1,2,4-Triazole - a versatile azole, proves and popular as an antifungal agent

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Abstract: Several five membered ring systems, e.g., triazole, oxadiazole dithiazole and thiadiazole with three heteroatoms at symmetrical or asymmetrical positions have been studied because of their interesting pharmacological properties. In this review our emphasis is on synthetic development and pharmacological activity of the 1,2,4-triazole moiety which exhibit a broad spectrum of pharmacological activity such as antifungal, antibacterial, anti-inflammatory and anticancer etc. Triazoles have increased our ability to treat many fungal infections, for example, candidiasis, cryptococcal meningitis, aspergillosis etc. However, mortality due to these infections even with antifungal therapy is still unacceptably high. Therefore, the development of new antifungal agents targeting specific fungal structures or functions is being actively pursued. Rapid developments in molecular mycology have led to a concentrated search for more target antifungals. Although we are entering a new era of antifungal therapy in which we will continue to be challenged by systemic fungal diseases, the options for treatment will have greatly expanded.

Keywords: 1,2,4-triazole, 1,3,4-triazole, standard drugs containing 1,2,4-triazole, synthetic drugs containing 1,2,4-triazole, antifungal agents.

Introduction

The alarming rates of the growing emergence of antimicrobial resistance are major concerns to the public health and scientific communities worldwide, especially in the field of multidrug-resistant bacteria and fungi [1,2]. These trends have emphasized the urgent need for new, more effective, less toxic and safe antimicrobial agents and the development of structurally new classes of antimicrobials with novel mechanisms of action as well as structural modifications to improve both their binding affinity and their spectrum of activity. One such strategy that has been pursued in recent years with increasing significance employs a combination of two different active fragments in one molecule [3]. With this strategy, various drug moieties have been designed to bind independently to different biological targets to produce beneficial effects [4]. The chemistry of N-bridged heterocyclic compounds, such as triazole, has received considerable attention in recent years due to their biological activities. Triazole is one of a pair of isomeric chemical compounds with the molecular formula C₃H₄N₂. It is a basic aromatic heterocyclic ring [5]. Triazole derivatives are known to exhibit various pharmacological properties such as antimicrobial [6-10], antitubercular[11], anticancer [12,13], anticonvulsant [14], anti-inflammatory, analgesic [15] and antiviral [16]. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs including H₁/H₂ histamine receptor blockers, CNS stimulants, anti-anxiety agents and sedatives [17]. The most important use, however, is as antimycotics in drugs such as fluconazole, itraconazole and voriconazole[18,19].
The triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding biomolecular targets as well as in increasing solubility [20]. Moreover, triazoles can function as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drug, and thus have become increasingly useful and important in constructing bioactive and functional molecules [21-23]. Notably, the bioisosteric replacement between triazole moiety and its bioisoster triazole has received special attention in medicinal chemistry, which represented an efficient concept for the discovery and development of novel triazole drugs, significantly extending the chemical space of triazole scaffolds possessing potent activities or enhancing biological activities [24]. Additionally, many investigations have shown that the addition of alkyl chains and/or various aromatic substituents, especially containing halogen atoms, has an important effect on the antimicrobial activities. The antifungal azoles are a class of synthetic compounds that possess one or more azole rings. Whilst both imidazole and triazole are five membered ring heterocycles, imidazole contains two ring nitrogen atoms, whereas triazoles have three. However, compared with imidazoles (clotrimazol, ketoconazol, miconazol), triazoles are less susceptible to metabolic degradation and have much greater target specificity, increased potency and an expanded spectrum of activity [25,26].

Chemistry of triazoles

Triazole refers to either one of a pair of isomeric chemical compounds with the molecular formula $C_2H_3N_3$, and has a five membered ring containing two carbon and three nitrogen atoms. Triazoles have two isomeric forms, i.e., $1,2,3$-triazole (1) and $1,2,4$-triazole (2) (Figure 1).

![Figure 1: Isomeric forms of triazole.](image)

Triazoles are basic aromatic heterocyclic compounds. $1,2,3$-Triazoles are surprisingly stable compared to other organic compounds with three adjacent nitrogen atoms. However, flash vacuum pyrolysis at 500 °C leads to loss of molecular nitrogen (N$_2$) to produce aziridine. Certain triazoles are relatively easy to cleave by ring–chain tautomerism.

Literature survey reviewing marketed drugs containing $1,2,4$-triazole moiety is depicted below with the help of table, in that salient features of $1,2,4$-triazole containing marketed drugs has been explained along with their chemical structures. [Mds.mol files]

**Table 1 Standard Marketed Drugs Containing 1,2,4-TRIAZOLE**

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Name of the drug</th>
<th>Chemical Structures</th>
<th>Salient features</th>
<th>References</th>
</tr>
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<tr>
<td></td>
<td>1. Voriconazole cleared <em>Candida</em> from the bloodstream as quickly as amphotericin B (median 2 days) and showed a trend toward better survival.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
4. RAVUCONAZOLE

1. RAVUCONAZOLE (BMS-207147 and ER-30346) is a potent triazole antifungal, being developed by Bristol-Myers Squibb, that is currently in phase I/II clinical trials.
2. The drug has shown to have a similar spectrum of activity to voriconazole, with an increased half-life. However, ravuconazole has limited activity against species of Fusarium, Scedosporium, and Zygomycetes.

5. TERCONAZOLE

1. Terconazole is an antifungal medication, primarily used to treat vaginal fungal infections.

6. ISAVUCONAZOLE

1. Isavuconazole (BAL4815) is an experimental triazole antifungal
7. **itraconazole**

1. Itraconazole has a broader spectrum of activity than fluconazole.

2. It is also licensed for use in blastomycosis, sporotrichosis, histoplasmosis, and onychomycosis.

3. Itraconazole is over 99% protein-bound and has virtually no penetration into cerebrospinal fluid. Therefore, it should never be used to treat meningitis or other central nervous system infections.

4. Itraconazole has also recently been explored as an anticancer agent for patients with basal cell carcinoma, non-small cell lung cancer, and prostate cancer.

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8. **Fluconazole**

1. Fluconazole is an antifungal medication that is administered by mouth or intravenously.

2. It is used to treat a variety of fungal infections, especially *Candida* infections of the vagina ("yeast infections"), mouth, throat, and bloodstream.

3. It is also used to prevent infections in people with weak immune systems, including those with neutropenia due to cancer chemotherapy, transplant patients, and premature babies.

4. Its mechanism of action involves interfering with synthesis of the fungal cell membrane.

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Efinaconazole

1. It is approved for use in Canada and the USA as a 10% topical solution for the treatment of onychomycosis (fungal infection of the nail).
2. Efinaconazole acts as a 14α-demethylase inhibitor.

wikipedia.org.in


### Table 2 Synthetic Drugs / Derivatives / Analogues Containing 1,2,4-TRIAZOLE

<table>
<thead>
<tr>
<th>Sr.no</th>
<th>Chemical Structures</th>
<th>Salient features and SAR</th>
<th>References</th>
</tr>
</thead>
</table>
| 1.    | ![Chemical Structure](image1) | 1. N-methyl group could form hydrophobic interaction with the surrounding residues and maintain the suitable conformation of the side chain in the CYP51 active site.  
| 2.    | ![Chemical Structure](image2) | 1. They showed excellent activity against most of the tested pathogenic fungi. For C. albicans and C. neoformans,  
| 3. | ![Chemical Structure](image) | 1. Molecular docking studies revealed that the hydrophobic and *van der Waals* interactions between the alkyl group and CACYP51 could compensate for the loss of TT–TT stacking interactions of the aromatic group.  
2. SAR results indicated that linkers (X) played important roles in their antifungal activities.  
3. *N*-methyl group and piperazinyl group are much better than hexahydropyrimidinyl and piperidin-4-imino group. The length of alkyl group is suitable for 3 or 4 carbon atoms. Various substitutions attached to the terminal phenyl group, such as halogens and nitro group, are favorable for the antifungal activity. |

| 4. | ![Chemical Structure](image) | 1. This compound target the biosynthesis of ergosterol by inhibiting the cytochrome P450-dependent lanosterol 14α-demethylase (Erg11p, CYP51), encoded by the ERG11 gene, resulting in accumulation of toxic methylsterols in membranes that may culminate in fungistatic effect or fungal death. |
1. Exhibits broad spectrum antifungal activity against candida species
2. Shows appreciable antifungal activity with mycostatin


1. Incorporation of triazole nucleus, a biologically important and accepted pharmacophore, into benzimidazole ring system makes it a versatile heterocycle possessing wide spectrum of antifungal activity against candida albicans and aspergillusniger.


1. Exhibit the capacity to overcome CDR and ERG11 gene upregulation and to maintain antifungal activity despite a recognized critical CYP51 substitution in C. albicans isolates.

2. Decreased intracellular accumulation of azoles due to the overexpression of genes encoding efflux transporters belonging to the ABC superfamily (CDR1 and CDR2) or major facilitator superfamily (MDR1)

3. Genetic alterations in the ERG11 gene leading to amino acid substitutions in the target enzyme CYP51 that decrease drug binding; alterations in the sterol biosynthesis pathway that bypass the accumulation of toxic sterols and overexpression of the ERG11 gene. Therefore, the antifungal


agent is overwhelmed, and routine therapeutic concentrations can no longer effectively inhibit ergosterol synthesis.

| 8 | ![Chemical Structure](image) | 1. The best MFC was 0.5 mg/mL that was observed for compounds A. against clinical Candida albicans and B. against standard Candida albicans and Candida kruzei.

2. Compounds A and B were also effective against all the tested fungi.

3. These compounds have imidazole ring and smaller size than the other compounds.

4. These compounds are very close to clotrimazole.

5. May be attributed to the better penetration into fungi cell. |

| 9 | ![Chemical Structure](image) | 1. Presence of chlorine and nitro substituent at the ortho and para position of the phenyl ring in A & B led to increase in activity.

2. Chlorine at ortho position of the phenyl ring provided activity to compound C.

3. Thetriazolyl ring clubbed with benzimidazole moiety in same molecule frame led to response in anthelmintic activity. |
1. A possessing smaller size than the other compounds and may be attributed to the better Penetration into fungi cell.

2. The activity was decreased by the presence of methoxy group on the triazoles and benzotriazoles Moiety in B.

3. Compounds C and D also possessed great inhibitory effect on tested fungus.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Activity</th>
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<tbody>
<tr>
<td>10. A.</td>
<td>1. Structure–activity relationship clearly suggested that introduction of a biaryloxy side chain greatly enhanced the antifungal activity of triazole</td>
</tr>
<tr>
<td>D.</td>
<td>Thiones group exhibiting significant antifungal activity against candida species.</td>
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<tr>
<td>Page</td>
<td>Image</td>
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<td>13</td>
<td><img src="image1.png" alt="Image" /></td>
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<tr>
<td>15</td>
<td><img src="image3.png" alt="Image" /></td>
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</tbody>
</table>
| 16   | ![Image](image4.png) | 1. Shows moderate antifungal activity against candida albicans.  
2. Nitro substitution at para position show antifungal activity as compared to ketoconazole. |
| 17   | ![Image](image5.png) | 1. Methoxy substituted triazole derivatives shows antifungal activity against candida albicans and aspergillus niger.  
2. Thiol group is also responsible to show antifungal activity. |
| 18   | ![Image](image6.png) | 1. Exhibits antifungal activity against fungal strains such as Candida albicans, Aspergillus fumigatus, Aspergillus flavus, and Aspergillus niger.  
2. Some compounds showed potent antifungal activity. |
Conclusion

The azole antifungal drugs have introduced a new era in antifungal chemotherapy. Although they all act through a similar mechanism, they vary widely in fungal spectrum, pharmacokinetics and toxicities. Other potent agents in earlier stages of development may further expand the options available in this remarkable group of compounds. Recent advances in antifungal chemotherapy and the addition of newer broad spectrum triazoles, offer clinicians more effective and less toxic alternatives to conventional amphotericin B. Even with the introduction of azole antifungal drugs and despite recent advances, mortality rates from invasive fungal infections remain high and there is a necessity for new treatment options. Earlier diagnosis, rapid restoration of the host immune system, the combination of antifungals and development of other compounds may improve the outcome of IFIs.

References:


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