Synthesis and Evaluation of *N*-Phenyl-(2-aminothiazol-4-yl)acetamides with Phenoxypropanolamine Moiety as Selective β3-Adrenergic Receptor Agonists

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

Drug Discovery Research, Astellas Pharma Inc.; 21 Miyukigaoka, Tsukuba, Ibaraki 305–8585, Japan.
Received January 29, 2012; accepted March 8, 2012

In the search for potent and selective human β3-adrenergic receptor (AR) agonists as potential drugs for use in treating obesity and non-insulin dependent (type 2) diabetes, a series of *N*-phenyl-(2-aminothiazol-4-yl)acetamides with phenoxypropanolamine moiety were prepared and their biological activities against human β3-, β2-, and β1-ARs were evaluated. Among these compounds, *N*-phenyl-(2-phenylaminothiazol-4-yl)acetamide (4g), *N*-phenyl-(2-benzylaminothiazol-4-yl)acetamide (4j), and *N*-phenyl-[2-(3-methoxyphenyl)-aminothiazol-4-yl]acetamide (6g) derivatives showed potent agonistic activity against the β3-AR with functional selectivity over the β1- and β2-ARs. In addition, these compounds exhibited significant hypoglycemic activity in a rodent model of diabetes.

Key words β3-adrenergic receptor; agonist; 2-aminothiazole; phenoxypropanolamine; diabetes

A major increase in the prevalence of obesity, non-insulin dependent (type 2) diabetes and related cardiovascular disorders has led to the search for new pharmacological approaches in the treatment of these conditions.[1,2] In the 1980s and 1990s, the β3-adrenergic receptor (AR) was identified as a possible therapeutic target for the treatment of type 2 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[7] (Fig. 1). Human clinical trials with these agents for use in treating 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, a notion supported by the discovery, cloning, and characterization of the human, rat, and mouse β3-ARs.[10–12]

Recent studies have 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] Several companies have reported developing a new generation of β3-AR agonists over the past few decades, including L-796568,[16] rafabegron,[17] ritobegron[18] and solabegron[19] (Fig. 1). The availability of appropriate human receptors has facilitated the design and synthesis of a new generation of highly potent β3-AR agonists. Subtype selectivity for β3-AR agonists must be kept specifically in mind, since activation of the β1- or β2-ARs could lead to undesirable side effects such as increased heart rate or muscle tremors.

We previously described efforts in this area that included the disclosure of acetanilide-based phenylethanolamine **1**, which showed potent β3-AR agonistic activity with functional selectivity over β1- and β2-ARs and oral hypoglycemic activity in diabetic kk mice.[20] Given our assumption that the (2-aminothiazol-4-yl)acetamide moiety of **1** might be a favorable pharmacophore for β3-AR agonistic activity and selectivity, we decided to apply this structure part in the phenoxypropanolamine analogue instead of the phenylethanolamine one. We therefore synthesized simple *N*-phenyl-(2-aminothiazol-4-yl)acetamide **4a**, which showed good partial agonistic activity at the β3-AR (EC_{50}=0.98 μM, IA=0.48) and functional selectivity over β1- and β2-ARs. This result encouraged us to attempt further modification of **4a** (Fig. 2).

Here, we describe the synthesis and structure–activity relationships (SARs) of these newly designed *N*-phenyl-(2-aminothiazol-4-yl)acetamides with phenoxypropanolamine moiety as β3-AR agonists.

Chemistry The syntheses of *N*-phenyl-(2-aminothiazol-4-yl)acetamides **4a**–**m** are shown in Chart 1. Treatment of aniline intermediate **2**[21] with the appropriate (2-aminothiazol-4-yl)acetic acids in the presence of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, followed by deprotection of the *tert*-butoxycarbonyl (Boc) group with hydrochloric acid, afforded the desired products **4a**–**m**. *N*-Phenyl-(2-phenylaminothiazol-4-yl)acetamides **6a**–**m** were also prepared from aniline intermediate **2** in the same manner as **4** (Chart 2). Compounds **9a** and **b** and **11** were synthesized, as illustrated in Chart 3. Aniline intermediates **7a** and **b**[21] were coupled with (2-phenylaminothiazol-4-yl)acetic acid, followed by cleavage of the Boc protecting group to afford the desired products **9a** and **b**. Meanwhile, treatment of **2** with (2-methylphenylaminothiazol-4-yl)acetic acid,[22] followed by deprotection with Boc group, afforded the desired product **11**. As starting materials, novel (2-aminothiazol-4-yl)acetic acids **14a**–**c** were synthesized from the treatment of methyl chloroacetylacetate with the appropriate thioureas **12a**–**c**, followed by saponification of **13a**–**c** (Chart 4).

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), are also shown for comparison in Table 1.

The authors declare no conflict of interest.

* To whom correspondence should be addressed. e-mail: tatsuya.maruyama@astellas.com

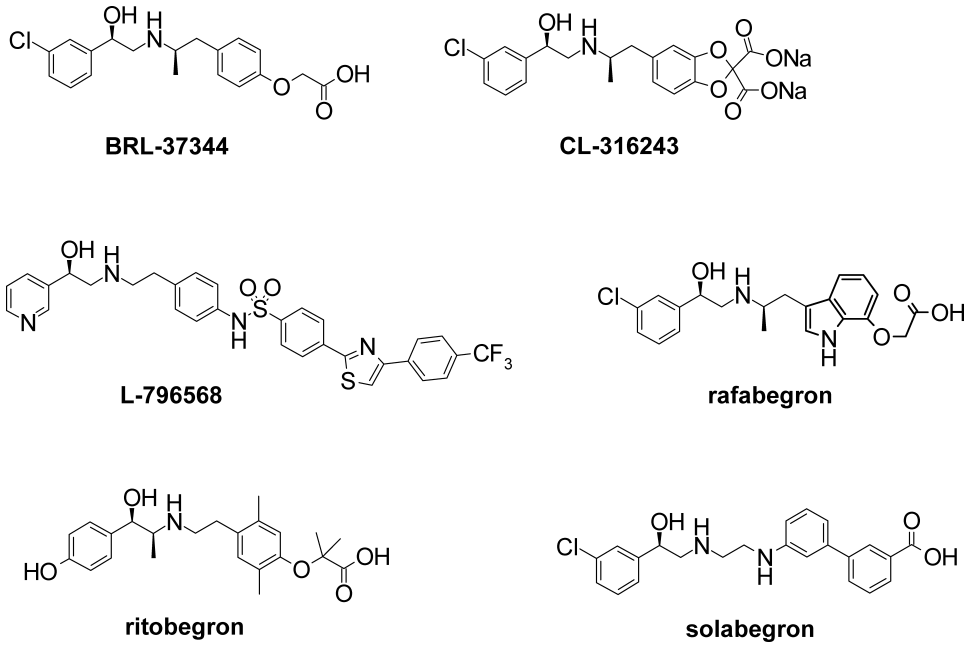


Fig. 1. Chemical Structure of β3-AR Agonists

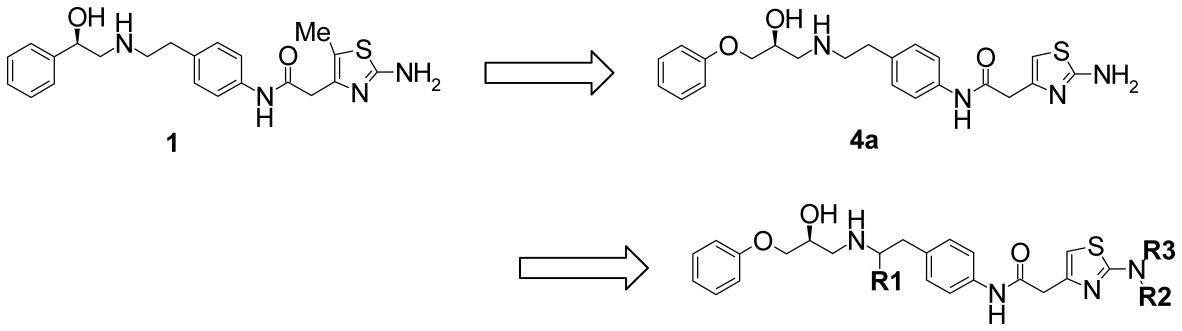
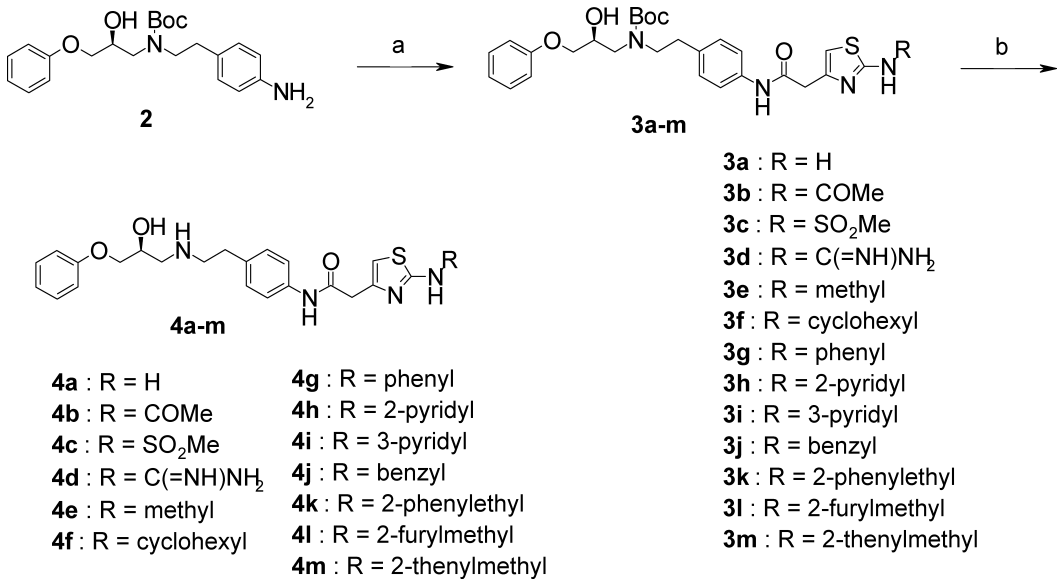


Fig. 2. Design of *N*-Phenyl-(2-aminothiazol-4-yl)acetamide Derivatives

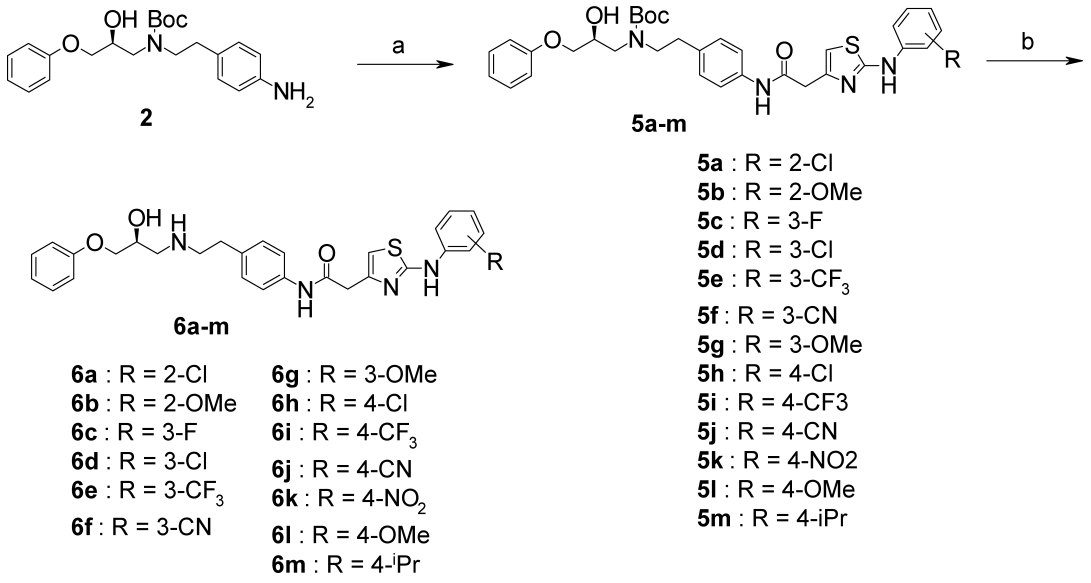


3a : R = H
3b : R = COMe
3c : R = SO_2Me
3d : R = $C(=NH)NH_2$
3e : R = methyl
3f : R = cyclohexyl
3g : R = phenyl
3h : R = 2-pyridyl
3i : R = 3-pyridyl
3j : R = benzyl
3k : R = 2-phenylethyl
3l : R = 2-furylmethyl
3m : R = 2-thenylmethyl

4a : R = H
4b : R = COMe
4c : R = SO_2Me
4d : R = $C(=NH)NH_2$
4e : R = methyl
4f : R = cyclohexyl
4g : R = phenyl
4h : R = 2-pyridyl
4i : R = 3-pyridyl
4j : R = benzyl
4k : R = 2-phenylethyl
4l : R = 2-furylmethyl
4m : R = 2-thenylmethyl

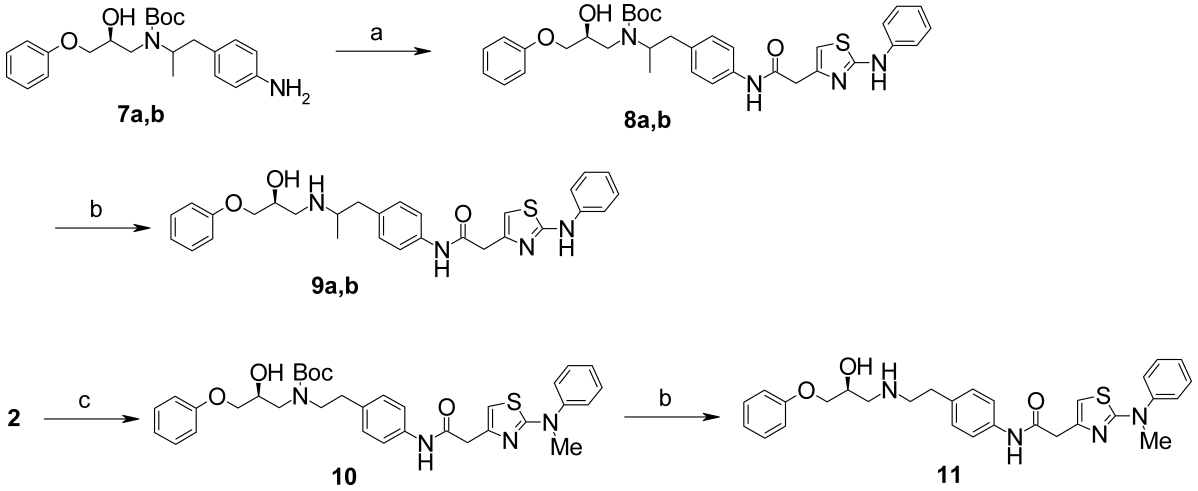
Reagents and conditions: (a) substituted 2-aminothiazol-4-ylacetic acid, EDC·HCl, HOBt, DMF; (b) 4 M HCl-EtOAc, MeOH.

Chart 1



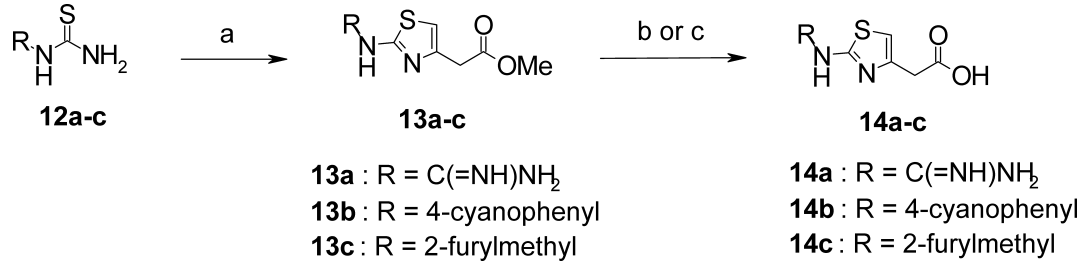
Reagents and conditions: (a) substituted 2-phenylaminothiazol-4-ylacetic acid, EDC·HCl, HOBt, DMF; (b) 4 M HCl–EtOAc, MeOH.

Chart 2



Reagents and conditions: (a) 2-phenylaminothiazol-4-ylacetic acid, EDC·HCl, HOBt, DMF; (b) 4 M HCl–EtOAc, MeOH; (c) 2-methylphenylaminothiazol-4-ylacetic acid, EDC·HCl, HOBt, DMF.

Chart 3

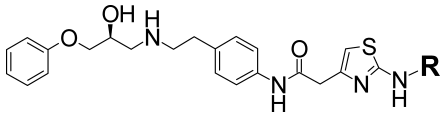


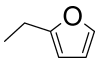
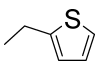
Reagents and conditions: (a) methyl chloroacetylacetate, MeOH, reflux; (b) 10% HClaq., reflux; (c) 1 M NaOHaq., MeOH, reflux.

Chart 4

Initially, introduction of substituent on the amino group of 2-aminothiazole moiety in **4a** was investigated as shown in Table 1. When *N*-phenyl-(2-aminothiazol-4-yl)acetamide containing phenoxypropanolamine moiety **4a** showed good partial agonistic activity at the β3-AR (EC_{50}=0.98 μM, IA=0.48) and functional selectivity over β1- and β2-ARs, 2-acetylamino derivative (**4b**) and 2-methanesulfonylamino derivative (**4c**) exhibited an extreme decrease in β3-AR agonistic activity. Further, 2-guanidino derivative (**4d**) showed 5-fold less agonistic activity against β3-AR (EC_{50}=4.6 μM) than did **4a**. These

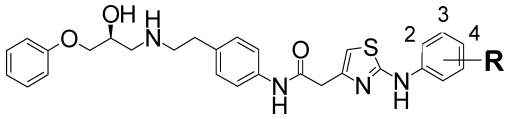
Table 1. β-AR Agonistic Activity Substituted *N*-Phenyl-(2-aminothiazol-4-yl)acetamides



Compound	R	EC_{50}, $\mu M^{a)}$ ($IA^{b)}$)		
		β3-AR	β2-AR	β1-AR
4a	H	0.98 (0.48)	>100 (0)	>100 (0)
4b	COMe	>100 (0.35)	>100 (0)	>100 (0.04)
4c	SO_2Me	14 (0.71)	>100 (0)	>100 (0.04)
4d	$C(=NH)NH_2$	4.6 (0.60)	>100 (0.01)	11 (0.16)
4e	Me	22 (0.58)	>100 (0.01)	0.44 (0.15)
4f	c-Hex	0.13 (0.55)	>100 (0.02)	0.39 (0.12)
4g	Ph	0.56 (0.90)	>100 (0.01)	>100 (0.06)
4h		1.6 (0.19)	>100 (0)	>100 (0.06)
4i		3.5 (0.73)	>100 (0.05)	0.65 (0.27)
4j	CH_2Ph	0.45 (0.79)	>100 (0)	>100 (0.06)
4k	CH_2CH_2Ph	0.51 (0.53)	>100 (0.02)	0.71 (0.11)
4l		4.6 (0.53)	>100 (0.05)	0.85 (0.34)
4m		0.91 (0.41)	>100 (0.05)	0.68 (0.30)
ISO		0.10 (1.00)	0.003 (1.00)	0.012 (1.00)

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

Table 2. β-AR Agonistic Activity of Substituted *N*-Phenyl-(2-phenylaminothiazol-4-yl)acetamides

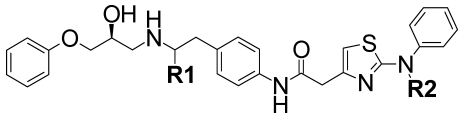


Compound	R	EC_{50}, $\mu M^{a)}$ ($IA^{b)}$)		
		β3-AR	β2-AR	β1-AR
4g	H	0.56 (0.90)	>100 (0.01)	>100 (0.06)
6a	2-Cl	0.16 (0.51)	>100 (0.01)	0.59 (0.15)
6b	2-OMe	0.28 (0.46)	>100 (0)	0.54 (0.15)
6c	3-F	0.16 (0.67)	>100 (0)	>100 (0.08)
6d	3-Cl	0.30 (0.58)	>100 (0.01)	>100 (0.10)
6e	$3\text{-}CF_3$	0.49 (0.56)	>100 (0.02)	>100 (0.06)
6f	3-CN	0.32 (0.65)	>100 (0.01)	4.3 (0.13)
6g	3-OMe	0.25 (0.70)	>100 (0)	>100 (0.07)
6h	4-Cl	2.2 (0.39)	>100 (0)	>100 (0.06)
6i	$4\text{-}CF_3$	3.0 (0.24)	>100 (0.01)	>100 (0.04)
6j	4-CN	0.87 (0.58)	>100 (0)	>100 (0.10)
6k	$4\text{-}NO_2$	0.98 (0.17)	>100 (0)	>100 (0.07)
6l	4-OMe	3.6 (0.29)	>100 (0)	>100 (0.07)
6m	$4\text{-}^{i}Pr$	11 (0.46)	>100 (0.10)	>100 (0.05)

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.

results suggested that the basic amino group of 2-aminothiazole moiety might be required for β3-AR agonistic activity. Introduction of methyl group at the 2-aminothiazole moiety (**4e**) resulted in a considerable decrease in agonistic activity against β3-AR (EC_{50}=22 μM) and an increase in agonistic activity against β1-AR. In contrast, the agonistic activity of

Table 3. β-AR Agonistic Activity of *N*-Phenyl-(2-phenylaminothiazol-4-yl)acetamide Derivatives



Compound	R1	R2	EC_{50}, μM[a] (IA[b])		
			β3-AR	β2-AR	β1-AR
4g	H	H	0.56 (0.90)	>100 (0.01)	>100 (0.06)
9a[c]	Me	H	0.21 (0.84)	>100 (0.06)	0.031 (0.21)
9b[d]	Me	H	0.23 (0.56)	>100 (0)	0.30 (0.20)
11	H	Me	0.62 (0.39)	3.7 (0.17)	2.0 (0.47)

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.

the cyclohexylamino derivative (**4f**) against β3-AR increased 7-fold (EC_{50}=0.13 μM) relative to that of **4a**, but **4f** was still partial agonist (IA=0.55). Interestingly, 2-phenylamino derivative (**4g**) exhibited 2-fold increased potency against β3-AR with high intrinsic activity (EC_{50}=0.56 μM, IA=0.90) relative to that of **4a** without agonistic activity at either β2- or β1-ARs. Given these findings, we therefore examined the effects of introducing an aryl-containing group on the amino group of the 2-aminothiazole moiety in **4a**. Both 2-(2-pyridyl)amino derivative (**4h**) and 2-(3-pyridyl)amino derivative (**4i**) showed decreased agonistic activity at the β3-AR relative to that of **4g**. Meanwhile, 2-benzylamino derivative (**4j**) exhibited good agonistic activity against β3-AR (EC_{50}=0.45 μM, IA=0.79) and functional selectivity over β1- and β2-ARs compared to **4g**. The introduction of 2-phenylethyl group (**4k**) on the amino group of the 2-aminothiazole moiety in **4a** resulted in decreased intrinsic activity at the β3-AR (IA=0.53) related to that of **4g**. Both 2-(2-furylmethyl)amino derivative (**4l**) and 2-(2-thenylmethyl)amino derivative (**4m**) showed decreased intrinsic activity at the β3-AR relative to that of **4j** and increased agonistic activity against β1-AR. These results indicated that phenyl group gave the most satisfied agonistic activity against β3-AR and functional selectivity over β1- and β2-ARs as a substituent on the amino group of the 2-aminothiazole moiety in **4a**.

In order to improve the potency of **4g** against β3-AR, introduction of substituent on the phenyl ring of 2-phenylaminothiazole moiety in **4g** was examined as shown in Table 2. Both 2-chlorophenyl derivative (**6a**) and 2-methoxyphenyl derivative (**6b**) showed slightly increased agonistic activity at the β3-AR (EC_{50}=0.16, 0.28 μM, respectively), however, their intrinsic activity at the β3-AR were decreased relative to that of **4g** (IA=0.51, 0.46, respectively). In addition, they exhibited slightly increased agonistic activity at the β1-AR. The results obtained for agonistic activity at the β3-AR on introduction of a substituent at the 3-position on the phenyl ring of the 2-phenylaminothiazole moiety (**6c**–**g**) were similar to those for introduction at the 2-position on the phenyl ring (EC_{50}=0.16–0.49 μM, IA=0.56–0.70), in which the 3-methoxyphenyl derivative (**6g**) gave the most satisfying results with respect to β3-AR agonistic activity (EC_{50}=0.25 μM, IA=0.70) and no agonistic activity for either the β2- and β1-AR. In contrast, introduction of a substituent at the 4-position on the phenyl ring of the 2-phenylaminothiazole moiety (**6h**–**m**) resulted in considerably decreased β3-AR agonistic activity (EC_{50}=0.87–11 μM, IA=0.17–0.58) relative to that of **4g**. These results suggested that introduction of a substituent on the phenyl ring at the 2- and 3-position on the phenyl ring of the 2-phenylaminothiazole moiety in **4g** may maintain agonistic activity against β3-AR, with similar results possible with both electron-withdrawing and electron-donating groups as substituents. Further, the non-substituted phenyl derivative (**4g**) was found to have the most potent agonistic activity against β3-AR.

Table 4. Oral Hypoglycemic Activity in kk Mice

Compound	Percent reduction in plasma glucose[a]	
	3 mg/kg *p.o.*	10 mg/kg *p.o.*
4g	55**[b]	58***
4j	28	46***
6g	23	50**

a) The compounds were administered orally to male kk mice for 4 d. *b*) Statistically significant at $^{**}p<0.01$, $^{***}p<0.001$.

Next, the introduction of a methyl group at the α-position of the secondary amine on the central part of **4g** was investigated, since it was reported to improve β3-AR agonistic activity in phenoxypropanolamine analogue[21] (Table 3). One diastereomer of the α-methyl derivative (**9a**) showed a 3-fold increase in potency at the β3-AR (EC_{50}=0.21 μM, IA=0.84) relative to that of **4g**, however, its functional selectivity over β1-AR was decreased. Another diastereomer of the α-methyl derivative (**9b**) showed a decrease in intrinsic activity against β3-AR (IA=0.56).

Lastly, we examined the introduction of a methyl group at the nitrogen of the 2-phenylaminothiazole moiety in **4g** (Table 3). This new compound **11** showed a dramatic decrease in intrinsic activity against β3-AR (IA=0.39) and functional selectivity over β2- and β1-ARs relative to that of **4g**, suggesting that the hydrogen on the amino group of the 2-phenylaminothiazole moiety may play an important role in the functional selectivity over β2- and β1-ARs, as most compounds in this series were selective for β3-AR.

Given the results of the *in vitro* study, compounds **4g**, **4j**, and **6g** were selected for *in vivo* evaluation in a rodent model of type 2 diabetes (Table 4). The effects on plasma glucose following four-day oral administration of compounds to diabetic kk mice were measured. All compounds induced a significant reduction in plasma glucose level at 10 mg/kg

(46–58% decrease), with **4g** showing the most potent hypoglycemic activity with a 55% decrease at 3 mg/kg.

Conclusion

Here, we have identified a new series of *N*-phenyl-(2-aminothiazol-4-yl)acetamides with phenoxypropanolamine moiety as β3-AR agonists and described their synthesis and SARs. Among these compounds, *N*-phenyl-(2-phenylaminothiazol-4-yl)acetamide (**4g**), *N*-phenyl-(2-benzylaminothiazol-4-yl)acetamide (**4j**), and *N*-phenyl-[2-(3-methoxyphenyl)aminothiazol-4-yl]acetamide (**6g**) derivatives showed potent agonistic activity against β3-AR (EC_{50}=0.56, 0.45, 0.25 μM, respectively) with high intrinsic activity (IA>0.70) and had functional selectivity over 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 $MgSO_4$.

***tert*-Butyl (*S*)-*N*-[2-(4-{[2-(2-Aminothiazol-4-yl)acetyl]amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (3a)** To a solution of **2** (0.58 g) and 2-aminothiazol-4-ylacetic acid (0.26 g) in *N*,*N*-dimethylformamide (20 mL) were added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.35 g) and 1-hydroxybenzotriazole (0.28 g), and the mixture was stirred at room temperature for 17 h. The resulting mixture was concentrated *in vacuo* and diluted with 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 (30 : 1) as the eluent to yield **3a** (0.40 g) as a colorless powder. 50% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.57 (9H, s), 2.75–2.86 (2H, m), 3.30–3.50 (4H, m), 3.71 (2H, s), 3.82–4.00 (2H, m), 4.09 (2H, brs), 6.73 (1H, s), 6.89 (2H, d, *J*=7.6 Hz), 6.96 (1H, t, *J*=7.2 Hz), 7.03–7.15 (2H, m), 7.29 (2H, d, *J*=7.6 Hz), 7.41 (2H, d, *J*=7.6 Hz), 8.64 (1H, brs); MS (FAB) *m*/*z*: 527 (MH^+).

***tert*-Butyl (*S*)-*N*-[2-(4-{[2-(2-Acetylaminothiazol-4-yl)acetyl]amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (3b)** The title compound was prepared in the same manner as described for **3a** using 2-acetylaminothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 98% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.29 (3H, s), 2.70–2.85 (2H, m), 3.30–3.52 (4H, m), 3.72 (2H, s), 3.80–4.00 (2H, m), 4.05–4.15 (1H, m), 6.78 (1H, s), 6.87–6.89 (2H, m), 6.96 (1H, t, *J*=7.6 Hz), 7.02–7.12 (2H, m), 7.27–7.30 (2H, m), 7.39–7.42 (2H, m), 8.51 (1H, brs); MS (FAB) *m*/*z*: 569 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-[2-(4-{[2-(2-methanesulfonylaminothiazol-4-yl)acetyl]amino}phenyl)ethyl]carbamate (3c)** The title compound was prepared in the same manner as described for **3a** using 2-methanesulfonylaminothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 87% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 2.73 (2H, t, *J*=7.6 Hz), 2.89 (3H, s), 3.30–3.42 (4H, m), 3.62 (2H, s), 3.79–3.87 (2H, m), 3.96 (1H, brs), 5.10–5.18 (1H, m), 6.56 (1H, s), 6.89–6.94 (3H, m), 7.11 (2H, d, *J*=8.4 Hz), 7.28 (2H, t, *J*=8.8 Hz), 7.49 (2H, d, *J*=8.8 Hz), 10.08 (1H, s), 12.47 (1H, s); MS (FAB) *m*/*z*: 603 [$(M-H)^-$)].

***tert*-Butyl (*S*)-*N*-[2-(4-{[2-(2-Guanidinothiazol-4-yl)acetyl]amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (3d)** The title compound was prepared in the same manner as described for **3a** using 2-guanidinothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 86% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.73–2.83 (2H, m), 3.30–3.48 (4H, m), 3.61 (2H, brs), 3.83–3.95 (2H, m), 4.00–4.11 (1H, m), 6.45 (1H, s), 6.83–7.40 (9H, m) 8.43 (1H, brs); MS (FAB) *m*/*z*: 569 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-[2-(4-{[2-(2-methylaminothiazol-4-yl)acetyl]amino}phenyl)ethyl]carbamate (3e)** The title compound was prepared in the same manner as described for **3a** using 2-methylaminothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 31% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.65–3.10 (5H, m), 3.30–4.25 (7H, m), 3.61 (2H, s), 6.30 (1H, s), 6.80–7.55 (9H, m); MS (FAB) *m*/*z*: 541 (MH^+).

***tert*-Butyl (*S*)-*N*-[2-(4-{[2-(2-Cyclohexylaminothiazol-4-yl)acetyl]amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (3f)** The title compound was prepared in the same manner as described for **3a** using 2-cyclohexylaminothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 88% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.25–1.50 (14H, m), 1.60–1.70 (1H, m), 1.75–1.85 (2H, m), 2.00–2.20 (2H, m), 2.70–2.90 (2H, m), 3.20–3.50 (5H, m), 3.65 (2H, s), 3.80–4.00 (2H, m), 4.05–4.15 (1H, m), 6.34 (1H, s), 6.80–7.90 (9H, m), 9.30 (1H, brs); MS (FAB) *m*/*z*: 609 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-[2-(4-{[2-(2-phenylaminothiazol-4-yl)acetyl]amino}phenyl)ethyl]carbamate (3g)** The title compound was prepared in the same manner as described for **3a** using 2-phenylaminothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 51% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.70–2.90 (2H, m), 3.30–3.50 (4H, m), 3.69 (2H, s), 3.80–4.00 (2H, m), 4.11 (1H, brs), 6.44 (1H, s), 6.89 (2H, d, *J*=8.0 Hz), 6.95 (1H, t, *J*=7.2 Hz), 7.02–7.14 (3H, m), 7.24–7.32 (2H, m), 7.37–7.44 (6H, m), 9.13 (1H, brs); MS (FAB) *m*/*z*: 603 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(2-pyridylamino)thiazol-4-yl]acetyl}amino)phenyl]ethyl}carbamate (3h)** The title compound was prepared in the same manner as described for **3a** using 2-(2-pyridylamino)-thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 44% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.87 (2H, m), 3.30–3.52 (4H, m), 3.73 (2H, s), 3.80–4.20 (3H, m), 6.63 (1H, s), 6.86–6.98 (6H, m), 7.02–7.13 (2H, m), 7.24–7.30 (1H, m), 7.43 (2H, d, *J*=8.4 Hz), 7.61–7.67 (1H, m), 8.33–8.42 (2H, m), 8.88 (1H, brs); MS (FAB) *m*/*z*: 604 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(3-pyridylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (3i)** To a solution of methyl

2-(3-pyridylamino)thiazol-4-ylacetate hydrochloride (**13i**) (1.52 g) in methanol (10 mL) were added 1 M NaOH aqueous solution (12 mL), and the mixture was stirred at reflux for 2 h. The resultant mixture was cooled in ice-water bath, and neutralized by addition of 1 M HCl aqueous solution (6 mL). The solvent was concentrated *in vacuo*, and diluted with water (10 mL). The precipitate was removed by filtration, washed with water and diethyl ether, and dried to yield the corresponding acid (0.91 g) as a colorless powder, which was used in next step. The title compound was prepared in the same manner as described for **3a** using above acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 90% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.75–2.85 (2H, m), 3.35–3.45 (4H, m), 3.62 (2H, s), 3.88–3.96 (2H, m), 4.11 (1H, brs), 4.68–4.69 (2H, m), 6.31 (1H, s), 6.48 (1H, brs), 6.88–7.06 (4H, m), 7.19–7.39 (6H, m), 7.66–7.71 (1H, m), 8.59–8.60 (1H, m), 9.32 (1H, brs); MS (FAB) *m/z*: 604 (MH^+).

***tert*-Butyl (*S*)-*N*-[2-(4-{[2-(2-Benzylaminothiazol-4-yl)acetyl]amino}phenyl)ethyl]-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (3j)** The title compound was prepared in the same manner as described for **3a** using 2-benzylaminothiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 58% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 2.70–2.75 (2H, m), 3.29–3.38 (4H, m), 3.48 (2H, s), 3.82–4.84 (2H, m), 3.96 (1H, brs), 4.41 (2H, d, *J*=6.0 Hz), 5.13 (1H, brs), 6.36 (1H, s), 6.89–6.94 (3H, m), 7.08 (2H, d, *J*=7.8 Hz), 7.23–7.35 (7H, m), 7.46 (2H, d, *J*=8.4 Hz), 8.04–8.07 (1H, m), 9.97 (1H, s); MS (FAB) *m/z*: 617 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(2-phenylethylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (3k)** The title compound was prepared in the same manner as described for **3a** using 2-(2-phenylethylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 86% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.35 (9H, s), 2.72 (2H, t, *J*=7.0 Hz), 2.84 (2H, t, *J*=7.0 Hz), 3.30–3.45 (6H, m), 3.49 (2H, s), 3.78–4.00 (3H, m), 6.35 (1H, s), 6.88–7.30 (11H, m), 7.51 (2H, d, *J*=8.0 Hz), 7.64 (1H, t, *J*=6.0 Hz); MS (FAB) *m/z*: 631 (MH^+).

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(2-Furylmethylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (3l)** The title compound was prepared in the same manner as described for **3i** using methyl 2-(2-furylmethylamino)thiazol-4-ylacetate hydrochloride instead of **13i** as a colorless powder. 72% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.66–2.78 (2H, m), 3.30–3.45 (4H, m), 3.63 (2H, s), 3.88–3.95 (2H, m), 4.08–4.15 (1H, m), 4.55 (2H, s), 6.30–6.35 (4H, m), 6.82–7.06 (5H, m), 7.22–7.41 (5H, m), 9.19 (1H, brs); MS (FAB) *m/z*: 607 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(2-thenylmethylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (3m)** The title compound was prepared in the same manner as described for **3a** using 2-(2-thenylmethylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 71% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.78 (2H, brs), 3.42 (4H, brs), 3.62 (2H, s), 3.88–3.96 (2H, m), 4.11–4.15 (1H, m), 4.73–4.75 (2H, m), 5.47 (1H, brs), 6.33 (1H, s), 6.85–7.07 (8H, m), 7.24–7.37 (4H, m), 9.18 (1H, brs); MS (FAB) *m/z*: 623 (MH^+).

(*S*)-2-(2-Aminothiazol-4-yl)-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (4a) To a solution of **3a** (0.38 g) in methanol (20 mL) was added 4 M HCl–EtOAc (10 mL), and the mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated *in vacuo*. The crude solid was purified by recrystallization from ethanol–ethyl acetate to yield **4a** (0.25 g) as a colorless solid. 70% yield; mp 167–170°C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.70–3.50 (6H, m), 3.65 (2H, s), 3.94–4.01 (2H, m), 4.23–4.25 (1H, m), 5.91 (1H, brs), 6.56 (1H, s), 6.94–6.97 (3H, m), 7.20 (2H, d, *J*=8.0 Hz), 7.28–7.32 (2H, m), 7.58 (2H, d, *J*=8.0 Hz), 8.35 (1H, brs), 8.91 (1H, brs), 9.16 (1H, brs), 10.38 (1H, s); MS (FAB) *m/z*: 427 (MH^+); *Anal.* Calcd for $C_{22}H_{26}N_4O_3S\cdot 2HCl\cdot 0.5H_2O$: C, 51.97; H, 5.75; N, 11.02; S, 6.31; Cl, 13.95. Found: C, 51.61; H, 5.53; N, 10.72; S, 5.93; Cl, 14.35.

(*S*)-2-(2-Acetylaminothiazol-4-yl)-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Hydrochloride (4b) The title compound was prepared in the same manner as described for **4a** using **3b** instead of **3a** as a colorless powder. 49% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.11 (3H, s), 2.90–3.23 (6H, m), 3.69 (2H, s), 3.94–4.02 (2H, m), 4.22–4.27 (1H, m), 5.00 (1H, brs), 6.93–6.97 (4H, m), 7.18 (2H, d, *J*=8.4 Hz), 7.30 (2H, d, *J*=8.0 Hz), 7.59 (2H, t, *J*=8.4 Hz), 8.92 (1H, brs), 9.18 (1H, brs), 10.26 (1H, s), 12.11 (1H, s); MS (FAB) *m/z*: 469 (MH^+); *Anal.* Calcd for $C_{24}H_{28}N_4O_4S\cdot 1.3HCl\cdot H_2O$: C, 53.98; H, 5.91; N, 10.49; S, 6.00; Cl, 8.63. Found: C, 54.05; H, 5.70; N, 10.56; S, 6.06; Cl, 8.72.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(2-methanesulfonylaminothiazol-4-yl)acetanilide Hydrochloride (4c) The title compound was prepared in the same manner as described for **4a** using **3c** instead of **3a** as a colorless solid. 57% yield; mp 249–254°C (decomp.) (MeOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.89 (3H, s), 2.92–3.24 (6H, m), 3.33 (2H, s), 3.65 (2H, s), 3.93–4.01 (2H, m), 4.21–4.23 (1H, m), 5.90 (1H, d, *J*=4.8 Hz), 6.58 (1H, s), 6.94–6.97 (3H, m), 7.20 (2H, d, *J*=8.4 Hz), 7.31 (2H, t, *J*=8.0 Hz), 7.57 (2H, d, *J*=8.4 Hz), 8.84 (1H, brs), 9.03 (1H, brs), 10.34 (1H, s), 12.54 (1H, s); MS (FAB) *m/z*: 505 (MH^+); *Anal.* Calcd for $C_{23}H_{28}N_4O_5S_2\cdot HCl\cdot 0.2H_2O$: C, 50.72; H, 5.44; N, 10.29; S, 11.77; Cl, 6.51. Found: C, 50.63; H, 5.29; N, 10.24; S, 11.77; Cl, 6.52.

(*S*)-2-(2-Guanidinothiazol-4-yl)-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (4d) The title compound was prepared in the same manner as described for **4a** using **3d** instead of **3a** as a colorless powder. 79% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.90–3.07 (3H, m), 3.14–3.22 (3H, m), 3.94–4.01 (2H, m), 4.22–4.27 (1H, m), 6.93–6.97 (3H, m), 7.12–7.32 (5H, m), 7.59 (2H, d, *J*=8.6 Hz), 8.38 (4H, brs), 8.92 (1H, brs), 9.18 (1H, brs), 10.41 (1H, s), 12.60 (1H, brs); MS (FAB) *m/z*: 469 (MH^+); *Anal.* Calcd for $C_{23}H_{28}N_6O_3S\cdot 2.1HCl\cdot 0.7H_2O$: C, 49.53; H, 5.69; N, 15.07; S, 5.75; Cl, 13.35. Found: C, 49.40; H, 5.44; N, 15.31; S, 5.92; Cl, 13.58.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(2-methylaminothiazol-4-yl)acetanilide Dihydrochloride (4e) The title compound was prepared in the same manner as described for **4a** using **3e** instead of **3a** as a colorless solid. 60% yield; mp 203–204°C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.04 (6H, m), 3.14–3.20 (3H, m), 3.70 (2H, s), 3.93–4.01 (2H, m), 4.22–4.25 (1H, m), 6.73 (1H, s), 6.94–6.97 (3H, m), 7.20 (2H, d, *J*=8.8 Hz), 7.28–7.33 (2H, m), 7.59 (2H,

d, J=8.8 Hz), 8.90 (1H, brs), 9.14 (1H, brs), 10.49 (1H, s); MS (FAB) *m/z*: 441 (MH^+); *Anal.* Calcd for $C_{23}H_{28}N_4O_3S\cdot 2HCl$: C, 53.80; H, 5.89; N, 10.91; S, 6.24; Cl, 13.81. Found: C, 53.56; H, 5.76; N, 10.88; S, 6.34; Cl, 13.88.

(*S*)-2-(2-Cyclohexylaminothiazol-4-yl)-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Hydrochloride (4f) The title compound was prepared in the same manner as described for **4a** using **3f** instead of **3a** as a colorless powder. 15% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.10–1.40 (5H, m), 1.45–1.70 (3H, m), 1.80–2.00 (2H, m), 2.80–3.55 (9H, m), 3.91–4.03 (2H, m), 4.17–4.28 (1H, m), 5.91 (1H, d, J=4.8 Hz), 6.33 (1H, s), 6.80–7.00 (3H, m), 7.10–7.70 (6H, m), 8.88 (1H, brs), 9.10 (1H, brs), 10.15 (1H, brs); MS (FAB) *m/z*: 509 (MH^+); *Anal.* Calcd for $C_{28}H_{36}N_4O_3S\cdot 1.2HCl\cdot 0.5H_2O$: C, 59.90; H, 6.86; N, 9.98; S, 5.71; Cl, 7.58. Found: C, 59.60; H, 6.83; N, 10.36; S, 5.64; Cl, 7.22.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(2-phenylaminothiazol-4-yl)acetanilide Dihydrochloride (4g) The title compound was prepared in the same manner as described for **4a** using **3g** instead of **3a** as a colorless powder. 33% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.93–3.04 (3H, m), 3.15–3.20 (3H, m), 3.66 (2H, s), 3.93–4.01 (2H, m), 4.20–4.27 (1H, m), 6.68 (1H, s), 6.94–6.98 (4H, m), 7.20 (2H, d, J=8.8 Hz), 7.26–7.61 (4H, m), 8.87 (1H, brs), 9.08 (1H, brs), 10.25 (1H, s), 10.45 (1H, brs); MS (FAB) *m/z*: 503 (MH^+); *Anal.* Calcd for $C_{28}H_{30}N_4O_3S\cdot 1.9HCl\cdot 0.7H_2O$: C, 57.54; H, 5.74; N, 9.59; S, 5.49; Cl, 11.52. Found: C, 57.60; H, 5.78; N, 9.41; S, 5.13; Cl, 11.57.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(2-pyridylamino)thiazol-4-yl]acetanilide Hydrochloride (4h) The title compound was prepared in the same manner as described for **4a** using **3h** instead of **3a** as a colorless powder. 20% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.90–3.10 (3H, m), 3.10–3.25 (3H, m), 3.66 (2H, s), 3.93–4.02 (2H, m), 4.17–4.26 (1H, m), 5.90 (1H, brs), 6.75 (1H, s), 6.89–7.03 (4H, m), 7.20 (2H, d, J=8.0 Hz), 7.31 (2H, t, J=7.6 Hz), 7.60 (2H, d, J=8.8 Hz), 7.68 (1H, t, J=7.2 Hz), 8.28 (1H, d, J=7.2 Hz), 8.80 (1H, brs), 8.96 (1H, brs), 10.19 (1H, s), 11.29 (1H, s); MS (FAB) *m/z*: 504 (MH^+); *Anal.* Calcd for $C_{27}H_{29}N_5O_3S\cdot 1.1HCl\cdot 0.5H_2O$: C, 58.67; H, 5.67; N, 12.67; S, 5.80; Cl, 7.06. Found: C, 58.46; H, 5.51; N, 12.73; S, 5.80; Cl, 6.92.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(3-pyridylamino)thiazol-4-yl]acetanilide Dihydrochloride (4i) The title compound was prepared in the same manner as described for **4a** using **3i** instead of **3a** as a colorless solid. 51% yield; mp 232–234°C (MeOH–EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.04 (3H, m), 3.13–3.19 (3H, m), 3.75 (2H, s), 3.94–4.04 (2H, m), 4.23–4.27 (1H, m), 6.92–7.00 (4H, m), 7.20 (2H, d, J=8.0 Hz), 7.24–7.32 (2H, m), 7.62–7.68 (2H, m), 7.94–7.98 (1H, m), 8.45 (1H, d, J=5.2 Hz), 8.63–8.66 (1H, m), 8.98 (1H, brs), 9.27 (1H, brs), 9.38 (1H, d, J=2.0 Hz), 10.40 (1H, s), 11.94 (1H, brs); MS (FAB) *m/z*: 504 (MH^+); *Anal.* Calcd for $C_{27}H_{29}N_5O_3S\cdot 2HCl\cdot 0.1H_2O$: C, 56.07; H, 5.44; N, 12.11; S, 5.54; Cl, 12.26. Found: C, 55.79; H, 5.25; N, 12.02; S, 5.58; Cl, 12.56.

(*S*)-2-(2-Benzylaminothiazol-4-yl)-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (4j) The title compound was prepared in the same manner as described for **4a** using **3j** instead of **3a** as a colorless solid. 62% yield; mp 193–196°C (MeOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.07 (3H, m), 3.14–3.22 (3H, m), 3.94–4.02 (2H, m), 4.22–4.26 (1H, m), 4.65 (2H, brs), 6.73 (1H, s), 6.94–6.97 (3H, m), 7.20 (2H, d, J=8.8 Hz), 7.28–7.43 (7H, m), 7.58 (2H, d, J=8.8 Hz), 8.94 (1H, brs), 9.22 (1H, brs), 10.25 (1H, brs), 10.52 (1H, s); MS (FAB) *m/z*: 517 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_3S\cdot 2HCl$: C, 59.08; H, 5.81; N, 9.50; S, 5.44; Cl, 12.03. Found: C, 58.97; H, 5.78; N, 9.38; S, 5.33; Cl, 12.00.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(2-phenylethylamino)thiazol-4-yl]acetanilide Dihydrochloride (4k) The title compound was prepared in the same manner as described for **4a** using **3k** instead of **3a** as a colorless solid. 71% yield; mp 214–215°C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.91–3.06 (5H, m), 3.13–3.19 (3H, m), 3.65 (2H, brs), 3.77 (2H, s), 3.94–4.01 (2H, m), 4.22–4.26 (1H, m), 6.72 (1H, s), 6.93–6.97 (3H, m), 7.19–7.35 (9H, m), 7.59 (2H, d, J=8.8 Hz), 8.93 (1H, brs), 9.19 (1H, brs), 10.53 (1H, s); MS (FAB) *m/z*: 531 (MH^+); *Anal.* Calcd for $C_{30}H_{34}N_4O_3S\cdot 2HCl$: C, 59.70; H, 6.01; N, 9.28; S, 5.31; Cl, 11.75. Found: C, 59.91; H, 6.01; N, 9.30; S, 5.31; Cl, 11.91.

(*S*)-2-[(2-Furylmethylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (4l) The title compound was prepared in the same manner as described for **4a** using **3l** instead of **3a** as a colorless solid. 60% yield; mp 184–189°C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.94–3.05 (3H, m), 3.14–3.18 (3H, m), 3.72 (2H, s), 3.93–4.01 (2H, m), 4.21–4.23 (1H, m), 4.61 (2H, s), 6.42–6.47 (2H, m), 6.69 (1H, s), 6.94–6.97 (3H, m), 7.20 (2H, d, J=8.8 Hz), 7.28–7.33 (2H, m), 7.58 (2H, d, J=8.4 Hz), 7.65 (1H, s), 8.84 (1H, brs), 9.04 (1H, brs), 10.38 (1H, s); MS (FAB) *m/z*: 507 (MH^+); *Anal.* Calcd for $C_{27}H_{30}N_4O_4S\cdot 2HCl$: C, 55.96; H, 5.57; N, 9.67; S, 5.53; Cl, 12.23. Found: C, 55.72; H, 5.35; N, 9.68; S, 5.45; Cl, 11.95.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(2-thenylmethylamino)thiazol-4-yl]acetanilide Dihydrochloride (4m) The title compound was prepared in the same manner as described for **4a** using **3m** instead of **3a** as a colorless solid. 77% yield; mp 204–207°C (MeOH–EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.07 (3H, m), 3.14–3.20 (3H, m), 3.77 (2H, s), 3.94–4.02 (2H, m), 4.23–4.26 (1H, m), 4.84 (2H, s), 6.74 (1H, s), 6.93–7.01 (4H, m), 7.19–7.21 (3H, m), 7.28–7.32 (2H, m), 7.49–7.51 (1H, m), 7.57–7.60 (2H, m), 8.95 (1H, brs), 9.22 (1H, brs), 10.11 (1H, brs), 10.50 (1H, s); MS (FAB) *m/z*: 523 (MH^+); *Anal.* Calcd for $C_{27}H_{30}N_4O_3S_2\cdot 2HCl$: C, 54.45; H, 5.42; N, 9.41; S, 10.77; Cl, 11.90. Found: C, 54.22; H, 5.22; N, 9.39; S, 10.77; Cl, 11.87.

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(2-Chlorophenylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (5a)** The title compound was prepared in the same manner as described for **3a** using 2-(2-chlorophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 55% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.65–2.80 (2H, m), 3.28–3.50 (4H, m), 3.72 (2H, s), 3.80–3.95 (2H, m), 4.10 (1H, brs), 6.54 (1H, brs), 6.83–7.50 (12H, m), 8.12–8.18 (1H, m), 8.99 (1H, s); MS (FAB) *m/z*: 637 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(2-methoxyphenylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (5b)** The title compound was prepared in the same manner as described for **3a** using 2-(2-methoxyphenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 33% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.82 (2H, m),

3.32–3.50 (4H, m), 3.75 (2H, s), 3.82–3.90 (2H, m), 3.92 (3H, s), 4.07–4.15 (1H, m), 6.44 (1H, s), 6.77–7.90 (13H, m), 9.24 (1H, brs); MS (FAB) *m/z*: 633 (MH^+).

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(3-Fluorophenylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (5c)** The title compound was prepared in the same manner as described for **3a** using 2-(3-fluorophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 27% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.71–2.82 (2H, m), 3.34–3.48 (4H, m), 3.68 (2H, s), 3.83–3.97 (2H, m), 4.07–4.16 (1H, m), 6.42 (1H, s), 6.65–7.45 (13H, m), 9.13 (1H, brs); MS (FAB) *m/z*: 621 (MH^+).

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(3-Chlorophenylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (5d)** The title compound was prepared in the same manner as described for **3a** using 2-(3-chlorophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 27% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.72–2.84 (2H, m), 3.30–3.50 (4H, m), 3.70 (2H, s), 3.82–3.99 (2H, m), 4.05–4.16 (1H, m), 6.47 (1H, s), 6.85–7.43 (12H, m), 7.58 (1H, s), 8.02 (1H, brs), 9.11 (1H, brs); MS (FAB) *m/z*: 637 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(3-trifluoromethylphenylamino)thiazol-4-yl]acetyl}-amino)phenyl]ethyl}carbamate (5e)** The title compound was prepared in the same manner as described for **3a** using 2-(3-trifluoromethylphenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 83% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.62–2.88 (2H, m), 3.28–3.52 (4H, m), 3.71 (2H, s), 3.80–4.00 (2H, m), 4.03–4.15 (1H, m), 6.51 (1H, s), 6.80–7.10 (5H, m), 7.20–7.76 (8H, m), 8.86 (1H, brs); MS (FAB) *m/z*: 671 (MH^+).

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(3-Cyanophenylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (5f)** The title compound was prepared in the same manner as described for **3a** using 2-(3-cyanophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 97% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.73–2.85 (2H, m), 3.35–3.46 (4H, m), 3.73 (2H, s), 3.82–3.95 (2H, m), 4.05–4.16 (1H, m), 6.54 (1H, s), 6.80–7.84 (13H, m), 8.76 (1H, s); MS (FAB) *m/z*: 628 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(3-methoxyphenylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (5g)** The title compound was prepared in the same manner as described for **3a** using 2-(3-methoxyphenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 66% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.70–2.88 (2H, m), 3.30–3.52 (4H, m), 3.69 (2H, s), 3.82–4.00 (2H, m), 3.82 (3H, s), 4.05–4.17 (1H, m), 6.45 (1H, s), 6.67 (1H, dd, J=4.8, 8.0 Hz), 6.89 (2H, d, J=8.4 Hz), 6.94–6.96 (2H, m), 7.02–7.12 (3H, m), 7.21–7.30 (3H, m), 7.43 (2H, d, J=8.4 Hz), 9.08 (1H, s); MS (FAB) *m/z*: 633 (MH^+).

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(4-Chlorophenylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (5h)** The title compound was prepared in the same manner as described for **3a** using 2-(4-chlorophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 40% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.75–2.85 (2H, m), 3.35–3.46 (4H, m), 3.72 (2H, s), 3.80–4.00 (2H, m), 4.10 (1H, t, J=5.5 Hz), 6.50 (1H, s), 6.80–7.80 (13H, m), 8.95 (1H, brs); MS (FAB) *m/z*: 637 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(4-trifluoromethylphenylamino)thiazol-4-yl]acetyl}-amino)phenyl]ethyl}carbamate (5i)** The title compound was prepared in the same manner as described for **3a** using 2-(4-trifluoromethylphenylamino)- thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 98% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.71–2.85 (2H, m), 3.31–3.51 (4H, m), 3.72 (2H, s), 3.81–3.99 (2H, m), 4.25 (1H, brs), 6.50 (1H, s), 6.83–6.98 (3H, m), 7.04 (2H, d, J=8.4 Hz), 7.22–7.29 (2H, m), 7.39 (2H, d, J=8.1 Hz), 7.57 (4H, s), 8.08 (1H, brs), 9.03 (1H, brs); MS (FAB) *m/z*: 671 (MH^+).

***tert*-Butyl (*S*)-*N*-{2-[4-({2-[2-(4-Cyanophenylamino)-thiazol-4-yl]acetyl}amino)phenyl]ethyl}-*N*-(2-hydroxy-3-phenoxypropyl)carbamate (5j)** The title compound was prepared in the same manner as described for **3a** using 2-(4-cyanophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 76% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.70–2.90 (2H, m), 3.20–3.50 (4H, m), 3.74 (2H, s), 3.80–4.00 (2H, m), 4.03–4.15 (1H, m), 6.61 (1H, s), 6.80–7.70 (13H, m), 8.68 (1H, brs); MS (FAB) *m/z*: 628 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(4-nitrophenylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (5k)** The title compound was prepared in the same manner as described for **3a** using 2-(4-nitrophenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 38% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.70–2.90 (2H, m), 3.34–3.51 (4H, m), 3.75 (2H, s), 3.88–4.15 (3H, m), 6.59 (1H, s), 6.86 (2H, d, J=8.1 Hz), 6.90–7.09 (3H, m), 7.20–7.44 (4H, m), 7.60 (2H, d, J=9.2 Hz), 8.13 (2H, d, J=9.2 Hz), 8.77 (1H, brs); MS (FAB) *m/z*: 648 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(4-methoxyphenylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (5l)** The title compound was prepared in the same manner as described for **3a** using 2-(4-methoxyphenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 27% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.73–2.84 (2H, m), 3.32–3.49 (4H, m), 3.65 (2H, s), 3.82 (3H, s), 3.83–3.98 (2H, m), 4.05–4.14 (1H, m), 6.35 (1H, s), 6.85–7.44 (13H, m), 9.17 (1H, s); MS (FAB) *m/z*: 633 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[4-({2-[2-(4-isopropylphenylamino)thiazol-4-yl]acetyl}amino)-phenyl]ethyl}carbamate (5m)** The title compound was prepared in the same manner as described for **3a** using 2-(4-isopropylphenylamino)thiazol-4-ylacetic acid instead of 2-aminothiazol-4-ylacetic acid as a colorless powder. 20% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, d, J=6.8 Hz), 1.46 (9H, s), 2.78 (2H, brs), 2.88–2.96 (1H, m), 3.43 (4H, brs), 3.68 (2H, s), 3.88–3.95 (2H, m), 4.11 (1H, brs), 6.41 (1H, s), 6.79–6.97 (3H, m), 7.04–7.13 (3H, m), 7.23–7.34 (5H, m), 7.42 (2H, d, J=8.4 Hz), 9.17 (1H, brs); MS (FAB) *m/z*: 645 (MH^+).

(*S*)-2-[(2-Chlorophenylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Hydrochloride (6a) The title compound was prepared in the same manner as described for **4a** using **5a** instead of **3a**

as a colorless powder. 20% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.88–3.30 (6H, m), 3.62 (2H, s), 3.93–4.01 (2H, m), 5.89 (1H, d, J=5.4 Hz), 6.70 (1H, s), 6.93–7.05 (4H, m), 7.16–7.59 (8H, m), 8.25–8.30 (1H, m), 8.60–8.90 (2H, m), 9.56 (1H, s), 10.15 (1H, s); MS (FAB) m/z: 537 (MH^+); *Anal.* Calcd for $C_{28}H_{29}N_4O_3S\cdot1.1HCl$: C, 58.27; H, 5.26; N, 9.71; S, 5.56; Cl, 12.90. Found: C, 57.97; H, 5.19; N, 9.77; S, 5.45; Cl, 12.73.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(2-methoxyphenylamino)thiazol-4-yl]acetanilide Hydrochloride (6b) The title compound was prepared in the same manner as described for **4a** using **5b** instead of **3a** as a colorless powder. 40% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.88–2.98 (2H, m), 2.99–3.08 (1H, m), 3.11–3.25 (2H, m), 3.61 (2H, s), 3.85 (3H, s), 3.92–4.01 (2H, m), 4.16–4.25 (1H, m), 5.89 (1H, brs), 6.60 (1H, s), 6.81–7.03 (6H, m), 7.20 (2H, d, J=8.6 Hz), 7.27–7.34 (2H, m), 7.58 (2H, d, J=8.0 Hz), 8.29 (1H, d, J=8.0 Hz), 8.75 (1H, brs), 8.86 (1H, brs), 9.45 (1H, brs), 10.18 (1H, s); MS (FAB) m/z: 533 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_4S\cdot HCl\cdot1.1H_2O$: C, 59.14; H, 6.02; N, 9.51; S, 5.44; Cl, 6.02. Found: C, 58.91; H, 5.71; N, 9.52; S, 5.38; Cl, 5.77.

(*S*)-2-[(3-Fluorophenylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (6c) The title compound was prepared in the same manner as described for **4a** using **5c** instead of **3a** as a colorless powder. 44% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.96–3.30 (6H, m), 3.65 (2H, s), 3.92–4.01 (2H, m), 4.12–4.23 (1H, m), 5.84–5.92 (1H, m), 6.72 (1H, s), 6.91–6.98 (4H, m), 7.19 (2H, d, J=8.8 Hz), 7.24–7.45 (4H, m), 7.59 (2H, d, J=8.3 Hz), 7.90 (1H, t, J=2.0 Hz), 8.60–8.80 (2H, m), 10.18 (1H, s), 10.40 (1H, s); MS (FAB) m/z: 521 (MH^+); *Anal.* Calcd for $C_{28}H_{29}N_4O_3FS\cdot1.8HCl\cdot0.5H_2O$: C, 56.50; H, 5.38; N, 9.41; F, 3.19; S, 5.39; Cl, 10.72. Found: C, 56.24; H, 5.38; N, 9.29; F, 2.97; S, 5.14; Cl, 10.74.

(*S*)-2-[(3-Chlorophenylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Hydrochloride (6d) The title compound was prepared in the same manner as described for **4a** using **5d** instead of **3a** as a colorless powder. 38% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.88–3.23 (6H, m), 3.64 (2H, s), 3.90–4.01 (2H, m), 4.16–4.26 (1H, m), 6.68–6.75 (2H, m), 6.93–6.98 (3H, m), 7.17–7.35 (6H, m), 7.59 (2H, d, J=8.3 Hz), 7.75 (1H, dt, J=2.4, 12.2 Hz), 8.77 (1H, brs), 8.91 (1H, brs), 10.21 (1H, s), 10.49 (1H, s); MS (FAB) m/z: 537 (MH^+); *Anal.* Calcd for $C_{28}H_{29}N_4O_3ClS\cdot1.1HCl\cdot1.5H_2O$: C, 55.66; H, 5.52; N, 9.27; S, 5.31; Cl, 12.32. Found: C, 55.54; H, 5.44; N, 9.35; S, 5.25; Cl, 12.09.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(3-trifluoromethylphenylamino)thiazol-4-yl]acetanilide Dihydrochloride (6e) The title compound was prepared in the same manner as described for **4a** using **5e** instead of **3a** as a colorless solid. 68% yield; mp 161–163°C (EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.93–3.07 (3H, m), 3.14–3.23 (3H, m), 3.68 (2H, s), 3.93–4.01 (2H, m), 4.22–4.25 (1H, m), 6.75 (1H, s), 6.93–6.97 (3H, m), 7.20 (2H, d, J=8.0 Hz), 7.23–7.33 (3H, m), 7.46–7.51 (1H, m), 7.59 (2H, d, J=8.4 Hz), 7.86 (1H, d, J=9.2 Hz), 8.12 (1H, s), 8.90 (1H, brs), 9.15 (1H, brs), 10.26 (1H, s), 10.77 (1H, brs); MS (FAB) m/z: 571 (MH^+); *Anal.* Calcd for $C_{29}H_{29}N_4O_3F_3S\cdot2HCl$: C, 54.12; H, 4.86; N, 8.71; F, 8.86; S, 4.98; Cl, 11.02. Found: C, 53.86; H, 4.89; N, 8.70; F, 8.81; S, 4.94; Cl, 10.93.

(*S*)-2-[(3-Cyanophenylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (6f) The title compound was prepared in the same manner as described for **4a** using **5f** instead of **3a** as a colorless solid. 46% yield; mp 166–171°C (MeOH–EtOH); ^{1}H-NMR (DMSO-d_6) δ: 2.94–3.05 (3H, m), 3.15–3.20 (3H, m), 3.68 (2H, s), 3.93–4.01 (2H, m), 4.21–4.23 (1H, m), 6.76 (1H, s), 6.94–7.97 (3H, m), 7.19 (2H, d, J=8.4 Hz), 7.28–7.36 (3H, m), 7.44–7.49 (1H, m), 7.61 (2H, d, J=8.4 Hz), 7.78–7.81 (1H, m), 8.25–8.26 (1H, m), 8.84 (1H, brs), 9.04 (1H, brs), 10.26 (1H, s), 10.75 (1H, brs); MS (FAB) m/z: 528 (MH^+); *Anal.* Calcd for $C_{29}H_{29}N_5O_3S\cdot2HCl$: C, 58.00; H, 5.20; N, 11.66; S, 5.34; Cl, 11.81. Found: C, 57.82; H, 5.37; N, 11.60; S, 5.30; Cl, 11.62.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(3-methoxyphenylamino)thiazol-4-yl]acetanilide Dihydrochloride (6g) The title compound was prepared in the same manner as described for **4a** using **5g** instead of **3a** as a colorless powder. 42% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.93–3.10 (3H, m), 3.10–3.26 (3H, m), 3.66 (2H, s), 3.67 (3H, s), 3.94–4.01 (2H, m), 4.22–4.24 (1H, m), 5.71 (1H, brs), 6.53 (1H, dd, J=8.0, 2.0 Hz), 6.68 (1H, s), 6.94–6.97 (3H, m), 7.03–7.06 (1H, m), 7.15–7.21 (3H, m), 7.28–7.40 (3H, m), 7.59 (2H, d, J=8.8 Hz), 8.87 (1H, brs), 9.09 (1H, brs), 10.26 (1H, s), 10.42 (1H, brs); MS (FAB) m/z: 533 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_4S\cdot1.9HCl\cdot0.6H_2O$: C, 56.85; H, 5.77; N, 9.14; S, 5.23; Cl, 10.99. Found: C, 57.16; H, 5.96; N, 8.94; S, 5.01; Cl, 10.64.

(*S*)-2-[(4-Chlorophenylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Hydrochloride (6h) The title compound was prepared in the same manner as described for **4a** using **5h** instead of **3a** as a colorless solid. 36% yield; mp 223–228°C (MeOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.86–3.24 (6H, m), 3.64 (2H, s), 3.92–4.01 (2H, m), 4.13–4.22 (1H, m), 5.88 (1H, d, J=5.4 Hz), 6.68 (1H, s), 6.93–6.99 (3H, m), 7.20 (2H, d, J=8.0 Hz), 7.26–7.34 (4H, m), 7.58 (2H, d, J=8.6 Hz), 7.65 (2H, d, J=9.1 Hz), 8.69 (1H, brs), 10.16 (1H, s), 10.33 (1H, s); MS (FAB) m/z: 537 (MH^+); *Anal.* Calcd for $C_{28}H_{29}N_4O_3ClS\cdot HCl\cdot0.15H_2O$: C, 58.30; H, 5.30; N, 9.72; S, 5.56; Cl, 12.31. Found: C, 58.03; H, 4.90; N, 9.77; S, 5.52; Cl, 12.39.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(4-trifluoromethylphenylamino)thiazol-4-yl]acetanilide Dihydrochloride (6i) The title compound was prepared in the same manner as described for **4a** using **5i** instead of **3a** as a colorless solid. 83% yield; mp 195–197°C (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, brs), 5.32 (2H, s), 5.90 (1H, brs), 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, brs), 9.02 (1H, brs), 10.28 (1H, s); MS (FAB) m/z: 571 (MH^+); *Anal.* Calcd for $C_{29}H_{29}N_4O_3F_3S\cdot2HCl$: C, 54.12; H, 4.86; N, 8.71; F, 8.86; S, 4.98; Cl, 11.02. Found: C, 53.90; H, 4.83; N, 8.62; F, 9.06; S, 5.00; Cl, 10.94.

(*S*)-2-[(4-Cyanophenylamino)thiazol-4-yl]-4′-{2-[(2-hydroxy-3-phenoxypropyl)amino]ethyl}acetanilide Dihydrochloride (6j) The title compound was prepared in the same manner as described for **4a** using **5j** instead of **3a** as a colorless solid. 55% yield; mp 224–225°C (MeOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.91–2.99 (3H, m), 3.02–3.08 (3H, m), 3.70 (2H, s), 3.94–4.02 (2H, m), 4.22–4.26 (1H, m), 6.82 (1H, s), 6.93–6.97 (3H, m), 7.21 (2H, d, J=8.4 Hz),

7.27–7.32 (2H, m), 7.61 (2H, d, J=8.8 Hz), 7.67–7.70 (2H, m), 7.81–7.84 (2H, m), 8.95 (1H, brs), 9.20 (1H, brs), 10.30 (1H, s), 11.01 (1H, brs); MS (FAB) m/z: 528 (MH^+); *Anal.* Calcd for $C_{29}H_{29}N_5O_3S \cdot 2HCl \cdot 0.3H_2O$: C, 57.48; H, 5.26; N, 11.56; S, 5.29; Cl, 11.70. Found: C, 57.50; H, 5.14; N, 11.40; S, 5.16; Cl, 11.42.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(4-nitrophenylamino)thiazol-4-yl]acetanilide Hydrochloride (6k) The title compound was prepared in the same manner as described for **4a** using **5k** instead of **3a** as a colorless solid. 42% yield; mp 227–229°C (MeOH–EtOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.90–3.05 (3H, m), 3.19–3.22 (3H, m), 3.70 (2H, s), 3.92–4.00 (2H, m), 4.19 (1H, brs), 5.89 (1H, d, J=4.8 Hz), 6.88 (1H, s), 6.93–6.97 (3H, m), 7.21 (2H, d, J=8.4 Hz), 7.28–7.33 (2H, m), 7.60 (2H, d, J=8.4 Hz), 7.81–7.85 (2H, m), 8.14 (2H, d, J=9.2 Hz), 10.22 (1H, s), 11.06 (1H, s); MS (FAB) m/z: 548 (MH^+); *Anal.* Calcd for $C_{28}H_{29}N_5O_5S \cdot HCl \cdot 0.1H_2O$: C, 57.40; H, 5.20; N, 11.95; S, 5.47; Cl, 6.05. Found: C, 57.16; H, 5.12; N, 11.90; S, 5.47; Cl, 6.01.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(4-methoxyphenylamino)thiazol-4-yl]acetanilide Hydrochloride (6l) The title compound was prepared in the same manner as described for **4a** using **5l** instead of **3a** as a colorless solid. 43% yield; mp 185–191°C (MeOH–EtOAc); ^{1}H-NMR (DMSO-d_6) δ: 2.85–3.25 (6H, m), 3.63 (2H, s), 3.70 (3H, s), 3.92 (2H, m), 4.13–4.23 (1H, m), 5.88 (1H, d, J=4.9 Hz), 6.56 (1H, s), 6.85 (2H, d, J=9.1 Hz), 6.93–6.99 (3H, m), 7.20 (2H, d, J=8.6 Hz), 7.28–7.34 (3H, m), 7.50 (2H, d, J=9.1 Hz), 7.58 (2H, d, J=8.6 Hz), 8.70–8.90 (2H, m), 9.94 (1H, s), 10.15 (1H, s); MS (FAB) m/z: 533 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_4S \cdot HCl \cdot 0.5H_2O$: C, 60.25; H, 5.93; N, 9.69; S, 5.55; Cl, 6.13. Found: C, 60.09; H, 5.81; N, 9.80; S, 5.65; Cl, 6.13.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-[(4-isopropylphenylamino)thiazol-4-yl]acetanilide Dihydrochloride (6m) The title compound was prepared in the same manner as described for **4a** using **5m** instead of **3a** as a colorless powder. 70% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.18 (6H, d, J=6.4 Hz), 2.79–3.05 (4H, m), 3.15–3.22 (3H, m), 3.65 (2H, s), 3.95–3.98 (2H, m), 4.53 (1H, brs), 6.64 (1H, s), 6.94–6.97 (3H, m), 7.14–7.21 (4H, m), 7.28–7.33 (2H, m), 7.48 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.4 Hz), 8.81 (1H, brs), 8.98 (1H, brs), 10.22 (1H, s), 10.33 (1H, brs); MS (FAB) m/z: 545 (MH^+); *Anal.* Calcd for $C_{31}H_{36}N_4O_3S \cdot 1.9HCl \cdot 0.75H_2O$: C, 59.34; H, 6.33; N, 8.93; S, 5.11; Cl, 10.73. Found: C, 59.32; H, 6.32; N, 8.92; S, 5.04; Cl, 10.80.

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[3-(4-{[2-(2-phenylaminothiazol-4-yl)acetyl]amino}phenyl)]-propyl}carbamate (8a)** The title compound was prepared in the same manner as described for **3a** using **7a** and 2-phenylaminothiazol-4-ylacetic acid instead of **2** and 2-*tert*-butoxycarbonylaminothiazol-4-ylacetic acid as a colorless oil. 80% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=6.8 Hz), 1.39 (9H, s), 2.60–2.80 (2H, m), 3.38 (1H, brs), 3.61–4.12 (5H, m), 3.69 (2H, s), 4.93 (1H, brs), 6.44 (1H, s), 6.81–7.31 (8H, m), 7.36–7.43 (6H, m), 9.11 (1H, brs); MS (FAB) m/z: 617 (MH^+).

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-{2-[3-(4-{[2-(2-phenylaminothiazol-4-yl)acetyl]amino}phenyl)]-propyl}carbamate (8b)** The title compound was prepared in the same manner as described for **3a** using **7b** and 2-phenylaminothiazol-4-ylacetic acid instead of **2** and 2-*tert*-butoxycarbonylaminothiazol-4-ylacetic acid as a colorless oil. 72% yield; ^{1}H-NMR ($CDCl_3$) δ: 1.15–1.25 (3H, m), 1.45 (9H, s), 2.62–2.71 (1H, m), 2.98–4.09 (6H, m), 4.52 (1H, brs), 6.43 (1H, s), 6.80–6.97 (4H, m), 7.07–7.13 (4H, m), 7.23–7.30 (4H, m), 7.36–7.43 (6H, m), 9.12 (1H, brs); MS (FAB) m/z: 617 (MH^+).

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]propyl}-2-(2-phenylaminothiazol-4-yl)acetanilide Dihydrochloride (9a) The title compound was prepared in the same manner as described for **4a** using **8a** instead of **3a** as a colorless powder. 64% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.11 (3H, d, J=6.2 Hz), 2.58–2.67 (1H, m), 3.07–3.23 (3H, m), 3.41–3.63 (3H, m), 3.95–4.03 (2H, m), 4.20–4.25 (1H, m), 6.65 (1H, s), 6.90–6.98 (4H, m), 7.17–7.33 (6H, m), 7.25–7.62 (4H, m), 8.67 (1H, s), 8.79 (1H, s), 10.18 (1H, s), 10.22 (1H, s); MS (FAB) m/z: 517 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_3S \cdot 2HCl \cdot 1.9H_2O$: C, 55.84; H, 6.11; N, 8.98; S, 5.14; Cl, 11.37. Found: C, 55.76; H, 5.95; N, 9.16; S, 5.24; Cl, 11.43.

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]propyl}-2-(2-phenylaminothiazol-4-yl)acetanilide Dihydrochloride (9b) The title compound was prepared in the same manner as described for **4a** using **8b** instead of **3a** as a colorless powder. 51% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, d, J=6.4 Hz), 2.58–2.65 (1H, m), 3.00–3.14 (1H, m), 3.20–3.30 (2H, m), 3.40–3.50 (1H, m), 3.69 (2H, s), 3.90–4.10 (2H, m), 4.24–4.32 (1H, m), 6.71 (1H, s), 6.93–7.03 (4H, m), 7.20 (2H, d, J=8.3 Hz), 7.28–7.33 (4H, m), 7.58–7.62 (4H, m), 8.81 (1H, s), 9.25 (1H, s), 10.32 (1H, s), 10.69 (1H, s); MS (FAB) m/z: 517 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_3S \cdot 1.9HCl \cdot 1.2H_2O$: C, 57.33; H, 6.02; N, 9.22; S, 5.28; Cl, 11.09. Found: C, 57.36; H, 6.29; N, 9.17; S, 5.13; Cl, 10.91.

***tert*-Butyl (*S*)-*N*-(2-Hydroxy-3-phenoxypropyl)-*N*-[2-(4-{[2-(2-methylphenylaminothiazol-4-yl)acetyl]amino}-phenyl)ethyl]carbamate (10)** The title compound was prepared in the same manner as described for **3a** using 2-methylphenylaminothiazol-4-ylacetic acid instead of 2-*tert*-butoxycarbonylaminothiazol-4-ylacetic acid as a colorless powder. 18% yield; ^{1}H-NMR (DMSO-d_6) δ: 1.36 (9H, s), 2.71–2.75 (2H, m), 3.28–3.43 (7H, m), 3.57 (2H, s), 3.82–3.83 (2H, m), 3.96 (1H, brs), 5.14 (1H, brs), 6.52 (1H, s), 6.89–6.94 (3H, m), 7.09–7.11 (2H, m), 7.25–7.30 (3H, m), 7.41–7.52 (6H, m), 10.03 (1H, s); MS (FAB) m/z: 617 (MH^+).

(*S*)-4′-{2-[(2-Hydroxy-3-phenoxypropyl)amino]ethyl}-2-(2-methylphenylaminothiazol-4-yl)acetanilide Hydrochloride (11) The title compound was prepared in the same manner as described for **4a** using **10** instead of **3a** as a colorless powder. 46% yield; ^{1}H-NMR (DMSO-d_6) δ: 2.80–3.50 (9H, m), 3.59 (2H, s), 3.91–4.02 (2H, m), 4.13–4.24 (1H, m), 5.89 (1H, brs), 6.53 (1H, s), 6.92–6.99 (3H, m), 7.16–7.70 (11H, m), 8.60–8.90 (1H, m), 10.13 (1H, brs); MS (FAB) m/z: 517 (MH^+); *Anal.* Calcd for $C_{29}H_{32}N_4O_3S \cdot HCl \cdot 0.5H_2O$: C, 61.96; H, 6.10; N, 9.97; S, 5.70; Cl, 6.31. Found: C, 61.98; H, 6.01; N, 10.02; S, 5.80; Cl, 6.48.

Methyl 2-(2-Guanidinothiazol-4-yl)acetate Hydrochloride (13a) A mixture of amidinothiourea (**12a**) (1.18 g) and methyl chloroacetylacetate (1.65 g) in methanol (20 mL) was heated at reflux for 4 h. After cooling to room temperature, the solvent was concentrated *in vacuo*. The residue was diluted with ethyl acetate, and then triturated. The precipitate was removed by filtration, washed with ethyl acetate, and dried to yield **13a** (2.25 g) as a colorless powder. 90% yield; ^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, s), 3.73 (3H, s), 6.81 (1H, s); MS (FAB) m/z: 215 (MH^+).

Methyl 2-[(4-Cyanophenylamino)thiazol-4-yl]acetate Hydrochloride (13b) The title compound was prepared in the same manner as described for **13a** using 4-cyanophenylthiourea instead of amidinothiourea as a colorless powder. 63% yield; ^{1}H-NMR ($CDCl_3$) δ: 3.72 (2H, s), 6.62 (1H, s), 7.44–7.48 (2H, m), 7.56–7.62 (2H, m); MS (FAB) *m/z*: 274 (MH^+).

Methyl 2-[(2-Furylmethylamino)thiazol-4-yl]acetate Hydrochloride (13c) The title compound was prepared in the same manner as described for **13a** using 2-furylmethylthiourea instead of amidinothiourea as a colorless powder. 83% yield; ^{1}H-NMR ($CDCl_3$) δ: 3.58 (2H, s), 3.70 (3H, s), 4.43 (2H, s), 6.06 (1H, br s), 6.25–6.35 (3H, m), 7.36 (1H, s); MS (FAB) *m/z*: 253 (MH^+).

2-(2-Guanidinothiazol-4-yl)acetic Acid Hydrochloride (14a) A mixture of **13a** (0.65 g) in 10% aqueous hydrochloric acid solution (10 mL) was heated at reflux for 1 h. After cooling to room temperature, the solvent was concentrated *in vacuo*. The residue was diluted with ethyl acetate, and then triturated. The precipitate was removed by filtration, washed with ethyl acetate and methanol, and dried to yield **14a** (0.6 g) as a colorless powder. 98% yield; ^{1}H-NMR (DMSO-d_6) δ: 3.66 (2H, s), 7.11 (1H, s), 8.28 (4H, br s), 12.46 (1H, s); MS (FAB) *m/z*: 201 (MH^+).

2-[(4-Cyanophenylamino)thiazol-4-yl]acetic Acid (14b) To a solution of **13b** (1.1 g) in methanol (10 mL) were added 1 M NaOH aqueous solution (4 mL), and the mixture was heated at reflux for 1 h. After cooling to room temperature, the solvent was concentrated *in vacuo*. The resultant mixture was neutralized by addition of 1 M HCl aqueous solution (4 mL), and stirred at room temperature. The precipitate was removed by filtration, washed with water, and dried to yield **14b** (0.95 g) as a colorless powder. 95% yield; ^{1}H-NMR (DMSO-d_6) δ: 3.58 (2H, s), 6.81 (1H, s), 7.72–7.78 (4H, m), 10.73 (1H, br s), 12.38 (1H, br s); MS (FAB) *m/z*: 260 (MH^+).

2-[(2-Furylmethylamino)thiazol-4-yl]acetic Acid (14c) The title compound was prepared in the same manner as described for **14b** using **13c** instead of **13b** as a colorless powder. 70% yield; ^{1}H-NMR ($CDCl_3$) δ: 3.51 (2H, s), 4.32 (2H, s), 6.25–6.26 (3H, m), 7.30–7.33 (1H, m).

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.

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 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.

Acknowledgment The authors are grateful to the staff of the Division of Analytical Science Laboratories for elemental analysis and spectral measurements.

References

1) Nisoli E., Tonello C., Carruba M. O., *Curr. Med. Chem. Central Nerv. Syst. Agents*, **3**, 257–273 (2003).
2) Moneva M. H., Dagogo-Jack S., *Curr. Drug Targets*, **3**, 203–221 (2002).
3) Arch J. R., Ainsworth A. T., Cawthorne M. A., Piercy V., Sennitt M. V., Thody V. E., Wilson C., Wilson S., *Nature* (London), **309**, 163–165 (1984).
4) Howe R., *Drugs Future*, **18**, 529–549 (1993).
5) Cantello B. C. C., Smith S. A., *Drugs Future*, **16**, 797–800 (1991).
6) Bloom J. D., Claus T. H., *Drugs Future*, **19**, 23–26 (1994).
7) Arch J. R. S., Wilson S., *Int. J. Obes.*, **20**, 191–199 (1996).
8) Lipworth B. J., *Br. J. Clin. Pharmacol.*, **42**, 291–300 (1996).
9) de Souza C. J., Burkey B. F., *Curr. Pharm. Des.*, **7**, 1433–1449 (2001).
10) Emorine L. J., Marullo S., Briend-Sutren M.-M., Patey G., Tate K., Delavier-Klutchko C., Strosberg A. D., *Science*, **245**, 1118–1121 (1989).
11) Emorine L. J., Fève B., Pairault J., Briend-Sutren M.-M., Nahmias C., Marullo S., Delavier-Klutchko C., Strosberg D. A., *Am. J. Clin. Nutr.*, **55** (Suppl.), 215S–218S (1992).
12) Tate K. M., Briend-Sutren M.-M., Emorine L. J., Delavier-Klutchko C., Marullo S., Strosberg A. D., *Eur. J. Biochem.*, **196**, 357–361 (1991).
13) Yamaguchi O., *Urology*, **59** (Suppl. 1), 25–29 (2002).
14) Nomiya M., Yamaguchi O., *J. Urol.*, **170**, 649–653 (2003).
15) Yamanishi T., Yasuda K., Kitahara S., Nakai H., Yoshida K.-I., Iizuka H., *Neurourol. Urodyn.*, **25**, 815–819 (2006).
16) Mathvink R. J., Tolman J. S., Chitty D., Candelore M. R., Cascieri M. A., Colwell L. F. Jr., Deng L., Feeney W. P., Forrest M. J., Hom G. J., MacIntyre D. E., Miller R. R., Stearns R. A., Tota L., Wyvratt M. J., Fisher M. H., Weber A. E., *J. Med. Chem.*, **43**, 3832–3836 (2000).
17) Harada H., Hirokawa Y., Suzuki K., Hiyama Y., Oue M., Kawashima H., Kato H., Yoshida N., Furutani Y., Kato S., *Chem. Pharm. Bull.*, **53**, 184–198 (2005).
18) Tanaka N., Tamai T., Mukaiyama H., Hirabayashi A., Muranaka H., Ishikawa T., Akahane S., Akahane M., *Bioorg. Med. Chem.*, **9**, 3265–3271 (2001).
19) Uehling D. E., Shearer B. G., Donaldson K. H., Chao E. Y., Deaton D. N., Adkison K. K., Brown K. K., Cariello N. F., Faison W. L., Lancaster M. E., Lin J., Hart R., Milliken T. O., Paulik M. A., Sherman B. W., Sugg E. E., Cowan C., *J. Med. Chem.*, **49**, 2758–2771 (2006).
20) Maruyama T., Onda K., Hayakawa M., Suzuki T., Kimizuka T., Matsui T., Takasu T., Nagase I., Hamada N., Ohta M., *Chem. Pharm. Bull.*, **58**, 533–545 (2010).
21) Maruyama T., Onda K., Hayakawa M., Seki N., Takahashi T., Moritomo H., Suzuki T., Matsui T., Takasu T., Nagase I., Ohta M., *Bioorg. Med. Chem.*, **17**, 3283–3294 (2009).
22) Maeda R., Hirose K., Jpn. Kokai Tokkyo Koho, JP50069076 (1975).