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Synthesis of new 1-[2-Azido-2-(2,4-dichlorophenyl)ethyl]-1H/-imidazoles and *in vitro* evaluation of their antifungal activity

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Abstract
New 1-[2-azido-2-(2,4-dichlorophenyl)ethyl]-1H/-imidazole were synthesized by nucleophilic substitution of various tertiary alcohols with azide anion in presence of boron trifluoride-diethyl etherate. Their antifungal activity was evaluated against *Candida albicans*, *Candida glabrata*, *Aspergillus fumigatus* and an azole-resistant petite mutant of *C. glabrata*. Preliminary SAR results are discussed.

Keywords: *Antifungal agents, Candida albicans, Candida glabrata, conazole, azide, resistance, Aspergillus fumigatus*

Introduction

In these past two or three decades, fungal infections have increased in frequency among severaly immuno-compromised hosts suffering from cancer or aids and in organ transplant cases. [1,2] On account of nephrotoxicity of amphotericin B [3] and despite the recent discovery of echinocandins [4], azoles which act by inhibiting cytochrome P450 14α-demethylase and present a low toxicity and a good distribution profile are usually preferred as first-line therapy [5]. However, the extensive use of azole compounds has given rise to the emergence of azole-resistant isolates in pathogenic yeasts which are often associated to an increased activity of the efflux pump [6]. Despite recent developements, there is still a need for a genuinely broad-spectrum and low toxicity antifungal azole agents capable to overcome this increased efflux [7,8] Considering this need, we recently reported the synthesis of new 2-aryl-1-azolyl-3-thienylbutan-2-ols [9], isoxazoles and isoxazolines [10] which kept a high activity against a *Candida glabrata* azole-resistant

strain which overexpressed genes coding for the efflux pump proteins. [6] These studies pointed out the utility of a five-membered heteroaromatic ring in the conazole side-chain for the escaping of the efflux pumps. Although modifications of the side-chain is very studied, some 2-position pharmacomodulations is less current. The most used conazole (fluconazole) was only modified by esterification between the 2-hydroxyl group and some carboxylic or phosphoric acids to form prodrugs with good solubility [11,12]. However, these prodrugs are less active than fluconazole and their hydrolysis capacity is weak. Therefore, it's very interesting to develop some new conazole with a pharmacomodulation in place of the 2-hydroxyl group. In this aim, we had worked on the subtitution of the 2-hydroxyl group by an azide anion. A such modification has ever encountered on griseofulvine with the substitution of the 2′-methoxy group while preserving the same antifungal activities against dermatophytes [13]. Although the azide group is recognized for his great toxicity, the used of

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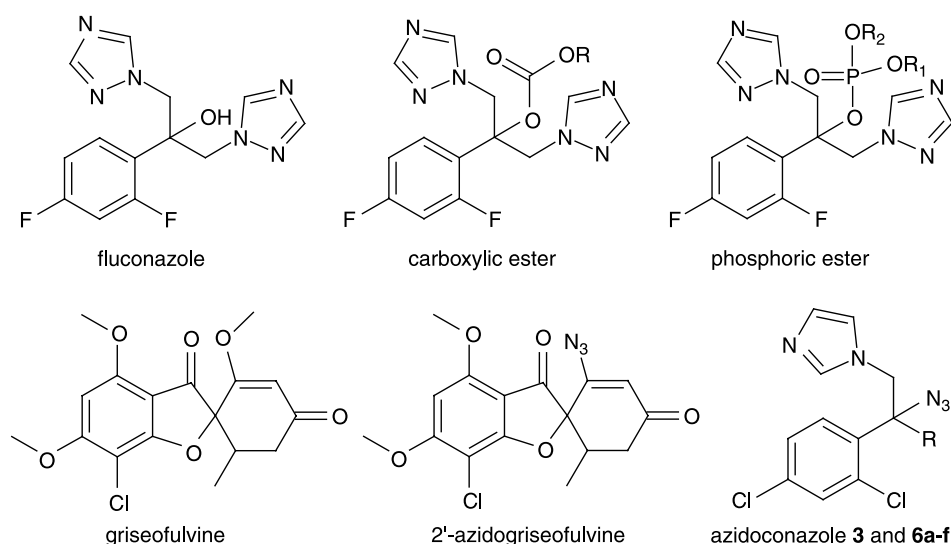
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Figure 1.   Antifungals used in therapeutic, and general structure of new synthesized compounds **3** and **6a-f** (R = H, butyl, vinyl, allyl, propargyl, phenyl, benzyl).

azidoconazoles could be justified for extremely infectious diseases caused by resistant strains. In this study, we have considered the antifungal potential of azide derivatives. So we would like to report herein the synthesis of new azide in the conazole series and an evaluation of their antifungal activity against an azole-resistant petite mutant of *C. glabrata* and its parent wild-type strain, but also on two other human pathogenic fungi, *i.e. C. albicans* and *Aspergillus fumigatus*.

Materials and methods

Chemistry

Instrumentation. Synthesis of **3** [14], **5a** [15], **5c** [16], **5d** [17], **5e** [18] and **5f** [19] were performed as previously described. Alcohol **1** [19] is commercially available from Acros Organics and ketone **4** [20] from Ugarit Chimie. Si gel 60 (Macherey-Nagel, 230-400 mesh) was used for column chromatography and precoated Si gel plates (Macherey-Nagel, SIL G/UV254, 0.25 mm) were used for preparative TLC. Infrared (IR) spectra were determined on a BRUKER FT IR Vector 22 using KBr discs for solids or neat liquid films for liquids. NMR spectra were recorded in CDCl$_3$ solution on a BRUKER AVANCE DRX 500 or a JEOL GSX 270 WB spectrometers.

Methanesulfonic acid 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethyl ester (2). At 0°C, methanesulfonyl chloride (1.1 mmol) was added to a solution of alcohol **1** (1.0 mmol) and triethylamine (1.1 mmol) in dichloromethane. After 2 h, the reaction was warmed to room temperature and water (20 mL) was then added. The organic phase was extracted with dichloromethane (2 × 20 mL), dried over Na$_2$SO$_4$,

filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO$_2$ with dichloromethane/ethanol (95/5) as eluent to give **2** (0,96 mmol; 96%). ^{1}H-NMR (270 MHz; CDCl$_3$): 2.71 (s, 3H, CH$_3$), 4.24 (dd, 1H, J = 7.5 and 15.2 Hz, CH$_{2a}$), 6.44 (dd, 1H, J = 3.0 and 15.2 Hz, CH$_{2b}$), 6.07 (dd, 1H, J = 3.0 and 7.5 Hz, CH), 6.95 (s, 1H$_{arom}$, H-2 imidazolyl), 7.09 (s, 1H$_{arom}$, H-3 imidazolyl), 7.31 (m, 2H$_{arom}$, H-5' and H-6'), 7.43 (s, 1H$_{arom}$, H-5 imidazolyl), 7.45 (m, 1H$_{arom}$, H-3'); ^{13}C-NMR (270 MHz; CDCl$_3$): 38.1 (CH$_3$), 50.4 (CH$_2$), 77.8 (CH), 127.9 (CH$_{arom}$), 128,1 (CH$_{arom}$), 128.3 (CH$_{arom}$), 129.3 (CH$_{arom}$), 129.6 (CH$_{arom}$), 129.8 (CH$_{arom}$), 131.2 (C$_{q/arom}$), 131.8 (C$_{q/arom}$), 136.0 (C$_{q/arom}$); HRMS (MeOH/H$_2$O, ESI+) m/z: 335,0033 (required: 335,0024).

2-(2,4-Dichlorophenyl)-1H-imidazol-1-yl-but-3-en-2-ol (5b). A solution of vinylmagnesium bromide (1 M in THF; 2.0 mmol) was dropped into a solution of ketone **4** (1.0 mmol) in freshly distilled THF (10 mL) and refluxed. The reaction was then quenched with water (20 mL) and THF was removed under reduced pressure. The organic phase was extracted with dichloromethane (2 × 20 mL), washed with a 10% aqueous solution of NaHCO$_3$, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on SiO$_2$ with dichloromethane/ethanol (97/3) as eluent to give **5b** (0,28 mmol; 28%). ^{1}H-NMR (270 MHz; CDCl$_3$): 4.37 (d, 1H, J = 14.1 Hz, CH$_{2a}$), 4.70 (d, 1H, J = 14.1 Hz, CH$_{2b}$), 5.26 (d, 1H$_{vinyl}$, J = 10.8 Hz, CH$_{2a}$), 5.30 (d, 1H$_{vinyl}$, J = 17.3 Hz, CH$_{2b}$), 6.46 (dd, 1H$_{vinyl}$, J = 10,8 and 17,3 Hz, CH), 6.74 (m, 2H$_{arom}$, H-2 imidazolyl and H-3 imidazolyl),

7.13 (dd, $1H_{arom}$, J = 2.1 and 8.7 Hz, H-5′), 7.33 (s, $1H_{arom}$, H-5 imidazolyl), 7.35 (d, $1H_{arom}$, J = 2.1 Hz, H-3′), 7.63 (d, $1H_{arom}$, J = 8.7 Hz, H-6′); ^{13}C-NMR (270 MHz; CDCl$_3$): 53.9 (CH$_2$), 76.1 (Cq), 117.1 (CH$_{2/vinyl}$), 120.4 (CH$_{arom}$), 127.2 (CH$_{arom}$), 127.3 (CH$_{arom}$), 129.9 (CH$_{arom}$), 130.4 (CH$_{arom}$), 131.1 (C$_{q/arom}$), 134.1 (C$_{q/arom}$), 137.9 (CH$_{arom}$), 138.3 (C$_{q/arom}$), 138.5 (CH$_{vinyl}$).

General procedure for compounds 6a–f. Boron trifluoride-diethyl etherate (1.97 mmol) was dropped at 0°C to a solution of sodium azide (1.54 mmol) and corresponding tertiary alcohol (0.16 mmol) in dried THF (10 mL). The mixture was stirred for 12 h, hydrolysed with water (1 mL) and concentrated. Then, dichloromethane (10 mL), water (10 mL) and a saturated aqueous solution of K$_2$CO$_3$ (2 mL) were added. The organic layer was extract with dichloromethane (2 × 10 mL), dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The product was purified by flash chromatography on SiO$_2$ with the adequat eluent.

1-(2-Azido-2-(2,4-dichlorophenyl)hexyl)-1H-imidazole (6a). Eluent: dichloromethane/ethanol (95/5), 75%; IR ν_{max}: 2100 (N$_3$) cm^{-1}; ^{1}H-NMR (270 MHz; CDCl$_3$): 0.93 (t, 3H, J = 7.5 Hz, CH$_3$), 1.33 (m, 2H, CH$_2$), 1.66 (m, 2H, CH$_2$), 2.74 (m, 2H, CH$_2$), 5.17 (d, 1H, J = 15.8 Hz, CH$_{2a}$), 5.32 (d, 1H, J = 15.8 Hz, CH$_{2b}$), 6.36 (s, $1H_{arom}$, H-2 imidazolyl), 7.17 (dd, $1H_{arom}$, J = 1.9 and 8.5 Hz, H-5′), 7.29 (d, $1H_{arom}$, J = 1.9 Hz, H-3′), 7.51 (d, $1H_{arom}$, J = 8.5 Hz, H-6′), 8.15 (s, $1H_{arom}$, H-3 imidazolyl), 8.51 (s, $1H_{arom}$, H-5 imidazolyl); ^{13}C-NMR (270 MHz; CDCl$_3$): 13.8 (CH$_3$), 22.3 (CH$_2$), 31.5 (CH$_2$), 35.9 (CH$_2$), 55.2 (CH$_2$), 74.5 (C$_q$), 121.3 (CH$_{arom}$), 121.9 (CH$_{arom}$), 127.7 (CH$_{arom}$), 134.6 (C$_{q/arom}$), 135.4 (C$_{q/arom}$), 135.9 (C$_{q/arom}$), 136.7 (CH$_{arom}$), 143.9 (CH$_{arom}$), 160.6 (C$_{q/arom}$).

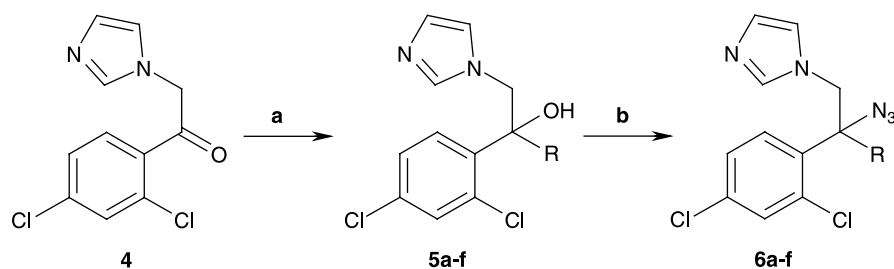*1-(2-Azido-2-(2,4-dichlorophenyl)but-3-enyl)-1H-imidazole (6b).* Eluent: dichloromethane/ethanol (96/4), 55%; IR ν_{max}: 2099 (N$_3$) cm^{-1}; ^{1}H-NMR (270 MHz; CDCl$_3$): 4.53 (d, 1H, J = 14.3 Hz, CH$_{2a}$), 4.88 (d, 1H, J = 14.3 Hz, CH$_{2b}$), 5.31 (d, $1H_{vinyl}$, J = 17.3 Hz, CH$_{2a'}$), 5.38 (d, $1H_{vinyl}$, J = 10.7 Hz, CH$_{2b'}$), 6.46 (dd, $1H_{vinyl}$, J = 10.7 and 17.3 Hz, CH), 6.76 (s, $1H_{arom}$, H-2 imidazolyl), 7.00 (s, $1H_{arom}$, H-3 imidazolyl), 7.21 (dd, $1H_{arom}$, J = 2.1 and 8.5 Hz, H-5′), 7.41 (d, $1H_{arom}$, J = 2.1 Hz, H-3′), 7.54 (d, $1H_{arom}$, J = 8.5 Hz, H-6′), 8.06 (s, $1H_{arom}$, H-5 imidazolyl); ^{13}C-NMR (270 MHz; CDCl$_3$): 70.5 (CH$_2$), 75.5 (C$_q$), 118.6 (CH$_{2/vinyl}$), 121.7 (CH$_{vinyl}$), 121.8 (CH$_{arom}$), 127.7 (CH$_{arom}$), 129.5 (CH$_{arom}$), 130.8 (CH$_{arom}$), 130.9 (CH$_{arom}$), 135.1 (C$_{q/arom}$), 136.0 (C$_{q/arom}$), 136.3 (C$_{q/arom}$), 137.4 (CH$_{arom}$).

1-(2-Azido-2-(2,4-dichlorophenyl)pent-4-enyl)-1H-imidazole (6c). Eluent: dichloromethane/ethanol (96/4), 37%; IR ν_{max}: 2097 (N$_3$) cm^{-1}; ^{1}H-NMR (270 MHz; CDCl$_3$): 2.47 (dd, 1H, J = 8.3 and 13.9 Hz, CH$_{2a}$), 3.46 (dd, 1H, J = 5.3 and 13.9 Hz, CH$_{2b}$), 4.31 (d, 1H, J = 14.1 Hz, CH$_{2a'}$), 4.91 (d, 1H, J = 14.1 Hz, CH$_{2b'}$), 5.19 (m, $2H_{vinyl}$, CH$_{2a''}$ and CH$_{2b''}$), 5.39 (m, $1H_{vinyl}$, CH), 6.77 (s, $1H_{arom}$, H-2 imidazolyl), 7.05 (s, $1H_{arom}$, H-3 imidazolyl), 7.18 (dd, $1H_{arom}$, J = 2.6 and 8.9 Hz, H-5′), 7.41 (d, $1H_{arom}$, J = 2.6 Hz, H-3′), 7.44 (d, $1H_{arom}$, J = 8.9 Hz, H-6′), 8.04 (s, $1H_{arom}$, H-5 imidazolyl); ^{13}C-NMR (270 MHz; CDCl$_3$): 41.1 (CH$_2$), 55.3 (CH$_2$), 75.0 (C$_q$), 121.6 (CH$_{vinyl}$), 121.9 (CH$_{arom}$), 122.1 (CH$_{2/vinyl}$), 127.7 (CH$_{arom}$), 127.9 (CH$_{arom}$), 135.1 (C$_{q/arom}$), 130.0 (CH$_{arom}$), 130.2 (CH$_{arom}$), 130.9 (CH$_{arom}$), 135.1 (C$_{q/arom}$), 135.9 (C$_{q/arom}$).

1-(2-Azido-2-(2,4-dichlorophenyl)pent-4-ynyl)-1H-imidazole (6d). Eluent: dichloromethane/ethanol (99/1), 15%; IR ν_{max}: 2098 (N$_3$) cm^{-1}; ^{1}H-NMR (270 MHz; CDCl$_3$): 2.19 (t, $1H_{alkyne}$, J = 2.5 Hz, CH), 3.09 (dd, 1H, J = 2.5 and 17.3 Hz, CH$_{2a}$), 3.26 (dd, 1H, J = 2.5 and 17.3 Hz, CH$_{2b}$), 4.55 (d, 1H, J = 14.5 Hz, CH$_{2a'}$), 4.95 (d, 1H, J = 14.5 Hz, CH$_{2b'}$), 6.76 (s, $1H_{arom}$, H-2 imidazolyl), 7.07 (s, $1H_{arom}$, H-3 imidazolyl), 7.23 (dd, $1H_{arom}$,
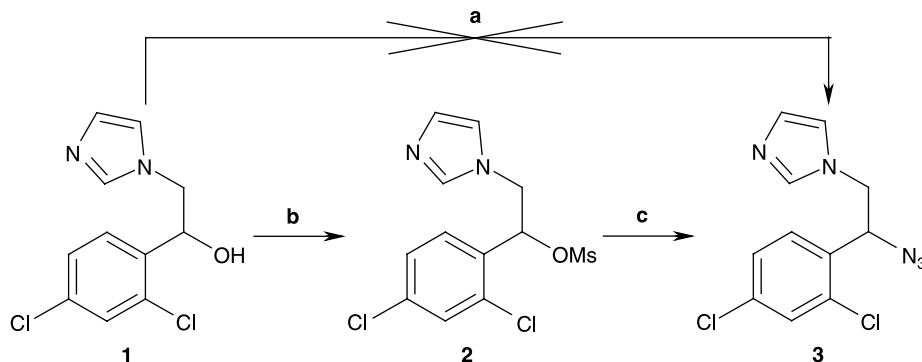
Scheme 1. Synthesis of compounds **2** and **3**. Reagent: (a) BF$_3$·Et$_2$O, NaN$_3$, THF, 0°C; (b) MsCl, NEt$_3$, CH$_2$Cl$_2$, 0°C, 99%; (c) NaN$_3$, DMF, RT, 92%.

Scheme 2.   Synthesis of compounds **5a-f** and **6a-f**. Reagents: (a) i-RMgBr, ii-RZnBr or iii-BuLi, THF; (b) $BF_3 \cdot Et_2O$, NaN_3, THF, 0°C.

Compound	R	Yield (%)	
		5	**6**
a	$(CH_2)_3CH_3$ [iii]	11	75
b	$CH=CH_2$ [i]	28	55
c	$CH_2\text{-}CH=CH_2$ [ii]	85	84
d	$CH_2\text{-}C\equiv CH$ [ii]	53	15
e	C_6H_5 [i]	6	44
f	$CH_2\text{-}C_6H_5$ [i]	55	90

J = 1.5 and 8.5 Hz, H-5'), 7.43 (d, $1H_{arom}$, J = 1.5 Hz, H-3'), 7.53 (d, $1H_{arom}$, J = 8.5 Hz, H-6'), 8.08 (s, $1H_{arom}$, H-5 imidazolyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 28.5 (CH_2), 54.3 (CH_2), 74.5 (C_q), 74.6 (CH_{alkyne}), 121.5 (CH_{arom}), 122.2 (CH_{arom}), 128.1 (CH_{arom}), 129.6 ($C_{q/arom}$), 130.1 (CH_{arom}), 130.4 (CH_{arom}), 135.1 ($C_{q/arom}$), 136.1 ($C_{q/arom}$), 136.3 (CH_{arom}).

1-(2-Azido-2-(2,4-dichlorophenyl)-2-phenylethyl)-1H-imidazole (6e). Eluent: dichloromethane/ethanol (97/3), 44%; IR ν_{max}: 2099 (N_3) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.84 (d, 1H, J = 13.2 Hz, CH_{2a}), 5.23 (d, 1H, J = 13.2 Hz, CH_{2b}), 6.60 (s, $1H_{arom}$, H-2 imidazolyl), 7.03 (s, $1H_{arom}$, H-3 imidazolyl), 7.16 (m, $2H_{arom}$, H-5' and H-3'), 7.33 (m, $5H_{arom}$, H-2'', H-3'', H-4'', H-5'' and H-6''), 7.56 (d, $1H_{arom}$, J = 8.5 Hz, H-6'), 7.94 (s, $1H_{arom}$, H-5 imidazolyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 55.7 (CH_2), 76.7 (C_q), 121.5 (CH_{arom}), 121.9 (CH_{arom}), 125.6 ($2CH_{arom}$), 127.5 (CH_{arom}), 128.8 (CH_{arom}), 129.9 ($2CH_{arom}$), 129.2 (CH_{arom}), 131.1 (CH_{arom}), 132.1 ($C_{q/arom}$), 135.2 ($C_{q/arom}$), 136.1 (CH_{arom}), 137.2 ($C_{q/arom}$), 141.0 ($C_{q/arom}$).

1-(2-Azido-2-(2,4-dichlorophenyl)-3-phenylpropyl)-1H-imidazole (6f). Eluent: dichloromethane/ethanol (95/5), 75%; IR ν_{max}: 2097 (N_3) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.05 (d, 1H, J = 13.7 Hz, CH_{2a}), 3.94 (d, 1H, J = 13.7 Hz, CH_{2b}), 4.44 (d, 1H, J = 14.3 Hz, $CH_{2a'}$), 5.12 (d, 1H, J = 14.3 Hz, $CH_{2b''}$), 6.77 (s, $1H_{arom}$, H-2 imidazolyl), 6.91 (m, $2H_{arom}$), 7.02 (m, $2H_{arom}$), 7.11 (m, $2H_{arom}$), 7.20 (m, $2H_{arom}$), 7.45 (d, 1Harom, J = 1.9 Hz, H-3'), 8.03 (s, $1H_{arom}$, H-5 imidazolyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 42.1 (CH_2), 55.4 (CH_2), 76.1

(C_q), 121.5 (CH_{arom}), 121.8 (CH_{arom}), 127.7 (CH_{arom}), 127.8 (CH_{arom}), 128.4 (CH_{arom}), 128.7 ($C_{q/arom}$), 128.8 ($2CH_{arom}$), 130.0 ($2CH_{arom}$), 130.6 (CH_{arom}), 130.8 (CH_{arom}), 133.1 ($C_{q/arom}$), 135.0 ($C_{q/arom}$), 135.8 ($C_{q/arom}$).

Antifungal activity

Test was performed following the guidelines of the approved reference method for yeasts [21]. Antifungal activity was evaluated against an azole-susceptible strain of *Candida glabrata* designated 94.5579 and its derived azole-resistant petite mutant. MICs (Minimum Inhibitory Concentration) were determined using a microdilution assay in RPMI-1640 culture medium, inoculated with $0.5–2.5 \times 10^3$ cells/mL. The test was performed using sterile 96 flat shaped-well microtitre plates. Serial two-fold drug dilutions were made in DMSO. Dilutions of the compounds were dispensed at a volume of 5 μL per well, to obtain final concentrations ranging from 250 μg/mL to the concentration where no inhibition was seen. After 48 h at 37°C, the absorbance was measured at 630 nm and $MICs_{90}$ were calculated at the minimum concentration required to inhibit at least 90% of the fungal growth compared to the drug-free control.

Results and discussion

Chemistry

Azidoconazoles **6a-f** were prepared by a two-step synthesis from ketone **4**. This last was reacted with various organometallic reagents to give alcohols **5a-f** as intermediates. The key step in this straightfoward

Table I.   MIC$_{90}$ for the tested compounds against several fungal strains.

Compounds	R	*Candida glabrata* parent	mutant	*C. albicans*	*A. fumigatus*
1	H	>250	>250	>250	>250
3		31	8	31	4
5a	$(CH_2)_3CH_3$	>250	>250	125	>250
6a		>250	>250	16	>250
5b	$CH{=}CH_2$	8	4	31	31
6b		4	1	250	>250
5c	$CH_2\text{-}CH{=}CH_2$	1	16	16	4
6c		2	4	8	8
5d	$CH_2\text{-}C{\equiv}CH$	4	16	16	62
6d		8	4	16	31
5e	C_6H_5	>250	>250	250	>250
6e		8	2	16	16
5f	$CH_2\text{-}C_6H_5$	0.25	4	2	16
6f		2	8	31	>250
fluconazole		8	>250	2	>250
voriconazole		0.5	>250	0.062	8

*Minimum Inhibitory Concentration required to inhibit at least 90% of the fungal growth compared to the drug-free control.

synthesis consisted in a nucleophilic substitution (SN_1) of the 2-hydroxyl group of tertiary alcohol **5a-f** with an azide anion in presence of a Lewis Acid, *i.e.* boron trifluoride-diethyl etherate [22]. This azido-substitution was very fast and efficient for the majority of compounds **6a-f**, excepted **6d** for which reaction yield did not exceed 15%. Azidoconazole **3** was also prepared with a two-step synthesis from secondary alcohol **1**. In this case, direct substitution of 2-hydroxyl group by an azide anion with Lewis Acid was unsuccessful. So, a more classical pathway was used with a mesylation of the secondary alcohol group followed by a nucleophilic substitution (SN_2) in DMF with NaN_3 [14].

Antifungal activity

In our approach for the discovery of new antifungal derivatives against *C. glabrata* petite mutant, a first compound **3** was synthesized. Evaluation of its antifungal activity pointed out that the azidoconazole **3** was much more active against *C. glabrata* (MIC$_{90}$ = 31 µg/mL) and *C. glabrata* petite mutant (MIC$_{90}$ = 8 µg/mL) than its alcoholic analog **1** whose for MICs$_{90}$ against *C. glabrata* and *C. glabrata* petite mutant were higher than 250 µg/mL. Morever, the pathogenic fungi *A. Fumigatus* was sensitive to azidoconazole **3** (MIC$_{90}$ = 4 µg/mL). Starting from this promising result that clearly demonstrated the sensitivity of various pathogenic fungi to secondary azidoconazole, more tertiary azidoconazoles **6a-f** were synthesized from conazoles **5a-f** bearing a hydroxyl group like last generation antifungal azoles (*i.e.* fluconazole or voriconazole). Results obtained for all compounds **6a-f** are heterogeneous. Among

alcohols derivatives **5**, compounds **5a** and **5e** are inactive against all tested strains. Substitution of the 2-hydroxyl group by an azide moiety lead to an increased activity. Azidoconazole **6e** was much more active than its hydroxylated analogue **5e** with MIC$_{90}$ values ranging from 2 to 16 µg/mL. A weak activity of **6a** was observed on the *C. albicans* strain (MIC$_{90}$ = 16 µg/mL). Activities of **5a** and **6a** pointed out the disfavorable effect of long saturated alkyl chain. However, introduction of unsaturated alkyl side chains (vinyl, allyl and propargyl) or aromatic ring seems to be favorable for the activity. Alcohols **5b-d** and azides **6b-d** are usually much more active against *C. glabrata* strains with MIC$_{90}$ values ranging from 1 to 8 mg/mL. This observation is less significant when alcohol **5e** and its azide analogue **6e** are considered. In these cases, there is no increasing of activity against *C. glabrata* when hydroxyl group was replaced by an azide. Against *C. glabrata* petite mutant, a decrease of MIC$_{90}$ showed that azidoconazole **6b**, **6c**, **6d** and **6e** are more active than their alcoholic analog **5b**, **5c**, **5d** and **5e** respectively and than frequently-used fluconazole and voriconazole. Also, one azidoconazole **6c** shown an interesting slightly broad-spectrum activity against *C. albicans* (MIC$_{90}$ = 8 µg/mL) and *A. Fumigatus* (MIC$_{90}$ = 8 µg/mL). In conclusion, the antifungal profile of the tested compounds showed that *C. glabrata* petite mutant seems to be more sensitive than its parent to azidoconazoles **6a-f**. Therefore, removing of the 2-hydroxyl group by an azido moiety using a nucleophilic substitution gave some azidoconazoles that could be specifically active against a conazole-resistant strain. Azido group seems to be an efficient parameter to consider in order to design new azoles with the aim to overcome the

increased activity of the efflux pumps which is the major mechanism of the acquired resistance to azoles in clinical isolates.

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References

[1] Fridkin SK, Jarvis WR. Clin Microbiol Rev 1996;9:499–511.
[2] Ablordeppey SY, Fan P, Ablordeppey JH, Mardenborough L. Curr Med Chem 1999;6:1151–1196.
[3] Kleinberg M. Int J Antimicrob Agents 2006;27(Suppl 1):12–16.
[4] Turner MS, Drew RH, Perfect JR. Expert Opin Emerg Drugs 2006;11:231–250.
[5] Richardson K, Cooper K, Marriott MS, Tarbit MH, Troke PF, Whittle PJ. Rev Infect Dis 1990;12(Suppl 3):267–271.
[6] Brun S, Bergès T, Poupard P, Vauzelle-Moreau C, Renier G, Chabasse D, Bouchara JP. Antimicrob Agents Chemother 2004;481:1788–1796.
[7] Chen A, Sobel JD. Expert Opin Emerg Drugs 2005;10:21–33.
[8] Sundriyal S, Sharma RK, Jain R. Curr Med Chem 2006;13:1321–1335.
[9] Chevreuil F, Landreau A, Séraphin D, Larcher G, Bouchara JP, Richomme P. J Enz Inhib Med Chem 2006;21:293–303.
[10] Chevreuil F, Landreau A, Séraphin D, Larcher G, Mallet S, Bouchara JP, Richomme P. J Enz Inhib Med Chem 2007;22:563–569.
[11] Nguyen-Hai N, Sardari S, Selecky M. Bioorgan Med Chem 2004;12:6255–6269.
[12] Bentley A, Butters M, Green SP. Organ Proc Res Develop 2002;6:109–112.
[13] Shapiro L, Ganguly AK. US3816472; Chem Abstr 1974;81:91336.
[14] Stuetz A, Egger H. DE3408127; Chem Abstr 1984;102:62244.
[15] Bawden D, Gymer GE, Marriott MS. Eur J Med Chem 1983;18(1):91–96.
[16] Jeager G, Boeckmann K, Buechel KH. DE3222191; Chem Abstr 1983;100:139121.
[17] Jiyooji AM, Haku FC. JP54027563; Chem Abstr 1979;91:57005.
[18] Scharwaechter P, Gutsche K, Kohlmann W. DE2623129; Chem Abstr 1977;88:89672.
[19] Godefroi EF, Heeres J, Van Custem J, Janssen PA. J Med Chem 1969;12:784–791.
[20] Perez ER, Loupy A, Liagre M, De Guzzi Plepis AM, Cordeiro PJ. Tetrahedron 2003;59:865–870.
[21] National Commitee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing yeasts. Approved standard M27-A. Villanova, PA: National Commitee for Clinical Standards; 1997.
[22] Harriman GCB, Shao J, Luly JR. Tetrahedron Lett 2000;41:8853–8856.

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