Synthesis and antifungal activity of phenacyl azoles

Ronald Nelson[a], Víctor Kesternich[a]*, Marcia Pérez-Fehrmann[a], Fernanda Salazar[a], Laurence Marcourt[b], Philippe Christen[b] and Patricio Godoy[c]

[a]*Departamento de Química, Facultad de Ciencias, Universidad Católica del Norte, Antofagasta, Chile*

[b]*School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland*

[c]*Instituto de Microbiología Clínica, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile*

A new *N*-(4-methoxyphenacyl)imidazole and three new substituted *N*-(phenacyl)triazoles were prepared by reaction of the heterocycle with a phenacyl halide. The former ketone and one example of the latter were reduced to the corresponding alcohols. All six compounds were screened *in vitro* for antifungal activity against two pathogenic fungal strains, *Candida albicans* (fluconazole-resistant) and *Aspergillus fumigatus*. The results revealed that most of the compounds showed activity against both strains at 100 μg mL^{-1} and 80 μg mL^{-1}, some comparable with control compound fluconazole. The alcohols were less active than the corresponding ketones.

Keywords: *N*-(4-methoxyphenacyl)imidazole, *N*-(phenacyl)-1,2,4-triazoles, fluconazole, antifungal activity

Fungal infections are an important complication, as well as the major cause of morbidity and mortality, in immunosuppressed patients such as transplant recipients and those with cancer and HIV.[1,2] Additionally, the appearance of microorganisms resistant to multiple conventional treatments has become a severe global health problem.[3] Therefore, there is an urgent need to develop new antifungal agents that are safe, effective and non-toxic with a broad spectrum of activity.[4]

In the last 30 years, only amphotericin B and 5-fluorocytosine have been used for the treatment of systemic fungal infections, although their effectiveness is unsatisfactory. A series of ergosterol synthesis inhibitors (the main sterol in fungal membranes) has shown excellent antifungal activity, and some are active after oral or parenteral administration.[5] Importantly, azoles such as imidazoles and triazoles (Fig. 1), inhibit fungal sterol synthesis by inhibiting cytochrome P450-dependent 14α-lanosterol demethylase (CYP51), ultimately affecting fungal growth and reproduction.[6–8]

Previous structure–activity relationship studies (SAR) have shown that azoles and phenyl rings are essential parts of the pharmacophore for this family of antifungal molecules.[9,10] We now report the synthesis of a new 4-methoxyphenacyl imidazole, three new substituted phenacyl triazoles and two related alcohols (Fig. 2), which possess the minimal pharmacophore structure, and evaluation of their antifungal activity against cultures of *Candida albicans* (fluconazole resistant) and *Aspergillus fumigatus*.

Results and discussion

Synthesis of α-bromoketones **2b** and **2c** (Scheme 1) was performed by brominating compounds **1b**–**c** in chloroform at room temperature.[11] Nucleophilic substitution of α-bromoketone **2b** with 1*H*-imidazole yielded the phenacyl imidazole **3b**,[12] while **2a** was converted to the phenacyl triazole derivative **5a** in alkaline medium under reflux using toluene and 1*H*-1,2,4-triazole in excess.[13] The phenacyl triazoles **5b** and **5c** were

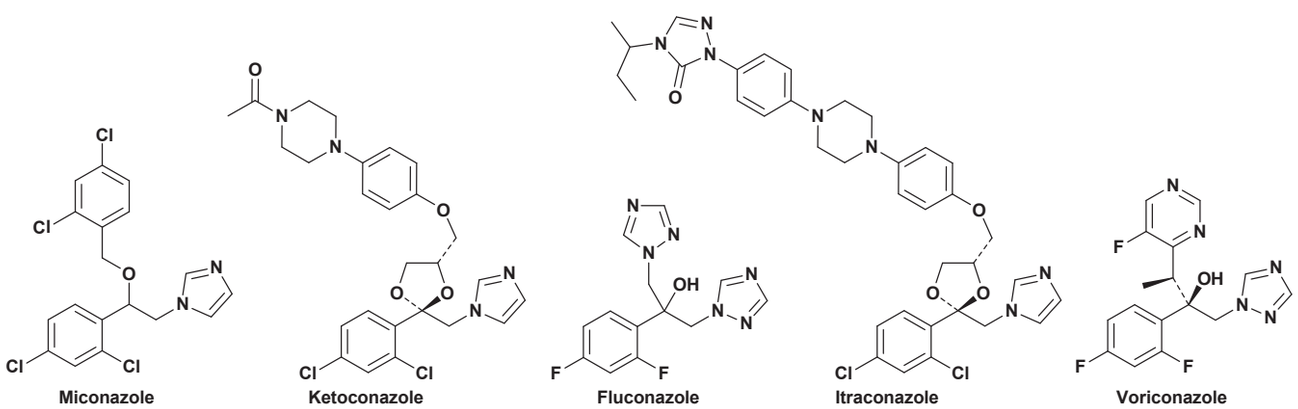
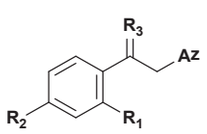


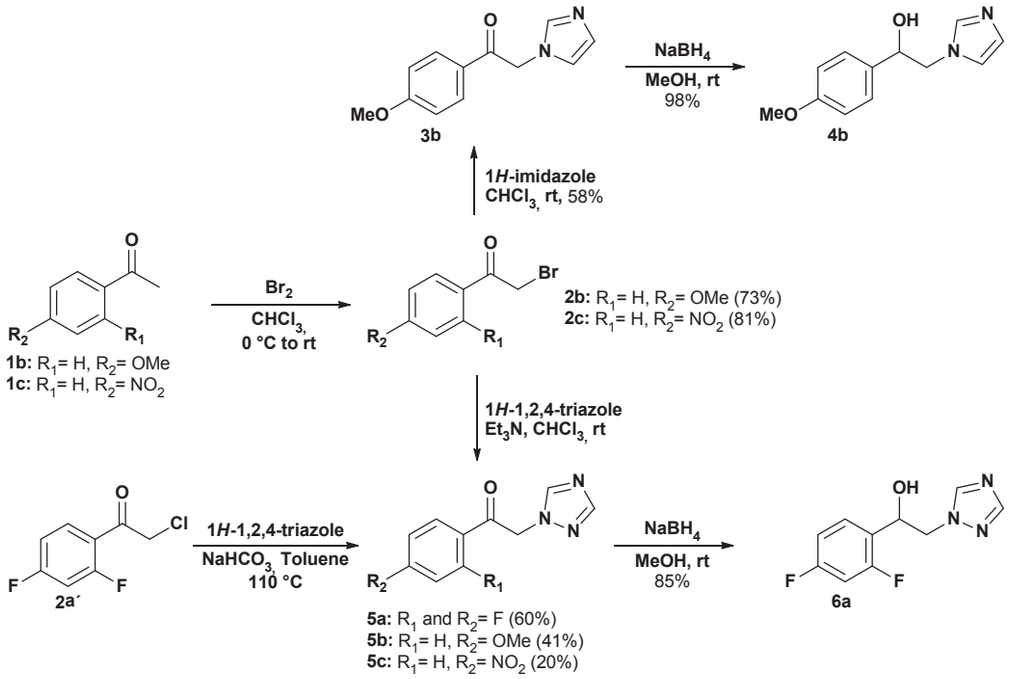
Fig. 1 Some antifungal azoles.



Az:1*H*-imidazol-1-yl; 1*H*-1,2,4-triazol-1-yl
R_1: H, F
R_2: F, OMe, NO
R_2: C=O; H,OH 2

Fig. 2 General structure of phenacyl azoles and related alcohols.

* Correspondent. E-mail: vkestern@ucn.cl



Scheme 1

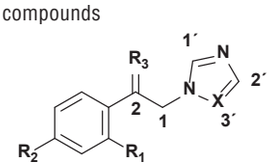
obtained from **2b** and **2c** through nucleophilic substitution at room temperature by adding 1*H*-1,2,4-triazole dissolved in chloroform and using triethylamine as the catalyst.[12,14] The reduction of ketones **3b** and **5a** with sodium borohydride in methanol produced alcohols **4b** and **6a** in good yields.[11]

Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR and MS) were consistent with the proposed structures of compounds **3**–**6** (Table 1). The imidazole ring of compounds **3b** and **4b** was characterised by the presence of a band at 1606 or 1610 cm^{-1} corresponding to C=N stretching in FT-IR and three broad singlets at δ_H 6.97 or 6.82 (H2′), 7.16 or 7.06 (H3′) and 7.65 or 7.45 (H1′) in the ^{1}H NMR spectrum. The IR spectra of compounds **5a**–**c** and **6a** showed absorption due to C=N stretching in the range of 1600–1609 cm^{-1}. In their ^{1}H NMR spectra, two singlets were observed in the aromatic region at δ_H 7.75–8.04 and 8.11–8.52 corresponding to H2′ and H1′ of the triazole ring, respectively. In the ^{13}C NMR spectra, chemical shifts at δ_C 144.2–145.7 and 150.7–151.9 were attributed to C1′ and C2′, respectively. Additionally, the structure of compound **5b** was confirmed by an X-ray diffraction study.[15] The structures of the alcohol derivatives **4b** and **6a** were characterised by an IR absorption band at 3181–3424 cm^{-1} attributed to O–H stretching. In their ^{1}H NMR spectra, the presence of an ABX system in the range of δ_H 4.01 to 5.15 corresponding to H1a, H1b and H2 protons was indicative of C2 reduction. The structure of compound **6a** was also confirmed by an X-ray diffraction study.[16]

The *in vitro* antifungal activity (percent inhibition) of azole compounds (**3**–**6**) was assessed against clinical isolates of *Candida albicans* (fluconazole-resistant) and *Aspergillus fumigatus* by the standard broth microdilution technique described in the NCCLS guidelines and using fluconazole as the standard for comparison (control antifungal).[17,18] The antifungal activities of the phenacyl azoles, expressed as percentages of inhibition at 80 and 100 μg mL^{-1}, are seen in Table 2. All azoles showed good activity at 100 μg mL^{-1} against both fungal strains. Moreover, compounds **3b**, **4b** and **5a** showed greater inhibition than fluconazole (control), though no significant differences were seen between compounds with imidazole or triazole rings. At 80 μg mL^{-1}, only phenacyl imidazole **3b** showed greater than 50% inhibition of *Candida albicans*, while for *Aspergillus fumigatus*, compounds **4b**, **5a** and **5b** showed greater activity than the control.

Our limited SAR study on the phenyl ring, revealed that when R_2 was a nitro group only weak activity was shown against *Candida albicans*, whereas a methoxyl substituent showed

Table 1 Spectroscopy data of phenacyl azole compounds



Comp.	X	IR/cm^{-1}			^{1}H NMR δ/ppm				^{13}C NMR δ/ppm			
		C=N	C=O	O–H	H1′	H2′	H3′	H2	C1′	C2′	C3′	C2
3b	CH	1606	1682	–	7.65	6.97	7.16	–	138.6	127.8	121.0	191.8
4b	CH	1610	–	3424	7.45	6.82	7.06	4.76	138.1	127.4	120.2	71.7
5a	N	1609	1689	–	8.15	7.91	–	–	145.0	151.9	–	187.7
5b	N	1600	1678	–	8.22	7.96	–	–	145.7	151.6	–	189.0
5c	N	1601	1704	–	8.52	8.04	–	–	145.5	151.3	–	192.0
6a	N	1618	–	3181	8.11	7.75	–	5.15	144.2	150.8	–	65.5

Table 2 Antifungal activity of phenacyl azoles

Compound	R_1	R_2	R_3	X	Inhibition/%			
					C. albicans		*A. fumigatus*	
					100 μg mL^{-1}	80 μg mL^{-1}	100 μg mL^{-1}	80 μg mL^{-1}
3b	H	OMe	C=O	CH	79	55	72	46
4b	H	OMe	H,OH	CH	74	39	73	47
5a	F	F	C=O	N	81	27	78	45
5b	H	OMe	C=O	N	60	35	64	48
5c	H	NO_2	C=O	N	23	16	93	12
6a	F	F	H,OH	N	44	24	54	38
Fluconazole					69	42	73	42

increased activity compared to difluorinated compounds **5a**, **6a** and fluconazole. With respect to alcoholic derivatives **4b** and **6a**, reduction of the C_2-carbonyl resulted in decreased activity of the fluorinated compounds, consistent with the findings recently described by Scipione *et al*.,[19] whereas antifungal activity for the methoxylated alcohol **4b** against both strains was similar to fluconazole.

Experimental

Melting points were determined on a Kofler-type apparatus and are uncorrected. The IR spectra were taken on a Perkin-Elmer 200 spectrophotometer in KBr discs. NMR spectra were obtained in DMSO-d_6 or $CDCl_3$ with a Varian Unity Inova 500 MHz spectrometer equipped with a 5 μL microflow probe from Protasis (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz). Chemical shifts were reported in parts per million (δ) using the residual solvent signals (DMSO-d_6: δ_H 2.50, δ_C 39.5) ($CDCl_3$; δ_H 7.26, δ_C 77.2) as the internal standards for ^{1}H and ^{13}C NMR and coupling constants (*J*) in Hz. UHPLC-TOFMS spectra were recorded on a Micromass-LCT Premier Time-of-Flight electrospray (ESI) spectrometer with an Acquity UHPLC (ultra-high performance liquid chromatography*)* interface system. TLC was performed on Al Si gel Merck 60 F_{254} and spots were visualised by spraying with phosphomolybdic acid reagent and heating. The starting materials and reagents used were acquired commercially from Sigma-Aldrich or Merck.

Synthesis of **2b** *and* **2c***; general procedure*

A solution of bromine (2.90 g, 18.0 mmol) in chloroform (150 mL) was slowly added to a cooled solution (0 °C) of acetophenone **1b**–**c** (17.0 mmol) in chloroform (150 mL), over a period of 1 h, the mixture stirred at room temperature for 15 h and quenched with ice-cold water. The organic layer was washed with saturated sodium bicarbonate solution, water and brine. The organic phase was dried over anhydrous sodium sulfate, concentrated under vacuum and purified on a silica gel (100–200 mesh) column. Elution with hexane–ethyl acetate (9 : 1) yielded pure compounds **2b and 2c**.

2-Bromo-1-(4-methoxyphenyl)ethanone (**2b):** White crystals; yield 73%; m.p. 67–69 °C (hexane-dichloromethane) (lit.[20] 69–73 °C). IR (cm^{-1}) ν: 3068 (CArH), 2980 and 2938 (Csp3-H), 1687 (C=O), 1599 and 1510 (CAr–CAr); ^{1}H NMR ($CDCl_3$) δ (ppm): 3.80 (s, 3H), 4.35 (s, 2H), 6.88 (d, 2H, *J*=8.9 Hz), 7.88 (d, 2H, *J*=8.9 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 31.0 (CH_2), 55.5 (CH_3), 114.0 (CH), 126.7 (C), 131.0 (CH), 164.0 (C), 189.8 (C=O); HRESIMS calcd for $C_9H_{10}BrO_2$ $[M+H]^+$ 228.9864, found 228.9865.

2-Bromo-1-(4-nitrophenyl)ethanone (**2c):** Yellow crystals (81%) m.p. 100–102 °C (hexane-dichloromethane) (lit.[21] m.p. 98–101 °C). IR (cm^{-1}) ν: 3102 and 3071 (CArH), 2937, 2853 and 2870 (Csp3-H), 1703 (C=O), 1599 and 1500 (Car–CAr); ^{1}H NMR (DMSO-d_6) δ (ppm): 5.00 (s, 2H), 8.21 (d, 2H, *J*=8.9 Hz), 8.33 (d, 2H, *J*=8.9 Hz).

*Synthesis of 2-(1H-imidazol-1-yl)-1-(4-methoxyphenyl)ethanone (***3b)**

A solution containing 2.00 g (8.73 mmol) of **2b**, 1.78 g (26.1 mmol) of imidazole and chloroform (100 mL) was stirred at room temperature for 24 h. Upon completion of the reaction, the mixture was concentrated on a rotary evaporator and the oil (**3b**) was purified by chromatography using dichloromethane as the eluent. Compound **3b** was obtained as a white solid, yield 58%; m.p. 134–136 °C. IR (cm^{-1}) ν: 3118 and 3014 (CArH), 2962, 2933 and 2838 (Csp3-H), 1682 (C=O), 1606 (C=N), 1509 (CAr–CAr); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.87 (s, 3H), 5.69 (s, 2H), 6.97 (brs, 1H), 7.11 (d, 2H, *J*=8.8 Hz), 7.16 (brs, 1H), 7.65 (brs, 1H), 8.02 (d, 2H, *J*=8.8 Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 52.4 (CH_2), 55.6 (CH_3), 114.1 (CH), 121.0 (CH), 127.3 (C), 127.8 (CH), 130.3 (CH), 138.6 (CH), 163.7 (C), 191.8 (C=O); HRESIMS calcd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$ 217.0977, found 217.0971.

*Synthesis of 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl) ethanone (***5a)**

A mixture of 2-chloro-2′,4′-difluroacetophenone (9.25 g, 48.53 mmol) (**2a**), 1*H*-1,2,4-triazole (4.01 g, 58.06 mmol) and sodium bicarbonate (4.90 g, 58.33 mmol) in toluene (50 mL) was refluxed for 5 h with magnetic stirring. Subsequently, cold water (50 mL) was added and the solution extracted with toluene (3 × 40 mL). The organic phase was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by chromatography using dichloromethane as the eluent. Compound **5a** was obtained as a white solid; yield 60%; m.p. 101–103 °C (lit.[22] 103–105 °C). IR (cm^{-1}) ν: 3045 (CArH), 2982 and 2946 (Csp3-H), 1689 (C=O), 1609 (C=N), 1592 and 1508 (CAr–CAr); ^{1}H NMR ($CDCl_3$) δ (ppm): 5.53 (s, 2H), 6.92 (ddd, 1H, *J*=11.0, 8.4, 2.3 Hz), 6.98 (ddd, 1H, *J*=9.6, 7.0, 2.3 Hz), 7.91 (s, 1H), 7.96 (td, 1H, *J*=8.5, 7.0 Hz), 8.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 58.4 (d, *J*=13.5 Hz, CH_2), 105.0 (t, *J*=26.6 Hz, CH), 113.2 (d, *J*=21.7 Hz, CH), 119.0 (d, *J*=11.4 Hz, CH), 133.1 (dd, *J*=10.7, 3.9 Hz, CH), 145.0 (CH), 151.9 (CH), 163.2 (dd, *J*=256.9, 12.7 Hz, C–F), 166.8 (dd, *J*=260.3, 12.6 Hz, C–F), 187.7 (C=O); HRESIMS calcd for $C_{10}H_8F_2N_3O$ $[M+H]^+$ 224.0635, found 224.0624.

Synthesis of compounds **5b** *and* **5c***; general procedure*

A solution containing 3.12 mmol of **2b** or **2c**, 0.64 g (9.27 mmol) of 1*H*-1,2,4-triazole, chloroform (50 mL) and triethylamine (500 μL) was stirred at room temperature for 48 h. Upon completion of the reaction, the mixture was filtered and the solvent distilled off under reduced pressure. The crude product was purified on a chromatographic column with dichloromethane as the mobile phase.

1-(4-Methoxyphenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (**5b**): White crystals; yield 41%; m.p. 98–99 °C (chloroform–methanol). IR (cm^{-1}) ν: 3121 and 3055 (CArH), 2973 and 2838 (Csp3-H), 1678 (C=O), 1600 (C=N), 1506 (CAr–CAr); ^{1}H NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 5.59 (s, 2H), 6.96 (d, 2H, *J*=8.6 Hz), 7.92 (d, 2H, *J*=8.6 Hz), 7.96 (s, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 54.8 (CH_2), 55.7 (CH_3), 114.4 (CH), 127.0 (C), 130.5 (CH), 145.7 (CH), 151.6 (CH), 164.6 (C), 189.0 (C=O); HRESIMS calcd for $C_{11}H_{12}N_3O_2$ $[M+H]^+$ 218.0930, found 218.0927.

1-(4-Nitrophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone (**5c**): Yellow solid; yield 20%; m.p. 148–149 °C. IR (cm^{-1}) ν: 3116 and 3067 (CArH); 2989, 2950 and 2856 (Csp3-H), 1704 (C=O), 1601 (C=N), 1518 (CAr–CAr and C–NO_2), 1347 (C–NO_2); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.08 (2H, s, H1), 8.04 (s, 1H), 8.28 (d, *J*=8.9 Hz, 2H), 8.41 (d, *J*=8.9 Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 55.6 (CH_2), 123.9 (CH), 129.6 (CH), 138.8 (C), 145.5 (CH), 150.4 (C), 151.3 (CH), 192.0 (C=O); HRESIMS calcd for $C_{10}H_9N_4O_3$ $[M+H]^+$ 233.0675, found 233.0674.

Synthesis of compounds **4b** *and* **6a**; *general procedure*

Sodium borohydride (0.15 g, 4.03 mmol) dissolved in methanol (20 mL) was added drop-wise to a mixture of 3.36 mmol **3b** or **6a** in 40 mL of methanol, and the reaction mixture was stirred at room temperature for 30 min and then taken to dryness by distillation. The solid product was suspended in saturated sodium bicarbonate and extracted with dichloromethane (3 × 40 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in a rotary evaporator.

2-(1H-Imidazol-1-yl)-1-(4-methoxyphenyl)ethanol (**4b):** White solid; yield 98%; m.p. 160–162 °C. IR (cm^{-1}) ν: 3424 (O–H), 2967, 2934 and 2844 (Csp3-H); 1610 (C=N), 1584 and 1512 (CAr–CAr); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.73 (s, 3H), 4.01 (dd, *J* = 13.8, 7.4 Hz, 1H), 4.09 (dd, *J* = 13.8, 7.4 Hz, 1H), 4.76 (dd, *J* = 7.4, 4.0 Hz, 1H), 5.59 (brs, 1H, OH), 6.82 (brs, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.06 (brs, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.45 (brs, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 53.7 (CH_2), 54.9 (CH_3), 71.7 (CH), 113.3 (CH), 120.2 (CH), 127.1 (CH), 127.4 (CH), 134.5 (C), 138.1 (CH), 158.5 (C); HRESIMS calcd for $C_{12}H_{15}N_2O_2$ $[M+H]^+$ 219.1134, found 219.1128.

1-(2,4-Difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanol (**6a**): White crystals; yield 85%; m.p. 118–120 °C (ethanol). IR (cm^{-1}) ν: 3182 (O–H), 3131 and 3071 (CArH), 2913, 2953 and 2865 (Csp3-H); 1618 (C=N), 1567 and 1504 (CAr–CAr); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 4.17 (dd, *J* = 13.6, 7.5 Hz, 1H), 4.31 (d, *J* = 13.6 Hz, 1H), 5.15 (d, *J* = 7.5 Hz, 2H), 6.66 (dt, *J* = 9.6, 1.9 Hz, 1H), 6.73 (ddd, *J* = 9.6, 7.0, 1.9 Hz, 1H), 7.32 (dt, *J* = 8.2, 7.0 Hz, 1H), 7.75 (s, 1H), 8.11 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ (ppm): 55.4 (CH_2), 65.5 (CH), 103.4 (t, *J* = 25.5 Hz, CH), 111.3 (d, *J* = 21.0 Hz, CH), 124.0 (d, *J* = 11.6 Hz, C), 128.5 (dd, *J* = 9.0, 6.0 Hz, CH), 144.3 (CH), 150.7 (CH), 159.3 (dd, *J* = 248.4, 11.9 Hz, C–F), 162.3 (dd, *J* = 248.5, 11.8 Hz, C–F); HRESIMS calcd for $C_{10}H_{10}F_2N_3O$ $[M+H]^+$ 226.0792, found 226.0787.

Antifungal activity

The percent inhibition of azole compounds against clinical isolates of *Candida albicans* (fluconazole-resistant) and *Aspergillus fumigatus* was determined by broth microdilution testing in accordance with the guidelines in NCCLS documents M27-A and M38-P. Briefly, testing was performed in flat-bottom 96-well tissue culture plates in RPMI 1640 medium buffered to pH 7.0 with 0.165 M MOPS (3-[morpholino]propanesulfonic acid). Stock solutions of fluconazole and compounds were prepared in DMSO and tested at 1–100 μg mL^{-1} (the final concentration of the solvent did not exceed 1% in any well). An inoculum of 1×10^3 to 5×10^3 CFU mL^{-1} was prepared by the UV spectroscopy method for each organism tested. The plates were incubated at 35 °C and absorbance at 530 nm recorded on a BioTek Symergy 2 apparatus after 48 h for *Candida albicans* and 72 h for *Aspergillus fumigatus*.

Conclusions

Several 2-(1*H*-azol-1-yl)-1-(substituted phenyl)ethanone (**3** and **5**) and 2-(1*H*-azol-1-yl)-1-(substituted phenyl)ethanol derivatives (**4** and **6**) were synthesised and their antifungal activity evaluated against two pathogenic fungal strains, *Candida albicans* (fluconazole-resistant) and *Aspergillus fumigatus*. Compounds with a methoxylated phenyl ring R_2 group (**3b**, **4b**, **5b**) or fluorine atoms [**5a** (R_1, R_2 = F)] exhibited inhibitory activity greater than fluconazole (control) against *Aspergillus fumigatus*, while only compound **3b** had activity equivalent to fluconazole against *Candida albicans*. The importance of this work lies in that these new compounds might be more efficacious anti-fungal drugs, which could be helpful in designing more potent antifungal agents for therapeutic use.

Samples of the compounds **3b**, **4b**, **5b** and **6a** are available from the authors.

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