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New azoles with antifungal activity: Design, synthesis, and molecular docking

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ABSTRACT

In order to search for many target compounds with excellent activities, a series of 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluoro-phenyl)-3-[(4-substituted phenyl)-piperazin-1-yl]-propan-2-ols were designed, synthesized, and evaluated as antifungal agents. Results of preliminary antifungal tests against eight human pathogenic fungi in vitro showed that all the title compounds exhibited excellent activities with broad spectrum. Moreover, a molecular model for the binding between **5a** and the active site of CACYP51 was provided based on the computational docking results.

Fungal infections pose a continuous and serious threat to human health and life especially to immunocompromised patients.[1–3] Many fungal infections are caused by opportunistic pathogens that may be endogenous (*Candida* infections) or acquired from the environment (*Cryptococcus, Aspergillus* infections). However, besides these known fungal species, new emerging fungal pathogens appear every year as the cause of morbidity and life-threatening infections in the immunocompromised hosts.[1,4]

Nowadays, numerous antifungal drugs with various structures and scaffolds spring up.[5] However, their clinical uses have been limited by the emergence of drug resistance, high risk of toxicity, insufficiencies in their antifungal activity and undesirable side effects. Hence, there is still a need to develop and extend the safe and efficient chemotherapeutic agents with potent antifungal activities.[6]

One of the most common classes of antifungal agents is azoles. For over a decade, azoles have been a mainstay of the antifungal armamentarium. Azoles inhibit the synthesis of ergosterol, the bulk sterol in fungal membranes, by binding to the heme cofactor located in the active site of the cytochrome P450 14α-demethylase (CYP51).[7] Unfortunately, the broad use of azoles has led to development of severe resistance, which significantly reduced their efficacy.[8,9] So the discovery of novel and potent antifungal azoles is the best way to overcome resistance and develop effective therapies.

Researches indicated that the structurally and functionally important regions, such as the heme group, the hydrophilic H-bonding region, the substrate access channel, and the active site have been recognized accurately. The binding mode of azoles with CACYP51 has been investigated by flexible molecular docking.[10–12] The molecular modeling, which gives the utilization of structural information of fungal CYP51s can accelerate the discovery of novel antifungal agents. In our letter, we used the strategy of structure-based rational drug design and find a series of new azoles with excellent in vitro antifungal activity and broad antifungal spectrum.

The general synthetic methodology for the preparation of title compounds 1-(1*H*-1,2,4-triazol-1-yl)-2-(2,4-difluoro-phenyl)-3-[(4-substitutedphenyl)-piperazin-1-yl]-propan-2-ols (**5a–q, 6a–q**) is outlined in Scheme 1. As a key intermediate of our designed triazole antifungals, the oxirane compound **1** was synthesized by the reported procedure.[13] And compound **2** were synthesized according to the literature.[14] The title compound **3** was synthesized by ring-open reaction of oxirane **1** with compound **2**. The good yield was obtained when the reaction was performed in a protic solvent ethanol in the presence of triethylamine as a base at 80 °C. Then the nitro group on the phenyl ring of compound **3** was reduced to an amino group in the presence of Ranney Ni and hydrazine hydrate. In the presence of DMAP (4-dimethylaminopyridine) and EDCI (1-ethyl-3-(3-dimethylaminopropyl) carbodii-mide HCl) in dichloromethane at room temperature, the aniline **4** was converted to title compounds by reacting with various substituted cinnamic acids. All the new compounds (**5a–q, 6a–q**) described above were characterized by IR, ESI, and NMR spectroscopic analysis.[15]

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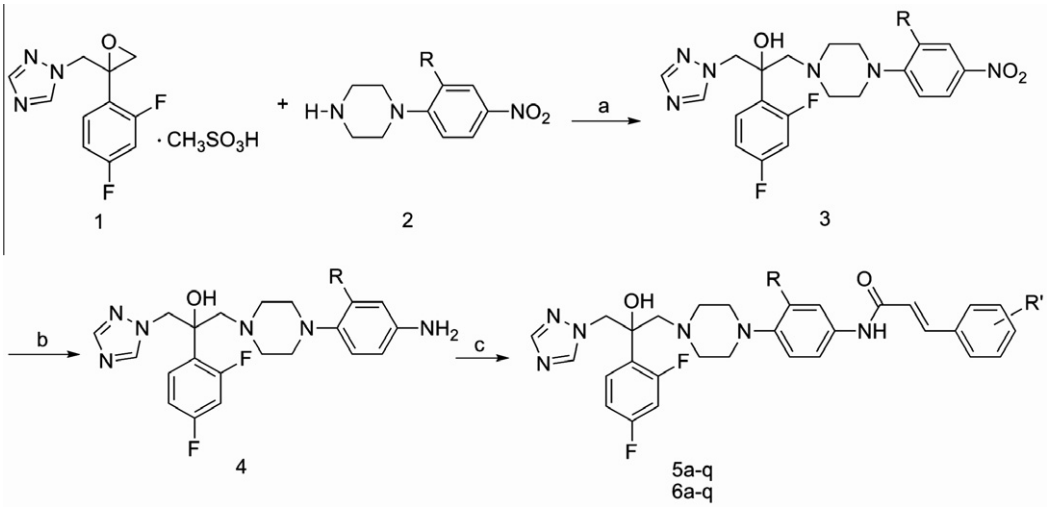

Scheme 1. Conditions: (a) CH_3CH_2OH, Et_3N, 80 °C, 5 h; (b) Ranney Ni, $NH_2NH_2{\cdot}H_2O$, CH_3CH_2OH, 80 °C, 3.5 h; (c) substituted cinnamic acids, DMAP, EDCI, CH_2Cl_2, 8 h.

The in vitro minimal inhibitory concentrations (MICs) of the compounds were determined by the micro-broth dilution method in 96-well microtestplates according to the methods defined by the National Committee for Clinical Laboratory Standards (NCCLS).[16] The MIC_{80} was defined as the first well with an approximate 80% reduction in growth compared to the growth of the drug-free well. For assays, the title compounds to be tested were dissolved in dimethyl sulfoxide (DMSO), serially diluted in growth medium, inoculated and incubated at 35 °C. Growth MIC was determined at 24 h for *Candida albicans* and at 72 h for *Cryptococcus neoformans*. Fluconazole (FLC), itraconazole (ICZ), and voriconazole (VCZ) served as the positive control were obtained from their respective manufacturers. The results of assays are summarized in Table 1. The data points from the mean of replicates. All of our susceptibility tests were performed three times by each antifungal agent.

Table 1
Antifungal activities of the title compounds in vitro (MIC_{80}, μg/mL)

Compound	R	R′	*C. albicans*	*C. parapsilosis*	*C. tropicalis*	*C. neoformans*	*T. rubrum*	*F. com.*	*M. gypseum*	*A. fumigatus*
5a	H	H	0.0156	0.0625	0.0625	0.25	0.0039	0.0625	0.25	16
5b	H	2-F	0.0039	0.0625	0.0156	0.0625	0.25	1	0.0625	>64
5c	H	3-F	0.0156	0.25	0.25	0.25	0.25	1	0.0156	4
5d	H	4-F	0.0625	0.25	0.25	0.25	0.0039	1	0.0625	0.0625
5e	H	2-Cl	0.0039	0.25	0.0625	0.25	0.0156	1	0.0156	4
5f	H	3-Cl	0.0625	1	0.25	1	1	64	0.0156	64
5g	H	4-Cl	0.0625	0.25	0.25	1	0.25	4	0.25	64
5h	H	3,4-Cl	0.0156	0.0625	0.0625	0.25	0.0156	0.25	0.25	4
5i	H	3-Br	0.0625	0.25	0.25	1	0.0625	1	1	16
5j	H	4-Br	0.0625	0.25	0.25	0.25	0.0156	1	0.25	4
5k	H	4-CH_3	0.0625	0.25	0.25	1	0.0156	16	0.25	64
5l	H	3,4-OCH_3	0.0156	0.0625	0.0625	0.25	0.25	1	0.25	4
5m	H	2,5-OCH_3	0.0156	0.25	0.0625	0.25	0.25	4	1	>64
5n	H	2-NO_2	0.0156	0.25	0.0625	1	0.0625	4	0.25	>64
5o	H	3-NO_2	0.0156	0.0625	0.25	0.25	0.0625	1	0.25	4
5p	H	4-NO_2	0.0625	1	0.25	1	0.0156	16	0.0625	4
5q	H	3-CN	0.0156	0.25	0.25	1	1	16	0.0625	>64
6a	2-F	H	0.25	0.0625	0.0625	0.0156	0.0625	0.25	0.25	1
6b	2-F	2-F	0.25	0.0625	0.0625	0.25	0.0625	1	0.25	4
6c	2-F	3-F	0.25	0.0156	0.25	0.25	0.25	0.25	0.25	4
6d	2-F	4-F	0.25	0.0156	0.0156	0.25	0.0625	0.25	0.25	1
6e	2-F	2-Cl	1	0.25	0.25	1	0.25	1	0.25	4
6f	2-F	3-Cl	1	0.25	0.0625	0.25	0.25	1	0.0625	1
6g	2-F	4-Cl	0.25	0.0156	0.0625	0.25	0.25	0.25	0.0625	1
6h	2-F	3,4-Cl	1	0.25	0.0625	1	0.0625	0.25	0.25	4
6i	2-F	3-Br	1	0.25	0.0625	0.0156	0.25	1	0.25	4
6j	2-F	4-Br	0.25	0.0625	0.0156	0.0156	0.0625	1	0.0625	1
6k	2-F	4-CH_3	0.25	1	0.0625	4	0.25	1	0.25	1
6l	2-F	3,4-OCH_3	0.25	0.25	1	1	4	4	0.25	>64
6m	2-F	2,5-OCH_3	0.0625	1	0.25	1	0.0625	64	1	>64
6n	2-F	2-NO_2	0.25	1	1	1	0.25	16	1	64
6o	2-F	3-NO_2	0.0039	0.0625	0.0625	0.0625	0.0625	0.0625	0.0625	>64
6p	2-F	4-NO_2	0.0156	0.25	0.25	1	0.0625	1	0.25	>64
6q	2-F	3-CN	0.25	1	1	1	4	64	4	>64
FCZ			4	1	1	1	0.25	16	0.25	64
ICZ			1	0.25	0.25	1	0.0152	0.25	0.0152	1
VCZ			0.0152	1	0.25	0.0152	0.0039	0.0152	0.0039	>64