CHAPTER-1

Introduction to Azoles Chemistry
1.1 Introduction to Azoles and its Derivatives

This chapter is an introductory summary of azoles (Fig.1) and its importance in medicinal chemistry. 1, 3 Azoles are important as heterocyclic components of many natural products, drugs, and biologically active molecules. Consequently, new efficient methodologies for the preparation of azole derivatives provide a valuable tool to synthetic organic chemists.

Fig.1.1: Azoles

An azole is a class of five-membered nitrogen heterocyclic ring compounds containing at least one other non-carbon atom of either nitrogen, sulfur, or oxygen. The parent compounds are aromatic and have two double bonds; there are successively reduced analogs (azolines and azolidines) with fewer. One, and only one, lone pair of electrons from each heteroatom in the ring is part of the aromatic bonding in an azole. Names of azoles maintain the prefix upon reduction (e.g. pyrazoline, pyrazolidine). The numbering of ring atoms in azoles starts with the heteroatom that is not part of a double bond, and then proceeds towards
the other heteroatom. Many azoles are used as antifungal drugs, inhibiting the fungal enzyme 14α-demethylase which produces ergosterol (an important component of the fungal plasma membrane).

1.2 History of Azole Chemistry

Since the earliest days of agriculture, insect pests, weeds and plant diseases have been some of the major problems of agriculture. Insect pests are visible and could, at least in some cases be countered by hand removal. A certain level of weed elimination was achieved by hoeing and hand weeding, and never ending task. However, rust, powdery mildew and smut being invisible enemies, spread throughout the fields like an unpredictable fate. Thus they occupied the imagination of rural folk, and magical concepts of disease control predominated in the early days of agriculture. Until the discovery of Bordeaux mixture in 1880, farmers had no real possibility of defending their crops against the ravages of fungal diseases. Fungi had only been identified a few years previously as the cause of plant diseases. Apart from a few empirical measures to prevent disease, active control was not possible. Massive disease epidemics often had catastrophic social consequences. The legacy of the Irish potato famine of the 1840's can be seen even today. It is difficult to imagine the significance of the pioneer fungicides, ones based on copper, sulphur and mercury had in their time.

The organic fungicides of the dithiocarbamate and phthalimide type (e.g. Captan) were a breakthrough in this field in the nineteen thirties
and forties. Although they only have protective activity and thus must be used prophylactically, they found broad applications due to their high plant compatibility and broad disease control spectrum. A further milestone in the development of fungicides was the discovery of the so-called systemic fungicides, chemicals that are taken up by the plant and transported within it. The fungicide classes found in the sixties, including the oxathiines, pyrimidines and organophosphates, are characterized by being absorbed by the leaves, often also by the seeds and roots, and being transported acropetally within the plant. These products have only a very narrow disease control spectrum. The oxathiines are active against Basidiomycetes, mainly against rusts and smuts; the pyrimidine derivatives are active against powdery mildews. The organophosphates are used for pyricularia control in rice.

The much wider disease control spectrum of the benzimidazole fungicides (eg. benomyl, BCM, thiabendazole)-permitted far wider usage. In the beginning, these were suitable for control of numerous plant diseases, but a new phenomenon soon emerged - resistance! due to the specific mode of action of these fungicides, resistance could appear quite rapidly. The conventional fungicides previously used had a broad biocidal activity and resistance had never been experienced.

With the class of 1-substituted imidazoles and 1, 2, 4-triazoles, we found a new group of highly active fungicides and antimycotics\textsuperscript{2, 3}. Since their discovery in the late sixties, several compounds from this chemical
class have been commercially developed and successfully used for the control of plant diseases and for the treatment of human fungal infections. These so called “azole fungicides and antimycotics” have set new standards in medicine and agriculture with respect to efficacy and range of disease control spectrum. Among this group, we find the most active compounds known today for control of plant diseases and human mycoses.

The synthetic routes to the systemic fungicide triadimefon (Bayleton) and the cereal seed dressing triadimenol (Baytan), starting from pinacolone, are representative for this very interesting group of azole derivatives (Figure 1.2).

![Diagram of synthetic pathways for triadimefon and triadimenol]

**Figure 1.2.** Pathways for the synthesis of triadimefon and triadimenol.

For the first time, they were able to synthesize azole fungicides that were systemic in plants and transported mainly upward in the direction of growth. Triadimefon is a potent systemic fungicide with particularly
high activity against powdery mildew and rust fungi. It is used in many different crops, but mainly in cereals and fruit. Triadimeno1 has excellent systemic properties making it suitable not only for the control of seed- and soil-borne fungal organisms but even of infections by wind-borne pathogens. Other important members of the azolyl-0,N-acetal family that have been marketed thus far are bitertanol (Baycor, Sibutol) and the imidazole derivative climbazole (Baypival). Bitertanol is not systemic, but penetrates plant tissue and thus possesses curative and eradicative properties combined with protective activity. It is used for control of foliar diseases of various crops such as tree fruit, peanuts and bananas. Climbazole is not an agricultural fungicide. It has a completely different antifungal profile than its triazole analogue, triadimefon, and has particularly high activity against mould fungi, yeasts and dermatophytes. It also has excellent activity against Pityro-sporum ovale and is thus used as an active ingredient in anti-dandruff formulations (Ceox).

These examples (Figure 1.3) clearly show that, although there are very close chemical relationships within a class of compounds, there may be remarkable differences in the biological and biophysical properties. This enables the use of various compounds for specific purposes although their biological spectrums may overlap.
The parent oxazole 1 was first prepared by Cornforth and Cornforth utilizing a rather lengthy and complex reaction sequence\textsuperscript{10}. More recently, however, a somewhat simpler approach to the synthesis was taken by Bredereck and Bangert\textsuperscript{11, 12}. Their method is an adaptation of an older synthesis of substituted oxazoles, i.e. the reaction of amides with \(\alpha\)-hydroxy ketones upon heating formamide with ethyl \(\alpha\)-hydroxyketosuccinate 2, diethyl oxazole-4, 5-dicarboxylate 3 is obtained. The diester was hydrolyzed with ether-ethanolic NaOH or aqueous Ba(OH)\textsubscript{2}, and decarboxylation of the acid salt 4 is effected by heating 4 in quinoline in the presence of quinoline sulfate and copper or copper oxide to give oxazole 1 in 30-50\% overall yield.
1.3 Biological Activity Azole Derivatives

The first report of antifungal activity of an azole compound, benzimidazole, was in 1944 by Woolley\textsuperscript{13}, who was studying biotin deficiency in animals and microbes. He noted the structural similarity of biotin and purines to benzimidazole, but the biological effects of benzimidazole were not reversed by biotin, whereas they were reversed by the purines adenine and guanine. Since mycotic diseases were of minimal interest in 1944, Woolley's initial discovery was largely ignored, although his data were confirmed in 1949. Thirty years later, Vanden Bossche observed that phenethylimidazole, another azole moiety with antifungal activity, inhibited the uptake of purines in yeast form Candida spp. by interference at the cell membrane\textsuperscript{14}. In 1952, Jerchel et al.\textsuperscript{15} revived Woolley's work and reported that certain substituted benzimidazole compounds had significant antifungal activity. This publication encouraged other investigators to screen this group of chemicals in search of a clinically useful antifungal agent. The breakthrough came in 1958 to 1959 when chlormidazole, a chlorobenzyl imidazole, was developed and studied in clinical trials\textsuperscript{16, 17}. 

**Scheme-1.1:**
Chlormidazole was sold as a 5% topical cream, the first azole derivative developed and marketed as an antifungal drug.

With the introduction of chlormidazole, interest in the antifungal activity of azole compounds began to increase. For example, after the introduction of thiabendazole, a thiazolyl-benzimidazole, in 1961 by Merck Sharp & Dohme for use as a broad-spectrum antihelminthic drug, Robinson et al. tested the compound for antifungal activity in vitro. It was effective against many dermatophytes and Aspergillus species, but since its activity against yeast-like fungi was minimal, the compound was not developed as an antifungal agent. Similarly, mebendazole, a benzoyl-benzimidazole developed by Janssen Pharmaceutica (Beerse, Belgium) in 1973 as a broad-spectrum antihelminthic agent, was shown to have antifungal activity.

Despite the fact that the antifungal activity of these two compounds was not pursued, the data supported the concept that two azole compounds had potential as antifungal drugs for human use. In the late 1960s, three compounds from two different laboratories were introduced in the literature; these drugs firmly established azoles as antifungal agents. Clotrimazole, developed by Bayer AG (Wuppertal, Federal Republic of Germany), and miconazole and econazole, developed by Janssen Pharmaceutica, were introduced within months of each other. This era of azole antifungal compounds was so new and competitive that the less descriptive report of clotrimazole antifungal activity was
published 3 years prior to the more detailed description of the chemical synthesis\textsuperscript{21}. These three imidazoles continue to be used today for treatment of fungal infections, demonstrating the success of these early discoveries. Unfortunately, their use also reveals the slow evolution of the azole class of antifungal drugs during the past two decades.

Although progress with this group of antifungal agents has been slow, several clinically useful compounds have been developed, and many, which appear promising, are presently under development and clinical evaluation. New triazole derivatives, e.g., fluconazole and itraconazole, appear to be less toxic and more active than ketoconazole\textsuperscript{22}. The azole antifungals include two classes, imidazoles and triazoles, which share the same mechanism of action. Imidazoles have a two-nitrogen azole ring; they are predominantly used topically and have been replaced for systemic administration by triazoles, which have three nitrogens in the azole ring.

Triazoles have a more favorable pharmacokinetic profile than imidazoles and do not significantly inhibit human sterol synthesis. They were introduced almost 30 years ago. Fluconazole and itraconazole were the first azoles in clinical practice. Voriconazole is structurally similar to fluconazole and posaconazole to itraconazole. These and several other biologically active azole derivatives are discussed in following chapters.
<table>
<thead>
<tr>
<th>S. No</th>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Chemical structure</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clotrimazole</td>
<td>Canesten, Mycelex, Mycelex-G, Lotrimin</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis</td>
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<td>2</td>
<td>Miconazole</td>
<td>Monistat, Monistat-Derm, MonistatIV.</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Systemic fungal infections, including coccidioidomycosis, candidiasis, cryptococcosis, and chronic mucocutaneous candidiasis</td>
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<tr>
<td>3</td>
<td>Econazole</td>
<td>Spectazole, Pevaryl</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis</td>
</tr>
<tr>
<td>4</td>
<td>Ketoconazole</td>
<td>Nizoral, Fungarol, Fungarest, Orifungal</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Systemic fungal infections, including blastomycosis, certain forms of coccidioidomycosis and histoplasmosis, chronic mucocutaneous candidiasis, chromoblastomycosis, paracoccidioidomycosis.</td>
</tr>
<tr>
<td>5</td>
<td>Bifonazole</td>
<td>Mycospor, Mycosporan</td>
<td><img src="image" alt="Chemical structure" /></td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous candidiasis</td>
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<tr>
<td>6</td>
<td>Butoconazole</td>
<td>Femstat</td>
<td>Vaginal candidiasis</td>
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<tr>
<td>7</td>
<td>Croconazole</td>
<td>Pilzcin</td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous candidiasis</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Isoconazole</td>
<td>Travogen Travogen</td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis</td>
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<tr>
<td>9</td>
<td>Fenticonazole</td>
<td>Lomexin</td>
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<td></td>
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<tr>
<td>10</td>
<td>Oxiconazole</td>
<td>Oceral Myfungar Gyno-Myfungar Okinazole Derimine</td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis</td>
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<tr>
<td>11</td>
<td>Sulconazole</td>
<td>Exelderm Sulcosyn</td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous candidiasis</td>
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<tr>
<td>12</td>
<td>Tioconazole</td>
<td>Trosyd Gyne-Trosyd</td>
<td>Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis</td>
<td></td>
</tr>
</tbody>
</table>
1.4. Literature for Synthesis of Azoles & Its Derivatives

K. Maruoka et al. reported\(^{23}\) that a chiral Ti(IV) catalyst 17 can be successfully utilized in the asymmetric 1, 3-dipolar cycloaddition reactions between various nitrones and acrolein to give the corresponding endo cycloadducts (isoxazolidines) 18 with high to excellent enantioselectivities (scheme-1.2).

**Scheme-1.2:**

Bratulescu et al. reported\(^{24}\) that starting from 1, 2-diketones and urotropine in the presence of ammonium acetate, a simple and efficient solventless microwave-assisted enabled the synthesis of 4, 5-disubstituted imidazoles 19 (scheme-1.3).

**Scheme-1.3:**

K. Bahrami reported\(^{25}\) a convenient method for the synthesis of 2-substituted benzimidazoles and benzothiazoles 20 offers short reaction times, large-scale synthesis, easy and quick isolation of the products,
excellent chemo selectivity, and excellent yields as main advantages (scheme-1.4).

**Scheme-1.4:**

```
R NH2
Y H Ar
+ H Ar
solvent-free
50°C, 9-70 min
```

Q. Yang et al. reported\(^2^6\) the synthesis of 1-monosubstituted aryl 1, 2, 3-triazoles 21 was achieved in good yields using calcium carbide as a source of acetylene. The copper-catalyzed 1, 3-dipolar cycloaddition reactions were carried out without nitrogen protection and in a MeCN-H\(_2\)O mixture (scheme-1.5).

**Scheme-1.5:**

```
Ar-N3 + 1.3 eq. CaC2
0.3 eq > Cul
0.3 eq. Na ascorbate
MeCN/H\(_2\)O (2:1)
rt., 2-20h
```

Q. Yang et al. reported\(^2^7\) that 4-Aryl-1H-1, 2, 3-triazoles 23 were synthesized from anti-3-aryl-2, 3-dibromopropionic acids 22 and sodium azide by a one-pot method using N, N-dimethylformamide as solvent in the presence of Pd\(_2\)(dba)\(_3\) and Xantphos (scheme-1.6).
Scheme-1.6:

R. C. Larock reported\(^{28}\) that a [3+2] cycloaddition of azides to benzyne affords a rapid and easy entry to a variety of substituted, functionalized benzotriazoles \(^{24}\) under mild conditions (scheme-1.7).

Scheme-1.7:

J. K. Sneed et.al reported\(^{29, 30}\) that 3, 5-Di (2-pyridyl) pyrazole \(^{26}\) was first obtained in the reaction of 1, 3-di (2-pyridyl) propane-1, 3-dione \(^{25}\) with hydrazine hydrate. A series of mono- and di (4-pyridyl)-substituted pyrazoles were synthesized using the same approach (scheme-1.8).

Scheme-1.8:
A. Silkhanova et.al reported\textsuperscript{31, 32} a large volume of the research was done by the authors who synthesized a series of symmetrical and unsymmetrical 3, 5-dipyridyl-substituted pyrazoles 27 and also a few 3, 5-dipyridyl-substituted isoxazoles 28 (scheme-1.9).

\textbf{Scheme-1.9:}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\( \text{R}^1 \)};
  \node (B) at (1,0) {\( \text{O} \)};
  \node (C) at (2,0) {\( \text{R}^2 \)};
  \node (D) at (3,0) {\( \text{O} \)};
  \node (E) at (4,0) {\( \text{N} \)};
  \node (F) at (5,0) {\( \text{N} \)};
  \node (G) at (6,0) {\( \text{\text{R}^3} \)};
  \node (H) at (0,-1) {\( \text{R}^1 \)};
  \node (I) at (1,-1) {\( \text{O} \)};
  \node (J) at (2,-1) {\( \text{R}^2 \)};
  \node (K) at (3,-1) {\( \text{O} \)};
  \node (L) at (4,-1) {\( \text{N} \)};
  \node (M) at (5,-1) {\( \text{N} \)};
  \node (N) at (6,-1) {\( \text{\text{R}^3} \)};
  \draw (A) -- (D) -- (E) -- (F) -- (G);
  \draw (H) -- (I) -- (J) -- (K) -- (L) -- (M) -- (N);
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\( \text{R}^1 \)};
  \node (B) at (1,0) {\( \text{O} \)};
  \node (C) at (2,0) {\( \text{R}^2 \)};
  \node (D) at (3,0) {\( \text{O} \)};
  \node (E) at (4,0) {\( \text{NH}_2\text{OH} \)};
  \node (F) at (0,-1) {\( \text{R}^1 \)};
  \node (G) at (1,-1) {\( \text{O} \)};
  \node (H) at (2,-1) {\( \text{R}^2 \)};
  \node (I) at (3,-1) {\( \text{O} \)};
  \node (J) at (4,-1) {\( \text{N} \)};
  \node (K) at (5,-1) {\( \text{O} \)};
  \node (L) at (6,-1) {\( \text{\text{R}^3} \)};
  \draw (A) -- (D) -- (E);
  \draw (F) -- (G) -- (H) -- (I) -- (J) -- (K) -- (L);
\end{tikzpicture}
\end{center}

J. Wang et.al reported\textsuperscript{33} one of the most convenient methods for the synthesis of 2, 4, 5-trisubstituted imidazoles is the reaction between 1, 2-diketones and aldehydes. In the case of derivatives of imidazole with pyridine substituents, however, the use of this method is restricted by the availability of the respective diketones. Thus, only the production of 4, 5-di (2-pyridyl) imidazoles 29 from the commercially a vailable 2, 2'-bipyridyl has been described in the literature. Here the imidazoles are obtained in a mixture with the corresponding imidazo [1, 5-\(\alpha\)]-pyridines 30 (scheme-1.10).
Scheme-1.10:

\[
\text{N} \quad \text{O} \quad \text{C} \quad \text{H} \quad \text{2} \quad \text{O} \\
\text{H} \quad \text{O} \quad \text{A} \quad \text{c} \quad \text{N} \quad \text{H} \quad \text{4} \quad \text{O} \\
\text{A} \quad \text{c} \\
\text{H} \quad \text{O} \quad \text{A} \quad \text{c} \\
\text{N} \quad \text{N} \quad \text{O} \\
\text{R} + \text{N} \quad \text{N} \quad \text{NH} \\
\text{R} \\
\text{R-H, Me, t, r-Pr. OMe, Cl, F, NO}_3
\]
1.5 References


