Synthesis and Evaluation of Novel Phenylethanolamine Derivatives containing Acetanilides as Potent and Selective β3-Adrenergic Receptor Agonists

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In the search for potent and selective human β3-adrenergic receptor (AR) agonists as potential pharmacotherapies for the treatment of obesity and non-insulin dependent (type II) diabetes, we prepared a novel series of phenylethanolamine derivatives containing acetanilides and evaluated their biological activities at the human β3-, β2-, and β1-ARs. Among these compounds, the 6-amino-2-pyridylacetanilide (36b), 2-amino-5-methylthiazol-4-ylacetanilide (36g), and 5-amino-1,2,4-thiadiazol-3-ylacetanilide (36h) derivatives showed potent agonistic activity at the β3-AR with functional selectivity over the β1- and β2-ARs. In addition, these compounds exhibited significant hypoglycemic activity in a rodent diabetic model.

Key words β_3-adrenergic receptor; agonist; phenylethanolamine; acetanilide; diabetes

A major increase in the prevalence of obesity and non-insulin dependent (type II) diabetes and related cardiovascular disorders has led to the search for new pharmacological approaches in the treatment of these conditions.[1,2] In the early 1980s, the β3-adrenergic receptor (AR) was identified as a possible therapeutic target for the treatment of type II diabetes and obesity.[3,4] Early potent and selective β3-AR agonists, such as BRL-37344[5] and CL-316243,[6] were reported to be effective anti-obesity and anti-diabetic agents in rodents (Fig. 1).[7] Human clinical trials with these agents for the treatment of metabolic disorders, however, have been disappointing due to a lack of efficacy or an unfavorable side-effect profile.[8,9] The clinical failure of such compounds has been attributed to a lack of sufficient β3-AR potency and selectivity relative to β1- and β2-ARs resulting from pharmacologic differences between rodent and human receptors, which was supported by the discovery, cloning, and characterization of the human, rat, and mouse β3-ARs.[10—12] 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.[13—15] The availability of appropriate human receptors has given rise to the design and synthesis of a new generation of β3-AR agonists with high potency. 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.

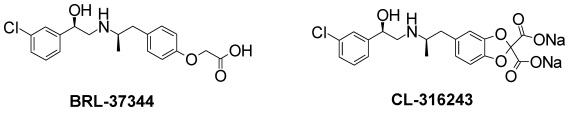

Fig. 1. Chemical Structure of Early β3-AR Agonists

We previously described efforts in this area, including the disclosure of acetanilide analogues exemplified by 2-pyridylacetanilide **1**, which showed potent β3-AR agonistic activity with modest functional selectivity over β1-AR and oral hypoglycemic activity in diabetic kk mice (Fig. 2).[16] Compound **1** was found, however, to exhibit poor bioavailability in rats (F=2%), probably due to the rapid metabolism of the 4-hydroxyphenoxy moiety on the left-hand side. Many kinds of phenylethanolamine-based β3-AR agonists have been reported (Fig. 3)[4,17] and we therefore decided to explore the alternative structures to the 4-hydroxyphenoxymethyl moiety. Subsequently, we attempted to modify the central part and the pyridyl moiety on the right-hand side (Fig. 2). In this paper, we describe the synthesis and structure–activity rela-

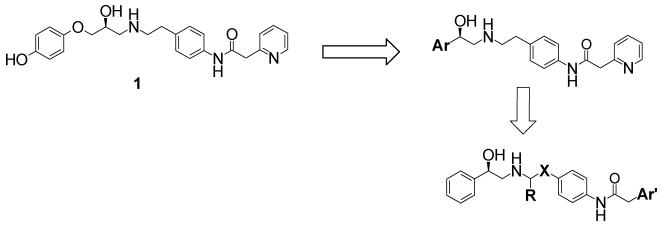

Fig. 2. Design of Phenylethanolamine Derivatives containing Acetanilides based on Compound **1**

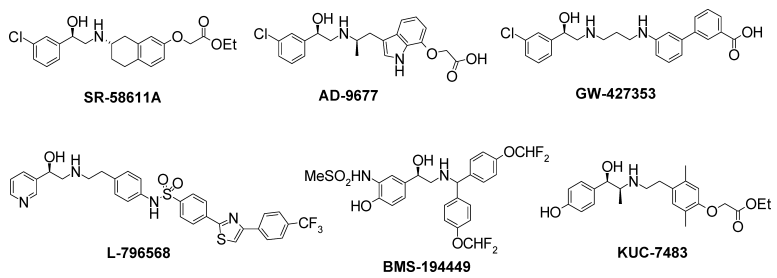

Fig. 3. Chemical Structure of Phenylethanolamine-based β3-AR Agonists

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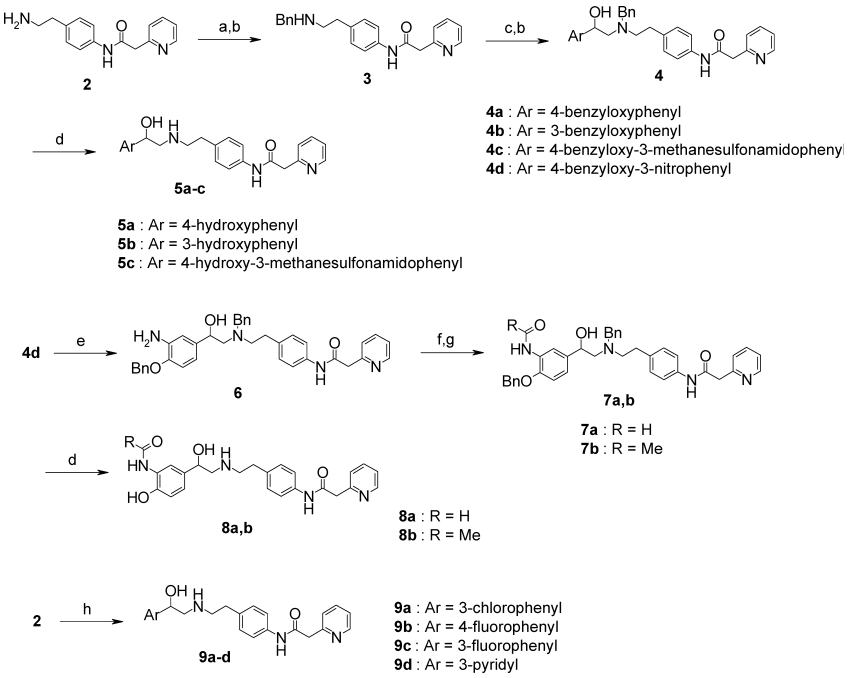
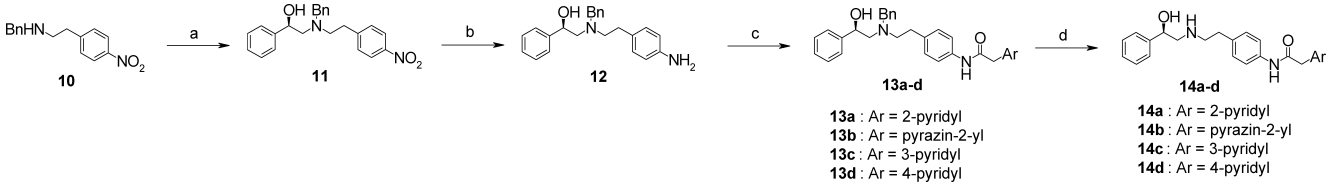


Reagents and conditions: (a) benzaldehyde, toluene, reflux; (b) $NaBH_4$, MeOH; (c) $ArCOCH_2Br$; $^iPr_2NEt$, 2-butanone, reflux; (d) H_2, Pd–C, MeOH, then 4 M HCl–EtOAc, MeOH; (e) Fe, HCl aq., MeOH; (f) RCO_2Ac, $CHCl_3$; (g) Na_2CO_3, MeOH aq.; (h) $ArCH(O)CH_2$, EtOH, reflux, and then 4 M HCl–EtOAc, EtOH.

Chart 1



Reagents and conditions: (a) (*R*)-styrene oxide, ^{i}PrOH, reflux; (b) Fe, HCl aq., MeOH; (c) $ArCH_2CO_2Me$, xylene, reflux, or $ArCH_2CO_2H$, EDC·HCl, HOBt, THF, DMF; (d) H_2, Pd–C, MeOH, and then 4 M HCl–EtOAc, MeOH.

Chart 2

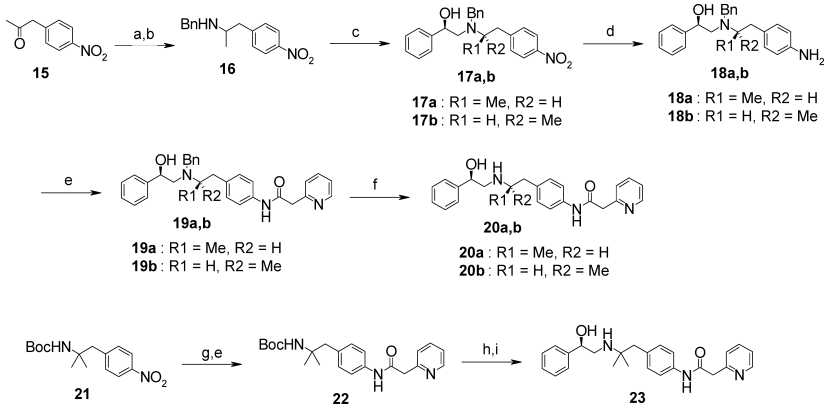
tionships (SARs) of these newly designed phenylethanolamine derivatives containing acetanilides as β3-AR agonists.

Chemistry The synthesis of 2-pyridylacetanilides **5a**—**c**, **8a**, **b**, and **9a**—**d** are shown in Chart 1. Treatment of 4′-(2-aminoethyl)-2-pyridylacetanilide (**2**)[16] with benzaldehyde, followed by reduction with sodium borohydride yielded a benzylamine intermediate (**3**). Compound **3** was coupled with the appropriate phenacyl bromides in the presence of diisopropylethylamine, followed by reduction of the ketone with sodium borohydride to yield the benzylamine derivatives **4a**—**d**. Deprotection of the benzyl groups by hydrogenolysis in **4a**—**c** afforded the desired products **5a**—**c**. Reduction of the nitro compound **4d** was accomplished by treatment with iron powder and provided aniline **6**, which was converted to the anilides **7a**, **b** by acylation. Deprotection of the benzyl groups by hydrogenolysis in **7a**, **b** afforded the desired products **8a**, **b**. Meanwhile, the coupling of compound **2** with the appropriate styrene oxide afforded the desired products **9a**—**d**.

Acetanilides **14a**—**d** were prepared from the aniline intermediate **12** as illustrated in Chart 2. Compound **12** was synthesized from *N*-benzyl-2-(4-nitrophenyl)ethylamine (**10**)[18] and (*R*)-styrene oxide, followed by reduction of the nitro group with iron powder. The coupling of **12** with the appropriate arylacetic acid derivatives, followed by deprotection of the benzyl group by hydrogenolysis afforded the desired products **14a**—**d**.

Chart 3 shows the synthesis of compounds **20a**, **b**, and **23**. Treatment of a commercially available 4-nitrophenylacetone (**15**) with benzylamine, followed by reduction with sodium borohydride gave compound **16**. The coupling of **16** with (*R*)-styrene oxide yielded the corresponding diastereomers **17a** and **17b**. The *S* configuration of the carbon atom that bound to the methyl group of **17b** was determined using single-crystal X-ray analysis (Fig. 4). Nitro compounds **17a**, **b** were reduced with iron powder, followed by coupling with 2-pyridylacetic acid to yield 2-pyridylacetanilides **19a**, **b**. Deprotection of the benzyl group by hydrogenolysis in **19a**, **b** afforded the desired products **20a**, **b**. Meanwhile, hydrogenation of *tert*-butyl *N*-[2-methyl-1-(4-nitrophenyl)-2-propyl]-carbamate (**21**)[19] followed by coupling with 2-pyridylacetic acid yielded compound **22**. Deprotection of the *tert*-butoxycarbonyl (Boc) group by treatment with hydrochloric acid in **22**, followed by coupling with (*R*)-styrene oxide afforded the desired product **23**.

Compounds **28a**, **b** were synthesized as illustrated in Chart 4. 4-(4-Nitrophenyl)butyric acid (**24**) was treated with diphenyl phosphoryl azide (DPPA) in the presence of trieth-



Reagents and conditions: (a) benzylamine, toluene, reflux; (b) $NaBH_4$, MeOH, THF; (c) (*R*)-styrene oxide, heat; (d) Fe, HCl aq., MeOH; (e) 2-pyridylacetic acid hydrochloride, EDC·HCl, HOBt, THF, DMF, or methyl 2-pyridylacetate, xylene, reflux; (f) H_2, Pd–C, MeOH, and then 4 M HCl–EtOAc, MeOH; (g) H_2, Pd–C, EtOH, THF; (h) 4 M HCl–EtOAc, MeOH; (i) (*R*)-styrene oxide, ^{i}PrOH, MeOH, reflux, and then 4 M HCl–EtOAc, MeOH.

Chart 3

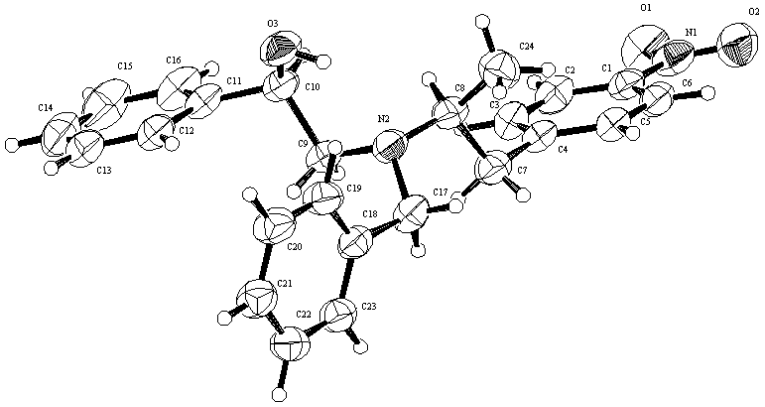
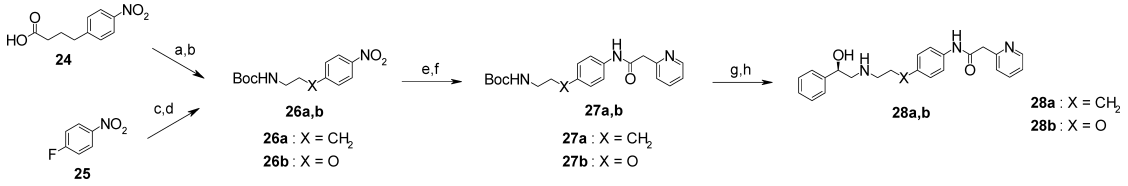


Fig. 4. The Molecular Structure of **17b** with the Crystallographic Numbering Scheme

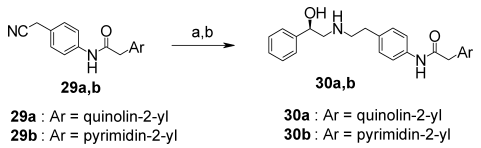


Reagents and conditions: (a) DPPA, Et_3N toluene, reflux; (b) ^{t}BuOH, reflux; (c) $H_2NCH_2CH_2OH$, NaH, THF; (d) $(Boc)_2O$, THF; (e) H_2, Pd–C, EtOH, THF; (f) 2-pyridylacetic acid hydrochloride, EDC·HCl, HOBt, THF; (g) 4 M HCl–EtOAc, MeOH; (i) (*R*)-styrene oxide, ^{i}PrOH, reflux, and then 4 M HCl–EtOAc, MeOH.

Chart 4

ylamine, followed by refluxing in *tert*-butanol to yield *tert*-butyl *N*-[3-(4-nitrophenyl)propyl]carbamate (**26a**). Meanwhile, treatment of 4-fluoronitrobenzene (**25**) with 2-aminoethanol in the presence of sodium hydride, followed by protection with the Boc group gave *tert*-butyl *N*-[2-(4-nitrophenoxy)ethyl]carbamate (**26b**). The nitro compounds **26a**, **b** were subjected to catalytic hydrogenation in the presence of palladium on charcoal, followed by coupling with 2-pyridylacetic acid to yield compounds **27a**, **b**. Deprotection of the Boc group in **27a**, **b** by treatment with hydrochloric acid followed by coupling with (*R*)-styrene oxide afforded the desired products **28a**, **b**.

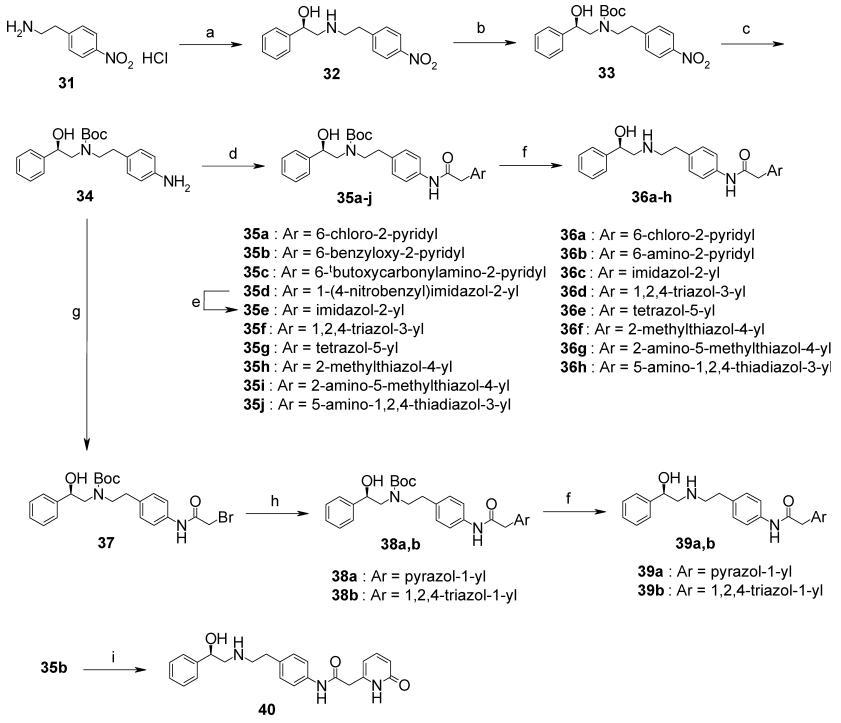
The acetanilides **30a**, **b** were prepared from the corresponding acetanilides **29a**, **b**,[16] as illustrated in Chart 5. Reduction of compounds **29a**, **b** was accomplished by hydrogenation in the presence of Raney-nickel, followed by coupling with (*R*)-styrene oxide to afford the desired products **30a**, **b**.



Reagents and conditions: (a) H_2, Raney-Ni, conc. NH_3 aq., EtOH, THF; (b) (*R*)-styrene oxide, ^{i}PrOH, reflux, and then 4 M HCl–EtOAc, MeOH.

Chart 5

Another process employing the aniline intermediate **34** is illustrated in Chart 6. A commercially available 2-(4-nitrophenyl)ethylamine hydrochloride (**31**) was treated with (*R*)-styrene oxide, followed by protection of the amine with a Boc group to provide nitro compound **33**. Hydrogenation of **33** in the presence of palladium on charcoal gave the aniline intermediate **34**. The coupling of **34** with the appropriate arylacetic acids, followed by deprotection of the Boc group



Reagents and conditions: (a) (*R*)-styrene oxide, ^{i}PrOH, reflux; (b) $(Boc)_2O$, THF; (c) H_2, Pd–C, EtOH; (d) $ArCH_2CO_2H$, EDC·HCl, HOBt, DMF; (e) H_2, Pd–C, HCl, MeOH; (f) 4 M HCl–EtOAc, EtOH; (g) $BrCH_2COBr$, $^{i}Pr_2NEt$, $CHCl_3$; (h) azole, K_2CO_3, MeCN; (i) CF_3CO_2H, tetramethylbenzene, and then 4 M HCl–EtOAc, EtOH.

Chart 6

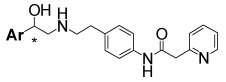
by treatment with hydrochloric acid, afforded the desired products **36a**, **b** and **36d**—**h**. The 4-nitrobenzyl group in 1-(4-nitrobenzyl)imidazol-2-ylacetanilide (**35d**) was removed by hydrogenation in the presence of palladium on charcoal, followed by deprotection of the Boc group to afford imidazol-2-ylacetanilide (**36c**). Meanwhile, the aniline intermediate **34** was coupled with 2-bromoacetyl bromide to yield bromoacetanilide **37**. The treatment of **37** with the appropriate azoles in the presence of potassium carbonate, followed by deprotection of the Boc group afforded the desired products **39a**, **b**. Deprotection of both the benzyl and Boc groups by treatment with trifluoroacetic acid in **35b** afforded the desired product **40**.

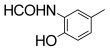
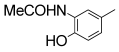
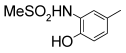
Results and Discussion

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 compound, isoproterenol (ISO; non-selective β-AR agonist), BRL-37344 and CL-316243, are also shown for comparison in Table 1.

Modification of the 4-hydroxyphenoxymethyl moiety on the left-hand side of **1** with several aryl moieties, which converted to phenylethanolamine derivatives, was investigated (Table 1). Initially, replacement of the 4-hydroxyphenoxymethyl of **1** with the 4-hydroxyphenyl group (**5a**) resulted in slightly improved potency at the β3-AR (50% effective concentration (EC_{50})=0.16 μM) with high intrinsic activity (IA=0.80), although there was an extreme decrease in the functional selectivity over both the β1- and β2-ARs. This prompted us to examine further phenylethanolamine analogues possessing 2-pyridylacetanilide in order to improve β3-AR agonistic activity and functional selectivity over β2- and β1-ARs. The β3-AR agonistic activity of the 3-hydroxyphenyl analogue (**5b**) was partial, and relative to **5a** there was no improvement in selectivity over β2- and β1-ARs. Introduction of a formamido group (**8a**) at 3-position of the phenyl ring in **5a** resulted in a dramatic increase in potency at the β2-AR while maintaining β3- and β1-AR agonistic activity, revealing that compound **8a** was a non-selective β-AR agonist. In contrast, introduction of an acetamido group (**8b**) at 3-position of the phenyl ring in **5a** led to a decrease in potency at all β-ARs relative to **5a**. The 4-hydroxy-3-methanesulfonylaminophenyl analogue (**5c**) showed a 20-fold increase in potency at the β3-AR (EC_{50}=0.081 μM) relative to **5a**, but adequate selectivity was not met over β2- and β1-ARs. These results indicated that replacement of the 4-hydroxyphenoxymethyl moiety in **1** with several hydroxyphenyl moieties was tolerable and maintained potency at the β3-AR, but this change may decrease functional selectivity over β2- and β1-ARs. Interestingly, removal of the 4-hydroxyl group (**14a**) in **5a** resulted in a substantial loss of both β2- and β1-AR agonistic activity while maintaining β3-AR agonistic activity (EC_{50}=0.41 μM, IA=0.67). We therefore selected the phenyl derivative (**14a**) as our new leading candidate and examined the modification of its phenyl ring. There was partial agonistic activity of the 4-fluorophenyl (**9b**) and 3-fluorophenyl (**9c**) derivatives at the β3-AR (IA=0.13 and 0.43, respectively), while the 3-chlorophenyl derivative (**9a**), known as a favorable β3-AR agonist chemical moiety and illustrated in Fig. 2, exhibited a considerable decrease in selectivity over β2- and β1-ARs while maintaining the same agonistic activity at the β3-AR (EC_{50}=0.56 μM, IA=0.59) as **14a**. The 3-pyridyl derivative (**9d**) showed a 5-fold decrease in potency at the β3-AR relative to **14a**.

Table 1. β-AR Agonistic Activity of Arylethanolamine Analogues



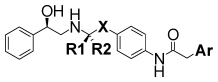
Compound	Ar	*Config.	EC_{50}, μM[a] (IA[b])		
			β3-AR	β2-AR	β1-AR
5a		*R*+*S*	0.16 (0.80)	10 (0.12)	0.81 (0.55)
5b		*R*+*S*	0.39 (0.55)	4.0 (0.43)	2.8 (0.32)
8a		*R*+*S*	0.11 (0.68)	0.32 (1.03)	1.1 (0.94)
8b		*R*+*S*	3.4 (0.38)	16 (0.25)	>100 (0.03)
5c		*R*+*S*	0.081 (0.75)	0.46 (0.63)	15 (0.19)
14a		*R*	0.41 (0.67)	>100 (0.01)	>100 (0.06)
9b		*R*+*S*	0.45 (0.13)	3.2 (0.11)	>100 (0.06)
9c		*R*+*S*	0.41 (0.43)	9.8 (0.42)	11 (0.13)
9a		*R*	0.56 (0.59)	29 (0.27)	3.9 (0.22)
9d		*R*+*S*	2.0 (0.56)	7.2 (0.22)	>100 (0.04)
1			0.29 (0.74)	>100 (0)	2.7 (0.14)
ISO			0.10 (1.00)	0.003 (1.00)	0.012 (1.00)
BRL-37344			0.46 (0.6)	0.36 (0.7)	1.29 (0.5)
CL-316243			4.43 (0.5)	>100 (0.1)	>100 (0)

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.

Next, in order to improve β3-AR agonistic activity while maintaining functional selectivity over β2- and β1-ARs, modification of the central part and the pyridyl moiety in **14a** was examined, as shown in Table 2. Initially, the effects of introducing a methyl group to the central methylene part in **14a** were investigated. Both β-methyl (**20a**) and α-methyl (**20b**) analogues showed respective 2- and 4-fold increases in potency at the β3-AR (EC_{50}=0.20 and 0.10 μM, respectively), but the functional selectivity over both the β1- and β2-ARs was decreased relative to **14a**. A dimethyl group (**23**) was also introduced on the central methylene part in **14a**, which yielded results similar to those of the methyl analogues (**20a**, **b**). These results showed that the introduction of a methyl group on the central methylene part in **14a** can improve potency at the β3-AR, but may not be efficacious for the functional selectivity over β2- and β1-ARs. In contrast, the propylene (**28a**) and ethylenoxy (**28b**) analogues exhibited respective 14- and 7-fold decreases in potency at the β3-AR (EC_{50}=5.9 and 2.8 μM, respectively) with lower selectivity over β2- and β1-ARs when compared to **14a**, which indicated that the ethylene moiety would be a favorable structure as a central part for conferring both potency at the β3-AR and functional selectivity. We then examined the nitrogen position and the substituents on the pyridine ring in **14a**. The 3-pyridyl (**14c**) and 4-pyridyl (**14d**) analogues were less potent at the β3-AR than the 2-pyridyl analogue (**14a**), results similar to those in the 4-hydroxyphenoxypropanolamine derivatives.[16] These results suggested that changing the position of the nitrogen atom on the 2-pyridyl moiety in **14a** would result in both potency at the β3-AR and functional selectivity over β2- and β1-ARs. Meanwhile, introduction of a chloro group at the 6-position on the pyridine ring (**36a**) resulted in a 5.5-fold improved potency at the β3-AR (EC_{50}=0.074 μM) with lower selectivity over β2- and β1-ARs when compared to **14a**, while the 2-pyridon-6-yl analogue (**40**) showed maintained potency at the β3-AR with lower intrinsic activity. Interestingly, the agonistic activity of the 6-amino-2-pyridylacetanilide derivative (**36b**) increased 4-fold at the β3-AR (EC_{50}=0.098 μM, IA=0.83) without agonistic activity at the β2- and β1-ARs. These results showed that introduction of substituents at the 6-position on the pyridine ring in **14a** allowed potency at the β3-AR to be maintained, although this change may affect functional selectivity over β2- and β1-ARs.

Lastly, replacement of the pyridine ring in **14a** with the appropriate nitrogen-containing heteroaromatic rings was investigated as shown in Table 3. The 2-quinolinyl analogue (**30a**) showed a considerable decrease in intrinsic activity at the β3-AR (IA=0.24). Further, although replacement of the pyridine ring in **14a** with a 6-membered basic heteroaromatic ring, such as pyrimidin-2-yl (**30b**) and pyrazin-2-yl (**14b**), maintained potency at the β3-AR (EC_{50}=0.66 and 0.20 μM, respectively), their intrinsic activities were decreased. The 5-membered basic heteroaromatic analogues, such as imidazol-2-yl (**36c**), pyrazol-1-yl (**39a**), 1,2,4-triazol-3-yl (**36d**), 1,2,4-triazol-1-yl (**39b**) and 2-methylthiazol-4-yl (**36f**), also showed a decrease in intrinsic activity at the β3-AR (IA=0.37—0.54). In contrast, the tetrazol-5-yl derivative (**36e**) as

Table 2. β-AR Agonistic Activity of Pyridylacetanilide Derivatives



Compound	R1	R2	X	Ar	EC_{50}, $\mu M^{a)}$ (IA$^{b)}$)		
					β3-AR	β2-AR	β1-AR
14a	H	H	CH_2		0.41 (0.67)	>100 (0.01)	>100 (0.06)
20a	Me	H	CH_2		0.20 (0.79)	0.54 (0.56)	0.62 (0.51)
20b	H	Me	CH_2		0.10 (0.61)	2.6 (0.13)	10 (0.27)
23	Me	Me	CH_2		0.13 (0.55)	0.28 (0.89)	2.5 (0.25)
28a	H	H	$(CH_2)_2$		5.9 (0.58)	2.2 (0.23)	>100 (0.03)
28b	H	H	CH_2O		2.8 (0.32)	3.6 (0.53)	2.7 (0.14)
14c	H	H	CH_2		2.5 (0.26)	4.1 (0.19)	3.7 (0.12)
14d	H	H	CH_2		3.5 (0.18)	150 (0.50)	4.4 (0.20)
36a	H	H	CH_2		0.074 (0.68)	4.9 (0.39)	7.9 (0.74)
40	H	H	CH_2		0.52 (0.40)	>100 (0.03)	5.5 (0.13)
36b	H	H	CH_2		0.098 (0.83)	>100 (0.02)	>100 (0.09)

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.

an acidic heteroaromatic analogue maintained potency and efficacy at the β3-AR (EC_{50}=0.45 μM, IA=0.89) with functional selectivity over β2- and β1-ARs when compared to **14a**. These results suggested that although replacement of the pyridine ring in **14a** with a basic 5- or 6-membered heteroaromatic ring allows potency at β3-AR to be maintained, this change may decrease intrinsic activity at the β3-AR. Since the introduction of an amino group on the pyridine ring in **14a** gave good results (**36b** *vs.* **14a**), we then examined some heteroaromatic rings possessing an amino group. Intrestingly, the 2-amino-5-methylthiazol-4-yl derivative (**36g**) showed a 30-fold increase in potency at the β3-AR (EC_{50}= 0.016 μM, IA=0.76) without agonistic activity at either β2- or β1-ARs when compared to **14a**, and **36g** was the most potent β3-AR agonist in this study. The 5-amino-1,2,4-thiadiazol-3-yl derivative (**36h**) also showed a 10-fold increase in potency at the β3-AR (EC_{50}=0.042 μM, IA=0.63) with agonistic activity completely abolished at both the β2- and β1-ARs when compared to **14a**.

Given the results of the *in vitro* study, compounds **36b**, **36g**, and **36h** were selected for *in vivo* evaluation in a rodent model of type II diabetes (Table 4). The compounds were administered orally for 4 d to diabetic kk mice and the effects on plasma glucose were measured. All compounds induced a significant reduction in plasma glucose levels at a dose of 10 mg/kg.

Conclusion

We identified a new series of phenylethanolamine derivatives containing acetanilides as β3-AR agonists, and described their synthesis and SARs. Among these compounds, the 6-amino-2-pyridylacetanilide (**36b**), 2-amino-5-methylthiazol-4-ylacetanilide (**36g**), and 5-amino-1,2,4-thiadiazol-3-ylacetanilide (**36h**) derivatives showed potent agonistic activity at the β3-AR (EC_{50}=0.098, 0.016, and 0.042 μM, respectively) with agonistic activity completely abolished at both the β1- and β2-ARs. In addition, these compounds exhibited significant hypoglycemic activity in diabetic kk mice.

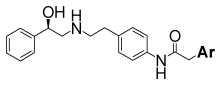
Experimental

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 magnesium sulfate.

4′-(2-Benzylaminoethyl)-2-pyridylacetanilide (3) A mixture of 4′-(2-aminoethyl)-2-pyridyl-acetanilide (**2**) (5.1 g) and benzaldehyde (2.1 ml) in toluene (50 ml) was refluxed for 3 h using a Dean–Stark trap. After cooling to room temperature, the resultant mixture was concentrated *in vacuo*. To the solution of the resultant in methanol (50 ml) was added sodium borohydride (1.0 g) at 0 °C, and the mixture was stirred for 1 h, and then concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (50 : 1) as the eluent to yield **3** (4.6 g) as a yellow solid. 66% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.76—2.80 (2H, m), 2.84—2.89 (2H, m), 3.78 (2H, s), 3.86 (2H, s), 7.14 (2H, d, J=8.4 Hz), 7.20—7.32 (7H, m), 7.46 (2H, d, J=8.0 Hz), 7.67—7.72 (1H, m), 8.61 (1H, d, J=5.2 Hz), 9.72 (1H, s); MS (FAB) m/z: 346 (MH^+).

4′-(2-{*N*-Benzyl-*N*-[2-(4-benzyloxyphenyl)-2-hydroxyethyl]amino}-ethyl)-2-(2-pyridyl)acetanilide (4a) A mixture of **3** (0.34 g), 4-benzyloxyphenacylbromide (0.30 g), and *N*,*N*-diisopropyl-*N*-ethylamine (175 ml)

Table 3. β-AR Agonistic Activity of Phenylethanolamine Derivatives containing Acetanilides



Compound	Ar	EC_{50}, $\mu M^{a)}$ ($IA^{b)}$)		
		β3-AR	β2-AR	β1-AR
14a		0.41 (0.67)	>100 (0.01)	>100 (0.06)
30a		0.56 (0.24)	1.3 (0.28)	4.9 (0.17)
30b		0.66 (0.31)	7.8 (0.12)	>100 (0.01)
14b		0.20 (0.51)	9.1 (0.15)	9.1 (0.22)
36c		0.54 (0.41)	6.8 (0.35)	0.26 (0.23)
39a		0.59 (0.54)	13 (0.11)	150 (0.34)
36d		0.59 (0.37)	>100 (0.09)	>100 (0.02)
39b		1.7 (0.38)	6.6 (0.22)	>100 (0.09)
36e		0.45 (0.89)	>100 (0.08)	>100 (0.05)
36f		0.31 (0.49)	4.0 (0.18)	>100 (0.01)
36g		0.016 (0.76)	>100 (0.04)	>100 (0.06)
36h		0.042 (0.63)	>100 (0.05)	>100 (0.06)

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 4. Oral Hypoglycemic Activity in kk Mice

Compound	Percent reduction in plasma glucose[a)]
36b	37*[b)]
36g	50**
36h	50**

a) The compounds were administered orally to male kk mice for 4 d at a dose of 10 mg/kg. *b*) Statistically significant at $*p<0.05$, $**p<0.01$.

in 2-butanone (20 ml) was refluxed for 3 h. After cooling to room temperature, the precipitate was removed by filtration, and the filtrate was then concentrated *in vacuo*. To the solution of the resultant in methanol (10 ml) was added sodium borohydride (0.12 g) at 0 °C, and the mixture was stirred for 1h, and then concentrated *in vacuo*. The residue was partitioned between chloroform and $NaHCO_3$ aqueous solution, and the organic layer was dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (100 : 1) as the eluent to yield **4a** (0.28 g) as a colorless powder. 50% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.54—2.94 (6H, m), 3.56 (1H, d, J=13.6 Hz), 3.86 (2H, s), 3.95 (1H, d, J=13.6 Hz), 4.57 (1H, dd, J=10.0, 4.0 Hz), 5.04 (2H, s), 6.90—6.94 (2H, m), 7.04—7.08 (2H, m), 7.18—7.48 (16H, m), 7.69 (1H, dt, J=2.0, 8.0 Hz), 8.62 (1H, d, J=4.8 Hz), 9.72 (1H, br s); MS (FAB) m/z: 572 (MH^+).

4′-(2-{*N*-Benzyl-*N*-[2-(3-benzyloxyphenyl)-2-hydroxyethyl]amino}-ethyl)-2-(2-pyridyl)acetanilide (4b) The title compound was prepared in the same manner as described for **4a** using 3-benzyloxyphenacylbromide instead of 4-benzyloxyphenacylbromide as a colorless powder. 53% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.56—2.90 (6H, m), 3.56 (1H, d, J=13.6 Hz), 3.86 (2H, s), 3.97 (1H, d, J=13.6 Hz), 4.60 (1H, dd, J=2.0, 8.0 Hz), 5.04 (2H, s), 6.83—6.90 (2H, m), 6.95—6.98 (1H, m), 7.03—7.08 (2H, m), 7.18—7.48 (15H, m), 7.69 (1H, dt, J=2.0, 8.0 Hz), 8.60—8.63 (1H, m), 9.72 (1H, br s); MS (FAB) m/z: 572 (MH^+).

4′-(2-{*N*-Benzyl-*N*-[2-(4-benzyloxy-3-methanesulfonamidophenyl)-2-hydroxyethyl]amino}ethyl)-2-(2-pyridyl)acetanilide (4c) The title compound was prepared in the same manner as described for **4a** using 4-benzyloxy-3-methanesulfonamidophenacylbromide[20)] instead of 4-benzyloxyphenacylbromide as a colorless powder. 43% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.91 (9H, m), 3.55 (1H, d, J=13.6 Hz), 3.85 (2H, s), 3.94 (1H, d, J=13.6 Hz), 4.56 (1H, dd, J=10.0, 3.6 Hz), 5.08 (2H, s), 6.83 (1H, br s), 6.94 (1H, d J=8.4 Hz), 7.04—7.12 (3H, m), 7.22—7.48 (15H, m), 7.69 (1H, dt, J=2.0, 8.0 Hz), 8.58—8.63 (1H, m), 9.70 (1H, br s); MS (FAB) m/z: 665 (MH^+).

4′-(2-{*N*-Benzyl-*N*-[2-(4-benzyloxy-3-nitrophenyl)-2-hydroxyethyl]-amino}ethyl)-2-(2-pyridyl)acetanilide (4d) The title compound was prepared in the same manner as described for **4a** using 4-benzyloxy-3-nitrophenacylbromide instead of 4-benzyloxyphenacylbromide as a colorless powder. 69% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.48—2.54 (1H, m), 2.64—2.94 (5H, m), 3.57 (1H, d, J=13.2 Hz), 3.75 (1H, br s), 3.86 (2H, s), 3.92 (1H, d, J=13.2 Hz), 4.53 (1H, dd, J=10.8, 3.6 Hz), 5.21 (2H, s), 7.03—7.08 (3H, m), 7.23—7.48 (15H, m), 7.67—7.75 (2H, m), 8.60—8.64 (1H, m), 9.75 (1H, s); MS (FAB) m/z: 617 (MH^+).

4′-(2-{[2-Hydroxy-2-(4-hydroxyphenyl)ethyl]amino}ethyl)-2-(2-pyridyl)acetanilide Hydrochloride (5a) To a solution of **4a** (0.27 g) in methanol (10 ml) was added palladium on carbon (10% w/w, 0.12 g), and the mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. To the solution of the residue in methanol (5 ml) was added 4 M HCl–EtOAc solution (450 ml), and the mixture was concentrated *in vacuo*. The residue was purified by recrystallization from MeOH–EtOH–Et_2O to yield **5a** (0.12 g) as a colorless solid. 60% yield; mp 211—212 °C (MeOH–EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.86—3.12 (6H, m), 3.84 (2H, s), 4.80—4.83 (1H, m), 6.00 (1H, d, J=1.2 Hz), 6.77 (2H, d, J=8.4 Hz), 7.16—7.19 (4H, m), 7.25—7.29 (1H, m), 7.39 (1H, d, J=8.0 Hz), 7.57 (2H, d, J=8.4 Hz), 7.73—7.78 (1H, m), 8.49 (1H, d, J=4.8 Hz), 8.71 (1H, br s), 8.91 (1H, br s), 9.46 (1H, s), 10.29 (1H, s); MS (FAB) m/z: 392 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_3\cdot HCl\cdot 0.5H_2O$: C, 63.22; H, 6.23; N, 9.62; Cl, 8.11. Found: C, 63.26; H, 6.04; N, 9.55; Cl, 7.87.

4′-(2-{[2-Hydroxy-2-(3-hydroxyphenyl)ethyl]amino}ethyl)-2-(2-pyridyl)acetanilide Hydrochloride (5b) The title compound was prepared in the same manner as described for **5a** using **4b** instead of **4a** as a colorless powder. 45% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.84—3.03 (3H, m), 3.06—3.20 (3H, m), 3.84 (2H, s), 4.80—4.89 (1H, m), 6.12 (1H, d, J=3.6 Hz), 6.70 (2H, dd, J=2.0, 8.0 Hz), 6.76—6.83 (2H, m), 7.13—7.20 (3H, m), 7.24—7.30 (1H, m), 7.39 (1H, d, J=8.0 Hz), 7.56—7.60 (2H, m), 7.76 (1H, dt, J=1.6, 7.2 Hz), 8.47—8.52 (1H, m), 8.72 (1H, br s), 8.92 (1H, br s), 9.49 (1H, br s), 10.28 (1H, br s); MS (FAB) m/z: 392 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_3\cdot 1.2HCl\cdot H_2O$: C, 60.95; H, 6.27; N, 9.27; Cl, 9.39. Found: C, 61.21; H, 6.08; N, 9.07; Cl, 9.21.

4′-(2-{[2-Hydroxy-2-(4-hydroxy-3-methylsulfonamidophenyl)-ethyl]amino}ethyl)-2-(2-pyridyl)acetanilide Hydrochloride (5c) The title compound was prepared in the same manner as described for **5a** using **4c** instead of **4a** as a colorless solid. 42% yield; mp 191—192 °C (MeOH–EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.84—3.01 (6H, m), 3.05—3.17 (3H, m), 3.84 (2H, s), 4.78—4.88 (1H, m), 6.05 (1H, br s), 6.92 (1H, d, J=8.0 Hz), 7.06 (1H, dd, J=2.0, 8.4 Hz), 7.14—7.29 (4H, m), 7.39 (1H, d, J=8.0 Hz), 7.54—7.60 (2H, m), 7.75 (1H, dt, J=2.0, 8.0 Hz), 8.47—8.51 (1H, m), 10.03 (1H, br s); MS (FAB) m/z: 485 (MH^+); *Anal.* Calcd for $C_{24}H_{28}N_4O_5S\cdot HCl\cdot 0.7H_2O$: C, 54.02; H, 5.74; N, 10.50; S, 6.01; Cl, 6.64. Found: C, 54.08; H, 5.66; N, 10.47; S, 6.12; Cl, 6.61.

4′-(2-{*N*-Benzyl-*N*-[2-(3-amino-4-benzyloxyphenyl)-2-hydroxyethyl]-amino}ethyl)-2-(2-pyridyl)acetanilide (6) To a solution of **4d** (1.83 g) in methanol (40 ml) were added 2.5 M HCl aqueous solution (2 ml) and iron powder (1.6 g), and the mixture was refluxed for 8 h. After cooling to room temperature, the resultant mixture was concentrated *in vacuo*. The residue was partitioned between chloroform and 1 M NaOH aqueous solution, and the precipitate was removed by filtration. 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 **6** (1.31 g) as a colorless powder. 75% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.59—2.88 (6H, m), 3.56 (1H, d, J=13.2 Hz), 3.67 (1H, br s), 3.81 (2H, br s), 3.86 (2H, s), 3.94 (1H, d, J=13.2 Hz), 4.49—4.52 (1H, m), 5.05 (2H, s), 6.59—6.79 (3H, m), 7.05—7.07 (2H, m), 7.23—7.46 (14H, m), 7.67—7.71 (1H, m), 8.61—8.62 (1H, m), 9.71 (1H, br s); MS (FAB) m/z: 587 (MH^+).

4′-(2-{*N*-Benzyl-*N*-[2-(4-benzyloxy-3-formamidophenyl)-2-hydroxy-

ethyl]amino}ethyl)-2-(2-pyridyl)acetanilide (7a) To a solution of **6** (0.67 g) in chloroform (10 ml) was added the mixture of formic acid and acetic anhydride (3 : 5, 1.0 ml), and the mixture was stirred at room temperature for 7 h, and the resulting mixture was then concentrated *in vacuo*. To the solution of the residue in methanol (15 ml) and water (1 ml) was added sodium carbonate (0.49 g), and the mixture was stirred at room temperature for 2 h. The precipitate was removed by filtration, and the filtrate was then concentrated *in vacuo*. The residue was partitioned between chloroform and water, and 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 (50 : 1) as the eluent to yield **7a** (0.59 g) as a colorless powder. 84% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.53—2.88 (6H, m), 3.55 (1H, d, J=13.6 Hz), 3.75 (1H, br s), 3.86 (2H, s), 3.94 (1H, d, J=13.6 Hz), 4.59—4.62 (1H, m), 5.06—5.08 (2H, m), 6.89—7.22 (5H, m), 7.23—7.48 (14H, m), 7.67—7.71 (1H, m), 7.78—8.72 (3H, m), 9.68—9.73 (1H, m); MS (FAB) *m/z*: 615 (MH^+).

4′-(2-{*N*-[2-(3-Acetamido-4-benzyloxyphenyl)-2-hydroxyethyl]-*N*-benzyl-amino}ethyl)-2-(2-pyridyl)acetanilide (7b) The title compound was prepared in the same manner as described for **7a** using acetic anhydride instead of the mixture of formic acid and acetic anhydride as a colorless powder. 83% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.58—2.87 (6H, m), 3.54 (1H, d, J=13.2 Hz), 3.74 (1H, br s), 3.86 (2H, s), 3.94 (1H, d, J=13.2 Hz), 4.56—4.64 (1H, m), 5.10 (2H, s), 6.90 (1H, d, J=8.4 Hz), 7.02—7.07 (3H, m), 7.22—7.46 (12H, m), 7.65—8.77 (2H, m), 8.28—8.32 (1H, m), 8.60—8.65 (1H, m), 9.69 (1H, s); MS (FAB) *m/z*: 629 (MH^+).

4′-(2-{[2-(3-Formamido-4-hydroxyphenyl)-2-hydroxyethyl]amino}-ethyl)-2-(2-pyridyl)acetanilide Hydrochloride (8a) The title compound was prepared in the same manner as described for **5a** using **7a** instead of **4a** as a colorless solid. 13% yield; mp 217—219 °C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.80—3.00 (3H, m), 3.00—3.20 (3H, m), 4.02 (2H, s), 4.83 (1H, d, J=8.0 Hz), 6.05 (1H, br s), 6.88—6.95 (2H, m), 7.14—7.20 (2H, m), 7.51—7.65 (4H, m), 8.05 (1H, t, J=7.2 Hz), 8.14—8.29 (2H, m), 8.64 (1H, d, J=4.8 Hz), 8.74 (1H, br s), 9.04 (1H, br s), 9.61 (1H, s), 10.12 (1H, s), 10.47 (1H, br s); MS (FAB) *m/z*: 435 (MH^+); *Anal.* Calcd for $C_{24}H_{26}N_4O_4 \cdot 1.5HCl \cdot 1.5H_2O$: C, 55.84; H, 5.96; N, 10.85; Cl, 10.30. Found: C, 55.70; H, 5.62; N, 10.86; Cl, 10.17.

4′-(2-{[2-(3-Acetamido-4-hydroxyphenyl)-2-hydroxyethyl]amino}-ethyl)-2-(2-pyridyl)acetanilide Hydrochloride (8b) The title compound was prepared in the same manner as described for **5a** using **7b** instead of **4a** as a colorless solid. 19% yield; mp 216—222 °C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.10 (3H, s), 2.87—3.02 (3H, m), 3.02—3.20 (3H, m), 3.83 (2H, s), 4.75—4.83 (1H, m), 6.05 (1H, d, J=3.6 Hz), 6.86 (1H, d, J=8.4 Hz), 6.94—6.96 (1H, m), 7.17 (2H, d, J=8.8 Hz), 7.26—7.29 (1H, m), 7.39 (1H, d, J=8.0 Hz), 7.57 (2H, d, J=8.8 Hz), 7.76 (1H, dt, J=8.0, 4.0 Hz), 7.81—7.84 (1H, m), 8.50 (1H, d, J=4.0 Hz), 8.66 (1H, br s), 8.79 (1H, br s), 9.31 (1H, s), 9.86 (1H, s), 10.26 (1H, br s); MS (FAB) *m/z*: 449 (MH^+); *Anal.* Calcd for $C_{25}H_{28}N_4O_4 \cdot 1.1HCl \cdot 0.5H_2O$: C, 60.34; H, 6.10; N, 11.26; Cl, 7.84. Found: C, 60.18; H, 6.06; N, 11.23; Cl, 7.99.

(*R*)-4′-(2-{[2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-2-(2-pyridyl)acetanilide Hydrochloride (9a) A mixture of **2** (1.0 g) and (*R*)-3-chlorostyrene oxide (0.59 g) in ethanol (20 ml) was refluxed for 12 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 (30 : 1) as the eluent to yield the free base product (0.66 g). To the solution of free base product in ethanol (5 ml) was added 4 M HCl–EtOAc solution (400 ml), and the mixture was concentrated *in vacuo*. The residue was purified by recrystallization from MeOH–EtOH to yield **9a** (0.33 g) as a colorless solid. 18% yield; mp 221—222 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.25 (6H, m), 3.85 (2H, s), 4.92—5.08 (1H, m), 6.35 (1H, d, J=3.6 Hz), 7.14—7.23 (2H, m), 7.23—7.31 (1H, m), 7.33—7.50 (5H, m), 7.54—7.64 (2H, m), 7.76 (1H, dt, J=1.6, 7.6 Hz), 8.43—8.55 (1H, m), 8.80—9.40 (2H, m), 10.36 (1H, br s); MS (FAB) *m/z*: 410 (MH^+); *Anal.* Calcd for $C_{23}H_{24}N_3O_2Cl \cdot HCl$: C, 61.89; H, 5.65; N, 9.41; Cl, 15.88. Found: C, 61.81; H, 5.58; N, 9.38; Cl, 15.58.

4′-(2-{[2-(4-Fluorophenyl)-2-hydroxyethyl]amino}ethyl)-2-(2-pyridyl)-acetanilide Hydrochloride (9b) The title compound was prepared in the same manner as described for **9a** using 4-fluorostyrene oxide instead of (*R*)-3-chlorostyrene oxide as a colorless solid. 18% yield; mp 223—225 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.88—3.06 (3H, m), 3.10—3.20 (3H, m), 3.84 (2H, s), 4.94—5.01 (1H, m), 6.24 (1H, d, J=4.0 Hz), 7.16—7.30 (5H, m), 7.38—7.46 (3H, m), 7.58 (2H, d, J=8.8 Hz), 7.76 (1H, dt, J=1.6, 7.6 Hz), 8.50 (2H, d, J=8.8 Hz), 8.83 (1H, s), 9.08 (1H, s), 10.31 (1H, s); MS (FAB) *m/z*: 394 (MH^+); *Anal.* Calcd for $C_{23}H_{24}N_3O_2F \cdot HCl$: C, 64.26; H, 5.86; N, 9.77; Cl, 8.25; F, 4.42. Found: C, 64.12; H, 5.90; N, 9.73; Cl, 8.36; F, 4.25.

4′-(2-{[2-(3-Fluorophenyl)-2-hydroxyethyl]amino}ethyl)-2-(2-pyridyl)-acetanilide Hydrochloride (9c) The title compound was prepared in the same manner as described for **9a** using 3-fluorostyrene oxide instead of (*R*)-3-chlorostyrene oxide as a colorless solid. 11% yield; mp 214—215 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.88—3.25 (6H, m), 3.85 (2H, s), 4.96—5.02 (1H, m), 6.33 (1H, d, J=3.8 Hz), 7.12—7.31 (6H, m), 7.39—7.48 (2H, m), 7.58 (2H, d, J=8.3 Hz), 7.74—7.80 (1H, m), 8.50 (1H, s), 8.82 (1H, s), 9.01 (1H, s), 10.30 (1H, s); MS (FAB) *m/z*: 394 (MH^+); *Anal.* Calcd for $C_{23}H_{24}N_3O_2F \cdot 1.5HCl \cdot 0.8H_2O$: C, 59.72; H, 5.90; N, 9.08; Cl, 11.50; F, 4.11. Found: C, 59.58; H, 5.62; N, 9.10; Cl, 11.75; F, 4.06.

4′-(2-{[2-Hydroxy-2-(3-pyridyl)ethyl]amino}ethyl)-2-(2-pyridyl)-acetanilide Hydrochloride (9d) The title compound was prepared in the same manner as described for **9a** using 2-(3-pyridyl)oxirane[21] instead of (*R*)-3-chlorostyrene oxide as a colorless solid. 20% yield; mp 204—205 °C (MeOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.85—3.28 (6H, m), 3.85 (2H, s), 5.02—5.14 (1H, m), 6.37 (1H, d, J=4.0 Hz), 7.14—7.32 (3H, m), 7.36—7.46 (2H, m), 7.55—7.64 (2H, m), 7.70—7.86 (2H, m), 8.46—8.56 (2H, m), 8.57—8.65 (1H, m), 9.13 (2H, br s), 10.37 (1H, br s); MS (FAB) *m/z*: 377 (MH^+); *Anal.* Calcd for $C_{22}H_{24}N_4O_2 \cdot HCl$: C, 63.99; H, 6.10; N, 13.57; Cl, 8.59. Found: C, 63.76; H, 5.90; N, 13.68; Cl, 8.46.

(*R*)-2-{*N*-Benzyl-*N*-[2-(4-nitrophenyl)ethyl]amino}-1-phenylethanol (11) A mixture of *N*-benzyl-2-(4-nitrophenyl)ethylamine (**10**) (11.96 g) and (*R*)-styrene oxide (7.21 g) in 2-propanol (80 ml) was refluxed for 20 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 (10 : 1) as the eluent to yield **11** (13.48 g) as a colorless powder. 76% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.63—2.99 (6H, m), 3.53—3.62 (1H, m), 3.57 (1H, d, J=13.2 Hz), 3.95 (1H, d, J=13.2 Hz), 4.65—4.70 (1H, m), 7.20—7.37 (7H, m), 8.09—8.12 (2H, m); MS (FAB) *m/z*: 377 (MH^+).

(*R*)-2-{*N*-[2-(4-Aminophenyl)ethyl]-*N*-benzylamino}-1-phenylethanol (12) The title compound was prepared in the same manner as described for **6** using **11** instead of **4d** as a colorless powder. 93% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.56—2.94 (6H, m), 3.40—3.65 (2H, m), 3.80 (1H, br s), 3.95 (1H, d, J=13.6 Hz), 4.62 (1H, dd, J=3.2, 10.0 Hz), 6.57—6.66 (2H, m), 6.87—6.98 (2H, m), 7.20—7.37 (10H, m); MS (FAB) *m/z*: 347 (MH^+).

(*R*)-4′-{2-[*N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)amino]ethyl}-2-(2-pyridyl)acetanilide (13a) A mixture of **12** (4.00 g) and methyl 2-pyridylacetate (1.90 g) in xylene (40 ml) was refluxed for 19 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 (1 : 3) as the eluent to yield **13a** (2.47 g) as a colorless powder. 45% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.54—2.98 (6H, m), 3.50—4.02 (5H, m), 3.80 (1H, br s), 4.62 (1H, dd, J=3.6, 10.0 Hz), 6.80—7.70 (17H, m), 8.60 (1H, d, J=5.6 Hz), 9.73 (1H, br s); MS (FAB) *m/z*: 466 (MH^+).

(*R*)-4′-{2-[*N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)amino]ethyl}-2-(pyrazin-2-yl)acetanilide (13b) The title compound was prepared in the same manner as described for **13a** using methyl 2-pyrazinylacetate instead of methyl 2-pyridylacetate as a colorless powder. 55% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.54—3.00 (6H, m), 3.57 (1H, d, J=13.6 Hz), 3.89 (2H, s), 3.95 (1H, d, J=13.6 Hz), 4.61 (1H, dd, J=3.6, 10.0 Hz), 7.00—7.50 (14H, m), 8.45—8.70 (3H, m), 8.91 (1H, br s); MS (FAB) *m/z*: 467 (MH^+).

(*R*)-4′-{2-[*N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)amino]ethyl}-2-(3-pyridyl)acetanilide (13c) To a solution of **12** (0.43 g) and 3-pyridylacetic acid hydrochloride (0.26 g) in tetrahydrofuran (5 ml) and *N*,*N*-dimethylformamide (2 ml) were added 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride (0.24 g) and 1-hydroxybenzotriazole (0.17 g), and the mixture was stirred at room temperature for 5 h. The resulting mixture was concentrated *in vacuo* and diluted with ethyl acetate. The organic layer was washed with $NaHCO_3$ aqueous solution, and then dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (100 : 1) as the eluent to yield **13b** (0.25 g) as a colorless powder. 43% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.54—2.98 (6H, m), 3.50—3.74 (3H, m), 3.96 (1H, d, J=13.6 Hz), 4.59 (1H, dd, J=3.6, 10.0 Hz), 7.00—7.80 (16H, m), 8.50—8.62 (2H, m); MS (FAB) *m/z*: 466 (MH^+).

(*R*)-4′-{2-[*N*-Benzyl-*N*-(2-hydroxy-2-phenylethyl)amino]ethyl}-2-(4-pyridyl)acetanilide (13d) The title compound was prepared in the same manner as described for **13c** using 4-pyridylacetic acid instead of 3-pyridylacetic acid as a colorless powder. 35% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.54—3.02 (6H, m), 3.50—3.75 (3H, m), 3.96 (1H, d, J=13.6 Hz), 4.59 (1H, dd, J=4.0, 10.0 Hz), 7.00—7.60 (16H, m), 8.55—8.65 (2H, m); MS (FAB) *m/z*: 466 (MH^+).

(*R*)-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethyl}-2-(2-pyridyl)ac-

etanilide Hydrochloride (14a) The title compound was prepared in the same manner as described for **5a** using **13a** instead of **4a** as a colorless solid. 62% yield; mp 223—224 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.86—3.22 (6H, m), 3.49 (2H, s), 4.93—5.03 (1H, m), 6.20 (1H, d, J=4.0 Hz), 7.15—7.43 (9H, m), 7.55—7.62 (2H, m), 7.75 (1H, dt, J=1.6, 8.0 Hz), 8.45—8.53 (1H, m), 8.06—9.50 (2H, m), 10.35 (1H, br s); MS (FAB) m/z: 376 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_2 \cdot HCl$: C, 67.06; H, 6.36; N, 10.20; Cl, 8.61. Found: C, 67.10; H, 6.55; N, 10.15; Cl, 8.53.

(*R*)-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethyl}-2-(pyrazin-2-yl)acetanilide Hydrochloride (14b) The title compound was prepared in the same manner as described for **5a** using **13b** instead of **4a** as a colorless solid. 28% yield; mp 236—238 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.86—3.24 (6H, m), 3.95 (2H, s), 4.91—5.01 (1H, m), 5.44 (2H, s), 6.19 (1H, d, J=4.4 Hz), 7.15—7.22 (2H, m), 7.27—7.43 (5H, m), 7.52—7.62 (2H, m), 8.50—8.69 (3H, m), 8.83 (1H, br s), 9.12 (1H, br s), 10.41 (1H, br s); MS (FAB) m/z: 377 (MH^+); *Anal.* Calcd for $C_{22}H_{24}N_4O_2 \cdot HCl$: C, 63.99; H, 6.10; N, 13.57; Cl, 8.59. Found: C, 63.85; H, 6.11; N, 13.54; Cl, 8.63.

(*R*)-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethyl}-2-(3-pyridyl)acetanilide Hydrochloride (14c) The title compound was prepared in the same manner as described for **5a** using **13c** instead of **4a** as a colorless solid. 52% yield; mp 236—238 °C (MeOH–EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.86—3.23 (6H, m), 3.72 (2H, s), 4.91—5.02 (1H, m), 6.20 (1H, d, J=4.0 Hz), 7.15—7.22 (2H, m), 7.27—7.45 (6H, m), 7.53—7.62 (2H, m), 7.73—7.82 (1H, m), 8.40—8.60 (2H, m), 8.84 (1H, br s), 9.16 (1H, br s), 10.35—10.50 (1H, m); MS (FAB) m/z: 376 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_2 \cdot 1.05HCl \cdot 0.3H_2O$: C, 65.91; H, 6.41; N, 10.03; Cl, 8.88. Found: C, 65.86; H, 6.40; N, 10.11; Cl, 8.84.

(*R*)-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethyl}-2-(4-pyridyl)acetanilide Hydrochloride (14d) The title compound was prepared in the same manner as described for **5a** using **13d** instead of **4a** as a colorless solid. 66% yield; mp 195—198 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.86—3.22 (6H, m), 3.73 (2H, s), 4.93—5.04 (1H, m), 6.15—6.25 (1H, m), 7.14—7.22 (2H, m), 7.28—7.43 (7H, m), 7.54—7.63 (2H, m), 8.47—8.53 (2H, m), 9.07 (2H, br s), 10.50 (1H, br s); MS (FAB) m/z: 376 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_2 \cdot 1.25HCl \cdot 0.8H_2O$: C, 63.44; H, 6.45; N, 9.65; Cl, 10.18. Found: C, 63.33; H, 6.36; N, 9.68; Cl, 10.11.

***N*-Benzyl-*N*-[1-(4-nitrophenyl)-2-propyl]amine (16)** A mixture of 4-nitrophenylacetone (**15**) (5.22 g) and benzylamine (3.43 g) in toluene (50 ml) was refluxed for 2 h using a Dean–Stark trap. After cooling to room temperature, the resultant mixture was concentrated *in vacuo*. To the solution of the resultant in methanol (100 ml) and tetrahydrofuran (30 ml) was added sodium borohydride (1.52 g) at 0 °C, and the mixture was stirred for 2 h at room temperature, and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, and the organic layer was dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (100 : 1) as the eluent to yield **16** (5.35 g) as a yellow solid. 67% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=6.4 Hz), 2.73 (1H, dd, J=6.4, 13.2 Hz), 2.89 (2H, dd, J=6.8, 13.2 Hz), 2.95—3.06 (1H, m), 3.76 (1H, d, J=13.2 Hz), 3.86 (1H, d, J=13.2 Hz), 7.16—7.40 (7H, m), 8.01—8.22 (2H, m); MS (FAB) m/z: 271 (MH^+).

2-{(2*R*)- and (2*S*)-*N*-Benzyl-*N*-[1-(4-nitrophenyl)-2-propyl]amino}-(1*R*)-1-phenylethanol (17a, 17b) A mixture of **16** (2.02 g) and (*R*)-styrene oxide (1.01 g) was heated at 150 °C for 5 h. After cooling to room temperature, the resultant was purified using column chromatography on silica gel with *n*-hexane/EtOAc (10 : 1) as the eluent to yield **17a** (0.87 g) as a yellow oil and **17b** (0.75 g) as a yellow solid.

17a: 29% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=6.4 Hz), 2.50—2.75 (3H, m), 2.88 (1H, dd, J=8.8, 13.6 Hz), 3.15—3.30 (1H, m), 3.51 (1H, d, J=13.2 Hz), 3.88 (1H, d, J=13.2 Hz), 4.62 (1H, dd, J=4.0, 10.4 Hz), 6.80—7.60 (12H, m), 8.00—8.15 (2H, m); MS (FAB) m/z: 391 (MH^+).

17b: 25% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, J=6.4 Hz), 2.47 (1H, dd, J=10.4, 14.4 Hz), 2.62—2.85 (2H, m), 3.03—3.18 (2H, m), 3.62 (1H, br s), 3.75 (1H, d, J=13.2 Hz), 3.89 (1H, d, J=13.2 Hz), 4.51 (1H, dd, J=3.2, 9.6 Hz), 7.14—7.44 (12H, m), 8.05—8.20 (2H, m); MS (FAB) m/z: 391 (MH^+).

2-{(2*R*)-*N*-Benzyl-*N*-[1-(4-aminophenyl)-2-propyl]amino}-(1*R*)-1-phenylethanol (18a) The title compound was prepared in the same manner as described for **6** using **17a** instead of **4d** as a colorless powder. 67% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, J=6.8 Hz), 2.45—2.77 (4H, m), 3.13—3.18 (1H, m), 3.40—3.78 (4H, m), 3.91 (1H, d, J=13.6 Hz), 4.56 (1H, dd, J=3.6, 10.4 Hz), 6.55—6.68 (2H, m), 6.80—6.93 (2H, m), 7.13—7.40 (10H, m); MS (FAB) m/z: 361 (MH^+).

2-{(2*S*)-*N*-Benzyl-*N*-[1-(4-aminophenyl)-2-propyl]amino}-(1*R*)-1-phenylethanol (18b) The title compound was prepared in the same manner as described for **6** using **17b** instead of **4d** as a colorless powder. 37% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J=6.8 Hz), 2.27 (1H, dd, J=9.6, 13.2 Hz), 2.62 (1H, dd, J=10.4, 13.2 Hz), 2.75 (1H, dd, J=4.0, 13.2 Hz), 3.30—4.10 (5H, m), 4.42 (1H, dd, J=4.0, 10.0 Hz), 6.55—6.68 (2H, m), 6.83—6.95 (2H, m), 7.20—7.40 (10H, m); MS (FAB) m/z: 361 (MH^+).

4′-{2-(2*R*)-[*N*-Benzyl-*N*-((2*R*)-2-hydroxy-2-phenylethyl)amino]-propyl}-2-(2-pyridyl)acetanilide (19a) The title compound was prepared in the same manner as described for **13a** using **18a** instead of **12** as a colorless powder. 40% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, J=6.8 Hz), 2.54—2.65 (3H, m), 2.70—2.82 (1H, m), 3.08—3.20 (1H, m), 3.44—3.98 (5H, m), 4.55 (1H, dd, J=3.6, 10.4 Hz), 6.80—7.60 (16H, m), 7.64—7.74 (1H, m), 8.50—8.70 (1H, m), 9.72 (1H, br s); MS (FAB) m/z: 480 (MH^+).

4′-{2-(2*S*)-[*N*-Benzyl-*N*-((2*R*)-2-hydroxy-2-phenylethyl)amino]-propyl}-2-(2-pyridyl)acetanilide (19b) The title compound was prepared in the same manner as described for **13a** using **18b** instead of **12** as a colorless powder. 51% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=6.8 Hz), 2.32 (1H, dd, J=8.8, 12.8 Hz), 2.63 (1H, dd, J=10.4, 13.2 Hz), 2.75 (1H, dd, J=3.6, 13.2 Hz), 2.95—3.10 (2H, m), 3.70—3.92 (4H, m), 4.44 (1H, dd, J=3.6, 9.6 Hz), 7.00—7.06 (2H, m), 7.16—7.38 (11H, m), 7.62—7.72 (2H, m), 8.61 (1H, d, J=4.4 Hz), 9.74 (1H, br s); MS (FAB) m/z: 480 (MH^+).

4′-{2-(2*R*)-[((2*R*)-2-Hydroxy-2-phenylethyl)amino]propyl}-2-(2-pyridyl)acetanilide Hydrochloride (20a) The title compound was prepared in the same manner as described for **5a** using **19a** instead of **4a** as a colorless powder. 40% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, d, J=6.4 Hz), 2.50—2.65 (2H, m), 2.90—3.15 (3H, m), 3.83 (2H, s), 4.80—4.94 (1H, m), 7.10—7.18 (2H, m), 7.23—7.45 (7H, m), 7.52—7.60 (2H, m), 7.71—7.80 (1H, m), 8.41—8.52 (1H, m), 10.25 (1H, br s); MS (FAB) m/z: 390 (MH^+); *Anal.* Calcd for $C_{24}H_{27}N_3O_2 \cdot 0.7HCl \cdot 0.8H_2O$: C, 67.13; H, 6.88; N, 9.79; Cl, 5.78. Found: C, 67.02; H, 7.08; N, 9.65; Cl, 5.98.

4′-{2-(2*S*)-[((2*R*)-2-Hydroxy-2-phenylethyl)amino]propyl}-2-(2-pyridyl)acetanilide Hydrochloride (20b) The title compound was prepared in the same manner as described for **5a** using **19b** instead of **4a** as a colorless solid. 52% yield; mp 203—204 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, d, J=6.4 Hz), 2.55—2.64 (1H, m), 3.00—3.50 (4H, m), 3.84 (2H, s), 4.92—5.02 (1H, m), 6.20 (1H, d, J=4.0 Hz), 7.13—7.20 (2H, m), 7.24—7.46 (7H, m), 7.54—7.60 (2H, m), 7.73—7.80 (1H, m), 8.51 (1H, br s), 8.67 (1H, br s), 9.13 (1H, br s), 10.31 (1H, br s); MS (FAB) m/z: 390 (MH^+); *Anal.* Calcd for $C_{24}H_{27}N_3O_2 \cdot HCl \cdot 0.1H_2O$: C, 67.39; H, 6.64; N, 9.82; Cl, 8.29. Found: C, 67.21; H, 6.58; N, 9.74; Cl, 8.34.

***tert*-Butyl *N*-[2-Methyl-1-(4-{[2-(2-pyridyl)acetyl]amino}phenyl)-2-propyl]carbamate (22)** To a solution of *tert*-butyl *N*-[2-methyl-1-(4-nitrophenyl)-2-propyl]carbamate (**21**)[19] (0.83 g) in ethanol (5 ml) and tetrahydrofuran (5 ml) was added palladium on carbon (10% w/w, 0.32 g), and the mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. To the solution of the resultant and 2-pyridylacetic acid hydrochloride (0.49 g) in tetrahydrofuran (10 ml) were added 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride (0.54 g) and 1-hydroxybenzotriazole (0.38 g), and the mixture was stirred at room temperature for 9 h, and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and $NaHCO_3$ aqueous solution, and the organic layer was dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (100 : 1) as the eluent to yield **22** (0.51 g) as colorless oil. 47% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, s), 1.46 (9H, s), 2.93 (2H, s), 3.87 (2H, s), 4.24 (1H, br s), 7.05—7.13 (2H, m), 7.18—7.33 (2H, m), 7.42—7.50 (2H, m), 7.66—7.73 (1H, m), 8.58—8.66 (1H, m), 9.73 (1H, br s); MS (FAB) m/z: 384 (MH^+).

(*R*)-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]-2-methylpropyl}-2-(2-pyridyl)acetanilide Hydrochloride (23) To a solution of **22** (0.49 g) in methanol (10 ml) was added 4 M HCl–EtOAc solution (30 ml), and the mixture was stirred at room temperature for 8 h. The resulting mixture was concentrated *in vacuo* and diluted with K_2CO_3 aqueous solution, and then extracted with chloroform–tetrahydrofuran. The organic layer was dried and concentrated *in vacuo*. To the solution of the resultant in 2-propanol (2 ml) and methanol (2 ml) was added (*R*)-styrene oxide (0.12 g), and the mixture was refluxed for 24 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 (30 : 1—5 : 1) as the eluent. To the solution of the resultant in methanol (5 ml) was added 4 M HCl–EtOAc solution (0.1 ml), and the mixture was concentrated *in vacuo*. The residue was purified using column chromatography on octadecylsilyl (ODS) silica gel with 50% MeOHaq. as the eluent to yield **23** (0.04 g) as colorless powder. 7% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.21 (6H, s), 2.85—3.23 (4H, m),

3.89 (2H, s), 4.90—5.00 (1H, m), 6.21 (1H, br s), 7.11—7.19 (2H, m), 7.28—7.50 (7H, m), 7.53—7.62 (2H, m), 7.78—7.90 (1H, m), 8.45—8.60 (2H, m), 9.00—9.10 (1H, m), 10.35 (1H, br s); MS (FAB) *m/z*: 404 (MH^+); *Anal.* Calcd for $C_{25}H_{29}N_3O_2 \cdot 1.3HCl \cdot 1.7H_2O$: C, 62.36; H, 7.05; N, 8.73; Cl, 9.57. Found: C, 62.37; H, 6.98; N, 9.45; Cl, 9.92.

***tert*-Butyl *N*-[3-(4-Nitrophenyl)propyl]carbamate (26a)** To a solution of 4-(4-nitrophenyl)-butyric acid (**24**) (5.32 g) in toluene (50 ml) were added diphenyl phosphoryl azide (7.00 g) and triethylamine (6.32 g), and the mixture was refluxed for 1 h. To the mixture was added *tert*-butanol (2.5 g), and the mixture was stirred at room temperature for 12 h, and then concentrated *in vacuo*. To the resultant was added *tert*-butanol (10 g), and the mixture was refluxed for 30 min. After cooling to room temperature, the resultant was concentrated *in vacuo* and diluted with ethyl acetate. The organic layer was washed with water, $NaHCO_3$ aqueous solution, and brine, and then dried and concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with *n*-hexane/EtOAc (5 : 1—2 : 1) as the eluent to yield **26a** (3.52 g) as a colorless solid. 49% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.42 (9H, s), 1.81—1.88 (2H, m), 2.73—2.77 (2H, m), 3.14—3.20 (2H, m), 4.58 (1H, br s), 7.34 (2H, d, J=8.0 Hz), 8.14 (2H, d, J=8.4 Hz); MS (FAB) *m/z*: 281 (MH^+).

***tert*-Butyl *N*-[2-(4-Nitrophenoxy)ethyl]carbamate (26b)** To a solution of 2-aminoethanol (3.25 g) in tetrahydrofuran (100 ml) was added sodium hydride (65% w/w, 2.00 g), and the mixture was stirred at room temperature for 30 min. To the mixture was added a solution of 4-fluoronitrobenzene (**25**) (5.00 g) in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 2 h. After that, to the mixture was added di-*tert*-butyl dicarbonate (12.00 g), and the mixture was stirred at room temperature for 9 h, and then concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with *n*-hexane/EtOAc (10 : 1) as the eluent to yield **26b** (6.92 g) as a colorless powder. 69% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.54—3.60 (2H, m), 4.12 (2H, t, J=5.1 Hz), 4.95 (1H, br s), 6.93—6.99 (2H, m), 8.18—8.24 (2H, m); MS (FAB) *m/z*: 283 (MH^+).

***tert*-Butyl *N*-[3-(4-{[2-(2-Pyridyl)acetyl]amino}phenyl)propyl]carbamate (27a)** The title compound was prepared in the same manner as described for **22** using **26a** instead of **21** as a colorless powder. 54% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.70—1.82 (2H, m), 2.59 (2H, t, J=8.0 Hz), 3.04—3.20 (2H, m), 3.86 (2H, s), 4.52 (1H, br s), 7.05—7.15 (2H, m), 7.20—7.33 (2H, m), 7.40—7.50 (2H, m), 7.69 (1H, dt, J=2.0, 8.0 Hz), 8.55—8.65 (1H, m), 9.70 (1H, br s); MS (FAB) *m/z*: 370 (MH^+).

***tert*-Butyl *N*-[2-(4-{[2-(2-Pyridyl)acetyl]amino}phenoxy)ethyl]carbamate (27b)** The title compound was prepared in the same manner as described for **22** using **26b** instead of **21** as a colorless powder. 42% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 3.42—3.60 (2H, m), 3.86 (2H, s), 3.98 (2H, t, J=5.2 Hz), 5.00 (1H, br s), 6.77—6.88 (2H, m), 7.21—7.28 (1H, m), 7.22 (1H, d, J=8.0 Hz), 7.40—7.50 (2H, m), 7.70 (1H, dt, J=2.0, 8.0 Hz), 8.57—8.65 (1H, m), 9.68 (1H, br s); MS (FAB) *m/z*: 372 (MH^+).

***(R)*-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(2-pyridyl)acetanilide Hydrochloride (28a)** To a solution of **27a** (1.54 g) in methanol (10 ml) was added 4 M HCl–EtOAc solution (20 ml), and the mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo*. The residue was partitioned between chloroform and 1 M NaOH aqueous solution, and the organic layer was dried and concentrated *in vacuo*. To the solution of the resultant in 2-propanol (10 ml) was added (*R*)-styrene oxide (0.15 g), and the mixture 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 $CHCl_3$/MeOH (30 : 1—10 : 1) as the eluent. To the solution of the resultant in methanol (5 ml) was added 4 M HCl–EtOAc solution (0.1 ml), and the mixture was concentrated *in vacuo*. The residue was purified by recrystallization from EtOH–Et_2O to yield **28a** (0.07 g) as a colorless solid. 4% yield; mp 183—184 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 1.85—2.05 (2H, m), 2.53—2.65 (2H, m), 2.83—3.03 (3H, m), 3.05—3.16 (1H, m), 3.88 (2H, s), 4.95 (1H, d, J=9.6 Hz), 6.15 (1H, br s), 7.10—7.18 (2H, m), 7.22—7.43 (7H, m), 7.50—7.60 (2H, m), 7.75 (1H, dt, J=1.6, 7.2 Hz), 8.45—8.53 (1H, m), 8.91 (2H, br s), 10.29 (1H, br s); MS (FAB) *m/z*: 390 (MH^+); *Anal.* Calcd for $C_{24}H_{27}N_3O_2 \cdot HCl$: C, 67.67; H, 6.63; N, 9.86; Cl, 8.32. Found: C, 67.56; H, 6.66; N, 9.80; Cl, 8.23.

***(R)*-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethoxy}-2-(2-pyridyl)acetanilide Hydrochloride (28b)** The title compound was prepared in the same manner as described for **28a** using **27b** instead of **27a** as a colorless solid. 10% yield; mp 225—226 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 3.02—3.14 (1H, m), 3.18—3.46 (3H, m), 3.84 (2H, s), 4.22—4.35 (2H, m), 4.98—5.08 (1H, m), 6.21 (1H, d, J=3.6 Hz), 6.90—6.97 (2H, m), 7.23—7.44 (7H, m), 7.53—7.62 (2H, m), 7.76 (1H, dt, J=1.6, 7.2 Hz), 8.45—8.54 (1H, m), 8.80—9.50 (2H, m), 10.29 (1H, br s); MS (FAB) *m/z*: 392 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_3 \cdot HCl$: C, 64.56; H, 6.12; N, 9.82; Cl, 8.28. Found: C, 64.39; H, 6.11; N, 9.98; Cl, 8.26.

***(R)*-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethyl}-2-(quinolin-2-yl)acetanilide Hydrochloride (30a)** To a solution of 4′-cyanomethyl-2-(quinolin-2-yl)acetanilide (**29a**) (0.41 g) and concentrated aqueous ammonia solution (1 ml) in ethanol (20 ml) and tetrahydrofuran (10 ml) was added Raney-nickel, and the mixture was stirred under hydrogen atmosphere for 6 h. The catalyst was removed by filtration over celite, and the filtrate was concentrated *in vacuo*. The residue was added to a solution of (*R*)-styrene oxide (0.08 g) in 2-propanol (10 ml), and the mixture was refluxed for 6 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 the solution of the resultant in methanol (5 ml) was added 4 M HCl–EtOAc solution (50 μl), and the mixture was concentrated *in vacuo*. The residue was purified by recrystallization from EtOH–Et_2O to yield **28a** (0.05 g) as a colorless solid. 8% yield; mp 234—235 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.94—3.25 (6H, m), 4.07 (2H, s), 4.90—5.02 (1H, m), 6.20 (1H, d, J=4.0 Hz), 7.16—7.23 (2H, m), 7.27—7.44 (5H, m), 7.53—7.65 (4H, m), 7.71—7.78 (1H, m), 7.94—8.00 (2H, m), 8.33 (1H, d, J=8.0 Hz), 8.50—9.25 (2H, m), 10.46 (1H, br s); MS (FAB) *m/z*: 426 (MH^+); *Anal.* Calcd for $C_{27}H_{27}N_3O_2 \cdot HCl$: C, 70.20; H, 6.11; N, 9.10; Cl, 7.67. Found: C, 69.98; H, 6.26; N, 9.08; Cl, 7.44.

***(R)*-4′-{2-[(2-Hydroxy-2-phenylethyl)amino]ethyl}-2-(pyrimidin-2-yl)acetanilide Hydrochloride (30b)** The title compound was prepared in the same manner as described for **30a** using 4′-cyanomethyl-2-(pyrimidin-2-yl)acetanilide (**29b**) instead of **29a** as a colorless solid. 12% yield; mp 208—210 °C (EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.88—3.24 (6H, m), 3.99 (2H, s), 4.90—5.01 (1H, m), 6.20 (1H, d, J=3.6 Hz), 7.15—7.24 (2H, m), 7.28—7.44 (6H, m), 7.53—7.62 (2H, m), 8.50—9.30 (4H, m), 10.33 (1H, br s); MS (FAB) *m/z*: 377 (MH^+); *Anal.* Calcd for $C_{22}H_{24}N_4O_2 \cdot HCl$: C, 63.99; H, 6.10; N, 13.57; Cl, 8.59. Found: C, 63.77; H, 6.20; N, 13.44; Cl, 8.53.

***(R)*-2-{[2-(4-Nitrophenyl)ethyl]amino}-1-phenylethanol (32)** 2-(4-Nitrophenyl)ethylamine hydrochloride (**31**) (25.2 g) was partitioned between ethyl acetate and 1 M NaOH aqueous solution, and the mixture was vigorously stirred at room temperature, and then the organic layer was dried and concentrated *in vacuo*. To the solution of resultant in 2-propanol (100 ml) was added (*R*)-styrene oxide (15.0 g), and the mixture was refluxed for 12 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 (100 : 1—10 : 1) as the eluent to yield **32** (8.05 g) as a colorless oil. 22% yield; ^{1}H-NMR ($CDCl_3$) δ: 2.75 (1H, dd, J=8.8, 12.4 Hz), 2.85—3.04 (5H, m), 4.70 (1H, dd, J=3.7, 8.8 Hz), 7.24—7.40 (7H, m), 8.10—8.20 (2H, m); MS (FAB) *m/z*: 287 (MH^+).

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-nitrophenyl)ethyl]-carbamate (33)** To a solution of **32** (8.02 g) in tetrahydrofuran (80 ml) was added di-*tert*-butyl dicarbonate (6.3 g). The mixture was stirred at room temperature for 12 h, 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 **33** (10.8 g) as a colorless oil. 99% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.75—3.10 (2H, m), 3.20—3.70 (4H, m), 4.93 (1H, br s), 7.25—7.40 (7H, m), 8.14 (2H, d, J=8.4 Hz); MS (FAB) *m/z*: 387 (MH^+).

***tert*-Butyl *N*-[2-(4-Aminophenyl)ethyl]-*N*-(2-hydroxy-2-phenylethyl)-carbamate (34)** To a solution of **33** (10.8 g) in ethanol (200 ml) was added palladium on carbon (10% w/w, 1.0 g), and the mixture was stirred under hydrogen atmosphere for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to yield **34** (9.5 g) as a colorless oil. 95% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.55—2.80 (2H, m), 3.20—3.40 (2H, m), 3.45—3.65 (2H, m), 4.87 (1H, br s), 6.57—6.65 (2H, m), 6.83—7.04 (2H, m), 7.25—7.40 (5H, m); MS (FAB) *m/z*: 357 (MH^+).

***tert*-Butyl *N*-[2-(4-{[2-(6-Chloro-2-pyridyl)acetyl]amino}phenyl)ethyl]-*N*-(2-hydroxy-2-phenylethyl)carbamate (35a)** To a solution of **34** (0.44 g) and 6-chloro-2-pyridylacetic acid (0.25 g) in *N*,*N*-dimethylformamide (15 ml) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.24 g) and 1-hydroxybenzotriazole (0.17 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 water. The organic layer was washed with $NaHCO_3$ aqueous solution, 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 **35a** (0.47 g) as a colorless powder. 75% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.60—2.80 (2H, m), 3.15—3.55 (4H, m), 3.82 (2H, s), 4.35 (1H, br s), 4.88 (1H, br s), 6.97—7.16 (2H, m), 7.22—7.38 (7H, m), 7.42—7.48

(2H, m), 7.66 (1H, t, J=8.0 Hz), 9.18 (1H, br s); MS (FAB) m/z: 510 $(MH)^+$.

***tert*-Butyl *N*-[2-(4-{[2-(6-Benzyloxy-2-pyridyl)acetyl]amino}phenyl)-ethyl]-*N*-(2-hydroxy-2-phenylethyl)carbamate (35b)** The title compound was prepared in the same manner as described for **35a** using 6-benzyloxy-2-pyridylacetic acid instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 56% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.60—2.85 (2H, m), 3.15—3.55 (4H, m), 3.77 (2H, s), 4.33 (1H, br s), 4.87 (1H, br s), 5.64 (2H, s), 6.77 (1H, d, J=8.4 Hz), 6.89 (1H, d, J=7.2 Hz), 6.94—7.12 (2H, m), 7.21—7.41 (10H, m), 7.43—7.48 (2H, m), 7.59 (1H, dd, J=7.2, 8.4 Hz), 9.05 (1H, br s); MS (FAB) m/z: 582 $(MH)^+$.

***tert*-Butyl *N*-[2-(4-{[2-(6-*tert*-Butoxycarbonylamino-2-pyridyl)acetyl]-amino}phenyl)ethyl]-*N*-(2-hydroxy-2-phenylethyl)carbamate (35c)** The title compound was prepared in the same manner as described for **35a** using 6-*tert*-butoxycarbonylamino-2-pyridylacetic acid[22] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 89% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.55 (9H, s), 2.55—2.85 (2H, m), 3.15—3.55 (4H, m), 3.76 (2H, s), 4.86 (1H, dd, J=3.2, 8.0 Hz), 6.94—7.15 (3H, m), 7.21—7.48 (6H, m), 7.63—7.84 (3H, m), 9.03 (1H, br s); MS (FAB) m/z: 591 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-{2-[4-({2-[1-(4-nitrobenzyl)imidazol-2-yl]acetyl}amino)phenyl]ethyl}carbamate (35d)** The title compound was prepared in the same manner as described for **35a** using 1-(4-nitrobenzyl)imidazol-2-ylacetic acid hydrochloride instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 77% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.50—2.80 (2H, m), 3.10—3.50 (4H, m), 3.70 (2H, s), 4.85—4.90 (1H, m), 5.30 (2H, s), 6.96—7.36 (11H, m), 7.41 (2H, d, J=8.3 Hz), 8.18 (2H, d, J=8.3 Hz); MS (FAB) m/z: 600 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-{[2-(1*H*-imidazol-2-yl)acetyl]amino}phenyl)ethyl]carbamate (35e)** To a solution of **35d** (0.91 g) in methanol (100 ml) was added 4 M HCl–EtOAc solution (2.0 ml). The mixture was stirred at room temperature for 5 min and concentrated *in vacuo*. To a solution of the residue in methanol (100 ml) was added palladium on carbon (10% w/w, 0.39 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*. The residue was partitioned between chloroform and 1 M NaOH aqueous solution. 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 (50 : 1) as the eluent to yield **35e** (0.31 g) as a colorless powder. 44% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.52—2.80 (2H, m), 3.10—3.60 (4H, m), 3.89 (2H, s), 4.85—4.95 (1H, m), 6.95—7.40 (9H, m), 7.49 (2H, d, J=8.4 Hz), 10.16 (1H, br s); MS (FAB) m/z: 465 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-{[2-(1*H*-1,2,4-triazol-3-yl)acetyl]amino}phenyl)ethyl]carbamate (35f)** The title compound was prepared in the same manner as described for **35a** using 1,2,4-triazol-3-ylacetic acid hydrochloride[23] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 36% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.60—3.36 (6H, m), 3.98 (2H, s), 4.81—4.89 (1H, m), 7.02—7.12 (2H, m), 7.29—7.50 (7H, m), 8.09 (1H, br s), 9.24 (1H, br s); MS (FAB) m/z: 466 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-{[2-(1*H*-tetrazol-5-yl)acetyl]amino}phenyl)ethyl]carbamate (35g)** The title compound was prepared in the same manner as described for **35a** using tetrazol-5-ylacetic acid instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 99% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.50—3.50 (6H, m), 4.23 (2H, s), 4.65—4.75 (1H, m), 7.07 (2H, d, J=8.0 Hz), 7.20—7.80 (7H, m), 9.26 (1H, br s); MS (FAB) m/z: 467 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-{[2-(2-methylthiazol-4-yl)acetyl]amino}phenyl)ethyl]carbamate (35h)** The title compound was prepared in the same manner as described for **35a** using 2-methylthiazol-4-ylacetic acid instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 99% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.34 (9H, s), 2.89 (3H, s), 3.06—3.36 (6H, m), 3.73 (2H, s), 4.72 (1H, s), 7.06—7.57 (10H, m), 10.10 (1H, s); MS (FAB) m/z: 496 $(MH)^+$.

***tert*-Butyl *N*-[2-(4-{[2-(2-Amino-5-methylthiazol-4-yl)acetyl]amino}-phenyl)ethyl]-*N*-(2-hydroxy-2-phenylethyl)carbamate (35i)** The title compound was prepared in the same manner as described for **35a** using 2-amino-5-methylhiazol-4-ylacetic acid hydrochloride[24] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 73% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.25 (3H, s), 2.60—3.50 (6H, m), 3.52 (2H, s), 4.83 (1H, s), 7.27—7.45 (9H, m), 9.01 (1H, br s); MS (FAB) m/z: 511 $(MH)^+$.

***tert*-Butyl *N*-[2-(4-{[2-(5-Amino-1,2,4-thiadiazol-3-yl)acetyl]amino}-phenyl)ethyl]-*N*-(2-hydroxy-2-phenylethyl)carbamate (35j)** The title compound was prepared in the same manner as described for **35a** using 5-amino-1,2,4-thiadiazol-3-ylacetic acid[25] hydrochloride instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 86% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.60—2.75 (2H, m), 3.10—3.55 (4H, m), 3.81 (2H, s), 4.81—4.87 (1H, m), 6.40—6.55 (2H, m), 7.02 (2H, d, J=7.3 Hz), 7.22—7.45 (7H, m), 9.26 (1H, s); MS (FAB) m/z: 496 $(M-H)^-$.

***(R)*-2-(6-Chloro-2-pyridyl)-4′-{3-[(2-hydroxy-2-phenylethyl)amino]-propyl}acetanilide Hydrochloride (36a)** To a solution of **35a** (0.45 g) in ethanol (10 ml) was added 4 M HCl–EtOAc solution (10 ml), and the mixture was stirred at room temperature for 2 h, and then concentrated *in vacuo*. The residue was purified by recrystallization from MeOH–EtOH–Et_2O to yield **36a** (0.25 g) as a colorless solid. 64% yield; mp 248—251 °C (MeOH–EtOH–Et_2O); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.08 (3H, m), 3.09—3.21 (3H, m), 3.88 (2H, s), 5.02 (1H, dd, J=2.4, 10.0 Hz), 6.20 (1H, br s), 7.16—7.22 (2H, m), 7.28—7.46 (7H, m), 7.57—7.63 (2H, m), 7.84 (1H, t, J=7.2 Hz), 8.95 (1H, br s), 9.40 (1H, br s), 10.48 (1H, br s); MS (FAB) m/z: 410 (MH^+); *Anal.* Calcd for $C_{23}H_{24}N_3O_2Cl\cdot HCl$: C, 61.89; H, 5.65; N, 9.41; Cl, 15.88. Found: C, 61.64; H, 5.57; N, 9.36; Cl, 15.82.

***(R)*-2-(6-Amino-2-pyridyl)-4′-{3-[(2-hydroxy-2-phenylethyl)amino]-propyl}acetanilide Dihydrochloride (36b)** The title compound was prepared in the same manner as described for **36a** using **35c** instead of **35a** as a colorless solid. 15% yield; mp 150—152 °C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.88—3.07 (3H, m), 3.08—3.21 (3H, m), 3.95 (2H, s), 5.00 (1H, dd, J=2.8, 10.0 Hz), 6.21 (1H, s), 6.82 (1H, d, J=7.6 Hz), 6.91 (1H, d, J=8.0 Hz), 7.17—7.23 (2H, m), 7.28—7.43 (5H, m), 7.55—7.62 (2H, m), 7.82—8.04 (3H, m), 8.90 (1H, br s), 9.31 (1H, br s), 10.67 (1H, br s), 14.07 (1H, br s); MS (FAB) m/z: 391 (MH^+); *Anal.* Calcd for $C_{23}H_{26}N_4O_2\cdot 2HCl\cdot 1.5H_2O$: C, 56.33; H, 6.37; N, 11.42; Cl, 14.46. Found: C, 56.37; H, 6.00; N, 11.37; Cl, 14.56.

***(R)*-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(1*H*-imidazol-2-yl)acetanilide Dihydrochloride (36c)** The title compound was prepared in the same manner as described for **36a** using **35e** instead of **35a** as a colorless solid. 89% yield; mp 203—207 °C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.92—3.08 (3H, m), 3.10—3.22 (3H, m), 4.28 (2H, s), 5.01 (1H, d, J=7.8 Hz), 6.21 (1H, br s), 7.22 (2H, d, J=8.3 Hz), 7.25—7.63 (4H, m), 8.93 (1H, br s), 9.38 (1H, br s), 10.86 (1H, s); MS (FAB) m/z: 365 (MH^+); *Anal.* Calcd for $C_{21}H_{24}N_4O_2\cdot 2HCl\cdot 0.2H_2O$: C, 57.20; H, 6.03; N, 12.71; Cl, 16.08. Found: C, 57.19; H, 6.06; N, 12.42; Cl, 16.37.

***(R)*-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(1*H*-1,2,4-triazol-3-yl)acetanilide Dihydrochloride (36d)** The title compound was prepared in the same manner as described for **36a** using **35f** instead of **35a** as a colorless solid. 78% yield; mp 221—224 °C (EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.07 (3H, m), 3.10—3.20 (3H, m), 4.05 (2H, s), 5.00 (1H, dd, J=2.7, 10.2 Hz), 7.21 (2H, d, J=8.6 Hz), 7.29—7.42 (5H, m), 7.58 (2H, d, J=8.6 Hz), 8.83 (1H, s), 8.91 (1H, br s), 9.32 (1H, br s), 10.62 (1H, s); MS (FAB) m/z: 366 (MH^+); *Anal.* Calcd for $C_{20}H_{23}N_5O_2\cdot 2HCl$: C, 54.80; H, 5.75; N, 15.98; Cl, 16.18. Found: C, 54.83; H, 5.80; N, 15.99; Cl, 16.18.

***(R)*-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(1*H*-tetrazol-5-yl)acetanilide Hydrochloride (36e)** The title compound was prepared in the same manner as described for **36a** using **35g** instead of **35a** as a colorless solid. 42% yield; mp 259—261 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.10 (3H, m), 3.10—3.25 (3H, m), 4.15 (2H, s), 4.97 (1H, d, J=10.8 Hz), 6.20 (1H, d, J=3.9 Hz), 7.21 (2H, d, J=8.8 Hz), 7.30—7.42 (5H, m), 7.57 (2H, d, J=8.8 Hz), 8.85 (1H, br s), 9.14 (1H, br s), 10.58 (1H, s); MS (FAB) m/z: 367 (MH^+); *Anal.* Calcd for $C_{19}H_{22}N_6O_2\cdot HCl$: C, 56.64; H, 5.75; N, 20.86; Cl, 8.80. Found: C, 56.43; H, 5.92; N, 20.78; Cl, 9.04.

***(R)*-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(2-methylthiazol-4-yl)acetanilide Dihydrochloride (36f)** The title compound was prepared in the same manner as described for **36a** using **35h** instead of **35a** as a colorless powder. 55% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.70 (3H, s), 2.86—3.27 (6H, m), 3.85 (2H, s), 5.00—5.05 (1H, m), 7.18—7.60 (10H, m), 10.43 (1H, s); MS (FAB) m/z: 396 (MH^+); *Anal.* Calcd for $C_{22}H_{25}N_3O_2S\cdot 2.3HCl\cdot 2H_2O$: C, 51.27; H, 6.12; N, 8.15; S, 6.22; Cl, 15.82. Found: C, 51.59; H, 5.98; N, 7.91; S, 6.32; Cl, 15.86.

***(R)*-2-(2-Amino-5-methylthiazol-4-yl)-4′-{3-[(2-hydroxy-2-phenylethyl)amino]propyl}acetanilide Dihydrochloride (36g)** The title compound was prepared in the same manner as described for **36a** using **35i** instead of **35a** as a colorless powder. 65% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 2.90—3.07 (3H, m), 3.10—3.20 (3H, m), 3.74 (2H, s), 5.00 (1H, dd, J=2.5, 10.3 Hz), 7.20 (2H, d, J=8.8 Hz), 7.28—7.42 (5H, m), 7.59 (2H, d, J=8.8 Hz), 8.91 (1H, br s), 9.13 (1H, br s), 9.33 (1H, br s), 10.58 (1H, s); MS (FAB) m/z: 411 (MH^+); *Anal.* Calcd for $C_{22}H_{26}N_4O_2S\cdot 2.15HCl\cdot H_2O$: C, 52.12; H, 5.99; N, 11.05; S, 6.33; Cl, 15.04. Found: C, 52.30; H, 6.28; N, 11.15; S, 6.50; Cl, 15.28.

***(R)*-2-(5-Amino-1,2,4-thiadiazol-3-yl)-4′-{3-[(2-hydroxy-2-phenylethyl)amino]propyl}acetanilide Dihydrochloride (36h)** The title compound was prepared in the same manner as described for **36a** using **35j**

instead of **35a** as a colorless solid. 74% yield; mp 205—208 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.08 (3H, m), 3.10—3.20 (3H, m), 3.67 (2H, s), 5.00 (1H, dd, J=2.4, 10.0 Hz), 7.19 (2H, d, J=8.3 Hz), 7.28—7.42 (5H, m), 7.57 (2H, d, J=8.3 Hz), 8.90 (1H, s), 9.31 (1H, s), 10.31 (1H, s); MS (FAB) m/z: 398 (MH^+); *Anal.* Calcd for $C_{20}H_{23}N_5O_2S\cdot 2HCl$: C, 51.06; H, 5.36; N, 14.89; S, 6.82; Cl, 15.07. Found: C, 50.81; H, 5.19; N, 14.84; S, 6.73; Cl, 14.86.

***tert*-Butyl *N*-(2-{4-[(2-Bromoacetyl)amino]phenyl}ethyl)-*N*-(2-hydroxy-2-phenylethyl)carbamate (37)** To a solution of **34** (1.87 g) and *N*,*N*-diisopropyl-*N*-ethylamine (1.05 g) in chloroform (40 ml) was added dropwise at 0 °C a solution of 2-bromoacetyl bromide (1.07 g) in chloroform (3 ml), and the mixture was stirred at 0 °C for 1 h. The resultant mixture was washed with 1 M HCl aqueous solution and brine. The organic layer was 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 **37** (2.15 g) as a colorless powder. 85% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.60—2.90 (2H, m), 3.16—3.56 (4H, m), 4.01 (2H, s), 4.20—4.30 (1H, m), 4.80—4.95 (1H, m), 7.00—7.20 (2H, m), 7.25—7.38 (5H, m), 7.44 (2H, d, J=8.4 Hz), 8.07 (1H, s); MS (FAB) m/z: 477, 479 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-{[2-(1*H*-pyrazol-1-yl)-acetyl]amino}phenyl)ethyl]carbamate (38a)** A mixture of **37** (0.62 g), pyrazole (0.42 g), and potassium carbonate (0.4 g) in acetonitrile (15 ml) was heated at 80 °C for 15 h. After cooling to room temperature, the precipitate was removed by filtration, and the filtrate was then concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (10 : 1) as the eluent to yield **38a** (0.55 g) as a colorless powder. 91% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.60—2.88 (2H, m), 3.10—3.54 (4H, m), 4.20—4.35 (1H, m), 4.85—4.90 (1H, m), 4.93 (2H, s), 6.38—6.40 (1H, m), 7.00—7.15 (2H, m), 7.30—7.40 (7H, m), 7.53 (1H, d, J=2.0 Hz), 7.71 (1H, d, J=2.0 Hz), 8.34 (1H, s); MS (FAB) m/z: 465 $(MH)^+$.

***tert*-Butyl *N*-(2-Hydroxy-2-phenylethyl)-*N*-[2-(4-{[2-(1*H*-1,2,4-triazol-1-yl)acetyl]amino}phenyl)ethyl]carbamate (38b)** The title compound was prepared in the same manner as described for **38a** using 1,2,4-triazole instead of pyrazole as a colorless powder. 84% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.60—2.84 (2H, m), 3.10—3.50 (4H, m), 4.14—4.28 (1H, m), 4.84—4.92 (1H, m), 5.00 (2H, s), 7.02—7.10 (2H, m), 7.30—7.40 (7H, m), 8.12 (1H, s), 8.24 (2H, s); MS (FAB) m/z: 466 $(MH)^+$.

(*R*)-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(1*H*-pyrazol-1-yl)acetanilide Hydrochloride (39a) The title compound was prepared in the same manner as described for **36a** using **38a** instead of **35a** as a colorless solid. 36% yield; mp 229—232 °C (EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.00 (3H, m), 3.10—3.18 (3H, m), 5.00 (1H, dd, J=2.8, 10.1 Hz), 5.03 (2H, s), 6.27 (1H, t, J=2.0 Hz), 7.20 (2H, d, J=8.8 Hz), 7.29—7.42 (5H, m), 7.46 (1H, d, J=2.4 Hz), 7.58 (2H, d, J=8.8 Hz), 7.77 (1H, d, J=2.0 Hz), 8.91 (1H, s), 9.32 (1H, s), 10.53 (1H, s); MS (FAB) m/z: 365 (MH^+); *Anal.* Calcd for $C_{21}H_{24}N_4O_2\cdot 1.1HCl\cdot 0.4C_2H_6O$: C, 61.90; H, 6.55; N, 13.25; Cl, 9.22. Found: C, 62.28; H, 6.23; N, 12.87; Cl, 9.34.

(*R*)-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(1*H*-1,2,4-triazol-1-yl)acetanilide Hydrochloride (39b) The title compound was prepared in the same manner as described for **36a** using **38b** instead of **35a** as a colorless solid. 64% yield; mp 237—240 °C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.90—3.08 (3H, m), 3.10—3.22 (3H, m), 4.96 (1H, dd, J=2.0, 10.0 Hz), 5.15 (2H, s), 7.21 (2H, d, J=8.0 Hz), 7.28—7.42 (5H, m), 7.56 (2H, d, J=8.4 Hz), 8.03 (1H, s), 8.61 (1H, s), 8.82 (1H, s), 9.09 (1H, s), 10.57 (1H, s); MS (FAB) m/z: 365 (MH^+); *Anal.* Calcd for $C_{20}H_{23}N_5O_2\cdot 1.8HCl\cdot 0.5H_2O$: C, 54.59; H, 5.91; N, 15.91; Cl, 14.50. Found: C, 54.51; H, 5.69; N, 15.89; Cl, 14.56.

(*R*)-4′-{3-[(2-Hydroxy-2-phenylethyl)amino]propyl}-2-(6-hydroxy-2-pyridyl)acetanilide Hydrochloride (40) To **35b** (0.35 g) were added pentamethylbenzene (0.48 g) and trifluoroacetic acid (5 ml), and the mixture was stirred at room temperature for 4 h, and then concentrated *in vacuo*. The resultant was diluted with K_2CO_3 aqueous solution, and extracted with chloroform–tetrahydrofuran (1 : 1). The organic layer was dried, and then concentrated *in vacuo*. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH (10 : 1—5 : 1) as the eluent. To the solution of the residue in ethanol (5 ml) was added 4 M HCl–EtOAc solution (100 ml), and the mixture was concentrated *in vacuo*. The residue was purified by recrystallization from EtOH–EtOAc to yield **40** (0.06 g) as a colorless solid. 24% yield; mp 214—216 °C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.86—3.24 (6H, m), 3.65 (2H, s), 4.98 (1H, dd, J=2.8, 10.4 Hz), 6.18 (1H, d, J=6.8 Hz), 6.28 (1H, d, J=8.8 Hz), 7.16—7.22 (2H, m), 7.28—7.45 (6H, m), 7.53—7.59 (2H, m), 8.85 (1H, br s), 9.18 (1H, br s), 10.36 (1H, br s); MS (FAB) m/z: 392 (MH^+); *Anal.* Calcd for $C_{23}H_{25}N_3O_3\cdot 1.4HCl\cdot 0.6H_2O$: C, 60.94; H, 6.14; N, 9.27; Cl, 10.95. Found: C, 61.05; H, 6.08; N, 9.31; Cl, 10.62.

Agonistic Activity on Human β3-, β2-, and β1-ARs The ability to stimulate human β3-, β2-, and β1-AR was 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} to 10^{-4} M) was investigated by incubating 10^5 cells/well of each type of cell 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.

Hypoglycemic Activity in kk Mice The blood sugar level of male kk mice (blood sugar level: not lower than 200 mg/dl) was measured under fed conditions, and then randomly classified into groups. The test compound was administered orally once daily for 4 d, and the blood sugar level 15 to 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.

Single-Crystal X-Ray Diffraction Analysis of 2-{(2*S*)-*N*-Benzyl-*N*-[1-(4-nitrophenyl)-2-propyl]amino}-(1*R*)-1-phenylethanol (17b) A light-yellow prismatic crystal of **17b** $C_{24}H_{26}N_2O_3$ (F.W.=390.48, 0.43 mm×0.40 mm×0.32 mm) was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Cu$K\alpha$ radiation and a rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $59.62<2\theta<60.02°$ corresponded to a primitive triclinic cell (P1, Z=2) with dimensions: a=9.523(5) Å, b=9.796(6) Å, c=13.333(4) Å, α=71.92(3)°, β=85.59(3)°, γ=63.64(4)°, V=1056.7(9) Å^3, the calculated density is 1.23 g/cm^3. The data were collected at a temperature of 25±1 °C using the $\theta-2\theta$ scan technique to a maximum 2θ value of 120.2°. Of the 3111 reflections that were collected, 2890 were unique (R_{int}=0.011). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied. The linear absorption coefficient, μ, for Cu$K\alpha$ radiation is 6.5 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.71 to 0.81. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods[26] and expanded using Fourier techniques.[27] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[28] was based on 2891 observed reflection s ($F^2>2.00\sigma(F^2)$, $2\theta<120.2°$) and 575 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: R=0.046, R_w=0.159, respectively. The goodness of fit[29] was 1.001. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.03 and −0.03 e/Å^3, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[30] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[31] All calculations were performed using the teXsan[32] crystallographic software package of Molecular Structure Corporation and CrystalStructure[33,34] crystallographic software package. The X-ray crystallographic data have been deposited at the Cambridge Crystallographic Centre (CCDC ref. No. 756207).

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