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A REVIEW ON AZOLE ANTIFUNGALS

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Abstract:
There has been a dramatic increase in the prevalence of serious invasive fungal infections over the past decade Up to 5% of the total infections in the world are caused by fungi. Fungal infections (mycoses), though not as frequent as bacterial or viral infections, have nonetheless been increasing in incidence in the human population. The design, synthesis and antimicrobial activity of azole derivatives have been extensively investigated and have become one of the highly active highlights in recent years, and the progress is quite rapid.

Keywords- *Chemistry*

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INTRODUCTION:

There has been a dramatic increase in the prevalence of serious invasive fungal infections over the past decade Up to 5% of the total infections in the world are caused by fungi. Fungal infections (mycoses), though not as frequent as bacterial or viral infections, have nonetheless been increasing in incidence in the human population. In addition, a number of fungal infections can be difficult to treat, even when the offending organism is identified and appropriate therapy is applied. Fungi have unique characteristics, distinct from their mammalian hosts, allowing for selective targeting of therapeutic drugs.

Fungi are, however, much more complex organisms in comparison to bacteria, are in fact eukaryotic and often grow fairly slowly. Consequently, only a few drugs are aimed at interfering with cell division and have limited use.

Some of the major factors behind the increasing incidences of fungal infections include greater use of broad-spectrum antibiotics; indwelling catheters; immunosuppressive drugs and increase in the number of individuals suffering from acquired immunodeficiency syndrome (AIDS).

The infections are mainly caused by fungi like *Candida* spp., *Cryptococcus neoformans*,*Aspergillus*spp., *Pneumocystis carinii*and *Histoplasmacapsulatum. Candida* species are most common cause of nosocomial bloodstream infections. For the treatment of such fungal infections several antifungal drugs have been produced as a result of advances in medicinal chemistry. Azoles are one of the most promising antifungal agents out of all. They are the largest class of synthetic antimycotics used to treat both superficial dermatophytic as well as systemic fungal infections. It is approved by FDA for treating candidiasis, chronic mucocutaneous candidiasis oral thrush, candiduria, coccidioidomycosis, histoplasmosis, chromomycosis and Para coccidioidomycosis.

The antifungal azoles belong to two main classes, namely the Imidazoles and the Triazoles. Although the earliest azole, Chlorimidazole was not very efficient but with gradual improvements over last 50 years, many new and more potent antifungal azole derivatives have been developed. The azole antifungal agents developed so far for clinical uses mainly include ketonazole, fluconazole, voriconazole and itraconazole.

Despite the implementation of several preventive measures and the use of antifungal chemoprophylaxis, physicians have witnessed an increased incidence of both mucosal and invasive fungal infections during the past two decades [1,2]. This increase is linked with progress in medical technology and novel therapeutic options and appears to be multifactorial. The widespread use of quinolone prophylaxis in neutropenic cancer patients and the availability of broad-spectrum antibacterial agents has virtually eliminated early death due to bacterial sepsis, thereby setting the stage for fungal colonization and putting patients at risk for subsequent mycotic infections. Medical procedures have become more invasive and aggressive; the accompanying disruption of protective anatomical barriers as a result of indwelling catheters, therapy-induced mucositis, viral infections, and graft-versus-host disease, or following major abdominal surgery or associated with extensive burns, allows fungi to reach normally sterile body sites. In addition, the community of vulnerable patients is continuously expanding as a result of the spread of human immunodeficiency virus (HIV) infections, the increased use of (novel) immunosuppressive drugs in autoimmune disorders and to prevent or treat rejection in the expanding area of transplant medicine, the popularity of dose-escalated, often myelo-ablative cytotoxic therapy, the improved survival rate in premature infants, and the availability of sophisticated life-saving medical techniques. Unfortunately, the attributable mortality rate of (systemic) fungal infections remains high. This may partly be explained by the difficulty of diagnosing these infections at an early stage of their development, because definite proof often requires time-consuming and labor-intensive approaches that cannot always be achieved in these severely ill patients. However, an additional explanation may be found in shortcomings of the current antifungal armamentaria [15].

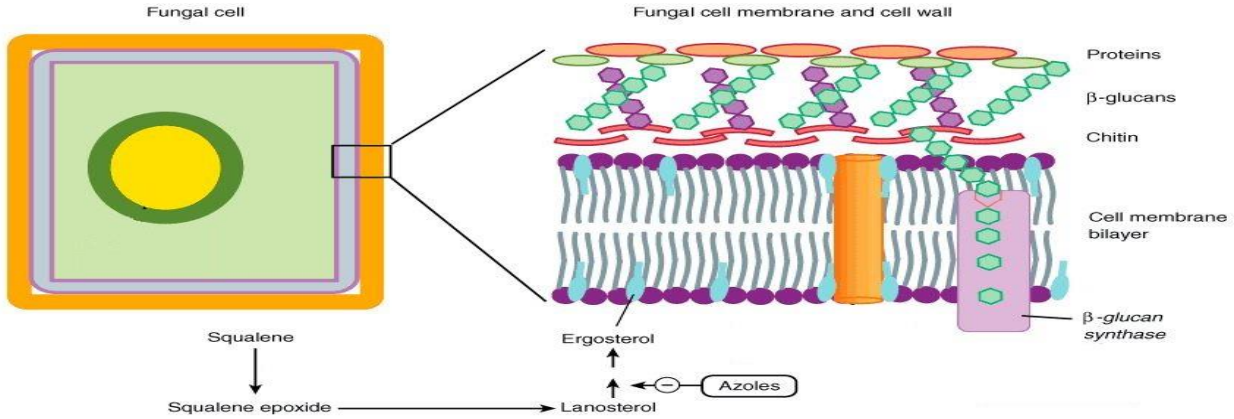
The design, synthesis and antimicrobial activity of azole derivatives have been extensively investigated and have become one of the highly active highlights in recent years, and the progress is quite rapid. It is hopeful that azole compounds may continue to serve as an important direction for the exploitation of azole-based antifungal drugs with better curative effect, lower toxicity, less side effects, especially fewer resistances and so on[3,5].

MECHANISM OF ACTION:

Azole antifungals are divided into the imidazoles (e.g. miconazole and ketoconazole) and the triazoles (e.g. itraconazole, fluconazole, voriconazole). The latter group has three instead of two nitrogen atoms in the azole ring. All of the azoles operate via a common mode of action: they prevent the synthesis

of ergosterol, the major sterol component of fungal plasmamembranes, through inhibition of the fungal cytochrome P450-dependent enzyme lanosterol 14-a demethylase. The resulting depletion of ergosterol and the concomitant accumulation of 14-a-methylated precursors interferes with the bulk function of ergosterol in fungal membranes and alters both the fluidity of the membrane and the activity of several membrane-bound enzymes (e.g. chitin synthase). The net effect is an inhibition of fungal growth and replication. In addition, a number of secondary effects, such as inhibition of the morphogenetic transformation of yeasts to the mycelialform, decreased fungal adherence, and direct toxic effects on membrane phospholipids, have been reported [5,6,18].

Unfortunately, as a result of the nonselective nature of the therapeutic target, cross-inhibition of P450-dependent enzymes involved in mammalian biosynthesis has been responsible for some toxicity, although significantly lower and less severe withfluconazole, itraconazoleand voriconazole than with the older compounds. The improved toxicity profile of the triazoles compared to the imidazoles(especially endocrine related(side-effects) can be explained by their greater affinity for fungal rather than mammalian P450-enzymes at therapeutic concentrations[15,16].



Mechanism of action of azoles

CLASSIFICATION

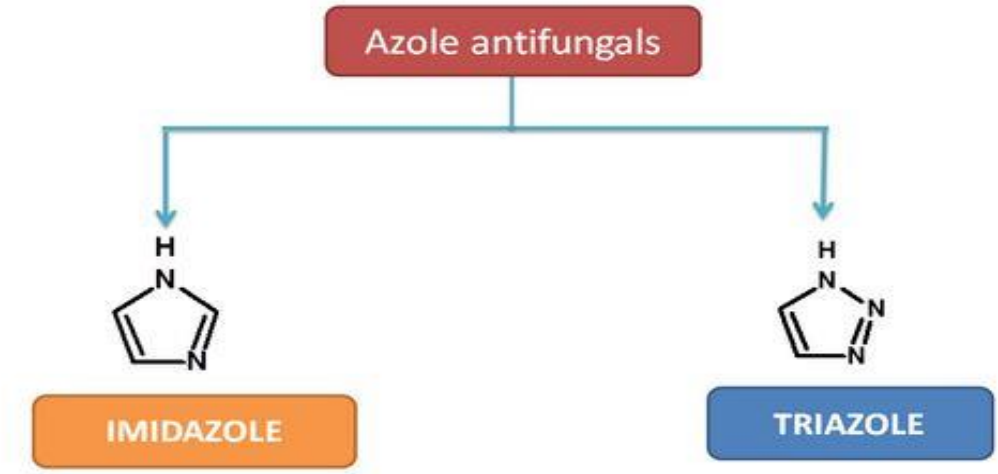
Azole antifungals are a group of medicines that contain an azole ring and inhibit the growth of a wide range of fungi. They are classified into two groups: those with two nitrogens in the azole ring, the imidazoles and those with three nitrogens in the azole ring, triazoles.

Class	Route of administration	Examples	Significance
Imidazole group	Topical agents	Clotrimazole, EconazoleMiconazole, Butaconazole	Their use is limited to topical administrations and has been replaced by Triazoles for systemic applications
	Systemic agent	Ketoconazole	
Triazole group	Topical agents	Teraconazole, Itraconazole	They are advantageous over Imidazoles in terms of having broad spectrum activity against both superficial and systemic fungal infections and having greater affinity for fungal rather than mammalian cytochrome P450 enzymes thus reducing the risk factors
	Systemic agents	Fluconazole, Itraconazole, Voriconazole	

Azole antifungal agents can be used to treat fungal infections of the body and skin, including athlete's foot, onychomycosis (fungal nail infections), ringworm, and vaginal candidiasis[1,2,15].

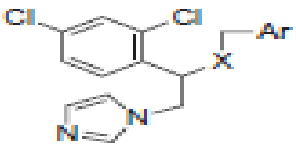
CHEMISTRY

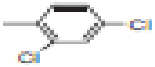
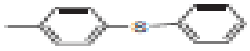
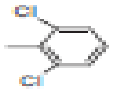
Azoles are basically five member heterocyclic compounds containing one or more different heteroatom out of which at least one must be nitrogen and other hetero atom may be nitrogen or other than nitrogen.

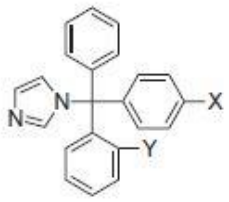


Azole compounds are an important class of nitrogen, heterocycles with electron-rich property. This special structure endows azole-based derivatives easily bind with the enzymes and receptors in organisms through noncovalent interactions such as hydrogen bonds, coordination bonds, ion-dipole, cation-π,π-π stacking and hydrophobic effect as well as van der Waals force etc., thereby possessing various applications in medicinal chemistry, especially their protrudent effects such as imidazoles and triazoles against fungal strains[1,2].

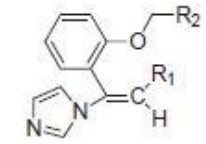
STRUTURAL ACTIVITY RELATIONSHIP

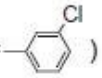


Generic name	X	Ar
Miconazole	O	
Econazole	O	
Sulconazole	S	Same
Fenticonazole	O	
Isoconazole	O	
Sertaconazole	O	
Tioconazole	O	

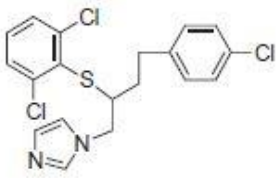


Clotrimazole (X = H, Y = Cl)
Flutrimazole (X = Y = F)

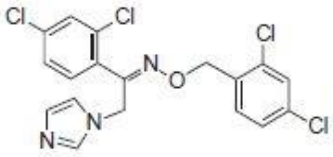


Croconazole (R_1 = H, R_2 = )

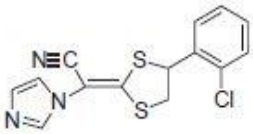
Neticonazole (R_1 = SCH_3, R_2 = n-C_4H_9)



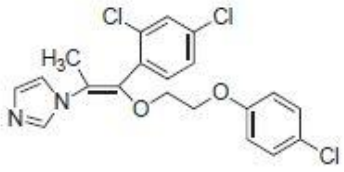
Butoconazole



Oxiconazole

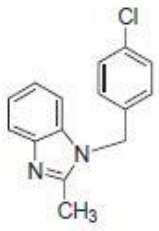


Lanoconazole



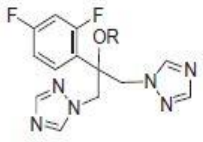
Omoconazole

Ketoconazole

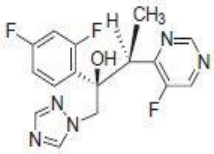


Chlormidazole

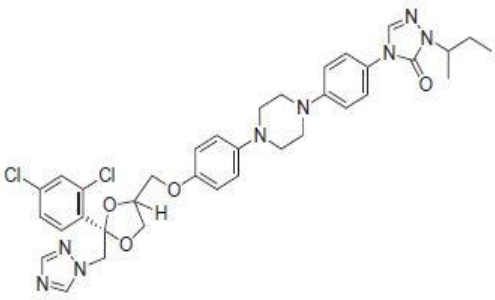
Imidazole antifungal agents



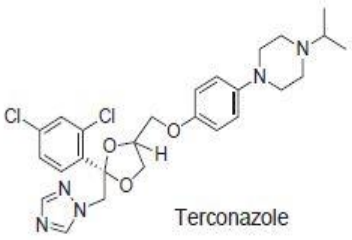
Fluconazole (R = H)
Fosfluconazole (R = )



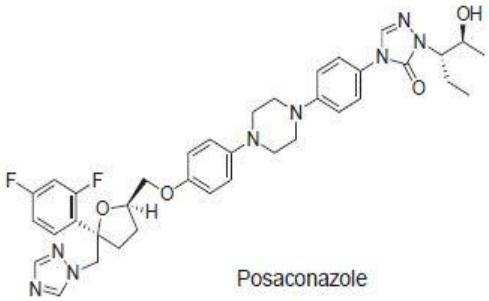
Voriconazole



Itraconazole



Terconazole



Posaconazole

Triazole antifungal agents

The basic structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pKa of 6.5–6.8) bonded by a nitrogen–carbon linkage to the rest of the structure.

At the molecular level, the amidine nitrogen atom (N-3 in the imidazoles, N-4 in the triazoles) is believed to bind to the heme iron of enzyme-bound cytochrome P450 to inhibit activation of molecular oxygen and prevent oxidation of steroidal substrates by the enzyme.

The most potent antifungal azoles possess two or three aromatic rings, at least one of which is halogen substituted (e.g., 2,4-dichlorophenyl, 4-chlorophenyl, 2,4-difluorophenyl), and other nonpolar functional groups. Only 2, and/or 2,4 substitution yields effective azole compounds.

The halogen atom that yields the most potent compounds is fluorine, although functional groups such as sulfonic acids have been shown to do the same.

Substitution at other positions of the ring yields inactive compounds. Presumably, the large nonpolar portion of these molecules mimics the nonpolar steroidal part of the substrate for lanosterol 14-demethylase, lanosterol, in shape and size.

The nonpolar functionality confers high lipophilicity to the antifungal azoles. The free bases are typically insoluble in water but are soluble in most organic solvents, such as ethanol. Fluconazole, which possesses two polar triazole moieties, is an exception, in that it is sufficiently water soluble to be injected intravenously as a solution of the free base [6,10].

CONCLUSION:

Thus we can conclude that azoles plays an important role in possessing the broad spectrum of activity against fungus.It is understood that each azoles are having specific antifugalactivity.On seeing the pharmacokinetics, the absorption of azoles are influenced by food and other drugs.Mectabolism takes in liver by phase I and phase II reaction. In case of excretion, major excretion takes by biliary route (80%) and a minor excretion by urine (20%). The expression of resistance to antifungal agents(azoles) by fungus is the inevitable consequence of using these azoles to treat human infection. Continued effects to study the mechanism of resistance and development of experimental studies will be the important component to limit the emergence of resistance to these agents and to develop safer and more potent compound for the future.

Drug-drug interaction do not only occur when therapy is initiated, but also become evident after the drug therapy is stopped, particularly if the agent is an enzyme inducer, because this might lead to toxic concentration. Therapeutic drug monitoring is a valuable tool for assessing the effect of a drug-drug interaction for both the antifungal azoles, and if possible, the co-administered drug.

Further advance in antifungal azole chemotherapy will be necessary to improve management in invasive mycoses in future.

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