Synthesis and in Vitro and in Vivo Structure−Activity Relationships of Novel Antifungal Triazoles for Dermatology

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In search for new compounds with potential for clinical use as antifungal agents in dermatology, a series of 12 azole compounds were synthesized stereospecifically and investigated specifically for their activity against dermatophyte fungal infections in animal models. This panel of azoles was studied in vitro and compared with itraconazole and terbinafine for their antifungal activity using a panel of 24 *Candida spp.* and 182 dermatophyte isolates. Three azoles (**1c**, **2c,** and **4c**) showed in vitro antifungal potency equivalent to itraconazole, but superior to terbinafine, against a panel of 24 *Candida spp.* with comparable or lower activity than that of itraconazole and terbinafine against 182 dermatophyte isolates and only rare activity against other pathogenic fungi. However, in vivo **1c** and **4c**, both given orally, demonstrated antifungal activity at least three times greater than itraconazole and were superior compared to terbinafine in *M. canis* infected guinea pigs. In a mouse model infected by *T. mentagrophytes*, again **4c**, but not **1c**, showed 5-fold superior activity over itraconazole and terbinafine. Compound **2c** was effective in both models but less effective than itraconazole in these models. On the basis of these promising results, **4c** is currently being clinically investigated for its potential as a novel antifungal agent against dermatophytosis.

Introduction

Traditionally, mycotic diseases have been divided into three broad categories including: cutaneous and mucocutaneous, subcutaneous, and systemic fungal infections. Although today's antifungal research is mainly focused on systemic fungal infections,[1] dermatomycoses are among the most widespread and common human superficial and cutaneous fungal infections.[2,3,4] These typically nonfatal conditions are difficult to treat, especially infections of toenails. Dermatomycoses are caused by filamentous fungi such as *Trichophyton*, *Microsporum*, or *Epidermophyton* species. For instance, tinea pedis, commonly known as "athlete's foot", is most frequently caused by either *Trichophyton* or *Epidermophyton* species. These filamentous fungi have a high affinity for keratin, an important component of hair, skin, and nails, which are the primary areas of infection by dermatophytes.

The antifungal agents currently marketed for dermatomycoses are mainly inhibitors of ergosterol biosynthesis,[5] except for griseofulvin, which interferes with mitotic separation of chromosomes.[6] Three different types of inhibitors of the ergosterol biosynthetic pathway have been proven to be clinically effective. These are azoles[7,8] such as ketoconazole,[9] itraconazole,[10] and fluconazole,[11] which act as 14-α-demethylase inhibitors; allylamines such as terbinafine,[12] which act as a squalene epoxidase inhibitor; and morpholines such as amorolfine,[13] a Δ^{14}-reductase and Δ^{8-7}-isomerase inhibitor. However, extensive use and prolonged therapy with azoles have led to resistance.[14] Hence, more effective antifungal azoles with fewer adverse effects and short-term action are deemed necessary to treat dermatophytosis. The second-generation antifungal azoles such as voriconazole,[15,16] posaconazole,[17] and ravuconazole[18] have shown broad spectrum antifungal activity comparable or slightly superior to itraconazole (Sporanox) against *Candida* species. These agents are marketed or currently in late stage clinical trials against life threatening systemic fungal infections. Voriconazole[19] and ravuconazole[20] have MIC values against dermatophytes comparable or lower than that of itraconazole, whereas antidermatophyte acitivity for posaconazole has not yet been reported.[21]

In the search for new compounds with potential for clinical use as antifungal agents in dermatology, a huge compound database was scanned for antifungal compounds with impressive activity against dermatophytes but not necessarily against *Candida*. Moreover, the overriding selection criterion was excellent activity against experimental guinea pig dermatophytosis models in vivo. This search was nominally structure−activity relationship (SAR)-based—structures supporting activity versus one fungal group without regard to

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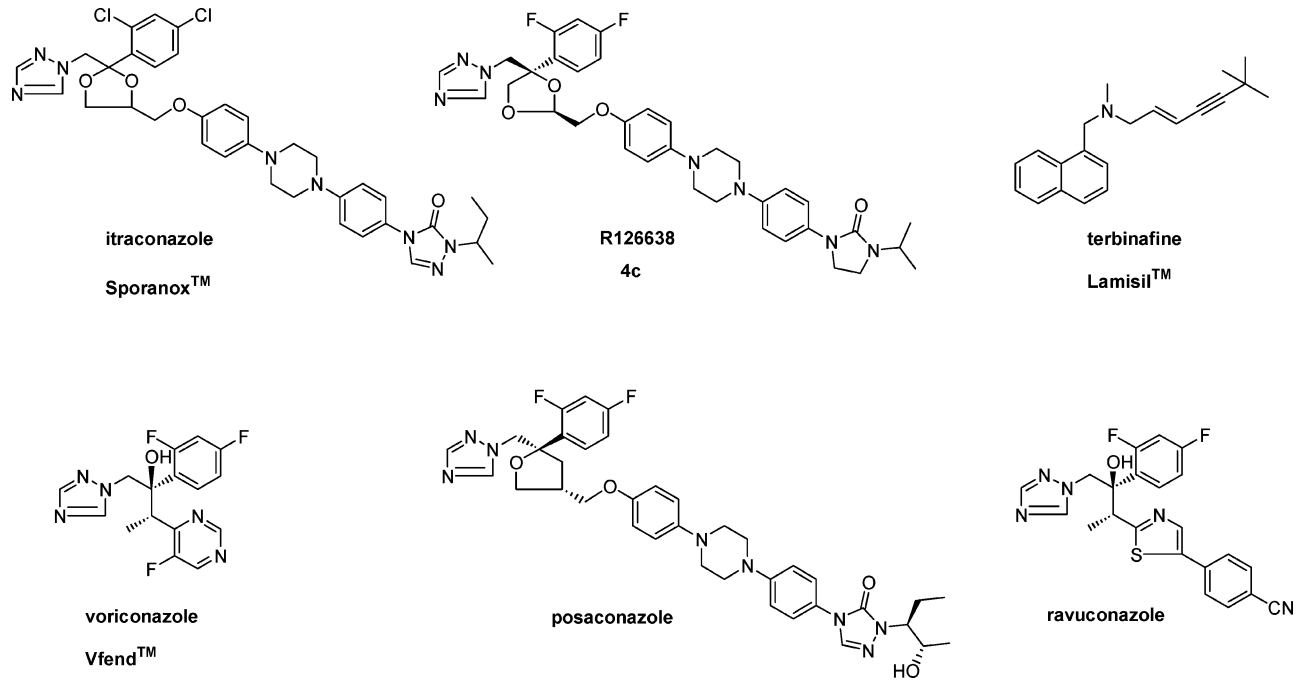


Figure 1.

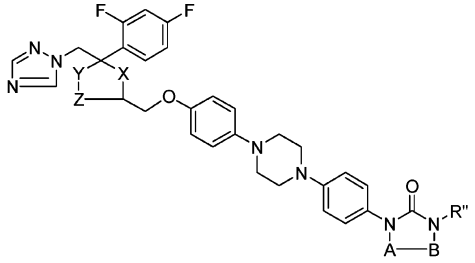
another. Having found prototype molecules, we designed new versions of them that incorporated the best modifications science has given us for azole antifungals over the years: 2,4-difluorophenyl substituted dioxolanes, triazole in place of imidazoles, and replacement of the triazolone moiety by other lypophilic heterocyclic moieties. In times of high-throughput screening and combinatorial chemistry, it might be surprising that only 12 combinations were needed to discover **4c**, a novel triazole for dermatomycoses.[22] In this paper, we report the synthesis and limited structure−activity relationships of derivatives and other antifungal compounds related to **4c**, which were tested for in vitro antifungal activity and against in vivo models for superficial mycoses and compared with itraconazole and terbinafine as drug standards.

Chemistry

The 12 target compounds, **1a**,**b**,**c**, **2a**,**b**,**c**, **3a**,**b**,**c**, and **4a**,**b**,**c**, are described in Table 1. Their syntheses are straightforward combinations of two enantiomeric pairs of *cis*-1,3-dioxolane-4-yl (**5b** and **6a**) and *cis*-1,3-dioxolane-2-yl (**8a** and **b**) with three phenolic heterocyclic substituents **12**, **15**, and **18**. Access to the enantiomerically pure dioxolanes was key in the synthesis of these novel azoles. Literature precedent[23,24] for the stereoselective synthesis of ketoconazole by transketalisation with optically pure solketal tosylates assisted us in the synthesis of 2,4-difluorophenyl dioxolane intermediates **5** and **6**. Recently, the same method was further optimized and used in the stereoselective synthesis of hydroxyitraconazole.[25] Ketalization of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone with (*R*)- and (*S*)-glyceryl tosylate[26,27] or mesylate[28,29] in a mixture of methanesulfonic acid and dichloromethane gave cis and trans diastereoisomers in an approximately 1.5:1 ratio, respectively, with moderate yields. For compound **6a**, NOESY correlations were observed between the 4-H dioxolane proton and the ortho proton of the 2,4-difluorophenyl ring, which was found to possess a cis configuration. The diol **7**, the precursor for intermediates **8a** and **8b**, has been documented in the literature to be a key intermediate in the synthesis of azole antifungals, and both racemic and enantioselective syntheses have been described.[30−35] In our hands, the diol **7** was obtained via two routes starting with 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone. In the first approach, the cyanohydrine of the ketone was formed. Hydrolysis of the nitrile and reduction of the carboxylic acid gave the diol compound **7** in 60% overall yield for the three-step synthesis. Alternatively, we used trimethylsulfoxonium iodide to form the epoxide, which was hydrolyzed with aqueous sulfuric acid at 60 °C to give the diol **7** with 50% overall yield for the two-step synthesis (Scheme 1). Acetalization of **7** with 1-bromo-2,2-diethoxyethane in the presence of methanesulfonic acid in dichloromethane at room temperature gave a mixture of *cis*- and *trans*-1,3-dioxolane-2-yl in a 1:1.9 ratio. Separation of the cis enantiomers on a Daicel Chiralcel OD HPLC column gave both enantiomers **8a** and **8b** in poor yield. The trans isomer was reclycled into a diasteroisomeric 1.3:1 cis and trans mixture under thermodynamic conditions in dichloromethane and methanesulfonic acid at reflux temperature for 2 days. NOESY experiments with compound **8a** revealed a clear correlation between the 2-H dioxolane proton and the ortho proton of the 2,4-difluorophenyl ring, confirming the cis configuration. In addition, X-ray diffraction measurements established the absolute configuration of **8a** as 2*S*-*cis*-1,3-dioxolane-2-yl.

The heterocyclic phenols **12**, **15**, and **18** were synthesized starting from the aniline **9**[36] using conventional heterocyclic synthesis as depicted in Scheme 2. As shown in Table 1, the target series **1**, **2**, **3**, and **4** were synthesized via a nucleophilic subtitution of the enantiomerically pure dioxolanes **5b**, **6a**, **8a**, and **8b** in combination with the heterocyclic phenols **12**, **15**, and **18**. All reactions were performed in dry dimethyl for-

Table 1. Target Compounds[3]



compounds		starting compound	Reaction time (procedure)	$[\alpha]_D^{20}$ (DMF)	Yield[(1)]
1a	*2S-cis*-1,3-dioxolan-4-yl	**12**	6h(a)	-10.69	61%
1b	*2S-cis*-1,3-dioxolan-4-yl	**15**	18h(a)	-10.69[(2)]	51%
1c	*2S-cis*-1,3-dioxolan-4-yl	**18**	16h(b)	-14.23	75%
2a	*2R-cis*-1,3-dioxolan-4-yl	**12**	18h(a)	11.55	43%
2b	*2R-cis*-1,3-dioxolan-4-yl	**15**	20h(a)	11.39	59%
2c	*2R-cis*-1,3-dioxolan-4-yl	**18**	16h(b)	13.54	70%
3a	*2R-cis*-1,3-dioxolan-2yl	**12**	6h(a)	-13.92	27%
3b	*2R-cis*-1,3-dioxolan-2yl	**15**	20h(a)	-14.52	49%
3c	*2R-cis*-1,3-dioxolan-2yl	**18**	16h(a)	-15.86	34%
4a	*2S-cis*-1,3-dioxolan-2-yl	**12**	6h(c)	14.73	14%
4b	*2S-cis*-1,3-dioxolan-2-yl	**15**	6h(c)	15.73	40%
4c	*2S-cis*-1,3-dioxolan-2-yl	**18**	16h(b)	17.83	63%

[1] Yields are calculated based upon mass of isolated and recrystalized compounds and were not optimized. [2] MeOH. [3] General procedure: (a) stirred in the presence of NaHMDS in DMF at 60 °C; (b) stirred in the presence of NaOH pellets in DMF at 60 °C; (c) stirred in the presence of NaH in DMF at 60 °C.

mamide in the presence of a base at 60 °C and gave moderate to good yields. Utilizing sodium hydroxide pellets as the base gave consistently better yields than either sodium bis(trimethylsilyl)amide or sodium hydride (Table 1).

Results and Discussion

The novel azoles series **1**, **2**, **3**, and **4** were screened against a panel of 182 dermatophytes consisting of *Epidermophyton*, *Microsporum*, and *Trichophyton* species (Table 2). These anamorphic genera were selected because they are the main cause for dermatophytic infections: tinea capitis, tinea barbae, tinea corporis, tinea cruris, tinea pedis, and onychomycosis. In addition, their potential antifungal activity against systemic fungal infections was determined via a panel of 24 *Candida* species, 8 *Aspergillus* species, and 13 other fungi including *Cryptococcus*, *Sporothrix*, and *Fusarium* species (Table 3). For all fungi, the susceptibility test method used was a microplate broth dilution method described previously.[22,37] This method is based on the recommendation of the National Committee for Clinical Laboratory Standards 2002 (NCCLS) and gives comparable results with the quality control yeast strains recommended by the NCCLS.[38]

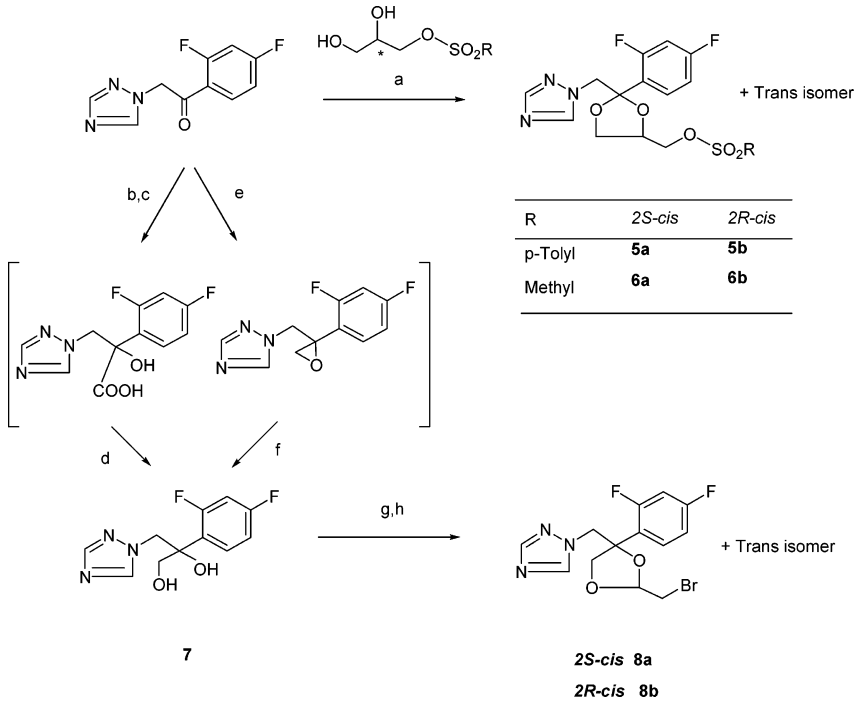
The imidazolidinone triazoles (c series: **1c**, **2c,** and **4c**) demonstrated a consistently greater potency compared to the pyrimidinetrione triazoles (a series) and triazinetrione triazoles (b series) against all dermatophytes tested (Table 2). For the 2*S-cis*-1,3-dioxolane-2-yl triazole series (**4a**,**b**,**c**), consistently high stereoselective antifungal activity against both yeasts and molds in vitro was found as opposed to the 2*R-cis* series (**3a**,**b**,**c**), which were almost inactive, especially for **3c** and **4c** when compared with the 1,3-dioxolane-4-yl congeners **1c** and **2c** the influence of stereochemistry was striking. The in vitro activity against *Epidermophyton* species for compounds **1c** and **4c** was comparable to itraconazole and terbinafine, both compounds were weaker against *Microsporum* species (Table 2). The overall activity of **1c** and **4c** against *Trichophyton* species was less than that of itraconazole, especially when compared to terbinafine (Table 2). Compound **2c** showed an overall lower potency, except for *Microsporum* species, when compared to itraconazole. Compounds **1c**, **2c**, and **4c** had similar potency against *Candida* species in vitro. A clearly lower effect was observed with these compounds on *A. fumigatus*, and a lack of activity against a panel of other fungi such as *Cryptococcus*, *Sporothrix*, and *Fusarium* species (Table 3) was observed with these compounds.

On the basis of the promising in vitro results, the same panel of novel triazoles was tested for their efficacy against dermatophyte infections in a guinea pig model infected with *Microsporum canis* and a mouse model infected with *Trichophyton mentagrophytes* (var. *T. quinckeanum*) according to the method previously described by Odds et al.[22] Tables 4 and 5 show results of various prophylactic oral treatment experiments, in which treatment was started at day 0, in the cutaneous infection models of *M. canis* in guinea pig and *T. mentagrophytes* in mice, respectively. In these tables, the effective dosages (ED_{50} values) of oral treatment experiments with various novel triazoles in comparison to itraconazole and terbinafine are given.

In the first model, it was confirmed that imidazolidinones (c series) have superiority over pyrimidinetrione and triazinetrione a and b series, respectively. In the cutaneous *M. canis* infection model in guinea pigs, compound **1c** (ED_{50} 0.33 to 0.44 mg/kg) was almost equipotent with **4c**, ED_{50} 0.31 mg/kg at all time intervals, and was at least two times more effective than its enatiomer **2c**, ED_{50} 0.89−1.29 mg/kg. In comparison to itraconazole, **4c** showed higher antifungal activity by at least a factor of 4. In this model, terbinafine was even shown to be less effective than itraconazole.

To confirm the promising in vivo results, the most active compounds were retested in the *T. mentagrophytes* mouse model (Table 5). From these experiments, confirmatory results were obtained. Compound **4c** was the most effective azole with an ED_{50} of <0.63 mg/kg, thereby showing superiority over itraconazole, ED_{50} 2.60 mg/kg, and terbinafine, $ED_{50} > 5.00$ mg/kg. After orally dosing for 4 days at 2.5 mg/kg in mice, evidence for the greater in vivo activity of **4c** over itraconazole was found with 5-fold and 3-fold higher plasma and skin levels in

Scheme 1. Synthesis of Dioxolane Intermediates[a]



R	*2S-cis*	*2R-cis*
p-Tolyl	**5a**	**5b**
Methyl	**6a**	**6b**

[a] Reagents and conditions: (a) CH_3SO_3H/CH_2Cl_2 (1.3:1 ratio), reflux, 20 h, 19% yield (for both **5a** and **5b**); (b) 2-hydroxy-2-methylpropionitrile, $NH_4OH_{cat.}$, room temperature, 50 h, 71% yield; (c) 12N HCl, reflux, 20 h, 96% yield; (d) $LiAlH_4$, THF, 24 h, 87% yield; or (e) $Me_3SO^+I^-$, 50% w/v NaOH, toluene, *N*-benzyltriethylammonium $chloride_{cat.}$, reflux, 24 h; (f) 10% v/v H_2SO_4/H_2O, room temperature, 50% yield (two-step synthesis); (g) CH_3SO_3H/CH_2Cl_2 (1:10 ratio), bromoacetaldehyde diethylacetal added at 0 to 10 °C, room temperature, 20 h; (h) Chiralcel OD **8a** (9% yield), **8b** (11% yield), (±)-trans (38% yield).

mice, 0.158 μg/mL and 0.093 μg/g, respectively. For itraconazole, plasma and skin levels were 0.0371 μg/mL and 0.032 μg/g, respectively.

Triazole **4c** was compared in vitro with itraconazole for their inhibitory effects on growth and ergosterol biosynthesis in *C. albicans* and *T. mentagrophytes* species and *Microsporum canis*.[39] In all species, inhibition of ergosterol synthesis coincided with the accumulation of 14-methylsterols, indicative for the P450 14α-demethylase, CYP51, as the target enzyme.

Conclusion

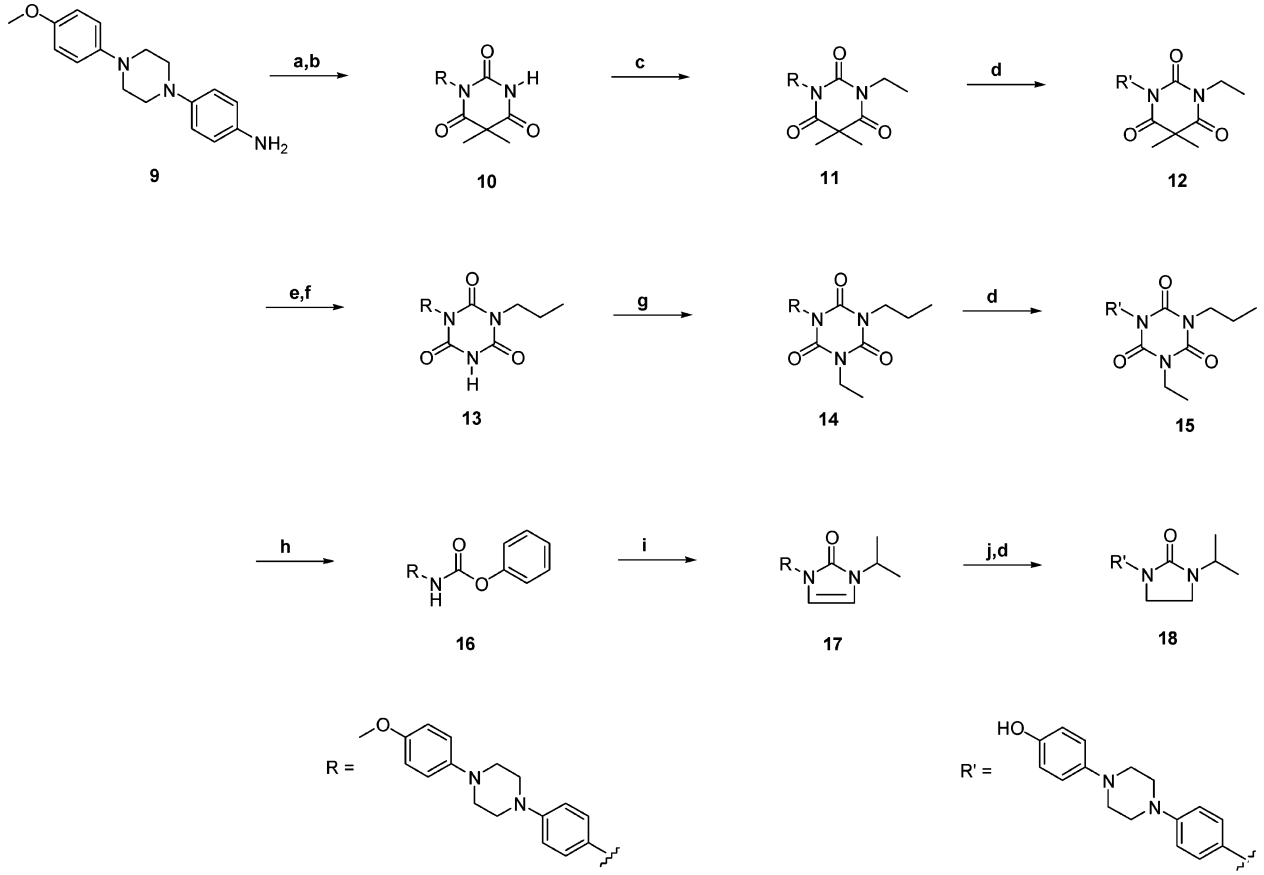
Twelve novel triazoles were compared in vitro and in vivo with itraconazole and terbinafine for their antifungal activity. The imidazolidinone series **1c**, **2c**, and **4c** showed antifungal potency equivalent to or slightly less than itraconazole against a panel of 24 Candida species, 2-fold or more lower activity against 182 dermatophyte isolates, and only rare activity against other pathogenic fungi. In animal models, **4c** consistently showed antifungal efficacy at least 4 times higher than that of itraconazole. These data indicate that if effects of **4c**, R126638, seen when it is used to treat animals can be extrapolated in humans, then it might be expected to show effects at doses lower than those used for existing drugs and, hence, present a lower risk for side effects.

Experimental Section

Chemistry. General Methods. Melting points were measured in open capillaries on a Buchi B545 instrument and are uncorrected. ^1H NMR spectra were recorded with Bruker Avance DPX 400 and 360 spectrometers, and chemical shifts (δ) are expressed in parts per million (ppm) with TMS as internal standard. Elemental analyses were performed with a Carlo-Erba EA1110 analyzer. Mass spectra were obtained with a Waters-Micromass ZQ mass spectrometer with an electrospray ionization source operated in positive and negative ionization modes. Mass spectra were acquired by scanning from 100 to 1000 mass units in 1 s using a dwell time of 0.1 s. The capillary needle voltage was 3 kV, and the source temperature was maintained at 140 °C. Nitrogen was used as the nebulizer gas. Cone voltage was 10 V for positive ionization mode and 20 V for negative ionization mode. Analytical results were within ±0.4% of the theoretical values, except when noted otherwise. Silica gel thin-layer chromatography was performed on precoated plates Kieselgel 60F254 (E. Merck, AG Darmstadt, Germany). Silica gel column chromatography was performed with Kiesel gel 60 (0.063−0.200 mm) (E. Merck, AG Darmstadt, Germany). Chiral HPLC purifications were performed on a Daicel cellulose normal phase Chiracel OD HPLC column purchased from Chiral Technologies Europe. Sensitive reactions were performed under nitrogen. Commercial solvents were used without any pretreatment. Brine is a saturated solution of sodium chloride in water. DMF (*N*,*N*-dimethylformamide), THF (tetrahydrofurane), MIK (4-methyl-2-pentanone), DIPE (diisopropyl ether), and 80% NaH (Sigma Aldrich) were washed free of oil with hexane prior to use.

(−)-(2*S*-*cis*)-1-Ethyl-3-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (1a). Sodium bis(trimethylsilyl)amide (24 mL, 0.024 mol) was added dropwise to a stirred mixture of **12** (5 g, 0.011 mol) in dry DMF (50 mL) at room temperature under inert nitrogen flow. The mixture was stirred for 10 min, and **6a** (5 g, 0.011 mol) was added. The mixture was stirred at 60 °C for 18 h in an oil bath, then cooled, poured out into H_2O, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated at reduced pressure. The residue was purified by silica gel column chromatography gradient elution, CH_2Cl_2/CH_3OH/EtOAc/hexane 49/1/30/20 toward 48/2/30/20, to give

Scheme 2. Synthesis of Phenol Precursors[a]



[a] Reagents and conditions: (a) KOCN, HCl, 4 h, room temperature, 100% yield; (b) 2,2-dimethylmalonyl chloride, sulfolane, 5 h, 50 °C, 83% yield; (c) NaH, EtI, DMF, 3 h, 85 °C, 40% yield; (d) 48% aqueous HBr, HBr/AcOH, $NaHSO_3$, 5 h, reflux; (e) *n*-PrNCO, CH_2Cl_2, overnight, room temperature, 86% yield; (f) chlorocarbonylisocyanate, 1,2-dichloroethane, 1 h, reflux, 88% yield; (g) EtBr, KOH, DMF, room temperature, overnight, 70% yield; (h) phenylchloroformate, Et_3N, CH_2Cl_2, overnight, room temperature, 100% yield; (i) *N*-(2,2-dimethoxyethyl)-2-propaneamine, DMAP, dioxane, reflux, 4 h; followed by HCOOH, 3 h, 70 °C, 75% yield; (j) H_2, AcOH, 10% Pd/C.

a solid which was crystallized from ethanol yielding **1a** (4.98 g, 61%): mp 155−157 °C. $[\alpha]^{20}_D$ −10.69° (c 1.0, DMF). MS (ESI) *m/z*: 716 (MH^+). ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.24 (t, J = 7.0 Hz, 3 H), 1.64 (s, 6 H), 3.23 (dd, J = 6.3, 3.8 Hz, 4 H), 3.39 (dd, J = 6.3, 3.8 Hz, 4 H), 3.49 (dd, J = 9.7, 6.3 Hz, 1 H), 3.79 (dd, J = 9.7, 4.7 Hz, 1 H), 3.82 (dd, J = 8.5, 5.2 Hz, 1 H), 3.98 (q, J = 7.0 Hz, 2 H), 3.98 (dd, J = 8.4, 6.5 Hz, 1 H), 4.41 (tt, J = 6.3, 5.1 Hz, 1 H), 4.68 (d, J = 14.7 Hz, 1 H), 4.74 (d, J = 14.7 Hz, 1 H), 6.80 (m, 2 H), 6.87 (m, 2 H), 6.94 (m, 2 H), 7.03 (m, 2 H), 7.07 (m, 2 H), 7.50 (td, J = 8.8, 6.5 Hz, 1 H), 7.89 (s, 1 H), 8.22 (s, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 13.2, 24.8, 37.7, 47.8, 49.0, 50.6, 54.5 (d, J = 4 Hz), 67.6, 74.9, 105.2 (t, J = 26 Hz), 106.7 (d, J = 4 Hz), 111.2 (dd, J = 21, 4 Hz), 115.2, 116.4, 118.4, 121.7 (dd, J = 13, 4 Hz), 125.8, 128.8, 129.2 (dd, J = 10, 5 Hz), 144.9, 146.1, 150.7, 151.3, 151.3, 152.6, 160.4 (dd, J = 252, 12 Hz), 163.7 (dd, J = 252, 12 Hz), 172.2, 172.8. Anal. ($C_{37}H_{39}F_2N_7O_6$) H, N; C calcd, 62.09; found, 61.23.

The synthetic methods for the following compounds **1b**, **2a**, **2b**, and **3a**−**c** were similar to the synthesis of compound **1a**.

(−)-(2*S*-*cis*)-1-Ethyl-3-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-5-propyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione hydrate (1:1) (1b). Yield 51%, crystallized from ethanol: mp 111−113 °C. $[\alpha]^{20}_D$ −10.69° (c 1.01, MeOH). MS (ESI) *m/z*: 731 (MH^+). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.96 (t, J = 7.5 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.72 (m, 2 H), 3.22 (dd, J = 6.1, 3.9 Hz, 4 H), 3.39 (dd, J = 6.3, 3.7 Hz, 4 H), 3.49 (dd, J = 9.7, 6.3 Hz, 1 H), 3.79 (dd, J = 9.7, 4.7 Hz, 1 H), 3.82 (dd, J = 8.5, 5.2 Hz, 1 H), 3.89 (m, 2 H), 3.99 (m, 3 H), 4.41 (tt, J = 6.3, 5.1 Hz, 1 H), 4.68 (d, J = 14.7 Hz, 1 H), 4.73 (d, J = 14.7 Hz, 1 H), 6.80 (m, 2 H), 6.88 (m, 2 H), 6.94 (m, 2 H), 7.03 (m, 2 H), 7.15 (m, 2 H), 7.50 (td, J = 8.8, 6.5 Hz, 1 H), 7.89 (s, 1 H), 8.22 (s, 1 H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 11.1, 13.1, 21.1, 38.5, 44.7, 48.9, 50.6, 54.5 (d, J = 3 Hz), 67.6 (d, J = 3 Hz), 74.9, 105.1 (t, J = 26 Hz), 106.7 (d, J = 4 Hz), 111.2 (dd, J = 21, 3 Hz), 115.2, 116.3, 118.4, 121.7 (dd, J = 13, 3 Hz), 125.2, 128.8, 129.2 (dd, J = 10, 5 Hz), 144.8, 146.0, 148.9, 149.0, 149.2, 151.3, 151.4, 152.5, 160.4 (dd, J = 252, 12 Hz), 163.7 (dd, J = 252, 12 Hz). Anal. ($C_{37}H_{40}F_2N_8O_6 \cdot H_2O$) C,H,N.

(−)-(2*S*-*cis*)-1-[4-[4-[4-[[4-(2,4-Difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone (1c). A mixture of **6a** (20 g, 0.053 mol), **18** (25 g, 0.053 mol), and NaOH pellets (5.3 g, 0.13 mol) in DMF (500 mL) was stirred at 60 °C under nitrogen flow for 24 h. The solvent was evaporated under reduced pressure. The residue was triturated with H_2O (250 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with H_2O (3 × 250 mL) and brine, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated at reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/hexane/EtOAc 50/20/30) to give an oil that was crystallized from EtOAc to give **1c** (26.2 g, 75.5%) as a white solid: mp 186.5−188.5 °C. $[\alpha]^{20}_D$ −14.23° (c 0.506, DMF). MS (ESI) *m/z*: 660 (MH^+). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, J = 7.0 Hz, 6 H), 3.18 (m, 8 H), 3.36 (m, 2 H), 3.72 (m, 5 H), 4.01 (m, 2 H), 4.40 (m, 1 H), 4.71 (m, 2 H), 6.84 (d, J = 9.1 Hz, 2 H), 6.96 (m, 4 H), 7.07 (td, J = 8.5, 2.6 Hz, 1 H), 7.32 (ddd, J = 11.4, 9.1, 2.5 Hz, 1 H), 7.44 (m, 3 H), 7.86 (s, 1 H), 8.41 (s, 1 H). ^{13}C NMR (101 MHz, DMSO−d_6): δ 19.2, 36.0, 42.3, 43.1, 49.1, 49.6, 54.0 (d, J = 3 Hz), 66.6, 67.7, 74.9, 104.9 (t, J = 26 Hz), 106.3 (d, J = 4 Hz), 111.1 (dd, J = 21, 3 Hz), 115.1, 116.2, 117.5, 118.2, 122.5 (dd, J = 13, 3 Hz), 129.3 (dd, J = 10, 5 Hz), 133.4, 145.4, 145.7, 146.1, 150.7, 151.8,

Table 2. MIC Values of Test Substances for Panels of Dermatophytes

	Epidermophyton floccosum (12)[a]			*Microsporum spp* (38)[a]			*Trichophyton mentagrophytes* (20)[a]		
entry	range[b]	50%[c]	90%[c]	range	50%	90%	range	50%	90%
1a	0.32−1	1	1	0.032−>20	3.2	>20	0.1−>20	1	>20
1b	0.32−3.2	1	3.2	0.01−>20[d]	1	>20	0.32−3.2	1	3.2
1c	0.01−0.1	0.032	0.093	0.0032−1	0.1	0.32	0.0005−0.1	0.032	0.032
2a	0.32−>20	3.2	>20	0.032−>20	10	>20	0.1−>20	1	>20
2b	0.32−3.2	1	3.2	0.032−>20	1	13	0.032−3.2	0.32	1
2c	0.032−3.2	0.406	2.98	0.0005−1	0.032	0.524	0.0032−0.1	0.021	0.032
3a	0.32−>20	>20	>20	1−>20	>20	>20	>20−>20	>20	>20
3b	10−>20	>20	>20	1−>20	>20	>20	>20−>20	>20	>20
3c	0.01−>20	1	>20	0.1−>20	2.1	>20	0.32−>20	1	>20
4a	1−3.2	1	2.98	0.1−>20	3.2	>20	1−10	3.2	3.2
4b	1−3.2	1	3.2	0.0032−>20	3.2	>20	0.32−3.2	1	3.2
4c	0.01−0.1	0.032	0.093	0.0005−>20	0.032	0.524	0.0032−0.032	0.01	0.032
itraconazole	0.01−0.32	0.032	0.093	0.0005−1	0.032	0.524	0.0032−1	0.01	0.1288
terbinafine	0.01−0.1	0.032	0.093	0.01−0.32	0.032	0.032	0.0032−0.01	0.01	0.01

	Trichophyton rubrum (14)[a]			*Trichophyton tonsurans* (18)[a]			Other *Trichophyton* spp. (80)[a]		
entry	range[b]	50%[c]	90%[c]	range	50%	90%	range	50%	90%
1a	1−>20	11.6	>20	3.2−>20	>20	>20	0.1−>20	>20	>20
1b	0.32−>20	3.2	>20	0.32−>20	>20	>20	0.1−>20	15	>20
1c	0.0032−1	0.32	0.934	0.1−1	1	1	0.0032−0.32	0.32	1
2a	1−>20	11.6	>20	1−>20	>20	>20	0.32−>20	>20	>20
2b	1−3.2	3.2	3.2	0.32−>20	3.2	10	0.32−>20	3.2	>20
2c	0.01−1	0.21	1	0.032−1	0.32	1	0.0005−>20	0.32	1
3a	>20−>20	>20	>20	>20−>20	>20	>20	1−>20	>20	>20
3b	>20−>20	>20	>20	3.2−>20	>20	>20	3.2−>20	>20	>20
3c	3.2−>20	>20	>20	1−>20	>20	>20	0.1−>20	>20	>20
4a	1−10	3.2	10	1−>20	3.2	13	0.1−>20	3.2	>20
4b	1−10	3.2	10	0.32−>20	10	>20	0.0005−>20	3.2	>20
4c	0.0032−1	0.32	0.796	0.01−1	0.32	1	0.0032−>20	0.1	1.22
itraconazole	0.01−1	0.1	0.32	0.01−1	0.32	0.524	0.0005−>20	0.1	1
terbinafine	0.0032−0.1	0.01	0.0254	0.01−3.2	0.032	0.0524	0.0005−>20	0.01	0.032

[a] Number of species tested. [b] MICs in μg/mL as the lowest concentrations of test compounds that reduced growth below 50% of the level of the control growth. [c] MICs at which 50% and 90% of the isolate in the test panel, respectively, are inhibited. [d] Number of *Microsporum* species tested is 37.

Table 3. MIC Values of Test Substances for Panels of Other Fungi

	Candida spp. (24)[a]			*Aspergillus spp.* (8)[a]			other fungi (13)[a]		
entry	range[b]	50%[c]	90%[c]	range	50%	90%	range	50%	90%
1a	0.01−>20	0.32	>20	>20−>20	>20	>20	0.1−>20	>20	>20
1b	0.01−>20	3.2	>20	10−>20	>20	>20	0.1−>20	>20	>20
1c	0.01−>20	0.32	>20	0.32−3.2	0.66	1.66	0.1−>20	>20	>20
2a	0.032−>20	0.66	>20	>20−>20	>20	>20	0.1−>20	>20	>20
2b	0.01−>20	1	10	3.2−>20	10	>20	0.32−>20	>20	>20
2c	0.01−>20	0.1	>20	0.1−1	0.32	0.524	0.032−>20	10	>20
3a	0.32−>20	15	>20	>20−>20	>20	>20	1−>20	>20	>20
3b	1−>20	10	>20	>20−>20	>20	>20	>20−>20	>20	>20
3c	0.1−>20	>20	>20	>20−>20	>20	>20	>20−>20	>20	>20
4a	0.01−>20	0.66	>20	>20−>20	>20	>20	0.32−>20	>20	>20
4b	0.01−>20	3.2	>20	10−>20	>20	>20	0.01−>20	>20	>20
4c	0.01−>20	0.1	>20	0.32−>20	>20	>20	0.1−>20	>20	>20
itraconazole	0.01−>20	0.1	17	0.032−3.2	0.32	1.184	0.032−20	1	>20
terbinafine	0.1−>20	>20	>20	0.032−3.2	0.32	1.66	0.1−3.2	0.32	3.2

[a] Number of species tested. [b] MICs in μg/mL as the lowest concentrations of test compounds that reduced growth below 50% of the level of the control growth. [c] MICs at which 50% and 90% of the isolate in the test panel, respectively, are inhibited.

156.8, 159.9 (dd, J = 251, 12 Hz), 162.8 (dd, J = 247, 12 Hz). Anal. ($C_{35}H_{39}F_2N_7O_4$.) C,H,N.

The synthetic methods for **2c** and **4c** were similar to the synthesis of compound **1c**.

(+)-(2*S*-*cis*)-1-Ethyl-3-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-5,5-dimethyl-2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione (4a). Under nitrogen flow, sodium hydride (0.4 g, 0.01 mol) was added to a stirred solution of compound **12** (4.4 g, 0.01 mol) in dry DMF (60 mL) and dry toluene (10 mL). After addition, the reaction was heated for 30 min at 50 °C, then a solution of **8a** (5.4 g, 0.015 mol) in dry DMF (20 mL) was added dropwise at 60 °C. After the reaction was stirred for 6 h at 60 °C, it was cooled, poured into an ice−water mixture, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O and brine, dried over anhydrous $MgSO_4$, and filtered, and the filtrate was evaporated at reduced pressure. The residue was purified by silica gel column chromatography (gradient elution CH_2Cl_2/CH_3OH/EtOAc/*n*-hexane 49/1/30/20 toward 48/2/30/20). The residue was crystallized from methanol to give **4a** (1 g, 14%): mp 115−117 °C. $[\alpha]^{20}_D$ +14.73° (c 1.0, DMF). MS (ESI) *m/z*: 716 (MH^+). ^{1}H NMR (360 MHz, $CDCl_3$) δ: 1.24 (t, J = 7.0 Hz, 3 H), 1.64 (s, 6 H), 3.24 (m, 4 H), 3.39 (m, 4 H), 3.98 (q, J = 7.0 Hz, 2 H), 4.03 (dd, J = 9.3, 1.4 Hz, 1 H), 4.11 (d, J = 3.1 Hz, 2 H), 4.54 (d, J = 14.3 Hz, 1 H), 4.67 (d, J = 14.4 Hz, 1 H), 4.71 (dd, J = 9.4, 3.4 Hz, 1 H), 5.31 (t, J = 3.1 Hz, 1 H), 6.85 (m, 2 H), 6.93 (m, 2 H), 6.97 (m, 2 H), 7.03 (m, 2 H), 7.07 (m, 2 H), 7.35 (td, J = 8.6, 6.4 Hz, 1 H), 7.78 (s, 1 H), 8.17 (s, 1 H). Anal. ($C_{37}H_{39}F_2N_7O_6$.) H, N; C calcd, 62.09; found, 61.22.

Table 4. ED_{50} Values in Guinea Pigs Infected with *M. Canis*[a]

entry	ED_{50} (mg/kg) assessed on day 7	14	21	doses tested (mg/kg) (number of animals)[b,c]
1a	1.18	3.28	2.35	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 12); 5
1b	1.18	1.94	1.94	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 8)
1c	0.33	0.44	0.33	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 8)
2a	>5.00	>5.00	>5.00	1.25; 2.5; 5
2b	>2.50	>2.50	>2.50	1.25; 2.5
2c	0.89	1.29	1.21	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 12); 5
3a	>2.50	>2.50	>2.50	1.25; 2.5
3b	>2.50	>2.50	>2.50	1.25; 2.5
3c	>2.50	>2.50	>2.50	1.25; 2.5
4a	2.35	2.35	2.35	1.25; 2.5
4b	1.25	2.35	>2.50	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 8)
4c	<0.31	<0.31	<0.31	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 12)
itraconazole	0.84	1.20	1.18	0.31; 0.63; 1.25 (n = 8); 2.5 (n = 12); 5; 10
terbinafine	>10	>10	>10	2.5; 5 (n = 8); 10

[a] Response was defined as a lesion score of less than 2; treatment started on day 0 and continued daily for 12 days. [b] The test groups comprised six animals each unless indicated otherwise in parentheses. [c] Untreated control group contained 18 animals.

Table 5. ED_{50} Values in Mice Infected with *T. Mentagrophytes*[a]

entry	ED_{50} (mg/kg) assessed on day 7	doses tested (mg/kg) (number of animals)[b,c]
1a	>2.50	0.63; 1.25 (n = 12); 2.5 (n = 12)
1b	2.86	0.63; 1.25 (n = 12); 2.5
1c	>2.50	0.63; 1.25 (n = 12); 2.5
2a	3.10	2.5; 5
2c	2.60	0.63; 1.25 (n = 12); 2.5 (n = 12); 5
4b	>1.25	0.63; 1.25
4c	<0.63	0.63; 1.25 (n = 12); 2.5 (n = 12); 5
itraconazole	2.60	0.63; 1.25 (n = 12); 2.5 (n = 12); 5
terbinafine	>5.00	2.5; 5

[a] Response was defined as a lesion score of less than 2; treatment started on day 0 and continued daily for 5 days. [b] The test groups comprised six animals each unless indicated otherwise in parentheses. [c] Untreated control group contained 18 animals.

(+)-(2*S*-*cis*)-1-Ethyl-3-[4-[4-[4-[[4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-5-propyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (4b) was synthesized according to the method described for **4a** to give **4b** (40%) crystallized from ethanol: mp 159−161 °C. $[\alpha]^{20}_D$ +15.73° (c 0.099, DMF). MS (ESI) *m/z*: 731 (MH^+). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.96 (t, J = 7.5 Hz, 3 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.72 (m, 2 H), 3.24 (m, 4 H), 3.39 (m, 4 H), 3.89 (m, 2 H), 4.00 (q, J = 7.0 Hz, 2 H), 4.03 (dd, J = 9.4, 1.5 Hz, 1 H), 4.11 (d, J = 3.1 Hz, 2 H), 4.54 (d, J = 14.3 Hz, 1 H), 4.67 (d, J = 14.4 Hz, 1 H), 4.71 (dd, J = 9. 5, 3.5 Hz, 1 H), 5.31 (t, J = 3.0 Hz, 1 H), 6.85 (m, 2 H), 6.95 (m, 4 H), 7.03 (m, 2 H), 7.15 (m, 2 H), 7.35 (td, J = 8.6, 6.3 Hz, 1 H), 7.78 (s, 1 H), 8.18 (s, 1 H). Anal. ($C_{37}H_{40}F_2N_8O_6$.) C, H, N.

(+)-(2*S*-*cis*)-1-[4-[4-[4-[[4-(2,4-Difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone (4c) (63%) was crystallized from DIPE/EtOAc: mp 178−180 °C. $[\alpha]^{20}_D$ +17.54° (c 0.05, DMF). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11 (d, J = 7.0 Hz, 6 H), 3.19 (m, 8 H), 3.36 (m, 2 H), 3.72 (m, 2 H), 4.02 (m, 3 H), 4.12 (dd, J = 11.0, 3.3 Hz, 1 H), 4.59 (m, 2 H), 4.68 (dd, J = 9.1, 3.3 Hz, 1 H), 5.28 (t, J = 3.5 Hz, 1 H), 6.92 (d, J = 9.1 Hz, 2 H), 6.97 (m, 4 H), 7.06 (td, J = 8.6, 2.2 Hz, 1 H), 7.34 (m, 2 H), 7.42 (d, J = 9.1 Hz, 2 H), 7.83 (s, 1 H), 8.36 (s, 1 H). ^{13}C NMR (101 MHz, DMSO−d_6): δ 19.2, 36.0, 42.3, 43.1, 49.1, 49.6, 55.0, 67.8, 72.4 (d, J = 6 Hz), 80.9 (d, J = 4 Hz), 102.3, 104.3 (t, J = 26 Hz), 111.5 (dd, J = 21, 3 Hz), 115.1, 116.2, 117.5, 118.2, 123.6 (dd, J = 15, 3 Hz), 128.6 (dd, J = 10, 7 Hz), 133.5, 145.1, 145.8, 146.1, 150.9, 151.8, 156.8, 158.8 (dd, J = 247, 13 Hz), 162.2 (dd, J = 247, 12 Hz). Anal. ($C_{35}H_{39}F_2N_7O_4$.) C, H, N.

(−)-(2*S*, *cis*)-2-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol 4-Methylbenzenesolfonate Ester 4-Methylbenzensulfonate Salt (1:1) (5a). In a two-neck flask provided with a Dean−Stark trap, methanesulfonic acid (200 mL) was added slowly to a solution of 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone[40] (44.6 g, 0.2 mol) and (2*S*)-1,2,3-propanetriol-1-(4- methylbenzenesulfonate) ester[27] (56 g, 0.227 mol) in CH_2Cl_2 (150 mL) at room temperature. After addition, the solution was heated to reflux for 24 h, cooled to room temperature, and slowly poured into a mixture of ice (500 g), water (800 mL), K_2CO_3 (400 g), and CH_2Cl_2 (500 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 250 mL). The combined CH_2Cl_2 layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, $CHCl_3$), and fractions containing the cis isomer were evaporated at reduced pressure and converted to its 4-methylbenzenesulfonate salt in MIK. The salt was crystallized from MIK to give **5a** (20.5 g, 16.4%): mp 182−184 °C. $[\alpha]^{20}_D$ −13.79° (c 1.0, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.12 (s, 3H), 4.44 (dd, 1H), 4.65 (dd, 1H), 4.84 (m, 2H), 5.40 (m, 1H), 5.81 (s, 2H), 8.59 (m, 2H), 9.21 (m, 3H), 9.75 (m, 3H), 10.15 (s, 1H). Anal. ($C_{20}H_{19}F_2N_3O_5S{\cdot}C_7H_8O_3S$) C, H, N.

(+)-(2*R*, *cis*)-2-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol 4-Methylbenzenesolfonate Ester 4-Methylbenzensulfonate Salt (1:1) (5b). The title compound was prepared from (2*R*)-1,2,3-propanetriol-1-(4-methylbenzenesulfonate) ester as a 4-methylbenzenesulfonate salt following the procedure described for compound **5a**. The salt was crystallized from MIK to give **5b** (20.6%): mp 183−185 °C. $[\alpha]^{20}_D$ +14.43° (c 1.0, MeOH).

(−)-(2*S*-*cis*)-2-(2,4-Difluorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-methanol Methanesulfonate Ester (6a). The title compound was prepared from (2*S*)-1,2,3-propanetriol-1-(methylsulfonate) ester following the procedure described for compound **5a** to give **6a** (22%) crystallized from MIK: mp 114.1−114.7 °C. $[\alpha]^{20}_D$ = −14.50 (c 0.2, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.26 (s, 3 H), 3.76 (dd, J = 8.8, 5.7 Hz, 1 H), 3.96 (dd, J = 8.7, 6.8 Hz, 1 H), 4.02 (dd, J = 11.0, 6.2 Hz, 1 H), 4.20 (dd, J = 11.0, 3.7 Hz, 1 H), 4.41 (dd, J = 6.2, 3.7 Hz, 1 H), 4.74 (m, 2 H), 7.05 (td, J = 8.5, 2.6 Hz, 1 H), 7.28 (dd, J = 11.4, 9.1, 2.5 Hz, 1 H), 7.41 (td, J = 8.8, 6.6 Hz, 1 H), 7.86 (s, 1 H), 8.42 (s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 36.8, 54.1 (d, J = 3 Hz), 66.0, 68.9, 74.2, 104.9 (t, J = 26 Hz), 106.7 (d, J = 4 Hz), 111.1 (dd, J = 21, 3 Hz), 122.1 (dd, J = 13, 3 Hz), 129.3 (dd, J = 10, 5 Hz), 145.3, 150.8, 159.9 (dd, J = 252, 13 Hz), 162.8 (dd, J = 250, 15 Hz). Anal. ($C_{14}H_{15}F_2N_3O_5S$) C, H, N.

(2*S*-*cis*)-1-[[2-(Bromomethyl)-4-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl]-1*H*-1,2,4-triazole (8a) and (2*R*-*cis*)-1-[[2-(Bromomethyl)-4-(2,4-difluorophenyl)-1,3-dioxolan-4-yl]methyl]-1*H*-1,2,4-triazole (8b). 1-Bromo-2,2-di-

ethoxyethane (40 g, 0.2 mmol) was added dropwise to a stirred solution of 2-(2,4-difluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)1,2-propanediol[30−35] (40.3 g, 0.16 mmol) in methanesulfonic acid (100 mL) and CH_2Cl_2 (1000 mL) at 10 °C. After addition, the mixture was allowed to warm at room temperature, stirred overnight, poured into a mixture of ice, H_2O (750 mL), $NaHCO_3$ (160 g), and extracted with CH_2Cl_2 (3 × 750 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was evaporated at reduced pressure. The residue was purified over silica gel (CH_2Cl_2/CH_3OH gradient elution from 100/0 to 98/2). The desired fractions were collected, and the solvent was evaporated under reduced pressure. The residue (cis and trans isomers) was purified by chiral column chromatography (Chiralcel OD, 20 μm, 1000 Å, hexane/ethanol 75/25) to give **8a** (5.1 g, 9%), **8b** (6.3 g, 11%), and trans isomer (21.8 g, 38%). **8a**: mp 165−167 °C. $[\alpha]^{20}_D$ +5.83° (c 0.94, DMF). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.64 (dd, J = 11.2, 4.2 Hz, 1 H), 3.70 (dd, J = 11.2, 3.4 Hz, 1 H), 4.03 (dd, J = 9.1, 1.5 Hz, 1 H), 4.60 (m, 2 H), 4.68 (dd, J = 9.0, 3.1 Hz, 1 H), 5.19 (t, J = 3.8 Hz, 1 H), 7.04 (td, J = 8.5, 2.4 Hz, 1 H), 7.29 (m, 2 H), 7.81 (s, 1 H), 8.39 (s, 1 H). Anal. ($C_{13}H_{12}BrF_2N_3O_2$) C, H, N; H, 3.79. **8b**: oil. $[\alpha]^{20}_D$ −4.26° (c 0.82, DMF). ^{1}H NMR (400 MHz, C_6D_6): δ 2.96 (dd, J = 11.3, 3.5 Hz, 1 H), 2.99 (dd, J = 11.3, 3.5 Hz, 1 H), 3.57 (dd, J = 9.2, 1.7 Hz, 1 H), 4.05 (d, J = 14.4 Hz, 1 H), 4.11 (d, J = 14.4 Hz, 1 H), 4.35 (dd, J = 9.2, 3.1 Hz, 1 H), 4.56 (t, J = 3.5 Hz, 1 H), 6.43 (m, 2 H), 6.96 (m, 1 H), 7.77 (s, 1 H), 7.91 (s, 1 H). *trans* isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (m, 2H), 4.25 (dd, J = 9.3 Hz, 1.7 Hz, 1H), 4.49 (m, 2H), 4.62 (d, J = 14.4 Hz, 1H), 5.26 (t, 1H), 6.87 (m, 2H), 7.48 (m,1H), 7.84 (s, 1H), 8.05 (s, 1H).

1-[4-[4-(4-Methoxyphenyl)-1-piperazinyl]phenyl]-5,5-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (10). A solution of potassium isocyanate (11.2 g, 0.138 mol) was added dropwise over a period of 3 h to a solution of **9** (13.02 g, 0.046 mol) in concentrated HCl (138 mL, 0.138 mol) and then stirred for an additional 1 h. The mixture was neutralized with NaOH, and the precipitate was filtered, washed with H_2O (3 × 75 mL), and dried in vacuo at 30 °C to give *N*-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]urea (15 g, 100%) as a white solid (mp 320 °C decomposition). 2,2-Dimethylmalonyl chloride (7.7 g, 0.046 mol) was added dropwise to a stirred solution of *N*-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]urea (15 g, 0.046 mol) in tetrahydrothiophene-1,1-dioxide (150 mL) at room temperature. After 15 min, the reaction was heated at 40 °C and stirred for 3 h followed by additional stirring at 50 °C for 2 h. The reaction mixture was allowed to stand overnight at room temperature. The product was precipitated by addition of diethyl ether, filtered, and crystallized from 2-propanol to give **10** (16.1 g, 83%) as a white solid: mp 218−222 °C. ^{1}H NMR (360 MHz, DMSO-d_6): δ 1.46 (s, 6 H), 3.16 (m, 4 H), 3.32 (m, 4 H), 3.70 (s, 3 H), 6.85 (d, J = 8.8 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.03 (d, J = 9.1 Hz, 2 H), 7.10 (d, J = 9.1 Hz, 2 H), 11.44 (s, 1 H). ^{13}C NMR (91 MHz, DMSO-d_6): δ 24.1, 46.7, 48.3, 49.8, 55.2, 114.3, 115.3, 117.7, 126.1, 129.3, 145.3, 150.5, 150.6, 153.2, 173.3, 173.6. Anal. ($C_{23}H_{26}N_4O_4$) C, H, N.

1-Ethyl-3-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]-5,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (11). Dry DMF (70 mL) was added to a flask containing the oil free NaH (0.52 g, 0.0174 mol) under argon. Compound **10** (7 g, 0.0166 mol) was added, after stirring for 30 min, ethyl iodide (1.41 mL, 0.0182 mol) was added dropwise, and the mixture was heated at 85 °C for 3 h. The mixture was cooled, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and filtered, and the filtrate was evaporated at reduced pressure. The residue was chromatographed on silica gel (2% MeOH in CH_2Cl_2), and the desired compound was crystallized from CH_3CN to give **11** (3 g, 40%): mp 184−185 °C.

1-Ethyl-3-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-5,5-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (12). Compound **11** (3.07 g, 6.8 mmol) was heated to reflux for 5 h in a mixture of 48% HBr (60 mL) and HBr saturated acetic acid (30 mL) in the presence of $NaHSO_3$ (1 g). The solvent was evaporated at reduced pressure, and aqueous K_2CO_3 was added to adjust the pH to 8. The mixture was extracted with CH_2Cl_2 (3 × 300 mL), and the combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and evaporated at reduced pressure. The residue was chromatographed on silica gel (2% MeOH in CH_2Cl_2). The desired fraction was recrystallized from CH_3CN to give **12** (1.2 g, 40%): mp 253−254 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, J = 7.1 Hz, 3 H), 1.49 (s, 6 H), 3.06−3.15 (m, 4 H), 3.27−3.35 (m, 4 H), 3.80 (q, J = 7.0 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 2 H), 6.86 (d, J = 8.8 Hz, 2 H), 7.03 (d, J = 9.1 Hz, 2 H), 7.10 (d, J = 9.1 Hz, 2 H), 8.86 (s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 12.9, 24.4, 36.6, 47.1, 48.3, 50.2, 115.3, 115.5, 118.1, 126.5, 129.2, 144.0, 150.6, 150.6, 151.2, 172.4, 172.7. Anal. ($C_{24}H_{28}N_4O_4$) C, H, N.

1-[4-[4-(4-Methoxyphenyl)-1-piperazinyl]phenyl]-3-propyl-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (13). Propylisocyanate (38.4 mL, 0.4 mol) was added to a solution of compound **9** (100 g, 0.35 mol) in CH_2Cl_2 (1 L), stirred overnight at room temperature, and evaporated under reduced pressure. The residue was triturated with MeOH (250 mL), and the precipitate was filtered and dried under reduced pressure at 60 °C to give *N*-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]-*N*′-propylurea (112 g, 86%). *N*-[4-[4-(4-Methoxyphenyl)-1-piperazinyl]phenyl]-*N*′-propylurea (50 g, 0.136 mol) was dissolved in 1,2-dichloroethane (500 mL) at reflux temperature. The mixture was cooled to room temperature, and chlorocarbonylisocyanate (10.9 mL, 0.136 mol) was added. The mixture was refluxed for 1 h and cooled to room temperature, and an aqueous saturated $NaHCO_3$ solution (150 mL) was added and stirred for 1 h. The precipitate was filtered, washed with H_2O (2 × 50 mL) and CH_2Cl_2 (50 mL), and dried to give **13** (47.5 g). Combined filtrates were separated, and the organic layer was washed with H_2O (2 × 100 mL) and brine (100 mL) and dried over anhydrous $MgSO_4$. The filtrate was evaporated at reduced pressure to give another crop of **13** (12.3 g). The combined crops were recrystallized from acetonitrile to give **13** (52.7 g, 88%): mp 233−235 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (t, J = 7.5 Hz, 3 H), 1.58 (m, 2 H), 3.16 (dd, J = 6.5, 3.6 Hz, 4 H), 3.32 (dd, J = 6.6, 3.5 Hz, 4 H), 3.67 (dd, J = 8.3, 6.2 Hz, 2 H), 3.70 (s, 3 H), 6.85 (d, J = 9.2 Hz, 2 H), 6.97 (d, J = 9.2 Hz, 2 H), 7.03 (d, J = 9.1 Hz, 2 H), 7.16 (d, J = 9.1 Hz, 2 H), 11.71 (s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 11.0, 20.6, 42.9, 48.2, 49.7, 55.2, 114.3, 115.3, 117.7, 125.5, 129.3, 145.2, 148.8, 148.9, 150.1, 150.7, 153.2. Anal. ($C_{23}H_{27}N_5O_4$) C, H, N.

5-Ethyl-1-[4-[4-(4-methoxyphenyl)-1-piperazinyl]phenyl]-3-propyl-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (14). Ethyl bromide (9.3 mL, 0.12 mol) was added to a mixture of compound **13** (50 g, 0.114 mol) and KOH pellets (12.7 g, 0.228 mol) in DMF (500 mL) and was stirred overnight at room temperature. The reaction mixture was then poured into a mixture of ice−water (400 mL). The precipitate was filtered, dissolved in CH_2Cl_2 (500 mL), washed with H_2O (2 × 100 mL) and brine (100 mL), and dried over anhydrous $MgSO_4$, and the filtrate was evaporated at reduced pressure. The residue was recrystallized from 2-propanol to give **14** (37 g, 70%): mp 177−179 °C. Anal. ($C_{23}H_{27}N_5O_4$) C, H, N.

5-Ethyl-1-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-3-propyl-1,3,5-triazine-2,4,6-(1H,3H,5H)-trione (15). Compound **15** was synthesized in 95% yield according to the method described for compound **12** and recrystallized from *n*-propanol: mp 256−258 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (t, J = 7.4 Hz, 3 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.60 (m, J = 7.4, 7.4, 7.4, 7.4, 7.4 Hz, 2 H), 3.11 (m, 4 H), 3.32 (m, 4 H), 3.73 (t, J = 7.3 Hz, 2 H), 3.82 (q, J = 7.0 Hz, 2 H), 6.68 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 7.03 (d, J = 8.7 Hz, 2 H), 7.17 (d, J = 8.7 Hz, 2 H), 8.86 (s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 11.1, 12.8, 20.6, 37.6, 43.8, 48.2, 50.1, 115.2, 115.5, 118.1, 125.8, 129.2, 144.0, 148.9, 148.9, 149.1, 150.8, 151.2. Anal. ($C_{24}H_{29}N_5O_4$) C, H, N.

1,3-Dihydro-1-[4-[4-(4-methoxyphenyl)-1-piperazinyl]-phenyl]-3-(1-methylethyl)-2H-imidazol-2-one (17). A mixture of compound **16**[36] (95 g, 0.23 mol), *N*-(2,2-dimethoxyethyl)-

2-propaneamine[41] (49 g, 0.23 mol), DMAP (17.6 g, 0.144 mol), and triethylamine (66 mL) in dioxane (880 mL) was refluxed for 4 h. The mixture was cooled to room temperature, and H_2O (880 mL) was added and stirred for 15 min. The precipitate was filtered, washed with H_2O (2 × 50 mL), and dried under reduced pressure. The solid was stirred in formic acid (440 mL) at 70 °C for 3 h followed by evaporation of the solvent at reduced pressure. The residue was dissolved in methylisobutyl ketone (500 mL), washed with aqueous saturated $NaHCO_3$ (2 × 100 mL), H_2O (100 mL), and brine (100 mL), dried over anhydrous $MgSO_4$, and evaporated at reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH/hexane/EtOAc, 48/2/20/30) to give an oil that was triturated with diisopropyl ether yielding **17** (68 g, 75%): mp 186.9 °C. MS *m/z*: 513 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.8 Hz, 6 H), 3.23 (m, 4 H), 3.33 (m, 4 H), 3.78 (s, 3 H), 4.47 (m, 1 H), 6.35 (d, J = 3.1 Hz, 1 H), 6.51 (d, J = 3.1 Hz, 1 H), 6.86 (d, J = 9.1 Hz, 2 H), 6.96 (d, J = 9.1 Hz, 2 H), 7.00 (d, J = 9.1 Hz, 2 H), 7.48 (d, J = 9.1 Hz, 2 H) 13C NMR (101 MHz, $CDCl_3$) δ 22.0, 44.5, 49.7, 50.8, 55.5, 107.3, 109.8, 114.5, 116.7, 118.5, 123.0, 130.0, 145.6, 149.3, 151.3, 154.1. Anal. ($C_{33}H_{28}N_4O_2$) C, H, N.

1-[4-[4-(4-Hydroxyphenyl)-1-piperazinyl]phenyl]-3-(1-methylethyl)-2-imidazolidinone (18). Compound **17** (67 g, 0.17 mol) was dissolved in acetic acid (2 L), 10% palladium on charcoal (8 g) was added, and the mixture was degassed three times. This mixture was hydrogenated overnight at atmospheric pressure and filtered, and the filtrate was evaporated at reduced pressure. The residue (47 g) was heated at reflux temperature for 2 h in 48% HBr (300 mL) and HBr saturated acetic acid (200 mL) in the presence of $NaHSO_3$ (3 g). The reaction was cooled to room temperature, and H_2O (500 mL) was added. After the reaction mixture was stirred for 30 min, the precipitate was filtered. The precipitate was stirred in H_2O (500 mL), and the mixture was neutralized with aqueous ammonia. The precipitate was filtered and recrystallized from 2-propanol to give **18** (52 g, 80% for the two steps): mp 234−237 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 1.10 (d, J = 6.6 Hz, 6 H), 3.09 (m, 4 H), 3.18 (m, 4 H), 3.36 (m, 2 H), 3.72 (m, 2 H), 4.01 (m, 1 H), 6.67 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 2 H), 8.83 (s, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 19.1, 36.0, 42.3, 43.1, 49.2, 50.1, 115.4, 116.1, 117.9, 118.2, 133.4, 144.0, 146.1, 151.0, 156.7. Anal. ($C_{22}H_{28}N_4O_2$) H, N; C calcd, 69.45; found, 68.90.

In Vitro Antifungal Activities. All fungi used for testing were originally isolated from humans or animals. They were stored at −80 °C, as part of the collection of the Department of Bacteriology and Mycology at the Janssen Research Foundation currently known as Johnson and Johnson Pharmaceutical Research and Development a division of Janssen Pharmaceutica N.V., in dilute casein hydrolysate yeast extract/glucose medium with 10% glycerol. The species tested and numbers of isolates of each tested were as follows: *Candida spp.* (24), (*Candida albicans* (5), *C. famata* (1), *C. glabrata* (4), *C. guilliermondii* (1), *C. kefyr* (2), *C. krusei* (2), *C. lusitaniae* (2), *C. parapsilosis* (3), *C. tropicalis* (4)), *Epidermophyton floccosum* (12), *Microsporum spp.* (38), (*Microsporum audouinii* (7), *M. canis* (22), *M. gypseum* (7), *M. nanum* (1), *M. vanbreuseghemii* (1)), *Trichophyton spp.* (132) (*Trichophyton ajelloi* (5), *T. concentricum* (6), *T. equinum* (17), *T. ferrugineum* (2), *T. gallinae* (2), *T. megninii* (1), *T. mentagrophytes* (20), *T. persicolor* (2), *T. quickeanum* (2), *T. rubrum* (14), *T. schoenleinii* (2), *T. soudanesis* (6), *T. sulfureum* (1), *T. terrestre* (5), *T. tonsurans* (18), *T. verrucosum* (20), *T. violaceum* (9)), *Aspergillus spp.* (8) (*Aspergillus fumigatus* (6), *Aspergillus niger* (1), *Aspergillus flavus* (1)), and other fungi (13) (*Mucor racemous* (1), *Rhizopus microsporum* (1), *Cumminghamella elegans* (1), *Fusarium oxysporum* (1), *Cryptococcus neoformans* (2), *Sporothrix schenckii* (2), *Exophilia dermatididis* (1), *Exophilia spinifera* (1), *Fonsecaea pedrosoi* (1), *Phialophora verrucosa* (2)). The test compounds were dissolved in dimethyl sulfoxide (DMSO), and a dilution series was prepared in DMSO to give concentrates that were stored at −20 °C. Concentrations of the stock solutions were 100 times the final concentration of each compound. For preparation of microdilution plates, 2 μL volumes of concentrate in DMSO were added to 100 μL volumes of sterile distilled water by means of a computer-controlled dispenser. Addition of 100 μL of inoculated culture medium as detailed below provided the final dilution step, creating cultures with 1% (v/v) DMSO. Earlier tests showed that this concentration of DMSO is not inhibitory for species tested; all control cultures also contained 1% DMSO.

Full experimental procedures for the in vitro and in vivo antifungal screening have been published recently.[22]

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Supporting Information Available: Analysis data for **2a**,**b**,**c** and **3a**,**b**,**c**, X-ray determination of absolute configuration of 4-methylbenzenesulfonate salt of compound **8a**, and elemental analysis data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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