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Short communication

Synthesis, antifungal activity and structure–activity relationships of 2-(alkyl or aryl)-2-(alkyl or polyazol-1-ylmethyl)-4-(polyazol-1-ylmethyl)-1,3-dioxolanes

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Summary — A series of 2-(alkyl or aryl)-2-(alkyl or polyazol-1-ylmethyl)-4-(polyazol-1-ylmethyl)-1,3-dioxolanes **Ia–u** was synthesized and tested in vitro against pathogenic fungi in man, animals and plants: *Candida albicans*, *Aspergillus flavus* and *Fusarium solani*. Compounds **Iq–t** with two polyazol groups have an in vitro activity against these fungi with MIC (minimum inhibitory concentration) value of 5 $\mu g\ mL^{-1}$.

antifungal activity / 1,3-dioxolane / imidazole / nitroimidazole / polyazol-1-ylmethyl / 1,2,4-triazole

Introduction

Recently we have reported the synthesis and in vitro antifungal activity of substituted 1,3-dioxolane derivatives related to ketoconazole, itraconazole and oxiconazole [1]. In the present communication, we report the synthesis and the antifungal activity of substituted 1,3-dioxolane derivatives **I**, which may be compared with antifungal agents for clinical use, econazole **IIa**, isoconazole **IIb** or miconazole **IIc** [2]. We intend to show the influence of antimycotic activity between a conformationally constrained structure (title compounds **I**) and a conformationally flexible structure **II**. This type of modification has already been used for the study of the conformationally constrained analogues of miconazole [3]. Redarding this, the *cis*-isomers were the most active [4–6].

Chemistry

Two synthetic methods were used to obtain the title compounds **I** according to the nature of R^2.

Method 1 (R^2 = H)

Substituted 1,3-dioxolanes **Ia–p** were obtained in three steps from appropriate arylmethylketones **1** (scheme 1). Condensation of ketones **1** with glycerol in the presence of *p*-Ts-OH·H_2O in a solution of toluene/*n*-butanol (2:1) heated at reflux through a Dean–Stark trap led to the corresponding 4-hydroxymethyldioxolanes **2** [5, 7]. Those alcohols **2**, esterified by *p*-Ts-Cl, gave the tosylates **3** [8]. Condensation of tosylates **3** with the appropriate polyazole [5] led to target compounds **Ia–p**. With 2'-polyazol-1-ylacetophenones as starting material ($R^2 \neq H$) no corresponding alcohols **2** were obtained, which led us to use another method.

Method 2 (R^2 = polyazol-1-yl)

The first step leading to alcohols **2** was similar to *Method 1*. Bromination under mild conditions of alcohols **2** led to derivatives **4** (scheme 2). Condensation of compounds **4** with Bz-Cl gave a mixture of two diastereomers, *cis*- and *trans*-benzoates **5a** and **5b**. The desired *cis*-isomer **5a** was separated and purified by several recrystallizations in absolute MeOH [9] or

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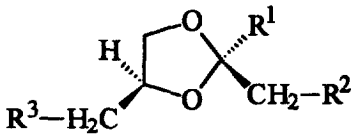
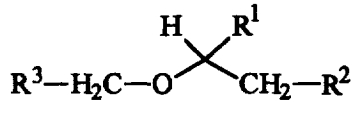


I

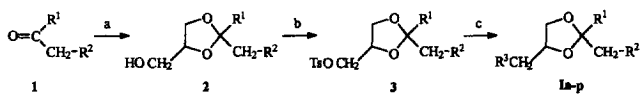


II

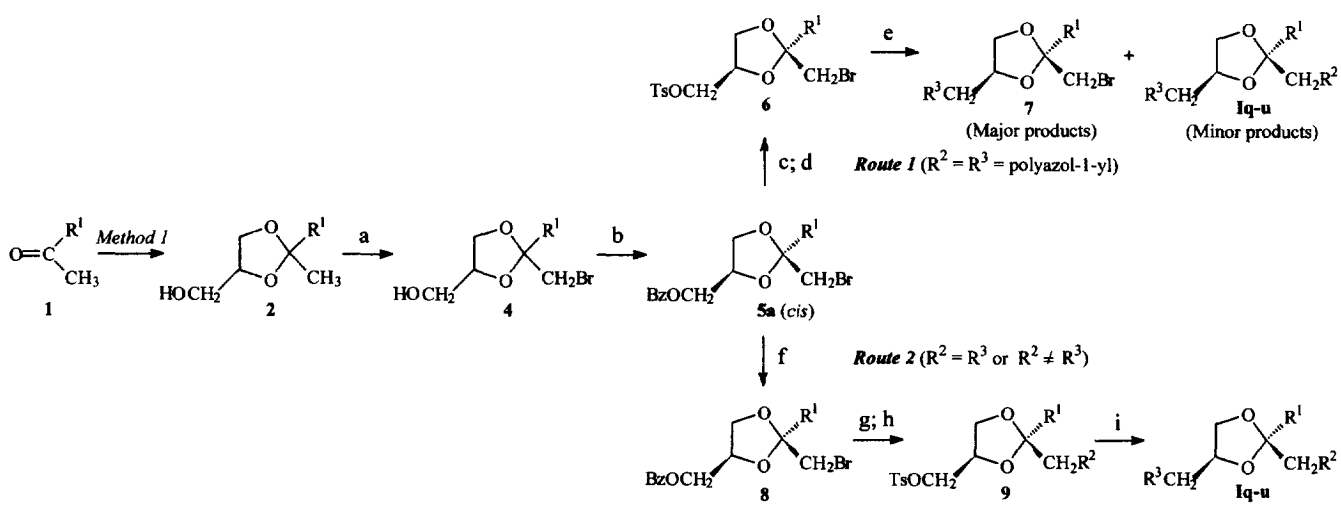
R^1 = CH_3, C_6H_5, 2-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$F_2C_6H_3$
R^2 = H, imidazol-1-yl, 1,2,4-triazol-1-yl
R^3 = imidazol-1-yl, 2-methyl-4-nitroimidazol-1-yl, 2-methyl-5-nitroimidazol-1-yl, 1,2,4-triazol-1-yl

II	R^1	R^2	R^3
a :	2,4-Cl_2Ph	Imidazol-1-yl	2-ClPh
b :	2,4-Cl_2Ph	Imidazol-1-yl	2,6-Cl_2Ph
c :	2,4-Cl_2Ph	Imidazol-1-yl	2,4-Cl_2Ph

Fig 1. Chemical structure of compounds **I** and **II**.



Scheme 1. R^1 (Me, Ph, 2- or 4-ClPh, 2,4-Cl_2Ph), R^2 (H), R^3 (imidazol-1-yl, 2-methyl-4 or 5-nitroimidazol-1-yl, 1,2,4-triazol-1-yl). For structure, physicochemical characteristics and ^{1}H-NMR data of each compound of **Ia–p**, see tables I and II. Reagents: a) glycerol, *p*-Ts-OH·H_2O, toluene/*n*-BuOH (2:1), reflux through a Dean–Stark trap, 24 h; b) *p*-Ts-Cl, pyridine, 0 °C, 1 h, then 20 °C, 48 h; c) imidazole, DMF, reflux 72 h for R^3 = imidazol-1-yl; 2-methyl-5-nitroimidazole, DMF, NaH, 80 °C, 5 h for R^3 = 2-methyl-4 or 5-nitroimidazole-1-yl; 1,2,4-triazole, DMF, NaH, 130 °C, 12 h for R^3 = 1,2,4-triazol-1-yl.



Scheme 2. R^1 (2,4-Cl_2Ph, 2,4-F_2Ph), R^2 (imidazol-1-yl, 1,2,4-triazol-1-yl), R^3 (imidazol-1-yl, 1,2,4-triazol-1-yl). For structure, physicochemical characteristics and ^{1}H-NMR data of each compound **Iq–u**, see tables I and II. Reagents: a) Br_2, $\theta < 30$ °C, 1h; b) Bz-Cl, anhydrous pyridine, 5 °C, 3 h; c) 5 N NaOH, dioxane, reflux, 1 h; d) *p*-Ts-Cl, anhydrous pyridine, 0 °C, 1 h, then 20 °C, 72 h; e and f) imidazole, anhydrous DMF, reflux, 96 h for R^2 = R^3 = imidazol-1-yl; 1,2,4-triazole, DMF, NaH, 130 °C, 12 h for R^2 = R^3 = 1,2,4-triazol-1-yl; g) 5 N NaOH, dioxane, reflux, 30 min; h) *p*-Ts-Cl, anhydrous pyridine, 0 °C, 1 h, then 20 °C, 48 h; i) imidazole, anhydrous DMF, reflux, 96 h for R^3 = imidazol-1-yl; 1,2,4-triazole, DMF, NaH, 20 °C, 1 h, then 130 °C, 12 h for R^3 = 1,2,4-triazol-1-yl.

by preparative column chromatography on silica gel (Merck, art 7734) with toluene as eluent.

Route 1

Using *Route 1*, $R^2 = R^3$ = polyazol-1-yl, saponification under mild conditions of *cis*-benzoates **5a** gave the corresponding carbinols which were converted to the *cis*-tosylates **6**. Condensation of these compounds with a large excess (five up to seven times the stoichiometric amount) of imidazole ($R^2 = R^3$ = imidazol-1-yl) or 1,2,4-triazole ($R^2 = R^3$ = 1,2,4-triazol-1-yl) (the latter in the presence of a base) led to compounds **7** [10] as major products and target compounds **I** as minor products. This lack of success compelled us to use a second route.

Route 2

Using *Route 2*, $R^2 = R^3$ or $R^2 \neq R^3$, condensation of *cis*-benzoates **5a**, in anhydrous DMF at reflux with imidazole or 1,2,4-triazole gave compounds **8** followed by saponification of *cis*-benzoates **8** with 5 N NaOH in dioxane at reflux, then esterified to *cis*-tosylates **9**. Condensation of the latter compounds with imidazole or 1,2,4-triazole in anhydrous DMF at reflux gave title compounds **Iq–u** in good yield.

The preparation of compounds **I** as described in *Route 2* gave target compounds **Iq–u** with substituents $R^2 = R^3$ or $R^2 \neq R^3$ and in a higher yield than by *Route 1*.

Results and discussion

Structure, physicochemical characteristics and ^{1}H-NMR data for compounds **Ia–u** are reported in tables I and II.

Method 1

Esterification of alcohol **2** (step b; scheme 1) by *p*-Ts-Cl as reported by several literature procedures [11–14] led to compounds **3** in a very low yield. We selected the Baer procedure [8] which, with some modifications, gave a real improvement in yields. It should, however, be noted that three parameters play a primordial part in the desired esterification, namely: (1) amount of pyridine: this amount must be the minimum, just enough to render the *p*-Ts-Cl soluble with heating; (2) reaction temperature: it is important to cool the mixture pyridine: *p*-Ts-Cl at 0 °C before adding alcohol **2** to the solution and to maintain for least 1 h the resulting mixture at 0 °C; (3) reaction time: the adequate time period is three days. According to the Baer procedure [8], the yield is 60% after 48 h, when under our experimental conditions and after 24 h in addition, the rate of esterification is really improved (85% yield).

p-Tosylates **3** reacted with imidazole, 2-methyl-5-nitroimidazole and 1,2,4-triazole in anhydrous DMF (step c; scheme 1). Substitution of the tosyl group with imidazole was performed with a good yield in anhydrous DMF under reflux for 3 days in the presence of a 3- to 5-fold excess of imidazole. In the presence of NaH, the yield was low and accompanied by several impurities. However, the *p*-tosyl substitution was successful for 1,2,4-triazole or 2-methyl-5-nitroimidazole with NaH as condensing agent. In the last case, it led to two products, purified by preparative-layer chromatography and identified with ^{1}H-NMR; ie, two geometrical isomers **Ib** and **Ic** (see scheme 3 and table I) obtained respectively in 8 and 64% yields. The mixture of isomers was obtained thanks to the mesomerism of the in situ formation of anionic intermediates **A** and **B** (scheme 3).

Method 2

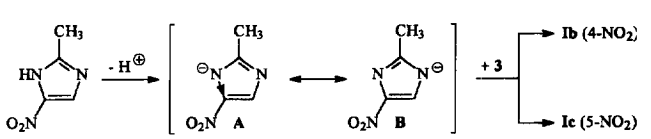
The structure of both diastereoisomeric benzoates *cis*-**5a** and *trans*-**5b** was identified by ^{1}H-NMR. Moreover, the structure of one of the diastereomers, precisely the *trans* form of 4-(benzoyloxymethyl)-2-(bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolane was confirmed by crystallographic X-ray diffraction analysis (fig 2; see *Experimental protocols* for data on crystal X-ray diffraction).

Antifungal activity

In the majority of fungi, ergosterol is needed for fungal growth. Inhibition of ergosterol biosynthesis inhibits fungal cell growth and can be achieved via a number of azole derivatives [15, 16]. In our experiment, the prepared polyazole derivatives **Ia–u** were evaluated for their antifungal activity against the pathogenic fungi for humans, animals and plants: *Candida albicans*, *Aspergillus flavus* and *Fusarium solani* (table III). All the studied compounds have a polyazolyl group (R^3) at the 4 position of the dioxolane ring.

*Compounds **Ia–d***

Compounds **Ia–d**, which possessed no chlorine atoms and no phenyl group at the 2 position of dioxolane



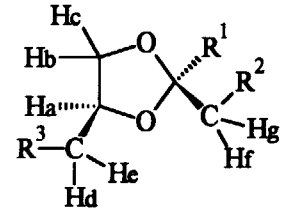
Scheme 3. Anionic intermediates **A** and **B**.

Table I. Data for *cis*-2-(alkyl or aryl)-2-(alkyl or polyazol-1-ylmethyl)-4-(polyazol-1-ylmethyl-1,3-dioxolanes **Ia–u**.

Compound I	*R¹*	*R²*	*R³*	*Formula (Mw)*	*Yield (%)*	*Recrystallization solvent*	*Mp (°C)*	ν_{max} *cm⁻¹*		
								$NO_{2\,sym}$	$NO_{2\,asym}$	$C–O_{ketal}$
a	CH_3	H	Imd	$C_9H_{14}N_2O_2$ (182.22)	40		Oil			1044, 1069, 1106, 1152
b	CH_3	H	2-CH_3-4-NO_2Imd	$C_{10}H_{15}N_3O_4$ (241.25)	8	IPE/*i*-PrOH	76	NR	NR	NR
c	CH_3	H	2-CH_3-5-NO_2Imd	$C_{10}H_{15}N_3O_4$ (241.25)	64	IPE/*i*-PrOH	89	1335	1536	1030, 1067, 1143
d	CH_3	H	1,2,4-Trz	$C_8H_{13}N_3O_2$ (183.21)	58		Oil			1044, 1070, 1115, 1138, 1176
e	2-ClC_6H_4	H	Imd	$C_{14}H_{15}ClN_2O_2$ (278.73)	58		Oil			1034, 1058, 1074, 1104, 1140
f	4-ClC_6H_4	H	Imd	$C_{14}H_{15}ClN_2O_2$ (278.73)	48		Oil			1036, 1058, 1076, 1091, 1198
g	2,4-$Cl_2C_6H_3$	H	Imd	$C_{14}H_{14}Cl_2N_2O_2$ (313.18)	47		Oil			1032, 1074, 1095, 1145, 1197
h	2-ClC_6H_4	H	2-CH_3-4-NO_2Imd	$C_{15}H_{16}ClN_3O_4$ (337.77)	15	Petroleum ether	113	1395	1540	1031, 1064, 1095, 1130, 1145, 1162, 1190
i	2-ClC_6H_4	H	2-CH_3-5-NO_2Imd	$C_{15}H_{16}ClN_3O_4$ (337.77)	55	IPE/*i*-PrOH	142	1343	1540	1036, 1049, 1099, 1136, 1158
j	4-ClC_6H_4	H	2-CH_3-4-NO_2Imd	$C_{15}H_{16}ClN_3O_4$ (337.77)	71	MeOH	154	1344	1537	1047, 1088, 1111, 1131, 1192
k	2,4-$Cl_2C_6H_3$	H	2-CH_3-4-NO_2Imd	$C_{15}H_{15}Cl_2N_3O_4$ (372.22)	10	EtOH	140	1374	1539	1034, 1094, 1144, 1161, 1199
l	2,4-$Cl_2C_6H_3$	H	2-CH_3-5-NO_2Imd	$C_{15}H_{15}Cl_2N_3O_4$ (372.22)	68	IPE/EtOH	144	1374	1537	1032, 1060, 1094, 1155, 1183
m	C_6H_5	H	1,2,4-Trz	$C_{13}H_{15}N_3O_2$ (245.28)	60	IPE/*i*-PrOH	88			1029, 1054, 1064, 1076, 1133
n	2-ClC_6H_4	H	1,2,4-Trz	$C_{13}H_{14}ClN_3O_2$ (279.72)	57	Hexane/*i*-PrOH	79			1034, 1059, 1098, 1138
o	4-ClC_6H_4	H	1,2,4-Trz	$C_{13}H_{14}ClN_3O_2$ (279.72)	67	Hexane/AcOEt	91			1039, 1062, 1092, 1138, 1174
p	2,4-$Cl_2C_6H_3$	H	1,2,4-Trz	$C_{13}H_{13}Cl_2N_3O_2$ (314.17)	72		Oil			1034, 1055, 1095, 1138, 1198
q	2,4-$Cl_2C_6H_3$	Imd	Imd	$C_{17}H_{16}Cl_2N_4O_2$ (379.26)	46	4-Methylpentan-2-one	142			1031, 1045, 1088, 1162
r	2,4-$Cl_2C_6H_3$	Imd	1,2,4-Trz	$C_{16}H_{15}Cl_2N_5O_2$ (380.24)	52	MeOH	153			1044, 1075, 1105, 1138, 1160
s	2,4-$Cl_2C_6H_3$	1,2,4-Trz	Imd	$C_{16}H_{15}Cl_2N_5O_2$ (380.24)	59	*i*-PrOH	145[a]			1044, 1070, 1104, 1135
t	2,4-$Cl_2C_6H_3$	1,2,4-Trz	1,2,4-Trz	$C_{15}H_{14}Cl_2N_6O_2$ (381.23)	43	EtOH	182[b]			1044, 1062, 1104, 1136
u	2,4-$F_2C_6H_3$	Imd	Imd	$C_{17}H_{16}F_2N_4O_2$ (346.35)	41	MeOH	114			1044, 1077, 1100, 1139, 1159

Imd: imidazol-1-yl; Trz: triazol-1-yl; IPE: isopropyl ether; NR: not recorded; [a]mp of oxalate of **I s**; [b]mp of nitrate of **I t**.

Table II. ^{1}H-NMR chemical shifts (δ in ppm with TMS as internal standard) and coupling constants J (Hz) of compounds **Ia–u**.



Ia-u

Compound I	*CH_3*	*H_a–H_g*	*HetAr-H*	*Ar-H*
a	1.35 (s, 3H) 1.40 (s, 3H)	3.65 (dd, J = 8.6; 6.0, 1H, $H_{b\ or\ c}$) 4.00–4.21 (m, 3H, $H_{c\ or\ b,\ d,\ e}$) 4.34 (qt, J = 5.7, 1H, H_a)	7.02 (s, 1H, H_5) 7.10 (s, 1H, H_4) 7.75 (s, 1H, H_2)	
a[a]	1.25 (s, 3H) 1.29 (s, 3H)	3.62 (dd, J = 8.5; 5.9, 1H, $H_{b\ or\ c}$) 4.00 (dd, J = 8.6; 6.4, 1H, $H_{c\ or\ b}$) 4.04 (part B of ABX, J_{AB} = 14.0, J_{BX} = 5.8, 1H, H_d) 4.17 (part A of ABX, J_{AB} = 14.4, J_{BX} = 4.1, 1H, H_e) 4.32 (qt, J = 6.3, 1H, H_a)	6.83 (s, 1H, H_5) 7.20 (s, 1H, H_4) 7.71 (s, 1H, H_2)	
b[a]	1.22 (s, 3H) 1.28 (s, 3H) 2.48 (s, 3H, CH_3 Imd)	3.66 (dd, J = 8.8; 5.7, 1H, $H_{b\ or\ c}$) 4.10 (dd, J= 8.6; 6.1, 1H, $H_{c\ or\ b}$) 4.28 (m, 2H, $H_{d,\ e}$) 4.54 (m, 1H, H_a)	8.04 (s, 1H, H_4)	
c[a]	1.28 (s, 3H) 1.32 (s, 3H) 2.41 (s, 3H, CH_3 Imd)	3.76 (dd, J = 8.8; 5.7, 1H, $H_{b\ or\ c}$) 4.08 (m in dd, J = 14.5; 7.7, 2H, $H_{c\ or\ b,\ d}$) 4.23 (dd, J = 14.4; 3.4, 1H, H_e) 4.42 (tdd, 1H, H_a)	8.28 (s, 1H, H_5)	
d	1.28 (s, 6H)	3.72 (dd, J = 8.6; 5.7, 1H, $H_{b\ or\ c}$) 4.03 (dd, J = 8.6; 6.3, 1H, $H_{c\ or\ b}$) 4.25 (m, 2H, $H_{d,\ e}$) 4.37 (qt, J = 5.6, 1H, H_a)	7.88 (s, 1H) 8.10 (s, 1H)	
e Z/E = 85:15	1.75 (s, 0.5H) 1.79 (s, 2.5H)	3.68 (m, 2H) 4.08–4.27 (m, 3H(including H_a))	7.32–7.60 (m, 3H)	6.94–7.07 (m, 2H) 7.17–7.25 (m, 2H)
f Z/E = 55:45	1.59 (s, 1.3H) 1.61 (s, 1.7H)	3.66 (m, 1H, $H_{b\ or\ c}$) 3.83–3.98 (m, 1H) 4.00–4.21 (m, 1H) 4.22–4.40(m, 2H (including H_a))	7.56 (s, 1H, H_2)	6.90–7.00 (m, 2H) 7.18–7.39 (m, 4H (including $H_{4,5}$ Imd))
g Z/E = 75:25	1.70 (s, 0.8H) 1.74 (s, 2.2H)	3.67–3.76 (m, 1H, $H_{b\ or\ c}$) 3.80–3.87 (m, 1H) 4.02–4.10 (m, 1H) 4.14–4.25 (m, 2H (including H_a))	7.34 (s, 1H, H_5) 7.48 (s, 1H, H_4) 7.53 (s, 1H, H_2)	6.91–7.03 (m, 2H) 7.13–7.19 (m, 1H)

Table II. *(Continued).*

Compound I	*CH_3*	*H_a–H_g*	*HetAr-H*	*Ar-H*
h[a]	1.65 (s, 3H) 2.34 (s, 3H, CH_3 Imd)	3.56 (dd, J = 8.2; 7.9, 1H, $H_{b\ or\ c}$) 3.87 (dd, J = 8.2; 7.9, 1H, H_d) 4.16-4.34 (m, 2H(including H_e)) 4.57 (m, 1H, H_a)	8.10 (s, 1H, H_5)	7.24–7.54 (m, 4H)
i[a]	1.68 (s, 3H) 2.47 (s, 3H, CH_3 Imd)	3.37 (dd, J = 8.8; 6.9, 1H, $H_{b\ or\ c}$) 3.90 (dd, J = 8.8; 4.3, 1H, $H_{c\ or\ b}$) 4.19 (dd, J = 15.0; 7.5, 1H, H_d) 4.34 (m, 2H, $H_{a,\ e}$)	8.40 (s, 1H, H_4)	7.31 (m, 4H)
j[a]	1.53 (s, 3H) 2.45 (s, 3H, CH_3 Imd)	3.72 (dd, J = 8.6; 7.2, 1H, $H_{b\ or\ c}$) 3.92 (dd, J = 8.6; 4.0, 1H, $H_{c\ or\ b}$) 4.14 (dd, J = 14.9; 7.1, 1H, H_d) 4.31 (m, 2H, $H_{a,\ e}$)	8.35 (s, 1H, H_4)	7.31 (m, 4H)
k[a]	1.66 (s, 3H) 2.28 (s, 3H, CH_3 Imd)	3.57 (dd, J = 8.3; 8.1, 1H, $H_{b\ or\ c}$) 3.93 (dd, J = 14.8; 6.6, 1H, H_d) 4.23 (m, 2H, $H_{c\ or\ b,\ e}$) 4.58 (m, 1H, H_a)	8.11 (s, 1H, H_5)	7.38 (dd, J = 8.5; 1.8, 1H, H_β) 7.52 (d, J = 8.5, 1H, H_α) 7.57 (d, J = 1.8, 1H, $H_{\beta'}$)
l	1.65 (s, 3H) 2.45 (s, 3H, CH_3 Imd)	3.76 (dd, J = 8.5; 7.3, 1H, $H_{b\ or\ c}$) 3.96 (dd, J = 8.9; 4.3, 1H, $H_{c\ or\ b}$) 4.17 (dd, J = 15.0; 7.4, 1H, H_d) 4.32 (m, 2H, $H_{a,\ e}$)	8.36 (s, 1H, H_4)	7.39 (dd, J = 8.4; 1.4, 1H, H_β) 7.55 (m, 2H, $H_{\alpha,\beta'}$)
m	1.61 (s, 3H)	3.70–3.90 (m, 2H (including $H_{b\ or\ c}$)) 4.27–4.40(m, 3H (including H_a))	7.95 (s, 1H) 8.24 (s, 1H)	7.25–7.34 (m, 3H) 7.36–7.42 (m, 2H)
n	1.72 (s, 3H)	3.62–3.80 (m, 1H, $H_{b\ or\ c}$) 3.86–3.95 (m, 1H) 4.02–4.43 (m, 3H (including H_a))	7.91 (s, 1H) 8.25 (s, 1H)	7.14–7.38 (m, 3H) 7.47–7.59 (m, 1H)
o	1.55 (s, 3H)	3.65–3.78 (m, 1H, $H_{b\ or\ c}$) 3.85–3.91 (m, 1H) 4.15–4.20 (m, 1H) 4.27–4.32 (m, 2H (including H_a))	7.93 (s, 1H)	7.23–7.34 (m, 4H)
p	1.64 (s, 3H)	3.58–3.75 (m, 1H, $H_{b\ or\ c}$) 3.83–3.89 (m, 1H, $H_{c\ or\ b}$) 4.17–4.29 (m, 3H (including H_a))	7.87 (s, 1H) 8.19 (s, 1H)	7.08–7.12 (m, 1H) 7.27–7.32 (m, 1H) 7.38–7.42 (m, 1H)
q[b]		3.64 (dd, J = 8.4; 6.0, 1H, $H_{b\ or\ c}$) 3.75 (part A of ABX, J_{AB} = 14.4, J_{BX} = 7.8, 1H, H_d) 3.97 (dd, J = 8.4; 6.8, 1H, $H_{c\ or\ b}$) 4.08 (part B of ABX, J_{AB} = 14.4, J_{BX} = 3.5, 1H, H_e) 4.38 (qt, 1H, H_a) 4.60 (s, 2H, $H_{f,\ g}$)	6.90 (s, 1H, H_5 Imd) 6.93 (s, 1H, H_5 Imd') 7.10 (s, 1H, H_4 Imd) 7.15 (s, 1H, H_4 Imd')	7.33 (dd, J = 8.4; 2.0, 1H, H_5) 7.52–7.57 (m, 4H(including H_2 Imd and H_2 Imd'))

Table II. *(Continued).*

Compound I	*CH_3*	*H_a–H_g*	*HetAr-H*	*Ar-H*
r[a]		3.68–3.92 (m, 3H, $H_{b, c, d}$) 4.13 (part B of ABX, J = 14.2; 3.1, 1H, H_c) 4.30 (qt, 1H, H_a) 4.81 (s, 2H, $H_{f, g}$)	6.94 (s, 1H, H_5 Imd) 7.25 (s, 1H, H_4 Imd) 7.70 (s, 1H, H_2 Imd) 7.91 (s, 1H, H Trz) 8.48 (s, 1H, H Trz)	7.36 (s, 2H) 7.65 (s, 1H)
s[b]		3.81–4.02 (m, 3H, $H_{b, c, d}$) 4.15 (part A of ABX, J = 14.1; 4.4, 1H, H_a) 4.52 (qt, 1H, H_a) 4.59 (s, 2H, $H_{f, g}$)	6.91 (s, 1H, H_5 Imd) 7.10 (s, 1H, H_4 Imd) 7.55 (s, 1H, H_2 Imd) 7.90 (s, 1H, H Trz) 8.37 (s, 1H, H Trz)	7.35 (dd, J = 8.4; 2.0, 1H, H_5) 7.54 (d, J = 8.4, 1H, H_6) 7.54 (d, J = 2.0, 1H, H_3)
t		3.67 (dd, J = 8.9; 5.1, 1H, $H_{b\ or\ c}$) 3.79 (t, J = 7.4, 1H, $H_{c\ or\ b}$) 3.81 (part A of ABX, J_{AB} = 11.8, J_{BX} = 7.0, 1H, H_d) 3.93 (part B of ABX, J_{AB} = 13.9, J_{BX} = 4.3, 1H, H_e) 4.66 (part A of AB, J = 14.8, 1H, H_f) 4.73 (part B of AB, J = 14.8, 1H, H_e)	7.86 (s, 1H, H Trz) 7.89 (s, 1H, H Trz) 8.12 (s, 1H, H Trz) 8.18 (s, 1H, H Trz)	7.16 (dd, J = 8.5; 1.7, 1H, H_5) 7.39 (d, J = 1.9, 1H, H_3) 7.45 (d, J = 7.8, 1H, H_6)
t[a]		3.82 and 3.83 (coalesced 2s, 2H, $H_{d, e}$) 4.07–4.33 (m, 2H, $H_{b, c}$) 4.42 (smoothed out qt, 1H, H_a)	7.90 (s, 1H, H Trz) 8.47 (s, 1H, H Trz) 8.04 (s, 1H, H Trz) 8.61 (s, 1H, H Trz)	7.36 (s, 2H) 7.65 (s, 1H)
u		3.32–3.47 (m, 1H, $H_{b\ or\ c}$) 3.53–3.68 (m, 2H, $H_{d, e}$) 3.80–3.97 (m, 1H, $H_{c\ or\ b}$) 4.10–4.50 (m, 1H, H_a) 4.26 (part A of AB, J = 14.5, 1H, H_f) 4.36 (part B of AB, J = 14.5, 1H, H_g)	7.01 (~ s, 4H, $H_{4, 5}$ Imd and $H_{4, 5}$ Imd') 7.40 (s, 1H, H_3 Imd) 7.52 (s, 1H, H_3 Imd')	6.70–6.83 (m, 2H, $H_{3, 5}$) 7.20–7.70 (m, 1H, H_6)

Except where otherwise indicated, the spectra were recorded in $CDCl_3$; [a]recorded in DMSO–d_6; [b]recorded in acetone–d_6; Imd: imidazol-1-yl; Trz: 1,2,4-triazol-1-yl.

Table III. In vitro antifungal activity of derivatives **Ia–u** (comparison of econazole, isoconazole and miconazole) against *C albicans*, *A flavus* and *F solani* after 24, 48 h, 7 and 14 days incubation expressed as the minimum inhibitory concentration (MIC) in $\mu g \cdot mL^{-1}$.

Strain		***Ia***	***Ib***	***Ic***	***Id***	***Ie***	***If***	***Ig***	***Ih***	***Ii***	***Ij***	***Ik***	***Il***	***Im***	***In***	***Io***	***Ip***	***Iq***	***Ir***	***Is***	***It***	***Iu***	*Eco*	*Mico*	*Isoco*
C albicans																									
	24h	> 25	> 25	> 25	> 25	≤ 25	≤ 25	≤ 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 5	≤ 5
	48h	> 25	> 25	> 25	> 25	≤ 25	≤ 25	≤ 25	> 25	≤ 25	≤ 25	> 25	> 25	≤ 25	≤ 25	≤ 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 5	≤ 5
	7d	> 25	> 25	> 25	> 25	≤ 25	≤ 25	≤ 25	> 25	≤ 25	≤ 25	> 25	> 25	≤ 25	≤ 25	≤ 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 10	≤ 10	≤ 5
	14d	> 25	> 25	> 25	> 25	≤ 25	≤ 25	≤ 25	> 25	≤ 25	≤ 25	> 25	> 25	≤ 25	≤ 25	≤ 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 10	≤ 10	≤ 5
A flavus																									
	24h	> 25	> 25	> 25	> 25	> 25	≤ 25	≤ 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 10	≤ 5
	48h	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 10	≤ 5
	7d	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 10	≥ 5
	14d	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 10	≥ 5
F solani																									
	24h	> 25	> 25	> 25	≤ 25	> 25	≤ 25	> 25	> 25	> 25	≤ 25	> 25	> 25	> 25	> 25	> 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 25	≤ 25
	48h	> 25	> 25	> 25	≤ 25	> 25	≤ 25	> 25	> 25	> 25	≤ 25	> 25	> 25	> 25	> 25	> 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 25	≤ 25
	7d	> 25	> 25	> 25	≤ 25	> 25	≤ 25	> 25	> 25	> 25	≤ 25	> 25	> 25	> 25	> 25	> 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 5	≤ 25	≤ 25
	14d	> 25	> 25	> 25	≤ 25	> 25	≤ 25	> 25	> 25	> 25	≤ 25	> 25	> 25	> 25	> 25	> 25	≤ 25	≤ 5	≤ 5	≤ 5	≤ 5	> 25	≤ 10	> 25	≤ 25

Eco: econazole; Mico: miconazole; Isoco: isoconazole.

were not very active towards the tested fungal strains (MIC > 25 μg•mL^{-1}) except for **Id**, carrying a triazole ring at the 4 position of dioxolane (MIC = 25 μg•mL^{-1} against *F solani*).

*Compounds **Ie–g***
Compounds **Ie–g**, which have at the 2 position of dioxolane one phenyl group carrying one *ortho-* or *para*-chlorine atom, or one *ortho-* and one *para*-chlorine atom respectively, possessed a significant activity at 25 μg•mL^{-1} against *C albicans*, but were not very active against *A flavus* and *F solani*, except for **If** against the latter (MIC = 25 μg•mL^{-1}).

*Compounds **Ih–k***
Compounds **Ih–k**, with a 2-methyl-4 or 5-nitroimidazol-1-yl group at the 4 position of dioxolane were not very active against the studied fungal strains, except for **Ic** against *C albicans* and **Ij** against *C albicans* and *F solani* (MIC = 25 μg•mL^{-1}).

*Compounds **Im–p***
Compounds **Im–p**, which carried a triazolyl group in the 4 position of dioxolane, possessed significant activity at 25 μg•mL^{-1} against *C albicans*, but were not very active against *A flavus* and *F solani* except for **Ip** against the latter (MIC = 25 μg•mL^{-1}).

*Compound **Iu***
Compound **Iu**, which possessed one polyazolyl group at the 2 and 4 positions and one *ortho-* and *para*-difluorophenyl group at the 2 position of the dioxolane ring, was not very active (MIC > 25 μg•mL^{-1}); meanwhile, replacement of fluorine atoms by chlorine atoms (compounds **Iq–t**) increased the antifungal activity. In our series, compounds **Iq–t** were the most active against all the tested fungi (MIC = 5 μg•mL^{-1}); compared to the following antifungal agents, they were: after 14 days incubation, more active than econazole, miconazole and isoconazole against *F solani*; after 14 days incubation, more active than miconazole and isoconazole, but as active as econazole against *A flavus*; after 14 days incubation, more active than econazole and miconazole, but as active as isoconazole against *C albicans*.

Conclusion

After examining table III, the following conclusions can be made. First, compounds **Ia–d**, which possessed no phenyl group bonded to C_2 of dioxolane, were not very active. Consequently, the presence of one phenyl group to C_2 was necessary for activity. For better antifungal activity, the chlorine atoms linked to the phenyl group at the *para* or/and *ortho* position(s) are essential (compounds **Ie–g**). Secondly, replacement of an imidazole ring to C_4 of the dioxolane by a triazole ring maintained the activity (compounds **Im–p**); on the other hand, 2-methyl-4 or 5-nitroimidazole decreased the activity (**Ih–l**).

Finally, to obtain higher antifungal activity in our series, the compounds have to carry on the C_2 of dioxolane a 2,4-dichlorophenyl group, and at the same time on C_2 and C_4 of dioxolane a polyazolylmethyl group (compounds **Iq–t**).

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}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, qt = quintuplet, 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_{254}). Preparative-layer chromatography (PLC) was performed on silica gel (Merck art 7748, silica-gel 60 $PF_{254+366}$) 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 **2***
Compounds **2** (except Solketal, a commercial product), used in the following synthesis (*Methods 1* and *2*), were prepared according to literature procedures [5, 7].

*2-(Alkyl or aryl)-2-methyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonates **3**: general procedure*
p-Ts-Cl (38 g, 0.20 mol) was suspended and stirred in 20 mL anhydrous pyridine and cooled with an ice–water bath. The appropriate 2-(alkyl or aryl)-2-methyl-1,3-dioxolane-4-methanol **2** (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 $MgSO_4$, evaporated to dryness and the residue purified by column chromatography on silica gel (Merck, art 7734) with hexane/ethyl acetate (7:3) as eluent.

*2,2-Dimethyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate **3a**.* 85% yield, mp = 49 °C from toluene. IR (KBr): ν 1175 ($SO_{2\ sym}$), 1367 ($SO_{2\ asym}$) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 2.45 (s, 3H, $PhCH_3$), 3.61 and 3.71 (parts A and B of ABX, J = 8.5; 5.1 Hz, 2H, CH_2 to C_4 of dioxolane), 3.90–4.10 (m, 2H, $H_{5\ and\ 5'}$ of dioxolane), 4.28 (qt, J = 5.8 Hz, 1H, H_4 of dioxolane), 7.36 (AA'BB', J = 8.3 Hz, 2H, $H_{3\ and\ 5}$ of Ph), 7.80 (AA'BB', J = 8.3 Hz, 2H, $H_{2\ and\ 6}$ of Ph).

*2-Methyl-2-phenyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate **3b**.* 80% yield, mp = 71 °C from toluene. IR (KBr): ν 1148 ($SO_{2\ sym}$), 1343 ($SO_{2\ asym}$) cm^{-1}.

2-(2-Chlorophenyl)-2-Methyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate ***3c***. 84% yield, oil. IR (KBr): ν 1147 ($SO_{2\,sym}$), 1356 ($SO_{2\,asym}$) cm^{-1}.

2-(4-Chlorophenyl)-2-Methyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate ***3d***. 78% yield. oil. IR (KBr): ν 1154 ($SO_{2\,sym}$), 1342 ($SO_{2\,asym}$) cm^{-1}.

2-(2,4-Dichlorophenyl)-2-Methyl-1,3-dioxolan-4-ylmethyl p-toluenesulfonate ***3e***. 84% yield, oil. IR (KBr): ν 1157 ($SO_{2\,sym}$), 1348 ($SO_{2\,asym}$) cm^{-1}.

2-(Alkyl or aryl)-2-methyl-4-(polyazol-1-ylmethyl)-1,3-dioxolanes ***1a–p****: general procedure*

R^3 = imidazol-1-yl. Under a nitrogen atmosphere, imidazole (3.1 g, 45 mmol) and *p*-tosylate **3** (15 mmol) were dissolved in 90 mL anhydrous DMF. The solution was refluxed by heating with an oil bath. After 72 h, the solution was evaporated to dryness and the residue dissolved in diethyl ether (100 mL). The organic layer was washed three times with 10 mL water and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by PLC with hexane/ethyl acetate (1:9) as eluent (tables I and II).

R^3 = 2-methyl-4 or 5-nitroimidazol-1-yl, 1,2,4-triazol-1-yl. Under a nitrogen atmosphere, sodium hydride (50% dispersion in mineral oil) (768 mg, 16 mmol) was suspended and stirred in 30 mL anhydrous DMF. To the suspension was added in small portions 2-methyl-5-nitroimidazole (1.91 g, 15 mmol) or 1,2,4-triazole (1.04 g, 15 mmol). The mixture was stirred for 1 h at room temperature. To the resulting solution was added dropwise an appropriate amount of *p*-tosylate **3** dissolved in 30 mL anhydrous DMF. The solution was stirred and heated with an oil bath at 80 °C for 5 h, R^3 = 2-methyl-4 or 5-nitroimidazol-1-yl; at 130 °C for 12 h, R^3 = 1,2,4-triazol-1-yl. The resulting precipitate was removed by filtration, the solvent was evaporated in vacuo and the residue dissolved in 100 mL chloroform, washed with water to pH 7, and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by PLC with hexane/ethyl acetate (7:3), then (9:1) as eluent for R^3 = 2-methyl-4 or 5-nitroimidazol-1-yl, hexane/ethyl acetate (1:9), then (4:1) as eluent for R^3 = 1,2,4-triazol-1-yl (tables I and II).

Method 2

cis- and trans-2-Bromomethyl-2-(2,4-dihalogenophenyl)-4-hydroxymethyl-1,3-dioxolanes ***4****: general procedure*
To 60 mL distilled anhydrous toluene was added alcohol **2** (120 mmol). After cooling and with temperature maintained at under 30 °C, bromine (19.2 g, 120 mmol) was added dropwise. After addition was completed, the mixture was stirred at room temperature for 1 h. The resulting solution was evaporated in vacuo and the residue poured into 100 mL ice–water and 100 mL chloroform was added in this solution. The organic layer was washed three times with 10 mL 6 N NaOH and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography on silica gel (Merck, art 7734) with toluene as eluent.

cis- and trans-2-Bromomethyl-2-(2,4-dichlorophenyl)-4-hydroxymethyl-1,3-dioxolane ***4a***. 87% yield, oil. IR (KBr): ν 1031 and 1104 (C-O ketal), 3418 (OH) cm^{-1}.

cis- and trans-2-Bromomethyl-2-(2,4-difluorophenyl)-4-hydroxymethyl-1,3-dioxolane ***4b***. 89% yield, oil. IR (KBr): ν 1043 and 1095 (C-O ketal), 3392 (OH) cm^{-1}.

cis-4-Benzoyloxymethyl-2-bromomethyl-2-(2,4-dihalogenophenyl)-1,3-dioxolanes ***5a****: general procedure*
Under a nitrogen atmosphere, *cis*- and *trans*-derivative **4** (91 mmol) was dissolved in 60 mL anhydrous pyridine. After cooling at 5 °C, Bz-Cl (14 g, 100 mmol) was added dropwise. After addition was completed, the mixture was stirred for 3 h. Pyridine was evaporated in vacuo and the residue was dissolved in chloroform. The organic layer was washed with water to pH 7, dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel (Merck, art 7734) with ethyl acetate as eluent.

cis-4-Benzoyloxymethyl-2-bromomethyl-2-(2,4-difluorophenyl)-1,3-dioxolane ***5a$_1$***. 62% yield, mp = 79.5 °C from absolute EtOH. IR (KBr): ν 1039 and 1093 (C-O ketal), 1722 (C=O ester) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.80 (~ s, 2H, CH_2 to C_4 of dioxolane), 4.03–4.17 (2dd, *J* = 9.4; 6.0 Hz, 2H, 2H to C_5 of dioxolane), 4.41–4.56 (m, 1H, H to C_4 of dioxolane), 4.54 (s, 2H, CH_2-Br), 6.78–6.92 (m, 2H, $H_{3\,and\,5}$ of 2,4-F_2Ph), 7.41–7.62 (m, 3H, $H_{\beta,\,\beta',\gamma}$ of PhCO), 7.46 (d, *J* = 7.5 Hz, 1H, H_6 of 2,4-F_2Ph), 8.07 (~ dd, J = 7.0; 1.5 Hz, 2H, $H_{\alpha,\,\alpha'}$ of PhCO).

trans-4-Benzoyloxymethyl-2-bromomethyl-2-(2,4-difluorophenyl)-1,3-dioxolane ***5b$_1$***. 38% yield, mp = 76 °C from absolute EtOH. IR (KBr): ν 1036 and 1091 (C-O ketal), 1714 (C=O ester) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.79 (s, 2H, CH_2 to C_4 of dioxolane), 3.94 (~ t, *J* = 7.9 Hz, 1H, H to C_5 of dioxolane), 4.31 (dd, *J* = 12.1; 4.1 Hz, 1H, H to C_5 of dioxolane), 4.41–4.56 (m, 2H, CH_2-Br), 4.74–4.85 (m, 1H, H to C_4 of dioxolane), 6.71–6.83 (m, 2H, $H_{3\,and\,5}$ of 2,4-F_2Ph), 7.33 (~ t, 1H, H_γ of PhCO), 7.38 (d, *J* = 7.6 Hz, 1H, H_6 of 2,4-F_2Ph), 7.51–7.64 (m, 2H, $HH_{\beta,\,\beta'}$ of PhCO), 7.77 (~ dd, *J* = 7.0; 1.5 Hz, 2H, $H_{\alpha,\,\alpha'}$ of PhCO).

cis-4-Benzoyloxymethyl-2-bromomethyl-2-(2,4-dichlorophenyl)-1,3-dioxolane ***5a$_2$***. 50% yield, mp = 118 °C from absolute EtOH). IR (KBr): ν 1058 and 1085 (C-O ketal), 1740 (C=O ester) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.83 (part A of AB, *J* = 11.2 Hz, 1H, H to CH_2 to C_4 of dioxolane), 3.92 (part B of AB, *J* = 11.2 Hz, 1H, H to CH_2 to C_4 of dioxolane), 4.00–4.23 (2dd, *J* = 8.1; 6.5 Hz, 2H, 2H to C_5 of dioxolane), 4.42 (~ qt, 1H, H to C_4 of dioxolane), 4.64 (s, 2H, CH_2-Br), 7.26 (dd, *J* = 8.5; 1.8 Hz, 1H, H_6 of 2,4-Cl_2Ph), 7.34–7.49 (m, 3H, $H_{\beta,\,\beta',\gamma}$ of PhCO), 7.55–7.65 (m, 2H, $H_{3\,and\,5}$ of 2,4-Cl_2Ph), 8.05 (d, *J* = 7.3 Hz, 2H, $H_{\alpha,\,\alpha'}$ of PhCO).

cis-4-Benzoyloxymethyl-2-(2,4-dihalogenophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolanes ***8****: general procedure*
A mixture of appropriate *cis*-benzoate **5a** (50 mmol), imidazole (10 g, 150 mmol) in 100 mL anhydrous DMF was refluxed by heating in an oil bath. After 96 h, the solution was evaporated in vacuo, the residue dissolved in 200 mL Et_2O, washed three times with 100 mL water, and dried over anhydrous $MgSO_4$. The organic layer was evaporated to dryness, and purified by column chromatography on silica gel (Merck, art 7734) with toluene as eluent.

cis-4-Benzoyloxymethyl-2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolane ***8a***. 55% yield, mp = 172 °C (nitrate) from *i*-Pr-OH/*i*-Pr_2O. IR (KBr): ν 1058 and 1085 (C-O ketal), 1740 (C=O ester) cm^{-1}.

cis-4-Benzoyloxymethyl-2-(2,4-difluorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolane ***8b***. 64% yield, oil. IR (KBr): ν 1012 and 1042 (C-O ketal), 1716 (C=O ester) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.58–3.65 (part A of ABX, 1H, H to C_5 of dioxolane), 3.89–3.96 (part B of ABX, 1H, H to C_5 of dioxolane),

4.07 and 4.08 (2d, J = 5.5 and 5.3 Hz, 2H, CH_2 to C_4 of dioxolane), 4.37 (qt, J = 5.5 Hz, 1H, H to C_4 of dioxolane), 4.35 (s, 2H, CH_2 to C_2 of dioxolane), 6.77–6.90 (m, 2H, $H_{3\text{ and }5}$ of 2,4-F_2Ph), 6.94 (~ s, 2H, $H_{4\text{ and }5}$ of imidazole), 7.12–7.26 (m, 1H, H_6 of 2,4-F_2Ph), 7.36–7.60 (m, 3H, $H_{\beta,\beta',\gamma}$ of PhCO), 7.47 (~ s, 1H, H_2 of imidazole), 7.99 (~ dd, J = 6.8; 1.7 Hz, 2H, $H_{\alpha,\alpha'}$ of PhCO).

cis-2-(2,4-Dihalogenophenyl)-4-hydroxymethyl-2-(imidazol-1-ylmethyl)-1,3-dioxolanes (step g, scheme 2): general procedure A mixture of *cis*-benzoate **8** (26 mmol) dissolved in 100 mL dioxane and 20 mL of 5 N NaOH was heated at reflux. After 30 min, the mixture was cooled to room temperature and then evaporated to dryness. The residue was dissolved in chloroform, washed with brine to pH 7, dried over $MgSO_4$ and evaporated in vacuo. The residue was precipitated and recrystallized from EtOH as a white solid.

cis-2-(2,4-Dichlorophenyl)-4-hydroxymethyl-2-(imidazol-1-ylmethyl)-1,3-dioxolane. 96% yield, mp = 140 °C from EtOH. IR (KBr): ν 3110 (OH_{bonded}) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.30 (part A of ABX, 1H, H of CH_2 to C_4 of dioxolane), 3.34 (part B of ABX, 1H, H of CH_2 to C_4 of dioxolane), 3.61 (dd, J = 7.7; 5.9 Hz, 1H, $H_{a\text{ or }b}$ to C_5 of dioxolane), 3.80 (dd, J = 7.8; 6.9 Hz, 1H, $H_{b\text{ or }a}$ to C_5 of dioxolane), 4.11 (qt, J = 5.7 Hz, 1H, H to C_4 of dioxolane), 4.36 (part A of AB, J = 14.7 Hz, 1H, H of CH_2 to C_2 of dioxolane), 4.50 (part B of AB, J = 14.7 Hz, 1H, H of CH_2 to C_2 of dioxolane), 6.96 (s, 2H, $H_{4\text{ and }5}$ of imidazole), 7.21 (dd, J = 8.5; 1.8 Hz, 1H, H_5 of 2,4-Cl_2Ph), 7.43 (d, J = 1.8 Hz, 1H, H_3 of 2,4-Cl_2Ph), 7.53 (s, 1H, H_2 of imidazole), 7.56 (d, J = 8.5, 1H, H_6 of 2,4-Cl_2Ph).

cis-2-(2,4-Difluorophenyl)-4-hydroxymethyl-2-(imidazol-1-ylmethyl)-1,3-dioxolane. 89% yield, mp = 142 °C from EtOH). IR (KBr): ν 3118 (OH_{bonded}) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.30 (d, J = 5.1 Hz, CH_2 to C_4 of dioxolane), 3.59 (dd, J = 8.1; 6.0 Hz, $H_{a\text{ or }b}$ to C_5 of dioxolane), 3.85 (dd, J = 7.9; 6.8 Hz, $H_{b\text{ or }a}$ to C_5 of dioxolane), 4.15 (qt, J = 5.6 Hz, 1H, H to C_4 of dioxolane), 4.28 (part A of AB, J = 14.7 Hz, 1H, H of CH_2 to C_2 of dioxolane), 4.38 (part B of AB, J = 14.7 Hz, 1H, H of CH_2 to C_2 of dioxolane), 6.81–6.92 (m, 2H, $H_{3\text{ and }5}$ of 2,4-F_2Ph), 6.98 (~ s, 2H, $H_{4\text{ and }5}$ of imidazole), 7.44–7.55 (m, 1H, H_6 of 2,4-F_2Ph), 7.54 (s, 1H, H_2 of imidazole).

cis-2-(2,4-Dichlorophenyl)-4-hydroxymethyl-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolane. Under a nitrogen atmosphere, sodium hydride (80% dispersion in mineral oil) (3.30 g, 110 mmol) was suspended and stirred in 100 mL anhydrous DMSO. To the suspension was added, in small portions, 1,2,4-triazole (6.90 g, 100 mmol). The mixture was stirred for 1 h at room temperature. To the resulting solution was added *cis*-benzoate **5a** (30 g, 67 mmol) in small portions. The solution was stirred and heated at 130 °C. After 12 h, the solution was poured in 20 mL ice–water and extracted with methylene chloride. The organic layer was washed with water to pH 7, dried over anhydrous $MgSO_4$ and evaporated to dryness. The resulting residue was dissolved in 180 mL of a mixture of dioxane/water (5:1). To this solution was added 200 mL 5 N NaOH. The solution was heated at reflux. After 2 h, the mixture was cooled to room temperature and then extracted with methylene chloride. The combined extracts were washed with brine to pH 7, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (Merck, art 7734) with chloroform/methanol (49:1) as eluent. The desired compound was obtained and recrystallized from a mixture of 4-methylpentan-2-one/*i*-Pr_2O as fine white crystals; 12.2 g (55%), mp = 138 °C, IR (KBr): ν 3110 (OH_{bonded}) cm^{-1}.

cis-2-(2,4-Dihalogenophenyl)-2-(polyazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl p-toluenesulfonates ***9****: general procedure* *p*-Ts-Cl (38 g, 0.20 mol) was suspended and stirred in 20 mL anhydrous pyridine and cooled with an ice–water bath. The appropriate alcohol as mentioned above (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 $MgSO_4$, evaporated to dryness and the residue purified by column chromatography on silica gel (Merck, art 7734) with hexane/ethyl acetate (7:3) as eluent.

cis-2-(2,4-Dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl p-toluenesulfonate ***9a****.* 75% yield, mp = 117 °C *from toluene.* IR (KBr): ν 1044 and 1105 (C-O ketal), 1152 ($SO_{2\,sym}$), 1325 ($SO_{2\,asym}$) cm^{-1}; ^{1}H-NMR (DMSO–d_6): δ 2.44 (s, 3H, CH_3 to *p*-Ts), 3.52 (m, 2H, CH_2 to C_4 of dioxolane), 3.71 (m, 1 H, $H_{a\text{ or }b}$ to C_5 of dioxolane), 3.84 (m, 1H, $H_{b\text{ or }a}$ to C_5 of dioxolane), 4.22 (~ qt, J = 4.5 Hz, 1H, H to C_4 of dioxolane), 4.47 (s, 2H, CH_2 to C_2 of dioxolane), 6.76 (s, 1H, H_5 of imidazole), 6.87 (s, 1H, H_4 of imidazole), 7.43 (~ s, 3H, $H_{3,5\text{ and }6}$ of 2,4-Cl_2Ph), 7.53 (AA'BB', J = 8.0 Hz, 2H, $H_{\beta,\beta'}$ of *p*-Ts), 7.67 (s, 1H, H_2 of imidazole), 7.82 (AA'BB', J = 8.0 Hz, $H_{\alpha,\alpha'}$ of *p*-Ts).

cis-2-(2,4-Difluorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl p-toluenesulfonate ***9b****.* 67% yield, paste. IR (KBr): ν 1043 and 1099 (C-O ketal), 1174 ($SO_{2\,sym}$), 1367 ($SO_{2\,asym}$) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3 of *p*-Ts), 3.30–3.41 (part A of ABX, 1H, H to C_5 of dioxolane), 3.50–3.57 (part B of ABX, 1H, H to C_5 of dioxolane), 3.70 (part A of ABX, 1H, H of CH_2 to C_4 of dioxolane), 3.80 (part B of ABX, 1H, H of CH_2 to C_4 of dioxolane), 4.17–4.34 (m, 1H, H to C_4 of dioxolane), 4.20 (part A of AB, J = 14.6 Hz, 1H, H of CH_2 to C_2 of dioxolane), 4.31 (part B of ABX, J = 14.6 Hz, H of CH_2 to C_2 of dioxolane), 6.78–6.89 (m, 1H, H_3 of 2,4-F_2Ph), 6.85 (~ s, 2H, $H_{4\text{ and }5}$ of imidazole), 7.31–7.43 (m, 2H, $H_{5\text{ and }6}$ of 2,4-F_2Ph), 7.35 (~ s, 1H, H_2 of imidazole), 7.36 (~ d, J = 8.1 Hz, $H_{\beta,\beta'}$ of *p*-Ts), 7.74 (~ d, J = 8.3 Hz, $H_{\alpha,\alpha'}$ of *p*-Ts).

cis-2-(2,4-Dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-ylmethyl p-toluenesulfonate ***9c****.* 75% yield, mp = 117 °C from toluene. IR (KBr): ν 1048 and 1176 (C-O ketal), 1149 ($SO_{2\,sym}$), 1342 ($SO_{2\,asym}$) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.46 (s, 3H, CH_3 of *p*-Ts), 3.49 (part A of ABX, J = 10.4; 6.2 Hz, 1H, H of CH_2 to C_4 of dioxolane), 3.69 (dd, J = 8.8; 4.7 Hz, 1H, H to C_5 of dioxolane), 3.76–3.85 (m, 2H, H (part B of ABX) of CH_2 to C_4 and H to C_5 of dioxolane), 4.25 (qt, J = 5.5 Hz, 1H, H to C_4 of dioxolane), 4.66 (part A of AB, J = 14.7 Hz, 1H, H of CH_2 to C_2 of dioxolane), 4.76 (part B of AB, J = 14.7 Hz, 1H, H of CH_2 to C_2 of dioxolane), 7.19 (dd, J = 8.4; 1.9 Hz, 1H, H_5 of 2,4-Cl_2Ph), 7.33 (AA'BB', J = 8.0 Hz, 2H, $H_{\beta,\beta'}$ of *p*-Ts), 7.43 (d, J = 8.4 Hz, 1H, H_6 of 2,4-Cl_2Ph), 7.44 (d, J = 2.0 Hz, 1H, H_3 of 2,4-Cl_2Ph), 7.76 (AA'BB', J = 8.6 Hz, 2H, $H_{\alpha,\alpha'}$ of *p*-Ts), 7.76 (s, 1H, H_3 of 1,2,4-triazole), 8.07 (s, 1H, H_5 of 1,2,4-triazole).

cis-2-(2,4-Dihalogenophenyl)-2-(polyazol-1-ylmethyl)-4-(imidazol-1-ylmethyl)-1,3-dioxolane ***Iq****,* ***s****,* ***u****: general procedure* Under a nitrogen atmosphere, a mixture of appropriate *cis*-tosylate **9** (5 mmol), imidazole (1.7 g, 25 mmol) in 50 mL anhydrous DMF was refluxed by heating with an oil bath. After 96 h, the solution was evaporated in vacuo, the residue dissol-

ved in 100 mL Et_2O, washed three times with 50 ml water, and dried over anhydrous $MgSO_4$. The organic layer was evaporated to dryness and purified by PLC with ethanol as eluent (tables I and II).

cis-2-(2,4-Dichlorophenyl)-2-(polyazol-1-ylmethyl)-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes ***Ir, t****: general procedure*
Under a nitrogen atmosphere, sodium hydride (80% dispersion in mineral oil) (480 mg, 16 mmol) was suspended and stirred in 30 mL anhydrous DMF. To the suspension was added in small portions 1,2,4-triazole (1.0 g, 15 mmol). The mixture was stirred for 1 h at room temperature. To the resulting solution was added *cis*-tosylate **9** (5 mmol) dissolved in 5 mL anhydrous DMF. The solution was stirred and heated at 130 °C. After 12 h, the resulting precipitate was removed by filtration, the solvent was evaporated in vacuo and the residue dissolved in 100 mL chloroform, washed with water to pH 7, and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by PLC with acetone as eluent (see tables I and II).

Molecular and crystal structure of trans-4-(benzoyloxymethyl)-2-(bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolane
The atomic coordinates and equivalent isotopic thermal parameters for all non-hydrogen atoms are given in table IV. A perspective view as shown in figure 2 reveals that the studied compound exibits a *trans* configuration. The dioxolane moiety is in a chair conformation, the C2 and C4 atoms lying at 0.4381(6) and –0.465(6) Å from the plane P1 defined by the basal atoms O1, O3 and C5. This is in contrast to the predominant 'envelope' conformation found in the structure of trimethyl[(*cis*-4-methyl-1,3-dioxolan-2-yl)methyl]ammonium iodide [17]. Moreover, the two asymmetric atoms C2 and C4 exhibit the 2 *RS*, 4 *RS* configurations since the studied compound crystallizes in the centrosymmetric space groups $P2_1/c$. Distances and angles within the dioxolane moiety do not differ significantly from those found in the structure of trimethyl[(*cis*-4-methyl-1,3-dioxolan-2-yl)methyl]ammonium iodide. The dihedral angles between the plane P1 and the mean plane P2 (defined by C17, C18, C19, C20, C21 and C22 atoms) on one side, P1 and the mean plane P3 (C10, C11, C12, C13, C14 and C15) on the other side, are respectively 90.1(3)° and 94.0(3)°, while the dihedral angle between P2, P3 is 50.3(2)°. The F18 and F20 atoms deviate from P2 by only 0.065(3) and –0.018(4) Å, and so lie nearly in this plane. The structure of the ester moiety can be compared with that of ethyl *p*-azoxybenzoate [18] with average carbon–oxygen bond lengths (1.194(6) and 1.320(7) Å). These values are very similar to those found in the studied compound, where the homologous bond lengths are 1.210(8) and 1.321(7) Å respectively. The torsion angles around the C8-O7 and C6-O7 bonds are –178.0(4), 2.5(8) and 168.0(5)° respectively for the C10-C8-O7-C6, O9-C8-O7-C6 and C4-C6-O7-C8 atoms. Many van der Waals contacts contri-

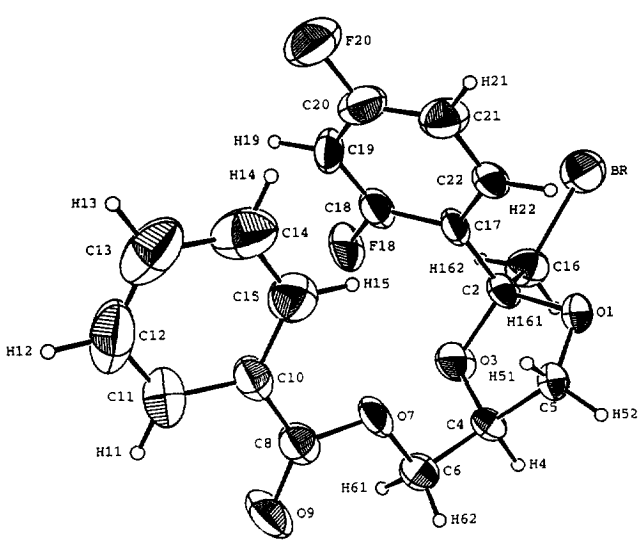


Fig 2. Molecular structure of *trans*-4-(benzoyloxymethyl)-2-(bromomethyl)-2-(2.4-difluorophenyl)-1,3-dioxolane, ORTEP view.

Table IV. Atomic coordinates and equivalent thermal parameters for the non-hydrogen atoms of *trans*-4-(benzoyloxymethyl)-2-(bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolane. The esd's are given in parentheses.

Atom	*x*	*y*	*z*	B_{eq} (Å²)
Br	0.54057 (4)	– 0.0695 (1)	0.83772 (5)	4.91 (2)
F (18)	0.6705 (2)	0.5078 (6)	0.8761 (2)	4.90 (9)
F (20)	0.8687 (2)	0.0747 (7)	0.8732 (3)	6.2 (1)
O (1)	0.6091 (2)	0.0549 (6)	1.0564 (2)	3.04 (8)
O (3)	0.6165 (2)	0.4189 (7)	1.0279 (2)	3.74 (9)
O (7)	0.7464 (2)	0.5052 (6)	1.1589 (3)	3.49 (9)
O (9)	0.7894 (2)	0.8218 (7)	1.2241 (3)	5.0 (1)
C (2)	0.6156 (3)	0.2060 (9)	0.9874 (4)	2.8 (1)
C (4)	0.6248 (3)	0.3946 (9)	1.1262 (4)	3.0 (1)
C (5)	0.6441 (3)	0.1555 (9)	1.1431 (4)	3.1 (1)
C (6)	0.6789 (3)	0.555 (1)	1.1772 (4)	3.4 (1)
C (8)	0.7971 (3)	0.653 (1)	1.1842 (4)	3.3 (1)
C (10)	0.8636 (3)	0.590 (1)	1.1594 (4)	3.5 (1)
C (11)	0.9185 (3)	0.740 (1)	1.1763 (5)	5.3 (2)
C (12)	0.9809 (4)	0.694 (2)	1.1547 (5)	6.9 (2)
C (13)	0.9897 (4)	0.495 (2)	1.1135 (5)	6.6 (2)
C (14)	0.9348 (3)	0.346 (1)	1.0964 (5)	6.1 (2)
C (15)	0.8718 (3)	0.391 (1)	1.1184 (4)	4.4 (2)
C (16)	0.5474 (3)	0.198 (1)	0.9090 (4)	3.8 (1)
C (17)	0.6835 (3)	0.1691 (9)	0.9558 (4)	2.6 (1)
C (18)	0.7088 (3)	0.321 (1)	0.9029 (4)	3.4 (1)
C (19)	0.7706 (3)	0.294 (1)	0.8758 (4)	3.9 (1)
C (20)	0.8068 (3)	0.104 (1)	0.9001 (4)	4.1 (2)
C (21)	0.7844 (3)	– 0.057 (1)	0.9501 (4)	4.1 (1)
C (22)	0.7221 (3)	– 0.0235 (9)	0.9768 (4)	3.2 (1)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a2 * B(1,1) + b2 * B(2,2) + c2 * B(3,3) + ab(cos γ) * B(1,2) + ac(cos β) * B(1,3) + bc (cos α) * B(2,3)].

bute to the cohesion of the crystal, the shortest 3.132(6) Å involving the atoms F20–C8^{i} (symmetry code i: x, 1/2 – y, – 1/2 + z).

Crystal data and X-ray structure analysis of trans-4-(benzoyloxymethyl)-2-(bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolane: experimental approach

$C_{18}H_{15}Br_2F_2O_2$ is crystallized from an ethanol solution. The refined cell constants and other relevant crystal data are presented in table V together with details on the intensity measurements. A white parallelepiped crystal of $C_{18}H_{15}Br_2F_2O_2$ with approximate dimensions of 0.150 × 0.180 × 0.350 mm^3 was used for all X-ray experiments which were carried out with an Enraf–Nonius CAD-4 diffractometer at 294 K with Mo K_α radiation (λ = 0.7107 Å). The lattice parameters of the monoclinic cystal with the space group $P2_1/c$ were refined using 25 reflections in the range θ = 9.0–11.05°. The data collection with $\omega/2\theta$ scan between θ = 2–28° resulted in 4077 intensity values. During the data collection, three intensity control reflections were monitored every 2 h, showing no loss of intensity. 1305 data with $I > 3\sigma(I)$ were used for structure determination. The data were corrected for Lorentz and polarization effects. The structure was solved by a combination of direct methods using the SIR procedure [19] and heavy atom techniques, and refined by full-matrix least-squares method based on F with weight = $1/\sigma^2(F)$. An empirical absorption correction with the DIFABS program was used. The structural parameters were refined with the non-hydrogen atoms refined anisotropically and the hydrogen atom isotropically. The current R factor was 0.038, and weighted factor wR 0.046. Neutral atom scattering factors used in all structure factor calculations were taken from [20]. Data processing and computations were carried out using the Enraf–Nonius MolEN program package [21]. Additional material concerning the structural part of this work can be ordered from D Nguyen-Huy.

Table V. Summary of crystal data and details of structure determination of *trans*-4-(benzoyloxymethyl)-2-(bromomethyl)-2-(2,4-difluorophenyl)-1,3-dioxolane.

Molecular formula	$C_{18}H_{15}Br_2F_2O_2$
Crystal system	Monoclinic
Space group	$P2_1/c$ (14)
M_r	413.22
Crystal size (mm)	0.150 × 0.180 × 0.350
Unit-cell dimensions	
a (Å)	19.432(5)
b (Å)	6.082(2)
c (Å)	14.834(7)
β (°)	104.17(3)
V (Å^3)	1700(2)
Z	4
D_x (g cm^{-3})	1.615
Linear absorption coefficient (Mo K_α radiation) (cm^{-1})	24.319
Minimum, maximum and average absorption correction	0.626/1.260/0.976
T (K)	294
Maximum values of $\sin\theta/\lambda$ reached in intensity measurement (Å^{-1})	0.660
h, k, l range	0, 9; 0, 12; –18, 18
Scan	ω/θ
Standard reflections	10, 0, –4/1, –3, 2/–4, 2, –3
Parameters refined	226
R	0.038
wR	0.046
Ratio of max LS shift to esd (Δ/σ)	0.01
Max $\Delta\rho$ in final difference electron density map (e Å^{-3})	–0.93, +0.90
Error in an observation of unit weight	1.224

Microbiology

Fungi and culture medium

Antifungal activities were tested in vitro on three species of pathogenic fungi for humans, animals and plants: *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 compounds studied for test

The substances were dissolved in DMSO (1 mg·mL^{-1}); further dilution with sterile water furnished 100 and 50 µg·mL^{-1} solutions. A 0.5 mL portion of each solution was added to 4.5 mL Casitone agar previously liquified and maintained at 44 °C (final concentrations respectively 10 and 5 µg·mL^{-1}). The solutions were dropped onto 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.

Preparation and sowing of inoculum

For *C albicans*, a sterile aqueous suspension containing 10^5 cells·mL^{-1} was prepared from the 48 h primoculture. For *A flavus* and *F solani*, the spores of the primoculture were collected in 1 mL sterile water. The suspension was vortexed and adjusted to 10^5 spores·mL^{-1}. 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, 7 and 14 d incubation for *C albicans*, *A flavus* and *F solani*.

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