Synthesis and Antifungal Activity of Novel Thiazole-Containing Triazole Antifungals. II.[1] Optically Active ER-30346 and Its Derivatives

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A series of novel thiazole-containing triazole antifungals was synthesized and evaluated for antifungal activity against a variety of clinically isolated pathogenic fungi *in vitro* and against systemic candidosis *in vivo*. These compounds showed potent antifungal activities *in vitro* and *in vivo*. In particular, (2*R*,3*R*)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12g; ER-30346) showed potent and well-balanced *in vitro* activities and potent *in vivo* efficacy, and had a good safety profile.

Key words thiazole-containing triazole antifungal; antifungal activity; ER-30346

Life-threatening, deep-seated fungal infections may become established in immunocompromised patients who have received cancer chemotherapy, or immunosuppressive agents. Patients with AIDS and AIDS-related complex are also susceptible to fungal infections.[2] For the treatment of these infections, orally active antifungal azoles, such as fluconazole[3] (FLCZ, **4**), and itraconazole[4] (ITZ, **5**), are in clinical use. However, in recent years, the development of resistance to FLCZ in *Candida* spp. has been reported.[5] Consequently, new antifungal agents are needed.

In a previous paper,[1] we reported the synthesis and antifungal activity of thiazole-containing triazole antifungals **1**. Among a series of triazoles **1**, we chose ER-24161 (**2**) as a candidate for further evaluation, based on its *in vitro* and *in vivo* activity. In a preliminary toxicological study in rats, however, ER-24161 (**2**) showed significant hepatotoxicity, and the evaluation was suspended. We continued to search for more effective, broader-spectrum, and safer drugs based on the fundamental structure **1**. We found that new thiazole-containing optically active triazoles represented by the general formula **3** (Chart 1) exhibited more potent antifungal activity and a better safety profile compared with the series of compounds **1**.[6] In this paper, we describe the synthesis and antifungal activity of a series of compounds **3** against *Aspergillus fumigatus* (*A. fumigatus*), *Candida albicans* (*C. albicans*), *Cryptococcus neoformans* (*C. neoformans*), and *Candida glabrata* (*C. glabrata*) *in vitro* and against *C. albicans in vivo*.

Chemistry In order to construct a thiazole or benzothiazole moiety in the general formula **3**, a cyano, thioamide or formyl substituent is necessary at the 3-position as a key precursor of the thiazole ring.

A series of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-substituted thiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**12a—j**) was synthesized from (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)methyloxirane (**6**) in three steps as shown in Chart 2. The most promising method to obtain a chiral β-hydroxy nitrile seemed to be ring-opening reaction of an oxirane with cyanide anion. The optically active oxirane (**6**) was prepared by using a known method.[7] Reaction of **6** with diethylaluminum cyanide (Et_2AlCN) in toluene at 50 °C gave the optically active nitrile (**7**) in 57% yield on gram-scale. This reaction proceeded in regio- and stereospecifically, and no other isomer of **7** was isolated. However, this method is not suitable for kilogram-scale synthesis because of the dangerous work-up with aqueous hydrochloric acid. So we also developed a practical synthetic process in which

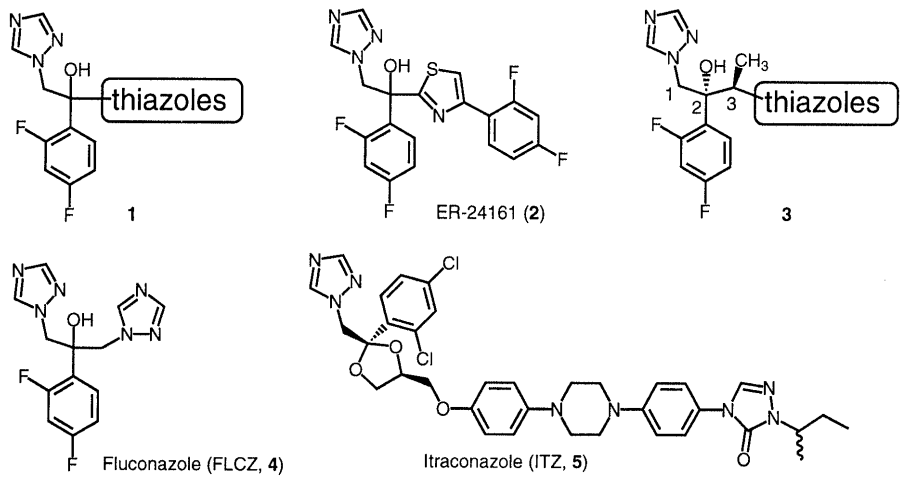

Chart 1

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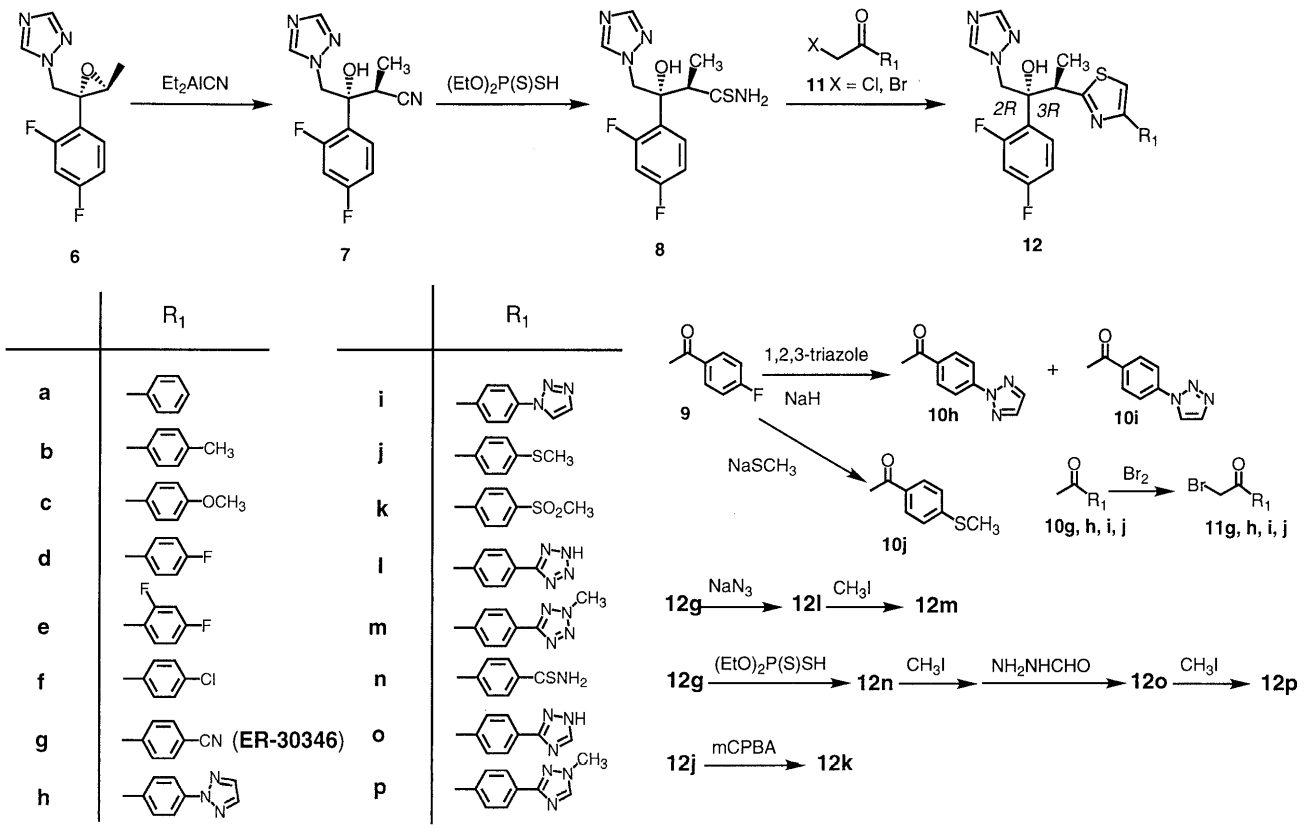


Chart 2

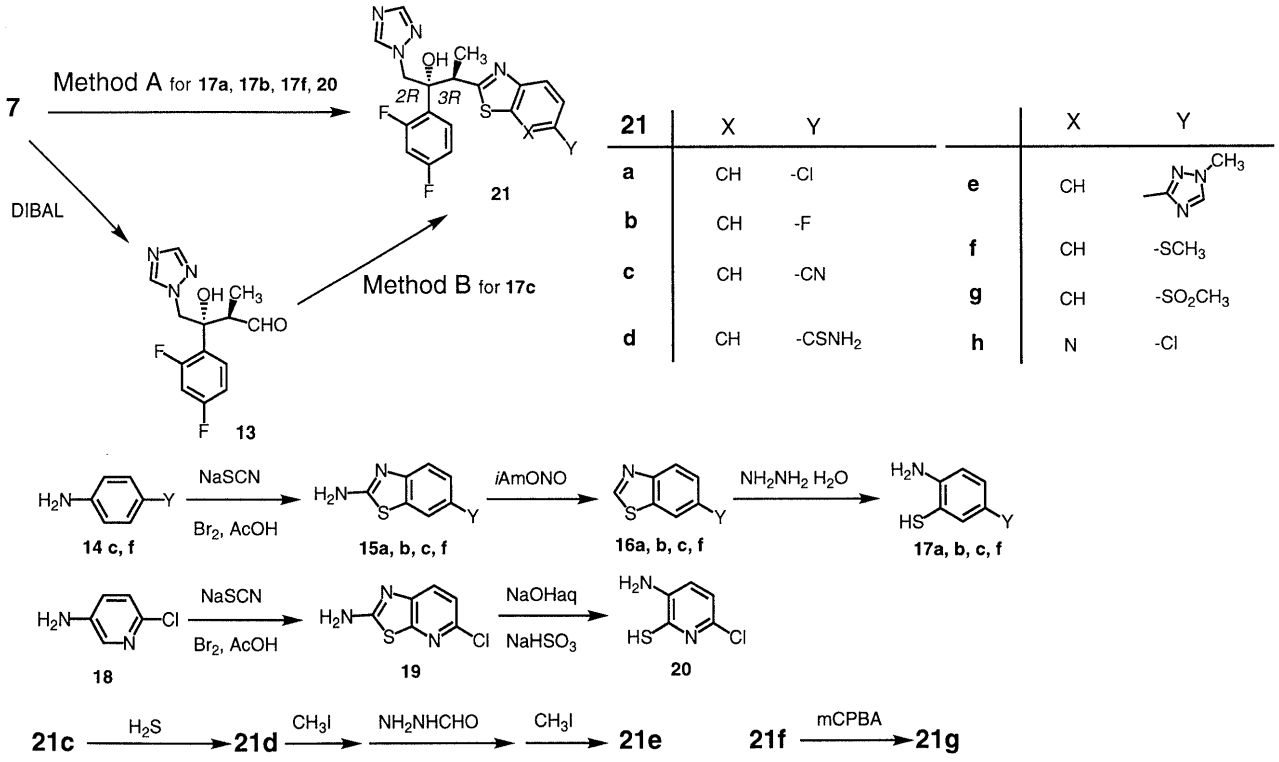
6 was converted to **7** by heating with LiCN.[8] The resultant nitrile (**7**) was reacted with diethyl dithiophosphate in aqueous 2-propanol (IPA) under reflux to afford the corresponding chiral thioamide (**8**) in 81% yield.

Several α-haloketones (**11a—f**) and **10g** were obtained from commercial suppliers. Others (**11g—j**) were prepared as described below (Chart 2). Reaction of 4′-fluoroacetophenone (**9**) with 1, 2, 3-triazole in the presence of sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) gave **10h** and **10i** in 50% and 23% yields, respectively. Reaction of 4′-fluoroacetophenone (**9**) with sodium thiomethoxide in DMF gave **10j** in 28% yield. Reaction of acetophenone derivatives (**10g—j**) with bromine gave the α-haloketones (**11g—j**) in 30—84% yield.[9] The thioamide (**8**) was reacted with **11a—j** in EtOH under reflux to afford the triazoles (**12a—j**) having a 4-substituted thiazole moiety in 60—93% yield.

4′-Substituents on the phenyl ring at the 4 position of the thiazole moiety were modified to obtain the derivatives **12k—p**. The methylsulfone (**12k**) was prepared from **12j** by treatment with *m*-chloroperbenzoic acid (mCPBA) in 67% yield. Tetrazole substituents (**12l**, **12m**) and triazole substituents (**12o**, **12p**) were derived from the nitrile group of **12g** as follows. Reaction of **12g** with sodium azide (NaN_3) in *N*-methylpyrrolidone gave a tetrazole (**12l**) in 60% yield. The tetrazole (**12l**) was reacted with iodomethane in the presence of cesium carbonate in DMF to afford **12m** in 55% yield. Reaction of **12g** with diethyl dithiophosphate in aqueous IPA gave a thioamide (**12n**). A triazole (**12o**) was prepared by thioimidation of **12n** with iodomethane followed by reaction with formic hydrazide. Methylation of **12o** with iodomethane in the presence of potassium carbonate in acetone gave **12p** in 67% yield.

A series of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(6-substituted benzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**21a—h**) was synthesized from **7** as shown in Chart 3. In general, 2-aminothiophenol derivatives having a halogen or an electron-donating group such as **17a**, **17b**, **17f** and **20** could react with the cyano group of **7** to generate the benzothiazole ring of **21**. As the reactivity of **17** having an electron-withdrawing group, such as a cyano group (**17c**), was decreased, the corresponding benzothiazole could not be obtained by method A. Therefore, the formyl derivative (**13**) obtained by reduction of **7** with diisobutylaluminum hydride (DIBAL) was employed as a precursor of **21**.

2-Aminothiophenol derivatives (**17a—c, f**) and the aza analogue (**20**) were prepared as follows (Chart 3). 2-Aminobenzothiazoles (**15a**, **15b**) were obtained from commercial suppliers. Reaction of aniline derivatives (**14c**, **14f**) with sodium thiocyanate (NaSCN) in the presence of bromine in acetic acid gave 2-aminobenzothiazoles (**15c**, **15f**). Deamination of **15** with isoamyl nitrite (*i*AmONO) gave benzothiazoles (**16a—c, f**). 2-Aminothiophenol derivatives (**17a—c, f**) were synthesized by reaction of benzothiazoles (**16a—c, f**) with hydrazine monohydrate. 5-Amino-2-chloropyridine (**18**) was converted to a 2-aminobenzothiazole (**19**) by treatment with NaSCN under the same conditions as described above. This compound (**19**) was treated with an aqueous solution of sodium hydroxide to afford **20**. The above 2-aminothiophenols (**17a—c, f, 20**) were used for the next reaction immediately without further purification because of their tendency to form the disulfides.



21	X	Y		X	Y
a	CH	-Cl	e	CH	
b	CH	-F	f	CH	$-SCH_3$
c	CH	-CN	g	CH	$-SO_2CH_3$
d	CH	$-CSNH_2$	h	N	-Cl

Chart 3

Compounds **21a, 21b**, **21f** and **21h** were prepared by the reaction of the nitrile (**7**) with **17a**, **17b**, **17f**, and **20** in the presence of diethyl dithiophosphate as an acid catalyst in chloroform ($CHCl_3$) under reflux (method A).

Compound **21c** was prepared according to method B. The aldehyde (**13**) was treated with **17c** in the presence of pyridinium *p*-toluenesulfonate (PPTS) in IPA to afford **21c** in 53% yield.

This compound (**21c**) was reacted with H_2S gas in the presence of Et_3N in DMF to afford the thioamide (**21d**). The methyltriazole (**21e**) was synthesized from **21c** by using the same procedure as described for **12p**. The methylsulfone (**21g**) was prepared from **21f** by treatment with mCPBA in 76% yield.

Antifungal Activity Antifungal activity of the thiazole-containing triazoles (**12a—p**, **21a—h**) was examined against clinical isolates of *A. fumigatus*, *C. albicans*, *C. neoformans*, and *C. glabrata*. Minimum antibiotic concentrations (MACs) were determined on Sabouraud dextrose agar incubated at 37 °C for 48 h. MAC was determined as the lowest drug concentration which showed clear inhibition of fungal growth compared with the control fungal growth. We also investigated the therapeutic effects of the compounds against experimental candidosis infection caused by *C. albicans* MCY8622 *in vivo*. *C. albicans* MCY8622 (2×10^6 cells/mouse) was given intravenously to mice and compounds were orally administered once at 1 h after infection. Efficacy was expressed in terms of the mean survival days calculated based on termination of the experiment 7 d after infection.

The results of *in vitro* and *in vivo* studies on (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-substituted thiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**12a—p**) are shown in Table 1. Compounds **12g** and **12m** showed excellent *in vitro* activity against *A. fumigatus*, comparable to that of ITZ (**5**). Other compounds showed moderate activity against *A. fumigatus*, whereas compounds **12e** and **12p** showed weak activity.

All compounds, except compounds **12l** and **12o**, which have a 2*H*-1,2,3,4-tetrazole group and a 2*H*-1,2,4-triazole group, respectively, on the phenyl substituent at the 4-position of the thiazole moiety, showed potent *in vitro* activity against *C. albicans*. In particular, compounds **12g**, **12j**, **12m** and **12p** showed excellent *in vitro* activity against *C. albicans*, comparable to that of ITZ (**5**). Compounds **12k**, **12l** and **12o** showed poor activity, whereas other compounds showed moderate to potent activity against *C. neoformans* and *C. glabrata*.

Compounds **12g**, and **12k**, which have an electron-withdrawing substituent such as a cyano group or sulfonylmethyl group, on the phenyl substituent at the 4-position of the thiazole moiety, showed potent protective effects comparable to that of FLCZ (**4**) in a murine candidosis model. Compounds **12h**, and **12p**, which have a triazole moiety on the phenyl substituent at the 4-position of the thiazole moiety, showed also potent protective effects comparable to that of FLCZ (**4**) in a murine candidosis model. Though the methyl sulfide (**12j**) also showed potent protective effects in a murine candidosis model, we found that **12j** was immediately metabolized to the methylsulfone (**12k**) *in vivo*.

On the other hand, compounds **12b** and **12c**, which have an electron-donating methyl group and methoxyl group, respectively, on the phenyl group, and compound **12a**, which has an unsubstituted phenyl group, showed poor activity *in vivo*. Compound **12l**, which have a tetrazole moiety on the phenyl substituent at the 4-position of the thiazole moiety, showed also poor activity *in vivo*.

Table 1. Antifungal Activity of (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(4-substituted thiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**12a—p**)

Compound No.	*In vitro* MAC (μg/ml)						*In vivo* murine systemic candidosis (mean survival days)	
	A. fumigatus TIMM0069	*A. fumigatus* TIMM0070	*C. albicans* MCY8622	*C. albicans* M1012	*C. neoformans* AJK4290	*C. glabrata* MCY86111	2.5 mg/kg	10 mg/kg
12a	0.05	0.2	0.013	0.013	0.1	0.05	3.4	4.6
12b	0.2	0.4	0.006	0.013	0.1	0.05	3.6	4.6
12c	0.2	0.2	0.006	0.013	0.1	0.05	4.2	5.0
12d	0.4	0.4	0.013	0.013	0.025	0.05	4.4	5.6
12e	0.8	0.8	0.013	0.006	0.05	0.025	5.0	6.8
12f	0.4	0.4	0.013	0.013	0.025	0.025	4.4	6.2
12g	<0.006	<0.006	<0.006	0.013	0.05	0.05	6.6	6.6
12h	0.2	0.2	0.013	0.013	0.05	0.1	7.0	7.0
12i	0.05	0.05	0.013	0.013	0.05	0.05	5.2	6.6
12j	0.013	0.013	<0.006	<0.006	0.1	0.1	6.8	7.0
12k	0.2	0.4	0.025	0.05	1.56	0.8	6.6	7.0
12l	0.1	0.4	0.1	0.8	3.13	3.13	2.4	3.4
12m	<0.006	<0.006	<0.006	0.025	0.2	0.1	5.6	6.2
12o	0.4	0.8	0.05	0.1	3.13	1.56	3.4	6.8
12p	0.8	1.56	0.006	0.006	0.8	0.2	7.0	7.0
FLCZ (**4**)	50	50	0.2	0.8	12.5	12.5	7.0	7.0
ITZ (**5**)	<0.006	<0.006	<0.006	<0.006	0.025	0.05	3.6	4.4
Control							2.6	

Table 2. Antifungal Activity of (2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(6-substituted benzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**21a—h**)

Compound No.	*In vitro* MAC (μg/ml)						*In vivo* murine systemic candidosis (mean survival days)	
	A. fumigatus TIMM0069	*A. fumigatus* TIMM0070	*C. albicans* MCY8622	*C. albicans* MCY1012	*C. neoformans* AJK4290	*C. glabrata* MCY86111	2.5 mg/kg	10 mg/kg
21a	<0.006	<0.006	<0.006	<0.006	0.025	0.025	7.0	7.0
21b	0.013	0.013	<0.006	0.013	0.025	0.025	7.0	6.2
21c	0.025	0.025	<0.006	<0.006	0.05	0.05	7.0	7.0
21d	0.05	0.05	0.013	0.05	0.2	0.4	6.6	6.0
21e	0.8	0.8	<0.006	0.025	0.2	0.2	7.0	7.0
21f	0.013	0.013	<0.006	<0.006	0.025	0.025	7.0	7.0
21g	0.025	0.025	0.025	0.1	1.56	1.56	7.0	7.0
21h	0.1	0.1	0.013	0.025	0.1	0.1	6.0	6.8
FLCZ (**4**)	50	50	0.2	0.8	12.5	12.5	7.0	7.0
ITZ (**5**)	<0.006	<0.006	<0.006	<0.006	0.025	0.05	3.6	4.4
Control							2.6	

The results of *in vitro* and *in vivo* studies on the (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(6-substituted benzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols (**21a—h**) are summarized in Table 2. Compound **21a** showed excellent *in vitro* activity against *A. fumigatus*, comparable to that of ITZ (**5**). Other compounds showed moderate to potent *in vitro* activity against *A. fumigatus*. Compounds **21a**, **21b**, **21c**, **21e** and **21f** showed excellent *in vitro* activity against *C. albicans*, comparable to that of ITZ (**5**). Other compounds showed potent *in vitro* activity against *C. albicans*. Compounds **21a**, **21b** and **21f** showed excellent *in vitro* activities against *C. neoformans* and *C. glabrata*, comparable to that of ITZ (**5**). Other compounds showed moderate to potent *in vitro* activity against *C. neoformans* and *C. glabrata*. The *in vivo* efficacy of all compounds against candidosis was comparable to that of FLCZ (**4**) and higher than that of ITZ (**5**).

In conclusion, we have synthesized a series of novel thiazole-containing triazole antifungals, some of which show potent antifungal activities *in vitro* against a variety of pathogenic fungi and *in vivo* against systemic candidosis.

After these compounds, which showed potent protective effects comparable to that of FLCZ (**4**) in a murine candidosis model, had been evaluated for efficacy against murine respiratory aspergillosis,[7,10] three candidates (**12g**; ER-30346, **12k**; ER-32408, **21h**; ER-29390) were selected. Finally, after preliminary pharmacokinetic and toxicological studies in rats and dogs, **12g** (ER-30346) was selected for further evaluation.[10]

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a Nicolet 205 FT-IR spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra (MS) were obtained on a JEOL JMS-HX100 mass spectrometer. The optical rotations were recorded with a JASCO DIP 1000 digital polarimeter.

Silica gel (Kieselgel 60, Merck) was used for column chromatography,

and silica gel (Kieselgel 60 F_{254}, layer thickness 0.25 mm, Merck) for analytical thin layer chromatography (TLC). All organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed with a rotary evaporator under reduced pressure.

(2*S*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butyronitrile (7) A 1.0 M solution of Et_2AlCN in toluene (80 ml, 80.0 mmol) was added to a solution of **6** (5 g, 20.0 mmol) in toluene (40 ml) and the mixture was heated at 50 °C for 12 h under an N_2 atmosphere, then cooled. Water (10 ml) and 1 N hydrochloric acid (120 ml) were added to it with stirring for 2 h at room temperature. The mixture was filtered, and the filtrate was extracted with ethyl acetate (AcOEt). The organic extract was washed with a mixture of water and brine (1 : 1, 4 times) and brine, dried, and evaporated. The resulting solid was washed with diisopropyl ether to give **7** (3.15 g, 57%) as pale grey prisms. mp 179—182 °C. $[\alpha]_D$ −26.9° (c=0.13, MeOH, 24 °C). IR ($CHCl_3$): 2225, 1434, 1141, 1069 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=7.2 Hz), 3.29 (1H, q, J=7.2 Hz), 4.82 (1H, d, J=14.0 Hz), 4.97 (1H, d, J=14.0 Hz), 5.44 (1H, d, J=0.8 Hz), 6.74—6.82 (2H, m), 7.39—7.46 (1H, m), 7.83 (1H, s), 7.84 (1H, s). *Anal.* Calcd for $C_{13}H_{12}F_2N_4O$: C, 56.11; H, 4.35; N, 20.13. Found: C, 56.27; H, 4.35; N, 20.24.

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)thiobutanamide (8) A mixture of **7** (130 g, 0.45 mol) and diethyl dithiophosphate (299 ml, 1.89 mol) in water (104 ml) and 2-propanol (130 ml) was heated under reflux for 3 h. After addition of AcOEt (500 ml) and 1 N NaOH (3.15 l) to the reaction mixture, the mixture was extracted with AcOEt (1 l). The organic extract was washed with a solution of 5% K_2CO_3 (1 l), water (1 l) and brine (1 l), dried, and evaporated. The resulting solid was recrystallized from diisopropyl ether (250 ml) to give **8** (127.4 g, 81%) as pale grey prisms. mp 132—134 °C. $[\alpha]_D$ −143.9° (c=0.16, MeOH, 24 °C). IR ($CHCl_3$): 1422, 1141, 1101 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=7.1 Hz), 3.67—3.72 (1H, m), 4.55 (1H, d, J=14.3 Hz), 6.71—6.80 (2H, m), 7.42—7.48 (1H, m), 7.80 (2H, br s), 7.94 (1H, s), 8.41 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}F_2N_4OS$: C, 49.99; H, 4.52; N, 17.94. Found: C, 50.11; H, 4.50; N, 17.92.

2-Bromo-4′-cyanoacetophenone (11g) Bromine (11.0 g, 70.0 mmol) was added dropwise to a mixture of 4-acetylbenzonitrile (10.0 g, 71.0 mmol) and aluminum chloride (0.2 g) in AcOEt (50 ml) with stirring at 10 °C for 5 min. The mixture was stirred at room temperature for 10 min, then evaporated. Methanol (40 ml) and water (40 ml) was added to the residue with stirring at room temperature. The precipitate was collected by filtration, and recrystallized from methanol to give **11g** (10.8 g, 70%) as colorless prisms. mp 82—84 °C. IR ($CHCl_3$): 2235, 1711, 1690, 1608, 1477 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.44 (2H, m), 7.81—7.84 (2H, m), 8.09 (1H, d, J=8 Hz), 8.23 (1H, d, J=8 Hz). *Anal.* Calcd for C_9H_6BrNO: C, 48.25; H, 2.70; N, 6.25. Found: C, 47.99; H, 2.72; N, 6.08.

4′-(2*H*-1,2,3-Triazol-2-yl)acetophenone (10h) and 4′-(1*H*-1,2,3-Triazol-1-yl)acetophenone (10i) NaH (2.74 g, 60% oil dispersion, 68.4 mmol) was added portionwise to a solution of 1,2,3-triazole (4.94 g, 71.5 mmol) in DMF (60 ml) with stirring at room temperature. The mixture was stirred for 15 min at the same temperature and a solution of 4′-fluoroacetophenone (8.58 g, 62.2 mmol) in DMF (10 ml) was added to it. The whole was heated at 80 °C for 1 h, then cooled, diluted with water, and extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The resulting solid was recrystallized from AcOEt to give **10h** (8.78 g, 50%) as colorless needles. The mother liquor was evaporated. The residue was chromatographed on silica gel (100 g, 5% MeOH–dichloromethane) to give **10i** (2.66 g, 23%) as colorless prisms. Compound **10h**: mp 101—102 °C. IR ($CHCl_3$): 1683, 1604, 1409, 1384 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (3H, s), 7.89 (2H, d, J=11.5 Hz), 7.90 (1H, d, J=1.5 Hz), 8.09 (1H, d, J=1.5 Hz), 8.14 (2H, d, J=11.5 Hz). *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.16; H, 4.87; N, 22.30. Compound **10i**: mp 169—172 °C. IR ($CHCl_3$): 1683, 1606, 1446, 1360 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 7.87 (2H, s), 8.10 (2H, d, J=11.5 Hz), 8.20 (2H, d, J=11.5 Hz). *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.28; H, 4.78; N, 22.62.

2-Bromo-4′-(2*H*-1,2,3-triazol-2-yl)acetophenone (11h) Compound **10h** (0.91 g, 4.87 mmol) and bromine (0.25 ml, 4.87 mmol) were treated according to the same procedure as described for the preparation of **11g** to afford **11h** (1.09 g, 84%) as colorless prisms. mp 134—136 °C. IR ($CHCl_3$): 1683, 1605, 1591, 1429, 1385 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.47 (2H, s), 7.91 (1H, d, J=1.5 Hz), 7.94 (2H, d, J=11.5 Hz), 8.10 (1H, d, J=1.5 Hz), 8.18 (2H, d, J=11.5 Hz). *Anal.* Calcd for $C_{10}H_8BrN_3O$: C, 45.14; H, 3.03; N, 15.79. Found: C, 45.15; H, 3.06; N, 15.69.

2-Bromo-4′-(1*H*-1,2,3-triazol-1-yl)acetophenone (11i) Compound **10i** (0.74 g, 3.97 mmol) and bromine (0.20 ml, 3.89 mmol) were treated according to the same procedure as described for the preparation of **11g** to afford **11i** (0.82 g, 78%). mp 213—217 °C. IR ($CHCl_3$): 1687, 1606, 1477, 1425 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.47 (2H, s), 7.89 (2H, s), 8.13 (2H, d, J=11 Hz), 8.24 (2H, d, J=11 Hz). *Anal.* Calcd for $C_{10}H_8BrN_3O$: C, 45.14; H, 3.03; N, 15.79. Found: C, 45.10; H, 2.94; N, 15.65.

4′-Methylthioacetophenone (10j) Sodium thiomethoxide (5.0 g, 71.43 mmol) in DMF (10 ml) was added to a solution of 4′-fluoroacetophenone (8.95 g, 64.86 mmol) in DMF (100 ml) with stirring at room temperature. The mixture was stirred at the same temperature for 4 h. The mixture was neutralized with 1 N HCl and then extracted with AcOEt. The organic extract was washed with water, and brine, dried, and evaporated. The resulting solid was recrystallized from diisopropyl ether to afford **10j** (2.98 g, 28%) as a pale brown solid. mp 50 °C. IR ($CHCl_3$): 1682, 1434, 1267 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.52 (3H, s), 2.57 (3H, s), 7.27 (2H, br d, J=8.4 Hz), 7.87 (2H, br d, J=8.4 Hz). *Anal.* Calcd for $C_9H_{10}OS$: C, 65.02; H, 6.06. Found: C, 64.87; H, 5.97.

2-Bromo-4′-methylthioacetophenone (11j) Compound **10j** (1000 mg, 6.05 mmol) and bromine (0.31 ml, 6.05 mmol) were treated according to the same procedure as described for the preparation of **11g** to afford **11j** (440 mg, 30%) as a pale brown solid. Compound **11j** was used for the next step without further purification. IR ($CHCl_3$): 1694, 1590, 1477, 1428 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.53 (3H, s), 4.40 (2H, s), 7.28 (2H, d, J=8.4 Hz), 7.89 (2H, d, J=8.4 Hz).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(4-phenylthiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12a) A mixture of **8** (500 mg, 1.6 mmol) and 2-bromoacetophenone (**11a**) (351 mg, 1.76 mmol) in EtOH (5 ml) was heated under reflux for 2 h. After addition of water, the mixture was extracted with AcOEt. The organic extract was washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, dried, and evaporated. The residue was chromatographed on silica gel (30 g, 1% MeOH–CH_2Cl_2) to give a solid (546 mg), which was recrystallized from diisopropyl ether–*n*-hexane to afford **12a** (395 mg, 60%) as a colorless powder. mp 95—96 °C. $[\alpha]_D$ −31.3° (c=0.15, MeOH, 24 °C). IR ($CHCl_3$): 1620, 1420, 1350, 1138 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=7.1 Hz), 4.07 (1H, q, J=7.1 Hz), 4.28 (1H, d, J=14.3 Hz), 4.90 (1H, d, J=14.3 Hz), 6.76—6.84 (2H, m), 7.37—7.41 (1H, m), 7.46—7.54 (4H, m), 7.67 (1H, s), 7.90—7.93 (2H, m), 7.95 (1H, s). *Anal.* Calcd for $C_{21}H_{18}F_2N_4OS$: C, 61.15; H, 4.40; N, 13.58. Found: C, 61.16; H, 4.45; N, 13.72.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-methylphenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12b) Compound **8** (1000 mg, 3.2 mmol) and 2-bromo-4′-methylacetophenone (**11b**) (750 mg, 3.5 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12b** (1210 mg, 89%) as a colorless amorphous solid. $[\alpha]_D$ −50.1° (c=0.13, MeOH, 24 °C). IR ($CHCl_3$): 1615, 1514 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.1 Hz), 2.41 (3H, s), 4.04 (1H, q, J=7.1 Hz), 4.28 (1H, d, J=14.3 Hz), 4.88 (1H, d, J=14.3 Hz), 6.24 (1H, s), 6.76—6.84 (2H, m), 7.27 (2H, d, J=8.3 Hz), 7.40 (1H, s), 7.47—7.53 (1H, m), 7.65 (1H, s), 7.87 (2H, d, J=8.3 Hz), 7.94 (1H, s). *Anal.* Calcd for $C_{22}H_{20}F_2N_4OS$: C, 61.96; H, 4.73; N, 13.14. Found: C, 61.83; H, 4.91; N, 12.76.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-methoxyphenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12c) Compound **8** (500 mg, 1.6 mmol) and 2-bromo-4′-methoxyacetophenone (**11c**) (403 mg, 1.8 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12c** (600 mg, 88%) as a colorless amorphous solid. $[\alpha]_D$ −30.1° (c=0.27, MeOH, 24 °C). IR ($CHCl_3$): 1614, 1440, 1421, 1303 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.1 Hz), 3.88 (3H, s), 4.04 (1H, q, J=7.1 Hz), 4.28 (1H, d, J=14.3 Hz), 4.87 (1H, d, J=14.3 Hz), 6.24 (1H, s), 6.76—6.84 (2H, m), 7.00 (2H, d, J=8.2 Hz), 7.32 (1H, s), 7.47—7.53 (1H, m), 7.65 (1H, s), 7.84 (2H, d, J=8.2 Hz), 7.94 (1H, s). *Anal.* Calcd for $C_{22}H_{20}F_2N_4O_2S$: C, 59.72; H, 4.56; N, 12.66. Found: C, 59.68; H, 4.60; N, 12.56.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-fluorophenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12d) Compound **8** (453 mg, 1.45 mmol) and 2-bromo-4′-fluoroacetophenone (**11d**) (331 mg, 1.52 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12d** (560 mg, 90%) as a colorless powder. mp 97—98 °C. $[\alpha]_D$ −41.1° (c=0.18, MeOH, 24 °C). IR ($CHCl_3$): 1619, 1274, 1158 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.1 Hz), 4.06 (1H, q, J=7.1 Hz), 4.28 (1H, d, J=14.4 Hz), 4.89 (1H, d, J=14.4 Hz),

6.04 (1H, s), 6.77—6.85 (2H, m), 7.13—7.17 (2H, m), 7.41 (1H, s), 7.47—7.55 (1H, m), 7.67 (1H, s), 7.85—7.92 (2H, m), 7.90 (1H, s). *Anal.* Calcd for $C_{21}H_{17}F_3N_4OS$: C, 58.76; H, 3.98; N, 13.02. Found: C, 58.60; H, 3.97; N, 12.99.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(2,4-difluorophenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12e) Compound **8** (500 mg, 1.6 mmol) and 2-chloro-2′,4′-difluoroacetophenone (**11e**) (335 mg, 1.8 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12e** (349 mg, 49%) as a colorless powder. mp 137—138 °C. $[\alpha]_D$ −42.4° (c=0.16, MeOH, 24 °C). IR ($CHCl_3$): 1618, 1276, 1139, 1101 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.1 Hz), 4.07 (1H, q, J=7.1 Hz), 4.26 (1H, d, J=14.4 Hz), 4.89 (1H, d, J=14.4 Hz), 5.93 (1H, s), 6.77—6.83 (2H, m), 6.92—6.98 (1H, m), 7.00—7.05 (1H, m), 7.47—7.54 (1H, m), 7.67 (1H, s), 7.68 (1H ,s), 7.88 (1H, s), 8.13—8.19 (1H, m). *Anal.* Calcd for $C_{21}H_{16}F_4N_4OS$: C, 56.25; H, 3.60; N, 12.49. Found: C, 56.26; H, 3.57; N, 12.61.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-chlorophenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12f) Compound **8** (453 mg, 1.45 mmol) and 2-bromo-4′-chloroacetophenone (**11f**) (356 mg, 1.52 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12f** (600 mg, 93%) as colorless prisms. mp 120—122 °C. $[\alpha]_D$ −37.6° (c=0.15, MeOH, 24 °C). IR ($CHCl_3$): 1139, 1091 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.1 Hz), 4.06 (1H, q, J=7.1 Hz), 4.27 (1H, d, J=14.4 Hz), 4.89 (1H, d, J=14.4 Hz), 5.97 (1H, s), 6.76—6.85 (2H, m), 7.40—7.55 (4H, m), 7.67 (1H, s), 7.72—7.77 (2H, m), 7.89 (1H, s). *Anal.* Calcd for $C_{21}H_{17}ClF_2N_4OS$: C, 56.44; H, 3.83; N, 12.54. Found: C, 56.40; H, 3.87; N, 12.38.

(2*R*,3*R*)-3-[4-(4-Cyanophenyl)thiazol-2-yl]-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12g) Compound **8** (13 g, 41.7 mmol) and 2-bromo-4′-cyanoacetophenone (**11g**) (10.3 g, 45.8 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12g** (6.9 g, 38%) as colorless prisms. mp 164—166 °C. $[\alpha]_D$ −29.1° (c=1.03, MeOH, 24 °C). IR ($CHCl_3$): 2230, 1610, 1436, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.0 Hz), 4.09 (1H, q, J=7.0 Hz), 4.26 (1H, d, J=14.3 Hz), 4.92 (1H, d, J=14.3 Hz), 5.74 (1H, s), 6.78—6.85 (2H, m), 7.48—7.54 (1H, m), 7.64 (1H, s), 7.69 (1H, s), 7.75 (2H, d, J=8.1 Hz), 7.85 (1H, s), 8.03 (2H, d, J=8.1 Hz). *Anal.* Calcd for $C_{22}H_{17}F_2N_5OS$: C, 60.40; H, 3.92; N, 16.01. Found: C, 60.51; H, 4.00; N, 16.03.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-{4-[4-(2*H*-1,2,3-triazol-2-yl)phenyl]-thiazol-2-yl}-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12h) Compound **8** (505 mg, 1.62 mmol) and 2-bromo-4′-(2*H*-1,2,3-triazol-2-yl)acetophenone (**11h**) (560 mg, 2.10 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12h** (659 mg, 85%) as colorless prisms. mp 157—158 °C. $[\alpha]_D$ −30.3° (c=0.15, MeOH, 24 °C). IR ($CHCl_3$): 1620, 1383, 1139 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.1 Hz), 4.09 (1H, q, J=7.1 Hz), 4.29 (1H, d, J=14.3 Hz), 4.92 (1H, d, J=14.3 Hz), 6.00 (1H, s), 6.78—6.86 (2H, m), 7.48—7.56 (1H, m), 7.53 (1H, s), 7.67 (1H, s), 7.86 (2H, s), 7.91 (1H, s), 8.04 (2H, d, J=8 Hz), 8.19 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{23}H_{19}F_2N_7OS$: C, 57.61; H, 3.99; N, 20.45. Found: C, 57.66; H, 3.97; N, 20.40.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-{4-[4-(1*H*-1,2,3-triazol-1-yl)phenyl]-thiazol-2-yl}-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12i) Compound **8** (510 mg, 1.63 mmol) and 2-bromo-4′-(1*H*-1,2,3-triazol-1-yl)acetophenone (**11i**) (1000 mg, 3.76 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12i** (475 mg, 61%) as colorless needles. mp 171—173 °C. $[\alpha]_D$ −20.6° (c=0.14, MeOH, 24 °C). IR ($CHCl_3$): 1619, 1410, 1139 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.1 Hz), 4.09 (1H, q, J=7.1 Hz), 4.31 (1H, d, J=14.2 Hz), 4.92 (1H, d, J=14.2 Hz), 5.93 (1H, s), 6.80—6.86 (1H, m), 7.48—7.56 (2H, m), 7.58 (1H, s), 7.68 (1H, s), 7.85—7.89 (4H, m), 8.07—8.89 (3H, m). *Anal.* Calcd for $C_{23}H_{19}F_2N_7OS$: C, 57.61; H, 3.99; N, 20.45. Found: C, 57.64; H, 3.96; N, 20.37.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-methylthiophenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12j) Compound **8** (1000 mg, 3.2 mmol) and 2-bromo-4′-methylthioacetophenone (**11j**) (824 mg, 3.36 mmol) were treated according to the same procedure as described for the preparation of **12a** to afford **12j** (1210 mg, 83%) as a yellow amorphous solid. $[\alpha]_D$ −26.3° (c=0.06, MeOH, 24 °C). IR ($CHCl_3$): 1621, 1405, 1139 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.2 Hz), 2.54 (3H, s), 4.05 (1H, q, J=7.2 Hz), 4.28 (1H, d, J=14.4 Hz), 4.88 (1H, d, J=14.4 Hz), 6.13 (1H, s), 6.75—6.85 (2H, m), 7.33 (2H, br d, J=8.4 Hz), 7.42 (1H, s), 7.46—7.54 (1H, m), 7.66 (1H, s), 7.82 (2H, br d, J=8.4 Hz), 7.92 (1H, s). *Anal.* Calcd for $C_{22}H_{20}F_2N_4OS_2$: C, 57.62; H, 4.40; N, 12.22. Found: C, 57.38; H, 4.31; N, 11.95.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-methylsulfonyphenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12k) mCPBA (215 mg, 1.2 mmol) was added to a solution of **12j** (138 mg, 0.30 mmol) in $CHCl_3$ (3 ml), and the mixture was stirred at room temperature for 1 h. After addition of water, the whole was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (5 g, 1% MeOH–CH_2Cl_2) to give **12k** (98.5 mg, 67%) as a colorless amorphous solid. $[\alpha]_D$ −30.3° (c=0.15, MeOH, 24 °C). IR ($CHCl_3$): 1455, 1139 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=7.2 Hz), 3.09 (3H, s), 4.09 (1H, q, J=7.2 Hz), 4.27 (1H, d, J=14.4 Hz), 4.91 (1H, d, J=14.4 Hz), 5.78 (1H, s), 6.78—6.85 (2H, m), 7.47—7.55 (1H, m), 7.67 (1H, s), 7.69 (1H, s), 8.02 (2H, br d, J=8.4 Hz), 8.10 (2H, br d, J=8.4 Hz). *Anal.* Calcd for $C_{22}H_{20}F_2N_4O_3S_2 \cdot 0.3H_2O$: C, 53.28; H, 4.19; N, 11.30. Found: C, 53.21; H, 3.96; N, 11.43.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-{4-[4-(2*H*-1,2,3,4-tetrazol-5-yl)-phenyl]thiazol-2-yl}-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12l) Sodium azide (537 mg, 8.26 mmol) and triethylamine hydrochloride (1137 mg, 8.26 mmol) were added to a solution of **12g** (1000 mg, 2.36 mmol) in *N*-methylpyrrolidone (10 ml) and the reaction mixture was heated at 100 °C for 8 h. After addition of water, the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (10 g, 5% MeOH–CH_2Cl_2) to give **12l** (679 mg, 60%) as a colorless solid. mp 203—204 °C. $[\alpha]_D$ −21.3° (c=0.10, MeOH, 24 °C). IR ($CHCl_3$): 1619, 1434, 1138 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, d, J=7.3 Hz), 4.11 (1H, q, J=7.3 Hz), 4.37 (1H, d, J=14.6 Hz), 4.87 (1H, d, J=14.6 Hz), 6.08 (1H, s), 6.91—6.96 (1H, m), 7.18—7.25 (1H, m), 7.27—7.34 (1H, m), 7.62 (1H, s), 8.11 (2H, d, J=8.5 Hz), 8.20 (2H, d, J=8.5 Hz), 8.22 (1H, s), 8.29 (1H, s). *Anal.* Calcd for $C_{22}H_{18}F_2N_8OS$: C, 54.99; H, 3.78; N, 23.32. Found: C, 54.90; H, 3.68; N, 23.38.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-{4-[4-(2-methyl-2*H*-1,2,3,4-tetrazol-5-yl)phenyl]thiazol-2-yl}-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12m) Cesium carbonate (236 mg, 0.71 mmol) was added to a solution of **12l** (331 mg, 0.71 mmol) in DMF (10 ml) and the mixture was heated at 60 °C for 1 h, then cooled to room temperature. Iodomethane (0.07 ml, 1.1 mmol) was added, and the reaction mixture was stirred at the same temperature for 1 h. After addition of water, the whole was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (40 g, 2% MeOH–CH_2Cl_2) to give **12m** (188 mg, 55%) as a colorless solid. mp 208—209 °C. $[\alpha]_D$ −29.0° (c=0.12, MeOH, 24 °C). IR ($CHCl_3$): 1446, 1138 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.0 Hz), 4.09 (1H, q, J=7.0 Hz), 4.29 (1H, d, J=14.0 Hz), 4.33 (3H, s), 4.92 (1H, d, J=14.0 Hz), 6.01 (1H, s), 6.77—6.85 (2H, m), 7.49—7.55 (1H, m), 7.58 (1H, s), 7.67 (1H, s), 7.91 (1H, s), 8.04 (2H, d, J=8.2 Hz), 8.24 (2H, d, J=8.2 Hz). *Anal.* Calcd for $C_{23}H_{20}F_2N_8OS \cdot 0.4H_2O$: C, 55.06; H, 4.18; N, 22.33. Found: C, 54.93; H, 3.98; N, 22.35.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[4-(4-thiocarbamoylphenyl)thiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12n) A mixture of **12g** (6.0 g, 13.72 mmol) and diethyl dithiophosphate (10.8 ml, 68.43 mmol) in water (3.0 ml) and IPA (6 ml) was heated under reflux for 0.5 h. After addition of water, the whole was extracted with AcOEt. The organic extract was washed with a saturated aqueous solution of sodium hydrogen carbonate, water and brine, dried, and evaporated to afford crude **12n** (8.05 g). The crude product was used for the next step without further purification. A part of it was purified by chromatography on silica gel to afford pure **12n** as a yellow solid. mp 191—193 °C. $[\alpha]_D$ −23.7° (c=0.13, MeOH, 24 °C). IR ($CHCl_3$): 1602, 1538, 1434, 1140 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.1 Hz), 4.12 (1H, q, J=7.1 Hz), 4.31 (1H, d, J=14.3 Hz), 4.89 (1H, d, J=14.3 Hz), 6.00 (1H, br s), 6.77—6.85 (2H, m), 7.48—7.54 (2H, m), 7.59 (1H, s), 7.67 (1H, s), 7.88 (1H, br s), 7.92 (2H, d, J=8.6 Hz), 7.96 (1H, s), 7.98 (2H, d, J=8.6 Hz). *Anal.* Calcd for $C_{22}H_{19}F_2N_5OS_2$: C, 56.04; H, 4.06; N, 14.85. Found: C, 55.88; H, 4.00; N, 14.72.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-{4-[4-(2*H*-1,2,4-triazol-5-yl)phenyl]-thiazol-2-yl}-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12o) Iodomethane (3.8 ml, 61.04 mmol) was added to a solution of **12n** (7.17 g, 15.21 mmol) in acetone (72 ml), and the mixture was heated at 40 °C for 1 h. The precipitate was collected by filtration, washed with AcOEt, and dried to afford a crude product (6.29 g), which was used for the next step without further purification. Formic hydrazide (1.07 g, 17.82 mmol), triethylamine (1.2 ml, 8.61 mmol) and sulfuric acid (0.1 ml) were added to a solution of the crude product (5.03 g) in ethanol (53 ml), and the mixture was

heated under reflux for 1 h. After addition of water, the whole was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (100 g, 3% MeOH–CH_2Cl_2) to give **12o** (1.85 g, 37%, 3 steps from **12g**) as a colorless solid. mp 140—143 °C. $[\alpha]_D$ −30.8° (c=0.11, MeOH, 24 °C). IR ($CHCl_3$): 1615, 1524, 1436, 1139 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=7.1 Hz), 4.08 (1H, q, J=7.1 Hz), 4.34 (1H, d, J=14.4 Hz), 4.91 (1H, d, J=14.4 Hz), 6.15 (1H, s), 6.79—6.85 (1H, m), 7.52—7.56 (2H, m), 7.69 (1H, s), 7.97—7.99 (3H, m), 8.14 (2H, d, J=8.2 Hz), 8.25 (1H, s). *Anal.* Calcd for $C_{23}H_{19}F_2N_7OS$: C, 57.61; H, 3.99; N, 20.45. Found: C, 57.48; H, 3.92; N, 20.31.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-{4-[4-(2-methyl-2*H*-1,2,4-triazol-5-yl)phenyl]thiazol-2-yl}-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12p) A mixture of **12o** (1.43 g, 2.98 mmol) and potassium carbonate (433 mg, 3.13 mmol) in acetone (36 ml) was treated with iodomethane (0.2 ml, 3.21 mmol) at room temperature, and the reaction mixture was stirred at the same temperature for 18 h. After addition of water, the whole was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (35 g, 2% MeOH–CH_2Cl_2) and then on a column of C18 silica gel (65% MeOH–water) to give **12p** (982 mg, 67%) as a colorless solid. mp 140—142 °C. $[\alpha]_D$ −26.6° (c=0.12, MeOH, 24 °C). IR ($CHCl_3$): 1619, 1454, 1139 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.1 Hz), 4.02 (3H, s), 4.09 (1H, q, J=7.1 Hz), 4.29 (1H, d, J=14.3 Hz), 4.93 (1H, d, J=14.3 Hz), 6.10 (1H, br s), 6.77—6.85 (2H, m), 7.48—7.53 (1H, m), 7.54 (1H, s), 7.68 (1H, s), 7.98—8.10 (3H, m), 8.20—8.22 (3H, m). *Anal.* Calcd for $C_{24}H_{21}F_2N_7OS$: C, 58.41; H, 4.29; N, 19.87. Found: C, 58.46; H, 4.27; N, 19.75.

(2*R*,3*R*)-3-(2,4-Difluorophenyl)-3-hydroxy-2-methyl-4-(1*H*-1,2,4-triazol-1-yl)butyraldehyde (13) A 1.0 M solution of DIBAL in *n*-hexane (9.0 ml, 9.0 mmol) was added to a solution of **7** (502 mg, 1.81 mmol) in CH_2Cl_2 (90 ml) at −70 °C and the mixture was stirred at the same temperature for 5 min. After addition of acetic acid (7 ml) and CH_2Cl_2 (7 ml), the organic layer was washed with a solution of saturated $NaHCO_3$ (3 times) and brine, dried, and evaporated. The resulting solid was recrystallized from toluene to give **12** (345 mg, 68%) as colorless cystals. mp 140—144 °C. $[\alpha]_D$ −48.7° (c=0.13, MeOH, 24 °C). IR ($CHCl_3$): 1721, 1615, 1457, 1278, 1141 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, J=7.2 Hz), 2.96—3.03 (1H, m), 4.62 (1H, d, J=14.0 Hz), 4.90 (1H, d, J=14.0 Hz), 5.16 (1H, s), 6.73—6.81 (2H, m), 7.37—7.44 (1H, m), 7.79 (1H, s), 7.86 (1H, s), 9.85 (1H, d, J=3.2 Hz). *Anal.* Calcd for $C_{13}H_{13}F_2N_3O_2$: C, 55.52; H, 4.66; N, 14.94. Found: C, 55.44; H, 4.68; N, 14.96.

2-Amino-6-cyanobenzothiazole (15c) Bromine (21 ml, 0.41 mol) was added dropwise to a mixture of 4-aminobenzonitrile (40.0 g, 0.34 mol) and sodium thiocyanate (82.3 g, 1.02 mol) in AcOH (150 ml) with stirring at 0 °C for 40 min. The mixture was heated at 100 °C for 3 h. After addition of 10 N NaOH (500 ml), the whole was filtered, and the filtrate was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated to afford **15c** (35 g, 59%). mp 203—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.39 (1H, dd, J=0.6, 8.4 Hz), 7.58 (1H, ddd, J=1.1, 1.7, 8.4 Hz), 8.02 (2H, s), 8.95 (1H, t, J=1.1 Hz). *Anal.* Calcd for $C_8H_5N_3S$: C, 54.84; H, 2.88; N, 23.98. Found: C, 54.71; H, 3.01; N, 23.94.

2-Amino-6-thiomethylbenzothiazole (15f) In the same manner as described for the preparation of **15c**, **15f** was obtained (87%) as a pale yellow solid. This compound was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s), 5.23 (2H, br s), 7.27 (1H, dd, J=2.0, 8.4 Hz), 7.45 (1H, d, J=8.4 Hz), 7.54 (1H, d, J=2.0 Hz).

6-Chlorobenzothiazole (16a) Isoamyl nitrite (1.92 ml, 14.3 mmol) was added dropwise to a solution of **15a** (1.20 g, 6.5 mmol) in tetrahydrofuran (10 ml) with stirring at room temperature. The mixture was heated under reflux for 30 min, then poured into ice-water, and the whole was extracted with AcOEt. The organic extract was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (25 g, CH_2Cl_2/*n*-hexane=6/1) to give **16a** (1.1 g, quant.). This compound was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.50 (1H, d, J=9.0 Hz), 7.95 (1H, s), 8.05 (1H, d, J=9.0 Hz), 9.0 (1H, s).

6-Fluorobenzothiazole (16b) In the same manner as described for the preparation of **16a**, **16b** was obtained (77%) as a pale brown solid. This compound was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 7.27 (1H, dt, J=2.6, 9.0 Hz), 7.64 (1H, dd, J=2.6, 8.1 Hz), 8.09 (1H, dd, J=4.8, 9.0 Hz), 8.95 (1H, s).

6-Cyanobenzothiazole (16c) In the same manner as described for the preparation of **16a**, **16c** was obtained (51%) as pale yellow needles. mp 137—138 °C. IR ($CHCl_3$): 2252, 1644, 1470, 1167 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, dt, J=1.9, 8.5 Hz), 8.24 (1H, dd, J=1.5, 8.5 Hz), 8.80 (1H, d, J=1.5 Hz), 9.65 (1H, d, J=1.9 Hz). *Anal.* Calcd for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49. Found: C, 59.71; H, 2.51; N, 17.42.

6-Thiomethylbenzothiazole (16f) In the same manner as described for the preparation of **16a**, **16f** was obtained (47%) as a solid. This compound was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s), 7.41 (1H, dd, J=2.0, 8.8 Hz), 7.78 (1H, d, J=2.0 Hz), 8.01 (1H, d, J=8.8 Hz), 8.89 (1H, s).

2-Amino-5-chlorothiophenol (17a) A mixture of **16a** (1.1 g, 6.7 mmol) and hydrazine monohydrate (2.4 ml, 49.9 mmol) in EtOH (11 ml) was heated at 80 °C for 1 h under an N_2 atmosphere. The mixture was evaporated, water (10 ml) was added to the residue, and the solution was adjusted to pH 5 with AcOH. The resultant precipitate was collected by filtration, washed with water, and dried to afford a crude product (0.85 g) as a pale red solid.

2-Amino-5-fluorothiophenol (17b) In the same manner as described for the preparation of **17a**, **17b** was obtained as a pale red solid.

2-Amino-5-cyanothiophenol (17c) In the same manner as described for the preparation of **17a**, **17c** was obtained as a pale yellow solid.

2-Amino-5-thiomethylthiophenol (17f) In the same manner as described for the preparation of **17a**, **17f** was obtained as a brown solid.

2-Amino-7-aza-6-chlorobenzothiazole (19) In the same manner as described for the preparation of **15c**, **19** was obtained (91%) as a pale red solid. This compound was used in the next step without further purification. ^{1}H-NMR (DMSO-d_6) δ: 7.28 (1H, d, J=8.4 Hz), 7.63 (1H, d, J=8.4 Hz), 7.91 (2H, s).

2-Amino-5-chloro-1-mercaptopyridine (20) A mixture of **19** (186 mg, 1.00 mmol) and $NaHSO_3$ (10 mg) in an aqueous solution of 20% NaOH (2 ml) was heated under reflux for 4 h. After addition of Et_2O, the mixture was adjusted to pH 6 with AcOH–H_2O. The precipitate was collected by filtration, washed with water, and dried to afford **20** (168 mg) as a pale yellow solid.

The above 2-aminothiophenols (**17a**, **17b**, **17c**, **17f**, **20**) were all used immediately for the next reaction without further purification because of their tendency readily to form the disulfides.

(2*R*,3*R*)-3-(6-Chlorobenzothiazol-2-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21a) Compound **17a** (188 mg, 1.18 mmol) and diethyl dithiophosphate (0.46 ml, 2.91 mmol) were added to a solution of **7** (164 mg, 0.59 mmol) in chloroform (1.6 ml) with stirring under reflux for 7 h under an N_2 atmosphere. After addition of water, the mixture was extracted with AcOEt. The organic extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (10 g, 0.5% MeOH–CH_2Cl_2) to give **21a** (23 mg, 9.3%) as a yellow caramel. $[\alpha]_D$ −41.3° (c=0.12, MeOH, 24 °C). IR ($CHCl_3$): 1557, 1470, 1274, 1169 cm^{-1}. FAB-MS m/z: 421 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.0 Hz), 4.09 (1H, q, J=7.0 Hz), 4.27 (1H, d, J=14.4 Hz), 4.93 (1H, d, J=14.4 Hz), 5.80 (1H, s), 6.78—6.85 (2H, m), 7.48 (1H, dd, J=2.4, 8.8 Hz), 7.49—7.55 (1H, m), 7.67 (1H, s), 7.87 (1H, s), 7.90 (1H, d, J=2.4 Hz), 7.94 (1H, d, J=8.8 Hz).

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(6-fluorobenzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21b) In the same manner as described for the preparation of **21a**, **21b** was obtained (15.5%) as a pale yellow solid. mp 130—131 °C. $[\alpha]_D$ −25.5° (c=0.12, MeOH, 24 °C). IR ($CHCl_3$): 1531, 1458, 1434, 1275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7.1 Hz), 4.08 (1H, q, J=7.1 Hz), 4.28 (1H, d, J=14.4 Hz), 4.93 (1H, d, J=14.4 Hz), 5.83 (1H, s), 6.77—6.85 (2H, m), 7.23—7.29 (1H, m), 7.49—7.56 (1H, m), 7.58—7.62 (1H, m), 7.67 (1H, s), 7.87 (1H, s), 7.96—8.00 (1H, m). *Anal.* Calcd for $C_{19}H_{15}F_3N_4OS \cdot 0.1H_2O$: C, 56.18; H, 3.77; N, 13.79. Found: C, 56.03; H, 3.70; N, 13.77.

(2*R*,3*R*)-3-(6-Cyanobenzothiazol-2-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21c) PPTS (120 mg, 0.48 mmol) was added to a solution of **13** (478 mg, 1.70 mmol) and **17c** (365 mg, 2.40 mmol) in IPA (10 ml) with stirring at room temperature for 2 h. The precipitate was collected by filtration, washed with diisopropyl ether, and dried to afford **21c** (374 mg, 53%) as a colorless powder. mp 183—185 °C. $[\alpha]_D$ −36.8° (c=0.09, MeOH, 24 °C). IR ($CHCl_3$): 2232, 1618, 1390 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7.2 Hz), 4.16 (1H, q, J=7.2 Hz), 4.24 (1H, d, J=14.0 Hz), 4.96 (1H, d, J=14.0 Hz), 5.67 (1H, s), 6.79—6.86 (2H, m), 7.49—7.56 (1H, m), 7.69 (1H, s), 7.77 (1H, dd, J=1.6, 8.4 Hz), 7.83 (1H, s), 8.11 (1H, d, J=8.4 Hz), 8.27 (1H, d, J=1.6 Hz). *Anal.* Calcd for $C_{20}H_{15}F_2N_5OS$: C, 58.39; H, 3.67; N, 17.02. Found: C, 58.22; H,

3.52; N, 16.92.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(6-thiocarbamoylbenzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21d) H_2S gas was introuced into a solution of **21c** (507 mg, 1.23 mmol) in DMF (5 ml) in the presence of Et_3N (0.1 ml) at room temperature and the mixture was left to stand for 6 h at the same temperature. After addition of water, the whole was extracted with AcOEt. The organic extract was washed with an aqueous solution of $NaHCO_3$, and brine, then dried, and evaporated. The residue was chromatographed on silica gel (30 g, 1% MeOH–CH_2Cl_2) to give **21d** (483 mg, 88%) as a yellow powder. mp 165—166 °C. $[\alpha]_D$ −50.1° (c=0.08, MeOH, 24 °C). IR ($CHCl_3$): 1602, 1477, 1423, 1333 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7.2 Hz), 4.13 (1H, q, J=7.2 Hz), 4.27 (1H, d, J=14.0 Hz), 4.94 (1H, d, J=14.0 Hz), 5.81 (1H, s), 6.78—6.85 (2H, m), 7.24—7.30 (1H, br s), 7.39—7.56 (1H, m), 7.66—7.72 (1H, br s), 7.86 (1H, s), 7.95 (1H, dd, J=2.0, 8.8 Hz), 8.02 (1H, d, J=8.8 Hz), 8.59 (1H, d, J=2.0 Hz). *Anal.* Calcd for $C_{20}H_{17}F_2N_5OS_2$: C, 53.92; H, 3.85; N, 15.72. Found: C, 53.79; H, 3.81; N, 15.68.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-[6-(2-methyl-2*H*-1,2,4-triazol-5-yl)-benzothiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21e) In the same manner as described for the preparation of **12o**, (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-[6-(2*H*-1,2,4-triazol-5-yl)benzothiazol-2-yl]-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol was obtained (33%) as a pale yellow solid. Next, in the same manner as described for the preparation of **12p**, **21e** was obtained (41%) as a pale yellow powder. mp 177—179 °C. $[\alpha]_D$ −39.0° (c=0.13, MeOH, 24 °C). IR ($CHCl_3$): 1619, 1477, 1394 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7.0 Hz), 4.01 (3H, s), 4.11 (1H, q, J=7.0 Hz), 4.32 (1H, d, J=14.0 Hz), 4.94 (1H, d, J=14.0 Hz), 5.99 (1H, s), 6.77—6.86 (2H, m), 7.50—7.57 (1H, m), 7.65 (1H, s), 7.91 (1H, s), 8.08 (1H, d, J=8.4 Hz), 8.10 (1H, s), 8.27 (1H, dd, J=1.6, 8.4 Hz), 8.67 (1H, d, J=1.6 Hz). *Anal.* Calcd for $C_{22}H_{19}F_2N_7OS$: C, 56.52; H, 4.10; N, 20.97. Found: C, 56.46; H, 4.08; N, 20.94.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(6-methylthiobenzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21f) In the same manner as described for the preparation of **21a**, **21f** was obtained (6.0%) as a pale yellow solid. mp 146—148 °C. $[\alpha]_D$ −41.3° (c=0.11, MeOH, 24 °C). IR ($CHCl_3$): 1644, 1471, 1385, 1168 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=7.0 Hz), 2.57 (3H, s), 4.06 (1H, q, J=7.0 Hz), 4.27 (1H, d, J=14.2 Hz), 4.92 (1H, d, J=14.2 Hz), 5.93 (1H, s), 6.76—6.84 (2H, m), 7.42 (1H, dd, J=2.0, 8.4 Hz), 7.47—7.55 (1H, m), 7.65 (1H, s), 7.76 (1H, d, J=2.0 Hz), 7.88 (1H, s), 7.92 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{20}H_{18}F_2N_4OS_2$: C, 55.54; H, 4.19; N, 12.95. Found: C, 55.39; H, 4.23; N, 12.80.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(6-methylsulfonylbenzothiazol-2-yl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21g) mCPBA (78 mg, 0.35 mmol) was added to a solution of **21f** (49 mg, 0.11 mmol) in chloroform (3 ml) with stirring at room temperature for 1 h. After addition of water, the mixture was extracted with $CHCl_3$. The organic extract was washed with water, a saturated aqueous solution of $NaHCO_3$ and brine, then dried, and evaporated. The residue was chromatographed on silica gel (10 g, 2% MeOH–CH_2Cl_2) to give **21g** (40 mg, 76%). mp 133—136 °C. $[\alpha]_D$ −34.9° (c=0.16, MeOH, 24 °C). FAB-MS m/z: 465 $(M+H)^+$. IR ($CHCl_3$): 1645, 1471, 1386, 1157 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=7.2 Hz), 3.13 (3H, s), 4.18 (1H, q, J=7.2 Hz), 4.24 (1H, d, J=14.2 Hz), 4.98 (1H, d, J=14.2 Hz), 5.68 (1H, s), 6.79—6.86 (2H, m), 7.49—7.56 (1H, m), 7.70 (1H, s), 7.84 (1H, s), 8.06 (1H, dd, J=2.0, 8.8 Hz), 8.19 (1H, d, J=8.8 Hz), 8.58 (1H, d, J=2.0 Hz).

(2*R*,3*R*)-3-(6-Chloro-7-azabenzothiazol-2-yl)-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21h) In the same manner as described for the preparation of **21a**, **21h** was obtained (66%) as pale yellow prisms. mp 170—172 °C. $[\alpha]_D$ −35.8° (c=0.13, MeOH, 24 °C). IR ($CHCl_3$): 1625, 1455, 1423, 1215 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7.2 Hz), 4.07 (1H, q, J=7.2 Hz), 4.27 (1H, d, J=14.0 Hz), 4.96 (1H, d, J=14.0 Hz), 5.63 (1H, s), 6.78—6.85 (2H, m), 7.47 (1H, d, J=8.4 Hz), 7.48—7.55 (1H, m), 7.70 (1H, s), 7.83 (1H, s), 8.19 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{18}H_{14}ClF_2N_5OS$: C, 51.25; H, 3.35; N, 16.60. Found: C, 51.10; H, 3.28; N, 16.62.

Determination of MACs MACs were determined by the two-fold agar dilution method with Sabouraud dextrose agar (SDA; Difco Laboratories, Detroit, Mich.). Yeasts were grown on SDA at 30 °C for 24 to 48 h and diluted to a final concentration of 10^5 cells per ml with sterilized saline. Filamentous fungi were grown on potato dextrose agar (PDA; Eiken Chemical Co., Tokyo, Japan) at 30 °C for 1 to 2 weeks, and diluted to a final concentration of 10^5 cells per ml with sterilized saline containing 0.05% Tween 80. Five microliters of each fungal suspension was spotted with a multiple-inoculum replicator (Microplanter; Sakuma Seisakusho, Tokyo, Japan) onto agar plates that contained twofold serial dilutions of antifungals. Fungal growth was observed 48 h after incubation at 37 °C. MAC was determined as the lowest drug concentration which visibly inhibited fungal growth compared with the control fungal growth.

Investigation of Therapeutic Effect in Experimental Systemic Infection by *C. albicans* *C. albicans* MCY8622 was incubated on SDA plates at 30 °C for 24 h, and challenge organisms were prepared in sterilized saline. Mice (age 4.5 weeks) (n=5) were infected *via* the tail vein with 2×10^6 cells. Drugs were orally administered in a volume of 0.2 ml per dose, 1 h after infection. Control groups received 10% DMSO in 0.5% CMC. Doses of drugs were 2.5 and 10 mg/kg. The mean survival days were calculated based on termination of the experiment 7 d after infection.

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