Chapter I

Introduction to Azoles
1.0. Introduction

From the earlier days of development of organic chemistry, heterocyclic chemistry has held center stage in the development of molecules to enhance quality of human life. For example, more than seventy percent of drugs used today are heterocyclic compounds. They are widely distributed in nature and are key intermediates in many biological processes. Generally, heterocyclic compounds isolated from natural sources act as lead compounds for the development of new molecules of biological interest. In addition, most of the heterocyclic drugs are synthesized from readily available fine chemicals. In this aspect, synthesis and characterization of new molecular entities incorporating heterocyclic structures is of high significance. There are multiple benefits exploring this type of research in organic chemistry. Firstly, it will help in unraveling intrinsic chemical behavior of small molecules which still remains mysterious. Secondly, it will immensely help in the development of new methods for synthesis. Thirdly, characterization of a set of compounds by spectral methods would create benchmarks for characterization of similar molecules. Finally, biological evaluation of the synthesized compounds may explore lead compounds for further structural fine tuning. Among organic compounds, those incorporating one or more sulphur or nitrogen atoms are of high significance because of their unique properties imparted by these elements.

Heterocyclic chemistry includes a large class of compounds, azoles being one among them. Azoles are five-membered heterocyclic compounds containing nitrogen atom and at least one other non-carbon atom of either nitrogen, sulphur, or oxygen [1]. It includes the following heterocyclic rings.

![Heterocyclic Rings Diagram](image-url)
Chapter I

Being main ingredients in many drugs, azoles are known for their broad spectrum of biological activities including antimicrobial, anti-inflammatory, analgesic, antimitotic, anticonvulsing, diuretic and many other uses [2-8]. They play an important role against skin diseases and secondary symptoms of AIDS. They are also used in the protection of plants and in industry (leather, wool, fibers). The rapid development in this field affords a comprehensive handbook about their uses and applications.
1.1. Reported activities of azoles

1.1.1. Azole drugs showing antifungal activity

The first report of antifungal activity of an azole compound, benzimidazole, was described in 1944 [9], it was however only after the introduction of topical chlormidazole in 1958 that researchers became interested in the antifungal activity ofazole compounds [9]. In the late 1960s, three new topical compounds were introduced [10] clotrimazole, developed by Bayer Ag, Germany [11], miconazole and econazole, both developed by Janssen Pharmaceutica, Belgium [12].

Miconazole, a phenethyl imidazole synthesized in 1969, was the first azole available for parenteral administration. Like other azoles, it interferes with the biosynthesis of fungal ergosterol, but at high concentrations. Miconazole may also cause direct membrane damage that result in leakage of cell constituents. It has been recently withdrawn from the markets because of toxicity. In 1981, Food and Drug Administration (FDA) approved the systemic use of ketoconazole, an imidazole derivative synthesized and developed by Janssen Pharmaceutica, Belgium [13].

![Chemical structures of azole drugs](image)

However, the poor response rates and frequent recurrences of major fungal infections, as well as the toxicity associated with ketoconazole therapy, led to the search for a second chemical group of azole derivatives, namely the triazoles. In general the triazoles demonstrate a broader spectrum of antifungal activity with reduced toxicity.
in comparison to imidazole antifungals. The serum half-life allows once-daily dosing of triazole based antifungals agents viz. fluconazole. In contrast to ketoconazole, renal clearance is the major route of elimination of fluconazole, with 70-80% of unchanged drug excreted in the urine [14].

Mechanism of action of azoles against fungal infection

Azoles inhibit the enzyme lanosterol 14 a-demethylase which is necessary to convert lanosterol to ergosterol. Diminution of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth [15]. Moreover, a number of secondary effects such as inhibition of the morphogenetic transformation of yeasts to the mycelia form, decreased fungal adherence and direct toxic effects on membrane phospholipids, have also been reported [16].

1.1.2. Azoles as antibacterial agents

The azole pharmacophore is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antimicrobial agents. Potential antibacterial
activities have been encountered with some azoles. Some of the potent azoles as antibacterial agents are as follows.

![Tazobactum](image1)

![Meloxicam](image2)

![Muscoride A](image3)

1.1.3. Azoles as Non-steroidal anti-inflammatory drugs (NSAIDs)

Azoles are one of the important class of compounds used as NSAIDs viz. Celecoxib etc. NSAIDs are non-narcotic drugs [17] that produce relief of pain and lower elevated body temperature. As these drugs do not have steroidal nucleus and also produce anti-inflammatory effect, they are known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are better in use than steroidal drugs. As a group, NSAIDs tend to cause gastric irritation and considerable effort has gone into preventing this complication or reducing its severity [18]. Furthermore, there are number of non azole NSAIDs present in the market to heal the inflammation but majority of them cause adverse side effects like gastric ulcer [19] and kidney damage [20] while some of the NSAIDs cause hepatotoxicity [21].

1.1.3.1. Properties of NSAIDs

- Mildly analgesic
- Antipyretic
- Anti-inflammatory
- Act on sub-cortical sites such as thalamus and hypothalamus
- No affinity for morphine receptors
- In addition, tolerance and drug dependence do not develop to these drugs in patients
1.1.3.2. **Classification of NSAIDs**

The NSAIDs are classified into different groups on the basis of their basic moieties and are listed in the table given below.

<table>
<thead>
<tr>
<th>Class</th>
<th>Structures</th>
<th>IUPAC Name</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazole derivatives</td>
<td><img src="structure1.png" alt="Pyrazole derivative structure" /></td>
<td>4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazolo-1-y1]benzenesulfonamide</td>
<td>Celecoxib</td>
</tr>
<tr>
<td>Oxicams derivatives</td>
<td><img src="structure2.png" alt="Oxicams derivative structure" /></td>
<td>4-hydroxy-2-methyl-N-2-pyridinyl-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide</td>
<td>Piroxicam</td>
</tr>
<tr>
<td>Indole acetic acid derivatives</td>
<td><img src="structure3.png" alt="Indole acetic acid derivative structure" /></td>
<td>1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Indole acetic acid derivatives</td>
<td><img src="structure4.png" alt="Indole acetic acid derivative structure" /></td>
<td>1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Pyrrole Alkanoic acid</td>
<td><img src="structure5.png" alt="Pyrrole Alkanoic acid structure" /></td>
<td>[1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl]acetic acid</td>
<td>Tolmetin</td>
</tr>
<tr>
<td>Salicylates</td>
<td><img src="structure6.png" alt="Salicylates structure" /></td>
<td>2-Acetoxybenzoic acid</td>
<td>Aspirin</td>
</tr>
<tr>
<td>p-aminophenol derivatives</td>
<td><img src="structure7.png" alt="p-aminophenol derivatives structure" /></td>
<td>N-(4-hydroxyphenyl) acetamide</td>
<td>Paracetamol</td>
</tr>
</tbody>
</table>
Mechanism of action of anti-inflammatory agents

The anti-inflammatory drugs inhibit inflammation by inhibiting the biosynthesis of prostaglandin [22]. Synthesis of prostaglandin is mediated by an enzyme called cyclooxygenase (COX or PGH2 synthase). It exists in two isoforms, COX-1 and COX-2. COX-1 is constitutive whereas COX-2 is inducible. COX-1 protects gastrointestinal mucosa and also maintains homeostasis, whereas COX-2 is responsible for inflammation, pain and fever. Most of the NSAIDs inhibit both isoforms of COX, which lead to other side effects (gastric ulcer and renal toxicity due to inhibition of COX-1).

Selective COX-2 inhibitors are better anti-inflammatory agents, because COX-2 is usually specific to inflamed tissue. Further, there is much less gastric irritation associated with COX-2 inhibitors, with a decreased risk of peptic ulceration. Selectivity for COX-2 is the main feature of azole based drugs such as celecoxib and other members of this class.
1.1.4. Azoles as antiviral and analgesic agents.

During the past few years several marine natural products with 2,4-disubstituted azoles have been isolated and synthesized [23]. Hennoxazole is an azole based potent antiherpes virus agent and peripheral analgesic containing a bioxazole unit [24].

![Diagram of COX-1 and COX-2 inhibitors and their effects]

1.1.4. Azoles as anticancer agents.

Azoles are known selective COX-2 inhibitors and also show anticancer properties [25]. COX-2 derived prostaglandin may accelerate the development of cancer by different mechanisms [26-28]. COX-2 inhibitors have been shown to reduce the occurrence of cancers and pre-cancerous growths [29]. One of the azoles with anticancer properties is carboxyamidotriazole [30].
RAF265 (CHIR-265; Novartis Pharmaceuticals, Basel, Switzerland), an orally bioavailable small molecule, under clinical trial phase-I, is a potent inhibitor of RAF (proto-oncogene) with a highly selective profile and is a derivative of benz azoles (Chiron, a subsidiary of Novartis) [31].

AZD6244 is an imidazole based anticancer agent under clinical trial Phase II (Astrazeneca), active against recurrent low grade ovarian cancer [32].
1.5. Conclusion

The usage of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side effects [33-36]. Therefore, the development of new and different antimicrobial drugs is a very important objective and much of the research program efforts are directed towards the design of new agents. Further several non steroidal anti-inflammatory drugs (NSAIDs) have been developed so far to heal the inflammation. The use of these NSAIDs has also been limited owing to their adverse effects like ulceration, hepatotoxicity, renal toxicity etc. [37-38]. Due to drug resistance and adverse side effects of the antimicrobial and anti-inflammatory agents present in the markets, there is need for undertaking research in this area for the development of new lead molecules. Since azole derivatives show numerous activities like anti-inflammatory and antimicrobial agents and are reported both from natural as well as synthetic sources, our main emphasis was on the development of azole based small molecule high affinity ligands (SHALs) with potent anti-inflammatory, analgesic and antimicrobial activities.
1.4. References


