N*-arylamine

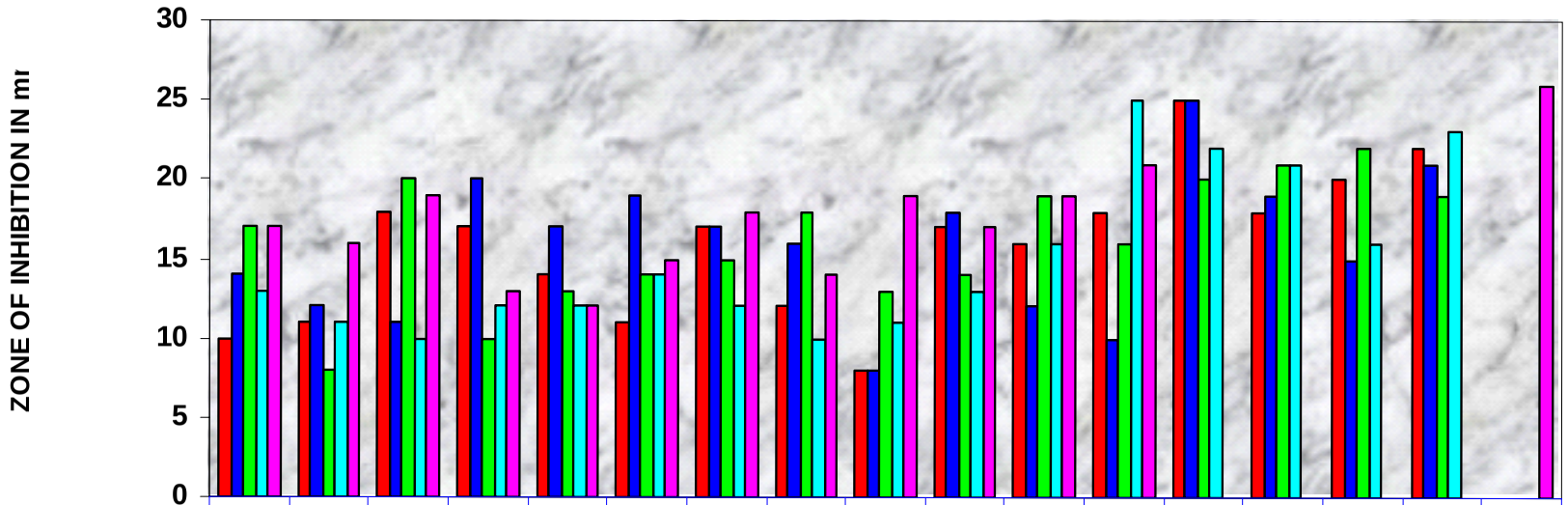
Antimicrobial testing was carried out as described in Part-I, Section-II (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 8.

TABLE : 8 PHYSICAL CONSTANTS OF *N*-{(1*E*)-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-ARYLAMINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
8a	C_6H_5-	$C_{20}H_{13}Cl_2N_3$	366.24	132	71	11.47	11.46	0.48	S_1
8b	4-CH_3-C_6H_4-	$C_{21}H_{15}Cl_2N_3$	380.26	190	65	11.05	11.00	0.53	S_2
8c	2-CH_3-C_6H_4-	$C_{21}H_{15}Cl_2N_3$	380.26	185	58	11.05	11.98	0.50	S_1
8d	2,5-$(CH_3)_2$-C_6H_3-	$C_{22}H_{17}Cl_2N_3$	394.29	165	55	10.66	10.65	0.56	S_2
8e	4-OCH_3-C_6H_4-	$C_{21}H_{15}Cl_2N_3O$	396.26	134	64	10.60	10.59	0.54	S_2
8f	2,5-$(Cl)_2$-C_6H_3-	$C_{20}H_{11}Cl_4N_3$	435.13	118	69	9.66	9.65	0.58	S_1
8g	4-Cl-C_6H_4-	$C_{20}H_{12}Cl_3N_3$	400.68	176	61	10.49	10.47	0.46	S_1
8h	3-Cl-C_6H_4-	$C_{20}H_{12}Cl_3N_3$	400.68	140	63	10.49	10.48	0.51	S_2
8i	4-F-C_6H_4-	$C_{20}H_{12}Cl_2FN_3$	384.23	126	50	10.94	10.93	0.59	S_2
8j	2-F-C_6H_4-	$C_{20}H_{12}Cl_2FN_3$	384.23	215	66	10.94	10.92	0.60	S_1
8k	3-NO_2-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	165	57	13.62	13.61	0.55	S_2
8l	4-NO_2-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	177	56	13.62	13.60	0.42	S_1

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

GRAPHICAL CHART NO. 8 : *N*-{(1*E*)-[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-*N*-ARYLAMINES

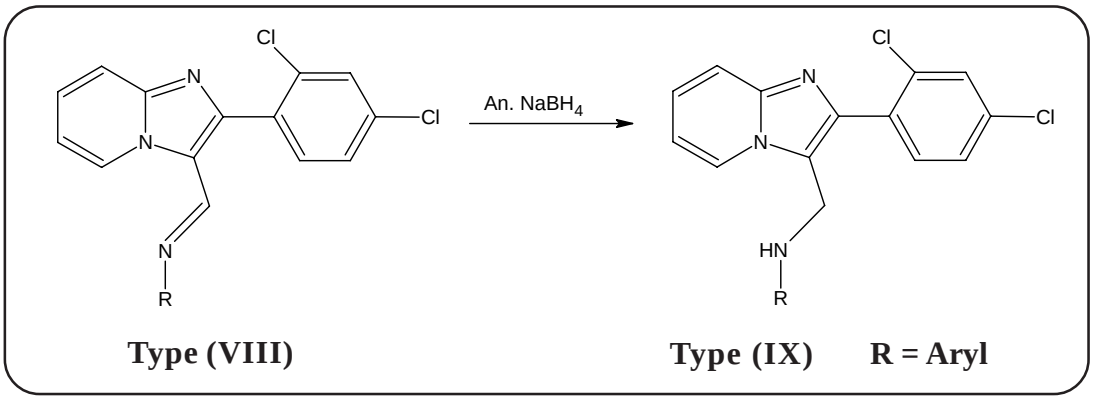


	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	Amoxycillin	Benzyl Penic	Ciprofloxacin	Erythromycin	Griseofulvin
B. Coccus	10	11	18	17	14	11	17	12	8	17	16	18	25	18	20	22	0
S. aureus	14	12	11	20	17	19	17	16	8	18	12	10	25	19	15	21	0
Aerogenes	17	8	20	10	13	14	15	18	13	14	19	16	20	21	22	19	0
Pseudomonas	13	11	10	12	12	14	12	10	11	13	16	25	22	21	16	23	0
A.niger	17	16	19	13	12	15	18	14	19	17	19	21	0	0	0	0	26

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*- ARYLAMINES

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 (imine group) Schiff's bases of Type (VIII) with sodium borohydride in controlled experimental condition as shown in the reaction scheme.

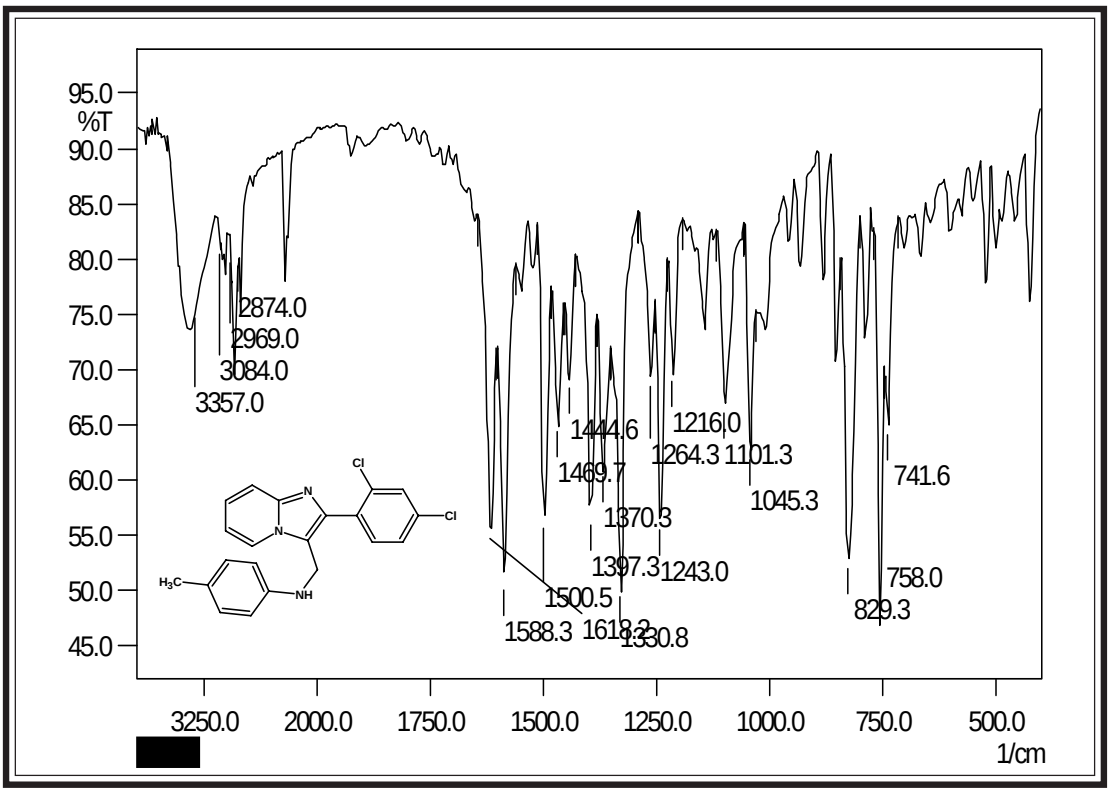


Type (VIII) **Type (IX)** **R = Aryl**

The constitution of the synthesised products have been characterised by using elemental analysis, infra red and ^{1}H nuclear magnetic resonance spectroscopy and mass spectrometry also.

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

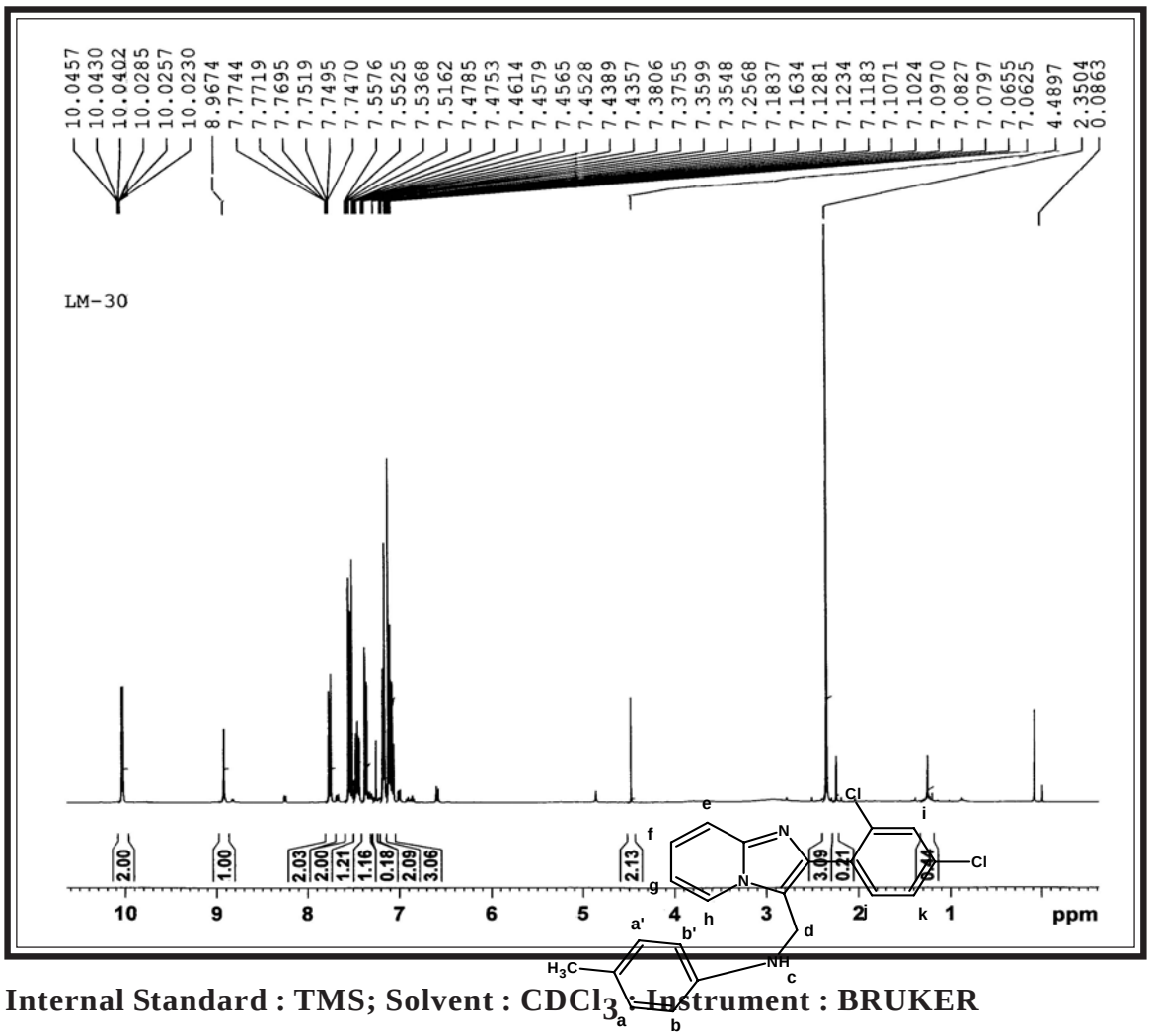
IR SPECTRAL STUDIES OF *N*-{[2-(2,4-DICHLOROPHENYL) IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*-(4-METHYLPHENYL) AMINE



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.)	2969	2975-2950	31
-CH_3	C-H str. (sym.)	2874	2880-2860	,,
	C-H def. (asym.)	1444	1470-1435	,,
	C-H def. (sym.)	1370	1390-1370	,,
Aromatic	C-H str.	3084	3090-3030	32
	C=C str.	1500	1540-1480	,,
		1101	1125-1090	,,
Halide	C-Cl str.	757	800-600	31
Imidazo[1,2-a]	C=N str.	1588	1612-1593	32
pyridine	C-N str.	1045	1220-1020	,,
Amine	N-H str.	3357	3400-3200	,,

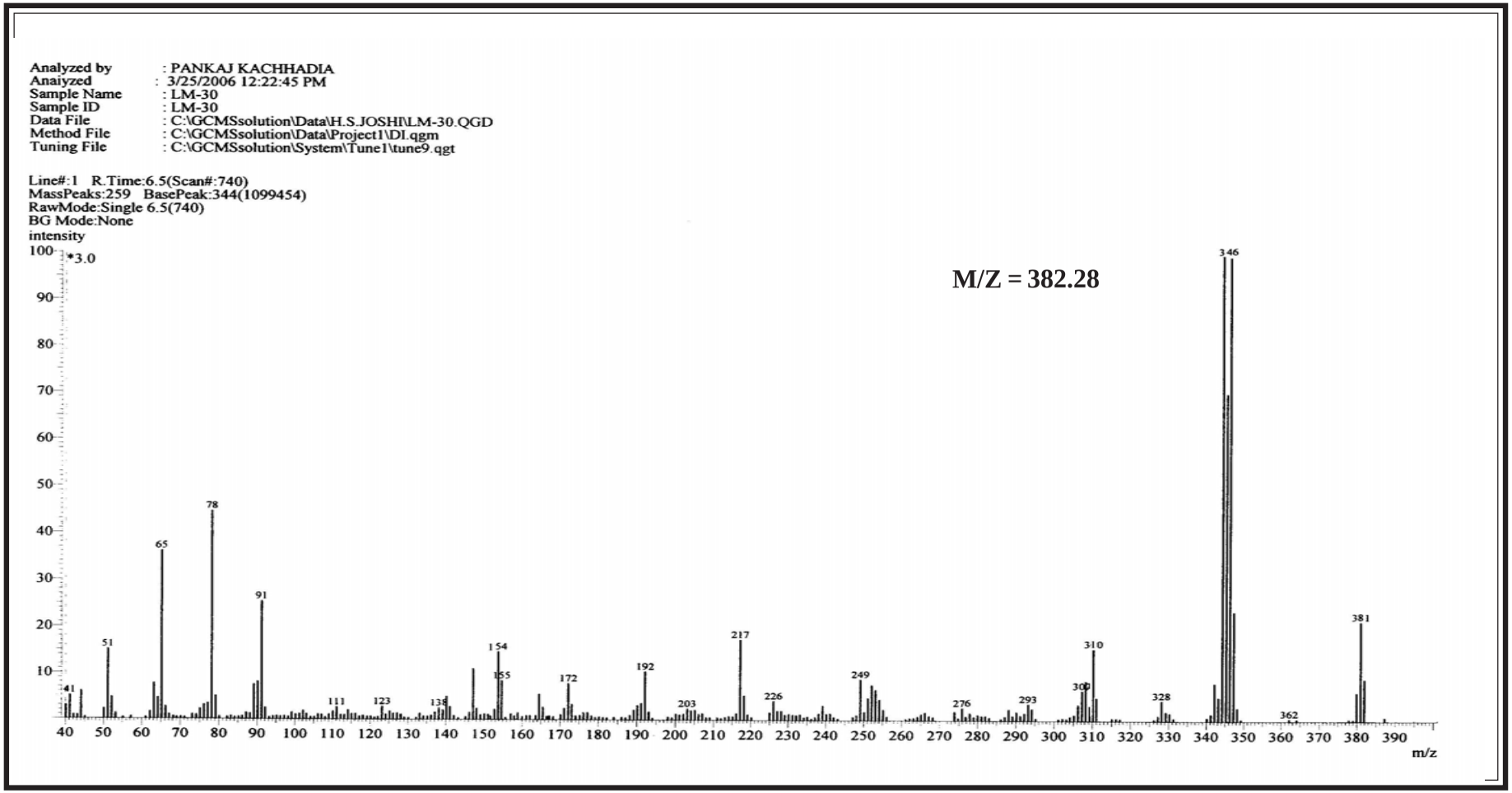
NMR SPECTRAL STUDIES OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO [1,2-a]PYRIDIN-3-YL]METHYL}-*N*-(4-METHYLPHENYL)AMINE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1.	2.3	3H	singlet	Ar-CH_3	-
2.	4.48	2H	singlet	C-CH_2 (d)	-
3.	7.06-7.18	4H	multiplet	Ar-CH (e,f,g,h)	-
4.	7.35-7.38	1H	doublet	Ar-CH (i)	J=1.7
5.	7.43-7.55	2H	multiplet	Ar-CH (j,k)	-
6.	7.74-7.77	2H	doublet	Ar-CH (a,a')	J=9
7.	8.96	1H	singlet	Ar-NH(c)	
8.	10.02-10.04	2H	doublet	Ar-CH (b,b')	J=6.2

TABLE-9 : MASS SPECTRAL STUDIES OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*- (4-METHYLPHENYL)AMINE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-{[2-(2,4-DICHLORO PHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*- ARYLAMINES

[A] Synthesis of *N*-{(1*E*)-[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-*N*-(4-methylphenyl)amine

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

[B] Synthesis of *N*-{[2-(2,4-Dichlorophenyl)imidazo[1,2-a]pyridin-3- yl] methyl}-*N*- (4-methylphenyl)amine

To a methanolic solution of *N*-{(1*E*)-[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-*N*-(4-methylphenyl)amine (0.01M, 3.80 g), sodium borohydride (0.15M, 0.57g) was added over a period of 30 minutes at temperature 5-10 ^{o}C. The reaction mixture was then kept over night at room temp. The excess borohydride was neutralized by adding water and the product was extracted with ether. The ether extract was washed with water untill neutral, then dried over anhydrous Na_2SO_4 and finally the ether was evaportated to give aminomethyl derivatives. Yield, 61%, m.p. 200^{o}C, $C_{21}H_{17}Cl_2N_3$; Found : C, 65.98%; H, 4.48%; N, 10.99%; Requires : C, 65.96%; H, 4.47%; N, 10.98%.

Similarly, other *N*-{[2-(2,4-dichlorophenyl)imidazo[1,2-a]pyridin-3-yl] methyl}-*N*- arylamines were prepared. The physical constants are recorded in Table No. 9.

[D] Biological screening of *N*-{[2-(2,4-Dichlorophenyl)imidazo[1,2-a]pyridin-3-yl]methyl}-*N*- arylamines

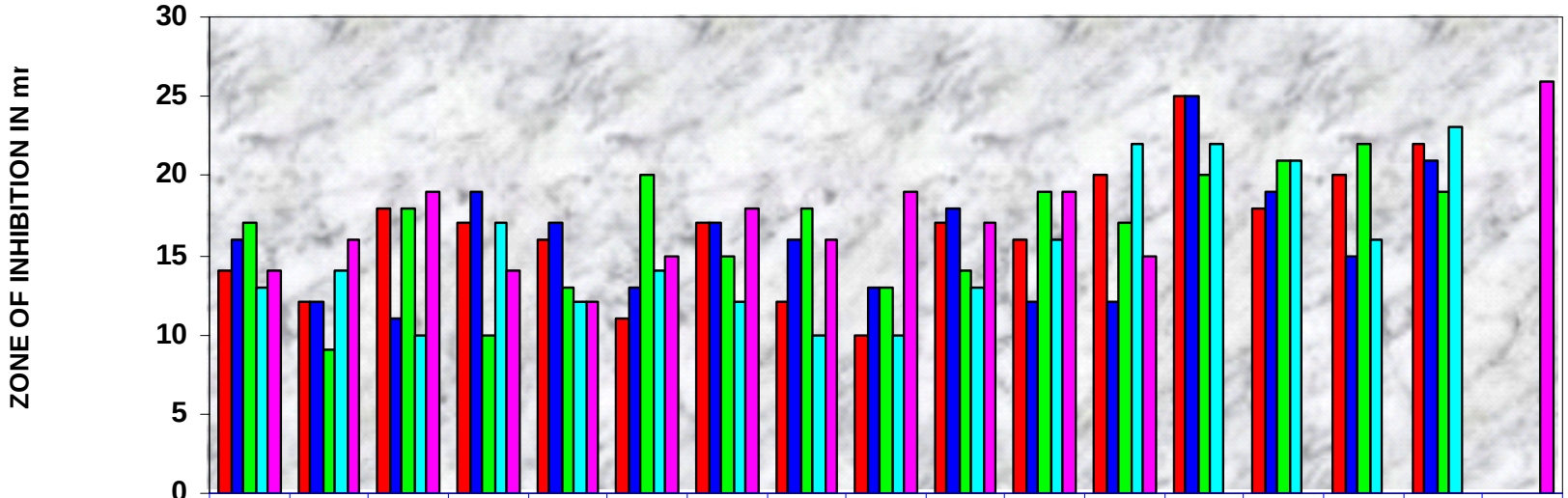
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 9.

TABLE : 9 PHYSICAL CONSTANTS OF *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*- ARYLAMINES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
9a	C_6H_5-	$C_{20}H_{15}Cl_2N_3$	368.25	148	68	11.41	11.40	0.47	S_2
9b	4-CH_3-C_6H_4-	$C_{21}H_{17}Cl_2N_3$	382.28	200	61	10.99	10.98	0.53	S_2
9c	2-CH_3-C_6H_4-	$C_{21}H_{17}Cl_2N_3$	382.28	185	58	10.99	10.97	0.49	S_1
9d	2,5-$(CH_3)_2$-C_6H_3-	$C_{22}H_{19}Cl_2N_3$	396.31	165	53	10.60	10.59	0.52	S_2
9e	4-OCH_3-C_6H_4-	$C_{21}H_{17}Cl_2N_3O$	398.28	134	64	10.55	10.54	0.57	S_2
9f	2,4-$(Cl)_2$-C_6H_3-	$C_{20}H_{13}Cl_4N_3$	437.14	118	69	9.61	9.60	0.50	S_1
9g	4-Cl-C_6H_4-	$C_{20}H_{14}Cl_3N_3$	402.70	126	61	10.43	10.42	0.58	S_1
9h	3-Cl-C_6H_4-	$C_{20}H_{14}Cl_3N_3$	402.70	140	63	10.43	10.41	0.54	S_2
9i	2-F-C_6H_4-	$C_{20}H_{14}Cl_2FN_3$	386.24	126	50	10.88	10.89	0.59	S_1
9j	4-F-C_6H_4-	$C_{20}H_{14}Cl_2FN_3$	386.24	146	66	10.88	10.86	0.60	S_1
9k	3-NO_2-C_6H_4-	$C_{20}H_{14}Cl_2N_4O_2$	413.25	165	57	13.56	13.54	0.55	S_2
9l	4-NO_2-C_6H_4-	$C_{20}H_{14}Cl_2N_4O_2$	413.25	136	55	13.56	13.55	0.45	S_1

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

GRAPHICAL CHART NO. 9 : *N*-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-a]PYRIDIN-3-YL]METHYL}-*N*-ARYL AMINES



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Amoxycillin	Benzyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	14	12	18	17	16	11	17	12	10	17	16	20	25	18	20	22	0
S. aureus	16	12	11	19	17	13	17	16	13	18	12	12	25	19	15	21	0
Aerogenes	17	9	18	10	13	20	15	18	13	14	19	17	20	21	22	19	0
Pseudomonas	13	14	10	17	12	14	12	10	10	13	16	22	22	21	16	23	0
A.niger	14	16	19	14	12	15	18	16	19	17	19	15	0	0	0	0	26

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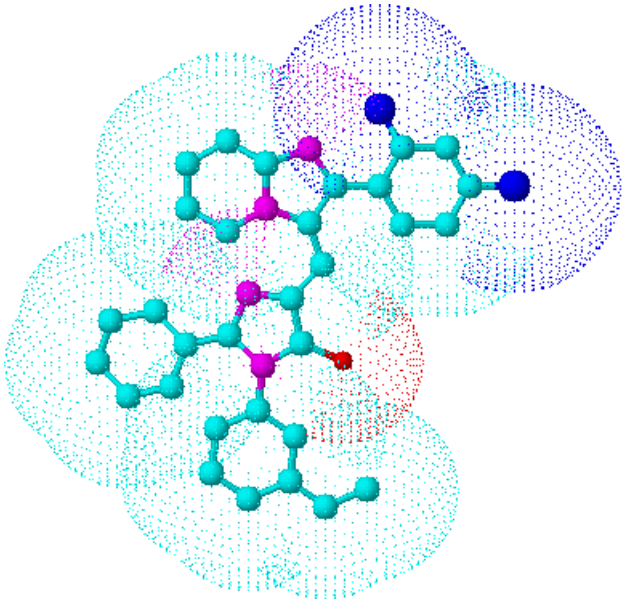


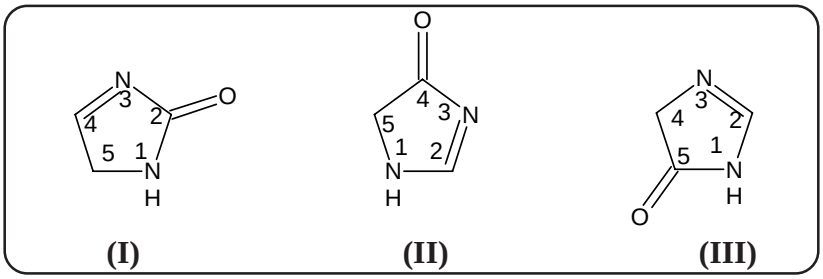
PART - VII

STUDIES ON

IMIDAZOLINONES

INTRODUCTION

Imidazolinone is a five membered heterocycle having 2-nitrogen atoms at 1 and 3 positions and C=O group at following positions : 2-oxo-imidazoline (I), 4-oxo-imidazoline (II), 5-oxo-imidazoline (III).

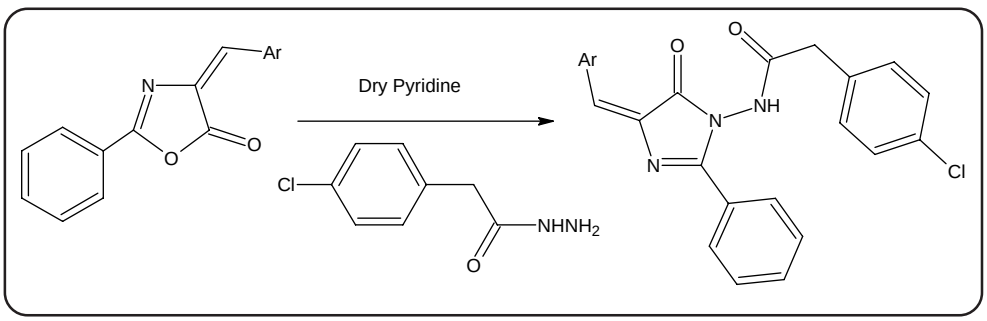


The discovery of the 2-substituted-5-imidazolines dates back to the year 1888, when A. W. Hoffman[1] for the first time discovered 5-oxo-imidazoline by heating N^1-diacetylethylene diamine in a stream of dry hydrogen chloride. Moreover, some compounds were prepared by A. Ladenburg[2] by the fusion of two equivalents of sodium acetate with one equivalent of ethylene diamine dihydrochloride.

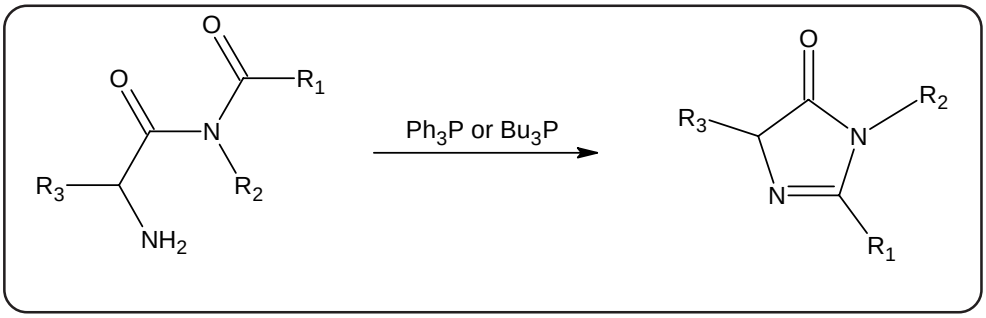
SYNTHETIC ASPECT

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

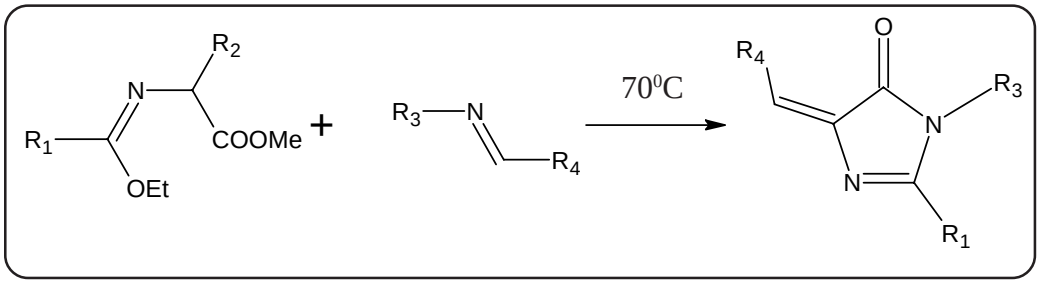
1. Allimony et al.[5] have synthesized new imidazolinone derivatives by conventional method.
2. Feng Jun Cai et al.[6] have reported 5-imidazolinone derivatives by microwaves irradiation.
3. A. Saxena et al.[7] have synthesized new imidazolinones as under.



4. Hisato Takeuchi et al.[8] have synthesized imidazolinones by the reaction of azido substituted imides with triphenylphosphine or tributylphosphine.

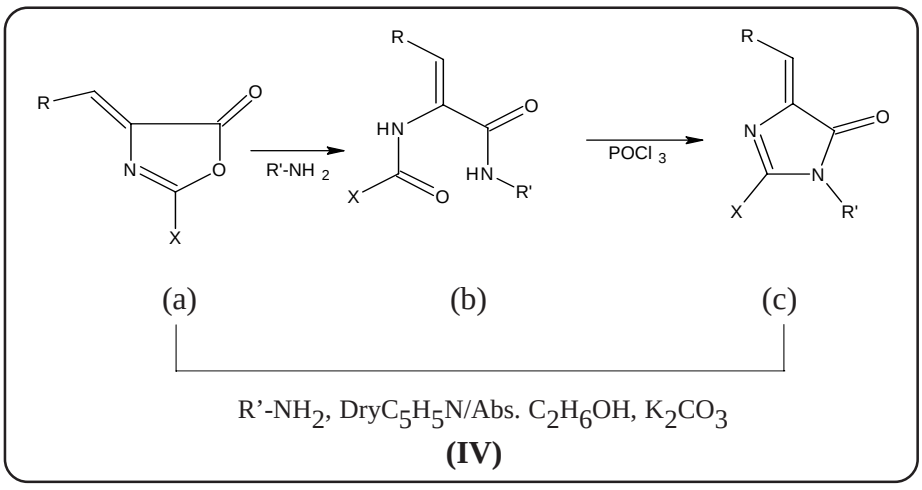


5. Jean Michel Lerestif et al.[9] have synthesized imidazolinone from α-aminoester.



MECHANISM

Azalactone reacts with variety of compounds such as water, alcohols, amines and hydrogen halides. Amides of α-acylamino acryclic acids obtained from the condensation of azalactone and primary amines can be converted into imidazolinones as shown in equation (IV). The ring closer can be affected under a variety of conditions. Substituted anilides have been converted to imidazolinone derivatives by the action of $POCl_3$.



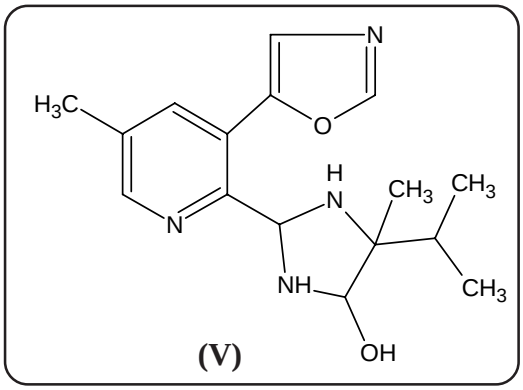
(IV)

THERAPEUTIC IMPORTANCE

Naphazoline hydrochloride, xylometazoline hydrochloride etc. are various imidazolinone derivatives which have been used as adrenergic stimulants and tolazoline and phenotolamine as adrenergic blocking agents. Various imidazolinones are known to exhibit a broad spectrum of biological activities such as,

1. Anticonvulsant[10,11]
2. Antihistaminic[12]
3. Antidiabatic[13]
4. Antitubercular[14]
5. Bactericidal[15,16]
6. Fungicidal[17,18]
7. Antiparkinsonian[19,20]
8. Anthelmintic[21]
9. Sedative and hypnotics[22]
10. Anticancer[23, 24]
11. Antimicrobial[25]
12. Potent CNS depressant[26, 27]
13. Insecticidal[28]
14. Antiviral[29]
15. Hypertensive[30]
16. Antiinflammatory[31-33]
17. Thrombin inhibitor[34]

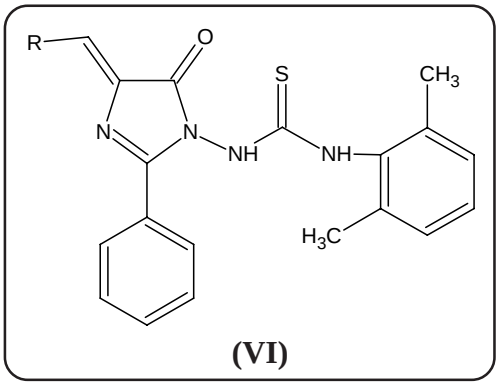
Christopher Preston and co-workers[35] have reported the triazolopyrimidine and imidazolinone as herbicides. U. Akyoshi et al.[36] have prepared some new imidazolinone derivatives (V) and reported their herbicidal activity. Agrochemical activity of imidazolinones have been reported by Bascou and co-workers.[37]



(V)

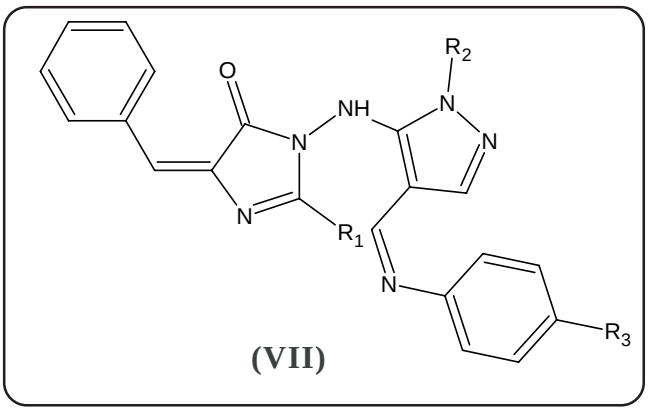
Moreover Yoneda Naoto et al.[38] have synthesized imidazolinones as antihypertensive agent. R. C. Dage et al.[39] have documented cardiotonic imidazolones. Rossello et al.[40] have prepared imidazolones as antifungal agent. Cooper A. B. and co-workers[41] have found that imidazolones are inhibitors of farnesyl protein transferase. Machii Daisuke et al.[42] have synthesized new imidazolones as a telomeres inhibitors and antitumor agents. Jean M. R. et al.[43] have synthesized imidazolones and tested as antileishmanial agent. Chafiq amdouchi et al.[44] have reported imidazolinones and screened for their potent and broad spectrum activity.

K. K. Awasthi et al.[45] have synthesized some new imidazolinone derivatives (VI) and reported their antimicrobial activity. A. J. Baxi and co-workers[46] have synthesized several imidazolinone derivatives by the condensation of some known sulpha drugs with 5-oxazolone derivatives, products have been screened for their *in vitro* growth inhibitory activity against several microorganisms and *in vivo* anticonvulsant activity.



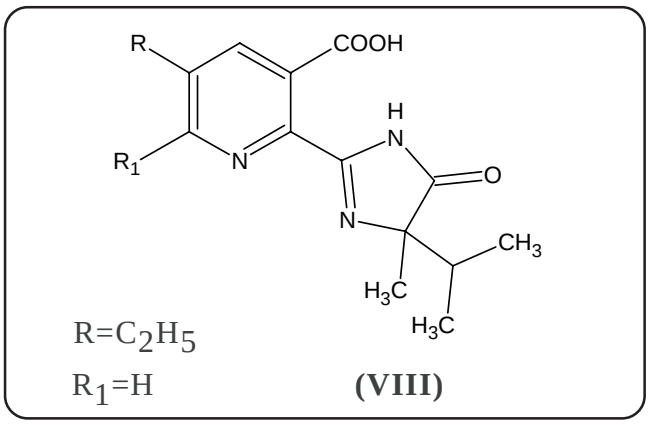
(VI)

Rama Sharma and co-workers[47] have reported antimicrobial activity of 5-oxo-imidazolines (VII).



(VII)

Xu Zhi-Feng et al.[48] have synthesized imidazolinones as biological agent. Farmshow Christopher Geoffrey et al.[49] and Pilkington et al.[50] have described and studied antifungal activity of imidazolinones. L. Joseph Peter and co-workers[51] have prepared substituted imidazolinones which inhibited the abnormal cell growth in human body. Stefama Lauter and co-workers[52] have isolated imidazoline from different methods and tested for the treatment of cytokine release. Imidazoline derivatives have been prepared by Declera arthur and co-workers[53] showing anti-HIV activity. Ding Ming Wu et al.[54] have prepared novel imidazolines and reported their antifungal activity. C. Alister and co-workers[55] have documented herbicidal activity of imidazolinone derivatives. Aleksey N. Vasiliev et al.[56] have synthesized imidazolinone derivatives (VIII) and reported their herbicidal activity.



(VIII)

Kolhe Vishnu et al.[57] have reported anti-AIDS, antibacterial and fungicidal activity of 5-oxo-imidazolines. B. R. Shah and co-workers[58] have prepared some new imidazolines and reported anticancer and anti HIV activity.

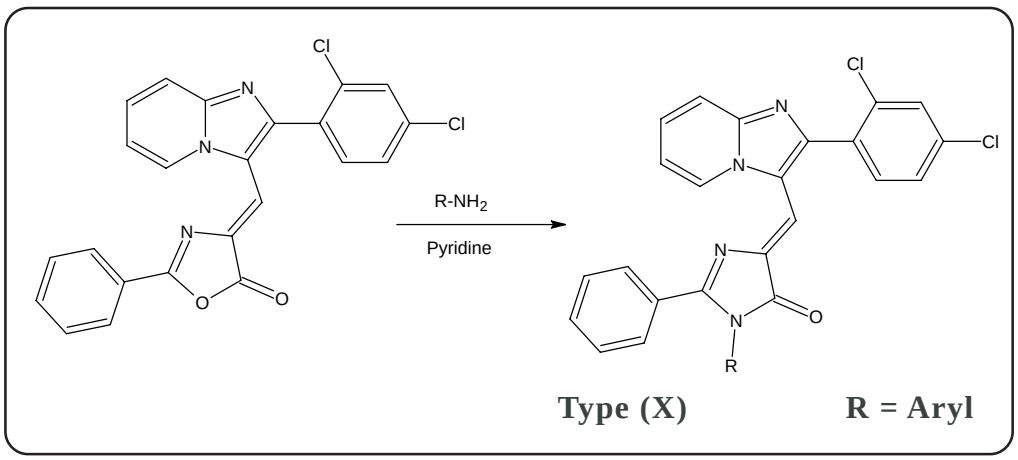
With a view to getting better therapeutic agent, it was contemplated to synthesize imidazolinones to enhance the overall activity of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF (5*Z*)-5-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-3-ARYL-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF (5*Z*)-5-{[2-(2,4-DI CHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-3-ARYL-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONES

Imidazolinones represent one of the most active class of compounds having a wide spectrum of biological activities. With an aim to getting better therapeutic agent, the preparation of (5*Z*)-5-{[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-3-aryl-2-phenyl-3,5-dihydro-4*H*-imidazol-4-ones of Type (X) have been undertaken by the condensation of azalactone with different aromatic amines as shown in reaction scheme.

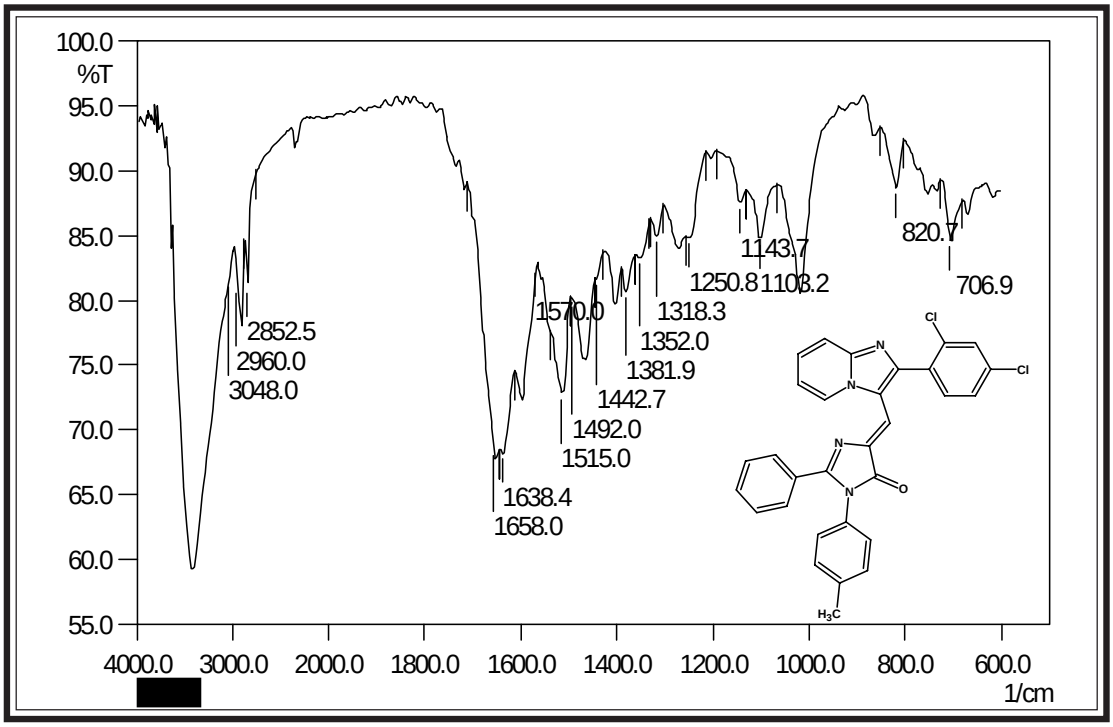


Type (X) **R = Aryl**

The constitution of the synthesized products have been characterized by using elemental analysis, infra red and ^{1}H-nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

All the products have been screened for their ***in vitro*** biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in **(A)** Part-I, Section-I (D).

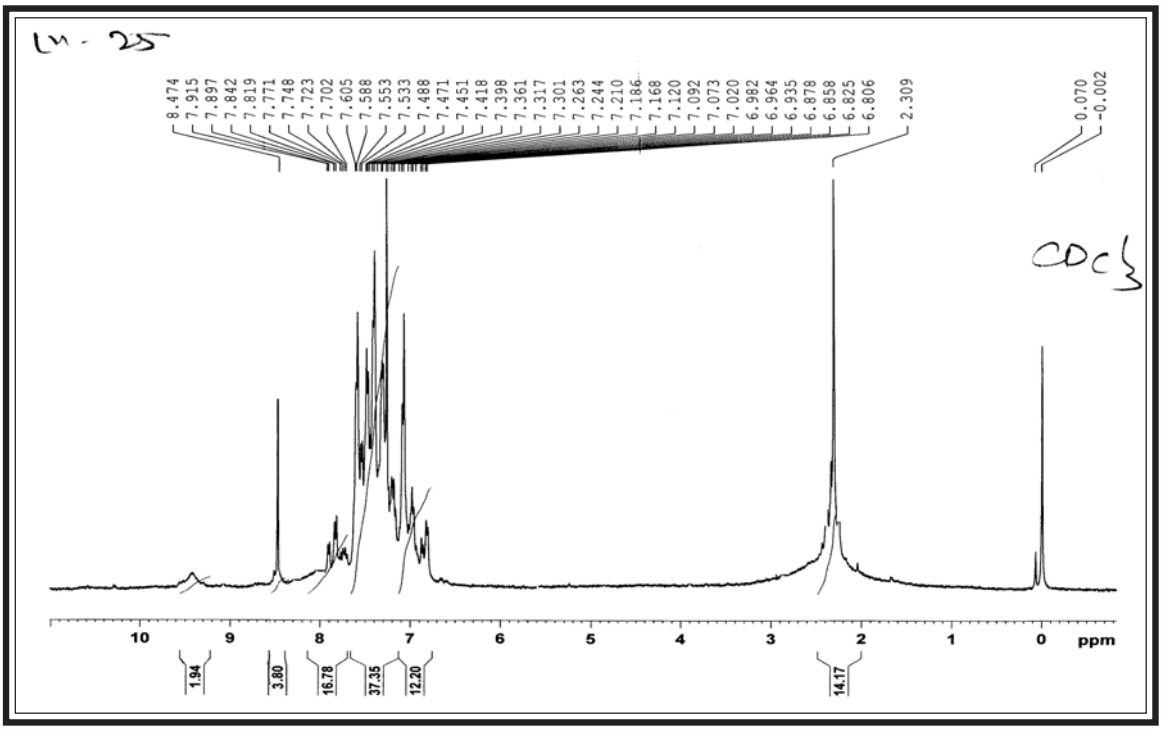
IR SPECTRAL STUDIES OF (5*Z*)-5-{[2-(2,4-DICHLOROPHENYL)IMIDAZO [1,2-*a*]PYRIDIN-3-YL]METHYLENE}-3-(4-METHYLPHENYL)-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONE



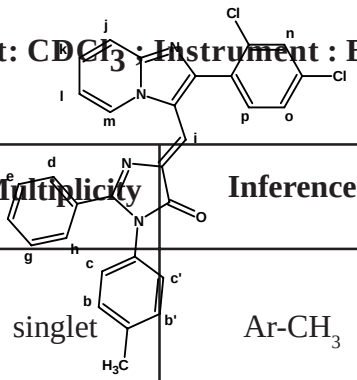
Instrument : SHIMADZU-FT-IR 8400-Spectrophotometer ; Frequency range : 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2960	2975-2950	59
-CH_3	C-H str. (sym.)	2852	2880-2860	,,
	C-H i.p.def. (asym.)	1442	1470-1435	,,
Aromatic	C-H str.	3048	3090-3030	60
	C=C str.	1514	1540-1480	,,
	C-H o.o.p. (def)	820	835-810	,,
Imidazo[1,2-a]	C=N str.	1638	1600-1650	,,
pyridine	C-N str.	1143	1220-1020	,,
Imidazole	C=O str.	1658	1760-1655	59
ring	C=N str.	1570	1650-1580	,,
	C=C str.	1492	1540-1480	,,
Halide	C-Cl str.	706	800-600	60

NMR SPECTRAL STUDIES OF (5Z)-5-{[2-(2,4-DICHLOROPHENYL) IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-3-(4-METHYLPHENYL)-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONE

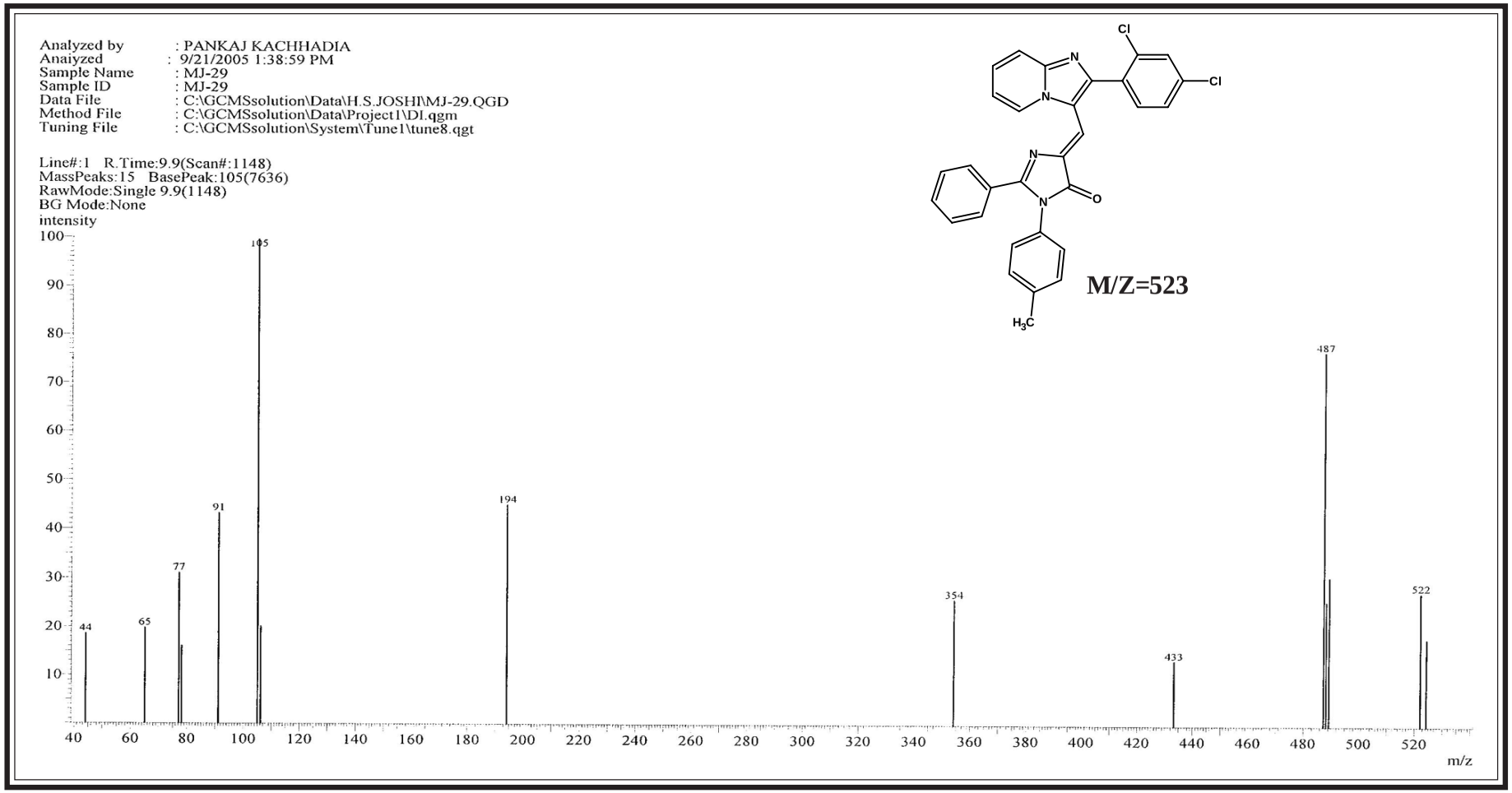


Instrumental Standard : TMS; Solvent: $CDCl_3$; Instrument : BRUKER Spectrometer (300MHz)



Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1.	2.309	3H	singlet	Ar-CH_3	-
2.	6.8-7.1	3H	multiplet	Ar-H(n,o,p)	-
3.	7.1-7.7	9H	multiplet	Ar-H (d,e,f,g,h,j,k,l,m)	-
4.	7.72-7.85	2H	doublet	Ar-H (b,b')	J=9
5.	7.87-7.95	2H	doublet	Ar-H (c,c')	J=6.2
6.	8.47	1H	singlet	Ar-H (i)	-

TABLE-10 : MASS SPECTRAL STUDIES OF (5*Z*)-5-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] METHYLENE}-3-(4-METHYLPHENYL)-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF (5*Z*)-5-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-3-ARYL-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONES

[A] Synthesis of 2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde

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

[B] Synthesis of (4*Z*)-4-{[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-2-phenyl-1,3-oxazol-5(4*H*)-one

A mixture of 2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (2.91 gm, 0.01 mol), acetic anhydride (7.6 ml, 0.075 mol), hippuric acid (4.4gm, 0.025 mol) and sodium acetate (2.46 gm 0.03 mol) was heated on a waterbath for 4-5 hr. The resulting solution was poured on to crushed ice, filtered and crystallized from dioxane. Yield, 68%, m.p. 232^{O}C.

[C] Synthesis of (5*Z*)-5-{[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-3-(4-methylphenyl)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one

To a solution of (4*Z*)-4-{[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-2-phenyl-1,3-oxazol-5(4*H*)-one (4.34 gm, 0.01 mol) and p-toluidine (1.27gm, 0.01 mol) in dry pyridine (25 ml) was refluxed for 12 hr. on oil bath. The content was poured on to crushed ice and neutralized with HCl, the isolated product crystallized from dioxane. Yield 66%, m.p. 142^{O}C; Anal. Calcd. for $C_{30}H_{20}Cl_2N_4O$; Requires : C, 68.84; H, 3.85; N, 10.70 %; Found : C, 68.82, H, 3.84, N, 10.71 %.

Similarly other (5*Z*)-5-{[2-(2,4-dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-3-aryl-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one were prepared. The physical constants are recorded in Table No. 10.

[D] Biological screening of (5*Z*)-5-{[2-(2,4-Dichlorophenyl)imidazo[1,2-*a*]pyridin-3-yl]methylene}-3-aryl-2-phenyl-3,5-dihydro-4*H*-imidazol-4-ones.

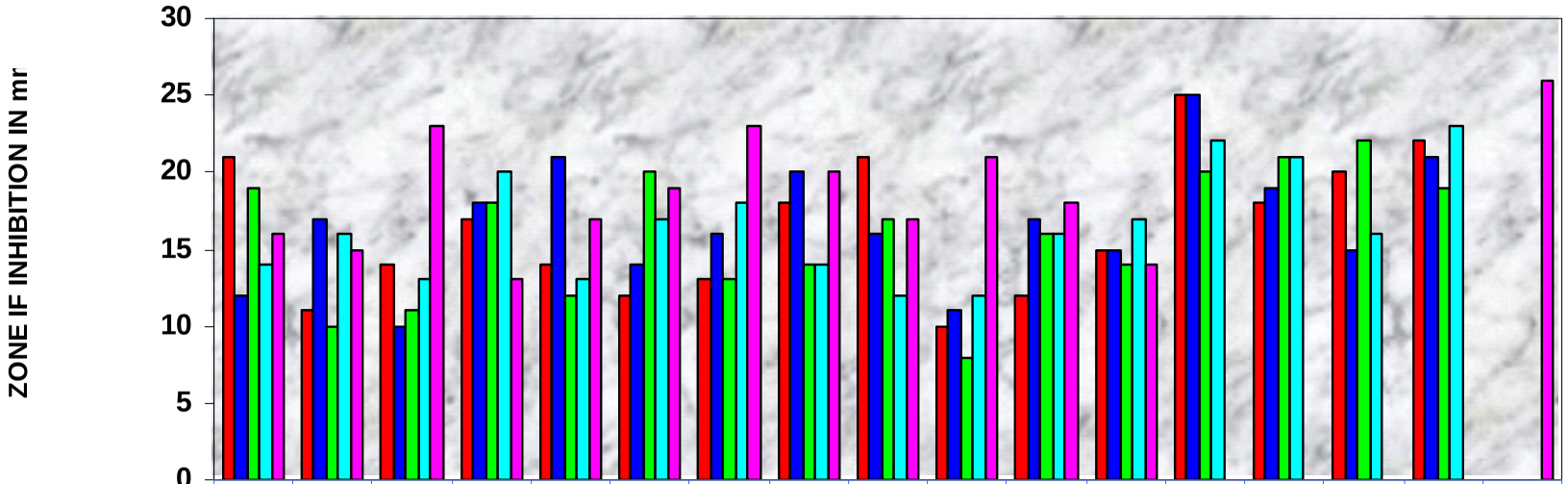
Antimicrobial activity was carried out as described in **(A)**Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 10

TABLE-10 : PHYSICAL CONSTANTS OF (5*Z*)-5-{[2-(2,4-DI CHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL] METHYLENE}-3-ARYL-2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONES

Sr. No.	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
10a	C_6H_5-	$C_{29}H_{18}Cl_2N_4O$	509.38	170	45	11.00	10.90	0.42	S1
10b	4-Cl-C_6H_4-	$C_{29}H_{17}Cl_3N_4O$	543.83	120	62	10.30	10.29	0.47	S2
10c	4-NO_2-C_6H_4-	$C_{29}H_{17}Cl_2N_5O_3$	554.38	151	68	12.63	12.62	0.53	S1
10d	2-CH_3-C_6H_4-	$C_{30}H_{20}Cl_2N_4O$	523.41	178	60	10.70	10.69	0.50	S2
10e	4-CH_3-C_6H_4-	$C_{30}H_{20}Cl_2N_4O$	523.41	142	66	10.70	10.71	0.58	S2
10f	2-OCH_3-C_6H_4-	$C_{30}H_{20}Cl_2N_4O_2$	539.41	251	68	10.39	10.38	0.41	S1
10g	4-OCH_3-C_6H_4-	$C_{30}H_{20}Cl_2N_4O_2$	539.41	168	74	10.39	10.37	0.59	S1
10h	4-F-C_6H_4-	$C_{29}H_{17}Cl_2FN_4O$	527.37	263	65	10.62	10.60	0.44	S2
10i	2-Cl-C_6H_4-	$C_{29}H_{17}Cl_3N_4O$	543.83	142	70	10.30	10.28	0.46	S2
10j	3,4-$(Cl)_2$-C_6H_4-	$C_{29}H_{16}Cl_4N_4O$	578.27	175	79	9.69	9.68	0.57	S1
10k	2,6-$(Cl)_2$-C_6H_4-	$C_{29}H_{16}Cl_4N_4O$	578.27	268	66	9.69	9.67	0.54	S2
10l	3-OH-C_6H_4-	$C_{29}H_{18}Cl_2N_4O_2$	525.38	198	59	10.66	10.65	0.56	S1

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

GRAPHICAL CHART NO. 10 : (5*Z*)-5-{[2-(2,4-DICHLOROPHENYL)IMIDAZO[1,2-*a*]PYRIDIN-3-YL]METHYLENE}-3-ARYL -2-PHENYL-3,5-DIHYDRO-4*H*-IMIDAZOL-4-ONES



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Amoxicillin	Benzoylpenic	Ciprofloxacin	Erythromycin	Griseofulvin
B. Coccus	21	11	14	17	14	12	13	18	21	10	12	15	25	18	20	22	0
S. aureus	12	17	10	18	21	14	16	20	16	11	17	15	25	19	15	21	0
Aerogenes	19	10	11	18	12	20	13	14	17	8	16	14	20	21	22	19	0
Pseudomonas	14	16	13	20	13	17	18	14	12	12	16	17	22	21	16	23	0
A.niger	16	15	23	13	17	19	23	20	17	21	18	14	0	0	0	0	26

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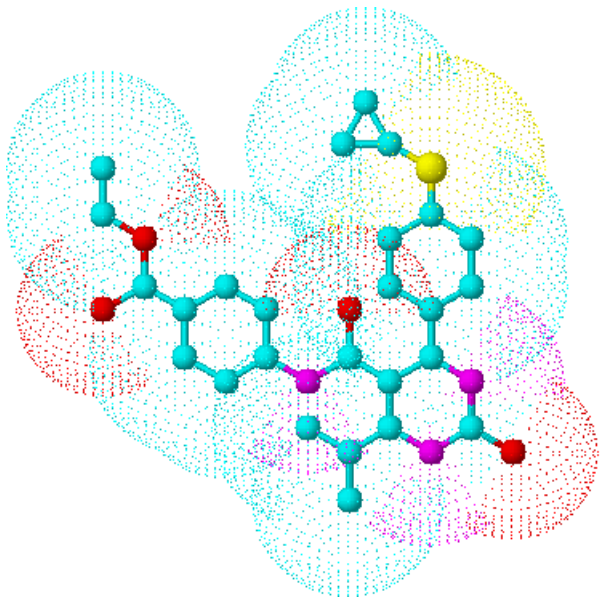


[B]

STUDIES ON

DIHYDROPYRIMIDINES

INTRODUCTION :

Dihydroyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Purines, uric acid, barbituric acid and antimalarial, antibacterial agents also contain the dihydropyrimidine ring. The chemistry of pyrimidine has been widely studied. Pyrimidine was first isolated by Gabriel and Colman in 1899. Despite the importance of dihydroazines (particularly those containing the 1,4-dihydropyrimidine and dihydropyridine moiety[1]) for clarifying a wide range of theoretical, medicinal and biological problems, the chemistry of this group of compounds is still extremely spotty. [2-6]

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.[7-11] Additionally, dihydropyridines have been found to actively transport medication across biological membranes.[12]

Until recently, most of the information available on dihydroazines centered around dihydropyridines, with very little data extending to the related dihydropyrimidines.

This lacuna has motivated our deep involvement in developing dihydropyrimidine chemistry, particularly dihydropyrimidines containing no substituents on the ring nitrogen.[13] These molecules have long been considered unstable for oxidation, polymerization or disproportionation reactions.[14]

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

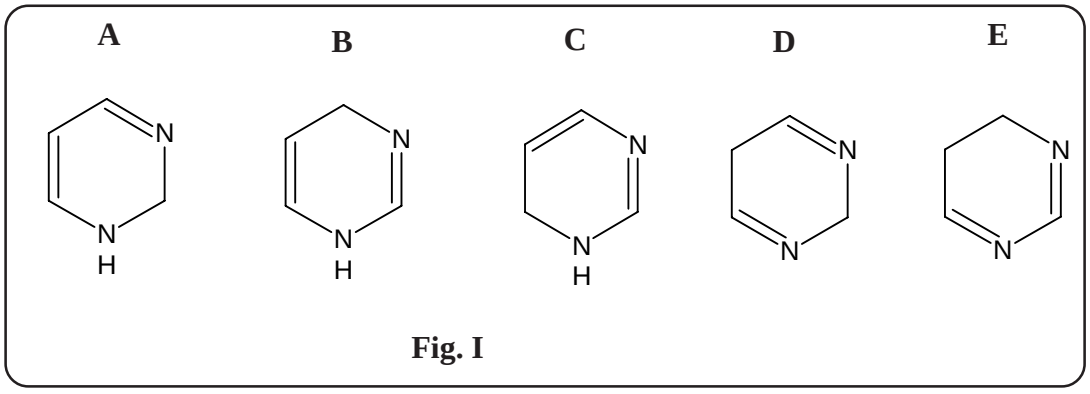


Fig. I

SYNTHETIC ASPECT :

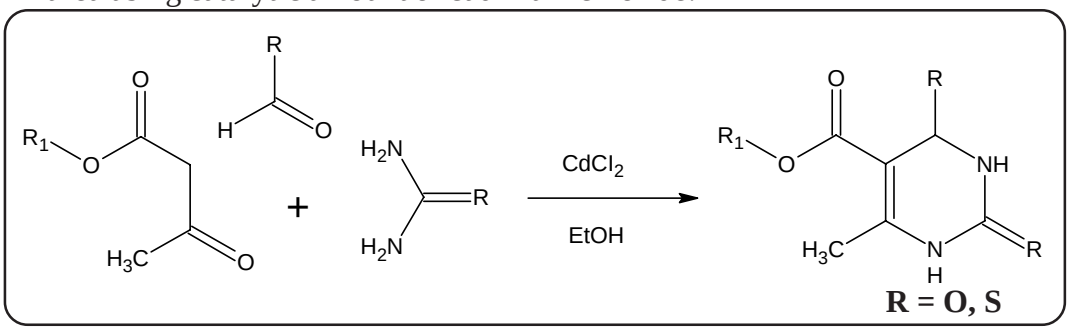
(1) A simple effective synthesis of DHPM-2(1H)-one derivatives is using $FeCl_3$ as catalyst by the reaction of an aldehyde, β-dicarbonyl compound and urea/ thiourea.[15]

(2) A novel one-pot condensation of an aldehyde, b-keto-ester and urea was performed using iodotrimethylsilane in acetonitrile for the first time at room temperature affording DHPMs.[16]

(3) Recently Kappe C. O.[17] demonstrated that by using neat polyphosphate ester(PPE) as reaction mediator coupled with microwave irradiation, excellent yield of variously substituted DHPMs can be obtain.

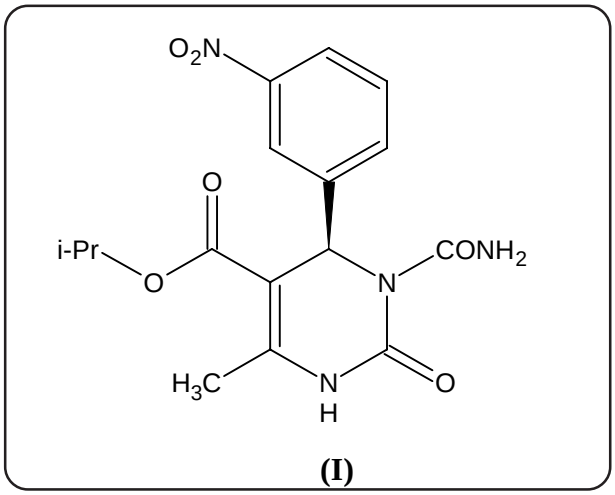
(4) Reddy et al.[18] described practical rout for the Biginelli reaction using zirconium tetrachloride as a catalyst. Three component condensation reaction of an aromatic aldehyde, β-ketoester and urea /thiourea in ethanol afforded the corresponding DHPM-2-(1H)-ones in high yield.

(5) Shingare M. S. et al.[19,20] examined a simple but effective procedure for Biginelli condensation reaction of an aldehyde, β–ketoester and urea/thio urea using catalytic amount of cadmium chloride.



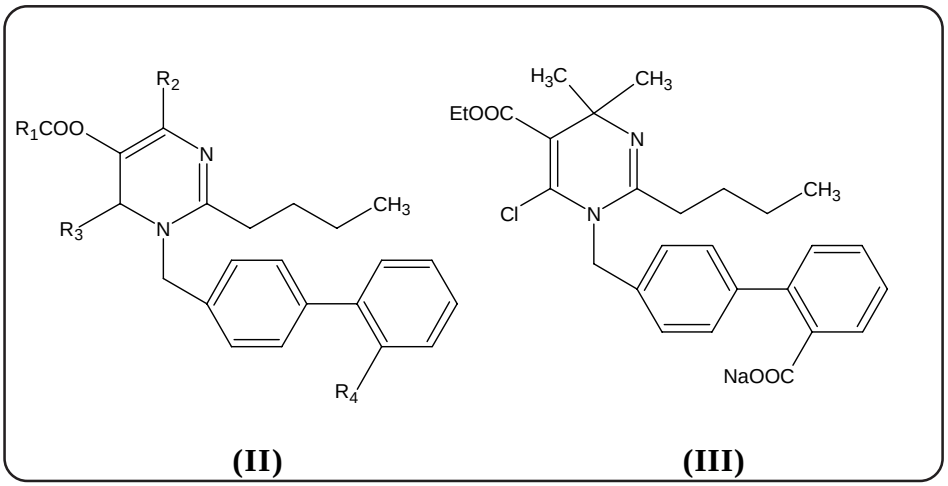
THERAPEUTIC IMPORTANCE :

Calcium ion plays a vital role in a large number of cellular processes, including excitation-contraction and stimulus-secretion.[21-23] In recent years interest has also focused on aza-analogs such as dihydropyrimidines (I) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[24-30]



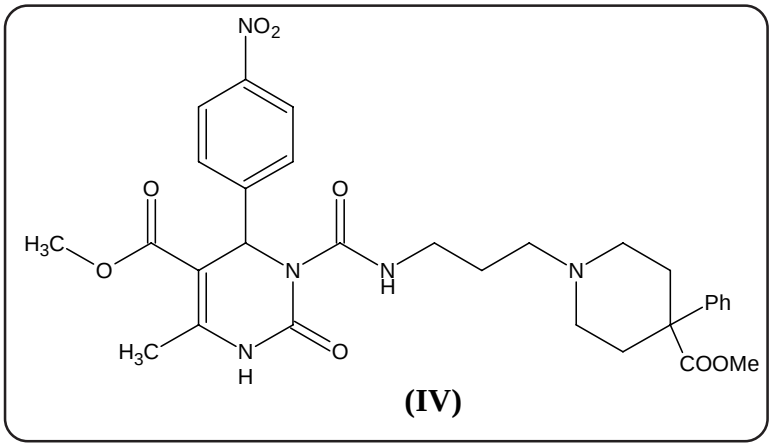
(I)

Hidetsura Cho et al.[24] have synthesized the novel calcium channel antagonists 3-N-substituted-3,4-dihydropyrimidines and 3-N-substituted-dihydropyrimidin-2(1H)-ones were regioselectively synthesized in good yields. Efforts of Atwal K. S. et al.[31] in this area have resulted in the discovery of dihydropyrimidines (II) and (III) as potent AII receptor antagonists



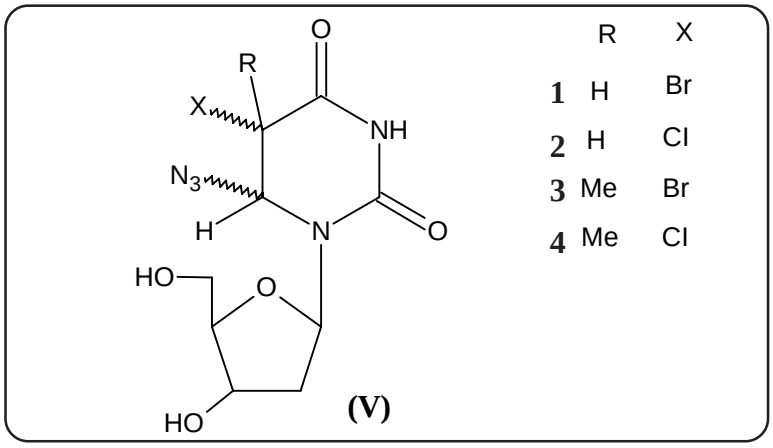
(II) **(III)**

Dhanapalan N. et al.[32] prepared dihydropyrimidinones (IV) exhibited high binding affinity and subtype selectivity for the cloned human a_{1a} receptor. James C. et al.[33] explores 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via C-5 amide as selective a_{1a} receptor subtype antagonists. Several recently isolated marine alkaloids with interesting biological activities also contain dihydropyrimidinone nucleus. Frederick C. et al.[204] described that a novel class of polyguanidine alkaloids isolated from the red Caribbean sponge *Batzella* sp.[34,35]



(IV)

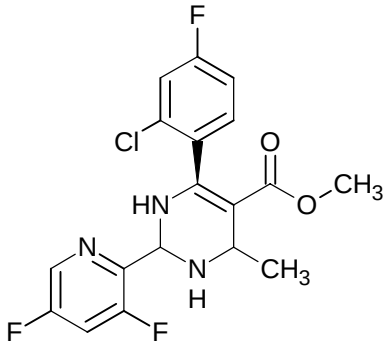
Rakesh Kumar[36] synthesized, antiviral and cytotoxic activities of 5-bromo (or chloro)-6-azido-5,6-dihydro-20-deoxyuridine **(1,2)** and thymidine **(3,4)**. Compounds (V) exhibited a broad spectrum of antiherpes activity against (HSV-1, HSV-2, HCMV, and VZV).



	R	X
1	H	Br
2	H	Cl
3	Me	Br
4	Me	Cl

(V)

4-Aryl-1,2,3,4-tetrahydropyrimidin-2-one derivatives[37] have been synthesized and examined for their activity against pathogenic strains of ***Aspergillus fumigatus*** and ***Candida albicans***.Recently many new molecules which are under study from phase-I to IV clinical trials for different pharmacological action have shown as under.



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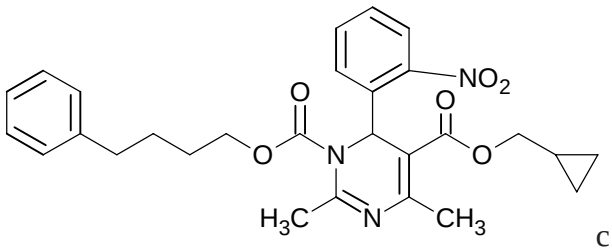
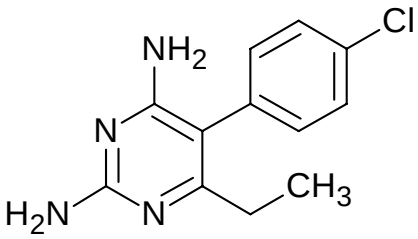
Anti Hepatitis B Virus Drugs[38]

Bayer



calcium channel blocker[39]



Antimalarial Agent.[40]

Primethamine

Literature survey reveals that dihydropyrimidine possess potential drug activity. Looking to the diversified biological activity, it appeared of interest to synthesize some new dihydropyrimidines, these studies are described in following parts.

PART - I : STUDIES ON DIHYDROPYRIMIDINONES

PART - II : STUDIES ON DIHYDROPYRIMIDINTHIONES

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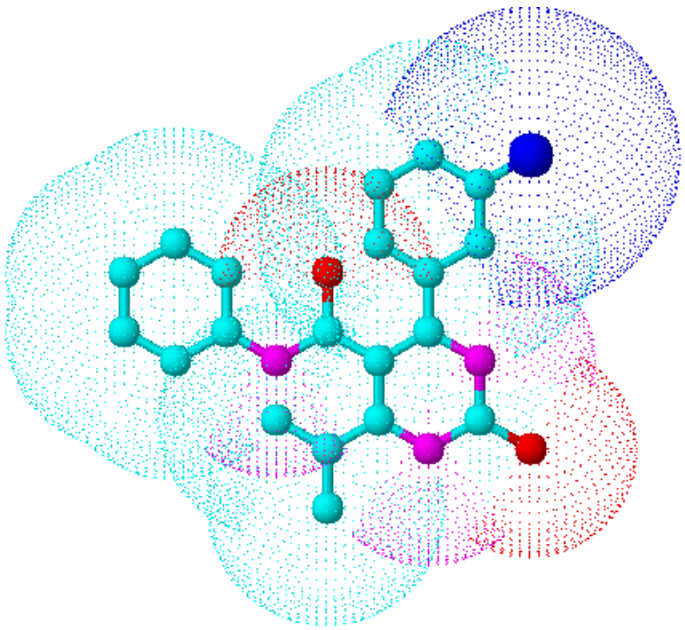


PART - I

STUDIES ON

DIHYDROPYRIMIDINONES

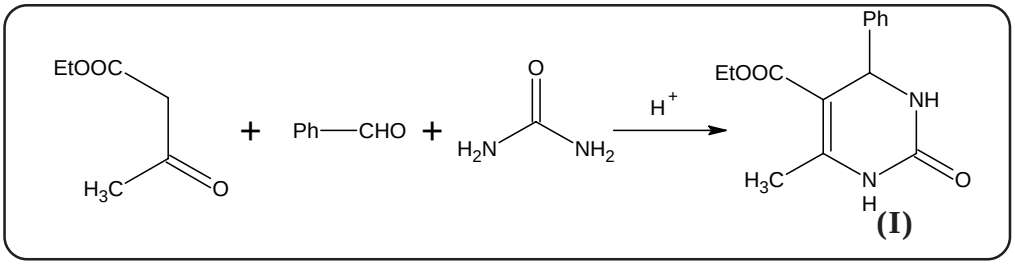
INTRODUCTION

Generally pyrimidine derivatives such as dihydropyrimidinones, dihydropyrimidinthiones are studied. Dihydropyrimidines have been isolated from the hydrolysis of the nucleic acid.

Dihydroyrimidines are among those molecules that make life possible, have been some of the building blocks of DNA and RNA. Several analogues of dihydropyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used. There are several other important groups of dihydropyrimidines with medicinal uses.

SYNTHETIC ASPECT

(1) In 1893 Pietro Biginelli reported the first synthesis of dihydropyrimidines (I) by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea under strongly acidic condition.[1,2]



(2) Substituted 3,4-DHPM-2(1H)-ones were prepared in high yield by Biginelli condensation of an aldehyde, dicarbonyl compounds and urea in ethanol using $CoCl_2.6H_2O$ catalyst.[3]

(3) DHPM-2-(1H)-one was prepared from three component i.e. β-diketone, aldehyde and urea coupling in ethanol catalyze by indium(III)tribromide ($InBr_3$).[4,5]

(4) A simple effective synthesis of DHPM-2-(1H)-one derivatives, using boric acid as a catalyst from an aldehyde 1,3-dicarbonyl compound and urea in glacial acetic acid is described.[6] Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yield 86-97% and the short reaction time (0.5-2hr).

(5) Subhas D. Bose et al.[7] describe a general and practical route for the Biginelli cyclocondensation reaction using cerium (III) chloride ($CeCl_3$)heptahydrate as catalyst.

(6) Recently, Indium (III) chloride was emerged as a powerful Lewis catalyst imparting high region and chemo selectivity in various chemical transformations Ranu C.et al.[8] described a simple synthesis of DHPM-2-(1H)-one derivatives, using indium (III) chloride (10 %) as a catalyst from an aldehyde, β-di carbonbyl compound and urea in THF.

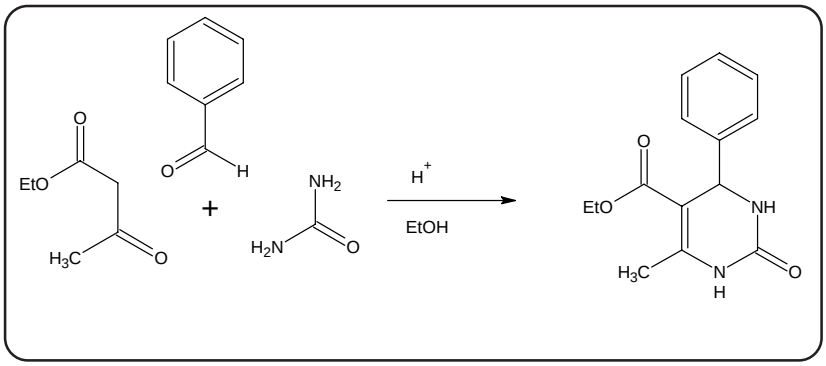
(7) A practical and green chemistry approach towards synthesis of DHPM-2-(1H)-one without any solvent or catalyst. This method was developed by Ranu C. et al.[9] Dihydropyrimidinone was prepared from three component β-diketone, aldehyde and urea was heated under stirring at 100-105 ^{0}C afford the corresponding DHPM-2-(1H)-one in high yield (82%) and purity (> 95%).

(8) DHPM-2(1H)-ones were prepared in high yield by Biginelli condensation of an aldehyde, a dicarbonly compound and urea in ethanol using $Mn(OAc)_3$ as a catalyst.[10]

(9) Oliver Kappe et al.[11] have synthesized dihydropyrimidine-5-carboxylicacid in two steps by multicomponent condensation of benzyl or allyl β-ketoesters with aldehyde and urea, followed by suitable benzyl or allyl deprotection strategies.

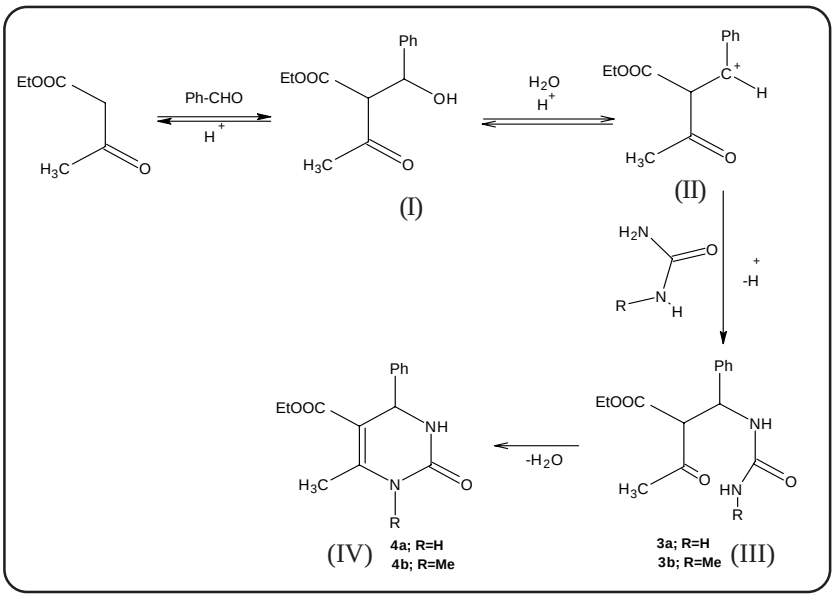
MECHANISM

Despite the importance and current interest in dihydropyrimidines of, the mechanism of the classical three-component Biginelli condensation has not been elucidated with certainly and remains disputed.[12]



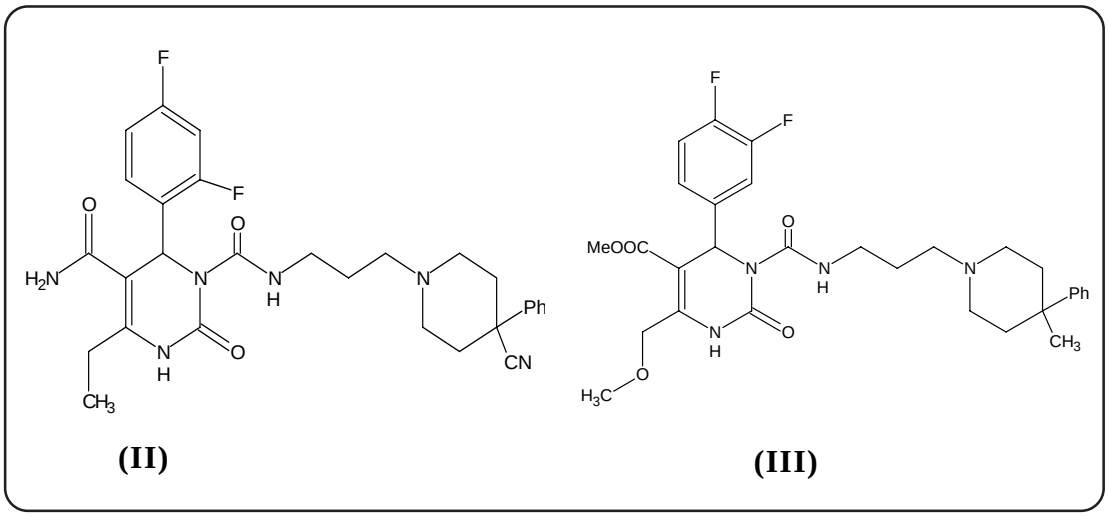
The "carbenium ion mechanism" was proposed by Sweet and Fissekis,[13] who investigated the reaction in 1973 and suggested that an acid-catalyzed aldol condensation is the first and limiting step of the Biginelli condensation. It was proposed that under acid catalysis benzaldehyde and ethyl acetoacetate would react in an aldol-type fashion to produce the corresponding aldol (I), which dehydrates in the presence of acid to the resonance-stabilized carbenium ion[13-15](II).

Interception of cation (II) by urea or *N*-methylurea then produces ureides (III), which ultimately cyclize to the Biginelli products[13] (IV).



THERAPEUTIC IMPORTANCE

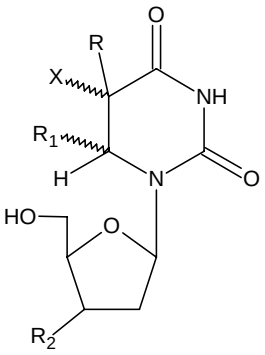
Atwal K. S. et al.[16] have described the potent antihypertensive activity of the modestly active (ICw = 3.2 pM) dihydropyrimidine calcium channel blocker. Kappe C. O. et al.[17] synthesize the polycyclic DHPM derivatives. T. G. Muralidhar et al.[18] have synthesized several DHPM-one analogues among this (II) and (III) give excellent selectivity (>880-fold) over α_{1b} and α_{1d} and also showed good selectivity over several other recombinant human G-protein coupled receptors.



(II) **(III)**

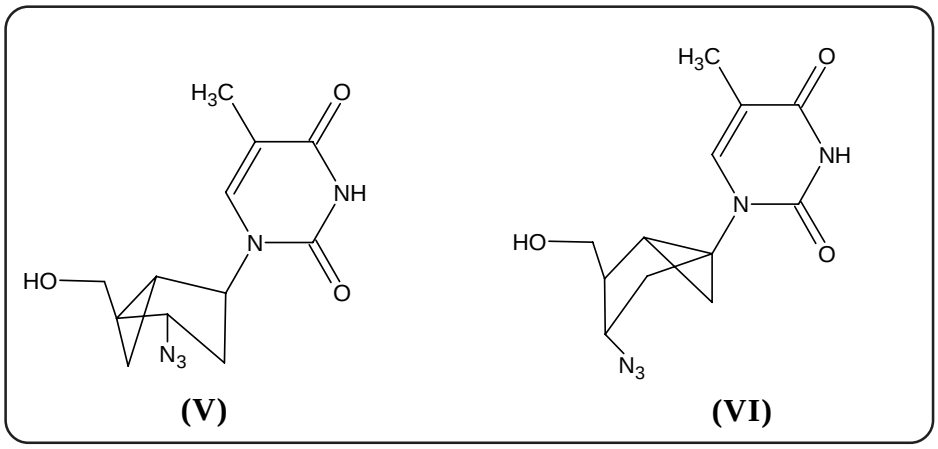
The 5,6-dihydropyrimidine nucleosides have attracted attention as potential antiviral and antitumor agents.[19,20] Physiological dihydro nucleosides play an important role in nucleic acid metabolism and appear frequently in the sequence of tRNA[21]. 5,6-Dihydro analogues of thymidine (IVc) can act as competitive substrates, to thymidine, for thymidine kinase.[22,23] 5-Fluoro-6-hydroxy (or acetoxy)-5,6-dihydro-2'-deoxyuridine diastereomers (IVa,b) have been investigated as prodrugs to 5-fluoro-2'-deoxyuridine.[19] The 5,6-dihydro derivatives (IVd–f) of antiviral pyrimidine nucleosides as potential prodrugs.[24-29] It was observed that the groups at C-5 and C-6 positions in the 5,6-dihydro derivatives created a potentially interesting enhancement of lipophilicity with respect to that of the parent nucleosides. It was also found that 5,6-dihydropyrimidine nucleosides (IVd–f) serve as slow releasers (prodrugs) of the parent nucleosides *in vivo* and were stable to glycosidic bond cleavage. These beneficial properties of 5,6-dihydropyrimidine nucleosides (IV d–f) encouraged us to further investigate 5,6-dihydro

derivatives of 2'-deoxyuridine and thymidine to study their biological activity.



	R	X	R_1	R_2
IV a	H	F	OH	OH
IV b	H	F	OAC	OH
IV c	Me	Br	alkoxy	OH
IV d	Et	helogen	alkoxy	OH
IV e	Me	helogen	alkoxy	N_3
IV f	Me	helogen	alkoxy	F

Victor E. M.et al.[30] synthesized 5'-triphosphates of (V) and (VI) and evaluated directly as reverse transcriptase (RT) inhibitors using both a recombinant enzyme and enzyme obtained and purified directly from wild type viruses.

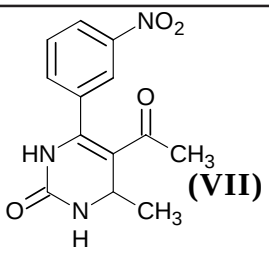


(V) **(VI)**

Sanjay Batra et al.[31] have synthesized 5-arylmethyl-4-imino-3-aryl-3,4-dihydro-1H-pyrimidin-2-ones which were tested for their antibacterial activity. Mai A. and coworkers[32] have investigate the dihydropyrimidines which are highly active against HIV-1. Herve Ganeste et al.[33] synthesized substituted 1H-pyrimidin-2-one with selective dopamine D_3-receptor antagonists activity.

New drug molecules under clinical study

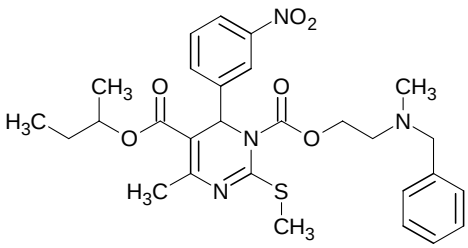
Recently many new molecules which are under study from phase-I to IV clinical trials for different pharmacological action have shown that the basic characteristic of morpholine to behave as hidden amine has attracted many medicinal chemists to incorporate this feature in drug design. Some interesting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



(VII)

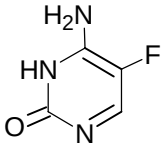
Calcium Channel Blokers[34]

Company Name: Merck & Co.



(VIII)

Calcium Channel Blockers[35]

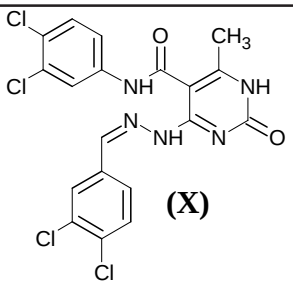


(IX)

Flucytosine

(fluorocytosine)

Antifungal Agent.[36]



(X)

Immunosuppressants

Oncolytic Drug

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

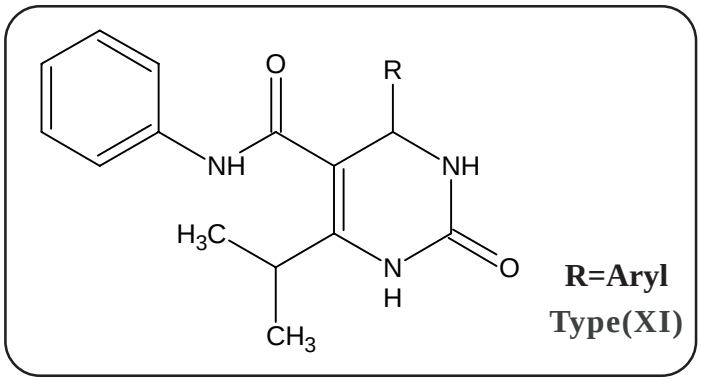
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISO PROPYL-4-ARYL-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISO PROPYL-4-ARYL-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-4-ARYL-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

Much interest have been focused around dihydropyrimidinone derivatives because of their wide variety of pharmacological properties and industrial applications. In view of these findings and achieve to better drug potency, we have synthesized 6-isopropyl-4-aryl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides of Type (XI) by the condensation of 4-methyl-3-oxo-N-phenylpentanamide with urea and aryl aldehydes.

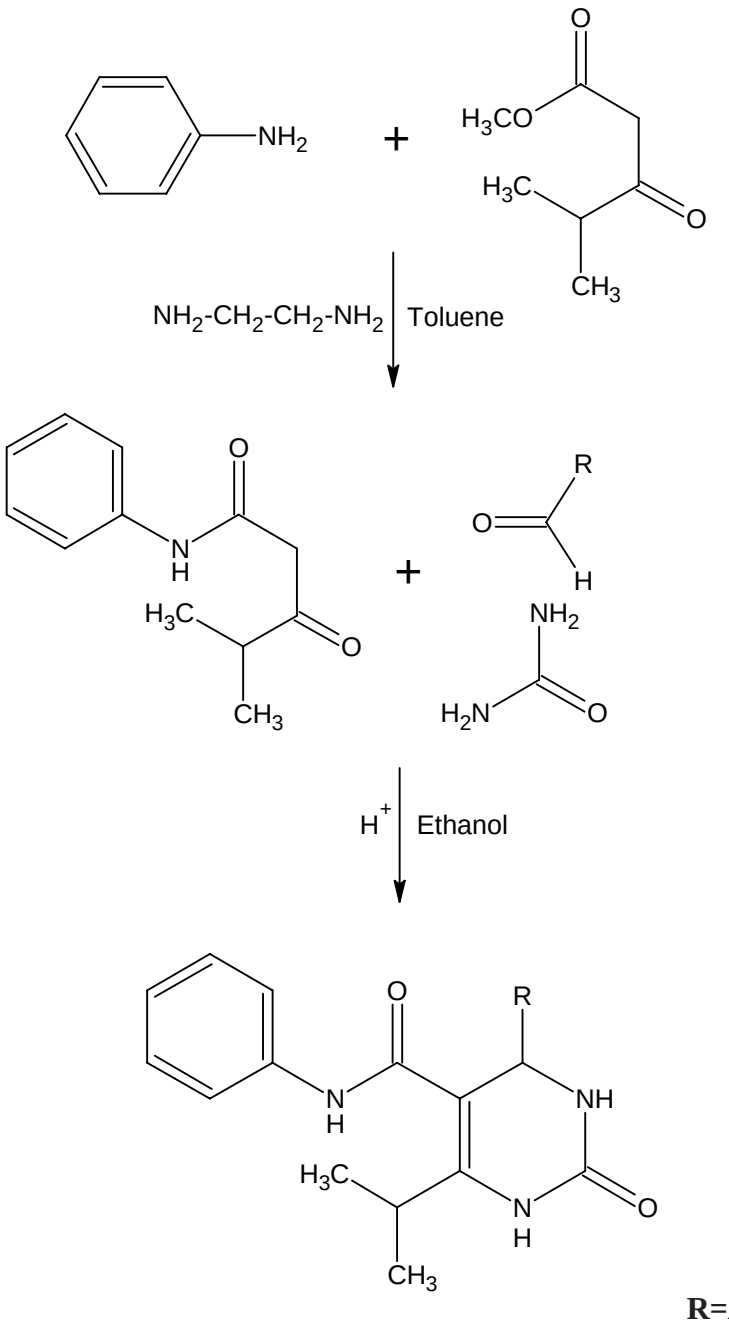


R=Aryl
Type(XI)

The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

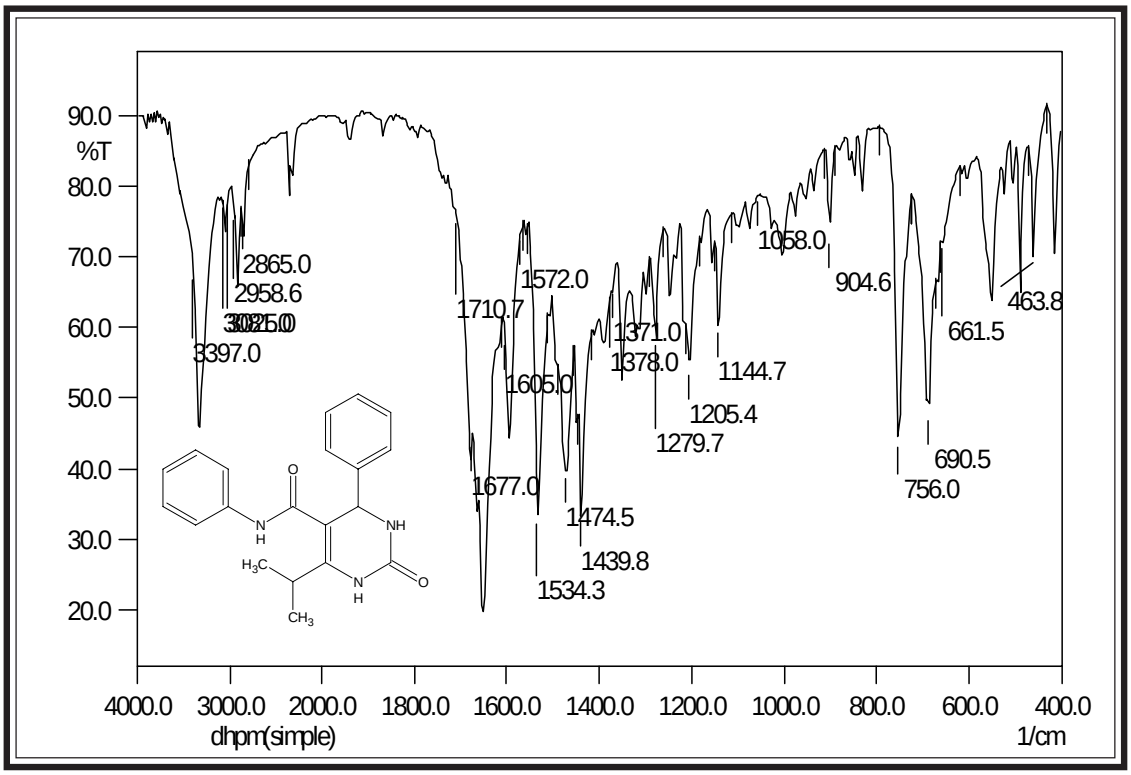
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds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

Reaction Scheme



R=Aryl

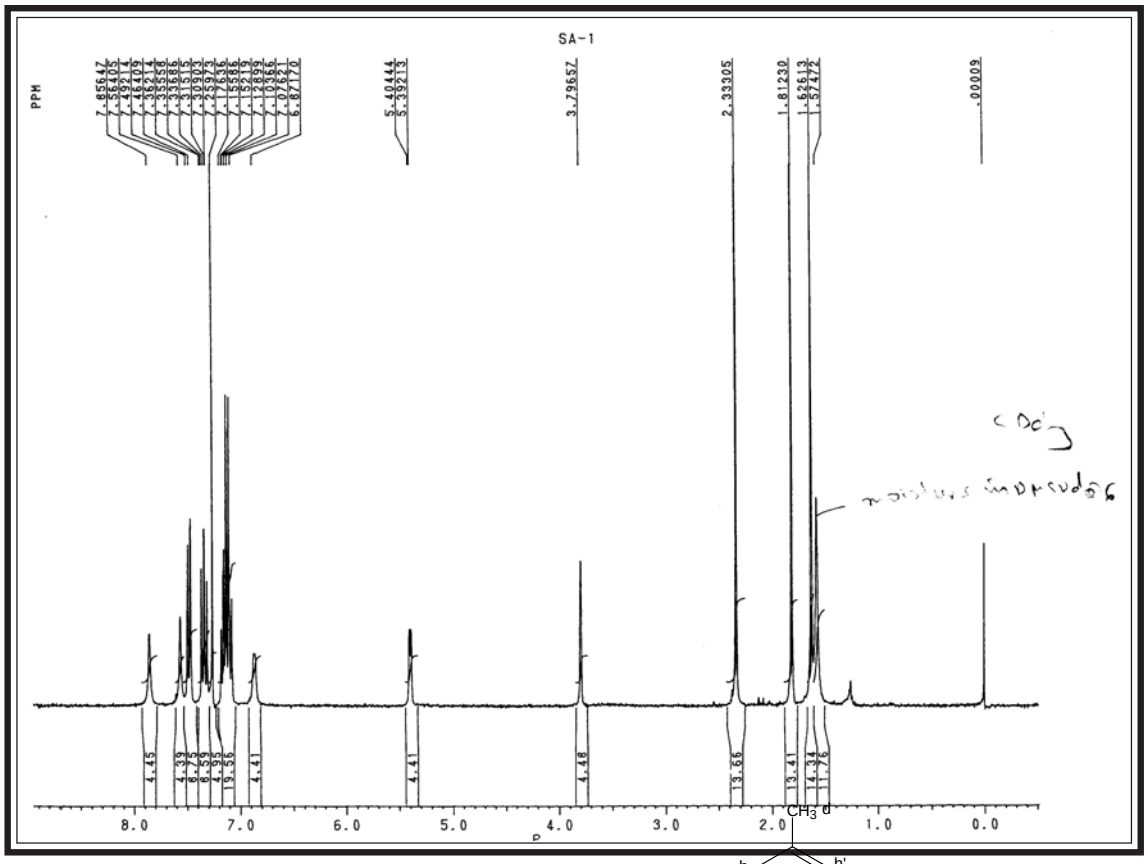
IR SPECTRAL STUDIES OF 6-ISOPROPYL-4-PHENYL-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



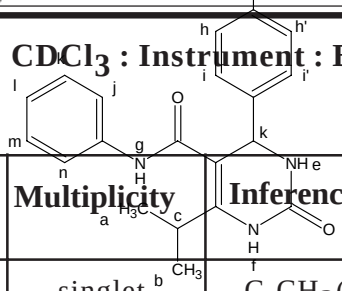
Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2958	2975-2950	37
$-CH_3$	C-H str. (sym.)	2865	2880-2860	,,
	C-H i.p.def. (asym.)	1439	1470-1435	,,
	C-H o.o.p. def. (sym.)	1378	1390-1370	,,
Aromatic	C-H str.	3081	3090-3030	38
	C=C str.	1534	1540-1480	,,
Pyrimidine	C=C str.	1572	1580-1520	,,
moity	C-H str.	3025	3080-3030	,,
	C-H i.p. def.	1058	1125-1090	,,
Amide	-NH str.	3397	3410-3380	37
	-NH def.	1605	1635-1595	,,
Carbonyl	-C=O str.	1710	1700-1725	,,
Amide	- C=O str.	1677	1690-1660	,,
Isopropyl	C-H str.	1371	1385-1365	,,

NMR SPECTRAL STUDIES OF 6-ISOPROPYL-4-(4-METHYLPHENYL)-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE

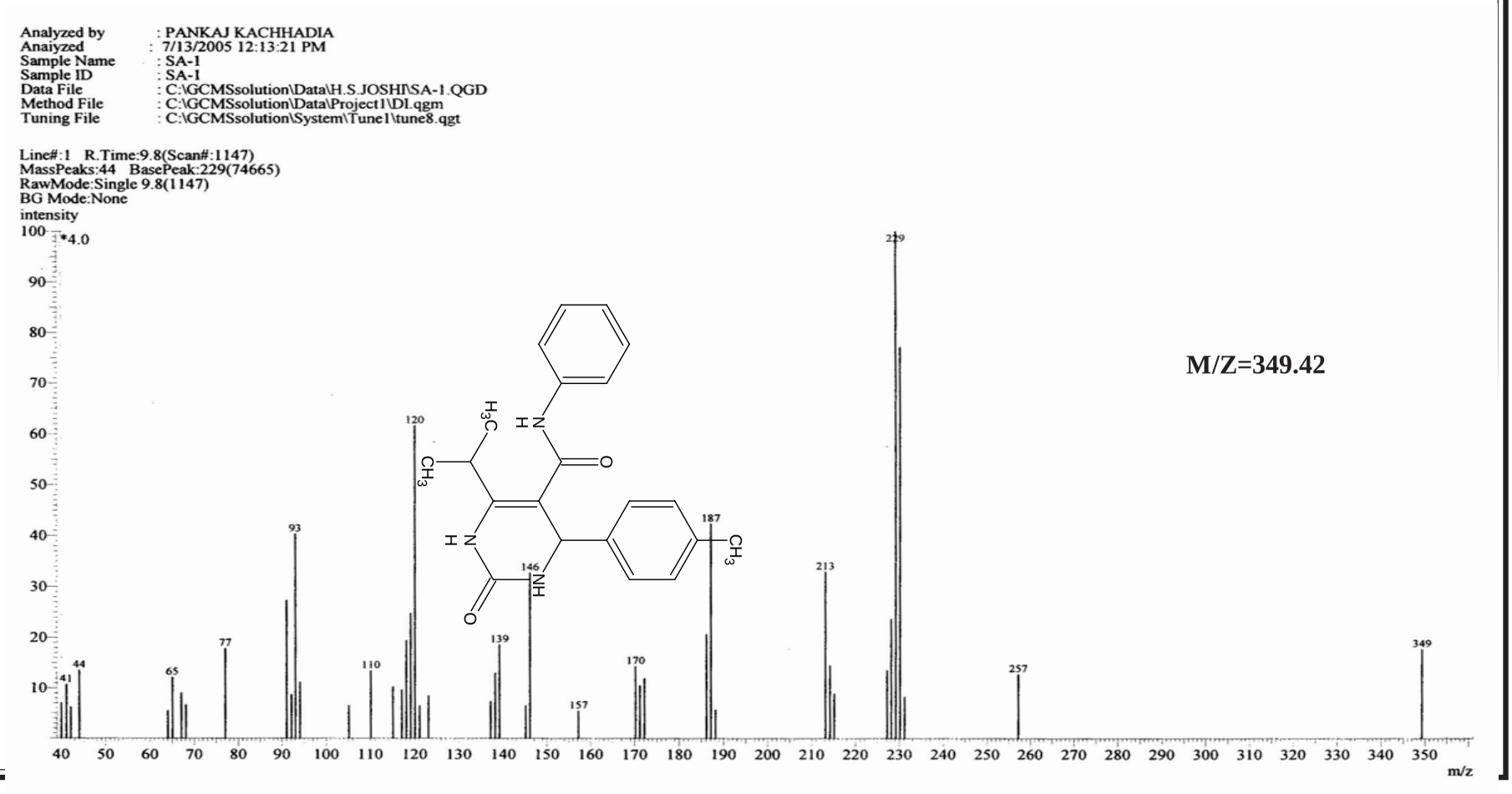


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)



Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.62	3H	singlet	C-CH_3(a)	-
2	1.81	3H	singlet	C-CH_3(b)	-
3	2.33	3H	singlet	Ar-CH_3(d)	-
4	3.79	1H	singlet	C-CH(c)	-
5	5.39	1H	doublet	Ar-CH(k)	J=3.6
6	6.87	1H	singlet	Ar-NH(g)	-
7	7.12-7.07	5H	multiplet	Ar-CH (j,k,l,m,n)	-
8	7.35	2H	doublet	Ar-CH(i,i')	J=6.4
9	7.47	2H	doublet	Ar-CH(h,h')	J=9.0
10	7.56	1H	singlet	Ar-NH(e)	
11	7.85	1H	singlet	Ar-NH(f)	

TABLE-11 : MASS SPECTRAL STUDIES OF 6-ISOPROPYL-4-(4-METHYLPHENYL)-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-4-ARYL-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

(A) Synthesis of 4-Methyl-3-oxo-N-phenylpentanamide

A mixture of methyl 4-methyl-3-oxopentanoate (methyl isobutrylacetate) (1.44 gm, 0.01 mol) and aniline (0.93 gm, 0.01 mol) in toluene containing few drops of ethylene diamine was refluxed for 12 hr and collect methanol using dean and stark. The resulting solution was cooled to 0^0C. Than add dilute HCL solution in toluene layer, the seperated toluene layer washed with three times water. and distilled out under vaccum. Yield 71%, m. p. 32^0C, Anal.Calcd. for C12H15NO2 Calcd: C, 70.22; H, 7.37; N, 6.82%, Found: C, 70.21; H, 7.36; N, 6.81%.

(B) Synthesis of 6-Isopropyl-4-(4-methylphenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide

A mixture of urea (0.60 gm, 0.01 mol), 4-methyl benzaldehyde (1.20 gm, 0.01 mol) and 4-methyl-3-oxo-N-phenylpentanamide (2.05 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 8 hr. The solution was allowed to stand for 12 hr. at room tempeture. The resulting solid mass separated was filtered and, crystallized from dioxane. Yield 41%, m. p. 266^0C, Anal.Calcd. for $C_{21}H_{23}N_3O_2$ Calcd: C,72.18; H,6.63; N, 12.03%, Found: C, 72.16; H, 6.62; N, 11.99 %.

Similarly, other 6-isopropyl-4-aryl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxamides were prepared. The physical data are recorded in Table No. 11

(C) Biological screening of 6-Isopropyl-4-aryl-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides

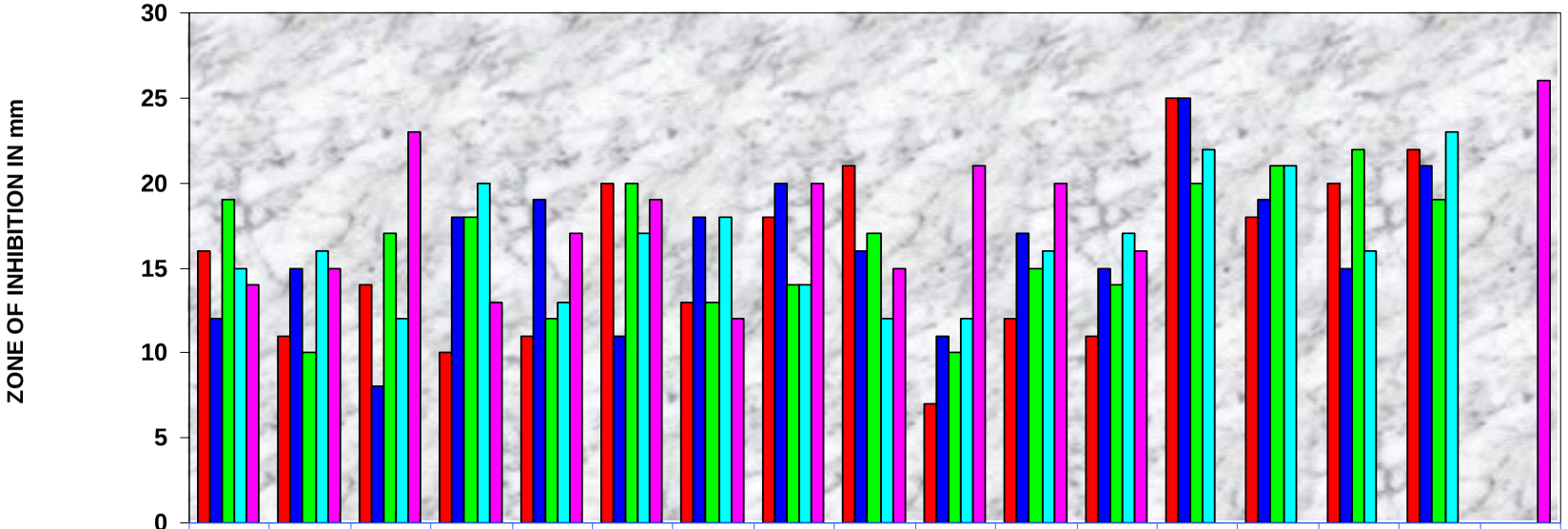
Antimicrobial activity was carried out as described in **(A)** Part-I, Section-I(D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 11

TABLE-11 : PHYSICAL CONSTANTS OF 6-ISOPROPYL-4-ARYL-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
11a	C_6H_5-	$C_{20}H_{21}N_3O_2$	335.39	230	45	12.53	12.52	0.50	S1
11b	4-NO_2-C_6H_4-	$C_{20}H_{20}N_4O_4$	380.39	245	36	14.73	14.72	0.44	S1
11c	3-NO_2-C_6H_4-	$C_{20}H_{20}N_4O_4$	380.39	225	47	14.73	14.71	0.53	S2
11d	4-CH_3-C_6H_4-	$C_{21}H_{23}N_3O_2$	349.42	266	41	12.03	11.99	0.55	S1
11e	2,4-Cl_2-C_6H_3-	$C_{20}H_{19}CI_2N_3O_2$	404.28	263	34	10.39	10.38	0.49	S2
11f	4-CI-C_6H_4-	$C_{20}H_{20}CIN_3O_2$	369.84	235	41	11.36	11.34	0.56	S1
11g	3-CI-C_6H_4-	$C_{20}H_{20}CIN_3O_2$	369.84	248	48	11.36	11.35	0.42	S2
11h	2-CI-C_6H_4-	$C_{20}H_{20}CIN_3O_2$	369.84	260	47	11.36	11.33	0.58	S1
11i	3-O-C_6H_5-C_6H_4-	$C_{26}H_{25}N_3O_3$	427.49	225	35	9.83	9.82	0.57	S1
11j	4-OCH_3-C_6H_4-	$C_{21}H_{23}N_3O_3$	365.42	240	39	11.50	11.49	0.47	S2
11k	4-F-C_6H_4-	$C_{20}H_{20}FN_3O_2$	353.39	235	37	11.89	11.88	0.54	S2
11l	3-Br-C_6H_4-	$C_{20}H_{20}BrN_3O_2$	414.29	222	51	10.14	10.13	0.43	S2

S1 Hexane : Ethyl acetate (8 : 2), S2 Hexane : Ethyl acetate (5 : 5)

GRAPHICAL CHART NO. 11 : 6-ISOPROPYL-4-ARYL-2-OXO-*N*-PHENYL-1,2,3,4-TETRAHYDROPYRIMIDINE -5-CARBOXAMIDES

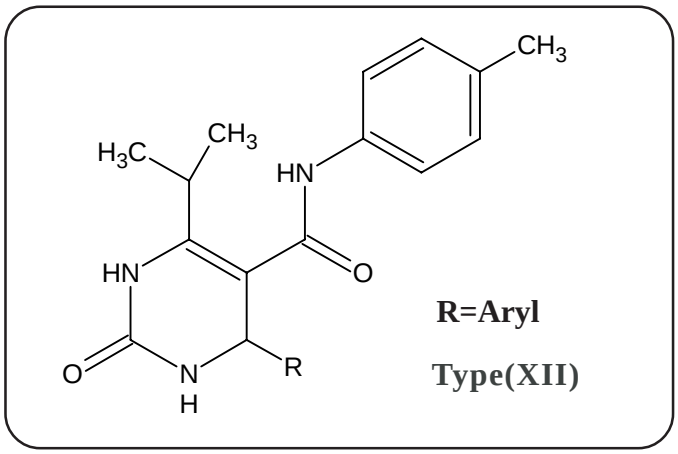


	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	Amoxicilllin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	16	11	14	10	11	20	13	18	21	7	12	11	25	18	20	22	0
S. aureus	12	15	8	18	19	11	18	20	16	11	17	15	25	19	15	21	0
Aerogenes	19	10	17	18	12	20	13	14	17	10	15	14	20	21	22	19	0
Pseudomonas	15	16	12	20	13	17	18	14	12	12	16	17	22	21	16	23	0
A.niger	14	15	23	13	17	19	12	20	15	21	20	16	0	0	0	0	26

SECTION - II

SYNTHSIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-4-ARYL-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

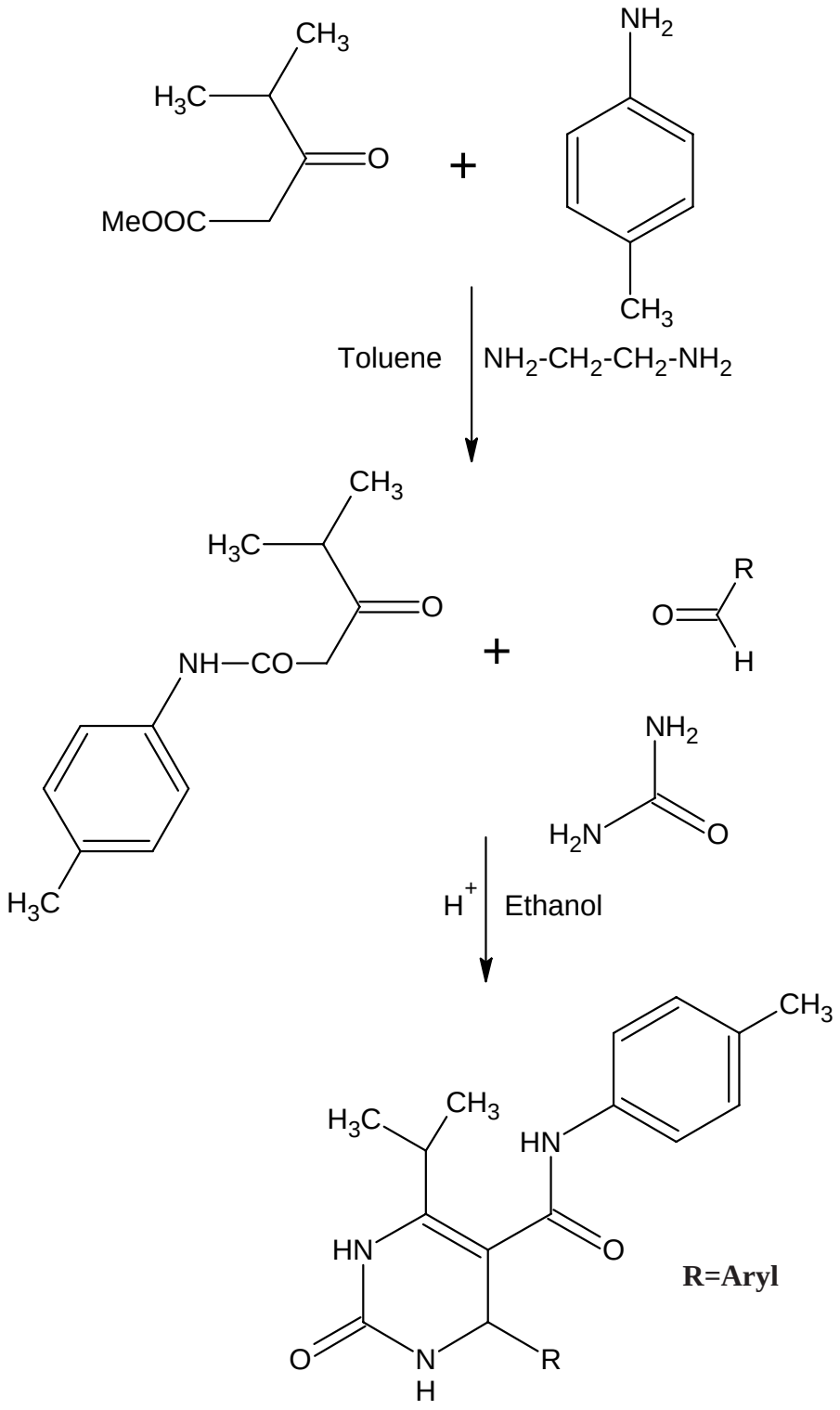
Compounds containing pyrimidine ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these reports, we have synthesized 6-isopropyl-4-aryl-*N*-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides of Type (XII) by the condensation of 4-Methyl-N-(4-methylphenyl)-3-oxopentanamide ,urea and aryl aldehydes.



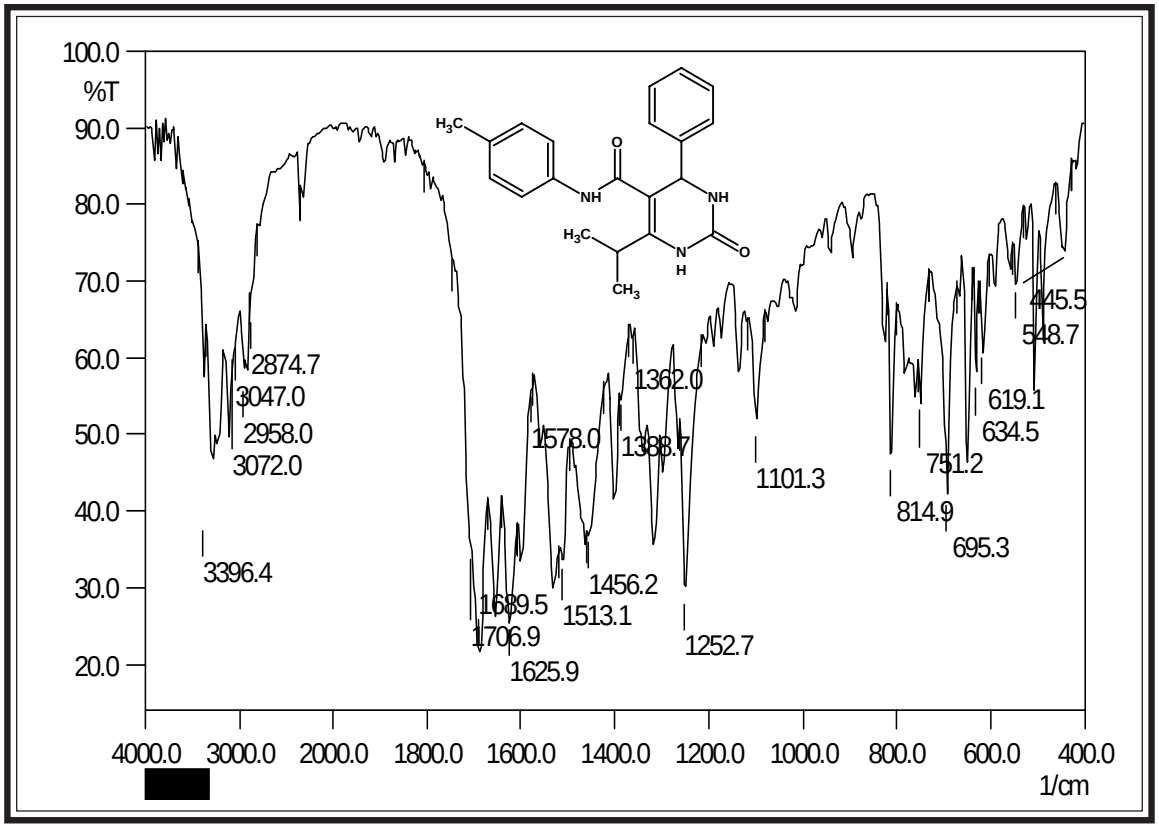
The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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.

Reaction Scheme



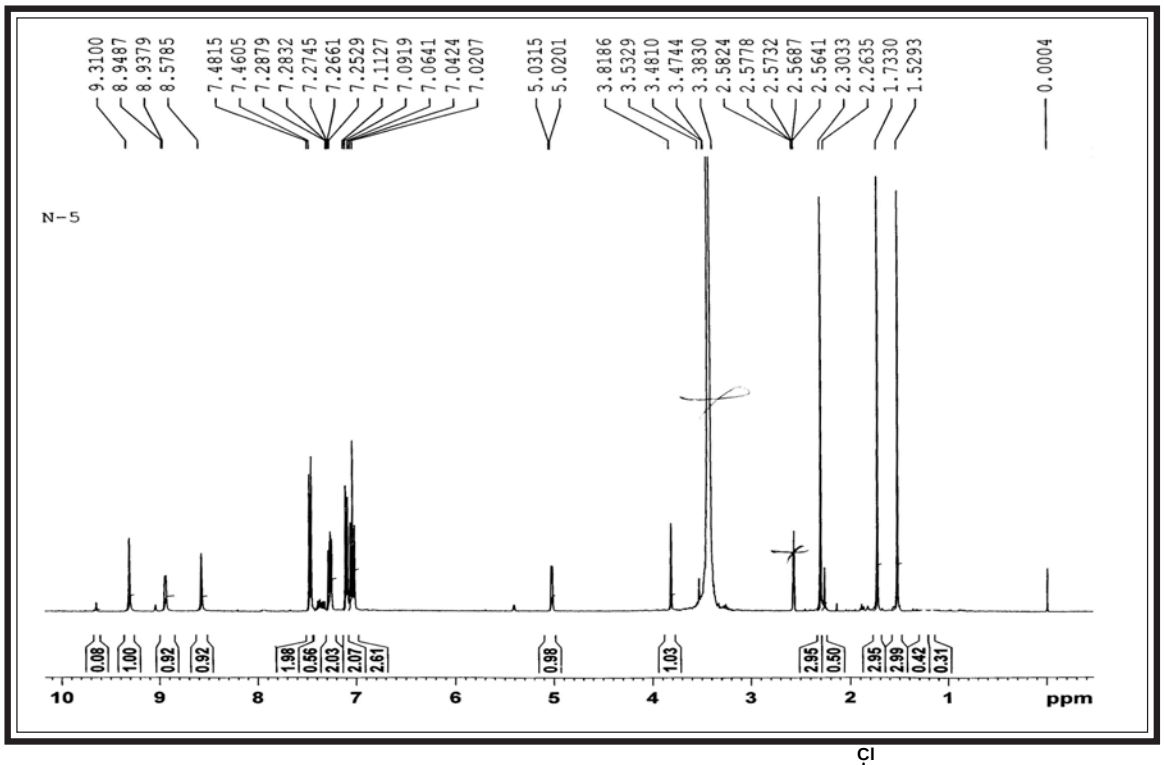
IR SPECTRAL STUDIES OF 6-ISOPROPYL-4-PHENYL-*N*-(4-METHYL PHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



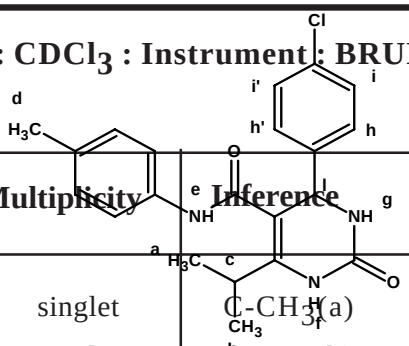
Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2958	2975-2950	37
-CH_3	C-H str. (sym.)	2874	2880-2860	,,
	C-H i.p.def. (asym.)	1456	1470-1435	,,
	C-H o.o.p. def. (sym.)	1388	1390-1370	,,
Aromatic	C-H str.	3047	3090-3030	38
	C=C str.	1513	1540-1480	,,
Pyrimidine	C=C str.	1578	1580-1520	,,
moity	C-H str.	3072	3080-3030	,,
	C-H i.p. def.	1101	1125-1090	,,
Amide	-NH str.	3396	3410-3380	37
	-NH def.	1625	1635-1595	,,
Carbonyl	-C=O str.	1706	1700-1725	,,
Amide	-C=O str.	1689	1690-1660	,,
Isopropyl	C-H str.	1362	1385-1365	,,

NMR SPECTRAL STUDIES OF 6-ISOPROPYL-4-(4-CHLOROPHENYL)-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE

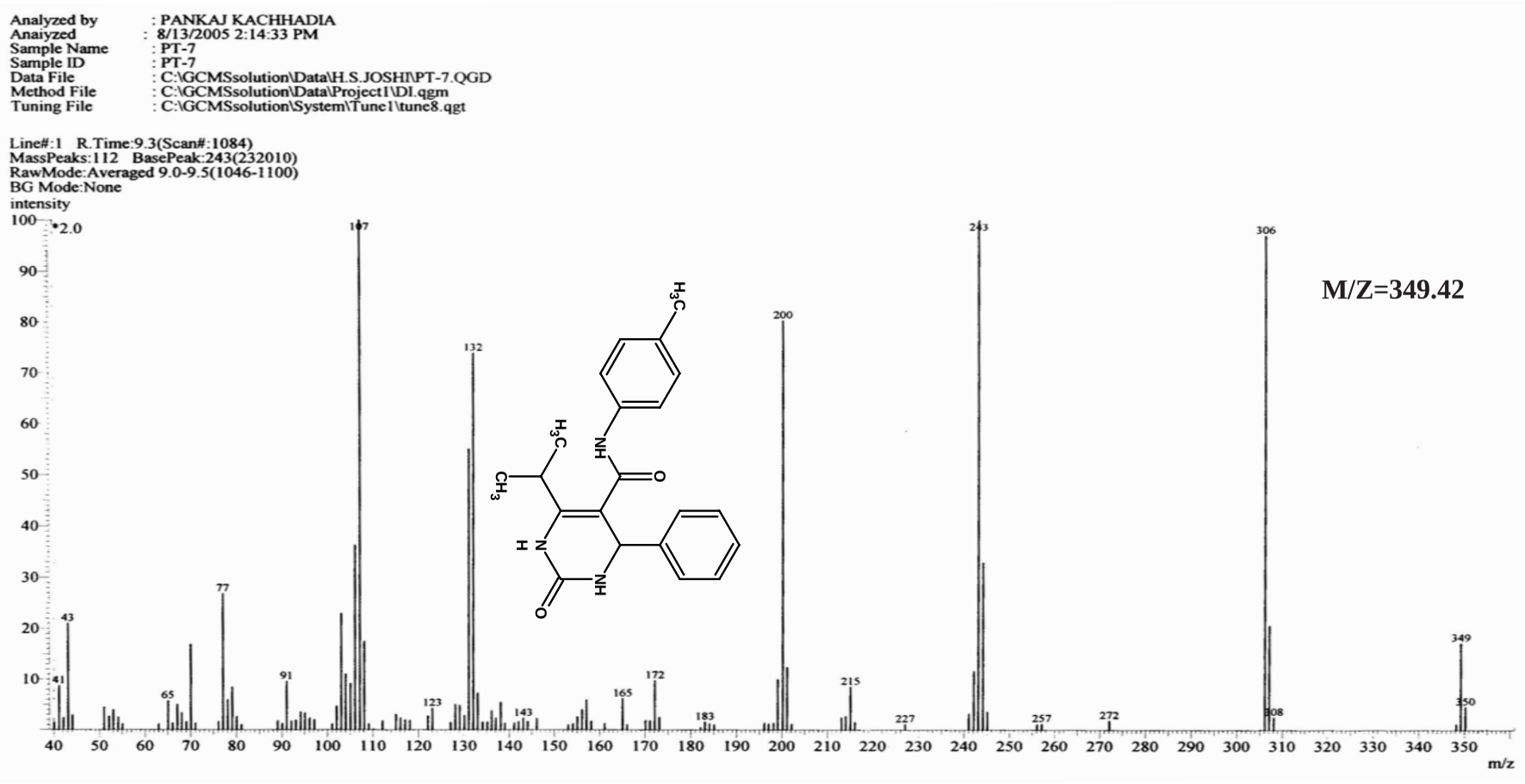


Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)



Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.52	3H	singlet	C-CH_3(a)	-
2	1.73	3H	singlet	C-CH_3(b)	-
3	2.30	3H	singlet	Ar-CH_3(d)	-
4	3.81	1H	singlet	C-CH(c)	-
5	5.03	1H	doublet	Ar-CH(l)	-
6	7.05	2H	doublet	Ar-CH(k,k')	J=6.6
7	7.10	2H	doublet	Ar-CH(j,j')	J=9.0
8	7.26	2H	doublet	Ar-CH(h,h')	J=6.0
9	7.47	2H	doublet	Ar-CH(i,i')	J=6.1
10	8.57	1H	singlet	Ar-NH(e)	-
11	8.93	1H	doublet	Ar-NH(g)	-
12	9.31	1H	singlet	Ar-NH(f)	-

TABLE-12 : MASS SPECTRAL STUDIES OF 6-ISOPROPYL-4-PHENYL-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-4-ARYL-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

(A) Synthesis of 4-Methyl-N-(4-methylphenyl)-3-oxo-pentanamide.

A mixture of methyl-4-methyl-3-oxopentanoate (methyl isobutrylacetate) (1.44 gm, 0.01 mol) and p-toluidine (1.07 gm, 0.01 mol) in toluene containing few drops of ethylene diamine was refluxed for 12 hr and collect methanol using dean and stark. The resulting solution was cooled to 0^0C. Add dilute HCL solution in to toluene layer, the seperated toluene layer was washed with three times water. The toluene distilled out under vaccum, the separated solid was crystallized from hexane-ethylacetate mixture. Yield-65%,m.p.58^{0}C, Anal.Calcd. for $C_{13}H_{17}NO_2$ Calcd: C, 71.21; H, 7.81;N,6.39, Found: C, 71.19; H, 7.80; N,6.40 %.

(B) Synthesis of 6-Isopropyl-4-(4-chlorophenyl)-*N*-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

A mixture of urea (0.60 gm, 0.01 mol), 4-chlorobenzaldehyde (1.40 gm, 0.01 mol) and 4-methyl-N-(4-methylphenyl)-3-oxo-pentanamide (2.19 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hr. The solution was allowed to stand for 12 hr. at room tempeture and the resulting solid mass separated was filtered and crystallized from dioxane.Yield 49%, m.p.247 ^{0}C, Anal.Calcd. for $C_{21}H_{22}CIN_3O_2$Calcd: C,65.71; H, 5.78; N, 10.95%, Found: C, 65.69; H, 5.77; N, 10.93 %.

Similarly, other 6-isopropyl-4-aryl-*N*-(4-methylphenyl)-2-oxo-1,2,3,4-tetra hydropyrimidine-5-carboxamides were prepared. The physical data are recorded in Table No. 12

(C) Biological screening of 6-Isopropyl-4-aryl-*N*-(4-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides

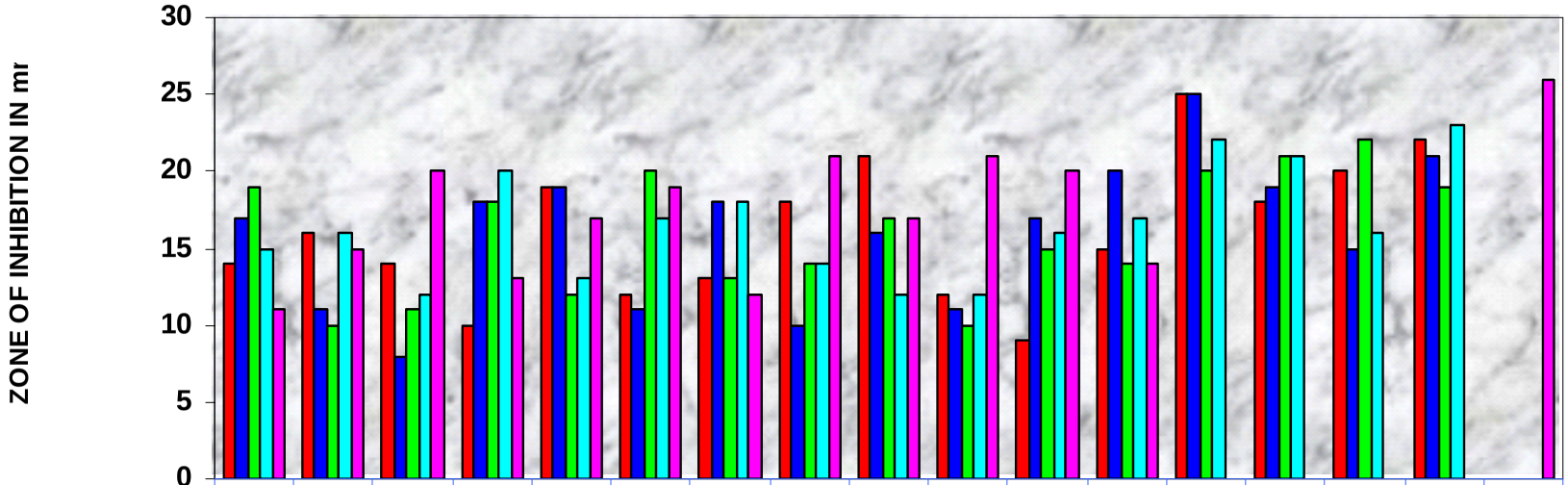
Antimicrobial testing were carried out as described in **(A)** Part-I Section-(D). The zones of inhibition of test solutions are recorded in Graphical Chart No.12

TABLE-12 : PHYSICAL CONSTANTS OF 6-ISOPROPYL-4-ARYL-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. °C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
12a	C_6H_5-	$C_{21}H_{23}N_3O_2$	349.42	267	34	12.03	12.00	0.50	S1
12b	4-NO_2-C_6H_4-	$C_{21}H_{22}N_4O_4$	394.42	262	46	14.20	14.19	0.48	S2
12c	3-NO_2-C_6H_4-	$C_{21}H_{22}N_4O_4$	394.42	264	48	14.20	14.18	0.55	S1
12d	4-$CH_3C_6H_4$-	$C_{22}H_{25}N_3O_2$	363.45	270	44	11.56	11.55	0.46	S1
12e	2,4-Cl_2-C_6H_3-	$C_{21}H_{21}CI_2N_3O_2$	418.31	289	38	10.05	10.00	0.58	S2
12f	4-CI-C_6H_4-	$C_{21}H_{22}CIN_3O_2$	383.87	247	49	10.95	10.93	0.54	S2
12g	3-CI-C_6H_4-	$C_{21}H_{22}CIN_3O_2$	383.87	245	45	10.95	10.94	0.42	S2
12h	2-CI-C_6H_4-	$C_{21}H_{22}CIN_3O_2$	383.87	240	48	10.95	10..92	0.57	S2
12i	3,4-$(OCH_3)_2$-C_6H_3-	$C_{23}H_{27}N_3O_4$	409.47	235	41	10.26	10.28	0.44	S1
12j	4-OCH_3-C_6H_4-	$C_{22}H_{25}N_3O_3$	379.45	230	32	11.07	11.06	0.49	S1
12k	4-F-C_6H_4-	$C_{21}H_{22}FN_3O_2$	367.41	220	51	11.44	11.42	0.53	S2
12l	3-Br-C_6H_4-	$C_{21}H_{22}BrN_3O_2$	428.32	240	56	9.81	9.80	0.56	S2

S1 Hexane : Ethyl acetate (7 : 3), S2 Hexane : Ethyl acetate (6 : 4)

GRAPHICAL CHART NO. 12 : 6-ISOPROPYL-4-ARYL-*N*-(4-METHYLPHENYL)-2-OXO-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Amoxicillin	Benzyl Penic	Ciprofloxacin	Erythromycin	Griseofulvin
B. Coccus	14	16	14	10	19	12	13	18	21	12	9	15	25	18	20	22	0
S. aureus	17	11	8	18	19	11	18	10	16	11	17	20	25	19	15	21	0
Aerogenes	19	10	11	18	12	20	13	14	17	10	15	14	20	21	22	19	0
Pseudomonas	15	16	12	20	13	17	18	14	12	12	16	17	22	21	16	23	0
A.niger	11	15	20	13	17	19	12	21	17	21	20	14	0	0	0	0	26

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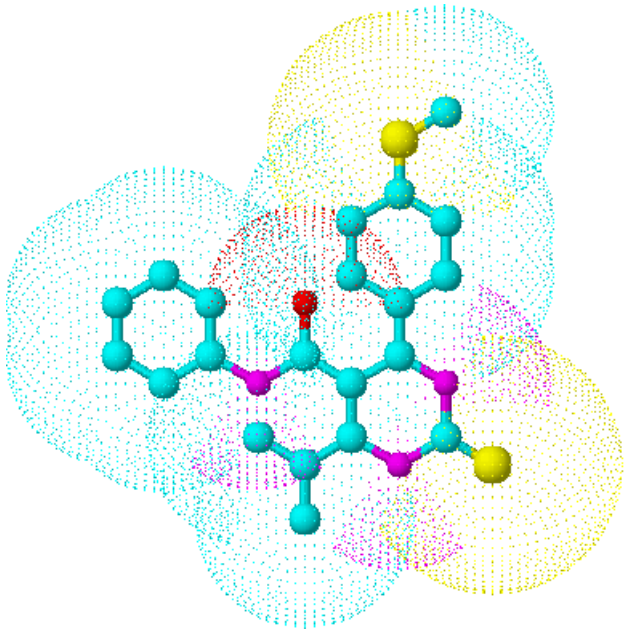


PART - II

STUDIES ON

DIHYDROPYRIMIDINTHIONES

INTRODUCTION

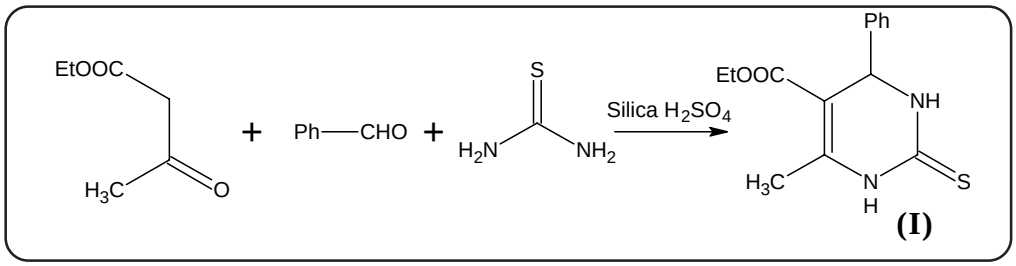
Thiourea itself was one of the first new drug employed to depress, the clinically over active thyroid in thyrotoxicosis[1] but some of the cyclic thiourea have been found better suited. All of these are prone of produce adverse reduction in susceptible patients and found more potent and less likely to produce side effect and is being used widely.[2]

Dihydropyrimidinthione ring carrying various subtituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other synthesis, which are complimentary rather than alternative to it. A second type of synthesis is the isomerisation or break down of another heterocycles such as an hydration of purine but such roots are frequently used.

From the biochemical point of view, 1,4-dihydropyrimidine 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, a central participant in metabolic processes in living organisms, participates in the reduction of various unsaturated functionalities.

SYNTHETIC ASPECT

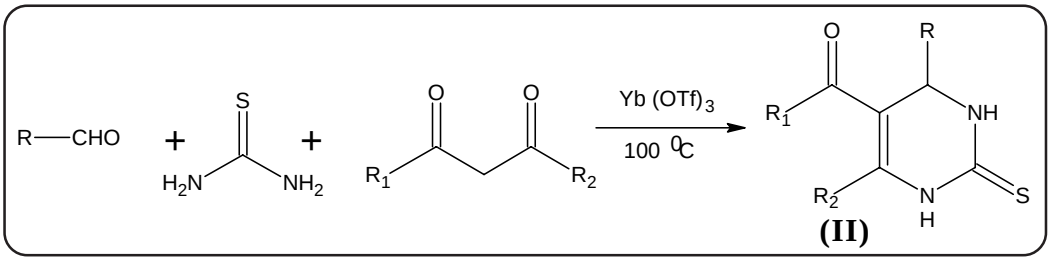
(1) Silica sulfuric acid efficiently catalyzes the three component Biginelli reaction between an aldehyde, β-dicarbonyl compound, and thiourea in ethanol to afford the corresponding dihydropyrimidines (I) in high yield.[3] The catalyst is reusable and can be applied several times without any decrease in the yield of the reaction.



(2) DHPM was prepared from three component β-diketone, aldehyde and thiourea coupling in ethanol catalyze by indium(III) tribromide($InBr_3$).[4,5] This modified one-pot Biginelli condensation provided not only simple preparation but also this modified Biginelli reaction was oxygen-bridge.

(3) Some Biginelli compounds were synthesized by using a photochemistry method. The Biginelli three component cyclocondensation reaction in THF medium using a mixture of β-ketoester or β-diketone, aryl aldehyde and thiourea under irradiation with a tungstan lamp light to gave DHPM-2-(1H)-thiones.[6]

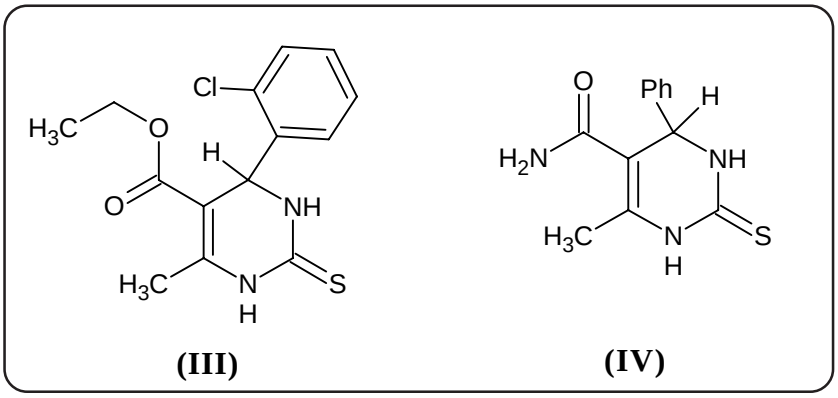
(4) Recently, Wang L. et al.[7-9] developed novel one pot Biginelli-type reaction. Aromatic or aliphatic aldehydes with β-dicarbonyl compound and thiourea in presence of catalytic amount of 5 % of $Yb(OTf)_3$ at 100 ^{0}C for 60-90 minute under solvent free condition proceeded smoothly to afford the corresponding DHPM thione (II).



(II)

THERAPEUTIC IMPORTANTS

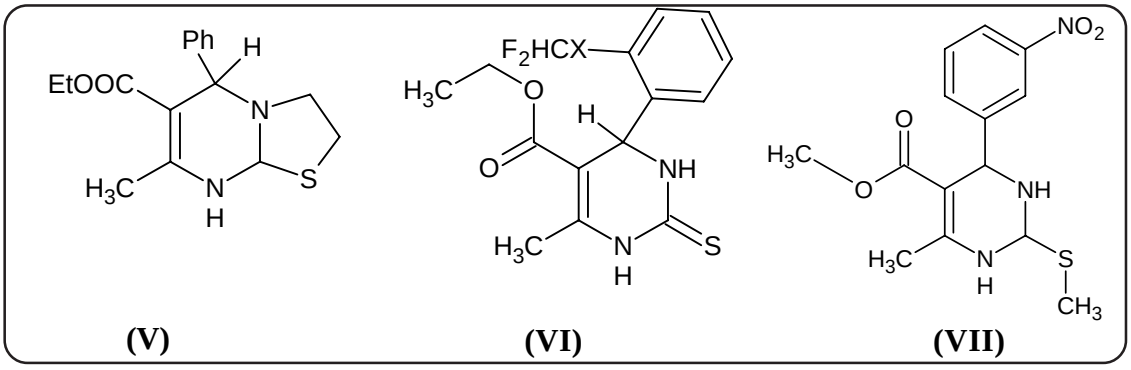
Biginelli compounds show a diverse range of biological activities. As early as 1930 simple derivatives (III) were patented as agent for the protection of wool against moths.[10] Later, interest focused on the antiviral activity of Biginelli compounds.[11]



(III) **(IV)**

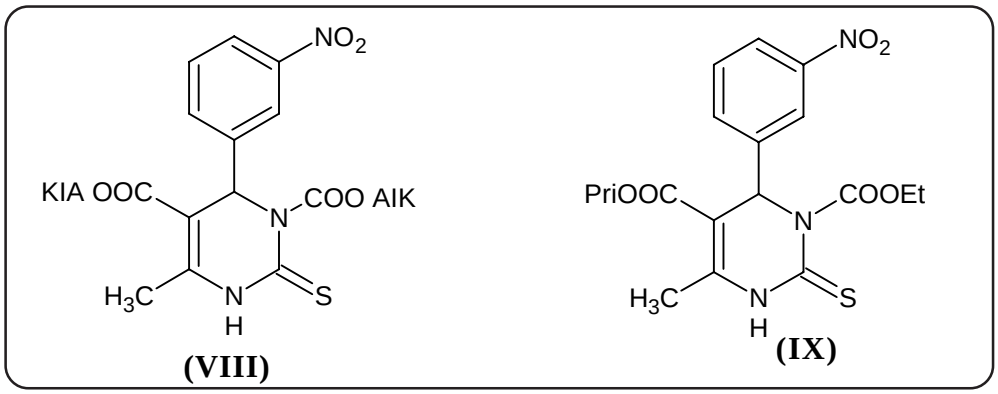
Pyrimidine-5-carboxamides derivatives (IV) were reported to possess anticarcinogencic activity,[12] antiinflammaroty,[13] analgesic[14] and blood platelet aggregation inhibitory activity.[15]

Simple modificatios of the aromatic ring are reported to give substances with only moderate cardiovascular activity, e.g. (V)[16], (VI),[17,18,19] and (VII) were shown to be potent calcium channel blockers,[20-22] but they do not show any significant antihypertensive activity[20] *in vivo*. This is also the case for bicyclic dihydropyrimidines[23,24] (V).

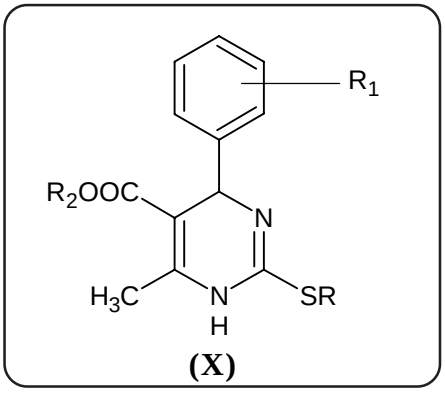


(V) **(VI)** **(VII)**

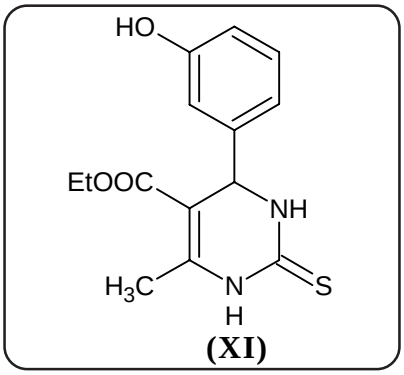
Among the most potent derivatives are Biginelli compounds bearing an ester group at N-3 (VIII), there by closely resembling the nifedipine structure.[25-28] Although the calcium channel blocking activity of these compounds, (IX) is comparable to dihydropyridines, most of them are devoid of antihypertensive activity[26] *in vivo*.



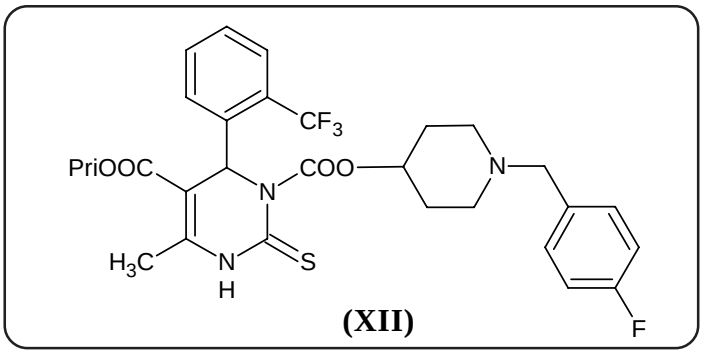
Atwal K. S. et al.[29] synthesized the 2-[[(4-methoxyphenyl)methyl]thio]-dihydropyrimidine (X) and investigated that pyrimidines are integral parts of such biologically important compounds as antiviral,[30,31] antitumor [32] and cardiovascular agent.[33]



A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol (XI) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest.[34] Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs.[35]

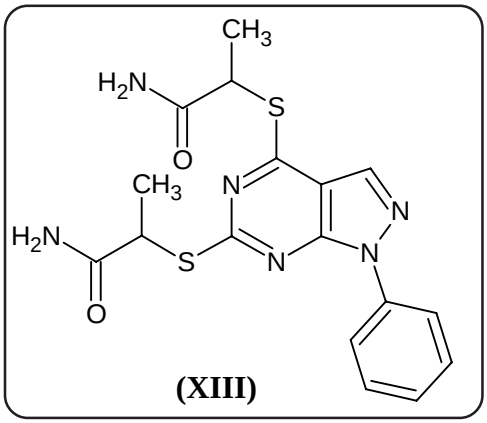


George C. et al.[36] prepared dihydropyrimidine (XII) was equipotent to nifedipine and amlodipine *in vitro*. In the spontaneously hypertensive rate, dihydropyrimidine (XII) is both more potent and longer acting than nifedipine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine (XII) has the potential advantage of being a single enantiomer.



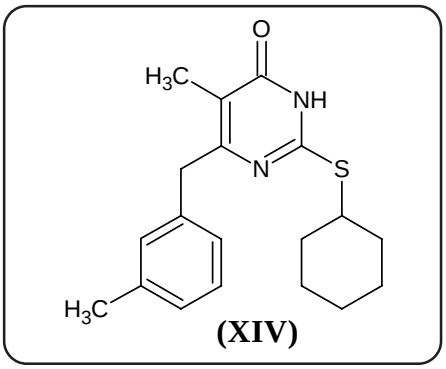
(XII)

Sally Ann P. et al.[37] synthesized 4,6-Bis[(R-carbamoylethyl)thio]-1-phenylpyrazolo[3,4- d]pyrimidine (XIII) was identified as a novel adenosine A_1 receptor antagonist, antagonizing adenosine stimulated cyclic adenosine mono phosphate generation in guinea pig brain slices.[38,39]



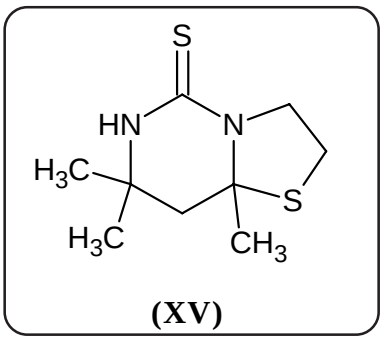
(XIII)

Atwal K. et al.[26] synthesized the 3-substituted 1,4-dihydropyrimidine and show that vasorelaxant activity. Novel compounds related to 2-(cyclohexylthio)-3,4-dihydro-5-methyl-6-(3-methylbenzyl)-4- oxopyrimidine (XIV) (MC 639) have been synthesized by Antonello M. et al.[40] and tested as inhibitors of Human Immunodeficiency virus type-1 (HIV-1).



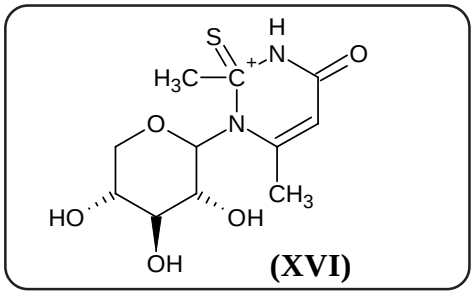
(XIV)

Various 2-thiopyrimidine derivatives have been synthesized by Sondhi S.M. et al.[41] One of the compound, 7,7,8a-trimethyl-hexahydro-thiazolo[3,2-c]pyrimidine-5-thione (XV) showed good antiinflammatory (37.4% at 100mg/kg p.o.) and analgesic activity (75% at 100 mg/kg p.o.). Twenty 5-alkyl-2-thiopyrimidine nucleosides were newly synthesized by Shigeta S. et al.[42] and examined for antiviral activities against Herpes Simplex virus (HSV), Varicella Zoster virus (VZV) and Human Cytomegalovirus (HCMV).



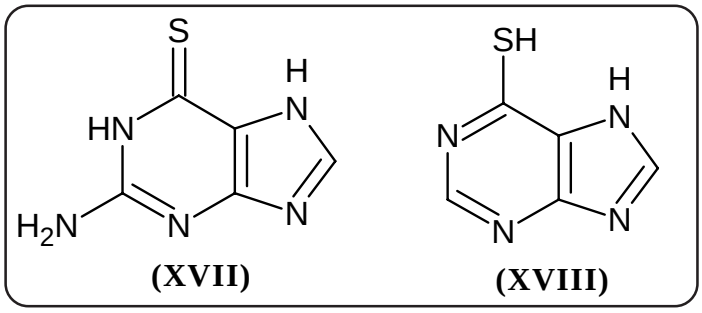
(XV)

Attia A. M. et al.[43] synthesized N3-beta-D-glucopyranosyl, galactopyranosyl and xylopyranosyl 6-methyl-2-methylthiouracil (XVI) and their 5-bromo derivatives by coupling an α-acetobromosugar with the corresponding thiouracil. The new modified thiouridine analogues were evaluated for their inhibitory activity against Human Immunodeficiency Virus (HIV) replication in MT-4 cells as well as for their cytotoxicity.

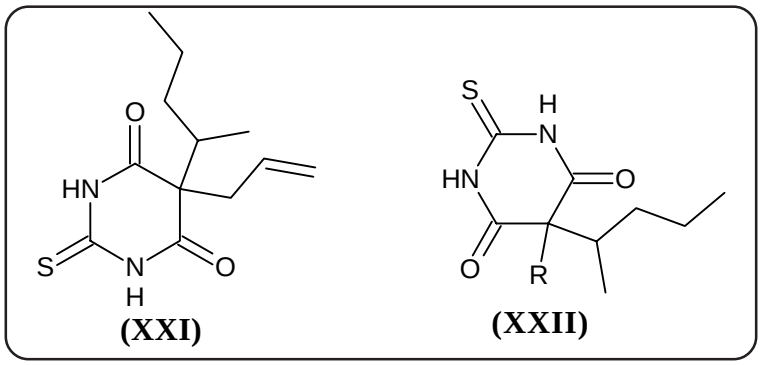


(XVI)

Massey A. et al.[44] described the thiopurines, 6-thioguanine (XVII) and 6-mercaptopurine (XVIII) are antileukemic agents that are incorporated into DNA following retrieval by the purine salvage pathway.



The metabolic rate of three pharmacologically significant thiopyrimidines has been investigated by Spector E. et al.[45] Incubation of thiamylal (XXI),5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid (XXII), with minced rat liver resulted in the formation of a metabolite which was isolated and identified as secobarbital.



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

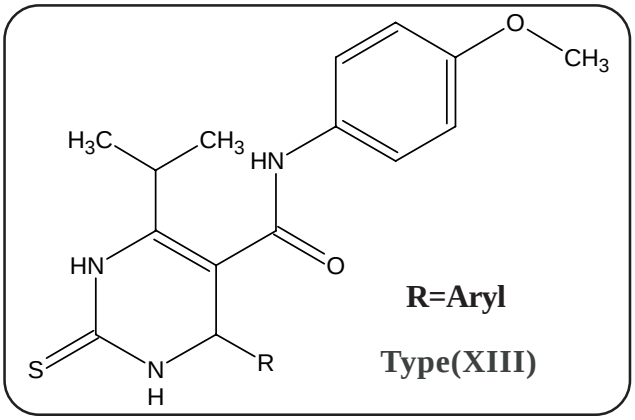
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISO PROPYL-*N*-(4-METHOXYPHENYL)-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDES

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE- 5-CARBOXAMIDES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES

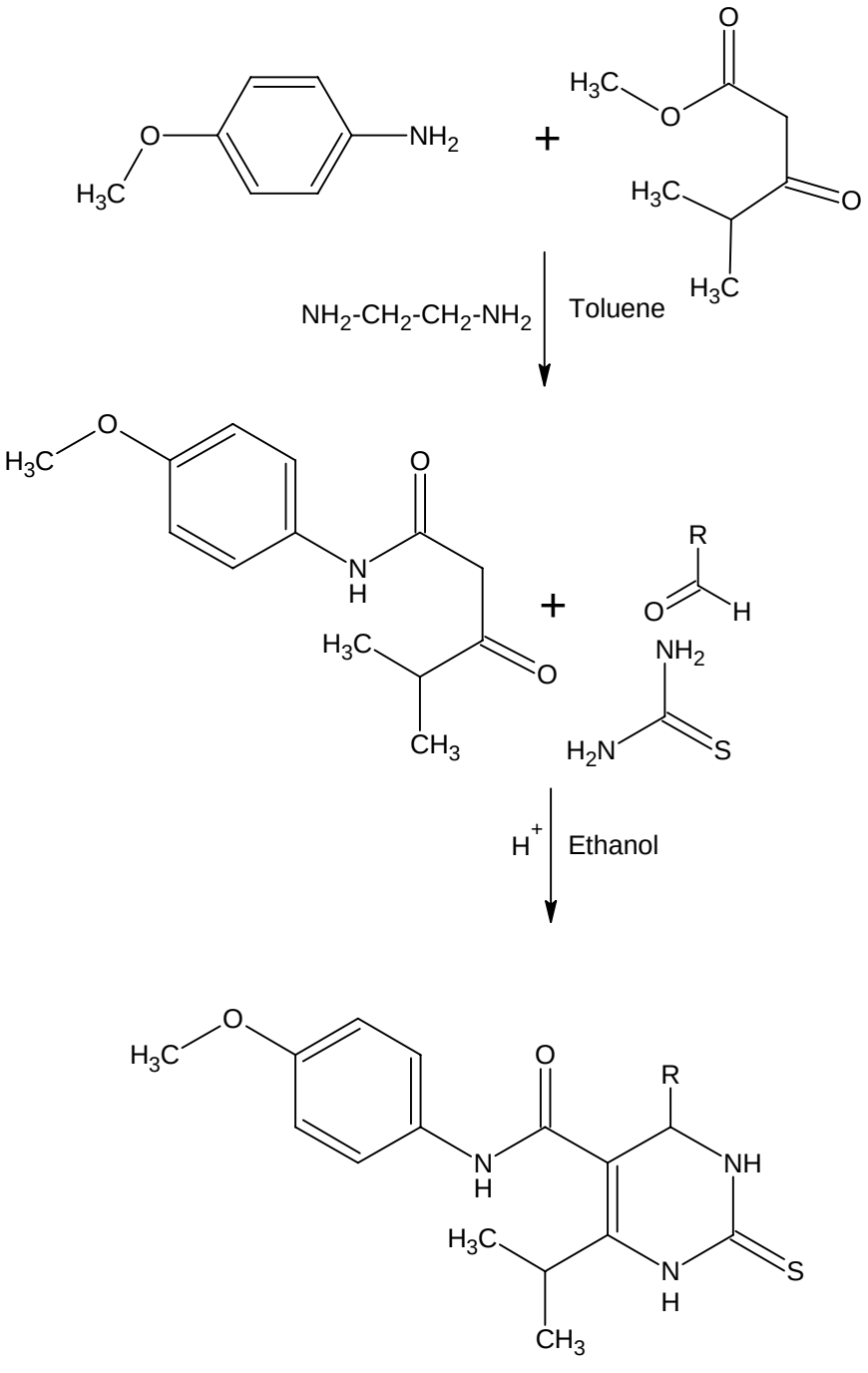
Much interest have been focused around dihydropyrimidinthione derivatives because of their wide variety of pharmacological properties and industrial applications. In view of these findings and achieve to better drug potency, we have synthesized 6-isopropyl-*N*-(4-methoxyphenyl)-4-aryl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamides of Type (XIII) by the cyclocondensation of 4-methyl-N-(4-methoxyphenyl)-3-oxopentanamide with thiourea and aryl aldehydes.



The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

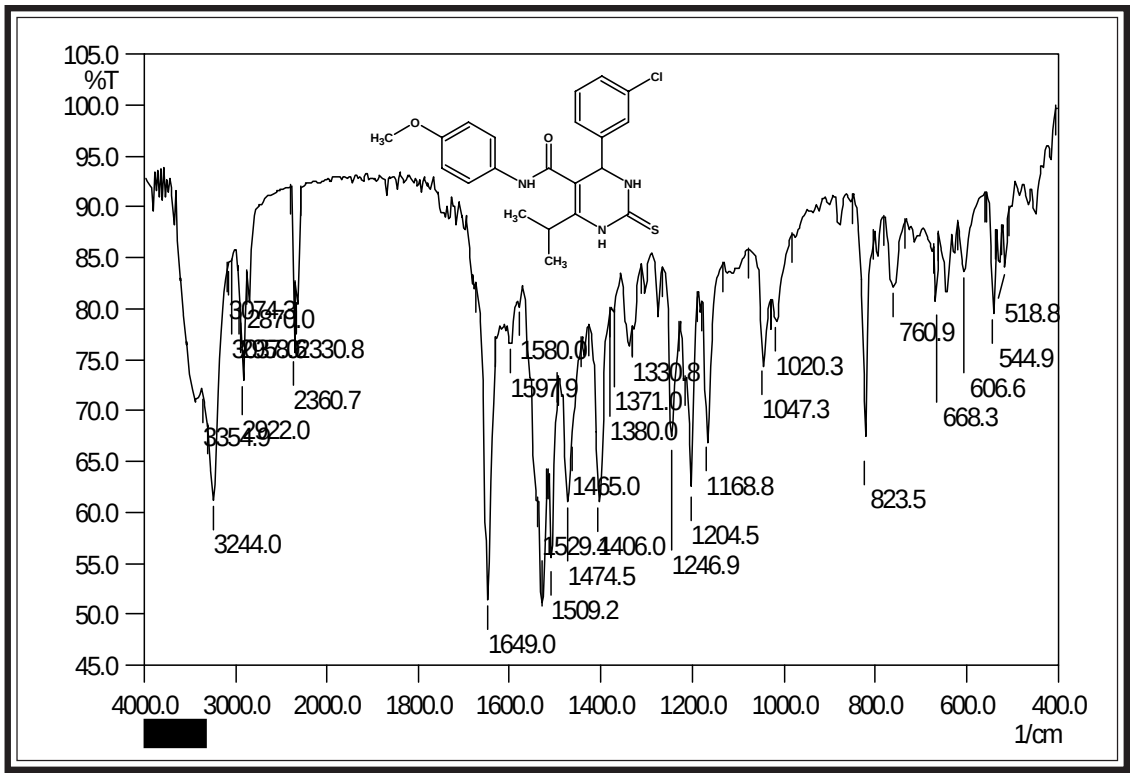
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds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

Reaction Scheme



R = Aryl

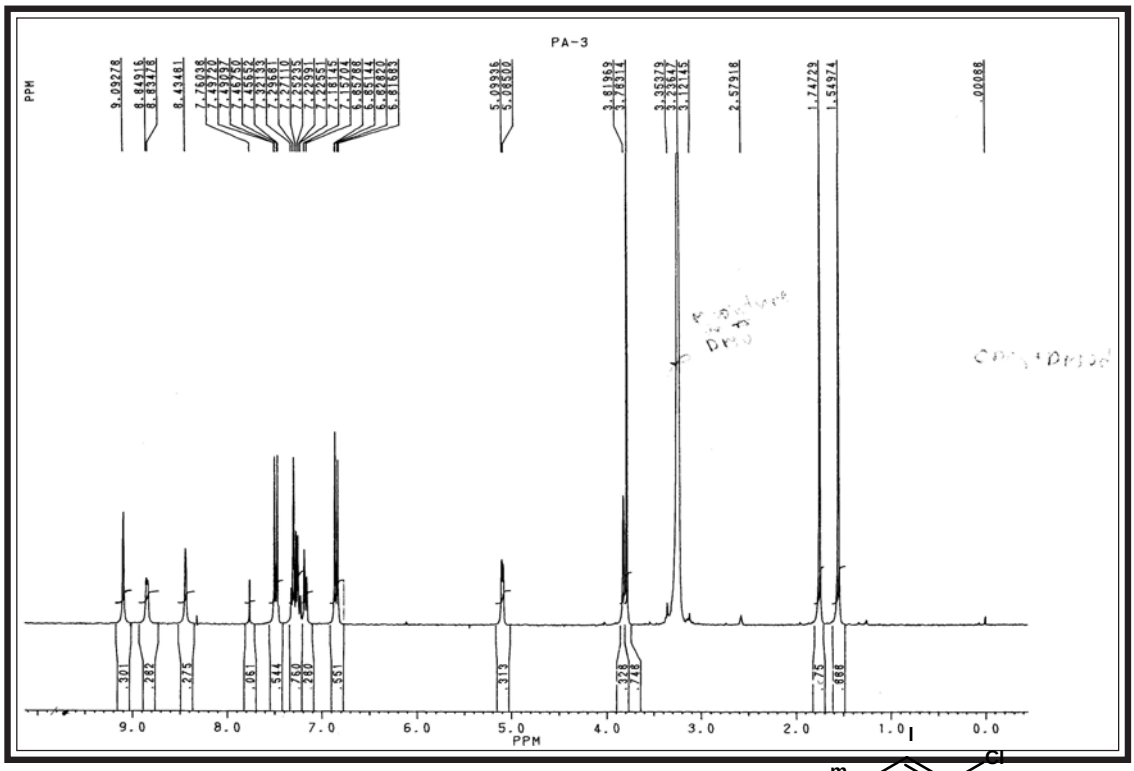
IR SPECTRAL STUDIES OF 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-(3-CHLOROPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



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	46
-CH3	C-H str. (sym.)	2870	2880-2860	,,
	C-H i.p.def. (asym.)	1465	1470-1435	,,
	C-H o.o.p. def. (sym.)	1371	1390-1370	,,
Aromatic	C-H str.	3074	3090-3030	47
	C=C str.	1509	1540-1480	,,
Pyrimidine	C=C str.	1529	1580-1520	,,
moity	C-H str.	3037	3080-3030	,,
	C-H i.p. def.	1047	1125-1090	,,
Amide	-NH str.	3354	3410-3380	46
	-NH def.	1597	1635-1595	,,
Carbonyl	-C=O str.	1706	1700-1725	,,
Amide	- C=O str.	1649	1690-1660	,,
Isopropyl	C-H str.	1380	1385-1365	,,

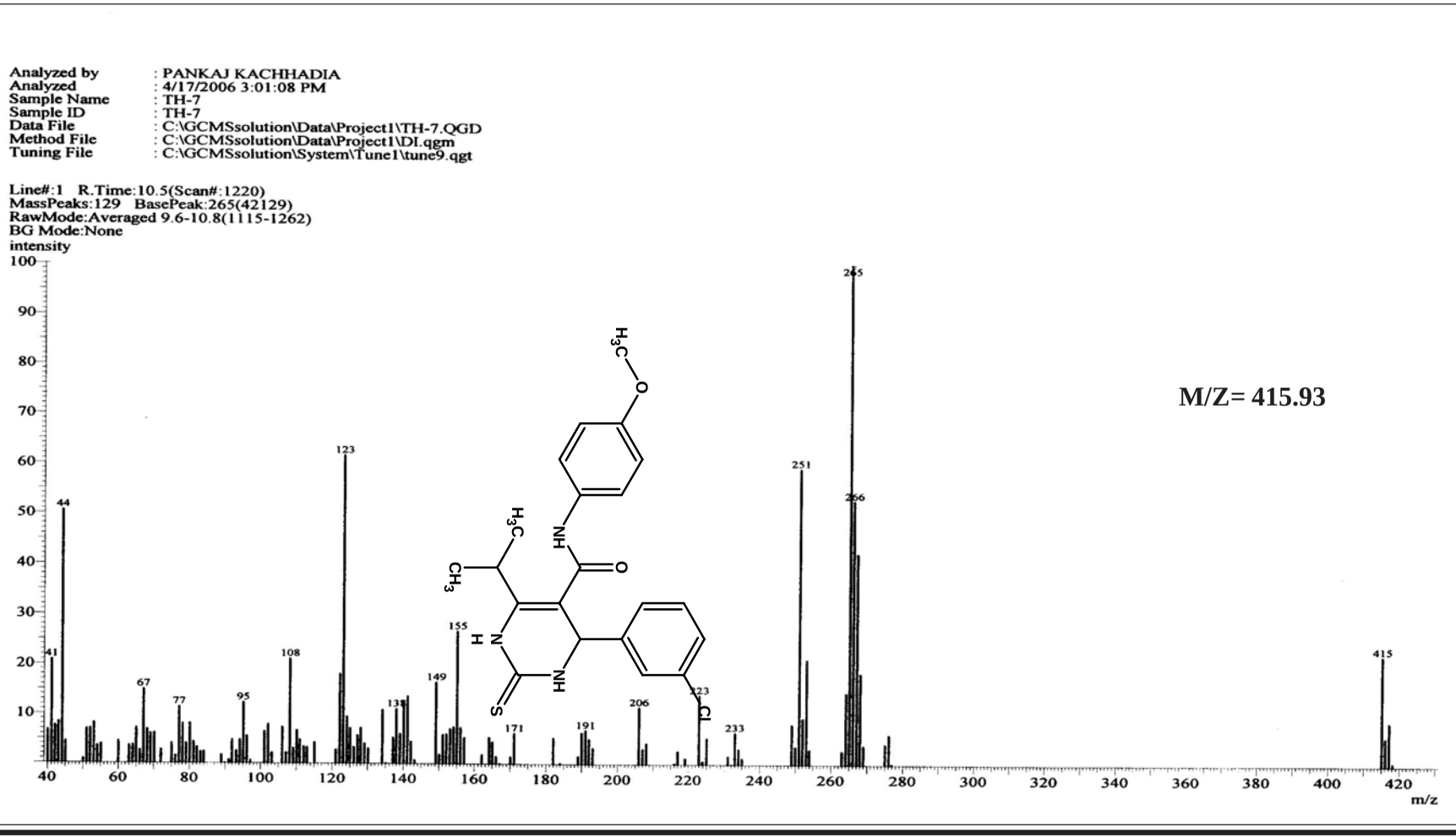
NMR SPECTRAL STUDY OF 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-(3-CHLOROPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.54	3H	singlet	C-CH_3(a)	-
2	1.74	3H	singlet	C-CH_3(b)	-
3	3.78	3H	singlet	Ar-OCH_3(d)	-
4	3.81	1H	singlet	C-CH(c)	-
5	5.08	1H	doublet	Ar-CH(H)	-
6	6.82	2H	doublet	Ar-CH(I,I')	J=9.0
7	7.15-7.32	4H	multiplet	Ar-CH(k,l,m,n)	-
8	7.42-7.55	2H	doublet	Ar-CH(j,j')	J=9.0
9	8.43	1H	singlet	Ar-NH(e)	-
10	8.83	1H	doublet	Ar-NH(f)	-
11	9.02	1H	singlet	Ar-NH(g)	-

TABLE-13 : MASS SPECTRAL STUDIES OF 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-(3-CHLOROPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES

(A) Synthesis of 4-Methyl-N-(4-methoxyphenyl)-3-oxo-pentanamide

A mixture of methyl-4-methyl-3-oxopentanoate (methyl isobutrylacetate) (1.44 gm, 0.01 mol) and 4-methoxyaniline (1.23 gm, 0.01 mol) in toluene containing few drops of ethylene diamine was refluxed for 12 hr. The excess methanol was collected in dean and stark. The resulting solution was cooled to 0^0C and trated with dilute HCL. The seperated toluene layer washed with three times water and distilled out under vaccum. Yield 61%, m. p. 36^0C, Anal.Calcd. for $C_{13}H_{17}NO_3$ Calcd: C, 66.36; H, 7.28; N, 5.95%, Found: C, 66.33; H, 7.30; N, 5.97%.

(B) Synthesis of 6-Isopropyl-*N*-(4-methoxyphenyl)-4-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

A mixture of thiourea (0.76 gm, 0.01 mol), 3-chlorobenzaldehyde (1.40 gm, 0.01 mol) and 4-methyl-N-(4-methoxyphenyl)-3-oxo-pentanamide (2.35 gm, 0.01 mol) in ethanol (15 ml) containing few drops of concentrated hydrochloric acid was refluxed with stirring for 24 hr. The solution was allowed to stand for 12 hr. at room temperature. The resulting solid mass separated was filtered and crystallized from dioxane. Yield 62%, m. p. 250^0C, Anal.Calcd. for $C_{21}H_{22}CIN_3O_2S$ Calcd: C, 60.64; H, 5.33; N, 10.10%, Found: C, 60.63; H, 5.32; N, 10.08%.

Similarly, other 6-isopropyl-*N*-(4-methoxyphenyl)-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides were prepared. The physical data are recorded in Table No. 13

(C) Biological screening of 6-Isopropyl-*N*-(4-methoxyphenyl)-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides

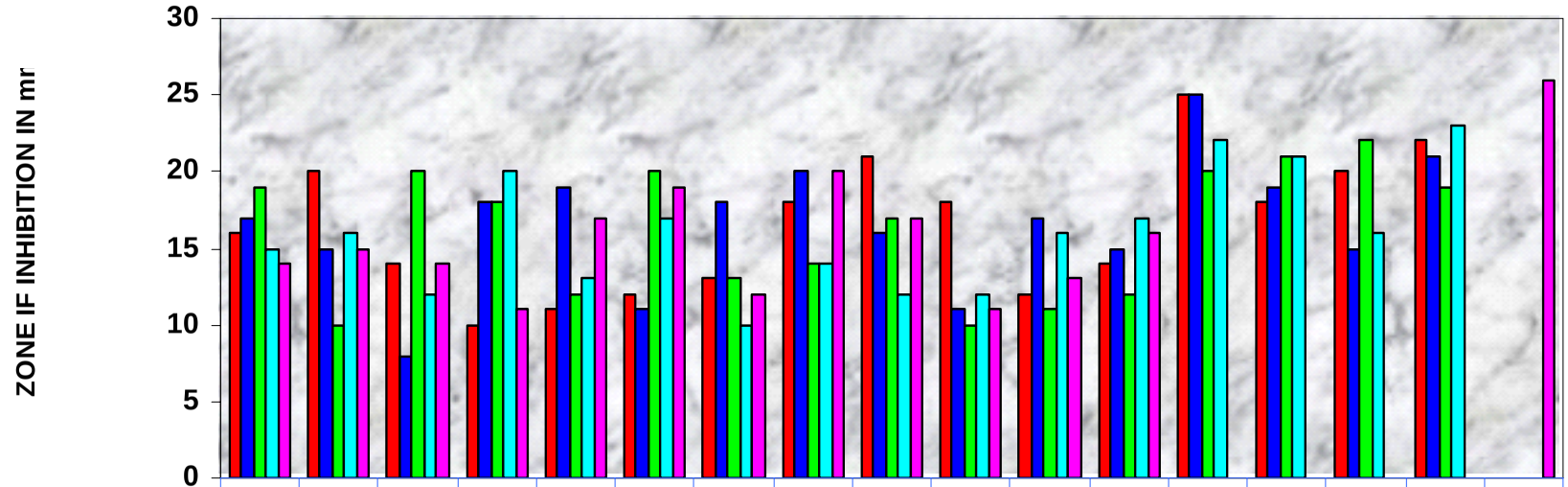
Antimicrobial testing were carried out as described in Part-I**(A)** Section-I(D). The zones of inhibition of test solutions are recorded in Graphical Chart No.13

TABLE-13 : PHYSICAL CONSTANTS OF 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
13a	C_6H_5-	$C_{21}H_{23}N_3O_2S$	381.49	262	49	11.01	11.00	0.50	S2
13b	4-NO_2-C_6H_4-	$C_{21}H_{22}N_4O_4S$	426.49	195	50	13.14	13.13	0.48	S2
13c	3-NO_2-C_6H_4-	$C_{21}H_{22}N_4O_4S$	426.49	260	56	13.14	13.13	0.49	S2
13d	4-$CH_3C_6H_4$-	$C_{22}H_{25}N_3O_2S$	395.51	268	49	10.62	10.61	0.61	S1
13e	2-CI-C_6H_4-	$C_{21}H_{22}CIN_3O_2S$	415.93	257	51	10.10	10.12	0.65	S1
13f	4-CI-C_6H_4-	$C_{21}H_{22}CIN_3O_2S$	415.93	255	44	10.10	10.09	0.61	S2
13g	3-CI-C_6H_4-	$C_{21}H_{22}CIN_3O_2S$	415.93	250	62	10.10	10.08	0.64	S2
13h	3,4-$(OCH_3)_2$-C_6H_4-	$C_{23}H_{27}N_3O_4S$	441.54	195	68	9.52	9.51	0.58	S1
13i	3-C_6H_5-O-C_6H_4-	$C_{27}H_{27}N_3O_3S$	473.58	230	40	8.87	8.86	0.44	S1
13j	4-OCH_3-C_6H_4-	$C_{22}H_{25}N_3O_3S$	411.51	242	68	10.21	10.20	0.43	S1
13k	4-F-C_6H_4-	$C_{21}H_{22}FN_3O_2S$	399.48	235	61	10.52	10.51	0.60	S2
13l	3-Br-C_6H_4-	$C_{21}H_{22}BrN_3O_2S$	460.38	257	56	9.13	9.12	0.41	S2

S1 Acetone:Benzene (0.5 : 9.5), S2 Hexane:Ethyl acetate (9 : 1)

GRAPHICAL CHART NO. 13 : 6-ISOPROPYL-*N*-(4-METHOXYPHENYL)-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDRO PYRIMIDINE-5-CARBOXAMIDES

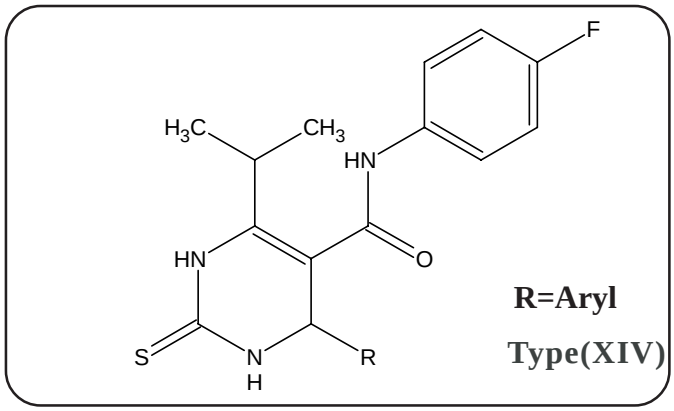


	13a	13b	13c	13d	13e	13f	13g	13h	13ii	13j	13k	13l	Amoxicillin	Benzyl Penic	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	16	20	14	10	11	12	13	18	21	18	12	14	25	18	20	22	0
S. aureus	17	15	8	18	19	11	18	20	16	11	17	15	25	19	15	21	0
Aerogenes	19	10	20	18	12	20	13	14	17	10	11	12	20	21	22	19	0
Pseudomonas	15	16	12	20	13	17	10	14	12	12	16	17	22	21	16	23	0
A.niger	14	15	14	11	17	19	12	20	17	11	13	16	0	0	0	0	26

SECTION - II

SYNTHSIS AND BIOLOGICAL SCREENING OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE- 5-CARBOXAMIDES

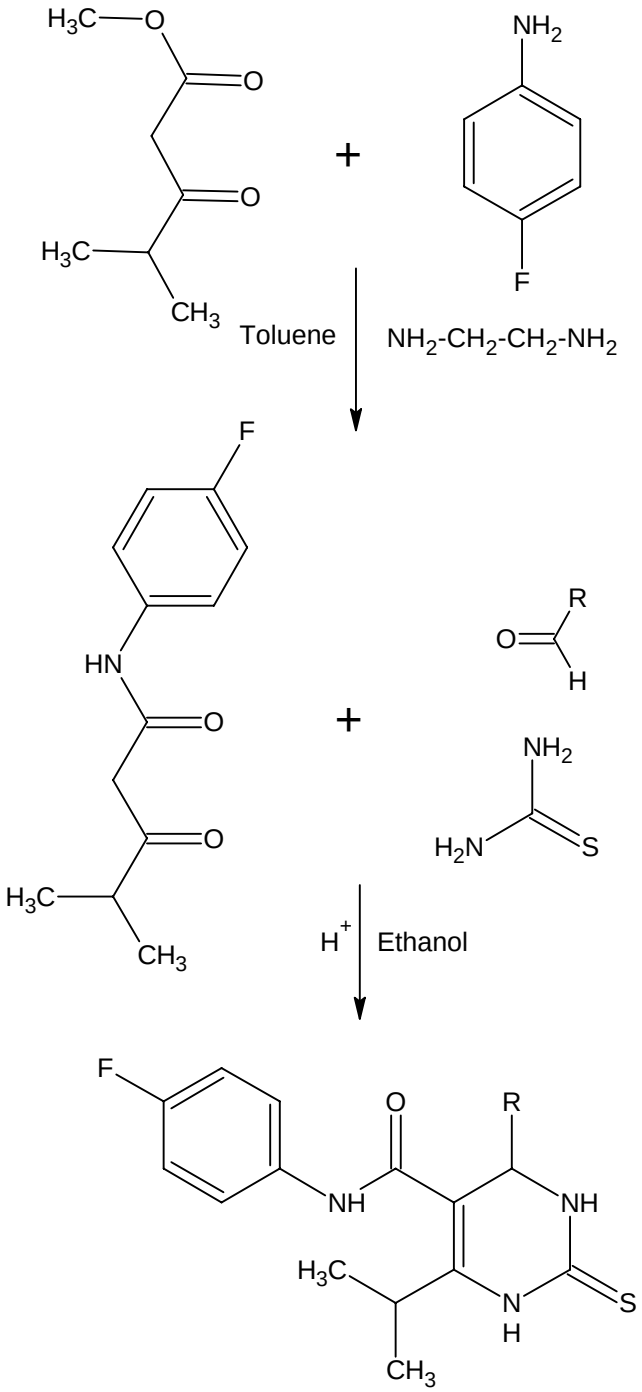
Compounds containing pyrimidine ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these report, we have synthesized *N*-(4-fluorophenyl)-6-isopropyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine- 5-carboxamides of Type (XIV) by the condensation of 4-methyl-N-(4-fluorohenyl)-3-oxo-pentanamide, thiourea and aryl aldehydes.



The structure elucidation of synthesized compounds has been done on the basis of elemental analysis, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

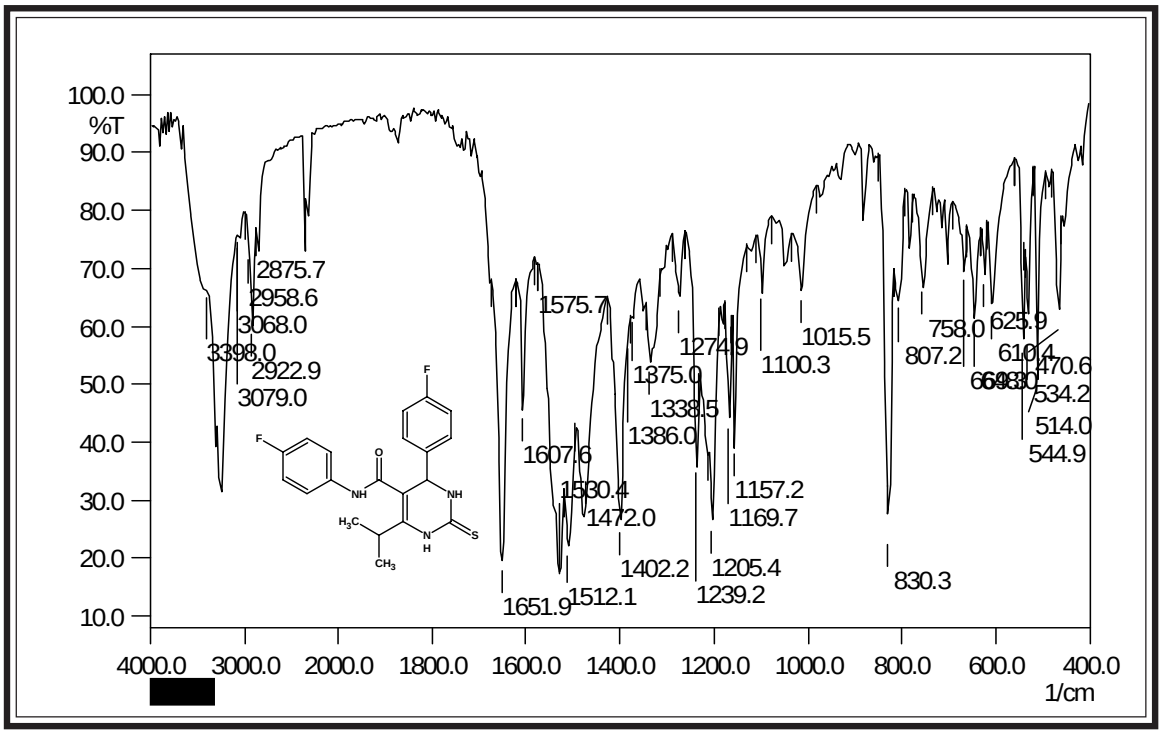
All the compounds have been evaluated for their **in vitro** biological assay like antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards **Aspergillus niger** at a concentration of 40µg/ml. The biological activities of synthesized compounds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

Reaction Scheme



R = Aryl

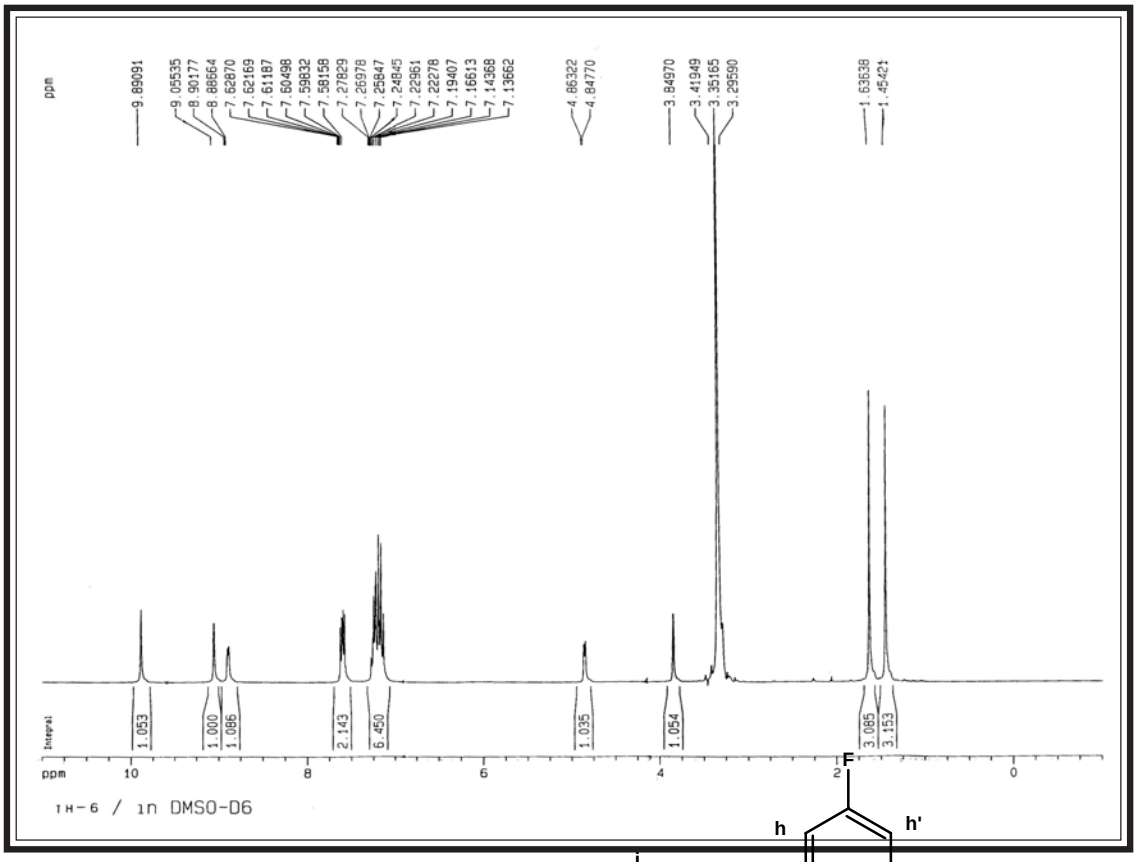
IR SPECTRAL STUDIES OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-(4-FLUOROPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



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	46
-CH3	C-H str. (sym.)	2875	2880-2860	,,
	C-H i.p.def. (asym.)	1472	1470-1435	,,
	C-H o.o.p. def. (sym.)	1386	1390-1370	,,
Aromatic	C-H str.	3079	3090-3030	47
	C=C str.	1512	1540-1480	,,
Pyrimidine	C=C str.	1530	1580-1520	,,
moity	C-H str.	3068	3080-3030	,,
	C-H i.p. def.	1100	1125-1090	,,
Amide	-NH str.	3398	3410-3380	46
	-NH def.	1607	1635-1595	,,
Carbonyl	-C=O str.	1706	1700-1725	,,
Amide	- C=O str.	1651	1690-1660	,,
Isopropyl	C-H str.	1375	1385-1365	,,

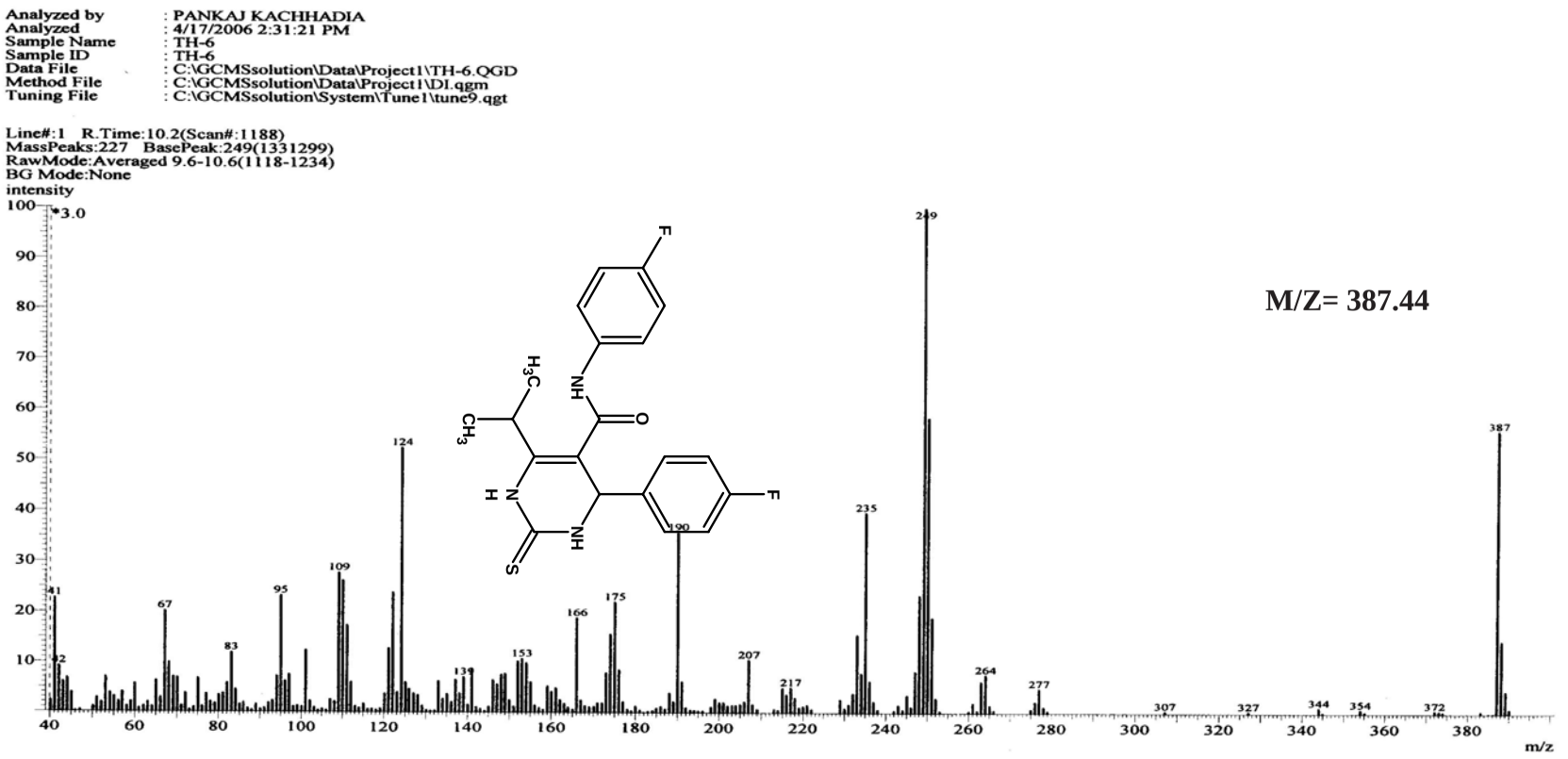
NMR SPECTRAL STUDIES OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-(4-FLUOROPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



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

Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.45	3H	singlet	C-CH_3(a)	-
2	1.63	3H	singlet	C-CH_3(b)	-
3	3.84	1H	singlet	Ar-CH(c)	-
4	4.85	1H	doublet	Ar-CH(d)	-
5	7.13-7.58	6H	multiplet	Ar-CH (h,h',j,j',k,k')	-
6	7.58-7.62	2H	dd	Ar-CH(i,i')	J=6.0
7	8.89	1H	singlet	Ar-NH(e)	-
8	9.05	1H	doublet	Ar-NH(g)	-
9	9.89	1H	singlet	Ar-NH(f)	-

TABLE-14 : MASS SPECTRAL STUDIES OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-(4-FLUOROPHENYL)-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXAMIDE



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE- 5-CARBOXAMIDES

(A) Synthesis of 4-Methyl-N-(4-fluorophenyl)-3-oxopentanamide

A mixture of methyl-4-methyl-3-oxopentanoate (methyl isobutrylacetate) (1.44 gm, 0.01 mol) and 4-fluoroaniline (1.23 gm, 0.01 mol) in toluene containing few drops of ethylene diamine was refluxed for 12 hr and collect methanol using dean and stark. The resulting solution was cooled to 0^0C. Than add dilute HCL solution in toluene layer, theseperated toluene layer washed with three times water and distilled out under vaccum. The seperated solid was crystallized from hexane-ethylacetate mixture Yield 67%, m. p. 65^0C, Anal.Calcd. for C12H14FNO2 Calcd: C, 64.56; H, 6.32; N, 6.27%, Found: C, 64.54; H, 6.29; N, 6.28%.

(B) Synthesis of *N*-(4-Fluorophenyl)-6-isopropyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine- 5-carboxamide

A mixture of thiourea (0.76 gm, 0.01 mol), p-fluorobenzaldehyde (1.24 gm, 0.01 mol) and 4-methyl-N-(4-fluorohenyl)-3-oxo-pentanamide (2.23 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hr. The solution was allowed to stand for 12 hr. at room temperature. The resulting solid mass separated was filtered and, crystallized from dioxane.Yield 52%, m.p.287^0C, Anal.Calcd. for $C_{20}H_{19}F_2N_3OS$ Calcd: C,62.00; H, 4.94; N, 10.85%, Found: C, 61.98; H, 4.93; N, 10.84%.

Similarly, other dihydropyrimidinthiones were prepared. The physical data are recorded in Table No. 14

(C) Biological screening *N*-(4-Fluorophenyl)-6-isopropyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine- 5-carboxamides

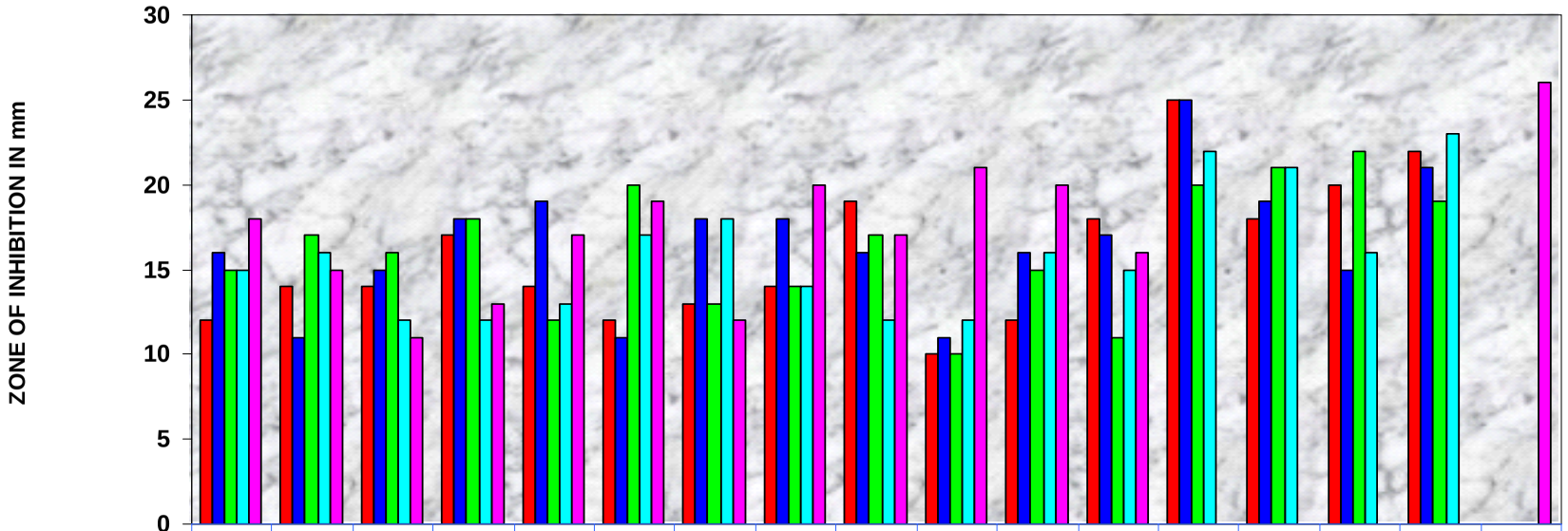
Antimicrobial testing were carried out as described in Part-I**(A)** Section-I(D). The zones of inhibition of test solutions are recorded in Graphical Chart No.14

TABLE-14 : PHYSICAL CONSTANTS OF *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-ARYL-2-THIOXO-1,2,3,4-TETRAHYDROPYRIMIDINE- 5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
14a	-C_6H_5-	$C_{20}H_{20}FN_3OS$	369.45	254	48	11.37	11.36	0.52	S2
14b	4-NO_2-C_6H_4-	$C_{20}H_{19}FN_4O_3S$	414.54	248	51	13.52	13.51	0.49	S2
14c	3-NO_2-C_6H_4-	$C_{20}H_{19}FN_4O_3S$	414.54	258	55	13.52	13.50	0.51	S2
14d	2-ClC_6H_4-	$C_{20}H_{19}ClFN_3OS$	403.90	235	47	10.40	10.39	0.58	S1
14e	4-CH_3-C_6H_4-	$C_{21}H_{22}FN_3OS$	383.48	274	59	10.96	10.98	0.54	S1
14f	4-CI-C_6H_4-	$C_{20}H_{19}ClFN_3OS$	403.90	256	47	10.40	10.39	0.61	S2
14g	3-CI-C_6H_4-	$C_{20}H_{19}ClFN_3OS$	403.90	254	62	10.40	10.38	0.68	S2
14h	3,4-$(OCH_3)_2$-C_6H_3-	$C_{22}H_{24}FN_3O_3S$	429.50	242	67	9.78	9.77	0.59	S1
14i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{24}FN_3O_2S$	461.55	250	41	9.10	9.08	0.47	S1
14j	4-OCH_3-C_6H_4-	$C_{21}H_{22}FN_3O_2S$	399.48	262	60	10.52	10.51	0.43	S1
14k	4-F-C_6H_4-	$C_{20}H_{19}F_2N_3OS$	387.44	287	52	10.85	10.84	0.57	S2
14l	3-Br-C_6H_4-	$C_{20}H_{19}BrFN_3OS$	448.35	272	56	9.37	9.36	0.42	S2

S1 Acetone:Benzene (0.5 : 9.5), S2 Hexane:Ethyl acetate (9 : 1)

GRAPHICAL CHART NO. 14 : *N*-(4-FLUOROPHENYL)-6-ISOPROPYL-4-ARYL-2-THIOXO-1,2,3,4 TETRAHYDRO PYRIMIDINE- 5-CARBOXAMIDES



	14a	14b	14c	14d	14e	14f	14g	14h	14i	14j	14k	14l	Amoxicilllin	Benzyl Penicillin	Ciprofloxacin	Erythromycin	Greseofulvin
B. Coccus	12	14	14	17	14	12	13	14	19	10	12	18	25	18	20	22	0
S. aureus	16	11	15	18	19	11	18	18	16	11	16	17	25	19	15	21	0
Aerogenes	15	17	16	18	12	20	13	14	17	10	15	11	20	21	22	19	0
Pseudomonas	15	16	12	12	13	17	18	14	12	12	16	15	22	21	16	23	0
A.niger	18	15	11	13	17	19	12	20	17	21	20	16	0	0	0	0	26

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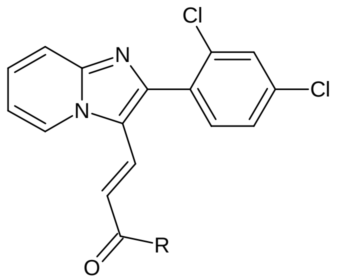
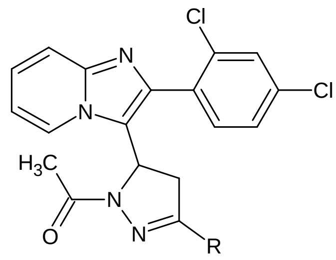
LIST OF NEW COMPOUNDS





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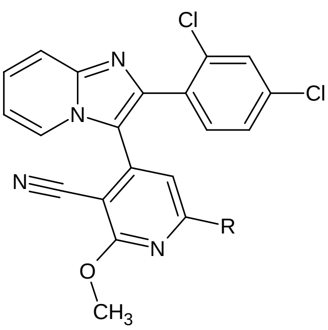
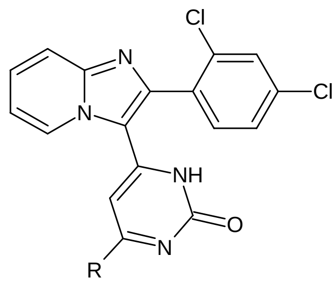
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
2-CH_3-C_6H_4-	2-CH_3-C_6H_4-
2,5-$(CH_3)_2$-C_6H_3-	2,5-$(CH_3)_2$-C_6H_3-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
2,4-$(Cl)_2$-C_6H_3-	2,4-$(Cl)_2$-C_6H_3-
4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-
4-S-CH_3-C_6H_4-	4-S-CH_3-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-





R	R
C_6H_5-	C_6H_5-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
2-CH_3-C_6H_4-	2-CH_3-C_6H_4-
2,5-$(CH_3)_2$-C_6H_3-	2,5-$(CH_3)_2$-C_6H_3-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
2,4-$(Cl)_2$-C_6H_3-	2,4-$(Cl)_2$-C_6H_3-
4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-Br-C_6H_4-	4-Br-C_6H_4-
4-S-CH_3-C_6H_4-	4-S-CH_3-C_6H_4-
4-F-C_6H_4-	4-F-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
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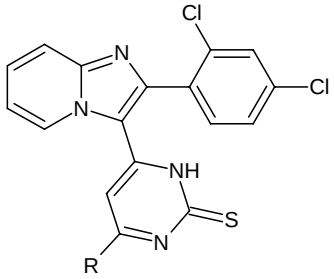

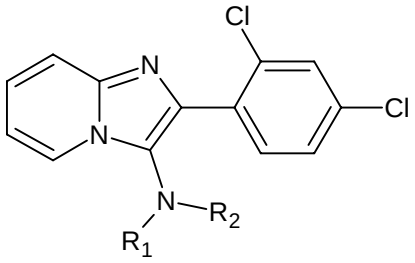

R	**R_1R_2**
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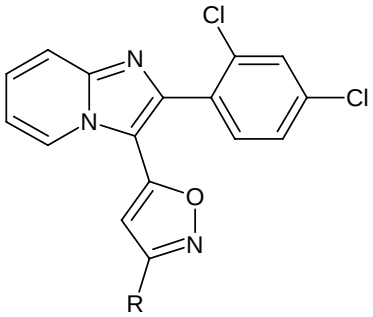
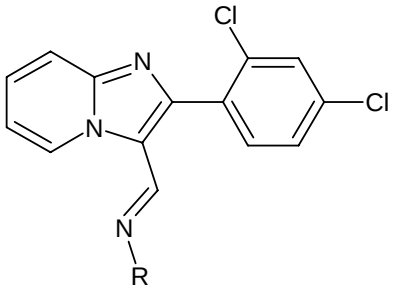
2-CH_3-C_6H_4-	$C_{11}H_{15}NO$-
2,5-$(CH_3)_2$-C_6H_3-	$C_6H_{13}NO$-
4-OCH_3-C_6H_4-	$C_6H_{13}N$-
2,4-$(Cl)_2$-C_6H_3-	$C_{10}H_{13}N$-
4-Cl-C_6H_4-	$C_5H_{11}N$-
4-Br-C_6H_4-	$C_{11}H_{15}N$-
4-S-CH_3-C_6H_4-	C_4H_8-
4-F-C_6H_4-	C_2H_6-
3-NO_2-C_6H_4-	C_4H_{10}-
4-NO_2-C_6H_4-	$C_{12}H_{10}$-





R	**R**
C_6H_5-	C_6H_5-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
2-CH_3-C_6H_4-	2-CH_3-C_6H_4-
2,5-$(CH_3)_2$-C_6H_3-	2,5-$(CH_3)_2$-C_6H_3-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-
2,4-$(Cl)_2$-C_6H_3-	2,5-$(Cl)_2$-C_6H_3-
4-Cl-C_6H_4-	4-Cl-C_6H_4-
4-Br-C_6H_4-	3-Cl-C_6H_4-
4-S-CH_3-C_6H_4-	4-F-C_6H_4-
4-F-C_6H_4-	2-F-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
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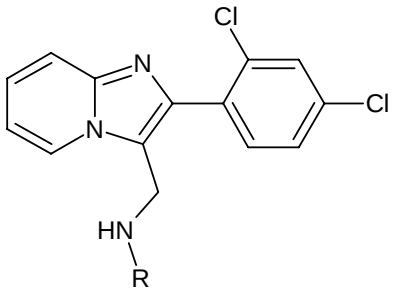

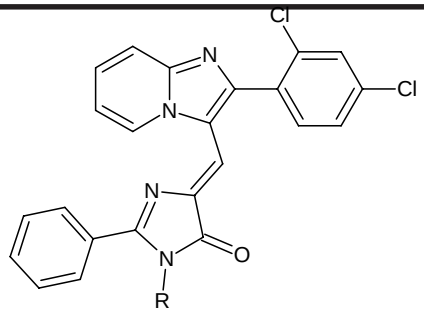

R	**R**
C_6H_5-	C_6H_5-
4-CH_3-C_6H_4-	4-Cl-C_6H_4-
2-CH_3-C_6H_4-	4-NO_2-C_6H_4-
2,5-$(CH_3)_2$-C_6H_3-	2-CH_3-C_6H_4-
4-OCH_3-C_6H_4-	4-CH_3-C_6H_4-
2,5-$(Cl)_2$-C_6H_3-	2-OCH_3-C_6H_4-
4-Cl-C_6H_4-	4-OCH_3-C_6H_4-
3-Cl-C_6H_4-	4-F-C_6H_4-
4-F-C_6H_4-	2-Cl-C_6H_4-
2-F-C_6H_4-	3,4-$(Cl)_2$-C_6H_3-
3-NO_2-C_6H_4-	2,6-$(Cl)_2$-C_6H_3-
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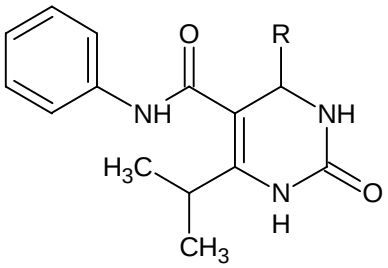
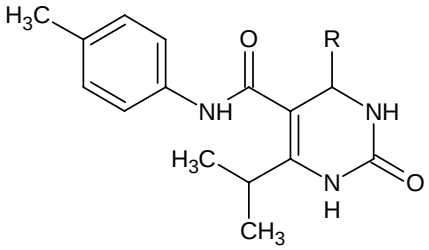
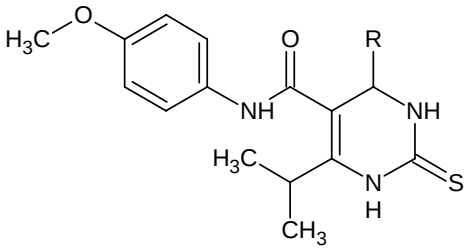
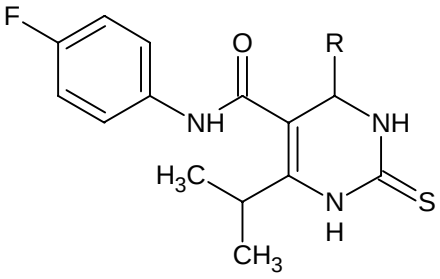




R	**R**
C_6H_5-	C_6H_5-
4-NO_2-C_6H_4-	4-NO_2-C_6H_4-
3-NO_2-C_6H_4-	3-NO_2-C_6H_4-
4-CH_3-C_6H_4-	4-CH_3-C_6H_4-
2,4-$(Cl)_2$-C_6H_3-	2,4-$(Cl)_2$-C_6H_3-
4-Cl-C_6H_4-	4-Cl-C_6H_4-
3-Cl-C_6H_4-	3-Cl-C_6H_4-
2-Cl-C_6H_4-	2-Cl-C_6H_4-
3,4-$(OCH_3)_2$-C_6H_3-	3-O-C_6H_5-C_6H_4-
4-OCH_3-C_6H_4-	4-OCH_3-C_6H_4-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





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