Structure–Activity Relationships of 3-Methyl and 3,3-Dimethyl Analogs of 2-(2,4-Difluorophenyl)-3-(ω-substituted alkyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-propanols

Hiroshi MIYAUCHI,* Koichi KOZUKI, Tomoharu TANIO, and Naohito OHASHI

Research Center, Sumitomo Pharmaceuticals Co., Ltd., 1–98, Kasugadenaka 3-chome, Konohana-ku, Osaka 554, Japan. Received October 16, 1995; accepted November 14, 1995

3-Methyl and 3,3-dimethyl analogs of 2-(2,4-difluorophenyl)-3-(ω-substituted alkyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-propanols were synthesized and evaluated for their antifungal activities against *Candida albicans* and *Aspergillus fumigatus*. The 3,3-dimethyl analogs were found to have more potent activity both *in vitro* and *in vivo* than the corresponding 3-mono-methyl analogs. The prophylactic efficacy of the lead compounds against murine systemic candidiasis and aspergillosis was improved significantly by dimethylation of the 3-position.

Key words triazole antifungal; antifungal activity; structure–activity relationship; synthesis; murine systemic aspergillosis

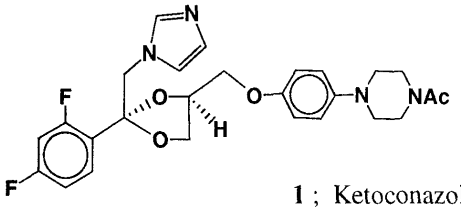
Systemic mycoses are more frequently being recognized as serious infections in a diverse and emergent group of patients. Opportunistic fungal infections represent a significant cause of morbidity and mortality in the immunocompromised patient.[1] An imidazole derivative, ketoconazole (**1**),[2] has been used as an orally active antifungal agent in Europe and the United States, however, it has the drawback of side effects including hepatotoxicity.[3] A triazole derivative, fluconazole (**2**),[4] has been widely used since it was launched in the market. Fluconazole (**2**) is claimed to have lower toxicity and more potent activity than ketoconazole, however, it is also reported that **2** does not show much activity against *Aspergillus species*.[5,6] On the other hand, our research group previously demonstrated that SM-8668 (**5**)[7] had higher potency against a wide range of mycoses in animal experiments than fluconazole.[6] Such strong activity of **5** may be due to the presence of the *threo*-methyl group at the 3-position, as shown in Chart 1.[8]

As a part of our search for active agents against systemic fungal infections, we synthesized 3-*threo*-methyl and 3,3-dimethyl analogs of 2-(2,4-difluorophenyl)-3-(ω-substituted alkyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-propanols, and examined their antifungal activities.

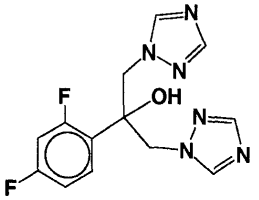
Chemistry 2-(2,4-Difluorophenyl)-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-propanol (**3**)[9] and its 3-*erythro*-methyl analog **4**[7a] and 3-*threo*-methyl analog **5** (SM-8668)[10] were prepared by the reported methods. The corresponding 3,3-dimethyl analog **6** was prepared from α-bromoketone **7**,[11,12] as shown in Chart 2. Displacement of the bromide in **7** to a methylthio group was carried out with aqueous sodium methanethiolate to give α-methylthioketone **8**. The reaction of the above obtained ketone **8** with dimethyloxosulfonium methylide[13] afforded oxirane **9**. Then, oxirane **9** was treated with 1*H*-1,2,4-triazole in the presence of sodium hydroxide in dimethyl sulfoxide (DMSO) to give triazolyl sulfide **10**. Finally, sulfide **10** was oxidized under acidic conditions with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate to give the desired sulfone **6** in high yield.[10]

The preparation methods for derivatives of 3-*threo*-methyl **5**, which have ω-substituted alkylthio or alkylsulfonyl groups instead of the methylsulfonyl group, are summarized in Chart 3. Sulfides **12a—c, f, g** were prepared by reaction of epoxide **11**[10] with various sodium thiolates (NaSR), as we recently reported.[8] These analogs were also prepared by reaction of thiol **14**[11,14–17] with halides (RX) under basic conditions.[15,16] Ethers **12d, e** were prepared by etherification of the corresponding alcohol **12a**. These sulfides were oxidized with hydrogen peroxide by the same method as described above to give the corresponding sulfones **13a—g** in high yields.

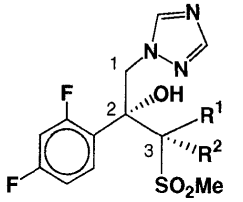
On the other hand, derivatives of 3,3-dimethyl sulfides **6**, which have ω-substituted alkylthio or alkylsulfonyl groups instead of the methylsulfonyl group, were prepared as follows. Sulfide **16a** was prepared by the same procedure as described for preparation of **6** (see Chart 2). Sulfides **16b, c, g** were prepared by reaction of thiol **15**[15] with halides (RX) under basic conditions, as shown in Chart 4. Ethers **16d, e** were prepared by etherification of the



1 ; Ketoconazole



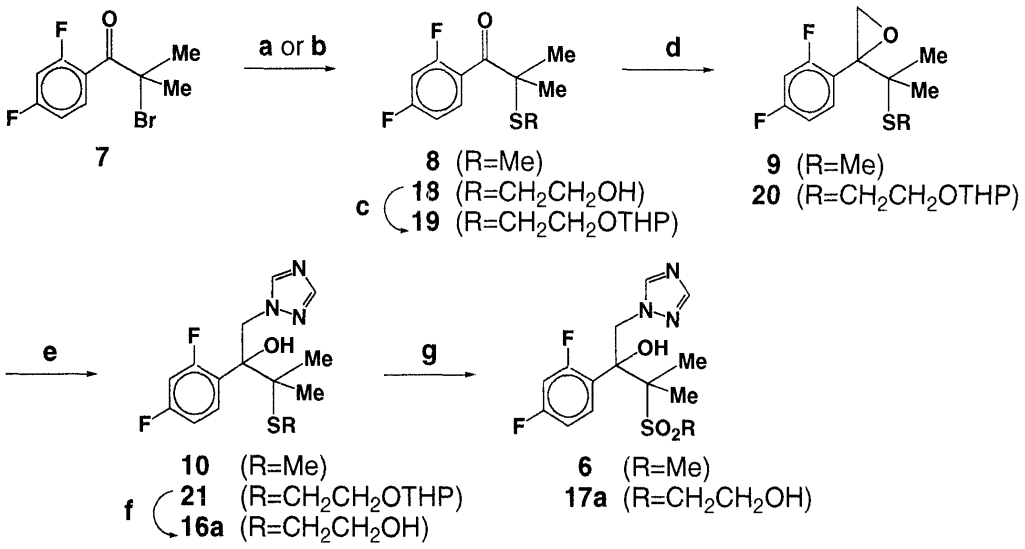
2 ; Fluconazole



3 ; $R^1 = R^2 = H$
4 ; $R^1 = H$, $R^2 = Me$ (*erythro*-)
5 ; $R^1 = Me$, $R^2 = H$ (*threo*-)
6 ; $R^1 = R^2 = Me$

Chart 1

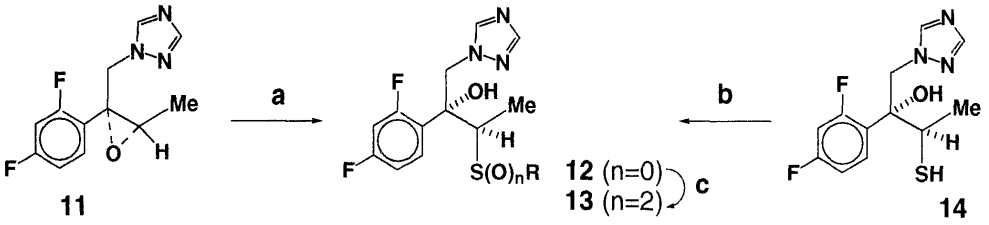
* To whom correspondence should be addressed.



Reagents and conditions:

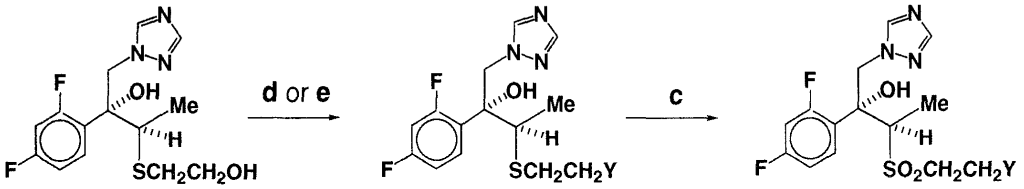
a) aq NaSMe,EtOH, -30 °C, 10 min (98%)
b) NaH, $HSCH_2CH_2OH$, DMF, -30 °C, 1 h (quant.)
c) DHP, PPTS, CH_2Cl_2, r.t., 20 h (quant.)
d) NaH, $Me_3S(O)^+ I^-$, DMSO-THF, r.t., 24 h
e) triazole, NaOH, DMSO, 80 °C, 3h, then 100 °C, 1h (58% from **8**, 55% from **19**)
f) *p*-TsOH, MeOH, r.t., 20 h (75%)
g) 31% aq H_2O_2, concd HCl, Na_2WO_4, MeOH, 60 °C, 1h (**6**; 84%, **17a**; 58%)

Chart 2



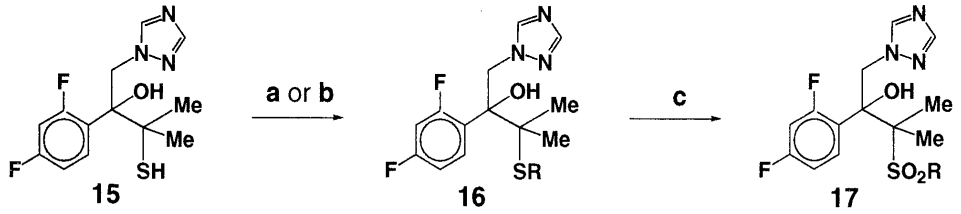
12a [R=$(CH_2)_2OH$, 43% from **11**]
12b [R=$(CH_2)_6OH$, 74% from **11**]
12c [R=$(CH_2)_7OH$, 39% from **11**]
12f [R=$(CH_2)_2NH_2$, 66% from **11**]
12g [R=CH_2CONH_2, 68% from **11**]

13a [R=$(CH_2)_2OH$, 82%]
13b [R=$(CH_2)_6OH$, 86%]
13c [R=$(CH_2)_7OH$, 95%]
13f [R=$(CH_2)_2NH_2$, 80%]
13g [R=CH_2CONH_2, 74%]

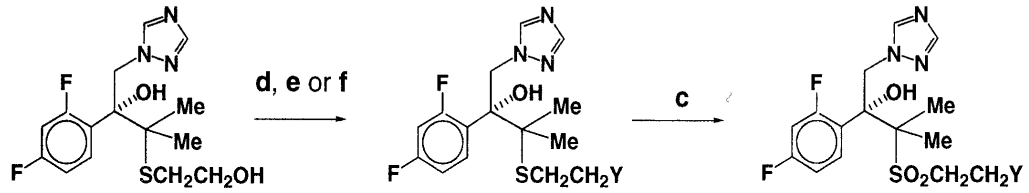


Reagents :
a) NaSR, DMF
b) NaH, RX (X=Br or I), DMF
c) 31% aq H_2O_2, concd HCl, Na_2WO_4, MeOH
d) NaH, MeI, DMF
e) NaH, BnBr, DMF

Chart 3



16b [R=$(CH_2)_6OH$, 98%] **17b** [R=$(CH_2)_6OH$, 78%]
16c [R=$(CH_2)_7OH$, 92%] **17c** [R=$(CH_2)_7OH$, 75%]
16g [R=CH_2CONH_2, 80%] **17g** [R=CH_2CONH_2, 73%]



16d (Y=OMe, 100%) **17d** (Y=OMe, 67%)
16e (Y=OCH_2Ph, 95%) **17e** (Y=OCH_2Ph, 99%)
16f (Y=NH_2, 37%) **17f** (Y=NH_2, 90%)

Reagents :
a) i) NaH, $THPO(CH_2)_mI$, DMF ii) *p*-TsOH, MeOH
b) NaH, $ClCH_2CONH_2$, DMF
c) 31% aq H_2O_2, concd HCl, Na_2WO_4, MeOH
d) NaH, MeI, DMF
e) NaH, BnBr, DMF
f) i) DEAD, Ph_3P, Phthalimide, THF ii) $H_2N\text{-}NH_2\cdot H_2O$, EtOH

Chart 4

corresponding alcohol **16a**. Amine **16f** was prepared by introduction of the phthalimido group into **16a**,[17] followed by treatment with hydrazine hydrate. These sulfides were also oxidized with hydrogen peroxide by the same method as described above to give the corresponding sulfones **17a—g** in high yields.

Results and Discussion

First, the antifungal activities of 3-desmethyl analog **3**, 3-*erythro*-methyl analog **4**, 3-*threo*-methyl analog **5** and 3,3-dimethyl analog **6** were compared to clarify the significance of 3-methylation.

The minimum inhibitory concentration values (MIC, μg/ml) of sulfones **3—6** against *Candida albicans* KB-8 and *Aspergillus fumigatus* MTU6001 are presented in Table 1. Their *in vitro* activity against *C. albicans* was found to increase in the order, desmethyl (**3**) < *erythro*-methyl (**4**) < *threo*-methyl (**5**) ≈ dimethyl (**6**). Their activity against *A. fumigatus* increased in a similar order, desmethyl (**3**) < *erythro*-methyl (**4**) < *threo*-methyl (**5**) < dimethyl (**6**).

The results on the prophylactic efficacy of sulfones **3—6** against murine systemic candidiasis and aspergillosis are summarized in Table 2. The orders of efficacy against candidiasis and aspergillosis are the same as those in *in vitro*, respectively, with the exception of 3-*erythro*-methyl analog **4**.[14] Particularly, 3-*threo*-methyl analog **5** and 3,3-dimethyl analog **6** showed high efficacy, even though the doses were low.

Table 1. *In Vitro* Antifungal Activity of Analogs **3**, **4**, **5** and **6**

Compound	Remarks	MIC (μg/ml)	
		C. albicans KB-8	*A. fumigatus* MTU4001
3	3-Desmethyl	6.25	>100
4	3-*erythro*-Methyl	0.39	100
5	3-*threo*-Methyl	0.20	12.5
6	3,3-Dimethyl	0.20	3.13
2	Fluconazole	0.78	400

Since 3,3-dimethyl analog **6** showed activity equal to or higher than that of 3-*threo*-methyl analog **5**, we were interested in the activity of further analogs of **6** which had ω-substituted alkylthio or alkylsulfonyl groups instead of the methylsulfonyl group. The evaluation data of such analogs, **16a—g** and **17a—g**, are summarized in Table 3, together with those of the corresponding 3-*threo*-methyl analogs **12a—g** and **13a—g**. With respect to sulfides, 3,3-dimethyl analogs **16a—g** showed higher *in vitro* activity against both *C. albicans* and *A. fumigatus* than the corresponding 3-*threo*-methyl analogs **12a—g** in all cases. Similar results were obtained for the relation between sulfones **13a—g** and **17a—g**. The prophylactic efficacy against murine systemic candidiasis and aspergillosis was also improved significantly by 3,3-dimethylation. Among the synthesized sulfides and 2-hydroxyethylsulfone de-

Table 2. Prophylactic Efficacy of Analogs **3**, **4**, **5** and **6**[a]

Compound	Remarks	Candidiasis[b]		Aspergillosis[c]	
		Dose (mg/kg)	Mean survival (d)[d]	Dose (mg/kg)	Mean survival (d)[d]
3	3-Desmethyl	1	0.8 (0.2)		
		10	7.6 (4.7)	50	1.6 (1.3)
4	3-*erythro*-Methyl	1	0.7 (0.7)		
		10	0.9 (0.7)		
5	3-*threo*-Methyl	1	9.6 (0.5)	5	5.7 (2.6)
		10	10 (0.5)	20	9.6 (2.6)
6	3,3-Dimethyl	1	9.6 (0.5)	5	10 (2.6)
		10	10 (0.5)	20	10 (2.6)
2	Fluconazole	1	7.1 (0.2)		
		10	10 (0.7)	100	2.8 (2.0)

a) Prophylactic efficacy was determined in mice. The triazole derivative was administered orally. *b*) Inoculated *via* tail vein with 2.0×10^6 cells of *C. albicans* KB-8. *c*) Inoculated *via* tail vein with 2.0×10^7 conidia of *A. fumigatus* MTU6001. *d*) Mean survival days of control mice under the same conditions are given in parentheses.

Table 3. Antifungal Activity of 3-*threo*-Methyl Derivatives **12** and **13**, and 3,3-Dimethyl Derivatives **16** and **17**

Compound	$S(O)_nR$	MIC (μg/ml)		Mean survival days[a]	
		C. albicans	*A. fumigatus*	*C. albicans*[b]	*A. fumigatus*[c]
12a	$S(CH_2)_2OH$	1.56	50	2.6 (2.0)	1.0 (1.0)
13a	$SO_2(CH_2)_2OH$	>6.25	>100	1.3 (2.0)	1.5 (1.0)
16a	$S(CH_2)_2OH$	0.05	3.13	9.1 (0.3)	9.4 (2.0)
17a	$SO_2(CH_2)_2OH$	0.78	50	9.4 (1.6)	10 (3.5)
12b	$S(CH_2)_6OH$	≤0.013	0.78	2.8 (1.1)	2.8 (2.3)
13b	$SO_2(CH_2)_6OH$	0.39	100	1.4 (0.9)	3.1 (1.8)
16b	$S(CH_2)_6OH$	≤0.013	≤0.20	10 (4.7)	10 (2.6)
17b	$SO_2(CH_2)_6OH$	0.10	n.t.	2.6 (4.7)	2.1 (2.6)
12c	$S(CH_2)_7OH$	≤0.013	0.78	10 (0.1)	9.7 (1.5)
13c	$SO_2(CH_2)_7OH$	0.39	25	n.t.[d]	1.2 (1.5)
16c	$S(CH_2)_7OH$	≤0.013	≤0.20	9.7 (0.5)	10 (1.7)
17c	$SO_2(CH_2)_7OH$	0.10	12.5	4.2 (1.1)	n.t.
12d	$S(CH_2)_2OMe$	≤0.013	6.25	n.t.	3.0 (3.7)
13d	$SO_2(CH_2)_2OMe$	0.39	>100	n.t.	1.8 (2.7)
16d	$S(CH_2)_2OMe$	≤0.013	1.56	9.3 (1.8)	9.5 (1.5)
17d	$SO_2(CH_2)_2OMe$	0.20	50	9.5 (1.8)	8.3 (1.5)
12e	$S(CH_2)_2OBn$[e]	≤0.013	1.57	0.2 (0.0)	2.1 (2.6)
13e	$SO_2(CH_2)_2Bn$	≤0.013	25	n.t.	1.2 (1.0)
16e	$S(CH_2)_2OBn$	≤0.013	≤0.20	8.9 (1.8)	10 (1.5)
17e	$SO_2(CH_2)_2OBn$	≤0.013	12.5	9.3 (0.5)	10 (1.6)
12f	$S(CH_2)_2NH_2$	0.78	>100	2.6 (2.0)	n.t.
13f	$SO_2(CH_2)_2NH_2$	6.25	>100	1.4 (2.0)	1.2 (1.3)
16f	$S(CH_2)_2NH_2$	0.20	12.5	8.8 (0.8)	10 (1.5)
17f	$SO_2(CH_2)_2NH_2$	1.56	>100	2.1 (0.3)	1.6 (1.6)
12g	SCH_2CONH_2	3.13	>100	8.5 (4.7)	1.4 (1.3)
13g	$SO_2CH_2CONH_2$	>6.25	>100	n.t.	n.t.
16g	SCH_2CONH_2	0.78	100	8.5 (0.2)	10 (2.2)
17g	$SO_2CH_2CONH_2$	>6.25	>100	3.4 (0.5)	4.0 (1.8)

a) Prophylactic efficacy was determined in mice. The triazole derivative was administered orally. Mean survival days of control mice under the same conditions are given in parentheses. *b*) 10 mg/kg/dose of the triazole derivative was used. *c*) 50 mg/kg/dose of the triazole derivative was used. *d*) n.t. means not tested. *e*) Bn means benzyl group (CH_2Ph).

rivatives, the 3,3-dimethyl analogs (**16a—g**, **17a**, **17d** and **17e**) showed higher efficacy against both candidiasis and aspergillosis than the corresponding 3-*threo*-methyl analogs (**12a—g**, **13a**, **13d** and **13e**). Especially, **16a**, **16b**, **16d**, **16e**, **16f**, **17a**, **17d** and **17e** showed significant efficacy, whereas their corresponding 3-*threo*-methyl derivatives did not show any efficacy. On the other hand, no significant efficacy was observed with the sulfone derivatives having a long chain (**17c**), 2-aminoethyl group (**17f**) or carbamoylmethyl group (**17g**) on the sulfur atom, or with the corresponding 3-*threo*-methyl analogs **13c**, **13f** and **13g**.

In conclusion, we found that the 3,3-dimethyl analogs had more efficient antifungal activity both *in vitro* and *in vivo* than the corresponding mono-methyl and desmethyl analogs. Moreover, they showed potent efficacy against not only murine systemic candidiasis, but also murine systemic aspergillosis. Further investigations are in progress to clarify the reason for those effects of the 3,3-dimethyl group.

Experimental

Melting points were determined on a Thomas–Hoover capillary melting point apparatus without correction. Infrared spectra (IR) were recorded on a JASCO A-102 IR spectrometer or a Perkin Elmer 1600 FTIR spectrometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR, 270 MHz) were obtained on a JEOL JNM-GX270 spectrometer in the designated solvent using tetramethylsilane as an internal standard (δ 0.00). TLC was performed on precoated glass sheets of Silica gel 60 F-254 (E. Merck). Chromatography columns were prepared with Silica gel 60 (70—230 mesh, E. Merck). All reagents were obtained from commercial suppliers and used as received unless otherwise indicated. *N*,*N*-Dimethylformamide (DMF) and dichloromethane were dried over molecular sieves 4A. Tetrahydrofuran (THF) and DMSO were dried over molecular sieves 5A.

1-(2,4-Difluorophenyl)-2-methyl-2-methylthio-1-propanone (8) A 15% aqueous solution of sodium methanethiolate (1.40 g, 3.00 mmol) at −30 °C was added dropwise to a cooled solution of α-bromoketone **7** (526 mg, 2.00 mmol) in ethanol (10.0 ml) at −30 °C over a 30 min period, and the mixture was stirred at −30 °C for an additional 10 min. Then, the mixture was diluted with toluene (50 ml), and washed with water (15 ml × 2) and brine (15 ml) in that order. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 20 g of silica gel eluting with hexane and toluene (1 : 1) to give **8** (451 mg, 98% yield) as a colorless oil. IR (KBr): 1695, 1620, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 6H, Me × 2), 2.01 (s, 3H, SMe), 6.80—6.91 (m, 2H, Ph-H), 7.64 (m, 1H, Ph-H).

2-(2,4-Difluorophenyl)-2-[1-methyl-1-(methylthio)ethyl]oxirane (9) Sodium hydride (60% assay, 1.41 g, 35.0 mmol) was added in a small portions to a solution of trimethyloxosulfonium iodide (8.45 g, 38.0 mmol) in DMSO (100 ml) at 15 °C, and the mixture was stirred at room temperature for 30 min. Then, a solution of ketone **8** (7.05 g, 30.6 mmol) in THF (30 ml) was added dropwise, and the whole was stirred at room temperature for 24 h. It was diluted with water (50 ml) and extracted with toluene (50 ml × 3). The combined organic layers were washed with water (50 ml × 3) and brine (50 ml × 2) in that order, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to give **9** (7.50 g, a quantitative yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (s, 3H, Me), 1.34 (s, 3H, Me), 2.15 (s, 3H, SMe), 2.73 (d, 1H, J = 5.0 Hz), 3.30 (d, 1H, J = 5.0 Hz), 6.72—6.91 (m, 2H, Ph-H), 7.50 (m, 1H, Ph-H).

2-(2,4-Difluorophenyl)-3-methyl-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (10) 1*H*-1,2,4-Triazole (3.32 g, 48.1 mmol) and sodium hydroxide (95% assay, 1.35 g, 32.1 mmol) were added to a solution of oxirane **9** obtained above (7.50 g) in DMSO (48 ml), and the resultant mixture was heated at 80 °C for 3 h and then 100 °C for 1 h. The reaction mixture was poured into water (50 ml), and the whole was extracted with toluene (100 ml × 2). The combined organic layers were washed with brine (50 ml × 5), dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 150 g of silica gel eluting with hexane and ethyl acetate (1 : 1) to give **10** (5.54 g, 58% yield from **8**) as a colorless crystalline powder, mp 56.0—58.0 °C. IR (KBr): 1615, 1600, 1520, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, Me), 1.34 (s, 3H, Me), 2.21 (s, 3H, SMe), 4.91 (d, 1H, J = 14.2 Hz), 5.26 (s, 1H, OH), 5.30 (d, 1H, J = 14.2 Hz), 6.63 (m, 1H, Ph-H), 6.80 (m, 1H, Ph-H), 7.67 (m, 1H, Ph-H), 7.73 (s, 1H, Tz-H), 8.08 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{17}F_2N_3OS$: C, 53.66; H, 5.47; N, 13.41. Found: C, 53.59; H, 5.49; N, 13.54.

2-(2,4-Difluorophenyl)-3-methyl-3-methylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (6) Sodium tungstate dihydrate (16 mg, 0.05 mmol) and concd hydrochloric acid (0.75 g, 7.20 mmol) were added to a suspension of sulfide **10** (1.50 g, 4.79 mmol) in methanol (9.0 ml), and the resultant mixture was stirred at room temperature while 31% aqueous H_2O_2 (1.58 g, 14.4 mmol) was added dropwise. The reaction mixture was stirred at 60 °C for 1 h, then cooled to room temperature, followed by addition of 10% aqueous sodium sulfite to reduce excess H_2O_2. The resulting mixture was neutralized with 10% aqueous sodium hydroxide, and the precipitated crystals were collected by filtration and dried under reduced pressure to give **6** (1.38 g, 84% yield) as a colorless crystalline powder, mp 172.0—174.0 °C. IR (KBr): 1615, 1600, 1520, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (s, 3H, Me), 1.50 (s, 3H, Me), 3.24 (s, 3H, SO_2Me), 5.27 (d, 1H, J = 14.2 Hz), 5.38 (d, 1H, J = 14.2 Hz), 6.04 (s, 1H, OH), 6.68 (m, 1H, Ph-H), 6.83 (m, 1H, Ph-H), 7.65 (m, 1H, Ph-H), 7.71 (s, 1H, Tz-H), 8.05 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{17}F_2N_3O_3S$: C, 48.69; H, 4.96; N, 12.18. Found: C, 48.66; H, 5.04; N, 12.09.

***threo*-2-(2,4-Difluorophenyl)-3-(2-hydroxyethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12a)** 2-Mercaptoethanol (1.88 g, 24.0 mmol) was added dropwise to a suspension of sodium hydride (0.88 g, 60% assay, 22.0 mmol) in DMF (30 ml) at 0 °C. After 10 min, a solution of oxirane **11** (5.02 g, 20.0 mmol) in DMF (10 ml) was added dropwise to the mixture, and the resultant solution was stirred at 0 °C for 1 h, then at room temperature for 1 h. It was poured into water (100 ml), followed by extraction with toluene (100 ml × 2). The organic layers were combined and washed with 4% sodium perchlorate solution (100 ml), water (100 ml × 2) and brine (100 ml) in that order. The toluene layer was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 200 g of silica gel eluting with hexane and ethyl acetate (1 : 2) to give **12a** (2.83 g, 43% yield) as a colorless crystalline powder, mp 132.0—134.0 °C. IR (KBr): 1620, 1600, 1520, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (d, 3H, J = 6.9 Hz, $CHC\underline{H}_3$), 2.05—2.25 (br, 2H, OH × 2), 2.82—3.04 (m, 2H, SCH_2), 3.41 (q, 1H, J = 6.9 Hz, $C\underline{H}CH_3$), 3.80—3.97 (m, 2H, $C\underline{H}_2OH$), 4.90 (d, 1H, J = 14.5 Hz), 5.21 (d, 1H, J = 14.5 Hz), 6.71—6.81 (m, 2H, Ph-H), 7.38 (m, 1H, Ph-H), 7.80 (s, 1H, Tz-H), 8.27 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{17}F_2N_3O_2S$: C, 51.05; H, 5.20; N, 12.76. Found: C, 50.85; H, 5.34; N, 12.77.

***threo*-2-(2,4-Difluorophenyl)-3-(6-hydroxyhexyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12b)** The title compound was obtained as a colorless crystalline powder in 74% yield by the same method as described for synthesis of **12a**, using 6-mercapto-1-hexanol, mp 95.0—98.0 °C. IR (KBr): 1620, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H, J = 6.9 Hz, $CHC\underline{H}_3$), 1.34—1.71 (m, 9H, $SCH_2(C\underline{H}_2)_4CH_2O\underline{H}$), 2.62—2.78 (m, 2H, SCH_2), 3.26 (q, 1H, J = 6.9 Hz, $C\underline{H}CH_3$), 3.68 (m, 2H, $C\underline{H}_2OH$), 4.63 (s, 1H, OH), 4.85 (d, 1H, J = 14.2 Hz), 5.07 (d, 1H, J = 14.2 Hz), 6.70—6.77 (m, 2H, Ph-H), 7.37 (m, 1H, Ph-H), 7.76 (s, 1H, Tz-H), 7.83 (s, 1H, Tz-H). *Anal.* Calcd for $C_{18}H_{25}F_2N_3O_2S \cdot 1/2H_2O$: C, 54.81; H, 6.64; N, 10.65. Found: C, 54.65; H, 6.50; N, 10.65.

***threo*-2-(2,4-Difluorophenyl)-3-(7-hydroxyheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12c)** The title compound was obtained as a colorless crystalline powder in 39% yield by the same method as described for synthesis of **12a**, using 7-mercapto-1-heptanol, mp 107.0—108.0 °C. IR (KBr): 1620, 1605, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H, J = 6.9 Hz, $CHC\underline{H}_3$), 1.33—1.47 (m, 6H, $SCH_2CH_2(C\underline{H}_2)_3$), 1.52—1.67 (m, 5H, $SCH_2C\underline{H}_2(CH_2)_3C\underline{H}_2CH_2O\underline{H}$), 2.64—2.75 (m, 2H, SCH_2), 3.26 (q, 1H, J = 6.9 Hz, $C\underline{H}CH_3$), 3.66 (m, 2H, $C\underline{H}_2OH$), 4.62 (s, 1H, OH), 4.85 (d, 1H, J = 14.2 Hz), 5.07 (d, 1H, J = 14.2 Hz), 6.70—6.77 (m, 2H, Ph-H), 7.35 (m, 1H, Ph-H), 7.76 (s, 1H, Tz-H), 7.84 (s, 1H, Tz-H). *Anal.* Calcd for $C_{19}H_{27}F_2N_3O_2S$: C, 57.12; H, 6.81; N, 10.52; S, 8.03. Found: C, 57.20; H, 6.79; N, 10.54; S, 8.15.

***threo*-2-(2,4-Difluorophenyl)-3-(2-methoxyethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12d)** A solution of alcohol **12a** (988 mg, 3.00 mmol) in DMF (3.0 ml) was added dropwise to a suspension of sodium hydride (144 mg, 60% assay, 3.60 mmol) in DMF (7.0 ml) at 0 °C, and the resultant solution was stirred at 0 °C for 15 min. Iodomethane (242 μl, 3.90 mmol) was added dropwise to the solution at 0 °C, and the mixture was stirred at 0 °C for 2 h. It was poured into water (20 ml), followed by extraction with toluene (50 ml × 2). The organic layers were combined and washed with water (20 ml) and brine (20 ml) in that order. The toluene layer was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 30 g of silica gel eluting with hexane and ethyl acetate (1 : 1) to give **12d** (1.01 g, 98% yield) as a colorless crystalline powder, mp 72.0—74.0 °C. IR (KBr): 1615, 1600, 1520, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (d, 3H, J = 6.9 Hz, $CHC\underline{H}_3$), 2.80—3.00 (m, 2H, SCH_2), 3.43 (q, 1H, J = 6.9 Hz, $C\underline{H}CH_3$), 3.45 (s, 3H, OMe), 3.61—3.71 (m, 2H, $SCH_2C\underline{H}_2O$), 4.85 (d, 1H, J = 14.2 Hz), 4.96 (br s, 1H, OH), 5.14 (d, 1H, J = 14.2 Hz), 6.70—6.79 (m, 2H, Ph-H), 7.37 (m, 1H, Ph-H), 7.77 (s, 1H, Tz-H), 7.91 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{19}F_2N_3O_2S$: C, 52.57; H, 5.58; N, 12.24. Found: C, 52.32; H, 5.64; N, 12.27.

***threo*-2-(2,4-Difluorophenyl)-3-(2-benzyloxyethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12e)** The title compound was obtained as a colorless crystalline powder in 71% yield by the same method as described for synthesis of **12d**, using benzyl bromide, mp 59.0—62.0 °C. IR (KBr): 1620, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H, J = 7.2 Hz, $CHC\underline{H}_3$), 2.83—3.03 (m, 2H, SCH_2), 3.41 (q, 1H, J = 7.2 Hz, $C\underline{H}CH_3$), 3.74 (t, 2H, J = 6.7 Hz, $SCH_2C\underline{H}_2O$), 4.61 (s, 2H, CH_2Ph),

4.77 (d, 1H, J=14.2 Hz), 4.84 (s, 1H, OH), 5.05 (d, 1H, J=14.2 Hz), 6.67—6.75 (m, 2H), 7.29—7.38 (m, 6H), 7.64 (s, 1H, Tz-H), 7.72 (s, 1H, Tz-H). *Anal.* Calcd for $C_{21}H_{23}F_2O_2N_3S$: C, 60.13; H, 5.53; N, 10.02. Found: C, 60.41; H, 5.58; N, 9.88.

***threo*-2-(2,4-Difluorophenyl)-3-(2-aminoethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12f)** The title compound was obtained as a pale yellow crystalline powder in 66% yield by the same method as described for synthesis of **12a**, using 2-aminoethanethiol, mp 80.0—83.0 °C. IR (KBr): 1620, 1595, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (d, 3H, J=7.2 Hz, $CHC\underline{H}_3$), 2.10—2.70 (m, 3H, NH_2 and OH), 2.71 (m, 4H, $SCH_2C\underline{H}_2N$), 3.37 (q, 1H, J=7.2 Hz, $C\underline{H}CH_3$), 4.80 (d, 1H, J=14.2 Hz), 5.15 (d, 1H, J=14.2 Hz), 6.71—6.79 (m, 2H, Ph-H), 7.41 (m, 1H, Ph-H), 7.75 (s, 1H, Tz-H), 7.84 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{18}F_2N_4OS\cdot H_2O$: C, 48.54; H, 5.82; N, 16.17. Found: C, 48.37; H, 5.78; N, 16.28.

***threo*-2-(2,4-Difluorophenyl)-3-carbamoylmethylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12g)** The title compound was obtained as a colorless crystalline powder in 68% yield by the same method as described for synthesis of **12a**, using carbamoylmethanethiol, mp 167.0—170.0 °C. IR (KBr): 1690, 1620, 1595, 1515, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.03 (d, 3H, J=6.9 Hz, $CHC\underline{H}_3$), 3.26 (s, 2H, SCH_2CO), 3.60 (q, 1H, J=7.2 Hz, $C\underline{H}CH_3$), 4.74 (d, 1H, J=14.2 Hz), 4.98 (d, 1H, J=14.2 Hz), 6.25 (s, 1H, OH), 6.88 (m, 1H, Ph-H), 7.09—7.26 (m, 3H, NH and Ph-H×2), 7.60 (m, 1H, NH), 7.62 (s, 1H, Tz-H), 8.27 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{16}F_2N_4O_2S$: C, 49.12; H, 4.71; N, 16.36. Found: C, 48.82; H, 4.77; N, 16.55.

***threo*-2-(2,4-Difluorophenyl)-3-(2-hydroxyethyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13a)** The title compound was obtained from sulfide **12a** as a colorless crystalline powder in 82% yield by the same method as described for synthesis of **6**, mp 195.0—197.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.11 (d, 3H, J=7.2 Hz, $CHC\underline{H}_3$), 3.18—3.57 (m, 3H, $SO_2C\underline{H}_2CH_2O\underline{H}$), 3.87 (m, 2H, $SO_2CH_2C\underline{H}_2O$), 4.03 (q, 1H, J=7.2 Hz, $C\underline{H}CH_3$), 4.86 (d, 1H, J=14.6 Hz), 5.32 (d, 1H, J=14.6 Hz), 6.38 (s, 1H, OH), 6.89 (m, 1H, Ph-H), 7.12—7.22 (m, 2H, Ph-H), 7.60 (s, 1H, Tz-H), 8.34 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{17}F_2N_3O_4S$: C, 46.53; H, 4.74; N, 11.63; S, 8.87. Found: C, 46.21; H, 4.84; N, 11.52; S, 8.78.

***threo*-2-(2,4-Difluorophenyl)-3-(6-hydroxyhexyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13b)** The title compound was obtained from sulfide **12b** as a colorless crystalline powder in 86% yield by the same method as described for synthesis of **6**, mp 110.5—112.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (d, 3H, J=7.2 Hz, $CHC\underline{H}_3$), 1.43—1.67 (m, 7H, $SO_2CH_2CH_2(C\underline{H}_2)_3CH_2O\underline{H}$), 1.86—2.04 (m, 2H, $SO_2CH_2C\underline{H}_2$), 3.18 (m, 1H), 3.36 (m, 1H), 3.59—3.71 (m, 3H, $C\underline{H}CH_3$ and $C\underline{H}_2OH$), 5.02 (d, 1H, J=14.2 Hz), 5.37 (d, 1H, J=14.2 Hz), 5.49 (s, 1H, OH), 6.71—6.81 (m, 2H, Ph-H), 7.29 (m, 1H, Ph-H), 7.76 (s, 1H, Tz-H), 7.79 (s, 1H, Tz-H). *Anal.* Calcd for $C_{18}H_{25}F_2N_3O_4S\cdot 3/5H_2O$: C, 50.48; H, 6.17; N, 9.81. Found: C, 50.28; H, 5.83; N, 9.78.

***threo*-2-(2,4-Difluorophenyl)-3-(7-hydroxyheptyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13c)** The title compound was obtained from sulfide **12c** as a colorless crystalline powder in 95% yield by the same method as described for synthesis of **6**, mp 85.0—86.5 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (d, 3H, J=7.2 Hz, $CHCH_3$), 1.30—1.65 (m, 8H, $SO_2CH_2CH_2(C\underline{H}_2)_4$), 1.75—2.00 (m, 3H, $SO_2CH_2C\underline{H}_2$ and $CH_2O\underline{H}$), 3.16 (m, 1H), 3.34 (m, 1H), 3.64 (q, 1H, J=7.2 Hz, $C\underline{H}CH_3$), 3.66 (t, 2H, J=6.4 Hz, $C\underline{H}_2OH$), 5.04 (d, 1H, J=14.5 Hz), 5.46 (d, 1H, J=14.5 Hz), 5.53 (br s, 1H, OH), 6.71—6.82 (m, 2H, Ph-H), 7.30 (m, 1H, Ph-H), 7.79 (s, 1H, Tz-H), 7.96 (s, 1H, Tz-H). *Anal.* Calcd for $C_{19}H_{27}F_2N_3O_4S\cdot 1/3H_2O$: C, 52.16; H, 6.37; N, 9.60. Found: C, 52.45; H, 6.45; N, 9.63.

***threo*-2-(2,4-Difluorophenyl)-3-(2-methoxyethyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13d)** The title compound was obtained from sulfide **12d** as a colorless crystalline powder in 62% yield by the same method as described for synthesis of **6**, mp 111.0—112.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (d, 3H, J=7.2 Hz, $CHC\underline{H}_3$), 3.44 (s, 3H, OMe), 3.38—3.61 (m, 2H, SO_2CH_2), 3.79—4.01 (m, 3H, $C\underline{H}CH_3$ and $SO_2CH_2CH_2O$), 5.03 (d, 1H, J=14.5 Hz), 5.38 (br s, 1H, OH), 5.40 (d, 1H, J=14.5 Hz), 6.71—6.82 (m, 2H, Ph-H), 7.31 (m, 1H, Ph-H), 7.75 (s, 1H, Tz-H), 7.94 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{19}F_2N_3O_4S\cdot 1/4H_2O$: C, 47.43; H, 5.17; N, 11.06. Found: C, 47.49; H, 5.12; N, 11.12.

***threo*-2-(2,4-Difluorophenyl)-3-(2-benzyloxyethyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13e)** The title compound was obtained from sulfide **12e** as a colorless crystalline powder in 62% yield by the same method as described for synthesis of **6**, mp 123.5—125.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (d, 3H, J=6.9 Hz, $CHC\underline{H}_3$), 3.44 (m, 1H), 3.60 (m, 1H), 3.84 (q, 1H, J=6.9 Hz, $C\underline{H}CH_3$), 3.93—4.14 (m, 2H, $SO_2CH_2C\underline{H}_2O$), 4.61 (s, 2H, CH_2Ph), 4.99 (d, 1H, J=14.5 Hz), 5.29 (s, 1H, OH), 5.35 (d, 1H, J=14.5 Hz), 6.69—6.77 (m, 2H), 7.23—7.40 (m, 6H), 7.71 (s, 1H, Tz-H), 7.79 (s, 1H, Tz-H). *Anal.* Calcd for $C_{21}H_{23}F_2N_3O_4S$: C, 55.87; H, 5.13; N, 9.31. Found: C, 56.01; H, 5.16; N, 9.22.

***threo*-2-(2,4-Difluorophenyl)-3-(2-aminoethyl)sulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13f)** The title compound was obtained from sulfide **12f** as a colorless crystalline powder in 80% yield by the same method as described for synthesis of **6**, mp 124.0—127.0 °C. IR (KBr): 1615, 1600, 1510, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (d, 3H, J=7.3 Hz, $CHC\underline{H}_3$), 1.50—2.50 (br, 3H, OH and NH_2), 3.27—3.41 (m, 3H), 3.56 (m, 1H), 3.69 (q, 1H, J=7.3 Hz, $C\underline{H}CH_3$), 5.00 (d, 1H, J=14.5 Hz), 5.41 (d, 1H, J=14.5 Hz), 6.71—6.82 (m, 2H, Ph-H), 7.29 (m, 1H, Ph-H), 7.75 (s, 1H, Tz-H), 7.76 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{18}F_2N_4O_3S\cdot 1/3H_2O$: C, 45.89; H, 5.14; N, 15.29. Found: C, 45.76; H, 4.98; N, 15.29.

***threo*-2-(2,4-Difluorophenyl)-3-carbamoylmethylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13g)** The title compound was obtained from sulfide **12g** as a colorless crystalline powder in 74% yield by the same method as described for synthesis of **6**, mp 178.0 °C (dec.). IR (KBr): 1690, 1620, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (d, 3H, J=6.9 Hz, $CHC\underline{H}_3$), 3.97 (d, 1H, J=14.2 Hz), 4.32 (d, 1H, J=14.2 Hz), 4.45 (q, 1H, J=6.9 Hz, $C\underline{H}CH_3$), 4.81 (d, 1H, J=14.5 Hz), 5.32 (d, 1H, J=14.5 Hz), 6.50 (s, 1H, OH), 6.89 (m, 1H, Ph-H), 7.13—7.21 (m, 2H, Ph-H), 7.58 (br, 1H, NH), 7.84 (br, 1H, NH), 7.85 (s, 1H, Tz-H), 8.32 (s, 1H, Tz-H). *Anal.* Calcd for $C_{14}H_{16}F_2N_4O_4S\cdot 1/4H_2O$: C, 44.38; H, 4.39; N, 14.79. Found: C, 44.25; H, 4.35; N, 14.74.

1-(2,4-Difluorophenyl)-2-(2-hydroxyethyl)thio-2-methyl-1-propanone (18) 2-Mercaptoethanol (5.90 ml, 83.8 mmol) was added dropwise to a suspension of sodium hydride (3.20 g, 60% assay, 80.0 mmol) in DMF (100 ml) at 0 °C, and the mixture was cooled to −40 °C. Then, a solution of α-bromoketone **7** (20.0 g, 76.0 mmol) in DMF (30 ml) was added dropwise at below −30 °C, and the mixture was stirred at −30 °C for an additional 1 h. The mixture was diluted with toluene (50 ml), and washed with water (15 ml×2) and brine (15 ml) in that order. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 300 g of silica gel eluting with hexane and ethyl acetate (5:2) to give **18** (19.80 g, a quantitative yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 6H, Me×2), 1.83 (t, 1H, J=6.0 Hz, OH), 2.74 (t, 2H, J=6.0 Hz, SCH_2), 3.78 (q, 2H, J=6.0 Hz, $C\underline{H}_2OH$), 6.73—6.93 (m, 2H, Ph-H), 7.69 (m, 1H, Ph-H).

1-(2,4-Difluorophenyl)-2-methyl-2-(2-tetrahydropyranyloxyethyl)thio-1-propanone (19) Dihydropyran (DHP, 6.50 ml, 71.1 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 120 mg, 0.48 mmol) were added to a solution of alcohol **18** (10.87 g, 41.8 mmol) in dichloromethane (100 ml) at 0 °C, and the mixture was stirred at room temperature for 20 h. Then, the mixture was diluted with dichloromethane (300 ml), and washed with 3% aqueous sodium hydrogen carbonate (100 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 280 g of silica gel eluting with hexane and ethyl acetate (4:1) to give **19** (14.34 g, a quantitative yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (s, 6H, Me×2), 1.50—1.80 (m, 6H), 2.74 (t, 2H, J=6.3 Hz), 3.53—3.62 (m, 2H), 3.83—3.93 (m, 2H), 4.62 (s-like, 1H), 6.79—6.90 (m, 2H, Ph-H), 7.77 (m, 1H, Ph-H).

2-(2,4-Difluorophenyl)-3-methyl-3-(2-tetrahydropyranyloxyethyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (21) The title compound was prepared from ketone **19** *via* oxirane **20** by the same method as described for synthesis of **10**. It was obtained as a colorless oil in 55% overall yield from **19**: ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, 6H, Me×2), 1.50—1.90 (m, 6H), 3.00—3.10 (m, 4H), 3.47—3.64 (m, 2H), 3.85—3.93 (m, 2H), 4.64 (br s, 1H), 4.97 (d, 1H, J=14.2 Hz), 5.28 (d, 1H, J=14.2 Hz), 5.31 (s, 1H, OH), 6.58—6.83 (m, 2H, Ph-H), 7.69 (m, 1H, Ph-H), 7.72 (s, 1H, Tz-H), 8.07 (s, 1H, Tz-H).

2-(2,4-Difluorophenyl)-3-(2-hydroxyethyl)thio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16a) A solution of THP ether **21** (2.397 g, 5.80 mmol) in methanol (12 ml) was treated with *p*-toluenesulfonic acid monohydrate (110 mg, 0.58 mmol) at 0 °C, and the mixture was stirred at room temperature for 20 h. Then, saturated sodium hydrogen carbonate (10 ml) was added to the reaction mixture, and the whole was

concentrated under reduced pressure. The residue was diluted with water (20 ml) and extracted with ethyl acetate (50 ml × 3). The combined organic layers were washed with brine (50 ml), dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting residue was crystallized from 2-propanol to give **16a** (1.486 g, 75% yield) as a colorless crystalline powder, mp 127.0—128.5 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (s, 3H, Me), 1.38 (s, 3H, Me), 2.23 (t, 1H, J=6.0 Hz, OH), 3.05 (m, 2H, SCH_2), 3.80 (q, 2H, J=6.0 Hz, $C\underline{H}_2OH$), 4.98 (d, 1H, J=14.2 Hz), 5.29 (d, 1H, J=14.2 Hz), 5.49 (s, 1H, OH), 6.64 (m, 1H, Ph-H), 6.81 (m, 1H, Ph-H), 7.69 (m, 1H, Ph-H), 7.73 (s, 1H, Tz-H), 8.07 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{19}F_2N_3O_2S$: C, 52.47; H, 5.58; N, 12.24. Found: C, 52.42; H, 5.80; N, 12.31.

2-(2,4-Difluorophenyl)-3-(6-hydroxyhexyl)thio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16b) A solution of thiol **15** (2.00 g, 6.69 mmol) in THF (15 ml) was added dropwise to a suspension of sodium hydride (417 mg, 60% assay, 10.4 mmol) in THF (17 ml) at 0 °C over a 10 min period, and the mixture was stirred at 0 °C for 1 h. Then, 6-iodohexyl tetrahydropyranyl ether (4.81 g, 15.4 mmol) was added dropwise to the reaction mixture at 0 °C over a 10 min period, and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into saturated ammonium chloride (50 ml) and extracted with ethyl acetate (50 ml × 2). The combined organic layers were washed with brine (50 ml), dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The resulting residue was purified by column chromatography on 80 g of silica gel eluting with hexane and ethyl acetate (2:1) to give THP ether of **16b** (3.258 g, a quantitative yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, Me), 1.35 (s, 3H, Me), 1.26—1.84 (m, 14H), 2.66—2.81 (m, 2H, SCH_2), 3.35—3.90 (m, 4H), 4.57 (br s, 1H), 4.91 (d, 1H, J=14.8 Hz), 5.25 (s, 1H, OH), 5.29 (d, 1H, J=14.8 Hz), 6.63 (m, 1H, Ph-H), 6.79 (m, 1H, Ph-H), 7.66 (m, 1H, Ph-H), 7.72 (s, 1H, Tz-H), 8.08 (s, 1H, Tz-H).

The THP ether was cleaved by the same method as described for synthesis of **16a**. Thus, the title compound **16b** (2.62 g) was obtained as a colorless oil in 98% overall yield from **15**. IR (neat): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, Me), 1.35 (s, 3H, Me), 1.30—1.60 (m, 9H, $SCH_2(C\underline{H}_2)_4CH_2O\underline{H}$), 2.66—2.88 (m, 2H, SCH_2), 3.64 (m, 2H, $C\underline{H}_2OH$), 4.91 (d, 1H, J=14.8 Hz), 5.25 (s, 1H, OH), 5.29 (d, 1H, J=14.8 Hz), 6.63 (m, 1H, Ph-H), 6.79 (m, 1H, Ph-H), 7.66 (m, 1H, Ph-H), 7.73 (s, 1H, Tz-H), 8.08 (s, 1H, Tz-H). *Anal.* Calcd for $C_{19}H_{27}F_2N_3O_2S \cdot 1/2H_2O$: C, 55.86; H, 6.91; N, 10.29. Found: C, 56.01; H, 6.68; N, 10.30.

2-(2,4-Difluorophenyl)-3-(7-hydroxyheptyl)thio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16c) The title compound was obtained from thiol **15** as a colorless oil in 92% overall yield by the same method as described for synthesis of **16b**, using 7-iodoheptyl tetrahydropyranyl ether. IR (neat): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, Me), 1.35 (s, 3H, Me), 1.30—1.46 (m, 7H, $SCH_2CH_2(C\underline{H}_2)_3CH_2CH_2O\underline{H}$), 1.51—1.60 (m, 4H, $SCH_2C\underline{H}_2(CH_2)_3C\underline{H}_2$), 2.62—2.83 (m, 2H, SCH_2), 3.61—3.67 (m, 2H, $C\underline{H}_2OH$), 4.91 (d, 1H, J=14.2 Hz), 5.24 (s, 1H, OH), 5.29 (d, 1H, J=14.2 Hz), 6.63 (m, 1H, Ph-H), 6.79 (m, 1H, Ph-H), 7.66 (m, 1H, Ph-H), 7.73 (s, 1H, Tz-H), 8.08 (s, 1H, Tz-H). *Anal.* Calcd for $C_{20}H_{29}F_2N_3O_2S$: C, 58.09; H, 7.03; N, 10.11. Found: C, 57.82; H, 7.23; N, 9.88.

2-(2,4-Difluorophenyl)-3-(2-methoxyethyl)thio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16d) The title compound was obtained from alcohol **16a** as a colorless oil in a quantitative yield by the same method as described for synthesis of **12d**. IR (neat): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 6H, Me × 2), 2.90—3.20 (m, 2H, SCH_2), 3.39 (s, 3H, OMe), 3.55—3.63 (m, 2H, CH_2O), 4.98 (d, 1H, J=14.2 Hz), 5.28 (d, 1H, J=14.2 Hz), 5.38 (s, 1H, OH), 6.64 (m, 1H, Ph-H), 6.79 (m, 1H, Ph-H), 7.67 (m, 1H, Ph-H), 7.73 (s, 1H, Tz-H), 8.07 (s, 1H, Tz-H). *Anal.* Calcd for $C_{16}H_{21}F_2N_3O_2S$: C, 53.77; H, 5.92; N, 11.76. Found: C, 53.39; H, 5.96; N, 11.61.

2-(2,4-Difluorophenyl)-3-(2-benzyloxyethyl)thio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16e) The title compound was obtained from alcohol **16a** as a colorless oil in 95% yield by the same method as described for synthesis of **12e**. IR (neat): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 6H, Me × 2), 2.98—3.14 (m, 2H, SCH_2), 3.63—3.69 (m, 2H, CH_2O), 4.56 (s, 2H, $C\underline{H}_2Ph$), 4.95 (d, 1H, J=14.2 Hz), 5.26 (d, 1H, J=14.2 Hz), 5.35 (s, 1H, OH), 6.62 (m, 1H, Ph-H), 6.78 (m, 1H, Ph-H), 7.27—7.35 (m, 5H, Ph-H), 7.65 (m, 1H, Ph-H), 7.71 (s, 1H, Tz-H), 8.02 (s, 1H, Tz-H). *Anal.* Calcd for $C_{22}H_{25}F_2N_3O_2S \cdot H_2O$: C, 58.52; H, 6.03; N, 9.31. Found: C, 58.80; H, 5.78; N, 9.34.

2-(2,4-Difluorophenyl)-3-(2-aminoethyl)thio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16f) A solution of diethyl azodicarboxylate (DEAD, 2.02 g, 11.60 mmol) in THF (40 ml) was added dropwise to a mixed solution of alcohol **16a** (2.00 g, 5.82 mmol), triphenylphosphine (3.05 g, 11.63 mmol) and phthalimide (1.71 g, 11.62 mmol) in THF (50 ml) at room temperature, and the mixture was stirred at room temperature for 20 h. It was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on 60 g of silica gel eluting with hexane and ethyl acetate (1:2) to give the imide (1.80 g, 65% yield) as a colorless crystalline powder. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 3H, Me), 1.35 (s, 3H, Me), 3.17 (t, 2H, J=6.9 Hz, $SC\underline{H}_2CH_2N$), 3.94 (t, 2H, J=6.9 Hz, $SCH_2C\underline{H}_2N$), 4.94 (d, 1H, J=14.5 Hz), 5.24 (d, 1H, J=14.5 Hz), 5.39 (s, 1H, OH), 6.60 (m, 1H, Ph-H), 6.76 (m, 1H, Ph-H), 7.65 (m, 1H, Ph-H), 7.70 (s, 1H, Tz-H), 7.72 (m, 2H), 7.86 (m, 2H), 8.05 (s, 1H, Tz-H).

The resultant imide was dissolved in ethanol (8.0 ml), and hydrazine hydrate (387 mg, 7.73 mmol) was added. The mixture was stirred at room temperature for 20 h, then poured into dichloromethane (50 ml), and the resultant precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in dichloromethane (50 ml). This solution was washed with 1 N HCl (20 ml). The aqueous layer was taken and added dropwise to a stirred mixture of dichloromethane (100 ml) and saturated sodium hydrogen carbonate (50 ml). The separated organic layer was washed with brine (50 ml), dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was crystallized from toluene to afford **16f** (823 mg, 37% overall yield from **16a**) as a colorless crystalline powder, mp 97.0—98.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 3H, Me), 1.37 (d, 3H, J=3.6 Hz, Me), 1.50—1.80 (br, 3H, NH_2 and OH), 2.85—3.00 (m, 4H, SCH_2CH_2N), 5.01 (d, 1H, J=14.2 Hz), 5.31 (d, 1H, J=14.2 Hz), 6.65 (m, 1H, Ph-H), 6.79 (m, 1H, Ph-H), 7.66 (m, 1H, Ph-H), 7.73 (s, 1H, Tz-H), 8.06 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{20}F_2N_4OS$: C, 52.62; H, 5.89; N, 16.36. Found: C, 52.76; H, 5.84; N, 16.06.

2-(2,4-Difluorophenyl)-3-carbamoylmethylthio-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16g) The title compound was obtained from thiol **15** as a colorless crystalline powder in 80% yield by a similar method to that described for synthesis of **16b**, using α-chloroacetamide, mp 79.0—81.5 °C. IR (KBr): 1660, 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (s, 3H, Me), 1.38 (d, 3H, J=3.2 Hz, Me), 3.53 (d, 1H, J=16.5 Hz), 3.63 (d, 1H, J=16.5 Hz), 5.01 (d, 1H, J=14.0 Hz), 5.27 (d, 1H, J=14.0 Hz), 5.75 (br s, 2H), 6.51 (br s, 1H), 6.66 (m, 1H, Ph-H), 6.83 (m, 1H, Ph-H), 7.65 (m, 1H, Ph-H), 7.66 (s, 1H, Tz-H), 8.08 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{18}F_2N_4O_2S \cdot 4/3H_2O$: C, 47.36; H, 5.48; N, 14.73. Found: C, 47.35; H, 5.39; N, 14.71.

2-(2,4-Difluorophenyl)-3-(2-hydroxyethyl)sulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17a) The title compound was obtained from sulfide ***16a*** as a colorless crystalline powder in 58% yield by the same method as described for synthesis of **6**, mp 141.5—142.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 3H, Me), 1.52 (s, 3H, Me), 2.85 (t, 1H, J=6.6 Hz, $CH_2O\underline{H}$), 3.67 (m, 1H), 3.84 (m, 1H), 4.26 (m, 2H, $C\underline{H}_2OH$), 5.25 (d, 1H, J=14.2 Hz), 5.37 (d, 1H, J=14.2 Hz), 6.10 (s, 1H, OH), 6.64—6.87 (m, 2H, Ph-H), 7.64 (m, 1H, Ph-H), 7.72 (s, 1H, Tz-H), 8.04 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{19}F_2N_3O_4S$: C, 47.99; H, 5.10; N, 11.19; F, 10.12; S, 8.54. Found: C, 48.11; H, 4.86; N, 11.31; F, 10.30; S, 8.73.

2-(2,4-Difluorophenyl)-3-(6-hydroxyhexyl)sulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17b) The title compound was obtained from sulfide **16b** as a colorless crystalline powder in 78% yield by the same method as described for synthesis of **6**, mp 68.5—70.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 3H, Me), 1.50 (s, 3H, Me), 1.40—1.70 (m, 7H, $SO_2CH_2CH_2(C\underline{H}_2)_3CH_2O\underline{H}$), 1.99 (m, 2H, $SO_2CH_2C\underline{H}_2$), 3.33 (m, 1H), 3.60 (m, 1H), 3.68 (m, 2H, $C\underline{H}_2OH$), 5.22 (d, 1H, J=14.5 Hz), 5.39 (d, 1H, J=14.5 Hz), 5.99 (s, 1H, OH), 6.67 (m, 1H, Ph-H), 6.83 (m, 1H, Ph-H), 7.64 (m, 1H, Ph-H), 7.71 (s, 1H, Tz-H), 8.05 (s, 1H, Tz-H). *Anal.* Calcd for $C_{19}H_{27}F_2N_3O_4S$: C, 52.89; H, 6.31; N, 9.74. Found: C, 52.73; H, 6.28; N, 9.66.

2-(2,4-Difluorophenyl)-3-(7-hydroxyheptyl)sulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17c) The title compound was obtained from sulfide **16c** as a colorless crystalline powder in 75% yield by the same method as described for synthesis of **6**, mp 80.0—83.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 3H, Me), 1.49 (d, 3H, J=4.0 Hz, Me), 1.41—1.58 (m, 9H, $SO_2CH_2CH_2(C\underline{H}_2)_4CH_2O\underline{H}$), 1.94—2.05 (m, 2H, $SO_2CH_2C\underline{H}_2$), 3.33 (m, 1H), 3.53 (m, 1H), 3.63—3.69 (m, 2H, $C\underline{H}_2OH$), 5.22 (d, 1H, J=14.2 Hz), 5.39 (d, 1H, J=14.2 Hz), 5.98 (s, 1H, OH), 6.68 (m, 1H, Ph-H), 6.82 (m, 1H, Ph-H),

7.64 (m, 1H, Ph-H), 7.71 (s, 1H, Tz-H), 8.05 (s, 1H, Tz-H). *Anal.* Calcd for $C_{20}H_{29}F_2N_3O_4S$: C, 53.92; H, 6.56; N, 9.43. Found: C, 53.70; H, 6.48; N, 9.41.

2-(2,4-Difluorophenyl)-3-(2-methoxyethyl)sulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17d) The title compound was obtained from sulfide **16d** as a colorless crystalline powder in 67% yield by the same method as described for synthesis of **6**. mp 116.0—120.0 °C. IR (KBr): 1615, 1600, 1515, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 3H, Me), 1.57 (d, 3H, J=3.8 Hz, Me), 3.44 (s, 3H, OMe), 3.68 (m, 1H), 3.88—4.02 (m, 3H), 5.25 (d, 1H, J=14.8 Hz), 5.37 (d, 1H, J=14.8 Hz), 6.06 (s, 1H, OH), 6.68 (m, 1H, Ph-H), 6.82 (m, 1H, Ph-H), 7.64 (m, 1H, Ph-H), 7.71 (s, 1H, Tz-H), 8.04 (s, 1H, Tz-H). *Anal.* Calcd for $C_{16}H_{21}F_2N_3O_4S$: C, 49.35; H, 5.43; N, 10.79. Found: C, 49.14; H, 5.45; N, 10.76.

2-(2,4-Difluorophenyl)-3-(2-benzyloxyethyl)sulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17e) The title compound was obtained from sulfide **16e** as a colorless oil in 99% yield by the same method as described for synthesis of **6**. IR (KBr): 1615, 1600, 1510, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 3H, Me), 1.50 (d, 3H, J=4.0 Hz, Me), 3.72 (m, 1H), 3.99 (m, 3H), 4.62 (s, 2H, CH_2Ph), 5.30 (d, 1H, J=14.5 Hz), 5.38 (d, 1H, J=14.5 Hz), 6.03 (s, 1H, OH), 6.67 (m, 1H, Ph-H), 6.81 (m, 1H, Ph-H), 7.29—7.38 (m, 5H, Ph-H), 7.62 (m, 1H, Ph-H), 7.70 (s, 1H, Tz-H), 8.03 (s, 1H, Tz-H). *Anal.* Calcd for $C_{22}H_{25}F_2N_3O_4S$: C, 56.76; H, 5.41; N, 9.03. Found: C, 56.37; H, 5.58; N, 8.74.

2-(2,4-Difluorophenyl)-3-(2-aminoethyl)sulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17f) The title compound was obtained from sulfide **16f** as a pale yellow crystalline powder in 90% yield by the same method as described for synthesis of **6**, mp 68.0—72.0 °C. IR (KBr): 1615, 1600, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 3H, Me), 1.49 (d, 3H, J=4.0 Hz, Me), 1.50—1.80 (br, 3H, OH and NH_2), 3.30—3.60 (m, 3H), 3.81 (m, 1H), 5.25 (d, 1H, J=14.2 Hz), 5.32 (d, 1H, J=14.2 Hz), 6.67 (m, 1H, Ph-H), 6.83 (m, 1H, Ph-H), 7.63 (m, 1H, Ph-H), 7.71 (s, 1H, Tz-H), 8.05 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{20}F_2N_4O_3S$: C, 48.12; H, 5.38; N, 14.96. Found: C, 48.28; H, 5.59; N, 14.66.

2-(2,4-Difluorophenyl)-3-carbamoylmethylsulfonyl-3-methyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17g) The title compound was obtained from sulfide **16g** as a colorless crystalline powder in 73% yield by the same method as described for synthesis of **6**, mp 174.5—177.0 °C. IR (KBr): 1660, 1615, 1600, 1520, 1500 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (s, 3H, Me), 1.56 (d, 3H, J=3.5 Hz, Me), 4.32 (d, 1H, J=14.9 Hz), 4.49 (d, 1H, J=14.9 Hz), 5.27 (d, 1H, J=14.3 Hz), 5.36 (d, 1H, J=14.3 Hz), 5.72 (br, 1H, NH), 6.26 (s, 1H, OH), 6.69 (m, 1H, Ph-H), 6.84 (m, 1H, Ph-H), 6.88 (br, 1H, NH), 7.64 (m, 1H, Ph-H), 7.70 (s, 1H, Tz-H), 8.04 (s, 1H, Tz-H). *Anal.* Calcd for $C_{15}H_{18}F_2N_4O_4S \cdot 4/5H_2O$: C, 44.73; H, 4.90; N, 13.91. Found: C, 45.00; H, 4.52; N, 13.55.

The *in Vitro* Activity against *C. albicans* KB-8 and *A. fumigatus* MTU6001 *C. albicans* KB-8 was grown at 37 °C on Sabouraud dextrose agar (SDA) for 24 h and transferred to glucose polypeptone yeast-extract broth for 24 h. *A. fumigatus* MTU6001 was grown at 30 °C on potato dextrose agar for 5 d. Approximately 10^3 saline-washed cells of *C. albicans* or conidia of *A. fumigatus* were inoculated into 1 ml of synthetic amino acid medium fungal (Gibco) containing a serially diluted triazole compound, and the plates were incubated at 37 °C for 24 h (*C. albicans*) or 30 °C for 2 d (*A. fumigatus*). The MIC was determined as the lowest concentration of the compound preventing visible fungal growth.

Prophylactic Efficiency against Murine Systemic Candidiasis and Aspergillosis Male albino ddY mice, five-week old, were inoculated *via* the tail vein with 2.0×10^6 cells of *C. albicans* KB-8 or 2.0×10^7 conidia of *A. fumigatus* MTU6001. An appropriate dose of a test compound in 0.5% methylcellulose or saline was orally administered to groups of 10 mice at 0, 24 and 48 h after infection. The survival rates were recorded for a period of 10 d. Almost all control mice died within 3 d after infection, whereas a considerable number of mice treated by oral administration of the triazole derivatives (1 or 10 mg/kg/dose for candidiasis, or 5, 20 or 50 mg/kg/dose for aspergillosis) survived significantly longer.

Acknowledgments We thank Drs. Ikutaro Saji and Hitoshi Fujita for valuable discussions, and Messrs. Mikiko Miyaguchi, Masahiko Tanaka and Kenko Kobayakawa for their technical assistance.

References

1) *a*) Gold J. W. M., *Am. J. Med.*, **76**, 458—463 (1984); *b*) Meunier F., *Rev. Infect. Dis.*, **9**, 408—416 (1987); *c*) Cairins M. R., *J. Electron Microscopy Techniques*, **8**, 115—131 (1988).
2) Heeres J., Backx L. J. J., Mostmans J. H., Van Cutsem J., *J. Med. Chem.*, **22**, 1003—1005 (1979).
3) *a*) Janssen P. A. J., Symoens J. E., *Am. J. Med.*, **74** (Suppl. 1B), 80—85 (1983); *b*) Lewis J. H., Zimmerman H. J., Benson G. D., Ishak K. G., *Gastroenterology*, **86**, 503—513 (1984).
4) *a*) Richardson K., Brammer K. W., Marriott M. S., Troke P. F., *Antimicrob. Agents Chemother.*, **27**, 832—835 (1985); *b*) Fromtling R. A., *Drugs of Today*, **26**, 547—556 (1990).
5) Kappe R., Osterziel K. J., Ruchel R., Siehl S., *J. Med. Veterinary Mycol.*, **31**, 259—261 (1993).
6) Tanio T., Ichise K., Nakajima T., Okuda T., *Antimicrob. Agents Chemother.*, **34**, 980—984 (1990).
7) *a*) Saji I., Tamoto K., Tanio T., Okuda T., Atsumi T., Abstracts of Papers, The 8th Medicinal Chemistry Symposium, Osaka, Nov. 1986, pp. 9—12; *b*) Saji I., Tanaka Y., Ichise K., Tanio T., Okuda T., Atsumi T., Eur. Patent EP-178533 (1986) [*Chem. Abstr.*, **105**, 35613 (1986)].
8) Miyauchi H., Kozuki K., Tanio T., Ohashi N., *Bioorg. Med. Chem. Lett.*, **5**, 1479—1482 (1995).
9) Gymer G. E., Richardson K., Eur. Patent EP-95828 (1983) [*Chem. Abstr.*, **100**, 85706 (1983)].
10) Saji I., Tamoto K., Tanaka Y., Miyauchi H., Fujimoto K., Ohashi N., *Bull. Chem. Soc. Jpn.*, **67**, 1427—1433 (1994).
11) Itoh K., Okonogi K., Tasaka A., Eur. Patent EP-510700 (1992) [*Chem. Abstr.*, **118**, 124544 (1992)].
12) Tomari M., Takagi J., Asahara N., Sakuma O., Ooto H., Iwase Y., Japan. Kokai Tokkyo Koho JP-05202005 (1993) [*Chem. Abstr.*, **120**, 134482 (1993)].
13) Corey E. J., Chaykovsky M., *J. Am. Chem. Soc.*, **87**, 1353—1364 (1965).
14) Tasaka A., Tamura N., Matsushita Y., Teranishi K., Hayashi R., Okonogi K., Itoh K., *Chem. Pharm. Bull.*, **41**, 1035—1042 (1993).
15) Oida S., Miyaoka T., Tajima Y., Konosu T., Takeda N., Yasuda H., Eur. Patent EP-473387 (1992) [*Chem. Abstr.*, **116**, 255617 (1992)].
16) Yamamoto N., Kodama H., Niwano Y., Yoshida M., Japan. Kokai Tokkyo Koho JP-05345768 (1993) [*Chem. Abstr.*, **120**, 245122 (1993)].
17) Mitsunobu O., Wada M., Sano T., *J. Am. Chem. Soc.*, **94**, 679—680 (1972).