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Synthesis and evaluation of novel phenoxypropanolamine derivatives containing acetanilides as potent and selective β3-adrenergic receptor agonists

Tatsuya Maruyama *, Kenichi Onda, Masahiko Hayakawa, Norio Seki, Takumi Takahashi, Hiroyuki Moritomo, Takayuki Suzuki, Tetsuo Matsui, Toshiyuki Takasu, Itsuro Nagase, Mitsuaki Ohta

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

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ABSTRACT

In the search for potent and selective human β3-adrenergic receptor (AR) agonists as potential drugs for the treatment of obesity and noninsulin-dependent (type II) diabetes, a novel series of phenoxypropanolamine derivatives containing acetanilides were prepared and their biological activities were evaluated at the human β3-, β2-, and β1-ARs. Several of the analogues (**21a**, **21b**, and **27a**) exhibited potent agonistic activity at the β3-AR. Among the compounds described herein, the *N*-methyl-1-benzylimidazol-2-ylacetanilide derivative (**21b**) was found to be the most potent and selective β3-AR agonist, with an EC_{50} value of 0.28 μM and no agonistic activity for either the β1- or β2-AR. In addition, **21b** showed significant hypoglycemic activity in a rodent diabetic model.

1. Introduction

A major increase in the prevalence of obesity and noninsulin-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, β3-adrenergic receptor (AR) was identified as a possible therapeutic opportunity 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] However, human clinical trials with these agents for the treatment of metabolic disorders have been disappointing due to a lack of efficacy or an unfavorable side-effect profile.[8] The clinical failure of such compounds has been attributed to a lack of sufficient β3-AR potency and selectivity over β1- or 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 in 1989.[9–11] 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 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.

We previously described efforts in this area that included 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.[12] However, compound **1** was found to exhibit poor bioavailability in rats ($F = 2\%$), probably due to the rapid metabolism of the 4-hydroxyphenoxy moiety on the left-hand side of **1**. Since many kinds of phenoxypropanolamine-based β3-agonists have been reported (Fig. 2),[13,14] we decided to explore the alternative structures instead of the 4-hydroxyphenoxy moiety of **1**, after which further attempts at modification of the pyridyl moiety on the right-hand side of **1** were made (Fig. 3). In this paper, we describe the synthesis and structure–activity relationships (SARs) of these newly designed phenoxypropanolamine derivatives containing acetanilides as β3-AR agonists.

2. Chemistry

2-Pyridylacetanilides **5a**–**f** were prepared from an amine intermediate **4**, as illustrated in Scheme 1. Compound **4** was synthesized from 2-pyridylacetic acid (**2**) and 4-aminobenzylcyanide,

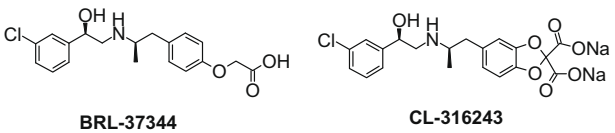

Figure 1. Chemical structure of early β3-AR agonists.

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

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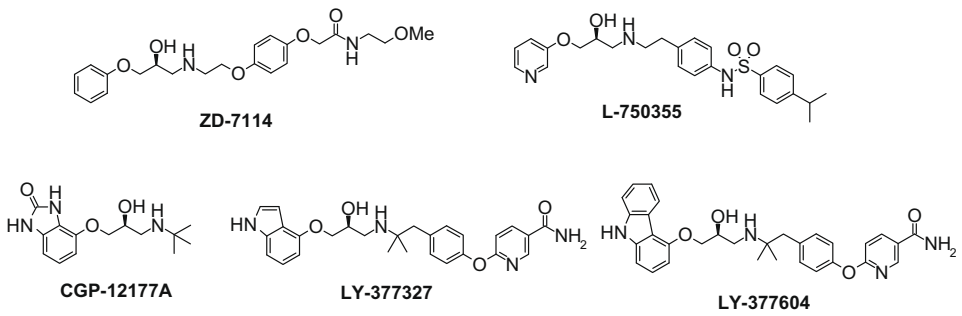


Figure 2. Chemical structure of phenoxypropanolamine-based β3-AR agonists.

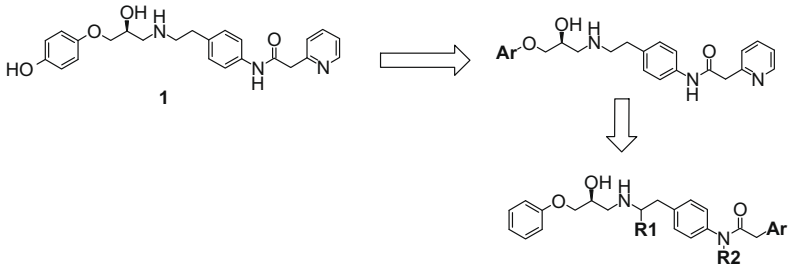
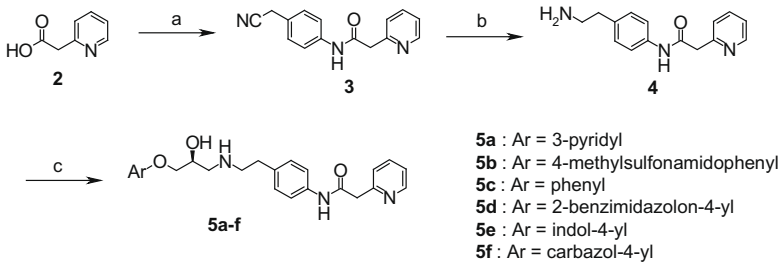


Figure 3. Design of phenoxypropanolamine analogues containing acetanilides based on compound **1**.



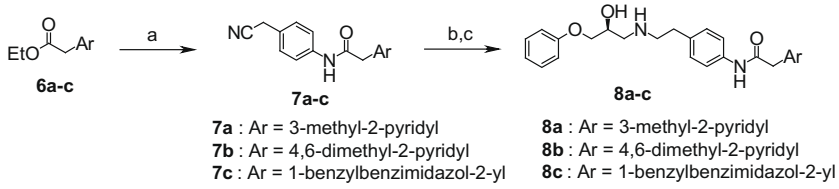
Scheme 1. Reagents and conditions: (a) 4-aminobenzylcyanide, EDC·HCl, HOBt, DMF; (b) H_2, Raney-Ni, NH_3 aq, THF, EtOH; (c) (*S*)-2-aryloxymethyloxirane, Et_3N, ^{i}PrOH, reflux, and then 4 M HCl–dioxane, acetone.

followed by hydrogenation of the cyano group with Raney-nickel. Compound **4** was coupled with appropriate (*S*)-2-aryloxymethyloxirane[15–18] to afford the desired products (**5a**–**f**).

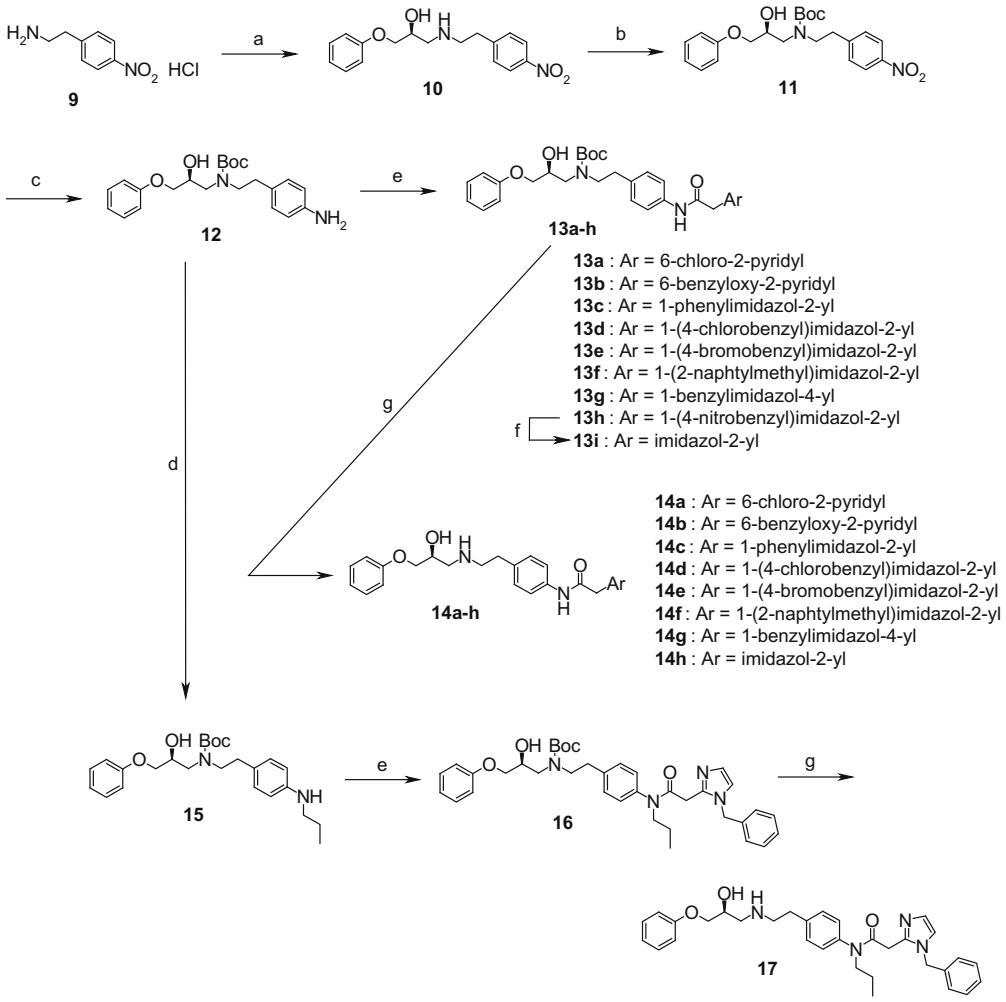
Acetanilides **8a**–**c** were prepared from the corresponding ethyl arylacetates **6a–c**, as illustrated in Scheme 2. Compounds **6a–c** were treated with 4-aminobenzylcyanide in refluxing xylene to provide anilides **7a–c**. The anilides **7a–c** were hydrogenated, followed by coupling with (*S*)-2-phenoxymethyloxirane to afford the desired products (**8a**–**c**).

Another route from aniline intermediate **12** was illustrated in Scheme 3. 2-(4-Nitrophenyl)ethylamine hydrochloride (**9**) was treated with (*S*)-2-phenoxymethyloxirane, followed by protection of the amine with a *tert*-butoxycarbonyl (Boc) group to provide nitro compound **11**. Hydrogenation of **11** yielded aniline intermediate **12**. The coupling of **12** with the appropriate acetic acids, followed by deprotection of the Boc group, afforded the desired products (**14a**–**g**). Deprotection of the 4-nitrobenzyl group of **13h** by catalytic hydrogenation, followed by deprotection of the Boc group afforded the imidazol-2-ylacetanilide derivative (**14h**). On the other hand, compound **12** was treated with propionaldehyde and borane to yield an *N*-propylaniline analogue **15**. The coupling of **15** with 1-benzylimidazol-2-ylacetic acid, followed by deprotection of the Boc group afforded *N*-propyl-1-benzylimidazol-2-ylacetanilide derivative (**17**).

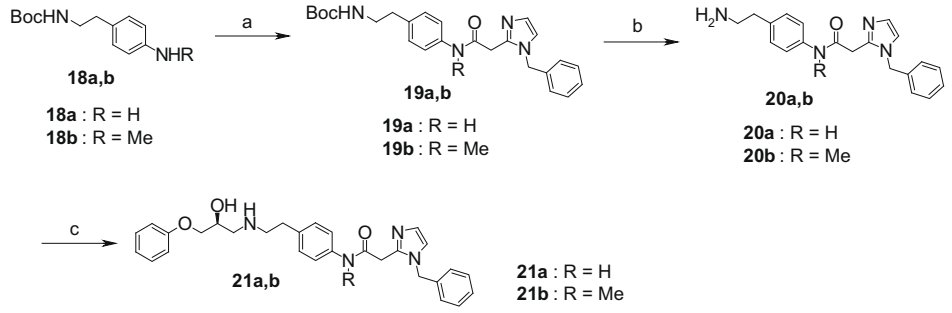
The synthesis of 1-benzylimidazol-2-ylacetanilide derivatives (**21a,b**) are shown in Scheme 4. 4-(2-*tert*-Butoxycarbonylamino-



Scheme 2. Reagents and conditions: (a) 4-aminobenzylcyanide, xylene, reflux; (b) H_2, Raney-Ni, concd NH_3 aq, EtOH–THF; (c) (*S*)-2-phenoxymethyloxirane, ^{i}PrOH, reflux, and then 4 M HCl–EtOAc, MeOH.



Scheme 3. Reagents and conditions: (a) (*S*)-2-phenoxymethyloxirane, Et_3N, $^{i}PrOH$, reflux; (b) $(Boc)_2O$, THF; (c) H_2, Pd/C, EtOH; (d) EtCHO, BH_3–THF; (e) $ArCH_2CO_2H$, EDC·HCl, HOBt, THF; (f) H_2, Pd/C, HCl, MeOH; (g) 4 M HCl–EtOAc, EtOH.

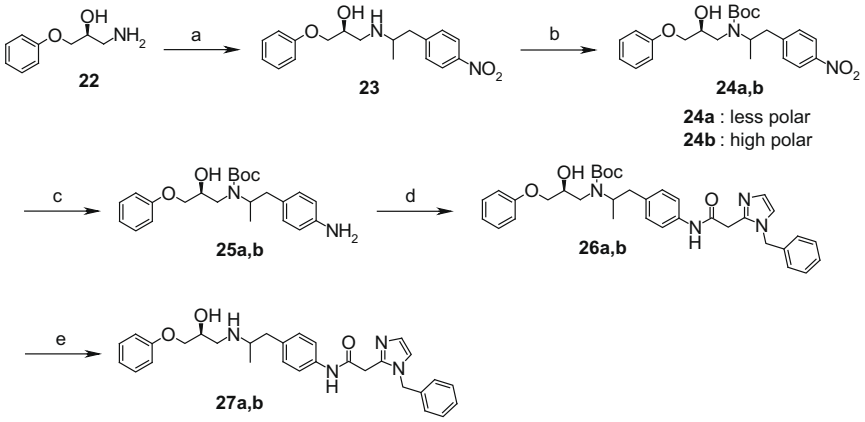


Scheme 4. Reagents and conditions: (a) 1-benzylimidazol-2-ylacetic acid, EDC·HCl, HOBt, DMF; (b) 4 M HCl–EtOAc, MeOH; (c) (*S*)-2-phenoxymethyloxirane, $^{i}PrOH$, reflux, and then 4 M HCl–EtOAc, MeOH.

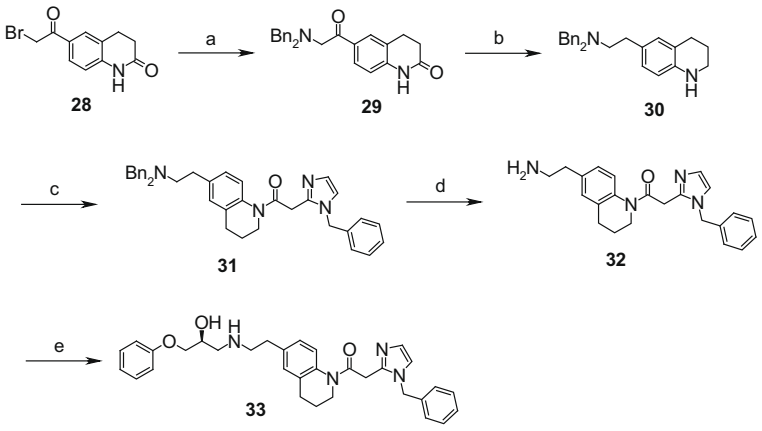
ethyl)anilines (**18a,b**) were coupled with 1-benzylimidazol-2-ylacetic acid, followed by deprotection of the Boc group, to provide amine intermediates **20a,b**. Compounds **20a,b** were treated with (*S*)-2-phenoxymethyloxirane to afford the desired products (**21a,b**).

Scheme 5 shows the synthesis of compounds **27a,b**. (*S*)-1-Amino-3-phenoxy-2-propanol (**22**) was treated with 4-nitrophenylacetone, followed by reduction with sodium borohydride to give nitro compound **23** as diastereomeric mixture. Compound **23** was protected with a *tert*-butoxycarbonyl (Boc) group, followed by separation using column chromatography to provide the less polar compound **24a** and the highly polar compound **24b** as single isomers. Hydrogenation of the nitro group of **24a,b** furnished the aniline intermediates **25a,b**, and subsequent coupling reaction with 1-benzylimidazol-2-ylacetic acid yielded anilides **26a,b**. Deprotection of the Boc group in **26a,b** afforded the desired products (**27a,b**).

The 1,2,3,4-tetrahydroquinoline derivative (**33**) was synthesized as illustrated in Scheme 6. 6-Bromoacetyl-1,2,3,4-tetrahydroquinolin-2-one (**28**) was treated with dibenzylamine, followed by reduction with borane to yield the 1,2,3,4-tetrahydroquinoline derivative (**30**). The coupling of **30** with 1-benzylimidazol-2-ylace-



Scheme 5. Reagents and conditions: (a) 4-nitrophenylacetone, benzene, reflux, then $NaBH_4$, MeOH; (b) $(Boc)_2O$, THF; (c) H_2, Pd/C, EtOH; (d) 1-benzylimidazol-2-ylacetic acid, EDC·HCl, HOBt, DMF; (e) 4 M HCl–EtOAc, MeOH.



Scheme 6. Reagents and conditions: (a) dibenzylamine, $^{i}Pr_2NEt$, DMF, 80 °C; (b) BH_3–THF, 80 °C; (c) 1-benzylimidazol-2-ylacetic acid, EDC·HCl, HOBt, DMF; (d) HCO_2NH_4, Pd/C, MeOH; (e) (*S*)-2-phenoxymethyloxirane, $^{i}PrOH$, reflux, then 4 M HCl–EtOAc, MeOH.

tic acid, followed by deprotection of the benzyl group, provided amine intermediate **32**. Compound **32** was treated with (*S*)-2-phenoxymethyloxirane to afford the desired product (**33**).

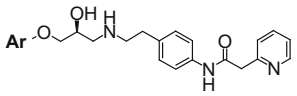
3. Results and discussion

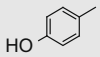
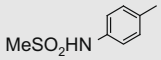
The prepared compounds were evaluated for their agonistic activities in stimulating an increase in cyclic AMP (cAMP) levels in Chinese hamster ovary (CHO) cells expressing the cloned human β3-, β2-, and β1-ARs. The results for the reference compound, isoproterenol (**ISO**; non-selective β-AR agonist),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

Modification of the 4-hydroxyphenyl moiety in **1** with the several aryloxy moieties illustrated in Figure 2 was investigated (Table 1). Replacement of the 4-hydroxyl group of **1** with the 4-methanesulfonylamino group (**5b**) resulted in a substantial loss of β3-AR agonistic activity. Removal of the 4-hydroxyl group (**5c**) of **1** resulted in a dramatic decrease in the potency of β3-AR (EC_{50} = 120 μM), while **5c** retained full agonistic activity (IA = 0.93) at the β3-AR. Next, replacement of the 4-hydroxyphenyl moiety in **1** with the 3-pyridyl (**5a**) and 2-benzimidazolinon-4-yl (**5d**) moieties resulted in a considerable decrease in intrinsic activity at the β3-AR (IA = 0.28 and 0.20, respectively). The indol-4-yl (**5e**) and carbazol-4-yl (**5f**) derivatives exhibited a decrease in agonistic activity at the β1-AR; however their β3-agonistic activity was only partial ('partial' is defined as IA < 0.75 in this paper). These results revealed that the replacement of the 4-hydroxyphenyl moiety in **1** with several heteroaromatic moieties was tolerated and allowed the potency of β3-AR to be maintained, but this change may decrease its intrinsic activity at the β3-AR. Thus, we selected the phenoxy derivative (**5c**) as our new leading candidate, because only this compound showed full β3-AR agonistic activity after altering the aromatic ring on the left-hand side of **1**. In addition, **5c** exhibited improved bioavailability in rats (*F* = 27%). In order to improve β3-AR agonistic activity while maintaining functional selectivity over β1- and β2-ARs, modification of the 2-pyridyl moiety in **5c** was examined.

The effects of pyridine ring modification in **5c** are shown in Table 2. Initially, the effects of the substituent on the pyridine ring in **5c** was investigated: introduction of a methyl group at this site (**8a** and **8b**) resulted in a dramatic increase in potency at both the β3- (EC_{50} = 0.33 and 0.28 μM, respectively) and β1-ARs (EC_{50} = 0.39 and 0.31 μM, respectively) relative to that of **5c**, but even with this increase, the agonistic activity was still only partial. The agonistic activity of the 6-chloro-2-pyridyl derivative (**14a**) at the β3-AR (EC_{50} = 0.043 μM, IA = 0.39) was much greater than that of **5c**, but it also increased β1-AR agonistic activity (EC_{50} = 0.055 μM, IA = 0.36). The 6-benzyloxy-2-pyridyl derivative (**14b**) showed results similar to that of **8a**. These results indicated that the introduction of a substituent on the pyridine ring in **5c** can improve the potency of β3-AR with lower intrinsic activity, but it may not be efficacious for improving functional selectivity over β1-AR. Next, we decided to replace the pyridine ring in **5c** with an imidazole ring because, like pyridine, it is a basic heteroaromatic ring. Replacement of the 2-pyridyl moiety in **5c** with the imidazol-2-yl

Table 1
β-AR agonistic activity of 2-pyridylacetanilide derivatives



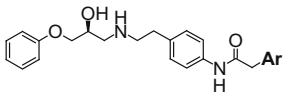
Compound	Ar	EC_{50}, μM[a] (IA[b])		
		β3-AR	β2-AR	β1-AR
1		0.29 (0.74)	>100 (0)	2.7 (0.14)
5b		>100 (0)	>100 (0.01)	>100 (0.01)
5c		120 (0.93)	>100 (0.01)	>100 (0.11)
5a		0.18 (0.28)	>100 (0.02)	>100 (0.06)
5d		0.28 (0.20)	>100 (0)	>100 (0.01)
5e		1.3 (0.49)	>100 (0.02)	>100 (0)
5f		0.25 (0.42)	>100 (0.01)	>100 (0.01)
ISO		0.10 (1.00)	0.003 (1.00)	0.012 (1.00)

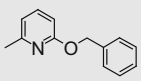
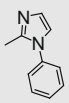
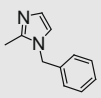
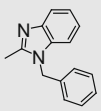
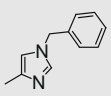
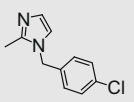
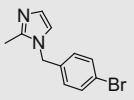
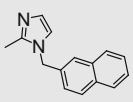
[a] Agonistic activity was assessed by measuring cAMP accumulation in CHO cells expressing β-ARs.
[b] Values in parentheses represent the intrinsic activity (IA) given as a fraction of the maximum stimulation with isoproterenol.

moiety (**14h**) resulted in a 12-fold increase in potency at the β3-AR (EC_{50} = 9.6 μM, IA = 0.62) with partial β1-AR agonistic activity (EC_{50} = 0.51 μM, IA = 0.26) relative to that of **5c**. This encouraged us to synthesize the substituted imidazole analogues. The 1-phenylimidazol-2-ylacetanilide derivative (**14c**) showed a 15-fold increase in potency at the β3-AR (EC_{50} = 0.65 μM, IA = 0.52) relative to that of **14h**. Furthermore, the 1-benzylimidazol-2-ylacetanilide derivative (**21a**) exhibited a 53-fold increase in potency at the β3-AR with good intrinsic activity (EC_{50} = 0.18 μM, IA = 0.77) and partial β1-AR agonistic activity (EC_{50} = 0.13 μM, IA = 0.20) relative to **14h**.

To improve the potency of β3-AR and functional selectivity over β1-AR of **21a**, we then examined the modification of the 1-benzylimidazol-2-yl moiety in **21a**. Replacement of the 1-benzylimidazol-2-yl moiety in **21a** with 1-benzylbenzimidazol-2-yl moiety (**8c**) resulted in a decrease in the intrinsic activity of β3-AR (EC_{50} = 0.14 μM, IA = 0.48). The 1-benzylimidazol-4-yl derivative (**14g**) displayed similar results to that of **8c**. These results indicated that such modification of the 1-benzylimidazol-2-yl moiety in **21a** may not improve the potency of β3-AR. On the other hand, the introduction of the chloro or bromo group (**14d** and **14e**) on the benzyl group of the imidazole ring in **21a** allowed the potency of β3-AR to be maintained, but induced a twofold increase in potency at the β1-AR. The results obtained for the 2-naphthylmethyl derivative (**14f**) were similar to that of **14d**. These results indicated that the modification of the benzyl group of the imidazol-2-yl moiety in **21a** may not be efficacious for improving a functional selectivity over β1-AR.

Table 2
β-AR agonistic activity of phenoxypropanolamine derivatives containing acetanilides



Compound	Ar	EC_{50}, μM[a] (IA[b])		
		β3-AR	β2-AR	β1-AR
5c		120 (0.93)	>100 (0.01)	>100 (0.11)
8a		0.33 (0.36)	>100 (0.01)	0.39 (0.18)
8b		0.28 (0.35)	>100 (0)	0.31 (0.17)
14a		0.043 (0.39)	>100 (0.02)	0.055 (0.36)
14b		2.5 (0.47)	>100 (0)	0.20 (0.12)
14h		9.6 (0.62)	>100 (0.09)	0.51 (0.26)
14c		0.65 (0.52)	>100 (0)	>100 (0.09)
21a		0.18 (0.77)	>100 (0)	0.13 (0.20)
8c		0.14 (0.48)	>100 (0)	>100 (0.02)
14g		0.13 (0.46)	>100 (0.02)	0.28 (0.06)
14d		0.27 (0.53)	>100 (0)	0.074 (0.13)
14e		0.19 (0.63)	>100 (0.02)	0.071 (0.30)
14f		0.26 (0.54)	>100 (0.01)	0.069 (0.17)

[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, the introduction of a methyl group at the α-position of the secondary amine on the central part of **21a** was investigated as shown in Table 3. One diastereomer of the α-methyl derivative **27a** showed a threefold increase in potency at the β3-AR (EC_{50} = 0.062 μM, IA = 0.64) relative to **21a**, and was the most potent β3-AR agonist in this study; however its functional selectivity over β1-AR was not improved. Another diastereomer of the α-methyl derivative **27b** showed a decrease in potency at both the β3- and β1-ARs relative to **21a**.

Lastly, we examined the introduction of a methyl group on the nitrogen of the acetanilide moiety in **21a**. This new compound **21b** maintained full agonistic activity at the β3-AR (EC_{50} = 0.28 μM, IA = 0.89) and dramatically decreased agonistic activity at the β1-AR (EC_{50} = >100 μM). Furthermore, the agonistic activity of the *N*-propylacetanilide derivative (**17**) at the β3-AR was comparable to that of **21b** (EC_{50} = 0.50 μM, IA = 0.90), with excellent functional selectivity over β1-AR. In contrast, the 1,2,3,4-tetrahydroquinoline derivative (**33**), a cyclic analogue of **17**, showed a decrease in intrinsic activity at the β3-AR (EC_{50} = 0.17 μM, IA = 0.33) relative to **21a**. These results suggested that the substituent on the nitrogen of the acetanilide moiety may play a very important role in diminishing β1-AR agonistic activity.

Given the results of the in vitro study, compounds **21a** and **21b** were selected for in vivo evaluation in a rodent model of type II diabetes (Table 4). The compounds were administered orally for 4 days in diabetic kk mice and the effects on plasma glucose were measured. Both compounds exhibited a significant reduction in plasma glucose levels at the dose of 30 mg/kg (43% and 38% decrease, respectively).

4. Conclusion

In this study, a new series of phenoxypropanolamine derivatives containing acetanilides as β3-AR agonists was identified, and their synthesis and SARs were described. Among these compounds, 1-benzylimidazol-2-ylacetanilide derivatives (**21a**, **21b**, and **27a**) showed potent agonistic activity at the β3-AR (EC_{50} = 0.18, 0.28, and 0.062 μM, respectively). With agonistic activity almost completely abolished at both the β1- and β2-ARs, the *N*-methyl-1-benzylimidazol-2-ylacetanilide derivative (**21b**) was found to be the most potent and selective β3-AR agonist in this study. In addition, **21b** exhibited significant hypoglycemic activity in diabetic kk mice.

Table 4
Oral hypoglycemic activity in kk mice

Compound	Percent reduction in plasma glucose[a]
21a	43[**b]
21b	38[**]

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

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.

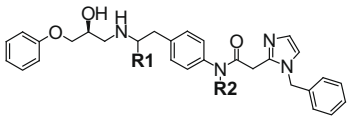
5.1.1. 4′-Cyanomethyl-2-(2-pyridyl)acetanilide (3)

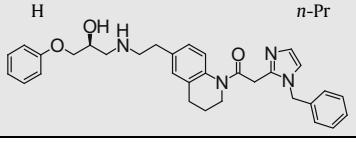
To a solution of 2-pyridylacetic acid hydrochloride (**2**) (10 g) and 4-aminobenzylcyanide (9.1 g) in *N,N*-dimethylformamide (500 mL) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (11.6 g) and 1-hydroxybenzotriazole hydrate (9.3 g), and the mixture was stirred at room temperature for 8 h. To the resulting mixture was added triethylamine (16.5 mL), and the 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 $CHCl_3$/MeOH (20:1) as the eluent to yield **3** (3.2 g) as a colorless solid. 22% yield; ^{1}H NMR ($CDCl_3$) δ: 3.70 (2H, s), 3.88 (2H, s), 7.15–7.33 (7H, m), 8.61–8.65 (1H, m), 10.02 (1H, br s); MS (FAB) *m/z*: 252 (MH^+).

5.1.2. 4′-(2-Aminoethyl)-2-(2-pyridyl)acetanilide (4)

To a solution of **3** (3.65 g) and concentrated aqueous ammonia solution (15 mL) in tetrahydrofuran (70 mL) and ethanol (70 mL)

Table 3
β-AR agonistic activity of 1-benzylimidazol-2-ylacetanilide derivatives



Compound	R1	R2	EC_{50}, μM[a] (IA[b])		
			β3-AR	β2-AR	β1-AR
21a	H	H	0.18 (0.77)	>100 (0)	0.13 (0.20)
27a[c]	Me	H	0.062 (0.64)	0.027 (0.09)	0.030 (0.16)
27b[d]	Me	H	0.35 (0.83)	>100 (0.02)	0.25 (0.19)
21b	H	Me	0.28 (0.89)	>100 (0)	>100 (0.04)
17	H	*n*-Pr	0.50 (0.90)	>100 (0)	>100 (0.01)
33			0.17 (0.33)	>100 (0)	0.12 (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.
[c] Less polar compound of diastereomer.
[d] High polar compound of diastereomer.

was added Raney-nickel, and the mixture was stirred under a hydrogen atmosphere for 16 h. The catalyst was removed by filtration over Celite, and the filtrate was concentrated in vacuo to yield **4** (3.7 g) as a colorless oil. 99% yield; ^{1}H NMR (DMSO-d_6) δ: 2.55–3.18 (4H, m), 3.57 (2H, br s), 3.82 (2H, s), 7.06–7.77 (7H, m), 8.50–8.52 (1H, m), 10.15 (1H, s); MS (FAB) *m/z*: 256 (MH^+).

5.1.3. (*S*)-4′-(2-{[2-Hydroxy-3-(3-pyridyloxy)propyl]amino}-ethyl)-2-(2-pyridyl)acetanilide hydrochloride (5a)

A mixture of **4** (0.51 g), (*S*)-2-(3-pyridyloxymethyl)oxirane[15] (0.3 g), and triethylamine (0.3 mL) in 2-propanol (10 mL) was heated at 70 °C for 2 h. After cooling to room temperature, the resultant mixture was concentrated in vacuo. The residue was partitioned between chloroform and $NaHCO_3$ aqueous solution, 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 as the eluent, followed by addition of 4 M HCl–dioxane in acetone to yield **5a** (0.14 g) as a colorless powder. 15% yield; ^{1}H NMR (DMSO-d_6) δ: 2.80–3.30 (6H, m), 3.75 (2H, s), 4.09 (2H, d, J = 5.6 Hz), 4.25–4.27 (1H, m), 5.98 (1H, br s), 7.19 (2H, d, J = 8.4 Hz), 7.34–7.41 (2H, m), 7.46–7.50 (2H, m), 7.59 (2H, d, J = 8.4 Hz), 7.83–7.88 (1H, m), 8.22 (1H, s), 8.35 (1H, s), 8.55 (1H, d, J = 3.6 Hz), 8.95 (1H, s), 9.19 (1H, s), 10.42 (1H, s); MS (FAB) *m/z*: 407 (MH^+); Anal. Calcd for $C_{23}H_{26}N_4O_3\cdot1.2HCl\cdot0.9H_2O$: C, 59.22; H, 6.27; N, 12.01; Cl, 9.12. Found: C, 59.32; H, 6.12; N, 11.96; Cl, 9.10.

5.1.4. (*S*)-4′-(2-{[2-Hydroxy-3-(4-methylsulfonamidophenoxy)-propyl]amino}ethyl)-2-(2-pyridyl)acetanilide hydrochloride (5b)

The title compound was prepared in the same manner as described for **5a** using (*S*)-2-[(4-methylsulfonylaminophenoxy)methyl]oxirane[16] instead of (*S*)-2-(3-pyridyloxymethyl)-oxirane as a colorless solid. 16% yield; mp 231–234 °C (dec.) (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.80–3.30 (6H, m), 2.88 (3H, s), 3.85 (2H, s), 3.92–3.98 (2H, m), 4.18–4.22 (1H, m), 5.90 (1H, d, J = 5.2 Hz), 6.93–6.96 (2H, m), 7.15–7.20 (4H, m), 7.25–7.28 (1H, m), 7.38–7.41 (1H, m), 7.57–7.60 (2H, m), 7.73–7.78 (1H, m), 8.48–8.50 (1H, m), 8.84 (1H, br s), 9.05 (1H, br s), 9.42 (1H, s), 10.33 (1H, s); MS (FAB) *m/z*: 499 (MH^+); Anal. Calcd for $C_{25}H_{30}N_4O_5S\cdot HCl$: C, 56.12; H, 5.84; N, 10.47; S, 5.99; Cl, 6.63. Found: C, 55.87; H, 5.80; N, 10.36; S, 6.02; Cl, 6.69.

5.1.5. (*S*)-4′-(2-{[2-Hydroxy-3-phenoxypropyl]amino}ethyl)-2-(2-pyridyl)acetanilide hydrochloride (5c)

The title compound was prepared in the same manner as described for **5a** using (*S*)-2-phenoxymethyloxirane instead of (*S*)-2-(3-pyridyloxymethyl)oxirane as a colorless solid. 35% yield; mp 205–207 °C (MeOH–EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.91–3.07 (3H, m), 3.14–3.20 (3H, m), 3.90 (2H, s), 3.93–4.01 (2H, m), 4.20–4.22 (1H, m), 5.90 (1H, br s), 6.94–6.97 (3H, m), 7.19 (2H, d, J = 8.8 Hz), 7.28–7.37 (3H, m), 7.48 (1H, d, J = 8.0 Hz), 7.58 (2H, d, J = 8.8 Hz), 7.84–7.88 (1H, m), 8.55 (1H, d, J = 4.8 Hz), 8.80 (1H, br s), 8.97 (1H, br s), 10.36 (1H, s); MS (FAB) *m/z*: 406 (MH^+); Anal. Calcd for $C_{25}H_{27}N_5O_4\cdot1.1HCl\cdot0.5H_2O$: C, 63.41; H, 6.45; N, 9.24; Cl, 8.58. Found: C, 63.12; H, 6.04; N, 9.13; Cl, 8.80.

5.1.6. (*S*)-4′-(2-{[2-Hydroxy-3-(2-benzimidazolon-4-yloxy)-propyl]amino}ethyl)-2-(2-pyridyl)-acetanilide hydrochloride (5d)

The title compound was prepared in the same manner as described for **5a** using (*S*)-2-[4-(2-benzimidazolon-4-yloxy)methyl]oxirane[17] instead of (*S*)-2-(3-pyridyloxymethyl)oxirane as a colorless powder. 36% yield; ^{1}H NMR (DMSO-d_6) δ: 2.92–3.02 (3H, m), 3.13–3.20 (3H, m), 3.84 (2H, s), 3.97–4.09 (2H, m), 4.17–4.25 (1H, m), 5.79 (1H, d, J = 4.8 Hz), 6.59–6.64 (2H, m), 6.85–6.89 (1H, m), 7.20 (2H, d, J = 8.8 Hz), 7.25–7.28 (1H, m), 7.40 (1H, d, J = 8.0 Hz), 7.59 (2H, d, J = 8.8 Hz), 7.73–7.78 (1H, m), 8.48–8.51 (1H, m), 8.83 (2H, br s), 10.31 (1H, s), 10.63 (1H, s), 10.69 (1H, s); MS (FAB) *m/z*: 462 (MH^+); Anal. Calcd for $C_{25}H_{27}N_5O_4\cdot HCl\cdot0.9H_2O$: C, 58.40; H, 5.84; N, 13.62; Cl, 6.89. Found: C, 58.52; H, 5.71; N, 13.61; Cl, 6.59.

5.1.7. (*S*)-4′-(2-{[2-Hydroxy-3-(indol-4-yloxy)propyl]amino}-ethyl)-2-(2-pyridyl)acetanilide hydrochloride (5e)

The title compound was prepared in the same manner as described for **5a** using (*S*)-2-(indol-4-yloxymethyl)oxirane[18] instead of (*S*)-2-(3-pyridyloxymethyl)oxirane as a colorless powder. 27% yield; ^{1}H NMR (DMSO-d_6) δ: 2.80–3.30 (6H, m), 4.02–4.13 (2H, m), 4.18 (2H, s), 4.26–4.34 (1H, m), 6.47–6.51 (2H, m), 6.96–7.03 (2H, m), 7.20–7.30 (3H, m), 7.58 (2H, d, J = 8.4 Hz), 7.72–7.78 (1H, m), 7.85 (1H, d, J = 8.0 Hz), 8.22 (1H, s), 8.25–8.35 (1H, m), 8.77 (1H, d, J = 4.4 Hz), 8.85 (1H, br s), 9.04 (1H, br s), 10.60 (1H, s), 11.12 (1H, s); MS (FAB) *m/z*: 445 (MH^+); Anal. Calcd for $C_{26}H_{28}N_4O_3\cdot1.8HCl\cdot1.6H_2O$: C, 57.94; H, 6.17; N, 10.40; Cl, 11.84. Found: C, 58.35; H, 6.23; N, 9.93; Cl, 11.93.

5.1.8. (*S*)-4′-(2-{[2-Hydroxy-3-(carbazol-4-yloxy)propyl]-amino}ethyl)-2-(2-pyridyl)acetanilide hydrochloride (5f)

The title compound was prepared in the same manner as described for **5a** using (*S*)-2-(carbazol-4-yloxymethyl)oxirane instead of (*S*)-2-(3-pyridyloxymethyl)oxirane as a colorless solid. 40% yield; mp 208–210 °C (MeOH–EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.40 (6H, m), 3.84 (2H, s), 4.18–4.27 (2H, m), 4.40–4.50 (1H, m), 6.04 (1H, d, J = 4.8 Hz), 6.71 (1H, d, J = 8.0 Hz), 7.09–7.47 (9H, m), 7.59 (2H, d, J = 8.0 Hz), 7.73–7.78 (1H, m), 8.23 (1H, d, J = 7.6 Hz), 8.50 (1H, d, J = 8.8 Hz), 8.92–9.03 (2H, m), 10.30 (1H, s), 11.31 (1H, s); MS (FAB) *m/z*: 495 (MH^+); Anal. Calcd for $C_{30}H_{30}N_4O_3\cdot HCl$: C, 67.85; H, 5.88; N, 10.55; Cl, 6.68. Found: C, 67.82; H, 5.84; N, 10.48; Cl, 6.57.

5.1.9. 4′-Cyanomethyl-2-(3-methyl-2-pyridyl)acetanilide (7a)

The mixture of ethyl (3-methyl-2-pyridyl)acetate (**6a**) (2.62 g) and 4-aminobenzylcyanide (1.63 g) in xylene (20 mL) was refluxed for 13 h. After cooling to room temperature, the resultant mixture was concentrated in vacuo. The residue was triturated in diethyl ether and filtered to yield **7a** (2.61 g) as a colorless solid. 65% yield; ^{1}H NMR ($CDCl_3$) δ: 2.40 (3H, s), 3.70 (2H, s), 3.89 (2H, s), 7.14–7.26 (3H, m), 7.52–7.59 (3H, m), 8.44–8.46 (1H, m), 10.06 (1H, s); MS (FAB) *m/z*: 266 (MH^+).

5.1.10. 4′-Cyanomethyl-2-(4,6-dimethyl-2-pyridyl)acetanilide (7b)

The title compound was prepared in the same manner as described for **7a** using **6b** instead of **6a** as a colorless solid. 87% yield; ^{1}H NMR ($CDCl_3$) δ: 2.31 (3H, s), 2.59 (3H, s), 3.71 (2H, s), 3.77 (2H, s), 6.90–6.93 (2H, m), 7.25–7.27 (2H, m), 7.56–7.60 (2H, m), 10.60 (1H, br s); MS (FAB) *m/z*: 280 (MH^+).

5.1.11. 4′-Cyanomethyl-2-(1-benzylbenzimidazol-2-yl)acetanilide (7c)

The title compound was prepared in the same manner as described for **7a** using **6c** instead of **6a** as a colorless solid. 85% yield; ^{1}H NMR ($CDCl_3$) δ: 3.71 (2H, s), 3.96 (2H, s), 5.43 (2H, s), 7.03–7.10 (2H, m), 7.24–7.38 (8H, m), 7.60 (2H, d, J = 8.8 Hz), 7.78–7.84 (1H, m), 10.80 (1H, br s); MS (FAB) *m/z*: 381 (MH^+).

5.1.12. (*S*)-4′-(2-{[2-Hydroxy-3-phenoxypropyl]amino}ethyl)-2-(3-methyl-2-pyridyl)acetanilide hydrochloride (8a)

To a mixture of **7a** (0.91 g) and concentrated aqueous ammonia solution (0.5 mL) in tetrahydrofuran (20 mL) was added Raney-nickel, and the mixture was stirred under a hydrogen atmosphere for 3 h. The catalyst was removed by filtration over Celite, and the filtrate was concentrated in vacuo. The residue was added to a solution of (*S*)-2-phenoxymethyl-oxirane (0.55 g) in 2-propanol (20 mL), and the mixture was refluxed for 4 h. After cooling to room temperature, the resultant mixture was concentrated in

vacuo. To a solution of the residue in methanol (5 mL) was added 4 M HCl–EtOAc solution (280 μL), and the mixture was concentrated in vacuo. The residue was purified by recrystallization to yield **8a** (0.37 g) as a colorless solid. 24% yield; mp 192–193 °C (MeOH–EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.39 (3H, s), 2.87–3.21 (6H, m), 3.74 (2H, s), 3.93–4.01 (2H, m), 4.15–4.25 (1H, m), 5.89 (1H, d, J = 4.8 Hz), 6.93–7.00 (5H, m), 7.19 (2H, d, J = 8.8 Hz), 7.28–7.32 (2H, m), 7.58 (2H, d, J = 8.8 Hz), 8.31 (1H, d, J = 4.4 Hz), 10.29 (1H, s); MS (FAB) m/z: 420 (MH^+); Anal. Calcd for $C_{25}H_{29}N_3O_3\cdot HCl\cdot 0.5H_2O$: C, 64.58; H, 6.72; N, 9.04; Cl, 7.62. Found: C, 64.63; H, 6.81; N, 9.00; Cl, 7.77.

5.1.13. (*S*)-4′-(2-{[2-Hydroxy-3-phenoxypropyl]amino}ethyl)-2-(4,6-dimethyl-2-pyridyl)-acetanilide hydrochloride (8b)

The title compound was prepared in the same manner as described for **8a** using **7b** instead of **7a** as a colorless solid. 30% yield; mp 191–192 °C (MeOH–EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.27 (3H, s), 2.40 (3H, s), 2.89–3.21 (6H, m), 3.74 (2H, s), 3.93–4.01 (2H, m), 4.15–4.25 (1H, m), 5.89 (1H, d, J = 4.8 Hz), 6.93–6.96 (4H, m), 7.01 (1H, s), 7.19 (2H, d, J = 8.4 Hz), 7.28–7.32 (2H, m), 7.58 (2H, d, J = 8.4 Hz), 10.29 (1H, s); MS (FAB) m/z: 434 (MH^+); Anal. Calcd for $C_{26}H_{31}N_3O_3\cdot HCl$: C, 66.44; H, 6.86; N, 8.94; Cl, 7.54. Found: C, 66.32; H, 6.85; N, 8.95; Cl, 7.84.

5.1.14. (*S*)-4′-(2-{[2-Hydroxy-3-phenoxypropyl]amino}ethyl)-2-(1-benzyl-benzimidazol-2-yl)-acetanilide hydrochloride (8c)

The title compound was prepared in the same manner as described for **8a** using **7c** instead of **7a** as a colorless solid. 12% yield; mp 226–227 °C (MeOH–EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.30 (6H, m), 3.93–4.01 (2H, m), 4.11 (2H, s), 4.15–4.25 (1H, m), 5.58 (2H, s), 5.89 (1H, d, J = 4.8 Hz), 6.93–6.97 (3H, m), 7.17–7.42 (12H, m), 7.54–7.62 (3H, m), 8.74 (1H, br s), 8.85 (1H, br s), 10.49 (1H, s); MS (FAB) m/z: 535 (MH^+); Anal. Calcd for $C_{33}H_{34}N_4O_3\cdot HCl\cdot 0.1H_2O$: C, 69.18; H, 6.19; N, 9.78; Cl, 6.19. Found: C, 69.07; H, 6.14; N, 9.69; Cl, 6.22.

5.1.15. (*S*)-1-[2-(4-Nitrophenyl)ethylamino]-3-phenoxy-2-propanol (10)

The mixture of 2-(4-nitrophenyl)ethylamine hydrochloride (**9**) (10.34 g), (*S*)-2-phenoxymethyloxirane (7.71 g), and triethylamine (5.20 g) in 2-propanol (100 mL) was refluxed for 9 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 **10** (6.35 g) as a colorless oil. 39% yield; ^{1}H NMR ($CDCl_3$) δ: 2.78–3.01 (6H, m), 3.97 (2H, d, J = 4.9 Hz), 4.01–4.05 (1H, m), 6.89 (2H, d, J = 7.9 Hz), 6.96 (1H, t, J = 7.3 Hz), 7.27 (2H, d, J = 7.3 Hz), 7.37 (2H, d, J = 9.2 Hz), 8.15 (2H, d, J = 8.6 Hz); MS (FAB) m/z: 317 (MH^+).

5.1.16. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxy)propyl-*N*-[2-(4-nitrophenyl)ethyl]carbamate (11)

To a solution of **10** (6.35 g) in tetrahydrofuran (110 mL) was added di-*tert*-butyl dicarbonate (4 g). The mixture was stirred at room temperature for 2 h, and concentrated in vacuo to yield **11** (7.94 g) as a colorless powder. 95% yield; ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.91–3.05 (2H, m), 3.40–3.60 (4H, m), 3.85–4.00 (2H, m), 4.10–4.20 (1H, m), 6.90 (2H, d, J = 8.0 Hz), 6.98 (1H, t, J = 7.0 Hz), 7.09–7.32 (4H, m), 8.15 (2H, d, J = 8.8 Hz); MS (FAB) m/z: 417 (MH^+).

5.1.17. *tert*-Butyl (*S*)-*N*-[2-(4-aminophenyl)ethyl]-*N*-(2-hydroxy-3-phenoxy)propylcarbamate (12)

To a solution of **11** (7.94 g) in ethanol (100 mL) was added palladium–carbon (10% w/w, 0.8 g), and the mixture was stirred under a hydrogen atmosphere for 2 h. The catalyst was removed by filtration, and the filtrate 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 **12** (5.15 g) as a colorless oil. 69% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.67–2.80 (2H, m), 3.30–3.48 (4H, m), 3.57 (2H, br s), 3.82–4.00 (2H, m), 4.06–4.20 (2H, m), 6.61 (2H, d, J = 8.0 Hz), 6.87–7.00 (5H, m), 7.25–7.32 (2H, m); MS (FAB) m/z: 387 (MH^+).

5.1.18. *tert*-Butyl (*S*)-*N*-[2-(4-{[2-(6-chloro-2-pyridyl)acetyl]-amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)-carbamate (13a)

To a solution of **12** (0.51 g) and 6-chloro-2-pyridylacetic acid (0.25 g) in tetrahydrofuran (15 mL) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.25 g) and 1-hydroxybenzotriazole (0.18 g), and the mixture was stirred at room temperature for 14 h. The resulting 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 *n*-hexane/EtOAc (1:1) as the eluent to yield **13a** (0.58 g) as a colorless powder. 81% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.85 (2H, m), 3.30–3.50 (4H, m), 3.83 (2H, s), 3.87–3.95 (2H, m), 4.09–4.13 (2H, m), 6.88–7.00 (3H, m), 7.06–7.14 (2H, m), 7.25–7.30 (4H, m), 7.47 (2H, d, J = 8.0 Hz), 7.52–7.68 (1H, m), 9.19 (1H, br s); MS (FAB) m/z: 540 (MH^+).

5.1.19. *tert*-Butyl (*S*)-*N*-[2-(4-{[2-(6-benzyloxy-2-pyridyl)acetyl]-amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (13b)

The title compound was prepared in the same manner as described for **13a** using 6-benzyloxy-2-pyridylacetic acid instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 60% yield; ^{1}H NMR ($CDCl_{3)\ \delta}$: 1.46 (9H, s), 2.72–2.85 (2H, m), 3.30–3.50 (4H, m), 3.78 (2H, s), 3.86–3.94 (2H, m), 4.11 (1H, br s), 5.46 (2H, s), 5.58–7.09 (7H, m), 7.22–7.40 (7H, m), 7.45–7.48 (2H, m), 7.57–7.61 (1H, m), 9.05 (1H, br s); MS (FAB) m/z: 612 (MH^+).

5.1.20. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxypropyl)-*N*-[2-(4-{[2-(1-phenylimidazol-2-yl)-acetyl]amino}phenyl)ethyl]-carbamate (13c)

The title compound was prepared in the same manner as described for **13a** using 1-phenylimidazol-2-ylacetic acid hydrochloride[19] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 75% yield; ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.75–2.85 (2H, m), 3.35–4.00 (4H, m), 3.73 (2H, s), 3.80–4.00 (2H, m), 4.05–4.10 (1H, m), 6.89–7.00 (3H, m), 7.10–7.18 (4H, m), 7.28–7.30 (4H, m), 7.47–7.53 (5H, m), 10.44 (1H, br s); MS (FAB) m/z: 571 (MH^+).

5.1.21. *tert*-Butyl (*S*)-*N*-{2-[4-({2-[1-(4-chlorobenzyl)imidazol-2-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxy-propyl)carbamate (13d)

The title compound was prepared in the same manner as described for **13a** using 1-(4-chlorobenzyl)imidazol-2-ylacetic acid hydrochloride[20] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 98% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.87 (2H, m), 3.30–3.50 (4H, m), 3.71 (2H, s), 3.80–4.00 (2H, m), 4.05–4.10 (1H, m), 5.21 (2H, s), 6.89–7.20 (10H, m), 7.25–7.30 (3H, m), 7.45 (2H, d, J = 8.3 Hz), 10.15 (1H, br s); MS (FAB) m/z: 619 (MH^+).

5.1.22. *tert*-Butyl (*S*)-*N*-{2-[4-({2-[1-(4-bromobenzyl)imidazol-2-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxy-propyl)carbamate (13e)

The title compound was prepared in the same manner as described for **13a** using 1-(4-bromobenzyl)imidazol-2-ylacetic acid hydrochloride[20] instead of 6-chloro-2-pyridylacetic acid as a

colorless powder. 68% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.85 (2H, m), 3.30–3.50 (4H, m), 3.70 (2H, s), 3.80–4.00 (2H, m), 4.05–4.15 (1H, m), 5.11 (2H, s), 6.89–6.98 (6H, m), 7.00–7.15 (3H, m), 7.20–7.35 (2H, m), 7.40–7.50 (4H, m), 10.14 (1H, br s); MS (FAB) *m/z*: 665 (MH^+).

5.1.23. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[1-(2-naphtylmethyl)-imidazol-2-yl]acetyl}amino)phenyl]-ethyl}carbamate (13f)

The title compound was prepared in the same manner as described for **13a** using 1-(2-naphtylmethyl)imidazol-2-ylacetic acid hydrochloride[20] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 63% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.85 (2H, m), 3.30–3.50 (4H, m), 3.76 (2H, s), 3.80–4.00 (2H, m), 4.00–4.05 (1H, m), 5.30 (2H, s), 6.89–7.12 (7H, m), 7.20–7.30 (3H, m), 7.44–7.50 (5H, m), 7.74–7.83 (3H, m), 10.30 (1H, br s); MS (FAB) *m/z*: 635 (MH^+).

5.1.24. *tert*-Butyl (*S*)-*N*-[2-(4-{[2-(1-benzylimidazol-4-yl)acetyl]-amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (13g)

The title compound was prepared in the same manner as described for **13a** using 1-benzylimidazol-4-ylacetic acid instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 81% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.78 (2H, br s), 3.30–3.50 (4H, m), 3.62 (2H, s), 3.89–3.94 (2H, m), 4.11 (1H, br s), 5.09 (2H, s), 6.80 (1H, s), 6.89 (2H, d, J = 8.3 Hz), 6.98 (1H, t, J = 7.2 Hz), 7.07 (2H, br s), 7.18 (2H, dd, J = 2.1, 7.2 Hz), 7.26–7.31 (2H, m), 7.36–7.40 (3H, m), 7.46 (2H, d, J = 8.3 Hz), 7.56 (1H, s), 9.44 (1H, br s); MS (FAB) *m/z*: 585 (MH^+).

5.1.25. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[1-(4-nitrobenzyl)imidazol-2-yl]acetyl}amino)phenyl]-ethyl}carbamate (13h)

The title compound was prepared in the same manner as described for **13a** using 1-(4-nitrobenzyl)imidazol-2-ylacetic acid[21] instead of 6-chloro-2-pyridylacetic acid as a colorless powder. 95% yield; ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.75–2.85 (2H, m), 3.30–3.50 (4H, m), 3.80–4.00 (4H, m), 4.05–4.10 (2H, m), 5.50 (2H, s), 6.88–6.98 (4H, m), 7.05–7.15 (3H, m), 7.25–7.75 (4H, m), 8.19 (2H, d, J = 8.8 Hz), 9.78 (1H, br s); MS (FAB) *m/z*: 639 (MH^+).

5.1.26. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxypropyl)-*N*-[2-(4-{[2-(*1H*-imidazol-2-yl)acetyl]-amino}phenyl)ethyl]carbamate (13i)

To a solution of **13h** (2.15 g) in methanol (200 mL) was added 4 M HCl–EtOAc solution (1.0 mL). The mixture was stirred at room temperature for 5 min and concentrated in vacuo. To a solution of the residue in methanol (150 mL) was added palladium on carbon (10% w/w, 0.67 g), and the mixture was stirred under hydrogen atmosphere for 5 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 **13i** (0.96 g) as a colorless powder. 56% yield; ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.85 (2H, m), 3.30–3.55 (4H, m), 3.80–4.00 (2H, m), 3.90 (2H, s), 4.05–4.15 (1H, m), 6.88–6.98 (3H, m), 7.00–7.20 (4H, m), 7.30–7.40 (2H, m), 7.50 (2H, d, J = 7.8 Hz), 10.03 (1H, br s); MS (FAB) *m/z*: 495 (MH^+).

5.1.27. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(6-chloro-2-pyridyl)acetanilide hydrochloride (14a)

To a solution of **13a** (0.56 g) in ethanol (10 mL) was added 4 M HCl–EtOAc (10 mL), and the mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated in vacuo. The crude solid was purified by recrystallization from methanol–ethanol–diethyl ether to yield **14a** (0.38 g) as a colorless solid. 77% yield; mp 234–236 °C (MeOH–EtOH–Et_2O); ^{1}H NMR (DMSO-d_6) δ: 2.92–3.08 (3H, m), 3.13–3.24 (3H, m), 3.89 (2H, s), 3.92–4.05 (2H, m), 4.24–4.29 (1H, m), 5.94 (1H, br s), 6.93–7.01 (3H, m), 7.20 (2H, d, J = 8.8 Hz), 7.27–7.32 (2H, m), 7.39–7.45 (2H, m), 7.61 (2H, d, J = 8.8 Hz), 7.80–7.86 (1H, m), 9.01 (1H, br s), 9.29 (1H, br s), 10.51 (1H, s); MS (FAB) *m/z*: 440 (MH^+); Anal. Calcd for $C_{24}H_{26}N_3O_3Cl$·HCl: C, 60.51; H, 5.71; N, 8.82; Cl, 14.88. Found: C, 60.40; H, 5.98; N, 8.71; Cl, 14.71.

5.1.28. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(6-benzyloxy-2-pyridyl)-acetanilide hydrochloride (14b)

The title compound was prepared in the same manner as described for **14a** using **13b** instead of **13a** as a colorless solid. 45% yield; mp 227–229 °C (MeOH–EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.88–3.05 (3H, m), 3.14–3.20 (3H, m), 3.77 (2H, s), 3.93–4.01 (2H, m), 4.22 (1H, br s), 5.32 (2H, s), 5.90 (1H, br s), 6.73 (1H, d, J = 8.3 Hz), 6.94–7.00 (4H, m), 7.20 (2H, d, J = 8.8 Hz), 7.26–7.33 (5H, m), 7.42–7.45 (2H, m), 7.60 (2H, d, J = 8.3 Hz), 7.65–7.70 (1H, m), 8.83 (1H, br s), 9.02 (1H, br s), 10.28 (1H, s); MS (FAB) *m/z*: 512 (MH^+); Anal. Calcd for $C_{31}H_{33}N_3O_4$·HCl: C, 67.94; H, 6.25; N, 7.67; Cl, 6.47. Found: C, 67.79; H, 6.31; N, 7.67; Cl, 6.47.

5.1.29. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(1-phenylimidazol-2-yl)-acetanilide dihydrochloride (14c)

The title compound was prepared in the same manner as described for **14a** using **13c** instead of **13a** as a colorless powder. 79% yield; ^{1}H NMR (DMSO-d_6) δ: 2.90–3.05 (3H, m), 3.05–3.25 (3H, m), 3.97 (2H, t, J = 5.4 Hz), 4.10–4.25 (3H, m), 5.92 (1H, br s), 6.93–6.98 (3H, m), 7.18 (2H, d, J = 8.6 Hz), 7.30 (2H, t, J = 8.0 Hz), 7.44 (2H, d, J = 8.0 Hz), 7.60–7.63 (5H, m), 7.85 (1H, d, J = 1.6 Hz), 7.97 (1H, d, J = 2.2 H), 8.90 (1H, br s), 9.16 (1H, br s), 10.62 (1H, s); MS (FAB) *m/z*: 471 (MH^+); Anal. Calcd for $C_{28}H_{30}N_4O_3$·2HCl·1.8H_2O: C, 58.40; H, 6.23; N, 9.73; Cl, 12.31. Found: C, 58.39; H, 6.16; N, 9.50; Cl, 12.44.

5.1.30. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[1-(4-chlorobenzyl)imidazol-2-yl]acetanilide dihydrochloride (14d)

The title compound was prepared in the same manner as described for **14a** using **13d** instead of **13a** as a colorless solid. 57% yield; mp 200–205 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.94–3.17 (6H, m), 3.94–4.04 (2H, m), 4.23–4.25 (1H, m), 4.44 (2H, s), 5.47 (2H, s), 5.92 (1H, br s), 6.93–6.97 (3H, m), 7.21 (2H, d, J = 8.8 Hz), 7.28–7.33 (2H, m), 7.37–7.45 (4H, m), 7.51–7.57 (2H, m), 7.69–7.71 (2H, m), 8.94 (1H, br s), 9.22 (1H, br s), 10.91 (1H, s); MS (FAB) *m/z*: 519 (MH^+); Anal. Calcd for $C_{29}H_{31}N_4O_3Cl$·2HCl·0.1H_2O: C, 58.66; H, 5.64; N, 9.44; Cl, 17.91. Found: C, 58.41; H, 5.47; N, 9.39; Cl, 18.08.

5.1.31. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[1-(4-bromobenzyl)imidazol-2-yl]acetanilide dihydrochloride (14e)

The title compound was prepared in the same manner as described for **14a** using **13e** instead of **13a** as a colorless solid. 89% yield; mp 207–210 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.95–3.18 (6H, m), 3.94–4.04 (2H, m), 4.23–4.25 (1H, m), 4.42 (2H, s), 5.46 (2H, s), 5.92 (1H, br s), 6.93–6.97 (3H, m), 7.21 (2H, d, J = 8.8 Hz), 7.28–7.33 (4H, m), 7.49–7.55 (4H, m), 7.70 (2H, s), 8.91 (1H, br s), 9.17 (1H, br s), 10.86 (1H, s); MS (FAB) *m/z*: 565 (MH^+); Anal. Calcd for $C_{29}H_{31}N_4O_3Br$·2HCl: C, 54.73; H, 5.23; N, 8.80; Cl, 11.14, Br, 12.56. Found: C, 54.56; H, 5.04; N, 8.76; Cl, 11.02, Br, 12.35.

5.1.32. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[1-(2-naphtylmethyl)imidazol-2-yl]acetanilide dihydrochloride (14f)

The title compound was prepared in the same manner as described for **14a** using **13f** instead of **13a** as a colorless solid. 75% yield; mp 215–218 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.94–3.15 (6H, m), 3.94–4.04 (2H, m), 4.23–4.25 (1H, m), 4.47 (2H, s), 5.63 (2H, s), 5.92 (1H, br s), 6.94–6.97 (3H, m), 7.17 (2H, d, J = 8.0 Hz), 7.28–7.33 (2H, m), 7.48–7.55 (5H, m), 7.71–7.93 (6H, m), 8.91 (1H, br s), 9.15 (1H, br s), 10.88 (1H, s); MS (FAB) m/z: 535 (MH^+); Anal. Calcd for $C_{33}H_{34}N_4O_3Cl{\cdot}2HCl{\cdot}0.5H_2O$: C, 64.28; H, 6.05; N, 9.09; Cl, 11.50. Found: C, 64.52; H, 5.96; N, 9.07; Cl, 11.52.

5.1.33. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(1-benzylimidazol-4-yl)-acetanilide dihydrochloride (14g)

The title compound was prepared in the same manner as described for **14a** using **13g** instead of **13a** as a colorless solid. 63% yield; mp 121–123 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.89–3.17 (6H, m), 3.92 (2H, s), 3.95–4.11 (2H, m), 4.27–4.29 (1H, m), 5.44 (2H, s), 6.93–6.97 (4H, m), 7.20 (2H, d, J = 8.3 Hz), 7.27–7.47 (7H, m), 7.58–7.66 (3H, m), 9.09 (1H, br s), 9.34 (1H, s), 9.42 (1H, br s), 10.74 (1H, s); MS (FAB) m/z: 485 (MH^+); Anal. Calcd for $C_{29}H_{32}N_4O_3{\cdot}2.4HCl{\cdot}1.3H_2O$: C, 58.49; H, 6.26; N, 9.41; Cl, 14.29. Found: C, 58.72; H, 6.12; N, 9.15; Cl, 14.04.

5.1.34. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(*1H*-imidazol-2-yl)acetanilide dihydrochloride (14h)

The title compound was prepared in the same manner as described for **14a** using **13i** instead of **13a** as a colorless solid. 94% yield; mp 195–201 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.99–3.17 (6H, m), 3.94–4.01 (2H, m), 4.21–4.25 (1H, m), 4.27 (2H, s), 5.91 (1H, br s), 6.94–6.97 (3H, m), 7.22 (2H, d, J = 8.4 Hz), 7.28–7.32 (2H, m), 7.57–7.62 (4H, m), 8.93 (1H, br s), 9.19 (1H, br s), 10.82 (1H, s); MS (FAB) m/z: 395 (MH^+); Anal. Calcd for $C_{22}H_{26}N_4O_3{\cdot}2HCl$: C, 56.54; H, 6.04; N, 11.99; Cl, 15.17. Found: C, 56.37; H, 6.07; N, 11.78; Cl, 15.38.

5.1.35. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxy)propyl-*N*-[2-(4-propylaminophenyl)ethyl]-carbamate (15)

To a solution of **12** (1.52 g), propionaldehyde (0.23 g), and acetic acid (0.34 mL) in tetrahydrofuran (30 mL) was added sodium triacetoxyborohydride (1.25 g). The mixture was stirred at room temperature for 2 h, and partitioned between ethyl acetate and water. 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 **15** (1.69 g) as a colorless powder. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7.0 Hz), 1.37 (9H, s), 1.45–1.75 (2H, m), 2.60 (2H, t, J = 7.0 Hz), 2.91 (2H, q, J = 7.0 Hz), 2.98–3.40 (4H, m), 3.78–4.00 (3H, m), 6.80–7.32 (7H, m); MS (FAB) m/z: 428 (M^+).

5.1.36. *tert*-Butyl (*S*)-*N*-[2-(4-{[2-(1-benzylimidazol-2-yl)acetyl]-*N*-(propyl)amino}phenyl)-ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (16)

The title compound was prepared in the same manner as described for **13a** using **15** and 1-benzylimidazol-2-ylacetic acid instead of **12** and 6-chloro-2-pyridylacetic acid as a colorless powder. 81% yield; ^{1}H NMR ($CDCl_3$) δ: 0.81 (3H, t, J = 7.0 Hz), 1.32 (9H, s), 1.30–1.45 (2H, m), 2.81 (2H, t, J = 7.0 Hz), 3.00–3.50 (4H, m), 3.26 (2H, s), 3.55 (2H, t, J = 7.0 Hz), 3.75–4.05 (3H, m), 5.04 (2H, s), 6.50–7.52 (16H, m); MS (FAB) m/z: 627 (MH^+).

5.1.37. (*S*)-*N*-Propyl-4′-{2-[(2-hydroxy-3-phenoxypropyl)-amino]ethyl}-2-(1-benzylimidazol-2-yl)acetanilide dihydrochloride (17)

The title compound was prepared in the same manner as described for **14a** using **16** instead of **13a** as a colorless powder. 62% yield; ^{1}H NMR (DMSO-d_6) δ: 0.82 (3H, t, J = 7.0 Hz), 1.36–1.46 (2H, m), 3.00–4.35 (9H, m), 3.56 (2H, t, J = 7.0 Hz), 3.95 (2H, s), 5.34 (2H, s), 6.92–7.66 (16H, m); MS (FAB) m/z: 527 (MH^+); Anal. Calcd for $C_{32}H_{38}N_4O_3{\cdot}2HCl{\cdot}H_2O$: C, 62.23; H, 6.85; N, 9.07; Cl, 11.48. Found: C, 62.19; H, 7.01; N, 9.09; Cl, 11.72.

5.1.38. 4′-[2-(*tert*-Butoxycarbonyl)aminoethyl]-2-(1-benzylimidazol-2-yl)acetanilide (19a)

To a solution of 4-[2-(*tert*-Butoxycarbonyl)aminoethyl]aniline (**18a**)[22] (0.95 g) and 1-benzylimidazol-2-ylacetic acid hydrochloride (1.00 g) in *N*,*N*-dimethylformamide (20 mL) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.85 g) and 1-hydroxybenzotriazole (0.68 g), and the mixture was stirred at room temperature for 19 h. The resulting 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/concd NH_3 aq (300:10:1) as the eluent to yield **19a** (1.14 g) as a colorless oil. 66% yield; ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.75 (2H, t, J = 6.8 Hz), 3.25–3.40 (2H, m), 3.74 (2H, s), 4.53 (1H, br s), 5.16 (2H, s), 6.94 (1H, d, J = 1.6 Hz), 7.06–7.14 (5H, m), 7.29–7.37 (3H, m), 7.47 (2H, d, J = 8.4 Hz), 10.44 (1H, s); MS (FAB) m/z: 435 (MH^+).

5.1.39. 4′-[2-(*tert*-Butoxycarbonyl)aminoethyl]-2-(1-benzylimidazol-2-yl)-*N*-methyl-acetanilide (19b)

The title compound was prepared in the same manner as described for **19a** using 4-[2-(*tert*-butoxycarbonyl)aminoethyl]-*N*-methylaniline (**18b**)[23] instead of **18a** as a colorless oil. 95% yield; ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.80 (2H, t, J = 6.8 Hz), 3.26 (3H, s), 3.36–3.38 (2H, m), 3.50 (2H, s), 5.17 (2H, s), 6.81 (1H, s), 6.95 (1H, s), 7.05 (2H, d, J = 6.8 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.27–7.33 (4H, m); MS (FAB) m/z: 449 (MH^+).

5.1.40. 4′-(2-Aminoethyl)-2-(1-benzylimidazol-2-yl)acetanilide (20a)

To a solution of **19a** (0.81 g) in methanol (25 mL) was added 4 M HCl–EtOAc solution (25 mL), and the mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated in vacuo and partitioned between chloroform and 1 M NaOH aqueous solution. The organic layer was washed with water and brine, and then dried and concentrated in vacuo to yield **20a** (0.48 g) as a yellow oil. 77% yield; ^{1}H NMR ($CDCl_3$) δ: 1.20 (2H, br s), 2.70 (2H, t, J = 6.8 Hz), 2.93 (2H, t, J = 6.8 Hz), 3.74 (2H, s), 5.15 (2H, s), 6.94 (2H, d, J = 1.2 Hz), 7.07–7.08 (3H, m), 7.13 (2H, d, J = 8.4 Hz), 7.29–7.36 (3H, m), 7.47 (2H, d, J = 8.4 Hz), 10.36 (1H, s); MS (FAB) m/z: 335 (MH^+).

5.1.41. 4′-(2-Aminoethyl)-2-(1-benzylimidazol-2-yl)-*N*-methyl-acetanilide (20b)

The title compound was prepared in the same manner as described for **20a** using **19b** instead of **19a** as a yellow oil. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 1.53 (2H, br s), 2.76 (2H, t, J = 6.8 Hz), 2.98 (2H, t, J = 6.8 Hz), 3.26 (3H, s), 3.50 (2H, s), 5.18 (2H, s), 6.81 (1H, s), 6.95 (1H, s), 7.06 (2H, d, J = 6.0 Hz), 7.14 (2H, d, J = 8.0 Hz), 7.22–7.33 (5H, m); MS (FAB) m/z: 349 (MH^+).

5.1.42. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(1-benzylimidazol-2-yl)-acetanilide hydrochloride (21a)

A mixture of **20a** (0.46 g) and (*S*)-2-phenoxymethyloxirane (0.2 g) in 2-propanol (10 mL) was heated at 90 °C for 22 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/concd NH_3 aq (200:10:1) as the eluent, followed by addition of 4 M HCl–EtOAc in methanol. The residue was purified by recrystallization to yield **21a** (0.13 g) as a colorless solid. 18% yield; mp 148–152 °C (EtOH–EtOAc); ^{1}H NMR (DMSO-d_6) δ: 2.90–3.22 (6H, m), 3.18–3.26 (3H, m), 3.80 (2H, s), 3.93–4.04 (2H, m), 4.20 (1H, br s), 5.25 (2H, s), 5.87 (1H, br s), 6.86 (1H, d, J = 1.2 Hz), 6.93–6.97 (3H, m), 7.13 (1H, d, J = 0.8 Hz), 7.18–7.22 (4H, m), 7.27–7.37 (5H, m), 7.54 (2H, d, J = 8.8 Hz), 10.37 (1H, s); MS (FAB) m/z: 485 (MH^+); Anal. Calcd for $C_{29}H_{32}N_4O_3$·HCl·0.1H_2O: C, 66.62; H, 6.40; N, 10.72; Cl, 6.78. Found: C, 66.38; H, 6.32; N, 10.74; Cl, 6.77.

5.1.43. (*S*)-*N*-Methyl-4′-{2-[(2-hydroxy-3-phenoxypropyl)-amino]ethyl}-2-(1-benzylimidazol-2-yl)acetanilide dihydrochloride (21b)

The title compound was prepared in the same manner as described for **21a** using **20b** instead of **20a** as a colorless powder. 32% yield; ^{1}H NMR (DMSO-d_6) δ: 3.07–3.11 (3H, m), 3.18–3.26 (3H, m), 3.16 (3H, s), 3.96–4.03 (4H, m), 4.28 (1H, br s), 5.34 (2H, s), 5.95 (1H, br s), 6.92–6.97 (3H, m), 7.28–7.45 (11H, m), 7.57 (1H, d, J = 1.6 Hz), 7.63 (1H, d, J = 1.6 Hz), 9.07 (1H, br s), 9.42 (1H, br s), 14.66 (1H, br s); MS (FAB) m/z: 499 (MH^+); Anal. Calcd for $C_{30}H_{34}N_4O_3$·2HCl·1.5H_2O: C, 60.20; H, 6.57; N, 9.36; Cl, 11.85. Found: C, 60.40; H, 6.72; N, 9.17; Cl, 11.77.

5.1.44. (*S*)-1-{2-[3-(4-Nitrophenyl)propyl]amino}-3-phenoxy-2-propanol (23)

A solution of (*S*)-1-amino-3-phenoxy-2-propanol (**22**) (4.90 g) and 4-nitrophenylacetone (5.20 g) in benzene (150 mL) was refluxed for 1 h using Dean-Stark trap. After cooling to room temperature, the resultant mixture was concentrated in vacuo. To a solution of the residue in methanol (80 mL) was added sodium borohydride (0.59 g) at 5 °C, and the mixture was stirred for 2 hs at 5 °C. 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 **23** (8.63 g) as a colorless solid. 89% yield; ^{1}H NMR ($CDCl_3$) δ: 1.10 (3H, d, J = 6.4 Hz), 2.68–3.02 (5H, m), 3.91–4.02 (3H, m), 6.86–6.98 (3H, m), 7.28–7.52 (4H, m), 8.13–8.18 (2H, m); MS (FAB) m/z: 331 (MH^+).

5.1.45. *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxypropyl)-*N*-{2-[3-(4-nitrophenyl)]propyl}-carbamate (24a) and *tert*-Butyl (*S*)-*N*-(2-hydroxy-3-phenoxypropyl)-*N*-*{2-[3-(4-nitrophenyl)]-propyl}carbamate (24b)*

To a solution of **23** (2.81 g) in tetrahydrofuran (50 mL) was added di-*tert*-butyl dicarbonate (1.93 g). The mixture was stirred at room temperature for 15 h, and concentrated in vacuo. The residue was purified using column chromatography on silica gel with benzene/EtOAc (10:1) as the eluent to yield a less polar compound **24a** (1.24 g) and a highly polar compound **24b** (1.06 g) as a colorless powder. Compound **24a**: 33% yield; ^{1}H NMR ($CDCl_3$) δ: 1.24–1.30 (3H, m), 1.35 (9H, s), 2.75–3.50 (4H, m), 3.80–3.90 (1H, m), 3.95–4.30 (3H, m), 6.89–7.00 (3H, m), 7.23–7.35 (4H, m), 8.15 (2H, d, J = 8.3 Hz); MS (FAB) m/z: 431 (MH^+); **24b**: 28% yield; ^{1}H NMR ($CDCl_3$) δ: 1.25–1.28 (3H, m), 1.44 (9H, s), 2.80–3.40 (4H, m), 3.80–3.90 (1H, m), 3.95–4.40 (3H, m), 6.85–7.00 (3H, m), 7.26–7.35 (4H, m), 8.12 (2H, d, J = 8.3 Hz); MS (FAB) m/z: 431 (MH^+).

5.1.46. *tert*-Butyl (*S*)-*N*-{2-[3-(4-aminophenyl)]propyl}-*N*-(2-hydroxy-3-phenoxypropyl)-carbamate (25a)

The title compound was prepared in the same manner as described for **12** using **24a** instead of **11** as a colorless powder. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 1.18–1.25 (3H, m), 1.38 (9H, s), 2.50–2.75 (2H, m), 3.30–3.60 (4H, m), 3.80–4.20 (4H, m), 6.57 (2H, d, J = 8.3 Hz), 6.85–7.00 (5H, m), 7.25–7.35 (2H, m); MS (FAB) m/z: 401 (MH^+).

5.1.47. *tert*-Butyl (*S*)-*N*-{2-[3-(4-aminophenyl)]propyl}-*N*-(2-hydroxy-3-phenoxypropyl)-carbamate (25b)

The title compound was prepared in the same manner as described for **12** using **24b** instead of **11** as a colorless powder. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 1.15–1.25 (3H, m), 1.45 (9H, s), 2.55–4.10 (8H, m), 6.55 (2H, d, J = 8.3 Hz), 6.85–7.00 (5H, m), 7.26–7.32 (2H, m); MS (FAB) m/z: 401 (MH^+).

5.1.48. *tert*-Butyl (*S*)-*N*-{2-[3-(4-{[2-(1-benzylimidazol-2-yl)-acetyl]amino}phenyl)]propyl}-*N*-(2-hydroxy-3-phenoxypropyl)-carbamate (26a)

The title compound was prepared in the same manner as described for **19a** using **25a** instead of **18a** as a colorless powder. 74% yield; ^{1}H NMR ($CDCl_3$) δ: 1.15–1.25 (3H, m), 1.39 (9H, s), 2.60–4.20 (8H, m), 3.75 (2H, s), 5.14 (2H, s), 6.85–7.00 (4H, m), 7.03–7.12 (5H, m), 7.26–7.37 (5H, m), 7.45–7.50 (2H, m), 10.35 (1H, s); MS (FAB) m/z: 599 (MH^+).

5.1.49. *tert*-Butyl (*S*)-*N*-{2-[3-(4-{[2-(1-benzylimidazol-2-yl)acetyl]amino}phenyl)]propyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (26b)

The title compound was prepared in the same manner as described for **19a** using **25b** instead of **18a** as a colorless powder. 82% yield; ^{1}H NMR ($CDCl_3$) δ: 1.15–1.25 (3H, m), 1.46 (9H, s), 2.60–4.20 (8H, m), 3.71 (2H, s), 5.14 (2H, s), 6.85–7.00 (4H, m), 7.05–7.14 (5H, m), 7.26–7.37 (5H, m), 7.44–7.48 (2H, m), 10.31 (1H, s); MS (FAB) m/z: 599 (MH^+).

5.1.50. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]propyl}-2-(1-benzylimidazol-2-yl)-acetanilide dihydrochloride (27a)

The title compound was prepared in the same manner as described for **14a** using **26a** instead of **13a** as a colorless powder. 71% yield; ^{1}H NMR (DMSO-d_6) δ: 1.11 (3H, d, J = 6.2 Hz), 2.60–2.66 (1H, m), 3.00–4.00 (4H, m), 3.96–4.04 (2H, m), 4.28–4.30 (1H, m), 4.44 (2H, s), 5.46 (2H, s), 6.94–6.98 (3H, m), 7.21 (2H, d, J = 8.3 Hz), 7.29–7.38 (7H, m), 7.54 (2H, d, J = 8.8 Hz), 7.67–7.74 (2H, m), 8.85 (1H, s), 9.22 (1H, s), 10.90 (1H, s); MS (FAB) m/z: 499 (MH^+); Anal. Calcd for $C_{30}H_{34}N_4O_3$·2.5HCl·1.2H_2O: C, 58.94; H, 6.41; N, 9.16; Cl, 14.50. Found: C, 58.88; H, 6.40; N, 9.19; Cl, 14.28.

5.1.51. (*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]propyl}-2-(1-benzylimidazol-2-yl)-acetanilide dihydrochloride (27b)

The title compound was prepared in the same manner as described for **14a** using **26b** instead of **13a** as a colorless powder. 78% yield; ^{1}H NMR (DMSO-d_6) δ: 1.13 (3H, d, J = 6.9 Hz), 2.58–2.67 (1H, m), 3.07–3.10 (1H, m), 3.24–3.47 (3H, m), 3.98–4.02 (2H, m), 4.23–4.32 (1H, m), 4.43 (2H, s), 5.46 (2H, s), 6.94–6.98 (3H, m), 7.21 (2H, d, J = 8.3 Hz), 7.29–7.37 (7H, m), 7.54 (2H, d, J = 8.3 Hz), 7.67–7.70 (2H, m), 8.78 (1H, s), 9.20 (1H, s), 10.87 (1H, s); MS (FAB) m/z: 499 (MH^+); Anal. Calcd for $C_{30}H_{34}N_4O_3$·2.2HCl·1.9H_2O: C, 58.78; H, 6.58; N, 9.14; Cl, 12.72. Found: C, 58.69; H, 6.53; N, 9.37; Cl, 12.95.

5.1.52. 6-[2-(Dibenzylamino)acetyl]-1,2,3,4-tetrahydroquinolin-2-one (29)

A solution of 6-bromoacetyl-1,2,3,4-tetrahydroquinolin-2-one (**28**) (8.63 g), dibenzylamine (7.60 g), and *N*,*N*-diisopropyl-*N*-ethylamine (7.8 mL) in 2-butanone (200 mL) was heated at 80 °C for 3 h. After cooling to room temperature, the resultant mixture was concentrated in vacuo. The resultant mixture was diluted with water and extracted 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 (60:1) as the eluent to yield **29** (10.97 g) as a colorless powder. 79% yield; ^{1}H NMR ($CDCl_3$) δ: 2.64–2.69 (2H, m), 2.94–2.98 (2H, m), 3.69–3.75 (6H, m), 6.78 (1H, d, J = 8.4 Hz), 7.23–7.35 (10H, m), 7.67–7.72 (2H, m), 8.91 (1H, s); MS (FAB) *m/z*: 385 (MH^+).

5.1.53. 6-(2-Dibenzylaminoethyl)-1,2,3,4-tetrahydroquinoline (30)

A mixture of **29** (9.45 g) and 1 M borane–THF solution (150 mL) was heated at 80 °C for 4 h. After cooling to room temperature, to the resultant mixture was added methanol (150 mL) and concentrated HCl aqueous solution (150 mL), and the mixture was heated at 100 °C for 1 h. After cooling to room temperature, the resultant mixture was concentrated in vacuo and partitioned between chloroform and 2 M NaOH aqueous solution. 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 *n*-hexane/EtOAc (6:1) as the eluent to yield **30** (9.62 g) as a colorless oil. 99% yield; ^{1}H NMR ($CDCl_3$) δ: 1.83–1.93 (2H, m), 2.65–2.71 (6H, m), 3.24–3.28 (2H, m), 3.56–3.71 (4H, m), 6.37 (1H, d, J = 10.4 Hz), 6.66–6.70 (2H, m), 7.18–7.35 (10H, m), 8.91 (1H, s); MS (FAB) *m/z*: 357 (MH^+).

5.1.54. 1-[(1-Benzylimidazol-2-yl)acetyl]-6-(2-dibenzylaminoethyl)-1,2,3,4-tetrahydroquinoline (31)

The title compound was prepared in the same manner as described for **19a** using **30** instead of **18a** as a colorless oil. 64% yield; ^{1}H NMR ($CDCl_3$) δ: 1.88–1.93 (2H, m), 2.61–2.76 (6H, m), 3.64 (4H, s), 3.82–3.89 (4H, m), 5.25 (2H, s), 6.84–6.90 (3H, m), 7.00 (1H, d, J = 1.6 Hz), 7.06–7.09 (2H, m), 7.18–7.33 (14H, m); MS (FAB) *m/z*: 555 (MH^+).

5.1.55. 6-(2-Aminoethyl)-1-[(1-benzylimidazol-2-yl)acetyl]-1,2,3,4-tetrahydroquinoline (32)

To a solution of **31** (4.56 g) in methanol (100 mL) were added ammonium formate (1.30 g) and palladium on carbon (10% w/w, 0.95 g). The mixture was stirred at room temperature for 15 h, after which the catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified using column chromatography on silica gel with $CHCl_3$/MeOH/concd NH_3 aq (100:10:1) as the eluent to yield **31** (0.55 g) as a colorless oil. 17% yield; ^{1}H NMR ($CDCl_3$) δ: 1.31 (2H, br s), 1.88–1.95 (2H, m), 2.67–2.72 (4H, m), 2.92–2.97 (2H, m), 3.84–4.05 (4H, m), 5.28 (2H, s), 6.86 (1H, d, J = 1.2 Hz), 6.97–7.11 (5H, m), 7.25–7.35 (4H, m); MS (FAB) *m/z*: 375 (MH^+).

5.1.56. (*S*)-1-[(2-{1-[(1-Benzylimidazol-2-yl)acetyl]-1,2,3,4-tetrahydroquinolin-6-yl}ethyl)-amino]-3-phenoxy-2-propanol dihydrochloride (33)

The title compound was prepared in the same manner as described for **21a** using **32** instead of **20a** as a colorless powder. 29% yield; ^{1}H NMR (DMSO-d_6) δ: 1.81–1.88 (2H, m), 2.67–2.71 (2H, m), 2.93–3.05 (6H, m), 3.67–3.71 (2H, m), 3.91–4.06 (4H, m), 4.20–4.22 (1H, m), 5.17 (2H, s), 5.87 (1H, br s), 6.83 (1H, s), 6.93–6.97 (3H, m), 7.02–7.16 (5H, m), 7.25–7.35 (5H, m), 7.55 (1H, br s); MS (FAB) *m/z*: 525 (MH^+); Anal. Calcd for $C_{32}H_{36}N_4O_3 \cdot 2HCl \cdot H_2O \cdot 0.5EtOAc$: C, 61.91; H, 6.72; N, 8.49; Cl, 10.75. Found: C, 61.79; H, 6.69; N, 8.42; Cl, 10.67.

5.2. Pharmacology

5.2.1. 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 are 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.

5.2.2. 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 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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