Review Article

Emerging Trends in 1, 2, 4 -Triazole as Antifungal Agents

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Fungal infections are on the increase and there exists a well recognised un-met clinical need for more effective anti-fungal agents that will combat drug resistance and not cause the severe side effects of some current therapies. The first antifungal agent griseofulvin, was isolated in 1939 and the first azole and polyene antifungal agents were reported in 1944 and 1949, respectively. With 15 different marketed drugs worldwide, the azoles are the most widely used and studied class of antifungal agents. This review focuses on the clinically important 1, 2, 4 - triazole antifungal agents currently marketed and some promising new agents under development.

Keywords: *Antifungal activity, azole antifungal agents, sterol biosynthesis inhibitors, 4-Amino-1, 2, 4 -triazole.*

Introduction

Modern medicine has greatly increased the number of immunocompromised patients. The incidence of fungal infection caused by opportunistic pathogens has increased significantly. The growing number of immunocompromised patients as a result of cancer chemotherapy and HIV infection are the major factors contributing to this incidence. Although some new drugs have recently been introduced to clinical practice, the number of available preparations to treat systemic fungal infections is still limited and more alternatives are needed, particularly with improved efficacy against emerging pathogens with limited susceptibility to the available preparations [1, 2]. Well-known azole derivatives, having a gem-phenyl-(1H-imidazol-1-ylmethyl) moiety (Fig. 1) which is thought to be largely responsible for imparting, antifungal activity, such as clotrimazole, miconazole (Fig. 2), econazole, and ketoconazole, have been developed for clinical uses. SAR studies revealed that imidazole and phenyl rings in these molecules can be replaced by the triazole [3].

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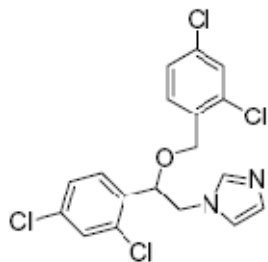**Figure 1:** Structure of gem-phenyl-(1H-imidazol-1-ylmethyl) moiety.

Figure 2: Structure of miconazole.

Sterols are essential lipid components of eukaryotes and are responsible for a number of important physical characteristics of membranes. Sterol biosynthesis is an essential eukaryotic metabolic pathway in animals (cholesterol biosynthesis), fungi (ergosterol biosynthesis) and plants (biosynthesis of sitosterol and an array of phytosterols)[4].The azole antifungals prevent the synthesis of ergosterol as are inhibitors of sterol 14α-demethylation (Fig. 3) and are the most widely discovered class of sterol biosynthesis inhibitors.[5]
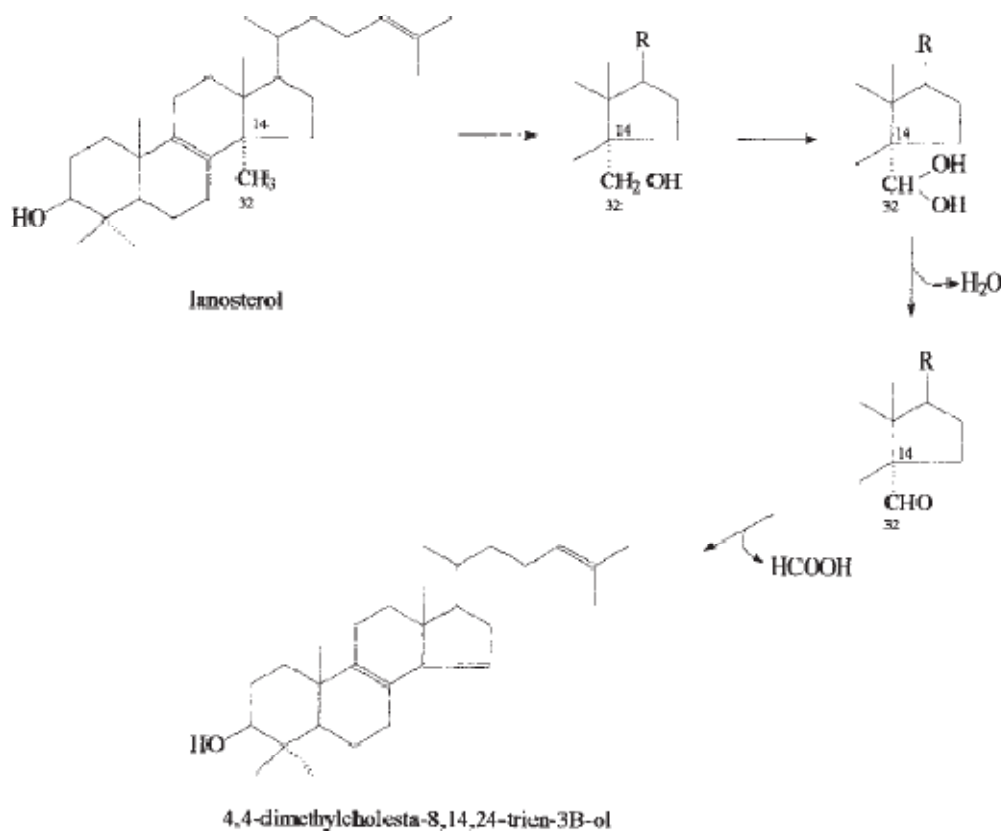

Figure 3: Chemical process of lanosterol 14α-demethylationcatalysed by CYP51.

The azoles inhibit the demethylation of 14α lanosterol in fungi, a process dependent on the cytochrome P450 system [6]. This action inhibits the production of ergosterol a key component in the fungal cell membrane. The mode of action of azole antifungals has been subject to much genetic and biochemical investigation [7] and is now open to investigation by post-genomic techniques.

The first agent with antifungal activity, griseofulvin,was isolated in 1939 [8] and the first azole and polyene antifungal agents were reported in 1944 and 1949, respectively. During the 1980s the azole antifungal compounds were introduced in orally administered forms, firstly with ketoconazole and then later with fluconazole and itraconazole(9). Fluconazole was first studied at Zeneca Agrochemicals (formerly ICI), as an agrochemical candidate, but recognized as a potent medical antimycotic by Pfizer. It has a good toxicological and pharmacokinetic profile, but is not active against all pathogens encountered clinically e.g. *Candida krusei*, *Aspergillus fumigatus*.

The azole antifungal agents in clinical use contain either two or three nitrogens in the azole ring and are thus classified as imidazoles (e.g., ketoconazole and miconazole, clotrimazole) or triazoles (e.g., itraconazole and fluconazole),

respectively [9]. Triazoles and in particular 1,2,4-triazole nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, antianxiety, antimicrobial agents.[10,11] antifungal activity. [12,13]

An ideal heterocyclic is the 4-amino-3-mercapto-4H-1,2,4 -triazole system which, by virtue of its vicinal nucleophiles amino and mercapto groups constitues a ready-made building block for construction of various organic heterocycles [14]. A series of 5 - [2-(substituted sulfamoyl) -4, 5-dimethoxy - benzyl] – 4 aryl -s-triazole-3-thiones showed significant antifungal activity against all the micromycetes. Differences in their activity depend on the substitution of different reactive groups. More specifically, best antifungal activity among synthetic analogues was shown with N-dimethylsulfamoyl group. Furthermore, it is apparent that different compounds reacted in different ways against bacteria. Gram (-) bacteria seem to be more sensitive to these compounds than Gram (+) species. [15]

A series of triazole antifungal agents,1-(1 H- 1, 2, 4-triazolyl)-2-(2,4-diflurophenyl) - 3-(4-substituted-1-piperazinyl)- 2-Propa-nols showed activity against the common pathogenic fungi to some extent and the activities against deep fungi were higher

than that against shallow fungi. In general, phenyl and pyridinyl analogues showed higher antifungal activity than that of the phenylacyl analogues.[16]

4-Amino-1,2,4 -triazole (Fig.4) has a CAS No. 584-13-4, molecular formula $C_2H_4N_4$ and molecular weight 84.08. It is a white crystalline powder with melting point 84 - 86 C. It is stable under ordinary conditions and is hygroscopic.
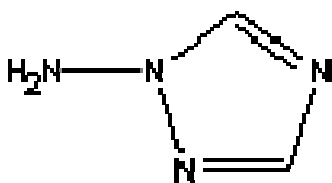

Figure 4: 4-Amino-1,2,4-triazole

Tetrazole-based triazole derivatives bearing an ethyl chain linked with an aryl-piperazine, possessed good antifungal activity against the different fungal cultures such as Candida species, C. neoformans and Aspergillus species(17). Among sulfones and sulfide derivatives of 1-(1 H – 1 , 2 ,4 – triazole - 1 –y l)- 2-(2,4-difluorophenyl)-3-substituted-2-propanols the sulfide derivatives exhibited potent activities against six kinds of common pathogenic fungi such as Microsporum lanosum, Cryptococcus neoformans, Candida albicans, Aspergillus fumigatus, Cladosporium carrionii, and Saccharomyces torulopsis in vitro, while the sulfone derivatives showed lower

antifungal activity(18). Ethyl 5-(2-furyl)-4-ethyl-1,2,4 -triazole-3-mercaptoacetate , 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide and a series of new *N*-alkylidene/arylidene-5-(2-furyl) -4- ethyl -1, 2, 4-triazole -3-mercaptoacetic acid hydrazides showed good antibacterial activity and antifungal activity [19].

Voriconazole is a second-generation new triazole antifungal agent whic.h can be given by either the intravenous or the oral route; the oral formulation has excellent bioavailability. The side effect of voriconazole include, non-sight-threatening, transient visual disturbances, rash (which can manifest as photosensitivity) and hepatitis. The potential for drug-drug interactions is high and requires , careful attention be given to dosage regimens. Voriconazole has been approved for the treatment of invasive aspergillosis and refractory infections with Pseudallescheria / Scedosporium and Fusarium species, and it will likely become the drug of choice for treatment of serious infections with those filamentous fungi [20].

FUTURE ROLE OF AZOLES IN ANTIFUNGAL THERAPY

Major developments in the azole class of antifungal agents during the 1990s have provided wide options for the treatment of

many opportunistic and endemic fungal infections. For over 20 years, amphotericin B was mainly used for treatment of serious systemic mycoses. The first oral azole, ketoconazole, introduced in the United States in 1981, provided an alternative to amphotericin B for nonmeningeal, non-life threatening infections and for outpatient treatment of histoplasmosis and blastomycosis [21]. Fluconazole has received widespread use for prophylaxis and treatment of candidal and cryptococcal infections, which are growing as the population of immunocompromised patients grows, and as single-dose oral therapy for vulvovaginal candidiasis. Although less widely used than fluconazole in AIDS patients and bone marrow transplant recipients due to variable absorption, itraconazole is used for the treatment of histoplasmosis and blastomycosis. It is considered drug of choice for the initial therapy of less severe cases of aspergillosis and for the treatment of onchomycosis due to both *Candida* and dermatophytes.[22,23] Expanded uses for the currently available azoles have been suggested.

Resistance to the available azole antifungal agents has become a major concern with their widespread use. In this review, we have discussed present and future uses of the currently available azole antifungal agents in the treatment of systemic and superficial fungal infections . Use of the currently available azoles in combination with other antifungal agents with different mechanisms of action is likely to provide increased efficacy. Some of the second-generation azoles and triazoles are being developed to provide extended coverage of opportunistic, endemic, and emerging fungal pathogens, as well as those in which resistance to older agents is becoming problematic. The use of combinations of fungicides is increasing in medicine and should be a route of choice for overcoming resistance. New azole compounds are under consideration, and in clinical trial. The emergence of resistance to these agents can be predicted and needs advance assessment to provide assistance for their proper integration into drug therapy.

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