Chapter -2

Literature Reviews
1. Chemistry of Piperazine:

Pharmaceutical chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have six membered two nitrogen containing heterocyclic ring in their structures. Two such important compound are piperazine. Structural frameworks have been described as privileged structures and in particular, Nitrogen containing polycyclic structures have been reported to be associated with a wide range of biological activity. In the field of six membered heterocyclic structures piperazine nucleus shows various properties. The high therapeutic properties of the piperazine related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Piperazine show numerous physiological effect such as-

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Molecular Formula</td>
<td>C_4H_{10}N_2</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>86.1356</td>
</tr>
<tr>
<td>Composition</td>
<td>C(55.78%)</td>
</tr>
<tr>
<td>H(11.70%) N(32.52%)</td>
<td></td>
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<tr>
<td>Molar Refractivity</td>
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</tr>
<tr>
<td>Molar Volume</td>
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</tr>
<tr>
<td>Parachor</td>
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<tr>
<td>Index of Refraction</td>
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<tr>
<td>Surface Tension</td>
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<tr>
<td>Density</td>
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<tr>
<td>Polarizability</td>
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<tr>
<td>Monoisotopic Mass</td>
<td>86.084398 Da</td>
</tr>
<tr>
<td>Nominal Mass</td>
<td>86 Da</td>
</tr>
<tr>
<td>Average Mass</td>
<td>86.1356 Da</td>
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Piperazine is an organic compound that consists of a six-membered ring containing two nitrogen atoms at opposite positions in the ring. Piperazine exists as small alkaline deliquescent crystals with a saline taste. The piperazines are a broad class of chemical compounds, many with important pharmacological properties, which contain a core piperazine functional group. Given below is a brief account of various alterations conducted on piperazine ring containing few important marketed drug and their associated biological activities.

Piperazine is an interesting heterocyclic moiety as constituent of several biologically active molecules. The polar nitrogen atoms in the piperazine ring confer bioactivity to molecules and enhance favorable interaction with macromolecules [1,2]. Piperazinyl-linked ciprofloxacin dimers are potent antibacterial agents against resistant strains, antimalarial agents and potential antipsychotic agents [3-5]. Piperazine derivatives containing tetrazole nucleus have been reported as antifungal agents [6]. Substituted benzamide piperazine derivatives have shown strong agonistic activity while the substituted acetamide piperazine derivative have better dopamine D4 receptor agonist activity as compared to substituted benzamide piperazine derivatives [7-8]. Diphenyl piperazine derivatives possess broad pharmacological action on central nervous system (CNS), especially on dopaminergic neurotransmission [9]. N-Sulfonamide derivatives of 1- [bis(4-fluorophenyl)-methyl]piperazine exhibit potent antibacterial activity against *E. coli*, *P. vulgaris* and *S. typhi* [10]. Most of the quinoline drugs, such as norfloxacin and ciprofloxacin having piperazine nucleus have shown broad spectrum activity against respiratory, urinary, gastrointestinal tract, skin and soft tissue infection caused by bacteria [11]. Various cyanopiperazine derivatives have been known for their use in the synthesis of pharmaceutical intermediates, peptide analogues and antibacterial drugs [12-14]. Cyano derivatives of *N*-alkyl and *N*-aryl substituted piperazine derivatives exhibit potent activity against *Pseudomonas aeruginosa* [15]. The new piperazine linked chalcone derivatives show potent antibacterial activity against *S. aureus, E. coli, P. vulgaris* and antifungal activity [16].

Piperazine-2-carboxylic acid is a valuable building block and constituent of many current and potential drug molecules. Such molecules include antagonists for *N*-
methyl-Daspartic acid (NMDA) type glutamate receptors [17], indinavir [18] used to treat HIV infections and inhibitors for TNF-α converting enzyme (TACE) [19] and farnesyl protein transferase [20].

The chemistry of piperazine-2,5-dione 1 is of great interest since many natural products contain this ring system [21-23]. Derivatives of 1 are useful in peptide synthesis [24], in the synthesis of pyrazines [25-26], and in Diels-Alder reactions as a 4p component [27]. Recent studies showed that 3-salicylidene piperazine-2,5-dione 3 was supposed to be the most promising precursor for the synthesis of spiro[benzofuran-2(3H)-2’-piperazine]-3’,6’-dione as a main skeleton of aspirochlorine [28-29]. N-methyl piperazine also possesses a variety of potent biological activities [30-31].

Piperazine ring has been found to exhibit wide spectrum of biological activities and it is used in many drugs against different diseases. Some are known to exhibit antihypertensive [32], antiinflammatory [33], antiallergenic [34], antitussive [35], antibacterial [36], antiserotonic [37], antipsychotic [38], anti-influenza [39], anticancer [40], antischizophrenia [41], or central nervous system CNS-depressant activity [42]. And since substitute effects antibacterial activity of nitrogen-carbon-linked agents for example (azolylphenyl) oxazolidinones the activity expanded against the fastidious gram-negative organisms Haemophilus influenzae and Moraxella catarrhalis [43]. A new study revealing the strong antifungal activity of a newly synthesized derivative containing piperazine and triazole moieties (Itraconazole) [44].

Piperazine derived compounds like N-benzylpiperazine (BZP), 1-(3,4-methylenedioxybenzyl) piperazine (MDBP), 1-(4-methoxyphenyl) piperazine (MeOPP), 1-(3-trifluoromethylphenyl) piperazine (TFMPP), and 1-(3-chlorophenyl)piperazine (mCPP) belong to one of these newer groups of designer drugs that are mentioned as psychoactive chemicals in “scene books”[45-46], seizures of these drugs have been
made throughout the world [47-56].

A known centrally active 1-arylpiperazine [57], is the most extensively investigated compound in this group as it is an active metabolite of well known therapeutics such as trazodone, mepiprazol [58-61], nefazodone [62], etoperidone [63-65], and Furthermore, the mCPP moiety is also part of the cloperidone and mefeclorazine structures [66].mCPP has been found to interact with different serotonin receptors [67-69], as well as with adrenergic and dopaminergic receptors [70] and it leads to serotonin release [71-72]. It has been used as a probe drug of serotonin function [73]. Concerning drug abuse, its psychological effects are of particular interest.

**Important marketing drugs and its biological activity.**

<table>
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<tr>
<th>Piperazine drugs</th>
<th>Uses</th>
<th>References</th>
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<tr>
<td><strong>Trimetazidine</strong></td>
<td></td>
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<tr>
<td><img src="image" alt="Trimetazidine" /></td>
<td>Antianginals</td>
<td>[74]</td>
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<tr>
<td>1-(2,3,4-trimethoxybenzyl)piperazine</td>
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<td><strong>Amoxapine</strong></td>
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<tr>
<td>2chloro11(piperazin1yl)dibenzo[b,f][1,4]oxazepine</td>
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<tr>
<td>Compound</td>
<td>Structure</td>
<td>Activity</td>
</tr>
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<td><strong>Befuraline</strong></td>
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</tr>
<tr>
<td></td>
<td>1-benzofuran-2-yl(4-benzylpiperazin-1-yl)methanone</td>
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<tr>
<td></td>
<td>8-[4-(4-pyrimidin-2-ylpiperazin-1-yl)butyl]-8-azaspiro[4.5]decane-7,9-dione</td>
<td></td>
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<tr>
<td><strong>Flesinoxan</strong></td>
<td><img src="image3" alt="Flesinoxan" /></td>
<td>Antidepressant</td>
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<tr>
<td></td>
<td>4-fluoro-N-(2-[4-[(2S)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-5-yl]piperazinyl]ethyl)benzamide</td>
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</tr>
<tr>
<td><strong>Ipsapirone</strong></td>
<td>Antidepressant</td>
<td>[79]</td>
</tr>
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<tr>
<td><img src="image1" alt="Ipsapirone" /></td>
<td>9,9-dioxo-8-[4-(4-pyrimidin-2-yl)piperazin-1-yl]butyl]-9(\lambda)6-thia-8-azabicyclo[4.3.0]nona-1,3,5-trien-7-one</td>
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<tr>
<td><img src="image2" alt="Nefazodone" /></td>
<td>1(3[4(3-chlorophenyl)piperazin-1-yl]propyl)-3-ethyl-4-(2-phenoxyethyl)-1H-1,2,4triazol-5(4H)-one</td>
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<th><strong>Piberaline</strong></th>
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<td><img src="image3" alt="Piberaline" /></td>
<td>[4-(phenylmethyl)piperazin-1-yl]-pyridin-2-ylmethanone</td>
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<td><img src="image4" alt="Tandospirone" /></td>
<td>(1R,2R,6S,7S)-4-[4-[4-(pyrimidin-2-yl)piperazin-1-yl]butyl]-4-azatricyclo[5.2.1.02,6]decane-3,5-dione</td>
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<td><strong>Trazodone</strong></td>
<td>2{3[4(3chlorophenyl)piperazin-1-yl]propyl}[1,2,4]triazolo[4,3-(a)]pyridin-3(2(H))-one</td>
<td>Antidepressant</td>
</tr>
<tr>
<td><strong>Vilazodone</strong></td>
<td>5-(4-[4-(5-cyano-1(H)-indol-3-yl)butyl]piperazin-1-yl)benzofuran-2-carboxamide</td>
<td>Antidepressant</td>
</tr>
<tr>
<td><strong>Zalospirone</strong></td>
<td>(3(\alpha),4(\alpha),4(\alpha)β,6(\alpha)β,7(\alpha),7(\alpha)α)hexahydro-2-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-4,7-etheno-1(H)cyclobut(f)isoindole-1,3(2(H))-dione</td>
<td>Antidepressant</td>
</tr>
<tr>
<td>Meclozine</td>
<td>Antihistamine</td>
<td>[86]</td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td>((RS)-1-[(4-chlorophenyl)(phenyl)methyl]-4-(3-methylbenzyl)piperazine)</td>
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<th>Cinnarizine</th>
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<td>1-benzhydryl-4-cinnamyl-piperazine</td>
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<th>Hydroxyzine</th>
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<td>((\pm)-2-(2-{4-[4-chlorophenyl]-phenylmethyl}piperazin-1-yl}ethoxy)ethanol)</td>
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<tr>
<td><strong>Cetirizine</strong></td>
<td>Antihistamine</td>
<td>[89]</td>
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<tr>
<td>(±)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperaziny]ethoxy]acetic acid</td>
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<td>2(2{4[(R)(4chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic acid</td>
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<td>N-{4-[4-(4-fluorophenyl)piperazin-1-yl]butan-2-yl}pyridine-3-carboxamide</td>
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<th>[92]</th>
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<tr>
<td>2-[4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]piperazin-1-yl]ethanol</td>
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<tr>
<td><strong>Perphenazine</strong></td>
<td>Antipsychotic</td>
<td>[93]</td>
</tr>
<tr>
<td>------------------</td>
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<td>-----</td>
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</tbody>
</table>
| \[
2-\left[4-\left(3-\left(2\text{-chloro-10H-phenothiazin-10-yl}\right)\text{propyl}\right)\text{piperazin-1-yl}\right]\text{ethanol}
\] | | |

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<th><strong>Prochlorperazine</strong></th>
<th>Antipsychotic</th>
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| \[
10-\left[3-\left(4\text{-methylpiperazin-1-yl}\right)\text{propyl}\right]-2\text{-}
\left(\text{trifluoromethyl}\right)-10H\text{-phenothiazine}
\] | | |

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<tr>
<th><strong>Prochlorperazine</strong></th>
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<th>[95]</th>
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| \[
2\text{-chloro-10-}\left[3-\left(4\text{-methyl-1-piperazinyl}\right)\text{propyl}\right]-10H\text{-phenothiazine}
\] | | |
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<thead>
<tr>
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<th>Description</th>
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</tr>
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<tbody>
<tr>
<td><strong>Thiothixene</strong></td>
<td>(9Z)-N,N-dimethyl-9-[3-(4-methylpiperazin-1-yl)propylidene]-9H-thioxanthene-2-sulfonamide</td>
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<tr>
<td><strong>Quipazine</strong></td>
<td>2-piperazin-1-ylquinoline</td>
<td>[97]</td>
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<tr>
<td><strong>Imatinib</strong></td>
<td>4-[(4-methylpiperazin-1-yl)methyl]-N-(4-methyl-3-[[4-(pyridin-3-yl)pyrimidin-2-yl]amino]phenyl)benzamide</td>
<td>[98]</td>
</tr>
<tr>
<td><strong>Fipexide</strong></td>
<td>1-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-2-(4-chlorophenoxy)ethanone</td>
<td>[99]</td>
</tr>
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</table>
Antrafenine

\[
\text{2-\{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl\}ethyl 2-\{[7-(trifluoromethyl)quinolin-4-yl]amino\}benzoate}
\]

acts as an analgesic and antiinflammatory drug

[100]

6-Nitroquipazine

\[
\text{6-nitro-2-piperazin-1-yl-quinoline}
\]

serotonin reuptake inhibitor

[101]

\underline{para-Fluorophenylpiperazine}

\[
\text{1-(4-fluorophenyl)piperazine}
\]

psychedelic and euphoriant effects

[102]

\underline{meta-Chlorophenylpiperazine}

\[
\text{1-(3-chlorophenyl)piperazine}
\]

Psychoactive drug

[103]
<table>
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td><strong>2C-B-BZP</strong></td>
<td>1-(4-bromo-2,5-dimethoxybenzyl)piperazine</td>
<td>[104]</td>
</tr>
<tr>
<td><strong>Benzylpiperazine</strong></td>
<td>1-benzylpiperazine</td>
<td>[105]</td>
</tr>
<tr>
<td><strong>Olanzapine</strong></td>
<td>2-methyl-4-(4-methyl-1-piperazinyl)-10Hthieno[2,3-b][1,5]benzodiazepine</td>
<td>[106]</td>
</tr>
<tr>
<td><strong>Perospirone</strong></td>
<td>(3aR,7aS)-2-{4-[4-(1,2-benzisothiazol-3-yl)piperazin-1-yl]butyl}hexahydro-1H-isoindole-1,3(2H)-dione</td>
<td>[107]</td>
</tr>
<tr>
<td>Compound</td>
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<td>Reference</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------------------------------------------------</td>
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<tr>
<td>Ziprasidone</td>
<td>5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one</td>
<td>[108]</td>
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<tr>
<td>MK-212</td>
<td>2-Chloro-6-(1-piperazinyl)pyrazine</td>
<td>[109]</td>
</tr>
<tr>
<td>WAY-161503</td>
<td>(R)-8,9-dichloro-2,3,4,4a-tetrahydro-1Hpyrazino[1,2-a]quinoxalin-5(6H)-one</td>
<td>[110]</td>
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REFERENCE:

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527-552,[1991].
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2. **Chemistry of 1, 2, 4-Triazoles**

The synthesis of high nitrogen containing heterocyclic systems has been attracting increasing interest over the past decade because of their utility in various applications, such as propellants, explosives, pyrotechnics and especially chemotherapy [1]. In the medicinal chemistry, azoles are widely used and studied class of antimicrobial agents due to their safety profile and high therapeutic index. Among these, Conazoles are a major class ofazole-based drugs such as Itraconazole, Fluconazole, Voriconazole, Ravuconazole etc [2–5]. Some of other major applications of conazoles are on crop protection. As pharmaceuticals, they are used for the treatment of local and systemic fungal infections, which are important problems in phytopathology and especially in medicine, and they are frequently observed in immune-compromised patients suffering from AIDS or subjected to invasive surgery, anti-cancer therapy or graft receivers.

The diseases caused by fungal species cause not only improve the cost of therapy but also may lead mortality. Due to the inadequacy of alone standard antibiotic therapy in certain circumstances, more efforts have been focused on addressing the problem of multidrug-resistant bacteria and the decreasing of costs and consequences the obtained results from this [6–8]. Tuberculosis (TB) that is another mortal infection, causes to death with approximately three million patients in the world every year. According to the World Health Organization (WHO), about 30 million people will be infected within next 20 years [9]. Thus, the treatment of infections has become an important and challenging problem because of the increasing number of multi-drug resistant microbial pathogens [10]. In spite of a large number of antibiotics and chemotherapeutics available for medical usage, the increasing resistance made it necessary to continue the search for new antimicrobial substances. Though various molecules designed and synthesized for this aim, the efforts have demonstrated that 1,2,4-triazoles and their derivatives could be considered as possible antimicrobial agents, some of them studied in our laboratories [11–23]. Many of the azoles comprise the ring system of several natural and synthetic compounds which are important for living system and also for synthesis of important drugs, dyes and agricultural chemicals.
The presence of additional nitrogen atoms in the five-membered ring has important effects on the properties of the ring system. The additional nitrogen atoms bear a lone pair of electron in the plane of the rings. This lone pair is not involved in the $\pi$-electron system and thus provide a favorable point of attack for protons and other electrophiles. The additional nitrogen atoms also cause lowering in the energy levels of the $\pi$-orbitals (compared benzene and pyridine) so that the heterocycles are less ‘$\pi$-electron rich’. The overall result is to make electrophilic attack at carbon less easy than in pyrole, furan or thiophene. On the other hand, the additional nitrogen atoms have an inductive electron-withdrawing effect and can provide stabilization to negatively charged reaction intermediates.

Two examples of reactions which are rarely observed in pyrole, furan or thiophene, but which are much more common in the azoles, are nucleophilic additional elimination and the deprotonation of substituent methyl groups. Reactions of this type become increasingly favored as the stabilization of the intermediate anions increases. All the azoles are aromatic though resonance energies for many of them have not been measured, and their electronic structures follow their relationship to pyrole, furan and thiophene. The lone pair of electrons on the hetero atom contributes towards the aromatic sextet. For the construction of the molecular orbital structure, each carbon atom contributes one $p_z$ electron, the nitrogen atom gives the fourth electron and the second heteroatom i.e. nitrogen in pyrazole or oxygen in oxazole give two electrons to complete the aromatic sextet. It is obvious that theazole nitrogen possesses an electron pair which is situated in orthogonal fashion to the molecular $\pi$-cloud. It is this pair of electrons which permits the azoles to behave as basic compounds and as nucleophiles.

The triazoles are numbered to indicate the relative positions of the nitrogen atoms, tetrazole and pentazole are unambiguous names. 1,2,3-triazoles are surprisingly stable, when one considers that they contain three directly-linked nitrogen atoms, but on flash vacuum pyrolysis at 500°C they do lose nitrogen to give 2H-azirines, probably via the 1H-isomers.[48-49].

\[
\begin{align*}
\text{NH} & \quad \text{NH} \\
N & \quad N \\
\text{NH} & \quad \text{NH}
\end{align*}
\]

Osotriazole

\[
\begin{align*}
pK_a \text{ (proton added)} & \quad 1.2 \\
pK_a \text{ (proton lost)} & \quad 9.4
\end{align*}
\]

Triazole

\[
\begin{align*}
pK_a \text{ (proton added)} & \quad 2.2 \\
pK_a \text{ (proton lost)} & \quad 10.3
\end{align*}
\]

The additional hetero atoms make these systems less basic but more acidic than comparable 1,2- and 1,3-azoles. Each is subject to the same kind of tautomerism as discussed for the 1,2- and 1,3-azoles, in which the tautomers are equivalent but also, in these systems, to tautomerism which generates different arrangements.

Molecular geometry and dimensions

The intuitive statistical argument from two ‘hydrazinic’ N centers against one ‘amine’ N favours the less symmetrical 1H rather than the symmetrical 4H structure for 1,2,4-triazole. On the evidence of X-ray diffraction analysis the solid parent triazole has a planar structure with hydrogen bridges between N-1 and N-4 of neighboring rings; of the two N-H bond lengths implied, only that leading to N-1 is of the order required by covalent bonding. Confirmation from similar studies carried out at 160°C proves the molecular dimensions as shown in
following table for one unit of a pleated sheet linked by hydrogen bridges. Slightly different values are obtained at room temperature or in substituted aromatic triazoles.

Molecular Geometry of 1,2,4-triazole\(^a\) at 160\(^\circ\)C

<table>
<thead>
<tr>
<th>Angle ((^\circ))</th>
<th>Bond</th>
<th>Bond length (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-1-4</td>
<td>110.2</td>
<td>1-2</td>
</tr>
<tr>
<td>1-2-3</td>
<td>102.1</td>
<td>2-3</td>
</tr>
<tr>
<td>2-3-4</td>
<td>114.6</td>
<td>3-4</td>
</tr>
<tr>
<td>3-4-5</td>
<td>103.0</td>
<td>4-5</td>
</tr>
<tr>
<td>4-5-1</td>
<td>110.1</td>
<td>5-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N(1)-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C(3)-H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C(5)-H</td>
</tr>
</tbody>
</table>

\(^a\)The numbering refers to annular centers in 1\(H\)-1,2,4-triazole.

Different routes for synthesis of triazoles

**A] Synthesis of triazole rings from acyclic compounds:**

**i Methods employing hydrazine derivatives:**

The ease of forming C-N and C=N bonds as compared with difficulty of N-N formation practically prescribes the use of hydrazines in the synthesis of 1, 2, 4-triazoles. In addition to hydrazine, acylhydrazine, amidrazone or acylamidrazone can also be used for the synthesis of triazole analogues.
ii  Nitrilimine methods

Huisgen’s studies of 1,3-dipolar cycloadditions leading to a great variety of heterocyclic systems are applicable to the synthesis of triazoles and derivatives. Nitrilimines (5) formed by dehydrohalogenation of C-halobenzyl idenephenyl hydrazones (4) react with C≡N, C=N (as in CNO) to afford triazoles and triazolines.
i. Destruction of non-triazole rings:

Methods of this type are best considered as reactions of the fused ring systems. The example illustrated in the given scheme is of potential interest in pharmacology. The conversion of the 1-aminoadenosine (9) into the imidazolyltriazole (10) amounts to triazole formation from an amidrazone intermediate and a formyl group derived from the pyrimidine moiety.

\[
\begin{align*}
\text{N} & \text{N} \\
\text{H}_2\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{R} & \text{N} \\
\end{align*}
\]

(9)

\[
\begin{align*}
\text{OH} \\
\rightarrow \\
\text{N} & \text{N} \\
\text{H} & \text{N} \\
\text{N} & \text{N} \\
\text{R} & \text{N} \\
\end{align*}
\]

(10)

Where R = D-1-ribosyl

ii. Cleavage and recyclization of non-triazole rings:

Following scheme summarizes the overall reaction much used for the conversion of 1,3,4-oxadiazoles (X=O) (11) and thiadiazoles (X=S) (11) to triazoles (12a) and (12b).

\[
\begin{align*}
\text{R'} \text{X} \text{R''} & \text{R'''} \text{H} \\
\rightarrow \\
\text{R'} \text{H} \text{N} & \text{R''} \text{X} \text{R'''} \text{H} \\
\rightarrow \\
\text{R'} \text{N} & \text{R''} \text{H} \text{N} \text{R'''X} \\
\rightarrow \\
\text{R'} \text{R''} \text{R'''X} & \text{R'''} \text{N} \\
\end{align*}
\]

(11)

Where X=O, S
R', R''=H, Alk, Ar

(12a)

R'''=Alk, Ar, OH, NH
R''=H

(12b)

C] Nitrilimines derived from non-triazole rings:

Nitrilimines for the preparation of triazoles are often generated from tetrazoles or from 1,3,4-oxadiazoline (13) derivatives, which themselves are obtainable by thermolysis of tetrazoles.
D] Introduction and modification of functions on the triazole ring:

Specific functions in specified positions of the triazole ring are available in three ways (a) constituent portions of the ring to be formed carry the functions (b) the preformed triazole ring is substituted and (c) existing functions are modified.

i. Alkyl and aryl groups:

Alkyl and aryl triazolium compounds are formed mostly by quaternization of preformed triazoles, more rarely by rearrangement of oxadiazoles proceeding through acylamidrazone intermediates. An unusual method is the addition of the alkoxydiazenium fluoroborate (14) to the Schiff base (15) to form the triazolium salt (16) through a mechanism that may involve a triazolidine intermediate.

ii. Halo groups:

The application of the amidrazone method is limited. Most of the other published preparations are equally divided between electrophilic halogenation, nucleophilic displacement of halogen or nitro groups, and displacement of diazo or nitrosamino groups. The conversion of triazolinones into chlorotriazoles with phosphorus chlorides may be regarded as a nucleophilic displacement reaction of the hydroxytriazole tautomer, while the preparation of chlorotriazoles by the action of chlorine on thiones is regarded as oxidative chlorination.
iii. **Carbonyl functions:**

The two major techniques for the preparation of triazolecarboxylic acids are the amidrazone method and transformations of replacements of existing functions. In the former case one can introduce the carboxylic acid through starting materials such as (17). Alternatively, cyclization of other amidrazone can be accomplished with derivatives of oxalic acid, e.g. by converting the acylamidrazone (18) into the amide (19) from which the acid may be liberated by hydrolysis.

![Chemical Structures](image)

E] **Intramolecular condensations[50]**

i. **Ring closures in alkaline media:**

Ring closure of acyl derivatives of semicarbazides, thiosemicarbazides, or aminoguanidines in alkaline solutions is a method widely applied for the preparation of s-triazoles. Gehlen [51] reported that 3-hydroxy-5-alkyl-s-triazoles (20) are produced in 40-50% yield by this method.

![Chemical Structures](image)

ii. **Ring closures in acidic media:**

In concentrated hydrochloric acid, thiourazole (21) has been obtained from carbamylthiosemicarbazide [52] (22, R=H), but phenylcarbamyl-thiosemicarbazide (22, R=C₆H₅) apparently is changed into 2-amino-5-hydroxythiadiazoles.[53] From (23) in concentrated hydrochloric acid, 4-aminodithiourazole is obtained.[54]
iii. **Oxidative ring closures in the presence of peroxide:**

From the S-methylthiosemicarbazone of benzaldehyde, 3-phenyl–5-methyl–thio-1,2,4-triazole is obtained in an unspecified good yield by peroxide oxidation.\[55\]

iv. **Thermally induced ring closure:**

Several acyl derivatives of semicarbazides, thiosemicarbazides, and aminoguanidines change into 1,2,4-triazoles when heated.

F] **Molecular rearrangements:**

Hydroxy-1,2,4-triazoles are obtained on pyrolysis of hydrazones of pyruvylhydroxamic acids, the Gastaldi reaction.\[56\] In an illustration of the reaction, 1-phenyl-3-methyl–5-hydroxy-1,2,4-triazole is obtained from the phenylhydrazone of pyruvylhydroxamic acid in propionic anhydride.
Unclassified methods:

Certain examples of \(s\)-triazole preparations appear unrelated to other methods and have remained undeveloped. In one instance, a triazolotriazole (29) obtained from benzalizine (28) and cyanic acid has been transformed into 1-benzyl-3-phenyl-5-hydroxy-1, 2, 4-triazole (30), identical with the product obtained on oxidation of the benzaldehyde derivative of 2-benzylsemicarbazide.[57]

Literature survey

Khosrow Zamani et al [58] and Monika Wujec et al [59] synthesized some new 3,5-disubstituted-1,2,4-triazoles (32) and their derivatives through the intramolecular cyclization of 1,4-disubstituted thiosemicarbazides (31).
Ranjitbhai K. Patel

Ph.D. Thesis

Chapter 2

Bahittin Kahveci et al [60] and Shirodkar P Y et al [61] synthesized different kinds of 1, 2, 4-triazole derivatives and screened for their antitumor activity and found to be weakly cytotoxic. Haydar Yuksek et al [62] synthesized 4-arylamino-4,5-dihydro-1H-1,2,4-triazole-5-one derivatives and checked acidic properties of these new potential biologically active compounds.

Among the triazole, studies for Loreclezole (33) have shown anticonvulsant [63] GABA agonist that binds allosterically to the GABA$_A$ receptor [64] and also showed antiepileptic [65] activity. Gadaginamath G S et al [66] synthesized triazoles (34) and were found to exhibit a wide spectrum of biological activities.[67-73] They have synthesized some bio-dynamic heterocyclic systems at position-5 linked through methoxy bridge with a view to prepare biheterocycles to enhance biological activities.

Xu Pengfei Y X et al.[74-81] have synthesized thiosemicarbazides, triazoles, thiadiazoles and oxadiazoles with 6-nitrobenzimidazoles (35) in one framework. Jingde Wu et al [82] synthesized novel derivatives of 4-amino-3-(2-furyl)-5-mercapto-1,2,4-

\[
\text{RNH}_2 + \text{CS}_2 / \text{NH}_3 + \text{Ph}(\text{NO})_2 \rightarrow \text{RNCS} + \text{RNH}_2
\]

Where R' = CH$_3$/C$_2$H$_5$/CH$_3$Ph/CH$_3$COOH
R = p-CH$_3$C$_6$H$_4$

Where Ar = Ary groups, R = Phenyl, 4-chlorophenyl
triazole (36) as potential HIV-1. Currently non-nucleoside reverse transcriptase inhibitors (NNRTIs) have found to be widespread use in HIV therapy in multidrug treatment regimes and in highly active antiretroviral therapy (HAART) [83].

Svensson [84] et al synthesized 2,4-dihydro-[1,2,4] triazole-3-thione (37). These compounds are inhibitors of the enzyme myeloperoxidase (MPO) and are thereby particularly useful in the treatment of prophylaxis of neuroinflammatory disorders. Hardtmann G E et al [85] have prepared tricyclic 1,2,4-triazoloquinazolines (38) and tested them for antibacterial activity. The synthesized compounds were also tested for anti-inflammatory activity at 3-200 mg/kg, tranquilizer at 5-200 mg/kg and virucidal against pot viruses at 0.01-10 µg/ml.

Udupi R.H. et al [86-88] synthesized different kinds of 1,2,4-triazole derivatives by treating acid hydroxide with alcoholic KOH/CS₂ and further with acid hydroxide and tested them for anti-inflammatory and analgesic activities. R.R. Kamble et al [89-90] have developed a 3’-substituted-2-aryl-5-methyl-5’-thioxo-[4,4’-bi-4H-1,2,4-triazol]-3(1’H,2H)-ones (39) and found interesting properties, such as antinociceptive [91], anticancer [92] and plant growth regulative activities. [93] Some 1,2,4-triazole
derivatives also exhibit bacteriostatic, hypoglycemic and antiviral activities. Kane J.M. et al [97] synthesized 1,2,4-triazole derivatives (40) as potential anti-tumor agents.

\[
\text{Where } R = \text{Aryl groups, } R' = \text{Alkyl groups}
\]

Goknur Aktay et al [98] have synthesized 3-[1-(4-(2-methylpropyl)phenyl)ethyl]-1,2,4-triazole-5-thione (41) and its bicyclic condensed derivatives 6-benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones (42) and demonstrated that they possess moderate anti-inflammatory activity against carrageenan induced mice paw edema.

\[
\text{Where } R = 4-\text{Cl}, 3-\text{CHCl}_3, 2-\text{OCH}_3
\]

Mhasalkar M Y et al [99] synthesized some 5-substituted, 4-(substituted aryl), 3-mercapto 1,2,4-triazoles (43) which showed antifungal activity. Similarly 5(p-sec-amylyphenyl) methoxy-3-mercapto1,2,4-triazole (44) showed good antifungal activity [100].

\[
\text{Where } R = \text{Aryl groups, } R' = \text{Alkyl groups}
\]
Carmen Lopez et al synthesized series of series of [1,2,4]triazolo[1,5-c]quinazolines (45) derivatives which are active against allergic asthma.

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{R} & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{N} & \quad \text{NH}_2
\end{align*}
\]

(45)

Where \( R = \text{Heteroaryl} \)

Importance of 1,2,4-triazoles as analytical reagents [101] Substituted 1,2,4-triazoles find many useful applications. Some of them are used as analytical reagents for determination of boron,[102] antimony[103] and cobalt.[104] Other triazoles find many synthetic uses as halogenating agents[105] or as activating polymeric reagents.[106]

Now 1,2,4-triazole derivatives are widely used as biocides [107] and as antifungal agents.[108] Several 1,2,4-triazoles derivatives find applications as photographic reagents.

**Commercially available 1,2,4-triazoles as antimicrobial agents**

Although dozens of 1,2,4-triazoles have been synthesized and reported, the most notable ones being developed, or used, as a medicine worldwide include Fluconazole,[109] Ribavirin,[110] Triazolam, Itraconazole, Viramidine,[111] Voriconazole [112] and Terconazole.
1,2,4-Triazole as agricultural importance

The Thazole moiety is an important and frequent insecticidal, agrochemical structural feature of many biologically active compounds such as cytochrome P450 enzyme inhibitors [113] and peptide analog inhibitors [114]. Recently, much attention has been focused on 1H-1,2,4-triazole derivatives for their broad-spectrum activities, such as fungicidal, herbicidal, anticonvulsant and plant growth regulatory activities [115-117]. Further, the disubstituted 1,2,4-triazole derivatives were also reported to show antifungal, insecticidal, herbicidal and anti-inflammatory properties which were similar to 1H-1,2,4-trizole derivatives [118-120]. 1,2,4-Triazole and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial, and biological activities [121-122] Some of agricultural 1,2,4-triazole derivatives such as Azocyclotin, Bitertanol, [123] Cyproconazole, Epoxiconazole, Flusilazole, Triadimenol, Propiconazole, Tebuconazole and Triazophos.
Commercially available 1,2,4-triazoles as antifungal agents

Looking to the pharmaceutical applications of 1,2,4-triazoles derivatives, in this section we have planned to synthesized some biologically active heterocyclic compounds which contain triazole moiety.
REFERENCE :
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82. Jingde Wu, Xinyong Liu, Xianchao Cheng, Yuan Cao & Defeng Wang; Molecules, 12, 2003 [2007].


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104. Calzolari C. & Favretto L.; Analyst, 93, 494 [1968].


3. Chemistry of Pyrazole:

Pyrazole refers both to the class of simple aromatic ring compounds of the heterocyclic series characterized by a five membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Being so composed and having pharmacological effects on humans, they are not known to occur in nature.

Pyrazole exhibits characteristic reactions of pyrrole and pyridine because of containing pyrrole type and pyridine type nitrogen atoms at the position-1 and position-2. Pyridine type nitrogen is susceptible to electrophilic attack but it is less nucleophilic than the pyridine nitrogen atom. The hydrogen atom attached to the nitrogen atom in pyrazole is more acidic than the pyrrolic N-H in pyrrole and can be easily removed by nucleophiles. Pyrazole exists in two tautomeric forms.

Heterocyclic compounds are predominant among the types of compounds used as pharmaceutical, agrochemical and veterinary products. One of the most useful classes in this category is pyrazole. The pyrazole ring consists of a doubly unsaturated five membered ring containing two adjacent nitrogen atoms. In 1983, Knorr [1-2] first
synthesized a compounds by the reaction of ethyl acetoacetate with phenylhydrazine, which yields 1-phenyl-3-methyl-5-pyrazoline. The name pyrazole was given to such compounds because the nucleus was derived from pyrrole by replacement of carbon by nitrogen \( [3] \). Much research has been carried out with the aim to find the therapeutic values of pyrazole moiety, since their discovery \( [4-6] \). Various pyrazole and its derivatives have been used in many drugs \( [7-9] \).

![Pyrazole Structure](image)

Different methods of preparation of pyrazole are available in literature. Palmey synthesized two structurally isomeric pyrazoles by the reaction of the substituted hydrazines with 1,3-dicarbonyl compound \( [10] \). By the reaction of ethyl acetoacetate with aryl hydrazine hydrate also, Esribano et al. synthesized some pyrazoles \( [11] \). Jacobs reported the synthesis by the reaction of acetylene with diazomethane \( [12] \) where as Singh and Ojha synthesized pyrazoles by the reaction of ethyl acetoacetate with aryl hydrazines \( [13] \). Sime Workes reported synthesis by reactions of acetonitrile derivatives with (DMF-DMA) \( [14] \), where as others synthesized by the cyclocondensation of monosubstituted hydrazines with enamiones afforded pyrazoles \( [15] \). Various methods for the preparation of pyrazole have been cited in literature.
(1) L. Knorr [16] has synthesized two structurally isomeric pyrazoles by the condensation of substituted hydrazines with 1,3-dicarbonyl compounds.

\[
\begin{align*}
R_1 & \quad + \quad H_2N-NH & \quad \rightarrow \quad R_1 & \quad + \quad H_2O \\
R_2 & \quad + \quad Ar & \quad \rightarrow \quad R_2 & \quad + \quad Ar \\
\text{(III)} & & \\
\end{align*}
\]


\[
\begin{align*}
\text{C}_6H_5-N=NC_6H_5 & \quad + \quad \text{Ph-CO} & \quad \rightarrow \quad \text{C}_6H_5-N=NC_6H_5 \quad + \quad \text{Ph-CO} \\
\text{KOH-MeOH} & \quad \rightarrow \quad \text{HO-C}_6H_5 \quad + \quad \text{Ph-CO} \\
\text{(IV)} & & \\
\end{align*}
\]

(3) R.C. Boruah [18] et al suggested one pot pyrazole from formylamides.
(4) by the reaction of 1,3-dinitroalkanes with hydrazines [19].

(5) H.V. Pechamann [20] has synthesized pyrazoles by the reaction of acetylene and diazomethane.
THEURAUPETIC IMPORTANCE

Pyrazole derivatives have been reported to be associated with diverse biological activities. Drug molecules having pyrazole nucleus with good pharmacological activities are listed below.
Zaleplon
(Sedative, Hypnotic)

Tepoxalin
(Antiinflammatory)

Celecixib
(Antiinflammatory)

Novalgin
(Antipyretic, Analgesic)
Pyrafluprole  
(Insectiside)

Oxyphenbutazone  
(Antiarthritic)

Chlorprazophos  
(Insectiside)

Stanozolol  
(Insectiside)
Pyrazole derivatives were prepared and tested for a variety of biological activities such as antitumor \([21,22]\), anticancer \([23]\), antiviral \([24]\), anti-inflammatory \([25]\), antiepileptic \([26]\), antiHIV \([27]\) etc. Many pyrazoles are known to be used as antiproliferature agent \([28]\), protein kinase inhibitors \([29]\), herbicidal \([30]\), CNS depressant \([31]\), antiulcer \([32]\), neurotoxin receptor \([33]\), immuno suppressants \([34]\) etc. Freddy et al reported the biological activity of 4-5-dihydro-3-phenyl-1H-pyrazols\([35]\). Shimzo and co-workers have also synthesized some pyrazoles derivatives and reported their herbicidal activity \([36]\). Feid-allah-hassan reported antidiabetic and antibacterial activity of some other pyrazoles \([37]\). El-emery et al synthesized 1,3-diphenyl pyrazole derivatives and reported their variety of biological activity (III) \([38]\). Edgardo et al reported the glycine transport-2 inhibitors activity of some pyrazoles \([39]\). Recently, Wilst et al discovered pyrazole as potential glucocorticoid receptor Ligand \([40]\) where as Prasanna and co-workers also reported pyrazoles as COX-2 inhibitors\([41]\).

Menozzi and co-workers \([42]\) have synthesized a series of N-substituted-4-carboxy-1-phenyl-1H-pyrazole-5-propanamides. In which some compounds showed a platelet antiaggregatin activity in vitro superior of comparable to that of acetyl-salicylic acid, as well as moderate anti-inflammatory, analgesic and antipyretic activities in rats or mice.

Naito et al \([43]\) have synthesized pyrimidinyl pyrazole derivatives which exhibited a potent cytotoxic activity against some tumor cell lines including multidrug resistant cell lines due to the overexpression of p-glycoprotein. Several new 1-methyl-5-[substituted-4-oxo-1,2,3-benzotrizin-3-yl]-1H-pyrazole-4-acetic acids and their ethyl ester derivatives were prepared and tested for analgesic and anti-inflammatory activities. Acute toxicity, ulcerogenic effect, and as in vitro inhibitors of 3a-hydroxy steroid dehydrogenase by Giuseppe daidone \([44]\). Ejima Akio et al \([45]\) have synthesized pyrazole derivatives as antitumoeor agents (VIII).
Steven W. Djuric and co-workers [46] have identified a series of bis(trifluoromethyl)pyrazoles (BTPs) as a novel inhibitor of cytokine production and even IL-2 production with a 10-fold enhancement over cyclosporine in an ex vivo assay.

Nagaaki sato et al [47] have prepared arylpyrazole derivatives and evaluated as neuropeptide Y5 receptor antagonist. One of the compound with chiral 2,3-dihydro-1H-cyclopenta[a] naphthalene moiety, showed good binding affinity and antagonistic activity for the Y5 receptor. Virinder S. Parmar et all [48] have synthesized pyrazole derivatives (IX) and studied their antiinvasive activity.

Carbau romuald and co-workers [49] have reported pyrazole derivatives useful as reverse transcriptase inhibitors for the treatment of HIV infection. J. Scott Sawyer et
al [50] have developed an interesting series of pyrazole based inhibitors of the transforming growth factor-b Type I receptor kinase domain. David L.S. et all [51] have reported pyrazoles as activators of the nitrile oxide receptor and soluble guanlate cyclase agent.

Akihiko Tanitame and co-workers [52] have synthesized new pyrazole derivatives and found that 5-[(E)-2-(5-chloroindol-3-yl)vinyl]pyrazole possesses potent antibacterial activity and selective inhibitory activity against bacterial topoisomerases. Many of the synthesized pyrazole derivatives were potent against clinically isolated quinolone of coumarin-resistant gram-positive strains.

T. van Herk et al [53] have demonstrated pyrazoles as nicotinic acid receptor(X). Atkinson R N et al [54] have synthesized pyrazoles as sodium channel blocker(XI). Pyrazole derivatives as TGF-13 inhibitors have been suggested by Gellibert francoise et al [55].

A series of 3-(4-phenoxy phenyl)-1H-Pyrazoles (XII) were synthesized and characterized as potent state-dependant sodium channel blockers by Ji Yang and co-workers [56].
Zainaba D. et al. [57] have investigated 1-phenyl-3-toluyl-4-[ortho-1-(N-ethyl-2’-methylpropylamine)] phenylpyrazole as antifungal agent and showed that mycelial growth and conodial germination of fungi were blocked by the compound. Adnan and Tarek [58] have synthesized pyrazole derivatives ((XIII) and tested for their anti-inflammatory, cyclooxygenase-2-inhibitory and antimicrobial activities.

A novel series of 1-thiocarmoyl-3,5-diaryl-4,5-dihydro-(1H)-Pyrazole derivatives have been synthesized by Franco chimenti et al. [59] and investigated for the
ability to inhibit selectively the activity of the A and B isoforms of monoamine oxidase (MAO).

Craig W. Lindsley et al [60] have investigated positive allosteric modulators for the metabotropic glutamate receptor form a series of N-(1,3-diphenyl-1H-pyrazole-5-yl) benzamides that potentiate receptor function in vivo. Several 5-substituted pyrazole derivatives have been prepared as potent CB1 antagonists by Raj K. Razdan [61]. These compounds have good binding affinity and also they may prove to be clinically useful for the treatment of obesity. Adrian I. Grill and Martyn Frederickson and co-workers [62] have identified pyrazole as a novel q 38a MAP Kinase inhibitors (XIV).

Recently, Bantwal Holla and co-workers [63] have synthesized pyrazole derivatives as potential antimicrobial agents. Antimalarial activity of 4-(5-triflouro methyl-1H-pyrazol-1-yl)-chloroquine analogus has been evaluated in vivo against a chloroquine resistant plasmodium falciparum clone by Antoniana U Krettli et al [64]. Pyrazole derivatives (XV) with nanomolar activity in the biochemical assay and able to efficiently inhibit CDK2-mediated tumor cell proliferation have been obtained by Paolo Pevarello et al [65].
Structure activity relationship (SAR) studies of the novel 2-[3-di and trifluoromethyl-5-alkylaminopyrazole-1-yl]-5-methanesulfonyl(SO$_2$Me)/sulfamoyl(SO$_2$NH$_2$)-pyridine derivatives for canine COX enzymes are described by Subas M.Sakya et al [66]. The studies led to the identification of (XVI) as lead with potent in vivo activity, selectivity, and in vivo activity in dogs and cats.

Bratenko et al [67] and Radadiya [68] synthesized new azomethines from 4-formyl-1-phenyl-3aryl (heteryl) pyrazoles shows good antimicrobial activity.
Literature survey reveals that the compounds bearing pyrazole moiety possess potential drug activity [69-75]. Looking to the diversified biological activity, it appeared of interest to synthesize some heterocyclic products based on 1-N-Phenyl-3-phenyl-4-Formyl-pyrazole (PFP). Hence, the study of post-heterocyclic compounds based on PFP compounds has been undertaken.

**Pyrazole derivative as therapeutic agents**

<table>
<thead>
<tr>
<th>Pyrazole derivative</th>
<th>Activity</th>
<th>Ref. No</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Pyrazole derivative" /></td>
<td>Antitumor Activity</td>
<td>[76]</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
R_1 & = 3, 4- \text{CH}_3 \\
R_2 & = 4- \text{OCH}_3
\end{align*}
\]
Anti-angiogenic activity [77]

Cyclin-dependent kinase inhibitory activities [78]
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Description</th>
<th>Reference</th>
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</thead>
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<td>[79]</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Antimicrobial Activity &amp; Antifungal Activity</td>
<td>[80]</td>
</tr>
</tbody>
</table>

**Legend:**
- $R_1$: NO$_2$
- $R_2$: OCH$_3$
### Antimicrobial Activity

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Antimicrobial Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>O</td>
<td>[81]</td>
</tr>
<tr>
<td>CH$_3$</td>
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</tr>
<tr>
<td>CO$_2$Et</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>CO$_2$Et</td>
<td>CH$_2$</td>
<td></td>
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<table>
<thead>
<tr>
<th>R</th>
<th>Antimicrobial Activity</th>
</tr>
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<tbody>
<tr>
<td>-4-NO$_2$-C$_6$H$_4$</td>
<td>[82]</td>
</tr>
<tr>
<td>-2-OH-C$_6$H$_4$</td>
<td></td>
</tr>
<tr>
<td>-4-Cl- C$_6$H$_4$</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>Anti-Inflammatory activity</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Image" /> ((A = 4-O(CH_2)_2O-4', R = Ph))</td>
<td>([83])</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /> (R = 4-CH_3C_6H_4)</td>
<td>([84])</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /> (R_7 = H,F,CH_3O)</td>
<td>([85])</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Activity</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------</td>
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<tr>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>Anti-Inflammatory activity</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
<td>Antiviral activity</td>
</tr>
</tbody>
</table>

(R = OCH₃, R’ = C₃H₅)

(R = Cl)
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Description</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Antiviral activity</td>
<td>[88]</td>
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<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>Anticonvulsant and antidepressant activity</td>
<td>[89]</td>
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REFERENCE:

1. Knorr; Ger. Pat., 26, 429, [1883].
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55. Francoise G., Glaxo Jeanne; PCT Int Appl.Wo 02 62781 (Cl.CO7D401/14); Chem.Abstr,137,169514d [2002].
4. Chemistry of Pyridine:

Pyridine is a colorless, hygroscopic liquid with a pungent, unpleasant odor. When anhydrous it boils at 115.2-115.3°C (239.4-239.5°F). Pyridine is miscible with organic solvents as well as with water. The pyridine system is aromatic. It is stable to heat, to acid, and to alkali. Pyridine is used as a solvent for organic and inorganic compounds, as an acid binder, as a basic catalyst, and as a reaction intermediate.

Pyridine is an irritant to skin (eczema) and other tissues (conjunctivitis), and chronic exposure has been known to cause liver and kidney damage. Repeated exposure to atmospheric levels greater than 5 parts per million is considered hazardous.

Pyridine is a simple aromatic heterocyclic organic compound with the chemical formula $C_5H_5N$ used as a precursor to agrochemicals and pharmaceuticals, and is also an important solvent and reagent. It is structurally related to benzene, wherein one CH group in the aromatic six-membered ring is replaced by a nitrogen atom. It exists as a colorless liquid with a distinctive, unpleasant fish-like odor. The pyridine ring occurs in many important compounds, including nicotinamides.

Pyridine was originally industrial produced by extraction from coal tar. It is currently synthesized from formaldehyde, ammonia and acetaldehyde:

$$\text{CH}_2\text{O} + \text{NH}_3 + 2 \text{CH}_3\text{CHO} \rightarrow \text{C}_5\text{H}_5\text{N} + 3 \text{H}_2\text{O} + \text{H}_2$$

This Process (Chichibabin pyridine synthesis) involves the intermediacy of acrolein. An estimated 26,000 tons were produced worldwide in 1989. Condensations of ammonia sources and related unsaturated carbon sources afford alkyl- and aryl-substituted pyridines, e.g. monomethyl compounds (picolines,) dimethyl compounds (lutidines), and trimethyl derivatives (collidines). Pyridine occurs in numerous plants although this can mostly recorded just by smell. Goris and larsonneau did show definite evidence of its presence in belladonna leaves, while Kuhn and Schäfer of its presence in the roots of the same plant.

For specialized applications, the synthesis of the pyridine skeleton is well developed. The Hantzsch pyridine synthesis, for example, is a multicomponent reaction involving formaldehyde, a keto-ester and a nitrogen donor. The Kröhnke pyridine synthesis involves the condensation of 1,5-diketones with ammonium acetate in acetic
acid followed by oxidation. The Ciamician-Dennstedt Rearrangement entails the ring-expansion of pyrrole with dichlorocarbene to 3-chloropyridine. In the Gattermann-Skita synthesis, a malonate ester salt reacts with dichloromethylamine.

4.1 Synthetic route for preparation of pyridine:

a. Hantzsch Dihydropyridine(pyridine)Synthesis:

\[ R-CHO + 2 \text{O} = C=O + \text{NH}_3 \rightarrow \text{COOR} \]

This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a \( \beta \)-ketoester in the presence of ammonia. Subsequent oxidation(or dehydrogenation)gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.

b. KrÖhnke Pyridine Synthesis:

1,4-Michael addition, q.v., of a-pyridinium methyl ketone salts to a, \( \beta \)-unsturated ketones, generating the 1,5-dicarbonyl compounds which undergo ammonium acetate-promoted ring closure, to yield substituted pyridines [1].
c. Chichibabin Pyridine Synthesis:

Condensation of caronyl compounds with ammonia or amines under pressure to form pyridine derivatives; the reaction is reversible and produces different pyridine derivatives along with byproducts [2].

\[
3 \text{RCH}_2\text{CHO} + \text{NH}_3 \rightarrow \text{R} \begin{array}{c}
\text{CH} \\
\text{RCH}_2
\end{array}
\]


d. Bohlmann-Rahtz Pyridine Synthesis:

Some methods that allow the synthesis of tri- and tetrasubstituted pyridines in a one-step procedure have recently been developed. Instead of using butynone as the substrate, Bagley screened different solvents for the conversion of the less volatile and cheaper 4-(trimethylsilyl)but-3-yn-2-one. It was shown that only EtOH and DMSO are suitable solvents, with EtOH clearly favored as being protic and polar solvent vs. DMSO as a polar aprotic solvent. In both solvents, spontaneous protodesilylation took place. Bagley has also shown that acid catalysis allowed the cyclodehydration to proceed at a significantly lower temperature.
As Brønsted acid catalysis also promotes the conjugate addition, a range of enamines were reacted with ethynyl ketones in a (5:1) mixture of toluene and acetic acid to afford functionalized pyridines in a single step in good to excellent yields.

4.2 Synthesis of 2-Chloro-5-Phenyl-3-Pyridine carboxaldehyde:
4.3 Pyridines and their fused derivatives:

Cyclocondensation of 2 with ethyl 3-aminocrotonate in methanol in the presence of potassium hydroxide under reflux afforded 1-amino-3-cyano-6-hydroxy-4-methyl-pyridine-2-one [3]

Scheme 1

Cyclocondensation of 2 with benzoyleacetone and/or benzoyl trifluoroacetone in refluxing ethanol containing a catalytic amount of diethyl amine yielded regioselectively 1-amino-4-alkyl-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile [4-5].

Scheme 2
Refluxing of 2 with benzylidenemalononitrile in ethanol in presence of piperidine gave pyridone derivative [6]

\[
\text{NH}_2\quad NC\quad O\quad NH_2
\]
\[
\text{NC}\quad O\quad NH_2\quad NC\quad CN\quad Ph\quad \text{EtOH/piperidine}
\]

Scheme 3

On heating 2 and arylidene of ethyl cyanoacetate in ethanol containing triethyl amine under reflux afforded diaminopyridine derivative rather than aminopyridine derivative [7-8].

\[
\text{NH}_2\quad NC\quad O\quad NH_2\quad NC\quad CN\quad Ph\quad \text{EtOH/}
\]
\[
\text{Ar}\quad \text{CO}_2\text{Et}\quad \text{EtN}\quad \text{EtN}
\]

\[
\text{NC}\quad \text{CO}_2\text{Et}\quad \text{Ar}\quad \text{NH}_2\quad \text{NC}\quad \text{CN}
\]

\[
\text{H}_2\quad \text{H}_2\quad \text{Ar}\quad \text{Ph}\quad 4-\text{Cl-Ph}_2\text{H}_4\quad \text{furyl}
\]

Scheme 4
The one-pot reaction of 2 with aldehyde and an activated nitrile in ethanol containing a catalytic amount of piperidine yielded pyridine-2-one derivative [9-11]

\[
\begin{align*}
\text{R} & = \text{H, Me, p-NO}_2\text{C}_6\text{H}_4, \text{ p-MeOC}_6\text{H}_4 \\
\text{X} & = \text{CN, COPh, CO}_2\text{Ph}
\end{align*}
\]

Scheme 5

Compound 2 reacted with (2E)-2-cyano-N-(4-methylphenyl)-3-phenylacrylamide in dry ethanol containing catalytic amount of piperidine under reflux to afford pyridine derivative instead of compound [12].

Scheme 6
Cyclocondensation of 2 with (4-methoxybenzylidene)malononitrile in ethanol in the presence of triethylamine afforded 1-aminopyridine derivative, which rearranged on heating in 95% aqueous ethanol/triethylamine to give 1,4-diamino-5-cyano-2-(4-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid [13].

Scheme 7

Martin and coworkers reinvestigated the cyclocondensation of 2 with (4-methoxybenzylidene)malononitrile. They have found that prolonged heating lead only to the formation of 1,6-diamino-4-(4-methoxyphenyl)-3,5-dicyano-2-pyridone. The structure of compound had been confirmed on the basis of chemical and spectroscopic evidence.[14].

Scheme 8
Treatment of 2 with arylidene cyanothioacetamide in ethanol containing catalytic amount of piperidine yielded pyridine-thione derivatives.

\[
\begin{align*}
\text{NC} & \quad \text{R} \\
\text{S} & \quad \text{NH}_2 \\
\text{S} & \quad \text{NH}_2 \\
\end{align*}
\]

2

\[
\begin{align*}
\text{NC} & \quad \text{R} \\
\text{S} & \quad \text{NH}_2 \\
\text{S} & \quad \text{NH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{EtOH} & \quad \text{Me} \\
\text{R} & \quad \text{H} \\
\text{H}_2 & \quad \text{EtOH/piperidine} \\
\end{align*}
\]

Scheme 9

Reaction of cyanoaceto-N-arylsulfonylhydrazide with 2-((thiophen-2-yl)methylene) malononitrile in ethanol containing a catalytic amount of piperidine furnished pyridin-2-one derivative [15].

\[
\begin{align*}
\text{NC} & \quad \text{O} \\
\text{HN} & \quad \text{SO}_2 \text{Ph} \\
\text{HN} & \quad \text{SO}_2 \text{Ph} \\
\end{align*}
\]

\[
\begin{align*}
\text{EtOH/piperidine} & \quad \text{EtOH/piperidine} \\
\text{EtOH/piperidine} & \quad \text{EtOH/piperidine} \\
\end{align*}
\]

Scheme 10
Refluxing of cyanoaceto-N-arylsulfonylhydrazide with arylidenecyanoacetate in presence of pyridines [16], afforded pyridone derivative, while in the presence of ethanol containing a catalytic amount of piperidine afforded pyridine-2-one derivative.

Scheme 11
Substituted $N$-benzoylaminopyridone was prepared by cyclocondensation of $N$benzoylcyaanoacetohydrazide with ethyl acetoacetate in presence of sodium methoxide\[17\].

Scheme 12

Cyclocondensation of 3-indolylidenecyanoacetohydrazide with ethyl benzylidenecyanoacetate in the presence of a base gave the corresponding 4-phenyl-3,5-dicyano-6-hydroxyl-1$N$-(3-indolyldene) pyridin-2-ones \[18\].

Scheme 13
On heating 2 with phenylhydrazono-3-oxobutyronitrile in refluxing ethanol containing acatalytic amount of triethyl amine yielded pyridine-2,6-dione derivative [19-20].

![Scheme 14](image)

**Scheme 14**

Elzanate *et al.* have been reported a novel synthetic route to nitrosopyridinone derivativ via the reaction of oxime derivative of β-ketoester with $N$-benzoylcyanoacetohydrazide[21].

![Scheme 15](image)

**Scheme 15**
The reaction of \( N \)-cyanoacetylhydrazone of epiandrosterone with malononitrile in ethanol in the presence of a catalytic amount of piperidine afforded pyridine-2-one derivative [21].

\[\text{Scheme 16}\]

Refluxing of 2 with 2-(4,5-dihydro-4-oxothiazol-2-yl)-3-phenylacrylonitrile in ethanol containing catalytic amount of piperidine gave 5-amino-8-cyano-3-oxo-7-phenyl-2,3-dihydro-7\(H\)-[1,3]thiazolo[3,2-\(a\)]pyridine-6-carboxylic acid.

\[\text{Scheme 17}\]
Cyclocondensation of 2 with 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde yielded 7-amino-3-methyl-6-oxo-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile [22].

![Scheme 18](image)

Cyclocondensation of 2 with (2E)-2-(1H-benzimidazol-2-yl)-3-arylacrylonitrile under reflux in the presence of a base gave 1-amino-3-aryl-4-cyanopyrido[1,2-a]benzimidazole-2-carbohydrazide [23]

![Scheme 19](image)
The reaction of 2 with α,β-unsaturated ketones in the presence of a base gave pyrazolo[3,4-b]pyridine-3-one erivative [24].

Scheme 20

Pyrazolopyridines were obtained via cyclocondensation of β-ketoaldehyde with 2 in alkaline medium [25].

Scheme 21
Pyrazolo[3,4-b]pyridine derivative was prepared via the reaction of α-benzoylcinnamonomitrile with N-acetyl cyanoacetohydrazide [26].

Scheme 22

Cyclocondensation of 2 with β-aminocrotononitrile in acidic medium yielded pyrazolo[3,4-b]pyridine derivative [27].

Scheme 23
The reaction of 2 with 3-acetylcoumarin in ethanol containing a catalytic amount of piperidine under reflux afforded 5-methyl-2,11c-dihydrochromeno[4,3-d]pyrazolo[3,4-b]pyridine-1,6-dione [28].

Scheme 24

Reaction of 2 with different aromatic aldehydes in ethanol under reflux afforded 1Naryl methylidene-2-cyanoacetohydrazides that were treated with benzylidenemalononitrile to give [1,2,4]triazolo[1,5-a]pyridin-5(3H)-one derivatives [29].
[1,2,4]Triazolo[1,5-α]pyridin-5(1H)-one derivatives were prepared in one pot reaction in excellent yields by the reaction of 2 with malononitrile and an aromatic aldehyde [30].

\[
\text{NC} - \text{NHN} = \text{C} - \text{CN} + \text{O} = \text{Ar} \rightarrow \begin{array}{c}
\text{NC} \\
\text{H}_2\text{N} \\
\text{NHNH}_2
\end{array}
\]

Scheme 26

Martin and coworkers have reported that an unexpected reaction between N-acetyl cyanoacetohydrazide and α-cyanocinnamonicitrile in ethanol containing catalytic amount of piperidine afforded a novel 2-methyl-5-oxo-7-phenyl-1,5-dihydro[1,2,4]triazolo[1,5-α]pyridine- 6,8-dicarbonitrile [31].

\[
\begin{array}{c}
\text{Ph} \\
\text{CN}
\end{array} + \begin{array}{c}
\text{NC} - \text{NHN} = \text{C} - \text{CN} \\
\text{EtOH/piperidine}
\end{array} \rightarrow \begin{array}{c}
\text{NC} \\
\text{N} \\
\text{N}
\end{array}
\]

Scheme 27
Refluxing of hydrazone derivative and appropriate arylidenes of activated nitriles in ethanolic piperidine yielded spiro[cyclohexane-1,2’-[1,2,4]triazolo[1,5-α]pyridine]-5’-(1’H)-one derivatives [32-33].

Scheme 28

The 3-indolyldeneacyanoacetohydrazide condensed with different arylidenemalononitriles in presence of a base to give 7-aryl-6,8-dicyano-2-(3-indolyl)[1,2,4]triazolo[1,5-α]-pyridin-5-ones

Scheme 29
When anthranilonitrile was fused on an oil bath at 170 °C with different N-arylidenes of cyanoacetohydrazide in presence of triethyl amine, it afforded triazolo[4,3-a]quinoline derivatives. Compounds are assumed to be formed by the initial Thorpe-Ziegler additions of the methylene group to the CN group of anthranilonitrile to afford the acyclic intermediates, followed by loss of a water molecule to afford the acyclic intermediates, which in turn undergo a further cyclization via addition of the NH to the activated C=N to give the final products [34].

Scheme 30
### 4.4 Pyridine derivatives as therapeutic agents:

<table>
<thead>
<tr>
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<th>Activities</th>
<th>Ref. No</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Neuroprotective, AntiAlzheimer agent, multi potent drug</td>
<td>[35]</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>COX-2 selective inhibitor</td>
<td>[36]</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>Antibacterial</td>
<td>[37]</td>
</tr>
<tr>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>Antiulcer</td>
<td>[38]</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Description</td>
<td>Reference</td>
</tr>
<tr>
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<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td><img src="image1" alt="Insecticide Structure" /></td>
<td>Insecticide</td>
<td>[39]</td>
</tr>
<tr>
<td><img src="image2" alt="Histaminic Structure" /></td>
<td>Histaminic</td>
<td>[40]</td>
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11. Hussein, A. H. M. Heteroatom Chem. 8, 1, [1997].


ISSN 1424-6376 Page 154 ©ARKAT [1996].
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5. Chemistry of Thiazoles:

Thiazole or 1, 3-Thiazole is a five member ring, in which two of the vertices of the ring are nitrogen and sulfur, and the other three are carbons. Thiazoles are a class of organic compounds related to azoles with a common thiazole functional group. Thiazoles are aromatic. The structure of thiazole has been approached using various theoretical methods [1]. Best set of numerical values introduce in to simple Huckel-type MO calculation. Thiazole substituted in 2-, or 4- position by XH groups (XH = NHR, OH, SH) is susceptible to protomerism, (Scheme 1).

![Scheme 1](image)

Scheme 1

The Thiazole moiety is a crucial part of Vitamin B1 (Thiamine). Thiamine (I) is one of only four nutrients associated with a pandemic human deficiency disease. It is essential for neural function and carbohydrate metabolism. Thiamin deficiency results in beriberi, a disease characterized by a bewildering variety of symptoms. Epothilone (II) also contain thiazole moiety, The Epothilones are a new class of cytotoxic molecules, including Epothilone A (II), Epothilone B, and Epothilone D, identified as potential chemotherapy drugs for treatment of cancer. Thiazoles are structurally similar to imidazoles. Like imidazoles, thiazoles have been used to give N-S free carbenes [2] and transition metal carbene complexes. Peniciline are also very important naturally occurring thiazolidine derivatieve. Luciferine, a natural product responsible for the
bioluminescence and chemiluminescence’s of fireflies, has a structure involving both a benzothiazole and a thiazole ring. A large number of natural flavors contain and aromas of foods contain the thiazole nucleus. The numerous syntheses of Thiazoles are reported in literature, and still lots of works are going on Thiazole moiety.

![Thiamine (I)](image1)

![Epothilone (II)](image2)

Pharmacologically, 2-aminothiazoles are among the most important classes of organic compounds. These compounds possess versatile type of biological activities; some of these are well known for their anti-inflammatory activities such as (Fentiazac- III) [3] and Meloxicam-4) [4]. Meloxicam contain 2-amino thiazole moiety which contain amide functionality. Meloxicam is an NSAID (Non-steroidal anti-inflammatory drug) and belongs to the class of drugs called the enolic acid group, structurally related to piroxicam. Meloxicam significantly decreased symptoms of pain, function, and stiffness in patients, with a low incidence of gastrointestinal side effects. In models, it exhibits anti-inflammatory, analgesic, and antipyretic activities. Its mechanism of action may be related to prostaglandin synthetase (cyclooxygenase) [5-6]. (COX) inhibition
Meloxicam has been shown, especially at its low therapeutic dose, to selectively inhibit COX-2 over COX-1. Fentizac (3) is a drug used for joint and muscular pain, which is 2, 4, 5-trisubstituted thiazole derivative having phenyl ring at 2- and 4- position and acetic acid functionality at 5- position.

![Fentiazac (III)](image)

![Meloxicam (IV)](image)

Compounds like Nizatidine (5) possess anti-ulcer activity [7]. 2,4-disubstituted thiazole derivative having secondary amine and thioethanol derivative. Nizatidine is a histamine H$_2$-receptor antagonist that inhibits stomach acid production, and commonly used in the treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD).

![Nizatidine (V)](image)

2-Aminothiazole derivatives are widely used as pharmaceuticals. For example, Talipexole [8] and Pramipexole [9] with a 2-aminothiazole moiety are used as antiparkinsonian drugs and dopamine agonists. Pramipexole is a medication indicated for treating Parkinson’s disease and restless legs syndrome (RLS). It is also sometimes used off-label as a treatment for cluster headache or to counteract the problems with low
libido experienced by some users of SSRI antidepressant drugs. Pramipexole (6) and Talipexol (7) are fused thiazole derivative having 2-amino functional group.

Pramipexole (VI)  
Talipexole (VII)

Thiazole derivatives are widely used in antibacterial drugs like Cefditoren pivoxil [10] is a third-generation oral cephalosporin with a broad spectrum of activity against pathogens, including both Gram-positive and -negative bacteria, and is stable to hydrolysis by many common [beta]-lactamases. 4-Methyl-5-formylthiazole (8) is a key intermediate for the synthesis of cefditoren pivoxil [11], which was first synthesized in 1939 [12].

(VIII)

5.1 Synthetic methods of Thiazoles:

The numerous syntheses of thiazoles are classified according to the nature of the components which join to form the ring system, following the scheme proposed by Sprague and Land [13] in case of thizole, thiazolines and thiazolidines the syntheses are classified as shown is, scheme - 2.

Scheme 2
Synthesis from α-halocarbonyl compounds (Type-A): Hantzsch’s synthesis

First described in 1887 [14] by Hantzsch, the cyclization of α-halocarbonyl compounds by a great variety of reactants bearing the N-C-S fragments of the ring is still the most widely used method of synthesis of thiazole.

(i) Reaction with thioamides

Thiazole itself can be obtained by condensing chloroacetaldehyde and thioformamide. The reaction is explosive and proceeds with low yield because of instability of the thioformamide under acidic condition. Higher thioamides are more stable and react under mild condition with substituted chloroacetaldehyde, affording 2,5-substituted thiazole in moderate yields. It is possible, and often preferable, to prepare the thioamide in situ in dioxane solution by the action of phosphorous pentasulfide on the corresponding amide and in the presence of solid MgCO₃, (Scheme 3).

Scheme 3

(ii) Reaction with N-Substituted thioamides

The application of Hantzsch synthesis to mono substituted thioamides affords the corresponding N-substituted thiazolium salts. This method is particularly valuable for the preparation of those thiazolium compounds in which the substituent on the ring nitrogen atom cannot be introduced by direct quaternization, (Scheme 4).

Scheme 4
(iii) Reaction with thiourea and substituted thiourea

Of all the methods described for the synthesis of thiazole compounds, the most efficient involves the condensation of equimolar quantities of thiourea and α-halo ketones or aldehyde yield the corresponding 2-aminothiazoles [15], (Scheme 5).

\[
\begin{align*}
\text{COR}_1 \quad &+ \quad \text{S} \quad \text{NH}_2 \\
\text{R}_2 \quad \text{Cl} \quad &\quad \longrightarrow \quad \text{R}_1 \\
&\quad \text{R}_2 \\
&\quad \text{NHR}_3
\end{align*}
\]

Scheme 5

(iv) Reaction with salt or ester of thiacarbamic acid.

The method, initiated by Merchesini in 1893 [16], consists of the condensation of an α-halocarbonyl compounds with ammonium thiocarbamate or its ester (Scheme 6). The reaction is carried out at low temperature in aqueous medium and then allowed to stand overnight.

\[
\begin{align*}
\text{COR}_1 \quad &+ \quad \text{S} \quad \text{NH}_2 \\
\text{R}_2 \quad \text{Cl} \quad &\quad \longrightarrow \quad \text{R}_1 \\
&\quad \text{R}_2 \\
&\quad \text{O} \quad \text{R}_3
\end{align*}
\]

Scheme 6

Synthesis from α-aminonitriles (Type-B) : Cook-Heilbron’s synthesis

This type of synthesis, which was investigated initially by cook and Heilborn in 1947, gives 5-aminothiazole with various substituents in the 2-position by reacting an α-aminonitrile with salts and esters of dithioacids, carbon disulfide, carbon oxysulfide, and isothiocyanates under exceptionally mild conditions [17].

(i) salts and ester of dithioacids : 5-Amino thiazole derivative.

By condensing the salts of the esters of either dithioformic or dithiophenacetic acids with α-aminonitriles, 5-aminothiazoles in which $R_1 = H$, Benzyl and $R_2 = \text{phenyl}$, ethoxycarbonyl or phenoxycarbonyl, are obtained in fairly good yields,(Scheme 7).
(ii) Carbon disulfide: 2-mercapto-5-aminothiazole derivatives

Carbon disulfide readily reacts with α-aminonitriles giving 5-amino-2-mercaptothiazoles which can be converted into 5-aminothiazoles unsubstituted in the 2-position. (Scheme - 8).

Scheme - 8

Synthesis from acylaminocarbonyl compounds and phosphorus pentasulfide and related condensation. (Type- C): Gabriel's synthesis.

The reaction was first described by Gabriel in 1910 [18-19] when he warmed an acyamino ketone with stochiometric amount of phosphorous pentasulfide. The reaction similar to that of cyclization of other five-membered oxygen and sulfur containing ring from 1,4-dicarbonyl compounds. The method is restricted to the preparation of alkyl-, ayl-, or alkoxy-thiazoles substituted mostly in the 2-, 5-, or 2,5-position. (Scheme 9).

Scheme 9
Synthesis from nitriles and α-mercapto ketones or acids: 2,4-disubstituted and 4-hydroxythiazole derivative (Type-D)

Beside α-halocarbonyl compounds, α-mercapto ketones and acids are also used for the preparation of thiazoles from nitriles and aldoximes. (Scheme 10)

![Scheme 10]

5.2 Applications of Thiazole derivative:

Natural occurrence:

The most important naturally occurring thiazole derivative is thiamine (Vitamin B1). Penicilins are also a very important naturally occurring thiazolidine derivative. They are produced by isolation from culture of mutant strain of the mold Penicillium chrysogenum. The most important id peniciline G (IX) but other natural, biosynthetic or semisynthetic penicillins are produced and used as antibiotics. Other natural antibiotics such as althiomycin [20] or micrococcin [21] contain thiazole ring as do many metabolic products of living organism such as 2-amino-4-(4-carboxy thiazol-2-yl)butyric acid (X), which has been isolated from the fungus Xerocomus subtomentosus [22] or aeruginoic acid which has been isolated from the culture medium of Pseudomonas aeruginosa and has the structure 2-o-hydroxyphenylthiazole-4-carboxylic [23]. Luciferin, a natural product responsible for the bioluminescence and chemiluminescence of fireflies, has structure involving both benzothiazole and a thiazoline ring [24].
A large number of natural flavors and aroma of foods contain the thiazole nucleus [25]. 4-Methyl-5-vinylthiazole (XI) is present in cocoa and passion fruit aromas, benzothiazole is a constitute of roast walnuts, coconut, cocoa, beer, and roast pork liver aromas while 2-acetylthiazole (XII) and 2-acetyl-5-methyl-thiazoline (XIII) are present in a beef aroma. 2-Isobutylthiazole (XIV) is the most important flavoring constituent of tomatoes. 2,4,5-trimethylthiazole and certain thiazolines, di- or tri-substituted by alkyl, acyl or alkoxy groups exhibit walnut and roast hazel nut flavors. Thiazoles have been detected in certain petroliums in small quantities.

Pharmaceutical features of the Thiazoles and their clinical applications Thiazole is one of important class of five member heterocyclic moiety in pharmaceutical industry. One of the first commercially synthetic drug containing thiazole was ‘sulphathiazole’ a simple sulfamide antibiotic derived from 2-amino thiazole (XV). More recently a large number of thiazole derivative have been found to exhibit pharmacological activity.
More specifically, 2-(p-chlorophenyl) thiazol-4-ylacetic acid (XVI) possesses anti-inflammatory properties [37]. ‘Thiabendazole’ or 2-(4-thiazolyl) benzimidazole (XVII) is widely used as an anthelmintic and fungicide. Other derivative such as 3-substituted 4-aminothiazoline-2-thiones (XVIII) possessed anti-fungal activity, inhibiting in *in-vivo* the growth of Xanthomonas oryzae [38].

\[
\begin{align*}
\text{(XV)} & \quad \text{(XVI)} \\
\text{(XVII)} & \quad \text{(XVIII)}
\end{align*}
\]

Yufu Sagara et al [39], synthesised a novel class of 2-Aminothiazole-4-carboxamides derivative (XIX) having Muscarinic M3 Selective Antagonists, which is target for treatment of pulmonary urinary diseases.

\[
\text{(XIX)}
\]

R= Aromatic and fused aromatic ring

Shigeo Ueda et al [40] synthesized a series of 2-amino thiazole (XX) for Inducible Nitric Oxide Synthase Inhibitors,
The chemistry and pharmacology of thiazole derivative have been of great interest to medicinal chemistry because thiazole derivatives have wide range of pharmacological properties like anti-inflammatory [41-49] antibacterial [50-58], Antiviral [59-68], anticancer [69-75].

Number of molecules having thiazole moiety as a core are in market for different therapeutic category (chart 1). Also number of molecules having thiazole moiety as a core are in different clinical trials (chart 2).
Chart-1: Drugs available in market having thiazole moiety

Acotiamide (Phase 3)
Gastric motility disorder

Lu-AA47070 (Phase 1)
Parkinsons disease

Mirabegron (Phase 3)
Non-insulin dependent diabetes

Tetomilast (Phase 3)
Inflammatory bowel disease
Chart-2: Drugs are in various clinical trial having thiazole moiety

5.3 BIOLOGICAL ACTIVITIES OF THIAZOLE DERIVATIVES

<table>
<thead>
<tr>
<th>Thiazole Derivatives</th>
<th>Activities</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Anticonvulsant activity" /></td>
<td>Anticonvulsant activity</td>
<td>[76]</td>
</tr>
<tr>
<td><img src="image2" alt="Anticonvulsant activity" /></td>
<td>Anticonvulsant activity</td>
<td>[77]</td>
</tr>
</tbody>
</table>

X = S, R = 4-OCH₃, X = S, R = 3-OCH₃, 4-OH
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Anticonvulsant Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>R_1 = Br, R_2 = OCH_3</td>
<td>[78]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>R = Cl, R_2 = Br</td>
<td>[79]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Compound 3" /></td>
<td>Moderate excellent activity</td>
<td>[80]</td>
</tr>
<tr>
<td><img src="image4.png" alt="Compound 4" /></td>
<td>R_1 = 3,4-CH_3C_6H_3, R_2 = CH_3</td>
<td>[81]</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Activity</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>Antibacterial and antifungal activity</td>
<td>[82]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
<td>Antifungal &amp; Antimicrobial activity</td>
<td>[83]</td>
</tr>
</tbody>
</table>

For the first structure: \( \text{Ar} = \text{Ar}_1 = \text{Ph} \)
\( \text{Ar} = \text{Ph}, \text{Ar}_1 = 4-\text{Br.C}_6\text{H}_4 \)
\( \text{Ar} = 4-\text{Cl.C}_6\text{H}_4, \text{Ar}_1 = \text{Ph} \)
\( \text{Ar} = 4-\text{Cl.C}_6\text{H}_4, \text{Ar}_1 = 4-\text{Br.C}_6\text{H}_4 \)

For the second structure:
\( \text{R} = \text{H}, \text{R}_1 = \text{C}_6\text{H}_5, \text{R}_2 = \text{OCH}_3 \)
\( \text{R} = \text{H}, \text{R}_1 = \text{C}_6\text{H}_5, \text{R}_2 = \text{Br} \)
\( \text{R} = \text{C}_6\text{H}_5, \text{R}_1 = -\text{CH(OH)}\text{C}_6\text{H}_5, \text{R}_2 = \text{Br} \)
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Anticonvulsant activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure 1" /></td>
<td>Anticonvulsant activity</td>
<td>[84]</td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure 2" /></td>
<td>Anticonvulsant activity</td>
<td>[85]</td>
</tr>
</tbody>
</table>

R = OCH₃, R = Br
Antimycobacterial activity

\[ R_1 = CH_3, R_2 = H, Ar = C_6H_5 \]
\[ R_1 = C_2H_5, R_2 = H, Ar = C_6H_5 \]
\[ R_1 = CH_3, R_2 = CH_3, Ar = C_6H_5 \]

\[ R_1 = CH_3, R_2 = H, Ar = 4\text{-}F\text{-}C_6H_4 \]
\[ R_1 = CH_3, R_2 = H, Ar = 4\text{-}OCH_3\text{-}C_6H_4 \]
\[ R_1 = CH_3, R_2 = CH_3, Ar = C_6H_5 \]
Potent activity

Ar = 3-pyridyl, Ar = biphenyl
Ar = 4-NO₂-C₆H₄, Ar = 4-Cl-C₆H₄

R = piperidino
R = 4-mercaptopyrazolopyrimi

Ar = 3-pyridyl, Ar = 4-NO₂
Antibacterial, antifungal and antitubercular activity

\[
\begin{align*}
R &= \text{C}_6\text{H}_5 \\
R &= 3,4,5-(OCH_3)_3\text{C}_6\text{H}_2 \\
R &= 4-\text{OH-C}_6\text{H}_4
\end{align*}
\]

Antifungal and antibacterial activity

\[
\begin{align*}
R_1 &= \text{OH, } R_2 = \text{I, } R_3 = \text{H, } R_4 = \text{Cl} \\
R_1 &= \text{OH, } R_2 = \text{Br, } R_3 = \text{H, } R_4 = \text{Cl} \\
R_1 &= \text{OH, } R_2 = \text{I, } R_3 = \text{H, } R_4 = \text{Cl} \\
R_1 &= \text{OH, } R_2 = \text{Br, } R_3 = \text{H, } R_4 = \text{Br} \\
R_1 &= \text{OH, } R_2 = \text{Cl, } R_3 = \text{H, } R_4 = \text{Cl}
\end{align*}
\]
<table>
<thead>
<tr>
<th>Compound</th>
<th>Antibacterial Activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical 1" /></td>
<td>( R = \text{C}_6\text{H}_5, R = 4\text{-F}\text{-C}_6\text{H}_4 ) ( R = \text{-CH}_2\text{-C}_6\text{H}_4 )</td>
<td>[90]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical 2" /></td>
<td>( R = \text{Br}, R = \text{OH} )</td>
<td>[91]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical 3" /></td>
<td>( R_1 = \text{OH}, R_2 = \text{H}, R_3 = \text{H}, R_4 = \text{Br} )</td>
<td></td>
</tr>
<tr>
<td><img src="image4.png" alt="Chemical 4" /></td>
<td>( R = 3\text{-OCH}_3, R = 4\text{-OH}, R = \text{OH} ) ( R = 2\text{-NO}_2, R = 2\text{-Cl}, R = 4\text{-Cl} )</td>
<td>[92]</td>
</tr>
</tbody>
</table>
Antibacterial activity [93]

R = H, OH, OCH₃, NO₂, Cl, Br, CH₃.

Anti-inflammatory activity [94]

R₁ = H, R₂ = OCH₃, R₃ = CH₃, R₄ = CH₃, R₅ = H
R₁ = H, R₂ = CH₃, R₃ = R₄ = H, R₅ = CH₃

Anti-inflammatory activity [95]
### Analgesic and antiinflammatory activity

<table>
<thead>
<tr>
<th>Structure</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Analgesic and antiinflammatory activity</td>
<td>[96]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Antiinflammatory activity</td>
<td>[97]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>Antiinflammatory activity</td>
<td>[98]</td>
</tr>
</tbody>
</table>

- **Structure 1**: \( R_3 = 6\text{-Cl}, R_2 = 6\text{-Br}, R_1 = 7\text{-Cl}, R_2 = 6\text{-Br} \)
  \( R_1 = 8\text{-CH}_3, R_3 = 6\text{'}\text{-Br}, R_4 = 6\text{-Cl}, R_4 = 6\text{'}\text{-Br} \)
  \( R_4 = 7\text{-Cl}, R_2 = 6\text{'}\text{-Br}, R_1 = 8\text{-CH}_3, R_2 = 6\text{'}\text{-Br} \)

- **Structure 2**: \( R_1 = \text{CH}_3, R_2 = \text{CH}_3, R_3 = 4\text{-Cl} \)
  \( R_1 = \text{p-Cl-Ph}, R_2 = \text{CH}_3, R_3 = 4\text{-Cl} \)

- **Structure 3**: \( \text{NHCO(CH}_2\text{)}_2\text{N(CH}_3\text{)}_2 \)
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Anti-inflammatory activity</th>
<th>Anticancer activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>[99]</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>[101]</td>
</tr>
</tbody>
</table>
Anticancer activity [102]

<table>
<thead>
<tr>
<th>R₁ = 3-NH₂, 4-OMe, R₂ = 3',4',5'-(OMe)₃, R₃ = H</th>
</tr>
</thead>
</table>

Antitumor activity [103]

<table>
<thead>
<tr>
<th>R₁ = 3-NH₂, 4-OMe, R₂ = 3',4',5'-(OMe)₃, R₃ = Cl</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Ar = 2-(4-OMe-C₆H₄NHCOCH₂O)-5-Cl-C₆H₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Structure</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td><img src="image1" alt="Chemical 1" /></td>
</tr>
<tr>
<td><img src="image2" alt="Chemical 2" /></td>
</tr>
<tr>
<td><img src="image3" alt="Chemical 3" /></td>
</tr>
<tr>
<td><img src="image4" alt="Chemical 4" /></td>
</tr>
</tbody>
</table>
\[
\text{Anti HIV-1 activity} \quad [108]
\]

\[
\text{Anti HIV-1 activity} \quad [109]
\]

\[
\text{Antiretroviral activity} \quad [110]
\]

\[
\text{Anti HIV-1 RT inhibitors activity} \quad [111]
\]
<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure 1" /></td>
<td>Anti HIV activity</td>
<td>[112]</td>
</tr>
<tr>
<td><img src="image2.png" alt="Chemical Structure 2" /></td>
<td>Hypotensive activities</td>
<td>[113]</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure 3" /></td>
<td>Hypotensive activities</td>
<td>[114]</td>
</tr>
<tr>
<td><img src="image4.png" alt="Chemical Structure 4" /></td>
<td>Antihypertensive activity</td>
<td>[115]</td>
</tr>
</tbody>
</table>
Looking to the prominent place of thiazole derivatives in medicinal chemistry, in this section we have synthesized some biologically active heterocyclic compounds which contain thiazole moiety.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Compound" /></td>
<td>Antihypertensive agent</td>
<td>[116]</td>
</tr>
<tr>
<td><img src="image2" alt="Compound" /></td>
<td>Free radical Scavenging activity</td>
<td>[117]</td>
</tr>
<tr>
<td><img src="image3" alt="Compound" /></td>
<td>Free radical Scavenging activity</td>
<td>[118]</td>
</tr>
<tr>
<td><img src="image4" alt="Compound" /></td>
<td>Antioxidant activity</td>
<td>[119]</td>
</tr>
</tbody>
</table>

**Chemical Structures:**
- ![Compound](image1) with R = H, R = 4-CH₃, R = 4-OCH₃, R = 4-OC₂H₅
- ![Compound](image2) with R = H, R = 4-Cl, R = 4-OCH₃, R = 4-OC₂H₅
- ![Compound](image3) with R = Cl, X = Cl, X₁ = H
- ![Compound](image4) with R = H, R = COCH₂CN
REFERENCE:

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6. Chemistry of Oxothiazole :

Oxothiazole derivatives are biologically interesting molecules that have established utility in the pharmaceutical and the industries compounds with these ring systems have a wide application range of biological activities and pharmacological actions [1-5], antibacterial [6-7] inhibitory activity [8-10]. Pyranopyridothiazole derivatives found a wide uses in the chemistry of dyes and pigments such as laser technologies [11-13], in colour and non colour photographic processes [14], in optical disk as recording media [15] and inks [16]. However, the structure activity relationship studies revealed that synthesized compounds is also an important in the many different fields [17]. The attempts have been made to synthesize a new fused and isolated heterocyclic compounds, Contain with oxothiazole system.

Literature survey revealed that thiazole, and pyrazole ring systems have occupied a unique position in the design and synthesis of novel biological active agents with remarkable analgesic and anti-inflammatory activities [18-21], in addition to their well documented potential antimicrobial activities [22-25]. Moreover, thiazoles have found application in drug development for the treatment of hypertension [26], schizophrenia [27], HIV infections [28], and as new inhibitors of bacterial DNA gyrase B [29].
REFERENCES:


7. Chemistry of Knoevlen Reaction:

The chemistry of bioactive thiazoles [1-7], rhodanines [8-10] and have been an interesting field of study for long time. The rapid syntheses of a variety of heterocyclic compounds under microwave. Study on the influence of structure on activity showed that sometimes, minor changes in heterocyclic nuclei enhance the pharmacological profile many folds than parent nuclei. The search for new, effective and safe nuclei has led to an improvement in the existing drugs by increasing their potency, duration of action and decreasing their toxic effects. This is achieved by creating new biologically active agents by molecular modifications.

Thiazolidinediones and rhodanines of type 1 (Fig.1) are an important and versatile class of compounds that show a wide variety of biological activities [11-12]. Compounds possessing these scaffolds have recently been shown to inhibit cholesterol esterase [13]. In addition, examples are known to have antifungal, [14] antibacterial, [15-16] antiviral [17] antitumor,[18] and antidiabetic potential [19]. Antibacterial activity is of particular importance given the dramatic rise of drug-resistant bacteria and the paucity of new agents currently in development [20-23].

![Thiazolidinedione and rhodanine structure](image)

Figure 1. Thiazolidinedione and rhodanine structure

5-Benzylidenerhodanine and 5-benzylidene-2-4-thiazolidinedione based derivative (Scheme -1 & 2) have been reported as antibacterial [24].
4-Thiazolidinones [25-26] are an important group of heterocyclic compounds, which have been subject to extensive study in the past years. One-pot, three component synthesis of 5-hydrazinoalkylidene rhodanines from 1,2 diaza-1,3-dienes was reported [27].
Rhodanine [28] and its derivatives possessing hydrogen attached to the nitrogen atom have been patented as fungicides while the compounds containing nitrogen atom [29] were patented as pesticides, with mention being made of their usefulness as fungicides. 5-Benzylidene-3-pheny-2-thioxo-thiazolidin-4-one core was shown to inhibit the Jun NH2-terminal kinase (Jnk) stimulatory phosphatase-1 (JSP-1). [30] In addition Rhodanine-based molecules are popular as small molecule inhibitors of numerous targets such as HCV NS3 protease, [31] aldose reductase, [32-33], b-lactamase ,[34] UDP-N-acetylmuramate/L-alanine UDP-N-acetylmuramate/L-alanine ligase, [35] antidiabetic agents, [36] cathepsin D,[37] and histidine decarboxylase. [38] Ankati,H. et al. have been prepared and evaluated biologically important compounds [39]. Microwave synthesis of novel class of rodanine derivative as potential HIV-1 and JSP-1 inhibitors were reported [40]. There fore we planned to synthesized rhodanine derivatives by knoevelgen reaction.
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8. Chemistrty of Benzylidene:

As a result of their pharmacological, biological, physiological, and medical significance, substituted and condensed benzylidine form class of compounds of importance and still growing interests. Facile synthesis of differently substituted 5-benzylidene-2-aryl-5,6-dihydro-4H-[1,3]oxazin-6-ones have been Synthesized by Rattan L. Sharma et al [1].

The Benzylidene derivatives of phenyloxazolones are exhibits biological and technological applicatons.[2–7] The compounds can be applied as inhibitors of the enzyme activity or as fluorescent sensors. The another effective heterocyclic compounds Benzothiazoles play a major role as antibacterial [8-10], antifungal activity, anti inflammatory activities [11-12], anthelmintic activity [13]. The reaction between benzaldehyde and D-mannitol has led to only two characterized products: dibenzylidene derivative. These structures are the equilibrium products predicted from the Barker-Bourne rules [14].
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