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Discovery of novel thiourea derivatives as potent and selective β3-adrenergic receptor agonists

Tatsuya Maruyama *, Norio Seki, Kenichi Onda, Takayuki Suzuki, Souichirou Kawazoe, Masahiko Hayakawa, Tetsuo Matsui, Toshiyuki Takasu, Mitsuaki Ohta

Drug Discovery Research, Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

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ABSTRACT

In the search for potent and selective human β3-adrenergic receptor (AR) agonists as potential drugs for the treatment of obesity and noninsulin-dependent (type II) diabetes, we prepared a novel series of phenoxypropanolamine derivatives containing the thiourea moiety and evaluated their biological activities at human β3-, β2-, and β1-ARs. Among these compounds, 4-nitrophenylthiourea (**18i**) and 3-methoxyphenylthiourea (**18k**) derivatives were found to exhibit potent agonistic activity at the β3-AR, with EC_{50} values of 0.10 and 0.16 μM, respectively, and no agonistic activity for either the β1- or β2-AR. In addition, they showed significant hypoglycemic activity in a rodent diabetic model.

1. Introduction

In 1984, β3-adrenergic receptors (ARs) were proposed as a third group of β-ARs present in rat adipose tissue that utilize various β-agonists.[1,2] In 1989, the primary structure of the β3-AR was identified and characterized using cloning and molecular pharmacological techniques.[3–5] β3-AR was found to play a significant role in regulating lipolysis and thermogenesis in both rodent and human adipose tissue. These findings suggest that β3-AR agonists are suitable for mediating thermogenesis for the purpose of obesity modulation and lowering plasma glucose and insulin levels, thereby ameliorating noninsulin-dependent (type II) diabetes. Recent studies indicated that, in addition to adipocytes, the β3-AR is also distributed in human urinary bladder detrusor tissue and its relaxation occurs mainly via β3-AR.[6–8] Subtype selectivity for β3-AR agonists must be kept specifically in mind since activation of the β1- or β2-ARs would cause undesirable side effects such as increased heart rate or muscle tremors. A number of laboratories have been engaged in developing potent and selective β3-AR agonists for the treatment of obesity and type II diabetes.[9,10] While early potent and selective rat β3-AR agonists, such as BRL-37344[11] and CL-316243,[12] were reported to be effective anti-obesity and anti-diabetic agents in rodents (Fig. 1),[13] clinical trials with these drugs for the treatment of metabolic disorders in humans have been disappointing due to a lack of selectivity and/or potency or poor pharmacokinetics.[14,15]

In 1998, researchers at Merck reported a 4-hydroxyphenoxypropanolamine derivative containing the benzenesulfonamide moiety (**1**) as one of the first selective human β3-AR agonists.[16] Owing to its rapid glucuronidation, however, the pharmacokinetic profile of this agent was poor.[17] Considering the structure of compound **1**, we assumed that the 4-hydroxyphenoxy moiety on the left-hand side of **1** might be easily metabolized. In fact, we found that the oral bioavailability of compound **1** in rats (5 mg/kg iv, 30 mg/kg po) was low (F = 4%). In contrast, its phenoxy analogue **2**[18] showed improved oral bioavailability in rats (F = 44%). In addition, compound **2** exhibited only a fivefold loss in potency at the β3-AR (EC_{50} = 0.41 μM, IA = 0.89) compared to **1** (EC_{50} = 0.078 μM, IA = 0.73).

Since compound **2** showed potent β3-AR agonistic activity and good pharmacokinetic profile, we chose compound **2** as our lead compound. Based on the structure of compound **2**, we decided to explore alternative structures instead of the sulfonamide moiety of **2**, and subsequently identified the thiourea derivative **14b**. We then further attempted to modify of the substituent on the

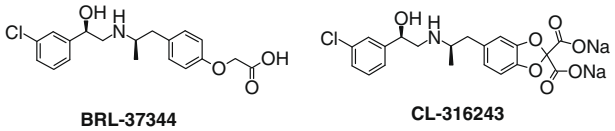

Figure 1. Chemical structure of early β3-AR agonists.

* Corresponding author. Tel.: +81 29 863 6749; fax: +81 29 852 5387.
E-mail address: tatsuya.maruyama@jp.astellas.com (T. Maruyama).

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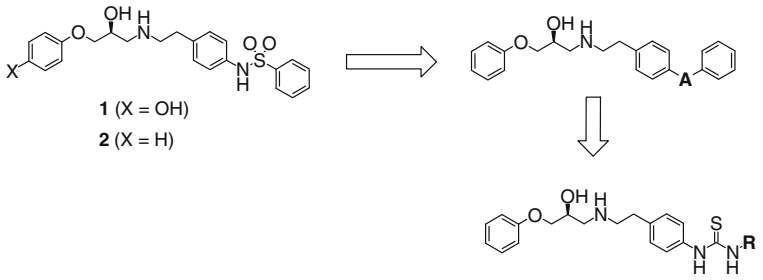


Figure 2. Design of compounds.

thiourea moiety (Fig. 2). In this paper, we describe the synthesis and structure–activity relationships (SARs) of these newly designed phenoxypropanolamine derivatives as β3-AR agonists.

2. Chemistry

Reverse sulfonamide derivative **4** and aniline derivative **9** were prepared as illustrated in Scheme 1. A commercially available *N*-phenyl-4-(2-aminoethyl)benzenesulfonamide (**3**) was coupled with (*S*)-2-(phenoxymethyl)oxirane to afford the desired product **4**. *N*-Benzyl-4-aminophenylacetamide (**5**)[19] was treated with triphenylbismuth in the presence of copper diacetate, followed by reduction of the amido moiety to give the 2-phenylethylamine **7**. Compound **7** was coupled with (*S*)-2-(phenoxymethyl)oxirane, followed by deprotection of the benzyl group to afford the desired product **9**.

Compounds **12** and **14** were prepared from aniline intermediate **10**[20] as illustrated in Scheme 2. The coupling of **10** with benzoyl chloride or phenyl chloroformate in the presence of triethylamine, followed by deprotection of the *tert*-butoxycarbonyl (Boc) group afforded the desired products **12a**,**b**. Compound **10** was coupled with phenylisocyanate or phenylisothiocyanate, followed by deprotection of the Boc group to afford the desired products **14a**,**b**.

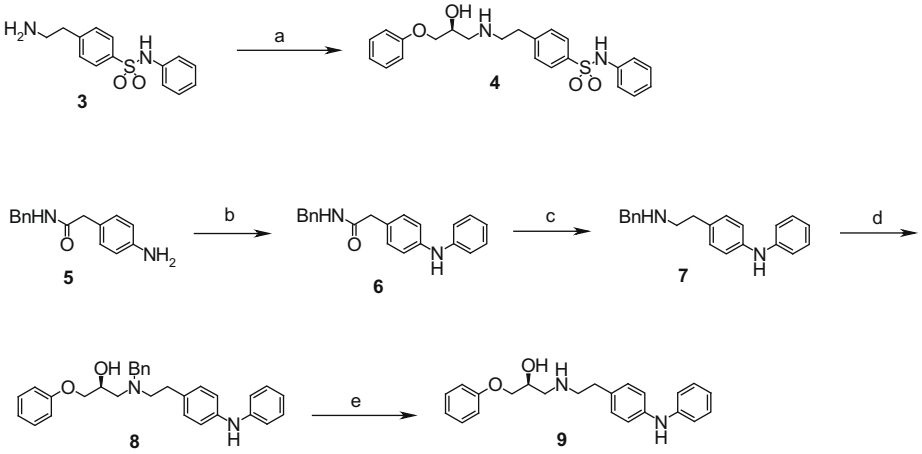
Scheme 3 shows the synthesis of cyanoguanidine derivative **16**. The thiourea moiety of **13b** was converted to a cyanoguanidine moiety by treatment with cyanamide and 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, followed by deprotection of the Boc group to afford the desired product **16**.

Thiourea derivatives **18a–r** were prepared in the same manner as the synthesis of **14b** as illustrated in Scheme 4. Compound **10** was coupled with the appropriate isothiocyanates, followed by deprotection of Boc group to afford the desired products **18a–r**.

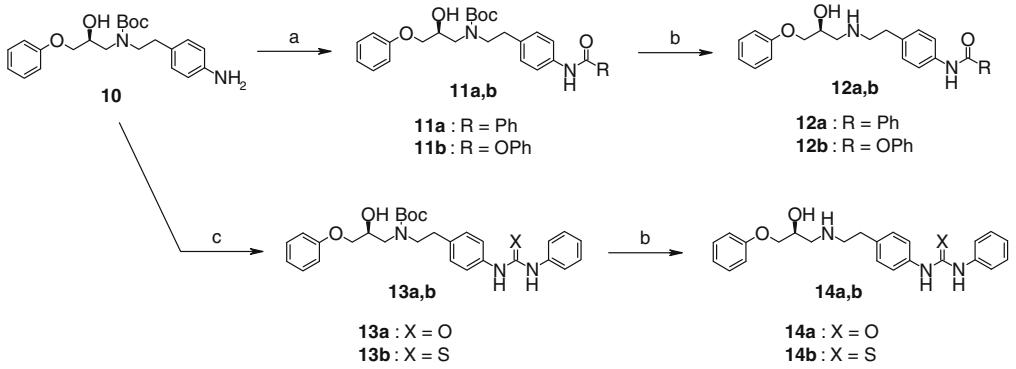
3. Results and discussion

The prepared compounds were evaluated for their agonistic activities in stimulating an increase in cyclic AMP (cAMP) levels in Chinese hamster ovary (CHO) cells expressing cloned human β3-, β2-, and β1-ARs. The results for the reference compounds, isoproterenol (**ISO**; non-selective β-AR agonist) and compound **1**, are also shown in Table 1 for comparison.

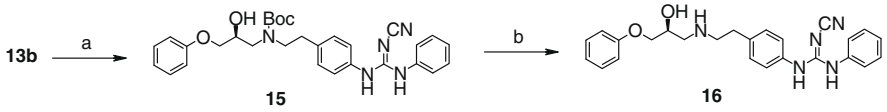
Compound **2** showed β3-, β2-, and β1-AR agonistic activity with EC_{50} values of 0.41, >100, and 78 μM, respectively. In order to improve β3-AR agonistic activity and functional selectivity over β1-AR, modification of the sulfonamido moiety in **2** with the other functional moieties containing the NH part was investigated (Table 1). Initially, reverse sulfonamide derivative **4** showed a fivefold decrease in potency at the β3-AR (EC_{50} = 2.0 μM) and a dramatic increase in potency at the β1-AR (EC_{50} = 0.25 μM) relative to **2**. These results indicated that the NH position is important for β3-AR agonistic activity and selectivity over β1-AR. Aniline derivative **9** was 30-fold less potent at the β3-AR (EC_{50} = 12 μM) and displayed a decrease in intrinsic activity (IA = 0.31) relative to **2**. This revealed that the basic aniline group may not be efficacious in improving agonistic activity at the β3-AR. Replacement of the sulfonamido moiety of **2** with the amido moiety (**12a**) resulted in dramatically decreased potency at the β3-AR (EC_{50} = 130 μM), while urethane derivative **12b** exhibited 23-fold decreased potency at the β3-AR (EC_{50} = 9.3 μM) relative to **2**. Next, replacement of the sulfonamido moiety in **2** with the ureido moiety (**14a**) resulted



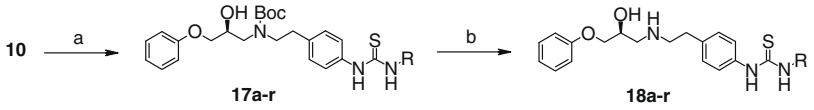
Scheme 1. Reagents and conditions: (a) (*S*)-2-(phenoxymethyl)oxirane, MeCN, reflux, and then 4 M HCl–dioxane, MeOH; (b) Ph_3Bi, $Cu(OAc)_2$, CH_2Cl_2, reflux; (c) 1 M BH_3–THF, THF, reflux; (d) (*S*)-2-(phenoxymethyl)oxirane, ^{i}PrOH, dioxane, reflux; (e) H_2, Pd/C, EtOH, and then 4 M HCl–EtOAc, MeOH.



Scheme 2. Reagents and conditions: (a) RCOCl, Et_3N, $CHCl_3$; (b) 4 M HCl–EtOAc, EtOH; (c) PhCNX, $CHCl_3$, 60–80 °C.



Scheme 3. Reagents and conditions: (a) H_2NCN, EDC·HCl, $^iPr_2NEt$, DMF, 50 °C; (b) CF_3CO_2H, and then 4 M HCl–dioxane.



17a : R = cyclohexyl
17b : R = benzyl
17c : R = 2-phenylethyl
17d : R = 2-chlorophenyl
17e : R = 3-chlorophenyl
17f : R = 4-chlorophenyl
17g : R = 2-nitrophenyl
17h : R = 3-nitrophenyl
17i : R = 4-nitrophenyl
17j : R = 2-methoxyphenyl
17k : R = 3-methoxyphenyl
17l : R = 4-methoxyphenyl
17m : R = 4-fluorophenyl
17n : R = 4-bromophenyl
17o : R = 4-iodophenyl
17p : R = 4-methoxycarbonylphenyl
17q : R = 4-sulfamoylphenyl
17r : R = 4-methylphenyl

18a : R = cyclohexyl
18b : R = benzyl
18c : R = 2-phenylethyl
18d : R = 2-chlorophenyl
18e : R = 3-chlorophenyl
18f : R = 4-chlorophenyl
18g : R = 2-nitrophenyl
18h : R = 3-nitrophenyl
18i : R = 4-nitrophenyl
18j : R = 2-methoxyphenyl
18k : R = 3-methoxyphenyl
18l : R = 4-methoxyphenyl
18m : R = 4-fluorophenyl
18n : R = 4-bromophenyl
18o : R = 4-iodophenyl
18p : R = 4-methoxycarbonylphenyl
18q : R = 4-sulfamoylphenyl
18r : R = 4-methylphenyl

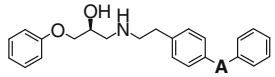
Scheme 4. Reagents and conditions: (a) RNCS, $CHCl_3$, 80 °C; (b) 4 M HCl–EtOAc, EtOH.

in a fivefold decrease in potency at the β3-AR with partial agonistic activity (EC_{50} = 1.9 μM, IA = 0.38) relative to **2**. In contrast, thiourea derivative **14b** showed comparable agonistic activity at the β3-AR (EC_{50} = 0.44 μM, IA = 0.70) relative to **2**, and no agonistic activity for either the β1- or β2-AR. These results indicated that the thiourea group played an important role in β3-AR agonistic activity and selectivity over β1-AR. However, cyanoguanidine derivative **16**, considered a bioisostere of thiourea, showed a 75-fold loss in potency at the β3-AR (EC_{50} = 33 μM) relative to **14b**. We therefore selected the thiourea derivative **14b** as our new leading candidate.

In order to improve β3-AR agonistic activity, modification of the substituent on the thiourea moiety in **14b** was examined as shown in Table 2. Replacement of the phenyl ring with a cyclohexyl ring (**18a**) resulted in threefold decreased potency at the β3-AR (EC_{50} = 1.4 μM) relative to **14b**. Both the benzyl (**18b**) and 2-phenylethyl (**18c**) derivatives exhibited maintained potency at the β3-AR, but their intrinsic activities were decreased (IA = 0.53 and 0.34, respectively). These results revealed that replacement of the phenyl ring with a cyclohexyl ring and the insertion of a methylene or ethylene group between the phenyl ring and thiourea moiety in **14b** may not have been efficacious for improving agonistic activity at the β3-AR.

We then examined the effects of substituents on the phenyl ring of the thiourea moiety in **14b** as shown in Table 3. The introduction of a chloro group as an electron-withdrawing group on the phenyl ring of the thiourea moiety in **14b** (**18d–f**) resulted in slightly increased potency at the β3-AR relative to **14b**, with an apparent rank order of potency of *para*- and *meta*-chloro (EC_{50} = 0.28 and 0.27 μM) > *ortho*-chloro (EC_{50} = 0.40 μM). The nitro group as a strong electron-withdrawing group was also introduced on the phenyl ring of the thiourea moiety (**18g–i**) to yield improved potency of the β3-AR relative to **14b**, with a similar rank order of potency to those of the chlorophenyl derivatives. When the intrinsic activities of β3-AR for 2-nitrophenyl (**18g**) and 3-nitrophenyl (**18h**) derivatives were partial, 4-nitrophenyl derivative **18i** showed full β3-AR agonistic activity (EC_{50} = 0.10 μM, IA = 0.88), and was the most potent in this series. The introduction of a methoxy group as an electron-donating group on the phenyl ring of the thiourea

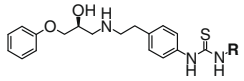
Table 1
β-AR agonistic activity of phenoxypropanolamine derivatives



Compound	A	EC_{50}[a] (μM) (IA[b])		
		β3-AR	β2-AR	β1-AR
2	$NHSO_2$	0.41 (0.89)	>100 (0)	78 (0.11)
4	SO_2NH	2.0 (0.52)	>100 (0.05)	0.25 (0.39)
9	NH	12 (0.31)	>100 (0)	>100 (0.01)
12a	NHCO	130 (0.33)	>100 (0)	>100 (0.02)
12b	$NHCO_2$	9.3 (0.57)	>100 (0)	>100 (0.04)
14a	NHCONH	1.9 (0.38)	>100 (0)	>100 (0.02)
14b	NHCSNH	0.44 (0.70)	>100 (0)	>100 (0.11)
16	NHC(NCN)NH	33 (0.55)	>100 (0.03)	0.056 (0.14)
1		0.078 (0.73)	>100 (0.02)	1.6 (0.21)
ISO		0.10 (1.00)	0.003 (1.00)	0.012 (1.00)

[a] Agonistic activity was assessed by measuring cAMP accumulation in CHO cells expressing β-ARs.
[b] Values in parentheses represent the intrinsic activity (IA) given as a fraction of the maximum stimulation with isoproterenol.

Table 2
β-AR agonistic activity of thiourea derivatives

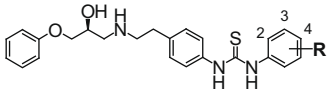


Compound	R	EC_{50}[a] (μM) (IA[b])		
		β3-AR	β2-AR	β1-AR
14b		0.44 (0.70)	>100 (0)	>100 (0.11)
18a		1.4 (0.46)	>100 (0.03)	>100 (0.05)
18b		0.47 (0.53)	>100 (0.03)	>100 (0.04)
18c		0.51 (0.34)	>100 (0.01)	>100 (0.03)

[a] Agonistic activity was assessed by measuring cAMP accumulation in CHO cells expressing β-ARs.
[b] Values in parentheses represent the intrinsic activity (IA) given as a fraction of the maximum stimulation with isoproterenol.

moiety in **14b** (**18j–l**) led to a several fold increase in the potency of β3-AR relative to **14b**, with a rank order of potency similar to those of the chlorophenyl derivatives The introduction of a *meta*-methoxy group (**18k**) led to a 2.8-fold increase in potency at the β3-AR (EC_{50} = 0.16 μM) relative to **14b**. These results revealed that the introduction of both electron-withdrawing and electron-donating groups at the 3- or 4-position on the phenyl ring of the thiourea moiety might be effective in improving agonistic activity at the β3-AR while maintaining functional selectivity over β1- and β2-ARs. Next, the introduction of another halogen group at the 4-position on the phenyl ring of the thiourea moiety in **14b** (**18m–o**) yielded similar results to those of 4-chlorophenyl derivative **18f**. Introduction of the methoxycarbonyl (**18p**) or sulfamoyl (**18q**) group at the 4-position on the phenyl ring of the thiourea moiety in **14b** resulted in slightly increased potency at the β3-AR relative to **14b**; however, their intrinsic activities were decreased (IA = 0.37 and 0.49, respectively). 4-Methylphenyl derivative **18r**

Table 3
β-AR agonistic activity of substituted phenylthiourea derivatives



Compound	R	EC_{50}[a] (μM) (IA[b])		
		β3-AR	β2-AR	β1-AR
14b	H	0.44 (0.70)	>100 (0)	>100 (0.11)
18d	2-Cl	0.40 (0.61)	>100 (0.04)	>100 (0.06)
18e	3-Cl	0.27 (0.61)	>100 (0.05)	>100 (0.10)
18f	4-Cl	0.28 (0.55)	>100 (0.03)	>100 (0.03)
18g	2-NO_2	0.34 (0.45)	>100 (0.02)	>100 (0.06)
18h	3-NO_2	0.10 (0.45)	>100 (0.03)	>100 (0.08)
18i	4-NO_2	0.10 (0.88)	>100 (0.02)	>100 (0.09)
18j	2-OMe	0.27 (0.76)	>100 (0.01)	0.34 (0.13)
18k	3-OMe	0.16 (0.81)	>100 (0.02)	>100 (0.07)
18l	4-OMe	0.20 (0.63)	>100 (0.02)	>100 (0.07)
18m	4-F	0.23 (0.58)	>100 (0.01)	>100 (0.09)
18n	4-Br	0.23 (0.46)	>100 (0.02)	>100 (0.07)
18o	4-I	0.47 (0.57)	>100 (0.01)	>100 (0.07)
18p	4-CO_2Me	0.17 (0.37)	>100 (0.01)	>100 (0.06)
18q	4-SO_2NH_2	0.32 (0.49)	>100 (0.01)	>100 (0.03)
18r	4-Me	0.65 (0.60)	>100 (0.01)	>100 (0.10)

[a] Agonistic activity was assessed by measuring cAMP accumulation in CHO cells expressing β-ARs.
[b] Values in parentheses represent the intrinsic activity (IA) given as a fraction of the maximum stimulation with isoproterenol.

showed a slight decrease in potency at β3-AR. These results indicated that the introduction of any substituent at the 4-position on the phenyl ring of the thiourea moiety in **14b** may maintain potency at β3-AR, but that intrinsic activity may tend to decrease.

Given the results of the in vitro study, compounds **18e**, **18i**, **18k**, and **18l** were selected for in vivo evaluation in a rodent model of type II diabetes (Table 4). The compounds were administered orally for 4 days in diabetic kk mice and the effects on plasma glucose were measured. All compounds induced a significant reduction in plasma glucose levels at the dose of 30 mg/kg. In particular, **18k** and **18l** exhibited more potent hypoglycemic activities (46% and 40% decrease, respectively) than **2** (15% decrease) at the dose of 10 mg/kg.

4. Conclusion

We have identified a new series of thiourea-based β3-AR agonists and described their synthesis and SARs. Among these compounds, the 4-nitrophenyl (**18i**), 3-methoxyphenyl (**18k**), and 4-methoxyphenyl (**18l**) derivatives showed potent agonistic activity at the β3-AR (EC_{50} = 0.10, 0.16, and 0.20 μM, respectively), and also had functional selectivity over β1- and β2-ARs. In addition, **18k** and **18l** exhibited significant hypoglycemic activity in diabetic kk mice at the dose of 10 mg/kg po.

Table 4
Oral hypoglycemic activity in kk mice

Compound	Percent reduction in plasma glucose[a]	
	10 mg/kg	30 mg/kg
18e	NT[b]	29**[c]
18i	NT	32**
18k	46**	49***
18l	40**	53***
2	15*	38**

[a] The compounds were administered orally to male kk mice for 4 days.
[b] Not tested.
[c] Statistically significant at (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

5. Experimental

5.1. Chemistry

Melting points were determined with a Yanaco MP-500D melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL EX90, EX400, or GX500 spectrometer, and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard (NMR description key: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad peak). Mass spectra were recorded on a Hitachi M-80 or JEOL JMS-DX300 spectrometer. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and were within ±0.4% of the theoretical values. During the work-up, all organic solutions were dried over anhydrous Mg_2SO_4.

5.1.1. (*S*)-*N*-Phenyl-4-{2-[(2-hydroxy-3-phenoxypropyl)amino]-ethyl}benzenesulfonamide hydrochloride (4)

A mixture of a commercially available *N*-phenyl-4-(2-aminoethyl)benzenesulfonamide (**3**) (0.13 g) and (*S*)-2-(phenoxymethyl)oxirane (0.07 g) in acetonitrile (5 ml) was refluxed for 24 h, and the resultant mixture was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (5:1) as the eluent to yield free base (0.10 g). To the solution of the residue in methanol (5 ml) was added 4 M HCl–dioxane (0.1 ml), and the resultant mixture was concentrated in vacuo. The residue was purified by recrystallization from methanol-isopropanol to yield **4** (0.06 g) as a colorless solid. 28% yield; mp 161–165 °C (MeOH–^{i}PrOH); ^{1}H NMR (DMSO-d_6) δ: 3.01–3.06 (3H, m), 3.15–3.25 (3H, m), 3.92–4.00 (2H, m), 4.19–4.21 (1H, m), 5.89 (1H, d, J = 4.9 Hz), 6.93–7.03 (4H, m), 7.09–7.12 (2H, m), 7.20–7.24 (2H, m), 7.28–7.32 (2H, m), 7.44 (2H, d, J = 8.3 Hz), 7.73 (2H, d, J = 8.3 Hz), 8.88 (1H, br s), 9.06 (1H, br s), 10.31 (1H, s); MS (FAB) *m/z*: 427 (MH^+). Anal. Calcd for $C_{23}H_{26}N_2O_4S\cdot HCl\cdot 0.5H_2O$: C, 58.53; H, 5.98; N, 5.94; S, 6.79; Cl, 7.51. Found: C, 58.49; H, 5.89; N, 5.91; S, 6.80; Cl, 7.67.

5.1.2. *N*-Benzyl-4-(phenylamino)phenylacetamide (6)

To a solution of *N*-benzyl-4-aminophenylacetamide (**5**) (1.26 g) in dichloromethane (70 ml) were added triphenylbismuth (3.86 g) and copper diacetate (0.96 g) at room temperature, and the mixture was refluxed for 3.5 h. After cooling to room temperature, the solid was removed by filtration over Celite, and the filtrate was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (40:1) as the eluent to yield **6** (1.27 g) as a colorless powder. 76% yield; ^{1}H NMR (DMSO-d_6) δ: 3.38 (2H, s), 3.07–3.09 (2H, m), 4.27 (2H, d, J = 6.1 Hz), 6.77–6.80 (1H, m), 7.00–7.04 (4H, m), 7.13–7.24 (7H, m), 7.28–7.32 (2H, m), 8.06 (1H, s), 8.43–8.46 (1H, m); MS (FAB) *m/z*: 317 (MH^+).

5.1.3. *N*-Benzyl-2-[4-(phenylamino)phenyl]ethylamine (7)

To a solution of compound **6** (1.25 g) in tetrahydrofuran (10 ml) was added 1 M borane–THF solution (12 ml), and the mixture was refluxed for 1 h. After cooling to room temperature, to the resultant mixture was added dropwise methanol (10 ml), and the mixture was refluxed for 30 min. To the mixture was added concentrated HCl aqueous solution (1.4 ml), and the mixture was heated at 80 °C for 2 h. After cooling to room temperature, the mixture was diluted with 1 M sodium hydroxide solution (15 ml) and stirred. The solid was isolated by filtration, and washed with water. The residue was purified by recrystallization from ethanol–ethyl acetate to yield **7** (0.79 g) as a colorless solid. 66% yield; ^{1}H NMR (DMSO-d_6) δ: 2.88–2.91 (2H, m), 3.07–3.09 (2H, m), 4.17 (2H, s), 6.80 (1H, t, J = 7.3 Hz), 7.02–7.11 (6H, m), 7.19–7.23 (2H, m), 7.42–7.47 (3H, m), 7.56 (2H, d, J = 6.1 Hz), 8.13 (1H, s), 9.27 (1H, s); MS (FAB) *m/z*: 303 (MH^+).

5.1.4. (*S*)-1-Phenoxy-3-(*N*-benzyl-{2-[4-(phenylamino)phenyl]-ethyl}amino)-2-propanol (8)

A mixture of compound **7** (0.27 g) and (*S*)-2-(phenoxymethyl)oxirane (0.31 g) in 2-propanol (15 ml) and dioxane (1 ml) was refluxed for 24 h, and the resultant mixture was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (50:1) as the eluent to yield **8** (0.36 g) as a colorless oil. 89% yield; ^{1}H NMR ($CDCl_3$) δ: 2.69–2.88 (6H, m), 3.61 (1H, d, J = 14.0 Hz), 3.84–3.94 (3H, m), 3.98–4.05 (1H, m), 5.60 (1H, s), 6.83–7.03 (10H, m), 7.21–7.33 (9H, m); MS (FAB) *m/z*: 453 (MH^+).

5.1.5. (*S*)-1-Phenoxy-3-({2-[4-(phenylamino)phenyl]ethyl}amino)-2-propanol hydrochloride (9)

To a solution of **8** (0.34 g) in ethanol (15 ml) was added palladium–carbon (10% w/w, 0.14 g), and the mixture was stirred under a hydrogen atmosphere for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. To the solution of the residue in methanol (10 ml) was added 1 M HCl–EtOAc (0.7 ml), and the resultant mixture was concentrated in vacuo. The residue was purified by recrystallization from ethanol–diethyl ether to yield **9** (0.13 g) as a colorless solid. 43% yield; mp 160–162 °C (EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.07 (3H, m), 3.12–3.24 (3H, m), 3.94–4.02 (2H, m), 4.21–4.25 (1H, m), 5.91 (1H, d, J = 5.6 Hz), 6.78–6.82 (1H, m), 6.94–6.97 (3H, m), 7.02–7.05 (4H, m), 7.20 (2H, d, J = 8.4 Hz), 7.19–7.23 (2H, m), 7.28–7.33 (2H, m), 8.15 (1H, s), 8.84 (1H, br s), 9.04 (1H, br s); MS (FAB) *m/z*: 363 (MH^+). Anal. Calcd for $C_{23}H_{26}N_2O_2\cdot 1.1HCl$: C, 67.41; H, 6.86; N, 6.84; Cl, 9.52. Found: C, 67.52; H, 6.63; N, 6.77; Cl, 9.58.

5.1.6. (*S*)-*N*-(4-{2-[*N*′-*tert*-Butoxycarbonyl-*N*′-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)benzamide (11a)

To a solution of *tert*-butyl (*S*)-*N*-[2-(4-aminophenyl)ethyl]-*N*-(2-hydroxy-3-phenoxy)propylcarbamate (**10**) (0.48 g) in chloroform (15 ml) were added triethylamine (0.15 g) and benzoyl chloride (0.19 g), and the mixture was stirred at room temperature for 30 min. The resulting mixture was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent to yield **11a** (0.48 g) as a colorless powder. 78% yield; ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.80–2.90 (2H, m), 3.28–3.50 (4H, m), 3.88–3.95 (2H, m), 4.11 (2H, br s), 6.89–6.98 (3H, m), 7.13–7.31 (4H, m), 7.47–7.57 (5H, m), 7.78–7.87 (3H, m); MS (FAB) *m/z*: 491 (MH^+).

5.1.7. Phenyl (*S*)-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)carbamate (11b)

The title compound was prepared in the same manner as described for **11a** using phenyl chloroformate instead of benzoyl chloride as a colorless powder. 77% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.90 (2H, m), 3.40–3.50 (4H, m), 3.89–3.95 (2H, m), 4.09 (2H, br s), 6.89–6.98 (3H, m), 7.12–7.41 (11H, m); MS (FAB) *m/z*: 507 (MH^+).

5.1.8. (*S*)-*N*-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl} phenyl)benzamide hydrochloride (12a)

To a solution of **11a** (0.47 g) in ethanol (10 ml) was added 4 M HCl–EtOAc (10 ml), and the mixture was stirred at room temperature for 30 min. The resulting mixture was concentrated in vacuo. The crude solid was purified by recrystallization from methanol to yield **12a** (0.20 g) as a colorless solid. 77% yield; mp 247–252 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ: 2.94–3.08 (3H, m), 3.17–3.20

(3H, m), 3.94–4.02 (2H, m), 4.21–4.23 (1H, m), 5.90 (1H, d, J = 4.8 Hz), 6.94–6.97 (3H, m), 7.23–7.33 (4H, m), 7.51–7.61 (3H, m), 7.75 (2H, d, J = 8.4 Hz), 7.94–7.97 (2H, m), 8.81 (1H, br s), 8.94 (1H, br s), 10.26 (1H, s); MS (FAB) *m/z*: 391 (MH^+). Anal. Calcd for $C_{24}H_{26}N_2O_3{\cdot}HCl{\cdot}0.1H_2O$: C, 67.23; H, 6.39; N, 6.53; Cl, 8.27. Found: C, 67.08; H, 6.34; N, 6.51; Cl, 8.08.

5.1.9. Phenyl (*S*)-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino] ethyl}phenyl)carbamate hydrochloride (12b)

The title compound was prepared in the same manner as described for **12a** using **11b** instead of **11a** as a colorless solid. 54% yield; mp 215–219 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.93–3.07 (3H, m), 3.15–3.22 (3H, m), 3.94–4.01 (2H, m), 4.21–4.24 (1H, m), 5.90 (1H, d, J = 4.8 Hz), 6.94–6.97 (3H, m), 7.20–7.33 (7H, m), 7.41–7.48 (4H, m), 8.85 (1H, br s), 9.03 (1H, br s), 10.22 (1H, s); MS (FAB) *m/z*: 407 (MH^+). Anal. Calcd for $C_{24}H_{26}N_2O_4{\cdot}HCl$: C, 65.08; H, 6.14; N, 6.32; Cl, 8.00. Found: C, 65.14; H, 5.90; N, 6.38; Cl, 7.89.

5.1.10. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-phenylurea (13a)

To a solution of **10** (0.49 g) in chloroform (15 ml) was added phenylisocyanate (0.17 g), and the mixture was stirred at 60 °C for 3 h. The resulting mixture was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent to yield **13a** (0.36 g) as a colorless powder. 56% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.90 (2H, m), 3.42–3.50 (4H, m), 3.88–3.95 (2H, m), 4.06–4.11 (2H, m), 6.60–6.67 (2H, m), 6.87–7.00 (3H, m), 7.05–7.12 (4H, m), 7.26–7.52 (7H, m); MS (FAB) *m/z*: 506 (MH^+).

5.1.11. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-phenylthiourea (13b)

To a solution of **10** (0.50 g) in chloroform (15 ml) was added phenylisothiocyanate (0.30 g), and the mixture was stirred at 80 °C for 15 h. The resulting mixture was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent to yield **13b** (0.35 g) as a colorless powder. 52% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.95 (2H, m), 3.36–3.55 (4H, m), 3.85–4.05 (3H, m), 4.05–4.15 (1H, m), 6.89 (2H, d, J = 8.0 Hz), 6.96 (1H, t, J = 7.2 Hz), 7.15–7.25 (2H, m), 7.26–7.45 (9H, m), 7.68 (1H, s), 7.73 (1H, s); MS (FAB) *m/z*: 522 (MH^+).

5.1.12. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl} phenyl)-3-phenylurea hydrochloride (14a)

The title compound was prepared in the same manner as described for **12a** using **13a** instead of **11a** as a colorless solid. 68% yield; mp 217–219 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ: 2.86–2.98 (2H, m), 3.03–3.06 (1H, m), 3.16–3.20 (3H, m), 3.93–4.01 (2H, m), 4.20 (1H, br s), 5.90 (1H, br s), 6.93–6.97 (4H, m), 7.17 (2H, d, J = 8.8 Hz), 7.24–7.33 (4H, m), 7.41–7.46 (4H, m), 8.73 (1H, br s), 8.84 (1H, br s), 9.05 (1H, d, J = 5.2 Hz); MS (FAB) *m/z*: 406 (MH^+). Anal. Calcd for $C_{24}H_{27}N_3O_3{\cdot}HCl$: C, 65.22; H, 6.39; N, 9.51; Cl, 8.02. Found: C, 65.12; H, 6.27; N, 9.53; Cl, 7.83.

5.1.13. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-phenylthiourea hydrochloride (14b)

The title compound was prepared in the same manner as described for **12a** using **13b** instead of **11a** as a colorless solid. 57% yield; mp 214–217 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.93–3.07 (3H, m), 3.15–3.25 (3H, m), 3.94–4.01 (2H, m), 4.19–4.23 (1H, m), 5.91 (1H, d, J = 4.4 Hz), 6.95–6.97 (3H, m), 7.09–7.13 (1H, m), 7.22 (2H, d, J = 8.0 Hz), 7.29–7.34 (4H, m), 7.50–7.55 (4H, m), 8.79 (1H, br s), 8.93 (1H, br s), 10.17 (1H, s), 10.18 (1H, s); MS (FAB) *m/z*: 422 (MH^+). Anal. Calcd for $C_{24}H_{27}N_3O_2S{\cdot}HCl$: C, 62.94; H, 6.16; N, 9.17; S, 7.00; Cl, 7.74. Found: C, 62.87; H, 6.03; N, 9.19; S, 6.85; Cl, 7.63.

5.1.14. (*S*)-2-Cyano-1-(4-{2-[*N*-*tert*-butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-phenylguanidine (15)

To a solution of **13b** (0.40 g) in *N*,*N*-dimethylformamide (10 ml) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.16 g), cyanamide (0.06 g) and diisopropylethylamine (0.01 g), and the mixture was heated at 50 °C for 20 h. The resulting mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The organic layer was washed with brine, and then dried and concentrated in vacuo. The residue was purified using column chromatography on silica gel with *n*-hexane/EtOAc (1:1) as the eluent to yield **15** (0.15 g) as a colorless oil. 37% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.90 (2H, m), 3.35–3.56 (4H, m), 3.82–4.10 (3H, m), 6.85–7.00 (4H, m), 7.20–7.44 (10H, m); MS (FAB) *m/z*: 530 (MH^+).

5.1.15. (*S*)-2-Cyano-1-(4-{2-[(2-hydroxy-3-phenoxypropyl)-amino]ethyl}phenyl)-3-phenylguanidine hydrochloride (16)

A mixture of **15** (0.15 g) in trifluoroacetic acid (5 ml) was stirred at room temperature for 5 min, and the resultant mixture was concentrated in vacuo. To the residue was added 4 M HCl–dioxane (5 ml), the mixture was stirred at room temperature for 30 min, and the resultant mixture was concentrated in vacuo. The residue was purified by recrystallization from aqueous methanol to yield **16** (0.05 g) as a colorless solid. 37% yield; mp 190–193 °C (MeOH–water); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.11 (3H, m), 3.12–3.30 (3H, m), 3.93–4.02 (2H, m), 4.21 (1H, br s), 5.90 (1H, d, J = 4.9 Hz), 6.93–6.99 (3H, m), 7.10–7.37 (11H, m), 8.78 (1H, br s), 8.94 (1H, br s), 9.50 (2H, br s); MS (FAB-nega.) *m/z*: 428 [$(M-H)^-$]. Anal. Calcd for $C_{25}H_{27}N_5O_2{\cdot}HCl{\cdot}0.3H_2O$: C, 63.70; H, 6.12; N, 14.86; Cl, 7.52. Found: C, 63.92; H, 6.04; N, 14.45; Cl, 7.54.

5.1.16. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-cyclohexylthiourea (17a)

The title compound was prepared in the same manner as described for **13b** using cyclohexylisothiocyanate instead of phenylisothiocyanate as a colorless oil. 20% yield; ^{1}H NMR ($CDCl_3$) δ: 1.05–1.20 (2H, m), 1.45 (9H, s), 1.30–1.70 (6H, m), 2.00–2.10 (2H, m), 2.70–3.00 (3H, m), 3.25–3.60 (4H, m), 3.80–4.00 (2H, m), 4.05–4.15 (1H, m), 4.20–4.35 (1H, m), 5.83 (1H, d, J = 8.0 Hz), 6.90 (2H, d, J = 7.6 Hz), 6.98 (1H, t, J = 7.2 Hz), 7.00 (2H, d, J = 8.0 Hz), 7.15–7.32 (5H, m), 7.39 (1H, s); MS (FAB) *m/z*: 528 (MH^+).

5.1.17. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-benzylthiourea (17b)

The title compound was prepared in the same manner as described for **13b** using benzylisothiocyanate instead of phenylisothiocyanate as a colorless oil. 55% yield; ^{1}H NMR ($CDCl_3$) δ: 1.42 (9H, s), 2.75–2.93 (2H, m), 3.40–3.50 (4H, m), 3.49 (2H, d, J = 7.6 Hz), 3.80–4.00 (2H, m), 4.00–4.10 (1H, m), 4.87 (1H, d, J = 7.2 Hz), 6.23 (1H, br s), 6.88 (2H, d, J = 8.4 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.08–7.44 (13H, m), 7.64 (1H, s); MS (FAB) *m/z*: 536 (MH^+).

5.1.18. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(2-phenylethyl)thiourea (17c)

The title compound was prepared in the same manner as described for **13b** using 2-phenylethylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 59% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.86–2.94 (4H, m), 3.34–3.54 (4H, m), 3.82–4.02 (5H, m), 4.04–4.12 (1H, m), 5.94 (1H, br s), 6.90 (4H, d, J = 8.4 Hz), 6.98 (1H, t, J = 7.2 Hz), 7.05–7.34 (9H, m), 7.54 (1H, s); MS (FAB) *m/z*: 550 (MH^+).

5.1.19. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(2-chlorophenyl)thiourea (17d)

The title compound was prepared in the same manner as described for **13b** using 2-chlorophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 34% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.95 (2H, m), 3.25–3.55 (4H, m), 3.80–4.00 (3H, m), 4.05–4.16 (1H, m), 6.89 (2H, d, J = 8.4 Hz), 6.95–7.00 (1H, m), 7.15–7.40 (10H, m), 7.71 (1H, s), 7.75 (1H, s); MS (FAB) *m/z*: 556 (MH^+).

5.1.20. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(3-chlorophenyl)thiourea (17e)

The title compound was prepared in the same manner as described for **13b** using 3-chlorophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 69% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.95 (2H, m), 3.40–3.60 (4H, m), 3.80–4.00 (3H, m), 4.00–4.10 (1H, m), 6.88 (2H, d, J = 8.0 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.20–7.40 (9H, m), 7.44 (1H, s), 7.60 (1H, s), 7.71 (1H, s); MS (FAB) *m/z*: 556 (MH^+).

5.1.21. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-chlorophenyl)thiourea (17f)

The title compound was prepared in the same manner as described for **13b** using 4-chlorophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 51% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.84–2.94 (2H, m), 3.37–3.54 (4H, m), 3.70–4.00 (3H, m), 4.00–4.20 (1H, m), 6.88 (2H, d, J = 8.0 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.55–7.70 (10H, m), 7.56 (1H, s), 7.65 (1H, s); MS (FAB) *m/z*: 556 (MH^+).

5.1.22. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(2-nitrophenyl)thiourea (17g)

The title compound was prepared in the same manner as described for **13b** using 2-nitrophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 85% yield; ^{1}H NMR ($CDCl_3$) δ: 1.38 (9H, s), 2.77–2.81 (2H, m), 3.10–3.18 (1H, m), 3.40–3.48 (3H, m), 3.82–3.88 (2H, m), 3.89–4.00 (1H, m), 5.15–5.18 (1H, m), 6.90–6.94 (3H, m), 7.18–7.19 (2H, m), 7.26–7.31 (2H, m), 7.39–7.43 (3H, m), 7.67–7.76 (2H, m), 8.00 (1H, dd, J = 8.4, 1.6 Hz), 9.84 (1H, s), 10.34 (1H, s); MS (FAB) *m/z*: 567 (MH^+).

5.1.23. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(3-nitrophenyl)thiourea (17h)

The title compound was prepared in the same manner as described for **13b** using 3-nitrophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 62% yield; ^{1}H NMR ($CDCl_3$) δ: 1.38 (9H, s), 2.77–2.80 (2H, m), 3.06–3.17 (1H, m), 3.37–3.44 (3H, m), 3.82–3.87 (2H, m), 3.99 (1H, br s), 5.15–5.18 (1H, m), 6.91–6.94 (3H, m), 7.16–7.19 (2H, m), 7.28 (2H, t, J = 8.4 Hz), 7.90 (1H, dd, J = 8.0, 2.0 Hz), 7.95 (1H, dd, J = 8.0, 2.0 Hz), 8.56 (1H, t, J = 2.0 Hz), 10.05 (1H, s), 10.08 (1H, s); MS (FAB) *m/z*: 567 (MH^+).

5.1.24. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-nitrophenyl)thiourea (17i)

The title compound was prepared in the same manner as described for **13b** using 4-nitrophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 88% yield; ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.85–3.00 (3H, m), 3.35–3.62 (3H, m), 3.80–4.05 (3H, m), 6.86 (2H, d, J = 7.6 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.20–7.32 (6H, m), 7.71 (2H, d, J = 8.8 Hz), 7.84 (1H, s), 7.99 (1H, s), 8.16 (2H, d, J = 8.8 Hz); MS (FAB) *m/z*: 567 (MH^+).

5.1.25. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(2-methoxyphenyl)thiourea (17j)

The title compound was prepared in the same manner as described for **13b** using 2-methoxyphenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 54% yield; ^{1}H NMR ($CDCl_3$) δ: 1.37 (9H, s), 2.49–2.51 (2H, m), 3.04–3.17 (1H, m), 3.38–3.44 (3H, m), 3.83–3.85 (5H, m), 3.98 (1H, br s), 5.14–5.19 (1H, m), 6.90–6.94 (4H, m), 7.04–7.06 (1H, m), 7.12–7.16 (3H, m), 7.26–7.30 (2H, m), 7.43 (2H, d, J = 8.0 Hz), 7.95 (1H, d, J = 7.6 Hz), 9.07 (1H, s), 9.89 (1H, s); MS (FAB) *m/z*: 552 (MH^+).

5.1.26. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(3-methoxyphenyl)thiourea (17k)

The title compound was prepared in the same manner as described for **13b** using 3-methoxyphenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 28% yield; ^{1}H NMR ($CDCl_3$) δ: 1.38 (9H, s), 2.74–2.79 (2H, m), 3.05–3.17 (1H, m), 3.38–3.43 (3H, m), 3.73 (3H, s), 3.83–3.88 (2H, m), 3.97–4.00 (1H, m), 5.14–5.19 (1H, m), 6.69 (1H, dd, J = 8.0, 2.0 Hz), 6.90–6.94 (3H, m), 7.01 (1H, dd, J = 8.0, 1.6 Hz), 7.12–7.14 (2H, m), 7.18–7.30 (4H, m), 7.38–7.40 (2H, m), 9.72 (2H, s); MS (FAB) *m/z*: 552 (MH^+).

5.1.27. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-methoxyphenyl)thiourea (17l)

The title compound was prepared in the same manner as described for **13b** using 4-methoxyphenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 53% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.95 (2H, m), 3.35–3.55 (4H, m), 3.82 (3H, s), 3.80–4.00 (3H, m), 4.05–4.15 (1H, m), 6.86–7.00 (6H, m), 7.13–7.20 (2H, m), 7.24–7.34 (5H, m), 7.51 (1H, s), 7.57 (1H, s); MS (FAB) *m/z*: 552 (MH^+).

5.1.28. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-fluorophenyl)thiourea (17m)

The title compound was prepared in the same manner as described for **13b** using 4-fluorophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 34% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.72–2.80 (2H, m), 3.34–3.46 (4H, m), 3.80–3.90 (2H, m), 3.93–4.03 (1H, m), 5.12–5.21 (1H, m), 6.90–6.95 (3H, m), 7.10–7.19 (4H, m), 7.26–7.30 (2H, m), 7.35–7.40 (2H, m), 7.43–7.48 (2H, m), 9.66 (1H, s), 9.72 (1H, s); MS (FAB) *m/z*: 540 (MH^+).

5.1.29. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-bromophenyl)thiourea (17n)

The title compound was prepared in the same manner as described for **13b** using 4-bromophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 37% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.95 (2H, m), 3.36–3.57 (4H, m), 3.80–4.00 (2H, m), 4.00–4.08 (1H, m), 6.88 (2H, d, J = 8.4 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.20–7.32 (8H, m), 7.48 (2H, d, J = 8.8 Hz), 7.57 (1H, s), 7.69 (1H, s); MS (FAB) *m/z*: 600 (MH^+).

5.1.30. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-iodophenyl)thiourea (17o)

The title compound was prepared in the same manner as described for **13b** using 4-iodophenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 43% yield; ^{1}H NMR

($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.95 (2H, m), 3.35–3.57 (4H, m), 3.80–4.00 (3H, m), 4.00–4.10 (1H, m), 6.88 (2H, d, J = 8.0 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.17 (2H, d, J = 8.4 Hz), 7.20–7.32 (6H, m), 7.58 (1H, s), 7.67 (2H, d, J = 8.4 Hz), 7.72 (1H, s); MS (FAB) m/z: 648 (MH^+).

5.1.31. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-methoxycarbonylphenyl)-thiourea (17p)

The title compound was prepared in the same manner as described for **13b** using 4-methoxycarbonylphenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 56% yield; ^1H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.80–2.96 (2H, m), 3.36–3.60 (4H, m), 3.84–4.00 (2H, m), 3.91 (3H, s), 4.00–4.04 (1H, m), 6.88 (2H, d, J = 8.0 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.22–7.32 (6H, m), 7.53 (2H, d, J = 8.4 Hz), 7.71 (1H, s), 7.77 (1H, s), 8.03 (2H, d, 6.88 (2H, d, J = 8.0 Hz); MS (FAB) m/z: 580 (MH^+).

5.1.32. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-sulfamoylphenyl)thiourea (17q)

The title compound was prepared in the same manner as described for **13b** using 4-sulfamoylphenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 61% yield; ^1H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.90 (2H, m), 3.20–3.55 (4H, m), 3.88–3.97 (2H, m), 4.05–4.15 (1H, m), 6.47 (2H, s), 6.88–6.97 (3H, m), 7.12–7.44 (6H, m), 7.73 (2H, d, J = 8.0 Hz), 7.87 (2H, d, J = 8.8 Hz), 9.32 (2H, br s); MS (FAB) m/z: 601 (MH^+).

5.1.33. (*S*)-1-(4-{2-[*N*-*tert*-Butoxycarbonyl-*N*-(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)-3-(4-methylphenyl) thiourea (17r)

The title compound was prepared in the same manner as described for **13b** using 4-methylphenylisothiocyanate instead of phenylisothiocyanate as a colorless powder. 41% yield; ^1H NMR ($CDCl_3$) δ: 1.38 (9H, s), 2.28 (3H, s), 2.74–2.78 (2H, m), 3.05–3.17 (1H, m), 3.36–3.44 (3H, m), 3.82–3.87 (2H, m), 3.98 (1H, br s), 5.13–5.17 (1H, m), 6.90–6.94 (3H, m), 7.12–7.14 (4H, m), 7.26–7.40 (6H, m), 9.60 (1H, s), 9.61 (1H, s); MS (FAB) m/z: 536 (MH^+).

5.1.34. (*S*)-1-Cyclohexyl-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)-amino]ethyl}phenyl)thiourea hydrochloride (18a)

The title compound was prepared in the same manner as described for **12a** using **17a** instead of **11a** as a colorless solid. 65% yield; mp 155–160 °C (EtOH–Et_2O); ^1H NMR (DMSO-d_6) δ: 1.10–1.36 (5H, m), 1.52–1.60 (1H, m), 1.64–1.72 (2H, m), 1.84–1.95 (2H, m), 2.86–3.28 (7H, m), 3.97 (2H, t, J = 4.4 Hz), 4.15–4.25 (1H, m), 5.88 (1H, br s), 6.93–7.00 (3H, m), 7.18 (2H, d, J = 8.4 Hz), 7.31 (2H, t, J = 8.0 Hz), 7.44 (2H, d, J = 8.4 Hz), 8.68 (2H, br s), 9.45 (1H, s); MS (FAB) m/z: 428 (MH^+). Anal. Calcd for $C_{24}H_{33}N_3O_2S{\cdot}1.3HCl{\cdot}0.4H_2O$: C, 59.78; H, 7.34; N, 8.71; S, 6.65; Cl, 9.56. Found: C, 59.88; H, 7.37; N, 8.36; S, 5.81; Cl, 9.45.

5.1.35. (*S*)-1-Benzyl-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino]-ethyl}phenyl)thiourea hydrochloride (18b)

The title compound was prepared in the same manner as described for **12a** using **17b** instead of **11a** as a colorless solid. 43% yield; mp 185–187 °C (EtOH-Et_2O); ^1H NMR (DMSO-d_6) δ: 2.88–3.10 (3H, m), 3.13–3.27 (3H, m), 3.93–4.02 (2H, m), 4.15–4.24 (1H, m), 4.73 (2H, d, J = 6.0 Hz), 5.89 (1H, d, J = 5.2 Hz), 6.94–6.98 (3H, m), 7.21 (2H, d, J = 8.4 Hz), 7.23–7.35 (7H, m), 7.44 (2H, d, J = 8.4 Hz), 8.28 (1H, br s), 8.73 (1H, br s), 8.84 (1H, br s), 9.79 (1H, br s); MS (FAB) m/z: 436 (MH^+). Anal. Calcd for $C_{25}H_{29}N_3O_2S{\cdot}HCl{\cdot}0.2H_2O$: C, 63.13; H, 6.44; N, 8.83; S, 6.74; Cl, 7.45. Found: C, 63.18; H, 6.35; N, 8.82; S, 6.78; Cl, 7.43.

5.1.36. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(2-phenylethyl)thiourea hydrochloride (18c)

The title compound was prepared in the same manner as described for **12a** using **17c** instead of **11a** as a colorless solid. 64% yield; mp 183–185 °C (MeOH–EtOH); ^1H NMR (DMSO-d_6) δ: 2.84–3.08 (5H, m), 3.16–3.23 (3H, m), 3.65–3.73 (2H, m), 3.94–4.01 (2H, m), 4.17–4.25 (1H, m), 5.90 (1H, d, J = 5.2 Hz), 6.94–6.98 (3H, m), 7.17–7.36 (11H, m), 7.87 (1H, br s), 8.79 (2H, br s), 9.73 (1H, br s); MS (FAB) m/z: 450 (MH^+). Anal. Calcd for $C_{26}H_{31}N_3O_2SCl{\cdot}HCl$: C, 64.25; H, 6.64; N, 8.64; S, 6.60; Cl, 7.29. Found: C, 64.11; H, 6.80; N, 8.56; S, 6.52; Cl, 7.42.

5.1.37. (*S*)-1-(2-Chlorophenyl)-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)thiourea hydrochloride (18d)

The title compound was prepared in the same manner as described for **12a** using **17d** instead of **11a** as a colorless solid. 43% yield; mp 157–160 °C (EtOH); ^1H NMR (DMSO-d_6) δ: 2.90–3.10 (3H, m), 3.15–3.26 (3H, m), 3.94–4.01 (2H, m), 4.16–4.25 (1H, m), 5.90 (1H, br s), 6.94–6.98 (3H, m), 7.20–7.36 (6H, m), 7.49–7.55 (3H, m), 7.61–7.64 (1H, m), 8.78 (1H, br s), 8.91 (1H, br s), 9.60 (1H, s), 10.30 (1H, s); MS (FAB) m/z: 456 (MH^+). Anal. Calcd for $C_{24}H_{26}N_3O_2SCl{\cdot}HCl$: C, 58.58; H, 5.53; N, 8.53; S, 6.51; Cl, 14.40. Found: C, 58.36; H, 5.52; N, 8.44; S, 6.27; Cl, 14.44.

5.1.38. (*S*)-1-(3-Chlorophenyl)-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)thiourea hydrochloride (18e)

The title compound was prepared in the same manner as described for **12a** using **17e** instead of **11a** as a colorless solid. 51% yield; mp 154–156 °C (EtOH); ^1H NMR (DMSO-d_6) δ: 2.91–3.09 (3H, m), 3.15–3.25 (3H, m), 3.94–4.01 (2H, m), 4.18–4.26 (1H, m), 5.91 (1H, br s), 6.94–6.97 (3H, m), 7.14–7.17 (1H, m), 7.23 (2H, d, J = 8.4 Hz), 7.29–7.36 (3H, m), 7.44–7.54 (3H, m), 7.82 (1H, t, J = 2.0 Hz), 8.79 (1H, br s), 8.93 (1H, br s), 10.38 (1H, s), 10.44 (1H, s); MS (FAB) m/z: 456 (MH^+). Anal. Calcd for $C_{24}H_{26}N_3O_2SCl{\cdot}HCl$: C, 58.58; H, 5.53; N, 8.53; S, 6.51; Cl, 14.40. Found: C, 58.26; H, 5.60; N, 8.43; S, 6.30; Cl, 14.47.

5.1.39. (*S*)-1-(4-Chlorophenyl)-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)thiourea hydrochloride (18f)

The title compound was prepared in the same manner as described for **12a** using **17f** instead of **11a** as a colorless solid. 57% yield; mp 211–214 °C (MeOH–EtOH); ^1H NMR (DMSO-d_6) δ: 2.90–3.08 (3H, m), 3.15–3.25 (3H, m), 3.94–4.01 (2H, m), 4.16–4.25 (1H, m), 5.90 (1H, d, J = 4.8 Hz), 6.94–6.98 (3H, m), 7.22 (2H, d, J = 8.4 Hz), 7.29–7.39 (4H, m), 7.49 (2H, d, J = 8.4 Hz), 7.58 (2H, d, J = 8.4 Hz), 8.78 (1H, br s), 8.89 (1H, br s), 10.26 (1H, s), 10.29 (1H, s); MS (FAB) m/z: 456 (MH^+). Anal. Calcd for $C_{24}H_{26}N_3O_2SCl{\cdot}HCl$: C, 58.58; H, 5.53; N, 8.53; S, 6.51; Cl, 14.40. Found: C, 58.24; H, 5.59; N, 8.42; S, 6.41; Cl, 14.40.

5.1.40. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(2-nitrophenyl)thiourea hydrochloride (18g)

The title compound was prepared in the same manner as described for **12a** using **17g** instead of **11a** as a colorless powder. 89% yield; ^1H NMR (DMSO-d_6) δ: 2.94–3.09 (3H, m), 3.16–3.24 (3H, m), 3.94–4.01 (2H, m), 4.20–4.25 (1H, m), 5.91 (1H, br s), 6.94–6.98 (3H, m), 7.25–7.33 (4H, m), 7.39–7.46 (1H, m), 7.50 (2H, d, J = 8.4 Hz), 7.70 (2H, d, J = 4.0 Hz), 8.01 (1H, d, J = 8.0 Hz), 10.09 (1H, s), 10.60 (1H, s); MS (FAB) m/z: 467 (MH^+). Anal. Calcd for $C_{24}H_{26}N_4O_4S{\cdot}HCl{\cdot}0.2H_2O$: C, 56.90; H, 5.45; N, 11.06; S, 6.33; Cl, 7.00. Found: C, 56.63; H, 5.33; N, 11.03; S, 6.39; Cl, 7.31.

5.1.41. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(3-nitrophenyl)thiourea hydrochloride (18h)

The title compound was prepared in the same manner as described for **12a** using **17h** instead of **11a** as a colorless powder. 34% yield; ^1H

NMR (DMSO-d_6) δ: 2.96–3.08 (3H, m), 3.19–3.24 (3H, m), 3.94–4.01 (2H, m), 4.22 (1H, br s), 5.90 (1H, br s), 6.95–6.97 (3H, m), 7.25–7.33 (4H, m), 7.50–7.52 (2H, m), 7.59–7.63 (1H, m), 7.92–7.96 (2H, m), 8.70 (1H, s), 10.52 (1H, s), 10.70 (1H, s); MS (FAB) *m/z*: 467 (MH^+). Anal. Calcd for $C_{24}H_{26}N_4O_4S{\cdot}HCl{\cdot}0.4H_2O$: C, 56.50; H, 5.49; N, 10.98; S, 6.28; Cl, 6.95. Found: C, 56.43; H, 5.38; N, 10.91; S, 6.20; Cl, 7.17.

5.1.42. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(4-nitrophenyl)thiourea hydrochloride (18i)

The title compound was prepared in the same manner as described for **12a** using **17i** instead of **11a** as a colorless solid. 55% yield; mp 152–154 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.91–3.10 (3H, m), 3.16–3.28 (3H, m), 3.94–4.02 (2H, m), 4.17–4.25 (1H, m), 5.90 (1H, br s), 6.94–6.98 (3H, m), 7.24–7.34 (4H, m), 7.53 (2H, d, *J* = 8.8 Hz), 7.95 (2H, d, *J* = 9.2 Hz), 8.21 (2H, d, *J* = 9.2 Hz), 8.76 (1H, br s), 10.69 (1H, s), 10.95 (1H, s); MS (FAB) *m/z*: 467 (MH^+). Anal. Calcd for $C_{24}H_{26}N_4O_4S{\cdot}HCl{\cdot}0.2H_2O$: C, 56.90; H, 5.45; N, 11.06; S, 6.33; Cl, 7.00. Found: C, 56.95; H, 5.42; N, 10.92; S, 6.14; Cl, 7.17.

5.1.43. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(2-methoxyphenyl)thiourea hydrochloride (18j)

The title compound was prepared in the same manner as described for **12a** using **17j** instead of **11a** as a colorless powder. 67% yield; ^{1}H NMR (DMSO-d_6) δ: 2.94–3.09 (3H, m), 3.16–3.24 (3H, m), 3.83 (3H, s), 3.96–4.00 (2H, m), 4.20–4.24 (1H, m), 5.91 (1H, br s), 6.90–6.98 (5H, m), 7.05–7.07 (1H, m), 7.13–7.17 (1H, m), 7.22 (2H, d, *J* = 8.0 Hz), 7.29–7.34 (2H, m), 7.53 (2H, d, *J* = 8.0 Hz), 7.91 (1H, d, *J* = 7.6, 1.2 Hz), 9.26 (1H, s), 10.18 (1H, s); MS (FAB) *m/z*: 452 (MH^+). Anal. Calcd for $C_{25}H_{29}N_3O_3S{\cdot}HCl{\cdot}1.2H_2O$: C, 58.92; H, 6.41; N, 8.24; S, 6.29; Cl, 6.96. Found: C, 59.11; H, 6.17; N, 7.98; S, 6.09; Cl, 7.17.

5.1.44. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(3-methoxyphenyl)thiourea hydrochloride (18k)

The title compound was prepared in the same manner as described for **12a** using **17k** instead of **11a** as a colorless solid. 50% yield; mp 151–152 °C (MeOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.09 (3H, m), 3.17–3.23 (3H, m), 3.73 (3H, s), 3.94–4.01 (2H, m), 4.18–4.25 (1H, m), 5.90 (1H, d, *J* = 4.8 Hz), 6.69 (1H, dd, *J* = 8.0, 2.0 Hz), 6.94–6.98 (3H, m), 7.05–7.08 (1H, m), 7.20–7.24 (3H, m), 7.28–7.33 (3H, m), 7.50 (2H, d, *J* = 8.4 Hz), 10.17 (1H, s), 10.18 (1H, s); MS (FAB) *m/z*: 452 (MH^+). Anal. Calcd for $C_{25}H_{29}N_3O_3S{\cdot}HCl$: C, 61.53; H, 6.20; N, 8.61; S, 6.57; Cl, 7.26. Found: C, 61.16; H, 6.25; N, 8.52; S, 6.47; Cl, 7.25.

5.1.45. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(4-methoxyphenyl)thiourea hydrochloride (18l)

The title compound was prepared in the same manner as described for **12a** using **17l** instead of **11a** as a colorless solid. 69% yield; mp 208–212 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.93–3.07 (3H, m), 3.15–3.25 (3H, m), 3.92–4.01 (2H, m), 4.21 (1H, br s), 5.91 (1H, br s), 6.88–6.92 (2H, m), 6.94–6.98 (3H, m), 7.21 (2H, d, *J* = 8.4 Hz), 7.29–7.37 (4H, m), 7.49 (2H, d, *J* = 8.4 Hz), 8.76 (1H, br s), 8.87 (1H, br s), 9.84–9.89 (2H, m); MS (FAB) *m/z*: 452 (MH^+). Anal. Calcd for $C_{25}H_{29}N_3O_3S{\cdot}HCl$: C, 61.53; H, 6.20; N, 8.61; S, 6.57; Cl, 7.26. Found: C, 61.28; H, 6.20; N, 8.51; S, 6.34; Cl, 7.38.

5.1.46. (*S*)-1-(4-Fluorophenyl)-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)thiourea hydrochloride (18m)

The title compound was prepared in the same manner as described for **12a** using **17m** instead of **11a** as a colorless solid. 63% yield; mp 211–213 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.10 (3H, m), 3.14–3.28 (3H, m), 3.92–4.02 (2H, m), 4.16–4.26 (1H, m), 5.89 (1H, br s), 6.94–6.98 (3H, m), 7.14–7.23 (4H, m), 7.20–7.24 (2H, m), 7.31 (2H, t, *J* = 7.2 Hz), 7.47–7.54 (4H, m), 8.74 (2H, br s), 10.04 (2H, br s); MS (FAB) *m/z*: 440 (MH^+). Anal. Calcd for $C_{24}H_{26}N_3O_2SFCl{\cdot}1.1HCl$: C, 60.10; H, 5.69; N, 8.76; S, 6.69; F, 3.96; Cl, 8.13. Found: C, 60.03; H, 5.67; N, 8.86; S, 6.44; F, 3.58; Cl, 7.83.

5.1.47. (*S*)-1-(4-Bromophenyl)-3-(4-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}phenyl)thiourea hydrochloride (18n)

The title compound was prepared in the same manner as described for **12a** using **17n** instead of **11a** as a colorless solid. 63% yield; mp 179–182 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.10 (3H, m), 3.14–3.28 (3H, m), 3.94–4.02 (2H, m), 4.16–4.25 (1H, m), 5.90 (1H, br s), 6.94–6.98 (3H, m), 7.23 (2H, d, *J* = 8.0 Hz), 7.31 (2H, t, *J* = 8.0 Hz), 7.48–7.56 (6H, m), 8.78 (1H, br s), 8.92 (1H, br s), 10.28 (1H, s), 10.31 (1H, s); MS (FAB) *m/z*: 500, 502 (MH^+). Anal. Calcd for $C_{24}H_{26}N_3O_2SBr{\cdot}HCl{\cdot}0.1H_2O$: C, 53.51; H, 5.09; N, 7.80; S, 5.95; Br, 14.83; Cl, 6.58. Found: C, 53.57; H, 5.05; N, 7.79; S, 5.89; Br, 14.46; Cl, 6.62.

5.1.48. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(4-iodophenyl)thiourea hydrochloride (18o)

The title compound was prepared in the same manner as described for **12a** using **17o** instead of **11a** as a colorless solid. 55% yield; mp 181–184 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ: 2.89–3.06 (3H, m), 3.15–3.25 (3H, m), 3.93–4.01 (2H, m), 4.18–4.22 (1H, m), 5.90 (1H, d, *J* = 5.2 Hz), 6.94–6.98 (3H, m), 7.22 (2H, d, *J* = 8.0 Hz), 7.29–7.33 (2H, m), 7.37–7.41 (2H, m), 7.48 (2H, d, *J* = 8.0 Hz), 7.63–7.67 (2H, m), 8.75 (1H, br s), 8.85 (1H, br s), 10.20 (1H, s), 10.21 (1H, s); MS (FAB) *m/z*: 548 (MH^+). Anal. Calcd for $C_{24}H_{26}N_3O_2SI{\cdot}HCl$: C, 49.37; H, 4.66; N, 7.20; S, 5.49; I, 21.73; Cl, 6.07. Found: C, 49.46; H, 4.56; N, 7.16; S, 5.48; I, 21.83; Cl, 6.28.

5.1.49. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(4-methoxycarbonylphenyl)thiourea hydrochloride (18p)

The title compound was prepared in the same manner as described for **12a** using **17p** instead of **11a** as a colorless solid. 40% yield; mp 178–181 °C (MeOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.10 (3H, m), 3.12–3.28 (3H, m), 3.83 (3H, s), 3.94–4.02 (2H, m), 4.16–4.26 (1H, m), 5.90 (1H, d, *J* = 4.4 Hz), 6.94–6.98 (3H, m), 7.24 (2H, d, *J* = 8.0 Hz), 7.31 (2H, t, *J* = 8.0 Hz), 7.52 (2H, d, *J* = 8.0 Hz), 7.80 (2H, dd, *J* = 8.8, 2.8 Hz), 7.91 (2H, d, *J* = 8.8 Hz), 8.78 (1H, br s), 8.91 (1H, br s), 10.51 (1H, s), 10.65 (1H, s); MS (FAB) *m/z*: 480 (MH^+). Anal. Calcd for $C_{26}H_{29}N_3O_4S{\cdot}1.05HCl$: C, 60.30; H, 5.85; N, 8.11; S, 6.19; Cl, 7.19. Found: C, 60.28; H, 5.87; N, 8.12; S, 6.16; Cl, 7.18.

5.1.50. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(4-sulfamoylphenyl)thiourea hydrochloride (18q)

The title compound was prepared in the same manner as described for **12a** using **17q** instead of **11a** as a colorless solid. 65% yield; mp 198–200 °C (MeOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.10 (3H, m), 3.15–3.25 (3H, m), 3.94–4.01 (2H, m), 4.15–4.25 (1H, m), 5.90 (1H, d, *J* = 5.2 Hz), 6.94–6.98 (3H, m), 7.23–7.33 (6H, m), 7.51 (2H, d, *J* = 8.0 Hz), 7.71–7.75 (4H, m), 8.75 (1H, br s), 8.83 (1H, br s), 10.37 (1H, s), 10.47 (1H, s); MS (FAB) *m/z*: 501 (MH^+). Anal. Calcd for $C_{24}H_{28}N_4O_4S_2{\cdot}HCl$: C, 53.67; H, 5.44; N, 10.43; S, 11.94; Cl, 6.60. Found: C, 53.46; H, 5.44; N, 10.42; S, 11.96; Cl, 6.79.

5.1.51. (*S*)-1-(4-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-phenyl)-3-(4-methylphenyl)thiourea hydrochloride (18r)

The title compound was prepared in the same manner as described for **12a** using **17r** instead of **11a** as a colorless powder.

60% yield; ^{1}H NMR (DMSO-d_6) δ: 2.28 (3H, s), 2.90–3.10 (3H, m), 3.17–3.23 (3H, m), 3.94–4.01 (2H, m), 4.17–4.23 (1H, m), 5.90 (1H, d, J = 5.2 Hz), 6.95–6.98 (3H, m), 7.13 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.37 (2H, d, J = 8.8 Hz), 7.49 (2H, d, J = 8.8 Hz), 9.93 (1H, s), 9.94 (1H, s); MS (FAB) m/z: 436 (MH^+). Anal. Calcd for $C_{25}H_{29}N_3O_2S{\cdot}HCl{\cdot}0.3H_2O$: C, 62.89; H, 6.46; N, 8.80; S, 6.72; Cl, 7.43. Found: C, 62.98; H, 6.38; N, 9.02; S, 6.62; Cl, 7.54.

5.2. Pharmacology

5.2.1. Agonistic activity on human β3-, β2-, and β1-ARs

Human β3-, β2-, and β1-stimulating activities were investigated using a CHO cell system (cells in which human β3-, β2-, and β1-ARs were compulsorily expressed were used). The agonistic activity of the compound (10^{-10}–10^{-4} M) was investigated by incubating 10^5 cells/well of each of the cells on a 24-well plate and checking the activity after 2 days' incubation (subconfluent state) using the production of cyclic AMP (cAMP) as an index. The amount of cAMP produced in each cell (pmol/ml) was measured using a radioimmunoassay method with ^{125}I-cAMP. The intensity of action among compounds was compared by calculating the EC_{50} and intrinsic activity (IA where the maximum reaction of 10^{-4} M isoproterenol was defined as 1.00) for each from the resulting dose–reaction curve.

5.2.2. Hypoglycemic activity in kk mice

Male kk mice (blood sugar level: not lower than 200 mg/dl) were subjected to measurement of blood sugar levels under fed conditions, and then randomly classified into groups. The test compound was administered orally once daily for 4 days, and the blood sugar level 15–18 h after final administration was compared with that before administration (n = 6). Blood samples were collected from the tail vein using a heparin-treated glass capillary tube after which the blood was deproteinized, and the amount of glucose in the supernatant (mg/dl) was determined calorimetrically by means of the glucose oxidase method.

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