Synthesis and Antifungal Activity of New Azole Derivatives Containing an *N*-Acylmorpholine Ring

Javier Bartroli,* Enric Turmo, Mònica Alguerό, Eulàlia Boncompte, Maria L. Vericat, Julián García-Rafanell, and Javier Forn

Research Center, J. Uriach & Cía. S.A., Degà Bahí 59–67, 08026 Barcelona, Spain

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A series of azole derivatives carrying an *N*-acylmorpholine ring are described. The compounds were chemically designed to simulate the lanosterol D ring, taking advantage of the conformational preferences of 2-alkyl-1-acylmorpholines. Three structural variables, the nature of the *N*-benzoyl group, the phenyl substituents, and the degree of oxidation at carbon 2 of the morpholine, were optimized for maximum activity. Only the (5*R*,6*R*) isomers showed antifungal activity. Cyclic hemiacetal (−)-**39a** (UR-9746) and cyclic ether (−)-**41** (UR-9751) were selected for further development. *In vitro*, (−)-**41** was clearly more active than (−)-**39a** and somewhat less active than the acyclic counterpart (−)-**7**. *In vivo* activity was assessed by a systemic (mouse) and a vaginal (rat) candidosis model. In the former, (−)-**39a**, (−)-**41**, and (−)-**7** at 1 mg/kg given 1, 4, and 24 h postinfection displayed 90−100% protection from mortality on day 9. Compound (−)-**39a** was slightly more potent than (−)-**41** and similar in potency to (−)-**7**. The three compounds were superior in potency to fluconazole and similar in potency to SCH-42427 in this test. In the vaginal model, (−)-**39a** and (−)-**41** given daily during 3 days after infection at 0.5 mg/kg showed high levels of protection on days 10 and 15. At 0.25 mg/kg, (−)-**39a** was slightly more potent than SCH-42427 and (−)-**7** and superior in potency to (−)-**41** and fluconazole in this model. Preliminary 28-day toxicity tests at 100 mg/kg/day *po* in rats indicated no or very mild adverse effects for the two UR compounds.

Introduction

While increasing success has been achieved in the management of bacterial infections, progress has been rather slow in the therapy for invasive mycoses. In fact, only two products, fluconazole (1) and itraconazole (**2**) (Figure 1), have reached the market for that indication in the last 15 years.[1] Given the worrying rise in fungal infections in the human population,[2,3] and the recent emergence of pathogens resistant to some of the commonly used antifungal agents,[4] the present medical situation is by no means satisfactory, and more effective and safe drugs are urgently needed.

In this regard, the azoles remain a promising class of compounds. Structure optimization within this family is currently producing new candidates with improved profiles (Figure 1). Some of these, such as D-0870 [(+)-**4**][5] and SCH-51048 [(−)-**5**][6] are presently undergoing clinical trials, and encouraging results are being obtained. Others, however, have been discontinued at various stages of development for a variety of reasons, often related to toxicity. Perhaps the most well-known case is that of the potent antifungal agent genaconazole [SCH-39304, (±)-**3**], or its active enantiomer SCH-42427 [(−)-**3**].[7] This product is one of the most active and broadest spectrum azole antifungal agents described to date, and it is still the reference in numerous studies. However, both (±)-**3** and (−)-**3** have been shown to induce hepatocellular adenomas and carcinomas in rats and mice after prolonged (18–24 months) exposure,[8] and consequently, they have had to be withdrawn from clinical trials.

New azole derivatives, nevertheless, continue to be discovered and tested. In this line, oxazolidine (−)-**6** and amido alcohol (−)-**7** have recently been described by researchers at Sankyo as potent antifungals.[9] According to the authors, these products inhibit cytochrome P450 14α-demethylase by fitting into the site normally occupied by the D ring of lanosterol, the enzyme's natural substrate. On the basis of this model, we sought to improve the conformational biases of the enzyme substrate and develop new, conformationally-locked azole derivatives with an optimized spatial orientation of their ring substituents. The present study reports the synthesis and the *in vitro* and *in vivo* activities of these new compounds, together with the preliminary toxicity results.

Design of New Drugs

Azole antifungals act by competitive inhibition through direct interaction with the cytochrome P450 14α-demethylase ($P450_{14DM}$), the enzyme that catalyses the 14-α-demethylation of lanosterol and eburicol in the biosynthesis of ergosterol, the main sterol in fungi.[10] Ergosterol depletion and the concomitant accumulation of 14α-methyl sterols impairs membrane functions and affects membrane-bound enzymes, like chitin synthase, causing a cessation of fungal growth. Researchers at Sankyo speculated that the oxazolidine ring of compound **6** might bind to the site in the receptor normally occupied by the five-membered ring of lanosterol and that the 4-methyl group and the 5-(triazolylmethyl) residue of **6** fill the positions of the 13-methyl and 14-methyl groups of lanosterol, respectively (Figure 2).[9] However, the X-ray structure of compound **6** indicates a dihedral angle for the Me−C(4)−C(5)−CH_2Tr unit of 137°,[11] far from the nearly antiperiplanar disposition of the Me−C(13)−C(14)−Me unit calculated for lanosterol.[12] In a second approach, Sankyo reported structure **7** as an alternative to **6**.[9b] The X-ray analysis of **7**

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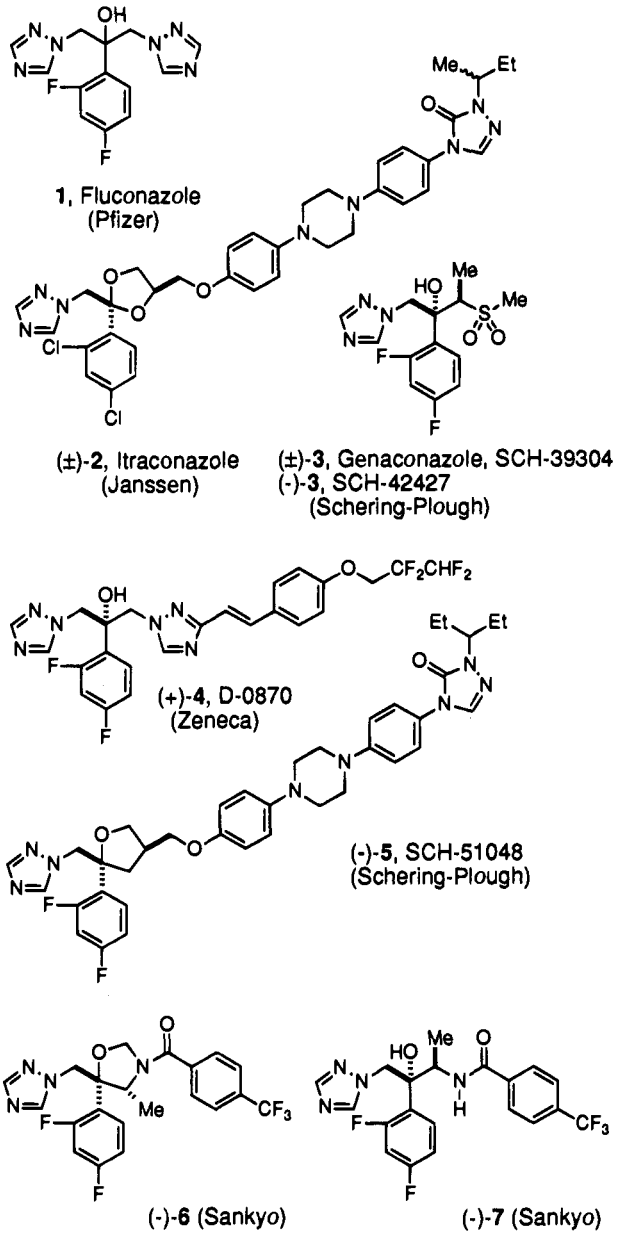


Figure 1. Azole antifungals.

is not available, but that of the related acyclic azido alcohol intermediate **8** (see Figure 2)[13] indicated a nearly antiperiplanar disposition (172°) of the unit in question, and this conformational preference was assumed to be maintained in the final product **7**.

On the basis of this model, one might justifiably assume that a conformationally restricted analogue of amido alcohol **7** that mimics the conformation of lanosterol should exhibit a higher level of intrinsic antifungal potency. We thus sought to synthesize new, conformationally locked molecules in which the dihedral angle between the methyl and the triazolylmethyl substituents approached antiperiplanarity.

It is known that 2,6-dialkyl-*N*-acylpiperidines exist in a chair conformation in which the alkyl substituents prefer the axial positions.[14] This bias has its origins in the planarity of the amide bond, which causes a severe 1,3-allylic interaction between the alkyl substituents and the amide group when the former are in the equatorial position (Figure 3). On the basis of this fact, it appeared to us that *N*-acyl morpholines of the type depicted in Figure 3 could provide good enzyme substrates. Thus, (5*R*,6*R*) *N*-acylmorpholines should adopt

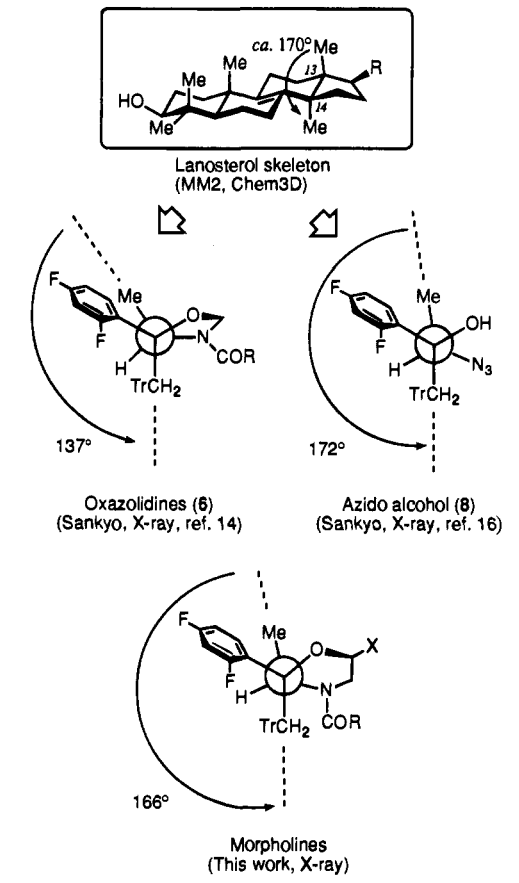


Figure 2. Relevant dihedral angles.

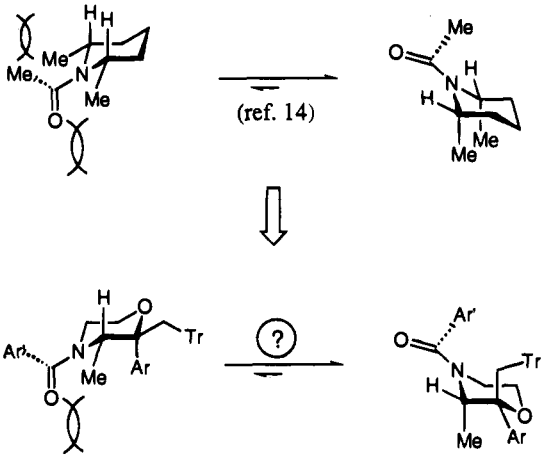


Figure 3. 1,3-Allylic strain.

a conformation in which the 5-methyl and the 6-triazolylmethyl groups are diaxial and antiperiplanar to one another, thus resembling the spatial disposition of the lanosterol D-ring substituents. In order to gain some insight into this assumption, a straightforward conformational study was conducted on morpholine **41**. Energy minimization[12] of the diaxial and diequatorial forms indicated that the (5,6)-diaxial conformation of **41** is 3 kcal·mol^{-1} more stable than the (5,6)-diequatorial form (Figure 4). Thermodynamically, this represents that at 25 °C 99.3% of the compound should be in the diaxial, bioactive form. Most importantly, the dihedral angle of the two substituents in this form was identical to that calculated for lanosterol (171°).

These assumptions were later corroborated by an X-ray analysis of the related compound **39a**, in which we further needed to determine the position of the anomeric OH. The X-ray study was performed on the

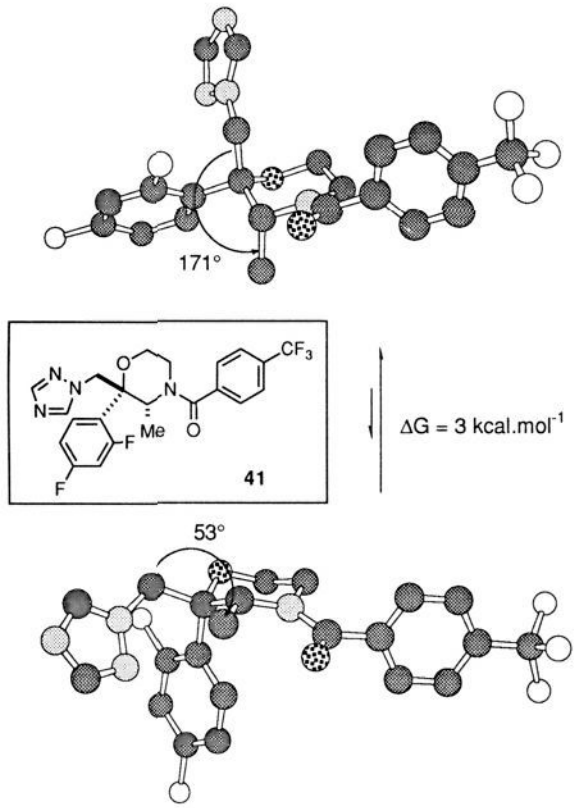


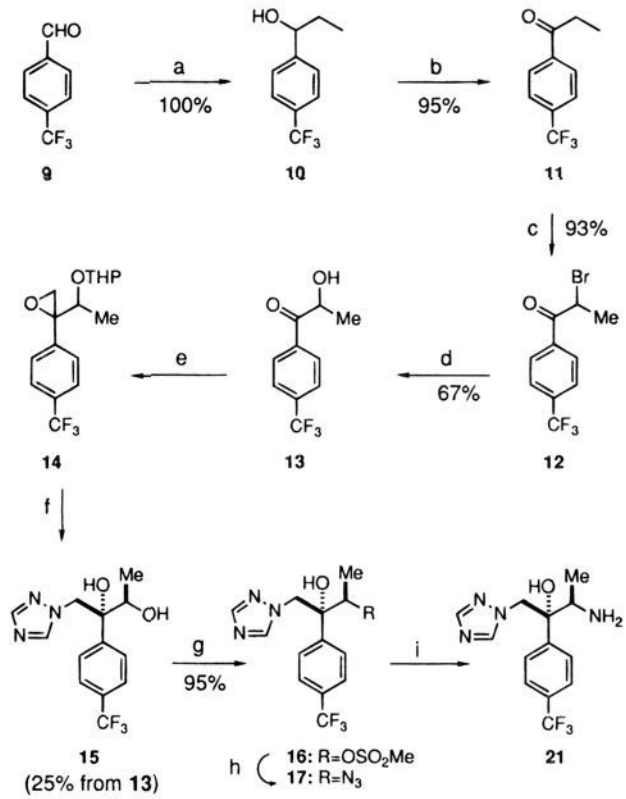
Figure 4. Chem3D-generated diaxial and diequatorial conformers of compound **41**.

ethanol solvate of the (5*R*,6*R*) enantiomer (−)-**39a**.[15] Crystallographic data indicated that the product indeed adopted the diaxial form (see Figure 5). The dihedral angle between the diaxial substituents was 166°, *i.e.* very close to the calculated value for **41**. The X-ray analysis also indicated that the compound crystallized as the α (2*S*) anomer, that is with the OH in the equatorial position.[16]

Chemistry

The racemic compounds were synthesized from 2,4-difluoro and 2,4-dichloro amino alcohols (±)-**18** and (±)-**20**, respectively, which were prepared from the corresponding 1,3-dihalobenzene in 10 steps according to a reported procedure.[9a] The new trifluoromethyl derivative (±)-**21** was obtained by a slight modification of the same general synthetic sequence (Scheme 1). Optically active intermediates (−)-**18** and (−)-**20** were first made following a modification of published syntheses starting from (*R*)-methyl lactate.[17,18] However, these preparations were long and required the use of protecting groups, and in some steps racemization was somewhat unpredictable. Furthermore, the carbinol asymmetric center was created in only 60% de. We therefore undertook a study aimed at obtaining these homochiral amino alcohols in a more practical manner. The new approach involved an unprecedented diastereoselective aldol reaction of a chiral enolate and an acetophenone derivative, tandem with a Curtius rearrangement (Scheme 2). Careful control of the reaction conditions and selection of the appropriate stereochemistry of the chiral auxiliary allowed the preparation of **18** or its carbinol epimer **19**, each in either enantiomeric form. The details of this new synthesis have been published elsewhere.[19]

Scheme 1. Synthesis of Amino Alcohol (±)-**21**[a]



[a] (a) EtMgBr, THF, 2 h, room temperature; (b) PCC, CH_2Cl_2, room temperature, 1 h; (c) Br_2, AcOH, 40 °C, 2.5 h; (d) LiOH, DMF−H_2O, 0 °C, 2 h; (e) (i) DHP, TsOH, CH_2Cl_2, room temperature, 24 h; (ii) Me_3SOI, NaH, DMSO, 60 °C, 2 h; (f) (i) triazole, *t*-BuOK, DMF, 100 °C, 1 h; (ii) TsOH, MeOH, room temperature, 2 h; (g) MsCl, pyr, room temperature, 2 h; (h) NaN_3, NH_4Cl, DMF, 115 °C, 15 h; (i) H_2, Pd−C 10%, EtOH, room temperature, 1 h.

With the amino alcohols **18**−**21** in hand, the final compounds were obtained by one of the three following procedures (we will subsequently refer to the 2,4-difluorophenyl compounds as representative of the synthesis). Lactones **31** were synthesized from **18** by the four-step sequence shown in Scheme 3 which included (a) *N*-alkylation ($BrCH_2CO_2Bn$, TEA, THF), (b) *N*-acylation with the desired acid chloride (RCOCl, TEA, $CHCl_3$), (c) benzyl ester deprotection (H_2, Pd−C, EtOH), and (d) δ-lactonization (TFAA, pyr). Cyclic hemiacetals (*i.e.* lactols) **39** and ethers **41** were prepared via

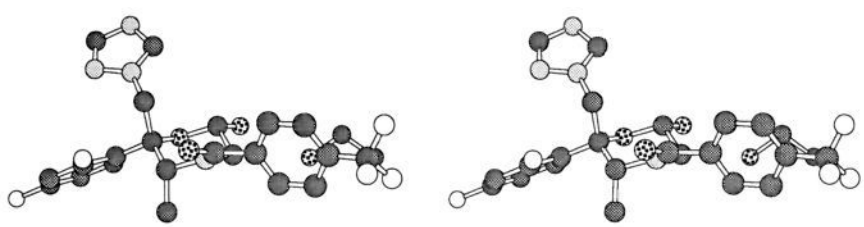
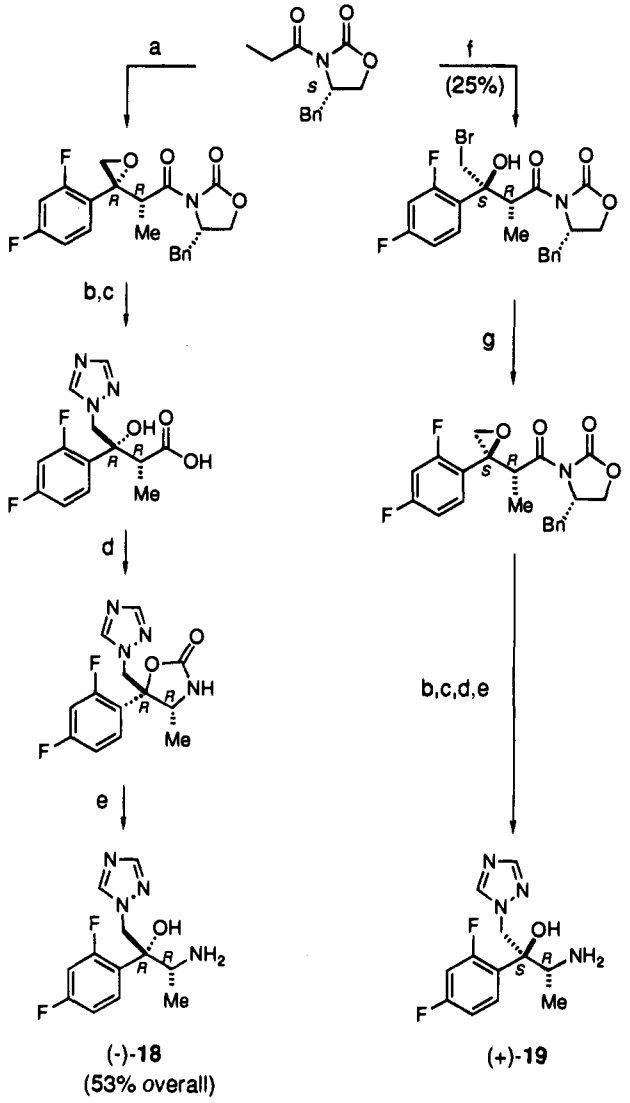


Figure 5. Stereoview of the X-ray structure of compound (−)-**39a**·EtOH solvate.

Scheme 2. Synthesis of Stereoisomers 18 and 19[14a]



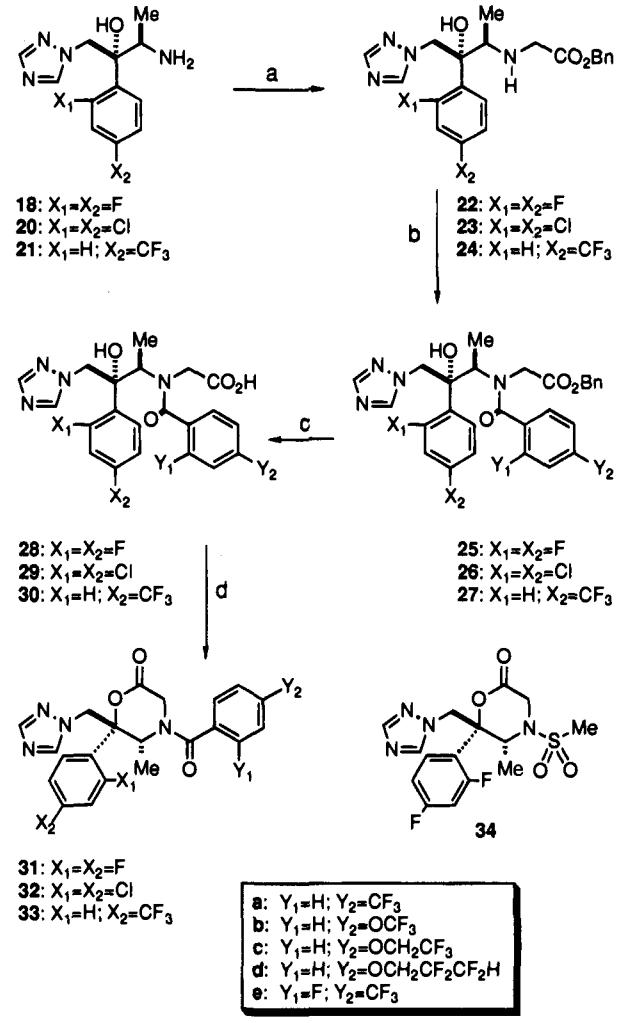
[a] (a) (i) NaHMDS, Et_2O, −78 °C, 30 min; (ii) 2,4-$F_2C_6H_3$−$COCH_2Br$, −78 °C, 1 h; (b) LiOH−H_2O_2−THF, 0 °C, 1 h; (c) Sodium triazolate, DMF, 60 °C, 3 h; (d) DPPA, pyr, 75 °C, 20 h; (e) HCl (concentrated), reflux, 2 days; (f) (i) LiHMDS, THF, −78 °C, 30 min; (ii) 2,4-$F_2C_6H_3$−$COCH_2Br$, −78 °C, 2 min; (g) NaHMDS, THF, −78 °C, 1 h (see ref 14 for experimental details). The corresponding enantiomers, (+)-**18** and (−)-**19**, were obtained departing from the (*R*)-oxazolidinone.

reduction (LAH, Et_2O) of an intermediate oxazolidine prepared by condensation of amino alcohol **18** with (benzyloxy)acetaldehyde (Scheme 4). The resulting *N*-substituted amine **35** was acylated with the desired acid chloride (RCOCl, TEA, $CHCl_3$) and deprotected to the free alcohol **37** (H_2, Pd−C, EtOH). Swern oxidation (DMSO, $(COCl)_2$, TEA, −78 °C) provided lactol **39**, whereas Mitsunobu's dehydration (DEAD, Bu_3P, THF) produced ether **41** in high yields. The optical purity of (−)-**41** was determined to be 99.92% ee by HPLC using a chiral column.

Results and Discussion

The antifungal activities of all the compounds were assessed both *in vivo* and *in vitro*. *In vitro* tests afford a more direct information on the impact of the structure upon activity against a variety of organisms, but a correlation with the *in vivo* results has frequently been unpredictable for some azole antifungals.[20] *In vivo* animal models of fungal infections better simulate the human disease, but they are tedious and SARs derived from them are the result of multiple factors including the enzyme inhibition, the pharmacokinetic profile of the compound, and, eventually, the metabolism to other structures. We thus used both methods, each one with its limitations, to progress in our optimization.

Scheme 3. Synthesis of Lactones[a]

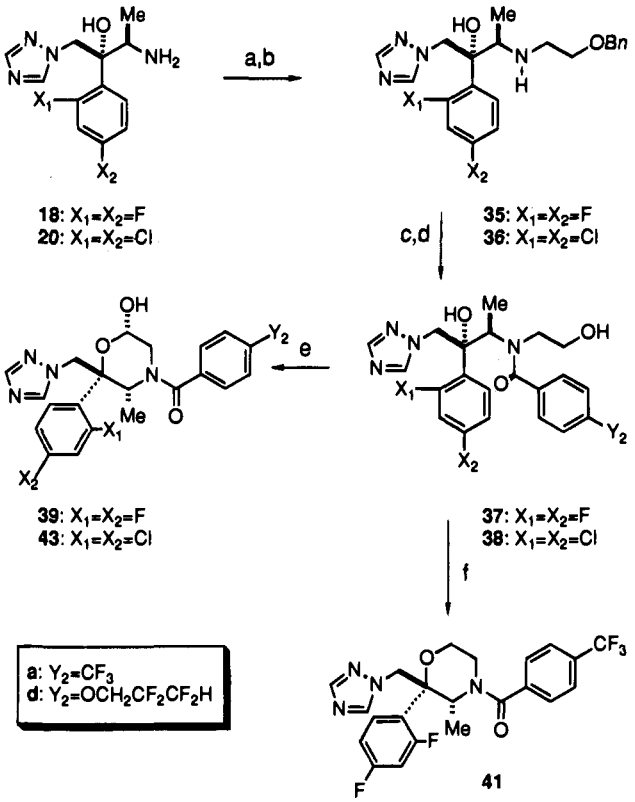


[a] (a) $BrCH_2CO_2Bn$, TEA, THF, room temperature, 3 h; (b) ArCOCl, TEA, $CHCl_3$, room temperature, 8 h; (c) H_2 (1 atm), Pd−C, EtOH, room temperature, 1 h; (d) TFAA, pyr, reflux, 1 h.

***In Vivo* Tests. Systemic Candidosis in Mice.** The *in vivo* screening test consisted in a murine systemic candidosis model in which the animals received three identical doses of the test compound 1, 4, and 24 h after infection.[9] The inoculum size was adjusted so that at least 90% of the control animals died within the first 3 days. Percent survival was noted on days 3, 5, 7, and 9. The compounds were tested at different doses (0.5−20 mg/kg) depending on their activity and were compared to the reference compounds fluconazole, SCH-42427, and (±)- and (−)-**7**. Interestingly, under these experimental conditions, fluconazole gave a consistent 25−60% mortality on day 9 over a dose range of 2.5−20 mg/kg, suggesting that a plateau of maximum protection had been reached. In our hands, itraconazole given as a PEG 200 solution showed no protection at 20 mg/kg in this model. Results are shown in Table 1.

Several general trends were tentatively drawn from the results obtained in the lactone series. First, 2,4-difluorophenyl (**31a**) and 2,4-dichlorophenyl (**32a**) derivatives were similar in potency, and both were

Scheme 4. Synthesis of Lactols and Cyclic Ethers[a]



[a] (a) $BnOCH_2CHO$, toluene, room temperature, 18 h; (b) LAH, THF, 0 °C, 4 h; (c) 4-$Y_2C_6H_4COCl$, TEA, $CHCl_3$, room temperature, 8 h; (d) H_2 (1 atm), Pd–C, EtOH, room temperature, 3 days; (e) TFAA, DMSO, TEA, −78 °C, 1 h; (f) DEAD, Bu_3P, THF, room temperature, 3 h.

significantly more active than the 4-trifluoromethyl derivative **33a**. A small series of fluorinated 4-alkyl- and 4-alkoxy benzoyl amides was tested, but this variable seemed not to play a crucial role upon protection as compounds with comparable overall activity were produced. A 2-fluoro-4-(trifluoromethyl)benzoyl group (**31e**) afforded very active compounds, as reported for a related series.[9] In the lactol family, however, a 2,2,3,3-tetrafluoropropoxy group significantly reduced mortality protection. On the basis of these facts and considering synthetic costs, a 4-CF_3 group was chosen as the benzoyl substituent. The possibility of replacing the amide bond with a sulfonamide was examined by preparing compound **34**. On the basis of our previous results in the acyclic sulfonamide series[21] we selected a methyl group for the sulfonamide unit. Nonetheless, this substitution resulted in a significant impairment of activity.

With regard to the influence of the C-2 oxidation stage, no differences were observed between racemic lactones (**31a**), lactols (**39a**), and ethers (**41**) at the higher doses (20 to 5 mg/kg). In this dose range, all three products showed 100% protection and were superior to fluconazole. However, at the lower dose of 1 mg/kg, lactols and ethers provided longer protection than lactones. This was attributed to the high susceptibility of the lactone function to hydrolysis.

As will be discussed in a separate section, stereochemistry played a crucial role as only the levo, (5*R*,6*R*) enantiomers displayed antifungal activity (Tables 1 and 3). We decided thus to pursue the study with only these stereoisomers. The mortality curve obtained for the most representative compounds at 1 mg/kg is represented in Figure 6. Lactone (−)-**31a** was somewhat more efficient than fluconazole, whereas products (−)-**39a** and (−)-**41** showed a clear improved activity. Products (−)-**39a**, SCH-42427, and (−)-**7** showed a 100% protection on day 9.

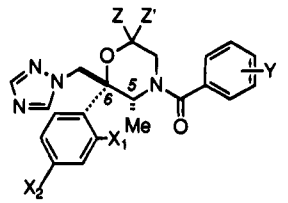
It has been shown that azoles form water-soluble inclusion complexes with certain types of cyclodextrins and that these agents significantly improve oral absorption in some cases.[22] In order to prove this effect in our series, cyclic ether (−)-**41** was administered at 0.5 mg/kg both as a solid suspension and as a water solution containing (hydroxypropyl)-β-cyclodextrin.[23] The observed survival evolution, however, was practically identical in both cases.

Vaginal Candidosis in the Rat. To further assess the anticandidal properties of the new compounds, enantiomers (−)-**31a**, (−)-**32a**, (−)-**39a**, and (−)-**41** were tested in a vaginal candidosis model in the rat and were compared to fluconazole, SCH-42427, and (−)-**7**. The compounds were administered once daily for 3 days, starting 3 days after infection. Vaginal samples were obtained for culture at days 10 and 15 after infection. The results are shown in Table 2. None of the control animals were culture-negative at days 10 and 15. At 0.25 mg/kg, both lactone (−)-**31a** and fluconazole gave little protection (10%) whereas the dichloro counterpart (−)-**32a** and ether (−)-**41** displayed a higher cure rate (50–70%). The most encouraging results were obtained with lactol (−)-**39a**, which, like SCH-42427 and amido alcohol (−)-**7**, protected all the animals against infection at the stated dose. When doses were reduced to 0.1 mg/kg/day, lactol (−)-**39a** still showed 50% protection on day 15, whereas (−)-**41**, SCH-42427, and (−)-**7** protected 20% of the animals at this dose.

***In Vitro* Results.** The susceptibilities of several microorganisms to the new compounds and to the reference products fluconazole, ketoconazole, itraconazole, SCH-42427, and (±)- and (−)-**7** were assessed *in vitro* by the agar dilution method. The MICs obtained are shown in Table 3. Under the conditions tested, lactones showed very little or no *in vitro* activity, except for (±)-**32d**. Sulfonamide (±)-**34**, as well as all the dextro enantiomers tested, were totally inactive. Lactols and fluconazole afforded intermediate MICs whereas itraconazole, SCH-42427, (−)-**7**, and (−)-**41** showed high activities.[25] Under our experimental conditions, ketoconazole showed the highest activity. In general, higher susceptibilities (lower MICs) were observed with yeasts, and poorer susceptibilities, with filamentous fungi.

Selected compounds (−)-**39a** and (−)-**41** were further tested *in vitro* by the broth macrodilution method against a variety of yeasts following the NCCLS guidelines and compared to (−)-**7**, fluconazole, and ketoconazole. Both, inhibitory and fungicidal values were calculated (Table 4). In general, amido alcohol (−)-**7** and ketoconazole showed comparably high activities. Cyclic ether (−)-**41** was 2–4 times less active than its acyclic counterpart (−)-**7**. Lactol (−)-**39a** showed the weakest activities, with MIC values slightly higher than those found for fluconazole against *C. albicans*, and clearly more resistant against non-*albicans* species. None of the azoles was cidal against the *C. albicans* tested. Ketoconazole and (−)-**7** showed cidal properties against non-*albicans* species. All the five compounds showed both good fungistatic and fungicidal properties against one strain of *Cryptococcus neoformans*.

Table 1. Antifungal Activities in an *in Vivo* Model of Murine Systemic Candidosis[a]



compd	stereochemistry	Z,Z'	X_1	X_2	Y	dose (mg/kg) po	*n*	% survival rate on day 3	5	7	9
					Lactones						
(±)-**31a**	5*R**,6*R**	=O	F	F	4-CF_3	2.5	20	100	100	95	70
						1	20	95	85	30	0
(−)-**31a**	5*R*,6*R*	=O	F	F	4-CF_3	1	10	100	100	90	10
(±)-**31b**	5*R**,6*R**	=O	F	F	4-OCF_3	2.5	10	100	100	100	90
(±)-**31c**	5*R**,6*R**	=O	F	F	4-OCH_2CF_3	2.5	10	100	100	100	70
(±)-**31d**	5*R**,6*R**	=O	F	F	4-$OCH_2CF_2CF_2H$	2.5	10	100	100	90	70
(±)-**31e**	5*R**,6*R**	=O	F	F	2-F-4-CF_3	2.5	10	100	100	100	90
(±)-**33a**	5*R**,6*R**	=O	H	CF_3	4-CF_3	2.5	10	20	20	10	10
(±)-**32a**	5*R**,6*R**	=O	Cl	Cl	4-CF_3	2.5	20	100	100	100	100
						1	20	100	80	55	45
(−)-**32a**	5*R*,6*R*	=O	Cl	Cl	4-CF_3	1	10	100	100	70	10
(+)-**32a**	5*S*,6*S*	=O	Cl	Cl	4-CF_3	1	10	0	0	0	0
(±)-**32d**	5*R**,6*R**	=O	Cl	Cl	4-$OCH_2CF_2CF_2H$	2.5	10	90	90	80	60
(±)-**34**	5*R**,6*R**					2.5	10	40	0	0	0
					Lactols						
(±)-**39a**	5*R**,6*R**	H,OH	F	F	4-CF_3	2.5	10	100	100	100	100
						1	20	85	85	55	25
(−)-**39a**	5*R*,6*R*	H,OH	F	F	4-CF_3	1	30	100	100	100	100
						0.5	10	100	100	80	40
(+)-**39a**	5*S*,6*S*	H,OH	F	F	4-CF_3	5	10	40	0	0	0
(±)-**39d**	5*R**,6*R**	H,OH	F	F	4-$OCH_2CF_2CF_2H$	1	10	80	50	0	0
(±)-**43a**	5*R**,6*R**	H,OH	Cl	Cl	4-CF_3	2.5	10	100	100	100	100
						1	10	100	100	90	70
					Cyclic Ethers						
(±)-**41**	5*R**,6*R**	H,H	F	F	4-CF_3	2.5	10	100	100	90	90
						1	10	80	70	10	0
(−)-**41**[b]	5*R*,6*R*	H,H	F	F	4-CF_3	1	10	100	100	100	70
						0.5	10	100	100	70	40
						0.5[c]	10	100	100	60	30
(+)-**41**[b]	5*S*,6*S*	H,H	F	F	4-CF_3	5	10	10	0	0	0
					Reference Compounds						
(±)-**7**						2.5	10	100	100	100	100
						1	10	100	100	80	60
(−)-**7**						1	10	100	100	100	100
						0.5	20	100	100	95	70
fluconazole						20	100	100	100	98	75
						10	10	100	100	80	60
						5	10	100	100	90	40
						2.5	20	100	100	95	70
						1	50	100	96	52	6
						0.5	10	100	90	20	10
SCH-42427						1	10	100	100	100	100
						0.5	10	100	100	100	100
control						vehicle	100	9	0	0	0

[a] See the Experimental Section for details. [b] Ethanol solvate. [c] As a water solution in (hydroxypropyl)-β-cyclodextrin.

At this point, comments must be made to some of the above results before conclusions are drawn. For example, the low *in vitro* activity of lactones could be due to their easy chemical conversion to the corresponding hydroxy acids **28**−**30**, which were proved to be inactive both *in vitro* and *in vivo*. Thus, although the chemical integrity of the lactones was monitored during sample preparation, variable hydrolytic cleavage during fungal growth cannot be discarded, and their MIC values should be interpreted carefully.

Other considerations must be taken into account regarding compound (−)-**39a**, which showed an unexpected low *in vitro* activity. First, the hemiacetal function in that structure may react, through its open hydroxy aldehyde form, with some of the components in the agar medium and form intermediates with diminished activities. Additionally, the physicochemical characteristics (dielectric constant, presence of hydrogen donors, etc.) of that medium might play an important role upon anomer equilibration and afford preferentially the β anomer, in which the bioactive conformation might be energetically unfavored. For these reasons, we believe that the most representative *in vitro* values are those of compound (−)-**41**, as no chemical transformation is to be expected for this structure. The results of Tables 3 and 4 show that the overall *in vitro* activity profile of this compound was good and somewhat lower than its acyclic counterpart (−)-**7**. The MICs of these two compounds against the strain of *C. albicans* used in the *in vivo* studies correlate well with these trends.

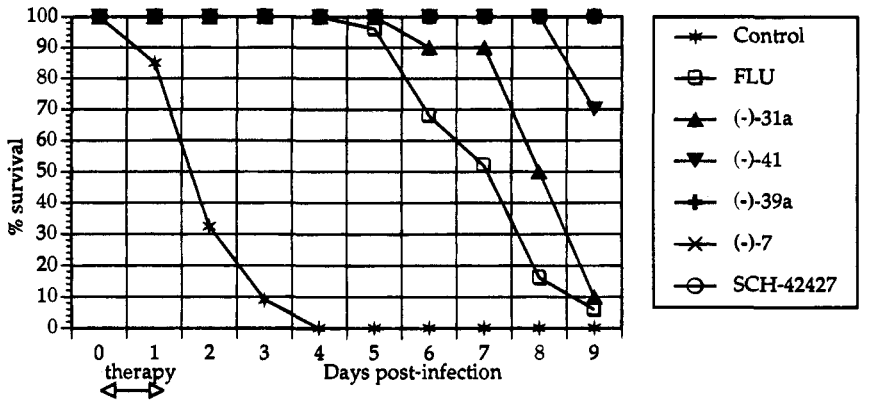


Figure 6. Cumulative mortality of mice infected with *C. albicans* and treated three times with 1 mg/kg of drug.

Table 2. *In Vivo* Antifungal Activities in a Rat Model of Vaginal Candidosis[a]

compd	*n*	dose (mg/kg/day) po	% curation rate on day 10	% curation rate on day 15
(−)-**31a**	10	0.5	90	90
	10	0.25	10	0
(−)-**32a**	10	0.5	80	100
	10	0.25	70	70
(−)-**39a**	20	0.25	95	100
	10	0.1	30	50
(−)-41	10	0.25	40	60
	10	0.1	10	20
(−)-**7**	10	0.25	100	100
	10	0.1	0	20
fluconazole	10	0.5	20	20
	20	0.25	10	25
SCH-42427	10	0.25	100	100
	10	0.1	20	20
control	30	vehicle	0	3

[a] See the Experimental Section for details.

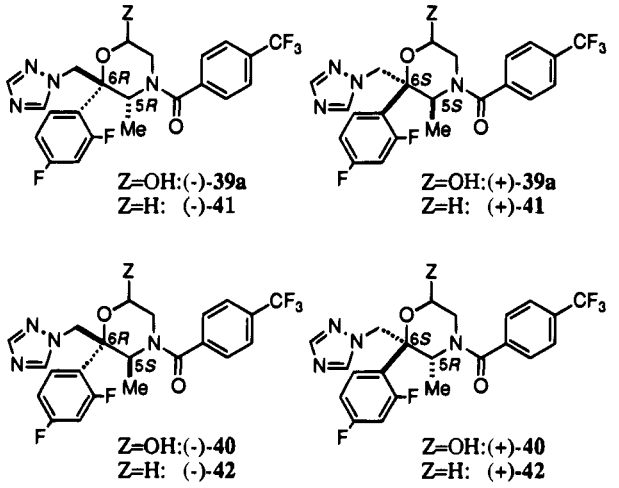


Figure 7. Structures of diastereomers.

Stereochemistry. The effect of the absolute stereochemistry of each of the two chiral centers was fully assessed for structures **39a** and **41** (Figure 7). Thus, the four diastereomers generated by the two asymmetric carbons in each of these two products were prepared, and their activity was tested *in vitro* and *in vivo* at a dose of 5 mg/kg. In both structures, only one diastereomer, the (5*R*,6*R*), showed activity (100% protection on day 9), the other three being virtually inactive both *in vivo* (0% protection from day 4) and *in vitro* (MICs > 80). It has been previously anticipated for other azole derivatives containing related asymmetric centers that the activity of the (*R**,*R**) racemate is due to the (*R*,*R*) enantiomer and that the (*S*,*S*) counterpart is devoid of activity.[9,12,24] However, there is only one previous case in which the individual potencies of the enantiomers forming the (*R**,*S**) racemate have been studied. Thus, for 2-(2,4-difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols, researchers at Takeda found that activity *in vivo* was observed only in the (2*R*,3*R*) derivative, but that *in vitro* both the (2*R*,3*R*) and the (2*R*,3*S*) derivatives displayed activity, and concluded that the (*R*) configuration of carbon C-2 (*i.e.* the carbinol center) might be the key factor for potent and broad antifungal activity *in vitro*.[12] This contrasts with our results, where the equivalent compounds having the (*R*)-carbinol configuration (*i.e.* (−)-**40** and (−)-**42**) were devoid of *in vitro* activity.

In summary one may tentatively conclude that the conformational restrictions imposed in the cyclic compounds maintain, but do not improve, the overall activity of the substrates. Thus, if antiperiplanarity is indeed a requisite for optimal enzyme recognition, the excellent profile observed for the acyclic analogue (−)-**7** implies that this skeleton must easily attain that conformation in the substrate−enzyme complex and that conformational lock does not appear to improve it.

Toxicity Tests. Preliminary toxicity data in the rat showed excellent tolerance upon exposure to the selected new drugs. Thus, compounds (−)-**31a**, (−)-**32a**, (−)-**39a**, (−)-**41**, and fluconazole were administered orally to rats at 100 mg/kg once daily for 28 days. A control group was treated with the vehicle only. All 10 animals in each group (five males, five females) survived treatment. Weight evolution in the females was comparable in all groups, including the control. In the males, the weight of the treated animals was slightly lower (10−15%) than those of the control group. This trend was more pronounced (≥20% weight reduction) in the dichloro derivative (−)-**32a**. Postmortem histopathological analysis of hepatic, renal, and adrenal samples indicated a severe hepatocytary vacuolization in the males treated with fluconazole whereas this effect was absent or mild in the rest of the groups. With regard to the renal and adrenal samples, no alteration of parameters was observed, either in the fluconazole group or in those treated with our compounds. For products (−)-**39a** and (−)-**41**, the histopathological analysis was extended to the thymus, lung, heart, spleen, testicles, uteri, and ovaries. Microscopic observation of these samples did not show any alteration.

On the basis of these results, compounds (−)-**39a** (UR-9746) and (−)-**41** (UR-9751) have been selected for further pharmacological development. Recent studies have proved efficacy against microorganisms other than *Candida*. Thus, the products have been shown to be

Table 3. *In Vitro* Antifungal Activities (Agar Dilution Method)[a]

comp	*C. alb.*[1]	*C. alb.*[2]	*C. alb.*[3]	*C. gui*	*C. kru*	*C. par*	*C. pse*	*C. tro*	*R. rub*	*T. gla*	*A. fl*	*A. fum*	*A. nig*	*M. can*	*M. gyp*	*T. men*	*T. rub*
(±)-**31a**	80	40	>80	>80	>80	>80	80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(−)-**31a**	40	40	80	>80	>80	>80	80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**31b**			80	>80	>80	>80	40		>40	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**31c**			80	>80	>80	>80	40		>40	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**31d**	10	10	>80	80	>80	80	80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**31e**	20	20	40	>80	>80	80	80	80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**33a**	>80	>80	>80	>80	>80	>80	80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**32a**	10	5	20	80	>80	40	20	80	80	>80	>80	>80	>80	>80	>80	>80	>80
(−)-**32a**	10	5	20	80	>80	40	10	40	>80	>80	>80	>80	>80	>80	>80	>80	>80
(+)-**32a**	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**32d**	2.5	1.25	20	80	>80	20	10	80	80	>80	>80	>80	>80	>80	80	>80	>80
(±)-**34**	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**39a**	10	2.5	>80	>80	>80	80	10	>80	>80	>80	>80	>80	>80	80	>80	>80	>80
(−)-**39a**[b]	2.5	1.25	10	80	>80	40	20	40	>80	>80	>80	80	>80	40	80	>80	40
(+)-**39a**[b]	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**39d**	5	1.25	80	80	>80	10	0.63	80	>80	>80	>80	>80	>80	>80	>80	>80	>80
(±)-**43a**	1.25	0.63	5	5	10	2.5	0.15	20	2.5	20	20	20	>80	40	40	40	40
(±)-**41**[c]	1.25	0.63	80	80	80	40	5	80	40	40	>80	40	>80	40	40	80	20
(−)-**41**[c]	0.31	0.15	1.25	20	40	10	40	40	5	10	40	40	80	20	20	40	10
(+)-**41**[c]	>80	>80	>80	>80	>80	>80	10	>80	>80	>80	>80	>80	>80	>80	>80	>80	80
(±)-**7**	0.63	0.31	80	2.5	>80	20	40	80	2.5	>80	>40	>80	>80	>80	>80	>80	>40
(−)-**7**	0.15	0.15	80	0.63	20	2.5	40	80	1.25	20	20	20	40	20	10	40	10
fluconazole	2.5	2.5	40	10	>80	20	80	80	>80	80	>80	>80	>80	>80	80	>80	>80
ketoconazole	≤0.03	≤0.03	0.15	≤0.03	1.25	0.07	10	2.5	0.07	1.25	2.5	5	40	2.5	0.63	5	1.25
itraconazole	0.07	<0.03	0.63	0.15	1.25	0.07	80	20	>80	>80	>80	0.15	>80	80	80	>80	0.63
SCH-42427	0.63	0.63	40	2.5	80	2.5	40	80	80	40	>80	10	40	10	20	10	10

[a] MIC values (μg/mL). See Experimental Section for details. [b] Hemiethylene glycol solvate, hemihydrate. [c] Ethanol solvate. *C. alb*[1], *C. albicans* 60, used in the *in vivo* tests; *C. alb*[2], *C. albicans* 406; *C. alb*[3], *C. albicans* 76; *C. gui*, *Candida guilliermondii* 26; *C. kru*, *Candida krusei* 70; *C. par*, *Candida parapsilosis* 61; *C. pse*, *Candida pseudotropicalis* 13; *C. tro*, *Candida tropicalis* 2.11; *R. rub*, *Rhodotorula rubra* 16; *T. gla*, *Torulopsis glabrata* 78; *A. fl*, *Aspergillus flavus* 19; *A. fum*, *Aspergillus fumigatus* 33; *A. nig*, *Aspergillus niger* 18; *M. can*, *Microsporum canis* 47; *M. gyp*, *Microsporum gypseum* 22; *T. men*, *Trichophyton mentagrophytes* 23; *T. rub*, *Trichophyton rubrum* 90.

approximately 10 times more potent than fluconazole in murine coccidioidomycosis[26a] and superior to itraconazole (CD complex) in murine histoplasmosis.[26b] Additionally, very encouraging results have also been obtained in *in vivo* models of murine cryptococcosis where the two compounds have demonstrated higher activity than fluconazole and amphotericin B.[26c-f] In general, (−)-**39a** has shown higher potency than (−)-**41**. The compounds, however, have failed so far to show any particular activity in murine models of aspergillosis.

Conclusions

A series of compounds containing a susbtituted *N*-acylmorpholine unit mimicking lanosterol D ring were designed for antifungal activity. The activity was strongly dependent on stereoisomerism. When compared to their acyclic analogue (−)-**7**, the *in vivo* activity of the new compounds was maintained, whereas the *in vitro* susceptibilities were somewhat impaired. Two products, (−)-**39a** (UR-9746) and (−)-**41** (UR-9751), have been selected for further testing. Both compounds have demonstrated high efficacy in animal models of systemic and vaginal candidosis, with a potency superior to fluconazole and comparable to SCH-42427. This anticandidal activity, lack of toxicity after a 28-day treatment of 100 mg/kg/day in rats, and the reported high activity against endemic mycoses are encouraging for the development of these compounds as oral antifungal agents.

Experimental Section

Chemistry. Tetrahydrofuran (THF) and ether were dried by distillation under argon from sodium metal. Flash chromatography was performed on SDS silica gel 60 (230–400 mesh). ^{1}H (80 MHz) and ^{13}C NMR (20 MHz) spectra were recorded on a Bruker AC-80 spectrometer. Coupling constants are reported in hertz. Melting points were recorded on Mettler FP-80, FP-81, and FP-82 apparatuses by heating a capillary tube containing the sample at a rate of 3 °C/min. IR spectra were recorded on a Perkin-Elmer 983 instrument. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature and at 589 nm using a sodium lamp and a 1 mL cell. Data are reported as follows: $[\alpha]_D$ (concentration g/100 mL, solvent). Elemental analysis was performed with a Carlo Erba EA-1108 instrument, and the results are within 0.4% of the theoretical values, except where noted. Analytical HPLC was performed on a Hewlett-Packard HP 1050 chromatograph coupled to a UV detector (210 nm). For routine HPLC analyses, a 4 mm × 25 cm Lichrospher 100RP18e 5 μm silica gel column was used. For optical purity assays, a CHIRAL AGP 100 × 4 mm column was employed. HPLC-MS analyses were performed using the same HPLC system coupled through a Hewlett-Packard particle-beam interface 59980 to a Hewlett-Packard 5988 mass spectrometer.

Water-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Racemic amines (±)-**18** and (±)-**20** and compound (−)-**7** were obtained according to a published procedure.[9] (Benzyloxy)acetaldehyde was obtained by oxidation of 3-(benzyloxy)-1,2-propanediol with $NaIO_4$. Fluconazole was synthesized in our research center, starting from 1,3-dichloroacetone and (2,4-difluorophenyl)-magnesium bromide and reacting the resulting mixture with sodium triazolate, following a published procedure.[27] SCH-42427 and itraconazole were kindly provided by Schering-Plough and Janssen, respectively.

All final products were assayed for homogeneity on analytical thin-layer chromatography (TLC) using Macherey-Nagel 0.25 mm silica gel SIL G-25 plates.

1-[4-(Trifluoromethyl)phenyl]-1-propanol [(±)-10]. Dry THF (700 mL), magnesium turnings (16.75 g, 0.69 mol), and an iodine crystal were placed in a flask, and the mixture was stirred intensively at room temperature. Bromoethane (68 g, 46.7 mL, 0.69 mol, 1.1 equiv) was added dropwise, and the resulting mixture was stirred for 30 min. The reaction mixture was then cooled to 0 °C and 4-(trifluoromethyl)benzaldehyde (100 g, 0.57 mol, 1 equiv) was added dropwise. After stirring at room temperature for 2 h, the reaction mixture was cooled to 0 °C and 1 *N* HCl (750 mL) was added carefully. The mixture was concentrated and the aqueous residue extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated *in vacuo* to afford (±)-**10** as a brown oil (117.8 g, 100% mass balance) that was used in the next step without

Table 4. *In Vitro* Antifungal Activities against Yeasts (Broth Macrodilution Method)[a]

microorganism	value	fluco	keto	(−)-**7**	(−)-**41**	(−)-**39a**
Candida albicans	MIC	1	0.063	0.125	0.25	2
2.01	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	0.25	≤0.031	≤0.031	0.125	0.5
31	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	2	0.063	0.063	0.25	0.5
ATCC 10231	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	0.5	≤0.031	≤0.031	0.25	1
60 (*in vivo* test)	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	0.25	≤0.031	≤0.031	0.125	1
76	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	0.25	0.063	≤0.031	0.25	1
C406	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	0.25	≤0.031	≤0.031	0.125	0.5
C52	MFC	>64	>16	>64	>64	>64
Candida albicans	MIC	0.5	≤0.031	≤0.031	0.125	1
C56	MFC	>64	>16	>64	>64	>64
Candida parapsilosis	MIC	4	0.063	0.125	2	16
ATCC 22019	MFC	64	4	2	4	32
Candida parapsilosis	MIC	2	0.5	1	32	>64
ATCC 141095	MFC	>64	16	32	>64	>64
Candida parapsilosis	MIC	1	0.063	0.063	1	4
2.07	MFC	>64	>16	64	>64	>64
Candida parapsilosis	MIC	1	0.125	0.063	2	8
C292	MFC	>64	16	4	>64	>64
Candida parapsilosis	MIC	0.25	0.063	≤0.031	0.5	2
C74	MFC	2	0.25	0.125	8	32
Candida guilliermondii	MIC	8	0.125	0.25	8	32
26	MFC	64	4	4	>64	>64
Candida krusei	MIC	32	2	2	32	>64
70	MFC	>64	4	8	>64	>64
Candida krusei	MIC	64	2	4	32	>64
C64	MFC	>64	8	16	>64	>64
Candida pseudotropicalis	MIC	0.5	0.063	≤0.031	0.125	0.5
ATCC 28838	MFC	32	>16	2	32	64
Candida tropicalis	MIC	8	2	1	16	>64
50	MFC	>64	>16	>64	>64	>64
Candida tropicalis	MIC	1	0.25	0.25	4	64
2.11	MFC	>64	8	64	>64	>64
Torulopsis glabrata	MIC	32	8	8	16	>64
78	MFC	>64	>16	>64	>64	>64
Cryptococcus neoformans	MIC	0.5	≤0.031	≤0.031	0.125	0.25
74	MFC	1	1	0.063	0.25	2
Cryptococcus neoformans	MIC	8	2	0.5	2	4
87	MFC	>64	16	64	>64	>64

[a] MIC and MFC values (μg/mL).

further purification: ^{1}H NMR ($CDCl_3$) δ 7.52 (q, J = 5.7, 4H, arom), 4.8–4.5 (m, 1H, C*H*OH), 1.73 (q, J = 6.8, 2H, CH_2), 0.92 (t, J = 6.8, 3H, Me).

4-(Trifluoromethyl)propiophenone (11). A solution of unpurified alcohol (±)-**10** (23 g, 0.11 mol) in CH_2Cl_2 (60 mL) was added dropwise to a suspension of PCC (36.6 g, 0.17 mol) and Celite (35 g) in CH_2Cl_2 (260 mL) at room temperature. The mixture was stirred for 1 h, and then diethyl ether (500 mL) was added. The resulting brown slurry was filtered through Celite and washed with CH_2Cl_2, the combined organic solution was washed with 1 *N* NaOH aqueous solution and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated *in vacuo* to a dark brown oil (20.7 g, 95% mass balance) that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.2, 2H, arom), 7.71 (d, J = 8.2, 2H, arom), 3.04 (q, J = 7.1, 2H, CH_2), 1.24 (t, J = 7.1, 3H, Me).

α-Bromo-4-(trifluoromethyl)propiophenone [(±)-12]. To a solution containing unpurified ketone 11 (37 g, 0.18 mol) in acetic acid (600 mL) was added dropwise a 5% solution of Br_2 in acetic acid (190 mL) at room temperature. When the addition was completed, the reaction mixture was stirred at 40 °C for 2.5 h. Then, acetic acid was distilled off, and the residue was diluted with EtOAc (300 mL) and washed with a 10% aqueous $NaHCO_3$ solution. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated *in vacuo* to afford (±)-**12** as an oil (46.9 g, 93% mass balance) that was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 8.13 (d, J = 8.2, 2H, arom), 7.74 (d, J = 8.2, 2H, arom), 5.26 (q, J = 6.6, 1H, CHBr), 1.92 (d, J = 6.6, 3H, Me).

α-Hydroxy-4-(trifluoromethyl)propiophenone [(±)-13]. To a solution of unpurified bromo derivative (±)-**12** (45.9 g, 0.16 mol) in a **4**:1 mixture of DMF and H_2O (460 mL) was added $LiOH·H_2O$ (6.9 g, 0.16 mol) at 0 °C, and the resulting mixture was stirred for 2 h. The reaction mixture was then poured into brine and EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford 39.81 g of a yellowish oil. Purification by chromatography on silica gel (EtOAc:hex mixtures of increasing polarity) yielded (±)-**13** as a colorless oil (23.46 g, 67%): ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8.2, 2H, arom), 7.74 (d, J = 8.2, 2H, arom), 5.2 (br q, 1H, CH), 1.45 (d, J = **7**, 3H, Me).

2-[1-(Tetrahydropyran-2-yloxy)ethyl]-2-[4-(trifluoromethyl)phenyl]oxirane [(±)-14]. A mixture containing alcohol (±)-**13** (23.46 g, 0.11 mol), 2,3-dihydropyran (12.6 mL, 0.14 mol), pyridinium *p*-toluenesulfonate (0.006 mol), and CH_2Cl_2 (260 mL) was stirred at room temperature for 24 h. Then, 10% aqueous $NaHCO_3$ solution was added, and the layers were separated. The organic layer was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated *in vacuo* to a thick oil (28.6 g) that was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 8.2–7.9 (m, 2H, arom), 7.71 (d, J = 8.2, 2H, arom), 5.3–4.5 (m, 2H), 4.2–3.3 (m, 2H), 2.0–1.3 (m, 9H).

Following, a suspension of 55% NaH (2.7 g, 0.11 mol) was added to anhydrous DMSO (300 mL), and the mixture was stirred at 60 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature, and trimethylsulfoxonium iodide (41.6 g, 0.19 mol) was added, after which the mixture was

allowed to react for 1 h. Then a solution containing unpurified α-(tetrahydropyran-2-yloxy)-4-(trifluoromethyl)propiophenone (28.6 g, 0.09 mol) in DMSO (200 mL) was added. After stirring for 2 h, the mixture was partitioned between benzene and water. The organic layer was separated and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated to afford (±)-**14** as a brown oil (29.7 g) that was used as obtained in the next step: ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 4H, arom), 5.4–4.6 (m, 1H, OCHO), 4.4–3.2 (m, 3H), 3.1 (m, 1H, epoxide), 2.7 (m, 1H, epoxide), 1.8–1.4 (m, 6H), 1.4–1.0 (m, 3H, Me).

(2*R,3*R**)-1-(1*H*-1,2,4-Triazol-1-yl)-2-[4-(trifluoromethyl)phenyl]-2,3-butanediol [(±)-15].** The unpurified epoxide (±)-**14** (29.7 g) was dissolved in DMF (300 mL) and treated with 1,2,4-triazole (26.0 g, 0.37 mol) and potassium *tert*-butoxide (21.12 g, 0.19 mol) at 100 °C for 1 h. DMF was distilled off, and the residue was partitioned between benzene and water. The organic phase was separated, washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated to afford a brown oil (36.28 g). This crude reaction mixture was then dissolved in methanol (300 mL) and treated with *p*-toluenesulfonic acid (17.9 g, 0.094 mol) at room temperature for 2 h. A 10% aqueous $NaHCO_3$ solution was added, and the volatiles were removed *in vacuo*. The aqueous residue was extracted with EtOAc and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated to a brown solid. Recrystallization from EtOAc yielded the pure (2*R**,3*R**) diastereomer [*i.e.* (±)-**15**] as a white solid (8.41 g, 25% from (±)-**13**): mp 177–178 °C; ^{1}H NMR (MeOH-d_4 + $CDCl_3$) δ 7.98 (s, 1H, CH triazole), 7.73 (s, 1H, CH triazole), 7.6–7.3 (m, 4H, arom), 4.72 (s, 2H, CH_2), 4.16 (q, J_q = 7.0, 1H, C*H*Me), 0.96 (d, J = 7, 3H, CH*Me*). Anal. ($C_{13}H_{14}F_3N_3O_2$) C, H, N.

(2*R,3*R**)-3-[(Methylsulfonyl)oxy]-2-[4-(trifluoromethyl)phenyl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-16].** To a cooled solution (0 °C) of diol (±)-**15** (8.4 g, 28 mmol) in pyridine (300 mL) was added methanesulfonyl chloride (5.11 g, 45 mmol, 1.6 equiv), and the reaction mixture was stirred at room temperature for 2 h. Then, pyridine was removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 and a 10% aqueous $NaHCO_3$ solution. The organic phase was separated, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated to an oil (9.37 g) that was used in the next step without further purification: ^{1}H NMR (MeOH-d_4 + $CDCl_3$) δ 8.00 (s, 1H, CH triazole), 7.72 (s, 1H, CH triazole), 7.54 (s, 4H, arom), 5.16 (q, J_q = 7, 1H, C*H*Me), 4.77 (s, 2H, CH_2), 3.16 (s, 3H, $MeSO_2$), 1.24 (d, J = 7, 3H, CH*Me*).

(2*R,3*R**)-3-Azido-1-(1*H*-1,2,4-triazol-1-yl)-2-[4-(trifluoromethyl)phenyl]-2-butanol [(±)-17].** A solution of mesylate (±)-**16** (9.4 g), sodium azide (8.4 g, 0.13 mol), and ammonium chloride (1.3 g, 0.025 mol) in DMF (140 mL) was heated at 115 °C for 15 h. DMF was distilled off, and the residue was partitioned between water and benzene. The organic layer was washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4, the drying agent was filtered off, and the filtrate was concentrated to afford (±)-**17** as a yellowish oil (8.7 g, 95% mass balance). Recrystallization from EtOAc:hex afforded an analytical sample as a white solid: mp 91–94 °C; IR (KBr) ν 3245, 2110, 1611, 1505, 1324 cm^{-1}; ^{1}H NMR (MeOH-d_4 + $CDCl_3$) δ 7.82 (s, 1H, CH triazole), 7.71 (s, 1H, CH triazole), 7.47 (AB q, Δν = 0.16, J = 8.4, 4H, arom), 5.16 (AB q, Δν = 0.20, J = 14.2, 2H, $TrCH_2$), 3.70 (q, J = 6.7, 1H, CHMe), 1.15 (d, J = 6.7, 3H, CH*Me*). Anal. ($C_{13}H_{13}F_3N_6O$) C, H; N: calcd, 25.76; found, 22.68.

(2*R,3*R**)-3-Amino-1-(1*H*-1,2,4-triazol-1-yl)-2-[4-(trifluoromethyl)phenyl]-2-butanol [(±)-21].** A suspension of azide (±)-**17** (0.5 g, 1.5 mmol) and 10% Pd/C (0.14 g) in ethanol (15 mL) was hydrogenated (H_2, 1 atm) at room temperature for 1 h with intensive stirring. The resulting mixture was filtered through Celite and concentrated to afford the title product as a white solid (0.45 g, 100%) pure by TLC analysis. An analytical sample was obtained by flash chromatography ($CHCl_3$:MeOH, 9:1) and recrystallization from EtOAc:Et_2O as a white solid: mp 141–144 °C; IR (KBr) ν 3329–2500, 1622, 1570, 1505, 1326 cm^{-1}; ^{1}H NMR (MeOH-d_4 + $CDCl_3$) δ 7.88 (s, 1H, CH triazole), 7.86 (s, 1H, CH triazole), 7.47 (q, J = 8, 4H, arom), 4.53 (s, 2H, CH_2), 3.38 (q, J_q = 7, 1H, C*H*Me), 0.85 (d, J = 7, 3H, CH*Me*). Anal. ($C_{13}H_{15}F_3N_4O$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-22] and the (2*R*,3*R*) Enantiomer (−)-22.** A solution containing (±)-**18** (14.9 g, 55.8 mmol) in dry THF (225 mL) was treated at room temperature with benzyl bromoacetate (19.2 g, 13.2 mL, 83.7 mmol, 1.5 equiv) and triethylamine (15.5 mL, 111 mmol, 2 equiv) for 20 h, resulting in the appearance of a white precipitate. The mixture was concentrated and partitioned between chloroform and 5% aqueous $NaHCO_3$. The aqueous phase was discarded, the organic layer was washed with 5% aqueous $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated to an oil (29 g) which was purified by flash chromatography (EtOAc) to afford (±)-**22** as a colorless oil (22.2 g, 95%).

(2*R,3*R**) [(±)-22]**: IR (KBr) ν 3600–2900, 1733, 1609, 1494, 1190, 1136 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H, triazole), 7.74 (s, 1H, triazole), 7.6–7.2 (m, 1H, arom), 7.37 (s, 5H, benzyl), 6.9–6.6 (m, 2H, arom), 5.19 (s, 2H, CH_2Ph), 4.83 (AB q, Δν = 0.023, J = 14.2, 2H, $TrCH_2$), 3.56 (s, 2H, CH_2CO), 3.3–3.0 (m, 1H, C*H*Me), 0.90 (d, J = 6.2, 3H, CH*Me*). Anal. ($C_{21}H_{22}F_2N_4O_3$) C, H, N.

(2*R*,3*R*) [(−)-22]: oil; [α]$_D$ −71.2° (*c* = 1, MeOH). Anal. ($C_{21}H_{22}F_2N_4O_3$) C, H, N.

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-23] and the (2*R*,3*R*) and (2*S*,3*S*) enantiomers [(−)-23 and (+)-23].** **(2*R**,3*R**) [(±)-23]**: yellowish oil, 20.0 g, 89% yield; IR (KBr) ν 3600–3100, 1734, 1187, 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H, triazole), 7.71 (s, 1H, triazole), 7.49 (d, J = 8.6, 1H, arom), 7.37 (s, 5H, benzyl), 7.27 (d, J = 2.1, 1H, arom), 7.06 (dd, J = 8.6, J = 2.1, 1H, arom), 5.20 (s, 2H, CH_2-Ph), 5.07 (AB q, Δν = 0.410, J = 14.4, 2H, $TrCH_2$), 3.70 (q, J = 6.5, 1H, C*H*Me), 3.60 (s, 2H, CH_2CO), 0. 80 (d, J = 6.5, 3H, CH*Me*). Anal. ($C_{21}H_{22}Cl_2N_4O_3$) C, H, N.

(2*R*,3*R*) [(−)-23]: [α]$_D$ −94.4° (*c* = 1, MeOH). Anal. ($C_{21}H_{22}Cl_2N_4O_3$) C, H, N.

(2*S*,3*S*) [(+)-23]: [α]$_D$ +90.0° (c = 1, MeOH). Anal. ($C_{21}H_{22}Cl_2N_4O_3$) C, H, N.

(2*R,3*R**)-2-[4-(Trifluoromethyl)phenyl]-3-[*N*-[(benzyloxycarbonyl)methyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-24]**: yellowish oil, 13.3 g, 90% yield; IR (KBr) ν 3600–3100, 1731, 1323, 1163, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91 (s, 1H, triazole), 7.80 (s, 1H, triazole), 7.6–7.2 (m, 4H, arom), 7.37 (s, 5H, benzyl), 5.29 (s, 2H, CH_2Ph), 4.73 (AB q, Δν = 0.308, J = 14.3, 2H, Tr-CH_2), 3.51 (AB q, Δν = 0.090, J = 17.8, 2H, CH_2CO), 2.82 (q, J = 6.6, 1H, C*H*Me), 0.96 (d, J = 6.6, 3H, CH*Me*).

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-25a] and the (2*R*,3*R*) Enantiomer (−)-25a.** A cooled (−15 °C) solution containing (±)-**22** (2.86 g, 6.87 mmol) and triethylamine (1.2 mL, 8,58 mmol, 1.25 equiv) in $CHCl_3$ (15 mL) was treated with 4-(trifluoromethyl)benzoyl chloride (1.57 g, 1.12 mL, 7.55 mmol, 1.1 equiv) and the mixture stirred at 0 °C for 30 min. A 5% $NaHCO_3$ aqueous solution was added, and the aqueous phase was separated and discarded. The organic phase was washed with brine and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated to an oil (4 g) which was purified by flash chromatography (EtOAc:hex, 1:1) to afford (±)-**25a** as a white solid (3.56 g, 88%).

(2*R,3*R**) [(±)-25a]**: mp 174–181 °C; IR 3500–2900, 1740, 1634, 1495, 1320, 1173, 1126 (KBr) ν cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 8.0–7.0 (complex signal, arom, 12H), 7.0–6.5 (m, 2H, arom), 5.5–4.0 (complex signal, 7H), 1.05 (br d, J = 7, 3H, Me). Anal. ($C_{29}H_{25}F_5N_4O_4$) C, H, N.

(2*R*,3*R*) [(−)-25a]: mp 115–118 °C; [α]$_D$ −68.1° (c = 1, MeOH). Anal. ($C_{29}H_{25}F_5N_4O_4$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[4-[(trifluoromethoxyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-25b]**: white solid, 503 mg, 85%; mp 153–155 °C; IR (KBr) ν 3500–2900, 1741, 1630, 1493, 1431, 1259, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H, triazole), 7.6–7.0 (m, triazole, arom), 6.9–6.5 (m, 2H,

arom), 5.3-4.2 (m, 7H), 1.05 (d, J = 6.2, 3H, CH*Me*). Anal. ($C_{29}H_{25}F_5N_4O_5$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[4-(2,2,2-trifluoroethoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-25c]**: white solid, 490 mg, 66%; mp 135–136 °C; IR (KBr) ν 3500–2900, 1738, 1630, 1498, 1427, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H, triazole), 7.6–7.1 (m, triazole, arom), 7.0–6.6 (m, arom), 5.4–4.8 (m), 4.6–4.1 (m), 1.05 (d, J = 6.8, 3H, CH*Me*). Anal. ($C_{30}H_{27}F_5N_4O_5$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-25d]**: white solid, 5.14 g, 82%; mp 133–134 °C; IR (KBr) ν 3500–2900, 1739, 1630, 1498, 1427, 1180, 1129 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H, triazole), 7.5–7.1 (m, triazole, arom), 7.34 (s, 5H, benzyl), 7.0-6.5 (m, arom), 6.06 (tt, J = 4.7, J = 53, 1H, CF_2H), 5.3–4.1 (m), 1.04 (d, J = 6.8, 3H, CH*Me*). Anal. ($C_{31}H_{28}F_6N_4O_5$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-25e]**: white solid, 950 mg, 60%; mp 70–73 °C; IR (KBr) ν 3500–2900, 1742, 1647, 1493, 1420, 1327, 1174, 1134 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.80 (s), 7.76 (s), 7.7–7.0 (complex signal, arom), 7.0–6.5 (m, 2H, arom), 5.6 (br q, J = 7, CHMe), 5.4–4.0 (complex signal), 1.07 and 1.0.2 (br d, J = 7, 3H, Me). Anal. ($C_{29}H_{24}F_6N_4O_4$) C, H, N.

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-26a] and the (2*R*,3*R*) and (2*S*,3*S*) Enantiomers (−)-26a and (+)-26a. (2*R**,3*R**) [(±)-26a]**: white solid, 24.3 g, 77%; mp 182–183 °C; IR (KBr) ν 3500–2900, 1752, 1622, 1320, 1171, 1129 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0–7.0 (complex signal, arom, 14H), 5.4–4.7 (m, H), 4.64 (s), 4.30 (s), 1.01 (dd, J_{C-F} = 2, 2, J = 6.7, 3H, Me). Anal. ($C_{29}H_{25}Cl_2F_3N_4O_4$) C, H, N.

(2*R*,3*R*) [(−)-26a]: mp 141–143 °C; $[\alpha]_D$ −76.3° (c = 1, MeOH). Anal. ($C_{29}H_{25}Cl_2F_3N_4O_4$) C, H, N.

(2*S*,3*S*) [(+)-26a]: mp 144–146 °C; $[\alpha]_D$ +76.4° (c = 1, MeOH). Anal. ($C_{29}H_{25}Cl_2F_3N_4O_4$) C, H, N.

(2*R,3*R**)-2-[4-(Trifluoromethyl)phenyl]-3-[*N*-[(benzyloxycarbonyl)methyl]-*N*-[4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-27a]**: white solid, 11.5 g, 64%; mp 139–140 °C (ether); IR (KBr) ν 3500–2900, 1740, 1626, 1323, 1169, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H, triazole), 7.64 (s, 1H, triazole), 7.51 (br s, arom), 7.4–7.2 (m, arom), 5.5–5.1 (m, 1H, *CH*Me), 5.09 (s, 2H, CH_2Ph), 4.98 (br s, 2H, CH_2Tr), 4.31 (s, 2H, CH_2CO), 1.03 (d, J = 7, 3H, CH*Me*).

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-(carboxymethyl)-*N*-[4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-28a] and the (2*R*,3*R*) Enantiomer (−)-28a.** To a solution of (±)-**25a** (3.4 g, 5.7 mmol) in ethanol (90 mL) was added 10% Pd on carbon (0.8 g), and the mixture was hydrogenated (1 atm) during 2 h. The mixture was filtered and the solvent removed *in vacuo* to afford the title product as a white solid (2.81 g, 99%):

(2*R,3*R**) [(±)-28a]**: mp 182–183 °C; IR (KBr) ν 3500–2500, 1727, 1610, 1493, 1321, 1167, 1130 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.24 and 8.18 (s, 1H, triazole), 8.0–7.6 (m, triazole, arom), 7.5–7.1 (m, 1H, arom), 7.0–6.6 (m, 2H, arom), 5.9–5.6 (m), 5.10 (br s), 4.97 (s), 4.76 (s), 4.60 (s), 4.50 (s), 4.32 (s), 1.11 (d, J = 6.8, 3H, CH*Me*). Anal. ($C_{22}H_{19}F_5N_4O_4$) C, H, N.

(2*R*,3*R*) [(−)-28a]: mp 122–130 °C; $[\alpha]_D$ −77.7° (c = 1, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_4{\cdot}^1/_2H_2O$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-(carboxymethyl)-*N*-[4-(trifluoromethoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-28b]**: white solid, 389 mg, 99%; mp 99–105 °C; IR (KBr) ν 3500–2500, 1727, 1611, 1437, 1257, 1216 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.19 (s, 1H, triazole), 7.8–7.0 (m, 6H, triazole, arom), 7.0–6.6 (m, 2H, arom), 5.2–4.2 (m, 5H), 1.10 (d, J = 6.8, 3H, CHMe). Anal. ($C_{22}H_{19}F_5N_4O_5$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-(carboxymethyl)-*N*-[4-(2,2,2-trifluoroethoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-28c]**: white solid, 383 mg, 98%; mp 168–177 °C; IR (KBr) ν 3500–2900, 1713, 1617, 1494, 1439, 1241, 1173 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.19 (s, 1H, triazole), 7.7–7.4 (m, 3H, triazole, arom), 7.3–7.0 (m, 3H, arom), 7.0–6.6 (m, 2H, arom), 5.1–4.2 (m), 1.09 (d, J = 6.8, 3H, CH*Me*). Anal. ($C_{23}H_{21}F_5N_4O_5$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-(carboxymethyl)-*N*-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-28d]**: white solid, 4.29 g, 98%; mp 183–184 °C; IR (KBr) ν 3500–2500, 1713, 1617, 1495, 1438, 1103 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ (*ca.* 1:1 mixture of rotamers) 8.23 and 8.19 (s, 1H, triazole), 8.0–7.5 (complex signal, 4H), 7.5–7.0 (complex signal, 1H), 7.0–6.6 (complex signal, 2H, arom), 5.73 (q, J = 7, 1H), 5.1 (br s), 4.77 (s), 4.5 (s), 4.7–4.2 (m), 4.3 (s), 1.12 and 1.07 (d, J = 7, 3H, CH*Me*). Anal. ($C_{24}H_{22}F_6N_4O_5$) C, H,N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-(carboxymethyl)-*N*-[2-fluoro-4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-28e]**: white solid, 630 mg, 82%; mp 191–192 °C; IR (KBr) ν 3500–2500, 1718, 1641, 1493, 1420, 1326, 1130, 1171 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.18 (s, 1H, triazole), 7.66 (s, 1H, triazole), 7.6–7.4 (m, 2H, arom), 7.3–6.6 (m, 5H, arom), 6.34 (m, 1H, CF_2H), 5.2–4.2 (m), 1.09 (d, J = 6.7, 3H, CH*Me*). Anal. ($C_{22}H_{18}F_6N_4O_4$) C, H; N: calcd, 10.85; found, 10.13.

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-(carboxymethyl)-*N*-[4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-29a] and the (2*R*,3*R*) and (2*S*,3*S*) enantiomers (−)-29a and (+)-29a. (2*R**,3*R**) [(±)-29a]**: white solid, 3.46 g, 96%; mp 183–189 °C; IR (KBr) ν 3500–2500, 1702, 1622, 1322, 1176, 1127 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.26 and 8.17 (s, 1H, triazole), 8.0–7.6 (m, triazole, arom), 7.5–7.1 (m, arom), 6.4–6.1 (m), 5.9–5.5 (m), 5.05 (br s), 4.54 (s), 4.25 (s), 1.05 (d, J = 6.9, 3H, CH*Me*). Anal. ($C_{22}H_{19}Cl_2F_3N_4O_4$) C, H, N.

(2*R*,3*R*) [(−)-29a]: mp 138–140 °C; $[\alpha]_D$ −87.8° (c = 1, MeOH). Anal. ($C_{22}H_{19}Cl_2F_3N_4O_4$) C, H, N.

(2*S*,3*S*) [(+)-29a]: mp 139–142 °C; $[\alpha]_D$ +93.8° (c = 1, MeOH). Anal. ($C_{22}H_{19}Cl_2F_3N_4O_4$) C, H, N.

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-(carboxymethyl)-*N*-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-29d]**: white solid, 635 mg, 95%, mp 192–193 °C; IR (KBr) ν 3500–2500, 1713, 1617, 1251, 1103 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.15 (s, 1H, triazole), 7.67 (s, 1H, triazole), 7.6–7.0 (m, arom), 6.34 (tt, J = 53, J = 4.8, 1H, CF_2H), 6.4–6.0 (m), 5.8–5.5 (m), 5.31 (q, J = 6.8, 1H, *CH*Me), 4.98 (AB q, $\Delta\nu$ = 0.103, J = 15, 2H, CH_2Tr), 4.52 (s), 4.38 (s), 1.04 (d, J = 6.8, 3H, CH*Me*). Anal. ($C_{24}H_{22}Cl_2F_4N_4O_5$) C, H, N.

(2*R,3*R**)-2-[4-(Trifluoromethyl)phenyl]-3-[*N*-(carboxymethyl)-*N*-[4-(trifluoromethyl)benzoyl]amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-30a]**: white solid, 8.75 g, 89%; mp 202–204 °C; IR (KBr) ν 3500–2500, 1725, 1627, 1324, 1108 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 8.16 (s, 1H, triazole), 7.9–7.5 (m, 9H, triazole, arom), 5.04 (s), 4.5–4.0 (m), 1.20 and 1.08 (d, J = 7, 3H, CH*Me*). Anal. ($C_{23}H_{20}F_6N_4O_4$) C, H, N.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-31a] and the (5*R*,6*R*) Enantiomer (−)-31a.** A cooled (−10 °C) solution containing the hydroxy acid (±)-**28a** (12.24 g, 24.55 mmol) in pyridine was treated with trifluoroacetic anhydride (5.2 mL, 36.83 mmol, 1.5 equiv). The mixture was stirred during 15 min at −10 °C and 2 h at 0 °C. The resulting red solution was then quenched by the addition of pH 7 phosphate buffer, it was concentrated *in vacuo*, and it was partitioned between water and chloroform. The aqueous phase was discarded, and the organic layer was washed with 5% aqueous $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated to a reddish solid which was flash chromatographed (EtOAc:hex, 2:1) to afford a white solid (10.0 g, 85%).

(5*R,6*R**) [(±)-31a]**: mp 197–198 °C; IR (KBr) ν 1740, 1641, 1497, 1432, 1321 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.9–7.3 (m, 7H, Tr, arom), 7.0–6.7 (m, 2H, arom), 4.79 (s), 4.4–4.0 (m), 1.12 (d, J = 6.9, 3H, CH*Me*). Anal. ($C_{22}H_{17}F_5N_4O_3$) C, H, N.

(5*R*,6*R*) [(−)-31a]: mp 189−190 °C; $[\alpha]_D$ −26.4° (*c* = 1, MeOH). Anal. ($C_{22}H_{17}F_5N_4O_3$) C, H, N.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-[4-(trifluoromethoxy)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-31b]**: white solid, 1.24 g, 43%; mp 180−181 °C (EtOAc:hex); IR (KBr) *ν* 1744, 1625, 1498, 1423, 1265, 1249, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.90 (s, 1H, triazole), 7.72 (s, 1H, triazole), 7.7−7.3 (m, 5H, arom), 7.1−6.7 (m, 2H, arom), 5.0−4.6 (m, 1H, *CH*Me), 4.81 (AB q, Δ*ν* = 0.133, *J* = 14.9, 2H, CH_2Tr), 4.33 (s), 4.09 (s), 1.11 (d, *J* = 6.9, 3H, CH*Me*). Anal. ($C_{22}H_{17}F_5N_4O_4$) C, H, N.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-[4-(2,2,2-trifluoroethoxy)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-31c]**: white solid, 750 mg, 51%; mp 162−163 °C (EtOAc:hex); IR (KBr) *ν* 1734, 1624, 1499, 1426, 1237, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.86 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.50 (d, *J* = 8.7, 2H, arom), 7.4−7.2 (m, 1H, arom), 7.06 (d, *J* = 8.7, 2H, arom), 6.9−6.7 (m, 2H, arom), 4.81 (AB q, Δ*ν* = 0.171, *J* = 14.9, 2H, CH_2Tr), 5.0−4.6 (m, 1H, *CH*Me), 4.44 (q, *J* = 8, 2H, CH_2CF_3), 4.36 (s), 4.11 (s), 1.11 (d, *J* = 7, 3H, CH*Me*). Anal. ($C_{23}H_{19}F_5N_4O_4$) C, H, N.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-31d]**: white solid, 320 mg, 57%; mp 78−83 °C; IR (KBr) *ν* 1754, 1635, 1498, 1421, 1253, 1118 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.92 (s, 1H, triazole), 7.71 (s, 1H, triazole), 7.6−6.8 (m, 7H, arom), 6.07 (tt, *J* = 4.6, *J* = 53, 1H, CF_2H), 5.1−4.0 (m), 1.11 (d, *J* = 7, 3H, CH*Me*). Anal. ($C_{24}H_{20}F_6N_4O_4$) C, H; N: calcd, 10.33; found, 9.75.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-[2-fluoro-4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-31e]**: white solid, 395 mg, 82%; mp 191−192 °C; IR (KBr) *ν* 1746, 1623, 1497, 1438, 1326, 1172, 1133 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* (*ca.* 1:1 mixture of rotamers) 7.9−7.2 (m, 6H, triazole, arom), 7.0−6.6 (m, 2H, arom), 5.84 (q, *J* = 7, 1H, *CH*Me), 5.1−4.7 (m), 4.81 (s), 4.7−4.3 (m), 4.2 (s), 1.14 and 1.04 (d, *J* = 7, 3H, CH*Me*). Anal. ($C_{22}H_{16}F_6N_4O_3$) C, H, N.

(5*R,6*R**)-6-(2,4-Dichlorophenyl)-5-methyl-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-32a] and the (5*R*,6*R*) and (5*S*,6*S*) Enantiomers (−)-32a and (+)-32a. (5*R**,6*R**) [(±)-32a]**: white solid, 13.5 g, 72%; mp 187−188 °C; IR (KBr) *ν* 1741, 1635, 1318 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.9−7.3 (m, triazole, arom), 7.3−7.1 (m, 1H, arom), 5.5−4.9 (m, 1H, *CH*Me), 5.01 (AB q, Δ*ν* = 0.444, *J* = 14.8, 2H, CH_2Tr), 4.29 (s), 4.05 (s), 1.08 (d, *J* = 6.8, 3H, CH*Me*); MS (M^+ (512−514), M^+ − 35). Anal. ($C_{22}H_{17}Cl_2F_3N_4O_3$) C, H, N.

(5*R*,6*R*) [(−)-32a]: mp 138−139 °C; $[\alpha]_D$ −54.1° (c = 1, MeOH). Anal. ($C_{22}H_{17}Cl_2F_3N_4O_3$) C, H, N.

(5*S*,6*S*) [(+)-32a]: mp 138−140 °C; $[\alpha]_D$ +55.0° (*c* = 1, MeOH). Anal. ($C_{22}H_{17}Cl_2F_3N_4O_3$) C, H, N.

(5*R,6*R**)-6-(2,4-Dichlorophenyl)-5-methyl-4-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-32d]**: white solid, 1.24 g, 43%; mp 88−94 °C (EtOAc:hex); IR (KBr) *ν* 1751, 1635, 1232, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.82 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.6−7.4 (m, arom), 7.3−6.9 (m, arom), 6.06 (tt, *J* = 53, *J* = 4.5, 1H, CF_2H), 5.23 (br s), 4.80 (s), 4.44 (br t, *J* = 11.8, 2H, CF_2CH_2), 4.33 (s), 4.10 (s), 1.08 (d, *J* = 7, 3H, CH*Me*). Anal. ($C_{24}H_{20}Cl_2F_4N_4O_4$) C, H, N.

(5*R,6*R**)-6-[4-(Trifluoromethyl)phenyl]-5-methyl-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-33a]**: white solid, 4.97 g, 76% yield; mp 189−190 °C (EtOAc:ether); IR (KBr) *ν* 1751, 1641, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.9−7.3 (m, 10H, triazole, arom), 4.73 (s), 4.5−4.0 (m), 1.10 (d, *J* = 6.9, 3H, CH*Me*). Anal. ($C_{23}H_{18}F_6N_4O_3$) C, H, N.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-(methanesulfonyl)-6-[(1*H*-1,2,4-triazol-1-yl)methyl]-2-morpholinone [(±)-34]**. Following a similar overall procedure, but starting from amine (±)-**22** and acylating with $MeSO_2Cl$, sulfonamide (±)-**34** was obtained as a white solid: mp 180−181 °C; IR (KBr) *ν* 1749, 1341, 1271, 1156 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.83 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.33 (dt, J_d = 6, J_t = 8.5, 1H, arom), 7.1−6.7 (m, 2H, arom), 4.92 (AB q, Δ*ν* = 0.11, 2H, Tr-CH_2), 5.1−4.7 (m, 1H, *CH*Me), 4.34 (AB q, Δ*ν* = 0.56, 2H, N-CH_2), 3.05 (s, 3H, $MeSO_2$), 1.10 (d, *J* = 6.9, 3H, *Me*CH). Anal. ($C_{15}H_{16}F_2N_4O_4S$) C, H, N, S.

(2*R,3*R**)-3-[[2-(Benzyloxy)ethyl]amino]-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-35] and the (2*R*,3*R*) and (2*S*,3*S*) Enantiomers (−)-35 and (+)-35.** A solution containing amino alcohol (±)-**18** (3.87 g, 14.42 mmol) in benzene was treated with (benzyloxy)acetaldehyde (2.17 g, 14.42 mmol, 1 equiv) and heated under reflux in the presence of a Dean−Stark collector for 4 h. After no more water distilled, the mixture was concentrated to an oil (6.01 g), diluted in THF (40 mL), cooled to 0 °C, and treated with $LiAlH_4$ (547 mg, 14 mmol). The reaction mixture was stirred 3 h at 0 °C and 1 h at room temperature, then re-cooled to 0 °C, and successively treated with 0.5 mL of water, 0.5 mL of 15% NaOH aqueous solution, and 1.5 mL of water. The resulting white suspension was filtered through Celite, and the filtrate was concentrated to an oily residue that was purified by flash chromatography (EtOAc) to afford (±)-**35** as a colorless oil (4.45 g, 80%).

(2*R,3*R**) [(±)-35]**: IR (KBr) *ν* 3600−3000, 1609, 1592, 1268, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.90 (s, 1H, triazole), 7.73 (s, 1H, triazole), 7.5−7.1 (m, 1H, arom), 7.33 (s, 5H, benzyl), 6.9−6.5 (m, 2H, arom), 4.77 (AB q, Δ*ν* = 0.074, 2H, $TrCH_2$), 4.53 (s, 2H, CH_2Ph), 3.7−3.4 (m, 2H), 3.3−2.5 (m, 3H), 0.90 (dd, *J* = 1.2, *J* = 7, 3H, CH*Me*). Anal. ($C_{21}H_{24}F_2N_4O_2$) C, H, N.

(2*R*,3*R*) [(−)-35]: $[\alpha]_D$ −55.4° (*c* = 1, MeOH). Anal. ($C_{21}H_{24}F_2N_4O_2$) C, H, N.

(2*S*,3*S*) [(+)-35]: $[\alpha]_D$ +54.8° (c = 1, MeOH). Anal. ($C_{21}H_{24}F_2N_4O_2$) C, H, N.

(2*R,3*R**)-3-[[2-(Benzyloxy)ethyl]amino]-2-(2,4-dichlorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-36]**: white solid, 25 g, 79%; mp 105−107 °C; IR (KBr) *ν* 3600−2800, 1580, 1513, 1448, 1138 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 7.82 (s, 1H, triazole), 7.68 (s, 1H, triazole), 7.49 (d, *J* = 8.6, 1H, arom), 7.33 (s, 5H, benzyl), 7.10 (dt, J_d = 2, J_t = 12.8, 2H, arom), 5.22 (d, *J* = 14.2, 1H, C*H*(H)), 4.71 (d, *J* = 14.2, 1H, CH(*H*)), 4.55 (s, 2H, CH_2Ph), 3.9−3.5 (m, 3H), 3.4−2.6 (m, 2H), 0.80 (d, *J* = 7, 3H, CH*Me*). Anal. ($C_{21}H_{24}Cl_2N_4O_2$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[4-(trifluoromethyl)benzoyl]-*N*-(2-hydroxyethyl)amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-37a] and the (2*R*,3*R*) Enantiomer (−)-37a.** To a solution of (±)-**35** (4.40 g, 11.4 mmol) in CH_2Cl_2 (40 mL) was added triethylamine (1.74 mL, 12.5 mmol). The resulting mixture was cooled in an ice bath, a solution of 4-(trifluoromethyl)benzoyl chloride (2.61 g, 12.5 mmol) in CH_2Cl_2 (5 mL) was carefully added, and the mixture was stirred for 1 h at 0 °C and 18 h at room temperature. The resulting solution was diluted with CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ solution. The organic phase was separated and dried over Na_2SO_4, and the solvent was removed *in vacuo*, to afford a thick oil (9.17 g) that was purified by chromatography on silica gel (EtOAc:hexane, 1:1). Anal. ($C_{29}H_{27}F_5N_4O_3$) C, H, N.

A mixture of this oil (1.68 g, 2.9 mmol), 10% palladium on charcoal (420 mg), and ethanol (20 mL) was hydrogenated at 1 atm under vigorous stirring for 18 h. The mixture was filtered through Celite and washed with ethanol. The filtrate was concentrated, and the residue was purified by flash chromatography (EtOAc:hex, 4:1 and then 1:0) to give (±)-**37a** as a white solid (718 mg, 51%).

(2*R,3*R**) [(±)-37a]**: mp 165−166 °C; IR (KBr) *ν* 3500−3000, 1623, 1320 cm^{-1}; ^1H NMR (DMSO-d_6) *δ* 8.30 and 8.17 (s, 1H, triazole), 8.0−6.7 (m, 8H, arom), 5.02 (br d, *J* = 14, 1H, C*H*(H)), 4.8−4.1 (m), 3.9−3.3 (m), 1.3−1.0 (d, *J* = 7, CH*Me*, 3H); MS (DIP, CI, CH_4) $M^+ + 1$ = 485. Anal. ($C_{22}H_{21}F_5N_4O_3$) C, H, N.

(2*R*,3*R*) [(−)-37a]: mp 170−171 °C; $[\alpha]_D$ −72.5° (*c* = 1, $CHCl_3$). Anal. ($C_{22}H_{21}F_5N_4O_3$) C, H, N.

(2*S*,3*S*) [(+)-37a]: mp 170−171 °C; $[\alpha]_D$ +69.8° (*c* = 1, $CHCl_3$). Anal. ($C_{22}H_{21}F_5N_4O_3$) C, H, N.

(2*R,3*R**)-2-(2,4-Difluorophenyl)-3-[*N*-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]-*N*-(2-hydroxyethyl)amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-37d]**: white solid, 9.3 g, 77%; mp 156−157 °C; IR (KBr) *ν* 3600−2900, 1604, 1495, 1462, 1172, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 8.26 (s, 1H, triazole), 8.0−

6.6 (m, 8H, triazole, arom), 6.06 (tt, $J = 4.7$, $J = 53$, 1H, CF_2H), 5.1–3.6 (m), 1.4–1.0 (m, 3H, CH*Me*). Anal. ($C_{24}H_{24}F_6N_4O_4$) C, H, N.

(2*R,3*R**)-2-(2,4-Dichlorophenyl)-3-[*N*-[4-(trifluoromethyl)benzoyl]-*N*-(2-hydroxyethyl)amino]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol [(±)-38a]**: white solid, 3.5 g, 62%; mp 185–189 °C; IR (KBr) ν 3600–2900, 1636, 1322 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0–7.0 (m, 9H, triazole, arom), 5.5–4.5 (m), 4.4–3.5 (m), 1.29 and 1.06 (d, $J = 7$, CH*Me*); MS (M^+ 517 and 519). Anal. ($C_{22}H_{21}Cl_2F_3N_4O_3$) C, H, N.

(2*S,5*R**,6*R**)-6-[2,4-Difluorophenyl]-5-methyl-2-hydroxy-4-[4-(trifluoromethyl)-benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(±)-39a] and the (2*S*,5*R*,6*R*) and (2*R*5*S*,6*S*) Enantiomers (−)-39a and (+)-39a Hemiethyleneglycolates.** To a cooled (−78 °C) solution containing anhydrous DMSO (9.52 mL, 134 mmol, 2.5 equiv) in CH_2Cl_2 (300 mL) was added a solution of trifluoroacetic anhydride (9.5 mL, 67 mmol, 1.25 equiv) in CH_2Cl_2 (9.5 mL) dropwise. Ten minutes after, it was added a solution of (±)-**37a** (26 g, 53.6 mmol, 1 equiv) in CH_2Cl_2 (300 mL). The mixture was stirred during 30 min, after which freshly distilled triethylamine (37 mL, 268 mmol, 5 equiv) was added. The reaction flask was then let warm to −40 °C, and the mixture was stirred at this temperature for 1.5 h and at −10 °C during 30 min. A 10% $NaHCO_3$ solution was then added, and the aqueous layer was back-extracted with $CHCl_3$. The combined organic layers were with water and brine. Drying over anhydrous Na_2SO_4, filtration, and concentration gave a crude solid (33 g). $CHCl_3$ was added, and the precipitated product was filtered to afford 22.5 g (87%) of pure (±)-**39a**. An analytical sample was obtained by flash chromatography (first EtOAc:hexane, 4:1, and then EtOAc) followed by recrystallization (EtOAc:hexane).

(2*S,5*R**,6*R**) [(±)-39a]**: mp 198–199 °C; IR (KBr) ν 3500–2900, 1620, 1323 cm^{-1}; ^1H NMR (MeOH-d_4) δ 8.0–7.2 (m, 7H, triazole, arom), 7.0–6.6 (m, 2H, arom), 5.9–5.3 (m, 2H, TrC*H*(H), OC*H*OH), 5.2–4.2 (m, 2H, TrCH(*H*), C*H*Me), 3.7 (br s, 2H, OCHCH_2), 1.13 (d, $J = 6.8$, 3H, CH*Me*). Anal. ($C_{22}H_{19}F_5N_4O_3$) C, H, N.

The synthesis starting from (−)- and (+)-**37a** provided the enantiomers, which were recrystallized from ethylene glycol:water to afford white needles of the hemietyleneglycol hemihydrate solvate.

(2*S*,5*R*,6*R*) [(−)-39a ($^1/_2C_2H_6O_2.^1/_2H_2O$ solvate)]: mp 189–190 °C; $[\alpha]_D$ −43.4° (c = 1, MeOH); HPLC–UV analysis (chiral AGP 100 × 4 mm column, 10 mM (pH 7.25) NaH_2PO4 buffer + 10.5% CH_3CN) [(*S*,*S*) t_R 6.2 min; (*R*,*R*) t_R 12 min] indicated an area relationship for these two products of (0.4:99.6). Anal. ($C_{22}H_{19}F_5N_4O_3{\cdot}^1/_2C_2H_6O_2{\cdot}^1/_2H_2O$) C, H, N.

(2*R*,5*S*,6*S*) [(+)-39a ($^1/_2C_2H_6O_2{\cdot}^1/_2H_2O$ solvate)]: mp 184–187 °C; $[\alpha]_D$ +43.6° (c = 1, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_3{\cdot}^1/_2C_2H_6O_2{\cdot}^1/_2H_2O$) C, H, N.

(5*R*,6*S*)-6-(2,4-Difluorophenyl)-5-methyl-2-hydroxy-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(+)-40] and the (5*S*,6*R*) Enantiomer [(−)-40]. Following an identical overall procedure, but starting from amines (+)-**19** and (−)-**19**, compounds (+)-**40** and (−)-**40** were obtained, respectively, as white solids after recrystallization from EtOAc:hexane.

(5*R*,6*S*) [(+)-40]: mp 172–174 °C; IR (KBr) ν 3600–2600, 1607, 1494, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.3–8.0 (complex signal), 7.69 (s), 7.58 (s), 7.22 (s), 7.12 (s), 7.0–6.4 (complex signal), 5.9–5.0 (m), 4.8–4.2 (m, 3H, TrCH_2, C*H*Me), 3.7–3.0 (m, 2H, OCHCH_2), 1.72 (d, $J = 6.6$, 3H, CH*Me*); $[\alpha]_D$ +44° (c = 0.2, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_3{\cdot}^1/_2H_2O$) C, H, N.

(5*S*,6*R*) [(−)-40]: mp 177–185 °C; $[\alpha]_D$ −39° (c = 0.1, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_3$) H, N; C: calcd, 54.78; found, 55.44.

(2*S,5*R**,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-2-hydroxy-4-[4-(2,2,3,3-tetrafluoropropoxy)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(±)-39d]**: white solid, 2.8 g, 67%; mp 209–210 °C; IR (KBr) ν 3500–2900, 1618, 1496, 1427 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85 (s, 1H, triazole), 7.70 (s, 1H, triazole), 7.6–6.8 (m, 7H, arom), 6.06 (tt, $J = 4.8$, $J = 53$, 1H, CF_2H), 5.9–5.4 (m, 2H), 5.2–4.5 (m, 2H), 4.41 (dt, $J = 11.9$, $J = 1.4$, 2H, CH_2CF_2), 4.0–3.1 (m, 2H), 1.10 (d, $J = 6.8$, 3H, CH*Me*). Anal. ($C_{24}H_{22}F_6N_4O_4$) C, H, N.

(2*S,5*R**,6*R**)-6-(2,4-Dichlorophenyl)-5-methyl-2-hydroxy-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(±)-43a]**: white solid, 552 mg, 56%; mp 153–156 °C; IR (KBr) ν 3500–2900, 1631, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (s, 1H, triazole), 7.8–7.0 (m, 8H, triazole, arom), 6.3–5.6 (m), 5.6–5.2 (m), 5.1–4.6 (m), 3.9–3.3 (m, 2H, OCHCH_2), 1.11 (d, $J = 7.2$, 3H, CH*Me*). Anal. ($C_{22}H_{19}Cl_2F_3N_4O_3$) C, H, N.

(5*R,6*R**)-6-(2,4-Difluorophenyl)-5-methyl-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(±)-41] Ethanol Solvate and the (5*R*,6*R*) and (5*S*,6*S*) Enantiomers (−)-41 and (+)-41 Ethanol Solvates.** A cooled (0 °C) solution containing (±)-**37a** (3.1 g, 6.4 mmol) in THF (50 mL) was treated with diethyl azadicarboxylate (1.67 g, 9.6 mmol, 1.5 equiv) and tributylphosphine (1.94 g, 9.6 mmol, 1.5 equiv) for 1 h. The volatiles were removed *in vacuo*, and the orange oily residue was purified by flash chromatography and recrystallized from ethanol to afford (±)-**41** (EtOH solvate) as a white solid (3.00 g, 92% yield).

(5*R,6*R**) [(±)-41 (EtOH solvate)]**: mp 177–178 °C; IR (KBr) ν 3500–3200, 1623, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (q, $J = 8$, 4H, triazole, arom), 7.72 (s), 7.4–7.1 (m, 2H, arom), 7.0–6.6 (complex signal, 2H, arom), 5.50 (br q, $J = 7$, 1H, CHMe), 5.32 (br s), 5.13 (br s), 4.9–3.3 (complex signal, 3H), 3.7 (q, $J = 7$, 2H, EtOH), 1.22 (t, $J = 7$, 3H, EtOH), 1.12 (br d, $J = 7$, 3H, Me); MS (CI, CH_4) 467 (M + 1). Anal. ($C_{22}H_{19}F_5N_4O_2{\cdot}C_2H_5OH$) C, H, N.

(5*R*,6*R*) [(−)-41 (EtOH solvate)]: mp 89–92 °C; $[\alpha]_D$ −63.6° (c = 1, MeOH). HPLC–UV analysis (chiral AGP 100 × 4 mm column, 10 mM (pH 6.75) NaH_2PO4 buffer + 16% CH_3CN) [(*S*,*S*) t_R 4.1 min; (*R*,*R*) t_R 5.8 min] indicated an area relationship for these two products of (0.04:99.96). Anal. ($C_{22}H_{19}F_5N_4O_2{\cdot}C_2H_5OH$) C, H, N.

(5*S*,6*S*) [(+)-41 (EtOH solvate)]: mp 86–93 °C; $[\alpha]_D$ +63.8° (c = 1, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_2{\cdot}C_2H_5OH$) C, H, N.

Obtention of an Aqueous Solution Containing (5*R*,6*R*)-6-(2,4-difluorophenyl)-5-methyl-4-[4-(trifluoromethyl)-benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(−)-41]. Compound (−)-**41**·EtOH solvate (275 mg) was placed in a 10 mL flask, and a solution containing 3.2 g of (hydroxypropyl)-β-cyclodextrin[22] in 7 mL of deionized water was added (2 × 1 mL rinses with additional water). The suspension was gradually dissolved by alternating short treatments with ultrasounds and heat (50 °C). The process took several minutes, and total solution proved highly dependent on small operational details, like time of heating and ultrasound. Once a clear solution was obtained, water was added to 10 mL. The solution was stable at room temperature (both in terms of transparency and HPLC assay) and contained 25 mg/ml of (−)-**41**. Lower concentrations could be obtained by diluting with deionized water.

(5*R*,6*S*)-6-(2,4-Difluorophenyl)-5-methyl-4-[4-(trifluoromethyl)benzoyl]-6-[(1*H*-1,2,4-triazol-1-yl)methyl]morpholine [(+)-42] and the (5*S*,6*R*) Enantiomer (−)-42. Following an identical overall to that described above, but starting from the amine (+)-**19** and (−)-**19**, compounds (+)-**42** and (−)-**42** were obtained, respectively, as white solids after recrystallization from ethylene glycol:water.

(5*R*,6*S*) [(+)-42]: mp 143–151 °C; IR (KBr) ν 3700–3300, 1624, 1322 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (br d, $J = 8$, 3H), 7.20 (br d, $J = 8$, 3H), 7.2–6.6 (complex signal, 3H, arom), 5.7–5.3 (br m, 1H, CHMe), 4.47 (br s), 4.1–3.2 (complex signal), 1.76 (d, $J = 7$, 3H, Me); $[\alpha]_D$ +38.3° (c = 1, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_2{\cdot}^1/_2H_2O$) C, H, N.

(5*S*,6*R*) [(−)-42]: mp 169–170 °C; $[\alpha]_D$ −44° (c = 0.2, MeOH). Anal. ($C_{22}H_{19}F_5N_4O_2.H_2O$) C, H, N.

X-ray diffraction analysis of (−)-39a (EtOH solvate): $C_{22}H_{19}F_6N_4O_2{\cdot}C_2H_5OH$, M = 528.478, monoclinic, $a = 13.684(4)$ Å, $b = 5.917(1)$ Å, c = 16.486(4) Å, $\beta = 104.47(2)°$, U = 1292.5 Å^3, $P2_1$ (C^2_2, No. 4), $Z = 2$, $D_c = 1.5454$ g cm^{-3}, Mo Kα radiation $\lambda = 0.710\,69$ Å, μ(Mo Kα) = 1.26 cm^{-1}. The colorless, transparent, brick-shaped crystal 0.3 × 0.3 × 0.5 mm, grown by the slow evaporation of an ethanol solution, was sealed in a Lindemann glass capillary and mounted on a CAD4 diffractometer. The unit cell dimensions and orientation matrix were determined at 293 K from 25 reflections with $8 < q < 14.3°$.

The intensity data were collected by $\omega/2\theta$ scan, and graphite monochromated Mo K radiation. A total of 2522 reflections were measured with $0 < \theta < 23°$, $-1 < h < 13$, $-1 < k < 5$, $-15 < l < 15$, which, after data reduction, gave 1847 unique reflections of which 1370 with $I \geq 3\sigma(I)$ were used in the structure analysis. Crystal orientation and decomposition was checked by hourly monitoring of three standard reflections, and a 4.3% loss in intensity of the standard reflections was recorded. Lorentz and polarization corrections were applied.

Direct methods (SHELXS) using default values led to the location of all non-hydrogen atoms in the molecule. In addition to the molecule of (−)-**39a** there was one molecule of ethanol solvate in the asymmetric unit. Initial refinement of the structure was followed by an empirical absorption correction (DIFABS minimum correction = 0.561, maximum correction = 1.236, Sheldrick merging $R = 2.4\%$). The model was further refined with anisotropic temperature factors until refinement converged. Electron density consistent with all the expected hydrogen atoms was observed in a difference map, and these were included in the model at calculated positions. The model, space parameters, and anisotropic temperature factors for all atoms except hydrogen atoms and the scale, 334 parameters in all, was refined to convergence by full matrix least squares analysis, minimizing $\Sigma w(F_o - Fc)^2$ unit weights were used initially and a five-term Chebychev polynomial weighting scheme for the final cycles. At convergence the final residuals were $R = 5.9\%$ and $R_w = 6.5\%$ and the root mean square shift/esd 0.033. A final difference map revealed no peaks above 0.03 e Å^{-3}, and the lowest density was −0.03 e Å^{-3}. Atomic scattering factors were taken from *International Tables for X-ray Crystallography*. Unless otherwise indicated, all calculations were carried out with the Oxford CRYSTALS system.

***In Vitro* Activity.** Test organisms were obtained from the ATCC or were clinical isolates.

(A) Agar Dilution Method. Suspensions of each microorganism were prepared to contain 10^5 colony forming units (cfu)/mL. All drugs were dissolved in ethanol 50% to obtain an stock solution of 800 μg/mL. The agar dilution method was performed using Kimmig's agar (KA, E. Merck) suplemented with 0.5% glycerol. Plates of KA containing twofold serial dilutions (80 to 0.025 μg/mL) of the drugs were inoculated with 10 μL of the fungal inocula and incubated at 25 °C during 48 h for yeasts and 120 h for dermatophytes and molds. Following incubation, MICs (minimal inhibitory concentrations) were determined.

(B) Broth Macrodilution Method. MIC determination of selected compounds was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) recommendations (document M27-P)[28] with RPMI-1640 (Sigma) buffered with 0.165 M MOPs (Sigma) as test medium. Fluconazol was dissolved in sterile purified water and the other drugs in DMSO. *Candida parapsilosis* ATCC 22019 was included as the reference strain in each run of the experiments. The MIC was defined as the lowest drug concentration which resulted in a culture with turbidity less than or equal to the 80% inhibition standard. From each tube without evident growth and from the control tube with no drug, 0.04 mL were removed and placed on a plate containing Sabouraud Dextrose Agar (Difco). The plates were incubated until growth from control tubes was evident. Minimal fungicidal concentration (MFC) was determined as the lowest concentration producing one or no colonies on the plate.

Systemic Candidosis in Mice. An *in vivo* murine candidosis model was used to monitor the antifungal activity of the test compounds. Groups of 10 male mice were inoculated iv with 0.2 mL of a suspension containing (2−8) × 10^7 cfu/mL of *C. albicans*. Compounds were administered orally at 20, 10, 5, 2.5, 1, or 0.5 mg/kg as suspensions in 1% Tween + 0.2% carboxymethylcellulose in distilled water, at times 1, 4, and 24 h after infection. The control group received only the vehicle. At least 90% of the animals in the control group died by day 3 of infection. The antifungal activity was assessed by the survival rate at days 3, 5, 7, and 9 postinfection.

Vaginal Candidosis in the Rat. Groups of 10 female Wistar rats were administered with estradiol (25 mg/kg) subcutaneously on day −5. On day 0, the vaginas of the rats were infected with an inoculum of *C. albicans* by means of a sterile hisope. On day 3 a vaginal frotis was performed on each rat, the hisope was transferred to a growing broth (TSB), and the next day the samples were cultured in agar Sabouraud to confirm infection. Compounds were administered orally once a day during days 3, 4, and 5. The control group received only the vehicle. Vaginal frotis were performed on days 10 and 15. The hisopes were cultured, and lectures were performed on the next day.

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