New Azole Antifungals. 2. Synthesis and Antifungal Activity of Heterocyclecarboxamide Derivatives of 3-Amino-2-aryl-1-azolyl-2-butanol[1]

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A series of 92 azole antifungals containing an amido alcohol unit was synthesized. The nature and substitution of the amide portion was systematically modified in search of improved antifungal activity, especially against filamentous fungi. The compounds were tested in vitro against a variety of clinically important pathogens and in vivo (po) in a murine candidosis model. Thiazole and thiophene carboxamides carrying both a substituted phenyl ring and a small alkyl group were best suited for activity against filamentous fungi. In a subset of these compounds, the amide portion was conformationally locked by means of a pyrimidone ring and it was proven that only an orthogonal orientation of the phenyl ring yields bioactive products. A tendency to display long plasma elimination half-lives was observed in both series. Two compounds, **74** and **107**, representative of the open and cyclic amides, respectively, were chosen for further studies, based on their excellent activity in in vivo murine models of candidosis and aspergillosis. This work describes the SARs found within this series. The next paper displays the results obtained in a related series of compounds, the quinazolinones.

Introduction

Marketing a new systemic antifungal drug has proved to be a difficult and costly task.[2,3] The need to perform lengthy in vivo screening tests, manage clinical trials in which patients suffer from other fatal diseases, and confront the appearance of toxicity effects at one stage or another have all contributed to slowing the launching of new drugs. In the meantime, resistance to many currently available antifungal agents continues to grow[4] while AIDS and other immunosuppressed patients wait for new, safer, and more potent drugs to overcome their fungal diseases.

Although various pharmaceutical companies are developing new therapeutic approaches, such as inhibition of the synthesis of cell wall components,[2] considerable effort is still concentrated in the azole area. Fluconazole (**1**) and itraconazole (**2**) are presently the azoles of choice for the treatment of deep mycoses (Figure 1).[5] Other drugs from this class currently under clinical research include Schering-Plough's SCH-56592 (**3**),[6] and Pfizer's voriconazole (**4**).[7] A plethora of other azole derivatives, such as Takeda's TAK-187 (**6**),[8] Eisai's ER-30346 (**7**),[9] and Sankyo's amido alcohol **8**,[10b] have also been described in the literature.

In this line, we have recently reported the discovery and structure–activity relationships of conformationally restricted analogues of **8** featuring an *N*-acylmorpholine ring as a surrogate of the lanosterol D ring.[1] It was our hope that, in addition to furnishing additional information about the binding, conformational restriction might afford enhanced potency. Contrary to our predictions, however, in vitro activity did not improve.[1,11a] Nonetheless, two compounds, UR-9746 (**9**) and UR-9751 (**10**) (Figure 2), were selected for further in vivo antifungal screening and preclinical tests. The products proved to be superior to fluconazole in murine models of candidosis,[1] coccidioidomycosis,[11b] cryptococcosis,[11c–f] and histoplasmosis.[11g] However, they were dropped from development because they suffered from two major drawbacks: low anti-*Aspergillus* activity, both in vitro and in vivo,[1,11h] and metabolism to amido alcohol **8**, a compound which we have found to have an extended plasma elimination half-life in the rat and dog.

Clinically, candidosis and aspergillosis account for between 80 and 90% of systemic fungal infections in immunocompromised patients, yet the difficulties in dealing with each of these two diseases are truly different. Whereas many drugs have proven effective against candidosis, infections due to *Aspergillus fumigatus* remain very hard to overcome. A drug active against both of these clinically important pathogens would be highly desirable. We thus undertook a study to chemically modify amido alcohol **8** in search of anti-*Aspergillus* efficacy. At the same time, we planned to shorten the half-life of the products to circumvent potential toxic effects. This paper presents the key structural elements that govern these two factors within the general structure depicted in Figure 2. The accompanying paper describes our related findings with the quinazolinone nucleus.

Chemistry

Studies have shown that only the (1*R*,2*R*) stereoisomers of 3-triazolyl-2-aryl-1-methylpropan-2-ol antifungals are responsible for activity.[1,8b,10,12,13] Consequently, all compounds in the present study (except racemic **102**) were directly prepared as the (*R*,*R*) enantiomers. Amides **I** were obtained by DCC coupling of amines **11**–**16** and the corresponding heterocyclecarboxylic acids **17**–**28** (Scheme 1). Optically active amines **11**–**14** and **16** were synthesized using Evans chiral oxazolidinones, following

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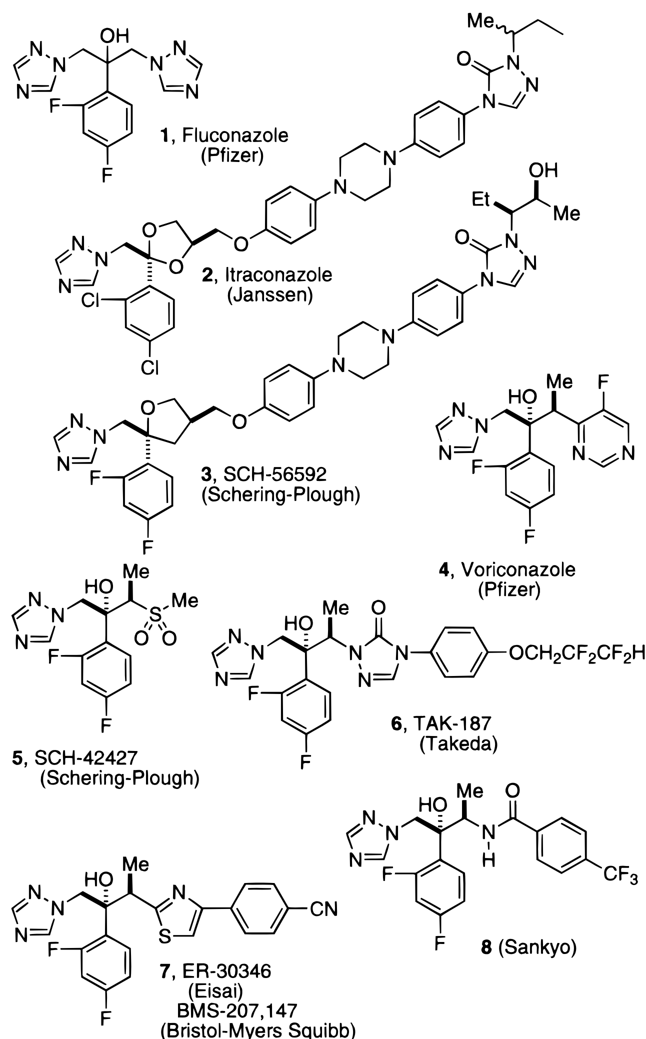


Figure 1. Azole antifungals (names and laboratory codes refer to single enantiomers, except itraconazole which is racemic).

our reported methodology.[14] The heterocyclecarboxylic acids **17**−**28** were obtained by slight modifications of published procedures[15−25] as summarized in Scheme 2, or they were commercially available. Pyrimidones **II** were prepared from **I** (D = H, B = NH_2) by heating with formamidine acetate in DMF. Compounds **70** and **71** were obtained by Suzuki's palladium-catalyzed coupling of the corresponding bromobenzoyl derivative with 4-chlorophenylboronic acid. Compounds **82**−**84**, **88**, **109**−**110**, **112**−**113**, and **116** were prepared by conventional nitrile and imidate chemistry.

Biological Tests

Compounds were tested in vitro by the agar dilution method against an assortment of 10 yeasts and 6 filamentous fungi. The individual minimum inhibitory concentrations (MICs, μg/mL) obtained for each compound are presented in Table 10 (Supporting Information). Two geometric means of the MICs were calculated to facilitate SARs, one for yeasts and another for filamentous fungi. Fluconazole, itraconazole, ketoconazole, SCH-42427 (**5**),[26] voriconazole (**4**), TAK-187 (**6**), ER-30346 (**7**), and **8** were also included for comparison purposes (see Figure 1 for structures). With the exception of the compounds with low in vitro activity, all of the products were also tested in vivo in a murine

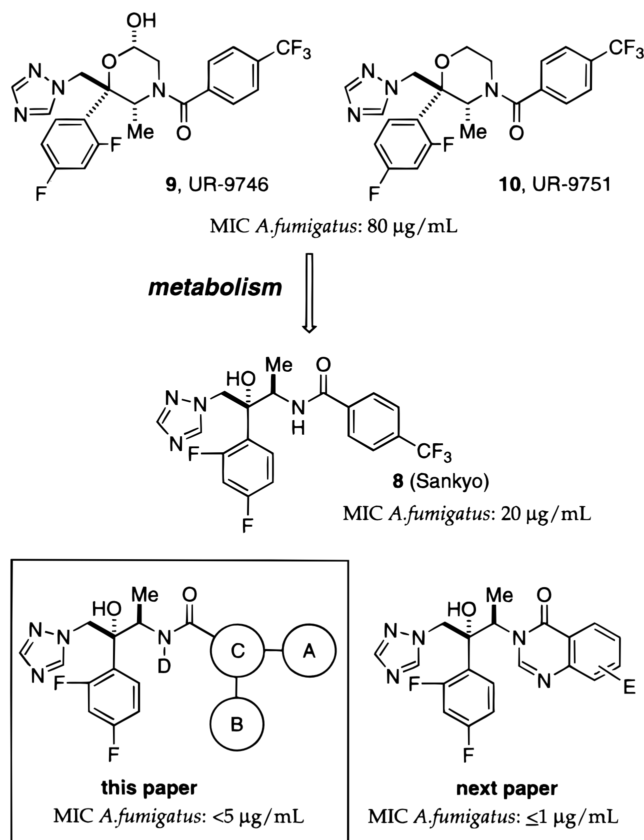
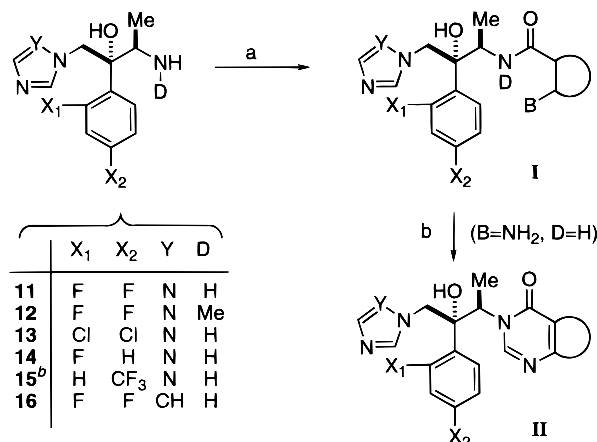


Figure 2. Previous selected compounds and new structures.

Scheme 1. Synthesis of Final Products[a]

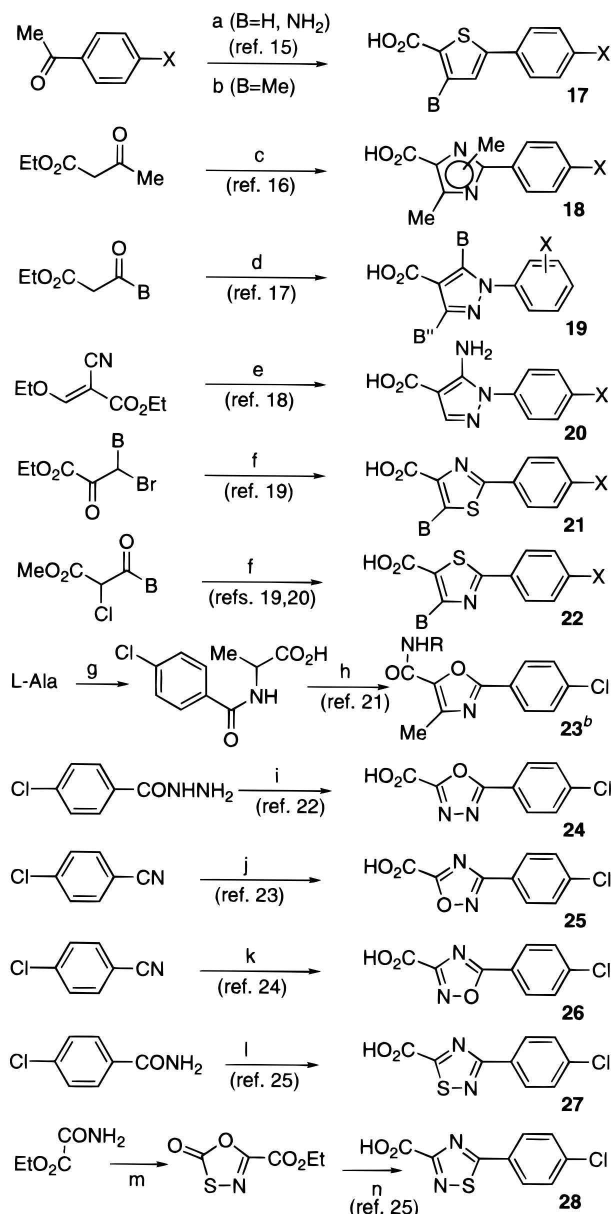


	X_1	X_2	Y	D
11	F	F	N	H
12	F	F	N	Me
13	Cl	Cl	N	H
14	F	H	N	H
15[b]	H	CF_3	N	H
16	F	F	CH	H

[a] Reagents: (a) acid **17**−**28**, DCC, HOBT, DMF, room temperature, 18 h; (b) HC(=NH)NH_2.HOAc, NMP, 130 °C, 24 h; [b]racemic.

systemic candidosis model.[10a] In these studies, the compounds were administered orally in groups of 10 animals, three times over the 24 h following infection, and observed for 9 days. Each study consisted of 10 groups, one of which was always a control group (infected but untreated), and another consisted of animals treated with fluconazole at the same dose as the test compound. Complete mortality in the control group was attained within 3 days, whereas in the fluconazole-treated group, 100% mortality was reached toward the end of each study, the exact day depending on the dose. Due to slight variations in the inocule virulence from study to study, comparison of the absolute in vivo protection levels was not possible for all the products. We thus report two figures for the in vivo

Scheme 2. Synthesis of Heterocyclecarboxylic Acids[a]



[a] Reagents: (a) (i) $POCl_3$, DMF, CH_2Cl_2, room temperature, 24 h; (ii) NaOAc, H_2O; (iii) $HSCH_2CO_2Et$, NaOEt, EtOH, reflux, 5 h; (iv) HO^-, H_2O; (b) (i) and (ii) as in (a); (iii) MeMgBr, 3*M* THF, −78 °C, 0.5 h; (iv) CrO_3, pyr, CH_2Cl_2, room temperature, 4 h; (v) $HSCH_2CO_2Et$, NaOEt, EtOH, reflux, 5 h; (vi) HO^-, H_2O. (c) (i) $NaNO_2$, H_2O, HOAc, 0 °C to room temperature, 15 h; (ii) 4-ClBnNH$_2$, MeCN, reflux, 18 h; (iii) MeI, K_2CO_3, DMF, 60 °C, 2 h; (iv) HO^-, H_2O; (d) (i) $(MeO)_2CHNMe_2$, C_6H_6, reflux, 1 h; (ii) X-C_6H_4-$NHNH_2$.HCl, EtOH, reflux, 8 h; (iii) HO^-, H_2O; (e) (i) 4-X-C_6H_4-$NHNH_2$.HCl, EtOH, reflux, 48 h; (ii) HO^-, H_2O; (f) (i) 4-X-$C_6H_4CSNH_2$, EtOH, reflux, 3 h; (ii) HO^-, H_2O; (g) 4-Cl−C_6H_4COCl, NaOH, H_2O, 1,4-dioxane, 0 °C, 3 h; (h) (i) $(COCl)_2$, C_6H_6, 45 °C, 3 h; (ii) 11, NEt_3, CH_2Cl_2, 0 °C, 0.5 h (iii) HO^-, H_2O. (i) (i) $(COCl)_2$, TEA, CH_2Cl_2, 0 °C, 3 h; (ii) $POCl_3$, 100 °C, 15 h; (iii) HO^-, H_2O; (j) (i) NH_2OH·HCl, K_2CO_3, EtOH, reflux, 20 h; (ii) EtO_2CCOCl, pyr, 0 °C, 1 h; (iii) HO^-, H_2O; (k) (i) $(EtO_2C)_2CHNO_2$, *n*-dodecane, 150 °C, 15 h; (ii) HO^-, H_2O; (l) (i) ClCOSCl, toluene, 110 °C, 15 h; (ii) EtO_2CCN, *n*-dodecane, 150 °C, 20 h; (iii) OH^-, H_2O; (m) ClCOSCl, toluene, 110 °C, 5 h. (n) (i) 4-Cl-C_6H_4CN, 190 °C, 72 h; (ii) HO^-, H_2O; [b]See Table 1 for the Definition of R.

activities. The first shows the intrinsic activity of the compound, and it is expressed as the percent survival observed in the treated group when all the untreated animals were dead (ca. day 3). The second reflects the potency of the compound compared to that of flucona-

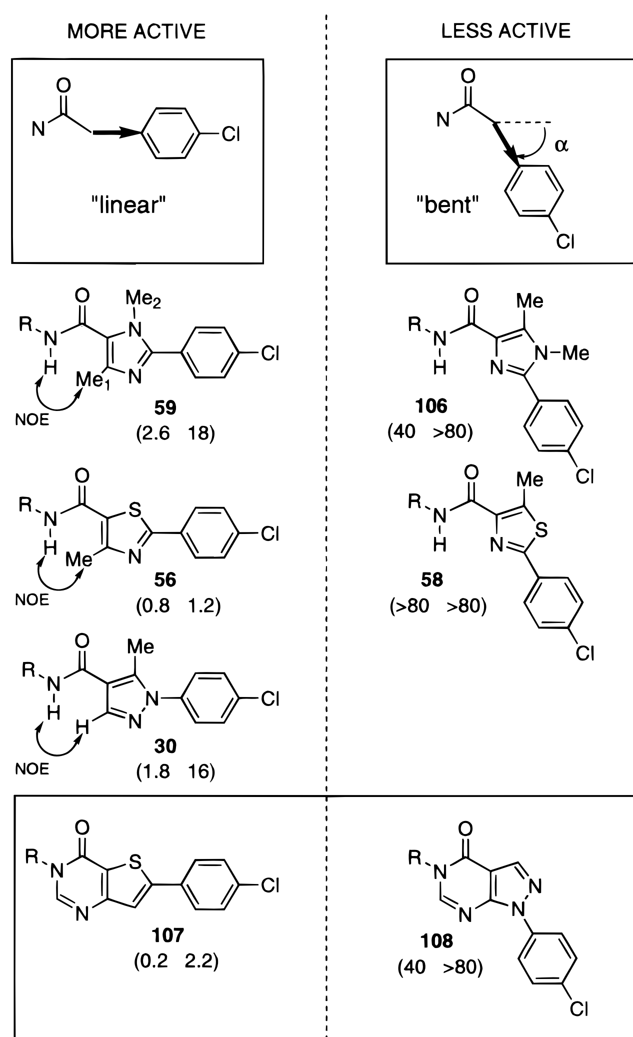


Figure 3. Conformation−activity working model (figures in parentheses indicate MIC geometric means for yeasts and filamentous fungi, respectively).

zole, and it is given as the percentage of surviving animals the day the group treated with fluconazole succumbed. These values, together with their mean in vitro activities, are presented in Tables 1−9. Compounds **74**, **107** (Figure 3), and **114** were tested in a second murine systemic candidosis model and compared to fluconazole, voriconazole, ER-30346, and SCH-42427. In this model the products were administered po daily for 5 days following infection, and the animals were observed for 65 days. The results are shown in Figure 4.

Selected compounds showing good in vivo activity in the murine candidosis model and low MIC values against *A. fumigatus* were evaluated in a murine model of aspergillosis. SCH-42427 (**5**) was the reference standard in this assay. The results are given in Figure 5.

For selected compounds, the serum half-life in the rat was calculated following iv administration of a single dose of 15 mg/kg ($n = 2$ per point). Their preliminary 28-day toxicologic profile was obtained in the rat ($n = 10$) after once daily administration of 100 mg/kg po.

Structure−Activity Studies

On the basis of amido alcohol **8** we first initiated an intensive search for anti-*Aspergillus* activity by modify-

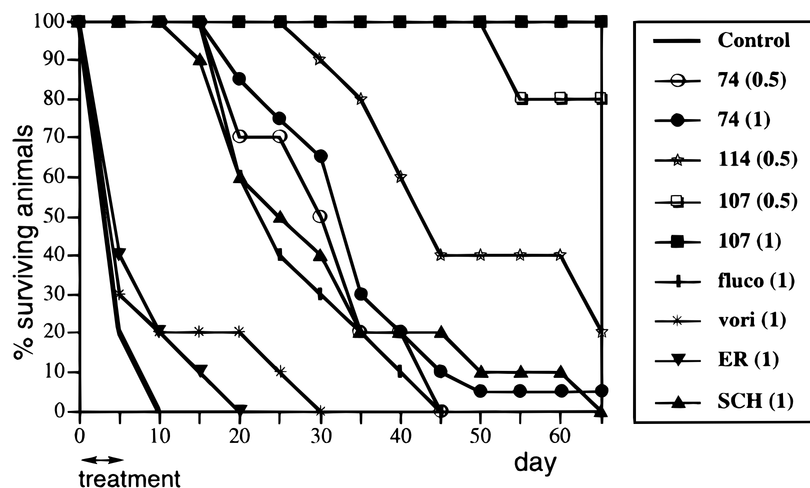


Figure 4. Murine systemic candidosis: survival rate ($n = 10$, except for control and **74** (**1**) for which $n = 20$). Figures in parentheses indicate dose in mg/kg/day (po, qd, 5 days). Compound **74** was administered as the mesylate salt: fluco = fluconazole; vori = voriconazole; ER = ER-30346; SCH = SCH-42427.

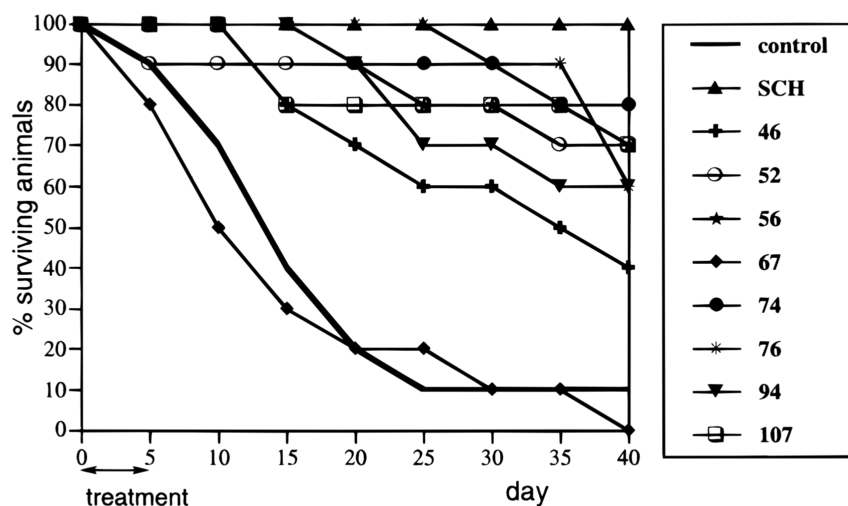


Figure 5. Murine aspergillosis: survival rate at 20 mg/kg/day po, qd, 5 days ($n = 10$). SCH = SCH-42427.

ing the acyl moiety of the amide bond (A, B, and C in Figure 2). A previous survey (not shown) clearly revealed that aromatic amides were preferred over aliphatic ones. Originally, pyrazolecarboxamide **46** (Table 1, MIC *A. fumigatus*: 5 μg/mL) was selected as a lead for structure optimization on the basis of its overall activity. Among the issues to be addressed were the importance of the pyrazole moiety, as well as the role of the phenyl and alkyl substituents.

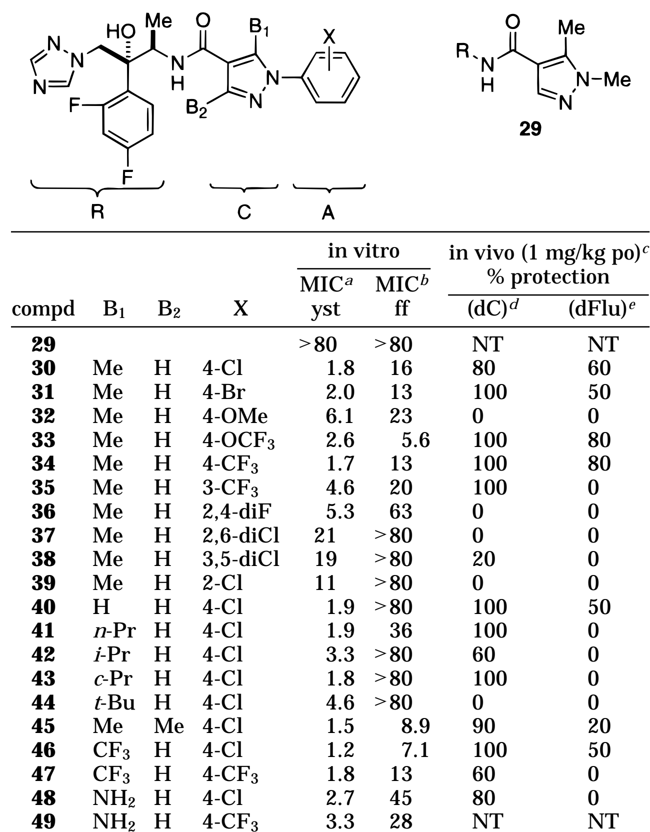
We first prepared a series of 21 pyrazoles in which the key elements of this new moiety were defined. Pyrazoles featured easy synthesis from a variety of commercially available substituted phenylhydrazines (Scheme 2). Table 1 shows the biological results. The first structural requirement discovered within the new acyl moiety was a phenyl ring (A) attached to ring C. The importance of this group was clearly demonstrated by the lack of activity obtained with the non-phenyl derivatives in the pyrazole (**29**) and the other series (thiazoles **72** and **73** in Table 5, and compounds **65**, **66**, and **68** in Table 3). When substitution within this phenyl ring was investigated, it was seen that in vitro activity was relatively similar for *para* and *meta* derivatives (**34** and **35**) and independent of the electron nature of the substituent (compare, for example, **32**). Ortho-substituted (**39**) or disubstituted derivatives (**36**−**38**) gave less active compounds, especially against filamentous fungi. Regarding in vivo activity, only the compounds carrying an EWG at the para position showed good protection. We attributed this fact to the greater metabolic stability conferred by this pattern.[27]

Introduction of one or two small alkyl substituents next to the carbonyl position of the pyrazole greatly increased the activity against filamentous fungi (**30** and **45** vs **40**, Table 1). This tendency was also observed with other heterocycles (see Table 2). Increasing the alkyl size (B_1 = *n*-Pr, *i*-Pr, c-Pr, and *t*-Bu) progressively reduced the susceptibility against filamentous fungi. Yeasts were much less sensitive to these steric changes. An amino group afforded derivatives with an intermediate activity between that of Me and H.

In view of the results obtained with pyrazoles, we proceeded to survey other cycles. For this purpose we prepared several pentaheterocycles (Table 2), fused heterocycles (Table 3), and biphenyl derivatives (Table 4). A *p*-chlorophenyl group in position 3′ to the carboxamide unit was kept as the standard A substituent.

Among the simple heterocycles, i.e., pyrrole (**50**), furan (**51**), and thiophene (**52**) (Table 2), the latter conferred the highest in vitro and in vivo activities. As

Table 1. Pyrazoles



compd	B_1	B_2	X	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (1 mg/kg po)[c] % protection (dC)[d]	in vivo (1 mg/kg po)[c] % protection (dFlu)[e]
29				>80	>80	NT	NT
30	Me	H	4-Cl	1.8	16	80	60
31	Me	H	4-Br	2.0	13	100	50
32	Me	H	4-OMe	6.1	23	0	0
33	Me	H	4-OCF_3	2.6	5.6	100	80
34	Me	H	4-CF_3	1.7	13	100	80
35	Me	H	3-CF_3	4.6	20	100	0
36	Me	H	2,4-diF	5.3	63	0	0
37	Me	H	2,6-diCl	21	>80	0	0
38	Me	H	3,5-diCl	19	>80	20	0
39	Me	H	2-Cl	11	>80	0	0
40	H	H	4-Cl	1.9	>80	100	50
41	*n*-Pr	H	4-Cl	1.9	36	100	0
42	*i*-Pr	H	4-Cl	3.3	>80	60	0
43	*c*-Pr	H	4-Cl	1.8	>80	100	0
44	*t*-Bu	H	4-Cl	4.6	>80	0	0
45	Me	Me	4-Cl	1.5	8.9	90	20
46	CF_3	H	4-Cl	1.2	7.1	100	50
47	CF_3	H	4-CF_3	1.8	13	60	0
48	NH_2	H	4-Cl	2.7	45	80	0
49	NH_2	H	4-CF_3	3.3	28	NT	NT

[a] Geometric mean of MIC values (μg/mL) against 10 yeasts (see Experimental Section). [b] Geometric mean of MIC values (μg/mL) against 6 filamentous fungi (see Experimental). [c] Murine systemic candidosis: three identical doses at 1, 4, and 24 h postinfection. [d] Percent protection the day that 100% mortality was attained in the untreated group (n = 10). [e] Percent protection the day that 100% mortality was attained in the fluconazole-treated group (n = 10). NT = not tested.

with pyrazoles, introduction of a methyl group in the ring improved the potency against filamentous fungi. In fact, compound **53** showed the highest in vitro activity of the whole series. Unfortunately, however, it performed only moderately in vivo.

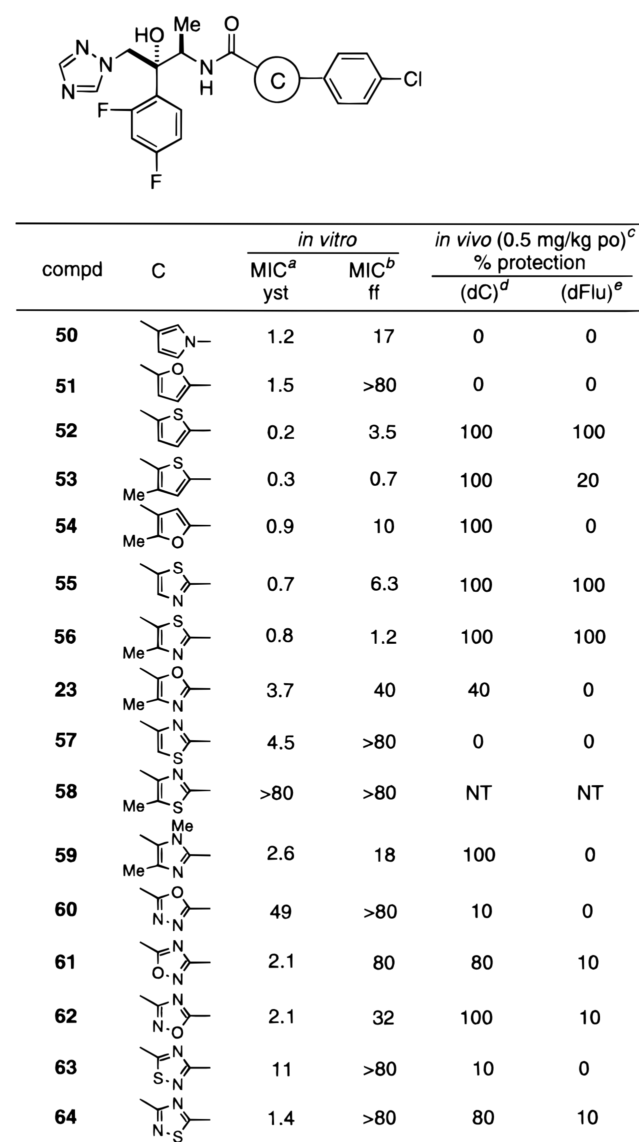
Among the azoles, thiazole **56** was clearly superior to pyrazole **30** (Table 1), oxazole **23**, and imidazole **59** (Table 2). Thiazole **56** further showed excellent in vivo efficacy, but was highly toxic after repeated administration to rats (vide infra). Particularly significant was the fact that its regioisomer, thiazole **58**, was virtually inactive. This unexpected result, together with the importance of methyl substitution, became the basis for constructing our conformation−activity model (vide infra).

A series of oxadiazoles and thiadiazoles was also prepared (**60**−**64**). The products showed a moderate to good anti-yeast spectrum, but they lacked activity against filamentous fungi.

We next prepared a small number of fused aromatic carboxamides (Table 3). As in the previous cases, compounds lacking the phenyl substituent were mostly inactive (**65**, **66**, and **68**). On the other hand, compound **67**, carrying a *p*-Cl-phenyl group, had excellent in vitro activity.

Finally, we decided to go back one step and determine the effect of adding our key *p*-Cl-phenyl ring to the

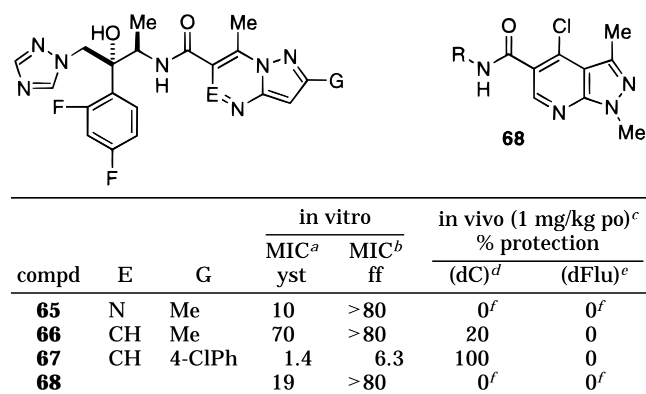
Table 2. The C Ring: Pentaheterocycles



compd	C	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (0.5 mg/kg po)[c] % protection (dC)[d]	in vivo (0.5 mg/kg po)[c] % protection (dFlu)[e]
50		1.2	17	0	0
51		1.5	>80	0	0
52		0.2	3.5	100	100
53		0.3	0.7	100	20
54		0.9	10	100	0
55		0.7	6.3	100	100
56		0.8	1.2	100	100
23		3.7	40	40	0
57		4.5	>80	0	0
58		>80	>80	NT	NT
59		2.6	18	100	0
60		49	>80	10	0
61		2.1	80	80	10
62		2.1	32	100	10
63		11	>80	10	0
64		1.4	>80	80	10

[a,b,c,d,e] See the corresponding footnotes in Table 1.

Table 3. The C Ring: Fused Heterocycles



compd	E	G	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (1 mg/kg po)[c] % protection (dC)[d]	in vivo (1 mg/kg po)[c] % protection (dFlu)[e]
65	N	Me	10	>80	0[f]	0[f]
66	CH	Me	70	>80	20	0
67	CH	4-ClPh	1.4	6.3	100	0
68			19	>80	0[f]	0[f]

[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] Dose: 2.5 mg/kg po.

benzamide unit of Sankyo's structure **69**[10b] (Table 4). We prepared both the para and meta biphenyl derivatives, **70** and **71**. When compared to **69** both compounds had improved in vitro activities against yeasts, but the susceptibility against filamentous fungi was lost in **71**

Table 4. The C Ring: Biphenyls

compd	in vitro		in vivo (0.5 mg/kg po)[c] % protection	
	MIC[a] yst	MIC[b] ff	(dC)[d]	(dFlu)[e]
69	3.9	11	0	0
70	0.3	18	100	100
71	0.3	>80	40	0

[a,b,c,d,e] See the corresponding footnotes in Table 1.

Table 5. Thiazoles

compd	B	L	X	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (0.5 mg/kg po)[c] % protection (dC)[d]	in vivo (0.5 mg/kg po)[c] % protection (dFlu)[e]
72				19	>80	0	0
73				4.6	32	NT	NT
55	H		Cl	0.7	6.3	100	100
74[f]	Me		CN	1.2	4.0	100	100
75	Me		F	1.1	1.8	100	80
56	Me		Cl	0.8	1.2	100	100
76	Me		Br	0.6	1.8	100	90
77	Me		CF_3	0.9	2.2	100	100
78	Me		OCF_3	1.3	1.6	100	100
79	Me		$OCH_2CF_2CF_2H$	1.3	2.2	100	0
80	Me		H	1.4	7.6	30	0
81	Me		*t*-Bu	2.1	8.9	0	0
82	Me		$CONH_2$	20	>80	0	0
83	Me		$C(=NOH)NH_2$	12	80	0	0
84	Me		$C(=NOAc)NH_2$	14	45	70	0
85	CF_3		CN	2.9	28	100	≤50
86	CF_3		Cl	2.0	8.9	100	≤70
87	CF_3		CF_3	1.6	17	90	≤20
88[g]	CF_3		5-tetrazolyl	75	>80	30	0
89	Me	O	Cl	1.5	4.0	10	0
90	Me	CH_2O	Cl	0.6	2.9	30	0
91	Me	SO_2	Cl	7.6	>80	0	0
92	Me	(4-methylthiazol-2,5-diyl)	Cl	1.8	>80	10	0

[a,b,d,e] See the corresponding footnotes in Table 1. [f] $MeSO_3H$ salt. [g] HCl salt.

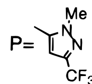
and only maintained in **70**. In vivo, compound **70** had greater efficacy than benzamide **69**.

Given the above results, thiazoles and thiophenes were selected for further optimization (Tables 5 and 6). Thiazoles having a phenyl substituted with a *p*-EWG (**74**–**79** and **55**–**56**), hydrogen (**80**), or an alkyl group (**81**) gave similar good in vitro activities, but again, only the former were clearly active in vivo. More polar

Table 6. Thiophenes

compd	type	B	Ar	Z	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (0.5 mg/kg po)[c] % protection (dC)[d]	in vivo (0.5 mg/kg po)[c] % protection (dFlu)[e]
52	I	H	4-ClPh		0.2	3.5	100	100
53	I	Me	4-ClPh		0.3	0.7	100	20
93	I	H	4-CNPh		0.8	>80	100	100
94	I	Me	4-CNPh		0.7	8.9	100	70
95	I	NH_2	4-ClPh		0.6	22	0	0
96	I	H	3-pyr		1.6	>80	60[f]	0[f]
97	I	H	P		2.3	28	10	0
98	II	NH_2		*n*-Pr	4.4	23	NT	NT
99	II	Me		4-ClPh	1.6	11	70[g]	0[g]
100	II	NH_2		4-ClPh	1.0	10	20	0

[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] Dose: 2.5 mg/kg po. [g] Dose: 1 mg/kg po.



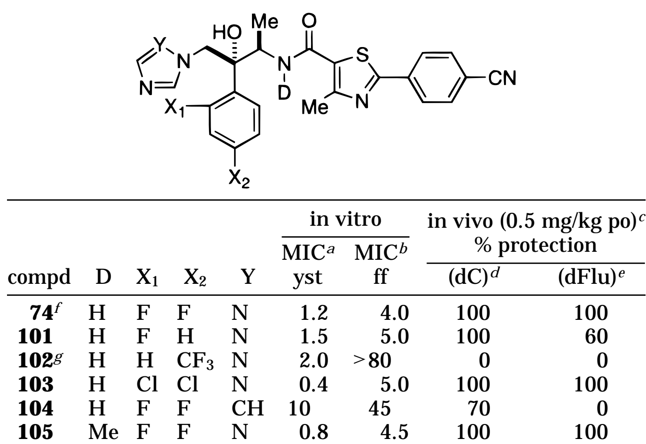
substituents such as amide, amidine derivatives, and 5-tetrazole afforded significantly less active products. Replacement of the thiazole CH_3 by a CF_3 group resulted in impaired activity. The effect of distance between ring A and heterocycle C was also studied. Thus, introduction of oxygen containing spacers in the thiazoles (**89** and **90**) did not substantially modify the in vitro activities but afforded products with diminished in vivo potencies. A sulfone (**91**) or a thiazolyl (**92**) spacer resulted in loss of both activity against filamentous fungi and oral efficacy. In the thiophenes (Table 6), introduction of a sulfone spacer in the 4-position gave moderately active compounds (**99** and **100**). In this series two other A substituents were tested, namely 3-pyridine and a substituted 5-pyrazole. Both compounds showed impaired activities over parent **52**.

In summary, Tables 1–6 suggest that both broad antifungal spectrum and high in vitro and in vivo activities are attained in these structures when the amide portion contains a *p*-EWG-substituted phenyl ring directly attached to a 5-thiazole or 2-thiophene ring, preferably substituted with a methyl group.

On the basis of the above findings, and given its good pharmacokinetic profile (vide infra), **74** (UR-9908) was chosen as the best overall compound. A few final modifications, this time in the left hand side substituent R, were examined on structure **74** (Table 7) without success. Thus, introducing *N*-amide substitution or changing the 2,4-diF pattern for 2,4-diCl or 2-F produced no major change. A 4-CF_3 group, on the other hand, was clearly negative. Replacement of the triazole by an imidazole surprisingly reduced the in vitro activity 10-fold.

Effect of Conformation. During the course of our study we were intrigued by the conformational preferences of the heterocycle-acyl, C–C bond. Whether the alkyl substituent of the heterocycle was syn or anti relative to the amide H seemed easy to determine by a NOE experiment (see Figure 3). Such a study would ultimately tell us the orientation of the phenyl ring

Table 7. Optimization of **74**



compd	D	X_1	X_2	Y	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (0.5 mg/kg po)[c] % protection (dC)[d]	in vivo (0.5 mg/kg po)[c] % protection (dFlu)[e]
74[f]	H	F	F	N	1.2	4.0	100	100
101	H	F	H	N	1.5	5.0	100	60
102[g]	H	H	CF_3	N	2.0	>80	0	0
103	H	Cl	Cl	N	0.4	5.0	100	100
104	H	F	F	CH	10	45	70	0
105	Me	F	F	N	0.8	4.5	100	100

[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] $MeSO_3H$ salt. [g] Racemic.

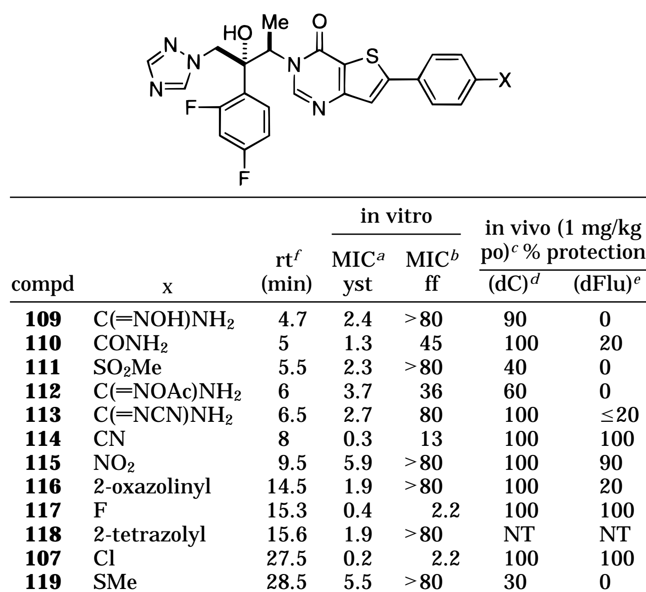
which, due to its strong impact on activity, should be very important for the design of new structures. The first hint came when we were trying to determine the structure of the two regioisomers **59** and **106** (Figure 3), of which the first was clearly more active than the second. Thus, when the amide H of the active isomer (**59**) was irradiated, a strong NOE for the Me_1 signal was observed, suggesting the proximity of these two groups. On the other hand, identical irradiation on the less active isomer (**106**) produced no methyl enhancement, indicating distance. The preferred conformations of each of these two compounds in solution were then seen as depicted in Figure 3, clearly differentiated by the phenyl orientation which we termed "linear" and "bent", respectively. More significant were the NOE results obtained with regioisomeric thiazoles **56** (very active) and **58** (virtually inactive). Again, the active isomer showed the linear conformation whereas the inactive compound was in the bent orientation. It therefore appeared that either a syn NH-Me relationship or a linear disposition of the phenyl ring, or both, were crucial for activity.

The pyrazoles then provided the answer, as the two variables acted in an opposite manner for this particular moiety (i.e., it was the anti NH-Me that yielded a linear phenyl). When the NH signal of **30** was irradiated, only the pyrazole H experienced enhancement, thereby confirming a linear disposition.This result indicated that *the antifungal activity was clearly related to a particular spatial orientation of the phenyl ring, independently of the anti or syn relative positions of the methyl substituent.*

We decided to demonstrate the above working hypothesis by chemically locking the two phenyl orientations. For this purpose we prepared thienopyrimidone **107** and pirazolopyrimidone **108** (Figure 3) and were glad to observe that only the structure emulating the linear conformer (**107**) was active, whereas the bent one (**108**) was not.

Given the good results obtained with compound **107**, thienopyrimidones were explored further (Table 8). Due to the tendency of the previous compounds to display long plasma elimination half-lives (vide infra), special emphasis was placed on increasing the molecule's polarity to facilitate renal elimination. Table 8 shows the results obtained with a series of thienopyrimidones listed in increasing order of hydrophobicity (HPLC). Unfortunately, however, polar substituents such as NO_2, SO_2Me, amide, and amidine derivatives considerably reduced the compounds' activities against filamentous fungi. Tetrazole and oxazoline rings also gave inactive products against those pathogens. The CN group, which helped to decrease the half-life in the open amide series (i.e., in compound **74**) gave a derivative (**114**) with only moderate activity against filamentous fungi. In summary only the 4-F (**117**) and the 4-Cl (**107**) derivatives showed attractive activity profiles.

Table 8. Phenylthienopyrimidones



compd	x	rt[f] (min)	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (1 mg/kg po)[c] % protection (dC)[d]	in vivo (1 mg/kg po)[c] % protection (dFlu)[e]
109	C(=NOH)NH_2	4.7	2.4	>80	90	0
110	$CONH_2$	5	1.3	45	100	20
111	SO_2Me	5.5	2.3	>80	40	0
112	C(=NOAc)NH_2	6	3.7	36	60	0
113	C(=NCN)NH_2	6.5	2.7	80	100	≤20
114	CN	8	0.3	13	100	100
115	NO_2	9.5	5.9	>80	100	90
116	2-oxazolinyl	14.5	1.9	>80	100	20
117	F	15.3	0.4	2.2	100	100
118	2-tetrazolyl	15.6	1.9	>80	NT	NT
107	Cl	27.5	0.2	2.2	100	100
119	SMe	28.5	5.5	>80	30	0

[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] HPLC retention time in a Lichrospher 100 RP-18e 220 × 4 mm column using $MeOH:H_2O$, 2:1.

Table 9. Comparison with Standards

compd	in vitro MIC[a] yst	in vitro MIC[b] ff	regimen 1[f] (dC)[d]	regimen 1[f] (dFlu)[e]	regimen 2[g] (dC)[d]	regimen 2[g] (dFlu)[e]
			in vivo candidosis % protection[c]			
74	1.2	4.0	100	100	100	10
107	0.2	2.2	100	100	100	100
114	0.3	13	100	100	100[h]	40[h]
fluconazole	30	>80	100		100	
itraconazole	5.2	63	0[i]	0[i]	NT	NT
voriconazole	0.6	0.5	0	0	20	0
SCH-43427	8.7	25	100	100	100	20
ER-30346	0.3	0.8	50	0	20	0
TAK-187	2.6	8.9	100	100	NT	NT
8	4.6	22	100	100	NT	NT

[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] Dose: 0.5 mg/kg (1, 4, 24 h) po. [g] Dose: 1 mg/kg/day (5 days) qd po. [h] Dose 0.5 mg/kg/day (5 days) qd po. [i] In PEG 400.

Comparison with Reference Compounds. Table 9 shows the in vitro and in vivo activities of thiazole amide **74** and thienopyrimidones **107** and **114** in comparison with fluconazole, voriconazole, SCH-42427, ER-30346, and TAK-187. In vitro, voriconazole, ER-30346, and **107** had comparably low MICs and a broad spectrum of activity. In vivo, two dose regimens were tested. Thus, under the conditions used for screening (three single doses of 0.5 mg/kg during the 24 h after infection), **74**, **107**, **114**, SCH-42427, TAK-187, and Sankyo's **8** showed 100% protection on the day that the last of the

fluconazole-treated animals died. Under the second conditions, where the products were administered once a day at 0.5 or 1 mg/kg for 5 days following infection, compounds **74** and SCH-42427 behaved more like fluconazole (Figure 4). The CN-substituted thienopyrimidone **114** showed improved levels of protection over the standards and **107** gave outstanding, long-lasting protection. In these two murine models, voriconazole[28] and ER-30346 showed little efficacy.

***In Vivo* Aspergillosis.** A reduced selection (eight products) of the new structures showing interesting in vivo anti-*Candida* and in vitro anti-*Aspergillus* activities were tested in vivo in a murine aspergillosis model at a dose of 20 mg/kg/day (5 days, qd, po). SCH-42427 (**5**) was the reference compound. The mortality curves (Figure 5) indicated that, except for product **67**, the new compounds were active in vivo, although less effective than SCH-42427. Thiophenes **52** and **94**, thiazoles **56**, **74**, and **76**, and thienopyrimidone **107** performed well, displaying efficacies from 60 to 80% protection at the end of the study (day 40). Pyrazole **46** was somewhat less active. The lack of activity of compound **67** could be related to reduced oral absorption as indicated by its poor activity in the in vivo candidosis test (see Table 3).

Kinetic and Toxicology Studies. At this point, we considered that the first of our objectives had been met: we had several compounds showing good in vitro and in vivo activity against a variety of fungi, including *A. fumigatus*. In view of the results, thiazoles **56**, **74**, and **77**, thiophenes **53** and **52**, and thienopyrimidones **107**, **114**, and **117** were subjected to pharmacokinetic and toxicologic screening in the rat. Among these products, only **74** displayed both a relatively short half-life (24 h, iv) and lack of toxicity upon treatment with 100 mg/kg/day po for 28 days. The other compounds showed both long (>48 h) plasma half-lives and high mortality rates appearing already in the second week of treatment. No new peaks indicating metabolism were observed in the plasma chromatograms in any of the kinetic studies under the used HPLC conditions. Since drug accumulation could be accounting for the toxicity observed for these compounds, **117** was also tested on a qod basis at 100 mg/kg for 28 days. Mortality was still obtained, although it was delayed to the third week. To test the pharmacokinetic behavior of these compounds in other species, compound **117** was further administered to monkeys ($n = 2$). Its plasma half-life was calculated to be 55 days, a truly unacceptable value for a drug candidate.

One possible explanation for such long half-lives may be that the high lipophilicity and metabolic stability of these compounds simply preclude their efficient renal elimination. Accordingly, only when the polarity of the molecule was increased (for example, by the introduction of a CN group in **74**) did the half-life start to reach acceptable levels. The in vivo test used in our screening program, consisting in monitoring survival 9 days after treatment, led to the identification of active compounds, but also implicitly favored those having long half-lives.

In conclusion, the results of the present study provide information on the antifungal activity of structures **I** and **II**. In addition, important functional features, such as a thiazole or thiophene rings carrying both a substituted phenyl and a small alkyl group, have been identified for anti-*Aspergillus* activity. However, most of the new compounds showed unacceptably long plasma half-lives and high toxicity rates in animal species. Consequently, and in light of the excellent results obtained with quinazolinone derivatives in an ongoing parallel study in our center, further investigation on structures **I** and **II** was temporarily interrupted. The results with the new derivatives are presented in the accompanying paper.

Experimental Section

Chemistry. Tetrahydrofuran (THF) and ether (Et_2O) were dried by distillation under argon from sodium metal. Flash chromatography was performed on SDS silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on AC-80 (80 MHz) or an Avance DPX (300 MHz) Bruker spectrometer and are reported in ppm on the δ scale from TMS (unless otherwise indicated). Coupling constants are reported in hertz. NMR interpretations are provided only for representative compounds. Melting points were determined on Mettler FP-80, FP-81, and FP-82 apparatuses 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. 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. GC–MS spectra were performed using a Hewlett-Packard 5980 chromatograph coupled to the above-mentioned mass spectrometer. For routine GC–MS analyses, a 12 m HP-5 column, with an injector temperature of 275 °C and an oven temperature gradient from 100 to 290 °C (25 °C/min), was used.

Water-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Fluconazole (**1**) was synthesized in our research center with 1,3-dichloroacetone and 2,4-difluorophenylmagnesium bromide as starting materials, and the resulting mixture was reacted with sodium triazolate, according to a published procedure.[29] SCH-42427 (**5**) and itraconazole (**2**) were kindly provided by Schering-Plough and Janssen, respectively. Voriconazole (**4**) was generously provided by Pfizer. Ketoconazole was purchased from Sigma. Compounds TAK-187,[8] ER-30346,[9] and **8**[10b] were synthesized in our center according to the published procedures. Acids **17–28** were commercially available (Aldrich, Maybridge) or were prepared as indicated in the Supporting Information.

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. Most of the chemical yields reported below are not optimized and correspond to reactions run only one time.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-methylamino-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12). The compound was obtained by a two step sequence from amine **11** ((a) *p*-CH_2O, C_6H_6, refl, 2 h, (b) LAH, Et_2O, room temperature, 1 h) according to a published procedure:[10b] mp 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.94 (s, 1H, triazole), 7.75 (s, 1H, triazole), 7.39 (m, 1H, ar), 6.8–6.7 (m, 2H, ar), 4.87 (d, $J = 14.2$, 1H, TrC*H*(H)), 4.76 (d, $J = 14.2$, 1H, TrCH(*H*)), 2.96 (dq, $J_d = 2.0$, $J_q = 6.6$, 1H, C*H*Me), 2.49 (s, 3H, N*Me*), 0.92 (dd, $J = 1.2$, $J = 6.6$, 3H, *Me*); $[\alpha]_D$ −102.7° (*c* 1, $CHCl_3$). Anal. ($C_{13}H_{16}F_2N_4O$) C, H, N.

(2*R*,3*R*)-3-Amino-2-(2-fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (14). The compound was obtained by adaptation of our previous published procedure:[14] mp 104−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.93 (s, 1H), 7.78 (s, 1H), 7.49 (dt, J_d = 1.8, J_t = 7.9, 1H), 7.28−7.18 (m, 1H), 7.1−6.9 (m, 2H), 4.71 (s, 2H), 3.64 (dq, J_d = 2.5, J_q = 6.6, 1H), 0.86 (dd, J = 0.8, J = 6.6, 3H); $[\alpha]_D$ −79.2° (*c* 1, $CHCl_3$). Anal. ($C_{12}H_{15}FN_4O$) C, H, N.

(2*R*,3*R*)-3-Amino-2-(2,4-difluorophenyl)-1-(1*H*-imidazol-1-yl)-2-butanol (16). The compound was obtained by adaptation of our previous published procedure:[14] white solid; mp 77−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.47 (dq, J_d = 1.5, J_q = 7.1, 1H, ar), 7.35 (s, 1H, imid), 6.87 (s, 1H, imid), 6.78 (s, 1H, imid), 6.8−6.7 (m, 2H), 4.31 (d, J = 14, 1H), 4.24 (d, J = 14, 1H), 3.64 (dq, J_d = 2.5, J_q = 6.6, 1H), 0.81 (d, J = 6.6, 3H); $[\alpha]_D$ −27.9° (*c* 1, $CHCl_3$). Anal. ($C_{13}H_{15}F_2N_3O$) C, H, N.

Hydrolysis of Esters. General Method A. A solution of the ethyl (or methyl) ester of acids **17**−**28** (10 mmol) in EtOH (or MeOH) (50 mL) and H_2O (10 mL) was treated with KOH (5 equiv) at 60 °C for 20 h. The reaction mixture was then concentrated and partitioned between H_2O and $CHCl_3$. The organic phase was discarded and the aqueous phase was acidified to pH 1 with 3 N HCl. Solid acids were obtained by filtration. Gummy acids were extracted with $CHCl_3$, dried, and concentrated.

Hydrolysis of esters. General Method B. For labile substrates, the following method was used. The ester (10 mmol) was dissolved in a mixture of MeOH (100 mL) and THF (50 mL). Next, a solution of LiOH·H_2O (5 equiv) in 10 mL of water was slowly added, and the resulting mixture was stirred at 30 °C for 8 h. The mixture was then evaporated to dryness. Water was added, and the mixture was filtered through Celite and acidified with 3 N HCl to pH 1.0−1.2, resulting in the appearance of a solid or a gum. This product was centrifuged, washed with cold water, centrifuged again if necessary, and then finally dried to afford the acid.

Amide Formation: General Method C. To a solution of the amine **11**−**16** (1 mmol) in DMF (6 mL) was added 1-hydroxybenzotriazole (1 equiv). Next, the acid **17**−**28** (1 equiv) and DCC (1.1 equiv) were added and the mixture was stirred at room temperature for 18 h. The reaction mixture was then cooled to 0 °C, and the dicyclohexylurea formed was filtered and washed with $CHCl_3$. The remaining solution was the evaporated to dryness and partitioned between 10% aqueous $NaHCO_3$ solution and $CHCl_3$. The layers were separated, and the organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hex:EtOAc 1:1 then 1:3) to give the title product, which was recrystallized from EtOAc:ether:hexane.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,5-dimethyl-1*H*-pyrazole-4-carboxamide (29). Method C (**11** + 1,5-dimethyl-1*H*-pyrazole-4-carboxylic acid[17]): white solid; mp 183−184 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (s, 2H, triazole), 7.69 (s, 1H, pyrazole), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H, ar), 6.9−6.7 (m, 2H, ar), 6.24 (br d, J = 9, 1H, N*H*), 5.33 (d, J = 1.3, 1H, O*H*), 5.02 (d, J = 14.3, 1H, TrC*H*(H)), 4.90 (quint, J = 7, 1H, C*H*Me), 4.49 (d, J = 14.3, 1H, TrCH(*H*)), 3.82 (s, 3H, *Me*-pyrazole), 2.59 (s, 3H, *Me*-pyrazole), 0.99 (d, J = 6.8, 3H, *Me*CH); $[\alpha]_D$ −117.2° (*c* 1, $CHCl_3$). Anal. ($C_{18}H_{20}F_2N_6O_2$) C, H, N.

(1*R*,2*R*)-1-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-5-methyl-1*H*-pyrazole-4-carboxamide (30). Method C (**11** + **19** [B = Me, B′ = H, X = 4-Cl]: white solid; mp 154−155 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 7.90 (s, 1H), 7.79 (s, 2H), 7.6−7.2 (m, 5H), 7.0−6.6 (m, 2H), 6.37 (br d, J = 9, 1H), 5.35 (d, J = 1.3, 1H), 5.06 (d, J = 14.5, 1H), 5.1−4.8 (m, 1H), 4.50 (d, J = 14.5, 1H), 2.61 (s, 3H), 1.02 (d, J = 7, 3H); $[\alpha]_D$ −91.4° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{21}ClF_2N_6O_2$) C, H, N.

(1*R*,2*R*)-1-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]pyrrole-3-carboxamide (50). Method C (**11** + 1-(4-chlorophenyl)-pyrrole-3-carboxylic acid[17c]): amorphous solid; ^{1}H NMR (80 MHz, $CDCl_3$) 7.79 (s, 2H), 7.63 (t, J = 2, 1H, pyrrole), 7.6−7.3 (m, 5H), 7.02 (t, J = 2, 1H, pyrrole), 7.0−6.6 (m, 2H), 6.63 (t, J = 2, 1H, pyrrole), 6.35 (br d, 1H), 5.36 (d, J = 1.3, 1H), 5.06 (d, J = 14.5, 1H), 5.1−4.8 (m, 1H), 4.50 (d, J = 14.5, 1H), 1.03 (d, J = 7, 3H); $[\alpha]_D$ −95.2° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{20}ClF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]furan-2-carboxamide (51). Method C (**11** + 5-(4-chlorophenyl)-furan-2-carboxylic acid [Maybridge]): white solid; mp 218−219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (s, 1H), 7.78 (s, 1H), 7.69 (dt, J_t = 2, J_d = 8.4, 2H), 7.42 (dt, J_t = 2, J_d = 8.4, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.25 (d, J = 3.6, 1H, furan), 6.88 (br d, J = 9.5, 1H), 6.8−6.6 (m, 2H), 6.76 (d, J = 3.6, 1H, furan), 5.39 (br s, 1H), 5.04 (d, J = 14.2, 1H), 4.96 (br quint, J = 7, 1H), 4.53 (d, J = 14.2, 1H), 1.05 (d, J = 6.8, 3H); GC−MS 248 and 250 ($C_{13}H_{11}ClNO_2$), 224 ($C_{10}H_8F_2N_3O$), 205 and 207 ($C_{11}H_6ClO_2$); $[\alpha]_D$ −173° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{19}ClF_2N_4O_3$·1/2EtOAc) C, H, N.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-thiophene-2-carboxamide (52). Method C (**11** + **17** [B = H, X = Cl]): white solid; mp 169−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (s, 1H), 7.78 (s, 1H), 7.55 (dt, J_t = 2.5, J_d = 6.6, 2H), 7.54 (d, J = 3.5, 1H, thiophene), 7.38 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.38 (dt, J_t = 2.5, J_d = 6.6, 2H), 7.25 (d, J = 3.5, 1H, thiophene), 6.8−6.6 (m, 2H), 6.53 (br d, J = 9.5, 1H), 5.35 (d, J = 1.5, 1H), 5.04 (d, J = 14.3, 1H), 4.93 (br quint, J = 7, 1H), 4.51 (d, J = 14.3, 1H), 1.02 (d, J = 6.8, 3H); MS 264 and 266 ($C_{13}H_{11}ClNOS$), 221 and 223 ($C_{11}H_6ClOS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −101.0° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{19}ClF_2N_4O_2S$) C, H, N, S.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-methylthiophene-2-carboxamide (53). Method C (**11** + **17** [B = Me, X = Cl]): amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) 7.84 (s, 1H), 7.82 (s, 1H), 7.56 (dt, J_t = 2.5, J_d = 6.6, 2H), 7.40 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.39 (d, J = 7, 2H), 7.14 (s, 1H, thiophene), 6.8−6.6 (m, 2H), 6.42 (br d, J = 9.3, 1H), 5.38 (br s, 1H), 5.08 (d, J = 14.5, 1H), 4.95 (br quint, J = 7, 1H), 4.55 (d, J = 14.5, 1H), 2.82 (s, 3H), 1.04 (d, J = 6.8, 3H); MS 278 and 280 ($C_{14}H_{13}ClNOS$), 235 and 237 ($C_{12}H_8ClOS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −114.9° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{21}ClF_2N_4O_2S$) C, H, N, S.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2-methylfuran-3-carboxamide (54). Method C (**11** + 5-(4-chlorophenyl)-2-methylfuran-3-carboxylic acid [Maybridge]): white solid; mp 189−190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (s, 1H), 7.79 (s, 1H), 7.59 (dt, J_t = 2, J_d = 8.4, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.37 (dt, J_t = 2, J_d = 8.4, 2H), 6.8−6.6 (m, 2H), 6.27 (s, 1H, furan), 6.29 (br d, J = 9.5, 1H), 5.35 (s, 1H), 5.04 (d, J = 14.2, 1H), 4.93 (br quint, J = 7, 1H), 4.51 (d, J = 14.2, 1H), 2.71 (s, 3H), 1.01 (d, J = 6.8, 3H); HPLC−MS 262 and 264 ($C_{14}H_{13}ClNO_2$), 219 and 221 ($C_{12}H_8ClO_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −131.2° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{21}ClF_2N_4O_3$) C, H, N.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiazole-5-carboxamide (55). Method C (**11** + **22** [B = H, X = Cl]): white solid; mp 194−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.25 (s, 1H, thiazole), 7.93 (dt, J_t = 2, J_d = 9, 2H), 7.81 (s, 1H), 7.79 (s, 1H), 7.45 (dt, J_t = 2, J_d = 9, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 2H), 6.55 (br d, J = 9.3, 1H), 5.40 (d, J = 1.6, 1H), 5.03 (d, J = 14.5, 1H), 4.95 (br quint, J = 7, 1H), 4.52 (d, J = 14.5, 1H), 1.04 (d, J = 6.8, 3H); HPLC−MS 265 and 267 ($C_{12}H_{10}ClN_2OS$), 222 ($C_{10}H_5ClNOS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −105.6° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{18}ClF_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-methylthiazole-5-carboxamide (56). Method C (**11** + **22** [B = Me, X = Cl]): white solid; mp 159−160 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.0−7.8 (m, 4H), 7.6−7.2 (m, 3H), 7.0−6.6 (m, 2H), 6.4 (br d, J = 10, 1H), 5.37 (d, J = 1.3, 1H), 5.06 (d, J = 14.5, 1H),

5.1−4.8 (m, 1H), 4.50 (d, $J = 14.5$, 1H), 2.80 (s, 3H), 1.02 (d, $J = 7$, 3H); MS 281 and 283 ($C_{13}H_{14}ClN_2OS$), 236 and 238 ($C_{11}H_7ClNOS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −117.1° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{20}ClF_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-methyloxazole-5-carboxamide (23). A solution of *N*-(4-chlorobenzoyl)-L-alanine (1.46 g, 6.41 mmol) in benzene (35 mL) was treated with oxalyl chloride (0.55 mL, 6.41 mmol) at 45 °C for 3 h. Next, a solution of (2*R*,3*R*)-3-amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (1.72 g, 6.41 mmol) and triethylamine (2.2 mL) in $CHCl_2$ (20 mL) was slowly added, and the reaction mixture was stirred at 0 °C for 0.5 h. The crude product was then poured into cold water and extracted with $CHCl_3$. The organic solution was dried over Na_2SO_4 and filtered, and the filtrate was concentrated in vacuo to give a mixture of several products (TLC) from which the title compound was isolated by flash chromatography as a white solid (140 mg): mp 89−93 °C; ^1H NMR (300 MHz, $CDCl_3$) 8.04 (d, $J = 8.5$, 2H), 7.79 (s, 1H), 7.78 (s, 1H), 7.49 (d, $J = 8.5$, 2H), 7.37 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.8−6.6 (m, 3H), 5.38 (d, $J = 1.1$, 1H), 5.04 (d, $J = 14.3$, 1H), 4.96 (br quint, $J = 7$, 1H), 4.53 (d, $J = 14.3$, 1H), 2.60 (s, 3H), 1.04 (d, $J = 6.8$, 3H); HPLC−MS 263 and 265 ($C_{13}H_{12}ClN_2O_2$), 220 and 222 ($C_{11}H_7ClNO_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −141° (*c* 0.5, $CHCl_3$). Anal. ($C_{23}H_{20}ClF_2N_5O_3$) C, H, N.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiazole-4-carboxamide (57). Method C (**11** + **21** [B = H, X = Cl]): white solid; mp 201−204 °C; ^1H NMR (80 MHz, $CDCl_3$) 8.15 (s, 1H, thiazole), 8.0−7.7 (m, 4H), 7.6−7.2 (m, 4H), 7.0−6.6 (m, 2H), 5.33 (d, $J = 1.3$, 1H), 5.06 (d, $J = 14.5$, 1H), 5.1−4.8 (m, 1H), 4.5 (d, $J = 14.5$, 1H), 1.07 (d, $J = 7$, 3H); $[\alpha]_D$ −130.7° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{18}ClF_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-5-methylthiazole-4-carboxamide (58). Method C (**11** + **21** [B = Me, X = Cl]): mp 166−167 °C; ^1H NMR (300 MHz, $CDCl_3$) 8.00 (br d, $J = 9.5$, 1H, N*H*), 7.87 (dt, $J_t = 2.4$, $J_d = 8.6$, 2H), 7.80 (s, 1H), 7.77 (s, 1H), 7.5−7.4 (m, 3H), 6.9−6.7 (m, 2H), 5.32 (d, $J = 1.5$, 1H), 5.05 (d, $J = 14.3$, 1H), 4.89 (br quint, $J = 7$, 1H), 4.57 (d, $J = 14.3$, 1H), 2.90 (s, 3H), 1.06 (d, $J = 6.8$, 3H); MS 281 and 283 ($C_{13}H_{14}ClN_2OS$), 236 and 238 ($C_{11}H_7ClNOS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −132.2° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{20}ClF_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3,5-dimethyl-3*H*-imidazole-4-carboxamide (59). Method C (**11** + **18**): the reaction produced two products which were separated by flash chromatography. The less polar product (TLC, EtOAc) was identified by NOE as the title compound and was isolated as a white amorphous solid: ^1H NMR (300 MHz, $CDCl_3$) 7.81 (s, 1H), 7.78 (s, 1H), 7.55 (d, $J = 8.5$, 2H), 7.45 (d, $J = 8.5$, 2H), 7.40 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.8−6.6 (m, 2H), 6.39 (d, $J = 9.5$, 1H), 5.37 (d, $J = 1.5$, 1H), 5.05 (d, $J = 14.3$, 1H), 4.96 (br quint, $J = 7$, 1H), 4.53 (d, $J = 14.3$, 1H), 3.87 (s, 3H, N-Me), 2.61 (s, 3H, *Me*-imidazol), 1.03 (d, $J = 6.8$, 3H); GC−MS 276 and 278 ($C_{14}H_{15}ClN_3O$), 198 and 200 ($C_{12}H_{10}N_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −71.4° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{23}ClF_2N_6O_2 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,5-dimethyl-1*H*-imidazole-4-carboxamide (106). The second product eluting from the column was identified by NOE as the title compound, and it was obtained as a white amorphous solid: ^1H NMR (300 MHz, $CDCl_3$) 7.81 (s, 1H), 7.73 (s, 1H), 7.68 (br d, $J = 9.4$, 1H, N*H*), 7.57 (d, $J = 8.5$, 2H), 7.48 (d, $J = 8.5$, 2H), 7.40 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.8−6.6 (m, 2H), 5.36 (d, $J = 1.5$, 1H), 5.03 (d, $J = 14.3$, 1H), 4.83 (br quint, $J = 7$, 1H), 4.56 (d, $J = 14.3$, 1H), 3.59 (s, 3H, N-*Me*), 2.68 (s, 3H, *Me*-imidazol), 1.04 (d, $J = 6.8$, 3H); GC−MS 276 and 278 ($C_{14}H_{15}ClN_3O$), 198 and 200 ($C_{12}H_{10}N_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −108.7° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{23}ClF_2N_6O_2 \cdot {}^1/_2EtOAc$) C, H, N.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,3,4-oxadiazole-2-carboxamide, Chloroform Solvate (60). Method C (**11** + **24**): white solid; mp 188−190 °C; ^1H NMR (300 MHz, MeOH-d_4) δ (MeOH-d_4) 8.24 (s, 1H), 7.9−7.8 (m, 2H), 7.68 (s, 1H), 7.52 (dt, $J_t = 2$, $J_d = 8.7$, 2H), 7.35 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.95 (ddd, $J = 2.4$, $J = 8.7$, $J = 11.5$, 1H), 6.81 (dt, $J_d = 2.0$, $J_t = 8.0$, 1H), 4.88 (d, $J = 14.4$, 1H), 4.82 (m, 1H), 4.54 (d, $J = 14.4$, 1H), 0.99 (d, $J = 6.8$, 3H); HPLC−MS 250 and 252 ($C_{11}H_9ClN_3O_2$), 207 and 209 ($C_9H_4ClN_2O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −66.5° (*c* 1, MeOH). Anal. ($C_{21}H_{17}ClF_2N_6O_3.CHCl_3$) C, H, N.

(1*R*,2*R*)-3-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,2,4-oxadiazole-5-carboxamide (61). Method C (**11** + **25**): white solid; mp 170−172 °C; ^1H NMR (300 MHz, $CDCl_3$) 8.10 (dt, $J_t = 2$, $J_d = 9$, 2H), 7.81 (s, 1H), 7.79 (s, 1H), 7.69 (br d, $J = 9.3$, 1H, N*H*), 7.52 (dt, $J_t = 2$, $J_d = 9$, 2H), 7.40 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.8−6.6 (m, 2H), 5.46 (d, $J = 1.5$, 1H), 5.02 (d, $J = 14.2$, 1H), 4.95 (br quint, $J = 7$, 1H), 4.52 (d, $J = 14.2$, 1H), 1.07 (d, $J = 6.8$, 3H); HPLC−MS 250 and 252 ($C_{11}H_9ClN_3O_2$), 207 and 209 ($C_9H_4ClN_2O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −81.8° (*c* 1, MeOH). Anal. ($C_{21}H_{17}ClF_2N_6O_3 \cdot {}^1/2EtOAc$) H, N; C: calcd, 53.24; found, 54.02.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,2,4-oxadiazole-3-carboxamide, Chloroform Solvate (62). Method C (**11** + **26**): white solid; mp 79−83 °C; ^1H NMR (300 MHz, $CDCl_3$) 8.16 (dt, $J_t = 1.8$, $J_d = 8.6$, 2H), 7.79 (br s, 2H), 7.60 (br d, $J = 9.3$, 1H, N*H*), 7.56 (dt, $J_t = 1.8$, $J_d = 8.6$, 2H), 7.40 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.8−6.6 (m, 2H), 5.38 (d, $J = 1.5$, 1H), 5.04 (d, $J = 14.4$, 1H), 4.95 (br quint, $J = 7$, 1H), 4.53 (d, $J = 14.4$, 1H), 1.06 (d, $J = 6.8$, 3H); HPLC−MS 250 and 252 ($C_{11}H_9ClN_3O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −67.4° (*c* 1, MeOH). Anal. ($C_{21}H_{17}ClF_2N_6O_3.CHCl_3$) C, H, N.

(1*R*,2*R*)-3-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,2,4-thiadiazole-5-carboxamide (63). Method C (**11** + **27**[25]): white solid; mp 215−220 °C; ^1H NMR (300 MHz, MeOH-d_4) δ (MeOH-d_4) 8.45 (dt, $J_t = 2$, $J_d = 7$, 2H), 8.32 (s, 1H), 7.75 (s, 1H), 7.65 (dt, $J_t = 2$, $J_d = 7$, 2H), 7.50 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 7.08 (ddd, $J = 2.4$, $J = 8.7$, $J = 11.5$, 1H), 6.94 (dt, $J_d = 2.0$, $J_t = 8.0$, 1H), 5.12 (q, $J = 6.8$, 1H), 5.05 (d, $J = 14.6$, 1H), 4.70 (d, $J = 14.6$, 1H), 1.18 (d, $J = 6.8$, 3H); HPLC−MS 266 and 268 ($C_{11}H_9ClN_3OS$), 223 and 225 ($C_9H_4ClN_2OS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −106.3° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{17}ClF_2N_6O_2S$) C, H, N, S.

(1*R*,2*R*)-5-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,2,4-thiadiazole-3-carboxamide (64). Method C (**11** + **28**[25]): white solid; mp 186−187 °C; ^1H NMR (300 MHz, MeOH-d_4) δ (MeOH) 8.32 (s, 1H), 8.22 (dt, $J_t = 2$, $J_d = 8.4$, 2H), 7.76 (s, 1H), 7.70 (dt, $J_t = 2$, $J_d = 8.4$, 2H), 7.49 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 7.08 (ddd, $J = 2.4$, $J = 8.7$, $J = 11.5$, 1H), 6.94 (dt, $J_d = 2.0$, $J_t = 8.0$, 1H), 5.15 (q, $J = 6.8$, 1H), 5.05 (d, $J = 14.6$, 1H), 4.70 (d, $J = 14.6$, 1H), 1.17 (d, $J = 6.8$, 3H); HPLC−MS 266 and 268 ($C_{11}H_9ClN_3OS$), 223 and 225 ($C_9H_4ClN_2OS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −80.8° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{17}ClF_2N_6O_2S$) C, H, N, S.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazine-3-carboxamide (65). Method C (**11** + 4,7-dimethylpyrazolo[5,1-*c*][1,2,4]triazine-3-carboxylic acid [Maybridge]): yellowish solid; mp 102−109 °C; ^1H NMR (80 MHz, $CDCl_3$) 8.80 (br d, $J = 9$, 1H, N*H*), 7.80 (s, 1H), 7.77 (s, 1H), 7.40 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 7.09 (s, 1H), 6.9−6.7 (m, 2H), 5.26 (br s, 1H), 5.2−4.8 (m, 2H), 4.58 (d, $J = 14.6$, 1H), 3.36 (s, 3H), 2.66 (s, 3H), 1.10 (d, $J = 7$, 3H); $[\alpha]_D$ −91.9° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{20}F_2N_8O_2$) C, H, N.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2,7-dimethylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide (66). Method C (**11** + 2,7-dimethylpyrazolo[1,5-*a*]pyrimidine-6-carboxamylic acid [Maybridge]): white solid; mp 97−101 °C; ^1H NMR (80 MHz, $CDCl_3$)

8.54 (s, 1H), 7.80 (s, 2H), 7.40 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.9−6.7 (m, 4H), 5.36 (d, J = 1.2, 1H), 5.09 (d, J = 14.5, 1H), 5.2−4.8 (m, 1H), 4.49 (d, J = 14.5, 1H), 3.04 (s, 3H), 2.55 (s, 3H), 1.04 (d, J = 7, 3H); [α]$_D$ −104.8° (c 1, $CHCl_3$). Anal. ($C_{21}H_{21}F_2N_7O_2$) C, H, N.

(1*R*,2*R*)-2-(4-Chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-methylpyrazolo[1,5-*a*]pyrimidine-6-carboxamide (67). Method C (**11** + 2-(4-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid [Maybridge]): white solid; mp 227−228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.61 (s, 1H), 7.99 (dt, J_t = 2.0, J_d = 8.6, 2H), 7.83 (s, 2H), 7.47 (dt, J_t = 2.0, J_d = 8.6, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.03 (s, 1H), 6.8−6.6 (m, 2H), 6.62 (br d, J = 9.4, 1H), 5.42 (s, 1H), 5.13 (d, J = 14.2, 1H), 5.02 (br quint, J = 7, 1H), 4.55 (d, J = 14.2, 1H), 3.13 (s, 3H), 1.09 (d, J = 6.8, 3H); MS 313 and 315 ($C_{16}H_{14}ClN_4O$), 270 and 272 ($C_{14}H_9ClN_3O$), 224 ($C_{10}H_8F_2N_3O$); [α]$_D$ −93.8° (c 1, $CHCl_3$). Anal. ($C_{26}H_{22}ClF_2N_7O_2$) C, H, N.

(1*R*,2*R*)-4-Chloro-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,3-dimethylpyrrolo[3,4-*b*]pyridine-5-carboxamide (68). Method C (**11** + 4-chloro-1,3-dimethylpyrrolo[3,4-*b*]pyridine-5-carboxylic acid [Maybridge]): white solid; mp 97−101 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.54 (s, 1H), 7.80 (s, 2H), 7.40 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.9−6.7 (m, 4H), 5.36 (d, J = 1.2, 1H), 5.09 (d, J = 14.5, 1H), 5.2−4.8 (m, 1H), 4.49 (d, J = 14.5, 1H), 3.04 (s, 3H), 2.55 (s, 3H), 1.04 (d, J = 7, 3H); [α]$_D$ −104.8° (c 1, $CHCl_3$). Anal. ($C_{21}H_{20}ClF_2N_7O_2$) C, H, N.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-chloro-*p*-biphenylcarboxamide (70). (a) Following the general method C (**11** + 4-bromobenzoic acid), (1*R*,2*R*)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-bromobenzamide was obtained as an amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (s, 1H), 7.77 (s, 1H), 7.72 (dt, J_t = 2.1, J_d = 8.6, 2H), 7.47 (dt, J_t = 2.1, J_d = 8.6, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 3H), 5.36 (s, 1H), 5.03 (d, J = 14.2, 1H), 4.96 (br quint, J = 7, 1H), 4.46 (d, J = 14.2, 1H), 1.01 (d, J = 6.8, 3H). Anal. ($C_{10}H_{17}BrF_2N_4O_2$)

(b) To a solution containing PPh_3 (37 mg, 0.14 mmol) and $Pd(AcO)_2$ (7 mg, 0.03 mmol) in DME (10 mL) and THF (2.5 mL) was added 4-chlorophenylboronic acid (305 mg, 2 mmol), and the mixture was stirred at room temperature for 30 min. Water (81 μL) and K_2CO_3 (641 mg, 4.6 mmol) were added, and the mixture was stirred for an additional 30 min. Finally, the product obtained in (a) was added to that mixture and the reaction was stirred at reflux for 15 h. Water was added and the volatiles were removed in vacuo. The residue was partitioned between $CHCl_3$ and water, the aqueous phase was discarded, the organic phase was washed with brine and dried with Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated to a brown foam that was purified by flash chromatography to afford a white solid (36% frrom amine **11**): mp 173−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.93 (dt, J_t = 1.7, J_d = 8.4, 2H), 7.79 (s, 2H), 7.66 (dt, J_t = 1.7, J_d = 8.4, 2H), 7.55 (dt, J_t = 2, J_d = 8.6, 2H), 7.44 (dt, J_t = 2, J_d = 8.6, 2H), 7.40 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 3H), 5.37 (br s, 1H), 5.08 (d, J = 14.3, 1H), 5.00 (br quint, J = 7, 1H), 4.50 (d, J = 14.3, 1H), 1.04 (d, J = 6.8, 3H); GC−MS 258 and 260 ($C_{15}H_{13}ClNO$), 224 ($C_{10}H_8F_2N_3O$), 215 and 217 ($C_{13}H_8ClO$); [α]$_D$ −110.2° (c 1, $CHCl_3$). Anal. ($C_{25}H_{21}ClF_2N_4O_2 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-chloro-*m*-biphenylcarboxamide (71). Following a similar procedure to that described above but using 3-(4-chlorophenyl)benzoic acid the title compound was obtained as a white solid (53% from **11**): mp 90−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.05 (t, J = 1.7, 1H), 7.80 (dt, J_t = 1.2, J_d = 8.3, 1H), 7.79 (s, 2H), 7.72 (dt, J_t = 1.2, J_d = 8.3, 1H), 7.56 (dt, J_t = 2, J_d = 8.7, 2H), 7.5−7.6 (m, 1H), 7.44 (dt, J_t = 2, J_d = 8.7, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 3H, ar), 5.36 (d, J = 1.2, 1H), 5.08 (d, J = 14.2, 1H), 5.01 (br quint, J = 7, 1H), 4.50 (d, J = 14.2, 1H), 1.05 (d, J = 6.8, 3H); GC−MS 258 and 260 ($C_{15}H_{13}ClNO$), 224 ($C_{10}H_8F_2N_3O$), 215 and 217 ($C_{13}H_8ClO$); [α]$_D$ −97.7° (c 1, $CHCl_3$). Anal. ($C_{25}H_{21}ClF_2N_4O_2 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2,4-dimethylthiazole-5-carboxamide (72). Method C (**11** + 2,4-dimethylthiazole-5-carboxylic acid [Maybridge]): mp 175−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (s, 1H), 7.77 (s, 1H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 2H), 6.28 (d, J = 9.5, 1H), 5.33 (d, J = 1.2, 1H), 5.02 (d, J = 14.2, 1H), 4.89 (br quint, J = 7, 1H), 4.48 (d, J = 14.2, 1H), 2.72 (s, 3H), 2.69 (s, 3H), 0.99 (d, J = 6.8, 3H); GC−MS 183 ($C_8H_{11}N_2OS$), 224 ($C_{10}H_8F_2N_3O$), 140 (C_6H_6NOS); [α]$_D$ −122.5° (c 1, $CHCl_3$). Anal. ($C_{18}H_{19}F_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-2-Bromo-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-methylthiazole-5-carboxamide (73). Method B (**11** + 2-bromo-4-methylthiazole-5-carboxylic acid[30]): white solid; mp 155−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81 (s, 1H), 7.78 (s, 1H), 7.35 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 2H), 6.36 (br d, J = 9.5, 1H), 5.4 (br s, 1H), 5.00 (d, J = 14.2, 1H), 4.90 (br quint, J = 7, 1H), 4.46 (d, J = 14.2, 1H), 2.74 (s, 3H), 0.99 (d, J = 6.8, 3H); [α]$_D$ −97.8° (c 1, $CHCl_3$). Anal. ($C_{17}H_{16}BrF_2N_5O_2S \cdot {}^1/_2EtOAc$) C, H, S; N: calcd, 13.56; found, 14.52.

(1*R*,2*R*)-2-(4-Cyanophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-methylthiazole-5-carboxamide (74, UR-9908). Method C (**11** + **22** [B = Me, X = CN]): white solid; mp 109−111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.07 (d, J = 8.3, 2H), 7.81 (s, 1H), 7.79 (s, 1H), 7.75 (d, J = 8.3, 2H), 7.37 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 2H), 6.46 (br d, J = 9.5, 1H), 5.40 (s, 1H), 5.03 (d, J = 14.5, 1H), 4.94 (br quint, J = 7, 1H), 4.50 (d, J = 14.5, 1H), 2.83 (s, 3H), 1.02 (d, J = 6.8, 3H); MS 270 ($C_{14}H_{12}N_3OS$), 227 ($C_{12}H_7N_2OS$), 224 ($C_{10}H_8F_2N_3O$); [α]$_D$ −120.8° (c 1, $CHCl_3$). Anal. ($C_{24}H_{20}F_2N_6O_2S \cdot {}^1/_2H_2O$) C, H, N, S.

(1*R*,2*R*)-2-(4-Cyanophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-methylthiazole-5-carboxamide, Methanesulfonic Acid Salt (74·MsOH). A solution of **74** (12.5 g, 25 mmol) in MeOH (300 mL) was treated with a solution of methanosulfonic acid (4.85 g, 50 mmol) in MeOH (10 mL) under heat, resulting in the slow appearance of fine white needles. After complete precipitation, the title product was obtained upon filtration (12.31 g, 83%): mp 126−138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (DMSO) 8.32 (s, 1H, triazole), 8.13 (d, J = 8.1, 2H, ar), 7.98 (d, J = 8.1, 2H, ar), 7.71 (s, 1H, triazole), 7.29 (q, J = 8.8, 1H, ar), 7.19 (ddd, J = 2.1, J = 9.3, J = 11.6, 1H, ar), 6.91 (dt, J_d = 2.2, J_t = 8.8, 1H, ar), 4.83 (br quint, J = 7, 1H, C*H*Me), 4.81 (d, J = 14.3, 1H, TrC*H*(H)), 4.50 (d, J = 14.3, 1H, TrCH(*H*)), 2.68 (s, 3H, *Me*-thiazole), 2.31 (t, J = 0.6, 3H, $MeSO_3H$), 0.92 (d, J = 6.8, 3H, *Me*CH); [α]$_D$ −71.0° (c 1, DMF). Anal. ($C_{24}H_{20}F_2N_6O_2S \cdot CH_3SO_3H \cdot H_2O$) C, H, N, S.

(1*R*,2*R*)-5-(4-Cyanophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiophene-2-carboxamide (93). Method C (**11** + **17** [B = H, X = CN]): white solid; mp 210−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (s, 1H), 7.79 (s, 1H), 7.71 (d, J = 8, 2H), 7.70 (d, J = 8, 2H), 7.58 (d, J = 3.9, 1H, thiophene), 7.41 (d, J = 3.9, 1H, thiophene), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 2H), 6.57 (br d, J = 9.4, 1H), 5.37 (d, J = 1.5, 1H), 5.05 (d, J = 14.3, 1H), 4.94 (br quint, J = 7, 1H), 4.52 (d, J = 14.3, 1H), 1.03 (d, J = 6.8, 3H); HPLC−MS 212 ($C_{12}H_6NOS$), 224 ($C_{10}H_8F_2N_3O$); [α]$_D$ −105.6° (c 1, $CHCl_3$). Anal. ($C_{24}H_{19}F_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-5-(4-Cyanophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-methylthiophene-2-carboxamide (94). Method C (**11** + **17** [B = Me, X = Cl]): white solid; mp 176−177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (s, 1H), 7.78 (s, 1H), 7.69 (s, 4H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.23 (s, 1H), 6.9−6.6 (m, 2H), 6.43 (br d, J = 9.4, 1H), 5.35 (d, J = 1.3, 1H), 5.04 (d, J = 14.2, 1H), 4.93 (br quint, J = 7, 1H), 4.52 (d, J = 14.2, 1H), 2.60 (s, 3H), 1.02 (d, J = 6.8, 3H); GC−MS 269 ($C_{15}H_{13}N_2OS$), 226 ($C_{13}H_8NOS$), 224 ($C_{10}H_8F_2N_3O$); [α]$_D$ −121.0° (c 1, $CHCl_3$). Anal. ($C_{25}H_{21}F_2N_5O_2S \cdot {}^1/_2H_2O$) C, H, N, S.

(1*R*,2*R*)-3-Amino-5-(4-chlorophenyl)-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiophene-2-carboxamide (95). Method C (**11** + **17** [B = NH_2, X = Cl]): yellow solid; mp 107−111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (s, 2H), 7.61 (dt, J_t = 2, J_d = 9, 2H), 7.39 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.37 (dt, J_t = 2, J_d = 9, 2H), 6.9−6.6 (m, 2H), 6.78 (s, 1H), 5.93 (br d, *J* = 9.3, 1H), 5.69 (br s, 2H, N*H*₂), 5.35 (d, *J* = 1.3, 1H), 5.02 (d, *J* = 14.3, 1H), 4.88 (br quint, *J* = 7, 1H,), 4.52 (d, *J* = 14.3, 1H), 1.01 (d, *J* = 6.8, 3H); HPLC−MS 279 and 281 ($C_{13}H_{12}ClN_2OS$), 236 ($C_{11}H_7ClNOS$); $[\alpha]_D$ −137.8° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{20}ClF_2N_5O_2S$) C, H, N; S: calcd, 6.36; found, 5.76.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-5-(2-pyridyl)thiophene-2-carboxamide (96). Method C (**11** + 5-(2-pyridyl)thiophene-2-carboxylic acid [Maybridge]): white solid; mp 212−213 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.60 (dt, J_t = 1, J_t = 5, 1H), 7.9−7.5 (m), 7.5−7.2 (m), 6.9−6.5 (m), 5.34 (d, *J* = 1.3, 1H), 5.05 (d, *J* = 14.5, 1H), 5.1−4.8 (m, 1H), 4.50 (d, *J* = 14.5, 1H), 1.02 (d, *J* = 7, 3H); $[\alpha]_D$ −116.8° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{19}F_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-*N*-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-5-[1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl]thiophene-2-carboxamide (97). Method C (**11** + 5-[1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl]thiophene-2-carboxylic acid [Maybridge]): white solid; mp 106−110 °C;^{1}H NMR (300 MHz, $CDCl_3$) 7.79 (s, 1H), 7.77 (s, 1H), 7.54 (d, *J* = 3.8, 1H, thiophene), 7.38 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.30 (d, *J* = 3.8, 1H, thiophene), 6.84 (s, 1H, pyrazole), 6.8−6.6 (m, 2H), 6.52 (br d, *J* = 9.3, 1H), 5.34 (d, *J* = 1.5, 1H), 5.03 (d, *J* = 14.3, 1H), 4.93 (br quint, *J* = 7, 1H), 4.52 (d, *J* = 14.3, 1H), 4.03 (s, 3H), 1.01 (d, *J* = 6.8, 3H); MS 302 ($C_{12}H_{11}F_3N_3OS$), 259 ($C_{10}H_6F_3N_2OS$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −90.1° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{19}F_5N_6O_2S$) C, H, N, S.

(1*R*,2*R*)-3-Amino-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[(1-propyl)sulfonyl]thiophene-2-carboxamide (98). Method C (**11** + 3-amino-4-[(1-propyl)sulfonyl]thiophene-2-carboxylic acid [Maybridge]): white amorphous solid; ^{1}H NMR (80 MHz, $CDCl_3$) 7.95 (s, 1H), 7.78 (s, 2H), 7.38 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.8−6.6 (m, 2H), 6.45 (br s, 2H, N*H*₂), 6.00 (br d, *J* = 9.3, 1H), 5.32 (br s, 1H), 5.03 (d, *J* = 14.5, 1H), 4.92 (br quint, *J* = 7, 1H), 4.48 (d, *J* = 14.5, 1H), 3.3−2.8 (m, 2H, Pr), 2.1−1.5 (m, 2H, Pr), 1.07 (d, *J* = 7, 3H), 1.03 (t, *J* = 7, 3H, Pr); $[\alpha]_D$ −78.2° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{23}F_2N_5O_4S_2 \cdot H_2O$) C, H, N; S: calcd, 12.39; found, 11.76.

(1*R*,2*R*)-4-[(4-Chlorophenyl)sulfonyl]-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-methylthiophene-2-carboxamide (99). Method C (**11** + 4-[(4-Chlorophenyl)sulfonyl]-3-methylthiophene-2-carboxylic acid [Maybridge]): white solid; mp 1001−102 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.33 (s, 1H), 7.85 (d, *J* = 8.8, 2H), 7.78 (s, 1H), 7.75 (s, 1H), 7.50 (d, *J* = 8.8, 2H), 7.41 (dt, J_d = 6.5, J_t = 9, 1H), 6.9−6.6 (m, 2H), 6.42 (br d, *J* = 9.5, 1H), 5.32 (d, *J* = 1.5, 1H), 4.99 (d, *J* = 14.5, 1H), 5.1−4.8 (m, 1H), 4.41 (d, *J* = 14.5, 1H), 2.54 (s, 3H), 0.98 (d, *J* = 7, 3H); $[\alpha]_D$ −84.3° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{21}ClF_2N_4O_4S_2$) C, H, N, S.

(1*R*,2*R*)-3-Amino-4-[(4-chlorophenyl)sulfonyl]-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thiophene-2-carboxamide (100). Method C (**11** + 3-amino-4-[(4-chlorophenyl)sulfonyl]thiophene-2-carboxylic acid [Maybridge]): hygroscopic amorphous solid; ^{1}H NMR (80 MHz, $CDCl_3$) 8.1−7.7 (m), 7.9−7.5 (m), 7.6−7.3 (m), 6.9−6.5 (m), 6.00 (br d, *J* = 9.5, 1H), 5.31 (d, *J* = 1.5, 1H), 4.95 (d, *J* = 14.5, 1H), 5.1−4.8 (m, 1H), 4.44 (d, *J* = 14.5, 1H), 0.96 (d, *J* = 7, 3H); $[\alpha]_D$ −59.2° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{20}ClF_2N_5O_4S_2$) C, H, N; S: calcd, 11.29; found, 10.65.

Method D. Formation of the Pyrimidone Ring. To a solution of the corresponding aminoheterocycle carboxamide (1 mmol) in NMP (5 mL) was added formamidine acetate (4.5 equiv), and the mixture was heated at 130 °C for 24 h. Water (75 mL) was added, and the solid that formed was collected by filtration and was then partitioned between aqueous 1 N NaOH solution and $CHCl_3$. The aqueous phase was discarded, and the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated and the residue purified by flash chromatography (ca. hex:EtOAc, 1:5) and recrystallized from a EtOAc:hexane:ether mixture to give the product.

(1*R*,2*R*)-6-(4-Chlorophenyl)-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thieno-[3,2-*d*]pyrimidin-4(3*H*)-one (107). Method D, using **95**, and recrystallizing the final product from MeCN: white solid; mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.60 (s, 1H, N = C*H*-N), 7.78 (s, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 6.6, 2H), 7.51 (s, 1H, thiophene), 7.50 (dt, J_d = 6.4, J_t = 8.8, 1H), 7.44 (d, *J* = 6.6, 2H), 6.9−6.7 (m, 2H), 5.98 (dq, J_d = 1.6, J_q = 7.3, 1H, MeC*H*), 5.54 (d, *J* = 1.6, 1H, O*H*), 5.19 (d, *J* = 14.2, 1H, TrCH(*H*)), 4.02 (d, *J* = 14.2, 1H, TrC*H*(H)), 1.31 (d, *J* = 7.3, 3H, CH*Me*); $[\alpha]_D$ +14.0° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{18}ClF_2N_5O_2S$) C, H, N, S.

(1*R*,2*R*)-1-(4-Chlorophenyl)-5-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one (108). Method C (**11** + **20** [X = Cl]) + method D: white solid: mp 237−238 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.58 (s, 1H, N = C*H*-N), 8.27 (s, 1H, pyrazole), 8.10 (d, *J* = 8.8, 2H), 7.76 (s, 1H), 7.73 (s, 1H), 7.49 (dt, J_d = 6.5, J_t = 9, 1H), 7.48 (d, *J* = 8.8, 2H), 6.9−6.7 (m, 2H), 5.97 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.54 (d, *J* = 1.5, 1H), 5.16 (d, *J* = 14.2, 1H), 3.96 (d, *J* = 14.2, 1H), 1.29 (d, *J* = 7.3, 3H); $[\alpha]_D$ −68.3° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{18}ClF_2N_7O_2$) C, H, N.

(1*R*,2*R*)-6-(4-Cyanophenyl)-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]thieno-[3,2-*d*]pyrimidin-4(3*H*)-one (114). Method C (**11** + **17** [B = NH_2, X = CN]) + method D: white solid: mp 231−232 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.62 (s, 1H), 7.83 (dt, J_d = 2, J_t = 8.6, 2H), 7.78 (s, 2H), 7.73 (dt, J_d = 2, J_t = 8.6, 2H), 7.64 (s, 1H), 7.49 (dt, J_d = 6.4, J_t = 8.8, 1H), 6.9−6.7 (m, 2H), 5.98 (dq, J_d = 1.6, J_q = 7.3, 1H), 5.57 (d, *J* = 1.6, 1H), 5.18 (d, *J* = 14.2, 1H), 4.02 (d, *J* = 14.2, 1H), 1.32 (d, *J* = 7.3, 3H); $[\alpha]_D$ +16.0° (*c* 1, $CHCl_3$). Anal. ($C_{25}H_{18}F_2N_6O_2S$) C, H, N, S.

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

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 a stock solution of 800 μg/mL. The agar dilution method was performed using Kimmig's agar (K. A., Merck) suplemented with 0.5% glycerol. Plates of K.A. containing 2-fold serial dilutions (80 to 0.03 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 filamentous fungi. Following incubation, MICs (minimal inhibitory concentrations) were determined. For the purpose of determining the geometric mean, MICs of >80 μg/mL were assumed to be 160 μg/mL and MICs of ≤0.03 μg/mL were assumed to be 0.03 μg/mL.

Systemic Candidosis in Mice. An in vivo murine candidosis model was used to monitor the antifungal activity of the test compounds.[10a] Groups of 10 male mice were inoculated iv with 0.2 mL of a suspension containing (2−8) × 10^7 cfu/mL of *Candida albicans*. Compounds were administered orally 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 1, 2, 3, 5, 7, and 9 postinfection and compared with both that of the control animals and that of the animals treated with fluconazole at the same dose.

Systemic Aspergillosis in Mice. Groups of 10 male mice were inoculated iv with 0.2 mL of a suspension containing 8.2 × 10^6 cfu/mL of *A. fumigatus* (Colección Española de Cultivos Tipo no. 2071). Compounds were administered daily orally at 20 mg/kg as suspensions in 1% Tween + 0.2% carboxymethylcellulose in distilled water, at days 0−4 after infection. The control group received only the vehicle. The antifungal activity was assessed by the survival rate at day 42 after infection.

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Supporting Information Available: Full experimental and spectroscopic details of acids **17**−**28**, their esters, final products, and individual MIC values for each final compound (Table 10) (25 pages). Ordering information is given on any current masthead page.

References

(1) For part I of this study, see: Bartroli, J.; Turmo, E.; Algueró, M.; Boncompte, E.; Vericat, M. L.; García-Rafanell, J.; Forn, J. Synthesis and Antifungal Activity of New Azole Derivatives Containing an *N*-Acylmorpholine Ring. *J. Med. Chem.* **1995**, *38*, 3918−3932.

(2) Maggon, K. K.; Slee, A. M.; Demos, C. H. Development of Antifungal Agents by the Pharmaceutical Industry. *Drugs Today* **1991**, *27*, 317−330.

(3) For an excellent update on current antifungal therapy, see: Turner, W. W.; Rodriguez, M. J. Recent Advances in the Medicinal Chemistry of Antifungal Agents. *Curr. Pharm. Des.* **1996**, *2*, 209−224.

(4) (a) Johnson, E. M.; Warnock, D. W.; Luker, J.; Porter, S. R.; Scully, C. Emergence of Azole Drug Resistance in Candida Species from HIV-infected Patients receiving Prolonged Fluconazole Therapy for Oral Candidosis. *J. Antimicrol. Chemother.* **1995**, *35*, 103−114. (b) Rex, J. H.; Rinaldi, M. G.; Pfaller, M. A. Resistance of Candida Species to Fluconazole (Minireview) *Antimicrob. Agents Chemother.* **1995**, *39*, 1−8, and references therein.

(5) For a recent review on the newer triazole derivatives in the clinic, see: Fung, J. C.; Bonner, D. P. Recent Developments in Pradimycin-benanomycin and Triazole Antibiotics *Exp. Opin. Invest. Drugs* **1997**, *6*, 129−145.

(6) For a recent review on SCH-56592, see: *Drugs Future* **1997**, *22*, 203−204.

(7) For a recent review on voriconazole, see: Voriconazole (UK-109496). *Drugs Future* **1997**, *22*, 326−327.

(8) (a) Itoh, K.; Okonogi, K.; Tasaka, A.; Hayashi, R.; Tamura, N.; Tsuchimori, N.; Kitazaki, T.; Matsushita, Y.; Obita, J. TAK-187, a New Antifungal Triazole: Synthesis and Antifungal Activity. 36nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1996, New Orleans, LA. (b) Tasaka, A.; Kitazaki, T.; Tamura, N.; Tsuchimori, N.; Matsushita, Y.; Hayashi, R.; Okonogi, K.; Itoh, K. Optically Active Antifungal Azoles. VII. Synthesis and Antifungal Activity of Stereoisomers of 2-[(1*R*, 2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3-(2*H*,4*H*)-1,2,4-triazolone (TAK-187). *Chem. Pharm. Bull.* **1997**, *45*, 321−326.

(9) Eisai's compound ER-30346 has been licensed to Bristol-Myers Squibb. The new laboratory code for this compound is BMS-207,-147. For a recent review on this compound, see: Naito, T.; Hata, K.; Tsuruoka, A. *Drugs Future* **1996**, *21*, 20−24.

(10) (a) Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. Triazole Antifungals. II. Synthesis and Antifungal Activities of 3-Acyl-4-methyloxazolidine Derivatives. *Chem. Pharm. Bull.* **1990**, *38*, 2476−2486. (b) Konosu, T.; Tajima, Y.; Takeda, N.; Miyaoka, T.; Kasahara, M.; Yasuda, H.; Oida, S. Triazole Antifungals. IV. Synthesis and Antifungal Activities of 3-Acylamino-2-aryl-2-butanol Derivatives. *Chem. Pharm. Bull.* **1991**, *39*, 2581−2589.

(11) (a) Stevens, D. A.; Devine, M. J.; Martinez, M.; Aristizabal, B. *In Vitro* Antifungal Activity of Novel Azole Derivatives with a Morpholine Ring, UR-9746 and UR-9751; Comparison with Fluconazole. 35 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1995, San Francisco, CA.; (b) Clemons, K. V.; Stevens, D. A. Efficacy of Two Novel Azole Derivatives Each Containing a Morpholine Ring, UR-9746 and UR-9751 against Systemic Murine Coccidioidomycosis. *Antimicrob. Agents Chemother.* **1997**, *41*, 200−203. (c) Bornay-Llinares, F. J.; Torres-Rodriguez, J. M. Anticryptococcal Activity of a New Azole Derivative (UR-9746) in a Murine Model. 35 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1995, San Francisco, CA. (d) Bornay-Llinares, F. J.; Mayol-Belda, M. S.; Onrubia-Pintado, J.; Torres-Rodriguez, J. M. Murine Cryptococcosis. Tissular Damage Decreases after Treatment with UR-9746. 35 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1995, San Francisco, CA. (e) Restrepo, M.; Najvar, L.; Barchiesi, F.; Graybill, J. R.; Treatment of Murine Cryptococcal Meningitis with UR-9751 and UR-9746. 35 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1995, San Francisco, CA. (f) Bornay-Llinares, F. J.; Torres-Rodriguez, J. M. Anticryptococcal Activity of a New Azole Derivative (UR-9746) in a Murine Model. Preliminary Results. 2nd Meeting of the European Confederation of Medical Mycology (ECMM), April 1995, Brussels, Belgium. (g) Improvisi, L.; García-Hermoso, D.; Provost, F.; Dromer, F.; Dupont, B. Evaluation of Two Novel Antifungal Agents, UR-9746 and UR-9751 in the Treatment of Experimental Murine Histoplasmosis. 35 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1995, San Francisco, CA. (h) Clemons, K.; Stevens, D. A. Personal communication.

(12) Loebenberg, D.; Cacciapuoti, A.; Parmegiani, R.; Moss, E. L., Jr.; Menzel, F., Jr.; Antonacci, B.; Norris, C.; Yarosh-Tomaine, T.; Hare, R. S.; Miller, G. H. *In Vitro* and *in Vivo* Activities of SCH 42427, the Active Enantiomer of the Antifungal Agent SCH 39304. *Antimicrob. Agents Chemother.* **1992**, *36*, 498−501.

(13) Tasaka, A.; Tamura, N.; Matsushita, Y.; Teranishi, K.; Hayashi, R.; Okonogi, K.; Itoh, K. Optically Active Antifungal Azoles. I. Synthesis and Antifungal Activity of (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-mercapto-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol and Its Stereoisomers. *Chem. Pharm. Bull.* **1993**, *41*, 1035−1042.

(14) Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. Aldol Condensation of Evans Chiral Enolates with Acetophenones. Its Application to the Stereoselective Synthesis of Homochiral Antifungal Agents. *J. Org. Chem.* **1995**, *60*, 3000−3012.

(15) (a) Alberola, A.; Andrés, J. M.; González, A.; Pedrosa, R.; Prádanos, P. Regioselective Synthesis of 2-Functionalized Thiophenes by Condensation of α-Mercapto Compounds with β-Amino enone Derivatives. *Chem. Commun.* **1990**, *20*, 2337−2547. (b) Hauptmann, S.; Weissenfels, M.; Scholz, M.; Werner, E.-M.; Köhler, H.-J.; Weisflog, J. Eine neue Synthese substituierter Thiophene und Pyrrole. *Tetrahedron Lett.* **1968**, 1317−1319. (c) Hartmann, H. A Simple Method for the Synthesis of 5-Aryl-3-amino-2-alkoxycarbonylthiophenes. *Synthesis* **1984**, 275−276.

(16) Veronose, A. C.; Cavicchioni, G.; Servadio, G.; Vecchiati, G. Syntheses of 2-Arylimidazole Derivatives through Annelations Employing Benzylamines. *J. Heterocycl. Chem.* **1980**, *17*, 1723−1725.

(17) (a) Menozzi, G.; Mosti, L.; Schenone, P. J. Reaction of 2-Dimethyalminomethylene-1,3-diones with Dinucleophiles. VI. Synthesis of Ethyl or Methyl 1,5-Disubstituted 1*H*-Pyrazole-4-carboxylates. *Heterocycl. Chem.* **1987**, *24*, 1669−1675. (b) For the compounds with B = H, carbethoxymalonaldehyde was obtained according to Panizzi, L. Investigations of β-dialdehydes. I. Carbethoxymalonaldehyde. *Gazz. Chim. Ital.* **1946**, *76*, 56−65. (c) Fabis, F.; Dallemagne, P.; Rault, S.; Robba, M. A New Efficient Synthesis of 3-Amino-1-phenylpyrrole. *Org. Prep. Proceed. Int.* **1995**, *27*, 236−239.

(18) Schmidt, P.; Eichenberger, K.; Wilhelm, M.; Druey, J. Pyrazolopyrimidine. III. Paraxanthin-, Theobromin- und Theophyllin-Analoga der Pyrazolo[3, 4-d]pyrimidin-Reihe. *Helv. Chim. Acta* **1959**, *1*, 349−359.

(19) Plouvier, B.; Bailly, C.; Houssin, R.; Hénichart, J.-P. Synthesis of Two New Thiazole-Containing Oligopeptides as Potential DNA Minor Groove Binding Analogs of Netropsin. *Heterocycles* **1991**, *32*, 693−701.

(20) Clemence, F.; Le Martret, O.; Fournex, R.; Dagnaux, M.; Plassard, G. Synthèse et Propriétés Antilipolytiques et Hypotriglycéridémiantes d'Acides Thiazole-5-carboxyliques. *Eur. J. Med. Chem.* **1976**, *11*, 567−570.

(21) Crooks, P. A.; Cynkowska, G.; Ashton, P.; Cynkowski, T. Unexpected Reaction in the Attempted Synthesis of a Drug-Amino Acid Ester Conjugate. Abstract 223. 209th ACS National Meeting, April 1995, Anaheim, CA.

(22) Dost, J.; Heschel, M.; Stein, J. Zur Herstellung von 1,3,4-Oxadiazol-2-carbonsäurederivative. *J. Prakt. Chem.* **1985**, *327*, 109−116.

(23) Diana, G. D.; Rudewicz, P.; Pevear, D. C.; Nitz, T.; Aldous, S.; Aldous, D. J.; Robinson, D. T. Draper, T.; Dutko, F. Picornavirus Inhibitors: Trifluoromethyl Substitution Provides a Global Protective Effect against Hepatic Metabolism. *J. Med. Chem.* **1995**, *38*, 1355−1371.

(24) Shimizu, T.; Hayashi, Y.; Teramura, K. A New Synthetic Method for Alkyl Carbonocyanidate *N*-oxides. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2519−2522.
(25) Howe, R. K.; Franz, J. E. Nitrile sulfides. Synthesis of 1,2,4-thiadiazoles. *J. Org. Chem.* **1974**, *39*, 962−964.
(26) Clinical trials for this product and its racemate (Genaconazole, SCH-39304) have been terminated. For a recent review, see: *Drugs Future* **1992**, *17*, 1145−1146.
(27) Klopman, G.; Ptchelinstev, D. Antifungal Triazole Alcohols: A Comparative Analysis of Structure−Activity, Structure-Teratogenity and Structure-Therapeutic Index Relationships using the Multiple Computer-Automated Structure Evaluation (Multi-CASE) Methodology. *J. Comput.-Aided Mol. Des.* **1993**, *7*, 349−362.
(28) Voriconazole is known to induce its own methabolism following multiple dose administration in sensitive rodent species and hence shows little efficacy in murine models. Jezequel, S. G.; Clark, M.; Cole, S.; Evans, K. M.; Wastall, P. UK-109,496, A Novel, Wide-Spectrum Triazole Derivative for the Treatment of Fungal Infections: Pre-clinical Pharmacokinetics. 35 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 1995, San Francisco, CA.
(29) Richardson, K. Antifungal 1,3-Bis-triazolyl-2-propanol Derivative. U.S. Patent 4,404,216, 1983.
(30) Abdel-Lateef, M.; Fath-Alla; Eckstein, Z. Nucleophilic Halogen Replacement of 2-Bromo-4-methyl-5-thiazolecarboxylic acid Derivatives and Their Anomalies. *Rocz. Chem.* **1972**, *46*, 1647−1658.
(31) Field, L.; Clark, R. D. Methyl *p*-Tolyl Sulfone. *Organic. Syntheses;* Wiley: New York, 1963; Collect. Vol. IV, p 674.

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