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Original article

New triazole derivatives containing substituted 1,2,3-triazole side chains: Design, synthesis and antifungal activity

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ABSTRACT

In order to discover new generation of triazole antifungal agents, a series of novel antifungal triazoles were designed and synthesized by structural simplification of our previously identified triazole-piperdine-heterocycle lead compounds. Several target compounds showed good antifungal activity with a broad spectrum. In particular, compound **7l** was highly active against *Candida albicans* and *Candida glabrata*. Moreover, compound **7l** showed potent *in vivo* antifungal efficacy in the *Caenorhabditis elegans–C. albicans* infection model.

1. Introduction

Recently, the incidence of invasive fungal infections (IFIs) and associated mortality has been increasing rapidly mainly due to the large number of immunocompromised patients and limited antifungal agents [1]. Most life-threatening IFIs are caused by *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*, whose mortality rate ranging from 20% to 90% [2,3]. However, there are only three classes of antifungal agents (*i.e.* polyenes, triazoles and echinocandins) available for the treatment of IFIs [4,5]. Clinical application of polyene antifungal agent amphotericin B is limited in some severe infections because of serious nephrotoxicity and many other side effects [6,7]. Echinocandins (*e.g.*, caspofungin and micafungin) have fungicidal activity, but they cannot be orally administrated. Clinically, triazole antifungal agents (*e.g.*, fluconazole, voriconazole, itraconazole, and posaconazole) are widely used as the first-line antifungal therapy for the prevention and treatment of IFIs (Fig. 1). However, broad application of the triazoles has caused severe drug resistance, which significantly reduced the clinical efficacy [8]. Thus, there is still an urgent need for the discovery and development of new generation of triazole antifungal agents [9–13]. For example, isavuconazole [14] was marketed in 2015 for treatment of invasive aspergillosis and invasive mucormycosis and albaconazole [15] are under late stages of clinical evaluations (Fig. 1).

Lanosterol 14α-demethylase (CYP51), a key enzyme in fungal membrane ergosterol biosynthesis, is the target of triazole antifungal agents. Due to the difficulties in solving structures of membrane-bound proteins, only one crystal structure of fungal CYP51 (*Saccharomyces cerevisiae* CYP51) has been reported [16]. However, the lack of high-resolution structural information for CYP51 from invasive fungal pathogens limited the structural optimization of the triazoles. Previously, we constructed three-dimensional models of *C. albicans* CYP51 (CACYP51), *C. neoformans* CYP51 (CNCYP51), and *A. fumigatus* CYP51 (AFCYP51) by homology modeling [17–19]. Guided by the binding modes of triazole antifungal agents [17,20,21], we rationally designed a number of highly potent new triazoles [21–34]. Among them, triazole **5** showed excellent *in vitro* antifungal activity with a broad antifungal spectrum (Fig. 2). Inspired by the results, further lead optimization was focused on improving the metabolic stability and *in vivo* antifungal potency. Herein a series of new 1,2,3-triazole containing triazole derivatives were designed and synthesized, which showed potent *in vitro* and *in vivo* antifungal activity.

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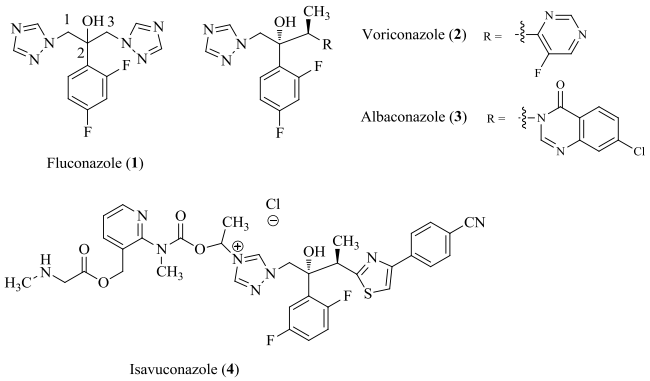

Fig. 1. Structures of triazole antifungal agents.

2. Results and discussion

2.1. Design rationale and molecular docking

In our previous studies, triazole **5** containing a benzyloxypiperidinyl side chain was identified as a potent antifungal agent with a broad spectrum (Fig. 2) [30]. However, it was metabolically unstable because of the benzyl alcohol substructure. Thus, lead compound **5** was further optimized by replacing the benzyl alcohol substructure with substituted heterocycles such as 1,2,3-triazole [31], 1,2,4-oxadiazole and 1,3,4-oxadiazole [34] (Fig. 2). Excellent antifungal activity was retained for these piperidinyl heterocylic derivatives [31,34]. Inspired by the results, we envisioned that the piperidinyl group can be further removed to reduce molecular weight and increase water solubility. Thus, a series of new traizole derivatives containing substituted 1,2,3-triazole side chains were synthesized and assayed because of its synthetic accessibility and usefulness in antifungal drug discovery [35–37].

In order to investigate whether the designed triazoles can bind well with the active site of CACYP51, the binding mode of compound **7l** was explored by molecular docking [31,34]. As shown in Fig. 3, the interactions between compound **7l** and CYP51 are similar to those observed in our previous studies [34]. The triazole ring formed a coordination bond with the Fe atom of the heme group and the difluorophenyl group was located into a hydrophobic pocket lined with Phe126 and Tyr132. The 1,2,3-triazole ring formed π–π interaction with Tyr118. Finally, the terminal cyclopropyl group interacted with Leu376, Phe380 through hydrophobic and Van der Waals interactions.

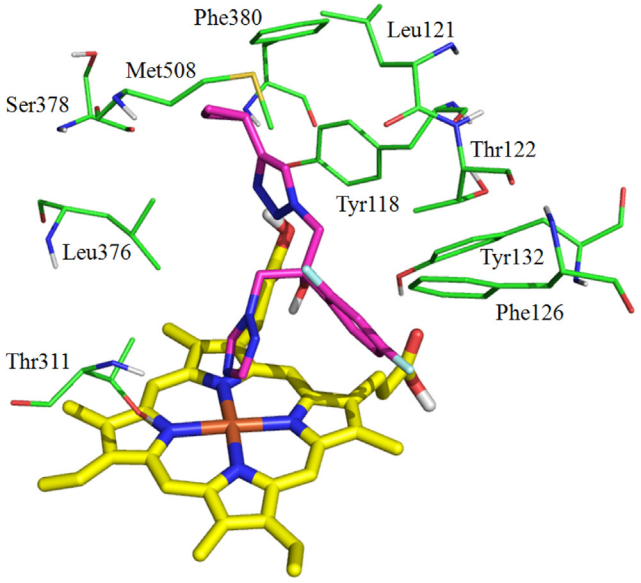

Fig. 3. The binding mode of compound **7l** in the active site of CACYP51.

2.2. In vitro antifungal activity

The inhibitory activity of the target compounds against clinically important pathogenic fungi was determined according to the protocols from National Committee for Clinical Laboratory Standards (NCCLS). The results revealed that most compounds generally showed moderate to excellent activity against the tested fungal pathogens (Table 1). Particularly, compounds **7f** (MIC = 0.125 μg/mL) and **7l** (MIC = 0.125 μg/mL) were highly active against *C. albicans*, which were more active than fluconazole (MIC = 0.5 μg/mL). In contrast, the target compounds generally showed improved activity against *Candida glabrata*, whereas they were less potent against *Candida parapsilosis*. For example, the activity of compounds **7j**, **7k**, **7l**, **8a** and **8b** (MIC range: 0.125–0.5 μg/mL) against *C. glabrata* were comparable or superior to that of fluconazole (MIC = 0.25 μg/mL). For *C. neoformans*, most compounds showed moderate activity except compound **8a** (MIC = 0.25 μg/mL), which was 8 fold more potent than fluconazole (MIC = 2 μg/mL). However, all the compounds as well as fluconazole were inactive against *A. fumigatus* (MIC > 64 μg/mL). For dematophytes (*Trichophyton* rubrum and *Microsporum* gypseum), the target compounds also showed moderate to good activity.In

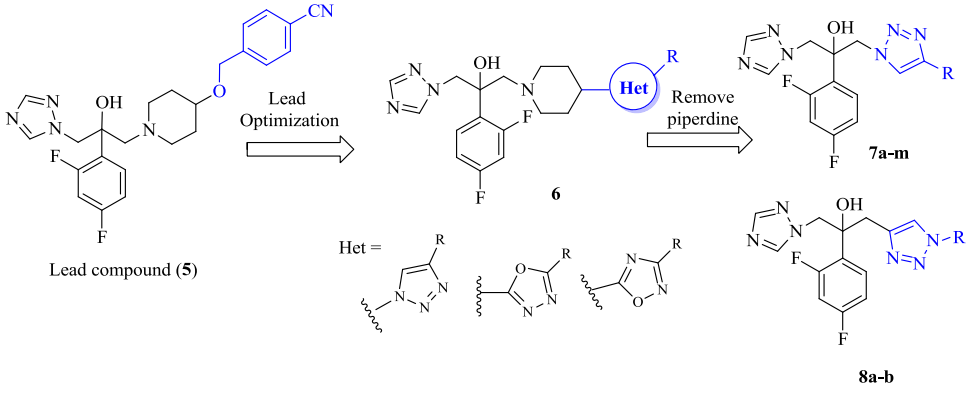

Fig. 2. Design rationale of the target compounds.