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Asymmetric Synthesis, Antifungal Activity and Molecular Modeling of Iodiconazole Isomers

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Iodiconazole is a novel antifungal agent that was developed in its racemic form. In order to investigate the effects of the chiral center on the antifungal activity, *R*- and *S*-isomers of iodiconazole were prepared on the basis of the asymmetric Sharpless epoxidation. (*S*)-Iodiconazole was proved to have better antifungal activity than the (*R*)-isomer. The binding modes of the two isomers with lanosterol 14α-demethylase were clarified by molecular docking.

Keywords iodiconazole, asymmetric synthesis, optically pure isomers, antifungal activity, molecular docking

Introduction

Fungal infections include superficial fungal infection and invasive fungal infection.[1] Superficial fungal infections (*e.g.* toenails and tinea pedis) are very common with worldwide distribution and often affect the skin or mucous membranes. Invasive fungal infections are often life-threatening, whose morbidity and mortality is increasing rapidly. Clinically, azole antifungal agents (*e.g.* fluconazole and voriconazole, Figure 1) are first-line antifungal agents that can be used to treat both superficial and invasive fungal infections. However, broad application of azole antifungal agents has led to severe resistance.[2] Also, the antifungal potency and spectrum of the azoles remains to be improved. The discovery and development of new generation of azole antifungal agents represents an active area of research interests.

Azole antifungals act by competitive inhibition of lanosterol 14α-demethylase (CYP51), an key enzyme involved in fungal sterol biosynthesis.[3] In our previous studies, three dimensional models of CYP51s from important fungal pathogens were built by homology modeling.[4,5] The azole-CYP51 interactions were investigated by molecular docking. On the basis of the active site properties of CYP51, a molecular design model for the optimization of azole antifungal agents was constructed.[6] Using this model, a number of highly potent azole antifungal agents were designed and synthesized. Among them, iodiconazole (Figure 1) was selected as a new antifungal drug for further development.[6] Iodiconazole showed excellent antifungal activity with a broad spectrum. Phase III clinical trial of iodiconazole for the treatment of tinea cruris and tinea pedis has been finished.[7,8] It should be noted that iodiconazole was developed in its racemic form. Due to the importance of developing chiral antifungal agents, it is interesting to know the effect of the chiral center on the antifungal activity. Herein, the *R*- and *S*-isomers of iodiconazole were prepared by asymmetric synthesis. *In vitro* antifungal activity of the two isomers was determined and their binding mode with CYP51 was investigated by molecular docking.

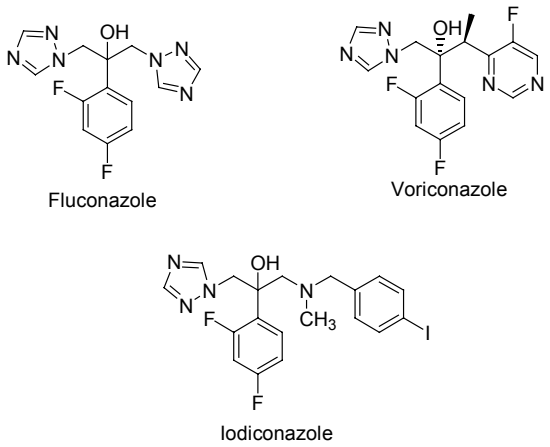

Figure 1 Chemical structures of fluconazole, voriconazole and iodiconazole.

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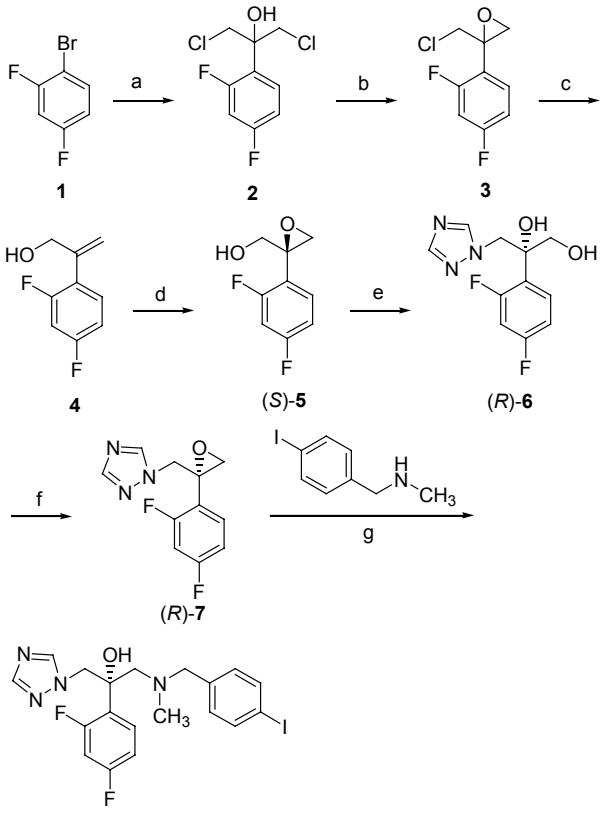
Experimental

General information

Commercial reagents were used as received, unless otherwise stated. Melting points were measured on an electrically heated XT4A instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 (500 MHz) or 300 (300 MHz) spectrometer ($CDCl_3$ or d_6-DMSO as solvent), and tetramethylsilane (TMS) was used as reference. High resolution mass spectrometry (HRMS) was recorded on an Agilent 6538 UHD Accurate-Mass Q-TOF LC/MS spectrometer. Analytical thin layer chromatography (TLC) was performed on silica gel GF254 (Qingdao Haiyang Chemical China). Flash chromatography was performed on silica gel 100—200 mesh with freshly distilled solvents. Enantioselectivities were determined by high performance liquid chromatography (HPLC) analysis employing a Daicel Chiralpak AD-H, OD-H. Optical rotations were measured in THF or ethyl acetate on an SGW-1 automatic polarimeter (Shanghai Precision Scientific Instrument CO., LTD) with a 0.8 mL cell (*c* given in g/100 mL).

Scheme 1 The asymmetric synthetic route of iodiconazole



Reaction conditions: (a) 1,3-dichloropropan-2-one, *n*-BuLi, Et_2O, –78 ℃; (b) NaH, DMF; (c) Te/NaOH (1 mol•L^{-1}), $NaHSO_2$•CH_2O•$2H_2O$, dioxane, 55—60 ℃; (d) Ti(OPr-*i*) 4, DCM, –20 ℃, diethyl-*L*-(+)-tartrate; (e) K_2CO_3, THF, 1,2,4-triazole, reflux, recrystallization with CH_3CN; (f) TEA, Et_2O, MsCl, r.t.; (g) TEA, EtOH, reflux, recrystallization with ethyl acetate and hexane.

1,3-Dichloro-2-(2,4-difluorophenyl)propan-2-ol (2) 2,4-Difluorobenzene (5.0 g, 25.9 mmol, 1.0 equiv.) was dissolved in diethyl ether (50 mL), *n*-butyl lithium (12.9 mL, 31.0 mmol, 1.2 equiv.) (2.4 mol•L^{-1} in hexane) was added dropwise at –78 ℃. After 0.5 h, the solution of 1,3-dichloroacetone (3.3 g, 25.9 mmol, 1.0 equiv.) in diethyl ether (30 mL) was added dropwise at –78 ℃. It was stirred for another 0.5 h, and quenched with the solution of acetic acid (2.0 g, 33.3 mmol, and 1.3 equiv.) in diethyl ether (5 mL) and ice water (10 mL). Then it was gradually raised to room temperature, and the organic phase was separated and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford **2** (5.1 g, 82% yield) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66—7.70 (m, 1H), 6.93—6.97 (m, 1H), 6.81—6.85 (m, 1H), 4.03 (s, 4H), 3.12 (brs, 1H).

2-(Chloromethyl)-2-(2,4-difluorophenyl)oxirane (3) Sodium hydride (60% oil) (1.0 g, 25.0 mmol, 1.2 equiv.) was suspended into dimethylformamide (25 mL). The solution of **2** (5.1 g, 21.1 mmol, 1.0 equiv.) in dimethylformamide (25 mL) was added dropwise at 0 ℃. The temperature was allowed to rise to r.t. and the resulted mixture was stirred overnight. Then it was poured into ice-water, and the pH was adjusted to 4 with HCl (4 mol•L^{-1}), extracted with ethyl acetate (50 mL×3), dried over anhydrous sodium sulphate, and the solvent was distilled off under reduced pressure. The crude product was purified through column chromatography over silica gel (hexane/EtOAc=30∶1) to afford **3** (2.3 g, 53% yield) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42—7.46 (m, 1H), 6.88—6.92 (m, 1H), 6.81—6.85 (m, 1H), 4.07 (d, J=11.9 Hz, 1H), 3.68 (d, J=11.9 Hz, 1H), 3.20 (d, J=5.0 Hz, 1H), 2.93 (d, J=5.0 Hz, 1H).

2-(2,4-Difluorophenyl)prop-2-en-1-ol (4) Metallic tellurium (0.95 g, 7.3 mmol, 1.0 equiv.) and sodium hydroxymethane-sulphinate (2.3 g, 14.9 mmol, 2.0 equiv.) were suspended in NaOH (1 mol•L^{-1}) (42 mL). The mixture was heated to 55—60 ℃ and stirred for 1 h under a nitrogen atomosphere, then a solution of **3** (1.5 g, 7.3 mmol, 1.0 equiv.) in dioxane (15 mL) was added dropwise and the mixture was stirred for another 0.5 h, cooled to r.t. After removing the insoluble pale-yellow solid through filtrating, the water phase was extracted with diethyl ether (30 mL×3), dried over anhydrous sodium sulphate, and concentrated to give **4** (0.9 g, 75% yield) as pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28—7.31 (m, 1H), 6.79—6.88 (m, 2H), 5.51 (s, 1H), 5.34 (s, 1H), 4.45 (s, 2H).

(*S*)-(2-(2,4-Difluorophenyl)oxiran-2-yl)methanol (5) Titanium tetraisopropoxide (32.9 g, 115.8 mmol, 2.0 equiv.) was dissolved into methylene chloride (200 mL) under a nitrogen atomosphere, and cooled to –20 ℃. A solution of diethyl-*L*-(+)-tartrate (13.2 g, 64.0 mmol, 1.1 equiv.) in methylene chloride (50 mL) was added dropwise. After stirring for 15 min, the solution of **4** (10.0 g, 58.8 mmol, 1.0 equiv.) in methylene chlo-

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ride (50 mL) and *tert*-butyl hydroperoxide (5.5 mol•L^{-1} in *n*-heptane) (34.4 mL, 189.2 mmol, 3.2 equiv.) was added into the solution successively. The resulted mixture was stirred for 8 h at –20 ℃, and quenched with tartaric acid (10%) (200 mL). It was warmed to room temperature gradually. Then the reaction mixture was filtered by celite and methylene chloride layer was separated, dried over anhydrous sodium sulphate, and concentrated to give the crude product. It was purified through column chromatography over silica gel with hexane/EtOAc (15∶1) as the eluent to yield **5** (4.7 g, 44% yield) as pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39－7.43 (m, 1H), 6.70－6.99 (m, 2H), 4.13 (d, J=11.3 Hz, 1H), 3.90 (d, J=12.6 Hz, 1H), 3.30 (d, J=5.0 Hz, 1H), 2.85 (d, J=5.2Hz, 1H). The *ee* value of **5** was determined when it was converted to **6**. HPLC (Chiralpak OD, ^{i}PrOH/hexane=10/90, flow rate 1.0 mL/min, λ=254 nm): t_{minor}=18.9 min (*R*), t_{major}=26.4 min (*S*), *ee*=68%; $[\alpha]_D^{25}$ –17.9 (c=0.3 in THF).

(*R*)-2-(2,4-Difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propane-1,2-diol (6) Compound **5** (4.7 g, 25.2 mmol, 1.0 equiv.) was dissolved into tetrahydrofuran (150 mL), and 1,2,4-triazole (3.5 g, 50.7 mmol, 2.0 equiv.) and anhydrous potassium carbonate (7.0 g, 50.6 mmol, 2.0 equiv.) were added. The mixture was heated under reflux for 48 h, then cooled to room temperature and concentrated in vacuum. The residue was dissolved into methylene chloride (200 mL), washed with brine (50 mL×3), dried over anhydrous sodium sulphate. After distilling off the solvent under reduced pressure, the residue was diluted with hexane (30 mL), stirred for 15 min, and filtered to afford 2.0 g of crude product, which was recrystallized from acetonitrile to give optically pure (***R***)-**6** (1.2 g, 18%) as white solid. m.p. 95－96 ℃ (m.p. 92－93 ℃, Ref: 10); $[\alpha]_D^{25}$ –65.0 (c=2.0 in MeOH). ^{1}H NMR (600 MHz, d_6-DMSO) δ: 8.29 (s, 1H), 7.71 (s, 1H), 7.37－7.41 (m, 1H), 7.11－7.15 (m, 1H), 6.94 (td, J=2.2, 8.1 Hz, 1H), 5.75 (brs, 1H), 5.07 (t, J=5.8 Hz, 1H), 4.59 (d, J=14.3 Hz, 1H), 4.56 (d, J=14.3 Hz, 1H), 3.70 (dd, J=4.6, 11.2 Hz, 1H), 3.64 (dd, J=4.6, 11.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.60 (dd, $J_{C\text{-}F}$=12.5, 245.0 Hz), 159.00 (dd, $J_{C\text{-}F}$=12.5, 245.0 Hz), 150.34, 144.80, 130.32 (dd, $J_{C\text{-}F}$=6.8, 9.0 Hz), 124.93 (d, $J_{C\text{-}F}$=13.2 Hz), 110.68 (d, $J_{C\text{-}F}$=18.2 Hz), 103.71 (t, $J_{C\text{-}F}$=26.3 Hz), 71.53 (d, $J_{C\text{-}F}$=5.0 Hz), 65.83, 54.14; HPLC (Chiralpak OD, ^{i}PrOH/hexane=10/90, flow rate 1.0 mL/min, λ=254 nm): t_{major}=18.9 min (*R*), t_{minor}=26.4 min (*S*), *ee*>99%; IR (neat) ν: 3439, 1599, 1556, 1499, 1278, 1140, 1123 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}F_2N_3O_2$ ($M+H^+$) 256.0892, found 256.0900.

(*S*)-1-((2-(2,4-Difluorophenyl)oxiran-2-yl)methyl)-1*H*-1,2,4-triazole (7) Methanesulphonyl chloride (0.4 g, 3.6 mmol, 1.5 equiv.) was added into a solution of compound **6** (0.6 g, 2.4 mmol, 1.0 equiv.) and triethylamine (1.1 g, 11.4 mmol, 4.7 equiv.) in diethyl ether (100 mL). After stirring for 1 h, water (50 mL) was added into this mixture and stirred for 1 h, then separated. The organic phase was mixed with water (50 mL) and its pH value was adjusted to 4 with HCl (1 mol•L^{-1}). The mixture was separated again, and the diethyl ether was washed with brine (50 mL×3), dried over anhydrous sodium sulphate, and concentrated to give (*S*)-**7** (0.4 g, 70% yield) as pale yellow oil. It was used directly in the next step without further purification. $[\alpha]_D^{25}$ 4.3 (c=0.8 in THF). ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.77 (s, 1H), 6.71－7.12 (m, 3H), 4.75 (d, J=14.9 Hz, 1H), 4.44 (d, J=14.9 Hz, 1H), 2.87 (d, J=4.6 Hz, 1H), 2.80 (d, J=4.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 163.12 (dd, $J_{C\text{-}F}$=10.6, 251.2 Hz), 160.59 (dd, $J_{C\text{-}F}$=111.9, 248.6 Hz), 151.78, 144.11, 129.59 (dd, $J_{C\text{-}F}$=5.2, 9.5 Hz), 119.52 (d, $J_{C\text{-}F}$=14.8 Hz), 111.68 (d, $J_{C\text{-}F}$=21.5 Hz), 104.00 (t, $J_{C\text{-}F}$=25.7 Hz), 56.21, 53.51, 52.14; IR (neat) ν: 3124, 1618, 1599, 1557, 1506, 1426, 1273, 1141 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_9F_2N_3O$ ($M+H^+$) 238.0786, found 238.0791.

(*S*)-Iodiconazole 1-(4-Iodophenyl)-*N*-methylmethanamine (1.6 g, 6.5 mmol, 3.8 equiv.) was added into the solution of compound **7** (0.4 g, 1.7 mmol, 1.0 equiv.) and triethylamine (0.6 g, 5.9 mmol, 3.5 equiv.) in ethanol (50 mL), and the resulting mixture was heated under reflux for 10 h. Then, ethanol was removed through evaporation, and the residue was dissolved into ethyl acetate (150 mL), washed with brine (50 mL×3), dried over anhydrous sodium sulphate, and concentrated to give the crude product. It was purified through column chromatography over silica gel with MeOH/DCM (1∶150) as the eluent to yield (*S*)-iodiconazole (0.6 g, 73% yield) as white solid. It was recrystallized from ethyl acetate and hexane and enantiomerically pure product was obtained in 59% recrystallization yield. m.p. 65－66 ℃; $[\alpha]_D^{25}$ 58.0 (c=0.4, ethyl acetate); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.74 (s, 1H), 7.59 (d, J=8.3 Hz, 2H), 754－7.58 (m, 1H), 6.86 (d, J=8.3 Hz, 2H), 6.75－6.82 (m, 3H), 5.20 (brs, 1H), 4.50 (d, J=14.5 Hz, 1H), 4.43 (d, J=14.5 Hz, 1H), 3.41 (d, J=13.2 Hz, 1H), 3.31 (d, J=13.2 Hz, 1H), 3.07 (d, J=13.8 Hz, 1H), 2.80 (d, J=13.8 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 162.17 (dd, $J_{C\text{-}F}$=11.5, 249.2 Hz), 158.27 (dd, $J_{C\text{-}F}$=111.9, 248.6 Hz), 151.78, 144.11, 129.59 (dd, $J_{C\text{-}F}$=5.2, 9.5 Hz), 119.52 (d, $J_{C\text{-}F}$=14.8 Hz), 111.68 (d, $J_{C\text{-}F}$=21.5 Hz), 104.00 (t, $J_{C\text{-}F}$=25.7 Hz), 56.21, 53.51, 52.14; HPLC (Chiralpak AD, ^{i}PrOH/hexane=10/90, flow rate 0.8 mL/min, λ=254 nm): t_{minor}=11.0 min (*R*), t_{major}=12.1 min (*S*), *ee*>99%; IR (neat) ν: 3384, 1616, 1598, 1556, 1498, 1421, 1272, 1204 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}F_2IN_4O$ ($M+H^+$) 485.0644, found 485.0661.

(*R*)-Iodiconazole The chiral center was generated through diethyl-*D*-(–)-tartrate induced asymmetric Sharpless epoxidation, and (*R*)-iodiconazole was prepared with a similar procedure as described above. m.p. 55－56 ℃; *ee*=92%; $[\alpha]_D^{25}$ –49.0 (c=0.5, ethyl acetate).

Results and Discussion

Asymmetric synthesis of iodiconazole isomers

Asymmetric Sharpless epoxidation was proven to be an efficient way to construct the chiral center of triazole antifungal agents.[9,10] Firstly, the key allyl alcohol intermediate **4** was prepared according to known procedure.[10] Then, starting from **4**, diethyl-*L*-(+)-tartrate induced asymmetric Sharpless epoxidation afforded (*S*)-**5** with a moderate enantioselectivity (68% *ee*). After the ring-opening reaction with 1,2,4-triazole, the resulting product was re-crystallized with acetonitrile to afford enantiomerically pure **6** (>99% *ee*). Its absolute configuration was determined by comparison with the specific rotation and retention time (HPLC) to the reported value.[11] After the formation of a new epoxide **7**, an epoxide-opening reaction with benzylamine afforded (*S*)-iodiconazole with a high enantioselectivity (>99% *ee*). Using a similar procedure, (*R*)-iodiconazole was prepared with a high *ee* value (92%).

In vitro antifungal activity of iodiconazole isomers

In vitro antifungal activity of (*R*)- and (*S*)-iodiconazole isomers is listed in Table 1 and fluconazole was used as a reference drug. The results revealed that both (*R*)- and (*S*)-iodiconazole isomers showed broad-spectrum inhibitory activity against the tested fungal pathogens. Iodiconazole revealed the best activity against two strains of *Candida albicans*, which ranks the fourth cause of bacterial/fungal nosocomial infectious diseases. Interestingly, the (*S*)-isomer was 16-fold more potent than the (*R*)-isomer. The same trend was also observed for other fungal pathogens except *Trichophyton rubrum*. For example, *Cryptococcus neoformans* and *Aspergillus fumigatus* caused significant mortality rate every year and (*S*)-iodiconazole was four fold more active than (*R*)-iodiconazole. For the dermatophytes, (*S*)-iodiconazole showed better activity against *Microsporum gypseum* than (*R*)-iodiconazole. Interestingly, both (*S*)-isomer (MIC=0.25 μg/mL) and (*R*)-isomer (MIC=0.125 μg/mL) showed similar inhibitory activity against *Trichophyton rubrum*. Because *Trichophyton rubrum* was the main cause of superficial fungal infections, it is reasonable to develop iodiconazole in its racemic form as a tropical antifungal agent. When iodiconazole is used to treat invasive fungal infections, it is better to develop its (*S*)-isomer.

Molecular docking of iodiconazole isomers

In order to investigate why (*S*)-iodiconazole generally showed better antifungal activity than (*R*)-iodiconazole, the two isomers were docked into the active site of *Candida albicans* CYP51. As depicted in Figure 2, the triazole ring and difluorophenyl group of the two isomers share a similar binding mode with CYP51. The N4 atom in the triazole ring interacts with the heme group through the formation of a coordination bond with the Fe atom. The difluorophenyl group forms hydrophobic interactions with Phe126 and Tyr132. It should be noted that the chiral center has important effect on the orientation of the C3-side chain. For the (*S*)-isomer, the *N*-methyl group forms hydrophobic and van der Waals interactions with Leu376 and Met508. However, these interactions were lost for the (*R*)-isomer. The terminal benzyl group of both isomers was extended into the CYP51 channel, which mainly forms hydrophobic and van der Waals interactions with the surrounding residues such as Met508, Leu121, Phe233, and Phe380. As shown in Table 2, the (*S*)-isomer of iodiconazole has higher GOLD fitness score than the (*R*)-isomer, which is consistent with their *in vitro* antifungal activity.

Table 1 *In vitro* antifungal activity of (*R*)-iodiconazole and (*S*)-iodiconazole (MIC_{80}, μg•mL^{-1})

Compd.	*C. alb.*	*C. para.*	*C. neo.*	*C. gla.*	*A. fum.*	*T. rub.*	*M. gyp.*
(*S*)-Iodiconazole	0.0156	0.125	0.125	0.0625	2	0.25	0.125
(*R*)-Iodiconazole	0.25	0.5	0.5	0.125	8	0.125	1
rac-Iodiconazole	0.032	0.25	0.125	0.125	8	0.25	0.5
Fluconazole	0.5	1	2	1	>64	0.5	16

Abbreviations: *C. alb.*, *Candida albicans*; *C. para.*, *Candida parapsilosis*; *C. neo.*, *Cryptococcus neoformans*; *C. gla.*, *Candida glabrata*; *A. fum.*, *Aspergillus fumigatus*; *T. rub.*, *Trichophyton rubrum*; *M. gyp.*, *Microsporum gypseum*.

Table 2 The GOLD docking scores of (*R*)-iodiconazole and (*S*)-iodiconazole with CYP51[a]

Compd.	Fitness[b]	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)
(*S*)-Iodiconazole	77.43	10.00	50.08	0.00	–1.42
(*R*)-Iodiconazole	72.93	10.00	48.40	0.00	–3.62

[a] S(hb_ext) is the protein-ligand hydrogen bond score; S(vdw_ext) is the protein-ligand van der Waals score; S(hb_int) is the score from intramolecular hydrogen bond in the ligand; S(int) is the score from intramolecular strain in the ligand. Gold FitnessScore=S(hb_ext)+1.375×S(vdw_ext)+S(hb_int)+S(int).

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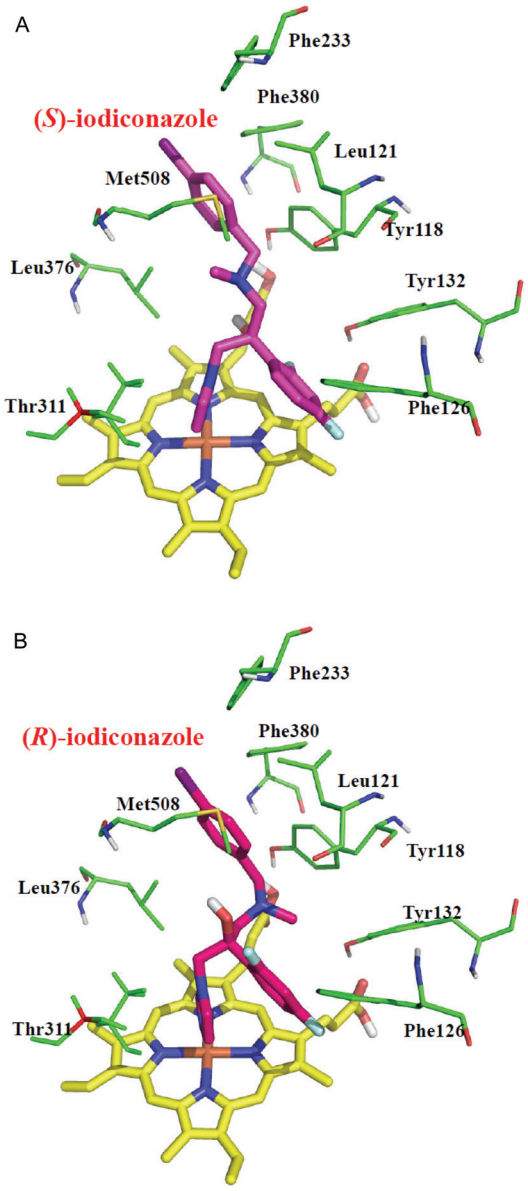

Figure 2 The binding mode of (*R*)-iodiconazole (A) and (*S*)-iodiconazole (B) with CYP51.

Conclusions

R- and *S*-isomers of iodiconazole were prepared by an asymmetric synthetic route. The antifungal activity assay revealed that (*S*)-iodiconazole was generally more active than the (*R*)-isomer. Molecular docking results indicated that the chiral center had an important effect on the position of *N*-methyl group, which led to different hydrophobic and van der Waals interactions with Leu376 and Met508. The pharmacokinetic evaluations of these two isomers were ongoing in our laboratory.

Acknowledgement

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