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Original article

Design and synthesis of novel triazole antifungal derivatives by structure-based bioisosterism

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ABSTRACT

The incidence of life-threatening fungal infections is increasing dramatically. In an attempt to develop novel antifungal agents, our previously synthesized phenoxyalkylpiperazine triazole derivatives were used as lead structures for further optimization. By means of structure-based bioisosterism, triazolone was used as a new bioisostere of oxygen atom. This type of bioisosteric replacement can improve the water solubility without loss of hydrogen-bonding interaction with the target enzyme. A series of triazolone-containing triazoles were rationally designed and synthesized. As compared with fluconazole, several compounds showed higher antifungal activity with broader spectrum, suggesting their potential for further evaluations.

1. Introduction

Over the past two decades, the incidence of systemic mycoses and associated mortality has increased dramatically [1,2]. This is primarily due to the increase in the number of immunocompromised individuals, such as patients receiving cancer chemotherapy or organ transplantation, and patients infected with human immunodeficiency virus. The most common fungal pathogens are species of *Candida*, *Cryptococcus* and *Aspergillus*. Clinically, amphotericin B (AmB) [3], triazoles (*e.g.* fluconazole and itraconazole, see Fig. 1) [4] and candins (*e.g.* caspofungin and micafungin) [5] are available to treat invasive fungal infections. However, these drugs were limited by their spectrum of activity, the development of resistance, non-optimal tolerability and drug–drug interactions. Therefore, there is an emergent need to develop novel antifungal agents with improved profiles.

Triazoles are the most widely used antifungal agents because of their high therapeutic index. They act by competitive inhibition of the lanosterol 14α-demethylase (CYP51), a key enzyme in sterol biosynthesis of fungi [6]. To overcome the drawbacks of clinically available triazoles, numerous medicinal chemistry efforts have been made to design and synthesize novel antifungal azoles. In order to improve the efficiency of azole optimization, we constructed three-dimensional (3D) models of fungal CYP51s by homology modeling [7–10]. Moreover, the CYP51-azole interactions were investigated by molecular docking [8,11]. On the basis of the results from molecular modeling, our group has designed highly potent azole derivatives with different C3-side chains [9,11–15]. Among them, azoles shown in Fig. 2 exhibited excellent *in vitro* activity with broad spectrum, representing promising leads for novel antifungal drug development [12]. Herein, triazolone was used as a new bioisostere of the side-chain oxygen atom in the lead structure. As a result, a series of potent antifungal triazoles were rationally designed and synthesized.

2. Chemistry

The oxirane intermediate **4** was synthesized by our previously reported procedure (Scheme 1) [11]. The triazolone-containing side chains **10a**–**t** were synthesized via six steps. In the presence of pyridine at ice bath, various substituted anilines **5a**–**t** were converted to phenylcarbamates **6a**–**t** by reacting with phenyl chloroformate. Phenylcarbamates **6a**–**t** was treated with hydrazine hydrate to give semicarbazide **7a**–**t**, which was subsequently reacted with formamidine acetate in the presence of DMF at 80 °C to give the triazolones **8a**–**t**. In the presence of K_2CO_3, compounds **8a**–**t** were treated with excess 1,3-dibromopropane in DMF at 65 °C

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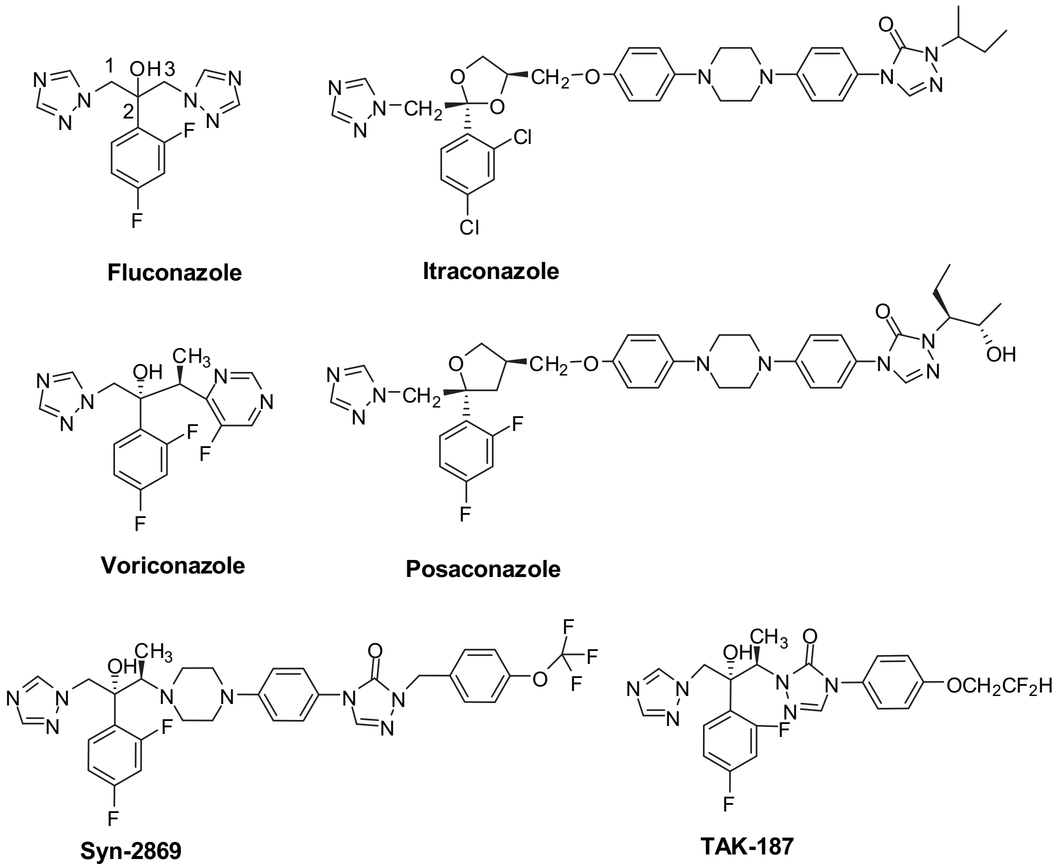

Fig. 1. Chemical structures of marketed and emerging triazole antifungal agents.

to afford compounds **9a**–**t**. Piperazine was substituted by **9a**–**t** using K_2CO_3 as base to yield triazolone side chains **10a**–**t**. The target compounds **11a**–**t** were obtained as racemates by a similar condition to our reported methods [12].

3. Microbiology

In vitro antifungal activity was measured according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations. The minimum inhibitory concentration (MIC) determination was performed by means of the serial dilution method in 96-well microtest plates with RPMI 1640 (Sigma) buffered with 0.165 M MOPS (Sigma) as the test medium. Fluconazole was used as the reference drug. Tested fungal strains were obtained from the ATCC or were clinical isolates. The MIC value was defined as the lowest concentration of test compounds that resulted in a culture with turbidity less than or equal to 80% inhibition when compared to the growth of the control. Test compounds were dissolved in DMSO serially diluted in growth medium. The yeasts were incubated at 35 °C, and the growth MIC was determined at 24 h for Candida species, at 72 h for *Cryptococcus neoformans*, and at 7 days for filamentous fungi.

4. Results and discussion

4.1. Design rationale: structure-based bioisosterism

In our previous studies, we reported a series of new azoles with phenoxyalkylpiperazine side chains (Fig. 2) [12]. Because these compounds showed good antifungal activity, they were selected as starting points for further structure–activity relationship (SAR) studies. Molecular docking studies revealed that the lead compounds could form good hydrophobic, *van der Waals* and hydrogen-bonding interactions with *Candida albicans* CYP51 (CACYP51) [12]. Our rationale was focused on modifying the side chain without loss of key interactions. In the present investigation, triazolone group was used as a new bioisostere of lead structures to afford target compounds **11a**–**t**. This type of bioisosteric

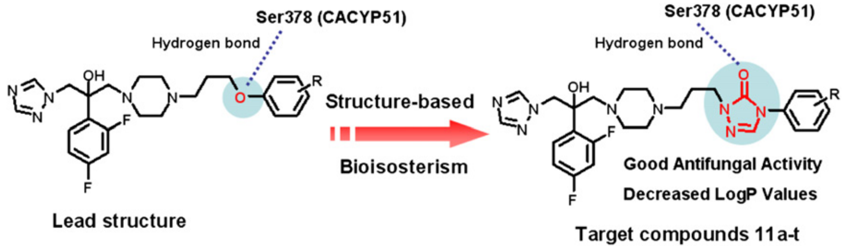

Fig. 2. Design rationale of the target compounds.