Discovery of a Novel Series of Benzoic Acid Derivatives as Potent and Selective Human β_3 Adrenergic Receptor Agonists with Good Oral Bioavailability. 3. Phenylethanolaminotetraline (PEAT) Skeleton Containing Biphenyl or Biphenyl Ether Moiety

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Received March 2, 2008

We designed a series of benzoic acid derivatives containing the biphenyl ether or biphenyl template on the RHS and a phenylethanolaminotetraline (PEAT) skeleton, which was prepared by highly stereoselective synthesis, to generate two structurally different lead compounds (**10c**, **10m**) with a good balance of potency, selectivity, and pharmacokinetic profile. Further optimization of the two lead compounds to improve potency led to several potential candidates (i.e., **11f**, **11l**, **11o**, **12b**). In particular, biphenyl analogue **12b** exhibited an excellent balance of high potency (EC_{50} = 0.38 nM) for β_3, high selectivity over β_1 and β_2, and good pharmacokinetic properties in rats, dogs, and monkeys.

Introduction

The β_3-adrenergic receptor (β-AR[a]), which is present on the surface of both white and brown adipocytes, plays a significant role in regulating lipolysis and thermogenesis in rodent and human adipocyte tissues.[1,2] It has been reported that stimulation of β_3-AR induces a variety of pharmacological effects such as an increase in fat oxidation, enhancement of energy expenditure, and improvement of insulin-mediated glucose uptake in rodent models, and thus, β_3-AR agonists have been developed as therapeutic candidates for obesity and type II diabetes.[3] Recent studies have indicated that in addition to adipocytes, the β_3-AR is also distributed in human heart, gall bladder, gastrointestinal tract, prostate,[4] and urinary bladder detrusor tissue; therefore, new therapeutic applications of β_3-AR agonists in the treatment of gastrointestinal and overactive bladder (OAB) have been studied.[5–8] On the other hand, the concomitant activation of β_1- or β_2-ARs would lead to undesirable side effects such as increased heart rate and/or muscle tremors. Thus, β_3-AR selectivity over β_1-AR and β_2-AR has been required for new therapeutic agents.

Early β_3 agonists (the "first generation" of potent and selective rat β_3-AR agonists) such as **1** (BRL37344),[9] **2** (CL316243),[9] **3** (SR58611A),[9] and **4** (FK175),[8c] as shown in Figure 1, have been reported to be effective antiobesity and antidiabetic agents in rodents. Unfortunately, **1**, **2**, and other β_3-AR agonists discovered during the 1980s were unsuccessful in the clinic either because of a lack of efficacy or an unfavorable cardiovascular side effect profile, and/or poor pharmacokinetics.[3] Thus, a second generation of orally bioavailable human β_3-AR agonists with minimal side effects associated with activation of human β_1- and β_2-ARs has been an important goal of recent research. In the past decade, drug discovery efforts have shifted toward the design of selective agonists for the β3-AR. Furthermore, several groups have reported a number of second generation of β_3-AR agonists with high potency and good selectivity with respect to human β_1 and β_2-ARs, as exemplified by the potent and selective β_3-AR agonists **5** (LY377604),[9,10] **6** (L796568),[11] and **7** (solabegron)[12] (see Figure 2), but these are still not sufficient in terms of the pharmacokinetic properties.[9,13,14]

In our laboratory, our first clinical candidate **4**, having a benzocycloheptene ring and carboxylic ester functionality (prodrug form) in the right-hand side (RHS) in Figure 1, showed good selectivity over human β_1 and β_2 ARs and good oral absorption in phase I clinical trials. However, it was still insufficient in terms of β_3-AR potency and long duration for OAB treatment, since in the field of treatment of urinary bladder dysfunction, there is an unmet medical need for a once daily oral administration. On the other hand, in the early 1990s, Sanofi-Midy (now Sanofi-Aventis) identified a series of a phenylethanolaminotetralines (PEATs), similar to **4** as a common structure for the RHS region, as selective β_3-AR agonists in rodents.[15] Among this series of PEATs, **3** was found to have the best profile as a β_3-AR agonist. Although **3** is less potent than isoproterenol (a nonselective β-AR agonist) and **4**, it was developed as a potential treatment for irritable bowel syndrome and obesity and then for depression.[13]

Recently, we have disclosed[16] a novel series of biphenylbenzoic acid derivatives as potent and selective human β_3-AR agonists that are orally bioavailable with a long duration. We demonstrated that the biphenyl **8** and biphenyl ether **9** templates with a benzoic acid moiety are essential for the good pharmacokinetic properties in our previous series.[16] To overcome several problems of **3** and **4**, we planned a discovery process for a novel tetraline series of second generation β_3-AR agonists, as shown in Figure 3. Our designed general β_3-AR agonist structure **10** (see Figure 3) involved construction of the PEAT skeleton with two chiral centers from **3** or **4**, and the biphenyl (**8**) or biphenyl ether (**9**) templates with a benzoic acid moiety,

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[a] Abbreviations: β-AR, β-adrenergic receptors; OAB, overactive bladder; SAR, structure−activity relationship; PEATs, phenylethanolaminotetralines; RHS, right-hand side; LHS, left-hand side; cAMP, cyclic adenosine monophosphate; ISP, isoproterenol; CHO, Chinese hamster ovary.

10.1021/jm800222k CCC: $40.75
Published on Web 07/24/2008

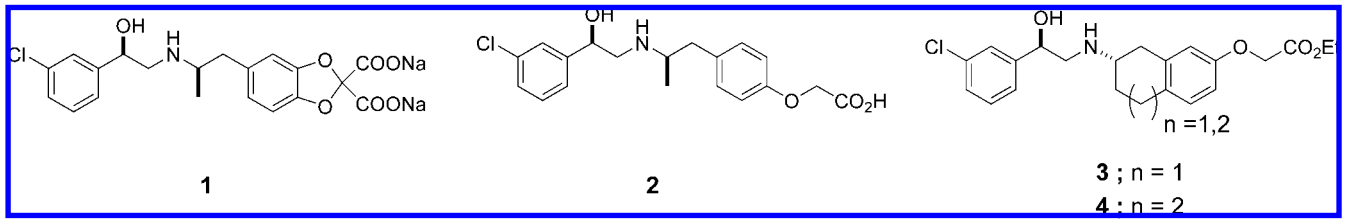


Figure 1. Representative first generation of β_3-AR agonists.

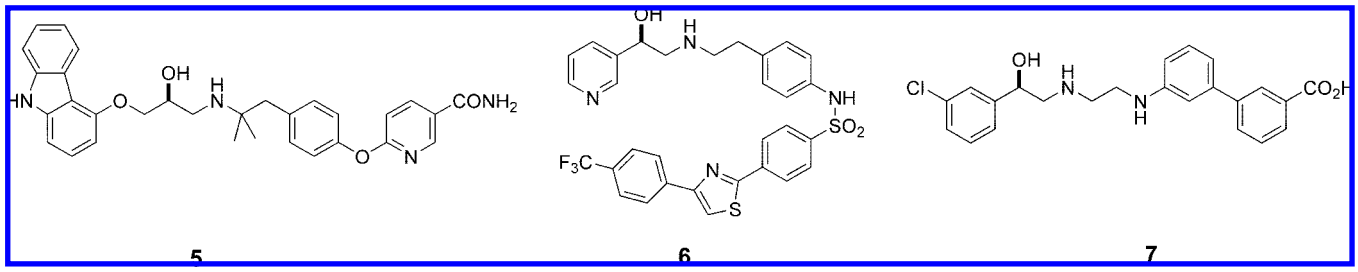


Figure 2. Representative second generation of β_3-AR agonists.

which are important for not only β_3-AR agonistic activity but also pharmacokinetic properties.

We investigated the structure−activity relationship (SAR) and pharmacokinetic properties of a PEAT series of compounds **10**, employing a cassette dosing assay by in vivo dog pharmacokinetic assay[17] to generate two different lead compounds (**10c**, **10k**) having biphenyl ether and biphenyl templates containing a benzoic acid moiety, with a good balance of potency, selectivity, and pharmacokinetic profile. Further optimization of the two different lead compounds (general structures **11** and **12**) to improve potency led to several potential candidates (i.e., **11f**, **11l**, **11o**, **12b**). The synthesis of these compounds with two chiral centers, the results of in vitro and cassette dosing assays, and the PK profiles of our drug candidates are described in detail in the following sections.

Chemistry

The requisite chiral amine intermediate **15** was prepared via asymmetric hydrogenation of the enamide **14**(Scheme 1). Since there are similar examples of highly enantioselective hydrogenation,[18] we applied this reaction to the asymmetric synthesis of the aminotetraline **18**, as shown in Scheme 1. Conversion of the 7-methoxy-2-tetralone **13** to the enamide **14** was accomplished by condensation with benzamide in the presence of Amberlyst-15 resin under Dean−Stark conditions, followed by asymmetric hydrogenation with a Ru complex. The screening of chiral ligands identified Ru(II)-(*S*)-SEGPOS **19** (by Takasago Co. Ltd.) as an optimal ligand to give a chiral amine **15** with high enantioselectivity. After recrystallization, **15** was obtained in 74% yield and 99.6% ee. Treatment of enantiomerically pure **15** with $BH_3 \cdot SMe_2$, affording the corresponding benzyl intermediate **16**, followed by removal methyl group with BBr_3 and hydrogenolysis of the benzyl group furnished aminotetraline **18** in 50% overall yield from **15**. The requisite intermediate PEATs derivatives **24**−**27** with two chiral centers were prepared as shown in Scheme 2. In general, coupling of the chiral amine **18** or **19**, which has previously been described,[19] with the chiral epoxides **21**−**23**, followed by protection of the amine with a Boc group gave phenol derivatives **24**−**27**.

The general synthetic route to biphenyl ether targets (**10a**−**i**) is shown in Schemes 3 and 4. The phenoxyacetic acid analogues (**10a**,**b**) were obtained by coupling of phenol derivative **24** with boronic acid using $Cu(OAc)_2$ and MS4 Å in CH_2Cl_2, followed by deprotection of TBS group, coupling with bromoethyl acetate, alkaline hydrolysis of the ester, and deprotection of the Boc group with 4 N HCl. Similarly, benzoic acid analogues (**10c**−**f**) were prepared from Boc amine derivatives **29a**−**d**, which were obtained by coupling of phenol derivative **24** or **26** with methoxycarbonylphenylboronic acid, followed by alkaline hydrolysis of the methyl ester derivatives (**29a**−**d**) and deprotection of the Boc group with 4 N HCl. The pyridine ether **10g** was obtained through nucleophilic displacement of commercially available ethyl 6-chloronicotinate with phenol **24**, followed by alkaline hydrolysis and deprotection of the Boc group (Scheme 6). Also, pyridine ether **10h** was obtained by selective oxidation of aldehyde **31**, followed by deprotection of the Boc group (Scheme 6). The thiophene analogue **10i** was prepared from phenol **24** according to the procedure described for the conversion of **24** to **10h.** The synthetic route to c **11a**−**o** is shown in Scheme 5. Similar to the conversion of **24** to **10c** in Scheme 3, the targets **11a**−**d**, **11k**−**l** were prepared by coupling of **24** or **25** or **27** with commercially available boronic acid **34**, **35**, or synthetic boronic acids **33** and **36** as shown in Scheme 11.[16] The amino analogues **11e**−**j** were synthesized from 4-amino intermediate **39**. Coupling of phenol **24** with nitrophenylboronic acid **37**, followed by reduction with Fe and NH_4Cl, gave **39**. The target **11e** was prepared by alkaline hydrolysis of **39**, followed by deprotection of the Boc group with 4 N HCl. Aniline **39** was coupled with acetic anhydride in the presence of pyridine, followed by the typical method to give acetyl analogue **11g**. The NMe_2 analogue **11f** was obtained through reductive amination of aniline **39** with formaldehyde with $NaBH(OAc)_3$, followed by alkaline hydrolysis and deprotection of the Boc group. In the same way, the *p*-chloropyridine analogue **11p** was prepared via coupling of phenol derivative **27** with nitrophenylboronic acid **37**. Similarly, the amino analogues **11i**, **11j** were prepared by reductive amination of aniline **32** with the corresponding ketones. The NH-*n*-Pr analogue **11h** was obtained from coupling of aniline **39** with *n*-Pr-I. The *p*-chlorophenyl or chloropyridine analogues **11k**,**l**,**n**,**o** were prepared via the coupling of phenol derivative **25** or **27** with commercially available boronic acids as shown in Scheme 5. In the same way, pyridine analogue **11m** was obtained from **27**, in an additional step, through dechlorination by catalytic hydrogenation in the presence of HCO_2NH_4.

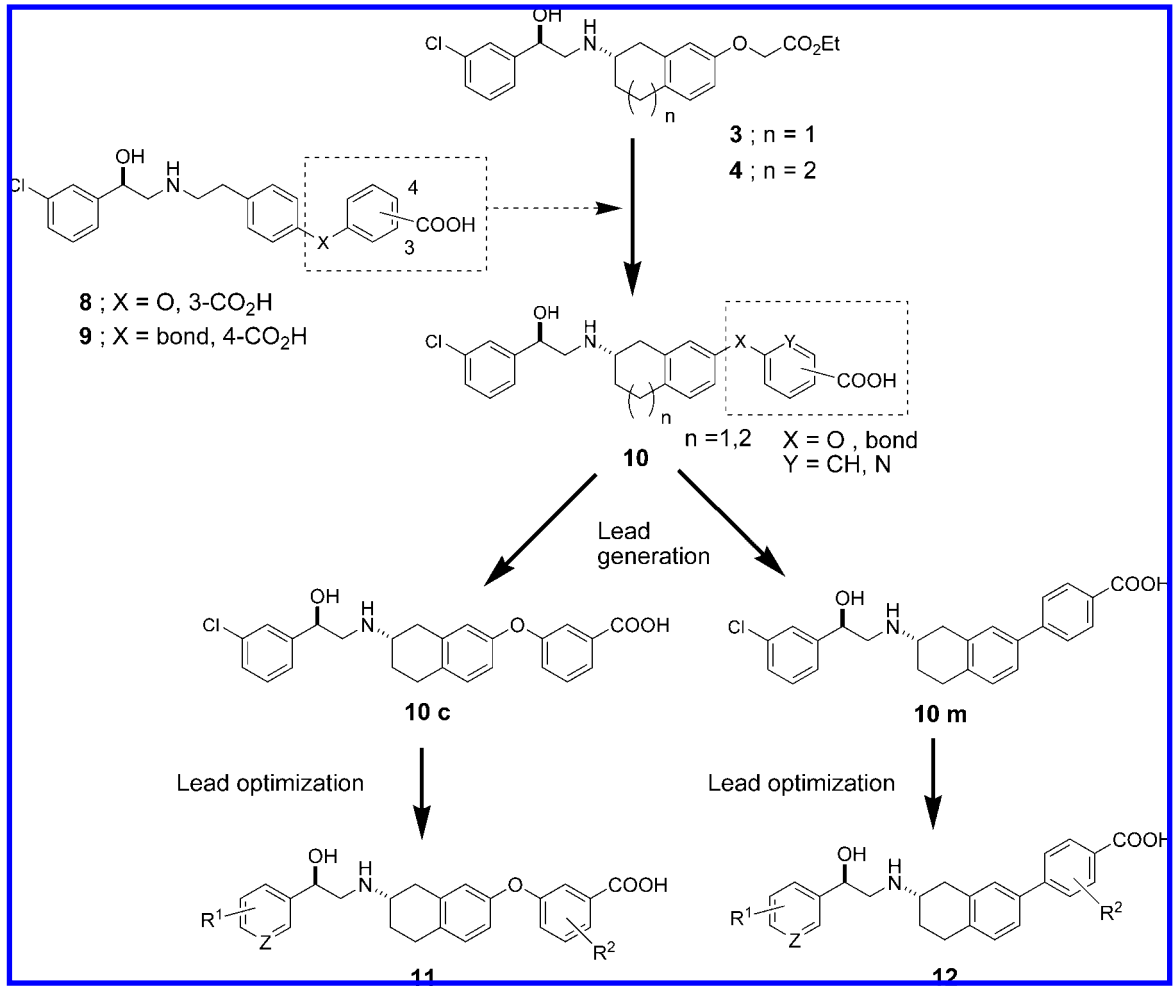
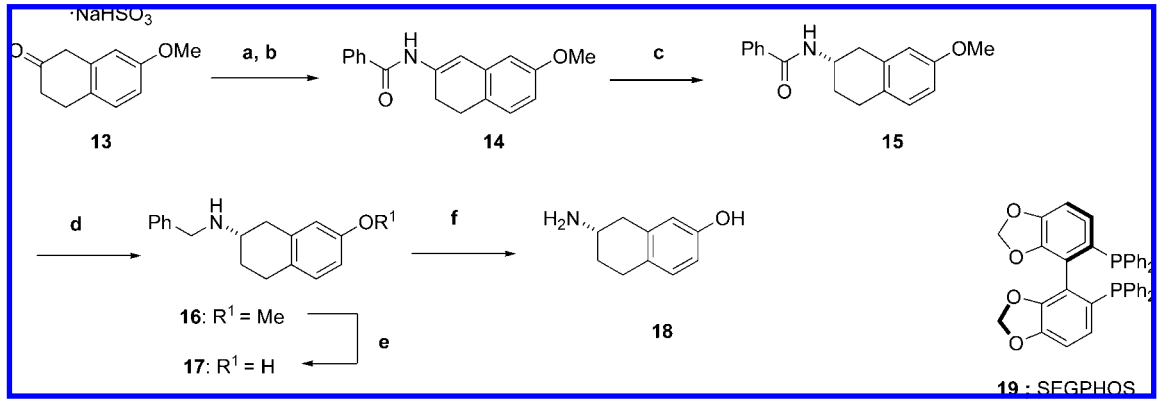


Figure 3. Design and discovery process of lead generation and lead optimization.

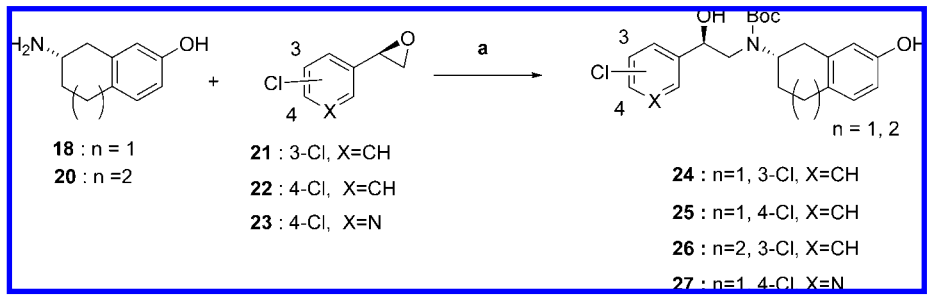
Scheme 1[a]



[a] (a) 3 N HCl, toluene; (b) $PhCONH_2$, Amberlyst-15 (50% wt %), toluene, reflux; (c) H_2 (30 atm), Ru(II)/SEGPHOS, MeOH, CH_2Cl_2; (d) $BH_3 \cdot SMe_2$, THF, then 6 N HCl; (e) BBr_3, CH_2Cl_2; (f) H_2, 10% Pd/C, MeOH.

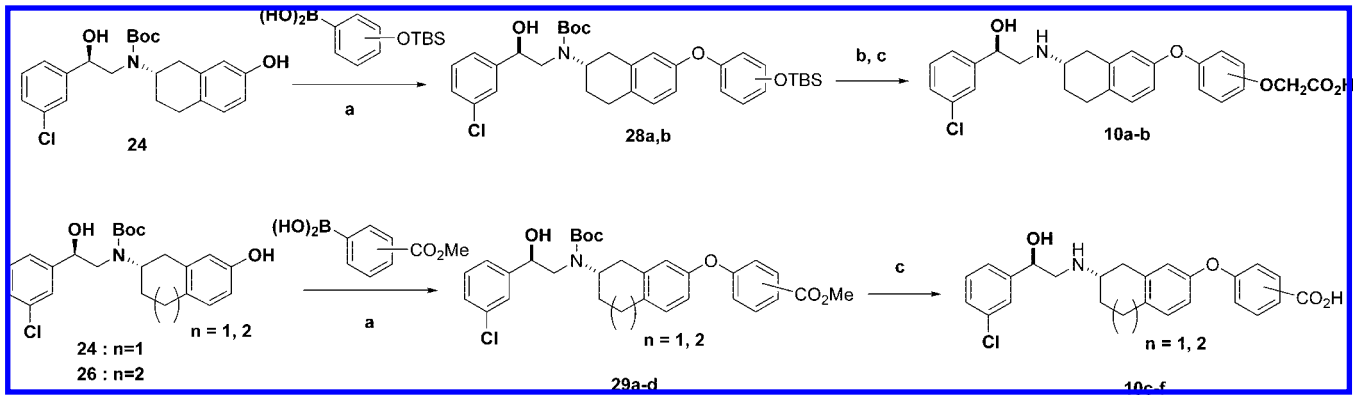
The general synthetic route to biphenyl targets (**10j**−**p**) is shown in Scheme 6. Suzuki cross-coupling of triflate derivatives, which were prepared by reaction of the corresponding phenol derivative **24** or **26** with Tf_2O/2,6-lutidine in CH_2Cl_2 at low temperature, with commercially available boronic acids, followed by alkaline hydrolysis of the methyl ester and deprotection of the Boc group with 4N HCl, provided biphenyl targets (**10l**−**o**). Similarly, the phenoxyacetic acid analogues **10j**,**k** were prepared from coupling product **38a,b**, followed by using the same method described for **10a**,**b**. The thiophene analogue **10p** was prepared from coupling product **40** followed by using the same method described for **10i.** The general synthetic route to biphenyl targets (**12a**,**b**,**d**−**f**,**h**) is shown in Scheme 7. The requisite biphenyl intermediate **43** was prepared as follows: the chiral aminotetraline **18** was protected with a Cbz group, and protection of the phenol **41** with a triflate group, followed by Suzuki coupling with boronic acid and deprotection of the Cbz group, furnished biphenyl intermediate **43**. As shown in Scheme 7, the required optically active epoxides (>97% ee) were prepared through the our previous asymmetric synthetic procedures[20] as shown in Scheme 10. Ring opening of epoxides with amine **43** in ethanol under reflux followed by alkaline

Scheme 2[a]



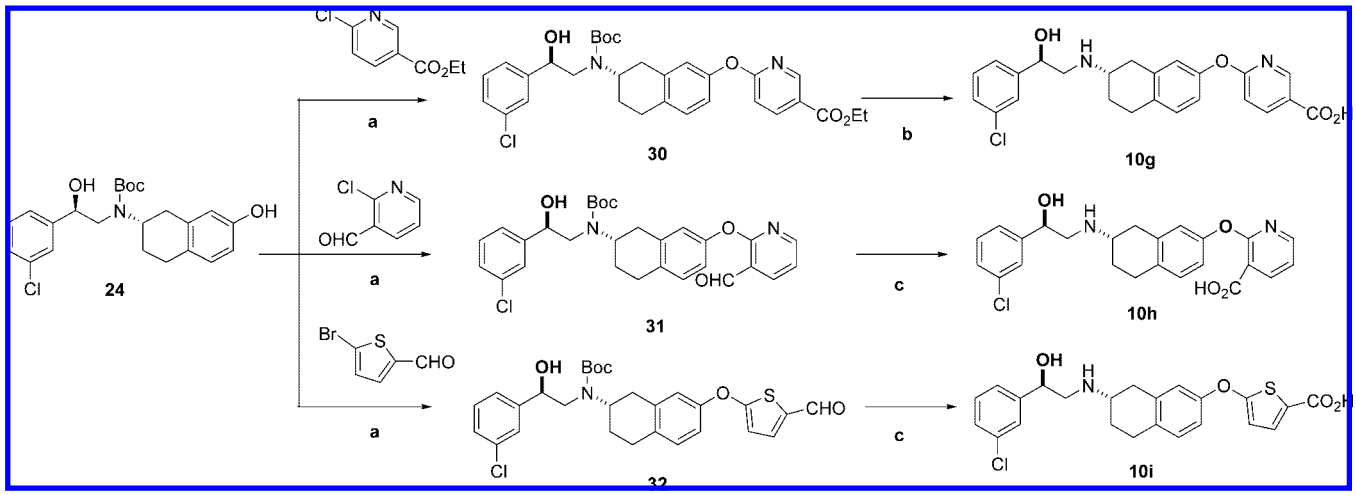
[a] EtOH, reflux, then $(Boc)_2O$, THF.

Scheme 3[a]



[a] (a) Boric acid, $Cu(OAc)_2$, 4 Å molecular sieves, CH_2Cl_2; (b) Bu_4NF (1 M in THF), THF, then $BrCH_2CO_2Et$, K_2CO_3, DMF; (c) 1 N aqueous NaOH, MeOH, then 4 N HCl/AcOEt or dioxane.

Scheme 4[a]



[a] (a) K_2CO_3, DMSO, 80°C; (b) 1 N aqueous NaOH, MeOH, then 4 N HCl/AcOEt or dioxane; (c) 30% H_2O_2, 80% $NaClO_2$, MeCN, then 4 N HCl/dioxane.

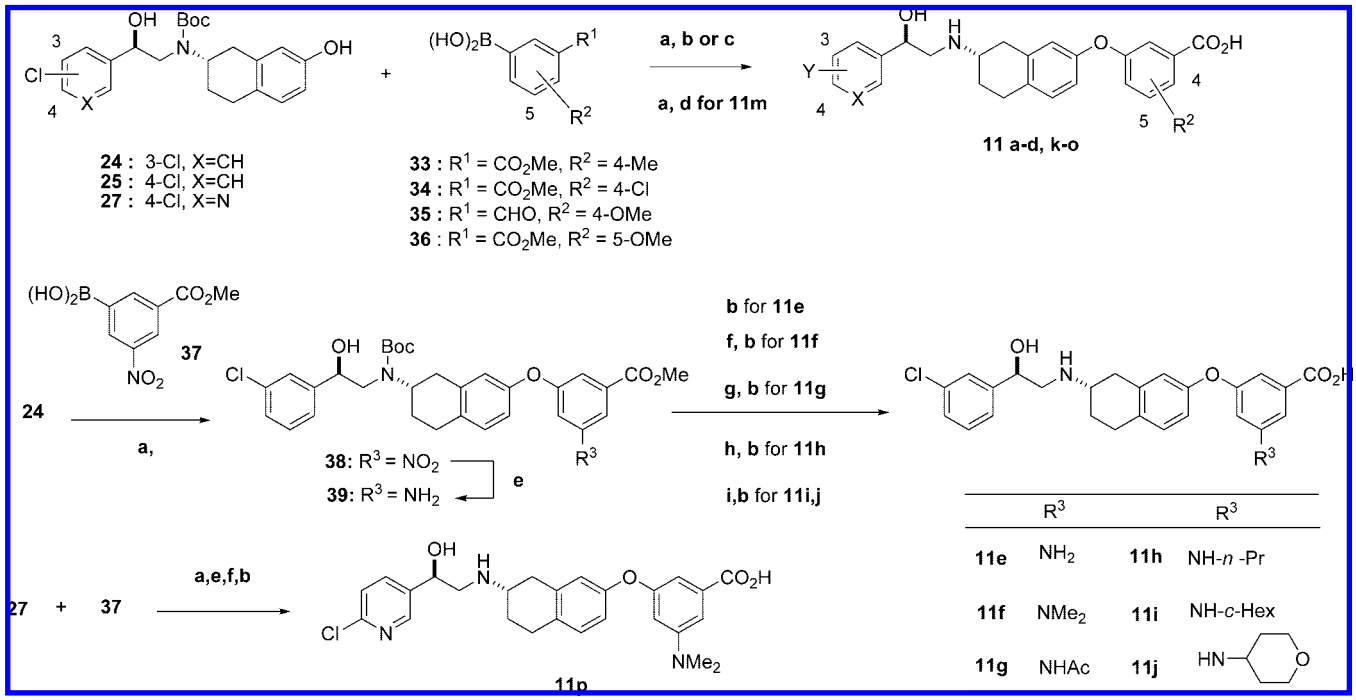
hydrolysis of the methyl ester provided the target compounds as sodium salts. Similarly, the biphenyl targets **12c** were prepared as hydrochloride salts by coupling of amine **43** with epoxide **44**, followed by alkaline hydrolysis, deprotection of the Boc group with 4 N HCl, as shown in Scheme 8. In a similar manner, pyridine analogue **12g** was obtained from **23** and **43**, in an additional step, through dechlorination by catalytic hydrogenation in the presence of HCO_2NH_4.

Finally, the synthetic route to substituted biphenyl analogues **12i−n** is shown in Scheme 9. Similar to the conversion of **24** to **1m** in Scheme 6, reaction of *p*-chlorophenyl derivative **25** with Tf_2O followed by Suzuki-coupling of the triflate derivative with R-substituted boronic acid, the synthesis of which has been previously described,[16] and ester hydrolysis and deprotection of the Boc group provided the target compounds **12i−n** as hydrochloride salts.

Results and Discussion

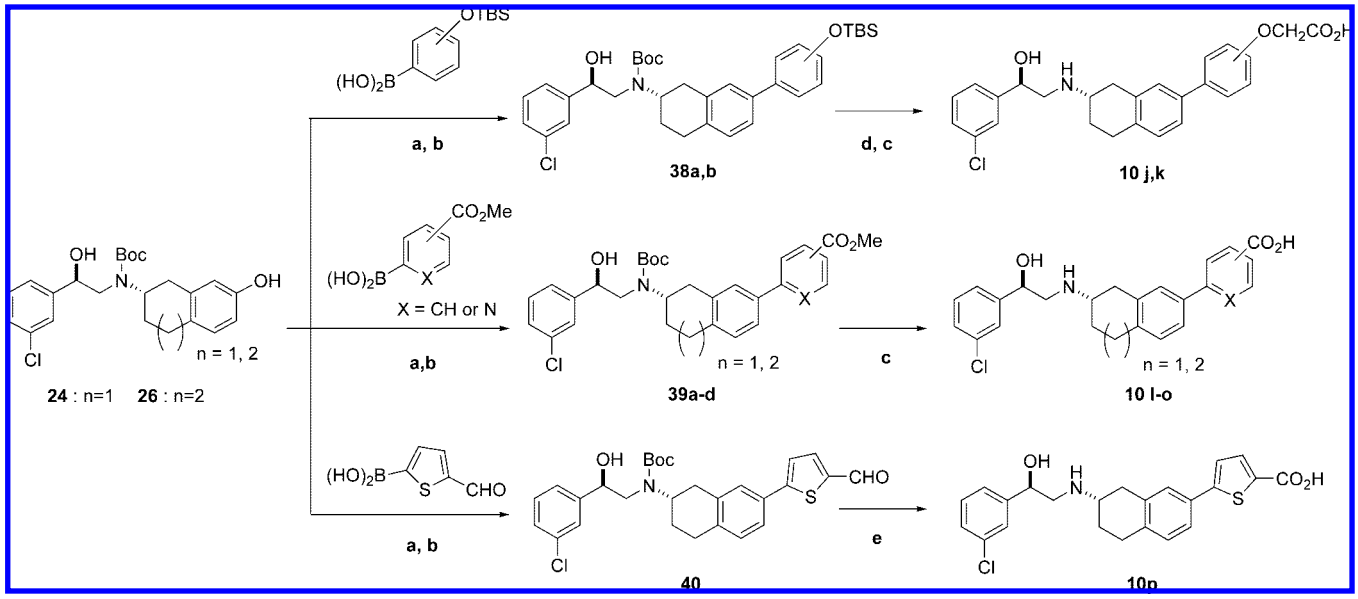
All compounds were evaluated for ability to produce cAMP in Chinese hamster ovary (CHO) cell lines expressing cloned human β3 and β1-ARs. Selected compounds were also evaluated for human β2 activity using a similar method.[16] The details are described in the Experiment Section. Pharmacokinetic properties of selected compounds were evaluated by cassette dosing assay

Scheme 5[a]



[a] (a) Cu(OAc) $_2$, 4 Å molecular sieves, CH_2Cl_2; (b) 1 N aqueous NaOH, MeOH, then 4 N HCl/AcOEt or dioxane; (c) 30% H_2O_2, 80% $NaClO_2$, MeCN, then 4 N HCl/dioxane; (d) 1 N aqueous NaOH, EtOH, then HCO_2NH_4, 10% Pd/C, MeOH, H_2O, reflux, then 4 N HCl/dioxane; (e) Fe (powder), NH_4Cl, EtOH, reflux; (f) 35% HCHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (g) Ac_2O, pyridine, CH_2Cl_2; (h) I-*n*-Pr, K_2CO_3, DMF, 80°C; (i) cyclohexanone or tetrahydro-4*H*-pyran-4-one, $NaBH(OAc)_3$, AcOH, CH_2Cl_2.

Scheme 6[a]

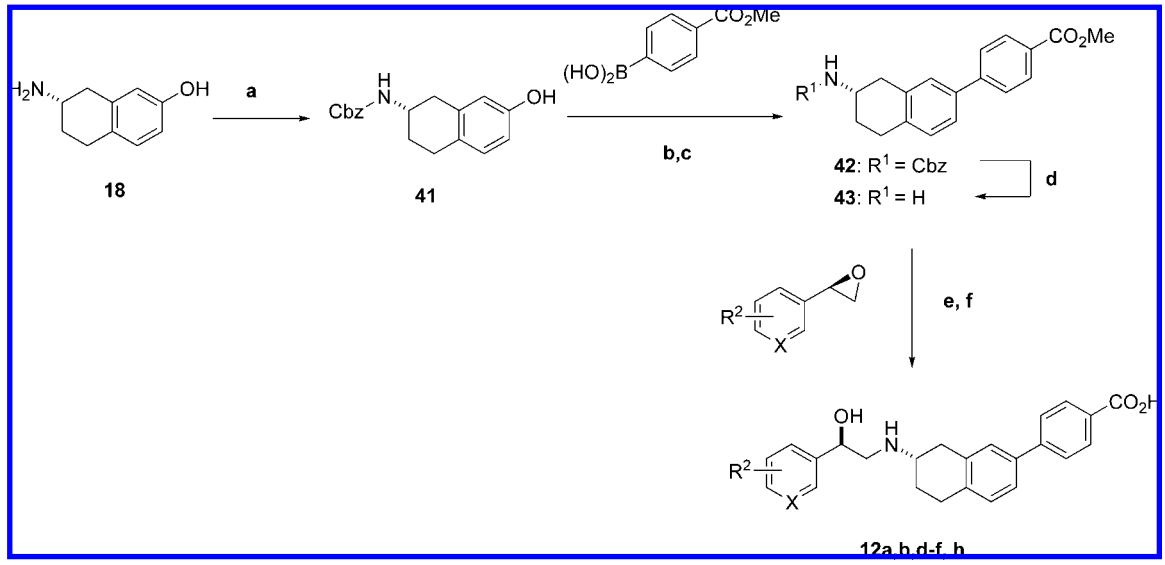


[a] (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C; (b) boric acid, $Pd(PPh_3)_4$, aqueous $NaHCO_3$, DME, 70°C; (c) 1 N aqueous NaOH, MeOH, then 4 N HCl/AcOEt or dioxane; (d) Bu_4NF (1 M in THF), THF, then $BrCH_2CO_2Et$, K_2CO_3, DMF; (e) 30% H_2O_2, 80% $NaClO_2$, MeCN, then 4 N HCl/dioxane.

in dogs.[21] The results with reference compound isoproterenol (ISP; nonselective β-AR agonist) are shown for comparison in Table 1.

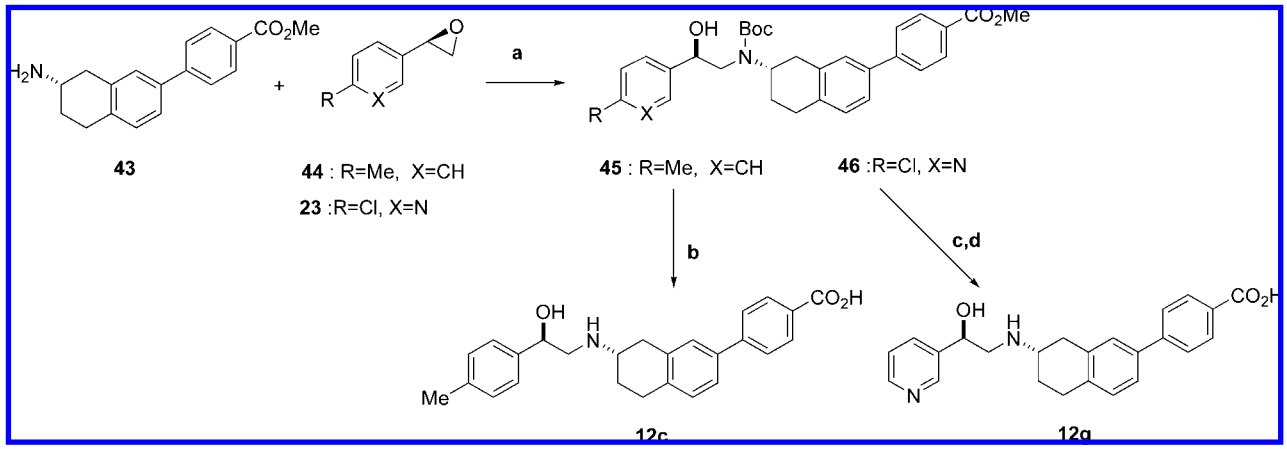
To assess the quality of our designed aminotetraline analogues (compound **10**) as potent, selective β3-AR agonists, we first prepared a series of biphenyl ethers with six-membered rings with phenoxyacetic acid in the terminal phenyl ring (Table 1, **10a**,**b**). Although phenoxyacetic acid analogues **10a**, **10b** showed moderate agonistic activity for the β3-AR, we felt that the profile of these compounds was insufficient in terms of potency for β3-AR. Next, we investigated the effect of modification of the carboxylic acid moiety. Biphenyl ether analogues (**10c**−**f**) having a benzoic acid moiety in both six- and seven-membered rings were prepared and examined. Analogues containing a meta carboxylic acid (**10c**, **10e**) showed improved β3-AR activity (**10c**, EC_{50} = 7.1 nM; **10e**, EC_{50} = 4.5 nM) relative to phenoxyacetic acid analogues (**10a**,**b**), **3** and **4**. On the other hand, para-position analogues (**10d**, **10f**) resulted in poor potency for β3-AR. The seven-membered ring analogue **10e** showed somewhat improved potency, although lower

Scheme 7[a]



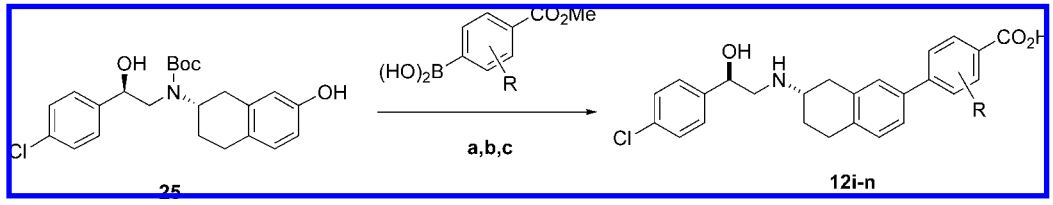
[a] (a) Cbz-Cl, THF, H_2O with aqueous NaOH (pH 7−8); (b) Tf_2O, 2,6-lutidine, CH_2Cl_2; (c) boric acid, $Pd(PPh_3)_4$, aqueous $NaHCO_3$, DME, 70°C; (d) H_2, 10% Pd/C, MeOH; (e) EtOH, reflux; (f) 1 N aqueous NaOH, EtOH.

Scheme 8[a]



[a] (a) EtOH, reflux, then $(Boc)_2O$, THF; (b) 1 N aqueous NaOH, MeOH, then 4 N HCl/AcOEt; (c) 1 N aqueous NaOH, EtOH, then HCO_2NH_4, 10% Pd/C, MeOH, H_2O, reflux; (d) 4 N HCl/dioxane.

Scheme 9[a]



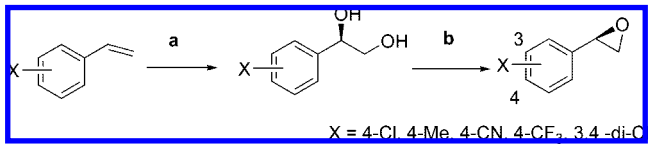
[a] (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78°C; (b) boric acid, $Pd(PPh_3)_4$, aqueous $NaHCO_3$, DME, 70°C; (c) 1 N aqueous NaOH, MeOH, then 4 N HCl/AcOEt or dioxane.

selectivity over β_1 activity (**10e**, $\beta_1/\beta_3 = 35$) compared to the six-membered ring analogue **10c** ($\beta_1/\beta_3 > 138$). Also, both **10c** and **10e** exhibited low activity for the β_2-AR ($EC_{50} > 1000$ nM).

Furthermore, biphenyl ether analogues (**10a**, **10c**, **10e**) were evaluated in the in vivo PK assay (cassette dosing assay, po) in dogs. As a baseline, the C_{max} and AUC ratio value of **10a** are presented as 1.0 for comparison in Table 1. The benzoic acid group (six-membered ring analogue **10c**) showed a superior C_{max} and AUC ratio relative to the phenoxyacetic acid analogue **10a**. On the other hand, seven-membered ring analogue **10e** showed a low C_{max} and AUC level relative to **10c**. This result (**10a** vs **10c**) in which the benzoic acid moiety may result in improvement of the C_{max} and AUC level indicated the same trend as we have previously demonstrated.[16] Actually, the C_{max} and AUC ratio of compound **10c** displayed a superior level compared with our previous compounds **8** and **9**.

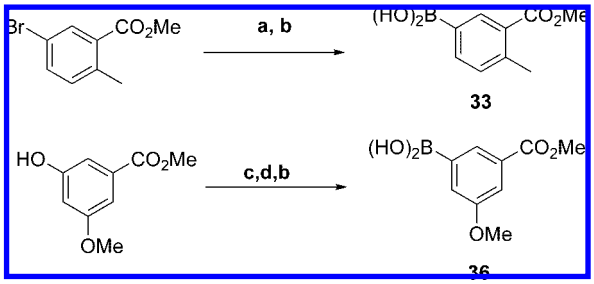
Next, we investigated replacement of the terminal phenyl ring of the biphenyl ether analogues with typical heterocycles. A pyridine analogue containing a *p*-carboxylic acid **10g** showed strong β3-AR agonistic activity ($EC_{50} = 1.4$ nM) but a lower $\beta1/\beta3$ selectivity ($\beta_1/\beta_3 = 50$) relative to the biphenyl ether

Scheme 10. General Synthetic Route to Optically Active Epoxides[a]



[a] (a) AD-mix-β, *t*-BuOH·H_2O, 0°C; (b) TMSCl, $MeC(OMe)_3$, CH_2Cl_2, 4 °C, then K_2CO_3, MeOH.

Scheme 11. Preparation of Phenylboronic Acids **33** and **36**[a]



[a] (a) KOAc, pinacol diborane, $PdCl_2(PPh_3)_2$, dioxane, 100°C; (b) $NaIO_4$, NH_4OAc, acetone, H_2O; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2; (d) KOAc, pinacol diborane, $PdCl_2(dppf)\cdot CHCl_3$, dioxane, 100°C.

analogue **10c**. Thiophene analogue **10i** showed somewhat increased potency (EC_{50} = 5.7 nM) and slightly decreased $\beta1/\beta3$ selectivity (β_1/β_3 = 117) relative to **10c**. These data (**10c**, **10g**, **10i**) suggested that a polar group such as pyridine appeared to influence the activity of $\beta1$ and $\beta3$-AR. In addition, cassette dosing assay of the heterocycle analogues (**10g**, **10i**) resulted in decreased C_{max} and AUC levels relative to phenyl analogue **10c**.

In analogy to the biphenyl ether analogues, a series of biphenyl analogues with six-membered rings (**10j**−**p**) were also synthesized. As seen in Table 1, *p*-phenoxyacetic acid analogue **10k** showed good potency (EC_{50} = 5.8 nM) and selectivity (β_1/β_3 > 170) relative to the *m*-phenoxyacetic acid analogue **10j** (EC_{50} = 10 nM). Furthermore, *p*-benzoic acid analogue **10m** showed higher potency (EC_{50} = 2.8 nM) relative to *m*-benzoic acid analogue **10l** (EC_{50} = 29 nM) and good selectivity for β_1 (β_1/β_3 > 138) and β_2. However, a seven-membered ring analogue having a *p*-benzoic acid moiety (**10n**) resulted in dramatically decreased potency for β_3-AR (EC_{50} > 100 nM) relative to the six-membered ring analogue **10m**. In addition, we attempted replacement of the terminal phenyl ring of **10m** with pyridine and thiophene. Although a pyridine analogue containing a *p*-carboxylic acid **10o** resulted in decreased potency (EC_{50} = 9.6 nM) and selectivity for β_1 (β_1/β_3 = 51), thiophene analogue **10p** maintained good potency (EC_{50} = 2.4 nM) and $\beta1/\beta3$ selectivity (β_1/β_3 > 417) relative to **10m**.

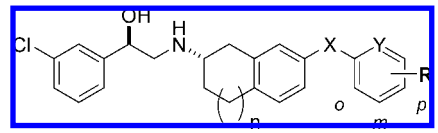
Next, biphenyl analogues **10k**, **10m**, **10p** with good in vitro profiles were evaluated in a cassette dosing assay. As expected, analogue **10m** having a benzoic acid moiety displayed a good C_{max} and AUC ratio similar to the biphenyl ether analogue **10c**. On the other hand, analogue **10k** having a phenoxyacetic acid moiety showed lower C_{max} and AUC revel relative to benzoic acid analogue **10m**. While thiophene analogue **10p** resulted in good C_{max} and AUC levels, the AUC ratio of **10p** showed 2.5-fold lower level relative to **10m**.

In consideration of the SAR study in Table 1, for both the biphenyl ether and biphenyl template, the position of the carboxylic acid moiety is important for $\beta3$-AR activity and selectivity. In addition, the six-membered ring series showed superior in vitro profiles (potency and selectivity) and PK profiles (C_{max} and AUC revel) relative to the seven-membered ring series. Table 2 shows pharmacokinetic data in dogs (cassette dosing assay, po and iv) of selected compounds (**10c**,**e**,**g**,**k**,**m**). All three biphenyl ether analogues (**10c**, **10e**, **10g**) showed good oral bioavailability (F > 60%). In particular, the benzoic acid six-membered ring analogue **10c** displayed lower total clearance (CL = 2.4 (mL/min)/kg), longer plasma half-life ($t_{1/2}$ = 7.9 h), and better bioavailability relative to seven-membered ring analogue **10e** and pyridine ring analogue **10g**. Likewise, biphenylbenzoic acid analogue **10m** exhibited a superior PK profile with lower total clearance (CL = 1.2 (mL/min)/kg), long plasma half-life ($t_{1/2}$ = 12.2 h), and good oral bioavailability (F = 71.4%) relative to the corresponding phenoxyacetic acid analogue **10k**. In comparison with **3** and **4** (see Table 5), both compounds **10c** and **10m** displayed an improvement of plasma half-life and lower total clearance and maintained good oral bioavailability. The results of the SAR study and cassette dosing assay led to the generation of two structurally different lead compounds **10c** and **10m** with a superior balance of potency, selectivity, and pharmacokinetic profile relative to both **3** and our previous clinical candidate **4**. Next, we focused our attention on further optimization of these series of biphenyl ether (see Table 3) and biphenyl analogues (see Table 4) to improve $\beta3$-AR potency.

First, in an effort to improve $\beta3$-AR potency of the biphenyl ether analogue **10c**, we initially investigated the effect of R^2-substituents on the terminal phenyl ring. Introduction of various substituents (Me, Cl, OMe) at the 4-position gave biphenyl ether analogues (**11a**−**c**). 4-Methoxy analogue **11c** maintained potency; however, **11a** and **11b** had less potency and selectivity for $\beta1$ than the original compound **10c**. Also, 5-methoxy analogue **11d** showed somewhat improved potency relative to **10c**. Next, we examined some amino substituents at the 5-position. The 5-NH_2 analogue **11e** and 5-N-Me_2 analogue **11f** displayed increased $\beta3$ potency $\beta3$ (EC_{50} = 3.2 nM), and **11f** showed good selectivity ($\beta1/\beta3$, $\beta2/\beta3$ > 312) relative to **10c**. In addition, 5-NH-acetyl analogue **11g** showed increased $\beta3$ potency by about 5.5-fold (EC_{50} = 1.3 nM) relative to **1c** and good selectivity for $\beta1$ ($\beta1/\beta3$ = 277).

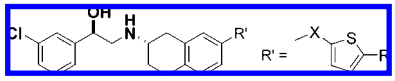
Furthermore, compounds **11e**−**g** were evaluated in a cassette dosing assay. As a result, the 3-NH_2 analogue **11e** and NH-acetyl analogue **11g** had a greatly lowered C_{max} and AUC ratio relative to the parent compound **11c**. On the other hand, 5-NMe_2 analogue **11f** maintained a good C_{max} and AUC level, similar to **11c**. We next tried to replace the acetyl group of **11g** (ClogP = 2.72) with a lipophilic alkyl group to improve potency and the PK properties of **11g**. The NH-*n*-Pr analogue **11h** (ClogP = 4.31) showed improved $\beta3$ potency (EC_{50} = 0.77 nM) but slightly lower selectivity ($\beta1/\beta3$ = 224). The more lipophilic and bulky cyclohexyl analogue **11i** (ClogP = 5.28) resulted in the same potency for $\beta3$ (EC_{50} = 0.78 nM) relative to the *n*-Pr analogue **11h** while showing increased potency for $\beta1$ and therefore a lower $\beta1/\beta3$ selectivity ($\beta1/\beta3$ = 88) compared with **11h**. This increased $\beta1$ activity of **11i** is likely due to the high lipophilicity of the cyclohexyl group; therefore, we tried to replace the cyclohexyl group with a tetrahydropyran group to adjust the lipophilicity of **11i**. As a result, 5-NH-tetrahydropyran analogue **11j** (ClogP = 2.88) maintained good $\beta3$ potency (EC_{50} = 1.0 nM) and improved selectivity ($\beta1/\beta3$ = 340) by about 4-fold relative to cyclohexyl analogue **11i.** However, in the cassette dosing assay, the C_{max} and AUC levels of **11j** showed poor results.

Table 1. SAR of Aminotetraline Analogues



compd	*n*	X	Y	R	human β_3 EC_{50}, nM[a] (IA[b])	human β_1 EC_{50}, nM[a]	β_1/β_3	human β_2 EC_{50}, nM[a]	cassette assay (po)[c] C_{max} ratio[d]	cassette assay (po)[c] AUC ratio[e]
10a	1	O	CH	*m*-OCH_2CO_2H	22 ± 4 (0.88)	>100	>4.5	NT	1.0	1.0
10b	1	O	CH	*p*-OCH_2CO_2H	24 ± 2 (0.88)	>100	>4.2	NT	NT	NT
10c	1	O	CH	*m*-CO_2H	7.1 ± 0.05 (0.89)	>1000	>138	>1000	2.96	5.27
10d	1	O	CH	*p*-CO_2H	37 (0.74)	>100	>2.7	NT	NT	NT
10e	2	O	CH	*m*-CO_2H	4.5 ± 0.7 (0.98)	160 ± 30	35	>1000	0.84	1.03
10f	2	O	CH	*p*-CO_2H	>100	>100		NT	NT	NT
10g	1	O	N	*p*-CO_2H	1.47 ± 0.3 (1.03)	70 ± 7.1	50	>1000	0.62	0.59
10h	1	O	N	*o*-CO_2H	49 (0.72)	>100	>2.0	NT	NT	NT
10i[f]	1	O		−CO_2H	5.7 ± 2 (0.99)	670 ± 96.2	117	>1000	0.57	0.47
10j	1	bond	CH	*m*-OCH_2CO_2H	10 ± 1 (0.78)	>100	>10	NT	NT	NT
10k	1	bond	CH	*p*-OCH_2CO_2H	5.8 ± 0.4 (0.80)	>1000	>170	>1000	0.44	0.58
10l	1	bond	CH	*m*-CO_2H	29 (0.68)	>100	>3.4	NT	NT	NT
10m	1	bond	CH	*p*-CO_2H	2.8 ± 0.3 (0.97)	>1000	>357	>1000	1.98	5.33
10n	2	bond	CH	*p*-CO_2H	>100	>100		NT	NT	NT
10o	1	bond	N	*p*-CO_2H	9.6 ± 0.4 (0.95)	490	51	NT	NT	NT
10p[f]	1	bond		−CO_2H	2.4 ± 0.06 (0.95)	>1000	>417	NT	1.45	2.17
3[g]					39	1500	38	>10000	NT	NT
4[g]					16 ± 2.0 (0.98)[h]	>3200[h]	>200	>10000	NT	NT
8					39 ± 1 (0.64)	>100	>2.6	NT	1.60	2.96
9					6.7 ± 0.3 (0.96)	280 ± 40	42	>1000	1.80	3.92
ISP[h]					0.97 ± 0.14 (1.0)	0.084 ± 0.02	0.087	2.0 ± 0.9	NT	NT

[a] The results are shown as the mean ± SE ($n \geq 3$) or presented as the average of two experiments. NT: not tested. [b] The intrinsic activity (IA) was defined as the ratio of the maximal effect of test compound to the maximal effect produced by isoproterenol (10^{-7} M). [c] Dose 0.32 or 0.2 mg/kg po ($n = 2-3$). See References for further details. NT: not tested. [d] The ratio was defined as the C_{max} of test compounds to the C_{max} of **10a**. The ratio value of **10a** was presented as 1.0. [e] The ratio was defined as the AUC of test compounds to the AUC of **10a**. The ratio value of **10a** was presented as 1.0. [f]



[g] Data for the carboxylic acid form. [h] Results are the mean ± SE of five experiments.

Table 2. Pharmacokinetic Profiles of Selected Compounds in Dogs[a]

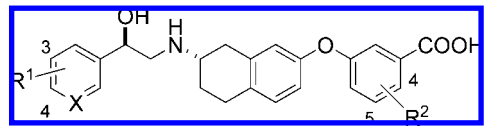
compd	po dose (mg/kg)	po C_{max} (ng/mL)	po AUC_{0-24h} (ng·h/mL)	iv dose (mg/mL)	iv $T_{1/2\beta}$ (h)	iv CL_{tot} ((mL/min)/kg)	*F* (%)[b]
10c	0.32	151.0	1998	0.1	7.9	2.4	81
10e	0.32	65.7	537.6	0.1	3.0	6.8	69
10g	0.32	49.0	319.7	0.1	2.8	10.8	61
10k	0.2	21.8	197.2	0.1	1.9	8.3	48
10m	0.2	97.4	1983	0.1	12.2	1.2	71

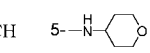
[a] Cassette assay data. $n = 2-3$. The results are presented as the average of two or three experiments. [b] *F* = bioavailability.

Next, we investigated replacement of the 3-chlorophenyl ring on the left-hand side (LHS) with 4-chlorophenyl or pyridyl ring groups, as shown in Table 3. 4-Chlorophenyl ring analogues **11k**, **11l** resulted in slightly improved potency relative to 3-chlorophenyl ring analogues (**10c**, **11c**), and 4-methoxy analogue **11l** showed superior selectivity ($\beta1$, $\beta2$; EC_{50} > 1000 nM, $\beta1$, $\beta2/\beta3$ > 217) relative to nonsubstituted analogue **11k**. Nonsubstituted pyridyl ring analogue **11m** showed decreased potency for $\beta3$ relative to **10c**. On the other hand, the 4-chloropyridyl ring derivatives (**11n**, **11o**) also had improved potency relative to **10c**, and 4-methoxy analogue **11o** exhibited higher selectivity for $\beta1$ ($\beta1$, $\beta2$; EC_{50} > 1000 nM, $\beta1$, $\beta2/\beta3$ > 277) relative to **11n**. In addition, the 5-NMe_2 substituted 4-chloropyridyl ring analogue **11p** showed significantly increased potency (EC_{50} = 1.8 nM) but lower selectivity relative to the 4-methoxy analogue **11o**. Therefore, 4-methoxy analogues **11l** and **11o** with good selectivity for $\beta1$ and $\beta2$ were evaluated in the cassette dosing assay. The 4-chlorophenyl ring analogue **11l** showed slightly decreased C_{max} and AUC ratio relative to the lead compound **10c**. The 4-chloropyridyl ring analogue **11o** also showed acceptable C_{max} and AUC levels.

Second, as can be seen in Table 4, in an effort to improve the $\beta3$-AR potency of biphenyl analogue **10m**, we initially attempted to modify the LHS because this modification in the biphenyl ether series in Table 3 resulted in improved potency for $\beta3$. Shift of the chloro group to the 2-position (**12a**) led to a substantial loss of potency. On the other hand, 4-chlorophenyl analogue **12b** resulted in 5.5-fold increased potency (EC_{50} = 0.38 nM) for $\beta3$ relative to 3-chlorophenyl analogue **10m** and high selectivity for $\beta1$ and $\beta2$ ($\beta1/\beta3$ = 2413, $\beta2/\beta3$ > 2630). On the basis of this result, we investigated replacement of chloro group with other substituents at the 4-position. As a result, the methyl analogue (**12c**) had 2-fold less potency (EC_{50} = 0.79 nM) for $\beta3$ relative to the chloro analogue **12b**, while the CN (**12d**) and CF_3 (**12e**) analogues showed decreased potency relative to **12b**. 3,4-Dichloro analogue **12f** was unfavorable for $\beta3$ agonistic activity relative to monochloro analogues **10m** and **12b**. In addition, we attempted replacement of the phenyl ring with a pyridine ring. Nonsubstituted pyridyl ring analogue **12g** showed decreased $\beta3$ potency relative to the lead compound **10m**. The 4-chloropyridyl ring analogue **12h**, as expected, showed increased potency relative to **12g**, although in com-

Table 3. SAR of Biphenyl Ether Analogues



compd	R^1	X	R^2	human β_3 EC_{50}, nM [a] (IA [b])	human β_1 EC_{50}, nM [a]	β_1/β_3	human β_2 EC_{50}, nM [a]	cassette assay (po) [c] Cmax Ratio [d]	cassette assay (po) [c] AUC Ratio [d]
10c	3-Cl	CH	H	7.1 ± 0.05 (0.89)	> 1000	> 138	> 1000	1.0	1.0
11a	3-Cl	CH	4-Me	9.0 ± 2 (0.91)	> 1000	> 111	NT	NT	NT
11b	3-Cl	CH	4-Cl	16 ± 2 (0.95)	> 1000	> 62	NT	NT	NT
11c	3-Cl	CH	4-OMe	6.0 ± 1 (0.97)	> 1000	> 166	> 1000	NT	NT
11d	3-Cl	CH	5-OMe	5.3 ± 0.1 (0.95)	890 ± 60.7	168	> 1000	NT	NT
11e	3-Cl	CH	5-NH_2	3.2 ± 0.2 (0.98)	480 ± 60	150	NT	0.26	0.20
11f	3-Cl	CH	5-NMe_2	3.2 ± 0.7 (0.91)	> 1000	> 312	> 1000	1.18	0.83
11g	3-Cl	CH	5-NH-Ac	1.3 ± 0.05 (0.92)	360 ± 98	277	NT	0.1	0.06
11h	3-Cl	CH	5-NH-*n*-Pr	0.77 ± 0.03 (1.04)	173 ± 33	224	NT	NT	NT
11i	3-Cl	CH	5-NH-*c*-Hex	0.78 ± 0.1 (0.98)	69 ± 8.9	88	NT	NT	NT
11j	3-Cl	CH		1.0 ± 0.05 (0.95)	340 ± 86	340	NT	0.06	0.02
11k	4-Cl	CH	H	4.8 ± 0.3 (0.98)	330 ± 15	69	NT	NT	NT
11l	4-Cl	CH	4-OMe	4.7 ± 0.6 (0.90)	> 1000	> 217	> 1000	0.64	0.76
11m	H	N	H	20 ± 4 (0.92)	> 100	> 5	NT	0.50	0.32
11n	4-Cl	N	H	4.1 ± 0.2 (0.90)	140	34	NT	NT	NT
11o	4-Cl	N	4-OMe	3.6 ± 0.3 (0.89)	> 1000	> 277	> 1000	0.50	0.48
11p	4-Cl	N	5-NMe_2	1.8 ± 0.5 (0.88)	270 ± 38	155	NT	NT	NT

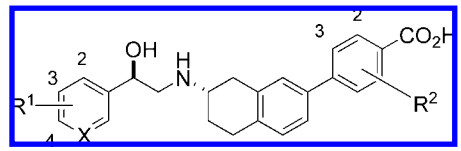
[a] The results are shown as the mean ± SE ($n = 3$) or presented as the average of two experiments. [b] The intrinsic activity (IA) was defined as the ratio of the maximal effect of test compound to the maximal effect produced by isoproterenol (10^{-7} M). [c] Dose 0.10 or 0.20 mg/kg po ($n = 2-3$). [d] The C_{max} ratio was defined as the C_{max} of test compounds to the C_{max} of **10c**, where the ratio value of **10c** was presented as 1.0. The AUC ratio was defined as the AUC of test compounds to the AUC of **10c**, where the ratio value of **10c** was presented as 1.0.

parison with **12b**, it exhibited a somewhat inferior in vitro profile (potency and selectivity). Furthermore, we examined the effect of R^2-substituents at the 2,3-position at the terminal phenyl ring of **12b**, since the 4-chloro analogue **12b** showed the best profile of potency and selectivity among **12a**−**h**. We introduced some substituents (2-Me, F, OMe) to give biphenyl analogues (**12i**−**k**). The 2-F and 2-OMe analogues **12j** and **12k** displayed good potency ($EC_{50} = 0.81$ and 0.78 nM, respectively) and good selectivity but decreased potency (~2-fold) relative to **12b**. In addition, our previous report had shown for a different biphenyl series that replacement of the R^2-substituents (OMe, F) at the 2-position with an O-*i*-Pr group provided improvement in potency and selectivity. This modification was incorporated into the current series at the 2-R^2-substituent. However, O-*i*-Pr analogue **12l** showed maintained potency for $\beta 3$ ($EC_{50} = 0.70$ nM) and somewhat decreased selectivity relative to **12j** and **12k**. Finally, we examined the effect of R^2-substituents (Me, F) at the 3-position in **12b**. The 3-Me and 3-F analogues **12m** and **12n** showed lower potency ($EC_{50} = 2.0$ and 1.4, respectively) relative to **12b**.

Next, we selected compounds (**12b**,**c**,**h**,**k**,**m**,**n**) in Table 4, which exhibited good in vitro profiles, and evaluated them in a cassette dosing assay. The 4-chlorophenyl ring analogue **12b** showed somewhat a decreased C_{max} ratio and improved AUC ratio relative to the 3-chloro analogue **10m**. The methyl analogue **12c** showed slightly decreased AUC ratio relative to **10m**. On the other hand, 4-chloropyridyl ring analogue **12h** showed decreased C_{max} and AUC levels (0.42-fold less). The R^2-substituented analogues **12k**,**m**,**n** (R^2 = 2-OMe, 3-Me, 3-F) were also evaluated. The 3-fluoro analogue **12n** displayed a good C_{max} ratio relative to **12k** and **12m** and the same AUC ratio relative to **10m**. As a result of the SAR study in Table 4, the 4-chlorophenyl ring analogue **12b** displayed the best profile of potency, selectivity, and oral exposure.

After SAR examination and study in the cassette dosing assay, we selected **11f**, **11l**, and **11o** in Table 3 and **12b** in Table 4 as

Table 4. SAR of Biphenyl Analogues



compd	R^1	X	R^2	human β_3 EC_{50}, nM[a] (IA[b])	human β_1 EC_{50}, nM[a]	β_1/β_3	human β_2 EC_{50}, nM[a]	cassette assay (po)[c] C_{max} ratio[d]	cassette assay (po)[c] AUC ratio[e]
10m	3-Cl	CH	H	2.8 ± 0.3 (0.97)	>100	>4.5	NT	1.0	1.0
12a	2-Cl	CH	H	38 (0.78)	620	16.3	NT	NT	NT
12b	4-Cl	CH	H	0.38 ± 0.02 (1.02)	917 ± 83	2413	>1000	0.71	1.25
12c	4-Me	CH	H	0.79 ± 0.02 (1.04)	>1000	>1265	NT	1.06	0.77
12d	4-CN	CH	H	28 (0.78)	>1000	>36	NT	NT	NT
12e	4-CF_3	CH	H	3.5 ± 0.5 (0.91)	775	221	>1000	NT	NT
12f	3,4-di-Cl	CH	H	33 (0.81)	>1000	>30	NT	NT	NT
12g	H	N	H	13 (0.82)	>1000	>77	NT	NT	NT
12h	4-Cl	N	H	0.85 ± 0.03 (0.80)	200	>1265	>1000	0.73	0.53
12i	4-Cl	CH	2-Me	1.8 (0.92)	825	458	NT	NT	NT
12j	4-Cl	CH	2-F	0.81 ± 0.06 (0.93)	650 ± 86	802	NT	NT	NT
12k	4-Cl	CH	2-OMe	0.78 ± 0.02 (0.95)	>1000	>1282	NT	0.62	0.53
12l	4-Cl	CH	2-O-*i*-Pr	0.70 ± 0.04 (0.93)	310	443	NT	NT	NT
12m	4-Cl	CH	3-Me	2.0 (0.87)	800	400	NT	0.72	0.64
12n	4-Cl	CH	3-F	1.4 ± 0.3 (0.84)	980	700	NT	1.13	1.01

[a] The results are shown as the mean ± SE ($n = 3$) or presented as the average of two experiments. NT: not tested. [b] The intrinsic activity (IA) was defined as the ratio of the maximal effect of test compound to the maximal effect produced by isoproterenol (10^{-7} M). [c] Dose 0.10 or 0.20 mg/kg po ($n = 2-3$). NT: not tested. [d] The ratio was defined as the C_{max} of the of test compounds to the C_{max} of **10m**. The ratio value of **10m** was presented as 1.0. [e] The ratio was defined as the AUC of test compounds to the AUC of **10m**. The ratio value of **10m** was presented as 1.0.

Table 5. Pharmacokinetic Profiles of Selected Compounds[a]

		po ($n = 2-3$)			iv ($n = 2-3$)			
compd	species	dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	dose (mg/kg)[g]	$T_{1/2\beta}$ (h)[g]	CL_{tot} ((mL/min)/kg)[g]	F (%)[b]
11f[c]	dog	0.20	189 ± 25	1467 ± 170	0.10	3.94	2.38	>95
11l[c]	rat	0.52	367 ± 0.5	4584 ± 616	0.50	11.9	2.0	>95
	dog	0.21	103 ± 2.5	1530 ± 72	0.10	8.3 ± 0.4	1.4 ± 0.1	64.2
	monkey	1.0	319 ± 51	1562 ± 212	0.32	6.7 ± 0.7	5.3 ± 0.7	48.0
11o[c]	rat	1.0	164 ± 0.5	1937 ± 552	0.51	15.3	2.5	27.3
	dog	0.2	64.4	860.1	0.1	5.9 ± 1.0	3.1 ± 0.1	76.8
	monkey	1.0	59 ± 3.3	313 ± 44	0.32	8.2 ± 0.3	15.7 ± 1.5	28.8
12b[c]	rat	0.5	65 ± 26	470 ± 107	0.50	13.6	11.4	63.4
	dog	0.2	113 ± 1.8	1980 ± 37	0.10	14.3 ± 1.6	1.7 ± 0.1	>95
	monkey	0.32	91.2 ± 14	722 ± 144	0.32	7.7 ± 0.4	6.7 ± 1.3	81.7
3[d]	rat	1.0	28.1 ± 7.7	177 ± 14	0.32	1.18	52.6	60.0
	dog[c]	0.2	92.5 ± 14	902 ± 99	0.12	3.8 ± 0.2	3.0 ± 0.5	83.2
4[d]	rat	1.0	38	83	0.83[e]	0.3	47.9	29
	dog	3.2	2070	10600	0.83[e]	1.63	3.7	73
	monkey	1.0	184 ± 22	398 ± 46	0.83[e]	2.28 ± 0.45	11.8 ± 0.8	35
	human[f]	1.0	1340 ± 300	4100 ± 800	NT	NT	NT	

[a] The results are shown as the mean ± SE ($n = 3$) or presented as the average of two experiments. [b] F = bioavailability. [c] Cassette assay data. [d] All parameters were calculated from the mean plasma concentration of the carboxylic acid form of **3** and **4**. See ref 22. [e] The dose of 0.83 mg/kg the carboxylic acid form of **4** was equivalent to 1 mg/kg **4**. [f] The results are shown as the mean ± SD ($n = 8$). [g] NT: not tested.

attractive compounds, since these compounds exhibited greater β3 potency relative to the corresponding lead compounds (**10c** or **10m**), high selectivity over β_1 and β_2, and good oral exposure. Table 5 shows the pharmacokinetic profiles in dog, rat, and monkey. The biphenyl ether analogue having a 5-NMe_2 group **11f** showed excellent oral bioavailability in dog ($F > 95\%$), while the plasma half-life ($t_{1/2} = 3.9$ h) was somewhat decreased relative to the lead compound **10c** (shown in Table 2). The 4-chlorophenyl ring analogue containing a 2-OMe group **11l** displayed low total clearance (CL, rats, 2.0 (mL/min)/kg; dogs, 1.4 (mL/min)/kg; monkeys, 5.3 (mL/min)/kg), long plasma half-life ($t_{1/2}$, iv, rats, 11.9 h; dogs, 8.3 h; monkeys, 6.7 h) and good oral bioavailability (rats, $F > 95\%$; dogs, $F = 64\%$; monkeys, $F = 48\%$) in all three species. On the other hand, the 4-chloropyridyl ring analogue **11o** displayed a good pharmacokinetic profile ($F = 76.8\%$, CL = 3.1 (mL/min)/kg, $t_{1/2} = 5.9$ h) in dog and showed moderate oral bioavailability (rats, $F = 27\%$; monkeys, $F = 29\%$) and long plasma half-life in rats (11.4 h) and monkeys (6.7 h). Next, biphenyl analogue **12b** having a 4-chlorophenyl ring on the LHS displayed good oral bioavailability in all three species ($F > 63\%$), and a long plasma half-life in dog (14.3 h), rat (13.6 h), and monkey (7.7 h). Compound **12b** provided a superior pharmacokinetic profile relative to both **3** and **4** in all two or three species.

Next, we examined the inhibitory effect of selected compounds (**11o**, **12b**) on carbachol-induced increase of intravesical pressure (IVP) in anesthetized dogs as an OAB model,[16] in comparison with the effects of our previous clinical compound **4**. Before conducting in vivo experiments, we confirmed the in vitro potency of these compounds to not only human β3-AR but also dog β3-AR activity in CHO cell lines, as shown in Table 6. In general, these tetraline analogues display some species differences between human and dog β3-AR activity, and the EC_{50} values for the dog β3-AR of compounds **11o** and

Table 6. Inhibitory Effect on Intravenous Administration of Selected Compounds (**11o**, **12b**) and **4** on Increase in IVP (Intravesical Pressure), Induced by Carbachol in Anesthetized Dogs[a]

	in vitro				
compd	human β_3 EC_{50}, nM	dog β_3 EC_{50}, nM	in vivo % inhibition (dose 32 μg/kg)	dog serum protein binding, %	ClogP[d]
control			0.0		
4	16 ± 2.0[b,c]	30 ± 9.0[b,c]	40.8 ± 2.6[b]	94[b]	
11o	3.6 ± 0.3	46	57	90	1.7
12b	0.38 ± 0.02	25	33	97	3.2

[a] The results are shown as the mean ± SE ($n = 3$) or presented as the average of two experiments. [b] Data for the carboxylic acid form of **4**. [c] Results are the mean ± SE of five experiments. [d] Biobyte CLOGP, version 4.3.

12b showed significantly reduced potency (**11o**, 12.8-fold; **12b**, 65.8-fold) relative to human β3-AR activity. Compound **12b** showed the same potency level, and compound **11o** showed less potent dog β3-AR activity relative to **4**. In the in vivo experiment, when intravenously (iv) administered, these compounds inhibited IVP increase at a dose of 32 μg/kg (Table 6). The 4-chloropyridyl analogue **11o** resulted in some improvement in inhibition % value, due to lower protein binding (**11o**, ClogP = 1.7, PB = 90%) relative to **4** (PB = 94%). On the other hand, 4-chlorophenyl analogue **12b**, having comparable in vitro dog β3-AR activity relative to **4**, showed a decreased inhibition % value due to higher protein binding (**12b**, ClogP = 3.2, PB = 97%) relative to **4**. However, compound **12b** displays higher human β3-AR activity (42-fold) compared to our previous clinical compound **4** and therefore may be an attractive candidate for the treatment of OAB.

Conclusions

Incorporation of the biphenyl ether or biphenyl template with a benzoic acid moiety on the RHS in **3** or **4** afforded two structurally different lead compounds (**10c**, **10m**) with improved β3 potency and plasma half-life relative to **3** and **4**, without the prodrug form. Importantly, our results suggested that the benzoic acid moiety on the RHS of either biphenyl ether and biphenyl analogues is essential for not only potency and selectivity but also the good pharmacokinetic properties of our current tetraline series, similar to our previous series. Next, in Tables 3 and 4, we investigated the effect of substituents on the terminal phenyl ring in the RHS and the replacement of the 3-chlorophenyl ring in the LHS of lead compounds (**10c**, **10m**). As a result, biphenyl ether analogues (**11f**, **11l**, **11o**) with a superior balance of potency, selectivity, and pharmacokinetic profiles, compared with **3** and our previous clinical candidate **4**, were identified and selected as the leading candidates. Furthermore, biphenyl analogue **12b** provided an excellent balance of high potency (EC_{50} = 0.38 nM), selectivity, and good pharmacokinetic properties ($F > 60\%$, $t_{1/2} > 7$ h in three species). In addition, compound **12b**, containing a 4-chlorophenylethanolaminotetraline skeleton, was prepared by high stereoselective synthesis of the two chiral centers. These findings suggest that these compounds (**11f**, **11l**, **11o, 12b**) had the good profiles and may be potential candidates for the treatment of OAB.

Experimental Section

Chemistry. General Methods. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel (Kanto Chemical, 63−210 μm) was used for chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from commercial sources. Proton NMR spectra were recorded on a Brucker BIOSPIN AVANCE400 or DPX200. Values in ppm relative to tetramethylsilane are given. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded with Micromass LCT. Chemical purity was given by HPLC analysis with a Shiseido Capcell pack C18 column (detection at 254 nm). Results of elemental analysis were recorded with Perkin-Elmer 2400II and were within 0.4% of the theoretical values calculated for C, H, and N unless otherwise noted.

***N*-[(2*S*)-7-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl]benzamide (15).** To a mixture of 7-methoxy-3,4-dihydronaphthalen-2(1*H*)-one sodium hydrogen carbonate **13** (20 g, 71.36 mmol) in toluene (150 mL) was added 3 N HCl (88 mL). The mixture was stirred at room temperature for 3 h. The mixture was partitioned between toluene and water. The organic layer was separated, washed with water, and concentrated in vacuo to give 7-methoxy-3,4-dihydronaphthalen-2(1*H*)-one (11.69 g, 92%). To the product (10.76 g, 60.55 mmol) in toluene (60 mL) was added benzamide (14.67 g, 121.1 mol) and Amberlyst 15E (6.8 g), and the mixture was refluxed for 5 h with continuous removal of water using a Dean−Stark trap. To the reaction mixture was added MeOH (30 mL) at 65 °C, and the mixture was cooled to room temperature. The mixture was filtered, and the residue of Amberlyst was washed with toluene−MeOH (1: 1). The combined solution was evaporated under reduced pressure. To the crude yellow solid was added MeOH, and the mixture was stirred at 50 °C for 1 h. The slurry was cooled to room temperature for 1 h, filtered, and washed with MeOH. After the sample was dried at 60 °C in vacuo, 7.54 g (41%) of the enamide **14** was obtained as a yellow solid.

A solution enamide **14** (5.55 g, 19.9 mmol) and Ru(II)-(*S*)-SEGPOS (0.0199 mmol) in MeOH (22 mL) and CH_2Cl_2 (22 mL) was deoxygenated using N_2 and charged into a stirred autoclave. The autoclave was pressurized with 30 atm of H_2 and stirred at 60 °C for 10 h. The solution was evaporated under reduced pressure. To the crude product was added MeOH (55 mL), and the mixture was stirred at 60 °C for 0.5 h. The slurry was cooled to room temperature for 3 h, filtered, and washed with cold MeOH. After the sample was dried at 60 °C in vacuo for 5 h, 3.95 g (74%) of the title compound was obtained as colorless crystals, mp 164.6 °C. MS (ES) *m/e*: 282 (M + H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.7−1.8 (1H, m), 2.0−2.1 (1H, m), 2.7−2.8 (3H, m), 2.9−3.0 (1H, m), 3.70 (3H, s), 4.1−4.2 (1H,m), 6.6−6.7 (2H, m), 7.01 (1H, d, J = 8.4 Hz), 7.44−7.55 (3H, m), 7.86−7.89 (2H, m), 8.40 (1H, d, J = 7.6 Hz). The optical purity was determined as 99.6% ee, given by HPLC analysis with two connected DAICELL Chiralcel OD-H columns (4.6 mm i.d. × 25 cm × 2.5 μm) eluted with hexane/2-propanol (70:30, 0.6 mL/min). Detection at 215 nm light; t_R (*R* isomer) = 24.26 min, t_R (*S* isomer) = 26.55 min.

(2*S*)-*N*-Benzyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (16). To a suspension of **15** (88.0 g, 313 mmol) in THF (500 mL) was added 2 M $BH_3 \cdot SMe_2$ in THF solution (380 mL) dropwise at approximately 4 °C over 40 min under nitrogen atomosphere. The reaction mixture was warmed to room temperature and refluxed for 4 h. To the mixture was added 6 N HCl (135 mL) dropwise at approximately 4 °C. The mixture was refluxed for1.5 h, and the solvent was removed. To the mixture, 3 N NaOH (500 mL) was added dropwise below 10 °C (pH ≈ 11). The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated

under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 97:3 to 95:5) to give 83.8 g (100%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.4−1.6 (1H, m), 1.8−2.1 (1H, m), 2.4−3.0 (5H, m), 3.68 (3H, s), 3.79 (2H, br s), 6.6−6.7 (2H, m), 6.94 (1H, d, J = 8.1 Hz), 7.19−7.38 (5H, m).

(7*S*)-7-(Benzylamino)-5,6,7,8-tetrahydronaphthalen-2-ol (17). To a solution of **16** (90.2 g, 337 mmol) in dichloromethane (600 mL) was added 2 M BBr_3 in CH_2Cl_2 (420 mL) dropwise at 4 °C over 1 h under nitrogen atomosphere. The mixture was warmed to room temperature and stirred over 2.5 h at same temperature. To the mixture was added 200 mL of cold water and 5 N NaOH (220 mL) dropwise at approximately 0 °C and then added saturated $NaHCO_3$ (500 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (500 mL × 3) and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol) to give 32.2 g (50.6%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.3−1.6 (1H, m), 1.9−2.1 (1H, m), 2.3−2.95 (5H, m), 3.78 (2H, br s), 6.4−6.5 (2H, m), 6.81 (1H, d, J = 8.1 Hz), 7.19−7.38 (5H, m), 8.97 (1H, br s). MS (ES) *m*/*e*: 254 (M + H).

(7*S*)-7-Amino-5,6,7,8-tetrahydronaphthalen-2-ol (18). A mixture of **17** (7.0 g, 23.5 mmol) in MeOH (70 mL) was hydrogenated over palladium on carbon (10% w/w, 50% wet, 700 mg) under hydrogen atmosphere for 2 h. The catalyst was filtered off, and the filtrate was evaporated to give 3.84 g (100%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.5−1.7 (1H, m), 1.8−2.3 (2H, br), 1.9−2.1 (1H, m), 2.4−2.6 (1H, m), 2.7−3.0 (3H, m), 3.1−3.25 (1H, m), 3.49 (1H, s), 6.52−6.63 (2H, m), 6.94 (1H, d, J = 8.2 Hz). MS (ES) *m*/*e*: 164 (M + H).

***tert*-Butyl (2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl[(2*S*)-7-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl]carbamate (25). Typical Procedure A.** A solution of **18** (11.2 g, 68.6 mmol) and (2*R*)-2-(4-chlorophenyl)oxirane **22** (9.02 g, 58.3 mmol) in ethanol (100 mL) was refluxed for 18 h. The mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform/methanol = 97: 3) to give 9.74 g (44.7%) of (7*S*)-7-{[(2*R*)-2-(4-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenol. MS (ES) *m*/*e*: 318 (M + H).

To a mixture of the obtained product (9.7 g, 30.7 mmol) in tetrahydrofuran (100 mL) was added di-*tert*-butyl dicarbonate (6.7 g, 30.7 mmol) at room temperature, and the mixture was stirred at the same temperature for 12 h. The resulting mixture was evaporated under pressure and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 12.2 g (95.3%) of the title compound as a colorless form. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.3 (1H, m), 3.4−3.7 (1H, m), 4.0−4.2 (1H, m), 4.8−5.0 (1H, m), 5.10 (1H, br s), 6.4−6.5 (1H, m), 6.62 (1H, dd, J = 2.5, 8.2 Hz), 6.93 (1H, d, J = 8.2 Hz), 7.28 (1H, d, J = 8.4 Hz), 7.2−7.4 (3H, m). MS (ES) *m*/*e*: 418 (M + H).

***tert*-Butyl [(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl][(2*S*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl]carbamate (24).** The title compound was synthesized from **18** and (2*R*)-2-(3-chlorophenyl)oxirane **21** according to procedure A (40.5%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 4.0−4.2 (1H, m), 4.7−4.9 (1H, m), 6.03 (1H, br s), 6.5−6.6 (2H, m), 6.62 (1H, dd, J = 2.4, 8.4 Hz), 6.90 (1H, d, J = 8.4 Hz), 7.3−7.5 (3H, m), 7.37 (1H, s). MS (ES) *m*/*e*: 440 (M + Na).

***tert*-Butyl [(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl][(6*S*)-3-hydroxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-6-yl]carbamate (26).** The title compound was synthesized from (8*S*)-8-amino-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-ol **20** and (2*R*)-2-(3-chlorophenyl)oxirane **21** according to procedure A (38.4%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50 (9H, s), 1.4−2.0 (4H, m), 2.6−2.8 (3H, m), 3.1−3.5 (4H, m), 4.8−5.0 (1H, m), 6.03 (1H, br s), 6.58 (2H, m), 6.92 (1H, m), 7.26 (3H, m), 7.41 (1H, s). MS (ES) *m*/*e*: 454 (M + Na).

***tert*-Butyl (2*R*)-2-(6-Chloro-3-pyridinyl)-2-hydroxyethyl[(2*S*)-7-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl]carbamate (27).** The title compound was synthesized from **18** and 2-chloro-5-[(2*R*)-oxiran-2-yl]pyridine **23** according to procedure A (47.7%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.6−1.9 (2H, m), 2.7−2.9 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 4.0−4.2 (1H, m), 4.8−5.0 (1H, m), 5.42 (1H, br), 6.5−6.7 (2H, m), 6.93 (1H, dd, J = 8.2 Hz), 7.32 (1H, d, J = 8.2 Hz), 7.73 (1H, dd, J = 2.3, 8.2 Hz), 8.34 (1H, d, J = 2.3 Hz). MS (ES) *m*/*e*: 419 (M + H).

3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy-]benzoic Acid Methyl Ester (29a). Typical Procedure B. To a mixture of **24** (400 mg, 0.96 mmol) in dichlorometane (10 mL) and triethylamine (1 mL) were added (3-methoxycarbonylphenyl-)boric acid (400 mg, 2.22 mmol) and copper acetate (400 mg, 2.20 mmol) and 4 Å molecular sieves (1 g) at room temperature, and the mixture was stirred at the same temperature for 12 h. The resulting mixture was filtered by Celite, and the mother layer was evaporated under pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give 240 mg (44%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 3.90 (3H, s), 4.0−4.2 (1H, m), 4.8−5.0 (1H, m), 6.6−6.9 (2H, m), 7.05 (1H, d, J = 8.4 Hz), 7.1−7.8 (8H, m). MS (ES) *m*/*e*: 574 (M + Na).

3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Hydrochloride (10c). Typical Procedure C. To a solution of the above coupling product **29a** (240 mg, 0.434 mmol) in methanol (3 mL) was added 1 N sodium hydroxide (1.5 mL) at room temperature, and the mixture was stirred at the same temperature for 12 h. The resulting mixture was evaporated under reduced pressure. The residue was diluted with a mixture of ethyl acetate or chloroform (30 mL) and 1 N HCl (1.5 mL), and the organic layer was washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure. The obtained benzoic acid was diluted with 4 N hydrogen chloride in dioxane or ethyl acetate (10 mL), and the mixture was allowed to keep at room temperature for 4 h. The mixture was evaporated under reduced pressure and the obtained solid was washed with ether to give 100 mg (50%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6) δ; 1.7−2,0 (1H, m), 2.1−2.3 (1H, m), 2.7−3.5 (7H, m), 5.0−5.1 (1H, m), 6.4 (br s), 6.8−7.0 (2H, m), 7.1−7.8 (9H, m). MS (ES) *m*/*e*: 438 (M + H). Anal. ($C_{25}H_{24}$ $Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.5H_2O$) C, H, N.

4-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy-]benzoic Acid Methyl Ester (29b). The title compound was synthesized from **24** and (4-methoxycarbonylphenyl)boric acid according to procedure B (49%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 3.89 (3H, s), 4.0−4.2 (1H, m), 4.8−5.0 (1H, m), 6.7−7.3 (8H, m), 7.39 (1H, s), 7.99 (2H, d, J = 8.6 Hz). MS (ES) *m*/*e*: 574 (M + Na).

4-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Hydrochloride (10d). The title compound was synthesized from **29b** according to procedure C (49%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2,0 (1H, m), 2.1−2.3 (1H, m), 2.7−3.5 (7H, m), 5.0−5.1 (1H, m), 6.4 (br s), 6.7−6.9 (2H, m), 6.99 (2H, d, J = 8.6 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.2−7.5 (4H, m), 7.93 (2H, d, J = 8.6 Hz). MS (ES) *m*/*e*: 438 (M + H). Anal. ($C_{25}H_{24}$ $Cl_1N_1O_4 \cdot 1.0HCl \cdot 1.3H_2O$) C, H, N.

{3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-phenoxy}-*tert*-butyldimethylsilane (28a). The title compound was synthesized from **24** and (3-{[*tert*-butyl(dimethyl)silyl]oxy}-phenyl)boronic acid according to procedure B (59%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.17 (6H, s), 0.95 (9H, s), 1.51 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 4.0−4.2 (1H, m), 4.8−5.0 (1H, m), 6.4−6.9 (5H, m), 7.0−7.5 (6H, m). MS (ES) *m*/*e*: 646 (M + Na).

{3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]phenoxy}acetic Acid Hydrochloride (10a). To a solution of **28a** (600 mg, 0.961 mmol) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride (5 mL, 1 M solution in THF) at room temperature, and the mixture was stirred for 3 h. The mixture was poured into water and ethyl acetate, and the organic layer was washed with 1 N HCl and brine and then dried over magnesium sulfate. After filtration, the solvent was evaporated, the residue was diluted in *N*,*N*-dimethylformamide (10 mL). To the solution were added K_2CO_3 (240 mg, 1.73 mmol) and bromoethylacetate (0.12 mL, 1.08 mmol) at room temperature, and the mixture was stirred for 4 h. The mixture was poured into water and ethyl acetate, and the organic layer was washed with 1 N HCl and brine and then dried over magnesium sulfate. After filtration, the solvent was evaporated, and the obtained residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 450 mg (72%) of {3-[((7*S*)-7-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]phenoxy}acetic acid ethy ester. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 6.8 Hz), 1.51 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 4.0−4.2 (1H, m), 4.21 (2H, q, J = 6.8 Hz), 4.58 (2H, s), 4.8−5.0 (1H, m), 6.5−6.9 (5H, m), 7.0−7.5 (6H, m). MS (ES) *m*/*e*: 618 (M + Na).

The title compound was synthesized from the obtained product according to procedure C (83%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2.0 (1H, m), 2.2−2.5 (1H, m), 2.6−3.6 (7H, m), 4.65 (2H, s), 5.07 (1H, m), 6.36 (1H, m), 6.5−6.8 (5H, m), 7.0−7.6 (6H, m), 8.97 (1H, m), 9.44 (1H, m). MS (ES) *m*/*e*: 468 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_5 \cdot 1.0HCl \cdot 0.5H_2O$) C, H, N.

{4-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]phenoxy}-*tert*-butyldimethylsilane (28b). The title compound was synthesized from **24** and (4-{[*tert*-butyl(dimethyl)silyl]oxy}-phenyl)boronic acid according to procedure B (44%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.17 (6H, s), 0.95 (9H, s), 1.51 (9H, s), 1.7−1.9 (2H, m), 2.7−3.0 (4H, m), 3.2−3.4 (1H, m), 3.4−3.7 (1H, m), 4.0−4.2 (1H, m), 4.8−5.0 (1H, m), 6.5−7.0 (6H, m), 7.2−7.4 (5H, m). MS (ES) *m*/*e*: 646 (M + Na).

{4-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]phenoxy}acetic Acid Hydrochloride (10b). The title compound was synthesized from **28b** according to the procedure described for the conversion of **28a** to **10a** (58%). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.7−2.0 (1H, m), 2.2−2.5 (1H, m), 2.6−3.6 (7H, m), 4.55 (2H, s), 5.04 (1H, m), 6.37 (1H, m), 6.6−7.0 (7H, m), 7.3−7.5 (4H, m). MS (ES) *m*/*e*: 468 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_5 \cdot 1.0HCl \cdot 1.5H_2O$) C, H, N.

3-[((8*S*)-8-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)oxy]benzoic Acid Methyl Ester (29c). The title compound was synthesized from **26** and (3-methoxycarbonylphenyl)boric acid according to procedure B (44%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.8−2.1 (2H, m), 2.5−2.8 (2H, m), 3.0−3.4 (3H, m), 3.91 (3H, s), 4.91 (1H, m), 6.6−6.8 (1H, m), 6.9−7.1 (1H, m), 7.1−7.8 (9H, m). MS (ES) *m*/*e*: 588 (M + Na).

3-[((8*S*)-8-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)oxy]benzoic Acid Hydrochloride (10e). The title compound was synthesized from **29c** according to procedure C (49%). ^{1}H NMR (200 MHz, DMSO-d_6) δ; 1.2−1.4 (1H, m), 1.7−2.1 (2H, m), 2.2−2.3 (1H, m), 2.7−3.4 (7H, m), 4.99 (1H, m), 6.32 (1H, br s), 6.85 (1H, dd, J = 2.4,8.0 Hz), 7.01 (1H, d, J = 2.4 Hz), 7.1−7.6 (8H, m), 7.68 (1 h, d, J = 8 Hz). MS (ES) *m*/*e*: 452 (M + H). Anal. ($C_{26}H_{26}$ $Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.8H_2O$) C, H, N.

4-[((8*S*)-8-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)oxy]benzoic Acid Methyl Ester (29d). The title compound was synthesized from **26** and (4-methoxycarbonylphenyl)boric acid according to procedure B (33%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.8−2.1 (2H, m), 2.5−2.8 (2H, m), 3.0−3.4 (3H, m), 3.91 (3H, s). 4.91 (1H, m), 6.9−7.8 (11H, m). MS (ES) *m*/*e*: 588 (M + Na).

4-[((8*S*)-8-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-2-yl)oxy]benzoic Acid Hydrochloride (10f). The title compound was synthesized from **29d** according to procedure C (49%). ^{1}H NMR (200 MHz, DMSO-d_6) δ; 1.2−1.4 (1H, m), 1.7−2.3 (3H, m), 2.7−3.4 (7H, m), 5.0 (1H, m), 6.32 (1H, s), 6.9−7.4 (9H, m), 7.93 (2H, d, J = 8 Hz). MS (ES) *m*/*e*: 452 (M + H). Anal. ($C_{26}H_{26}$ $Cl_1N_1O_4 \cdot 1.0HCl \cdot 1.2H_2O$) C, H, N.

6-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]nicotinic Acid Ethyl Ester (30). Typical Procedure D. To a mixture of **24** (300 mg, 0.718 mmol) in dimethyl sulfoxide (10 mL) were added ethyl 6-chloronicotinate (300 mg, 1.61 mmol) and K_2CO_3 (800 mg, 5.78 mmol) at room temperature, and the mixture was stirred at 80 °C for 2 h. The resulting mixture was poured into a mixture of ethyl acetate and water, and the organic layer was washed with brine. After the solvent was evaporated under pressure, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) to give 300 mg (77%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (3H, t, J = 7.0 Hz), 1.52 (9H, s), 1.7−2.0 (2H, m), 2.6−3.0 (4H, m), 3.2−3.6 (2H, m), 4.35 (2H, q, J = 7.0 Hz), 4.90 (1H, m), 6.8−7.2 (4H, m), 7.2−7.4 (4H, m), 8.27 (1H, dd, J = 2.2, 8.4 Hz), 8.81 (1H, dd, J = 2.2 Hz). MS (ES) *m*/*e*: 589 (M + Na).

6-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]nicotinic Acid Dihydrochloride (10g). The title compound was synthesized from **30** according to procedure C (73%). ^{1}H NMR (200 MHz, DMSO-d_6) δ; 1.7−2.0 (1H, m), 2.3−2.5 (1H, m), 2.7−3.7 (7H, m), 5.12 (1H, m), 6.8−7.0 (2H, m), 7.0−7.3 (2H, m), 7.4−7.6 (4H, m), 8.27 (1H, dd, J = 2.2,8.6 Hz), 8.64 (1H, d, J = 2.2 Hz), 9.0 (1H, br s), 9.6 (1H, br s). MS (ES) *m*/*e*: 439 (M + H). Anal. ($C_{24}H_{23}$ $Cl_1N_2O_4 \cdot 2.0HCl \cdot 1.0H_2O$) C, H, N.

2-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-3-pyridinylcarboxaldehyde (31). The title compound was synthesized from **24** and 2-chloronicotinaldehyde according to procedure D (91%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56 (9H, s), 1.7−2.0 (2H, m), 2.7−3.0 (4H, m), 3.1−3.7 (2H, m), 4.0−4.2 (1H, m), 4.88 (1H, m), 6.8−7.2 (7H, m), 7.39 (1H, s), 8.23 (1H, dd, J = 2.2, 7.2 Hz), 8.36 (1H, dd, J = 2.2 Hz), 10.52 (1H, s). MS (ES) *m*/*e*: 523 (M + H).

2-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]nicotinic Acid Hydrochloride (10h). Typical Procedure E. To a mixture of **31** (300 mg, 0.573 mmol), acetonitrile (5 mL), pH 4 buffer solution (sodium dihydrogen phosphate) (0.25 mL), and 30% hydrogen peroxide solution (0.12 mL) was added sodium chlorite (500 mg, 5.52 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 4 h, diluted with ethyl acetate (50 mL), washed with water followed by brine, dried over magnesium sulfate, and evaporated to give the corresponding acid. The obtained acid was diluted with 4 N hydrogen chloride in dioxane (10 mL), and the mixture was allowed to keep at room temperature for 4 h. The mixture was evaporated under reduced pressure and the obtained solid was washed with ether to give 200 mg (62%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2.0 (1H, m), 2.3−2.5 (1H, m), 2.7−3.7 (7H, m), 5.12 (1H, m), 6.37 (1H, m), 6.7−7.0 (2H, m), 7.1−7.3 (2H, m), 7.4−7.7 (4H, m), 8.1−8.3 (2H, m), 8.9 (1H, m), 9.5 (1H, m). MS (ES) *m*/*e*: 439 (M + H). Anal. ($C_{24}H_{22}$ $Cl_1N_2O_4 \cdot 1.0HCl \cdot 1.2H_2O$) C, H, N.

5-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-thiophenecarboxaldehyde (32). The title compound was synthesized from **24** and 5-bromothiophene-2-carbaldehyde according to procedure D (78%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.7−2.0 (2H, m), 2.7−3.0 (4H, m), 3.1−3.3 (1H, m), 2.3−2.5

(1H, m), 4.0−4.3 (1H, m), 4.8−5.0 (1H, m), 6.5−6.8 (2H, m), 6.8−7.6 (7H, m), 9.70 (1H, s). MS (ES) *m/e*: 550 (M + Na).

5-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-thiophenecarboxylic Acid Hydrochloride (10i). The title compound was synthesized from **32** according to procedure E (56%). ^{1}H NMR (200 MHz, DMSO-d_6) δ; 1.8−2.2 (2H, m), 2.4−3.4 (7H, m), 5.05 (1H, m), 6.36 (1H, m), 6.5−7.5 (9H, m), 8.93 (1H, m), 9.38 (1H, m). MS (ES) *m/e*: 444(M + 1). HRMS $(M + H)^+$ found: 444.1034. Calcd for $C_{23}H_{22}Cl_1N_1O_4S$ 444.1036. Anal. ($C_{24}H_{26}Cl_1N_1O_4S_1 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

3-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic Acid Methyl Ester (39a). Typical Procedure F. To a mixture of **24** (400 mg, 0.957 mmol) in dichloromethane (10 mL) were added 2,6-lutidine (0.22 mL, 1.89 mmol) and trifluoromethanesulfonic anhydride (0.162 mL, 0.96 mmol) at −78 °C under N_2, and the mixture was stirred for 1 h at the same temperature. The mixture was poured into water, and the organic layer was washed with 1 N HCl and brine, then dried over magnesium sulfate. After filtration, the solvent was evaporated, and the obtained residue was purified by column chromatography on silica gel with ethyl acetate and hexane (1: 2) to give 473 mg (90%) of (7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.8−2.0 (2H, m), 2.8−3.0 (4H, m), 3.31 (1H, m), 3.4−3.6 (1H, m), 3.9−4.1 (1H, m), 4.91 (1H, m), 6.97 (1H, s), 7.01 (1H, m), 7.14 (1H, m), 7.22−7.305 (3H, m), 7.40 (1H, s). MS (ES) *m/e*: 572 (M + Na). To a solution of the sulfonate (470 mg, 0.855 mmol) in diethoxymethane (10 mL) were added (3-methoxycarbonylphenyl)boric acid (200 mg, 1.11 mmol) and $Pd(PPh_3)_4$ (110 mg, 0.095 mmol) and 2 N Na_2CO_3 (2.0 mL) at room temperature, and the mixture was stirred at 80 °C for 2 h. The resulting mixture was filtrated by Celite, and the mother layer was evaporated under pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 350 mg (69%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.8−2.0 (2H, m), 2.8−3.1 (4H, m), 3.2−3.7 (2H, m), 3.95 (3H, s), 4.0−4.3 (1H, m), 4.93 (1H, m), 7.0−7.5 (8H, m), 7.78 (1H, d, J = 8 Hz), 7.99 (1H, d, J = 8 Hz), 8.26 (1H, s). MS (ES) *m/e*: 558 (M + Na).

3-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic Acid Hydrochloride (10l). The title compound was synthesized from **39a** according to procedure C (64%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2.0 (1H, m), 2.1−2.3 (1H, m), 2.5−3.7 (7H, m), 5.07 (1H, m), 6.4 (1H, m), 7.24 (1H, d, J = 8.0 Hz), 7.3−7.7 (7H, m), 7.90 (2H, m), 8.16 (1H, s), 8.94 (1H, m), 9.28 (1H, m). MS (ES) *m/e*: 422 (M + H). Anal. ($C_{25}H_{24}Cl_1N_1O_3 \cdot 1.0HCl \cdot 1.5H_2O$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic Acid Methy Ester (39b). The title compound was synthesized from **24** and (4-methoxycarbonylphenyl)boric acid according to procedure F (78%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.8−2.0 (2H, m), 2.8−3.1 (4H, m), 3.2−3.7 (2H, m), 3.94 (3H, s), 4.0−4.3 (1H, m), 4.93 (1H, m), 7.1−7.4 (8H, m), 7.64 (2H, d, J = 8.4 Hz), 8.09 (2H, d, J = 8.4 Hz), 8.48 (1H, s). MS (ES) *m/e*: 558 (M + Na).

4-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic Acid Hydrochloride (10m). The title compound was synthesized from **39b** according to procedure C (77%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2.0 (1H, m), 2.1−2.3 (1H, m), 2.5−3.7 (7H, m), 5.07 (1H, m), 6.38 (1H, m), 7.24 (1H, d, J = 8.0 Hz), 7.3−7.6 (6H, m), 7.76 (2H, d, J = 8.4 Hz), 8.01 (2H, d, J = 8.4 Hz). MS (ES) *m/e*: 422 (M + H). Anal. ($C_{25}H_{24}Cl_1N_1O_3 \cdot 1.0HCl \cdot 0.5H_2O$) C, H, N.

4-[(8*S*)-8-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-2-yl]benzoic Acid Hydrochloride (10n). 39c was synthesized from **26** and (4-methoxycarbonylphenyl)boric acid according to procedure F (61%). MS (ES) *m/e*: 572 (M + Na). The title compound was synthesized from **39c** according to procedure C (80%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2−1.4 (1H, m), 1.8−2.1 (2H, m), 2.2−2.3 (1H, m), 2.7−2.8 (2H, m), 3.0−3.4 (5H, m), 5.0 (1H, m), 6.33 (1H, br s), 7.26 (1H, m), 7.35−7.65 (5H, m), 7.68 (1H, s), 7.76 (2H, d, J = 8.4 Hz), 8.01 (2H, d, J = 8.3 Hz). MS (ES) *m/e*: 436 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_3 \cdot 1.0HCl \cdot 1.7H_2O$) C, H, N.

6-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)nicotinic Acid Dihydrochloride (10o). 39d was synthesized from **24** and (4-methoxycarbonylphenyl)boric acid according to procedure F (52%). MS (ES) *m/e*: 559 (M + Na). The title compound was synthesized from **39d** according to procedure C (83%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.74−1.99 (2H, m), 2.32−2.49 (2H, m), 2.85−3.04 (4H, m), 3.38 (1H, br), 3.52 (1H, br), 5.07 (1H, d, J = 8.0 Hz), 7.28 (1H, d, J = 7.9 Hz), 7.47−7.59 (4H, m), 7.94 (1H, d, J = 7.8 Hz), 7.96 (1H, s), 8.07 (1H, d, J = 8.3 Hz), 8.29−8.34 (1H, m), 8.97 (1H, br), 9.12 (1H, s), 9.31 (1H, br). MS (ES) *m/e*: 421 (M − H). Anal. ($C_{24}H_{23}Cl_1N_2O_3 \cdot 2.0HCl \cdot 2.5H_2O$) C, H, N.

[4-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)phenoxy]-*tert*-butyldimethylsilane (38a). The title compound was synthesized from **24** and (4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-boronic acid according to procedure F (38%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.21 (6H, s), 1.01 (9H, s), 1.57 (9H, s), 1.8−2.0 (2H, m), 2.8−3.1 (4H, m), 3.2−3.7 (2H, m), 4.0−4.3 (1H, m), 4.9 (1H, m), 6.89 (2H, d, J = 8 Hz), 7.12 (1H, d, J = 8 Hz), 7.2−7.5 (8H, m). MS (ES) *m/e*: 630 (M + Na).

4-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)phenoxy]acetic Acid Hydrochloride (10k). The title compound was synthesized from **38a** according to the procedure described for the conversion of **28a** to **10a** (40%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2.0 (1H, m), 2.1−2.3 (1H, m), 2.5−3.7 (7H, m), 4.71 (2H, s), 5.08 (1H, m), 6.38 (1H, m), 6.98 (2H, d, J = 8.4 Hz), 7.09 (1H, d, J = 8.4 Hz), 7.2−7.7 (8H, m), 8.97 (1H, m), 9.41 (1H, m). MS (ES) *m/e*: 452 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_4 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

[3-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]-*tert*-butyloxycarbonylamino}-5,6,7,8-tetrahydro-2-naphthalenyl)phenoxy]-*tert*-butyldimethylsilane (38b). The title compound was synthesized from **24** and (3-{[*tert*-butyl(dimethyl)-silyl]oxy}phenyl)boronic acid according to procedure F (33%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.19 (6H, s), 0.96 (9H, s), 1.54 (9H, s), 1.8−2.0 (2H, m), 2.8−3.1 (4H, m), 3.2−3.7 (2H, m), 4.0−4.3 (1H, m), 4.9 (1H, m), 6.8−7.0 (1H, m), 7.0−7.4 (10H, m). MS (ES) *m/e*: 630 (M + Na).

[3-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)phenoxy]acetic Acid Hydrochloride (10j). The title compound was synthesized from **38b** according to the procedure described for the conversion of **28a** to **10a** (68%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.7−2.0 (1H, m), 2.1−2.3 (1H, m), 2.5−3.7 (7H, m), 4.79 (2H, s), 5.05 (1H, m), 6.38 (1H, m), 6.89 (1H, dd, J = 8.4, 2.2 Hz), 7.0−7.4 (10H, m). MS (ES) *m/e*: 452 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_4 \cdot 1.0HCl \cdot 1.5H_2O$) C, H, N.

5-((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-2-thiophenecarboxylic Acid Hydrochloride (10p). Compound **40** was synthesized from **24** and (5-formyl-2-thienyl)boronic acid according to procedure F (36%). MS (ES) *m/e*: 512 (M + H). The title compound was synthesized from **40** according to procedure E (33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ; 1.74−1.77 (1H, m), 1.80−1.95 (1H, m), 2.30−2.33 (1H, m), 2.80−2.95 (3H, m), 3.13−3.16 (1H, m), 3.29−3.36 (1H, m), 3.52−3.62 (2H, m), 5.04 (1H, d, J = 9.2 Hz), 6.36 (1H, br), 7.20 (1H, d, J = 8.0 Hz), 7.39−7.53 (7H, m), 7.71 (1H, d, J = 4.0 Hz), 9.01 (1H, br), 13.1 (1H, br). MS (ES) *m/e*: 426 (M − H). Anal. ($C_{23}H_{23}Cl_1N_1O_3S_1 \cdot 1.0HCl \cdot 1.4H_2O$) C, H, N.

5-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-methylbenzoic Acid Hydrochloride (11a). The title compound was synthesized from **24** and [3-(methoxycarbonyl)-4-methylphenyl]boronic acid **33** according to the procedure described for the conversion of **24** to **10c** (33%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.71−1.90 (1H, m),

2.14−2.21 (1H, m), 2.46 (3H, s), 2.65−3.50 (7H, m), 4.88−4.93 (1H, m), 6.72−7.47 (10H, m). MS (ES) *m/e*: 450 (M − H). Anal. ($C_{26}H_{26}Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

2-Chloro-5-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Hydrochloride (11b). The title compound was synthesized from **24** and [3-(methoxycarbonyl)-4-chlorophenyl]boronic acid **34** according to the procedure described for the conversion of **24** to **10c** (51%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.12−1.28 (1H, m), 1.83−1.91 (2H, m), 2.32−2.57 (1H, m), 2.83−3.13 (2H, m), 3.24−3.56 (2H, m), 3.64−3.73 (1H, m), 5.09−5.13 (1H, m), 6.38 (1H, m), 6.84−7.71 (10H, m), 9.03 (1H, br s), 9.61 (1H, br s), 13.38 (1H, br s). MS (ES) *m/e*: 470 (M − H). Anal. ($C_{25}H_{23}Cl_2N_1O_4 \cdot 1.0HCl \cdot 1.75H_2O$) C, H, N.

5-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-methoxybenzoic Acid Hydrochloride (11c). The title compound was synthesized from **24** and (3-formyl-4-methoxyphenyl)boronic acid **35** according to procedures B and E (20%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.79−1.91 (1H, m), 2.28−2.33 (1H, m), 2.77−2.91 (2H, m), 3.16−3.61 (5H, m), 3.80 (3H, s), 5.04−5.08 (1H, m), 6.34−6.36 (1H, m), 6.69−7.50 (10H, m), 8.94 (1H, br s), 9.40 (1H, br s), 12.72 (1H, br s). MS (ES) *m/e*: 482 (M + Na). Anal. ($C_{26}H_{26}Cl_1N_1O_5 \cdot 1.0HCl \cdot 3.5H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-5-methoxybenzoic Acid Hydrochloride (11d). The title compound was synthesized from **24** and [3-methoxy-5-(methoxycarbonyl)phenyl]boronic acid **36** according to the procedure described for the conversion of **24** to **10c** (40%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15−1.25 (1H, m), 1.83−1.88 (2H, m), 2.27−2.32 (1H, m), 2.78−2.86 (2H, m), 3.08−3.48 (2H, m), 3.68−3.73 (1H, m), 3.80 (3H, s), 5.02−5.05 (1H, m), 6.35−6.37 (1H, m), 6.82−7.50 (10H, m), 8.91 (1H, br s), 9.32 (1H, br s). MS (ES) *m/e*: 466 (M − H). Anal. ($C_{26}H_{27}Cl_1N_1O_5 \cdot 1.0HCl \cdot 1.5H_2O$) C, H, N.

Methyl 3-[((7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-5-nitrobenzoate (38). The title compound was synthesized from **24** and [3-(methoxycarbonyl)-5-nitrophenyl]boronic acid **37** according to procedure B (54%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.36 (9H, s), 1.9−2.1 (2H, m), 2.6−3.0 (4H, m), 3.3−3.4 (3H, m), 3.90 (3H, s), 4.7−4.9 (1H, m), 5.5−5.6 (1H, m), 6.8−7.0 (2H, m), 7.1−7.4 (5H, m), 7.7−7.8 (1H, m), 7.9−8.0 (1H, m), 8.30−8.35 (1H, m). MS (ES) *m/e*: 619 (M + Na).

Methyl 3-Amino-5-[((7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoate (39). To a solution of **38** (150 mg, 0.25 mmol) in a mixed solution of ethanol (1.5 mL) and water (0.5 mL) were added iron powder (42.1 mg, 0.75 mmol) and ammmonium chloride (6.72 mg, 0.126 mmol). The solution was heated under reflux for 2 h. After the mixture was cooled to room temperature, the precipitate was filtered through a pad of Celite. After concentration under reduced pressure, the residue was extracted with ethyl acetate, successively washed with saturated aqueous sodium hydrogen carbonate and brine, and dried over magnesium sulfate. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel with ethyl acetate and hexane (1: 3) to give 132 mg (93%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.36 (9H, s), 1.9−2.0 (2H, m), 2.5−2.9 (4H, m), 3.2−3.4 (3H, m), 3.76 (3H, s), 4.7−4.8 (1H, m), 5.50−5.7 (3H, br), 6.3−6.4 (1H, m), 6.5−6.8 (2H, m), 6.75 (1H, d, J = 8.3 Hz), 6.9−7.0 (1H, m), 7.08 (1H, d, J = 8.3 Hz), 7.2−7.4 (4H, m). MS (ES) *m/e*: 589 (M + Na).

3-Amino-5-[((7*S*)-7-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Dihydrochloride (11e). The title compound was synthesized from **39** according to procedure C (57%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.83−0.89 (1H, m), 1.45−1.51 (1H, m), 1.84−1.91 (1H, m), 2.29−2.35 (1H, m), 2.80−2.93 (2H, m), 3.13−3.89 (3H, m), 5.03−5.07 (1H, m), 6.60−6.61 (1H, m), 6.76−7.50 (13H, m), 8.94 (1H, br s), 9.33 (1H, br s). MS (ES) *m/e*: 453 (M + H). Anal. ($C_{25}H_{25}Cl_1N_2O_4 \cdot 2.0HCl \cdot 2.5H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-5-(dimethylamino)benzoic Acid Dihydrochloride (11f). To a solution of **39** (80 mg, 0.141mmol) in dichloromethane (2 mL) were added sodium triacetoxyborohydride (49.0 mg, 0.232mmol), acetic acid (47 μL), and 35% formaldehyde solution (0.328 mL, 1.41 mmol). The solution was stirred at room temperature for 17 h. The solution was concentrated under reduced pressure. The residue was extracted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate and water. The extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate and hexane to give 70.5 mg (84%) of methyl 3-[((7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-5-(dimethylamino)benzoate. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.36 (9H, s), 1.8−2.0 (2H, m), 2.5−2.9 (4H, m), 3.33 (6H, s), 3.2−3.4 (3H, m), 3.78 (3H, s), 4.7−4.8 (1H, m), 5.5−5.6 (1H, m), 6.3−6.4 (1H, m), 6.6−6.8 (4H, m), 6.95−7.15 (2H, m), 7.25−7.42 (4H, m). MS (ES) *m/e*: 617 (M + Na).

The title compound was synthesized from the obtained product according to procedure C (78%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.51−1.55 (1H, m), 1.75−1.90 (2H, m), 2.28−2.33 (1H, m), 2.73−2.85 (2H, m), 2.93 (6H, s), 3.14−3.27 (2H, m), 3.38−3.50 (1H, m) 5.02−5.06 (1H, m), 6.63−6.64 (1H, m), 6.77−7.50 (10H, m), 8.90 (1H, br s), 9.26 (1H, br s). MS (ES) *m/e*: 479 (M − H). Anal. ($C_{27}H_{29}Cl_1N_2O_4 \cdot 2.0HCl \cdot 4.5H_2O$) C, H, N.

3-(Acetylamino)-5-[((7*S*)-7-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Hydrochloride (11g). To a solution of **39** (73 mg, 0.129 mmol) and pyridine (0.021 mL, 0.257 mmol) in dichloromethane (1.0 mL) was added acetic anhydride (13.4 μL, 0.142 mmol) dropwise at 4 °C. The solution was stirred at room temperature for 2 h. To the solution was added water, and the solution was extracted with ethyl acetate and washed with water and brine. The extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate and hexane to give 75 mg (95%) of methyl 3-(acetylamino)-5-[((7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoate. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.36 (9H, s), 1.9−2.1 (2H, m), 2.08 (3H, s), 2.2−2.3 (2H, m), 2.7−3.0 (2H, m), 3.2−3.4 (3H, m), 3.82 (3H, s), 4.7−4.8 (1H, m), 5.5−5.6 (1H, m), 6.7−6.9 (2H, m), 7.1−7.2 (2H, m), 7.3−7.4 (4H, m), 7.50 (1H, br s), 7.97 (1H, s), 10.20 (1H, s). MS (ES) *m/e*: 607 (M-H).

The title compound was synthesized from the obtained product according to procedure C (89%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.45−1.65 (1H, m), 1.74−1.91 (2H, m), 2.03 (3H, s), 2.28−2.33 (1H, m), 2.78−2.93 (2H, m), 3.10−3.64 (3H, m), 4.97−5.02 (1H, m), 6.33−6.36 (1H, m), 6.88−7.88 (10H, m), 8.95 (2H, br), 10.21 (1H, s), 13.06 (1H, br s). MS (ES) *m/e*: 493 (M − H). Anal. ($C_{27}H_{27}Cl_1N_2O_5 \cdot 1.0HCl \cdot 2.5H_2O$) C, H, N.

3-{[(7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-5-(propylamino)benzoic Acid Dihydrochloride (11h). To a mixture of **39** (123 mg, 0.217 mmol) in DMF (2.0 mL) was added ethyl *n*-propyl iodide (47 μL, 0.60 mmol) and K_2CO_3 (100 mg, 0.72 mmol) at room temperature, and the mixture was stirred at 80 °C for 22 h. The resulting mixture was poured into a mixture of ethyl acetate and water, and the organic layer was washed with brine. After the solvent was evaporated under pressure, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give 54 mg (41%) of methyl 3-{[(7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-5-(propylamino)benzoate. ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.8−1.0 (5H, m), 1.36 (9H, s), 1.4−1.6 (2H, m), 1.8−2.0 (2H, m), 2.5−2.9 (4H, m), 3.33 (6H, s), 3.2−3.4 (3H, m), 3.78 (3H, s), 4.7−4.8 (1H, m), 5.5−5.6 (1H, m), 6.3−6.4 (1H, m),

6.5−6.6 (1H, m), 6.7−6.95 (4H, m), 7.1−7.2 (1H, m), 7.3−7.5 (4H, m). MS (ES) *m/e*: 631 (M + Na).

The title compound was synthesized from the above product according to procedure B (94%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.8−1.0 (5H, m), 1.4−1.6 (2H, m), 1.7−1.9 (1H, m), 2.2−2.4 (1H, m), 2.7−3.0 (4H, m), 3.04−3.2 (2H, m), 3.4−3.6 (2H, m), 4.2−4.8 (1H, br), 5.0−5.1 (1H, m), 6.45 (1H, br s), 6.5 (1H, m), 6.77−6.87 (3H, m), 6.95 (1H, s), 7.1−7.2 (1H, m), 7.35−7.51 (3H, m), 8.92 (1H, br s), 9.27 (1H, br s). MS (ES) *m/e*: 493 (M − H). Anal. ($C_{28}H_{31}Cl_1N_2O_4 \cdot 2.0HCl \cdot 2.5H_2O$) C, H, N.

3-{[(7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-5-(cyclohexylamino)benzoic Acid Dihydrochloride (11i). The title compound was synthesized from **39** and cyclohexanone according to the procedure described for the conversion of **39** to **11f** (40%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.1−2.0 (11H, m), 2.2−2.4 (1H, m), 2.7−3.2 (6H, m), 2.4−2.63 (2H, m), 4.22 (1H, br), 5.08 (1H, m), 6.72−6.88 (4H, m), 7.16 (2H, d, J = 8.3 Hz), 7.41−7.51 (4H, m), 8.95 (1H, br), 9.47 (1H, br). MS (ES) *m/e*: 533 (M − H). Anal. ($C_{31}H_{35}Cl_1N_2O_4 \cdot 2.0HCl \cdot 2.0H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-5-(tetrahydro-2*H*-pyran-4-ylamino)benzoic Acid Dihydrochloride (11j). The title compound was synthesized from **39** and tetrahydro-4*H*-pyran-4-one according to the procedure described for the conversion of **39** to **11f** (34%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.5−2.2 (5H, m), 2.1−3.0 (3H, m), 3.0−3.8 (8H, m), 4.66 (1H, m), 4.97 (1H, m), 6.33 (1H, m), 6.8−7.0 (4H, m), 7.18 (2H, d, J = 8.4 Hz), 7.3−7.6 (4H, m). MS (ES) *m/e*: 537 (M + H). Anal. ($C_{301}H_{33}Cl_1N_2O_5 \cdot 2.0HCl \cdot 2.0H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Hydrochloride (11k). The title compound was synthesized from **25** according to the procedure described for the conversion of **24** to **10c** (46%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.85−2.05 (1H, m), 2.30−2.50 (1H, m), 2.70−3.60 (7H, m), 5.10−5.20 (1H, m), 6.80−6.90 (2H, m), 7.20−7.80 (9H, m). MS (ES) *m/e*: 438 (M + H). Anal. ($C_{25}H_{24}Cl_1N_1O_4 \cdot 1.0HCl \cdot 2.6H_2O$) C, H, N.

5-[((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-methoxybenzoic Acid Hydrochloride (11l). The title compound was synthesized from **25** according to the procedure described for the conversion of **24** to **11c** (35%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.75−2.00 (1H, m), 2.20−2.40 (1H, m), 2.60−3.60 (7H, m), 3.80 (3H, s), 5.05−5.15 (1H, m), 6.75−6.90 (2H, m), 7.05−7.25 (4H, m), 7.40−7.50 (4H, m). MS (ES) *m/e*: 468 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_5 \cdot 1.0HCl \cdot 2.5H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-Hydroxy-2-(3-pyridinyl)ethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Dihydrochloride (11m). The title compound was synthesized from **27** according to procedure B (20%), followed by the procedure described for the conversion of **46** to **12g** (38%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.90−2.05 (1H, m), 2.30−2.40 (1H, m), 2.70−3.10 (3H, m), 3.20−3.60 (4H, m), 5.30−5.45 (1H, m), 6.80−6.95 (2H, m), 7.10−7.70 (6H, m), 8.00 (1H, dd, J = 5 Hz, 8 Hz), 8.60 (1H, d, J = 8 Hz), 8.85 (1H, d, J = 5 Hz). MS (ES) *m/e*: 405 (M + H). Anal. ($C_{24}H_{24}N_2O_4 \cdot 2.0HCl \cdot 1.0H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-(6-Chloro-3-pyridinyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]benzoic Acid Dihydrochloride (11n). The title compound was synthesized from **27** according to the procedure described for the conversion of **24** to **10c** (11%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.80−1.90 (1H, m), 2.30−2.40 (1H, m), 2.50−3.50 (7H, m), 5.10−5.20 (1H, m), 6.80−7.00 (2H, m), 7.15−7.70 (6H, m), 7.90−8.00 (1H, m), 8.48 (1H,s).MS(ES)*m/e*:439(M+H).Anal.($C_{24}H_{23}Cl_1N_2O_4 \cdot 2.0HCl \cdot 3.5H_2O$) C, H, N.

5-[((7*S*)-7-{[(2*R*)-2-(6-Chloro-3-pyridinyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-2-methoxybenzoic Acid Dihydrochloride (11o). The title compound was synthesized from **27** according to the procedure described for the conversion of **24** to **11c** (20%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.75−1.85 (1H, m), 2.30−2.40 (1H, m), 2.70−3.30 (7H, m), 3.80 (3H, s), 5.00−5.10 (1H, m), 6.65−6.80 (2H, m), 7.00−7.20 (4H, m), 7.55 (1H, d, J = 8 Hz), 7.90 (1H, dd, J = 2 Hz, 8 Hz), 8.45 (1H, d, J = 2 Hz). MS (ES) *m/e*: 469 (M + H). Anal. ($C_{25}H_{25}Cl_1N_2O_5 \cdot 2.0HCl \cdot 0.5H_2O$) C, H, N.

3-[((7*S*)-7-{[(2*R*)-2-(6-Chloro-3-pyridinyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)oxy]-5-(dimethylamino)benzoic Acid Dihydrochloride (11p). The title compound was synthesized from **27** according to the procedure described for the conversion of **24** to **11f** (22%). HPLC purity: 95%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.8−2.0 (1H, m), 2.96 (6H, s), 3.0−4.0 (5H, m), 5.15 (1H, m), 6.5−7.3 (6H, m), 7.56 (1H, d, J = 8.4 Hz), 7.91 (1H, m), 8.46 (1H, m), 9.01 (1H, m), 9.58 (1H, m). MS (ES) *m/e*: 482 (M + H). HRMS(M + H)$^+$ found: 482.1836. Calcd for $C_{26}H_{28}Cl_1N_3O_4$ 482.1847.

[3-(Methoxycarbonyl)-4-methylphenyl]boronic Acid (33). To a solution of methyl 5-bromo-2-methylbenzoate (6.4 g, 27.9 mmol) in 1,4-dioxane (70 mL) were added bis(pinacolate)diboron (7.09 g, 27.9 mmol), potassium acetate (8.23 g, 83.8 mmol), and dichlorobis(triphenylphosphine)palladium(II) (1.57 g, 2.24 mmol). The mixture was stirred at 100 °C for 2 h. To the mixture was added 1 N hydrogen chloride. The mixture was extracted with ethyl acetate and washed with 1 N hydrogen chloride and water. The extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the corresponding boronic ester. To a solution of the boronic ester in a mixed solution of acetone (120 mL) and water (120 mL) were added sodium periodate (17.9 g, 83.7 mmol) and ammonium acetate (6.45 g, 83.7 mmol). The mixture was stirred at room temperature for 17 h. The precipitate was filtered, and the filtrate was concentrated under reduced pressure. The residue was extracted with ethyl acetate and washed with water. The extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate and hexane (1:1) to give 4.05 g (75%) of the title compound as a pale-brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.53 (3H, s), 3.86 (3H, s), 7.29 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 8.27 (1H, s),.8.31 (2H, s). MS (ES) *m/e*: 193 (M − H).

[3-Methoxy-5-(methoxycarbonyl)phenyl]boronic Acid (36). To a mixture of methyl 3-hydroxy-5-methoxybenzoate (1.5 g, 8.23 mmol) in dichloromethane (15 mL) were added 2,6-lutidine (1.05 mL, 9.06 mmol) and trifluoromethanesulfonic anhydride (1.52 mL, 9.06 mmol) at 4 °C under N_2, and the mixture was stirred for 1 h at the room temperature. The mixture was poured into water, and the organic layer was washed with 1 N HCl and brine and then dried over magnesium sulfate to give the corresponding sulfonate. The title compound was synthesized from the obtained sulfonate according to the procedure described for the conversion of methyl 5-bromo-2-methylbenzoate to **33** except that the Pd catalyst was $PdCl_2(dppf) \cdot CHCl_3$ (21%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.81 (3H, s), 3.85 (3H, s), 7.46 (1H, m), 7.61 (1H, m), 8.01 (1H, s), 8.27 (2H, s). MS (ES) *m/e*: 209 (M − H).

Benzyl [(2*S*)-7-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl]-carbamate (41). To a mixture of (7*S*)-7-amino-5,6,7,8-tetrahydro-2-naphthalenol **18** (7.16 g, 43.9 mmol) in THF(70 mL) and water (50 mL) was added benzyl chlorocarbonate (6.58 mL, 46.1 mmol) at room temperature. The pH was kept between 7 and 8 by using 1 N aqueous NaOH. The mixture was stirred at room temperature for 1 h. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform/methanol = 20/1) to give 12.5 g (96%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60−1.85 (1H, m), 1.92−2.12 (1H, m), 2.4−3.1 (4H, m), 3.87−4.12 (1H, m), 4.8−5.0 (1H, m), 5.11 (2H, s), 5.86 (1H, s), 6.51 (1H, d, J = 2.6 Hz), 6.63 (1H, dd, J = 2.6, 8.2 Hz), 7.26−7.40 (5H, m).

Methyl 4-((7*S*)-7-{[(Benzyloxy)carbonyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (42). The title compound was synthesized from **41** and 4-(methoxycarbonyl)phenylboronic acid according to procedure F (72%). ^{1}H NMR (200 MHz, $CDCl_3$): δ

1.6−1.9 (1H, m), 2.0−2.2 (1H, m), 2.6−2.8 (1H, m), 2.82−3.0 (1H, m), 3.1−3.3 (1H, m), 3.95 (3H, s), 4.0−4.2 (1H, m), 4.84 (1H, br s), 5.12 (2H, s), 5.86 (1H, s), 7.17−7.41 (7H, m), 7.61 (1H, d, J = 8 Hz), 8.10 (1H, d, J = 8 Hz). MS (ES) *m/e*: 416 (M + H).

Methyl 4-[(7*S*)-7-Amino-5,6,7,8-tetrahydro-2-naphthalenyl]-benzoate (43). A mixture of **42** (580 mg, 1.4 mmol) in MeOH (50 mL) was hydrogenated over palladium on carbon (10% w/w, 50% wet, 58 mg) under hydrogen atmosphere for 1 h. The catalyst was filtered off, and the filtrate was evaporated to give 395 mg (100%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.6−1.9 (1H, m), 2.0−2.2 (1H, m), 2.6−2.8 (1H, m), 2.8−3.0 (3H, m), 3.2−3.6 (1H, m), 3.87 (3H, s), 3.8−3.9 (1H, m), 7.2−7.5 (3H, m), 7.82 (1H, d, J = 8 Hz), 8.02 (1H, d, J = 8 Hz), 8.19 (2H, br). MS (ES) *m/e*: 282 (M + H).

(2*R*)-2-(4-Chlorophenyl)oxirane (22). Typical Procedure G. To a solution of AD-mix-β (10.1 g) in *tert*-butanol (60 mL) and water (60 mL) was added 1-chloro-4-vinylbenzene (1.0 g, 7.22 mmol) on ice-cooling, and the mixture was stirred at the same temperature for 4 h. To the mixture was added sodium sulfite (19 g). The resulting mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1/1) to give 1.04 g (83.5%) of (1*R*)-1-(4-chlorophenyl)-1,2-ethanediol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.50−3.80 (2H, m), 4.70−4.85 (1H, m), 7.20−7.40 (4H, m).

Trimethylsilyl chloride (0.956 mL, 7.53 mmol) was added to a solution of (1*R*)-1-(4-chlorophenyl)-1,2-ethanediol (1.0 g, 5.79 mmol) and trimethyl orthoacetate (0.87 mL, 6.89 mmol) in dichloromethane (30 mL) on ice-cooling. The mixture was stirred for 1 h and evaporated. The crude product was dissolved in dry methanol, and potassium carbonate (1.97 g, 14.3 mmol) was added. The suspension was stirred vigorously for 100 min and then filtered, and the residue was washed with dichloromethane. The filtrate was washed with brine, dried over magnesium sulfate, and evaporated to give 700 mg (83.2%) of the title compound as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.75 (1H, dd, J = 2.5, 5.5 Hz), 3.14 (1H, dd, J = 4.0, 5.5 Hz), 3.80−3.86 (1H, m), 7.18−7.40 (4H, m). The optical purity was determined as 98.6% ee by chiral HPLC (Chiralcel OD); eluent, 2-propanol/hexane = 0.25%.

(2*R*)-2-(4-Methylphenyl)oxirane (44). The title compound was synthesized from 1-methyl-4-vinylbenzene according to procedure G (93%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (3H, s), 2.80 (1H, dd, J = 2.5, 5.5 Hz), 3.13 (1H, dd, J = 4 Hz, 5.5 Hz), 3.82 (1H, dd, J = 2.5, 4 Hz), 7.10−7.30 (4H, m). The optical purity was determined as 97.8% ee by chiral HPLC (Chiralcel OD).

Sodium 4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (12b). Typical Procedure H. A solution of methyl 4-[(7*S*)-7-amino-5,6,7,8-tetrahydro-2-naphthalenyl]benzoate **43** (142 mg, 0.505 mmol), and (2*R*)-2-(4-chlorophenyl)oxirane **22** (70.2 mg, 0.454 mmol) in ethanol (10 mL) was refluxed for 18 h. The mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform/methanol = 100:1) to give 130 mg (59.1%) of methyl 4-((7*S*)-7-{[(2*R*)-2-(4-chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.4−1.6 (1H, m), 1.9−2.0 (1H, m), 2.6−3.2 (6H, m), 4.6−4.7 (1H, m), 5.4−5.5 (1H, m), 7.17(1H, d, J = 8.5 Hz), 7.3−7.5 (6H, m), 7.78 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz). MS (ES) *m/e*: 436 (M + H).

To a solution of the obtained product (130 mg, 0.298 mmol) in ethanol (3.0 mL) was added 1 N sodium hydroxide (0.75 mL), and the mixture was refluxed for 3 h. After the mixture was cooled to room temperature, the precipitates were collected by filtration, washed with a small amount of ethanol, and dried under reduced pressure at 40−50 °C to give 120 mg (92.1%) of the title compound as a colorless powder. HPLC purity: 99%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.40−1.60 (1H, m), 1.90−2.10 (1H, m), 2.50−3.20 (6H, m), 4.60−4.70 (1H, m), 7.05 (1H, d, J = 8.0 Hz), 7.30−7.40 (6H, m), 7.50 (2H, d, J = 8.0 Hz), 7.90 (2H, d, J = 8.0 Hz). MS (ES) *m/e*: 422 (M + H). HRMS (M + H)$^+$ found: 422.1523. Calcd for $C_{25}H_{24}Cl_1N_1O_3$ 422.1523. Anal. ($C_{25}H_{23}Cl_1N_1O_3 \cdot 1.0Na \cdot 1.8H_2O \cdot 0.5CHCl_3$) C, H, N.

Sodium 4-((7*S*)-7-{[(2*R*)-2-(2-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (12a). The title compound was synthesized from **43** according to procedure H (45%). HPLC purity: 97%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.8−3.0 (9H, m), 4.97 (1H, m), 7.0−7.7 (9H, m), 7.8−8.0 (2H, m). MS (ES) *m/e*: 420 (M − H). HRMS (M + H)$^+$ found: 422.1513. Calcd for $C_{25}H_{24}Cl_1N_1O_3$ 422.1523.

Sodium 4-((7*S*)-7-{[(2*R*)-2-(4-Cyanophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (12d). The title compound was synthesized from **43** according to procedure H (71%). HPLC purity: 98%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.4−3.0 (9H, m), 4.72 (1H, m), 7.12 (1H, d, J = 8.2 Hz), 7.2−7.6 (6H, m), 8.82 (2H, d, J = 8.4 Hz), 7.92 (2H, d, J = 8.4 Hz). MS (ES) *m/e*: 413 (M + H). HRMS (M + H)$^+$ found: 413.1859. Calcd for $C_{26}H_{24}N_2O_3$ 413.1865.

Sodium 4-((7*S*)-7-{[(2*R*)-2-(4-trifluorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (12e). The title compound was synthesized from **43** according to procedure H (56%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.8−3.2 (9H, m), 4.73 (1H, m), 7.11 (1H, d, J = 8.6 Hz), 7.3−7.8 (8H, m), 7.88 (2H, d, J = 8.2 Hz). MS (ES) *m/e*: 456 (M + H). Anal. ($C_{26}H_{23}F_3N_1O_3 \cdot 1.0Na \cdot 0.5H_2O \cdot 1.0CHCl_3$) C, H, N.

Sodium 4-((7*S*)-7-{[(2*R*)-2-(3,4-Dichlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (12f). The title compound was synthesized from **43** according to procedure H (54%). HPLC purity: 97%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.8−3.0 (9H, m), 4.66 (1H, m), 7.0−7.2 (1H, m), 7.2−7.9 (9H, m). MS (ES) *m/e*: 472 (M + H). HRMS(M + H)$^+$ found: 456.1126. Calcd for $C_{25}H_{23}Cl_2N_1O_3$ 456.1133.

Sodium 4-((7*S*)-7-{[(2*R*)-2-(6-Chloro-3-pyridinyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (12h). The title compound was synthesized from **43** according to procedure H (42%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.50−1.70 (1H, m), 1.90−2.10 (1H, m), 2.50−3.50 (7H, m), 4.70−4.80 (1H, m), 7.10−7.15 (1H, m), 7.20−7.60 (5H, m), 7.70−8.00 (3H, m), 8.40 1H, s). MS (ES) *m/e*: 423 (M + H). Anal. ($C_{24}H_{22}Cl_1N_2O_3 \cdot 1.0Na \cdot 2.25H_2O$) C, H, N.

Methyl 4-[(7*S*)-7-{(*tert*-Butoxycarbonyl)[(2*R*)-2-hydroxy-2-(4-methylphenyl)ethyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl]benzoate (45). The title compound was synthesized from **43** and (2*R*)-2-(4-methylphenyl)oxirane **44** according to procedure A (29%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.8−2.0 (2H, m), 2.34 (3H, s), 2.8−3.1 (4H, m), 3.2−3.7 (2H, m), 3.94 (3H, s), 4.1−4.2 (1H, m), 4.90 (1H, m), 7.13−7.42 (7H, m), 7.64 (2H, d, J = 8.5 Hz), 8.09 (2H, d, J = 8.5 Hz). MS (ES) *m/e*: 516 (M + H).

4-((7*S*)-7-{[(2*R*)-2-Hydroxy-2-(4-methylphenyl)ethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic Acid Hydrochloride (12c). The title compound was synthesized from **45** according to procedure C (46.4%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.80−2.00 (1H, m), 2.31 (3H, s), 2.25−2.50 (1H, m), 2.70−3.70 (7H, m), 5.00−5.10 (1H, m), 6.85−6.95 (2H, m), 7.10−7.55 (7H, m), 7.80 (2H, d, J = 8 Hz), 8.00 (2H, d, J = 8 Hz). MS (ES) *m/e*: 402 (M + H). Anal. ($C_{26}H_{27}NO_3 \cdot 1.0HCl$) C, H, N.

Methyl 4-((7*S*)-7-{(*tert*-Butoxycarbonyl)[(2*R*)-2-(6-chloro-3-pyridinyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoate (46). The title compound was synthesized from **43** and 2-chloro-5-[(2*R*)-oxiran-2-yl]pyridine **23** according to procedure A (36.7%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.8−2.0 (2H, m), 2.8−3.1 (4H, m), 3.2−3.7 (2H, m), 3.94 (3H, s), 4.1−4.2 (1H, m), 4.97 (1H, m), 7.16−7.42 (4H, m), 7.63 (2H, d, J = 8.4 Hz), 7.73 (1H, dd, J = 2.4, 8.3 Hz), 8.09 (2H, d, J = 8.4 Hz), 8.38 (1H, d, J = 2.4 Hz). MS (ES) *m/e*: 537 (M + H).

4-((7*S*)-7-{[(2*R*)-2-Hydroxy-2-(3-pyridinyl)ethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic Acid Dihydrochloride (12g). To a solution of **46** (1.0 g, 1.86 mmol) in ethanol (15.0 mL) was added 1 N sodium hydroxide (5.0 mL), and the mixture was stirred

for 2 h at room temperature. The mixture was diluted with ethyl acetate and 1 N hydrochloride. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. A mixture of the obtained benzoic acid (800 mg, 1.53 mmol), ammonium formate (300 mg), and palladium on carbon powder (100 mg) in methanol (25 mL) and water (5.0 mL) was refluxed for 15 min. The reaction mixture was filtered, poured into water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform−methanol) to give 620 mg (68%) of 4-((7*S*)-7-{(*tert*-butoxycarbonyl)[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)benzoic acid as a colorless form. MS (ES) *m/e*: 489 (M + H).

A solution of the obtained product (620 mg, 1.27 mmol) and 4 N hydrochloric acid in dioxane (10 mL) was stirred at room temperature for 24 h. The resultant solid was collected by filtration and dried to give 450 mg (75%) of the title compound as a white solid. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.80−1.90 (1H, m), 2.30−2.40 (1H, m), 2.80−3.50 (6H, m), 5.30−5.40 (1H, m), 7.20 (1H, d, J = 8 Hz), 7.40−7.50 (2H, m), 7.77 (2H, d, J = 8 Hz), 7.90−8.05 (3H, m), 8.60 (1H, d, J = 8 Hz), 8.88 (1H, d, J = 8 Hz), 8.99 (1H, s). MS (ES) *m/e*: 389 (M + H). Anal. ($C_{24}H_{24}N_2O_3 \cdot 2.0HCl \cdot 2.5H_2O$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-2-methylbenzoic Acid Hydrochloride (12i). The title compound was synthesized from **25** and [4-(methoxycarbonyl)-3-methylphenyl]boronic acid according to the procedure described for the conversion of **24** to **10m** (44%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.80−2.00 (1H, m), 2.30−2.40 (1H, m), 2.59 (3H, s), 2.70−3.70 (7H, m), 5.05−5.15 (1H, m), 7.24 (1H, d, J = 8 Hz), 7.30−7.65 (8H, m), 7.90(1H, d, J = 8 Hz). MS (ES) *m/e*: 436 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_3 \cdot 1.0HCl \cdot 2.5H_2O$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-2-fluorobenzoic Acid Hydrochloride (12j). The title compound was synthesized from **25** and [3-fluoro-4-(methoxycarbonyl)phenyl]boronic acid according to the procedure described for the conversion of **24** to **10m** (34%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.80−1.95 (1H, m), 2.25−2.40 (1H, m), 2.70−3.60 (7H, m), 5.00−5.10 (1H, m), 7.20 (1H, d, J = 8 Hz), 7.40−7.65 (8H, m), 7.90 (1H, d, J = 8 Hz). MS (ES) *m/e*: 440 (M + H). HRMS (M + H)$^+$ found: 440.1432. Calcd for $C_{25}H_{23}Cl_1F_1N_1O_3$ 440.1429. Anal. ($C_{25}H_{23}Cl_1F_1N_1O_3 \cdot 0.5HCl$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-2-methoxybenzoic Acid Hydrochloride (12k). The title compound was synthesized from **25** and [3-methoxy-4-(methoxycarbonyl)phenyl]boronic acid according to the procedure described for the conversion of **24** to **10m** (65%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.80−1.90 (1H, m), 2.30−2.40 (1H, m), 2.80−3.20 (6H, m), 3.90 (3H, s), 5.00−5,05 (1H, m), 7.10−7.30 (3H, m), 7.50−7.60 (6H, m), 7.70 (2H, d, J = 8 Hz). MS (ES) *m/e*: 452 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.2H_2O$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-2-isopropoxybenzoic Acid Hydrochloride (12l). The title compound was synthesized from **25** and [3-isopropoxy-4-(methoxycarbonyl)phenyl]boronic acid according to the procedure described for the conversion of **24** to **10m** (67%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.25 (6H, d, J = 6.0 Hz), 1.5−3.5 (10H, m), 4.77 (1H, m), 5.02 (1H, m), 6.2−7.0 (3H, m), 7.1−7.6 (5H, m), 7.68 (2H, d, J = 8.4 Hz). MS (ES) *m/e*: 480 (M + H). Anal. ($C_{28}H_{30}Cl_1N_1O_4 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-3-methylbenzoic Acid Hydrochloride (12m). The title compound was synthesized from **25** and [4-(methoxycarbonyl)-2-methylphenyl]boronic acid according to the procedure described for the conversion of **24** to **10m** (39%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.75−1.85 (1H, m), 2.40 (3H, s), 2.40−2.50 (1H, m), 2.70−3.00 (7H, m), 5.00−5.10 (1H, m), 7.00−7.30 (4H, m), 7.35−7.45 (5H, m), 7.80−7.90 (1H, m). MS (ES) *m/e*: 436 (M + H). Anal. ($C_{26}H_{26}Cl_1N_1O_3 \cdot 1.0HCl \cdot 0.8H_2O$) C, H, N.

4-((7*S*)-7-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}-5,6,7,8-tetrahydro-2-naphthalenyl)-3-fluorobenzoic Acid Hydrochloride (12n). The title compound was synthesized from **25** and [2-fluoro-4-(methoxycarbonyl)phenyl]boronic acid according to the procedure described for the conversion of **24** to **10m** (63%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.70−1.95 (1H, m), 2.30−2.40 (1H, m), 2.70−3.50 (7H, m), 5.00−5.10 (1H, m), 7.20−7.90 (10H, m). MS (ES) *m/e*: 440 (M + H). Anal. ($C_{25}H_{23}Cl_1F_1N_1O_3 \cdot 1.0HCl \cdot 3.0H_2O$) C, H, N.

Biological Materials and Methods. In Vitro Experiments. (1) Cell Culture. We used stably transfected Chinese hamster ovary (CHO) cells expressing recombinant human β1-, β2-, β3-ARs and recombinant canine β3-AR. CHO cells were seeded 2 days before the assays in 96-well plates at a density of (1−1.3) × 10^4 cell/well.

(2) cAMP Accumulation Assay. CHO cells grown to confluence were washed twice with assay buffer [130 mM NaCl, 5 mM KCl, 1 mM $MgCl_2 \cdot 6H_2O$, 1.5 mM $CaCl_2 \cdot 2H_2O$, 10 mM glucose, 10 mM HEPES, 0.1% bovine serum albumin, pH7.4] and incubated with 180 μL of assay buffer containing 0.5 mM 3-isobutylmethylxanthine (IBMX) at 37 °C for 10 min. Test compound (20 μL) dissolved in assay buffer containing 1% DMSO was then added, and cells were incubated at 37 °C for 15 min. The reaction was stopped by addition of 80 μL of 0.1 M HCl. After 1 h at 4 °C, cells were centrifuged at 2000 rpm for 5 min at 4 °C. The amount of cAMP in the supernatant was determined using a cAMP enzymeimmunoassay (EIA) kit (Amersham Biosciences). The supernatant was frozen below −80 °C until the measurement of cAMP levels.

(3) Data Analysis. cAMP acumulation elicited by test compounds were expressed as a percentage of the maximal response to isoproterenol. Fifty percent effective concentration (EC_{50}) values were calculated using GraphPad Prism (version 3.03) from the concentration−response curve.

Acknowledgment. We thank Dr. Xiaoyong Zhang (Takasago Co.) for the screening of asymmetric hydrogenation to prepare a chiral amine **15**. We express our thanks to Dr. David Barrett for his critical reading of the manuscript.

Supporting Information Available: Combustion analysis data and biological method for in vivo experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM800222K