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Design synthesis and biological evaluation of 3-substituted triazole derivatives

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Abstract

Based on the active site of lanosterol 14α-demethylase of azole antifungal agents, sixteen 1-(1*H*-1,2,4-triazole-1-yl)- 2-(2,4-difluorophenyl)-3-(*N*-*n*-butyl-*N*-1-substitutedbenzyl-4-methylene-1*H*-1,2,3-triazole)-2-propanols have been designed, synthesized and evaluated as antifungal agents. Results of preliminary antifungal tests against eight human pathogenic fungi *in vitro* showed that some of the compounds exhibited excellent activities with broad spectrum.

Keywords: Synthesis; Triazole; Antifungal activity; 1,3-Dipolar cycloaddition

During the past two decades, fungal infections have caused a number of disease and mortality, particularly in individuals with immunocompromised hosts, such as patients undergoing anticancer chemotherapy or organ transplants and patients with AIDS [1]. Clinically, triazoles such as fluconazole, voriconazole, and itraconazole (Fig. 1) are widely used as antifungal agents for their significant activity against most yeasts and filamentous fungi. However, triazole drugs are often associated with hepatotoxicity and limited antifungal spectrum [2,3]. Moreover, resistance to azoles is emerging and may pose a serious health problem in the future [4]. Therefore, the research on low-toxicity and broad spectrum antifungal agents has a great significance.

The antifungal activity of azoles are exerted through inhibiting the lanosterol 14α-demethylase (CYP51) [5]. A three-dimensional model of CYP51 of *Candida albicans* and its interaction with azole antifungals were reported by Ji *et al*. [6]. In general, the active site of CYP51 for ligand binding can be divided into four subsites: a coordination bond with iron of the heme group, the hydrophilic H-bonding region, the hydrophobic region, and the narrow hydrophobic cleft formed by the residues in the helix B′-meander 1 loop and *N*-terminus of helix I [7]. According to the active site of CYP51, the classical structure of the triazoles, propanols-triazole-2,4-difluorophenyl, was reserved. The hydroxy of propanols could form H-bonding with the H-bonding region, the N4 atom of triazole could be coordinated to iron atom of the heme and the 2,4-difluorophenyl group could be located in to the hydrophobic pocket. In addition, a series of

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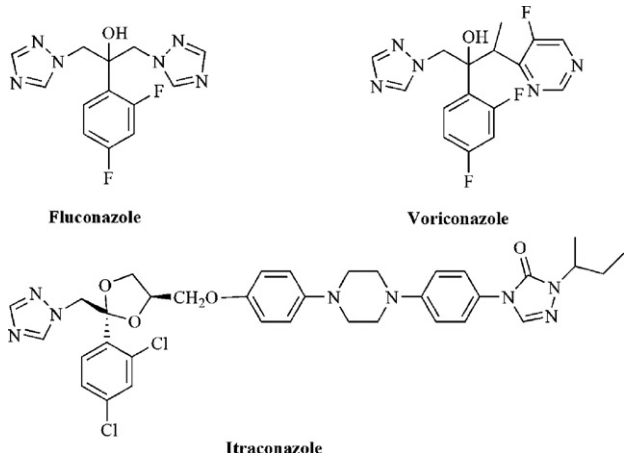
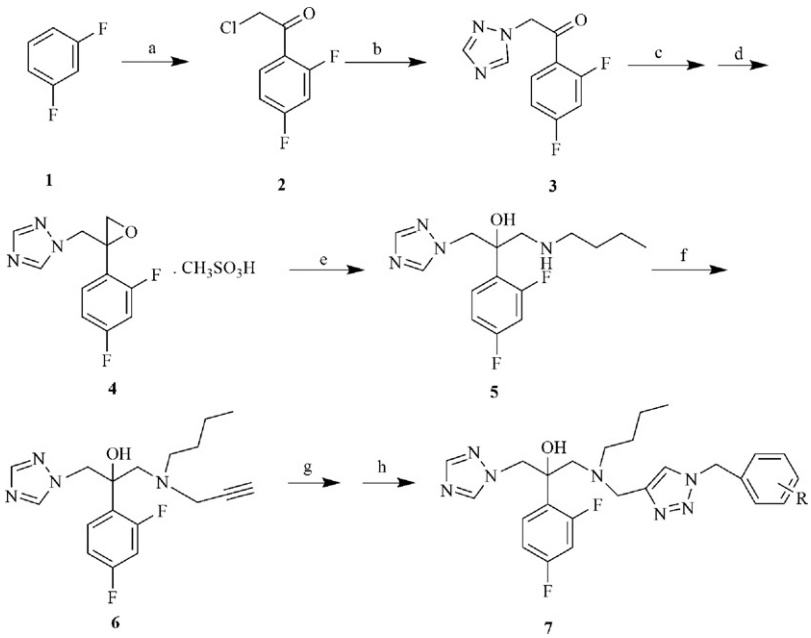


Fig. 1. The structure of fluconazole, voriconazole and itraconazole.

triazoles containing the 1,2,3-triazole side chain, considering the special property of it, was designed and synthesized in order to improve the activity of the title compounds.

The synthetic route of title compounds was outlined in the Scheme 1. The intermediate oxirane **4** was synthesized with known procedures [8]. 1-(1*H*-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-[*N*-*n*-butylamino]-2-propanol **5** was obtained by the reaction of compound **4** and *n*-butylamine in EtOH in the presence of Et_3N. Compound **6** was obtained by the reaction of **5** and propargyl bromide in CH_3CN in the presence of K_2CO_3. The sodium azide and substituted benzyl bromide were mixed and stirred in DMSO for 12 h and **6** was allowed to add into the mixture without purification and react *via* $CuSO_4{\cdot}5H_2O$ and sodium ascorbate catalyzing. By the intermolecular 1,3-dipolar cycloaddition, the title compounds **7a**–**p** were obtained.

In vitro antifungal activity was measured by means of the minimal inhibitory concentrations (MIC) using the serial dilution method in 96-well microtest plates. Test fungal strains were obtained from the ATCC or clinical isolates. The



Scheme 1. Conditions: (a) $ClCH_2COCl$, $AlCl_3$, 50 °C, 5 h, in 80.0% yield; (b) $C_6H_5CH_3$, $NaHCO_3$, 1*H*-1,2,4-triazole, reflux, 5 h, in 41.7% yield; (c) $C_6H_5CH_3$, $(CH_3)_3SOI$, NaOH, cetyltrimethylammonium bromide, 60 °C, 3 h; (d) CH_3SO_3H, 0 °C, 1 h, in 52.6% yield; (e) CH_3CH_2OH, Et_3N, *n*-butylamine, reflux, 6 h, in 91% yield; (f) CH_3CN, propargyl bromide, rt. 6 h, in 62.2% yield; (g) DMSO, NaN_3, substituted benzyl bromide, rt. 5–6 h; (h) $CuSO_4.5H_2O$, VitC-Na, in 90.0–95.0% yield, two steps.

Table 1
Structure and *in vitro* antifungal activity of the title compounds.

Compounds	R	MIC_{80} (μg/mL)							
		C.alb SC5314	*C.neo*	*C.alb Y0109*	*C.par*	*C.tro*	*T.rub*	*C.kef*	*A.fum*
7a	2-F	1	8	16	2	2	4	1	>64
7b	3-F	<0.125	1	4	0.25	<0.125	1	0.0156	>64
7c	4-F	<0.125	2	0.0625	0.25	0.5	1	0.625	>64
7d	3-Cl	<0.125	1	16	0.25	<0.125	0.25	0.0156	>64
7e	4-Cl	<0.125	2	16	<0.125	<0.125	<0.125	0.0039	>64
7f	2-Br	4	64	0.5	8	0.5	4	0.0156	>64
7g	3-Br	4	>64	1	>64	32	8	>64	>64
7h	4-Br	4	>64	1	8	8	0.5	>64	>64
7i	4-CH_3	<0.125	2	<0.125	<0.125	<0.125	2	0.25	>64
7j	2-NO_2	2	64	4	4	2	4	16	>64
7k	3-NO_2	4	64	4	8	8	8	0.0625	>64
7l	4-NO_2	2	64	4	4	8	32	0.0625	>64
7m	2-CN	1	64	16	4	1	16	0.0625	>64
7n	3-CN	4	64	16	16	>64	16	4	>64
7o	2-Cl,4-Cl	4	>64	4	8	32	32	16	>64
7p	2-Cl,6-Cl	16	>64	8	64	8	32	16	>64
ICZ	–	<0.0625	0.125	0.625	0.0625	<0.0625	0.0625	0.0625	2
FCZ	–	0.5	8	0.5	<0.125	<0.125	2	1	>64

Abbreviations: *C.alb* SC5314, *Candida albicans* SC5314; *C.neo*, *Cryptococcus neoformans*; *C.alb* Y0109, *Candida albicans* Y0109; *C par*, *Candida parapsilosis*; *C.tro*, *Candida tropicalis*; *T.rub*, *Trichophyton rubrum*; *C.kef*, *Candida kefyr*; *A.fum*, *Aspergillus fumigatus*.ICZ, Itraconazole; FCZ, Fluconazole.

MIC determination was performed according to the national committee for clinical laboratory standards (NCCLS) recommendations [9]. The results of antifungal activities *in vitro* of the target compounds were listed in Table 1.

All the title compounds containing 1,2,3-triazole are first reported and their structures were confirmed by ^{1}H NMR, MS, IR and elemental analysis.

Although 1,2,3-triazole moiety does not occur in nature, it is attractive as a connecting group thanks to the stability of metabolic degradation and capability of hydrogen bonding, which can be favorable in binding of biomolecular targets and for solubility [10]. The group of Pore *et al*. had reported some 1,2,3-triazole molecules containing molecules as azole antifungals and the molecules exhibited excellent activities against Candida species [11]. In addition, the Cu(I) catalyzed intermolecular 1,3-dipolar cycloaddition used to introduce the side chain containing 1,4-disubstituted-1,2,3-triazole was in excellent yield and easy to purify.

The structure and *in vitro* antifungal activities were listed in Table 1. All the title compounds were active against eight pathogenic fungi to such an extent. The activities against *Candida albicans SC5314* and *Candida kefyr* of some of the title compounds are stronger than those of fluconazole and itraconazole. Some of the target compounds showed good MIC values less than 0.0156 μg/mL and proved to be more potent than fluconazole and are comparable with that of itraconazole. Compounds **7b, 7d, 7e** and **7h** exhibited strong antifungal activities against eight test fungi comparable to the control drug itraconazole except *Aspergillus fumigatus*. The study also proved that the long side chain containing the 1,4-disubstituted-1,2,3-triazole can improve the activities against fungi of the target compounds. In addition, the substituent R on phenyl group has a great influence on antifungal activities. The activities of compounds **7j–p** containing the strong electron-withdrawing group such as –CN, –NO_2 or two halogen were lower than other compounds, respectively, suggesting that the 1,2,3-triazole group could form hydrogen-bonding interaction with the enzyme and the electron-donating conjugation can firm the interaction. To clarify the binding mode of our synthesized compounds, the mode of action of this class of compounds will be explored by molecular modeling. These results may provide some guidance for novel azole antifungal research.

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