

Short communication

## Synthesis and antifungal activity of novel (1-aryl-2-heterocyclyl)ethylideneaminooxymethyl-substituted dioxolanes

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**Summary** — A novel series of (1-aryl-2-heterocyclyl)ethylideneaminooxymethyl-substituted dioxolanes **IIIa–n** were synthesized by condensation of substituted 1,3-dioxolan-4-ylmethyl *p*-toluenesulfonates **4** with 1-(hydroxyimino)-1-aryl-2-heterocyclylethanes **5**. Compounds **IIIa–n** were found to have effective *in vitro* antifungal activity when evaluated against the pathogenic fungi *Candida albicans*, *Aspergillus flavus* and *Fusarium solani* with MIC (minimum inhibitory concentration) values of 10 µg·ml<sup>-1</sup> for **IIIa–l** and 5 µg·ml<sup>-1</sup> for **IIIm,n**.

antifungal activity / 1,3-dioxolane / ethylideneaminooxy / imidazole / 1,2,4-triazole

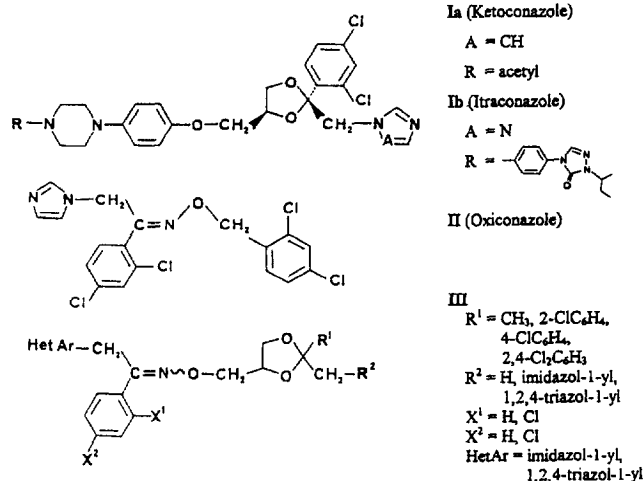
### Introduction

AIDS, a disease that first appeared in the 1980s, debilitates the immune system of patients, and requires aggressive therapy. The subsequent immunological defects have caused an increase in the occurrence and extent of fungal infections and consequently there is a growing need for new antifungal agents. The most active antifungal agents contain an imidazole or triazole ring. Those presently on the European market include two compounds with a 1,3-dioxolane skeleton, sold in France as Ketoconazole **Ia** (since 1983) and Itraconazole **Ib** (since 1994), and a compound possessing an oxime group, Oxiconazole **II**, sold in Belgium and Switzerland (since the 1980s).

After examination of the structure of these antifungals, we decided to synthesize and evaluate the antifungal activity of the diversely substituted structure **III**, including a 1,3-dioxolane cycle, an oxime function and an imidazole or triazole ring.

### Chemistry

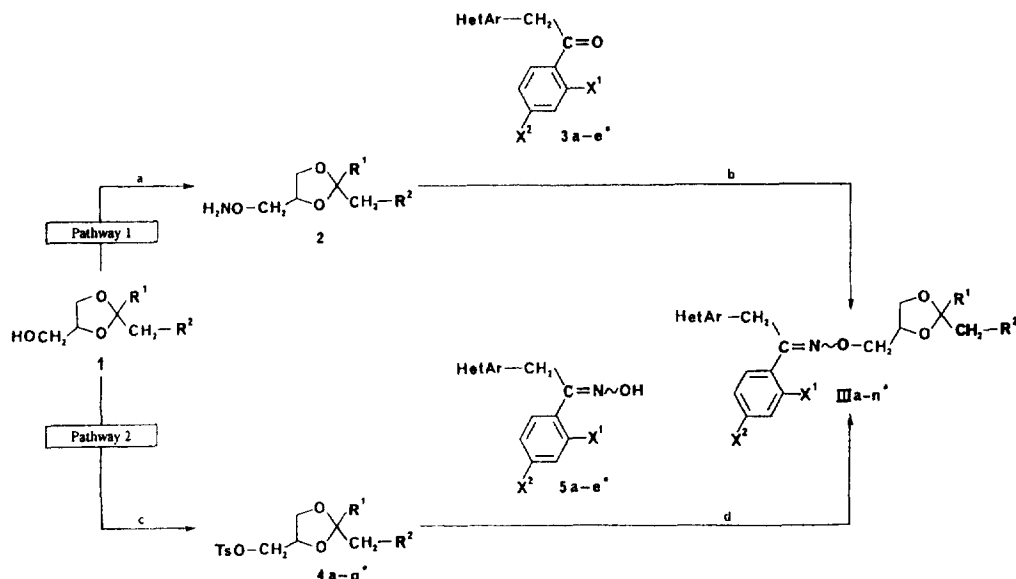
Two synthetic methods were used to obtain the title compounds **III** (scheme 1).



### Method 1

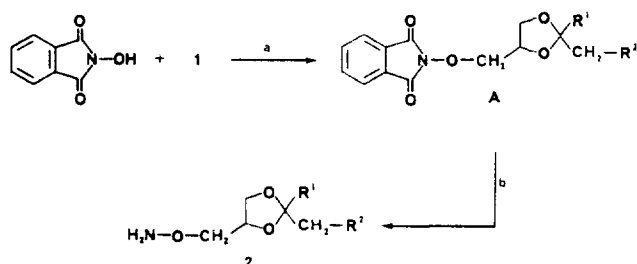
The O-substituted oximes **III** were prepared by condensation of ketones **3** with O-substituted hydroxylamines **2**. Products **2** were prepared (scheme 2) by condensation of alcohol **1** (see *Experimental protocols* for the preparation of **1**) and *N*-hydroxyphthalimide in THF in the presence of the Mitsunobu reagent (a mixture of triphenylphosphine and diethyl azodicarboxylate) according to Bailey's method [1]. This led to intermediates **A** accompanied by triphenyl-

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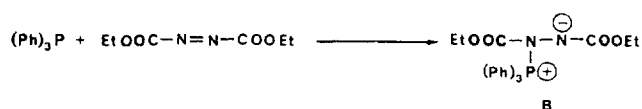


**Scheme 1.** R<sup>1</sup> (Me, Ph, 2- or 4-ClPh), R<sup>2</sup> (H, imidazol-1-yl, 1,2,4-triazol-1-yl), X<sup>1</sup> and X<sup>2</sup> (H, Cl), HetAr (imidazol-1-yl, 1,2,4-triazol-1-yl). \*For each compound, see tables I (for **3a-e**), II (for **4a-g**), III (for **5a-e**) and IV (for **IIIa-n**). Reagents: a) 1) *N*-hydroxyphthalimide, triphenylphosphine, diethyl azodicarboxylate, THF, 20°C, 18 h; 2) methylhydrazine, dichloromethane, 20°C; b) *p*-TsOH·H<sub>2</sub>O, benzene/*n*-butanol (2:1), reflux, 24 h; c) *p*-TsCl, pyridine, 0°C, 1 h; then 20°C, 48 h; d) K<sub>2</sub>CO<sub>3</sub>, DMF, 50°C, 15 h.

phosphine oxide and diethyl hydrazinedicarboxylate as by-products. The role of the Mitsunobu reagent in this synthesis is to facilitate the dehydration reaction *via* the *in situ* formation of zwitterion **B** (scheme 3), which activates the *N*-hydroxyphthalimide [2–7] lead-



**Scheme 2.** Reagents: a) triphenylphosphine, diethyl azodicarboxylate, THF, 20°C, 18 h; b) methylhydrazine, dichloromethane, 20°C.



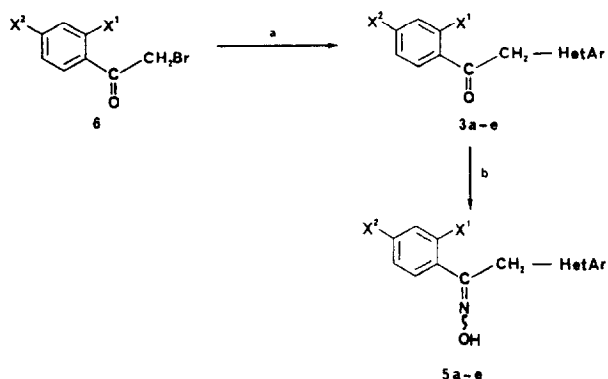
**Scheme 3.** Formation *in situ* of zwitterion **B**.

ing to condensation of alcohol **1** and then substituted phthalimides **A**.

The intermediates **A** then led to *O*-substituted hydroxylamines **2** (scheme 2) by using methylhydrazine at ambient temperature, and not hydrazine, which generally requires heating [8–10]. These mild conditions of methylhydrazinolysis means that the ketal function does not have to be used. Compounds **2** were then reacted with substituted acetophenones **3** according to the Heeres' procedure [11]. If R<sup>1</sup> = Me and R<sup>2</sup> = H, the corresponding oxime **IIIa** is obtained in a very low yield (8%). This lack of success compelled us to reject this synthetic route and to use another route to obtain the title compounds **III**.

#### Method 2

Tosylates **4** were prepared from alcohols **1** as reported by Baer and Fischer [12]. They were then condensed with oximes **5**. Those oximes were synthesized from bromoacetophenones **6** by substitution of bromine by an imidazole or triazole ring as reported by Godefroi *et al* [13] (scheme 4). *para*-Halogenacetophenone reacts easily with nucleophiles, even weak ones, and so it was not necessary to use a base (*eg*, NaH or K<sub>2</sub>CO<sub>3</sub>) to obtain the desired substitution. However, in the other cases, excess imidazole or 1,2,4-triazole is absolutely necessary (respectively five and three times the stoichiometric amount to obtain good yields).



**Scheme 4.** Reagents: a) imidazole or 1,2,4-triazole, DMF, 0°C, 2 h [13]; b)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ , EtOH 95%; 15 N NaOH until pH 11, reflux 3 h.

Oximes **5** were obtained by condensation of hydroxylamine with corresponding acetophenones **3**.

A solution of oximes **5** and tosylates **4** in anhydrous DMF was stirred in the presence of  $\text{K}_2\text{CO}_3$  at 50°C for 15 h (scheme 1). Because of the acidity of oximes, it is not necessary to use such a strong base as NaH to obtain the corresponding nucleophilic species. Indeed, its use gives several by-products and is not advisable.

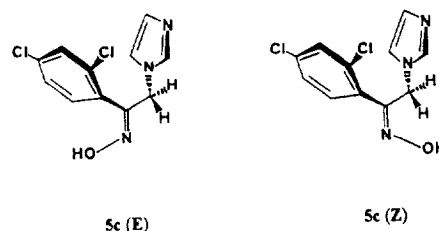
*Method 2* gave a great improvement of yields (up to about nine times) (*Method 1*: 8% yield; *Method 2*: 70% yield).

## Results and discussion

Physical data for compounds **3a-e**, **4a-g**, **5a-e** and **IIIa-n** are presented in tables I–IV. The unsubstituted

oximes **5a-e** (table III) were isolated pure (**5a**, **5b** and **5d**) or as a mixture of isomers (**5c** and **5e**). The mixture **5c** was more interesting because the two geometrical isomers were found in the proportion 70:30.  $^1\text{H}$  NMR spectroscopy was used to assign the *E* or *Z* configuration to the isomers of compounds **5** (table V), and it was possible to allocate the signals to the two different isomers. The strongest spectrum had one unshielded singlet, corresponding to the methylene ( $\Delta\delta = +0.25$  ppm), three slightly shielded singlets ( $\Delta\delta = -0.10$  ppm), corresponding to the protons of imidazole, and a clearly unshielded singlet for the proton of hydroxyl group ( $\Delta\delta = +0.60$  ppm). The methylene is unshielded by the presence of the nearly hydroxyl function and must therefore be the *Z* isomer, which agrees with previously published data [14–18]. Thus, compounds **5a** and **5b** are *Z* isomers ( $\delta\text{CH}_2 > 5.30$  ppm). By analogy, in the mixture of triazoles **5e** (*Z/E* = 50:50), the *Z* isomer differed from the *E* isomer by the displacement of this singlet: 5.50 versus 5.38 ppm. Similarly, the proton of the hydroxyl in **5e** (*E*) appeared at 12.53 versus 12.46 ppm. Compound **5d** was an *s*-triazole derivative of configuration *E*.

For imidazole derivatives in series *Z*, the protons of both the methylene ( $\Delta\delta = -0.3$  ppm) and the heterocycle ( $\Delta\delta = -0.10$  ppm) were shielded; in imidazole



**Table I.** Data for 2' (or 4', or 2',4'-di)-chloro-2-heterocyclylacetophenones **3a-e**.

Compound <b>3</b>	$X^1$	$X^2$	HetAr	Formula ( $M_w$ )	Yield (%)	Mp (°C)	$\nu_{\text{max}}$ ( $\text{cm}^{-1}$ ) C=O
<b>a</b>	H	H	Imidazol-1-yl	$\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$ (186.21)	62	118 <sup>a</sup>	1690
<b>b</b>	Cl	Cl	Imidazol-1-yl	$\text{C}_{11}\text{H}_8\text{Cl}_2\text{N}_2\text{O}$ (255.10)	71	170 <sup>a</sup>	1680
<b>c</b>	Cl	Cl	1,2,4-Triazol-1-yl	$\text{C}_{10}\text{H}_7\text{Cl}_2\text{N}_3\text{O}$ (256.09)	80	203 <sup>a</sup>	1682
<b>d</b>	H	Cl	Imidazol-1-yl	$\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}$ (220.66)	76	161 <sup>b</sup>	1694
<b>e</b>	H	Cl	1,2,4-Triazol-1-yl	$\text{C}_{10}\text{H}_8\text{ClN}_3\text{O}$ (221.64)	82	194 <sup>b</sup>	1686

<sup>a</sup>Mp of nitrate of **3**, recrystallized from EtOH; <sup>b</sup>recrystallized from acetonitrile.

**Table II.** Data for 2-(alkyl or aryl)-2-(alkyl or heterocyclylmethyl)-1,3-dioxolan-4-ylmethyl *p*-toluenesulfonates **4a–g**.

Compound <b>4</b>	$R^1$	$R^2$	Formula (Mw)	Yield (%)	Mp <sup>a</sup> (°C)	$\nu_{\max}$ (cm <sup>-1</sup> ) $SO_2$ sym	$SO_2$ asym
<b>a</b>	CH <sub>3</sub>	H	C <sub>13</sub> H <sub>8</sub> O <sub>5</sub> S (276.26)	85	49	1175	1367
<b>b</b>	C <sub>6</sub> H <sub>5</sub>	H	C <sub>18</sub> H <sub>10</sub> O <sub>5</sub> S (338.32)	80	71	1148	1343
<b>c</b>	2-ClC <sub>6</sub> H <sub>4</sub>	H	C <sub>18</sub> H <sub>9</sub> ClO <sub>5</sub> S (382.85)	84	Oil	1147	1356
<b>d</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	C <sub>18</sub> H <sub>9</sub> ClO <sub>5</sub> S (382.85)	78	Oil	1154	1342
<b>e</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	C <sub>18</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>5</sub> S (417.29)	84	Oil	1157	1348
<b>f</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Imidazol-1-yl	C <sub>21</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>5</sub> S (473.28)	89	107	1152	1325
<b>g</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1,2,4-Triazol-1-yl	C <sub>20</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>5</sub> S (484.34)	75	117	1149	1342

<sup>a</sup>Recrystallized from toluene.**Table III.** Data for 1-aryl-2-heterocyclyl-1-hydroxyiminoethanes **5a–e**.

Compound <b>5</b>	$X^1$	$X^2$	HetAr	Formula (Mw)	Yield (%)	Mp <sup>a</sup> (°C)	$\nu_{\max}$ (cm <sup>-1</sup> ) $C=N_{oxime}$	$OH_{bonded}$
<b>a</b> ( <i>Z</i> )	H	H	Imidazol-1-yl	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O (201.22)	74	166	1625	3100
<b>b</b> ( <i>Z</i> )	H	Cl	Imidazol-1-yl	C <sub>11</sub> H <sub>10</sub> ClN <sub>3</sub> O (235.66)	87	210	1623	3142
<b>c</b> ( <i>Z/E</i> = 70:30)	Cl	Cl	Imidazol-1-yl	C <sub>11</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> O (270.11)	80	230	1647	3121
<b>d</b> ( <i>E</i> )	H	Cl	1,2,4-Triazol-4-yl	C <sub>10</sub> H <sub>6</sub> ClN <sub>4</sub> O (236.66)	91	201	1625	3118
<b>e</b> ( <i>Z/E</i> = 50:50)	Cl	Cl	1,2,4-Triazol-1-yl	C <sub>10</sub> H <sub>5</sub> Cl <sub>2</sub> N <sub>4</sub> O (271.10)	82	264	1647	3119

<sup>a</sup>Solvent of recrystallization: diisopropyl ether/isopropanol.

derivatives in series *E* (compound **5c**), the proton of hydroxyl was shielded at 0.60 ppm. This can be explained as follows. The increasing steric crowding caused by the chlorine of the phenyl group, which was already inclined compared with the plane of the imino bond (see Ortep view [19]), increased the inclination. This was confirmed by IR spectra in which the  $\nu_{OH\ bonded}$  and  $\nu_{C=N}$  frequencies of **5a** appeared at 3100 and 1625 cm<sup>-1</sup>. The +M effect of the *para*-chlorine in **5b** increased  $\nu_{OH}$  by 42 cm<sup>-1</sup> and decreased  $\nu_{C=N}$  by 2 cm<sup>-1</sup>. However, the *ortho*-chlorine partially reduced the conjugation and  $\nu_{OH}$  decreased by 22 cm<sup>-1</sup>, while  $\nu_{C=N}$  increased by 24 cm<sup>-1</sup> in **5c** and **5d** compared with

**5b**. The inclination of phenyl group was responsible for an increased shielding of the protons of the methylene and imidazole, and the proton of the hydroxyl in the *E* form.

The shielding induced on the imidazole ring suggests that the ring of imidazole and phenyl are close enough and offset, otherwise the effect of unshielding of oxygen would give an opposite effect in oximes (*Z*).

The <sup>1</sup>H NMR spectra of substituted oximes **III**m and **n** (table VI) provoked the same observations. Compounds **III**e–**h** were obtained as complex mixtures formed by two pairs of diastereomers (*E* and *Z*).

### Antifungal activity

The antifungal activity of ketoconazole and related azoles is based upon the blockage of the conversion of lanosterol into ergosterol, which is necessary for maintaining the integrity of the organism's cell membrane. The oxidative removal of the C-14 methyl group of lanosterol (lanosterol 14 $\alpha$ -demethylase) is due to the inhibition of the enzyme cytochrome P-450 [20–22]. For example, stereoisomers of the ketoconazole were evaluated for their effectiveness as inhibitors of a number of cytochrome P-450 enzymes [23]. In our experiment, compounds **IIIa–n** were evaluated for their antifungal activity against the pathogenic fungi *Candida albicans*, *Aspergillus flavus* and *Fusarium solani* (table VII).

### Compounds **IIIa–d**

Compound **IIIa**, which possesses no chlorine atoms, was totally inactive towards the fungal strains used. Compounds **IIIb** and **IIIc**, whose phenyl groups carry one *para*-chlorine atom, or one *ortho*- and one *para*-chlorine atom respectively, possessed a significant activity at 10  $\mu\text{g}\cdot\text{ml}^{-1}$ . The *para*-chloro derivative **IIIc** was still active against *C. albicans* after 7 d. However, it ceased to be active against *A. flavus* after 24 h and against *F. solani* after 48 h. The most active compound was the dichloro derivative **IIIb**, but its antifungal power against *A. flavus* decreased after 7 d.

### Compounds **IIIe–l**

All the products **IIIe–l** were active against *C. albicans* at 10  $\mu\text{g}\cdot\text{ml}^{-1}$  after 24 h and up to 7 d. Similar results

**Table IV.** Data for 2-(alkyl or aryl)-2-(alkyl or heterocyclylmethyl)-4-[(1-aryl-2-heterocyclyl)ethylideneaminoxymethyl]-1,3-dioxolanes **IIIa–n**.

Compound <b>III</b>	$R^1$	$R^2$	$X^1$	$X^2$	HetAr	Formula (Mw)	Yield (%)	Mp(°C) (oxalate of <b>III</b> ) <sup>a</sup>	$\nu_{\text{max}}$ ( $\text{cm}^{-1}$ ) $\text{C}=\text{N}_{\text{oxime}}$ $\text{C}-\text{O}_{\text{ketal}}$
<b>a</b>	CH <sub>3</sub>	H	H	H	Imidazol-1-yl	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> (315.36)	60	105	1673    1047, 1078
<b>b</b>	CH <sub>3</sub>	H	Cl	Cl	Imidazol-1-yl	C <sub>17</sub> H <sub>19</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> (384.25)	57	92	1613    1026, 1061
<b>c</b>	CH <sub>3</sub>	H	Cl	Cl	1,2,4-Triazol-1-yl	C <sub>16</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>3</sub> (385.24)	52	80	1637    1056, 1076
<b>d</b>	CH <sub>3</sub>	H	H	Cl	Imidazol-1-yl	C <sub>17</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>3</sub> (349.80)	52	143	1676    1048, 1078
<b>e</b>	2-ClC <sub>6</sub> H <sub>4</sub>	H	H	Cl	Imidazol-1-yl	C <sub>22</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> (446.32)	62	137	1671    1048, 1078
<b>f</b>	2-ClC <sub>6</sub> H <sub>4</sub>	H	Cl	Cl	Imidazol-1-yl	C <sub>22</sub> H <sub>20</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>3</sub> (480.77)	60	125	1673    1047, 1077
<b>g</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	H	H	Imidazol-1-yl	C <sub>22</sub> H <sub>22</sub> ClN <sub>3</sub> O <sub>3</sub> (411.87)	64	94	1674    1048, 1078
<b>h</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	H	Cl	Imidazol-1-yl	C <sub>22</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> (446.32)	63	118	1674    1048, 1078
<b>i</b>	4-ClC <sub>6</sub> H <sub>4</sub>	H	Cl	Cl	Imidazol-1-yl	C <sub>22</sub> H <sub>20</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>3</sub> (480.77)	65	123	1674    1048, 1078
<b>j</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	H	H	Imidazol-1-yl	C <sub>22</sub> H <sub>21</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>3</sub> (446.32)	65	116	1674    1048, 1078
<b>k</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	H	Cl	Imidazol-1-yl	C <sub>22</sub> H <sub>20</sub> Cl <sub>3</sub> N <sub>3</sub> O <sub>3</sub> (480.77)	64	110	1674    1048, 1078
<b>l</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	Cl	Cl	Imidazol-1-yl	C <sub>22</sub> H <sub>19</sub> Cl <sub>4</sub> N <sub>3</sub> O <sub>3</sub> (543.24)	62	120	1674    1048, 1078
<b>m</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Imidazol-1-yl	Cl	Cl	Imidazol-1-yl	C <sub>25</sub> H <sub>21</sub> Cl <sub>4</sub> N <sub>5</sub> O <sub>3</sub> (581.29)	59	98 <sup>b</sup>	1674    1047, 1078
<b>n</b>	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1,2,4-Triazol-1-yl	Cl	Cl	Imidazol-1-yl	C <sub>24</sub> H <sub>20</sub> Cl <sub>4</sub> N <sub>6</sub> O <sub>3</sub> (582.28)	46	168 <sup>b</sup>	1673    1023, 1078

<sup>a</sup>Recrystallized from isopropanol; <sup>b</sup>Mp of nitrate of **III**, recrystallized from EtOH.

**Table V.**  $^1\text{H}$  NMR<sup>a</sup> chemical shifts (ppm) and coupling constants  $J$  (Hz) of 1-aryl-2-heterocyclyl-1-hydroxyiminoethanes **5a–e**.

Compounds <b>5</b>	$\text{CH}_2$	HetAr-H	Ar-H	$\text{C}=\text{N}-\text{OH}^b$
<b>a</b> (Z)	5.33 (s, 2H)	6.82 (s, 1H, $\text{H}_5$ ) 7.05 (s, 1H, $\text{H}_4$ ) 7.68 (s, 1H, $\text{H}_2$ )	7.38 (m, 3H) 7.68 (m, 2H)	12.08 (s, 1H)
<b>b</b> (Z)	5.32 (s, 2H)	6.81 (s, 1H, $\text{H}_5$ ) 7.03 (s, 1H, $\text{H}_4$ ) 7.65 (s, 1H, $\text{H}_2$ )	7.40 (d, $J = 7.8$ , 2H) 7.67 (d, $J = 7.8$ , 2H)	12.16 (s, 1H)
<b>c</b> (Z/E = 70:30)	5.04 (s, 0.6H) (E) 5.30 (s, 1.4H) (Z)	6.73 (s, 0.7H, $\text{H}_5$ ) 6.96 (s, 0.7H, $\text{H}_4$ ) 7.58 (s, 0.7H, $\text{H}_2$ ) 6.86 (s, 0.3H, $\text{H}_5$ ) 7.05 (s, 0.3H, $\text{H}_4$ ) 7.65 (s, 0.3H, $\text{H}_2$ )	7.28–7.45 (m, 2H) 7.5 (s, 1H)	11.57 (s, 0.3H) 12.17 (s, 0.7H)
<b>d</b> (E)	5.04 (s, 0.6H)	8.47 (s, 2H)	7.22 (d, $J = 8.4$ , 2H) 7.46 (d, $J = 8.4$ , 2H)	12.33 (s, 1H)
<b>e</b> (Z/E = 50:50)	5.38 (s, 1H) (E) 5.50 (s, 1H) (Z)	8.36 (s, 1H) (Z) 8.46 (s, 1H) (E)	7.30–7.50 (m, 2H) 7.57 (s, 1H)	12.46 (s, 0.5H) (E) 12.53 (s, 0.5H) (Z)

<sup>a</sup>Recorded in  $\text{DMSO}-d_6$ ; <sup>b</sup>exchangeable with MeOD.

were found for *F. solani*, except for **IIIe**, whose power weakened after 14 d. These compounds were only active against *A. flavus* for 48 h and the fungus proliferated after 7 d. This actually represented a partial inhibition, expressed by a lengthening of the lag phase.

#### Compounds **III m–n**

Compounds **III m** and **n** were the most active. They were active against *C. albicans*, *A. flavus* and *F. solani* at  $5\text{ }\mu\text{g}\cdot\text{mL}^{-1}$  after 24 h and up to 14 d.

## Conclusion

After examining table VII, we can conclude the following. First, chlorine atoms linked to the phenyl group at the *para* or *ortho* positions are essential to antifungal activity. Compound **IIIa**, which did not have a chlorine atom, was totally inactive. Substitutions by chlorine in the *ortho* and *para* positions (compound **IIIb**) were more suitable to antifungal activity than *para* substitution (compound **III d**). Secondly, replacement of one of the methyls at the 2 position of the dioxolane, by an aryl that is monosubstituted (*ortho* or *para*, compounds **III e–i**) or disubstituted (*ortho* and *para*, compounds **III j–n**) by chlorine atom(s) increased the antifungal activity. Such a substitution actually makes the product active for the longest time against *F. solani*. Consequently, the presence of the

aryl group bonded to  $\text{C}_2$  of the dioxolane was necessary for real activity. At  $10\text{ }\mu\text{g}\cdot\text{mL}^{-1}$ , for compounds **III e–n**, the position and number of chlorine atoms seemed to have no influence on the activity, but it is likely that at least one chlorine atom is necessary to maintain the activity.

## Experimental protocols

### Chemistry

Melting points were determined on a Kofler bench and are uncorrected. IR spectra were recorded in KBr pellets for solids and between KBr disks for liquids with a Perkin-Elmer 881 IR spectrometer.  $^1\text{H}$ -NMR spectra were recorded on a Bruker AC 200 spectrometer (200 MHz) using tetramethylsilane (TMS) as the internal standard. Splitting patterns are designated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, and m = multiplet. All reactions were carried out under a nitrogen atmosphere. Thin-layer chromatography was performed on silica-gel pre-coated plates (Merck art 5554, silica-gel 60F<sub>254</sub>). Preparative-layer chromatography was performed on silica-gel (Merck art 7748, silica-gel 60 PF<sub>254+366</sub>) pre-coated plates. Compounds were detected under UV light (254 nm) or by exposure to iodine vapor. For all reactions, anhydrous organic solvents were used.

### Method 1

**Synthesis of compounds 1.** Compounds **1** (except solketal, commercial product), used in the following syntheses (*Methods 1* and *2*), were prepared according to literature procedures [11, 24].

**2,2-Dimethyl-4-phthalimidooxymethyl-1,3-dioxolane A.** Under a nitrogen atmosphere, *N*-hydroxyphthalimide (8.2 g, 50 mmol) was dissolved in 200 ml anhydrous THF. To the solution was added successively and in small portions, triphenylphosphine (13.1 g, 50 mmol) and 2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane **1** ( $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) (6.6 g, 50 mmol). After cooling at 0°C, diethyl azodicarboxylate (11.5 g, 66 mmol) was added dropwise. The solution became deep red, and the color disappeared after 10 min. The solution was stirred at room temperature for 18 h. THF was evaporated *in vacuo* and the residue dissolved in diethyl ether (200 ml). The organic layer was washed three times with 10 ml water and dried over anhydrous  $\text{MgSO}_4$ . The solvent was evaporated and the residue purified by preparative layer chromatography with hexane/acetone (1:3) as eluent. Compound **A** was obtained as fine white crystals; 12.6 g (91%).

TLC:  $R_f = 0.45$ ; mp = 100°C; IR (KBr):  $\nu$  1610, 1730 and 1790 ( $\text{C=O}$ )  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  1.35 (s, 3H,  $\text{CH}_3$ ), 1.41 (s, 3H,  $\text{CH}_3$ ), 3.99 (dd,  $J = 5.5$ ; 8.8 Hz, 1H,  $\text{H}_{5\text{ or }5'}$  of dioxolane), 4.17 (m, 2H,  $\text{H}_{5\text{ or }5'}$  of dioxolane and H of  $\text{CH}_2$  attached to  $\text{C}_4$  of dioxolane), 4.32 (dd,  $J = 5.7$ ; 10.1 Hz, 1H, H of  $\text{CH}_2$  bonded to  $\text{C}_4$  of dioxolane), 4.5 (q, 1H,  $\text{H}_4$  of dioxolane), 7.5 ppm (m, 4H,  $\text{H}_{\text{arom}}$ ).

**4-Aminooxymethyl-2,2-dimethyl-1,3-dioxolane 2.** The phthalimide derivative **A** (10 g, 36 mmol) was dissolved in anhydrous dichloromethane (150 ml) and cooled to 0°C. Methylhydrazine (3.3 g, 72 mmol) was added dropwise. The solution was stirred at 20°C up to complete hydrolysis, and controlled by TLC with ethyl acetate as eluent. The precipitate was removed by filtration, the solvent was evaporated *in vacuo* and the residue was purified by preparative layer chromatography with ethyl acetate as eluent. Compound **2** was obtained as a pale yellow oil; 4.9 g (93%).

TLC:  $R_f = 0.6$ ; IR (film):  $\nu$  3550 ( $\text{NH}_2$ )  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$  1.38 (s, 3H,  $\text{CH}_3$ ), 1.44 (s, 3H,  $\text{CH}_3$ ), 3.73 (m, 3H,  $\text{H}_{5\text{ or }5'}$  of dioxolane and  $\text{CH}_2$  attached to  $\text{C}_4$  of dioxolane), 4.07 (dd,  $J = 6.4$ ; 8.2 Hz,  $\text{H}_{5\text{ or }5'}$  of dioxolane), 4.35 (q, 1H,  $\text{H}_4$  of dioxolane), 5.56 ppm (s, 2H,  $\text{NH}_2$  exchangeable with  $\text{D}_2\text{O}$ ).

**2', 4'- or 2',4'-Dichloro-2-heterocyclylacetophenones 3a-e (general procedure).** To 25 ml distilled anhydrous DMF, was added imidazole (or 1,2,4-triazole) (0.52 mol). To the solution was added, the appropriate 2-bromo-2'-(or 4', or 2',4'-di)-chloroacetophenone (0.10 mol) in small portions. The temperature of the mixture must not exceed 15°C. After addition was completed, the mixture was stirred at 0°C for 2 h. The resulting solution was poured into 500 ml water and 100 ml benzene was added in this solution. Abundant crude product of compound **3** was precipitated out of the resulting mixture and recrystallized from the appropriate solvent (see table I).

**2,2-Dimethyl-4-[(2-imidazol-1-yl-1-phenyl)ethylideneaminoxymethyl]-1,3-dioxolane IIIa.** A mixture of acetophenone **3a** (1.2 g, 10 mmol), amine **2** (2.1 g, 11 mmol) and *p*-TsOH· $\text{H}_2\text{O}$  (120 mg) in 10 ml of a solution of benzene/*n*-butanol (2:1) was heated at reflux through a Dean-Stark trap. After 24 h, the mixture was cooled to room temperature and then evaporated to dryness. The residue was dissolved in chloroform, washed with water to pH 7, dried over  $\text{MgSO}_4$  and evaporated *in vacuo*. The yellow oil residue was obtained and purified by column chromatography on silica gel (Merck, art 7734) with ethyl acetate as an eluent. Compound **IIIa** was obtained as a pale yellow oil; 324 mg (8%) (see tables IV and VI).

## Method 2

**2-Alkyl or 2-aryl-2-(alkyl or heterocyclylmethyl)-1,3-dioxolan-4-yl-methyl *p*-toluenesulfonates 4a-g.** *p*-TsCl (0.20 mol) was suspended and stirred in 20 ml anhydrous pyridine and cooled with an ice and water bath. The appropriate 2-(alkyl or aryl)-2-(alkyl or heterocyclylmethyl)-1,3-dioxolane-4-methanol **1** (0.20 mol) was added dropwise. The mixture was maintained at 0°C for 1 h, and stirred at room temperature. After 48 h, the solution was poured in 500 ml ice-water and extracted with diethyl ether. The combined ether extracts were washed with ice-cold aqueous 5% sodium hydrogen carbonate, and then with water to pH 7. The organic layer was dried over anhydrous  $\text{MgSO}_4$ , evaporated to dryness and the residue purified by preparative layer chromatography with hexane/ethyl acetate (7:3) as eluent. Compounds **4c**, **4d** and **4e** were obtained as colorless oils and **4a**, **4b**, **4f** and **4g** as precipitates, recrystallized from toluene (see table II).

**1-Aryl-2-heterocyclyl-1-hydroxyiminoethanes 5a-e.** To 150 ml of 95% EtOH, was added the appropriate acetophenone **3** (0.15 mol). Hydroxylamine hydrochloride (0.20 mol) was added and the pH of the mixture was adjusted to 11 with 15 N NaOH. The solution was refluxed by heating with an oil bath. After 3 h, the solution was evaporated in dryness and gave a solid that was solubilized in water. The aqueous layer was acidified with 1 N HCl to pH 5, and then adjusted to pH 9 with a solution of aqueous saturated sodium hydrogen carbonate. The mixture was cooled and compound **5** was precipitated out of solution and recrystallized from a mixture of diisopropyl ether/isopropanol as a white amorphous solid (see tables III and V).

**2-Alkyl or 2-aryl-2-(alkyl or heterocyclylmethyl)-4-[(1-aryl-2-heterocyclyl)ethylideneaminoxymethyl]-1,3-dioxolanes IIIa-n.** The appropriate oxime **5** (10 mmol) and  $\text{K}_2\text{CO}_3$  (10 mmol) were suspended and stirred in 10 ml anhydrous DMF. The mixture was heated at 50°C with an oil bath. The appropriate tosylate **4** (10 mmol) dissolved in 5 ml anhydrous DMF was added dropwise and stirred. After 15 h, the solution was evaporated *in vacuo*, the residue dissolved in 50 ml methylene chloride, washed three times with 10 ml water, and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The organic layer was evaporated to dryness, and purified by preparative layer chromatography with ethyl acetate/triethylamine as eluent. Compound **III** was obtained as an oil, dissolved in absolute ethanol and condensed with a stoichiometric amount of oxalic acid. The precipitate was recrystallized from isopropanol (see tables IV and VI).

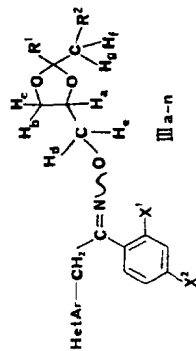
## Microbiology

### Fungi and medium of culture

Antifungal activities were tested *in vitro* on three species of pathogenic fungi for men and animals: *C. albicans*, *A. flavus* and *F. solani*. Before the experiment, the strains (preserved by freezing) were subcultured on Casitone IP agar at 26°C for 48 h for *C. albicans* and 8 d for *A. flavus* and *F. solani*.

### Range of studied compounds for the test

The substances were dissolved in DMSO (1 mg·ml<sup>-1</sup>); further dilution with sterile water furnished 100 and 50  $\mu\text{g}\cdot\text{ml}^{-1}$  solutions. A 0.5 ml portion of each solution was added to 4.5 ml of Casitone agar previously liquified and maintained at 44°C (final concentrations respectively 10 and 5  $\mu\text{g}\cdot\text{ml}^{-1}$ ). These solutions were dropped on Petri dishes. The medium was solidified at room temperature and the open Petri dishes were dried at 37°C for 30 min. Meanwhile, one control without the tested compounds and another with DMSO were prepared.



Compounds III	CH <sub>3</sub>	CH <sub>2</sub>	H <sub>a</sub> -H <sub>g</sub>	HetAr-H	Ar-H
<b>a</b> Z	1.37 (s, 3H) 1.44 (s, 3H)	5.18 (s, 2H)	3.79 (dd, <i>J</i> = 8.3; 5.9, 1H, H <sub>b</sub> or c) 4.09 (dd, <i>J</i> = 8.3; 3.0, 1H, H <sub>c</sub> or b) 4.42 (dd, <i>J</i> = 11.3; 5.5, 1H, H <sub>d</sub> ) 4.30 (m, 2H, H <sub>a</sub> and d)	6.92 (s, 1H, H <sub>c</sub> ) 6.98 (s, 1H, H <sub>a</sub> ) 7.53 (s, 1H, H <sub>2</sub> )	7.35 (m, 3H) 7.53 (m, 2H)
<b>b</b> Z/E = 70:30	1.31 (s, 0.9H) (E) 1.31 (s, 0.9H) (E) 1.38 (s, 2.1H) (Z) 1.45 (s, 2.1H) (Z)	4.88 (s, 0.6H) (E) 5.21 (s, 1.4H) (Z)	3.70 (dd, <i>J</i> = 8.1; 5.8, 0.3H) (E) 3.78 (dd, <i>J</i> = 8.4; 6.1, 0.7H) (Z) 3.98 (dd, <i>J</i> = 8.2; 6.3, 0.3H) (E) 4.08 (dd, <i>J</i> = 8.2; 6.4, 0.7H) (Z) 4.41 (dd, <i>J</i> = 11.3; 5.8, 1H, H <sub>d</sub> ) 4.31 (m, 2H, H <sub>a</sub> and e)	6.59 (s, 0.3H, H <sub>5</sub> ) (E) 6.90 (s, 0.7H, H <sub>5</sub> ) (Z) 6.77 and 6.84 (2s, 1H, H <sub>4</sub> ) 6.98 and 7.01 (2s, 1H, H <sub>2</sub> )	7.13–7.37 (m, 3H)
<b>c</b> Z/E = 50:50	1.20 (s, 1.5H) (E) 1.24 (s, 1.5H) (E) 1.31 (s, 1.5H) (Z) 1.38 (s, 1.5H) (Z)	5.33 (s, 1H) (E) 5.56 (s, 1H) (Z)	3.63 (dd, <i>J</i> = 13.8; 7.2, 0.5H, H <sub>b</sub> or c) 3.77 (dd, <i>J</i> = 13.2; 6.7, 0.5H, H <sub>c</sub> or b) 3.98 and 4.34 (dd and dd, <i>J</i> = 14.2; 6.4 and <i>J</i> = 10.7; 5.7, 1H, H <sub>b</sub> or c) 4.0–4.28 (m, 3H, H <sub>a</sub> , c and d)	7.83 (s, 0.5H) 7.97 (s, 0.5H) 8.46 (s, 0.5H) 8.51 (s, 0.5H)	7.64 (d, <i>J</i> = 11, 1H) 7.3–7.5 (m, 2H)
<b>d</b> Z	1.38 (s, 3H) 1.46 (s, 3H)	5.19 (s, 2H)	3.80 (dd, <i>J</i> = 8.2; 5.9, 1H, H <sub>b</sub> or c) 4.10 (dd, <i>J</i> = 8.2; 6.3, 1H, H <sub>c</sub> or b) 4.43 (dd, <i>J</i> = 10.8; 5.4, 1H, H <sub>d</sub> ) 4.35 (m, 2H, H <sub>a</sub> and e)	6.93 (s, 1H, H <sub>c</sub> ) 7.01 (s, 1H, H <sub>4</sub> ) 7.57 (s, 1H, H <sub>2</sub> )	7.34 (d, <i>J</i> = 8.5, 2H) 7.50 (d, <i>J</i> = 8.5, 2H)
<b>e</b> 80:20 <sup>b</sup>	1.71 (s, 0.2H) 1.74 (s, 0.4H) 1.79 (s, 0.6H) 1.83 (s, 1.8H)	4.90 (s, 0.1H) 4.96 (s, 0.3H) 5.16 (s, 0.4H) 5.20 (s, 1.2H)	3.63–3.95 (m, 2H) 4.18–4.35 (m, 2H) 4.40–4.45 (m, 1H, H <sub>a</sub> )	6.97 and 7.01 (2s, 1.6H, H <sub>5</sub> and 4) 6.69 and 6.84 (2s, 0.4H, H <sub>5</sub> and 4) 7.60–7.70 (m, 1H, H <sub>2</sub> and 2 <sup>c</sup> )	7.33 and 7.49 (2d, <i>J</i> = 8.5 and <i>J</i> = 8.5, 4H) (ArCl) 7.3–7.6 (m, 4H) (ArCl)
<b>f</b> 50:20:30 <sup>b</sup>	1.73 (s, 0.9H) 1.78 (s, 0.6H) 1.84 (s, 1.5H)	4.90 (s, 0.4H) 4.95 (s, 0.6H) 5.24 (s, 0.4H) 5.26 (s, 0.6H)	3.67–3.92 (m, 2H) 4.12–4.31 (m, 2H) 4.32–4.38 (m, 1H, H <sub>a</sub> )	6.69 and 6.72 (2s, 1H, H <sub>5</sub> and 4) 6.90 and 6.94 (2s, 1H, H <sub>5</sub> and 4) 7.01 and 7.09 (2s, 1H, H <sub>2</sub> and 2 <sup>c</sup> )	7.14 and 7.20 (2m coalesced, 3H) (ArH) 7.36 and 7.60 (2m, 4H) (ArH)
<b>g</b> 80:20 <sup>b</sup>	1.61 (s, 0.6H) 1.65 (s, 2.4H)	4.98 (s, 0.4H) 5.19 (s, 1.6H)	3.74–3.91 (m, 2H) 4.17–4.32 (m, 2H) 4.36 (m, 1H, H <sub>a</sub> )	6.95 and 6.98 (2s, 1.6H, H <sub>5</sub> and 4) 6.95 and 6.89 (2s, 0.4H, H <sub>5</sub> and 4) 7.2–7.5 (m, 1H, H <sub>2</sub> and 2 <sup>c</sup> )	7.39 (m, 5H) (ArH) 7.55 (m, 4H) (ArH)
<b>h</b> 60:40 <sup>b</sup>	1.62 (s, 1.1H) 1.66 (s, 1.9H)	4.97 (s, 0.8H) 5.18 (s, 1.2H)	3.75–3.91 (m, 1.6H) 4.18–4.32 (m, 2H) 4.37–4.40 (m, 1.4H)	6.96 and 6.99 (2s, 1.2H, H <sub>5</sub> and 4) 6.00 and 6.84 (2s, 0.8H, H <sub>5</sub> and 4 <sup>c</sup> )	7.17–7.55 (m, 9H (including H <sub>2</sub> and H <sub>2</sub> '))



Table VI. (Continued.)

Compounds <b>III</b>	CH <sub>3</sub>	CH <sub>2</sub>	H <sub>a</sub> -H <sub>g</sub>	HetAr-H	Ar-H
<b>i</b> 25:20:20:35 <sup>b</sup>	1.56 (s, 0.8H) 1.60 (s, 0.6H) 1.62 (s, 0.6H) 1.68 (s, 1.0H)	5.02 (s, 0.8H) 5.24 (s, 1.2H)	3.45–3.95 (m, 3H) 4.0–4.38 (m, 2H)	6.82, 6.93, 7.00 and 7.14 (4s, 3H)	7.18–7.50 (m, 7H)
<b>j</b> 25:25:50 <sup>b</sup>	1.68 (s, 0.7H) 1.77 (s, 0.8H) 1.80 (s, 1.5H)	5.02 (s, 0.5H) 5.20 (s, 1.0H) 5.28 (s, 0.5H)	3.51–4.00, 4.00–4.37, 4.37–4.43 (3m, 5H)	6.98 (s, 1H) 7.23–8.00 (m, 5H)	7.37 (s, 5H, C <sub>6</sub> H <sub>5</sub> )
<b>k</b> 30:30:15:25 <sup>b</sup>	1.71 (s, 0.9H) 1.76 (s, 0.9H) 1.80 (s, 0.5H) 1.82 (s, 0.7H)	5.06 (s, 1.4H) 5.27 (s, 0.3H) 5.30 (s, 0.3H)	3.49–3.97, 4.05–4.35, 4.37–4.42 (3m, 5H)	7.05 (s, 1H) 7.13–8.02 (m, 9H)	
<b>l</b> 25:25:50 <sup>b</sup>	1.68 (s, 0.7H) 1.75 (s, 0.8H) 1.80 (s, 1.5H)	4.94 (s, 0.2H) 5.25 (s, 0.3H) 5.22 (s, 1.5H)	3.47–3.92 (m, 2H) 4.00–4.30 (m, 2H) 4.35 (m, 1H, H <sub>g</sub> )	6.80, 7.98 and 6.87–7.63 (2s and m, 9H)	
<b>m</b> <sup>a</sup> 75:25 <sup>b</sup>		5.09 (s, 1.5H) 5.10 (s, 0.5H)	3.70–4.05 (m, 4H, H <sub>b</sub> , c, d and e) 4.22 (q, 0.2H) 4.32 (q, 0.8H) 4.44 (s, 0.4H, H <sub>f</sub> or g) 4.56 (s, 1.6, H <sub>g</sub> or f)	6.75–7.25 (m, 4H (including H <sub>4</sub> and H <sub>5</sub> )) 7.33–7.70 (m, 8H (including H <sub>2</sub> ))	
<b>n</b> <sup>a</sup> 85:15 <sup>b</sup>		5.12 (s, 1.7H) 5.36 (s, 0.3H)	3.84–4.10 (m, 3H, H <sub>b</sub> , c, d and e) 3.58–3.65 (m, 1H, H <sub>b</sub> or e) 4.24 (q, 1H, H <sub>g</sub> ) 4.71 (s, 1.7H, H <sub>f</sub> or g) 4.86 (s, 0.3H, H <sub>g</sub> or f)	6.88 (s, 1H, H <sub>5</sub> imidazole) 7.06 (s, 1H, H <sub>4</sub> imidazole) 7.18 (d, <i>J</i> = 8.3, 1H, H <sub>3</sub> triazole) 7.85 and 7.91 (s, 0.85H and s, 0.15H, H <sub>2</sub> imidazole) 8.40 and 8.49 (s, 0.85H and s, 0.15H, H <sub>5</sub> triazole)	7.3–7.8 (m, 6H, Ar-H)

Except where otherwise indicated, the spectra were recorded in CDCl<sub>3</sub>. <sup>a</sup>Recorded in DMSO-*d*<sub>6</sub>. <sup>b</sup>Mixture of diastereomers.

**Table VII.** *In vitro* antifungal activity of derivatives **IIIa,b,d-n** (comparison of ketoconazole and oxiconazole) against *C albicans*, *A flavus* and *F solani* after 24, 48 h, 7 and 14 d incubation expressed as the minimum inhibitory concentration (MIC) in  $\mu\text{g}\cdot\text{ml}^{-1}$ .

Strain	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh	IIIi	IIIj	IIIk	IIIl	IIIm	IIIn	Ketoconazole	Oxiconazole
<i>C albicans</i>																
24 h	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
48 h	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
7 d	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	12.5	6.25
<i>A flavus</i>																
24 h	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
48 h	> 10	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
7 d	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	≤ 5	≤ 5	ND	ND
14 d	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	> 10	≤ 5	≤ 5	6.25	12.5
<i>F solani</i>																
24 h	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
48 h	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
7 d	> 10	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	ND	ND
14 d	> 10	> 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 10	≤ 5	≤ 5	> 25	> 25

ND = not determined.

#### Preparation of inoculum and sowing

*C albicans*. A sterile aqueous suspension containing  $10^5$  cells·ml<sup>-1</sup> was prepared from the 48 h primoculture.

*A flavus* and *F solani*. The spores of the primoculture were collected in 1 ml of sterile water. The suspension was vortexed and adjusted to  $10^5$  spores/ml. One millilitre of each suspension was placed on the medium containing the tested products and kept at 26°C.

#### Data collection

Data were recorded after 24, 48 h and 7 d incubation for *C albicans*, and 24, 48 h, 7 and 14 d incubation for *A flavus* and *F solani*.

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