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Short communication

Aromatic ethers of 1-aryl 2-(1*H*-azolyl)ethanol: study of antifungal activity

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Summary — Aromatic ethers related to antifungal azole miconazole were synthesized and tested against various strains of *Candida*. We found that activity is related to the nature of the aromatic ring and the position of substituents on this ring. Activity is more strongly dependent on the substituent in the 2 position of the ethyl chain than on the aromatic group linked through the oxygen. Triazoles were always less potent than the corresponding imidazole analogues.

imidazole / 1,2,4-triazole / antifungal activity / yeast / structure–activity relationship

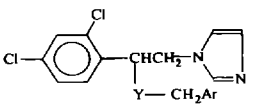
Introduction

Numerous ethers of 1-(2,4-dichlorophenyl)-2-(1*H*-imidazolyl)ethanol have been developed as antifungal agents for clinical uses, *eg*, econazole **1a**, miconazole **1b** and sulconazole **1c** (fig 1) [1]. Various molecules have been synthesized by replacing the benzylic group with other substituents [2] or by cyclization, which gives conformationally constrained analogues of miconazole [3].

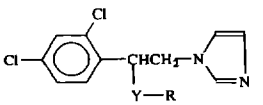
In a previous paper [4], we studied aliphatic esters and ethers of 1-(2,4-dichlorophenyl)-2-(1*H*-imidazolyl)ethanol **2** and **3** and showed that hydrophobicity plays an important role in the activity of these compounds. In this paper, we study the influence of different aromatic groups in miconazole-like structures on lipophilic parameters and antifungal activity. The substitution of the imidazole ring by the 1,2,4-triazole moiety in some target compounds was also evaluated for the same parameters.

Chemistry

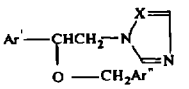
Target compounds **4** or **5** were obtained in four steps from ketones **6**. Bromination of ketones followed by condensation with 1*H*-imidazole or 1*H*-1,2,4-triazole led to azole ketones **8** or **9**. Reduction with $NaBH_4$ gave secondary alcohols **10** and **11**, which were converted into target compounds **4** or **5** by etherification (scheme 1). Structures, physicochemical characteristics and ^1H NMR data for derivatives **4** and **5** and intermediates **8**–**11** are reported in tables I–VI.



Y = O; Ar = 4-chlorophenyl: econazole **1a**
Y = O; Ar = 2,4-dichlorophenyl: miconazole **1b**
Y = S; Ar = 2,4-dichlorophenyl: sulconazole **1c**



R = Aliphatic
Y = OCO: **2**
Y = O: **3**



X = CH: **4**
X = N: **5**

Fig 1. Structure of azole derivatives.

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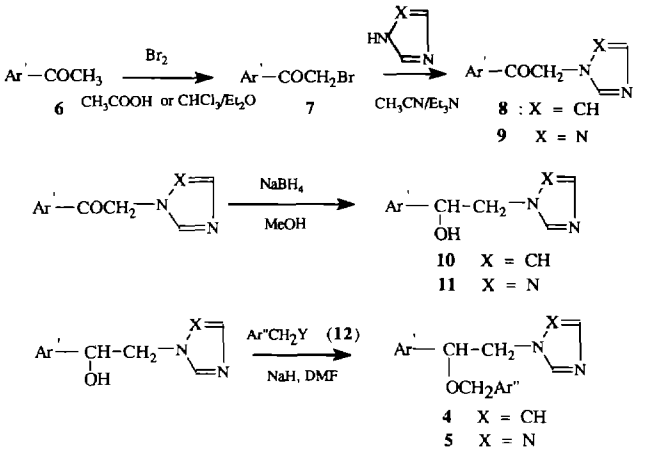

Scheme 1. Preparation of derivatives **4** and **5**.

Results and discussion

Lipophilicity parameters

The lipophilicity parameters of **4** and **5** (R_m retention time and log k_w capacity factor) were measured by reverse-phase liquid chromatography and thin-layer chromatography. These results are reported in table VII and compared with those of miconazole.

As expected, the molecules bearing the same substituents have very similar parameters (*eg*, **4a** and **4f**, **4b** and **4g**, **4c** and **4h**), while the introduction of a triazole ring always decreases the lipophilicity, with the exception of **5a**, which is closely related to reference miconazole. Only four molecules (**4c**, **4d**, **4h** and **4i**) have values in the range observed for the three reference compounds.

Table I. Physicochemical data for ketones **8** and **9**.

Compound	*Ar'*	*X*	*Formula*	*Mp*	*Yield (%)*
8b	3,4-Dimethoxyphenyl	CH	$C_{13}H_{14}N_2O_3$	165	52
8c	3,4-Methylenedioxyphenyl	CH	$C_{12}H_{10}N_2O_3$	152	55
8d	1-Naphthyl	CH	$C_{15}H_{12}N_2O$	114[a]	30
8e	2-Naphthyl	CH	$C_{15}H_{12}N_2O$	119[b]	55
8f	2-Benzofuranyl	CH	$C_{13}H_{10}N_2O_2$	152[c]	40
9a	2,4-Dichlorophenyl	N	$C_{10}H_7Cl_2N_3O$	116[d]	35
9b	3,4-Dimethoxyphenyl	N	$C_{12}H_{13}N_3O_3$	150	48
9c	3,4-Methylenedioxyphenyl	N	$C_{11}H_9N_3O_3$	179	51
9d	1-Naphthyl	N	$C_{14}H_{11}N_3O$	132	20
9e	2-Naphthyl	N	$C_{14}H_{11}N_3O$	157	21
9f	2-Benzofuranyl	N	$C_{12}H_9N_3O_2$	172	30

[a]Reference [10]: 112–115°C; [b]reference [8]: 113.5–117°C; [c]reference [8]: 226–228°C (hydrochloride); [d]reference [9]: 117°C.

Table II. Physicochemical data for alcohols **10** and **11**.

Compound	*Ar'*	*X*	*Formula*	*Mp*	*Yield (%)*
10b	3,4-Dimethoxyphenyl	CH	$C_{13}H_{16}N_2O_3$	110	83
10c	3,4-Methylenedioxyphenyl	CH	$C_{12}H_{12}N_2O_3$	135	79
10d	1-Naphthyl	CH	$C_{15}H_{14}N_2O$	110[a]	75
10e	2-Naphthyl	CH	$C_{15}H_{14}N_2O$	153[b]	80
10f	2-Benzofuranyl	CH	$C_{13}H_{12}N_2O_2$	92	74
11a	2,4-Dichlorophenyl	N	$C_{10}H_9Cl_2N_3O$	90[c]	72
11b	3,4-Dimethoxyphenyl	N	$C_{12}H_{15}N_3O_3$	76	82
11c	3,4-Methylenedioxyphenyl	N	$C_{11}H_{11}N_3O_3$	117	81
11d	1-Naphthyl	N	$C_{14}H_{13}N_3O$	122	69
11e	2-Naphthyl	N	$C_{14}H_{13}N_3O$	153[d]	86
11f	2-Benzofuranyl	N	$C_{12}H_{11}N_3O_2$	73	67

[a]Reference [10]: 112°C; [b]reference [10]: 156–160°C; [c]reference [9]: 90°C; reference [11]: 93–96°C; [d]reference [10]: 156–160°C.

Table III. Physicochemical data for ethers **4** and **5**.

Compound	*Ar'*	*Ar''*	*X*	*Formula*	*Mp (n_D 21°C)*	*Yield (%)*
4a	2,4-Dichlorophenyl	3,4-Dimethoxyphenyl	CH	$C_{20}H_{20}Cl_2N_2O_3$	90	32
4b	2,4-Dichlorophenyl	3,4-Methylenedioxyphenyl	CH	$C_{19}H_{16}Cl_2N_2O_3$	(1.5864)	31
4c	2,4-Dichlorophenyl	1-Naphthyl	CH	$C_{22}H_{18}Cl_2N_2O$	120	22
4d	2,4-Dichlorophenyl	2-Naphthyl	CH	$C_{22}H_{18}Cl_2N_2O$	70	16
4e	2,4-Dichlorophenyl	2-Benzofuryl	CH	$C_{20}H_{16}Cl_2N_2O_2$	(1.5648)	27
4f	3,4-Dimethoxyphenyl	2,4-Dichlorophenyl	CH	$C_{20}H_{20}Cl_2N_2O_3$	(1.5678)	39
4g	3,4-Methylenedioxyphenyl	2,4-Dichlorophenyl	CH	$C_{19}H_{16}Cl_2N_2O_3$	91	48
4h	1-Naphthyl	2,4-Dichlorophenyl	CH	$C_{22}H_{18}Cl_2N_2O$	< 50[a]	15
4i	2-Naphthyl	2,4-Dichlorophenyl	CH	$C_{22}H_{18}Cl_2N_2O$	91[a]	27
4j	2-Benzofuryl	2,4-Dichlorophenyl	CH	$C_{20}H_{16}Cl_2N_2O_2$	85	30
5a	2 4-Dichlorophenyl	2,4-Dichlorophenyl	N	$C_{17}H_{13}Cl_4N_3O$	86[b]	41
5b	2,4-Dichlorophenyl	3,4-Dimethoxyphenyl	N	$C_{19}H_{19}Cl_2N_3O_3$	(1.5788)	32
5c	2,4-Dichlorophenyl	3,4-Methylenedioxyphenyl	N	$C_{18}H_{15}Cl_2N_3O_3$	133	32
5d	2,4-Dichlorophenyl	1-Naphthyl	N	$C_{21}H_{17}Cl_2N_3O$	127	37
5e	2,4-Dichlorophenyl	2-Naphthyl	N	$C_{21}H_{17}Cl_2N_3O$	1.6204	38
5f	2,4-Dichlorophenyl	2-Benzofuryl	N	$C_{19}H_{15}Cl_2N_3O_2$	< 50	31
5g	3,4-Dimethoxyphenyl	2,4-Dichlorophenyl	N	$C_{19}H_{19}Cl_2N_3O_3$	61	25
5h	3,4-Methylenedioxyphenyl	2,4-Dichlorophenyl	N	$C_{18}H_{15}Cl_2N_3O_3$	114	25
5i	1-Naphthyl	2,4-Dichlorophenyl	N	$C_{21}H_{17}Cl_2N_3O$	100	34
5j	2-Naphthyl	2,4-Dichlorophenyl	N	$C_{21}H_{17}Cl_2N_3O$	86	42
5k	2-Benzofuryl	2,4-Dichlorophenyl	N	$C_{19}H_{15}Cl_2N_3O_2$	< 50	30

[a]Reference [10]: reported but not described; [b]reference [9]: 84°C.

Table IV. ^{1}H NMR data for ketone derivatives **8** and **9**.

Compound	*$COCH_2$*	*Azole (H)*	*Aromatic (H')*	*Others*
8b	5.39	7.51 (s, H_2), 6.93 and 7.02 (2s, H_4 and H_5)	7.49 (d, $H_{2'}$), 6.90 (d, $H_{5'}$), 7.60 (dd, $H_{6'}$)	3.87 and 3.92 (2s, 6H, 2(CH_3O))
8c	4.09	7.52 (s, H_2), 6.85 and 7.02 (2s, H_4 and H_5)	7.40 (d, $H_{2'}$), 6.90 (d, $H_{5'}$), 7.60 (dd, $H_{6'}$)	6.09 (s, 2H, OCH_2O)
8d	5.41	6.92 and 7.08 (2s, H_4 and H_5)	7.40–8.00 (m, 8H, H_2 and aromatics)	–
8e	5.54	6.91 and 7.01 (2s, H_4 and H_5)	7.50–8.00 (m, 8H, H_2 and aromatics)	–
8f	5.39	6.91 and 7.01 (2s, H_4 and H_5)	7.30–7.70 (m, 6H, H_2 and benzofuryl)	–
9a	5.60	7.92 and 8.03 (2s, H_3 and H_5) 7. 58 (d, $H_{6'}$)	7.50 (d, $H_{3'}$), 7.30 (dd, $H_{5'}$)	–
9b	5.68	8.20 and 8.23 (2s, H_3 and H_5)	7.40 (d, H_2), 6.90 (d, H_5), 7.58 (dd, H_6)	3.92 and 3.96 (2s, 6H, 2(CH_3O))
9c	5.59	8.03 and 8.18 (2s, H_3 and H_5)	7.39 (d, H_2), 6.88 (d, H_5), 7.60 (dd, H_6)	6.13 (s, 2H, OCH_2O)
9d	5.69	8.02 and 8.21 (2s, H_4 and H_5)	7.50–7.90 (m, 7H)	–
9e	4.47	8.13 and 8.21 (2s, H_3 and H_5)	7.50–8.10	–
9f	6.04	8.17 and 8.25 (2s, H_3 and H_5)	7.50–8.40 (m, 4H), 6.44 (s, $H_{3'}$)	–

Table V. ^{1}H NMR data for alcohol derivatives **10** and **11**.

Compound	*CH_2*[a]	*CH*[b]	*OH*	*Azole (H)*	*Aromatics (H')*	*Others*
10b	4.18, 4.02	4.88	5.10	7.37 (s, H_2), 6.85 and 7.02 (2s, H_4 and H_5)	6.80 (m, 3H)	3.85 and 3.88 (2s, 6H, 2(CH_3O))
10c	4.15, 4.03	4.82	4.90	7.48 (s, H_2), 6.92 and 7.03 (2s, H_4 and H_5)	6.80 (m, 3H)	5.97 (s, 2H OCH_2O)
10d	4.70, 4.30	5.51	5.73	7.48 (s,H_2), 6.75 and 6.98 (2s, H_4 and H_5)	7.30–7.90 (m, 7H)	–
10e	4.20, 4.05	4.59	5.21	7.17–8.08 (m, 10H aromatics and azole)		–
10f	4.25, 4.10	5.05	6.23	6.85 and 7.02 (2s, H_4 and H_5)	6.65 (s, H_2), 7.15–7.50 (m, 5H)	–
11a	4.28, 4.12	4.59	4.08	8.07 and 8.20 (2s, H_4 and H_5)	7.40 (d, $H_{3'}$), 7.30 (dd, $H_{5'}$), 7.50 (d, $H_{6'}$)	–
11b	4.32, 4.12	5.03	4.56	7.98 and 8.05 (2s, H_4 and H_5)	6.00–6.90 (m, 3H)	3.85 and 3.87 (2s, 6H, 2(CH_3O))
11c	4.35, 4.14	5.08	3.58	7.92 and 8.01 (2s, H_4 and H_5)	6.70–6.90 (m, 3H)	5.97 (s, 2H, OCH_2O)
11d	4.60, 4.33	5.53	4.07	6.90–8.00 (m, 9H aromatics and azole)		–
11e	4.46, 4.34	4.8	4.04	6.90–8.08 (m, 9H aromatics and azole)		–
11f	4.20, 4.00	5.02	6.18	7.93 and 8.04 (2s, H_4 and H_5)	6.6–7.20 (m, 5H)	–

[a]2dd, J_2 = 14 Hz, J_3 = 8 and 2.5 Hz; [b]dd.

Antifungal activity

All the compounds **4** and **5** and their references were tested against an array of clinical isolates: three *Candida albicans*, two *C glabrata*, two *C krusei* (*Issatchenkia orientalis*), two *C parapsilosis* and two *C tropicalis*. The results of *in vitro* activities are reported in tables VIII and IX. IC_{90} are the medians of the values observed for different strains of the same species.

Derivatives **4** (imidazole ring) are generally more potent than analogues **5** (triazole ring). This is related to the difference between the lipophilic parameters between the two groups. Although molecules with the same substituents in different positions (by exchange of Ar' and Ar") and the same lipophilicity generally have different activities, derivatives with Ar' = 2,4-dichlorophenyl are more potent, except against *C krusei*, which is more sensitive to compounds with Ar" = 2,4-dichlorophenyl. Imidazoles **4d** and **4e** are the most efficient compounds with IC_{90} less than IC_{90} of miconazole against *C parapsilosis* and *C glabrata*. The best activity for triazole derivatives are found for **5g**, **5i** and **5j** against *C krusei*.

Compounds **4c**, **4d** and **5a** have similar lipophilicity parameters to the reference compounds and show an acceptable to good antifungal activity. The triazoles generally have differing parameters, except for **5a**. This compound is also the most active triazole derivative of the series, except for **5g** with respect to *C krusei*. We must bear in mind that the reference compounds are imidazoles. Therefore, because molecules with equivalent parameters (by exchange of an aromatic group) may have very different levels of activity, we can conclude that lipophilicity is a necessary condition but not the only determining parameter.

Table VI. ^{1}H NMR data for derivatives **4** and **5**.

Compound	*CH_2*[a]	*CH*[b]	*OCH_2*[c]	*Azole*	*Aromatics (Ar') and others*	*Aromatics (Ar") and others*
4a	4.15, 4.01	4.93	4.43, 4.14	7.49 (H_2), 6.84 and 7.01 (2s, H_4 and H_5)	7.45 (d, $H_{3'}$), 7.20 (dd, $H_{5'}$), 7.40 (d, H_6)	6.54 (d, $H_{2''}$), 6.80 (d, $H_{5''}$), 6.68 (dd, $H_{6''}$), 3.83 and 3.86 (2s, 6H, 2(CH_3O))
4b	4.17, 4.01	4.90	4.43, 4.12	7.42 (H_2), 6.88 and 7.02 (2s, H_4 and H_5)	7.20–7.40 (m, 3H, $H_{3'}$, H_4, $H_{6'}$)	6.60 (d, $H_{2''}$), 6.70 (d, $H_{5''}$), 6.48(dd, $H_{6''}$), 5.93 (s, 2H, OCH_2O)
4c	4.17, 4.01	5.03	4.85, 4.68	6.87 and 7.01 (2s, H_4 and H_5)	7.1–7.9 (m, 11H, H_2 and aromatics)	
4d	4.19, 4.03	5.05	4.68, 4.92	6.87 and 7.01 (2s, H_4 and H_5)	7.1–7.8 (m, 11H, H_2 and aromatics)	
4e	4.08, 3.98	5.06	4.60, 4.39	6.87 and 7.01 (2s, H_4 and H_5)	7.2–7.5 (m, 8H, H_2 and aromatics), 6.47 (s, H3")	
4f	4.16, 4.02	4.80	4.34, 4.10	7.42 (s, H_2), 6.87 and 7.01 (2s, H_4 and H_5)	6.6 (d, $H_{2'}$), 6.80 (d, H_5), 6.7 (dd, H_6), 3.83 and 3.89 (2s, 6H, 2(CH_3O))	7.3 (d, $H_{3''}$), 7.20 (dd, $H_{5''}$), 7.10 (d, $H_{6''}$)
4g	4.21, 4.05	4.55	4.60, 4.36	7.42 (H_2), 6.89 and 7.02 (2s, H_4 and H_5)	6.70 (d, H_2), 6.80 (d, $H_{5'}$), 6.60 (dd, H_6), 5.98 (s, 2H, OCH_2O)	7.3 (d, $H_{3''}$), 7.20 (dd, $H_{5''}$), 7.10 (d, $H_{6''}$)
4h	4.38, 4.22	5.36	4.62, 4 43	6.94 and 7.04 (2s, H_4 and H_5)	7.10–8.00 (m, 11 H, aromatics and H_2)	
4i	4.34, 4.20	4.74	4.51, 4.38	6.91 and 7.03 (2s, H_4 and H_5)	7.10–8.90 (m, 11 H, aromatics and H_2), 4.40	
4j	4.52, 4.28	4.72	4.62, 4.43	6.91 and 7.03 (2s, H_4 and H_5)	7.10–7.60 (m, 8 H, aromatics and H_2), 6.72 (s, $H_{3'}$)	
5a	4.47, 4.30	5.21	4.48, 4.31	7.91 and 8.11 (2s, H_4 and H_5)	7.07–7.46 (m, 6 H, aromatics)	
5b	4.49, 4.31	5.10	4.30	7.91 and 8.14 (2s, H_4 and H_5)	7.40 (s, $H_{3'}$), 7.30 (d, $H_{5'}$), 7.50 (d, $H_{6'}$)	6.5 (d, $H_{2''}$), 6.80 (d, $H_{5''}$), 6.60 (dd, $H_{6''}$), 3.83 and 3.86 (2s, 6H, 2(CH_3O))
5c	4.43, 4.08	5.13	4.68, 4.35	7.93 and 8.11 (2s, H_4 and H_5)	7.20–7.40 (m, $H_{3'}$, $H_{5'}$, H_6)	6.50 to 6.70 (m, $H_{2''}$, $H_{5''}$, $H_{6''}$), 5.95 (s, 2H, OCH_2O)
5d	4.35, 4.15	5.26	4.83, 4.64	7.85 and 7.98 (2s, H_4 and H_5)	7.20–7.70 (m, 10 H, aromatics)	
5e	4.56, 4.20	5.21	4.51, 4.31	7.91 and 8.15 (2s, H_4 and H_5)	7.20–7.70 (m, 10 H, aromatics)	

[a]2dd; [b]dd; [c]2d.

Table VI. *(Continued).*

Compound	CH_2[a]	CH[b]	OCH_2[c]	*Azole*	*Aromatics (Ar') and others*	*Aromatics (Ar") and others*
5f	4.20, 4.04	5.22	4.46, 4.31	7.78 and 8.13 (2s, H_4 and H_5)	7.1–7.5 (m, 7 H, aromatics), 6.5 (s, $H_{3''}$)	
5g	4.43, 4.26	4.70	4.64, 4.38	7.94 and 8.06 (2s, H_3 and H_5)	6.7–6.9 (m, 3H $H_{2'}$, $H_{5'}$, $H_{6'}$), 3.86 and 3.90 (2s, 6H, $2(CH_3O)$)	7.3 (d, $H_{3''}$), 7.2 (dd, $H_{5''}$), 7.0 (d, $H_{6''}$)
5h	4.30, 4.12	4.70	4.65, 4.32	7.92 and 8.03 (2s, H_3 and H_5)	6.6–6.8 (m, 3H $H_{2'}$, $H_{5'}$, H_6), 6.01 (d, 2H, OCH_2O)	7.0 (d, $H_{3''}$), 7.2 (dd, $H_{5''}$), 7.3 (d, $H_{6''}$)
5i	4.47, 4.30	4.68	4.46, 4.30	7.98 and 8.12 (2s, H_3 and H_5)	7.5–7.7 (m, 7H)	7.0 (d, $H_{3''}$), 7.2 (dd, $H_{5''}$), 7.3 (d, $H_{6''}$)
5j	4.40, 4.26	4.95	4.51, 4.33	7.95 and 8.09 (2s, H_3 and H_5)	7.46–7.85 (m, 7H)	7.0 (d, $H_{3''}$), 7.2 (d, $H_{5''}$), 7.1 (d, $H_{6''}$)
5k	4.40, 4.80 (m, 5H)			7.93 and 8.12 (2s, H_3 and H_5)	6.8–7.4 (m, 7H, aromatics), 6.78 (s, $H_{3'}$)	

[a]2dd; [b]dd; [c]2d.

Table VII. Lipophilicity parameters for derivatives **4** and **5**.

Compound	R_f	R_m	$\log k_w$
4a	0.40	0.17	3.47
4b	0.39	0.19	4.54
4c	0.30	0.36	5.43
4d	0.34	0.28	5.26
4e	0.38	0.21	4.82
4f	0.39	0.19	3.47
4g	0.37	0.23	4.65
4h	0.30	0.36	5.03
4i	0.27	0.43	5.55
4j	0.39	0.19	4.82
5a	0.43	0.12	5.01
5b	0.60	–0.17	3.40
5c	0.60	–0.17	3.31
5d	0.57	–0.12	4.43
5e	0.54	–0.06	4.45
5f	0.58	–0.14	3.76
5g	0.58	–0.14	3.30
5h	0.58	–0.14	3.34
5i	0.49	0.01	4.50
5j	0.49	0.01	4.30
5k	0.56	–0.10	3.68
Miconazole	0.39	0.19	5.86

Experimental protocols

Chemistry

*Method for preparation of bromoketones **7a–c** [5]*
To a stirred solution of the ketone (100 mmol) in a chloroform/diethyl oxide mixture (100 ml/500 ml) at 0°C was slowly added (over 4 h) a solution of bromine in chloroform (100 mmol in 150 ml). After return to room temperature, the mixture was washed with 100 ml of cold 5% NaOH solution and then with 100 ml of cold water. The organic layer was dried on $MgSO_4$ and evaporated under reduced pressure at < 40°C and the crude residue crystallized in ethanol.

*Method for preparation of bromoketones **7d** and **7e** [6]*
To a solution of 100 mmol of the convenient ketone in 100 ml acetic acid, was added dropwise a solution of 100 mmol bromine in 15 ml of acetic acid and the mixture was stirred at room temperature for 2 h. The acetic acid was then evaporated under reduced pressure at < 40°C. Crystallization of the crude residue was performed in ethanol.

*General method for preparation of **8** and **9***
To a solution of 200 mmol of 1*H*-imidazole or 1*H*-1,2,4-triazole in 200 ml acetonitrile was added 200 mmol triethylamine, and then dropwise 100 mmol **7** and the mixture stirred at room temperature for 4 h. The solution was concentrated under reduced pressure, and the residue suspended in water and extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and then evaporated to dryness. The crude residue was purified by chromatography on a silica-gel column and crystallization in ethanol.

Table VIII. IC_{90} of compounds **4a–j** (μg/ml).

Compound	IC_{90} (μg/ml)				
	C albicans	*C glabrata*	*C krusei*	*C parapsilosis*	*C tropicalis*
4a	59	81	> 100	>100	61
4b	10.7	1.7	> 100	5.9	17.8
4c	23 8	70	> 100	76	57
4d	16.2	0.2	> 100	0.1	12.8
4e	26.8	2.5	66	0.08	15.1
4f	> 100	> 100	58	> 100	> 100
4g	> 100	> 100	60	> 100	> 100
4h	> 100	> 100	52	> 100	> 100
4i	86	> 100	5.6	> 100	> 100
4j	62	> 100	14.10	> 100	> 100
Miconazole	1 9	2.0	3.9	2.2	0.4

Table IX. IC_{90} of compounds **5a–k** (μg/ml).

Compound	IC_{90} (μg/ml)				
	C albicans	*C glabrata*	*C krusei*	*C parapsilosis*	*C tropicalis*
5a	56	12.9	58	0.7	> 100
5b	> 100	85	> 100	34	80
5c	> 100	> 100	> 100	> 100	> 100
5d	> 100	> 100	> 100	> 100	> 100
5e	> 100	22.5	> 100	> 100	> 100
5f	> 100	> 100	> 100	> 100	> 100
5g	65	51	36.3	2.5	> 100
5h	> 100	> 100	> 100	> 100	> 100
5i	> 100	> 100	58	> 100	> 100
5j	> 100	> 100	34	> 100	> 100
5k	> 100	53	> 100	> 100	> 100
Miconazole	1 9	2.0	3.9	2.2	0.4

*General method for preparation of **10** and **11***

To 30 mmol of **8** or **9** in 300 ml methanol was added 30 mmol (1.14 g) of sodium borohydride over 2 h and in small fractions. The mixture was then evaporated to dryness and the residue suspended in water and extracted with methylene chloride. The organic layer was dried on $MgSO_4$ and then evaporated to dryness. The crude residue was used without further purification.

*General method for preparation of **4** and **5** [7]*

To 20 mmol of **10** or **11** in 40 ml DMF was added 25 mmol NaH in small fractions to prevent any heating. The appropriate arylchloromethyl compound **12** in 20 ml of DMF was then added dropwise. The mixture was stirred at room temperature for 2 h and the excess of hydride was decomposed with a small amount of methyl alcohol. After evaporation to dryness under reduced pressure, the crude residue was suspended with water (80 ml) and extracted with methylene chloride. The organic layer was dried on $MgSO_4$ and then evaporated to dryness to afford a crude residue purified by chromatography on a silica-gel column (ethyl acetate/methylene chloride 30:70).

*Physicochemical data for compounds **4–11***

Physicochemical characteristics and yields are given in tables I–III. Melting points were determined on a Kofler bank and refraction values on an Abbe refractometer. Infrared spectrometric data (in KBr pellets or liquid films) were recorded on a Perkin-Elmer 983G: **8b–9f** (ν in cm^{-1}): 3100 (CH azole), 3050 (CH aromatics), 1680–1710 (C=O), 1615, 1580 (C=C, C=N); **10b–11f** (ν in cm^{-1}): 3400–2700 (OH), 1625, 1575 (C=C, C=N); **4a–5k** (ν in cm^{-1}): 3120 (CH azole), 3040 (CH aromatics), 1600, 1585 (C=C, C=N), 1100 (C-O).

^1H NMR data (in $CDCl_3$) at 200 MHz with the Me_4Si as an internal standard are reported in tables IV–VI. Elemental analyses are in agreement with the accepted norms and are not reported. Halides **12** were prepared as described in the literature in [7].

Lipophilicity parameters and antifungal activity

Experimental protocols were described elsewhere [4]. R_m and log k_w are reported in table VII; IC_{90} are reported in tables VIII and IX.

References

1 Godefroi EF, Heeres J, Van Custem J, Janssen PA (1969) *J Med Chem* 12, 784–791
2 Zinngibl L (1983) *Prog Drug Res* 27, 253–383
3 Lovey RG, Elliot AJ, Kaminski JJ (1992) *J Med Chem* 35, 4221–4229
4 Wahbi Y, Tournaire C, Caujolle R, Payard M, Linas MD, Seguela JP (1994) *Eur J Med Chem* 29, 701–706
5 Fuji T, Yoshfuji S, Ohba M (1978) *Chem Pharm Bull* 26, 3218–3222
6 Langley WD, Clarke HT, Boutwell PW (1958) *Organic Synthesis* 2nd ed John Wiley, London 1, 127–128
7 Wahbi Y (1995) PhD thesis, Univ Toulouse, N° 1991
8 Walker KAM, Wallach MB, Hirschfeld DR (1981) *J Med Chem* 24, 67–74
9 Bayer AG (1977) *German patent* 2547953, *Chem Abstr* 87, 53318n
10 Syntex (1978) *US patent* 4172141; *Chem Abstr* 92, 146763x
11 BASF (1977) *German patent* 2556319, *Chem Abstr* 87, 152212e