Chinese Chemical Letters Vol. 15, No. 9, pp 1011-1014, 2004 1011
http://www.imm.ac.cn/journal/ccl.html

Synthesis of Novel Antifungal Triazole Compounds

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Abstract: Based on our previous studies of 3D-QSAR, 38 novel objective compounds belonging to 4 series were designed and successfully synthesized directed by the idea of reconstructing the structure of non-pharmacophores while reserving essential ones in triazoles. *In vitro* pilot studies on their antifungal activities showed that most compounds have inhibitory effects on *C.albicans* and some inhibit *S.cerevisiae* also. The effects on *C.albicans* of 5 compounds are more potent than or equal to that of fluconazole or itraconazole.

Keywords: Triazole, antifungal, synthesis, bioactivity.

During the past two decades, the frequencies and types of systemic fungal infections have increased dramatically in patients suffered with tumors, immunodeficiency or immunosuppression and have become one of the important fatal causes. New antifungal drugs with higher activity and lower toxicity are clinically in urgent. Triazole antifungals can exactly fulfil such a need, and so the studies of it have become a highlight in this field recently.

The results of our previous studies of 3D-QSAR on triazole antifungals showed that azoles having a substituent connecting to the chiral carbon in the middle of their basic structures with bulky volume or high density of negative charges might present higher antifungal activities. Based on it and the molecular mechanisms of azoles' antifungal function, 38 novel triazole compounds belonging to four series, as showing in **Scheme 1,** were designed and successfully synthesized. Two essential pharmacophores of azoles, that is, 1, 2, 4-triazole and 2, 4-difluorinphenyl were reserved while a number of large groups with different volume and charges or various long chains were inducted to occupy appropriate sites in specific leading compounds. All the introduced fragments had ever been reported to have certain antifungal activities[1-5]. Compounds **MI** and **MII** series include 11 objects, into which indole and quinolinone derivatives were inducted. **MIII** series consist of 12 compounds, into which various long chains were inducted. **MIV** series include 15 compounds, into which both large groups and long chains were inducted and especially were worth to be explored further since they represent a novel kind of triazoles. All of the objects were firstly reported and their structures were confirmed by ^{1}HNMR, IR and MS.

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Scheme 1 The synthetic routes of the objective compounds and the structures of five objects with better activity

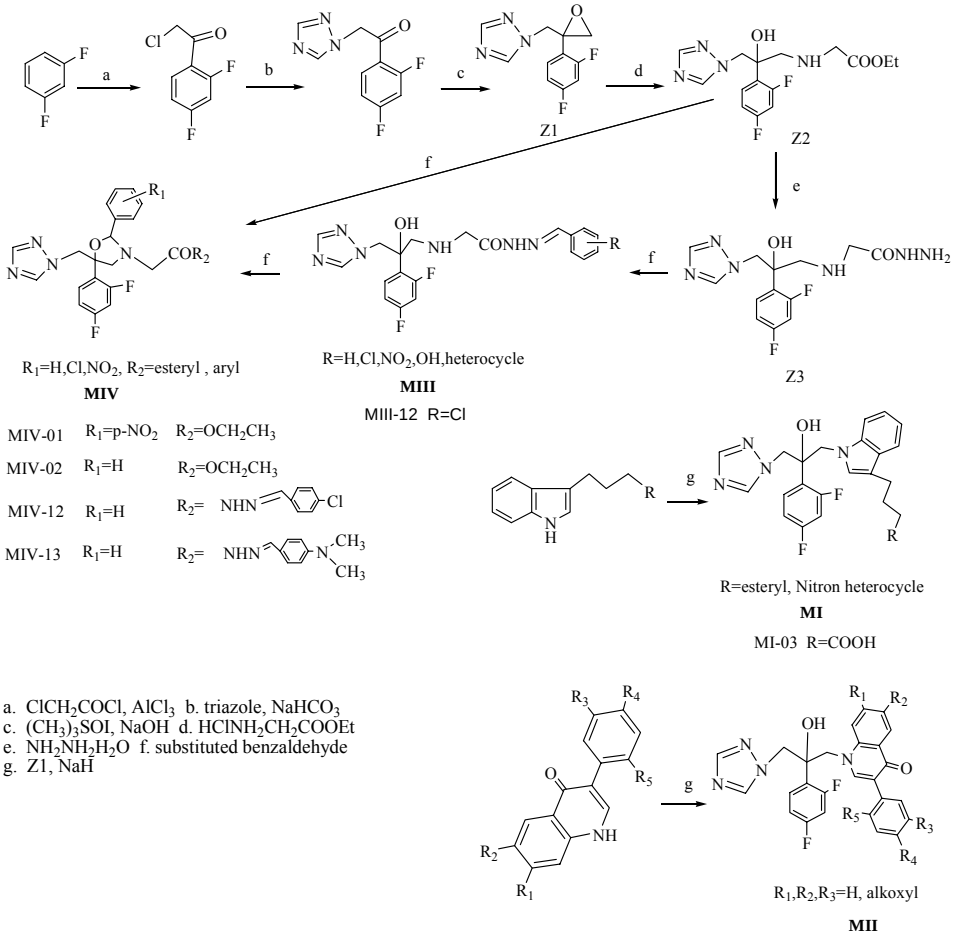

Table 1 *in vitro* MIC_{90} (μg/mL) values of five compounds

Entry		*A.niger*	*C.neoformans.*	*S.cerevisiae*
fluconazole	32	64	8	16
MI-03	32	764	2	0.125
MIV-01	2			0.125
MIV-02	4			4
MIV-12	＞128			＞128
MIV-13	2			＞128

The results of *In vitro* inhibitory tests showed that most of objects showed different inhibitory effects on *C.albicans*, some can inhibit the growth of *S.cerevisiae* also. Five compounds even presented more potent or equal inhibiting effects on *C.albicans* and *S.cerevisiae* comparing with fluconazole or itraconazole. Nevertheless, it seems that none of these compounds showed visible effect on *A.niger* and *C.neoformans*.

Experimental

Melting points were determined on a WRS-1B digital melting point apparatus. MS, IR and NMR spectra were respectively determined on Hitachi M-80A GC/MS spectrometer, PE-983 spectrophotometer and Barian INVOA-400 spectrometer.

*Representative synthesis of compounds **MI** and **MII***

4-(1-(2-(2,4-Difluorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl) propyl)-1H-indol-3-yl) butanoic acid (**MI-03**)：Ethyl 4-(1H-indol-3-yl)butanoate (4 g, 20 mmol) and anhydrous potassium carbonate powder (5 g, 36 mmol) were stirred in 40 mL of anhydrous DMF at 25°C until air bubble completely disappeared, and then compound **Z1** (5 g, 15 mmol) and polyethylene glycol 600 (0.6 g, 1 mmol) were added to the reaction mixture which was then warmed to 80°C for 24 h. The solution was then poured into ice-cold water and extracted with ethyl acetate. After the organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*, the residue was purified by silica gel chromatography using dichloromethane-methanol (v:v 50:1) to give the **MI-03** as an brown powder (2 g，yield: 33%). mp 108°C ~110°C. IR (KBr, cm^{-1}) 3350, 1730. ^{1}HNMR ($CDCl_3$, δppm) 8.07(s, 1H), 7.95(s, 1H), 7.77(s, 1H), 7.52(d, 1H, J=7.6Hz), 7.49~7.45(m, 1H), 7.31(d, 1H, J=8Hz), 7.21~7.04(m, 2H), 6.90(s, 1H), 6.77~6.69(m, 1H), 4.60(AB q, 2H, J=13.6Hz, △υ=39Hz), 4.32(d of AB q, 2H, J=1.2, 11.8Hz, △υ=36Hz), 3.55(s, 1H), 2.69(t, 2H, J=7.2Hz), 2.31(t, 2H, J=7.2Hz), 1.962~1.889(m, 2H). MS *m/z* Calcd. 440.17(M^+), Found. 441$(M+1)^+$, 224$(M-216)^+$, 83$(M-357)^+$.

*Representative synthesis of compounds **MIII***

1′-(4′-Chlorobenzylidene) -2-(2-(2,4-difluorophenyl) -2-hydroxy-3- (1H-1,2,4-triazol-1-yl) propylamino) acetohydrazone（**MIII-12**）：Triethylamine (4 mL, 60 mmol), compound **Z1** (3.33 g, 10 mmol) and ethyl 2-aminoacetate hydrochloride (2.78 g, 20 mmol) in 40 mL of methanol were refluxed for 18 h under vigorous stirring. After concentrated *in vacuo*, the residue was extracted with ethyl acetate and the organic layer was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to afforded a solid, which was recrystallized from a mixture of ethyl acetate and ether to give the intermediate **Z2** as a white solid (3.1 g, yield: 90%), mp 49 °C～51 °C. Compound **Z2** (3 g, 8.8 mmol) was dissolved in a mixture of ethanol and hydrazine hydrate and then refluxed for 24 h. After concentrated *in vacuo*, the residue was recrystallized form hexane to give compound **Z3** as a white crystal (1.88 g，yield: 65%), mp 138 °C～140 °C. Compound **Z3** (1 g, 3 mmol) and 4-chlorobenzaldehyde (0.5 g, 3.3 mmol) in 200 mL of absolute ethanol were heated at 80 °C for 8 h. After concentrated *in vacuo*, the residue was recrystallized form ethyl acetate to give **MIII-12** as a white powder (0.5 g，yield: 38%). mp 167 °C～168 °C. ^{1}HNMR (DMSO-d_6, δppm)11.36(s, 1H), 8.29(s, 1H), 7.93(s, 1H), 8.15~6.92(m, 7H), 5.97(s, 1H), 4.57(s, 2H), 3.64(s, 2H), 3.06~2.88 (m, 2H). MS *m/z* Calcd. 448.12 (M^+), Found. 449.4$(M+1)^+$, 181.4$(M-267)^+$.

*Representative synthesis of compounds **MIV***

Ethyl 2-(5-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(2,4-difluorophenyl)-2-(4-nitrophenyl) oxaz olidin-3-yl)acetate (**MIV-01**)：A solution of compound **Z2** (6.5 g, 19 mmol) and 4-nitrobenzaldehyde (3.2 g, 21 mmol) in 200 mL of toluene refluxed for 18 h. Removal of solvent *in vacuo* gave red oil, which was purified by silica gel chromatography using petroleum ether-ethyl acetate (v:v 2:1) to give compound

MIV-01 as light yellow powder (6.4 g，yield: 71%). mp 103 °C ~104 °C. ^{1}HNMR ($CDCl_3$, δppm) 8.32(s, 1H), 8.02(s, 1H), 8.00~6.61(m, 7H), 5.27(s, 1H), 4.36(AB q, 2H, J=14Hz, △υ=30Hz), 3.95(q, 2H, J=7Hz), 3.19(d, 1H, J=7.2Hz), 2.84(d, 1H, J=7.2Hz), 2.96(d, H, J=7Hz), 2.89(d, H, J=7Hz), 1.31(t, 3H, J=7.2Hz). MS *m/z* Calcd. 473.15(M^+), Found. 475.5(M+2)$^+$, 405.5(M-68)$^+$, 321.5(M-151)$^+$.

MIV-02: ^{1}HNMR ($CDCl_3$, δppm), 7.88(s, 1H), 7.63(s, 1H), 7.46~6.66(m, 8H), 5.08(s, 1H), 4.63(AB q, 2H, J=14Hz, △υ=26.6Hz), 4.14(dd, 1H, J=4, 10Hz), 4.01(q, 2H, J=7.2Hz), 3.08(AB q, 2H, J=17Hz, △υ=120.6Hz), 3.04(dd, 1H, J=1.2, 10Hz), 1.12(t, 3H, J=7.2Hz). MS *m/z* Calcd. 428.17(M^+), Found. 429.4(M+1)$^+$, 341.4(M-87)$^+$, 323.3(M-106)$^+$, 254.4(M-106-68)$^+$.

MIV-12: mp 142 °C ~144 °C. ^{1}HNMR ($CDCl_3$, δppm), 10.03(s, 1H), 8.90(s, 1H), 7.84(s, 1H), 7.82(s, 1H), 8.79~6.48(m, 12H), 5.35(s, 1H), 4.49(AB q, 2H, J=14Hz, △υ=72Hz), 3.90(d, H, J=16Hz), 3.39(d, H, J=16Hz), 3.18(d, 1H, J=13Hz), 2.84(d, 1H, J=13Hz). MS *m/z* Calcd. 536.15(M^+), Found. 537.8(M+1)$^+$, 431.3(M-106)$^+$.

MIV-13: mp 176 °C ~178 °C. ^{1}HNMR ($CDCl_3$, δppm), 10.02(s, 1H), 8.58(s, 1H), 7.87(s, 1H), 7.86(s, 1H), 7.80~6.51(m, 12H), 5.56(s, 1H), 4.48(AB q, 2H, J=13.6Hz, △υ=69Hz), 3.84(d, 1H, J=15.2Hz), 3.36(d, 1H, J=15.2Hz), 3.16(d, 1H, J=13Hz), 3.05(d, 1H, J=13Hz), 2.98(s, 3H), 2.83(s, 3H). MS *m/z* Calcd. 545.24(M^+), Found. 546.2(M+1)$^+$, 371.2(M-106-68)$^+$, 321.3(M-147-77)$^+$, 147.2(M-399)$^+$.

Acknowledgments

We thank the West China Pharmacy School of Sichuan University and the drug research center of Sichuan Institute of Antibiotic Industry for support of this research.

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Received 21 July, 2003