1. INTRODUCTION

Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure their fitness. There is a lot of collaboration between chemists and biologists while searching for a lead on a new drug or doing research on a preclinical drug candidate. While looking into the drug safety profile, collaboration with toxicologists and pharmacologists is required. Drug discovery research is a highly creative and stimulating work environment where people are driven to succeed by personal and scientific objectives.

Heterocyclic compounds are organic compounds that contain a ring structure containing atom in addition to carbon, such as sulphur, oxygen, nitrogen as part of the ring. Many of the heterocyclic ring systems are of fundamental importance to living systems. For instance, nucleic acids are derivatives of the purine and pyrimidine ring systems. Many heterocycles have important pharmaceutical properties and have a wide range of applications: they are predominant among the types of compounds used as pharmaceuticals, as agro chemicals and as veterinary products. They are also used as optical brightening agents, as antioxidants, as copolymers, solvents, photographic sensitizers, corrosion inhibitors and additives with a variety of other functions. Many dye stuffs and pigments have heterocyclic structures.

Heterocyclic compounds are of fundamental importance to biological process and are widespread of natural products. Heterocyclic compounds are finding an increasing use as intermediates in organic synthesis. They offer a high degree of structural diversity and have proven to be broadly and economically useful as
therapeutic agents. Some heterocyclic amines (HCAs) found in cooked meat are known carcinogens.

1.1. 1,8-NAPHTHYRIDINE

Naphthyridine is the name commonly given to the fused-ring system resulting from the fusion of two pyridine rings through two adjacent carbon atoms, each ring thus containing only one nitrogen atom. This name was suggested by Reissert, who, in 1893, made the first representative of the series, since 1,8-naphthyridine was considered to be the naphthalene analogue of pyridine. Six possible naphthyridines are:

1,5-naphthyridine (1)
1,6-naphthyridine (2)
1,7-naphthyridine (3)
1,8-naphthyridine (4)
2,6-naphthyridine (5)
2,7-naphthyridine (6)

1,8-Naphthyridine derivatives are reported to possess a wide spectrum of biological activities such as diuretic, antimalarial, anti-inflammatory, antitumor, antihypertensive and antibacterial activities. 1,8-Naphthyridine derivatives have attracted considerable attention because the 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances, with various biological activities. Nalidixic acid (7), for example, possesses strong antibacterial activity and used mainly for the treatment of urinary tract infections.
with gram negative pathogens. In addition, Gemifloxacin (8) is antimicrobial and antibacterial. It is known that \((E)\) and \((Z)\)-\(O\)-(diethylamino)ethyl oximes of 1,8-naphthrydine series (9) are potential drugs for local anaesthesia\(^8\), and 1-(2-fluorobenzyl)-3-(2-tolyl)-1,8-naphthyridin-2(1H)-one (10) is used for the treatment of memory disorders, in particular, Alzheimer’s disease\(^9\). 2-Amino-\(N\)-hydroxy-1,8-naphthyridine-3-carboxamidine(11) possesses herbicidal properties and used for the selective control of weeds in barley, wheat, maize, sorghum and rice crops\(^{10}\).
Halogeno-1, 8-naphthyridine have proved to be valuable intermediates. Halogeno-1,8-napthyridine shows different antimicrobial activities. Examples are Enoxacin, Tosufloxacin, Trovafloxacin etc. 1,8-Naphthyridine derivatives also react with adenosine receptors of subtypes A₁ and A₂. The important biological properties just described stimulated studies on the synthesis of various functionalized (particularly, at positions 2, 4 and 7) 1,8-naphthyridines, with the goal of designing new drugs for oral administration. Some 3-phenyl-1,8-naphthyridines which carry piperidyl, piperazinyl or morpholinyl groups or an N-diethanolamine side-chain in the 2- or 7- and 2,7- positions have been reported to show significant activity as inhibitors of human platelets aggregation induced by arachidonate and collagen. In addition, 4-(N-methyleneacycloalkylamino)-1,8-naphthyridine derivatives substituted in positions 2 and 7 are effective as antihypertensive agents. 7-Amino-2-(4-carbethoxypiperazin-1-yl)-4-phenyl-1,8-naphthyridine has recently been synthesized and reported to have marked activity against mycobacterium tuberculosis.

1.1.1 Primary synthesis of 1,8-naphthyridine

Primary synthesis of 1,8-naphthyridines may be done by cyclization of appropriate aliphatic substrates, with or without auxiliary synthons, by cyclization of appropriate substituted pyridines with or without sythons or from other heterocyclic substrates by several process.
From a single pyridine substrate

5-Methyl-3-(m-tolylethynyl)-2-pyridinamine (12) on treatment with sodium ethoxide in the presence of ethanol on cyclisation produced 4-ethoxy-6-methyl-2-m-tolyl-1,8-naphthyridine (13). From (2-Ethoxycarbonylvinyl)-2-pyridinamine (14) on treatment with sodium ethoxide underwent cyclisation to form 1,8-naphthyridin-2(1H)-one (7) in ethanol.

\[
\text{C}_2\text{H}_3\text{ONa} \quad \text{(12)} \quad \text{C}_2\text{H}_3\text{ONa} \quad \text{(13)}
\]

\[
\text{N} \quad \text{NH}_2 \quad \text{CH}=\text{CHCO}_2\text{C}_2\text{H}_5 \quad \text{N} \quad \text{NH}_2 \quad \text{C}_2\text{H}_3\text{ONa} \quad \text{(14)} \quad \text{C}_2\text{H}_3\text{ONa} \quad \text{(15)}
\]

2,5-Bis (3-aminopropyl)pyridine (16) on treatment with NaNH₂ in toluene after cyclisation gave 2-(3-aminopropyl)-1,2,3,4-tetrahydro-1,8-naphthyridine (17). 6-(2-acetyl-1-methylethylidene) amino-2-pyridinamine (18) gives 5,7-dimethyl-1,8-naphthyridin-2-amine (19) after cyclisation on treatment with NaNH₂ in presence of phosphoric acid at 100°C.
\textbf{From pyridine substrate and synthon(S)}

3-(2-Nitrovinyl)-2-pyridinamine (20) underwent condensation with benzaldehyde (PhCHO) in xylene and gave 3-nitro-2-phenyl-1,8-naphthyridine (21)\textsuperscript{23}. 2-Pyridinamine (22) on treatment with benzaldehyde and subsequently with acetic acid produced 2-phenyl-1,8-naphthyridine-4-carboxylic acid (23) in ethanol\textsuperscript{24}.
2-Amino-3-pyridinecarbonitrile (24) on treatment with m-chlorobenzyl cyanide, KOH/H$_2$O on microwave irradiation produced 3-m-chlorophenyl-1,8 naphthyridin-2-amine (25). The same substrate (23) with ethyl cyano acetate in ethanol and trace amounts of piper dine gave 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (26)$^{25}$

- From other heterocyclic substrates
- Pyrido[2,3-d]pyrimidines as substrates

Pyrido[2,3-d] pyrimidine (27) with malononitrile in methanol, gave 2-amino-1,8-naphthyridine-3-carbonitrile (28) and with ethyl cyano acetate gave ethyl 2-amino-1,8-naphthyridine-3-carboxylate.(29)$^{26}$
Pyrrolo[2,3-b]pyridines as substrates

Pyrrolo[2,3-b]pyridines (30) underwent pyrolysis in chloroform to give a separable mixture of 1,8-naphthyridine (R=H) and 3-chloro-1,8-naphthyridine .(R= Cl) (31)

\[
\begin{align*}
\text{CHCl}_3 & \quad \text{N} \quad \text{N} \quad R \\
(30) & \quad \text{N} \quad \text{N} \\
(31)
\end{align*}
\]

1.1.2 Reactions of 1,8-naphthyridines

- **C-Amination**

  1,8-Naphthyridine (32) on treatment with NaNH₂ in NH₃ and then KMnO₄ gave 1,8-naphthyridin-2-amine (34) the intermediate dihydro adduct (33) was clearly involved.

\[
\begin{align*}
\text{NaNH}_2 & \quad \text{NH}_3 & \quad \text{[O]} \\
(32) & \quad (33) & \quad (34)
\end{align*}
\]

- **Halogenation**

  1,8-Naphthyridine hydro bromide (35) gave a separable mixture of 3-bromo-1,8-naphthyridine (36) and 3,6-dibromo-1,8-naphthyridine (37) on treatment with Br₂ in PhNO₂ at 175°C yield was 30% each.
N-oxidation

1,8-naphthyridine undergo oxidation in the presence of $\text{H}_2\text{O}_2$ and benzoic acid to form its 1-oxide derivative.$^{29}$

\[
\begin{align*}
\text{N-N} & \quad \text{H}_2\text{O}_2 \\
\end{align*}
\]

1,8-Naphthyridine-1-oxide (39) with o-methoxyphenyllithium gave 2-o-methoxyphenyl-1,8-naphthyridine (40) in diethylether.$^{30}$

\[
\begin{align*}
\text{N-N} & \quad \text{LiC}_6\text{H}_4\text{OMe} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{C}_6\text{H}_4\text{OMe} \\
\end{align*}
\]

1.2 Synthetic routes of 1,4-napthyridine nucleus

Four routes involved in synthesis of 1,8-napthyridine ring

a) Niementowski synthesis  b) Friedlander synthesis  c) Reductive cyclization  d) Intramolecular nucleophilic cyclization

Niementowski synthesis

In the first route Hitherto$^{31}$ described was an extension of the Niementowski synthesis to the preparation of 1,8-naphthyridine-2,4-diols. 7-phenyl - 1,8-naphthyridine-2,4-diols (42) by the condensation of ethyl-2-amino-6-phenyl nicotinate (41) with simple esters in the presence of sodium.
In the second route Friedlander was described for the synthesis of \([1,8]\) naphthyridine derivatives containing phosphorus. The first 2, 3 alkene substituted \([1,8]\) naphthyridine (44) bearing a phosphorus moiety have been synthesized by the Friedlander annulations of 2-aminonicotinaldehyde (43) with diphenyl phosphoryl cyclopentanones.

The Friedlander condensation of 2- amino nicotinaldehyde with active methylene compounds in the presence of catalyst Lithium chloride under the two non-conventional methods like microwave Irradiation and by grinding in a mortar afforded the corresponding 1,8 – Naphthyridines (45). Both these methodologies are attractive as they are relatively nontoxic, economical and highly effective. The results shows that microwave procedure as slightly superior to the solid-state methods in terms of reduced time period and better yields.
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- **Reductive cyclization**

The third route was investigated for synthesis of 1,2-dihydro-1-hydroxy 2-oxo-1,8-napthyridine-3-carboxylate (47) by reductive cyclization of B-(3-nitro-4-pyridyl)acrylic acid (46).34

![Reductive cyclization reaction](image)

- **Intramolecular nucleophilic cyclization**

The fourth route was investigated for synthesis of 1,2,3,4-Tetrahydro-3-phenyl-1,8-napthyridine (49) by intramolecular nucleophilic cyclization of a 3-(3-pyridyl)-propylamine (48) in the presence of sodium.

![Intramolecular nucleophilic cyclization reaction](image)

1.3 Preparation of halogeno-1,8-napthyridine

**Halogenolysis of 1,8-naptyridinones**

1,8-napthyridine-2-one reacts with phosphoryl chloride in microwave irradiation forms 2-chloro-3-substituted-1,8-napthyridine (50).35
1.3.1 Reactions of halogeno-1,8-napthyridine

Aminolysis

4-Bromo-1,8-napthyridine (51) gave 1,8-naphthyridin-4-amine (52) on treatment with NH$_3$ in phenol at 170\(^\circ\)C.

\[
\begin{align*}
\text{Br} & \quad \text{NH}_3/\text{C}_6\text{H}_5\text{OH} \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} & \quad \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

\[\text{Br} \quad \text{NH}_3/\text{C}_6\text{H}_5\text{OH} \quad \begin{align*}
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} & \quad \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{align*}\]

2-chloro-3-nitro-1,8-naphthyridine (53) gave 3-nitro-1,8-naphthyridin-2-amine (54) on treatment with NH$_3$ in ethanol at 110\(^\circ\)C.$^{36,37}$

\[
\begin{align*}
\text{Cl} & \quad \text{NH}_3/\text{C}_2\text{H}_5\text{OH} \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} & \quad \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{align*}
\]

\[\begin{align*}
\text{Cl} & \quad \text{NH}_3/\text{C}_2\text{H}_5\text{OH} \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} & \quad \\
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{align*}\]

Hydrolysis

In alkaline hydrolysis 2-chloro-1,8-napthyridine reacts with NaOH to from 1,8-napthyridine-2-(1H)-one$^{38}$ (55). In acidic condition 4-bromo-1,8-napthyridine with Hcl to from 1,8-napthyridine-2(1H)-one.$^{39}$
1.4 Preparation of amino-1,8-naphthyridine

❖ From Acylamino-1,8-naphthyridine

2-Acetamido-7-ethoxy-4-phenyl-1,8-naphthyridine (56) reflux with sodium ethoxide in ethanol gave 7-ethoxy-4-phenyl-1,8-naphthyridin-2-amine (57).\(^{40}\)

❖ Conversion of azido to amino naphthyridine

4-Azido-7-methyl-2-phenyl-1,8-naphthyridine (58) gave 7-methyl-2-phenyl-1,8-naphthyridin-4-amine (59) with Pd/C in methanol, H\(_2\)O at 20\(^{\circ}\)C\(^{41}\)
1.4.1 Reactions of amino-1,8-naphthyridine

2-p-(Benzyldeneamino) phenyl-1,8-naphthyridine (60) underwent oxidation to give 2-p-benzamidophenyl-1,8-naphthyridine (61) on treatment with $m$-ClC$_6$H$_4$CO$_3$H.$^{42,43}$

$$\begin{array}{c}
\text{N} = \text{CHC}_6\text{H}_5 \\
\text{N} = \text{C}_6\text{H}_5
\end{array}$$

(60) $\xrightarrow{\text{m-ClC}_6\text{H}_4\text{CO}_3\text{H}}$ (61)

1,8-Naphthyridine-2,7-diamine (62) with nitrosobenzene gave 2,7-bis phenylazo-1,8-naphthyridine (63) on treatment with alcoholic KOH in H$_2$O.$^{44}$

$$\begin{array}{c}
\text{N} = \text{Ph} \\
\text{N} = \text{NPh}
\end{array}$$

(62) $\xrightarrow{\text{C}_6\text{H}_5\text{NO}, \text{KOH}}$ (63)

5,7-Dimethyl-1,8-naphthyridin-2-amine (64, $R = \text{NH}_2$) gave 2-isocyanato-5,7-dimethyl-1,8-naphthyridine (65, $R = \text{NCO}$) as a minor product (7%) via an imidazo[1,2-a][1,8]naphthyridine intermediate. The same substrate (64, $R = \text{NH}_2$) with butyl isocyanate afforded 2-N-butylureido-5,7-dimethyl-1,8-naphthyridine (66, $R = \text{NHCONHBu}$) on reflux with toluene.$^{45}$

$$\begin{array}{c}
\text{R-NH}_2 \quad \text{(64)} \\
\text{(65)} = \text{R-NCO} \\
\text{(66)} = \text{NHCONHBu}
\end{array}$$
1.5 Preparation of 1,8-naphthyridine carboxylic acid

- By hydrolysis of 1,8-naphthyridinecarbonitriles

2-Phenyl-1,8-naphthyridine-3-carbonitrile (67, R= CN) gave the corresponding 3-carboxylic acid (68, R= CO₂H) on reflux with alcoholic KOH in water for 14 h at 70°C, the yield was found to be 76%.\(^4\)

\[
\begin{array}{c}
\text{N} \\
\text{Ph} \\
\text{CN} \\
\text{KOH/C₂H₅OH} \\
\text{N} \\
\text{Ph} \\
\text{COOH}
\end{array}
\xrightarrow{	ext{(67)}}
\begin{array}{c}
\text{N} \\
\text{Ph} \\
\text{N} \\
\text{CO₂H}
\end{array}
\]

- By oxidation of 1,8-naphthyridinecarbaldehydes

1,8-Naphthyridine-2,7-dicarbaldehyde (69, R= H) gave 1,8-naphthyridine-2,7-dicarboxylic acid (70, R =H) on refluxing with 80% HNO₃.\(^4\)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} \\
\text{CHO} \\
\text{R} \\
\text{OHC} \\
\text{HNO₃(R=H)or} \\
\text{NaClO₂(R=OC₈H₁₇)}
\end{array}
\xrightarrow{	ext{(69)}}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} \\
\text{CO₂H}
\end{array}
\]

1.5.1 Reaction of 1,8-naphthyridine carboxylic acid

Decarboxylation

7-Amino-4-oxo-1,4-dihydro-1,8-naphthyridine-2-carboxylic acid (65) gave 2-phenyl-1,8-naphthyridine (72) on treating with Cu bronze at 260°C.
1.6. Pyrazolones and Isoxazolinone:

1.6.1. Chemistry of Pyrazolones

The oxo derivatives of pyrazolines, known as pyrazolones, are best classified as follows: 5-pyrazolone, also called 2-pyrazolin-5-one (73); 4-pyrazolone, also called 2-pyrazolin-4-one (74); and 3-pyrazolone, also called 3-pyrazolin-5-one (75). Within each class of pyrazolones many tautomeric forms are possible; for simplicity only one form is shown.

Substitution at N1 decreases the possible number of tautomers: for 3-pyrazolones, two tautomeric forms are possible, (76) and (77), which in non polar
solvents are both present in about the same ratio. 5-pyrazolones exhibit similar behavior.

In 4-pyrazolones, the enol form predominates, although the keto form has also been observed. The tautomeric character of the pyrazolones is also illustrated by the mixture of products isolated aftercertain reactions. Thus alkylation normally takes place at C4, but on occasion it is accompanied by alkylation on O and N. Similar problems can arise during acylation and carbamoylation reactions, which also favor C4. Pyrazolones react with aldehydes and ketones at C4 to form a carbon–carbon double bond, eg (78). Coupling takes place when pyrazolones react with diazonium salts to produce azo compounds, eg (79).

Compounds of type (79) are widely used in the dye industry. The Mannich reaction also takes place at C4, as does halogenation and nitration. The important analgesic aminoantipyrine (80)on photolysis in methanol undergoes ringfission to yield (81).
1.6.2 Synthesis of pyrazolone derivatives

The pyrazolone-3-carboxylic acid (83) has been isolated by reaction of oxazolone (82) with hydrazonyl chloride.\textsuperscript{49}

The preferred synthetic method for the title compounds utilizes the reaction of hydrazines with bifunctional compounds, such as $\beta$-diketones and esters, and $\beta$-keto acetylenic compounds. In an alternative procedure, diazo compounds replace
hydrazines and ring formation takes place via 1,3-dipolar cycloaddition. Pyrazoles and pyrazolones are widely used in the pharmaceutical industry to alleviate inflammation, fever, pain, and infections. To a lesser extent, they are also used as insecticides and herbicides. Pyrazolones linked to azo compounds are extensively used in the dye industry; some pyrazolines display insecticidal activity.\textsuperscript{50}

Pyrazolones with a free NH group are easily nitrosated and give rise to nitrosamines, which cause tumors in the liver of test animals. The analgesics antipyrine (85) and aminopyrine (86), if admixed with nitrites, are mutagenic when tested \textit{in vitro}; however, when tested in the absence of nitrites, negative results are obtained\textsuperscript{51}.

\begin{center}
\begin{tikzpicture}
\t\node[draw,rectangle] (a) at (0,0) {\text{\textsuperscript{1}H\textsuperscript{2}N\textsuperscript{3}CH\textsuperscript{4}O}}; \\
\t\node[draw,rectangle] (b) at (0,2) {\text{\textsuperscript{5}CH\textsuperscript{6}CH\textsuperscript{7}}}; \\
\t\node[draw,rectangle] (c) at (1,0) {\text{\textsuperscript{1}H\textsuperscript{2}N\textsuperscript{3}CH\textsuperscript{4}}}; \\
\t\node[draw,rectangle] (d) at (1,2) {\text{\textsuperscript{5}CH\textsuperscript{6}CH\textsuperscript{7}}}; \\
\t\node[draw,rectangle] (e) at (2,0) {\text{\textsuperscript{1}H\textsuperscript{2}N\textsuperscript{3}CH\textsuperscript{4}}}; \\
\t\node[draw,rectangle] (f) at (2,2) {\text{\textsuperscript{5}CH\textsuperscript{6}CH\textsuperscript{7}}}; \\
\end{tikzpicture}
\end{center}

Pyrazolone-type drugs, such as phenylbutazone and febrylpyrazone, are metabolized in the liver by micro-somal enzymes, forming glucuronide metabolites that are easily excreted because of enhanced water solubility.

The pyrazolone derivatives, which include dipyrone (87), antipyrine (85), aminopyrine (86) and propyphenazone, are widely used analgesics. Dipyone, the most widely used pyrazolone, has been the most studied. Dipyone is an inhibitor of cyclo-oxygenase but, unlike aspirin, its effect is rapidly reversible. The inhibition of prostaglandin biosynthesis contributes to the analgesic activity of the pyrazolone
derivatives. Unlike the Non-steroidal anti-inflammatory agents (NSAIDs) generally, the pyrazolone derivatives antipyrine, aminopyrine and propyphenazone are minimally bound to plasma proteins. The pyrazolones undergo extensive biotransformation, aminopyrine and dipyrone being converted to active metabolites. The most frequently reported side effects of the pyrazolone derivatives are skin rashes. Gastrointestinal side effects are rare.

\[
\text{(87)}
\]

1.6.3 Important pyrazolone and isoxazoline derivative in pharmaceuticals:

Some of the pharmaceuticals that incorporate the pyrazole nucleus are given below. Their main uses are as antipyretic, anti-inflammatory, and analgesic agents. To a lesser extent, they have shown efficacy as antibacterial/antimicrobial, antipsychotic, anti-emetic, and diuretic agents. The analgesic aminopyrine, the antipyretic dipyrone, and the anti-inflammatory phenylbutazone (88), though once widely prescribed, are rarely used in the 1990s on account of their tendency to cause agranulocytosis. Pyrazolone derivatives as like benzimidazole derivatives have been found to possess some interesting pharmacological activities. eg. antipyrine, ampyrone, edaravone, etc.
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(88) 

(89) butaglycon

(90) feclobuzo,

(91) kebuzone

(92) sulfinpyrazone
Pyrazolones react with diazonium salts, an important process in the dye industry. The majority of dyes are having pyrazolone nucleus with an azo linkage attached at C4, eg, (97) and (98).
The survey of the pertinent literature reveals that isoxazolines have been found to possess a wide range of biological activity such as anti bacterial,\textsuperscript{52} anti HIV\textsuperscript{53}, anti-inflammatory\textsuperscript{54}, anticancer\textsuperscript{55}, etc. Some Isoxazole derivatives (99) have been reported as anti-tubercular, anti bacterial and antifungal agents.\textsuperscript{56}

![Isoxazole derivative (99)](image)

Azopyrazoles (100) and azoisoxazoles (101) are possessing good antifungal activity\textsuperscript{57}. Similarly, 2-alkyl isoxazolidine derivatives have been as antifungal agents.\textsuperscript{58}

![Azopyrazole (100) and AzoIsoxazole (101)](image)

1.7 PYRAZOLE

1.7.1 CHEMISTRY OF PYRAZOLE RING SYSTEM:

Pyrazole is a hetero aromatic compound, consists of doubly unsaturated five membered ring containing two adjacent nitrogen atoms (102). Pyrazole is a 1,2-diazole and as its name implies, it may be considered as an azapyrrole. Many drugs and medicinal (e.g. antipyrine) contain a pyrazole ring and many dye stuffs are derived from it.
Knorr introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by replacement of a carbon by nitrogen and he synthesized many members of the class and systemically investigated their properties.

**Chemical properties:**

1. Pyrazoles are aromatic compounds and the ring system is more stable than pyrrole and less reactive.
2. Electrophilic substitution reactions occur readily, the attack being at the 4th position.
3. Bromination can be effected in organic solvents using hypobromite to yield 4-bromo derivative.
4. Direct iodination occur using iodine and sodium acetate.
5. Nitration and sulphonation reactions are less facile.

The pyrazoles are class of heterocyclic compounds and the pyrazole skeleton constitutes an important central template for a wide variety of biologically active compounds. The pyrazole nucleus has been reported to possess a wide spectrum of biological activities such as anti-inflammatory, antibacterial, analgesic, antifungal, anti viral, Hypoglycemic, anticancer and antitubercular.
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Pyrazole related marketed drugs:

- Celecoxib
- Rofecoxib
- Valdecoxib
- Etoricoxib
- Deracoxib
- Meloxicam

1.8 Isoxazole

Isoxazole (103) is a five membered heterocyclic compound having two hetero atoms: oxygen at position 1 and nitrogen at position 2. Claisen first reported an isoxazole (103) for a product from the reaction of 1,3 diketone with hydroxylamine hydrochloride. Isoxazole nucleus has been reported to possess a wide spectrum of biological activities such as anti-inflammatory, analgesic, antituberculosis, Hypoglycemic, and antcancer.
1.8.1 Chemistry of Isoxazole

Isoxazoles can be prepared by various methods; some of them are described as under.

Crawley L. S. and Fan Shawe W. J. \(^{72}\) have prepared substituted isoxazole (104) from \(\alpha,\beta\)-unsaturated carbonyl compounds, hydroxyl amine hydrochloride and KOH in methanol.

\[
\begin{align*}
R-CH=CH-R^1 + \text{NH}_2\text{OH.HCl} & \rightarrow \text{R}^1
\end{align*}
\]

Kalirajan et al. \(^{73}\) have synthesized and check antimicrobial screening against various gram positive and gram negative bacteria and anti fungal activity against various fungal stains compared with standard drug (Ampicillin and Ketoconazole) using solvent control. \(^{74}\)
Isoxazole related marketed drugs:

\[
\begin{align*}
\text{Sulfisoxazole} & \quad \text{O} \quad \text{N} \quad \text{O} \quad \text{NH}_2 \\
\text{Zonisamide} & \quad \text{O} \quad \text{CH}_2 \text{SO} \quad \text{NH}_2
\end{align*}
\]

1.9 Pyrimidine-2-one

Pyridones, which belongs to an important group of heterocyclic compounds, have been extensively explored for their applications in the field of medicinal chemistry.

Pyridones, with a carbonyl group at position 2 (106) have been subject of extensive study in recent past.

Pyridone derivatives have been found to possess variety of therapeutic activities like antiviral\textsuperscript{75}, antimicrobial\textsuperscript{76}, anticancer\textsuperscript{77}, antiHIV\textsuperscript{78}, Pesticidal\textsuperscript{79}, Herbicidal.\textsuperscript{80} Pyridones are derivatives of pyrimidines with carbonyl group at 2-position (I). Some 2-pyridones are physiologically as well as pharmacologically important which areas under, eg. Ciclopirox (107), and Amrinone (108).
1.9.1 Chemistry of pyrimidine-2-one

K. Folkers and S. A. Harris have synthesized 3-cyano-2-pyridone (109) by the condensation of cyano acetamide with 1,3-diketone or 3-ketoester.

\[
\text{CH}_3\text{COCH}_2\text{COCH}_2\text{OC}_2\text{H}_5 + \text{NH}_2\text{COCH}_2\text{CN} \rightarrow \text{CH}_2\text{OC}_2\text{H}_5
\]

Pednekar have synthesized fused 2-pyridone derivatives (110), (111) and (112) as useful heterocyclic moieties as they possess broad spectrum of biological activities such as antiviral, CNS depressant, bactericidal and ulcer inhibitor.
Upadhyay et al.\textsuperscript{83} have documented cyanopyridone derivatives, which showed antifungal and antileishmanial activities. E. Amer\textsuperscript{84} prepared 3-cyano-2-pyridonederivatives (113) displaying high antimicrobial activity. Abou El-Fotooh and co-workers.\textsuperscript{85} have demonstrated pyridones (114) as anticancer agent.

\begin{align*}
\text{(113)} & \\
\text{(114)} & 
\end{align*}

1.10. **Introduction of analgesic activity**

1.10.1 **pain**

The struggle to relieve pain began with the origin of humanity. Ancient writings, both serious and fanciful, dealt with secret remedies, religious rituals and other methods of pain relief, slowly paving way to the present modern era of synthetic analgesics.

Tainter has divided the history of analgesic drugs into 4 major eras, namely:

a) The period of discovery and use of naturally occurring plant drugs.

b) The isolation of pure plant principles from the natural sources and their identification with analgesic action.

c) The development of organic chemistry and the first synthetic analgesics.
d) The development of modern pharmacologic techniques, making it possible to undertake a systematic testing of new analgesics.

Pain is sensation transmitted from sensory nerves through the spinal cord to the sensory area of the cerebrum where the sensations are perceived.

It is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Pain is referred to as the sensation of an injured tissue:

- Whenever there is a damage to a tissue
- During onset of a disease
- Due to inflammation
- Pain may be external (due to any injury; e.g. cut) or may be internal (due to onset of a disease; e.g. headache, muscular pain, etc.).

### 1.10.2 Types of pain

Pain can be classified as acute or chronic. The distinction between acute and chronic pain is not based on its duration of sensation, but rather the nature of the pain itself. In general, physicians are more comfortable treating acute pain, which has as its source soft tissue damage, infection and/or inflammation. It can be modulated and removed by treating its cause and through combined strategies using analgesics to treat the pain and antibiotics to treat the infection. In general, while it is uncomfortable to experience,
it is easy to treat; is distinguished by having a specific cause and purpose, and generally produces no persistent psychological reaction.\(^{86}\)

- **Acute pain** is also called as fast pain, perception is very rapid, usually within 0.1 second after a stimulus is applied, because the nerve impulses conduct along medium-diameter, myelinated axons called A-delta fibres. This type of pain also known as fast, sharp, or pricking pain. The pain felt from a needle puncture or knife cut to the skin. Acute pain is not felt in deeper tissues of the body.\(^{87}\)

- **Chronic pain** is also called as slow pain, by contrast, begins a second or more after stimuli is applied and then gradually increases in intensity over a period of several seconds or minutes. Impulses for slow pain conduct along small-diameter, unmyelinated C fibers. This type of pain, which may be excruciating, is also referred to as burning, aching, or throbbing pain. Slow pain can occur both in the and in deeper tissue or internal organs.\(^{87}\)

- **Cutaneous pain** is caused by injury to the skin or superficial tissues. Cutaneous nociceptors terminate just below the skin, and due to the high concentration of nerve endings, produce a well-defined, localized pain of short duration. Examples of injuries that produce cutaneous pain include paper cuts, minor cuts, minor (first degree) burns and lacerations.\(^{87}\)

- **Somatic Pain** is due to stimulation of nociceptors in the integument and supporting structures, namely, striated muscles, joints, periosteum, bones, and nerve trunks by direct extension through fascial planes and lymphatic spread.\(^{77}\)
Visceral pain, The cause for visceral pain could be spasm of the smooth muscles of hollow viscus, distention of the capsule of solid organs, inflammation, chemical irritation, traction or twisting of mesentery, ischemia and necrosis, or tumour encroachment of the pelvis and presacral regions.  

Referred pain the pain is felt in or just deep to the skin that overlies the stimulated organ. This pain may also felt in surface area far from the stimulated organ. In general, the visceral organ involved and the area to which the pain is referred are served by the same segment of the spinal cord. 

Phantom limb pain is the sensation of pain from a limb that has been lost or from which a person no longer receives physical signals like itching, pressure, tingling. Cerebral cortex interprets impulses arising in the proximal portions of sensory neurons that previously carried impulses from the limb as coming from the nonexistent limb. 

Neuropathic pain, or "neuralgia", can occur as a result of injury or disease to the nerve tissue itself. This can disrupt the ability of the sensory nerves to transmit correct information to the thalamus, and hence the brain interprets painful stimuli even though there is no obvious or known physiologic cause for the pain. Neuropathic pain is, as stated above, the disease of pain. It is not the sole definition for chronic pain, but does meet its criteria.
1.10.3 Physiology of nociception (Commonly physiology of pain)

- This section, except in the paragraph on pain in consciousness, for historical reasons uses pain to refer to nociception. Where both a historical pain term and a modern nociception term are common, a bracketed pain term is included. E.g. Nociceptors (Pain receptors).

- "Nociception is the term introduced almost 100 years ago by the great physiologist Sherrington in 1906 to make clear the distinction between detection of a noxious event or a potentially harmful event and the psychological and other responses to it\textsuperscript{90}.

- Nociception is the system which carries information about noxious stimulus, usually associated with tissue damage to the spinal cord and brain.

1.10.4 Transmission of nociception (pain) signals

There are 2 pathways for transmission of nociception in the central nervous system. These are the neospinothalamic tract (for fast pain) and the paleospinothalamic tract (for slow pain) as shown in Fig 1.1
Fig 1.1. Physiology of nociception

- **Fast pain** travels via type Aδ fibers to terminate on lamina I (lamina marginalis) of the dorsal horn of the spinal cord. Second order neurons of the neospinothalamic tract then take off and give rise to long fibres which cross the midline through the grey commissure and pass upwards in the contralateral anterolateral columns. These fibres then terminate on the reticular formation, Ventrobasal Complex (VBC) of the thalamus. From here, third order neurons communicate with the somatosensory cortex. Fast pain can be localised easily if Aδ fibres are stimulated together with tactile receptors.

- **Slow pain** is transmitted via slower type C fibres to laminae II and III of the dorsal horns, together known as the substantia gelatinosa. Second order neurons take off and terminate in lamina V, also in the dorsal horn. Third order neurons then join fibers from the fast pathway, crossing to the opposite side via the grey
commisure, and traveling upwards through the anterolateral pathway. These neurons terminate widely in the brain stem, with one tenth of fibres stopping in the thalamus, and the rest stopping in the medulla, pons and tectum of midbrain mesencephalon, periaqueductal grey. Slow pain is poorly localized.91

1.11 Introduction of anti-inflammatory activity

1.11.1 Inflammation

Inflammation92 is defined as the local response of living mammalian tissues to the injury due to an agent.

Agents causing inflammation are

- Physical agents like heat, cold, radiation, mechanical trauma.
- Chemical agents like organic and inorganic poisons.
- Infective agents like bacteria, viruses and their toxins.
- Immunological agents like cell-mediated and antigen-antibody reactions earliest response to tissue injury. These alterations include: haemodynamic changes and changes in vascular permeability.

- Cellular events:

The cellular phase of inflammation consists of 2 processes:

**Exudation of leukocytes:**

The escape of leukocytes from the lumen of microvasculature to the intestinal tissue is the most important feature of inflammatory response. In acute inflammation,
polymorphonuclear neutrophils (PMNs) comprise the first line of body defence, followed later by monocytes and macrophages.

1.11.2 Signs of inflammation

The Roman writer Celsus in 1st century A.D. named the famous 4 cardinal signs of inflammations as:

- Rubor (Redness)
- Tumour (Swelling)
- Calor (Heat)
- Dolor (Pain)

To these, fifth sign functio laesa (loss of function) was later added by Virchow.

As evident from the above discussion Inflammation is one of the causes of Pain, while Pain is one of the signs of Inflammation. Thus it can be inferred that Pain and Inflammation often occurs simultaneously.

1.11.3 Types of inflammation

Depending upon the defense capacity of the host and duration of response, inflammation can be classified as acute and chronic.

- Acute Inflammation is of short duration and represents the early body reaction and is usually followed by repair.
- Chronic Inflammation is of longer duration and occurs either after the causative agent of acute inflammation persists for a long time, or the stimulus is such that it induces chronic inflammation from the beginning.
Chronic inflammation is subdivided into 2 types

- Non-Specific, which the irritant substance produces a non-specific chronic inflammatory reaction with formation of granulation tissue and healing by fibrosis e.g. osteomyelitis, chronic ulcer.

- Specific, when the injurious agent causes a characteristic histologic tissue response e.g. tuberculosis, leprosy, syphilis.

### 1.11.4 Characteristics

Inflammation has two main components: **cellular and exudative**.

The **cellular component** involves the movement of white blood cells from blood vessels into the inflamed tissue. The white blood cells, or leukocytes, take on an important role in inflammation; they extravasate (filter out) from the capillaries into tissue, and act as phagocytes, picking up bacteria and cellular debris. They may also aid by walling off an infection and preventing its spread.

The **exudative component** involves the movement of fluid, usually containing many important proteins such as fibrin and immunoglobulins (antibodies). Blood vessels are dilated upstream of an infection (causing redness and heat) and constricted downstream while capillary permeability to the affected tissue is increased, resulting in a net loss of blood plasma into the tissue, giving rise to edema or swelling. The swelling distends the tissues, compresses nerve endings, and thus causes pain.\(^{93}\)

If inflammation of the affected site persists, released cytokines IL-1 and TNF will activate endothelial cells to up regulate receptors VCAM-1, ICAM-1, E-selectin, and L-selectin for various immune cells. Receptor up regulation increases extravasation of
Neutrophils, monocytes, activated T-helper and T-cytotoxic, and memory T and B cells to the infected site. Neutrophils are characteristic of inflammation in the early stages. They are the first cells to appear in an infected area, and any section of recently inflamed (within a couple of days or so) tissue viewed under a microscope will appear packed with them. They are easily identified by their multilobed nuclei and granular cytoplasm and perform many important functions, including phagocytosis and the release of extracellular chemical messengers. Neutrophils only live for a couple days in these interstitial areas, so if the inflammation persists for a longer duration then they are gradually replaced by longer lived monocytes.

1.11.5 Leukocytes and Cytokines

Various leukocytes are involved in the initiation and maintenance of inflammation. Generally speaking, acute inflammation is mediated by granulocytes or polymorphonuclear leukocytes, while chronic inflammation is mediated by mononuclear cells such as monocytes and macrophages.

These cells can be further stimulated to maintain inflammation through the action of an adaptive cascade involving lymphocytes: T cells, B cells, and antibodies as shown in Fig 1.2. These inflammatory cells are

- **Mast cells**, which release histamine and prostaglandin in response to activation of stretch receptors. This is especially important in cases of trauma.
• **Macrophages** which release TNF-α, IL-1 in response to activation of toll-like receptors.

![Figure- 1.2 Mechanism action of cox-2 receptor](image)

### 1.11.6 Remedies of pain and inflammation

An Analgesic may be defined as a drug bringing about insensibility to pain without loss of consciousness. In other words, agents that decrease pain or which relieves pain are called as Analgesics or Analgetics meaning Pain-killers. Although ‘Analgetic’ is grammatically correct, common use has made the term ‘Analgesic’ to ‘Analgetic’ for the description of pain killing drugs. Pain relieving agents are also called as antinociceptives. The effect of pain-killing is known as Analgesia. The effect is brought about by increasing the threshold of pain which is felt when an internal or external stimulus is given.

\[
\text{Threshold of Pain} = \frac{\text{Lowest perceptible degree}}{\text{Intensity of Pain}}
\]

From the above equation it is evident that as the **Threshold of Pain** is increased, the **Intensity of Pain** is decreased.

Analgesic drugs can be classified into two groups:
1.11.7 Opioids: Narcotic analgesics

Opioids analgesics are also known as narcotic analgesics. They are used to relieve severe pain and are often prescribed to patients recovering from operations and serious injuries. They are basically centrally-acting analgesics i.e they exert their action by acting on the Central Nervous System. Opioid analgesics are classified into two categories viz. Morphine drivatives and Phenanthrene derivatives. Example of opioid analgesics include morphine, papaverine.

![Figure: 1.3 – Inflammatory Pathways](image)

1.11.8 Non-opioids or NSAIDs:

Non-opioids, also called non-narcotic drugs or Non-steroidal anti-inflammatory drugs, usually abbreviated to NSAIDs, are drugs with analgesic, antipyretic and anti-inflammatory effects - they reduce pain, fever and inflammation. The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range
of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. They are basically peripherally-acting analgesics and exert their action by interfering with the formation of the eicosanoids from arachidonic acid. Many non-opioid analgesics can be bought over-the-counter at chemists and supermarkets. Clinical use of NSAIDs is associated with significant toxicity particularly in the gastrointestinal tract and kidney. Various approaches such as formulation & co-administration (of agents to protect the stomach), chemical manipulation and synthesis of new safer anti-inflammatory drugs are reported to overcome the toxicity of NSAIDs. The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen partly because they are available over-the-counter in many areas. Paracetamol (acetaminophen) has negligible anti-inflammatory activity, and is strictly speaking not an NSAID. NSAIDs within a group will tend to have similar characteristics and tolerability. There is little difference in clinical efficacy between the NSAIDs when used at equivalent doses. Rather, differences between compounds tended to be with regards to dosing regimens (related to the compound's elimination half-life), route of administration, and tolerability profile. NSAID drugs sometimes referred to as non-narcotic analgesic or aspirin-like drugs. The NSAIDs are classified as follows:

- **Salicylates e.g. Aspirin**
- **Arylalkanoic acids e.g. Diclofenac**
- **2-Arylpropionic acids (profens) e.g. Ibuprofen**
- **N-Arylanthranilic acids (fenamic acids) e.g. Mefenamic acid**
- **Pyrazolidine derivatives e.g. Phenybutazone**
- Oxicams e.g. Piroxicam
- COX-2 Inhibitors e.g. Celecoxib (FDA alert [1])
- Sulphonanilides e.g. Nimesulide
- Others e.g. Licofelone

### 1.11.9 Pharmacological actions of NSAIDs

All the NSAIDs have actions very similar to those of aspirin. The three main therapeutic effects are:

- An anti-inflammatory effect: modification of the inflammatory action,
- An analgesic effect: reduction of pain, and
- An antipyretic effect: lowering of body temperature when this is raised in disease. (i.e. fever)

In addition, all the NSAIDs share, to a greater or lesser degree, the same type of mechanism-based side effects. These include:

- Gastric irritation, which may range from simple discomfort to ulcer formation
- An effect on renal blood flow in the compromised kidney
- A tendency to prolong bleeding through inhibition of platelet function.

Controversially, it is argued that they may also all-but especially COX-2 selective drugs-increase the likelihood of thrombotic events such as myocardial infarction by inhibiting prostaglandin (PG I₂) synthesis.

A number of aryl and heteroaryl substituted compounds such as Diclofenac⁹⁷, lumiracoxib⁹⁸ Etodolac ⁹⁷ have been characterized as non-steroidal anti-inflammatory drugs (NSAIDS).
Important Marketed Non-Steroidal Anti-Inflammatory Drugs:

Diclofenac
Indomethacin
sulindac

PROFEN DERIVATIVES

Ibuprofen
Flubiprofen
Ketoprofen
Naproxen

OXICAMS
1.12 Introduction of antibacterial activity

A drug which kills or inhibits the growth of microbes is known as antimicrobial agent. In vitro tests are used as screening procedure for new agents to test the susceptibility if individual isolates from infections to determine which of the available drugs might be useful therapeutically. Due to development of sulfonamides and penicillin’s in vitro measurement of susceptibility of microbes to chemotherapeutic agents have been used. A drug is considered to be bacteriostatic or fungistatic when they inhibit the growth of bacteria or fungi respectively and bactericidal or fungicidal due to its ability to kill bacteria or fungi.

Important factors for antimicrobial activity are size of the inoculums, metabolic state of microbes, pH, temperature and duration of interaction, concentration of inhibitor and presence of interference substances. The development of resistance among various pathogenic microbes towards antibiotics has increased the impetus for investigating new antimicrobial agents.
index, a new series of related compounds are synthesized in the hope that one of them would be more effective than the existing one.

1.12.1 Anti bacterial activity:

The emergence of resistance to the major classes of antibacterial agent is recognized as a significant medical crisis and serious health concern. Particularly, the emergence of multi drug-resistance strains of Gram-positive bacterial pathogens is a problem of ever increasing significance. As the limited number of antimicrobial classes and the common occurrence of resistance within and between classes, the search for antibacterial agents with novel mechanism of actions is always remains an important and challenging task.

The control of microorganism is critical for the prevention and treatment of disease. Microorganisms also grow on and within other organism, and microbial colonization can lead to disease, disability, and death. Thus the control or destruction of microorganisms residing within the bodies of humans and other animals is great importance.

Modern medicine is dependant on chemotherapeutic agents, chemical agents that are used to treat disease. Chemotherapeutic agents destroy pathogenic microorganisms or inhibit their growth at concentrations low enough to avoid undesirable damage to the host. Most of these agents are antibiotics, microbial products or their derivatives that can kill susceptible microorganisms or inhibit their growth. Drugs such as the sulfonamides are sometimes called antibiotics although they are synthetic chemotherapeutic agents, not microbially synthesized.
Antibiotics are chemical substances excreted by some microorganism which inhibit the growth and development of other microbes. Some of these drugs that were obtained naturally were put to chemical modifications in attempts to enhance beneficial effects while minimizing the toxic effects. The resultant modified product is termed as semi synthetic antibiotics. Most antibiotic currently used are semi synthetic. The chemist has synthesized many drugs that have got the antibacterial property and less toxicity. These drugs are called synthetic antibiotic drugs. Naturally occurring antibiotic, their semisynthetic derivatives and synthetic antibiotics have got the same target. i.e., antimicrobial action. Hence all these drugs were put together to be called antimicrobial agents.

1.12.2. Drug resistance:

The emergence of drug resistance bacteria is posing a major problem in antimicrobial therapy. The frequency varies with the organism and the antibiotic used. At first, there is an emergence of a small number of drug resistant bacteria which sooner multiplies selectively in the presence of the drug at the cost of sensitive bacteria.

1.12.3. Types of drug resistance:

Drug resistance is of two types, primary and acquired.

1. Primary resistance: some bacteria possess an innate property of resistance to certain drug, e.g. resistance of *E.coli* to penicillin.

2. Acquired resistance: it results either from mutation or gene transfer.
1.12.4. Recent targets for finding antibacterial agents

Beta-Ketoacyl-acyl carrier protein (KAS) synthase III encoded by the fabH gene is thought to catalyze the first elongation reaction of type II fatty acid synthesis in bacteria and plant plastids. Beta-ketoacyl-acyl carrier protein synthase (KAS) I is an important enzyme system for the construction of the unsaturated fatty acid carbon skeletons characterizing E. coli membrane lipids. Recent research reported that Type II fatty acid synthesis (FAS II) pathway is an attractive target for their efficacy against infections caused by multi-resistant Gram-positive bacteria and Gram-negative bacteria. Among the related FAS II enzymes, beta ketoacyl-acyl carrier protein synthase (KAS) is an essential target for novel antibacterial drug design.

The enzyme bacterial peptide deformylase (PDF) is another novel target for novel antibacterial agents. The metalloproteases enzyme, Bacterial peptide deformylase (PDF) deformsylates the N-formyl methionine of newly synthesized polypeptides through Fe$^{2+}$-mediated catalytic reaction. PDF is essential in prokaryotes and this enzyme is absent in mammalian cells and provides a unique target for antimicrobial chemotherapy. Thus, it may be another target for new chemotherapeutic agents.

Lipopolysaccharides constitute the outer leaflet of the outer membrane of Gram-negative bacteria and are therefore essential for cell growth and viability. The glycosyltransferase (GT) enzyme, heptosyltransferase WaaC involved in the synthesis of the inner core region of lipopolysaccharides. It catalyzes the addition of the first L-glycero-d-manno-heptose molecule to one molecule of 3-deoxy-d-manno-oct-2-ulose acid (Kdo) residue of the Kdo2-lipid A molecule. These heptose is an essential
component of the Lipopolysaccharides core domain; its absence results in a truncated lipopolysaccharide associated with the deep-rough phenotype causing a greater susceptibility to antibiotic. Thus, WaaC represents a promising target in antibacterial drug design.\textsuperscript{106}

1.12.5 Anti fungal activity:

The object of antifungal drug discovery has become a subject of greater challenge due to increasing incidences of fungal drug resistance. This appears due largely to the extensive use of antifungal agents to treat fungal infections. In the past decade, number of patients diagnosed with fungal infections have increased drastically, whereas, relatively very few clinically useful drugs were discovered. The azole derivatives such as such as clotrimazole, fluconazole, itraconazole, ketoconazole, etc. have been widely used to treat a verity of fungal infections. These azole derivatives inhibit the fungal enzyme 14-alpha demethylase which is essential for the ergosterol synthesis pathway leads to the depletion of this steroidal compound in the cell membrane and accumulation of toxic intermediate sterols, leads increased membrane permeability and inhibition of fungal growth\textsuperscript{107-109}. But broad usage of these drugs led to development of acquired resistance especially among\textit{ Candida albicans}. Thus, searching not only improved version of existing drug but also for new drug targets has become an urgent need\textsuperscript{110}.recent reports showed that 2-glutamine, D-fructose-6-phosphate aminotransferase known as a new target for antifungals, it catalyzes a complex reaction involving ammonia transfer from L-glutamine to fructose-6-phosphate, followed by isomerisation of the formed fructosamine-6-phosphate to glucosamine-6-phosphate.\textsuperscript{111}