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ORIGINAL ARTICLE

Triazole hybrids as new type of anti-fungal agents

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Abstract The present work involves synthesis of novel anti-fungal agents containing triazole scaffold. The newly designed compounds were synthesized on the trails of ketoconazole using the molecular hybridization approach. A series of 10 compounds having (2-((1H-1,2,4-triazol-1-yl)methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methyl esters (**4a**–**j**) were prepared by conventional synthetic approach. The synthesized compounds were subjected for *in vitro* anti-fungal screening against *Aspergillus niger*, *Aspergillus fumigatus*, *Candida albicans* and *Penicillium notatum*. Out of 10 newly synthesized compounds, six compounds (**4b**–**f** and **j**) showed remarkable anti-fungal activity (MIC range 6.5–25 μg/ml), whereas compound **4d** (MIC 6.5 μg/ml) was more potent than standard drug ketoconazole (MIC 12.5 μg/ml). These triazole hybrids can be considered as potential anti-fungal agents.

1. Introduction

Fungal infections pose a continuous and serious threat to human life. The severity of infection ranges from minor irritations such as athlete's foot to life-threatening systemic infections caused by *Aspergillus fumigates* (Uchida et al., 2008). Hence the development of a potent, safe and selective antifungal agent is of prime importance for medicinal chemist in the quest for effective chemotherapeutic treatment for fungal diseases (Rezaei et al., 2009). At present antifungal treatment with existing drugs proved to be less effective, due to drug toxicity and drug resistance against a wide variety of fungal species (Behbehani et al., 2011).

Triazole is an antifungal scaffold because of its high potency and low toxicity (Xu et al., 2004). Hence many potent antifungal compounds were developed in recent past by bioisosteric replacement of imidazole moiety with triazole (Acetti et al., 2009). Triazole derivatives competitively inhibit lanosterol 14α-demethylase (CYP51), a key enzyme in sterol biosynthesis of fungi. Based on the structure of the active site of CYP51 and the extensive investigation of azole antifungals, triazole inhibitors are able to fit in the active site by H-bonding, hydrophobic interactions and π–π stacking within the heme

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environment of the enzyme (Upadhayaya et al., 2009; Kamal et al., 2011).

The literature survey revealed that, many researchers developed potent anti-fungal agents by the molecular hybridization approach using dioxolone with diazole/triazole moiety (Hiromichi and Yasushi, 2000; Dariusz and Andrzej, 2007; Fringuelli and Giacche, 2009; Xu and Cao, 2011). Well known drugs *viz*. terconazole and itraconazole were developed as molecular hybrids of triazole and dioxolone, whereas triazole moiety was replaced by diazole in ketoconazole. The three crucial features of clinically active anti-fungal agents are diazole/triazole ring, aromatic ring and side chains (Fig. 1). Hence novel compounds were developed on the trails of the above mentioned molecular hybridization approach (Fig. 1).

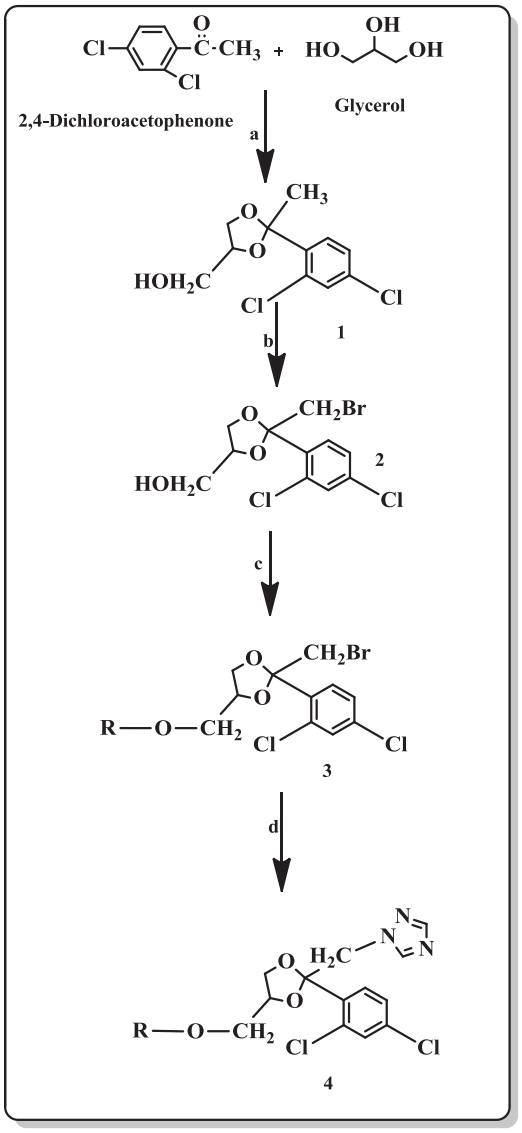
2. Results and discussion

2.1. Chemistry

The targeted compounds were synthesized by a four-step reaction process (Scheme 1). In the first step, glycerol and 2,4-dichloroacetophenone were used to synthesize (2-(2,4-dichlorophenyl)-2-methyl-1,3-dioxolan-4-yl)methanol **(1)** in the presence of *p*-toluene sulfonic acid. Compound **(1)** was brominated by using bromine and glacial acetic acid to obtain (2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methanol **(2)**. Intermediate **(2)** was converted into (2-(bromomethyl)-2-(2,4-dichloroacetophenyl)-1,3-dioxolan-4-yl) methyl ester **(3)** by reaction with corresponding aliphatic/substituted and unsubstituted aromatic acid chlorides. Finally, compounds **(3)** was stirred overnight with 50% sodium hydride and 1,2,4-triazole to obtain (2-((1H-1,2,4-triazol-1-yl)-methyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methyl esters (**4a**–**j**) (Table 1).

2.2. Biological activity

The anti-fungal activities of **4a**–**j** were performed against *Aspergillus niger*, *Penicillium notatum*, *A. fumigatus* and *Candida albicans* (Odds and Vanden Bossche, 2000) and results with respect to zone of inhibition and MIC are summarized in Tables 2 and 3. Compound **4d** which is benzenesulfonyl methylester (MIC 6.5 μg/ml) was found more potent than reference standard ketoconazole (MIC 12.5 μg/ml), while compound **4c**, cinnamoyl methylester (MIC 12.5 μg/ml) was at par with the reference standard. It was observed that in case of compounds **4a** and **b** esterification with aliphatic acid chlorides and *o* and *m* substituted aromatic methyl esters *viz*. **4f**–**i**



Scheme 1 Synthesis scheme for **4a**–**j** compounds. R = Aliphatic/aromatic acid chloride; **a** = *n*-BuOH, Benzene, *p*-TsOH; **b** = Br2, 25 °C;**c** = Pyridine, 5 °C, substituted acid chlorides; **d** = NaH, Triazole, DMSO, 130 °C.

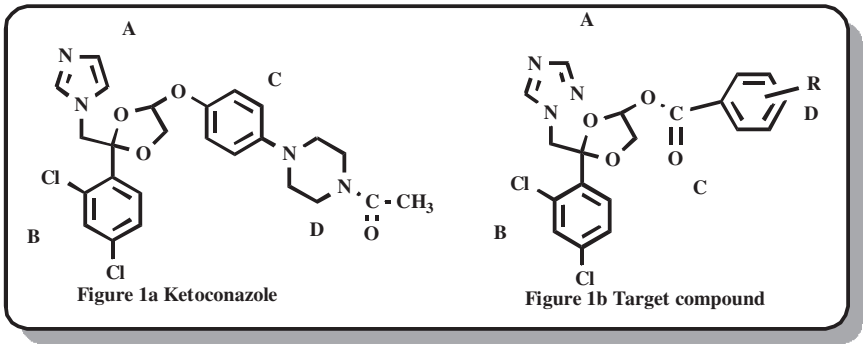


Figure 1 Comparison of ketoconazole and targeted anti-fungal agent. A = Iron coordinating group (diazole/triazole moiety); B = Aromatic group; C = Second aromatic ring; D = Additional hydrophobic group (side chain).