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Original article

Design, synthesis and structure–activity relationships of new triazole derivatives containing *N*-substituted phenoxypropylamino side chains

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ABSTRACT

The incidence of invasive fungal infections and resistance to antifungal agents is increasing dramatically. It is highly desirable to develop novel azoles with improved biological profiles. The structure–activity relationship (SAR) of the *N*-substitutions was investigated in this study. *In vitro* antifungal activities revealed that sterically large groups were not favored for the *N*-substitutions. The removal of the *N*-substitutions had little effect on the antifungal activity. Two compounds with free amine group (*i.e.* **9a** and **10a**) showed excellent activity with broad antifungal spectrum. The SAR results were supported by molecular docking and the *N*-substitutions were found to be important for the conformation of the side chains. The SAR and binding mode of the azoles are useful for further lead optimization.

1. Introduction

During the past two decades, the incidence of systemic fungal infections has been increasing dramatically due to an increasing number of immunocompromised hosts, such as patients undergoing organ transplants or anticancer chemotherapy and patients with AIDS. However, there is a lack of effective antifungal agents that can be used for life-threatening fungal infections. Clinically available antifungal agents include amphotericin B, 5-fluorocytosine, azoles (*e.g.* fluconazole and itraconazole), and echinocandins (*e.g.* caspofungin and micafungin).

Azoles are currently the most widely used agents in antifungal chemotherapy. They possess the antifungal activity by competitive inhibition of lanosterol 14α-demethylase (CYP51) [1]. Sterol δ^{22} desaturase (CYP61), a cytochrome P450 enzyme involved in the last step of ergosterol biosynthesis, has also been described as the second target for the azole antifungals [2,3]. Fluconazole (FLC) shows good antifungal activity and relatively low toxicity, which is used as the first-line agent in treating *Candida* infections [4]. However, FLC is not effective against invasive aspergillosis and has suffered severe drug resistance [5,6]. In comparison with FLC, itraconazole (ITR) has a broader antifungal spectrum and better toleration but its variable oral absorption and low bioavailability have hampered its clinical use. Several novel azole antifungal agents, such as voriconazole [7], posaconazole [8], ravuconazole [9] and albaconazole [10], are marketed or currently in the late stages of clinical trials.

Nowadays, fungal resistance caused by the broad use of azoles is becoming serious, which has significantly reduced the therapeutic efficacy of them. The mechanism of drug resistance includes mutation or abnormal expression of CYP51 [11,12], over expression of drug excretion genes (*e.g.* CDR1, CDR2 and MDR1) [13], the formation of biofilm changes [14], and so on. The severe resistance has led to an ongoing search for new azoles [15–22].

In our previous studies, new azoles with substituted phenoxypropylamino side chain (Fig. 1) were designed and synthesized. Most of them showed excellent *in vitro* antifungal activity with broad spectrum, representing promising leads for further optimization [23–25]. In order to get more information of structure–activity relationships (SARs), the influence of *N*-substituents on the antifungal activity was investigated in the present study (Fig. 1). Their *in vitro* antifungal activity in combination with binding modes obtained from molecular docking can provide useful information for further optimization.

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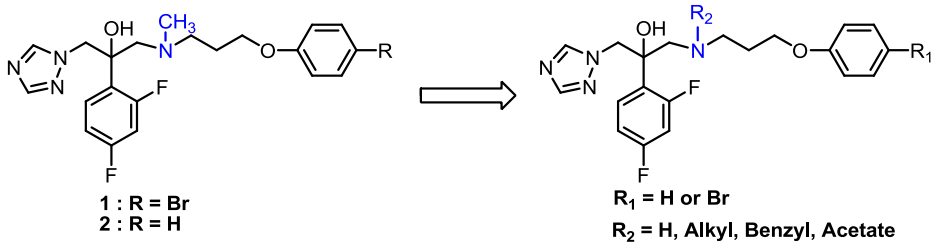


Fig. 1. Design rationale of the target compounds.

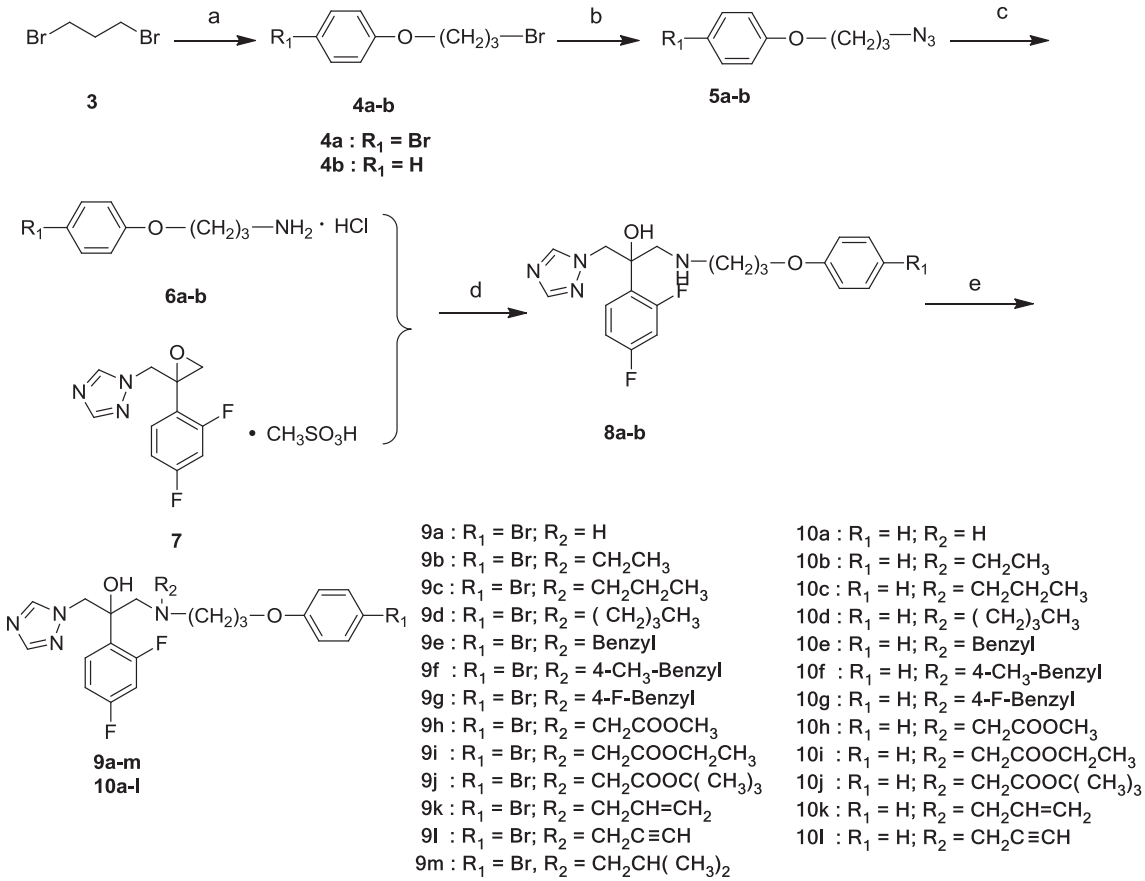
2. Chemistry

The chemical synthesis of the target compounds was outlined in Scheme 1. The oxirane intermediate **7** was synthesized by our reported procedure [26]. The phenoxypropylamino side chains **6a**, **b** were synthesized via three steps. Excess 1,3-dibromopropane was treated with phenols to give bromopropoxybenzene **4a**, **b**. Then, compounds **4a**, **b** reacted with NaN_3 in DMSO at room temperature to afford azides **5a**, **b**. The azide groups of compounds **5a**, **b** were reduced to amino groups in the presence of Ph_3P and MeOH. After treating with EtOAc saturated by hydrogen chloride, the side chains **6a**, **b** were obtained. Ring-open reactions were performed between compounds **6a**, **b** and oxirane **7** to give intermediates **8a**, **b**. In the presence of KI and K_2CO_3, various halogen substituted reagents were reacted with compounds **8a**, **b** to afford the target compounds **9a**–**m** and **10a**–**l**. All the target compounds were obtained as racemates.

3. Results and discussion

3.1. In vitro antifungal activity

The *in vitro* antifungal activity is shown in Table 1. Six important fungal pathogens were chosen for assaying. FLC and ITR were used as positive controls. The synthesized compounds showed moderate to excellent antifungal activity against the tested fungal pathogens. Several compounds, such as **9a**, **10a**, **10b** and **10k**, showed better antifungal activity than FLC. On the *Candida albicans* strain, compounds **9a**, **10a**, and **10b** displayed the highest activity with their MIC_{80} in the range of 0.0313–0.0625 μg/mL, which was more potent than FLC and ITR. In addition, compounds **9l**, **10k** and **10l** also showed comparable activity to FLC (MIC_{80} range: 0.25–0.5 μg/mL). Particularly, compounds **9a** and **10a** also displayed broad spectrum. Their inhibitory activity toward *Candida tropicalis* and *Candida krusei* ($MIC_{80} < 0.125$ μg/mL) was better than FLC and lead



Scheme 1. The synthetic route for target compounds **9a**–**10l**. Reagents and conditions: a. phenol, K_2CO_3, EtOH, reflux, 4 h, 75–82%; b. Sodium azide, DMSO, rt, 88–91%; c. Ph_3P, MeOH, reflux; HCl, EtOAc, rt, 44–56%; d. EtOH, $(Et)_3N$, reflux, 58–65%; e. K_2CO_3, KI, CH_3CN, reflux, 9 h, 21–58%.