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Synthesis and Antifungal Activity of Alkylthio and Alkylsulfonyl Derivatives of SM-8668

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Abstract—Triazole analogues which contained alkylthio or alkylsulfonyl groups where synthesized as derivatives of antifungal SM-8668 and estimated for their in vitro and in vivo activity. Derivatives having pentylthio, heptylthio or nonylthio groups showed excellent efficacy against both candidiasis and aspergillosis. Introduction of a hydrophilic group at the end of their alkyl chain made their activity stronger. Especially, 5-hydroxypentylthio and 7-hydroxyheptylthio derivatives showed the strongest antifungal activity.

Introduction

Imidazole and triazole antifungals are known as potent inhibitors of the cytochrome P_{450} monooxygenase in the process of fungal biosynthesis of ergosterol,[1,2] which is an important constituent of fungal cell membranes. This enzyme oxidatively removes the 14-α-methyl group of lanosterol (**1**) by using O_2 and NADPH.[3] Inhibition of this enzyme causes the accumulation of precursor 14-α-methyl sterols such as lanosterol and its biosynthetic derivatives, which leads to the destruction of cell membrane integrity.[4] Imidazole and triazole antifungals are believed to inhibit this enzyme by binding to the heterocyclic nitrogen atom (at the 3-position of the imidazolyl group or the 4-position of the triazolyl group) to the protoheme iron atom and exclude the oxygen atom which would normally take part in the reaction.[2,5] Since the target of the enzyme is the 14-α-methyl group of lanosterol, a logical inhibitor could be a lanosterol derivative with a heme binding component at the 14-α-methyl position. Indeed, such a derivative **2** was reported to be an inhibitor of fungal ergosterol biosynthesis and was active in vitro against *Candida* and dermatophyte strains.[6]

On the other hand, our research group previously reported that SM-8668 (**3**, DL-*threo*-isomer)[7] was demonstrated to have higher potency against a wide range of mycoses in animal experiments than fluconazole.[8,9] Interestingly, the corresponding *erythro*-isomer showed much lower activity than **3** both in vitro and in vivo.[7] Moreover, the potent antifungal activity of **3** depended only on the (2*R*,3*R*)-isomer and was scarcely dependent on the (2*S*,3*S*)-isomer, as we recently reported.[10] As shown in Chart 1, it seems that (2*R*,3*R*)-**3** has a similar structure to lanosterol as well as **2**, since the aromatic ring of **3** can be regarded as the B ring of **1**, and the methyl group at the 4-position and the methylene group at the 1-position of **3** can also be regarded as the 13-β-methyl group and the 14-α-methyl group of **1**, respectively. On the basis of these results, we considered (2*R*,3*R*)-**3** as a logical inhibitor of the cytochrome P_{450} monooxygenase. As part of our search for active antifungal agents, we synthesized a new series of analogues of **3** having a long alkyl group on sulfur atom.[11] Such substituents should be reasonable because they are regarded as the side chain of **1**.

Results and Discussion

Corresponding alkyl derivatives **4a–j** and **5b–j** were synthesized as shown in Chart 2, in order to investigate the structure–activity relationships on the length of R.

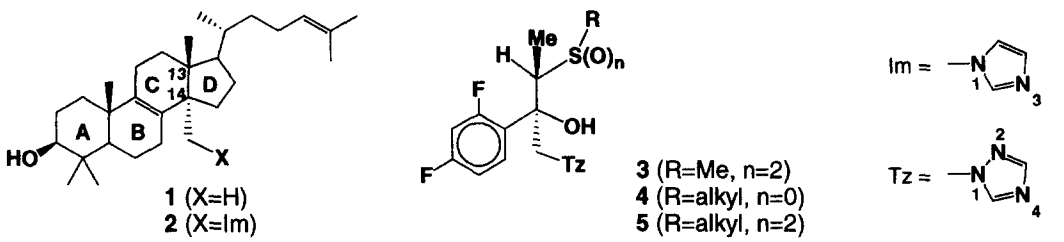

Chart 1.

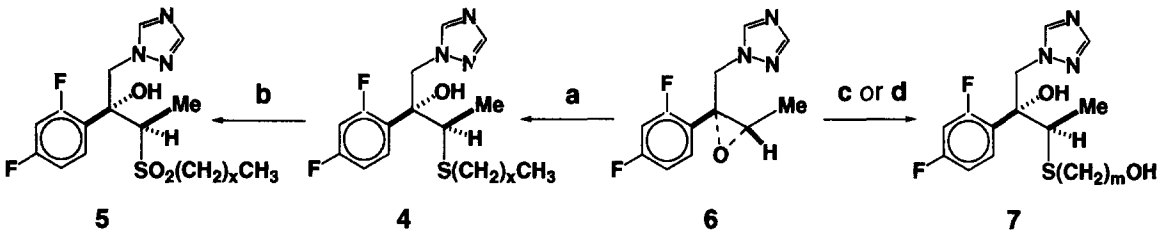

Chart 2. (a) NaH, $CH_3(CH_2)_xSH$, DMF; (b) H_2O_2, concd HCl, Na_2WO_4, MeOH; (c) $AcS(CH_2)_mOH$, 48% aq NaOH, DMSO; (d) (i) $AcS(CH_2)_mOSiMe_2{}^tBu$, K_2CO_3, MeOH; (ii) $^nBu_4NF$, THF.

Sulfides **4a–j** were obtained by reaction of oxirane **6**[12] with sodium alkylthiolate in dimethylformamide. Sulfides **4a–j** were respectively oxidized under acidic conditions with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate to give sulfones **5b–j** in high yields.[12]

The minimum inhibitory concentration values (MIC, μg mL^{-1}) of these alkyl derivatives **4a–j** and **5b–j** against *Candida albicans* KB-8 and *Aspergillus fumigatus* MTU6001 are presented in Table 1. All the derivatives showed higher activity against *C. albicans* than **3**. In contrast, the highest activity against *A. fumigatus* was observed when the number of carbon atoms on the alkyl group was six (**4f**, in the case of the sulfide series) or eight (**5h**, in the case of the sulfone series). However, these in vitro activities could not be directly reflected in their in vivo activity.

The results of the prophylactic efficiency against murine systemic candidiasis and aspergillosis of alkyl derivatives **4a–j** and **5b–j** are also summarized in Table 1. Almost all control mice died within 3 days after infection, whereas a considerable number of mice treated by oral administration of the triazole derivatives (10 mg kg^{-1} $dose^{-1}$ for candidiasis or 50 mg kg^{-1} $dose^{-1}$ for aspergillosis) survived appreciably longer. Alkylsulfides having odd carbon atoms (**4a,e,g,i**) and alkylsulfones having less than two carbon atoms (**3** and **5b**) were shown to have good efficiency against candidiasis and aspergillosis. Especially, sulfide **4a** and sulfones **3** and **5b** were shown to have potent activity, even though their in vitro activity was lower than those of longer side chain derivatives. Perhaps because of their excellent pharmacokinetics[9] based on their hydrophilic property, they show such strong activity in spite of their relatively weak in vitro activity. These

Table 1. Antifungal activity of sulfur-containing triazole derivatives **4** and **5**

Compound	R or R′	MIC (μg mL^{-1})		Mean survival days (d)[a]	
		C. albicans	*A. fumigatus*	*C. albicans*[b]	*A. fumigatus*[c]
Fluconazole		0.78	400	10.0 (0.7)	2.8 (2.0)[d]
SM-8668 (**3**)	methyl	0.20	12.5	10.0 (1.6)	10.0 (2.1)
Sulfides **4**					
4a	methyl	0.025	1.56	10.0 (0.8)	9.8 (1.3)
4b	ethyl	0.10	12.5	4.4 (0.6)	1.0 (1.0)
4c	*n*-propyl	≤0.013	0.78	9.9 (0.6)	2.5 (1.0)
4d	*n*-butyl	≤0.013	0.78	9.9 (0.6)	2.5 (1.0)
4e	*n*-pentyl	≤0.013	0.39	9.2 (2.4)	6.8 (1.8)
4f	*n*-hexyl	≤0.013	≤0.20	10.0 (0.7)	2.2 (2.5)
4g	*n*-heptyl	≤0.013	0.39	8.6 (0.0)	7.2 (1.5)
4h	*n*-octyl	≤0.013	3.13	5.0 (0.8)	1.8 (1.0)
4i	*n*-nonyl	≤0.013	0.78	9.1 (0.6)	8.0 (2.1)
4j	*n*-decyl	≤0.013	25	5.8 (0.8)	1.6 (1.3)
Sulfones **5**					
5b	ethyl	0.20	6.25	8.3 (2.0)	10.0 (2.1)
5c	*n*-propyl	0.20	12.5	7.6 (0.6)	4.1 (3.7)
5d	*n*-butyl	0.20	25	0.4 (0.8)	3.6 (3.7)
5e	*n*-pentyl	0.10	12.5	2.6 (0.8)	1.6 (2.6)
5f	*n*-hexyl	≤0.013	6.25	0.9 (0.4)	1.1 (2.5)
5g	*n*-heptyl	≤0.013	3.13	1.3 (0.8)	1.6 (1.5)
5h	*n*-octyl	≤0.013	0.78	0.6 (0.8)	1.0 (1.0)
5i	*n*-nonyl	≤0.013	≤0.20	3.9 (0.6)	1.5 (2.1)
5j	*n*-decyl	≤0.013	3.13	1.1 (0.8)	1.6 (1.3)

[a]Prophylactic efficacy was determined in mice. The triazole derivative was administered orally. Mean survival days of control mice on the same conditions are given in parentheses.
[b]10 mg kg^{-1} $dose^{-1}$ of the triazole derivative was used.
[c]50 mg kg^{-1} $dose^{-1}$ of the triazole derivative was used.
[d]Only in this case, 100 mg kg^{-1} of fluconazole was used.

hydrophilic derivatives should show higher serum concentration in protein-free form, owing to their low affinity for serum proteins. Actually, affinity of **3** for human serum albumin (HSA) was measured to be only 10%, while that of octylthio derivative **4h** was more than 95%. On the other hand, it is surprising that sulfides **4e,g,i** showed remarkable activity against both candidiasis and aspergillosis though they were expected to be much more hydrophobic than **3**, **4a** or **5b**.

On the basis of these results, we prepared their hydrophilic analogues which had a hydroxyl group at the end of the alkylthio group, as shown in Chart 2. Introduction of the hydroxyl group is known to be one of the most effective ways to lower the log P values.[13] Such derivatives **7d–h** were respectively obtained by reaction of oxirane **6** with (ω-hydroxyalkyl)thioacetates in alkaline conditions. As summarized in Table 2, the hydroxyl analogues **7e** and **7g** showed more excellent prophylactic efficiency against both candidiasis and aspergillosis than their corresponding alkyl analogues **4e** and **4g**. In this connection, log P values of alcohols **7e** and **7g** were calculated to be 2.7 and 3.7, respectively. In contrast, those of **4e** and **4g** were calculated to be 1.6 point higher, respectively, namely 4.3 and 5.3. These log P values were calculated by the reported method[13] and corrected by the observed value for the methylthio derivative **4a** (log $P^* = 2.16$).[14]

Further derived analogues of **4g** which had other hydrophilic substituents such as amino, substituted nitrile, or carboxyl groups were also synthesized and estimated. These analogues were prepared from the hydroxyheptylthio derivative **7g** by substitution of its hydroxyl group to iodide **8g**[15] followed by substitution by other functional groups, as shown in Chart 3. Amine derivative **10g** was prepared via succinimide **9g**. Several kinds of substituted amino group and nitrile group were introduced directly by substitution of iodide on **8g**. Carboxyl derivatives **18g** and **19g** were prepared from nitrile **17g**. Thus obtained compounds **10g–17g** showed efficient activity against candidiasis, as shown in Table 2. However, their antifungal activity against aspergillosis was not so valuable in comparison with that of **7e** or **7g**. On the other hand, carboxyl derivatives **18g** and **19g** did not show any activity in vivo.

In conclusion, we synthesized SM-8668 analogues having a long alkyl group on the sulfur atom, and found that pentylthio and heptylthio derivatives **4e** and **4g** showed efficient antifungal activity. Moreover, introduction of a hydroxyl group at the end of their alkyl chain made their activity stronger. Further evaluations on hydroxyl analogues **7e** and **7g** are currently in progress.

Experimental

Melting points were determined on Thomas–Hoover capillary melting point apparatus and uncorrected. 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) and carbon-13 nuclear magnetic resonance spectra (^{13}C NMR; 67.5 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

Table 2. Antifungal activity of substituted alkylthio derivatives

Compound	R or R′	MIC (μg mL^{-1})		Mean survival days (d)[a]	
		C. albicans	*A. fumigatus*	*C. albicans*[b]	*A. fumigatus*[c]
7d	$(CH_2)_4OH$	0.20	6.25	2.5 (0.1)	3.2 (2.6)
7e	$(CH_2)_5OH$	0.025	0.78	9.8 (1.6)	10.0 (3.5)
7f	$(CH_2)_6OH$	≤0.013	0.78	2.8 (1.1)	2.8 (2.3)
7g	$(CH_2)_7OH$	≤0.013	0.78	10.0 (0.1)	9.7 (1.5)
7h	$(CH_2)_8OH$	≤0.013	≤0.20	4.3 (2.0)	3.5 (5.3)
10g	$(CH_2)_7NH_2$	0.05	6.25	9.9 (0.7)	3.0 (2.5)
11g	$(CH_2)_7NHAc$	0.05	3.13	9.9 (0.6)	2.8 (1.8)
12g	$(CH_2)_7$Morpholino	≤0.013	12.5	8.6 (0.9)	5.5 (1.8)
13g	$(CH_2)_7$Thiomorpholino	≤0.013	6.25	9.7 (0.7)	2.4 (2.0)
14g	$(CH_2)_7$Piperazino	≤0.013	6.25	9.8 (0.9)	1.6 (1.8)
15g	$(Ch_2)_7$Methylpiperazino	≤0.013	12.5	10.0 (0.7)	2.0 (2.0)
16g	$(CH_2)_7$Pyrrolidino	0.10	25	9.7 (0.7)	1.4 (2.0)
17g	$(CH_2)_7CN$	≤0.013	≤0.20	9.9 (0.1)	6.8 (2.6)
18g	$(CH_2)_7CONH_2$	0.20	1.56	0.3 (0.0)	1.3 (2.5)
19g	$(CH_2)_7CO_2H$	1.56	100	1.6 (0.4)	

[a]Prophylactic efficacy was determined in mice. The triazole derivative was administered orally. Mean survival days of control mice on the same conditions are given in parentheses.
[b]10 mg kg^{-1} dose^{-1} of the triazole derivative was used.
[c]50 mg kg^{-1} dose^{-1} of the triazole derivative was used.

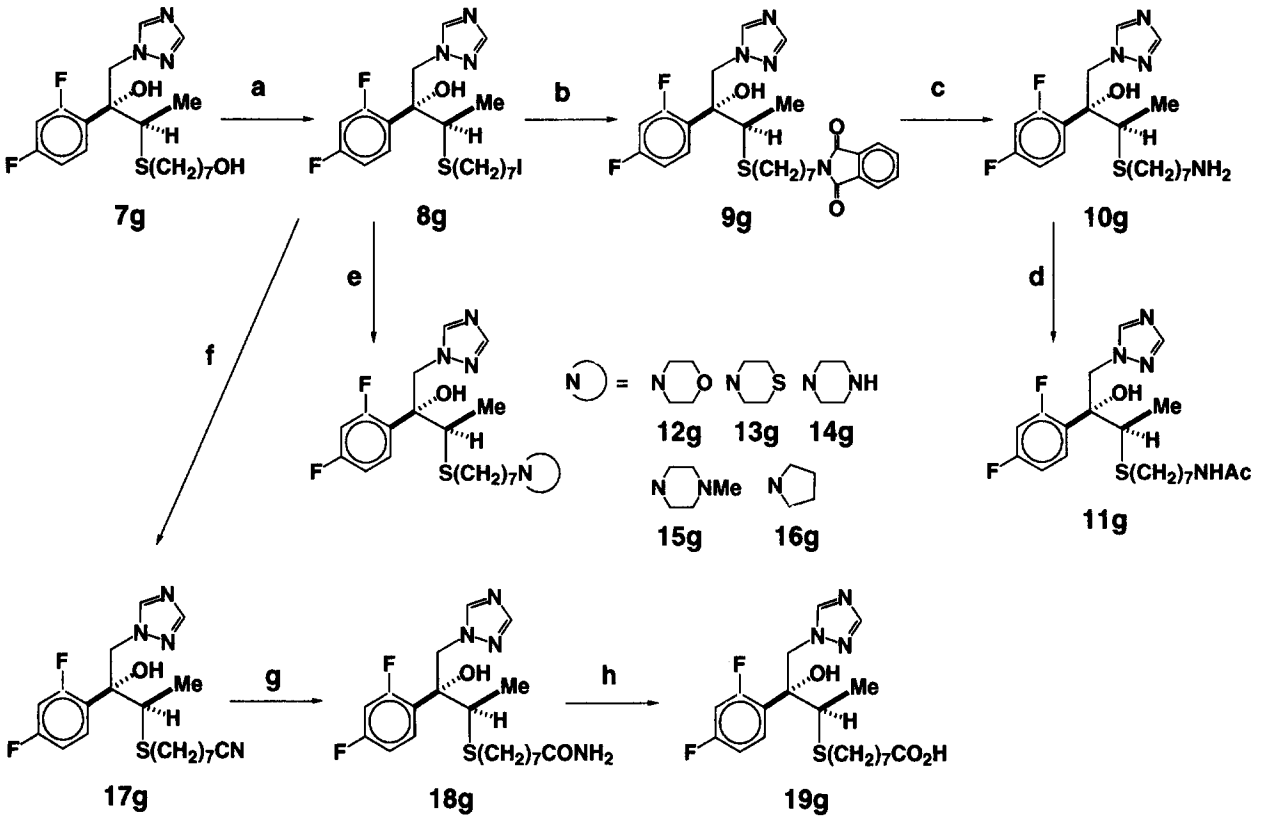

Chart 3. (a) I_2, Ph_3P, imidazole, CH_2Cl_2, MeCN; (b) potassium phtalimide, DMF; (c) $NH_2NH_2 \cdot H_2O$, EtOH; (d) Ac_2O, pyridine, CH_2Cl_2; (e) HN⌒, DMF; (f) KCN, DMF; (g) concd HCl; (h) KOH, H_2O, EtOH.

received unless otherwise indicated. Dimethylformamide (DMF) and dichloromethane were dried over molecular sieves 4 Å, respectively.

***threo*-2-(2,4-Difluorophenyl)-3-methylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4a).** The title compound was obtained by reaction of oxirane **6** with 15% aqueous sodium methanethiolate as described in a previous report.[12]

***threo*-2-(2,4-Difluorophenyl)-3-ethylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4b).** To a suspension of sodium hydride (1.20 g, 60% assay, 30.0 mmol) in DMF (30 mL) was added dropwise ethanethiol (2.29 mL, 97% assay, 30.0 mmol) at 0 °C. After 10 min, a solution of oxirane **6** (5.02 g, 20.0 mmol) in DMF (10 mL) was added to the mixture, and the resultant solution was stirred at 0 °C for 1.5 h, followed by stirring at room temperature for 1 h. Then it was poured into water (100 mL), followed by extraction with toluene (100 mL × 2). The organic layers were combined together and washed with 4% sodium hypochlorate solution (100 mL), water (100 mL × 2) and brine (100 mL) in order. The toluene layer was then 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 (2:1) to give **4b** (5.19 g, 83% yield): a colorless crystalline powder; mp 93.5–95.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHC\underline{H}_3$), 1.33 (3H, t, J=7.2 Hz, $SCH_2C\underline{H}_3$), 2.74 (2H, m, $S\underline{CH}_2CH_3$), 3.36 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 4.75 (1H, s, OH), 4.92 (1H, d, J=14.2 Hz, $\underline{CH}_2$Tz), 5.24 (1H, d, J=14.2 Hz, $\underline{CH}_2$Tz), 6.70–6.81 (2H, m), 7.36 (1H, m), 7.77 (1H, s) and 7.82 (1H, s). Found: C, 53.48; H, 5.52; N, 13.32; S, 10.22%. Calcd for $C_{14}H_{17}F_2N_3OS$: C, 53.66; H, 5.47; N, 13.41; S, 10.23%.

***threo*-2-(2,4-Difluorophenyl)-3-propylthio-1-(1*H*-1,2,4-triazol-1-yl-2-butanol (4c).** The title compound was obtained by the same method as described in the synthesis of **4b** (72% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 1.04 (3H, t, J=7.3 Hz, $S(CH_2)_2\underline{CH}_3$), 1.15 (3H, d, J=7.2 Hz, $CHC\underline{H}_3$), 1.61–1.74 (2H, m, $SCH_2\underline{CH}_2CH_3$), 2.62–2.71 (2H, m, $S\underline{CH}_2CH_2CH_3$), 3.27 (1H, q, J=7.2 Hz, $\underline{CH}CH_3$), 4.62 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, $\underline{CH}_2$Tz), 5.07 (1H, d, J=14.2 Hz, $\underline{CH}_2$Tz), 6.69–6.76 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). The oily **4c** was treated with ethereal hydrochloric acid to give HCl salt of **4c**: a colorless crystalline powder; mp 155.0–158.0 °C; IR (KBr) 3400, 3050, 1620 and 1500 cm^{-1}. Found: C, 49.73; H, 5.73; N, 11.32; Cl, 9.31%. Calcd for $C_{15}H_{19}F_2N_3OS \cdot HCl$: C, 49.52; H, 5.54; N, 11.55; Cl, 9.74%.

***threo*-2-(2,4-Difluorophenyl)-3-butylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4d).** The title compound was obtained by the same method as described in the synthesis of **4b** (87% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J=7.3 Hz, $S(CH_2)_3\underline{CH}_3$), 1.15 (3H, d, J=7.2 Hz, $CHC\underline{H}_3$), 1.41–1.52 (2H, m, SCH_2-

$CH_2\underline{CH_2}CH_3$), 1.57–1.68 (2H, m, $SCH_2\underline{CH_2}CH_2CH_3$), 2.61–2.75 (2H, m, $S\underline{CH_2}(CH_2)_2CH_3$), 3.27 (1H, q, $J=7.2$ Hz, $\underline{CH}CH_3$), 4.61 (1H, s, OH), 4.85 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.07 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.69–6.78 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). The oily **4d** was treated with ethereal hydrochloric acid to give HCl salt of **4d**: a colorless crystalline powder; mp 149.0–151.5 °C; IR (KBr) 3400, 3050, 1620 and 1500 cm^{-1}. Found: C, 50.81; H, 6.00; N, 11.09; Cl, 9.19; S, 8.72%. Calcd for $C_{16}H_{21}F_2N_3OS\cdot HCl$: C, 50.86; H, 5.87; N, 11.12; Cl, 9.38; S, 8.48%.

***threo*-2-(2,4-Difluorophenyl)-3-pentylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4e)**. The title compound was obtained by the same method as described in the synthesis of **4b** (78% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, $J=7.3$ Hz, $S(CH_2)_4\underline{CH_3}$), 1.15 (3H, d, $J=6.9$ Hz, $CH\underline{CH_3}$), 1.26–1.46 (4H, m, $SCH_2CH_2(\underline{CH_2})_2CH_3$), 1.58–1.70 (2H, m, $SCH_2\underline{CH_2}(CH_2)_2CH_3$), 2.60–2.77 (2H, m, $S\underline{CH_2}(CH_2)_3CH_3$), 3.27 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.62 (1H, s, OH), 4.85 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.06 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.70–6.77 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). The oily **4e** was treated with ethereal hydrochloric acid to give HCl salt of **4e**: a colorless crystalline powder; mp 150.0–153.0 °C; IR (KBr) 3250, 3050, 1620 and 1500 cm^{-1}. Found: C, 52.18; H, 6.27; N, 10.70; Cl, 8.71; S, 8.25%. Calcd for $C_{17}H_{23}F_2N_3OS\cdot HCl$: C, 52.10; H, 6.17; N, 10.72; Cl, 9.05; S, 8.18%.

***threo*-2-(2,4-Difluorophenyl)-3-hexylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4f)**. The title compound was obtained by the same method as described in the synthesis of **4b** (57% yield): a colorless crystalline powder; mp 57.0–58.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, $J=7.3$ Hz, $S(CH_2)_5\underline{CH_3}$), 1.15 (3H, d, $J=6.9$ Hz, $CH\underline{CH_3}$), 1.28–1.48 (6H, m, $SCH_2CH_2(\underline{CH_2})_3CH_3$), 1.55–1.69 (2H, m, $SCH_2\underline{CH_2}(CH_2)_3CH_3$), 2.60–2.77 (2H, m, $S\underline{CH_2}$-$(CH_2)_4CH_3$), 3.27 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.61 (1H, s, OH), 4.85 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.06 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.65–6.77 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 58.65; H, 6.80; N, 11.42; S, 8.90%. Calcd for $C_{18}H_{25}F_2N_3OS$: C, 58.52; H, 6.82; N, 11.37; S, 8.68%.

***threo*-2-(2,4-Difluorophenyl)-3-heptylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4g)**. The title compound was obtained by the same method as described in the synthesis of **4b** (79% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, $J=7.2$ Hz, $S(CH_2)_6\underline{CH_3}$), 1.15 (3H, d, $J=6.9$ Hz, $CH\underline{CH_3}$), 1.23–1.45 (8H, m, $SCH_2CH_2(\underline{CH_2})_4CH_3$), 1.58–1.69 (2H, m, $SCH_2\underline{CH_2}(CH_2)_4CH_3$), 2.60–2.78 (2H, m, $S\underline{CH_2}(CH_2)_5CH_3$), 3.27 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.62 (1H, s, OH), 4.85 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.07 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.70–6.78 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.85 (1H, s). The oily **4g** was treated with ethereal hydrochloric acid to give HCl salt of **4g**: a colorless crystalline powder; mp 139.5–142.0 °C; IR (KBr) 3430, 3050, 2930, 1620 and 1500 cm^{-1}. Found: C, 54.41; H, 6.83; N, 10.02; Cl, 8.98; S, 8.00%. Calcd for $C_{19}H_{27}F_2N_3OS\cdot HCl$: C, 54.34; H, 6.72; N, 10.01; Cl, 8.44; S, 7.63%.

***threo*-2-(2,4-Difluorophenyl)-3-octylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4h)**. The title compound was obtained by the same method as described in the synthesis of **4b** (79% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, $J=6.6$ Hz, $S(CH_2)_7\underline{CH_3}$), 1.15 (3H, d, $J=6.9$ Hz, $CH\underline{CH_3}$), 1.29–1.50 (10H, m, $SCH_2CH_2(\underline{CH_2})_5CH_3$), 1.58–1.69 (2H, m, $SCH_2\underline{CH_2}$-$(CH_2)_5CH_3$), 2.60–2.77 (2H, m, $S\underline{CH_2}(CH_2)_6CH_3$), 3.27 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.61 (1H, s, OH), 4.85 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.06 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.70–6.80 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). The oily **4h** was treated with ethereal hydrochloric acid to give HCl salt of **4h**: a colorless crystalline powder; mp 133.0–137.0 °C; IR (KBr) 3400, 3050, 2930, 1620 and 1500 cm^{-1}. Found: C, 55.41; H, 7.06; N, 9.75; Cl, 8.06; S, 7.51%. Calcd for $C_{20}H_{29}F_2N_3OS\cdot HCl$: C, 55.35; H, 6.97; N, 9.68; Cl, 8.17; S, 7.39%.

***threo*-2-(2,4-Difluorophenyl)-3-nonylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4i)**. The title compound was obtained by the same method as described in the synthesis of **4b** (71% yield): a colorless oil; IR (neat) 3200, 2950, 1615, 1605, 1520 and 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J=6.6$ Hz, $S(CH_2)_8\underline{CH_3}$), 1.14 (3H, d, $J=6.9$ Hz, $CH\underline{CH_3}$), 1.23–1.45 (12H, m, $SCH_2CH_2(\underline{CH_2})_6CH_3$), 1.58–1.68 (2H, m, $SCH_2\underline{CH_2}$-$(CH_2)_6CH_3$), 2.60–2.78 (2H, m, $S\underline{CH_2}(CH_2)_7CH_3$), 3.32 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.70 (1H, s, OH), 4.90 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.70 (1H, s, OH), 4.90 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.17 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.69–6.80 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 60.92; H, 7.58; N, 10.27; S, 7.91%. Calcd for $C_{21}H_{31}F_2N_3OS$: C, 61.29; H, 7.59; N, 10.21; S, 7.79%.

***threo*-2-(2,4-Difluorophenyl)-3-decylthio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (4j)**. The title compound was obtained by the same method as described in the synthesis of **4b** (73% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J=6.9$ Hz, $S(CH_2)_9\underline{CH_3}$), 1.15 (3H, d, $J=6.9$ Hz, $CH\underline{CH_3}$), 1.23–1.42 (14H, m, $SCH_2CH_2(\underline{CH_2})_7CH_3$), 1.58–1.69 (2H, m, SCH_2 CH_2 (CH_2) CH_3), 2.63–2.74 (2H, m, $SCH_2\underline{CH_2})_8CH_3$), 3.27 (1H, q, $J=6.9$ Hz, $\underline{CH}CH_3$), 4.61 (1H, s, OH), 4.85 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 5.06 (1H, d, $J=14.2$ Hz, $\underline{CH_2}Tz$), 6.69–6.78 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). The oily **4j** was treated with ethereal hydrochloric acid to give HCl salt of **4j**: a colorless crystalline powder; mp 114.0–118.0 °C; IR (KBr) 3430, 3050, 2930, 1620 and 1500 cm^{-1}. Found: C, 57.17; H, 7.54; N, 9.12; Cl, 7.46; S, 7.06%. Calcd for $C_{22}H_{33}F_2N_3OS\cdot HCl$: C, 57.19; H, 7.42; N, 9.09; Cl, 7.67; S, 6.94%.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-ethylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5b). To a solution of sulfide **4b** (385 mg, 1.23 mmol) in methanol (4 mL) were added sodium tungstate dihydrate (12.3 mg, 0.037

mmol) and concd hydrochloric acid (0.19 g, 35% assay, 1.82 mmol), and the mixture was stirred at room temperature while 31% aqueous hydrogen peroxide (0.41 g, 3.74 mmol) was added dropwise. After stirring at 40 °C for 1 h, the resulting mixture was cooled to room temperature, followed by addition of 10% aqueous sodium sulfite to reduce excess hydrogen peroxide (checked by potassium iodide starch paper). Then it was neutralized with 10% sodium hydroxide, and the precipitated crystals were collected by filtration to give sulfone **5b** (375 mg, 88% yield): colorless crystals; mp 148.0–149.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (3H, d, J=7.2 Hz, $CHCH_3$), 1.47 (3H, t, J=7.6 Hz, $SO_2CH_2CH_3$), 3.23 (1H, dd, J=7.6 and 13.5 Hz, $SO_2CH_2CH_3$), 3.38 (1H, dd, J=7.6 and 13.5 Hz, $SO_2CH_2CG_3$), 3.68 (1H, q, J=7.2 Hz, $CHCH_3$), 5.06 (1H, d, J=14.5 Hz, CH_2Tz), 5.41 (1H, d, J=14.5 Hz, CH_2Tz), 5.51 (1H, br, OH), 6.70–6.82 (2H, m), 7.30 (1H, m), 7.79 (1H, s) and 8.02 (1H, s). Found: C, 48.67; H, 4.92; N, 12.17; S, 9.49%. Calcd for $C_{14}H_{17}F_2N_3O_3S$: C, 48.69; H, 4.96; N, 12.17; S, 9.28%.

***threo*-2-(2,4-Difluorophenyl)-3-propylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5c)**. The title compound was obtained by the same method as described in the synthesis of **5b** (79%) yield): colorless crystals; mp 121.5–122.5 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J=7.3 Hz, $SO_2(CH_2)_2CH_3$), 1.26 (3H, d, J=7.2 Hz, $CHCH_3$), 1.19–2.07 (2H, m, $SO_2CH_2CH_2CH_3$), 3.16 (1H, m, $SO_2CH_2CH_3$), 3.33 (1H, m, $SO_2CH_2CH_2CH_3$), 3.61 (1H, q, J=7.2 Hz, $CHCH_3$), 5.02 (1H, d, J=14.5 Hz, CH_2Tz), 5.38 (1H, d, J=14.5 Hz, CH_2Tz), 5.47 (1H, s, OH), 6.71–6.81 (2H, m), 7.31 (1H, m), 7.75 (1H, s) and 7.79 (1H, s). Found: C, 49.33; H, 5.25; N, 11.47%. Calcd for $C_{15}H_{19}F_2N_3O_3S{\cdot}1/4\ H_2O$: C, 49.51; H, 5.40; N, 11.55%.

***threo*-2-(2,4-Difluorophenyl)-3-butylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5d)**. The title compound was obtained by the same method as described in the synthesis of **5b** (a quantitative yield): colorless crystals; mp 124.0–125.5 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (3H, t, J=7.3 Hz, $SO_2(CH_2)_3CH_3$), 1.26 (3H, d, J=7.2 Hz, $CHCH_3$), 1.46–1.60 (2H, m, $SO_2CH_2CH_2CH_3$), 1.85–2.08 (2H, m, $SO_2CH_2CH_2CH_2CH_3$), 3.17 (1H, m, $SO_2CH_2(CH_2)_2CH_3$), 3.34 (1H, m, $SO_2CH_2(CH_2)_2CH_3$), 3.63 (1H, q, J=7.2 Hz, $CHCH_3$), 5.03 (1H, d, J=14.5 Hz, CH_2Tz), 5.38 (1H, d, J=14.5 Hz, CH_2Tz), 5.47 (1H, s, OH), 6.71–6.81 (2H, m), 7.30 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 51.86; H, 5.72; N, 11.13; S, 8.92%. Calcd for $C_{16}H_{21}F_2N_3O_3S$: C, 51.46; H, 5.67; N, 11.25; S, 8.59%.

***threo*-2-(2,4-Difluorophenyl)-3-pentylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5e)**. The title compound was obtained by the same method as described in the synthesis of **5b** (87% yield): colorless crystals; mp 102.0–105.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, J=7.3 Hz, $SO_2(CH_2)_4CH_3$), 1.26 (3H, d, J=7.2 Hz, $CHCH_3$), 1.34–1.54 (4H, m, $SO_2CH_2(CH_2CH_3)$), 1.84–2.01 (2H, m, $SO_2CH_2CH_2(CH_2)_2CH_3$), 3.17 (1H, m, $SO_2CH_2(CH_2)_3CH_3$), 3.30 (1H, m, $SO_2CH_2(CH_2)_3CH_3$), 3.63 (1H, q, J=7.2 Hz, $CHCH_3$), 5.03 (1H, d, J=14.5 Hz, CH_2Tz), 5.37 (1H, d, J=14.5 Hz, CH_2Tz), 5.47 (1H, s, OH), 6.71–6.81 (2H, m), 7.29 (1H, m), 7.75 (1H, s) and 7.79 (1H, s). Found: C, 52.64; H, 5.95; N, 10.82; S, 8.46%. Calcd for $C_{17}H_{23}F_2N_3O_3S$: C, 52.70; H, 5.98; N, 10.85; S, 8.27%.

***threo*-2-(2,4-Difluorophenyl)-3-hexylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5f)**. The title compound was obtained by the same method as described in the synthesis of **5b** (82% yield): colorless crystals; mp 77.5–78.5 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3H, t, J=6.9 Hz, $SO_2(CH_2)_5CH_3$), 1.26 (3H, d, J=7.2 Hz, $CHCH_3$), 1.32–1.55 (6H, m, $SO_2CH_2(CH_2(CH_2)_3CH_3$, 1.89–1.98 (2H, m, $SO_2CH_2CH_2(CH_2)_3CH_3$), 3.17 (1H, m, $SO_2CH_2(CH_2)_4CH_3$), 3.32 (1H, m, $SO_2CH_2(CH_2)_4CH_3$), 3.63 (1H, q, J=7.2 Hz, $CHCH_3$), 5.03 (1H, d, J=14.5 Hz, CH_2Tz), 5.37 (1H, d, J=14.5 Hz, CH_2Tz), 5.47 (1H, s, OH), 6.71–6.81 (2H, m), 7.30 (1H, m), 7.75 (1H, s) and 7.79 (1H, s). Found: C, 53.85; H, 6.16; N, 10.44; S, 8.10%. Calcd for $C_{18}H_{25}F_2N_3O_3S$: C, 53.85; H, 6.28; N, 10.47; S, 7.99%.

***threo*-2-(2,4-Difluorophenyl)-3-heptylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5g)**. The title compound was obtained by the same method as described in the synthesis of **5b** (93% yield): colorless crystals; mp 119.0–120.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, t, J=6.6 Hz, $SO_2(CH_2)_6CH_3$), 1.26 (3H, d, J=7.2 Hz, $CHCH_3$), 1.23–1.49 (8H, m, $SO_2CH_2CH_2(CH_2)_4CH_3$), 1.86–2.01 (2H, m, $SO_2CH_2CH_2(CH_2)_4CH_3$), 3.16 (1H, m, $SO_2CH_2(CH_2)_5CH_3$), 3.33 (1H, m, $SO_2CH_2(CH_2)_5CH_3$), 3.63 (1H, q, J=7.2 Hz, $CHCH_3$), 5.02 (1H, d, J=14.5 Hz, CH_2Tz), 5.37 (1H, d, J=14.5 Hz, CH_2Tz), 5.47 (1H, s, OH), 6.71–6.81 (2H, m), 7.29 (1H, m), 7.75 (1H, s) and 7.79 (1H, s). Found: C, 54.92; H, 6.71; N, 9.83; S, 8.06%. Calcd for $C_{19}H_{27}F_2N_3O_3S$: C, 54.92; H, 6.55; N, 10.11; S, 7.72%.

***threo*-2-(2,4-Difluorophenyl)-3-octylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5h)**. The title compound was obtained by the same method as described in the synthesis of **5b** (94% yield): colorless crystals; mp 109.0–112.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J=6.6 Hz, $SO_2(CH_2)_7CH_3$), 1.26 (3H, d, J=7.2 Hz, $CHCH_3$), 1.30–1.54 (10H, m, $SO_2CH_2CH_2(CH_2)_5CH_3$), 1.81–2.07 (2H, m, $SO_2CH_2CH_2(CH_2)_5CH_3$), 3.15 (1H, m, $SO_2CH_2(CH_2)_6CH_3$), 3.34 (1H, m, $SO_2CH_2(CH_2)_6CH_3$), 3.63 (1H, q, J=7.2 Hz, $CHCH_3$), 5.03 (1H, d, J=14.9 Hz, CH_2Tz), 5.37 (1H, d, J=14.9 Hz, CH_2Tz), 5.47 (1H, s, OH), 6.71–6.81 (2H, m), 7.30 (1H, m), 7.75 (1H, s) and 7.80 (1H, s). Found: C, 55.45; H, 6.72; N, 9.72; S, 7.55%. Calcd for $C_{20}H_{29}F_2N_3O_3S$: C, 55.93; H, 6.72; N, 9.72; S, 7.55%.

***threo*-2-(2,4-Difluorophenyl)-3-nonylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5i).** The title compound was obtained by the same method as described in the synthesis of **5b** (a quantitative yield): colorless crystals; mp 91.0–92.5 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J=6.6 Hz, $SO_2(CH_2)_8\underline{CH_3}$), 1.26 (3H, d, J=7.2 Hz, $CH\underline{CH_3}$), 1.18–1.51 (12H, m, $SO_2CH_2CH_2(\underline{CH_2})_6CH_3$), 1.82–2.02 (2H, m, $SO_2CH_2\underline{CH_2}(CH_2)_6CH_3$), 3.15 (1H, m, $SO_2\underline{CH_2}(CH_2)_7CH_3$), 3.32 (1H, m, $SO_2\underline{CH_2}(CH_2)_7CH_3$), 3.65 (1H, q, J=7.2 Hz, $\underline{CH}CH_3$), 5.05 (1H, d, J=14.3 Hz, $\underline{CH_2}Tz$), 5.41 (1H, d, J=14.3 Hz, $\underline{CH_2}Tz$), 5.50 (1H, br, OH), 6.71–6.82 (2H, m), 7.30 (1H, m), 7.80 (1H, s) and 8.04 (1H, s). Found: C, 56.97; H, 6.88; N, 9.30; S, 7.42%. Calcd for $C_{21}H_{31}F_2N_3O_3S$: C, 56.87; H, 7.04; N, 9.47; S, 7.23%.

***threo*-2-(2,4-Difluorophenyl)-3-decylsulfonyl-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (5j).** The title compound was obtained by the same method as described in the synthesis of **5b** (73%): colorless crystals; mp 69.5–71.0 °C; IR (KBr) 3100, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3H, t, J=6.9 Hz, $SO_2(CH_2)_9\underline{CH_3}$), 1.26 (3H, d, J=7.2 Hz, $CH\underline{CH_3}$), 1.11–1.51 (14H, m, $SO_2CH_2CH_2(\underline{CH_2})_7CH_3$), 1.80–2.07 (2H, m, $SO_2CH_2\underline{CH_2}(CH_2)_7CH_3$), 3.19 (1H, m, $SO_2\underline{CH_2}(CH_2)_8CH_3$), 3.34 (1H, m, $SO_2\underline{CH_2}(CH_2)_8CH_3$), 3.64 (1H, q, J=7.2 Hz, $\underline{CH}CH_3$), 5.04 (1H, d, J=14.5 Hz, $\underline{CH_2}Tz$), 5.40 (1H, d, J=14.5 Hz, $\underline{CH_2}Tz$), 5.48 (1H, s, OH), 6.71–6.82 (2H, m), 7.30 (1H, m), 7.78 (1H, s) and 7.94 (1H, s). Found: C, 55.09; H, 7.06; N, 8.74%. Calcd for $C_{22}H_{33}F_2N_3O_3S\cdot 6/5\ H_2O$: C, 55.14; H, 7.44; N, 8.77%.

***threo*-2-(2,4-Difluorophenyl)-3-(4-hydroxybutyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7d).** To a solution of potassium thioacetate (5.14 g, 45.0 mmol) in DMF (60 mL) was added dropwise 4-chloro-1-butanol (3.26 g, 30.0 mmol) at room temperature. After stirring for 2 h, it was poured into water (50 mL), followed by extraction with ethyl acetate (100 mL × 2). The organic layers were combined together and washed with brine (50 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography to give 4-acetylthio-1-butanol (1.50 g, 34% yield) as a pale yellow oil. 4-Acetylthio-1-butanol obtained above (1.48 g, 10.0 mmol) was added dropwise to a stirred mixture of 48% aqueous sodium hydroxide (1.04 g, 12.5 mmol) and dimethyl sulfoxide (15 mL) at room temperature. After stirring for 20 min, a solution of oxirane **6** (2.07 g, 8.33 mmol) in dimethyl sulfoxide (5.0 mL) was added to the mixture, and the resultant solution was stirred at room temperature for 2 h. Then, it was poured into water (50 mL), followed by extraction with ethyl acetate (100 mL × 2). The organic layers were combined together and washed with brine (50 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 50 g of silica gel eluting with hexane and ethyl acetate (2:1) to give **7d** (0.962 g, 32% yield): a colorless crystalline powder; mp 59.0–62.0 °C; IR (KBr) 3150, 2940, 2860, 1620, 1600, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (3H, d, J=6.9 Hz, $CH\underline{CH_3}$), 1.68–1.77 (5H, m, $SCH_2\underline{(CH_2)_2CH_2OH}$), 2.69–2.78 (2H, m, $S\underline{CH_2}$), 3.28 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.71 (2H, m, $\underline{CH_2}OH$), 4.69 (1H, s, OH), 4.86 (1H, d, J=14.2 Hz, $\underline{CH_2}Tz$), 5.07 (1H, d, J=14.2 Hz, $\underline{CH_2}Tz$), 6.69–6.77 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.82 (1H, s). Found: 52.86; H, 5.98; N, 11.48; S, 8.53%. Calcd for $C_{16}H_{21}F_2N_3O_2S\cdot 1/3H_2O$: C, 53.02; H, 6.03; N, 11.59; S, 8.85%.

***threo*-2-(2,4-Difluorophenyl)-3-(5-hydroxypentyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7e).** To a solution of potassium thioacetate (9.87 g, 86.5 mmol) in DMF (150 ml) was added dropwise 5-chloro-1-butanol (9.43 g, 86.5 mmol) at room temperature. After stirring for 3 h, it was poured into water (100 mL), followed by extraction with ethyl acetate (200 mL × 2). The organic layers were combined together and washed with brine (100 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was dissolved in DMF (200 mL) and the solution was cooled to 0 °C. Imidazole (8.83 g, 129.7 mmol) and *tert*-butyldimethylsilyl chloride (15.64 g, 103.8 mmol) were added to the solution, and the mixture was stirred at 0 °C for 2 h. Then, it was poured into water (100 mL), followed by extraction with ethyl acetate (200 mL × 2). The organic layers were combined together and washed with brine (100 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography to give 5-acetylthio-1-(trimethylsilyloxy)butane (17.78 g, 73% yield): a pale yellow oil; ^1H NMR ($CDCl_3$) δ 0.04 (6H, s, $SiMe\times 2$), 0.89 (9H, s, $SiCMe_3$), 1.36–1.64 (6H, m, $SCH_2\underline{(CH_2)_3CH_2O}$), 2.32 (3H, s, SAc), 2.87 (2H, t, J=7.2 Hz, $S\underline{CH_2}$), 3.59 (2H, t, J=6.3 Hz, CH_2O).

Above-obtained 5-acetylthio-1-(trimethylsilyloxy)butane (1.66 g, 6.00 mmol) was added to a stirred suspension of anhydrous potassium carbonate (0.83 g, 6.0 mmol) in methanol (8.0 mL) at room temperature. After stirring for 1 h, oxirane **6** was added to the mixture. The mixture was warmed to 60 °C and stirred at the temperature for 8 h. Then, it was poured into water (25 mL), followed by extraction with ethyl acetate (50 mL × 2). The organic layers were combined together and washed with brine (25 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography to give *O*-silyl derivative of **7e** (1.09 g, 56% yield): a colorless oil; ^1H NMR ($CDCl_3$) δ 0.05 (6H, s, $SiMe\times 2$), 0.89 (9H, s, $SiCMe_3$), 1.14 (3H, d, J=7.2 Hz, $CH\underline{CH_3}$), 1.46–1.72 (6H, m, $SCH_2\underline{(CH_2)_3CH_2O}$), 2.69 (2H, m, $S\underline{CH_2}$), 3.27 (1H, q, J=7.2 Hz, $\underline{CH}CH_3$), 3.62 (2H, m, $\underline{CH_2}O$), 4.63 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, $\underline{CH_2}Tz$), 5.06 (1H, d, J=14.2 Hz, $\underline{CH_2}Tz$), 6.69–6.77 (2H, m), 7.36 (1H, m), 7.75 (1H, s) and 7.83 (1H, s).

Finally, thus obtained *O*-silyl derivative of **7e** (1.09 g, 2.26 mmol) was dissolved in tetrahydrofuran (5.0 mL),

and 1.1 M tetrabutylammonium fluoride solution in tetrahydrofuran (4.62 mL, 5.08 mmol) was added to the solution at room temperature. After stirring for 1.5 h, it was poured into water (25 mL), followed by extraction with ethyl acetate (50 mL × 2). The organic layers were combined together and washed with brine (25 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography to give **7e** (0.73 g, 87% yield): a colorless crystalline powder; mp 115.0–117.5 °C; IR (KBr) 3150, 2930, 2855, 1620, 1600, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHC\underline{H}_3$), 1.43 (1H, t, J=5.3 Hz, OH), 1.48–1.71 (6H, m, $SCH_2(\underline{CH}_2)_3CH_2OH$), 2.72 (2H, m, $S\underline{CH}_2$), 3.27 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.68 (2H, m, $\underline{CH}_2OH$), 4.66 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 5.07 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 6.69–6.78 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 54.58; H, 6.24; N, 11.10; S, 8.87%. Calcd for $C_{17}H_{23}F_2N_3O_2S$: C, 54.97; H, 6.24; N, 11.31; S, 8.63%.

***threo*-2-(2,4-Difluorophenyl)-3-(6-hydroxyhexyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7f)**. The title compound was obtained in 74% yield by the same method as described in the synthesis of **7d** using 6-acetylthio-1-hexanol: a colorless crystalline powder; mp 95.0–98.0 °C; IR (KBr) 3200, 2930, 2855, 1620, 1600, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHC\underline{H}_3$), 1.34–1.71 (9H, m, $SCH_2(\underline{CH}_2)_4CH_2OH$), 2.62–2.78 (2H, m, $S\underline{CH}_2$), 3.26 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.68 (2H, m, $\underline{CH}_2OH$), 4.63 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 5.07 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 6.70–6.77 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 54.65; H, 6.50; N, 10.65%. Calcd for $C_{18}H_{25}F_2N_3O_2S \cdot 1/2H_2O$: C, 54.81; H, 6.64; N, 10.65%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-hydroxyheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7g)**. The title compound was obtained in 39% yield by the same method as described in the synthesis of **7d** using 7-acetylthio-1-heptanol: a colorless crystalline powder; mp 107.0–108.0 °C; IR (KBr) 3150, 2930, 2855, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHC\underline{H}_3$), 1.33–1.47 (6H, m, $SCH_2CH_2(\underline{CH}_2)_3CH_2CH_2OH$), 1.52–1.67 (5H, m, $SCH_2\underline{CH}_2(CH_2)_3\underline{CH}_2CH_2OH$), 2.64–2.75 (2H, m, $S\underline{CH}_2$), 3.26 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.66 (2H, m, $\underline{CH}_2OH$), 4.62 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 5.07 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 6.70–6.77 (2H, m), 7.35 (1H, m), 7.76 (1H, s) and 7.84 (1H, s); ^{13}C NMR ($CDCl_3$) δ 17.5, 25.5, 28.7, 28.8, 30.0, 31.7, 32.5, 47.1, 56.6, 62.5, 78.6, 103.8 (dd, J=25 and 28 Hz), 111.4 (dd, J=4 and 20 Hz), 124.0 (dd, J=4 and 13 Hz), 130.3 (dd, J=6 and 9 Hz), 143.8, 151.2, 158.0 (dd, J=12 and 246 Hz), 162.5 (dd, J=13 and 250 Hz). Found: 57.20; H, 6.79; N, 10.54; S, 8.15%. Calcd for $C_{19}H_{27}F_2N_3O_2S$: C, 57.12; H, 6.81; N, 10.52; S, 8.03%.

***threo*-2-(2,4-Difluorophenyl)-3-(8-hydroxyoctyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (7h)**. The title compound was obtained in 49% yield by the same method as described in the synthesis of **7d** using 8-acetylthio-1-octanol: a colorless crystalline powder; mp 77.0–78.0 °C; IR (KBr) 3200, 2930, 2855, 1620, 1605, 1515 and 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHC\underline{H}_3$), 1.30–1.50 (8H, m, $SCH_2CH_2(\underline{CH}_2)_4CH_2CH_2OH$), 1.51–1.70 (5H, m, $SCH_2\underline{CH}_2(CH_2)_4\underline{CH}_2CH_2OH$), 2.63–2.77 (2H, m, $S\underline{CH}_2$), 3.26 (1H, q, J=6.9 Hz, $\underline{CH}CH_3$), 3.64 (2H, m, $\underline{CH}_2OH$), 4.61 (1H, s, OH), 4.84 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 5.06 (1H, d, J=14.2 Hz, $\underline{CH}_2Tz$), 6.70–6.76 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 57.12; H, 6.99; N, 9.96; S, 8.00%. Calcd for $C_{20}H_{29}F_2N_3O_2S \cdot 1/3H_2O$: C, 57.26; H, 7.13; N, 10.02; S, 7.64%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-iodoheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (8g)**. To a solution of alcohol **7g** (399.5 mg, 1.00 mmol) in dichloromethane (5.0 mL) and acetonitrile (1.0 mL) were added imidazole (170.2 mg, 2.50 mmol), triphenylphosphine (655.7 mg, 2.50 mmol), and iodine (507.6 mg, 2.00 mmol), in order at 0 °C.[15] The mixture was stirred at room temperature for 30 min and then it was filtered off. The filtrate was diluted with dichloromethane (100 mL) and washed with saturated sodium sulfite (30 mL × 2) and brine (30 mL) in order. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to give iodide **8g**, which was subjected to the sequential reactions without further purification: a pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHCH_3$), 1.33–1.52 (6H, m, $SCH_2CH_2(\underline{CH}_2)_3CH_2CH_2I$), 1.58–1.71 (2H, m, $SCH_2\underline{CH}_2$), 1.75–1.90 (2H, m, $\underline{CH}_2CH_2I$), 2.69 (2H, m, SCH_2), 3.20 (2H, t, J=6.9 Hz, CH_2I), 3.27 (1H, q, J=6.9 Hz, $CHCH_3$), 4.64 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH_2Tz), 5.07 (1H, d, J=14.2 Hz, CH_2Tz), 6.70–6.77 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.83 (1H, s).

***threo*-2-(2,4-Difluorophenyl)-3-(7-phthaliminoheptyl)-thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (9g)**. Potassium phthalimide (1.39 g, 7.50 mmol) was added to a mixture of DMF (30 mL) and iodide **8g** which was generated from alcohol **7g** (1.00 g, 2.50 mmol) by the method described above. The mixture was warmed to 40 °C and stirred at the temperature for 1 h. Then it was poured into water (100 mL), followed by extraction with the 1:1 mixture of toluene and ethyl acetate (100 mL × 2). The organic layers were combined together and washed with brine (50 mL). It was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography on 100 g of silica gel eluting with hexane and ethyl acetate (1:1) to give **9g** (1.12 g, 85% yield from **7g**): a colorless oil; IR (neat) 3500–3100, 2950, 2870, 1780, 1710, 1620, 1600, 1520 and 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, d, J=6.9 Hz, $CHC\underline{H}_3$), 1.39–1.45 (6H, m, $SCH_2CH_2(\underline{CH}_2)_3CH_2CH_2N$), 1.66–1.77 (4H, m, $SCH_2\underline{CH}_2(CH_2)_3\underline{CH}_2CH_2N$), 2.62–2.73 (2H, m, $SCH_2\underline{CH}_2(CH_2)_3\underline{CH}_2CH_2N$), 2.62–2.73 (2H, m, $S\underline{CH}_2$), 3.26 (1H, q, J=6.9 Hz,

CHCH$_3$), 3.69 (2H, t, J=7.3 Hz, CH$_2$N), 4.63 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.06 (1H, d, J=14.2 Hz, CH$_2$Tz), 6.68–6.76 (2H, m), 7.36 (1H, m), 7.69–7.74 (3H, m, Phthal-H×2 and Tz-H) and 7.75–7.85 (3H, m Phthal-H×2 and Tz-H).

***threo*-2-(2,4-Difluorophenyl)-3-(7-aminoheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (10g).** To a solution of phthalimide **9g** (1.12 g, 2.12 mmol) in ethanol (30 mL) was added hydrazine hydrate (530 mg, 10.59 mmol) at room temperature. After stirring at room temperature for 3 h, the mixture was diluted with dichloromethane (100 mL), filtered off and the filtrate was concentrated under the reduced pressure. Diluted sodium hydroxide solution (pH=9, 50 mL) and dichloromethane (100 mL) were added to the residue, and the mixture was stirred vigorously for 10 min. The organic layer was separated, washed with brine (50 mL) and dried over anhydrous magnesium sulfate. It was then filtered and evaporated in vacuo. The resulting residue was crystallized from the mixture of ether and hexane to afford **10g** (867 mg, a quantitative yield from **7g**): a colorless oil; IR (neat) 3400–3100, 2950, 2870, 1620, 1600, 1520 and 1505 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3H, d, J=6.9 Hz, CHCH$_3$), 1.33–1.58 (9H, m, SCH$_2$CH$_2$(CH$_2$)$_3$CH$_2$CH$_2$NH$_2$ and OH), 1.59–1.69 (4H, m, SCH$_2$CH$_2$(CH$_2$)$_3$CH$_2$CH$_2$NH$_2$), 2.61–2.77 (4H, m, SCH$_2$ and CH$_2$NH$_2$), 3.27 (1H, q, J=6.9 Hz, CHCH$_3$), 4.85 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.06 (1H, d, J=14.2 Hz, CH$_2$Tz), 6.69–6.78 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.84 (1H, s). Found: C, 57.38; H, 7.02; N, 14.33%. Calcd for C$_{19}$H$_{28}$F$_2$N$_4$OS: C, 57.27; H, 7.08; N, 14.06%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-acetoaminoheptyl)-thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (11g).** To a solution of amine **10g** (455 mg, 1.14 mmol) in dichloromethane (3.0 mL) were added pyridine (271 mg, 3.43 mmol) and acetic anhydride (175 mg, 1.71 mmol) at room temperature. After stirring at room temperature for 2 h, the mixture was diluted with ethyl acetate (50 mL), and washed with 10% aqueous copper(II) sulfate (20 mL), water (20 mL), saturated sodium hydrogen carbonate and brine (20 mL) in order. The organic layer was dried over anhydrous magnesium sulfate, then filtered and evaporated in vacuo. The resulting residue was purified by column chromatography to afford **11g** (360 mg, 72% yield): a colorless oil; IR (neat) 3300, 3100, 2950, 2870, 1655, 1620, 1600, 1560, 1545, 1510 and 1500 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3H, d, J=6.9 Hz, CHCH$_3$), 1.27–1.66 (10H, m, SCH$_2$(CH$_2$)$_5$CH$_2$N), 1.97 (3H, s, NHAc), 2.60–2.77 (2H, m, SCH$_2$), 3.21–3.28 (3H, m, CH$_2$N and CH$_2$CH$_3$), 4.64 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.06 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.40 (1H, br, NH), 6.69–6.78 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.85 (1H, s). Found: C, 57.48; H, 6.97; N, 12.70%. Calcd for C$_{21}$H$_{30}$F$_2$N$_4$O$_2$S: C, 57.25; H, 6.86; N, 12.72%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-morpholinoheptyl)-thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (12g).** Morpholine (2.18 mL, 25.0 mmol) was added to a mixture of toluene (5.0 mL) and iodide **8g** which was generated from alcohol **7g** (1.00 g, 2.50 mmol) by the method described above. The mixture was warmed to 45 °C and stirred at the temperature for 2 h. Then it was diluted with toluene (50 mL) and washed with water 20 mL×2) and brine (20 mL) in order. The organic layer was then dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo. The resulting residue was crystallized from ether to give **12g** (519 mg, 50% yield from **7g**): a colorless crystalline powder; mp 60.0–61.5 °C; IR (KBr) 3120, 2930, 2855, 1620, 1600, 1520 and 1500 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3H, d, J=6.9 Hz, CHCH$_3$), 1.32–1.69 (10H, m, SCh$_2$(CH$_2$)$_5$CH$_2$N), 2.29–2.35 (2H, m, CH$_2$N), 2.42–2.52 (4H, m, morpholino-H), 2.62–2.77 (2H, m, SCH$_2$)3.26 (1H, q, J=6.9 Hz, CHCH$_3$), 3.72 (4H, t, J=4.6 Hz, morpholino-H), 4.62 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.06 (1H, d, J=14.2 Hz, CH$_2$Tz), 6.67–6.77 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.84 (1H, s). Found: C, 58.03; H, 7.19; N, 11.52; S, 6.74%. Calcd for C$_{23}$H$_{34}$F$_2$N$_4$O$_2$S·1/2H$_2$O: C, 57.84; H, 7.39; N, 11.73; S, 6.71%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-thiomorpholinoheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (13g).** The title compound was obtained in 70% yield by the same method as described in synthesis of **12g** using thiomorpholine (2.0 equiv): a colorless crystalline powder; mp 56.0–57.0 °C; IR (KBr) 3150, 2930, 2855, 1620, 1605, 1515 and 1500 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3H, d, J=6.9 Hz, CHCH$_3$), 1.22–2.17 (10H, m, SCH$_2$(CH$_2$)$_5$CH$_2$N), 2.55 (2H, t, J=6.9 Hz, CH$_2$N), 2.63–2.77 (6H, m, thiomorpholino-H and SCH$_2$), 3.27 (1H, q, J=6.9 Hz, CHCH$_3$), 3.62–3.66 (4H, m, thiomorpholino-H), 4.63 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.07 (1H, d, J=14.2 Hz, CH$_2$Tz), 6.69–6.78 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.85 (1H, s). Found: C, 57.32; H, 7.22; N, 11.89%. Calcd for C$_{23}$H$_{34}$F$_2$N$_4$OS$_2$: C, 57.00; H, 7.07; N, 11.56%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-piperazinoheptyl)-thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (14g).** The title compound was obtained in 70% yield by the same method as described in synthesis of **12g** using piperazine (10 equiv): a pale yellow oil; IR (neat) 3300, 2950, 1620, 1600, 1520 and 1505 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.15 (3H, d, J=6.9 Hz, CHCH$_3$), 1.21–1.66 (11H, m, SCH$_2$(CH$_2$)$_5$CH$_2$N and NH), 2.28–2.34 (2H, m, CH$_2$N), 2.34–2.45 (4H, m, piperazino-H), 2.60–2.76 (2H, m, SCH$_2$), 2.90 (4H, t, J=5.0 Hz, piperazino-H), 3.27 (1H, q, J=6.9 Hz, CHCH$_3$), 4.62 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH$_2$Tz), 5.06 (1H, d, J=14.2 Hz, CH$_2$Tz), 6.70–6.76 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: 59.46; H, 7.86; N, 14.75%. Calcd for C$_{23}$H$_{35}$F$_2$N$_5$OS: C, 59.08; H, 7.54; N, 14.98%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-methylpiperazinoheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (15g).** The title compound was obtained in 89% yield by the same method as described in synthesis of **12g** using methylpiperazine (2.0 equiv): a pale yellow oil; IR (neat) 3200, 2950, 2860, 1620, 1605, 1515 and 1500

cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHCH_3$), 1.30–1.80 (10H, m, $SCH_2(CH_2)_5CH_2N$), 2.29 (3H, s, NCH_3), 2.31–2.76 (10H, m, methylpiperazino-H and NCH_2), 3.26 (1H, q, J=6.9 Hz, $CHCH_3$), 4.61 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH_2Tz), 5.06 (1H, d, J=14.2 Hz, CH_2Tz), 6.69–6.76 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 55.84; H, 7.61; N, 13.26; S, 6.10%. Calcd for $C_{24}H_{37}F_2N_5OS\cdot 2H_2O$: C, 55.68; H, 7.98; N, 13.53; S, 6.19%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-pyrrolidinoheptyl)-thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (16g).** The title compound was obtained in 88% yield by the same method as described in synthesis of **12g** using pyrrolidine (2.0 equiv): a pale yellow oil; IR (neat) 3300, 2950, 1620, 1600, 1515 and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J=7.2 Hz, $CHCH_3$), 1.27–2.19 (14H, m, $SCH_2(CH_2)_5CH_2N$ and pyrrolidino-H), 2.29–2.41 (6H, m, CH_2N and pyrrolidino-H), 2.60–2.74 (2H, m, SCH_2), 3.27 (1H, q, J=7.2 Hz, $CHCH_3$), 4.61 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH_2Tz), 5.06 (1H, d, J=14.2 Hz, CH_2Tz), 6.69–6.77 (2H, m), 7.37 (1H, m), 7.76 (1H, s) and 7.83 (1H, s). Found: C, 61.42; H, 7.84; N, 12.05%. Calcd for $C_{23}H_{34}F_2N_4OS$: C, 61.04; H, 7.57; N, 12.38%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-cyanoheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (17g).** The title compound was obtained in 88% yield by the same method as described in synthesis of **9g** using potassium cyanide (3.0 equiv): a colorless oil; IR (neat) 3150, 2930, 2860, 2250, 1615, 1600 and 1500 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHCH_3$), 1.34–1.54 (6H, m, $SCH_2CH_2(CH_2)_3CH_2CH_2CN$), 1.63–1.73 (4H, m, $SCH_2CH_2(CH_2)_3CH_2CH_2CN$), 2.36 (2H, t, J=6.9 Hz, CHCHN), 2.62–2.78 (2H, m, SCH_2), 3.28 (1H, q, J=6.9 Hz, $CHCH_3$), 4.71 (1H, s, OH), 4.86 (1H, d, J=14.2 Hz, CH_2Tz), 5.06 (1H, d, J=14.2 Hz, CH_2Tz), 6.70–6.78 (2H, m), 7.34 (1H, m), 7.75 (1H, s) and 7.86 (1H, s). Found: C, 58.31; H, 6.46; N, 13.34; S, 7.75%. Calcd for $C_{20}H_{26}F_2N_4OS\cdot 1/4H_2O$: C, 58.16; H, 6.47; N, 13.57; S, 7.76%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-carbamoylheptyl)-thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (18g).** Nitrile **17g** (954 mg, 2.34 mmol) was dissolved in 35% aqueous hydrochloric acid (10 mL), and the mixture was stirred at room temperature for 14 h. After adding water (30 mL), pH was adjusted to 10 with 2 N sodium hydroxide solution, and the mixture was extracted with chloroform (50 mL×3). The organic layer was combined together, washed with brine (50 mL) and dried over anhydrous magnesium sulfate. It was then filtered and evaporated in vacuo. The resulting residue was purified by column chromatography and crystallized from ether to give **18g** (549 mg, 55% yield): colorless crystals; mp 76.0–77.0 °C; IR (KBr) 3350, 3200, 2930, 2860, 1670, 1615, 1600 and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, d, J=6.9 Hz, $CHCH_3$), 1.35–1.49 (6H, m, $SCH_2(CH_2)_3CH_2CH_2$), 1.54–1.71 (4H, m, $SCH_2CH_2(CH_2)_3CH_2CH_2$), 2.23 (2H, t, J=7.3 Hz, CH_2CONH_2), 2.60–2.77 (2H, m, SCH_2), 3.27 (1H, q, J=6.9 Hz, $CHCH_3$), 4.64 (1H, s, OH), 4.85 (1H, d, J=14.2 Hz, CH_2Tz), 5.06 (1H, d, J=14.2 Hz, CH_2Tz), 5.21–5.51 (2H, br, CH_2CONH_2), 6.69–6.79 (2H, m), 7.36 (1H, m), 7.76 (1H, s) and 7.85 (1H, s). Found: C, 55.74; H, 6.59; N, 12.98; S, 7.67%. Calcd for $C_{20}H_{28}F_2N_4O_2S\cdot 1/4H_2O$: C, 55.73; H, 6.66; N, 13.00; S, 7.44%.

***threo*-2-(2,4-Difluorophenyl)-3-(7-carboxylheptyl)thio-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (19g).** To a solution of amido **18g** (517 mg, 1.21 mmol) in ethanol (5.0 mL) was added 5% aqueous potassium hydroxide (7.2 mL), and the mixture was stirred under the refluxed temperature for 17 h. After adding water (10 mL), pH was adjusted to 4 with 2 N hydrochloric acid solution, and the mixture was extracted with ethyl acetate (40 mL×3). The organic layer was combined together, washed with brine (30 mL) and dried over anhydrous magnesium sulfate. It was then filtered and evaporated in vacuo. The resulting residue was purified by column chromatography and crystallized from ether to give **19g** (523 mg, a quantitative yield): colorless crystals; mp 77.0–78.0 °C; IR (KBr) 2930, 2860, 1710, 1615, 1600 and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$ δ 1.15 (3H, d, J=6.9 Hz, $CHCH_3$), 1.29–1.52 (6H, m, $SCH_2CH_2(CH_2)_3CH_2CH_2$), 1.58–1.68 (4H, m, $SCH_2CH_2(CH_2)_3CH_2CH_2$), 2.36 (2H, t, J=7.3 Hz, CH_2CO_2H), 2.60–2.77 (2H, m, SCH_2), 3.27 (1H, q, J=6.9 Hz, $CHCH_3$), 4.65 (1H, br, OH), 4.85 (1H, d, J=14.2 Hz, CH_2Tz), 5.07 (1H, d, J=14.2 Hz, CH_2Tz), 6.68–6.78 (2H, m), 7.36 (1H, m), 7.77 (1H, s) and 7.90 (1H, s). Found: C, 55.77; H, 6.34; N, 9.72; S, 7.40%. Calcd for $C_{20}H_{27}F_2N_3O_3S\cdot 1/4H_2O$: C, 55.60; H, 6.42; N, 9.73; S, 7.42%.

The in vitro activity against *C. albicans* KB-8 and *A. fumigatus* MTU6001

Candida albicans KB-8 was grown at 37 °C on Sabouraud dextrose agar (SDA) for 24 h and transferred in glucose polypeptone yeast extract broth for 24 h. *Aspergillus fumigatus* MTU6001 was grown at 30 °C on potatodextrose agar for 5 days. 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 serially diluted triazole compound and incubated at 37 °C for 24 h for *C. albicans* or 30 °C for 2 days for *A. fumigatus*. The MIC was determined as the lowest concentration of compound preventing visible fungal growth.

The prophylactic efficiency against murine systemic candidiasis and aspergillosis

Male albino ddY mice, five weeks old, were inoculated via tail vein with 2.0×10^6 cells of *C. albicans* KB-8 or 2×10^7 conidia of *A. fumigatus* MTU6001. Appropriate doses of each compound in 0.5% methylcellulose or saline were 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 days.

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