New Azole Antifungals. 3. Synthesis and Antifungal Activity of 3-Substituted-4(3*H*)-quinazolinones[1,2]

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A series of azole antifungal agents featuring a quinazolinone nucleus have been subjected to studies of structure−activity relationships. In general, these compounds displayed higher in vitro activities against filamentous fungi and shorter half-lives than the structures described in our preceding paper. The most potent products in vitro carried a halogen (or an isostere) at the 7-position of the quinazolinone ring. Using a murine model of systemic candidosis, oral activity was found to be dependent on hydrophobicity, which, in turn, modulated the compound's half-life. The 7-Cl derivative, (1*R*,2*R*)-7-chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (**20**, UR-9825), was selected for further testing due to its high in vitro activity, low toxicity, good pharmacokinetic profile, and ease of obtention. Compound **20** is the (1*R*,2*R*) isomer of four possible stereoisomers. The other three isomers were also prepared and tested. The enantiomer (1*S*,2*S*) and the (1*R*,2*S*) epimer were inactive, whereas the (1*S*,2*R*) epimer retained some activity. In vitro **20** was superior to fluconazole, itraconazole, SCH-42427, and TAK-187 and roughly similar to voriconazole and ER-30346. In vivo, **20** was only moderately active in a mouse model of systemic candidosis when administration was limited to the first day. This was attributed to its short half-life in that species ($t_{1/2}$ = 1 h po). Protection levels comparable to or higher than those of fluconazole, however, were observed in systemic candidosis models in rat and rabbit, where the half-life of the compound was found to be 6 and 9 h, respectively. Finally, **20** showed excellent protection levels in an immunocompromised rat model of disseminated aspergillosis. The compound showed low toxicity signs when administered to rats at 250 mg/kg qd or at 100 mg/kg bid during 28 days.

Introduction

Since the launching of fluconazole (**1**) and itraconazole (**2**) for the treatment of systemic mycoses a decade ago, the race to market a new azole continues. Although new structures in this class are frequently reported in the patent[3] and the scientific[4] literature (Figure 1), announcements about their clinical discontinuation are unfortunately also common. The medical need for new, more effective azole antifungal drugs persists.

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 quite different. Whereas many drugs have proven effective against candidosis, only two, amphotericin B and itraconazole, are currently available to treat infections due to *Aspergillus fumigatus,* and both have only moderate response rates. A drug active against those two clinically important pathogens would thus be highly desirable.

Our accompanying paper[2b] described the development of a series of carboxamides with high potency against both yeasts and filamentous fungi based on Sankyo's benzamide **8**.[5] Two compounds, **9** and **10**, representing, respectively, the open and conformationally constrained versions of these amide derivatives, were selected and studied further (Figure 2). It was suggested that a heterocyclecarboxamide unit carrying a substituted phenyl ring specifically oriented in the space could be responsible for the improved activity and spectrum. However, a tendency to display long plasma elimination half-lives in animal species was clearly observed for those and related structures. Attempts to decrease that pharmacokinetic parameter in the rat by means of increasing the compound's polarity generally resulted in diminished activity.

During the course of that study, a very active class of compounds containing a quinazolinone unit caught our interest, as their structure lacked the phenyl substituent. The new products were less hydrophobic, a characteristic that might potentially facilitate body clearance. But most importantly, they were particularly active against *A. fumigatus*. The present paper describes the synthesis and SARs found in this new family of antifungal agents and the selection of compound **20** (UR-9825) for preclinical development.

Chemistry

Quinazolinones were readily synthesized from enantiomerically pure amines **11**−**14**[5,6] by a two-step procedure (Scheme 1) consisting of a DCC coupling with the corresponding anthranilic acid, followed by heating the resulting intermediate with triethylorthoformate or formamidine acetate in NMP. Final compounds carrying a NR_1R_2, OR, or SR substituent at the 7-position were obtained by nucleophile aromatic substitution of the 7-F derivative **24**. All of the screened compounds

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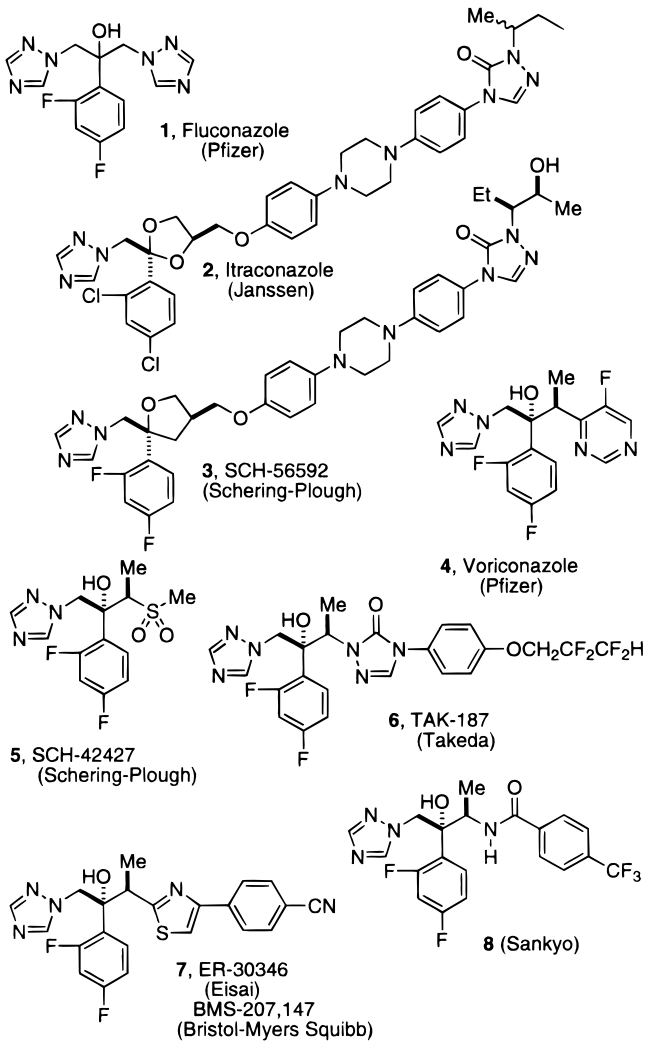


Figure 1. Azole antifungals (names and laboratory codes refer to single enantiomers, except itraconazole which is racemic).

were prepared as the enantiomerically pure (1*R*,2*R*) isomers. The four stereoisomers of structure **20** were synthesized from the corresponding stereoisomeric amines[6] and their activity tested. The total synthesis of **20** is outlined in Scheme 2. The process does not require chromatographic purifications and presently produces **20** in the kilogram scale with high enantiomeric purity (>99.9% ee, chiral HPLC) and chemical yield (35% overall).

Biological Tests

Compounds were tested in vitro by the agar dilution method against an assortment of 10 yeast and 6 filamentous fungi. The individual minimum inhibitory concentrations (MICs, μg/mL) obtained for each product 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 (**1**), itraconazole (**2**), voriconazole (**4**),[7] SCH-42427 (**5**),[8] TAK-187 (**6**),[9] ER-30346 (**7**),[10] and **8**[5] 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 systemic candidosis model. In these studies, the compounds were administered orally three times over the 24 h following

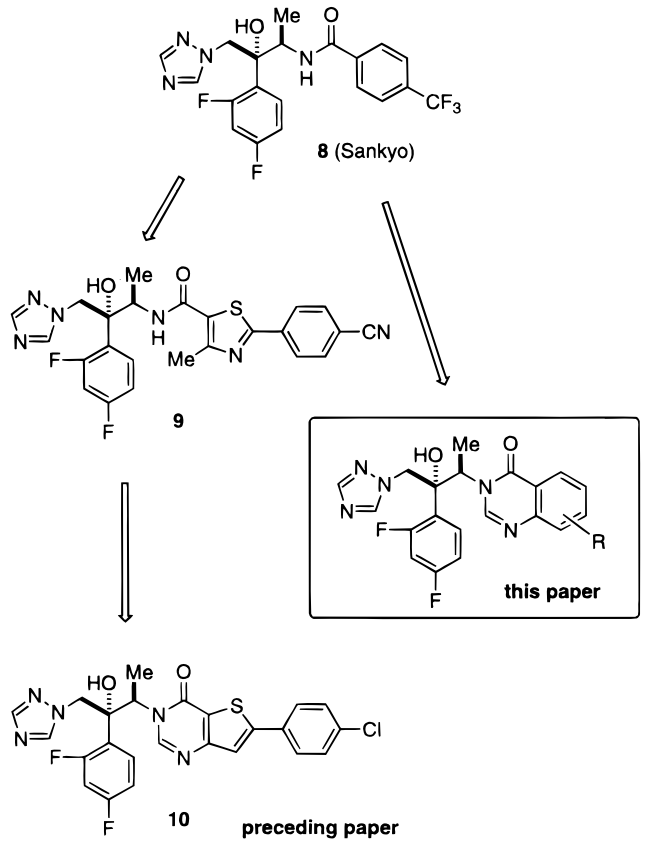
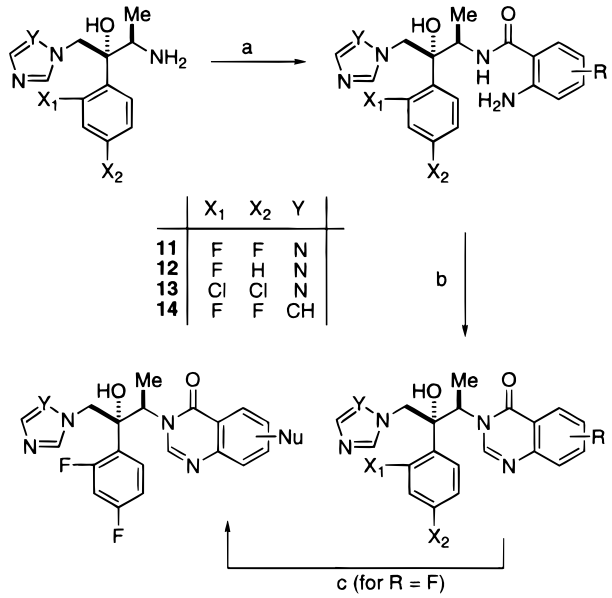


Figure 2. Structure evolution.

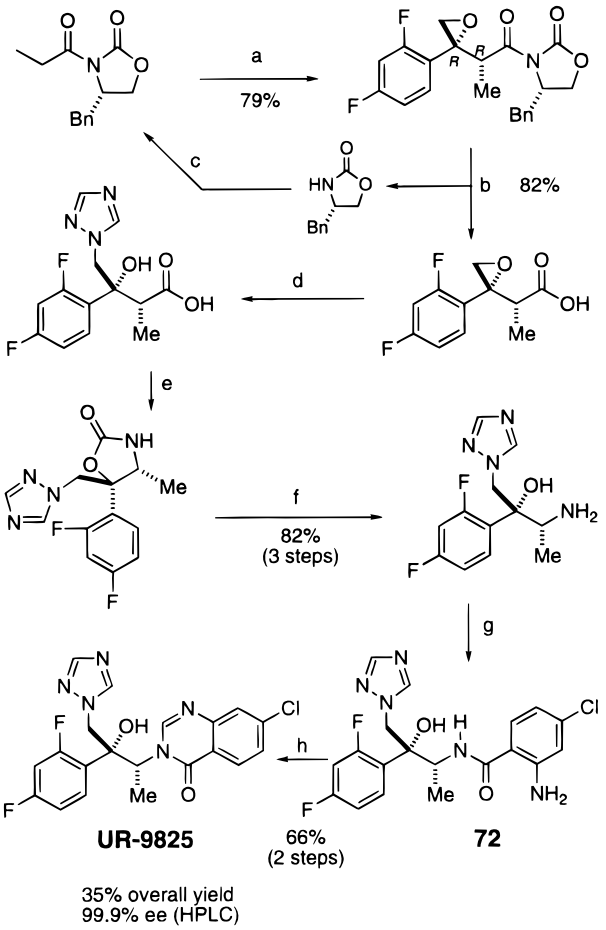
Scheme 1. Synthesis of Quinazolinones[a]



[a] Reagents: (a) DCC, HOBT, NEt_3, DMF, room temperature, 18 h; (b) $(EtO)_3CH$, NMP, 110 °C, 18 h; (c) HNu, NaH, NMP, heat.

infection. 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

Scheme 2. Synthesis of **20**[a] (ref 6)



[a] Reagents: (a) (i) NaHMDS, THF−Et_2O, −78 °C, 30 min; (ii) 2,4-diF-C_6H_3-$COCH_2Br$, −78 °C, 1 h; (b) LiOH, H_2O_2, THF, H_2O, 0 °C, 30 min; (c) $(EtCO)_2O$, LiCl, TEA, THF, 25 °C; (d) triazole, NaH, DMF, 60 °C, 3 h; (e) DPPA, pyr, 80 °C, 10 h; (f) 10 N HCl, refl, 7 days; (g) 2-NH_2-4-Cl-$C_6H_3CO_2H$, DCC, HOBT, room temperature, 18 h; (h) $HC(OEt)_3$, HCl (cat.), dioxane−NMP, 110 °C, 18 h.

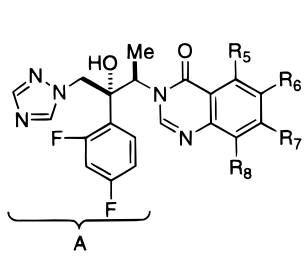
levels was not possible for all the products. We thus report two figures for the in vivo activities. The first shows the intrinsic activity of the compound, and it is expressed as the percent survival observed in the treated group when all the untreated animals were dead (ca. day 3). The second reflects the potency of the compound compared to that of fluconazole, 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 1−5, 8, and 9. Using the same model of infection, compound **20** was also administered once or twice daily during 5 days and compared to different standards (Table 5).

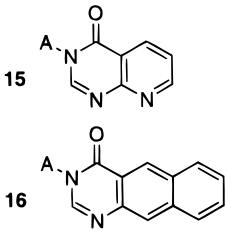
Compound **20** was further tested in vivo in a model of systemic candidosis in the rabbit and compared to fluconazole (Table 6), and in an immunocompromised rat model of disseminated aspergillosis in comparison with amphotericin B (Table 7).

For selected compounds, the plasma half-life in the rat was calculated following iv administration of a single dose of 15 mg/kg ($n = 2$ per point).

For compound **20**, a preliminary 28-day toxicology profile was obtained in the rat ($n = 10$) after oral qd or bid administration.

Table 1. Effect of Benzo Substitution





					in vitro		in vivo (1 mg/kg po)[c] % protection	
compd	R_5	R_6	R_7	R_8	MIC[a] yst	MIC[b] ff	(dC)[d]	(dFlu)[e]
15					43	>80	0[f]	0[f]
16					0.4	45	30	0
17	H	H	H	H	1.2	8.9	10	0
18	Cl	H	H	H	3.1	71	0	0
19	H	Cl	H	H	1.0	50	40	0
20	H	H	Cl	H	0.3	0.7	0	0
21	H	H	H	Cl	2.5	45	0[f]	0[f]
22	F	H	H	H	4.3	57	0	0
23	H	F	H	H	2.4	>80	0	0
24	H	H	F	H	0.9	2.5	0	0
25	H	Br	H	H	1.6	45	100	0
26	H	H	Br	H	0.4	0.8	30	0
27	H	F	F	H	1.7	70	10	0
28	H	Cl	H	Cl	1.7	>80	100	0
29	H	Br	H	Br	2.6	>80	10	0
30	Me	H	H	H	2.6	40	0	0
31	H	Me	H	H	1.4	45	40	0
32	H	H	H	Me	2.3	80	10	0
33	H	Me	H	Me	3.8	>80	0	0
34	H	Me	H	Br	2.1	>80	0	0
35	H	H	H	OMe	10	>80	0[f]	0[f]
36	H	OMe	OMe	H	7.6	80	0[f]	0[f]
37	H	F	NMe_2	H	1.4	22	0	0
38	H	F	NH_2	H	8.7	50	NT	NT
39	H	F	$NHCOCF_3$	H	8.1	80	NT	NT

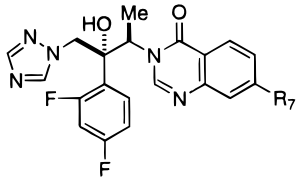
[a] Geometric mean of MIC values (μg/mL) against 10 yeasts (see Experimental Section). [b] Geometric mean of MIC values (μg/mL) against 6 filamentous fungi (see Experimental Section). [c] Murine systemic candidosis: three identical doses at 1, 4, and 24 h postinfection. [d] Percent protection the day 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 ($n = 10$). [f] Dose: 2.5 mg/kg po. NT = not tested.

Structure−Activity Studies

In Vitro. Pyrimidones fused with three different types of ring (**15**, **16**, and **17**) were first evaluated for antifungal activity. Of these, **15** ([*b*]pyridine) was essentially inactive, **16** ([*b*]naphthyl) showed activity against yeasts only, and **17** (phenyl) was active against both yeasts and filamentous fungi (Table 1). Given this result, and the ready availability of a wide range of starting anthranilic acids, we decided to fully explore the benzo nucleus of **17**. The effect of positional substitution was first investigated by preparing all four possible chloro regioisomers. The products gave good potency against yeasts, but only the 7-derivative (**20**) showed high activity against filamentous fungi. The same trend was found within the Br and F derivatives. Disubstitution (**27**−**29**), methyl substitution (**30**−**34**), and introduction of electron-donating groups (**35**−**36**) all resulted in poorer compounds.

In view of the activities shown in Table 1, we focused on the 7-position for further optimization (Table 2). Thus, all four halogens were tested and found to be

Table 2. Effect of Substitution at the 7-Position



compd	R_7	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]
24	F	0.9	2.5	0[f]	0[f]
20	Cl	0.3	0.7	0	0
26	Br	0.4	0.8	30	0
40	I	0.3	0.9	100	0
41	CN	0.8	3.5	10[f]	0[f]
42	CF_3	0.7	2.2	100	60
43	OCH_2CH_2F	1.4	28	0	0
44	OCH_2CHF_2	1.4	25	100	0
45	OCH_2CF_3	1.0	15	100	100
46	$OCH_2CF_2CHF_2$	0.4	18	100	100
47	SMe	0.5	3.8	100	40
48	SO_2Me	11	>80	100	80
49	SPh	0.7	2.0	0	0
50	SO_2Ph	1.2	8.7	0	0
51	O-(p-ClPh)	0.7	7.1	100	80
52	1-triazolyl	6.6	80	70	≤50
53	2-tetrazolyl	1.5	57	NT	NT
54	3-oxazolidin-2-one	8.7	80	NT	NT
55	morpholine	1.9	35	20	0
56	*N*-methylpiperazine	19	>80	20	0
57	$NHNH_2$	15	>80	NT	NT
58	NHBn	1.2	11	40	0
59	NMe_2	1.3	71	0[f]	0[f]
60	$CONH_2$	25	>80	NT	NT
61	$C(=NSO_2NH_2)NH_2$	40	>80	0	0

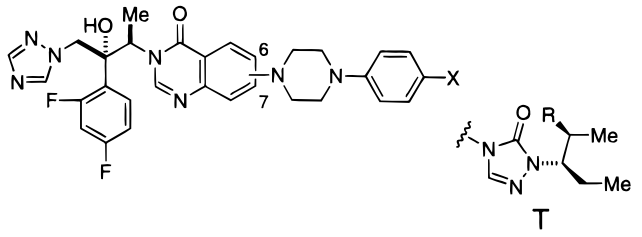
[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] Dose: 1 mg/kg po.

mostly equipotent, except for the F derivative **24** which was slightly poorer. Similar impaired activity was seen for the CN, SMe, SPh, O-*p*-ClPh, and CF_3 derivatives. This was more pronounced in the polyfluoroalkoxy series (**43**−**46**), where the compounds showed only moderate activity against filamentous fungi. More deleterious was the introduction of polarity-enhancing substituents, such as $C(=NSO_2NH_2)NH_2$, $CONH_2$, $NHNH_2$, SO_2Me, amine derivatives, 3-oxazolidin-2-one, tetrazole, or triazole, which resulted in compounds with diminished or complete loss of in vitro activity against filamentous fungi.

Finally, a small series of compounds carrying a phenylpiperazine substituent of the general type found in the structure of itraconazole (**2**) and SCH-56592 (**3**)[11] (see Figure 1) was prepared (Table 3). Compound **63**, featuring a *p*-chlorophenylpiperazine ring pendent from the 7-position, displayed high and broad activity, but low oral absorption in the rat. The nitro equivalent (**62**) had lower in vitro activity. Three pentyltriazolone derivatives of the type found in Schering's newest series were also tested, one of them at the 6-position of the quinazolinone nucleus. None of these products displayed interesting activity levels.

In Vivo. Although we were quite pleased with the levels of in vitro activity obtained with some of the above compounds, the preliminary in vivo results using our previous murine candidosis model[2] were in general disappointing.

Table 3. Phenylpiperazine Analogues



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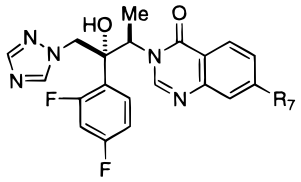
compd	position	X	R	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (0.5 mg/kg po)[c] % protection (dC)[d]	in vivo (0.5 mg/kg po)[c] % protection (dFlu)[e]
62	7	NO_2		7.9	>80	NT	NT
63	7	Cl		0.2	2.8	60	0
64	7	T	H	2.3	>80	20	0
65	6	T	H	3.7	28	0	0
66	7	T	OH	32	>80	NT	NT

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

Table 4. In Vivo Activity−Polarity Relationships in the 7-Halo Series



compd	R_7	c log P[a]	HPLC t_R (min)[b]	in vitro MIC *C. albicans*[f]	in vivo (0.5 mg/kg po)[c] % protection (dC)[d]	in vivo (0.5 mg/kg po)[c] % protection (dFlu)[e]	$t_{1/2}$[g] iv (h)
24	F	2.16	6.44	≤0.03	0	0	1.4
20	Cl	2.50	9.44	≤0.03	0	0	2.9
26	Br	2.82	10.61	≤0.03	30	0	−
40	I	3.31	11.96	≤0.03	100	0	>48

[a] Calculated using Molecular Design's Chem-X. [b] HPLC retention time in a Lichrospher 100 RP-18e 220 × 4 mm column using MeOH:H_2O, 2:1. [c,d,e] See the corresponding footnotes in Table 1. [f] Strain of *C. albicans* used in the in vivo test. [g] Rat.

Quantitative estimates of lipophilicity have proven to be useful parameters of biological behavior in several systems. Table 4 shows the calculated log *P* values of the 7-halo-substituted quinazolinones together with their in vivo anticandidal activity in mice and their half-lives in rat. The retention times recorded for these compounds using a reverse phase HPLC column are also included for comparison purposes. Since the four compounds had similar in vitro activities against *C. albicans* we hypothesize that the differences in the in vivo efficacies are due to their different half-lives, which, in turn, seem to be related to the compound's polarity.

For nonmetabolizable compounds, long half-lives in mice tend to convert into even longer half-lives in larger species, including humans. We therefore sought to select a derivative with high in vitro activity and a relatively short half-life in the rat to ensure clinical viability. A compound that seemed to fulfill these conditions was the 7-chloro derivative, compound **20**. Compound **20** further featured an expeditious and low-cost synthesis (4-chloroanthranilic acid is inexpensive), excellent oral bioavailability (nearly 80% in rats and 100% in dogs), and lack of toxicity in preliminary repeated-dose tests (vide infra).

Table 5. Comparison with Standards

compd	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (% protection, mice) model 1[f] (dC)[d]	model 1[f] (dFlu)[e]	model 2[g] (dC)[d]	model 2[g] (dFlu)[e]
20	0.3	0.7	0	0	90[h]	0[h]
fluconazole	30	>80	100	–	100[h]	–
itraconazole	5.2	63	0[i]	0[i]	NT	NT
voriconazole	0.6	0.5	0	0	20	0
SCH-42427	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,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 (days 1 through 5) qd po. [h] Dose: 5 mg/kg/day (days 1 through 5) bid po. [i] In PEG 400.

Comparison with Reference Compounds. Table 5 shows the in vitro and anti-*Candida*, in vivo activities of **20** compared to those of fluconazole, itraconazole, voriconazole, SCH-42427, ER-30346, TAK-187, and **8**. In vitro, voriconazole, ER-30346, and **20** had comparable low MICs and broad spectra of activity. In vivo, two dose regimens were tested. Under the conditions used for the in vivo screening (three single doses over the first 24 h after infection), SCH-42427, TAK-187, and Sankyo's **8** showed 100% survival the day that the last of the fluconazole-treated animals died, ER-30346 showed an incipient activity, and compound **20**, itraconazole, and voriconazole[14] showed no protection at all. In the second model, where the products were administered qd or bid throughout the 5 days following infection, compound **20** (5 mg/kg, bid), fluconazole (5 mg/kg, bid), and SCH-42427 (1 mg/kg, qd) had comparably good levels of protection, whereas voriconazole and ER-30346 (both at 1 mg/kg qd) were mostly inactive.

Pharmacokinetics. A pharmacokinetic study in the mouse indicated that drug levels of **20** declined very rapidly in that species and that they were already undetectable 6 h postadministration. The half-life was calculated to be 1 h. Such fast kinetics certainly precluded maintaining drug levels effective for overcoming infection. We were therefore quite happy to observe that when the dose regime was changed to bid administration of 5 mg/kg over 5 days, **20** showed activity comparable to that of fluconazole.

As expected, excellent levels of activity started to appear when **20** was tested in species in which the compound's half-life was longer. Thus, in a systemic candidosis model in the rat ($t_{1/2}$ = 3 h iv; 6 h po) compound **20** administered at 1 mg/kg bid po (5 days) gave 100% survival at the end of the study (day 45) in an experiment where all the control (untreated) animals were dead by day 6. Fluconazole under the same regime was equally effective. In the rabbit, where the compound's half-life was found 9 h (po), once a day administration was sufficient to observe high levels of activity. Thus, the group treated with 0.5 mg/kg of **20** gave significantly lower cfu counts in the lung and kidneys than the control group or the group treated with 12.5 mg/kg of fluconazole (Table 6).

In summary, it was not until the end of this study that we realized that the mouse might not have been the ideal species for screening this type of compounds. Since mouse models are widely used in the study of new agents, emphasis must be placed on observing the pharmacokinetics of compounds so selected. Indeed, due to the fungistatic nature of azoles against *C. albicans*, long-term protection might not be merely indicative of high activity but rather a consequence of persistently high drug levels. Products with fast elimination rates in mice, on the other hand, but with potentially acceptable half-lives in humans (such as **20**) would show little in vivo activity in murine models and could be incorrectly rejected in a screening program.

Table 6. In Vivo Activity of **20** in a Rabbit Systemic Candidosis Model[a]

compd	dose (mg/kg, qd, po)	log cfu/g (kidney)	log cfu/g (lung)
20	0.5	0.68	0.39
	2.5	0.30	0.12
	12.5	0.35	0.0
fluconazole	12.5	1.29	1.44
control	vehicle	4.48	3.04

[a] See the Experimental Section for details.

Table 7. In Vivo Activity of **20** in an Immunocompromised Rat Model of Disseminated Aspergillosis[a]

compd	dose (mg/kg, bid, po)	log cfu/g (liver)
20	1	1.59
	5	1.22
	25	0.48
	50	0.0
AmB	2[b]	0.10
control	vehicle	2.27

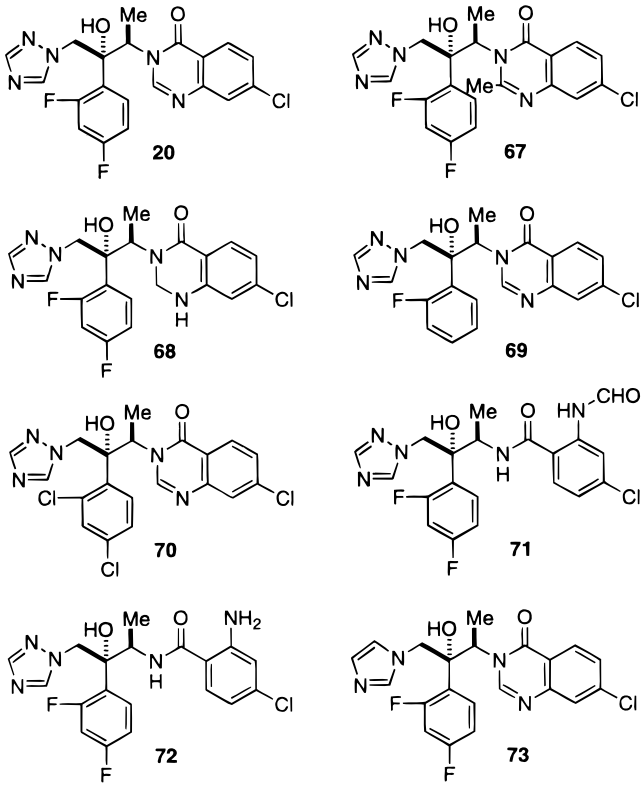
[a] See the Experimental Section for details. [b] qd, iv.

Systemic Aspergillosis. Compound **20** was also tested in an immunocompromised rat model of disseminated aspergillosis and compared to amphotericin B. Activity was measured by reduction of fungal loads (cfu counts) in the liver 24 h after the last administration. Table 7 shows that compound **20** protected rats infected with conidia of *A. fumigatus* in a dose-related fashion. At 50 mg/kg bid po, compound **20** gave 100% protection (log cfu/g = 0), whereas amphotericin B at 2 mg/kg qd iv gave a mean log cfu/g of 0.10.

Toxicity Tests. Repeated dose toxicity tests performed with compound **20** in rats indicated a low incidence of toxic effects. Thus, when compound **20** was administered orally to rats for 28 consecutive days at 100 mg/kg bid or at 250 mg/kg qd, no mortality or even external signs of toxicity were observed. Slight hepatomegaly and a mild increase in alanine aminotransferase (females, 250 mg/kg) suggested that the liver is the main target organ.

Other Modifications. After the selection of product **20**, an attempt to further optimize its structure was undertaken (Table 8). Some features proved critical for maintenance of the antifungal profile while others were more flexible. Thus, different substitution patterns of the phenyl unit (2-F and 2,4-diCl) afforded equally active compounds (**69** and **70**). Chemical reduction to the dihydro analogue (**68**) also maintained the in vitro activity. However, amide **72** was 1 order of magnitude less active than the parent compound **20**, proving that conformational restraint to the quinazolinone nucleus enhances potency. Introduction of a methyl group at the pyrimidone ring (**67**) had a deleterious effect. The imidazole counterpart (**73**) also showed impaired activ-

Table 8. Derivatives of **20**



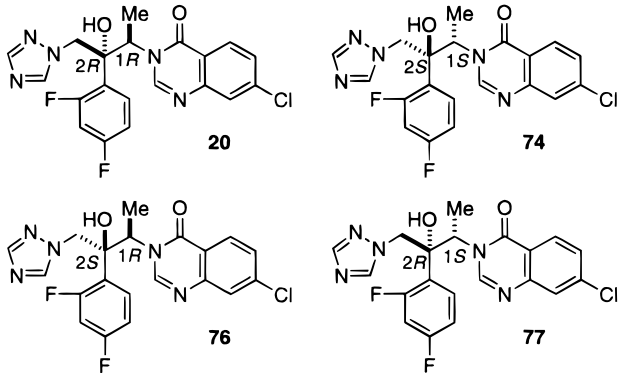
compd	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (2.5 mg/kg po)[c] % protection (dC)[d]	in vivo (2.5 mg/kg po)[c] % protection (dFlu)[e]
20	0.3	0.7	60	0
67	6.6	36	NT	NT
68	0.8	2.8	30	0
69	0.7	1.1	20	0
70	0.2	1.6	80	0
71[f]	0.3	0.9	0	0
72	3.7	8.9	20	0
73	2.0	28	0	0

[a,b,c,d,e] See the corresponding footnotes in Table 1. [f] Dehydrates to **20** upon standing in organic solutions.

ity. Finally, the partially hydrolyzed derivative **71** was also prepared. The in vitro activity of this compound was strikingly similar to that of **20**. However, we later found (HPLC) that this compound reverts to **20** upon standing in organic solutions or in the culture medium, for which reason these values should be interpreted with care.

Stereochemistry. We[2a] and others[12] have previously demonstrated that for antifungal azoles carrying a 3-triazolyl-2-aryl-1-methyl-2-propanol unit, the (1*R*,2*R*) stereoisomer has the highest activity. To further prove this rule in our series and examine the influence of each center's absolute configuration upon activity, the three stereoisomers of compound **20** (i.e., (1*S*,2*S*) **74**, (1*R*,2*S*) **76**, and (1*S*,2*R*) **77**), and its racemate (1*R**,2*R**) **75** were synthesized and tested in vitro and in vivo (Table 9). In the anti series, only the (1*R*,2*R*) enantiomer (**20**) showed high activity, whereas the (1*S*,2*S*) (**74**) was virtually inactive. The racemic compound (**75**) showed the expected MIC values against yeasts (i.e., nearly 2-fold those of **20**) but it proved suprisingly poor against molds. At this point, it is unknown if this was due to deleterious, active participation of the enantiomer or if

Table 9. Stereochemistry



compd	abs config	in vitro MIC[a] yst	in vitro MIC[b] ff	in vivo (2.5 mg/kg po)[c] % protection (dC)[d]	in vivo (2.5 mg/kg po)[c] % protection (dFlu)[e]
20	(1*R*,2*R*)	0.3	0.7	60	0
74	(1*S*,2*S*)	40	>80	0	0
75	(1*R**,2*R**)	1.0	33	NT	NT
76	(1*R*,2*S*)	>80	>80	0	0
77	(1*S*,2*R*)	7.4	65	0	0

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

the high insolubility of racemate **75** (mp 242 °C) compared to that of the pure enantiomer **20** (amorphous solid) was physically impairing membrane penetration.

In the syn series, comparison of the MIC values obtained for epimers **76** and **77** indicated that the impact of the absolute stereochemistry of the carbinol center (C-2) is greater than that of the methine carbon (C-1). All of the above findings support the assumption that this type of structure fits in the same chiral pocket as the lanosterol D ring in the target enzyme, cytochrome $P450_{14}DM$.[5]

Conformational Studies. Right from the beginning of the study we observed the presence of a set of small (5−10%) parallel signals in the ^1H NMR spectra of all the anti quinazolinones. We first thought that they might be due to an impurity, but the signals failed to disappear upon product recrystallization. Nor did the HPLC analyses show the presence of other peaks. This effect was most evident in the syn quinazolinone **77**, where the two set of signals approached a 1:1 ratio.

A 2D EXSY (exchange spectroscopy) experiment in $CDCl_3$ was performed on **20** and **77**. This method shows chemical exchange before line broadening occurs, with the particular advantage that cross signals for all exchanging species can be seen. Examination of the resulting 2D NMR map clearly indicated that the duplicity of the signals were due to rotaisomerism.

CPK model analysis of **20** showed that rotation about the C−N bond that links the propanol unit to the quinazolinone is severely restricted. Parallel MM calculations[13] further indicated conformer *m* to be 2.1 kcal/mol higher in energy than *M* (Figure 3). Contrarily, no difference in energy was found for the two corresponding conformers of the syn isomer (**77**). These findings were in full accordance with the above-mentioned ratios observed in the NMR spectra of the two isomers.

For further investigation of the dynamic process, GROESY (1D-ROE with pulse field gradients) spectra were recorded at different temperatures. Thus, irradiation of each methyl signal of **77** at −50 °C produced

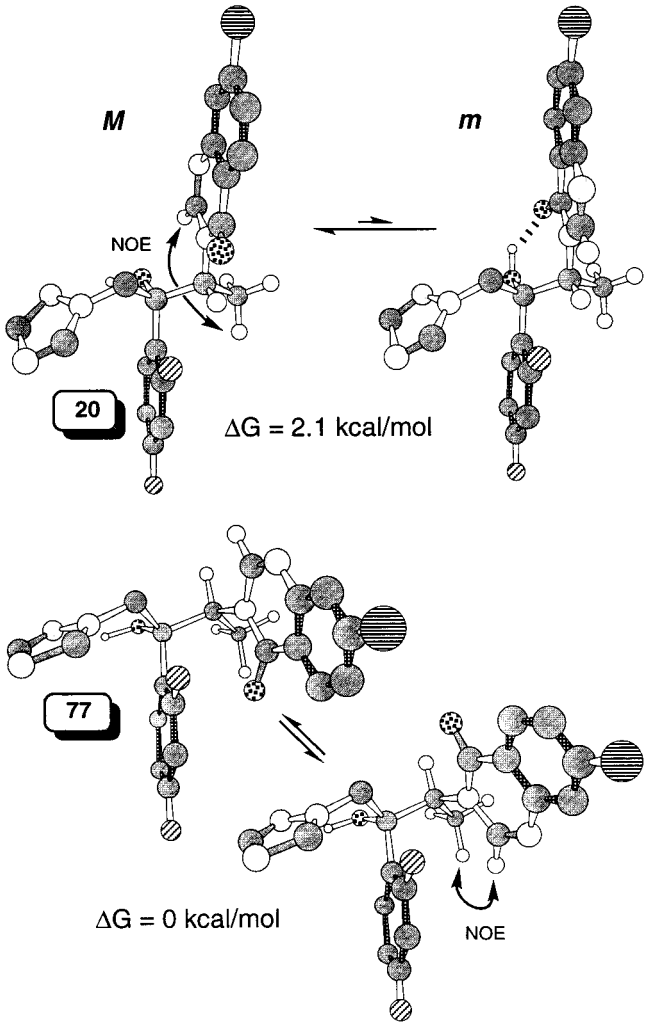


Figure 3. Conformational analysis of the anti (**20**) and syn (**77**) stereoisomers.[13]

enhancement of the quinazolinone methine in one rotamer but not in the other (Figure 3), proving that there is no rotamer interconversion at this temperature. In **20**, where the conformer ratio approached 97:3, irradiation of the methyl signal of the major rotamer *M* at −50 °C produced methine enhancement, proving in this way the assigned conformations depicted in Figure 3.

Conclusions

The acyl moiety of (1*R*,2*R*)-3-azole-2-aryl-1-methyl-2-butanol-1-acylamino antifungal agents possess enough structural flexibility to allow product optimization. In the preceding paper we demonstrated that the antifungal spectrum can be broadened by introducing a specifically oriented phenyl substituent in a five-member ring acyl unit. The resulting compounds, however, suffered from extremely long plasma half-lives. In the present paper we demonstrate that the quinazolinones, which lack the phenyl substituent, have both a broader spectrum of activity and faster elimination rates. Summarizing the findings of Tables 1−9, we can conclude that the best-suited quinazolinone derivatives are those carrying a halogen or an isostere at the 7-position and no substituent at the pyrimidone unit. Diastereomers with a stereochemistry other than (*R*,*R*) are far less active. After thorough evaluation that included studies of in vitro and in vivo activity in different species (including *Aspergillus fumigatus*), pharmacokinetics, and ease of synthesis, compound **20** was selected for further development.

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 for representative compounds. All the (*R*,*R*) quinazolinone derivatives appeared as a ca. 95:5−90:10 mixture of rotamers in the ^{1}H NMR spectrum. For simplicity, we will describe the signals of the major rotamer only, except for compound **20** where a full description is reported. 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. 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 mentioned mass spectrometer. For routine GC−MS analyses, a 12 m HP-5 column with an injector temperature of 275 °C and a gradient oven temperature 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, following a published procedure.[15] 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 **6**,[9] **7**,[10] and **8**[5] were synthesized in our center according to the published procedures. Amine **13** was obtained as described in the literature.[5] Amines **11**, **12**, and **14** were prepared according to our previous procedure.[6]

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. The majority of the chemical yields reported below are not optimized and correspond to reactions ran only one time.

Preparation of Quinazolinones: General Method. To a cooled (0 °C) solution of amine **11**−**14** in DMF (1 M) were added the corresponding anthranilic acid (1.05 equiv), HOBT (containing 17% H_2O, 1.05 equiv), and DCC (1.05 equiv). The cooling bath was removed and the solution stirred at room temperature for 18 h. The solid formed (dicyclohexylurea, DCU) was filtered off and washed with $CHCl_3$. The filtrate was concentrated (oil pump). The residue was taken off with EtOAc and washed with aqueous 5% $NaHCO_3$. The product was extracted from the organic phase with aqueous 2 N HCl. The aqueous phase was then brought to pH 7 with aqueous 20% NaOH, and the emulsion formed was extracted with $CHCl_3$, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to a colored foam containing

EtOAc. The mixture was then dissolved in $CHCl_3$ and passed through a short column of silica using EtOAc as the eluent to afford the corresponding anthranylamide as a cream-colored foam in 90−100% yield.

To a solution of the above intermediate in *N*-methylpyrrolidone (NMP, 1 M) were added triethyl orthoformate (3 equiv) and 5 N HCl in 1,4-dioxane (ca. 0.5 equiv). The solution was heated at 110 °C for 18 h or until TLC analysis indicated completion. After the mixture was cooled to room temperature, water (75 mL) was added and the pH brought to 5.5 with saturated $NaHCO_3$. The mixture was extracted with EtOAc (4×). The collected organic fractions were washed with water (4×) and brine, (1×) and dried over Na_2SO_4 and the drying agent filtered. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography (hex:EtOAc, 1:5) and recrystallized from an EtOAc:hexane: ether mixture (50−90% yield). In general, the quinazolinones tended to form crystalline solvates with the solvent of recrystallization. A free of solvent, amorphous solid could be obtained by adding water to a solution of the product in EtOH.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (15): white solid; mp 210−211 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 9.03 (dd, J = 2, J = 4.5, 1H, ar), 8.81 (s, 1H, N=C*H*-N), 8.67 (dd, J = 2, J = 8.7, 1H, ar), 7.77 (s, 1H, triazole), 7.73 (s, 1H, triazole), 7.6−7.3 (m, 2H, arom), 6.9−6.7 (m, 2H, ar), 5.90 (dq, J_d = 1.6, J_q = 7, 1H, MeC*H*), 5.61 (d, J = 1.6, 1H, O*H*), 5.14 (d, J = 14, 1H, CH(*H*)), 4.05 (d, J = 14, 1H, C*H*(H)), 1.32 (d, J = 7, 3H, CH*Me*); GC/MS 224 ($C_{10}H_8F_2N_3O$), 175 ($C_{19}H_9N_3O$); $[\alpha]_D$ +0.8° (*c* 1, $CHCl_3$). Anal. ($C_{19}H_{16}F_2N_6O_2$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]benzo[*g*]quinazolin-4(3*H*)-one (16): yellowish solid; mp 200−202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.95 (s, 1H, arom), 8.57 (s, 1H, N=C*H*-N), 8.24 (s, 1H, arom), 8.2−7.9 (m, 2H, arom), 7.77 (s, 1H, triazole), 7.72 (s, 1H, triazole), 7.7−7.3 (m, 3H, arom), 6.9−6.8 (m, 2H, arom), 5.98 (dq, J_d = 1.2, J_q = 7.3, 1H, MeC*H*), 5.51 (d, J = 1.6, 1H, O*H*), 5.21 (d, J = 14.1, 1H, CH(*H*)), 4.08 (d, J = 14.1, 1H, C*H*(H)), 1.32 (d, J = 7.3, 3H, CH*Me*); HPLC−MS 224 ($C_{14}H_{12}N_2O$ and $C_{10}H_8F_2N_3O$); $[\alpha]_D$ +3.6° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{19}F_2N_5O_2 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl] quinazolin-4(3*H*)-one (17). Precipitated from EtOH/water: white solid; mp 164−165 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.59 (s, 1H), 8.35 (d, J = 8.5, 1H), 8.0−7.4 (m, 6H, arom), 6.9−6.7 (m, 2H), 5.95 (dq, J_d = 1.6, J_q = 7, 1H), 5.50 (d, J = 1.6, 1H), 5.18 (d, J = 14, 1H), 4.02 (d, J = 14, 1H), 1.31 (d, J = 7, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 174 ($C_{10}H_{10}N_2O$); $[\alpha]_D$ −3.36° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{17}F_2N_5O_2$) C, H, N.

(1*R*,2*R*)-5-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (18): white solid; mp 114−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.59 (s, 1H), 7.79 (s, 1H), 7.76 (s, 1H), 7.8−7.5 (m, 3H), 7.50 (dt, J_d = 6.4, J_t = 8.8, 1H), 6.9−6.7 (m, 2H), 5.95 (dq, J_d = 1.7, J_q = 7.3, 1H), 5.58 (d, J = 1.7, 1H), 5.23 (d, J = 14.2, 1H), 4.08 (d, J = 14.2, 1H), 1.29 (d, J = 7.3, 3H); GC/MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ +39.5° ($CHCl_3$, *c* 1). Anal. ($C_{20}H_{16}ClF_2N_5O_2 \cdot {}^1/_3H_2O$) C, H, N.

(1*R*,2*R*)-6-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (19): white solid; mp 188−189 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.56 (s, 1H), 8.30 (t, J = 1.3, 1H), 7.75−7.70 (m, 3H), 7.7−7.3 (m, 2H), 7.0−6.6 (m, 2H), 5.93 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.52 (d, J = 1.5, 1H), 5.15 (d, J = 14, 1H), 3.98 (d, J = 14, 1H), 1.30 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ +14.6° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}ClF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (20, UR-9825). Precipitated from EtOH/H_2O (66% yield from amine **11**): white amorphous solid; mp 93−110 °C (wide range); IR (KBr) ν 1675, 1601, 1554, 1498 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 8.58 (s, 1H, N=C*H*-N), 8.26 (d, J = 8.6, 1H, arom), 8.11 (d, J = 5.7, trace rotamer), 7.76 (s, 2H, triazol), 7.74 (d, J = 5.3, 1H, arom), 7.5 (m, 2H, arom), 7.10 (s, trace rotamer), 6.9−6.7 (m, 2H, arom), 5.91 (dq, J_d = 2, J_q = 7, 1H, MeC*H*), 5.54 (d, J = 2, 1H, O*H*), 5.15 (d, J = 14.2 1H, CH(*H*)), 4.9−4.7 (m, trace rotamer), 4.30 (d, trace rotamer), 3.99 (d, J = 14.2, 1H, C*H*(H)), 1.46 (d, J = 6.9, trace rotamer), 1.29 (d, J = 7, 3H, CH*Me*); GC−MS 224 (Tr-CH_2COHAr, $C_{10}H_8F_2N_3O$), 208 (group *N*-ethylheterocycle, $C_{10}H_9ClN_2O$); $[\alpha]_D$ −8.0° (*c* 1, $CHCl_3$). Chiral HPLC (column, CicloBond SN 1; eluent, MeOH: Et_3NHOAc in H_2O at pH7 1:1; retention times: (*S*,*S*) (**74**) t_R 12.6 min; (*R*,*R*) (**20**) t_R 13.7 min). Area ratio: 0.01: 99.99. Anal. ($C_{20}H_{16}ClF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-8-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (21): white solid; mp 110−113 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.73 (s, 1H), 8.27 (dd, J = 1.5, J = 8, 1H), 7.84 (dt, J_d = 1.5, J_t = 7.7, 1H), 7.74 (broad s, 2H), 7.7−7.3 (m, 2H), 7.0−6.6 (m, 2H), 5.90 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.55 (d, J = 1.5, 1H), 5.15 (d, J = 14, 1H), 4.00 (d, J = 14, 1H), 1.30 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ −21.8° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}ClF_2N_5O_2 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-5-fluoroquinazolin-4(3*H*)-one (22): white amorphous solid; mp 94−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.57 (s, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.73 (dd, J = 8.2, J = 1.5, 1H), 7.8−7.5 (m, 1H), 7.49 (dt, J_d = 6.4, J_t = 8.8, 1H), 7.20 (ddd, J = 1.0, J = 8.0, J = 10.7, 1H), 6.9−6.7 (m, 2H), 5.96 (dq, J_d = 1.7, J_q = 7.3, 1H), 5.57 (d, J = 1.7, 1H), 5.23 (d, J = 14.2, 1H), 4.07 (d, J = 14.2, 1H), 1.30 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 192 ($C_{10}H_9FN_2O$); $[\alpha]_D$ +18.1° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}F_3N_5O_2 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6-fluoroquinazolin-4(3*H*)-one (23): white solid; mp 192−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.57 (s, 1H), 7.98 (dd, J = 2.9, J = 8.4, 1H), 7.8−7.7 (m, 3H), 7.6−7.4 (m, 3H), 6.9−6.7 (m, 2H), 5.95 (dq, J_d = 1.6, J_q = 7.3, 1H), 5.54 (d, J = 1.7, 1H), 5.18 (d, J = 14.2, 1H), 4.02 (d, J = 14.2, 1H), 1.32 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 192 ($C_{10}H_9FN_2O$); $[\alpha]_D$ −2.3° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}F_3N_5O_2$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-fluoroquinazolin-4(3*H*)-one (24): white solid; mp 139−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.60 (s, 1H), 8.37 (dd, J = 6.0, J = 8.9, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.49 (dt, J_d = 6.5, J_t = 8.7, 1H), 7.42 (dd, J = 2.4, J = 9.4, 1H), 7.27 (dt, J_d = 2.5, J_t = 8.7, 1H), 6.9−6.7 (m, 2H), 5.94 (dq, J_d = 1.7, J_q = 7.3, 1H), 5.54 (d, J = 1.7, 1H), 5.17 (d, J = 14.1, 1H), 4.03 (d, J = 14.1, 1H), 1.31 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 192 ($C_{10}H_9FN_2O$); $[\alpha]_D$ −4.1° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}F_3N_5O_2 \cdot {}^1/_2$EtOAc) C, H, N.

(1*R*,2*R*)-6-Bromo-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (25): white solid; mp 198−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.59 (s, 1H), 8.47 (d, J = 2.2, 1H), 7.88 (dd, J = 2.2, J = 8.6, 1H), 7.78 (s, 1H), 7.74 (s, 1H), 7.64 (d, J = 8.6, 1H), 7.48 (dt, J_d = 6.5, J_t = 8.8, 1H), 6.9−6.7 (m, 2H), 5.93 (dq, J_d = 1.7, J_q = 7.3, 1H), 5.54 (d, J = 1.7, 1H), 5.16 (d, J = 14.1, 1H), 4.01 (d, J = 14.1, 1H), 1.31 (d, J = 7.3, 3H); GC−MS 252 and 254 ($C_{10}H_9BrN_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ +17.6° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}BrF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-7-Benzylamino-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (58). A solution of **24** (1.85 g, 4.4 mmol) and benzylamine (1.45 g, 13.4 mmol) in 40 mL of NMP was heated at 120 °C for 4 days. Once the reaction was completed, water and EtOAc were added. The aqueous phase was separated and reextracted with additional EtOAc. The combined extracts were washed with water and brine and dried over Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated to an oil which was purified by flash chromatography to give the title compound as an amorphous white solid (1.45 g, 66%): mp 100−107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.45 (s, 1H), 8.09 (d, J = 8.5, 1H), 7.76 (s, 1H), 7.73 (s, 1H),

7.48 (dt, $J_d = 6.4$, $J_t = 8.8$, 1H), 7.5−7.3 (m, 5H), 6.9−6.7 (m, 4H), 5.90 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.42 (d, $J = 1.5$, 1H), 5.17 (d, $J = 14.2$, 1H), 4.72 (broad t, $J = 4.8$, 1H, N*H*), 4.47 (d, $J = 5.5$, 2H, NCH_2), 4.03 (d, $J = 14.2$, 1H), 1.26 (d, $J = 7.3$, 3H); GC−MS 279 ($C_{17}H_{17}N_3O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −32.3° (*c* 1, $CHCl_3$). Anal. ($C_{27}H_{24}F_2N_6O_2$) C, H, N.

(1*R*,2*R*)-7-Bromo-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (26). (a) To a solution of **58** (1.45 g, 2.8 mmol) in MeOH (10 mL) was added 10% Pd/C (250 mg) and a solution of ammonium formate (700 mg, 11.2 mmol) in H_2O (2.5 mL). The mixture was refluxed for 24 h and then filtered through Celite. The filtrate was concentrated to give (1*R*,2*R*)-7-amino-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one as an off-white solid (1.16 g, 93%): mp 103−109 °C; ^{1}H NMR (300 MHz, MeOH-d_4) δ (MeOH) 8.39 (s, 1H), 8.17 (s, 1H), 7.98 (d, $J = 8.7$, 1H), 7.63 (s, 1H), 7.5−7.2 (m, 2H), 7.03 (ddd, $J_d = 2.5$, $J_d = 8.5$, $J_d = 14$, 1H), 6.9−6.8 (m, 2H), 6.03 (q, $J = 7.3$, 1H), 5.06 (d, $J = 14.2$, 1H), 4.14 (d, $J = 14.2$, 1H), 1.26 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 189 ($C_{10}H_{11}N_3O$); $[\alpha]_D$ −11.6° (*c* 0.5, $CHCl_3$).

(b) To a cooled (0 °C) solution of the product obtained above (300 mg, 0.7 mmol) in 48% HBr (3 mL) was added a solution of $NaNO_2$ (48 mg, 0.7 mmol) in H_2O (0.5 mL). The mixture was poured into a mixture of CuBr (55 mg, 0.4 mmol) in 48% HBr (1 mL). The reaction mixture was then refluxed for 2 h. Next, H_2O and EtOAc were added, the layers were separated, and the organic phase was washed with 1 N NaOH and with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to give the title product as a white solid (145 mg, 43%): mp 109−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.58 (s, 1H), 8.19 (d, $J = 8.5$, 1H), 7.94 (d, $J = 1.8$, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.64 (dd, $J = 1.8$, $J = 8.5$, 1H), 7.48 (dt, $J_d = 6.4$, $J_t = 8.8$, 1H), 6.9−6.7 (m, 2H), 5.91 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.54 (d, $J = 1.5$, 1H), 5.14 (d, $J = 14.2$, 1H), 4.00 (d, $J = 14.2$, 1H), 1.29 (d, $J = 7.3$, 3H); GC−MS 252 and 254 ($C_{10}H_9BrN_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −10.8° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}BrF_2N_5O_2 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-6,7-Difluoro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (27): white solid; mp 212−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.56 (s, 1H), 8.09 (dd, $J = 8.4$, $J = 9.9$, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.54 (dd, $J = 7.0$, $J = 9.9$, 1H), 7.6−7.4 (m, 1H), 6.9−6.7 (m, 2H), 5.89 (dq, $J_d = 1.7$, $J_q = 7.3$, 1H), 5.55 (d, $J = 1.6$, 1H), 5.14 (d, $J = 14.2$, 1H), 3.99 (d, $J = 14.2$, 1H), 1.29 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 210 ($C_{10}H_8F_2N_2O$); $[\alpha]_D$ −4.5° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{15}F_4N_5O_2$) C, H, N.

(1*R*,2*R*)-6,8-Dichloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (28): white solid; mp 158−160 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.71 (s, 1H), 8.24 (d, $J = 2.2$, 1H), 7.92 (d, $J = 2.2$, 1H), 7.75 (s, 2H), 7.6−7.1 (m, 1H), 7.0−6.6 (m, 2H), 5.90 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.58 (d, $J = 1.5$, 1H), 5.12 (d, $J = 14$, 1H), 3.99 (d, $J = 14$, 1H), 1.30 (d, $J = 7.3$, 3H); GC−MS 242 and 244 ($C_{10}H_8Cl_2N_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −6.8° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{15}Cl_2F_2N_5O_2$) C, H, N.

(1*R*,2*R*)-6,8-Dibromo-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (29): white solid; mp 134−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.75 (s, 1H), 8.46 (d, $J = 2$, 1H), 8.20 (d, $J = 2$, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.49 (dt, $J_d = 6.5$, $J_t = 8.8$, 1H), 6.9−6.7 (m, 2H), 5.90 (dq, $J_d = 1.7$, $J_q = 7.3$, 1H), 5.58 (d, $J = 1.6$, 1H), 5.13 (d, $J = 14.1$, 1H), 4.00 (d, $J = 14.1$, 1H), 1.31 (d, $J = 7.3$, 3H); GC−MS 330, 332, and 334 ($C_{10}H_8Br_2N_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −10.2° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{15}Br_2F_2N_5O_2 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-5-methylquinazolin-4(3*H*)-one (30): white solid; mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.54 (s, 1H), 7.79 (s, 1H), 7.75 (s, 1H), 7.7−7.6 (m, 2H), 7.49 (dt, $J_d = 6.4$, $J_t = 8.8$, 1H), 7.30 (dt, $J_t = 0.8$, $J_d = 6.7$, 1H), 6.9−6.8 (m, 2H), 5.94 (dq, $J_d = 1.7$, $J_q = 7.3$, 1H), 5.49 (d, $J = 1.7$, 1H), 5.19 (d, $J = 14.2$, 1H), 4.09 (d, $J = 14.2$, 1H), 2.95 (s, 3H, *Me*), 1.29 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 188 ($C_{11}H_{12}N_2O$); $[\alpha]_D$ +10.9° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{19}F_2N_5O_2 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6-methylquinazolin-4(3*H*)-one (31): white solid; mp 189−190 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.53 (s, 1H), 8.13 (s, 1H), 7.76 (s, 1H), 7.71 (s, 1H), 7.9−7.3 (m, 3H), 6.9−6.7 (m, 2H), 5.95 (dq, $J_d = 1.7$, $J_q = 7.3$, 1H), 5.48 (d, $J = 1.5$, 1H), 5.14 (d, $J = 14.2$, 1H), 3.97 (d, $J = 14.2$, 1H), 2.51 (s, 3H, *Me*), 1.30 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 188 ($C_{11}H_{12}N_2O$); $[\alpha]_D$ −17.0° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{19}F_2N_5O_2$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-8-methylquinazolin-4(3*H*)-one (32): white solid; mp 141−144 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.63 (s, 1H), 8.20 (dd, $J = 1.5$, $J = 8$, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.8−7.3 (m, 3H), 7.0−6.5 (m, 2H), 5.95 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.48 (d, $J = 1.5$, 1H), 5.19 (d, $J = 14$, 1H), 3.98 (d, $J = 14$, 1H), 2.66 (s, 3H, *Me*), 1.31 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 188 ($C_{11}H_{12}N_2O$); $[\alpha]_D$ −49.3° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{19}F_2N_5O_2$) H, N; C: calcd, 61.31; found, 61.72.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6,8-dimethylquinazolin-4(3*H*)-one (33): white amorphous solid; mp 95−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.58 (s, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.49 (dt, $J_d = 6.4$, $J_t = 8.8$, 1H), 7.48 (s, 1H), 6.9−6.8 (m, 2H), 5.94 (dq, $J_d = 1.7$, $J_q = 7.3$, 1H), 5.44 (d, $J = 1.6$, 1H), 5.18 (d, $J = 14.2$, 1H), 4.00 (d, $J = 14.2$, 1H), 2.62 (s, 3H, *Me*), 2.47 (s, 3H, *Me*), 1.29 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 202 ($C_{12}H_{14}N_2O$); $[\alpha]_D$ −11.1° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{21}F_2N_5O_2 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-8-Bromo-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6-methylquinazolin-4(3*H*)-one (34): white solid; mp 116−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.71 (s, 1H), 8.11 (q, $J = 0.85$, 1H), 7.93 (d, $J = 1.88$, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 7.50 (dt, $J_d = 6.4$, $J_t = 8.8$, 1H), 6.9−6.7 (m, 2H), 5.92 (dq, $J_d = 1.7$, $J_q = 7.3$, 1H), 5.53 (d, $J = 1.7$, 1H), 5.15 (d, $J = 14.2$, 1H), 4.00 (d, $J = 14.2$, 1H), 2.51 (s, 3H, *Me*), 1.31 (d, $J = 7.3$, 3H); GC−MS 266 and 268 ($C_{11}H_{11}BrN_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −20.6° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{18}BrF_2N_5O_2 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-8-methoxyquinazolin-4(3*H*)-one (35): white solid; mp 117−121 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.60 (s, 1H), 7.92 (dd, $J = 1.3$, $J = 7.7$, 1H), 7.74 (s, 1H), 7.71 (s, 1H), 7.6−7.3 (m), 7.0−6.6 (m, 2H), 5.95 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.48 (d, $J = 1.5$, 1H), 5.15 (d, $J = 14$, 1H), 4.05 (s, 3H, O*Me*), 3.98 (d, $J = 14$, 1H,), 1.29 (d, $J = 7.3$, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 204 ($C_{11}H_{12}N_2O_2$); $[\alpha]_D$ −19.7° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{19}F_2N_5O_3 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (36): white solid; mp 144−159 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.70 (s, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.66 (s, 1H), 7.6−7.3 (m, 1H), 7.15 (s, 1H), 7.0−6.5 (m, 2H), 5.97 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.47 (d, $J = 1.5$, 1H), 5.18 (d, $J = 14$, 1H), 4.01 (s, 6H, 2 O*Me*), 3.98 (d, $J = 14$, 1H), 1.30 (d, $J = 7.3$, 3H); GC−MS 234 ($C_{12}H_{14}N_2O_3$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −11.7° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{21}F_2N_5O_4 \cdot {}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(dimethylamino)-6-fluoroquinazolin-4(3*H*)-one (37). This compound was obtained as a byproduct when the preparation of compound **27** was carried out in DMF instead of NMP (22% yield): white solid; mp 197−198 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.45 (s, 1H), 7.91 (s, 1H), 7.74 (broad s, 3H), 7.7−7.3 (m, 1H), 7.0−6.6 (m, 2H), 5.90 (dq, $J_d = 1.5$, $J_q = 7.3$, 1H), 5.46 (d, $J = 1.5$, 1H), 5.16 (d, $J = 14$, 1H), 4.00 (d, $J = 14$, 1H), 3.06 (s, 6H, NMe_2), 1.25 (d, $J = 7.3$, 3H); MS 458 (M^+); $[\alpha]_D$ −36° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{21}F_3N_6O_2 \cdot {}^1/_2$ Et$_2$O) C, H, N.

(1*R*,2*R*)-7-Amino-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6-fluoroquinazolin-4(3*H*)-one (38). This compound was obtained as a byprod-

uct when the preparation of compound **27** was carried out using formamidine acetate instead of triethyl orthoformate and 5 N HCl in 1,4-dioxane (43% yield): white solid; mp 124−125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.45 (s, 1H), 7.86 (d, J = 11, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.6−7.4 (m, 1H), 6.97 (d, J = 8.0, 1H), 6.9−6.7 (m, 2H), 5.89 (dq, J_d = 1.7, J_q = 7.3, 1H), 5.46 (d, J = 1.7, 1H), 5.15 (d, J = 14.2, 1H), 4.43 (broad s, 2H, N*H*$_2$), 4.01 (d, J = 14.2, 1H), 1.26 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 207 ($C_{10}H_{10}FN_3O$); $[\alpha]_D$ −0.31° (*c* 1, MeOH). Anal. ($C_{20}H_{17}F_3N_6O_2\cdot{}^1/_2H_2O$) C, H; N: calcd, 19.13; found, 17.42.

(1*R*,2*R*)-*N*-[3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6-fluoro-4-oxo-3,4-dihydroquinazolin-7-yl]-2,2,2-trifluoroacetamide (39). A solution of **38** (500 mg, 1.16 mmol) in pyridine (5 mL) was treated with trifluoroacetic anhydride (488 mg, 2.3 mmol) at 0 °C for 1 h. Next aqueous Na_2CO_3 solution was added, pyridine was removed in vacuo, and the residue was partitioned between water and $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to an oil that was purified by flash chromatography to give the title product as a white solid (412 mg, 67%): mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.77 (d, J = 7, 1H), 8.58 (s, 1H), 8.33 (broad s, 1H, N*H*), 8.07 (d, J = 10.6, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.49 (dt, J_d = 6.5, J_t = 9, 1H), 6.9−6.7 (m, 2H), 5.91 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.56 (d, J = 1.7, 1H), 5.13 (d, J = 14.2, 1H), 4.02 (d, J = 14.2, 1H), 1.30 (d, J = 7.3, 3H); GC−MS 303 ($C_{12}H_9F_4N_3O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −38.4° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{16}F_6N_6O_3\cdot{}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-iodoquinazolin-4(3*H*)-one (40). To a cooled (0 °C) solution of (1*R*,2*R*)-7-amino-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (see section (a) of preparation of **26**) (500 mg, 1.2 mmol) in a mixture of concentrated HCl (3 mL) and ice (4 mL) was added a solution of $NaNO_2$ (88 mg, 1.3 mmol) in H_2O (0.5 mL). After 15 min, the resulting mixture was poured to a mixture of KI (1.9 g, 12 mmol) in H_2O (10 mL). The reaction mixture was stirred at 25 °C for 15 h. Then, H_2O and EtOAc were added, the layers were separated, and the organic phase was washed with 1 N NaOH and with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to give the title product as a white solid (225 mg, 35%): mp 155−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.56 (s, 1H), 8.18 (d, J = 1.5, 1H), 8.02 (d, J = 8.5, 1H), 7.85 (dd, J = 1.5, J = 8.5, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.48 (dt, J_d = 6.4, J_t = 8.8, 1H), 6.9−6.7 (m, 2H), 5.91 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.53 (d, J = 1.5, 1H), 5.14 (d, J = 14.2, 1H), 4.00 (d, J = 14.2, 1H), 1.29 (d, J = 7.3, 3H); GC−MS 300 ($C_{10}H_9IN_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −19.3° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}IF_2N_5O_2\cdot H_2O$) C, H; N: calcd, 12.94; found, 12.23.

(1*R*,2*R*)-7-Cyano-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (41). 4-Cyanoanthranilic acid was prepared as described in the literature:[16] white solid; mp 168−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.64 (s, 1H), 8.43 (d, J = 8.2, 1H), 8.08 (d, J = 1.1, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.73 (dd, J = 1.5, J = 8.2, 1H), 7.47 (dt, J_d = 6.4, J_t = 8.8, 1H), 6.9−6.8 (m, 2H), 5.91 (dq, J_d = 1.2, J_q = 7.3, 1H), 5.60 (d, J = 1.3, 1H), 5.13 (d, J = 14.1, 1H), 4.00 (d, J = 14.1, 1H), 1.31 (d, J = 7.3, 3H); GC−MS 423 (M^+ + 1), 224 ($C_{10}H_8F_2N_3O$), 198 ($C_{11}H_8N_3O$); $[\alpha]_D$ −0.95° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{16}F_2N_6O_2\cdot H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-trifluoromethylquinazolin-4(3*H*)-one (42): white solid; mp 142−143 °C (MeCN); ^{1}H NMR (300 MHz, $CDCl_3$) 8.65 (s, 1H), 8.46 (d, J = 8.3, 1H), 8.04 (s, 1H), 7.76 (s, 1H), 7.74 (d, J = 8.6, 1H), 7.73 (s, 1H), 7.48 (q, J = 8.5, 1H), 6.9−6.7 (m, 2H), 5.94 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.57 (d, J = 1.5, 1H), 5.15 (d, J = 14.1, 1H), 4.00 (d, J = 14.2, 1H), 1.31 (d, J = 7.3, 3H); GC−MS 242 ($C_{11}H_9F_3N_2O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ +4.2° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{16}F_5N_5O_2$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(2,2,3,3-tetrafluoropropoxy)quinazolin-4(3*H*)-one (46). A solution of 2,2,3,3-tetrafluoropropanol (381 mg, 2.9 mmol) in anhydrous NMP (10 mL) was treated with NaH (55% oil dispersion, 126 mg, 2.9 mmol) for 10 min at room temperature. Once H_2 ceased to evolve, compound **24** (400 mg, 0.96 mmol) was added and the mixture was stirred at 120 °C overnight. Once the reaction was completed, water and EtOAc were added. The aqueous phase was separated and reextracted with additional EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash chromatography to give the title compound as an amorphous white solid (200 mg, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) 8.56 (s, 1H), 8.29 (d, J = 9.5, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.48 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.15 (m, 2H), 6.9−6.7 (m, 2H), 6.08 (tt, J = 4.5, J = 53, 1H, C*H*F$_2$), 5.92 (dq, J_d = 2, J_q = 7.3, 1H), 5.51 (d, J = 1.5, 1H), 5.16 (d, J = 14.3, 1H), 4.49 (tt, J = 1.5, J = 12, 2H, C*H*$_2$), 4.01 (d, J = 14.3, 1H), 1.29 (d, J = 7.3, 3H); GC−MS 304 ($C_{13}H_{12}F_4N_2O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −16.7° (*c* 1, $CHCl_3$). Anal. ($C_{23}H_{19}F_6N_5O_3\cdot{}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(2-fluoroethoxy)quinazolin-4(3*H*)-one (43). Obtained in an analogous way from the reaction of **24** and 2-fluoroethanol (23% yield): white solid; mp 191−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.54 (s, 1H), 8.29 (d, J = 9.5, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.48 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.3−7.1 (m, 2H), 6.9−6.7 (m, 2H), 5.93 (dq, J_d = 2, J_q = 7.3, 1H), 5.49 (d, J = 1.5, 1H), 5.17 (d, J = 14.3, 1H), 4.90 (t, J = 4, 1H), 4.75 (t, J = 4, 1H), 4.40 (t, J = 4, 1H), 4.31 (t, J = 4, 1H), 4.02 (d, J = 14.3, 1H), 1.29 (d, J = 7.3, 3H); GC−MS 236 ($C_{12}H_{13}FN_2O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −22.9° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{20}F_3N_5O_3\cdot{}^1/_2$EtOAc) C, H, N.

(1*R*,2*R*)-7-(2,2-Difluoroethoxy)-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (44). Obtained in an analogous way from the reaction of **24** and 2,2-difluoroethanol (60% yield): white solid; mp 96−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.55 (s, 1H), 8.27 (d, J = 9.5, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.49 (dt, J_d = 6.5, J_t = 8.8, 1H), 7.15 (m, 2H), 6.9−6.7 (m, 2H), 6.16 (tt, J = 4, J = 55, 1H, C*H*F$_2$), 5.93 (dq, J_d = 2, J_q = 7.3, 1H), 5.50 (d, J = 1.5, 1H), 5.16 (d, J = 14.3, 1H), 4.32 (dt, J_d = 4, J_t = 13, 2H, OC*H*$_2$), 4.02 (d, J = 14.3, 1H), 1.29 (d, J = 7.3, 3H); GC−MS 254 ($C_{12}H_{12}F_2N_2O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −25.7° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{19}F_4N_5O_3$) C, H; N: calcd, 14.67; found, 13.21.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(2,2,2-trifluoroethoxy)-quinazolin-4(3*H*)-one (45). Obtained in an analogous way from the reaction of **24** and 2,2,2-trifluoroethanol (21% yield): white amorphous solid, contaminated with ca. 15% of the product resulting from substitution of the 2,4-difluorophenyl ring; ^{1}H NMR (300 MHz, $CDCl_3$) 8.56 (s, 1H), 8.29 (d, J = 8.8, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.4−7.1 (m, 3H), 6.9−6.7 (m, 2H), 5.93 (dq, J_d = 2, J_q = 7.3, 1H), 5.51 (d, J = 1.5, 1H), 5.16 (d, J = 14.3, 1H), 4.49 (q, J = 7.9, 2H, C*H*$_2$), 4.02 (d, J = 14.3, 1H), 1.29 (d, J = 7.3, 3H); GC−MS 272 ($C_{12}H_{11}F_3N_2O_2$), 224 ($C_{10}H_8F_2N_3O$).

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(methylthio)quinazolin-4(3*H*)-one (47). Obtained in an analogous way from the reaction of **24** and sodium thiomethoxide (89% yield): white solid; mp 152−153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.55 (s, 1H), 8.17 (d, J = 8.9, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.6−7.4 (m, 2H), 7.36 (dd, J = 1.7, J = 8.5, 1H), 6.9−6.7 (m, 2H), 5.92 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.50 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.02 (d, J = 14.2, 1H), 2.59 (s, 3H, S*Me*), 1.29 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 220 ($C_{11}H_{12}N_2OS$); $[\alpha]_D$ −53.6° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{19}F_2N_5O_2S$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(methylsulfonyl)quinazolin-4(3*H*)-one (48). A solution of compound **47** (0.22 g, 0.49 mmol) in CH_2Cl_2 (10 mL) was treated with a dried (Na_2SO_4)

solution of MCPBA (55%, 0.62 g, 1.98 mmol) in CH_2Cl_2 (10 mL) at 25 °C for 18 h. The solid formed was filtered, and the filtrate was then washed with 10% aqueous $Na_2S_2O_3$ solution, 1 N NaOH, and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated, purified by flash chromatography, and recrystallized from EtOAc:ether to give the title product as a white solid (141 mg, 56%): mp 223−224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (s, 1H), 8.53 (d, J = 8.4, 1H), 8.36 (d, J = 1.6, 1H), 8.03 (dd, J = 1.6, J = 8.3, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.48 (dt, J_d = 6.4, J_t = 8.8, 1H), 6.9−6.7 (m, 2H), 5.92 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.59 (d, J = 1.5, 1H), 5.15 (d, J = 14.2, 1H), 4.00 (d, J = 14.2, 1H), 3.13 (s, 3H, SO_2Me), 1.32 (d, J = 7.3, 3H); GC−MS 252 ($C_{11}H_{12}N_2O_3S$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ +2.1° (*c* 0.5, $CHCl_3$). Anal. ($C_{21}H_{19}F_2N_5O_4S\cdot{}^1/_2H_2O$) C, H, N, S.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(phenylthio)quinazolin-4(3*H*)-one (49). Obtained from the reaction of **24** and sodium thiophenoxide (66% yield): white solid, contaminated with ca. 20% of the product resulting from substitution of the 2,4-difluorophenyl ring: ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (s, 1H), 8.17 (d, J = 8.5, 1H), 7.75 (s, 1H), 7.76 (s, 1H), 7.6−7.3 (m, 8H), 6.9−6.7 (m, 2H), 5.90 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.48 (d, J = 1.5, 1H), 5.15 (d, J = 14.2, 1H), 3.99 (d, J = 14.2, 1H), 1.27 (d, J = 7.3, 3H); GC−MS 282 ($C_{16}H_{14}N_2OS$), 224 ($C_{10}H_8F_2N_3O$). Anal. ($C_{26}H_{21}F_2N_5O_2S$) C, H, S; N: calcd, 13.85; found, 13.04.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-phenylsulfonylquinazolin-4(3*H*)-one (50). Same oxidation procedure as for **48** (29% yield): white solid; mp 125−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.63 (s, 1H), 8.44 (d, J = 8.4, 1H), 8.35 (d, J = 1.6, 1H), 8.02 (d, J = 8.3, 3H), 7.77 (s, 1H), 7.73 (s, 1H), 7.6−7.4 (m, 4H), 6.9−6.7 (m, 2H), 5.90 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.55 (d, J = 1.5, 1H), 5.12 (d, J = 14.2, 1H), 3.94 (d, J = 14.2, 1H), 1.28 (d, J = 7.3, 3H); GC−MS 314 ($C_{16}H_{14}N_2O_3S$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ +7.0° (*c* 1, $CHCl_3$).

(1*R*,2*R*)-7-(4-Chlorophenoxy)-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (51). Obtained from the reaction of compound **24** and sodium 4-chlorophenoxide (40% yield): white solid; mp 198−199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (s, 1H), 8.26 (d, J = 8.7, 1H), 7.75 (s, 1H), 7.68 (s, 1H), 7.47 (dt, J_d = 6.5, J_t = 9, 1H), 7.34 (d, J = 8.6, 2H), 7.15 (dd, J = 2.4, J = 8.6, 1H), 7.13 (d, J = 2.2, 1H), 7.03 (d, J = 8.6, 2H), 6.9−6.7 (m, 2H), 5.97 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.58 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 3.96 (d, J = 14.2, 1H), 1.30 (d, J = 7.3, 3H); GC−MS 300 and 302 ($C_{16}H_{13}ClN_2O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −22° (*c* 0.1, $CHCl_3$). Anal. ($C_{26}H_{20}ClF_2N_5O_3$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(1*H*-1,2,4-triazol-1-yl)-quinazolin-4(3*H*)-one (52). Obtained from the reaction of compound **24** and the sodium salt of 1,2,4-triazole (52% yield): white solid; mp 236−237 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ (DMSO) 9.58 (s, 1H, triazole), 8.46 (s, 1H), 8.38 (d, J = 8.7, 1H), 8.34 (s, 1H, triazole), 8.24 (d, J = 1,5, 1H), 8.19 (s, 1H, triazole), 8.11 (dd, J = 2, J = 8.5, 1H), 7.55 (s, 1H, triazole), 7.3−7.2 (m, 2H), 6.95 (dt, J_d = 2.3, J_t = 8.4, 1H), 6.35 (s, 1H), 5.86 (q, J = 7.3, 1H), 4.84 (d, J = 14.5, 1H), 4.22 (d, J = 14.5, 1H), 1.20 (d, J = 7.3, 3H); GC−MS 240 ($C_{12}H_{11}N_5O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ +61.7° (*c* 1, DMF). Anal. ($C_{22}H_{18}F_2N_8O_2\cdot{}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(2-tetrazolyl)quinazolin-4(3*H*)-one (53). Obtained from the reaction of compound **24** and sodium tetrazolate (9% yield): white solid; mp 198−201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.74 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.54 (d, J = 9.4, 1H), 8.36 (dd, J = 2.0, J = 8.7, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.47 (dt, J_d = 6.5, J_t = 9, 1H), 6.9−6.7 (m, 2H), 5.95 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.60 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.05 (d, J = 14.2, 1H), 1.33 (d, J = 7.3, 3H); DIP-MS 242 ($C_{11}H_{10}N_6O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −16.9° (*c* 0.2, $CHCl_3$). Anal. ($C_{21}H_{17}F_2N_9O_2\cdot{}^1/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(2-oxazolidinone-3-yl)-quinazolin-4(3*H*)-one (54). Obtained from the reaction of compound **24** and the sodium salt of 2-oxazolidinone (10% yield): white solid; mp 294−295 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 8.38 (s, 1H), 8.21 (d, J = 8.9, 1H), 8.18 (s, 1H), 7.85 (dd, J = 2.0, J = 8.8, 1H), 7.79 (d, J = 8.9, 1H), 7.54 (s, 1H), 7.3−7.2 (m, 2H), 6.94 (dt, J_d = 2.3, J_t = 8.4, 1H), 6.33 (s, 1H), 5.84 (q, J = 7.2, 1H), 4.84 (d, J = 14.4, 1H), 4.96 (t, J = 7.7, 2H), 4.2−4.1 (m, 3H), 1.17 (d, J = 7.2, 3H); $[\alpha]_D$ +32.4° (*c* 0.5, DMSO). Anal. ($C_{23}H_{20}F_2N_6O_4\cdot{}^1/_2$EtOAc) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(4-morpholinyl)quinazolin-4(3*H*)-one (55). Obtained from the reaction of compound **24** and morpholine (64% yield): white solid; mp 196−197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.49 (s, 1H), 8.18 (d, J = 9.0, 1H), 7.75 (s, 1H), 7.73 (s, 1H), 7.5−7.4 (m, 1H), 7.09 (dd, J = 2.4, J = 9.0, 1H), 7.02 (d, J = 2.4, 1H), 6.9−6.6 (m, 2H), 5.91 (dq, J_d = 1.6, J_q = 7.3, 1H), 5.45 (d, J = 1.6, 1H), 5.17 (d, J = 14.2, 1H), 4.03 (d, J = 14.2, 1H), 3.88 (m, 4H, morph), 3.38 (m, 4H, morph), 1.27 (d, J = 7.3, 3H); GC−MS 259 ($C_{14}H_{17}N_3O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −37.9° (*c* 1, $CHCl_3$). Anal. ($C_{24}H_{24}F_2N_6O_3$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-(4-methyl-1-piperazinyl)-quinazolin-4(3*H*)-one (56). Obtained from the reaction of compound **24** and *N*-methylpiperazine (55% yield): white solid; mp 121−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.47 (s, 1H), 8.15 (d, J = 9.0, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.5−7.4 (m, 1H), 7.10 (dd, J = 2.4, J = 9.0, 1H), 7.02 (d, J = 2.3, 1H), 6.9−6.6 (m, 2H), 5.91 (dq, J_d = 1.6, J_q = 7.3, 1H), 5.44 (d, J = 1.6, 1H), 5.17 (d, J = 14.2, 1H), 4.02 (d, J = 14.2, 1H), 3.45 (m, 4H, pip), 2.58 (m, 4H, pip), 2.36 (s, 3H, N*Me*), 1.27 (d, J = 7.3, 3H); GC−MS 271 and 272 ($C_{15}H_{20}N_4O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −14.3° (*c* 1, $CHCl_3$). Anal. ($C_{25}H_{27}F_2N_7O_2\cdot{}^1/_2$EtOAc) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-hydrazinoquinazolin-4(3*H*)-one (57). This compound was obtained as a byproduct in the preparation of compound **53** (22% yield): white solid; mp 227−230 °C; ^{1}H NMR (300 MHz, MeOH-d_4) 8.52 (s, 1H), 8.28 (d, J = 8.6, 1H), 8.18 (s, 1H), 7.64 (s, 1H), 7.40 (dt, J_d = 6.5, J_t = 8.9, 1H), 7.3−7.2 (m, 2H), 7.04 (ddd, J_d = 2.5, J_d = 8.5, J_d = 14, 1H), 6.88 (dt, J_d = 2.5, J_t = 8.5, 1H), 6.04 (q, J = 7.2, 1H), 5.05 (d, J = 14.4, 1H), 4.17 (d, J = 14.4, 1H), 1.29 (d, J = 7.2, 3H); $[\alpha]_D$ +2.4° (*c* 0.2, DMSO). Anal. ($C_{20}H_{19}F_2N_7O_2\cdot{}^1/_4$EtOAc) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-dimethylaminoquinazolin-4(3*H*)-one (59). This compound was obtained as a byproduct when the preparation of compound **24** was carried out in DMF instead of NMP (44% yield): white solid; mp 201−201 °C; ^{1}H NMR (80 MHz, $CDCl_3$) 8.45 (s, 1H), 8.15 (d, J = 8, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.7−7.3 (m), 7.1−6.5 (m), 5.92 (dq, J_d = 2, J_q = 7.3, 1H), 5.43 (d, J = 2, 1H), 5.18 (d, J = 14, 1H), 4.05 (d, J = 14, 1H), 3.11 (s, 6H, NMe_2), 1.27 (d, J = 7.3, 3H); GC−MS 440 (M^+), 216 ($C_{12}H_{14}N_3O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −43° (*c* 1, $CHCl_3$). Anal. ($C_{22}H_{22}F_2N_6O_2$) C, H, N.

(1*R*,2*R*)-7-Carbamoyl-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (60). A solution of compound **41** (500 mg, 1.2 mmol) in MeOH (5 mL) and $CHCl_3$ (5 mL) was cooled to 0 °C, and HCl gas was bubbled until saturation (1.5 h). The mixture was allowed to stand at 0 °C overnight and was then concentrated, and the residue was slowly added to aqueous K_2CO_3 solution (2.5 g). The yellowish precipitate formed was filtered, dried, taken up in methanol, and allowed to react with sulfamide (350 mg, 3.6 mmol) at reflux for 3 h. The reaction mixture was then concentrated and partitioned between water and $CHCl_3$. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated, and the resulting residue (a mixture of three spots on the TLC plate) was chromatographed on silica. The first compound to elute was identified as the methyl imidate and was discarded. The second compound was identified as the amide (12 mg, 2%, title compound): off-white

solid; mp 235−236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.63 (s, 1H), 8.42 (d, J = 8.2, 1H), 8.13 (d, J = 1.5, 1H), 7.98 (dd, J = 8.2, J = 1.5, 1H), 7.77 (s, 1H), 7.74 (s, 1H), 7.48 (dt, J_d = 6.4, J_t = 8.8, 1H), 6.9−6.8 (m, 2H), 6.3 (br s, 2H, NH_2), 5.92 (dq, J_d = 1.2, J_q = 7.3, 1H), 5.56 (d, J = 1.3, 1H), 5.16 (d, J = 14.1, 1H), 4.03 (d, J = 14.1, 1H), 1.32 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 216 ($C_{11}H_{11}N_3O_2$).

(1*R*,2*R*)-7-[(Aminosulfonylamino)iminomethyl]-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (61). Proceeding with the above flash chromatography the title product eluted in the third place (80 mg, 13%): white solid; mp 203−206 °C; ^{1}H NMR (300 MHz, MeOH-d_4) 8.59 (s, 1H), 8.39 (d, J = 8.4, 1H), 8.19 (dd, J = 1.5, J = 8.5, 1H), 8.17 (s, 1H), 8.02 (dd, J = 1.7, J = 8.4, 1H), 7.63 (s, 1H), 7.42 (dt, J_t = 6.5, J_d = 9, 1H), 7.05 (ddd, J_d = 2.5, J_d = 8.5, J_d = 14, 1H), 6.89 (dt, J_d = 2.5, J_t = 8.5, 1H), 6.06 (q, J = 7.3, 1H), 5.06 (d, J = 14.2, 1H), 4.22 (d, J = 14.2, 1H), 1.31 (d, J = 7.3, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 199 ($C_{11}H_9N_3O$); $[\alpha]_D$ +35.5° (*c* 0.2, MeOH). Anal. ($C_{21}H_{20}F_2N_8O_4S$) C, H; N: calcd, 21.61; found, 20.19; S: calcd, 6.18; S, 5.49.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-[4-(4-nitrophenyl)-1-piperazinyl]quinazolin-4(3*H*)-one (62). Obtained from the reaction of compound **24** and 4-(4-nitrophenyl)piperazine (57% yield): orange-colored solid; mp 287−289 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (s, 1H), 8.3−8.1 (m, 3H), 7.76 (s, 1H), 7.73 (s, 1H), 7.47 (dt, J_d = 6.5, J_t = 9, 1H), 7.10 (dd, J = 2.3, J = 9.0, 1H), 7.03 (d, J = 2.3, 1H), 6.9−6.7 (m, 4H), 5.92 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.46 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.03 (d, J = 14.2, 1H), 3.67 (s, 8H, pip), 1.28 (d, J = 7.3, 3H); $[\alpha]_D$ −41° (*c* 0.2, $CHCl_3$). Anal. ($C_{30}H_{28}F_2N_8O_4$) C, H, N.

(1*R*,2*R*)-7-[4-(4-Chlorophenyl)-1-piperazinyl]-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (63). Obtained from the reaction of compound **24** and 4-(4-chlorophenyl)piperazine (61% yield): white solid; mp 218−219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.49 (s, 1H), 8.19 (d, J = 8.9, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.47 (dt, J_d = 6.5, J_t = 9, 1H), 7.24 (dt, J_t = 2.8, J_d = 9.6, 2H), 7.14 (dd, J = 2.4, J = 9.0, 1H), 7.06 (d, J = 2.3, 1H), 6.89 (dt, J_t = 2.8, J_d = 9.6, 2H), 6.9−6.7 (m, 2H), 5.91 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.46 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.03 (d, J = 14.2, 1H), 3.6−3.5 (m, 4H, pip), 3.4−3.3 (m, 4H, pip), 1.28 (d, J = 7.3, 3H); MS (DIP) 367 ($C_{20}H_{20}ClN_4O$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ −34.1° (*c* 1, $CHCl_3$). Anal. ($C_{30}H_{28}ClF_2N_7O_2 \cdot {}^1/_2$EtOAc) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-[4-[4-(2,4-dihydro-3*H*-1,2,4-triazol-3-one-4-yl)phenyl]-1-piperazinyl] quinazolin-4(3*H*)-one. (a) A solution of **62** (1.3 g, 2.1 mmol) in EtOH (200 mL) and $CHCl_3$ (5 mL) was treated with Pd/C (5%, 1 g) and H_2 at 1 atm for 24 h. The catalyst was filtered off, and the resulting solution was evaporated to dryness to give the amino derivative as a slighly greenish solid (1.2 g, 100%): mp 170−173 °C; ^{1}H NMR (300 MHz, MeOH-d_4) 8.57 (s, 1H, N=C*H*-N), 8.2−8.0 (m, 2H), 7.90 (s, 1H), 7.39 (dt, J_d = 6.5, J_t = 9, 1H), 7.4−7.0 (m), 7.29 (dt, J_t = 2.2, J_d = 9.3, 1H), 7.15 (ddd, J = 2.4, J = 8.7, J = 11.5, 1H), 6.89 (dt, J_d = 2.5, J_t = 8.5, 1H), 6.05 (q, J_q = 7.3, 1H), 5.06 (d, J = 14.2, 1H), 4.18 (d, J = 14.2, 1H), 3.7−3.5 (m, 4H), 3.5−3.3 (m, 4H), 1.29 (d, J = 7.3, 3H).

(b) A solution of the above product (1.2 g, 2.1 mmol) in pyridine (75 mL) was treated with phenyl chloroformate (393 mg, 2.5 mmol) at 25 °C for 3 h. The reaction was quenched by the addition of 10% aqueous $NaHCO_3$ solution. Next, most of the pyridine was removed in vacuo, and the residue was partitioned between $CHCl_3$ and H_2O. The layers were separated, and the organic phase was dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to give the corresponding phenyl carbamate as a yellowish solid (1.2 g, 83%): mp 137−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ($CDCl_3$) 8.49 (s, 1H), 8.19 (d, J = 8.9, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.47 (dt, J_d = 6.5, J_t = 9, 1H), 7.4−6.5 (m), 5.92 (q, J_q = 7.3, 1H), 5.45 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.03 (d, J = 14.2, 1H), 3.6−3.5 (m, 4H, pip), 3.4−3.3 (m, 4H, pip), 1.28 (d, J = 7.3, 3H); $[\alpha]_D$ +6.0° (*c* 0.2, MeOH).

(c) The above product (1.2 g, 1.7 mmol) was dissolved in 1,2-dimethoxyethane (25 mL) and was treated with hydrazine hydrate (693 mg, 14 mmol) at 80 °C for 3 h. Solvents were removed in vacuo, and the resulting yellowish residue was recrystallized from MeOH−H_2O to give the corresponding semicarbazide as an off-white solid (900 mg, 84%): mp 190−193 °C; ^{1}H NMR (300 MHz, MeOH-d_4) δ (MeOH) 8.45 (s, 1H), 8.17 (s, 1H), 8.12 (d, J = 9.0, 1H), 7.64 (s, 1H), 7.5−7.2 (m), 7.2−6.7 (m), 6.04 (q, J_q = 7.3, 1H), 5.07 (d, J = 14.2, 1H), 4.13 (d, J = 14.2, 1H), 3.6−3.5 (m, 4H, pip), 3.4−3.3 (m, 4H, pip), 1.27 (d, J = 7.3, 3H); $[\alpha]_D$ +5.2° (*c* 0.2, MeOH).

(d) The compound obtained above (900 mg) was dissolved in DMF (10 mL) and treated with formamidine acetate (665 mg, 6.3 mmol) at 80 °C for 3 h. The resulting product was isolated in a manner similar to that described in section (c), and finally it was flash chromatographed to give the title product as an off-white solid (450 mg, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) 10.4 (br s, 1H, N*H*), 8.50 (s, 1H), 8.19 (d, J = 8.9, 1H), 7.77 (s, 1H), 7.72 (s, 1H), 7.63 (s, 1H, triazolone), 7.44 (d, J = 9, 2H), 7.5−7.4 (m, 1H), 7.14 (dd, J = 2.3, J = 9.0, 1H), 7.07 (d, J = 2.3, 1H), 7.00 (d, J = 9, 2H), 6.9−6.7 (m, 2H), 5.90 (q, J = 7.3, 1H), 5.46 (br s, 1H), 5.18 (d, J = 14.2, 1H), 4.03 (d, J = 14.2, 1H), 3.60 (m, 4H, pip), 3.40 (m, 4H, pip), 1.27 (d, J = 7.3, 3H).

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-[4-[4-[2,4-dihydro-2-(3-pentyl)-3*H*-1,2,4-triazol-3-one-4-yl]phenyl]-1-piperazinyl]-quinazolin-4(3*H*)-one (64). A solution of the product obtained above (100 mg) in DMF (5 mL) was treated with Cs_2CO_3 (50 mg, 0.16 mmol) and 3-bromopentane (47 mg, 0.32 mmol) at 65 °C for 18 h. The mixture was partitioned between EtOAc and H_2O, and the organic phase was separated, dried, concentrated, and purified by flash chromatography to give the title compound as a cream-colored solid (70 mg, 27%): mp 206−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.49 (s, 1H), 8.18 (d, J = 8.9, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.64 (s, 1H, triazolone), 7.44 (d, J = 9, 2H), 7.5−7.4 (m, 1H), 7.14 (dd, J = 2.3, J = 9.0, 1H), 7.06 (d, J = 2.3, 1H), 7.02 (d, J = 9, 2H), 6.9−6.7 (m, 2H), 5.91 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.46 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.1−3.9 (m, 1H, C*H*Et$_2$), 4.03 (d, J = 14.2, 1H), 3.60 (m, 4H, pip), 3.39 (m, 4H, pip), 1.9−1.6 (m, 4H, CH(CH_2CH$_3$)$_2$), 1.27 (d, J = 7.3, 3H), 0.88 (t, J = 7.3, 6H, CH-(CH$_2$CH_3)$_2$); MS (DIP) 711 (M^+), 486 ($C_{27}H_{32}N_7O_2$), 224 (C_{10}-$H_8F_2N_3O$); $[\alpha]_D$ −30.3° (*c* 1, $CHCl_3$). Anal. ($C_{37}H_{40}F_2N_{10}O_3$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-6-[4-[4-[2,4-dihydro-2-(3-pentyl)-3*H*-1,2,4-triazol-3-one-4-yl]phenyl]-1-piperazinyl]-quinazolin-4(3*H*)-one (65). Obtained by reaction of 4-[4-[2,4-dihydro-2-(3-pentyl)-3*H*-1,2,4-triazol-3-one-4-yl]phenyl]-1-piperazine and **23** (31% yield): cream-colored solid; 81−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.46 (s, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.7 (m, 2H), 7.64 (s, 1H, triazolone), 7.46 (d, J = 9, 2H), 7.5−7.4 (m, 2H), 7.05 (d,J = 9.0, 2H), 6.9−6.7 (m, 2H), 5.96 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.46 (d, J = 1.5, 1H), 5.19 (d, J = 14.2, 1H), 4.1−3.9 (m, 1H, C*H*Et$_2$), 4.01 (d, J = 14.2, 1H), 3.60 (m, 4H, pip), 3.39 (m, 4H, pip), 1.9−1.6 (m, 4H, CH(CH_2CH$_3$)$_2$), 1.30 (d, J = 7.3, 3H), 0.89 (t, J = 7.3, 6H, CH(CH$_2$CH_3)$_2$); GC−MS 486 ($C_{27}H_{32}N_7O_2$), 224 ($C_{10}H_8F_2N_3O$); $[\alpha]_D$ +20.3° (*c* 1, $CHCl_3$). Anal. ($C_{37}H_{40}F_2N_{10}O_3 \cdot {}^3/_2H_2O$) C, H, N.

(1*R*,2*R*)-3-[2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-7-[4-[4-[2,4-dihydro-2-[(*S*)-1-ethyl-2(*S*)-hydroxypropyl]-3*H*-1,2,4-triazol-3-one-4-yl]-phenyl]-1-piperazinyl]quinazolin-4(3*H*)-one (66). Obtained as **64** but using (3*R*,2*S*)-3-brosyloxy-2-pentanol[17] (23% yield): cream-colored solid; mp 249−252 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.49 (s, 1H), 8.19 (d, J = 8.9, 1H), 7.76 (s, 1H), 7.73 (s, 1H), 7.67 (s, 1H, triazolone), 7.45 (d, J = 9, 2H), 7.5−7.4 (m, 1H), 7.14 (dd, J = 2.3, J = 9.0, 1H), 7.06 (d, J = 2.3, 1H), 7.02 (d, J = 9, 2H), 6.9−6.7 (m, 2H), 5.92 (dq, J_d = 1.5, J_q = 7.3, 1H), 5.46 (d, J = 1.5, 1H), 5.17 (d, J = 14.2, 1H), 4.1−3.9 (m, 2H, C*H*OH and C*H*N), 4.03 (d, J = 14.2, 1H), 3.60 (m, 4H,

pip), 3.39 (m, 4H, pip), 3.08 (d, J = 8.7, 1H, O*H*), 2.1−1.8 (m, 2H, CHCH_2CH$_3$), 1.28 (d, J = 7.3, 3H), 1.22 (d, J = 6.2, 3H, HOCHCH_3), 0.94 (t, J = 7.4, 3H, CHCH$_2$CH_3); $[\alpha]_D$ −26.7° (*c* 0.5, $CHCl_3$). Anal. ($C_{37}H_{40}F_2N_{10}O_4$) C, H, N.

(1*R*,2*R*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2-methylquinazolin-4(3*H*)-one (67). Obtained following the general quinazolinone ring formation procedure but using triethyl orthoacetate (59%): white solid; mp 200−201 °C (EtOH/H_2O); ^{1}H NMR (300 MHz, $CDCl_3$) 8.20 (d, J = 8.6, 1H), 8.17 (s, 1H), 7.8−7.6 (m, 2H), 7.68 (s, 1H), 7.47 (dd, J = 1.9, J = 8.6, 1H), 7.45 (s, 1H), 6.9−6.7 (m, 2H), 5.18 (q, J = 6.9, 1H), 4.80 (dd, J = 1.1, J = 14.0, 1H), 4.32 (d, J = 14.0, 1H), 2.87 (s, 3H, CH_3), 1.39 (d, J = 6.9, 3H); GC/MS 224 ($C_{10}H_8F_2N_3O$), 221 ($C_{11}H_{10}ClN_2O$); $[\alpha]_D$ −59.2° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{18}ClF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2,3-dihydroquinazolin-4(1*H*)-one (68). The procedure described in the literature for a similar reaction was followed.[18] To a solution of compound **20** (250 mg, 0.59 mmol) in EtOH (3 mL) was added aqueous formaldehyde (46 mcL, 0.59 mmol), and the solution was heated at reflux for 4 h. An 80% NaOH aqueous solution (0.2 mL) was added, and the solution was stirred at reflux for 20 min. The cooled mixture was concentrated and partitioned between $CHCl_3$ and water. The organic solution was dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography to a white amorphous solid (190 mg, 74%); mp 62−75 °C (wide range); ^{1}H RMN (300 MHz, $CDCl_3$) 7.9 (d, J = 8.4, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 7.38 (dt, J_d = 6.5, J_t = 9, 1H), 6.89 (dd, J = 1.6, J = 8.4, 1H), 6.9−6.7 (m, 3H), 5.44 (q, J = 6.9, 1H), 5.3−5.1 (m, 3H), 4.75 (dd, J = 1.7, J = 9.9, 1H), 4.50 (s, 1H), 4.48 (d, J = 14.2, 1H), 1.00 (d, J = 6.9, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 209 ($C_{10}H_{10}ClN_2O$); $[\alpha]_D$ −134.0° (*c* 0.5, $CHCl_3$). Anal. ($C_{20}H_{18}ClF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-7-Chloro-3-[2-(2-fluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (69). Obtained following the general procedure using amine **12**:[6] white solid; mp 124−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.65 (s, 1H), 8.31 (d, J = 8.5, 1H), 7.80 (d, J = 1.9, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.6−7.4 (m, 2H), 7.3−7.2 (m, 1H), 7.2−7.0 (m, 2H), 6.02 (dq, J_d = 1.2, J_q = 7.3, 1H), 5.47 (d, J = 1.3, 1H), 5.24 (d, J = 14.1, 1H), 4.05 (d, J = 14.1, 1H), 1.31 (d, J = 7.3, 3H); GC−MS 207 ($C_{10}H_9ClN_2O$), 206 ($C_{10}H_9FN_3O$); $[\alpha]_D$ −9.0° (*c* 0.5, $CHCl_3$). Anal. ($C_{20}H_{17}ClFN_5O_2$) C, H, N.

(1*R*,2*R*)-7-Chloro-3-[2-(2,4-dichlorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (70). Obtained following the general procedure using amine **13**:[5] white solid; mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.57 (s, 1H), 8.26 (d, J = 8.6, 1H), 7.81 (s, 1H), 7.76 (d, J = 2, 1H), 7.73 (s, 1H), 7.62 (d, J = 8.6, 1H), 7.49 (dd, J = 2, J = 8.6, 1H), 7.38 (d, J = 2.2, 1H), 7.17 (dd, J = 2.2, J = 8.6, 1H), 6.40 (dq, J_d=1.7, J_q=7.3, 1H), 5.74 (d, J = 14.3, 1H) 5.64 (d, J = 1.8, 1H), 3.96 (d, J = 14.3, 1H), 1.26 (d, J = 7.3, 3H); GC−MS 208 and 210 ($C_{10}H_9ClN_2O$), 256 and 258 ($C_{10}H_8Cl_2N_3O$); $[\alpha]_D$= −46.6° (*c* 0.12, $CHCl_3$). Anal. ($C_{20}H_{16}Cl_3N_5O_2$) C, H, N.

(1*R*,2*R*)-4-Chloro-2-formamido*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]benzamide (71). To a solution of 3.0 g of **20** (7 mmol) in 75 mL of THF was added 150 mL of 0.1 N NaOH aqueous solution. The mixture was stirred at room temperature for 3 h. The product was extracted with EtOAc (×3). The collected organic fractions were washed with 0.1 N HCl aqueous solution and brine and dried over anhydrous Na_2SO_4, the drying agent was filtered, and the filtrate was concentrated and purified by flash chromatography to give the title compound (25% yield): white solid; mp 160−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 11.22 (br s, 1H), 8.78 (d, J = 1.9, 1H), 8.48 (d, J = 1.3, 1H), 7.81 (s, 1H), 7.78 (s, 1H), 7.53 (d, J = 8.5, 1H), 7.37 (dt, J_d = 6.5, J_t = 9, 1H), 7.15 (dd, J = 2.0, J = 8.4, 1H), 6.8−6.7 (m, 3H), 5.40 (d, J = 1.3, 1H), 5.01 (d, J = 14.2, 1H), 4.93 (quint, J = 6.9, 1H), 4.46 (d, J = 14.2, 1H), 1.02 (d, J = 6.9, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ −99.8° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{18}ClF_2N_5O_3$) C, H, N.

(1*R*,2*R*)-2-Amino-4-chloro-*N*-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]benzamide (72). Obtained from the reaction of amine **11** and 4-chloroanthranilic acid, following the general procedure (first step) (ca. 100% yield): white foam; ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 (s, 1H), 7.77 (s, 1H), 7.37 (dt, J_d = 6.5, J_t = 9, 1H), 7.33 (d, J = 8.4, 1H), 6.8−6.6 (m, 4H), 6.59 (br d, J = 9.3, 1H, N*H*), 5.74 (br s, 2H, NH_2), 5.32 (d, J = 1.3, 1H), 5.02 (d, J = 14.2, 1H), 4.94 (quint, J = 6.9, 1H), 4.48 (d, J = 14.2, 1H), 0.99 (d, J = 6.9, 3H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 197 ($C_9H_{10}ClN_2O$), 154 (C_7H_5ClNO); $[\alpha]_D$ −90.8° (*c* 1, $CHCl_3$). Anal. ($C_{19}H_{18}ClF_2N_5O_2$) C, H, N.

(1*R*,2*R*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-imidazol-1-yl)propyl]quinazolin-4(3*H*)-one (73). Obtained following the general procedure using amine **14**:[6] white solid; mp 142−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (ca. 1:1 mixture of two rotamers) 8.50 (s, $^1/_2$H), 8.32 (d, J = 8.6, $^1/_2$H), 8.27 (d, J = 8.6, $^1/_2$H), 8.12 (s, $^1/_2$H), 7.8−7.5 (m), 7.28 (s), 7.04 (s, $^1/_2$H), 7.0−6.7 (m), 6.32 (s, $^1/_2$H), 6.07 (s, $^1/_2$H), 5.89 (q, J = 7.3, $^1/_2$H), 4.83 (d, J = 14.5, $^1/_2$H), 4.68 (q, J = 6.9, $^1/_2$H) 4.48 (dd, J = 2.4, J = 14.2, $^1/_2$H), 3.92 (d, J = 14.2, $^1/_2$H), 3.72 (d, J = 14.5, $^1/_2$H), 1.44 (d, J = 6.9, $^3/_2$H), 1.27 (d, J = 7.2, $^3/_2$H); GC−MS 430 (M^+), 223 ($C_{11}H_9F_2N_2O$), 207 ($C_{10}H_8ClN_2O$); $[\alpha]_D$ +72.5° (*c* 1, $CHCl_3$). Anal. ($C_{21}H_{17}ClF_2N_4O_2\cdot{}^1/_2$EtOAc) C, H, N.

(1*S*,2*S*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (74). Obtained as a white amorphous solid, from the diastereomer (1*S*,2*S*) of amine **11**:[6] GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ +8.8° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}ClF_2N_5O_2$) C, H, N.

(1*R,2*R**)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (75).** Obtained as a white solid, from racemic amine **11**:[5] mp 242−243 °C; GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$). Anal. ($C_{20}H_{16}ClF_2N_5O_2$) C, H, N.

(1*R*,2*S*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (76). Obtained as a white, amorphous solid, from the diastereomer (1*R*,2*S*) of amine **11**:[6] mp 85−89 °C (EtOH/H_2O); ^{1}H NMR (300 MHz, $CDCl_3$) (ca. 1:1 mixture of two rotamers) 8.41 (s, $^1/_2$H), 8.17 (s, $^1/_2$H), 8.02 (d, J = 8.6, $^1/_2$H), 7.9−7.8 (m), 7.79 (s, $^1/_2$H), 7.75 (s, $^1/_2$H), 7.60 (s, 1H), 7.5−7.2 (m), 7.12 (q, J = 8.8, $^1/_2$H), 6.89 (s, $^1/_2$H), 6.8−6.6 (m, $^3/_2$H), 6.43 (t, J = 7.4, $^1/_2$H), 5.85 (q, J = 6.8, $^1/_2$H), 5.47 (s, $^1/_2$H), 5.15 (d, J = 14, $^1/_2$H), 4.85 (q, J = 6.9, $^1/_2$H), 4.65 (s, $^1/_2$H), 4.60 (d, J = 14, $^1/_2$H), 1.74 (d, J = 7.1, $^3/_2$H), 1.51 (d, J = 6.9, $^3/_2$H); GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ +45.0° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}ClF_2N_5O_2\cdot{}^1/_2H_2O$) C, H, N.

(1*S*,2*R*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one (77). Obtained as a white amorphous solid from the diastereomer (1*S*,2*R*) of amine **11**:[6] mp 83−87 °C (EtOH/H_2O); GC−MS 224 ($C_{10}H_8F_2N_3O$), 208 ($C_{10}H_9ClN_2O$); $[\alpha]_D$ −46.1° (*c* 1, $CHCl_3$). Anal. ($C_{20}H_{16}ClF_2N_5O_2\cdot{}^1/_2H_2O$) C, H, N.

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 an 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, μg/mL) 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.

Systemic Candidosis in Mice. An in vivo murine candidosis model was used to monitor the antifungal activity of

the test compounds.[2] Groups of 10 male mice were inoculated iv with 0.2 mL of a suspension containing 2 to 8 × 10^7 cfu/mL of *C. 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 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 dosis.

Systemic Candidosis in Rabbit. Groups of 10 male New Zealand rabbits were inoculated iv with *C. albicans* (1.2 × 10^7 cfu/kg). Compounds were administered orally as suspensions in 1% Tween 80 + 0.2% carboxymethylcellulose in distilled water, 4 h after infection (day 0), qd (i.e., once a day) for 6 additional days. The control group received only the vehicle. Rabbits were killed on day 7. Kidneys and lungs were excised and homogenized in 1 mL saline per gram of wet tissue. An aliquot of the homogenate was added to Sabouraud agar and incubated for cell count (37 °C, 7 days). Results were expressed as the log cfu per gram of wet tissue.

Systemic Aspergillosis in Rat. Groups of 10 male Sprague−Dawley rats were immunosuppressed with 1 mg/kg/day po of dexamethasone 21-acetate, starting 4 days before the iv inoculation of *A. fumigatus* (4.6 × 10^5 cfu/animal). Compound **20** was administered orally as a suspension in 1% Tween 80 + 0.2% carboxymethylcellulose in distilled water, 1 and 8 h after infection (day 0), and bid (i.e., twice daily) for 6 additional days. Amphotericin B was administered iv qd and served as a positive standard. The control group received po, twice daily the vehicle used with compound **20**. Rats were killed on day 7. Livers were excised and homogenized in 1 mL saline per gram of wet tissue. An aliquot of the homogenate was added to Sabouraud agar and incubated for cell count (37 °C, 7 days). Results were expressed as the log cfu per gram of liver.

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Supporting Information Available: Individual MIC values for each final compound (Table 10) (3 pages). Ordering information is given on any current masthead page.

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