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DESIGN AND SYNTHESIS OF SOME MEDICINALLY IMPORTANT HETEROCYLES

A THESIS
SUBMITTED TO THE SAURASHTRA UNIVERSITY FOR THE DEGREE OF

Doctor of Philosophy
IN THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE OF

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RAJKOT - 360 005.
INDIA
2006
Dedicated to
My Beloved
Lt. Grandfather
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Bhavin P. Thanki
The research work incorporated in the thesis with title “DESIGN AND SYNTHESIS OF SOME MEDICINALLY IMPORTANT HETEROCYCLES” has been described as under.

[A] STUDIES ON DIHYDROPYRIMIDINES
[B] STUDIES ON PYRIMIDINES
[C] STUDIES ON MICROWAVE INDUCED ORGANIC REACTION ENHANCEMENT

[A] STUDIES ON DIHYDROPYRIMIDINES

Recently, the interest in the synthesis of dihydropyrimidine derivatives is increasing tremendously because of their therapeutic activities such as antiviral, antitumor, antibacterial and antiinflammatory. Many of them are pharmacologically important since they behave as calcium channel blockers, antihypertensive agents and α1a antagonists.

In order to developing better medicinally important compounds, it was considered of interest to synthesise some new dihydropyrimidinone and dihydropyrimidine thione derivatives shown as under.

PART-I : STUDIES ON DIHYDROPYRIMIDINTHIONES

Dihydropyrimidinethione and its derivatives have been center of interest for research chemist as they possess varied therapeutic activities such as significant in vitro activity against unrelated DNA and RNA virus, antimalarial, diuretic, antimicrobial, antileukemic and antineoplastic. The above observations created the interest for the synthesis of the series of dihydropyrimidinethiones which is described as under.

SECTION-I : Synthesis and biological screening of 6-Isopropyl-5-[N-phenyl aminocarbonyl]-4-aryl-3,4-dihydropyrimidine-2(1H)-thiones.
The thiopyrimidines of type (I) have been synthesized by the condensation of 4-methyl-3-oxo-N-phenyl pentanamide, thiourea and aryl aldehydes.

SECTION-II : Synthesis and biological screening of 6-Isopropyl-5-[N-(4-methyl phenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones

The thiopyrimidines of type (II) have been synthesized by the condensation of 4-methyl-N-(4-methylphenyl)-3-oxo-pentanamide, thiourea and aryl aldehydes.

SECTION-III : Synthesis and biological screening of 6-Isopropyl-5-[N-phenyl aminocarbonyl]-4-aryl-2-methylthio-3,4-dihydropyrimidines
The thiopyrimidines of type (III) have been synthesized by the condensation of 2-benzylidene-4-methyl-3-oxo-N-phenyl pentanamide with methyl imidothio carbamate.

**PART-II : STUDIES ON DIHYDROPYRIMIDINONES**

Dihydropyrimidinone derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activities. They have been found to possess wide therapeutic activities like antiinflammatory, antiviral, antibacterial, calcium channel blockers, antihypertensive agent and anticancer. In view of these facts, we have undertaken the synthesis of compounds as shown under.

**SECTION-I : Synthesis and biological screening of 6-Isopropyl-5-[N-(4-methoxy phenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones**
The oxopyrimidines of type (IV) have been synthesized by the condensation of 4-methyl-N-(4-methoxyphenyl)-3-oxo pentanamide, urea and aryl aldehydes.

SECTION-II : Synthesis and biological screening of 6-Isopropyl-5-[N-(4-fluoro phenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones

The oxopyrimidines of type (V) have been synthesized by the condensation of 4-methyl-N-(4-fluorophenyl)-3-oxo-pentanamide, urea and aryl aldehydes.

[B] STUDIES ON PYRIMIDINES

Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Pyrimidine derivatives have a wide range of applications and are found to possess most effective therapeutic activities like antibacterial, antimalarial, antiinflammatory, antiviral, CNS depressant etc.

These finding prompted us to design and synthesize some derivatives like chalcones, pyrazolines, cyanopyridines, cyanopyridones, isoxazoles and to study their pharmacological profile against several microbes. The study is described in the following parts.
PART-I  STUDIES ON PYRAZOLINES

Pyrazolines constitute one of the modest class of compounds possessing diversified biological applications such as anticancer, analgesic, antiinflammatory, anticonvulsant, antimicrobial and antipyretic. Literature survey reveals that various pyrazolines have attracted considerable attention as they are also endowed with wide range of pharmacological activities like herbicidal and insecticidal. Prompted by above facts, some new pyrazolines have been prepared which have been described as under.

SECTION-I :  Synthesis and biological screening of 1-Aryl-3-[2’-amino pyrimidin-5’-yl]-propen-2-ones

The chalcone derivative of type (VI) have been synthesized by the condensation of 2-amino-5-formyl pyrimidine with different aryl ketones in the presence of 40% alcoholic KOH.

SECTION-II :  Synthesis and biological screening of 1-Acetyl-3-aryl-5-[2’-aminopyrimidin-5’-yl]-pyrazolines
The pyrazoline derivatives of type (VII) have been synthesized by the reaction of chalcones of type (VI) with hydrazine hydrate in glacial acetic acid.

PART-II : STUDIES ON CYANOPYRIDINES

In continuation to our synthetic manipulations about pharmacologically active cyanopyridine derivatives have been found to be associated with various pharmacological activities such as antifungal, antidiabatic, anticholestermic and antihypertensive. On the basis of these results, we have synthesised new derivatives which have been described as under.

SECTION-I : Synthesis and biological screening of 3-Cyano-2-methoxy-4-[2’-aminopyrimidin-5’-yl]-6-aryl-pyridines

![Chemical Structure](image)

2-Methoxy-3-cyanopyridines of type (VIII) have been synthesized by the condensation of chalcones of type (VI) with malononitrile and sodium methoxide.

PART-III STUDIES ON CYANOPYRIDONES

Cyanopyridone ring systems possess a prominent feature in medicinal chemistry and associated with biological activities such as analgesic, antibacterial, antidiabetic, anticonvulsant etc. In view of these facts, it was contemplated to synthesize cyanopyridone derivative which have been described as under.
SECTION-I : Synthesis and biological screening of 3-Cyano-4-[2’-aminopyrimidin-5’-yl]-6-aryl-1,2-dihydro-2-pyridones

The cyanopyridones of type (IX) have been synthesized by the condensation of chalcones of type (VI) with ethylcyanoacetate and ammonium acetate.

PART-IV STUDIES OF ISOXAZOLES

Isoxazole derivatives are of considerable interest due to many bioactivities which they possess such as antibacterial, antifungal, antidiabetic, analgesic, hypnotics and sedatives etc. In view of these valid observations it was contemplated to synthesise some new isoxazoles possessing higher biological activity which have been described as under.

SECTION-I : Synthesis and biological screening of 3-Aryl-5-[2’-amino pyrimidin-5’-yl]-isoxazoles

The isoxazole derivatives of type (X) have been synthesized by the condensation of chalcones of type (VI) with anhydrous sodium acetate and hydroxylamine hydrochloride in glacial acetic acid.
[C] STUDIES ON MICROWAVE INDUCED ORGANIC REACTION ENHANCEMENT

In coming years microwave synthesis will become a widely used technique for process development as well as drug discovery by enlightened scientists in the pharmaceutical and fine chemical industries. We have developed Microwave-induced Organic Reaction Enhancement (MORE) techniques which is characterized by simple, rapid reaction, high selectivity in some cases, increased atom economy, low energy consumption (no refluxing and therefore no wasted latent heat of vaporization) and safe operation. Led by these considerations, we have synthesised some new acetylpyrazoline and dihydrothiopyrimidinethione derivatives.

SECTION-I : Synthesis and biological screening of 6-Isopropyl-5-[N-phenyl aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones

Dihydropyrimidinthiones of type (I) have been synthesized by the condensation of 4-methyl-N-phenyl-3-oxo-pentanamide, thiourea and aryl aldehydes under microwave irradiation in few minutes. The advantages of microwave synthesis has been reported.

SECTION-II : Synthesis and biological screening of 1-Acetyl-3-aryl-5-[2’-amino pyrimidin-5’-yl]-pyrazolines
The pyrazoline derivatives of type (VII) have been synthesized by the reaction of chalcones of type (VI) with hydrazine hydrate in glacial acetic acid under microwave irradiation in few minutes.

**CHARACTERISATION**

The constitution of newly synthesised products have been supported by using elemental analyses, Infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

**In vitro study on multiple biological activities**

(i) All the compounds have been evaluated for their antibacterial activity towards *Gram positive* and *Gram negative* bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 $\mu$g. The biological activity of the synthesised compounds have been compared with standard drugs.

(ii) Selected compounds have been evaluated for their *in vitro* biological assay like antitubercular activity towards a strain of *Mycobacterium tuberculosis H37Rv* at a concentration of 6.25$\mu$g/ml using Rifampin as a standard drug, which have been tested by Tuberculosis Antimicrobial Acquisition Coordinating Facility (TAACF), Alabama, U.S.A.
DESIGN AND SYNTHESIS OF SOME MEDICINALLY IMPORTANT HETEROCYCLES
INTRODUCTION

The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds. Inorganic compounds continue to be important in therapy but organic molecules with increasingly specific pharmacological activities are clearly dominant. The primary objective of medicinal chemistry is the design and synthesis of new compounds that are suitable for use as drugs. This process requires a team effort. It not only involves chemists but also workers from a wide range of disciplines such as biology, biochemistry, pharmacology, medicine and others.

A great deal of research carried out in chemistry is devoted to the study of heterocyclic chemistry. It is a vast and expanding area of chemistry because of the obvious applications of compounds derived from heterocyclic ring in pharmacy, medicine, agriculture and other fields. Heterocyclic compounds show vital role in the field of pharmaceuticals. Heterocyclic compounds are used because they have a specific clinical reactivity, for example epoxides, aziridines and β-lactams. The introduction of heterocyclic group into drugs may affect their physical properties, for example the dissociation constants of sulphur drugs or modify their patterns of absorption, metabolism or toxicity.

Heterocyclic compounds are also widely distributed in nature. Many are of fundamental importance to living systems: it is striking how often a heterocyclic compound is found as a key component in biological processes. For example, nucleic acid bases, which are derivatives of the pyrimidine and purine ring systems, as being crucial to the mechanism of replication. Chlorophyll and haemin, which are derivatives of the porphyrin ring systems are the components
required for photosynthesis and for oxygen transport in higher plants and in animals, respectively. Essential diet ingredients such as thiamine (Vitamin B₁) and ascorbic acid (Vitamin C) are heterocyclic compounds of the twenty amino acids commonly found in proteins, three namely histidine, proline and tryptophan are heterocyclic. It is not surprising, therefore, that a great deal of current research work is concerned with methods of synthesis and properties of heterocyclic compounds.

Research in the field of pharmaceutical has its most important task in the development of new & better drugs and their successful introduction into clinical practice. Central to these efforts, accordingly stand the search for pharmaceutical substances and preparation which are new and original. In addition to these objectives, we may search for newer drugs which exhibit some clear advantages over a drug already known. Such advantages may be qualitative or quantitative improvement in activity, the absence of undesirable side effects, lower toxicity, improved stability or decreased cost.

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

Drugs action is believed to be due to the interaction of the drug with enzymes, receptors and other molecules found in the biological system. The binding of a drug to the active or other sites of an enzyme usually has the effect of preventing the normal operation of that enzyme. The drug’s therapeutic effect will depend on the stability of the drug-enzyme complex as well as the fraction of active and allosteric sites occupied by the drug. The stronger the binding of the drug to the enzyme and greater the number of sites occupied, the more effective the drug is likely to be in inhibiting the action of the enzyme.
The degree of drug activity is directly related to the concentration of the drug in the aqueous medium in contact with the active or receptor site. The factors affecting this concentration in a biological system can be classified into two phases.

(I) The pharmacokinetic phase

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

(II) The pharmacodynamic phase

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

The role of the medicinal chemist is to design a drug structure that has the maximum beneficial effects with a minimum of side effects. This design has to take into account the stereoelectronic characteristics of the target active or receptor site and also such factors as the drug’s stability in situ, its polarity and its relative solubilities in aqueous media and lipids. The stereochemistry of the drug is particularly important because stereoisomers often have different biological effects that range from inactive to highly toxic.

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 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.

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.

AIMS AND OBJECTIVES

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

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

- To generate several derivatives like dihdropyrimidinthiones and dihydropyrimidinones.
To generate derivatives like pyrazolines, cyanopyridines, cyanopyridones and isoxazoles bearing pyrimidine nucleus.

To synthesise biologically active dihydropyrimidine thiones and acetyl pyrazolines bearing pyrimidine nucleus using microwave induced synthesis method.

To check purity of all the compounds using thin layer chromatography.

To characterise these products for stucture elucidation using spectroscopic techniques like IR, PMR and Mass spectral studies.

To evaluate new products for better drug potential against different strains of bacteria, fungi and for antitubercular activity against *Mycobacterium Tuberculosis H37Rv*. 
[A]

STUDIES ON DIHYDROPYRIMIDINES
INTRODUCTION

The chemistry of dihydropyrimidines and their derivatives has been studied for over a century due to the association of these systems with a variety of biological properties. Over 100 years ago, 4-aryl-3,4-dihydropyrimidin-2(1H)-ones of type (I) (DHPMs) were reported for the first time in the literature. In 1893, Italian chemist Pietro Biginelli discovered a multicomponent reaction that produced these multifunctionalized dihydropyrimidones (I), in a simple one-pot process. Since the early 1980s however, interest in dihydropyrimidones of type (I) has increased significantly\(^1\). This was originally due to the apparent structural similarity of DHPMs to the well-known dihydropyridine calcium channel modulators of the Hantzsch type (II). It was soon established that DHPMs exhibit a similar pharmacological profile to DHP calcium channel modulators of the nifedipine type and much activity has been observed in this area throughout the 1980s and 1990s\(^2\).\(^3\).\(^4\).

From the biochemical point of view, dihydroazines are of intense interest because of presence of this group at the active site of the “hydrogen transferring coenzyme” NADH (reduced nicotinamide adenine dinucleotide). This nucleotide, a central participant in metabolic processes in living organisms, participates in the reduction of various unsaturated functionalities.
Despite the importance of dihydroazines for clarifying a wide range of theoretical, medicinal and biological problems, the chemistry of this group of compounds is still extremely spotty\textsuperscript{5-9}.

The growing demand for biologically active compounds made multicomponent reactions attractive. The multicomponent condensation (MCC) approach is especially appealing as the products are formed in single step and the diversity can be readily achieved by varying the components. A variety of heterocyclic compounds can be rapidly assembled employing this approach as demonstrated by the synthesis of dihydropyrimidin using Biginelli reaction.

In the area of drug development, dihydroazines show great promise, particularly since the 4-aryldihydropyridines exhibit powerful vasodilation activity via modifying the calcium ion membrane channel\textsuperscript{10-14}. Additionally, dihydropyridines have been found to actively transport medication across biological membranes\textsuperscript{15}.

Until recently, most of the information available on dihydroazines centered around dihydropyridines, with very little data extending to the related dihydropyrimidines. This lacuna has motivated our deep involvement in developing dihydropyrimidine chemistry, particularly dihydropyrimidines containing no substituents on the ring nitrogen\textsuperscript{16}. 
CONCEPT OF MCRs

In MCRs, "three or more reactants come together in a single reaction vessel to form product that contains portions of all the components".

First officially reported MCR was the Strecker synthesis of α-amino crotononitrile in 1850. Some of the important MCR are given below.

(1) **Strecker synthesis**\(^{17}\) (1850).

(2) **Hantzsch dihydropyridine synthesis**\(^{18}\) (1882).

(3) **Radziszewski imidazole synthesis**\(^{19}\) (1882).

(4) **Hantzsch pyrrole synthesis**\(^{20}\) (1890).
(5) Biginelli reaction\textsuperscript{21} (1893).

\[
\text{CHO} + \underset{R}{\text{C}} - \text{O} + \text{NH}_2 \text{CONH}_2 \xrightarrow{\text{Ethanol, con HCl}} \text{O}
\]

(6) Mannich reaction\textsuperscript{22} (1912).

\[
\text{R} + \text{H}_2\text{C} = \text{NH} + \text{R}_1\text{C} = \text{O} + \text{R}_2\text{C} = \text{O} \xrightarrow{\text{H}^+} \text{R} + \text{R}_1\text{R}_2\text{C} = \text{O}
\]

(7) Robinsons synthesis of tropinone\textsuperscript{23} (1917).

\[
\begin{align*}
\text{CHO} + \text{CH}_3\text{NH}_2 + \text{O} = \text{C} \xrightarrow{} \text{H}_3\text{N} - \text{C} = \text{O}
\end{align*}
\]

(8) Passerini reaction\textsuperscript{24} (1921).

\[
\text{R}_1\text{N} = \text{C}^- + \text{R}_2\text{C} = \text{O} + \text{R}_3\text{C} = \text{O} \xrightarrow{} \text{R}_1\text{R}_2\text{R}_3\text{C} = \text{O}
\]

(9) Bucherer-Bergs hydantoin synthesis\textsuperscript{25} (1929).

\[
\begin{align*}
\text{R}_1\text{R}_2\text{C} = \text{O} + \text{NH}_3 + \text{CO}_2 + \text{KCN} \xrightarrow{} \text{R}_2\text{R}_1\text{N} = \text{C} \equiv \text{O}
\end{align*}
\]
(10) Ugi reaction\textsuperscript{26} (1959).

\[
\begin{align*}
R_2CHO + R-COOH + R_3NC + R_1NH_2 & \rightarrow \quad \text{N} \quad \text{NH-R}_3 \\
\text{R}_2\text{C}=\text{N}\text{R}_1 & \quad \text{O} \\
\text{R} & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{R}_3 \\
\text{R} & \quad \text{R}_2
\end{align*}
\]

\text{(XII)}

**MECHANISTIC STUDIES**

Since the 1930s several mechanistic pathways have been proposed for the Biginelli reaction. In 1933, Folkers and Johnson reported that one of three intermediates (XIII-XV) was likely to be present in this reaction\textsuperscript{27}. These included bisureide (XIII) which was formed by a condensation reaction between the aryl aldehyde and the urea followed by subsequent attack of the resultant imine with another equivalent of urea. Also, 3-urido ethyl acrylate (XIV) arose from a condensation reaction between the $\beta$-ketoester and urea. Finally, the reaction of the $\beta$-ketoester and the aldehyde delivered the aldol adduct (XV).

\[
\begin{align*}
\text{PhNH}_2&\quad\text{NH}_2 \\
\text{O} & \quad \text{NH} \\
\text{H}_2\text{N} & \quad \text{NH} \\
\text{Ph} & \quad \text{NH}_2 \\
\text{O} & \quad \text{NH} \\
\text{H}_2\text{N} & \quad \text{NH} \\
(XIII) & \quad (XIV) \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{Ph} & \quad \text{O} \\
\text{EtOOC} & \quad \text{OEt} \\
(XV)
\end{align*}
\]

Sweet and Fissekis proposed a more detailed pathway involving a carbenium ion species\textsuperscript{28}. According to these authors the first step involved an aldol condensation between ethyl acetoacetate (XVI) and benzaldehyde (XVII) to deliver the aldol adduct (XVIII). Subsequent dehydration of (XVIII) furnished the key carbenium ion (XIX) which was in equilibrium with enone (XX). Nucleophilic attack of (XIX) by urea then delivered ureide (XXI). Intramolecular cyclisation produced a hemiaminal which underwent dehydration to afford dihyropyrimidinone (XXII). These authors demonstrated that the carbenium species was viable through
synthesis. After enone (XX) was synthesised, it was allowed to react with N-methyl urea to deliver the mono-N-methylated derivative of DHPM (XXII).

The mechanism was then reexamined 25 years later in 1997 by Kappe\textsuperscript{29}. Kappe used \textsuperscript{1}H and \textsuperscript{13}C spectroscopy to support the argument that the key intermediate in the Biginelli reaction was iminium species (XXIII). In the event, benzaldehyde reacted with urea to form an intermediate "hamiaminal" (XXIV) which subsequently dehydrated to deliver (XXIII). Iminium cation (XXIII) then reacted with (XVI) to give (XXII), which underwent facile cyclodehydration to give (XXII). Kappe also noted that in the absence of (XVI), bisureide (XIII) was afforded as a consequence of nucleophilic attack of (XXIII) by urea. This discovery confirmed the conclusion of Folkers and Johnson in 1933. As far as the proposal form 25 years earlier by Sweet and Fissekis, Kappe show no evidence by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy that a carbenium ion was a required species in the Biginelli reaction. When benzaldehyde (XVII) and ethyl acetoacetate(XVI) were mixed under
Biginelli conditions the requisite aldol product (XVIII), which was necessary for the formation of carbenium ion (XIX), was not detected.

**POSSIBLE MANIPULATION IN DHPM NUCLEUS**

Looking below to the structure of the DHPM ring, it requires following modification in it's structure for generating new molecules for further screening. So many, scientists have synthesised huge libraries for the screening of new molecules.

1. Partial or full oxidation.
2. Reduction of the ring to the hexahydropyrimidine.
3. Alkylation and acylation of the heteroatoms.
4. Manipulation of the ester at C₅
5. Manipulation of the methyl group at C₆
   (halogenation, nitration, sulphonation etc.)
6. Ring condensing reaction to make bi,tri-cycles
PART - I

STUDIES ON DIHYDROPYRIMIDINE THIONES
INTRODUCTION

Recent years could be featured with the significant increase of an interest to the chemistry of 3,4-dihydropyrimidine-2(H)-ones and thiones. It is related to an equal degree with their both usage as synthones for obtaining more complex compounds, including naturally occurred ones and biological activity. The structural features of these heterocyclic systems move them forward as unique synthones in pyrimidine derivatives synthesis.

Dihydropyrimidinthione and its derivatives have been center of interest for reaction for research chemist as they possess varied therapeutic activities such as significant in vitro activity against unrelated DNA and RNA viruses, antimalarial, diuretic, antimicrobial, antileukemic and antineoplastic\textsuperscript{30}.

SYNTHETIC ASPECTS

Literature survey reveals that several publications and patents described the synthesis of dihydropyrimidinthiones as under.

1. Polyphosphate ester (PPE) serves as an excellent reaction mediator in the three component Biginelli reaction\textsuperscript{31}.

2. Indium(III) chloride was emerged as a powerful Lewis catalyst imparting high region and chemo selectivity in various chemical transformations\textsuperscript{32}.
3. DHPM was prepared from three component β-diketone, aldehyde and thiourea coupling in ethanol catalyzed by indium(III) tribromide (In Br₃)\textsuperscript{33,34}. This modified one-pot Biginelli condensation provided not only simple preparation but also this modified Biginelli reaction was oxygen-bridge.

4. Silica Sulfuric acid efficiently catalyzes the three component Biginelli reaction as shown under\textsuperscript{35}.

5. Subhas D. Bose et al\textsuperscript{36} describe a general and practical route for the Biginelli cyclocondensation reaction using cerium(III) chloride (CeCl₃) heptahydrate as the catalyst.

6. Shrinivas et al\textsuperscript{37} developed iodine catalysed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-thiones.
7. De. S. K. et al.\textsuperscript{38} reported Biginelli-type reaction in the presence of catalytic amount of 5% of Sc(OTf)\textsubscript{3} at 100\textdegree C.

\[
\begin{array}{c}
\text{R}_2\text{O} - \text{C} = \text{O} + \text{R} - \text{CHO} + \text{H}_2\text{N}-\text{S}-\text{NH}_2 \\
\xrightarrow{\text{Sc(OTf)}_3} \ 100\textdegree C \\
\text{R}_1\text{O} - \text{C} = \text{O}
\end{array}
\]

(VI)

8. Zhang X et al.\textsuperscript{39} developed a novel series of 4-substituted 3,4-dihydropyrimidin-2(1H)-thiones employing magnesium perchlorate as an efficinet catalyst under ultrasound irradiation.

\[
\begin{array}{c}
\text{R}_3\text{O} - \text{C} = \text{O} + \text{R}_1 - \text{CHO} + \text{H}_2\text{N}-\text{S}-\text{NH}_2 \\
\xrightarrow{[\text{Mg(ClO}_4)_2]} \\
\text{R}_2\text{O} - \text{C} = \text{O}
\end{array}
\]

(VII)

ATWAL MODIFICATION

Apart from the traditional Biginelli condensation, there are only a few other synthetic methods available that lead to DHPMs, none of these have any significance today. One noticeable exception is the so-called “Atwal modification” of the Biginelli reaction\textsuperscript{40-42}. Here, an enone of type (VIII) is first condensed with a suitable protected urea or thiourea derivative (IX) under almost neutral conditions.

\[
\begin{array}{c}
\text{O} - \text{C} = \text{O} + \text{H}_2\text{N}-\text{S}-\text{R} \\
\xrightarrow{\text{NaHCO}_3} \text{DMF} \\
\text{Ar}\text{O} - \text{C} = \text{O}
\end{array}
\]

(VIII) (IX) (X)
**THERAPEUTIC IMPORTANCE**

Dihydropyrimidines of Biginelli-type have come a long way since their discovery in 1893 and the first patent on DHPM derivatives in 1930, describing agents for the protection of wool against moths.\(^{43}\)

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

- Antiviral\(^{44-46}\)
- Antibacterial\(^{47}\)
- Antitumor\(^{48,49}\)
- Cardiovascular\(^{50}\)
- Antiplasmat\(^{51}\)
- Anticarcinogenic\(^{52}\)
- Calcium channel modulator\(^{53,54}\)
- Antihypertensive\(^{55,56}\)
- Vasodialative\(^{57}\)
- Blood platelet aggregation inhibitor\(^{58}\)
- Antiinflammatory\(^{59}\)
- Analgesic\(^{59}\)
- Antileukemic\(^{60}\)
- \(\alpha_{1a}\)-Adrenergic receptor antagonist\(^{61,62}\)

Atwal K. et al\(^{63}\) synthesized 3-substituted 1,4-dihydropyrimidines (XI) and show that vasorelaxant activity was critically dependent on the size of the C5 ester group, isopropyl ester being the best, a variety of substituents (carbamate, acyl, sulfonyl, alkyl) were tolerated at N3. Dihydropyridine enantiomer usually show 10-15-fold difference in activity, the enantiomers of dihydropyrimidine (XII) show more than a 1000-fold difference in activity. These results strengthen the requirement of an enaminoo ester for binding to the dihydropyrimidine receptor and indicate a nonspecific role for the N3-substituent.
George C. et al.\textsuperscript{64} prepared dihydropyrimidine (XIII) which was equipotent to nifedipine and amlodipine \textit{in vitro}. In the spontaneously hypertensive rat, dihydropyrimidine (XIII) is both more potent and longer acting than nifedipine and compares most favorably with the long-acting dihydropyridine derivative amlodipine.

Sally Ann et al.\textsuperscript{65} synthesized 4,6-bis[(R-carbamoylethyl)thio]-1-phenylpyrazolo[3,4-d] pyrimidine (XIV) and identified as a novel adenosine A1 receptor antagonist, antagonizing adenosine-stimulated cyclic adenosine monophosphate generation in guinea pig brain slices.\textsuperscript{66,67}
A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol (XV) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest. Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs.\textsuperscript{68,69} Ghorab and coworkers exploited the classical Biginelli reaction to synthesize a variety of potentially active antifungal agents such as (XVI)\textsuperscript{70}.

![Chemical Structure](image1)

As a demonstration of this new concept in the Biginelli reaction, the synthesis of two C\textsubscript{4} epimer monastrol analogues bearing the ribofuranosyl moiety at C\textsubscript{6} (XVII),(XVIII),(XIX) has been synthesized by Alessandro D. et al.\textsuperscript{71}

![Chemical Structures](image2)
Salvatore B. et al.\textsuperscript{72} studied the stopped-flow fluorometry indicates that monastrol inhibits ADP release by forming an Eg5-ADP-monastrol ternary complex. Monastrol reversibly inhibits the motility of human Eg5. Monastrol has no inhibitory effect on the following members of the kinesin superfamily.

Recently, Edward J. et al.\textsuperscript{73} employed difference infrared spectroscopy to probe structural changes that occur in the motor protein with monastrol in the presence of either ADP or ATP.

Various 2-thiopyrimidine derivatives have been synthesized by Sondhi S.M. et al.\textsuperscript{74} One of the compound, 7,7,8a-trimethyl-hexahydro-thiazolo[3,2-c]pyrimidine-5-thione (XX) showed good anti-inflammatory (37.4% at 100mg/kg p.o.) and analgesic activity (75% at 100mg/kg p.o.). 7-(1-Mercapto-3,3,4a-trimethyl-4,4a,5,9b-tetrahydro-3H-pyrido[4,3-b]indol-7-yl)-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-c]pyrimidine-1-thiol (XXI) showed moderate activity against CDK-1 (IC(50)=5muM). The other compounds showed moderate anti-inflammatory (5-20%), analgesic (25-75%) and protein kinase (CDK-5, GSK-3) inhibitory activities (IC(50)>10muM).

Dennis Russowsky et al.\textsuperscript{75} have reported monastrol was shown to be more active than its oxo-analogue, except for HT-29 cell line, suggesting the importance of the sulfur atom for the antiproliferative activity. Monastrol and the thio-derivatives displayed relevant antiproliferative properties with 3,4-
methylenedioxy derivative being approximately more than 30 times potent against colon cancer (HT-29) cell line.

Keeping the association of dihydropyrimidinonthione derivatives with varid biological activity, it was thought worthwhile to synthesize some new dihydropyrimidinonthione derivatives as under.

SECTION - I : SYNTHEsis AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

SECTION - II : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-METHYLPHENYL) AMINOCARBONYL]-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-THIONES

SECTION - III : SYNTHEsis AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-2-METHYLTHIO-1,4-DIHYDROPYRIMIDINES
SECTION - 1

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

Much interest have been focused around dihydropyrimidinthione derivatives because of their wide variety of pharmacological properties and industrial applications. In view of these findings and to achieve better drug potency, we have synthesized 6-isopropyl-5-(N-phenylaminocarbonyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones of type (I) by the cyclocondensation of 4-methyl-3-oxo-N-phenyl pentanamide with thiourea and aryl aldehydes.

![Chemical Structure](image)

R = Aryl  Type (I)

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the compounds have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 µg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 1.
**Reaction Scheme**

NH$_2$ + O

Reflux Toluene

NH$_2$ S

Ethanol

R = Cl, Br, CH$_3$, etc
IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINO CARBONYL)-4-(4'-METHYLPHENYL)-3,4-DIHYDROPYRIDIN-2(1H)-THIONE

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
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</thead>
<tbody>
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<td>2975-2950</td>
</tr>
<tr>
<td>–CH(_3)</td>
<td>C – H str. (sym.)</td>
<td>2854</td>
<td>2880-2860</td>
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<td></td>
<td>C – H def. (asym.)</td>
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<td>1470-1435</td>
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<td></td>
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<td>1385-1370</td>
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<td>–C (CH(_3))(_2)</td>
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<td>1175-1140</td>
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<td>3048</td>
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<td>C = C str.</td>
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<td>1580-1450</td>
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<td></td>
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<td></td>
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<td>C = C str.</td>
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<td>1580-1520</td>
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<td></td>
<td>C – N str.</td>
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<tr>
<td>Carbonyl</td>
<td>C = O str.</td>
<td>1675</td>
<td>1680-1630</td>
</tr>
</tbody>
</table>
NMR SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINO CARBONYL)-4-(4'-METHOXYPHENYL)-3,4-DIHYDROPYRIDIMIDIN-2(1H)-THIONE.

Internal Standard: TMS; Solvent: CDCl₃; Instrument: BRUKER Spectrometer (300 MHz)

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
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<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>C–CH₃</td>
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<td>Ar–CH</td>
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<td>2H</td>
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<td>Ar–H&lt;sub&gt;bb'&lt;/sub&gt;</td>
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<td>2H</td>
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<td>singlet</td>
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<td>–</td>
<td>–NH(3)</td>
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</table>
EXPANDED AROMATIC REGION

IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINO CARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

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

<table>
<thead>
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<th>Sr. No.</th>
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<td>3-Cl-C(_6)H(_4)-</td>
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<tr>
<td>1d</td>
<td>4-Cl-C(_6)H(_4)-</td>
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<td>1e</td>
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<td>1k</td>
<td>4-NO(_2)-C(_6)H(_4)-</td>
<td>1674</td>
</tr>
<tr>
<td>1l</td>
<td>3-C(_6)H(_5)-O-C(_6)H(_4)-</td>
<td>1675</td>
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</tbody>
</table>
MASS SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-(4'-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE.
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

[A] Synthesis of 4-Methyl-3-oxo-N-phenylpentanamide\textsuperscript{445}

A mixture of methyl isobutryl acetate (1.44 gm, 0.01 mol) and aniline (0.93 gm, 0.01 mol) in toluene, containing few drop of ethylene diamine, was refluxed for 12 hrs and methanol was collected using Dean & Stark apparatus. The resulting solution was cooled to 0°C and dilute hydrochloric acid solution was added into toluene layer which was seperated and washed three times with water. Finally toluene was distilled out under vaccum. Yield 71\%, m. p. 32°C, Anal.Calcd. for C\textsubscript{12}H\textsubscript{15}NO\textsubscript{2} Calcd: C, 70.22; H, 7.37; N, 6.82\%, Found: C, 70.71; H, 7.36; N, 6.81\%.

[B] Synthesis of 6-Isopropyl-5-(N-phenylaminocarbonyl)-4-(4’-methylphenyl)-3,4-dihydropyrimidin-2(1H)-thione

A mixture of thiourea (0.76 gm, 0.01 mol), 4-methylbenzaldehyde (1.20 gm, 0.01 mol) and 4-methyl-3-oxo-N-phenylpentanamide (2.05 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 8 hrs. The solution was allowed to stand for 12 hrs. at room temperture. The resulting solid mass was separated, filtered and crystallised from dioxane. Yield 55\%, m. p. 252°C, Anal.Calcd. for C\textsubscript{21}H\textsubscript{23}N\textsubscript{3}O S Calcd: C,72.18; H,6.63; N, 11.50\%, Found: C, 72.16; H, 6.62; N, 11.00\%.

Similarly, other 6-isopropyl-5-(N-phenylaminocarbonyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones were prepared. The physical data are recorded in Table No. 1.
[C] Biological screening of 6-isopropyl-5-(N-phenylaminocarbonyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones.

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

(a) Antimicrobial activity

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

(I) Antibacterial activity

The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hrs old subcultures of B. coccus, B. subtilis, P. vulgaris, E. coli in separate conical flasks at 40-50°C and mixed well by gently shaking. About 25 ml content of the flask were poured and evenly spreaded in a petridish (13 cm in diameter and allowed to set for 2 hrs. The cups 10 mm in diameter were formed by the help of borer in agar medium and filled with 0.04 ml (40 μg) solution of sample in DMF.

The plates were incubated at 37°C for 24 hrs and the control was also maintained with 0.04ml of DMF in a similar manner and zones of inhibition of the bacterial growth were measured in millimeter and are recorded in Graphical Chart No. 1.

The antibacterial activity data of the synthesised compounds have been compared with standard antibiotics like amoxycillin, benzoylpenicillin, ciprofloxacin and erythromycin.

(II) Antifungal activity

Aspergillus niger was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar slants. Sterilised Subouraud's agar medium was inoculated with 72 hrs old 0.5 ml suspension of fungal spores in separate flask. About 25 ml of the inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in
diameter) were punched and filled with 0.04 ml (40 μg) solution of sample in DMF. The plates were incubated at 30°C for 48 hrs. After the completion of incubation period, the zones of inhibition of growth of fungi in the form of diameter in mm were measured. Along the test solution in each petridish one cup was filled up with solvent act as control. The zones of inhibition were compared with standard antifungal Greseofulvin. The zones of inhibition are recorded in Graphical Chart No. 1.

(b) Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition and co-ordinating Facility (TAACF), U.S.A., primary screening of the compounds for antitubercular activity have been conducted at 6.25 μg towards Mycobacterium Tuberculosis H₃₇Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demonstrating atleast > 90% inhibition in the primary screen have been retested at lower Mycobacterium Tuberculosis H₃₇Rv to determine the actual minimum inhibition concentration (MIC) in the BACTEC 460.

The antitubercular activity data have been compared with standard drug Rifampin at 6.25 μg/ml concentration and it showed 98% inhibition.
ANTIMICROBIAL ACTIVITY

<table>
<thead>
<tr>
<th>Method</th>
<th>Cup-Plate\textsuperscript{76}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive bacteria</td>
<td>\textit{Bacillus coccus}</td>
</tr>
<tr>
<td></td>
<td>\textit{Staphylococcus aureus}</td>
</tr>
<tr>
<td>Gram negative bacteria</td>
<td>\textit{Enterobacter aerogenes}</td>
</tr>
<tr>
<td></td>
<td>\textit{Pseudomonas aeroginosa}</td>
</tr>
<tr>
<td>Fungi</td>
<td>\textit{Aspergillus niger}</td>
</tr>
<tr>
<td>Concentration</td>
<td>40 µg/ml</td>
</tr>
<tr>
<td>Solvent</td>
<td>Dimethyl formamide</td>
</tr>
<tr>
<td>Standard drugs</td>
<td>Amoxicillin, Ampicillin, Benzyl penicillin, Norfloxacin, Greseofulvin</td>
</tr>
</tbody>
</table>

The antimicrobial activity was compared with standard drug viz Amoxicillin, Ampicillin, Benzyl penicillin, Norfloxacin, Greseofulvin and antifungal activity was compared with viz Greseofulvin. The inhibition zones measured in mm.

ANTITUBERCULAR ACTIVITY

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF) U.S.A.

<table>
<thead>
<tr>
<th>Method</th>
<th>BACTEC 460 Radiometric system.</th>
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</thead>
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<tr>
<td>Bacteria</td>
<td>\textit{Mycobacterium Tuberculosis H37Rv}</td>
</tr>
<tr>
<td>Concentration</td>
<td>6.25 mg/ml.</td>
</tr>
<tr>
<td>Standard drug</td>
<td>Rifampin.</td>
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</table>
TABLE NO. 1 : PHYSICAL CONSTANTS OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDINE-2(1H)-THIONES

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅⁻</td>
<td>C₂₀H₂₁N₃OS</td>
<td>351</td>
<td>238</td>
<td>0.54</td>
<td>55</td>
<td>11.96</td>
<td>11.40</td>
</tr>
<tr>
<td>1a</td>
<td>2-Cl-C₆H₄⁻</td>
<td>C₂₀H₂₀N₃OSCl</td>
<td>385</td>
<td>258</td>
<td>0.59</td>
<td>42</td>
<td>10.89</td>
<td>10.10</td>
</tr>
<tr>
<td>1b</td>
<td>3-Cl-C₆H₄⁻</td>
<td>C₂₀H₂₀N₃OSCl</td>
<td>385</td>
<td>244</td>
<td>0.44</td>
<td>48</td>
<td>10.89</td>
<td>10.20</td>
</tr>
<tr>
<td>1c</td>
<td>4-Cl-C₆H₄⁻</td>
<td>C₂₀H₂₀N₃OSCl</td>
<td>385</td>
<td>221</td>
<td>0.55</td>
<td>46</td>
<td>10.89</td>
<td>10.07</td>
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<tr>
<td>1d</td>
<td>2,4-(Cl)₂-C₆H₃⁻</td>
<td>C₂₀H₁₉N₃OSCl₂</td>
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<td>1e</td>
<td>3-Br-C₆H₄⁻</td>
<td>C₂₀H₂₀N₃OSBr</td>
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<td>232</td>
<td>0.42</td>
<td>50</td>
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<td>9.01</td>
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<td>1f</td>
<td>4-F-C₆H₄⁻</td>
<td>C₂₀H₂₀N₃OSF</td>
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<td>10.85</td>
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<td>1g</td>
<td>4-CH₃-C₆H₄⁻</td>
<td>C₂₁H₂₃N₃OS</td>
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<td>252</td>
<td>0.45</td>
<td>55</td>
<td>11.50</td>
<td>11.00</td>
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<tr>
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<td>4-OCH₃-C₆H₄⁻</td>
<td>C₂₁H₂₃N₃OS₂</td>
<td>381</td>
<td>236</td>
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<td>1i</td>
<td>3-NO₂-C₆H₄⁻</td>
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<td>1j</td>
<td>4-NO₂-C₆H₄⁻</td>
<td>C₂₀H₂₀N₄O₃S</td>
<td>396</td>
<td>248</td>
<td>0.56</td>
<td>35</td>
<td>14.13</td>
<td>13.81</td>
</tr>
<tr>
<td>1k</td>
<td>3-C₆H₅-O-C₆H₄⁻</td>
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<td>236</td>
<td>0.41</td>
<td>48</td>
<td>9.47</td>
<td>8.90</td>
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</tbody>
</table>

*TLC Solvent System : Hexane:Ethyl acetate(7:3)*
GRAPHICAL CHART NO. 1 : ANTIMICROBIAL ACTIVITY OF 6-ISOPROPYL-5-(N-PHENYLAMINO CARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDINE-2(1H)-THIONES

![Graphical Chart](image_url)
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

It has been concluded from the experimental data that all the compounds of type (I) significantly inhibit the growth of Gram positive bacteria and also Gram negative bacteria.

Maximum activity was observed in compounds bearing R=phenyl, 4-nitrophenyl, 3-phenoxyphenyl-thienyl against \textit{B.coccus} and R=3-chlorophenyl and 4-chlorophenyl against \textit{S.aureus}.

In case of \textit{E.aerogenes} significant activity was displayed by compounds bearing R=phenyl, 4-methylphenyl and 4-nitrophenyl. Compounds with R=phenyl and 3-chlorophenyl showed highest activity against \textit{P.aeruginosa}.

ANTIFUNGAL ACTIVITY

The compounds were tested against fungal species \textit{A.niger}. It has been concluded that all the compounds were active against \textit{A.niger}. Maximum activity was displayed by the compounds bearing R=phenyl, 3-chlorophenyl and 4-fluorophenyl.

The antibacterial activity was compared with standard drug viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. gresefulvin.
SECTION - II

SYNTHESES AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-METHYLPHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-THIONES

Compounds containing pyrimidine ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these report, we have synthesized 6-Isopropyl-5-[N-(4’-methylphenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones of type (II) by the condensation of 4-methyl-N-(4-methylphenyl)-3-oxo-pentanamide, thiourea and aryl aldehydes.

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the compounds have been screened for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards Aspergillus niger at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 2.
Reaction Scheme

\[ \text{Toluene} \xrightarrow{\text{Reflux}} \text{R} \text{H}_2\text{C} - \text{NH}_2 + \text{H}_3\text{C} - \text{CO} - \text{CH}_3 \xrightarrow{\text{H}^+ \text{Ethanol}} \text{R} \text{H}_2\text{C} - \text{NH} - \text{CH}_3 + \text{H}_2\text{N} - \text{CH}_2 \text{S} \xrightarrow{\text{Type (II)}} \text{R} \text{H}_2\text{C} - \text{NH} - \text{CH}_3 - \text{NH} - \text{CH}_2 - \text{S} \]

\[ R = \text{Cl, Br, CH}_3, \text{etc} \]
IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4'-METHYLPHENYL)AMINOCARBONYL]-4-(4'-FLUOROPHENYL)-3,4-DIHYDROPYRIDIN-2(1H)-THIONE

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Reported</td>
<td></td>
</tr>
<tr>
<td>Alkane</td>
<td>C - H str. (asym.)</td>
<td>2919</td>
<td>2975-2950</td>
</tr>
<tr>
<td>-CH(_3)</td>
<td>C - H str. (sym.)</td>
<td>2855</td>
<td>2880-2860</td>
</tr>
<tr>
<td></td>
<td>C - H def. (asym.)</td>
<td>1401</td>
<td>1470-1435</td>
</tr>
<tr>
<td></td>
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<td>1337</td>
<td>1385-1370</td>
</tr>
<tr>
<td>-C (CH(_3))(_2)</td>
<td>C - H def.</td>
<td>1383</td>
<td>1385-1365</td>
</tr>
<tr>
<td>Aromatic</td>
<td>C - H str.</td>
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<td>3090-3030</td>
</tr>
<tr>
<td></td>
<td>C = C str.</td>
<td>1605</td>
<td>1620-1590</td>
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<tr>
<td></td>
<td>C - H i.p. (def.)</td>
<td>1053</td>
<td>1177-1027</td>
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<td></td>
<td>C - H o.o.p. (def.)</td>
<td>834</td>
<td>832-802</td>
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<tr>
<td>Pyrimidine</td>
<td>N - H str.</td>
<td>3332</td>
<td>3360-3320</td>
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<tr>
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<td>3267</td>
<td>3220-3180</td>
<td>&quot;</td>
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<tr>
<td>Carbonyl</td>
<td>C - H str.</td>
<td>3049</td>
<td>3060-3010</td>
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<td>1580-1520</td>
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<tr>
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<td>C - N str.</td>
<td>1275</td>
<td>1305-1200</td>
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<td>C = S str.</td>
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<td>1300-1100</td>
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<tr>
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<td>1680-1630</td>
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<tr>
<td></td>
<td>C - F str.</td>
<td>1099</td>
<td>1110-1000</td>
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NMR SPECTRAL STUDIES OF 6-ISOPROPYL-5-{N-(4'-METHYLPHENYL) AMINOCARBONYL}-4-(4'-FLUOROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE

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

<table>
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<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
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<td>1</td>
<td>1.52</td>
<td>singlet</td>
<td>3H</td>
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<td>C–CH₃</td>
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<td>1.73</td>
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<td>C–CH₃</td>
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<tr>
<td>3</td>
<td>2.30</td>
<td>singlet</td>
<td>3H</td>
<td></td>
<td>Ar–CH₃</td>
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<td>singlet</td>
<td>1H</td>
<td></td>
<td>C–CH</td>
</tr>
<tr>
<td>5</td>
<td>5.02–5.03</td>
<td>doublet</td>
<td>1H</td>
<td>J=4.56</td>
<td>Ar–CH</td>
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<td>6</td>
<td>7.02–7.04</td>
<td>doublet</td>
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<td>Jₐc=8.68</td>
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<td>7</td>
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<td>doublet</td>
<td>2H</td>
<td>Jₐb=8.32</td>
<td>Ar–H bb'</td>
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<td>8</td>
<td>7.26–7.28</td>
<td>doublet</td>
<td>2H</td>
<td>Jₐd=8.72</td>
<td>Ar–H cc'</td>
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<td>2H</td>
<td>Jₐb=8.40</td>
<td>Ar–H aa'</td>
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<td>1H</td>
<td>J=4.32</td>
<td>–</td>
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<tr>
<td>11</td>
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<td>doublet</td>
<td>1H</td>
<td></td>
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<tr>
<td>12</td>
<td>9.31</td>
<td>singlet</td>
<td>1H</td>
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IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4'-METHYLPHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

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

<table>
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<tr>
<th>Sr. No.</th>
<th>R</th>
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<tbody>
<tr>
<td>2a</td>
<td>C₆H₅⁻</td>
<td>1651</td>
</tr>
<tr>
<td>2b</td>
<td>2-Cl-C₆H₄⁻</td>
<td>1650</td>
</tr>
<tr>
<td>2c</td>
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<tr>
<td>2d</td>
<td>4-Cl-C₆H₄⁻</td>
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</tr>
<tr>
<td>2e</td>
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<td>2f</td>
<td>3-Br-C₆H₄⁻</td>
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<td>2g</td>
<td>4-F-C₆H₄⁻</td>
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<tr>
<td>2h</td>
<td>4-CH₃-C₆H₄⁻</td>
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</tr>
<tr>
<td>2i</td>
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<td>4-NO₂-C₆H₄⁻</td>
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<tr>
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<td>3-C₆H₅-O-C₆H₄⁻</td>
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</table>
m/z = 383
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-METHYLPHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-THIONES


A mixture of methyl isobutryl acetate (1.44 gm, 0.01 mol) and p-toluidine (1.07 gm, 0.01 mol) in toluene, containing few drop of ethylene diamine, was refluxed for 12 hrs and methanol was collected using Dean & Stark apparatus. The resulting solution was cooled to 0°C and dilute hydrochloric acid solution was added into toluene layer, which was seperated and washed three times with water. Finally toluene was distilled out under vaccum, the residue was crystallise from hexane-ethyl acetate mixture. Yield-65%, m.p.58°C, Anal. Calcd. for C_{13}H_{17}NO_2 Calcd: C, 71.21; H, 7.81;N,6.39, Found: C, 71.19; H, 7.80; N,6.40 %.

[B] Synthesis of 6-Isopropyl-5-[N-(4’-methylphenyl)aminocarbonyl]-4-(4’-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-thione.

A mixture of thiourea (0.76 gm, 0.01 mol), 4-chlorobenzaldehyde (1.40 gm, 0.01 mol) and 4-methyl-N-(4-methylphenyl)-3-oxo-pentanamide (2.19 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 8 hrs. The solution was allowed to stand for 12 hrs. at room temperature and the resulting solid mass was separated, filtered and crystallised from dioxane. Yield 49%, m.p.221°C, Anal. Calcd. for C_{21}H_{22}N_3OSCI Calcd: C,65.71; H, 5.78; N, 10.51%, Found: C, 65.69; H, 5.77; N, 10.32%.

Similarly, other 6-isopropyl-5-[N-(4’-methylphenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones were prepared. The physical data are recorded in Table No. 2.

[C] Biological screening of 6-Isopropyl-5-[N-(4’-methylphenyl) aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-thione.

Antimicrobial testing were carried out as described in Part-I Section-I (C). The zones of inhibition of test solutions are recorded in Graphical Chart No. 2.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>Found</th>
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<tr>
<td>2a</td>
<td>C₆H₅⁻</td>
<td>C₂₁H₂₃N₃OS</td>
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<td>C₂₁H₂₂N₂OSCl</td>
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<td>10.01</td>
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<tr>
<td>2c</td>
<td>3-Cl-C₆H₄⁻</td>
<td>C₂₁H₂₂N₂OSCl</td>
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<td>210</td>
<td>0.59</td>
<td>44</td>
<td>10.51</td>
<td>10.05</td>
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<tr>
<td>2d</td>
<td>4-Cl-C₆H₄⁻</td>
<td>C₂₁H₂₂N₂OSCl</td>
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<td>221</td>
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<td>49</td>
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<td>10.32</td>
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<tr>
<td>2e</td>
<td>2,4-(Cl)₂-C₆H₃⁻</td>
<td>C₂₁H₂₂N₂OSCl₂</td>
<td>434</td>
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<td>3-Br-C₆H₄⁻</td>
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<td>2g</td>
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<td>9.81</td>
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<tr>
<td>2h</td>
<td>4-CH₃-C₆H₄⁻</td>
<td>C₂₂H₂₅N₃OS</td>
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<td>252</td>
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<td>52</td>
<td>11.07</td>
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<td>2i</td>
<td>4-OCH₃-C₆H₄⁻</td>
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<td>4-NO₂-C₆H₄⁻</td>
<td>C₂₁H₂₂N₄O₃S</td>
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<tr>
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*TLC Solvent System: Hexane:Ethyl acetate (7:3)
GRAPHICAL CHART NO. 2 : ANTIMICROBIAL ACTIVITY OF 6-ISOPROPYL-5-[N-(4’-METHYLPHENYL) AMINOCARBONYL]-4-ARYL-3,4-DIHYDRO-PYRIMIDINE-2(1H)-THIONES

ZONE OF INHIBITION IN mm

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<thead>
<tr>
<th></th>
<th>2a</th>
<th>2b</th>
<th>2c</th>
<th>2d</th>
<th>2e</th>
<th>2f</th>
<th>2g</th>
<th>2h</th>
<th>2i</th>
<th>2j</th>
<th>2k</th>
<th>2l</th>
<th>Amoxicillin</th>
<th>Benzoylpenicillin</th>
<th>Ciprofloxacin</th>
<th>Erythromycin</th>
<th>Gram</th>
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<td>B. coccus</td>
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<td>22</td>
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<td>21</td>
<td>18</td>
<td>14</td>
<td>17</td>
<td>20</td>
<td>25</td>
<td>18</td>
<td>20</td>
<td>22</td>
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<tr>
<td>S. aureus</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>24</td>
<td>15</td>
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<td>19</td>
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<td>25</td>
<td>19</td>
<td>15</td>
<td>21</td>
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<tr>
<td>E. aerogenes</td>
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<td>15</td>
<td>19</td>
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<td>22</td>
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<tr>
<td>P. aeruginosa</td>
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<td>17</td>
<td>13</td>
<td>22</td>
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<td>22</td>
<td>21</td>
<td>16</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>A. niger</td>
<td>16</td>
<td>19</td>
<td>20</td>
<td>15</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td>19</td>
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<td>2</td>
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</tr>
</tbody>
</table>

0 5 10 15 20 25 30

ZONE OF INHIBITION IN mm
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

From the experimental data it has been observed that all the compounds of type (II) were active against Gram positive and Gram negative bacterial species.

It was observed that the compounds showed good activity against Gram positive bacteria. Maximum activity was observed in compounds having R=2-chloro phenyl, 4-methylphenyl and 3-phenoxyphenyl against \textit{B. coccus}. The compounds bearing R=4-chloro, 4-fluorophenyl and 3-nytropheynyl have highly inhibited the growth of \textit{S. aureus}.

Compounds with R=2-dichlorophenyl, 4-fluorophenyl and 3-phenoxyphenyl showed significant activity against \textit{E. aerogenes}. While the compounds bearing R=4-chlorophenyl, 2-dichlorophenyl and 4-methoxyphenyl have fairly inhibited the growth \textit{Paeruginosa}.

ANTIFUNGAL ACTIVITY

All the compounds were active against \textit{A. niger}. Maximum activity was observed by the compounds bearing R=3-chlorophenyl, 4-methoxyphenyl, 3-nitrophenyl and 3-phenoxyphenyl.

The antibacterial activity was compared with standard drug viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.
SECTION - III

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-2-METHYLTII0-1,4-DIHYDROPYRIMIDINES

It is well known that 1,4-dihydropyrimidines and related compounds exhibit a wide range of biological activities. Looking to the interesting therapeutic activity, compounds of type (III) have been synthesized by the condensation of 2-benzylidene-4-methyl-3-oxo-N-phenyl pentanamide with s-methylisothiourea.

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the compounds have been screened for their *in vitro* biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 3.
Reaction Scheme

\[
\begin{align*}
\text{O} & \quad \text{Me} & + & \quad \text{NH}_2 \\
\text{H}_3\text{C} & \quad \text{O} & \quad \text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{NH} & \quad \text{O} & \quad \text{NH} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{NH} & \quad \text{O} & \quad \text{O} & \quad \text{NH} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{R} & \quad \text{S} & \quad \text{NH} & \quad \text{CH}_3 \\
\text{R} & \quad \text{S} & \quad \text{NH} & \quad \text{CH}_3 \\
\text{DMSO} & \quad \text{KHCO}_3 & \quad \text{H}_2\text{SO}_4 \quad \text{H}_2\text{SO}_4 \\
\text{Type (III)} & \quad \text{R} = \text{Aryl}
\end{align*}
\]
IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-PHENYL-2-METHYLTHIO-1,4-DIHYDROPYRIMIDINE

![IR Spectrum Graph]

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm⁻¹</th>
<th>Ref.</th>
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</thead>
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<td>Alkane</td>
<td>C – H str.(asym.)</td>
<td>2923</td>
<td>2975-2950</td>
</tr>
<tr>
<td>–CH₃</td>
<td>C – H str. (sym.)</td>
<td>2868</td>
<td>2880-2860</td>
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<td></td>
<td>C – H def. (asym.)</td>
<td>1439</td>
<td>1470-1435</td>
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<tr>
<td></td>
<td>C – H def. (sym.)</td>
<td>1356</td>
<td>1385-1370</td>
</tr>
<tr>
<td>–C(CH₃)₂</td>
<td>C – H def.</td>
<td>1382</td>
<td>1385-1365</td>
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<td></td>
<td>1175</td>
<td>1175-1140</td>
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<tr>
<td>Aromatic</td>
<td>C – H str.</td>
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<td>3090-3030</td>
</tr>
<tr>
<td></td>
<td>C = C str.</td>
<td>1605</td>
<td>1620-1590</td>
</tr>
<tr>
<td></td>
<td>C – H i.p. (def)</td>
<td>1028</td>
<td>1177-1027</td>
</tr>
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<td>C – H o.o.p. (def)</td>
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<td>832-802</td>
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<td>Pyrimidine</td>
<td>N – H str.</td>
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<td>3360-3320</td>
</tr>
<tr>
<td></td>
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<td>1000-960</td>
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<td>Carbonyl</td>
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<td>1680-1630</td>
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<tr>
<td></td>
<td>C – S – C str.</td>
<td>699</td>
<td>700-650</td>
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NMR SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-(4'-CHLOROPHENYL)-2-METHYLTHIO-1,4-DIHYDROPYRIMIDINE

Internal Standard : TMS; Solvent : CDCl₃ : Instrument : BRUKER Spectrometer (300 MHz)

<table>
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<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
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<td>3H</td>
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<td>C–CH₃</td>
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<td>C–CH₃</td>
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<td>S–CH₃</td>
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<td>1H</td>
<td>-</td>
<td>Ar–CH</td>
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<td>7</td>
<td>7.30–7.36</td>
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<td>8</td>
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<td>1H</td>
<td>-</td>
<td>N–H (2)</td>
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**EXPANDED AROMATIC REGION**

**IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-2-METHYLTHIO-1,4-DIHYDROPYRIMIDINES.**

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

<table>
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<tr>
<th>Sr. No.</th>
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<tr>
<td>3b</td>
<td>2-Cl-C(_6)H(_4)(^-)</td>
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<tr>
<td>3c</td>
<td>3-Cl-C(_6)H(_4)(^-)</td>
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<td>3d</td>
<td>4-Cl-C(_6)H(_4)(^-)</td>
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<td>3l</td>
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MASS SPECTRAL STUDIES OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-PHENYL-2-METHYLTIO-1,4-DIHYDROPYRIMIDINE

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

m/z = 365

chemical structure of the compound

Mass Peaks: 223, Base Peak 275 (m/z 275)
Base Mode: Averaged 4.0-5.9 (1449-621)
BG Mode: None

intensity

m/z

40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-2-METHYLTHIO-1,4-DIHYDROPYRIMIDINES

[A] Synthesis of 4-Methyl-3-oxo-N-phenylpentanamide

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

[B] Synthesis of 2-Benzylidene-4-methyl-3-oxo-N-phenylpentanamide

Toluene, 4-methyl-3-oxo-N-phenylpentanamide (2.05 gm, 0.01 mol), benzaldehyde (1.06 gm, 0.01 mol), morpholine and acetic acid was charged in round bottom flask. The reaction mixture was refluxed for 14-16 hrs. and the contents were cooled to room temperature. Sodium bisulphite solution was added and stirred for 15 minutes and allowed to settle down for 15 minutes. Toluene layer was separated and washed with sodium bicarbonate solution, for 15 minutes and allowed to settle for 15 minute again. Toluene layer was separated, washed with distilled water. The product, crystallize in haxane. Yield 80%, m.p. 144°C, Anal. Calcd. for $\text{C}_19\text{H}_18\text{NO}_2$ Calcd: C, 77.79; H, 6.53; N, 4.77%. Found: C, 77.07; H, 6.11; N, 4.09%

[C] Synthesis of 6-Isopropyl-5-(N-phenylaminocarbonyl)-4-phenyl-2-methylthio-1,4-dihydropyrimidine

s-Methylisothiourea (1.88 gm, 0.01 mol) and DMSO was added in the round bottom flask, the reaction mixture was stirred for 10 minute. Sodium bicarbonate (1 gm.) was added at 20-25°C, and the reaction mixture was refluxed for 20 minute, then 2-benzylidene-4-methyl-3-oxo-N-phenylpentanamide (2.93 gm, 0.01 mol) was added and refluxed for 8 hrs. at 80°C. The reaction mixture was cooled to room temperature and dumped into cold water. Toluene (20 ml) was added and reaction mixture stirred for 15 minute. Toluene layer was separated
and 25 ml. ammonia added during 15 minutes. Then toluene layer was separated and washed with distilled water. IPA:HCl solution was added till acidic pH at 20-25°C. The reaction mixture was stired for 5 hrs. The material was filtered and washed with toluene. The wet material was dumped into toluene-water (1:1) solution and liq. ammonia was added till 8-9 pH. The toluene layer was separated and finally toluene was distilled out under vaccum. Yield 36%, m.p. 225°C. Anal. Calcd. for C_{21}H_{23}N_{3}O S Calcd: C, 69.01; H, 6.34; N, 11.43%, Found: C, 68.50; H, 6.01; N, 10.35%.

Similarly, other 6-Isopropyl-5-(N-phenylaminocarbonyl)-4-aryl-2-methylthio-1,4-dihydropyrimidines were prepared. The physical data are recorded in Table No.3.

(D) Biological screening of 6-Isopropyl-5-(N-phenylaminocarbonyl)-4-aryl-2-methylthio-1,4-dihydropyrimidines

Antimicrobial testing were carried out as described in Part-I Section-I (C). The zones of inhibition of test solutions are recorded in Graphical Chart No.3.
TABLE NO. 3: PHYSICAL CONSTANTS OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-2-METHYLTHIO-1,4-DIHYDROPYRIMIDINES

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C_6H_5^-</td>
<td>C_{21}H_{23}N_{3}OS</td>
<td>365</td>
<td>225</td>
<td>0.54</td>
<td>36</td>
<td>11.43</td>
<td>10.35</td>
</tr>
<tr>
<td>3b</td>
<td>2-Cl-C_6H_4^-</td>
<td>C_{21}H_{22}N_{3}OSCl</td>
<td>399</td>
<td>238</td>
<td>0.52</td>
<td>47</td>
<td>10.45</td>
<td>10.01</td>
</tr>
<tr>
<td>3c</td>
<td>3-Cl-C_6H_4^-</td>
<td>C_{21}H_{22}N_{3}OSCl</td>
<td>399</td>
<td>232</td>
<td>0.49</td>
<td>39</td>
<td>10.45</td>
<td>9.90</td>
</tr>
<tr>
<td>3d</td>
<td>4-Cl-C_6H_4^-</td>
<td>C_{21}H_{22}N_{3}OSCl</td>
<td>399</td>
<td>252</td>
<td>0.50</td>
<td>37</td>
<td>10.45</td>
<td>9.86</td>
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<tr>
<td>3e</td>
<td>3-Br-C_6H_4^-</td>
<td>C_{21}H_{22}N_{3}OSBr</td>
<td>444</td>
<td>262</td>
<td>0.48</td>
<td>33</td>
<td>9.41</td>
<td>8.95</td>
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<tr>
<td>3f</td>
<td>4-F-C_6H_4^-</td>
<td>C_{21}H_{22}N_{3}OSF</td>
<td>383</td>
<td>271</td>
<td>0.32</td>
<td>40</td>
<td>10.90</td>
<td>9.71</td>
</tr>
<tr>
<td>3g</td>
<td>4-CH_3-C_6H_4^-</td>
<td>C_{22}H_{25}N_{3}OS</td>
<td>379</td>
<td>257</td>
<td>0.50</td>
<td>47</td>
<td>10.01</td>
<td>9.32</td>
</tr>
<tr>
<td>3h</td>
<td>4-OCH_3-C_6H_4^-</td>
<td>C_{22}H_{25}N_{3}O_S</td>
<td>395</td>
<td>220</td>
<td>0.44</td>
<td>49</td>
<td>10.57</td>
<td>9.42</td>
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<tr>
<td>3i</td>
<td>3,4-(OCH_3)_{2}-C_6H_3^-</td>
<td>C_{23}H_{27}N_{3}O_S</td>
<td>425</td>
<td>240</td>
<td>0.54</td>
<td>41</td>
<td>9.83</td>
<td>8.72</td>
</tr>
<tr>
<td>3j</td>
<td>3-NO_2-C_6H_4^-</td>
<td>C_{21}H_{22}N_{4}O_S</td>
<td>410</td>
<td>248</td>
<td>0.46</td>
<td>35</td>
<td>13.58</td>
<td>12.48</td>
</tr>
<tr>
<td>3k</td>
<td>4-NO_2-C_6H_4^-</td>
<td>C_{21}H_{22}N_{4}O_S</td>
<td>410</td>
<td>268</td>
<td>0.42</td>
<td>42</td>
<td>13.58</td>
<td>12.46</td>
</tr>
<tr>
<td>3l</td>
<td>3-C_6H_5-O-C_6H_4^-</td>
<td>C_{27}H_{27}N_{3}O_S</td>
<td>457</td>
<td>230</td>
<td>0.50</td>
<td>45</td>
<td>9.14</td>
<td>8.08</td>
</tr>
</tbody>
</table>

*TLC Solvent System: Hexane:Ethyl acetate (7:3)
ANTIMICROBIAL ACTIVITY OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-2-METHYLTHIO-1,4-DIHYROPYRIMIDINES
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

It has been concluded from the experimental data that the compounds bearing R=phenyl, 4-methylphenyl and 4-nitrophenyl have displayed good activity against *B. coccus*. The compounds bearing R=3-chlorophenyl, 4-methylphenyl and 4-methoxyphenyl have show considerable activity against *S. aureus*.

In case of Gram negative bacterial strains all the compounds were inactive against *E. aerogenes* except the compound bearing R=4-fluorophenyl. While the compounds bearing R=phenyl, 4-fluorophenyl, 4-methylphenyl and 3-phenoxyphenyl showed significant activity against *P. aeruginosa*.

ANTIFUNGAL ACTIVITY

All the compounds exhibited moderate to poor activity against the tested species. However, the compounds having R=2-chlorophenyl and 4-methoxyphenyl displayed highest activity against *A. niger*.

The antibacterial activity was compared with standard drug viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. griseofulvin.
PART - II

STUDIES ON DIHYDRO PYRIMIDINONES
INTRODUCTION

During the last 20 years extensive studies on the pharmacology of this ring system have been reported, with an initial focus on developing calcium channel blockers that possess superior pharmacological profiles to Hantzsch-type dihydropyridines. Because of the pharmacological potency of the DHPM scaffold, novel dihydropyrimidines, with important biological properties, will undoubtedly be discovered in the future by combining combinatorial synthesis and high throughput screening (HTS) techniques.

Dihydropyrimidinone and their derivatives represent one of the most active class of compounds in their own right possessing a wide spectrum of biological activities such as antiinflammatory, antiviral, antibacterial, antitumor, antihypertensive and anticancer. Certain dihydropyrimidinones have been shown to act as $\alpha_{1a}$-adrenergic receptor antagonists, mitotic kinesin inhibitors and neuropeptide Y (NPY) antagonists\textsuperscript{77,78}.

SYNTHETIC ASPECTS

Several methods have been reported in the literature for the preparation of dihydropyrimidinones. The procedure for synthesising 3,4-dihydropyrimidin-2(1H)-ones have been described as under.

1. Unprecedented catalytic three-component one-pot condensation reaction is described by Essa E. H. et. al.\textsuperscript{79}
2. Recently, Bigl\textsuperscript{80} reported that the Biginelli reaction could be performed under solvent less conditions using KSF montmorillonite.

3. 3,4-DHPM-2(1H)-ones were prepared in high yield by Biginelli condensation of an aldehyde, a dicarbonyl compound and urea in ethanol using LiClO\textsubscript{4} as catalyst\textsuperscript{81}.

4. Dihydropyrimidinone was prepared from three component β-diketone, aldehyde and urea which was heated under stirring at 100-105°C to afford the corresponding DHPM-2-(1H)-one\textsuperscript{82}.

5. A simple effective synthesis of DHPM-2-(1H)-one derivatives, using boric acid as a catalyst from an aldehyde 1,3-dicarbonyl compound and urea in glacial acetic acid is described\textsuperscript{83}.

6. Shingare M. S. et al.\textsuperscript{84,85} reported use of catalytic amount of cadmium chloride.
7. An important stage in process development is kilo scale preparation of the target compound. For this reason, a procedure involving water-based biphasic media has been developed for conducting some exothermic reactions on large scale\textsuperscript{86}.

8. Abdelmadjid et. al.\textsuperscript{87} synthesised 3,4-dihydropyrimidine derivative using phenylboronic acid as catalyst.
THERAPEUTIC IMPORTANCE

Dihydropyrimidinone derivatives exhibit broad spectrum of therapeutic activities. The several biological activities associated with dihydropyrimidinones have been described as under.

Antitumor\textsuperscript{88}
Coronary dilatory\textsuperscript{89}
Cardiovascular activity\textsuperscript{90,91}
Antihypertensive\textsuperscript{92}
Calcium channel modulator\textsuperscript{93,94}
Antiviral\textsuperscript{95}
Anti-ischemic\textsuperscript{96}
Blood platelet aggregation inhibitor\textsuperscript{97}
Anti-inflammatory\textsuperscript{98}
Neuropeptide Y (NPY) antagonist\textsuperscript{99}
Mitotic Kinesin inhibitor\textsuperscript{100}
metabotropic glutamate receptor antagonist\textsuperscript{101}

Calcium ion plays a vital role in a large number of cellular processes, including excitation-contraction and stimulus-secretion.\textsuperscript{102,104} The use of agents known as calcium channel antagonists, which inhibit the movement of calcium through certain membrane channel.\textsuperscript{103,105,106}

Hidetsura Cho et. al.\textsuperscript{107} synthesized the novel calcium antagonists 3-N-substituted-3,4-dihydropyrimidines (VII) and 3-N-substituted-dihydropyrimidin-2(1H)-ones (VIII) regioselectively.
Atwal K. S. et al.\textsuperscript{108} described that in order to explain the potent antihypertensive activity of the modestly active dihydropyrimidine calcium channel blocker (IX), they carried out drug metabolism studies in the rat and found (IX) is metabolized to compounds (X-XIII). Two of the metabolites, (X) and (XI) were found to be responsible for the antihypertensive activity of compound (IX). Potential metabolism of (X) into (XI) \textit{in vivo}. Structure-activity studies aimed at identifying additional aryl-substituted analogues of (XI) led to (XV,XVI,XVII) with comparable potential \textit{in vivo}, though these compounds were less potent than (XI) \textit{in vitro}.

The results demonstrate that the active R-(\texttt{-})-enantiomer (XVIII) of (XI) is both more potent and longer acting than nifedipine as an antihypertensive agent in the SHR. The \textit{in vivo} potency and duration of (XVIII) is comparable to the long-acting dihydropyridine amlodipine.
Dhanapalan N. et al.\textsuperscript{109} prepared dihydropyrimidinones such as compound (XIX) exhibited high binding affinity and subtype selectivity for the cloned human $\alpha_{1a}$ receptor. Systematic modifications of (XIX) led to identification of highly potent and subtype-selective compounds such as (+)-(XX) and (+)-(XXI), with high binding affinity for $\alpha_{1a}$ receptor and greater than 1500-fold selectivity over $\alpha_{1b}$ and $\alpha_{1d}$ adrenoceptors. Compound (+)-(XXI) exhibited excellent selectivity to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood pressure (DBP) in mongrel dogs ($K_b$(DBP)$/K_b$(IUP)) = 40) suggesting uroselectivity for $\alpha_{1a}$-selective compounds.
T. G. Muralidhar et al.\textsuperscript{110} have synthesized several DHPM-one analogues, among this (+)-(XXII) and (+)-(XXIII) gave excellent selectivity (>880-fold) over $\alpha_{1b}$ and $\alpha_{1d}$ also showed good selectivity over several other recombinant human G-protein coupled receptors.

![Muralidhar et al. (XXII and XXIII)](image)

James C. et al.\textsuperscript{111} explores 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpyridine via a C-5 amide as selective $\alpha_{1a}$-receptor subtype antagonists. In receptor binding assays, these types of compounds generally display $K_1$ values for the $\alpha_{1a}$-receptor subtype <1 nM while being greater than 100-fold selective versus the $\alpha_{1b}$ and $\alpha_{1d}$ receptor subtypes. While many of the compounds tested displayed poor pharmacokinetics, compound (XXIV) was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs.

![James C. et al. (XXIV)](image)

Baldev Kumar et. al.\textsuperscript{112} have prepared some new oxo-pyrimidine derivatives (XXV) and reported them as potent calcium channel blockers. Abd. El-Galil and M. Abdulla\textsuperscript{113} have synthesised some fused steroidal oxo-pyrimidine derivatives (XXVI) and reported them as androgenic anabolic agent as well as antiinflammatory agent.
Recently, Vladimir N. Belov et. al.\textsuperscript{114} have documented enantioselective synthesis of the novel antiinfective TAN-1057A via aminomethyl-substituted dihydropyrimidinone heterocycle (XXVII). Rajni Garg et. al.\textsuperscript{115} suggest that the balance of hydrophobicity and a volume-dependent polarizability plays a key role in the inhibition of the viral proteas by these (XXVIII) inhibitors.

Christopher Blackburn et. al.\textsuperscript{116} described that lipophilic ester substituents at the 5-position and substitution at the para-position (optimal group -NO\textsubscript{2} and CF\textsubscript{3}) of the 4-aryl group led to active compounds (XXIX,XXX)
NEW DRUG MOLECULES UNDER CLINICAL STUDY

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

![Molecule Diagram](image)

Treatment of Hypertension
Calcium Channel Blockers

(XXXI)

Calcium Channel Blockers\(^{117}\)
Company Name: Merck & Co.

(XXXII)

Moreover one of the compound\(^{118}\) is very active against non-nucleoside inhibitor of human hepatitis B virus (IC\(_{50} = 53\) nM for reduction of HBV DNA in human hepatoma HepG2.2.15 cells) with low cytotoxicity in uninfected cells (CC\(_{50} = 7\) mcM). Compound inhibited both viral DNA and viral cores in HepG2.2.15 cells and HBV-transfected cell lines, whereas it did not affect the activity of endopolymerase and had no effect on other DNA or RNA viruses.
Name: Bay-41-4109
Anti Hepatitis B Virus Drugs\textsuperscript{119}
Bayer

Calcium channel blocker\textsuperscript{120}

MAR-99
Leukotrine Antagonist\textsuperscript{121}
(Known anti-asthmatic agent, now reported to possess anti-ulcerative and gastric antisecretory activities, which inhibits hydrochloric acid-ethanol-, stress- and indomethacin-induced ulcers in rat.)

Calcium Channel Blockers\textsuperscript{122}
<table>
<thead>
<tr>
<th>Structure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td>Flucytosine (fluorocytosine) Antifungal Agent. In vitro susceptibility of Candida species isolated from cancer patients against some antifungal agents.</td>
</tr>
<tr>
<td><img src="image2" alt="Image" /></td>
<td>Primethamine Antimalarial Agent.</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td>Dipyridamole Acute Myocardial Infection Treatment of Antiplatelet Therapy.</td>
</tr>
<tr>
<td><img src="image4" alt="Image" /></td>
<td>Immunosuppressants Oncolytic Drug</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td>Antibacterial Drugs 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F1808 In vitro activity of novel 6-aminouracils targeted to DNA polymerase III of Gram-positive bacteria</td>
</tr>
<tr>
<td><img src="image6" alt="Image" /></td>
<td>TNK-6123 Anti HIV Agent Reverse Transcriptase Inhibitors. Non-nucleoside HIV-1 reverse transcriptase inhibitor Compound was active not only against wild type HIV-1 strains (IC50 = 3 nM against III B and NL43 HIV-1) strains but also showed nanomolar</td>
</tr>
</tbody>
</table>

XXXVII

XXXVIII

XXXIX

XXXX

XXXXI

XXXXII
Thus the important role displayed by dihydropyrimidinone derivatives for various therapeutic and pharmaceutical activities prompted us to synthesise some new dihydropyrimidinones in order to achieving better drug potential. The study is described as under.

SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-METHOXYPHENYL) AMINOCARBONYL]-4-ARYL-3,4-DIHYDRO PYRIMIDIN- 2(1H)-ONES.

SECTION - II : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-FLUOROPHENYL) AMINOCARBONYL]-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-ONES.
SECTION - 1

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-METHOXYPHENYL)AMINOCARBONYL-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

The broad spectrums of pharmacological properties have been demonstrated by the dihydropyrimidinone nucleus. Inspired by these facts, novel dihydropyrimidinone derivatives of type(IV) have been synthesized by the condensation of N-(4-methoxyphenyl)-4-methyl-3-oxopentanamide, urea and aryl aldehydes.

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the compounds have been screened for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards Aspergillus niger at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 4.
**Reaction Scheme**

\[
\begin{align*}
\text{H}_3\text{CO-} \text{NH}_2 + \text{H}_3\text{CO} \text{CH}_3 \text{CO} & \xrightarrow{\text{Reflux,Toluene}} \text{R-} \text{NH} \text{CO-} \text{H} \\
\text{H}_3\text{CO-} \text{NH} \text{C} \text{H}_3 \text{CO} & \xrightarrow{\text{H}^+, \text{Ethanol}} \text{R-} \text{NH} \text{C} \text{H}_3 \text{CO}
\end{align*}
\]

Type (IV) \hspace{1cm} R = \text{Cl, Br, CH}_3, \text{ etc}

IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4'- METHOXYPHENYL) AMINOCARBONYL-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE.

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkane</td>
<td>C – H str. (asym.)</td>
<td>2929</td>
<td>2975-2950</td>
</tr>
<tr>
<td>–CH(_3)</td>
<td>C – H str. (sym.)</td>
<td>2833</td>
<td>2880-2860</td>
</tr>
<tr>
<td></td>
<td>C – H def. (asym.)</td>
<td>1464</td>
<td>1470-1435</td>
</tr>
<tr>
<td>–C (CH(_3))(_2)</td>
<td>C – H def.</td>
<td>1366</td>
<td>1385-1370</td>
</tr>
<tr>
<td>Aromatic</td>
<td>C – H str.</td>
<td>3028</td>
<td>3090-3030</td>
</tr>
<tr>
<td></td>
<td>C = C</td>
<td>1600</td>
<td>1620-1590</td>
</tr>
<tr>
<td></td>
<td>C – H i.p. (def)</td>
<td>1139</td>
<td>1177-1027</td>
</tr>
<tr>
<td></td>
<td>C – H o.o.p. (def)</td>
<td>830</td>
<td>832-802</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td>N – H str.</td>
<td>3301</td>
<td>3360-3320</td>
</tr>
<tr>
<td></td>
<td>C – H str.</td>
<td>3233</td>
<td>3220-3180</td>
</tr>
<tr>
<td></td>
<td>C = C str.</td>
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<td>3060-3010</td>
</tr>
<tr>
<td></td>
<td>C – N str.</td>
<td>1539</td>
<td>1580-1520</td>
</tr>
<tr>
<td></td>
<td>C – O</td>
<td>1245</td>
<td>1305-1200</td>
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<tr>
<td></td>
<td>C – H i.p. (def)</td>
<td>1037</td>
<td>1300-1100</td>
</tr>
<tr>
<td></td>
<td>C = O</td>
<td>946</td>
<td>1000-960</td>
</tr>
<tr>
<td></td>
<td>C = O (amide)</td>
<td>1692</td>
<td>1700-1660</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1660</td>
<td>1680-1630</td>
</tr>
</tbody>
</table>
NMR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4’-METHOXYPHENYL)AMINOCARBONYL-4-(3’-CHLOROPHENYL)-3,4-DIHYDROPYRIDIMIDIN-2(1H)-ONE

Internal Standard: TMS; Solvent: CDCl₃; Instrument: BRUKER Spectrometer (300 MHz)

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.54</td>
<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>C-CH₃</td>
</tr>
<tr>
<td>2.</td>
<td>1.74</td>
<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>C-CH₃</td>
</tr>
<tr>
<td>3.</td>
<td>3.78</td>
<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>Ar-OCH₃</td>
</tr>
<tr>
<td>4.</td>
<td>3.81</td>
<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>C-CH</td>
</tr>
<tr>
<td>5.</td>
<td>5.08–5.09</td>
<td>doublet</td>
<td>1H</td>
<td>J=4.30</td>
<td>Ar–CH</td>
</tr>
<tr>
<td>6.</td>
<td>6.82–6.85</td>
<td>doublet</td>
<td>2H</td>
<td>Jₑ=8.90</td>
<td>Ar–Hᶠᵉ</td>
</tr>
<tr>
<td>7.</td>
<td>7.15–7.18</td>
<td>doublet</td>
<td>1H</td>
<td>–</td>
<td>Ar–Hᶠ</td>
</tr>
<tr>
<td>8.</td>
<td>7.22–7.32</td>
<td>multiplet</td>
<td>3H</td>
<td>–</td>
<td>Ar–Hᶠᵃ,ᵇ,ᶜ</td>
</tr>
<tr>
<td>9.</td>
<td>7.46–7.49</td>
<td>doublet</td>
<td>2H</td>
<td>Jₑ=8.91</td>
<td>Ar–Hᶠᵉˡ</td>
</tr>
<tr>
<td>10.</td>
<td>8.43</td>
<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>N–H (1)</td>
</tr>
<tr>
<td>11.</td>
<td>8.83–8.84</td>
<td>doublet</td>
<td>1H</td>
<td>J=4.31</td>
<td>N–H (2)</td>
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<tr>
<td>12.</td>
<td>9.09</td>
<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>N–H (3)</td>
</tr>
</tbody>
</table>
IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4’-METHOXYPHENYL) AMINOCARBONYL-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES.

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

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>C=O str.</th>
<th>C=O str. (amide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C(_6)H(_5)^-</td>
<td>1692</td>
<td>1660</td>
</tr>
<tr>
<td>4b</td>
<td>2-Cl-C(_6)H(_4)^-</td>
<td>1692</td>
<td>1658</td>
</tr>
<tr>
<td>4c</td>
<td>3-Cl-C(_6)H(_4)^-</td>
<td>1692</td>
<td>1658</td>
</tr>
<tr>
<td>4d</td>
<td>4-Cl-C(_6)H(_4)^-</td>
<td>1692</td>
<td>1658</td>
</tr>
<tr>
<td>4e</td>
<td>3-Br-C(_6)H(_4)^-</td>
<td>1694</td>
<td>1656</td>
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<tr>
<td>4f</td>
<td>4-F-C(_6)H(_4)^-</td>
<td>1694</td>
<td>1656</td>
</tr>
<tr>
<td>4g</td>
<td>4-CH(_3)-C(_6)H(_4)^-</td>
<td>1698</td>
<td>1660</td>
</tr>
<tr>
<td>4h</td>
<td>4-OCH(_3)-C(_6)H(_4)^-</td>
<td>1698</td>
<td>1660</td>
</tr>
<tr>
<td>4i</td>
<td>3,4-(OCH(_3))(_2)-C(_6)H(_3)^-</td>
<td>1696</td>
<td>1661</td>
</tr>
<tr>
<td>4j</td>
<td>3-NO(_2)-C(_6)H(_4)^-</td>
<td>1690</td>
<td>1657</td>
</tr>
<tr>
<td>4k</td>
<td>4-NO(_2)-C(_6)H(_4)^-</td>
<td>1691</td>
<td>1657</td>
</tr>
<tr>
<td>4l</td>
<td>3-C(_6)H(_5)-O-C(_6)H(_4)^-</td>
<td>1692</td>
<td>1658</td>
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MASS SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4'-METHOXYPHENYL)AMINOCARBONYL-4-(3'-NITROPHENYL)-3,4-
DIHYDROPYRIMIDIN-2(1H)-ONE

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

mass = 410

\[ \text{m/z} = 410 \]

NH
N
CH\(_3\)
CH\(_3\)
O
NH
O
H\(_3\)CO

NO\(_2\)
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-METHOXYPHENYL)AMINOCARBONYL-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES.]

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

A mixture of methyl isobutryl acetate (1.44 gm, 0.01 mol) and 4-methoxyaniline (1.23 gm, 0.01 mol) in toluene, containing few drop of ethylene diamine, was refluxed for 12 hrs and methanol was collected using Dean & Stark apparatus. The resulting solution was cooled to 0°C and then dilute hydrochloric acid solution was added into toluene layer, which was separated and washed three times with water. Finally toluene was distilled out under vaccum. Yield 61%, m. p. 36°C, Anal.Calcd. for C₁₃H₁₇NO₃ Calcd: C, 66.36; H, 7.28; N, 5.95% , Found: C, 66.33; H, 7.30; N, 5.97%.

[B] Synthesis of 6-Isopropyl-5-[N-(4’-methoxyphenyl)aminocarbonyl]-4-(4’-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one.

A mixture of urea (0.60 gm, 0.01 mol), 4-chlorobenzaldehyde (1.40 gm, 0.01 mol) and 4-methyl-N-(4-methoxyphenyl)-3-oxo-pentanamide (2.35 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 8 hrs. The solution was allowed to stand for 12 hrs. at room temperature. The resulting solid mass was separated, filtered and crystallized from dioxane. Yield 49%, m. p. 278°C, Anal.Calcd. for C₂₁H₂₂N₃O₃Cl Calcd: C, 60.64; H, 5.33; N, 10.51%, Found: C, 60.63; H, 5.32; N, 10.39%.

Similarly, other 6-isopropyl-5-[N-(4’-methoxyphenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones were prepared. The physical data are recorded in Table No. 4.

[C] Biological screening of 6-Isopropyl-5-[N-(4’-methoxyphenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones.

Antimicrobial testing were carried out as described in Part-I Section-I (C). The zones of inhibition of test solutions are recorded in Graphical Chart No. 4.
### TABLE NO. 4 : PHYSICAL ONSTANTS OF 6-ISOPROPYL-5-[N-(4’-METHOXY PHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcld.</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C₆H₅⁻</td>
<td>C₂₁H₂₃N₃O₃</td>
<td>365</td>
<td>214</td>
<td>0.43</td>
<td>52</td>
<td>11.50</td>
<td>10.40</td>
</tr>
<tr>
<td>4b</td>
<td>2-Cl-C₆H₄⁻₆⁻</td>
<td>C₂₁H₂₂N₃O₃Cl</td>
<td>399</td>
<td>284</td>
<td>0.54</td>
<td>41</td>
<td>10.51</td>
<td>9.25</td>
</tr>
<tr>
<td>4c</td>
<td>3-Cl-C₆H₄⁻₆⁻</td>
<td>C₂₁H₂₂N₃O₃Cl</td>
<td>399</td>
<td>297</td>
<td>0.55</td>
<td>45</td>
<td>10.51</td>
<td>9.44</td>
</tr>
<tr>
<td>4d</td>
<td>4-Cl-C₆H₄⁻₆⁻</td>
<td>C₂₁H₂₂N₃O₃Cl</td>
<td>399</td>
<td>278</td>
<td>0.50</td>
<td>49</td>
<td>10.51</td>
<td>10.39</td>
</tr>
<tr>
<td>4e</td>
<td>3-Br-C₆H₄⁻₆⁻</td>
<td>C₂₁H₂₂N₃O₃Br</td>
<td>444</td>
<td>227</td>
<td>0.48</td>
<td>44</td>
<td>9.46</td>
<td>8.42</td>
</tr>
<tr>
<td>4f</td>
<td>4-F-C₆H₄⁻₆⁻</td>
<td>C₂₁H₂₂N₃O₃F</td>
<td>383</td>
<td>245</td>
<td>0.32</td>
<td>42</td>
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<td>4g</td>
<td>4-CH₃-C₆H₄⁻₆⁻</td>
<td>C₂₂H₂₅N₃O₃</td>
<td>379</td>
<td>296</td>
<td>0.56</td>
<td>55</td>
<td>11.07</td>
<td>10.02</td>
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<tr>
<td>4h</td>
<td>4-OCH₃-C₆H₄⁻₆⁻</td>
<td>C₂₂H₂₅N₃O₄</td>
<td>395</td>
<td>231</td>
<td>0.52</td>
<td>56</td>
<td>10.63</td>
<td>9.52</td>
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<tr>
<td>4i</td>
<td>3,4-(OCH₂)₂C₆H₃⁻₆⁻</td>
<td>C₂₃H₂₇N₃O₅</td>
<td>425</td>
<td>248</td>
<td>0.42</td>
<td>52</td>
<td>9.88</td>
<td>8.71</td>
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<td>3-NO₂-C₆H₄⁻₆⁻</td>
<td>C₂₁H₂₂N₄O₅</td>
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<td>266</td>
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<td>3-C₆H₅-O-C₆H₄⁻₆⁻</td>
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<td>255</td>
<td>0.54</td>
<td>44</td>
<td>9.18</td>
<td>8.01</td>
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</tbody>
</table>

*TLC Solvent System : Hexane:Ethyl acetate(7:3)
GRAPHICAL CHART NO. 4 : ANTIMICROBIAL ACTIVITY OF 6-ISOPROPYL-5-[N-(4'-METHOXY PHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDINE-2(1H)-ONES

<table>
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<tr>
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<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4g</th>
<th>4h</th>
<th>4i</th>
<th>4j</th>
<th>4k</th>
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<td>13</td>
<td>17</td>
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<td>22</td>
<td>18</td>
<td>19</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>S. aureus</td>
<td>14</td>
<td>22</td>
<td>14</td>
<td>16</td>
<td>21</td>
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<td>13</td>
</tr>
<tr>
<td>E. aerogenes</td>
<td>16</td>
<td>13</td>
<td>18</td>
<td>14</td>
<td>17</td>
<td>14</td>
<td>21</td>
<td>16</td>
<td>13</td>
<td>16</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>19</td>
<td>17</td>
<td>21</td>
<td>18</td>
<td>17</td>
<td>14</td>
<td>18</td>
<td>19</td>
<td>21</td>
<td>18</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>A. niger</td>
<td>18</td>
<td>21</td>
<td>17</td>
<td>16</td>
<td>14</td>
<td>20</td>
<td>19</td>
<td>18</td>
<td>14</td>
<td>16</td>
<td>13</td>
<td>21</td>
</tr>
</tbody>
</table>

- Amoxicillin
- Benzoylpenicillin
- Ciprofloxacin
- Erythromycin
- Gentamicin
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

It has been observed from the experimental data that all compounds of type (IV) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

However, the significant activity was observed in compounds bearing R=4-fluorophenyl against *B. coccus*. The maximum activity was observed in compounds bearing R=2-chlorophenyl and 3-bromophenyl against *S. aureus*.

In case of *E. aerogenes* all the compounds were least active except R=4-methylphenyl. The maximum activity was displayed by the compounds bearing R=3-chlorophenyl and 3,4-dimethoxyphenyl against *Paeruginosa*.

ANTIFUNGAL ACTIVITY

All the compounds were mildly active against *A. niger* except compounds bearing R=2-chlorophenyl, 4-fluorophenyl and 3-phenoxyphenyl which showed good activity.

The antibacterial activity was compared with standard drug viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.
SECTION - II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-FLUOROPHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES.

Compounds containing dihydropyrimidinone ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these reports, we have synthesized 6-isopropyl-5-[N-(4’-fluorophenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones of type (V) by the condensation of N-(4-fluorophenyl)-4-methyl-3-oxopentanamide, urea and aryl aldehydes.

![Chemical Structure](image)

R=Aryl  Type(V)

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and \(^1\)H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the compounds have been screened for their \textit{in vitro} biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards \textit{Aspergillus niger} at a concentration of 40 \(\mu\)g. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 5.
Reaction Scheme

\[
\begin{align*}
\text{F-NH}_2 - \text{NH}_2 & + \text{H}_2\text{CO} - \text{CH}_3\text{CO} \\
\text{Reflux} & \rightarrow \text{Toluene} \\
\text{F-} & + \text{CH}_3\text{NH} - \text{NH}_2 \\
\text{H}^+ & \rightarrow \text{Ethanol} \\
& \rightarrow \text{Product} \quad \text{R} = \text{Cl, Br, CH}_3, \text{etc}
\end{align*}
\]
### IR Spectral Studies of 6-Isopropyl-5-[N-(4'-Fluorophenyl)aminocarbonyl]-4-Phenyl-3,4-Dihydropyrimidin-2(1H)-One

![](image.png)

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
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<td>Alkane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-CH(_3)</td>
<td>C – H str. (asym.)</td>
<td>2922</td>
<td>2975-2950</td>
</tr>
<tr>
<td></td>
<td>C – H str. (sym.)</td>
<td>2857</td>
<td>2880-2860</td>
</tr>
<tr>
<td></td>
<td>C – H def. (asym.)</td>
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<td>1470-1435</td>
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<td></td>
<td>C – H def. (sym.)</td>
<td>1375</td>
<td>1385-1370</td>
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<tr>
<td>-C (CH(_3))(_2)</td>
<td>C – H def.</td>
<td>1353</td>
<td>1385-1365</td>
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<tr>
<td>Aromatic</td>
<td>C – H str.</td>
<td>3074</td>
<td>3090-3030</td>
</tr>
<tr>
<td></td>
<td>C = C</td>
<td>1610</td>
<td>1620-1590</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1475</td>
<td>1580-1450</td>
</tr>
<tr>
<td></td>
<td>C – H i.p. (def)</td>
<td>1144</td>
<td>1177-1027</td>
</tr>
<tr>
<td></td>
<td>C – H o.o.p. (def)</td>
<td>833</td>
<td>832-802</td>
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<tr>
<td>Pyrimidine</td>
<td>N – H str.</td>
<td>3344</td>
<td>3360-3320</td>
</tr>
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<td></td>
<td>C – H str.</td>
<td>3049</td>
<td>3060-3010</td>
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<tr>
<td></td>
<td>C = C str.</td>
<td>1534</td>
<td>1580-1520</td>
</tr>
<tr>
<td></td>
<td>C – N str.</td>
<td>1278</td>
<td>1305-1200</td>
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<td></td>
<td>C – H i.p. (def)</td>
<td>1003</td>
<td>1000-960</td>
</tr>
<tr>
<td></td>
<td>C = O</td>
<td>1677</td>
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</tr>
<tr>
<td></td>
<td>C =O (amide)</td>
<td>1649</td>
<td>1680-1630</td>
</tr>
<tr>
<td></td>
<td>C – F</td>
<td>1102</td>
<td>1110-1000</td>
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NMR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4'-FLUOROPHENYL)AMINO CARBONYL]-4-(4'-FLUOROPHENYL)-3,4-DIHYDROPYRIDIN-2(1H)-ONE

Internal Standard: TMS; Solvent: CDCl₃; Instrument: BRUKER Spectrometer (300 MHz)

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.46</td>
<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>C–CH₃</td>
</tr>
<tr>
<td>2.</td>
<td>1.57</td>
<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>C–CH₃</td>
</tr>
<tr>
<td>3.</td>
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<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>C–CH</td>
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<tr>
<td>4.</td>
<td>4.77-4.79</td>
<td>doublet</td>
<td>1H</td>
<td>J=4.6</td>
<td>Ar–CH</td>
</tr>
<tr>
<td>5.</td>
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<td>2H</td>
<td>Jₐc=9.0</td>
<td>Ar–Hₐd'</td>
</tr>
<tr>
<td>6.</td>
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<td>2H</td>
<td>Jₐb=9.0</td>
<td>Ar–Hₐb'</td>
</tr>
<tr>
<td>7.</td>
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<td>Jₐd=8.6</td>
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<tr>
<td>8.</td>
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<td>2H</td>
<td>Jₐb=9.0</td>
<td>Ar–Hₐa'</td>
</tr>
<tr>
<td>9.</td>
<td>7.88</td>
<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>N–H (1)</td>
</tr>
<tr>
<td>10.</td>
<td>9.30</td>
<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>N–H (2)</td>
</tr>
<tr>
<td>11.</td>
<td>9.91</td>
<td>singlet</td>
<td>1H</td>
<td>–</td>
<td>N–H (3)</td>
</tr>
</tbody>
</table>
IR SPECTRAL STUDIES OF 6-ISOPROPYL-5-[N-(4'-FLUOROPHENYL)AMINO CARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

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

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>C=O str.</th>
<th>C=O str. (amide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>C(_6)(_5)-</td>
<td>1677</td>
<td>1649</td>
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<td>1677</td>
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<td>1647</td>
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<td>5j</td>
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<tr>
<td>5k</td>
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STUDIES OF 6-ISOPROPYL-5-[N-(4’-FLUOROPHENYL) AMINOCARBONYL]-4-(4’-CHLOROPHENYL)-3,4-
DIHYDROPYRIDIMIDIN-2(1H)-ONE

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

m/z = 387
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-(4’-FLUOROPHENYL) AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES

[A] Synthesis of 4-Methyl-N-(4-fluorophenyl)-3-oxo-pentanamide

A mixture of methyl isobutryl acetate (1.44 gm, 0.01 mol) and 4-fluoroaniline (1.23 gm, 0.01 mol) in toluene, containing few drop of ethylene diamine, was refluxed for 12 hrs and methanol was collected using Dean & Stark apparatus. The resulting solution was cooled to 0°C and then dilute hydrochloric acid solution was added into toluene layer, which was seperated and washed three times with water. Finally toluene was distilled out under vaccum and crystallised from hexane-ethyl acetate mixture. Yield 67%, m.p. 65°C, Anal.Calcd. for C_{12}H_{14}FNO_{2} Calcd: C, 64.56; H, 6.32; N, 6.27%, Found: C, 64.54; H, 6.29; N, 6.28%.

[B] Synthesis of 6-Isopropyl-5-[N-(4’-fluorophenyl)aminocarbonyl]-4-(4’-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one

A mixture of urea (0.60 gm, 0.01 mol), p-fluorobenzaldehyde (1.24 gm, 0.01 mol) and 4-methyl-N-(4-fluorophenyl)-3-oxo-pentanamide (2.23 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 8 hrs. The solution was allowed to stand for 12 hrs. at room temperature. The resulting solid mass was separated, filtered and crystallised from dioxane. Yield 48%, m.p.250°C, Anal.Calcd. for C_{20}H_{19}N_{3}O_{2}F_{2} Calcd: C,62.00; H, 4.94; N, 11.31%, Found: C, 61.00; H, 4.93; N, 11.20%.

Similarly, other 6-isopropyl-5-[N-(4’-fluorophenyl)aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones were prepared. The physical data are recorded in Table No. 5.

[C] Biological screening of 6-Isopropyl-5-[N-(4’-fluorophenyl) aminocarbonyl]-4-aryl-3,4-dihydropyrimidin-2(1H)-ones.

Antimicrobial testing were carried out as described in Part-I Section-I (C). The zones of inhibition of test solutions are recorded in Graphical Chart No. 5.
TABLE NO. 5: PHYSICAL CONSTANTS OF 6-ISOPROPYL-5-[N-(4’-FLUOROPHENYL)AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDINE-2(1H)-ONES

<table>
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<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
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</table>

*TLC Solvent System: Hexane:Ethyl acetate (7:3)*
GRAPHICAL CHART NO. 5 : ANTIMICROBIAL ACTIVITY OF 6-ISOPROPYL-5-[N-(4’-FLUOROPHENYL) AMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDINE-2(1H)-ONES.

ZONE OF INHIBITION IN mm

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<th>5c</th>
<th>5d</th>
<th>5e</th>
<th>5f</th>
<th>5g</th>
<th>5h</th>
<th>5i</th>
<th>5j</th>
<th>5k</th>
<th>5l</th>
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<th>Benzoylpenicillin</th>
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<tr>
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RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

From the experimental data it has been observed that all the compounds of type (V) were active against Gram positive and Gram negative bacterial species.

It was observed that the compounds showed good activity against Gram positive bacteria. Maximum activity was observed in compounds having R=4-methylphenyl and 2-chlorophenyl against B.coccus. The compounds bearing R=phenyl, 4-chlorophenyl and 4-methoxyphenyl have fairly inhibited the growth of S.aureus.

Compounds with R=4-fluorophenyl and 3-nitrophenyl showed significant activity against E.aerogenes. Almost all compounds were found to be mildly active against Paeruginosa except R=3-chlorophenyl and 4-methylphenyl.

ANTIFUNGAL ACTIVITY

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds bearing R=3-bromo phenyl against A.niger.

The antibacterial activity was compared with standard drug viz. amoxicillin, benzoilpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.
[B]
STUDIES ON
PYRIMIDINES
INTRODUCTION

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

![Pyrimidine](image)

Generally pyrimidine derivatives such as 2-hydroxy substituted, 2-mercaptop-substituted and 2-amino substituted pyrimidines are studied. Pyrimidines have been isolated from the nucleic acid hydrolysates.

Pyrimidines are among those molecules that make life possible, have been some of the building blocks of DNA and RNA. Several analogues of 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. Some pyrimidines are perhaps the most widely used in medicines i.e. veronal, luminal are used as hypnotics while pentothal is used as an anaesthetic. Several important sulfa drugs are pyrimidine derivatives namely sulfadiazine, sulfamerazine and sulfadimidine\textsuperscript{125,126}.

SYNTHETIC ASPECTS

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\textsuperscript{127-136}. It is also possible to prepare pyrimidines from other heterocyclic compounds such as pyrrole\textsuperscript{137}, imidazole\textsuperscript{138}, isoxazole and
oxazole$^{139,140}$, pyridine$^{141}$, pyrazine$^{142}$, 1,3,5-triazine$^{143}$, oxazine$^{144}$, thiazine$^{145}$ by different processes.

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

1. The condensation of urea and malonic acid leads to the formation of pyrimidines$^{146}$.
2. The condensation of malonic ester and urea leads to formation of pyrimidines$^{147}$.
3. The condensation of formamidine with phenylazomalononitrile leads to the formation of 4,5,6-triamino pyrimidines$^{148}$.
4. The condensation of aromatic aldehydes, $\beta$-ketoester or substituted $\beta$-ketoester with urea or thiourea yields of pyrimidines$^{149}$.
5. The condensation of thiourea and substituted $\beta$-ketoester in the presence of sodium ethoxide affords 2-mercapto pyrimidines$^{150}$.
6. By the condensation of chalcones with dicyandiamide in the presence of piperidine, pyrimidines$^{151}$ are obtained.

**THERAPEUTIC IMPORTANCE**

Several pyrimidine derivatives reported to possess pharmacological activity whose structures are shown below.
Literature survey revealed that various pyrimidines have resulted in many potential drugs and are known to exhibit a broad spectrum of biological activities such as:

1. Platelet aggregation inhibitor\textsuperscript{152,153}
2. Antithyroid\textsuperscript{154,155}
3. Anticonvulsant\textsuperscript{156}
4. Anthelmintic\textsuperscript{157}
5. Antihistamine\textsuperscript{158,159}
6. Antihypertensive\textsuperscript{160-162}
7. Cardiovascular\textsuperscript{163-165}
8. Antiinflammatory\textsuperscript{166,167}
9. Antitubercular\textsuperscript{168}
10. Anti-HIV\textsuperscript{169,170}
11. Antineoplastic\textsuperscript{171,172}
12. Antitumor\textsuperscript{173,174}
13. Antiviral\textsuperscript{175-178}
14. Antimicrobial\textsuperscript{179-183}

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, chrotic acid, willardiline, tetradoxine, becimethrian (II), blasticidine (III), cougerotin, amicetin, bamicetin and plicacetin, phleomicine, blemycin and related families (IV).
5-Azacytidine (V), the most active of the azapyrimidines, shows substantial activity in the treatment of murine and human leukaemias, but little useful activity against solid tumors\textsuperscript{184}. It is phosphorylated in vivo to the mono-, di- and triphosphate levels, and inhibits nucleic acid synthesis and function.

A number of other pyrimidine antagonists displaying antitumor activity, in which the base is conjugated to a modified sugar ring have been reported. 5-Bromo- and 5-iodo-D-arabinofuranosyl uridine inhibits the growth of sarcoma 180 and L1210 cells in culture\textsuperscript{185}. Other thymidine analogues with similar activity include 5-azidomethyl-, 5-aminomethyl and 5-hydroxymethyl-2'-deoxyuridine\textsuperscript{186}. 3’-Amino-3’-deoxy thymidine\textsuperscript{187} and 3’-amino-2’,3’-dideoxycytidine\textsuperscript{188} also possess strong activity against L1210 leukaemia. 2’-Deoxy-2’-fluoro-5-methyl-1-B-D-arabinofuranosyluracil (FMAU; 29) is highly active against arabinofranosyl cytidine (ara-C) resistant L1210 and P815 cell lines.
both in vitro and in vivo\textsuperscript{189}. 2-B-D-Ribofuranosylthiazole-4-carboxamide (Tiazofurin; 30) has aroused much interest recently for its activity against solid tumor 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\textsuperscript{190}.

Hisaki Masakatsu\textsuperscript{191} et. al. have synthesized some aminopyrimidines which are useful in the treatment of rotaviral diseases. Robson C. et al.\textsuperscript{192} have prepared aminopyrimidine derivatives as antifungal agents in P9P and MRP over expressive tumor cell lines.

Hernandez et al.\textsuperscript{193} and Secrist J. et al.\textsuperscript{194} have documented aminopyrimidines showing antitumor activity. Glazier A. et al.\textsuperscript{195} and Singh J.\textsuperscript{196} found aminopyrimidines as antiviral agents. Pan S.\textsuperscript{197} have reported 2-methylthio-4-amino-6-(3,5-diacylphenyl-amino)-pyrimidines which show anti-HIV activity in H9 cell cultures. Aminopyrimidine derivatives also possess antimicrobial,\textsuperscript{198} anti-HIV\textsuperscript{199} and antitumor\textsuperscript{200} activities.

Bargiotti, Alberto et al.\textsuperscript{201} have studied 1,7-disubstituted guanine derivatives for their therapeutic use as telomerase inhibitors and anticancer agent. Amjad Ali and co-workers\textsuperscript{202} have designed and synthesized pyrimidine derivatives (VI) as newer antibacterial agents with inhibitor activity against DNA polymerase-II.

Aleem Gangjee et al.\textsuperscript{203} have reported 2-amino pyrimidine derivative(VII) as antiangiogenic and antitumor agents.
Marie Gompel and co-workers\textsuperscript{204} have showed that meridianins inhibit various protein kinases such as cyclin-dependent kinases, glycogen synthase kinase-3, cyclic nucleotide-dependent kinases and casein kinase (VIII).

Alistair H. et al.\textsuperscript{205} have synthesized a novel series of aminopyrimidine IKK2 inhibitors which show excellent in vitro inhibition of this enzyme and good selectivity over the IKK1 isoform. The relative potency and selectivity of these compounds have been rationalized using QSAR and structure-based modelling (IX).

Recently, Mai A. et al.\textsuperscript{206} have synthesized 5-alkyl-2-alkylamino-6-(2,6-difluorophenylalkyl)-3,4-dihydropyrimidin-4(3H)-ones, a new series of potent, broad-spectrum non-nucleoside reverse transcriptase inhibitors belonging to the DABO family. Vadim A. Makarov et al.\textsuperscript{207} have demonstrated 2-amino, 3-nitropyrazolo(1, 5-a) pyrimidines (X) as anticoxsackievirus. Antonello Mai et al.\textsuperscript{208} have described 2-alkylamino-6-[1-(2,6-difluorophenyl)alkyl]-3,4-dihydro-5-alkylpyrimidin-4(3H)-ones (F$_2$-NH-DABOs) 4, 5 belonging to the dihydro-alkoxybenzyl-oxopyrimidine family and bearing different alkyl and arylamino side chains at the C$_2$-position of the pyrimidine ring were designed as active against wild type human immunodeficiency virus (HIV-1) and some relevant HIV-1 mutants (XI).
Maria T. Cocco and co-workers\textsuperscript{209} have synthesized pyrimidine derivatives (XII) and reported their antitumor activity. Ha-Soon Choi et al.\textsuperscript{210} have designed and synthesised pyrimidine derivatives (XIII) as potent FAK inhibitor.

Looking to the diversified biological activities, it appeared of interest to synthesise some pyrazolines, cyanopyridines, cyanopyridones and isoxazoles bearing pyrimidine moiety, in order to achieving compounds having better therapeutic importance. These study are described in following parts.

[B] STUDIES ON PYRIMIDINES

\begin{itemize}
  \item \textbf{PART - I} : STUDIES ON PYRAZOLINES
  \item \textbf{PART I - II} : STUDIES ON CYANOPYRIDINES
  \item \textbf{PART - III} : STUDIES ON CYANOPYRIDONES
  \item \textbf{PART - IV} : STUDIES ON ISOXAZOLES
\end{itemize}
PART-I
STUDIES ON
PYRAZOLINES
INTRODUCTION

Amongst nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful framework for biological activities. Pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activity associated with them. The chemistry of pyrazoline was reviewed by Jorbe in 1967, which have been studied extensively for their biodynamic behaviour\textsuperscript{211} and industrial applications. Pyrazoline has three possible tautomeric structures, but the structure shown is the most stable, which can be prepared from hydrazine hydrate and acrolein.

SYNTHETIC ASPECT

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

1. The most common procedure for the synthesis of 2-pyrazolines is the reaction of an aliphatic or aromatic hydrazine with $\alpha,\beta$-unsaturated carbonyl compounds.

2. 3-Amino-2-pyrazolines can be prepared by condensation of $\alpha,\beta$-unsaturated nitriles with hydrazine.
3. 2-Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate$^{212}$.
4. 2-Pyrazolines can be prepared by condensation of chalcone dibromide with hydrazines$^{213}$.
5. 2-Pyrazoline derivatives can be prepared by intramolecular 1,3-dipolar addition of diarylnitrilimines generated from 2,5-diaryl tetrazoles$^{214}$.
6. Epoxidation of chalcones have epoxy ketones which reacts with hydrazine and phenyl hydrazine to give pyrazolines$^{215}$.
7. Dipolar cycloaddition of nitrilimines of dimethyl fumarate, fumaronitrile and the N-aryl maleimides yields the corresponding pyrazolines$^{216}$.

**REACTION MECHANISM**

The following mechanism seems to be operable for the condensation of chalcones with hydrazine hydrate$^{217}$.

Nucleophilic attack by hydrazine at the $\beta$-carbon of the $\alpha,\beta$-unsaturated carbonyl system forms species (II), in which the negative charge is mainly accommodated by the electronegative oxygen atom. Proton transfer from the nitrogen to oxygen produces an intermediate end which simultaneously ketonises to ketoamine (III). Another intramolecular nucleophilic attack by the primary
amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to hydroxyl amine (IV). The later with a hydroxy group and amine group on the same carbon loses water easily to yield the pyrazolines.

**THERAPEUTIC IMPORTANCE**

From the literature survey, it was revealed that 2-pyrazolines are potential therapeutic agents. Some of the activities are mentioned below.

1. Antiallergic
2. Anticonvulsant
3. Antibacterial
4. Antiimplantation
5. Antiinflammatory
6. Antitumor
7. Antineoplastic
8. Antiandrogenic
9. Antidepressant
10. Antimicrobial
11. Analgesic
12. Fungicidal
13. Herbicidal
14. Hypoglycemic
15. Insecticidal

F. Manna and coworkers have described 1-acetyl-5-(2'-bromophenyl)-4,5-dihydro-3-(2'-hydroxyphenyl)-1H-pyrazolines (V) and its derivatives which acts as potent antiinflammatory, analgesic and antipyretic agents.
Fuche Rainer et al.\textsuperscript{240} have investigated some new 1H-pyrazoline (VI) derivatives and reported them as pesticides. Tsuboi et al.\textsuperscript{241} have synthesized some new phenylcarbonyl pyrazolines (VII) as an insecticide and at 40\% concentration shows 100\% mortality of spodopetra litura larve after seven drop.

Tuntawy Atif and coworkers\textsuperscript{242} have patented 3-methyl-4'-(substituted phenylazo)-pyrazol-5-ones as antibacterial agent. Almstead J. et al.\textsuperscript{243} have prepared pyrazolines as vascularization agent. G. N. Mishirika et al.\textsuperscript{244} have also prepared 2-pyrazolines of salicylic acid (VIII) possessing antimicrobial properties.
Nisha Singh and co-workers\textsuperscript{245} have synthesised 1-acetyl pyrazolines (IX) and reported them as potent pesticides and fungicides. Nugent Richard et al.\textsuperscript{246} have investigated pyrazolines bis phosphonate as novel antiinflammatory and antiarthritis agents.

\begin{equation}
\text{IX}
\end{equation}

Shulabh Sharma et al.\textsuperscript{247} have synthesised some pyrazoline derivatives (X) of anthranilic acid and reported them as antiinflammatory agents.

\begin{equation}
\text{X}
\end{equation}

**CONTRIBUTION FROM OUR LABORATORY**

Jatin Upadhyay et al.\textsuperscript{248} have synthesised 1-acetyl-4,5 dihydro-5-(4-hydroxy-3-methoxyphenyl)-3-(4-phenyl sulphonamidophenyl)-1H-pyrazoline and other derivatives for their antimicrobial activity. Vikani and co-workers\textsuperscript{249} have synthesised pyrazoline derivatives from arsanilic acid for their antimicrobial activity against different strains of bacteria and fungi. P. Patel et al.\textsuperscript{250} have reported some novel pyrazoline derivatives as antimicrobial agents. P. M. Patel and A. R. Parikh\textsuperscript{251} have investigated 3-(3'-bromo-4'-acetamidophenyl)-5-aryl-1H/1-acetyl-2-pyrazolines. Akhil H. Bhatt and H. H. Parekh et al.\textsuperscript{252} have shown moderate antimicrobial activity of some pyrazoline derivatives. N. S. Shah and A. R. Parikh et al.\textsuperscript{253} have synthesised pyrazolines and reported them as potent antimicrobial agents. Fatema Bharmal et al.\textsuperscript{254} have shown good biological activity of pyrazolines.
Recently, Ahn J. H. et al.\textsuperscript{255} have reported DP-IV inhibition of cyano-pyrazoline derivatives as potent antidiabetic agents. Jeong T. S. et al.\textsuperscript{256} have investigated some novel 3,5-diaryl pyrazolines as human acyl-CoA:cholesterol acyltransferase inhibitors. Nasr M. N. et al.\textsuperscript{257} have suggested the synthesis of novel 3,3a,4,5,6,7-hexahydroindazole and arylthiazolylpyrazoline derivatives as antiinflammatory agent. Ucar et al.\textsuperscript{258} have documented pyrazolines as cholinesterase and selective monoamine oxidase β-inhibitors for the treatment of Parkinson’s and Alzheimer’s diseases.

Bhat and co-workers\textsuperscript{259} reported cytotoxic properties of pyrazoline derivatives. Y. Rajendra Prasad et al.\textsuperscript{260} have synthesised some 1,3,5-triphenyl-2-pyrazolines and 3-(2"-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines and reported them as antidepressant (XI) & (XII).

Mohammad Abid and Amir Azam\textsuperscript{261} have synthesized 1-N-substituted cyclised pyrazoline of thiosemicarbazones (XIII) and reported as antiamoebic agent. Abd El-Galil E. Amr et. al.\textsuperscript{262} have screened some new 3-substituted androstano[17,16-c]-52-aryl-pyrazolines and reported their antiandrogenic activity. John R. Goodell. et al.\textsuperscript{263} have synthesized some newer 1,3,5-trisubstituted pyrazoline derivatives which shows anti west nile virus activity (XIV).
Led by these considerations, several derivatives of chalcones and pyrazolines bearing pyrimidine nucleus have been investigated and described as under.

SECTION - I: SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ARYL-3-[2’-AMINOPYRIMIDIN-5’-YL]-PROPEN-2-ONES

SECTION - II: SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES
SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ARYL-3-[2’-AMINO-PYRIMIDIN-5’-YL]-PROPEN-2-ONES

With a view to getting better therapeutic agents and considering the association of various biological activities of pyrimidine heterocycles, the preparation of chalcones of type (I) have been undertaken by the condensation of 2-amino-5-formyl pyrimidine with various aromatic ketones in the presence of alkali.

![Chemical structure of Type-(I) R = Aryl]

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

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

The synthesised compounds have been screened for their in vitro biological assay like antitubercular activity towards a strain of Mycobacterium tuberculosis $H_{37}Rv$ at concentration of 6.25 µg/ml using Rifampin as standard drug.
IR SPECTRAL STUDIES OF 1-(p-ANISYL)-3-[2'-AMINOPYRIMIDIN-5'-YL]-PROPEN-2-ONE

![IR Spectrum Image]

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm⁻¹</th>
<th>Ref.</th>
</tr>
</thead>
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<td>Alkane</td>
<td>C-H (asym.)</td>
<td>2933</td>
<td>2975-2950</td>
</tr>
<tr>
<td>-CH₃</td>
<td>C-H (sym.)</td>
<td>2838</td>
<td>2880-2860</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>C-H (sym.) (def.)</td>
<td>1376</td>
<td>1385-1350</td>
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<tr>
<td>Aromatic</td>
<td>C-H str.</td>
<td>3017</td>
<td>3080-3030</td>
</tr>
<tr>
<td></td>
<td>C=C str.</td>
<td>1494</td>
<td>1585-1480</td>
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<tr>
<td></td>
<td>C-H i.p. (def.)</td>
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<td>1175-1140</td>
</tr>
<tr>
<td></td>
<td>C-H o.o.p. (def.)</td>
<td>829</td>
<td>850-800</td>
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<tr>
<td>Pyrimidine</td>
<td>N-H str.</td>
<td>3308</td>
<td>3360-3320</td>
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<tr>
<td></td>
<td></td>
<td>3162</td>
<td>3220-3180</td>
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<tr>
<td></td>
<td>C=N str.</td>
<td>1594</td>
<td>1650-1580</td>
</tr>
<tr>
<td></td>
<td>C-N str.</td>
<td>1229</td>
<td>1300-1200</td>
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<tr>
<td></td>
<td>C-H (def.)</td>
<td>980</td>
<td>1000-960</td>
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<tr>
<td>Ether</td>
<td>C-O-C str.</td>
<td>1022</td>
<td>1070-1020</td>
</tr>
<tr>
<td>Carbonyl</td>
<td>C=O str.</td>
<td>1651</td>
<td>1760-1650</td>
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</table>
NMR SPECTRAL STUDIES OF 1-\((p\text{-ANISYL})\)-3-\([2'\text{-AMINOPYRIMIDIN-5'\text{-YL}}]\)\-PROPEN-2-ONE

Internal Standard : TMS; Solvent : CDCl\textsubscript{3}; Instrument : BRUKER Spectrometer (200 MHz)

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>(J) value in Hz</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
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<td>3.87</td>
<td>singlet</td>
<td>3H</td>
<td>–</td>
<td>Ar–OCH\textsubscript{3}</td>
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<tr>
<td>2.</td>
<td>7.05–7.10</td>
<td>doublet</td>
<td>2H</td>
<td>(J_{ba} = 8.8)</td>
<td>Ar–H\textsubscript{bb}'</td>
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<tr>
<td>3.</td>
<td>7.27</td>
<td>singlet</td>
<td>2H</td>
<td>–</td>
<td>Ar–NH\textsubscript{2}</td>
</tr>
<tr>
<td>4.</td>
<td>7.52–7.60</td>
<td>doublet</td>
<td>1H</td>
<td>(J_{AB} = 15.6)</td>
<td>C–H\textsubscript{A} (vinyllic)</td>
</tr>
<tr>
<td>5.</td>
<td>7.82–7.90</td>
<td>doublet</td>
<td>1H</td>
<td>(J_{BA} = 15.6)</td>
<td>C–H\textsubscript{B} (vinyllic)</td>
</tr>
<tr>
<td>6.</td>
<td>8.13–8.17</td>
<td>doublet</td>
<td>2H</td>
<td>(J_{ab} = 8.6)</td>
<td>Ar–H\textsubscript{aa}'</td>
</tr>
<tr>
<td>7.</td>
<td>8.78</td>
<td>singlet</td>
<td>2H</td>
<td>–</td>
<td>Ar–H\textsubscript{cc}'</td>
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</tbody>
</table>
EXPANDED AROMATIC REGION

IR SPECTRAL STUDIES OF 1-ARYL-3-[2'-AMINOPYRIMIDIN-5'-YL]-PROPEN-2-ONES

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

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>C=O str.</th>
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</thead>
<tbody>
<tr>
<td>6a</td>
<td>C₆H₅⁻</td>
<td>1652</td>
</tr>
<tr>
<td>6b</td>
<td>4-CH₃-C₆H₄⁻</td>
<td>1650</td>
</tr>
<tr>
<td>6c</td>
<td>4-OCH₃-C₆H₄⁻</td>
<td>1651</td>
</tr>
<tr>
<td>6d</td>
<td>4-Cl-C₆H₄⁻</td>
<td>1660</td>
</tr>
<tr>
<td>6e</td>
<td>4-Br-C₆H₄⁻</td>
<td>1661</td>
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<tr>
<td>6f</td>
<td>4-F-C₆H₄⁻</td>
<td>1658</td>
</tr>
<tr>
<td>6g</td>
<td>2-OH-C₆H₄⁻</td>
<td>1654</td>
</tr>
<tr>
<td>6h</td>
<td>4-OH-C₆H₄⁻</td>
<td>1654</td>
</tr>
<tr>
<td>6i</td>
<td>3-NO₂-C₆H₄⁻</td>
<td>1651</td>
</tr>
<tr>
<td>6j</td>
<td>4-NO₂-C₆H₄⁻</td>
<td>1652</td>
</tr>
<tr>
<td>6k</td>
<td>4-NH₂-C₆H₄⁻</td>
<td>1650</td>
</tr>
<tr>
<td>6l</td>
<td>2,4-(Cl₂)-C₆H₃⁻</td>
<td>1662</td>
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</table>
EXPERIMENTAL
SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ARYL-3-[2’-AMINOPYRIMIDIN-5’-YL]-PROPEN-2-ONES

[A] Synthesis of 2-Amino-5-formyl pyrimidine

Different steps involved in the formation of 2-amino-5-formyl pyrimidine are as under:

(I) Preparation of phosphonoacetic acid

(II) Preparation of 2-Dimethylaminomethylene-1,3-bis (dimethyl immonio) propane bisperchlorate from phosphonoacetic acid.

A 500 ml, three-necked flask was equipped with a condenser, magnetic stirring, thermometer and a nitrogen atmosphere. Phosphorous oxychloride (3.3 g, 0.022 mole) and N,N-dimethylformamide (2.5 g, 0.043 mole) were added to the flask along with (1.4 g 0.01 mole) of phosphonoacetic acid. This mixture was heated at 100-105°C for 4 hours. The reaction mixture was cooled to room temperature and carefully poured into a cold solution 3.01 g of perchloric acid in 13 ml of methanol. The cold solution was allowed to stand for a few minutes and the resulting solid was removed by filtration and dried at room temperature in vacuo. yield 2.2 g, 59% m.p. 222-223°C.

(III) Preparation of 2-Amino-5-formyl pyrimidine.

A 250 ml, three-necked flask was equipped with a condenser, magnetic stirring, thermometer and a nitrogen atmosphere. Sodium metal (0.73 g, 0.032 mole) was added to 97 ml. n-propanol. Bisvinimidinium salt (3.8 g, 0.01 mole) and guanidine carbonate (0.83 g, 0.0069 mole) was added in above solution, the reaction mixture was refluxed for 3 hrs. at 93°C. Excess n-propanol was distilled off and the reaction mixture was cooled to isolate the product. Yield 1.2 g, 93%, m.p. 190-192°C.
[B] Synthesis of 1-(p-Methoxy)-3-[2’-aminopyrimidin-5’-yl]-propan-2-ones

A solution of p-methoxyacetophenone (1.5 g, 0.01 mol) in minimum quantity of ethanol (5 ml) was added to a mixture of 2-amino-5-formyl pyrimidine (1.23 g, 0.01 mol) in DMF (20 ml) and 40% KOH was added to make it alkaline. The reaction mixture was then stirred for 24 hrs. at room temperature. The product was isolated and crystallised from DMF. Yield 54%, m.p. 181°C, Anal. Calcd. required for C_{14}H_{13}N_{3}O_{2}: C, 65.87%; H, 5.13%; N, 16.46%; found C, 65.27%; H, 5.10%; N, 16.12%.

Similarly other 1-aryl-3-[2’-aminopyrimidin-5’-yl]-propan-2-ones were prepared. The physical constants are recorded in Table No. 6.

[C] Biological screening of 1-Aryl-3-[2’-aminopyrimidin-5’-yl]-propan-2-ones

Antimicrobial testing were carried out as described in Part-I, Section-I (C). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 6.

Antitubercular screening of the compounds of type (VI) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 6a.
TABLE NO. 6 :  PHYSICAL CONSTANTS OF 1-ARYL-3-[2’-AMINOPYRIMIDIN-5’-YL]-PROPEN-2-ONES

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>6a</td>
<td>C₆H₅⁻</td>
<td>C₁₃H₁₁N₃O</td>
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<td>200</td>
<td>0.33</td>
<td>73</td>
<td>18.56</td>
<td>18.08</td>
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<tr>
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<td>C₁₄H₁₃N₃O</td>
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<td>207</td>
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<td>60</td>
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<td>4-OCH₃C₆H₄⁻</td>
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<td>16.46</td>
<td>16.12</td>
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<td>221</td>
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<td>57</td>
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<td>230</td>
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*TLC Solvent System : Hexane:Ethyl acetate(1:9)
GRAPHICAL CHART NO. 6: ANTIMICROBIAL ACTIVITY OF 1-ARYL-3-[2’-AMINOPYRIMIDIN-5’-YL]-PROPEN-2-ONES

ZONE OF INHIBITION IN mm

<table>
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<th>6a</th>
<th>6b</th>
<th>6c</th>
<th>6d</th>
<th>6e</th>
<th>6f</th>
<th>6g</th>
<th>6h</th>
<th>6i</th>
<th>6j</th>
<th>6k</th>
<th>6l</th>
<th>Amoxicillin</th>
<th>Benzylpenicillin</th>
<th>Ciprofloxacin</th>
<th>Erythromycin</th>
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<td>26</td>
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B. coccus
S. aureus
E. aerogenes
P. aeruginosa
A. niger
TABLE NO. 6a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY

![Chemical Structure]

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Corp ID</th>
<th>Where, ( R = )</th>
<th>Assay</th>
<th>Mtb Strain</th>
<th>Mic ( \mu g/ml )</th>
<th>% Inhib</th>
<th>Activity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>295527</td>
<td>BT-1</td>
<td>( \text{C}_6\text{H}_5^- )</td>
<td>Alamar</td>
<td>( \text{H}_3\text{Rv} )</td>
<td>&gt;6.25</td>
<td>3</td>
<td>-</td>
<td>Mic Rifampin = 0.25 ( \mu g/ml ) @ 98% Inhibition</td>
</tr>
<tr>
<td>295528</td>
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<td>4-CH(_3)C(_6)H(_4)(^-)</td>
<td>Alamar</td>
<td>( \text{H}_3\text{Rv} )</td>
<td>&gt;6.25</td>
<td>0</td>
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<tr>
<td>295529</td>
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<td>4-OCH(_3)C(_6)H(_4)(^-)</td>
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<td>( \text{H}_3\text{Rv} )</td>
<td>&gt;6.25</td>
<td>8</td>
<td>-</td>
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</tr>
<tr>
<td>295530</td>
<td>BT-4</td>
<td>4-ClC(_6)H(_4)(^-)</td>
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<td>( \text{H}_3\text{Rv} )</td>
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<td>-</td>
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<tr>
<td>295531</td>
<td>BT-5</td>
<td>4-BrC(_6)H(_4)(^-)</td>
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<td>( \text{H}_3\text{Rv} )</td>
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<td>-</td>
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<tr>
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<td>4-FC(_6)H(_4)(^-)</td>
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<td>( \text{H}_3\text{Rv} )</td>
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<td>-</td>
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<td>2-OHC(_6)H(_4)(^-)</td>
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<td>4-NHC(_6)H(_4)(^-)</td>
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<td>-</td>
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</tbody>
</table>

TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

Antibacterial activity

It has been observed from the experimental data that all the chalcones of type (VI) markedly inhibited the growth of Gram positive and also Gram negative bacteria.

However, comparatively significant activity was observed in compounds with R = 4-fluorophenyl and 2-hydroxyphenyl against \textit{B. coccus} and R = 4-hydroxyphenyl and 4-aminophenyl against \textit{S. aureus}. Compounds bearing R = 4-hydroxyphenyl, 4-methylphenyl and dichlorophenyl showed considerable activity against \textit{E. aerogenes}. Maximum activity was observed in compounds bearing R = 3-nitrophenyl and 4-fluorophenyl against \textit{P. aeruginosa}.

Antifungal activity

All the compounds were active against \textit{A. niger}. Maximum activity was shown by the compounds bearing R = 4 bromophenyl and 4-nitrophenyl.

The antibacterial activity was compared with standard drugs viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. gresefulvin.

Antitubercular activity

Some compounds displayed antitubercular activity against \textit{Mycobacterium tuberculosis H37Rv} ranging from 3 to 90% inhibition. Compounds with R = 4-fluorophenyl exhibited maximum activity upto 90% inhibition.
SECTION - II
SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES

During the past years, considerable evidence has been accumulated to demonstrate the efficiency of pyrazolines in including variety of therapeutic activity. To further assess the potential of such a class of compounds as good therapeutic agents, a series of pyrazolines of type (VII) have been synthesised by the condensation of chalcones with hydrazine hydrate in glacial acetic acid.

![Reaction scheme](image)

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the compounds have been screened for their \textit{in vitro} biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards \textit{Aspergillus niger} at a concentration of 40 μg. The biological activity of the synthesised compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No.7.

The synthesised compounds have been screened for their \textit{in vitro} biological assay like antitubercular activity towards a strain of \textit{Mycobacterium tuberculosis} $H_{37}Rv$ at concentration of 6.25 μg/ml using Rifampin as standard drug.
IR SPECTRAL STUDIES OF 1-ACETYLC-3-(p-ANISYL)-5-[2'-AMINOPYRIMIDIN-5'-YL]-PYRAZOLINE

![IR Spectral Study Image]

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

<table>
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<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm⁻¹ (Observed)</th>
<th>Frequency in cm⁻¹ (Reported)</th>
<th>Ref.</th>
</tr>
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<tbody>
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<td>Alkane</td>
<td>C-H (asym.)</td>
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<td>2975-2950</td>
<td>440</td>
</tr>
<tr>
<td>-CH₃</td>
<td>C-H (sym.)</td>
<td>2840</td>
<td>2880-2860</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>C-H (asym.)</td>
<td>1406</td>
<td>1470-1435</td>
<td>&quot;</td>
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<tr>
<td>Aromatic</td>
<td>C-H (sym.)</td>
<td>1363</td>
<td>1385-1350</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td>C-H str.</td>
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<td>3080-3030</td>
<td>444</td>
</tr>
<tr>
<td></td>
<td>C=C str.</td>
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<td>1585-1480</td>
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<tr>
<td></td>
<td>C-H i.p. (def.)</td>
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<td>1175-1140</td>
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<tr>
<td></td>
<td>C-H o.o.p. (def.)</td>
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<td>850-800</td>
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<tr>
<td>Pyrimidine</td>
<td>N-H str.</td>
<td>3317</td>
<td>3360-3320</td>
<td>443</td>
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<tr>
<td></td>
<td></td>
<td>3168</td>
<td>3220-3180</td>
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<tr>
<td></td>
<td>C=N str.</td>
<td>1605</td>
<td>1650-1580</td>
<td>&quot;</td>
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<tr>
<td></td>
<td>C-N str.</td>
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<td>1300-1200</td>
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<tr>
<td></td>
<td>C-H (def.)</td>
<td>957</td>
<td>1000-960</td>
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<tr>
<td>Ether</td>
<td>C-O-C str.</td>
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<td>1070-1020</td>
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<td>Carbonyl</td>
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<td>1760-1650</td>
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<tr>
<td>Pyrazoline</td>
<td>C=C str.</td>
<td>1446</td>
<td>1650-1580</td>
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</tr>
<tr>
<td></td>
<td>C=N str.</td>
<td>1562</td>
<td>1585-1480</td>
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</table>
NMR SPECTRAL STUDIES OF 1-ACETYL-3-(p-ANISYL)-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINE

Internal Standard: TMS; Solvent: CDCl₃; Instrument: BRUKER Spectrometer (300 MHz)

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2.37</td>
<td>singlet</td>
<td>3H</td>
<td>-</td>
<td>Ar-CH₃</td>
</tr>
<tr>
<td>2.</td>
<td>3.10-3.17</td>
<td>d. doublet</td>
<td>1H</td>
<td>J_{AB} = 17.6</td>
<td>C-H_A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>J_{AX} = 4.8</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>3.70-3.75</td>
<td>d. doublet</td>
<td>1H</td>
<td>J_{BA} = 17.6</td>
<td>C-H_B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>J_{BX} = 11.8</td>
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</tr>
<tr>
<td>4.</td>
<td>3.85</td>
<td>singlet</td>
<td>3H</td>
<td>-</td>
<td>Ar-OCCH₃</td>
</tr>
<tr>
<td>5.</td>
<td>5.27</td>
<td>broad</td>
<td>2H</td>
<td>-</td>
<td>Ar-NH₂</td>
</tr>
<tr>
<td>6.</td>
<td>5.42-5.46</td>
<td>d. doublet</td>
<td>1H</td>
<td>J_{XA} = 11.8</td>
<td>C-H_X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>J_{XB} = 4.5</td>
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</tr>
<tr>
<td>7.</td>
<td>6.94-6.97</td>
<td>doublet</td>
<td>2H</td>
<td>J_{ba} = 9.5</td>
<td>Ar-H_{bb’}</td>
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<tr>
<td>8.</td>
<td>7.67-7.70</td>
<td>doublet</td>
<td>2H</td>
<td>J_{ab} = 9.5</td>
<td>Ar-H_{aa’}</td>
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<tr>
<td>9.</td>
<td>8.21</td>
<td>singlet</td>
<td>2H</td>
<td>-</td>
<td>Ar-H_{cc’}</td>
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</table>

Diagram showing the NMR spectrum with peaks and assignments.
EXPANDED AROMATIC REGION

IR SPECTRAL STUDIES OF 1-ACETYL-3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES

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

<table>
<thead>
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<th>Sr. No.</th>
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<td>7a</td>
<td>C(_6)H(_5)-</td>
<td>1654</td>
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<tr>
<td>7b</td>
<td>4-CH(_3)-C(_6)H(_4)-</td>
<td>1656</td>
</tr>
<tr>
<td>7c</td>
<td>4-OCH(_3)-C(_6)H(_4)-</td>
<td>1655</td>
</tr>
<tr>
<td>7d</td>
<td>4-Cl-C(_6)H(_4)-</td>
<td>1668</td>
</tr>
<tr>
<td>7e</td>
<td>4-Br-C(_6)H(_4)-</td>
<td>1660</td>
</tr>
<tr>
<td>7f</td>
<td>4-F-C(_6)H(_4)-</td>
<td>1662</td>
</tr>
<tr>
<td>7g</td>
<td>2-OH-C(_6)H(_4)-</td>
<td>1659</td>
</tr>
<tr>
<td>7h</td>
<td>4-OH-C(_6)H(_4)-</td>
<td>1656</td>
</tr>
<tr>
<td>7i</td>
<td>3-NO(_2)-C(_6)H(_4)-</td>
<td>1659</td>
</tr>
<tr>
<td>7j</td>
<td>4-NO(_2)-C(_6)H(_4)-</td>
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</tr>
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<td>7k</td>
<td>4-NH(_2)-C(_6)H(_4)-</td>
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</tr>
<tr>
<td>7l</td>
<td>2,4-(Cl(_2))-C(_6)H(_3)-</td>
<td>1668</td>
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</table>
EXPERIMENTAL
SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES

[A] Synthesis of 1-Aryl-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones
See, Part-VI, Section-I (B).

[B] Synthesis of 1-Acetyl-3-(p-anisyl)-5-[2’-aminopyrimidin-5-yl]-pyrazolines
A mixture of 1-Aryl-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones (2.55 g, 0.01mol) and hydrazine hydrate (2 ml, 0.04 mol) in 30 ml acetic acid was refluxed for 10 hrs. The resulting solution was poured into crushed ice and crystallised from DMF. Yield 70%, m.p. 163°C, Anal. Calcd. required for C_{17}H_{18}N_{5}O_{2}: C, 62.67%; H, 5.26%; N, 22.49%, found C, 66.56; H, 5.23; N, 22.36%.

Similarly, other 1-acetyl-3-aryl-5-[2’-aminopyrimidine-5-yl]-pyrazolines were prepared. The physical data are recorded in Table No. 7.

[C] Biological screening of 1-Acetyl-3-aryl-5-[2’-aminopyrimidine-5-yl]-pyrazolines
Antimicrobial testing were carried out as described in Part-I, Section-I (C). The zone of inhibition of the test solution are recorded in Graphical Chart No. 7.

Antitubercular screening of the compounds of type (VII) were carried out by TAACF, the Southern Research Institute, U.S.A. as described In Part-I, Section-I (D) and the percentage of inhibition data of the compounds are recorded in Table No. 7a.
<table>
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<th>Molecular Weight</th>
<th>M.P. 0°C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
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<tr>
<td>7b</td>
<td>4-CH₂C₆H₄⁻</td>
<td>C₁₆H₁₇N₅O</td>
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<td>209</td>
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<td>55</td>
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<td>7c</td>
<td>4-OCH₃C₆H₄⁻</td>
<td>C₁₆H₁₇N₅O₂</td>
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<td>163</td>
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<td>22.18</td>
<td>22.10</td>
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*TLC Solvent System*: Hexane:Ethyl acetate(1:9)
GRAPHICAL CHART NO. 7: ANTIMICROBIAL ACTIVITY OF 1-ACETYL-3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES

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<th>7d</th>
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<th>7f</th>
<th>7g</th>
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<td><strong>S. aureus</strong></td>
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<td>19</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

- Amox: Amoxicillin
- Ben: Benzylpenicillin
- Cipro: Ciprofloxacin
- Eryth: Erythromycin
- Geo: G. ovina

ZONES OF INHIBITION IN mm
TABLE NO. 7a : PRIMARY ASSAY OF ANTIMICROBIAL ACTIVITY

```
\[
\text{\[
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{Sample ID} & \text{Corp ID} & \text{Where, } R = & \text{Assay} & \text{Mtb Strain} & \text{Mic \( \mu g/ml \)} & \text{% Inhib} & \text{Activity} & \text{Comment} \\
\hline
295539 & BT-13 & C\textsubscript{6}H\textsubscript{5}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 0 & - & Mic Rifampin = 0.25 \mu g/ml @ 98\% Inhibition \\
295540 & BT-14 & 4-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 13 & - & " \\
295542 & BT-16 & 4-OCH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 3 & - & " \\
295543 & BT-17 & 4-Cl-C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 32 & - & " \\
295544 & BT-18 & 4-Br-C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 13 & - & " \\
295545 & BT-19 & 4-F-C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 15 & - & " \\
295546 & BT-20 & 2-OH-C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 14 & - & " \\
295547 & BT-21 & 4-OH-C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 15 & - & " \\
295548 & BT-22 & 3-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 0 & - & " \\
295549 & BT-23 & 4-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 14 & - & " \\
295550 & BT-24 & 4-NH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}\textsuperscript{-} & Alamar & H\textsubscript{37}Rv & >6.25 & 0 & - & " \\
\hline
\end{array}
\]}
```

TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. H. H. Parekh
Saurashtra University
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

Antibacterial activity

From the experimental data it has been observed that all the compounds of type (VII) were active against Gram positive and Gram negative bacterial species.

It was observed that the compounds showed good activity against Gram positive bacteria. Maximum activity was observed in compounds having R=3-nitrophenyl, 4-hydroxyphenyl, 2,4-dichlorophenyl, against B. coccus. The compounds bearing R=4-hydroxyphenyl, 4-fluorophenyl and 4-methylphenyl have fairly inhibited the growth of S. aureus. Compounds with R=4-bromophenyl and 4-nitrophenyl showed highest activity against E. aerogenes. Almost all compounds were found to be markedly active against Paeruginosa like R=4-methylphenyl and 4-hydroxyphenyl.

Antifungal activity

It has been found that all the compounds were moderately active against A. niger. The maximum activity was displayed by the compounds bearing R=2-hydroxyphenyl against A. niger.

The antibacterial activity was compared with standard drugs viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.

Antitubercular activity

All the compounds of type (VII) were found to be less active against Mycobacterium tuberculosis H$_{37}$Rv.

The antitubercular activity data have been compared with standard drug Rifampin.
PART-II
STUDIES ON
CYNOPYRIDINES
INTRODUCTION

Pyridine, the simplest and perhaps is the best known heterocyclic compound. The credit for the discovery of pyridine goes to Anbderson who first obtained it from bone oil. Pyridine ring system is highly distributed in nature as pyridine derivatives and in many important alkaloids.

Pyridine is the parent of a series of agriculture, medicine and industrial chemistry. Although many polysubstituted pyridine compounds like other heterocyclic compounds are synthesised with their functional group present from acyclic compounds, most derivatives are prepared by manipulation of pyridine and its simple homologues in a manner similar to the chemistry of the benzenoid chemistry. However, the simple pyridine compounds are prepared by the cyclisation of aliphatic raw materials.

SYNTHETIC ASPECTS

Preparation of 3-cyanopyridines is available in the literature\textsuperscript{266-270} with different methods.

1. Samour and co-workers\textsuperscript{271} have prepared substituted cyanopyridines(I) by the condensation of chalcones with malononitriles in presence of ammonium acetate.

2. Feng Shi and co-workers\textsuperscript{272} have prepared 2-amino-3-cyanopyridine derivative by the reaction of aromatic aldehyde, ketone, malononitriles and ammonium acetate under microwave irradiation without solvent.
3. Dao-Lin & Kimiaki\textsuperscript{273} have prepared 2-methoxy-3-cyano pyridine derivatives by the condensation of chalcones with malononitrile in sodium methoxide.

\begin{center}
\textbf{MECHANISM}
\end{center}

The reaction proceeds through conjugate addition of active methylene compounds to the \( \alpha,\beta \)-unsaturated system as shown below.
THERAPEUTIC IMPORTANCE

The extensive use of cyanopyridine derivatives have been established in medicine due to its variety of therapeutic activity shown as under.
1. Analgesic\textsuperscript{274}
2. Insecticidal\textsuperscript{275}
3. Antisoriasis\textsuperscript{276}
4. Antihypertensive\textsuperscript{277}
5. Antifungal\textsuperscript{278}
6. Antiepileptic\textsuperscript{279}
7. Antibacterial\textsuperscript{280}
8. Anticonvulsant\textsuperscript{281}

F. Manna et. al.\textsuperscript{282} have prepared 3-cyanopyridine derivatives as antiinflammatory, analgesic and antipyretic agents. Aivars Krauze et. al.\textsuperscript{283} have synthesised 3-cyanopyridine derivatives & shown their neurotropic activity. Fatma Goda & co-workers\textsuperscript{284} have synthesised 2-alkoxy pyridines (III) and studied their antimicrobial activity. H. Yoshida et. al.\textsuperscript{285} have studied the antihistamic & antiallergic activity of 3-cyanopyridine derivatives. Gadaginamath and co-workers\textsuperscript{286} have synthesised various cyanopyridyl derivatives (IV) and documented their variety of biological activities.
Hammung E. G. and co-workers\textsuperscript{287} have studied the anticancer and anti-HIV activity of 3-cyanopyridines. Abdallah Navine et. al.\textsuperscript{288} have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity.

Abu and co-workers\textsuperscript{289} have described novel fused cyanopyridines (V) for the treatment and preparation of systemic fungal infection. S. V. Roman et. al.\textsuperscript{290} have investigated 2-amino-3-cyanopyridine derivatives and reported their biological activity. El-Tawell and co-workers\textsuperscript{291} have described cyanopyridine derivatives (VI) and showed their significant biological activity.

Pyachenko V. D. and co-workers\textsuperscript{292} have shown some cyanopyridines (VII) useful in treatment of retroviral disease. Hironori et. al.\textsuperscript{293} have prepared cyanopyridines and screened for their large conductance calcium activated potassium channel opener activity.
CONTRIBUTION FROM OUR LABORATORY

Akhil Bhatt and co-workers\textsuperscript{294} have synthesised cyanopyridines as potential antimicrobial agents. R. C. Khunt et. al.\textsuperscript{295} have screened cyanopyridine derivatives used as biologically active agents. Synthesis and antimicrobial activity of cyanopyridines is shown by B. P. Kansagara et. al.\textsuperscript{296} J. R. Patel & co-workers\textsuperscript{297} have prepared cyanopyridines bearing 2-chloro-6-bromoquinoline nucleus as potential anticancer agents.

Synthesis and biological evaluation of cyanopyridines is screened by Pankaj Patel & co-workers\textsuperscript{298}. Rajeev Doshi and co-workers\textsuperscript{299} have described some novel cyanopyridines as a new class of potential antitubercular agents. Cyanopyridines have been screened by A. V. Dobaria et. al.\textsuperscript{300} and showed their significant biological activity. Ketan Hirpara & co-workers\textsuperscript{301} have discovered cyanopyridines as antitubercular agents (VIII).

\begin{center}
\includegraphics[width=0.5\textwidth]{figure.png}
\end{center}

Recently, Marco J. L. et al.\textsuperscript{302} have synthesized acetylcholinesterase inhibitors. Moustafa M. A. et al.\textsuperscript{303} have prepared cyanopyridines as antibacterial agents. Eduardo H. S. Sousa et al.\textsuperscript{304} documented thionicotinamide coordinated to the model system for the \textit{in vitro} activation of thioamides antituberculosis drugs. Rosentreter Ulrich et al.\textsuperscript{305} have synthesized a new cyanopyridine as receptor agonists in the treatment of cardiac or urogenital disease cancer, inflammation, neurodegenerative disease (IX). Gary T. Wang and co-workers\textsuperscript{306} have synthesized o-trifluoromethylbiphenyl substituted 2-amino-nicotinonitriles as inhibitors of farnesyl transferase (X).
Henryk foks et al.\textsuperscript{307} investigated new 3-cyanopyridine derivatives showing an antibacterial activity. Abdel-Galil E. Amr and Mohamed M. Abdulla\textsuperscript{308} have synthesized pyridine derivatives (XI) fused with steroidal structure. Initially the acute toxicity of the compounds was assayed via the determination of their LD\textsubscript{50}. Thus, diverse biological activities have been encountered in compounds containing cyanopyridine ring system. To further assess the potential of such a type of compounds, study of cyanopyridines have been carried out as under.

**SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-2-METHOXY-4-\([2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-PYRIDINES**
SECTIO\-\-I
SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-2-METHOXY-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-PYRIDINES

Pyridine nucleus plays an important role in medicine, agriculture and industrial chemistry. In the light of these biological activities and variety of industrial applications, some new 3-cyano-2-methoxy-4-[2’-aminopyrimidin-5’-yl]-6-aryl-pyridine derivatives of type (VIII) have been prepared, by the cyclocondensation of 1-aryl-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones of type (VI) with malononitrile in the presence of sodium methoxide.

![Chemical Structure]

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the 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 $\mu$g/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 8.
IR SPECTRAL STUDIES OF 3-CYANO-2-METHOXY-4-[2'-AMINOPYRIMIDIN-5'-YL]-6-(p-ANISYL)-PYRIDINE

![IR Spectroscopy of the compound](image)

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observed</td>
<td>Reported</td>
</tr>
<tr>
<td>Alkane</td>
<td>C-H (asym.)</td>
<td>2950</td>
<td>2975-2950</td>
</tr>
<tr>
<td></td>
<td>C-H (sym.)</td>
<td>2848</td>
<td>2880-2860</td>
</tr>
<tr>
<td></td>
<td>C-H (asym.) (def.)</td>
<td>1419</td>
<td>1470-1435</td>
</tr>
<tr>
<td></td>
<td>C-H (sym.) (def.)</td>
<td>1387</td>
<td>1385-1350</td>
</tr>
<tr>
<td>Aromatic</td>
<td>C-H str.</td>
<td>3017</td>
<td>3080-3030</td>
</tr>
<tr>
<td></td>
<td>C=C str.</td>
<td>1510</td>
<td>1585-1480</td>
</tr>
<tr>
<td></td>
<td>C-H i.p. (def.)</td>
<td>1179</td>
<td>1175-1140</td>
</tr>
<tr>
<td></td>
<td>C-H o.o.p. (def.)</td>
<td>828</td>
<td>850-800</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td>N-H str.</td>
<td>3346</td>
<td>3360-3320</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3192</td>
<td>3220-3180</td>
</tr>
<tr>
<td></td>
<td>C=N str.</td>
<td>1606</td>
<td>1650-1580</td>
</tr>
<tr>
<td></td>
<td>C-N str.</td>
<td>1247</td>
<td>1300-1200</td>
</tr>
<tr>
<td></td>
<td>C-H (def.)</td>
<td>964</td>
<td>1000-960</td>
</tr>
<tr>
<td>Ether</td>
<td>C-O-C str.</td>
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<td>1070-1020</td>
</tr>
<tr>
<td>Pyridine</td>
<td>C=C str.</td>
<td>1584</td>
<td>1650-1580</td>
</tr>
<tr>
<td></td>
<td>C=N str.</td>
<td>1557</td>
<td>1585-1480</td>
</tr>
<tr>
<td>Cynide</td>
<td>C ≡ N str.</td>
<td>2215</td>
<td>2240-2120</td>
</tr>
</tbody>
</table>
NMR SPECTRAL STUDIES OF 3-CYANO-2-METHOXY-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-(p-ANISYL)-PYRIDINE

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

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>3.89</td>
<td>singlet</td>
<td>3H</td>
<td>-</td>
<td>Ar-OCH₃</td>
</tr>
<tr>
<td>2.</td>
<td>4.18</td>
<td>singlet</td>
<td>3H</td>
<td>-</td>
<td>Ar-OCH₃</td>
</tr>
<tr>
<td>3.</td>
<td>6.5</td>
<td>broad</td>
<td>2H</td>
<td>-</td>
<td>Ar-NH₂</td>
</tr>
<tr>
<td>4.</td>
<td>7.00-7.03</td>
<td>doublet</td>
<td>2H</td>
<td>J₉ba = 8.9</td>
<td>Ar-Hbb’</td>
</tr>
<tr>
<td>5.</td>
<td>7.41</td>
<td>singlet</td>
<td>1H</td>
<td>-</td>
<td>Ar-Hd</td>
</tr>
<tr>
<td>6.</td>
<td>8.09-8.11</td>
<td>doublet</td>
<td>2H</td>
<td>J₉ab = 8.9</td>
<td>Ar-Haa’</td>
</tr>
<tr>
<td>7.</td>
<td>8.62</td>
<td>singlet</td>
<td>2H</td>
<td>-</td>
<td>Ar-Hcc’</td>
</tr>
</tbody>
</table>
### IR SPECTRAL STUDIES OF 3-CYANO-2-METHOXY-4-[2'-AMINOPYRIMIDIN-5'-YL]-6-ARYL-PYRIDINES

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

<table>
<thead>
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<th>Sr. No.</th>
<th>R</th>
<th>C=(\equiv)N str.</th>
</tr>
</thead>
<tbody>
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<td>(\text{C}_6\text{H}_5^-)</td>
<td>2208</td>
</tr>
<tr>
<td>8b</td>
<td>4-(\text{CH}_3)-(\text{C}_6\text{H}_4^-)</td>
<td>2196</td>
</tr>
<tr>
<td>8c</td>
<td>4-(\text{OCH}_3)-(\text{C}_6\text{H}_4^-)</td>
<td>2215</td>
</tr>
<tr>
<td>8d</td>
<td>4-Cl-(\text{C}_6\text{H}_4^-)</td>
<td>2191</td>
</tr>
<tr>
<td>8e</td>
<td>4-Br-(\text{C}_6\text{H}_4^-)</td>
<td>2212</td>
</tr>
<tr>
<td>8f</td>
<td>4-F-(\text{C}_6\text{H}_4^-)</td>
<td>2200</td>
</tr>
<tr>
<td>8g</td>
<td>2-(\text{OH})-(\text{C}_6\text{H}_4^-)</td>
<td>2218</td>
</tr>
<tr>
<td>8h</td>
<td>4-(\text{OH})-(\text{C}_6\text{H}_4^-)</td>
<td>2220</td>
</tr>
<tr>
<td>8i</td>
<td>3-(\text{NO}_2)-(\text{C}_6\text{H}_4^-)</td>
<td>2205</td>
</tr>
<tr>
<td>8j</td>
<td>4-(\text{NO}_2)-(\text{C}_6\text{H}_4^-)</td>
<td>2196</td>
</tr>
<tr>
<td>8k</td>
<td>4-(\text{NH}_2)-(\text{C}_6\text{H}_4^-)</td>
<td>2212</td>
</tr>
<tr>
<td>8l</td>
<td>2,4-((\text{Cl}_2))-(\text{C}_6\text{H}_3^-)</td>
<td>2215</td>
</tr>
</tbody>
</table>
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-2-METHOXY-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-PYRIDINES

[A] Synthesis of 1-Aryl-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones

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

[B] Synthesis of 3-Cyano-2-methoxy-4-[2’-aminopyrimidin-5’-yl]-6-(p-anisyl)-pyridine

To a solution of 1-(p-methoxy)-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones (2.55 g, 0.01 mol), malononitrile (0.60g, 0.01 mol) in DMF (20ml) and sodium methoxide, which was prepared from sodium (46mg) and absolute methanol (20ml), was added. The content was heated under reflux with stirring for 12 hr. The reaction mixture was diluted with water and extracted with chloroform. The excess solvent was distilled off and residue was crystallized from DMF. Yield 63%, m.p. 222°C, Anal. Calcd. required for C_{18}H_{15}N_{5}O_{2} : C, 64.86%; H, 4.54%; N, 21.01%; found: C, 64.43 %; H, 4.08%; N,20.60%.

Similarly, other 3-cyano-2-methoxy-4-[2’-aminopyrimidin-5’-yl]-6-aryl-pyridine were prepared. The physical data are recorded in Table No. 8.

[C] Biological screening of 3-Cyano-2-methoxy-4-[2’-aminopyrimidin-5’-yl]-6-aryl-pyridine

Antimicrobial testing were carried out as described in Part-I, Section-I [C]. The zones of inhabitation of test solution are recorded in Graphical Chart No. 8.
**TABLE NO. 8 : PHYSICAL CONSTANTS OF 3-CYANO-2-METHOXY-4-[2'-AMINOPYRIMIDIN-5'-YL]-6-ARYL-PYRIDINES**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calc'd.</th>
<th>% of Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>C₆H₅⁻</td>
<td>C₁₇H₁₃N₅O</td>
<td>303</td>
<td>197</td>
<td>0.30</td>
<td>69</td>
<td>23.09</td>
<td>22.65</td>
</tr>
<tr>
<td>8b</td>
<td>4-CH₃C₆H₄⁻</td>
<td>C₁₈H₁₅N₅O</td>
<td>317</td>
<td>162</td>
<td>0.32</td>
<td>59</td>
<td>22.07</td>
<td>21.80</td>
</tr>
<tr>
<td>8c</td>
<td>4-OCH₃C₆H₄⁻</td>
<td>C₁₈H₁₅N₅O₂</td>
<td>333</td>
<td>222</td>
<td>0.41</td>
<td>63</td>
<td>21.01</td>
<td>20.60</td>
</tr>
<tr>
<td>8d</td>
<td>4-ClC₆H₄⁻</td>
<td>C₁₇H₁₂N₅OCl</td>
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<td>209</td>
<td>0.36</td>
<td>56</td>
<td>20.73</td>
<td>20.12</td>
</tr>
<tr>
<td>8e</td>
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<td>C₁₇H₁₂N₅OBr</td>
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<td>204</td>
<td>0.45</td>
<td>68</td>
<td>18.32</td>
<td>18.00</td>
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<tr>
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<td>321</td>
<td>192</td>
<td>0.51</td>
<td>70</td>
<td>21.80</td>
<td>21.10</td>
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<td>8g</td>
<td>2-OHC₆H₄⁻</td>
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<td>187</td>
<td>0.50</td>
<td>60</td>
<td>21.93</td>
<td>21.22</td>
</tr>
<tr>
<td>8h</td>
<td>4-OHC₆H₄⁻</td>
<td>C₁₇H₁₃N₅O₂</td>
<td>319</td>
<td>163</td>
<td>0.48</td>
<td>62</td>
<td>21.93</td>
<td>21.25</td>
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<tr>
<td>8i</td>
<td>3-NO₂C₆H₄⁻</td>
<td>C₁₇H₁₂N₆O₃</td>
<td>348</td>
<td>216</td>
<td>0.55</td>
<td>56</td>
<td>24.13</td>
<td>23.85</td>
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<tr>
<td>8j</td>
<td>4-NO₂C₆H₄⁻</td>
<td>C₁₇H₁₂N₆O₃</td>
<td>348</td>
<td>167</td>
<td>0.36</td>
<td>64</td>
<td>24.13</td>
<td>23.62</td>
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<tr>
<td>8k</td>
<td>4-NHC₆H₄⁻</td>
<td>C₁₇H₁₄N₆O</td>
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<td>238</td>
<td>0.40</td>
<td>58</td>
<td>26.40</td>
<td>25.92</td>
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</table>

*TLC Solvent System*: Hexane:Ethyl acetate(1:9)
GRAPHICAL CHART NO. 8: ANTIMICROBIAL ACTIVITY OF 3-CYANO-2-METHOXY-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-PYRIDINES

ZONE OF INHIBITION IN mm

<table>
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<th>8c</th>
<th>8d</th>
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<th>8f</th>
<th>8g</th>
<th>8h</th>
<th>8i</th>
<th>8j</th>
<th>8k</th>
<th>8l</th>
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<th>Benzoylpenicillin</th>
<th>Ciprofloxacin</th>
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<tr>
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RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

Antibacterial activity

It has been observed from the experimental data that all compounds of type (VIII) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

However, comparatively good activity was observed in compounds with R=4-nitrophenyl and 4-fluorophenyl against *B. coccus*; R=4-chlorophenyl, 3-nitrophenyle and 4-nitrophenyl against *S. aureus*.

In case of Gram negative bacterial strains, the maximum activity was displayed by the compounds bearing R=4-bromophenyl, 2,4-dichlorophenyl and 2-hydroxyphenyl against *E. aerogenes*. While the compounds bearing R=4-chlorophenyl and 4-nitrophenyl have shown considerable activity against *P. aeruginosa*.

Antifungal activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds bearing R=4-chlorophenyl against *A. niger*.

The antibacterial activity was compared with standard drugs viz. amoxicillin, benzoylpenicillin, ciprofloxacin, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.
PART-III
STUDIES ON CYANOPYRIDONES
INTRODUCTION

Pyridones, which belong to an important group of heterocyclic compounds have been extensively explored for their applications in the field of medicine. Pyridones, with a carbonyl group at position 2 (I) have been subject of extensive study in recent past. Numerous reports have appeared in the literature which highlight their chemistry and use.

![Pyridone structure](image)

Some 2-pyridones are physiologically as well as pharmacologically important which are as under: eg. amrinone (II), ciclopirox (III) and methylprylon (IV).

![Pyridone derivatives](image)

Synthetic pyridone derivatives contribute much to the searchable literature of pyridone derivatives in huge libraries owing to their wide applicability in different fields.

SYNTHETIC ASPECTS

Different methods for preparation of cyanopyridones are as follows:

1. Rajul Jain et al.\textsuperscript{309} have synthesised 3-cyano-2-pyridones by the reaction of various enones with cyanoacetamide in presence of t-BuOK in DMSO under O\textsubscript{2} atmosphere.
2. K. Follkers and S. A. Harris\textsuperscript{310} have synthesised 3-cyano-2-pyridones by the condensation of cyanoacetamide with 1,3-diketone or 3-ketoester.

3. W. Russel Bowman et. al.\textsuperscript{311} have synthesised cyanopyridones from 2,6-dibromopyridine in the presence of chlorotrimethylsilane and sodium iodide in acetonitrile.

**MECHANISM**

The addition reaction between ethylcyanoacetale and $\alpha,\beta$-unsaturated ketone give cyanopyridone via Michael addition. Here, $\alpha,\beta$-unsaturated compound is known as acceptor and active methylene group containing compound known as addender. It involves nucleophilic addition of carbanion to the C=C of the acceptor.
THERAPEUTIC IMPORTANCE

Pyridone derivatives have been found to possess variety of therapeutic activities as shown below:

1. Anticancer
2. Herbicidal
3. Angiotensin II antagonist
4. Antimicrobial
5. Pesticidal
6. Antiviral
7. AntiHIV

F. Peter and co-workers have prepared pyridinylmethyl substituted pyridines and pyridones as angiotensin II antagonist. H. Posnes synthesized 2-pyridones and 2-pyriones as physiologically active compounds. Mukhtar Hussain Khan and co-workers have prepared 2-pyridone derivatives (VIII) and (IX) which possess insecticidal and pesticidal activity.
M. K. Morishita et al.\(^{326}\) have synthesised m-(2-oxo-1,2-dihydropyridyl) urea derivatives (X) possessing cholesterol acyltransterase (ACAT) inhibitory activity and are useful for the treatment of hyperlipidemia and arteriosclerosis.

I.J. Collins et al.\(^{327}\) prepared heteroaryl pyridones as GABA \(\alpha_2/\alpha_3\) ligands. Pednecker\(^{328}\) synthesised fused 2-pyridone derivatives (XI), (XII) and (XIII) as useful heterocyclic moieties as they possess a broad spectrum of biological activities such as antiviral, CNS depressant, bactericidal and ulcer inhibitor.

Moreover, several co-workers have prepared 2-pyridones as S3 site of thrombin inhibitor\(^{329}\), herbicidal\(^{330}\), SH\(_2\) domain inhibitor\(^{331}\), antimicrobial\(^{332}\), GABA-receptor\(^{333}\) and antiinflammatory\(^{334}\).

Upadhyay and co-workers\(^{335}\) have synthesised cyanopyridine derivatives which showed antifungal and antileishmanial activities. E. Amer\(^{336}\) prepared 3-cyano-2-pyridone derivatives (XIV) displaying high antimicrobial activity. Abou El-Fotooh and co-worker\(^{337}\) have demonstrated pyridones (XV) as anticancer agent.
M. G. Nizamuddin et al.\textsuperscript{338} have prepared cyanopyridone derivatives \textup{(XVI)} and documented their antifungal activity. Tanaka Akira et al.\textsuperscript{339} have prepared pyrazolo pyridone derivatives. \textup{(XVII)} Moreover, several co-workers have prepared 2-pyridones as nuclear receptors, including liver x receptor and antiinflammatory\textsuperscript{340}.

Recently, Devdas B. et al.\textsuperscript{341} have synthesised pyridone derivatives \textup{(XVIII)} which are useful for treating diseases and conditions caused or exacerbated by unregulated P38 MAP kinase and/or TNF activity, such as inflammation, ischemia, viral infections and autoimmune diseases. Wang S. and co-workers\textsuperscript{342} have prepared 2-pyridone containing tricyclic alkaloid derivatives as potential inhibitors of tumor cell proliferation by regioselective intramolecular N- and C-acylation of 2-pyridone. A novel series of pyridone inhibitors has been identified through
pharmacophore analysis as potent and selective VLA-4 integrin antagonists by Jason Witherington et. al.\textsuperscript{343} Jiang Q. and co-workers\textsuperscript{344} have identified a series of novel pyridones as kinase inhibitors of ALK.

Thus the important role played by cyanopyridone nucleus for various physiological activities prompted us to explore cyanopyridone chemistry by synthesising its derivatives bearing pyrimidine ring systems of therapeutic importance, in order to achieving compounds having better drug potential which has been described as under.

**SECTION - I :** SYNTHESES AND BIOLOGICAL SCREENING OF 3-CYANO-4-[2'-AMINOPYRIMIDIN-5-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES
SECTION - 1
SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

The growing potent literature of recent years demonstrates that the cyanopyridone derivative are used as better therapeutic agents. Prompted by these facts, the preparation of cyanopyridone derivative of type (IX) by the condensation of chalcone with ethylcyanoacetate in presence of ammonium acetate.

![Chemical structure of Type-(IX) R=Aryl]

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the 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 $\mu$g/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 9.
IR SPECTRAL STUDIES OF 3-CYANO-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-(p-ANISYL)-1,2-DIHYDRO-2-PYRIDONE

![Chemical Structure](image)

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

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<th>Ref.</th>
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<td>-CH₃</td>
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<td></td>
<td>C-H (sym.) (def.)</td>
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<td>1385-1350</td>
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<td>C≡N str.</td>
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NMR SPECTRAL STUDIES OF 3-CYANO-4-[2'-AMINOPYRIMIDIN-5'-YL]-6-(p-TOLYL)-1,2-DIHYDRO-2-PYRIDONE

Internal Standard: TMS; Solvent: CDCl₃; Instrument: BRUKER Spectrometer (300 MHz)

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<th>J. value in Hz</th>
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<td>J&lt;sub&gt;ab&lt;/sub&gt; = 8.11</td>
<td>Ar-H&lt;sub&gt;aa'&lt;/sub&gt;</td>
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<tr>
<td>4.</td>
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<td>2H</td>
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<td>Ar-H&lt;sub&gt;bb'&lt;/sub&gt;</td>
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<td>-</td>
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<td>6.</td>
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<td>singlet</td>
<td>2H</td>
<td>-</td>
<td>Ar-H&lt;sub&gt;cc'&lt;/sub&gt;</td>
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</table>
EXPANDED AROMATIC REGION

IR SPECTRAL STUDIES OF 3-CYANO-4-[2'-AMINOPYRIMIDIN-5-YL]-6ARYL-1,2-DIHYDRO-2-PYRIDONES

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

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<td>4-CH₃C₆H₄⁻</td>
<td>1639</td>
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<tr>
<td>9c</td>
<td>4-OCH₃C₆H₄⁻</td>
<td>1637</td>
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<td>9d</td>
<td>4-ClC₆H₄⁻</td>
<td>1645</td>
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<td>9e</td>
<td>4-BrC₆H₄⁻</td>
<td>1644</td>
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<td>9f</td>
<td>4-FC₆H₄⁻</td>
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<td>9g</td>
<td>2-OHC₆H₄⁻</td>
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<td>9k</td>
<td>4-NH₂C₆H₄⁻</td>
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<td>9l</td>
<td>2,4-(Cl₂)C₆H₃⁻</td>
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MASS SPECTRAL STUDIES 3-CYANO-4-[2'-AMINOPYRIMIDIN-5'-YL]-6-(p-ANISYL)-1,2-DIHYDRO-2-PYRIDONE

Line#1 R.Time:9.8(Scan#:1135)
MassPeaks:38 BasePeak: 233(29840)
RawMode:Single 9.8(1135)
BG Mode:None

intensity

m/z
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

[A] Synthesis of 1-Aryl-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones

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

[B] Synthesis of 3-Cyano-4-[2’-aminopyrimidin-5’-yl]-6-(p-tolyl)-1,2-dihydro-2-pyridones

A solution of 1-(p-tolyl)-3-[2’-aminopyrimidin-5’-yl]-propen-2-ones (2.39 gm, 0.01 mol), ethyl cyanoacetate (1.13 gm, 0.01 mol) and ammonium acetate (6.16 gm, 0.08 mol) in DMF was refluxed for 10 hrs. The reaction mixture was poured into crushed ice and product was isolated and crystallized from DMF. Yield 57%, m.p. 238°C, Anal. Calcd. required for C_{17}H_{13}N_{5}O : C, 67.32%; H, 4.32%; N, 23.09 %; found: C, 66.10%; H, 4.14%; N, 23.00 %.

Similarly other 3-cyano-4-[2’-aminopyrimidin-5-yl]-6-aryl-1,2-dihydro-2-pyridones were prepared. The physical data are recorded in Table No. 9.

[C] Biological screening of 3-Cyano-4-[2’-aminopyrimidin-5-yl]-6-aryl-1,2-dihydro-2-pyridones

Antimicrobial testing was carried out as described in Part-I, Section-I [C]. The zone of inhibition of the test solutions are recorded in Graphical Chart No. 9.
### TABLE NO. 9: PHYSICAL CONSTANTS OF 3-CYANO-4-[2’-AMINOPYRIMIDIN-5-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

<table>
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<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
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<td>18.92</td>
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<td>188</td>
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<td>63</td>
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<td>22.92</td>
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<td>9i</td>
<td>3-NO₂C₆H₄⁻</td>
<td>C₁₆H₁₁N₆O₃</td>
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<td>245</td>
<td>0.52</td>
<td>66</td>
<td>25.14</td>
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<td>9j</td>
<td>4-NO₂C₆H₄⁻</td>
<td>C₁₆H₁₁N₆O₃</td>
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<td>250</td>
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<td>C₁₆H₉N₅OCl₂</td>
<td>358</td>
<td>261</td>
<td>0.42</td>
<td>65</td>
<td>19.55</td>
<td>19.28</td>
</tr>
</tbody>
</table>

*TLC Solvent System: Hexane:Ethyl acetate (1:9)*
GRAPHICAL CHART NO. 9: ANTIMICROBIAL ACTIVITY OF 3-CYANO-4-[2’-AMINOPYRIMIDIN-5’-YL]-6-ARYL-1,2-DIHYDRO-2-PYRIDONES

<table>
<thead>
<tr>
<th></th>
<th>9a</th>
<th>9b</th>
<th>9c</th>
<th>9d</th>
<th>9e</th>
<th>9f</th>
<th>9g</th>
<th>9h</th>
<th>9i</th>
<th>9j</th>
<th>9k</th>
<th>9l</th>
<th>Amoxicillin</th>
<th>Benzoylpenicillin</th>
<th>Ciprofloxacin</th>
<th>Erythromycin</th>
<th>Grevicol</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. coccus</td>
<td>13</td>
<td>21</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>16</td>
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<td>17</td>
<td>25</td>
<td>18</td>
<td>20</td>
<td>22</td>
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</tr>
<tr>
<td>S. aureus</td>
<td>17</td>
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<td>14</td>
<td>20</td>
<td>25</td>
<td>19</td>
<td>15</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>E. aerogenes</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>19</td>
<td>15</td>
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<td>20</td>
<td>21</td>
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<tr>
<td>P. aeruginosa</td>
<td>15</td>
<td>17</td>
<td>16</td>
<td>20</td>
<td>18</td>
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<td>17</td>
<td>22</td>
<td>21</td>
<td>16</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>A. niger</td>
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<td>14</td>
<td>16</td>
<td>18</td>
<td>19</td>
<td>16</td>
<td>15</td>
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<td>14</td>
<td>17</td>
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<td>17</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
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</tbody>
</table>
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

Antibacterial activity:

It has been concluded from the experimental data that all the cyanopyridones of type (IX) are active against different strains of Gram positive and Gram negative bacteria.

The significant activity was observed in compounds bearing \( R = 4\)-methylphenyl, 3-nitrophenyl and 2,4-dichlorophenyl against \textit{B.coccus} and \textit{S.aureus}.

The maximum activity was observed in compounds bearing \( R = 4\)-nitrophenyl, 4-chlorophenyl and 2-hydroxyphenyl against \textit{E.aerogenes} and \( R = 4\)-chlorophenyl against \textit{P.aeruginosa}.

Antifungal activity

All the compounds exhibited mild activity against \textit{A.niger} except compounds bearing \( R = 4\)-bromophenyl which showed good activity against \textit{A.niger}. 
PART-IV
STUDIES ON
ISOXAZOLES
INTRODUCTION

Isoxazoles are a group of heterocyclic compounds containing two heteroatoms in five membered ring: Nitrogen and Oxygen. In 1888, Claisen first suggested an isoxazole structure (I), for a product from the reaction of 1,3-diketone with hydroxylamine\textsuperscript{345}. Subsequently, a solid foundation for the chemistry of isoxazole was laid down by Claisen and his students\textsuperscript{346,347}.

![Diagram of Isocycle]

The next important contribution to the chemistry of isoxazoles was made by Quilico in 1946, when he began to study the formation of isoxazoles from nitrile N-oxides and unsaturated compounds. Well known sulpha drug, sulphamethoxazole and antibiotic oxamycin or cycloserin is D\textsubscript{4}-amino-3-oxazolidinone, both contains isoxazole type of nucleus.

It was shown to possess the typical properties of an aromatic system but under certain reaction conditions, particularly in reducing or basic media, it becomes very highly labile. Isoxazole when substituted in the 3,5-position are stable to alkali but when 3-position is vacant, the ring is opened in the presence of cold alkaline media to give keto nitriles and when 5-position is vacant, the ring is opened in the presence of hot alkali media to yield nitriles and carboxylic acids.

![Diagram of Reaction]

Where $R = \text{CH}_3$.
SYNTHETIC ASPECTS

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

1. Crawley L. S. and Fanshawe W. J.\textsuperscript{348} prepared isoxazole from \(\alpha,\beta\)-unsaturated carbonyl compounds and hydroxyl amine

\[
\begin{align*}
\text{R-CH=CHR}_1 + \text{NH}_2\text{OH.HCl} & \xrightarrow{\text{KOH}} \text{R-CHR}_2 \text{O} \\
\end{align*}
\]

2. Dawood Kamal et al.\textsuperscript{349} prepared isoxazole derivatives from enamino nitriles.

3. Tayade V. B. et al.\textsuperscript{350} synthesized some new 3,5-diarylisoxazoles from the reaction of 2-aryl acetophenones with hydroxylamine hydrochloride in presence of alkali.

4. Mark Lautens and Ame´lie Roy\textsuperscript{351} have prepared isoxazoles in good yields by using \(N\)-acetoacetyl derivatives.

\[
\begin{align*}
\text{H}_3\text{C}-\text{CH}=\text{CH}_3 \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{H}_3\text{C} \xrightarrow{\text{NaOAc, MeOH}} \text{H}_3\text{C} - \text{NCH}_3 \\
\end{align*}
\]

5. Keisuke Suzuki et al.\textsuperscript{352} have synthesized functionalized isoxazole derivatives by cyclocondensation of C-chlorooximes with cyclic 1,3 diketone, hydrochloride and KOH in methanol.

\[
\begin{align*}
\text{H}_3\text{C} \xrightarrow{\text{PrOH, NaO/Pr}} \text{H}_3\text{C} \\
\end{align*}
\]
6. A variety of 3,5-disubstituted 4-bromoisoxazoles\textsuperscript{353} are prepared in good to excellent yields under mild reaction conditions by the reaction of 2-alkyn-1-one O-methyl oximes with Br\textsubscript{2}.

![Chemical reaction diagram](image)

**REACTION MECHANISM**

**THERAPEUTIC IMPORTANCE**

A class of isoxazole derivatives has been disclosed as having immuno suppressant activity. These heterocycles are rapidly converted \textit{in vivo} to ring opened metabolites, hydroxyalkylidene-cynoacetamides, which we believed to be the active therapeutic agents. Leflunomide (VI) is the lead compound of this new group of isoxazole derivatives that have been developed at Hoechst.
The physiological effects of this class of compounds, analogues of A77 1726 (VII) and the parent isoxazoles were disclosed as useful for treatment of cancer\textsuperscript{354}. These compounds exert an antiproliferative effect through inhibition of receptor tyrosine kinases and have little effect on proliferation of normal cells since their inhibitory effect on DHOdehase is weak. The Dihydro isoxazoles can be used as linkers for joining chemically sensitive moieties. This is the case for isozazole-linked nitromidazole-carborane (VIII) used for targeting to hypoxic tumors\textsuperscript{355}.

Some isoxazole analogs of retinoids exhibited good antiproliferative activity and capability to induce differentiation of \textit{in vitro} culture tumor cell lines\textsuperscript{356}. Compound (IX) is a representative example of bis-isoxazole derivatives disclosed to have anticancer properties\textsuperscript{357}.
The compound (X) is chosen among a wide series of 1-amino-3-phenoxy propane derivatives claimed as antineoplastic enhancers which are able to modulate the multi-drug resistance of tumor cells to various chemotherapeutic agents\textsuperscript{358}.

Over and above the isoxazole posses wide range of therapeutic activites like,

1. Cardovascular\textsuperscript{359,360}
2. Antiviral\textsuperscript{361,362}
3. CNS active\textsuperscript{363,364}
4. Analgesic\textsuperscript{365}
5. Anticonvulsant\textsuperscript{366}
6. Fungicidal\textsuperscript{367}
7. Anticholestermic\textsuperscript{368}
8. Hypoglycemic\textsuperscript{369}
9. Antileukemic\textsuperscript{370}
10. Antipyretic\textsuperscript{371}
11. Antiinflammatory\textsuperscript{372}
12. Nematocidal\textsuperscript{373}
13. Muscle relaxant\textsuperscript{374}
14. Antidiabetic\textsuperscript{375}

The Isoxicam\textsuperscript{376} (XI) and Activicin\textsuperscript{377} (XII) bearing isoxzoles possess antiinflammatory\textsuperscript{378} and antitumor activity.
Morohashi and co-workers\textsuperscript{379} have synthesised some new isoxazole (XIII) and reported their effect to correct abnormalities in the immune system and therefore it is useful towards rhumatism or as anticancer agent.

J. J. Talley and co-workers\textsuperscript{380} prepared some new isoxazoles and reported them as selective inhibitors of COX-2 for paratetal administration. Sun Chang-Jun et al.\textsuperscript{381} prepared isoxazole derivatives (XIV) and studied their antitumor activity.

Archana et al.\textsuperscript{382} have prepared isoxazole derivatives and screened for their anticonvulsant activity. Chengde and co-workers\textsuperscript{383} have synthesised isoxazole derivatives which are used in the treatment of endothelin mediated disorder. F. Gallemi and co-workers\textsuperscript{384} have prepared some new isoxazoles (XV) and reported them as antibiotics and antitumor agent.
CONTRIBUTION FROM OUR LABORATORY

V. B. Patel and co-workers\textsuperscript{385} have prepared isoxazoles bearing sulphonamide moiety and reported their antimicrobial activity. R. C. Khunt, A. R. Parikh and co-workers\textsuperscript{386} have prepared isoxazole derivatives which possess antimicrobial activity. Rajeev Doshi and co-workers\textsuperscript{387} have discovered isoxazoles as a new class of potential antitubercular agents. Ketan Hirpara et. al.\textsuperscript{388} have synthesised isoxazoles as antitubercular agents. A. V. Dobaria et. al.\textsuperscript{389} have described the isoxazole derivatives and their use as antimicrobial agents. B. P. Kansagara et. al.\textsuperscript{390} have demonstrated various isoxazole and tested their antimicrobial activity.

Recently, Kaifan Cheng and Yousef Al-Abed\textsuperscript{391} have reported isoxazole derivatives (XVI) and found 20-fold more potent than 3-(3-fluro-4-hydroxyphenyl)-4,5-dihydro-5-acetic acid methyl ester isoxazole which inhibits MIF tautomerase with an IC\textsubscript{50} of 550 nM. Novel cyclohexyl drug resistance modulators\textsuperscript{392} (XVII) were synthesized and evaluated for in vitro inhibition of the drug resistance transporter, MRP1.
Stefano Chimichi and co-workers\textsuperscript{393} have investigated cytotoxic activity of 3-quinolinoyl isoxazoles (XVIII) against leukemia-and adenocarcinoma-derived cell lines in comparison to the normal human keratinocytes. Julia Kaffy et al.\textsuperscript{394} have synthesized various five membered heterocycles with oxygen and nitrogen atoms. The 4,5 diarylisoxazole (XIV) exhibited greater antitubulin activity, but modest antiproliferative activity.

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

\textbf{SECTION -I : SYNTHEIS AND BIOLOGICAL SCREENING OF 3-ARYL-5-[2'-AMINOPYRIMIDIN-5'-YL]-ISOXAZOLES}
SECTION - I
SYNTHESIS AND BIOLOGICAL SCREENING OF 3-ARYL-5-[2’-AMINOPYRIDIN-5’-YL]-Isoxazoles

Isoxazole derivatives occupy a unique place in the field of medicinal chemistry due to a wide range of biological activities exhibited by them. Looking at the interesting therapeutic activity of isoxazoles, it was considered to synthesise a series of isoxazoles of type (X) for obtaining biologically potent agents which were prepared by the condensation of chalcones with hydroxylamine hydrochloride in the presence of sodium acetate in glacial acetic acid.

The constitution of the synthesized compounds have been supported by using elemental analyses, infrared and $^{1}$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds have been checked by thin layer chromatography.

All the 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 $\mu$g/ml. The biological activity of the synthesized compounds have been compared with standard drugs. Some compounds have been found to have moderate activity as compared to known antibiotics recorded on Graphical Chart No. 10.
IR SPECTRAL STUDIES OF 3-(p-ANISYL)-5-[2′-AMINOPYRIMIDIN-5′-YL]-ISOXAZOLE

![Graph showing IR spectrum](image)

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration mode</th>
<th>Frequency in cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkane</td>
<td>C-H (asym.)</td>
<td>Observed: 2923</td>
</tr>
<tr>
<td>C-H (sym.)</td>
<td>2841</td>
<td>2880-2860</td>
</tr>
<tr>
<td>C-H (asym.) (def.)</td>
<td>1436</td>
<td>1470-1435</td>
</tr>
<tr>
<td>C-H (sym.) (def.)</td>
<td>1380</td>
<td>1385-1350</td>
</tr>
<tr>
<td>Aromatic</td>
<td>C-H str.</td>
<td>3020</td>
</tr>
<tr>
<td>C=C str.</td>
<td>1498</td>
<td>1585-1480</td>
</tr>
<tr>
<td>C-H i.p. (def.)</td>
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<td>1175-1140</td>
</tr>
<tr>
<td>C-H o.o.p. (def.)</td>
<td>831</td>
<td>850-800</td>
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<tr>
<td>Pyrimidine</td>
<td>N-H str.</td>
<td>3317</td>
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<tr>
<td>C=N str.</td>
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<td>3220-3180</td>
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<tr>
<td>C-N str.</td>
<td>1616</td>
<td>1650-1580</td>
</tr>
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<td>C-H (def.)</td>
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<td>1300-1200</td>
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<tr>
<td>Ether</td>
<td>C-O-C str.</td>
<td>947</td>
</tr>
<tr>
<td>Isoxazole</td>
<td>C=C str.</td>
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</tr>
<tr>
<td>C=N str.</td>
<td>1591</td>
<td>1650-1580</td>
</tr>
<tr>
<td>N-O str.</td>
<td>1550</td>
<td>1585-1480</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>850-800</td>
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</tbody>
</table>
**NMR SPECTRAL STUDIES OF 3-*(p-TOLYL)-5-[2’-AMINOPYRIMIDIN-5’-YL]-ISOXAZOLE**

![NMR Spectral Image]

Internal Standard: TMS; Solvent: CDCl₃; Instrument: BRUKER Spectrometer (300 MHz)

<table>
<thead>
<tr>
<th>Signal No.</th>
<th>Signal Position (δ ppm)</th>
<th>Multiplicity</th>
<th>Relative No. of Protons</th>
<th>J. value in Hz</th>
<th>Inference</th>
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<tr>
<td>1</td>
<td>2.24</td>
<td>singlet</td>
<td>3H</td>
<td>-</td>
<td>Ar-CH₃</td>
</tr>
<tr>
<td>2</td>
<td>5.86</td>
<td>broad</td>
<td>2H</td>
<td>-</td>
<td>Ar-NH₂</td>
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<tr>
<td>3</td>
<td>6.71-6.73</td>
<td>doublet</td>
<td>2H</td>
<td>Jₐb = 9.64</td>
<td>Ar-Hₐa</td>
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<tr>
<td>4</td>
<td>7.01-7.03</td>
<td>doublet</td>
<td>2H</td>
<td>J₉bₐ = 9.64</td>
<td>Ar-H₉b</td>
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<tr>
<td>5</td>
<td>7.78</td>
<td>singlet</td>
<td>1H</td>
<td>-</td>
<td>Ar-H₉d</td>
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<tr>
<td>6</td>
<td>8.43</td>
<td>singlet</td>
<td>2H</td>
<td>-</td>
<td>Ar-H₉c</td>
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</table>
EXPANDED AROMATIC REGION

MASS SPECTRAL STUDIES OF 3-(p-ANISYL)-5-[2'-AMINOPYRIMIDIN-5'-YL]-ISOXAZOLE
EXPERIMENTAL
SYNTHESIS AND BIOLOGICAL SCREENING OF 3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-ISOXAZOLES

[A] Synthesis of 1-Aryl-3-[2’-aminopyrimidin-5’-yl]-propan-2-ones
See, Part-VI, Section-I (B).

[B] Synthesis of 3-(p-tolyl)-5-[2’-aminopyrimidin-5’-yl]-isoaxazole
A solution of anhydrous sodium acetate (0.739g, 0.01 mol) in a minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (0.59 g, 0.01 mol) in DMF (20 ml). This solution was added to a solution of 1-(p-tolyl-3-[2’-aminopyrimidin-5’-yl]-propan-2-one (2.39 g, 0.01 mol) in DMF (25 ml). The mixture was heated under reflux on oilbath for 12 hrs. The product was isolated and recrystallised from DMF. Yield 56%, m.p. 239°C, C_{14}H_{12}N_{4}O; Required : C, 66.65; H, 4.79; N, 22.21; Found : C, 66.54; H, 4.71; N, 22.16%.

Similarly other 3-aryl-5-[2’-aminopyrimidin-5’-yl]-isoaxazoles were prepared. The physical data are recorded in Table No. 10.

[C] Biological screening of 3-Aryl-5-[2’-aminopyrimidin-5’-yl]-isoaxazoles
Antimicrobial testing were carried out as described in Part - I, Section - I (C). The zones of inhibition of test solution are reported in Graphical Chart No. 10.
**TABLE NO. 10 : PHYSICAL CONSTANTS OF 3-ARYL-5-[2’-AMINOPYRIDIN-5’-YL]-ISOXAZOLES**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. °C</th>
<th>Rf* Value</th>
<th>Yield %</th>
<th>% of Nitrogen Calcd.</th>
<th>% of Nitrogen Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td>C₆H₅⁻</td>
<td>C₁₃H₁₀N₄O</td>
<td>238</td>
<td>210</td>
<td>0.51</td>
<td>50</td>
<td>23.52</td>
<td>23.38</td>
</tr>
<tr>
<td>10b</td>
<td>4-CH₃C₆H₄⁻</td>
<td>C₁₄H₁₂N₄O</td>
<td>252</td>
<td>239</td>
<td>0.55</td>
<td>56</td>
<td>22.21</td>
<td>22.16</td>
</tr>
<tr>
<td>10c</td>
<td>4-OCH₃C₆H₄⁻</td>
<td>C₁₄H₁₂N₄O₂</td>
<td>268</td>
<td>230</td>
<td>0.40</td>
<td>60</td>
<td>20.88</td>
<td>20.61</td>
</tr>
<tr>
<td>10d</td>
<td>4-ClC₆H₄⁻</td>
<td>C₁₃H₉N₄OCl</td>
<td>272</td>
<td>196</td>
<td>0.48</td>
<td>68</td>
<td>20.55</td>
<td>20.47</td>
</tr>
<tr>
<td>10e</td>
<td>4-BrC₆H₄⁻</td>
<td>C₁₃H₉N₄Br</td>
<td>317</td>
<td>190</td>
<td>0.42</td>
<td>48</td>
<td>17.67</td>
<td>17.54</td>
</tr>
<tr>
<td>10f</td>
<td>4-FC₆H₄⁻</td>
<td>C₁₃H₉N₄OBr</td>
<td>256</td>
<td>181</td>
<td>0.55</td>
<td>50</td>
<td>21.87</td>
<td>21.72</td>
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<td>10g</td>
<td>2-OHC₆H₄⁻</td>
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<td>202</td>
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<td>67</td>
<td>22.04</td>
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<tr>
<td>10h</td>
<td>4-OHC₆H₄⁻</td>
<td>C₁₃H₁₀N₄O₂</td>
<td>254</td>
<td>216</td>
<td>0.66</td>
<td>62</td>
<td>22.04</td>
<td>23.98</td>
</tr>
<tr>
<td>10i</td>
<td>3-NO₂C₆H₄⁻</td>
<td>C₁₃H₉N₄O₃</td>
<td>283</td>
<td>241</td>
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<td>52</td>
<td>24.73</td>
<td>24.65</td>
</tr>
<tr>
<td>10j</td>
<td>4-NO₂C₆H₄⁻</td>
<td>C₁₃H₉N₄O₃</td>
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<td>249</td>
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<td>56</td>
<td>24.73</td>
<td>24.69</td>
</tr>
<tr>
<td>10k</td>
<td>4-NHC₆H₄⁻</td>
<td>C₁₃H₁₁N₅</td>
<td>253</td>
<td>255</td>
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<td>27.57</td>
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<tr>
<td>10l</td>
<td>2,4-(Cl₂)C₆H₃⁻</td>
<td>C₁₃H₈N₄OCl₂</td>
<td>307</td>
<td>261</td>
<td>0.44</td>
<td>44</td>
<td>18.24</td>
<td>18.21</td>
</tr>
</tbody>
</table>

*TLC Solvent System : Hexane:Ethyl acetate(1:9)*
GRAPHICAL CHART NO. 10 : ANTIMICROBIAL ACTIVITY OF 3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-ISOXAZOLES
RESULTS & DISCUSSION

ANTIMICROBIAL ACTIVITY

Antibacterial activity

From the experimental data it has been concluded that the compounds bearing \( R = 4 \)-aminophenyl, 2-hydroxyphenyl and 3-hydroxyphenyl have shown maximum activity against \textit{B. coccus}. The compounds bearing \( R = 4 \)-hydroxyphenyl, 4-methoxyphenyl, 4-flourophenyl, 3-nitrophenyl and 4-aminophenyl displayed considerable activity against \textit{S aureus}.

In case of Gram negative bacterial strains, the significant activity was displayed by the compounds bearing \( R = 4 \)-hydroxyphenyl and 4-chloro phenyl against \textit{E. aerogenes}. and \( R = 4 \)-fluoro phenyl, 4-methoxyphenyl and 4-hydroxyphenyl against \textit{P. aeruginosa}.

Antifungal activity

All the compounds displayed mild activity except compound bearing \( R = 4 \)-2-hydroxyphenyl and 4-aminophenyl against \textit{A.niger}.

The antibacterial activity was compared with standard drugs viz. amoxicillin, benzoylpenicillin, ciprofloxacinc, erythromycin and antifungal activity was compared with standard drug viz. greseofulvin.
[C]

STUDIES ON
MICROWAVE INDUCED
ORGANIC REACTION
ENHANCEMENT
INTRODUCTION

In the last few years Microwave induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis\textsuperscript{395} & many researchers have described accelerated organic reaction and a large number of papers has appeared proving the synthetic utility of MORE chemistry in routing organic synthesis. It can be termed as "e-chemistry' because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry.

Microwave assisted synthesis in general is likely to have a large impact on synthetic organic chemistry in particular the medicinal/combinatorial chemistry communities compared to tradition processing of organic synthesis, microwave enhanced chemistry saves significant time and very often improves yields.

GENERAL PRINCIPLES

The microwave region of the electromagnetic spectrum lies between 1 cm and 1 m and in order to avoid interfering with radar and telecommunication activities which operate within this region, most domestic and commercial microwave instruments operate at 2.45 GHz. The heating effect utilised in microwave assisted organic transformations is due in the main, to dielectric polarisation, although conduction losses can be important particularly at higher temperatures. Whilst the polarisability of a molecule (determined by the Debye equation) is the sum of a number of contributions, only dipolar and interfacial polarisation are important to heating effects associated with microwave irradiation. When a molecule is irradiated with microwaves it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation and consequently the molecule continually attempts to realign itself with the changing field and energy is absorbed. It is particularly
convenient that qualitatively, the larger the dielectric constant the great the coupling with microwaves. Thus solvents such as water, methanol, DMF, ethyl acetate, acetone, chloroform, acetic acid and dichloromethane are all heated when irradiated with microwaves. Solvents such as hexane, toluene, diethyl ether, \( \text{CCl}_4 \), do not couple and therefore do not heat with microwave irradiation although it is of course possible to use mixtures comprising microwave active/microwave inactive solvents.

**POWER SOURCES**

The development of electron in tubes including those for the most microwave range, has been a mature field. Today it is feasible to generate almost any desired power level for microwave frequencies of practical interest limited only by cost.

Power sources in the millimeter wave range are mostly in the category of extended interaction Klystrons or narrow band backward wave oscillators. They are quite expensive and suffer from low life and efficiency. The most dramatic evolution of a microwave power is one of the cooker magnetron for microwave ovens. These tubes generate well over 700 Watt 2450 MHz into a matched load and exhibit a tube efficiency on the order of 70\%. It is feasible to utilize a number of such tubes to generate large total power eq. 25 or 50 Kw.

**APPLICATIONS IN ORGANIC SYNTHESIS**

The first applications of microwave ovens in organic synthesis began very recently. In the first experiments, Gedye\(^{396}\) and then Giguere\(^{397}\), provided evidence for dramatic accelerations in some classical organic reactions and these were ascribed to temperature and pressure effects, when performed in closed teflon vessels. Since solvents were used in these experiments, some problems with safe operation appeared, and explosions sometimes resulted. Further developments demonstrated the potential of solvent free reactions to solve these problems and to facilitate the scale up of preparative runs.
Three types of solvent free procedures can be coupled with microwave activation.

(i) Reactions between heat reactants, needing at least one polar molecule, as liquid-liquid or liquid solid systems. In this later case, reactions presumably occur at the interface due to adsorption of the liquid reactant at the surface of the solid one.

(ii) Reactions between supported reagents on solid mineral supports in dry media by impregnation of compounds on alumina, silicas or clays.

(iii) Phase Transfer Catalysis (PTC) conditions in the absence of organic solvent, i.e. when a liquid reagent acts both as a reactant and an organic phase. This last methodology can also be improved under sonochemical activation.

Microwaves constitute very original procedure for heating materials, clearly different from the classical ways. Their main advantages derived from the almost instantaneous "in core" heating of materials, in an homogeneous and selective manner. This technique proves to be excellent in case where traditional heating has a low efficiency because of poor heat transmission and hence local overheating is a major inconvenience.

The main interests can thus be listed as the rapid transfer of energy into the bulk of the reaction mixture, without inertia since only the product is heated and the ease of utilization. Furthermore as the depth of penetration in materials of the same order of magnitude as the wavelength, microwaves interact with substance of appreciable thickness (about 10 cm).

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions. Microwave reaction under solvent-free conditions are attractive in offering reduced pollution and offer low cost together with simplicity in processing and handling. The recent introduction of microwave synthesis has gained acceptance and popularity among the synthetic chemist community.
& it includes virtually all types of chemical reactions such as Diels-Alder, Claisen, Vilsmeier, Oxidation, Substitution, Cyclisation, Catalytic transfer hydrogenation, Knoevenagel condensation, oxime synthesis, alkylation, decarboxylation etc.

Malhotra V. et. al. have demonstrated one-pot condensation of chalcones with thiosemicarbazide in ethanol under strongly basic condensation. Microwave enhanced esterification of \( \alpha, \beta \)-unsaturated acids have been carried out by Kumar Mitra & co-workers. Microwave assisted fungicidal 1,2,4-triazines, 1,2,4-tetrazoles, pyrazoles and triazoles have been synthesised by Mazahir Kidwai & co-workers.

Some other organic synthesis like 1,2-dihydropyridines, phthalimide, & quinazolinone derivatives etc. and also enhanced by the microwave irradiation.

Recently, microwave assisted some new organic reactions have been carried out which include synthesis of pyrazolines, isoxazoles, cyanopyridines, quinoxalines and heterocyclic pyrazines, N-aryl phthalamic acids, substituted 2-pyridones, sulfonylbenzimidazole-4,7-diones and dihydropyrimidines with better biological activities.

As a part of ongoing research towards the non-traditional approach to the experimental setup of organic reaction, the concept of microwave enhanced reaction has been utilised from rapid and efficient synthesis of 6-isopropyl-5-(N-phenylaminocarbonyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thiones and 1-acetyl-3-aryl-5-[2’-aminopyrimidin-5’-yl]-pyrazolines. Q. Pro-M Microwave Oven is used as a microwave irradiation source. Conventional method & microwave technique has been compared in terms of yield and reaction period and data are cited in Table No. 1a and 7a.
SECTION-I : SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-(N-PHENYLAMINOCARBONYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES USING MICROWAVE INDUCED SYNTHESIS

SECTION-II : SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-ARYL-5-[2'-AMINOPYRIMIDIN-5'-YL]-PYRAZOLINES USING MICROWAVE INDUCED SYNTHESIS
SECTION - I
SYNTHESIS AND BIOLOGICAL SCREENING OF 6-ISOPROPYL-5-[N-PHENYLAMINOCARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

As microwave used to creat effect in organic synthesis, the “in situ” generation of heat is very efficient and can be used to significantly reduce reaction times of synthetically useful organic transformations. Thus microwave assisted organic synthesis has advantages over conventional technology. We have synthesised dihydropyrimidinethiones of type (I) by the condensation of 4-methyl-N-phenyl-3-oxo-pentanamide, thiourea and aryl aldehydes under microwave irradiation in few minutes.

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

The compounds of type (I) have been already synthesised using conventional method as reported earlier in Part-I, section-I (B), page No. 37.

Q. Pro-M Microwave Oven, Questron Technologies corporation-CANADA, sample preparation system : 220 VAC, 60 Hz is used as a microwave irradiation source and data are compared in terms of yield and reaction period have been cited in Table No. 1a.
TABLE NO. 1a : COMPARISION OF CONVENTIONAL METHOD AND MICROWAVE METHOD OF 6-ISOPROPYL-5-[N-PHENYLAMINO CARBONYL]-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONES

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>Thermal Reaction Period (hr.)</th>
<th>Yield (%)</th>
<th>Microwave Reaction Period (min.)</th>
<th>Yield (%)</th>
<th>M.P. °C</th>
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<tr>
<td>1a</td>
<td>C₆H₅⁻</td>
<td>8</td>
<td>55</td>
<td>3</td>
<td>61</td>
<td>238</td>
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<td>1b</td>
<td>2-Cl-C₆H₄⁻⁻</td>
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<td>42</td>
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<td>3-Cl-C₆H₄⁻⁻</td>
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<td>4</td>
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<td>1d</td>
<td>4-Cl-C₆H₄⁻⁻</td>
<td>9</td>
<td>46</td>
<td>3</td>
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<td>221</td>
</tr>
<tr>
<td>1e</td>
<td>2,4-(Cl)₂-C₆H₃⁻⁻</td>
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<td>40</td>
<td>4</td>
<td>49</td>
<td>261</td>
</tr>
<tr>
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<td>3-Br-C₆H₄⁻⁻</td>
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<td>50</td>
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<td>4-OCH₃-C₆H₄⁻⁻</td>
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<td>52</td>
<td>4</td>
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<tr>
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<td>38</td>
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<td>35</td>
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<td>48</td>
<td>4</td>
<td>55</td>
<td>236</td>
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SECTION - II
SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-ARYL-5-[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES BY MICROWAVE METHOD

As a part of our research programme towards the non traditional approach to the experimental set up of organic reactions, the concept of “Microwave induced Organic Reaction Enhancement” (MORE) chemistry has been utilised for rapid and efficient synthesis of some acetyl pyrazolines which is described as under. The synthesis was carried out by irradiating condensation of chalcone of type (VII) with hydrazine hydrate in glacial acetic acid.

![Chemical Reaction Diagram]

The constitution of the synthesized products have been characterized by using elemental analyses, infrared and $^1$H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

The compounds of type (VII) have been already synthesised using conventional method as reported earlier in Part-I, section-II (B), page No. 134

Q. Pro-M Microwave Oven, Questron Technologies corporation-CANADA, sample preparation system : 220 VAC, 60 Hz is used as a microwave irradiation source and data are compared in terms of yield and reaction period have been cited in Table No. 7a.
TABLE NO. 7a : COMPARISON OF CONVENTIONAL METHOD AND MICROWAVE METHOD OF 1-ACETYL-3-ARYL-5-
[2’-AMINOPYRIMIDIN-5’-YL]-PYRAZOLINES

<table>
<thead>
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<th>Comp. No.</th>
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<th>Thermal Reaction Period (hr.)</th>
<th>Yield %</th>
<th>Microwave Reaction Period (min.)</th>
<th>Yield %</th>
<th>M.P. °C</th>
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<td>55</td>
<td>8</td>
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<td>7c</td>
<td>4-OCH₃C₆H₄⁻</td>
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<td>70</td>
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<td>4-BrC₆H₄⁻</td>
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<td>9</td>
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<td>7h</td>
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</tr>
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<td>7i</td>
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<td>7j</td>
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<tr>
<td>7l</td>
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<td>50</td>
<td>10</td>
<td>57</td>
<td>180</td>
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</tbody>
</table>

CONCLUSION

We have demonstrated a rapid and general synthesis of acetyl pyrazolines and dihydropyrimidinithiones using a microwave oven. Microwave technology is emerging as an alternative energy source powerful enough to accomplish chemical transformation in minutes, instead of hours. Consequently, reactions exhibit cleaner products and more facile work-up procedures. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis. Moreover, it can lead to improve isolated yields compared to conventional technology.
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233. Mohammad Abid and Amir Azam;  
234. Ekta Bansal, V. K. Srivastava and Ashok Kumar;  
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268. U. P. Dayochenko; 

269. G. H. Sayed, R. R. Kassab; 

270. Okazoe Takashi; 

271. A. Samour, Y. Akhnoook and H. Jahine; 

272. Feng Shi, Shujiang Tu, Fung Fung and Tuanjie Li; 

273. Dao-Lin Wang & Kimiaki Imafu; 

274. Thiele Kurt, Von Be Benburg and Walter E; 

275. B. John ED., Freeman and Petey F. M.; 

276. V. Scott and Joseph; 

277. J. J. Baldwin, A. Scrilrine, G. S. Ponticello, E. L. Engelhardt and C. S. Sweet; 

278. N. Latif, M. Mishrky and N. S. Girgis; 

279. W. Von Behenburg, J. Engel, J. Heese and K. Thiele; 

280. L. Castedo, J. M. Quintela and R. Riguers; 


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283. Aivars Kruaze, Gunars Duburs, et. al.; 

284. Fatma E. Goda, Alaa A. M. Abdel-Aziz & Omer; 

286. G. S. Gadaginamath, A. S. Shya Digeri and R. R. Kavali; 

287. E. G. Hammung Abou, El-Hafezu Najia A. Abd, Midarus Wandall; 

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293. Harada Hironori, Takuwa Tomofumi, Okazaki Toshio, Hiranu Yusuke; 

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309. Rajul Jain, Frank Roschangar, Marco A. Ciufolini;
310. K. Folkers, S. A. Harris;
311. W. Russel Bowman, Colin F. Bridge, Philip Brookes, Martin O. Cloonan and David C. Leach;
312. Hu Zhiyong, and Wang Huilai;
313. U. Toru, T. Susumu, E. Masayuki and S. M. Sahara;
314. H. K. Rudolf, H. Walter D. Juergen and F. Peter;
315. H. Michael, Aasslein Jean-luc and H. Bertrand;
316. P. Fey, H. K. Rudolf H. Walter and K. Thomas;
318. R. W. Hartann, N. Reichert and S. Gozhring;
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321. F. Al-Omar, A. Abdul Zahar, A. El-Khair, and A. Adel;
322. F. Peter, D. Juergem, H. Rudolg, H. Walter and K. Thomas;
323. H. Posnes;
324. Mukhtar Hussain Khan, Raizul Haque and Nizamuddin;
325. Mukhtar Hussain Khan, Raizul Haque, Taruna Agrawal and Nizamuddin;  

326. M. K. Morishita, A. Sagisa and J. Masashi;  

327. I. J. Collins, L. P. David and M. C. Richard;  

328. Pednecker;  

329. J. E. Reiner, Lim-Wilby, R. S. Margeu, T. K. Brunck and Ha-Vong;  

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332. S. Asmaa, and S. Salem;  

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334. B. Shivakumar and L. G. Nargund;  

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416. Mazaahir Kidwai, Yogesh Goel & Rajesh Kumar;,
418. Abdol Reza Hajipoor, Shadpour E. Mallakpour and Gholamhasan Imanzadeh;
420. Vimesh M. Patel and Kishor R. Desai;
421. Werner-Seebacher, Giinther Michl, Ferdinand Belaj, Reto Brun, Robert Saf and Robert Weis;
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425. Vera L. M. Sena, Rajendra M. Srivastava, Shalom P. Oliveira and Vera L. M. Lima;
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427. Narimene Boufatah, Armand Gellis, Jose Maldonado and Patrice Vanelle;
428. Jiajian Peng and Youquan Deng:  

429 Jean Jacques Vanden Eynede, Nancy Hecq, Olga Kataeva and C. Oliver Kappe:  

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434. Weike Su, Jianjun Li, Zhiguo Zheng and Yinchu Shen:  

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440. V. M. Parikh;  

441. C. N. R. Rao;  

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R

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