

## Aliphatic ethers of 1-(2,4-dichlorophenyl)-2-(1-*H*-imidazolyl)ethanol: influence of ramification and/or unsaturation on lipophilicity and antifungal activity

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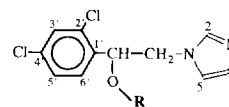
**Summary** — Ethers of 1-(2,4-dichlorophenyl)-2-(1-*H*-imidazolyl)ethanol bearing ramified and/or unsaturated chains have been synthesized in order to specify the role of lipophilicity or steric contributions on antifungal activity against yeast for miconazole-like structures. The presence of ramifications on aliphatic chains (between 4 and 7 carbons) or unsaturation at the end, increases antifungal activity. For these compounds, lipophilicity seems to be counterbalanced by steric contributions.

**imidazole / antifungal activity / lipophilicity / structure–activity relationship**

### Introduction

Many azole derivatives are used as antifungal agents; this type of compounds exhibits activity by interfering with ergosterol biosynthesis through the inhibition of lanosterol 14 $\alpha$ -demethylation catalysed by cytochrome *P*-450<sub>14 DM</sub> [1–5]. Imidazoles, the first group to be developed, contain several ethers of 1-(2,4-dichlorophenyl)-2-(1-*H*-imidazolyl)ethanol such as econazole or miconazole. In a previous paper [6], we demonstrated that the replacement of the 1-(2,4-dichlorophenyl) moiety (fig 1) by different aromatic groups on econazole-like structures decreases both antifungal activity and lipophilicity.

As hydrophobicity plays an important role in structure–activity relationships, we also studied [7] the contribution of lipophilic character to antifungal activity of aliphatic ethers of 1-(2,4-dichlorophenyl)-2-(1-*H*-imidazolyl)ethanol bearing saturated chains (1 to 12 carbons). We concluded that a chain length near to six carbons is optimal for antifungal activity, ethers with linear chains under 3 carbons or over 8 carbons are ineffective. The affinity of an azole antifungal



**Econazole:** R = 4-chlorophenyl

**Miconazole:** R = 2,4-dichlorophenyl

**Fig 1.** Structure of miconazole and econazole.

agent for cytochrome *P*-450<sub>14 DM</sub> is dependent on how the hydrophobic groups and the azole nitrogen fit the active site of the cytochrome in order to interact with the substrate-binding site and the heme. However, steric contributions related to the substituent size may also be involved in this interaction.

We synthesized ethers with ramified alkyl chains in order to underline the contributions of hydrophobicity or the size of the alkyl moiety to antifungal activity. Imazalil [8]: an unsaturated ether of 2,4-dichlorophenyl-2-(1-*H*-imidazolyl)ethanol is active against a wide range of fungi affecting fruits and vegetables and is largely used as an agricultural antifungal [9–10], therefore we also studied the influence of unsaturation on antifungal activity.

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## Chemistry

The ethers were synthesized by condensation of 1-(2,4-dichlorophenyl)-2-(1-*H*-imidazolyl)ethanol with the appropriate alkyl bromide RX (scheme 1).

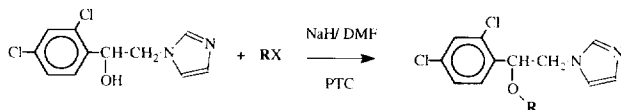
The Williamson reaction is a classical way for the preparation of unsymmetrical ethers; this method involves reaction between the halide and alkoxide ion generated from an alcohol. The reaction is not successful for tertiary alkyl groups (because of elimination) and very low yields are obtained with secondary alkyl groups.

Phase transfer catalysis (PTC) is a convenient substitute for the rigorous conditions usually required for the Williamson standard synthesis of ethers. Alkyl ethers can be prepared through this method from primary or secondary alkyl halides [11, 12].

Optimum conditions are achieved when a two-phase mixture consisting of at least a five-fold excess of 50% aqueous sodium hydroxide over alcohol, an excess of alkyl chloride (conveniently used as solvent) and 5 mol-% of tetrabutylammonium bisulfate as catalyst is stirred at 25–70 °C. 2,4-Dichlorophenyl-2-(1-*H*-imidazolyl)ethanol is more rapidly alkylated by primary halides; the reaction requires more time with secondary halides. Physicochemical data of ethers are shown in tables I and II.

## Results and discussion

Capacity factors ( $\log k_w$ ) may supply a good alternative for the evaluation of lipophilicity for a set of closely related compounds [13–15]. The lipophilicity parameters  $\log k_w$  were measured by reversed-phase liquid chromatography. In a previous work, we reported the linear relation between  $\log k_w$  and the number of carbons for a set of aliphatic ethers with linear saturated chains between 1 and 12 carbons. We are now demonstrating that  $\log k_w$  can be modulated by the presence of a ramified chain (fig 2), depending on the position of the ramification and on the primary or the secondary nature of the chain. Unsaturation slightly lower lipophilicity according to the additive relations of Hansch [16, 17] but when the chain is also ramified (compounds **5** and **10**), the effect is much more significant.



**Scheme 1.** General scheme for the synthesis of the compounds.

All compounds were tested with regard to an array of clinical isolates: 3 *Candida albicans*, 2 *Candida glabrata*, 2 *Candida parapsilosis*, 2 *Candida tropicalis*, 2 *Candida krusei*. The results of in vitro activities  $IC_{90}$  are reported in table III. In order to improve the study of structure–activity relationships on miconazole-like structures and for an easier comparison with ethers bearing linear chains between 3 and 8 carbons,  $IC_{90}$  previously obtained [7] for those compounds are recalled in table III.

For the most potent linear ethers (5 and 6 carbons), we have previously shown that  $\log k_w$  (5.04 and 5.60) was close to  $\log k_w$  of miconazole (5.85). In the case of ramified chains, lipophilicity seems less discriminant for antifungal activity. Actually, even if  $\log k_w$  is not so close to  $\log k_w$  of miconazole, compounds **2**, **3**, **6**, **7** and **8** are more potent than their analogues with linear chains. We can suppose that steric contributions introduced by ramifications counterbalance the poor lipophilicity contribution.

$IC_{90}$  values are close for compounds bearing between 4 and 6 carbons on the chain (**2**, **3**, **5**, **6**, **7** and **11**), consequently, the number of carbons is not so restrictive for activity when the chain is ramified by comparison with linear chains. Unsaturation clearly enhance activity when they are at the end of chains and compounds **4**, **5** and **9** are more potent than their saturated analogues.

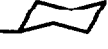
With the aim to establish a relation between antifungal activity and the nature of the chain, we performed a QSAR study. The ASP software [18] was used to take the 3D-structure into account. This software optimizes the relative orientation of a molecule in relation to a lead compound (miconazole), under energetical control (flexible fit) and then calculates similarity indices which can be used in a 3D-QSAR study (Carbo indices). On the other hand, parameters of shape and physical properties were computed from the ASP-optimized structures (see Experimental protocols).

Stepwise Discriminant Analysis (SDA) was used as a statistical technique to perform a qualitative classification of compounds. For that purpose, they were divided into three classes according to their antifungal activity (A: active, I: Inactive and M: medium, see table III).

The SDA results are given in table IV. 14 compounds out of 16 were well classified by the introduction of three variables in the stepwise process (Carbo shape, B1 Verloop and Chi 3 valence indices). The classification could not be improved by the introduction of an additional parameter.

Figure 3 shows the 2D plot of these compounds in the plane constituted by the two discriminant axes. The active compound **9** is dramatically positioned onto the medium-group and in a less obvious way, the

**Table I.** Physicochemical data.

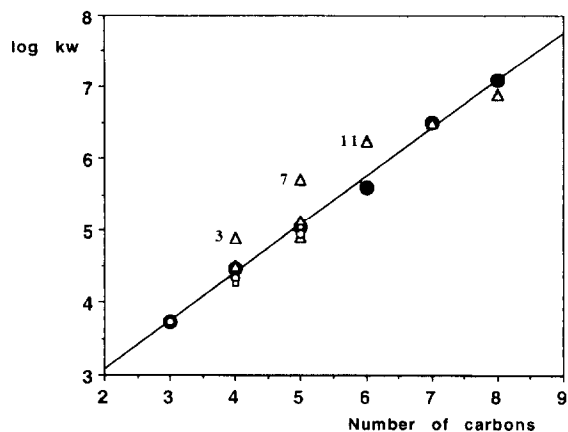
Compounds	R	$n^{20^\circ}$ (D)	Log $k_w^a$	Yield (%)
1 <sup>b,c</sup>	$-\text{CH}_2\text{CH}=\text{CH}_2$	1.5609	3.73	17 <sup>d</sup>
2	$-\text{CH} \begin{cases} \text{CH}_2\text{CH}_3 \\ \text{CH}_3 \end{cases}$	1.5419	4.50	16 <sup>e</sup>
3	$-\text{CH}_2\text{CH} \begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$	1.5430	4.88	42 <sup>e</sup>
4	$-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$	1.5408	4.33	40 <sup>e</sup>
5	$-\text{CH}_2\overset{\text{CH}_3}{\text{C}}=\text{CH}_2$	1.5505	4.26	35 <sup>e</sup>
6	$-\text{CH} \begin{cases} (\text{CH}_3)_2\text{CH}_3 \\ \text{CH}_3 \end{cases}$	1.5380	4.90	15 <sup>e</sup>
7	$-(\text{CH}_2)_2\text{CH} \begin{cases} \text{CH}_3 \\ \text{CH}_3 \end{cases}$	1.5359	5.71	11 <sup>d</sup>
8	$-\text{CH} \begin{cases} \text{CH}_2\text{CH}_3 \\ \text{CH}_2\text{CH}_3 \end{cases}$	1.5415	5.13	20 <sup>e</sup>
9	$-(\text{CH}_2)_3\text{CH}=\text{CH}_2$	1.5445	4.94	62 <sup>e</sup>
10	$-\text{CH}_2\text{CH}=\overset{\text{CH}_3}{\text{C}} \begin{cases} \text{CH}_3 \end{cases}$	1.5490	5.04	25 <sup>d</sup>
11	$-\text{CH}_2\text{CH} \begin{cases} \text{CH}_2\text{CH}_3 \\ \text{CH}_2\text{CH}_3 \end{cases}$	1.5345	6.24	22 <sup>d</sup>
12	$-\text{CH}_2$ 	1.5440	6.50	42 <sup>e</sup>
13	$-\text{CH}_2\text{CH} \begin{cases} (\text{CH}_2)_3\text{CH}_3 \\ \text{CH}_2\text{CH}_3 \end{cases}$	1.5294	6.89	60 <sup>e</sup>

<sup>a</sup>Experimental determination of log  $k_w$  (log  $k_w$  of miconazole = 5.85); <sup>b</sup>bimazalil; <sup>c</sup>nitrate: mp 89 °C [8]; <sup>d</sup>yields by Williamson reaction; <sup>e</sup>yields by phase transfer catalysis.

**Table II.** <sup>1</sup>H-NMR data (CDCl<sub>3</sub>).

<i>Compounds</i>	<i>CH<sub>2</sub><sup>a</sup></i>	<i>CH<sup>b</sup></i>	<i>Azole</i>	<i>Aromatic</i>	<i>R</i>
<b>1</b>	3.97, 4.15	4.89	6.89, 6.98 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.42 (s, H <sub>2</sub> )	7.24 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.37 (m, H <sub>3</sub> )	3.71, 3.90 (2 m, =CH <sub>2</sub> ), 5.74 (m, =CH), 5.14 (m, OCH <sub>2</sub> )
<b>2</b>	3.96, 4.14	4.92	6.91, 6.99 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.44 (s, H <sub>2</sub> )	7.34 (m, H <sub>3</sub> , H <sub>5</sub> , H <sub>6</sub> )	0.67, 0.98 (m, 2 CH <sub>3</sub> ) 1.34 (m, CH <sub>2</sub> ), 3.16 (m, CH)
<b>3</b>	3.96, 4.16	4.82	6.91, 7.00 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.43 (s, H <sub>2</sub> )	7.23 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.39 (m, H <sub>3</sub> )	0.83, 0.86 (2d, 2 CH <sub>3</sub> ) 1.82 (m, CH), 3.05 (m, OCH <sub>2</sub> )
<b>4</b>	3.99, 4.19	4.83	6.90, 6.97 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.44 (s, H <sub>2</sub> )	7.24 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.39 (m, H <sub>3</sub> )	2.26 (m, 2H, CH <sub>2</sub> -CH=) 3.32 (m, OCH <sub>2</sub> ), 5.04 (m, =CH <sub>2</sub> ) 5.73 (m, CH=)
<b>5</b>	3.94, 4.05	4.90	6.90, 6.94 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.42 (s, H <sub>2</sub> )	7.25 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.39 (m, H <sub>3</sub> )	1.57 (s, CH <sub>3</sub> ), 3.63 (m, OCH <sub>2</sub> ) 4.81, 4.85 (2s, =CH <sub>2</sub> )
<b>6</b>	3.93, 4.06	4.93	6.91, 6.99 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.43 (m, H <sub>2</sub> )	7.32 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.37 (m, H <sub>3</sub> )	0.8, 0.91 (m, 2CH <sub>3</sub> ) 1.18, 1.31 (m, 2CH <sub>2</sub> ), 3.23 (m, CH)
<b>7</b>	3.97, 4.12	4.80	6.89, 7.00 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.47 (s, H <sub>2</sub> )	7.24 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.39 (m, H <sub>3</sub> )	0.80, 0.84 (2d, 2 CH <sub>3</sub> ), 1.39 (m, CH <sub>2</sub> ), 1.67 (m, CH) 3.28 (m, OCH <sub>2</sub> )
<b>8</b>	3.98, 4.12	5.00	6.92, 7.02 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.44 (s, H <sub>2</sub> )	7.21 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.38 (m, H <sub>3</sub> )	0.69, 0.80 (2t, 2 CH <sub>3</sub> ) 1.41 (2 CH <sub>2</sub> ), 3.06 (q, OCH)
<b>9</b>	3.94, 4.12	4.82	6.89, 6.99 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.42 (s, H <sub>2</sub> )	7.23 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.37 (m, H <sub>3</sub> )	1.61, 2.02 (2m, 2 CH <sub>2</sub> ) 3.22, 3.32 (2m, OCH <sub>2</sub> ) 4.93 (m, =CH <sub>2</sub> ), 5.70 (m, CH=)
<b>10</b>	3.92, 4.10	4.86	6.88, 6.97 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.41 (s, H <sub>2</sub> )	7.24 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.36 (m, H <sub>3</sub> )	1.46, 1.67 (2s, 2 CH <sub>3</sub> ) 3.82 (m, CH=), 5.15 (m, OCH <sub>2</sub> )
<b>11</b>	3.94, 4.13	4.79	6.87, 6.97 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.37 (m, H <sub>2</sub> )	7.21 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.37 (m, H <sub>3</sub> )	0.77 (t, 2 CH <sub>3</sub> ), 1.29 (CH(CH <sub>2</sub> ) <sub>2</sub> -), 3.08, 3.20 (2dd, OCH <sub>2</sub> )
<b>12</b>	3.87, 4.00	4.67	6.90, 6.98 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.43 (s, H <sub>2</sub> )	7.23 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.38 (m, H <sub>3</sub> )	0.84–1.66 (m, C <sub>6</sub> H <sub>11</sub> ) 4.05 (2dd, OCH <sub>2</sub> )
<b>13</b>	3.94, 4.13	4.79	6.88, 6.98 (2s, H <sub>4</sub> , H <sub>5</sub> ) 7.38 (s, H <sub>2</sub> )	7.24 (m, H <sub>5</sub> , H <sub>6</sub> ) 7.38 (m, H <sub>3</sub> )	0.77, 0.85 (2t, 2 CH <sub>3</sub> ) 1.28 (m, 9H, CH, CH <sub>2</sub> )

<sup>a</sup>2dd, *J*<sub>2</sub> = 14 Hz, *J*<sub>3</sub> = 8 and 2.5 Hz; <sup>b</sup>dd, *J*<sub>3</sub> = 8 and 2.5 Hz.



**Fig 2.** Log  $k_w$  as a function of the number of carbons for saturated (●), ramified (Δ), unsaturated (□), or both ramified and unsaturated (○) chains.

moderately active **4** compound is classified as inactive. So, only **9** is really wrongly classified.

This model allows to point out the significant role of the shape and to express the incidence of the level of ramification and of the length of the side chain, on its orientation and on the molecular volume it fills.

The Carbo shape index expresses the fact that the molecules must have common structural features to exhibit antifungal activity. Nevertheless this structural information must be completed by more specific data about the aliphatic chain. The B1 Verloop parameter which reflects the minimum width of the chain probably expresses an optimal size of the cavity capable of accomodating it.

This information is completed by the third selected parameter (existence of third-order clusters according to Kier classification) which constitutes an indicator of the level of both ramification and insaturation of the side chain.

**Table III.** IC<sub>90</sub> (μg/mL) of ethers<sup>a</sup>.

Compounds	Number of carbons of R	Groups of activity <sup>b</sup>	C albicans	C glabrata	C krusei	C tropicalis	C parapsilosis
Linear chains <sup>c</sup>	3	I	66.8	90	75.6	17.5–100	10.8
	4		31.9	21.7–100	26.9	18.2	4.3–56.9
	5		33.8	3.2–42	45.0–93.0	26.6	6.4
	6	M	26.9	1.9	24.7	16.2	5.4
	7		17.6–100	2.7	52–100	19.6	9.7
	8	I	22.5–100	1.2–34.0	> 100	23.6	0.81–14.2
<b>1</b>	3	I	20.4–100	7	18	> 100	8.9–100
<b>2</b>	4	A	5.7	1.2–12.8	9.2	17.6	5.7
<b>3</b>	4	A	9.9	2.5	15.2	84	4.2
<b>4</b>	4	M	4.5–80	5.8	11	34–85	14.7
<b>5</b>	4	A	2–25	5.2	13.5	85	11.1
<b>6</b>	5	A	5.2	6.6	14	26–39	5.5
<b>7</b>	5	A	10.1	3.3	17.5	> 100	6.1
<b>8</b>	5	A	7.5	1.4–10.3	3.2–19	38	5.2
<b>9</b>	5	A	3.7–20	2.7	5.2	15–40.3	4.6
<b>10</b>	5	M	29–75	10.9	10.6	46–100	6.3–22.9
<b>11</b>	6	M	10.2	0.9–17	15–50	> 100	9.7
<b>12</b>	7	M	4.5–41	4.2	15–35	82	7.4
<b>13</b>	8	I	45–100	28.5	90	47–100	34–70
Miconazole			5.5	0.04	1.9	0.2	0.8

<sup>a</sup>IC<sub>90</sub> determinations have been made in triplicates, we reported a median value or a range when IC<sub>90</sub> values were too far.

<sup>b</sup>Groups of activity used in the QSAR studies: I: inactive, A: active, M: medium. <sup>c</sup>See [7].

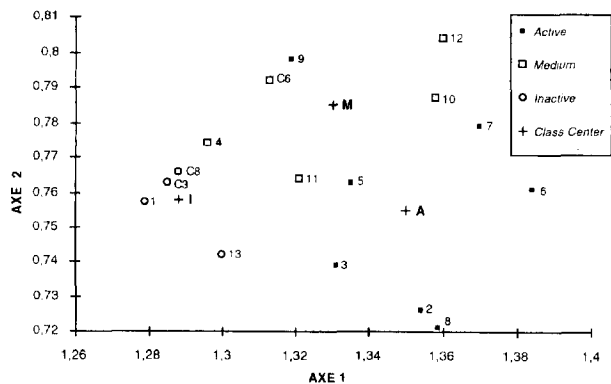
**Table IV.** Fraction of compounds well classified at each step of the SDA and confidence estimates.

Number in class	Class	Well classified fraction per class			
		Step 1: Carbo Shape	Step 2: BI (Verloop)	Step 3: Chi 3v	Confidence estimate
7	Active	0.143	0.429	0.857	0.571
5	Medium	0.6	0.6	0.8	0.40
4	Inactive	1	1	1	0.25
Total fraction well classified		0.50	0.625	0.875	0.438

## Conclusion

Except for *C tropicalis* which is not very sensitive to these compounds, IC<sub>90</sub> values are smaller than 15 µg/mL for ethers bearing ramified chains between 4 to 6 carbons; for others compounds, IC<sub>90</sub> values are most generally superior to 15 µg/mL. These results point out the significant role of the ramification and the shape of the side chain on the level of activity. The presence of a double bond does not modify the activity significantly.

The results obtained for compound **10** fully agrees with those of Aoyama [19] showing that the spectrophotometric modifications of P<sub>450</sub> cytochrome observed in the presence of the compound came from a one-to-one complex with P<sub>450</sub>, and we may suppose that the antifungal effect of **10** could be directly correlated with P<sub>450</sub> interaction. As a result, we can note therefore that enilconazole **1** is not very efficient against *Candida* species but exhibits a better activity than its saturated analogue.



**Fig 3.** Results of the SDA; projection of compounds onto the two discriminant axes.

## Experimental protocols

### Physicochemical data

Physicochemical data and yields are given in table I.

<sup>1</sup>H-NMR data (in CDCl<sub>3</sub>) at 200 MHz (Brüker apparatus) with Me<sub>4</sub>Si as an internal standard are reported in table II. Elemental analyses are in good agreement with the accepted norms and are not reported.

Infrared spectrometric data (liquid films) were recorded with a Perkin-Elmer 983 G (ν in cm<sup>-1</sup>), 3120: CH imidazole; 2970–2860: CH<sub>3</sub>, CH<sub>2</sub>, CH; 1640–1550: C=C, C=N.

Refraction values were determined on an Abbe refractometer.

### Protocols for synthesis by phase transfer catalysis

A two-phase mixture of (2,4-dichlorophenyl)-2-(1-*H*-imidazolyl)ethanol (5 mmol) dissolved in 50% aqueous NaOH (4 mL) and alkyl bromide was vigorously stirred in the presence of a small amount of [CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>]<sub>4</sub>NHSO<sub>4</sub> (0.44 mmol).

(1) *With saturated halides*: a large excess of alkyl bromide (20 mmol) was used, the mixture was stirred for 4 h at 65 °C.

(2) *With unsaturated halides*: only 5 mmol of alkyl bromide was used, and the mixture was stirred at room temperature for 4 h.

(3) In the case of 3-bromo-2-methylpropene, the reaction was stopped after 10 min to give compound **10** (yield 35%) because the yield decreased when the mixture was stirred longer.

Ethers were extracted with diethyl oxide. The organic layer was dried on MgSO<sub>4</sub>, concentrated and purified by chromatography on a silica column (eluant: ethyl acetate/methylene chloride, 3:7).

### Determination of lipophilicity parameters and antifungal activity

Experimental protocols for the determination of both lipophilicity parameters and antifungal activity were described in a previous work [6–7].

Lipophilicity parameters log *k*<sub>w</sub> were determined by reversed-phase chromatography using a methanol/sodium acetate buffer (pH 8.6) mixture as eluant. Antifungal activity was determined in vitro against different strains of *Candida*. From stock solutions of antifungal agents ((100 µg/mL) in a water/DMSO mixture (70:30)) with Tween-80, 5 dilutions were obtained with sterile distilled water (25, 10, 5, 2, 1) for antifungal evaluation.

## Structure-activity relationships

The MAD V2.3 [18] molecular modeling system was used for molecular building and manipulations. The molecular structures were optimized by molecular mechanics computations, using the MM2 force field [20, 21]. The coordinates of the MM2-minimized structures were used for further energy optimization with the semiempirical quantum mechanical AM1 method [22] included in the MOPAC version 6.0 package [23]. In the case of miconazole, calculations were performed starting from the crystallographic structure [24].

The measures of similarity between miconazole on the one hand and the studied compounds on the other hand were performed with the ASP V3.11b program [18]. This software calculates similarity indices between a reference compound (miconazole) and a second molecule, based on physical properties. For this purpose, a 3D-grid is set up around the two molecules to be compared and the properties are calculated at each grid point. The relative orientation of the two compounds to be compared can be optimised to yield a maximum value of similarity by translations and/or torsions of dihedral angles of the comparison molecule, under energetical control [25].

The calculated similarity indices (Carbo indices) vary from 0 to 1 according to the level of similarity. The electrostatic potentials and the shape of molecules may be used as structural properties [26–28]. In order to calculate molecular electrostatic potentials, atomic charges were determined using the AM1 Hamiltonian.

Physical properties and parameters of shape (Verloop's steric parameters [29], molecular surface areas, dipole moment, polarizability and inertia moments) were computed using either the AM1 Hamiltonian or the TSAR V2.41a [18] package. Verloop's parameters give a measure of the dimensions of a molecule in its five principal directions and are very useful in quantitative structure-activity studies. The structural descriptors elaborated by Kier and Hall [30, 31], ie, Kappa and Chi indices, were also determined. Kappa indices are molecular shape parameters. The Chi indices which are adapted to the study of flexibility and ramification of chains, reflect the atom identities, bonding environments and number of bonding hydrogens. These descriptors can easily be calculated for any molecule from its connectivity matrix. The experimental  $\log k_w$  values were introduced as lipophilic parameters.

TSAR software was also used to perform statistical analyses. All simulations were computed on a Silicon Graphics Indigo R3000 workstation.

## References

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