# "STUDIES ON SOME HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST"

**A THESIS**
**SUBMITTED TO THE**
**SAURASHTRA UNIVERSITY**
**FOR THE DEGREE OF**

## DOCTOR OF PHILOSOPHY

**IN**

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**BY**


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

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

Date: -05-2011

Place: Morbi

**(Rajesh G. Rupala)**

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

Date : -05-2011

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*Dedicated*
*to my*
*beloved parents*

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First and foremost I wish to bow my head humbly before THE ALMIGHTY, "THE WONDERFUL CHEMIST" of this lovely world. Without his blessings this task would have not been accomplished.

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*I feel a deep sense of gratitude to my wife Aekta who had a dream for my doctorate. With their untiring cooperation, which I received in the form of love, everlasting inspiration and moral support during the period of my study, which was instrumental for the successful completion of the work.*

*The never ending process of enlightenment, love and affection which was showered upon me by my Late. Sister Nayana has reached to an important mile stone. I am really staggered to realize, just how much efforts has been put in by them as well as all my sisters and brother.*

*And finally, still there are many more my family Members ,well Wishers, Friends, Relatives, who directly and indirectly rendered me valuable help and moral strength to complete this academic endeavor. I have deep reverence for all of them.*

*Rajesh G. Rupala*

# CONTENTS

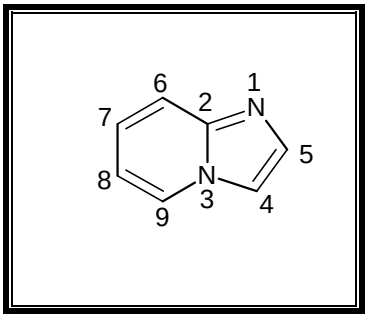
# *SYNOPSIS*

# "STUDIES ON SOME HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST"

A brief summary of the work to be incorporated in the thesis entitled, **"STUDIES ON SOME HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST"** has been summarized as under.

## A. Studies on imidazo pyridine derivatives

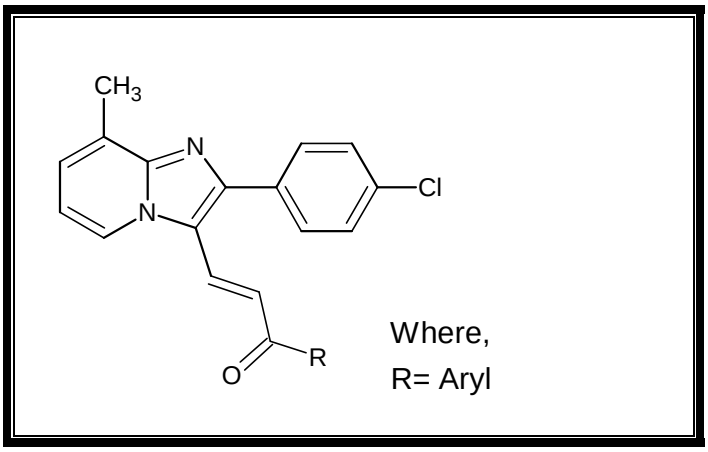
The aza-indolizine contains a phenyl ring fused to a imidazole ring as indicated in the structure, hence it is also known as imidazo[1,2-*a*]pyridine.The constitution of imidazo[1,2-*a*]pyridine was represented by W.L.Mosby.




The group of compound containing imidazo[1,2-*a*]pyridine moiety are prominent structural feature in a variety of natural products as well as in other compounds of medicinal interest and have attracted attention for their biological activities.

## PART-I : SYNTHESIS OF (2Z)-3-[2-(4-CHLOROPHENYL)-8-METHYL IMIDAZO [1,2-*a*]PYRIDINE-3-YL]-1-ARYL PROP-2-EN-1-ONE.

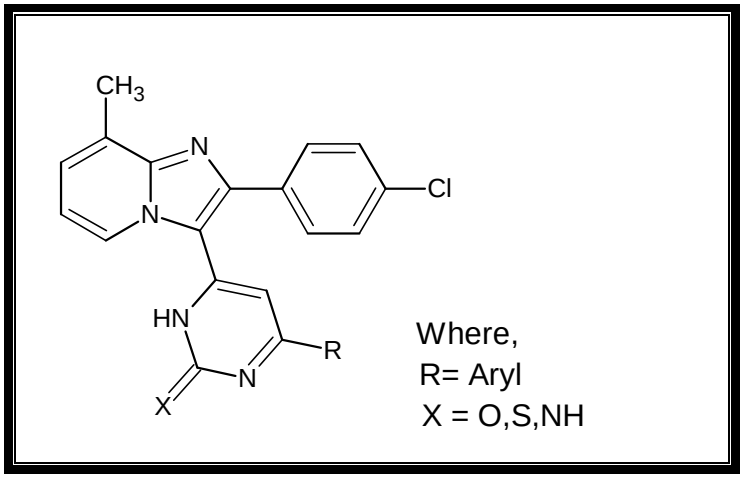
Chalcone derivatives have been found to be associated with various pharmacological activities. These finding encouraged as to synthesize some new novel synthesis.




(2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one derivatives prepared by the condensation of 2-(4-chlorophenyl)-6-methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde with various substituted ketone in methanol.

**PART-II : SYNTHESIS OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO [1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(*H*)-ONE.**

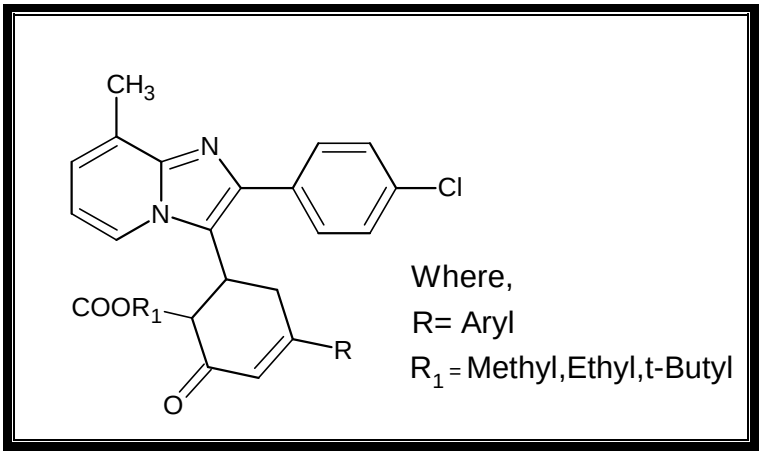
Pyrimidine derivatives have been reported to possess various pharmacological activities like antibacterial, antifungal, insecticide etc. In order to achive better potency, we have synthesized pyrimidine derivatives.



Pyrimidine derivatives have been prepared by the reaction of (2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one and Urea/Thiourea/Guanidine in basic media and methanol as a solvents.

**PART-III : SYNTHESIS OF ETHYL-6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL-2-OXOCYCLOHEX-3-ENE-CARBOXYLATE.**

Cyclohexenone derivatives have been reported to possess various Pharmacological activities like antibacterial, antifungal etc. In order to achieve better potency, we have synthesized Cyclohexenone derivatives.

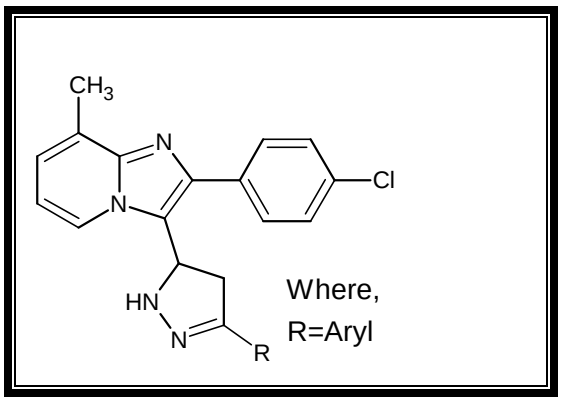



Cyclohexenone derivatives have been prepared by the reaction of (2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one and Methylacetoacetate/Ethylacetoacetate/t-Butylacetoacetate with $Na_2CO_3$ in acetone as solvent.

**PART-IV : SYNTHESIS OF 2-(4-CHLOROPHENYL)-3-(4,5-DIHYDRO-3-ARYL-1*H*-PYRAZOL-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**

Pyrazoline derivatives are endowed with various antimicrobial activities.

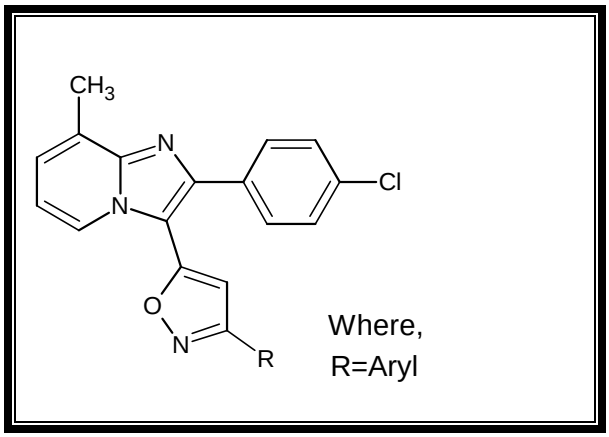
Looking at their versatile therapeutic importance and with an aim to getting better drug. It was considered worthwhile to synthesized some new pyrazoline.




The preparation of 2-(4-chlorophenyl)-3-(4,5-dihydro-3-aryl-1*H*-pyrazol-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine derivatives has been undertaken by the cyclo-condensation of chalcone with hydrazine hydrate and glacial acetic acid.

**PART-V : SYNTHESIS OF 2-(4-CHLOROPHENYL)-3-(3-ARYL ISOXAZOLE-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**

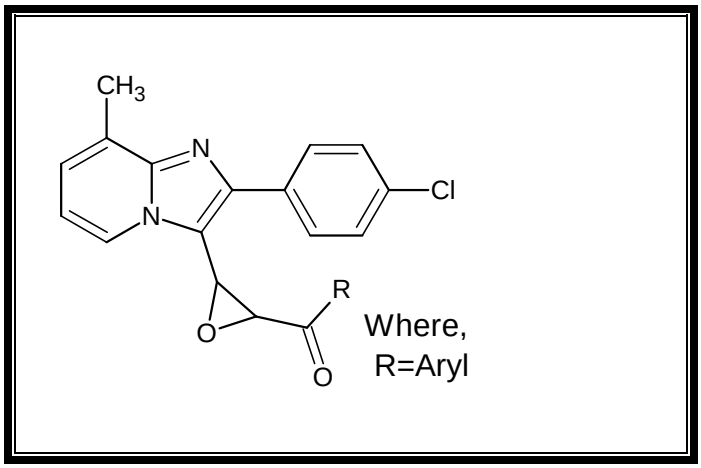
Isoxazole have been found to be associated with broad spectrum of biological activities like antibacterial, antifungal, insecticidal, anesthetic, analgesic and antidaibetic.



Isoxazole derivative synthesized by the reaction of (2Z)-3-[2-(4-chloro phenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one and hydroxyl amine hydrochloride in ethanol containing sodium hydroxide was refluxed for 11hrs, the product was isolated by pouring the alcoholic solution on to crushed ice, then filtered, dried it.

**PART-VI : SYNTHESIS OF (3-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*- IMIDAZO [1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL) ARYL METHANONE.**

Oxirane derivatives have been reported to possess various pharmacological activities like antibacterial, antifungal etc. In order to achive better potency, we have synthesized oxirane derivatives.




Oxirane or Epoxide derivatives synthesized by the reaction of (2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-arylprop-2-en-1-one in mixture of acetone and methanol with 8% aqueous sodium hydroxide followed by addition of 30% hydrogen peroxide, the solution was shaken and heated to the boiling point for 1h, then allowed to stand overnight at room temperature, then water was added in the solution was extracted with ether. The ether layer was evaporated to give Epoxide derivative compound.

The reaction monitoring of the all compounds done by thin layer chromatography using two different solvent systems **($Rf_1$ & $Rf_2$)**.The constitution of newly synthesized compounds have been delineated by **elemental analysis, FT-IR, $^1$H NMR** and **Mass spectroscopy.**

The compounds have been screened for their ***in vitro*** therapeutic assay like antibacterial activities towards ***Gram positive*** and ***Gram negative*** bacterial strain and antifungal activity towards fungal strain at different concentration (**Minimum Inhibitory Concentration).**The biological activities of synthesized compounds have been compared with standard drugs at different concentrations.

# *"STUDIES ON SOME HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST"*

## GENERAL INTRODUCTION

### (A) Drug

The word drug is derived from the French word “drogue” which means ‘a dry herb’. It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease. This disease oriented definition of drug does not include contraceptives or use of drugs for improvement of health. 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 as pathological status for the benefit of the recipient”.

### (B) Pharmacology

Pharmacology is the science of drugs. In a broad sense, it deals with interaction of exogenously administered chemical molecules (drugs) with living system. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purposes. For thousands of years most drugs were crude natural products of unknown composition and limited efficiency. Only the over effects of these substances on the body were rather imprecisely known, but how the same were produced was entirely unknown. Over the past 100 years or so, drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs has been developed. The two main divisions of pharmacology are pharmacodynamics and pharmaco kinetics.

**(a) Pharmacodynamics:** It is derived from the Greek word “dynamic” means Power. What the drug does to the body ? This includes physiological and biochemical effects of drugs and their mechanism of action at macromolecular / sub cellular organ systems.

**(b) Pharmacokinetics:** It is derived from the Greek word 'Kinesis' means movement. What the body does to the drug? This refers to movements of the drug in and alternation of the drug by the body; includes absorption, distribution, binding / localization / storage, biotransformation and excretion of the drug.

Some other important aspects of pharmacology are given as under :

- **Pharmacotherapeutics :** It is the application of pharmacodynamics information together with knowledge of the disease for its prevention, mitigation or cure.

- **Clinical Pharmacology:** It is the scientific study of drug in man. It includes Pharmacodynamics and pharmacokinetic investigation in healthy volunteers and in patients; evaluation of efficiency and safety of drugs and comparative trials with other forms of treatments; surveillance of patterns of drug uses, adverse effects, etc.

- **Chemotherapy :** It is the treatment of systemic infection/malignancy with specific drugs that have selective toxicity for the infecting organism/malignant cell with less effect on the host cells.

Drugs in general, can thus be divided into :

- **Pharmacodynamic agents :** These are chemical substances designed to have pharmacodynamics effect in the recipient.
- **Chemotherapeutic agents :** These are chemical substances designed for the treatment of infectious diseases or by the proliferation of malignant cells.

**(c) Essential Drug Concept :** The 'WHO' has defined Essential Drugs as "those that satisfy the healthcare needs of majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage form". It

has been realized that only a handful of drugs out of the multitude available can meet the health needs of majority of the people in any country, and that may be well tested and cheaper drugs are equally (or more) efficient and safe as their newer more expensive congeners. For optimum utilization of resources, governments (specially in developing countries) should concentrate on these drugs by identifying them as Essential Drugs. The “WHO” has laid down criteria guide

**Selection of an essential drug:**

(I) Adequate data on its efficiency and safety should be available from clinical studies.

(II) It should be available in a form in which quality, including bioavailability, and stability on storage can be assured.

(III) Its choice should depend upon pattern of prevalent diseases; availability of facilities and trained personnel; financial resources; genetic, demographic and environmental factors.

(IV) In case of two or more similar drugs, choice should be made on the basis of their relative efficiency, safety, quality, price, availability and cost benefit ratio should be a major consideration.

(V) Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.

(VI) Most essential drug should be single compound. Fixed ratio combination products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage.

(VII) Selection of essential drug should be a continuous process which should take into account the changing priorities for public health action, epidemiological condition as well as availability of better drugs/ formulations and progress in pharmacological knowledge.

**(C) Drug Development**

Many natural products by trial and error, came into practice for combating Human ailments existent during early human observation. With the advent of modern scientific approach, various plant medicines came under chemical scrutiny, ultimately leading to the isolation of active principles since early.

Such compounds either in extract form or in pure form became a part of pharmacopoeias. For instance, though the Chinese drug, Mauhang was in use for over 5000 years for the treatment of various types of fever and respiratory ailments, its active principle, Ephedrine was isolated in 1887. In 1925 chemical investigations followed by pharmacological evaluation led this compound into the modern medicine. Similarly during this period, urea stibamine was introduced as the first drug in 1920 for the treatment of Kala-azar. In 1930, De Rauwolfia preparations were first employed for sedative and hypotensive properties.

A drug is a substance having abnormal effect on certain body functions eg. Strychnine stimulates the action of heart and aspirin retards its action. Since both of them effects abnormally, the two substances are known as drugs. Chemical sciences contributed extensively new discoveries leading to useful drugs since after 1930.

The modern concept of drug discovery started in 1933 by Gerhand Domagk with his finding of **"Prontosil Red"**, a compound responsible for the antibacterial activity. The advent of **sulphonamides** drew the attention for the different activities of various chemicals for bacterial and human cells, this important factor prompted Florey and Chain in 1939 to investigate **penicillin** which was discovered ten years earlier by Alexander Fleming. The spectacular chemotherapeutical properties of penicillin and its dramatic war-time development for the treatment of wounds made **penicillin,** a most commonly used inexpensive drug.

A large number of important drugs have been introduced during the period of 1940 to 1980. This period is known as “Golden period” of new drug discovery. Thus starting from 1933 - the first antibacterial drug **prontosil** leading to various sulpha drugs ; 1940 - **penicillin** ; 1945 - **chloroquine** - antimalarial ; 1950 **Methyldopa** - anti-hypertensive; 1967 - **chlorothiazine -** diuretic ; 1958 adrenergic beta blockers coronary vasodilatory; 1960 - semi synthetic **penicillin**-antibacterial ; 1965 – **trimethoprim** - antimicrobial ;1967 **disodium chromoglycoate** -antiallergic; 1972 - **cimetidine** $H_2$ -antagonist; 1975 - **verapamil** - calciumantagonist and 1981 - **captopril** - antihypertensive. There are some specific examples representing new therapeuticagent eg. **Metormine, glipizide** antidiabetic.

**(D) Latest Drug Developments**

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

Today, the chief source of agents for the cure, the mitigation or the prevention of diseases are the organic compounds, natural or synthetic, together with so called organometallics. Such agents have their origin in a number of ways (a) from naturally occurring materials of both plant and animal origin, and (b) from the isolation of organic compounds synthesized in laboratory whose structures are closely related to those of naturally occurring compounds for eg.**atropine, steroids, morphine, cocaine** etc. that have been known to possess useful medicinal properties.

The process of drug design is extensively driven by the instinct and experience of pharmaceutical research scientists. It is often instructive to attempt to "capture" these experiences by analyzing the historical record that are successful drug design projects of the past. From this analysis, the inferences are drawn which play an important role in shaping our current and future projects. Towards this region, we would like to analyse the structures of a large number of drugs – 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.

Different kinds of drugs are developed for different types of diseases *viz*. which can be defined with their names of the modern drugs are as under.

**(a) Anticancer drugs**

The drugs, which stop the abnormal growth of cell tissues in human body, are termed as anticancer drug. **Vinblastin** and **Busulphan** are the novel anticancer drugs.

**(b) Hepatoprotective drugs**

Drug, which gives vitality to liver and protects liver by giving immunity power against antibodies, are termed as Hepatoprotective drug.

**(c) Antimalarial drugs**

Drug, which kills the plasmodium causing malaria are called antimalarial drug. Combination of **Sulphamethoxazole** with **Pyrimethamine** is a novel antimalarial drug.

**(d) Drug for meningitis**

Drugs, which cures the inflammation of meningitis, are termed as meningitis drugs **Cifalexin** is a novel meningitis drug.

**(e) Drug for typhoid**

Drugs, which kills the bacteria of Salmonella typhi causing typhoid, are known as typhoid drugs. A novel drug for typhoid is **Ciprofloxacin.**

**(f) Antidiabetic drugs**

Drugs, which converts the excess glucose of blood into glycogen are termed as antidiabetic drugs. Novel antidiabetic drugs are **Metformin** and **Glipizide.**

**(g) Antitubercular drugs**

Drugs, which kills the bacteria of mycobacterium tuberculosis and thus cures lesions of pleural cavity. An antitubercular drug is **Ethambutol**.

**(h) Antiasthamatic drugs**

Drugs, which prevents the attack of asthama and gives relax respiration are called antiasthamatic drugs. Novel antiasthamatic drugs are **Ethophylline, Theophylline** and **Asmon**.

**(i) Antihypertensive drugs**

Drugs, which normalizes the blood pressure by dilating blood vessels are called antihypertensive drugs. Novel antihypertensive drugs are **Atenolol, Amlodipine** and **Nifedipine.**

**(j) Anti-AIDS drugs**

Drugs, which kills the viruses of AIDS **i.e**., *HIV-1* and *HIV*-2 are called anti-AIDS drugs. Novel drugs are **Zidovudine, Acyclovir** and **Didanosine**.

**(k) Antacid drugs**

Drugs, which neutralize the acid in stomach and stops excessive secretion of acid, are called antacid drugs. Novel antacid drugs are **Omeprazole** and **Lansoprazole.**

**(l) Non steroidal anti-inflammatory drugs (NSAID)**

Drugs, which gives relief from fever, pain and inflammation are called NSAID. Novel NSAID are **Pyroxicam**, **Meloxicam** and **Nimesulide.**

Different kind of drugs generally used are designed as anesthetic,antiviral, antibacterials,antifungal,antianxiety,antiinflammatory,analgesic,antipyretic,antiulcer and hypnotics which prompted us to synthesis drugs having **Imidazo[1,2-*a*]pyridine** moieties as a better therapeutic activity.

**AIMS & OBJECTIVES**

Aims and objectives of the present investigation are:

(a) To generate several Chalcone,Pyrimidine,Isoxazole,Pyrazoline,Cyclohexinone, Oxirane derivatives bearing Imidazo[1,2-*a*]pyridine moiety.

(b) To characterize these products for their structural assignment using various Spectroscopic techniques like IR, $^{1}$H NMR and Mass spectroscopy.

(c) To screen these new derivatives for their antimicrobial activity using different Strains of bacteria and fungi and to compare antimicrobial activity with different known drugs at different concentrations for their MIC values.

In view of these facts, the research work presented in thesis are as follows.

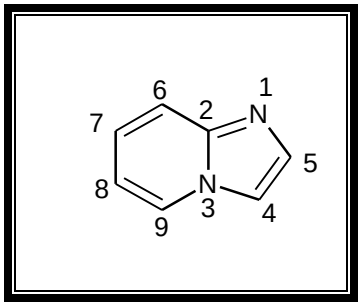
**STUDIES ON IMIDAZO[1,2-*a*]PYRIDINE**

**Part-I : STUDIES ON CHALCONES**
**Part-II : STUDIES ON PYRIMIDINES**
**Part-III : STUDIES ON CYCLOHEXINONES**
**Part-IV : STUDIES ON PYRAZOLINES**
**Part-V : STUDIES ON ISOXAZOLES**
**Part-IV : STUDIES ON OXIRANES**

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

## INTRODUCTION

The aza-indolizine contains a phenyl ring fused to a imidazole ring as indicated in the structure, hence it is also known as imidazo[1,2-*a*]pyridine.[1] The constitution of imidazo[1,2-*a*]pyridine was represented by W.L.Mosby.[2]




The group of compound containing imidazo[1,2-*a*]pyridine moiety are prominent structural feature in a variety of natural products as well as in other compounds of medicinal interest and have attracted attention for their biological activities.

## SYNTHETIC ASPECT

Classical approaches of imidazo[1,2-*a*]pyridine involving different type of reaction has been described as under:

(i) Reaction of (arylacetyl) imidazoles with acetylnedicarboxylic esters.[3]

(ii) Reaction of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogen.[4]

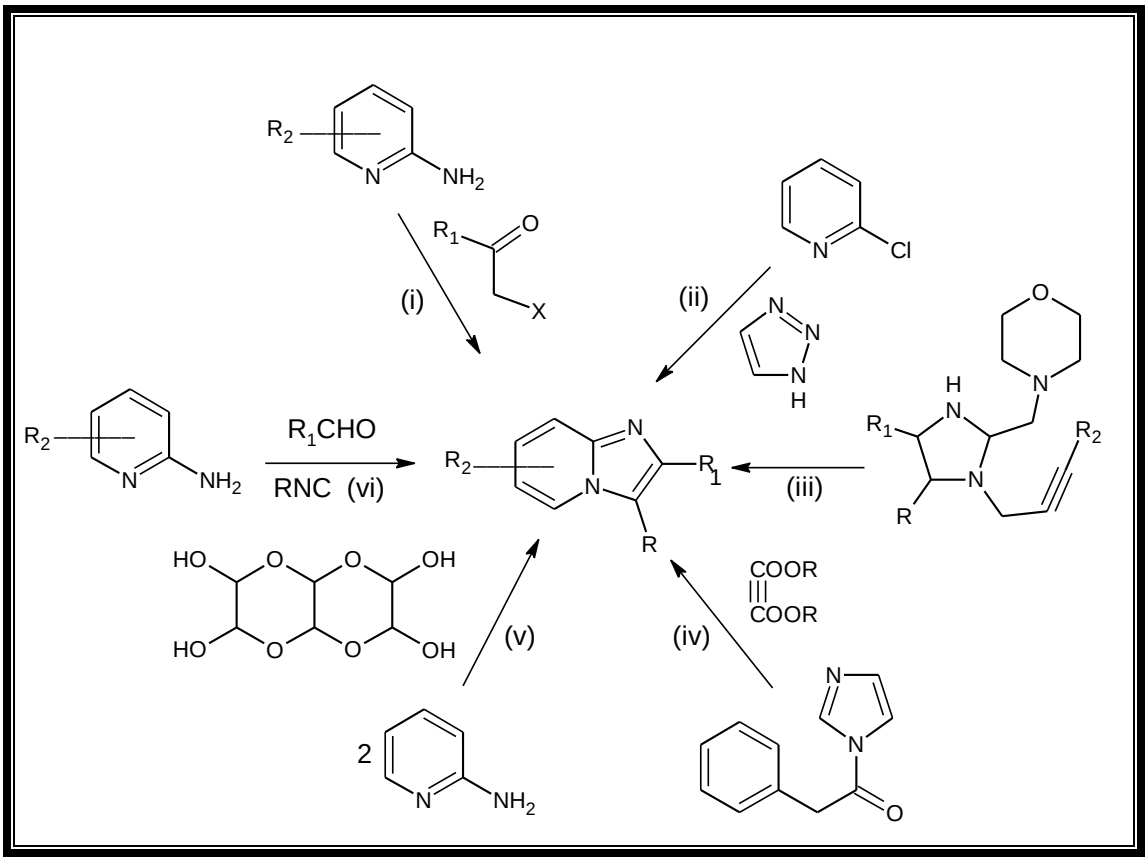
(iii) Cyclizations of 1-(2-alkynyl)-2-aminomethylimidazoles,which are obtained from substituted via six steps.[5]

(iv) Coupling reaction of 2-aminopyridines with α-halo carbonyl compounds.[6,7]

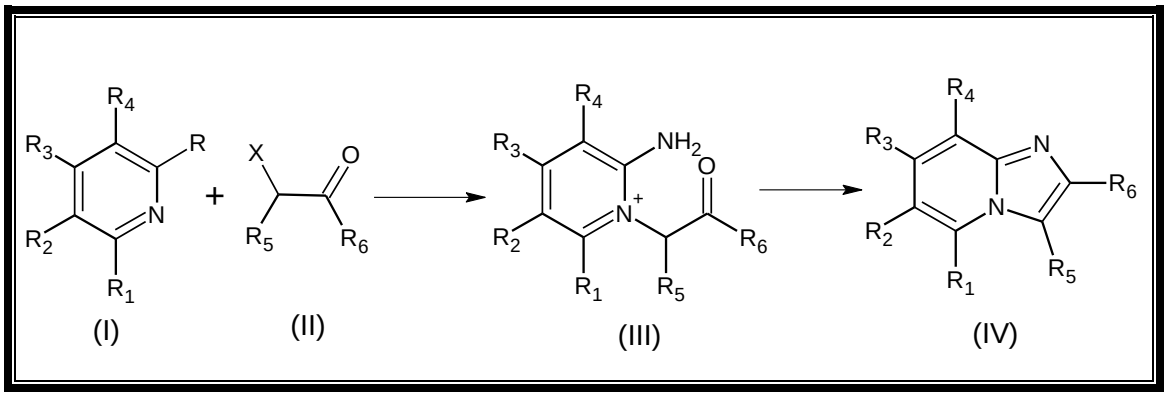
(v) Condensation of 2-aminopyridine with global trimer dehydrate in aqueous $NaHSO_3$.[8]

(vi) One-pot condensations of aldehydes, isonitriles,and 2-aminopyridines.[9]

Moreover, methods ( i ) and ( vi ) are also used for the preparation of imidazo [1,2-*a*]pyrimidines.[10,]




**MECHANISM**



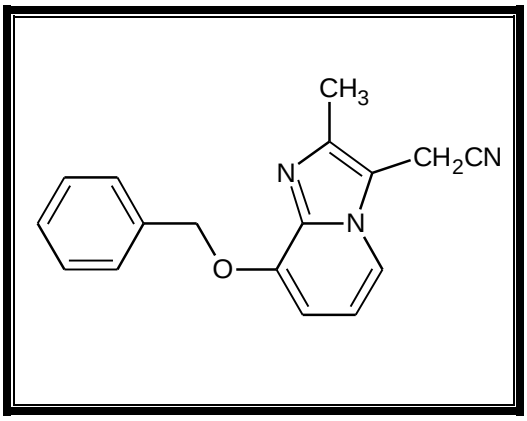

The majority of imidazo[1,2-*a*]pyridine (IV) have been prepared by the reaction of a 2-aminopyridine (I) with a *α* -halo carbonyl compound (II) gives form (III). Which is further cyclize at room temperature and gives imidazo[1,2-*a*]pyridine.

## PHARMACEUTICAL IMPORTANT

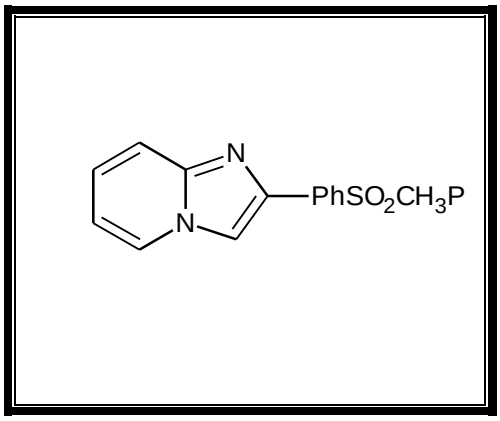
Much research has been carried out with the aim to finding therapeutic value of aza-indolizine moiety since their discovery. A large number of substituted aza-indolizine derivatives are prepared and tested for variety of biological activities.

1. Gastric antisecretory[12,13]
2. Local anesthetic[14]
3. Antiviral[15,16]
4. Hypnotic[17]
5. Antianxiety[18]
6. Antibacterials[19,20]
7. Antifungal agents[21]
8. Calcium channel blockers[22]
9. Antiherputic activity[23, 24]
10. Antiinflammatory,analgesic,antipyretic[25, 26]
11. Antiulcer[27]
12. Hypnoselective and anxioselective activities[28]
13. $\alpha$–Amyloid formation inhibitors[29]
14. Active nonpeptide bradykinin $\beta_2$ receptor antagonists[30]
15. Nonsedative antioxytic[31]
16. Benzodiazepine receptor agonists[32]
17. Anticytomegalo-zoster and antivaricella-zoster virus[33-35]
18. Cardiotonic agents[36]

James J. Kaminski and co-workers[37] had investigated the imidazo[1,2-*a*] pyridine derivatives 3-(cyanomethyl)-2-methyl-8-(phenylmethoxy) imidazo[1,2-*a*] pyridine Type-II as an antiulcer activity. On the basis of the reported metabolism of zolimidine.They reported that the 3-cynomethyl and 8-phenylmethoxy groups have been established as metabolic sites in Type-II.

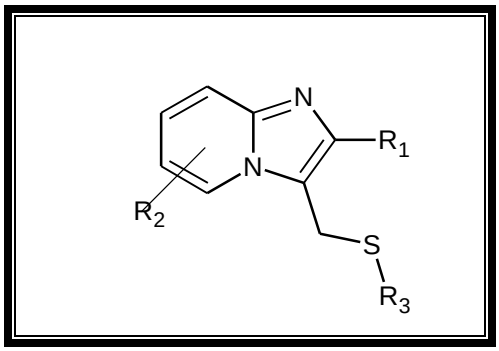



Type-II

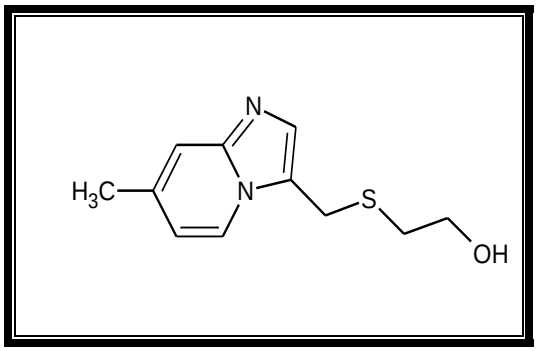



(Zolimidine)

Alain Gueiffier and co-worker[38] are reported the synthesis and the antiviral activities of C-3 acyclic nucleoside analogues of imidazo[1,2-*a*]pyridine and pyrimidine. In contrast, some derivatives in the imidazo[1,2-*a*]pyrimidines series were devoid of antiviral activity.[39] Some compounds showed a marked activity against cytomegalovirus and varicella-zoster virus. The most potent was Type-III (C), but this compound also showed marked cytotoxicity. Substantial antiviral activity again CMV was also noted for a,b,d,e, while compounds a, b and c proved to be active against VZV replication and they also synthesized 3-[[(hydroxyethyl)thio]methyl]-7-methyl imidazo[1,2-*a*]pyridine (Type-IV). Which shows antiviral activity against TK varicella-zoster virus.



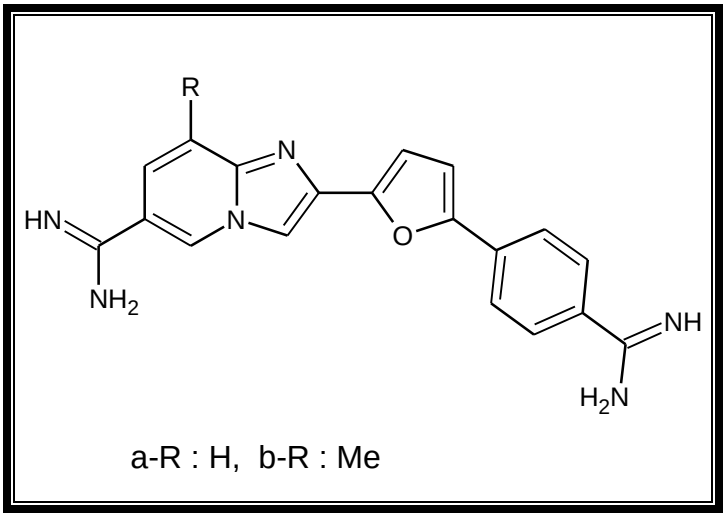

Type-III




Type-IV

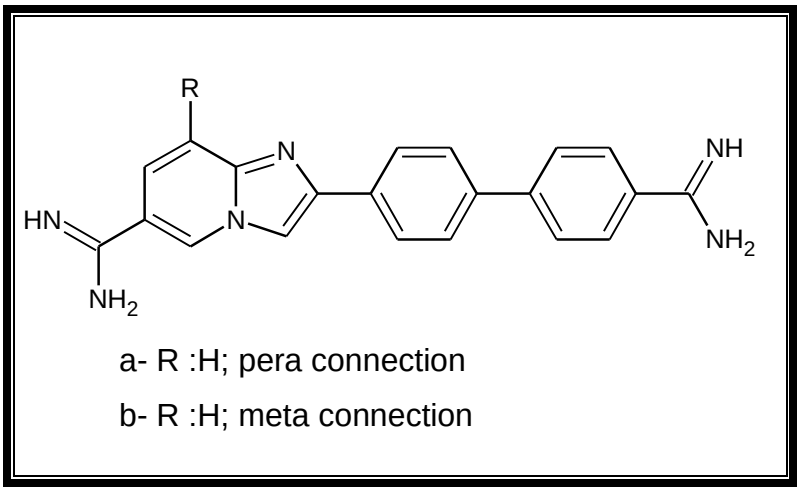
| Compd. | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a :- | H | 7-Me-6,8-$Br_2$ | $CH_2C_6H_5$ |
| b :- | H | 8-Me | $CH_2CH_3$ |
| c :- | H | 8-Me | $CH_2C_6H_5$ |
| d :- | H | 8-Me | $CH_2CH_2OH$ |
| e :- | H | 5,7-$Me_2$-6,8-$Br_2$ | $CH_2C_6H_5$ |

The imidazo[1,2-*a*]pyridine units appear as important building blocks in both natural and synthesis compounds.[41-43] Such alterations in structure offer the potential to change the base pair recognition on DNA binding and to yield different pharmacokinetics profiles. Mohamed A.Ismail[44] and co-workers synthesized some novel diamidino imidazo[1,2-*a*]pyridines like (Type-V) & (Type-VI) and 5,6,7,8-tetrahydro imidazo[1,2-*a*]pyridines and their corresponding *N*-hydroxy and *N*-methoxy analogues which are potential prodrugs for this series and their evaluation versus ***Trypanosoma b.rhodesiense (T.b.rhodesiense*)** and ***Plasmodium falciparum (P.falcipaarum)***. Aromatic diamidines exhibit broad-spectrum antimicrobial activity including effectiveness against the protozoan diseases caused by ***Trypanosoma sp*** and ***Plasmodium sp***.[45]




a-R : H, b-R : Me

Type-V

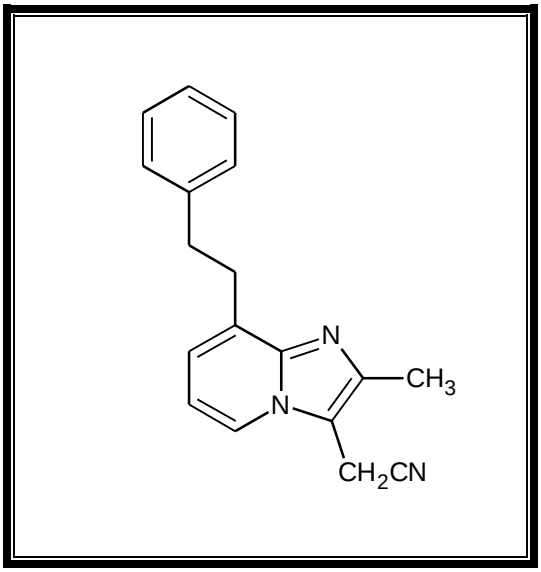



a- R :H; pera connection

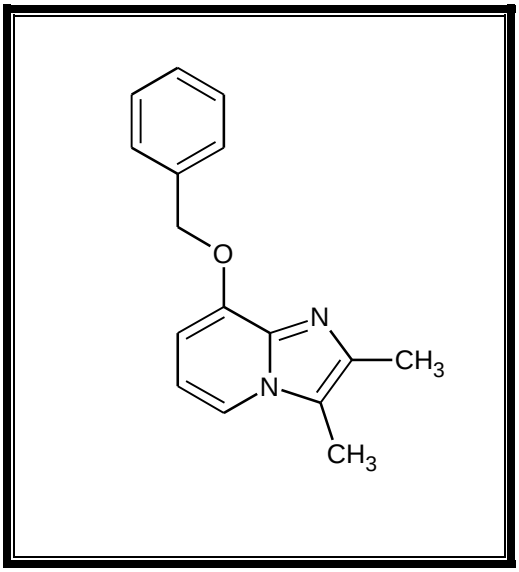
b- R :H; meta connection

Type-VI

James J. Kaminski and co-workers[46] had been synthesized some novel compounds such as 3-(cyanomethyl)-2-methyl-8-(2-phenylethyl) imidazo [1,2-*a*]pyridine (Type-VII) and 2,3-dimethyl-8-(phenylmethoxy)imidazo[1,2-*a*]pyridine (Type-VIII). Which shows Gastric-Antisecretory and Cytoprotective Properties.

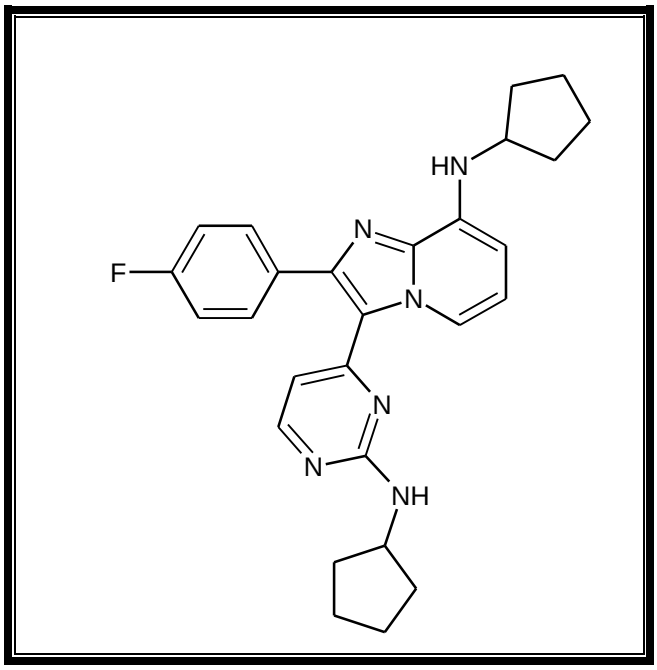



Type-VII




Type-VIII

S. Kristjan, Gudmundsson and A. Brain Johns[47] and A.Chaouni-Bendallah et al.[48] worked on synthesis of a novel imidazo[1,2-*a*]pyridine shown in Type-IX with potent activity against herpes simpex viruses.




Type-IX

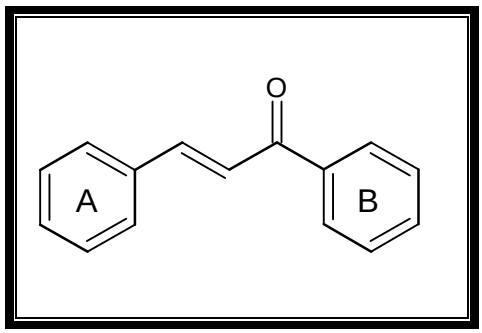
Thus the important role displayed by imidazo[1,2-*a*]pyridine and it's derivatives for various therapeutic and biological activities promoted us to synthesise some chalcone and acetylpyrazoline derivatives bearing imidazo[1,2-*a*] pyridine moiety in order to achive compounds having better activities.

# PART-I

# STUDIES ON CHALCONES

**STUDIES ON IMIDAZOPYRIDINE DERIVATIVE**

**INTRODUCTION**




Type-I

The chemistry of chalcones have generated intensive scientific studies throughout the world, specially interesting are their biological and industrial applications. Chalcones are coloured compounds because of presence of the chromophore and auxochromes.They are known as benzalacetophenones or benzylidene acetophenones. Kostanecki and Tambor[49] gave the name “Chalcone”. Chalcones are characterized by their possession of a structure in which two aromatic ring A and B are linked by an aliphatic three carbon chain.

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

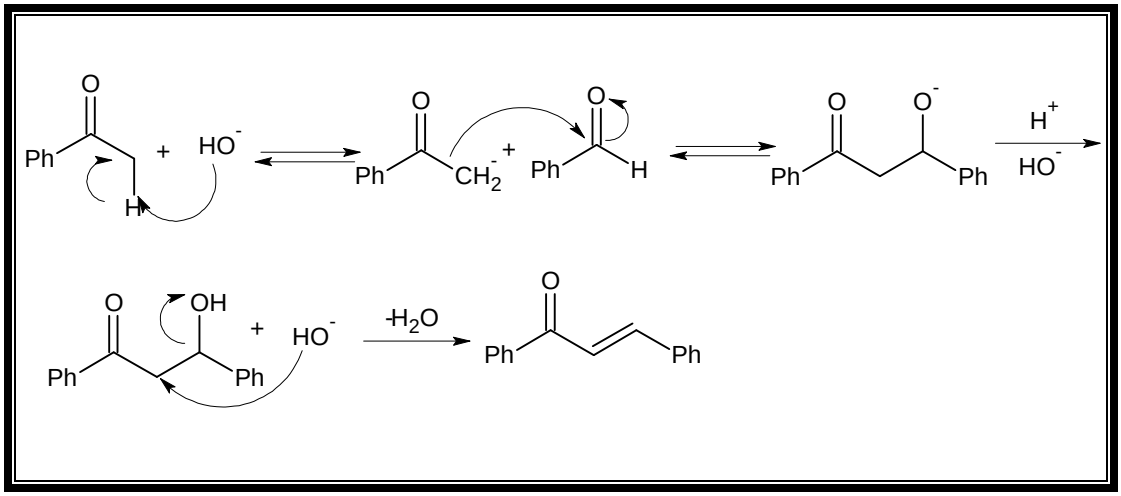
**SHYNTHETIC ASPECT**

A considerable variety of methods are available for the synthesis of chalcones. The most convenient method is the one that involves the Claisenschimdt condensation of equimolar quantities of an arylmethyl ketone with arylaldehyde in the presence of alcoholic alkali.[50]

Several condensing agents used are alkali of different strength[51,52] hydrogen chloride[53,54], phosphorous oxychloride[55], piperidine[56], anhydrous aluminium chloride[57], boron trifluoride[58], aq.solution of borax[59], amino acids[60], and perchloric acid[61] etc.

**MECHANISM**

Chalcone formation proceeds through Aldol type condensation and the process is catalysed by the presence of alkali.[62]Following are the steps of the reaction mechanism.




The intermediate Aldol type of products formed readily undergoes dehydration even under mild condition.

**REACTIVITY OF CHALCONES**

The chalcones have been found to be a very good synthone to form heterocyclic compounds are as under.

(a) Chalcones with monoethanolamine in ethanol gives 1,4-oxazepines.[63]

(b) Chalcones with 2-amino thiophenol in acetic acid produces 1,5-thiazepines.[64]

(c) Chalcones on reaction with semicarbazide hydrochloride in ethanol affords 1-carboxamide pyrazolines.[65]

(d) Chalcones on reaction with 2-aminopyridine in glacial acetic acid affords pyridopyrimidines.[66]

(e) Oxiran[67] can be prepared by the reaction of chalcone with $H_2O_2$ in basic media.

(f) Cynopyridone[68] derivatives can be prepared by the condensation of chalcone with ethyl cynoacetate.

(g) Chalcone on reaction with barbituric acid gave barbitone[69] derivatives.

(h) Chalcone give imine derivatives with amine in presence of sulfuric acid as catalyst.[70]

(i) Pyrazolines[71]and its derivative can prepared by the condensation of chalcones with hydrazine hydrate and acetic acid.

(j) Chalcones on condensation with malononitrile and ammonium acetate yields 2-amino-3-cyano pyridines.[72]

(k) Isoxazoles[73] can be prepared by the treatment of chalcones with hydroxylamine hydrochloride and sodium acetate.

(l) Chalcones on condensation with malononitrile in pyridine forms 2-amino-3-cyanopyrans.[74]

(m) Chalcones on treatment with urea in presence of alkali affords 2-oxopyrimidines.[75]

(n) Chalcones on treatment with thiourea in presence of alkali/acid yields 2-thienopyrimidines.[76]

(o) Chalcones on treatment with guanidine in presence of alkali affords 2-aminopyrimidines.[77]

(p) Chalcone reacts with sodium nitrile in presence of glacial acetic acid in ethanol produces 2-1*H*-pyrimidines.[79]

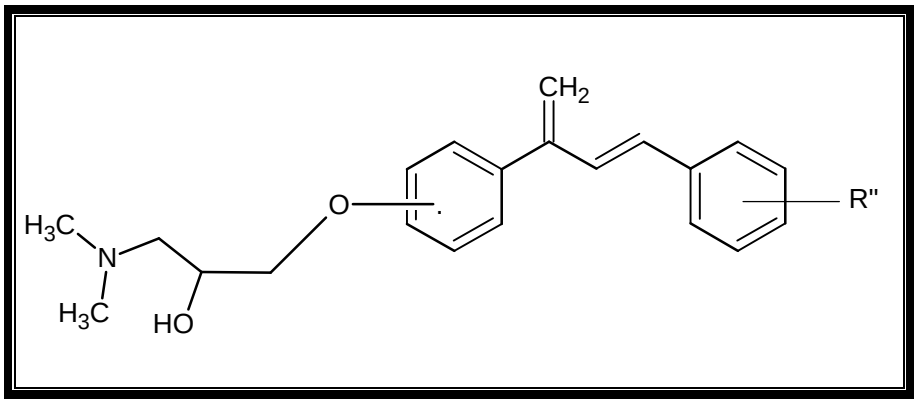
**THERAPEUTIC INTEREST**

Chalcones are potential biocides, some naturally occurring antibiotics and amino chalcones probably own their biological activity to the presence of *α*, *β* - unsaturated carbonyl group. Chalcone derivatives are associated with diverse biological activity.

1. Antiallergic[80]
2. Carboxygenase inhibitir[81]
3. Antitumor[82,83]
4. Antimalatial[84]
5. Anticancer[85]
6. Antieishmanial[86]
7. Insecticidal[87,88]
8. Antiulcer[89]
9. Antiinflammatory[90,91]
10. Bactericidal[92,93]
11. fungicidal[94,95]
12. antiviral[96]
13. Anthelmintics[97]

Recently, Ni Liming et al.[98] have synthesized chalcones and screened for their antiinflammatory and cardiovascular activity. Kumar Srinivas et al.[99] have synthesised chalcones as an antitumor agent. Ko horng-Huey et al.[100] have prepared chalcones as an antiinflammatory agent. Nakahara Kazuhiko et al.[101] have synthesised chalcones as carcinogen inhibitors. Antitubercular agents of chalcone derivatives have been prepared by Lin Yuh-Meei et al.[102] Ezico et al.[103] have demonstrated that chalcone possess a valuable antiproliferation activity both on sensitive cancereous cell and on cell which are resistant to common chemotherapeutic drugs.Some of the chalcones have been patented for their use for treatment of glueoma[104] and showed antifungal[105,106] aldose reductase inhibitores[107], anticancer[108] and antimicrobial[109,110] activities.

Das B.P. et al.[111] have found that chalcones possesses larvicidal properties. Kim Min-Young et al.[112] have synthesized chalcones and tested for their matrix metalloproteinase inhibitor activity. Satyanarayana M. et al.[113] have synthesised chalcone derivatives as antihyperglycemic activity (Type-II)

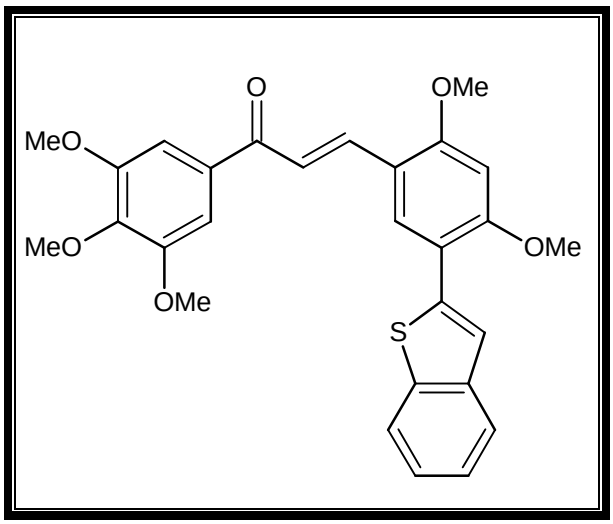



Type-II

Moreover, synthesis and antibacterial activity of substituted chalcone derivatives have been reported by Modi et al.[114] and Attia A.[115], V. Mudalir et al.[116] have prepared phenoxy chalcones and observed their insecticidal activity, Kammei et al.[117] have synthesised chalcone derivatives having antitumor activity. De Vincenzo et al.[118] and Han et al.[119] have reported chalcone derivatives for their antiinflammatory activity.

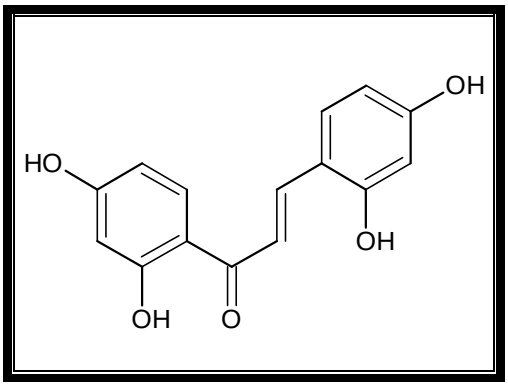
Aldose reductanse inhibitor activity of chalcone derivatives have been reported by Okuyama et al.[120] Chalcones are also associated with antitumor and antifungal activity as reported by A. Tsotitns and co-worker.[121] Antifeedant activity of chalcones have been observed by Sarma and Sreenivasulu.[122] Liu Mei et al.[123] have prepared antimalarial chalcones. Opletalova Veronika et al.[124] have synthesised chalcones and screened as cardiovascular agents. Moreover, it has been found that chalcone derivatives possesses nitric oxide inhibitor[125,126] anti *HIV*[127,128] and antiproliferative[129,130] activities.

Meng C.Q.et al.[131] discovered of novel heteroaryl substituted chalcones as inhibitors of TNF-alpha-induced VCAM-1 expression (Type-III).



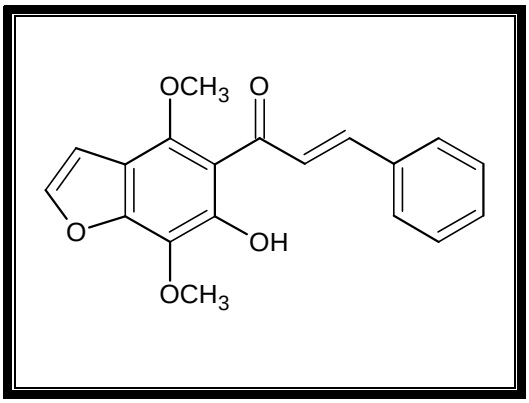

Type-III

Moreover, Khatib S.et al.[132] synthesized some novel chalcones as potent inhibitors (IV). Ko H.H. et al.[133] have prepared some new chalcones as potent inhibition of platelet aggregation. Ziegler HL, et al.[134] reported some new chalcones as antiparasitic. Go ML,et al.[135] have described the synthesis and biological activities of chalcones as Antiplasmodial. Xue CX et al.[136] synthesized as antimalarial agents. Fu Y et al.[137] have synthesized Licochalcone-A Type-IV.




Type-IV

Furthermore, Alcaraz M.J, et al.[138] have described the role of nuclear factor-kappa $\beta$ and heme oxygenase-1 in the mechanism of action of anti-inflammatory chalcone derivative in RAW 264.7 cells. Nerya O et al.[139] have prepared some new Chalcones as potent tryosinase inhibitors.




Type-V

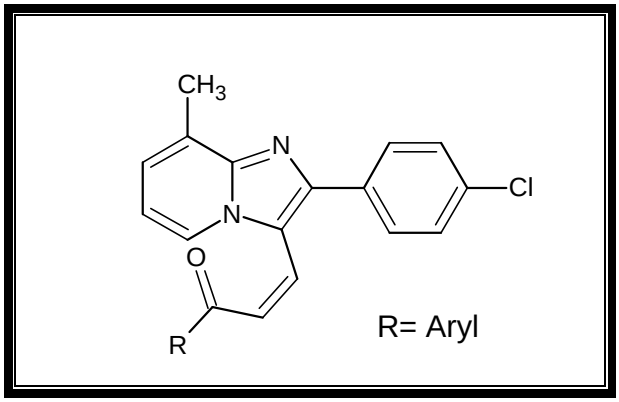
Sabzevari O. et al.[140] have constructed some new chalcone derivatives as Molecular cytotoxic mechanism of anticancer hydroxy chalcones (Type-V).

Recently, Ban H.S. et al.[141] synthesized some novel chalcones as inhibition of lipopolysaccharide-induced expression of inducible nitric oxide synthesis and tumor necrosis factor-alpha by 2'-hydroxychalcone derivatives in RAW 264.7 cells. Hollosy F.et al.[142] have prepared some new chalcones as Plant-derived protein tyrosine kinase inhibitors as anticancer agents.

Chalcone beaing a very good synthon variety of novel heterocycles with good pharmacological profile can be designed. These valid observation led us to explore chalcone chemistry by synthesising several derivatives like pyrazolines, cyanopyridines, cyanopyridones, cyclohexenones, indazoles and aminopyrimidines bearing different heterocyclic ring systems for medicinal value, in order to achieving better therapeutic agents, this study described as under.

**SYNTHESIS AND THERAPEUTIC EVALUTION OF (2Z)-3-[2-(4-CHLOROPHENYL) -8-METHYL IMIDAZO[1,2-*a*]PYRIDINE-3-YL]-1-ARYL PROP-2-EN-1-ONE.**

Chalcone derivatives have been found to be associated with various pharmacological activities. These finding encouraged as to synthesize, some new novel synthesis. (2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one derivatives Type-I synthesized by the condensation of 2-(4-chlorophenyl)-6-methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde with various substituted ketone in methanol.

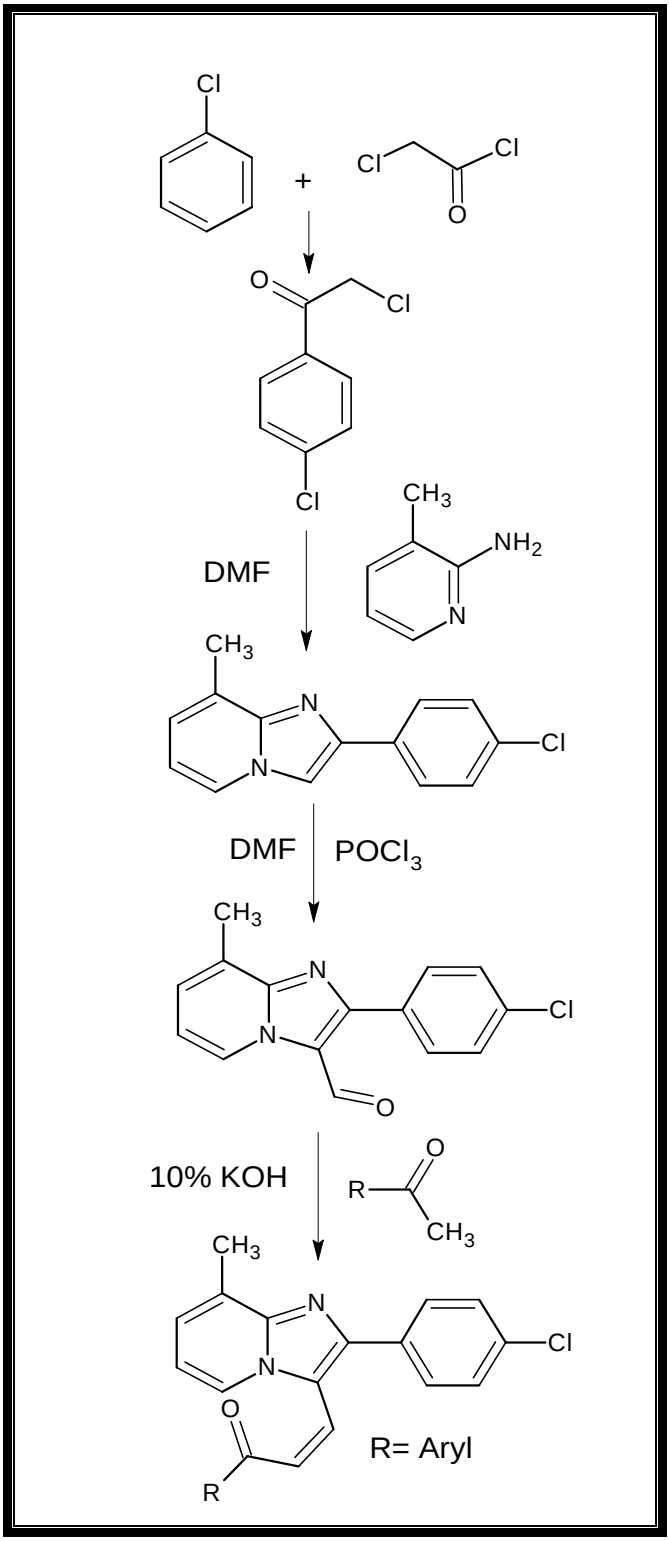



Type-I

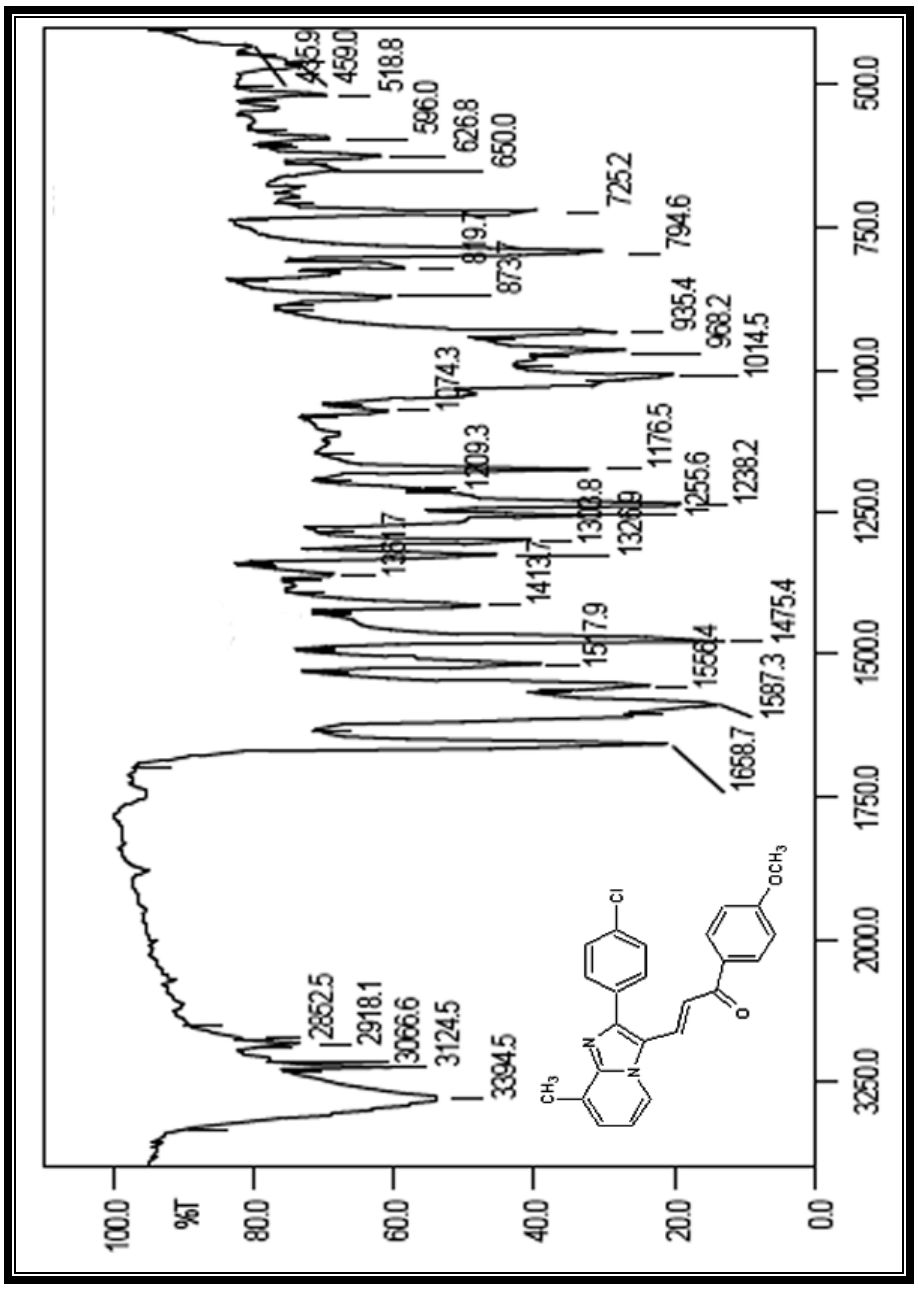
The constitution of the synthesized products have been characterized by using elemental analyses, infrared and $^{1}$H-nucleur magnetic resonance spectroscopy and further supported by mass spectroscopy.

All the products have been screened for their ***in vitro*** biological assay like antimicrobial activity towards ***Gram positive*** and ***Gram negative*** bacterial strains and antifungal activity toward ***Aspergillus niger*** at a concentration of 40µg/ml.The biological activities of the synthesized compound were compared with standard drugs. The detail have been cited in Part-I Experimental - (E).

## REACTION SCHEME



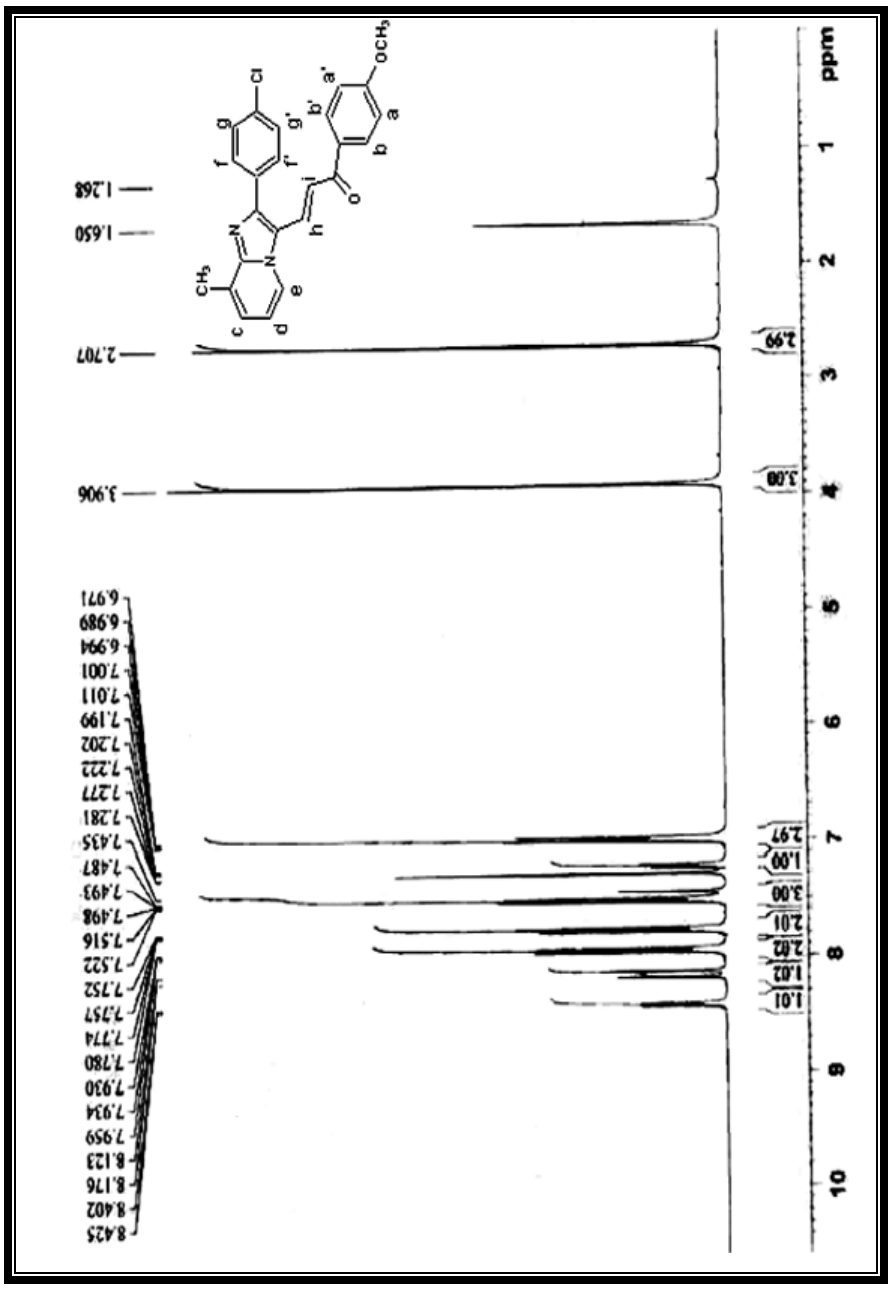
**IR SPECTRAL STUDIES OF (2Z)-3-[2-(4-CHLOROPHENYL)-8-METHYL IMIDAZO[1,2-*a*]PYRIDINE-3-YL]-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2918 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2852 | 2880-2860 | " |
| | C-H i.p.def | 1475 | 1470-1435 | " |
| | C-H o.o.p.def. | 1361 | 1395-1370 | " |
| Aromatic | C-H str. | 3066 | 3090-3030 | 143-b |
| | C=C Str. | 1517 | 1520-1480 | " |
| | C-H i.p.def | 1014 | 1070-1000 | " |
| | C-H o.o.p.def. | 819 | 835-810 | " |
| Moiety | C=N str. | 1587 | 1610-1590 | 143-c |
| | C-N str. | 1176 | 1230-1020 | " |
| | C-Cl str. | 795 | 800-750 | " |
| Chalcone | C=O str. | 1658 | 1700-1640 | 143-d |
| | CH=CH- str. | 1640 | 1644-1618 | " |

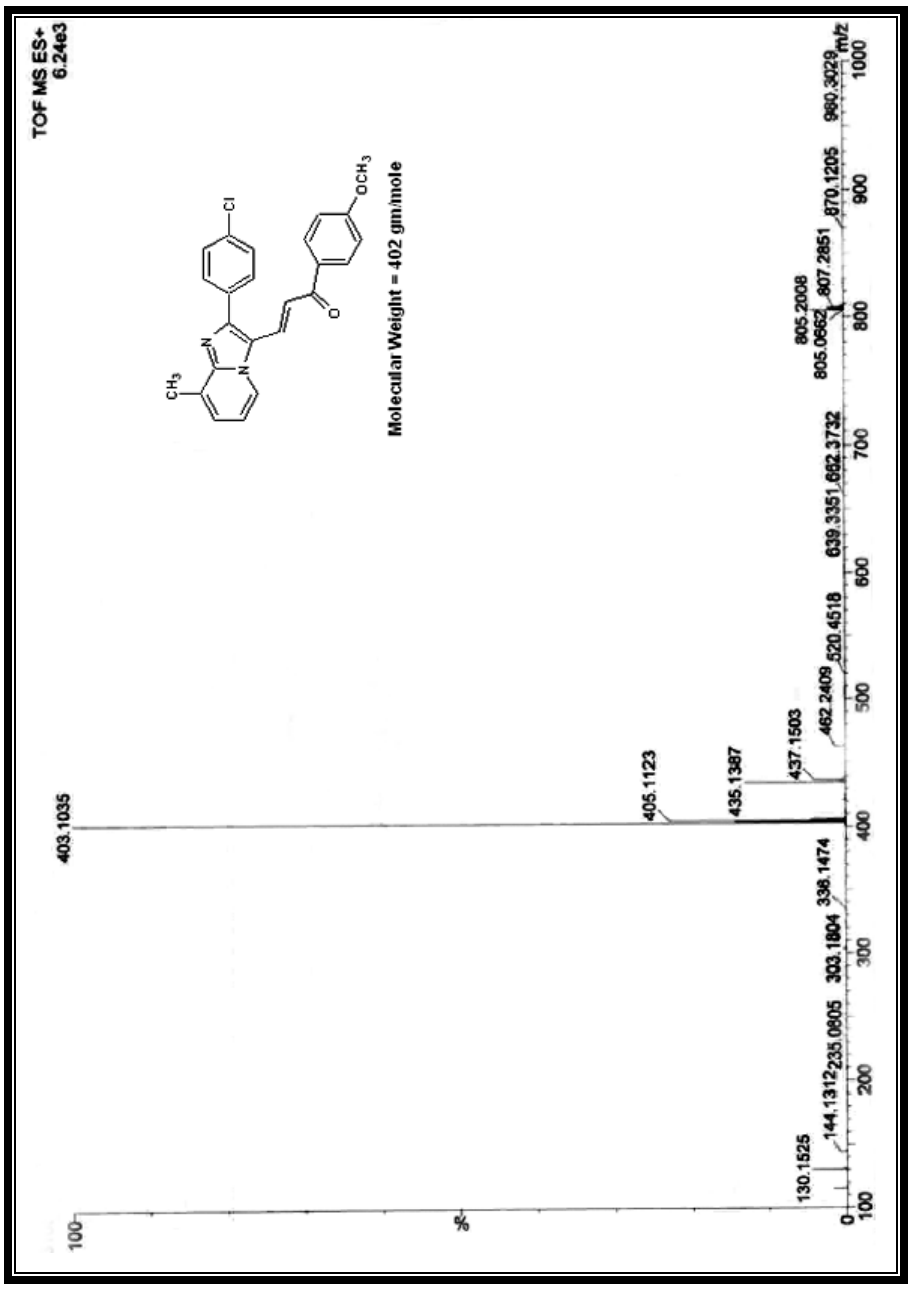
**NMR SPECTRAL STUDIES OF (2Z)-3-[2-(4-CHLOROPHENYL)-8-METHYL IMIDAZO[1,2-*a*]PYRIDINE-3-YL]-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.70 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.90 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 7.55 | 2H | doublet | Ar-H(b,b') |
| 4 | 7.00 | 1H | triplet | Ar-Hd |
| 5 | 6.97 | 2H | doublet | Ar-H(a,a') |
| 6 | 7.55 | 1H | doublet | Ar-Hi |
| 7 | 7.95 | 2H | doublet | Ar-H(f,f') |
| 8 | 8.15 | 1H | doublet | Ar-Hh |
| 9 | 7.75 | 2H | doublet | Ar-H(g,g') |
| 10 | 7.27 | 1H | doublet | Ar-Hc |
| 11 | 8.43 | 1H | doublet | Ar-He |

**MASS SPECTRAL STUDIES OF (2Z)-3-[2-(4-CHLOROPHENYL)-8-METHYL IMIDAZO[1,2-*a*]PYRIDINE-3-YL]-1-(4-METHOXYPHENYL)PROP-2-EN-1-ONE.**



## ANTIMICROBIAL ACTIVITY

| | | |
|---|---|---|
| Products | : | Chalcones |
| Method | : | Cup-plate |
| Gram positive bacteria | : | *Staphylococcus aureus* |
| | | *Bacillus coccus* |
| Gram negative bacteria | : | *Pseudomonas* |
| | | *E. coli* |
| Fungi | : | *Aspergillus niger* |
| Concentration | : | 40µg |
| Solvent | : | Dimethyl formamide |
| Standard drug | : | Ampicillin, Amoxicillin, Ciprofloxacin, Norfloxacin, Greseofulvin. |

The antimicrobial activity was compare with standard drug *viz* ciprofloxacin, Amoxicillin, Benzyl-penicillin and antifungal activity was compared with *viz* greseofulvin. The zone of inhibition were measured in mm.

All the compounds have been evaluated for antimicrobial activity using Cup-plate agar diffusion method at a concentration of 40µg using DMF as a solvent against different strains of bacteria and fungi as describe in experimental (E).

## EXPERIMENTAL

**Synthesis of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-(4-methoxyphenyl)prop-2-en-1-one.**

**[A] Preparation of 2-chloro-1-(*p*-chlorophenyl)ethanone.**

A mixture of chlorobenzene (1.13gm,0.01m) and di-chloromethane is maintain at 0 °C, then add anhydrous $AlCl_3$ (1.8gm,0.01m) and Chloracetyl Chloride (1.13gm, 0.01m) Stirred reaction mixture at 20 °C for about 10 hrs. Finally pour the reaction mixture on crushed ice then add cons. HCl and solid product was isolated with help of di-chloromethane and wash with petrolium ether. Yield 85% (1.60gm) ; m.p.95 °C ; ($C_8H_6Cl_2O$ ; Found : C,50.90%;H,3.25%; Required : C,50.83%;H,3.20%)

TLC solvent system : Ethyl acetate : Hexane ( 3:7)

**[B] Preparation of 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine**

A mixture of 2-chloro-1-(*p*-chlorophenyl)ethanone (1.89gm,0.01m) and 2-amino-3-methyl pyridine (1.08gm,0.01m) in DMF was refluxed at 140 °C for about 6 hrs. Finally pour the reaction mixture on crushed ice then solid product was isolated and purified by methanol. Yield 83% (2.0gm) ; m.p.150 °C ; ($C_{14}H_{11}N_2Cl$ ; Found : C,69.39%;H,4.65%;N,11.62% ; Required : C,69.28%;H,4.57%;N,11.54%)

TLC solvent system : Ethyl acetate : Hexane ( 2:8)

**[C] Preparation of 2-(*p*-chlorophenyl)- 8- methyl imidazo[1,2-*a*]pyridine- 3-carbaldehyde.**

A compound 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine (2.43gm, 0.01m) was added in a mixture et Vilsmeire-Haack reagent (prepared by dropwise addition of 3.27ml $POCl_3$ in ice cooled 27ml DMF) and refluxed for 6 hrs.

The reaction mixture was poured on to crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from DMF. Yield 80% (2.34gm) ; m.p.179 °C ; ($C_{15}H_{11}N_2OCl$ ; Found : C,66.63%;H,4.18%; N,10.43 ; Required : C,66.55%;H,4.10%;N,10.35%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

**[D] Preparation of (2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine -3-yl]-1-(4-methoxyphenyl)prop-2-en-1-one.**

A mixture 2-(4-chlorophenyl)-8-methylimidazo[1,2-*a*]pyridine-3-carbaldehyde (2.70gm,0.01m) and 1-(4-methoxyphenyl)ethanone (1.50gm,0.01m) was refluxed in methanol for 6 hrs. NaOH is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 75% (3.01gm) ; m.p. 189 °C ; ($C_{24}H_{19}N_2O_2Cl$; Found : C,71.29%;H,4.52%;N,6.69% ; Required : C,71.55%;H,4.75%;N,6.95%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Chalcone derivatives have been obtained. The physical data are recorded in Table No.- 1(B).

**[E] Antimicrobial activity of (2Z)-3-[2-(4-chlorophenyl)-8-methyl imidazo [1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one.**

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

**(a) Antimicrobial activity**

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

**(I) Antibacterial activity**

The purified products were screened for their antimicrobial activity. The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of ***B.cocus, S.aureus, Pseudomonas*** and ***E.coli*** in separate conical flask at 40-50 °C and mixed well by gentle sacking. About 25ml content of the flask were poured and evenly spreaded in a petridish (13mm in diameter) and allowed to set for 2 hrs. The cups (10mm in diameter) were formed by the help of borar in agar medium and filled with 0.04ml (40mg) solution of sample in DMF.

The plates were incubated at 37 °C for 24.0 hrs. and the control was also maintained with 0.04 mole of DMF in a similar manner and the zones of inhibition of bacterial growth were measured in millimeter.

**(II) Antifungal activity**

***A.Niger*** was employed for testing antifungal activity using cup-plate method. The culture was maintained on Subouraud's agar slants. Steriled Subouraud's agar medium was inoculated with 72 hrs. Old 0.5ml suspension of fungal spores in a separate flask.

About 25ml of inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in diameters) were punched in petridish and loaded with (0.04gm) of solution of sample in DMF. The plates were incubated at 30 °C for 48 hrs. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled with solvent which act as control. The zones of inhibition are recorded in Table No.- 1(A).

**TABLE NO.- 1A BIOLOGICAL SCREENING OF (2Z)-3-[2-(4-CHLOROPHENYL) -8-METHYL IMIDAZO[1,2-*a*]PYRIDINE-3-YL]-1-ARYL PROP-2-EN-1-ONE.**

| Sr. No. | R | Zone of Inhibition in m.m. | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **1a** | $C_6H_5$- | 17 | 16 | 13 | 12 | **19** |
| **1b** | 4-$CH_3$-$C_6H_4$- | 15 | 13 | 15 | 14 | 13 |
| **1c** | 4-$OCH_3$-$C_6H_4$- | 16 | 15 | 14 | 15 | 12 |
| **1d** | 4-Cl-$C_6H_4$- | 18 | **18** | 15 | 16 | 14 |
| **1e** | 4-F-$C_6H_4$- | 16 | 14 | 15 | 15 | 16 |
| **1f** | 4-Br-$C_6H_4$- | 14 | 12 | 13 | 12 | 13 |
| **1g** | 4-$NH_2$-$C_6H_4$- | 15 | 14 | 14 | 13 | 15 |
| **1h** | 4-$NO_2$-$C_6H_4$- | 13 | 12 | 13 | 14 | 15 |
| **1i** | 4-OH-$C_6H_4$- | **19** | 16 | **18** | **18** | 18 |
| **Std$^n$** | Ampicillin | 20 | 19 | 21 | 22 | - |
| **"** | Amoxicillin | 22 | 20 | 20 | 21 | - |
| **"** | Ciprofloxacin | 24 | 23 | 22 | 20 | - |
| **"** | Norfloxacin | 23 | 21 | 21 | 22 | - |
| **"** | Greseofulvin | - | - | - | - | 24 |

**TABLE NO.- 1B PHYSICAL CONSTANTS OF (2Z)-3-[2-(4-CHLOROPHENYL) -8-METHYL IMIDAZO[1,2-*a*]PYRIDINE-3-YL]-1-ARYL PROP-2-EN-1-ONE.**

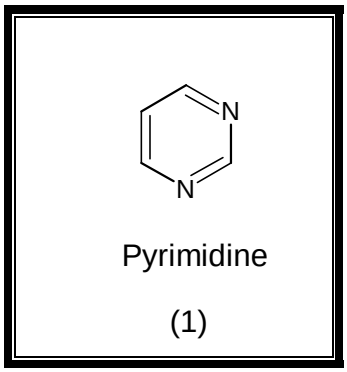
| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **1a** | $C_6H_5$ - | $C_{23}H_{17}ClN_2O$ | 372.5 | 215.0 | 0.54 | 59.0 | 7.51 | 7.36 |
| **1b** | 4-$CH_3$-$C_6H_4$ - | $C_{24}H_{19}ClN_2O$ | 386.5 | 262.0 | 0.58 | 56.0 | 7.24 | 7.12 |
| **1c** | 4-$OCH_3$-$C_6H_4$- | $C_{24}H_{19}ClN_2O_2$ | 402.5 | 189.0 | 0.60 | 75.0 | 6.95 | 6.78 |
| **1d** | 4-Cl-$C_6H_4$ - | $C_{23}H_{16}Cl_2N_2O$ | 407.0 | 185.0 | 0.59 | 72.0 | 6.88 | 6.76 |
| **1e** | 4-F-$C_6H_4$ - | $C_{23}H_{16}ClFN_2O$ | 390.5 | 140.0 | 0.44 | 65.0 | 7.17 | 6.98 |
| **1f** | 4-Br-$C_6H_4$ - | $C_{23}H_{16}ClBrN_2O$ | 451.5 | 243.0 | 0.62 | 57.0 | 6.20 | 6.15 |
| **1g** | 4-$NH_2$-$C_6H_4$ - | $C_{23}H_{18}ClN_3O$ | 387.5 | 165.0 | 0.56 | 55.0 | 10.83 | 10.79 |
| **1h** | 4-$NO_2$-$C_6H_4$ - | $C_{23}H_{16}ClN_3O_3$ | 417.5 | 161.0 | 0.56 | 70.0 | 10.06 | 9.88 |
| **1i** | 4-OH-$C_6H_4$ - | $C_{23}H_{17}ClN_2O_2$ | 388.5 | 149.0 | 0.49 | 54.0 | 7.20 | 7.04 |
| **Solvent System : Ethyl acetate : Hexane (5:5)** | | | | | | | | |

# PART-II

# STUDIES ON PYRIMIDINES

## INTRODUCTION

Pyrimidine (1) is a six membered heterocyclic compound consisting of two nitrogen atoms at 1 and 3 positions of heterocyclic ring.



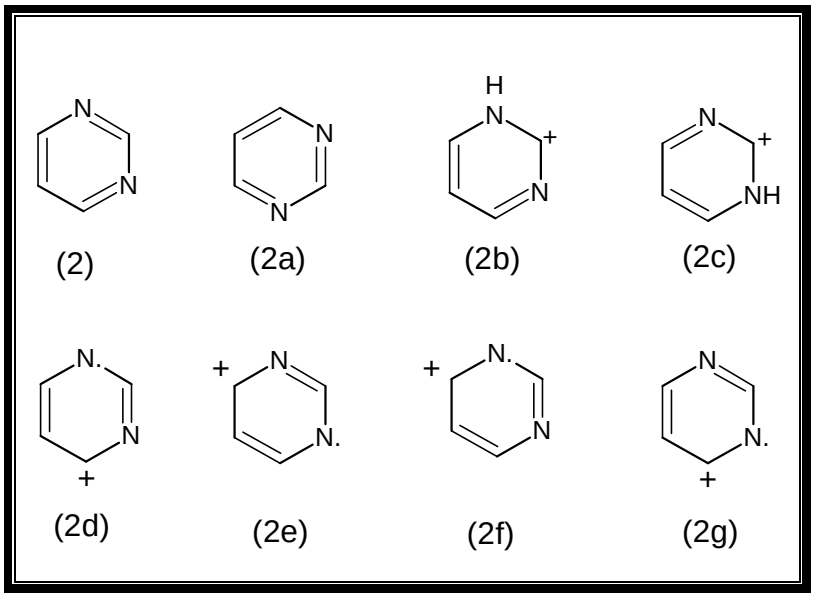

Pyrimidine

(1)

Generally Pyrimidine derivatives such as 2-hydroxy-substituted-pyrimidine, 2-mercapto-substituted-pyrimidine and 2-amino-substituted-pyrimidine are studied. Pyrimidines have been isolated from the nucleic acid hydrolysates. Pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used.[143] There are several other important groups of pyrimidines with medicinal uses.

Pyrimidine ring carrying various substituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other syntheses, which are complimentary rather than alternative to it. An alternative method of synthesis is the isomerisation or break down of another heterocycles such as hydration of purine, but such methods are rarely used. Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent Kekule structures 2 and 2a and charged structures 2b and 2g contributes.

The self consistent (pi) electron densities required for the ground state of pyrimidines are 0.776, 0.825 and 1.103 for positions 2, 4 and 5 respectively[144]. Despite considerable localization of (pi) electrons at nitrogen atoms of pyrimidines the ring system is still sufficiently aromatic to possess substantial stability. This has a great advantage in the primary synthesis of pyrimidines.




The first primary synthesis from aliphatic fragments was carried out by Frankland et al. in 1848. Since then a many distinct primary synthetic methods have been devised.[145-154] It is also possible to prepare pyrimidines from other heterocyclic compounds such as **pyrrole**[155], **imidazole**[156], **isoxazole** and **oxazole** [157-158], **pyridine**[159], **pyrazine**[160], **1,3,5-triazine**[161], **oxazine**[162], **thiazine**[163] by different processes.

**SYNTHETIC METHODS FOR PYRIMIDINES**

Various methods for synthesis of **pyrimidines** which are reported in the literature are as follows.

(a) By the condensation of **urea** and **malonic acid** led to formation of **pyrimidine**.[164]

(b) By the condensation of **malonic ester** and **urea** led to formation of **pyrimidine**.[165]

(c) By the condensation of **formamidine** with **phenylazomalononitrile** led to formation of **4,5,6 – triaminopyrimidine**.[166]

(d) By the condensation of aromatic **aldehydes**, ***ß*-ketoester** or substituted ***ß*-ketoester** with urea or **thiourea** led to formation of **pyrimidines**.[167]

(e) By the condensation of **thiourea** and substituted ***ß*-ketoester** in presence of **sodium ethoxid** e led to formation of **2-mercaptopyrimidines**.[168]

(f) By the condensation of **chalcones** with **dicyandiamide** in presence of **piperidine** led to formation of **pyrimidines**.[169]

(g) By thermal or microwave irridiation of **thiourea** and substituted ***ß* -ketoester** in presence of **dimethylformamide** led to formation of substituted **tetrahydropyrimidines**.[170]

(h) One pot synthesis of substituted **dihydropyrimidin-2-ones** catalysed by **$CuCl_2$**.[171]

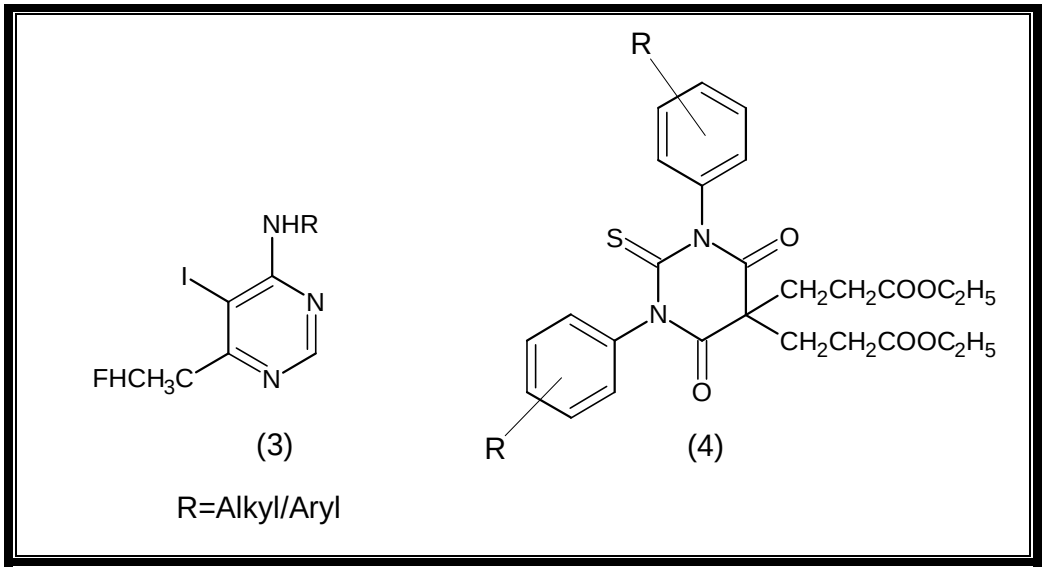
(i) Synthesis of **3,4-dihydropyrimidin- 2- (1*H*)- ones/thiones** under micro wave irradiation.[172]

(j) One pot efficient and novel synthesis of **dihydropyrimidin-2-(1*H*)-ones** catalysed by **Tin (II) chloride ($SnCl_2$)**.[173]

(k) By microwave induced eco-friendly solvent free Biginelli reaction catalysed by **calcium chloride**.[174]

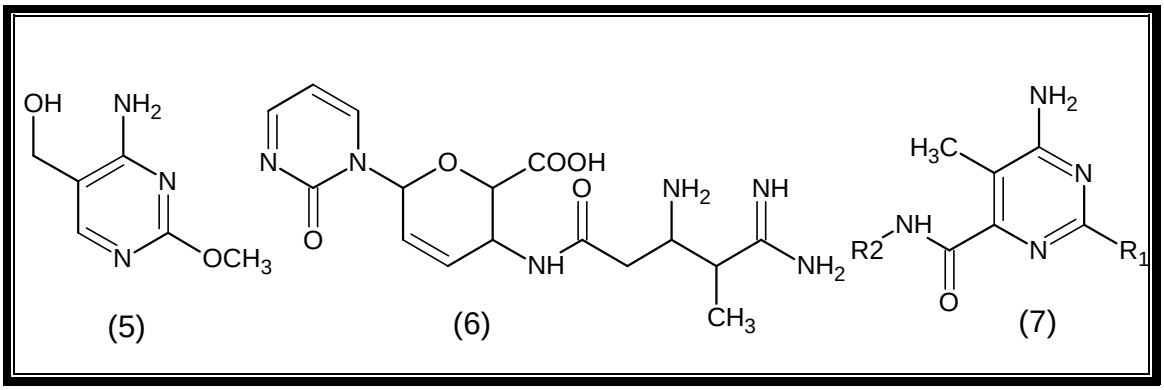
**Pyrimidines** have found their applications as **herbicidal**[175] and **pesticidal**[176-177] agents. Yoshida et al.[178] have synthesized **4-amino-5-formyl-2-mercapto pyrimidines** as agrochemical intermediates. C. Srivastava et al.[179] have synthesized new substituted **pyrimidines** (3) as potential insecticides. N. Yasushi et al.[180] synthesized **6-(1-fluoroethyl)-5-iodo-4-alkylamino Pyrimidines**(4) as pesticides for agriculture and horticulture. Besides such a great biological importance of **pyrimidines** they also contribute to an important

class of dye *viz*. **trichloro pyrimidine**[181] dye which is a reactive dye. **Pyrimidines** also have applications in liquid crystal composition.[182] Many synthetic members of **pyrimidines** are important as vulcanizing accelerator agents and photography stabilizer.[183]




**PHARMACOLOGICAL IMPORTANCE OF PYRIMIDINES**

Numerous **pyrimidines** are well known drugs for variety of diseases. They may be placed in four categories *viz*. **barbiturates**, **sulfonamides**, **antimicrobials** and **antitumor** agents. **Uracil**, **thymine**, **alloxan**, **vicine** and **divicine**, **cytosine**, **chroticacid**, **willardiline**, **tetradotoxine**, **becimethrian** (5),**blasticidine** (6) , **cougerotin** , **amicetin** , **bamicetin** and **plicacetin, phleomicine**, **blemycin** and related families (7).



**Pyrimidine** derivatives have wide varieties of usages. **Pyrimidine** ring system is also present in **Vitamin $B_2$** and **folic acid**. **Pyrimidine** ring system having a mercapto group occupy a unique position in medicinal chemistry.[184] These types of derivatives play a vital role in biological processes[185-187] as well as synthetic drugs.[188]

Some of the therapeutic activities of **pyrimidine** derivatives can be summarized as follows.

(a) **Antithyroid** [189-190]
(b) **Antitumor**[191-193]
(c) **Antihypertensive**[194-196]
(d) **Antiinflammatory**[197-199]
(e) **Diuretic**[200]
(f) **Antimalarial**[201-203]
(g) **Antispasmodic** [204]
(h) **Anticonvulsant**[205]
(i) **Antineoplastic** [206,207]
(j) **Anthelmintic**[208]
(k) **Antimicrobial**[209-234]
(l) **Cardiovascular**[235-237]
(m) **Antiviral**[238-241]
(n) **Platelet aggregation inhibitor**[242,243]
(o) **Antihistamine**[244,245]
(p) **Anti-HIV**[246,247]
(q) **Antitubercular**[248]

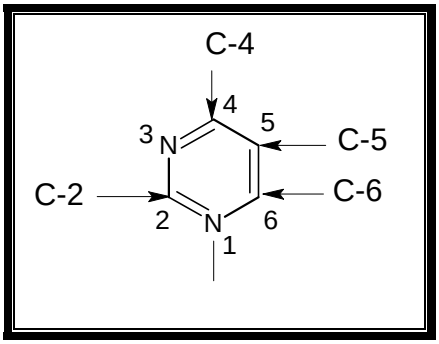
The basis of any rational drug discovery programme is fundamently, the Medicinal Chemistry. Although the synthesis of modified nucleic acids has been a subject of interest for some time, the intense focus on the medicinal chemistry of **oligonucleotides** dates perhaps to not more than five years. As a result of this, the scope of medicinal chemistry has recently been expanded enormously, but the biological data of supporting the conclusions about synthetic strategies have just begun to emerge.

Modifications in the base, sugar and phosphate moieties of oligonucleotides and oligonucleotide conjugates have been reported. The subjects of medicinal chemical programmes include approaches to create enhanced affinity and more selective affinity for **RNA** or duplex structures, the

ability to cleave **nucleic acid** targets, enhanced nuclease stability, cellular uptake and distribution, ***in vivo*** tissue distribution, metabolism and clearance. Although substantial progress in the medicinal chemistry of oligonucleotides has been made in the past three years, it is not yet possible to reach the conclusion about the therapeutic ability of the novel modifications. Preliminary data on effects on nuclease stability and hybridization properties for a few modifications and activity ***in vitro*** suggest that the next generation of oligonucleotides may display substantially improved potencies and selectivity.

**PYRIMIDINE MODIFICATIONS (Nucleotide)**

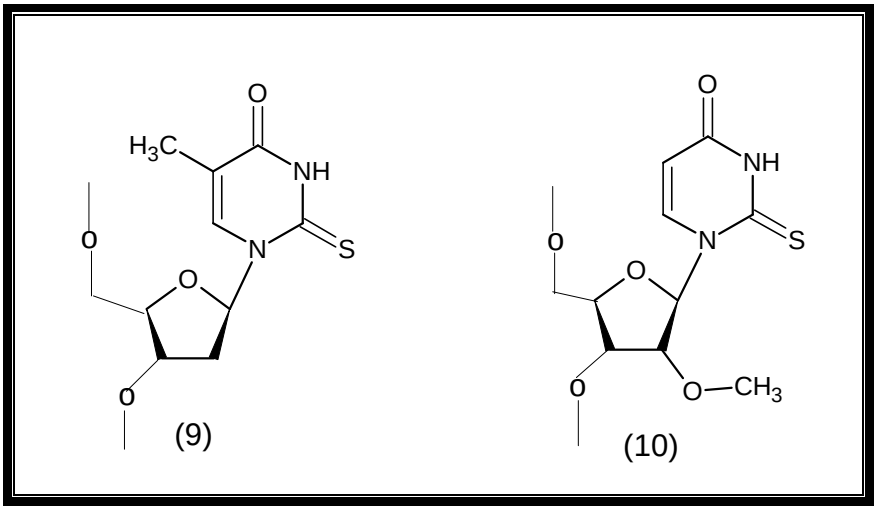
A relatively large number of modified **pyrimidines** have been synthesized and now incorporated into **oligonucleotides** and evaluated. The principle sites of modification are C-2, C-4, C-5 and C-6 (8). These and other **nucleoside** analogues have recently been thoroughly reviewed.[250]



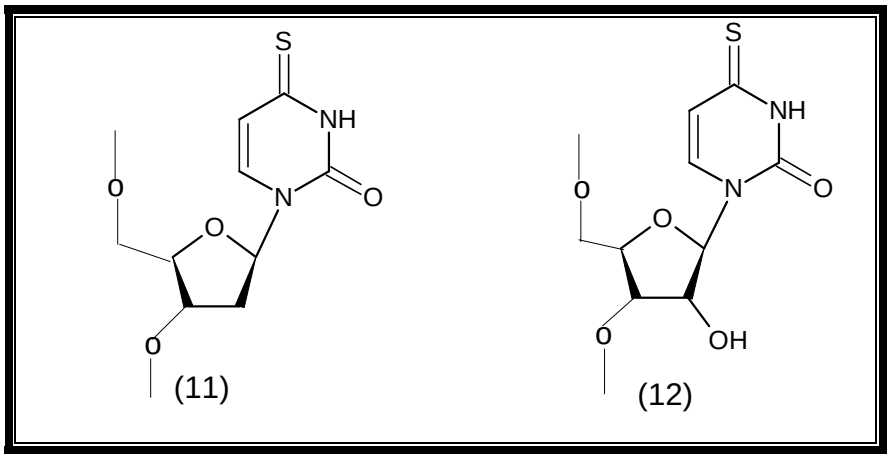

**Sites of Pyrimidine Modification (8)**

In as much as the C-2 position is involved in Watson-Crick hybridization, **oligonucleotides** containing C-2 alkyl modified **pyrimidines** have shown unattractive hybridization characters. However, an oligonucleotide containing **2-thiopyrimidine**(9) was found to hybridize well to **DNA** and, in fact even better to **RNA** with a thermal melting temperature (∆Tm) value of 1.5 ° C/modification. In a different study, **oligoribonucleotides** with **2'-o-methyl-2-thiouridine** (10)

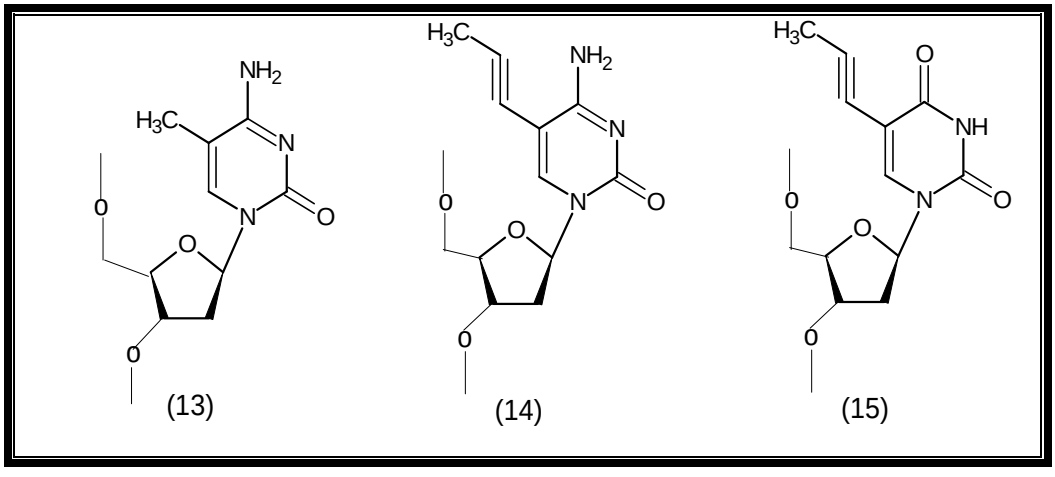
exhibited a thermal melting temperature (ΔTm) value of +5.5 °C/modification when hybridized against **RNA** resulting from a highlly preoganized **RNA**-like C-3' endo conformation (attributed to the combination of 2-thio modification and **2'-o-Mesubstituent)**. Oligonucleotides with this modification also exhibit better hybridization discrimination for the wobble uracil-guanosine (U-G) base pair formation compared to the (8) **Sites of Pyrimidine Modification** normal **uracil-adenine** (U-A) base pair. This selectivity is a result of weaker hydrogen bonding and increased steric bulk of the **2-thiocarbonyl group**.[251]



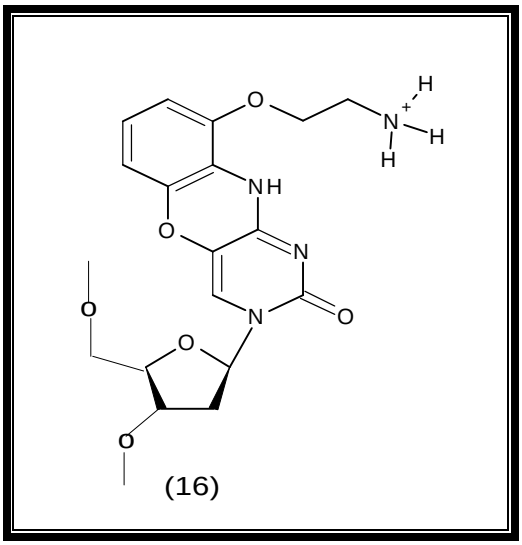

In contrast, the **Pyrimidine** modifications in 4-position with interesting properties have been reported. **4-Thiopyrimidines** (11,12) have been incorporated into oligonucleotides with no significant negative effect on hybridization. However, recent studies have shown destabilization in the normal **uraciladenin** (U-A) base pair formation and stabilization of the wobble **uracil guanosine** (U-G) base pair for **4-thiouridine**. A bicyclic 4-methoxy analog of **cytosine** were shown to hybridize with both purine bases in **DNA** with thermal melting temperature (Tm) values approximately equal to that of natural base pairs. Additionally, a fluorescent base has been incorporated into **oligonucleotides** and shown to enhance **DNA-DNA duplex** stability.[252]




The **Pyrimidine** modification at C-5 position including **halogenated nucleosides** have been reported. Although the stability of duplexes may be enhanced by incorporation **5-halogenated uracil** containing nucleosides, the occasional mispairing with guanidine and the potential that the **oligonucleotide** might degrade and release toxic nucleosides analogs cause concern. **Oligo-nucleotides** containing **5-propynylpyrimidine** (14,15) modification have been shown to enhance the duplex stability thermal melting temperature ($\Delta$Tm = 1.6 °C/modification),and support RNase H activity. The **5-heteroaryl-pyrimidines** were also shown to increase the stability of duplexes. A more dramatic influence was reported for the **tricyclic 2'-deoxycytidine** analoges, termed phenoxazine, exhibiting an enhancement of 2-5 °C/modification, depending on the positioning of the modified bases.[253]



As expected, modifications in the C-6 position of pyrimidines are highly destabilizing. Oligonucleotides containing **6-azapyrimidines** (16) have been shown not only to reduce the thermal melting temperature (Tm) value by 1-2 °C per modification, but also to enhance the nuclease stability of **oligonucleotides** and to support ***E. coli*** RNase H-induced deradation of **RNA** targets.[254]

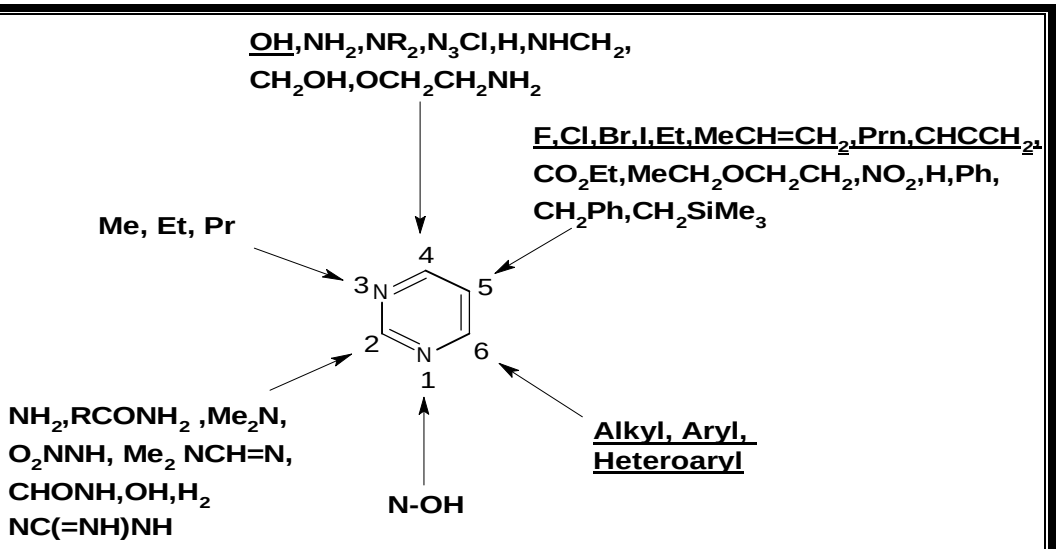



(16)

**PYRIMIDINE MODIFICATIONS (Non-nucleotide)**

The increasing interest in the early 1970s in properties and use of interferon (IFN) together with the difficulty in producing useful amounts of interferon (IFN) led to the search for agents that would induce IFN in the host. Precedenced at that time for interferon (IFN) inducers included viruses and bacterial wall constituents and entities of large molecular weight such as the polynucleotides. There were also several examples of low molecular weight substances such as certain **antibiotics** and the **antiviral** agent, tilorone.[255] In 1976 it was reported that **6-methyl pyrimidinone (2-amino-5-bromo-6-methyl-4-(3*H*) pyrimidinone, ABMP)** induced circulating levels of interferon (IFN) in several animal specis upon oral or intraperitoneal administration.[256] Subsequent structure-activity studies yielded a more potent and less toxic 6-phenyl ananlog

called **ABPP** or **bropirimine(2-amino-5-bromo-6-phenyl-4-(3*H*)-pyrimidinone)** (figure 1 and Table 1).[257,258] **Bropirimine** and related **6-aryl analogs** were examined extensively for efficacy in virus and tumor models, along with their immunomodulatory properties and overall pharmacological effects.[259]




Where, Preliminary SAR of **antiviral activity of pyrimidinones** (underlined substituents were active)

**Table - I**

**Antiviral Activity**

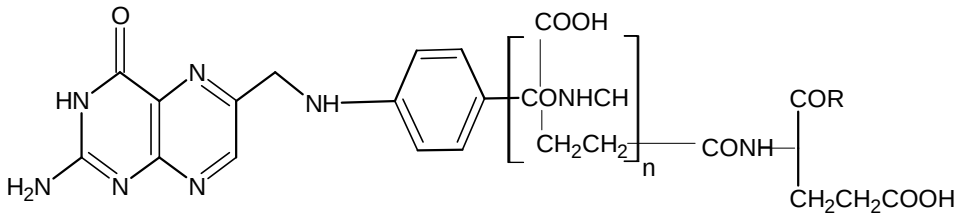
| | Monosubstituted | Disubstituted | Heterocyclic |
|---|---|---|---|
| **Active** | 2-F,OMe, Me | 3,5-OMe | 1Naphthyl |
| | 3-F,OMe, Cl, $NO_2$ | 2,5-$Cl_2$ | 2-Pyrazyl |
| | Me, $CF_3$, $MeCH_2CH_2O$, | 3,5-OMe | 2,3-pyridyl |
| | Br,I | 3,4-$Cl_2$ | 2-Furyl |
| | 4-F, Cl | 3,5-$Cl_2$ | |
| **Inactive** | 4-Me, CN, Butyl, | 2,3-OMe | 2-Napthyl |
| | $OH,OCH_2Ph$, OMe | | 1-Furyl |
| | | | 4-Pyridyl |
| | | | 2Quinoline |

As with the polynucleotides, the **pyrimidinones** exhibited significant activity against **interferon (IFN)** sensitive viruses such as Semliki Forest virus ***in vivo***. How ever, in addition, they exhibited **prophylactic** and **therapeutic** activity upon either local or systemic administration to rodents infected with a variety of **DNA viruses**, such as the **herpes viruses (*HSV-1, HSV-2*, CMV** and **pseudorabies**), and when administered intranasally for upper respiratory infections, such as infectious bovine **rhinortacheites**, **influenza A** and **para-influenza-3**.Particularly interestion activity was noted with **bropirimine** on intravaginal administration in protection against ***HSV-2*** intravaginal infection in guinea pigs, an important model for genital **herpes** in humans.[260] **Bropirimine** also exhibited activity when given either intraperitoneally or orally to mice infected with **Listera monocytogenes**. The efficacy in this model was not abrogated by the addition of **anti-interferon (IFN) antibody.**[261]

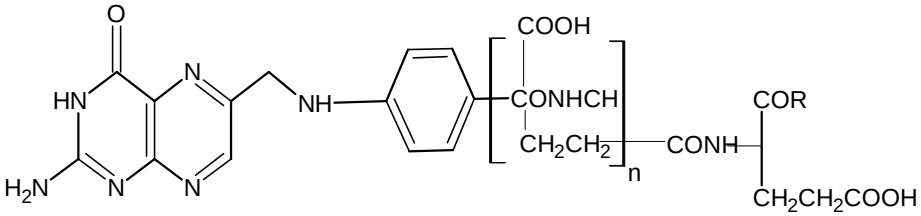
**Pyrimidines as Antifolates**

During a preliminary clinical trial designed to establish safety and suitability for use in the treatment of **cancer**, Farber found the **folic acid** derivatives **pteroyldiglutamic acid** (17) and **pteroyltriglutamic acid** (18) were accelerating the growth of malignant cells in the bone marrow of patients with acute leukaemia. He obtained the newly synthesized antifolate **pteroylaspartic acid** from Subba Row, from which encouraging results were obtained in children with acute leukaemia. Better responses were observed with the **aminopterin** (19) and methotrexate (20). Injections of **methotrexate** induced temporary remissions in 30% of children, but Farber and his colleagues later combined it with drugs such as **cortisone** and **mercaptopurine** to achieve results which paved the way towards the currentposition where most children can be cured of the disease if given the appropriate treatment. The precise model of action of the antifolates became apparent in 1952. This was the inhibition of dihydrofolate reductase, the enzymes that catalysed the transformation of folic

acid so that it could be utilized for the synthesis of thymine for incorporation into **DNA**. Surprisingly, no other antifolate has emerged to rival **methotrexate** in the treatment of either acute **leukaemia** or **cancers**.




(17) n = 0, R = NHCH(COOH)$CH_2CH_2$COOH (18) n =2, R = OH

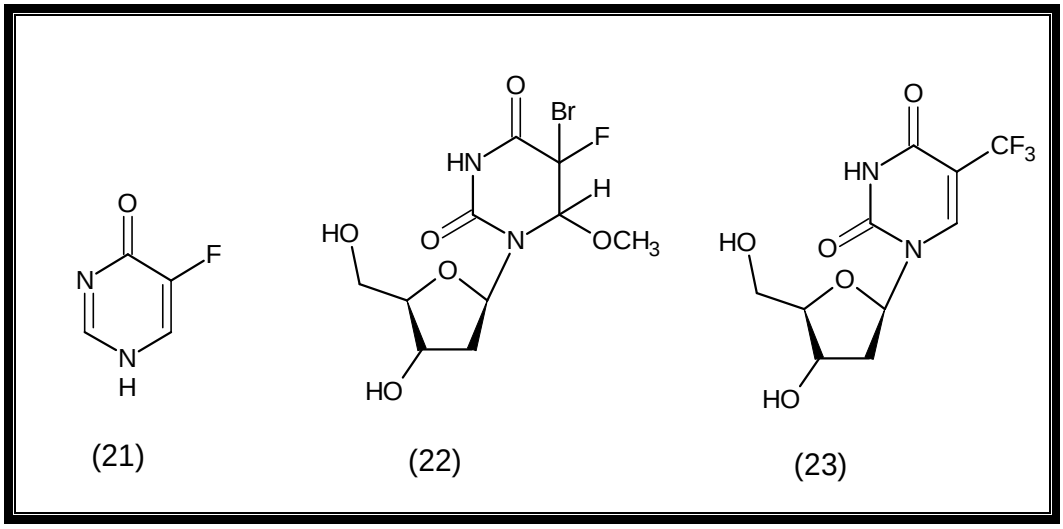



(19) R = H (20) R = Me

Of the various halogenated **pyrimidines** which have been prepared, only the fluorinated **pyrimidines** and nucleosides have useful **antitumour** activity, and of these the most significant are **5-fluorouracil (FU)** and it's **2'-deoxyribonucleside (FUdR; Floxuridine)**. Both of these drugs have found wide uses in patients suffering from metastatic **cancer**, and have been administered both singly and in combination therapy. The presence of flourine, which cannot be abstracted by base, halts the process. In contrast, the **5'-monophosphate** of **5-chloro-**, **5-bromo-** and **5- iodo- 2'-deoxyuridine**, in which the halogen atom is bulkier and less electro- negative, have little or no useful inhibitory activity for the enzyme. The drugs of

**fluorouracil (FU)** showing good **antitumour** activity includes it's **1-t-butyl carbamoyl**[262], **1-hexylcarbamoyl**[263] and **1-methoxycarbonylmethyl carbamoyl**[264] derivatives, **5'- deoxy-5-fluorouridine**[265] and **methyl-1-(5-fluoro-1-H-2-oxopyrimidin- 4- yl)-BD- glucopyranuronate** (21).[266] All of these contain in essence the **fluorouracil (FU)** moiety, ready via oxidative or hydrolytic means. **5-Fluoropyrimidin-4(1*H*)-one**, with activity against **tumours** in experimental animals, is a different type of prodrug, being oxidized to **5-fluorouracil (FU)** by **xanthine oxidase**.[267]

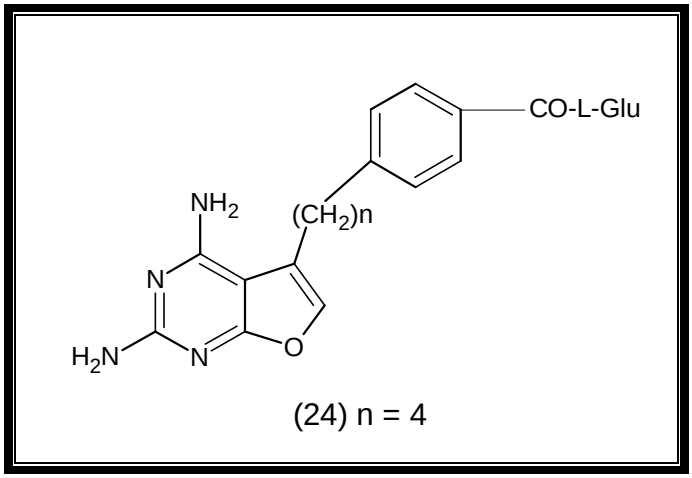
A number of prodrugs of FUdR have also been prepared a notably potent member being **5-bromo-6-methoxydihydro-5-fluro-2'-deoxyuridine** (22).[268] Finally, a different species of **fluoropyrimidine** derivative, which as its 5' mono phosphate inhibits **thymixylate** synthetase is **5-trifluoromethyl-2'-deoxyuridine( Trifluridine);** (23) it possesses a higher therapeutic index against **adenocar-cinoma** 755 in mice than **2'-deoxyribo-nucleoside (FUdR; Floxuridine).**[269]




(21) (22) (23)

As part of a continuing effort of develop novel classical antifolates as **dihydrofolates (DHFR)** inhibitors and as **antitumor** agents, A. Gangjee et al.[270]

have reported the **5-substitutedfuro [2,3-*d*] pyrimidines** (24) for enzyme inhibitoryactivity and **antitumor** activity.

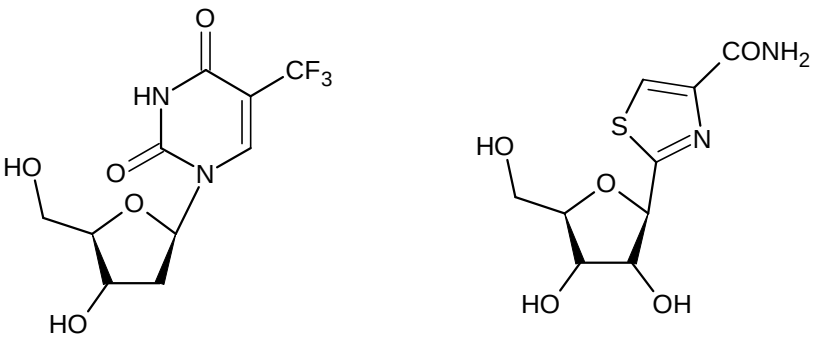



(24) n = 4

**PYRIMIDINES AS ANTITUMOUR AGENTS**

A number of other **pyrimidine** antagonists displaying **antitumour** activity, in which the base is conjugated to a modified suger ring have been reported. Although D-Arabinofuranosyl **uridine** (ara-uridine) shows no useful acitivity and **5-bromo-** and **5-iodo-D-arabinofuranosyl uridine** inhibit the growth of **sarcoma** 180 and L1210 cells in culture.[271] Other **thymidine** analogues with similar activity include **5-azidomethyl-,5-aminomethyl** and **5-hydroxymethyl-2'-deoxyuridine**[272]. **3'-Amino-3'-deoxy thymidine**[273] and 3**'-amino-2',3'-dideoxycytidine**[274] also posses strong activity against L1210 **leukaemia 2'-Deoxy-2'-fluoro-5-methyl-1-B-D-arabinofuranosyluracil (FMAU);**(25) is highly active against **arabinofuranosyl cytidine (ara-C)** resistant L1210 and P815 cell lines both ***in vitro*** and ***in vivo***.[275] **2-B-D-Ribofuranosylthiazole-4-carbox amide (Tiazofurin; 26)** has aroused much interest recently for its activity against solid **tumour** such as lung **carcinoma**. It is metabolized to an analogue of **NAD** in which the **thiazole-4-carboxamide** moiety replaces the **nicotinamide** ring.

However, it also depresses the synthesis of **DNA** and **RNA**, and thus merits inclusion as an **antagonist** of normal **purine** and **pyrimidine** metabolism.[276]




(25) (26)

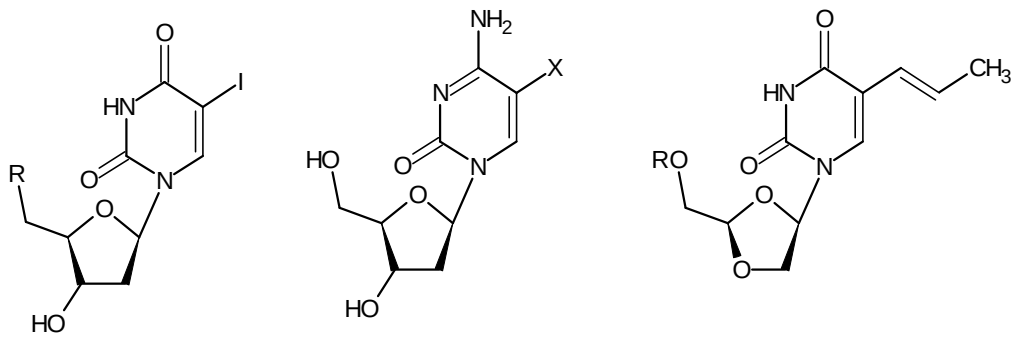
**Targets for Antiviral Chemotherapy**

Viral chemotherapy presents a quite different problem from **tumor** chemotherapy. A **virus**[277] consists of a core of nuclear material, **DNA** or **RNA**, containing specific viral genes, which may be associated with 'core proteins', and which is surrounded by a protective proteincoat. The coat may have functional protein appendages, and there may be present an 'envelope', rich in lipoprotein and glycoprotein. The virus possesses no energy-producing or protein synthesizing machinery of its own. In order to reproduce, it must therefore become adsorbed to a host cell, be transported across the cell membrane, and uncoat in order that its viral genes may be expressed. The genome may require to be transported to the cytoplasm or the nucleus. The nuclear material must then be replicated, and the viral genes also transcribed into **RNA** (assuming that we are dealing with a **DNA** virus) and translated into virally specified protein. In addition to the coat protein, viral enzymes will be produced in this process, and these are vital for suborning the host cell's internal biochemistry to serve the requirements of the virus. Before the viral proteins can be made, a process of

maturation of the viral **mRNA** molecules, involving guanylylation and methylation to produce a 'cap' structure containing **7-methylguanosine 5'-phosphate** in a **5'- 5'-pyrophosphate** structure at the 5'- end of the **mRNA**, must occur. Once the synthesis of the components needed to make fresh viral particles has been completed, maturatian occurs, in which the nucleic acid and protein components are assmbled to from the complete viral particle or virion, and finally this is released from the cell as a new , infective virus. **RNA** viruses require that their nucleic acid be replicated also, in order that new viral particles can form. Some **RNA** viruses code for an enzyme 'transcriptase' or 'replicase' (**RNA**-directed **RNA** polymerase), which replicates **RNA** strands directly without involving **DNA**[278] while others encode an enzyme 'reverse transcriptase' (**RNA**-directed **DNA** polymerase), which transcribes the RNA sequence into **DNA**-the reverse of the usual sequence which can subsequently become integrated into the host cell chromosome and is transcribed to from copies of the viral **RNA**.[279] Purine and **pyrimidine** antimetabolites which are active against viruses are thus most likely to be effective by inhibiting specifically the viral enzymes which are required to replicate the viral nucleic acids, or inhibiting the viral enzymes responsible for transcription and capping of **mRNA**, without inhibiting the corresponding enzymes of the host cell.

Alternatively, incorporation of an antimetabolite into a viral **nucleic acid** causing the cessation of strand synthesis, or otherwise disturbing the normal function of the nucleic acid in replication or in directing protein synthesis, offers another way of preventing the replication of functional virus.[280] Again, it is important that the integrity of the nuclear material of the host cell should not be compromised.One therefore seeks to exploit the differences between the viral enzymes to the discomfiture of the virus. **5'-Amino- 5- iodo- 2',5'-dideoxyuridine(Aminoidoxuridine;**28**)** displays good **antiherpes** activity and is less cytotoxic than (27).[281,282] The Phosphorylation of **Aminoidoxuridine** (28) is catalyzed specifically by virus-induced thymidine kinase, and thus

**Aminoidoxuridine**(28) is only potentiated in virus-infected cells. It inhibits the synthesis of **DNA** in infected cells. The **5-bromo-**, **5-chloro-** and **5-trifluoro**methyl derivatives of **5'-amino-2',5'-dideoxyuridine** also exhibit **antiviral** activity.[283] **5-Iodo-2'-deoxcytidine** (29) and **5-bromo-2'-deoxycytidine** (30) also show useful activity against **herpes** viruses and vaccinia with less cytotoxicity than the uridine compounds and more selective inhibition of virus replication. C. K.Chu[284] et al. have prepared **pyrimidine** nucleosides (31) and reported ***in vitro*** **antiviral** activity against **varicella zoster virus (VZV)**.



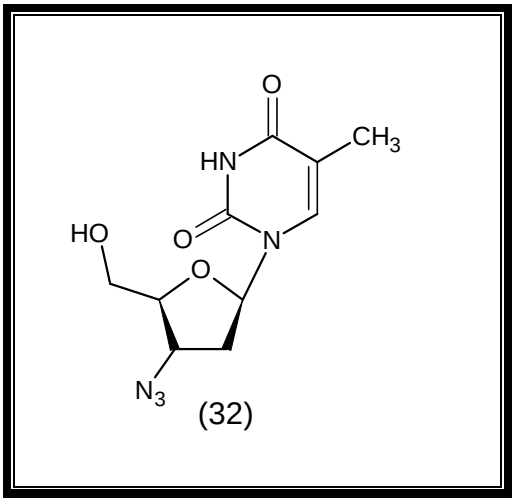
(27, 28) R = OH, $NH_2$ (29,30) X = I, Br (31) X = Cl, Br, I

**PYRIMIDINES AS ANTI-HIV AGENTS**

The strategy of designing nucleoside analogs that are selective for viral **DNA** polymerases is the most well-studied and successful approach to viral chemotherapy, and has led to the discovery of several clinically useful **antiviral** drugs.This strategy, however, has inherent limitations. Human **DNA** polymerases also required dNTP's and the chemical mechanisms of polymerization by the viral and human enzymes are similar. Nucleoside analogs often have significant host toxicity that is probably related to inhibition of host cell **DNA** synthesis.

Nevertheless, these compounds constitute the major class of **antiviral** drugs,and this approach is likely to yield additional active compounds in the near future. For the long term, however, other strategies may ultimately lead tumor selective agent within lower toxicity.

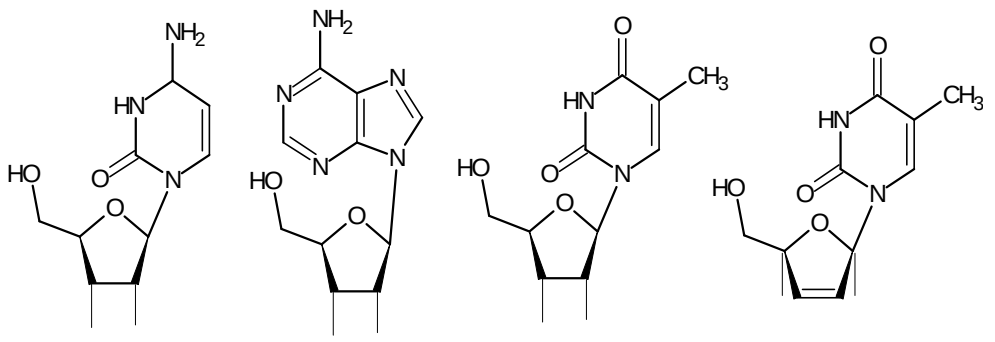
Obviously, the key to design analogue with a lower affinity for the host enzyme than the viral enzyme, which requires that there be structural differences between the enzyme active sites. For reverse transcriptase, the most well studied inhibitor is **3'-azido-3'-deoxythymidine (AZT; 32)**, which is currently used clinically to treat **AIDS**.[285,286]




(32)

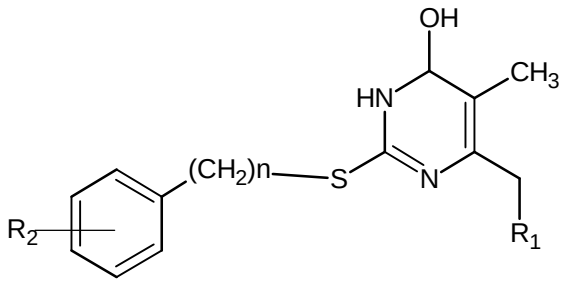
3'-azido-3'-deoxythymidine (AZT) inhibits HIV reverse transcriptase with an IC50 of 40nM[287], but is 100-300 times less active against mammalian **DNA** polymerase $\alpha$ and **DNA** polymerase $\gamma$. The reason for this selectivity is not clear since **3'-azido-3'-deoxythymidine (AZT)** is a chain terminator for mammalian **DNA** polymerases and inhibits normal cellular **DNA** synthesis.[288] Several other **dideoxy nucleoside** analogs have been shown to be potent inhibitors of ***HIV*** replication ***in vitro***.[289,290] In general, these compounds have the same mechanism of action as **3'-azido- 3'-deoxythymidine (AZT)**, that is, intracellular

conversion to the triphosphate derivative and subsequent inhibition of ***HIV*** **reverse transcriptase**. Some of these compounds are simply analogs of the natural **2'-deoxy- nucleoside** in which the 3'-OH group has been replaced with a hydrogen, such as **2',3'-dideoxycytidine**(33), **2',3'-dideoxyadenosine**(34) and **2',3'-dideoxy thymidine**(35)**.** Other analogs contain a 2'-3' double bond, such as **2'3'- dide-hydro-2',3'-dideoxythymidine** (36). Several related analogs with other modifications to the ribose ring or the heterocyclic base moiety have also been reported to have activity against ***HIV*** or ***HIV*** **reverse transcriptase**.[291,292]



(33) (34) (35) (36)

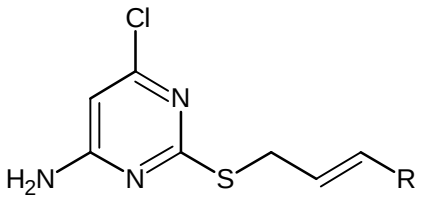
Recently, P. Khalili et al.[293] have carried out biochemical and pharmacokinetic evaluation of a novel nitric oxide donor **pyrimidine** nucleoside hybrid drug as a potential **anticancer** / **antiviral** agent. Rostom et al.[294] have synthesized and screened certain **2-(benzoxazol-2-yl-amino)-3*H*-4-oxopyrimidines** for ***in vitro*** **anti-HIV** activity. R. A. Nugent et al.[295] have synthesized **pyrimidine** thio ethers (37) and evaluated for inhibitory properties against wild-type ***HIV-1*** reverse transcriptase. F. Manetti et al.[296] have synthesized novel **pyrimidines** (38) with nanomolar activity toward recombinant ***HIV-1*** and mutant ***HIV-1*** strains.




R1= 2,6-$(Cl)_2$, 4-F

R2=4-$OCH_3$,4-$NO_2$, 4-CN, 4-Br

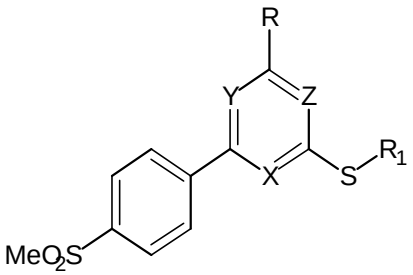
(37)



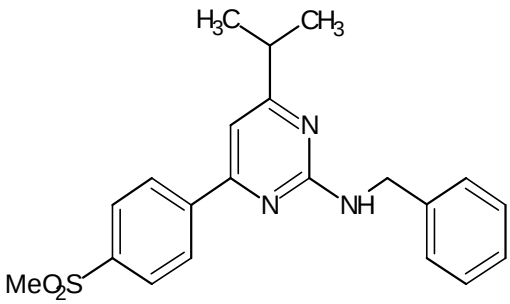

R=Ph,Me,$CO_2$Me,$CONMe_2$,$CONEt_2$

(38)

A family of tri substituted **pyrimidines** has been described as selective **COX- 2 inhibitors**. To explore the usefulness of **pyrimidine** derivatives as potential **NSAIDs**. Aurelio Orjales et al.[297] have synthesized novel **pyrimidine** derivatives(39) and (40). ***In vitro*** biological evaluation of these compounds has provided information to determine the structural features necessary for **COX-2 inhibitory** activity.




(39) Y = CH; X, Z = N




(40) Y, Z = N; X = CH

In view of procuring highly potent biodynamic agents and after reviewing recent literature survey on **oxo/thio/amino pyrimidines** for their various methods of synthesis and different pharmacological activities, synthesis of **pyrimidines** have been undertaken which can be summarized in the following sections as follows:

**SECTION - I :** Synthesis and therapeutic evaluation of 6-(2-(4-chlorophenyl) - 8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-aryl pyrimidine-2(*H*)-one.

**SECTION - II :** Synthesis and therapeutic evaluation of 6-(2-(4-chlorophenyl) - 8-methyl-1*H*-imidazo[1,2-*a*]pyridine- 3-yl)- 4-aryl pyrimidine-2(*H*)-thione.

**SECTION – III :** Synthesis and therapeutic evaluation of 4-(2-(4-chlorophenyl) - 8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)- 6-aryl pyrimidine-2-amine.

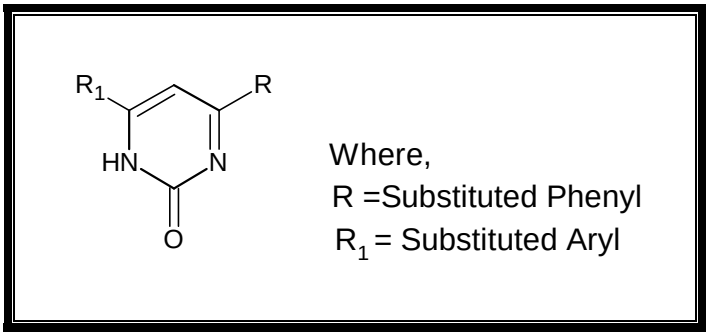
# SECTION-I

# STUDIES ON

# OXOPYRIMIDINES

## INTRODUCTION

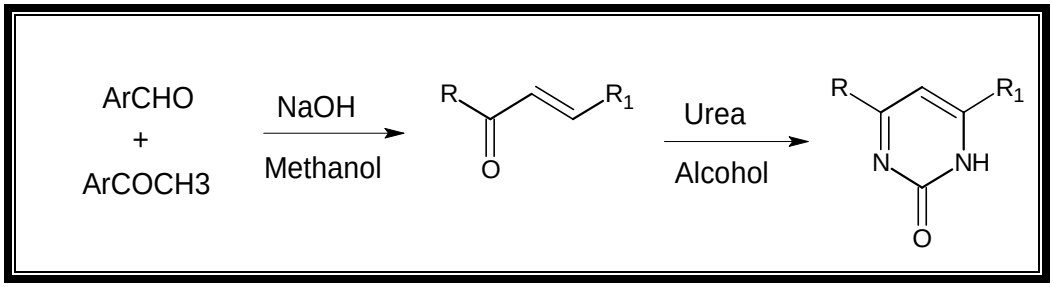
Oxopyrimidines represent one of the most active class of compounds possessing a wide spectrum of biological activities, such as significant ***in vitro*** activity against unrelated DNA and RNA viruses including polio and Herpes viruses, diuretic, Antitubercular spermicidal, etc.




## SYNTHETIC ASPECT :

Different methods are available in literature.

1. By the condensation of *β*–keto esters with *N*- Substituted urea.
2. By the condensation of *β*-dintriles with urea.
3. By the reaction of *β*- aldehydo nitrile with formamidine and urea.
4. By substituted benzaldehyde and substituted acetophenone were subjected to the Claisen-Schmidt condensation in the presence of alkali alcoholate and and yielded 1-(1-naphthyl)-3-aryl-prop-2-en-1-ones. Compounds reacted with an alcohol solution of Urea in aqueous sodium hydroxide to yield the corresponding 2-Oxopyrimidines.[298]



## PHARMACEUTICAL IMPORTANCE

In recent years, dihydropyrimidinones and their derivatives have received considerable attention in natural and synthetic organic chemistry because of their therapeutic and pharmacological properties.[299-306]

Oxopyrimidine derivatives have wide variety of uses. In particular as biologically active compounds in medicine

1. Antihypertensive[299-302]
2. *α*-1a-antagonists[299-302]
3. Neuropeptide Y antagonists.[299-302]
4. *HIV* gp-120-CDA inhibitors [299-302]
5. Antibacterial[303-306]

Due to various biodynamic activities of pyrimidines and with a view to have potent therapeutic agents, the synthesis of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-aryl pyrimidine-2(*H*)-one have been undertaken by the condensation of different substituted chalcones with urea in basic medium.

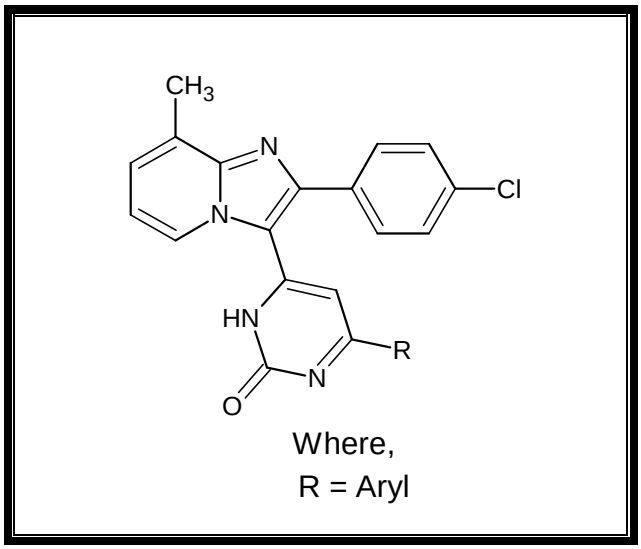
The constitution of the products have been delineated by elemental analyses, IR, $^{1}$H NMR and Mass spectral data. The products were assayed for their ***in vitro*** biological assay like antibacterial activity toward ***A. niger***.

Looking to the interesting biological properties of oxopyrimidine it is worthwhile to prepare some new derivative of oxopyrimidine bearing different heterocyclic systems of medicinal value in order to achieve better therapeutic agents. It has been described in the following section-I.

**Section-I : Synthesis and therapeutic evaluation of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-aryl pyrimidine-2(*H*)-one.**

**SYNTHESIS AND THERAPEUTIC EVALUATION OF 6-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(*H*)-ONE.**

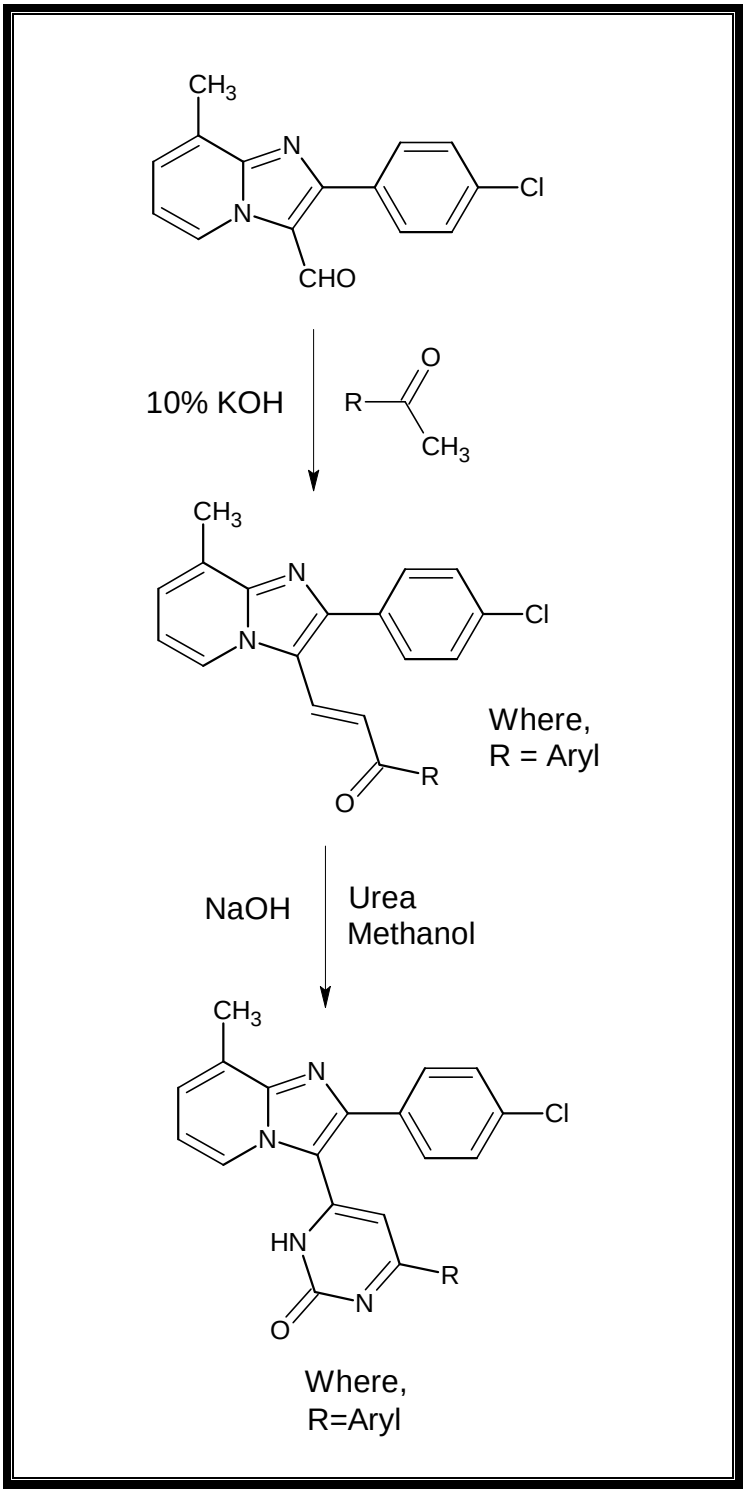
Oxopyrimidine derivatives synthesized by condensation of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one with urea in basic media and methanol as a solvents.



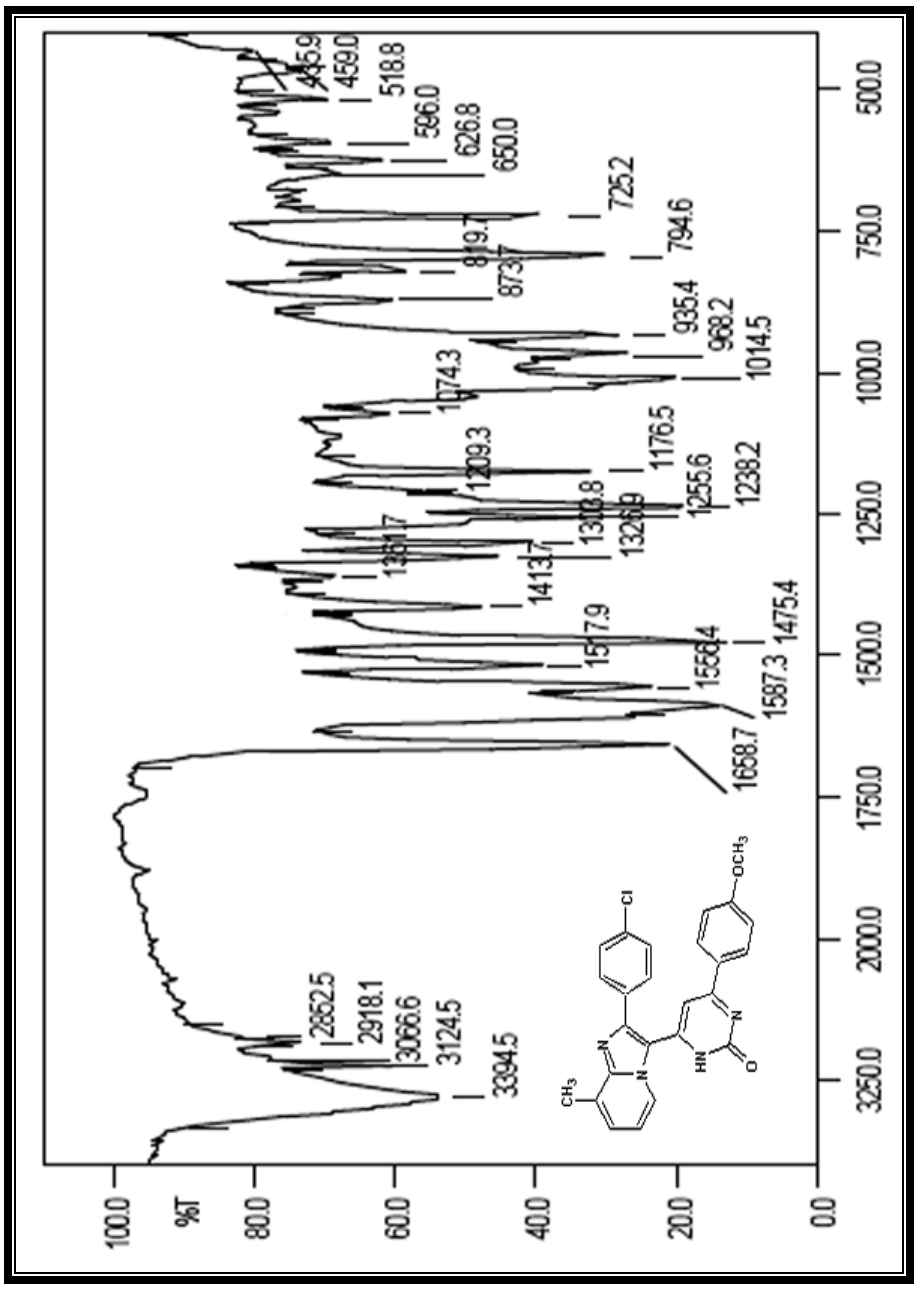

The constitution of the synthesised products have been characterized using elemental analyses, Infrared and $^{1}$H-nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

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 ***A. niger*** at a concentration 40µg. The biological activities of synthesized compounds recorded in table.

## REACTION SCHEME



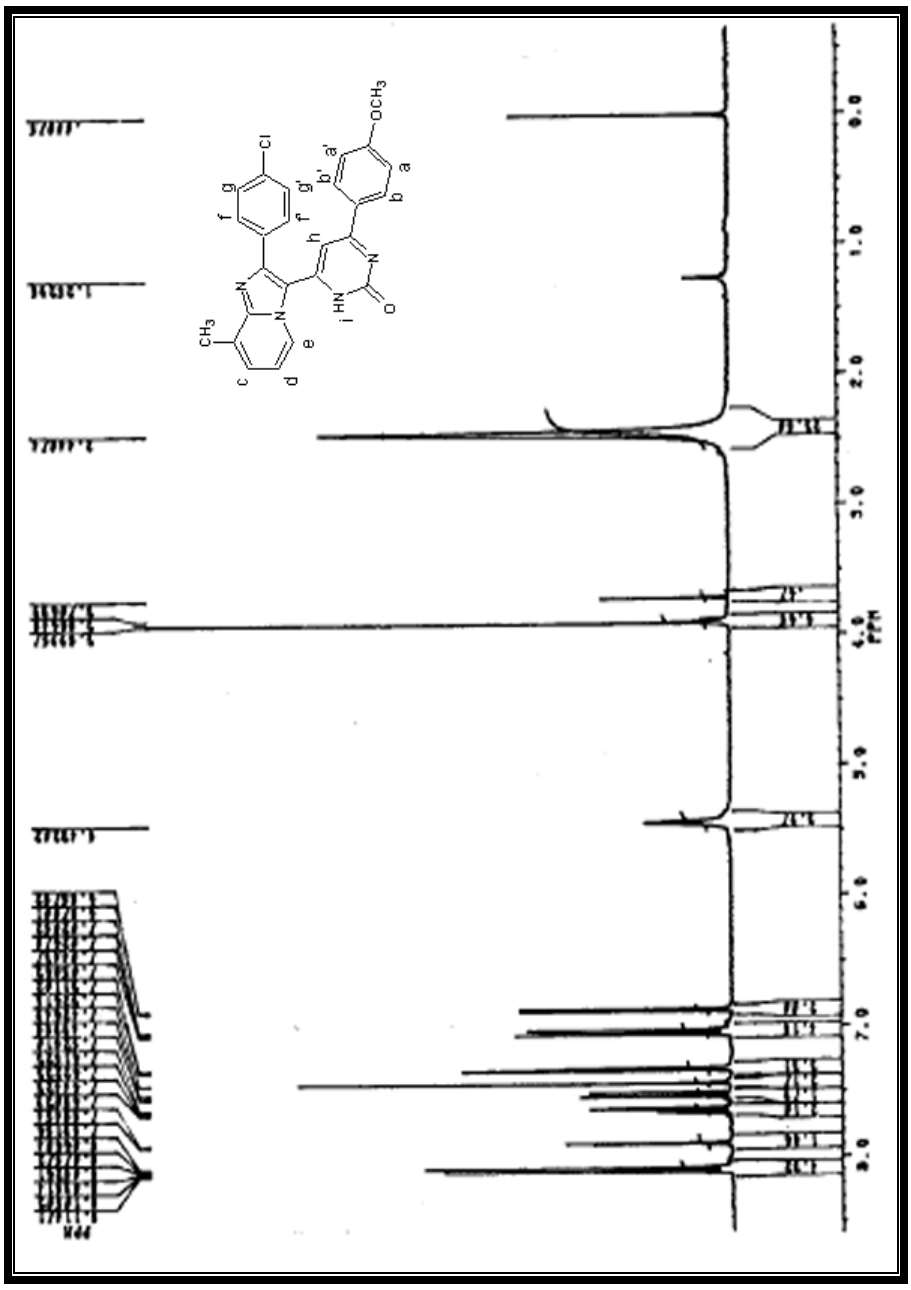
**IR SPECTRAL STUDIES OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)PYRIMIDINE-2(*H*)-ONE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2918 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2852 | 2880-2860 | ” |
| | C-H i.p.def | 1475 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1361 | 1395-1370 | ” |
| Aromatic | C-H str. | 3066 | 3090-3030 | 143-b |
| | C=C Str. | 1517 | 1520-1480 | ” |
| | C-H i.p.def | 1015 | 1070-1000 | ” |
| | C-H o.o.p.def. | 820 | 835-810 | ” |
| Moiety | C=N str. | 1587 | 1610-1590 | 143-c |
| | C-N str. | 1176 | 1230-1020 | ” |
| | C-Cl str. | 794 | 800-750 | ” |
| Pyrimidine | -NH str.(sym.) | 3394 | 3450-3350 | 143-d |
| | C=O str. | 1658 | 1700-1640 | ” |

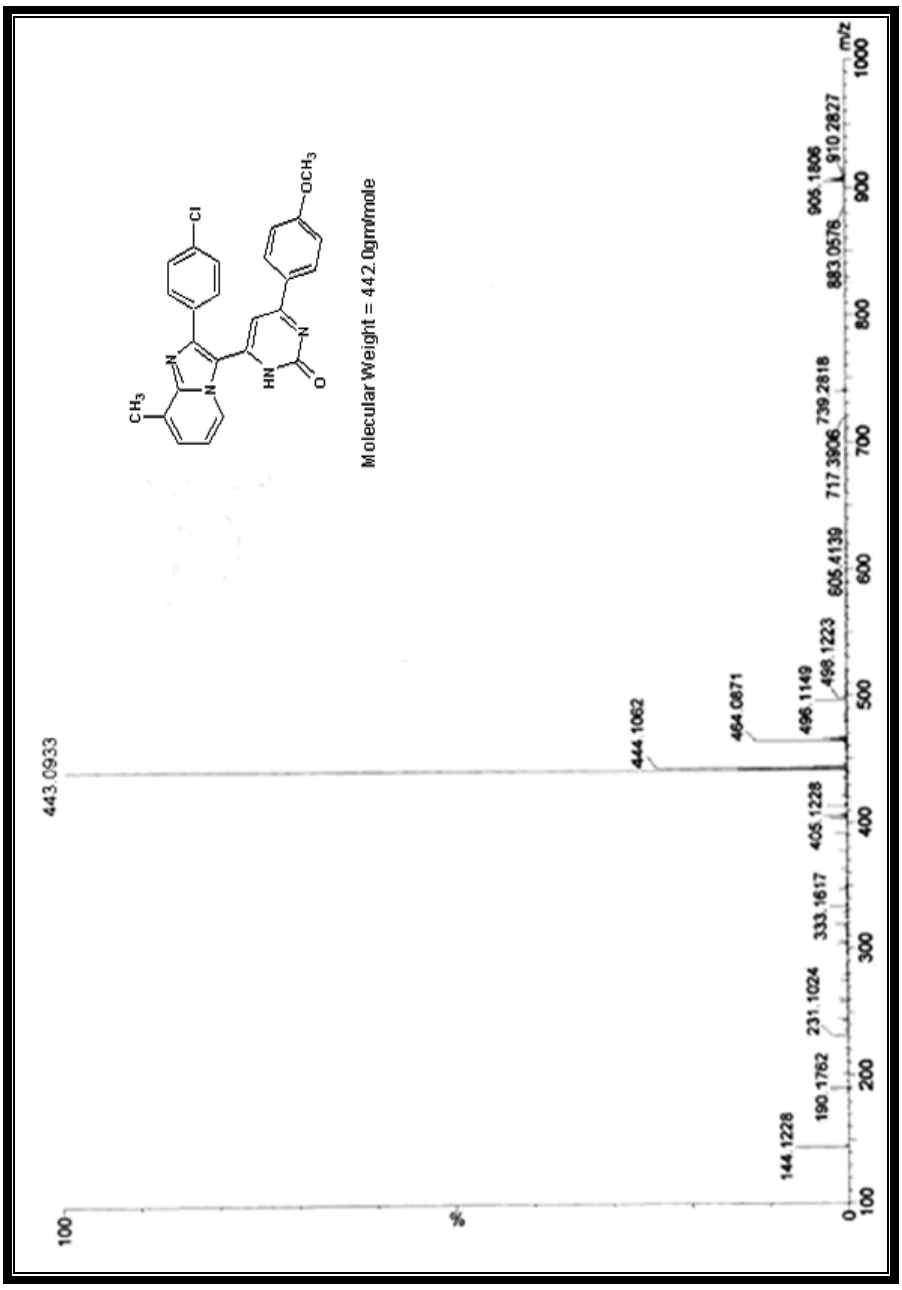
**NMR SPECTRAL STUDIES OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)PYRIMIDINE-2(*H*)-ONE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.40 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.95 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 5.40 | 1H | singlet | Ar-Hh |
| 4 | 7.20 | 1H | triplet | Ar-Hd |
| 5 | 6.95 | 2H | doublet | Ar-H(a,a') |
| 6 | 7.00 | 2H | doublet | Ar-H(b,b') |
| 7 | 7.53 | 2H | doublet | Ar-H(f,f') |
| 8 | 7.45 | 2H | doublet | Ar-H(g,g') |
| 9 | 7.30 | 1H | doublet | Ar-Hc |
| 10 | 8.07 | 1H | doublet | Ar-He |
| 11 | 8.00 | 1H | singlet | -NH- |

**MASS SPECTRAL STUDIES OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)PYRIMIDINE-2(*H*)-ONE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-(4-methoxyphenyl)pyrimidine-2(*H*)-one.**

**[A] Preparation of 2-chloro-1-(*p*-chlorophenyl)ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2- (*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine -3-yl]-1-aryl prop-2-en-1-one.**

See on Page No. 38 Part-I (D)

**[E] Preparation of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine -3-yl)-4-(4-methoxyphenyl)pyrimidine-2(*H*)-one.**

A mixture (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one.(4.02gm,0.01m) and Urea (0.60gm,0.01m) was refluxed in methanol for 6-8 hrs. NaOH is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 59% (2.60gm) ; m.p.177 °C ; ($C_{25}H_{19}ClN_4O$ ; Found : C,67.78%;H,4.30%;N,12.60% ; Required : C,67.80%;H,4.32%;N,12.65%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Oxopyrimidines derivatives have been obtained. The physical data are recorded in Table No.- 2(IB).

**[F] Antimicrobial activity of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo [1,2-*a*]pyridine-3-yl)- 4-aryl pyrimidine-2(*H*)-one.**

Antimicrobial testing was carried out as described in **part- I Experimental Section [E]** Page No. 38. The zone of inhibition of the test solution are recorded in Table No.- 2(IA).

**TABLE NO.- 2(IA) BIOLOGICAL SCREENING OF 6-(2-(4-CHLOROPHENYL -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(*H*)-ONE.**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **2(Ia)** | $C_6H_5$- | 16 | 15 | 14 | 13 | **17** |
| **2(Ib)** | 4-$CH_3$-$C_6H_4$ - | 14 | 13 | 13 | 14 | 15 |
| **2(Ic)** | 4-$OCH_3$ -$C_6H_4$- | 16 | 14 | 15 | 16 | 13 |
| **2(Id)** | 4-Cl-$C_6H_4$ - | **19** | **18** | 16 | 17 | 14 |
| **2(Ie)** | 4-F-$C_6H_4$ - | 15 | 14 | 13 | 16 | 13 |
| **2(If)** | 4-Br-$C_6H_4$ - | 14 | 13 | 15 | 13 | 14 |
| **2(Ig)** | 4-$NH_2$-$C_6H_4$ - | 16 | 15 | 14 | 14 | 15 |
| **2(Ih)** | 4-$NO_2$-$C_6H_4$ - | 14 | 13 | 12 | 15 | 16 |
| **2(Ii)** | 4-OH-$C_6H_4$ - | 18 | 17 | **17** | **19** | **18** |
| **Std$^n$** | Ampicillin | 21 | 20 | 23 | 22 | - |
| **”** | Amoxicillin | 23 | 21 | 20 | 22 | - |
| **”** | Ciprofloxacin | 24 | 23 | 22 | 21 | - |
| **”** | Norfloxacin | 22 | 22 | 24 | 23 | - |
| **”** | Greseofulvin | - | - | - | - | 23 |

**TABLE NO.- 2(IB) PHYSICAL CONSTANTS OF 6-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(*H*)-ONE.**

| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **2(Ia)** | $C_6H_5$ - | $C_{24}H_{17}ClN_4O$ | 412.0 | 165.0 | 0.54 | 52.0 | 13.57 | 13.50 |
| **2(Ib)** | 4-$CH_3$-$C_6H_4$ - | $C_{25}H_{19}ClN_4O$ | 426.0 | 175.0 | 0.56 | 55.0 | 13.12 | 12.90 |
| **2(Ic)** | 4-$OCH_3$-$C_6H_4$- | $C_{25}H_{19}ClN_4O_2$ | 442.5 | 177.0 | 0.55 | 59.0 | 12.65 | 12.60 |
| **2(Id)** | 4-Cl-$C_6H_4$ - | $C_{24}H_{16}Cl_2N_4O$ | 446.0 | 170.0 | 0.56 | 60.0 | 12.53 | 12.40 |
| **2(Ie)** | 4-F-$C_6H_4$ - | $C_{24}H_{16}ClFN_4O$ | 430.0 | 162.0 | 0.53 | 54.0 | 13.00 | 12.97 |
| **2(If)** | 4-Br-$C_6H_4$ - | $C_{24}H_{16}ClBrN_4O$ | 490.0 | 155.0 | 0.59 | 57.0 | 11.39 | 11.00 |
| **2(Ig)** | 4-$NH_2$-$C_6H_4$ - | $C_{24}H_{18}ClN_5O$ | 427.0 | 169.0 | 0.57 | 58.0 | 16.37 | 16.35 |
| **2(Ih)** | 4-$NO_2$-$C_6H_4$ - | $C_{24}H_{16}ClN_5O_3$ | 457.0 | 180.0 | 0.56 | 61.0 | 15.30 | 15.19 |
| **2(Ii)** | 4-OH-$C_6H_4$ - | $C_{24}H_{17}ClN_4O_2$ | 428.0 | 172.0 | 0.52 | 58.0 | 13.06 | 13.02 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

# SECTION-II

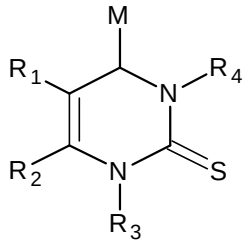
# STUDIES ON

# THIOPYRIMIDINES

## INTRODUCTION

Thiopyrimidine derivatives first primary synthesise from aliphatic fragments was carried out by Frankland and Kolbs in 1848. Since then a many distinct primary synthetic method have been derived.[307-316] It is also possible to prepare from other heterocyclic compounds.[317-320]

M = Sub. Ph
$R_1$ = H, $NO_2$
$R_2$ = H, alkyl
$R_3$ = H, alkyl
$R_4$ = amino cycloalkyl




Selective antagonists for human α/A receptors

## SYNTHETIC ASPECT :

Different methods are available in literature.

1. By the condensation of *β*–keto esters with *N*-methyl thiourea.[321]
2. By the condensation of *β*-dintriles with thiourea and gaunidines.[322-324]
3. By the reaction of *β*- aldehydo nitrile with formamidine and thiourea.[325-326]
4. By the condensation of *β*- keto esters with amidino acetamide.[327]

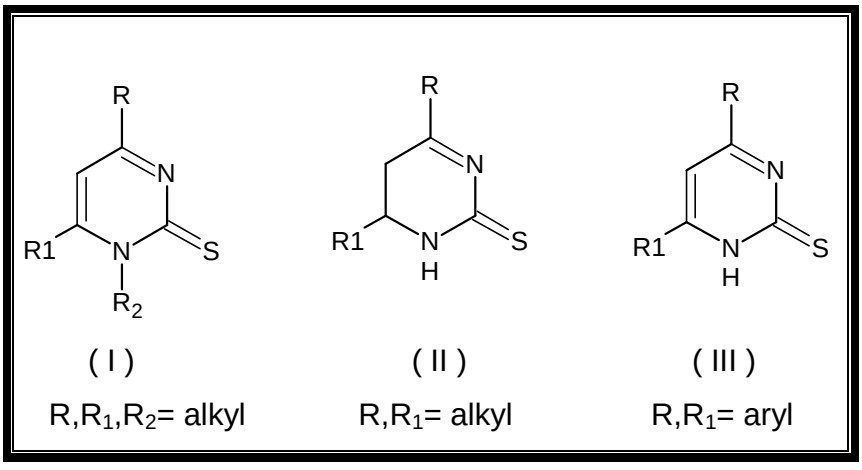
## PHARMACEUTICAL IMPORTANCE

Thiopyrimidine derivatives have wide variety of uses. In particular as biologically active compounds in medicine, so thiopyrimidine derivatives play a vital role in many biological processes and as synthetic drugs.

1. Antifungal[328]
2. Anticancer[329,330,331]

3. Antitumor[332]
4. Cellobiase activity[333]
5. Antimicrobial[334]
6. Antineoplastic[335]
7. Antibacterial[336,337]
8. Antiinflammatory[338,339]
9. Antibiotics[340]
10. Antiviral[341,342]
11. Insecticidal[343]
12. Antifilarial[344]
13. Anti AIDS[345]
14. Antitubercular[346]
15. Antagonist[347]
16. Analgesic[348]

Thiopyrimidine derivatives as a antibacterial and fungicidal drugs ( I ), ( II ) reported by Kashima[349] and ( III ) reported by Naik S. K.[350]

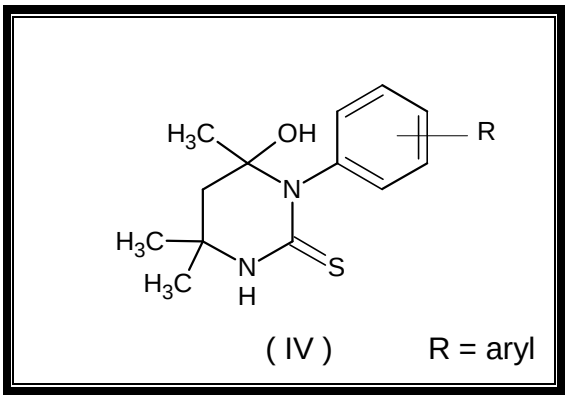



( I ) R,$R_1$,$R_2$= alkyl

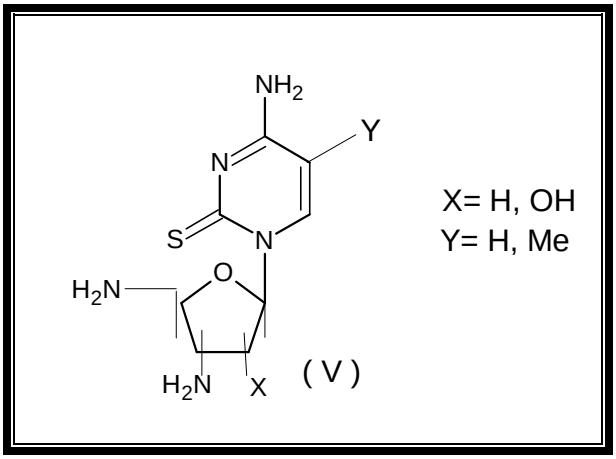
( II ) R,$R_1$= alkyl

( III ) R,$R_1$= aryl

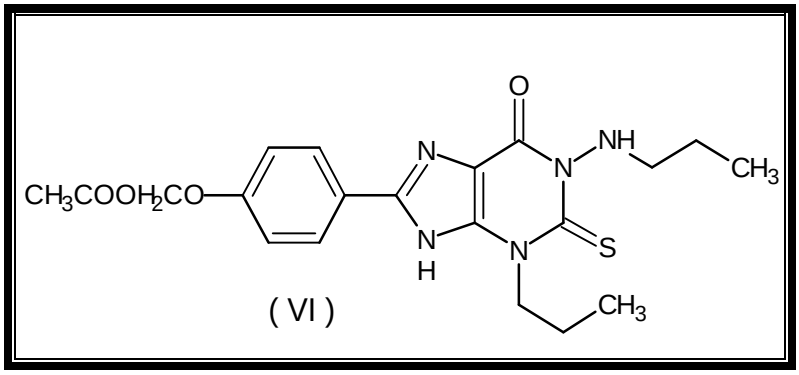
Guseva N. N. and co-workers[351] prepared fungicidal active thiopyrimidine derivative. (IV)



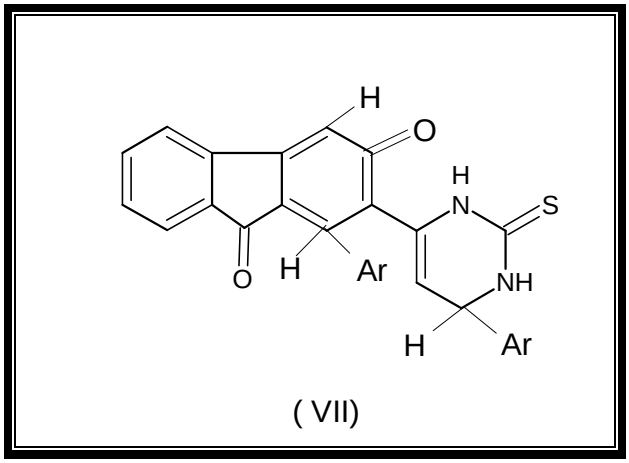

Saneyoshi, Mineo, Wakayama and co-workers[352] have prepared 3'-amino-2-thiopyrimidine nucleosides as anticancer drugs. (V)




C. J. Shishoo and K. S. Jain[353] have prepared thiopyrimidine derivative as a $A_2$ receptor antagonists. (VI)



M.A. Salama and S. A. El Essa[354], have prepared substituted tetrahydro thiopyrimidine derivative as a antimicrobial activity. (VII)



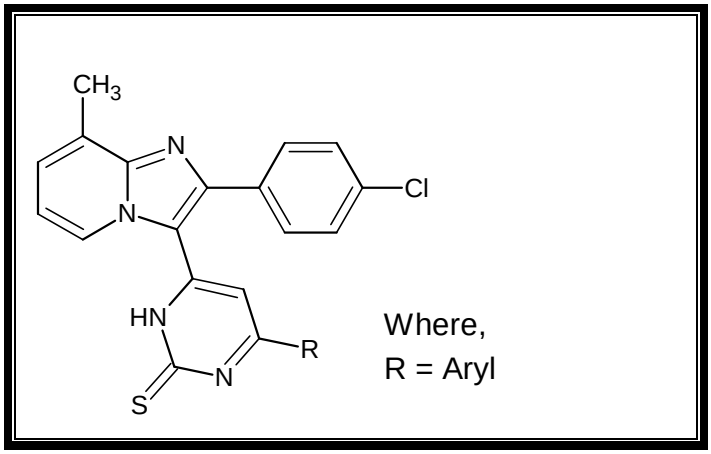

( VII)

Looking to the interesting biological properties of thiopyrimidine it is worthwhile to prepare thiopyrimidine bearing different heterocyclic systems of medicinal value in order to achieve better therapeutic agents. It has been described in the following section-II.

**Section-II : Synthesis and therapeutic evaluation of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-midazo[1,2-*a*]pyridine-3-yl)-4-aryl pyrimidine-2(*H*)-thione.**

**SYNTHESIS AND THERAPEUTIC EVALUATION OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(*H*)-THIONE.**

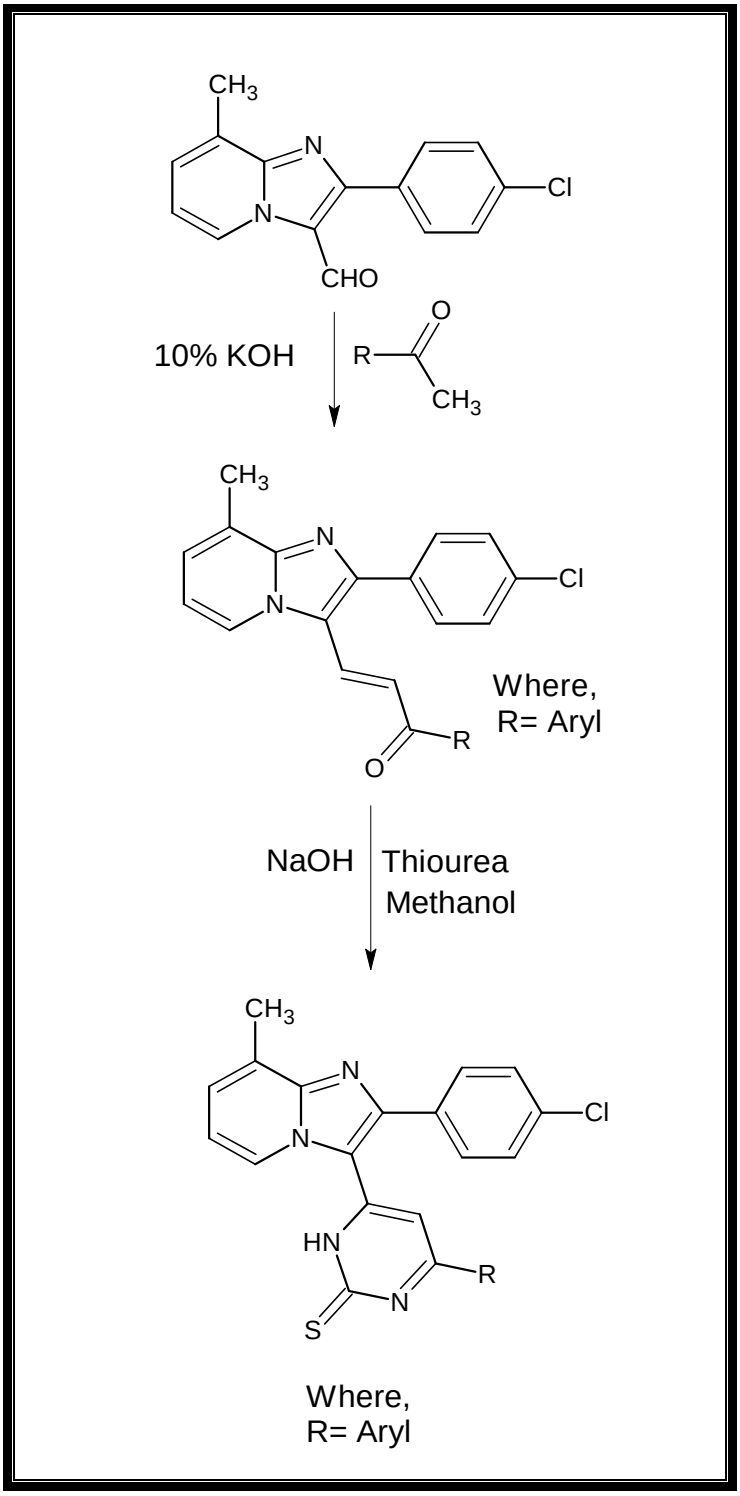
Thiopyrimidines represent one of the most active class of compounds possessing a wide spectrum of biological activities, such as significant ***in vitro*** activity against unrelated DNA and RNA viruses including polio and herpes viruses, diuretic, antitubercular, spermicidal, etc. In view of these facts, It was contemplated to synthesize thiopyrimidine derivatives by condensation of (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one with thiourea in basic media and methanol as a solvents.



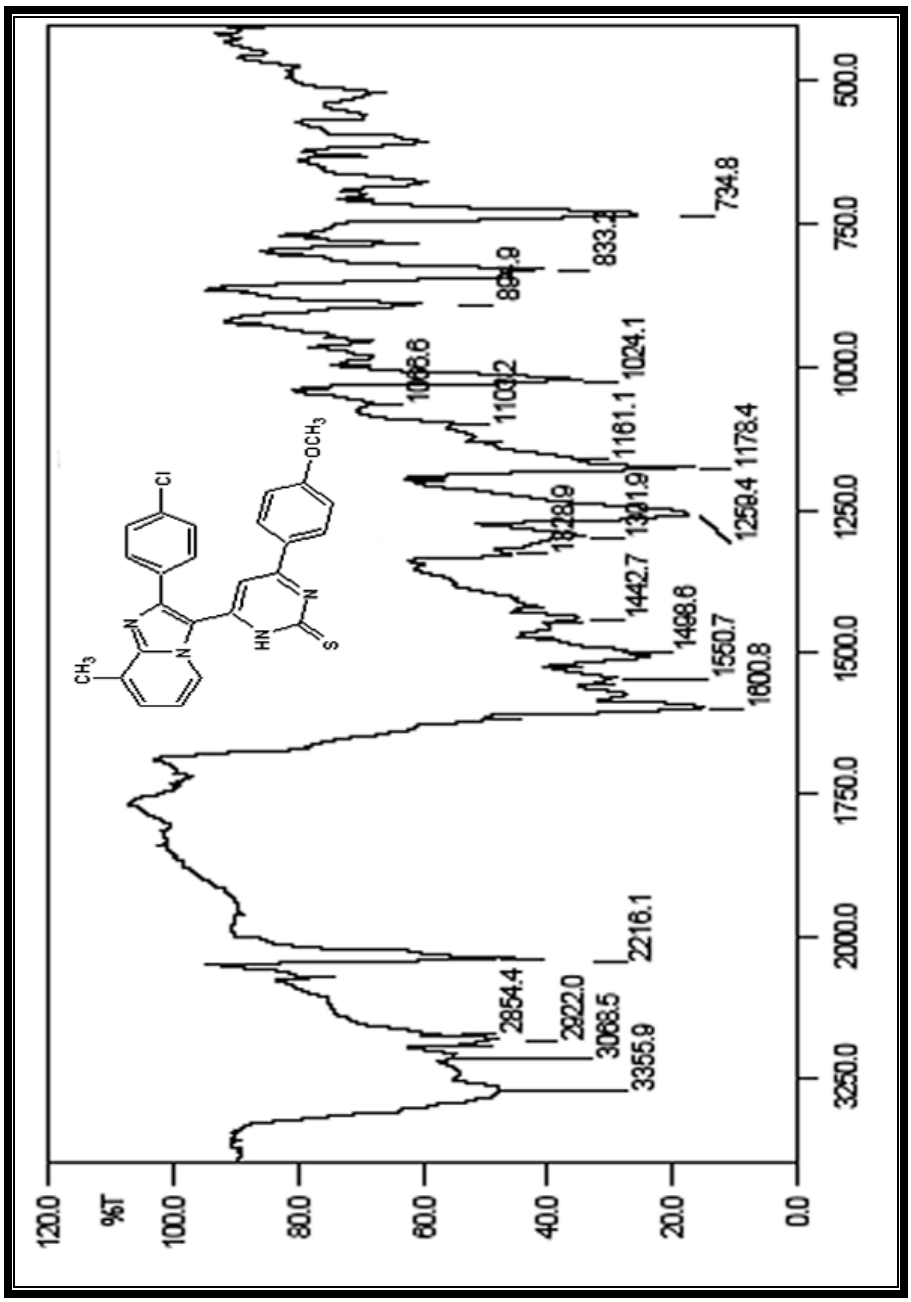

The constitution of the synthesized products have been characterized using elemental analyses, Infrared and $^{1}H$ nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

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 ***A. niger*** at a concentration 40µg. The biological activities of synthesized compounds recorded in table.

## REACTION SCHEME



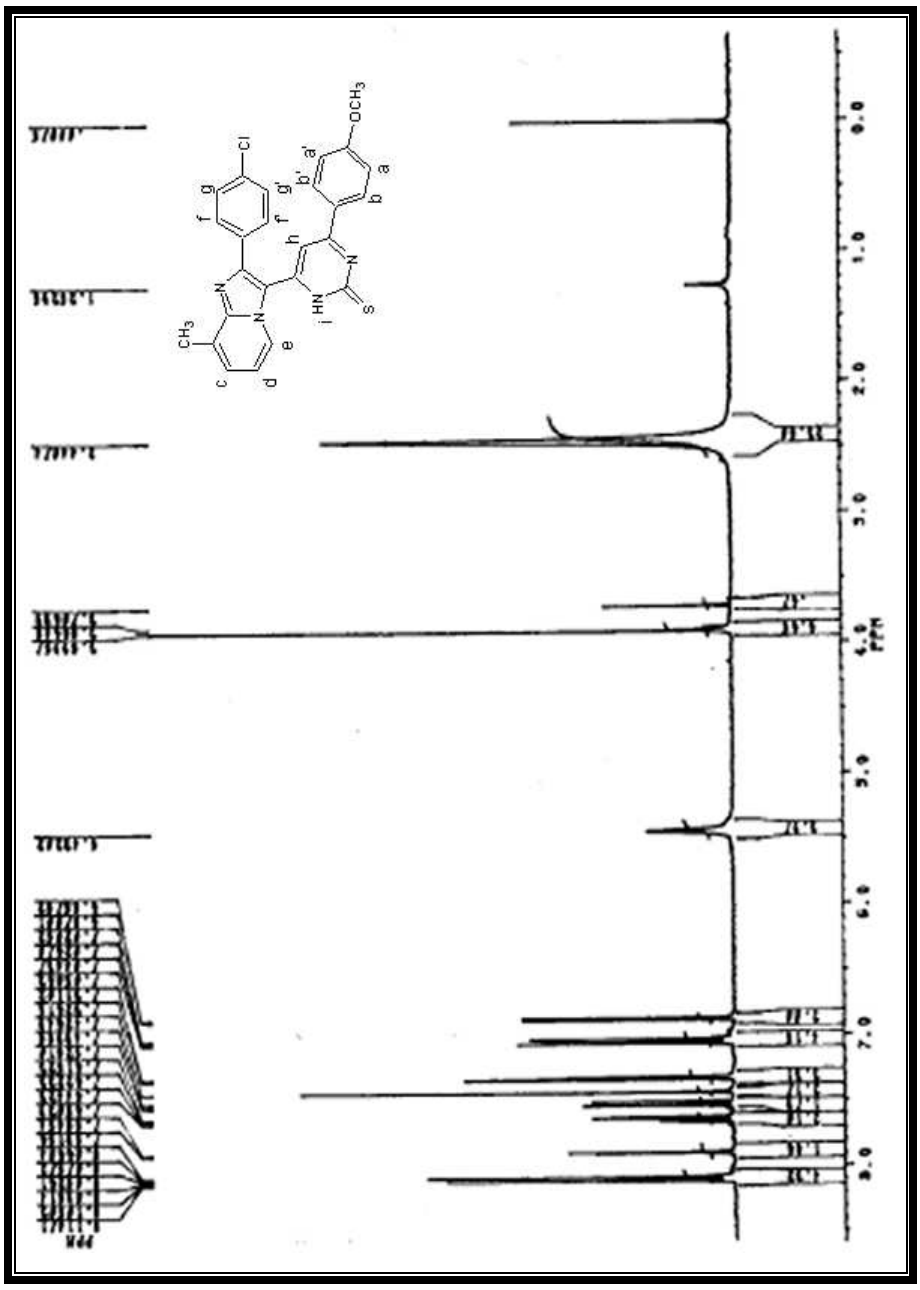
**IR SPECTRAL STUDIES OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO [1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)PYRIMIDINE-2(*H*)-THIONE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2922 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2854 | 2880-2860 | ” |
| | C-H i.p.def | 1442 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1391 | 1395-1370 | ” |
| Aromatic | C-H str. | 3088 | 3090-3030 | 143-b |
| | C=C Str. | 1498 | 1520-1480 | ” |
| | C-H i.p.def | 1178 | 1125-1090 | ” |
| | C-H o.o.p.def. | 833 | 835-810 | ” |
| Moiety | C=N str. | 1600 | 1610-1590 | 143-c |
| | C-N str. | 1178 | 1230-1020 | ” |
| | C-Cl str. | 800 | 800-750 | ” |
| Pyrimidine | C=S str.(asym) | 1259 | 1275-1190 | 143-d |
| | C=S str.(sym.) | 735 | 700-600 | ” |

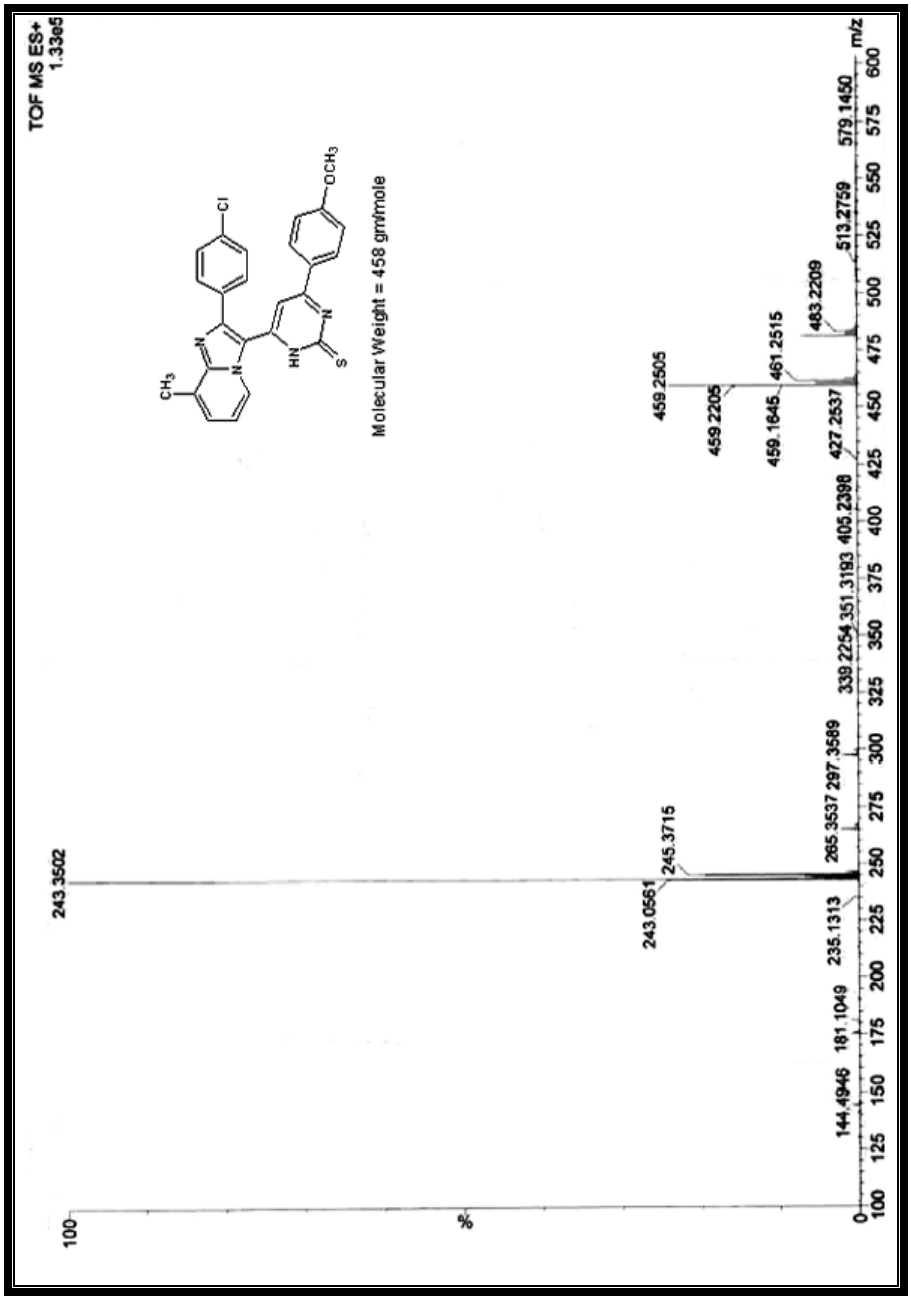
**NMR SPECTRAL STUDIES OF 6-(2-(4-CHLOROPHENYL)-8-METHYL -1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)PYRIMIDINE-2(*H*)-THIONE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.44 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.95 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 5.42 | 1H | singlet | Ar-Hh |
| 4 | 7.20 | 1H | triplet | Ar-Hd |
| 5 | 7.00 | 2H | doublet | Ar-H(a,a') |
| 6 | 7.05 | 2H | doublet | Ar-H(b,b') |
| 7 | 7.50 | 2H | doublet | Ar-H(f,f') |
| 8 | 7.45 | 2H | doublet | Ar-H(g,g') |
| 9 | 7.30 | 1H | doublet | Ar-Hc |
| 10 | 8.05 | 1H | doublet | Ar-He |

**MASS SPECTRAL STUDIES OF 6-(2-(4-CHLOROPHENYL)-8-METHYL -1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)PYRIMIDINE-2(*H*)-THIONE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-(4-methoxyphenyl)pyrimidine-2(*H*)-thione.**

**[A] Preparation of 2-chloro-1-(*p*-chlorophenyl) ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methylimidazo[1,2-*a*]pyridine -3-yl]-1-aryl prop-2-en-1-one.**

See on Page No. 38 Part-I (D)

**[E] Preparation of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine - 3- yl)-4-(4-methoxyphenyl)pyrimidine-2(*H*)-thione.**

A mixture (2z)-3-[2-(4-chlorophenyl)- 8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one.(4.20gm,0.01m) and Thiourea (0.76gm,0.01m) was refluxed in methanol for 6 hrs. NaOH is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 63% (3.0gm) ; m.p.187 °C ; ($C_{25}H_{19}ClN_4OS$ ; Found : C,65.25%;H,4.10%;N,12.15% ; Required : C,65.42%;H,4.17%;N,12.21%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Thiopyrimidines derivatives have been obtained. The physical data are recorded in Table No.- 2(IIB).

**[F] Antimicrobial activity of 6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo [1,2-*a*]pyridine-3-yl)-4-aryl pyrimidine-2(*H*)-thione.**

Antimicrobial testing was carried out as described in **part- I Experimental Section [E]** Page No. 38. The zone of inhibition of the test solution are recorded in Table No.- 2(IIA).

**TABLE NO.- 2(IIA) BIOLOGICAL SCREENING OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(H)-THIONE.**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **2(IIa)** | $C_6H_5$- | 16 | 15 | 16 | **18** | 16 |
| **2(IIb)** | 4-$CH_3$-$C_6H_4$ - | 15 | 14 | 12 | 13 | 14 |
| **2(IIc)** | 4-$OCH_3$ -$C_6H_4$- | 14 | 13 | 15 | 12 | 13 |
| **2(IId)** | 4-Cl-$C_6H_4$ - | 16 | **17** | 14 | 16 | **18** |
| **2(IIe)** | 4-F-$C_6H_4$ - | 15 | 16 | 12 | 14 | 14 |
| **2(IIf)** | 4-Br-$C_6H_4$ - | 13 | 12 | 13 | 14 | 15 |
| **2(IIg)** | 4-$NH_2$-$C_6H_4$ - | 15 | 13 | 14 | 12 | 16 |
| **2(IIh)** | 4-$NO_2$-$C_6H_4$ - | 12 | 14 | 12 | 14 | 15 |
| **2(IIi)** | 4-OH-$C_6H_4$ - | **17** | 16 | **18** | 17 | 16 |
| **Std$^n$** | Ampicillin | 20 | 21 | 22 | 21 | - |
| **”** | Amoxicillin | 22 | 23 | 21 | 20 | - |
| **”** | Ciprofloxacin | 23 | 22 | 24 | 22 | - |
| **”** | Norfloxacin | 21 | 24 | 22 | 23 | - |
| **”** | Greseofulvin | - | - | - | - | 25 |

**TABLE NO.- 2(IIB) PHYSICAL CONSTANTS OF 6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL PYRIMIDINE-2(*H*)-THIONE.**

| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **2(IIa)** | $C_6H_5$ - | $C_{24}H_{17}ClN_4S$ | 428.0 | 173.0 | 0.54 | 59.0 | 13.06 | 13.02 |
| **2(IIb)** | 4-$CH_3$-$C_6H_4$ - | $C_{25}H_{19}ClN_4S$ | 442.0 | 182.0 | 0.58 | 56.0 | 12.65 | 12.62 |
| **2(IIc)** | 4-$OCH_3$-$C_6H_4$- | $C_{25}H_{19}ClN_4OS$ | 458.0 | 187.0 | 0.56 | 63.0 | 12.21 | 12.15 |
| **2(IId)** | 4-Cl-$C_6H_4$ - | $C_{24}H_{16}Cl_2N_4S$ | 462.0 | 175.0 | 0.57 | 60.0 | 12.09 | 11.98 |
| **2(IIe)** | 4-F-$C_6H_4$ - | $C_{24}H_{16}ClFN_4S$ | 446.0 | 160.0 | 0.44 | 65.0 | 12.54 | 12.50 |
| **2(IIf)** | 4-Br-$C_6H_4$ - | $C_{24}H_{16}ClBrN_4S$ | 506.0 | 166.0 | 0.60 | 57.0 | 11.03 | 11.00 |
| **2(IIg)** | 4-$NH_2$-$C_6H_4$ - | $C_{24}H_{18}ClN_5S$ | 443.0 | 171.0 | 0.55 | 55.0 | 15.78 | 15.75 |
| **2(IIh)** | 4-$NO_2$-$C_6H_4$ - | $C_{24}H_{16}ClN_5O_2S$ | 473.0 | 175.0 | 0.56 | 67.0 | 14.78 | 14.70 |
| **2(IIi)** | 4-OH-$C_6H_4$ - | $C_{24}H_{17}ClN_4OS$ | 444.0 | 158.0 | 0.49 | 54.0 | 12.59 | 12.46 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

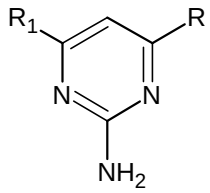
# SECTION-III

# STUDIES ON AMINOPYRIMIDINES

## INTRODUCTION

Amino pyrimidine is the most important member of all the diazine as this ring system occurs widely in living organisms. Pyrimidine was first isolated by Gabriel and Colman in 1899. 2-Amino pyrimidine and its derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activities.

Pyrimidine and its derivatives have gained prominence because of their potential pharmaceutical values. They are among those molecules that make life possible as being some of the building blocks of DNA and RNA. Pyrimidine is considered to be a resonance hybrid of the charged and uncharged canonical structures, its resonance energy has been found to be less than benzene or pyridine.

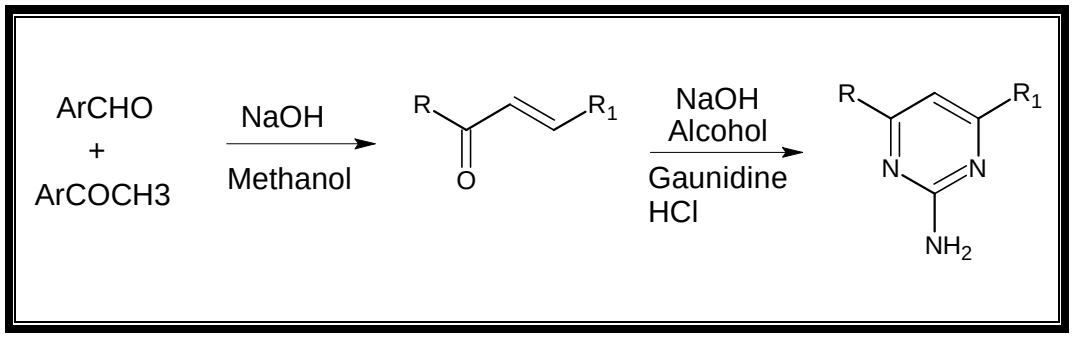



Where,
R=Substituted Phenyl
$R_1$= Substituted Aryl

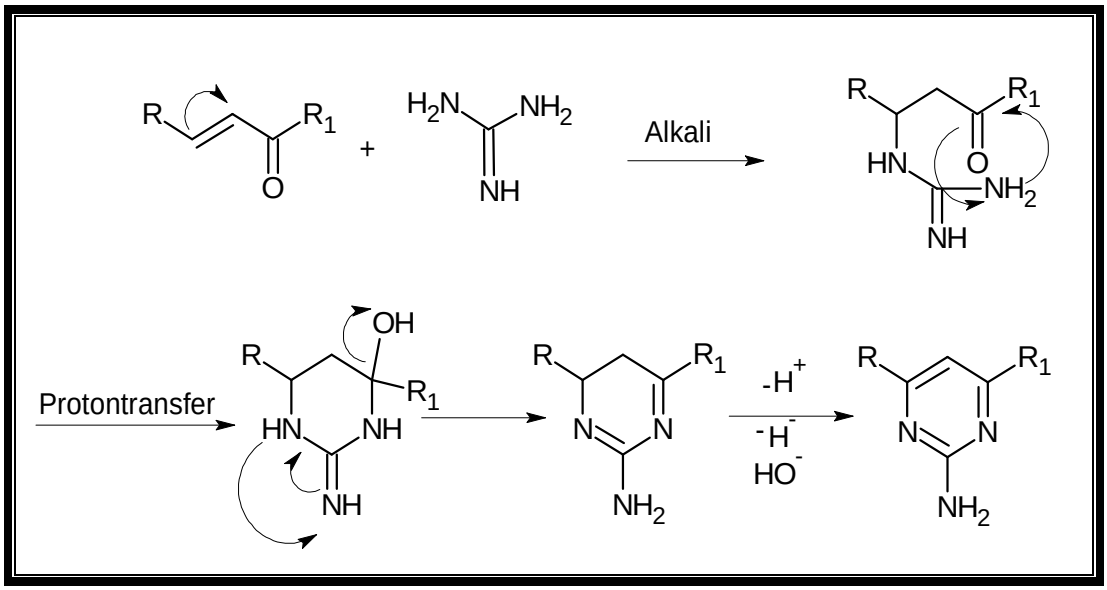
## SYNTHETIC ASPECT :

Different methods are available in literature.

1. By the condensation of *β*–keto esters with N- Substituted guanidine[321].
2. By the condensation of *β*-dintriles with gaunidines[322-324].
3. By the reaction of *β*- aldehydo nitrile with formamidine and guanidine [325-326].
4. By substituted benzaldehyde and Substituted Acetophenone were subjected to the Claisen-Schmidt condensation in the presence of alkali alcoholate and and yielded 1-(1-naphthyl)-3-aryl prop-2-en-1-ones. Compounds reacted with an alcohol solution of Guanidine hydrochloride in aqueous sodium hydroxide to yield the corresponding 2-Aminopyrimidines.[298]




**MECHANISM :**




**PHARMACEUTICAL IMPORTANCE**

Aminopyrimidine derivatives have wide variety of uses. In particular as biologically active compounds in medicine

1 Antitumor
2 Cellobiase activity
3 Antimicrobial
4 Antineoplast
5 Antibacterial

6 Antiinflammatory
7 Antibiotics
8 Antiviral
9 Insecticidal
10 Antagonist[298]
11 Analgesic
12 Antifungal

Due to various biodynamic activities189-248 of pyrimidines and with a view to have potent therapeutic agents, the synthesis of 4-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-6-aryl pyrimidine-2-amine have been undertaken by the condensation of different substituted Chalcones with Guanidine hydrochloride in basic Medium.

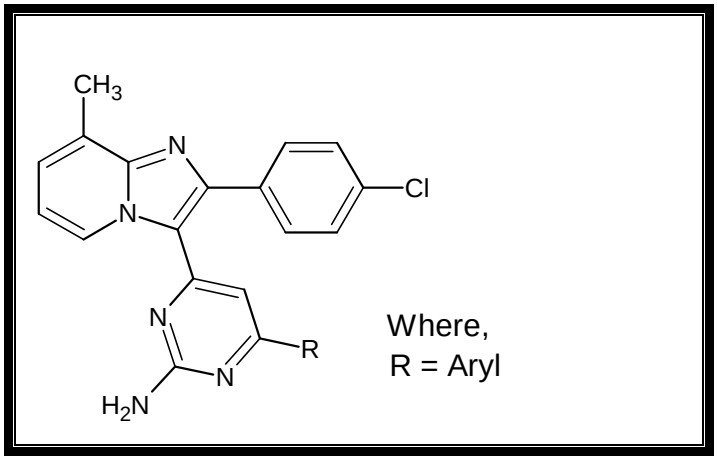
The constitution of the products have been delineated by elemental analyses, IR, $^{1}$H NMR and further supported by Mass spectroscopy. The products were assayed for their ***in vitro*** biological assay like antibacterial activity towards

Looking to the interesting biological properties of Aminopyrimidine it is worthwhile to prepare Aminopyrimidine bearing different heterocyclic systems of medicinal value in order to achieve better therapeutic agents. It has been described in the following section-III.

**Section-III : Synthesis and therapeutic evaluation of 4-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-6-aryl pyrimidine-2-amine.**

**SYNTHESIS AND THERAPEUTIC EVALUATION OF 4-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-6-ARYL PYRIMIDINE-2-AMINE.**

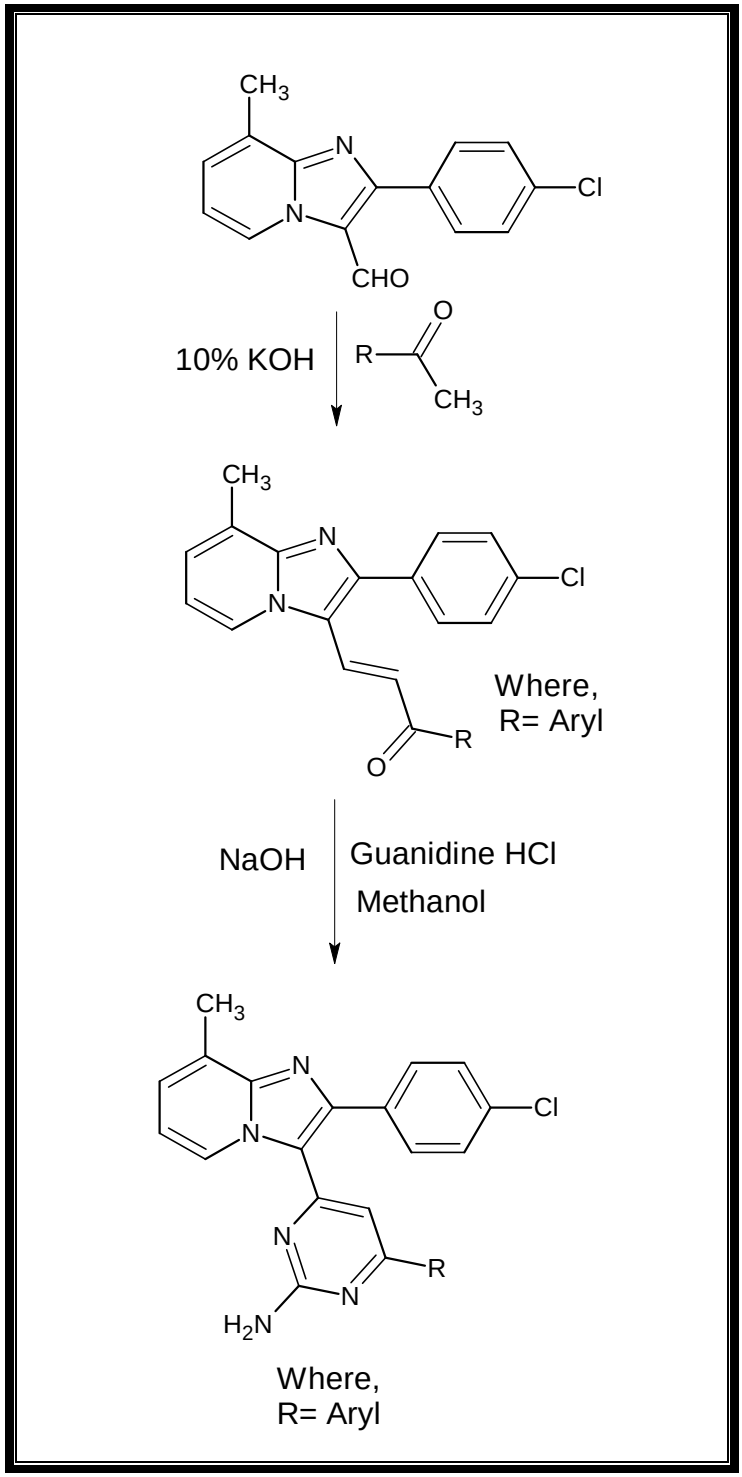
Looking to the interesting pharmacological and agriculture activity of pyrimidine ring system, it was considered worthwhile to synthesise. Amino pyrimidine derivatives synthesized by condensation of (2z)-3-[2-(4-chlorophenyl) -8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one with guanidine hydrochloride in basic media and methanol as a solvent for study their biological activities.



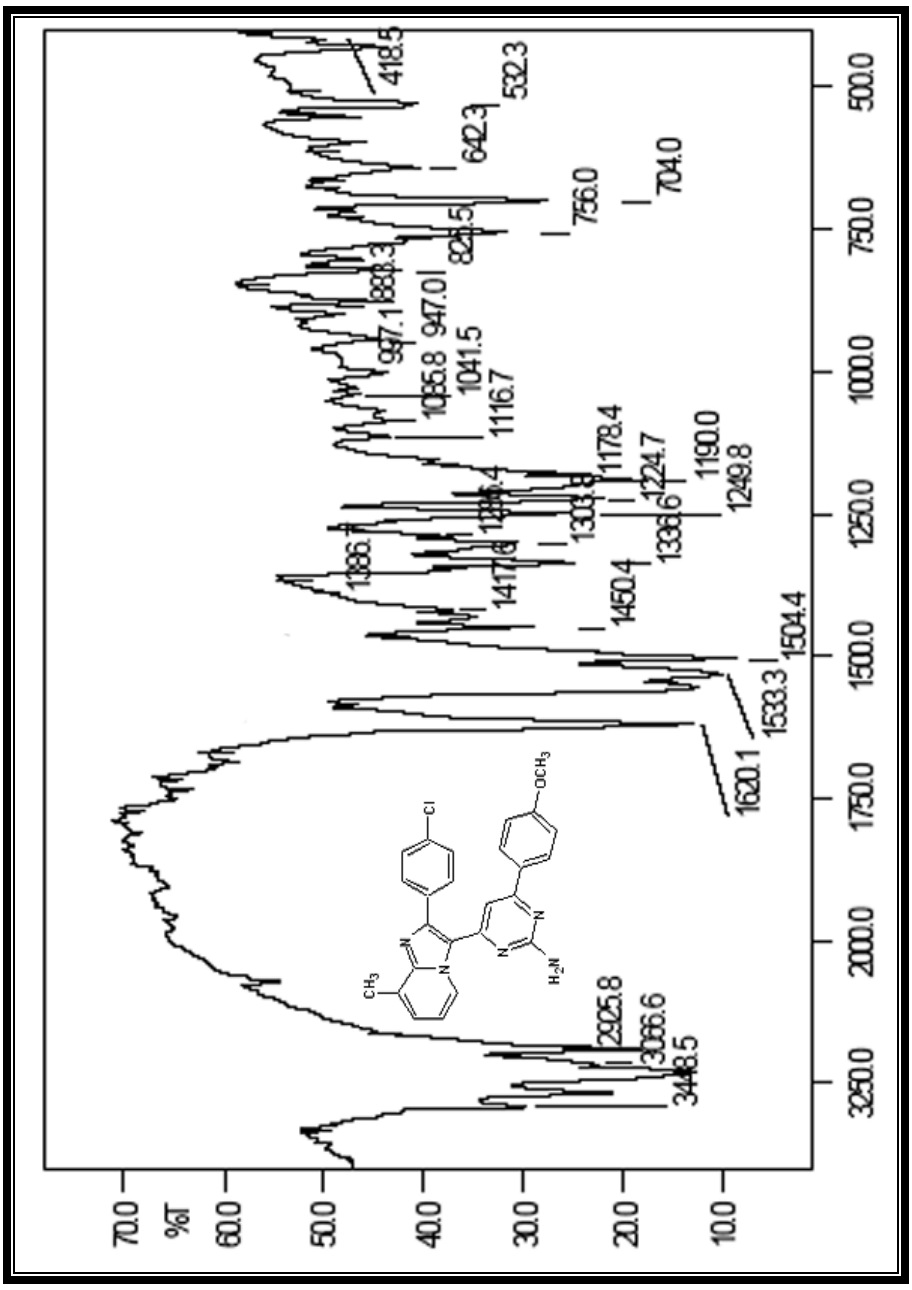

The constitution of the synthesized products have been characterized using elemental analyses, Infrared and $^{1}H$ nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

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 ***A. Niger*** at a concentration 40µg. The biological activities of synthesized compounds recorded in table.

## REACTION SCHEME



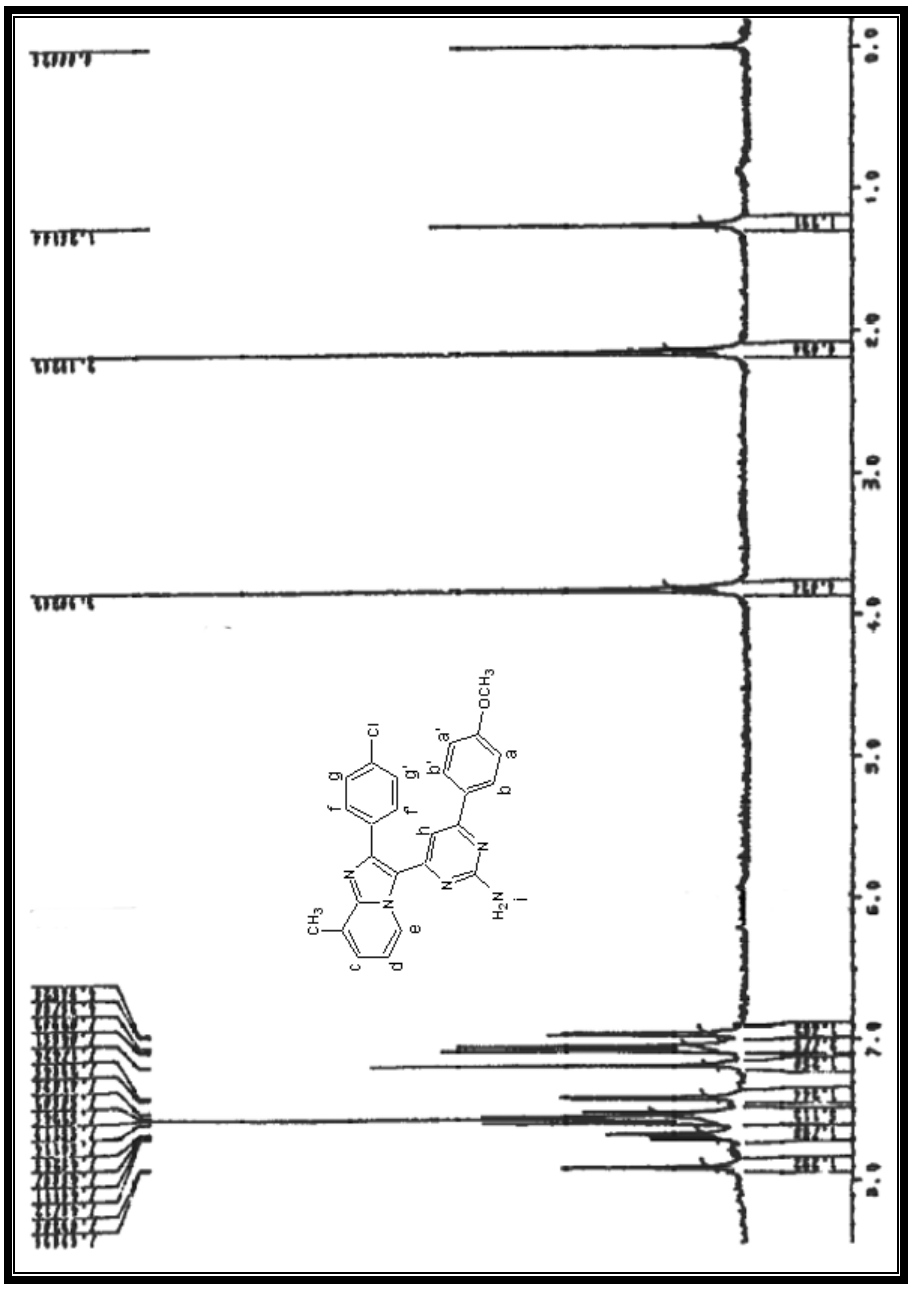
**IR SPECTRAL STUDIES OF 4-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO [1,2-*a*]PYRIDINE-3-YL)-6-(4-METHOXYPHENYL)PYRIMIDINE-2-AMINE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2925 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2880 | 2880-2860 | ” |
| | C-H i.p.def | 1450 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1386 | 1395-1370 | ” |
| Aromatic | C-H str. | 3066 | 3090-3030 | 143-b |
| | C=C Str. | 1504 | 1520-1480 | ” |
| | C-H i.p.def | 1041 | 1070-1000 | ” |
| | C-H o.o.p.def. | 825 | 835-810 | ” |
| Moiety | C=N str. | 1620 | 1610-1590 | 143-c |
| | C-N str. | 1190 | 1230-1020 | ” |
| | C-Cl str. | 756 | 800-750 | ” |
| Pyrimidine | N-H str.(sym) | 3448 | 3450-3350 | 143-d |
| | C-N str. | 1190 | 1220-1020 | ” |

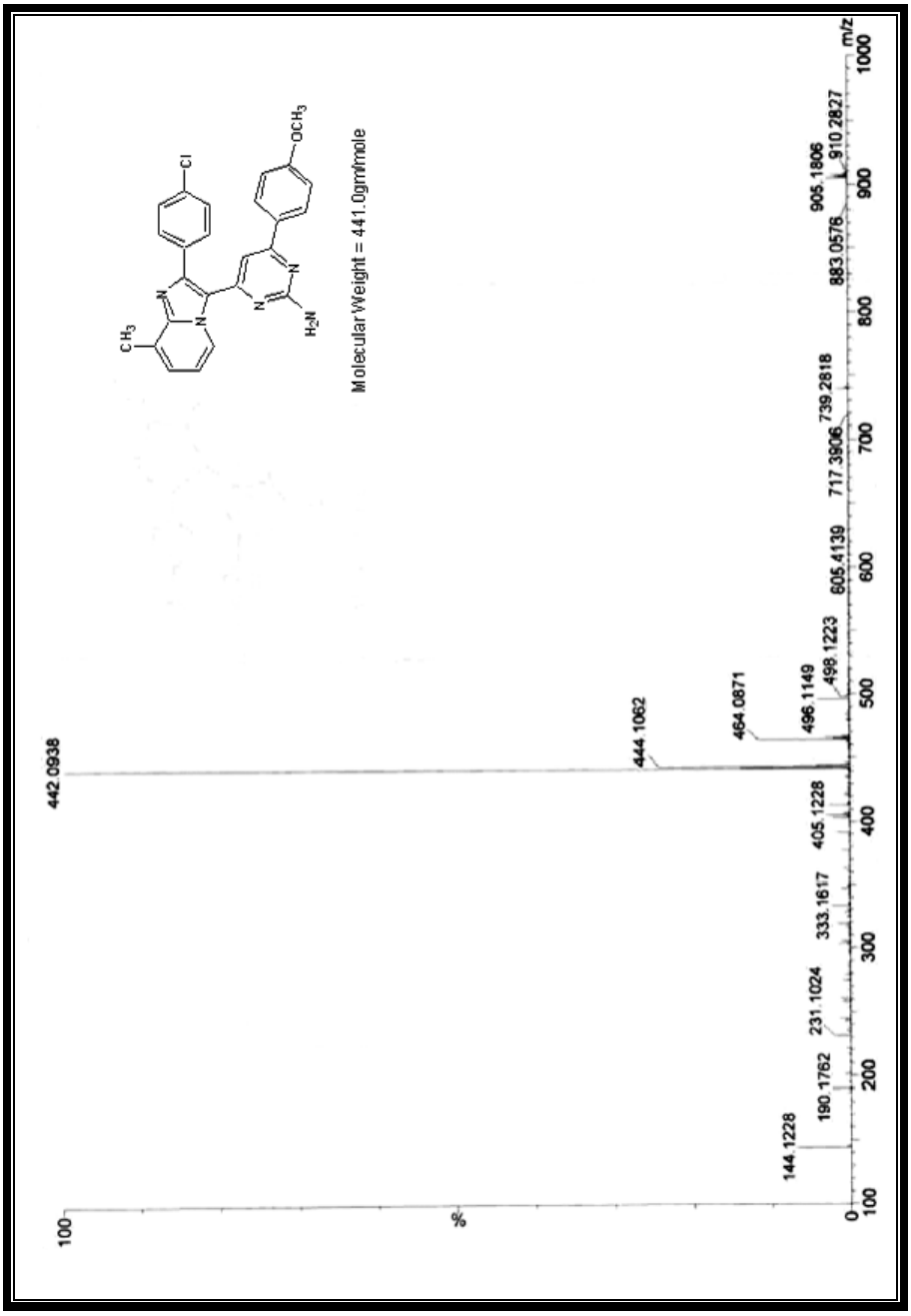
**NMR SPECTRAL STUDIES OF 4-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-6-(4-METHOXYPHENYL)PYRIMIDINE-2-AMINE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.30 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.80 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 7.40 | 1H | triplet | Ar-Hd |
| 4 | 6.90 | 2H | doublet | Ar-H(a,a') |
| 5 | 7.10 | 2H | doublet | Ar-H(b,b') |
| 6 | 7.75 | 2H | doublet | Ar-H(f,f') |
| 7 | 7.60 | 2H | doublet | Ar-H(g,g') |
| 8 | 7.00 | 1H | doublet | Ar-Hc |
| 9 | 7.95 | 1H | doublet | Ar-He |
| 10 | 7.50 | 1H | singlet | Ar-Hh |

**MASS SPECTRAL STUDIES OF 4-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-6-(4-METHOXYPHENYL)PYRIMIDINE-2-AMINE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of 4-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-6-(4-methoxyphenyl)pyrimidine-2-amine.**

**[A] Preparation of 2-chloro-1-(*p*-chlorophenyl) ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine -3-yl]-1-aryl prop-2-en-1-one.**

See on Page No. 38 Part-I (D)

**[E] Preparation of 4-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine - 3- yl)-6-(4-methoxyphenyl)pyrimidine-2-amine.**

A mixture (2z)-3-[2-(4-chlorophenyl)-8-methy imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one.(4.02gm,0.01m) and Guanidine hydrochloride (0.59gm,0.01m) was refluxed in methanol for 6-8 hrs. NaOH is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloro methane. Yield 61% (2.9gm); m.p.165 °C; ($C_{25}H_{20}ClN_5O$; Found:C,67.85%;H,4.55%; N,15.83% ; Required : C,67.95%;H,4.56%;N,15.85%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Aminopyrimidines derivatives have been obtained. The physical data are recorded in Table No.- 2(IIIB).

**[F] Antimicrobial activity of 4-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo [1,2-*a*]pyridine-3-yl)-6-aryl pyrimidine-2-amine.**

Antimicrobial testing was carried out as described in **Part- I Experimental Section [E]** Page No. 38 . The zone of inhibition of the test solution are recorded in Table No.- 2(IIIA).

**TABLE NO.- 2(IIIA) BIOLOGICAL SCREENING OF (4-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-6-ARYL PYRIMIDINE-2-AMINE.**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **2(IIIa)** | $C_6H_5$- | 18 | 17 | 15 | **17** | 15 |
| **2(IIIb)** | 4-$CH_3$-$C_6H_4$ - | 16 | 15 | 13 | 14 | 14 |
| **2(IIIc)** | 4-$OCH_3$ -$C_6H_4$- | 15 | 14 | 15 | 13 | 12 |
| **2(IIId)** | 4-Cl-$C_6H_4$ - | 17 | 18 | **18** | 16 | 17 |
| **2(IIIe)** | 4-F-$C_6H_4$ - | 16 | 15 | 14 | 15 | 14 |
| **2(IIIf)** | 4-Br-$C_6H_4$ - | 14 | 13 | 15 | 14 | 13 |
| **2(IIIg)** | 4-$NH_2$-$C_6H_4$ - | 16 | 14 | 13 | 15 | 12 |
| **2(IIIh)** | 4-$NO_2$-$C_6H_4$ - | 13 | 15 | 14 | 14 | 16 |
| **2(IIIi)** | 4-OH-$C_6H_4$ - | **20** | **19** | 17 | 16 | 19 |
| **Std$^n$** | Ampicillin | 21 | 21 | 22 | 22 | - |
| **”** | Amoxicillin | 23 | 23 | 21 | 21 | - |
| **”** | Ciprofloxacin | 24 | 22 | 24 | 23 | - |
| **”** | Norfloxacin | 22 | 24 | 23 | 23 | - |
| **”** | Greseofulvin | - | - | - | - | 24 |

**TABLE NO.- 2(IIIB) PHYSICAL CONSTANTS OF (4-((2-(4-CHLOROPHENYL) - 8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-6-ARYL PYRIMIDINE-2-AMINE.**

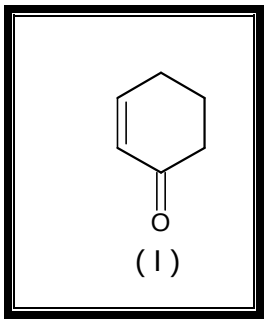
| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **2(IIIa)** | $C_6H_5$ - | $C_{24}H_{18}ClN_5$ | 411.0 | 162.0 | 0.56 | 59.0 | 17.00 | 16.97 |
| **2(IIIb)** | 4-$CH_3$-$C_6H_4$ - | $C_{25}H_{20}ClN_5$ | 425.0 | 170.0 | 0.58 | 56.0 | 16.44 | 16.37 |
| **2(IIIc)** | 4-$OCH_3$-$C_6H_4$- | $C_{25}H_{20}ClN_5O$ | 441.0 | 165.0 | 0.55 | 61.0 | 15.85 | 15.83 |
| **2(IIId)** | 4-Cl-$C_6H_4$ - | $C_{24}H_{17}Cl_2N_5$ | 445.0 | 159.0 | 0.53 | 59.0 | 15.69 | 15.62 |
| **2(IIIe)** | 4-F-$C_6H_4$ - | $C_{24}H_{17}ClFN_5$ | 429.0 | 152.0 | 0.52 | 55.0 | 16.29 | 16.18 |
| **2(IIIf)** | 4-Br-$C_6H_4$ - | $C_{24}H_{17}ClBrN_5$ | 489.0 | 149.0 | 0.60 | 57.0 | 14.27 | 14.26 |
| **2(IIIg)** | 4-$NH_2$-$C_6H_4$ - | $C_{24}H_{19}ClN_6$ | 426.0 | 160.0 | 0.55 | 58.0 | 19.69 | 19.60 |
| **2(IIIh)** | 4-$NO_2$-$C_6H_4$ - | $C_{24}H_{17}ClN_6O_2$ | 456.0 | 168.0 | 0.56 | 60.0 | 18.39 | 18.35 |
| **2(IIIi)** | 4-OH-$C_6H_4$ - | $C_{24}H_{18}ClN_5O$ | 427.0 | 156.0 | 0.50 | 54.0 | 16.37 | 16.31 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

# PART-III

# STUDIES ON CYCLOHEXENONES

## INTRODUCTION

Cyclohexenone is the parent of a series of compounds that is important in agricultural and medicinal chemistry. Cyclohexenones are derivatives of cyclo hexane with carbonyl group at 1-position and double bond at 2-position (I). Cyclohexenones can be conveniently synthesised by the treatment of *α,β* - unsaturated carbonyl compounds with ethylacetoacetate in basic media.



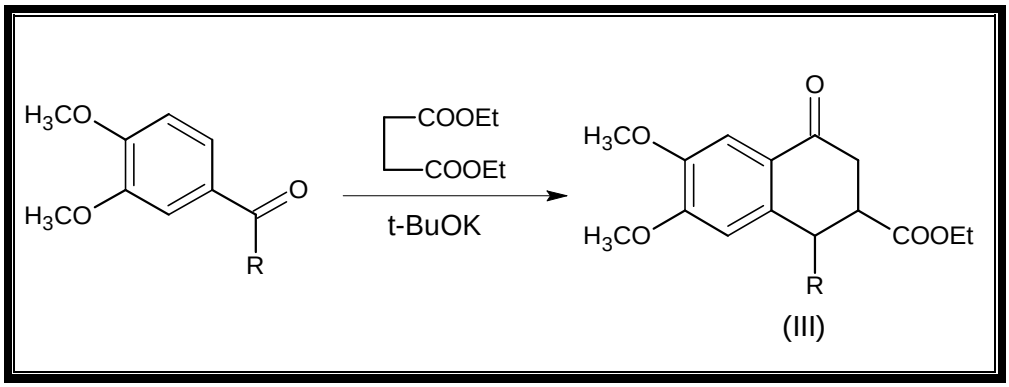

( I )

In recent years cyclohexenone derivatives have gained lots of interest because of its prominent pharmaceutical properties.

## SYNTHETIC ASPECT

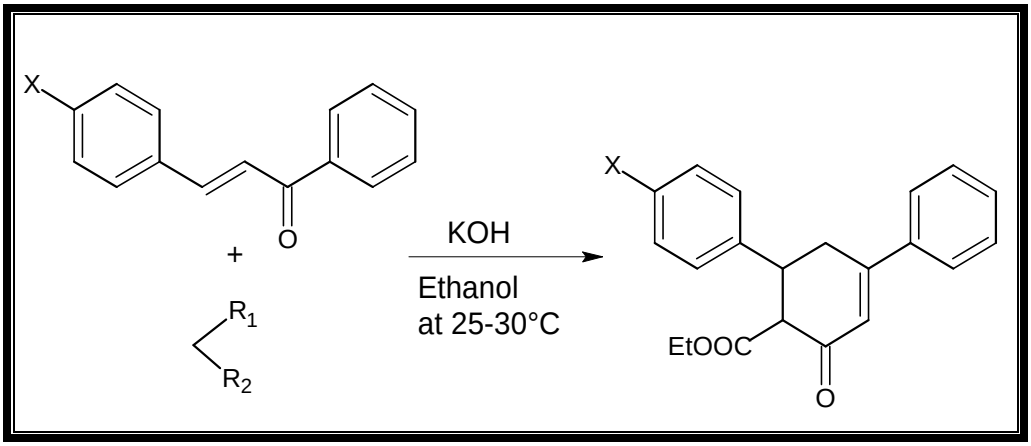
Different methods for the synthesis of cyclohexenone derivatives have been described in literature.[355-361]

1. N. Nanjundaswami et al.[362] have prepared 6,7-dimethoxy-1-aryl-4-oxo-2-naphthoate derivatives (III) by the reaction of dimethoxyphenyl aryl ketone with diethyl succinate in presence of t-potassium butoxide.

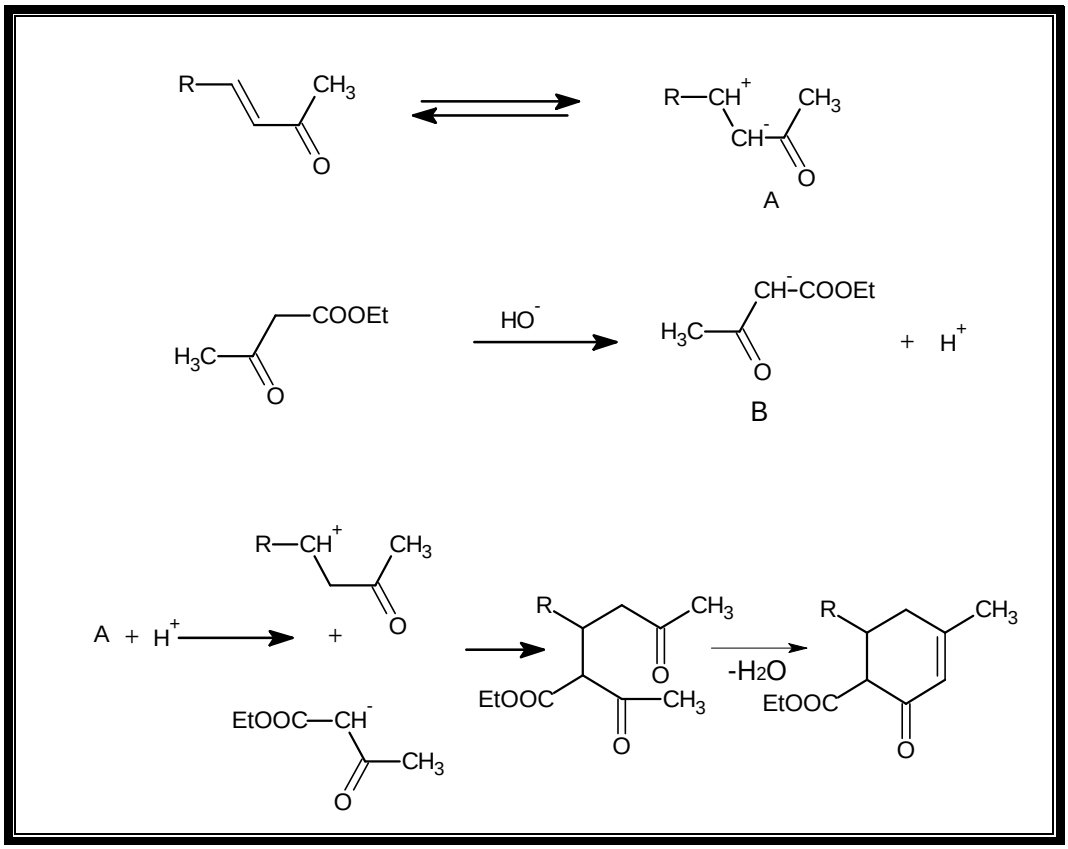



(III)

2. Michael addition of chalcone with active methylene compound such as diethyl malonate, nitro methane and ethyl aceto acetate catalyzed by potassium hydroxide in anhydrous ethanol results Michael adducts in 75–98% yield under ultrasound irradiation in 25–90 min.[363]




**MECHANISM**



The addition reaction between ethylacetoacetate and *α*,*β*-unsaturated ketone give cyclohexenone *via.* Michael addition. This reaction has been carried out in basic media by using sodium ethoxide or anhy. $K_2CO_3$ in acetone. During the reaction nucleophillic addition of carbanion take place to the C=C of the acceptor. The *α,β*-unsaturated compound is known as acceptor and ethylacetoacetate is known as donor.

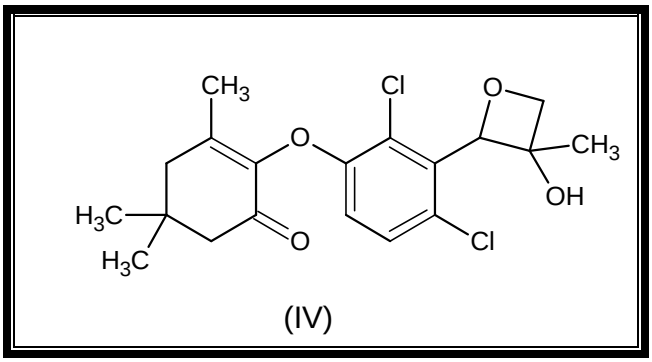
**THERAPEUTIC EVALUATION**

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

1. Herbicidal[364]
2. Analgesic[365]
3. Antiinflammatory[366]
4. Anticonvulsant[367]
5. Antibacterial[368]
6. Antithrombitics[369]
7. Antagonist[370]
8. Antibiotic[371,372]
9. Cardiovascular[373]

Cyclohexenone derivatives which possess plant growth regulatory activity have been reported.[374,375] Nagao et al.[376] have reported antiarrhythmic cyclo-hexenones. Collins and co-workers[377] have documented cyclohexenone derivatives which possess estrogenic activity. Tvanov et al.[378] have reported antimicrobial activity of some cyclohexenone derivatives. V. K. Ahluwalia and co-workers[379] have assessed cyclohexenone derivatives for anti *HIV-I*, gastric secretion inhibitors and pesticidal activity. Cyclohexenone derivatives have been reported to be active as allergy inhibitors, platelet aggregation inhibitors and fibrinogen antagonist.[380]

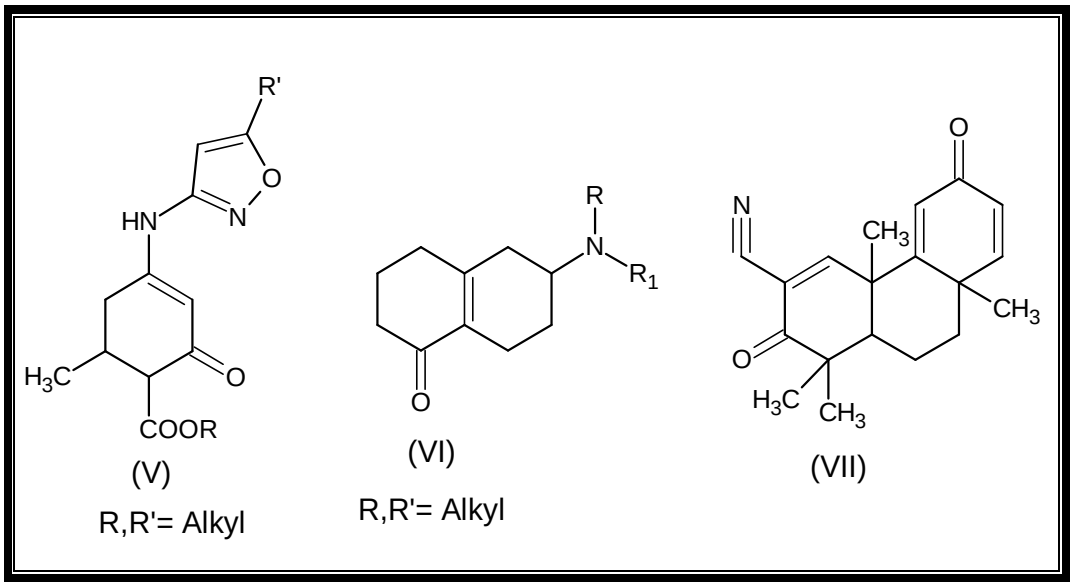
Rheinheimer J. et al.[381] have synthesised 5-(dioxabicyclohept-6-yl) cyclohexenone oxime ethers as herbicides and plant growth regulators. Harimaya and co-workers[382] have synthesised new cyclohexenone derivatives possessing progesteron receptor binding inhibitory activity. The herbicidal activity of cyclohexenone derivatives (IV) has been investigated.[383]




(IV)

Antimicrobial activity of cyclohexenone derivatives has been studied by Salama and Atshikh[384.] Takehiro and co-workers[385] have reported cyclohexenones possessing neutropeptide *γ*-receptor antagonist activity. Kimura and co-workers[386] have prepared cyclohexenones which possess inhibitory activity of penienone and they exhibit the remarkable inhibitory activity against the growth of lettuce seedlings. Broughton H. et al.[387] have demonstrated cyclohexenones as GABA $\alpha_5$ receptor ligands for enhancing cognition properties.

Hermann S. et al.[388] have reported cyclohexenones as herbicides. Anticonvulsant activity of some cyclohexenone derivatives (V) have been reported by Natalie D. et al.[389] Bastiaan and co-workers[390] have synthesised novel cyclohexenone derivatives (VI) which are useful in the treatment of perkinson's disease. Cyclohexenones (VII) as anticancer and antiinflammatory agents have been investigated.[391]



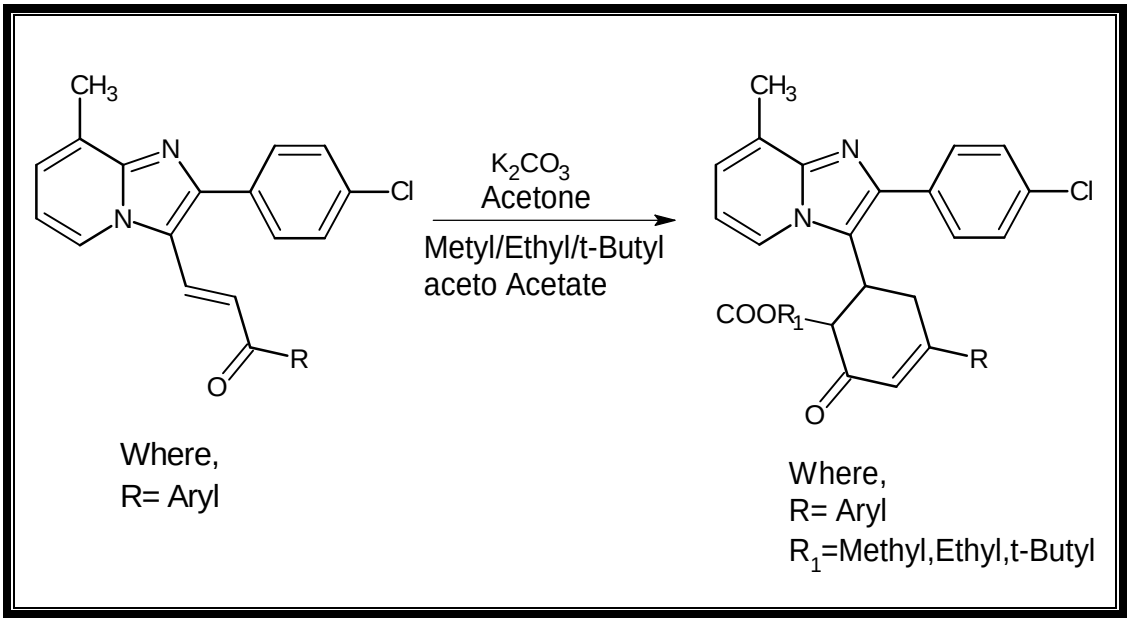

Moreover, H. H. Parekh and co-workers[392] have synthesised 6-carbethoxy -5-(4'-cinnamoyloxyphenyl)-3-aryl-2-cyclohexenones and all the products have been evaluated for their antimicrobial activity. Zhang C. et al.[393] have prepared tricyclic heterocycles, containing furan and cyclohexenone nucleus for treating hyperproliferative disorders. Under the high-speed vibration milling conditions, $K_2CO_3$ was found to be a very efficient catalyst for the solvent-free Michael reactions of 1,3-dicarbonyl compounds with chalcones,e.g., I (X=CH) and aza chalcones,e.g., I (X=N). In most cases, conventional side reactions were avoided and excellent yields were achieved. The influences of other catalysts and the vibration frequency on the Michael reaction were also investigated.[394]

With a view to getting better therapeutic agent, it was contemplated to synthesised cyclohexenones bearing furan nucleus to enhance the overall activity of resulting compounds, which have been described as under.

**Synthesis and therapeutic evaluation of ethyl-6-(2-(4-chlorophenyl)-8-methyl -1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-aryl-2-oxocyclohex-3-ene-carboxylate.**

**SYNTHESIS AND THERAPEUTIC EVALUATION OF ETHYL-6-(2-(4-CHLORO PHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL-2-OXOCYCLO HEX-3-ENE CARBOXYLATE.**

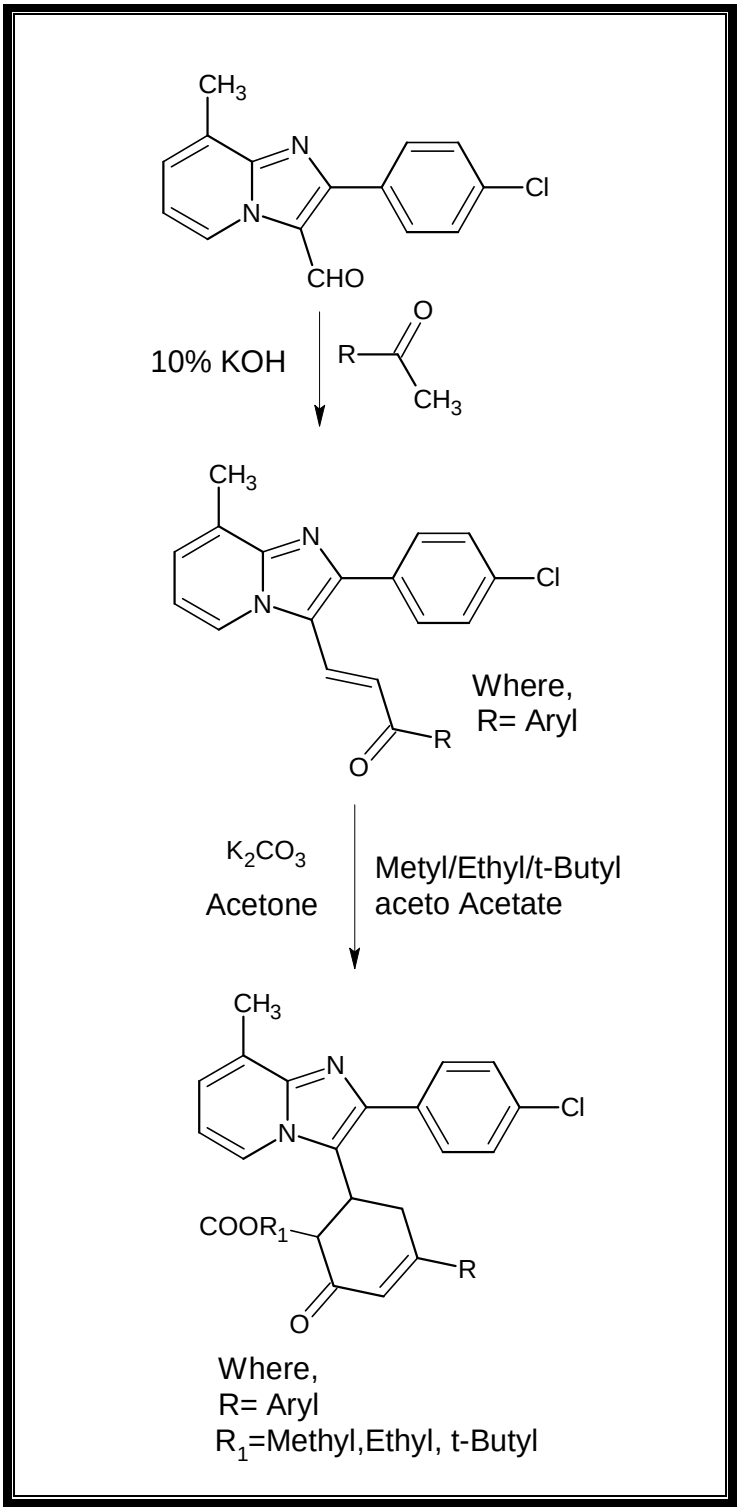
The growing potent literature of recent years demonstrates that the cyclohexenone derivatives are used as better therapeutic agents. These findings prompted us to synthesize a series of ethyl-6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-aryl-2-oxocyclohex-3-ene-carboxylate. The synthesis was carried out by the condensation of chalcones with ethylacetoacetate in acetone.



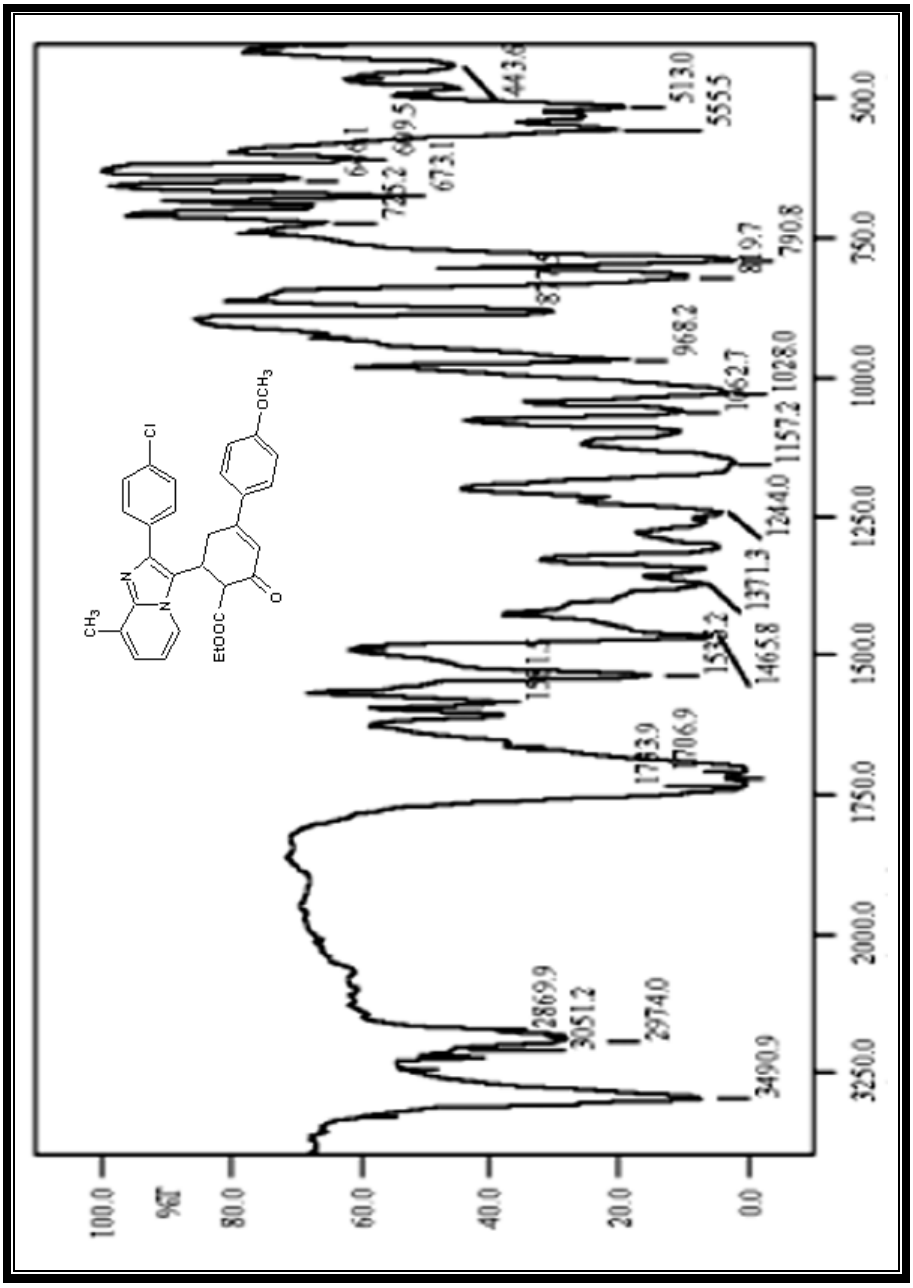

The constitution of the synthesized products have been characterized using elemental analyses, IR and $^{1}H$ nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

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

## REACTION SCHEME



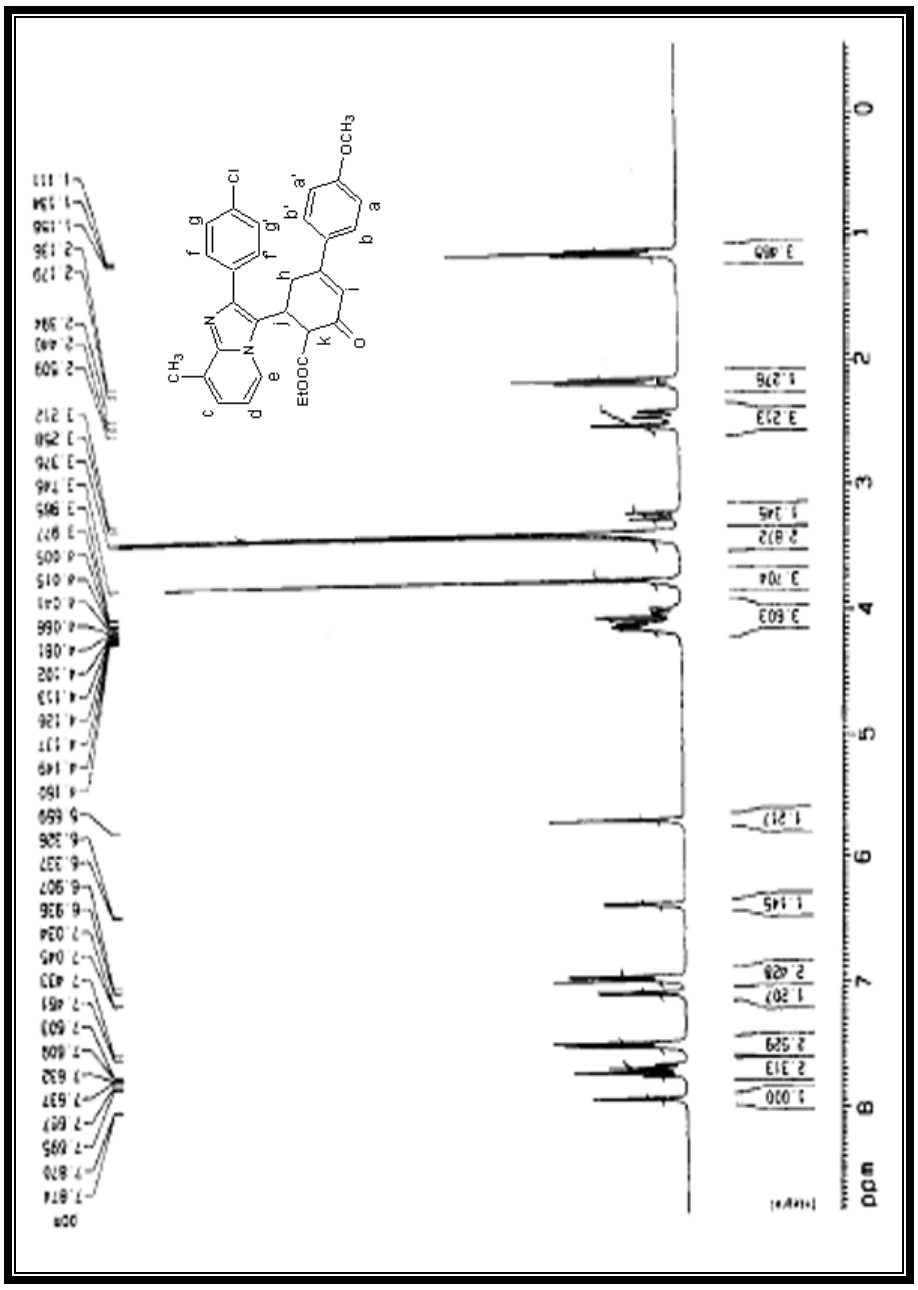
**IR SPECTRAL STUDIES OF ETHYL-6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)-2-OXOCYCLOHEX-3-ENE-CARBOXYLATE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2974 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2870 | 2880-2860 | ” |
| | C-H i.p.def | 1465 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1371 | 1395-1370 | ” |
| Aromatic | C-H str. | 3051 | 3090-3030 | 143-b |
| | C=C Str. | 1535 | 1520-1480 | ” |
| | C-H i.p.def | 1157 | 1125-1090 | ” |
| | C-H o.o.p.def. | 819 | 835-810 | ” |
| Moiety | C=N str. | 1581 | 1610-1590 | 143-c |
| | C-N str. | 1028 | 1230-1020 | ” |
| | C-Cl str. | 790 | 800-750 | ” |
| Cyclo- | C=O str. of ester | 1733 | 1750-1725 | 143-d |
| hexenone | C=O str. of cyclohexenone | 1706 | 1720-1690 | ” |

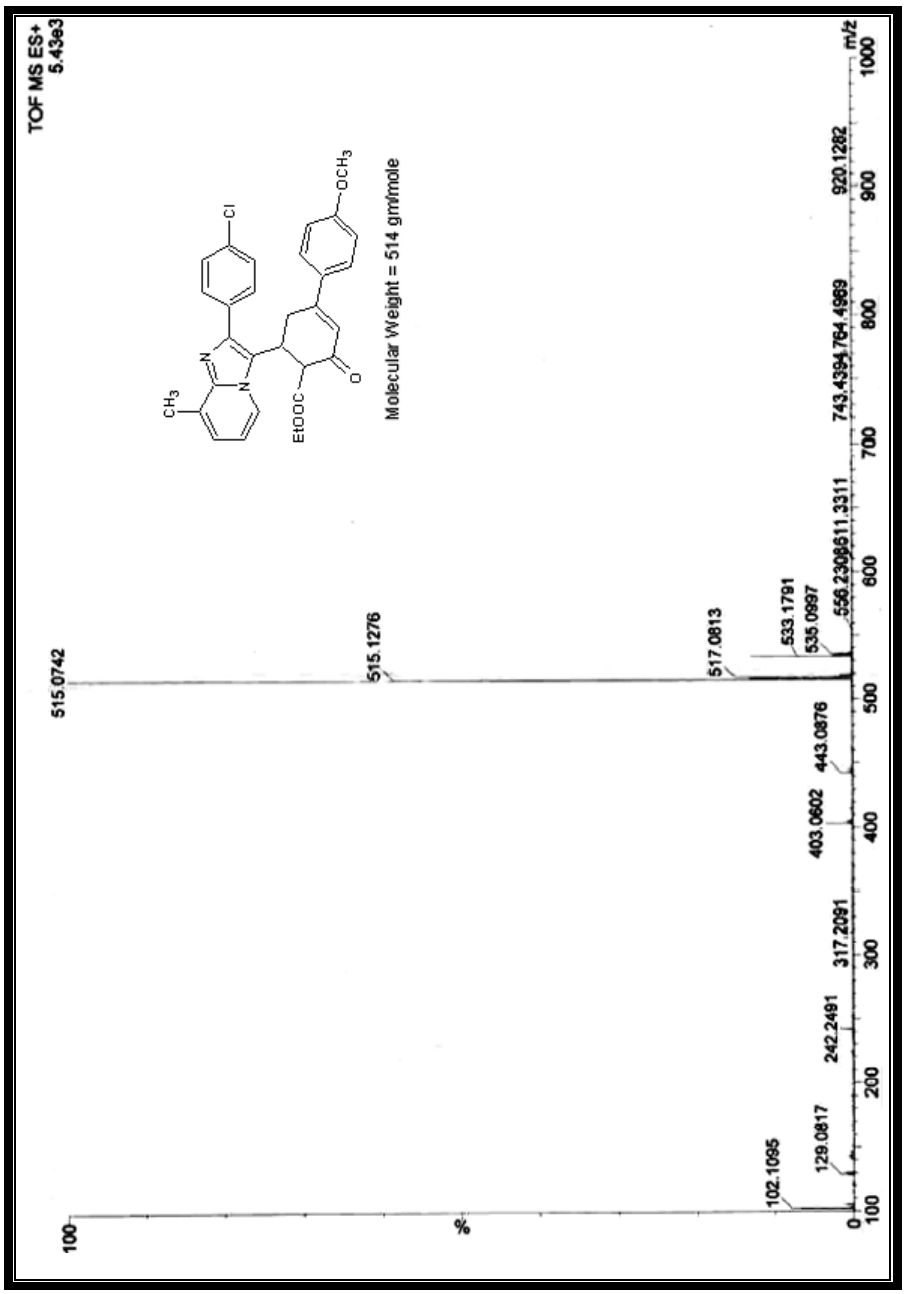
**NMR SPECTRAL STUDIES OF ETHYL-6-(2-(4-CHLOROPHENYL)-8-METHY-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)-2-OXOCYCLOHEX-3-ENE-CARBOXYLATE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.30 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.80 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 1.30 | 3H | triplet | Alk.-$CH_3$ |
| 4 | 4.10 | 2H | quatrate | Alk.-$CH_2$ |
| 5 | 6.30 | 1H | singlet | CHi |
| 6 | 2.40 | 2H | doublet | CHh |
| 7 | 4.00 | 1H | quatrate | CHj |
| 8 | 3.21 | 1H | singlet | CHk |
| 9 | 6.50 | 1H | triplet | Ar-Hd |
| 10 | 6.90 | 2H | doublet | Ar-H(a,a') |
| 11 | 7.10 | 2H | doublet | Ar-H(b,b') |
| 12 | 7.70 | 2H | doublet | Ar-H(f,f') |
| 13 | 7.55 | 2H | doublet | Ar-H(g,g') |
| 14 | 7.05 | 1H | doublet | Ar-Hc |
| 15 | 7.90 | 1H | doublet | Ar-He |

**MASS SPECTRAL STUDIES OF ETHYL-6-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-(4-METHOXYPHENYL)-2-OXOCYCLOHEX-3-ENE-CARBOXYLATE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of ethyl-6-(2-(4-chlorophenyl)-8 - methyl-1*H* -imidazo[1,2-*a*]pyridine-3-yl)-4-(4-methoxyphenyl)-2-oxocyclohex-3-ene carboxylate.**

**[A] Preparation of 2-chloro- 1-(*p*-chlorophenyl)ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)- 8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2- (*p*-chlorophenyl)- 8-methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine -3-yl]-1-arylprop-2-en-1-one.**

See on Page No. 38 Part-I (D)

**[E] Preparation of ethyl-6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*] pyridine-3-yl)-4-(4-methoxyphenyl)-2-oxocyclohex-3-ene-carboxylate.**

A mixture (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*] pyridine-3-yl]-1-aryl prop-2-en-1-one.(4.02gm,0.01m) and Ethylacetoacetate (1.30gm,0.01m) was refluxed in Acetone for 6-8 hrs.$K_2CO_3$ is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 59% (3.05gm) ; m.p.163 °C ; ($C_{30}H_{27}ClN_2O$ ; Found : C,69.43%;H,5.21%;N,5.35% ; Required : C,69.97%;H,5.28%;N,5.44%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Cyclohexenone derivatives have been obtained. The physical data are recorded in Table No.- 3(B).

**[F] Antimicrobial activity of ethyl-6-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)-4-aryl-2-oxocyclohex-3-ene-carboxylate.**

Antimicrobial testing was carried out as described in **Part- I Experimental Section [E]** Page No. 38. The zone of inhibition of the test solution are recorded in Table No.- 3(A).

**TABLE NO.- 3(A) BIOLOGICAL SCREENING OF ETHYL-6-(2-(4-CHLORO PHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL-2-OXOCYCLO-HEX-3-ENE-CARBOXYLATE.**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **3a** | $C_6H_5$- | **18** | 17 | 15 | **17** | 16 |
| **3b** | 4-$CH_3$-$C_6H_4$ - | 15 | 16 | 14 | 15 | 15 |
| **3c** | 4-$OCH_3$ -$C_6H_4$- | 14 | 15 | 13 | 12 | 14 |
| **3d** | 4-Cl-$C_6H_4$ - | 16 | **19** | 15 | 16 | 17 |
| **3e** | 4-F-$C_6H_4$ - | 16 | 15 | 14 | 13 | 15 |
| **3f** | 4-Br-$C_6H_4$ - | 15 | 12 | 13 | 14 | 14 |
| **3g** | 4-$NH_2$-$C_6H_4$ - | 14 | 13 | 15 | 12 | 13 |
| **3h** | 4-$NO_2$-$C_6H_4$ - | 13 | 15 | 14 | 14 | 16 |
| **3i** | 4-OH-$C_6H_4$ - | 17 | 16 | **17** | 15 | **18** |
| **Std$^n$** | Ampicillin | 20 | 22 | 21 | 22 | - |
| **”** | Amoxicillin | 22 | 20 | 21 | 23 | - |
| **”** | Ciprofloxacin | 23 | 24 | 22 | 22 | - |
| **”** | Norfloxacin | 21 | 23 | 23 | 24 | - |
| **”** | Greseofulvin | - | - | - | - | 24 |

**TABLE NO.- 3(B) PHYSICAL CONSTANTS OF ETHYL-6-(2-(4-CHLORO PHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)-4-ARYL-2-OXOCYCLO-HEX-3-ENE-CARBOXYLATE.**

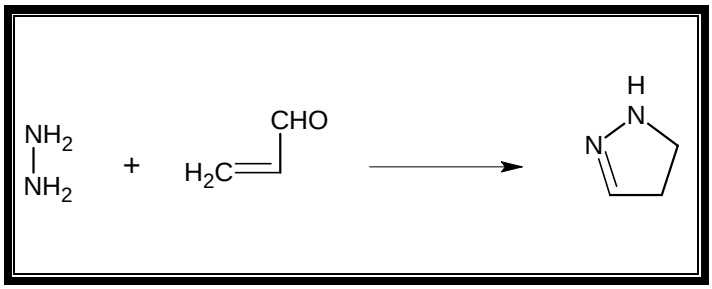
| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **3a** | $C_6H_5$ - | $C_{29}H_{25}ClN_2O_3$ | 484.0 | 160.0 | 0.58 | 58.0 | 5.78 | 5.71 |
| **3b** | 4-$CH_3$-$C_6H_4$ - | $C_{30}H_{27}ClN_2O_3$ | 498.0 | 161.0 | 0.57 | 54.0 | 5.61 | 5.60 |
| **3c** | 4-$OCH_3$-$C_6H_4$- | $C_{30}H_{27}ClN_2O_4$ | 514.0 | 163.0 | 0.56 | 59.0 | 5.44 | 5.35 |
| **3d** | 4-Cl-$C_6H_4$ - | $C_{29}H_{24}Cl_2N_2O_3$ | 518.0 | 155.0 | 0.52 | 61.0 | 5.39 | 5.35 |
| **3e** | 4-F-$C_6H_4$ - | $C_{29}H_{24}ClFN_2O_3$ | 502.0 | 150.0 | 0.53 | 57.0 | 5.57 | 5.55 |
| **3f** | 4-Br-$C_6H_4$ - | $C_{29}H_{24}ClBrN_2O_3$ | 562.0 | 152.0 | 0.60 | 55.0 | 4.97 | 4.90 |
| **3g** | 4-$NH_2$-$C_6H_4$ - | $C_{29}H_{26}ClN_3O_3$ | 499.5 | 159.0 | 0.54 | 60.0 | 8.40 | 8.37 |
| **3h** | 4-$NO_2$-$C_6H_4$ - | $C_{29}H_{24}ClN_3O_5$ | 529.0 | 157.0 | 0.53 | 56.0 | 7.93 | 7.89 |
| **3i** | 4-OH-$C_6H_4$ - | $C_{29}H_{25}ClN_2O_4$ | 500.0 | 149.0 | 0.49 | 58.0 | 5.59 | 5.56 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

# PART-IV

# STUDIES ON PYRAZOLINES

**INTRODUCTION :**

The chemistry of Pyrazoline was reviewed by Jarboe in 1967. Pyrazoline has three possible tautomeric structures, but the structure shown is the most stable which can be prepared by hydrazine hydrate and acrolein.

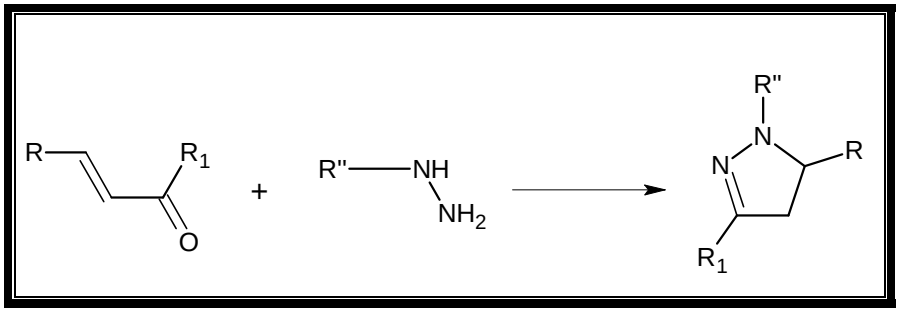


The interesting biological activities of a novel heterocycle like pyrazolines have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system.

**SYNTHETIC ASPECT :**

Different methods for the preparation of 2-Pyrazolines are as per follows :

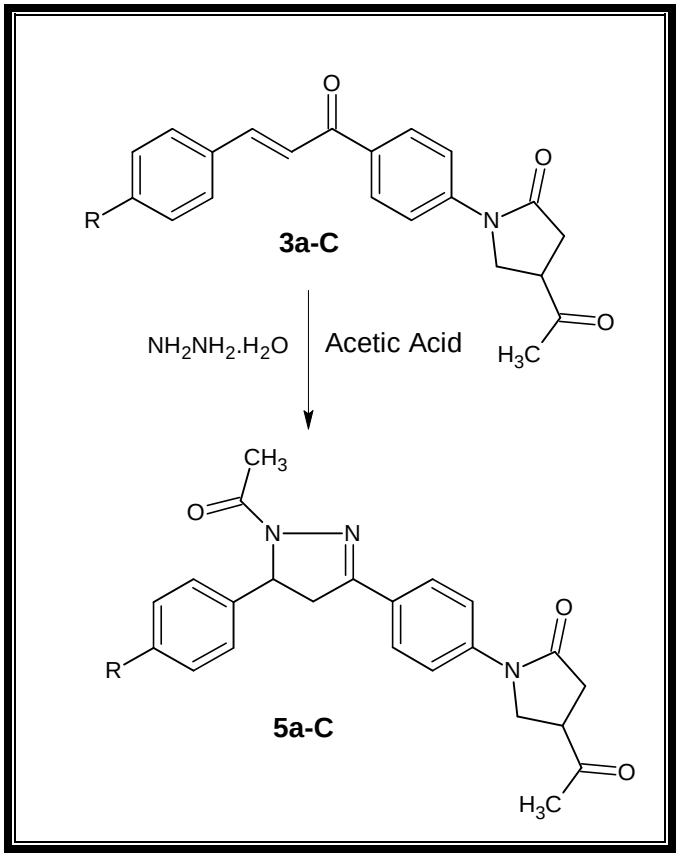
(1) The most common procedure for the synthesis of an aliphatic or aromatic hydrazine with *α, β* - unsaturated carbonyl compounds.



(2) 3-Amino-2-Pyrazolines can be prepared by condentation of *α, β* - unsaturated nitriles with hydrazine.


(3) 2 - Pyrazolines can also be synthesised by the condensation of chalcones with hydrazine hydrate[395].

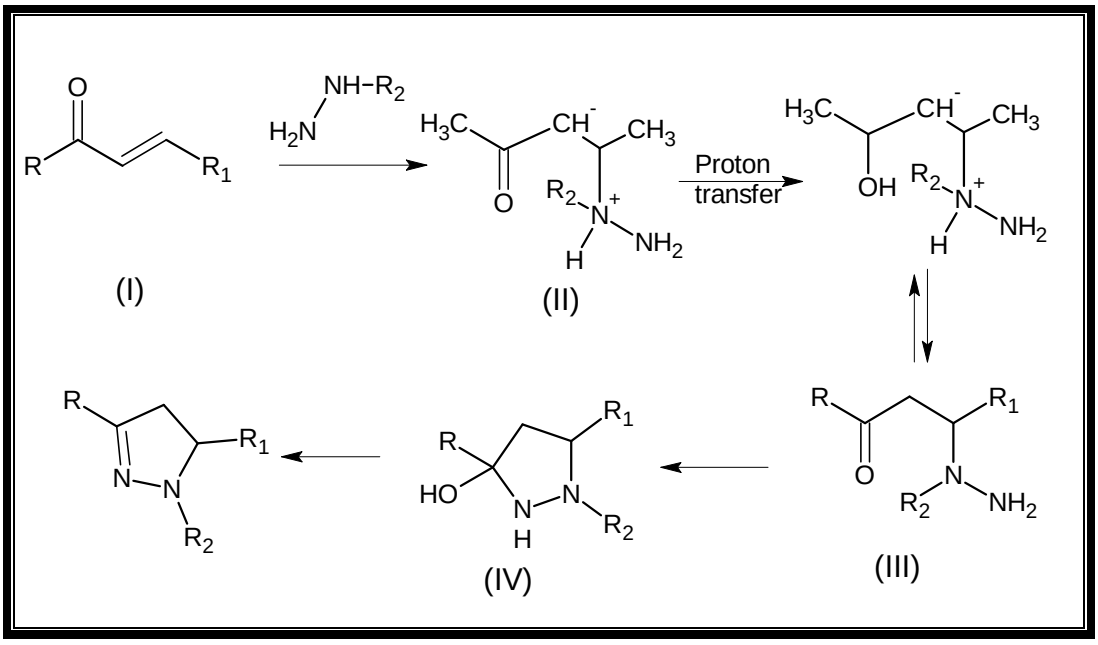
(4) A solution of 0.002 mol of the corresponding chalcones **3a-C**, 0.3 g (0.006 mol) of hydrazine hydrate and 10 ml of acetic acid was refluxed for 5 hours, then catalytic amount of HCI (4-5 drops) was added and yet refluxed for 30 min. After cooling 30 ml water was added and the resulting precipitate was filtered, washed with water.[396]



(5) Iodobenzene diacetate, a relatively nonmetallic oxidant, has been utilized efficiently for the oxidation of *N*-substituted hydrazones of chalcones to afford 1,3,5- trisubstituted pyrazoles under mild reaction conditions.[397]

**REACTION MECHANISM :**

The following mechanism seems for the condensation of chalcones with hydrazine hydrate.




Nucleophillic attack by hydrazine at the *β*–carbon of the *α,β*–unsaturated carbonyl system forms species (II), in which the negative charge is mainly accommodated by the electronegative oxygen atom. Proton transfer from nitrogen to oxygen produces an intermediate and which simultaneously ketonises to ketoamine (III). Another intramolecular Nucleophillic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen lead ultimately to hydroxyl amine (IV). The later with a hydroxyl group and amine group on the same carbon lose water easily to yield the pyrazolines.

**PHARMACEUTICAL IMPORTANCE :**

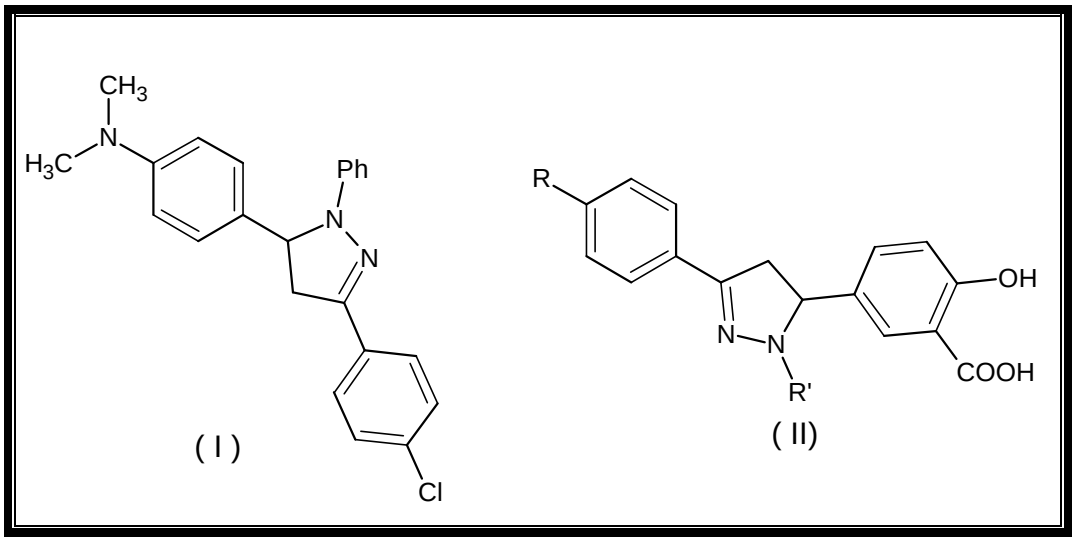
2- Pyrazolines have been found to possess very interesting range of important therapeutic activities shown below :

1. Bactericidal[395]
2. Anticonvulsant[398]
3. Diuretic[399]
4. Analgesic[400]
5. Antiinflammatoty[401]
6. Insecticidal[402]
7. Antibacterial[403]
8. Herbicidal[404]

3-N-Arylamino-1-(4,5,6,7-tetrahydro-thiazol-yl)-2-pyrazolines are found to be useful as an antiinflammatory and allergy inhibitor agents.[405] K. Trena and Zolzislaw[406] have tested 2-Pyrazolines on rats and observed comparatively good response as hypoglycemic agents. Moreover, several pyrazolines have been reported to possess antimicrobial activity[407]. Some new 2-pyrazolines (I) have been synthesised and their antimicrobial properties have been reported by Koos et al.[408] More over, use of some pyrazolines as cardiovascular agent along with their synthesis[409] is also reported in literature. Subbanward et al.[410] have prepared and tested some novel pyrazoline derivatives for their antimicrobial activity.

Recently Abl El-Latif and co-workers[411] have synthesized pyrazoline derivatives. Ismail et al.[412] have prepared pyrazoline derivatives bearing sulphonamide moiety and tested their antimicrobial activity. Sarah and co-workers[413] have synthesised pyrazoline derivatives and reported antibacterial, analgesic and antiinflammatory activities. Wang et al.[414] have synthesised pyrazoline derivatives which showed bactericidal activity.

4,5-Dihydro-1,3-dimethyl- 5- (2,4,6-trimethyl- 2-cynohexan- 1-yl)-1*H*- pyrazole and other derivatives are observed as versatile compounds having perfume fragrance by D. Francois et al.[415] F. Manna and co- workers[416] have repoted pyrazoline derivatives which act as potent antiinflammatory, analgesic and antipyretics agent. Grant and co-worker[417] found pyrazoline (II) having good antimicrobial properties.




Jatin Upadhyay et al.[418] have synthesised 1- actyl- 4,5-dihyro-5-(4-hydroxy -3-methanoxyphenyl)-3-(4-phenylsulphonamidophenyl)-1*H*-pyrazole and other derivatives. Vikani and co-workers[419] have prepared pyrazoline derivatives from arsanillic acid for their antimicrobial and antifungal activities. Patel et al.[420] have synthesised and reported antimicrobial activity of pyrazolines. Fernandes et al.[421] have synthesised and tested for their activity against different strains of bacteria and fungi. Sorathia et al.[422] have reported new derivatives of pyrazoline as antimicrobial agents.

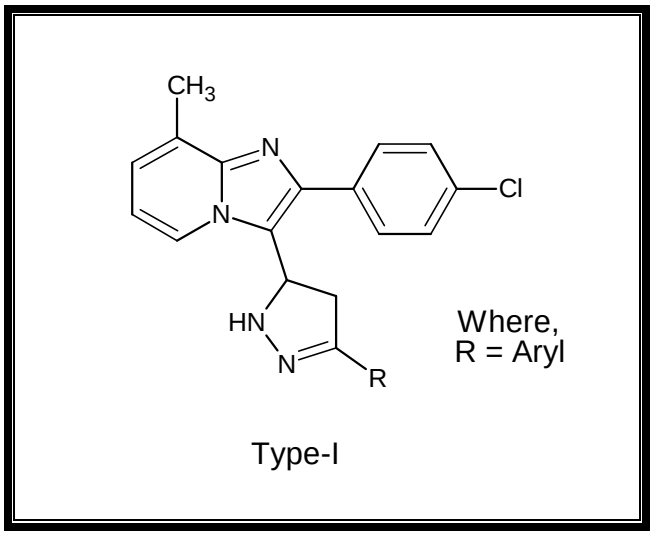
More Udupi and co- worker[423] have reported pyrazolines having analgesic, bactericidal, antifungal, antitubercular and antiinflammatory agents. Moreover, fungicidal, herbicidal and plant growth regulatory activity has also been observed by

Kadu et al.[424] and antimicrobial by patil et al.[425] Thus interesting biological activities of a novel heterocycles like pyrazolines have stimulated considerable research work in recent years. In our search for new potential antimicrobial compounds, the reaction of series of chalcone with hydrazine hydrate under different conditions have been investigated and pharmacological profile of the compounds have been studied and describes as under.

**Synthesis and therapeutic evaluation of 2-(4-chlorophenyl)-3-(4,5-dihydro-3-aryl-1*H*-pyrazol-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine**.

**SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-(4-CHLOROPHENYL) - 3-(4,5-DIHYDRO- 3-ARYL-1*H*-PYRAZOL- 5-YL)- 8- METHYL-1*H*-IMIDAZO[1,2-*a*] PYRIDINE.**

Pyrazoline derivatives have attracted considerable attention as it appeared of interest to possess wide range of therapeutic activities. With an attempt to getting better therapeutic agents, pyrazolines of Type-I have been prepared by the condensation of chalcone with hydrazine hydrate.

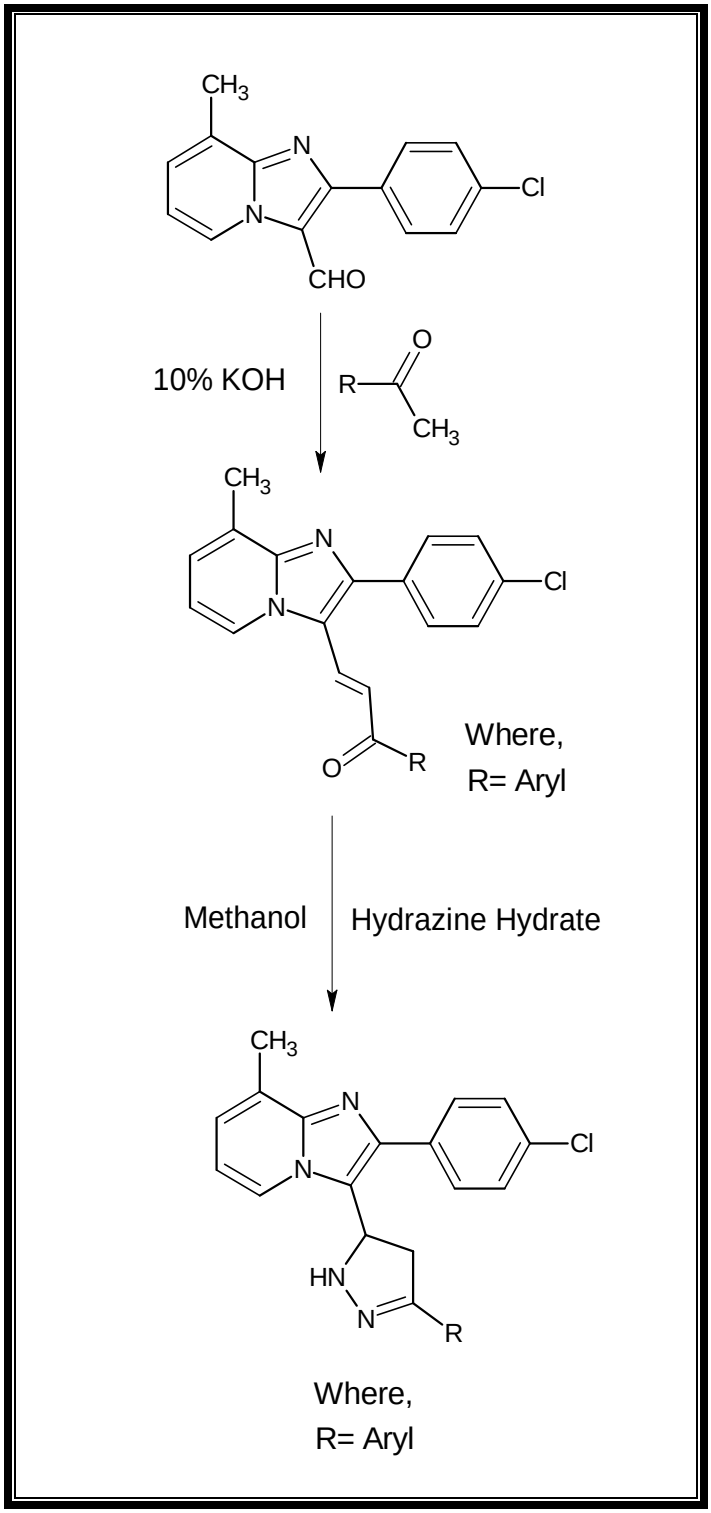



Type-I

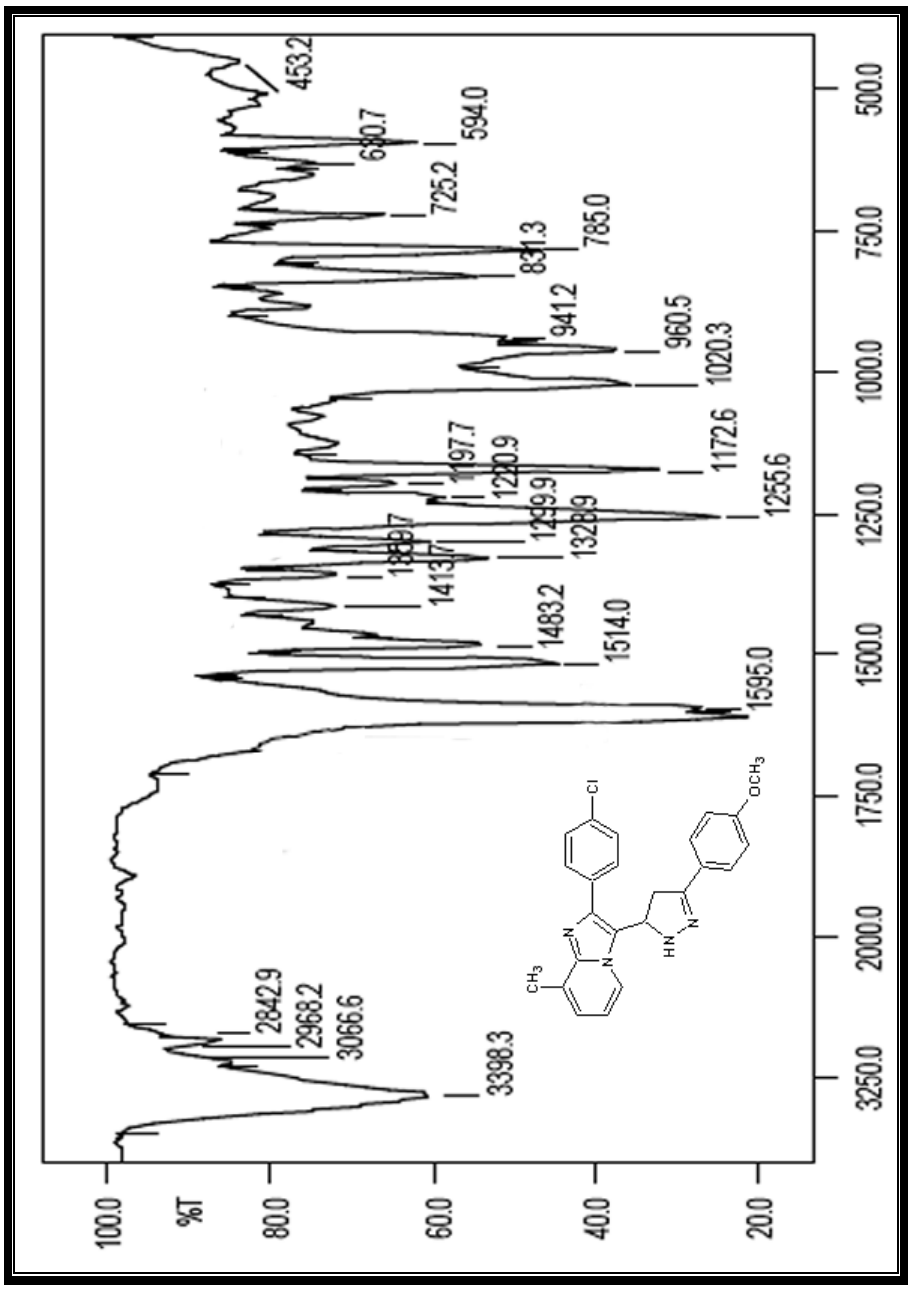
The constitution of the synthesized products has been characterized by using elemental analyses, infra red and $^{1}H$ nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

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 40µg. The biological activities of the synthesized compounds have been compared with standard drugs.

## REACTION SCHEME



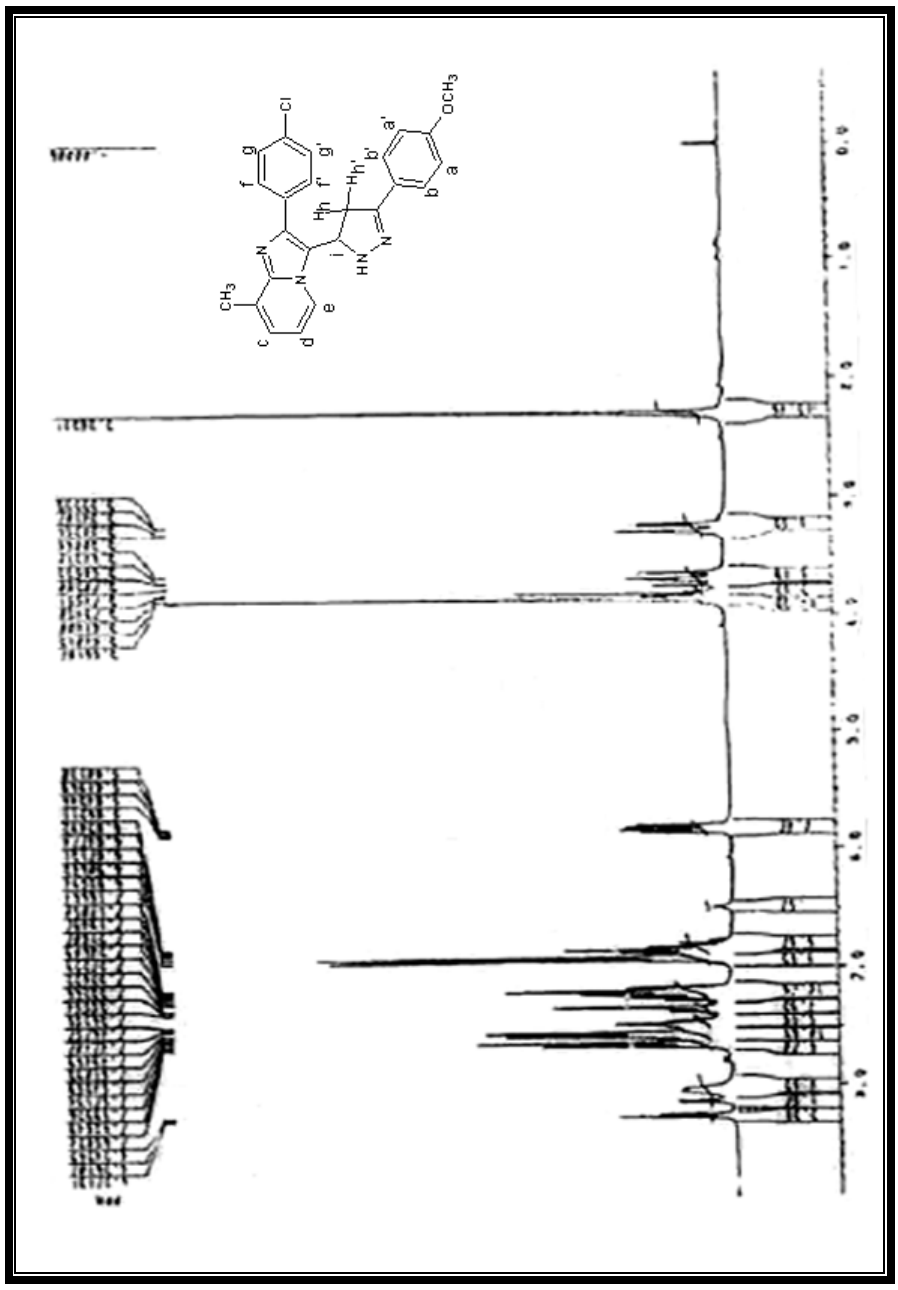
**IR SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-3-(4,5-DIHYDRO - 3-(4-METHOXYPHENYL)-1*H*-PYRAZOL- 5-YL)- 8- METHYL-1*H*-IMIDAZO[1,2-*a*] PYRIDINE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2968 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2842 | 2880-2860 | ” |
| | C-H i.p.def | 1483 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1389 | 1395-1370 | ” |
| Aromatic | C-H str. | 3066 | 3090-3030 | 143-b |
| | C=C Str. | 1483 | 1520-1480 | ” |
| | C-H i.p.def | 1100 | 1125-1090 | ” |
| | C-H o.o.p.def. | 831 | 835-810 | ” |
| Moiety | C=N str. | 1595 | 1610-1590 | 143-c |
| | C-N str. | 1172 | 1230-1020 | ” |
| | C-Cl str. | 785 | 800-750 | ” |
| Pyrazoline | C=N str. | 1595 | 1655-1550 | 143-d |

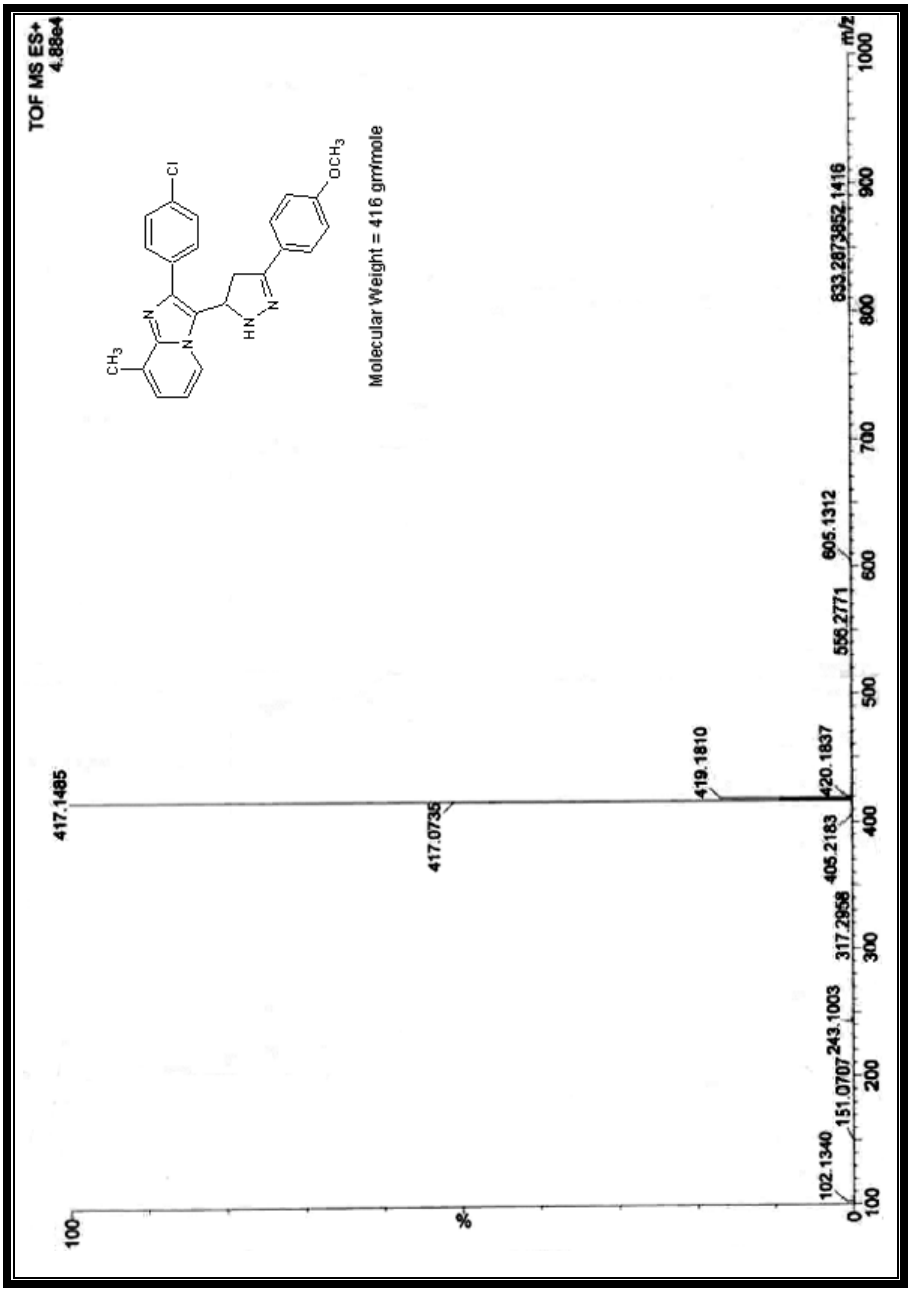
**NMR SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-3-(4,5-DIHYDRO - 3-(4-METHOXYPHENYL)-1*H*-PYRAZOL- 5-YL)- 8- METHYL-1*H*-IMIDAZO[1,2-*a*] PYRIDINE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.30 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.90 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 3.24 | 1H | doublet | CHh |
| 4 | 3.80 | 1H | doublet | CHh' |
| 5 | 3.65 | 1H | triplet | Ar-Hi |
| 6 | 6.50 | 1H | triplet | Ar-Hd |
| 7 | 6.90 | 2H | doublet | Ar-H(a,a') |
| 8 | 7.10 | 2H | doublet | Ar-H(b,b') |
| 9 | 7.75 | 2H | doublet | Ar-H(f,f') |
| 10 | 7.60 | 2H | doublet | Ar-H(g,g') |
| 11 | 7.00 | 1H | doublet | Ar-Hc |
| 12 | 8.00 | 1H | doublet | Ar-He |

**MASS SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-3-(4,5-DIHYDRO - 3-(4-METHOXYPHENYL)-1*H*-PYRAZOL- 5-YL)- 8- METHYL-1*H*-IMIDAZO[1,2-*a*] PYRIDINE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of 2-(4-chlorophenyl)-3-(4,5-dihydro-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine.**

**[A] Preparation of 2-chloro-1-(*p*-chlorophenyl)ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)- 8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2-(*p*-chlorophenyl)- 8- methyl imidazo[1,2-*a*]pyridine-3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine -3-yl]-1-aryl prop-2-en-1-one.**

See on Page No. 38 Part-I (D)

**[E] Preparation of 2-(4-chlorophenyl)-3-(4,5-dihydro-3-(4-methoxyphenyl) -1*H*-pyrazol-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine.**

A mixture (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one. (4.02gm,0.01m) and hydrazine hydrate (0.32gm,0.01m) was refluxed in methanol in acidic media for 6-8 hrs. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 56% (2.6gm); m.p.136 °C; ($C_{24}H_{21}ClN_4$; Found : C,69.02%;H,4.95%;N,13.35%; Required : C,69.14%;H,5.08%;N,13.44%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Pyrazoline derivatives have been obtained. The physical data are recorded in Table No.- 4(B).

**[F] Antimicrobial activity of 2-(4-chlorophenyl)-3-(4,5-dihydro-3-aryl-1*H*-pyrazol-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine.**

Antimicrobial testing was carried out as described in **part- I Experimental Section [E]** Page No. 38. The zone of inhibition of the test solution are recorded in Table No.- 4(A).

**TABLE NO.- 4(A) BIOLOGICAL SCREENING OF 2-(4-CHLOROPHENYL)-3-(4,5-DIHYDRO-3-ARYL-1*H*-PYRAZOL-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **4a** | $C_6H_5$- | 16 | 15 | 14 | 15 | 16 |
| **4b** | 4-$CH_3$-$C_6H_4$ - | 15 | 14 | 12 | 13 | 15 |
| **4c** | 4-$OCH_3$ -$C_6H_4$- | 13 | 12 | 15 | 14 | 12 |
| **4d** | 4-Cl-$C_6H_4$ - | 17 | 16 | **18** | 16 | **19** |
| **4e** | 4-F-$C_6H_4$ - | 15 | 14 | 16 | 13 | 15 |
| **4f** | 4-Br-$C_6H_4$ - | 12 | 15 | 14 | 15 | 14 |
| **4g** | 4-$NH_2$-$C_6H_4$ - | 15 | 14 | 13 | 12 | 15 |
| **4h** | 4-$NO_2$-$C_6H_4$ - | 14 | 13 | 15 | 14 | 16 |
| **4i** | 4-OH-$C_6H_4$ - | **18** | **19** | 16 | **17** | 15 |
| **Std$^n$** | Ampicillin | 22 | 20 | 21 | 21 | - |
| **”** | Amoxicillin | 21 | 22 | 23 | 22 | - |
| **”** | Ciprofloxacin | 24 | 23 | 22 | 23 | - |
| **”** | Norfloxacin | 23 | 24 | 24 | 23 | - |
| **”** | Greseofulvin | - | - | - | - | 23 |

**TABLE NO.- 4(B) PHYSICAL CONSTANTS OF 2-(4-CHLOROPHENYL)-3-(4,5-DIHYDRO-3-ARYL-1*H*-PYRAZOL-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**

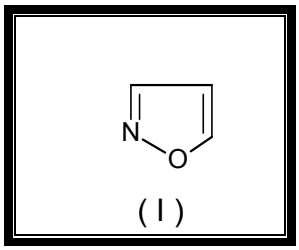
| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **4a** | $C_6H_5$ - | $C_{23}H_{19}ClN_4$ | 386.5 | 154.0 | 0.59 | 60.0 | 14.48 | 14.33 |
| **4b** | 4-$CH_3$-$C_6H_4$ - | $C_{24}H_{21}ClN_4$ | 400.5 | 123.0 | 0.61 | 68.0 | 13.98 | 13.89 |
| **4c** | 4-$OCH_3$-$C_6H_4$- | $C_{24}H_{21}ClN_4O$ | 416.5 | 136.0 | 0.55 | 56.0 | 13.44 | 13.35 |
| **4d** | 4-Cl-$C_6H_4$ - | $C_{23}H_{18}Cl_2N_4$ | 421.0 | 146.0 | 0.62 | 59.0 | 13.30 | 13.25 |
| **4e** | 4-F-$C_6H_4$ - | $C_{23}H_{18}ClFN_4$ | 404.1 | 168.0 | 0.48 | 62.0 | 13.84 | 13.80 |
| **4f** | 4-Br-$C_6H_4$ - | $C_{23}H_{18}ClBrN_4$ | 465.5 | 109.0 | 0.66 | 55.0 | 12.03 | 12.00 |
| **4g** | 4-$NH_2$-$C_6H_4$ - | $C_{23}H_{20}ClN_5$ | 401.5 | 131.0 | 0.51 | 60.0 | 17.43 | 17.36 |
| **4h** | 4-$NO_2$-$C_6H_4$ - | $C_{23}H_{18}ClN_5O_2$ | 431.5 | 143.0 | 0.58 | 59.0 | 16.22 | 16.05 |
| **4i** | 4-OH-$C_6H_4$ - | $C_{23}H_{19}ClN_4O$ | 402.5 | 121.0 | 0.43 | 48.0 | 13.91 | 13.83 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

# PART-V

# STUDIES ON ISOXAZOLES

**INTRODUCTION:**

Isoxazole come under the class of compounds containing two heteroatom in five membered ring, Oxygen and Nitrogen.

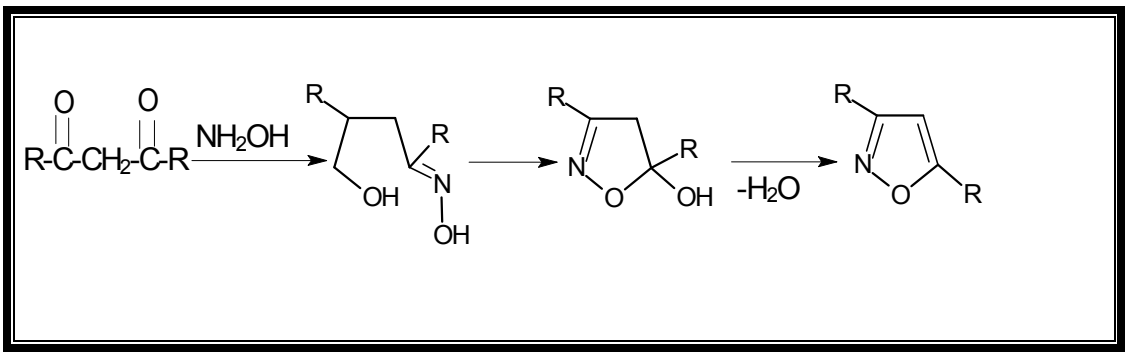



( I )

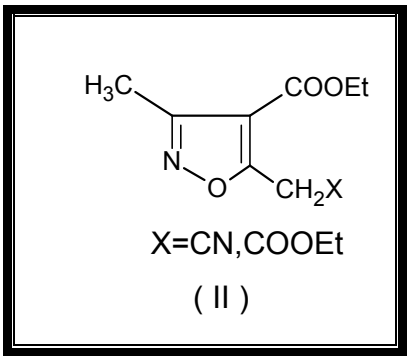
This type of structure (I) was first reported by Claisen for the product obtained by the reaction of 1,3-Diketone with hydroxylamine.[426] More work for Isoxazole was done by Claisen and his students[427,428] to provide solid foundation of Isoxazole chemistry. Not only that, other scientist Cremlico gave important contribution to understand Isoxazole chemistry. Isoxazoles shows typical properties of an aromatic system, but under the conditions, particularly reducing or basic media, it becomes highly labile.

**SYNTHETIC ASPECT :**

Isoxazoles may be prepared by reaction between hydroxylamine and *α, β*-dicarbonyl compound. The reaction proceeds via the formation of an oxime, which possibly undergoes cyclisation.



Substituted Isoxazoles were prepared from hydroxylamine hydrochloride and chalcones.[429] Naik and co-workers[430] have synthesised Isoxazoles by bromination of chalcones, followed by cyclocondensation of the *α,β*-dibrominated, satd. Chalcones with hydroxylamine hydrochloride in ethanol, in presence of KOH. Other method was reported by El.Kholy et al.[431] The Isoxazole of type (II) was prepared by the reaction of ethyl-3-oxo-butanoate with malononitrile and ethyl cyano acetate.




X=CN,COOEt

( II )

Chalcones of 2-(4'-chlorophenylamino)-4-(4'-fluorophenylamino)-6-(4'-acety lphenylamino)-s-triazine have been synthesized by condensation with different aromatic aldehydes. These chalcones on treatment with hydroxylamine hydrochloride in presence of alkali give isoxazoles and on treatment with malononitrile in presence of ammonium acetate give cyanopyridines.[432]

A series of 2,4-bis-(4'-chloro phenyl amino) -6- [4'-{1''- acetyl- 5''-aryl- 2''-pyrazolin-3''-yl}phenyl amino]-s-triazines have been prepared by the reaction of chalcone and hydrazine hydrate in presence of glacial acetic acid and 2,4-bis-(4'-chlorophenylamino)-6-[4'-{5''-aryl-2''-isoxazol-3''-yl}phenylamino]-s-triazines were similarly prepared with hydroxylamine hydrochloride in presence of alkali. All the synthesized compounds have been screened for their antimicrobial activity. The structure of synthesized compds. have been confirmed on the basis of elemental anal., IR and $^{1}$H NMR spectral data.[433]

**PHARMACEUTICAL IMPORTANCE :**

Isoxazoles shows various biological activities which are shown below.

1. Antiviral[434]
2. Herbicidal[435]
3. Nematocidal[436]
4. Anticonvulsant[437]
5. Central muscle relaxing[438]
6. Neuroleptic[439]
7. Anticholestermic[440]

B.Victor [441] have reported antipyretic antiarthitic and immunoregulating activities of some Isoxazole derivatives. Herbicidal activity of some isoxazoles have been reported by Alfred et al.[442] and fungicidal activity observed by Mackie et al.[443] Some Isoxazole derivatives have been prepared which showed broad spectrum of physiological properties *viz.* antitumor[444], antileukemia[445], antiinflammatory[446], antimicrobial[447] and anthelmintic[448] activities.

Moreover Isoxazole have been prepared which showed broad spectrum of activities *viz*. antitumor[449] anthelmitic[450] antiinflammatory[451] antimicrobial[452] antileukemia[453] and herbicidal[454]. Recently, Isoxazole derivatives possessing fungicidal[455] and herbicidal[456] properties are also reported. Rajeev Jain et al.[457] prepared isoxazoles are hypoglycemic agents. Inani et al.[458] synthesised isoxazoles as an inflammation inhibitors and analgesics agents. A.R. Parikh[459] and coworkers have prepared isoxazoles as an antimicrobial agents. Masui et al.[460] have prepared isoxazoles having pesticidal activity. Some excellent herbicidal results obtained by Reddy et al.[461] Moreover, isoxazoles found to possess remarkable anxiolytic and antihypertensive effect, reported by Nyitrai et al.[462] Mishra et al.[463] have synthesised and reported isoxazoles as useful agents for analgesic and antiinflammatory activities. Aicher et al.[464] cited some Isoxazole derivatives possessing hypoglycemic agents.

Doshi Rajeev et al.[465] have synthesised and screened antitubercular activity. Some, isoxazoles are found to possess herbicidal[466], potential antiinflammatory[467] and antimicrobial agents.[468]

Cyclocondensation of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones on reaction with hydroxylamine hydrochloride in presence of acetic acid and sodium acetate to give 3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-isoxazoles. The compounds were tested against different microbes for their antimicrobial activity and antitubercular activity.[469]

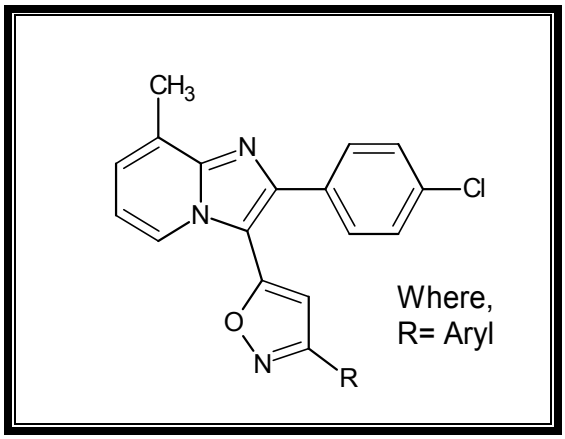
5-(Substituted phenyl)-{3-[4-2-methyl-4-(4-hydroxybenzylidene)-5-oxoimidazo -1-yl)]phenyl}-Isoxazole have been prepared by the refluxation for 10 hrs. of 4-(4-hydroxybenzylidene)-1-{4-[3-(substituted phenyl)prop-2-enoyl]phenyl}-2-methyl imidazol-5-one with hydroxylamine hydrochloride and 40% potassium hydroxide solution in dioxane. The intermediate 4-(4-hydroxybenzylidene)-1-{4-[3(substituted phenyl)prop-2-enoyl]phenyl}-2-methyl-imidazol-5-one was synthesized by the condensation of 1-(4-acetylphenyl)-4-(4-hydroxy benzyl idene)-2-methyl-3,5-dihydro imidazol-5-one with various aldehydes.The antimicrobial activities of these isoxazoles were also studied.[470]

Thus, significant biological properties associated with isoxazoles have aroused considerable interest to design the compounds in which benzimidazole moiety is incorporated. Such compounds have been synthesized and described as under.

**Synthesis and therapeutic evaluation of 2-(4-chlorophenyl)-3-(3-aryl-isoxazole-5-yl)-8-methyl-1*H*-Imidazo[1,2-*a*]pyridine.**

**SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-(4-CHLOROPHENYL) -3-(3-ARYL-ISOXAZOLE-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**

Isoxazole derivatives have created interest in the field of medicinal chemistry, due to wide rage of biological activities exhibited by them. Prompted by these facts, the preparation of Isoxazole of type (III) was carried out by condensing chalcones with hydroxylamine hydrochloride in the presence of sodium acetate.

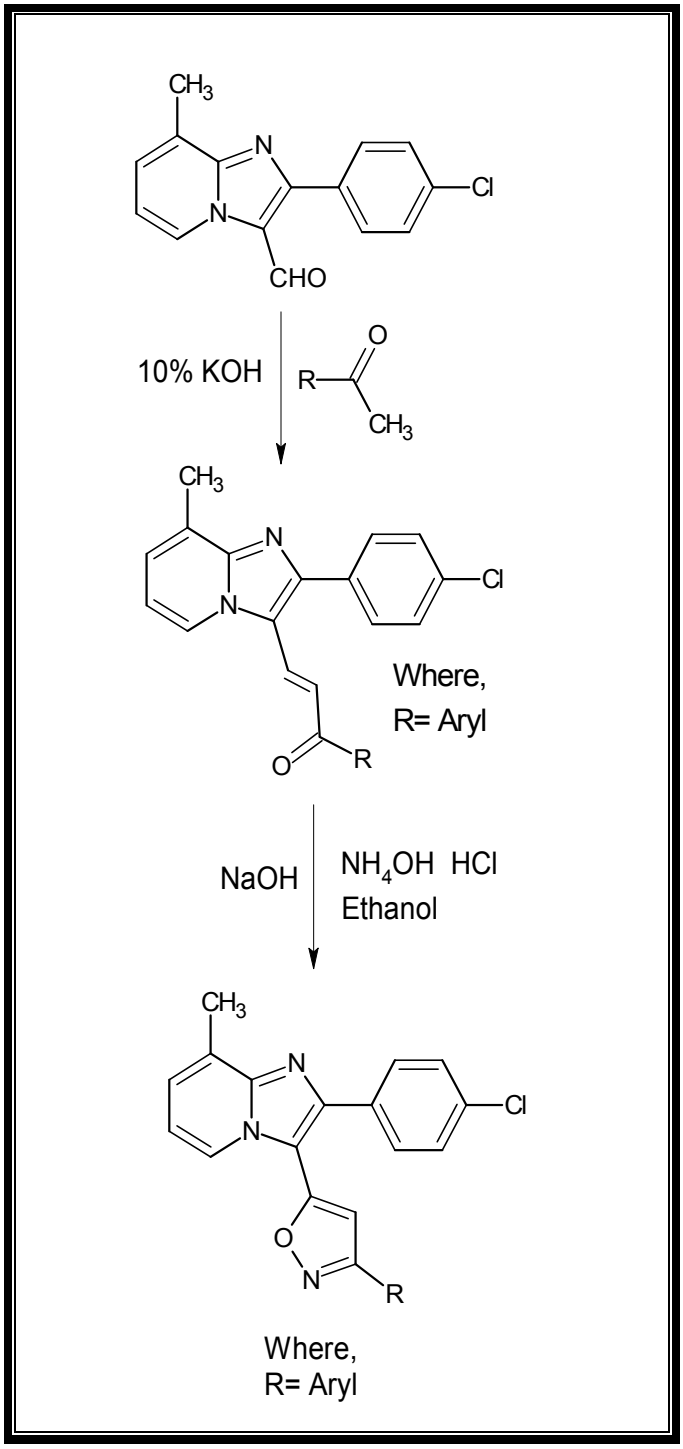



Type (III)

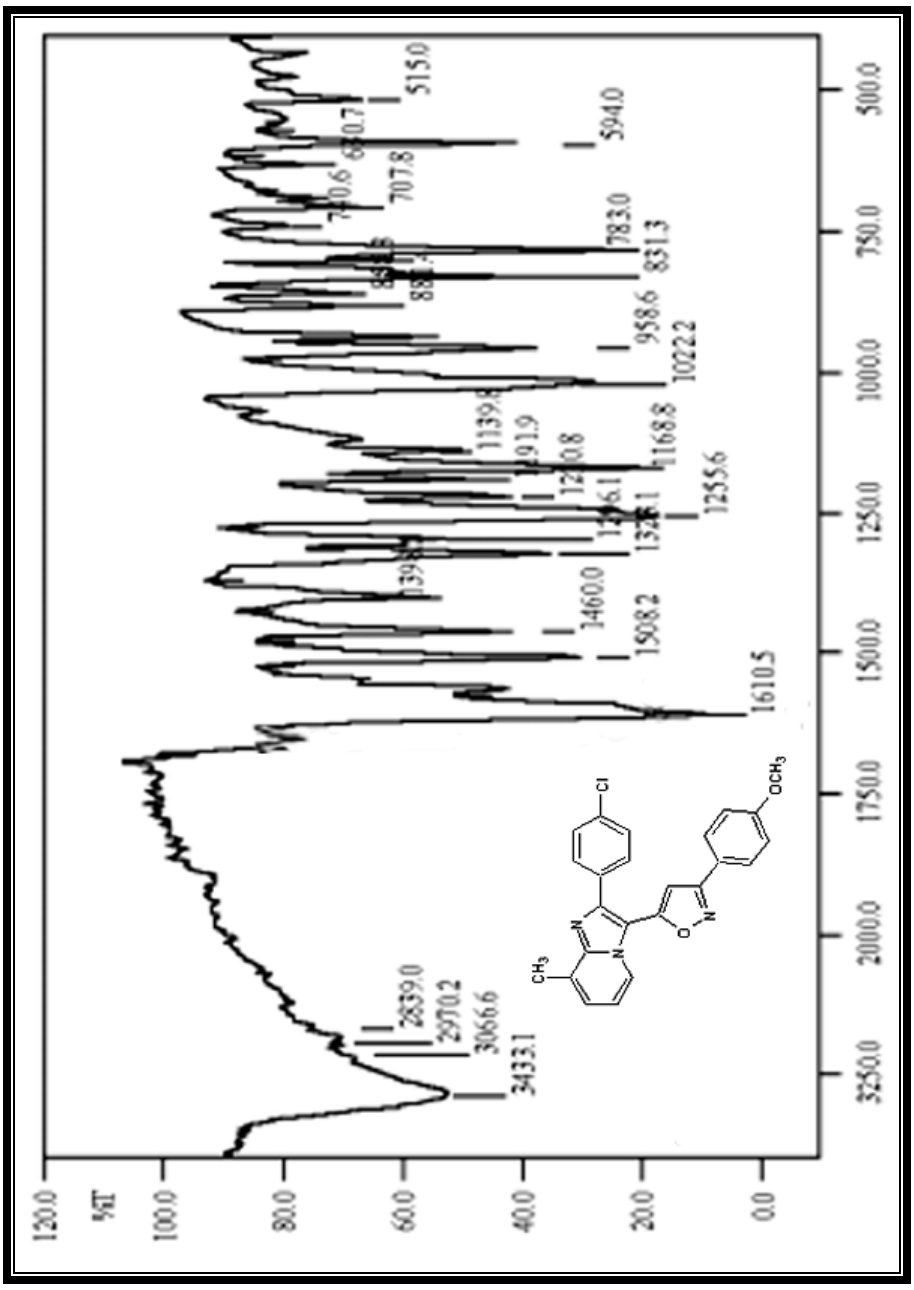
The constitution of the synthesized products has been characterized by using elemental analyses, infra red and $^{1}H$ nuclear magnetic resonance spectroscopy and further supported by mass spectroscopy.

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 40µg. The biological activities of the synthesized compounds have been compared with standard drugs.

## REACTION SCHEME



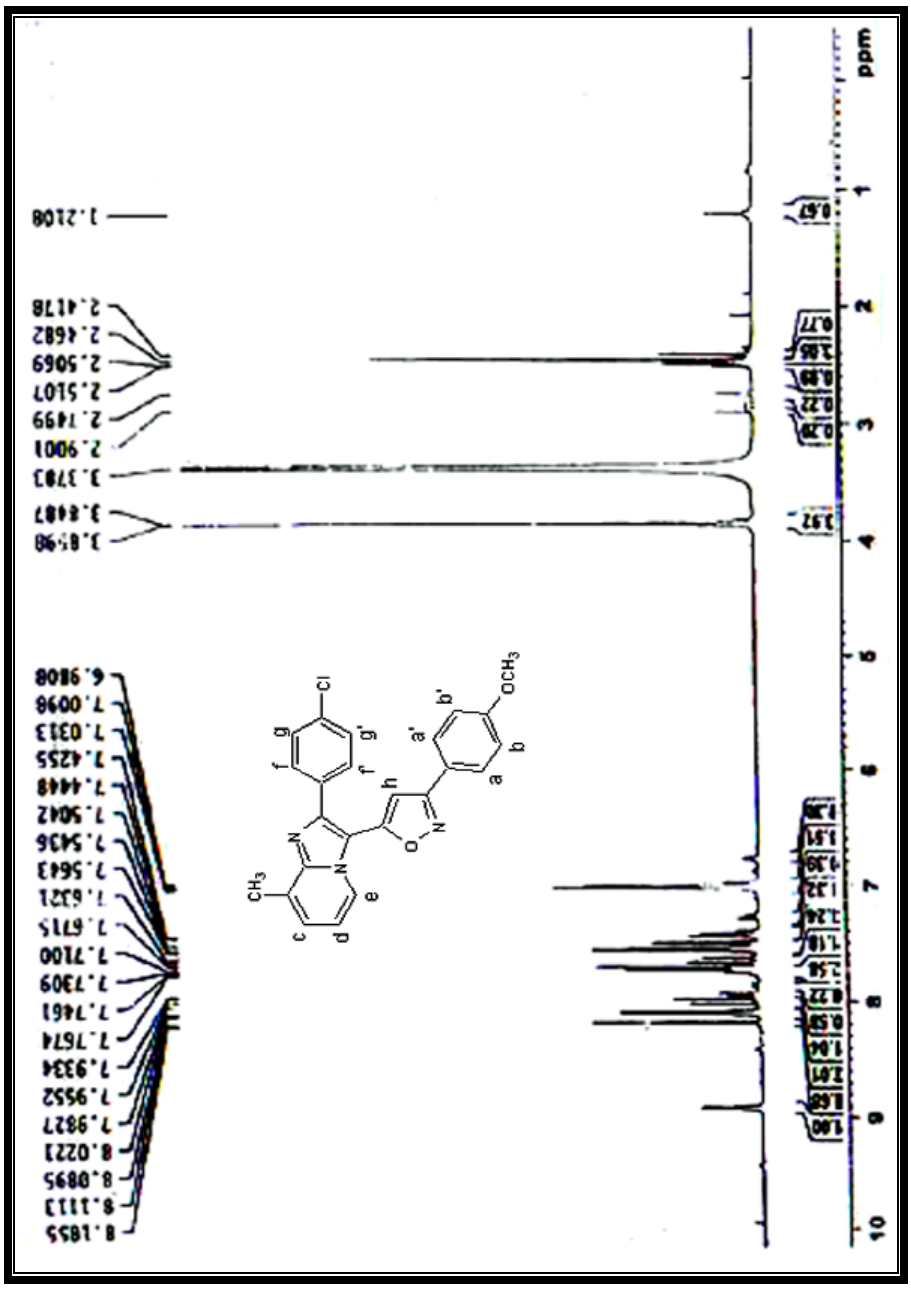
**IR SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-3-(3-(4-METHOXYPHENYL) ISOXAZOLE-5-YL)-8 METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2970 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2839 | 2880-2860 | ” |
| | C-H i.p.def | 1460 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1398 | 1395-1370 | ” |
| Aromatic | C-H str. | 3066 | 3090-3030 | 143-b |
| | C=C Str. | 1508 | 1520-1480 | ” |
| | C-H i.p.def | 1139 | 1125-1090 | ” |
| | C-H o.o.p.def. | 831 | 835-810 | ” |
| Moiety | C=N str. | 1610 | 1610-1590 | 143-c |
| | C-N str. | 1191 | 1230-1020 | ” |
| | C-Cl str. | 783 | 800-750 | ” |
| Isoxazole | C=C str. | 1538 | 1580-1550 | 143-d |
| | C=N str. | 1460 | 1470-1460 | ” |
| | N-O str. | 850 | 850-810 | ” |

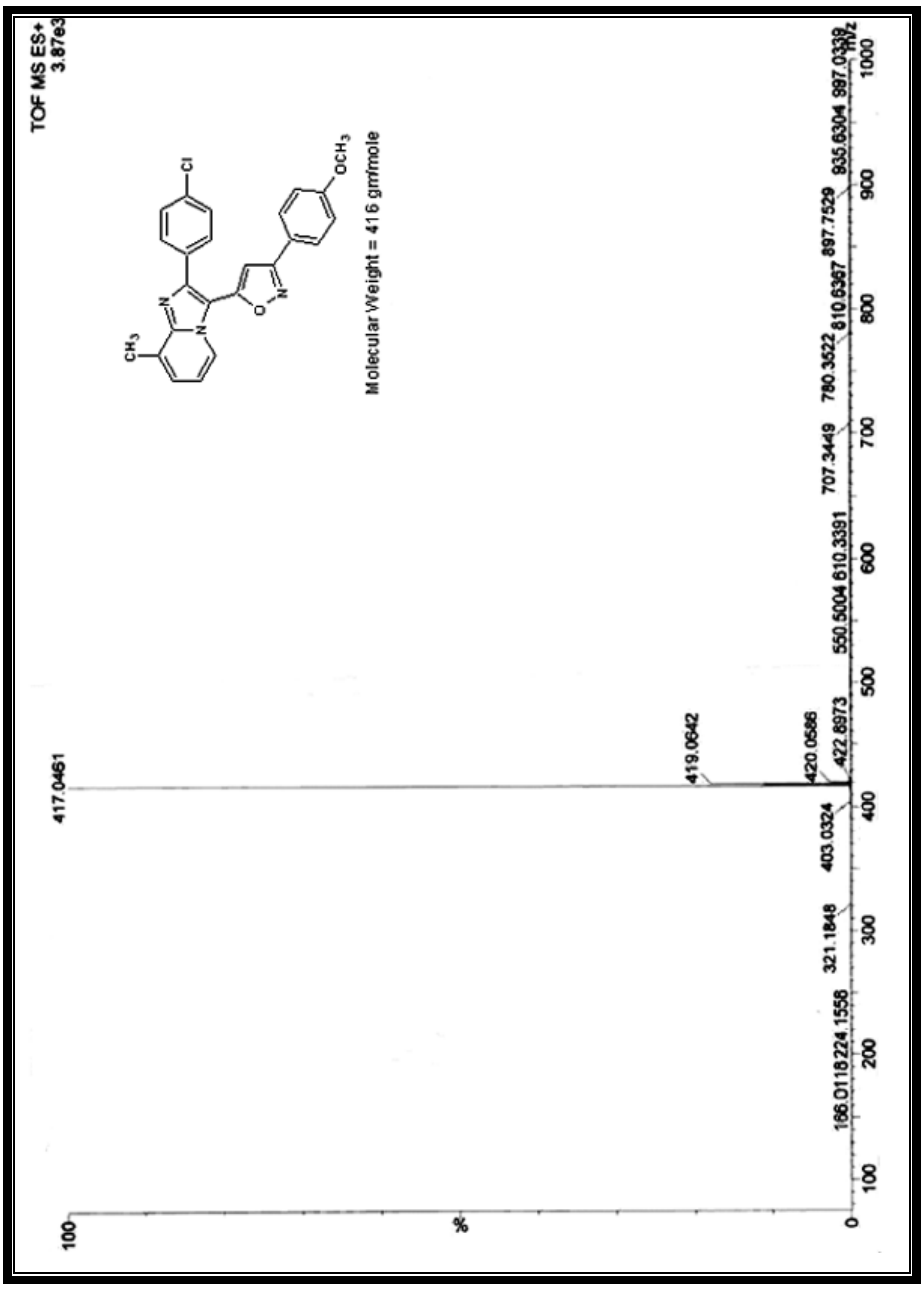
**NMR SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-3-(3-(4-METHOXY PHENYL)ISOXAZOLE-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.42 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.86 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 6.95 | 1H | singlet | CHh |
| 4 | 7.00 | 1H | triplet | Ar-Hd |
| 5 | 7.35 | 2H | doublet | Ar-H(a,a') |
| 6 | 7.50 | 2H | doublet | Ar-H(b,b') |
| 7 | 7.90 | 2H | doublet | Ar-H(f,f') |
| 8 | 7.75 | 2H | doublet | Ar-H(g,g') |
| 9 | 7.05 | 1H | doublet | Ar-Hc |
| 10 | 8.20 | 1H | doublet | Ar-He |

**MASS SPECTRAL STUDIES OF 2-(4-CHLOROPHENYL)-3-(3-(4-METHOXY PHENYL)ISOXAZOLE-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of 2-(4-chlorophenyl)-3-(3-(4-methoxy phenyl)isoxazole-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine.**

**[A] Preparation of 2-chloro-1- (*p*-chlorophenyl)ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)- 8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2-(*p*-chlorophenyl)- 8- methyl imidazo[1,2-*a*]pyridine- 3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine -3-yl]-1-aryl prop-2-en-1-one.**

See on Page No.38 Part-I (D)

**[E] Preparation of 2-(4-chlorophenyl)-3-(3-(4-methoxyphenyl)isoxazole-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine.**

A mixture (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl] aryl prop-2-en-1-one. (4.02gm,0.01m) and hydroxylamine hydrochloride (0.7gm, 0.01m) was refluxed in ethanol for 11 hrs. NaOH is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 63% (3.0gm); m.p.165 °C ; ($C_{24}H_{18}ClN_3O_2$; Found : C,69.15%; H,4.24%; N,9.87%; Required : C,69.31%:H,4.36%;N,10.10%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Isoxazole derivatives have been obtained. The physical data are recorded in Table No.- 5(B).

**[F] Antimicrobial activity of 2-(4-chlorophenyl)-3-(3-aryl-isoxazole-5-yl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine.**

Antimicrobial testing was carried out as described in **part- I Experimental Section [E]** Page No. 38. The zone of inhibition of the test solution are recorded in Table No.- 5(A).

**TABLE NO.- 5(A) BIOLOGICAL SCREENING OF 2-(4-CHLOROPHENYL)-3-(3-ARYL-ISOXAZOLE-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | ***B.coccus*** | ***S.aureus*** | ***Pseudo mona*** | ***E.coli*** | ***A.niger*** |
| **5a** | $C_6H_5$- | 17 | **18** | **19** | 16 | **18** |
| **5b** | 4-$CH_3$-$C_6H_4$ - | 14 | 15 | 13 | 14 | 15 |
| **5c** | 4-$OCH_3$ -$C_6H_4$- | 13 | 12 | 14 | 15 | 13 |
| **5d** | 4-Cl-$C_6H_4$ - | **19** | 15 | 16 | 17 | 16 |
| **5e** | 4-F-$C_6H_4$ - | 14 | 13 | 15 | 12 | 14 |
| **5f** | 4-Br-$C_6H_4$ - | 13 | 14 | 12 | 15 | 13 |
| **5g** | 4-$NH_2$-$C_6H_4$ - | 15 | 13 | 14 | 13 | 12 |
| **5h** | 4-$NO_2$-$C_6H_4$ - | 12 | 14 | 15 | 14 | 15 |
| **5i** | 4-OH-$C_6H_4$ - | 16 | 17 | 16 | **18** | 16 |
| **Std$^n$** | Ampicillin | 20 | 22 | 21 | 21 | - |
| ” | Amoxicillin | 22 | 21 | 22 | 23 | - |
| ” | Ciprofloxacin | 23 | 24 | 24 | 23 | - |
| ” | Norfloxacin | 23 | 23 | 24 | 24 | - |
| ” | Greseofulvin | - | - | - | - | 23 |

**TABLE NO.- 5(B) PHYSICAL CONSTANTS OF 2-(4-CHLOROPHENYL)-3-(3-ARYL-ISOXAZOLE-5-YL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE.**

| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **5a** | $C_6H_5$ - | $C_{23}H_{16}ClN_3O$ | 385.5 | 171.0 | 0.51 | 54.0 | 10.89 | 10.85 |
| **5b** | 4-$CH_3$-$C_6H_4$ - | $C_{24}H_{18}ClN_3O$ | 399.5 | 158.0 | 0.53 | 60.0 | 10.51 | 10.46 |
| **5c** | 4-$OCH_3$-$C_6H_4$- | $C_{24}H_{18}ClN_3O_2$ | 415.5 | 165.0 | 0.54 | 63.0 | 10.10 | 9.98 |
| **5d** | 4-Cl-$C_6H_4$ - | $C_{23}H_{15}Cl_2N_3O$ | 420.0 | 149.0 | 0.59 | 59.0 | 10.00 | 9.91 |
| **5e** | 4-F-$C_6H_4$ - | $C_{23}H_{15}ClFN_3O$ | 403.5 | 152.0 | 0.50 | 57.0 | 10.41 | 10.23 |
| **5f** | 4-Br-$C_6H_4$ - | $C_{23}H_{15}ClBrN_3O$ | 464.5 | 143.0 | 0.61 | 50.0 | 9.04 | 9.01 |
| **5g** | 4-$NH_2$-$C_6H_4$ - | $C_{23}H_{17}ClN_4O$ | 400.5 | 155.0 | 0.53 | 55.0 | 13.98 | 13.00 |
| **5h** | 4-$NO_2$-$C_6H_4$ - | $C_{23}H_{15}ClN_4O_3$ | 430.5 | 139.0 | 0.59 | 53.0 | 13.00 | 12.90 |
| **5i** | 4-OH-$C_6H_4$ - | $C_{23}H_{16}ClN_3O_2$ | 401.5 | 150.0 | 0.50 | 52.0 | 10.46 | 10.40 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

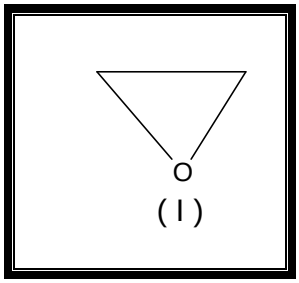
# PART-VI

# STUDIES ON OXIRANES

## INTRODUCTION

The saturated Heterocyclic three-member ring containing one oxygen atom is known as Oxirane ( I ). Oxirane and its derivatives have been known for a long time and have been used as key intermediates in the synthesis of great variety of organic compounds. The Oxirane ring has also designated as “epoxide”, “ethylene oxide”, “ glycide” or some times as “*α, β*–epoxy ethane” and “1,2-oxido ethane”

Wurtz[471] first discovered Oxirane or ethylene oxide in 1859.




( I )

## SYNTHETIC ASPECT

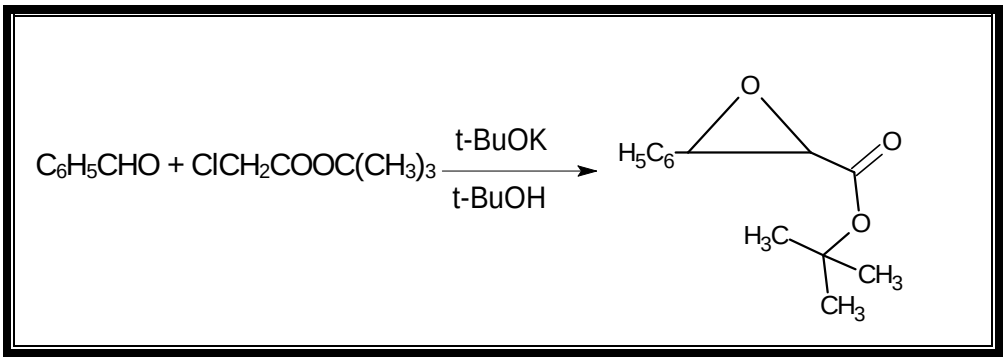
There are so many procedures have been cited in the literature to synthesise oxiranes.

( i ) The simplest method of preparing the parent compound oxirane is the direct oxidation of alkene by air over a silver catalyst at elevated temperature or it’s oxidation to epoxide can be usefully accomplished with organic per acids.[472] Some times epoxidation is carried out by a more reagent alkaline $H_2O_2$.[473]

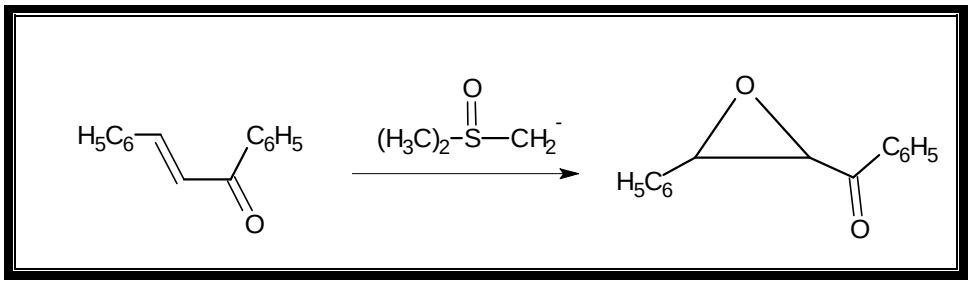
( ii ) Payne and co-workers[474,475] have used a mixture of benzonitrile and $H_2O_2$ in methanol which produces peroxy carboximidic acid which is an efficient oxidizing agent.

( iii ) Epoxidation can also been carried out by using sodium hypochloride catalysed by transition metal complexes.[476]

( iv ) An excellent method for the introduction of an epoxide ring involves various ring closure procedure. A major synthetic pathway of ring closure methods is the Darzens condensation.[477] For example, benzaldehyde is converted into corresponding glycide described as under.[478]

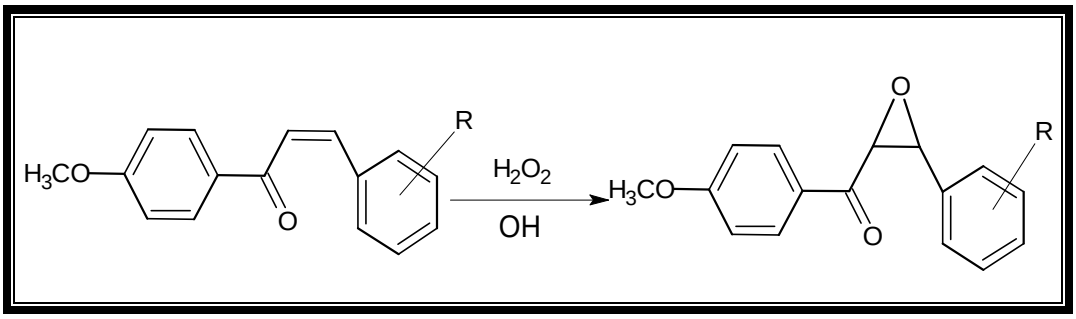



( v ) Coreys and Chakowski[479] discovered an ingenious application of dimethyl sulfoxonium methylides as methylene transfer agents to the carbonyl group for oxirane formation.




( vi ) Rasaki Abayomi Osisany et al.[480] have been synthesized chalcone epoxide by using hydrogen peroxide in alkaline medium.

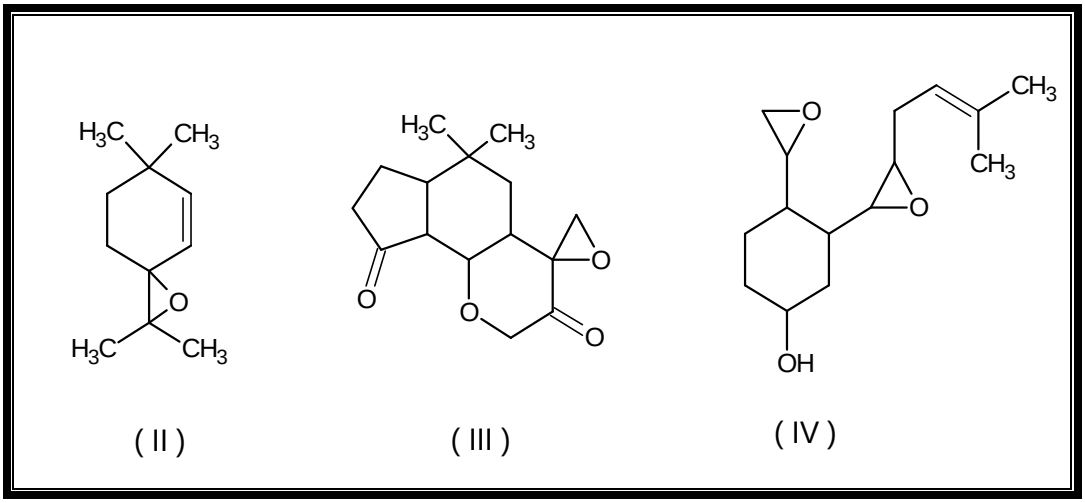
( vii ) Straub Thomas S. et al.[481] reported that *α, β* - unsaturated carbonyl compounds rapidly converted to epoxy ketones at room temp. in aqueous sodium perborate in the presence of phase transfer catalyst.



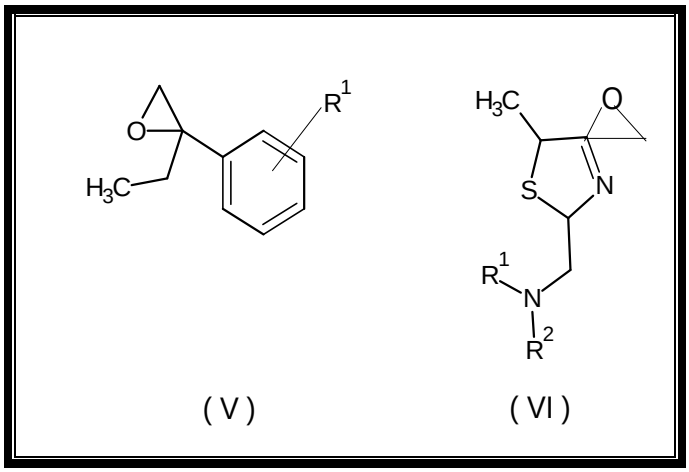

(Viii) An efficient epoxidation of chalcones with urea-hydrogen peroxide under ultrasound irradn. was carried out in 78-93% yields. Compared with the classical method, the advantages of protocol are to use a safer oxidant, mild conditions, no toxic solvent and shorter reaction time.[482]

**PHARMACEUTICAL IMPORTANCE :**

The growing importance of epoxides in the field of natural product chemistry indicates that epoxides from a part of a large number of naturally occurring compounds.[483] Epoxides have been known to form a part of terpens like linalool epoxide[484] (II) and also antitumor[485] agent and antibiotics[486] such as Stranmonin B ( III ) and Fumaglillin ( IV ).

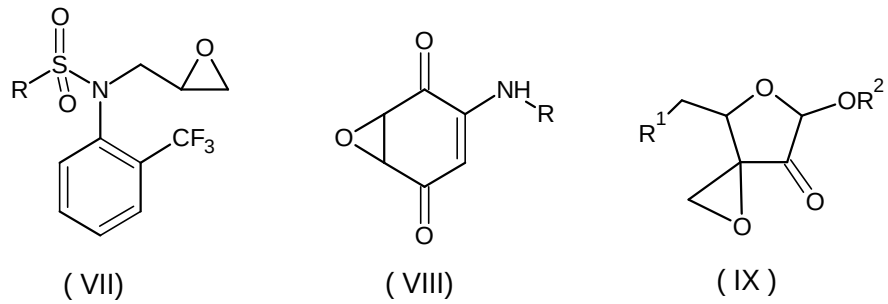


Moreover, Nomura Yutaka et al.[487] synthesized epoxy succinic acid derivatives which are useful in the prevention of treatement of bone diseases such as osteoporosis, Malignant hyperalemia and in the treatment of osteoarthritis and rheumatold arthritis. Kikkawa Kosi[488] and co-workers synthesised epoxide derivatives (V) which exhibited 100% herbicidal activity against panciu, crusgalli and scirpus juncoides respectively with no damage on rice.




( V ) ( VI )

Moder Kennteth Philip[489] have reported epoxides ( VI ) as antiulcer agents. Some oxirane carboxylic acid and esters are useful as intermediate for hypoglycemics and hypolipeacics Rose Henry J.[490] synthesised epoxide derivatives having potent fungicidal activity. Some epoxides have been reported as insecticides and pesticides. Hamaguchi Shigeki et. al.[491] synthesized some optically active halo methyl oxirane useful as insect pheromones. Neef Gunter and co-worker[492] prepared Gonene epoxide and reported that it can be used as intermediates for antigestanenes and antiglucocorticoides. Oesch F. et al.[493] reported enzyme inhibitor activity of oxirane. Tsunemoto Daiei et. al. and Kawamura Yasuo et al.[494] synthesized oxirane derivatives (VII) which are useful as herbicides.



( VII)



( VIII)



( IX )

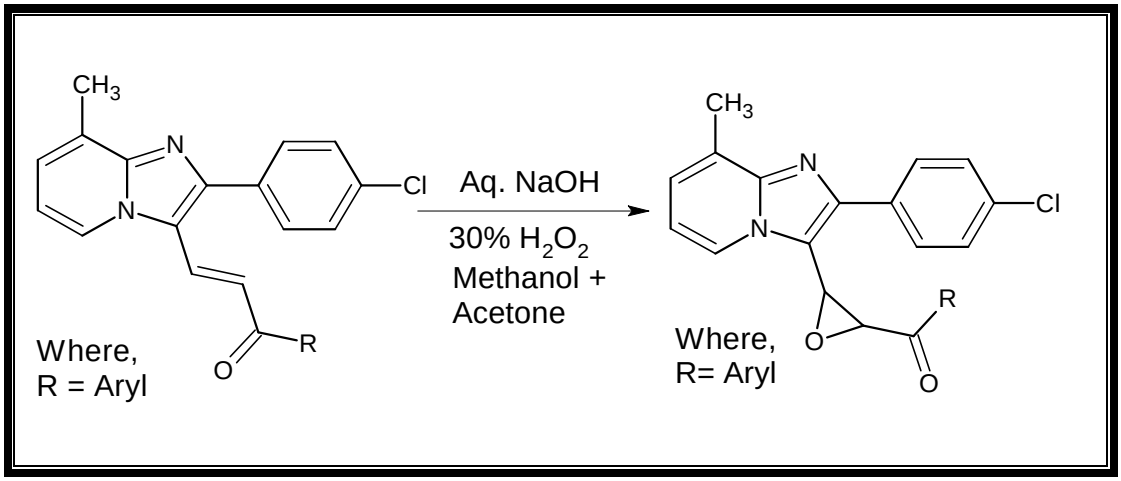
Janada Kim D.[495] synthesised a series of novel oxirane derivatives. Which are useful for inhibiting HIV-1 protease. Kaneko Masami et al.[496] synthesized epoxy cyclohexene dione (VIII) and reported as antibacterial and antitumor agent. Salqdino Raffaele et al.[497] prepared new 6-oxiranyl uracils which showed a potent and selective antiviral activity against the Para influenza 1-virus replication. Tamogami Shigeru et al.[498] prepared epoxy cyclopentyl benzyl ether derivatives which possess 100% herbicidal activity against Echinochloa Crus-galli at 1ppm concentration. Some epoxy keto furanosides (IX) have been reported as antitumor agents by Kobayashi Shin et al.[499] Further more, several derivatives of oxirane have been patented for their use as antitumor[500], antibacterial agents[501], herbicides[502], HIV-protease[503] inhibitors etc. Target compounds and intermediates were assayed for anti-inflammatory effects on superoxide anion generation and elastase release by human neutrophils in response to fMLP /CB, and for cytotoxic activity against nasopharyngeal (KB), vincristine-resistant nasopharyngeal (KBvin), lung (A549) and prostate (DU-145) human cancer cell lines.[504]

Led by this consideration several chalcone epoxides have been synthesised and evaluated for their biological screening described as under.

**Synthesis and therapeutic evaluation of (3-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)oxirane-2-yl) aryl methanone.**

**SYNTHESIS AND THERAPEUTIC EVALUATION OF (3-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL) ARYL METHAN-ONE.**

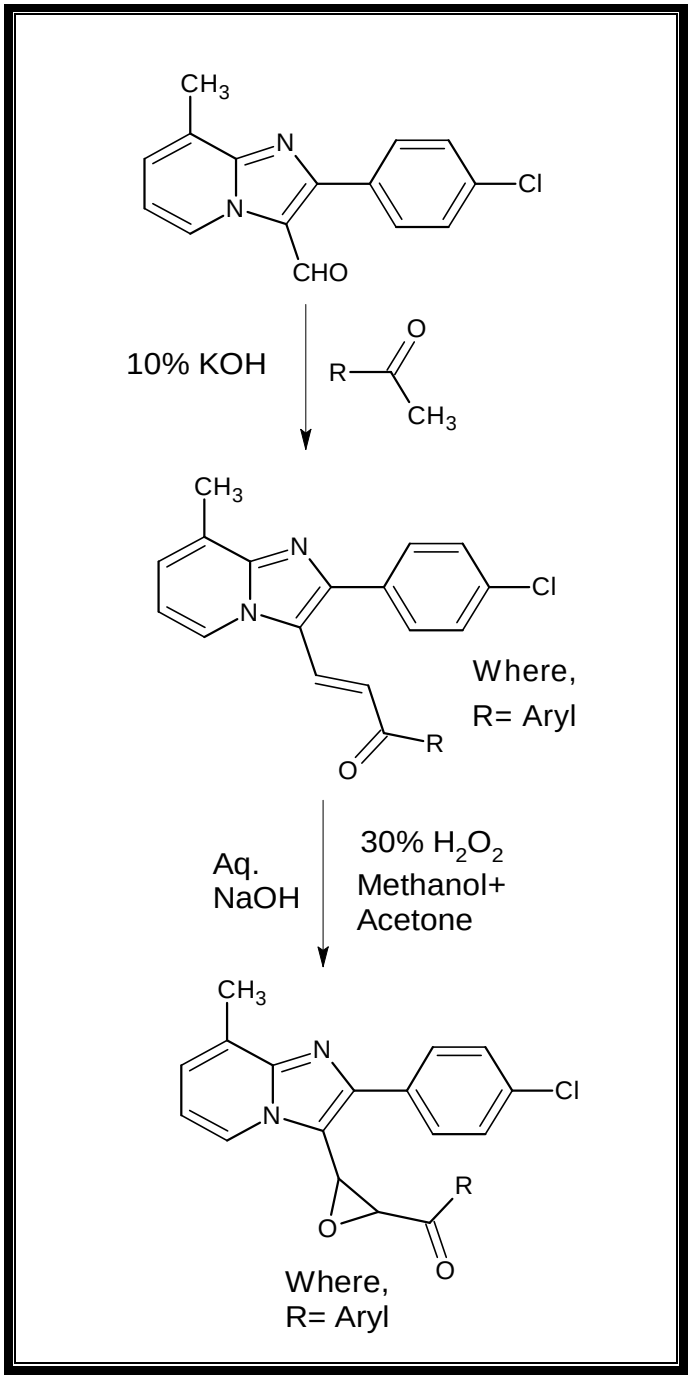
The chemistry of oxiranes has assumed importance because of their versatility in the synthesis of many heterocycles and polymeric compounds. Further more, epoxides are also associated with spectrum of biological activities. Keeping this in view, we have prepared some oxiranes compounds by the oxidation of Chalcone using alkaline $H_2O_2$ shown as under.



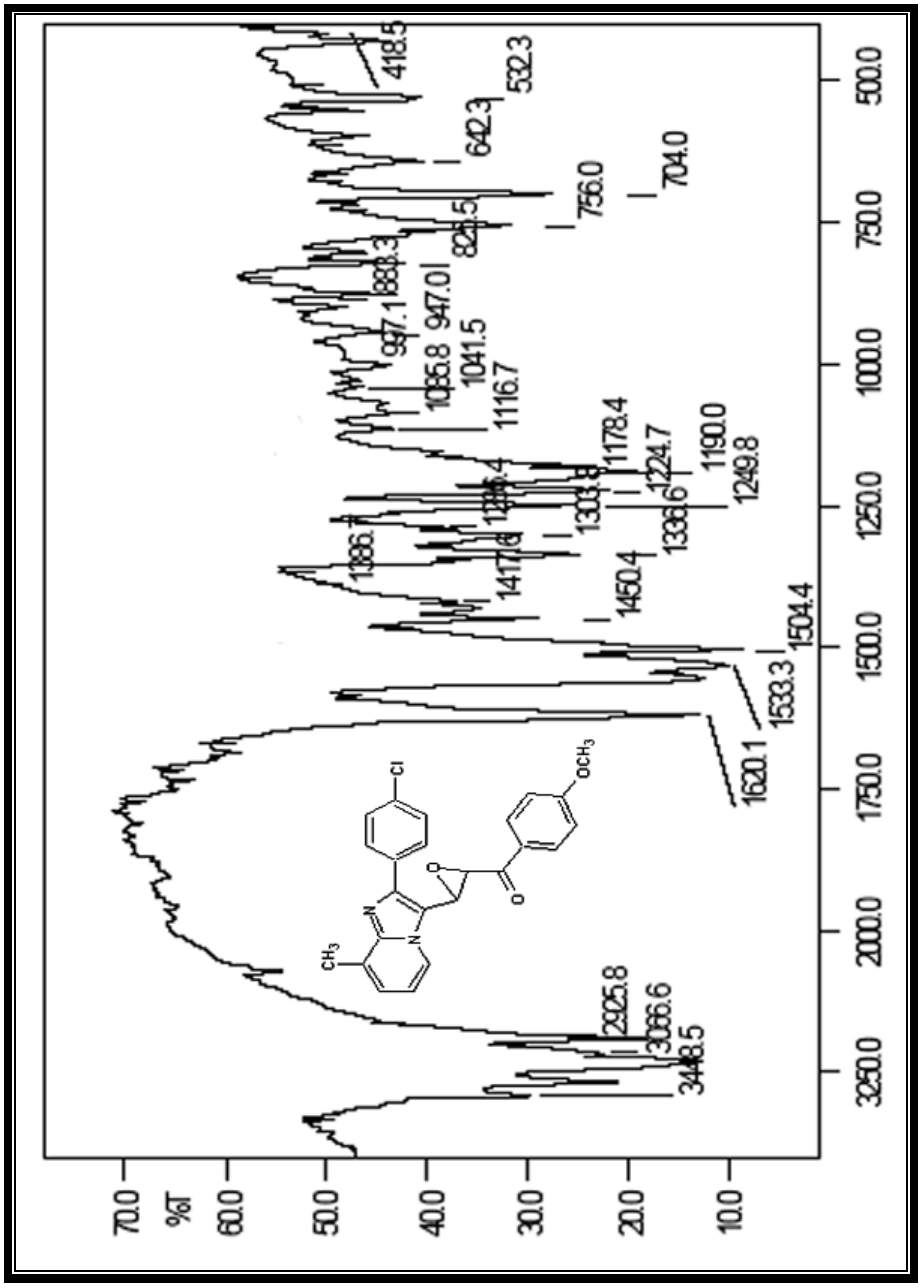

The structure elucidation of the synthesized compounds have been done on the basis of elemental analyses, Infrared and $^1$H-nuclear magnetic resonance spectroscopy and further supported by Mass spectroscopy.

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

## REACTION SCHEME



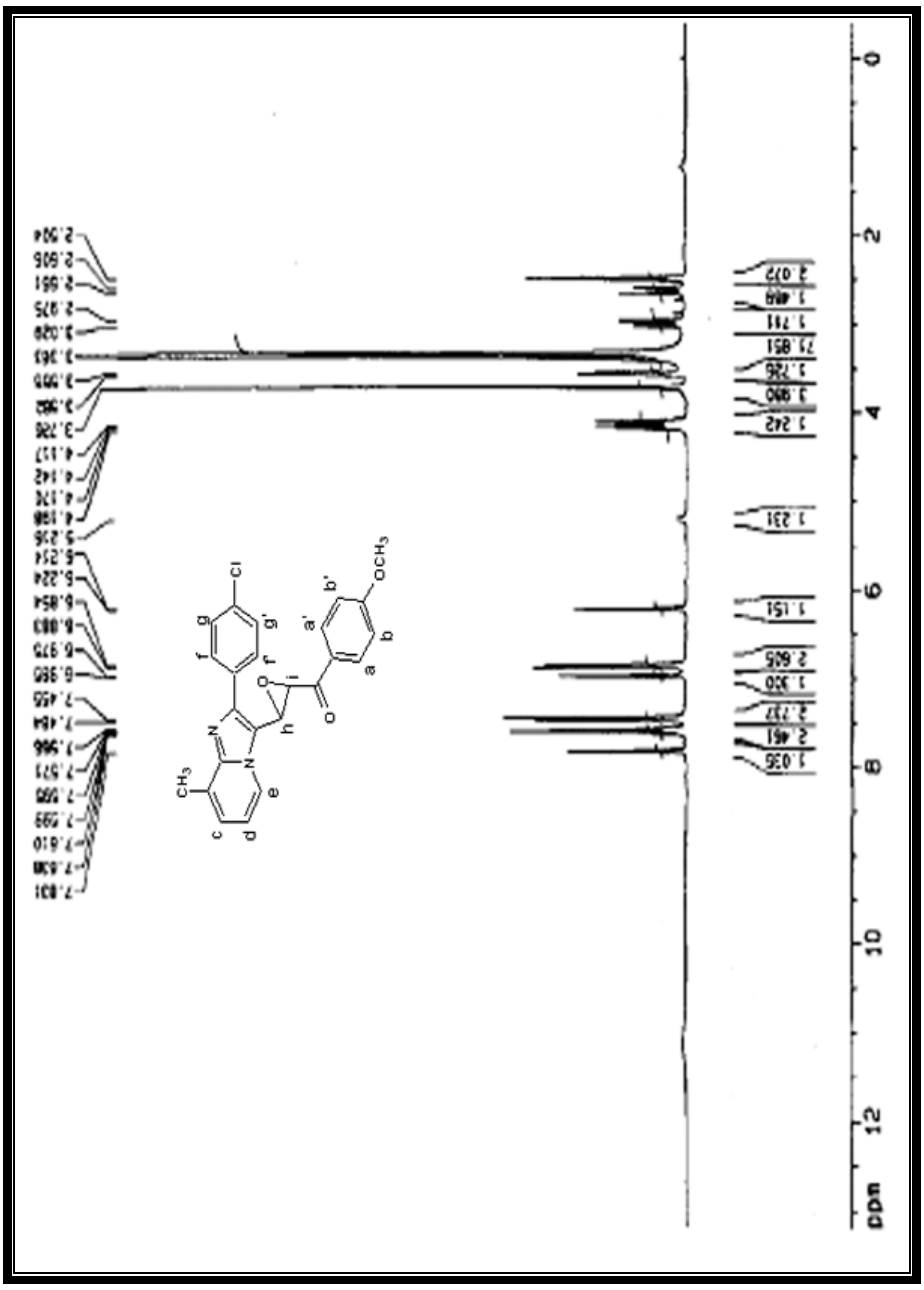
**IR SPECTRAL STUDIES OF (3-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL)(4-METHOXYPHENYL)METHANONE.**



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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2925 | 2975-2950 | 143-a |
| $-CH_3$ | C-H str.(sym.) | 2880 | 2880-2860 | ” |
| | C-H i.p.def | 1450 | 1470-1435 | ” |
| | C-H o.o.p.def. | 1386 | 1395-1370 | ” |
| Aromatic | C-H str. | 3066 | 3090-3030 | 143-b |
| | C=C Str. | 1504 | 1520-1480 | ” |
| | C-H i.p.def | 1116 | 1125-1090 | ” |
| | C-H o.o.p.def. | 835 | 835-810 | ” |
| Moiety | C=N str. | 1620 | 1610-1590 | 143-c |
| | C-N str. | 1190 | 1230-1020 | ” |
| | C-Cl str. | 756 | 800-750 | ” |
| | C=O str. | 1620 | 1700-1640 | ” |
| Ether (Epoxide) | C-O-C str. | 825 | 865-785 | 143-d |

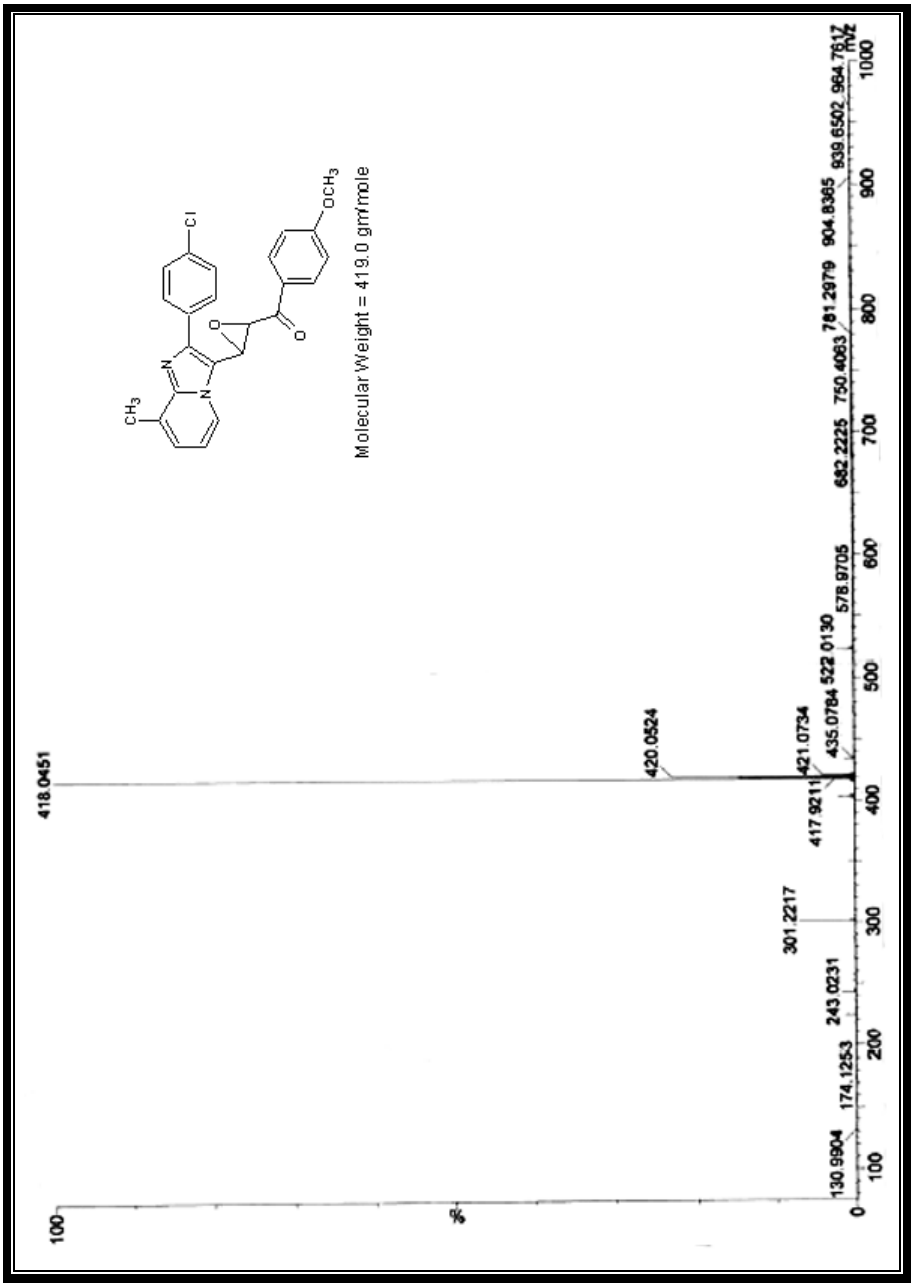
**NMR SPECTRAL STUDIES OF (3-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL)(4-METHOXYPHENYL)METHANONE.**




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

| Signal No. | Signal Position (δppm) | Relative No. of protons | Multiplicity | Inference |
|---|---|---|---|---|
| 1 | 2.50 | 3H | singlet | Ar-$CH_3$ |
| 2 | 3.73 | 3H | singlet | Ar-$OCH_3$ |
| 3 | 4.20 | 1H | doublet | CHh |
| 4 | 3.50 | 1H | doublet | Ar-Hi |
| 5 | 6.85 | 2H | doublet | Ar-H(a,a') |
| 6 | 6.95 | 2H | doublet | Ar-H(b,b') |
| 7 | 7.80 | 2H | doublet | Ar-H(f,f') |
| 8 | 7.62 | 2H | doublet | Ar-H(g,g') |
| 9 | 6.95 | 1H | doublet | Ar-Hc |
| 10 | 7.90 | 1H | doublet | Ar-He |
| 11 | 6.35 | 1H | triplet | Ar-Hd |

**MASS SPECTRAL STUDIES OF (3-(2-(4-CHLOROPHENYL)-8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL)(4-METHOXYPHENYL)METHANONE.**



## EXPERIMENTAL

**Synthesis and therapeutic evaluation of (3-(2-(4-chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*]pyridine-3-yl)oxirane-2-yl)(4-methoxyphenyl)methanone.**

**[A] Preparation of 2-chloro-1- (*p*-chlorophenyl)ethanone.**

See on Page No. 37 Part-I (A)

**[B] Preparation of 2-(*p*-chlorophenyl)- 8-methyl imidazo[1,2-*a*]pyridine**

See on Page No. 37 Part-I (B)

**[C] Preparation of 2-(*p*-chlorophenyl)- 8- methyl imidazo[1,2-*a*]pyridine- 3-carbaldehyde.**

See on Page No. 37 Part-I (C)

**[D] Preparation of (2Z)-3-[2-(*p*-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine - 3-yl]-1-aryl prop-2-en-1-one.**

See on Page No. 38 Part-I (D)

**[E] Preparation of (3-(2-(4-Chlorophenyl)-8-methyl-1*H*-imidazo[1,2-*a*] pyridine-3-yl)oxirane-2-yl)(4-methoxyphenyl)methanone.**

A mixture (2z)-3-[2-(4-chlorophenyl)-8-methyl imidazo[1,2-*a*]pyridine-3-yl]-1-aryl prop-2-en-1-one (4.02gm,0.01m) and 30% $H_2O_2$ solution (0.34,0.01m) was refluxed in Mixture of methanol and acetone for 1-2 hrs. Aq. NaOH solution is used as catalyst. The contents were poured on to crushed ice and product isolated was crystallized from di-chloromethane. Yield 60% (2.55gm); m.p.171 °C;($C_{24}H_{19}ClN_2O_3$ ; Found: C,68.75%;H,4.55%;N,6.60%; Required : C,68.82%;H,4.57%;N,,6.69%)

TLC solvent system : Ethyl acetate : Hexane ( 4:6)

Similarly, other Oxirane derivatives have been obtained. The physical data are recorded in Table No.- 6(B).

**[F] Antimicrobial activity of (3-(2-(4-Chlorophenyl)-8-methyl-1*H*-imidazo [1,2-*a*]pyridine-3-yl)oxirane-2-yl) aryl methanone.**

Antimicrobial testing was carried out as described in **part- I Experimental Section [E]** Page No. 38. The zone of inhibition of the test solution are recorded in Table No.- 6(A).

**TABLE NO.- 6(A) BIOLOGICAL SCREENING OF (3-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL) ARYL METHAN-ONE.**

| Sr. No. | R | Zone of inhibition in m.m | | | | |
|---|---|---|---|---|---|---|
| | | Antibacterial | | | | Antifungal |
| | | *B.coccus* | *S.aureus* | *Pseudo mona* | *E.coli* | *A.niger* |
| **6a** | $C_6H_5$- | 17 | 16 | 15 | **18** | 16 |
| **6b** | 4-$CH_3$-$C_6H_4$ - | 14 | 14 | 12 | 13 | 14 |
| **6c** | 4-$OCH_3$ -$C_6H_4$- | 13 | 12 | 13 | 14 | 13 |
| **6d** | 4-Cl-$C_6H_4$ - | **18** | 15 | **17** | 16 | **19** |
| **6e** | 4-F-$C_6H_4$ - | 14 | 13 | 14 | 12 | 12 |
| **6f** | 4-Br-$C_6H_4$ - | 12 | 12 | 13 | 14 | 13 |
| **6g** | 4-$NH_2$-$C_6H_4$ - | 15 | 13 | 14 | 13 | 12 |
| **6h** | 4-$NO_2$-$C_6H_4$ - | 13 | 14 | 15 | 15 | 14 |
| **6i** | 4-OH-$C_6H_4$ - | 15 | **19** | 16 | 16 | 17 |
| **Std$^n$** | Ampicillin | 20 | 21 | 21 | 20 | - |
| **”** | Amoxicillin | 22 | 21 | 22 | 22 | - |
| **”** | Ciprofloxacin | 24 | 22 | 23 | 22 | - |
| **”** | Norfloxacin | 23 | 23 | 23 | 23 | - |
| **”** | Greseofulvin | - | - | - | - | 24 |

**TABLE NO.- 6(B) PHYSICAL CONSTANTS OF (3-(2-(4-CHLOROPHENYL) -8-METHYL-1*H*-IMIDAZO[1,2-*a*]PYRIDINE-3-YL)OXIRANE-2-YL) ARYL METHAN-ONE.**

| Sr. No. | R | Molecular Formula | M.W. | M.P. °C | Rf* Value | % Yield | % Nitrogen | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Calcd. | Found |
| **6a** | $C_6H_5$ - | $C_{23}H_{17}ClN_2O_2$ | 388.5 | 158.0 | 0.54 | 57.0 | 7.20 | 7.09 |
| **6b** | 4-$CH_3$-$C_6H_4$ - | $C_{24}H_{19}ClN_2O_2$ | 402.5 | 162.0 | 0.52 | 61.0 | 6.95 | 6.85 |
| **6c** | 4-$OCH_3$-$C_6H_4$- | $C_{24}H_{19}ClN_2O_3$ | 418.5 | 171.0 | 0.53 | 60.0 | 6.69 | 6.60 |
| **6d** | 4-Cl-$C_6H_4$ - | $C_{23}H_{16}Cl_2N_2O_2$ | 423.0 | 160.0 | 0.58 | 59.0 | 6.62 | 6.50 |
| **6e** | 4-F-$C_6H_4$ - | $C_{23}H_{16}ClFN_2O_2$ | 406.5 | 165.0 | 0.55 | 58.0 | 6.89 | 6.77 |
| **6f** | 4-Br-$C_6H_4$ - | $C_{23}H_{16}ClBrN_2O_2$ | 467.5 | 154.0 | 0.59 | 53.0 | 5.99 | 5.88 |
| **6g** | 4-$NH_2$-$C_6H_4$ - | $C_{23}H_{18}ClN_3O_2$ | 403.5 | 168.0 | 0.57 | 56.0 | 10.40 | 10.32 |
| **6h** | 4-$NO_2$-$C_6H_4$ - | $C_{23}H_{16}ClN_3O_4$ | 433.5 | 152.0 | 0.60 | 55.0 | 9.69 | 9.63 |
| **6i** | 4-OH-$C_6H_4$ - | $C_{23}H_{17}ClN_2O_3$ | 404.5 | 158.0 | 0.52 | 50.0 | 6.92 | 6.85 |
| **Solvent System : Ethyl acetate : Hexane (4:6)** | | | | | | | | |

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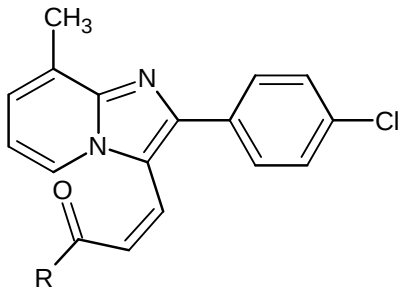
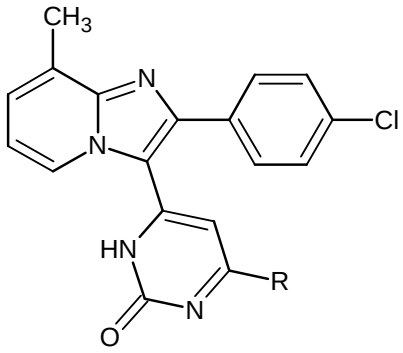
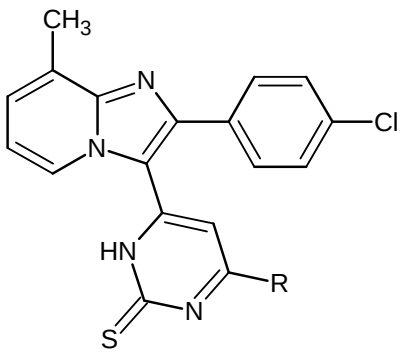
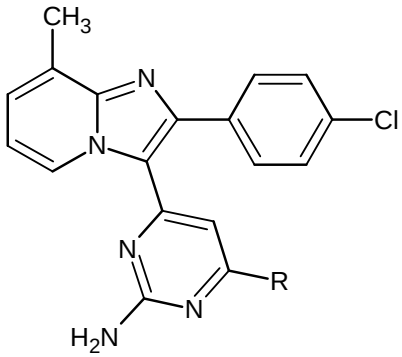
# *LIST OF NEW COMPOUNDS*



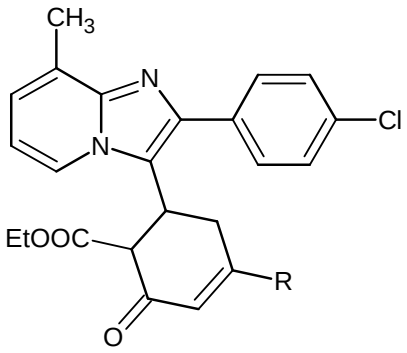



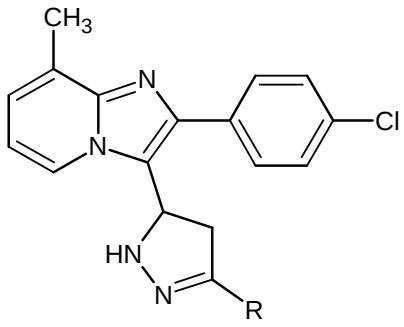

| R | R |
|---|---|
| $C_6H_5$- | $C_6H_5$- |
| 4-$CH_3$-$C_6H_4$ - | 4-$CH_3$-$C_6H_4$ - |
| 4-$OCH_3$-$C_6H_4$ - | 4-$OCH_3$-$C_6H_4$ - |
| 4-Cl-$C_6H_4$ - | 4-Cl-$C_6H_4$ - |
| 4-F-$C_6H_4$ - | 4-F-$C_6H_4$ |
| 4-Br-$C_6H_4$ - | 4-Br-$C_6H_4$ - |
| 4-$NH_2$-$C_6H_4$ - | 4-$NH_2$-$C_6H_4$ - |
| 4-$NO_2$-$C_6H_4$ - | 4-$NO_2$-$C_6H_4$ - |
| 4-OH-$C_6H_4$ - | 4-OH-$C_6H_4$ - |



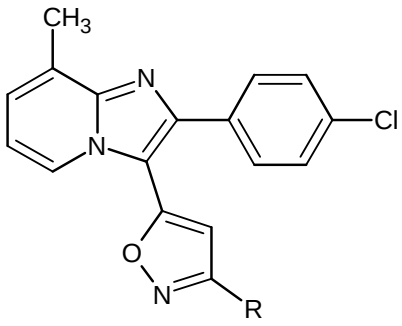



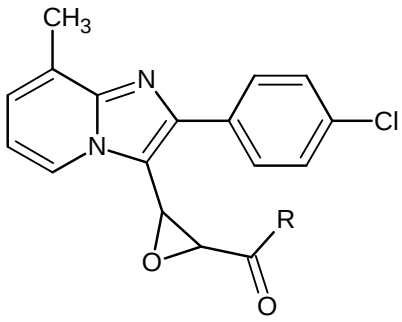

| R | R |
|---|---|
| $C_6H_5$- | $C_6H_5$- |
| 4-$CH_3$-$C_6H_4$ - | 4-$CH_3$-$C_6H_4$ - |
| 4-$OCH_3$-$C_6H_4$ - | 4-$OCH_3$-$C_6H_4$ - |
| 4-Cl-$C_6H_4$ - | 4-Cl-$C_6H_4$ - |
| 4-F-$C_6H_4$ - | 4-F-$C_6H_4$ |
| 4-Br-$C_6H_4$ - | 4-Br-$C_6H_4$ - |
| 4-$NH_2$-$C_6H_4$ - | 4-$NH_2$-$C_6H_4$ - |
| 4-$NO_2$-$C_6H_4$ - | 4-$NO_2$-$C_6H_4$ - |
| 4-OH-$C_6H_4$ - | 4-OH-$C_6H_4$ - |




| R | R |
|---|---|
| $C_6H_5$- | $C_6H_5$- |
| 4-$CH_3$-$C_6H_4$ - | 4-$CH_3$-$C_6H_4$ - |
| 4-$OCH_3$-$C_6H_4$ - | 4-$OCH_3$-$C_6H_4$ - |
| 4-Cl-$C_6H_4$ - | 4-Cl-$C_6H_4$ - |
| 4-F-$C_6H_4$ - | 4-F-$C_6H_4$ |
| 4-Br-$C_6H_4$ - | 4-Br-$C_6H_4$ - |
| 4-$NH_2$-$C_6H_4$ - | 4-$NH_2$-$C_6H_4$ - |
| 4-$NO_2$-$C_6H_4$ - | 4-$NO_2$-$C_6H_4$ - |
| 4-OH-$C_6H_4$ - | 4-OH-$C_6H_4$ - |




| R | R |
|---|---|
| $C_6H_5$- | $C_6H_5$- |
| 4-$CH_3$-$C_6H_4$ - | 4-$CH_3$-$C_6H_4$ - |
| 4-$OCH_3$-$C_6H_4$ - | 4-$OCH_3$-$C_6H_4$ - |
| 4-Cl-$C_6H_4$ - | 4-Cl-$C_6H_4$ - |
| 4-F-$C_6H_4$ - | 4-F-$C_6H_4$ |
| 4-Br-$C_6H_4$ - | 4-Br-$C_6H_4$ - |
| 4-$NH_2$-$C_6H_4$ - | 4-$NH_2$-$C_6H_4$ - |
| 4-$NO_2$-$C_6H_4$ - | 4-$NO_2$-$C_6H_4$ - |
| 4-OH-$C_6H_4$ - | 4-OH-$C_6H_4$ - |