"STUDIES ON SOME HETEROCYCLIC COMPOUNDS OF THERAPEUTIC INTEREST"

A THESIS

SUBMITTED TO THE

SAURASHTRA UNIVERSITY

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

Vipul V. Bhuva

UNDER THE GUIDANCE
OF
Dr. D. M. Purohit

Shree M. & N. Virani Science College,
Department of Chemistry,
Kalawad Road,
Rajkot – 360 005
Gujarat, INDIA

2009

Date: / /2009

Dr. D. M. Purohit
M. Sc. Ph. D.,
Lecturer,
Shree M. & N. Virani Science College
Department of chemistry,
Kalawad Road
Rajkot – 360 005

Residence:
Dr.D.M.Purohit
B-149,"shandilya"
Shastrinagar,
Nana Mova Road,
Rajkot – 360 005
Gujarat (India).

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

The work included in the thesis is my own work under the supervision of **Dr. D. M. Purohit** and leads to some contribution in Chemistry subsidised by a number of references.

Date: / /2009

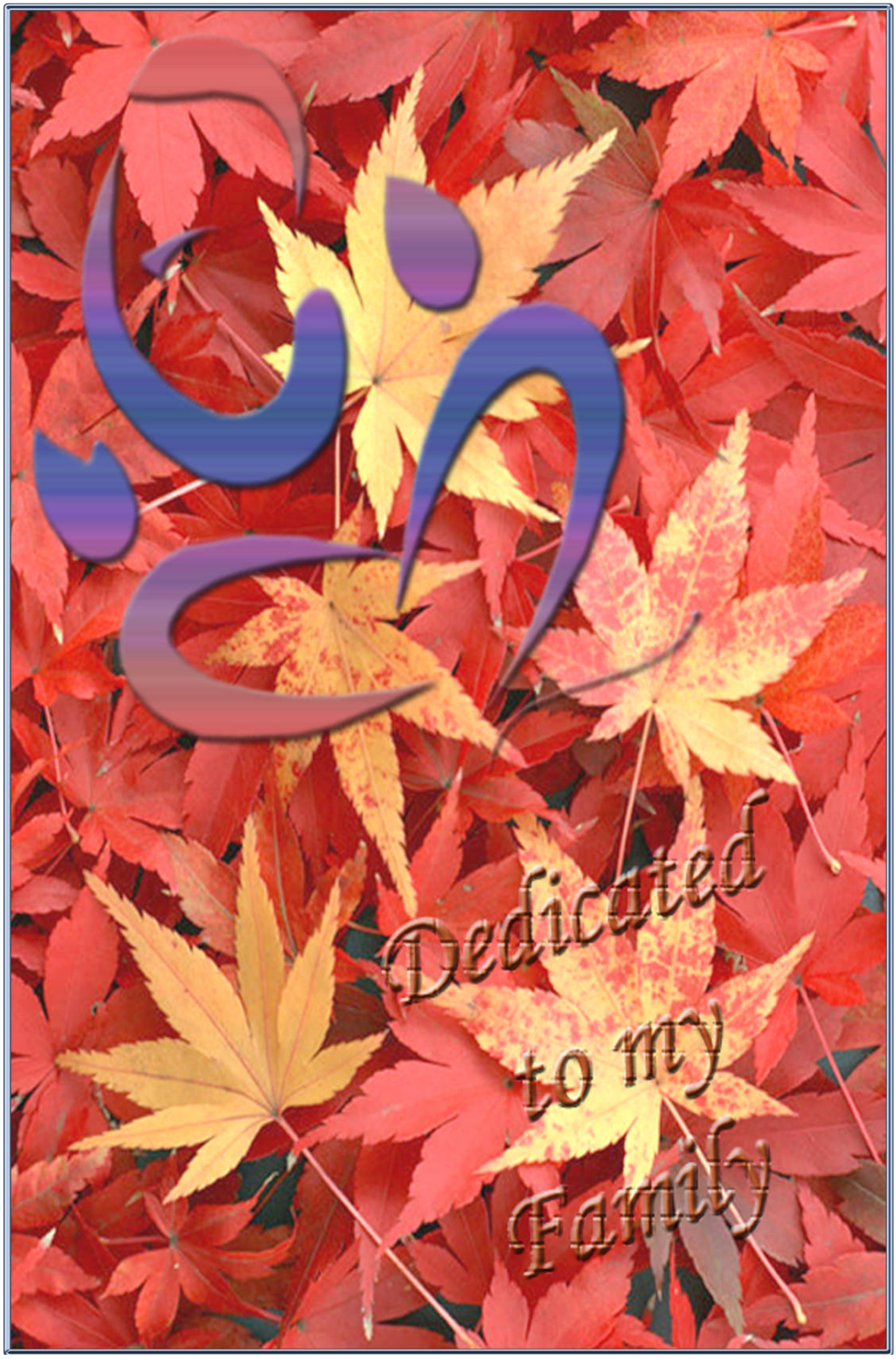
Place: Rajkot. **(Vipul V. Bhuva)**

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

Date: / /2009

Place: Rajkot.

(Dr. D. M. Purohit)
Lecturer,
Shree M. & N. Virani Science College
Department of Chemistry
Kalawad Road.
Rajkot – 360 005.
Gujarat (India).


Dedicated
to my
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 “***Jay Adya shakti Mataji***”.

An endeavour such as a Ph.D. is impossible to accomplish without the generous help and support of my family, friends and colleagues. I would like to take this opportunity to thank those whom I was fortunate to know, work, and form friendship with over the past three years.

First I would like to express my deep appreciation and gratitude to my co-traveler and guide ***Dr. D. M. Purohit*** Lecturer, Chemistry Department shree M.& N. Virani science college Rajkot. His dedication to science, unwavering demand for excellence from himself has set up a high standard for his students to look up to and to follow. I appreciated the freedom he allowed, which permitted me to develop scientific thoughts and experimental skills independently, lofty research methodology and the motivation as well as them highly punctual, affectionate.

I also owe to, from the deepest corner of heart, deepest sense of gratitude and indebtedness to ***Dr.V. N. Patolia*** ,Head Chemistry Department, Kamani science college,Amreli. as I have been constantly benefited with them .

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 their gift to us, so I am at loss of words in which to own my most esteemed father late. ***Shri vallabhbhai*** and My loving mother ***Smt. shardaben*** . I would be remised if I failed to express my special gratitude to my younger Sister **Jayshree** and elder Sister **Asmita and vaishali** whose unstopping flow of love helped me to reach the goal and most venerated grand father late ***Bhanabapa*** grand mother late **Jamanaba**.

Through the stress and strain of this study, my wife ***Deepti*** has encouraged me to reach my destination.

I am deeply indebted to the Dr. Jitendra G. Dobaria for his help, suggestions, encouragement and kindness that made my research work success.

I feel great pleasur to acknowledge my deepest sense of indebtedness to **Mr. Mahendra G. Dobaria** and **Mr. Kalpesh vadodaria** for her invaluable inspiration and moral support throught the course of my research work.

I wish to thank Jayesh V. Guna and Mahendra savalia for his most willing co-operation and comprehensive exchange of ideas during the course of my research work.

I offer my heart full gratitude to Dr. Viral Parekh Dr. Mayur Joshi Dr. Harshad Sangani Dr. Vijay Lunagariya, Dr. Sunil Rokad , Dr.Ranjan, Dr.Hitin, Ramesh Kanparia Paresh Kathiria Bhavin Marvania, Satish, Chirag, vivek, prashant and gatti. my research colleagues for their support and much fruitful discussion at various stages. I am most thankful to all my Juniors for their valuable co-operation and help during the course of my work.

I am thankful to Principal and Management of shree M. & N. Virani science college, Rajkot. for their kind support and providing chemicals research place and glasswares on time his co-operation in magnifying the presentation of my work in the form of thesis.

I Gratefully acknowledge the most willing help and co-operation shown by Department of chemistry. Saurastra university, Rajkot. CSMCRI Bhavnagar,CIL Chandigadh for spectral studies .

Finally, I express my grateful acknowledgment to Chemistry Department shree M. & N. Virani science college. for providing me the excellent laboratory facilities .

Vipul V. Bhuva

STUDIES ON SOME HETEROCYCLIC COMPOUNDS OF THERAPEUTIC INTEREST

CONTENTS

.

. . . .

. .

SYNOPSIS

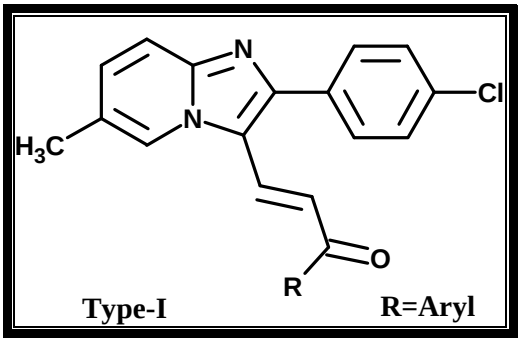
The research work incorporated in the thesis with entitled **"STUDIES ON SOME HETEROCYCLIC COMPOUNDS OF THERAPEUTIC INTEREST"** has been described as under.

These valid observations prompted us to design and synthesize some heterocycles like chalcones, pyrazolines, cynopyridines, pyrimidines, isoxazoles, Barbitones, Mannich bases, Schiff's base etc., bearing imidazo [1,2-a] pyridine ring.

PART – I : STUDIES ON CHALCONES

Chalcones are phenylstyrylketones containing reactive keto- ethylenic group. Literature survey reveals that chalcone derivatives possess antibacterial, antiviral, antispasmodic activities. Hence it was thougth worth while to synthesize chalcone derivatives, which have been described as under.

SECTION-I : Synthesis and biological Screening of 2 - (4'-chlorophenyl) - 6-methyl-3-(1"-aryl-2"-propene-1"-one-3-yl)-imidazo[1,2-a] pyridines



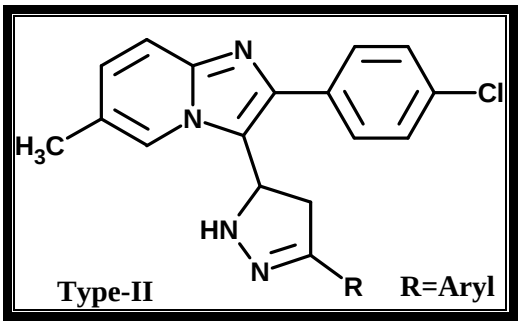
Type-I **R=Aryl**

The Chalcones of Type - (I) have been synthesized by the condensation of 2-(4-chlorophenyl)-6-methylimidazo [1, 2-a] pyridine-3-carboxaldehyde with aromatic ketones in the presence of aqueous NaOH.

PART-II : STUDIES ON PYRAZOLINES

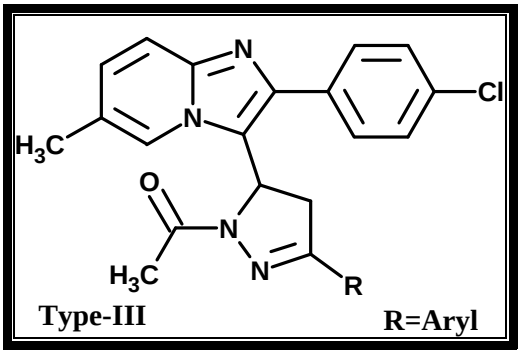
Pyrazoline derivatives are one of the most active therapeutic activity such as antibacterial, analgesic, anthelminetic, anti-inflammatory, anti-tubercular etc. This valid observation led us to sythesize some new pyrazoline derivatives, which have been described as under.

SECTION-I : Synthesis and biological Screening of 2 - (4' - chlorophenyl)-6-Methyl-3-(3"-aryl -4", 5"-dihydro-1"-H-pyrazol-5"-yl) imidazo [1, 2-a] pyridines.



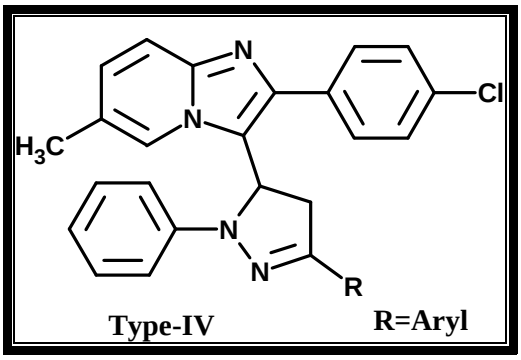
Pyrazoline derivatives of Type- (II) have been synthesized by the condensation of chalcones of Type -(I) with hydrazine hydrate.

SECTION-II : Synthesis and biological Screening of 2-(4'-chlorophenyl)-6-Methyl-3-(3"-aryl -1"acetyl-4", 5"-dihydropyrazol-5"-yl) imidazo [1, 2-a] pyridines.



Acetyl pyrazoline derivatives of Type (III) have been synthesized by the condensation of chalcones of Type- (I) with hydrazine hydrate and glacial acetic acid.

SECTION-III : Synthesis and biological Screening of 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl-1"-phenyl-4", 5"-dihydropyrazol-5"-yl) imidazo [1, 2-a]pyridines.



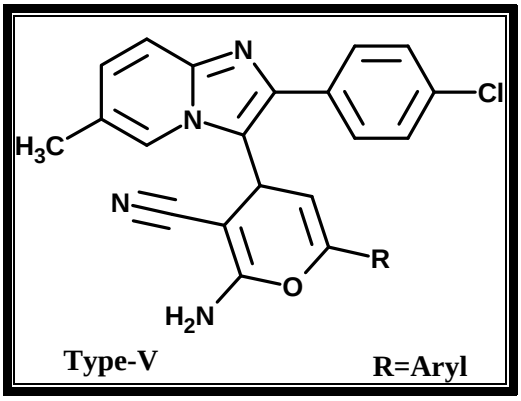
Type-IV **R=Aryl**

Phenyl pyrazoline derivatives of Type (IV) have been synthesized by the condensation of chalcones of Type- (I) with phenyl hydrazine.

PART - III : STUDIES ON CYANOPYRANS

Cyanopyran derivatives represents one of the modest classes of the compounds possessing wide range of therapeutic activities such as antibecterial, antifungal, antiviral and anticonvulsant etc. In view of these facts, it was contemplated to sythesized some new Cyanopyrans, which have been described as under.

SECTION-I : Synthesis and biological Screening of 2" – amino - 4" - [2 - (4'-chlorophenyl) - 6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl- 4"-H-pyran-3"- carbonitriles.



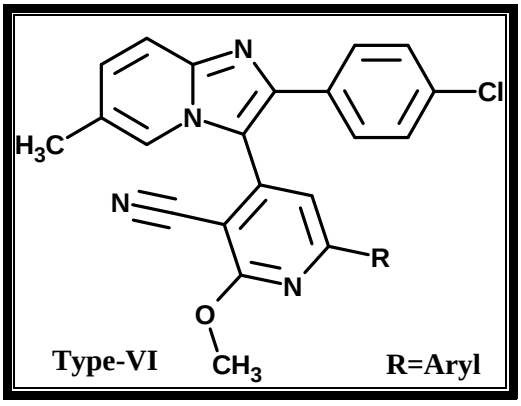
Type-V **R=Aryl**

Cyanopyran derivatives of Type-(V) have been synthesized by the Condensation of chalcones of Type- (I) with malononitrile in pyridine**.**

PART-IV : STUDIES ON CYANOPYRIDINES

Cyanopyridines nucleus possess remarkable pharmaceutical importance and biological activities. Cyanopyridine derivatives have been reported to be active as antifungal, antidiabetic, anticholestemic and antihypertensive etc. On the basis of these results, prompted us to synthesize some new cyanopyridines derivatives, which have been described as under.

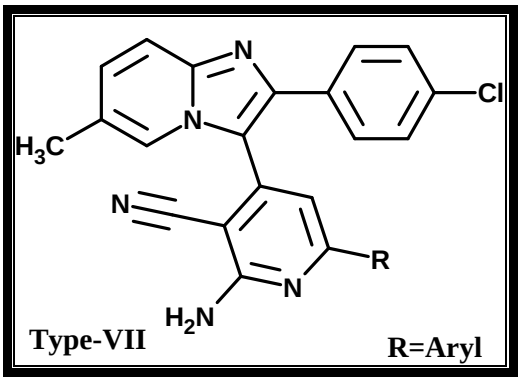
SECTION-I : Synthesis and biological Screening of 2"-methoxy - 4"- [2 - (4'-chlorophenyl)-6- methyl imidazo [1, 2-a] pyridine – 3 - yl]-6"-aryl nicotinonitriles.



Type-VI **R=Aryl**

Cyanopyridine derivatives of Type- (VI) have been synthesized by the Condensation of chalcones of Type- (I) with malononitrile and sodium methoxide.

SECTION-Il : Synthesis and biological Screening of 2"-amino-4"-[2-(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-arylnicotinonitriles.



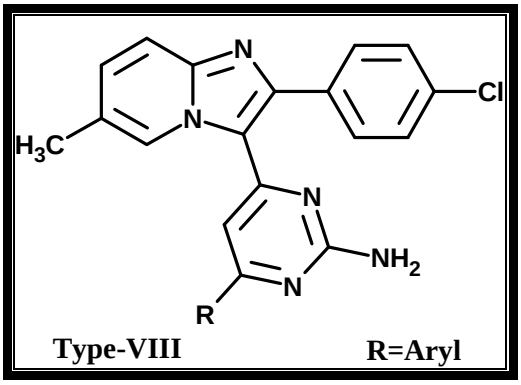
Type-VII **R=Aryl**

Cyanopyridine derivatives of Type -(VIl) have been synthesized by the condensation of chalcones of Type- (I) with malononitrile and ammonium acetate.

PART-V : 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, antibacterial, antimalarial, antifungal etc. These valid observations prompted us to synthesize some new substituted pyrimidines, which have been described as under.

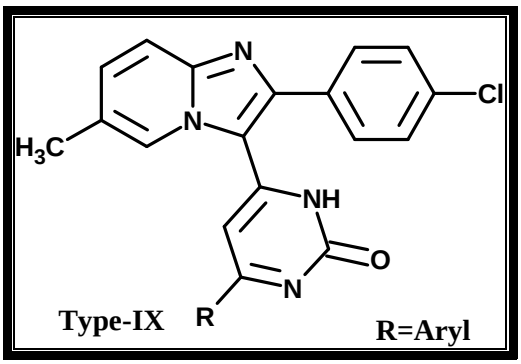
SECTION-I : Synthesis and biological Screening of 4"-[2-(4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-6"-aryl-2"-aminopyrimidines.



Type-VIII **R=Aryl**

Aminopyrimidine derivatives of Type- (VIII) have been synthesized by the condensation of chalcone of Type- (I) with guanidine hydrochloride.

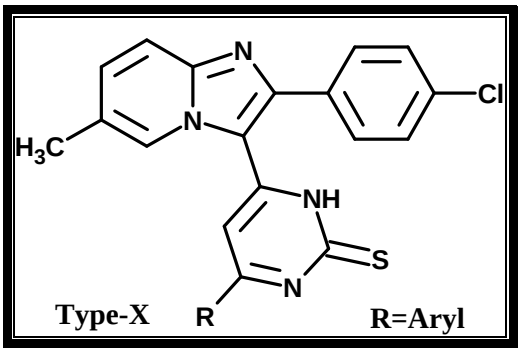
SECTION-II : Synthesis and biological Screening of 6"-[2-(4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-4"-arylpyrimidin-2"(1"H)-ones.



Type-IX **R=Aryl**

Pyrimidinone derivatives of Type-(IX) have been synthesized by the cyclization of chalcones of Type- (I) with urea in presence of basic catalyst KOH.

SECTION-III: Synthesis and biological Screening of 6"-[2-(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridine – 3 – yl -4"-aryl pyrimidine-2"-(1"H)-thiones.



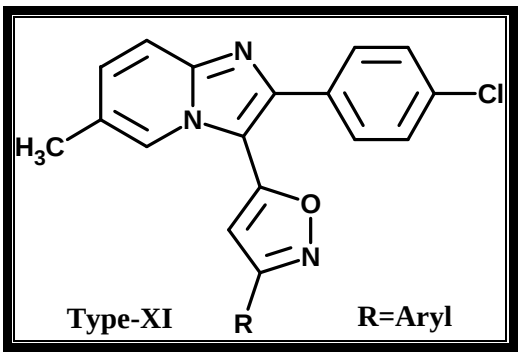
Type-X **R=Aryl**

Thio Pyrimidine derivatives of Type-(X) have been synthesized by the cyclocondensation of chalcones of Type - (I) with thiourea in presence of basic catalyst KOH.

PART-VI : STUDIES ON ISOXAZOLES

Isoxazole derivatives represent one of the modest class of compound possessing broad range of biological activities such as antidepresants, skeleton muscle relaxant, antidiabetic, anti-inflammatory, analgesic, antimicrobial etc. These valid observations prompted us to synthesize some new isoxazole derivatives described as under.

SECTION-I : Synthesis and biological Screening of 2-(4'-chlorophenyl)-6-methyl- 3-(3"-aryl isoxazol-5"-yl) imidazo [1, 2-a] pyridines.



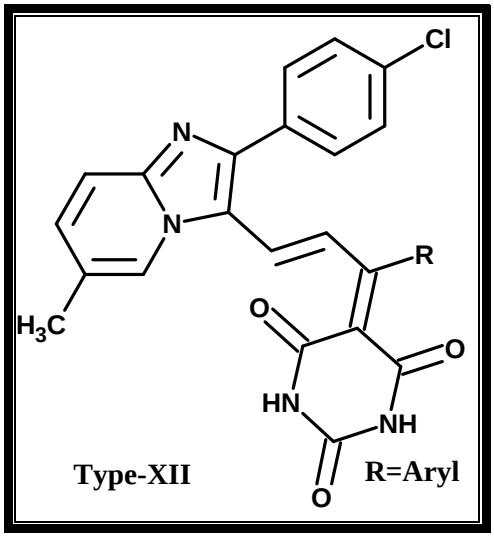
Type-XI **R=Aryl**

Isoxazole derivatives of Type-(XI) have been synthesized by the cyclocondesation of chalcones of Type- (I) with hydroxylamine hydrochloride.

PART-VII : STUDIES ON BARBITONES

Barbitone derivatives have been found to biological activities viz. anticonvulsant, hypnotic, sedatives, anti-inflammatory etc. Promoted by above facts, some new barbitones have been synthesized as under.

SECTION-I : Synthesis and biological Screening of 2-[(4'-chlorophenyl)-6-methylimidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)-pyrimidine-2"',4"',6"'-(3"'H, 5"'H)-triones.



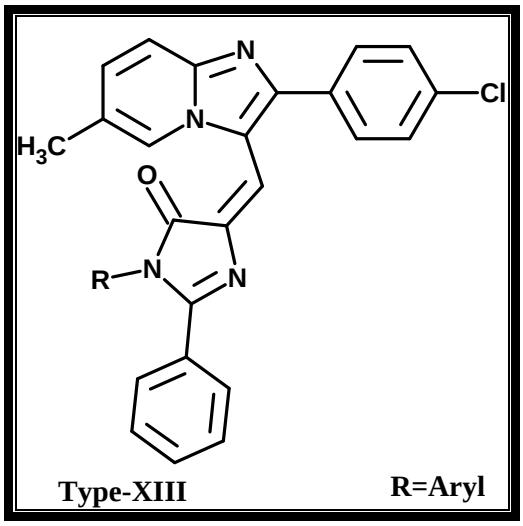
Type-XII **R=Aryl**

The barbitone derivatives of Type- (XII) have been synthesised by the condensation of chalcone of Type- (I) with barbituric acid in glacial acetic acid**.**

PART – VIII : STUDIES ON 5-OXO-IMIDAZOLINES

5–Oxo-imidazoline derivatives have been reported to be active as anticonvulsant, potent CNS depressant, anti-inflammatory, anticancer, hypnotics and as mono aminooxidase (MAO) inhibitor.These valid observations prompted us to synthesize some new 5-oxo-imidazoline derivatives. which have been described as under.

SECTION-I: Synthesis and biological Screening of 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene-1"-aryl-2"-phenyl-5"-oxo- imidazolines.



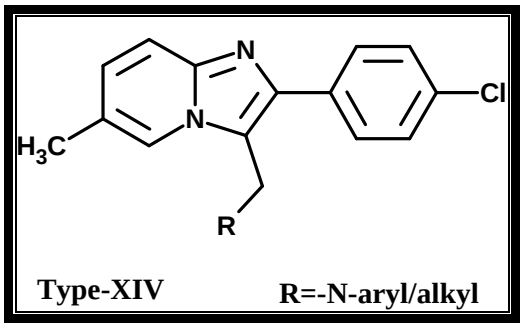
Type-XIII **R=Aryl**

5-Oxo-imidazoline of Type- (XIII) have been synthesized by the condensation of 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone with aromatic amine.

PART – IX : STUDIES ON MANNICH BASES

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

SECTION-I : Synthesis and biological Screening of 2-(4'-chlorophenyl)-6-methyl-(3-N, N'-diaryl/dialkyl amino methyl)-imidazo [1, 2-a] pyridines.



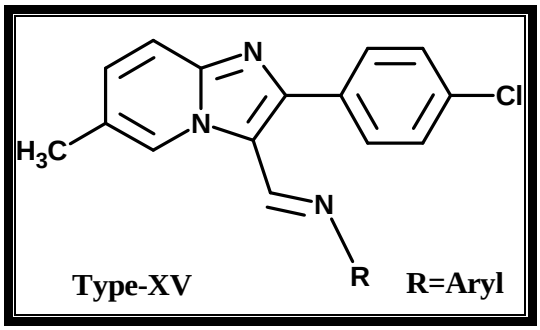
Type-XIV **R=-N-aryl/alkyl**

Mannich bases of Type- (XIV) have been synthesized by the condensation of 2-(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridine with different secondary amines and formaldehyde in the presence of acidic catalyst like HCl.

PART – X : STUDIES ON SCHIFF'S BASES

Arylaminomethyl derivatives represent one of the modest class of biological active agent which have been deeply studies during search on new potential agent. These have been reported to be active as antimicrobial, antitubercular, anticancer and insecticidal etc. In view of these valid observation, it was contemplated to synthesize some new schiff's base derivatives possessing wide biological activities which have been described as under.

SECTION-I : Synthesis and biological Screening of 2-[(4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]- methylene arylamines



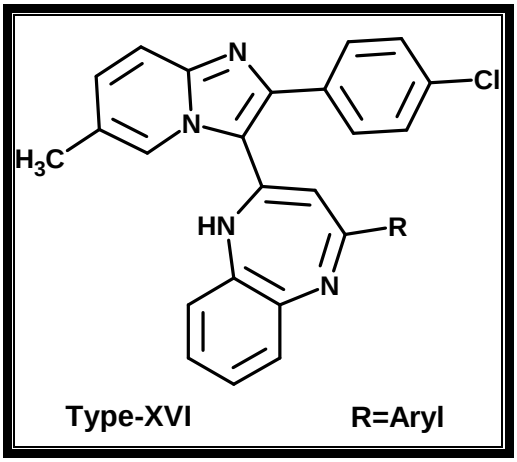
Type-XV **R=Aryl**

Schiff's base of Type - (XV) have been synthesized by the condensation of 2 -(4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridine-3-carboxaldehyde with aromatic amine.

ART – XI : STUDIES ON BENZODIAZEPINES.

Benzodiazepines derivatives have been found to possess wide range of therapeutic activities, like anthelmintic ,anticonvulsant, antimicrobial etc. Prompted by these facts new Benzodiazepines have been synthesize which are described as under**.**

SECTION-I : Synthesis and biological Screening of-4"-aryl-2"-yl-[2-(4'-chlorophenyl-6-methyl imidazo [1, 2-a] pyridin]-1"H,-1",5" benzodiazepines



Bnzodiazepines derivatives of Type- (XVI) have been synthesized by the reaction of chalcones of Type -(I) with o-phenylene diamine in presence of acidic medium.

Characterization:

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

Studies on biological activities.

All the compounds have been also evaluated for their antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity toward at a concentration of 50 µg/ml. The biological activity of the sythesized compounds have been compared with known standard drugs.

STUDIES ON SOME HETEROCYCLIC COMPOUNDS OF THERAPEUTIC INTEREST

INTRODUCTION

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

The focus of drug design has switched from structure oriented to target oriented research, e.g. development of the antiulcer agent cimetidine. histamine was the lead compound for the project and various strategies were used to find an analog that would prevent it fitting its receptor. once an antagonist was developed, a theory was proposed on how it might interact with the histamine receptor at a molecular level. further analogs were then synthesized to test theory and the theory was continuously modified as required.

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

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

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

instance, exist largely in the form of five membered. Vitamin B_6 (Pyridoxine) is a derivative of pyrimidine essential in amino acid metabolism.

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

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

The ultimate product of a successful drug design effort. Our goal for this is to begin to deconvolute this information in order to apply it to design of new drugs. Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing imidazo[1,2-a]pyridine nucleus. The placement of a wide variety of substituents of these nuclei has been designed in order to evaluate the synthesized products for their pharmacological profile against several strains of bacteria and fungi.

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

Taking in view of the applicability of heterocyclic compounds, we have undertaken the preparation of heterocycles bearing imidazo[1,2-a]pyridine nucleus The placement of a wide variety of substituents of these nuclei have been designed in order to evaluate the synthesized products for their pharmacological profile against several strains

Of becteria and fungi.

AIMS AND OBJECTIVES

In the pharmaceutical field, there is a need for new and novel chemical inhibitors of biological functions. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interesting heter ocyclic compounds of widely different composition. During the course of research work looking to the applications of heterocyclic compounds, several entities have been designed, generated and

characterized using spectral studies. The aims and objectives of the work carried out are as under.

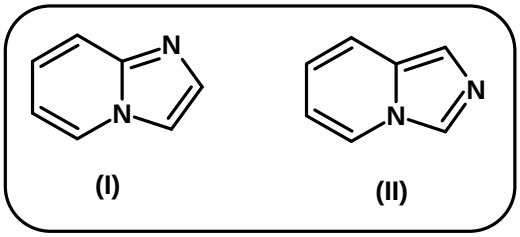
1. To synthesize pharmacologically active entities like chalcones, cyanopyridines, pyrazolines, schiffbases, cynopyrans, isoxazoles, Mannichbases, Barbitones,Pyrimidines,Benzodiazipines, cyanopyrimidines, 5-Oxo-imidazolines etc.
2. To characterise these products for structural elucidation using spectroscopic techniques like IR,[1] HNMR and Mass spectral studies .
3. To check the purity of all compounds using thin layer chromatography.
4. To evaluate these new products for better drug potential against different strains of bacteria and fungi.

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

SUBJECT
INTRODUCTION OF
IMIDAZO[1,2-a]PYRIDINE

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).



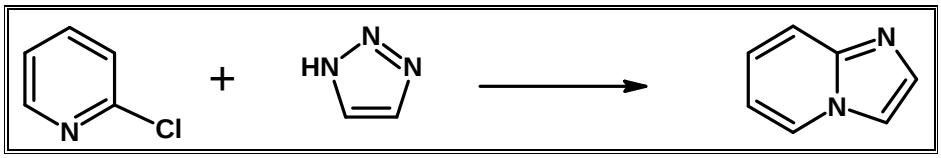
The aza-indolizine contains a pyridine ring fused to a imidazole ring is indicated in the structure, hence it is also known as imidazo[1,2-a]pyridine[2]. Many drugs contain imidazo[1,2-a] nucleus. Several procedure for their synthesis have been extensively studied. Such studies have been stimulated by various promising applications, especially in the case of bridge head 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].

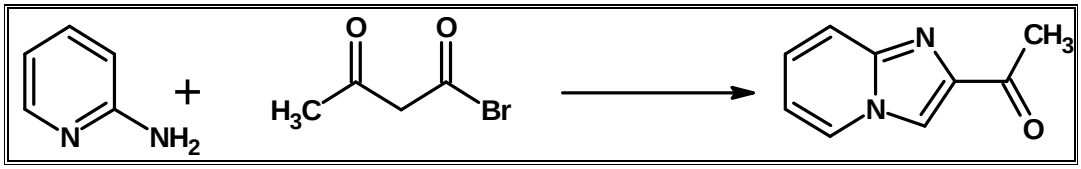
SYNTHETIC ASPECT:

Classical 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.

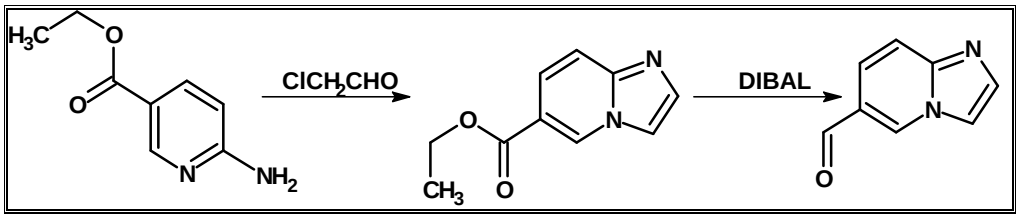
1. The synthesis of imidazo[1,2-a]pyridine from 2-aminopyridine with α-bromoacetophenone was reported by Tschitschibabine[5].
2. Reaction of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogens give the imidazo[1,2-a]pyridine[6].



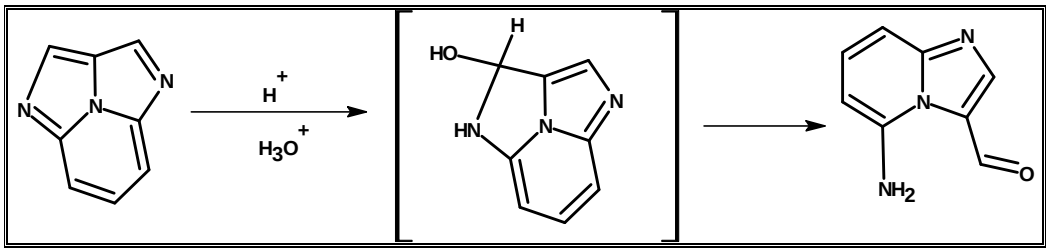
3 2-Acetylimidazo[1,2-a]pyridine[7] can be constructed by the cyclocodensation of 2-aminopyridine with bromo butanedione.



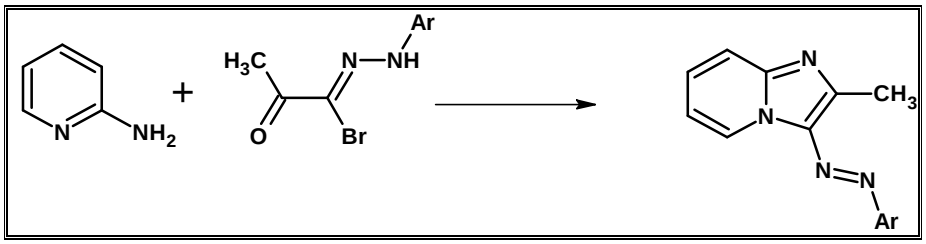
4. Condensation of ethyl-6-aminonicotinate with chloroacetaldehyde according To Hand's procedure gave imidazo[1,2-a]pyridine-6-carbaldehyde[8].



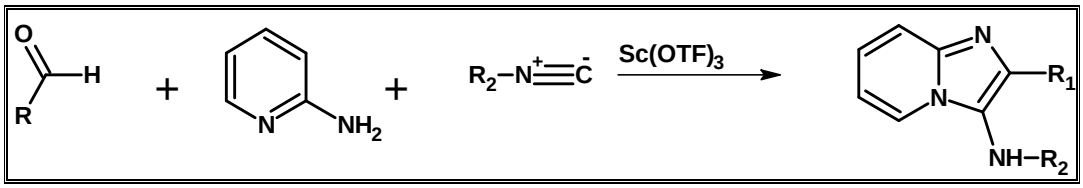
5. Paudler et al.[9] have synthesized 5-amino-3-formylimidazo[1,2-a]pyridine from acid catalyzed hydrolysis of 1,4-diazacycl[3,2,2]azine.



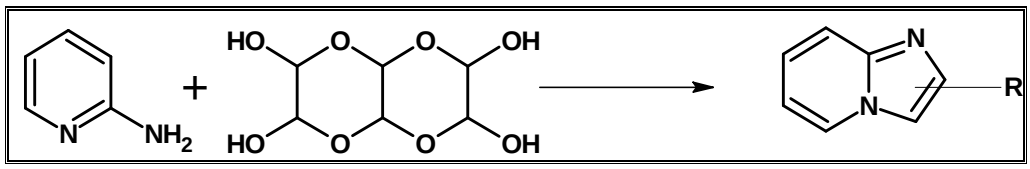
6 Imidazo[1,2-a]pyridine[10] nucleus can be also synthesized by the reaction of ά-ketohydrazidoyl halide with heterocyclic amines.



7. Tsai et al.[11] have been prepared 3-amino imidazo[1,2-a]pyridine derivatives by a three component condensation reaction between 2-aminopyridine, aldehyde and isonitrile in the presence of scandiumtriflate as a catalyst.

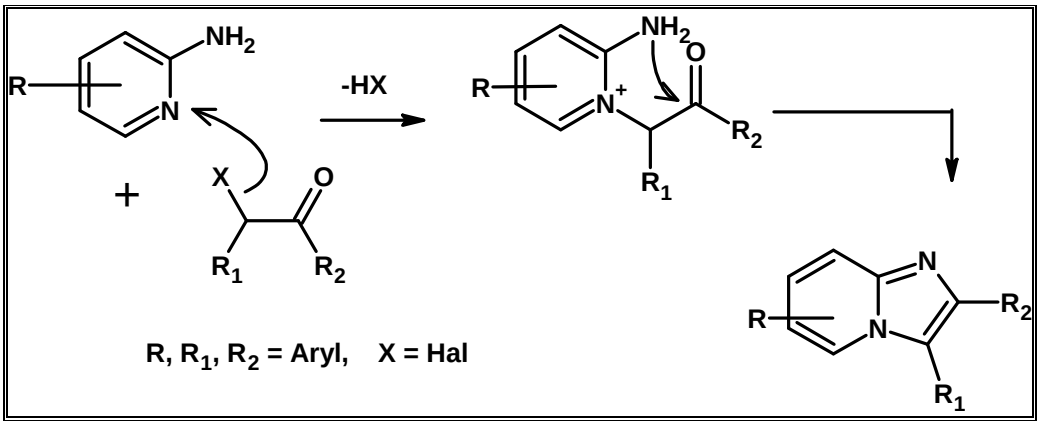


8. Groziak et al.[12] have synthesized substituted imidazo[1,2-a]pyridine derivatives by the condensation of 2-aminopyridine with glyoxal trimer dehydrate in aqueous $NaHSO_3$.



MECHANISM

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



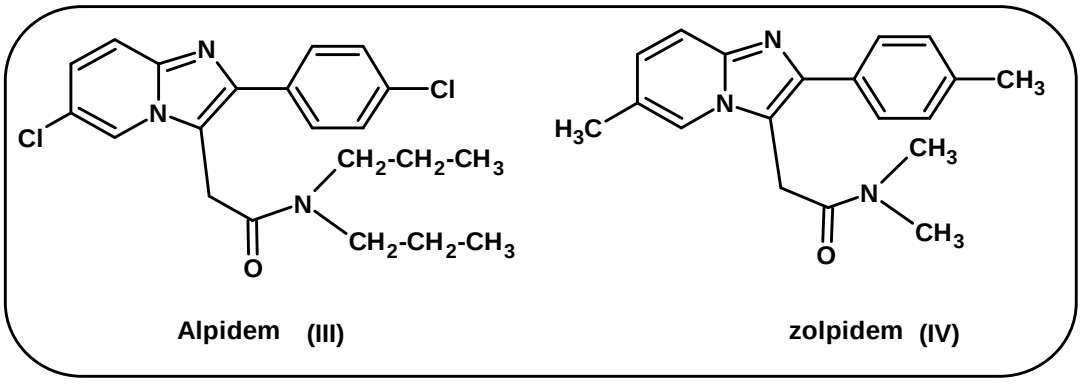
THERAPEUTIC IMPORTANCE

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 such as,

1. Anti-inflammatory, analgesic, antipyretic[13,14]
2. Antiviral[15,16]
3. Antianxiety[17]
4. Antiulcer[18,19]
5. Antifungal agents[20]
6. Anthelmintic[21]
7. Antibacterials[22,23]

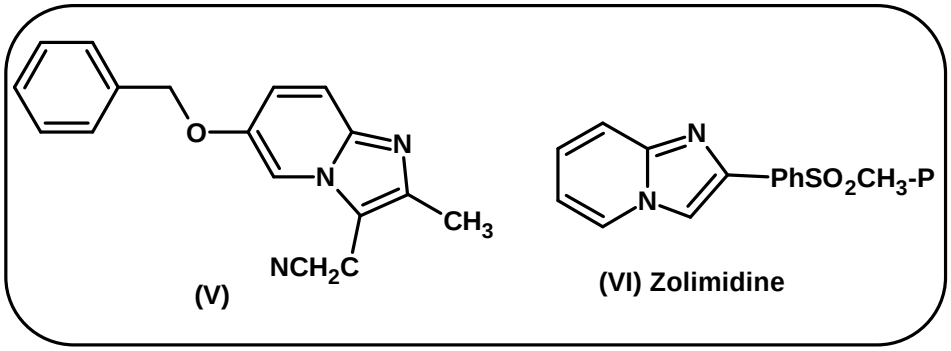
8. Hypnotic[24]
9. Antiherpetie[25,26]
10. Gastric antisecretory[27,28]
11. Hypnoselective and anxioselective[29]
12. b-Amyloid formation inhibitors[30]
13. Benzodiazepine receptor agonists[31]
14. Nonsedative anxiolytic[32]
15. Active nonpeptide bradykinin B2 receptor antagonists[33]
16. Cardiotonic agents[34]
17. Anticytomegalo-zoster and antivaricellazoster virus[35-37]
18. Long-acting local anesthetic[38]
19. Calcium channel blockers[39]

Some imidazo[1,2-a]pyridines already in market include **alpidem[40] (III)**[a ligand of both the central benzodiazepine receptors and the peripheral type benzodiazepine receptor] has sedative and anxiolytic properties and **zolpidem[40](IV)** [a selective ligand for the central benzodiazepine receptor] is a hypnotic drug. Bothalpidem and zolpidem have higher affinity for enzodiazpine-1 than for benzodiazepine-2 receptors[41] and their interaction with various receptor types has beenreported[42]

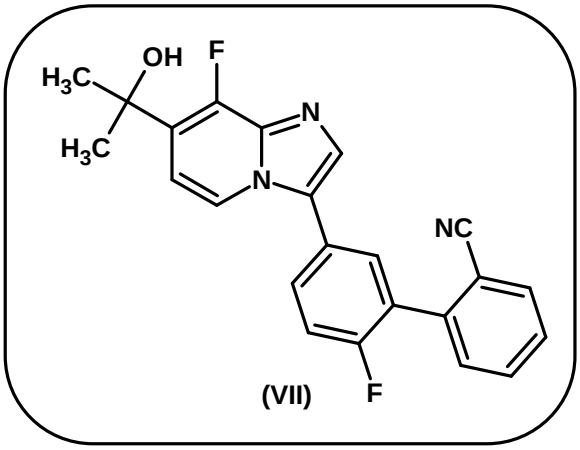


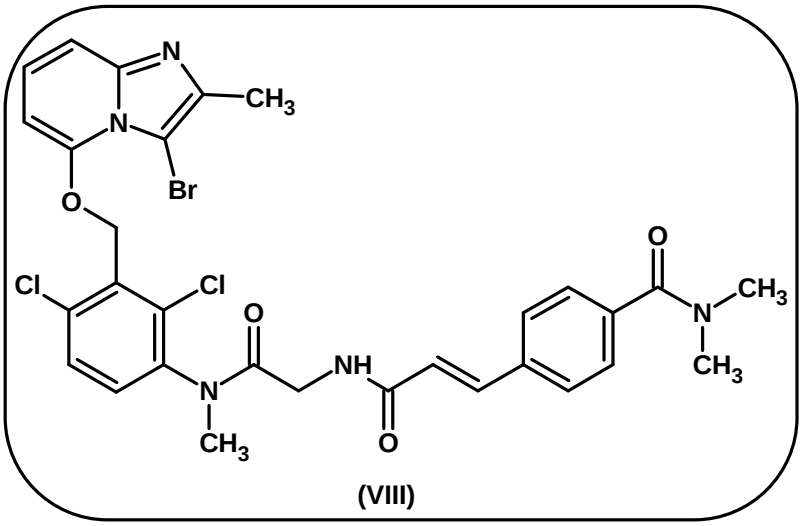
Alpidem (III) **zolpidem (IV)**

J. J. Kaminski and co-workers[43] have investigated the imidazo[1,2-a]pyridine derivative 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (V) as an antiulcer agent. On the basis of the reported metabolism of **zolimidine(VI)**, they reported that the 3-cyanomethyl and 8-phenylmethoxy group have been established as metabolic sites in.



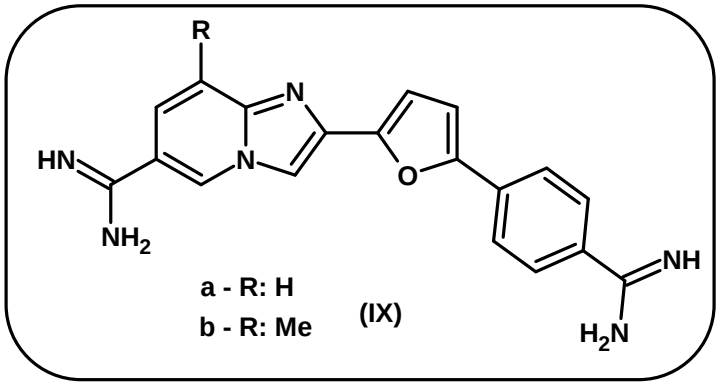
Pharmaceutical research requires an increasing number of novel compounds to cover previously unexplored areas in the chemical space. there is also a need to increase the quality of the newly prepared molecules regarding their drug likeness and other predefined physicochemical parameters. C. Alexander.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

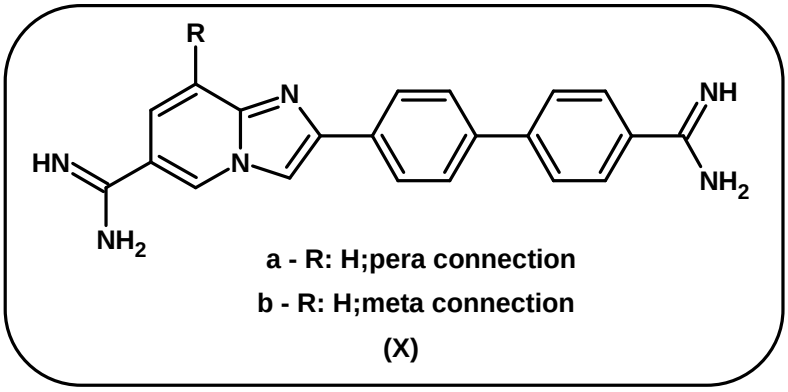




Evaluated as a bioisosteric replacement for imidazo[1,2-a]pyridine in an allosteric modulator ligand of the GABAA receptor. Kristian S. Gudmundsson[44] have reported the synthesis and antiviral activities of newer Erythrofuranosyl imidazo[1,2-a]pyridine C-nucleosides. I. Aramori et al.[45] have been synthesized highly potent and selective non-peptide bradykinin receptor antagonist (VIII).A Novel Class of Orally Active Non-Peptide Bradykinin B2 Receptor Antagonist and Discovering Bioisosteres of the Imidazo[1,2-a]pyridine Moiety reported by Yoshito Abe.[46]Synthesis of Acyclo-C-nucleosides in the Imidazo[1,2-a]pyridine and Pyrimidine Series as Antiviral Agents.[47] Dubinsky B and A.H.Vaidya.[48] has defined like imidazo [1,2-a] pyridine deri. is a new nonbenzodiazepine anxiolytic.

The imidazo[1,2-a]pyridine bearing a very good synthon variety of building blocks in both natural and synthetic bioactive compounds.[49-51] Mohamed A. Ismail [53] have recently synthesized some novel diamidine imidazo[1,2-a]pyridine like (IX) and (X) 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 and plasmodium falciparum. More ever synthesise Aromatic diamidines exhibit broad spectrum antimicrobial activity including effectiveness against the protozoa disease caused by trypanosoma SP and plasmodium SP. Novel substituted imidazo [1,2-a] pyridine compounds are disclosed which have a high degree of anthelmintic activity. Processes for the preparation of such compounds are also disclosed as well as active ingredients for the treatment of helminthiasis and anti ulsurative.



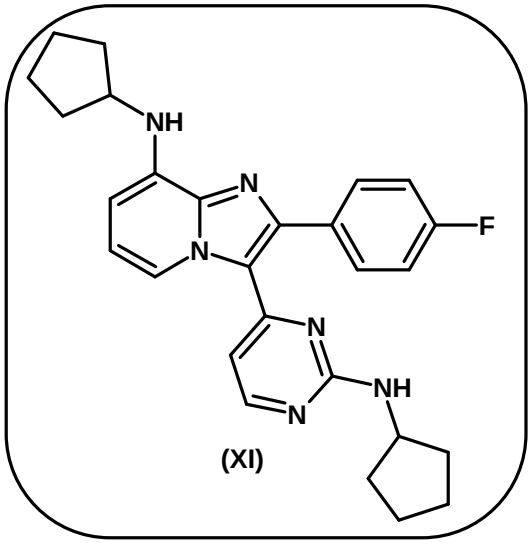


a - R: H;pera connection

b - R: H;meta connection

(X)

Kristjan S., Gudmundsson, Brian Johns A.[53]and Chaouni Bendallay A. et al.[54] have worked on synthesis of a novel imidazo[1,2-a] pyridine shown in (XI) with potent activity against herpes simplex viruses.



(XI)

Thus the important role displayed by imidazo[1,2-a]pyridine and its derivatives for various therapeutic and biological activities prompted us to synthesise some Chalcones, Phenyl pyrazolines, Cyano pyridines, Thiozolidinones, Cyclohexenone, Schiff's base, Aryl amino methyl derivatives bearing imidazo[1,2-a]pyridine moiety in order to active compounds having better biological activities as described in the following parts.

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

PART – I : STUDIES ON CHALCONES

PART- II : STUDIES ON PYRAZOLINES

PART - III : STUDIES ON CYANOPYRANS

PART- IV : STUDIES ON CYANOPYRIDINES

PART- V : STUDIES ON PYRIMIDINES

PART- VI : STUDIES ON ISOXAZOLES

PART- VII : STUDIES ON BARBITONES

PART – VIII : STUDIES ON 5-OXO-IMIDAZOLINES

PART – IX : STUDIES ON MANNICH BASES

PART – X : STUDIES ON SCHIFF BASES

PART – XI : STUDIES ON BENZODIAZEPINES

PART-I

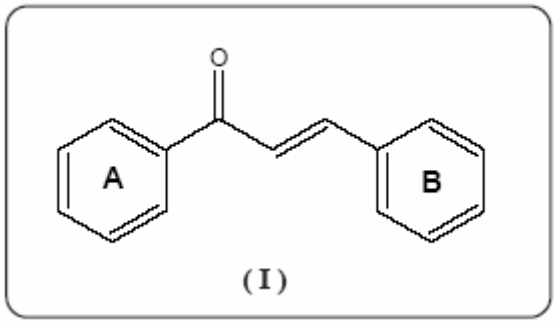
STUDIES ON CHALCONES

STUDIES ON CHALCONES

INTRODUCTION

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. Kostanecki and Tambor[55] gave the name Chalcone.

Chalcones 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.

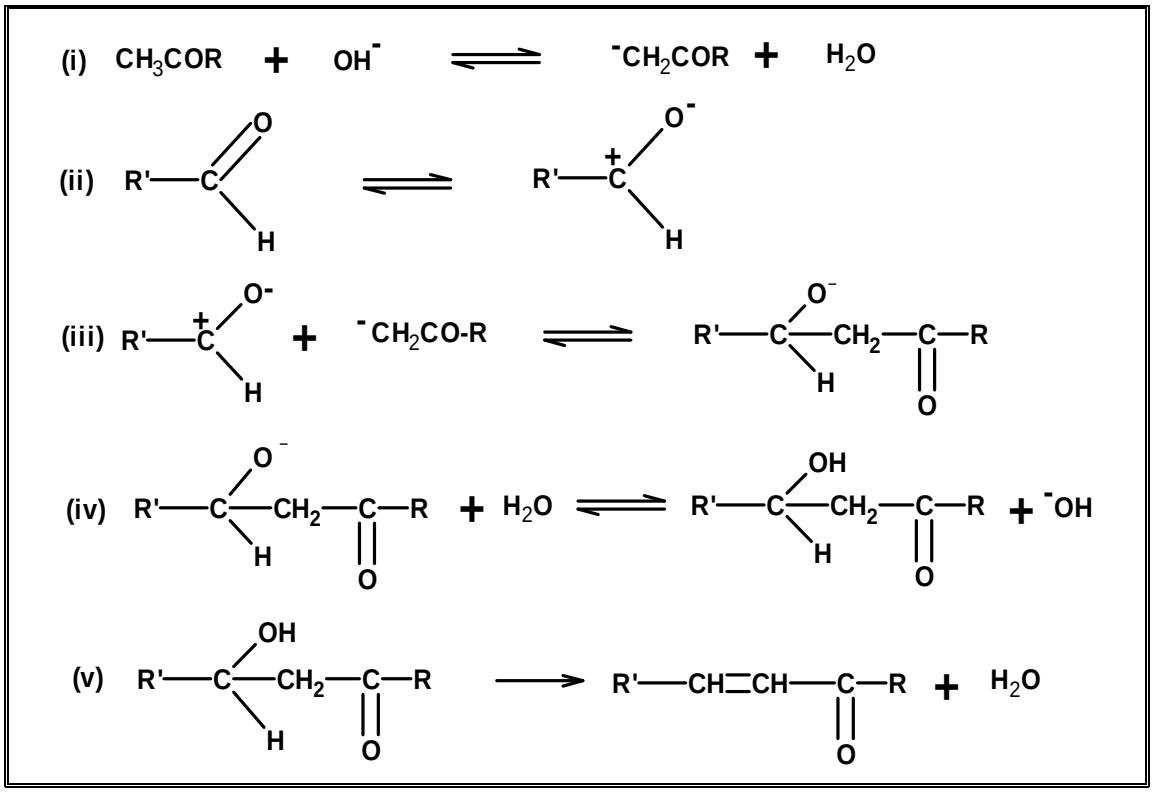
SYNTHETIC ASPECT :

A variety of 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.[56, 57] Various condensing agent used for the synthesis of chalcones are alkali of different strength.[58-59] Hydrogen chloride[60-61] Phosphorous oxychloride[62], Piperidine[63], Anhydrous AluminiumChloride[64], Borontrifluoride[65], Borax[66], Aminoacids[67], Perchloricacid[68] etc.

MECHANISM

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

Carbanion formation observes in presence of alkali media and the intermediate aldol type products formed readily undergoes dehydration even under mild condition and form unsaturated α,β -keto derivatives.



REACTIVITY OF CHALCONES

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

1. Chalcones are intermediate compounds for the synthesis of some naturally occuring heterocyclic compounds like flavones, flavanones, flavanoid, dihydro flavanols, benzal coumarinones, anthocyanins etc.
2. Chalcone contain a keto-ethylenic group and therefore reactive towards number of reagents yielding various heterocyclic compounds exhibiting significant biological activities viz. pyrazolines[69], cyanopyridines[70], cyanopyrans[71], cyanopyridones[72], pyrimidines[73-75], isoxazoles[76], indazole[77] etc.
3. They have been useful in providing structure of some natural products like cyanomulcurin[78], eviodictoyl[79], hemlocktanin[80], narighenin[81], plioretin[82] etc.
4. Chalcones are also useful for the detection of Fe (II) [83] and Ca (II) [84] ions in presence of Barium and Stronsium as it reacts with number of metal ions.

Trihydroxy chalcones was used as an analytical reagent for amperometric estimation of Copper[85] and for spectrophotomatric study of the Germanium [86].

5. Chalcones and their derivatives are also found to be applicable as light Chalcone

and their derivatives are also found to be applicable as light stabilizing agent[87], sweetening agent[88], organic brightening agent, photo sensitive material, polymerisation catalyst, scintillators as well as fluorescent whitening agent.

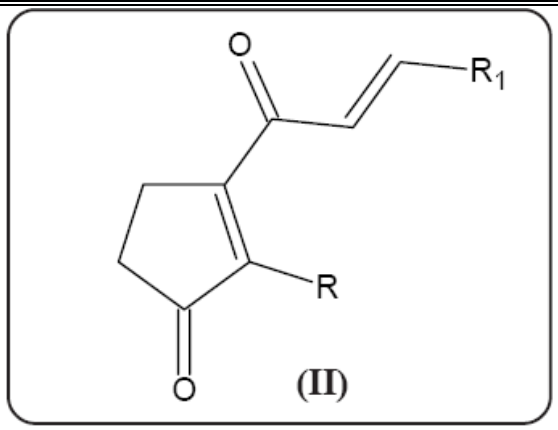
6. The chalcones are natural biocides[89, 90] and are well-known key intermidiate in the synthesis of heterocyclic compounds possessing biodynamic behaviour [91-92].

THERAPEUTIC INTEREST :

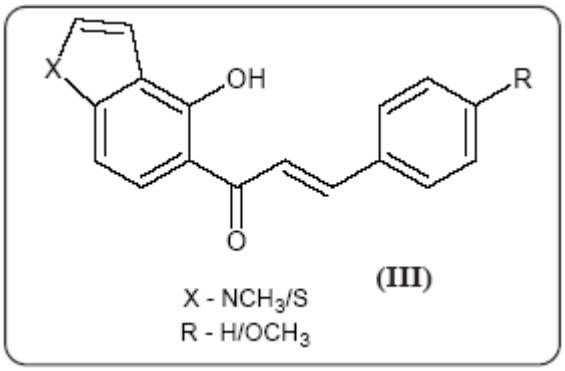
Chalcones derivatives have been found to possess wide range of therapeutic activities as shown below

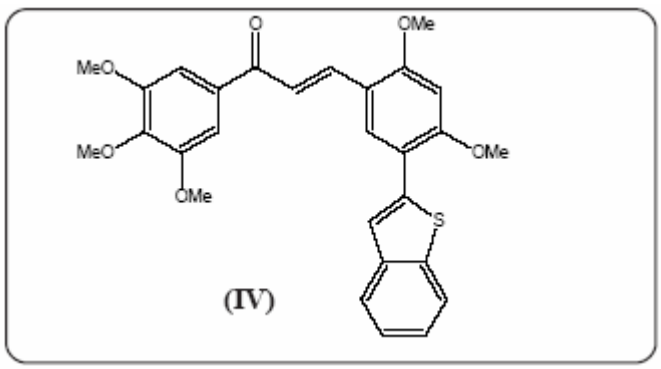
1. Antiallergic[93]
2. Antiinflammatory[94, 95]
3. Antitumor[96, 97]
4. Antispasmodic[98]
5. Antiulcer[99, 100]
6. Anthelmintics[101, 102]
7. Anticancer[103, 104]
8. Antiviral and Antitubercular[105]
9. Anti HIV[106]
10. Bactericidal[107, 108]
11. Cardiovascular[109]
12. Fungicidal[110-112]
13. Herbicidal[113]
14. Insecticidal[114-116]

Chalcones are potential biocides, because some naturally occurring antibiotics[117] and aminochalcones[118, 119] probably own their biological activity in the presence of the α, β-unsaturated carbonyl group. G. L. Nelson[120] has synthesized the analogues of prostaglandin (II).



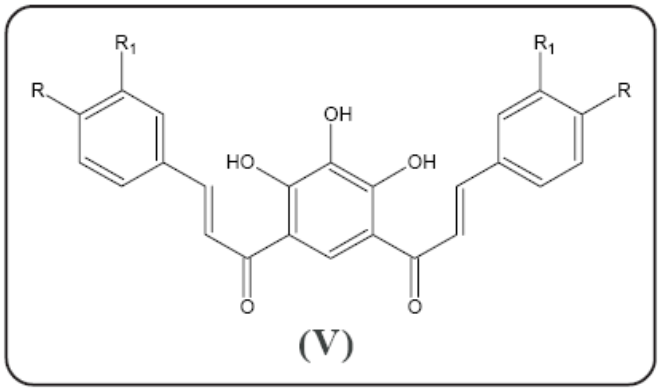
Prem P. Yadav and co-workers[121] have synthesized nitrogen and sulfur containing furanoflavonoids and thiophenylflavonoids (III), Which have been screened fo antifungal and antibacterial activity. C. Q. Meng et al.[122] discovered some novel heteroaryl substituted chalcones (IV) as inhibitors of TNF-alpha-induced VCAM-1 expression.





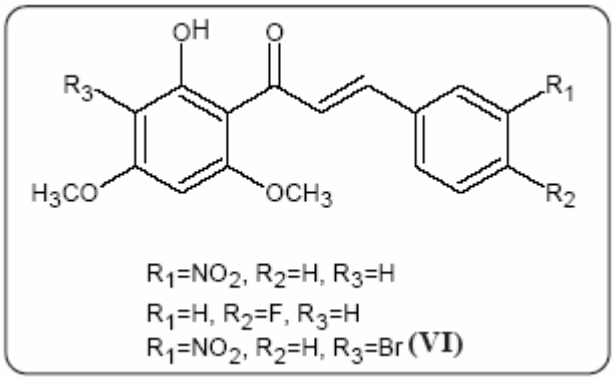
Some dihydrochalcones are well known for their sweetening property[123, 124] and appear to be non-nutritive sweeteners. A dihydrochalcone **Uvaretin** from *Uvaria acuminata* has shown antitumor activity[125] in lymphocytic leukemia test.

V.K. Ahluwalia et al.[126] have noted that 5-cinnamoylchalcones (V) have shown good as antibacterial activity.



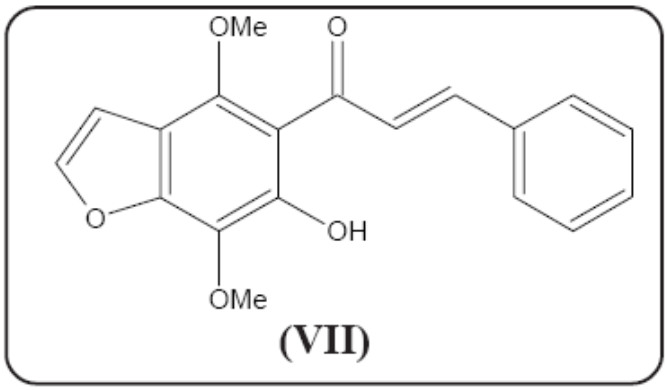
(V)

Paula Boeck et al.[127] 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.

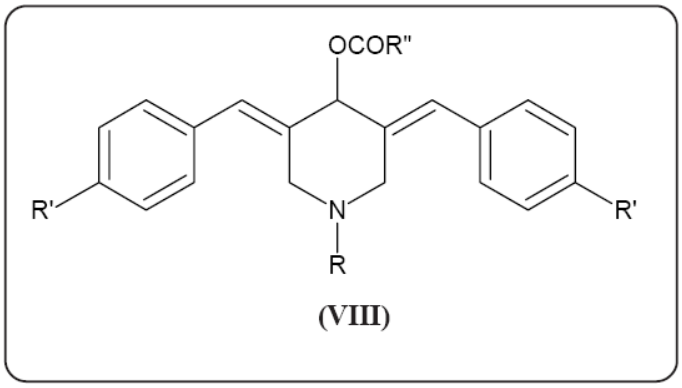


(VI)

Furthermore, M. J. Alcaraz et al.[128] have described the role of nuclear factor-kappaB and heme oxygenase-1 in the mechanism of action of an antiinflammatory activity of chalcone derivative. O. Nerya et al.[129] have prepared chalcones as potent tyrosinase inhibitors. O. Sabzevari et al.[130] have constructed some new chalcone derivatives (VII) as molecular cytotoxic mechanisms for anticancer activity. Aneta Modzelewska et al.[131] have prepared novel chalcone and bis chalcone derivatives (VIII) having anticancer activity.



(VII)



(VIII)

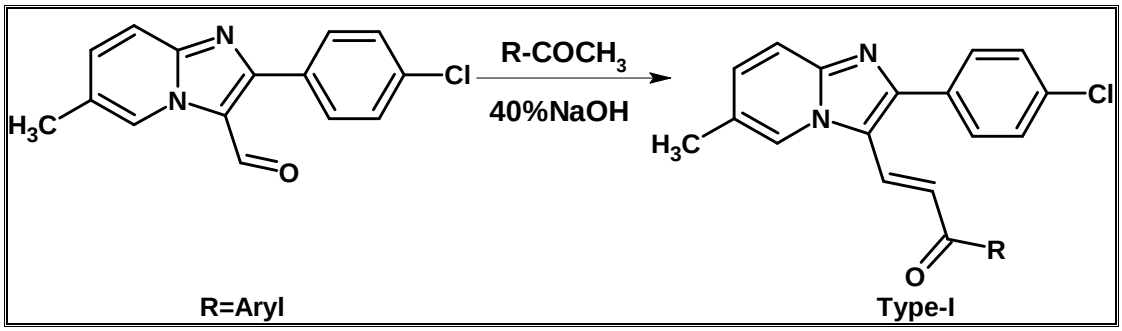
Chalcones have been proved to be an important intermediate for the synthesis of many heterocyclic compounds in organic chemistry. These facts prompted us to synthesize some new chalcone derivatives bearing imidazo[1,2-a]pyridine as a nucleus. In view of getting to synthesised chalcone derivative, Which also wide use in pharmaceutical field the chalcone derivatives are represented as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)- 6-METHYL- 3-[1"-ARYL- 2"-PROPENE-1"ONE-3-YL]-IMIDAZO[1,2-a]PYRIDINES.

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-[1"-ARYL- 2"-PROPENE-1"-ONE-3-YL]-IMIDAZO[1,2-a] PYRIDINES.

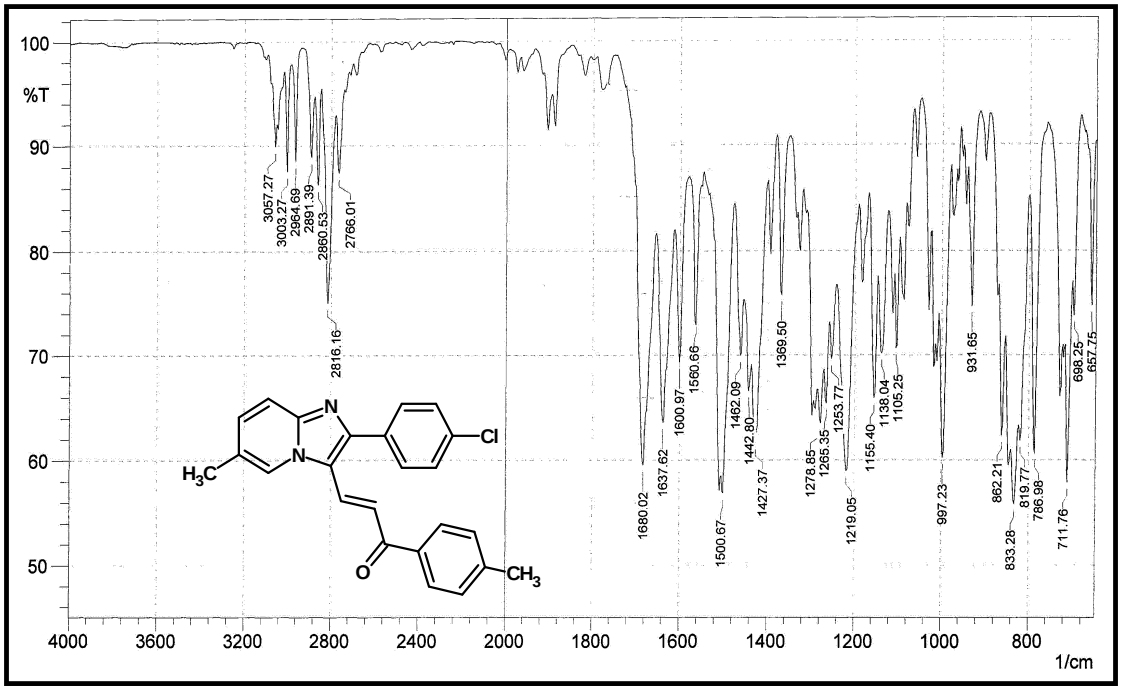
Recently much interest has been focused on the synthesis and biodynamic activities of chalcones and it is a good synthon for various heterocyclic rings, the interest has been focused on the synthesis of new chalcones. With a view to obtained compounds having better therapeutic activity, we have synthesized 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl-2"propene-1"-one-3-yl]-imidazo[1,2-a]pyridine by the condensation of 2-(4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridine-3-carboxaldehyde with various aromatic ketones in the presence of aqueous NaOH.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I,page no.41.

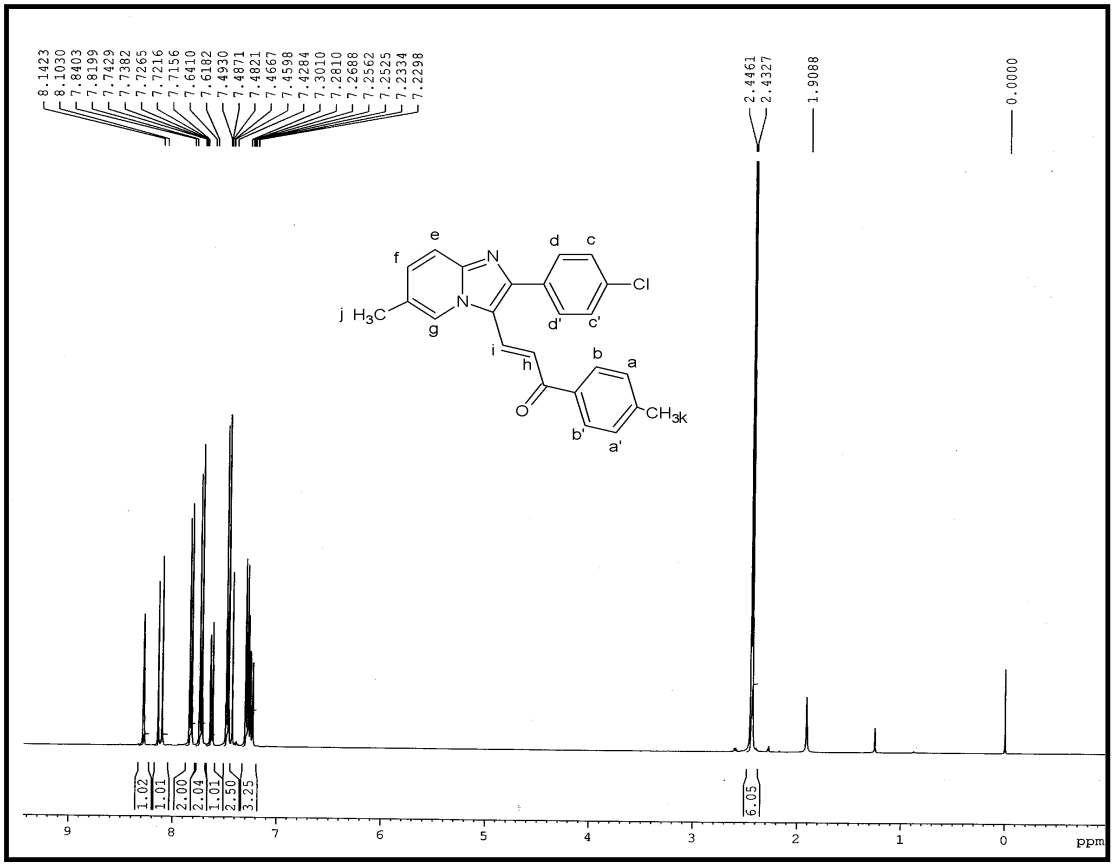
IR SPECTRAL STUDY OF 2 - (4' – CHLOROPHENYL)-6-METHYL- 3-[1"-(4'''-METHYLPHENYL)- 2" – PROPENE - 1" –ONE- 3-YL]-IMIDAZO [1,2-a] PYRIDINE



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2964	2990-2850	648
	C-H str. (sym.)	2860	2880-2860	"
	C-H def. (asym.)	1442	1470-1435	"
	C-H def. (sym.)	1369	1390-1370	"
Aromatic	C-H str.	3057	3090-3030	"
	C=C str	1500	1450-1600	"
	C-H i.p. (def.)	1138	1300-1100	649
Ketone	C=O str.	1680	1700-1640	"
Imidazo[1,2-a] pyridine	C-N str.	1105	1220-1020	"
	C=N str.	1600	1630-1593	"
Vinyl	CH=CH	3003	3050-3000	"
Ether	C-O-C	1219	1260-1200	"
Halide	C-Cl str.	711	800-600	"

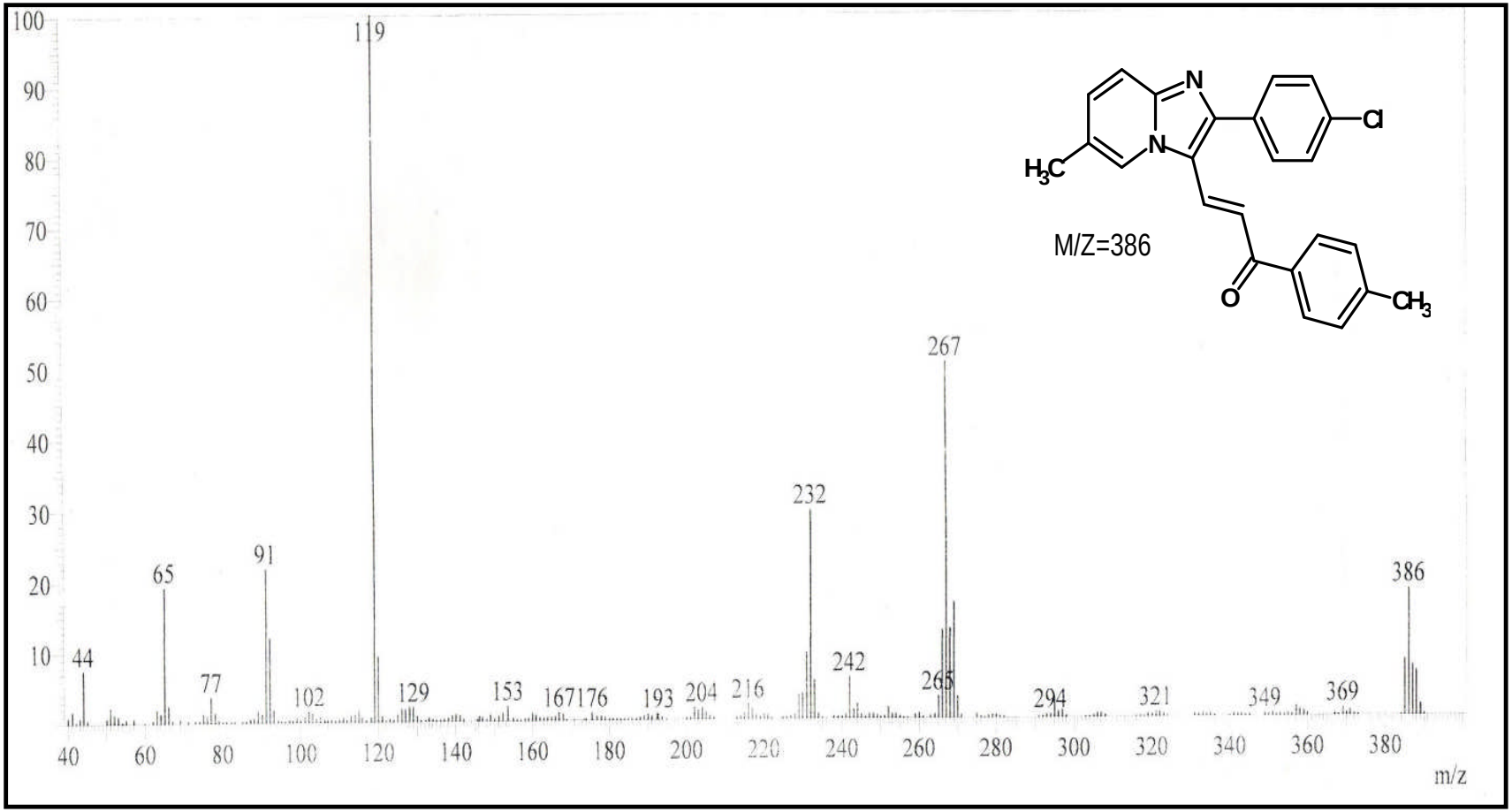
NMR SPECTRAL STUDY OF 2 - (4' – CHLOROPHENYL)-6-METHYL- 3-[1"-(4'''-METHYLPHENYL)- 2"-PROPENE-1"-ONE-3-YL]-IMIDAZO [1,2-a] PYRIDINE.

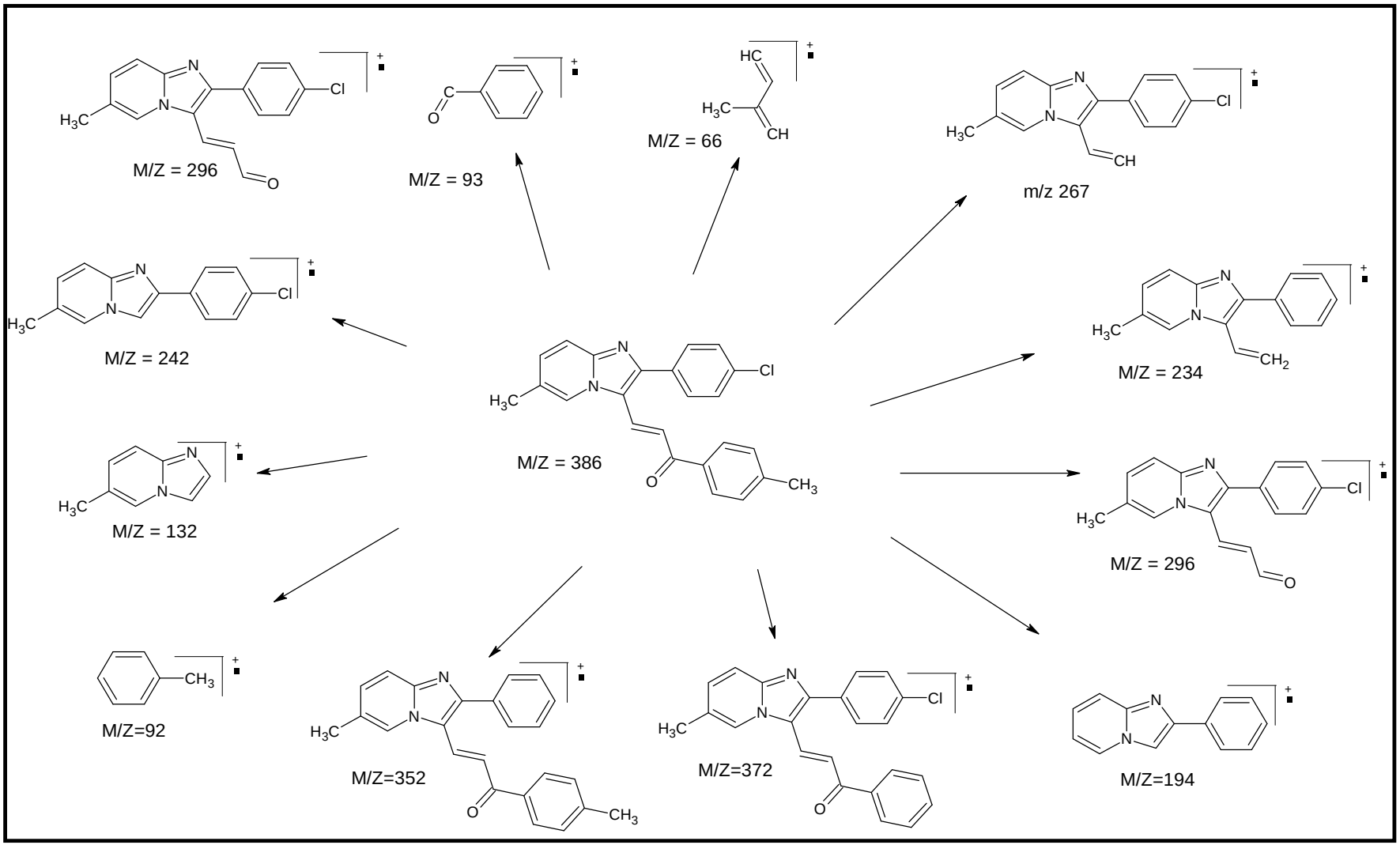


InternalStandard:TMS;Solvent : $CDCl_3$;Instument Bruker Spectometer (300MHz)

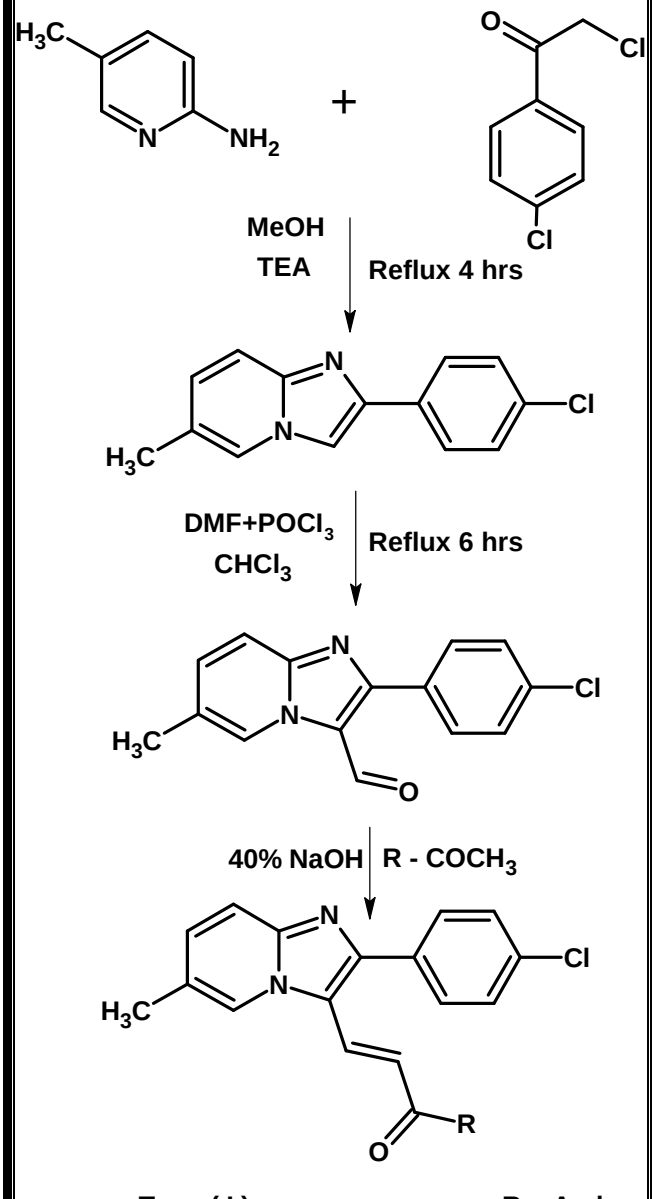
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.43	3H	singlet	Ar-CH_3(j)
2	2.44	3H	singlet	Ar-CH_3(k)
3	7.22-7.25	1H	doublet	Ar-H(f)
4	7.26-7.30	2H	doublet	Ar-H(aa')
5	7.45-7.49	3H	doublet	Ar-H(cc',e)
6	7.61-7.64	1H	doublet	CH=CH(h)
7	7.71-7.74	2H	doublet	Ar-H(dd')
8	7.81-7.84	2H	doublet	Ar-H(bb')
9	8.10-8.14	1H	doublet	Ar-H(i)
10	8.21	1H	singlet	Ar-H(g')

MASS SPECTRAL STUDY OF 2 - (4' – CHLOROPHENYL)-6-METHYL- 3-[1"-(4"'-METHYLPHENYL)- 2"-ROPENE-1"-ON E -3-YL]-IMIDAZO [1,2-a] PYRIDINE.




M/Z = 296
M/Z = 93
M/Z = 66
m/z 267
M/Z = 242
M/Z = 234
M/Z = 386
M/Z = 132
M/Z = 296
M/Z=92
M/Z=352
M/Z=372
M/Z=194

REACTION SCHEME



Type-(I) R = Aryl

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-[1"-ARYL- 2"-PROPENE-1"-ONE-3-YL]-IMIDAZO [1,2- a] PYRIDINES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine :

Arranged 1.0 lit 4/N RBF equipped with stirrer tharmopoket and condensor. Charge 100ml methanol and 21.3g (0.1 mole) (4-chlorophenyl)acetyl chloride and then charge 11.9g (0.11mole) 2-amino 5- methyl pyridine at room temperature stir till clear solution. Add drop wise 5.9g (0.055mol) triethylamine at room temperature till P^H adjust 8 to 9. After addition complete heat 60-65 ^oC for 3 to 4 hrs, then check TLC. After complies TLC cool reaction mass at room temperature and pour in crused ice filter and dry it.Yield 86%, m.p200 ^oC.

($C_{14}H_{11}ClN_2$; Required : C, 69.28; H, 4.53; N, 11.54%; found : C, 69.26; H, 4.52; N, 11.50%).

[B] Synthesis of 6 – methyl – 2 - (4' - chlorolphenyl)imidazo [1,2-a] pyridine – 3 - carboxaldehyde :

Arranged 2.0 lit 4/N RBF equipped with stirrer, tharmopocket and condensor in water bath. Charge 84ml DMF and 1.0 lit $CHCl_3$ in RBF and cool at 0 - 5 ^oC. Start drop wise addition of 165ml $POCl_3$ within 1.0 hrs. (exothermicity observe) stir 30 min at 0-5 ^oC. Add 50g (0.225 mole) 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine slowly temp. raise up to reflux for 6 hrs. Remove $CHCl_3$ by vacuum distillation. Cool the reaction mass at room temperature and pour in crused ice. P^H adjust neutral by coustic solution. Filter and crystallized from methanol. Yield 70%, mp180 ^oC.

($C_{15}H_{11}ClN_2O$; Required : C, 71.33; H, 5.99; N, 11.55%; found : C, 71.33; H, 5.99; N, 11.55%).

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (1i)

Dissolve - 6 - methyl – 2 - (4' – chlorophenyl) imidazo [1,2 – a] pyridine 3-carboxaldehyde (2.91gm,0.01mol) in a mixture of methanol (50 ml) + DMF (50 ml). To this add p-methylacetophenone (1.40gm, 0.01mol) and methanol (50 ml). Stirr the content at room temperature for 24 hr. in presence of catalytical amount of 40% NaOH. The resulting solution was poured on to crushed ice, thus the solid 0seprated was filterated and crystallized from ethanol, Yield 56 %, m. p. 184^oC

($C_{24}H_{19}ClN_2O$; Required : C, 74.51; H, 4.95; N, 7.24%; found : C, 74.50; H, 4.93; N, 7.22%;

Similarly, other2-(4'-chlorophenyl)-6-methyl- 3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine compounds were prepared. The physical data are recorded in Table no.1

[D] Biological Screening of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

All the compounds have been evaluated for their biological screening represented in graphical chart no.-1

(I) Antibacterial activity[650]

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 megaterium, Salmonella taphimurium, staphylo coccus aureus, Escherichia coli*** in separate conical flasks at 40-50 ^oC and mixxed well by gentle shaking. About 25 ml content of the flask was poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hrs. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.05ml (50μg) solution of sample in DMF.

The plates were incubated at 37 ^oC for 24 hrs. and the control was also maintained with 0.05ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in millimeter and recorded in Table No-A.

(II) Antifungal activity[650]

***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 hrs. 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 hrs, the cups (10mm diameter) were punched. The plates were incubated at 30 ^oC for 48 hrs.

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 zones of inhibition of test solution are recorded in TableNo. A

BIOLOGICAL SCREENING

Method	:	**Cup-Plate[650]**
Gram positive bacteria	:	***Bacillus megaterium,*** ***Salmonella taphimurium,***
Gram negative bacteria	:	***staphylo coccus aureus,*** ***Escherichia coli***
Fungi	:	***Aspergillus niger***
Concentration	:	**50µg/ml**
Solvent	:	**Dimethyl formamide**
Standard drugs	:	**Ampicillin,Chloramphenicol,** **Norfloxacin** **Greseofulvin**.

The biological screening was compared with standard drug viz Ampicillin, Chloramphenicol**,** Norfloxacin, and antifungal activity was compared with viz Greseofulvin. The inhibition zones were measured in mm,The zones of inhibition that displayed by standared drugs are recorded in part-I, page no.41, Table no-A.

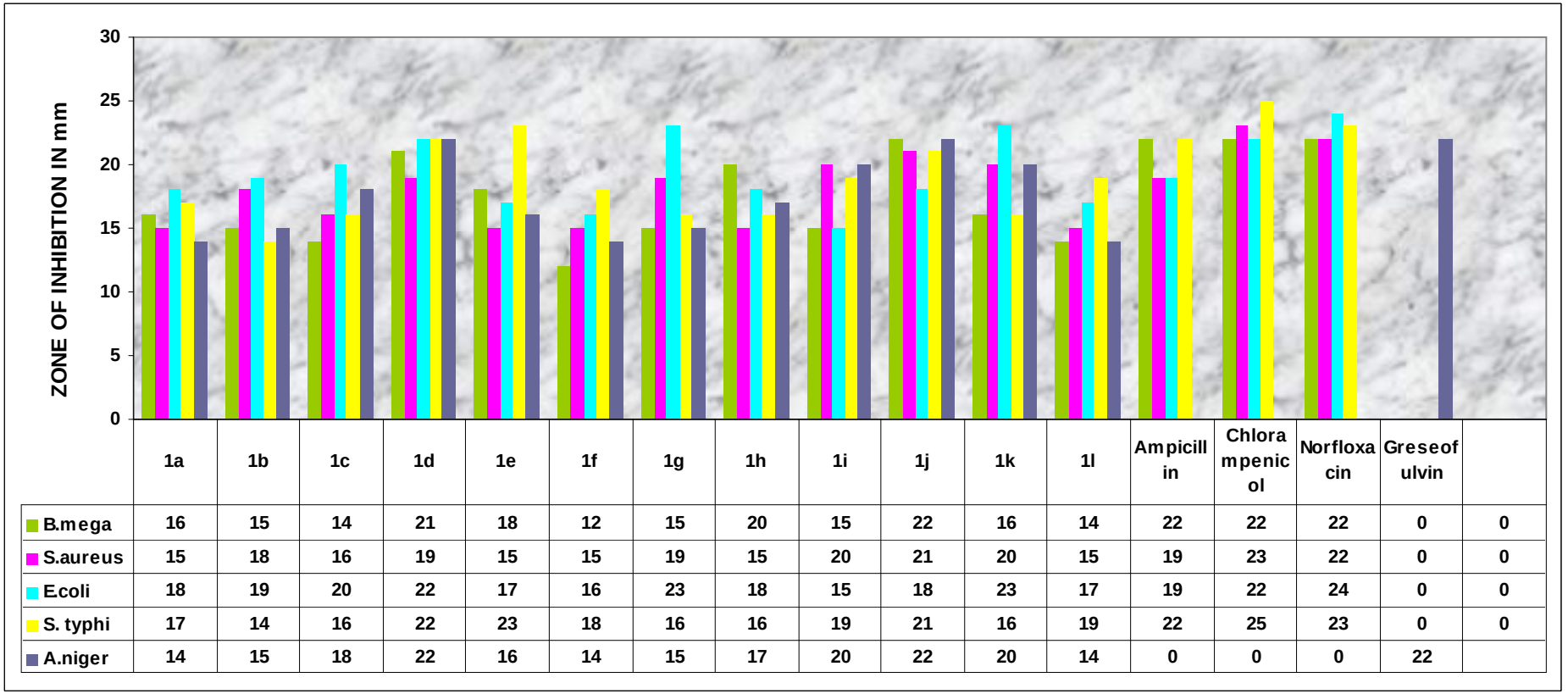
TABLE NO.A : ANTIMICROBIAL ACTIVITY ZONE OF INHIBITION OF STANDARD DRUGS.

	Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
Drugs	***B. mega***	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
Ampicillin (50 µg)	**22**	**19**	**19**	**22**	**--**
Chloramphenicol(50 µg)	**22**	**23**	**22**	**25**	**--**
Norfloxacin (50 µg)	**22**	**22**	**24**	**23**	**--**
Greseofulvin (50 µg)	**--**	**--**	**--**	**--**	**22**

TABLE NO.1 PHYSICAL CONSTANTS OF 2 - (4' – CHLOROPHENYL)-6-METHYL- 3-[1"-(ARYL)- 2"-ROPENE-1"-ONE-3-YL]-IMIDAZO [1,2-a] PYRIDINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
1a	C_6H_{5-}	$C_{23}H_{17}ClN_2O$	372.5	101	61	7.51	7.49
1b	3-Cl-C_6H_4 -	$C_{23}H_{16}Cl_2N_2O$	407.0	245	63	6.88	6.86
1c	4-Cl-C_6H_4 -	$C_{23}H_{16}Cl_2N_2O$	407.0	250	59	6.88	6.86
1d	2-4-$(Cl)_2$-C_6H_3-	$C_{23}H_{15}Cl_3N_2O$	441.5	205	55	6.34	6.32
1e	4 -F-C_6H_4-	$C_{23}H_{16}ClFN_2O$	390.5	126	69	7.17	7.15
1f	4-Br-C_6H_4-	$C_{23}H_{16}BrClN_2O$	451.5	170	60	6.20	6.17
1g	4 -OH-C_6H_4-	$C_{23}H_{17}ClN_2O_2$	388.5	140	51	7.20	7.18
1h	4-NH_2-C_6H_4	$C_{23}H_{18}ClN_3O$	387.5	190	58	10.83	10.82
1i	4-CH_3-C_6H_4-	$C_{24}H_{19}ClN_2O$	386.5	184	56	7.24	7.22
1j	4-OCH_3-C_6H_4-	$C_{24}H_{19}ClN_2\ O_2$	402.5	180	70	6.95	6.93
1k	3-NO_2-C_6H_4-	$C_{23}H_{16}ClN_3O_3$	417.5	111	69	10.06	10.04
1l	4-NO_2-C_6H_4-	$C_{23}H_{16}ClN_3O_3$	417.5	250	50	10.06	10.04

GRAPHICAL CHART NO.1: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-[1"-(ARYL)- 2"-PROPENE- 1"-ONE-3-YL]-IMIDAZO [1,2-a]PYRIDINES.



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	16	15	14	21	18	12	15	20	15	22	16	14	22	22	22	0	0
S.aureus	15	18	16	19	15	15	19	15	20	21	20	15	19	23	22	0	0
E.coli	18	19	20	22	17	16	23	18	15	18	23	17	19	22	24	0	0
S. typhi	17	14	16	22	23	18	16	16	19	21	16	19	22	25	23	0	0
A.niger	14	15	18	22	16	14	15	17	20	22	20	14	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-I

SECTION – I: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-[1"-ARYL - 2"- PROPENE-1"-ONE-3-YL]-IMIDAZO [1,2-a]PYRIDINES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E. coli***	***S. typhi***	***A. Niger***
		1d-(21)	**1d-(19)**	**1c-(20)**	**1d-(22)**	**1d-(22)**
		1h-(20)	**1g-(19)**	**1d-(22)**	**1e-(23)**	**1i- (20)**
		1j-(22)	**1i- (20)**	**1g-(23)**	**1j-(21)**	**1k-(20)**
			1j-(21)	**1k-(23)**		**1j-(22)**
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

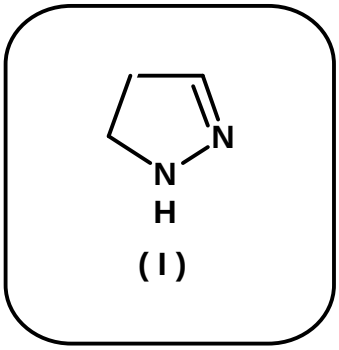
PART-II

STUDIES ON PYRAZOLINES

STUDIES ON PYRAZOLINES

INTRODUCTION

Amongst nitrogen containing five member heterocycles, pyrazolines have proved to be the most useful frame work for biological activities.The chemistry of pyrazoline was reviewed by Jarobe in 1967. The chemistry of pyrazolines, which have been studied extensively for their biodynamic behavior[132]. Pyrazoline has three possible tautomeric structures, but the structure (I) shown is the most stable.

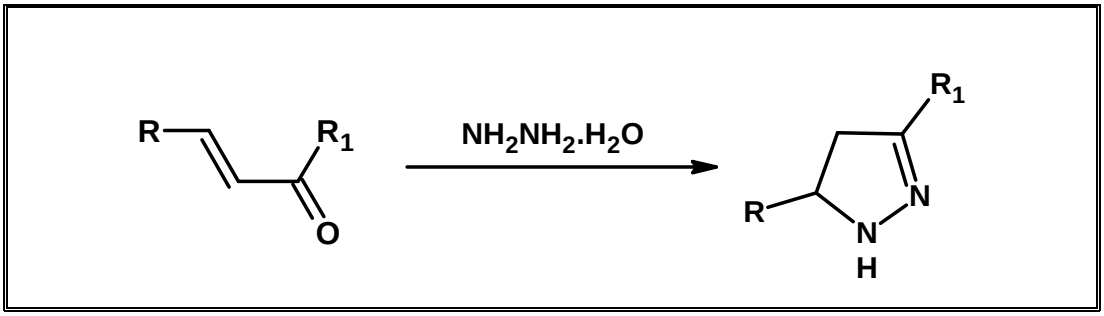


(I)

SYNTHETIC ASPECT

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

1. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate[133].

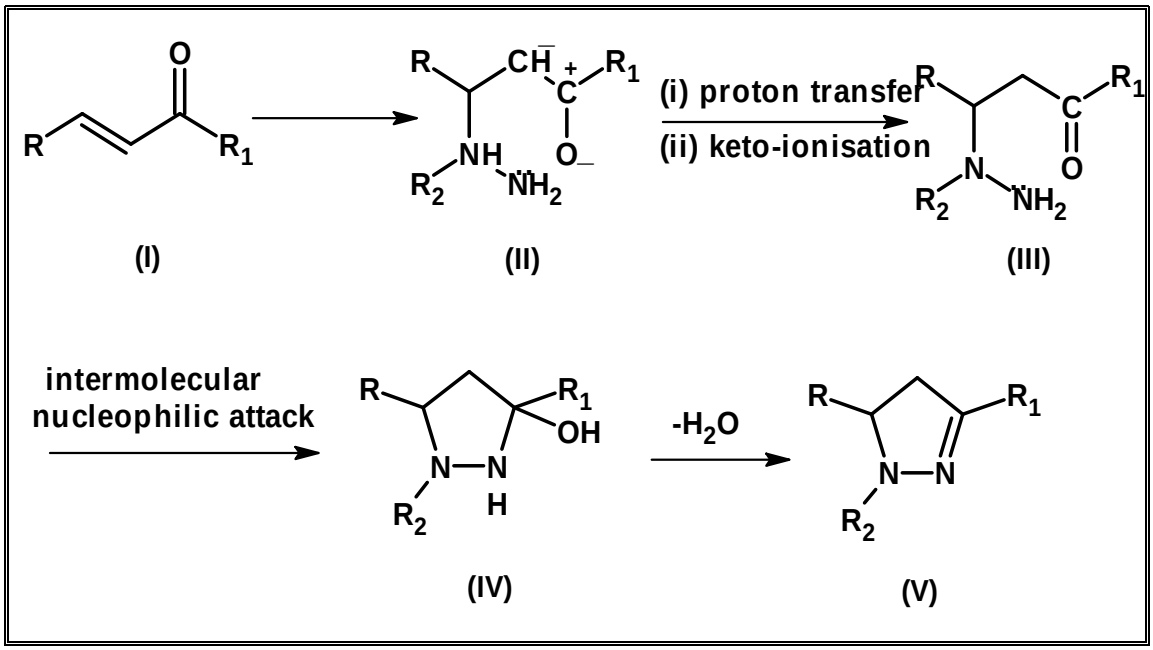


2. 2-Pyrazolines can be synthesized by the cycloaddition of diazomethane to substituted chalcone[134].
3. Dipolar cycloaddition of nitrileimines of dimethyl fumarate, fumaronitrile and the N-aryl maleimides yielded the corresponding pyrazolines[135].
4. Epoxidation of chalcones with epoxy ketones on reaction with hydrazine hydrate and phenyl hydrazine to give pyrazolines[136].

5. 2 - Pyrazolines can also be prepared by the condensation of chalcone dibromide with hydrazine[137]. Furthermore, Gyassi B.et al[138]have investigated the one pot synthesis of some pyrazolines in dry media under microwave irradiation. Paul S.et al.[139]and Dandia Anshu et al.[140] have also described the microwave synthesis of 2-pyrazolines.

MECHANISM :

The following mechanism seems to be operable for pyrazoline by the condensation of chalcones with hydrazine hydrate[141].



.

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

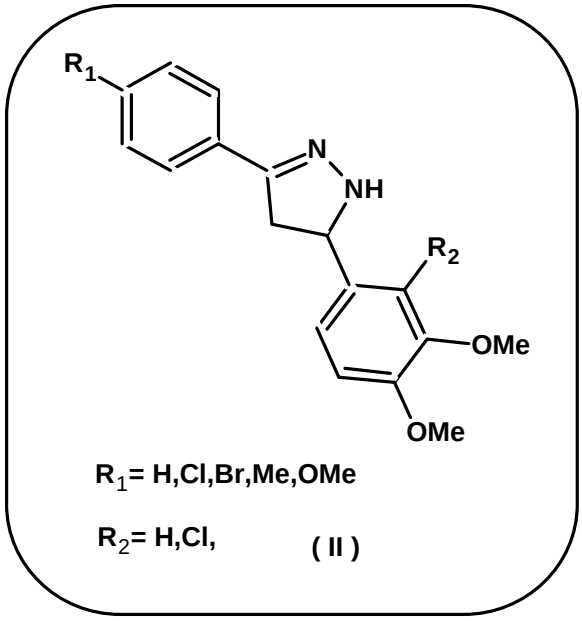
Proton transfer from the nitrogen to -ve oxygen produces an intermediate enol which simultaneously ketonises to ketoamine (III). Another intramolecular nucleophilic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately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

THERAPEUTIC IMPORTANCE :

From the literature survey, it was revealed that 2-pyrazolines are better therapeutic agents like,

1. Antimicrobial[142]
2. Antiinflammatory[143, 144]
3. Antiallergic[145]
4. Anticonvulsant and Antidepressant[146]
5. Antidiabatic[147]
6. Antiimplantation[148]
7. Antitumor[149]
8. Antineoplastic[150]
9. Analgesic[151,152]
10. Fungicidal[153,154]
11. Bactericidal[155,156]
12. Herbicidal[157]
13. Cardiovascular[158]
14. Antiamoebic[159]
15. Tranquilizer[160]

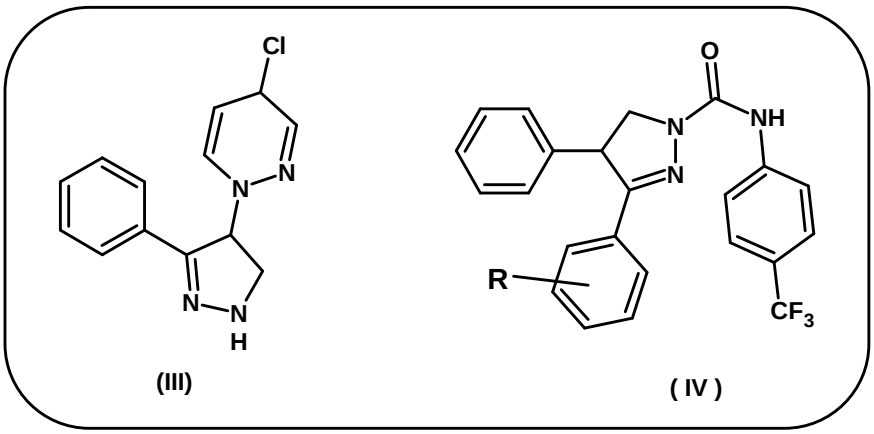
E. Palska et al.[161] have prepared 3,5-diphenyl-2-pyrazolines (II) and cited their antidepressant activity. N. Gokhan et al.[162] reported pyrazolines as cholinstearase and selective monoamine oxidase B inhibitiors .T. M. Stivenson et al.[163]have also investigated N-substituted pyrazoline type insecticides. Tanka Katsoshori[164] have patented pyrazoline derivatives as herbicides and Johannes et al.[165] have reported as insecticides.



(II)

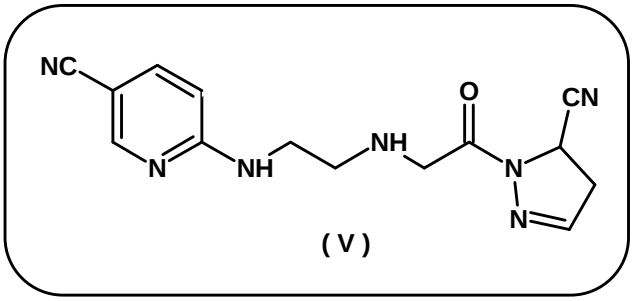
M. M. Abdalla et al.[166] have synthesized pyrazolines and tested their antiandrogenic activity. M. A.Berghot et al.[167] have prepared pyrazolines as antibacterial agents. Maurer Fritz et al.[168] have synthesized pyrazoles and screened for their pesticidal activity.

A. R. Udupi and A. R.Bhatt [169] have reported the synthesis and biological activity of Mannich bases of certain 1,2-pyrazolines. Nugent Richard[170] investigated pyrazolines bis phosphonate ester as novel antiinflammatory and antiarthritic agent. Fuche Rainer etal.[171] have prepared some new 1H-pyrazoline derivatives (III) and reported them as pesticides. Furthermore, Tsubai et al.[172] have synthesized some new (phenylcarbamoyl) pyrazolines (IV) as an insecticides and at 40% concentration shows 100% mortality ofspodopetra litura larve after seven drops.



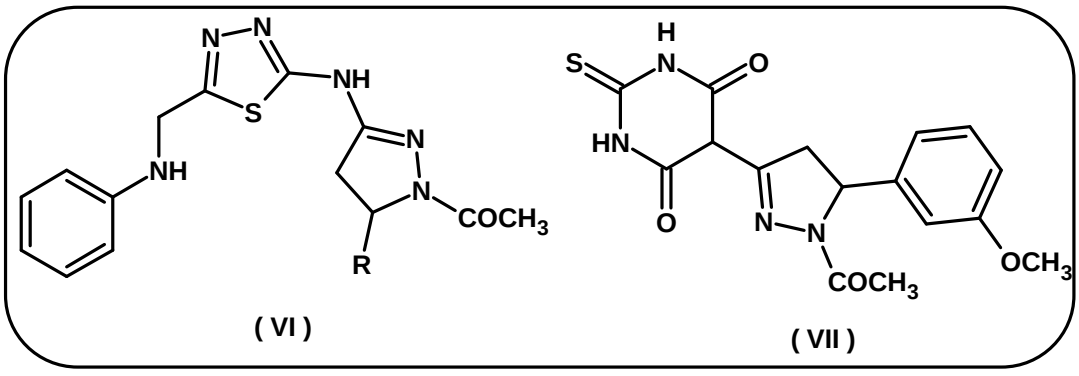
(III) (IV)

Moreover, J. H.Ahn et al.[173] have described the synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent antidiabetic agents(V). J. H. Jeong. et al.[174] have synthesized some novel 3,5-diaryl pyrazolines as cholesterol acyl transferase inhibitors. M. N Nasr. et al.[175] have reported the synthesis of Novel 3,3a,4,5,6,7-hexahydroindazole and aryl thiazolylpyrazoline derivatives as antiinflammatory agents. M. A Berghot. et al.[176] have prepared for convergentsynthesis and antibacterial activity of pyrazole and pyrazoline derivatives of diazepam.



(V)

J. Almstead et al.[177] have prepared pyrazolines as vascularization agent. Guniz Kucukguzel et al.[178] have synthesized pyrazolines as a anticonvulsant agents. T. Gulhan and coworkers[179] have prepared pyrazolines as a hypotensive agent. Shalabh Sharma et al.[180] have synthesized pyrazolines and tested their anti-inflammatory activity (VI). Ashok Kumar et al.[181] have synthesized pyrazolines as anticonvulsant agents (VII). Maurer Fritz et al.[182] have synthesized pyrazoles and screened for their pesticidal activity**.**



(VI) (VII)

Recently, N. Gokhan et al.[183] have synthesized the pyrazoline derivatives of 1-N-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazolines as MAO inhibitors. J. Matysiak et al.[184] have reported some novel pyrazoline derivatives as antimycotic activity of N-azolyl-2,4-dihydroxythiobenzamides. Z. Tabarelli et al.[185] have prepared

some pyrazole derivative showed activity of antinociceptive effect of novel pyrazolines in mice.

S. S. Sonarc et al.[186] have synthesized-3-(2-acetoxy-4-methoxyphenyl)-5-(substituted phenyl)-pyrazolines and tested their antimicrobial activity. H. S. Joshi[187] et al. have also synthesized some new pyrazolines as an antimicrobial agent. G. N. Mishirikaet al.[188] have prepared 2-pyrazolines of salicyclic acid possessing antimicrobial properties. Tunfawy Atif and co-workers[189] have patented 3-methyl-4'-(substituted phenylazo)-pyrazol-5-ones as antibacterial agents.

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

SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-(3"-ARYL -4", 5"-DIHYDRO-1"H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

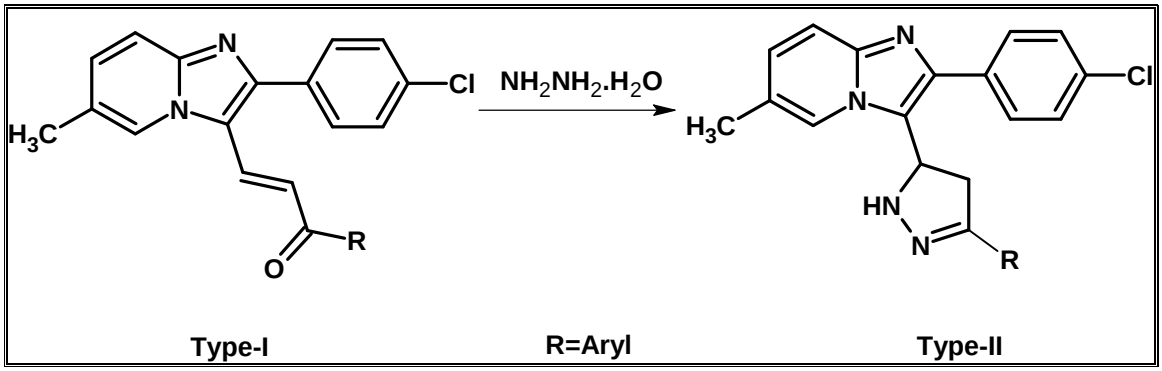
SECTION-II: SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-(3"-ARYL -1"-ACETYL-4", 5"- DIHYDROPYRAZOL-5"-YL) IMIDAZO [1, 2a] PYRIDINES.

SECTION-III: SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6- METHYL-3-(3"-ARYL-1"-PHENYL-4", 5"-DIHYDROPYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

SECTION – I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" - ARYL - 4", 5" – DIHYDRO -1"H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

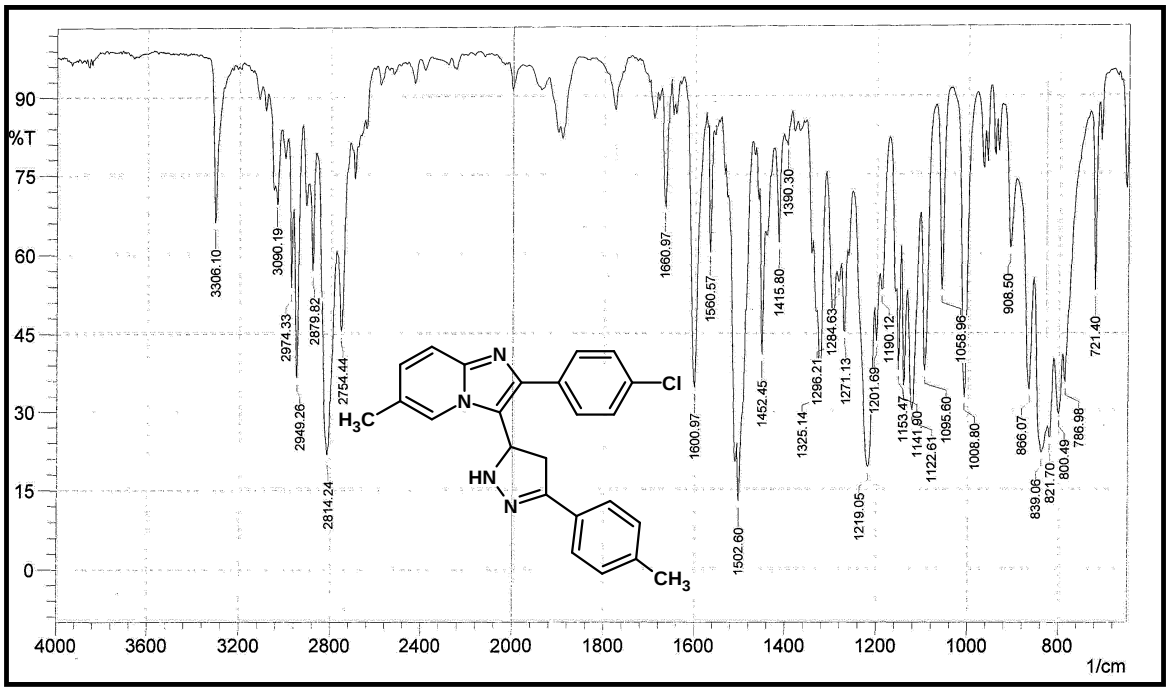
The broad spectrums of pharmacological properties have been demonstrated by the pyrazoline nucleus. Inspired by these facts, new pyrazoline derivatives of 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl -4", 5"-dihydro-1"H-pyrazol-5"-yl) imidazo [1, 2-a] pyridines of Type (II) have been synthesized by condensation of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine of Type (I) with hydrazine hydrate in methanol .



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared,^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs.The details have been cited in part-I,section-I , page no. 41,Table no. A

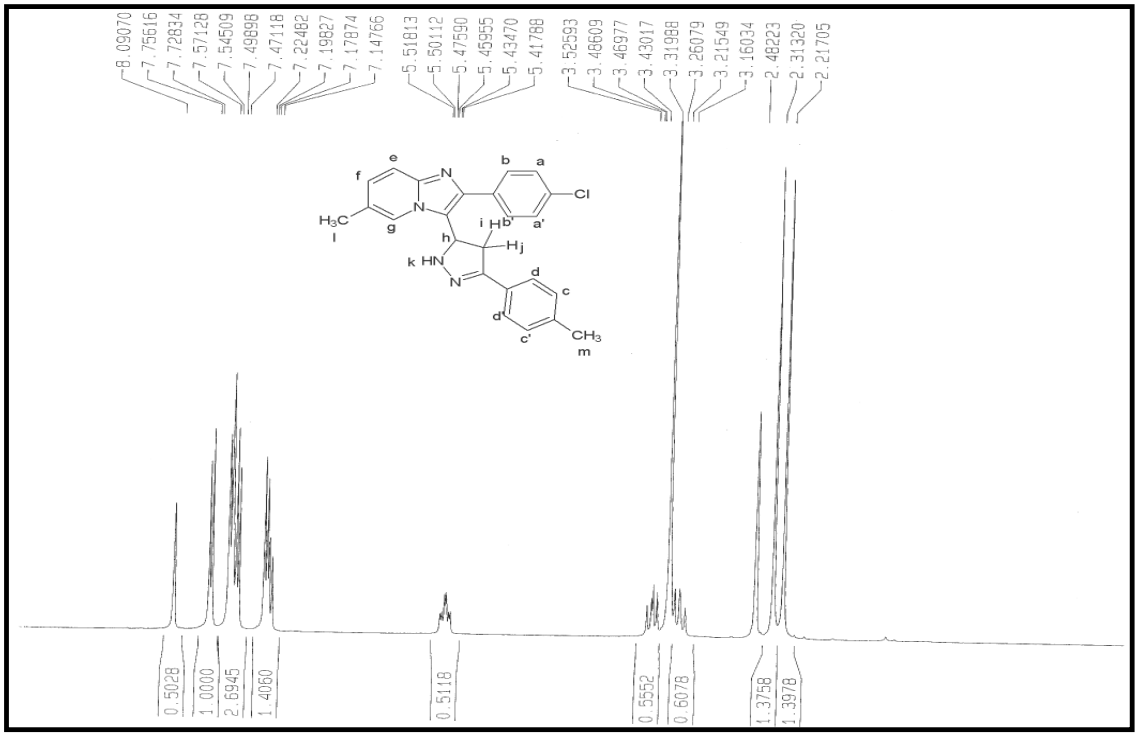
IR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4'''-METHYLPHENYL)-4",5"-DIHYDRO-1"H-PYRAZOL-5"-YL] IMIDAZO [1, 2-a] PYRIDINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2949	2990-2850	648
	C-H str. (sym.)	2879	2880-2860	"
	C-H def. (asym.)	1452	1470-1435	"
	C-H def. (sym.)	1390	1390-1370	"
Aromatic	C-H str.	3090	3090-3030	"
	C=C str	1502	1600-1450	"
	C-H i.p. (def.)	1122	1300-1100	"
Pyrazoline	C-N str	1095	1230-1020	649
	C=N str	1560	1650-1550	"
	N-H str	3306	3320-3140	"
	-CH-$(CH)_2$ str.	2754	2850-1790	"
Imidazo[1,2-a] pyridine	C-N str.	1058	1220-1020	"
	C=N str.	1600	1612-1593	"
Halide	C-Cl str.	721	800-600	"

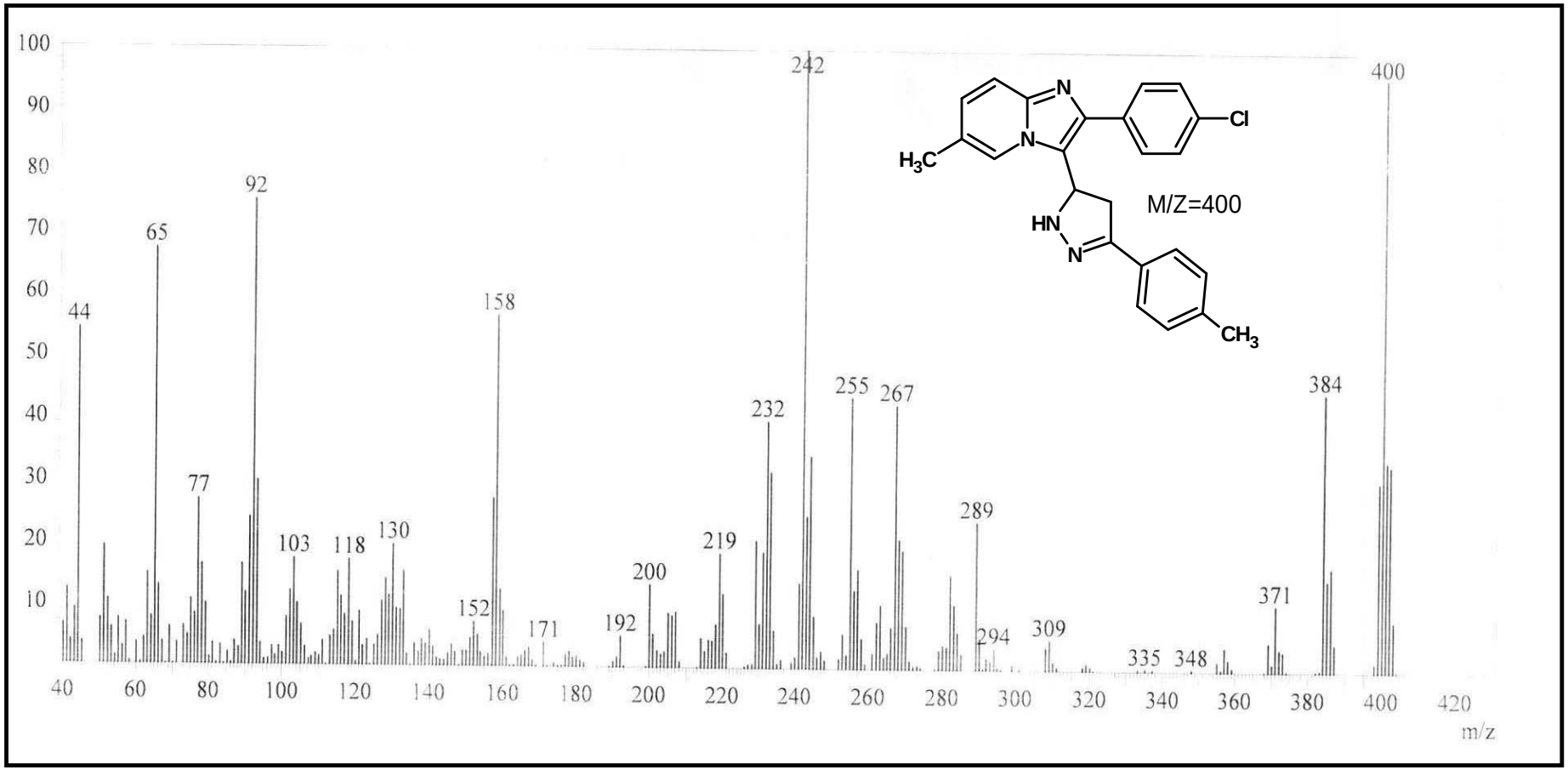
NMR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4'''-METHYLPHENYL]4",5"-DIHYDRO-1"H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINE.

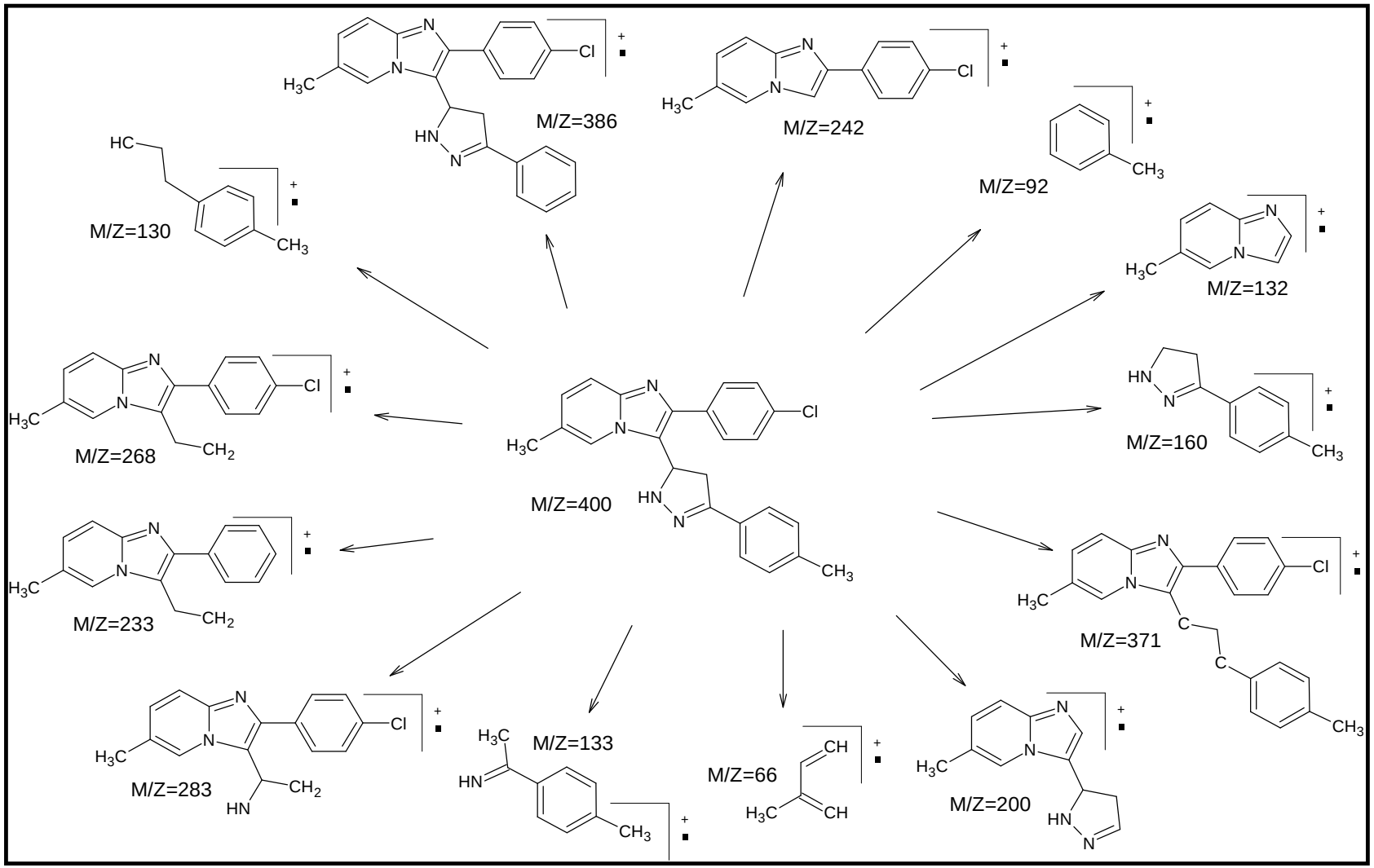


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

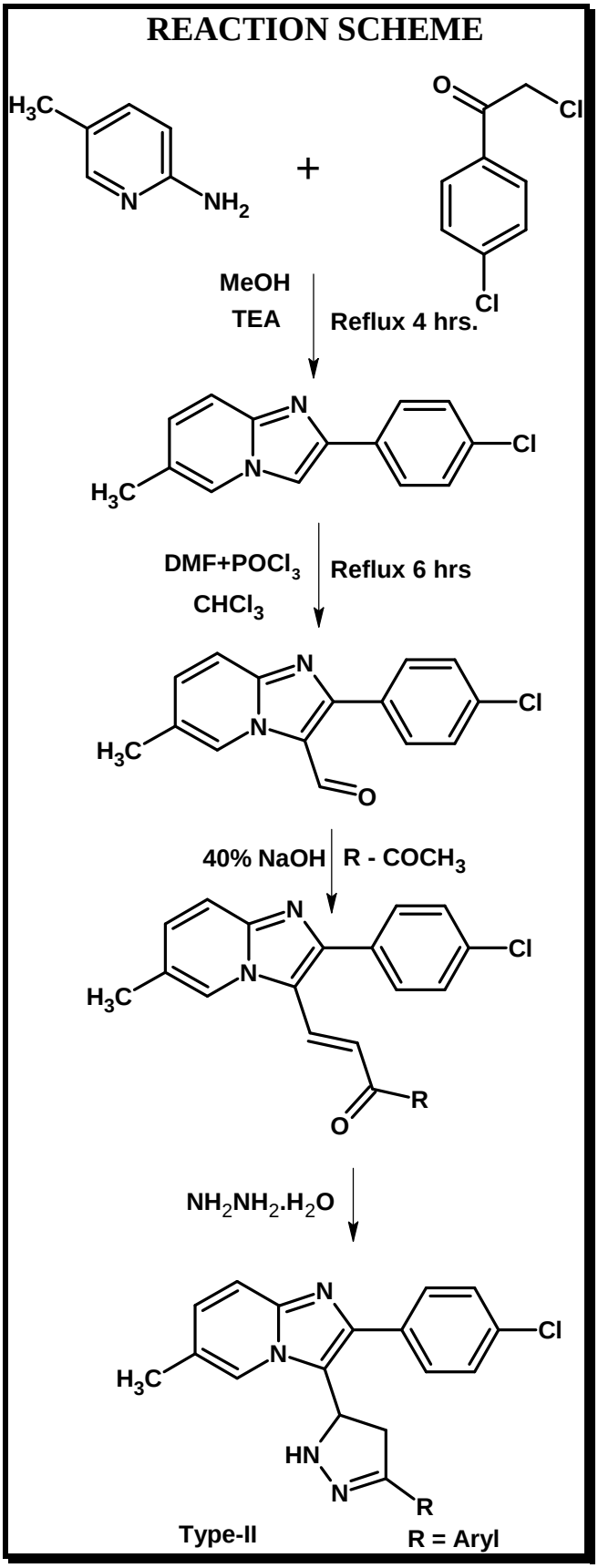
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.21	3H	Singlet	Ar-CH_3(k)
2	2.31	3H	Singlet	Ar-CH_3(l)
3	3.16-3.31	1H	ddoublet	Ar- H(i)
4	3.43-3.52	1H	ddoublet	Ar-H(j)
5	5.41-3.51	1H	quatret	Ar-H(h)
6	7.14-7.17	1H	doublet	Ar-H(f)
7	7.19-7.22	2H	doublet	Ar-H(cc')
8	7.47-7.57	5H	multiplate	Ar-H(aa',bb',e)
9	7.72-7.75	2H	doublet	Ar-H(dd')
10	8.09	1H	Singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL)-4",5"-DIHYDRO-1"-H-PYRAZOL-5"-YL] IMIDAZO [1, 2-a] PYRIDINE.




M/Z=386
M/Z=242
M/Z=92
M/Z=132
M/Z=160
M/Z=371
M/Z=200
M/Z=66
M/Z=133
M/Z=283
M/Z=233
M/Z=268
M/Z=130
M/Z=400

REACTION SCHEME



EXPERIMENTAL

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

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I,on page no.37

[B] Synthesis of 6-methyl-2-(-4'chlorolphenyl)imidazo[1,2-a]pyridine-3-Carboxaldehyde.

See, Part-I, Section-I , on page no.37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I,on page no.37

[D] Synthesis of 2-(4'-chlorophenyl)-6-methyl-3-[3"-(4"'-methylphenyl) -4", 5"-dihydro-1"-H-pyrazol-5"-yl] imidazo [1, 2-a] pyridines(2i).

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a] pyridine (3.82 g, 0.01 mol) and hydrazine hydrate 1.0g (0.02mol) in 25 ml methanol. The reaction mixture was reflux for 5 hrs. the content was poured in to crused an ice,filtered dried and recrystllized from ethanol. Yield 72 %, m.p. 170^{o}C.

($C_{24}H_{21}ClN_4$ Requires : C,71.90, H,5.28, N,13.98%, Found : C,71.88, H,5.26, N,13.95%).

Similarly, other 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl) -4", 5"-dihydro-1"-H-pyrazol-5"-yl) imidazo [1, 2-a] pyridines were prepared. The physical data are recorded in Table no.2.

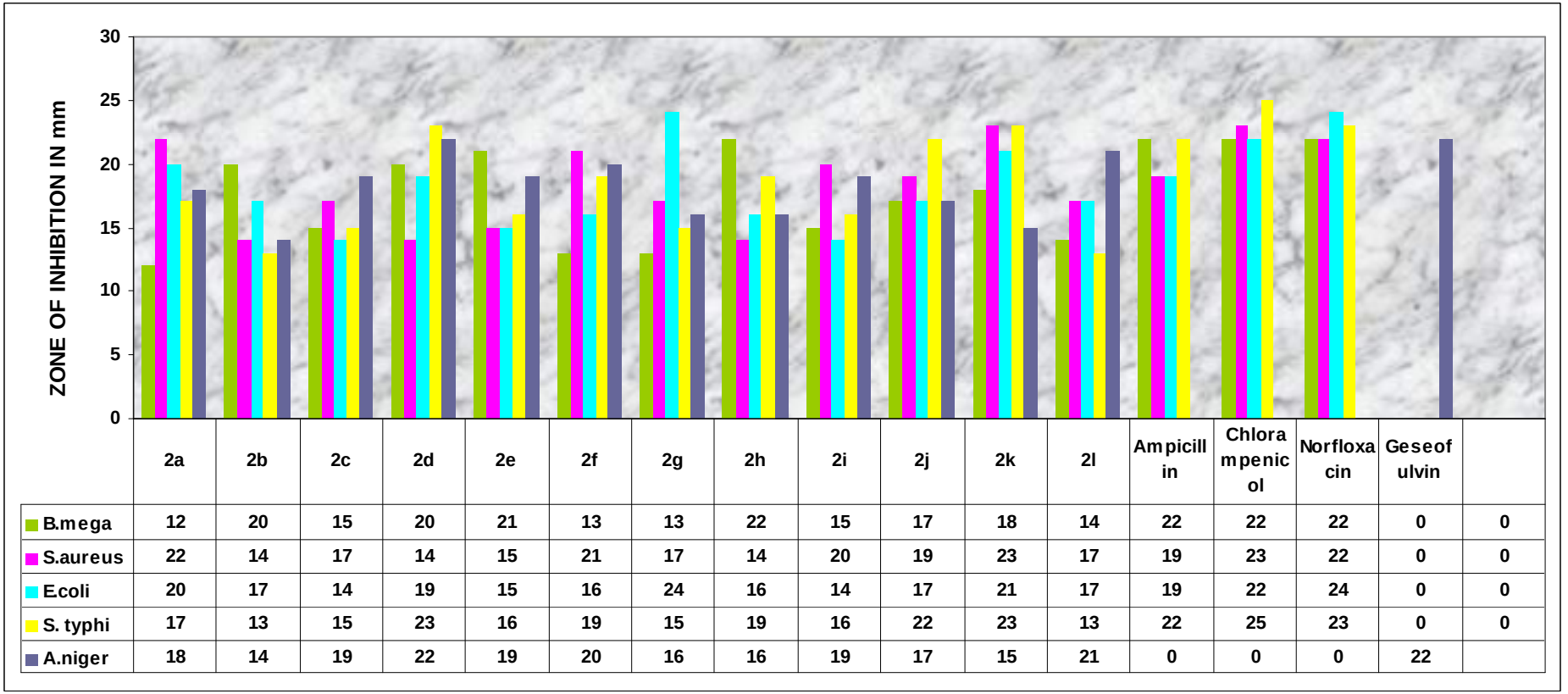
[E] Biological screening of 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl) -4", 5"-dihydro-1"-H-pyrazol-5"-yl) imidazo [1, 2-a] pyridines.

Biological screening were carried out as described in Part-I, Section-I. page no. 38,The zones of inhibition of test solutions are recorded in Graphical Chart no.2.

TABLE NO. 2 PHYSICAL COSTANTS OF 2- (4'-CHLOROPHENYL)-6-METHYL-3-(3"-ARYL -4", 5"-DIHYDRO-1"-H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

Sr.No.	R	MoleculerFormula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
2a	C_6H_5-	$C_{23}H_{19}ClN_4$	386.5	160	65	14.48	14.45
2b	3-Cl-C_6H_4 -	$C_{23}H_{18}Cl_2N_4$	421.0	155	72	13.30	13.27
2c	4-Cl-C_6H_4 -	$C_{23}H_{18}Cl_2N_4$	421.0	145	55	13.30	13.27
2d	2-4-$(Cl)_2$-C_6H_3-	$C_{23}H_{17}Cl_3N_4$	455.5	205	50	12.29	12.27
2e	4 -F-C_6H_4-	$C_{23}H_{18}ClFN_4$	404.5	185	65	13.84	13.81
2f	4-Br-C_6H_4-	$C_{23}H_{18}BrClN_4$	465.5	198	60	12.04	12.01
2g	4 -OH-C_6H_4-	$C_{23}H_{19}ClN_4O$	402.5	182	59	13.91	13.88
2h	4-NH_2-C_6H_4	$C_{23}H_{20}ClN_5$	401.5	210	62	17.43	17.40
2i	4-CH_3-C_6H_4-	$C_{24}H_{21}ClN_4$	400.5	170	72	13.98	13.95
2j	4-OCH_3-C_6H_4-	$C_{24}H_{21}ClN_4O$	416.5	165	50	13.44	13.41
2k	3-NO_2-C_6H_4-	$C_{23}H_{18}ClN_5O_2$	431.5	150	58	16.22	16.20
2l	4-NO_2-C_6H_4-	$C_{23}H_{18}ClN_5O_2$	431.5	190	66	16.22	16.20

GRAPHICAL CHART NO. 2 : BIOLOGICAL SCREENING OF 2 - (4' – CHLOROPHENYL) – 6 – METHYL -3 - (3"- ARYL - 4", 5"DIHYDRO-1"-H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Ampicillin	Chloramphenicol	Norfloxacin	Geseofulvin	
B.mega	12	20	15	20	21	13	13	22	15	17	18	14	22	22	22	0	0
S.aureus	22	14	17	14	15	21	17	14	20	19	23	17	19	23	22	0	0
E.coli	20	17	14	19	15	16	24	16	14	17	21	17	19	22	24	0	0
S. typhi	17	13	15	23	16	19	15	19	16	22	23	13	22	25	23	0	0
A.niger	18	14	19	22	19	20	16	16	19	17	15	21	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-II

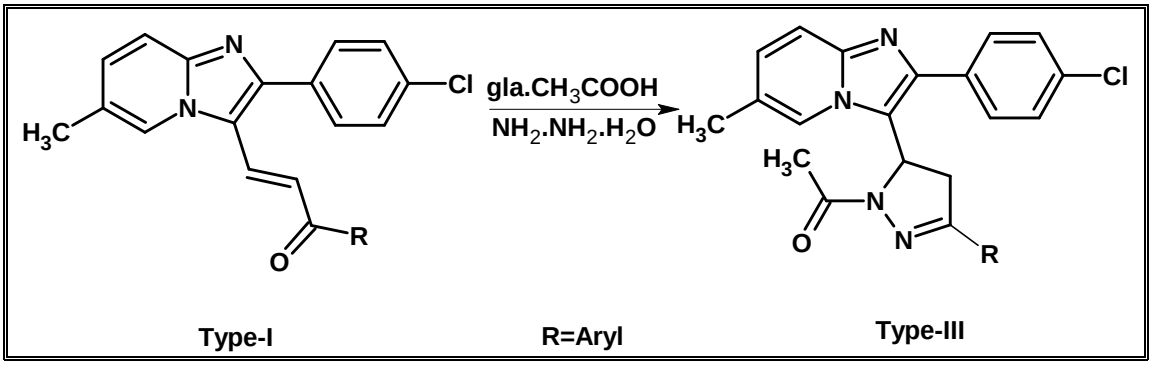
SECTION – I: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-(3"-ARYL -4", 5"DIHYDRO-1"-H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E. coli***	***S. typhi***	***A. Niger***
		2b-(20)	**2a-(22)**	**2a-(20)**	**2d-(23)**	**2d-(22)**
		2d-(20)	**2f-(21)**	**2d-(19)**	**2j- (22)**	**2f- (20)**
		2e-(21)	**2i- (20)**	**2g-(24)**	**2k-(23)**	**2l-(21)**
		2h-(22)	**2j-(19)**	**2k-(21)**		
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-(3"-ARYL) -1"ACETYL-4", 5"-DIHYDROPYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

Acetyl pyrazoline derivetives procuring better therapeutic and antimicrobial activities. Looking at their versatile therapeutic importance and with an aim to getting better potential drug, it was considered worthwhile to synthesized some new pyrazolines. The preparation of 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl) -1"-acetyl-4", 5"-dihydropyrazol-5"-yl) imidazo [1, 2-a] pyridines of Type (III) have been undertaken by cyclocondensation of chalcones of Type (I) with hydrazine hydrate in glacial acetic acid.

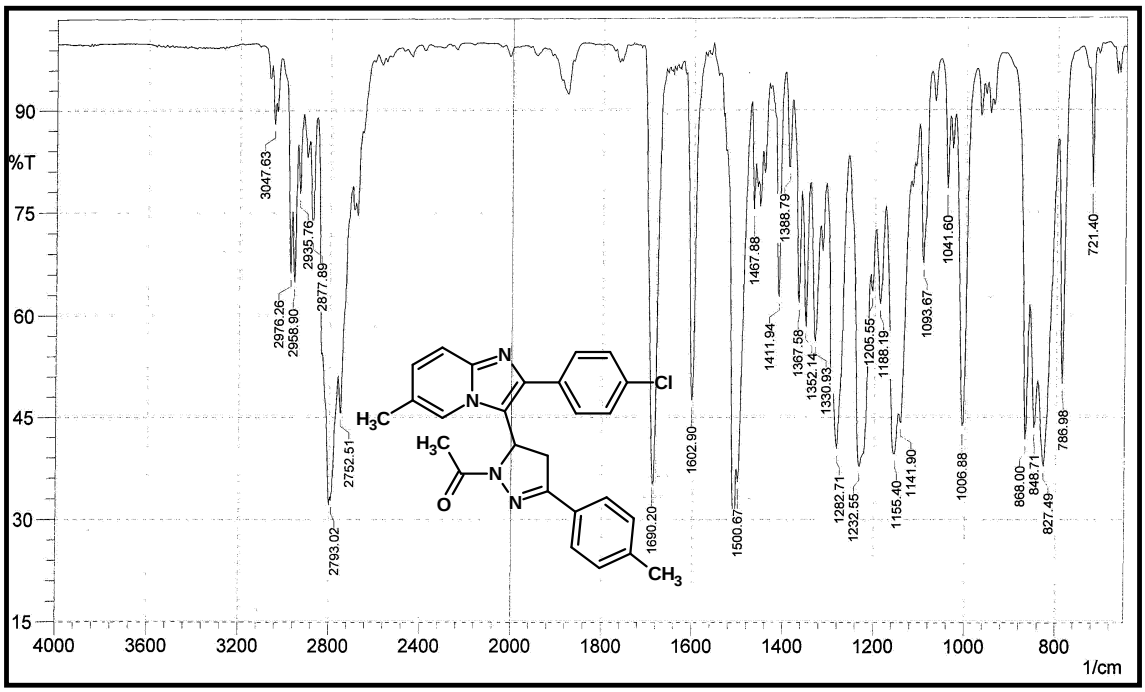


The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I , page no. 41

.

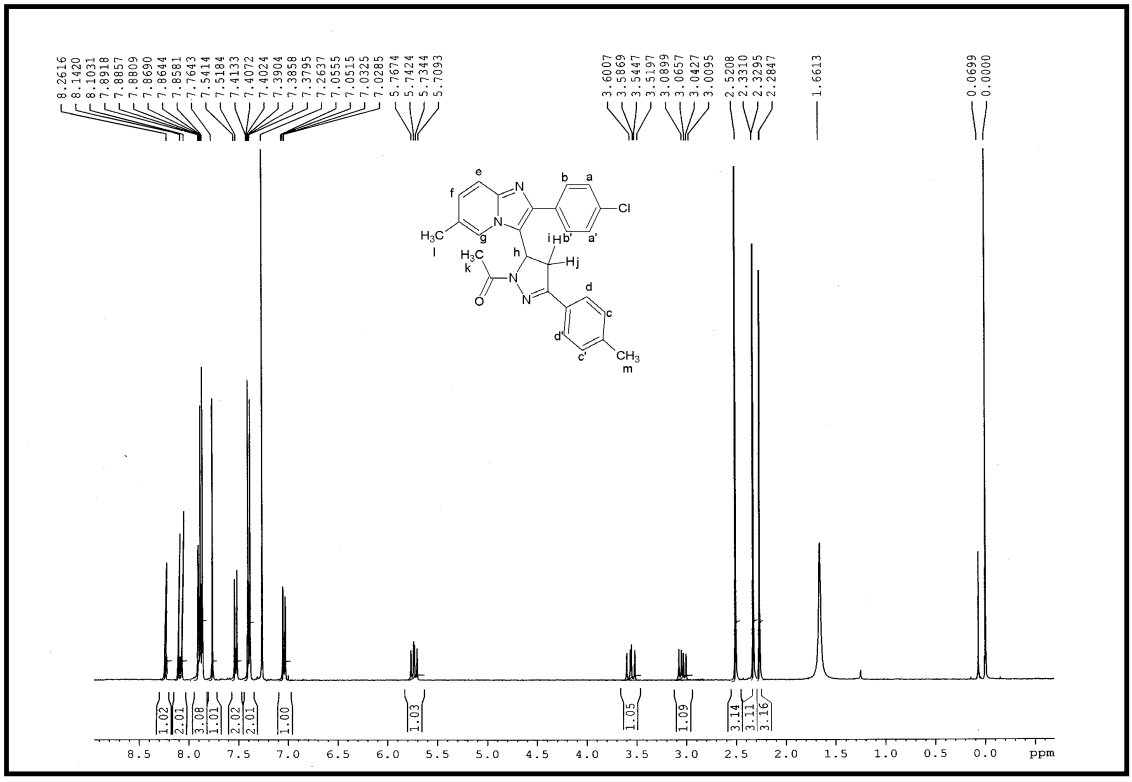
IR SPECTRAL STUDY OF 2 - (4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL) - 1" –ACETYL -4", 5" – DIHYDROPYRAZOL - 5" – YL] IMIDAZO [1, 2-a] PYRIDINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2958	2990-2850	648
	C-H str. (sym.)	2877	2880-2860	"
	C-H def. (asym.	1467	1470-1435	
	C-H def. (sym.)	1388	1390-1370	"
Aromatic	C-H str.	3047	3090-3030	"
	C=C str	1467	1600-1450	"
	C-H i.p. (def.)	1141	1300-1100	"
Pyrazoline	C=O str	1690	1705-1650	"
	C=N str	1602	1650-1550	649
	-CH-$(CH)_2$ str.	2793	2850-1790	"
Imidazo[1,2-a] pyridine	C-N str.	1093	1220-1020	"
	C=N str.	1600	1612-1593	"
Halide	C-Cl str.	721	800-600	"

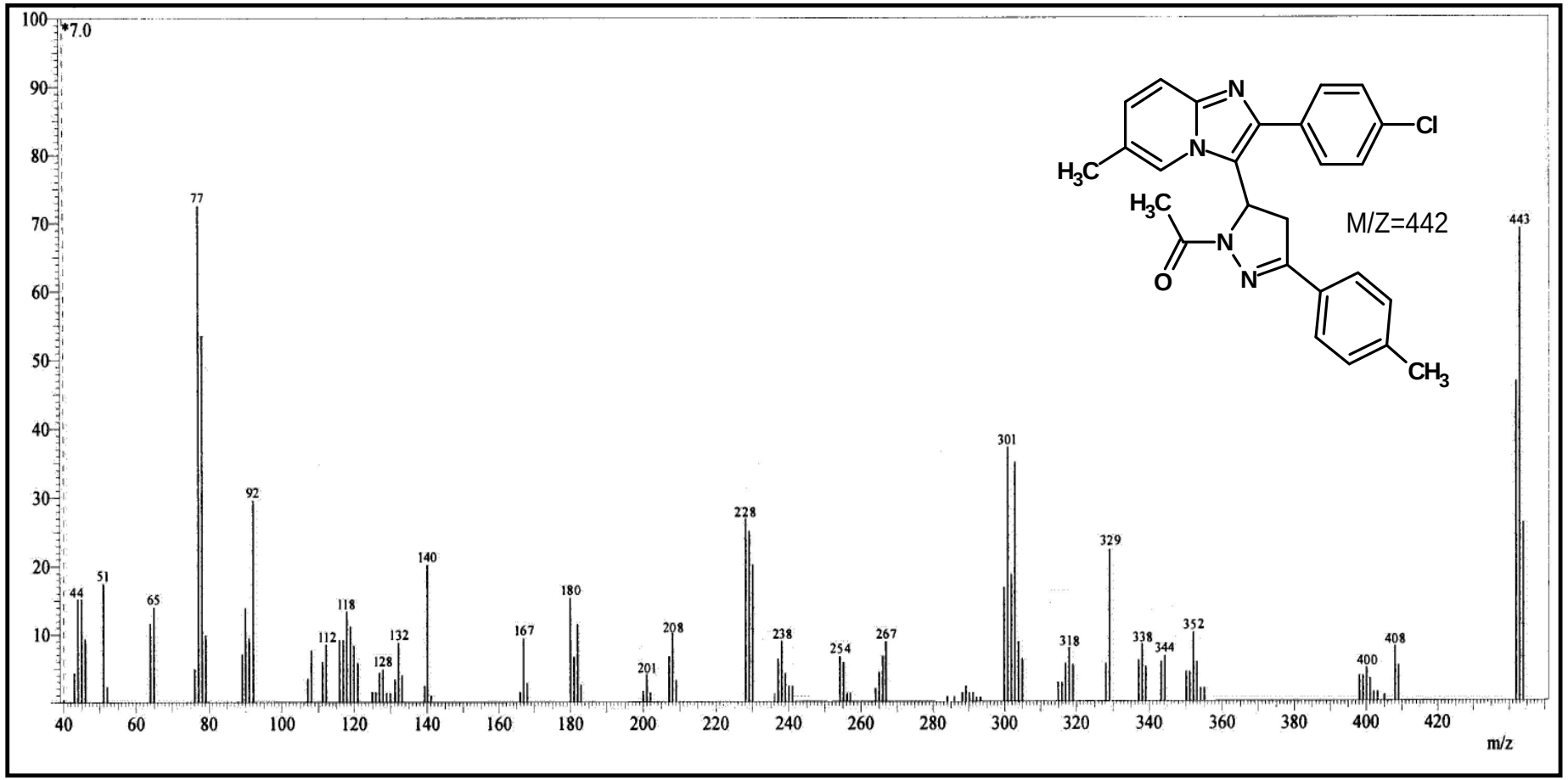
NMR SPECTRAL STUDY OF 2 - (4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL) - 1" –ACETYL -4", 5" – DIHYDROPYRAZOL - 5" – YL] IMIDAZO [1, 2-a] PYRIDINE.

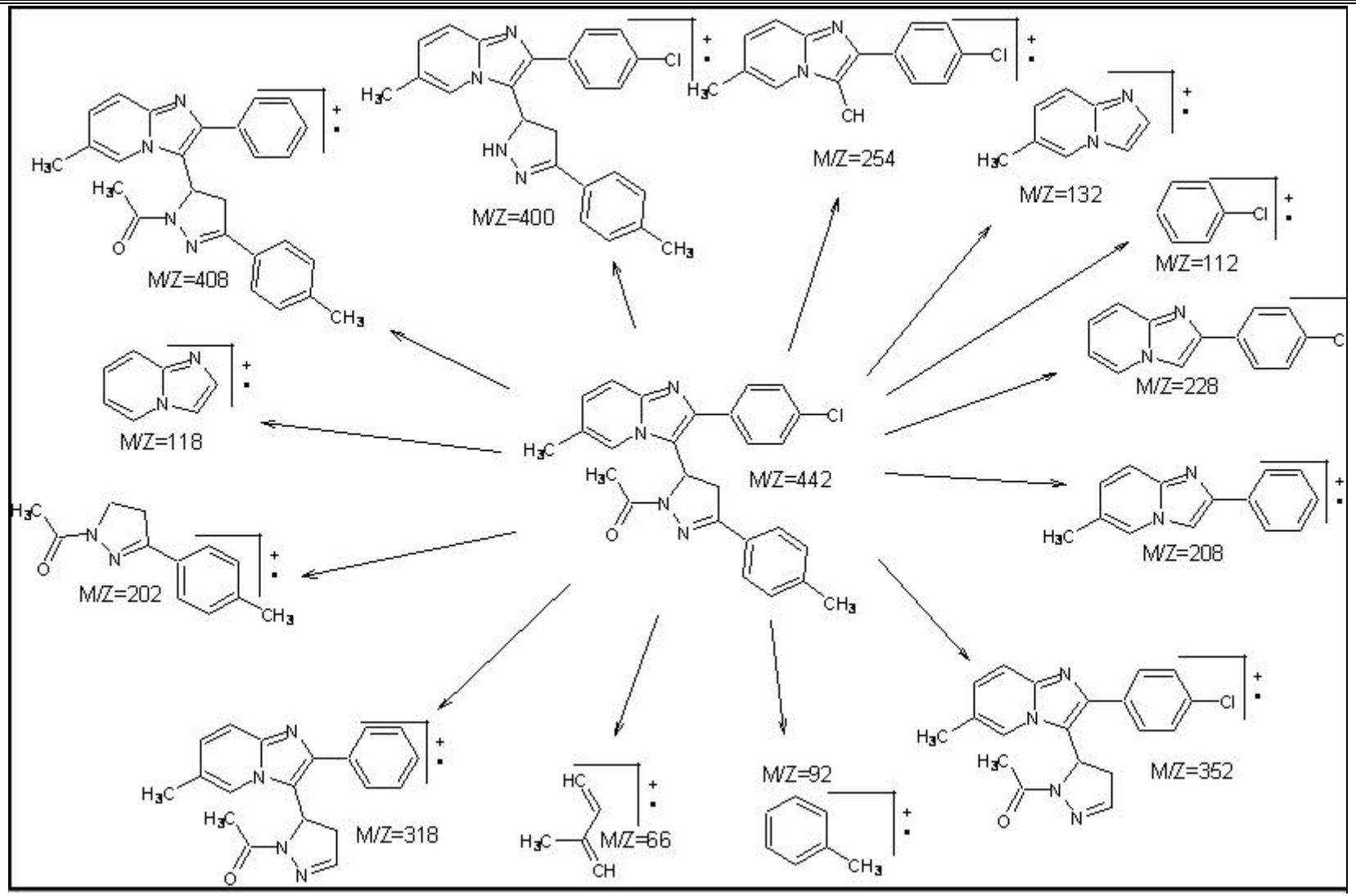


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

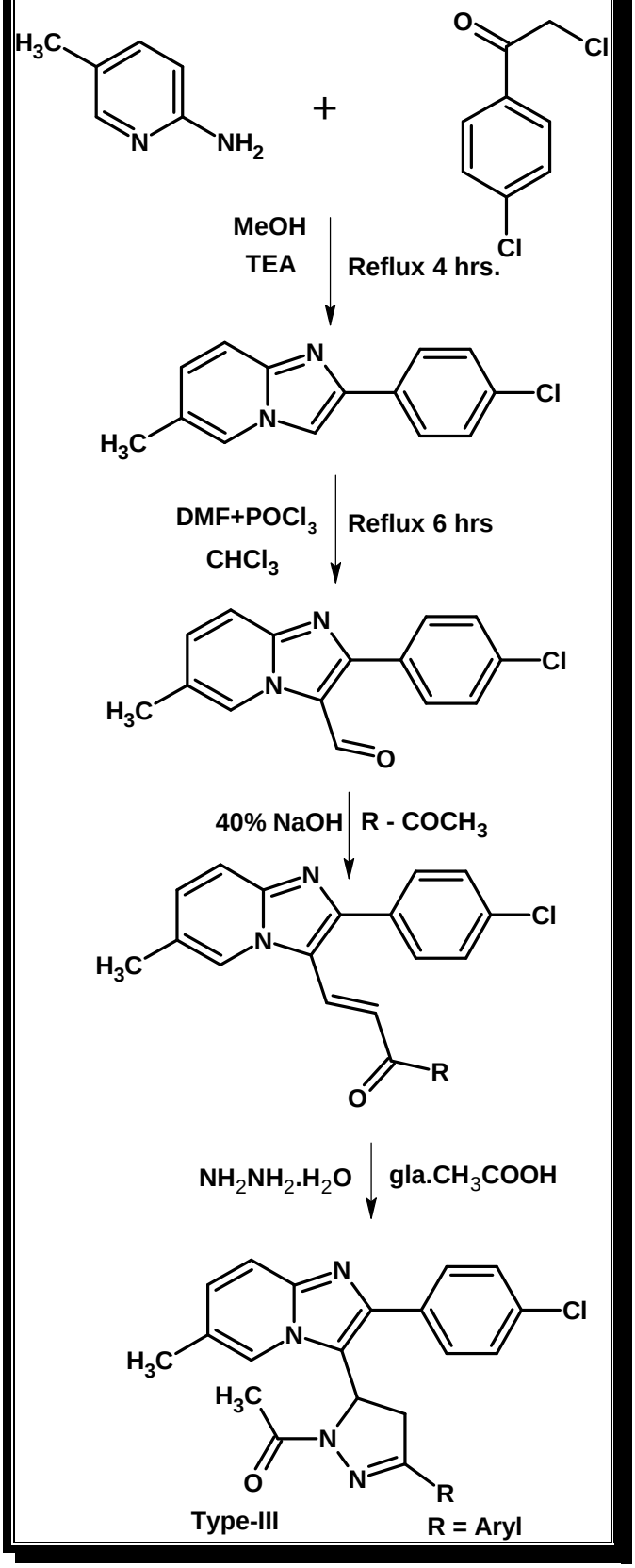
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.28	3H	singlet	Ar-CO-CH_3(k)
2	2.32-2.33	3H	singlet	Ar-CH_3(l)
3	2.52	3H	singlet	Ar-CH_3(m)
4	3.00-3.08	1H	doublet	Ar-H(i)
5	3.51-3.60	1H	doublet	Ar-H(j)
6	5.70-5.76	1H	quatret	Ar-H(h)
7	7.02-7.05	1H	doublet	Ar-H(f)
8	7.37-7.41	2H	doublet	Ar-H(aa')
9	7.51-7.41	2H	doublet	Ar-H(cc')
10	7.85-7.89	3H	doublet	Ar-H(bb',e)
11	8.10-8.14	2H	doublet	Ar-H(dd')
12	8.26	1H	singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 2 - (4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL) - 1" –ACETYL -4", 5" – DIHYDROPYRAZOL - 5" – YL] IMIDAZO [1, 2-a] PYRIDINE.




M/Z=408
M/Z=400
M/Z=254
M/Z=132
M/Z=112
M/Z=228
M/Z=118
M/Z=442
M/Z=208
M/Z=202
M/Z=352
M/Z=318
M/Z=66
M/Z=92

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-(3"-ARYL) -1"-ACETYL-4", 5"-DIHYDROPYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine.

See, Part-I, Section-I ,on page no.37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde.

See, Part-I, Section-I , on page no.37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I,on page no.37

[D] Synthesis of 2-(4'-chlorophenyl)-6-methyl-3-[3"-(4"'-methylphenyl) – 1"-acetyl-4", 5"-dihydropyrazol-5"-yl] imidazo [1, 2-a] pyridines(3i).

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyle) - 2"-propene 1"-one-3-yl]-imidazo [1,2-a]pyridine. (3.88 gm, 0.01 mol) and hydrazine hydrate (0.5 gm, 0.01 mol), glacial acetic acid (2 ml) and methenol was refluxed for 10 hrs. The reaction mixture poured in to crused an ice, filterd and dried it and crystallized from ethanol. Yield 65%, m.p. 203^{o}C.

($C_{26}H_{23}ClN_4O$; Required : C, 70.50; H, 5.23; N, 12.65%; found : C, 70.48; H, 5.20; N, 12.63%;)

Similarly,Other 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl – 1"-acetyl-4", 5"-dihydropyrazol-5"-yl) imidazo [1, 2-a] pyridines were prepared. The physical data are recorded in Table No.3

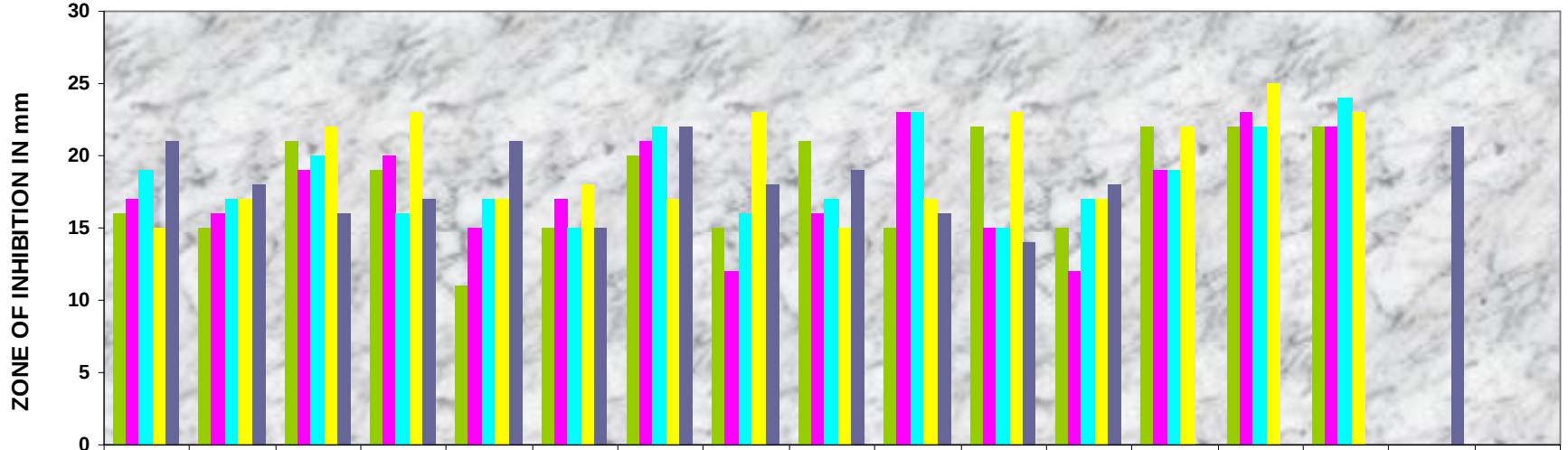
[E] Biological Screening of 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl)-1"- acetyl-4", 5"-dihydropyrazol-5"-yl) imidazo [1, 2-a] pyridines.

Biological Screening testing were carried out as described in Part-I , Section-I. page no.38 The zones of inhibition of test solutions are recorded in Graphical Chart No.3

TABLE CNO. 3 PHYSICAL CONSTANTS OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" - ARYL -1"-ACETYL -4",5"-DIHYDROPYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
3a	C_6H_5-	$C_{25}H_{21}ClN_4O$	428.5	150	58	13.06	13.04
3b	3-Cl-C_6H_4 -	$C_{25}H_{20}Cl_2N_4O$	463.0	190	51	12.09	12.07
3c	4-Cl-C_6H_4 -	$C_{25}H_{20}Cl_2N_4O$	463.0	155	68	12.09	12.07
3d	2-4-$(Cl)_2$-C_6H_3-	$C_{25}H_{19}Cl_3N_4O$	497.5	180	60	11.25	11.23
3e	4 -F-C_6H_4-	$C_{25}H_{20}ClFN_4O$	446.5	145	60	12.54	12.52
3f	4-Br-C_6H_4-	$C_{25}H_{20}BrClN_4O$	507.5	198	55	11.03	11.01
3g	4 -OH-C_6H_4-	$C_{25}H_{21}ClN_4O_2$	441.5	158	64	12.59	12.56
3h	4-NH_2-C_6H_4	$C_{25}H_{22}ClN_5O$	443.5	165	59	15.78	15.76
3i	4-CH_3-C_6H_4-	$C_{26}H_{23}ClN_4O$	442.5	203	65	12.65	12.63
3j	4-OCH_3-C_6H_4-	$C_{26}H_{23}ClN_4O_2$	458.5	200	70	12.21	12.2
3k	3-NO_2-C_6H_4-	$C_{25}H_{20}ClN_5O_3$	473.5	167	54	14.78	14.76
3l	4-NO_2-C_6H_4-	$C_{25}H_{20}ClN_5O_3$	473.5	170	55	14.78	14.76

GRAPHICAL CHART NO. 3 : BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" – ARYL -1"-ACETYL- 4",5"-DIHYDROPYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	3l	Ampicillin	Amoxycillin	Norfloxacin	Greseofulvin	
B.mega	16	15	21	19	11	15	20	15	21	15	22	15	22	22	22	0	0
S.aureus	17	16	19	20	15	17	21	12	16	23	15	12	19	23	22	0	0
E.coli	19	17	20	16	17	15	22	16	17	23	15	17	19	22	24	0	0
S. typhi	15	17	22	23	17	18	17	23	15	17	23	17	22	25	23	0	0
A.niger	21	18	16	17	21	15	22	18	19	16	14	18	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-II

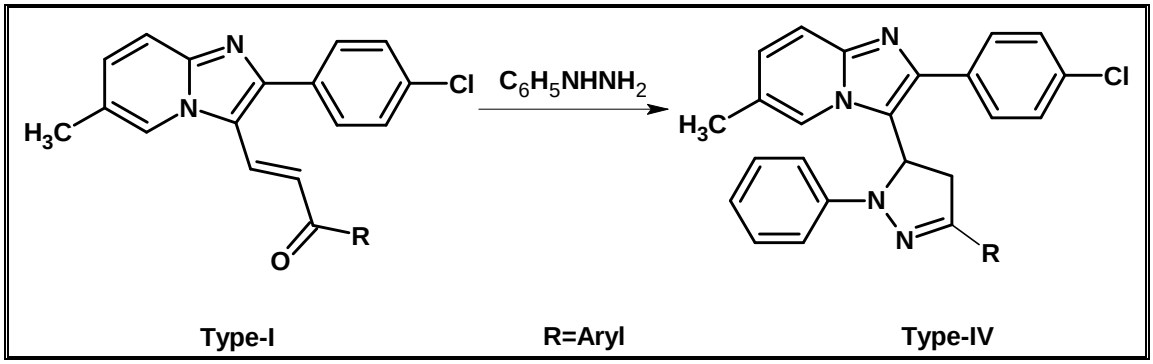
SECTION – II: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" – ARYL -1"-ACETYL-4",5"-DIHYDROPYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E. coli***	***S. typhi***	***A. niger***
		3c-(21)	**3c-(19)**	**3a-(19)**	**3c-(22)**	**3a-(21)**
		3g-(20)	**3d-(20)**	**3c-(20)**	**3d- (23)**	**3e-(21)**
		3i- (21)	**3g-(21)**	**3g-(22)**	**3h-(23)**	**3g- (22)**
		3k-(22)	**3j- (23)**	**3j-(23)**	**3k-(23)**	
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

SECTION-III

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL -3 - (3"- (ARYL)-1"-PHENYL-4",5"DIHYDROPYRAZOL-5"-YL IMIDAZO [1, 2-a] PYRIDINES.

Various derivatives of phenyl pyrazolines exhibit interesting biological properties like anticancer, antiinflammatory, anticonvulsant, antipyretic etc. With a view to prepare more potential phenyl pyrazoline drug compounds, we have carried out the synthesis of phenyl pyrazoline of 2-(4'-chlorophenyl)-6-methyl -3 - (3"- aryl-1"-phenyl-4",5"dihydropyrazol-5"-yl)imidazo [1, 2-a] pyridines of Type-(IV), which have been prepared by the condensation of chalcone of Type-(I) with phenyl hydrazine in presence of piperidine as a catalyst, which have been described as under.

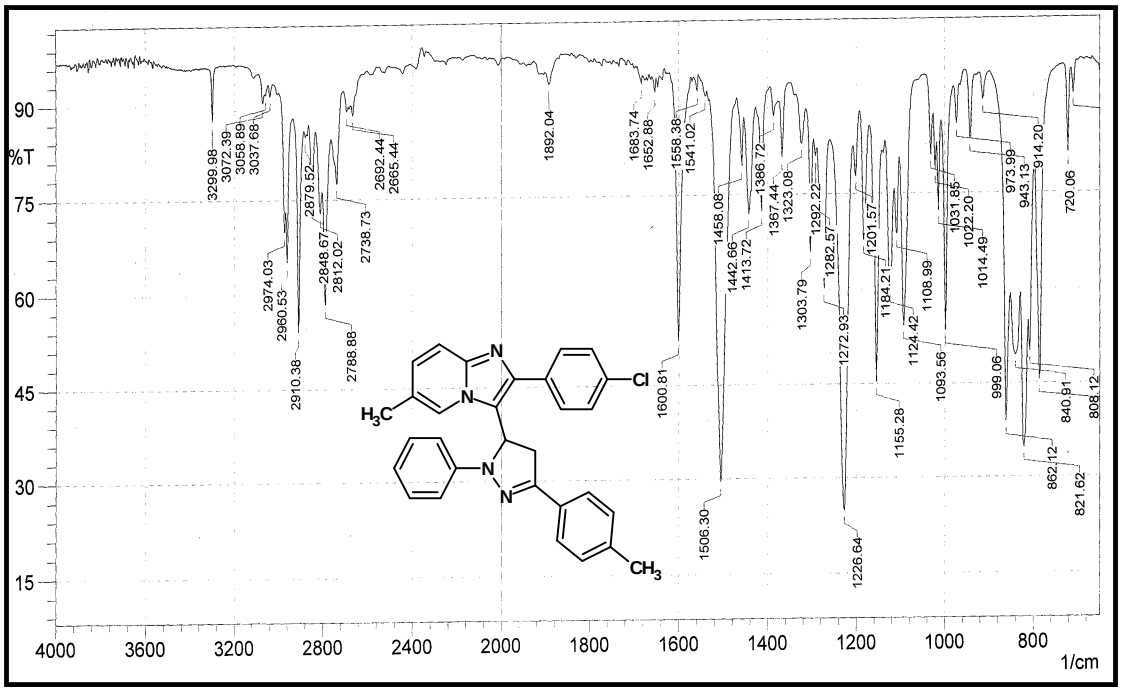


Type-I **R=Aryl** **Type-IV**

The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I ,page no. 41

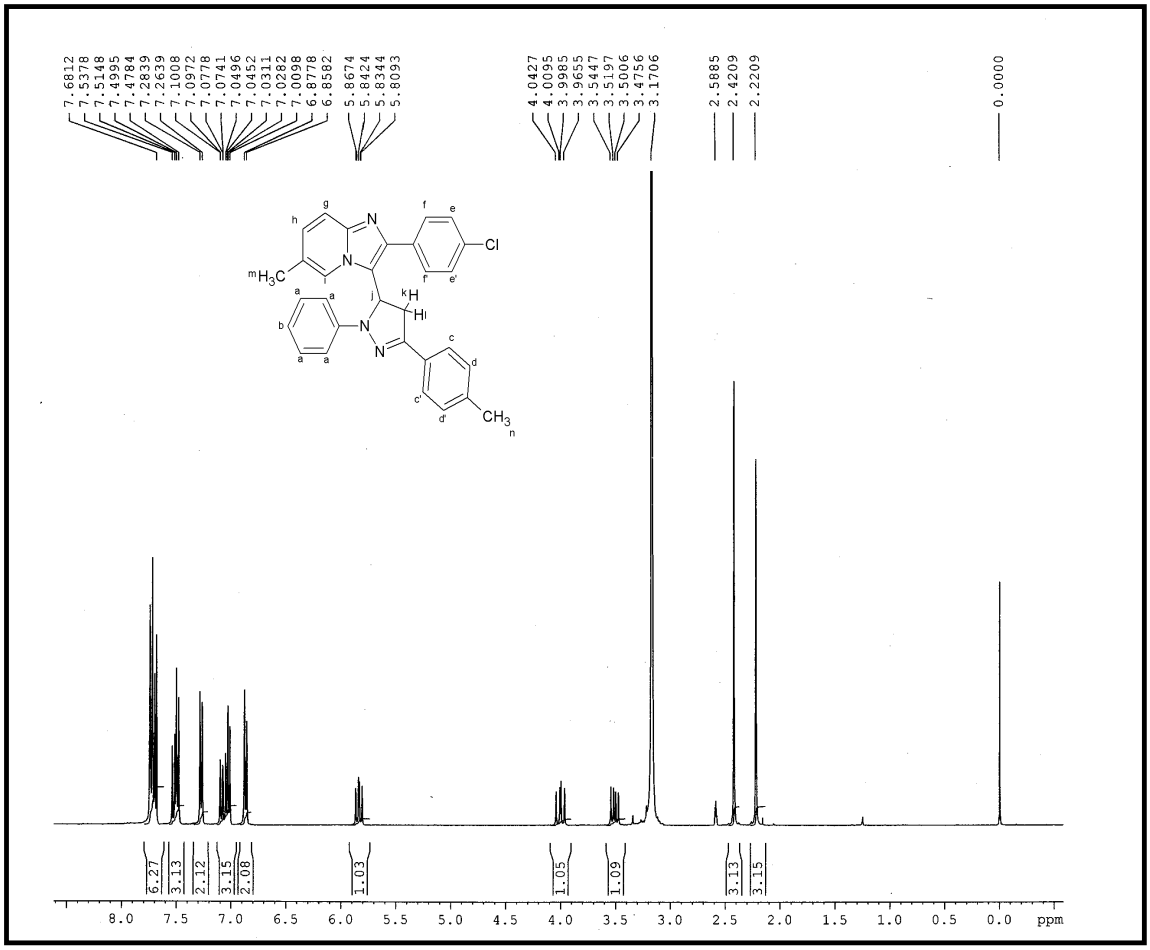
IR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL) - 1" – PHENYL - 4" ,5" – DIHYDROPYRAZOL - 5"-YL]IMIDAZO [1, 2-a] PYRIDINE



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

Type	Vibretion Mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2974	2990-2850	648
	C-H str. (sym.)	2881	2880-2860	"
	C-H def. (asym.)	1442	1470-1435	"
	C-H def. (sym.)	1386	1390-1370	"
Aromatic	C-H str.	3037	3090-3030	"
	C=C str	1506	1600-1450	"
	C-H i.p. (def.)	1155	1300-1100	"
Pyrazoline	C-N str	1226	1230-1020	649
	C=N str	1558	1650-1550	"
	-CH-$(CH)_2$ str.	2788	2850-1790	"
Imidazo[1,2-a] pyridine	C-N str.	1093	1220-1020	"
	C=N str.	1600	1612-1593	"
Halide	C-Cl str.	720	600-800	"

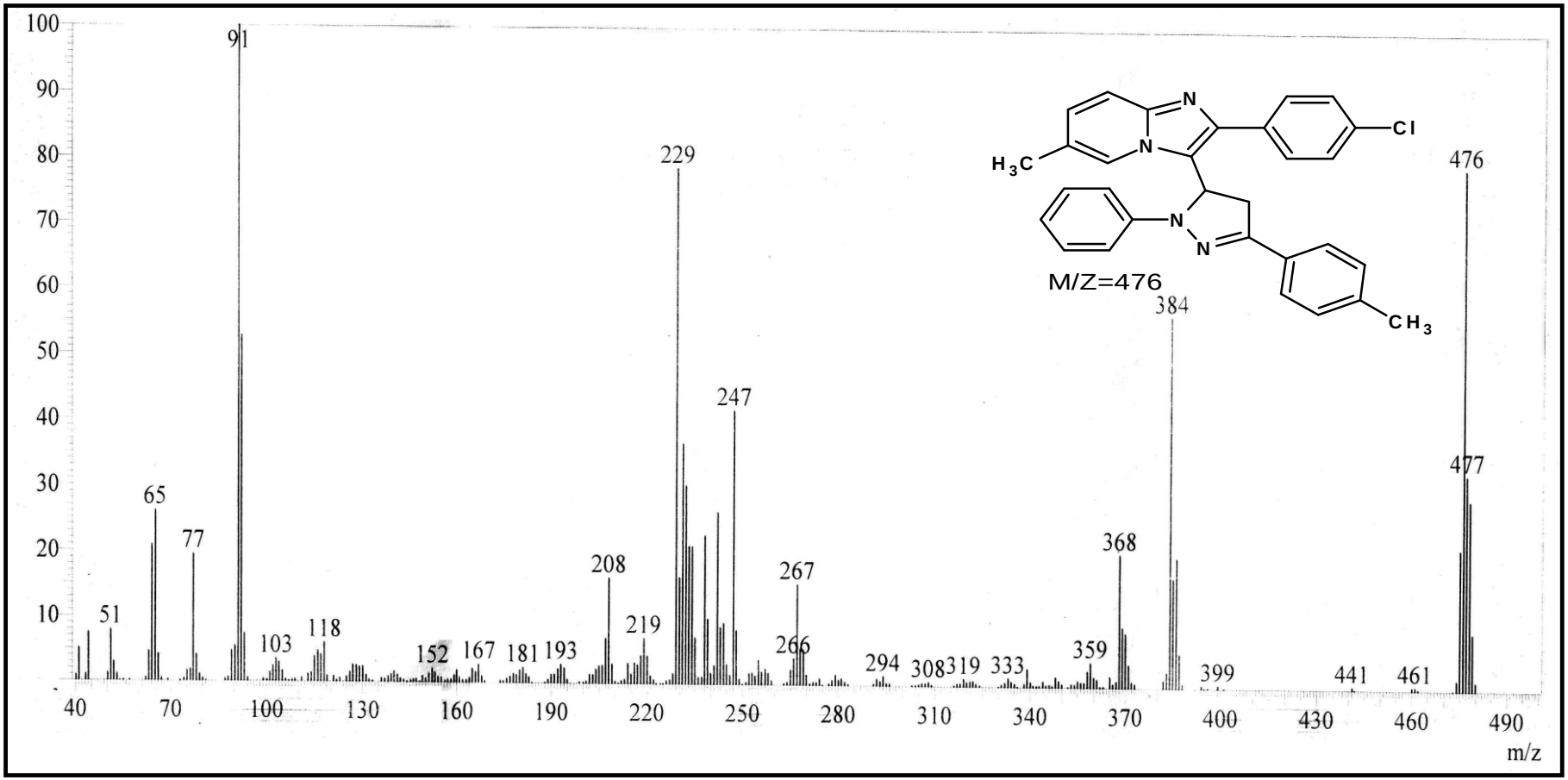
NMR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'- METHYLPHENYL) - 1" – PHENYL - 4",5" – DIHYDROPYRAZOL -5"-YL]IMIDAZO [1, 2-a] PYRIDINE.

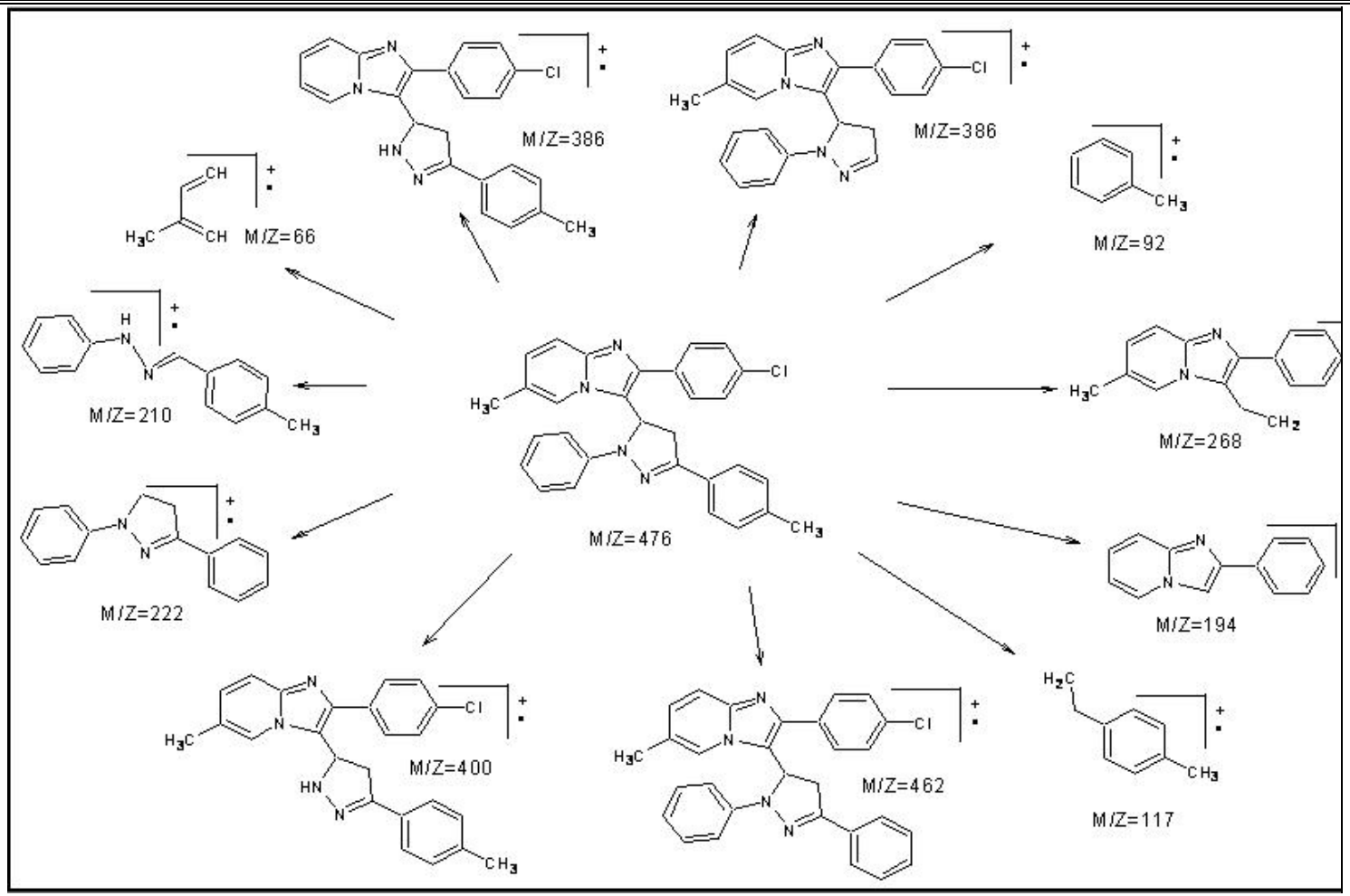


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

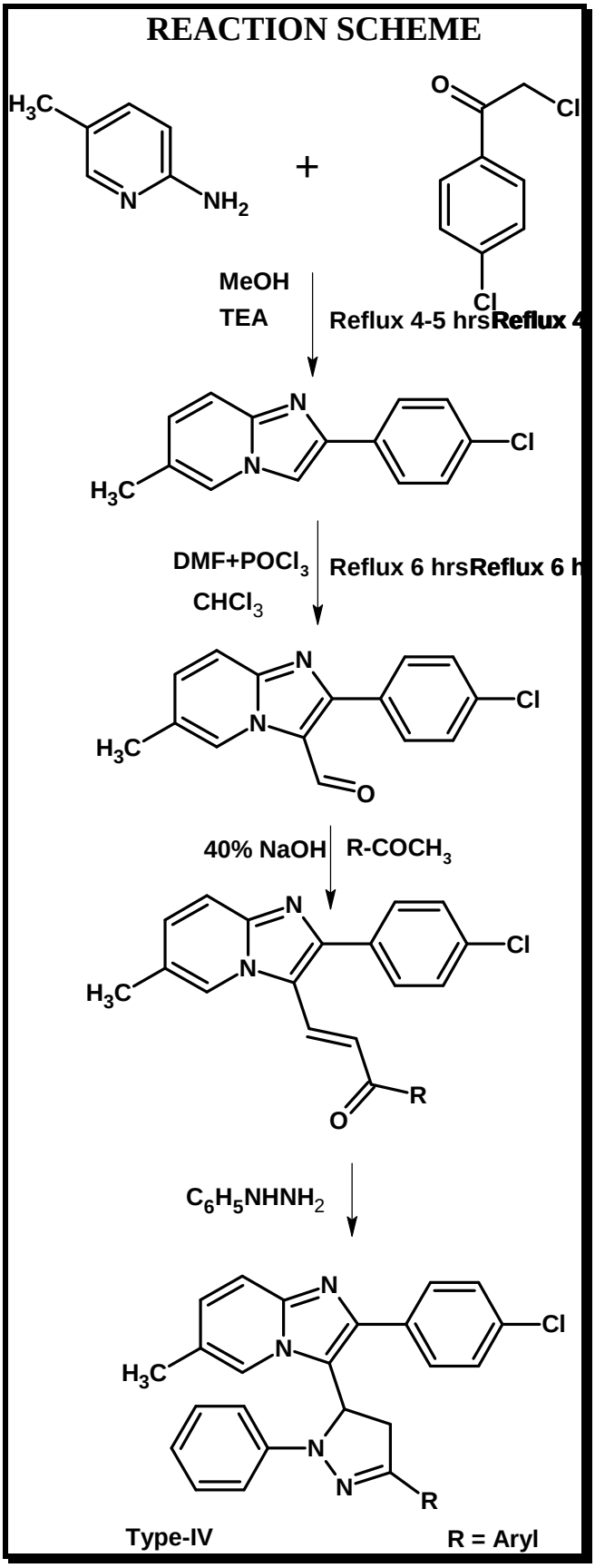
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.33	3H	Singlet	Ar-CH_3(k)
2	2.43	3H	Singlet	Ar-CH_3(i)
3	4.24	3H	Singlet	Ar-OCH3(j)
4	7.17-7.20	1H	Doublet	Ar-H(f)
5	7.29-7.31	4H	Doublet	Ar-H(aa',cc')
6	7.44	1H	Singlet	Ar-H(h)
7	7.55-7.56	2H	Doublet	Ar-H(bb'')
8	7.63-7.65	1H	Doublet	Ar-H(e)
9	7.69	1H	Singlet	Ar-H(g')
10	7.91-7.93	2H	Doublet	Ar-H(dd')

MASS SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'- METHYLPHENYL) - 1" – PHENYL - 4",5" – DIHYDROPYRAZOL -5"YL]IMIDAZO [1, 2-a] PYRIDINE.




M/Z=386
M/Z=386
M/Z=66
M/Z=92
M/Z=210
M/Z=268
M/Z=476
M/Z=222
M/Z=194
M/Z=400
M/Z=462
M/Z=117

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-(3"-(ARYL)-1"-PHENYL-4",5"-DIHYDROPYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6-methyl-2-(-4'chlorolphenyl)imidazo[1,2-a]pyridine-3-carbaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I,on page no. 37

[D] Synthesis of 2-(4'-chlorophenyl)-6-methyl-3-[3"-(4"'-methylphenyl)-1"-phenyl-4",5"-dihydropyrazol-5"-yl] imidazo [1, 2-a] pyridine(4i).

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (4.21g ,0.01 mol), and phenyl hydrazine (1.18g ,0.01 mol) in 25 ml methanol reflux for 10 hrs. poured the reaction mass in to the ice chilled water. The product was filter dryied and recrystllized from ethanol. Yield 78 %, m.p.185 ^{o}C,

($C_{30}H_{25}ClN_4$; Required : C, 75.54; H, 5.28; N, 11.75%; found : : C, 75.52; H, 5.25; N, 11.73%;)

Similarly Others 2 - (4' – chlorophenyl) 6-methyl-3-(3"-(aryl)-1"-phenyl 4",5"-dihydropyrazol-5"-yl) imidazo [1, 2-a] pyridines. other were prepared. The physical data are recorded in Table no.4.

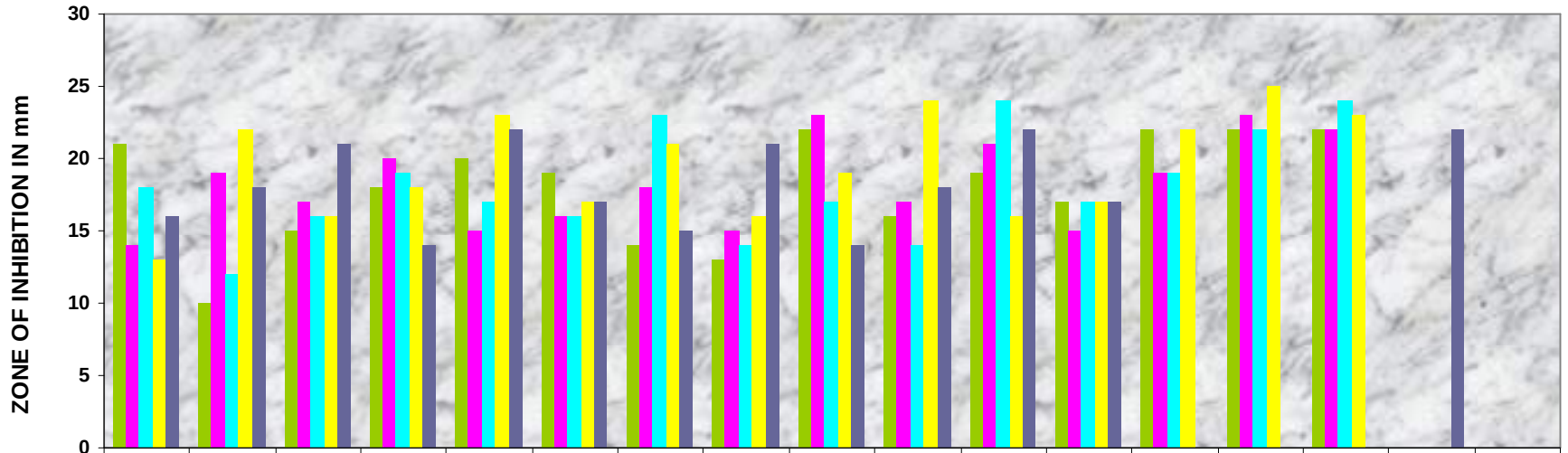
[E] Biological screening of 2-(4'-chlorophenyl)-6-methyl-3-(3"-aryl-1"-phenyl-4",5"-dihydropyrazol-5"-yl) imidazo [1, 2-a] pyridines.

Biological screening were carried out as described in Part-I, Section-I,page no.38, The zones of inhibition of test solutions are recorded in Graphical Chart no.4.

TABLE NO. 4 PHYSICAL CONSTANTS OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" – ARYL -1"-PHENYL-4",5"-DIHYDRO PYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
4a	C_6H_{5-}	$C_{29}H_{23}ClN_4$	462.5	165	60	12.10	12.08
4b	3-Cl-C_6H_4 -	$C_{29}H_{22}Cl_2N_4$	497.0	168	65	11.26	11.24
4c	4-Cl-C_6H_4 -	$C_{29}H_{22}Cl_2N_4$	497.0	175	68	11.26	11.24
4d	2-4-$(Cl)_2$-C_6H_{3-}	$C_{29}H_{21}Cl_3N_4$	531.5	160	55	10.53	10.51
4e	4 -F-C_6H_{4-}	$C_{29}H_{22}ClFN_4$	480.5	175	63	11.65	11.64
4f	4-Br-C_6H_{4-}	$C_{29}H_{22}BrClN_4$	541.5	160	72	10.34	10.32
4g	4 -OH-C_6H_{4-}	$C_{29}H_{23}ClN_4O$	478.5	163	60	11.70	11.68
4h	4-NH_2-C_6H_4	$C_{29}H_{24}ClN_5$	477.5	163	75	14.65	14.63
4i	4-CH_3-C_6H_{4-}	$C_{30}H_{25}ClN_4$	476.5	185	78	11.75	11.73
4j	4-OCH_3-C_6H_{4-}	$C_{30}H_{25}ClN_4O$	492.5	165	66	11.36	11.33
4k	3-NO_2-C_6H_{4-}	$C_{29}H_{22}ClN_5O_2$	507.5	185	65	13.79	13.78
4l	4-NO_2-C_6H_{4-}	$C_{29}H_{22}ClN_5O_2$	507.5	195	68	13.79	13.78

GRAPHICAL CHART NO. 4 : BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" - ARYL –1"- PHENYL-4",5"- DIHYDRO PYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.



	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Ampicillin	Amoxycillin	Norfloxacin	Greseofulvin	
B.mega	21	10	15	18	20	19	14	13	22	16	19	17	22	22	22	0	0
S.aureus	14	19	17	20	15	16	18	15	23	17	21	15	19	23	22	0	0
E.coli	18	12	16	19	17	16	23	14	17	14	24	17	19	22	24	0	0
S. typhi	13	22	16	18	23	17	21	16	19	24	16	17	22	25	23	0	0
A.niger	16	18	21	14	22	17	15	21	14	18	22	17	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-II

SECTION – III: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL) – 6 – METHYL – 3 - (3" - ARYL –1"-PHENYL-4",5"-DIHYDRO PYRAZOL-5"-YL)IMIDAZO [1, 2-a] PYRIDINES.

	Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
	B. mega	***S. aureus***	***E. coli***	***S. typhi***	***A. niger***
	4a-(21)	4b-(19)	4a-(18)	4b-(22)	4c-(21)
	4e-(20)	4d-(20)	4d-(19)	4e-(23)	4e-(22)
	4i- (22)	4i- (23)	4g-(23)	4g- (21)	4h-(21)
		4k-(21)	4k-(24)	4j- (24)	4k-(22)
Ampicillin (50 µg)	22	19	19	22	--
Chloramphenicol (50 µg)	22	23	22	25	--
Norfloxacin (50 µg)	22	22	24	23	--
Greseofulvin (50 µg)	--	--	--	--	22

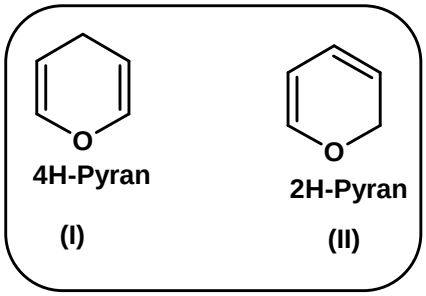
PART-III

STUDIES ON CYNOPYRANS

STUDIES ON CYANOPYRANS

INTRODUCTION

Heterocyclic compounds such as pyran derivatives continue to be a rich source of innovative chemistry because a number of pharmaceutical, dyestuff, sweety-smelling substances, insecticide possess this ring system. Pyran ring system is also present in large number of neturally ocuring coloured compounds, in vitamin-E, hemorrhagic compounds in cloves, in certain alkaloids and other substances.



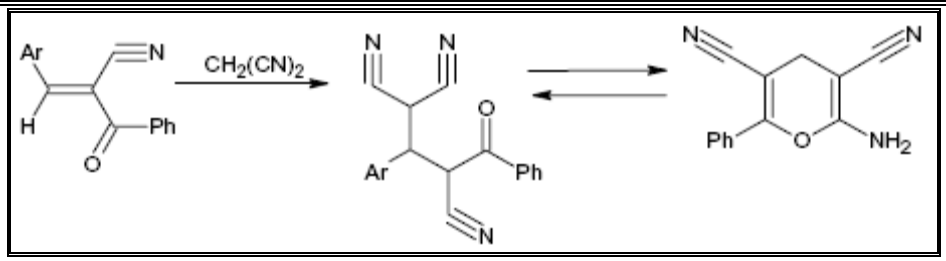
Pyran is a doubly unsaturated six membered ring system with a single oxygen as hetero atom. The two double bonds may be conjugated as α,β. or 1,2-pyran or isolated as in α,δ or 1,4-pyran.

A degree of stabilisation of the pyran nucleus is achieved by substituting phenyl group in the 2 or 4 and preferably also in the 6 position.

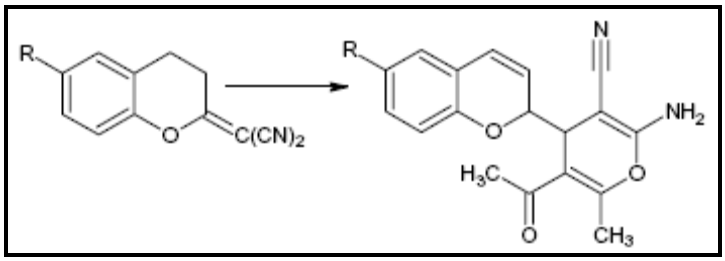
SYNTHETIC ASPECT

Various methods for the preparation of pyran derivatives have been cited in the literature.[190-199]

1. Reaction between α,β-unsaturated carbonyl system with $(CH_2CN)_2$ led to corresponding 2-amino-3-cyano-4H-pyrans.[200]
2. Some alkylidene 2H-pyrans were synthesized[201] by thermal electrolyting ring closure of divinyl alkenyl.
3. J. Svete et al.[202] have synthesized fused 3-amino-2H-pyran-2-ones by solid phase synthesis and by solution phase paralled synthesis.
4. N. M. Abed and co-workers[203] have synthesized pyran derivatives.

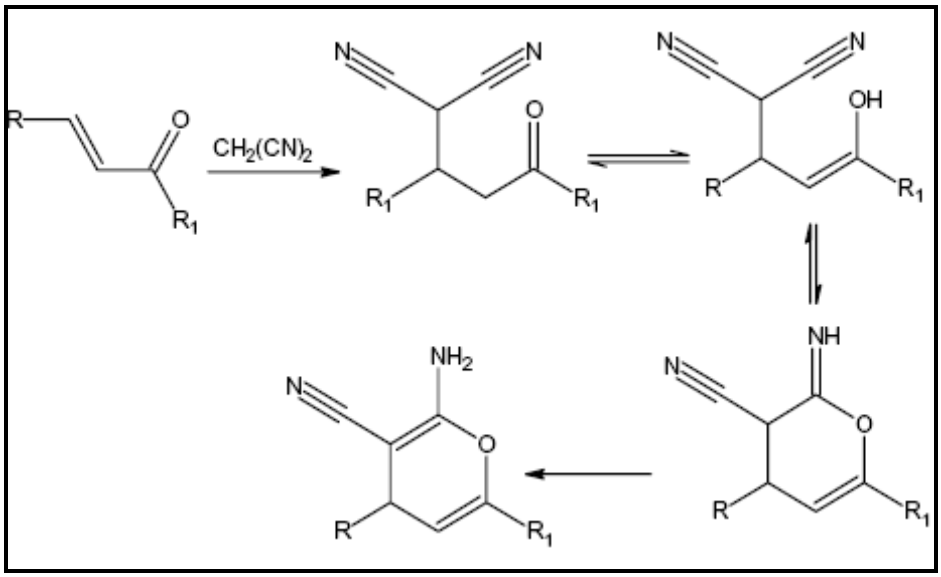


5. H. Abdel Ghany et al.[204] have prepared new pyran derivatives by condentation of 2-coumarylidene malononitriles with active methylene containing compound.



MECHANISM

The reaction of malononitrile with α,β -unsaturated system leads to the formation of cyano 4H-pyran via Michael addition as shown in figure.



THERAPEUTIC IMPORTANCE

Literature survey revealed that various pyrans have resulted in many potential drugs and are known to possess a broad biological activity such as,

1. Anti HIV[205, 206]
2. Antifungal[207-209]

3. Antiallergic[210]

4. Analgesic[211]

5. Antagonist[212,213]

6. Antitumor[214]

7. CNS active agent[215]

8. Cytotoxic[216]

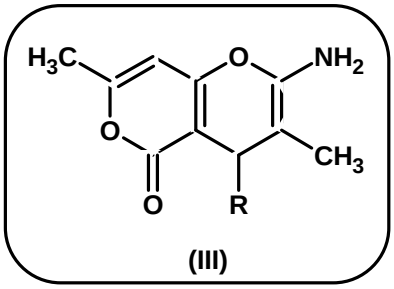
9. Inhibitors of cell proliferation[217]

10. Gastric acid secretion inhibitor[218]

11. Antimicrobial[219]

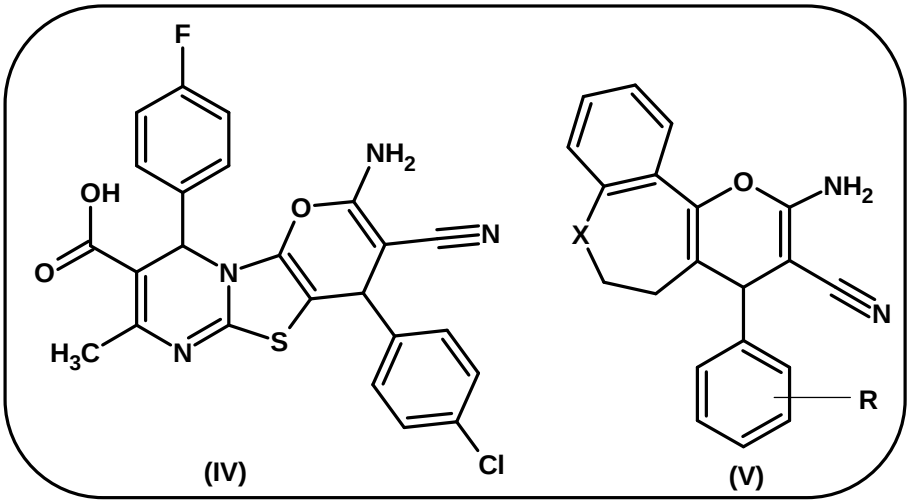
12. Hypolipidemic[220]

Zwaagstra Mariel[221] have newly synthesised pyran derivatives and tested for antiashamatic activity. Boyer Frederick et. al.[222] have prepared some new- 2-amino-3-cyano-4H-pyran and reported anti HIV agent and antiviral activity. Y. U. A. Sharanin et al.[223] have suggested new 2-amino-3-cyano-4H-pyran derivatives (III).



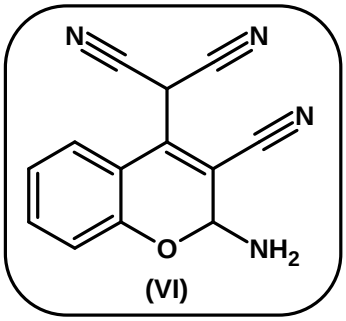
(III)

Synthesis and anticancer activity of pyran (IV) containing flourine have been reported by Mohamed S. El-gaby et. al.[224] 4H-pyran of type (V) were prepared to enhance the anticancer and anti- HIV activity.



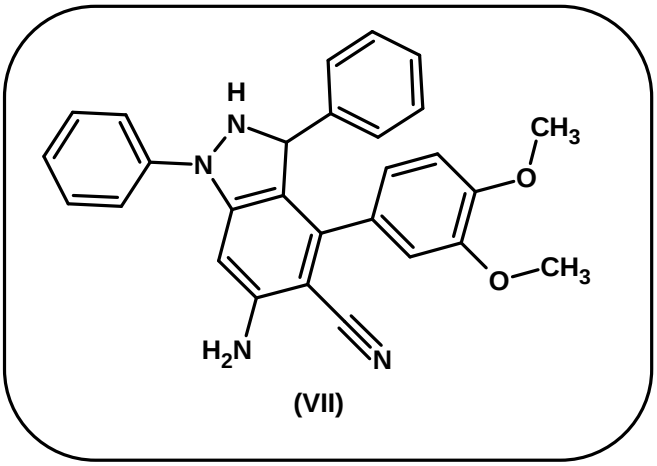
(IV) (V)

Some of the pyran derivatives (VI) have been patented for their use as antihypertensive[225], antiestogens[226], antagonist[227,228], antitumor[229] and antiviral[230] activities. Synthesis and biological activity of pyran ring system have been reported by O'Brien et al.[231]



(VI)

El-Subbagh and co-workers[232] have synthesized cyanopyran derivatives and showed their antiviral activity. Corbou Romuld et al.[233] have reported cyanopyran derivatives (VII) which have significant pharmacological activity.



(VII)

Moreover, Fathy F. Abdel-Latif et al.[234] have reported the synthesis of 2-amino-3-cyanopyran derivatives and studied their biological activity. P. M. Zhu et. al.[235] have prepared biologically active 2-amino pyran derivatives.

Y. Iwahashi and co-workers[236] have synthesized 4-hydroxy-4H-furo[3,2c]pyran-2(6H)-one, is one of the best characterized and most widely disseminated mycotoxinsfound in agriculrueal products. Y. Osada et al.[237] investigated antioxidative activity of 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one.

Recently, T. Hanafusa et al.[238] have reported some new cyanopyran as functional promoter upstream p53 regulatory sequence of $IGFBP_3$ that is silenced by tumor specific methylation. H. S. Williamson et al.[239] have described pyran as a truncated protein from enteropathogenic Escherichia coli acts as an antagonist. H. Yeo and Y.Li et al.[240] have described the synthesis and antiviral activity of helioxanthin analogues. M. H DavidCordonnier. et al.[241] have synthesized pyrano compounds as antitumor agents.

Morever, C. Asche et al.[242] have reported some novel cyanopyran for antitumour activity and structure-activity relationships of 5H-benzo[b]carbazoles. C. H Moon et al.[243] have found some novel benzopyran analog, attenuates hypoxia-induced cell death via mitochondrial KATP channel and protein kinase C-epsilon in heart-derived H9c2 cells. A.Y Howe. et al.[244] have described some novel nonnucleoside inhibitor of hepatitis C virus RNA-dependent RNA polymerase. K. Y. Kim et al.[245] investigated anti-apoptotic action of (2S,3S,4R)-N"-cyano-N-(6-amino-3,4-dihydro-3-hydroxy-2-methyl-2-dimethoxymethyl-2H-benzopyran-4-yl)-N'-benzylguanidine.

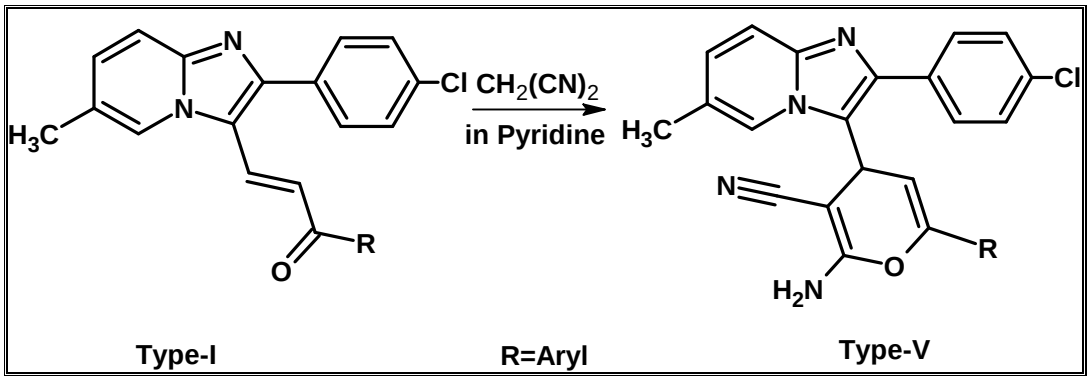
With this in view and in continuation of our research worck on new heterocyclics of pharmacological interest, we report here in some new cynopyran derivatives.

SECTION – I :SYNTHESIS AND BIOLOGICAL SCREENING OF 2"-AMINO -4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL-4"-H-PYRAN-3"- CARBONITRILES

SECTION – I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL- 4"-H-PYRAN-3"- CARBONITRILES.

3-Cyano-4,6-disubstituted 4H-pyrans are endowed with a variety of pharmacodynamic activities such as anticonvulsant, antiinflammatory, antihypertensive, antitumor etc. Looking to the interesting properties of cyanopyrans, it was considered worthwhile to synthesis some new 2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl- 4"-H-pyran-3"-carbonitriles of Type (V) have been synthesized by condensation of chalcone of Type (I) with malononitrile in presence of pyridine as shown below.

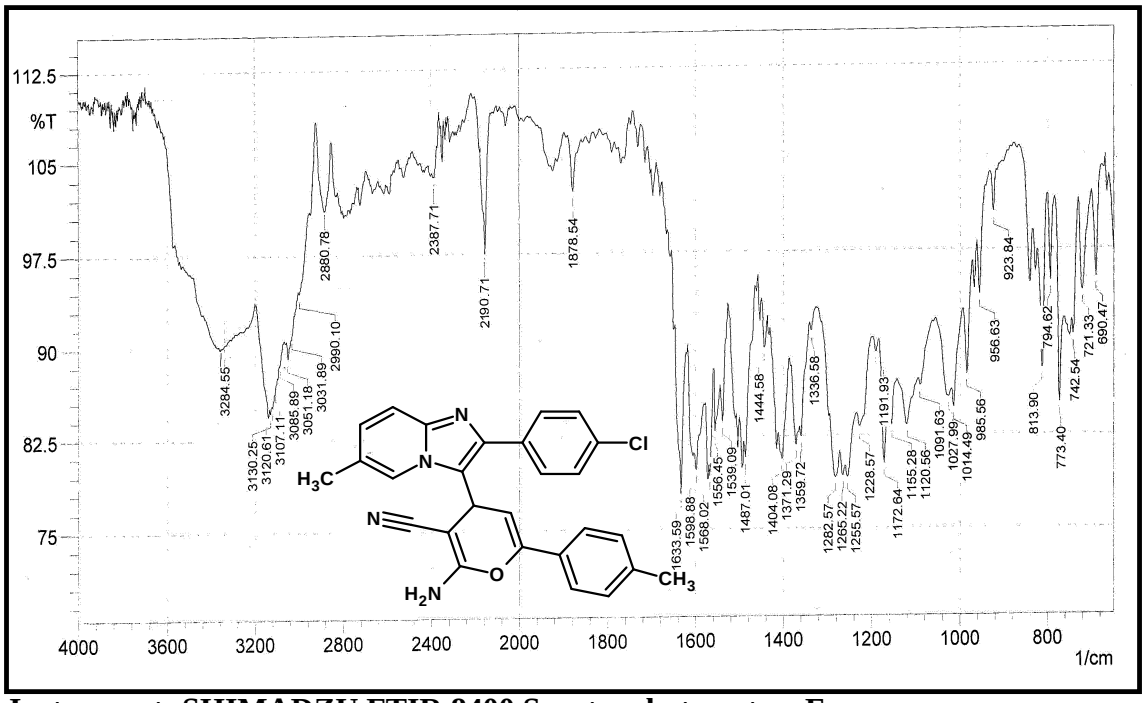


Type-I **R=Aryl** **Type-V**

The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I,page no. 41

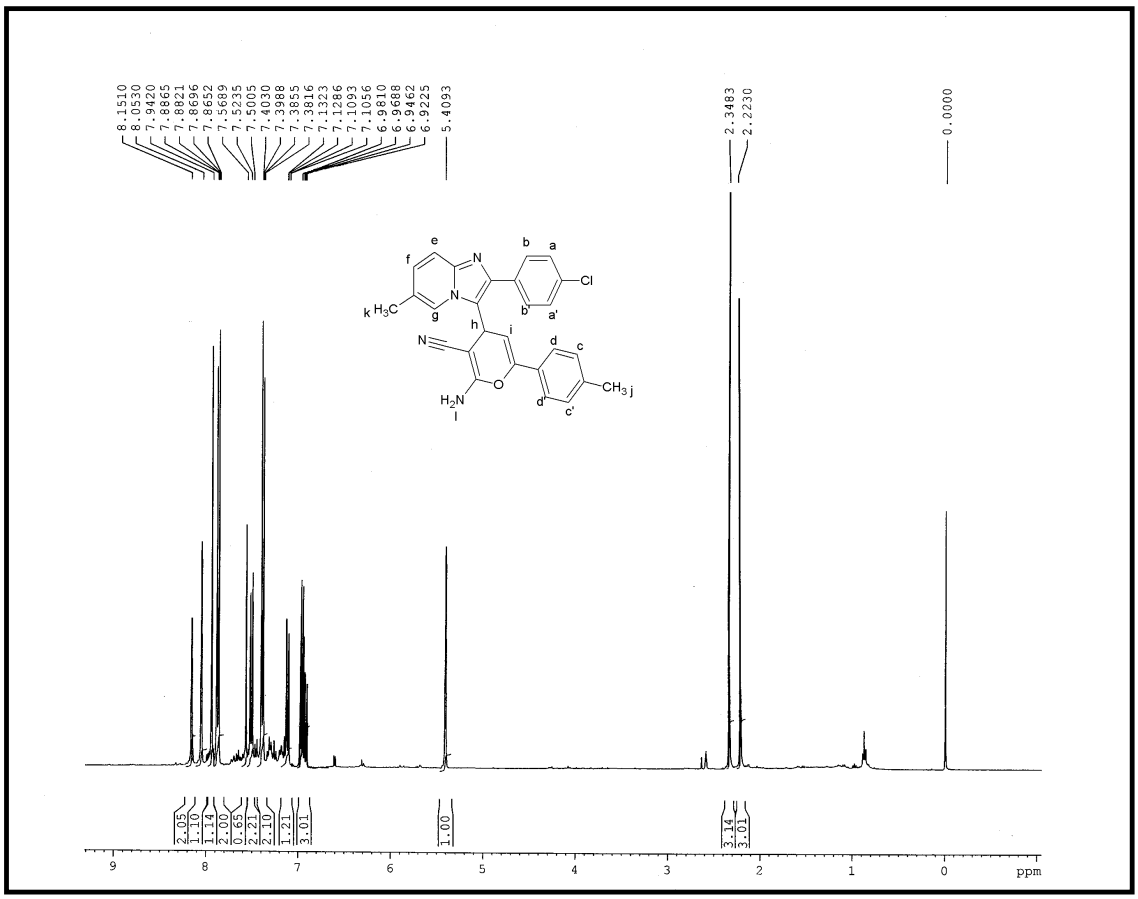
IR SPECTRAL STUDY OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(4"'-METHYLPHENYL)- 4"-H-PYRAN-3"- CARBONITRILE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2990	2990-2850	648
	C-H str. (sym.)	2880	2880-2860	"
	C-H def. (asym.	1444	1470-1430	"
	C-H def. (sym.)	1359	1395-1370	"
Aromatic	C-H str.	3051	3090-3030	"
	C=C str	1487	1600-1450	"
	C-H i.p. (def.)	1120	1300-1100	"
Imidazo[1,2-a] pyridine	C=N str.	1598	1612-1593	649
	C-N str.	1027	1220-1020	"
Pyrane	N=H str. (-NH_2)	3284	3350-3250	"
Nitril	C=N str.	2190	2240-2120	"
	C-N str.	1633	1650-1520	"
Ether	C-O-C	1228	1260-1200	"
Halide	C-Cl str.	721	800-600	"

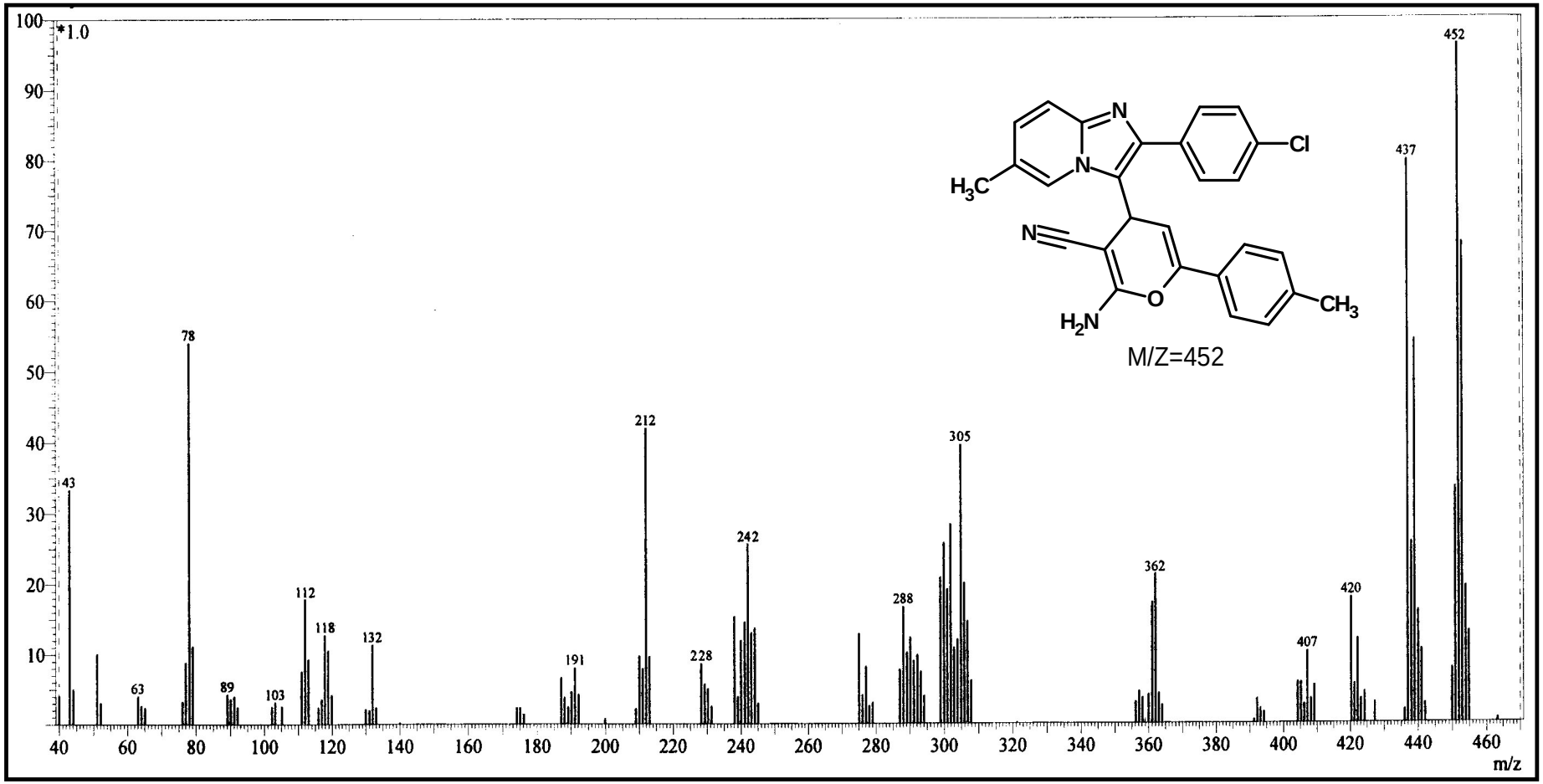
NMR SPECTRAL STUDY OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(4"'-METHYLPHENYL)- 4"-H-PYRAN-3"- CARBONITRILE.

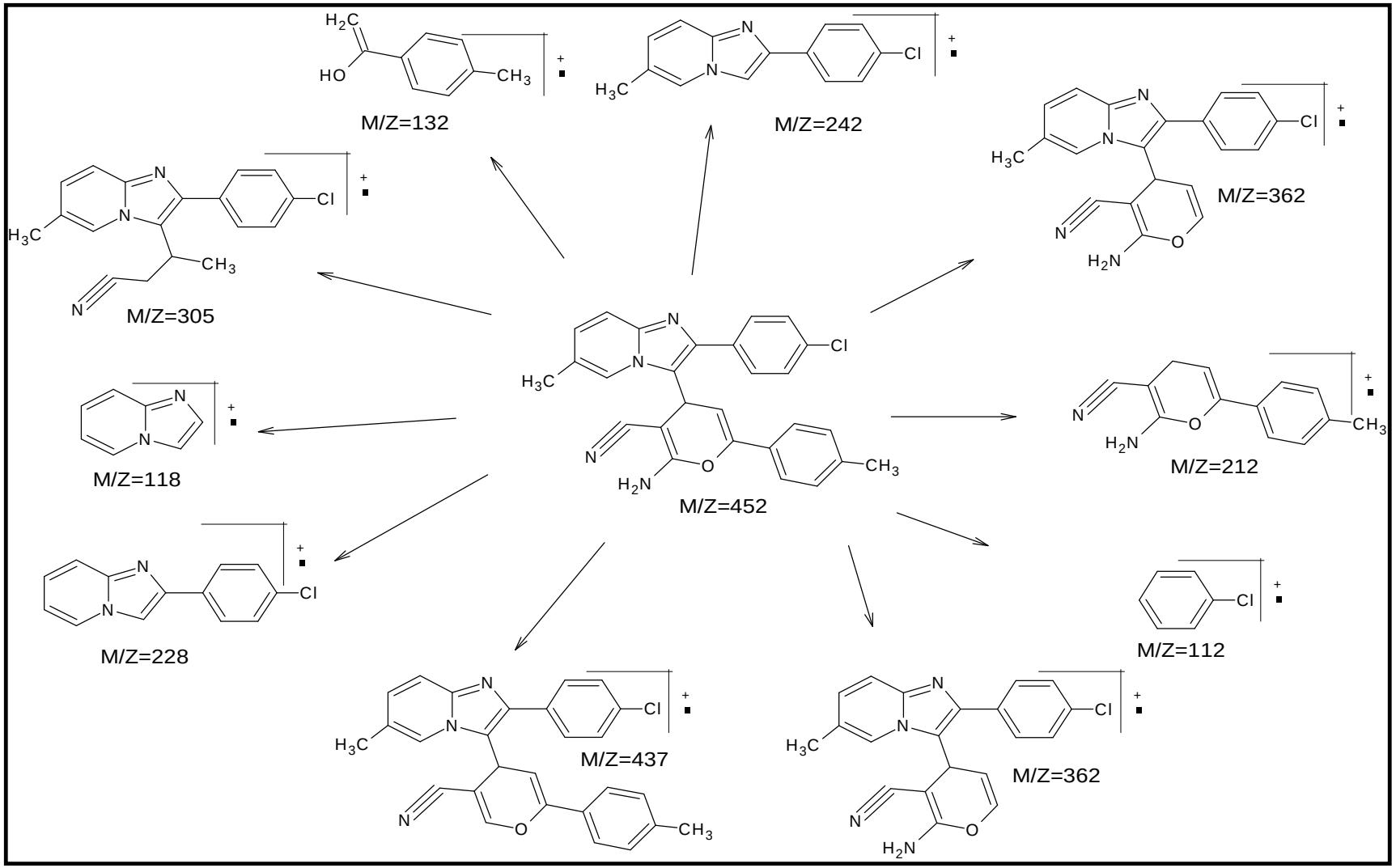


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

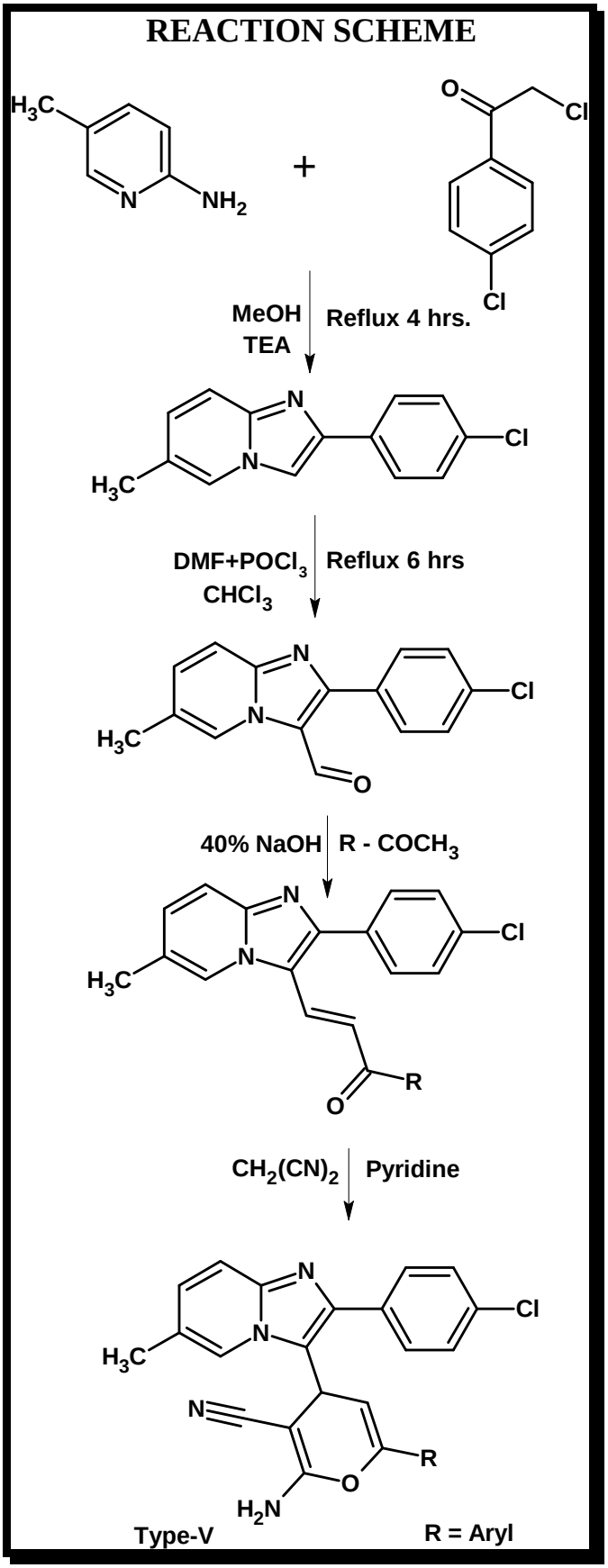
Signal No.	Signal Position (δppm)	Relative No.of protons	Multiplicity	Inference
1	2.33	3H	singlet	Ar-CH_3(k)
2	2.43	3H	singlet	Ar-CH_3(i)
3	4.24	3H	singlet	Ar-OCH3(j)
4	7.17-7.20	1H	doublet	Ar-H(f)
5	7.29-7.31	4H	doublet	Ar-H(aa',cc')
6	7.44	1H	singlet	Ar-H(h)
7	7.55-7.56	2H	doublet	Ar-H(bb'')
8	7.63-7.65	1H	doublet	Ar-H(e)
9	7.69	1H	singlet	Ar-H(g')
10	7.91-7.93	2H	doublet	Ar-H(dd')

MASS SPECTRAL STUDY OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(4'''-METHYLPHENYL)- 4"-H-PYRAN-3"- CARBONITRILE.




M/Z=132
M/Z=242
M/Z=362
M/Z=305
M/Z=452
M/Z=212
M/Z=118
M/Z=228
M/Z=112
M/Z=437
M/Z=362

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL- 4"-H-PYRAN-3"- CARBONITRILES

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyle)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no.37

[D] Synthesis of 2"-amino-4"-[2-(4'-chlorophenyl)-6-methylimidazo[1, 2-a] pyridin-3-yl]-6"-(4"'-methylphenyl)-4"-H-pyran-3"-carbonitrile(5i).

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (2.74 gm, 0.01 mol) and malononitrile (0.66gm, 0.01 mol) in pyridine (20 ml), was heated under reflux for 12 hrs. on oilbath. The reaction mixture was cooled and poured on to crushed ice. The product was neutralized with 20% HCl, where upon a solid separated out, which was filtered dried and crystallized from ethanol. Yield 65%, m.p.165^{o}C

($C_{27}H_{21}ClN_4O$; Required : C, 71.60; H, 4.67; N, 12.37%; found C, 71.58; H, 4.65; N, 12.35%;)

Similarly, other 2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl - 4"-H-pyran-3"- carbonitriles were prepared. The physical data are recorded in Table No.5

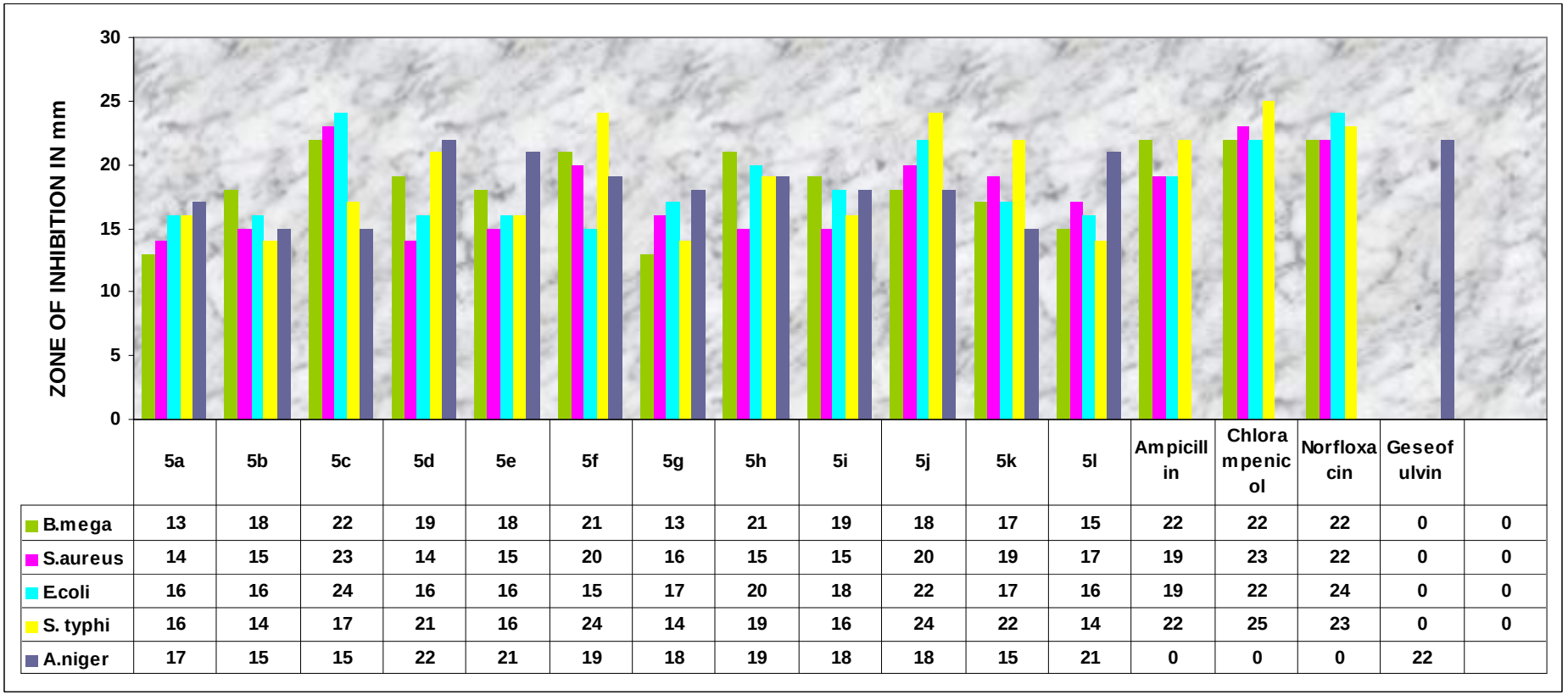
[E] Biological Screening of 2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"- (aryl) - 4"-H-pyran-3"- carbonitriles.

Biological Screening were carried out as described in Part-I , Section-1,page no.38 The zones of inhebition of test solution are recorded in Graphical Chart No 5.

TABLE NO. 5 PHYSICAL CONSTANTS OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL)- 4"-H-PYRAN-3"- CARBONITRILES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
5a	C_6H_{5-}	$C_{26}H_{19}ClN_4O$	438.5	180	48	12.77	12.72
5b	3-Cl-C_6H_4 -	$C_{26}H_{18}Cl_2N_4O$	473.0	165	72	11.84	11.81
5c	4-Cl-C_6H_4 -	$C_{26}H_{18}Cl_2N_4O$	473.0	155	68	11.84	11.80
5d	2-4-$(Cl)_2$-C_6H_{3-}	$C_{26}H_{17}Cl_3N_4O$	507.5	195	65	11.03	11.01
5e	4 -F-C_6H_{4-}	$C_{26}H_{18}ClFN_4O$	456.5	183	55	12.26	12.22
5f	4-Br-C_6H_{4-}	$C_{26}H_{18}BrClN_4O$	517.5	200	53	10.82	10.80
5g	4 -OH-C_6H_{4-}	$C_{26}H_{19}ClN_4O_2$	454.5	175	60	12.32	12.30
5h	4-NH_2-C_6H_{4-}	$C_{26}H_{20}ClN_5O$	453.5	210	50	15.43	15.41
5i	4-CH_3-C_6H_{4-}	$C_{27}H_{21}ClN_4O$	452.5	165	65	12.37	12.35
5j	4-OCH_3-C_6H_{4-}	$C_{27}H_{21}ClN_4O_2$	468.5	190	63	11.95	11.90
5k	3-NO_2-C_6H_{4-}	$C_{26}H_{18}ClN_5O_3$	483.5	166	58	14.97	14.91
5l	4-NO_2-C_6H_{4-}	$C_{26}H_{18}ClN_5O_3$	483.5	177	55	14.97	14.95

GRAPHICAL CHART NO. 5 : BIOLOGICAL SCREENING OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL)- 4"-H-PYRAN-3"- CARBONITRILES.



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	Ampicillin	Chloramphenicol	Norfloxacin	Geseofulvin	
B.mega	13	18	22	19	18	21	13	21	19	18	17	15	22	22	22	0	0
S.aureus	14	15	23	14	15	20	16	15	15	20	19	17	19	23	22	0	0
E.coli	16	16	24	16	16	15	17	20	18	22	17	16	19	22	24	0	0
S. typhi	16	14	17	21	16	24	14	19	16	24	22	14	22	25	23	0	0
A.niger	17	15	15	22	21	19	18	19	18	18	15	21	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-III

SECTION – I: BIOLOGICAL SCREENING OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL)- 4"-H-PYRAN-3"- CARBONITRILES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
		5c-(22)	**5c-(23)**		**5c-(24)**	**5d-(21)**	**5d-(22)**
		5f-(21)	**5f- (20)**		**5h-(20)**	**5f- (24)**	**5e-(21)**
		5h-(21)	**5j-(20)**		**5i- (18)**	**5j- (24)**	**5l- (21)**
			5k-(19)		**5j-(22)**	**5k-(22)**	
Ampicillin	**(50 µg)**	**22**	**19**		**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**		**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**		**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**		**--**	**--**	**22**

PART-IV

STUDIES ON CYNOPYRIDINES

STUDIES ON CYANOPYRIDINES

INTRODUCTION

Pyridine, nucleus has been extensively explored for their applications in the field of medicine, agriculture and industrial chemistry. 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 2"–methoxy-4"-[2-(4'-Chlorophenyl)–6 - methyl imidazo [1, 2 – a] pyridine - 3 –yl]- 6"-aryl nicotinonitriles via chlacones.

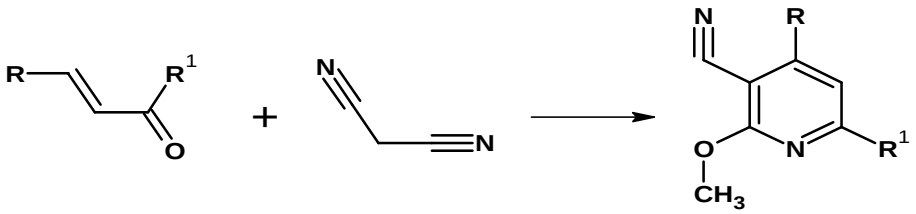
SYNTHETIC ASPECT :

Different methods for the preparation of 3-cyanopyridines are available in literature.[246-252]

The well known methods are:

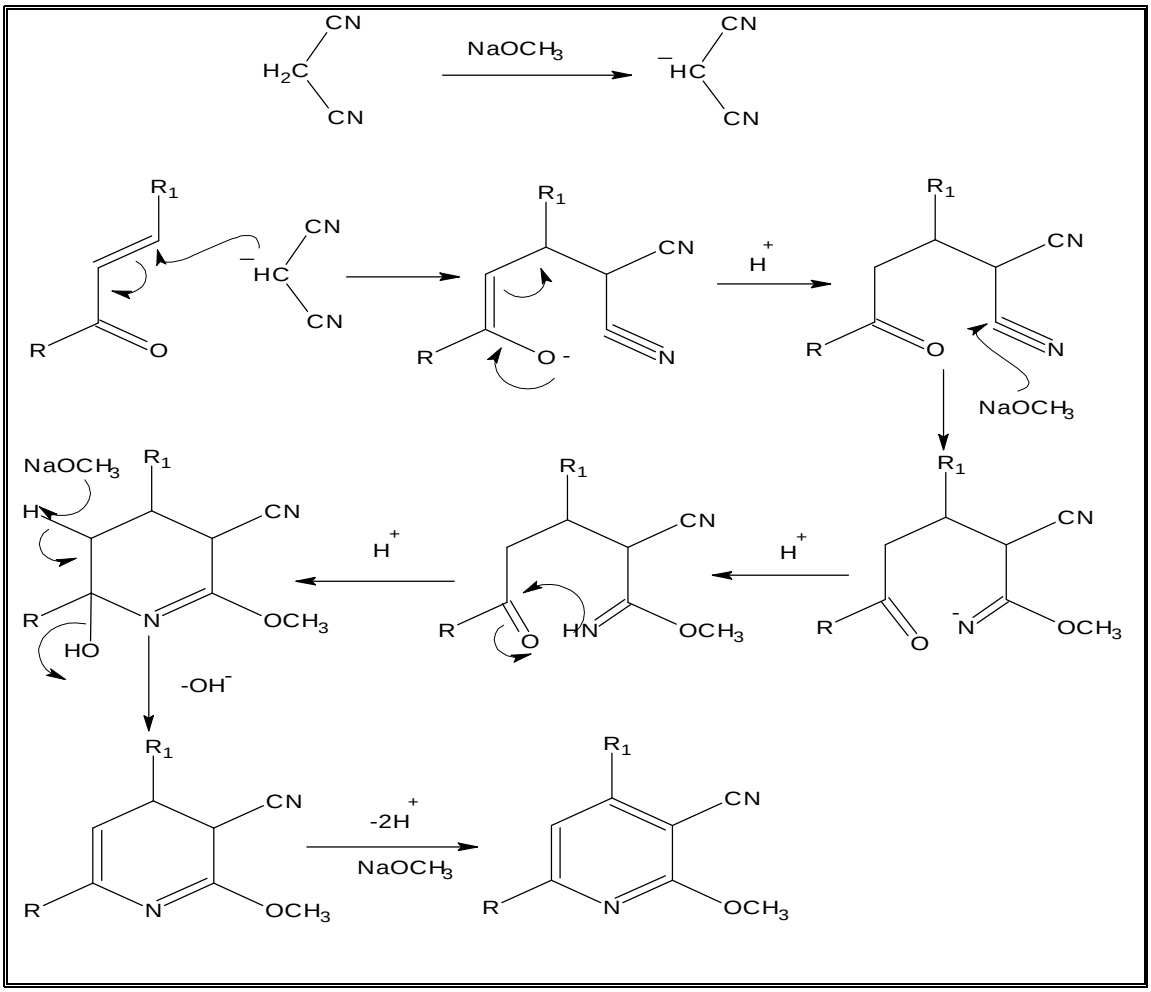
1. Substituted cyanopyridine derivatives were prepared from 3-substituted phenyl pyrazolone derivatives with malononitrile.[253]
2. A.Samour and co-workers[254] have prepared substituted cyanopyridines by the condensation of chalcones with malononitrile in presence of ammonium acetate.
3. A.Sakurai and Midorikaw[255, 256] have reported that malononitrile reacts with α, β-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines.
4. D. Bowman Matthew et al.[257] have synthesized fluorescent cyanopyridine and deazalumazine dyes using small molecule macroarrays.
5. Dao-Lin& wengetal[258] have prepared 2-methoxy -3-cyano pyridine derivatives by

the condensation of α,β-unsaturated ketones with malano nitrile in sodium methoxide



MECHANISM:

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



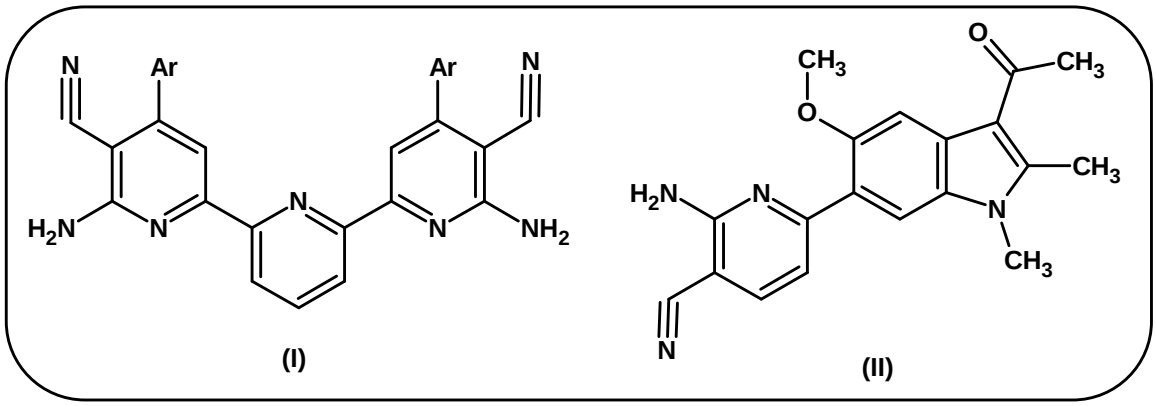
THERAPEUTIC IMPORTANCE

Cyanopyridine have attracted considerable attention as they appeared of interest to possess antibacterial, anticholestermic, antifungal, antihypertensive and antidiabetic activities. Few of them reported as shown below.

1. Antifungal[259]
2. Antiepileptic[260]
3. Antibacterial[261]
4. Anticonvulsant[262]
5. Antitubercular[263]
6. Analgesic[264]
7. Insecticidal[265]
8. Antisoriasis[266]
9. Antihypertensive[267]

E.G.Hammana Abou and co-workers[268] have studied anticancer and anti-HIV activity of 3-cyanopyridines. N. A. Abdallah et al.[269] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity. M. Fedele and co-workers[270] have reported the antiinflammatory activity of 3-cyanopyridines. H. Yoshida et al[271] have studied the antihistamic and antiallergic activity of 3-cyanopyridine derivatives.

A. El-Galil and co-workers[272] have prepared 3-cyanopyridines (I) and studied their pharmacological activity. G.S. Gadaginamath and co-workers[273] have synthesized various cyanopyridyl derivatives (II) and documented their variety of biological activities.

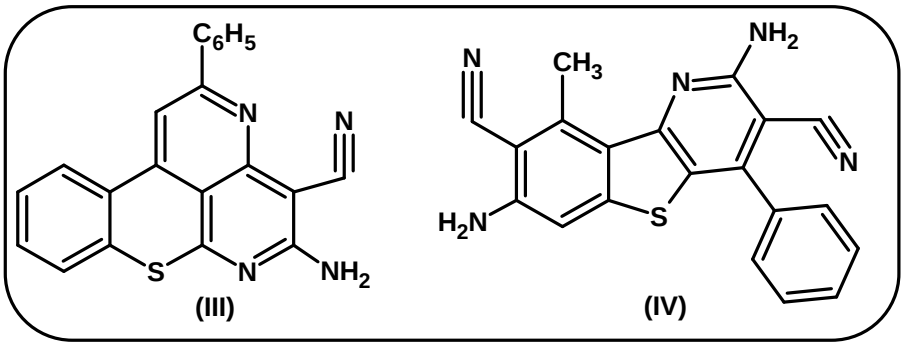


S. V. Roman et al.[274] have synthesized 2-amino-3-cyanopyridines and reported their biological activity. F.M.A.El-Taweel and co-workers[275] have prepared cyanopyridine derivatives and showed their significant biological activity.

M. Hussan and co-workers[276] have prepared 3-cyanopyridines and reported their pharmacological activity. U. D. Pyachenko et al.[277] have synthesized some cyanopyridines which are useful in the treatment of retroviral disease. K.Thiele et al.[278] have studied the analgesic activity of substituted 3-cyanopyridines.

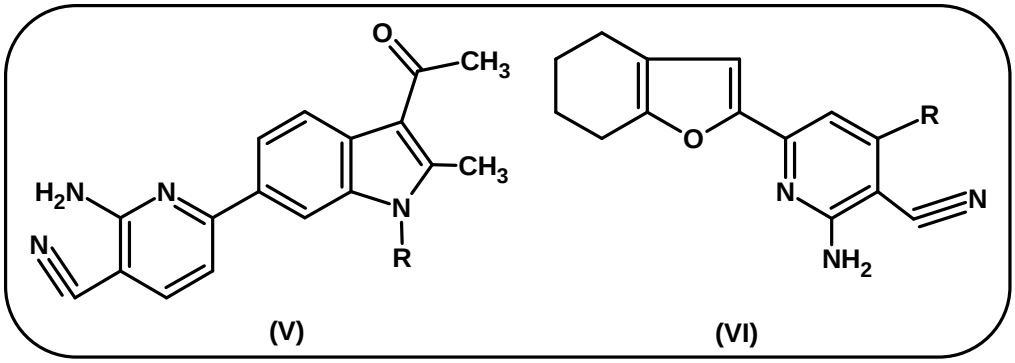
N. Latif and co-workers[279] have reported the antibacterial and antifungal activity of 2-amino-3-cyano-4,6-disubstituted pyridines. M. Bernard et al.[280] have reported the anticonvulsant activity of 3-cyanopyridines. D. G. Bhatt et al.[281] have prepared 3-cyanopyridines as an immunosuppressisve agent. U. Teu and co-workers[282] have shown cyanopyridine as agrochemical fungicides.

J. A. Vann Allan et al.[283] have prepared fused heterocyclic 3-cyanopyridine (III). Abu and co-workers[284] have prepared novel fused cyanopyridines (IV) for the treatment and preparation of systemic fungal infection



A.Streightoff1[285] and Seydal[286] have studied the bacteriostatic effect of somesubstituted 3-cyanopyridines.E. Francis and co-worker[287] have studied the effectof some substituted pyridines on the growth of the walker carcinosarcome in tissue culture. E.D.Barton et. al.[288] have reported fungicidal and insecticidalproperties. W. Veb leuna and co-worker[289] have studied 3- and 4-cyanopyridinesas tuberculosis arresting agents.

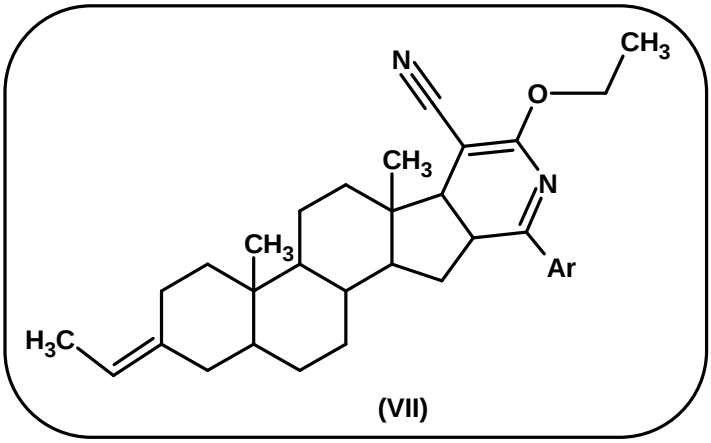
El-Nabawia et al.[290] have prepared 2-amino-3-cyano pyridine derivatives (V) and studied their antimicrobial activity. S. Guru et al.[291] have synthesized various cyanopyridyl derivatives (VI) and documented their multiple biological activities.



K. Kadlec and Hanslian[292] showed that 2-methyl-3-nitro-4-methoxyethyl-5-cyano-6-chloro pyridines caused occupational eczema in Vitamin B6 factory workers. Rigterink and H.Raymond[293] have studied the pesticidal activity of 3-cyanopyridines. M. R. Pavia et al.[294] have prepared N-substituted 2- aminopyridines which possess anticonvulsant property. 3-Cyanopyridines reported by L. Castedo et al.[295] showed a minimum inhibitory concentration of 1.56 µg/ml against S. aureus.

W. Von Benbenburg and co-workers[296] have synthesized 2-amino-3,6-disubstituted pyridines as antiepileptic agents. V. Scott and E. Joseph[297, 298] have prepared 2-amino-3-cyanopyridine derivatives which were found to be useful as antipsoriasis pharmaceuticals.

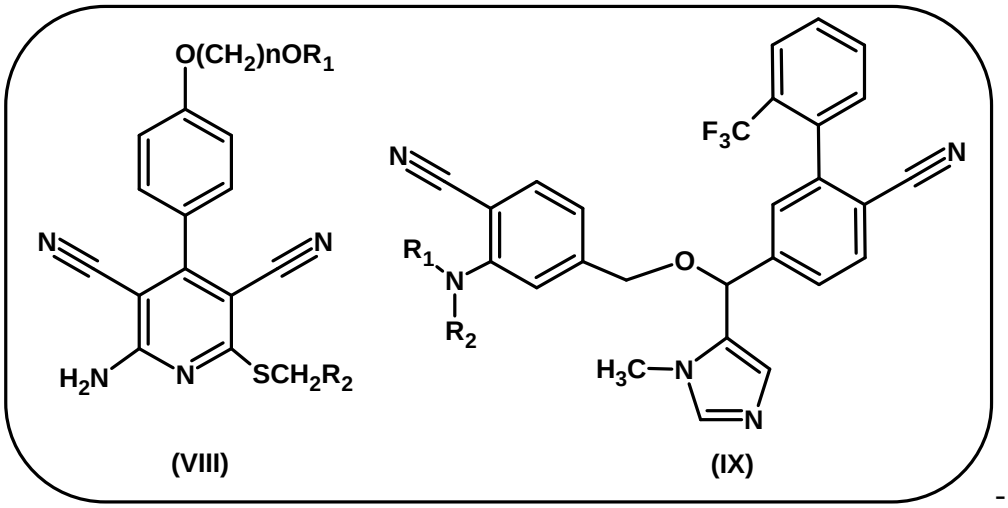
E.Abdel-Galil Amr and Mohamed M. Abdulla[299] have synthesized heterocyclic pyridine derivatives (VII) fused with steroidal structure. Initially the acute toxicity of the compounds was assayed via the determination of their LD50. Heterocyclic pyridine fused with steroid structure are active as anti inflammatory agents.



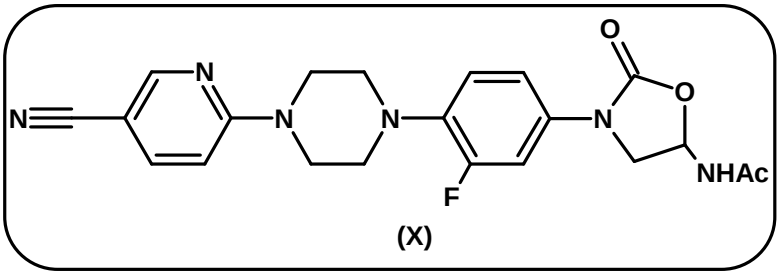
W. Von Benbenburg and co-workers[300] have synthesized 2-amino-3,6-disubstituted pyridines as antiepileptic agents. V. Scott and E. Joseph[301, 302] have prepared 2-amino-3-cyanopyridine derivatives which were found to be useful as antipsoriasis pharmaceuticals.

Dipeptidyl peptidase (DPP-IV) inhibition has the potential to become a valuable therapy for diabetes. Edwin B. Villhauer and co-workers[303] 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.

J. L Marco. et al.[304] have synthesized cyanopyridine and reported as acetylcholinesterase inhibitors. M. A.Moustafa et al.[305] have prepared cyanopyridine as antibacterial agents. H. S. Eduardo Sousa et al.[306] documented thionicotinamide coordinated to the a model system for the in vitro activation of thioamides antituberculosis drugs. Rosentreter Ulrich et al.[307] have synthesized a new cyanopyridine as receptor agonists in the treatment of cardiac or urogenital disease cancer, inflammation, neurodegenerative disease(VIII). Gary T. Wang and co-workers[308] have synthesized o-trifluoromethylbiphenyl substituted 2-amino-nicotinonitriles as inhibitors of farnesyl transferase(IX)



A John. Tucker et al.[309] have synthesized novel Piperazinyl Oxazolidinone containing cyanopyridine (X) as an antibacterial agents.



(X)

In view of therapeutic activities shown by cyanopyridines, it was contemplated to synthesize some new cyanopyridines in described as under.

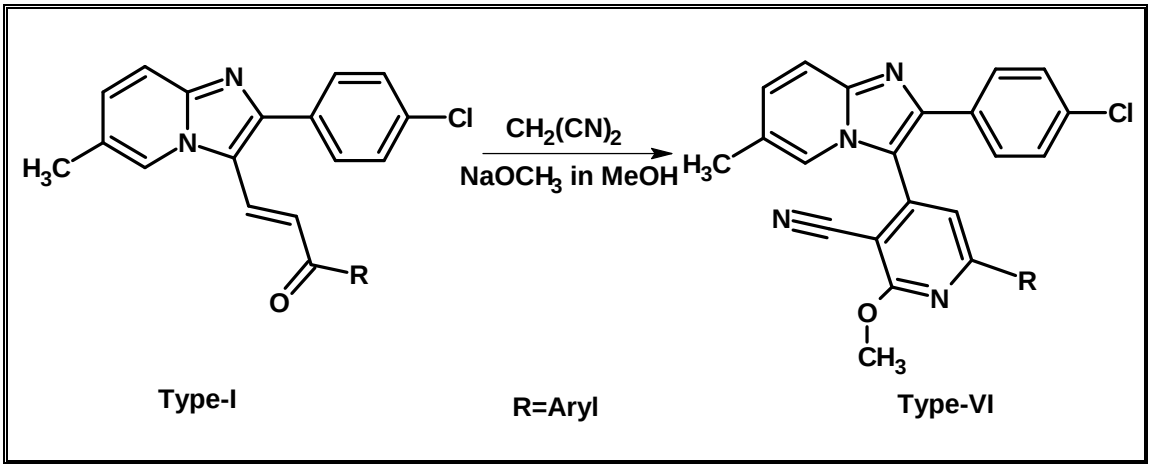
SECTION-I : Synthesis and biological Screening of 2" – methoxy - 4" - [2 - (4'-Chlorophenyl)–6-methyl imidazo [1, 2 – a] pyridine -3–yl]- 6"- aryl nicotinonitryles.

SECTION-II : Synthesis and biological Screening of 2" – amino - 4" - [2 - (4'-chlorophenyl)–6-methyl imidazo [1, 2 – a] pyridine – 3 –yl]-6"- arylnicotinonitryles

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2" – METHOXY - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL NICOTINONITRILES.

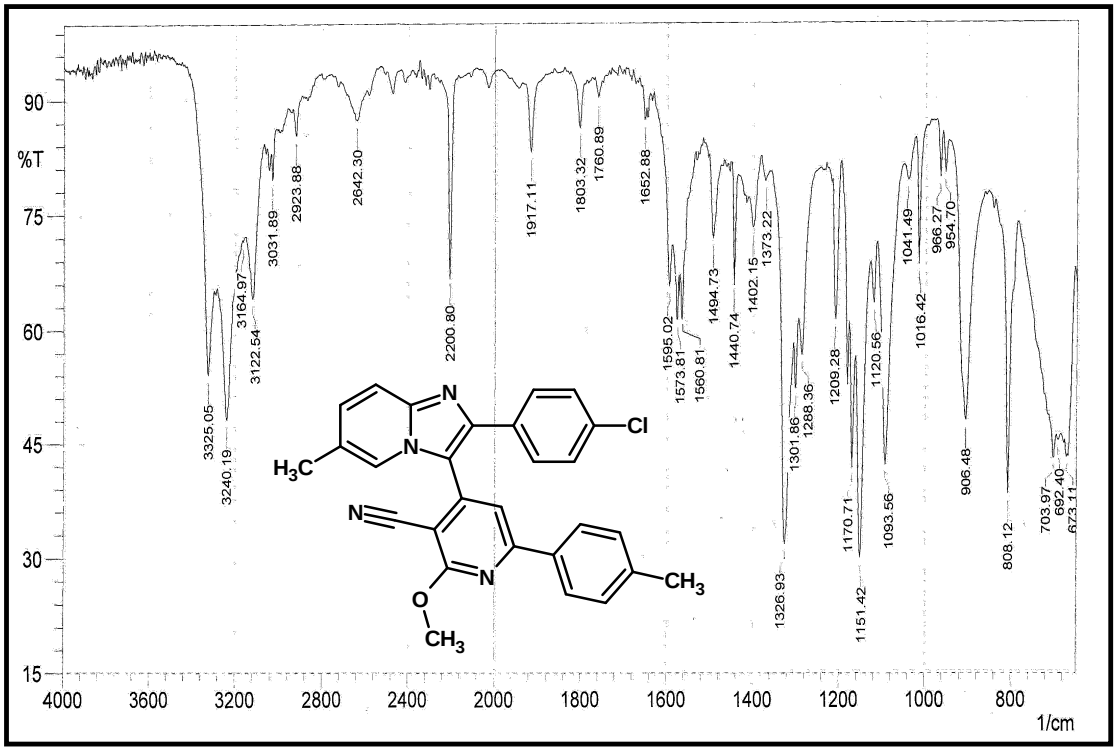
Pyridine nucleus plays an important role in medicine, agriculture and industrial chemistry. With a view of biological activities and variety of industrial applications, some new 2" – methoxy - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl nicotinonitriles derivative of Type (VI) have been prepared by the cyclocondensation of 2-(4'-chlorophenyl)-6-methyl- 3-(1"-aryl-2"-propene-1"-one-3-yl) -imidazo [1,2-a] pyridines of Type (I) with malononitrile in presence of sodium methoxide.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I ,page no. 41

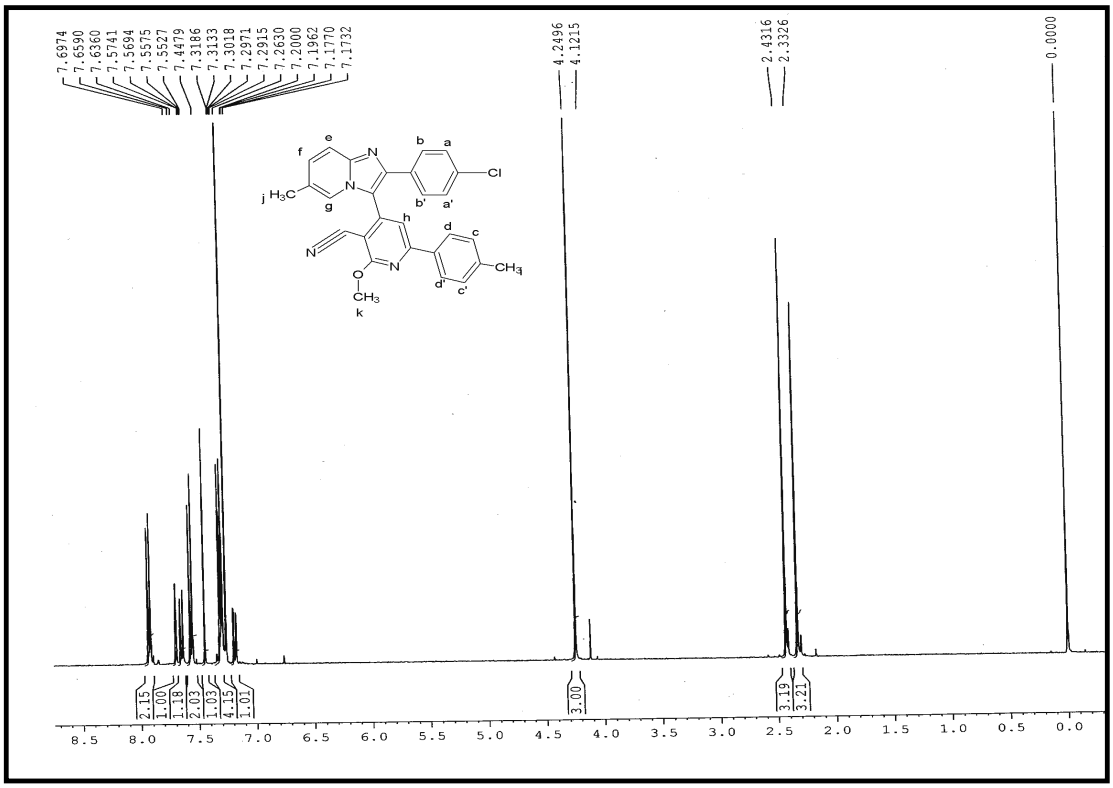
IR SPECTRAL STUDY OF 2" – METHOXY - 4" - [2 - (4' - CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(4"'-METHYLPHENYL) NICOTINONITRILE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2923	2990-2850	648
	C-H str. (sym.)	2894	2880-2860	"
	C-H def. (asym.	1440	1470-1430	"
	C-H def. (sym.)	1373	1395-1370	"
Aromatic	C-H str.	3031	3090-3030	"
	C=C str	1494	1600-1450	"
	C-H i.p. (def.)	1151	1300-1100	"
Imidazo[1,2-a] pyridine	C=N str.	1595	1612-1593	649
	C-N str.	1117	1220-1020	"
Pyridine Nitril	C=N	1573	1580-1550	"
	C=N str.	2200	2240-2120	"
	C-N str.	1560	1650-1520	"
Ether	C-O-C	1209	1260-1200	"
Halide	C-Cl str.	703	800-600	"

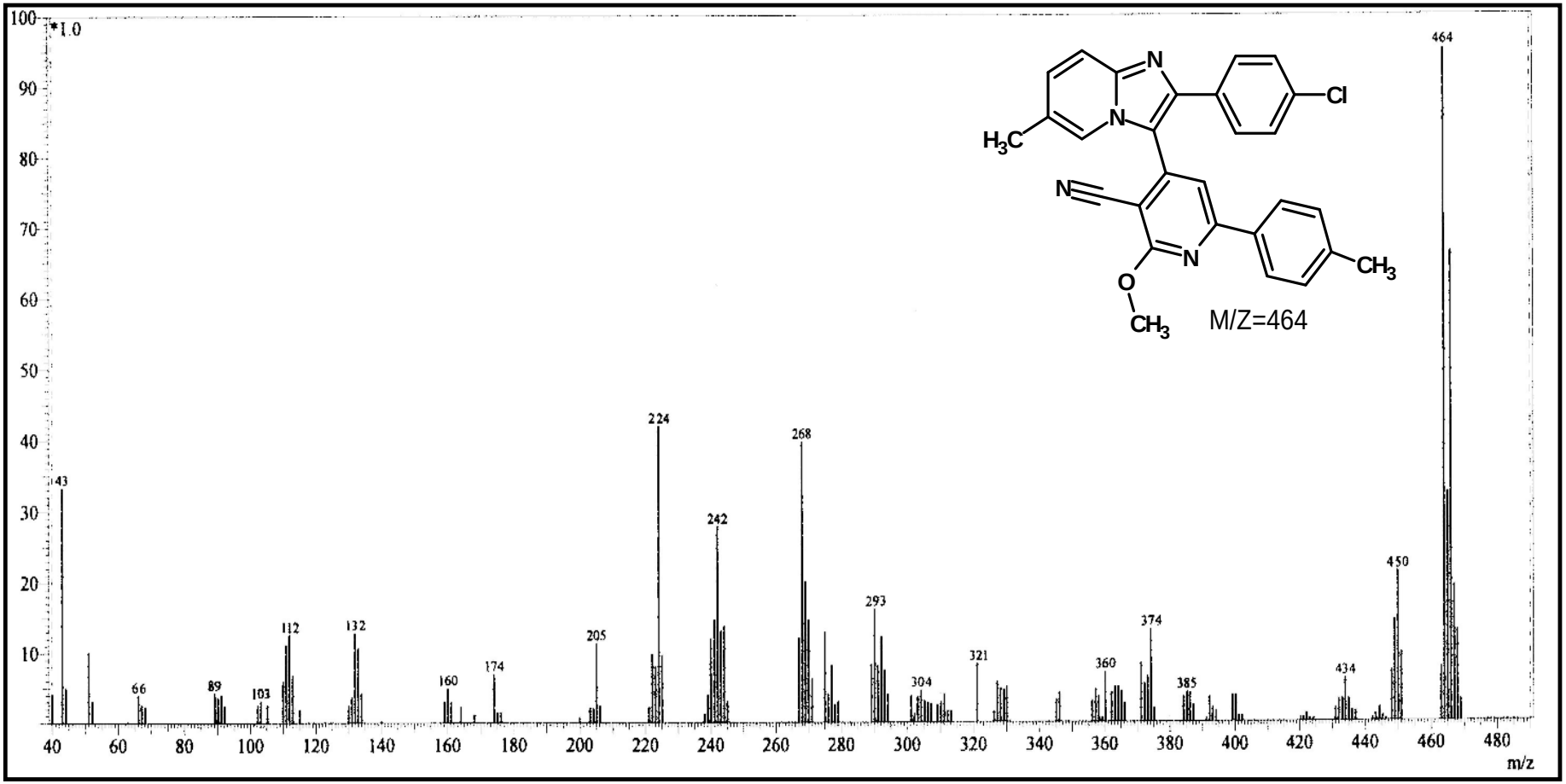
NMR SPECTRAL STUDY OF 2" – METHOXY - 4" - [2 - (4' - CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(4"'-METHYLPHENYL) NICOTINONITRILE.

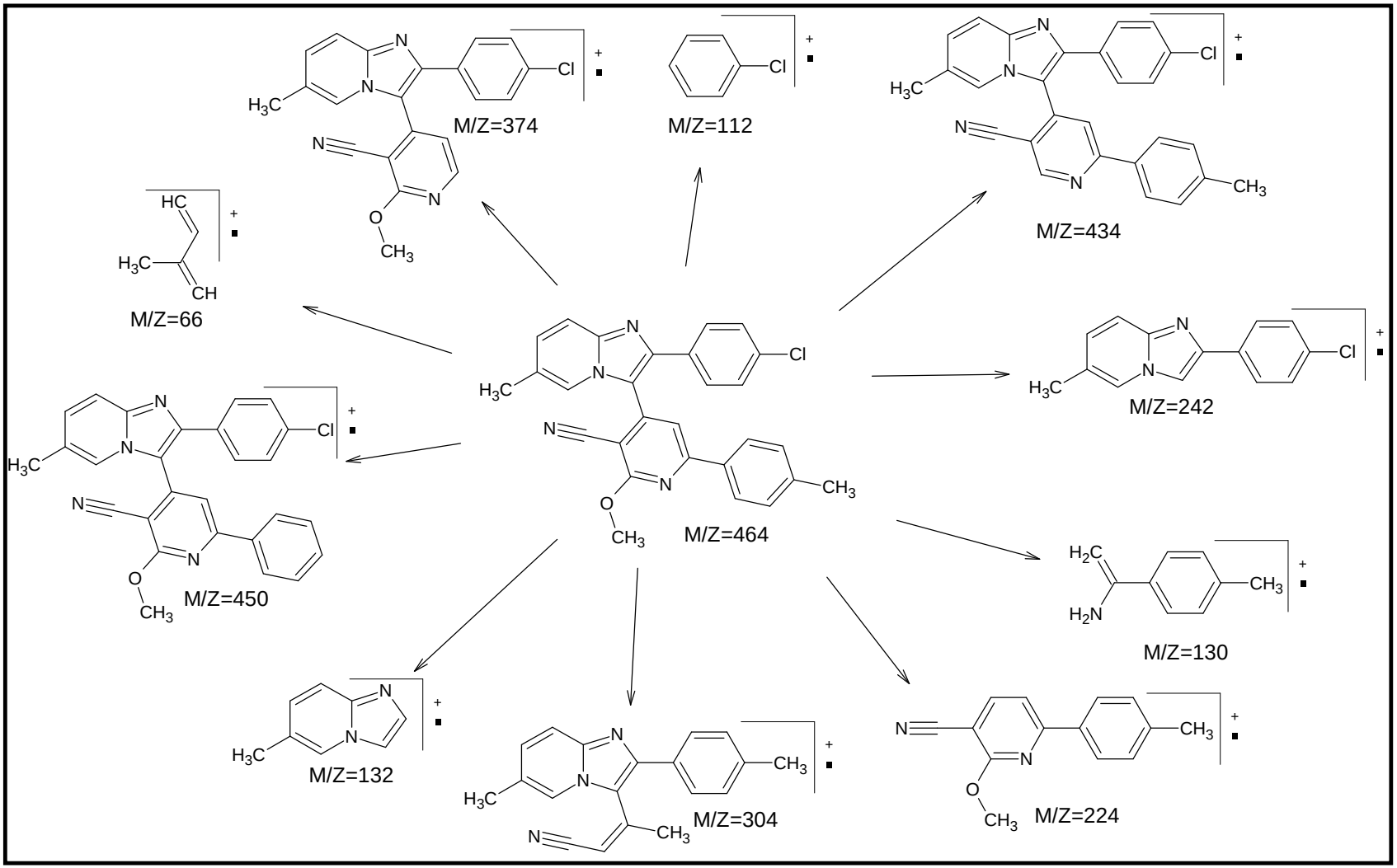


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

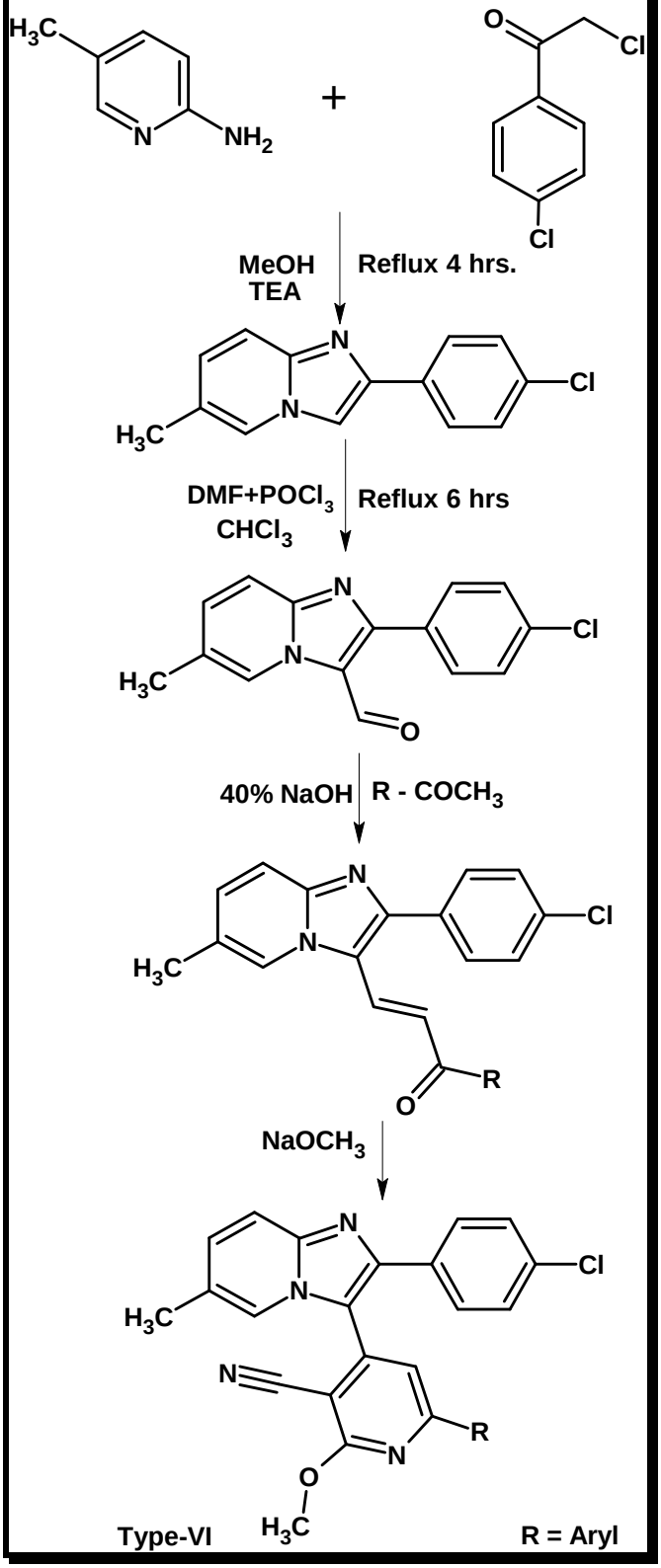
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.33	3H	Singlet	Ar-CH_3(k)
2	2.43	3H	Singlet	Ar-CH_3(i)
3	4.24	3H	Singlet	Ar-OCH3(j)
4	7.17-7.20	1H	doublet	Ar-H(f)
5	7.29-7.31	4H	doublet	Ar-H(aa',cc')
6	7.44	1H	Singlet	Ar-H(h)
7	7.55-7.56	2H	doublet	Ar-H(bb'')
8	7.63-7.65	1H	doublet	Ar-H(e)
9	7.69	1H	Singlet	Ar-H(g')
10	7.91-7.93	2H	doublet	Ar-H(dd')

MASS SPECTRAL STUDY OF 2" – METHOXY - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(4'"-METHYLPHENYL) NICOTINONITRILE.




M/Z=374
M/Z=112
M/Z=434
M/Z=66
M/Z=242
M/Z=450
M/Z=464
M/Z=130
M/Z=132
M/Z=304
M/Z=224

REACTION SCHEME



EXPERIMENTALS

SYNTHESIS AND BIOLOGICAL SCREENING OF 2" – METHOXY - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL NICOTINONITRILES.

[A] Synthesis of 6– methy –2 - (4' -chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6–methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesisof2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyle)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no. 37

[D] Synthesis of 2" –methoxy -4" -[2 -(4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-(4"'-methylphenyle) nicotinonitriles(6i)

To a solution of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyle)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (3.88 gm, 0.01 mol), malononitrile (0.60gm, 0.01 mol) and sodium methoxide in methanol (25ml). The content was heated under reflux with stirring for 12 hrs. The reaction mixture was diluted with water and extracted with chloroform. The excess solvent was distilled out and product was crystallized from ethanol. Yield 62%, m.p. 159^{o}C.

($C_{28}H_{21}ClN_4O$; Required : C, 72.33; H, 4.55; N, 12.05 %; found : C, 71.31; H, 4.53; N, 12.03 %;)

Similarly, other 2" – methoxy - 4" - [2 - (4' -chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-6"- aryl nicotinonitriles were prepared. The physical data are recorded in Table No.-6

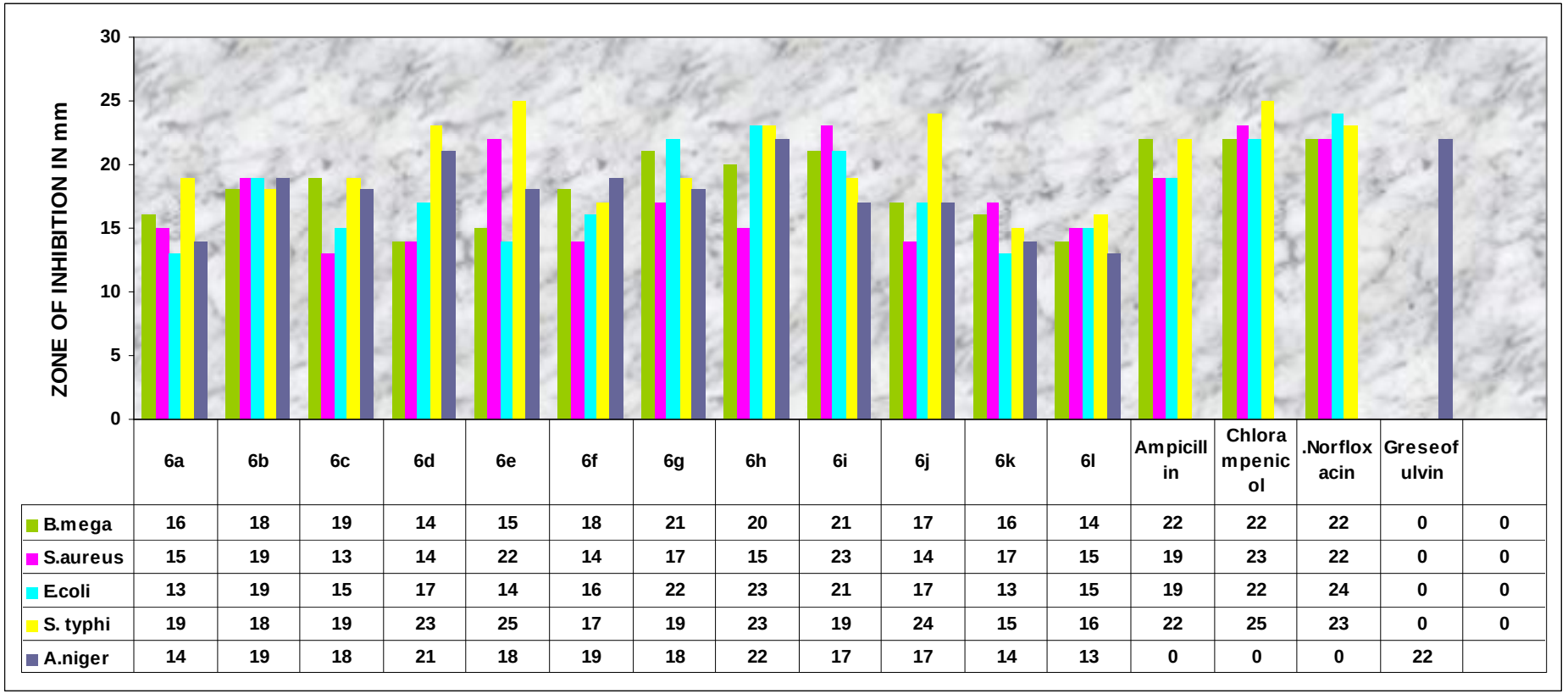
[E] Biological Screening of 2" – methoxy - 4" - [2 - (4' -chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-6"- aryl nicotinonitryles

Biological Screening were carried out as described in Part-I , Section-1,page no. 38The zones of inhabition of test solution are recorded in Graphical Chart No.-6

TABLE NO. 6 PHYSICAL COSTANTS OF 2" – METHOXY - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL) NICOTINONITRILES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
6a	C_6H_5-	$C_{27}H_{19}ClN_4O$	450.5	190	65	12.43	12.40
6b	3-Cl-C_6H_4 -	$C_{27}H_{18}Cl_2N_4O$	485.0	185	59	11.54	11.51
6c	4-Cl-C_6H_4 -	$C_{27}H_{18}Cl_2N_4O$	485.0	170	52	11.54	11.52
6d	2-4-$(Cl)_2$-C_6H_3-	$C_{27}H_{17}Cl_3N_4O$	519.5	195	75	10.78	10.76
6e	4 -F-C_6H_4-	$C_{27}H_{18}ClFN_4O$	468.5	200	68	11.95	11.93
6f	4-Br-C_6H_4-	$C_{27}H_{18}BrClN_4O$	529.5	222	72	10.57	10.55
6g	4 -OH-C_6H_4-	$C_{27}H_{19}ClN_4O_2$	466.5	180	48	12.00	12.00
6h	4-NH_2-C_6H_4-	$C_{27}H_{20}ClN_5O$	465.5	165	59	15.03	15.01
6i	4-CH_3-C_6H_4-	$C_{28}H_{21}ClN_4O$	464.5	159	62	12.05	12.02
6j	4-OCH_3-C_6H_4-	$C_{28}H_{21}ClN_4O_2$	480.5	160	60	11.65	11.61
6k	3-NO_2-C_6H_4-	$C_{27}H_{18}ClN_5O_3$	495.5	167	71	14.12	14.10
6l	4-NO_2-C_6H_4-	$C_{27}H_{18}ClN_5O_3$	495.5	188	66	14.12	14.11

GRAPHICAL CHART NO. 6 : BIOLOGICAL SCREENING OF 2" – METHOXY - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL) NICOTINONITRILES.



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Ampicillin	Chloramphenicol	.Norfloxacin	Greseofulvin	
B.mega	16	18	19	14	15	18	21	20	21	17	16	14	22	22	22	0	0
S.aureus	15	19	13	14	22	14	17	15	23	14	17	15	19	23	22	0	0
E.coli	13	19	15	17	14	16	22	23	21	17	13	15	19	22	24	0	0
S. typhi	19	18	19	23	25	17	19	23	19	24	15	16	22	25	23	0	0
A.niger	14	19	18	21	18	19	18	22	17	17	14	13	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-IV

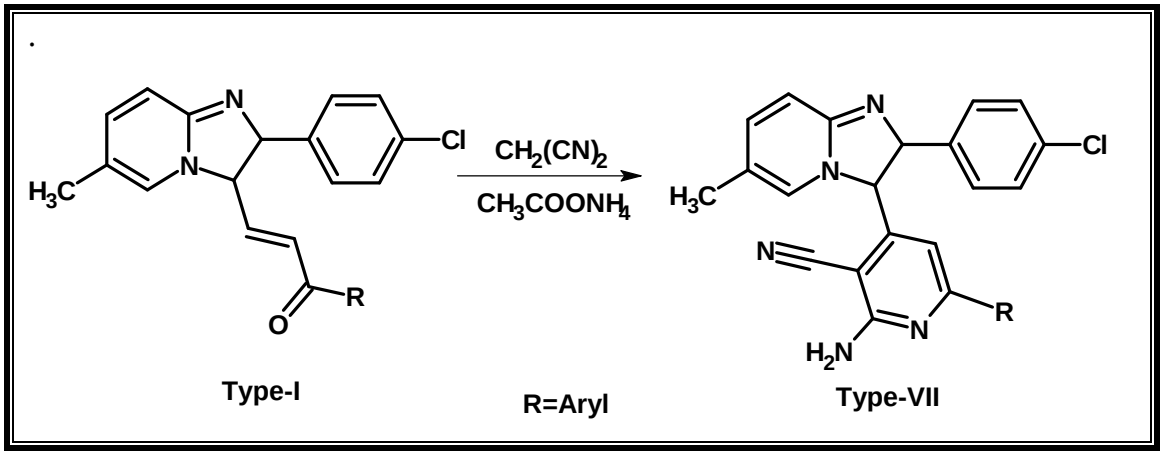
SECTION – I: BIOLOGICAL SCREENING OF 2" – METHOXY - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL) NICOTINONITRILES.

	Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
	B. mega	***S. aureus***	***E. coli***	***S. typhi***	***A. niger***
	6g-(21)	**6b-(19)**	**6b-(19)**	**6d-(23)**	**6d-(21)**
	6h-(20)	**6e-(22)**	**6g-(22)**	**6e-(25)**	**6h-(22)**
	6i- (21)	**6i-(23)**	**6h-(23)**	**6h-(23)**	
			6i- (21)	**6j-(24)**	
Ampicillin (50 µg)	**22**	**19**	**19**	**22**	**--**
Chloramphenicol(50 µg)	**22**	**23**	**22**	**25**	**--**
Norfloxacin (50 µg)	**22**	**22**	**24**	**23**	**--**
Greseofulvin (50 µg)	**--**	**--**	**--**	**--**	**22**

SECTION – II

SYNTHESIS AND BIOLOGICAL SCREENING OF 2" – AMINO - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL NICOTINONITRILES.

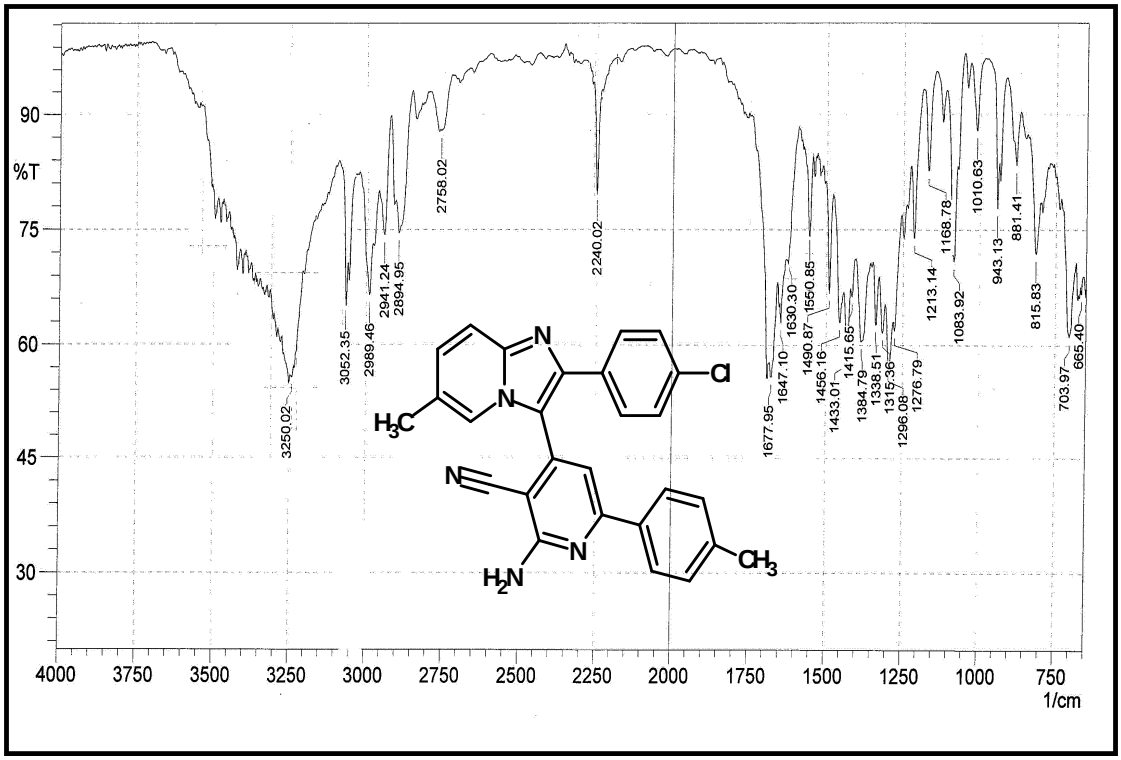
In the past years, considerable evidence has been accumulated to demonstrate the efficiency of cyanopyridines. To further assess the potential of such class of compounds, cyanopyridine derivatives of 2" – amino - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl nicotinonitryles of Type (VII) have been prepared, by the cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-(1"-aryl- 2"-propene-1"-one-3-yl) -imidazo [1,2-a] pyridines of Type (I) with with malononitrile in presence of ammonium acetate.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I ,page no. 41

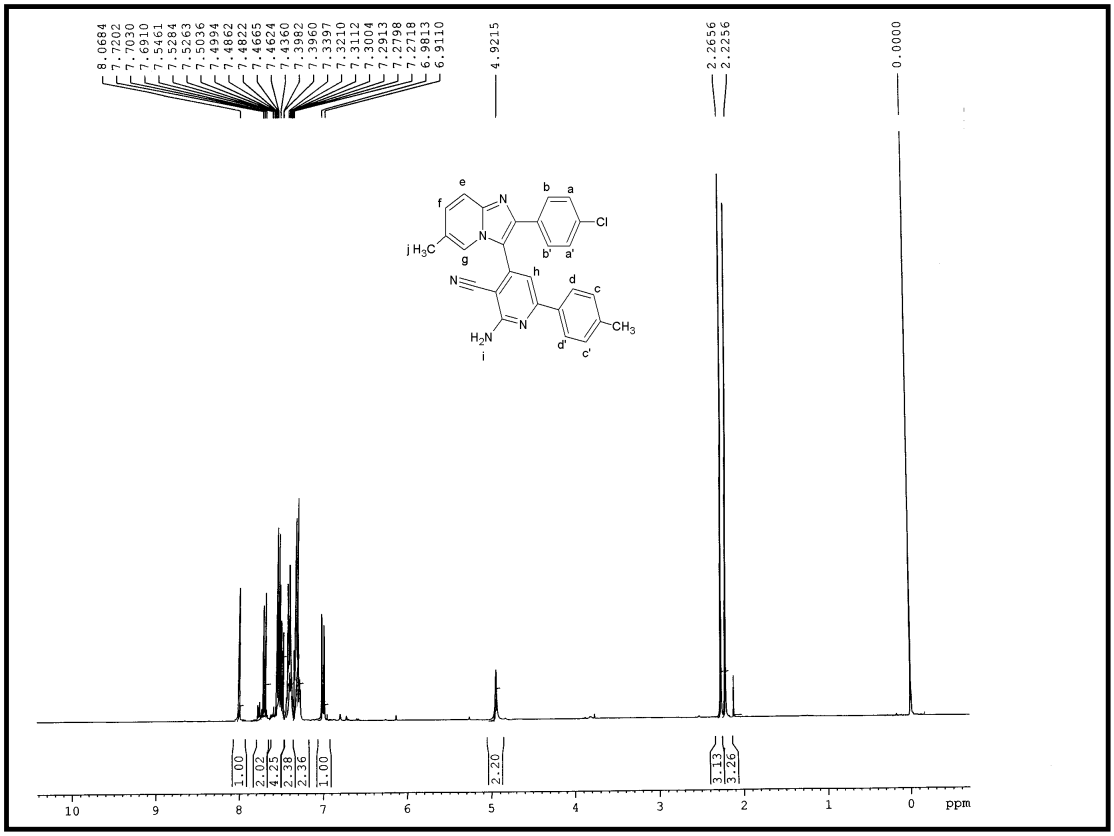
IR SPECTRAL STUDY OF 2" – AMINO - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN-3-YL]-6"-(4'''-METHYLPHENYL) NICOTINONITRILE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2941	2990-2850	648
	C-H str. (sym.)	2894	2880-2860	"
	C-H def. (asym.	1456	1470-1430	"
	C-H def. (sym.)	1384	1395-1370	"
Aromatic	C-H str.	3052	3090-3030	"
	C=C str	1490	1600-1450	"
	C-H i.p. (def.)	1168	1300-1100	"
Imidazo[1,2-a] pyridine	C=N str.	1598	1612-1593	649
	C-N str.	1083	1220-1020	"
Pyridine Nitril	N-H str. (-NH_2)	3250	3350-3250	"
	C=N str.	1558	1612-1550	"
	C-N str.	1186	1220-1020	"
Halid	C-Cl str.	703	600-800	"

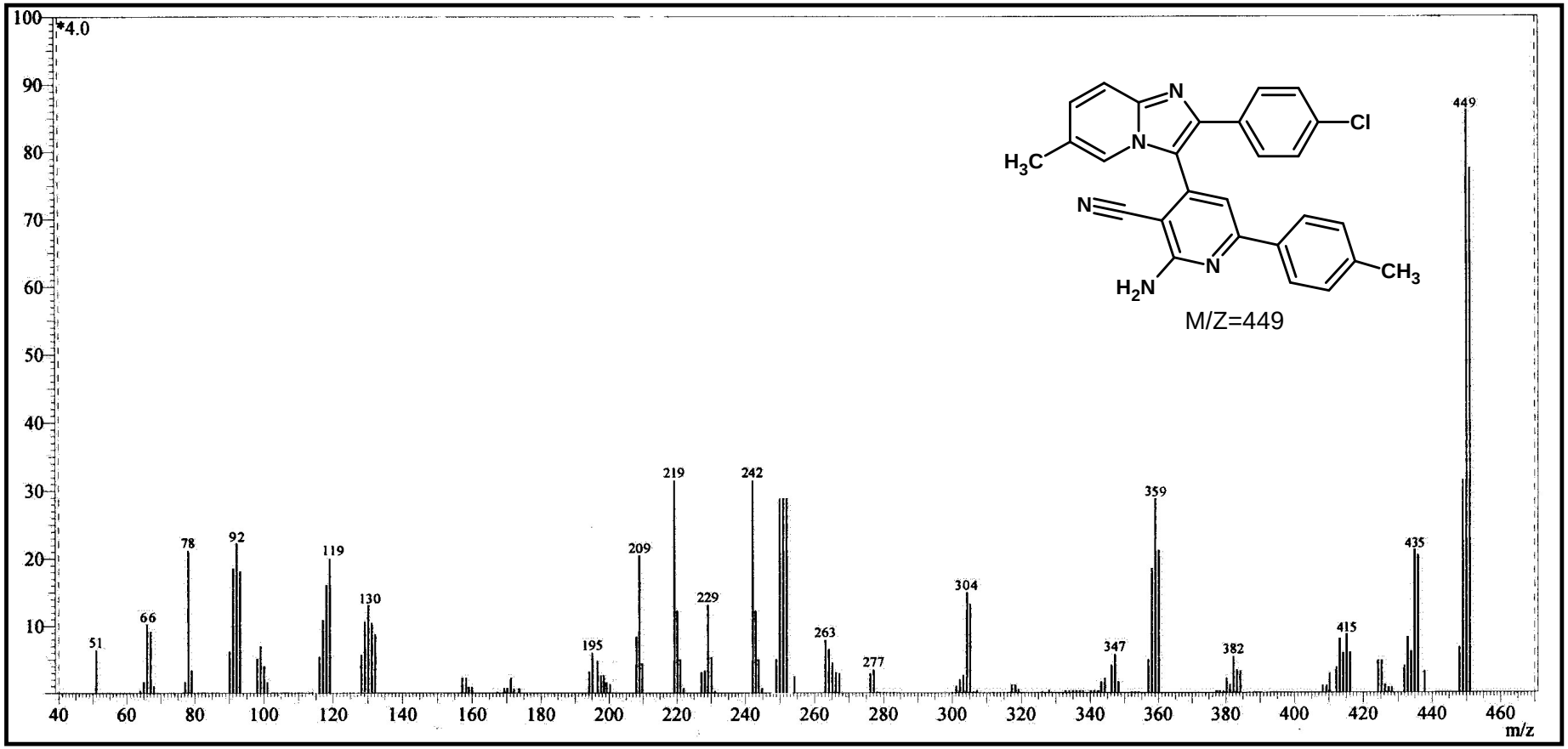
NMR SPECTRAL STUDY OF 2" – AMINO - 4" - [2 - (4' - CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN-3-YL]-6"-(4"'-METHYLPHENYL) NICOTINONITRILE.

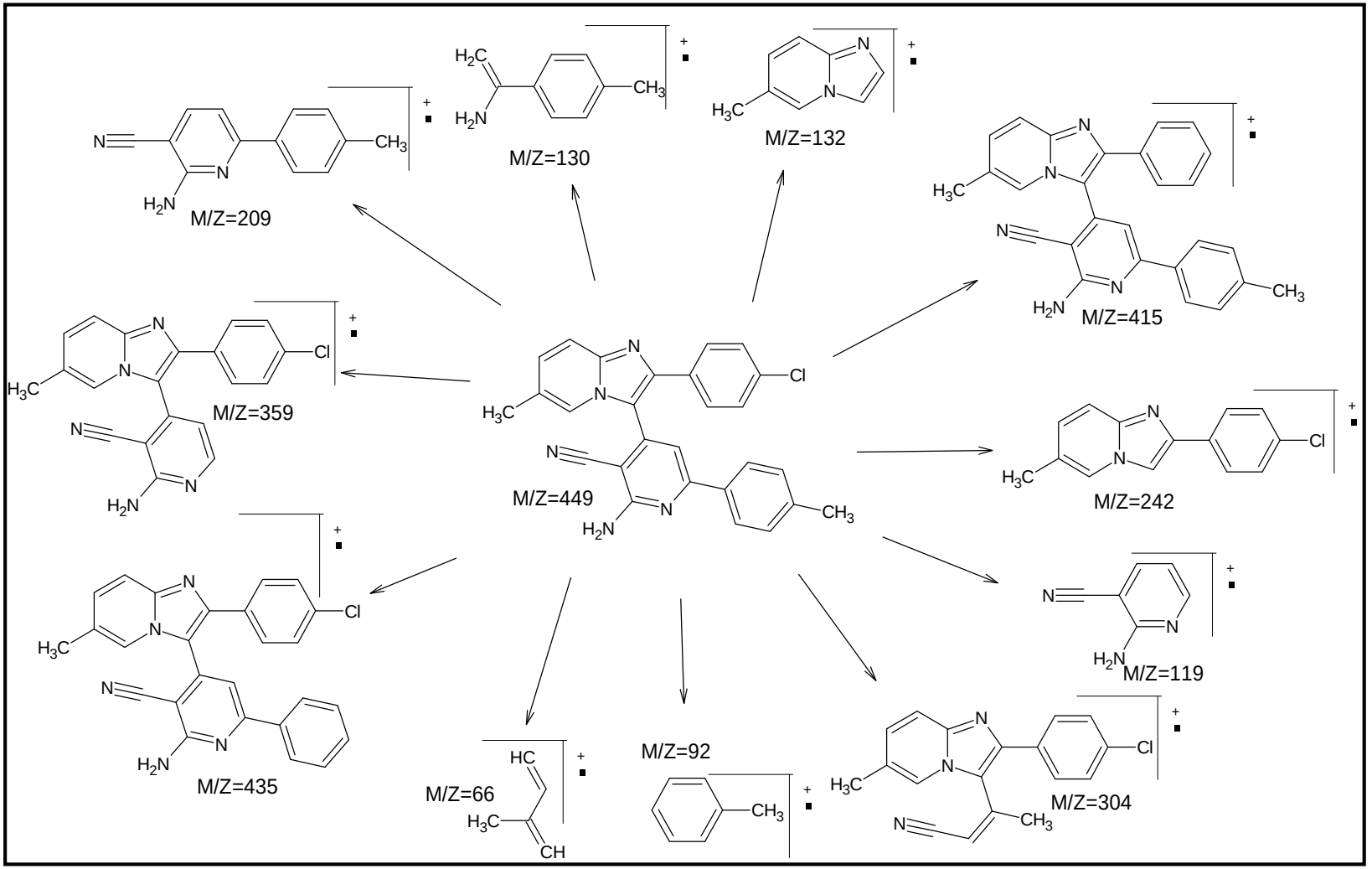


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300MHz)

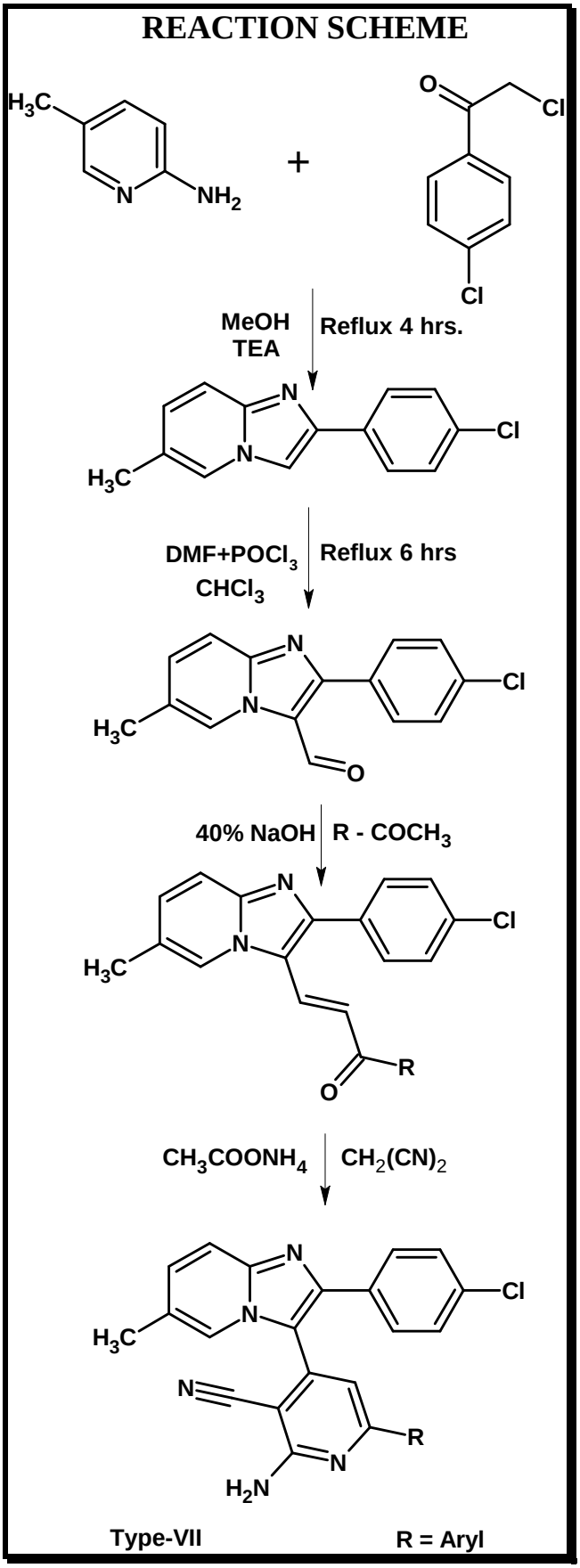
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.22	3H	singlet	Ar-CH_3 (k)
2	2.26	3H	singlet	Ar-CH_3 (j)
3	4.92	2H	singlet	Ar-NH_2 (i)
4	6.91-6.98	1H	doublet	Ar-H (f)
5	7.27-7.33	2H	doublet	Ar-H(dd')
6	7.39-7.43	2H	singlet	Ar-H (aa')
7	7.46-7.54	4H	multiplet	Ar-H (bb',e,h)
8	7.69-7.72	2H	doublet	Ar-H (cc')
9	8.06	1H	singlet	Ar-H (g)

MASS SPECTRAL STUDY OF 2" – AMINO - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN-3-YL]-6"-(4'''-METHYLPHENYL) NICOTINONITRILE.




M/Z=209
M/Z=130
M/Z=132
M/Z=415
M/Z=359
M/Z=449
M/Z=242
M/Z=119
M/Z=435
M/Z=66
M/Z=92
M/Z=304

REACTION SCHEME



Type-VII **R = Aryl**

EXPERIMENTALS

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

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'- methylphenyle)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no. 37

[D] Synthesis of 2"–amino - 4"-[2 -(4'–chlorophenyl) – 6 - methyl imidazo [1, 2– a] pyridin –3–yl]- 6"-(4"'-methylphenyl) nicotinonitriles(7i).

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"' -methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine. (3.40 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) and ammonium acetate (2.31 g, 0.03 mol) in DMF (30 ml) was refluxed for 8 hrs., The content was poured in to crushed ice. The solid was obtained filtered, washed with water and crystallised from dioxane. Yield 58%, m.p. 159 ^{o}C.

($C_{27}H_{20}ClN_5$; Required : C, 72.07; H, 4.48; N, 15.57 %; found : C, 72.07; H, 4.48; N, 15.56 %;)

Similarly other 2" – amino - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridine 3-yl]-6"-aryl nicotinonitriles were synthesized. The physical data are recorded in Table No.7

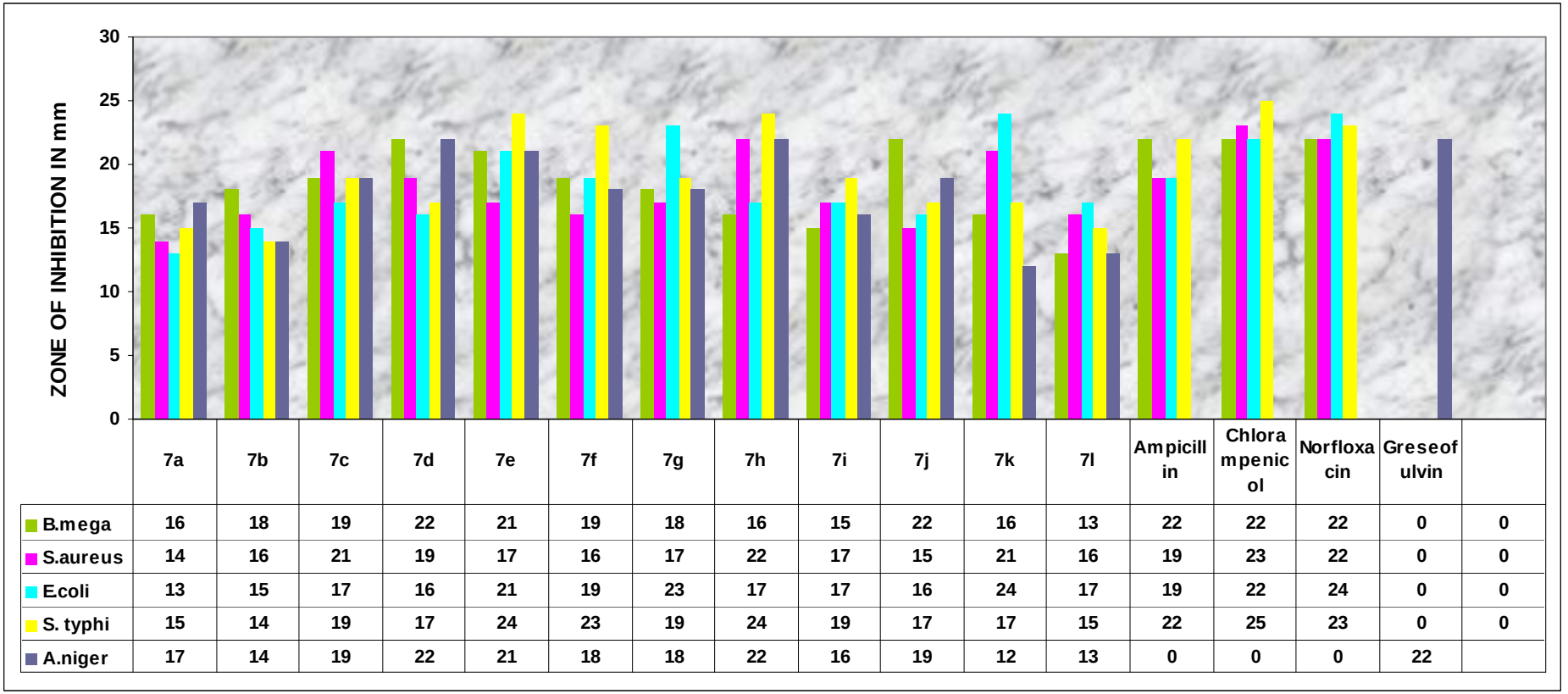
[E] Biological Screening of 2" – amino - 4" - [2 - (4' - chlorophenyl) - 6-methylimidazo [1, 2-a] pyridin-3-yl]-6"- (aryl) nicotinonitriles

Biological Screening were carried out as described in Part-I , Section-1 page no.38 The zones of inhabition of test solution are recorded in Graphical Chart No. 7.

TABLE NO. 7 PHYSICAL COSTANTS OF 2" – AMINO - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN-3-YL]-6"-(ARYL) NICOTINONITRILES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
7a	C_6H_{5-}	$C_{26}H_{18}ClN_5$	435.5	210	72	16.07	16.05
7b	3-Cl-C_6H_4 -	$C_{26}H_{17}Cl_2N_5$	470.0	180	62	14.89	14.87
7c	4-Cl-C_6H_4 -	$C_{26}H_{17}Cl_2N_5$	470.0	195	55	14.89	14.86
7d	2-4-$(Cl)_2$-C_6H_3-	$C_{26}H_{16}Cl_3N_5$	504.5	160	68	13.87	13.85
7e	4 -F-C_6H_4-	$C_{26}H_{17}ClFN_5$	453.5	205	75	15.43	15.41
7f	4-Br-C_6H_4-	$C_{26}H_{17}BrClN_5$	514.5	165	55	13.60	13.59
7g	4 -OH-C_6H_4-	$C_{26}H_{18}ClN_5O$	451.5	190	62	15.50	15.48
7h	4-NH_2-C_6H_4-	$C_{26}H_{19}ClN_6$	450.5	150	54	18.64	18.62
7i	4-CH_3-C_6H_4-	$C_{27}H_{20}ClN_5$	449.5	159	58	15.57	15.56
7j	4-OCH_3-C_6H_4-	$C_{27}H_{20}ClN_5O$	465.5	169	66	15.03	15.01
7k	3-NO_2-C_6H_4-	$C_{26}H_{17}ClN_6O_2$	480.5	177	71	17.48	17.45
7l	4-NO_2-C_6H_4-	$C_{26}H_{17}ClN_6O_2$	480.5	185	70	17.48	17.46

GRAPHICAL CHART NO. 7 : BIOLOGICAL SCREENING OF 2" – AMINO - 4" - [2 - (4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN-3-YL]-6"-(ARYL)NICOTINONITRILES.



	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	7k	7l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	16	18	19	22	21	19	18	16	15	22	16	13	22	22	22	0	0
S.aureus	14	16	21	19	17	16	17	22	17	15	21	16	19	23	22	0	0
E.coli	13	15	17	16	21	19	23	17	17	16	24	17	19	22	24	0	0
S. typhi	15	14	19	17	24	23	19	24	19	17	17	15	22	25	23	0	0
A.niger	17	14	19	22	21	18	18	22	16	19	12	13	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-III

SECTION – I: BIOLOGICAL SCREENING OF 2"-AMINO-4"-[2-(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-(ARYL)- 4"-H-PYRAN-3"- CARBONITRILES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
		5c-(22)	**5c-(23)**	**5c-(24)**	**5d-(21)**	**5d-(22)**
		5f-(21)	**5f- (20)**	**5h-(20)**	**5f- (24)**	**5e-(21)**
		5h-(21)	**5j-(20)**	**5i- (18)**	**5j- (24)**	**5l- (21)**
			5k-(19)	**5j-(22)**	**5k-(22)**	
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

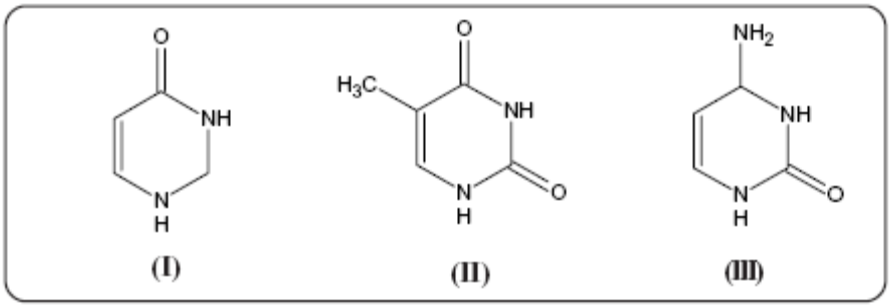
PART-V

STUDIES ON PYRIMIDINES

STUDIES ON PYRIMIDINES

INTRODUCTION

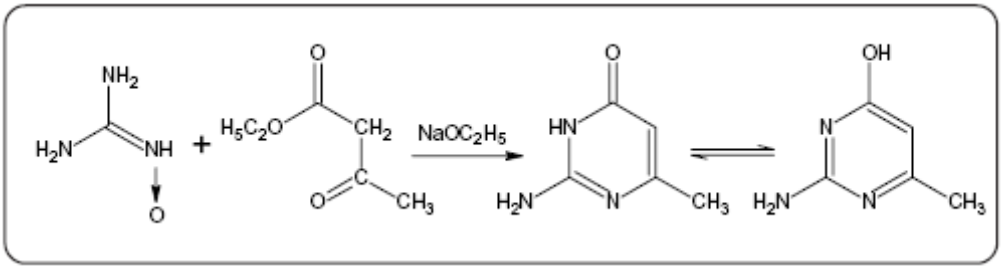
Pyrimidine derivatives like **uracil** (I), **thymine** (II) and **cytosine** (III) occur widely in nature showing remarkable pharmaceutical importance because of their diverse pharmacological activities. Pyrimidine derivatives which occurs in natural products[310] like nucleic acid, vitamin-B and having remarkable pharmaceutical importance because of their broad spectrum of biological 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. Pyrimidines are among those molecules that make like possible as being some of the building blockers of DNA and RNA.



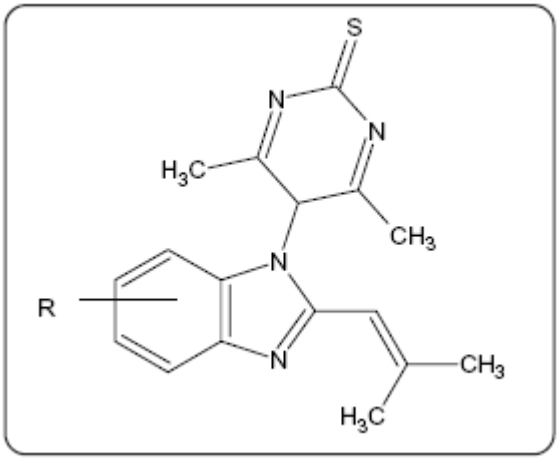
Pyrimidine is considered to be a resonance hybrid of the charged and uncharged cannonical structures, its resonance energy has been found to be less than benzene or pyridine. The naturally occuring pyrimidine derivatives was first isolated by Gabrial and Colman in 1870, and its structure was confirmed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

SYNTHETIC ASPECT

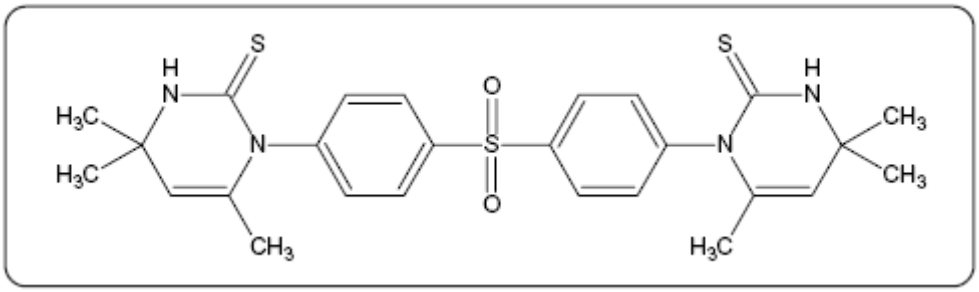
A very important general method for preparing pyrimidines is the condensation between a three carbon compounds of the type YCH_2Z, where Y and Z = COR, CO_2R, CN, and compounds having the amidine structure $R(C=NH)NH_2$, where R=R (an amidine), SH or SR (thiourea or its s-derivative), NH_2 (guanidine); 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.



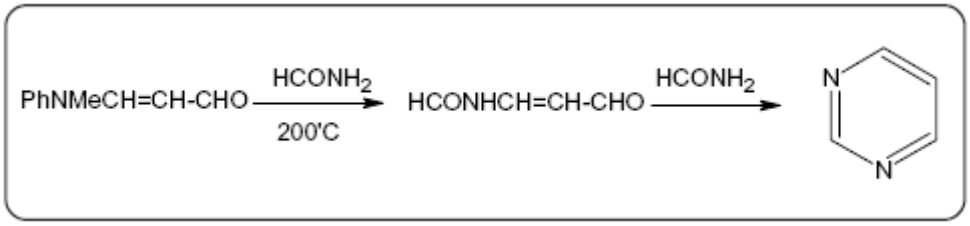
The reaction of chalcone with guanidine hydrochloride in presence of potassium t-butoxide in t-butanol yielded corresponding 2-amino pyrimidine derivatives[311]. Pratibha Sharma and co-workers[312] have investigated the insertion of dimethylvinylidene carbine into azo moiety was investigated in order to synthesize 4,6-dimethyl-5-[2-(2-methylprop-1-enyl)-1*H*-benzimidazol-1-yl]pyrimidine-2(5*H*)-thiones under kinetically controlled phase transfer catalysis conditions.



Rasaki[313] synthesized 2-amino-pyrimidine by the reaction of chalcone epoxides with guanidine carbonate in xylene. Sham M. Sondhi et al.[314] have synthesized pyrimidinederivatives by an efficient, one-pot reaction of functionalized amines with either4-isothiocyanato-4-methyl-2-pentanone or 3-isothiocyanatobutanal.

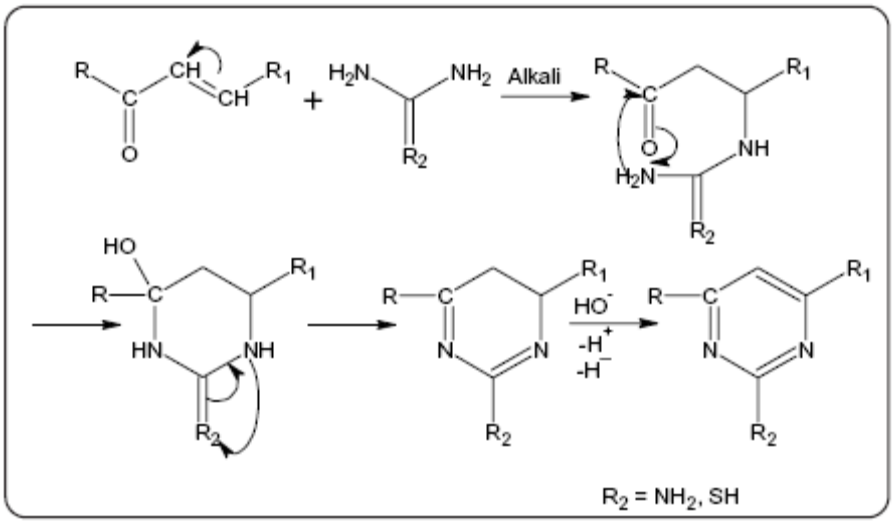


There are many other methods of pyrimidine ring synthesis which are of more limited scope. The reaction of 1,3-dicarbonyl compound or an equivalent reagent with formamide provides a route of several pyrimidine which are unsubstituted at the 2-position.



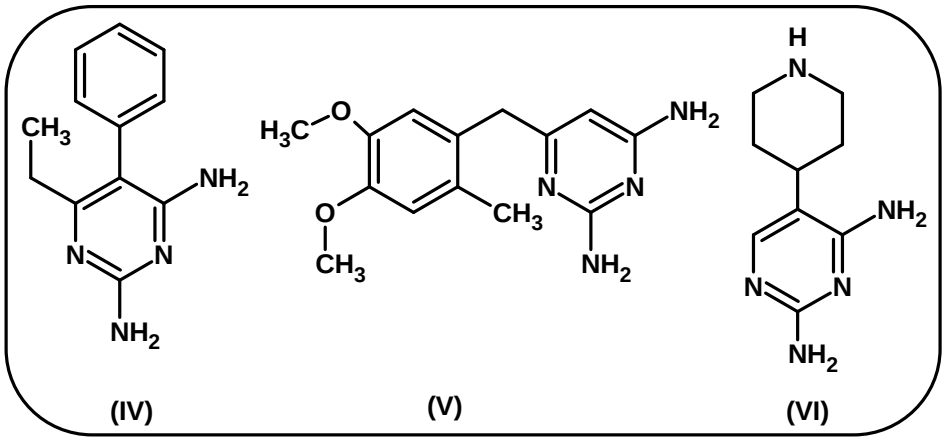
REACTION MECHANISM

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



THERAPEUTIC IMPORTANCE

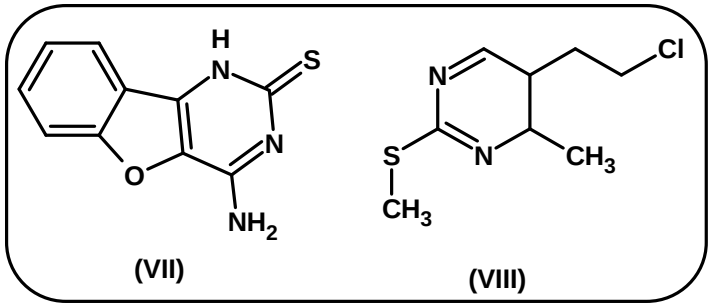
Large number of drugs possess pyrimidine ring system. Well-known antimalarial agents like hypotensive agent like minoxidil (IV), pyrimethamine (V), antibacterial agent like ormetraprim (VI) possess pyrimidine ring system.



Pyrimidine derivatives exhibit a wide spectrum of pharmacological activities few of them are as under.

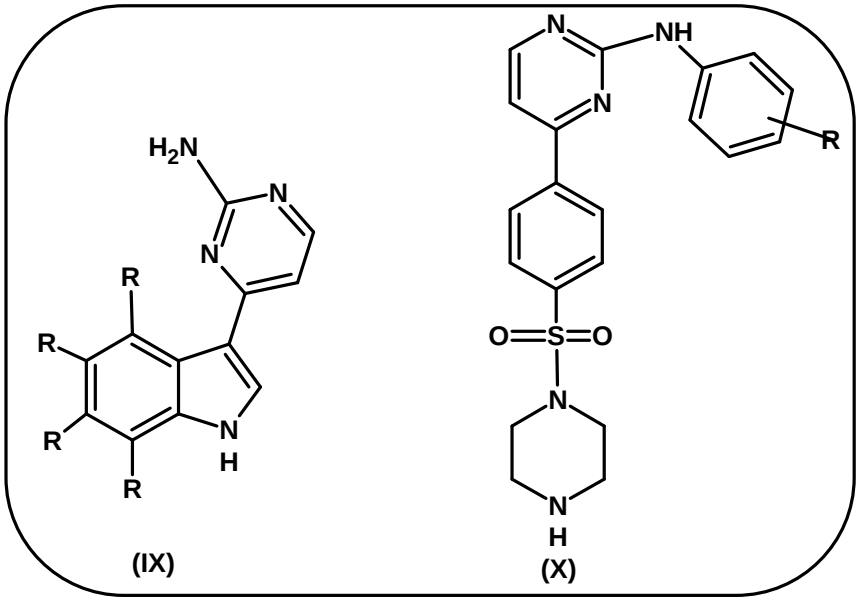
1. Antitubercular[315]
2. Antidiabetic[316]
3. Anticonvulsant[317]
4. Fungicidal[318]
5. Insecticidal[319]
6. Analgesic[320]
7. Tranquilizing[321]
8. Antibacterial[322]
9. Diuretic[323]
10. Antihypertensive[324]

S. S. Sangopure[325] have tested the antimicrobial activity of benzofuro[3,2 d]pyrimidine derivatives (VII). El Sayed[326] have synthesized alkylated substituted mercapto pyrimidine derivatives (VIII) and studied their anticancer and antineoplastic activity. H. Y. Moustafa[327] have reported some pyrimidine derivatives and studied their biological activities.



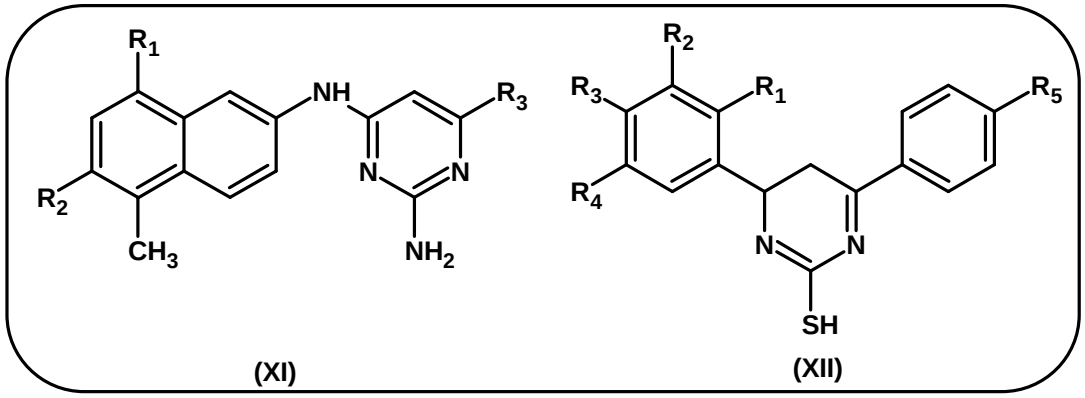
(VII) (VIII)

Marie Gompel and co-workers[328] have showed that meridianins inhibit various protein kinases such as cyclin-dependent kinases, glycogen Synthase kinase-3, cyclic nucleotide-dependent kinases and casein kinase (IX). H. Alistair et al.[329] have Synthesized a novel series of aminopyrimidine IKK-2 inhibitors which show excellent *in vitro* inhibition of this enzyme and good selectivity over the IKK1 isoform. The relativen potency and selectivity of these compounds has been rationalized using QSAR and structure based modelling (X).



(IX) (X)

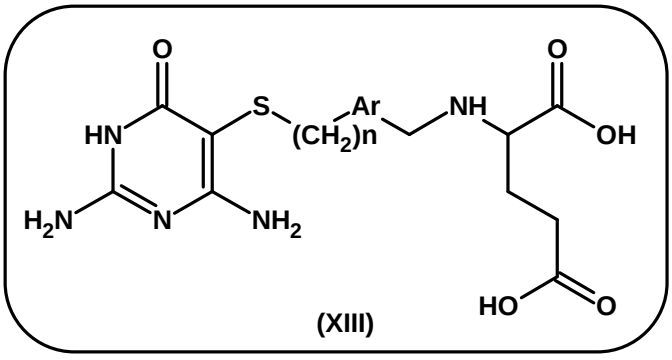
L. R Patil. et al.[330] have synthesized some new pyrimidines bearing paracetamol and imidazolyl moieties. B. J. Ghiya et al.[331] synthesized some mercapto pyrimidine derivatives (XI) and screened for their anticancer, antitubercular and anti HIV activities. N. V. Kaplina and co-workers[332] shows herpes inhibiting activity of some mercapto pyrimidine derivatives (XII).



(XI) (XII)

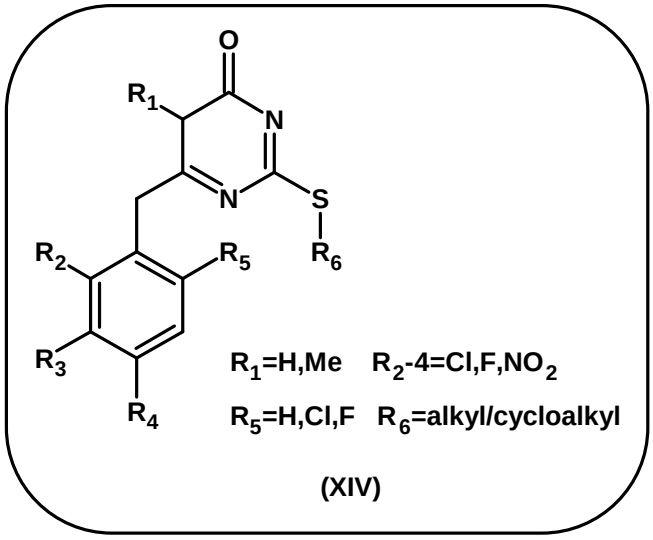
Moreover, B. Chaudhari et al.[333] prepared N6-(2-aminopyrimidin-4-yl)-quinoline-4,6-diamine as N-type calcium channel antagonists for the treatment of pain. E.Devi Sree and co-workers[334] have prepared pyrimidine derivatives and tested for antimicrobial activity. A. L Kovalenko.[335] synthesized and reported antifungal activity of pyrimidine derivatives. P. Shiv Singh and co-workers[336] synthesized 4-(4-pyrazolyl)-2-aminopyrimidines and tested them for their antimicrobial activity.

D.Michael Varney and co-workers[337] 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.



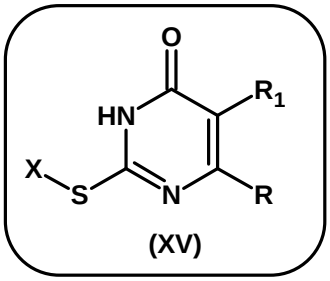
(XIII)

Paolo La Colla et al.[338] have synthesized various 5-alkyl-2-(alkyl/cycloalkkyl thio)-6-(2,6-dichloro/2,6-difluoro phenylmethyl)-3,4-dihydropyrimidin-4(3H)-ones (XIV) and tested as anti-HIV agents in both cell-based and enzyme (recombinant reverse transcriptase)assay.



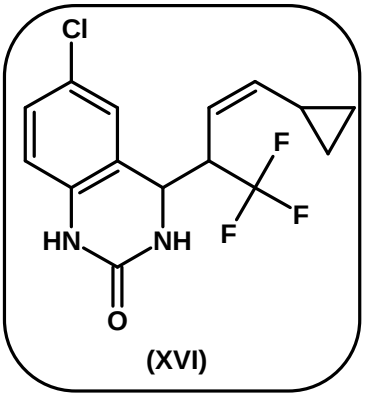
(XIV)

V. Lather and co-workers[339] have been proposed to predict the anti-HIV activity of dihydro (alkylthio) (naphthylmethyl) oxopyrimidines (XV). These models are capable of providing lead structures for development of potent but safe anti-HIV agents.



(XV)

J. L. Whittingham et al.[340] have described pyrimidine ring as a platform for antimalarial drug. G. Z. Han et al.[341] documented the pyrimidine derivatives as anticancer actions of 2-methoxyestradiol and microtubule-disrupting agents in human breast cancer. D. K. Tack et al.[342] reported anthracycline *vs* nonanthracycline therapy for breast cancer. P. Cano-Soldado et al.[343] have described pyrimidine nucleus as an inhibitors of HIV-1 reverse transcriptase. M. Gompel et al.[344] have isolated pyrimidine derivatives,a new family of protein kinase inhibitors from the ascidian aplidium meridianum. Junmei Wang et al.[345] have prepared pyrimidine (XVI) as HIV-1 Reverse Transcriptase.

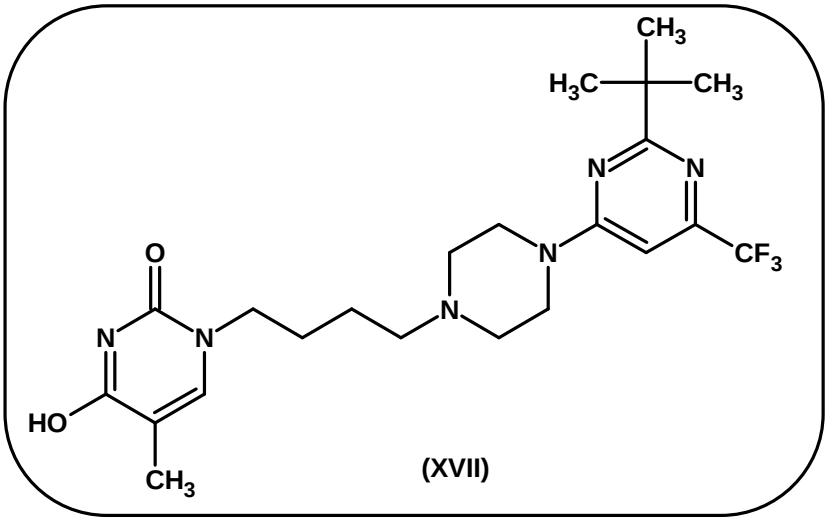


(XVI)

T. Shimizu co-workers[346] have described N3-substituted pyridine and related pyrimidine nucleosides as antinociceptive effects in mice. C. Sanmartin et al.[347] have prepared new symmetrical derivatives as cytotoxic agents and apoptosis inducers. A. Agarwal et al.[348] have synthesized 2,4,6-trisubstituted pyrimidine derivatives as pregnancy interceptive agents.

S. Shigeta et al.[349] 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[350] synthesized substituted 1H-pyrimidin-2-one (XVII) with selective dopamine D3-receptor antagonists activity.

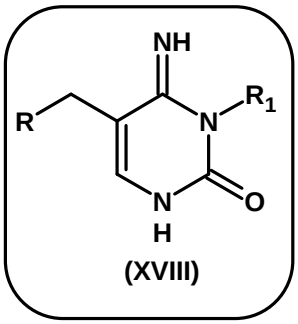


(XVII)

A. Mai et al.[351] 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. I. Yamamoto et al.[352] have reported some oxopyrimidines searching for the

novel antagonist or agonist of barbiturates to the sleep mechanism based on the uridine receptor. Y.L. Huang et al.[353] have synthesized non classical antifolates, 5-(Nphenylpyrrolidin – 3 – yl) - 2, 4, 6 – triaminopyrimidinesand 2, 4 -diamino-6(5H)-oxopyrimidinesas antitumor activity.

S. batra et al.[354] 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 (XVIII). All the compounds were tested for their antibacterial activity.



(XVIII)

2-(Arylcarbonylmethyl)thio-6-alpha-naphthylmethyl derivatives of dihydro alkoxy benzyl oxopyrimidines[355] (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 research 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 4" -[2 -(4'-chlorophenyl -6 - methylimidazo [1, 2 – a] pyridin – 3 – yl] - 6" – aryl - 2" - aminopyrimidines.

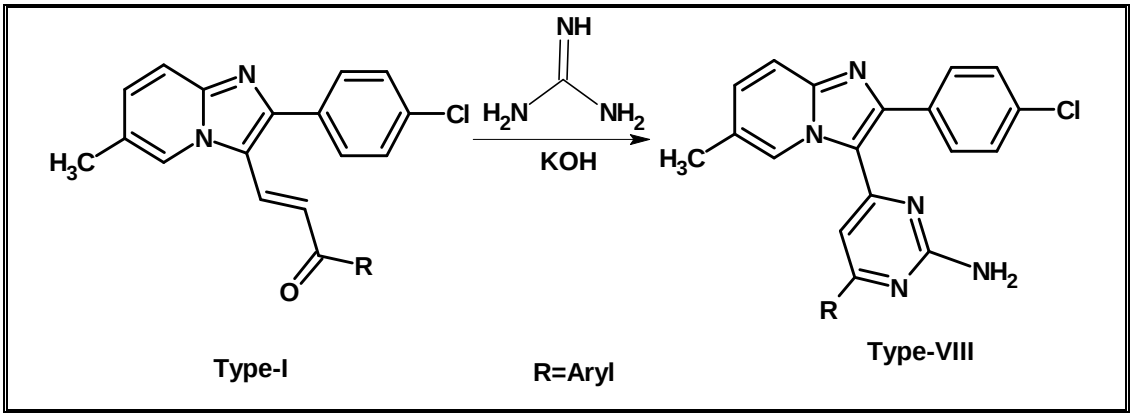
SECTION-II :Synthesis and biological Screening of 6"-[2-(4'- chlorophenyl) -6 - methylimidazo [1, 2 – a] pyridine – 3-yl]- 4"-arylpyrimidin-2"(1"H)-ones.

SECTION-III :Synthesis and biological Screening of 6"-[2-(4'- chlorophenyl) -6-methyl imidazo [1, 2 – a] pyridin-3-yl] - 4" - aryl pyrimidine-2"- (1"H)-thiones.

SECTION – I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]-6"-ARYL-2"-AMINOPYRIMIDINES.

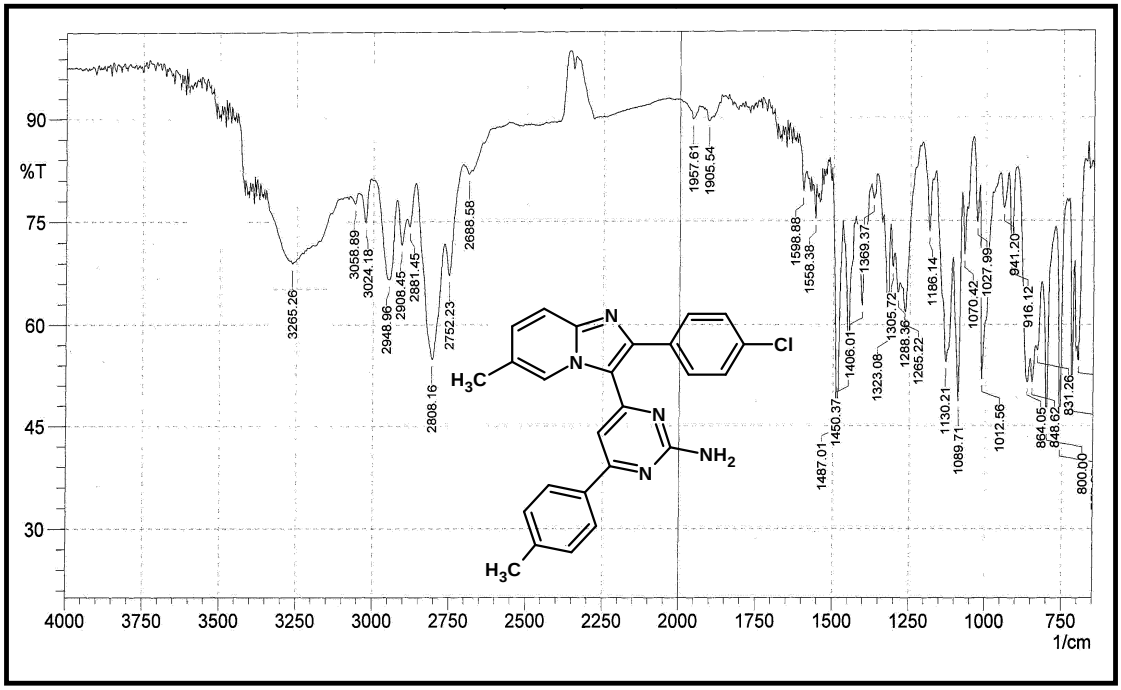
Aminopyrimidines represent one of the most active classes of compounds possessing a wide spectrum of biological activities, such as significant *in vitro* activity against DNA and RNA viruses including polio viruses, diuretic, antitubercular activity etc. These valid observation led us to synthesize 4" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl-2"-aminopyrimidines of Type (VIII) by cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl- 2"-propene-1"one-3-yl]-imidazo[1,2-a]pyridine of Type (I) and guanidine hydrochloride in presence of KOH as catalyst.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared,^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I page no. 41

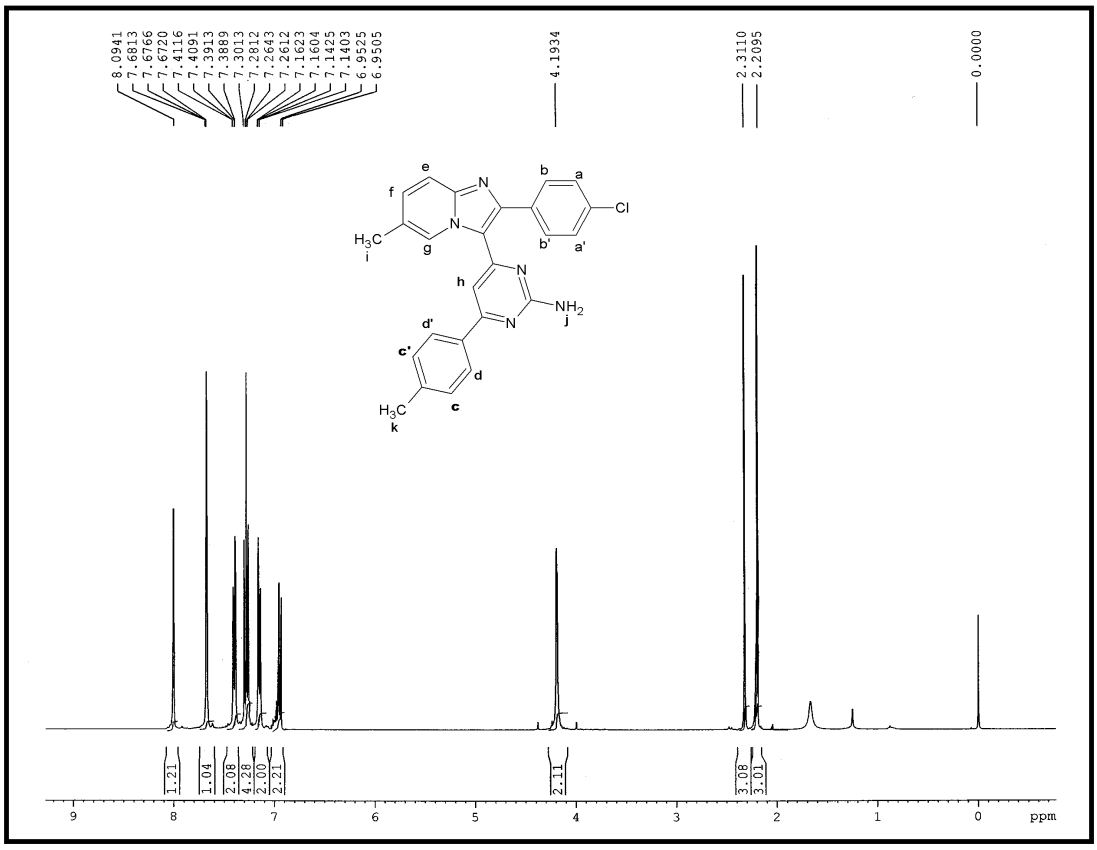
IR SPECTRAL STUDY OF 4" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2 – a] PYRIDIN – 3 – YL] - 6"-(4'''-METHYLPHENYL)-2"-AMINOPYRIMIDINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2908	2990-2850	648
	C-H str. (sym.)	2880	2880-2860	"
	C-H def. (asym.	1450	1470-1430	"
	C-H def. (sym.)	1369	1395-1370	"
Aromatic	C-H str.	3058	3090-3030	"
	C=C str	1450	1600-1450	"
	C-H i.p. (def.)	1130	1300-1100	"
Imidazo[1,2-a] pyridine	C=N str.	1630	1612-1593	649
	C-N str.	1070	1220-1020	"
Pyrimidine	N-H str. (-NH_2)	3265	3350-3250	"
	C=N str.	1558	1612-1550	"
	C-N str.	1186	1220-1020	"
Halide	C-Cl str.	800	600-800	"

NMR SPECTRAL STUDY OF 4" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN -3-YL]- 6"-(4"'-METHYLPHENYL)-2"-AMINOPYRIMIDINE.



Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

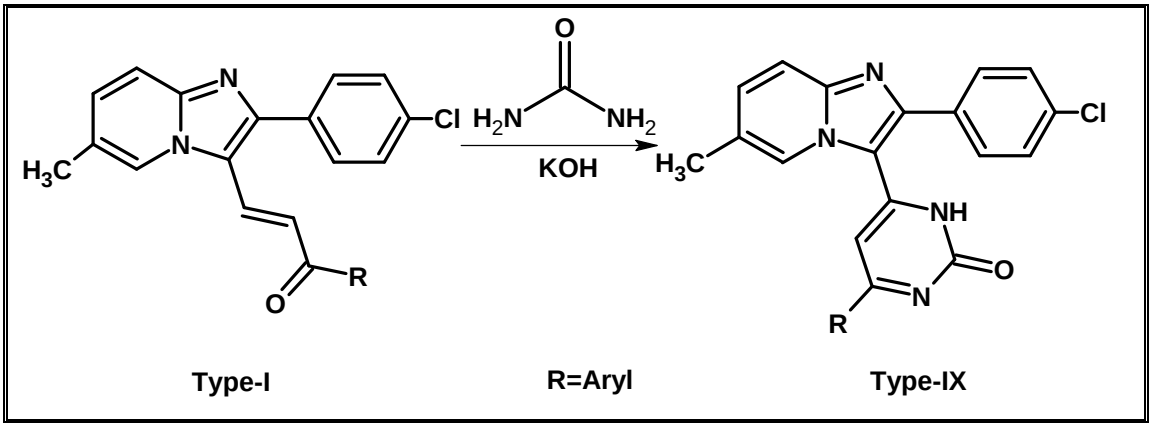
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.20	3H	Singlet	Ar-CH_3(j)
2	2.31	3H	Singlet	Ar-CH_3(k)
3	4.19	2H	Singlet	Ar-NH_2(i)
4	6.95	2H	doublet	Ar-H(f,h)
5	7.14 -7.16	2H	doublet	Ar-H(cc')
6	7.26-7.30	4H	doublet	Ar-H(aa',dd')
7	7.38-7.41	2H	doublet	Ar-H(bb')
8	7.69-7.68	1H	singlet	Ar-H(e)
9	8.09	1H	Singlet	Ar-H(g')

MASS SPECTRAL STUDY OF 4" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 6"-(4"'-METHYLPHENYL)-2"-AMINOPYRIMIDINE.

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6" - [2 - (4' - CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-ARYLPYRIMIDIN-2"(1"H)-ONES.

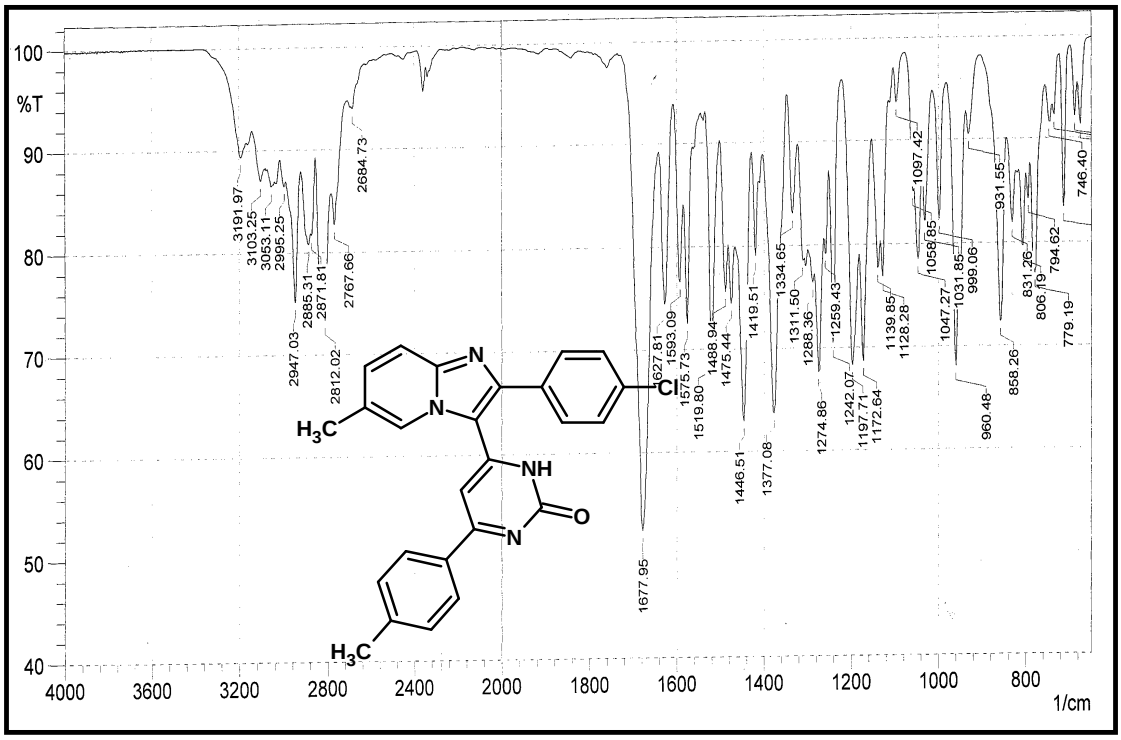
Looking to the interesting therapeutic activity of pyrimidinone ring system, It was considered worthwile to synthesis compounds bearing pyrimidine liked to the pyrimidinone nucleus. In the past years considerable evidence has been accumulated to demonstrate the efficiency of pyrimidinones. The compounds of 6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]- 4"-arylpyrimidin-2"(1"H)-ones of Type (IX) have been prepared by the condensation of 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo[1,2-a]pyridine of Type (I) with urea in presence of basic catalyst.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared,^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I page no. 41

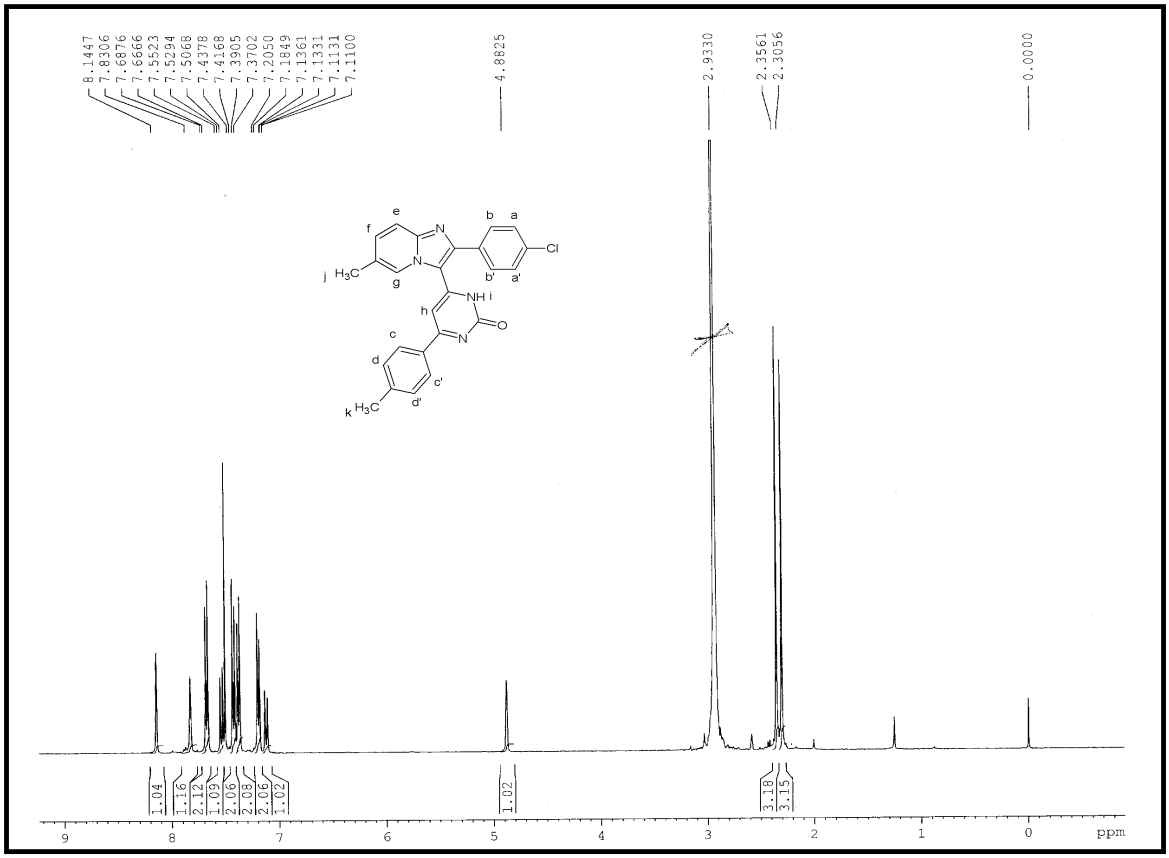
IR SPECTRAL STUDY OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL] - 4" - (4''' – METHYLPHENYL) PYRIMIDIN-2"-(1"H) ONE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2994	2990-2850	648
	C-H str. (sym.)	2871	2880-2860	"
	C-H def. (asym.)	1446	1470-1435	"
	C-H def. (sym.)	1377	1390-1370	"
Aromatic	C-H str.	3053	3090-3030	"
	C=C str	1475	1450-1600	"
	C-H i.p. (def.)	1197	1300-1100	"
Oxopyri.	C=O str.	1677	1680-1652	649
Imidazo[1,2-a] pyridine	C=N str.	1627	1630-1593	"
	C-N str.	1128	1220-1020	"
Halide	C-Cl str.	779	800-600	"

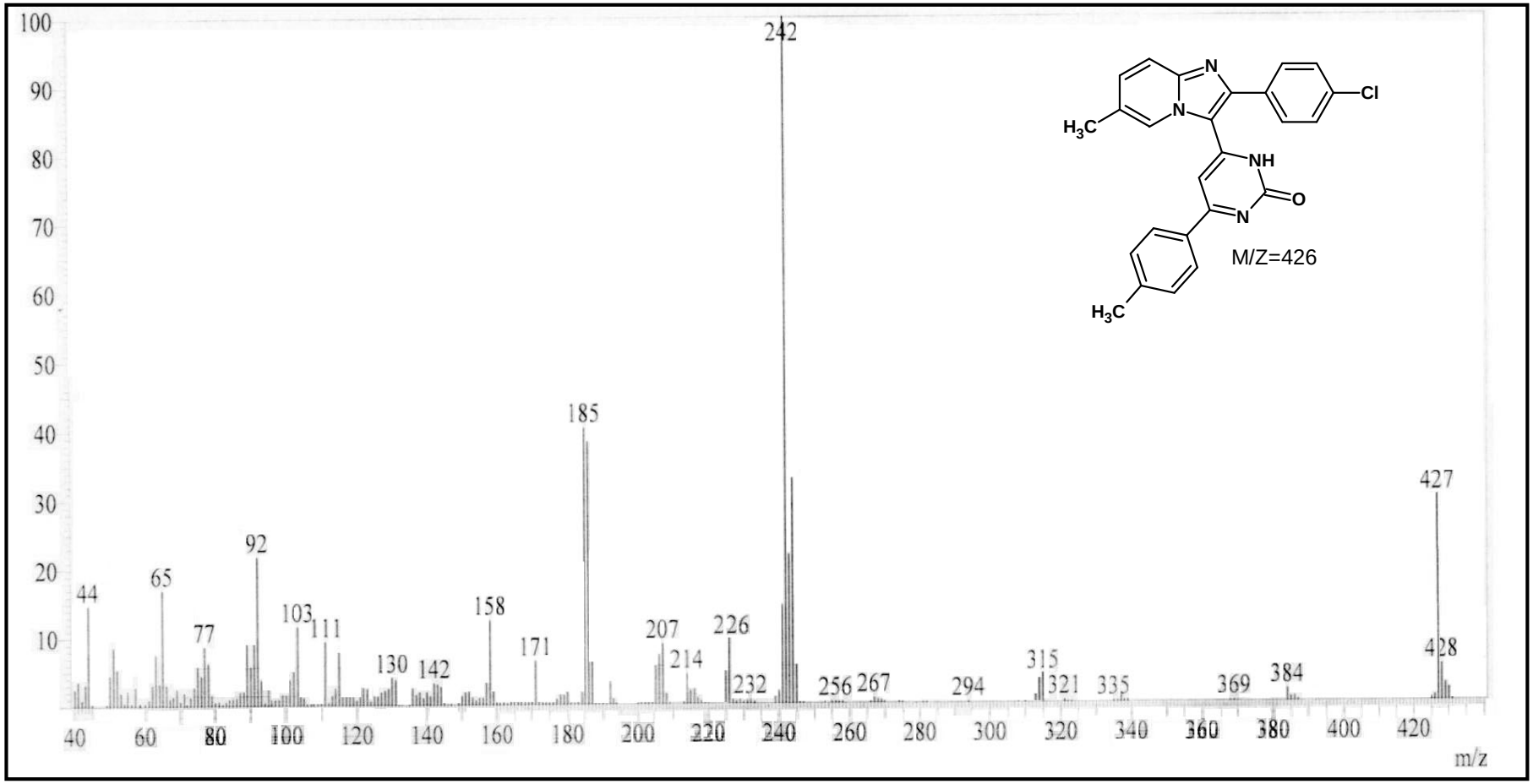
NMR SPECTRAL STUDY OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL] - 4" - (4''' – METHYLPHENYL) PYRIMIDIN-2"-(1"-H) ONE.

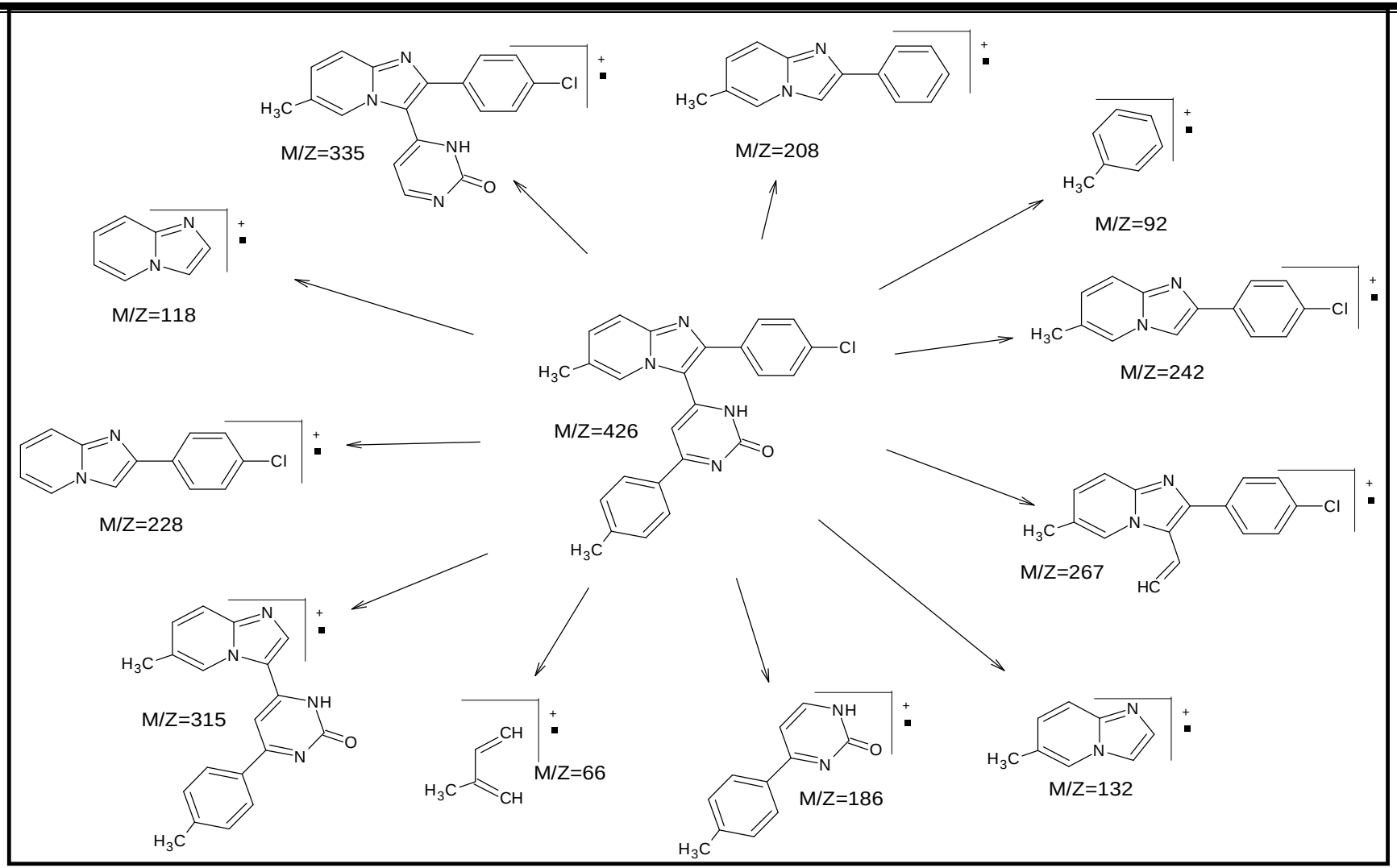


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

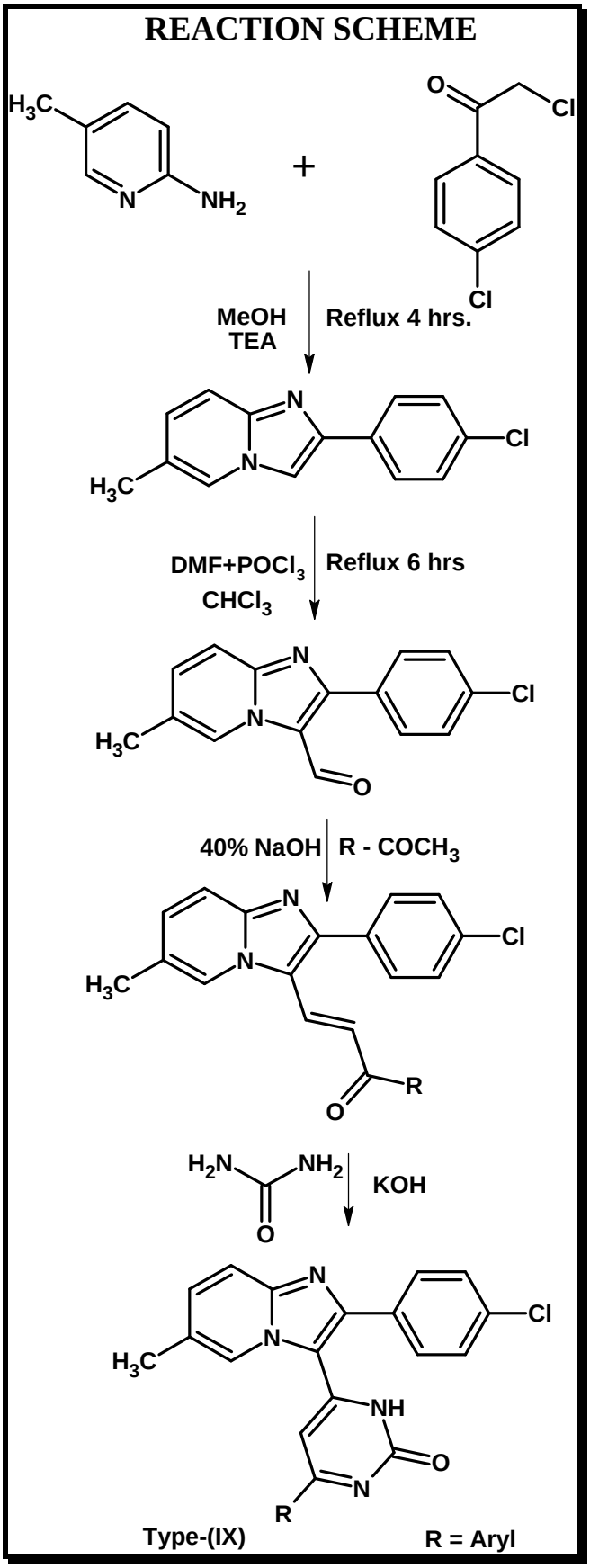
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.30	3H	singlet	Ar-CH_3(j)
2	2.35	3H	singlet	Ar-CH_3(k)
3	4.88	1H	singlet	Ar-H(h)
4	7.11-7.13	1H	doublet	Ar-H(f)
5	7.18 -7.20	2H	doublet	Ar-H(dd')
6	7.37-7.39	2H	doublet	Ar-H(aa')
7	7.41-7.43	2H	doublet	Ar-H(cc')
8	7.52-7.55	1H	doublet	Ar-H(e)
9	7.66-7.68	2H	doublet	Ar-H(bb')
10	7.83	1H	singlet	Ar-NH(i)
11	8.14	1H	singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL] - 4" - (4''' – METHYLPHENYL) PYRIMIDIN-2"(1"-H) -ONE.




M/Z=335
M/Z=208
M/Z=92
M/Z=118
M/Z=242
M/Z=426
M/Z=228
M/Z=267
M/Z=315
M/Z=66
M/Z=186
M/Z=132

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-ARYLPYRIMIDIN-2"(1"H)-ONES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See(A), Part-I, Section-I (A),on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'methylphenyl)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no. 37

[D] Synthesis of 6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3- yl]- 4"-(4"'methylphenyl)pyrimidin-2"(1"H)-ones(9i).

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (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 hrs. The excess solvent was distilled out and the product was poured in to crused ice, the separated solid was filtered out and crystallized from ethanol. Yield 65 %, m.p. 165^{o}C ($C_{25}H_{19}ClN_4O$; Required : C, 70.34; H, 4.49; N, 13.12%; found : C, 70.33; H, 4.45; N, 13.11%;)

Similarly, other 6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridine 3- yl]- 4"-arylpyrimidin-2"(1"H)-ones. were prepared. The physical data are recorded in Table No.9

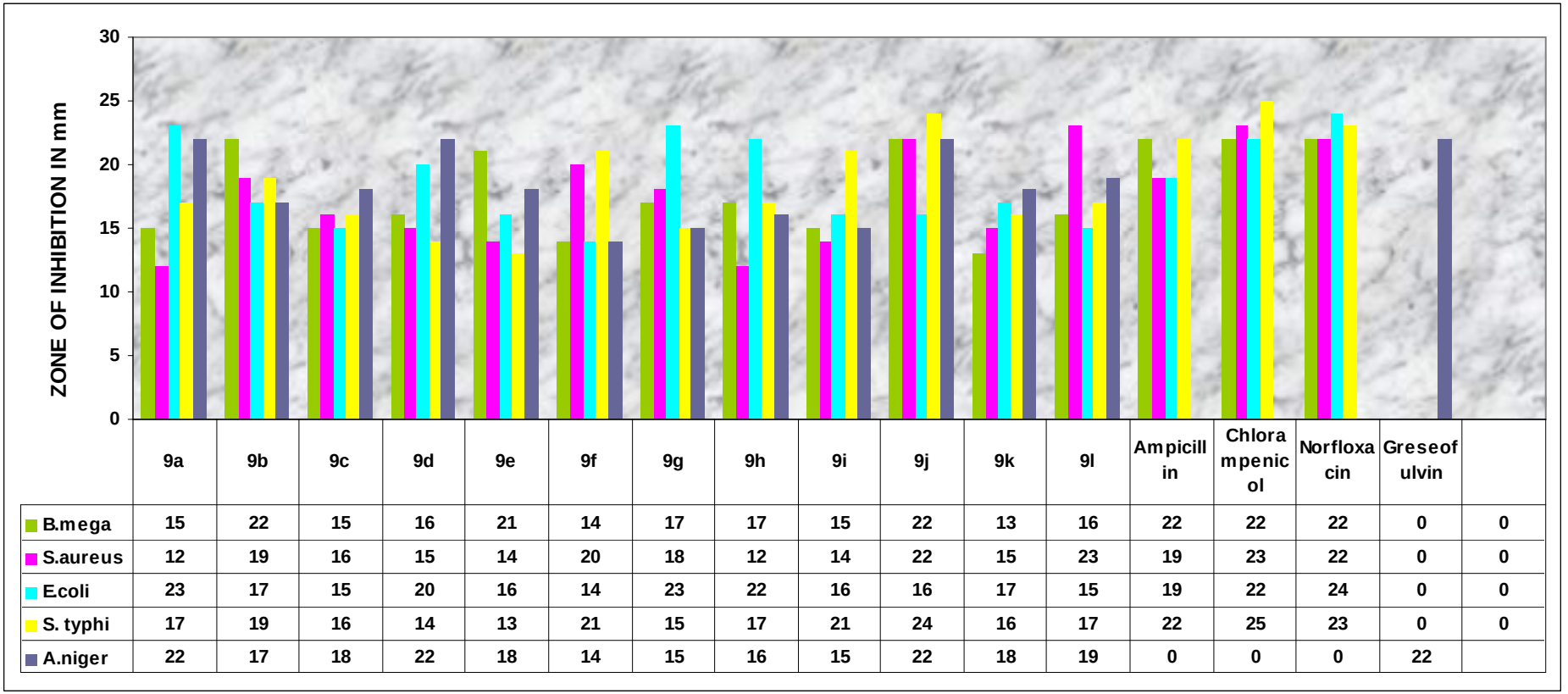
[E] Biological Screening of of 6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin- 3- yl]- 4"-aryl pyrimidin-2"(1"H)-ones.

Biological Screening were carried out as described in Part-I, Section-1 page no.38 The zones of inhebition of test solution are recorded in Graphical Chart no-9.

TABLE NO. 9 PHYSICAL COSTANTS OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL] - 4" – (ARYL) PYRIMIDIN-2"-(1"H)- ONES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
9a	C_6H_{5-}	$C_{24}H_{17}ClN_4O$	412.5	189	60	13.57	13.56
9b	3-Cl-C_6H_4 -	$C_{24}H_{16}Cl_2N_4O$	447.0	168	68	12.53	12.51
9c	4-Cl-C_6H_4 -	$C_{24}H_{16}Cl_2N_4O$	447.0	155	74	12.53	12.51
9d	2-4-$(Cl)_2$-C_6H_{3-}	$C_{24}H_{15}Cl_3N_4O$	481.5	190	55	11.63	11.60
9e	4 -F-C_6H_{4-}	$C_{24}H_{16}ClFN_4O$	430.5	183	59	13.00	13.00
9f	4-Br-C_6H_{4-}	$C_{24}H_{16}BrClN_4O$	491.5	192	66	11.39	11.35
9g	4 -OH-C_6H_{4-}	$C_{24}H_{17}ClN_4O_2$	428.5	170	63	13.06	13.03
9h	4-NH_2-C_6H_{4-}	$C_{24}H_{18}ClN_5O$	427.5	205	70	16.37	16.35
9i	4-CH_3-C_6H_{4-}	$C_{25}H_{19}ClN_4O$	426.5	165	65	13.12	13.11
9j	4-OCH_3-C_6H_{4-}	$C_{25}H_{19}ClN_4O_2$	442.5	198	56	12.65	12.63
9k	3-NO_2-C_6H_{4-}	$C_{24}H_{16}ClN_5O_3$	457.5	166	67	15.30	15.28
9l	4-NO_2-C_6H_{4-}	$C_{24}H_{16}ClN_5O_3$	457.5	174	60	15.30	15.27

GRAPHICAL CHART NO. 9: BIOLOGICAL SCREENING OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL] –4" – (ARYL) PYRIMIDIN-2"-(1"H)- ONES.



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	15	22	15	16	21	14	17	17	15	22	13	16	22	22	22	0	0
S.aureus	12	19	16	15	14	20	18	12	14	22	15	23	19	23	22	0	0
E.coli	23	17	15	20	16	14	23	22	16	16	17	15	19	22	24	0	0
S. typhi	17	19	16	14	13	21	15	17	21	24	16	17	22	25	23	0	0
A.niger	22	17	18	22	18	14	15	16	15	22	18	19	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-V

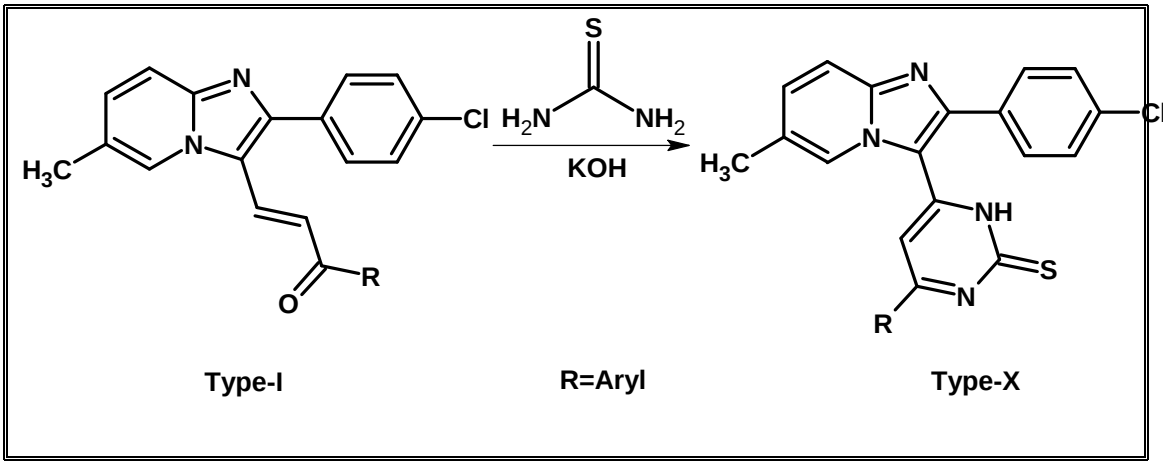
SECTION – II: BIOLOGICAL SCREENING OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1, 2-a] PYRIDIN-3-YL] – 4" – (ARYL) PYRIMIDIN-2"-(1"H)- ONES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E. coli***	***S. typhi***	***A. niger***
		9b-(22)	**9b-(19)**	**9a-(23)**	**9f-(21)**	**9a-(22)**
		9e-(21)	**9f-(20)**	**9d-(20)**	**9i-(21)**	**9d-(22)**
		9j- (22)	**9j-(22)**	**9g-(23)**	**9j-(24)**	**9j-(22)**
			9l-(23)	**9h-(22)**		
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

SECTION-III

SYNTHESIS AND BIOLOGICAL SCREENING OF 6"-[2 -(4' -CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-ARYL PYRIMIDINE-2"-(1"H)-THIONES

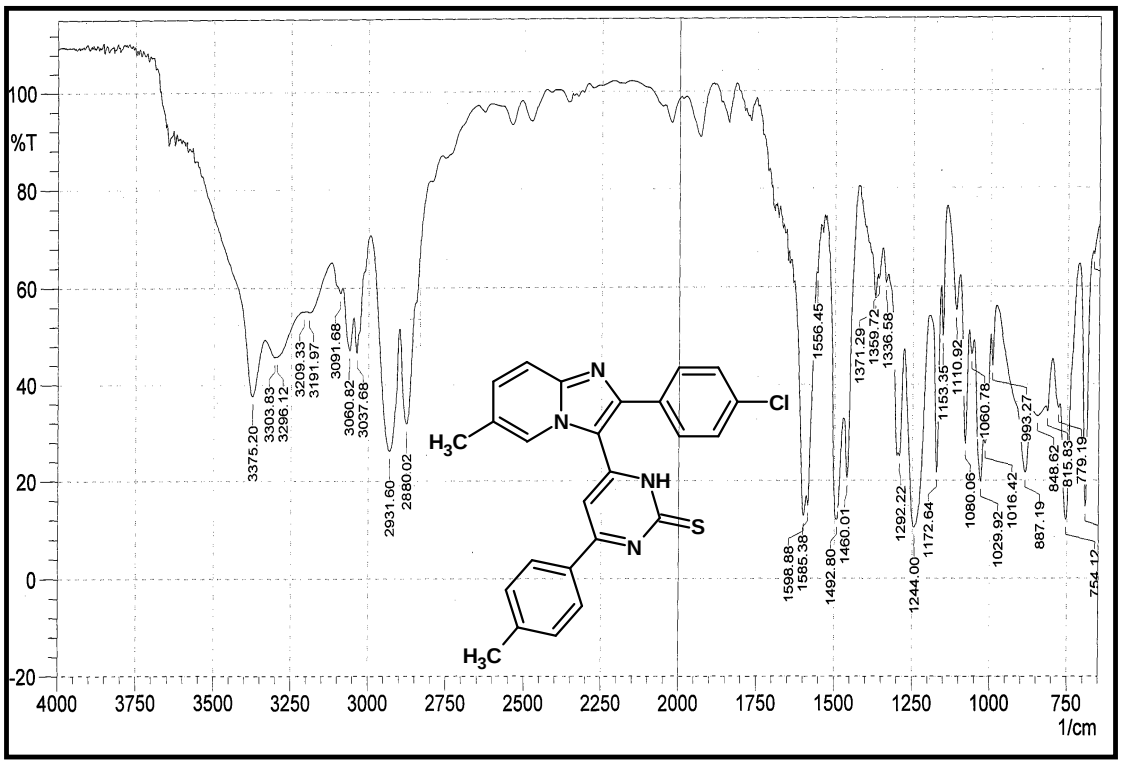
Compounds containing pyrimidine ring are widely available in nature. Many thio pyrimidine derivatives are reported to possess different therapeutic activities. In view of these findings, it was considered worthwhile to synthesize some new 6" -[2-(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones of Type (X) have been prepared by the reaction of 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo[1,2-a]pyridine of Type (I) with thiourea in presence of basic catalyst KOH.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I page no. 41

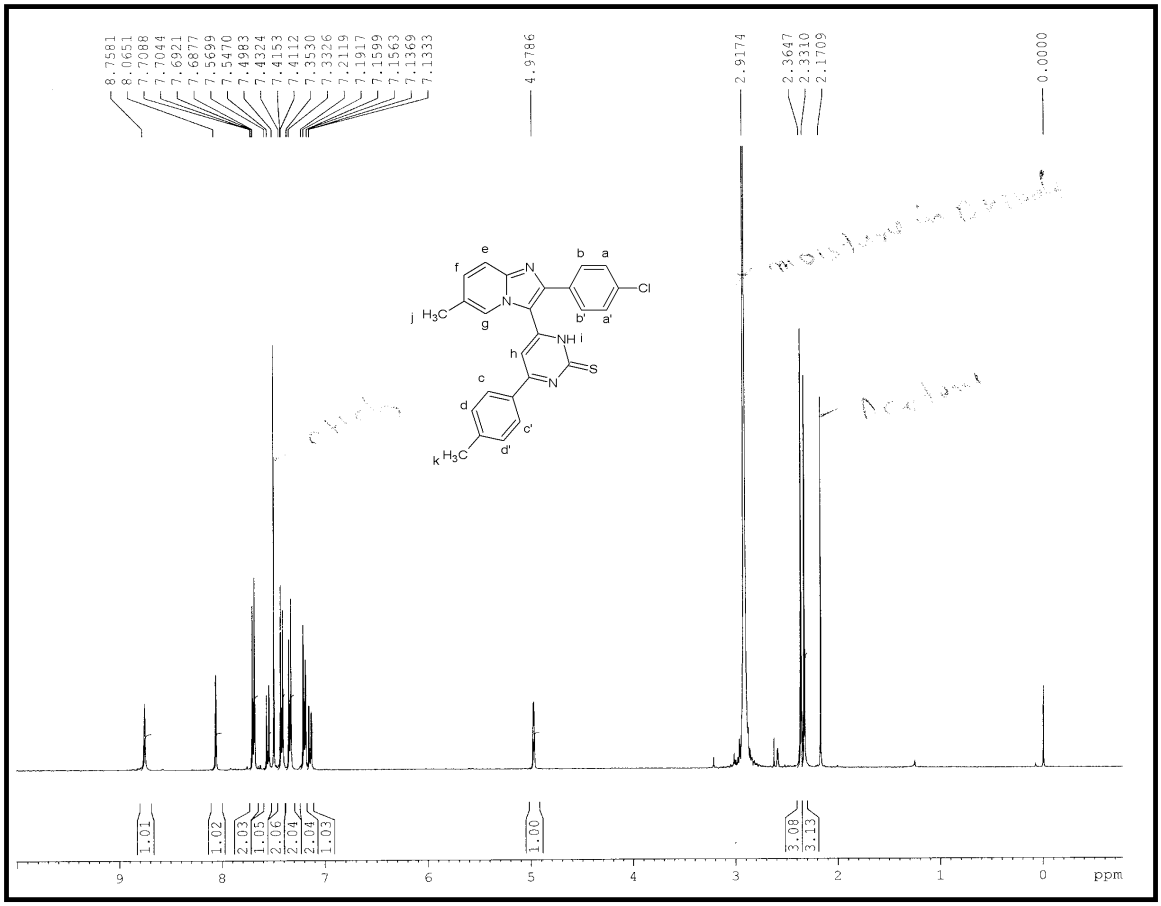
IR SPECTRAL STUDY OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-(4'''-METHYLPHENYL) PYRIMIDINE-2"-(1"H)-THIONE.



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

Type	Vibretion Mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2931	2990-2850	648
	C-H str. (sym.)	2880	2880-2860	"
	C-H def. (asym.	1460	1470-1435	"
	C-H def. (sym.)	1371	1390-1370	"
Aromatic	C-H str.	3060	3090-3030	"
	C=C str	1492	1450-1600	649
	C-H i.p. (def.)	1172	1300-1100	"
Thiopyri.	C=S str.	1158	1590-1550	"
Imidazo[1,2-a] pyridine	C=N str.	1598	1630-1593	
	C-N str.	1080	1220-1020	"
Halide	C-Cl str.	779	800-600	"

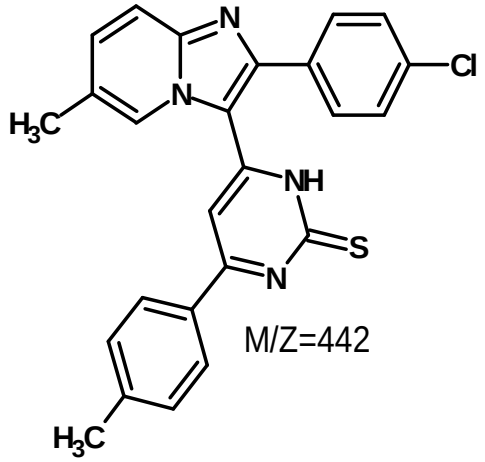
NMR SPECTRAL STUDY OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-(4'''-METHYLPHENYL) PYRIMIDINE-2"-(1"H)-THIONE.

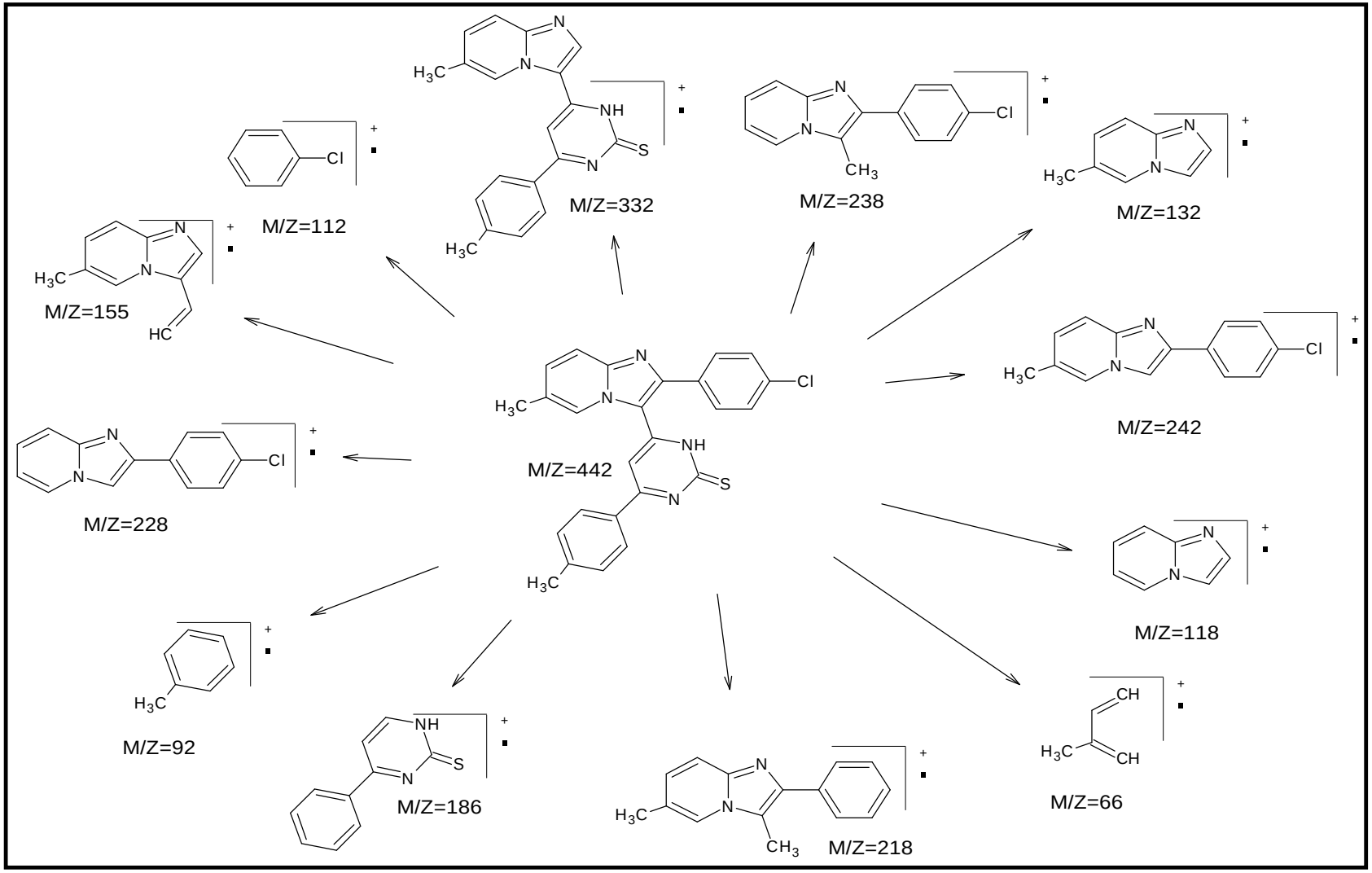


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

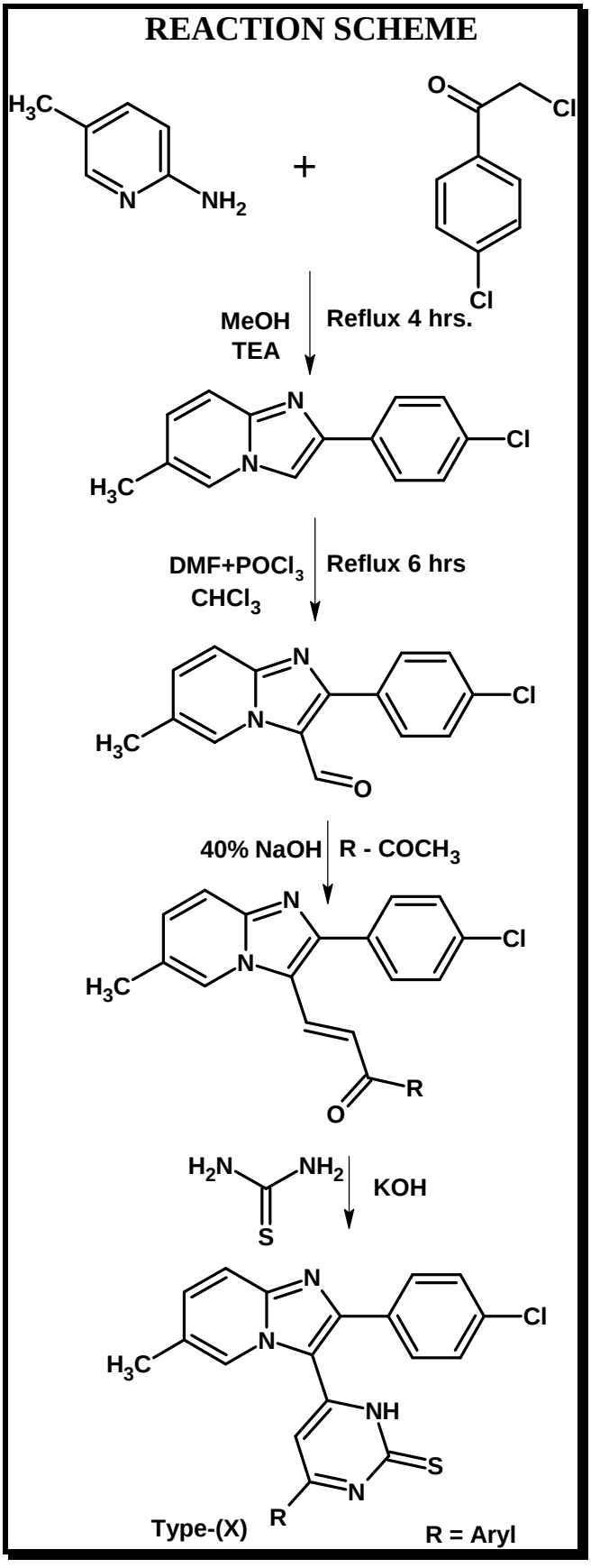
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.33	3H	singlet	Ar-CH_3(j)
2	2.36	3H	singlet	Ar-CH_3(k)
3	4.97	1H	singlet	Ar-H(h)
4	7.13-7.15	1H	doublet	Ar-H(f)
5	7.19 -7.21	2H	doublet	Ar-H(aa')
6	7.33-7.35	2H	doublet	Ar-H(cc')
7	7.41-7.43	2H	doublet	Ar-H(bb')
8	7.54-7.56	1H	doublet	Ar-H(e)
9	7.68-7.70	2H	doublet	Ar-H(dd')
10	8.06	1H	singlet	Ar-NH(g)
11	8.75	1H	singlet	Ar-H(i)

MASS SPECTRAL STUDY OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-(4"'-METHYLPHENYL) PYRIMIDINE-2"-(1"-H)-THIONE.




M/Z=442
M/Z=332
M/Z=238
M/Z=132
M/Z=242
M/Z=118
M/Z=66
M/Z=218
M/Z=186
M/Z=92
M/Z=228
M/Z=155
M/Z=112

REACTION SCHEME



EXPERIMENTALS

SYNTHESIS AND BIOLOGICAL SCREENING OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-ARYL PYRIMIDINE-2"-(1"H)-THIONES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde.

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'- methylphenyl)-2"-propene-1"one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no.37

[D] Synthesis of 6" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-(4"'methylphenyl) pyrimidine-2"-(1"H)-thiones(10i).

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'methylphenyl)- 2"-prop-en-1"ones-3-yl]-imidazo [1,2-a]pyridine (4.27gm, 0.01 mol) and thiourea (0.60gm, 0.01 mol) in ethanol (20 ml) was refluxed in presence of alcoholic KOH for 12 hr. The excess solvent was distilled out and the residue was poured in to crused ice, the separated solid was filtered out and crystallized from ethanol. Yield 68 %, m.p. 170^{o}C ($C_{25}H_{19}ClN_4S$; Required : C, 67.79; H, 4.32; N, 12.65 %; found : C, 67.77; H, 4.30; N, 12.63 %;)

Similarly, other of 6" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones . were prepared. The physical data are recorded in Table No.10

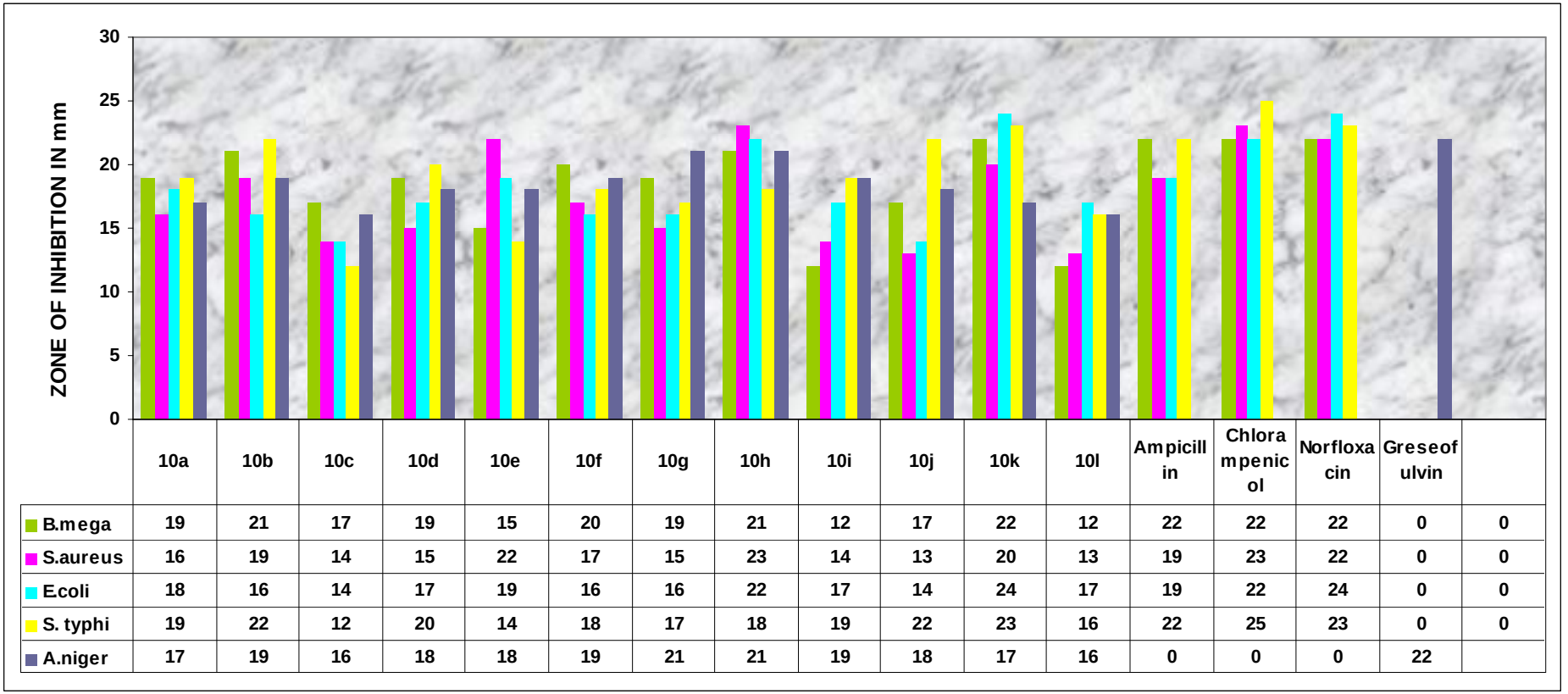
[E] Biological Screening of of 6" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones.

Biological Screening were carried out as described in Part-I, Section-1.page no. 38 The zones of inhebition of test solution are recorded in Graphical Chart No.10

TABLE NO. 10 PHYSICAL COSTANTS OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-(ARYL) PYRIMIDINE-2"-(1"H)-THIONES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
10a	C_6H_{5-}	$C_{24}H_{17}ClN_4S$	428.5	195	79	13.06	13.05
10b	3-Cl-C_6H_4 -	$C_{24}H_{16}Cl_2N_4S$	463.0	188	68	12.09	12.07
10c	4-Cl-C_6H_4 -	$C_{24}H_{16}Cl_2N_4S$	463.0	175	59	12.09	12.08
10d	2-4-$(Cl)_2$-C_6H_{3-}	$C_{24}H_{15}Cl_3N_4S$	497.5	165	72	11.25	11.23
10e	4 -F-C_6H_{4-}	$C_{24}H_{16}ClFN_4S$	446.5	178	66	12.54	12.51
10f	4-Br-C_6H_{4-}	$C_{24}H_{16}BrClN_4S$	507.5	190	55	11.03	11.01
10g	4 -OH-C_6H_{4-}	$C_{24}H_{17}ClN_4OS$	444.5	200	70	12.59	12.56
10h	4-NH_2-C_6H_{4-}	$C_{24}H_{18}ClN_5S$	443.5	168	62	15.78	15.77
10i	4-CH_3-C_6H_{4-}	$C_{25}H_{19}ClN_4S$	442.5	170	68	12.65	12.64
10j	4-OCH_3-C_6H_{4-}	$C_{25}H_{19}ClN_4OS$	458.5	177	63	12.21	12.20
10k	3-NO_2-C_6H_{4-}	$C_{24}H_{16}ClN_5O_2S$	473.5	160	58	14.78	14.76
10l	4-NO_2-C_6H_{4-}	$C_{24}H_{16}ClN_5O_2S$	473.5	180	64	14.78	14.75

GRAPHICAL CHART NO. 10 : BIOLOGICAL SCREENING OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-(ARYL) PYRIMIDINE-2"-(1"H)-THIONES.



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	19	21	17	19	15	20	19	21	12	17	22	12	22	22	22	0	0
S.aureus	16	19	14	15	22	17	15	23	14	13	20	13	19	23	22	0	0
E.coli	18	16	14	17	19	16	16	22	17	14	24	17	19	22	24	0	0
S. typhi	19	22	12	20	14	18	17	18	19	22	23	16	22	25	23	0	0
A.niger	17	19	16	18	18	19	21	21	19	18	17	16	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-V

SECTION – III : BIOLOGICAL SCREENING OF 6" - [2 - (4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2-a] PYRIDIN-3-YL]- 4"-(ARYL) PYRIMIDINE-2"-(1"H)-THIONES.

		Antibacterial activity Zone of inhibition in m. m.		Antifungal activity Zone of inhibition in m. m.		
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
		10b-(21)	**10b-(19)**	**10a-(18)**	**10b-(22)**	**10g-(21)**
		10f-(20)	**10e-(22)**	**10e-(19)**	**10i-(20)**	**10h-(21)**
		10h-(21)	**10h-(23)**	**10h-(22)**	**10j-(22)**	
		10k-(22)	**10k-(20)**	**10k-(24)**	**10k-(23)**	
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

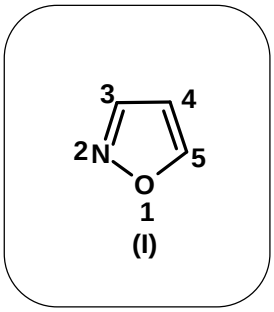
PART-VI

STUDIES ON ISOXAZOLES

STUDIES ON ISOXAZOLES.

INTRODUCTION

Isoxazole 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.[356] 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.

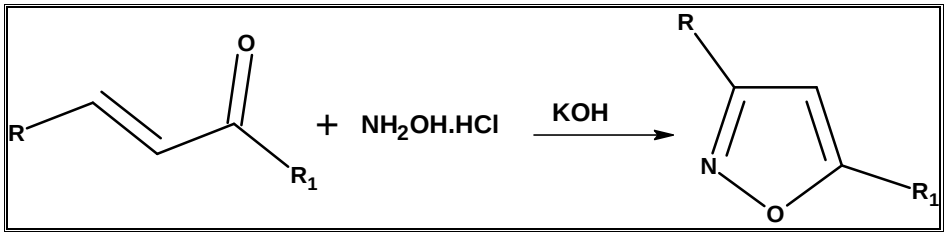


(I)

The next important contribution to the chemistry of isoxazoles was made by A. Quelico[357] in 1945, when he begane to study the formation of isoxazoles from nitrile N-oxide and unsaturated compounds.

SYNTHETIC ASPECT

1. L.S.Crawley and W.J.Fanshawe[358] were prepared isoxazole from α-βunsaturated carbonyl compounds, hydroxyl amine hydrochloride and KOH in methanol.

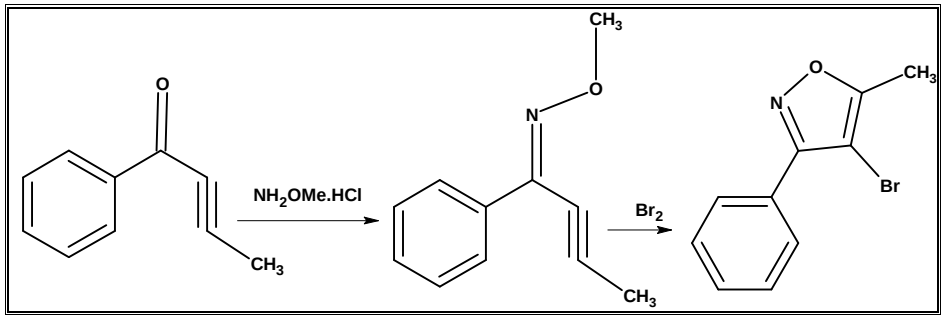


2. Dawood Kamal et al[359] have prepared isoxazole derivatives from enamino nitriles

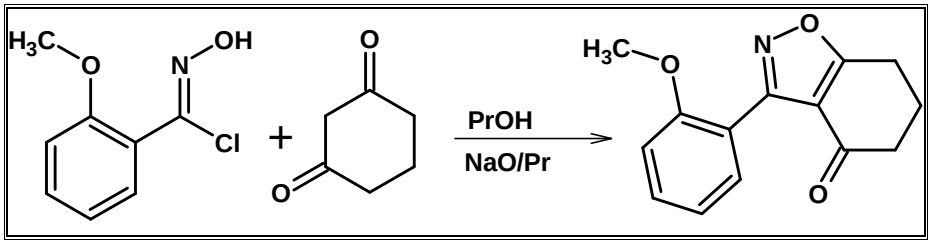
3. V.B.Tayade et al [360] synthesized some new 3,5-diarylisoxazoles from the reaction of 2-aryl acetophenones with hydroxyl amine hydrochloride in presence of alkali.

4. Solid phase synthesis of isoxazole derivatives based on aminoacids was reported by Lidia De Luca and co-workers[361] in the presence of basic catalyst and dichloro methane used as a solvent. One-Pot synthesis of polyfunctionalized isoxazoles[362] have been prepared by the reaction of dipyrrolidinium 3,3-dimethylpentanedinitrile -2,4-dinitronate and acetyl chloride in benzene.

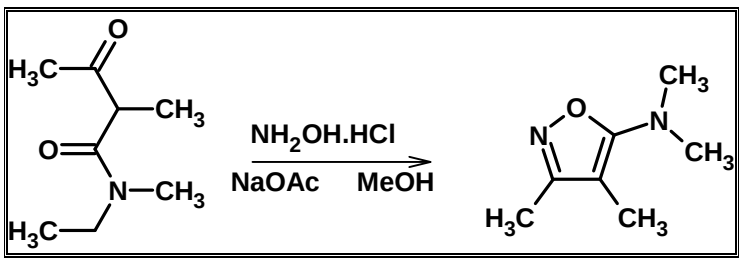
5. A variety of 3,5-disubstituted 4-bromoisoxazoles[363-365] were prepared in good to excellent yields under mild reaction conditions as under.



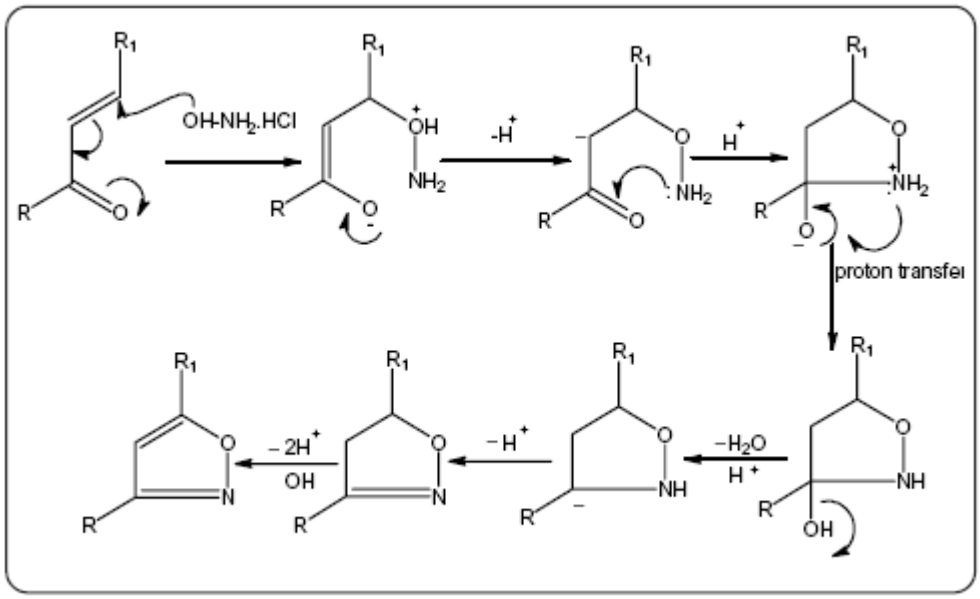
6. Keisuke Suzuki et al[366] have synthesized functionalized isoxazole derivatives by cyclocondensation of C-chlorooximes with cyclic 1,3-diketones.



7. Mark Lautens and Ame´lie Roy[367] have constructed isoxazoles , were achieved in good yields in a rapid and simple way by using *N*-acetoacetyl derivatives.



REACTION MECHANISM



THERAPEUTIC IMPORTANCE

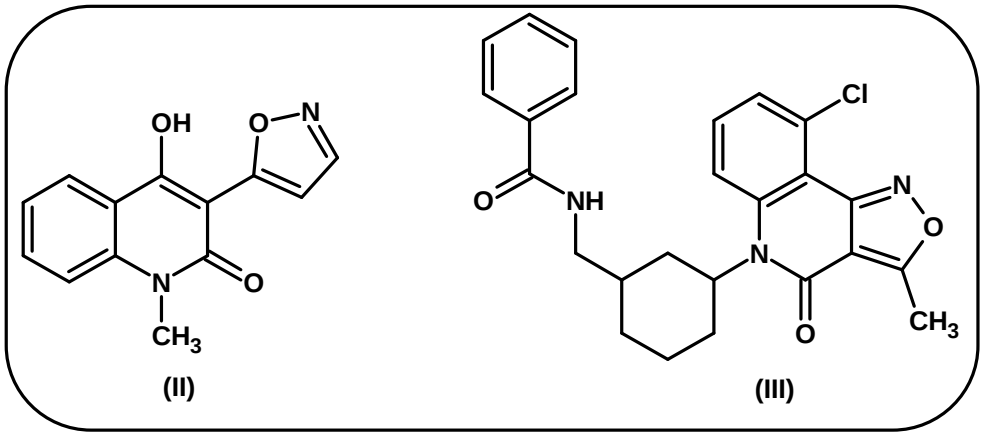
Isoxazole derivatives exhibit various biological activities such as,

1. Antibacterial[368, 369]
2. Anticonvulsant[370, 371]
3. Anticholestermic[372]
4. Anticancer[373]
5. Anthelmintics[374]
6. Antiinflammatory[375-378]
7. Adenosine antagonist[379]
8. Fungicidal[380-382]
9. Herbicidal[383, 384]
10. Hypoglycemic[385]
11. Muscle relaxant[386,387]
12. Nematocidal[388]
13. Insecticidal[389]
14. Antiviral[390]
15. Antimicrobial[391]

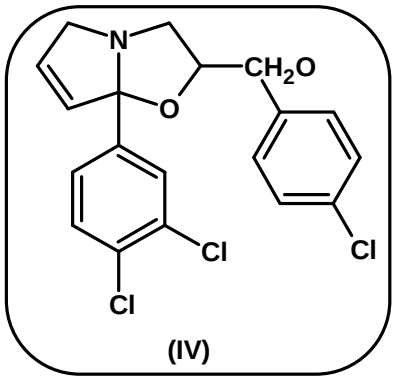
P. M. Welsing et al.[392] have documented the isoxazoles as tumornecrosis factor blocking agents and leflunomide for treating rheumatoid arthritis in the Netherlands.

S. J. Bingham et al.[393]have synthesized isoxazole derivatives as an antiuclear agents.M. R Barbachyn et al.[394] have described the phenylisoxazolines as novel and viable antibacterial agents active against *Gram-positive* pathogens.

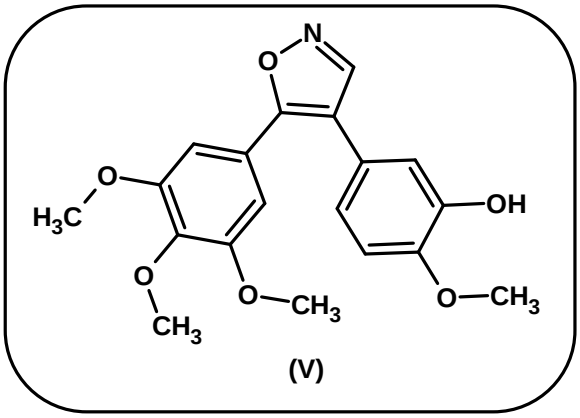
Stefano Chimichi and co-workers[395] have investigated cytotoxic activity of 3-quinolinoyl isoxazoles (II) against leukemia and adenocarcinoma derived cell lines in comparison to the normal human keratinocytes. Novel cyclohexyl drug resistance modulators[396] (III) were synthesized and evaluated for *in vitro* inhibition of the drug resistance transporter, MRP1.



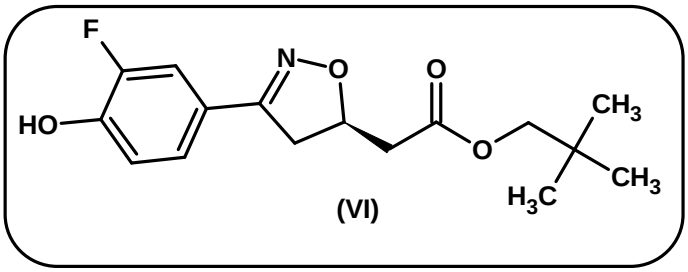
T. D. Aicher et al.[397] reported isoxazoles (IV) as hypoglycemic agents. M. Masui et al.[398] have prepared isoxazoles having pesticidal activity. Some excellent herbicidal results obtained by K.V. Reddy et al.[399]C. B. Xue et al.[400] have reported an oralantiplatelet effect in dogs.



Julia Kaffy et al.[401] have been synthesized various five membered heterocycles with oxygen and nitrogen atoms. The 4,5-diarylisoxazole (V) exhibited greater antitubulin activity, but modest antiproliferative activity. Kai Fan Cheng[402] have been synthesized 3-(4-hydroxyphenyl)-4,5-dihydro-5-aceticacidmethylester isoxazole, an inhibitor of the proinflammatory cytokine MIF, two critical modifications and chiral resolution have significantly improved the potency of the inhibition.Compound (VI) inhibits MIF tautomerase with an IC50 of 550 nM.



(V)



(VI)

Moreover, S. Rung and D. Dus[403] have synthesized some new isoxazoles as remedy for leukemia. M. Scobie and co-workers[404] have prepared isoxazole derivatives and studied their antitumor activity. G. Daidone et al.[405] synthesized 3-(isoxazol- 3-yl)-quinazolin-4-(3H)-one derivative and tested for their analgesic and antiinflammatory activities as well as for their acute toxicity and ulcerogeniceffect. M. W. Salter et al.[406] have prepared some isoxazole as cellular neuroplasticity mechanisms mediating pain persistence. M. Matringe et al.[407] have reported some new p-hydroxyphenylpyruvate dioxygenase inhibitor resistant plants. D. R. Mehlisch et al.[408] have synthesized isoxazole derivative as analgesic efficacy of intramuscular parecoxib sodium in postoperative dental pain. W. A. Ray et al.[409] have reported isoxazole derivative as cardiovascular toxicity of valdecoxib.

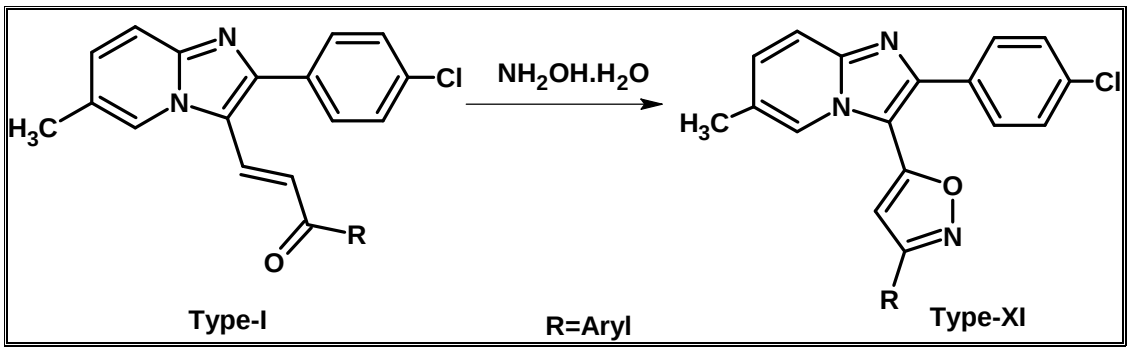
With an intension of preparing the compounds possessing better therapeutic activity, we have under taken the preparation of isoxazoles bearing imidazo[1,2-a]pyridine nucleus which have been described as follows.

SECTION I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2 - (4' - CHLOROPHENYL)-6-METHYL- 3-(3"-ARYL ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-ARYL ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

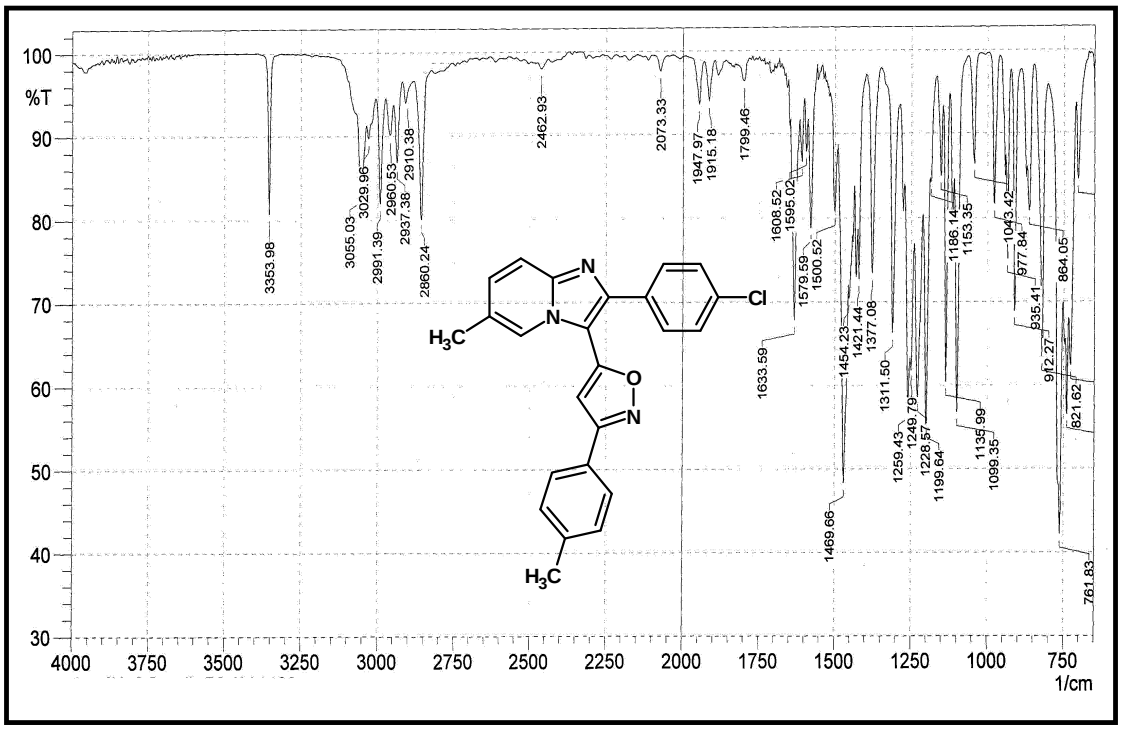
Isoxazoles have been reported to have various pharmacological activities like antibacterial, antifungal, insecticidal etc. In order to achieving better drug potency, we have prepared isoxazole derivatives of Type (XI) by the cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo[1,2-a]pyridine of Type (I) with hydroxylamine hydrochloride.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC,

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I ,Page No. 41

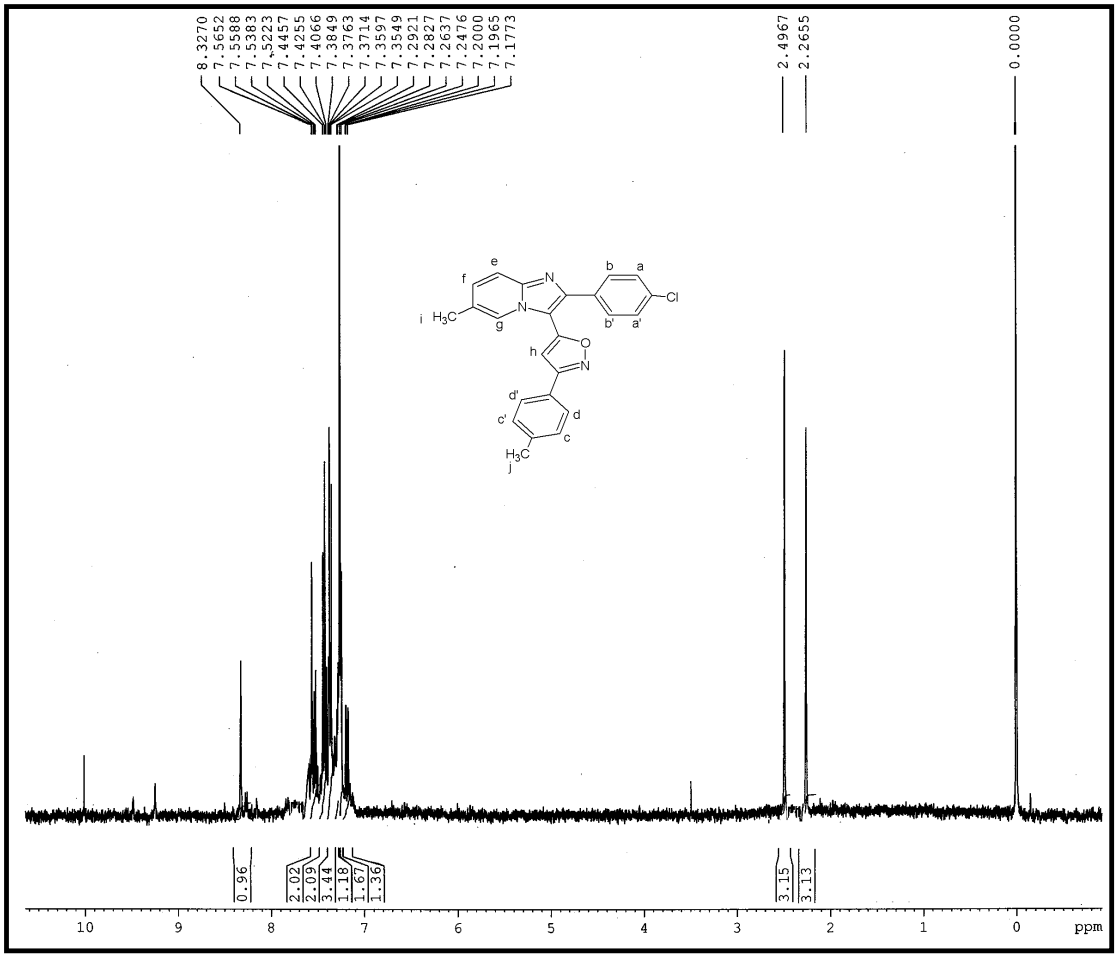
IR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-(4"'-METHYLPHENYL) ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2960	2990-2850	648
	C-H str. (sym.)	2860	2880-2860	"
	C-H def. (asym.)	1469	1470-1435	"
	C-H def. (sym.)	1377	1390-1370	"
Aromatic	C-H str.	3055	3090-3030	649
	C=C str	1500	1600-1450	"
	C-H i.p. (def.)	1199	1300-1100	"
Isoxazole	C=C str	1633	1680-1550	"
	C=N str	1579	1690-1460	"
	N-O str.	821	850-810	"
Imidazo[1,2-a] pyridine	C-N str.	1099	1220-1020	"
	C=N str.	1608	1612-1593	"
Halide	C-Cl str.	761	800-600	"

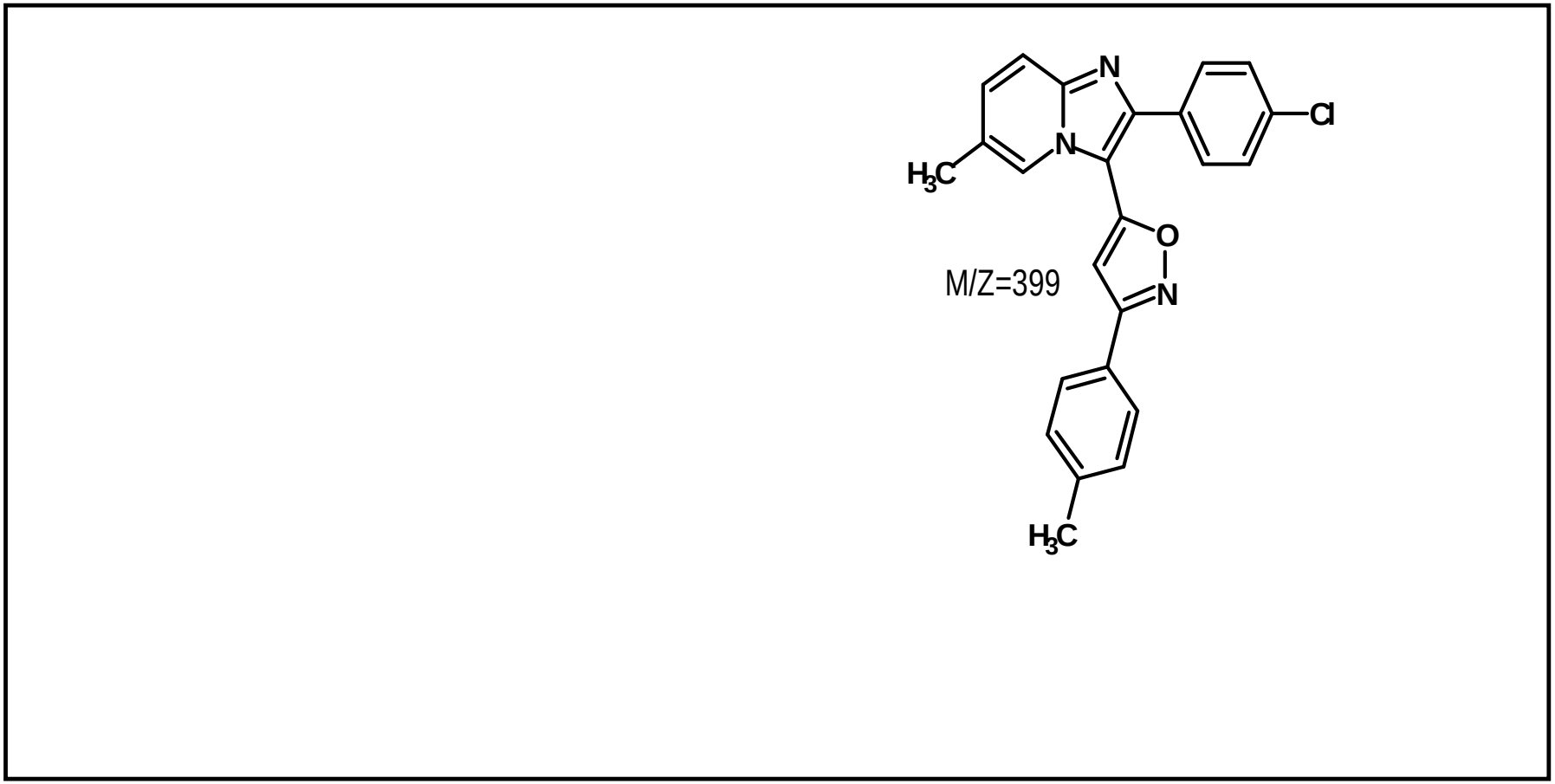
NMR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-(4'''-METHYLPHENYL) ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINE.

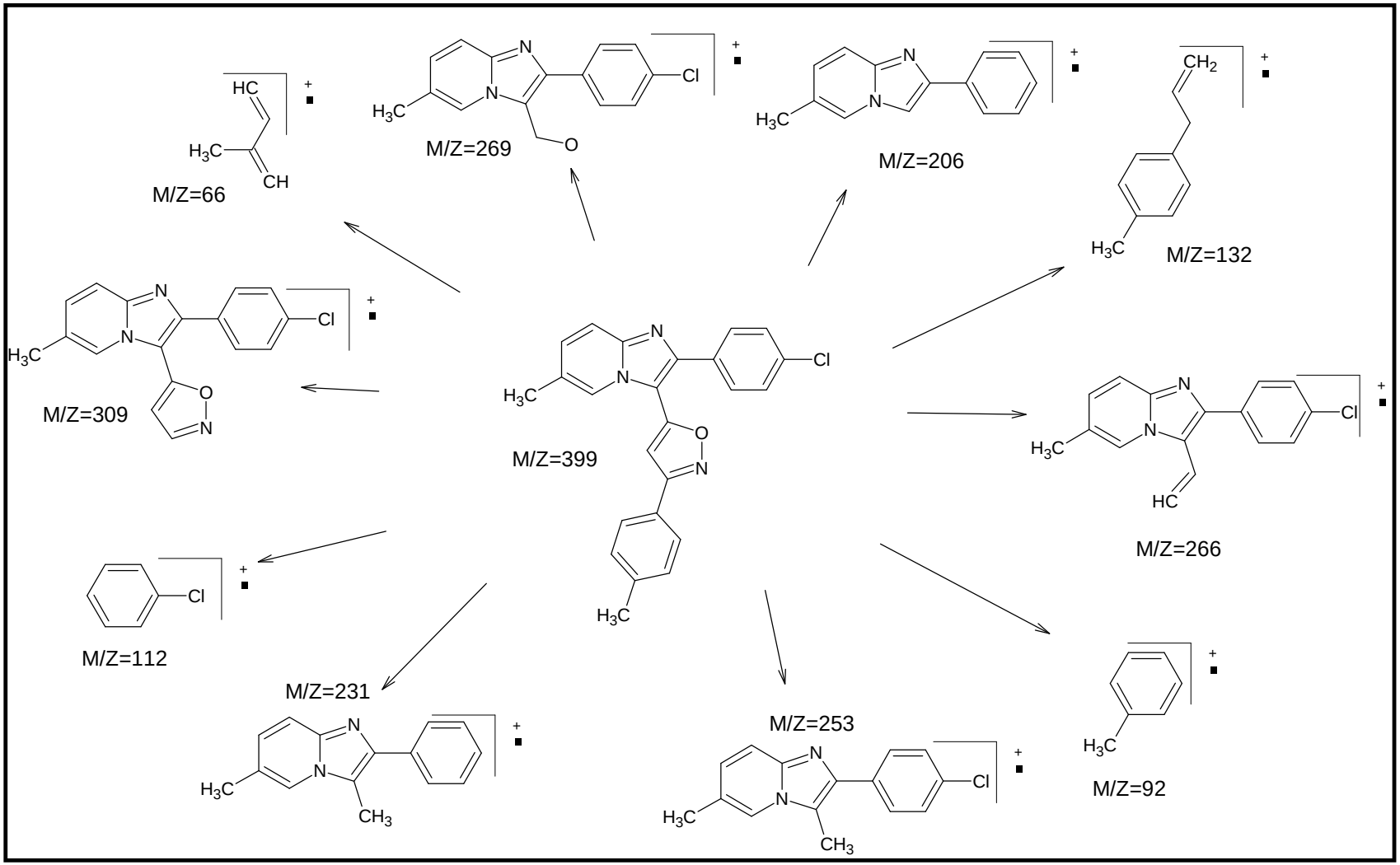


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

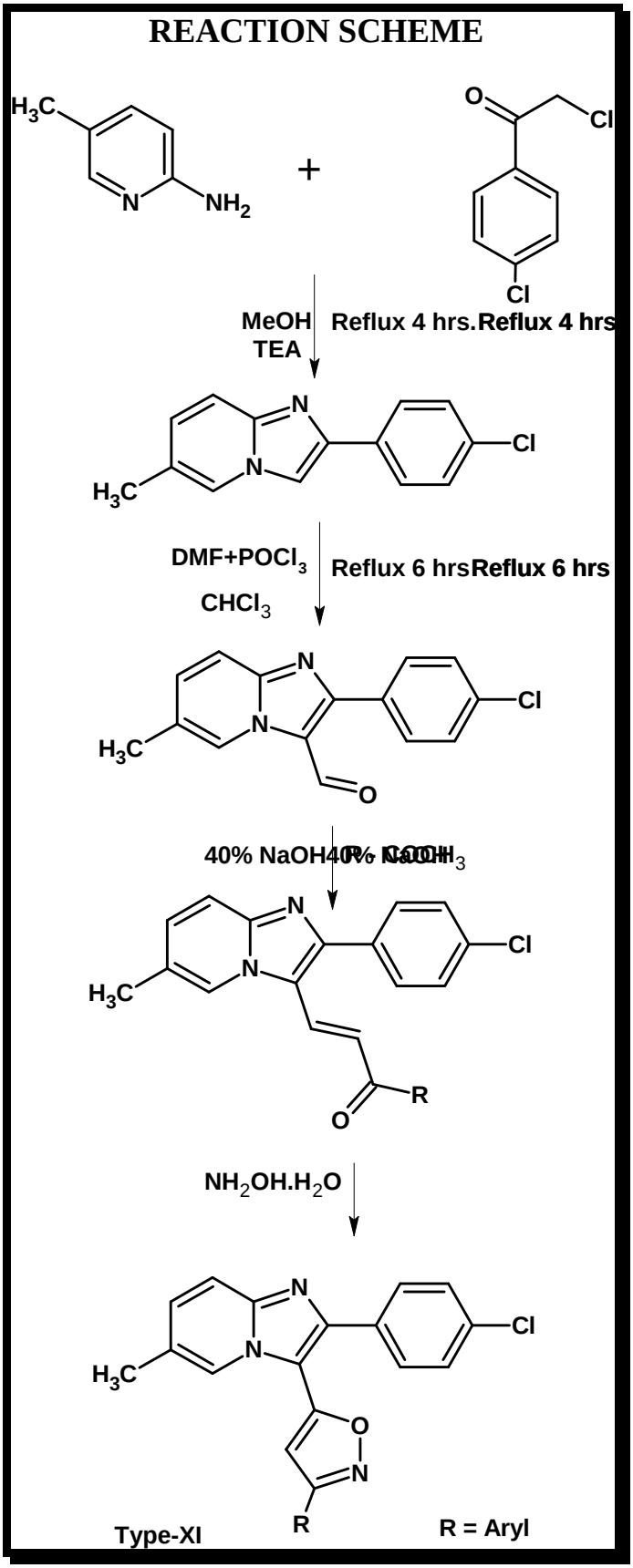
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.26	3H	Singlet	Ar-CH_3(j)
2	2.49	3H	Singlet	Ar-CH_3(i)
3	7.17-7.20	1H	doublet	Ar-H(f)
4	7.24-7.29	3H	Quatret	Ar-H(cc',h)
5	7.35-7.38	3H	Quartet	Ar-H(bb,e')
6	7.40-7.44	2H	doublet	Ar-H(aa')
7	7.52-7.56	2H	doublet	Ar-H(dd')
8	8.32	1H	singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-(4"'-METHYLPHENYL) ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINE.




M/Z=66
M/Z=269
M/Z=206
M/Z=132
M/Z=309
M/Z=399
M/Z=266
M/Z=112
M/Z=231
M/Z=253
M/Z=92

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-ARYL ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no. 37

[D] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[3"-(4"'-methylphenyl) isoxazol-5"-yl] imidazo [1, 2-a] pyridines(11i).

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (3.93 gm, 0.01 mol) in ethanol (50 ml), and hydroxylamine hydrochloride (0.59 gm, 0.01 mol) were added. The reaction mixture was refluxed on oil bath for 10 hrs. The product was isolated and crystallized from ethanol. Yield 54 %, m.p. 156^{o}C.

($C_{24}H_{18}ClN_3O$; Required : C, 72.09; H, 4.54; N, 10.51%; found : C, 72.07; H, 4.52; N, 10.49%)

Similarly,other 2-(4'-chlorophenyl)-6-methyl- 3-(3"-aryl isoxazol-5"-yl) imidazo [1, 2-a] pyridines. were prepared. The physical data are recorded in Table No.11.

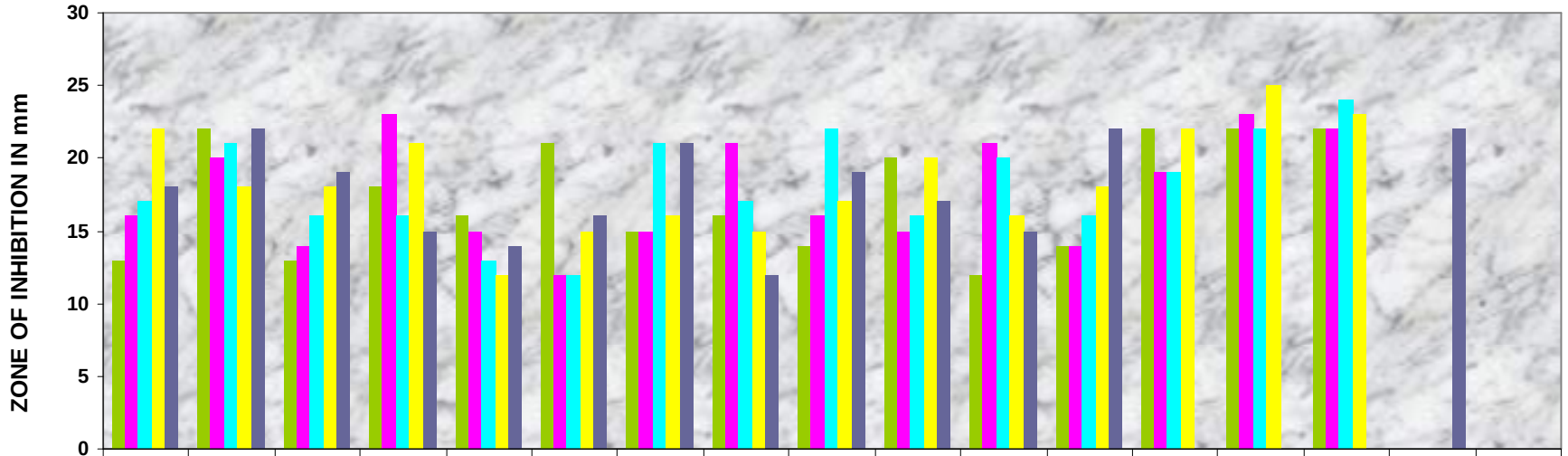
[C] Biological Screening of 2-(4'-chlorophenyl)-6-methyl- 3-(3"-aryl isoxazol-5"-yl) imidazo [1, 2-a] pyridines.

Biological Screening were carried out as described in Part-I Section-1 page no.38. .The zones of inhibition of test solution are recorded in Graphical Chart No 11.

TABLE NO. 11 PHYSICAL CONSTANTS OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-[(3"-(ARYL) ISOXAZOL-5"-YL)] IMIDAZO [1, 2-a] PYRIDINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
11a	C_6H_{5-}	$C_{22}H_{16}ClN_3O$	385.5	180	71	10.89	10.86
11b	3-Cl-C_6H_4 -	$C_{23}H_{15}Cl_2N_3O$	420.0	174	65	10.00	9.98
11c	4-Cl-C_6H_4 -	$C_{23}H_{15}Cl_2N_3O$	420.0	168	68	10.00	9.98
11d	2-4-$(Cl)_2$-C_6H_{3-}	$C_{23}H_{14}Cl_3N_3O$	454.5	165	59	9.24	9.22
11e	4 -F-C_6H_{4-}	$C_{23}H_{15}ClFN_3O$	403.5	152	63	10.41	10.39
11f	4-Br-C_6H_{4-}	$C_{23}H_{15}BrClN_3O$	464.5	192	72	9.04	9.01
11g	4 -OH-C_6H_{4-}	$C_{23}H_{16}ClN_3O_2$	401.5	185	60	10.46	10.44
11h	4-NH_2-C_6H_4	$C_{23}H_{17}ClN_4O$	400.5	180	55	13.98	13.95
11i	4-CH_3-C_6H_{4-}	$C_{24}H_{18}ClN_3O$	399.5	156	54	10.51	10.49
11j	4-OCH_3-C_6H_{4-}	$C_{24}H_{18}ClN_3O_2$	415.5	185	60	10.10	10.07
11k	3-NO_2-C_6H_{4-}	$C_{23}H_{15}ClN_4O_3$	430.5	195	51	13.00	12.97
11l	4-NO_2-C_6H_{4-}	$C_{23}H_{15}ClN_4O_3$	430.5	190	52	13.00	12.97

GRAPHICAL CHART NO. 11 : BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-ARYL -ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	Ampicillin	Amoxycillin	Norfloxacin	Greseofulvin	
B.mega	13	22	13	18	16	21	15	16	14	20	12	14	22	22	22	0	0
S.aureus	16	20	14	23	15	12	15	21	16	15	21	14	19	23	22	0	0
E.coli	17	21	16	16	13	12	21	17	22	16	20	16	19	22	24	0	0
S. typhi	22	18	18	21	12	15	16	15	17	20	16	18	22	25	23	0	0
A.niger	18	22	19	15	14	16	21	12	19	17	15	22	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-VI

SECTION – I: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL- 3-(3"-ARYL -ISOXAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

	Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
	B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
	11b-(22)	**11b-(20)**	**11b-(21)**	**11a-(22)**	**11b-(22)**
	11f-(21)	**11d-(23)**	**11g-(21)**	**11d-(21)**	**11g-(21)**
	11j-(20)	**11h-(21)**	**11i- (22)**	**11j-(20)**	**11l- (22)**
		11k-(21)	**11k-(20)**		
Ampicillin (50 µg)	**22**	**19**	**19**	**22**	**--**
Chloramphenicol(50 µg)	**22**	**23**	**22**	**25**	**--**
Norfloxacin (50 µg)	**22**	**22**	**24**	**23**	**--**
Greseofulvin (50 µg)	**--**	**--**	**--**	**--**	**22**

PART-VII

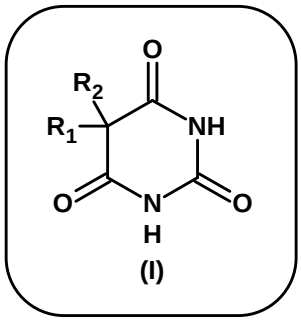
STUDIES ON BARBITONES

STUDIES ON BARBITONES

INTRODUCTION

Barbitones, which belongs to an important group of nitrogen containing heterocyclic compounds have been extensively explored for their application in the field of medicine. Most important is the effect of barbiturates on CNS. Barbituric aicd derivatives constitute an important class of compounds possessing diverse type of biological properties including hyphotic, sedative, anticonvulsant,cardiovascular etc.

Barbituric acid usually represented as the trione was first made about 1864 and it has no hypnotic properties. The origin of the name is lost, although there are several plausible explanations associated with St. Barbara's feast day, a favourite Munchen *Kellnerin* rejoicing in that given name, and even the *barba* which is a beard of the business end of a key.

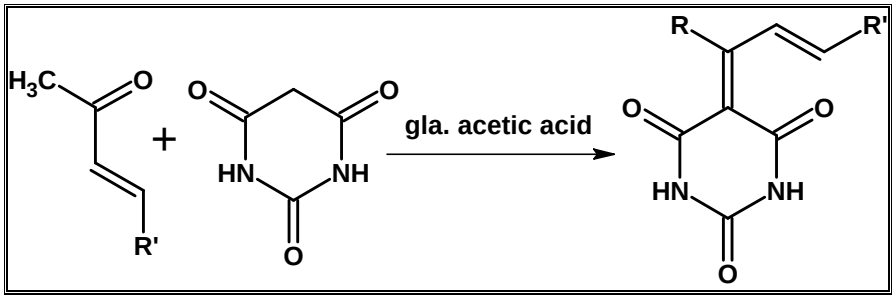


(I)

SYNTHETIC ASPECT

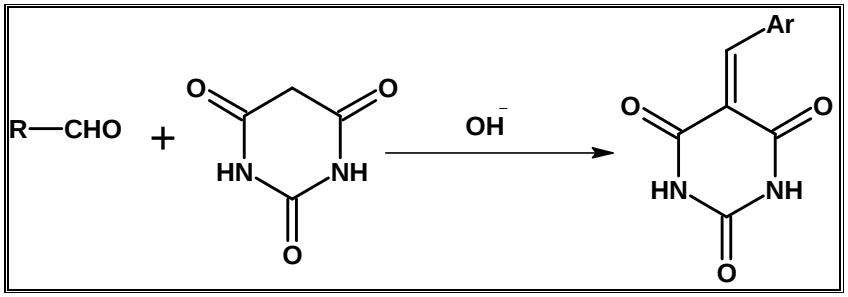
Different methods are used for the preparation of barbitones in literature[410, 411]

1. M. R. Mahmoud et. al.[412] have synthesised barbituric acid derivatives from chalcone.



2. Cao-Yan Weu et. al.[413] have prepared barbitones by reaction of different aldehydes

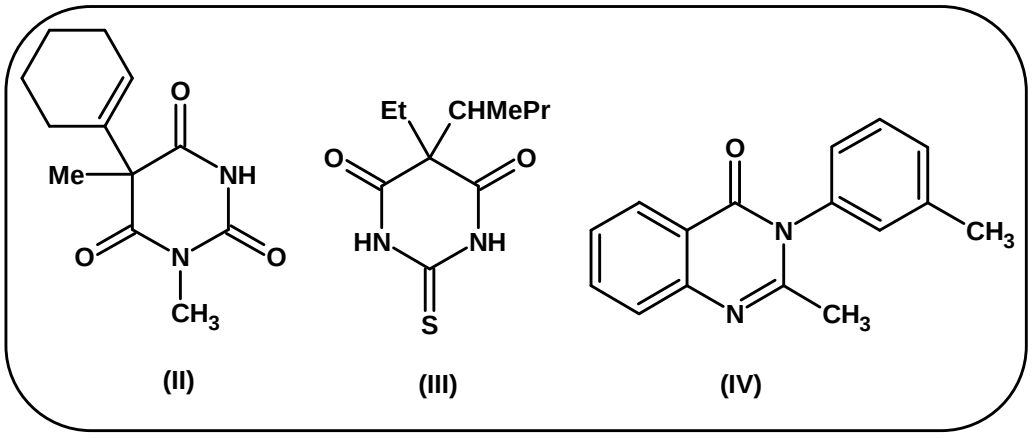
with barbituric acid in basic media.



3. Ogus Funda et. al.[414] have prepared barbitones by the reaction of acetone and barbituric aicd.

THERAPEUTIC IMPORTANCE

The first hyphotic barbiturate, 5,5-diethyl barbituric acid (barbital, Veronal ; I; R_1R_2=Et) was made in 1904, was introduced into medicine in 1905, and is still used sometimes; the second was 5-ethyl-5-phenylbarbituric acid (phenobarbital, Luminal, I; R_1=Et, R_2=Ph), also prepared in 1904 but used as a long acting CNS depressant only from 1912 until the present day. Several thousand active barbiturates were made subsequently but scarcely a dozen are still used to any extent. Among these are pentobarbital (Nembutal; I; $R_1=C_2H_5$, R_2=CHMePr), amobarbital (Amytal ; I; $R1=C_2H_5$, $R_2=CH_2CH_2CHMe_2$),secobarbital (Seconal; I; $R_1=CH_2$ $CH=CH_2$, R_2=CHMePr), hexobarbital (Sombulex/Evipal; II), thiopental (Pentothal ; III). The whole subject is well reviewed[415-417]

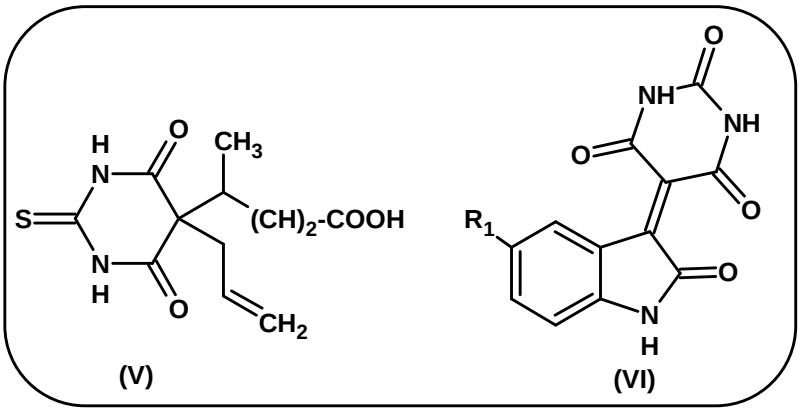


The 'pseudo-barbiturate', 2-methyl-3-o-tolylquinazolin-4(3H)-one (methaqualone, Revonal; IV) has an ever winder spectrum of activities that do the barbiturates proper; it

appears to be quite widely used as a sedative, hyphotic, anticonvulsant, antispasmodic and local anaesthetic agent[418].

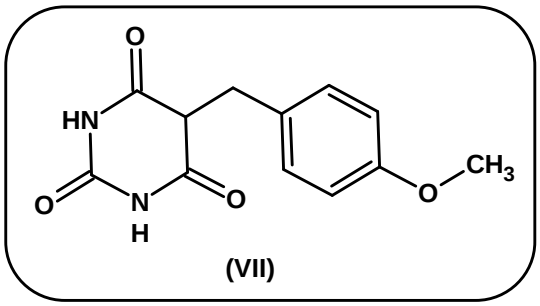
Some barbituric acid derivatives used as sedative and hyphotic iscarbubarb[419], which is used as veternary anaesthetics. Some isoxazolo pyrimidines have been studied because of their potential as pesticidal[420,421] activity. Some barbiturates showing cardiovascular[422-424] and analgesics and antiinflammatory activities[425] have been reported. Some isoxazolopyrimidines have been extensively studied and reported as antagonist[426] and antitumor[427] activity. Wolf-Gang et. al.[428] have reported 5-(3-Benzylthiazolidin-2-ylidene)-1,3-dimethyl hexahydropyrimidin-2,4,6-trione having agricultural activity. Andre Roland et. al.[429] demonstrated some barbituric acid derivatives used as herbicidal and insecticides.

M. T.Omar [430] has synthesised barbitone derivatives, showing antimicrobial activity. Sakai et. al.[431] have synthesised new barbitones which were assessed for bone and cartilage disease. Ambrogio Oliva et. al.[432] have synthesized barbitones possessing antimetastatic and antitumor activity. W. Weber et. al.[433] have synthesised barbitones as main metabolite (V). Frank Grams et. al.[434] have synthesised barbitones and found to be metalloprotease inhibitors. R T Pardasani et. al.[435] have synthesised new barbitones for antibacterial agents. (VI).



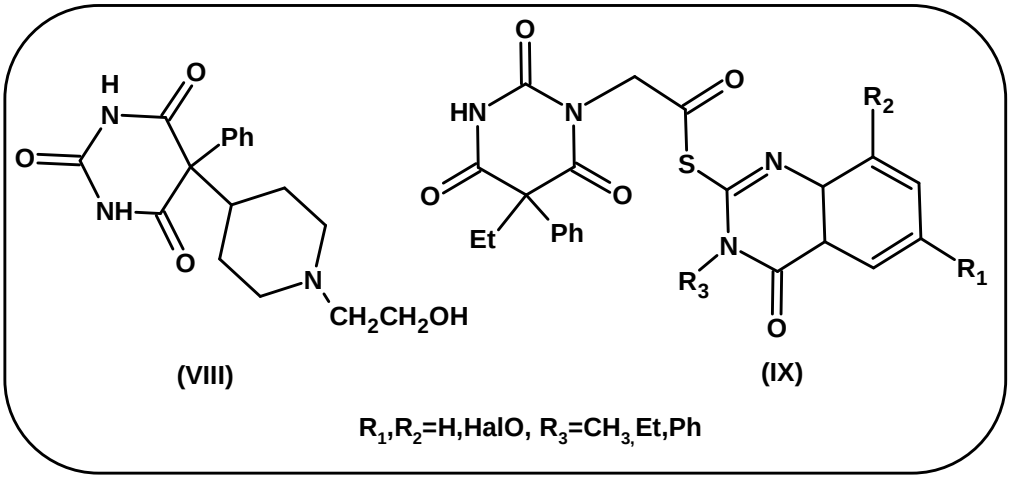
Ulf Wellmar et. al.[436] have synthesised some uracil derivatives and screened for antiviral activity[437,438]. Raymond et. al.[439] have synthesized some barbiturates (VII),

which showed anticancer activity. M. R. Mahmoud et. al.[440] synthesised barbituric acid derivatives and reported their antimicrobial activity.



(VII)

D. L. Levesque et. al.[441] have synthesised barbitones as uridine phosphoralase inhibitors. I. M Wyzlic. et. al.[442] have synthesised and tested barbitones as anticonvulsant agent. A. N. Shivanyuk and co-worker[443] have prepared barbitones as Porphyrin Melamine Calixarene receptor. Gursu Esin et. al.[444] have prepared barbitone as biological activity agent. Bosies Elmar and co-worker[445] have prepared barbitones as metalloproteinase inhibitor (VIII).



(VIII) (IX)

R_1,R_2=H,HalO, R_3=CH_3, Et,Ph

S. G. Abdel Hamide et. al.[446] have prepared barbitone as anticonvulsant agent (IX). Li Laizhong et. al. [447] have synthesised barbitones and screened for their anticonvulsant activity.

Recently, Geppert Dangmar et. al.[448] have synthesised barbitones and tested their metalloproteinase inhibitory activity.

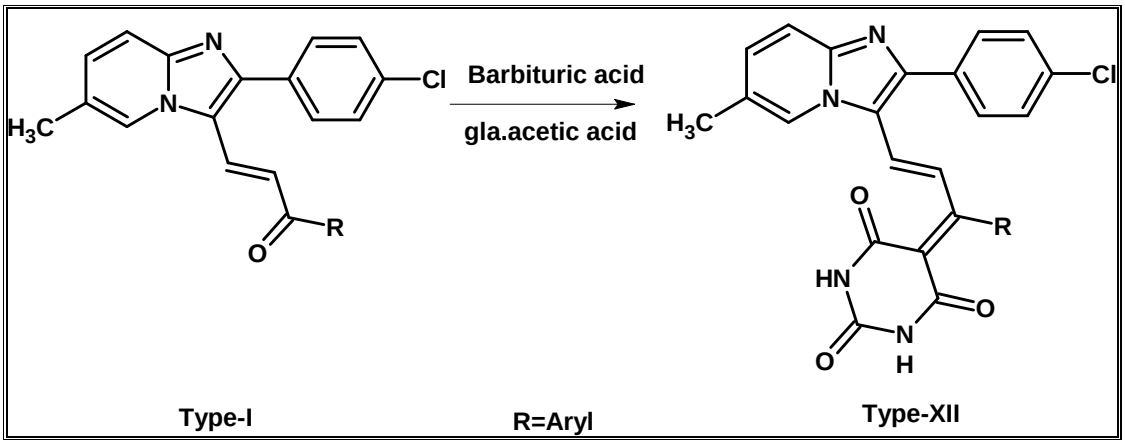
These observations led us to explore barbitone chemistry by synthesizing its derivatives in order to achieve better therapeutic agents. It has been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2 - [(4' - CHLOROPHENYL) – 6 - METHYL IMIDAZO [1,2-a] PYRIDIN-3-YL] - (1" – PROPENE - 3" – ARYL - 3" – YL) - PYRIMIDINE - 2"',4"',6"'-(3"'H, 5"'H)-TRIONES.

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1,2-a] PYRIDIN-3-YL]-(1"-PROPENE-3"-ARYL-3"-YL)-PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONES.

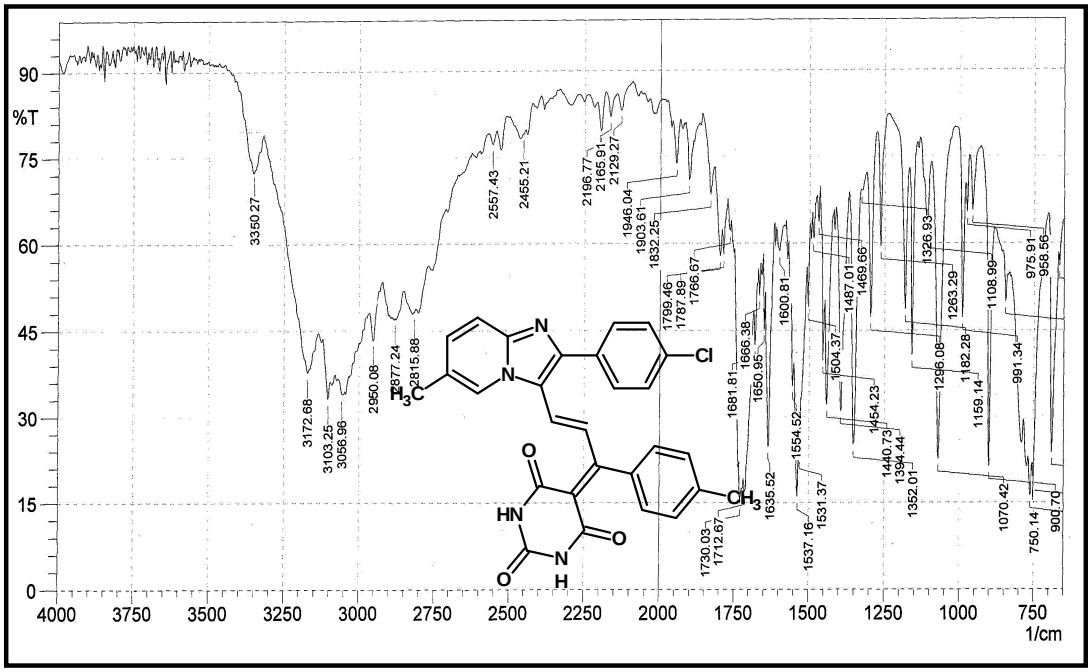
Barbiturates derivatives possess good therapeutic activity in the field of medicinal chemistry, Prompted by these facts, the preparation of 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine- 2"',4"',6"'-(3"'H, 5"'H)-triones. of type (XII) have been synthesised by the reaction with chalcone of Type (I) with barbituric acid in glacial acetic acid.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I Page no. 41

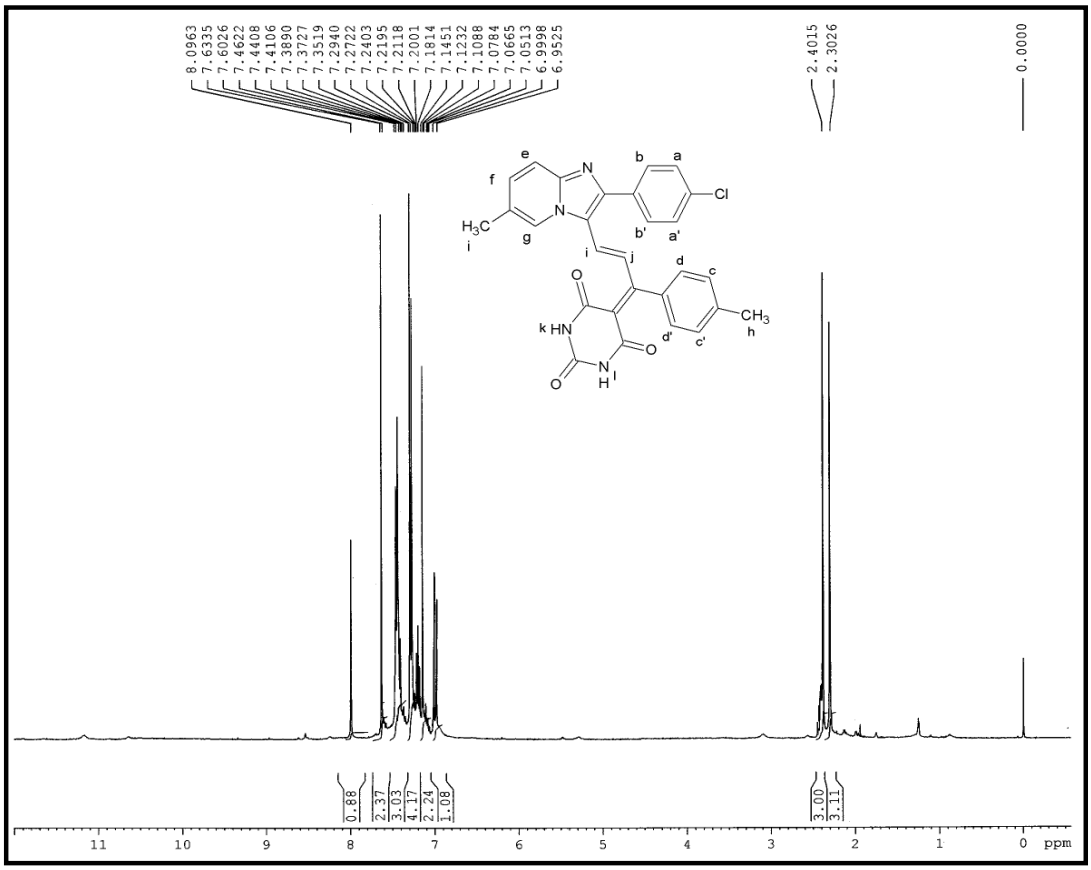
IR SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO[1,2-a] PYRIDIN-3-YL]-(1"-PROPENE-3"-(4"''-METHYLPHENYL) -3"-YL)- PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2887	2990-2850	648
	C-H str. (sym.)	2877	2880-2860	"
	C-H def. (asym.)	1440	1470-1430	"
	C-H def. (sym.)	1394	1395-1370	"
Aromatic	C-H str.	3056	3090-3030	"
	C=C str	1537	1600-1450	"
	C-H i.p. (def.)	1296	1300-1100	649
Imidazo[1,2-a] pyridine	C=N str.	1600	1612-1593	"
	C-N str.	1070	1220-1020	"
Barbitones	N-H str.	3350	3350-3250	"
	C=O	1712	1750-1610	"
	C=O	1730	1750-1610	"
	C-H str.(asym.)	2950	2950-2850	"
Halide	C-Cl str.	750	600-800	

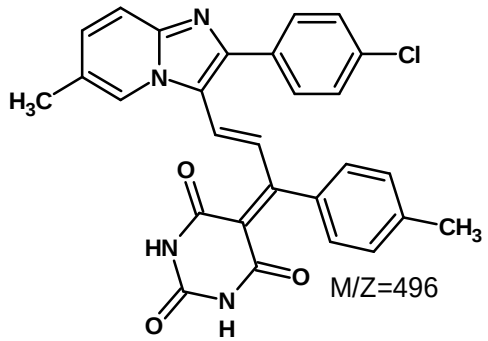
NMR SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO[1,2-a] PYRIDIN-3-YL]-(1"-PROPENE-3"-(4'''-METHYLPHENYL) -3"-YL)- PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONE.

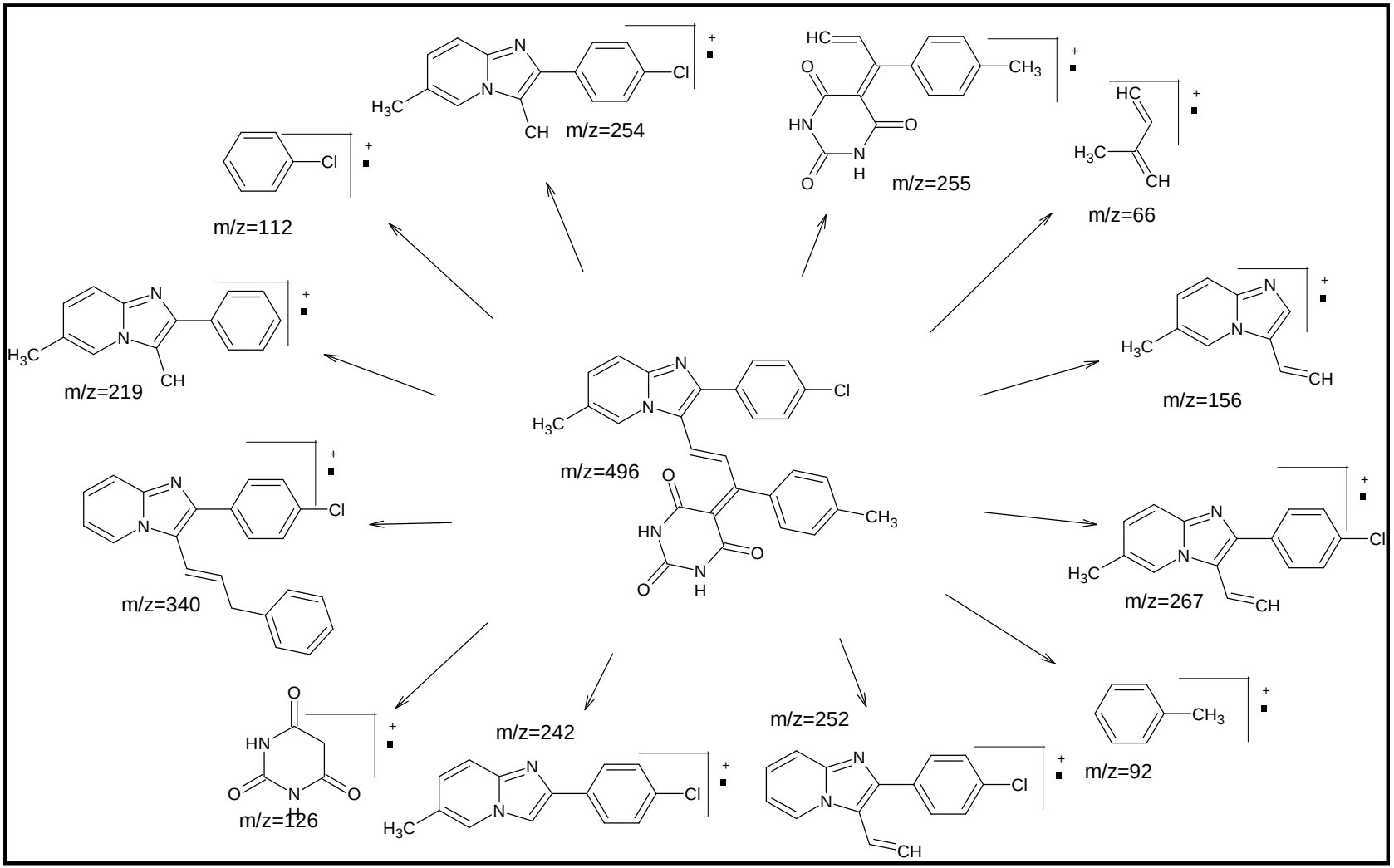


Internal Standard:TMS;Solvent :$CDCl_3$;Instument Bruker Spectometer (300MHz)

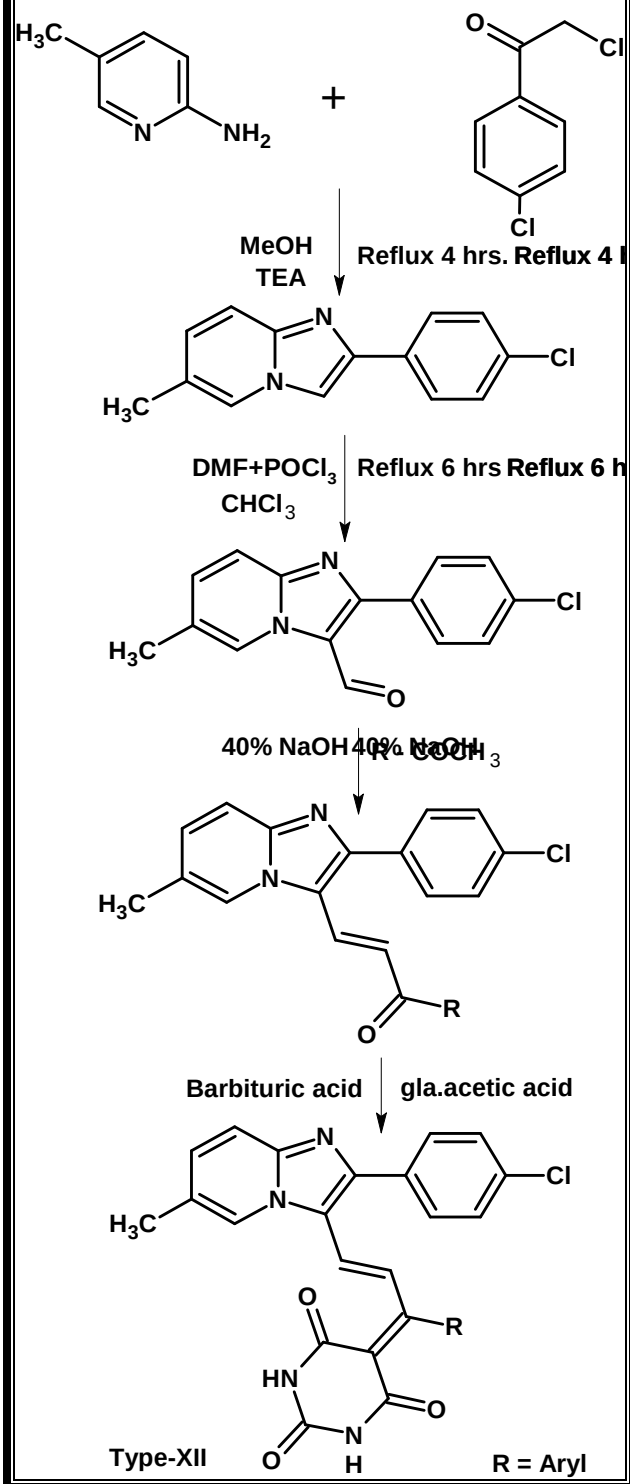
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.30	3H	singlet	Ar-CH_3(h)
2	2.40	3H	singlet	Ar-CH_3(i)
3	6.95-6.99	1H	doublet	Ar-H(j)
4	7.14-7.18	2H	doublet	Ar-H(f,k)
5	7.20-7.29	4H	multiplet	Ar-H(cc',dd')
6	7.35-7.46	3H	doublet	Ar-H (bb',e)
7	7.60-7.63	2H	doublet	Ar-H(aa')
8	8.09	1H	singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO[1,2-a] PYRIDIN-3-YL]-(1"-PROPENE-3"-(4'''-METHYLPHENYL)-3"-YL)- PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONE.




m/z=496
m/z=254
m/z=255
m/z=66
m/z=112
m/z=219
m/z=156
m/z=340
m/z=267
m/z=126
m/z=242
m/z=252
m/z=92

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGOCAL SCREENING OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1,2-a] PYRIDIN-3-YL]-(1"-PROPENE-3"-ARYL-3"-YL)-PYRIMIDINE 2"',4"',6"'-(3"'H, 5"'H)-TRIONES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I,on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no. 37

[D] Synthesis of 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-(4"'-methylphenyl)-3"-yl)-pyrimidine- 2"',4"',6"'(3"'H, 5"'-H)-triones(12i).

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (3.8 g, 0.01 mol), barbituric acid (1.28 g, 0.01 mol) in glacial acetic acid was refluxed for 10 hrs. in oil bath. The contents were poured in to ice and product was isolated, crystallized from DMF. Yield, 69%, m.p.170^{o}C. ($C_{28}H_{21}ClN_4O_3$; Required : C, 67.67; H, 4.26; N, 11.27%; found : C, 67.65; H, 4.25; N, 11.25%;)

Similarly other barbitones have been prepared. The physical data are recorded in Table No. 12

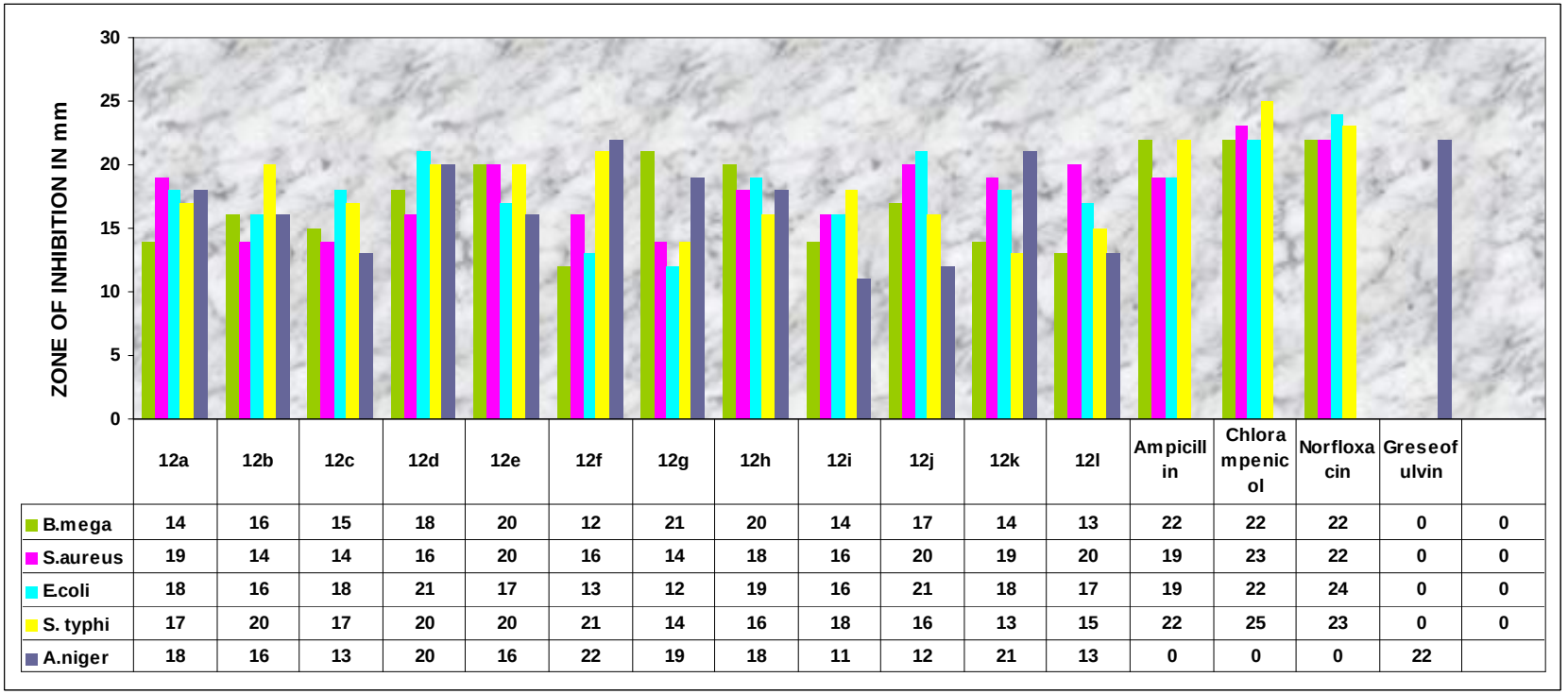
[E]] Biological Screening of 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine- 2"',4"',6"'-(3"'H, 5"'H)-triones .

Biological Screening was carried out as described in Part-I, Section-I Page no.38 The zone for inhibition of the test solutions are recorded in Graphical Chart No. 12

TABLE NO. 12 PHYSICAL CONSTANTS OF 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2-a] PYRIDIN-3-YL]-(1"- PROPENE-3"-ARYL-3"-YL)- PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
12a	C_6H_5-	$C_{27}H_{19}ClN_4O_3$	482.5	165	67	11.60	11.58
12b	3-Cl-C_6H_4 -	$C_{27}H_{18}Cl_2N_4O_3$	517.0	195	55	10.83	10.81
12c	4-Cl-C_6H_4 -	$C_{27}H_{18}Cl_2N_4O_3$	517.0	155	59	10.83	10.80
12d	2-4-$(Cl)_2$-C_6H_3-	$C_{27}H_{17}Cl_3N_4O_3$	551.5	205	70	10.15	10.12
12e	4 -F-C_6H_4-	$C_{27}H_{18}ClFN_4O_3$	500.5	190	65	11.19	11.17
12f	4-Br-C_6H_4-	$C_{27}H_{18}BrClN_4O_3$	561.5	167	69	9.97	9.96
12g	4 -OH-C_6H_4-	$C_{27}H_{19}ClN_4O_4$	498.5	158	72	11.23	11.21
12h	4-NH_2-C_6H_4-	$C_{27}H_{20}ClN_5O_3$	497.5	165	57	14.06	14.04
12i	4-CH_3-C_6H_4-	$C_{28}H_{21}ClN_4O_3$	496.5	170	69	11.27	11.25
12j	4-OCH_3-C_6H_4-	$C_{28}H_{21}ClN_4O_4$	512.5	200	75	10.92	10.90
12k	3-NO_2-C_6H_4-	$C_{27}H_{18}ClN_5O_5$	527.5	165	64	13.27	13.24
12l	4-NO_2-C_6H_4-	$C_{27}H_{18}ClN_5O_5$	527.5	177	50	13.27	13.25

GRAPHICAL CHART NO. 12: BIOLOGICAL SCREENING OF 2 - [(4' – CHLOROPHENYL) – 6 - METHYLIMIDAZO [1,2-a] PYRIDIN – 3 – YL] - (1" – PROPENE - 3" ARYL-3"-YL)- PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONES.



	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	12k	12l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	14	16	15	18	20	12	21	20	14	17	14	13	22	22	22	0	0
S.aureus	19	14	14	16	20	16	14	18	16	20	19	20	19	23	22	0	0
E.coli	18	16	18	21	17	13	12	19	16	21	18	17	19	22	24	0	0
S. typhi	17	20	17	20	20	21	14	16	18	16	13	15	22	25	23	0	0
A.niger	18	16	13	20	16	22	19	18	11	12	21	13	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-VII

SECTION – I: BIOLOGICAL SCREENING OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1,2-a] PYRIDIN-3-YL]-(1"- PROPENE-3"-ARYL-3"-YL)- PYRIMIDINE- 2"',4"',6"'-(3"'H, 5"'H)-TRIONES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
		12e-(20)	**12a-(19)**	**12a-(18)**	**12b-(20)**	**12d-(20)**
		12g-(21)	**12e-(20)**	**12c-(18)**	**12d-(20)**	**12f- (22)**
		12h-(20)	**12k-(19)**	**12d- (21)**	**12e-(20)**	**12k-(21)**
			12l-(20)	**12h-(19)**	**12f-(21)**	
				12j-(21)		
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

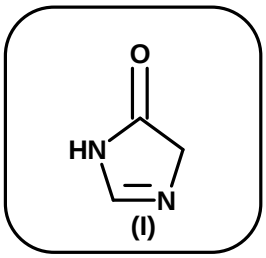
PART-VIII

STUDIES ON 5-OXO-MIDAZOLINES

STUDIES ON 5-OXO-IMIDAZOLINES

INTRODUCTION

The five membered heterocyclic ring system 5-oxo-imidazolines have two nitrogen atom at 1- and 3-positions and a carbonyl group at 5-position.



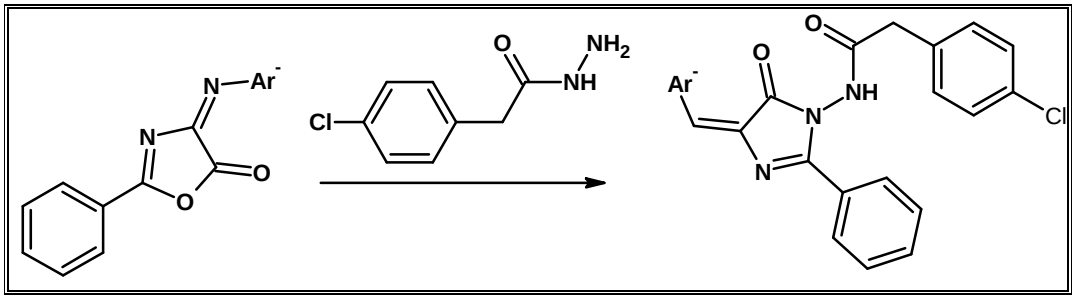
(I)

The discovery of the 2-substituted-5-imidazolines dates back to the year 1888, when A. W. Hoffman[449] for the first time discovered 5-oxo-imidazoline by heating N-diacetylethylene diamine in a stream of dry hydrogen chloride. Moreover, some compounds were prepared by A. Ladenburg[450] 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[451]. Aminolysis of oxazolone with amine leads to the formation of imidazolinones which has been reported in literature[452].

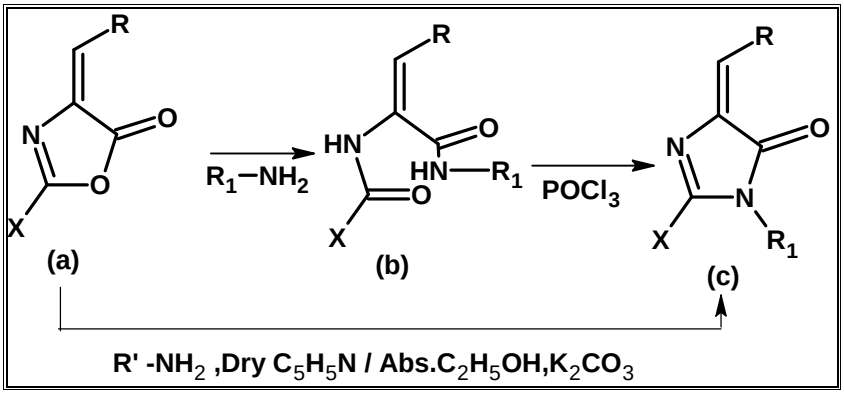
1. Feng-Jun-Cai et. al.[453] have synthesised 5-imidazolinone derivatives by micro-waves irradiation.
2. A. Saxena et. al.[454] have synthesised new imidazolinones



3. H.A. Allimony et. al.[455] have synthesised new imidazolinone derivatives by conventional method.

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 amine can be converted to imidazolinones as shown in reaction.



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

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. Antitubercular[456]
2. Potent CNS depressant[457, 458]
3. Insecticidal[459]
4. Antiviral[460]
5. Hypertensive[461]
6. Antiinflammatory[462-464]
7. Glucagon antagonists[465]
8. Antimicrobial[466]
9. Thrombin inhibitor[467]
10. Anticonvulsant[468, 469]
11. Sedative and hypnotics[470]
12. Bactericidal[471, 472]
13. Fungicidal[473, 474]

14. Antiparkinson[475, 476]

15. Anthelmintic[477]

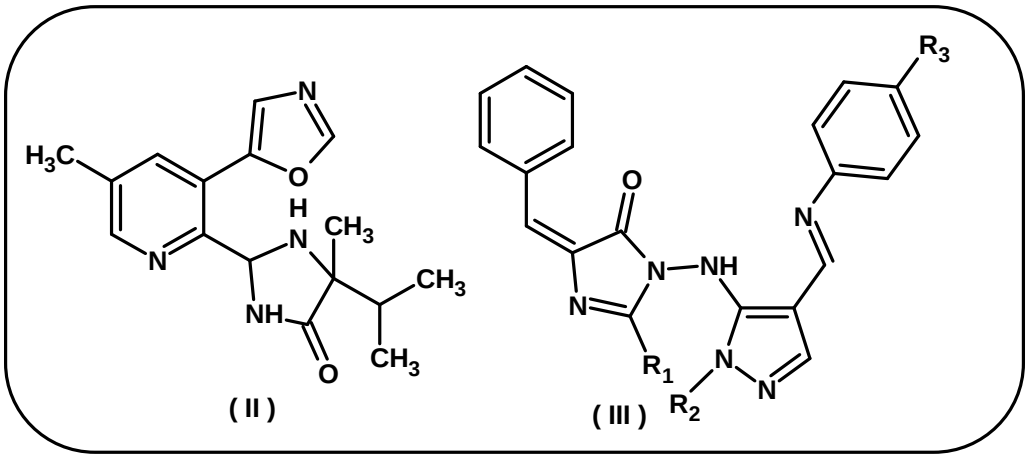
16. Antihistaminic[478]

17. Anticancer[479, 480]

18. Antidiabatic[481]

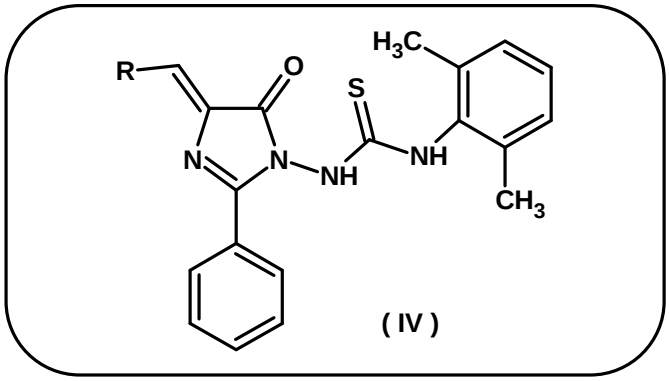
F. C. Geoffrey et. al [482] and B. L. Pilkington et. Al[483] have synthesised and studied antifungal activity of imidazolinones. L. J. Peter and Co-worker[484] have prepared substituted imidazolinones which inhibited the abnormal cell growth in human body. S. Lauter and Co-worker[485] have isolated imidazoline from different methods and tested for the treatment of cytokine release. Imidazoline derivatives have been prepared by Erick and co-worker[486] showing anti-HIV activity. Ding Ming-Wu et. Al[487] have prepared novel imidazolines and reported their antifungal activity.

K. Vishnu et. al.[488] has reported anti-AIDS, antibacterial and fungicidal activity of 5-oxo-imidazolines. B. R. Shah and co-worker[489] have prepared some new imidazolines and reported anticancer and anti HIV activity.



V. Akyoshi et. al.[490] have prepared some new imidazolinone derivatives (II) and reported their herbicidal activity. Agrochemical activity of imidazolinones has been reported by J. P. Bascou and co-workers[491].

R. Sharma and co-workers[492] have reported antimicrobial activity of 5-oxo-imidazolines (III). K. K. Awasthi et. al.[493] (IV) have synthesised some new imidazolinone derivatives and reported their antimicrobial activity**.**

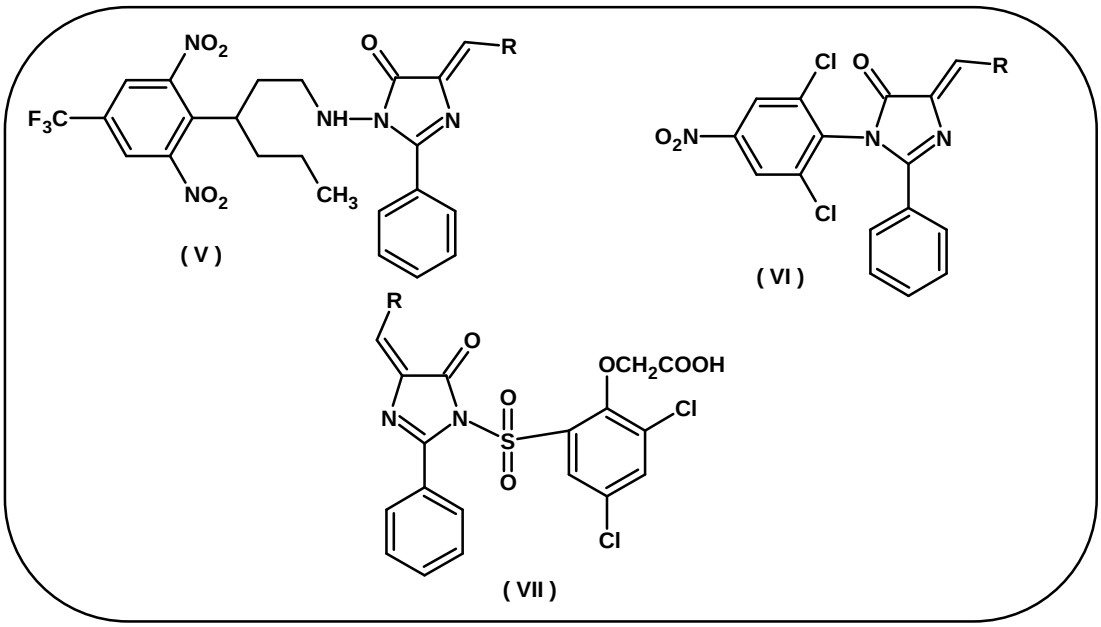


(IV)

CONTRIBUTION FROM OUR LABORATORY

A. R. Parikh et. Al[494] have synthesised imidazolinones bearing thiazole as moderately active bactericidal and fungicidal. H. H. Parekh et. Al[495] have elaborated better activity for some imidazolinones with activated benzylidene group at 5-position.

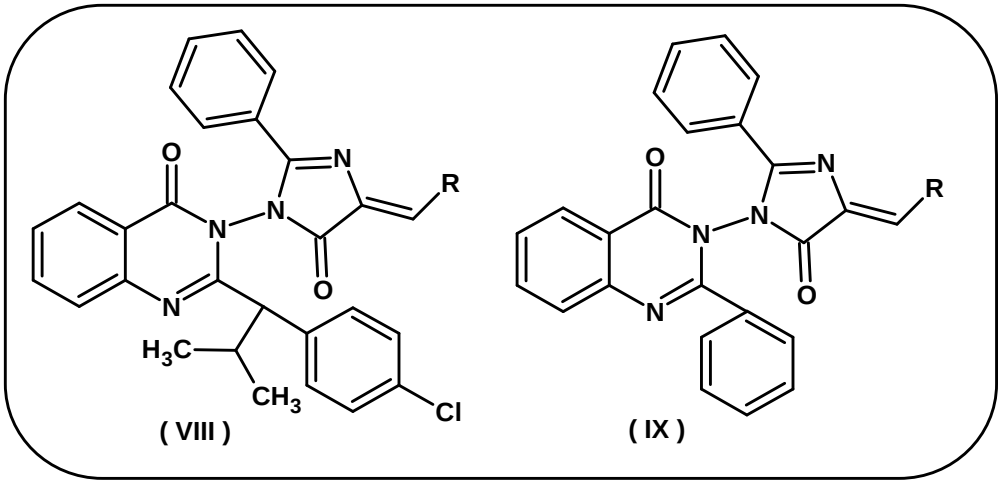
D. M. Purohit et al[496] synthesized 5-oxo-imidazoline (V) derivatives in "Fluchloralin" moiety. D. M. Purohit et al[497, 498] have synthesized 5-oxo-imidazolines (VI) in "dichlorine" nucleus. D. M. Purohit et al [499] have synthesized 5-oxo-imidazolines (VII) in 2, 4-D derivatives.



(V) (VI)

(VII)

V. N. Patoliya et al [500, 501] have synthesized 5-oxo-imidazolines (VIII, IX) evaluated its antimicrobial activity.



A. R. Parikh et. al. have synthesized imidazolinones bearing phthalazine[502], 2-base of chloramphenicol[503] moiety at one position which were evaluated for their antimicrobial activity. A. R. Parikh et. al. [504] have reported 4-(4'-Arylidine-2'- phenyl-5'-oxo-imidazolin-1-yl) benzophenones which were screened for their antimicrobial activity. Biplabde et. al. [505] have reported some new 5-oxoimidazoline as antimicrobial agents.Imidazolinones have been reported to possess antioxidant activity.

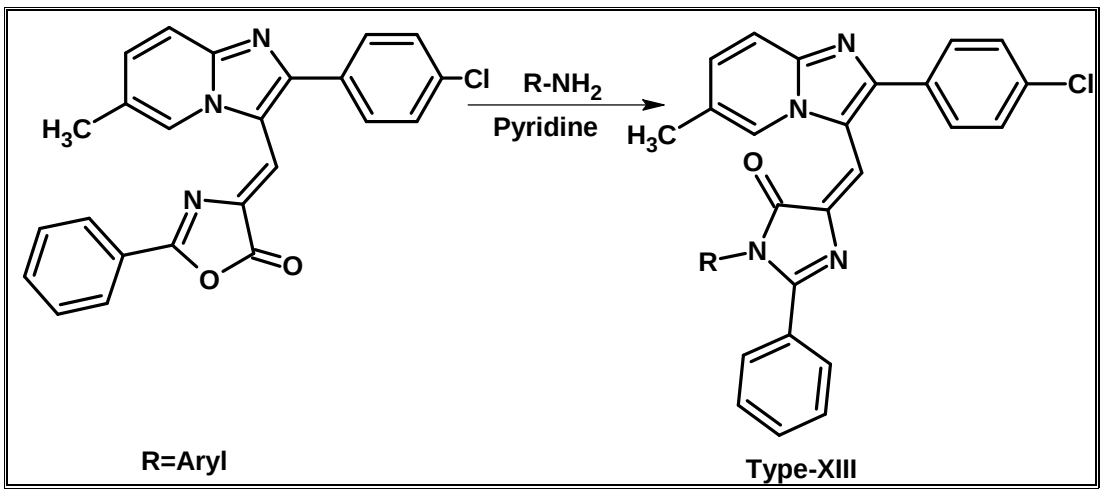
Moreover Yoneda Naoto et. Al[506] have synthesised imidazolinones as antihypertensive agent. R. C. Dage et. al.[507] have synthesised cardiotonic imidazolones. Armando Rossello et. al. [508] have synthesised imidazolones as antifungal agent. A. B. Cooper and co-workers[509] have found that imidazolones are inhibitors of farnesyl protein transferase. Machii Daisuke et. al.[510] have synthesised new imidazolones as a telomerase inhibitors and antitumor agents M. R. Jean et. al. [511] have synthesised imidazolones and tested as antileishmanial agent. Chafiq Hamdouchi et. al. [512] have synthesised imidazolinones and screened for their potent and broad spectrum activity. M. L. Irene et al.[513] have synthesised imidazolinones and tested as antiretroviral activity (IX). Xu Zhi-Feng et. al. [514] have synthesised imidazolinones as biological agent. With a view to getting better therapeutic agent, it was contemplated to synthesized imidazolinones to enhance the overall activity of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2 [(4'-CHLOROPHENYL)-6-METHYLIMIDAZO[1,2 -a]PYRIDIN-3-YL] METHYLENE - 1" – ARYL - 2" - PHENYL - 5" - OXO-IMIDAZOLINES.

SECTION:-I

SYNTHESIS AND BIOLOGICAL SCREENING 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2 – a] PYRIDIN – 3 – YL] METHYLENE - 1" – ARYL -2" PHENYL-5"-OXO-IMIDAZOLINES.

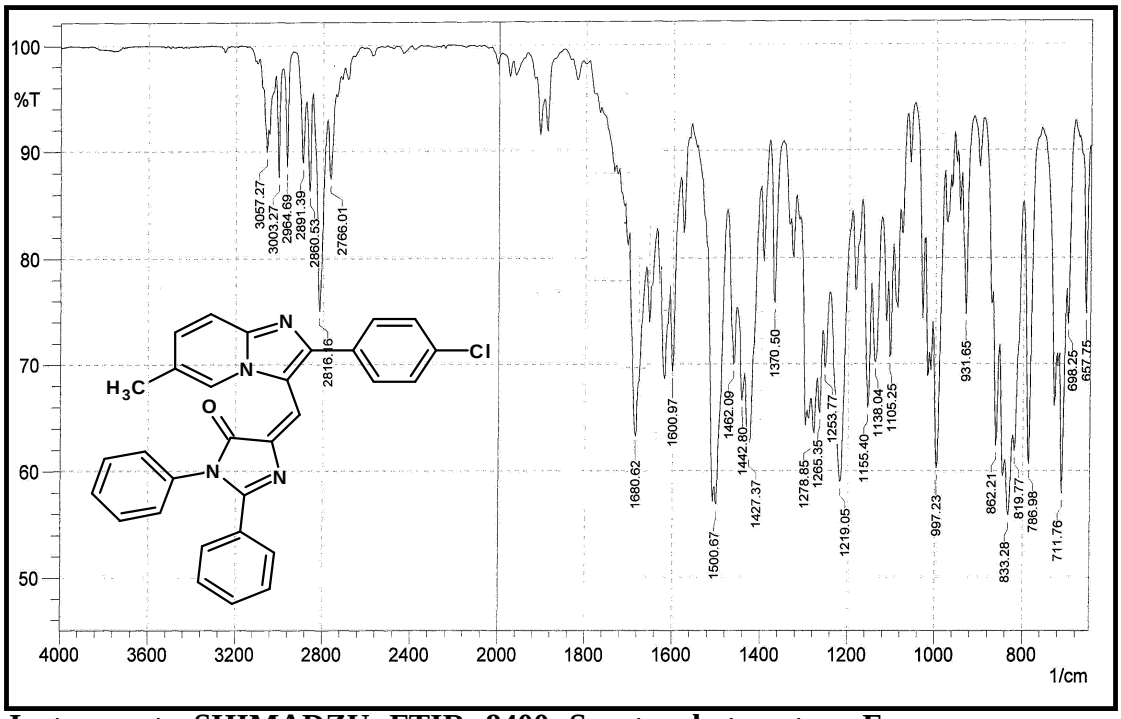
Imidazolinones represent one of the most active classes of compounds having a wide spectrum of biological activities with an aim to getting better therapeutic agent. The preparations of 2-[(4'-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methylene-1"-aryl-2"-phenyl-5"-oxo-imidazolines. of Type (XIII) have been undertaken by the condensation of 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone with aromatic amines.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I, section-I Page no. 41

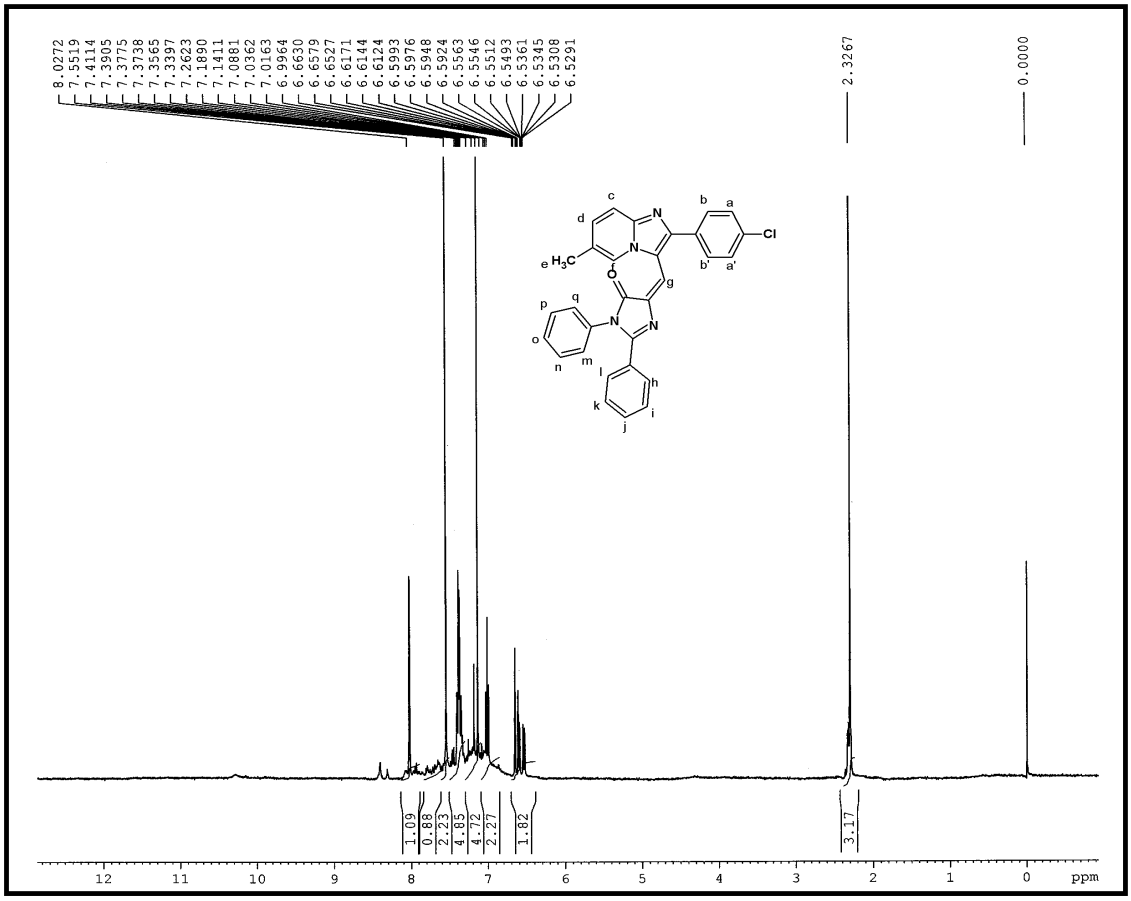
IR SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2- a] PYRIDIN – 3 - Yl] METHYLENE - 1" - (PHENYL)- 2"-PHENYL -5"-OXO-IMIDAZOLINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2964	2990-2850	648
	C-H str. (sym.)	2860	2880-2860	"
	C-H def. (asym.)	1442	1470-1435	"
	C-H def. (sym.)	1370	1390-1370	"
Aromatic	C-H str.	3057	3090-3030	649
	C=C str	1462	1450-1600	"
	C-H i.p. (def.)	1219	1300-1100	"
Imidazole ring	C=O str.	1680	1760-1655	"
	C=N str.	1600	1650-1580	"
	C=C str.	1500	1540-1480	"
Imidazo[1,2-a] pyridine	C=N str.	1627	1630-1593	"
	C-N str.	1128	1220-1020	"
Halide	C-Cl str.	786	800-600	"

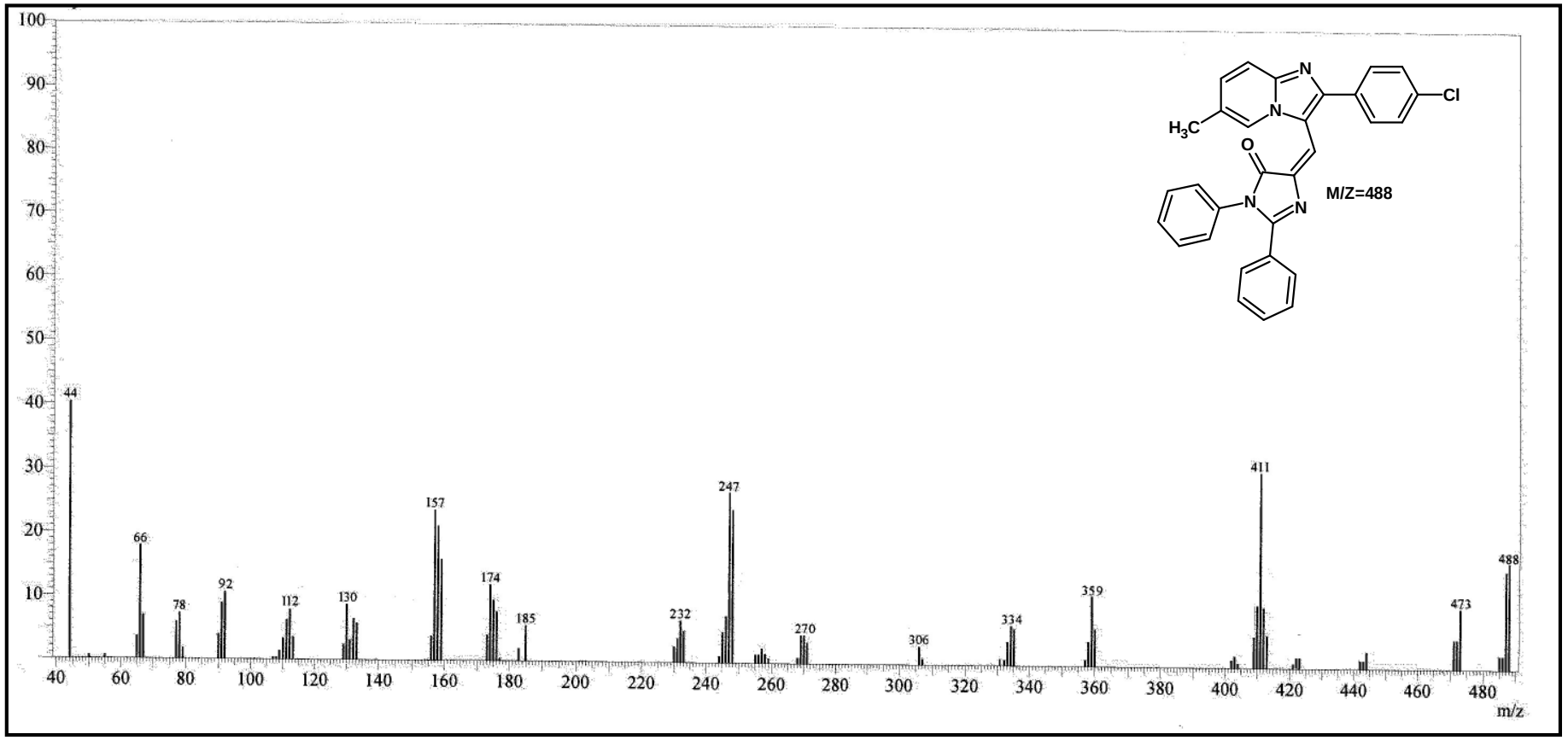
NMR SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2- a] PYRIDIN – 3 - Yl] METHYLENE - 1" - (PHENYL)- 2"-PHENYL -5"-OXO-IMIDAZOLINE.

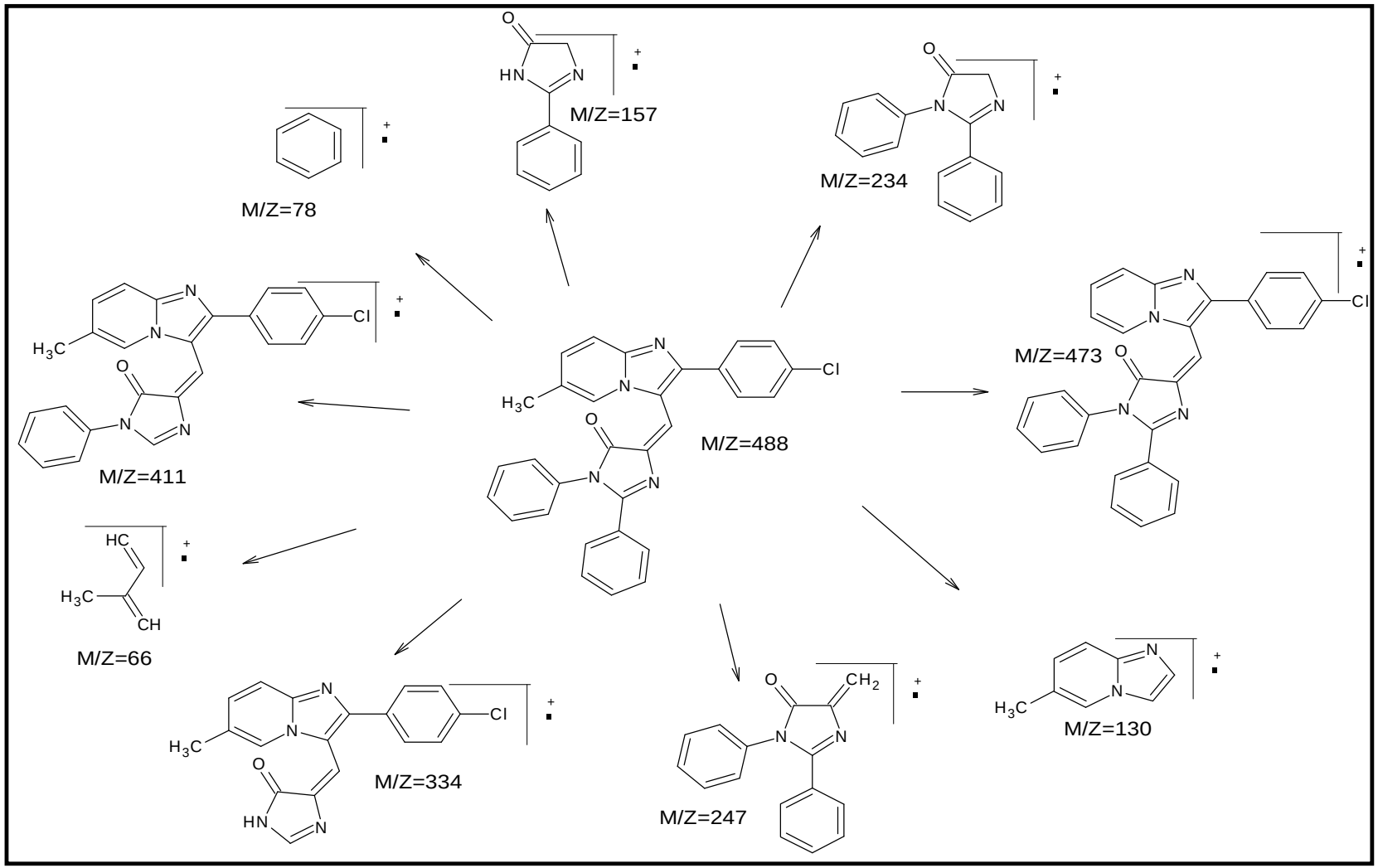


Internal Standard:TMS;Solvent :$CDCl_3$;Instument Bruker Spectometer (300MHz)

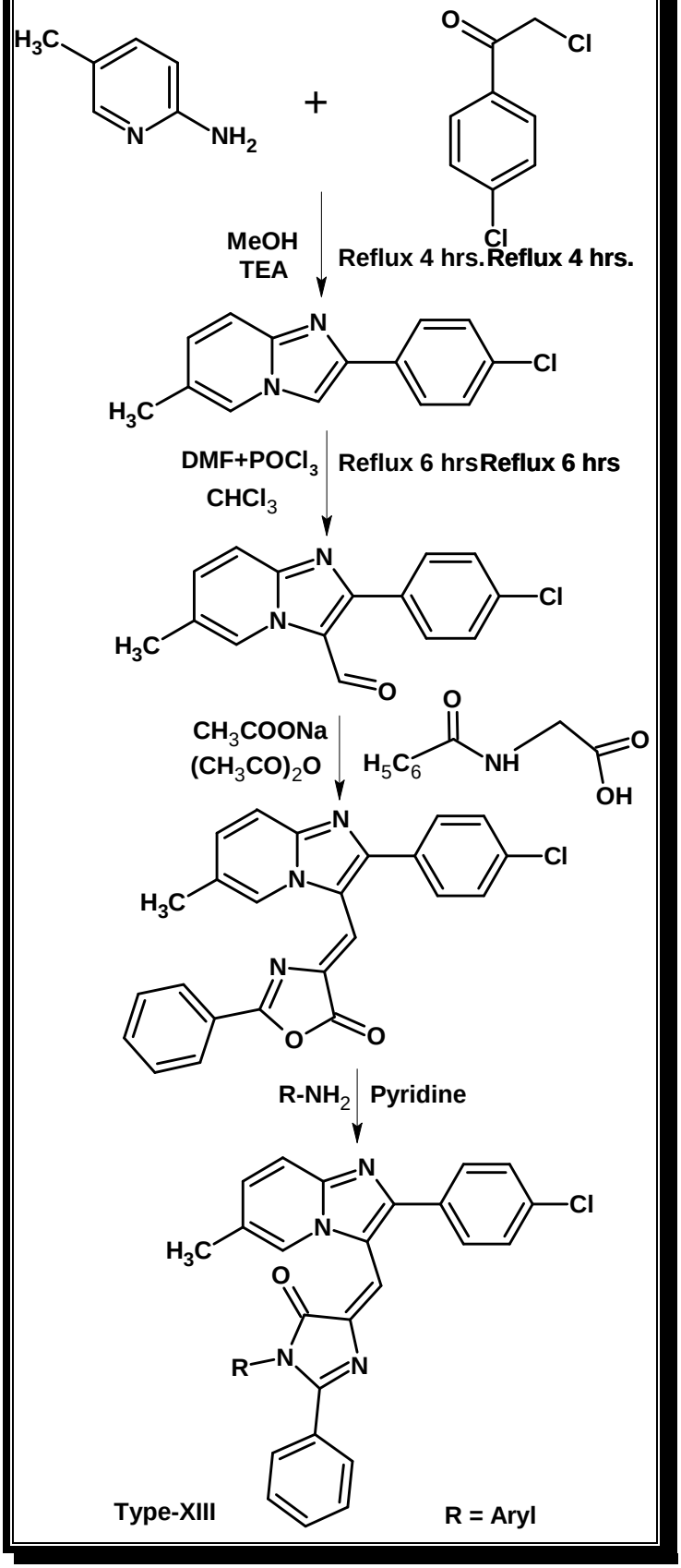
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.32	3H	singlet	Ar-CH_3(e)
2	6.52-6.66	2H	multiplet	Ar-H(d,o)
3	6.99-7.03	2H	triplet	Ar-H(p,n)
4	7.08-7.26	5H	multiplet	Ar-H(aa',i,j,k)
5	7.33-7.41	5H	multiplet	Ar-H(h,l,g,q,m)
6	7.55	3H	multiplet	Ar-H(bb',c)
7	8.02	1H	singlet	Ar-H(f)

MASS SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2- a] PYRIDIN – 3 - Yl] METHYLENE - 1" - (PHENYL)- 2"-PHENYL -5"-OXO-IMIDAZOLINE.




M/Z=157
M/Z=78
M/Z=234
M/Z=411
M/Z=488
M/Z=473
M/Z=66
M/Z=334
M/Z=247
M/Z=130

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO[1,2-a]PYRIDIN-3-YL]METHYLENE-1"-ARYL-2"-PHENYL-5"-OXO-IMIDAZOLINES.

(A) synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See(A), Part-I, Section-I (A),on page no. 37

(B) Synthesis of 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone.

A mixture of benzoylaminoacetic acid (6.0 gm,0.029 mol),acetic anhydride(4.27 gm,0.032 mol),sodium acetate(2.62 gm,0.032 mol**)** and 6 – methyl – 2 - (4' - chlorolphenyl)imidazo [1,2-a] pyridine – 3 - carboxaldehyde (4.36 gm,0.032 mol) was heated on a waterbath for 4 hrs. Resulting mass poured into ice cold water,filtered and crystallized from DMF.yield,66%,m.p.143 ^{o}C.

(C) Synthesis of 2-[(4'-chlorophenyl)-6-methylimidazo [1,2-a] pyridin-3-yl] methylene-1"-(phenyl)-2"-phenyl-5"-oxo- imidazolines(13a)

A mixture of phenyl amine (3.0 g, 0.01 mol) and 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone (4.26 g, 0.01 mol) in dry pyridine (30 ml) was refluxed for 10 hrs. in oil bath. Resulting mass was poured into crushed ice and neutralised with HCl, filtered and crystallized from dioxane. Yield 65%, mp. 155ºC.

($C_{30}H_{21}ClN_4O$; Required : C, 73.69; H, 4.33; N, 11.46%; found : C, 73.67; H, 4.30; N, 11.44%)

Similarly other 5-oxo-imidazolines have been prepared. The physicalconstants are recorded in Table No.13.

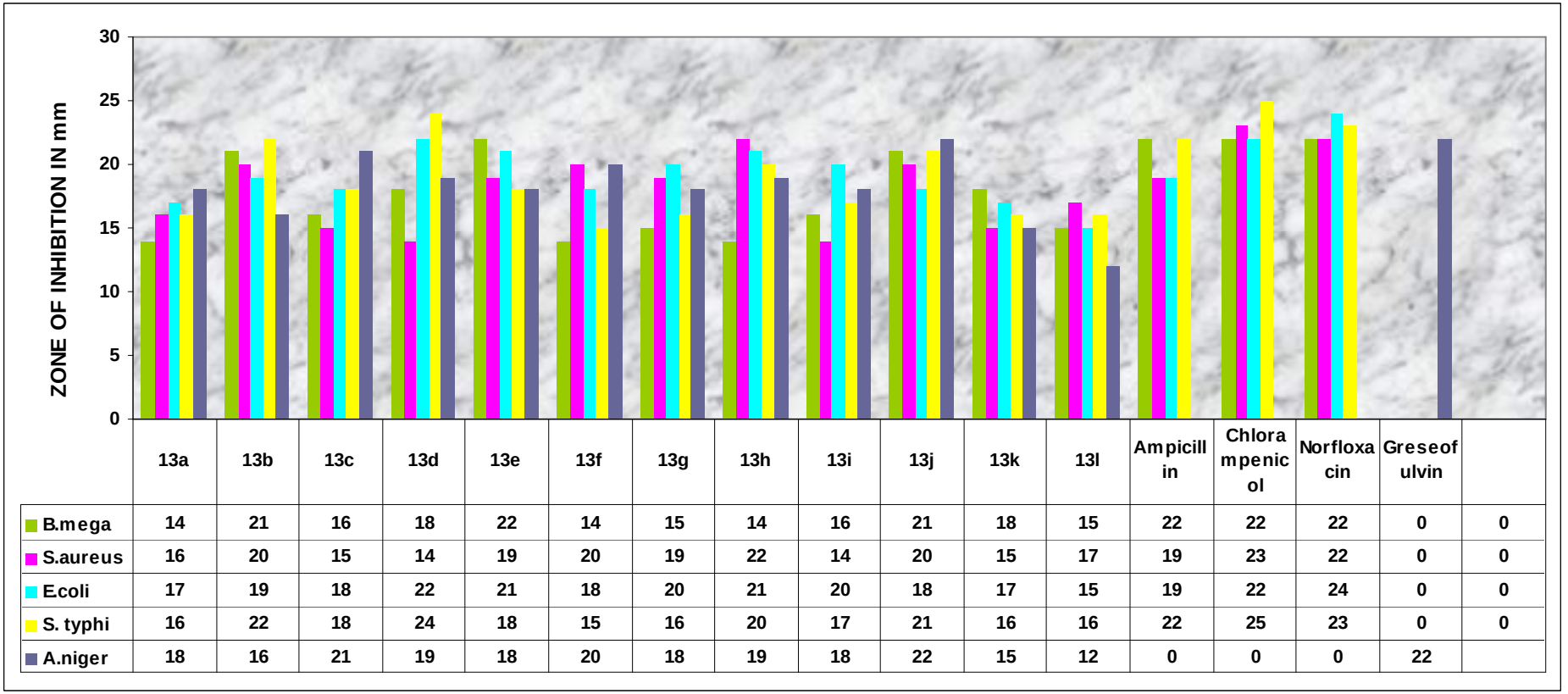
(D) Biological Screening of 2-[(4'-chlorophenyl)-6-methylimidazo [1,2-a] pyridin-3-yl] methylene-1"-aryl-2"-phenyl-5"-oxo- imidazolines.

Biological Screening was carried out as describe in Part-I,Section-I,page no.38.the zone of inhibition of the test solutions are recorded in graphical chart No.13

TABLE CNO. 13 PHYSICAL CONSTANTS OF 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2- a] PYRIDIN – 3 -] METHYLENE - 1" - (PHENYL)- 2"PHENYL -5"-OXO-IMIDAZOLINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
13a	C_6H_5-	$C_{30}H_{21}ClN_4O$	488.5	155	65	11.46	11.44
13b	3-Cl-C_6H_4 -	$C_{30}H_{20}Cl_2N_4O$	523.0	195	61	10.70	10.68
13c	4-Cl-C_6H_4 -	$C_{30}H_{20}Cl_2N_4O$	523.0	173	70	10.70	10.68
13d	2-4-$(Cl)_2$-C_6H_3-	$C_{30}H_{19}Cl_3N_4O$	557.5	180	75	10.04	10.02
13e	4 -F-C_6H_4-	$C_{30}H_{20}ClFN_4O$	506.5	165	62	11.05	11.03
13f	4-Br-C_6H_4-	$C_{30}H_{20}BrClN_4O$	567.5	190	66	9.87	9.85
13g	4 -OH-C_6H_4-	$C_{30}H_{21}ClN_4O_2$	504.5	168	60	11.10	11.08
13h	4-NH_2-C_6H_4-	$C_{30}H_{22}ClN_5O$	503.5	166	58	13.90	13.89
13i	4-CH_3-C_6H_4-	$C_{31}H_{23}ClN_4O$	502.5	163	55	11.14	11.11
13j	4-OCH_3-C_6H_4-	$C_{31}H_{23}ClN_4O_2$	518.5	200	69	10.80	10.79
13k	3-NO_2-C_6H_4-	$C_{30}H_{20}ClN_5O_3$	533.5	182	48	13.12	13.10
13l	4-NO_2-C_6H_4-	$C_{30}H_{20}ClN_5O_3$	533.5	198	59	13.12	13.10

GRAPHICAL CHART NO. 13: BIOLOGICAL SCREENING OF 2 - [(4' – CHLOROPHENYL) – 6 - METHYLIMIDAZO [1,2- a] PYRIDIN – 3 -] METHYLENE - 1" - (ARYL)- 2"-PHENYL -5"-OXO-IMIDAZOLINES.



	13a	13b	13c	13d	13e	13f	13g	13h	13i	13j	13k	13l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	14	21	16	18	22	14	15	14	16	21	18	15	22	22	22	0	0
S.aureus	16	20	15	14	19	20	19	22	14	20	15	17	19	23	22	0	0
E.coli	17	19	18	22	21	18	20	21	20	18	17	15	19	22	24	0	0
S. typhi	16	22	18	24	18	15	16	20	17	21	16	16	22	25	23	0	0
A.niger	18	16	21	19	18	20	18	19	18	22	15	12	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-VIII

SECTION – I: BIOLOGICAL SCREENING OF 2-[(4'-CHLOROPHENYL)-6-METHYLIMIDAZO [1,2- a] PYRIDIN – 3 -] METHYLENE - 1" - (ARYL)- 2"-PHENYL -5"-OXO-IMIDAZOLINES.

	Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
	B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
	13b-(21)	**13b-(20)**	**13b-(19)**	**13b-(22)**	**13c-(21)**
	13e-(22)	**13e-(19)**	**13d-(22)**	**13d-(24)**	**13f-(20)**
	13j-(21)	**13f- (20)**	**13e- (21)**	**13h-(20)**	**13j-(22)**
		13h-(22)	**13h-(21)**	**13j-(21)**	
		13j-(20)	**13i-(20)**		
Ampicillin (50 µg)	**22**	**19**	**19**	**22**	**--**
Chloramphenicol(50 µg)	**22**	**23**	**22**	**25**	**--**
Norfloxacin (50 µg)	**22**	**22**	**24**	**23**	**--**
Greseofulvin (50 µg)	**--**	**--**	**--**	**--**	**22**

PART-IX

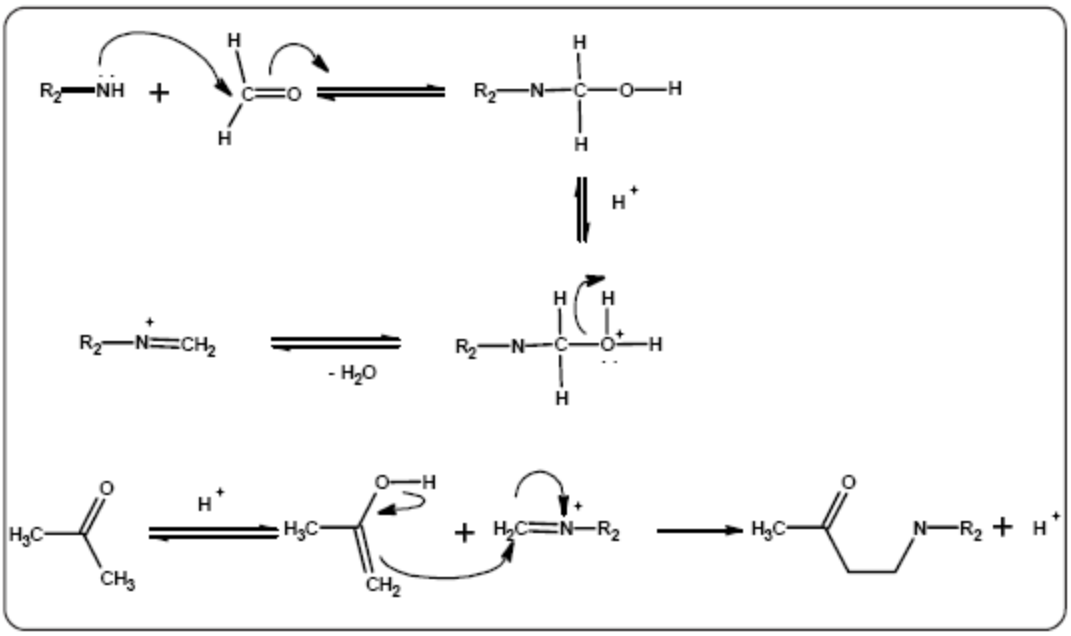
STUDIES ON MANNICH BASES

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 pharmacological and industrial applications. Mannich bases are also employed as intermediate in chemical synthesis.[515-517] Mannich base derivatives with bridge N-atom have been found to be potent drug in medicinal science and possess wide range of biological activities like anticancer, antibacterial, antimalarial, analgesic etc. Mannich bases have gained important because of their technological applications in polymer chemistry[518], especially as paints and surface. active agents and exhibits complexation characteristic with many transition metal ions. Over the years there has been much contraversy about the mechanism of the Mannich reaction. Studies of the reaction kinetics have led to the following mechanistic proposals.

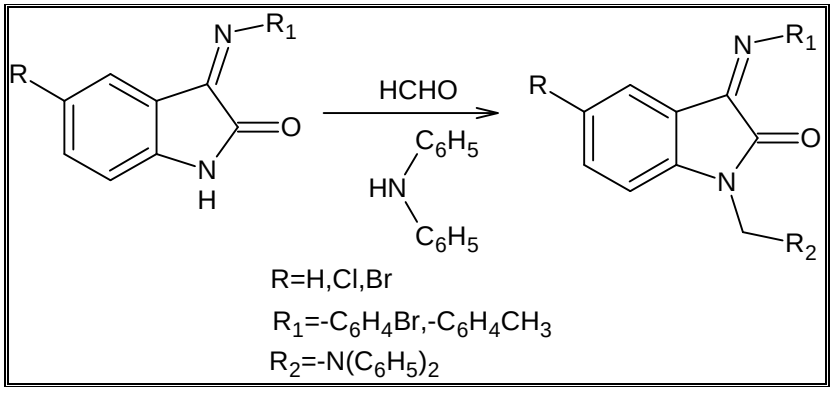
MECHANISM



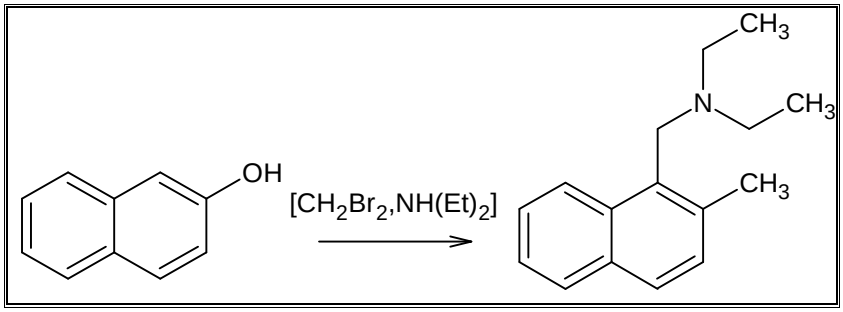
SYNTHETIC ASPECT

Different methods have cited in literature to synthesize Mannich bases by several workers[519, 520] using various interesting substractes.

1. P.G. Venkatesha and D. Vanappayya [521] have synthesized aminobenzylated Mannich bases by the condensation reaction between heterocyclic secondary amines and benzaldehyde.
2. Seshaiah Krishnan et al[522] have synthesized Mannich bases from the schiff bases of isatin in presence of formaldehyde and diphenyl amine.



3. Yung-son Hon et al[523]. have prepared Mannich base from the reaction of phenolic compounds with a preheated mixture of dibromomethane and diethylamine.



4. S. N. Pandeya and D. Sriram Dave[524] have synthesized Mannich bases by the condensationofthe acidic group of isatin with formaldehyde and secondary amines.
5. K.W. Chi and co-workers[525] have synthesized Mannich base using 1,4,10,13-tetraoxa-7,16 diazacyclooctadecane, formaldehyde and phenolic derivatives in benzene.
6. A. Christos Kontogiorgis et al.[526] have synthesized Mannich base of coumarine

THERAPEUTIC IMPORTANCE

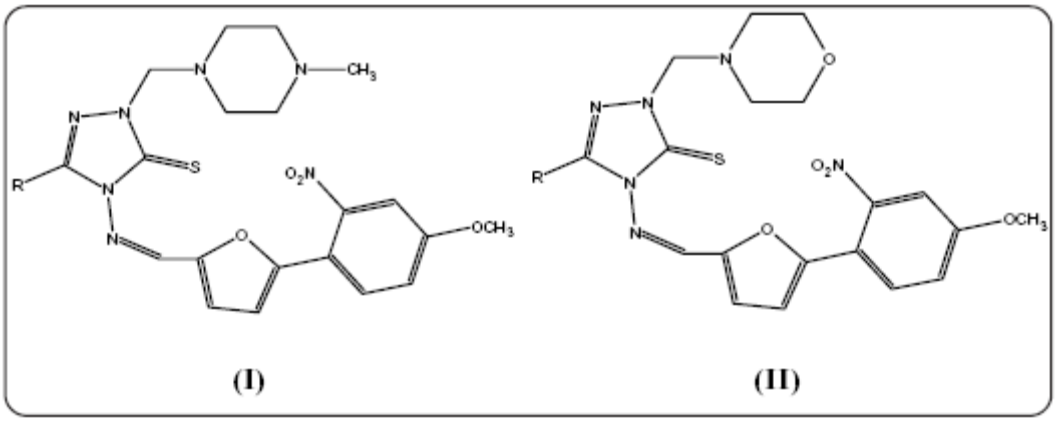
Mannich bases are associated with a wide variety of biological activities and therapeutic applications such as,

1. Anti-inflammatory[527-529]
2. Antifungal[530]
3. Antitumor[531]
4. Analgesic[532]
5. Cytotoxic and anticancer[533]
6. Antibacterial[534]
7. Antipsychotic[535]
8. Tranquilizer[536,537]
9. Antileishmanial[538]
10. Antimalarial[539]

T. Lorand and B Kocsis [540] have synthesized some new Mannich ketones and reported their antibacterial activity. D. D. Erol A.rosen et al.[541] have synthesized some novel mannich base derivatives from 6-acyl-3-(3,5-dimethylpiperidinomethyl)-2(3H)-benzoxazolones and reported their biological activities. H. M. Hassan[542] have synthesized some new Mannich bases containing 1,8-napthyridine moiety and reported their antimicrobial activity.

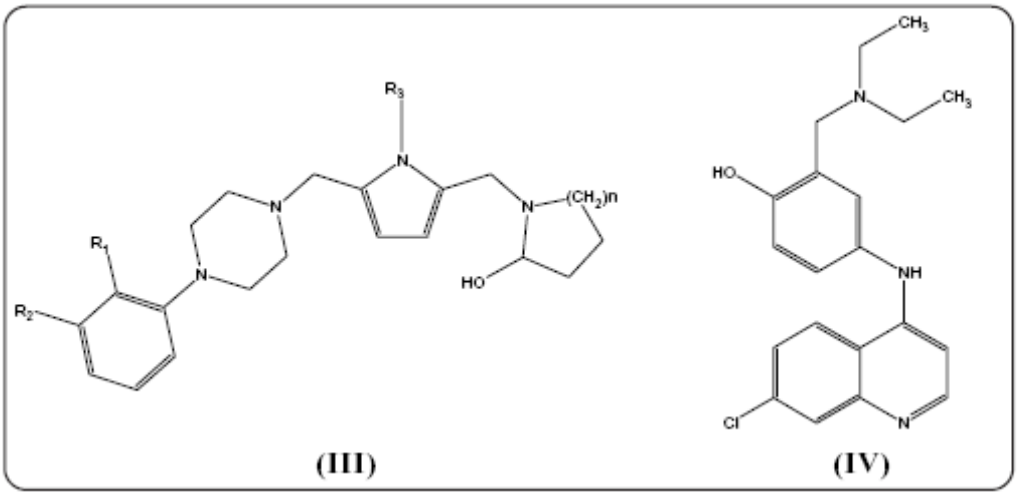
M. Movrin and D. Maysinger [543] have synthesized Mannich bases from nitroxoline and reported them as biologically active agents. T. Ojanen and coworkers[544] have reported antifungal activity of some mono, bis and quaternary mannich bases derived from acetophenone. Y. Li, Z. S. Yang et al[545]have synthesized some mannich base derivatives and reported their antimalarial activity.

B. Shivarama Holla et al.[546] have prepared Mannich bases and tested them for anthelmintic activity (I) and all the newly synthesized compounds (II) were tested for their antibacterial and antifungal activity.



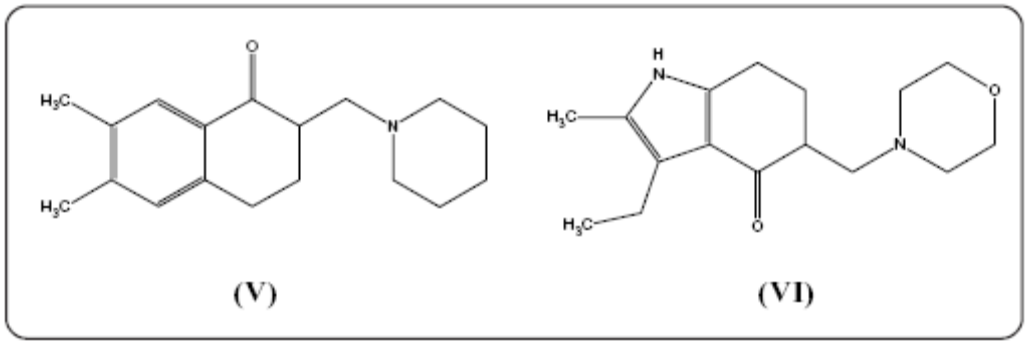
(I) **(II)**

Amodiaquine[547,548], Mannich base derivatives (III) which shown an antimalarial activity superior than chloroquine in areas of high chloroquine resistance. M. L. Edwards et al.[549] have prepared the mannich base of 4-phenyl-3-buten-2-one as an antiherps agent. K. Malcolm Scott and co-workers[550] have prepared the pyrrole mannich base (IV) as a potent antipsychotic agents.

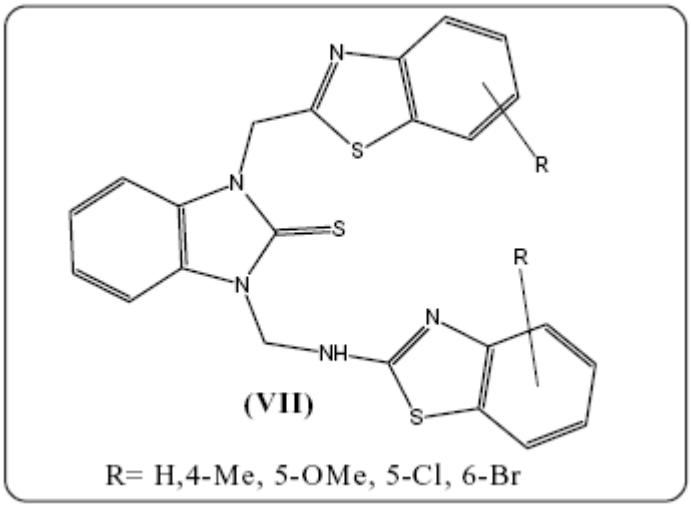


(III) **(IV)**

J. Knoll et al.[551] have prepared the mannich base (V) which was the most potent neuroleptic compound of a series of aryl substituted analogues. Molindone (VI) which has been reported to demostrate potent neuroleptic activity[552]. Jan Balzarini and co-workers[553] have prepared the mannich bases of chalcone shows cytotoxic activities.



H. I. Gul et al[554 ,555] have documented antifungal activity of bis mannich bases derived from acetophenones and some mono mannich bases evaluated for their anticonvulsant activity. M. S. Shingare et al[556] have described the synthesis and the antiviral activity of mannich bases (VII).



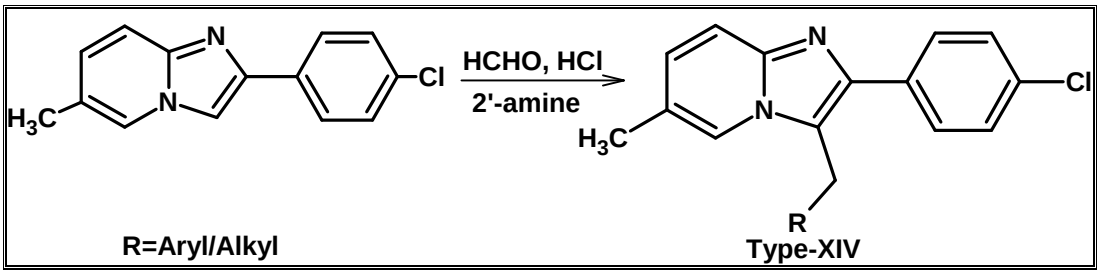
In view of the importance of mannich bases as versatile synthetic intermediates and the availability of scanty literature on therapeutic properties, we have undertaken the preparation of mannich bases in following sections.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2 - (4' - CHLOROPHENYL)-6-METHYL- (3-N, N'-DIARYL/DIALKYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2- (4'-CHLOROPHENYL)-6-METHYL- (3-N, N'-DIARYL/DIALKYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINES.

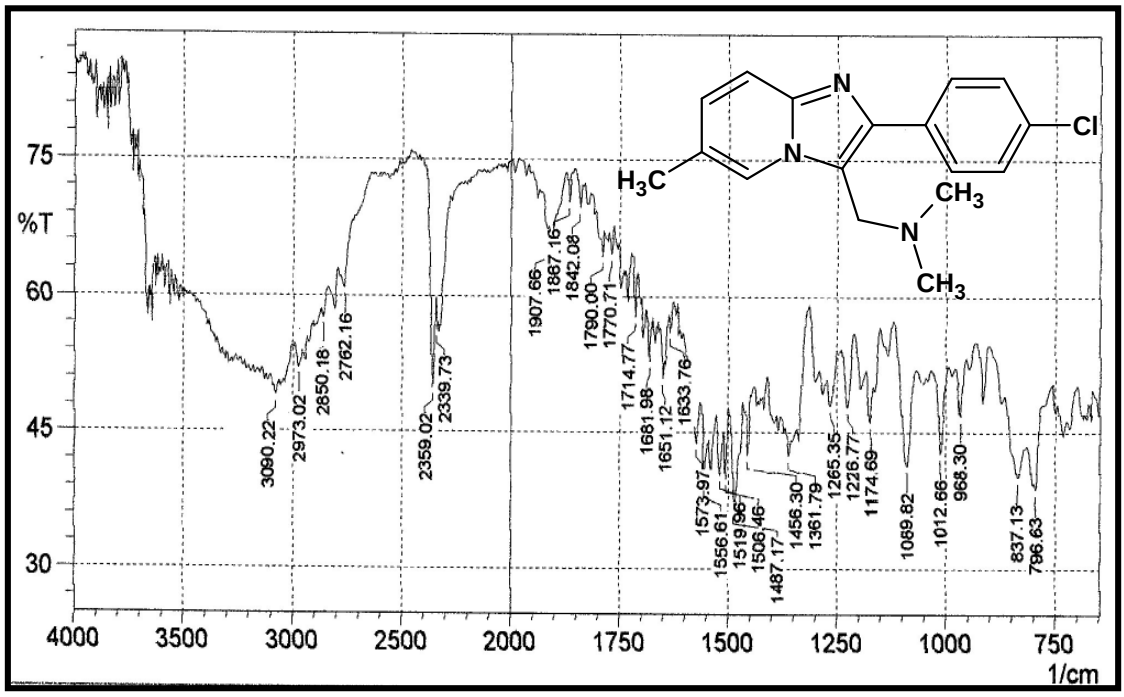
In view of getting better therapeutic agent and considering the association of various biological activity with imidazo[1,2-a]pyridine nucleus, the preparation of 2 -(4'chlorophenyl)-6-methyl- (3-N, N'-diaryl/dialkyl amino methyl)-imidazo [1, 2-a] pyridines. of Type(XIV) have been synthesised from 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine with aryl/alkyl amines, formaldehyde and HCl in methanol.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared,[1]H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I ,page no. 41

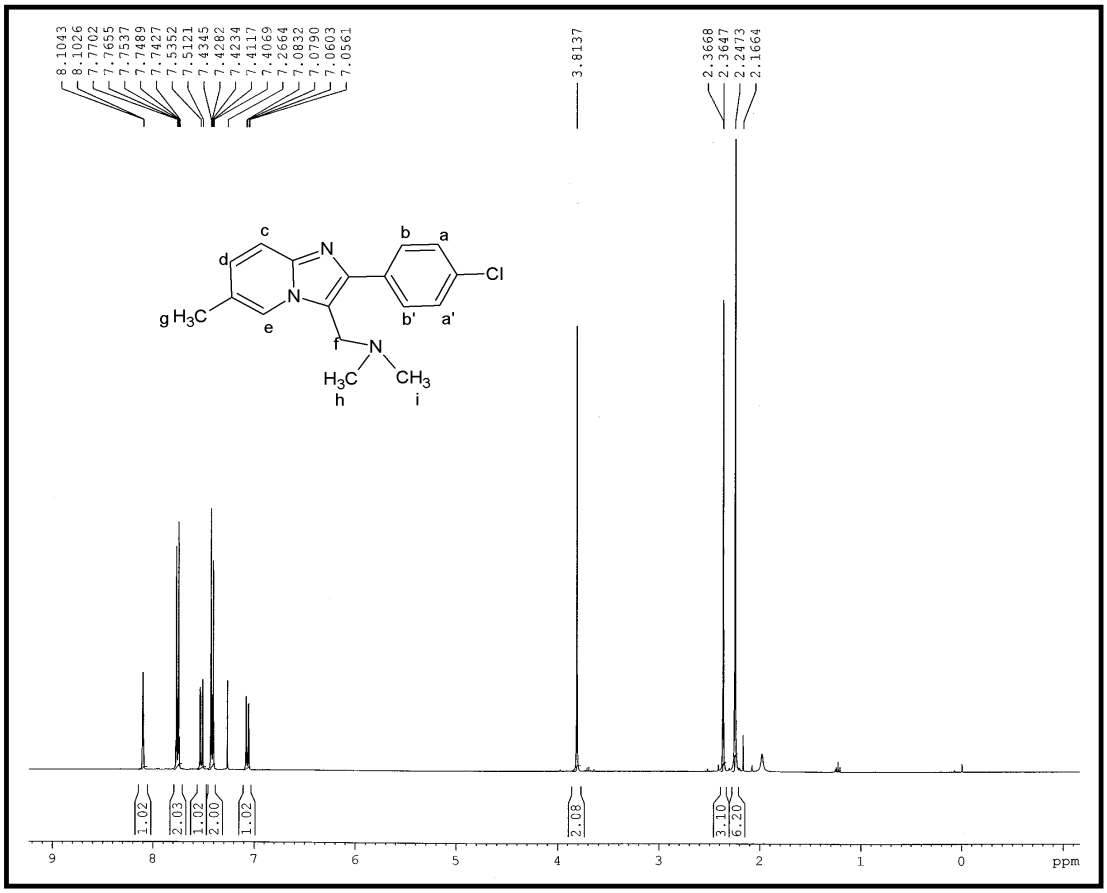
IR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL- (3-N, N'-DIMETHYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2973	2990-2850	648
	C-H str. (sym.)	2881	2880-2860	"
	C-H def. (asym.)	1442	1470-1435	"
	C-H def. (sym.)	1361	1390-1370	"
Aromatic	C-H str.	3090	3090-3030	649
	C=C str	1487	1600-1450	"
	C-H i.p. (def.)	1265	1300-1100	"
Imidazo[1,2-a] Pyridine	C-N str.	1174	1220-1020	"
	C=N str.	1633	1612-1593	"
Halide	C-Cl str.	796	800-600	"
Alkene	$-CH_2$ str.	2762	2850-1790	"

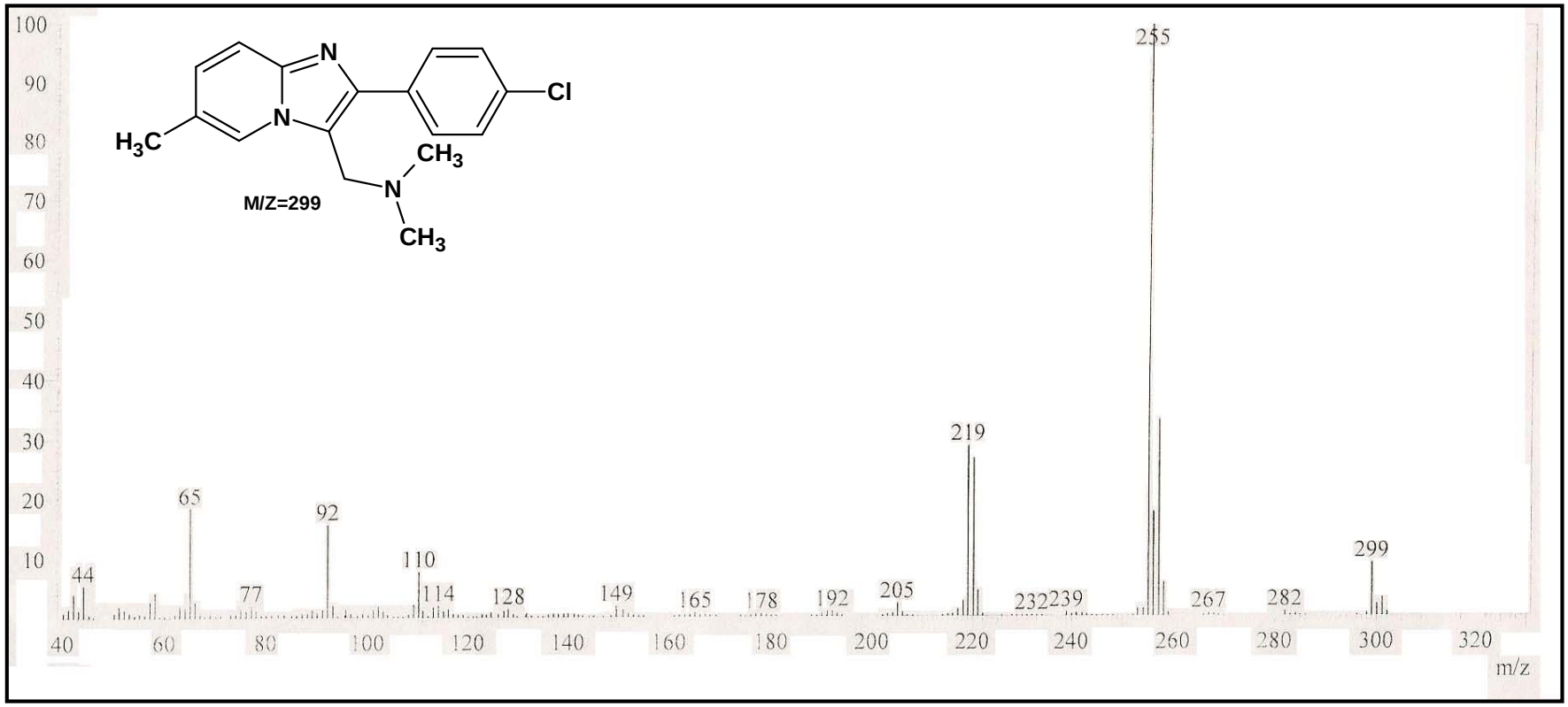
NMR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL- (3-N, N'-DIMETHYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINE.

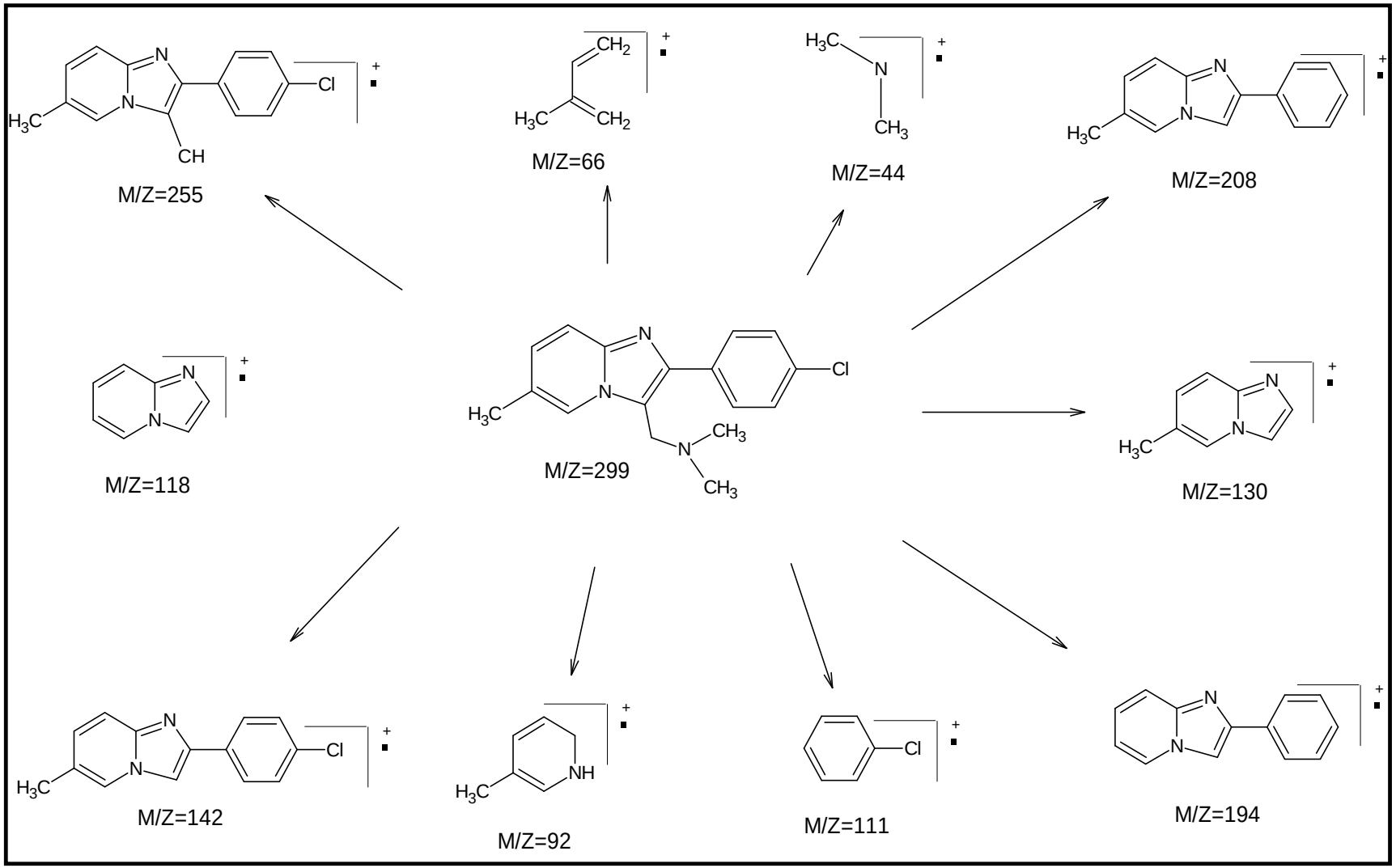


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

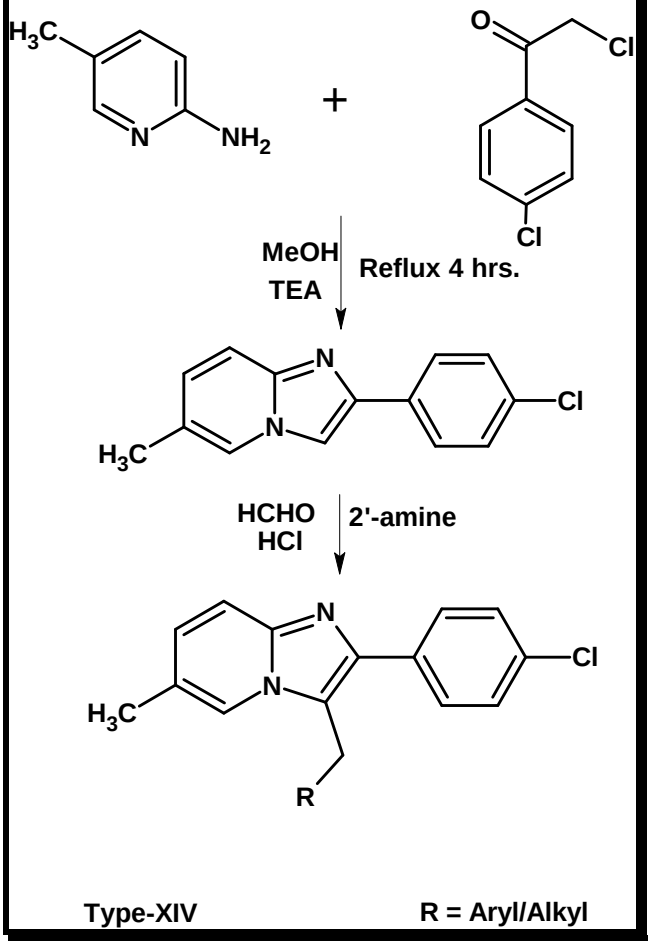
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.24	6H	singlet	N-$(CH_3)_2$(i,j)
2	2.36	3H	singlet	Ar-CH_3(g)
3	3.81	2H	singlet	Ar-H(f)
4	7.05-7.08	1H	doublet	Ar-H(d)
5	7.40-7.43	2H	doublet	Ar-H(aa')
6	7.51-7.53	1H	doublet	Ar-H(c)
7	7.74-7.77	2H	doublet	Ar-H(bb')
8	8.10	1H	singlet	Ar-H(e)

MASS SPECTRAL STUDY OF 2-(4'CHLOROPHENYL)-6-METHYL- (3-N, N'-DIMETHYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINE.




M/Z=255
M/Z=66
M/Z=44
M/Z=208
M/Z=118
M/Z=299
M/Z=130
M/Z=142
M/Z=92
M/Z=111
M/Z=194

REACTION SCHEME



Type-XIV **R = Aryl/Alkyl**

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-(3-N,N'-DIARYL/DIALKYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINES.

[A] Synthesis of 2-(4'-chlorophenyl)6-methyl imidazo[1,2-a]pyridine

See, Part-I, Section-I,on page no. 37

[B] Synthesis of 2-(4'-chlorophenyl)-6-methyl-(3-N, N'-di methyl aminomethyl)-imidazo [1, 2-a] pyridines(14a).

A mixture of 2-(4'-chlorophenyl)-6-methyl imidazo[1,2-*a*]pyridine (2.88 gm, 0.01 mol), formaldehyde (0.3 gm, 0.01 mol) and dimethyl amine (0.87 gm, 0.01 mol) and HCl in methanol (50 ml) was refluxed for 8 hrs. The product was poured on to crushed ice. The product was isolated, dried and recrystallised from hexane Yield 65%, m.p. 170^{o}C.

($C_{17}H_{18}ClN_3$; Required : C, 68.11; H, 6.05; N, 14.02%; found : C, 68.10; H, 6.03; N, 14.00%)

Similarly other 2-(4'-chlorophenyl)–6–methyl-(3-N,N'-diaryl/dialkyl aminomethyl)-imidazo [1, 2-a] pyridines compouns were prepared. The physical constants are recorded in Table No.14.

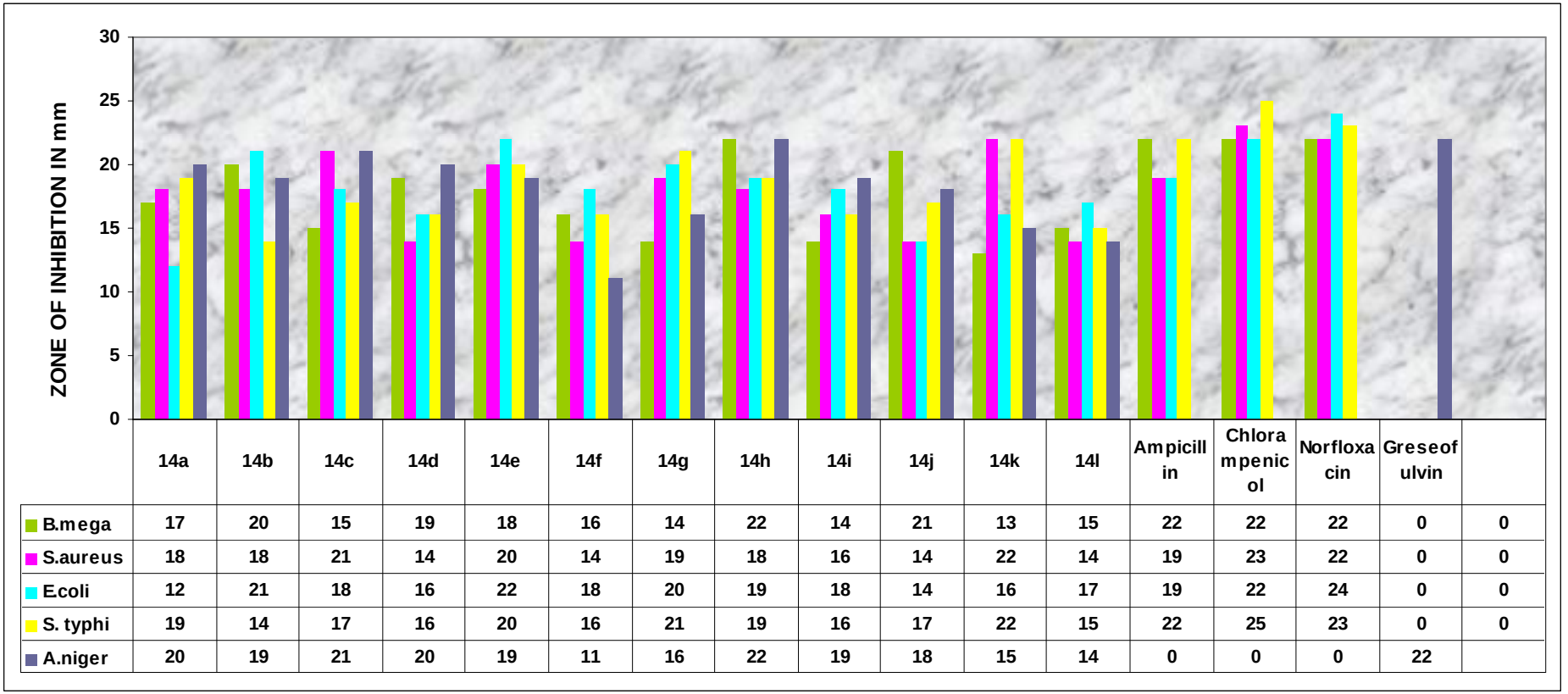
[E] Biological screening of 2 - (4'- chlorophenyl) – 6 – methyl - (3-N,N'-diaryl/dialkylaminomethyl)-imidazo [1, 2-a] pyridines.

Biological screening were carried out as described in Part-I, Section-I, page no. 38 The zones of inhibition of test solutions are recorded in Graphical Chart no.14.

TABLE NO. 14 PHYSICAL CONSTANTS OF 2-(4'CHLOROPHENYL)-6-METHYL-(3-N,N'-DIALKYL/DIARYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
14a	$(CH_3)_2N$-(DMA)	$C_{17}H_{18}ClN_3$	299.5	170	65	14.02	14.00
14b	C_4H_8NO-(Morpholine)	$C_{19}H_{20}ClN_3$	341.5	150	62	12.29	12.26
14c	$C_4H_9N_2$-(Piprazine)	$C_{19}H_{21}ClN_4$	340.5	190	69	16.44	16.40
14d	$(C_2H_5)_2N$-(DEthylA)	$C_{19}H_{22}ClN_3$	327.5	150	55	12.82	12.81
14e	$(C_6H_5)_2N$-(Diphenyl amine)	$C_{27}H_{22}ClN_3$	423.5	210	63	9.91	9.90
14f	C_4H_8N-(Pipiridine)	$C_{19}H_{20}ClN_3$	325.5	170	70	12.90	12.88
14g	$(C_2H_4Cl)_2N$-(Bis-2-Chloro)	$C_{19}H_{20}Cl_3N_3$	396.5	121	62	10.59	10.58
14h	$(C_3H_7)_2N$-(Isopropylamine)	$C_{21}H_{26}ClN_3$	355.5	180	69	11.81	11.80
14i	$C_{10}H_{13}N_2$-(N-Phenyl piprazine)	$C_{25}H_{25}ClN_4$	416.5	216	62	13.44	13.42
14j	$C_5H_{11}N_2$-(N-Methyl piprazine)	$C_{20}H_{23}ClN_4$	354.5	180	72	15.79	15.76
14k	$C_{11}H_{15}N_2O$ –(Benz hyd pip.)	$C_{26}H_{27}ClN_4O$	446.5	190	60	12.53	12.51
14l	$(OHCH_2CH_2)_2N$ –(Di-ethenol A)	$C_{19}H_{20}ClN_3O$	359.5	195	70	11.68	11.65

GRAPHICAL CHART NO. 14 : BIOLOGICAL SCREENING OF 2 - (4' – CHLOROPHENYL) - 6 - METHYL - (3 - N, N'-DIARYL/DIALKYLAMINOMETHYL)-IMIDAZO [1, 2-a] PYRIDINES.



	14a	14b	14c	14d	14e	14f	14g	14h	14i	14j	14k	14l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	17	20	15	19	18	16	14	22	14	21	13	15	22	22	22	0	0
S.aureus	18	18	21	14	20	14	19	18	16	14	22	14	19	23	22	0	0
E.coli	12	21	18	16	22	18	20	19	18	14	16	17	19	22	24	0	0
S. typhi	19	14	17	16	20	16	21	19	16	17	22	15	22	25	23	0	0
A.niger	20	19	21	20	19	11	16	22	19	18	15	14	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-IX

SECTION – I: BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL)-6-METHYL-(3-N,N'- DIARYL/DIALKYL AMINO METHYL)-IMIDAZO [1, 2-a] PYRIDINES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
		14b-(20)	**14b-(18)**	**14b-(21)**	**14e-(20)**	**14c-(21)**
		14h-(22)	**14c-(21)**	**14f-(18)**	**14g-(21)**	**14d-(20)**
		14j-(21)	**14e- (20)**	**14e-(22)**	**14k-(22)**	**14h-(22)**
			14g-(19)	**14g-(20)**		
			14k-(22)	**14h-(19)**		
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

PART-X

STUDIES ON SCHIFF'S BASES

STUDIES ON SCHIFF'S BASES

INTRODUCTION

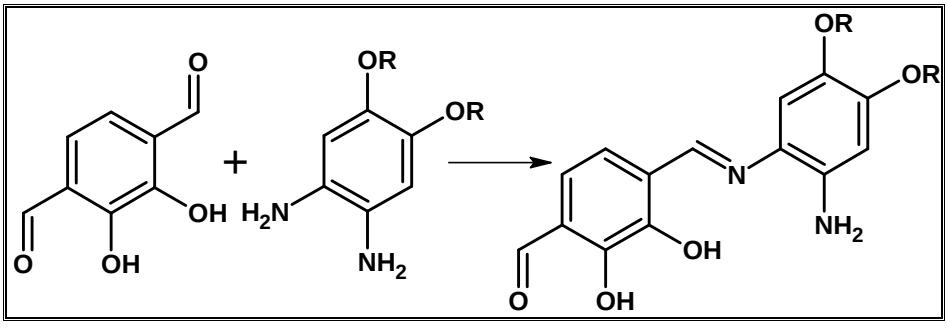
In recent years, interest has also focused on aza-analogs such as azomethine derivatives which show a very similar pharmacological profile to classical Over the past few years, several lead-compounds have been developed.Azomethines are also known as schiff's bases and they are well known intermediates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

Azomethines are obtained mainly by warming the aldehyde & aromatic amine togather. Howeve, it is more convenient to work in a solvent such as alcohol, dilute acetic acid or glacial acetic acid. Some time the reaction is aided by trace of acid in other cases the hydrochloride of the amines can be used in the synthesis. In general Schiff's bases do not react further with either of the reagents used in their preparation as do most of the other types of simple intermediates.Synthetic Schiff's base derivatives contribute in huge libraries owing to their wide applicability in different fields.

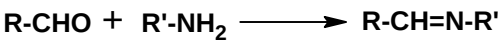
SYNTHETIC ASPECT

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

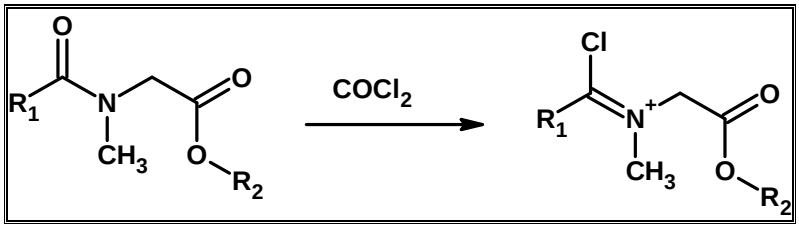
1. A. J. Gallant et al.[557] have prepared schiff's bases by condensation of equimolar quantity of 3,6 diformyl catechol and substituted o-phenylenediamine.



2. General account of the summary of reaction of aldehydes with amine (aromatic or aliphatic) has been reviewed by M. S.Murray[558].

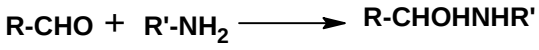


3. A new one pot procedure for the generation of azomethine has been investigated by R. J. Anderson and co-workers[559].

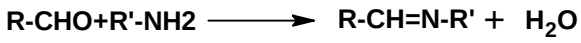


4. Strache[560] and Van Alphen[561] have prepared imine involves in two steps.

a. Add. of the amine to the aldehyde gives aldol. Which are rarely capable of isolation.

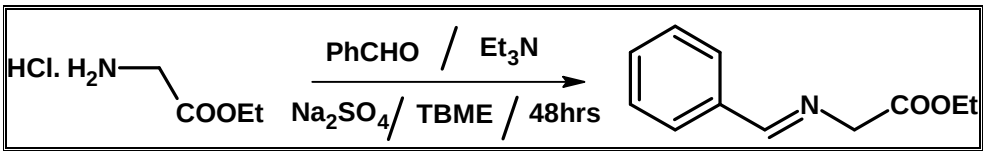


b. The loss of water to give an imine (azomethine), this corresponds to the "crotonaldehyde stage" of the aldol condensation.



5. Oddo and Tognacchini[562] have introduced the comparative rates of formation of Schiff 's base from aniline & substituted aniline & aromatic aldehyde using a cryscopic method follow the course of reaction.

P. L. Beaulieu and co-workers[563] have synthesized (*E*)-*N*-phenyl methylene glycine ethyl ester by the cyclocondensation of glycine ethyl ester hydrochloride, *t*-butylmethyl ether (TBME), benzaldehyde was added followed by anhydrous Na_2SO_4 and triethylamine



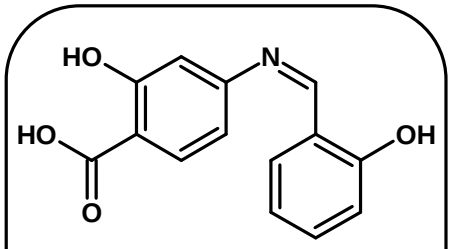
THERAPEUTIC IMPORTANCE

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

1. Antiviral[564]
2. Antifungal[565]
3. Antiparasitic[566]

4. Antibacterial[567]
5. Antipyretic[568]
6. Antiinflammatory[569]
7. Plant harmone activity[570]
8. Antitubercular[571]

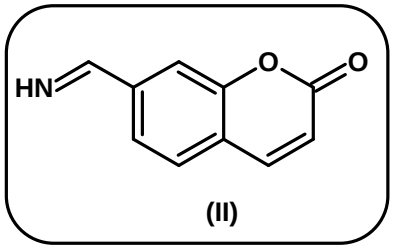
Smalders et al.[572] synthesized some new azomethine as potential antitumor agents. Sharaf El-Din, and Nabaweyal[573] have synthesized some azomethine derivatives (I) having good antibacterial activity.Chohan et al.[574] have synthesized azomethines, which have been screened and compared for their antibacterial action against bacterial species Escherichia coli, Pesudomonas aeruginose and Klebisella pneumoniase.



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

(I)

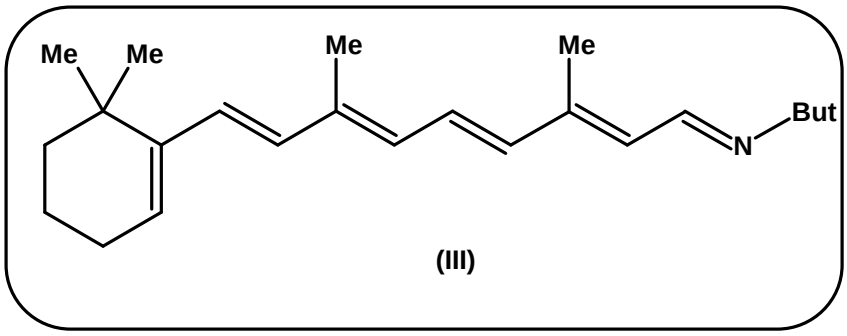
Schiff's bases exhibit a wide range of pharmacological activities like antifungal, antibacterial, antiviral, anti-inflammatory etc. R. H. Mehta et al.[575] have synthesized coummarin schiff's base derivatives (II) and examined for their antibacterial activity. A. K. Khalafallah and M. E Hassan.[576] have prepared some styryl Schiff's bases spiro derivatives as potential antibacterial and antifungal activity.



(II)

Chohan et al.[577] have synthesized azomethines, which have been screened and compared for their antibacterial action against bacterial species Escherichia coli, Pesudomonus aeruginoase and Klebisella pneumoniase. Das Joydip[578] have synthesized trans-N-refinylidene-n-butylamine (III) 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. V. M. Patel [579] have synthesized some new Schiff's bases having good antibacterial activity.



(III)

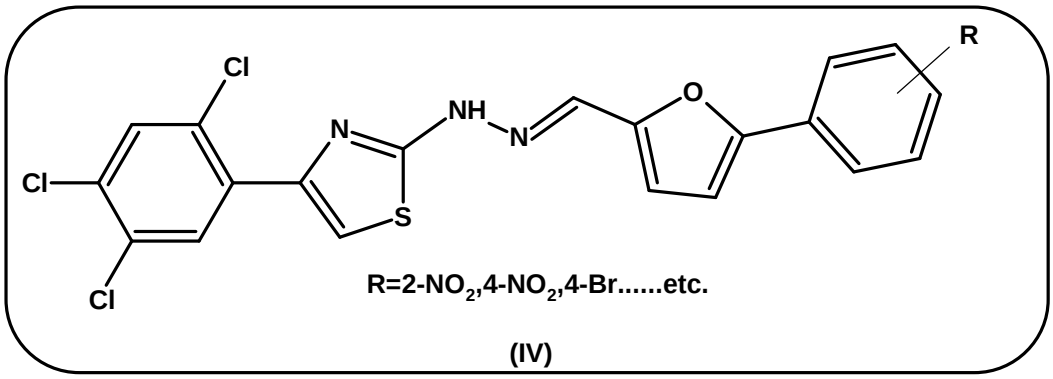
M. D. Deshmukh. and A. G. Doshi [580] prepared some new Schiff's bases show good antimicrobial activity against test organism *S. aureus, E. coli, Saigella dysenteridse* and *Salmonella typhi*. Wang and Yangang[581] have synthesize diazomethines having plant hormone activity. Das Arima et al.[582] have prepared Schiff's bases of aminohydroxy guanidine (SB-AHG5) and tested for antiviral activity against Herpes Simplex virus (HSV-1) and adenovirus (Ad-5) along with 11 other heterocyclic SB-AHG5.

S. Castellano et. al.[583] have prepared azomethine derivatives and evaluated in vitro against several pathogenic fungi responsible for human disease. B. Shivarama Holla et. al.[584] have documented antibacterial, antifungal and herbicidal activity of azomethine derivatives.Wang, Yangsng and co-workers[585] have screened some azomethines having good plant homone activity. Pascal Rotheist et. al.[586]have reported soe new azomethines as antiparasitic agents.

B. Shivarama Holla., et al.[587] have synthesized azomethines having antibacterial and anti-inflammatory activity. J. R. Dimmoch et. al.[588] have reported azomethines as cytotoxic agents.Adnan A. et. al.[589] have synthesised azomethines possessing significant antibacterial and antifungal activity.

C. Alexandru et al.[590] have synthesized azomethines, which have good analgesic and antipyretic properties. S. N. Pandeya et al.[591] 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).

R. V. Chambhare et al.[592] have prepared some azomethines and tested for their antimicrobial activity. B. Shivarama Holla et. al.[593] have synthesized azomethines of (IV) having antibacterial and anti-inflammatory activity.



(IV)

R, Tilak et al.[594] have synthesized some Schiff's bases, thiazolidinones 4-triazolines, and formazones of 2-chloro phenothiazines and screened against carrageenininduced edema in albino rats. The thiazolidinones showed promising anti-inflammatory activity.

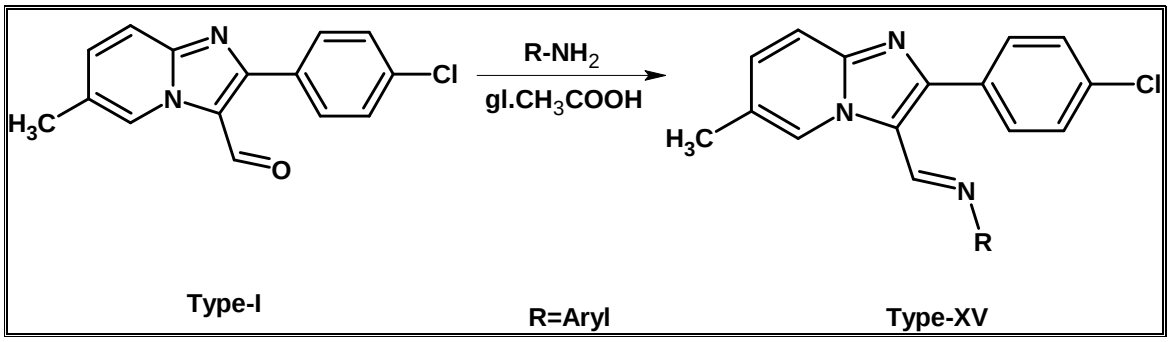
Looking to the interesting properties of azomethines, we have synthesized some new azomethines, which have been described as under.

SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE ARYLAMINES.

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENEARYLAMINES.

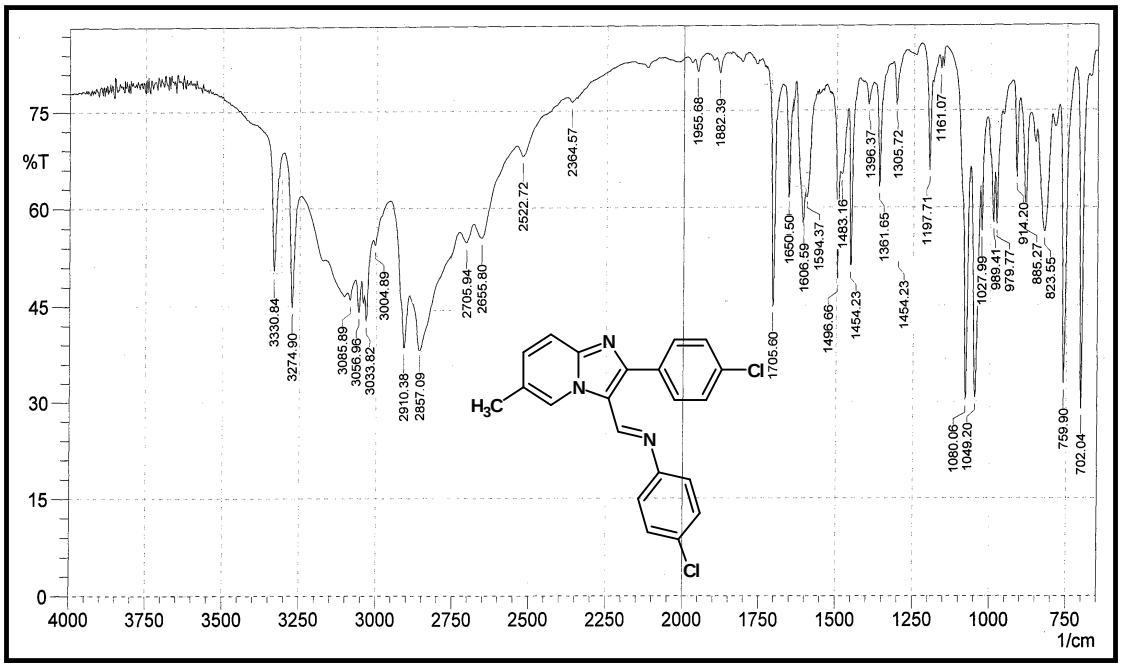
Looking to the interesting properties of azomethines, with an intension tosynthesising better therapeutic agents, azomethine derivatives of Type (XV) have been synthesized by the condensation of 6-methyl-2-(4'-methylphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde with different aromatic amines in order to study their biodynamic behavior.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared, ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC,

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I page no. 41

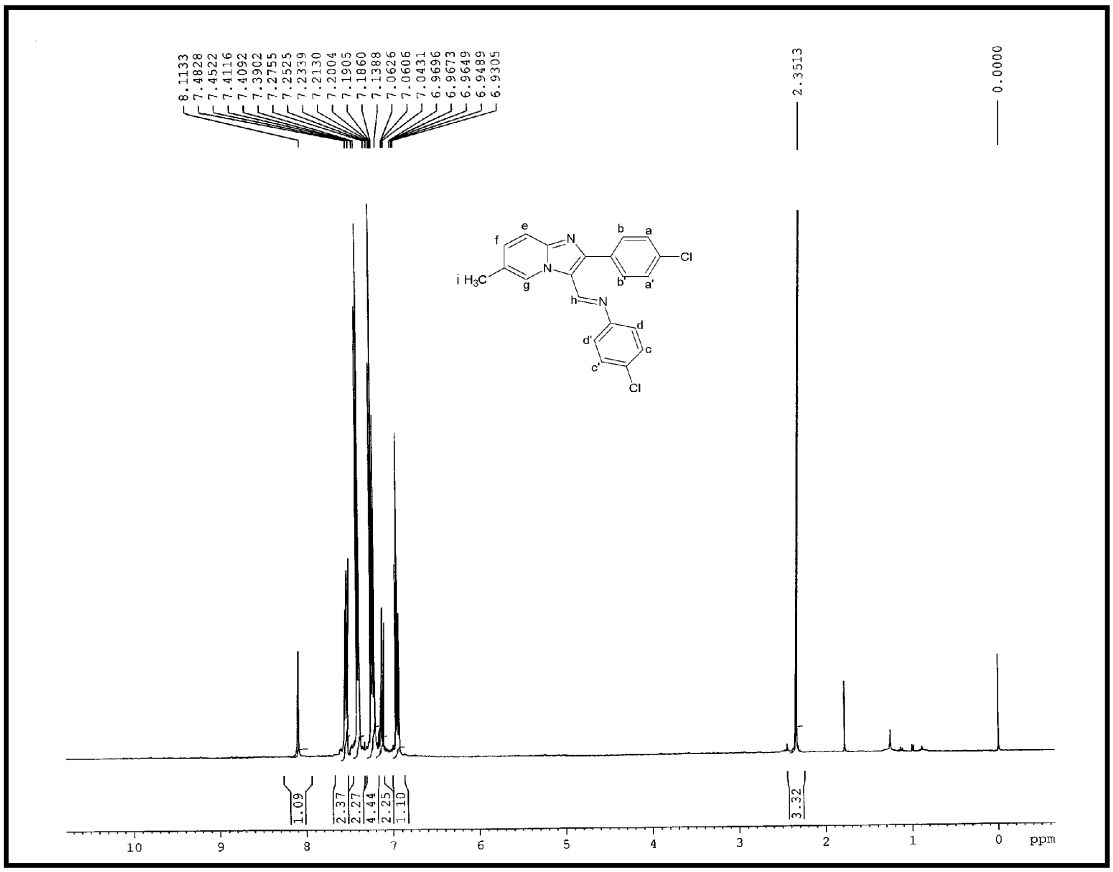
IR SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE (4'''-CHLOROPHENYL)AMINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2910	2990-2850	648
	C-H str. (sym.)	2860	2880-2860	"
	C-H def. (asym).	1454	1470-1435	"
	C-H def. (sym.)	1396	1390-1370	"
Aromatic	C-H str.	3033	3090-3030	649
	C=C str	1483	1600-1450	"
	C-H i.p. (def.)	1300	1300-1100	"
Schiff base	C-N str	1049	1220-1020	"
	C=N str	1705	1710-1650	"
Imidazo[1,2-a] pyridine	C-N str.	1080	1220-1020	"
	C=N str.	1694	1612-1593	"
Halide	C-Cl str.	702	800-600	"

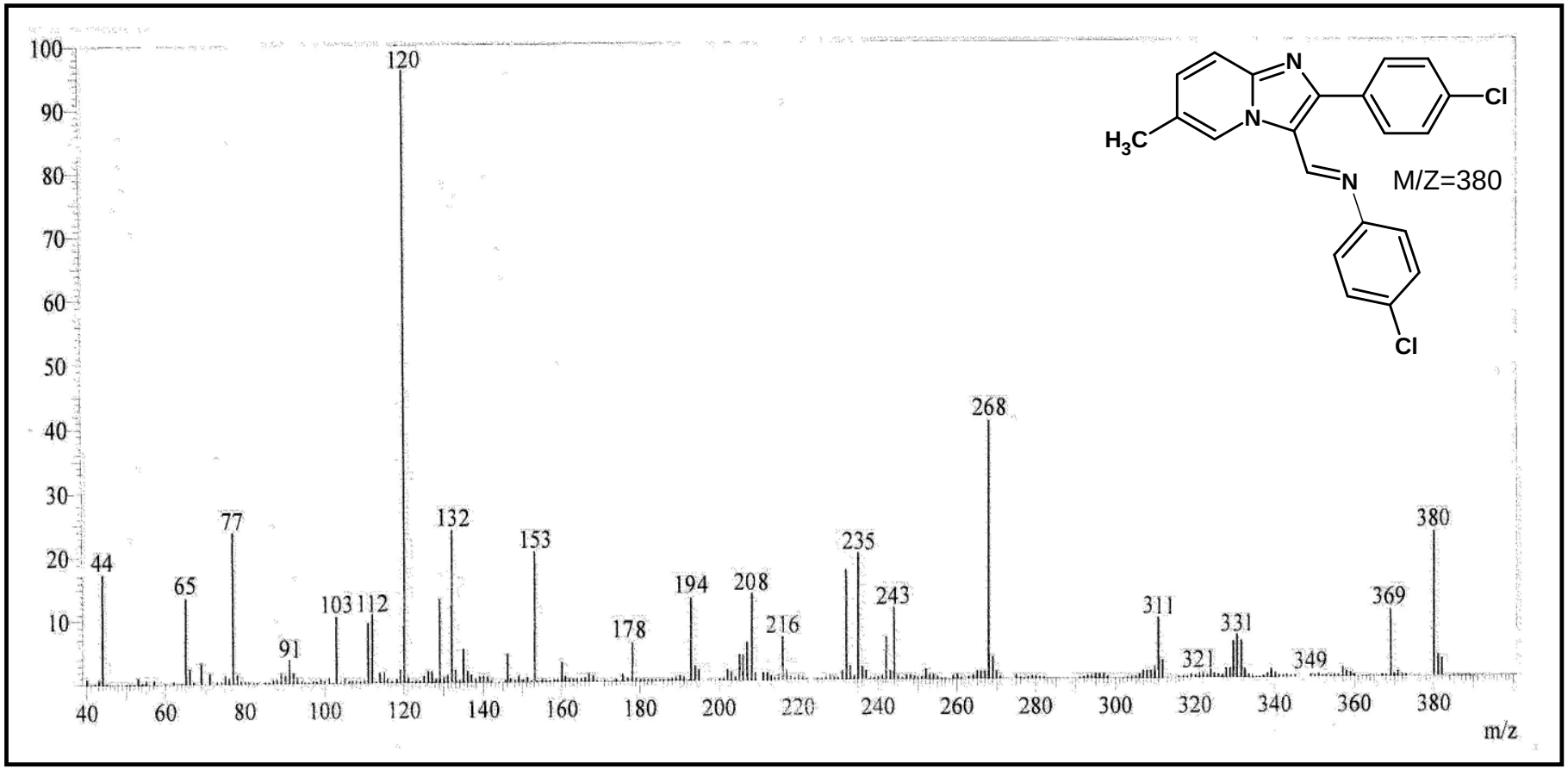
NMR SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE (4'''-CHLOROPHENYL)AMINE.

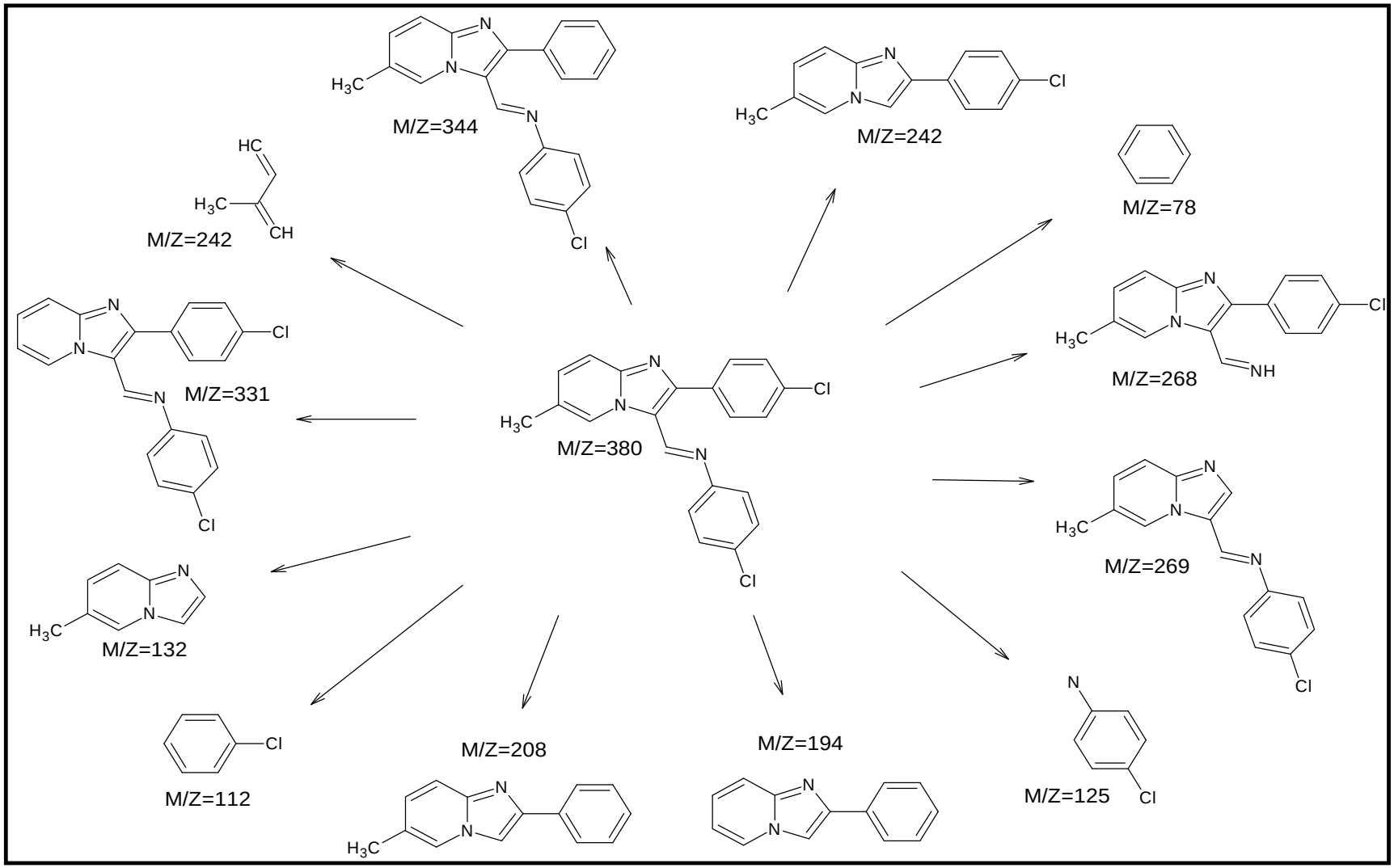


Internal Standard: TMS;Solvent :CDCl3; Instument Bruker Spectometer (300 MHz)

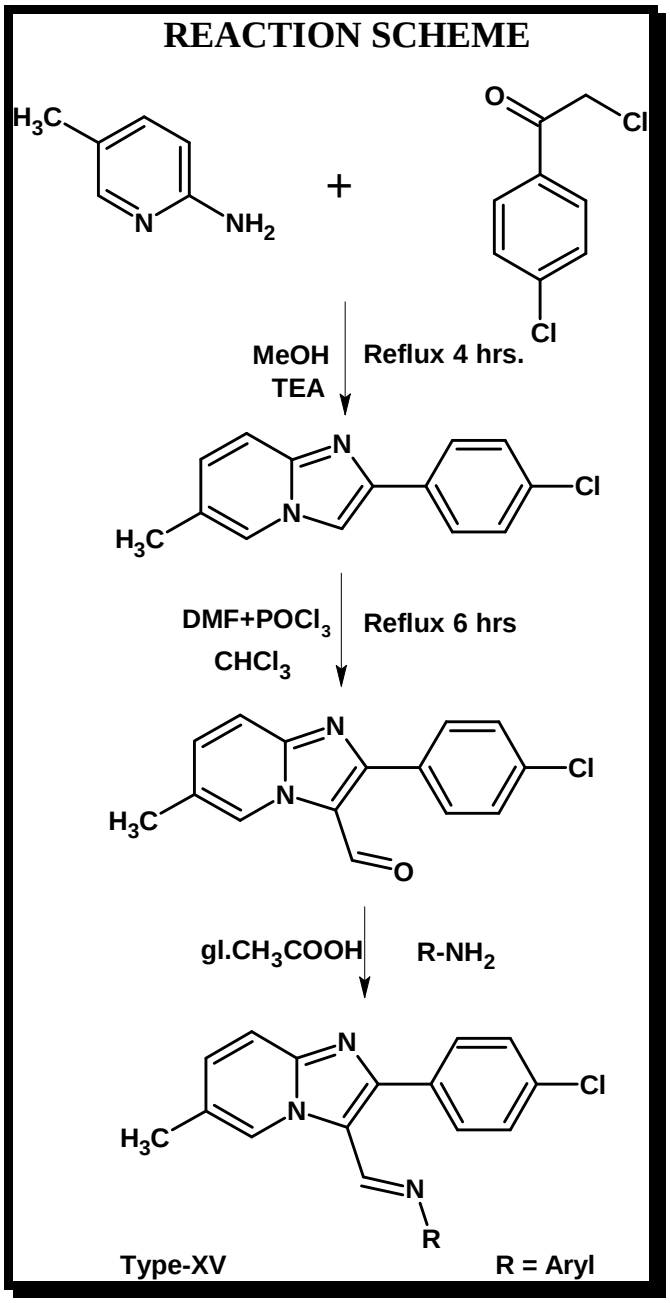
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.35	3H	singlet	Ar-(CH_3)(i)
2	6.93-6.96	1H	singlet	Ar-H(f)
3	7.06	2H	singlet	Ar-H(dd')
4	7.18-7.27	4H	doublet	Ar-H(aa',cc')
5	7.39-7.41	2H	doublet	Ar-H(bb')
6	7.45-7.48	2H	doublet	Ar-H(e,h)
7	8.11	1H	doublet	Ar-H(g)

MASS SPECTRAL STUDY OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE (4'''-CHLOROPHENYL) AMINE.




M/Z=344
M/Z=242
M/Z=78
M/Z=242
M/Z=331
M/Z=268
M/Z=380
M/Z=269
M/Z=132
M/Z=112
M/Z=208
M/Z=194
M/Z=125

REACTION SCHEME



Type-XV R = Aryl

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-[(4'-CHLOROPHENYL) -6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE ARYLAMINES.

[A] Synthesis of -2-(4'-chlorophenyl)6-methyl imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 2-(4'-chlorolphenyl)-6-methyl imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-[(4'-chlorophenyl)-6-methyl imidazo [1, 2- a] pyridin – 3- yl] methylene-(4"'-Chlorophenyl)amines(15c)

A mixture of 2-(4'-chlorophenyl) 6-methyl imidazo[1,2-*a*]pyridine-3-carboxaldehyde (2.28gm, 0.01 mol) and p-Chloroaniline (1.08 gm, 0.01 mol) in toluene (20 ml) in presence of catalytic amount of glacial acetic acid was refluxed for 6 hr. The contents were cooled and poured in crushed ice product was isolated crystallized from methanol. Yield, 76%, m.p. 195^{o}C,

($C_{21}H_{15}Cl_2N_3$; Required : C, 66.33; H, 3.98; N, 11.05%; found : C, 66.30; H, 3.95; N, 11.04%)

Similarly, other2-[(4'-chlorophenyl)-6-methyl imidazo [1, 2- a] pyridin – 3 - yl] methylene arylamines were prepared. The physical constants are recorded in Table No. 15.

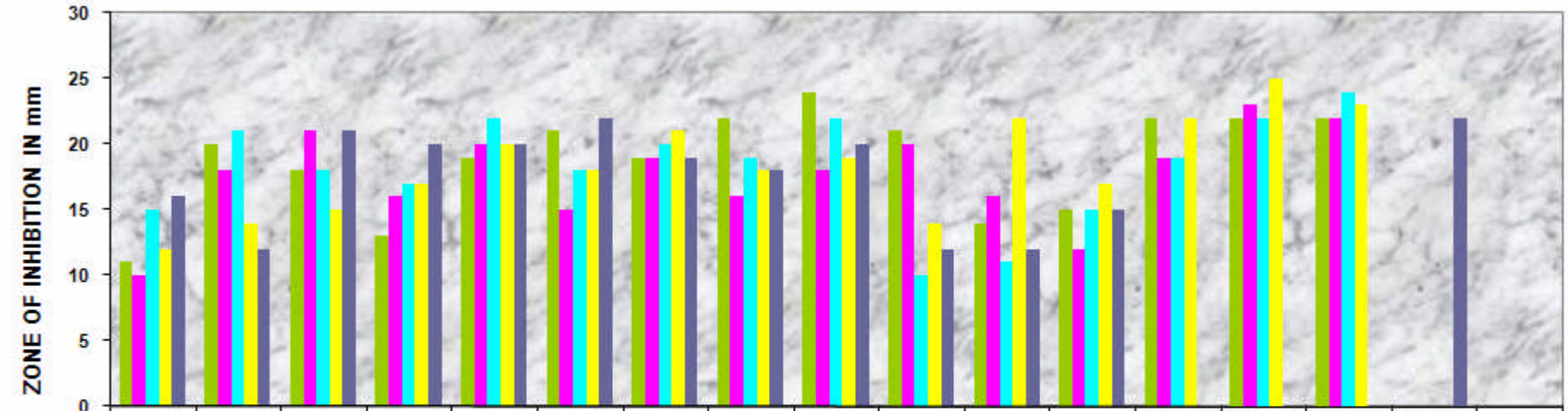
[D] Biological Screening 2-[(4'-chlorophenyl)-6-methyl imidazo [1, 2- a] pyridin – 3 - yl] methylene arylamines

Biological Screening was carried out as described in Part-I , Section-I ,Page no.38 The zone of inhibition of the test solution are recorded in Graphical Chart No. 15

TABLE NO. 15 PHYSICALCONSTANTS OF 2- [(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE (ARYL) AMINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^0C	Yield %	%of Nitrogen	
						calcd.	Found.
15a	C_6H_5-	$C_{21}H_{16}ClN_3$	345.5	155	62	12.15	12.13
15b	3-Cl-C_6H_4-	$C_{21}H_{15}Cl_2N_3$	380.0	160	66	11.05	11.02
15c	4-Cl-C_6H_4-	$C_{21}H_{15}Cl_2N_3$	380.0	195	76	11.05	11.02
15d	2-4-$(Cl)_2$-C_6H_3-	$C_{21}H_{14}Cl_3N_3$	414.5	138	75	10.13	10.10
15e	2 -F-C_6H_4-	$C_{21}H_{15}ClFN_3$	363.5	180	50	11.55	11.52
15f	4 -F-C_6H_4-	$C_{21}H_{15}ClFN_3$	363.5	121	60	11.55	11.52
15g	4-CH_3-C_6H_4-	$C_{22}H_{18}ClN_3$	359.5	193	55	11.68	11.65
15h	4-OCH_3-C_6H_4-	$C_{22}H_{18}ClN_3O$	375.5	136	59	17.18	17.16
15i	4-6-$(OCH_3)_2$ - C_4 N_2-	$C_{21}H_{18}ClN_5O_2$	407.5	170	60	17.17	17.15
15j	3-NO_2-C_6H_4-	$C_{21}H_{15}ClN_4O_2$	390.5	215	65	14.34	14.32
15k	4-NO_2-C_6H_4-	$C_{21}H_{15}ClN_4O_2$	390.5	216	66	14.34	14.32
15l	5-CH_3-C_5H_3N-	$C_{21}H_{17}ClN_4$	360.5	175	50	15.53	15.51

GRAPHICAL CHART NO. 15 : BIOLOGICAL SCREENING OF 2 -[(4' - CHLOROPHENYL) -6 - METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE(ARYL)AMINES.



	15a	15b	15c	15d	15e	15f	15g	15h	15i	15j	15k	15l	1.Ampicillin	2.Chloramphenicol	3.Norfloxacin	4.Greseofulvin	
B.mega	11	20	18	13	19	21	19	22	24	21	14	15	22	22	22	0	0
S.aureus	10	18	21	16	20	15	19	16	18	20	16	12	19	23	22	0	0
E.coli	15	21	18	17	22	18	20	19	22	10	11	15	19	22	24	0	0
S. typhi	12	14	15	17	20	18	21	18	19	14	22	17	22	25	23	0	0
A.niger	16	12	21	20	20	22	19	18	20	12	12	15	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS

PART-X

SECTION – I : BIOLOGICAL SCREENING OF 2-[(4'-CHLOROPHENYL)-6-METHYL IMIDAZO [1, 2- a] PYRIDIN – 3 - YL] METHYLENE (ARYL)AMINES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. niger***
		15b-(20)	**15b-(18)**	**15b-(21)**	**15e-(20)**	**15c-(21)**
		15h(22)	**15c-(21)**	**15c-(18)**	**15g-(21)**	**15d-(20)**
		15j-(21)	**15e-(20)**	**15e-(22)**	**15k-(22)**	**15f- (22)**
			15g-(19)	**15g-(20)**		
			15j-(20)	**15h-(19)**		
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

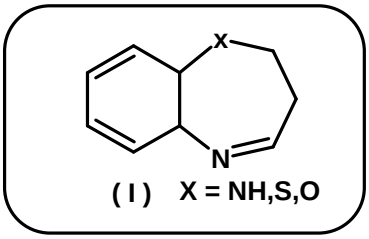
PART-XI

STUDIES ON BENZODIAZEPINES

STUDIES ON BENZODIAZEPINES.

INTRODUCTION

Benzodiazepines are characterized by their possession of fused benzene ring with seven membered heterocyclic ring containing amino group at five position and nitrogen, sulphur or oxygen at one position with double bond in between forth carbon and fifth nitrogen atom.



(I) X = NH,S,O

1,5-Benzodiazepines viz. benzodiazepine, benzothiazepines and benzoxazepines are very important compounds because of their pharmacological properties. Some of the popular drugs based on these compounds are Thiazesim, Diltiazem[595] and Clentienzem[596]etc.

Many pharmacological compositions of benzodiazepines have been patented.[597-600]

SYNTHETIC ASPECT

The literature survey revealed that the most explored route for the synthesis of 1,5-benzodiazepines is the reaction either of o-phenylene diamine with 1,3-disubstituted-2-propen-1-ones (chalcone). 1,5-Benzodiazepines are also synthesized by cyclocondensation of the corresponding 2-substitutted anilines with suitable enones or 1,3 or (α, β-dicarbonyl compounds.

Different methods for preparation of 1, 5-benzodiazepines are reportd in literature as under.

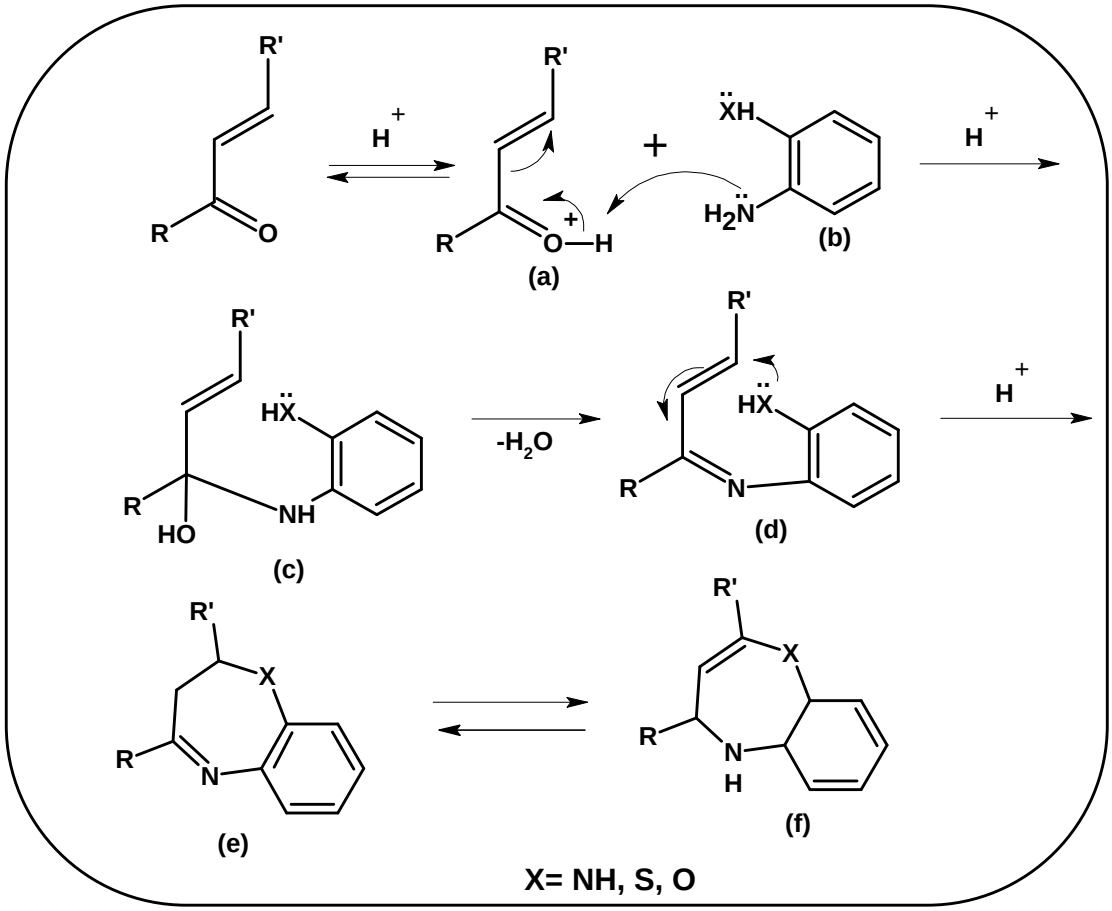
Methods for the preparation of 1,5-benzodiazepines are as under.

1. By the condensation of o-phenylenediamine with α, β̃-unsaturated carbonyl compounds.[601-603]

2. By the condensation of o-phenylenediamine with α-haloketones.[604]

3. By the condensation of o-phenylenediamine with ketones in the presence of polyphosphoric acid, silica gel[605], MgO and $POCl_3$.[606]

MECHANISM



The mechanism includes the attack of lone pair of electron of nitrogen atom of 2-substituted aniline (b) on keto-enol form of 1,3-disubstituted-2-propen-1-ones (a) affords hydrated product (c) which on dehydration yields intermediate product (d). Intermediate (d), on intramolecular cyclization yield dihydro intermediate (e) in the presence of acid. (e) On tautomerises to the final product (f).

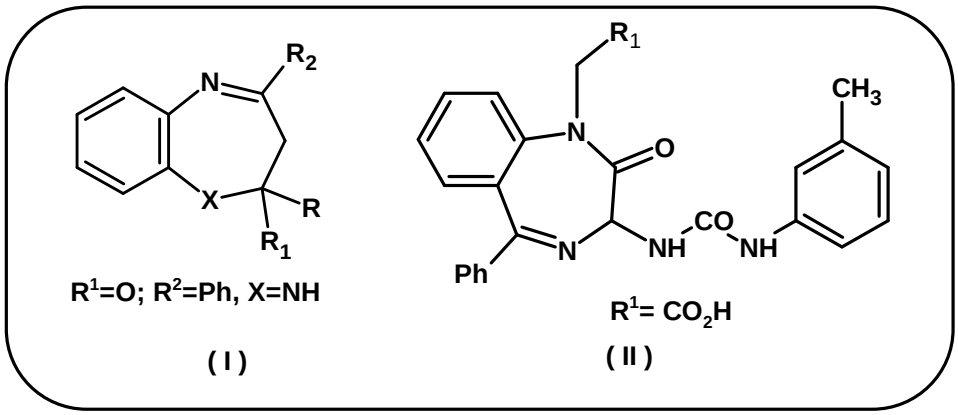
MEDICINAL INTEREST

Considerable research has been undertaken to extend the activity and reduce toxicity of benzodiazepines . The specific biological activities to Benzoheterozepines have been summarized as under.

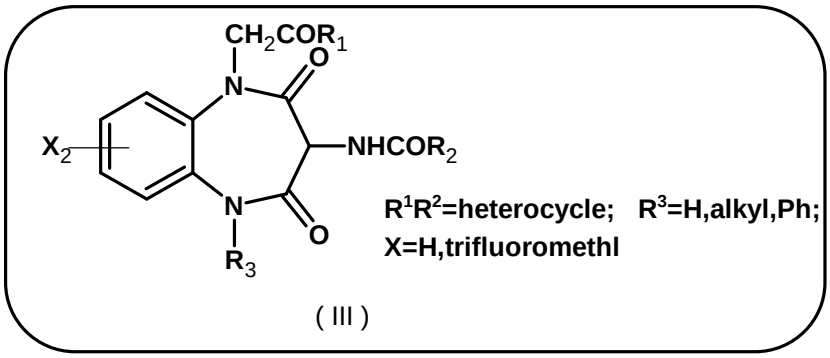
1. Central nervous stimulating agent [607, 608]
2. Tranquilizer[609]
3. Antidepressant[610]
4. Antitumor activity[611, 612]
5. Antimicrobial activity[613, 614]

6. Platelet aggregation inhibitors[615]
7. Antipyretic[616]
8. Ca-channel antagonist[617]
9. Antifeedant[618]
10. Analgesic[619]
11. Anticonvulsant activity[620]

A. Bauer et. al.[621] have synthesized 4-amino-1,5-benzodiazepines having psychotropic activity. R. G. Smith et. al.[622] have synthesized pyrazino benzodiazepines possessing anxiolytic activity. G.B. De Sarro et. al.,[623] have synthesized 1,5-benzodiazepines (I) derivatives possessing anticonvulsant activity. H.F. Miranda et.al.[624] has reported antinociceptive action benzodiazepines. H. Yamaji et.al.[625] have prepared benzodiazepines derivatives (II) as gastrin receptor antagonists.



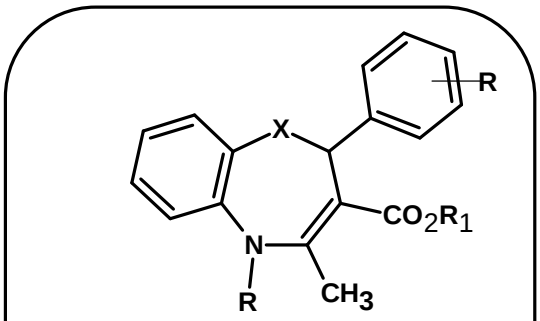
A. Farese et. al. [626] have synthesized benzodiazepines and evaluated their biological activities by luciferase transactivation and anti-viral assay. De S. Giovambattista et. al.[627] have synthesized 1,4-benzodiazepine derivatives as anticonvulsant agents. S. E. Ellen [628] has prepared 1,5-benzodiazepines (III) having cholecystokininantagonistic or agonistic activity.



(III)

K.A. Rao et. al.[629] have synthesized 1,4-benzodiazepines as DNA-interactive antitumor antibiotics. L. Wang et. al.[630] have synthesized benzodiazepine derivatives as CDK5 inhibitors. R. Kumar et. al.[631] have synthesized 3H-1,5-benzodiazepine derivatives and screened for anthelmintic activities. S. Joseph et. al.[632] have reported benzodiazepines that activates cardiac slow delayed rectifier K^+ currents.

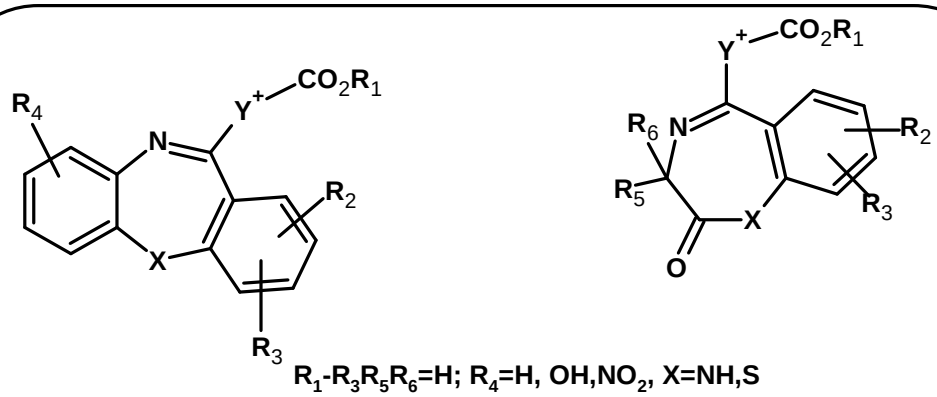
T. Nagao et.al.[633] have synthesized 1,5-benzothiazepine derivatives and tested their coronary vasodilating effect. K.S. Atwal et. al.[634] have synthesized 1,5-benzothiazepines (IV) ,which are calcium channel blockers. V. Ambrogi et. al.[635] have synthesized 1,5-benzothiazepines and screened for their CNS activity.



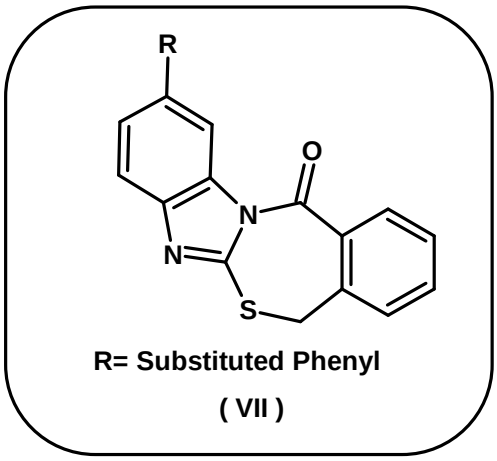
X=S, R_1=H, R=Substituted phenyl

(IV)

C. Saturnino et. al. [636] have synthesized 1,5-benzothiazepines and examined *in vitro* for their calcium antagonist activity compared to the diltiazem. S. Koichi et. al.[637] have prepared benzodiazepines, benzothiazepines and benzoxazepines compounds (V),(VI) of potentiating retinoid.

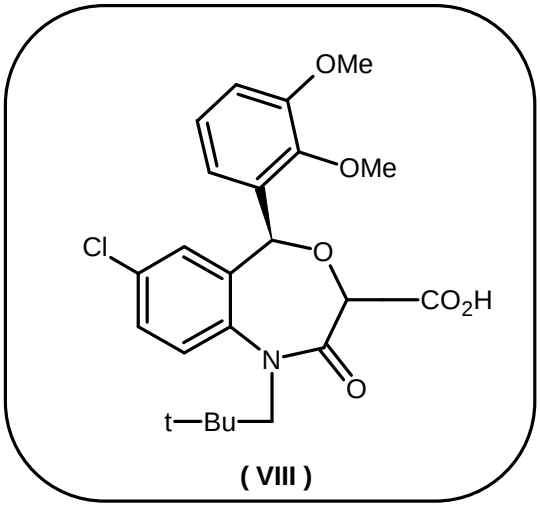


C. Sanchez-Mateo et. al. [638] have studied neuropharmacological activity of hetero[2,1] benzothiazepines. F. L. Ansari et. al.[639] have synthesized 1,5-benzothiazepine derivatives and studied their urease and α-glucosidase inhibitors properties. N. Rastkari et. al.[640] have synthesized benzothiazepine derivatives (VII) and reported their antidiabetic ctivities.



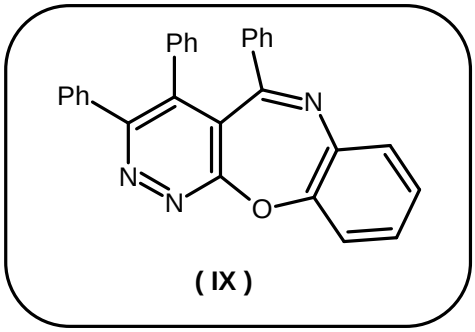
L.R.Swettt et. al. [641] have reported anti-inflammatory activity of 4,5-dihydro benzoxazepine derivatives. D. M. Zisterer et al[642] have reported pyrrolo-1,5-benzoxazepines as a new class of apoptotic agents.

P. B. Bharucha and H. B. Naik[643] have prepared 1,4-oxazipine derivatives and studied their antimicrobial activity. M. Takashi et. al. [644] have synthesized 4,1-benzoxazepine (VII) derivatives with potent squalene synthase inhibitory activities.



(VIII)

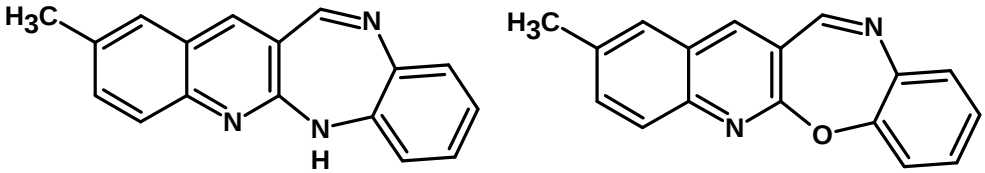
Shalaby and Alyaa A.[645] has synthesized pyrrolo-1,5-benzoxazepine-6 derivatives (IX) and reported as microtubule-targeting agent, in both STl-5H-sensitiveand resistant Bcr-Abl-positive human chronic myeloid leukemia cells.



(IX)

Younes Laras et. al.[646] have prepared various substituted 4,5-dihydro-3H-spiro [1,5]-benzoxazepine-2,4'-piperidine and assayed as the possible aspartyl protease inhibitors HIV Protease (HIV-1) and B-Secretase (BACF-1).

B. Basavaraju et al[647] have synthesized methylquinolono[3,2-b][1,5] benzodiazepine (X) and methylquinolono[3,2-b][1,5] benzoxazepine (XI) and its various metal complexes and screened for antimicrobial activity.



(X)

(XI)

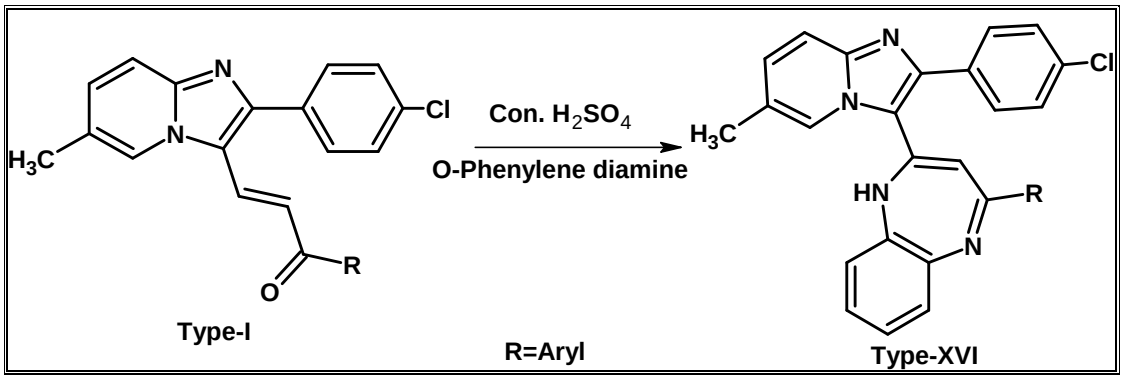
In light of wide varieties of biological activities exhibited by 1,5-benzoheterozepines it appeared of interest to synthesize 1,5-benzoheterozepines derivatives, in order to achieving compounds having better therapeutic activity described as under.

SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF-4"-ARYL-2"-YL-[2-(4'-CHLOROPHENYL -6-METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5" BENZODIAZEPINES

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4"-ARYL-2"-YL-[2-(4'-CHLOROPHENYL -6-METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5" BENZODIAZEPINES

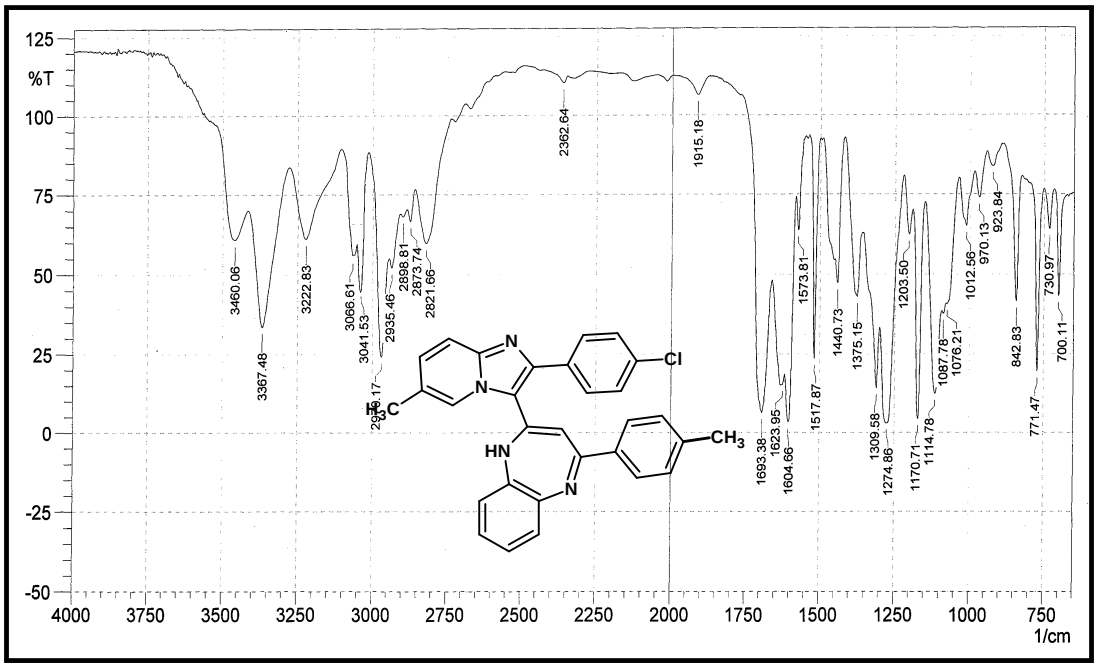
Benzodiazepines have been reported to various pharmacological activities like therapeutic activities, like anthelmintic ,anticonvulsant, antimicrobial etc. . In order to achieving better drug potency, we have prepared benzodiazepines derivatives of 4"-aryl-2"-yl-[2-(4'-chlorophenyl -6-methyl imidazo [1, 2-a] pyridin]-1"-H,-1",5" benzodiazepines**.** Type (XVI) by the cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl- 2"-propene1"-one-3-yl]-imidazo[1,2-a]pyridine of Type (I) with o-phenylene diamine in presence of acidic medium.



The constitution of the synthesized compounds have been characterized by using elemental analyses, infrared,[1]H nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy and TLC.

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 50 µg/ml. The biological activities of the synthesized compounds were compared with standard drugs. The details have been cited in part-I,section-I , Page no. 41

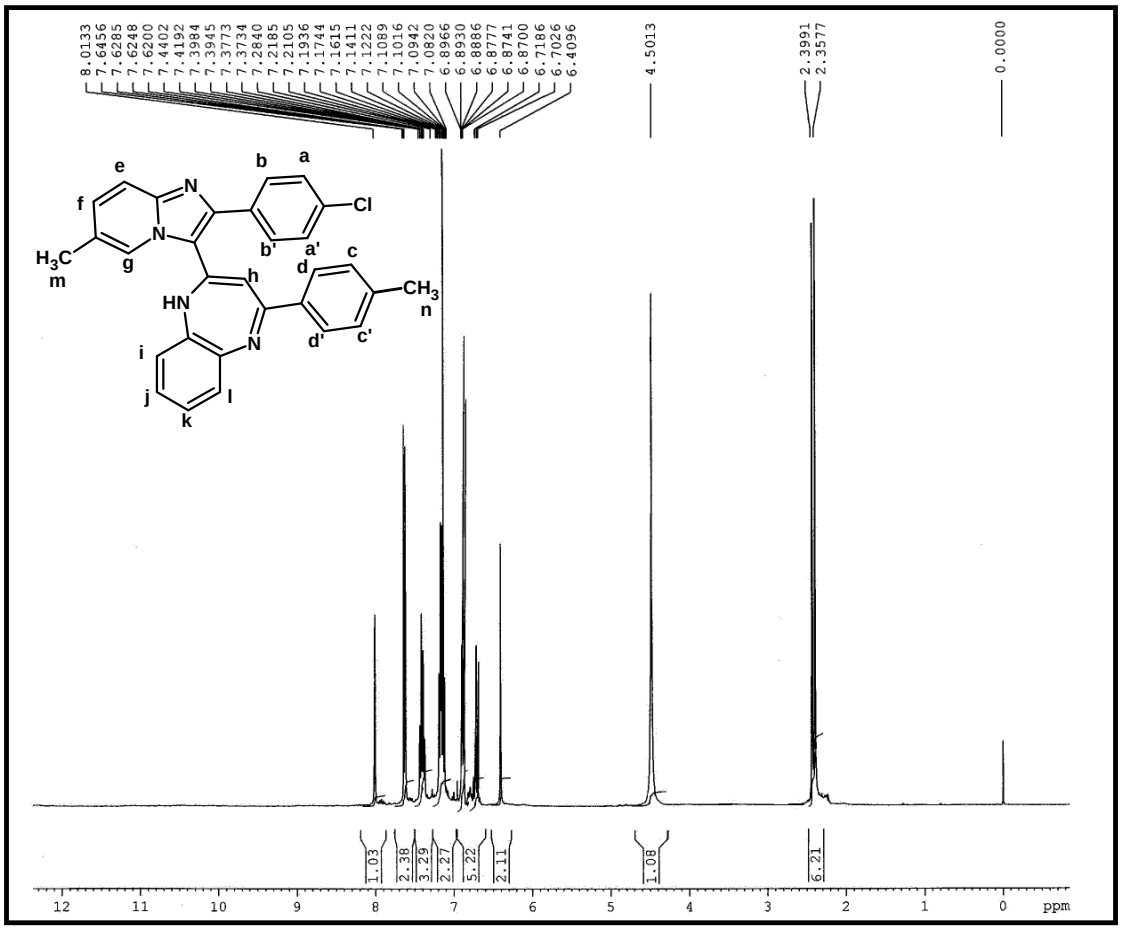
IR SPECTRAL STUDY OF 4"-(4'''-METHYLPHENYL)-2"-YL-[2-(4'-CHLOROPHENYL -6 – METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5" BENZODIAZEPINE.



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

Type	Vibretion mode	Frequency in cm^{-1}		Ref.
		Observd	Reported	
Alkane	C-H str.(asym.)	2935	2990-2850	648
	C-H str. (sym.)	2873	2880-2860	"
	C-H def. (asym.	1440	1470-1435	"
	C-H def. (sym.)	1375	1390-1370	"
Aromatic	C-H str.	3041	3090-3030	649
	C=C str	1517	1600-1450	"
	C-H i.p. (def.)	1170	1300-1100	"
Benzdiazipine	C-N str	1076	1220-1020	"
	C=N str	1693	1710-1650	"
	N-H str.	3350	3350-3250	"
Imidazo[1,2-a] pyridine	C-N str.	1087	1220-1020	"
	C=N str.	1604	1612-1593	"
Halide	C-Cl str.	730	800-600	"

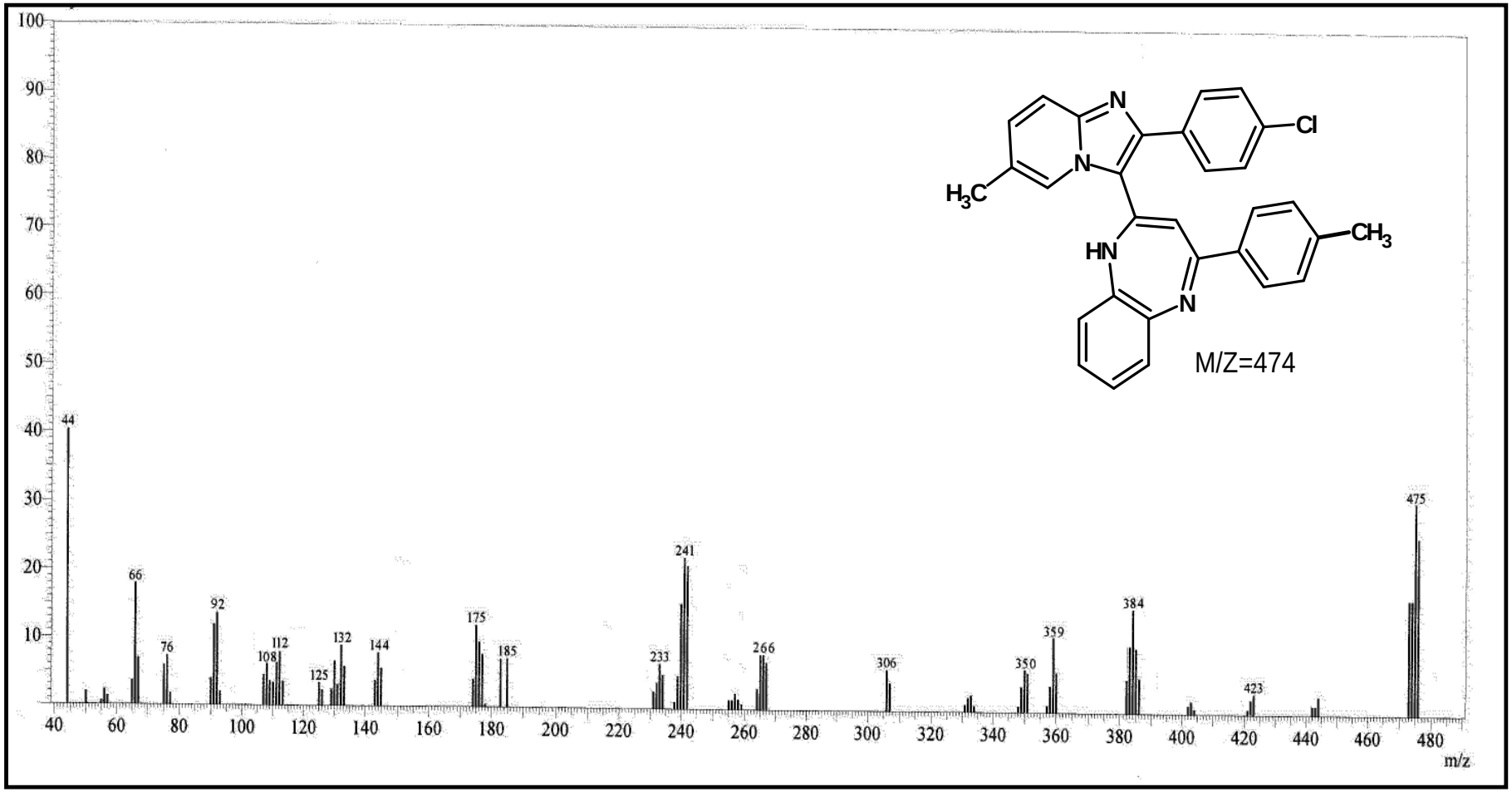
NMR SPECTRAL STUDY OF 4"-(4'''-METHYLPHENYL)-2"-YL-[2-(4'-CHLOROPHENYL -6 – METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5" BENZODIAZEPINE.

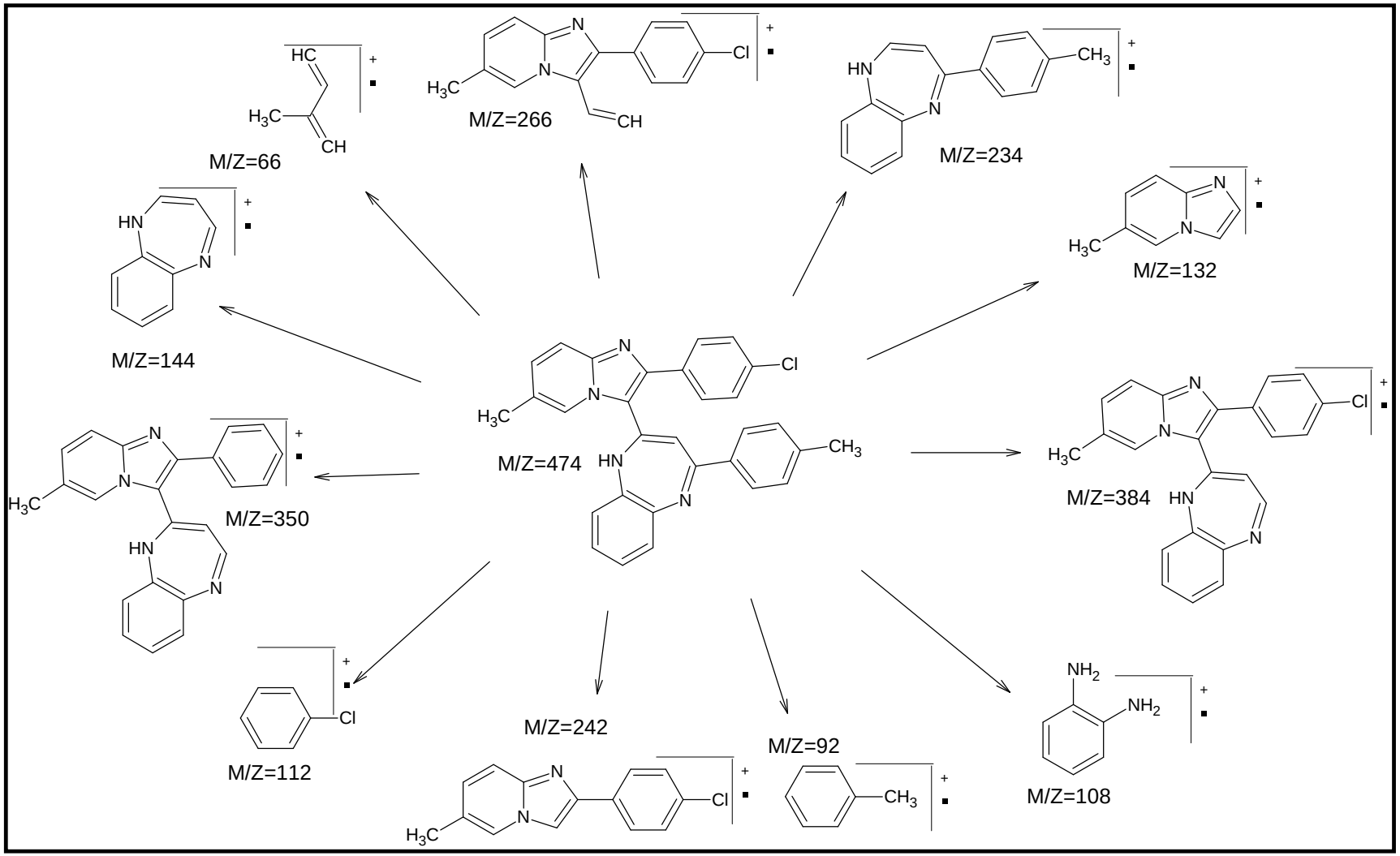


Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

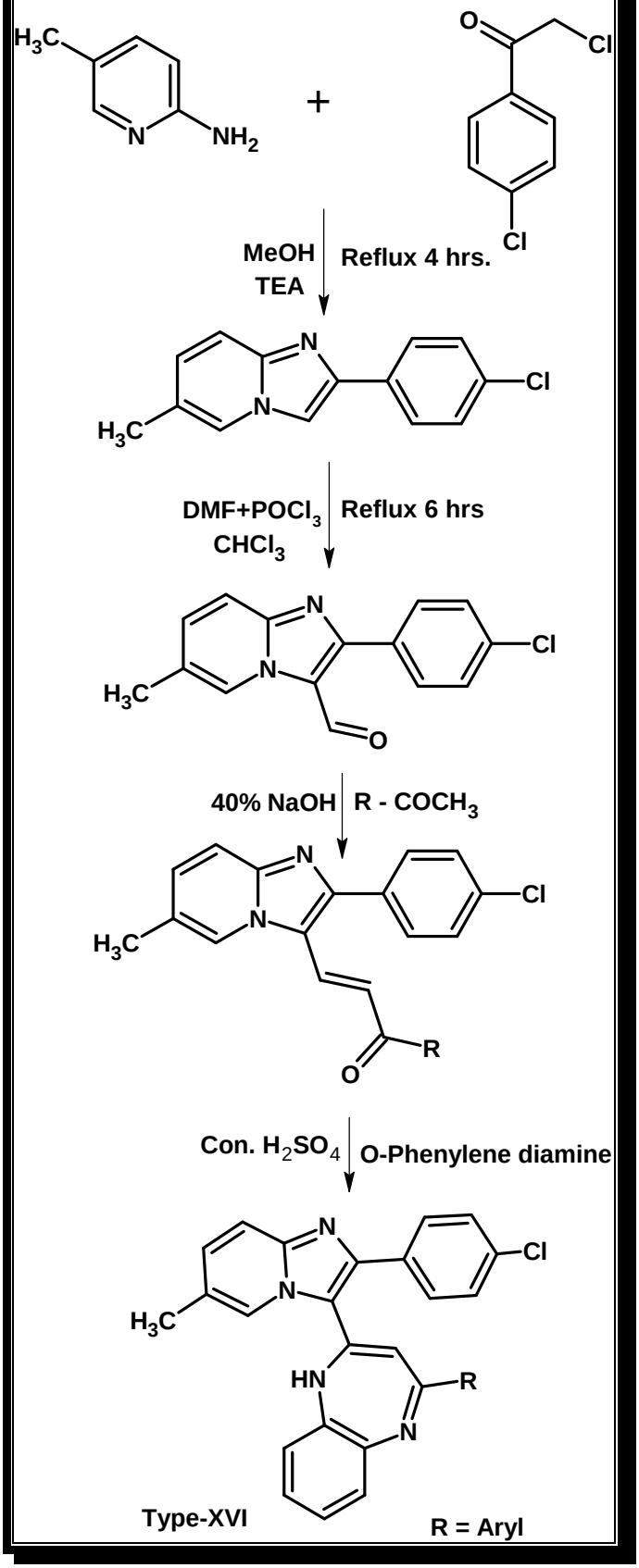
Signal No.	Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
1	2.35	3H	singlet	Ar-CH_3(n)
2	2.39	3H	singlet	Ar-CH_3(m)
3	4.50	1H	singlet	Ar-H(h)
4	6.40	2H	singlet	Ar-H(i,k)
5	6.70-6.89	5H	multiplate	Ar-H(cc',j.l,f)
6	7.09-7.014	2H	doublet	Ar-H(aa')
7	7.21-7.39	3H	doublet	Ar-H(bb',e)
8	7.62-7.64	2H	doublet	Ar-H(dd')
9	8.01	1H	singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 4"-(4"'-METHYLPHENYL)-2"-YL-[2-(4'-CHLOROPHENYL -6 – METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"-H,-1",5" BENZODIAZEPINE.




M/Z=66
M/Z=266
M/Z=234
M/Z=132
M/Z=144
M/Z=474
M/Z=350
M/Z=384
M/Z=112
M/Z=242
M/Z=92
M/Z=108

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF -4"-ARYL-2"-YL-[2-(4'-CHLOROPHENYL -6-METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5" BENZODIAZEPINES.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl)imidazo[1,2-a]pyridine

See, Part-I, Section-I ,on page no. 37

[B] Synthesis of 6-methyl-2-(4'-chlorolphenyl)imidazo[1,2-a]pyridine-3-carboxaldehyde

See, Part-I, Section-I , on page no. 37

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)-2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine.

See, Part-I, Section-I ,on page no. 37

[D] Synthesis of -4"-(4"'methylphenyl)-2"-yl-[2-(4'-chlorophenyl -6-methyl imidazo [1, 2-a]pyridin]-1"H,-1",5" benzodiazepines(16i).

A Mixture of solution of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (2.74 gm, 0.01 mol) and O-phenylene diamine (1.10gm, 0.01 mol) in toluene (20 ml)and sulphuric acid was heated under reflux for 12 hrs. on oilbath . The excess solvent was distilled out than reaction mixture was cooled and poured on to crushed ice. where upon a solid separated out, which was filtered and crystallized from ethanol. Yield 70%, m.p.175^{o}C

($C_{30}H_{23}ClN_4$; Required : C, 75.86; H, 4.88; N, 11.80%; found C, 75.85; H, 4.87; N, 11.78%;)

Similarly, other-4"-aryl-2"-yl-[2-(4'-chlorophenyl -6-methyl imidazo [1, 2-a]pyridin]-1"H,-1",5" benzodiazepines were prepared. The physical data are recorded in Table No.16

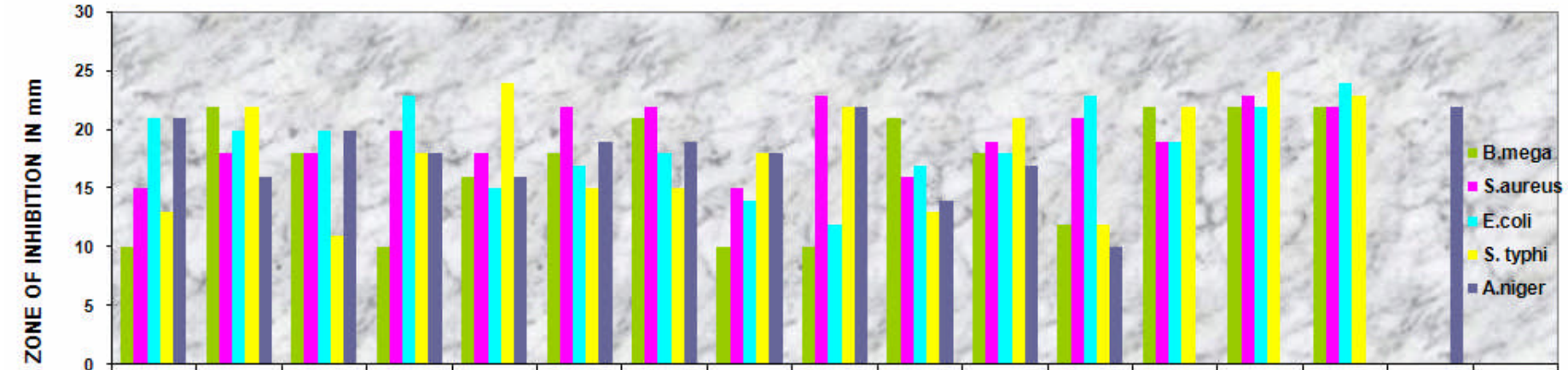
[E] Biological Screening of-4"-aryl-2"-yl-[2-(4'-chlorophenyl -6-methyl imidazo [1, 2-a]pyridin]-1"H,-1",5" benzodiazepines.

Biological Screening were carried out as described in Part-I , Section-1,Page no. 38 The zones of inhabition of test solution are recorded in Graphical Chart No 16.

TABLE NO. 16 PHYSICAL COSTANTS OF -4"-(ARYL)-2"-YL-[2-(4'-CHLOROPHENYL -6 – METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5"- BENZODIAZEPINES.

Sr.No.	R	Moleculer Formula	M.W.	M.P ^{0}C	Yield %	%of Nitrogen	
						calcd.	Found.
16a	C_6H_5-	$C_{29}H_{21}ClN_4$	460.5	199	69	12.15	12.13
16b	3-Cl-C_6H_4 -	$C_{29}H_{20}Cl_2N_4$	495.0	210	56	11.31	11.30
16c	4-Cl-C_6H_4 -	$C_{29}H_{20}Cl_2N_4$	495.0	170	67	11.31	11.31
16d	2-4-$(Cl)_2$-C_6H_3-	$C_{29}H_{19}Cl_3N_4$	529.5	180	55	10.57	10.56
16e	4 -F-C_6H_4-	$C_{29}H_{20}ClFN_4$	478.5	230	73	11.70	11.68
16f	4-Br-C_6H_4-	$C_{29}H_{20}BrClN_4$	539.5	198	59	10.38	10.35
16g	4 -OH-C_6H_4-	$C_{29}H_{21}ClN_4O$	476.5	185	67	11.75	11.73
16h	4-NH_2-C_6H_4-	$C_{29}H_{22}ClN_5$	475.5	195	60	14.71	14.70
16i	4-CH_3-C_6H_4-	$C_{30}H_{23}ClN_4$	474.5	175	70	11.80	11.78
16j	4-OCH_3-C_6H_4-	$C_{30}H_{23}ClN_4O$	490.5	200	55	11.41	11.40
16k	3-NO_2-C_6H_4-	$C_{29}H_{20}ClN_5O_2$	505.5	167	49	13.84	13.82
16l	4-NO_2-C_6H_4-	$C_{29}H_{20}ClN_5O_2$	505.5	188	50	13.84	13.83

GRAPHICAL CHART NO.16: BIOLOGICAL SCREENING OF -4"-(ARYL)-2"-YL-[2-(4'-CHLOROPHENYL -6 – METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5"- BENZODIAZEPINES.



	16a	16b	16c	16d	16e	16f	16g	16h	16i	16j	16k	16l	Ampicillin	Chloramphenicol	Norfloxacin	Greseofulvin	
B.mega	10	22	18	10	16	18	21	10	10	21	18	12	22	22	22	0	0
S.aureus	15	18	18	20	18	22	22	15	23	16	19	21	19	23	22	0	0
E.coli	21	20	20	23	15	17	18	14	12	17	18	23	19	22	24	0	0
S. typhi	13	22	11	18	24	15	15	18	22	13	21	12	22	25	23	0	0
A.niger	21	16	20	18	16	19	19	18	22	14	17	10	0	0	0	22	

COMPARATIVE BIOLOGICAL SCREENING STUDY WITH KNOWN STANDARD DRUGS
PART-XI
SECTION – I : BIOLOGICAL SCREENING OF 4"-ARYL-2"-YL-[2-(4'-CHLOROPHENYL -6 – METHYL IMIDAZO [1, 2-a] PYRIDIN]-1"H,-1",5" BENZODIAZEPINES.

		Antibacterial activity Zone of inhibition in m. m.			Antifungal activity Zone of inhibition in m. m.	
		B. mega	***S. aureus***	***E-coli***	***S. typhi***	***A. Niger***
		16b-(22)	**16d-(20)**	**16a-(21)**	**16b-(22)**	**16a-(21)**
		16g(21)	**16f-(22)**	**16b-(20)**	**16e-(24)**	**16c-(20)**
		16j-(21)	**16g-(22)**	**16c-(20)**	**16i- (22)**	**16i-(22)**
			16i- (23)	**16d-(24)**	**16k-(21)**	
			15l-(21)	**16l-(23)**		
Ampicillin	**(50 µg)**	**22**	**19**	**19**	**22**	**--**
Chloramphenicol	**(50 µg)**	**22**	**23**	**22**	**25**	**--**
Norfloxacin	**(50 µg)**	**22**	**22**	**24**	**23**	**--**
Greseofulvin	**(50 µg)**	**--**	**--**	**--**	**--**	**22**

REFERENCES:

1. J. Silvestre, P. A. Leeson, J. Castaner;
   Drugs Fut., 23, 598-601 (1998).
2. J. A. Joule and K. Mills;
   Heterocyclic Chemistry 4th Ed.492.
3. W. L Mosby.;
   Chem. Heterocycl. Compd., 15(1), 460 (1961).
4. Fikret Karci and Aykut Demircali;
   Dyes and Pigments, 71(2), 97-102 (2006).
5. A. E. Tschitschibabine;
   Ber., 58, 1704 (1925).
6. A. J. Hubert, H. Reimlinger;
   Chem. Ber., 103, 3811 (1970).
7. J. A Montgomery., J. A Secrist.;
   Comprehensive Heterocyclic Chemistry; A. R. Katrisky, C. W. Rees,
   Potts K. T., Eds; Pergamon; Oxford, 5, 607 (1984).
8. E. S. Hand , W. W. Paudler;
   J. Org. Chem., 43, 2900 (1978).
9. W. William Paudler, A. Richard Vandahm and Young N. Park;
   J. Heterocyclic Chem., 9, 81 (1972).
10. O. Abdou Abdelhamid, M. Hamid Hassaneen and Ahmad S. Shawli;
    J. Heterocyclic Chem., 20, 639 (1983).
11. Christopher Blackburn, Bing Guan and Shriling Tsai;
    Tetrahedron Letters, 39(22), 3655-3638 (1998).
12. M. P. Groziak, S. R. Wilson, G. L. Clauson;
    J. Am. Chem. Soc., 108, 8002 (1986).
13. E. Abignente;
    Actual. Chim. Ther., 18, 193 (1991); Chem. Abstr., 115, 256028n (1991).
14. E Abignente, F Arena., E Luraschi., C. Saturnino, F Rossi.;
    Rend. Atti. Accad. Sci. Med. Chir., 139, 313 (1985); Chem. Abstr., 105,
    126822z (1986).

15. A. Gueiffier, S. Mavel., J. Balzarini, J. P. Chapat;
J. Med. Chem., 41, 5108-5112 (1998).
16. M. Lhassani, O Chavignon., A. Gueiffier;
Eur. J. Med. Chem., 34, 271-274 (1999).
17. P. George., G Rossey., B. Zivkovic;
Eds; Raven Press Ltd.; New York, 49-59 (1993).
18. Y. Katsura, S. Nishino;
Chem. Pharma. Bull., 40, 371 (1992).
19. J. E.Starrett, T. A Montzka., R. L.Cavanagh;
J. Med. Chem., 32, 2204 (1989).
20. Y. Rival, G Grassy., A Taudou., R Ecalle.;
J. Eur. Med. Chem., 26, 13 (1991).
21. J. H Fischer., A Lusi.;
J. Med. Chem., 15, 982 (1972).
22. Y. Rival, G. Grassy, G Michel.;
Chem. Pharma. Bull., 40, 1170 (1992).
23. J. C Teulade., G Grassy., J. P Girard., J. P Chapat.;
Eur. J. Med. Chem., 13, 271 (1978).
24. J. P Kaplan., P. George;
Eur. Patent 0050563, (1982); Chem. Abstr., 97, 149531a (2002).
25. A. Chaouni, C Galtier., Allouchi H., Teulade J. C. et al.;
Chem. Pharma. Bull., 49, 1631 (2001).
26. S. Mavel, J. L Renou., Galtier C., Snoeck R., Andrei G.;
Arzneimittel-Forschung, 51, 304 (2001).
27. J. J Kaminnski., J. A. Bristol, A. T. Mcphail;
J. Med. Chem., 28, 876-892 (1985).
28. J. J Kaminnski, A. M Doweyko.;
J. Med. Chem., 40, 427-436 (1997).
29. G. Bartholini;
L. E. R. S. Monogr. Ser., 8, 1 (1993); Chem. Abstr., 124, 164079n (1996).
30. K Fuchs., M. Romig, K Mendla., H Briem., K. Fechteler;
WO, 14 313, (2002); Chem. Abstr., 136, 183824r (2002).
31. W. R Tully., C. R. Grder, R. J. Gillespie, R Westwood.;
J. Med. Chem., 34, 2060 (1991).

32. S. Z Langer., S Arbilla., J. Benavides, B Scatton.;
Adv. Biochem Psychopharmacol, 46, 61 (1990).

33. Y Abe., H Kayakiri., S Satoh., T. Inoue, H. Tanaka;
J. Med. Chem., 41, 564 (1998).

34. D. Dvey, Paul W. Erhardt, William C. Lumma, Elinor Cantor;
J. Med. Chem., 30(8), 1337-1342 (1987).

35. A Elhakmaoui., A Gueiffier., J. C Milhavet., Declercq E.;
Bioorg. Med. Chem. Lett., 4, 1937 (1994).

36. L. B. Townsend, J. C Drach.;
WO, 27, 205 (1997); Chem. Abstr., 127, 190983j (1997).

37. S Mavel., J. L Renou., C Galtier., R Snoeck., A Gueiffier.;
Arzneim-Forsch., 51, 304 (2001); Chem. Abstr., 135, 131730s (2001).

38. B. Dubinsky, D. A. Shriver, M. E Rosenthale.;
Drug. Dev. Res., 21, 277 (1990).

39. P. J. Sanfilippo, M. Urbanski, J. B Press., J. B. Moore;
J. Med. Chem. , 31, 2221 (1998).

40. K. A. Wafford, P. J. Whitting, J. A.Kemp;
Mol. Pharmocol., 43, 240 (1993); Chem. Abstr., 118, 77084 (1996).

41. C Faure Hally., D Graham., S Arbilla. and S. Z Langer.;
Eur. J. Pharmocol. Mol. Pharmacol. Sect., 246, 283 (1993).

42. J James. Kaminski, D. G Perkins., J. D. Frantz, James F. Long;
J. Med. Chem., 30, 2047-2051 (1987).

43. Alexander C. Humphries, Emanuela Ganeia, T . Myra. Gilligan;
Bioorganic and Medicinal Chemistry Letters, 16(6), 1518-1522 (2006).

44. S Kristjan. Gudmundsson, D. John Williams, Leroy B. Townsend;
J. Med. Chem. , 46, 1449-1455 (2003).

45. I Aramori., Zenkoh J., N Morikawa., Y Notsu.;
Mol. Pharmacol., 51, 171-176 (1997).

46. Yoshito Abe`, Hiroshi Kayakiri;
J. of medicinal chem. ,41,4062-4079 (1998).

47. Alain Gueiffier,, Mohammed Lhassani;
J. Med. Chem. , 39, 2856-2859 (1996).

48. B Dubinsky. and A.H. Vaidya;
J Pharmacol Exp Ther. Nov,303(2):777-90 (2002).

49 C Hamdouchi., J Blass., M.Prade, L Vance.;J. Med. Chem., 42, 50-59 (1999).

50. W. S. Hamama, H. H Zoorob.;
Tetrahedron, 58, 6143-6162 (2002).

51. R. J Sundberg., S Biswas., Murthi K.K., Rowe D.;
J. Med. Chem., 41, 4317-4328 (1998).

52. A Mohamed. Ismail, Reto Burn, David W. Boykin;
J. Med. Chem., 47, 3658-3664 (2004).

53. S Krisjan. Gudmundsson and Brian A. Johns;
Org. Lett., 5(8), 1369-1372 (2003).

54. A Chaouni-Bendallah, Galtier C., Teulade J. C. et al.;

55. S. V. Kostanecki and J. Tambor; *Chem. Ber.,* **32,** 1921 (1899).

56. B. S. Holla and S. Y. Ambekar;
J. Indian Chem. Soc., **50,** 673 (1973); *Chem. Abstr.,* **80,** 132961 (1974).

57. K. Kazauki, K. Htayama, S. Yokomor and T. Soki;
Japan Kokai **75**, 140, 429, (Cl. C07 C A61K) 11 Nov. 1975, Appl. 74, 44, 152, 19 Apr. 1974; 4, p.p.*; Chem. Abstr.,* **85,** 5913 (1976).

58. H. Rupe and D. Wasserzug; *Chem. Ber.,* **34,** 3527 (1901).

59. T. Szell;
Chem. Ber., **92,** 1672 (1959); *Chem. Abstr.,* **53,** 21913 (1959).

60. R. E. Lyle and L. P. Paradis;
J. American Chem. Soc., **77,** 6667 (1955); *Chem. Abstr.,* **50,** 10057 (1956).

61. S. A. Hermes;
SPAN 346, **599**, 16 Dec. 1968, appl. 31, Oct. 1967, 5 p.p.*; Chem. Abstr.,* **70,** 96422h (1969).

62. A. A. Rawal and N. M. Shah;
Indian J. Chem., **21**, 234 (1962).

63. P. L. Cheng, P. Fournari and J. Tirouflet;
Bull. Soc. Chim. France, 102248 (1963); *Chem Abstr.*, **60**, 1683 (1964).

64. C. Kurodo and T. Matsukuma;
Sci. Papers Inst. Phys. Chem. Res. (Tokyo), **18,** 51 (1932); *Chem. Abstr.,* **26,** 2442 (1932).

65. D. S. Breslow and C. R. Houser;
J. American Chem. Soc., **62,** 2385 (1940); *Chem. Abstr.,* **34**. 7875 (1940).

66. G. V. Jadav and V. G. Kulkarni; *Curr. Sci.,* (1944).

67. L. Reichel;
Naturwissenschallen, **32,** 215 (1944); *Chem. Abstr.,* **10,** 2441 (1946).

68. V. M. Vlasov;
Izu. Sib. Otd, Akad. Nauk. SSSR Ser. Khim. Nauk., **2,** 96 (1971); *Chem. Abstr.,* **76,,**140411d (1972).

69. A. M. Fahmy, M. Hussan, A. A. Khalt, R. A. Ahmedi;
Rev. Roum-Chim., **33(7),** 755-61 (1988); *Chem. Abstr.,* **111,** 77898 (1989).

70. A. Sakari and H. Midorikawa;
Bull. Soc. Japan, **41,** 430 (1968); *Chem. Abstr.,* **69,** 18985 (1968).

71. A. Samour, Y. Akjnoukh nd H. Jahine (Pal. Sci. Ain Sharm Uni. Cario UAK);
J. Chem. 1970 pub., 13(4), 421-37 (Eng.) (1971); *Chem. Abstr.,* **77**, 101348 (1977).

72. Hartann R. W., Reichert N and Grzarinh S;
Eur. J. Med. Chem., **29(11)**, 807-817 (1994); *Chem. Abstr.,* **122**, 239500n (1995).

73. N. Latif, N. Mishriky and N. S. Girgis;
Indian Journal Of Chemistry, **20B,** 147-149 (1981).

74. H. G. Garg and P. P. Singh; *J. Med. Chem.,* **11,** 1104 (1968).

75. B. S. Hastak and B. J. Ghiya;
Indian Journal of Heterocyclic Chemistry, **2,** 135-136 (1992).

76. S. B. Lohiya and B. J. Ghiya;
Indian J. Chem., 279-82 (1986).

77. A. C. Jain, A. Mehta and P. Arya;
Indian Jornal of Chemistry, **26B,** 150-153 (1987).

78. Arito et al.;
Japan p., 1956, 294; *Chem. Abstr.,* **51,** 4054 (1957).

79. Shinoda and Sato;
J. Pharm. Soc. Japan, **49,** 64 (1929); *Chem. Abstr.,* **23,** 4210 (1929).

80. Prafulchandra Mitter and Shirishkumar Shah;
J. Indian Chem. Soc., **11,** 257 (1934).

81. Shinoda and Sato;
J. Pharm. Soc. Japan, **48,** 933 (1928); *Chem. Abstr.,* **23,** 2956 (1929).

82. Shinoda, Sato and Kawagoe;
J. Pharm. Soc. Japan, **49,** 548 (1929); *Chem. Abstr.,* **24,** 604 (1930).

83. K. Shyama Sundar;
Proc. Indian Acad. Sci., **59A**, 241 (1964).

84. Magyar Kimiai;
Folyoirat, 60, 373 (1954); *Hung. Tech. Abstr.,* **3,** 7 (1955).

85. K. Shyam Sundar; *Proc. Indian Acad. Sci.,* **67,** 259, (1964).

86. K. Shyam Sundar;
Proc. *Indian Acad. Sci.,* **67,** 90, (1968).

87. Arita et al.;
Japan 294(56) Jan. 20, US 2, 769, 786 Nov. 6, 1956 See Britt 740, 886, (C. A. 50, 10445e).*; Chem. Abstr.,* **51,** 4054, (1957).

88. Krbeckek;
J. Agr. Food. Chem., **16**, 108 (1968).

89. D. H. Marian, P. B. Russel and A. R. Todd;
J. Chem. Soc., 1419 (1947).

90. D. N. Dhar;
Chemistry of Chalcones, *Wiley*, *New York*, (1981).

91. S. S. Misra and B. Nath;
Indian J. Appl. Chem., **34,** 260 (1971).

92. R. Aries; *Ger. Pat.,* **2,** 341-514 (1979); 146152 (1974).

93. E. T. Ogansyna et al.;
Khim. Farm. Zh., **25(8)**, 18 (1991); *Chem. Abstr.,* **115,** 247497n (1991).

94. Hsieh, Hasin, Kaw, Lee-Tai-Hua Wang, Jih-Pyang. Wang. et al.;
Chem. Abstr., **128,** 225684n (1998).

95. A. E. Vanstone, G. K. Maile and L. K. Nalbantoglu;
Ger. Offen. DE, **3**, 537, 207 (Cl. 07 c 65/40) (1986); *Chem. Abstr.,* **106,** 49778f (1987).

96. Kamei, Hideo, Koide, Tatsurou, Hashimoto Yoko, Kojima et al.;
Cancer Biother Radio Pharm., **12(1)**, 51-54 (Eng.) (1997)*; Chem. Abstr.,* **126,** 258666v (1997).

97. Tsotitus Andreas, Kalosorooulou Theodara et al.;
PCT Int. Appl., WO **99,** 54, 278 (1999); *Chem. Abstr.,* **131,** 28260z (1999).

98. A. C. Grosscurt, H. R. Van and K. Wellinga;
J. Agric. Food Chem., **27(2),** 406 (1979); *Chem. Abstr.,* **91,** 15123x (1979).

99. Tashio Pharmaceutical Co Ltd.;

Japan, Kokai Tokkyo Koho Jp., **51,** 12, 094 (Cl A 61 K 31/215); *Chem. Abstr.,* **101,**54722j (1984).

100. K. Kyogoku et al.;
Chem. Pharm. Bull., **27(12),** 2943 (1979); *Chem. Abstr.,* **93,** 26047r (1980).

101. M. R. Bell;
US Appl., **637,** 931 (1984); *Chem. Abstr.,* **113,** 211828t (1990).

102. L. Real, C. David and B. Francois;
Can J. Pharm. Sci., **2,** 37 (1967); Chem. Abstr., 67, 98058f (1967).

103. Guo Zongru, Han Rui;
CN **1**, 13, 909, *Chem. Abstr.,* **125,** 103768 (1996).

104. G Achanta., A Modzelewska., L Feng., S R. Khans, P. Hang;
Mol. Pharmacol., April-24 (2006).

105. N. Lall, A. A. Hussein and J. J. M. Meyer;
Fitoterapia, **77(3)**, 230-232 (2006).

106. Sarot Cheenpracha, Chatehanok Karalai, Supinya Tewtrakul;
Bioorganic & Medicinal Chemistry, **14(6)**, 1710-1714 (2006).

107. Y. Inamori et al.;
Chem. Pharm. Bull., **39(6)**, 1604 (1991); *Chem. Abstr.,* **115,** 105547c (1991).

108. K. Bowden; P. A. Dal and C. K. Shah;
J. Chem. Res. Synop., **12,** 2801 (1990); *Chem. Abstr.,* **114,** 160570m (1991).

109. E. Marmo, A. P. Caputi and S. Cataldi;
Farmaco Ed. Prat., **28(3),** 132 (1973); *Chem. Abstr.,* **79,** 13501v (1973).

110. V. M. Gaurav and D. B. Ingle;
Indian J. Chem., **25B (8)**, 868 (1986); *Chem. Abstr.,* **103,** 17, 39321h (1987).

111. A. K. Pedersen and G. A. Fitz Gerald;
J. Pharm. Sci., **74(2)**, 188 (1985); *Chem. Abstr.,* **103,** 87592n (1999).

112. B. B Kalashnikow., B. B Kalashnikovax;
Russ. J. Ger. Chem., 1998; *Chem. Abstr.,* **130,** 296596n (1999).

113. S.Parmar Virinder, C. Jain Subhash et al.;
Indian J. Chem., Sect. B., Org. Chem. Incl Med. Chem., **37B(7)**, 628-643 (Eng.) (1998).
CSIR, *Chem. Abstr.,* **129,** 289910m (1998).

114. S. R. Modi and H. B. Naik;
Orient J. Chem., **10(1),** 85-6 (1994); *Chem. Abstr.,* **122**, 81186c (1995).

115. Nissan Chemical Industries Ltd.,
Japan Kokai Tokkyo Koho Japan, **38**, 08, 035, (1983); *Chem. Abstr.*, **98,** 178974q (1983).

116. A. C. Gross Curt, H. R. Van and K. Wellinga;
J. Agric. Food. Chem., **27(2),** 406 (1979); *Chem. Abstr.*, **91,** 15132x (1979).

117. W. B.Geiger and J. E.Conn;
J. Am. Chem. Soc., **67** 112 (1945).

118. D. H Marrian., P. B. Russell and A. R. Todd; *J. Chem. Soc.*, 1419 (1947).

119. D. N.Dhar;
Chemistry of Chalcones; Wiley, New York, (1981).

120. L. Nelson George;
U.S. US **4**,338,499 (Cl. 568-343; CO7C49/597), 06 Jul (1982), *Appl.* 250, 366, 02 Apr (1981);7 pp.

121. P. Prem. Yadav, P. K.Prasoon Gupta, Shukla and Rakesh Mavrya;
Bioorganic & Medicinal Chemistry, **13(5)**, 1497-1505 (2005).

122. C. Q.Meng and X. S.Zheng;
Bioorg Med. Chem. Lett., **14(6),** 1513-1517 (2004)

123. B.Crammer, R.Ikan;
Chem. Soc. Rev., **6**, 431 (1977).

124. S. Antus, L.Farkas, A.Gottsegen, M.Nogradi and T Pfleigel.;
Acta Chim Hung., **98**, 225 (1978). *Chem. Abstr*., **90**, 86935b (1979).

125. J. R.Cole, S. J.Torrance, R. H.Weiedgopf, S. K.Arora and R. B.Bates;
J. Org. Chem., **41**, 1852 (1976).

126. V. K. Ahluwalia, Neelu Kaila and Shashi Bala;
Indian J. Chem., **25B**, 663 (1986).

127. Paula Boeck, Camila Alves and Bartira Rossi-Bergmann;
Bioorganic & Medicinal Chemistry, **14(5)**, 1533-1545 (2006).

128. M. J.Alcaraz, A. M.Vicente, A.Araico, J. N.Dominguez, M. C.Terencio;
Br. J. Pharmacol., **142(7),** 1191-9 (2004).

129. O.Nerya, R.Musa, S. Khatib, S.Tamir, J. Vaya;
Photochemistry., **65(10),** 1389-95 (2004).

130. O Sabzevari., G.Galati, M. Y.Moridani, A. O Siraki, P. J Brien.;
Chem. Biol. Interact, 148(1-2), 57-67 (2004).

131. Aneta Modzelewska, Catherina Pettit, Geetha Achanta and Saeed R. Khan;

Bioorganic & Medicinal Chemistry, 14(10), 3491-3495 (2006).

132. J. Elguero ;
In Comprehensive Heterocyclic Chemistry, eds., A. R. Katritzky and C. W. res., Vol 5, 168 (1984)

133. A. M Fahmy. , M. Hassan., A. A. Khalf., R. A. Ahmed.;
Rev. Roum. Chim., 33(7), 755-61 (1988); Chem. Abstr., 111, 77898 (1989).

134. V.Gohanmukkala , A.Subbaraju A, R. Naykula and D. P Armeswara,
Indian J. Heterocyclic Chem., 4, 87-92 (1994).

135. M. Hassaneen Hamdi, Hamad A. E., Hiyam A. H. M.;
Salter Lett., 8(5), 27582 (1989); Chem. Abstr., 111, 57611 (1989).

136. M.Hashsh, El-Kady, M. A Saiyed., A. A Elsawy.;
Egypt. J. Chem., 27(6), 715-21 (1985); Chem. Abstr., 105, 20868u (1986).

137. A. K Padya., K Jaggi, V.Lakshminarayana , C. S. Pande ;
J. Indian Chem. Soc., 75(2), 104-105 (1998).

138. G.Gyassi, K.Bourin , M.Lamiri, M.Soufiaoui ;
New Journal of Chemistry, 22(12), 1545-1548 (1998).

139. S.Paul, R. Gupta.;
Indian J. Chem., 37B, 1279-1282 (1998).

140. A. D. Andia, H.Taneja , C. S. Sharma ;
Indian J. Heterocycl. Chem., 1999; Chem. Abstr., 132, 265161d (2000).

141. A. K., Reda, A. A. Khalaf , M. T.Zimaltu , A. M.Khalil , A. M. Kaddah.;
J. Indian Chem. Soc., 68, 47-51 (1991).

142. J.Panda S. V. Srinivas , M. E.Rao;
J. Indian Chem. Soc., **79(9)**, 770-1 (2002); *Chem. Abstr.*, **138**, 153499n (2003).

143. F. F. Barsoum., H. M.Hosni , A. S.Girgis ;
Bioorg. Med. Chem., Feb 3 (2006).

144. A. A.Bekhit , H. H. Ashour, A. A.Guemei ;
Arch. Pharm.(*Weinheim*), **338(4)**, 167-174 (2005).

145. B. Roman;
Pharmazie, **45**, 214 (1990).

146. O.Ruhoglu , Z.Ozdemir , A. A. Bilgin ;
Arzneimittelforschung, **55(8)**, 431-436 (2005).

147. H. G. Garg and P. P. Singh;

J. Chem. Soc., **2,** 1141 (1936).

148. D. B. Reddy, T. Senshuna and M. V. Ramma Reddy;
Indian J. Chem., **30B,** 46 (1991).

149. W. I. Ronald, A. Adriano;
Chem. Abstr., **126**, 181346f (1997).

150. H. M. Mokhtar, H. M. Faidallah;
Pharmazie, **42,** 482 (1987).

151. Delay Francois (Fermenich S. A.) Patent Schrift (Switz);
Chem. Abstr., **117**, 90276f (1992).

152. G.Ayses , D.Seref, C.Gultaze , E.Kevser, V.Kamil;
Eur. J. Med. Chem., **35,** 359-64 (2002).

153. S. S. Nayal and C.P. Singh;
Asian J. Chem., **11,** 1, 207-212 (1999).

154. O.A.Fathalla , S. M Awad, M. S. Mohamed ;
Arch. Pharm. Res., **28(11)**, 1205-1212 (2005).

155. P. Desaea, A. Nunrich, M. Carderny and G. Devaux;
Eur. J. Med. Chem., **25**, 285 (1990).

156. B. Kalluraya , R. Chimabalkar, G.Rai , R.Gururaja , S.Shenoy ;
J. Indian Coun. Chemi., **18(2)**, 39-43 (2001); *Chem. Abstr.,* **138**, 238061.

157. K. Wellinga, H. H. Eussen Jacobus;
Eur. Pat. Ep., **269**, 141 (Cl C07D 231/06) (1988); *Chem. Abstr.,* **110**, 8204 (1989).

158. Y. Hiroyuti, O. Mocoto, et al.;
Eur. Pat. Appl. Ep., 295695 (Cl. C07D 40/16) (1988); *Chem. Abstr.,* **111**, 23510 (1989).

159. A.Budakoti , M.Abid , A. Azam ;B.Hans, R. Rolf and R.Rudolf;
US. Pat. 3, 822, 283 (1974); Chem. Abstr., 81, 105494r (1974).

160. K. Zalgislaw , and V.Seffan ;
Acta. Pol. Pharm., 36(6), 645 (1979); Chem. Abstr., 93, 204525e (1980).

161. E. Palaska , M. Aytemir , I. T.Uzboy , D.Erol ;
Europian Journal of Medicinal Chemistry, 36(6), 539-543 (Eng.) (2001);
Chem. Abstr.,136, 18374v (2002).

162. N.Gokhan , A. Yesilada and A. A.Bilgin ;
Neuroscience letters, 382, 327 (2003).

163. T. M.Stavenson, D. W Piotrowski., M. A. H Fahmy. , R. L L owe, K.L Monaco ;
Chem. Abstr., 130, 29 AGRO (1999).

164. T. Katsushori, A.Hiroyuki , K.Masumij ;
PCT Int. Appl. WO 98, 56, 760; Chem. Abstr., 130, 66492w (1999).

165. K.Johannes, J. Fuchs, R.Erdelen ;
U.S. US 5, 525, 622 (cl. 514-403; A 0N 43/56). Jun. 1996, DE Appl. 4, 128, 564, Aug.(1991); 574; Chem. Abstr., 125, 1427199 (1996).

166. N. A Abdel-latif. Amr-Ael-G., and M. M Abdalla.;
Bioorg. Med. Chem.,14(2), 373-384 (2006).

167. M. A. Berghot.and E.B. Maowad;
Eur. J. Pharm. Sci., 20(2), 173-179 (2006).

168. A. Turberg.Maurer Fritz, Fuchs Rainer, Erdelen Chritoph,;
PCT Int ppl. WO, 03, 59, 887 (Cl. C07 D231/28) (2003);Chem. Abstr.,139,117441z (2003).

169. R. H. Udupi, A. R. Bhatt, K. Kumar;
Indian J. Hete. Chem., **8(2)**, 143-146 (1998);

170. N. Richard, M. Megan et al.;
J. Med. Chem., **36(1)**, 134-139 (1993); *Chem. Abstr.*, **118**, 191847u (1993).

171. F. Rainer, E. Christoph;
Ger. Offen. DE., **4**, 336, 307 (Cl. C07D 231/16) (1995); *Chem. Abstr.*, **123**, 256703u (1995).

172. Tsubai Shinichiwada, Katshaki et al.;
Eur. Pat. Appl. EP., 537-580 (Cl C07D 401/64) (1993); *JP Appl.* 91/297; 772 (1991);*Chem. Abstr.*, **119**, 139220r (1993).

173. J.H Ahn., H.M. Kim, S.H. Jung, S.K Kang.and K.R Kim.;
Bioorg Med Chem Lett. 14(17), 4461-5 (2004).

174. T.S. Jeong , K.S Kim , An S.J., K.H.Cho , S. Lee, W.S Lee ;
Bioorg Med Chem Lett. 14(11), 2715-7 (2004).

175. M.N.Nasr, S.A Said ;
Arch Pharm (Weinheim). 336(12), 551-9 (2003).

176. M.A Berghot., E.B. Moawad
Eur J Pharm Sci. 20(2), 173-9 (2003).

177. D. R. Jones,Almstead Ji - In Kim, 1220 N. J.;

PCT Int. Appl. WO 02 89, 799 (Cl. A61K31/4439) (2002); Chem. Abstr., 137, 370086j (2002).

178. Guniz Kucukguzel, Sevin Rollas, Habibe Erdeniz, Muammer Kiraz, A. Cevdet Ekinci,; Eur. J. Med. Chem., 35, 761-77 (2000).

179. T. Z Gulhan., Pierre Chevallet, S.K.Fatma ,Kevser Erol.; Eur. J. Med. Chem., 35, 635-41 (2000).

180. Shalabh Sharma, Virendra Kishor Srivastava, Ashok Kumar; Eur. J. Med. Chem., 37, 689-97 (2002).

181. V. K. Archana Srivastava, Kumar Ashok; Arzneimittel. Forschung, 52(11), 787-91 (2002); Chem. Abstr., 138, 353758 (2003).

182. A. Turberg Maurer Fritz, Fuchs Rainer, Erdelen Chritoph,.; PCT Int. Appl. WO 03 59, 887 (Cl. C07 D231/28) (2003); Chem. Abstr., 139, 117441z (2003).

183. N.Gokhan, A.Yesilada, G.Ucar, K.Erol, A.A Bilgin ; Arch Pharm (Weinheim). 336(8) , 362-71 (2003).

184. J.Matysiak , A. Niewiadomy ; Bioorg Med Chem. 11(10), 2285-91(2003).

185. Z.Tabarelli, M.A Rubin, D.B. Berlese, P.D Sauzem , T.P. Missio , M.V. Teixeira ; Braz J Med Biol Res. 37(10), 1531-40 (2004).

186. S. S. Sonarc; Asian J. Chem., 10(3), 591-593 (1998); Chem. Abstr., 129, 633, 54317j (1998).

187. V. J. Fernandes, H. H. Parekh; J. Indian Chem. Soc., 74(3), 238 (1997) (Eng.).

188. G. N. Mishrika, N. Assod, F. M. Fawzy; Pharmazie, 53(8), 543-547 (1998); Chem. Abstr., 129, 260380 (1998).

189. T. Atif, E. Fatema, A. M. Abdela; Chim Pharm. J., 47(1), 37-45 (1995); Chem. Abstr., 123, 228016d (1995).

190. M. Augustin, P. Jeschke; *J. Peact. Chem*., (1987); *Chem. Abstr.*, **111**, 7246d (1989).

191. P. M. Zhu, I. Kimiaki; *Tetrahedron Lett.*, **38(30)**, 5301-62 (1997); *Chem. Abstr.*, **127**, 190659h (1997).

192. A. Chan Seng H., Brlinble margaret;
Aust. J. Chem., (1998); *Chem. Abstr.*, **129**, 16105f (1998).

193. M. R. Selim Al-Azhar;
Bull. Sci., (1997); *Chem. Abstr.*, **130**, 110131d (1999).

194. A. A. Hassanien, M. D. Zahran, M. S. A. El-Gaby, M. M. Ghorab;
J. Indian Chem. Soc., (1999); *Chem. Abstr.*, **131**, 214249k (1999).

195. M. R. Hallet, J. E. Painter, Q. Peter, R. Deam;
Tetrahedron Lett., (1998); *Chem. Abstr.*, **129**, 16105f (1998).

196. A. M. El-Sayed, A. M. El-Saghier, M. M. Abbas Ali, El-Shafei Ahmed Kamal;
Gaaz. Chim. Ital, (1997); *Chem. Abstr.*, **129**, 4604c (1998).

197. R. P. Hsung, C. A. Zificsak, Wei Lin-Li, L. R. Zehnder, P. Francis, K. M. Tran;*J. Org. Chem.*, (1999); *Chem. Abstr.*, **132**, 49557f (2000).

198. S. P. Anatoliy, M. Niazimbetova, Z. I. Evans, H. Dennis, M. E. Nizazymbetor;
Heterocycles, (1999); *Chem. Abstr.*, **131**, 44712m (2000).

199. G. V. Klokol, S. G. Kaivokolysko, V. D. Dya Chenko, V. P. Litninov;
Chem. Heterocycl. Compd., (N. Y.) (1999); *Chem. Abstr.*, **133**, 43477t (2000).

200. S. S Emorsy., O. M Habib. and M. A.Mutwally;
An. Quim., **83(7-8)**, 711-713 (1993); *Chem. Abstr.*, **121**, 108724v (1994).

201. R. De Lero Angel, Torrado Alicia, Rey Jose and Loper Susana;
Tetrahedron Lett., **38(42)**, 7421-7424 (1997); *Chem. Abstr.*, **128**, 13179b (1998).

202. P.Cebasek, D.Bevk, S. Pirc., B. Stanovnik., J.Svete;
J. Comb. Chem., **8(1)**, 95-102 (2006).

203. N. M. Abed, N. S. Ibrahim and M. H. Elnagedi;
Z. Naturforsch., **416**, 925 (1986); *IJHC*, **3**, 15-18 (1993).

204. H.Abdel-Ghany, H. M.Moustafa and A. Khodeairy;
Syth-Commun., **28(18)**, 3431-3441 (1998); *Chem. Abstr.*, **129**, 260360w (1998).

205. X. Zhang, B. Hinkle (a), L. Ballantyne (a); S. Gonzales (a) and M. R. Pena;
J. Heterocycl. Chem., **34**, 1061 (1997).

206. T. P. Kosta, B. M. Turner, S. Ronald, D. John et. al.;
Eur. Pat. Appl. WO 807, 629; *Chem. Abstr.*, **128**, 34684c (1998).

207. M. J. Anne, O'Mahony Mary Josephine, L. Stephen, D. Jacqueline;

PCT Int. Appl. WO **98** 27, 080; *Chem. Abstr.*, **129**, 81666d (1998).

208. A. Z. Elassar, A. Abdel Zaher;
Pharmazie 1998; *Chem. Abstr.*, **129**, 4562a (1998).

209 R. M. Shaker;
Pharmazie 1996, 51(3); *Chem. Abstr.*, **125**, 10762p (1996).

210. D. B. Shinde, M. S. Shingare;
Indian J. Chem., **30B**, 450 (1991).

211. P. Pere, G. Elisa;
Span ES 511, 501.

212. G. A. Kileigil and R. Ertan;
J. Heterocycl. Chem., **35,** 1485 (1998).

213. Saheyla Ozbey and Engin Kendi;
J. Heterocycl. Chem., **35**, 1485 (1998).

214. W. Wuri, Li Tiechao, M. Robert, J. Yares, E. Hinnart, M. J. Luzzio, S. A. Noble, Attardo Giorgio;*Bio. Org. Med. Chem. Lett.* 1998; *Chem. Abstr.*, **129**, 202833s (1998).

215. Y. D. Kulkarni, D. Srivastava, A. Bishnoi, P. R. Dua;
J. Indian Chem. Soc., **73(45)**; *Chem. Abstr.*, **125**, 86440c (1996).

216. R. Judith, B. Geneviere, T Francois, R. Pierre, L. Stephane, P. Alan, A. Gharem; *Chem. Pharm.Bull.* 1998; *Chem. Abstr.*, **128**, 180349p (1998).

217. Dell Colin Peter, Williams Andrew Carwyn;
Eur. Pat. Appl. EP 599, 514; *Chem. Abstr.*, **121**, 108765j (1994).

218. L. H. Jochem, V. W. E. Gerlach, B. J. Chim, E. H. Christian, M. Hropot;
Eur. Pat. Appl. EP 807, 629; *Chem. Abstr.*, **128**, 34684c (1998).

219. A. Dandia, V. Sehgal and P. Singh;
Indian J. of Chem., **32B**, 1288-91 (1993).

220. A. Orjales; A. Berisa and L. Alonso-Cires;
Indian J. of Chem., **33B**, 27-31 (1994).

221. M. E. Zwaagstra, R. E. M. Korthouwer, T. Henk, Z. Ming-Quinng;
Eur. J. Med. Chem., 1998; *Chem. Abstr.*, **129**, 16039n (1998).

222. E. Boyer Frederick Jr., D. J. Michael, E. E. Lee, G. C. Andrew, H. S. Elizabeth;*PCT Int. Appl. WO* **98** (1997); *Chem. Abstr.*, **129**, 16055q (1998)

223. Y. U. A. Sharanin, L. Y. U. Sukharevskaya, V. V. Shelyakin;
Russ. Journal of Org. Chem., (1998); *Chem. Abstr.*, **130**, 209617d (1999).

224. M. S. El-Gaby, Abd. El-Aal, S. G. Abdel-Hamide, M. M. Ghorab;
Acta. Pharm. (Zagreb) 1999; *Chem. Abstr.*, **132**, 93278d (2000).

225 . A. A. Miky Jehan, H. H. Sharaf;
Indian J. Chem., **37B**, (1998); *Chem. Abstr.*, **129**, 95421g (1998).

226. J. J. Chon, P. S. Dae, L. H. Sukim Ju Su, K. S. Jin, M. Kuzumi;
PCT Int. Appl., WO **98**, 25, 916; *Chem. Abstr.*, **129**, 81667q (1998).

227. F. Katsumi, M. Isamu, T. Natsuku, I. Y. Iijima;
Jpn. Kokai Tokkyo Koho JP, **09**, 301, 915; *Chem. Abstr.*, **128**, 13147q (1998).

228. K. A. Jacobson, Jiang Ji-Long, K. Y. Chul; K. Yishi, A. M. Van Rhee;
PCT Int. Appl., WO **97**, 27, 177 (1996); *Chem. Abstr.*, **127**, 190650y (1997).

229. A. Tsutomu, V. Kimihisa;
Saito Synthesis, (1997); *Chem. Abstr.*, **128**, 14002e (1998).

230. T. Mladen, L. Zrinlca, K. Zeljko, P. Ljerka;
Eur. Pat. Appl. EP, 820, 998; *Chem. Abstr.*, **128**, 15401g (1998).

231. O'Brien, John E., Mc. Murry et. al.;
Chem. Abstr., **130**, (1999).

232. El-Subbagh, I. Hussein, Abu-Zaid, M. Sunair;
J. Med. Chem., (2000), **43(15)**, 2915-2921 (2000).

233. Carbou Romuald, Mowbary, Charles Erie, Perros Manoussos;
Chem. Abstr., **136**, 118423v (2002).

234. F. F. Abdel-Latif, R. M. Shanker, N. S. Abdel-Aziz;
Heterocyclic Communication, Vol. **3**, 245-252 (1997).

235. P. M. Zhu, I. Kimiaki;
Chem. Abstr., **127**, 190659h (1997).

236. Iwahashi Y., Hosoda H., Park J. H., Lee J. H., Suzuki Y. and Iwahashi H.;
J. Agric. Food Chem., **54(5)**, 1936-1942 (2006).

237. Y. Osada and T. Shibamoto;
Food Chemistry, **98(3)**, 522-528 (2006).

238. T.Hanafusa, Shinji T., Shiraha H., Nouso K.;
Cancer., **5(1)**, 9 (2005).

239. Williamson H. S., Free A.;
Mol Microbiol., **55(3)**, 808-827 (2005).

240. H. Yeo, Y.Li, Fu L., J. L.Zhu, E. A.Gullen, G. E.Dutschman;
J. Med. Chem., **48(2)**, 534-546 (2005).

241. M. H.David Cordonnier, W.Laine, A Lansiaux., F.Rosu, P.Colson;
Mol Cancer Ther., **4(1)**, 71-80 (2005).

242. C.Asche, W.Frank, A.Albert, U.Kucklaender;
Bioorg Med Chem., **13(3)**, 819-37 (2005).

243. C. H.Moon, E. J.Baik, Y. S.Jung;
Eur J Pharmacol., **506(1)**, 27-35 (2004).

244. A. Y.Howe, J.Bloom, C. J.Baldick, C. A. Benetatos, H. Cheng, J Christensen. S.;*Antimicrob Agents Chemother.*, **48(12)**, 4813-21(2004).

245. K. Y.Kim, Lee J. H., Park J. H., Yoo M. A., Kwak Y. G., Kim S. O.;
Eur J. Pharmacol., **497(3)**, 267-77 (2004).

246. S. G. Krivokolysko;
Chem. Heterocycl. Compd., (N.Y.) (1999)

247. A. Samour, Y. Akhnookh and H. Jahine;
U. A .R. J. Chem., 13(4), 421-37 (1971); Chem. Abstr., 77, 101348 (1972)

248. M. L. Crossley, V. L. King, L. H. Northey, T. E. Scholz;
U.S. US, 02 491, 253 (1949); Chem. Abstr., 45, 4746 (1961)

249. U. D. Dayochenko;
Russ. J. Org. Chem., 34(4), 554-56 (1998); Chem. Abstr., 130, 223222c (1999)

250. M. Kanded Ez-El-Din;
Chin. Pharm. J., (1999); Chem. Abstr., 132, 321784y (2000)

251. Okazoe Takashi;
PCT Int. Appl. WO 00 06, 347; Chem. Abstr., 132, 321784y (2000).

252. G. H. Sayed, R. R. Kassab;
Bull. Fac. Pharma., (1998); Chem. Abstr., 131, 15727p (1999).

253. C. Pierre. Wyss, Paul Gerber, G.Peter Hartman, Christian Hubschwerlen, Martin
J.Stahl; Med. Chem., 46(12), 2304-2311 (2003).

254. A. Samour, Y. Akhnookh and H. Jahine;
J. Chem., 13(4), 421-37 (Eng.) (1970); Chem. Abstr., 77, 101348 (1972).

255. A. Sakuri and H. Midorikwa;
Bull. Chem. Soc. Japan, 40, 1680 (1967); Chem. Abstr., 67, 9021d (1968).

256. A. Sakuri and H. Midorikaw;
Bull. Chem. Soc. Japan, 41(2), 430 (1968); Chem. Abstr., 69, 1898s (1968).

257. D. Matthew Bowman, M. Megan Jacobson, and Helen E. Blackwell; Organic Letters, 8(8), 1645-1648 (2006).

258. Dao-Lin Wang and Kimiaki Imafuky; J.Heterocyclic chem.,37, 1019-1032,(2000).

259. N. Latif, N. Mishrky and N. S. Girgis; Indian J. Chem., 20B, 147-149 (1981).

260. W. von Behenburg, J. Engel, J. Heese and K. Thiele; Ger. Often., D.E., 3, 337, 593 (Cl C07D 213/72) 1984; Chem. Abstr., 101, 130595n (1984).

261. L. Castedo, J. M. Quintela and R. Riguers; Eur. J. Med. Chem. Chim. Ther., 19(6), 555 (1984); Chem. Abstr., 103, 37337 (1985).

262. M. R. Pavia, C. P. Taylor, F. M. Hershenson and S. J. Lobbestael; J. Med. Chem., 30, 1210 (1987).

263. W. L. Hoefling, D. Elhaner and E. Reckling; VEB Leund-Werke "Walter Ulbricht" Ger., 1,193, 506 (1965); Chem. Abstr., 63, 6979 (1965).

264. Thiele Kurt, Von Be Benburg and Walter E.; S. African 6, 905, 06, 13 Feb. (1970).

265. B. John E.D., F. M. Peter and Freeman Ger. Often., 2, 029, 079 (Cl. A 01 N007d) (1971); Brist. Appl. (1969); Chem . Abstr., 74, 99891d (1971).

266. V. Scott and Joseph; Jap. Pat., 2, 803, 592 (1979); Chem. Abstr., 92, 47216 (1980).

267. J. J. Baldwin, A. Scrialrine, G. S. Ponticeello, E. L. Engelhardt and C. S. Sweeti; J. Heterocycl. Chem., 17(3), 425 (1980); Chem. Abstr., 93, 186222, (1980).

268. E. G. Hammana Abou, El-Hafeza Nagla A. Abd, Midurus Wandall, Z. Naturforsch B.;Chem. Sci., (2000).

269. N. A. Abdallah, E. A. Zakimagdi; Acta Pharm (Zagreb) 1999; Chem. Abstr., 132, 137287n (2000).

270. M. Fedele, C. Franco, B. Adriana, B. Bruna, F. Walter, F. Amelia, G. Luigi; Eur. J. Med. Chem., 34(3), 245-254 (1999); Chem. Abstr., 130, 352178s (1999).

271. H. Yoshida, K. Omori, Y. Yasuyuki, F. Kensaku;
Jpn. Kokai Tokkyo Koh. JP, 10, 120, 677; Chem. Abstr., 129, 16062q (1998).

272. A. El-Galil and E. Amr;
Indian J. Heterocyclic Chem., 10, 49-54 (2000).

273. G. S. Gadaginamath, A. S. Shyadigeri and R. R. Kavali;
Indian J. Chem., 37B, 1137c (1998).

274. S. V. Roman, U. D. Pyachenko;
Chem. Abstr., 136, 325448x (2002).

275. F. M. A. El-Taweel, M. A. Sofan;
Egyptian J. Med. Chem., 36(2), 539-544 (2002) (Egy); Chem. Abstr., 137, 63154w (2002).

276. M. Hussans, H. A. Eman., A. A. El-maghruby
Chem. Abstr., **127**, 638p, 190698 (1997).

277. U. D. Pyachenko., S. V Roman ;
National nogo Uni., 495-59-64 (Russ.); *Chem. Abstr.*, **136(21)**, p-807, 325448x (2002).

278. Thiele Kurt, Von be Benburg, Walter E;
S. African., **6**, 905-06 (1970).

279. N. Latif, N. Mishry and N. S. Girgis;
Indian J. Chem., **20 (B)**, 147-149 (1981).

280. M. Bernard, W. Johan, p. Lionel, L. Didier;
J. Med. Chem., **41(17)**, 3239-3244 (1998); *Chem. Abstr.*, **129**, 202846y (1998).

281. D. G. Bhatt, J. J. Petraitis, S. R. Sherk, R. A. Copeland;
Bioorg. Med. Chem., Lett., **8(13)**, 1745-1750 (1998); *Chem. Abstr.*, **129**, 202848a(1998).

282. U. Teu, K. M. Takuro, M. Shinkya, K. Seiikhi;
Jpn. Kokai Tokkyo Koho JP, **09**, 95, 489 (1997); *Chem. Abstr.*, **127**, 17699y (1997).

283. J. A. Van Allan, C. C. Petropoulos, G. A. Reynolds and D. P. Maier;
J. Heterocycl. Chem.,**7**, 1364 (1970).

284. Abu-Shana B, Fathi A, Satyed Ahmed Z, El-Gaby;

285. A. Streightoff;
J. Bacteriol, **85**, 42-8 (1963); *Chem. Abstr.*, **58**, 4836a (1963).

286. J. Seydel;
Antibiot. Chemotherapia, **12**, 137-47 (1946) (Ger.); *Chem. Abstr.*, **61**, 4833a (1964).

287. E. Francis J. H. Reinhart, Gray and William G. Batt;
J. Franklin Inst., 261, 669-70 (1966); *Chem. Abstr.*, **50**, 10930c (1956).

288. E. D. Barton John , F. M. Freeman Peter
Ger. Offen, **2** 029, 079 (Cl. AOIN007d), 21 Jan. 1971, Brit. Appl. 12 June (1969);
Chem. Abstr.,**74**, 99891d (1971).

289. VEB Leuna-Werke, "walter Ulbricht" (by W. L. Hoefling, D. Ethaner and G. Reckling);Ger., 1 193, 506 (Cl C07D) may 26 (1965); Chem. Abstr., 63, 6979 (1965).

290. El-Nabawia El-Said Goda, F. Alexandria;
S. Pharm. Sci., 1999; Chem. Abstr., 132, 151650g (2000).

291. Guru S. Goda Ginamath, Ashok S. Shya digeri and Rajesh R. Kavall;
Ind. J. Chem., 37(B), 1137C (1998).

292. K. Kadlec and L. Hanslian;
Symp. Dermatol Corpus Lecteonum Uni., Carolina Prague 1, 302-13 (1960) (Ger.); Chem. Abstr., 61, 7596 (1964).

293. H. Rigterink, Raymond (Don Chemical Co.);
US, 3 899, 205 (CE 260-294-8) 27 Aug (1968); Chem. Abstr., 69, 96483h (1968).

294. M. R. Pavia, C. P. Taylor, F. M. Hershenson and S. J. Lobbestael;
J.Med. Chem., 30, 1210 (1987)

295. L. Castedo, J. M. Quintela, and R. Rignera;
Eur. J. Med. Chem. Chim. Ther., 19(6), 555 (1984); Chem. Abstr., 103, 37337 (1985).

296. W. Von Behenburg, J. Engel, J. Heese and K. Thiele;
Ger. Offen., D. E., 3, 337, 593 (Cl. C 07D 213/72) 1984; Chem. Abstr., 101, 130595n (1984).

297. V. Scott and E. Joseph;
Jap. Pat. 7 99 8338 (1979); Chem. Abstr., 92, 82428 (1980).

298. V. Scott and E. Joseph;
Jap. Pat., 2, 803, 592 (1979); Chem. Abstr., 92, 47216 (1980).

299. E.Abdel-Galil Amr and Mohamed M. Abdulla;
Bioorganic & Medicinal Chemistry, **14(13)**, 4341-4352 (2006).

300. W. Von Behenburg, J. Engel, J. Heese and K. Thiele;
Ger. Offen., D. E., **3,** 337**,** 593 (Cl. C 07D 213/72) 1984; *Chem. Abstr.*, **101,** 130595n (1984).

301. V. Scott and E. Joseph;
Jap. Pat. **7** 99 8338 (1979); *Chem. Abstr.*, **92**, 82428 (1980).

302. V. Scott and E. Joseph;
Jap. Pat., **2,** 803, 592 (1979); *Chem. Abstr.*, **92,** 47216 (1980).

303. B. Edwin Villhauer, A. John Brinkman, B. Goli Naderi, E. Beth Dunning, Bonnie L.; *J. Med. Chem.*, **45,** 2362-2365 (2002)

304. J. L. Marco, M. C. Carreiras.;
Mini. Rev. Med. Chem., **3(6),** 518-24, (2003).

305. M. A. Moustafa., M. N. Nasr., M. M. Gineinah., W. A. Bayoumi.;
Arch Pharm. (Weinheim), **337(3)**, 164-70, (2004).

306. H. S. Eduardo Sousa, L. Daniel Pontes, C. N. Izaura Diógenes, G. F. Luiz Lope; *Journal of Inorganic Biochemistry*, 368-375, (2005).

307. Rosentreter Ulrich, Kraemer Thomas et al.;
Ger. Otten. DE 10, 238, 113 (Cl,CO 7D213/60) (2003).

308. T.Gary Wang, , Xilu Wang, Weibo Wang, A.Lisa Hasvold, Gerry Sullivan, W.Charles ;
Bioorganic & Medicinal Chemistry lett., **15(1),** 153-158, (2005).

309. A.John Tucker, A.Debra Allwine, C.Kevin Grega et al.;
J. Med. Chem., **41,** 3727-3735 (1998).

310. Williams R. R. and Cline J. K.;
J. Amer. Chem. Soc., **58**, 1504 (1936).

311. Y. L. N. Murthy and G. Jagmohan;
Indian J. Heterocyclic Chem., **8**, 277-80.

312. Pratibha Sharma, Ashok Kumar and Manisha Sharma;
Journal of Molecular Catalysis A: *Chemical*, **237 (1-2)**, 191-198 (2005).

313. Rasaki Abayomi Osisanya and James Olabisi Oluwadiya;
J. Heterocyclic Chem., **26**, 947 (1989).

314. S. M. Sondhi, Rajendra N. Goyal and Ram Raghubir;
Bioorganic & Medicinal Chemistry, **13(9)**, 3185-3195 (2005).

316. A. S. Noranyan, Oranisyan A. Sr., Grigoryan G. O., Vartanyan S. et al.; *Chem Abstr.*, **126**, 70176f (1997).

317. Mochida Pharmaceutical Co. Ltd. JP, **81**, 127, 383 (1981).

318. N.Henrie Robert, J Peake Clinton., G.Cullen Thomas et al.; *PCT Int Appl., WO* **98**,20,878, Appl. 96/08,17748 (1996); *Chem Abstr.*, **129**, 16136s (1998).

319. M. M. Ghorob and S. G. Abdel-Hamid; *Indian J. Heterocycl. Chem.*, **4**, 103-06 (1994).

320. Obatokio Fujii, Katsu Toshi, Narita Isami et al.; *Jpn. Kokai Tpkkyo Koho JP*, 08,269,021 (1995); *Chem Abstr.*, **126**, 74864b (1997).

321. R. K. Russell, J. B. Press, R. A. Rampulla, J. J. Mc Nally et al.; *J. Med. Chem.*, **31**, 1786 (1988).

322. Ranise Angelo, Bruno Olga, Schenone Silvia, Bondalalli Franceso et al.; *Farmaco*, **52(8-9)**, 547-55 (1997); *Chem. Abstr.*, **128**, 238986n (1986).

323. Y. S. Sadanandan, N. M. Shetty and P. V. Diwan; *Chem. Abstr.*, **117**, 7885k (1990).

324. A. K. Khalafallah, F. M. Abd-El Latif and M. A. Salim; *Asian J. Chem.*, **5**, 988-94 (1993).

325. S. S. Sangopure and A. M. Mulogi; *Indian J. Heterocyclic Chem.*, **10**, 27-30 (2000).

326. El-Sayed and A. M. Badaway; *J. Heterocyclic Chem.*, **33**, 229 (1996); **7**, 273-76 (1998).

327. H. Y. Moustafa; *Indian J. Heterocyclic Chem.*, **7**, 273-76 (1998).

328. Marie Gompel, Maryse Leost, Elisa Bal De Kier Joffe, Lydia Puricelli, *Bioorganic and Medicinal Chemistry Letteres*, **14**, 1703-1707 (2004).

329. H.Alistair Bingham , Richard J. Davenport, Lewis Gowers , Roland L.; *Bioorg Med Chem Lett.*, **14(2)**, 409-12 (2004).

330. L. R. Patil, Ingle V. S., Bondge S. P., Bhingolikar V. E., Mane R. A.; *Indian Journal of Chem.*, **40B**, 131-134 (2001).

331. B. J. Ghiya and Manoj Prabjavat; *Indian J. Heterocyclic Chem.*, **7**, 311-12 (1992).

332. N. V. Kaplina, Griner A. N., Sherdor V. I., Fomina A. N. et al.;

Chem Abstr., **123**, 228207s (1995).

333. Chaudhari Bipinchandra, Chapdelaine Mare, Hostetler Greg, Kemp Lucius, Mc Cauley; *John PCT Int. Appl.* WO **02** 36, 586 (Cl. CO7D401/12), 10 May (2002); SE Appl. (2000)**4**, 053, 6 Nov, 56 pp. (Eng) (2000).

334. E.Devi Sree, Prakash E. Om, Rao J. T.;
Journal of the Institution of Chemists (India), **74(5)**, 167-168 (Eng) (2002).

335. A. L.Kovalenko, Krutika V. I., Zolotukhina M. M. and Alekseeva L. E.;
Zh. Obsch. Khim., **62(6)**, 1363-66 (1992); *Chem Abstr*., **118**, 101909r (1993).

336. Shiv P. Singh and Hitesh Batra;
Indian J. Heterocyclic Chem., **9**, 73-74 (1999).

337. Michael D. Varney, Clindy L. Palmer, Eleanor J. Howland and Rosanne Ferre;
J. Med. Chem., **40**, 2502-2524 (1997).

338. Antonello Mai, Marino Artico, Gianluca Sbardella and Paolo La Colla;
J. Med. Chem., **42**, 619-627 (1999).

339. Vin`ey Lather and A. K. Madan;
Bioorganic and Medicinal Chemistry Letters, **13,** 1599-1604, (2005).

340. J. L.Whittingham, I. Leal, C.Nguyen, G.Kasinathan, E.Bell;
Structure (Camb)., **13(2)**, 329-38 (2005).

341. G. Z.Han, Z. J.Liu, K. Shimoi, B. T.Zhu;
Cancer Res., **65(2)**, 387-93 (2005).

342. D. K.Tack, F. M.Palmieri, E. A.Perez;
Oncology (Huntingt), **18(11)**, 1367-76 (2004).

343. P.Cano-Soldado, I. M.Lorrayoz, M. Molina-Arcas, F. J.Casado, Martinez-Picado J.;*Antivir. Ther*., **9(6)**, 993-1002 (2004).

344. M.Gompel, M.Leost, E. B.De Kier Joffe, L. Puricelli, L. H.Franco, J.Palermo;
Bioorg. Med. Chem. Lett., **14(7)**, 1703-7 (2004).

345. Junmei Wang, Xinshan Kang, Irwin D. Kuntz, and Peter A. Kollman.;
Journal of medicinal chemistry, **27**, (2004).

346. T.Shimizu, T.Kimura, T.Funahashi, K.Watanabe, Ho I. K., Yamamoto I.;
Chem Pharm. Bull. (Tokyo), **53(3)**, 313-8 (2005).

347. C.Sanmartin, M.Echeverria, B.Mendivil, L.Cordeu, E. Cubedo, Garcia-Foncillas J.;*Bioorg. Med. Chem*., **13(6)**, 2031-44 (2005).

348. A Agarwal., B Kumar., P. K.Mehrotra P. M Chauhan.;

Bioorg. Med. Chem., **13(6)**, 1893-9 (2005).

349. S.Shigeta, S Mori, F. Watanabe, M .Saneyoshi.;
Antivir. Chem. Chemother., **13(2)**, 67-82 (2002).

350. Herve Geneste, Gisela Backfisch, Wilfried Braje, Wolfgang Wernet;
Bioorganic & Medicinal Chemistry Letters, **16(3)**, 490-494 (2006).

351. A .Mai., M.Artico, R.Ragno, G.Sbardella;
Bioorg. Med. Chem.,**13(6)**, 2065-2077 (2005).

352. I.Yamamoto;
Yakugaku Zasshi., **125(1)**, 73-120 (2005).

353. Y. L.Huang, C. F Lin., Y. J Lee., W. W .Li., T. C. Chao.;
Bioorg. Med. Chem., **11(1)**, 145-57 (2003).

354. Somnath Nag, Richa pathak, Manish kumar, P. K. Shukla and Sanjay Batra;
Bioorganic &Medicinal Chemistry, **16(14)**, 3824-3828(2006).

355. G. F .Sun., Y. Y. Kuang., F. E. Chen De Clercq, C.Pannecouque;
Arch. Pharm. (Weinheim), **338(10)**, 457-61 (2005).

356. L. Claisen and O. Lowmann;
Chem. Ber., **21**, 1149 (1888).

357. A. Quelico;
Chem. Heterocycl.Compd., **17**, 1 (1962).

358. L. S. Crawley and W.J. Fanshawe;
J. Heterocycl. Chem., **14**, 531 (1977).

359. Dawood Kamal M., Kundeel Zaghku E., Faraq Ahmed M;
J. Chem. Res. Synp., **(4)**, 208-209 (1998); *Chem. Abstr*., **129**, 67759e (1998).

360. Tayade V. B., Jamode V. S.;
Asian J. Chem., **9(4)**, 866-68 (1997); *Chem. Abstr.*, **128**, 88824s (1998).

361. Lidia De Luca, Giampaolo Giacomelli, and Antonella Riu;
J. Org. Chem., **66**, 6823-6825 (2001).

362. Nagatoshi Nishiwaki, Tomoko Nogami and Masahiro Ariga;
J. Org. Chem., **64(17)**, 6476-6478 (1999).

363. P. Jesse Waldo and Richard C. Larock;
Organic Letters, **7(23)**, 5203-5205 (2005).

364. Jeffrey W. Bode, Yoshifami Hachisu and Keisuke Suzuki;
Organic Letters, **5(4)**, 391-394 (2003).

365. Mark Lautens and Ame´lie Roy;

Organic Letters, **2(4)**, 555-557 (2000).

366. S. Suzuki, K. Ueno and K. Mori;
Yakugaku Kenkua, **34**, 224-31 (1962); *Chem. Abstr.*, **57**, 16754 (1962).

367. B. Victor, J. Safir and R. Sidney;
Brit., 1, **178**, 604 (Cl. C07D), 21 Jan. 1970, US *Appl*. 21 Mar. 1966; 8 p.p.; *Chem. Abstr.*,**72**, 79017d (1970).

368. G. P. Reddy, E. Rajendra and A. K. Murthy;
Indian J. Heterocycl., **3**, 233 (1994); *Chem. Abstr.*, **122**, 105724e (1995).

370. T. Tochiro, K. Shrji, I. Shinji, M. Hiroshi, S. Akira, V. Hiroshi;
Gen. Offen. DE, **3**, 237,149 (Cl. CO7A 261114) (1983); *Chem. Abstr.*, **99**, 88188(1984).

371. T. U. Quazi;
Pak. J. Sci. Ind. Res., **27**, 326 (1984); *Chem. Abstr.*,**103**, 12339m (1985).

372. R. Major, B. Eisele, P. Mutler and H. Grube;
Ger. Offen. DE, 3621372 (1988); *Chem. Abstr.*, **108**, 67456r (1988).

373. D. R P.Li W. Hwang Chen Shen C. W., C. L Huang c., Chen T. W.,
J. Med. Chem., **46**, 1706 (2003).

374. S. Rung and D. Dus;
Pharmazie, **49**, 727 (1994); *Chem. Abstr.*, **122**, 55934h (1995).

375. Vamanauchi Pharm. Co. Ltd.;
Jpn Kokai Koho JP, **58**, 148, 858 (Cl. CO7D 207/333) (1982); *Chem. Abstr.*, **100**, 34538 (1984).

376. P. T. Gallagher, T. A. Hicka and G. W. Mullier;
Eur. Pat. Ep., **2**, 57, 882 (1988); *Chem. Abstr.*, **108**, 6499K (1988).

377. A. Ando and R. W. Stevens;
PCT Int. Appl. WO, **94**, 12, 481 (Cl. C07 D 261/04); *Chem. Abstr.*, **122**, 56037x (1995).

378. W. Wells, A. Michele, H. Todd, H. Dennis;
J. (USA), US Pat. Appl. Publ. US (2002), **49**, 213, (Cl. 514-252, 05; C07D 413/02), 25 Apr. 2002, US Appl. PV 209, 6 Jun. 2000, 19 p.p. (Eng.); *Chem. Abstr.*,**136**, 340680j (2002).

379. I. A. Shehata and R. A. Glannoh;
J. Heterocycl. Chem., **24**, 1291 (1987).

380. M. D. Mackie, H. S. Anthony, W. J. R. Howe, S. P. John and W. S. Marry;

Brit.; *UK Pat. Appl. GB* **2**, 265, 371 (Cl. C07 D 261/06); *Chem. Abstr.*, **120**, 164153z (1994).

381. G. D. Diana and C. P. Michel;
S. African ZA, **81**, 03, 105 (1981); *Chem. Abstr.*, **98**, 1667, (1983).

382. M. Moriyusu, H. Yusui;
Gen. Offen. DE, **3**, 237,149 (Cl. CO7A 261114) (1983); *Chem. Abstr.*, **99**, 88188 (1984).

383. A. K. Banerjee;
Arzneim Forsch., **44**, 863 (1994); *Chem. Abstr.*, **122**, 160522n (1995).

384. M. Tibor, P. S. Neil and S. P. Henry, Gount;
PCT Int. Appl. Wo, 9414, 782 (Cl. C 07D 261/08); Chem. Abstr., **121**, 255784t (1994).

385. Inai Masatoshi, Tanaka Akie, Goto Kyoto;
Jpn Kokai Tokkyo Koho JP, **07**, 215, 952 (95, 215, 952) (1995); *Chem. Abstr.*, **124**, 86995s (1996).

386. Nippon Chemiphar Co. Ltd.;
Jpn. Kokai Koho JP, **58**, 46,077 (Cl. CO7A 261/14) (1983); *Chem. Abstr.*, **99**, 17574 (1984).

387. T. Taate, K. Natira and H. Fukhola;
Chem. Pharm. Buld., **35(9)**, 37769 (1987); *Chem. Abstr.*, **108**, 186621e (1988).

388. D. J. David, D. B. Allon and E. A. Frederick;
Ger. Offen., **2**, 723,688 (Cl. A01N 9/28) (1977); *Chem. Abstr.*, **88**, 132015k (1978).

389. Sezer Ozkan, Debak Kudir, Anac Okay, Akar Ahmet;
Heterocycl. Commun., (1999); *Chem. Abstr.*, **131**, 5221f (1999).

390. C. P. Alfred, C. David Herman, D. Nancy, B. Daniel;
PCT Int. Appl. WO, **95**, 22, 9103 (1995); *Chem. Abstr.*, **124**, 3055m (1996).

391. K., Tomita Takahi Y. and H.; Vdaira H.;
Ann. Sankyo Res. Lab., **1**, 25 (1973).

392. P. M Welsing.. J. L Severens., M Hartman , M., P. L.van Riel P. L., Laan R. F
Arthritis. Rheum., **51(6)**, 964-73 (2004).

393. S. J., Bingham ., M. H., Buch , M. A Kerr., Emery P., Valadao Barcelos A.
Arthritis. Rheum., **50(12)**, 4072-3 (2004).

394. M. R., Barbachyn M. R., G. J., Cleek, L. A Dolak., S. A Garmon., Morris J., E Seest *J. Med. Chem.,* **46(2),** 284-302 (2003).

395. Stefano Chimichi, Macro Boccalini and Massimo Carini; *Tetrahedron*, **62(1)**, 90-96 (2006).

396. H. Bryan Norman, A. Peter Lander and Anne H. Dantzig; *Bioorganic & Medicinal Chemistry Letters*, **15(24)**, 5526-5530 (2005).

397. T. D. Aicher, B. Balkam, P. A. Bell, L. J. Brand et al.; *J. Med. Chem.*, **14(1)**, 151-152 (1998); *Chem. Abstr.*, **129**, 343429b (1998).

398. M. Masui, H. Yasushi; *PCT Int. Appl.* WO 97, 43, 248 (Cl. C 07 C 251/50), 20 Nov. 1997, JP Appl. 96/117,370, 13 May 1996; 68 pp (Japan); *Chem. Abstr.* **128,** 13256z (1998).

399. K. V. Reddy, S.G. Rao, A. V. Subba; *Indian J. Chemistry,* **37(B)**, 677-99 (1998); *Chem. Abstr.*, **129,** 260397p (1998).

400. C. B. Xue, J. Roderick, S. Mousa, R. E. Olason, W. F. Degrado; *Bioorg. Med. Chem. Lett.*, **8(24)b**, 3499-3504 (1998).

401. Julia Kaffy, Renee Pontikis, Daniele Carrez and Jean Claude Florent; *Bioorganic & Medicinal Chemistry*, **14(12)**, 4067-4077 (2006).

402. Kai Fan Cheng and Yousef Al-Abed; *Bioorganic & Medicinal Chemistry Letters*, **16(13)**, 3376-3379 (2005).

403. S. Rung and D. Dus; *Pharmazie*, **49**, 727 (1994); *Chem. Abstr.*, **122**, 559344 (1995).

404. M. Scobie and M. D. Threadosill; *J. Org. Chem.*, **59**, 7008 (1994); *Chem. Abstr.*, **122**, 10090f (1995).

405. G. Daidone, D. Raffa, B. Maggio, F. Plescia, C. Cutuli; *Archiv Der Pharmazie*, **332(2)**, 50-54 (1999).

406. M. W.Salter *J. Orofac Pain.,* **18(4)**, 318-24 (2004).

407. Matringe M., Sailland A., Pelissier B., Rolland A., Zink O.; *Pest Manag Sci.* (2005).

408. D. R., Mehlisch P. J.Desjardins S Daniels., R. C Hubbard.; *J Am Dent Assoc.,* **135(11)**, 1578-90 (2004).

409. W. A Ray., M. R Griffin., C. M Stein.; *N Engl J Med.,* **351(26)**, 2767 (2004).

410. J. B. Dickey and A. R. Gray;
Org. Syn. Coll. **2,** 60 (1943).

411. C. B. Reese and S. R. James;
Tetrahedron Letters, **29** 15 (1975).

412. M. R. Mahamoud, Awatef E. F. Ebrahim, M. S. Abd El-Halim and A. M. Radwan;
Indian J. Heterocyclic Chem., **4,** 131-36 (1994).

413. Cao-Yan Weu, Chai Xain Dong, Jiang Yue-Shan et al.;
Gaodeng Xuexiao Huaxue Xuebao, **16(2),** 225-29 (1995); *Chem. Abstr.,* **123,** 33021u (1995).

414. Ougus Funda and Dogan Liknur;
Chem. Abstr., **129,** 16097e (1998).

415. S. C. Harvey in "The Pharmacological Basis of Therapeutics" ed. L. S. Goodmann and A. Gilman;
Macmillan, New York, 5th edition, p. 102 (1975).

416. S. C. Harvey in "The Pharmacological Basis of Therapeutics" ed. L. S. Goodmann and A. Gilman;
Macmillan, New York, 5th edition, p. 124 (1975).

417. L. Weinstein in "The Pharmacological Basis of Therapeutics" ed. L. S. Goodmann and A. Gilman;
Macmillan, New York, 5th edition, p. 1113 (1975).

418. C. I. Chappel and C. Von Seeman;
Prog. Med. Chem. **3**, 89 (1963).

419. Malcom Daniels and Alec Grimison;
U. S. US Pat. **13**, 150, 137 (1964); *Chem. Abstr.*, **59**, 7539c (1963).

420. J. M. Cox, C. D. Snowling and M. C. Shepard;
German Often, **2,** 812, 367 (1978); *Chem. Abstr.,* **90,** 82129u (1978).

421. Z. H. Khalil, A. I. M. Koraiem and R. M. Abu-El-Hammed;
J. Chem. Technol., Biotechnol., **36,** 473 (1986).

422. Y. K. Gupta, K. P. Bhargava, K. Shanker and J. C. Agarwal;
Indian J. Chem., **20B,** 714 (1981).

423. J. C. Agarwal, Y. K. Gupta, P. Kumar, C. Nath, K. P. Bhargava and K. Shanker;
Indian J. Chem., **22B,** 955 (1983).

424. G. P. Gupta, Sharda Singh and K. Shanker;
Indian J. Chem., **24B,** 1094 (1985).

425. Y. Furukawa;
European Patent Appl. EP. **88** 413 (1983); *Chem. Abstr.,* **100,** 22688 (1983).

426. R. F. Burns;
Biochim, Pharmacol., **30,** 325 (1981); *J. Heterocyclic Chem.,* **33,** 1025 (1996).

427. A. G. Manukyan, R. G. Malik and B. T. Guri. bidzhanyan;
Khim-Pharm, Zh., **19,** 685 (1985); *Chem. Abstr.,* **104,** 207622s (1996).

428. Wolf-Gang, Hanefeld and Helge Hurms;
Indian J. Heterocyclic Chem., **34,** 509 (1997).

429. Andre Roland, Dollinger Markus and Erdelen Christopher;
Ger. Offen DE **19,** 715, 017 (Cl. CO7D 401/12) (1998), Appl. 19, 715, 017, (1997); *Chem.Abstr.,* **129,** 302655d (1998).

430. M. T.;Omar *Egypt J. Pharma. Sci.* 1997, **38 (4-6)**, 281-89 (1997), *Chem. Abstr.,* **131,** 257514k (1999).

431. Sakai, Kunikazu, Satoh, Yusuke;
PCT Int. Appl. WO **99** 50, 252 (Cl. CO7D 239/62), Chem. Abstr., **131,** 243286a (1999).

432. Ambrogio Oliva, De Cillis, Gianpiero; Grams Frank, Livi Valeria et. al.;
PCT Int. Appl. WO **98** 58, 925 (Cl. C07D 401/12); *Chem. Abstr.*, **130**, 95560x (1999).

433. W. Weber., J. Jaeger., M.Doelker, Eger K.;
Pharmazie, **53(11)**, 771-75 (1998); *Chem. Abstr.*, **130**, 95531p (1999).

434. Frank Grams, Zimmermann Gerd;
PCT Int. Appl. WO **98** 58, 915 (Cl. C07 D 239/00); *Chem. Abstr.*, **130**, 95559d (1999).

435. R. T. Pardasani, S. K. Jain, S.K. Yadav and I. Sharma;
Indian J. Heterocycl. Chem., **12,** 179-180 (2002).

436. Ulf Wellmar, Anna-Britta Hornfield and Salo Gromowitz;
J. Heterocyclic Chem., **32,** 1159 (1995).

437. D. Peters, A. B. Hornfield and S. Gromowitz;
J. Heterocycl. Chem., **27**, 2165 (1990).

438. P. A. M. Herdwijin;

Antiviral Chem. Chemother., **5,** 131, (1994); *J. Heterocyclic Chem.*, **32,** 1159, (1995).

439. P. Raymond L. Daine, Dan-Chang Wei, Wang;
J. Heterocyclic Chem., **30,** 1399 (1993).

440. M. R. Mahmound, M. S. Abd, El-Halim and A. M. Radwan;
Indian J. Heterocyclic Chem., **4,** 131-36 (1994).

441. D. L. Levesque., E. C. wang., D. C. Wei C. C Tzeng., R. P. Panzica.;
J. Heterocycl. Chem., **30(5)**, 1399-1404 (1993); *Chem. Abstr.*, **120**, 217540g (1994).

442. I. M. Wyzlic W. Tjarks, A. H. Soloway., D. J. Perkins.,
Inorg. Chem., **35(16)**, 4541-47 (1996); *Chem. Abstr.*, **125**, 168582q (1996).

443. Shivanyuk Alexander. N., Rudkevich D. M., Reinhoudt D. N.;
Tetrahedron Lett., **37(52)**, 9341-44 (1996); *Chem. Abstr.*, **126**, 144028h (1997).

444. Gursu Esin, Ulusoy Nuray;
Acta. Pharm. Turc., **38(4)**, 107-9 (1996); *Chem. Abstr.*, **126**, 59802m (1997).

445. Bosies Elmar, Eswein A., Gram Frank, Krell Hans Willi;
Ger. Offen., DE **19**, 548, 624 (Cl. C07D 401/04) (1997); *Chem. Abstr.*, **127**, 121746x (1997).

446. Abdel Hamide S. G., El-Hakim A. El-Helby A. A.;
Al-Azhar J. Pharm. Sci., **17**, 35-40 (1996).

447. Li Laizhong, Liu Qingjian, Huang Ruqi, Wang hailing;
Hecheng Huaxue, **5(2)**, 197-8 (1997); *Chem. Abstr.*, **128**, 217351m (1998).

448. H. W. Krell, Gepper Dangmar, Grams Frank,., H Leinert., E Menta ;
PCT Int. Appl. WO **02** 79, 170 (Cl. C07D 239/62); *Chem. Abstr.*, **137**, 294967e (2002).

449. A. W. Hoffman;
Ber., **21**, 2332 (1880).

450. A. Ladenburg;
Ibid., **27**, 2952 (1894).

451. Zednikova Gabriela, Nalepa Karela;

Acta Univ. Palacki Olamuc., Fac. Rerum Nat. Chem., 1998; *Chem. Abstr.,* **131**, 116188v (1999).

452. C. Granachar and G. Gulbas;
Helv. Chem. Acta., **10**, 818-26 (1927); *Chem. Abstr.*, **22**, 781 (1928).

453. Feng Jun-Cai, Meng Quing-Hug, Liu Yang, Dai-Li;
Org. Prep. Proceed Int., (1997); *Chem. Abstr.,* **128**, 61455k (1998).

454. A. Saxena, N. C. Desai, Kesha K. Awasthi;
Indian J. Chem., **40(B)**, 201 (2001).

455. H. A. Allimony, Sadd H. A. and F. A. A. el-Mariah;
Indian J. Chem., **38(B),** 445 (1999).

456. B. S. Vashi, D. S. Mehta and V. H. Shah;
Indian J. of Chem., **34B,** 802 (1995); *Chem. Abstr.,* **123,** 339793z (1995).

457. E. Bousquet, G. Romeo, N.A. Santagati, T. Lancetta, A. Caruso, V. Leone, and A. Felice; *Farmaco.,* **44(9),** 851-63 (1989); *Chem. Abstr.,* **112,** 191378t (1990).

458. R. Agarwal, C. Chaudhary and V. S. Misra;
Indian J. Chem., **22(B)**, 308 (1983); *Chem. Abstr.,* **99**, 881280 (1983).

459. C. R. Sharma and D. R. Shridhar;
Indian Pat. IN 154-314 (1984); *Chem. Abstr.,* **105,** 133738 (1986).

460. A.J. Srivastava, Sanjay Swaroop, V. K. Saxena and P. Srivastava;
Indian J. Pharma. Sci., **51(6),** 23 (1989).

461. Hussieny Hamed Moharram, R. Samiya El-Amin and Ahmed El-Dawany; *J. Serb. Chem. Soc.,* **54(7)**, 335-42 (1989); *Chem. Abstr.,* **114**, 101822x (1991).

462. S. M. Sethna and R. C. Shah;
J. Indian Chem. Sci., 1459 (1993).

463. Sanjay Swaroop, V. K. Saxena and S.R. Chowdhary;
Indian J. Pharma. Soc., **51(4),** 124-27 (1989).

464. M. Verma, A. K. Chaturvedi, A. Chaudhari, S. S. Parmar;
J. Phar. Sci., **63,** 1740-44 (1974); *Chem. Abstr.,* **82,** 51358y (1975).

465. Chang Lind di;
PCT Int. Appl. WO **98** 22, 208 (1998); *Chem. Abstr.,* **129,** 41134x, (1998).

466. K. K. Kataryna, E. Szymanska, M. Motyl, W. Holzer, A. Bialecka, Kasprowicze; *Pharmazie,* **53(10),** 680-684 (1998); *Chem. Abstr.,* **130,** 3606f (1999).

467. Altenburger J. M., Gilbert L.;
Chem. Abstr., **131,** 76653y (1999).

468. A. Sudhir and P. C. Dandiya;
Proc. Dec. Conf. Ind. Pharmacal. Soc. Abs. No. **88** (1977).

469. M. D. Shah, N. C. Desai, K. K. Awasthi, and A. K. Saxena;
Ind. J. Chem., **40B,** 201-208; March 2001.

470. M. W. Goldberg and H. H. Lehr;
US, U. S. **2,** 602,086 (1952); *Chem. Abstr.,* **47,** 6987d (1953).

471. K. C. Mathur and R. Sahay;
J. Indian Chem. Soc., **67,** 856 (1990).

472. S. A. Agripat;
Neth. Appl. **6,** 611,087 (1967); *Chem. Abstr.,* **68,** 29699z (1968).

473. M. B. Gravestock and J. F. Ryley;
``*Antifungal Chemotherapy in annual reports in medicinal chemistry.''* **19,** 127 (1984).

474. V. K. Pandey and (Ms.) Meenal Tandon;
Ind. J. Chem., **40B,** 527-29 (2001).

475. P. K. Naithani, V. K. Srivastava, J. P. Barthwal, A. K. Saxena, T. K. Gupta and K. Shanker; *Indian J. Chem.,* **28B,** 990-92 (1989).

476. K. A. Johnnes, K. Kauko, O. A. Seppo, Sulevi Lennart;
Eur. Pat. Appl. EP **58** 047; *Chem. Abstr.,* **98,** 16692m (1983).

477. Thomas I. Kalman;
PCT Int. Appl. WO **94** 21,658 (1994); *Chem. Abstr.,* **122,** 315045k (1995).

478. R. R. Grenshaw and Luke George M.;
Can. CA., **1,** 130, 306; *Chem. Abstr.,* **98,** 16649p (1983).

479. Desalns S Jane, Shaw Anthony W.;
PCT Int. Appl. WO **99** 8,096 (Cl. C07 P401/02) (1999); *Chem. Abstr.,* **131,** 167431z (1999).

480. Arnould Jean-Cldude, Francis Thomas Boyle;
PCT Int. Appl. WO **98** 32,741 (1998); *Chem. Abstr.,* **129,** 16156f (1998).

481. K. Kawasaki, H. Kobayashi, S. Ehara, Hideaki Sato;
PCT Int. Appl. WO **98** 32, 740 (Cl. C07D 223/60) (1998); *JP. Appl.* 97, 110, 114
(1997); *Chem. Abstr.,* **129,** 148945h (1998).

482. Farmshow Christopher Geoffrey, Hough T. L., Mitchell D. R.;
PCT Int. Appl., WO **98,** 51,673 (1998); *Chem. Abstr.*, **130,** 13990g (1999).

483. B. L. Pilkington, R. S. Elizabeth;
Brit. UK Pat. Appl. GB. **2** 3,29,180; *Chem. Abstr.*, **130,** 448172 (1999).

484. L. Joseph Peter, Yang Bingwei Vera;
Eur. Pat. Appl. WO **100,** 6, 113; *Chem. Abstr.*, **133,** 307296 (2000).

485. Stefama Lauter, Hans Gunther, Gerd Wagnewr;
J. Medicinal Chem., VIK-**45,** 4695-4705 (2002).

486. Declera Erickl, Van Aerschot Arthur, Herdeciln Piet;
PCT Int. Appl. WO **02** 68, 395 (Cl. C07D 235/84) (2002); *Chem. Abstr.*, **137,** 201308c (2002).

487. Ding Ming Wu, Zhifeng Ziu, Ying Yong, Hy axye;
Chem. Abstr., **136,** 5497 (2002).

488. Kolhe Vishnu, Dhingra Vinod;
Ind. J. Heterocycl. Chem., **4(1),** 69-70 (1994); *Chem. Abstr.*, **122,** 105757l (1995).

489. B. R. Shah, J. J. Bhatt, H. N. Patel, N. K. Undavia;
Indian J. Chem., **34B**, 201-8 (1995).

490. V.Akyoshi, Myazawa Yasuyuki;
Jpn. Kokai Tokkyo Koho, JP **7** 206, 829 (1995); *Chem. Abstr.*, **123,** 283031 (1995).

491. Bascou J. P., Lacrox G., Perez J. O. and Schmitz C.;
PCT Int. Appl. WO **94** 01, 410, 20 Jan. (1994); *Chem. Abstr.*, **121**, 83334c (1994).

492. Rama Sharma and Bipiab De;
Ind. J. Heterocycl. Chem., **9,** 185-188 (2000).

493. K. K. Awashthi; A. K. Saxena;
Indian J. Chem., **40B,** 207 (2001).

494. N. S. Shah, P. Kagathra, V. H. Thakrar and A. R. Parikh;
J. Inst. Chemists (India), **69,** Part-II, (1997), pp. 63.

495. H. B. Oza, D. G. Joshi, H. H. Parekh;
J. Inst. Chemists (India), vol **69,** Part-II (1997). pp. 57.

496. D. M. Purohit and V. H. shah, Heterocyclic communications vol 3(2). 139-145 (1997).

497. D. M. purohit and V. H. shah; I.J.H.C. Vol 8, Jul- sept 67-70 (1998).

498. D. M. Purohit and V. H. shah, I.J.H.C. Vol 8-Jan- March, (213-216)(1999).

499. D. M. Purohit and V. H. Shah; I,J,H.C. Vol 8 Oct-Dec;133-138(1998).

500. V. R.Radadiya, D. M. Purohit and V. N. Patoliya; J.Inst. Chemists (India),Vol 78(1) 14-16(2006).

501. V. R. Radadiya, D. M. Purohit and V. N. Patoliya; J. Inst. Chemist (India) Vol. 78(1), 11-13 (2006).

502. V. C. Soni and A. R. Parikh;
Indian J. Pharm. Sci., **53**, 185 (1991); *Chem. Abstr.*, **116**, 151653, (1992).

503. R. R. Shah, V. H. Shah, A. R. Parikh;
J. Inst. Chem., **65(5),** 169-70 (1993).

504. A. H. Bhatt, K. A. Parikh and A. R. Parikh;
Ind. J. Chem., **38(5)B,** 628-631 (1999).

505. Biplab De and G. U. S. Ram Sarma;
Indian J. Heterocyclic Chem., **9,** 185 (2000).

506. Y. Naoto, K. Jyoji, H. Kimiaki, O. Takashi, K. Keizo;
Eur. Pat. Appl. EP **95,** 163 (Cl. C07 C103/52); *Chem. Abstr.*, **100,** 174827y (1984).

507. R. C. Dage, Palopoli F. P., Schnettler R. A., Grisar J. M.;
U.S. US. **4,** 405,628 (Cl. 424-263; A61K 31/415); *Chem. Abstr.*, **100,** 6516c (1984).

508. Armando Rossello, S. Bertini, A. Lapucci, M. Machi, A. Martinelli, S. Rapposelli, E. Herreros and B. M. Acchia;
J. Med. Chem., **45(22),** 4903-12 (2002).

509. A. B Cooper,., R. J Doll., J. A Ferreira., A Ganguly., V. M.Girijavallabhan A. G Taveras. J.P Chao., J.J Baldmin., C. Y.Huang Li Ge;
Chem. Abstr., **137,** 154949n (2002).

510. Machii Daisuke, H. Koji, A. Akira, A. Hitoshi, Y. Yoshinori, Chin A.C., M. A M. A Piatyszek.; *Chem. Abstr.*, **137,** 93750e (2002).

511. M. R.Jean Carolin Sabourin, Nidia Alvorez, R. P.Sylvie Guillaume L. B., Patrice.; *Eur. J. Med. Chem.* **38,** 711-718 (2003).

512. Chafiq Hamdouchi, Concha Sanchez, Joseph Gruber, Miriamdel Prado;
J. Medicinal Chem., **46,** 4333-4341 (2003).

513. M. L Irene., P Christophe., Arthur A Van., Myriam Witwrouw, Zeger Debyser;*J. Med. Chem.*, **46(8),** 1546 (2003).

514. Xu Zhi-Feng, Ding Ming-Wu;
Chem. Abstr., **139,** 101228z (2003).

515. R. Caganiat, G. Kirsch, M. Wierzbicki, K. Lepage et al.;
Eur. J. Med. Chem., **15**, 439 (1980).

516. J. R. Dimmock, S. K. Raghavan, B. M. Logan and G.E. Begam;
J. Med. Chem., **18**, 249 (1983).

517. Maurilio Tramontini and Luigi Angiolini;
Chemistry and uses (CRC Press, Ann Aror,-Londan) (1994).

518. M. Traimontini, L. Angolini and N. Ghedini;
Polymer, **29**, 271 (1988).

519. Mannich and kathuer;
Arch. Pharm., **18**, 257 (1919).

520. A.Sabastiyan and D Venkappyya.;
J. Indian chem. Soc., **61**, 16 (1984).

521. Venkatesha Prabhu G. and Vanappayya D.;
J.Indian Chem.Soc., **72**,511-514,681-684 (1995).

522. Seshaiah Krishnan, Sridhar et al.;
Biol. Pharm. Bull, **24(10)**, 1149-1152 (2001).

523. Yung-Son Hon, Yu-Yu Chou and I-Che Wu;
Synthetic Comunication, **34(12)**,2253-2267 (2004).

524. S. N Pandeya., D Sriram.;
Acta Pharm. Turc., **40(1)**, 33-38(Eng.) (1998),
Chem.Abstr., **129**, 109060c, (1998).

525. K.W.Chi, H. C.Wei T. Kottke., R. J. Lagow.;
J. Org. Chem., **61**, 5684 (1996).

526. A Christos. Kontogiorgis and Dimitra J. Hadjipavlou-Litina;
J. Med. Chem., **48**, 6400-6408 (2005).

527. D. Hadjipavlou Litina., A.Geronikaki, E. Sotiropoulou;
Res. Commun. Chem. Pathol. Pharm., **790**, 355-362 (1993).

528. A.Gavalas, L. Hadjipetrou, P. Kourounakis;
J. Pharm. Pharmacol., **50**, 583-591 (1998).

529. D. Satyanarayana, S. Gorge, E. V.Subrahmanyam B. Kalluraya;

Boll. Chim. Farm., **140**, 228-232 (2001).

530. J. M. Pattanaik., M. Pattanaik, D.Bhatta;
Indian J. Heterocycl. Chem., **8(1)**, 75-76(1998); *Chem.Abstr*., **130**,66444g (1999).

531. Piao Riyang, Liu Baili, J. Zhizhong et al.;
Zhongguo Yaowu Huaxue Zazhi Bianjibu, **8(3)**, 157-162(ch) (1998).

532. R. H. K. Foster and A. J. Carman;
J. Pharmacol. Exp. Ther., **91**, 195 (1947).

533. J. R. Dimmock and P. Kumar;
Curr. Med. Chem., **4**, 1-22 (1997).

534. J. N.Gadre, C. S. Thatte and Pramod Vele;
Indian J. heterocyclic Chem., **8**, 71-74 (1998).

535. Rae Ducan Robertson and Gibson Samuel George;
PCT Int. Appl. Wo, 98, 21, 206, EP Appl.96/203,175 (1996);
Chem.Abstr.,**129**,27899u (1998).

536. J. Knoll;
Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol., **236**, 92 (1959).

537. J. Knoll;
Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol., **238**, 114 (1960).

538. V. J. Ram and N. Haque;
Indian J. Chem., **34**, 514 (1995).

539. L. H. Schmidt and Ruth Crosby;
Antimicrobial agents and Chemotherapy, **15(5)**, 672-679 (1978).

540. T. Lorand, B. Kocsis et al.;
Eur. J. Med. Chem., **37(10)**, 803-12 (2002).

541. D. D Erol., A. Rosen et al.;
Arzneimittelforschung, **39(8)**, 851-3 (1989).

542. H. M. Hassan, S. A. M. Shedid;
J. Serb.Chem. Soc., **63(2)**, 125-130 (1996).

543. Movrin M., Maysinger D. et al.;
Pharmazie, **35(8)**, 458-60 (1998).

544. H. I.Gul., T. Ojanen et al.;
Arzneimittelforschung, **51(1)**,72-5 (2001).

545. Y. Li, Z. S.Yang et al.;

Bioorg. Med. Chem.,**11(20)**, 4363-8 (2003).

546. B. Shivarama Holla, B. Veerendra, M. K. Shivananda, K. P. Latha, V. P. Vaidya;
Indian J. Heterocycl. Chem., **13(1)**, 61-64 (2003).

547. C. G.Nevill F. H Verhoeff., C. G. Munafu H. J. VanderKaay
E. AFR. Med. J., **71**, 167-170 (1994).

548. L. K. Panali L. Assicoulibaly B. Kaptue, D. Konan, A. Ehouman.;
Bull. Soc. Path. Exo., **87**, 244-247 (1994).

549. M. L. Edwards, H. W. Ritter, D. M. Stemerick and K. T. Stewart;
J. Med. Chem., **26**, 431-436 (1983).

550. Malcolm K. Scoott, Gregory E. Martin, Deena L. DiStefano and J. L. Vaught;
J. Med. Chem., **35**, 552-558 (1992).

551. J. Knoll, K. Nador, B. Knoll, J. Heidt and J. G. Nievel;
Arch. Int. Pharmacodyn. Ther., **130**, 155 (1961).

552. D. M. Gallant and M. P. Bishop;
Curr. Ther. Res., Clin. Exp., **10**, 441 (1968).

553. Jonathan R. Dimmock, N. Murthi Kandepu, Erik De Clercq and Jan Balzarini;
J. Med. Chem., **41**, 1014-1026 (1998).

554. H. I..Gul T. Ojanen et al.;
Biol. Pharm. Bull., **25(10)**, 1307-10 (2002).

555. H. I. Gul., U. Calis et al.;
Bioorg Med.Chem., **11(20)**, 4363-8 (2003).

556. M. S.Shingare D.V.Mane D. B Shinde. S. N Thore.;
Asian J.Chem., **8(2)**, 225-8 (1996).

557. J. Amanda Gallant, O. Brian Patrick and Mark J. Maclachlan;
J. Org. Chem., **69**, 8739-8744 (2004).

558. M. S. Murray;
Chemical Review **26,** 297-338 (1940).

559. J. Rosaleen J. Anderson, S. Anderi Batsanov, Natalia Belskaia, Paul W. Groundwoqer,Andrey Zaytsev;
Tetrahedron Letters., **45(5)**, 943-946, Jan. 2004.

560. Strache; *Bre*., **21,** 2361 (1888).

561. Van Alphen;
Dec. Tran Chi., **54**, 93 (1935).

562. Oddo & Tognacchini;
Gazz. Chim. Ital., **52,** II, 347, (1922).

563. L. Pierre Beaulieu, James Gillard and Bruno Simoneau;
J. Org. Chem., **70**, 5869-5879 (2005).

564. Das, Arima, Lien, Eric J. Trousdale, Melvin D.;
Chin. Pharm. J. (Taipet) 49 (2), 89-102 (Eng.) (1997) ;
Chem. Abstr., 128 (18), 217259n (1998).

565. Ergenc, Nedime, Uinsoy, Nuray, Capangultate, Soruis, Aulten O tuk, Kiraz, Mnammer;
Arch. Pharm. 329 (8-9), 427-430 (1996); Chem. Abstr., 126, 1, 8031b (1997).

566. Pascal Rathelst, Nadine Azos, Hussain El-Kashef, Forence Delwasi;
Eur. J. Med. Chem., 57, 671-679 (2002).

567. R. P. Pawar Anduskary N. M., Vibhute V. B.;
J. Indian Chem. Soc., 76(5), 271-72 (Eng.) (1999); Chem. Abstr., 131, 677, 271829y (1999).

568. C. Alexandru, Stocia, Gheorghe-Zaharia, Berdan, Ioan ;
Rom. RO, 106, 403 (Cl. CO7D 231/04) (1993), Appl. 143, 707, 15, (1990);
Chem.Abstr.,129, 2, 491, 16120g (1998).

569. A. Adnan A. Bekhil, Heshan T. V. Fahwy, Azzaim Baraka et. al.;
Eur. J. Med. Chem., 38, 27-56 (2003).

570. Wang, Yangang, Ye, Wenfa, Yang Jun., Lou, Aihong; Wuhan Daxue Xuebao, Ziran; Kexueban;

571. M.J. Hearn and M.H Cynamon.;
JAC., 53, 185-191 (2004).
Chem. Abstr., 125 (13), 167488b (1996).
Delta J. Sci., **15(1)**, 47-56 (1991); *Chem. Abstr.*, **118**, 168756e (1993).

572. Smalders, Robert Rene, Brunin, Dominique, Sarten, Frederic;
Bull.Soc.Chim. Belg., (1988), 97 (11-12), 941-4 (Fr); Chem. Abstr.,112, 511, 21055t (1990).

573. Sharaf El-Din, Nabaweya;
Delta J. Sci., 1991, 15(1), 47-56; Chem. Abstr., 118, 168756e (1993).

574. Chohan, Zahid Hussain, Kusuar, Somina;
Chem. Pharm., Bull.,41(5), (1993), 951-3 (Eng.); Chem. Abstr., 120, 1034,134406s (1994).

575. R. H Mehta., Shah Sonal, Vyas Rajeev;
J. Indian. Chem. Soc., 69(9), 590-2 (Eng.) (1992); Chem. Abstr., 119, 1088, 95268f (1993).

576. Khalafallah A. K. and Hassan M. E.;
Aswan Sci. Technol. Bull., 12, 82-90 (Eng.) (1991); Chem. Abstr., 118, 918, 191392s (1993).

577. Chohan, Zahid Hussain, Kusuar Somina;
Chem. Pharm., Bull., **41(5)**, 951-3 (Eng.) (1993); *Chem. Abstr.,* **120**, 1034, 134406s (1994).

578. Das Joydip, Singh Anilk;
Indian J. Chem., Sec. B. Org., Chem. Incl. Med. Chem., **33B(7)**, 615-17 (Eng.) (1994);
Chem. Abstr., **121**, 1212, 205726e (1994).

579. Solankee Anjani, Mistry Pankaj, Patel V. M.;
*Orient. J. Chem.,***13(3)**, 289-292 (Eng.) (1997); *Chem. Abstr.,* **128**, 16, 192584z (1998).

580. Deshmukh M. D., Doshi A. G.;
Orient. J. Chem., **11(1)**, 85-6 (Eng.) (1995); *Chem. Abstr.,* **123**, 1111, 256269g (1995).

581. Wang Yangang, Ye Wenta, Yang Jun., Lou Aihong;
Wuhan Daxue Xuebao Ziran Kexueban, 191-194 (Ch.) (1996); *Chem. Abstr.,* **125(13)**,167488b (1996).

582. Das Arima, Lien Eric J., Trousdale Melvin D.;
Chin. Pharm. J. (Taipei.), **49(2)**, 89-102 (Eng)(1997); *Chem. Abstr.,* **128(18)**, 217259n(1998).

583. Sabrina Castellano, Paolo La Colla, Chiara Musia, Giorgio Stefancich;
Archiv der Pharmazie, 333, 6, 162-166 (2000).

584. Shivarama Holla B., Sooryanarayana RaoB., Shridhara K. & Akberali P. M.;
IL Farmaco, 55, 5, 338-344, May (2000).

585. Wang, Yangang, Ye, Wenfa, Yang, Jun. Lou, Aihong; Wuhan Dexue Xuebao, Ziran Kesueban;
Chem. Abstr.,125(13), 167488b (1996).

586. Pascal Rathelst, Nadine Azoes, Hassain El-Kashef, Forence Delwas;
Eur. J. Med. Chem., 57, 671-679 (2002).

587. Holla B. Shivarama, MaliniK. V., Sooryanarayan B. , Raw B. K., Sarojini N.; Eur. J. Med. Chem., 38, 313-318 (2003).

588. J. R Dimmock., A ,Jha., G. A., Zello G. A., T. M Allen., Santos C. L.; Pharmazie, 58 (4), 227-232 (Eng.) (2003); Chem. Abstr., 139, 149383 (2003).

589. A. Adnan A. Bekhil, Heshan T. U. Fahwy, Azzaim Baraka et. al.; Eur. J. Med. Chem., 38, 27-56 (2003).

590. Cascaval Alexandru, Stocia, Gheorghe-Zaharia, Berdan, Ioan; *Rom. RO*, **106,** 403, (Cl. C07D 231/04), 1993, Appl. 143, 707, 15, (1990); *Chem.Abstr.*, **129**, 2, 491, 16120g (1998).

591. S. N Pandeya., D Sriram.; *Acta. Pharm. Ture.*,**40(1)**, 33-38 (Eng.) (1998); *Chem. Abstr.*, **129**, 9, 641, 109060 (1998).

592. V Ravindra. Chambhare, Barsu, G. Khudse, Anil S. Bobde, Rajesh H. Bahekar; *Eur. J. Med. Chem.*, **38**, 89-100 (2003).

593. B Holla. Shivarama, V MaliniK. B. Sooryanarayan, B. K. Raw, N. Sarojini, Suchetha Kumari; *Eur. J. Med. Chem.*, **38**, 313-318 (2003).

594. Ram Tilak, Tyagi Ritu, Goel Bhawna, Saxena K. K., Shrivastava V. K., Kumar Ashok; *Indian Drugs.*, **35(4),** 216-221 (Eng.) (1998); *Chem. Abstr.*, **129**, 9, 641, 109052r (1998).

595. P. Nygren, R. Larsson, L. Slater, *J. Cell Pharmacol.*, 1991, **2(4)**, 202 (1991).

596. K. Kikkawa, S. Muraa, H. Iwasaki, W. Toriumi, K. Banno, T. Nagao, *Arzneim. Forsch.*, **42(6)**, 781 (1992).

597. A. Odawara, Y. Sasaki, S. Murata, H. Narita (Tanabe Seiyaku co. Ltd); *Eur Pat. Appl* . EP **476**, 854 (Cl. A 61 K 31/62), 25 Mar. 1992, JP Appl. 90/243, 728, 17 Sep. 1990;6 pp., *Chem. Abstr*., **117**, 11427 (1992).

598. S. Ishikawa (Tanabe Seiyaku co. Ltd); *Eur Pat.Appl* EP **463**, 877 (Cl. A 61 K 9/54),02 Jan 1992, JP Appl. 90/171, 762, 28 Jun 1990; 14 pp. ; *Chem. Abstr*., **116**, 91426 (1992).

599. I. R. Buxton, A. Brown, H. Critchlly, Leslie, T. Stewart, S. Malkowska, A. Therese, D. A. Prater, R. B. Miller (Euroceltique SA); *Eur Pat.Appl* EP **527**, 638 (Cl. A 61 K31/55), 17 Feb 1993, G. B. Appl. EP 527, 638; *Chem. Abstr*., **118**, 240944 (1993).

600. D. Hendrickson, D. C. Dimmitt, M. S. Willaims, P. F. Skultely, M. J. Balterzor (Marion Mersell Dow INc); *Eur Pat.Appl* EP **514**, 814 (Cl. A 61 K 31/550), 25 Nov. 1992, 45 Appl 702, 567., 20 May 191; 24 pp.; *Chem. Abstr.*, **118**, 66884 (1993).

601. R. J Reddy; D.Ashok; P. N.Sarma, *Indian J. Chem.*, **32B**, 404, Sect. B (1993).

602. K.Satyanarayana, M. N. A.Rao, *Indian j. Pharm. Sci.*, **55**, 230 (1993).

603. G.DeSarro, A.Chimirri, A.DeSarro, R.Gitto, S.Grasso, M.Zappala, *Eur. J. Med. Chem.*, **30**, 925 (1995).

604. P.Stahlhofen, W.Ried, *Chem. Ber*. **90**,815 (1957).

605. D. I. Jung, T. W. Choi, Y. Y. Kim, M. Y. Park, Y. G. Lee, and D. H. Jung, *Synth. Commun.*, **29**, 1941 (1999).

606. M. Pozarentzi, J. Stephanidou-Stephanatou, and C. A. Tsoleridis, *Tetrahedron Lett.*, **43**, 1755 (2002).

607. W.Ried, E.Torinus. ; *Chem. Ber.*, **92**, 2902 (1959).

608. D. I.Jung, T. W.Choi, Y. Y. Kim, I.S.Kim, Y.M.Park; Y.G.Lee, Jung,D.H. *Synth. Commun*., **29**,1941 (1999).

609. M.S.Balakrishna, B.Kaboundin, *Tetrahedron Lett*. **42**, 1127 (2001).

610. Kawashima Co. Ltd., Jpn Kokai Tokkyo Koho Jp 6056, 972 [8556, 972] (Cl. CO 7 D 281/10), 02 Apr. 1985, Appl. 88/163, 884, 06 Sep. 1983; 4 pp. *Chem. Abstr.*, **103**, 105014 (1985).

611. H. Kogita, H. Inoue, M. Ikezki, S. Takeo; Ger. Offen., 1, 805, 714 (Cl. CO7 D A 61k), 19 Jun 1969; *Chem. Abstr.*, **71**, 7065 (1969).

612. J. Bernsten (Squibb, E.R. and Sons Inc); Brit. 1, 198; 853 (ClCO7 d) 15 July 1970, Appl. 13 Jun 1967 ; 8 pp., *Chem. Abstr.*, **73**, 77295 (1970).

613. Hamari Yakuhin Kogyo Co. Ltd., Jpn Kokai Tokkyo Koho Jp 59, 101, 497 [84, 101, 497] (Cl CO 7 F 5/02), 12 Jun. 1984, Appl. 82/212 314, 02 Dec. 1982; 6 pp. *Chem. Abstr.*, **101**, 171292 (1984).

614. Hamari Yakuhin Kogyo Co. Ltd., Jpn Kokai Tokkyo Koho Jp 59, 101, 498 [84, 101, 498] (Cl CO 7 F 5/02), 12 Jun. 1984, Appl. 82/212 315, 02 Dec. 1982; 6 pp. *Chem. Abstr.*, **101**, 171292 (1984).

615. F. Yang., S. Jin., Q. Xing, Youji Huaxzle **3**, 212 (1985).

616. K. Kikkawa, S. Muraa, H. Iwasaki, W. Toriumi, K. Banno, T. Nagao, *Arzneium, forsch.*,**42(6)**, 781 (1992).

617. Tanabe Seiyaku Co. Ltd., Jpn Kokai Tokkyo Koho Jp 6025, 982, 498 [85, 25, 982](Cl CO 7 D 281/10), 08 Feb 1983, Appl. 83/ 134 923, 22 Jul. 1983; 4pp.,*Chem. Abstr.*, **103**, 87918 (1985).

618. Hamari Yakuhin Kogyo Co. Ltd., Jpn Kokai Tokkyo Koho Jp 60 72, 8785 [85, 92, 875] (Cl CO 7 D 1/10), 24, Apr. 1985, Appl. 83/181 085, 28 Sep. 1983; 8 pp. *Chem. Abstr.*, **103**, 142032 (1985).

619. A. Soriabine, J. Cardiovaso; *Pharmacol.*, **9**, 53, (1987).

620. J. Svetlik, V. Hanus J. Betia, *Liabig Ann. Chem.*, **11**, 91 (1989).

621. A. Bauer; Danneberg P; Weber K H; Minck K; *Journal of medicinal Chemistry., 16(9),* 1011-4 (1973).

622. R.G. Smith; Lucas R A; Wasley J W; *Journal of Medicinal Chemistry*., **23(8)**, 952-5 (1980).

623. DeSarro, G.; Chimirri, A.; DeSarro, A.; Gitto, R.; Zappala, M., *Eur. J. Med. Chem*., **30**, 925 (1995).

624. H. F. Miranda, Sierralta, F.; *General Pharmacology*., **24(4)**, 891-4 (1993).

625. Hagishita, Yamaji; Seno, Kaoru; Myakoshi, Masanori; Tsushima, Tadahiko; Ishihara, Yasunobu.; *Jpn. Kokai Tokkyo Koho*, 17pp (1994).

626. A. Farese; Peytou, V.; Condom, R.; Sinet, M.; Patino, n.; Kim, A,; Moog, C.; Abbertin, A. M.; Guedj, R.; *European Journal of Medicinal Chemistry*., **31(6)**, 497-505 (1996).

627. De Sarro, Giovambattista; Gitto, Rosaria; Rizzo, Milena; Zappia, Mario; De Sarro, Angela; *General Pharmacology*., **27(6)**, 935-41 (1996).

628. Sugg, Elizabeth Ellen; *PCT Int. Appl*. 18pp (1996).

629. Kamal, Ahmed; Rao, maddamsetty V.; Laxaman, N.; Ramesh, G.; Reddy, G.S.K.; *Current Medicinal Chemistry*., **2(2)**, 215-254 (2002).

630. Hui-Ling Wang; Xiong, Xiaoling; Abstracts of paper, 229th ACS National Meeting, San Diego, CA, US, March 13-17, 2005.

631. Rajesh Kumar; Joshi, Y. C.; *Indian Chemical Society*., **84(12)**, 1261-65 (2007).

632. Salata, Joseph j.; Jurkiewicz, nancy K,; Wang, Jixin; Evans, Ben E,; Orme, Heidi T.; Sanguinetti, Michael C.; *Molecular Pharmacology*, **54(1)**, 220-230 (1998).

633. Taku,Nagao; Sato, Masanori; Nakajima, Hiromichi; Kiyomoto, Akio.; *Chemical and Pharmaceutical Bulletin*., **21(1)**, 92-7 (1973).

634. S. Kamail Atwal; Bergey, James L.; Hedberg, Anders; Moreland, Suzanne.; *Journal of Medicinal Chemistry*., **30(4)**, 635-40 (1987).

635. V. Ambrogi; Giampietri A; Grandolini G; Perioli L; Ricci M; Tuttobello L.; *Archiv der Phamazie.*, **325(9)**, 569-77 (1992).

636. C. Saturnino; Saturnino P.; De Martino G; Lancelot J C; Perrine D; Rault S; Robba M; Rossi F; *Penta Italia Farmaco*., **52(3)**, 183-6 (1997).

.637 Shudo, Koichi; *Pct Int. Appl*. 56pp (1997).

638. C. Candelaria, Sanchez-Mateo; Darias, Victoriano; Exposito-Orta, Auxiliadora; Albertos, Luz M.; *Farmaco*., **58(1)**, 1-10 (2003).

639. Farzana L. Ansari; Umbreen, Sumaira; Hussain, Latif; Makhmoor, Talat; Nawaz, Sarfraz A.; Lodhi, Muhammad A.; Atta-ur-Rahman.; *Chemistry and Biodiversity*., **2(4)**, 487-96 (2005).

640. Noushin, Rastkari; Abdollahi, Mohmmad; Ahmadkhaniha, Reza; Shafiee, Abbas.; *Archiv der Pharmazie*., **341(1)**, 49-54 (2008).

641 Stein, Robert G.; Kimura, Eugene T.; *Journal of Medicinal Chemistry*., **15(1)**, 42-5 (1972).

642. D. M. Zisterer, M. M. McGee, G. Campiani, A. Ramunno, C. Fattorusso, V, Nacci, M. Lawlar and D.C. williams.,*Biochemical Society transactions* (2001).

643. P. B. Bharucha, and Naik, H.B., *Asian J. Chem*., **12**, 318-320 (2002).

644. Miki, Takashi; Kori, Masakuni; Mabuchi, Hiroshi; Banno, Hiroshi; Tozawa, Ryu-507ichi; Nakamura, masahira; Itokawa, Shigekazu; Sugiyama, Yasuo; Yukimasa, Hidefumi; *Bioorganic and Medicinal Chemistry*., **10(2)**, 401-414 (2001).

645. Shalaby, Alyaa A., *Phosphorus, Sulphur and Silicon and the related elements;* **178(2),**199-210 (2003).

646. Younes Laras, N. Pietrancosta, V Moret, S. Marc, C. Garino, A. Rolland, V. Monnier and J. Kraus., *Australian Journal of chemistry*, **59(11)**, 812-828 (2006).

647 B. Basavaraju, H. S. Bhojya Naik and M. C. Prabhakara., *E-Journal of chemistry* **4(1)**, 32-38 (2007).

648 V. M. Parikh; *"Absorption spectroscopy of organic molecules"*, Addition-Wesley Pub. Co. London 243, 258 (1978). A. Hand book of spectroscopic data by B. D. Mishtry; 1st ed. ABD Press,Jaipur 11-36 (2000).

649 A. R. Kartizky and R. Alans Jones; *J. Chem. Soc.*, 2942 (1960). Introduction of Infra red and Raman spectroscopy by Norman,B. Colthup, Lowrence H. Daly and Stephan E. Wiberluy. Academic Press (1975).

650 A. L. Barry;

The Antimicrobial Suceptibility test Principle and Practices edited by Illus Lea and Febiger,(Philadelphia Pel USA) 180; Bio. Abstra., 64,25183 (1976).

LIST OF PAPER PUBLICATION

LIST OF PAPER PUBLISED.

1. Synthesis of 2-(4'-Chlorophenyl)-6-methyl-3-[1"-aryl-2"-propene-1"-one-3-yl]/3"-aryl-4",5"- dihydro - 1" – H – pyrazole - 5" –yl) / (3"-arylisoxazole-5"-yl)-imidazo[1,2-a]pyridine
   (V.V. Bhuva, V.N. patolia, A.U. patel, D. M. Purohit*)
   Organic Chemistry;
   An Indian journal
   Vol. 5(1)(104-108)2009.

2. Synthesis and biological screening of 2-(4'-Chlorophenyl)-6-methyl-3-(3"-aryl1"-acetyl/phenyl-4",5" – dihydropyrazol - 5" - yl)-imidazo[1,2-a]pyridines.
   (V.V. Bhuva, V.N. patolia, A.U. patel,D. M. Purohit*)
   Organic Chemistry;
   An Indian journal
   Vol. 5(1)(92-95)2009.

LIST OF PAPER ACCEPTED FOR PUBLICATION:

1. Synthesis and biological Screening of 2"–amino-4"- [2-(4'- chlorophenyl) - 6-methyl imidazo[1,2-a] pyridin-3-yl]-6"-aryl- 4"- H-pyran-3"- carbonitriles. H-pyran-3"- carbonitriles.
   (V.V. Bhuva, V.N. patolia, D. M. Purohit*)

2. Synthesis and biological Screening of 2"-methoxy-4"-[2-(4'- chlorophenyl) -6- methyl imidazo [1, 2-a] pyridine – 3 - yl]-6"-aryl nicotinonitriles.
   (V.V. Bhuva, V.N. patolia, D. M. Purohit*)

3. Synthesis and biological Screening of 2"-amino-4"-[2-(4'- chlorophenyl) -6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"- arylnicotinonitriles.
   (V.V. Bhuva, V.N. patolia, D. M. Purohit*)