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Synthesis and Antifungal Activity of Structural Analogues of Bifonazole and Ketoconazole

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The synthesis and antifungal activities of the *cis*- and *trans*-1-acetyl-4-{4-[[2-(1,1'-biphenyl-4-yl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methoxy]phenyl}piperazines **3** and **4** are reported. Stereochemical assignments to diastereomeric pairs of *cis/trans* isomers were made on the basis of ^{1}H- and ^{13}C-NMR data. Among test derivatives the best activity was shown by the benzoyl esters of the *cis*- and *trans*-[2-(1,1'-biphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methanols **9** and **10**.

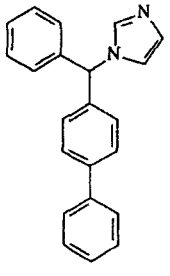
Antibakterielle und antimykotische Verbindungen, 15. Mitt.[1]: Synthese und antimykotische Aktivität von Strukturanalogen des Bifonazols und Ketoconazols

Über Synthese und antimykotische Aktivität der *cis*- und *trans*-1-Acetyl-4-{4[[2-(1,1'-diphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl}piperazine wird berichtet. Aufgrund von ^{1}H- und ^{13}C-NMR-Daten wurde die Stereochemie der diastereomeren *cis/trans*-Isomeren zugeordnet. Die Benzoylester der *cis*- und *trans*-[-2-(1,1'-Diphenyl-4-yl-)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]-methanole zeigten die höchste Aktivität innerhalb der geprüften Verbindungen.

Imidazole derivatives represent a class of antimycotics with an extraordinarily wide range of antimicrobial activity. Bifonazole (**1**) is a member of this type claimed to be active against dermatophytes, yeast, and aspergilli, and to be devoid of toxicity[2]. It has been marketed in Germany by *Bayer* as Mycospor® for the treatment of mycoses and dermatomycoses, such as interdigital mycoses, *tinea corporis*, *tinea inguinalis*, *pityriasis versicolor*, superficial candidoses, and erythrasma[3].

We recently were engaged in a search devoted to the synthesis and the microbiological assays of compounds strictly related to bifonazole[1,4-6]. Substitution of the biphenyl portion by the 4-(1*H*-pyrrol-1-yl)phenyl moiety and replacement of the phenyl by a thiophene ring in the bifonazole structure furnished very active compounds with antifungal power comparable or sometimes superior to that of the parent structure.

These encouraging results led us to pursue search on novel potent antifungal agents and we decided to prepare new compounds which incorporate the biphenyl portion of bifonazole into the structure of ketoconazole (**2**), a substance active against systemic and subcutaneous pathogens marketed in the UK as Nizoral® [7].



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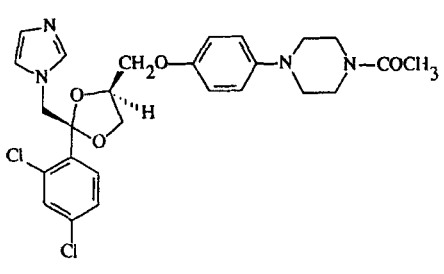

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In this paper we present the synthesis of *cis*- and *trans*-1-acetyl-4-{4-[[2-(1,1'-biphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl}piperazines **3** and **4**. *In vitro* antimycotic activities of these compounds and their precursors against *Candida Albicans* and *Candida* spp are also reported.

Chemistry

As described in Scheme 1, ketalization of 1-(1,1'-biphenyl-4-yl)-2-bromoethan-1-one with 1,2,3-propanetriol in toluene in the presence of *p*-toluenesulfonic acid as catalyst provided a mixture of the *cis*- and *trans*-[2-(1,1'-biphenyl-4-yl)-2-bromomethyl-1,3-dioxolan-4-yl]methanols **5**, which were converted into the benzoates **6** by benzoyl chloride in pyridine.

Displacement of bromine by imidazole furnished the *cis*- and *trans*-[2-(1,1'-biphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl benzoates **7** and **8**, respectively, which were separated by chromatography on a silica gel column. Hydrolysis of the benzoates with NaOH furnished the corresponding alcohols **9** and **10**, and subsequent acylation with methanesulfonyl chloride formed the *cis*- and *trans*-methanesulfonates **11** and **12**, respectively. Nucleophilic displacements of such sulfonates by the phenoxide ion from 1-acetyl-4-(4-hydroxyphenyl)piperazine led to the required *cis*- and *trans*-1-acetyl-4-{4-[[2-(1,1'-biphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl}piperazines **3** and **4**.

1-Acetyl-4-(4-hydroxyphenyl)piperazine was synthetized starting from 4-(1-piperazinyl)anisole dihydrochloride which was converted by HBr into 1-(4-hydroxyphenyl)piperazine dihydrobromide. Acetylation led to the ester-

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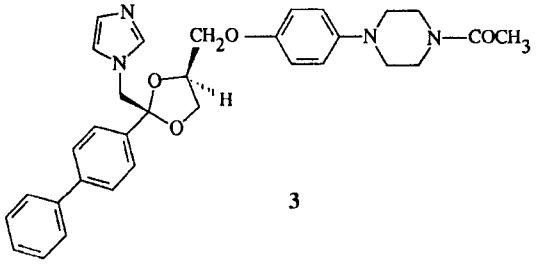
amide, which was partially hydrolyzed to the required phenolic amide. A similar pathway for the synthesis of 1-acetyl-4-(4-hydroxyphenyl)piperazine has been recently reported[8].



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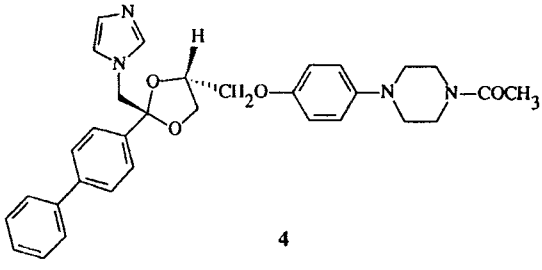

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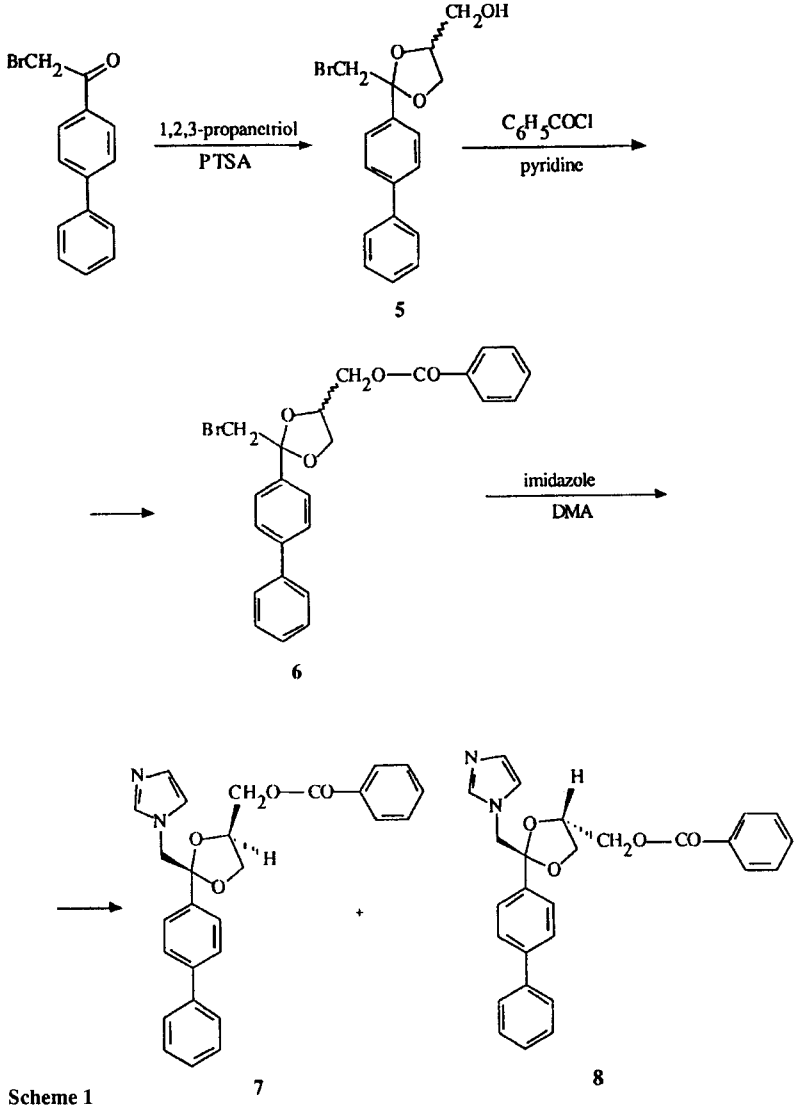
Identification of Diastereomers

The relative orientation of the substituents in the two couples of diastereomeric 1,3-dioxolane derivatives *cis-/trans*-[2-(1,1'-biphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl benzoates **7** and **8** and *cis/trans*-[2-(1,1'-biphenyl-4-yl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methanols **9** and **10** was deduced on the basis of ^{1}H- and ^{13}C-NMR data (Tables 1-4). It has already been reported by a research group at *Janssen* that stereochemical information can be obtained from the NMR spectra of the ketoconazole precursors **13** and **14** which are *cis* isomers[9]. Unfortunately, a detailed description of this result has not been published. The NMR data have been furthermore confirmed by X-ray diffraction[9,10].

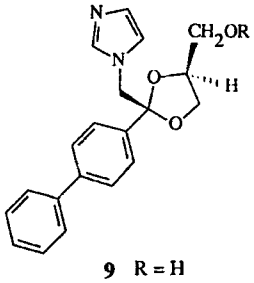
As shown in Table 1, ester **7** and alcohol **9** exhibit ^{1}H-NMR spectra well in agreement, in terms of both chemical shifts and multiplicities, with those observed for *cis*-derivatives **13** and **14**, respectively.

Addition of the shift reagent $Eu(DPM)_3$[11] to $CDCl_3$ solutions of esters **7**, **8**, and **13** and of alcohols **9**, **10**, and **14** caused downfield shifts of all protons consistent with com-

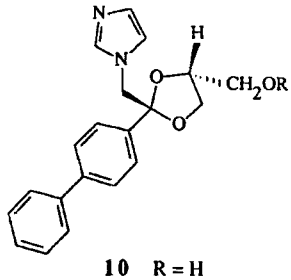


Scheme 1

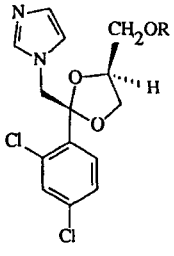
plex formation occurring specifically (for esters) and preferably (for alcohols) at the basic 3-nitrogen of the imidazole ring (Tables 2 and 3)[12].



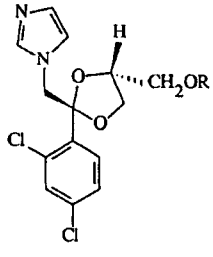
9 R = H
11 R = SO_2CH_3



10 R = H
12 R = SO_2CH_3



13 R = COC_6H_5
14 R = H



15 R = COC_6H_5
16 R = H

The methylene protons of $-CH_2OCOC_6H_5$ and $-CH_2OH$ groups were shifted downfield to a greater extent in the *cis* isomers **7** and **9** in comparison with the *trans* isomers **8** and **10**, while a reverse behaviour was shown by the methine proton of the 1,3-dioxolane ring, *i.e.*, the methine protons of **8** and **10** were shifted more strongly than those of **7** and **9**, respectively. A close similarity in induced shifts of all protons was observed between **7** and **13** and, again, between **9** and **14**.

In *Dreiding* models[13] $CH_2OCOC_6H_5$ and CH_2OH protons are closer to the coordination site in the *cis* isomer. A reverse situation exists for the methine protons, which are located in the *cis* isomer opposite to the imidazolylmethyl group and thus farther from the metal.

The findings summarized in Tables 1, 2, and 3 provide, therefore, good evidence for the conclusion that compounds **7** and **9** are the *cis* isomers while compounds **8** and **10** are the *trans* counterparts.

Very recently, stereochemical assignments to the diastereomeric pairs of a series of *cis*- and *trans*-[2-(haloaryl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methanols, **13**, **15** and **14**, **16** included, have been made, based on one major ^{13}C-chemical shift difference, namely that of C-4 in the dioxolane ring[14]. More precisely, the chemical shift of the *cis* isomers was found without exceptions 1.0-2.5 ppm upfield from that of the *trans* isomers.

The only other noticeable but definitely smaller differences (between 0.5 and 1.5 ppm) come from the methylene C-atoms attached at C-2 of the dioxolane ring. A similar trend was observed by us for the two couples **7**, **8** and **9**, **10** (Table 4), thus providing further support to the aforementioned conclusion.

Microbiological Part

Materials and Methods

The antimycotic activity against *Candida albicans* and *Candida* spp at pH 7.2 and pH 5.8 have been calculated by means of the minimal inhibitory concentrations (MIC) using the serial dilution test in a liquid nutrient medium[15]. Dilution series have been prepared by dissolving 5 mg of substance in DMSO (1 ml) and dilution with distilled water (9 ml) on shaking. Further dilutions with cultural medium gave the required concentrations in the range from 0.25 to 256 µg/ml. Blanks were prepared in the test medium with the above reported quantities of DMSO and water.

MIC was defined as the lowest concentration of test substances at which there was no visible growth in comparison with a blank after the preset incubation time. Bifonazole, ketoconazole, and miconazole were used as standards.

Strains with MIC > 256 µg/ml were regarded as resistant (R) but not excluded from MICs calculation. MIC_{50}, MIC_{90}, and mean MIC values nX have been calculated as reported[1].

All microorganisms used for tests were preliminarily incubated at 37°C on Sabouraud (BBL) dextrose broth for 18 h. Antimicrobial tests were then performed in the same medium using inocula of 10^3 cells/ml. MICs were determined after 36 h at 37°C.

44 Strains of *Candida albicans* and 6 strains of *Candida spp.* (1 *C. glabrata*, 1 *C. parapsilosis*, 1 *C. stellatoidea*, 1 *C. guilliermondii*, 2 *C. lypolitica*) were used, freshly isolated from hospitalized patients and identified by standard methodologies and stocked in the Institute of Microbiology of Rome University.

Results and Discussion

The results of the antifungal screening of derivatives **3** and **4** and those of their precursors **7**-**12** against *Candida albicans* and *Candida spp* measured at pH 7.2 and pH 5.8 are reported in Table 5. Data refer to R%, nX, MIC_{50}, and MIC_{90} values in comparison with those of miconazole, bifonazole, and ketoconazole.

At pH 7.2 only compounds **4**, **8**, and **12** showed no resistant strains against *Candida albicans*. This result was confirmed at pH 5.8 for derivatives **4** and **8** and no resistant strains were observed for derivative **8** also against *Candida* spp at this pH. Various strains are resistant to all other test compounds.

As regard to all test strains a comparison between **3** and **4**, the biphenyl analogues of ketoconazole showed the *trans* isomer to be more active than the *cis* one at pH 7.2 and 5.8, respectively. On the contrary, ketoconazole ist the *cis* isomer of the couple of diastereomeric 1,3-dioxolane derivatives. Data of Table 5 clearly indicate that the most potent derivatives are the benzoyl ester **7** (*cis*-isomer) and **8** (*trans*-isomer). In particular, the *trans*-isomer is active at both pHs against either *Candida albicans* or *Candida* spp, although always less potent, from twice to four times, than the standards.

On the contrary, its *cis*-isomer **7** showed at pH 5.8 very good values of nX and MIC_{90}, superior for *Candida* spp to those of ketoconazole and comparable in potency to the nX and MIC_{90} values of miconazole and bifonazole against either *Candida albicans* or *Candida* spp. The lower pH may favorably influence the activity of drug, perhaps allowing higher concentration of the active nonprotonated form[16].

Further studies are now in progress to improve the activity of **7** by replacing the benzoyl portion by aroyl, and heteroaromatic carbonyl moieties.

Chemical Experimental Part

M.p.: Electrothermal IA6304 (uncorr.).- IR-spectra (nujol mulls): Perkin Elmer 1310.- ^1H- and ^{13}C-NMR-spectra: Varian XL-300 MHz ($CDCl_3$, TMS).- Column chromatography: silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh).- TLC: Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator).- Microanalyses: Prof. A. Pietrogrande, University of Padova (Italy).- Organic extracts were dried over anhydrous Na_2SO_4.- Evaporation of the solvents under reduced pressure.- Chemical and physical data of compounds: Tables 1-4 and 6.

cis/trans-[2-(1,1'-Biphenyl-4-yl)-2-bromomethyl-1,3-dioxolan-4-yl] methanoles (**5**)

A mixture of 1-(1,1'-biphenyl-4-yl)-2-bromoethan-1-one (40.0 g; 0.145 mol), anhydrous 1,2,3-propanetriol (40.0 g; 0.43 mol), *p*-toluenesulfonic acid monohydrate (2 g) and toluene (200 ml) was refluxed overnight with azeotropic removal of water by a Dean-Stark trap. After cooling, the mixture was filtered, the solution was washed with brine and dried. Removal of the solvent gave a residue, which was purified on alumina column/chloroform. The central eluates were collected to provide 40 g of **5** (*cis-trans* mixture) as a viscous oil, which solidified on standing (m.p. 65-68°C). No attempt was made to further purify or separate the isomers of **5**.

cis/trans-[2-(1,1'-Biphenyl-4-yl)-2-bromomethyl-1,3-dioxolan-4-yl]methyl Benzoates (**6**)

Benzoyl chloride (14.0 g; 0.10 mol) was added dropwise to an ice-cooled solution of **5** (31.4 g; 0.09 mol) in dry pyridine (60 ml). The mixture was stirred at 0°C for 2.5 h, then diluted with water. After extraction with chloroform the org. layer was washed with 6 N HCl and with brine and then dried. Evaporation of the solvent gave 39.0 g of the *cis-trans* mixture of **6** as an oil, which was used in the next step without further purification.

cis- **7** *and trans-[2-(1,1'-Biphenyl-4-yl)-2(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl Benzoates* (**8**)

A solution of **6** (23.5 g; 0.052 mol) and imidazole (10.6 g; 0.156 mol) in dry N,N-dimethylacetamide (300 ml) was refluxed for 4 days. Evaporation of the solvent gave a residue which was dissolved in chloroform. The solution was washed with brine, dried, and evaporated to provide a residue which was chromatographed on a silica gel column (88 x 5 cm)/ethyl acetate. After discarding initial fractions, subsequent elution furnished the *cis* isomer **7** (6.4 g; 28%) as an oil. Further eluates gave the *trans* isomer **8** (2.7 g; 12%) as a solid (Table 6).

cis-[2-(1,1'-Biphenyl-4-yl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methanol (**9**)

A solution of **7** (3.2 g; 0.007 mol) in 1,4-dioxane (28 ml) and water (5.6 ml) was heated with 50% NaOH solution (5.6 ml) at 100°C for 0.5 h. After cooling, the mixture was diluted with water and the resultant solid was filtered and then dissolved in chloroform. The org. phase was washed with brine, dried and the solvent evaporated to yield 1.7 g (70%) of *cis* isomer **9** after crystallization (Table 6).

trans-[2-(1,1'-Biphenyl-4-yl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methanol (**10**)

Prepared as **9** in 96% yield starting from **8** (Table 6).

cis-[2-(1,1'-Biphenyl-4-yl)-2(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl Methanesulfonate **11**

Methanesulfonyl chloride (2.3 g; 0.02 mol) was added dropwise during 10 min to a well-stirred cooled (0-5°C) solution of **9** (6.3 g; 0.018 mol) in dry pyridine (100 ml). After stirring for 5 h at room temp., water was added and the resultant solid was filtered. Dissolution of the solid in chloroform gave a solution, which was washed with brine, dried, and then evaporated to afford 7.4 g (95%) of *cis* isomer **11** after crystallization (Table 6).

trans-[2-(1,1'-Biphenyl-4-yl)-2(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl Methanesulfonate **12**

Prepared as **11** in 77% yield starting from **10** (Table 6).

cis-1-Acetyl-4-{4-[[2-(1,1'-biphenyl-4-yl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl}piperazine (**3**)

1-Acetyl-4-(4-hydroxyphenyl)piperazine (1.48 g; 0.0067 mol) was added to a suspension of NaH (80% in white oil) (0.25 g; 0.008 mol) in dry DMSO (41 ml). The suspension was stirred at room temp. for 1 h, then **11** (2.8 g; 0.0067 mol) was added and stirring was continued for 5 h at 80°C. The mixture was cooled and water was added. After extraction with chloroform, the org. layer was washed with brine, dried, and evaporated. The crude residue was purified on a silica gel column/ethyl acetate:ethanol 9:1. Initial fractions were discarded and the central fractions gave 2.1 g (60%) of *cis*-isomer **3** (Table 6).

trans-1-Acetyl-4-{4-[[2-(1,1'-biphenyl-4-yl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl}piperazine (**4**)

Prepared as described for **3** in 61% yield starting from **12**. Chromatography: the fractions collected by elution with ethyl acetate/ethanol 9:1 were discarded and elution was continued with ethyl acetate/ethanol 1:1. Evaporation furnished **4** as a glassy material (Table 6).

1-(4-Hydroxyphenyl)piperazine Dihydrobromide

A solution of commercially available 1-(4-methoxyphenyl)piperazine (90%, 17.0 g; 0.058 mol) in 48% HBr (200 ml) was refluxed overnight. After evaporation, the residue was triturated with aceton, filtered, and washed with aceton. 1-(4-Hydroxyphenyl)piperazine dihydrobromide was obtained as a white solid (19.7 g; 100% yield) (Table 6).

1-(4-Acetoxyphenyl)-4-acetylpiperazine

A mixture of 1-(4-hydroxyphenyl)piperazine dihydrobromide (17.0 g; 0.05 mol), anhydrous sodium acetate (8.2 g; 0.1 mol), and glacial acetic acid (50 ml) was stirred at room temp. for 30 min. Acetic anhydride (50 ml) was added and the mixture was refluxed for 45 min. After evaporation, cooled (0-5°C) water and solid $NaHCO_3$ were added (ice-cooling). Extraction with chloroform, followed by washing with brine, drying, and evaporation gave 13.1 g (100%) of 1-(4-acetoxyphenyl)-4-acetylpiperazine as an oil which solidified after trituration with CCl_4 (Table 6).

1-Acetyl-4-(4-hydroxyphenyl)piperazine

A mixture of 1-(4-acetoxyphenyl)-4-acetylpiperazine (15.3 g; 0.058 mol), $KHCO_3$ (8.7 g; 0.087 mol), methanol (320 ml), and water (32 ml) was stirred at room temp. overnight. After evaporation, the residue was

Table 1: ^{1}H-NMR Data for compounds **3, 4, 7-14.**

Nr.	δ
3	2.14 (3H, s, $COCH_3$), 3.05 (4H, m, piperazine 3-H and 5-H), 3.25 and 3.68 (2H, AM of AMX, J_{AM} = 9.5 Hz, J_{AX} = 6.8 Hz, J_{MX} = 5.4 Hz, CH_2OPh), 3.62 (2H, m, piperazine 2-H and 6-H), 3.73-3.79 (3H, m, piperazine 2-H and 6-H, OC*H*HCHO), 3.91 (1H, dd, J = 8.3 and 6.4 Hz, OCH*H*CHO), 4.20 and 4.26 (2H, ABq, J = 14.9 Hz, CH_2N), 4.39 (1H, m, OCH_2CHO), 6.77 and 6.89 (AA'BB', J = 9.0 Hz, OPh), 7.01 (2H, br s, imidazole 4-H and 5-H), 7.35-7.64 (10H, m, ArH and imidazole 2-H).
4	2.12 (3H, s, $COCH_3$), 2.99 (4H, m, piperazine 3-H and 5-H), 3.58 (2H, m, piperazine 2-H and 6-H), 3.68-3.76 (4H, m, piperazine 2-H and 6-H, OC*H*HCHO, C*H*HOPh), 3.86-3.94 (2H, m, OCH*H*CHO, CH*H*OPh), 4.18 (1H, m, OCH_2CHO), 4.21 (2H, s, CH_2N), 6.72 and 6.81 (AA'BB', J= 9.1 Hz, OPh), 7.04 (2H, m, imidazole 4-H and 5-H), 7.35-7.60 (10H, m, ArH and imidazole 2-H).
7	3.70 and 3.94 (2H, AM of AMX, J_{AM} = 8.3 Hz, J_{AX} = 5.4 Hz, J_{MX} = 6.8 Hz, OCH_2CHO), 4.10 and 4.15 (2H, AB of ABX, J_{AB} = 11.7 Hz, J_{AX} = 5.3 Hz, J_{BX} = 5.6 Hz, CH_2OCOPh), 4.24 (2H, s, CH_2N), 4.38 (1H, m, OCH_2CHO), 6.99 (2H, s, imidazole 4-H and 5-H), 7.34-8.04 (15 H, m, ArH and imidazole 2-H).
8	3.76 and 3.94 (2H, AM of AMX, J_{AM} = 8.0 Hz, J_{AX} = 8.0 Hz, J_{MX} = 6.1 Hz, OCH_2CHO), 4.11 (1H, m, OCH_2CHO), 4.19 (2H, s, CH_2N), 4.20 and 4.38 (2H, BC of ABC, J_{BC} = 12.1 Hz, J_{AB} = 4.3 Hz, J_{AC} = 4.2 Hz, CH_2OCOPh), 7.05 (2H, app d, J= 3.6 Hz, imidazole 4-H and 5-H), 7.25-7.74 (15 H, m, ArH and imidazole 2-H).
9	2.03 (1H, m, O*H*), 3.27 and 3.43 (2H, AB of ABX, J_{AB} = 11.8 Hz, J_{AX} = 5.2 Hz, J_{BX} 4.1 Hz, CH_2OH), 3.69 and 3.83 (2H, AB of ABX, J_{AB} = 8.0 Hz, J_{AX} = 5.4 Hz, J_{BX} = 8.0 Hz, OCH_2CHO), 4.16 (1H, m, OCH_2CHO), 4.19 and 4.26 (2H, ABq, J = 14.8 Hz, CH_2N), 7.04 (2H, app d, J = 2.3 Hz, imidazole 4-H and 5-H), 7.35-7.64 (10H, m, ArH and imidazole 2-H).
10	1.93 (1H, m, O*H*), 3.45 and 3.59 (2H, AB of ABX, J_{AB} = 12.1 Hz, J_{AX} = 4.6 Hz, J_{BX} = 3.6 Hz, CH_2OH), 3.67 (1H, t, J = 10.2 Hz, OC*H*HCHO), 3.87 (2H, m, OCH*H*CHO and OCH_2CHO), 4.18 (2H, s, CH_2N), 7.01 (2H, app d, J = 4.3 Hz, imidazole 4-H and 5-H), 7.35-7.62 (10H, m, ArH and imidazole 2-H).
11	3.03 (3H, s, OSO_2CH_3), 3.64 and 3.80 (2H, AB of ABX, J_{AB} = 10.6 Hz, J_{AX} = 5.5 Hz, J_{BX} = 5.8 Hz, $CH_2OSO_2CH_3$), 3.72 and 3.87 (2H, AB of ABX, J_{AB} = 8.7 Hz, J_{AX} = 4.3 Hz, J_{BX} = 6.8 Hz, OCH_2CHO), 4.20 and 4.26 (2H, ABq, J = 14.9 Hz, CH_2N), 4.34 (1H, m, OCH_2CHO), 7.04 (2H, app d, J = 3.9 Hz, imidazole 4-H and 5-H), 7.36-7.64 (10H, m, ArH and imidazole 2-H).
12	2.83 (3H, s, OSO_2CH_3), 3.66 and 3.86 (2H, AM of AMX, J_{AM} = 8.3 Hz, J_{AX} = 6.3 Hz, J_{MX} = 5.6 Hz, OCH_2CHO), 4.06 (2H, s, $CH_2OSO_2CH_3$), 4.07 (1H, m, OCH_2CHO), 4.19 (2H, s, CH_2N), 7.03 (2H, app d, J = 11.0 Hz, imidazole 4-H and 5-H), 7.36-7.63 (10H, m, ArH and imidazole 2-H).
13	3.67 and 3.91 (2H, AM of AMX, J_{AM} = 8.3 Hz, J_{AX} = 5.6 Hz, J_{MX} = 6.6 Hz, OCH_2CHO), 4.11 and 4.17 (2H, AB of ABX, J_{AB} = 11.7 Hz, J_{AX} = 5.2 Hz, J_{BX} = 5.6 Hz, CH_2OCOPh), 4.35 (1H, m, OCH_2CHO), 4.44 and 4.52 (2H, ABq, J = 14.6 Hz, CH_2N), 6.96 (2H, br s, imidazole 4-H and 5-H), 7.20-8.04 (9H, m, ArH and imidazole 2-H).
14	1.90 (1H, m, O*H*), 3.31 and 3.40 (2H, AB of ABX, J_{AB} = 11.7 Hz, J_{AX} = 5.1 Hz, J_{BX} = 4.4 Hz, CH_2OH), 3.65 and 3.81 (2H, AB of ABX, J_{AB} = 8.0 Hz, J_{AX} = 5.8 Hz, J_{BX} = 7.0 Hz, OCH_2CHO), 4.12 (1H, m, OCH_2CHO), 4.39 and 4.51 (ABq, J = 14.7 Hz, CH_2N), 7.01 (2H, app d, J = 3.0 Hz, imidazole 4-H and 5-H), 7.24-7.60 (4H, m, ArH and imidazole 2-H).

Table 2: Eu(DPM)3 induced paramagnetic shifts of esters **7**, **8**, and **13**[a]

Nr.	Molar Ratio[b]	-OCH$_2$CHO-		-OCH$_2$CHO-		-CH$_2$OCO Ph		$-CH_2N\langle$	
		δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ
7	0.0	3.70, 3.94[c]	-	4.38[c]	-	4.10, 4.15[c]	-	4.24[c]	-
	0.2	4.01, 4.11	0.31, 0.17	4.57	0.19	4.40	0.30, 0.25	4.76	0.52
	0.4	4.52, 4.40	0.82, 0.46	4.86	0.48	4.86	0.76, 0.71	5.64	1.40
8	0.0	3.76, 3.94[c]	-	4.11[c]	-	4.20, 4.38[c]	-	4.19[c]	-
	0.2	3.93, 4.27	0.17, 0.33	4.51	0.40	4.30, 4.49	0.10, 0.11	4.71	0.52
	0.4	4.21, 4.76	0.45, 0.82	5.14	1.03	4.46, 4.66	0.26, 0.28	5.52	1.33
13	0.0	3.67, 3.91[c]	-	4.35[c]	-	4.11, 4.17[c]	-	4.44, 4.52[c]	-
	0.2	4.02, 4.09	0.35, 0.18	4.53	0.18	4.42	0.31, 0.25	4.96, 5.05	0.52, 0.53
	0.4	4.60, 4.40	0.93, 0.49	4.93	0.58	4.87	0.76, 0.70	5.95	1.51, 1.43

[a] δ values relative to TMS in $CDCl_3$ and related Δδ values are expressed in ppm.
[b] Molar ratio of Eu(DPM)$_3$ to substrate.
[c] δ values (ppm) of uncomplexed substrate.

Table 3: Eu(DPM)3 induced paramagnetic shifts of alkohols **9**, **10**, and **14**[a]

Nr.	Molar Ratio[b]	-OCH$_2$CHO-		-OCH$_2$CHO-		-CH$_2$OH		-CH$_2$N$\langle$	
		δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ
9	0.0	3.69, 3.83[c]	-	4.16[c]	-	3.27, 3.43[c]	-	4.19, 4.26[c]	-
	0.2	3.98	0.29, 0.15	4.33	0.17	3.58, 3.64	0.31, 0.21	4.62, 4.67	0.43, 0.41
	0.4	4.44, 4.26	0.75, 0.43	4.65	0.49	4.08	0.81, 0.65	5.44, 5.45	1.25, 1.19
10	0.0	3.67, 3.87[c]	-	3.87[c]	-	3.45, 3.59[c]	-	4.18[c]	-
	0.2	3.91, 4.24	0.24, 0.37	4.41	0.54	3.65, 3.80	0.20, 0.21	4.75	0.57
	0.4	4.28, 4.78	0.61, 0.91	5.20	1.33	3.95, 4.12	0.50, 0.53	5.63	1.45
14	0.0	3.65, 3.81[c]	-	4.12[c]	-	3.31, 3.40[c]	-	4.39, 4.51[c]	-
	0.2	4.03	0.38, 0.22	4.34	0.22	3.70	0.39, 0.30	4.97, 5.07	0.58, 0.56
	0.4	4.58, 4.31	0.93, 0.50	4.67	0.55	4.23, 4.15	0.92, 0.75	5.79, 5.92	1.40, 1.41

[a] δ values relative to TMS in $CDCl_3$ and related Δδ values are expressed in ppm.
[b] Molar ratio of Eu(DPM)$_3$ to substrate.
[c] δ values (ppm) of uncomplexed substrate.

Table 4: ^{13}C Chemical shift differences of compounds **7/8**, **9/10**, **13/15**, **14/16**[a]

Cis-trans Isomers	1,3-Dioxolane Ring Carbons			Methylene C's on Ring	
	C-2	C-4	C-5	2-CH$_2$	4-CH$_2$
7/8	0.0	-1.6	0.1	-0.9	1.1
9/10	-0.3	-2.0	-0.7	-1.2	0.2
13/15[b]	-0.1	-1.6	0.2	-0.8	1.3
14/16[b]	-0.2	-1.5	-0.2	-0.9	0.2

[a] Δδ values (ppm) in $CDCl_3$ solution.
[b] Values reported by *Chapman* and *Bauer*[14].

Table 5: Antimycotic activities of derivatives **3, 4, 7-12** at pH 7.2 and pH 5.8 against 44 strains of *Candida albicans* and 6 strains of *Candida spp.* (1 *C. glabrata*, 1 *C. parapsilosis*, 1 *C. stellatoidea*, 1 *C. guiliermondii*, 2 *C. lipolytica*)

pH 7.2

Tested substance	Fungi (n° of strains tested)									
	Candida albicans (44)					*Candida* spp. (6)				
	Range (µg/ml)	nX	MIC_{50}	MIC_{90}	R%	Range (µg/ml)	nX	MIC_{50}	MIC_{90}	R%
a	1-8	5.7	4	8	0	1-8	4.3	4	8	0
b	0.25-8	4.1	4	8	0	1-4	2.3	2	4	0
c	0.25-32	5.6	2	16	0	2-32	16.2	8	32	0
3	8->256	>256	>256	>256	61.3	128->256	>256	>256	>256	66.7
4	2-128	29.7	32	64	0	8->256	218.4	32	>256	40
7*	4->256	100.3	16	>256	12.9	8->256	166	128	>256	25
8	4-32	15.9	16	32	0	8-32	16	16	32	0
9	4->256	143.9	32	>256	23.7	8->256	166.4	128	>256	20
10	2->256	151.1	32	>256	24.3	4->256	>256	>256	>256	60
11	0.5->256	>256	>256	>256	57.9	256->256	>256	>256	>256	80
12	4-128	94.1	64	128	0	32->256	166.4	128	>256	20

pH 5.8

Tested substance	Fungi (n° of strains tested)									
	Candida albicans (44)					*Candida* spp. (6)				
	Range (µg/ml)	nX	MIC_{50}	MIC_{90}	R%	Range (µg/ml)	nX	MIC_{50}	MIC_{90}	R%
a	0.5-8	4.4	2	8	0	0.5-16	8.1	4	16	0
b	1-16	4.76	4	8	0	4-16	11	4	16	0
c	0.5-32	6.92	1	16	0	2-32	11	2	32	0
3	32->256	>256	>256	>256	54	256->256	>256	>256	>256	80
4	4-256	53.9	32	128	0	8->256	>256	>256	>256	60
7*	0.25-32	7.6	8	16	0	4-16	8.8	8	16	0
8	2-64	18.6	8	64	0	2-64	28.4	8	64	0
9	8->256	79.8	64	128	2.5	64->256	217	128	>256	20
10	32-256	102	128	128	0	32->256	160	64	>256	20
11	4->256	198	64	>256	28.2	16->256	233	64	>256	40
12	16->256	110.4	64	256	2.5	16->256	>256	>256	>256	60

a = miconazole; b = bifonazole; c = ketoconazole; * mononitrate

Table 6: Analytical Data

Nr.	Formula (mol. weight)	M.p. (°C) Solvent	Analysis (%): Found Calcd. C	H	N	Br	S
3	$C_{32}H_{34}N_4O_4$	193-194	71.20	6.26	10.35	-	-
	(538.62)	butan-2-one	71.35	6.36	10.40	-	-
4	$C_{32}H_{34}N_4O_4$	-	71.15	6.15	10.29	-	-
	(538.62)	-	71.35	6.36	10.40	-	-
7	$C_{27}H_{25}N_3O_7$ [a]	151-153	64.16	4.88	8.53	-	-
	(503.49)	propan-2-ol	64.40	5.01	8.35	-	-
8	$C_{27}H_{24}N_2O_4$	125-126	73.41	5.56	6.30	-	-
	(440.40)	cyclohexane	73.62	5.49	6.36	-	-
9	$C_{20}H_{20}N_2O_3$	178-179	71.11	6.13	8.14	-	-
	(336.38)	toluene	71.41	5.99	8.33	-	-
10	$C_{20}H_{20}N_2O_3$	179-181	71.69	6.12	8.41	-	-
	(336.38)	toluene	71.41	5.99	8.33	-	-
11	$C_{21}H_{22}N_2O_5S$	112-114	60.66	5.44	6.70	-	7.49
	(414.46)	benzene/petroleum ether	60.85	5.35	6.76	-	7.73
12	$C_{21}H_{22}N_2O_5S$	137-140	61.04	5.62	6.55	-	7.43
	(414.46)	benzene/petroleum ether	60.85	5.35	6.76	-	7.73
*	$C_{10}H_{16}Br_2N_2O$	300-302	35.09	4.58	8.32	47.08	-
	(340.07)	ethanol	35.31	4.74	8.23	46.99	-
**	$C_{14}H_{18}N_2O_3$	74-76	63.90	6.72	10.55	-	-
	(262.30)	toluene/ligroin	64.10	6.92	10.68	-	-
***	$C_{12}H_{16}N_2O_2$	184-186	65.26	7.45	12.78	-	-
	(220.26)	ethanol	65.43	7.32	12.72	-	-

[a] mononitrate.

* 1-(4-Hydroxyphenyl)piperazine Dihydrobromide: lit.[8]: mp 286-289 °C; ref. therein cited: 291-293 °C.

** 1-(4-Acetoxyphenyl)-4-acetylpiperazine: lit.[8]: analytical data are not reported.

*** 1-Acetyl-4-(4-hydroxyphenyl)piperazine: lit.[8]: mp 177-178 °C; ref. therein cited: mp 181.3 °C.

dissolved in methanol and the solution passed on Celite® 545. Evaporation gave a crude product, which was crystallized to furnish 11.7 g (92%) of 1-acetyl-4-(4-hydroxyphenyl)piperazine (Table 6).

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