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Original article

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

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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, a novel series of acetanilide-based analogues were prepared and their biological activities were evaluated at the human β3-, β2-, and β1-ARs. Among these compounds, 2-pyridylacetanilide (**2f**), pyrimidin-2-ylacetanilide (**2u**), and pyrazin-2-ylacetanilide (**2v**) derivatives exhibited potent agonistic activity at the β3-AR with functional selectivity over the β1- and β2-ARs. In particular, compound **2u** was found to be the most potent and selective β3-AR agonist with an EC_{50} value of 0.11 μM and no agonistic activity for either the β1- or β2-AR. In addition, **2f**, **2u**, and **2v** showed significant hypoglycemic activity in a rodent diabetic model.

1. Introduction

In 1984, β3-adrenergic receptors (ARs) were proposed as the 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 the plasma glucose and insulin levels, thereby ameliorating noninsulin-dependent (type II) diabetes. Subtype selectivity for β3-AR agonists specifically must be kept 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 [6,7]. Early potent and selective rat β3-AR agonists, such as BRL-37344 [8] and CL-316243 [9], were reported to be effective anti-obesity and anti-diabetic agents in rodents (Fig. 1) [10]. However, human clinical trials with these drugs for the treatment of metabolic disorders have been disappointing due to a lack of selectivity and/or potency or poor pharmacokinetics [11].

As our lead compound in the search for novel potent and selective human β3-AR agonists, we chose the benzenesulfonanilide derivative (**1**) reported by Merck scientists to be one of the first selective human β3-AR agonists [12]. Based on the structure of compound **1**, we hypothesized that the position of the two benzene rings in the benzenesulfonanilide moiety of **1** would play an important role in its β3-AR agonistic activity and/or its selectivity over β1- and β2-ARs. We also assumed that the relative position of the two benzene rings on both benzenesulfonanilide and phenylacetanilide would be similar to that shown in Fig. 2. Thus, we planned to design and synthesize the phenylacetanilide derivative (**2a**) by converting the sulfonamide moiety of **1** into an acetamide moiety. Since compound **2a** showed good β3-AR agonistic activity, further attempts at modification were made (Fig. 3). In this paper, we describe the synthesis and structure–activity relationships (SARs) of these newly designed acetanilide-based β3-AR agonists.

2. Chemistry

Acetanilides **2a**–**h** were prepared from aniline intermediate **5**, as illustrated in Scheme 1. Compound **5** was synthesized from (*S*)-2-[(4-benzyloxyphenoxy)methyl]oxirane (**3**) [13] and *N*-benzyl-*N*-[2-(4-nitrophenyl)ethyl]amine [14], followed by reduction of the nitro group with iron. Compound **5** was coupled with the appropriate acetyl chlorides or acetic acids, followed by deprotection of the benzyl group to afford the desired products **2a**–**h**. Another route starting from aniline intermediate **11** is illustrated in Scheme 2. (*S*)-2-{[4-(Methoxymethoxy)phenoxy]methyl}-oxirane (**8a**) was prepared from 4-(methoxymethoxy)phenol (**7a**) [15] and (*R*)-epichlorohydrin. Compound **8a** was treated with a commercially

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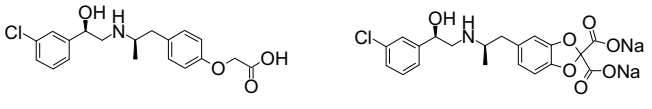


Fig. 1. Chemical structure of early β3-AR agonists.

available 2-(4-nitrophenyl)ethylamine hydrochloride, followed by protection of the amine with a *tert*-butoxycarbonyl (Boc) group to provide nitro compound **10**. Hydrogenation of **10** yielded aniline intermediate **11**. The coupling of **11** with the appropriate acetyl chlorides or acetic acids, followed by deprotection of the methoxymethyl (MOM) and Boc groups afforded the desired products **2i–r**. An alternate route was developed for the synthesis of acetanilides **2s–v**, as illustrated in Scheme 3, because the corresponding acetic acids were unstable. 4-Aminobenzylcyanide (**13**) was treated with the appropriate esters in refluxing xylene to provide anilides **14a–d**. Anilides **14a–d** was then hydrogenated in the presence of Raney-nickel, followed by coupling with (*S*)-2-{[4-(2-methoxyethoxymethoxy)phenoxy]methyl}-oxirane (**8b**) to afford compounds **15a–d**. Deprotection of the 2-methoxyethoxymethyl (MEM) group in **15a–d** yielded the desired products **2s–v**.

3. Results and discussion

All compounds listed in Tables 1 and 2 were evaluated for their agonistic activities in stimulating an increase in cyclic AMP (cAMP) levels in Chinese hamster ovary (CHO) cells expressing the cloned human β3-, β2-, and β1-ARs. The results for reference compounds, isoproterenol (**ISO**; non-selective β-AR agonist) and compound **1**, are also shown for comparison in Table 1.

The phenylacetanilide derivative (**2a**) of our lead compound was found to be a modestly potent β3-AR agonist ($EC_{50} = 1.7$ μM, IA = 0.91) with a lower potency for the β2-AR ($EC_{50} = >100$ μM); however compound **2a** also showed modest β1-AR agonistic activity ($EC_{50} = 0.76$ μM, IA = 0.50). In order to improve β3-AR agonistic activity and functional selectivity over β1-AR, modification of the phenylacetyl moiety in **2a** was examined.

Initially, introduction of substituent at the α-position of the phenylacetyl moiety in **2a** was investigated as shown in Table 1. Introduction of the phenyl group at the α-position of the phenylacetyl moiety (**2b**) resulted in a considerable increase in agonistic activity (14-fold) at the β3-AR ($EC_{50} = 0.12$ μM, IA = 1.05) and a 4-fold increase in agonistic activity at the β1-AR ($EC_{50} = 0.18$ μM, IA = 0.65) relative to that of **2a**. This indicated that **2b** was a non-selective β3- and β1-AR agonist. Next, the introduction of a hydrogen bond donor or acceptor at the α-position of the phenylacetyl moiety in **2a** was examined, because the sulfonanilide moiety of **1** possessed two oxygen atoms. Both the hydroxyl (**2i**) and amino (**2j**) derivatives exhibited a slight increase in agonistic activity (1.8-fold) at the β3-AR without diminishing β1-AR agonistic activity relative to **2a**. The introduction of a hydroxyl group to **2a** led to full agonistic activity (IA = 1.12) at the β1-AR, with only partial β1-AR agonism. These results indicated that the introduction of a substituent at the α-position of the phenylacetyl moiety in **2a** was tolerated while maintaining β3-AR agonistic activity, but this change may not improve functional selectivity over β1-AR.

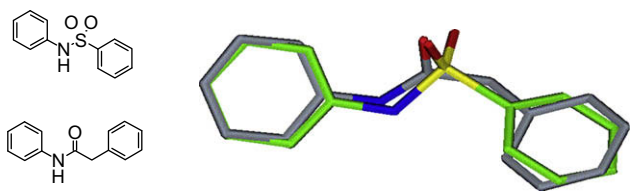


Fig. 2. Flexible alignment of phenylacetanilide and benzenesulfonanilide.

We then examined the effects of the substituents on the phenyl ring of the phenylacetyl moiety in **2a**. The introduction of the chloro group as an electron-withdrawing group on the phenyl ring of the phenylacetyl moiety (**2k–m**) resulted in slightly increased agonistic activity at the β3-AR relative to **2a**, and the rank of order of potency seemed to be *ortho*-chloro ($EC_{50} = 0.74$ μM) > *meta*-chloro ($EC_{50} = 0.89$ μM) > *para*-chloro ($EC_{50} = 1.2$ μM); however β1-AR agonistic activity did not decrease for any of these. The methoxy group as an electron-donating group was also introduced on the phenyl ring of the phenylacetyl moiety (**2n–p**), which yielded results similar to those of the chlorophenyl derivatives, the introduction of an *ortho*-methoxy group (**2n**) led to a 5-fold increase in agonistic activity at the β3-AR ($EC_{50} = 0.36$ μM, IA = 0.88) relative to **2a**. These results revealed that the introduction of a substituent on the phenyl ring of the phenylacetyl moiety in **2a** allowed the potency of β3-AR to be maintained, but may not be efficacious for improving functional selectivity over β1-AR.

Next, the modification of the phenyl ring in the phenylacetyl moiety of **2a** into other aromatic rings was investigated as shown in Table 2. Replacement of the phenyl ring with 1-naphthyl (**2c**) and indol-3-yl (**2e**) ring resulted in slightly increased agonistic activity (3-fold) at the β3-AR relative to **2a** without decreasing β1-AR agonistic activity. The 2-naphthylacetanilide derivative (**2d**) showed an improvement in potency of more than 5-fold for both β3- and β1-AR relative to **2a**. The thenylacetanilide derivatives (**2q**,**r**) showed results similar to those of **2e**. These results suggested that altering the aromatic rings may not be sufficient to decrease agonistic activity at the β1-AR.

Replacement of the phenyl ring with a pyridine ring yielded interesting results. The agonistic activity of the 2-pyridylacetanilide derivative (**2f**) increased 6-fold at the β3-AR ($EC_{50} = 0.29$ μM, IA = 0.74), but decreased 3.5-fold at the β1-AR. In addition its intrinsic activity decreased ($EC_{50} = 2.7$ μM, IA = 0.14) relative to **2a**, which indicated that **2f** was a potent and functionally selective β3-AR agonist. In contrast, the intrinsic activity of the 3-pyridylacetanilide (**2g**) and 4-pyridylacetanilide (**2h**) derivatives decreased at the β3-AR (IA = 0.48 and 0.49, respectively) relative to **2a** without decreasing agonistic activity at the β1-AR. These results suggested that changing the position of the nitrogen atom on the 2-pyridyl moiety in **2f** would result in both potency at the β3-AR and functional selectivity over β1-AR; this promoted us to synthesize benzene-fused 2-pyridyl analogues. The results obtained for quinolin-2-ylacetanilide derivative (**2s**) were similar to those of **2f**, with EC_{50} values of 0.65 μM at the β3-AR and 1.7 μM at the β1-AR, respectively; however, **2s** was less potent and less functionally selective than **2f**. The agonistic activity of the isoquinolin-3-ylacetanilide derivative (**2t**) at the β3-AR ($EC_{50} = 0.14$ μM, IA = 0.77) was much greater than that of **2a**, but it did not decrease β1-AR agonistic activity ($EC_{50} = 0.35$ μM, IA = 0.36).

Lastly, we replaced the phenyl ring with a heteroaromatic ring containing two nitrogens. The pyrimidin-2-ylacetanilide derivative (**2u**) increased agonistic activity at the β3-AR 15-fold ($EC_{50} = 0.11$ μM, IA = 0.57), relative to **2a**, and dramatically decreased agonistic activity at the β1-AR ($EC_{50} = >100$ μM), which suggested that the two nitrogen atoms at 1- and 3-positions on the pyrimidin-2-yl moiety may play a very important role in the improvement of β3-AR agonistic activity and the substantial loss of β1-AR agonistic activity. Furthermore, the pyrazin-2-ylacetanilide derivative (**2v**) exhibited a 20-fold increase in agonistic activity at the β3-AR ($EC_{50} = 0.083$ μM, IA = 0.64) relative to **2a**, and was the most potent β3-AR agonist in this study. Compound **2v** induced

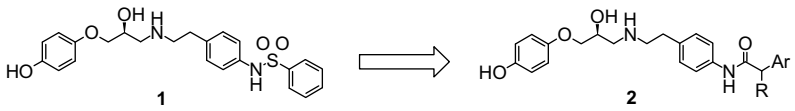


Fig. 3. Design of acetanilides based on compound **1**.

a 4-fold decrease in agonistic activity at the β1-AR ($EC_{50} = 3.1$ μM, IA = 0.18) relative to **2a** and its potency for β3-AR and functional selectivity over β1-AR was comparable to that of compound **1**.

Given the results of the *in vitro* study, compounds **2f**, **2u**, and **2v** were selected for *in vivo* evaluation in a rodent model of type II diabetes (Table 3). The compounds were administered orally for 4 days in diabetic kk mice and the effects on plasma glucose were measured. All compounds exhibited a significant reduction in plasma glucose levels at the dose of 30 mg/kg. In particular, **2f** showed the most potent hypoglycemic activity (32% decrease).

4. Conclusion

We have identified a new series of acetanilide-based β3-AR agonists and described their synthesis and SARs. Among these compounds, the 2-pyridylacetanilide (**2f**), pyrimidin-2-ylacetanilide (**2u**), and pyrazin-2-ylacetanilide (**2v**) derivatives showed potent agonistic activity at the β3-AR ($EC_{50} = 0.29$, 0.11, and 0.083 μM, respectively), with functional selectivity over β1- and β2-ARs. With agonistic activity almost completely abolished at both the β1- and β2-ARs, the pyrimidin-2-ylacetanilide derivative (**2u**) was found to be the most potent and selective β3-AR agonist in this study. In addition, these compounds exhibited significant hypoglycemic activity in diabetic kk mice.

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*)-1-{N-*Benzyl*-N-*[2-(4-nitrophenyl)ethyl]amino}-3-(4-benzyloxyphenoxy)-2-propanol (**4**)

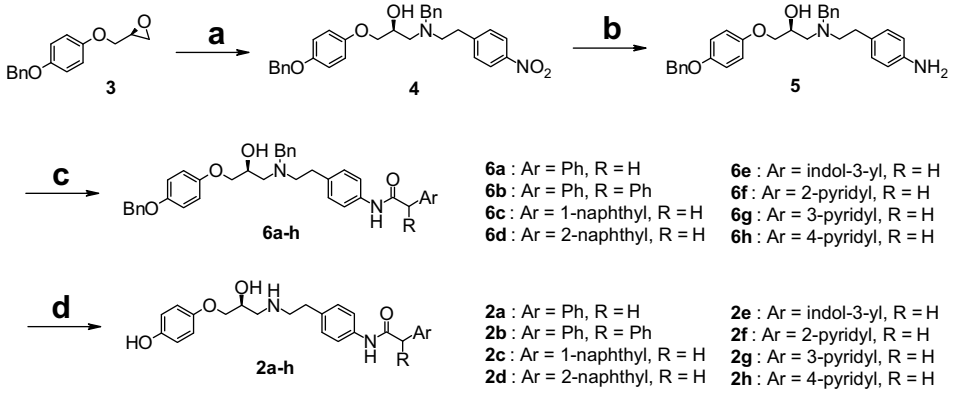
A mixture of (*S*)-2-[(4-benzyloxyphenoxy)methyl]oxirane (**3**) (3.48 g) and *N*-benzyl-*N*-[2-(4-nitrophenyl)ethyl]amine (3.22 g) in 2-propanol (70 mL) was refluxed for 4 h. After cooling to room temperature, the resultant mixture was concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with *n*-hexane/EtOAc (3:1) as the eluent to yield **4** (5.91 g) as a colorless oil. 84% yield; ^{1}H NMR ($CDCl_3$) δ: 2.69–2.93 (6H, m), 3.05 (3H, br s), 3.60 (1H, d, $J = 13.4$ Hz), 3.82 (1H, d, $J = 13.4$ Hz), 3.85–3.88 (2H, m), 3.97–4.01 (1H, m), 5.02 (2H, s), 6.79 (2H, d, $J = 9.2$ Hz), 6.89 (2H, d, $J = 9.2$ Hz), 7.20–7.43 (12H, m), 8.08 (2H, d, $J = 8.6$ Hz); MS (FAB) *m*/*z*: 513 (MH^+).

5.1.2. (*S*)-1-{N-*[2-(4-Aminophenyl)ethyl]*-N-*benzylamino}*-3-(4-benzyloxyphenoxy)-2-propanol (**5**)

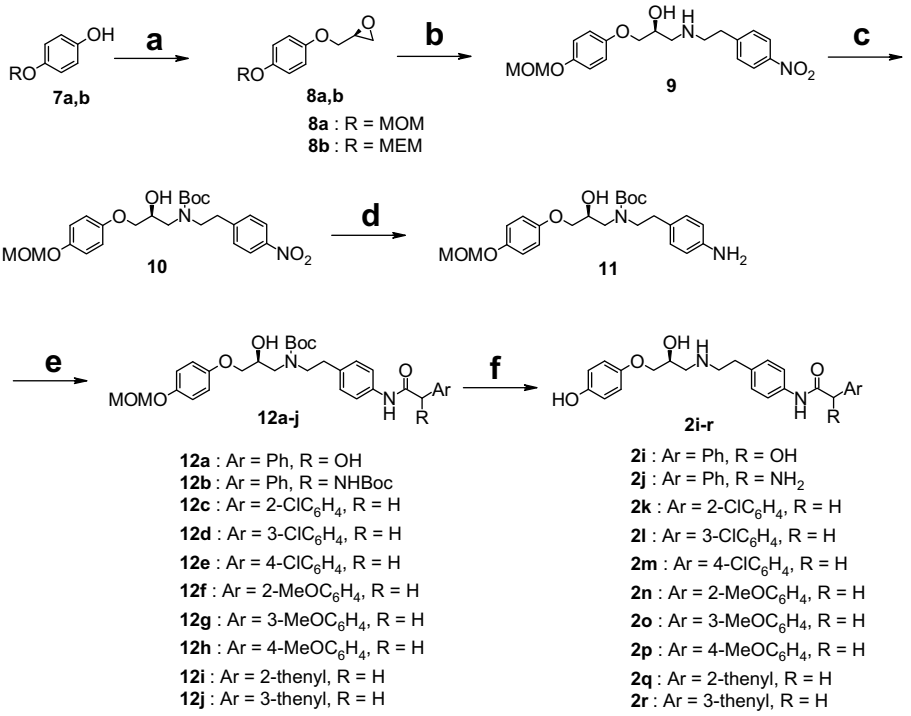
To a solution of **4** (4.07 g) in methanol (60 mL) were added 2 M HCl aqueous solution (8 mL) and iron powder (0.45 g), and the mixture was refluxed for 1 h. After cooling to room temperature, the excess iron was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 M NaOH aqueous solution, and the organic layer was washed with water and brine, and then dried and concentrated *in vacuo* to yield **5** (3.62 g) as a colorless oil. 94% yield; ^{1}H NMR ($CDCl_3$) δ: 2.63–2.82 (6H, m), 3.25 (1H, br s), 3.53 (2H, br s), 3.59 (1H, d, $J = 13.4$ Hz), 3.83–3.87 (3H, m), 3.94–3.97 (1H, m), 5.01 (2H, s), 6.59 (2H, d, $J = 7.3$ Hz), 6.80 (2H, d, $J = 7.9$ Hz), 6.87–6.94 (4H, m), 7.24–7.42 (10H, m); MS (FAB) *m*/*z*: 483 (MH^+).

5.1.3. (*S*)-4′-(2-{N-*Benzyl*-N-*[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-phenylacetanilide (**6a**)

To a solution of **5** (0.38 g) and triethylamine (0.86 g) in chloroform (7 mL) was added phenylacetyl chloride (0.13 g) at 0 °C, and the mixture was stirred at room temperature for 1 h. The resultant mixture was partitioned between chloroform and water. The organic layer was washed with water and brine, and then dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with chloroform as the eluent to yield **4** (0.43 g) as a colorless powder. 91% yield; ^{1}H NMR ($CDCl_3$) δ: 2.62–2.82 (6H, m), 3.16 (1H, br s), 3.58 (1H, d, $J = 13.4$ Hz), 3.72 (2H, s),



Scheme 1. Reagents and conditions: (a) *N*-benzyl-*N*-[2-(4-nitrophenyl)ethyl]amine, ^{i}PrOH, reflux; (b) Fe, 2 M HCl aq., MeOH; (c) ArCH(R)COCl, Et_3N, $CHCl_3$; or $ArCH_2CO_2H$, EDC·HCl, HOBt, DMF; (d) H_2, Pd/C, EtOH, and then 4 M HCl–EtOAc, MeOH.



Scheme 2. Reagents and conditions: (a) (*R*)-epichlorohydrin, KOH aq.; (b) 2-(4-nitrophenyl)ethylamine hydrochloride, Et_3N, ^iPrOH, reflux; (c) $(Boc)_2O$, THF; (d) H_2, Pd/C, EtOH; (e) $ArCH(R)CO_2H$, EDC·HCl, HOBt, DMF; or $ArCH_2COCl$, Et_3N, $CHCl_3$; (f) 4 M HCl–EtOAc, MeOH.

3.78–3.85 (3H, m), 3.93–3.96 (1H, m), 5.01 (2H, s), 6.78 (2H, d, $J = 9.1$ Hz), 6.86–6.91 (2H, m), 6.99–7.03 (2H, m), 7.21–7.42 (17H, m); MS (FAB) *m*/*z*: 601 (MH^+).

5.1.4. (*S*)-4′-(2-{N-*Benzyl*-N-*[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2,2-diphenylacetanilide (*6b*)

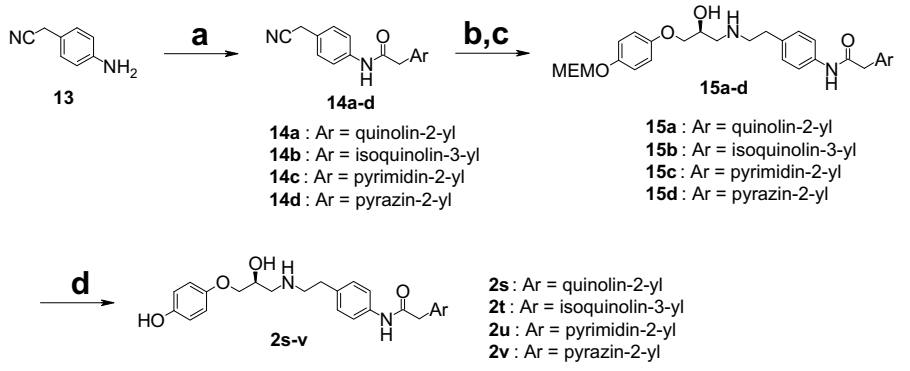
The title compound was prepared in the same manner as described for **6a** using diphenylacetyl chloride instead of phenylacetyl chloride as a colorless powder. 86% yield; ^1H NMR ($CDCl_3$) δ: 2.63–2.83 (6H, m), 3.17 (1H, br s), 3.58 (1H, d, $J = 13.4$ Hz), 3.80–3.86 (3H, m), 3.94–3.97 (1H, m), 5.00 (2H, s), 5.06 (1H, s), 6.78 (2H, d, $J = 9.2$ Hz), 6.88 (2H, d, $J = 9.2$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 7.21–7.42 (22H, m); MS (FAB) *m*/*z*: 677 (MH^+).

5.1.5. (*S*)-4′-(2-{N-*Benzyl*-N-*[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-(1-naphthyl)acetanilide (*6c*)

The title compound was prepared in the same manner as described for **6a** using 1-naphthylacetyl chloride instead of phenylacetyl chloride as a colorless powder. 51% yield; ^1H NMR ($CDCl_3$) δ: 2.62–2.78 (6H, m), 3.55 (1H, d, $J = 13.5$ Hz), 3.78–3.84 (2H, m), 3.91–3.94 (1H, m), 4.17 (2H, s), 5.00 (2H, s), 6.77 (2H, d, $J = 9.1$ Hz), 6.86–6.90 (2H, m), 6.96 (2H, d, $J = 8.6$ Hz), 7.15–7.56 (17H, m), 7.86–7.91 (2H, m), 8.02 (1H, d, $J = 8.0$ Hz); MS (FAB) *m*/*z*: 651 (MH^+).

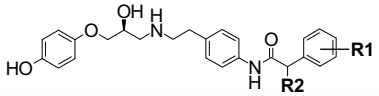
5.1.6. (*S*)-4′-(2-{N-*Benzyl*-N-*[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-(2-naphthyl)acetanilide (*6d*)

To a solution of **5** (0.8 g) and 2-naphthylacetic acid (0.31 g) in *N*,*N*-dimethylformamide (10 mL) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.32 g) and 1-hydroxybenzotriazole (0.22 g), and the mixture was stirred at room temperature for 13 h. The resulting mixture was concentrated *in vacuo*, and partitioned between ethyl acetate and $NaHCO_3$ aqueous solution. The organic layer was dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with *n*-hexane/EtOAc (3:2) as the eluent to yield **6d** (0.61 g) as a colorless powder. 57% yield; ^1H NMR ($CDCl_3$) δ: 2.61–2.83 (6H, m), 3.56 (1H, br s), 3.57 (1H, d, $J = 13.4$ Hz), 3.78–3.95 (6H, m), 5.00 (2H, s), 6.77 (2H, d, $J = 9.1$ Hz), 6.87 (2H, d, $J = 9.1$ Hz), 7.00



Scheme 3. Reagents and conditions: (a) $ArCH_2CO_2Et$, xylene, reflux; (b) H_2, Raney-Ni, conc. NH_3 aq., EtOH–THF; (c) **8b**, 2-propanol, reflux; (d) 4 M HCl–EtOAc, MeOH.

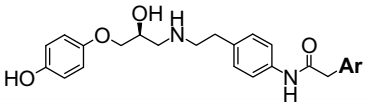
Table 1
β-AR agonistic activity of substituted phenylacetanilide derivatives.

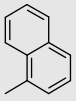
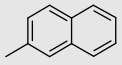
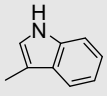


Compound	R1	R2	EC_{50}, μM[a] (IA[b])		
			β3-AR	β2-AR	β1-AR
2a	H	H	1.7 (0.91)	>100 (0.03)	0.76 (0.50)
2b	H	Ph	0.12 (1.05)	>100 (0.02)	0.18 (0.65)
2i	H	OH	0.96 (0.82)	>100 (0)	0.59 (1.12)
2j	H	NH_2	0.96 (0.68)	>100 (0)	0.66 (0.50)
2k	2-Cl	H	0.74 (0.90)	>100 (0.01)	0.72 (0.51)
2l	3-Cl	H	0.89 (0.96)	>100 (0.03)	0.083 (0.55)
2m	4-Cl	H	1.2 (1.10)	>100 (0.02)	0.19 (0.47)
2n	2-MeO	H	0.36 (0.88)	>100 (0)	0.96 (0.69)
2o	3-MeO	H	0.56 (0.85)	>100 (0.01)	0.71 (0.84)
2p	4-MeO	H	1.7 (0.86)	>100 (0.01)	0.28 (0.49)
ISO			0.10 (1.00)	0.003 (1.00)	0.012 (1.00)
1			0.078 (0.73)	>100 (0.02)	1.6 (0.21)

[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.

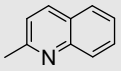
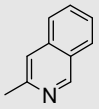
Table 2
β-AR agonistic activity of arylacetanilide derivatives.



Compound	Ar	EC_{50}, μM[a] (IA[b])		
		β3-AR	β2-AR	β1-AR
2a		1.7 (0.91)	>100 (0.03)	0.76 (0.50)
2c		0.47 (0.96)	>100 (0)	0.60 (0.47)
2d		0.24 (0.90)	>100 (0.01)	0.15 (0.40)
2e		0.49 (1.01)	>100 (0)	0.55 (0.28)
2q		0.50 (0.79)	>100 (0)	0.55 (0.28)
2r		0.55 (0.80)	>100 (0.04)	0.49 (0.37)
2f		0.29 (0.74)	>100 (0)	2.7 (0.14)

(*continued on next page*)

Table 2 (*continued*)

Compound	Ar	EC_{50}, μM[a] (IA[b])		
		β3-AR	β2-AR	β1-AR
2g		1.5 (0.48)	>100 (0)	0.91 (0.35)
2h		0.52 (0.49)	>100 (0.03)	0.26 (0.38)
2s		0.65 (0.71)	>100 (0.01)	1.7 (0.29)
2t		0.14 (0.77)	>100 (0.02)	0.35 (0.36)
2u		0.11 (0.57)	>100 (0)	>100 (0.07)
2v		0.083 (0.64)	>100 (0.01)	3.1 (0.18)

[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.

(2H, d, $J = 7.9$ Hz), 7.08 (1H, s), 7.21–7.52 (14H, m), 7.52–7.87 (3H, m); MS (FAB) *m*/*z*: 651 (MH^+).

*5.1.7. (S)-4′-(2-{N-Benzyl-N-[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-(3-indolyl)acetanilide (**6e**)*

The title compound was prepared in the same manner as described for **6d** using 3-indolylacetic acid instead of 2-naphthylacetic acid as a colorless powder. 52% yield; ^{1}H NMR ($CDCl_3$) δ: 2.61–2.78 (6H, m), 3.56–3.63 (2H, m), 3.81–3.89 (4H, m), 5.01 (2H, s), 5.20–5.22 (1H, m), 6.67 (2H, d, $J = 8.5$ Hz), 6.83–6.86 (2H, m), 6.92 (2H, d, $J = 8.5$ Hz), 7.03–7.07 (2H, m), 7.14–7.44 (13H, m), 7.55–7.62 (2H, m), 8.09 (1H, s), 8.21 (1H, s); MS (FAB) *m*/*z*: 640 (MH^+).

*5.1.8. (S)-4′-(2-{N-Benzyl-N-[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-(2-pyridyl)acetanilide (**6f**)*

The title compound was prepared in the same manner as described for **6d** using 2-pyridylacetic acid instead of 2-naphthylacetic acid as a colorless powder. 52% yield; ^{1}H NMR ($CDCl_3$) δ: 2.62–2.87 (6H, m), 3.22 (1H, br s), 3.59 (1H, d, $J = 13.2$ Hz), 3.80–3.88 (5H, m), 3.92–4.00 (1H, m), 5.00 (2H, s), 6.75–6.82 (2H, m), 6.85–6.90 (2H, m), 7.02–7.07 (2H, m), 7.20–7.47 (8H, m), 7.65–7.72 (1H, m), 8.58–8.65 (1H, m), 9.71 (1H, br s); MS (FAB) *m*/*z*: 602 (MH^+).

Table 3
Oral hypoglycemic activity in kk mice.

Compound	Percent reduction in plasma glucose[a]
2f	32**[,b]
2u	20*
2v	13**

[a] The compounds were administered orally to male kk mice for 4 days at the dose of 30 mg/kg.
[b] Statistically significant at $^*p < 0.05$, $^{**}p < 0.01$.

*5.1.9. (S)-4′-(2-{N-Benzyl-N-[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-(3-pyridyl)acetanilide (**6g**)*

The title compound was prepared in the same manner as described for **6d** using 3-pyridylacetic acid instead of 2-naphthylacetic acid as a colorless powder. 61% yield; ^{1}H NMR ($CDCl_3$) δ: 2.60–2.85 (6H, m), 3.18 (1H, br s), 3.59 (1H, d, J = 13.5 Hz), 3.68 (2H, s), 3.80–3.85 (3H, m), 3.93–3.96 (1H, m), 5.01 (2H, s), 6.78 (2H, d, J = 9.0 Hz), 6.88 (2H, d, J = 9.5 Hz), 7.05 (2H, d, J = 9.0 Hz), 7.19–7.42 (13H, m), 7.72 (1H, d, J = 8.0 Hz), 8.55–8.57 (2H, m); MS (FAB) m/z: 602 (MH^+).

*5.1.10. (S)-4′-(2-{N-Benzyl-N-[3-(4-benzyloxyphenoxy)-2-hydroxypropyl]amino}ethyl)-2-(4-pyridyl)acetanilide (**6h**)*

The title compound was prepared in the same manner as described for **6d** using 4-pyridylacetic acid instead of 2-naphthylacetic acid as a colorless powder. 69% yield; ^{1}H NMR ($CDCl_3$) δ: 2.60–2.89 (6H, m), 3.17 (1H, br s), 3.59 (1H, d, J = 13.6 Hz), 3.66 (2H, s), 3.77–3.87 (3H, m), 3.90–3.98 (1H, m), 5.00 (2H, s), 6.74–6.79 (2H, m), 6.85–6.89 (2H, m), 7.03–7.08 (2H, m), 7.22–7.43 (14H, m), 8.58–8.60 (2H, m); MS (FAB) m/z: 602 (MH^+).

*5.1.11. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-phenylacetanilide hydrochloride (**2a**)*

To a mixture of **6a** (0.41 g) in ethanol (50 mL) was added palladium on carbon (10% w/w, 0.1 g), and the mixture was stirred under hydrogen atmosphere for 15 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in methanol (10 mL), and 4 M HCl–EtOAc solution (0.2 mL) was added, and then the mixture was concentrated *in vacuo*. The crude solid was purified by recrystallization from ethanol to yield **2a** (0.1 g) as a colorless solid. 32% yield; mp 243–245 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.88–3.03 (3H, m), 3.10–3.20 (3H, m), 3.63 (2H, s), 3.80–3.90 (2H, m), 4.05–4.20 (1H, m), 5.82 (1H, d, J = 4.9 Hz), 6.68 (2H, d, J = 8.4 Hz), 6.77 (2H, d, J = 8.8 Hz), 7.18 (2H, d, J = 8.3 Hz), 7.22–7.26 (1H, m), 7.29–7.33 (4H, m), 7.56 (1H, d, J = 8.3 Hz), 8.76 (2H, br s), 8.97 (1H, s), 10.22 (1H, s); MS (FAB) m/z: 421 (MH^+); Anal. Calcd for $C_{25}H_{28}N_2O_4\cdot HCl$: C, 65.71; H, 6.40; N, 6.13; Cl, 7.76. Found: C, 65.68; H, 6.42; N, 6.06; Cl, 7.83.

*5.1.12. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2,2-diphenylacetanilide hydrochloride (**2b**)*

The title compound was prepared in the same manner as described for **2a** using **6b** instead of **6a** as a colorless powder. 88% yield; ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.05–3.20 (3H, m), 3.80–3.90 (2H, m), 4.05–4.20 (1H, m), 5.20 (1H, s), 5.82 (1H, d, J = 4.9 Hz), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 9.3 Hz), 7.19 (2H, d, J = 8.3 Hz), 7.20–7.50 (10H, m), 7.59 (1H, d, J = 8.3 Hz), 8.77 (2H, br s), 8.97 (1H, s), 10.50 (1H, s); MS (FAB) m/z: 497 (MH^+); Anal. Calcd for $C_{31}H_{32}N_2O_4\cdot HCl$: C, 69.85; H, 6.24; N, 5.26; Cl, 6.65. Found: C, 69.66; H, 6.27; N, 5.02; Cl, 6.48.

*5.1.13. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(1-naphthyl)acetanilide hydrochloride (**2c**)*

The title compound was prepared in the same manner as described for **2a** using **6c** instead of **6a** as a colorless solid. 43% yield; mp 226–228 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.83–3.87 (2H, m), 4.10–4.20 (3H, m), 5.80 (1H, br s), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 7.18 (2H, d, J = 8.8 Hz), 7.47–7.59 (6H, m), 7.85 (1H, d, J = 7.3 Hz), 7.94 (1H, d, J = 7.3 Hz), 8.13 (1H, d, J = 7.8 Hz), 8.72 (2H, br s), 8.97 (1H, s), 10.39 (1H, s); MS (FAB) m/z: 471 (MH^+); Anal. Calcd for $C_{29}H_{30}N_2O_4\cdot HCl$: C, 68.70; H, 6.16; N, 5.53; Cl, 6.99. Found: C, 68.41; H, 6.09; N, 5.48; Cl, 7.09.

*5.1.14. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(2-naphthyl)acetanilide hydrochloride (**2d**)*

The title compound was prepared in the same manner as described for **2a** using **6d** instead of **6a** as a colorless solid. 35% yield; mp 258–260 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.93–3.03 (3H, m), 3.12–3.19 (3H, m), 3.81–3.90 (4H, m), 4.17 (1H, br s), 5.84 (1H, d, J = 4.9 Hz), 6.69 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 9.3 Hz), 7.18 (2H, d, J = 8.3 Hz), 7.46–7.53 (3H, m), 7.60 (2H, d, J = 8.8 Hz), 7.84–7.90 (4H, m), 9.00 (3H, br s), 10.39 (1H, s); MS (FAB) m/z: 471 (MH^+); Anal. Calcd for $C_{29}H_{30}N_2O_4\cdot HCl$: C, 68.70; H, 6.16; N, 5.53; Cl, 6.99. Found: C, 68.76; H, 6.24; N, 5.52; Cl, 6.92.

*5.1.15. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(indol-3-yl)acetanilide hydrochloride (**2e**)*

The title compound was prepared in the same manner as described for **2a** using **6e** instead of **6a** as a colorless solid. 66% yield; mp 204–206 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.91–3.05 (3H, m), 3.10–3.20 (3H, m), 3.73 (2H, s), 3.81–3.90 (2H, m), 4.16 (1H, br s), 5.83 (1H, d, J = 4.9 Hz), 6.69 (2H, d, J = 9.3 Hz), 6.77 (2H, d, J = 9.3 Hz), 6.97 (1H, t, J = 7.3 Hz), 7.06 (1H, t, J = 7.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 7.25 (1H, d, J = 2.0 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.57–7.62 (3H, m), 8.78–8.99 (3H, m), 10.18 (1H, s), 10.93 (1H, s); MS (FAB) m/z: 460 (MH^+); Anal. Calcd for $C_{27}H_{29}N_3O_4\cdot HCl$: C, 65.38; H, 6.10; N, 8.47; Cl, 7.15. Found: C, 65.20; H, 6.05; N, 8.43; Cl, 6.93.

*5.1.16. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(2-pyridyl)acetanilide hydrochloride (**2f**)*

The title compound was prepared in the same manner as described for **2a** using **6f** instead of **6a** as a colorless solid. 37% yield; mp 206–207 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.83–3.87 (4H, m), 4.12 (1H, br s), 5.80 (1H, br s), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 7.18 (1H, d, J = 8.3 Hz), 7.20–7.30 (1H, m), 7.39 (1H, d, J = 7.8 Hz), 7.57 (2H, d, J = 8.3 Hz), 7.70–7.80 (1H, m), 8.50 (1H, d, J = 4.9 Hz), 8.65 (1H, br s), 8.97 (1H, s), 10.27 (1H, s); MS (FAB) m/z: 422 (MH^+); Anal. Calcd for $C_{24}H_{27}N_3O_4\cdot HCl\cdot 0.2H_2O$: C, 62.45; H, 6.20; N, 9.10; Cl, 7.68. Found: C, 62.57; H, 6.18; N, 9.12; Cl, 7.54.

*5.1.17. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(3-pyridyl)acetanilide dihydrochloride (**2g**)*

The title compound was prepared in the same manner as described for **2a** using **6g** instead of **6a** as a colorless powder. 63% yield; ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.25 (3H, m), 3.80–3.95 (2H, m), 3.99 (2H, s), 4.15–4.25 (1H, m), 6.65–6.80 (4H, m), 7.20 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.93–7.96 (1H, m), 8.43 (1H, d, J = 8.0 Hz), 8.78–8.87 (3H, m), 9.10 (1H, br s), 10.61 (1H, s); MS (FAB) m/z: 422 (MH^+); Anal. Calcd for $C_{24}H_{27}N_3O_4\cdot 2HCl\cdot 1.8H_2O$: C, 54.72; H, 6.24; N, 7.98; Cl, 13.46. Found: C, 54.81; H, 6.60; N, 7.82; Cl, 13.53.

*5.1.18. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(4-pyridyl)acetanilide hydrochloride (**2h**)*

The title compound was prepared in the same manner as described for **2a** using **6h** instead of **6a** as a colorless solid. 28% yield; mp 228–229 °C (MeOH–EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.91–3.03 (3H, m), 3.13–3.19 (3H, m), 3.71 (2H, s), 3.81–3.90 (2H, m), 4.14 (1H, br s), 5.81–5.83 (1H, m), 6.67–6.70 (2H, m),

6.75–6.78 (2H, m), 7.19 (2H, d, $J = 8.4$ Hz), 7.33–7.35 (2H, m), 7.56 (2H, d, $J = 8.4$ Hz), 8.50 (2H, d, $J = 6.0$ Hz), 8.97 (1H, s), 10.34 (1H, br s); MS (FAB) *m/z*: 422 (MH^+); Anal. Calcd for $C_{24}H_{27}N_3O_4 \cdot HCl$: C, 62.95; H, 6.16; N, 9.18; Cl, 7.74. Found: C, 62.84; H, 6.28; N, 9.09; Cl, 7.89.

*5.1.19. (S)-2-{[4-(Methoxymethoxy)phenoxy]methyl}oxirane (**8a**)*

A mixture of 4-(methoxymethoxy)phenol (**7a**) (3.11 g), (*R*)-epichlorohydrin (1.06 g) and KOH (1.1 g) in water (30 mL) was stirred at room temperature for 15 h. The resultant mixture was 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 (3:1) as the eluent to yield **8a** (2.87 g) as a colorless oil. 67% yield; ^{1}H NMR ($CDCl_3$) δ: 2.73–2.75 (1H, m), 2.88–2.90 (1H, m), 3.31–3.35 (1H, m), 3.47 (3H, s), 3.90–3.94 (1H, m), 4.11–4.19 (1H, m), 5.10 (2H, s), 6.85 (2H, d, $J = 9.2$ Hz), 6.97 (2H, d, $J = 9.2$ Hz); MS (EI) *m/z*: 210 (M^+).

*5.1.20. (S)-2-{[4-(2-Methoxyethoxymethoxy)phenoxy]methyl}oxirane (**8b**)*

The title compound was prepared in the same manner as described for **8a** using 4-(2-methoxyethoxymethoxy)phenol (**7b**) [16] instead of **7a** as a colorless oil. 58% yield; ^{1}H NMR ($CDCl_3$) δ: 2.74 (1H, dd, $J = 4.8$, 2.4 Hz), 2.89 (1H, t, $J = 40$ Hz), 3.31–3.36 (1H, m), 3.38 (3H, s), 3.54–3.58 (2H, m), 3.81–3.84 (2H, m), 3.92 (1H, dd, $J = 5.2$, 11.2 Hz), 4.17 (1H, dd, $J = 3.6$, 10.4 Hz), 5.20 (2H, s), 6.82–6.87 (2H, m), 6.97–7.01 (2H, m); MS (EI) *m/z*: 254 (M^+).

*5.1.21. (S)-1-[4-(Methoxymethoxy)phenoxy]-3-[2-(4-nitrophenyl)ethylamino]-2-propanol (**9**)*

A mixture of **8a** (10.16 g), 2-(4-nitrophenyl)ethylamine hydrochloride (9.6 g), and triethylamine (5.05 g) in 2-propanol (100 mL) was refluxed for 8 h. After cooling to room temperature, the resultant mixture was concentrated *in vacuo* and diluted with ethyl acetate. The organic layer was washed with water and brine, and then dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (10:1) as the eluent to yield **9** (6.97 g) as a colorless oil. 38% yield; ^{1}H NMR ($CDCl_3$) δ: 2.77–3.00 (6H, m), 3.48 (3H, s), 3.92 (2H, d, $J = 4.9$ Hz), 3.99–4.03 (1H, m), 5.11 (2H, s), 6.81 (2H, d, $J = 9.2$ Hz), 6.96 (2H, d, $J = 8.6$ Hz), 7.36 (2H, d, $J = 8.5$ Hz), 8.15 (2H, d, $J = 8.6$ Hz); MS (FAB) *m/z*: 377 (MH^+).

5.1.22. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*[2-(4-nitrophenyl)-ethyl]carbamate (**10**)*

To a solution of **9** (6.97 g) in tetrahydrofuran (80 mL) was added di-*tert*-butyl dicarbonate (4.11 g). The mixture was stirred at room temperature for 1 h, and then concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent to yield **10** (8.45 g) as a colorless oil. 96% yield; ^{1}H NMR ($CDCl_3$) δ: 1.43 (9H, s), 2.90–3.10 (2H, m), 3.40–3.60 (4H, m), 3.70 (3H, s), 3.80–3.95 (2H, m), 4.05–4.15 (1H, m), 5.11 (2H, s), 6.82 (2H, d, $J = 8.8$ Hz), 6.98 (2H, d, $J = 9.3$ Hz), 7.25–7.40 (2H, m), 8.15 (2H, d, $J = 8.3$ Hz); MS (EI) *m/z*: 476 (M^+).

5.1.23. tert-*Butyl (S)*-N-*[2-(4-aminophenyl)ethyl]*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]-propyl}carbamate (**11**)*

To a solution of **10** (8.45 g) in ethanol (100 mL) was added palladium on carbon (10% w/w, 0.5 g), and the mixture was stirred under hydrogen atmosphere for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to yield **11** (7.85 g) as a colorless oil. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.65–2.80 (2H, m), 3.30–3.50 (4H, m), 3.48 (3H, s), 3.57 (2H, br s), 3.80–3.95 (2H, m), 4.05–4.15 (2H, m), 5.11 (2H, s), 6.61 (2H, d, $J = 8.3$ Hz), 6.82 (2H, d, $J = 9.3$ Hz), 6.85–7.00 (2H, m), 6.97 (2H, d, $J = 9.3$ Hz); MS (EI) *m/z*: 446 (M^+).

5.1.24. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*(2-{4-[(2-hydroxy-2-phenylacetyl)amino]phenyl}ethyl)carbamate (**12a**)*

To a solution of **11** (0.47 g) and DL-mandelic acid (0.18 g) in *N*,*N*-dimethylformamide (15 mL) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g) and 1-hydroxybenzotriazole (0.16 g), and the mixture was stirred at room temperature for 15 h. The resulting mixture was diluted with ethyl acetate and washed with water twice. 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 $CHCl_3$/MeOH (30:1) as the eluent to yield **12a** (0.61 g) as a yellow oil. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.75–2.90 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.81–3.90 (2H, m), 4.04 (2H, br s), 5.10 (2H, s), 5.19 (1H, d, $J = 3.4$ Hz), 6.81 (2H, d, $J = 8.8$ Hz), 6.96 (2H, d, $J = 8.8$ Hz), 7.05–7.20 (2H, m), 7.35–7.49 (7H, m), 8.08 (1H, br s); MS (FAB) *m/z*: 580 (M^+).

5.1.25. tert-*Butyl (S)*-N-*(2-{4-[(2-tert-butoxycarbonylamino-2-phenylacetyl)amino]phenyl}ethyl)*-N-*[2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl]carbamate (**12b**)*

The title compound was prepared in the same manner as described for **12a** using *N*-Boc-phenylglycine instead of DL-mandelic acid as a colorless oil. 82% yield; ^{1}H NMR ($CDCl_3$) δ: 1.41 (9H, s), 1.43 (9H, s), 2.70–2.90 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.80–3.95 (2H, m), 4.00–4.10 (2H, m), 5.10 (2H, s), 5.27 (1H, br s), 5.77 (1H, br s), 6.81 (2H, d, $J = 8.8$ Hz), 6.96 (2H, d, $J = 9.3$ Hz), 7.00–7.15 (2H, m), 7.33–7.44 (7H, m), 7.55 (1H, br s); MS (FAB) *m/z*: 679 (M^+).

5.1.26. tert-*Butyl (S)*-N-*[2-(4-{[2-(2-chlorophenyl)acetyl]amino}phenyl)ethyl]*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}carbamate (**12c**)*

To a solution of **11** (0.5 g) and triethylamine (0.19 g) in chloroform (15 mL) was added dropwise a solution of 2-chlorophenylacetyl chloride (0.24 g) in benzene (2 mL), and the mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated *in vacuo*, and the residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent to yield **12c** (0.51 g) as a yellow oil. 81% yield; ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.70–2.85 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.75–3.95 (2H, m), 3.85 (2H, s), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.80–6.84 (2H, m), 6.91–7.00 (2H, m), 7.05–7.13 (2H, m), 7.26–7.52 (6H, m); MS (FAB) *m/z*: 598 (MH^+).

5.1.27. tert-*Butyl (S)*-N-*[2-(4-{[2-(3-chlorophenyl)acetyl]amino}phenyl)ethyl]*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}carbamate (**12d**)*

The title compound was prepared in the same manner as described for **12c** using 3-chlorophenylacetyl chloride instead of 2-chlorophenylacetyl chloride as a yellow oil. 98% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.90 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.69 (2H, s), 3.75–3.95 (2H, m), 4.00–4.20 (2H, m), 5.10 (2H, s), 6.79–6.83 (2H, m), 6.91–7.00 (2H, m), 7.05–7.20 (2H, m), 7.21–7.52 (6H, m); MS (FAB) *m/z*: 598 (MH^+).

5.1.28. tert-*Butyl (S)*-N-*[2-(4-{[2-(4-chlorophenyl)acetyl]amino}phenyl)ethyl]*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}carbamate (**12e**)*

The title compound was prepared in the same manner as described for **12c** using 4-chlorophenylacetyl chloride instead of

2-chlorophenylacetyl chloride as a yellow oil. 90% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.90 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.69 (2H, s), 3.75–3.90 (2H, m), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.79–6.83 (2H, m), 6.90–7.20 (5H, m), 7.21–7.34 (5H, m); MS (FAB) *m*/*z*: 598 (MH^+).

5.1.29. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*[2-(4-{[2-(2-methoxyphenyl)acetyl]amino}phenyl)ethyl]carbamate (**12f**)*

The title compound was prepared in the same manner as described for **12c** using 2-methoxyphenylacetyl chloride instead of 2-chlorophenylacetyl chloride as a yellow oil. 72% yield; ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.70–2.85 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.70 (2H, s), 3.80–3.95 (2H, m), 3.92 (3H, s), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.81 (2H, d, J = 8.8 Hz), 6.90–7.10 (6H, m), 7.20–7.34 (2H, m), 7.61 (1H, br s); MS (FAB) *m*/*z*: 595 (MH^+).

5.1.30. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*[2-(4-{[2-(3-methoxyphenyl)acetyl]amino}phenyl)ethyl]carbamate (**12g**)*

The title compound was prepared in the same manner as described for **12c** using 3-methoxyphenylacetyl chloride instead of 2-chlorophenylacetyl chloride as a yellow oil. 86% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.85 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.70 (2H, s), 3.75–3.95 (2H, m), 3.82 (3H, s), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.79–7.06 (10H, m), 7.26–7.34 (2H, m); MS (FAB) *m*/*z*: 594 (M^+).

5.1.31. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*[2-(4-{[2-(4-methoxyphenyl)acetyl]amino}phenyl)ethyl]carbamate (**12h**)*

The title compound was prepared in the same manner as described for **12c** using 4-methoxyphenylacetyl chloride instead of 2-chlorophenylacetyl chloride as a yellow oil. 85% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.85 (2H, m), 3.30–3.50 (4H, m), 3.47 (3H, s), 3.67 (2H, s), 3.75–3.95 (2H, m), 3.83 (3H, s), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.79–6.84 (2H, m), 6.90–7.15 (6H, m), 7.23–7.26 (2H, m), 7.32 (2H, d, J = 8.3 Hz); MS (FAB) *m*/*z*: 594 (M^+).

5.1.32. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*[2-(4-{[2-(2-thenyl)-acetyl]amino}phenyl)ethyl]carbamate (**12i**)*

The title compound was prepared in the same manner as described for **12c** using 2-thenylacetyl chloride instead of 2-chlorophenylacetyl chloride as a colorless oil. 74% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.85 (2H, m), 3.30–3.50 (4H, m), 3.48 (3H, s), 3.80–3.90 (2H, m), 3.94 (2H, s), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.81 (2H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.00–7.15 (3H, m), 7.20–7.36 (4H, m); MS (FAB) *m*/*z*: 570 (M^+).

5.1.33. tert-*Butyl (S)*-N-*{2-hydroxy-3-[4-(methoxymethoxy)phenoxy]propyl}*-N-*[2-(4-{[2-(3-thenyl)-acetyl]amino}phenyl)ethyl]carbamate (**12j**)*

The title compound was prepared in the same manner as described for **12c** using 3-thenylacetyl chloride instead of 2-chlorophenylacetyl chloride as a colorless oil. 66% yield; ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.85 (2H, m), 3.30–3.50 (4H, m), 3.48 (3H, s), 3.76 (2H, s), 3.80–3.90 (2H, m), 4.00–4.15 (2H, m), 5.10 (2H, s), 6.80–6.83 (2H, m), 6.95–6.98 (2H, m), 7.06–7.08 (3H, m), 7.24–7.52 (4H, m); MS (FAB) *m*/*z*: 571 (MH^+).

*5.1.34. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-hydroxy-2-phenylacetanilide hydrochloride (**2i**)*

To a solution of **12a** (0.6 g) in methanol (10 mL) was added 4 M HCl–EtOAc solution (10 mL), and the mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated *in vacuo*, and the residue was solidified by trituration. The crude solid was purified by recrystallization from EtOH–Et_2O to yield **2i** (0.22 g) as a colorless solid. 44% yield; mp 173–176 °C (EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.83–3.87 (2H, m), 4.12 (1H, br s), 5.10 (1H, s), 5.80 (1H, br s), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 9.3 Hz), 7.17 (2H, d, J = 8.3 Hz), 7.28–7.37 (3H, m), 7.51 (2H, d, J = 7.3 Hz), 7.66 (2H, d, J = 8.3 Hz), 8.60–8.80 (2H, m), 8.97 (1H, br s), 9.93 (1H, s); MS (FAB) *m*/*z*: 437 (MH^+); Anal. Calcd for $C_{25}H_{28}N_2O_5 \cdot 1.1HCl$: C, 63.00; H, 6.15; N, 5.88; Cl, 8.18. Found: C, 62.61; H, 6.16; N, 5.99; Cl, 8.01.

*5.1.35. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-amino-2-phenylacetanilide dihydrochloride (**2j**)*

The title compound was prepared in the same manner as described for **2i** using **12b** instead of **12a** as a colorless powder. 80% yield; ^{1}H NMR (DMSO-d_6) δ: 2.85–3.00 (3H, m), 3.10–3.20 (3H, m), 3.80–3.90 (2H, m), 4.16 (1H, br s), 5.29 (1H, br s), 6.68 (2H, d, J = 9.3 Hz), 6.77 (2H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.8 Hz), 7.42–7.48 (3H, m), 7.59 (2H, d, J = 8.8 Hz), 7.68 (2H, d, J = 6.8 Hz), 8.80–9.10 (5H, m), 11.18 (1H, s); MS (FAB) *m*/*z*: 436 (MH^+); Anal. Calcd for $C_{25}H_{29}N_3O_4 \cdot 2.2HCl \cdot 3.4H_2O$: C, 52.04; H, 6.64; N, 7.28; Cl, 13.52. Found: C, 51.94; H, 6.98; N, 7.67; Cl, 13.55.

*5.1.36. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(2-chlorophenyl)acetanilide hydrochloride (**2k**)*

The title compound was prepared in the same manner as described for **2i** using **12c** instead of **12a** as a colorless solid. 43% yield; mp 236–239 °C (MeOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.81–3.90 (2H, m), 3.83 (2H, s), 4.16 (1H, br s), 5.83 (1H, br s), 6.67–6.71 (2H, m), 6.75–6.78 (2H, m), 7.19 (2H, d, J = 8.3 Hz), 7.27–7.33 (2H, m), 7.40–7.45 (2H, m), 7.57 (2H, d, J = 8.8 Hz), 8.78 (1H, br s), 8.98 (2H, br s), 10.29 (1H, s); MS (FAB) *m*/*z*: 455 (MH^+); Anal. Calcd for $C_{25}H_{27}N_2O_4Cl \cdot HCl$: C, 61.10; H, 5.74; N, 5.70; Cl, 14.43. Found: C, 60.92; H, 5.72; N, 5.60; Cl, 14.74.

*5.1.37. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(3-chlorophenyl)acetanilide hydrochloride (**2l**)*

The title compound was prepared in the same manner as described for **2i** using **12d** instead of **12a** as a colorless solid. 31% yield; mp 229–232 °C (MeOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.67 (2H, s), 3.81–3.90 (2H, m), 4.14 (1H, br s), 5.82 (1H, d, J = 4.9 Hz), 6.67–6.71 (2H, m), 6.75–6.78 (2H, m), 7.19 (2H, d, J = 8.8 Hz), 7.28–7.41 (4H, m), 7.56 (2H, d, J = 8.3 Hz), 8.70 (1H, br s), 8.82 (1H, br s), 8.67 (1H, s), 10.28 (1H, s); MS (FAB) *m*/*z*: 455 (MH^+); Anal. Calcd for $C_{25}H_{27}N_2O_4Cl \cdot HCl$: C, 61.10; H, 5.74; N, 5.70; Cl, 14.43. Found: C, 61.23; H, 5.72; N, 5.69; Cl, 14.58.

*5.1.38. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(4-chlorophenyl)acetanilide hydrochloride (**2m**)*

The title compound was prepared in the same manner as described for **2i** using **12e** instead of **12a** as a colorless solid. 49% yield; mp 245–250 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.65 (2H, s), 3.81–3.90 (2H, m), 4.13 (1H, br s), 5.82 (1H, br s), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 7.18 (2H, d, J = 8.3 Hz), 7.33–7.40 (4H, m), 7.55 (2H, d, J = 8.3 Hz), 8.69 (1H, br s), 8.78 (1H, br s), 8.97 (1H, s), 10.25 (1H, s); MS (FAB) *m*/*z*: 455 (MH^+); Anal. Calcd for $C_{25}H_{27}N_2O_4Cl \cdot HCl \cdot 0.2H_2O$: C, 60.66; H, 5.78; N, 5.66; Cl, 14.32. Found: C, 60.53; H, 5.66; N, 5.55; Cl, 14.68.

*5.1.39. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(2-methoxyphenyl)acetanilide hydrochloride (**2n**)*

The title compound was prepared in the same manner as described for **2i** using **12f** instead of **12a** as a colorless solid. 38% yield; mp 179–181 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.61 (2H, s), 3.76 (3H, s), 3.83–3.87 (2H, m), 4.10–4.20 (1H, m), 5.82 (1H, d, J = 4.4 Hz), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 6.90 (1H, t, J = 7.3 Hz), 6.98 (1H, d, J = 7.8 Hz), 7.16–7.24 (4H, m), 7.56 (2H, d, J = 8.3 Hz), 8.65 (2H, br s), 8.96 (1H, s), 10.05 (1H, s); MS (FAB) m/z: 451 (MH^+); Anal. Calcd for $C_{26}H_{30}N_2O_5 \cdot HCl \cdot 0.1H_2O$: C, 63.89; H, 6.43; N, 5.73; Cl, 7.25. Found: C, 63.77; H, 6.40; N, 5.68; Cl, 7.49.

*5.1.40. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(3-methoxyphenyl)acetanilide hydrochloride (**2o**)*

The title compound was prepared in the same manner as described for **2i** using **12g** instead of **12a** as a colorless solid. 43% yield; mp 214–217 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.59 (2H, s), 3.74 (3H, s), 3.81–3.90 (2H, m), 4.13 (1H, br s), 5.81 (1H, d, J = 4.9 Hz), 6.68 (2H, d, J = 8.8 Hz), 6.75–6.91 (5H, m), 7.16–7.25 (3H, m), 7.56 (2H, d, J = 8.3 Hz), 8.67 (2H, br s), 8.96 (1H, s), 10.18 (1H, s); MS (FAB) m/z: 451 (MH^+); Anal. Calcd for $C_{26}H_{30}N_2O_5 \cdot HCl$: C, 64.13; H, 6.42; N, 5.75; Cl, 7.28. Found: C, 63.87; H, 6.34; N, 5.68; Cl, 7.61.

*5.1.41. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(4-methoxyphenyl)acetanilide hydrochloride (**2p**)*

The title compound was prepared in the same manner as described for **2i** using **12h** instead of **12a** as a colorless solid. 52% yield; mp 241–244 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.85–3.05 (3H, m), 3.10–3.20 (3H, m), 3.55 (2H, s), 3.72 (3H, s), 3.81–3.90 (2H, m), 4.16 (1H, br s), 5.84 (1H, br s), 6.69 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.17 (2H, d, J = 8.3 Hz), 7.25 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.3 Hz), 8.77 (1H, br s), 8.98 (2H, br s), 10.21 (1H, s); MS (FAB) m/z: 451 (MH^+); Anal. Calcd for $C_{26}H_{30}N_2O_5 \cdot HCl \cdot 0.1H_2O$: C, 63.89; H, 6.43; N, 5.73; Cl, 7.25. Found: C, 63.65; H, 6.31; N, 5.62; Cl, 7.46.

*5.1.42. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(2-thenyl)acetanilide hydrochloride (**2q**)*

The title compound was prepared in the same manner as described for **2i** using **12i** instead of **12a** as a colorless solid. 55% yield; mp 219–223 °C (MeOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.89–3.02 (3H, m), 3.16 (3H, br s), 3.81–3.90 (2H, m), 3.87 (2H, s), 4.14 (1H, br s), 5.83 (1H, br s), 6.68 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 6.96–6.98 (2H, m), 7.19 (2H, d, J = 8.3 Hz), 7.37–7.39 (1H, m), 7.56 (2H, d, J = 7.8 Hz), 8.72 (1H, br s), 8.85 (1H, br s), 8.97 (1H, s), 10.27 (1H, s); MS (FAB) m/z: 427 (MH^+); Anal. Calcd for $C_{23}H_{26}N_2O_4S \cdot HCl \cdot 0.1H_2O$: C, 59.44; H, 5.90; N, 6.03; S, 6.90; Cl, 7.63. Found: C, 59.33; H, 5.85; N, 6.01; S, 6.77; Cl, 7.89.

*5.1.43. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(3-thenyl)acetanilide hydrochloride (**2r**)*

The title compound was prepared in the same manner as described for **2i** using **12j** instead of **12a** as a colorless solid. 32% yield; mp 233–235 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ: 2.89–3.02 (3H, m), 3.16 (3H, br s), 3.65 (2H, s), 3.81–3.90 (2H, m), 4.13 (1H, br s), 5.82 (1H, d, J = 4.8 Hz), 6.67–6.70 (2H, m), 6.75–6.78 (2H, m), 7.07 (1H, d, J = 5.2 Hz), 7.18 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 2.0 Hz), 7.46–7.49 (1H, m), 7.56 (2H, d, J = 8.4 Hz), 8.67 (2H, br s), 8.96 (1H, s), 10.16 (1H, s); MS (FAB) m/z: 427 (MH^+); Anal. Calcd for $C_{23}H_{26}N_2O_4S \cdot HCl$: C, 59.67; H, 5.88; N, 6.05; S, 6.93; Cl, 7.66. Found: C, 59.41; H, 5.91; N, 6.04; S, 6.79; Cl, 7.87.

*5.1.44. 4′-Cyanomethyl-2-(quinolin-2-yl)acetanilide (**14a**)*

A mixture of 4-aminobenzylcyanide (1.07 g) and ethyl 2-quinolinylacetate (1.04 g) in xylene (15 mL) was refluxed for 19 h. After cooling to room temperature, the resultant mixture was concentrated *in vacuo*. The residue was purified by recrystallization from *n*-hexane–EtOAc to yield **14a** (1.22 g) as a colorless solid. 79% yield; ^{1}H NMR ($CDCl_3$) δ: 3.71 (2H, s), 4.08 (2H, s), 7.25–7.30 (2H, m), 7.40 (1H, d, J = 8.4 Hz), 7.57–7.66 (3H, m), 7.77–7.89 (2H, m), 8.12 (1H, d, J = 8.4 Hz), 8.20 (1H, d, J = 8.4 Hz), 10.75 (1H, br s); MS (FAB) m/z: 302 (MH^+).

*5.1.45. 4′-Cyanomethyl-2-(isoquinolin-3-yl)acetanilide (**14b**)*

The title compound was prepared in the same manner as described for **14a** using ethyl 3-isoquinolinylacetate [17] instead of ethyl 2-quinolinylacetate as a colorless solid. 67% yield; ^{1}H NMR ($CDCl_3$) δ: 3.70 (2H, s), 4.01 (2H, s), 7.23–7.28 (2H, m), 7.56–7.68 (4H, m), 7.71–7.76 (1H, m), 8.01 (1H, d, J = 8.1 Hz), 9.29 (1H, s), 9.88 (1H, br s); MS (FAB) m/z: 302 (MH^+).

*5.1.46. 4′-Cyanomethyl-2-(pyrimidin-2-yl)acetanilide (**14c**)*

The title compound was prepared in the same manner as described for **14a** using ethyl 2-pyrimidinylacetate instead of ethyl 2-quinolinylacetate as a colorless solid. 89% yield; ^{1}H NMR ($CDCl_3$) δ: 3.72 (2H, s), 4.13 (2H, s), 7.26–7.31 (3H, m), 7.59–7.62 (2H, m), 8.78 (2H, d, J = 5.2 Hz), 9.82 (1H, s); MS (FAB) m/z: 253 (MH^+).

*5.1.47. 4′-Cyanomethyl-2-(pyrazin-2-yl)acetanilide (**14d**)*

The title compound was prepared in the same manner as described for **14a** using ethyl 2-pyrazinylacetate [18] instead of ethyl 2-quinolinylacetate as a colorless solid. 76% yield; ^{1}H NMR ($CDCl_3$) δ: 3.71 (2H, s), 3.92 (2H, s), 7.26–7.29 (2H, m), 7.55–7.58 (2H, m), 8.57–8.60 (2H, m), 8.65 (1H, s), 9.12 (1H, s); MS (FAB) m/z: 253 (MH^+).

*5.1.48. (S)-4′-[2-({2-Hydroxy-3-[4-(2-methoxyethoxymethoxy)phenoxy]propyl}amino)ethyl]-2-(quinolin-2-yl)acetanilide (**15a**)*

To a mixture of **14a** (2.09 g) and concentrated aqueous ammonia solution (1 mL) in tetrahydrofuran (40 mL) was added Raney-nickel, and the mixture was stirred under hydrogen atmosphere for 4 h. The catalyst was removed by filtration over Celite, and the filtrate was concentrated *in vacuo*. The residue was added to a solution of **8b** (1.44 g) in 2-propanol (40 mL), and the mixture was refluxed for 1 h. After cooling to room temperature, the resultant mixture was concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (20:1) as the eluent to yield **15a** (1.27 g) as a colorless powder. 32% yield; ^{1}H NMR ($CDCl_3$) δ: 2.70–2.93 (6H, m), 3.37 (3H, s), 3.54–3.57 (2H, m), 3.79–3.84 (2H, m), 3.88–3.93 (2H, m), 3.95–4.04 (1H, m), 4.06 (2H, s), 5.18 (2H, s), 6.77–6.85 (2H, m), 6.93–7.00 (2H, m), 7.15 (2H, d, J = 4.0 Hz), 7.41 (1H, d, J = 8.4 Hz), 7.50–7.60 (3H, m), 7.75–7.87 (2H, m), 8.11 (1H, d, J = 8.4 Hz), 8.17 (1H, d, J = 8.0 Hz), 10.42 (1H, br s); MS (FAB) m/z: 560 (MH^+).

*5.1.49. (S)-4′-[2-({2-Hydroxy-3-[4-(2-methoxyethoxymethoxy)phenoxy]propyl}amino)ethyl]-2-(isoquinolin-3-yl)acetanilide (**15b**)*

The title compound was prepared in the same manner as described for **15a** using **14b** instead of **14a** as a colorless powder. 44% yield; ^{1}H NMR ($CDCl_3$) δ: 2.70–2.95 (6H, m), 3.37 (3H, s), 3.53–3.57 (2H, m), 3.79–3.88 (2H, m), 3.87–3.92 (2H, m), 3.95–4.03 (3H,

m), 5.19 (2H, s), 6.78–6.83 (2H, m), 6.94–7.00 (2H, m), 7.13 (2H, d, $J = 8.4$ Hz), 7.47 (2H, d, $J = 8.4$ Hz), 7.59–7.75 (4H, m), 7.99 (1H, d, $J = 7.9$ Hz), 9.28 (1H, s), 9.62 (1H, br s); MS (FAB) m/z: 560 (MH^+).

*5.1.50. (S)-4′-[2-({2-Hydroxy-3-[4-(2-methoxyethoxymethoxy)phenoxy]propyl}amino)ethyl]-2-(pyrimidin-2-yl)acetanilide (**15c**)*

The title compound was prepared in the same manner as described for **15a** using **14c** instead of **14a** as a colorless powder. 24% yield; ^{1}H NMR ($CDCl_3$) δ: 2.78–2.85 (3H, m), 2.90–2.99 (3H, m), 3.37 (3H, s), 3.54–3.57 (2H, m), 3.80–3.83 (2H, m), 3.90–3.92 (2H, m), 4.04–4.08 (1H, m), 4.12 (2H, s), 5.19 (2H, s), 6.78–6.82 (2H, m), 6.95–6.98 (2H, m), 7.17 (2H, d, $J = 8.4$ Hz), 7.23–7.29 (1H, m), 7.50 (2H, d, $J = 8.0$ Hz), 8.76–8.78 (2H, m), 9.61 (1H, s); MS (FAB) m/z: 511 (MH^+).

*5.1.51. (S)-4′-[2-({2-Hydroxy-3-[4-(2-methoxyethoxymethoxy)phenoxy]propyl}amino)ethyl]-2-(pyrazin-2-yl)acetanilide (**15d**)*

The title compound was prepared in the same manner as described for **15a** using **14d** instead of **14a** as a colorless powder. 33% yield; ^{1}H NMR ($CDCl_3$) δ: 2.78–2.85 (3H, m), 2.91–2.99 (3H, m), 3.37 (3H, s), 3.54–3.57 (2H, m), 3.80–3.83 (2H, m), 3.90–3.92 (2H, m), 4.04–4.08 (1H, m), 4.12 (2H, s), 5.19 (2H, s), 6.78–6.82 (2H, m), 6.95–6.98 (2H, m), 7.17 (2H, d, $J = 8.4$ Hz), 7.23–7.29 (1H, m), 7.51 (2H, d, $J = 8.0$ Hz), 8.76–8.78 (2H, m), 9.61 (1H, s); MS (FAB) m/z: 511 (MH^+).

*5.1.52. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(quinolin-2-yl)acetanilide hydrochloride (**2s**)*

The title compound was prepared in the same manner as described for **2i** using **15a** instead of **12a** as a colorless solid. 51% yield; mp 226–227 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.87–3.02 (3H, m), 3.16 (3H, br s), 3.81–3.90 (2H, m), 4.01 (2H, s), 4.16 (1H, br s), 5.84–5.85 (1H, m), 6.67–6.71 (2H, m), 6.75–6.78 (2H, m), 7.20 (2H, d, $J = 8.4$ Hz), 7.57–7.61 (4H, m), 7.73–7.77 (1H, m), 7.97 (2H, d, $J = 8.8$ Hz), 8.34 (1H, d, $J = 8.4$ Hz), 8.77 (1H, br s), 8.93 (1H, br s), 8.99 (1H, s), 10.45 (1H, s); MS (FAB) m/z: 472 (MH^+); Anal. Calcd for $C_{28}H_{29}N_3O_4 \cdot HCl$: C, 66.20; H, 5.95; N, 8.27; Cl, 6.98. Found: C, 65.96; H, 5.98; N, 8.27; Cl, 7.10.

*5.1.53. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(isoquinolin-3-yl)acetanilide hydrochloride (**2t**)*

The title compound was prepared in the same manner as described for **2i** using **15b** instead of **12a** as a colorless solid. 56% yield; mp 214–216 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.02 (3H, m), 3.16 (3H, br s), 3.81–3.90 (2H, m), 4.00 (2H, s), 4.15 (1H, br s), 5.83–5.84 (1H, m), 6.66–6.71 (2H, m), 6.76–6.78 (2H, m), 7.19 (2H, d, $J = 8.8$ Hz), 7.59–7.68 (3H, m), 7.75–7.80 (2H, m), 7.95 (1H, d, $J = 8.4$ Hz), 8.12 (1H, d, $J = 8.0$ Hz), 8.73 (1H, br s), 8.86 (1H, br s), 8.98 (1H, s), 9.27 (1H, s), 10.33 (1H, s); MS (FAB) m/z: 472 (MH^+); Anal. Calcd for $C_{28}H_{29}N_3O_4 \cdot HCl \cdot 0.1H_2O$: C, 65.97; H, 5.97; N, 8.24; Cl, 6.95. Found: C, 65.83; H, 5.90; N, 8.23; Cl, 6.82.

*5.1.54. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(pyrimidin-2-yl)acetanilide hydrochloride (**2u**)*

The title compound was prepared in the same manner as described for **2i** using **15c** instead of **12a** as a colorless solid. 53% yield; mp 193–194 °C (MeOH–EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.02 (3H, m), 3.16 (3H, br s), 3.81–3.90 (2H, m), 3.99 (2H, s), 4.15 (1H, br s), 5.84 (1H, br s), 6.69 (2H, d, $J = 8.8$ Hz), 6.77 (2H, d, $J = 8.8$ Hz), 7.20 (2H, d, $J = 8.8$ Hz), 7.41 (1H, t, $J = 4.8$ Hz), 7.57 (2H, d, $J = 8.8$ Hz), 8.69 (2H, br), 8.77 (2H, d, $J = 5.2$ Hz), 8.98 (1H, s), 10.29 (1H, s); MS (FAB) m/z: 423 (MH^+); Anal. Calcd for $C_{23}H_{26}N_4O_4 \cdot 1.1HCl$: C, 59.72; H, 5.90; N, 12.11; Cl, 8.43. Found: C, 59.49; H, 5.87; N, 11.83; Cl, 8.13.

*5.1.55. (S)-4′-(2-{[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino}ethyl)-2-(pyrazin-2-yl)acetanilide hydrochloride (**2v**)*

The title compound was prepared in the same manner as described for **2i** using **15d** instead of **12a** as a colorless solid. 79% yield; mp 218–219 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.88–3.02 (3H, m), 3.16 (3H, br), 3.81–3.90 (2H, m), 3.94 (2H, s), 4.15 (1H, br), 5.82–5.84 (1H, m), 6.66–6.71 (2H, m), 6.75–6.78 (2H, m), 7.19 (2H, d, $J = 8.4$ Hz), 7.57 (2H, d, $J = 8.0$ Hz), 8.54 (1H, d, $J = 2.8$ Hz), 8.58 (1H, br s), 8.67 (1H, s), 8.74 (1H, br s), 8.89 (1H, br s), 8.98 (1H, s), 10.38 (1H, s); MS (FAB) m/z: 423 (MH^+); Anal. Calcd for $C_{23}H_{26}N_4O_4 \cdot HCl \cdot 0.2H_2O$: C, 59.72; H, 5.97; N, 12.11; Cl, 7.66. Found: C, 59.59; H, 5.91; N, 12.06; Cl, 7.97.

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 are compulsorily expressed were used). The agonistic activity of the compound (final concentrations of 10^{-10} to 10^{-4} M) was investigated by incubating 10^5 cells/well of each 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 level 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 glass capillary tube (previously treated with heparin) 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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