Triazol derivatives with improved in vitro antifungal activity over azole drugs

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Abstract: A series of triazole antifungal agents with piperidine side chains was designed and synthesized. The results of antifungal tests against eight human pathogenic fungi in vitro showed that all the compounds exhibited moderate-to-excellent activities. Molecular docking between 8d and the active site of Candida albicans CYP51 was provided based on the computational docking results. The triazole interacts with the iron of the heme group. The difluorophenyl group is located in the S3 subsite and its fluorine atom (2-F) can form H-bonds with Gly307. The side chain is oriented into the S4 subsite and formed hydrophobic and van der Waals interactions with the amino residues. Moreover, the phenyl group in the side chain interacts with the phenol group of Phe380 through the formation of π–π face-to-edge interactions.

Keywords: synthesis, CYP51, molecular docking,azole agents

Introduction

Over the past two decades, a dramatically significant increase in fungal infections has been observed. Among these, the widespread diffusion of topical and systemic infectious diseases caused by the opportunistic pathogen Candida albicans is often related to the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs.1-2 One of the principal problems in the treatment of Candida albicans infections is the spread of antifungal drug resistance, mainly in patients chronically subjected to antimycotic therapy such as HIV-infected individuals.3,4

More recently, there has been an expansion in the number of antifungal drugs available. Major classes of antifungal compounds are currently in clinical use: polyenes, azole derivatives, allylamines, thiocarbamates, echinocandins, and fluoropyrimidines.5-8 Despite this growing list of antifungal agents, treatment of fungal diseases remains unsatisfactory. In a word, the limitations of current antifungal drugs, increased incidence of systemic fungal infections, and rapid development of drug resistance have highlighted the need for new antifungal agents with a new structure of compounds and with fewer side effects.9-13

The current standard of therapies is the fungicidal polyenes, amphotericin B (very good antifungal activity, but liver and kidney toxicity), and the safe azoles (not fungicidal, but fungistatic). In particular, the azoles are important antifungal agents widely used in clinics.14 Azoles exert antifungal activity through the inhibition of cytochrome P450 14α-demethylase (CYP51), which is crucial in the process of ergosterol biosynthesis. The CYP51 enzyme contains an iron protoporphyrin unit located in its active site, which catalyzes the oxidative removal of the 14α-methyl group of lanosterol by
typical monooxygenase activity. Azole antifungal agents bind to the iron of the porphyrin and cause the blockade of the fungal ergosterol biosynthesis pathway by preventing the access of the natural substrate lanosterol to the active site of the enzyme. The depletion of ergosterol and accumulation of 14α-methylated sterols alter membrane fluidity, with concomitant reduction in activity of membrane-associated enzymes and increased permeability. The net effect is to inhibit fungal growth and replication.

In our previous research, numerous studies on the structure-activity relationships (SAR) of antifungal azoles had been developed, and these studies had led to new compounds endowed with better biological and pharmaceutical properties. Molecular docking studies indicated that the triazole ring, the difluorophenyl group, and the hydroxyl group were the pharmacophores of antifungal agents; the side chains can be oriented into substrate access channel 2 (FG loop) and form hydrophobic and van der Waals interactions. In view of the importance of the piperazinyl for antifungal activity in our previous study, we sought to investigate this further with the piperidine ring, which contains an oxygen atom. This oxygen atom could improve the flexibility of the molecule, making the side chain more easily lock into its proper position. Also, it may interact with the amino acid residues through hydrogen bonding.

We focused our attention on installing various substituted acids to form piperidonol ester. In order to study the SAR of the new compounds, we inserted aromatic groups (6a–c) and alkyl groups (compounds 7a–m) into the side chains. We also inserted halogens, and alkoxy, nitro, and cyano groups into the phenyl group (compounds 8a–r) of the side chains, respectively. Almost all of the azole antifungal drugs have halogens present, which play a very important role in these drugs. They are very useful to modulate the electronic effects on the phenyl rings of drugs. For example, chlorine has strong inductive electron-attracting effects, while those of fluorine are very weak. Moreover, these atoms may also influence the steric characteristics and the hydrophilic–hydrophobic balance of the molecules.

**Chemistry**

The general synthetic methodology for the preparation of the title compounds (6a–c, 7a–m, and 8a–r) is outlined in Figure 1. As a key intermediate of our designed triazole antifungals, the oxirane compound 4 was synthesized using the reported procedure. The intermediate 5 was synthesized by ring-open reaction of oxirane 4 with piperidinol. The title compounds were synthesized and a good yield was obtained when the reaction was performed in CH₂Cl₂ in the presence of 4-dimethylaminopyridine (DMAP) and 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDCI). All the new compounds (6a–c, 7a–m, and 8a–r) described above were characterized by infra-red (IR), high-resolution electrospray ionization mass spectra (HR-MS), and nuclear magnetic resonance (NMR) spectroscopic analysis.

**Pharmacology**

The in vitro antifungal activities of all the title compounds were evaluated against eight human pathogenic fungi: *Candida albicans* (C. alb.), *Candida parapsilosis* (C. para.), *Candida tropicalis* (C. tro.), *Cryptococcus neoformans* (C. neo.), *Fonsecaea compacta* (F. com.), *Trichophyton rubrum* (T. rub.), *Microsporum gypseum* (M. gyp.), and *Aspergillus fumigatus* (A. fum.), which are often encountered clinically, and were compared with fluconazole (FCZ), itraconazole (ICZ), voriconazole (VCZ). *C. alb.* and *C. neo.* were provided by Shanghai Changzheng Hospital (Shanghai, People’s Republic of China); *C. par., C. tro., F. com., T. rub., M. gyp., and A. fum.* were provided by Shanghai Changjiang Hospital. *C. alb.* (ATCCY0109) and *C. neo.* (ATCCBLS108) were used as the quality control strains, and tested in each assay. FCZ, ICZ, and VCZ served as the positive control, and were obtained from their respective manufacturers.

The antifungal potency was evaluated by means of the minimum inhibitory concentrations (MICs) using the serial test in the broth microdilution modification method published by the Clinical and Laboratory Standards Institute (CLSI) method M 27-A2. The MIC 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 MICs were determined at 24 hours for *C. alb.* and at 72 hours for *C. neo.* The data points were calculated from the mean of replicates (three times). All of our susceptibility tests were performed in triplicate using each antifungal agent.

**Materials and methods**

In our studies, the 3D structures of the designed azoles were built using the Builder module within the Insight II 2000 software package of Discovery Studio 2.5 from Accelrys (San
Diego, CA, USA). The flexible ligand-docking procedure in the Affinity module within Insight II was used to define the lowest energy position for the substrate using a Monte Carlo docking protocol.

Melting points (Mp) were measured on a Yamanaka MP-21 melting-point apparatus (Tokyo, Japan) and are uncorrected. IR spectra were recorded in potassium bromide disks on a Hitachi 270-50 spectrophotometer (Tokyo, Japan). 

$^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ unless otherwise indicated with a Bruker Avance II 500 spectrometer (Billerica, MA, USA), using tetramethylsilane (TMS) as the internal standard. HR-MS was performed on an Agilent 6538 Q-TOF mass spectrometer (Santa Clara, CA, USA). Thin layer chromatography (TLC) analysis was carried out on silica gel plates GF254 (Qingdao Haiyang Chemical, Qingdao, People's Republic of China). Column chromatography was performed with silica gel 60 G (Qindao Haiyang Chemical).

The solvents and reagents were used as received or dried prior to use as needed.

**Preparation of compounds**

1-(2-[2,4-difluorophenyl]-2-hydroxy-3-[1H-1,2,4-triazol-1-yl]propyl)piperidin-4-ol (5)

To a stirred mixture of: 1-(2-[2,4-difluorophenyl]-2,3-epoxypropyl)-1H-1,2,4-triazole methanesulfonate (4) (1.65 g, 0.005 mol), C$_2$H$_5$OH (30 mL), N(C$_2$H$_5$)$_3$ (3 mL), 4-piperidinol (2) (0.70g, 0.006 mol) were added and heated at 70°C–80°C for 5 hours. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure. Water (30 mL) was added to the residue, which was then extracted with ethyl acetate (80 mL ×3). The extract was washed with saturated NaCl solution (20 mL ×3), dried over anhydrous Na$_2$SO$_4$, and evaporated. The residue was separated and purified readily.
by chromatography on silica gel to afford compound 5 (1.23g), with a 70.2% yield. Mp: 79°C~82°C; 'H NMR (500 MHz, CDCl₃) δ: 8.12 (1H, s, triazole-C₃-H), 7.79 (1H, s, triazole-C₇-H), 6.65–7.23 (3H, m, Ar-H), 5.25 (1H, br, OH), 3.76–3.91 (1H, m, CH-O), 4.56 (1H, d, J=14.0 Hz, triazole-CHA), 4.52 (1H, d, J=14.0 Hz, triazole-CHb), 3.15 (1H, d, J=13.6 Hz, NCHa), 2.78 (1H, d, J=13.6 Hz, NCHb), 1.50–2.33 (8H, m, piperidine-H); 13C NMR (125 MHz, CDCl₃) δ: 162.5, 161.8, 150.8, 143.1, 130.2, 115.8, 110.4, 104.6, 69.8, 63.7, 55.5, 51.7, 47.1, 46.8, 31.8, 31.4; IR (KBr): 3420, 3084, 2952, 1414, 1363, 1320, 1266, 1175, 1134, 1082, 1012, 965, 885, 864, 749, 714, 672, 651, 561, 510, 456; HR-MS (ESI): m/z calculated for C₁₀H₁₂F₂N₄O₂ [M+H]+ 339.1554; found: 339.1567.

**General procedure for the target compounds 6a–c, 7a–m, and 8a–r**

To a stirred mixture of: 1-(2-[2,4-difluorophenyl]-2-hydroxy-3-[1H-1,2,4-triazol-1-yl] propyl)piperidin-4-ol (5) (0.338 g, 0.001 mol), DMAP (100 mg) and EDCI (200 mg) in 50 mL dichloromethane at 0°C and substituted acid (0.001 mol) were added and stirred for 8–12 hours. The reaction was monitored by TLC. After filtration, the filtrate was evaporated under reduced pressure to afford a yellowish oil. Then the product was purified by silica gel column chromatography with ethyl acetate–methanol (9 : 1, v/v) as eluent.

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**Table 1 Antifungal activities of the title compounds in vitro (MIC₈₀, nmol/mL)**

| Compound | C. alb. | C. par. | C. tro. | C. neo. | F. com. | T. rub. | M. gyp. | A. fum. |
|----------|---------|---------|---------|---------|---------|---------|---------|---------|
| 6a       | 0.034   | 0.137   | 0.137   | 0.137   | 0.548   | 0.137   | 0.137   | 2.192   |
| 6b       | 0.126   | 0.032   | 0.126   | 2.019   | 0.505   | 0.505   | 0.126   | 8.078   |
| 6c       | 0.479   | 0.479   | 0.479   | 7.660   | 1.915   | 0.479   | 1.915   | 1.047   |
| 7a       | 0.164   | 2.630   | 0.658   | 2.630   | 0.658   | 0.658   | 10.521  |
| 7b       | 0.159   | 0.634   | 0.159   | 0.634   | 0.634   | 0.634   | 10.47   |
| 7c       | 0.153   | 0.153   | 0.153   | 0.153   | 0.153   | 0.153   | 2.450   |
| 7d       | 0.153   | 0.612   | 0.612   | 0.612   | 0.612   | 0.612   | 9.799   |
| 7e       | 0.148   | 0.592   | 0.148   | 0.592   | 0.592   | 0.592   | 9.474   |
| 7f       | 0.036   | 0.573   | 0.573   | 0.573   | 0.573   | 0.573   | 9.170   |
| 7g       | 0.009   | 0.139   | 0.139   | 0.139   | 0.139   | 0.555   | 0.193   |
| 7h       | 0.034   | 0.538   | 0.615   | 0.034   | 2.154   | 0.135   | 0.135   |
| 7i       | 0.508   | 2.031   | 0.508   | 0.508   | 2.031   | 2.031   | 2.031   |
| 7j       | 0.480   | 1.922   | 1.922   | 0.480   | 7.688   | 1.922   | 0.480   |
| 7k       | 2.304   | 9.214   | 2.304   | 36.858  | 36.858  | 9.214   | 2.304   | 147.431 |
| 7l       | 2.222   | 35.548  | 2.222   | 35.548  | 35.548  | 8.887   | 35.548  | 142.191 |
| 7m       | 0.604   | 9.660   | 2.415   | 9.660   | 9.660   | 9.660   | 9.660   |
| 8a       | 0.033   | 0.008   | 0.033   | 0.033   | 0.133   | 0.133   | 0.133   |
| 8b       | 0.032   | 0.129   | 0.129   | 0.129   | 0.129   | 0.129   | 2.057   |
| 8c       | 0.005   | 0.129   | 0.129   | 0.129   | 0.129   | 0.129   | 2.057   |
| 8d       | 0.005   | 0.129   | 0.129   | 0.129   | 0.129   | 0.129   | 2.057   |
| 8e       | 0.124   | 0.498   | 0.124   | 0.498   | 0.498   | 0.498   | 0.498   |
| 8f       | 0.124   | 0.124   | 0.498   | 0.498   | 0.498   | 0.498   | 0.498   |
| 8g       | 0.124   | 0.124   | 0.498   | 0.498   | 0.498   | 0.498   | 0.498   |
| 8h       | 0.114   | 0.458   | 0.458   | 0.458   | 0.458   | 0.458   |
| 8i       | 0.114   | 0.458   | 0.458   | 0.458   |
| 8j       | 0.007   | 0.458   | 0.458   | 0.458   |
| 8k       | 0.117   | 0.466   | 0.466   | 0.466   |
| 8l       | 0.032   | 0.130   | 0.032   |
| 8m       | 0.031   | 0.125   | 0.125   |
| 8n       | 0.030   | 0.118   | 0.118   |
| 8o       | 0.030   | 0.487   | 0.122   |
| 8p       | 0.122   | 0.122   |
| 8q       | 0.030   | 0.122   |
| 8r       | 0.032   | 0.507   |
| ICZ      | 0.089   | 0.354   |
| VCZ      | 0.011   | 0.045   |
| FCZ      | 0.816   | 0.816   |

**Notes:** C. alb., Candida albicans; C. par., Candida parapsilosis; C. tro., Candida tropicalis; C. neo., Cryptococcus neoformans; F. com., Fonsecaea compacta; T. rub., Trichophyton rubrum; M. gyp., Microsporum gypseum; A. fum., Aspergillus fumigatus, ICZ, itraconazole; VCZ, voriconazole; FCZ, fluconazole; MIC₈₀: 80% minimal inhibitory concentration; FCZ, fluconazole; ICZ, itraconazole; VCZ, voriconazole.
reduced pressure. The residue was then extracted with ethyl acetate (60 mL × 3). The extract was washed with saturated NaCl solution (20 mL × 3), dried over anhydrous Na₂SO₄, and evaporated. The residue was crystallized from ethyl acetate to afford the title compounds, with 67.0%-85.0% yield.

1-[(2-[2,4-difluorophenyl]-2-hydroxy-3-[1H-1,2,4-triazol-1-yl]propyl)piperidin-4-yl]-2-phenylacetate (6a)

Mp: 93°C–95°C; ¹H NMR (500 MHz, CDCl₃) δ: 8.13 (1H, s, triazole-C-H), 7.78 (1H, s, triazole-C-H), 6.80–7.54 (8H, m, Ar-H), 5.20 (1H, br, OH), 4.72–4.74 (1H, m, CH-O), 4.55 (1H, d, J=14.0 Hz, triazole-CHa), 4.50 (1H, d, J=14.0 Hz, triazole-CHb), 3.57 (2H, s, ArCH₂N), 3.10 (1H, d, J=13.6 Hz, NCHa), 2.70 (1H, d, J=13.6 Hz, NCHb), 1.52–2.40 (8H, m, piperidine-H); ¹³C NMR (125 MHz, CDCl₃) δ: 167.6, 152.8, 146.5, 135.7, 131.2, 130.8, 130.6, 130.2, 129.8, 128.6, 119.8, 112.2, 105.8, 105.5, 105.2, 73.8, 69.5, 63.4, 55.2, 51.9, 46.8, 32.2; IR (KBr): 3,426, 3,082, 1,709, 1,669, 1,617, 1,568, 1,543, 1,384, 1,282, 1,220, 1,197, 1,143, 1,084, 1,042, 1,010, 962, 882, 818, 795, 760, 710, 677, 657, 631, 577, 515, 470, 439; HR-MS (ESI): m/z calculated for C₂₄H₂₆F₂N₄O₃, [M+H]+ 457.1973; found: 457.2034.

Results and discussion

The in vitro antifungal activities of newly synthesizedazole derivatives 6a–c, 7a–m, and 8a–r against eight strains of important pathogenic fungi are reported in Table 1, together with the positive controls FCZ, ICZ, and V CZ. From the in vitro antifungal activity assay, we can see that all the synthesized compounds show moderate-to-excellent activity against nearly all the tested fungal pathogens. The MIC values of compounds 7k–7m against C. alb. were decreased from 2.304 nmol/mL to 0.604 nmol/mL, while compounds 7a–7j ranged from 0.009 nmol/mL to 0.480 nmol/mL. From that, we can see that the activity of type 7 would be weakened when the H atom of the alkyl group side chain is substituted by a halogen atom. Furthermore, the activity got lower when the halogen electron-withdrawing action ability was enhanced. Tested against C. alb., compounds 8c and 8d showed MICs about 18-fold greater than that of ICZ (with a MIC value of 0.089 nmol/mL), and was also comparable to that of VCZ (with a MIC value of 0.011 nmol/mL). Additionally, compounds 7g and 8j showed MIC values of 0.009 nmol/mL and 0.007 nmol/mL, respectively. The activity of all the title compounds except compounds 7k and 7l exhibited moderate activity against A. fum., and showed higher activity than FCZ (with a MIC value of 208.97 nmol/mL). VCZ is an antifungal agent, which is characterized by a broad spectrum of activity in vitro and which shows fungistatic activity against fungi such as A. fum. Compounds 8a, 8d, 8i, 8p, and 8q exhibited similar activity against A. fum. when compared to VCZ (with a MIC value of 0.716 nmol/mL). Compound 8a was about six-fold more active in MIC values against C. par. than VCZ (with a MIC value of 0.045 nmol/mL); in addition, it was about 100-fold more potent than FCZ. Lastly, compound 6b showed a MIC value of 0.032 nmol/mL, which is comparable to the positive control VCZ, and was

| Compd. | Fitness[a] | S(hb_ext)[b] | S(vdw_ext)[c] | S(int)[d] |
|--------|------------|--------------|---------------|----------|
| 6a     | 78.17      | 10.00        | 50.36         | –4.36    |
| 6b     | 73.14      | 10.00        | 46.61         | –3.64    |
| 6c     | 65.10      | 10.00        | 44.94         | –5.94    |
| 7a     | 62.71      | 10.00        | 39.59         | –2.45    |
| 7b     | 61.46      | 10.00        | 36.66         | –4.92    |
| 7c     | 59.81      | 10.00        | 36.66         | –5.01    |
| 7d     | 57.63      | 10.00        | 41.64         | –3.54    |
| 7e     | 46.65      | 10.00        | 33.37         | –2.72    |
| 7f     | 70.35      | 10.00        | 45.98         | –8.14    |
| 7g     | 73.25      | 9.99         | 45.02         | –9.02    |
| 7h     | 75.95      | 10.02        | 48.93         | –8.30    |
| 7i     | 67.84      | 9.91         | 42.52         | –9.97    |
| 7j     | 57.35      | 0.98         | 59.92         | –12.74   |
| 7k     | 45.01      | 0.99         | 34.76         | –3.06    |
| 7l     | 55.36      | 10.00        | 35.51         | –6.25    |
| 7m     | 57.96      | 5.98         | 39.04         | –4.22    |
| 7n     | 57.74      | 10.00        | 45.59         | –7.14    |
| 7o     | 67.40      | 10.00        | 46.72         | –10.98   |
| 7p     | 72.29      | 8.49         | 44.33         | –7.96    |
| 7q     | 81.00      | 10.00        | 53.18         | –10.62   |
| 7r     | 75.74      | 10.00        | 51.74         | –13.38   |
| 8a     | 72.74      | 10.00        | 53.99         | –6.20    |
| 8b     | 78.32      | 10.00        | 53.18         | –9.25    |
| 8c     | 72.40      | 9.95         | 49.20         | –11.49   |
| 8d     | 79.29      | 10.00        | 50.50         | –8.60    |
| 8e     | 76.98      | 10.00        | 52.48         | –8.07    |
| 8f     | 80.81      | 10.00        | 47.47         | –6.72    |
| 8g     | 64.76      | 10.00        | 43.77         | –13.54   |
| 8h     | 76.32      | 10.00        | 54.23         | –13.53   |
| 8i     | 74.95      | 9.21         | 50.87         | –15.00   |
| 8j     | 66.78      | 10.00        | 49.55         | –10.18   |
| 8k     | 70.70      | 9.98         | 44.58         | –12.44   |
| 8l     | 61.20      | 0.03         | 50.35         | –7.03    |

Notes: [a] Fitness, the negative of the sum of the component energy terms; [b] S(hb_ext), protein-ligand hydrogen bond energy; [c] S(vdw_ext), protein-ligand interaction energy; [d] S(int), the sum of ligand internal vdw energy and ligand torsional strain energy.
found to be a potent inhibitor of fungal growth even on fungi strains resistant to FCZ.

In this study, we docked all the compounds to clarify their binding modes with Candida albicans CYP51 (CACYP51) using the flexible docking in the Affinity module within the Insight II 2000 software package and which provided information for further optimization. As shown in Table 2, compounds 6a, 7g, 7h, 8b, 8c, 8d, 8j, 8n, and 8o have relatively higher fitness scores, which are consistent with their antifungal activity. In contrast, weakly active compounds such as 7i, 7j, 7k, 7l, and 7m have relatively lower fitness scores. The good correlation between antifungal activity and docking score indicates that a suitable side chain has a great impact on antifungal activity.

Figure 2 shows the binding mode of the designed compound 8d to the active site of CYP51. The active site of CYP51 was constructed in previous studies. Molecular docking results revealed that the compound 8d binds to the active site of CACYP51 through the formation of a coordination bond with the iron of the heme group. The difluorophenyl group is located in the S3 subsite, which is a narrow hydrophobic cleft formed by Phe126, Leu121, Tyr118, Met306, and Gly307. The fluorine atom (2-F) can form H-bonds with the residue Gly307. The side chain of the compound 8d is oriented in the S4 subsite and forms hydrophobic and van der Waals interactions with Tyr64, Met92, Ala117, Tyr118, Phe228, Pro230, Leu376, Ile379, Phe380, and Met508. Moreover, the phenyl group attached to the piperidinol of the side chain interacts with the phenol group of Phe380 through the formation of π–π face-to-edge interactions.

Conclusion
In conclusion, a series of triazoles was successfully synthesized and characterized by IR, HR-MS, and NMR spectroscopic analysis. This study was undertaken to evaluate the effects on the antifungal properties of the designed compounds. The data of the in vitro antifungal activity indicates that all the synthesized compounds show
moderate-to-excellent activity against nearly all the tested fungal pathogens. The activity of type 7 is weakened when the alkyl group is substituted by a halogen atom. Moreover, the activity got lower when the halogen electron-withdrawing action ability was enhanced. Halogens are common in antifungal agents and, together with alkyl, alkoxy, nitro, and cyano groups, were inserted into the phenyl of the side chains. However, in our research, the introduction of the halogens on the phenyl group of the designed compounds did not improve activity. Conversely, antifungal activity to some other fungi strains was decreased and the antifungal spectrum was narrowed to \textit{C. par}, \textit{C. tro}, \textit{C. neo.}, and \textit{F. com.}

Molecular docking results revealed that the compound 8d binds to the active site of CACYP51 through the formation of a coordination bond with the iron of the heme group. The difluorophenyl group is located in the S3 subsite. The fluorine (2-F) can form H-bonds with the residue Gly307. The side chain of the compound 8d is oriented in the S4 subsite and formed hydrophobic and van der Waals interactions with the amino residues. Moreover, the phenyl group attached to the piperidinol of the side chain interacts with the phenol group of Phe380 through the formation of π–π face-to-edge interactions. More insightful observations of the active site would give us some key information about the SAR for further design of broad-spectrum antifungal agents.

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Disclosure

The authors report no conflicts of interest in this work.

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