Discovery of a Novel Series of Biphenyl Benzoic Acid Derivatives as Highly Potent and Selective Human β3 Adrenergic Receptor Agonists with Good Oral Bioavailability. Part II

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The left-hand side (LHS) and central part of our first generation biphenyl (FGB) series was modified to improve in vitro and in vivo β3-AR potency without loss of oral bioavailability. First, in this study, we focused our efforts on replacement of the 3-chlorophenyl moiety in the LHS of FGB analogues with 3-pyridyl ring analogues to adjust the lipophilicity. Second, we investigated the replacement of the central part of this series and discovered that introduction of a methyl group into the α-position of the phenethylamine moiety greatly enhanced potency keeping good oral availability. Finally, the replacement of the two carbon linker of the central part with an ethoxy-based linker provided improved potency and PK profiles. As a result of these studies, several analogues (i.e., **9h**, **9k**, **9l**, **10g, 10m**, **10p**, **10r**, **11b**, and **11l**) were identified that displayed an excellent balance of very higher human β3-AR potency compared to the FGB compounds, high selectivity, and good pharmacokinetic profiles. Furthermore, these several compounds showed high in vivo efficacy in an overactive bladder (OAB) model. These findings suggest that our selected second generation biphenyl (SGB) series compounds may be attractive new successful therapeutic candidates for the treatment of OAB.

Introduction

The β3-adrenergic receptor (β3-AR)[a] has been shown to mediate various pharmacological and physiological effects such as lipolysis, thermogenesis,[1] intestinal smooth muscle relaxation,[2] and urinary bladder detrusor muscle relaxation.[3,4] Thus, the activation of the human β3-AR has attracted much attention as a potential approach toward the treatment of obesity, noninsulin-dependent diabetes mellitus (NIDDM), irritable bowel syndrome, and overactive bladder, and the β3-AR is therefore recognized as an attractive target for drug discovery.[5] Recently, on the other hand, β3-AR selectivity over β1-AR and β2-AR is also important because stimulation of β1-AR and β2-AR may induce severe side effects such as enhancement of heart rate and tracheal relaxation, respectively. 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 potent and selective human β3-AR chemotypes (see Figure 1), but these are still not sufficient in terms of the pharmacokinetic properties.[5b,6]

Previous work in our laboratory has described the discovery of a series of first generation biphenyl (FGB) analogues containing a benzoic acid moiety on the right-hand side (RHS), represented by **8** (Figure 2), which exhibited good oral bioavailability and a long plasma half-life.[7] The structure−activity relationship (SAR) studies at the R position of the terminal phenyl ring on the RHS indicated that introduction of more lipophilic substitution increased β3-AR activity (*O*-cyclohexyl, **8c** > O-*iso*-pr, **8b** > O-Me, **8a**) but decreased oral bioavailability (**8a** > **8b** > **8c**) (see Figure 2). On the basis of these results, we selected lead candidate **8b** with a good balance of potency, selectivity, and pharmacokinetic profile. We extended optimization of the FGB series to further improve β3-AR activity without loss of the good oral bioavailability.

Our designed second generation biphenyl (SGB) series (**9**−**11**) is shown in Figure 3. First of all, we focused our efforts on replacement of the 3-chlorophenyl moiety in the left-hand side (LHS) with several identified partial structures such as present in compounds **1**,[8] **2**,[9] **3**,[10] and **4**[11] (see Figure 1). Second, we investigated the replacement of the central part of this series, through introduction of a methyl groups adjacent to the secondary amino group, such as in compounds **5**[12] and **6**.[13] Finally, we modified the two carbon linker region, such as in compounds **4** and **7**[14] (see Figure 1).

In this paper, we describe synthesis and SAR studies in which we have varied the LHS and central part of the SGB series and simultaneously evaluated the pharmacokinetic profile by cassette dosing assay in dogs, as previously described. These studies have led to the successful discovery of several clinical drug candidates with an excellent balance of very high potency, selectivity and good pharmacokinetic profile.

Chemistry. As shown in the first and second reactions of Scheme 1, in general, the requisite left and center part intermediate Boc amine derivatives (**17**−**19**) were synthesized by coupling of amino ethanol derivatives (**12**,[15] **13**, **14**) with carboxylic acid derivatives (**15**, **16**) to afford the corresponding amide intermediate, followed by selective reduction of the amide moiety with $BH_3 \cdot SMe_2$ to unmask the amino ethanol, followed

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[a] Abbreviations: β-AR, β-adrenergic receptors; OAB, overactive bladder; FGB, first generation biphenyl; SGB, second generation biphenyl; LHS, left-hand side; RHS, right-hand side; cAMP, cyclic adenosine monophosphate; ISP, isoproterenol; CHO, Chinese hamster ovary; IVP, intravesical pressure; PAMPA, parallel artificial membrane permeation assay; PB, protein binding.

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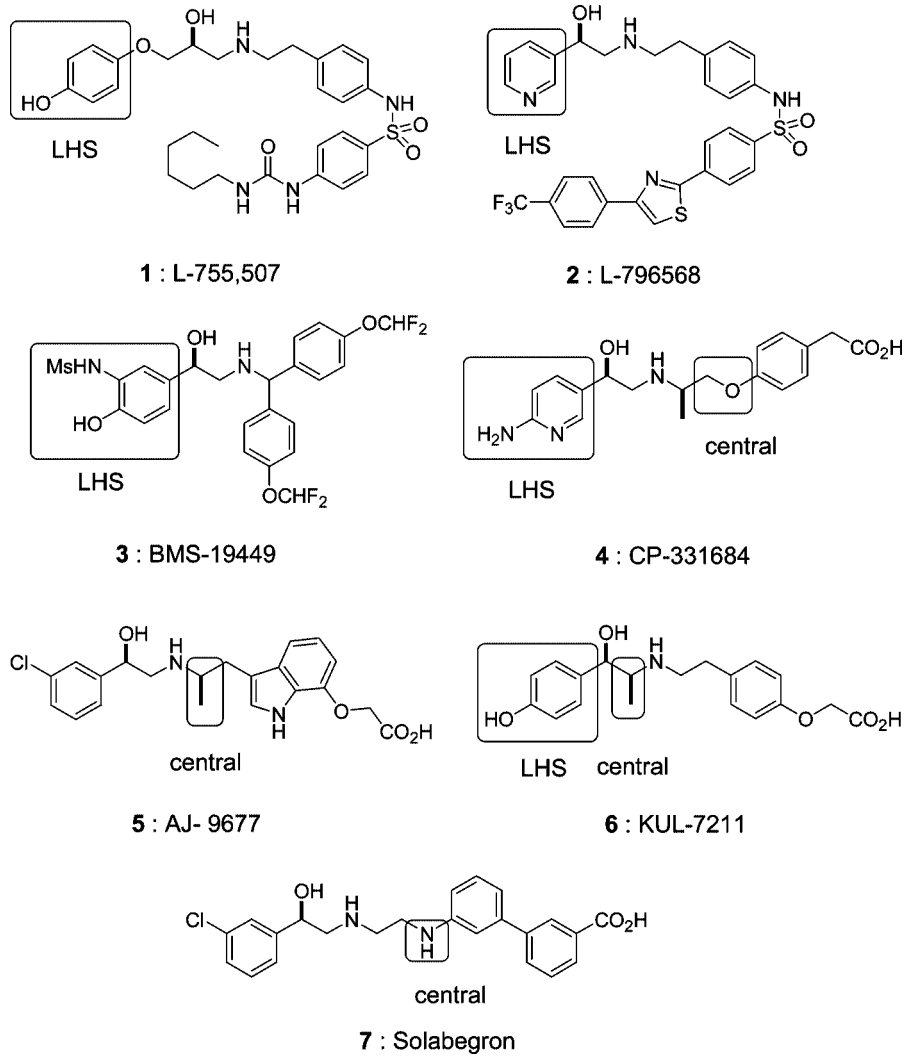
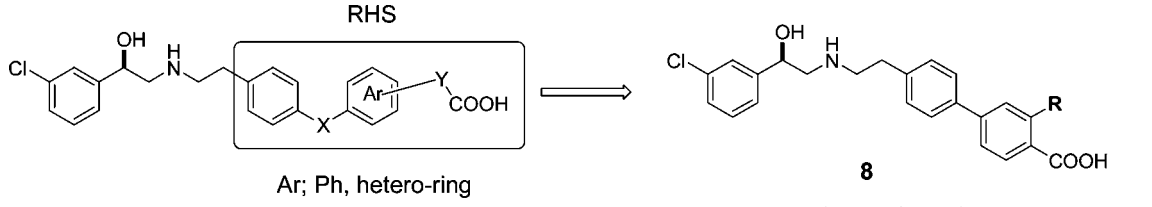


Figure 1. Structures of some β-3 AR agonists



	human β 3 EC_{50} (nM)	human β 1/β 3	dog Ba (%)
8a: R = OMe	4.8	52	58
8b: R = O-*i* - Pr	1.1	654	45
8c: R = O-*c* - Hex	0.46	120	0

Figure 2. First generation biphenyl (FGB) series.

by protection of the amine with a Boc group. In a similar way, the requisite intermediate 4-iodophenyl derivatives (**24**−**26**) were synthesized by coupling of commercially available mandelic acid derivatives **20** or **21** with amines **22**, **23**, which were synthesized as outlined in Scheme 2.

The requisite intermediate Boc amine derivatives **28**−**32** containing a phenyl ethanol moiety were prepared as shown in the third and fourth reactions of Scheme 1. Coupling of optically active epoxides,[16,17] in the presence of BSU with 4-bromophenyl ethylamine **27**, followed by protection of the amine with a Boc group, gave the corresponding Boc amine derivatives **28**−**32**. In a similar manner, the requisite intermediate 4-iodophenyl derivatives (**38**−**41**) were synthesized by reaction of optically active epoxides **33** or **34**, which are commercially available, or 2-chloro-5-[(2*R*)-2-oxiranyl]pyridine **35** prepared through known synthetic procedures, and with the chiral amines **36** or **37**, and subsequently protection with a Boc group, respectively. As shown in Scheme 2, the optically active amine intermediate **36** containing a chiral methyl group was prepared in five steps starting from commercially available (2*S*)-2-amino-3-phenyl-

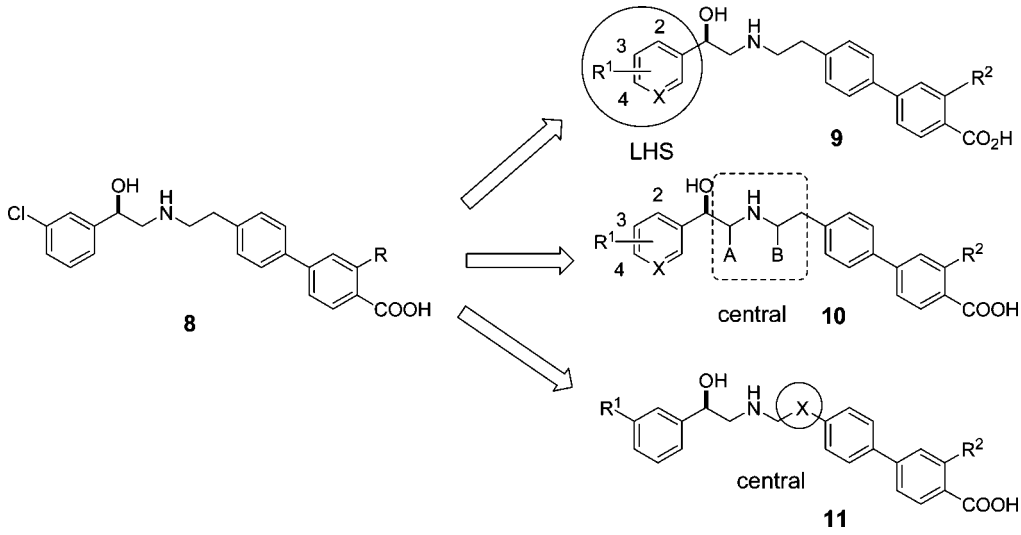


Figure 3. Second generation biphenyl (SGB) series.

1-propanol **47**. The optically active amino propanol intermediate **37** was prepared by reduction of commercially available (2*S*)-2-amino-3-(4-iodophenyl)propanoic acid with $NaBH_4$ in the presence of H_2SO_4.

As shown in the fifth and sixth reactions of Scheme 1, the intermediate Boc amine derivatives **43** and **44** containing an amino-pyridine moiety in the left part were prepared. Coupling of tosylate **42**, which was prepared through known synthetic procedures,[18] with 4-bromophenyl ethylamine **27** or 4-iodophenoxyethylamine **22** afforded a secondary amine, which was protected by protected with Boc to give the corresponding Boc amine derivatives **43** and **44**. 4-Hydroxyphenyl intermediate **46** was prepared by coupling of commercially available (*aS*,*bR*)-4-hydroxynorephedrine **45** with 4-bromophenylethylbromide, followed by protection with a Boc group.

The general synthetic route to biphenyl targets (**9a**,**b**,**h**,**j**,**k**, **10a**−**i**,**g**−**k**, **11a**−**k**) is shown in Scheme 3. Suzuki cross-coupling of Boc amine intermediates with boronic acids (**53a**−**h**), the syntheses of which have been previously described,[7] followed by alkaline hydrolysis of the methyl ester, and deprotection of the Boc group with 4 N HCl provided the target compounds as hydrochloride salts. In a similar manner, pyridine analogues (**10p**−**s**) were obtained from **40**, in an additional step, through dechlorination by catalytic hydrogenation in the presence of HCO_2NH_4. The amino pyridine analogues (**9i**,**l**,**m**, **11l**) were prepared by coupling of **43** or **44** with boronic acids (**53b**,**e**,**f**) in the presence of a catalytic amount of $PdCl_2(dppf)\cdot CHCl_3$, followed by alkaline hydrolysis, and subsequent deprotection of the Boc amine silyl ether using 4 N HCl.

The preparation methods for the final targets **9c**−**f** are shown in Scheme 4. The phenol analogue **9c** was obtained through a Suzuki coupling of Boc amine derivative **30** and boronic acid **53b**, followed by deprotection of the benzyl group by catalytic hydrogenation, followed by using the same methods as described for **9a**. In a similar manner, the aniline analogues **9e**,**f** were obtained from **31** and **32**, through an additional step of reduction of the nitro group with iron powder in the presence of NH_4Cl. The methane sulfonamide analogue **9d** was obtained from **31**, in an additional step, through acylation of the NH_2 group with Ms-Cl.

The preparation of the final target **9g** is shown in Scheme 5. The requisite intermediate **56** containing the methane sulfonamide moiety was obtained by reduction of the corresponding nitro derivative **55**, followed by coupling with Ms-Cl. The nitro derivative **55** was prepared from chiral oxirane **54**, which has been previously described[19] similar to procedures described for the third and fourth reactions of Scheme 1 using Cbz-Cl instead of Boc_2O. The target **9g** was obtained through a Suzuki coupling of Cbz derivative **56** and boronic ester **58**, which was prepared from bromide **57** followed by deprotection of the Cbz group by catalytic hydrogenation.

As shown in Scheme 6, the target **10j** with a dimethyl group was synthesized from **61**, similar to the preparation of **10d**. The requisite intermediate **61** was prepared by protection of the amino group of commercially available **59** with trifluoro-acetyl, followed by para-selective iodination.

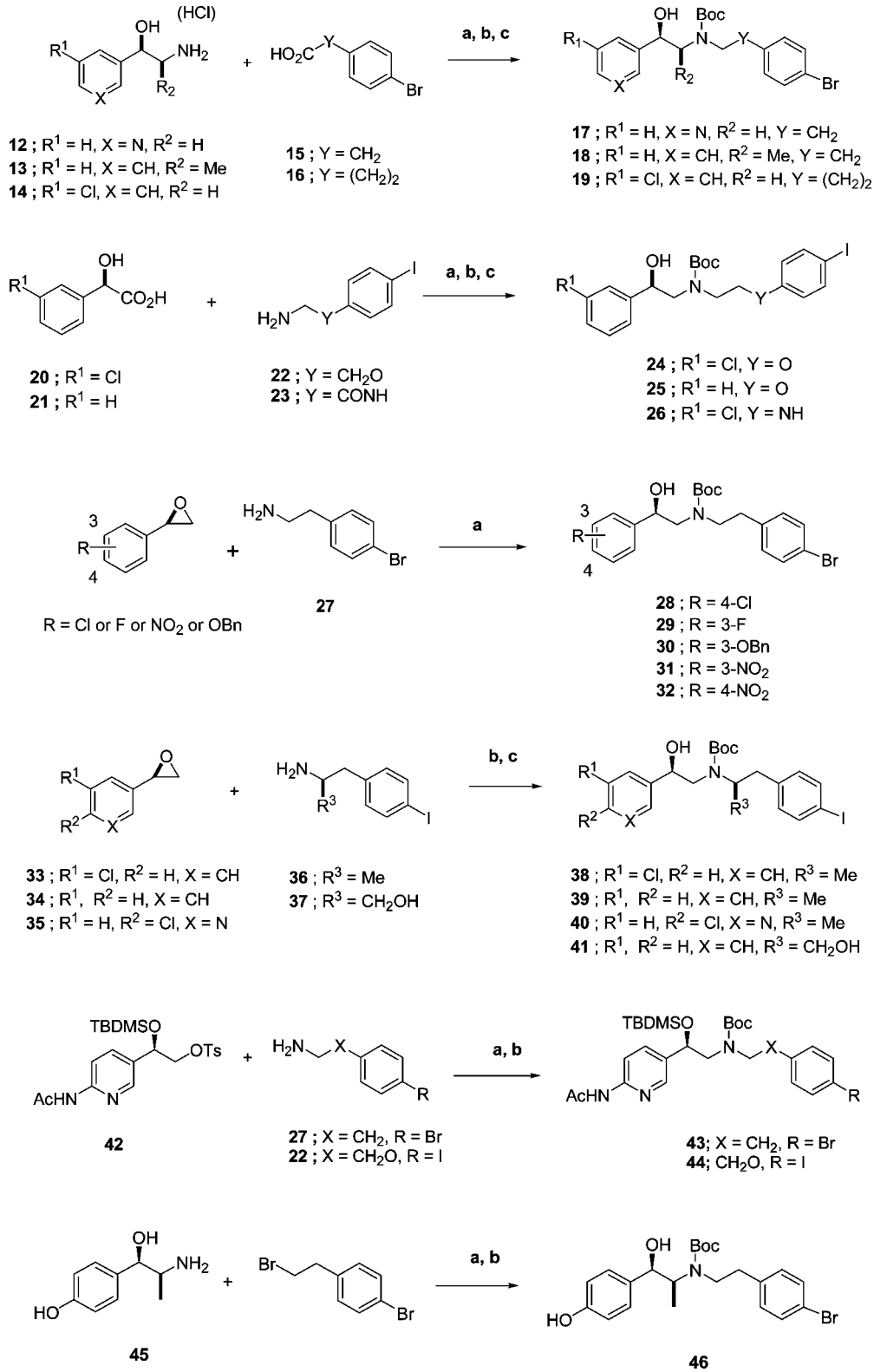
Results and Discussion

All compounds were evaluated for the 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, as previously described.[7,20] The results for reference compound, isoproterenol (ISP, nonselective β-AR agonist) are shown for comparison in Table 1. In addition, pharmacokinetic properties of selected compounds were evaluated by cassette dosing assay in dogs.[7,21]

As shown in Figure 2 and Table 1, in a previous article, we reported that our leading candidate **8b** showed potent β3-AR activity (EC_{50} = 1.1 nM), good selectivity relative to β1 and β2 activity, and good pharmacokinetics in all three species examined (rat, dog, and monkey). The *O*-cyclohexyl analogue (**8c**) with enhanced lipophilicity, resulted in a further improvement in β3-AR potency (EC_{50} = 0.46 nM) but poor bioavailability. We also investigated the removal of the chloro atom on the LHS phenyl ring. More lipophilic isobutyl (**8e**) and O-*c*-hex (**8f**) analogues, relative to the O-*iso*-pr derivative (**8d**), showed improved β3-AR activity and selectivity compared to **8d**. However, in the cassette dosing assay, both analogues displayed decreased C_{max} levels. (These compounds showed high passive permeability in PAMPA.) These results indicated SAR trends as for the 3-chlorophenyl analogues that we have previously reported.[7]

First of all, to improve the β3-AR activity of **8b**, we focused on replacement of the LHS 3-chlorophenyl moiety with several substituted phenyl groups. Shift of the chloro group to the

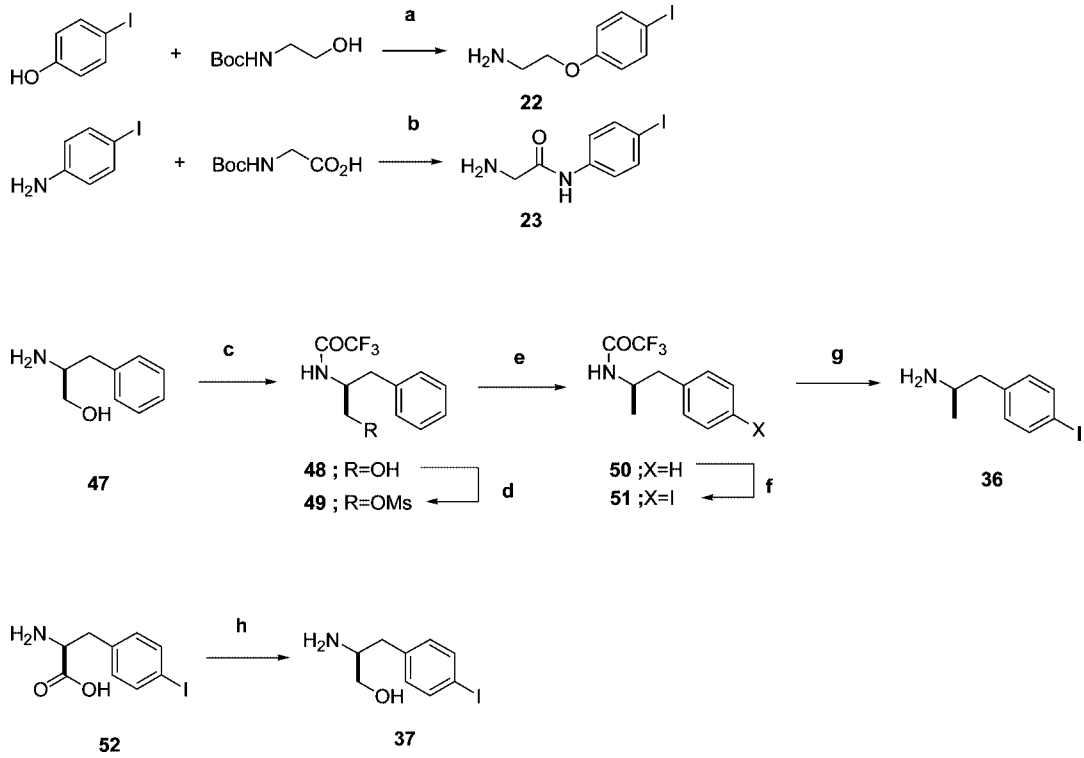
Scheme 1. Preparation of Left and Center Part Intermediates[a]



[a] For first and second reactions: (a) HOBt, WSCD, DMF; (b) $BH_3 \cdot SMe_2$, THF, DMI, then c. HCl; (c) $(Boc)_2O$, THF, aq NaOH (pH = 7−8). For third and fourth reactions: (a) BSU, DMSO, 65 °C, then $(Boc)_2O$, THF, H_2O; (b) EtOH, reflux; (c) $(Boc)_2O$, THF, H_2O, 1 N NaOH aq. For fifth and sixth reactions: (a) i-Pr_2NEt, DMSO or DMF, 80 °C; (b) $(Boc)_2O$, THF.

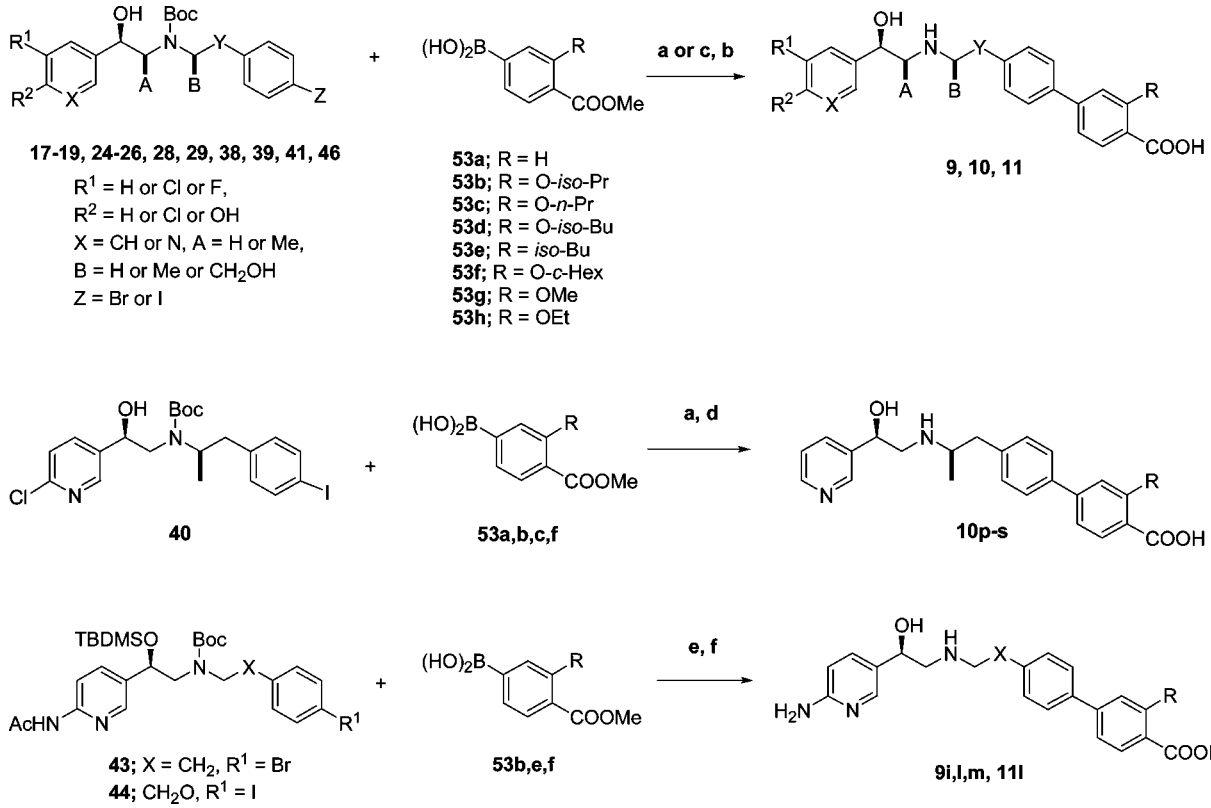
4-position (**9a**) and the fluoro analogue (**9b**) resulted in slightly decreased β3-AR activity relative to **8b**. We investigated replacement of the chloro group with a hydroxy group at the 3-position, such as in compounds **1** or **6** (Figure 1). As a result, the phenol analogue (**9c**) resulted in 18-fold increased potency (EC_{50} = 0.062 nM) for β3 relative to **8b** and high selectivity for β1. However, **9c** showed lower C_{max} levels relative to **8b** in the cassette dosing assay. On the basis of this result, our efforts were focused on improving the PK properties of **9c** by replacing the phenol part with isosteric functionalities. The methylsul-

Scheme 2. Preparation of Alkyl Amine of Center Part Intermediates[a]



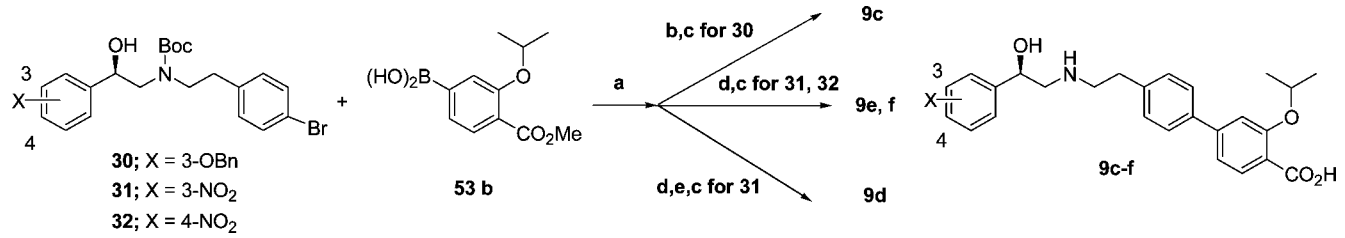
[a] (a) PPh_3, 40% DEAD in toluene, 4 °C−room temp, then 4 N HCl/AcOEt; (b) HOBt, WSCD, DMF, then 4 N HCl/AcOEt; (c) CF_3CO_2Et, MeOH; (d) MsCl, Et_3N, THF; (e) Zn(powder), NaI, AcOH, DME, reflux; (f) I_2, $HIO_4 \cdot 2H_2O$, AcOH, H_2SO_4, H_2O, 80 °C; (g) 1 N NaOH aq, dioxane, 50 °C; (h) $NaBH_4$, THF, H_2SO_4, Et_2O.

Scheme 3. General Synthesis Route to Targets **9**, **10**, **11**[a]



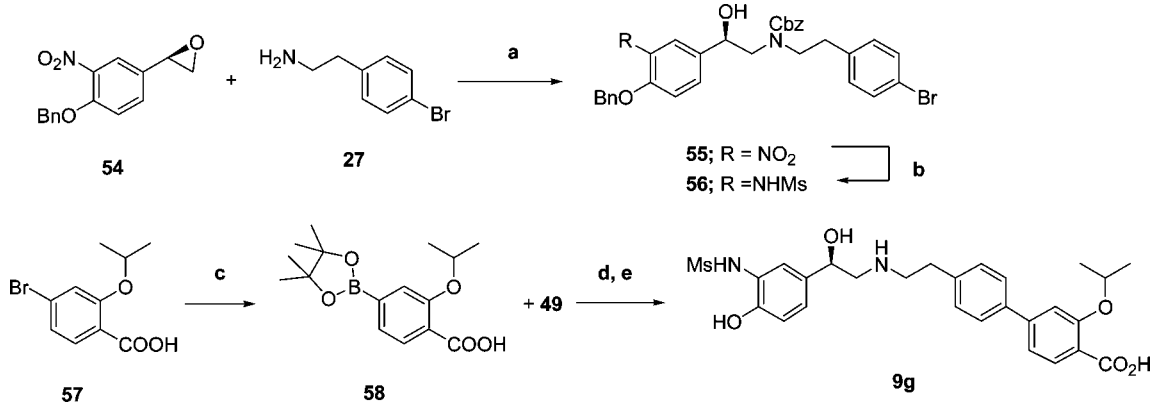
[a] (a) $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70 °C; (b) 1 N NaOH aq, EtOH, THF, then 4 N HCl/AcOEt; (c) $PdCl_2$(dppf) CH_2Cl_2, dppf, aq Na_2CO_3, toluene, EtOH, 75 °C (d) 1 N NaOH aq, EtOH, THF, then HCO_2NH_4, 10% Pd/C, MeOH, H_2O, reflux, then 4 N HCl/dioxane; (e) $PdCl_2$(dppf) CH_2Cl_2, dppf, aq Na_2CO_3, DMF, 80 °C; (f) 1 N NaOH aq, EtOH, 100 °C, then 4 N HCl/dioxane, MeOH.

Scheme 4. Synthesis Route to Targets **9c−f**[a]



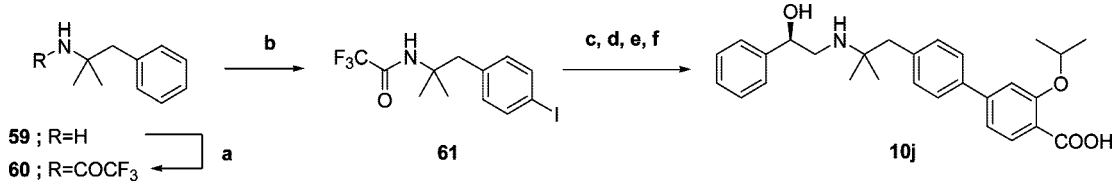
[a] (a) $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70 °C; (b) H_2 (gas), 10% Pd/C, MeOH; (c) 1 N NaOH aq, EtOH, THF, then 4 N HCl/AcOEt (d) Fe (powder), NH_4Cl, EtOH, reflux, (e) MsCl, pyridine.

Scheme 5. Synthesis Route to Targets **9g**[a]



[a] (a) BSU, DMSO, 65 °C, then Cbz-Cl, THF, H_2O; (b) Fe (powder), NH_4Cl, EtOH, reflux, then MsCl, pyridine;(c) KOAc, pinacol diborane, $PdCl_2$(dppf)-$CHCl_3$, dioxane, 90 °C; (d) $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70 °C; (e) H_2 (gas), 10% Pd/C, MeOH, then 4 N HCl/AcOEt.

Scheme 6. Synthesis Route to Targets **10j**[a]



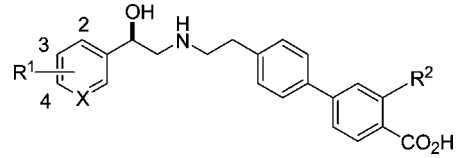
[a] (a) $(CF_3CO)_2O$, Et_3N, THF; (b) I_2, $HIO_4 \cdot 2H_2O$, AcOH, H_2SO_4, H_2O, 80 °C; (c) 1 N NaOH aq, dioxane, 50 °C, then **34**, EtOH, reflux; (d) $(Boc)_2O$, THF, H_2O, 1 N NaOHaq (pH = 8−8.5); (e) **53b**, $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70 °C; (f) 1 N NaOH aq, EtOH, THF, then 4 N HCl/AcOEt.

fonamide analogue **9d** resulted in a substantial loss of potency (EC_{50} = 30 nM) for β3 relative to **9c**, and the C_{max} level was not improved. The 3-aniline analogue **9e** showed significantly decreased potency for β3 (EC_{50} = 8.1 nM). The 4-aniline analogue **9f** resulted in slightly decreased β_3-AR activity (EC_{50} = 2.6 nM) relative to **8b**, but **9f** had an improved C_{max} level relative to the phenol analogue **9c**. 4-Hydroxy-3-methylsulfonamide analogue **9g** displayed stronger β3-AR activity but lower C_{max} levels relative to **8b**.

We next investigated the replacement of LHS the 3-chlorophenyl ring with pyridine derivatives. The pyridine analogue **9h** resulted in similar β3-AR activity (EC_{50} = 1.5 nM) relative to **8b** and **8d**. Next, an amino-pyridine derivative was prepared and examined. As a result, compound **9i** had greatly increased β3-AR activity (EC_{50} = 0.19 nM) relative to the corresponding pyridine analogue **9h** and phenyl analogues **8b** and **8d**, respectively. In addition, the pyridine analogue **9h** and the amino-pyridine analogue **9i** showed acceptable C_{max} levels relative to **8b** and **8d** in the cassette dosing assay.

On the basis of these findings, we attempted further optimization of the R^2 substituent of pyridine and amino-pyridine analogues. Both the pyridine analogue **9h** and the amino-pyridine analogue **9i** had reduced lipophilicity (**9h**, *C* log *P* = 1.09; **9i**, *C* log *P* = 0.79) relative to chloro-phenyl **8b** and phenyl **8d** analogues (**8b**, *C* log *P* = 3.30; **8d**, *C*log *P* = 2.58). By analogy to the phenyl ring analogues (**8e**,**f**), the 3-pyridine derivatives with R^2 = isobutyl (**9j**) and O-*c*-hex (**9k**) were prepared, respectively. As predicted, the isobutyl analogue **9j** (EC_{50} = 0.26 nM) and the O-*c*-hex analogue **9k** (EC_{50} = 0.26 nM) exhibited higher potent β3-AR activity and selectivity relative to the O-*iso*-pr analogue **9h**. Furthermore, compounds **9j** and **9k** were evaluated in the cassette dosing assay. It is noteworthy that these more lipophilic compounds (**9j**,**9k**) displayed acceptable C_{max} levels relative to the O-*iso*-pr analogue **9h**. In particular, the O-*c*-hex analogue (**9k**) showed a remarkable improvement of C_{max} level relative to the same O-*c*-hex group analogues **8c** and **8f**. In consideration of the superior PK profile of **9k** (**9k**, *C* log *P* = 2.28) compared with **8c** or **8f** (**8c**, *C* log *P* = 4.49; **8f**, *C* log *P* = 3.73), adjusting the lipophilicity by incorporation of the pyridine ring to the LHS may result in the improved PK profile. Therefore, the pyridine analogue **9k** provided the best combination of high potency and C_{max} level.

Table 1. Effect of Conversion of Left-Hand Side of SGB 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]	β_2/β_3	cassette (po) [c] C_{max} ratio [d]	*C* log *P* [e]
8b	3-Cl	CH	O-*iso*-Pr	1.1 ± 0.1 (0.98)	720 ± 106	654	>10000	>9090	1.0	3.30
8c	3-Cl	CH	O-*c*-Hex	0.46 ± 0.1 (1.0)	55 ± 5	120	NT	NT	0.0	4.49
8d	H	CH	O-*iso*-Pr	2.0 ± 0.06 (0.97)	>1000	>500	>10000	>5000	0.90	2.58
8e	H	CH	*iso*-Bu	0.60 ± 0.12 (0.99)	>1000	>1667	>10000	>16670	0.25	3.09
8f	H	CH	O-*c*-Hex	0.30 ± 0.02 (1.0)	260 ± 45	867	NT	NT	0.0	3.73
9a	4-Cl	CH	O-*iso*-Pr	2.4 ± 0.03 (0.96)	500 ± 40	208	NT	NT	NT	3.30
9b	3-F	CH	O-*iso*-Pr	2.1 ± 0.2 (0.99)	320 ± 38	152	NT	NT	0.61	2.73
9c	3-OH	CH	O-*iso*-Pr	0.062 ± 0.04 (0.99)	440 ± 26	7100	NT	NT	0.10	1.92
9d	3-NHMs	CH	O-*iso*-Pr	30 (0.74)	>1000	>33	NT	NT	0.15	1.39
9e	3-NH_2	CH	O-*iso*-Pr	8.1 ± 0.6 (0.99)	>1000	>123	NT	NT	NT	1.36
9f	4-NH_2	CH	O-*iso*-Pr	2.6 ± 0.3 (0.98)	>1000	>380	NT	NT	0.35	1.36
9g	3-NHMs 4-OH	CH	O-*iso*-Pr	0.26 ± 0.03 (1.0)	150 ± 8.8	577	NT	NT	0.06	0.73
9h	H	N	O-*iso*-Pr	1.5 ± 0.1 (0.97)	>1000	>667	>10000	>6667	0.65	1.09
9i	4-NH_2	N	O-*iso*-Pr	0.19 ± 0.02 (1.0)	130 ± 11	760	>10000	>58800	0.49	0.76
9j	H	N	*iso*-Bu	0.26 ± 0.01 (0.99)	>1000	>3846	NT	NT	0.36	1.71
9k	H	N	O-*c*-Hex	0.26 ± 0.02 (1.0)	480 ± 52	1769	>10000	>38400	0.48	2.28
9l	4-NH_2	N	*iso*-Bu	0.066 ± 0.004 (0.97)	150 ± 5	2300	3200	48480	0.36	1.27
9m	4-NH_2	N	O-*c*-Hex	0.035 ± 0.005 (0.99)	39 ± 0.5	1114	1100	31420	0.09	1.95
ISP [f]				0.97 ± 0.14 (1.0)	0.084 ± 0.02	0.087	2.0 ± 0.9	2.1	NT	

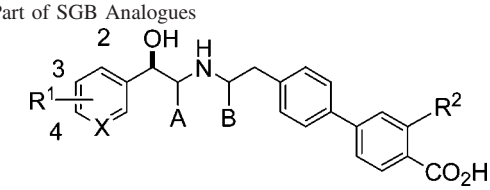
[a] The results are shown as the mean ± SE ($n = 3$) or presented as the average of two experiments. [b] The intrinsic activity (IA) was defined as the ratio between the maximal effect of test compound and the maximal effect produced by isoproterenol. [c] Dose 0.1 mg/kg po ($n = 2-3$). See References section for further details. [d] The ratio was defined between the C_{max} of test compounds and the C_{max} of **1b**. The ratio value of **1b** was presented as 1.0. [e] Biobyte *C* log *P* version 4.3. [f] Isoproterenol. NT: not tested.

On the other hand, the amino-pyridine derivatives with R^2 = isobutyl (**9l**) and O-*c*-hex (**9m**) had greatly increased β3-AR activity (**9l**, $EC_{50} = 0.066$ nM; **9m**, $EC_{50} = 0.035$ nM) relative to the parent pyridine analogues (**9j**,**9k**), respectively. In addition, the isobutyl analogue **9l** maintained C_{max} levels relative to the pyridine analogues and the corresponding O-*iso*-pr analogue **9i**. Compound **9l** showed the best profile of potency, selectivity, and C_{max} level in Table 1. Unfortunately, the most potent amino-pyridine analogue with a O-*c*-hex moiety, **9m**, showed poor C_{max} levels in spite of the moderate *C* log *P* level (**9m**, *C* log $P = 1.95$).

Second, as can be seen in Figure 3, we shifted our attention to modification of biphenyl series **10**, in which substituents were introduced at the α-position of the secondary amino group, such as in compounds **5** and **6** (see Figure 1), to improve β3-AR activity relative to **8b**. From studies on the β3-AR activity of the four optical isomers of **5**[12] and {2-[4-[(2*R*)-2-[[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxy]}acetic acid (BRL-37344),[22] the (*R,R*)-configuration was shown to be important for enhancing β3-AR activity. As can be seen in Table 2, introduction of a methyl group into the α-position of the phenethylamine moiety of our nonsubstituted biphenyl series gave the (*R*)-methyl optical isomer, which exhibited more potent β3-AR activity (**10a**, $EC_{50} = 0.18$ nM) compared with the corresponding (*S*)-methyl isomer (**10b**, $EC_{50} = 6.0$ nM). By analogy to previous SAR studies, introducing at the R^2 position of the terminal phenyl ring on the RHS with an O-*iso*-pr group maintained β3-AR activity (**10c**, $EC_{50} = 0.19$ nM) and improved $\beta3/\beta1$ selectivity (**10c**, $\beta3/\beta1 = 195$) relative to **10a**. The nonsubstituted LHS phenyl ring derivatives with R^2 = H (**10d**), OMe (**10e**), OEt (**10f**), O-*i*-pr (**10g**), O-*i*-butyl (**10h**), and O-*c*-hex (**10i**) were next prepared and examined. Similar to the previous SAR trends, the order of potency at the R^2 position was OMe (**10e**) < H (**10d**), OEt (**10f**) < O-*i*-pr (**10g**) < O-*i*-butyl (**10h**), O-*c*-hex (**10i**) and selectivity for β_1/β_3 was H (**10d**), OMe (**10e**) < OEt (**10f**) < O-*i*-pr (**10g**), O-*c*-hex (**10i**) < O-*i*-butyl (**10h**). On the other hand, in the cassette dosing assay, the order of their C_{max} levels was OMe (**10e**), OEt (**10f**) > O-*i*-pr (**10g**) ≫ O-*i*-butyl (**10h**), O-*c*-hex (**10i**). These results also showed the same trends as previously demonstrated. Furthermore, these compounds (**10f**, **10g**, **10h**, **10i**) were evaluated in the cassette dosing assay (iv) in dogs, and their pharmacokinetic parameters are shown in Table 3. The results indicated that introduction of more lipophilic substitution at the R^2 position increased total clearance (**10f**, OEt < **10g**, O-*i*-pr ≪ **10h**, O-*i*-butyl < **10i**, O-*c*-hex) and decreased oral exposure (AUC) and bioavailability (**10f**, OEt > **10g**, O-*i*-pr ≫ **10h**, O-*i*-butyl, **10i**, O-*c*-hex). Actually, both O-*i*-pr analogue **10g** and O-*c*-hex analogue **10i** are predicted to have good passive permeability as previously reported (based on PAMPA data) and, in liver microsomes, **10g** and **10i** showed good stability to dog and other species in terms of in vitro clearance (see Table 4). These results suggested that the high total clearance of the O-*i*-butyl (**10h**) and O-*c*-hex (**10i**) analogues may be due to a conjugation metabolism and/or elimination, hence these compounds showed poor C_{max} levels and oral exposure. On the other hand, compound **10g** displayed an excellent balance of high β3-AR potency, high selectivity, and good pharmacokinetic profiles.

Furthermore, replacement of the methyl group of **10g** with a dimethyl group (**10j**) resulted in a 10-fold decrease in β3-AR activity. Compound **10k**, having a hydroxy methyl group (*R*-configuration)[23] exhibited significantly decreased potency but improved C_{max} levels in the cassette dosing assay relative to **10g**. The Kissei group have studied a series of 4′-hydroxynorepherine derivatives, such as compound **6** (see Figure 1). In our study, compound **10l** having a 4′-hydroxynorepherine

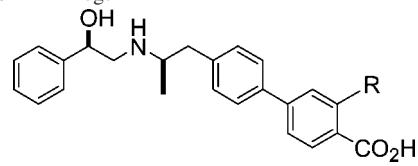
Table 2. Effect of Conversion of the Central Part of SGB Analogues



compd	R^1	X	A	B	R^2	human β_3 EC_{50}, nM [a] (IA^b)	human β_1 EC_{50}, nM [a] (IA^b)	β_1/β_3	human β_2 EC_{50}, nM [a]	β_2/β_3	cassette (po) [c] C_{max} ratio [d]
8b	3-Cl	CH	H	H	O-*iso*-Pr	1.1 ± 0.1 (0.98)	720 ± 106	654	>10000	>9090	1.0
10a	3-Cl	CH	H	Me (*R*)	H	0.18 ± 0.02 (0.96)	13 ± 2	72	NT	NT	NT
10b	3-Cl	CH	H	Me (*S*)	H	6.0 ± 0.4 (0.98)	12 ± 1	2	NT	NT	NT
10c	3-Cl	CH	H	Me (*R*)	O-*iso*-Pr	0.19 ± 0.02 (0.96)	37 ± 2	195	NT	NT	0.80
10d	H	CH	H	Me (*R*)	H	0.30± 0.02 (0.93)	22 ± 2	73	>1000	>3300	NT
10e	H	CH	H	Me (*R*)	O-Me	0.79 ± 0.02 (0.90)	83	105	NT	NT	2.82
10f	H	CH	H	Me (*R*)	O-Et	0.31 ± 0.07 (0.97)	62	200	NT	NT	2.83
10g	H	CH	H	Me (*R*)	O-*iso*-Pr	0.091 ± 0.01 (1.01)	86 ± 7	945	>10000	>10000	0.63
10h	H	CH	H	Me (*R*)	O-*iso*-Bu	0.041 ± 0.001 (0.97)	130 ± 17	3170	NT	NT	0.01
10i	H	CH	H	Me (*R*)	O-*c*-Hex	0.042 ± 0.006 (1.07)	28 ± 7	667	NT	NT	0.00
10j	H	CH	H	Me_2	O-*iso*-Pr	0.91 ± 0.09 (1.0)	280 ± 38	307	NT	NT	0.43
10k	H	CH	H	CH_2OH(*R*)	O-*iso*-Pr	7.4 ± 1 (0.98)	>1000	>135	NT	NT	1.37
10l	4-OH	CH	Me (*S*)	H	O-*iso*-Pr	0.14 ± 0.01 (0.97)	500 ± 9.8	3570	NT	NT	0.04
10m	H	CH	Me (*S*)	H	O-*iso*-Pr	0.81 ± 0.04 (0.97)	780 ± 26	980	>10000	>12300	0.42
10n	H	CH	Me (*S*)	H	O-*n*-Pr	0.43 ± 0.07 (0.98)	690 ± 75	1607	>10000	>23200	0.13
10o	H	CH	Me (*S*)	H	*iso*-Bu	0.14 ± 0.01 (0.98)	300 ± 17	2124	NT	NT	0.16
10p	H	N	H	Me (*R*)	H	0.49 ± 0.005 (0.98)	75 ± 5	153	>1000	>2040	2.3
10q	H	N	H	Me (*R*)	O-*iso*-Pr	0.099 ± 0.002 (1.0)	80 ± 10	808	>1000	>10000	0.58
10r	H	N	H	Me (*R*)	O-*n*-Pr	0.064 ± 0.002 (1.0)	190 ± 15	2930	>1000	>15625	0.29
10s	H	N	H	Me (*R*)	O-*c*-Hex	0.069 ± 0.01 (1.06)	24 ± 4	348	NT	NT	NT

[a] The results are shown as the mean ± SE ($n = 3$). [b] The intrinsic activity (IA) was defined as the ratio between the maximal effect of test compound and the maximal effect produced by isoproterenol. [c] Dose 0.1 or 0.2 mg/kg po ($n = 2-3$). See References section for further details. [d] The ratio was defined between the C_{max} of test compounds and the C_{max} of **8b**. The ratio value of **8b** was presented as 1.0. NT: not tested.

Table 3. Pharmacokinetic Profiles of Compounds **10f−i** in Dogs [a,b]



		po, ($n = 2-3$)	iv, ($n = 2-3$)				
compd	R	AUC_{0-2h} (ng·h/mL)	$T_{1/2\beta}$ (hr)	V_{dss}(L/kg)	AUC_{0-24h} (ng·h/mL)	CL_{tot} (mL/min/kg)	*F* (%)[c]
10f	O-Et	350 ± 60	9.9	1.9	477	3.5	73
10g	O-*iso*-Pr	106	15.5	5.4	260	6.5	41
10h	O-*iso*-Bu	0.2 ± 0.2	17.7 ± 0.9	30.8 ± 3.4	44.5 ± 3.0	39.0 ± 2.4	0.4
10i	O-*c*-Hex	0	0.35	1.13	24.3	68.9	0

[a] Cassette assay data. The results are shown as the mean ± SE ($n = 3$) or presented as the average of two experiments. [b] Dose 0.1 mg/kg. po and iv ($n = 2-3$). [c] *F* = bioavailability.

Table 4. In Vitro Metabolism in Liver Microsomes CL_{int} (mL/min/kg)[a,b]

compd	rat	dog	monkey	human
9l	<2.0	<2.0	3.8	2.2
10g	ND[c]	ND[c]	<1.0	ND[c]
10i	NT	ND[c]	NT	NT

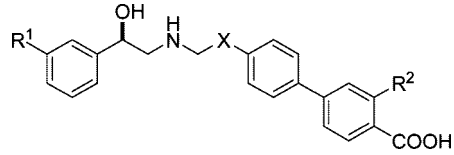
[a] Each compound was incubated at 37 °C with live microsomes from rats, dogs, monkeys and humans in the presence of the NADPH-generating system. [b] The results are presented as the average of two experiments. [c] ND: not determined (<0.1 mL/min/kg). NT: not tested.

unit with the (*S*,*R*)-configuration in the LHS, was prepared and characterized. Compound **10l** showed greatly improved β3-AR activity (ca. 8-fold) relative to the original compound **8b**, while the C_{max} level showed a substantial loss, similar to the phenol analogue **9c** (see Table 1). On the basis of this result, we examined the removal of the hydroxy group of **10l** to improve oral absorption. As expected, compound **10m** showed improvement at the C_{max} level, however, the β3-AR activity of **10m** was decreased by ca. 6-fold relative to **10l**. Analogues **10n** and **10o** containing a O-*n*-pr and isobutyl group at the R^2 position, respectively, showed good β3-AR activity, while their C_{max} levels in the cassette dosing assay were decreased relative to **10m**.

Pyridine derivatives with R^2 = H (**10p**), O-*i*-pr (**10q**), O-*n*-pr (**10r**), and O-*c*-hex (**10s**) were next prepared. The O-*n*-pr analogue (**10r**) provided the best in vitro profile (β3-AR, EC_{50} = 0.064 nM; $\beta3/\beta1$ = 2930, $\beta3/\beta2$ > 15625), and the nonsubstituted analogue **10p** showed decreased potency relative to the 3-chlorophenyl ring analogue **10a**. The O-*c*-hex analogue **10s** showed comparable high potency (EC_{50} = 0.069 nM) but a lower selectivity for $\beta3/\beta1$ relative to **10r**. In the cassette dosing assay, the nonsubstituted analogue **10p** exhibited a significantly higher C_{max} level relative to **10b**, and the O-*n*-pr analogue **10r** showed an acceptable C_{max} level.

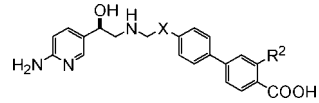
Last, as can be seen in Table 5, we investigated modification of the two carbon linker between the secondary amine and the biphenyl part. The Pfizer group have reported that replacement of the two carbon linker with an ethoxy-based linker in their

Table 5. Effect of Conversion of the Two Carbon Linker of SGB Analogues



compd	R^1	X	R^2	human β_3 EC_{50}, nM [a] (IA[b])	human β_1 EC_{50}, nM [b] (IA[b])	β_1/β_3	cassette (po) [c] C_{max} Ratio [d]
8b	Cl	CH_2	O-*iso*-Pr	1.1 ± 0.1 (0.98)	720 ± 106	654	1.0
11a	Cl	CH_2O	O-*iso*-Pr	0.50 ± 0.02 (0.96)	84 ± 7	168	NT
11b	Cl	CH_2O	O-*n*-Pr	0.21 ± 0.03 (0.99)	120 ± 13	571	2.43
11c	Cl	CH_2O	O-*iso*-Bu	0.32 ± 0.08 (0.98)	110 ± 16	340	NT
11d	Cl	CH_2O	*iso*-Bu	0.68 ± 0.07 (0.99)	15 ± 0.6	22	1.12
11e	Cl	CH_2O	O-*c*-Hex	0.27 ± 0.05 (1.0)	52 ± 6	193	NT
11f	H	CH_2O	O-*iso*-Pr	2.4 (0.95)	510	212	NT
11g	H	CH_2O	O-*n*-Pr	1.2 ± 0.05 (0.98)	210 ± 35	175	NT
11h	H	CH_2O	O-*iso*-Bu	0.55 ± 0.05 (0.99)	400 ± 44	727	0.22
11i	H	CH_2O	O-*c*-Hex	0.16 ± 0.03 (1.1)	91 ± 6	570	NT
11j	Cl	$(CH_2)_2$	O-*n*-Pr	0.7 (1.0)	180	126	NT
11k	Cl	CH_2NH	O-*n*-Pr	0.21 (0.97)	11	52	NT
11l [e]		CH_2O	*iso*-Bu	0.059 ± 0.006 (1.01)	12 ± 0.6	200	0.70

[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 between the maximal effect of test compound and the maximal effect produced by isoproterenol. [c] Dose 0.1 mg/kg po ($n = 2-3$). See References section for further details. [d] The ratio was defined between the C_{max} of test compounds and the C_{max} of **8**. The ratio value of **8b** was presented as 1.0. NT: not tested. [e]



series provided an increase in potency[24] and discovered potent and selective β3-AR agonists such as compound **4** (see Figure 1). This modification was incorporated into the FGB series compound **8b**. The O-*i*-pr analogue **11a** showed an improvement in β3-AR activity, although $\beta3/\beta1$ selectivity was lower relative to **8b**. Furthermore, to improve the in vitro profile of **11a**, the ethoxy-based linker derivatives of R^2 = O-*n*-pr (**11b**), O-*i*-u (**11c**), isobutyl (**11d**), and O-*c*-hex (**11e**) were prepared. Interestingly, the O-*n*-pr analogue **11b** showed much more potent β3-AR activity (EC_{50} = 0.21 nM) and better selectivity ($\beta3/\beta1$ = 571) compared with **11c**, **11d**, and **11e**. These SAR results were different from the previous SAR results for two carbon linker derivatives, suggesting that the O-*n*-pr group (**11b**) had to the most favorable lipophilicity for β3-AR binding affinity. On the other hand, analogues (**11f**−**i**) containing a LHS phenyl ring showed a similar SAR trend to the previous two carbon linker derivatives. Therefore, the O-*c*-hex analogue (**11i**) provided the most potent β3-AR activity (EC_{50} = 0.16 nM). Next, we investigated the effect of incorporation of oxygen into the two carbon linker of pharmacokinetic properties. The O-*n*-pr analogue (**11b**) displayed a significant increase in C_{max} level relative to the lead compound **8b**. Similar to this result, the isobutyl analogue **11d** showed an improved C_{max} level compared with the corresponding isobutyl analogue (**8e** in Table 1) having a two carbon linker. However, the O-isobutyl analogue **11h** showed dramatically decreased C_{max} levels relative to the O-*n*-pr analogue (**11b**). This trend in the PK property for R^2 substituted analogues is similar to the two carbon linker derivatives. We next investigated the replacement of the oxygen atom in **11b** with nitrogen and carbon atoms because the O-*n*-pr analogue **11b** exhibited better potency relative to **8b** (5-fold), good selectivity, and an excellent C_{max} level. Analogue **11j**, having a three carbon linker, showed reduced potency (4.5-fold) and $\beta3/\beta1$ selectivity (2.7-fold) relative to **11b**. The ethylamine-based linker derivative **11k** maintained high potency for the β3-AR relative to **11b** but poor selectivity for $\beta3/\beta1$. On the basis of these results, we attempted to utilize the effect of incorporation of the oxygen in the two carbon linker with the amino-pyridine analogue **9l**. As expected, the amino-pyridine analogue **11l** displayed very high β3-AR potency (EC_{50} = 0.059 nM) and improved C_{max} levels (2-fold) relative to the original compound **9l**, although the $\beta3/\beta1$ selectivity was lower than **9l**.

After SAR examination and study in the cassette dosing assay, we selected **9h**, **9k**, and **9l** in Table 1, **10g**, **10m**, **10p** and **10r** in Table 2 and **11b** and **11l** in Table 5 as potential candidates. Table 6 shows the pharmacokinetic profiles in rats, dogs, and monkeys for the selected compounds.[25] The pyridine analogue with an O-*iso*-pr moiety (**9h**) displayed good to moderate oral bioavailability in all three species (rats, F = 61.5%; dogs, F = 63.2%; monkeys, F = 25.7%) and had a long plasma half-life in dogs ($t_{1/2\beta}$ = 9.9 h). On the other hand, the pyridine analogue with a O-*c*-hex moiety (**9k**), which had higher β3-AR potency, showed good oral bioavailability in dogs (F = 60%) and rats (F = 82.5%). The amino-pyridine analogue with an isobutyl moiety (**9l**) showed good to moderate oral bioavailability in dogs and monkeys (dogs, F = 27%; monkeys, F = 48.6%) and had a long plasma half-life in dogs ($t_{1/2\beta}$ = 7.6 h). Next, both phenyl analogues **10g** and **10m**, having a methyl group at the α-position of the phenethylamine moiety, exhibited good oral bioavailability in all three species (**10g**: F = 69.7% in rats, F = 79.6% in dogs, F = 52.8% in monkeys; **10m**: F = 100% in rats, F = 63.9% in dogs, F = 88.2% in monkeys) and had a long plasma half-life (**10g**: $t_{1/2\beta}$ = 14.3 h in dogs; **10m**: $t_{1/2\beta}$ = 14.3 h in dogs, $t_{1/2\beta}$ = 29 h in monkeys). Pyridine analogue **10p** exhibited good to moderate oral bioavailability in rats and dogs (rats, F = 25.2%; dogs, F = 59.7%) and had a moderate plasma half-life in dogs ($t_{1/2\beta}$ = 6.4 h). A similar pyridine analogue with an O-*iso*-pr moiety (**10r**) also showed good oral bioavailability in dogs (F = 55%) and monkeys (F = 57%). Last, the ethoxy-

Table 6. Pharmacokinetic Profiles of Selected Members of the SGB Series [a]

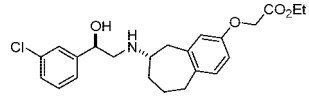
			po ($n = 3$)		iv ($n = 2-3$)		
compd	species	dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	$T_{1/2\beta}$ (hr)	CL_{tot} (mL/min/kg)	F (%) [b]
9h	rat	1.0	171.9 ± 5.7	548.2 ± 5.7	3.5 ± 1	16.0 ± 0.6	61.5
	dog	0.32	27.0 ± 4.5	461.3 ± 85.7	9.9 ± 1	6.4 ± 0.5	63.2
	monkey[c]	0.27	11.0 ± 1.0	77.5 ± 26.0	2.2	22.8	25.7
9k	rat [c]	0.26	72.4 ± 12.7	245.1 ± 27.4	3.3	15.8	82.5
	dog	0.32	11.4 ± 6.4	58.1 ± 10.3	*d*	47.7 ± 3.3	60.0
	monkey[c]	0.28	18.6 ± 2.5	153.3 ± 48.3	10.3	3.4	10.7
9l	rat	1.0	21.9 ± 0.5	208.0 ± 40.8	1.9 ± 0.7	8.5 ± 0.3	12.4
	dog	0.32	49.1 ± 1.8	177.2 ± 70.1	7.6 ± 2	7.9 ± 1	27.0
	monkey[c]	0.32	12.4 ± 6.2	90.8 ± 25.4	5.9	24.3	48.6
10g	rat[c]	1.0	116.5 ± 5.9	1640 ± 131	*d*	7.2	69.7
	dog	0.1	8.5 ± 0.81	162.1 ± 21.3	14.3 ± 2.9	7.83 ± 1.2	79.6
	monkey[c]	0.32	128.3 ± 45.9	1304.7 ± 345.4	*d*	1.8 ± 0.3	52.8
10m	rat[c]	0.34	125.1 ± 14.1	879.7 ± 41.9	8.2	6.8	100
	dog	0.1	7.4 ± 0.1	134.3 ± 0.8	14.3 ± 0.6	7.3 ± 0.6	63.9
	monkey[c]	0.32	178.2 ± 31.7	1803.1 ± 236.6	29.0 ± 1.0	2.5 ± 0.2	88.2
10p	rat	1.0	22.0 ± 5.8	102.9 ± 4.5	1.91	34.3	25.2
	dog	0.1	30.5 ± 5.5	206.8 ± 72.3	6.4 ± 0.3	4.4 ± 0.5	59.7
10r	dog	0.1	3.0 ± 0.5	35.5 ± 5.4	*d*	24.3 ± 2.1	54.9
	monkey[c]	0.30	8.2 ± 2.3	65.2 ± 14.9	*d*	47.0	57.2
11b	dog[c]	0.1	40.6 ± 1.8	419.7 ± 14.5	10.9	2.9	69.7
11l	dog [c]	0.1	11.6 ± 2.9	38.2 ± 8.6	9.5	14.2	34.8

[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] Not calculated.

Table 7. Inhibitory Effect on Intraduodenal Administration of Selected Compounds and **62** (FK175)[f], **8d** on Increase in IVP (Intravesical Pressure), Induced by Carbachol in Anesthetized Dogs [a]

	in vitro		in vivo			
compd	human β_3 EC_{50}, nM (IA^b)	dog β_3 EC_{50}, nM (IA^b)	ED_{50} (μg/kg)	EC_{50} (nM)	dog serum protein binding	C log P[e]
62	16 ± 2.0 (0.98)[c,d]	30 ± 9.0 (0.91) [c,d]	270 ± 12	352 ± 16 [c]	94% [c]	
8d	2.0 ± 0.06 (0.97)	2.9 ± 0.4 (0.97)	25.9 ± 4.6	20 ± 4	86%	2.58
9h	1.5 ± 0.1 (0.97)	11 ± 0.8 (0.87)	28.4 ± 9.1	7.8 ± 0.8	77%	1.09
9k	0.26 ± 0.02 (1.0)	1.3 ± 0.2 (0.94)	65.0 ± 32	4.0 ± 0.5	90%	2.28
9l	0.066 ± 0.004 (0.97)	3.2 ± 0.4 (1.0)	16.1 ± 9.5	1.8 ± 1	80%	1.27
10g	0.091 ± 0.01 (1.01)	0.19 ± 0.04 (1.07)	3.5 ± 1	2.5 ± 0.3	86%	2.89
10m	0.81 ± 0.04 (0.97)	3.7 ± 0.8 (0.89)	20.0 ± 12	9.5 ± 2	86%	2.89
10r	0.064 ± 0.002 (1.0)	0.51 ± 0.09 (1.03)	4.80 ± 2.5	0.28 ± 0.05	82%	1.62

[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 between the maximal effect of test compound and the maximal effect produced by isoproterenol. [c] Data for the carboxylic acid form of **62**. [d] Results are the mean ± SE of five experiments. [e] Biobyte C log P ver 4.3. [f]



based linker analogue **11b** displayed good oral bioavailability in dogs ($F = 70\%$) as well as a long plasma half-life ($t_{1/2\beta} =$ 10 h) and low clearance. Compound **11l** had an improved PK profile in dogs ($F = 38\%$, $t_{1/2\beta} = 9.5$ h) relative to the corresponding amino-pyridine analogue **9l**.

Next, we examined the inhibitory effect of selected compounds (**9h**,**k**,**l**, **10g**,**m**,**r**) on carbachol-induced increase of intravesical pressure (IVP) in anesthetized dogs as an OAB model, and which has been previously described,[20] in comparison with the effects of our previous clinical compound **62** and FBG analogue **8d**. Before conducting in vivo experiments, we confirmed the in vitro potency of these selected compounds for not only human β3-AR activity but also dog β3-AR activity in CHO cell lines, as shown in Table 7.[20] In general, SBG analogues have some species differences between human and dog β3-AR activity, except for **10g**, and the EC_{50} values for dog β3-AR activity of all the selected compounds showed much less potency relative to human β3-AR activity. Compounds **10g** and **10r**, having a methyl group, showed more potent dog β_3-AR activity relative to **8d**. Compounds **9k**, **9l**, and **10m** showed the same potency level, and compound **9h** showed less potent dog β_3-AR activity relative to **8d**. In the in vivo experiment,

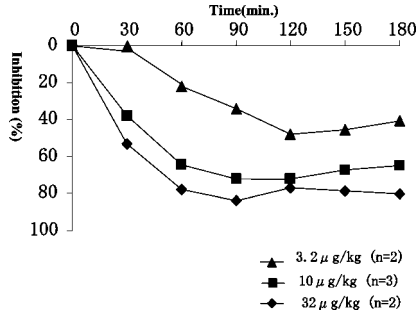


Figure 4. Time course of inhibitory effect of intraduodenal administration of **10g** on increase in IVP (intravesical pressure) induced by carbachol in anesthetized dogs. The results are presented as the average of two or three experiments.

Intraduodenally (i.d.) administered selected compounds inhibited the IVP increase in a dose-dependent manner with the ED_{50} and EC_{50} values listed in Table 7, respectively. Phenyl analogues with a methyl group (**10g**) and (**10m**) possessed the same level of lipophilicity (**10g**, **10m**: *C* log *P* = 2.89) and protein binding (PB) in dog (**10g**, **10m**: PB = 86%) compared to **8d** (**8d**: *C* log *P* = 2.58, PB = 86%). Compound **10g** resulted in a 7−8-fold improvement in the in vivo EC_{50} values (**10g**: EC_{50} = 2.5 nM) due to the improvement of the in vitro dog β3-AR potency compared to **8d** (EC_{50} = 20 nM). As shown in Figure 4, intraduodenally administered **10g**, which provided the best ED_{50} of the selected compounds, inhibited the IVP increase in a dose-dependent manner with a long duration of action. On the other hand, compound **10m** resulted in a 2-fold improvement in in vivo EC_{50} value (**10m**: EC_{50} = 9.5 nM), in spite of the same potency level for in vitro dog β3-AR activity, relative to **8d**. Similarly, the 3-pyridine and amino-pyridine analogues (**9h**, **9k**, **9l**), having comparable or less potency for in vitro dog β3-AR activity, resulted in a 2.4−10-fold improvement in the in vivo EC_{50} values compared to phenyl analogue **8d**. Furthermore, the 3-pyridyl analogue **10r** with a methyl group, which showed 2.6-fold less potency for in vitro dog β3-AR activity compared to the phenyl analogue with a methyl group **10g**, was the most potent of the selected compounds and showed more than 8 times better in vivo activity (**10r**, EC_{50} = 0.28 nM) relative to **10g** (EC_{50} = 2.5 nM). These results suggested that the improvement in the in vivo EC_{50} with pyridine or amino-pyridine ring analogues relative to phenyl ring analogues (compare **9h**, **9k**, **9l** vs **8d**, and **10r** vs **10g**) may be due to not only lower protein binding but also improvement in the pharmacokinetic properties for the in vivo efficacy. We will describe the correlation of in vitro and in vivo activity for designing efficacious compounds in the near future.

Conclusions

First, in this study, replacement of the 3-chlorophenyl moiety in the LHS of FGB analogues with 3-pyridine afforded compound (**9k**), having an O-*c*-hex group in the RHS, with not only highly potency (EC_{50} = 0.26 nM) and selectivity but also good oral bioavailability in both dogs (*F* = 60%) and rats (*F* = 82.5%), without loss of oral bioavailability, such as with **8c** and **8f** (see Table 1). In addition, amino-pyridine analogues resulted in increased potency relative to pyridine analogues, and in particular, the isobutyl analogue **9l** showed highly potent β3-AR activity (EC_{50} = 0.066 nM) and displayed moderate to good oral bioavailability in dogs (*F* = 27%) and monkeys (*F* = 48.6%). It is interesting note that adjusting the lipophilicity by incorporation of the pyridine/amino pyridine moiety to the LHS may result in the improved pharmacokinetic properties. Furthermore, in a carbachol-induced IVP model in dogs, these pyridine and amino-pyridine analogues **9h**, **9k**, **9l** resulted in improved in vivo EC_{50} values relative to FGB phenyl analogue **8d**, probably due to both lower serum protein binding and improvement of pharmacokinetic properties for the in vivo efficacy.

Next, we investigated the effect of substituents on the position adjacent to the secondary amino group and discovered that introduction of a methyl group (*R*-configuration) into the α-position of the phenethylamine moiety greatly enhanced potency while keeping good oral availability. Amang these analogues, compounds **10g** and **10r** provided an excellent balance of high potency for human β3-AR (**10g**, EC_{50} = 0.091nM; **10r**, EC_{50} = 0.069nM), selectivity, and good oral bioavailability (*F* > 50% in two or three species). Further, in vivo, these two compounds resulted in 5−7-fold improved ED_{50} values compared to FBG analogue **8d**. In particular, compound **10r**, having a combination of a methyl group at the α-position and a pyridine ring in the LHS, resulted in a greater than 70-fold increase in vivo EC_{50} value relative to the FBG analogue **8d**.

Lastly, the replacement of the two carbon linker with an ethoxy-based linker provided improved potency and PK profiles. The O-*n*-pr analogue **11b** exhibited good potency (EC_{50} = 0.21 nM) and an excellent PK profile in dogs (*F* = 70%, $t_{1/2\beta}$ = 10.9 h). This modification was incorporated into amino-pyridine analogue **9l**. As a result, compound **11l** maintained high potency (EC_{50} = 0.059 nM) and an improved PK profile in dogs (*F* = 38%, $t_{1/2\beta}$ = 9.5 h).

Although our SGB compounds (**9h**, **9k**, **9l**, **10g**, **10m**, **10p**, **10r**, **11b**, and **11l**) were all of potential interest as possible drug candidates, the pyridine and amino pyridine analogues **9h**, **9l**, and **10r** were of particular interest because of extremely improved in vivo efficacy compared to the FGB compound **8d** and **62**, and phenyl analogue **10g** was of particular interest because of its high human β3-AR potency, selectivity, and excellent PK profiles in three species. Therefore, these SGB compounds may be attractive as new successful therapeutic candidates for the treatment of OAB.[26]

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: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded with Micromass LCT. Chemical pPurity 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, were within 0.4% of the theoretical values calculated for C, H, and N unless otherwise noted.

4′-(2-{[(2*R*)-2-(4-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (9a). Compound **9a** was synthesized from **28** and **53b** according to the procedure D (71%). NMR (200 MHz, DMSO-d_6) δ: 1.29 (6H, t, *J* = 6.0 Hz), 2.9−3.4 (6H, m), 4.84 (1H, m), 4.9−5.1 (1H, m), 6.30 (1H, m), 7.1−7.8 (11H, m). MS (ES) *m*/*e*: 454 (M + H). Anal. ($C_{26}H_{28}Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.5H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Fluorophenyl)-2-hydroxyethyl]amino}ethyl)-3-isopropoxy-1,1′-biphenyl-4-carboxylic acid hydrochloride (9b). Compound **9b** was synthesized from **29** and **53b** according to the procedure D (54%). NMR (200 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.0 Hz), 2.9−3.4 (6H, m), 4.81 (1H, m), 4.9−5.1 (1H, m), 6.22(1H, m), 7.1−7.8 (11H, m). MS (ES) *m/e*: 438 (M + H). Anal. ($C_{26}H_{28}F_1N_1O_4 \cdot 1.0HCl \cdot 0.5H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-(3-hydroxyphenyl)ethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (9c). Compound **30** and **53b** were reacted according to the typical Suzuki coupling procedure (procedure D) to give methyl 4′-{2-[{(2*R*)-2-[3-(benzyloxy)phenyl]-2-hydroxyethyl}(*tert*-butoxycarbonyl)amino]ethyl}-3-isobutylbiphenyl-4-carboxylate (72%). MS (ES) *m/e*: 660 (M + Na).

The product was subjected to the hydrogenation procedure used to supply compound **9g** to give phenol product. **9c** was synthesized from the phenol product according to the hydrolysis, followed by deprotection procedure used typical procedure D (48%). NMR (200 MHz, DMSO-d_6) δ: 1.26 (6H, d, J = 5.9 Hz), 2.8−3.5 (6H, m), 4.76 (1H, m), 4.94(1H, m), 6.15 (1H, m), 6.6−7.8 (11H, m). MS (ES) *m/e*: 436 (M + H). Anal. ($C_{26}H_{29}N_1O_5 \cdot 1.0HCl \cdot 1.8H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Methansulfonylaminophenyl)-2-hydroxyethyl]-amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid dihydrochloride (9d). Methyl 4′-(2-{[(2*R*)-2-(3-aminophenyl)-2-hydroxyethyl](*tert*-butoxycarbonyl)amino}ethyl)-3-isopropoxybiphenyl-4-carboxylate and MsCl were reacted according to the procedure used to supply intermediate **56**, followed by hydrolysis and deprotection procedure used typical procedure D to give **9d** (55%). NMR (200 MHz, DMSO-d_6) δ: 1.25 (6H, d, J = 5.9 Hz), 2.8−3.5 (6H, m), 4.89 (1H, m), 4.94 (1H, m), 6.15 (1H, m), 7.0−7.8 (11H, m). MS (ES) *m/e*: 513 (M + H). Anal. ($C_{27}H_{32}N_2O_6 \cdot 1.0HCl \cdot 3.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Aminophenyl)-2-hydroxyethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid dihydrochloride (9e). Compound **31** and **53b** were reacted according to the typical Suzuki coupling procedure (procedure D), followed by reduction procedure used for **55** to give methyl 4′-(2-{[(2*R*)-2-(3-aminophenyl)-2-hydroxyethyl](*tert*-butoxycarbonyl)amino}ethyl)-3-isopropoxybiphenyl-4-carboxylate (69%). MS (ES) *m/e*: 549 (M + H).

Compound **9e** was synthesized from the aniline product according to the hydrolysis, followed by deprotection procedure used typical procedure D (62%). NMR (200 MHz, DMSO-d_6) δ: 1.26 (6H, d, J = 5.9 Hz), 2.8−3.5 (6H, m), 4.82 (1H, m), 5.02 (1H, m), 6.15 (1H, m), 7.2−7.8 (11H, m). MS (ES) *m/e*: 435 (M + H). Anal. ($C_{26}H_{30}N_2O_4 \cdot 2.0HCl \cdot 1.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(4-Aminophenyl)-2-hydroxyethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid dihydrochloride (9f). Compound **9f** was synthesized from **32** according to the procedure described for the conversion of **31** to **9e** (42%). NMR (200 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.0 Hz), 3.0−3.3 (6H, m), 4.82 (1H, m), 5.02 (1H, m), 7.1−7.5 (8H, m), 7.6−7.9 (3H, m), 8.9 (1H, m), 9.2 (1H, m). MS (ES) *m/e*: 435 (M + H). Anal. ($C_{26}H_{30}N_2O_4 \cdot 2.0HCl \cdot 1.0H_2O$) C, H, N.

4′-{2-[((2*R*)-2-Hydroxy-2-{4-hydroxy-3-[(methylsulfonyl)amino]-phenyl}ethyl)amino]ethyl}-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (9g). To a solution of **56** (200 mg, 0.31 mmol) and benzoic acid **58** (120 mg, 0.39 mmol) in 1,2-dimethoxyethane (4 mL) were added $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and aqueous solution of Na_2CO_3 (2M, 0.68 mL), and the mixture was stirred at 70 °C for 10 h under nitrogen. The mixture was poured into 1 N aqueous HCl solution and EtOAc, added active carbon, and stirred for 2 h. The mixture was filtered and partitioned. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/3) to give a biphenyl product. A suspension of the product in MeOH (6 mL) was hydrogenated over palladium on carbon (10% w/w, 50% wet, 50 mg) under hydrogen atmosphere for 40 min, and the catalyst was filtered off. To the filtrate was added 4 N HCl in EtOAc (40 μL) and evaporated to give 62 mg (22.7%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.0 Hz), 2.95 (3H, s), 2.83−3.34 (6H, m), 4.76−4.88 (2H, m), 6.11 (1H, m), 6.92 (1H, d, J = 6.0 Hz), 7.07 (1H, dd, J = 1.7, 8.4 Hz), 7.25−7.39 (5H, m), 7.68−7.72 (3H, m), 8.81 (1H, br), 10.03 (1H, br). MS (ES) *m/e*: 527 (M-H). Anal. ($C_{27}H_{32}N_2O_7S_1 \cdot 1.0HCl \cdot 2.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-(3-pyridinyl)ethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid dihydrochloride (9h). Compound **9h** was synthesized from **17** and **53b** according to the procedure D (40%). NMR (200 MHz, DMSO-d_6) δ: 1.29 (6H, d, J = 6.0 Hz), 2.9−3.4 (6H, m), 4.84 (1H, m), 4.9−5.1(1H, m), 7.2−7.5 (4H, m), 7.6−7.9 (4H, m), 8.2−8.5 (1H, m), 8.7−8.9 (2H, m), 9.0−9.4 (2H, m). MS (ES) *m/e*: 421 (M + H). Anal. ($C_{25}H_{28}N_2O_4 \cdot 2.0HCl \cdot 0.2H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(6-Amino-3-pyridinyl)-2-hydroxyethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid dihydrochloride (9i). Compound **9i** was synthesized from **43** and **53b** according to the procedure G (25%). HPLC purity: 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.2 Hz), 3.02−3.26 (6H, m), 4.82 (1H, heptuplet, J = 6,.2 Hz), 4.98 (1H, br), 6.44 (1H, br), 7.03 (1H, d, J = 9.5 Hz), 7.27 (1H, dd, J = 1.5, 8.1 Hz), 7.32 (1H, d, J = 1.5 Hz), 7.38 (2H, d, J = 8.4 Hz), 7.70 (1H, d, J = 8.1 Hz), 7.71 (2H, d, J = 8.4 Hz), 7.93−7.96 (2H, m), 8.11 (2H, br), 9.07 (1H, br), 9.22 (1H, br), 12.5 (1H, br), 14.0 (1H, br). MS (ES) *m/e*: 434 (M − H). HRMS (M + H)$^+$: found 436.2232; calcd for $C_{25}H_{29}N_3O_3$ 436.2236.

4′-(2-{[(2*R*)-2-Hydroxy-2-(3-pyridinyl)ethyl]amino}ethyl)-3-isobutyl-4-biphenylcarboxylic acid dihydrochloride (9j). Compound **9j** was synthesized from **17** and **53e** according to the procedure D (37%). NMR (200 MHz, DMSO-d_6) δ: 0.88 (6H, d, J = 6.53 Hz), 1.73−1.97 (1H, m), 2.99−3.52 (6H, m), 5.24−5.38 (1H, m), 7.39 (2H, d, J = 8.03 Hz), 7.49−7.62 (2H, m), 7.70 (2H, d, J = 8.03 Hz), 7.87 (1H, d, J = 8.53 Hz), 7.93−8.05 (1H, m), 8.50 (1H, d, J = 8.53 Hz), 8.79−8.96 (2H, m). MS (ES) *m/e*: 417 (M − H). Anal. ($C_{26}H_{30}N_2O_3 \cdot 2.0HCl \cdot 0.5H_2O$) C, H, N.

3-(Cyclohexyloxy)-4′-(2-{[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]amino}-ethyl)-4-biphenylcarboxylic acid dihydrochloride (9k). Typical Procedure D. To a solution of **17** (1.3 g, 3.08 mol) in 1,2-dimethoxyethane (20 mL) were added boronic acid **53f** (0.95 g, 3.41 mol), $Pd(PPh_3)_4$ (210 mg, 0.18 mmol), and aqueous solution of Na_2CO_3 (2 M, 3.4 mL), and the mixture was stirred at 70 °C for 5 h under nitrogen. The mixture was diluted with 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 (hexane/EtOAc = 1/1−1/4) to give 1.12 g (63%) of methyl 4′-(2-{(*tert*-butoxycarbonyl)[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]amino}ethyl)-3-(cyclohexyloxy)-4-biphenylcarboxylate as pale-yellow foam. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.17−1.98 (10H, m), 1.27 (9H, s), 2.65−2.81 (2H, m), 3.1−3.55 (4H, m), 3.79 (3H, s), 4.6−4.85 (2H, m), 5.61−5.68 (1H, m), 7.22−7.72 (9H, m), 8.44−8.49 (2H, m). MS (ESI): 575 (M + H).

To a solution of the product (750 mg, 1.3 mmol) in MeOH (7.5 mL) and THF (3.5 mL) was added 1 N aqueous NaOH (3.9 mL, 3.0 equiv), and the mixture was stirred at room temperature for 16 h. The solvent was removed by evaporation, and the aqueous solution was neutralized with 1 N aqueous HCl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a benzoic acid product. To a solution of the product in EtOAc (7.0 mL) was added 4 N HCl in EtOAc (7 mL), and the mixture was stirred at room temperature for 12 h. The resultant solid was collected by filtration and dried to give 574 mg (81%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 1.0−2.0 (10H, m), 2.9−3.4 (6H, m), 4.65 (1H, m), 5.02−5.31 (1H, m), 7.22−7.50 (4H, m), 8.4−8.6 (1H, m), 8.7−8.9 (2H, m). 9.0−9.4 (2H, m). MS (ES) *m/e*: 461 (M − H). Anal. ($C_{28}H_{32}N_2O_4 \cdot 2.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(6-Amino-3-pyridinyl)-2-hydroxyethyl]amino}ethyl)-3-isobutyl-4-biphenylcarboxylic acid dihydrochloride (9l). Typical Procedure G. A mixture of bromide **43** (400 mg, 0.675 mol), boronic acid **53e** (191 mg, 0.81 mol), $PdCl_2(dppf) \cdot CHCl_3$ (1:1, 82 mg, 0.10

mmol), dppf (56 mg, 0.10 mmol), DMF (8 mL), and 2 N sodium carbonate solution (1.0 mL) was stirred at 80 °C for 3 h. After cooling to room temperature, the mixture was quenched by the addition of water and extracted with EtOAc. The combined extracts were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to give 351 mg (74%) of methyl 4′-(2-{[(2*R*)-2-[6-(acetylamino)-3-pyridinyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl](*tert*-butoxycarbonyl)amino}ethyl)-3-isobutyl-4-biphenylcarboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ: −0.14 (3H, s), −0.01 (3H, s), 0.81 (9H, s), 0.87 (6H, d, J = 6.6 Hz), 1.30 (9H, brs), 1.82(1H, m), 2.01 (s, 3H), 2.7−2.9 (4H, m), 3.2−3.4 (4H, m), 4.9−5.0 (1H, m), 7.1 −8.22 (10H, m), 10.5 (1H, s). MS (ES) *m/e*: 704 (M + H).

To a solution of the product (345 mg, 0.490 mmol) in EtOH (3.45 mL) was added 1 N aqueous NaOH solution (4.9 mL, 4.90 mmol) and the mixture was stirred at 100 °C for 24 h. After cooling to room temperature, the mixture was quenched by the addition of 1 N aqueous HCl solution (4.9 mL, 4.9 mmol) and the solvent was removed by evaporation. To the residual brown solid were added 4 N HCl in dioxane (4 mL) and MeOH (1 mL) and the mixture was stirred at room temperature for 6.5 h. The solvent was removed by evaporation and the residual brown solid was chromatographed on ODS column (eluent: water/methanol = 100/0, 90/10, 80/20, 70/30, 60/40, 50/50, and 40/60). The fractions containing the target compound were acidified by 1 N HCl (1 mL) and concentrated in vacuo to give the title compound (103 mg, 42%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (6H, d, J = 6.6 Hz), 1.85 (1H, heptuplet, J = 6.6 Hz), 2.91 (2H, d, J = 6.6 Hz), 3.04−3.22 (6H, m), 4.98 (1H, d, J = 7.3 Hz), 6.45 (1H, br), 7.03 (1H, d, J = 9.9 Hz), 7.38 (2H, d, J = 8.1 Hz), 7.52 (1H, s), 7.58 (1H, dd, J = 1.8, 8.1 Hz), 7.70 (2H, d, J = 8.1 Hz), 7.87 (1H, d, J = 8.1 Hz), 7.93−7.98 (2H, m), 8.14 (2H, br), 9.07 (1H, br), 9.21 (1H, br), 12.8 (1H, br), 14.0 (1H, br). MS (ES) *m/e*: 432 (M − H). Anal. ($C_{26}H_{31}N_3O_3\cdot 2.0HCl\cdot 2.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(6-Amino-3-pyridinyl)-2-hydroxyethyl]amino}ethyl)-3-(cyclohexyloxy)-4-biphenylcarboxylic acid (9m). Compound **9m** was synthesized from **43** and **53f** according to the procedure G. The crude product **9m** (187 mg, 0.393 mmol) was dissolved in 4 N HCl in dioxane (3 mL) and the solution was stirred at room temperature for 14 h. The solvent was concentrated in vacuo and the residual solid was dissolved in water (5 mL) and treated with activated carbon. The mixture was filtered and the filtrate was adjusted to pH 7 by the addition of 1 N aqueous NaOH solution. The precipitates were collected by filtration, washed with water, and dried under reduced pressure at 50 °C to give the title compound (103 mg, 46%) as a off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.28−1.61 (6H, m), 1.69−1.78 (2H, m), 1.82−1.91 (2H, m), 2.72−2.98 (6H, m), 4.52−4.65 (2H, m), 5.82 (2H, brs), 6.41 (1H, d, J = 8.1 Hz), 7.21−7.38 (5H, m), 7.61−7.66 (3H, m), 7.85 (1H, br). MS (ES) *m/e*: 474 (M − H). Anal. ($C_{28}H_{33}N_3O_4\cdot 2.0H_2O$) C, H, N.

4′-[(2*R*)-2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl]-4-biphenylcarboxylic acid hydrochloride (10a). Compound **10a** was synthesized from **38** and **53a** according to the procedure D (65%). NMR (400 MHz, DMSO-d_6) δ: 0.88 (3H, d, J = 6.5 Hz), 2.7−2.8 (1H, m), 3.1−3.4 (3H, m), 3.53 (1H, m), 5.05 (1H, m), 6.37 (1H, m), 7.37−7.47 (6H, m), 7.73 (2H, d, J = 8.3 Hz), 7.79−7.82 (2H, m), 8.00−8.03 (2H, m), 8.81 (1H, br s), 9.18 (1H, br s), 12.9 (1H, br s). MS (ES) *m/e*: 410 (M + H). Anal. ($C_{24}H_{24}Cl_1N_1O_3\cdot 1.0HCl\cdot 0.5H_2O$) C, H, N.

4′-[(2*S*)-2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl]-4-biphenylcarboxylic acid hydrochloride (10b). Compound **10b** was prepared from (2*R*)-2-amino-3-phenyl-1-propanol according to the same procedures described for the conversion of (2*S*)-2-amino-3-phenyl-1-propanol **47** to **10a**. NMR (400 MHz, DMSO-d_6) δ: 1.17 (3H, d, J = 6.5 Hz), 2.7−2.8 (1H, m), 3.1−3.3 (2H, m), 3.27 (1H, m), 3.50 (1H, m), 5.01 (1H, m), 6.36 (1H, m), 7.32−7.46 (6H, m), 7.72 (2H, d, J = 8.3 Hz), 7.77−7.81 (2H, m), 8.00−8.03 (2H, m), 8.95 (1H, br s), 9.11 (1H, br s), 12.9 (1H, br s). MS (ES) *m/e*: 410 (M + H). Anal. ($C_{24}H_{24}Cl_1N_1O_3\cdot 1.0HCl\cdot 0.5H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (10c). Compound **10c** was synthesized from **38** and **53b** according to the procedure D (71%). NMR (200 MHz, DMSO-d_6) δ: 1.14 (3H, d, J = 6.4 Hz), 1.30 (6H, d, J = 5.8 Hz), 2.8−3.8 (5H, m), 4.6−4.9 (1H, m), 5.0−5.3 (1H, m), 6.2−6.4 (1H, m), 7.2−7.8 (11H, m), 8.82 (1H, br.s), 9.24 (1H, br.s). MS (ES) *m/e*: 468 (M + H). HRMS (M + H)$^+$: found 468.1949; calcd for $C_{27}H_{30}Cl_1N_1O_4$ 468.1942. Anal. ($C_{27}H_{30}Cl_1N_1O_4\cdot 1.0HCl\cdot 1.5H_2O$) C, H, N.

4′-[(2*R*)-2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}propyl]biphenyl-4-carboxylic acid hydrochloride (10d). Compound **10d** was synthesized from **39** and **53a** according to the procedure D (67%). NMR (400 MHz, DMSO-d_6) δ: 1.15 (3H, d, J = 6.5 Hz), 2.6−2.8 (1H, m), 3.0−3.3 (3H, m), 3.54 (1H, m), 5.00 (1H, m), 6.22 (1H, m), 7.32−7.46 (7H, m), 7.73 (2H, d, J = 8.0 Hz), 7.80 (2H, d, J = 8.0 Hz), 8.00−8.03 (2H, m), 8.77 (1H, br s), 9.02 (1H, br s), 12.9 (1H, br s). MS (ES) *m/e*: 374 (M − H). Anal. ($C_{24}H_{25}N_1O_3\cdot 1.0HCl\cdot 0.5H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Phenyl-2-hydroxyethyl]amino}propyl)-3-methoxy-1,1′-biphenyl-4-carboxylic acid hydrochloride (10e). Compound **10e** was synthesized from **39** and **53g** according to the procedure D (69%). NMR (200 MHz, DMSO-d_6) δ: 1.15 (3H, d, J = 6.4 Hz), 2.8−3.8 (5H, m), 3.92 (3H, s), 5.0−5.2 (1H, m), 6.3−6.4 (1H, m), 7.2−7.6 (9H, m), 7.7−7.9 (3H, m), 8.81 (1H, br.s), 9.31 (1H, br.s). MS (ES) *m/e*: 406 (M + H). Anal. ($C_{25}H_{27}N_1O_4\cdot 1.0HCl\cdot 0.5H_2O$) C, H, N.

3-Ethoxy-4′-[(2*R*)-2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}propyl]-biphenyl-4-carboxylic acid hydrochloride (10f). Compound **10f** was synthesized from **39** and **53h** according to the procedure D (75%). NMR (200 MHz, DMSO-d_6) δ: 1.15 (3H, d, J = 6.4 Hz), 1.36 (3H, t, J = 7.0 Hz), 2.6−3.2 (5H, m), 4.21 (2H, q, J = 7.0 Hz), 4.9−5.1 (1H, m), 6.23 (1H, m), 7.2−7.7 (11H, m). MS (ES) *m/e*: 418 (M − H). Anal. ($C_{26}H_{29}N_1O_4\cdot 1.0HCl\cdot 0.8\ H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}propyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (10g). Compound **10g** was synthesized from **39** and **53b** according to the procedure D (59%). NMR (200 MHz, DMSO-d_6) δ: 1.12 (3H, d, J = 6.4 Hz), 1.30 (6H, d, J = 5.8 Hz), 2.8−3.8 (5H, m), 4.6−4.9 (1H, m), 5.0−5.3 (1H, m), 6.2−6.4 (1H, m), 7.2−7.8 (12H, m), 8.82 (1H, br.s). MS (ES) *m/e*: 434 (M + H). Anal. ($C_{27}H_{31}N_1O_4\cdot 1.0HCl$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}propyl)-3-isobutoxy-4-biphenylcarboxylic acid hydrochloride (10h). Compound **10h** was synthesized from **39** and **53d** according to the procedure D (59%). NMR (200 MHz, DMSO-d_6) δ: 1.03 (6H, t, J = 6.2 Hz), 1.16 (3H, d, J = 6.4 Hz), 1.8−2.2 (1H, m), 2.6−3.2 (5H, m), 3.93 (2H, d, J = 6.2 Hz), 4.9−5.1 (1H, m), 6.23 (1H, m), 7.2−7.7 (11H, m). MS (ES) *m/e*: 448 (M + H). Anal. ($C_{28}H_{33}N_1O_4\cdot 1.0HCl\cdot 0.5H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Phenyl-2-hydroxyethyl]amino}propyl)-3-cyclohexyloxy-1,1′-biphenyl-4-carboxylic acid hydrochloride (10i). Compound **10i** was synthesized from **39** and **53f** according to the procedure D (55%). NMR (200 MHz, DMSO-d_6) δ: 1.14 (3H, d, J = 6.4 Hz), 1.2−2.0 (10H, m), 2.8−3.8 (5H, m), 4.65 (1H, m), 4.9−5.1 (1H, m), 6.23 (1H, m), 7.1−7.9 (12H, m). MS (ES) *m/e*: 474 (M + H). Anal. ($C_{30}H_{35}N_1O_4\cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}-2-methylpropyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (10j). Compound **10j** was prepared from **61** according to the procedures described for the conversion of **51** to **10g** in 29% yield. NMR (200 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.0 Hz), 1.35 (6H, s), 2.8−3.5 (5H, m), 4.82 (1H, m), 5.02 (1H, m), 6.17 (1H, m), 7.2−7.5 (9H, m), 7.6−7.9 (3H, m). MS (ES) *m/e*: 448 (M + H). Anal. ($C_{28}H_{33}N_1O_4\cdot 1.0HCl\cdot 0.75H_2O$) C, H, N.

4′-((2*S*)-3-Hydroxy-2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}propyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (10k). Compound **10k** was synthesized from **41** and **53b** according to the procedure D (66%). NMR (200 MHz, DMSO-d$_6$) δ: 1.31(6H, d, J = 6 Hz), 2.8−3.5 (7H, m), 4.82 (1H, m), 5.00 (1H, m), 5.41 (1H, m), 6.23 (1H, m), 7.2−7.8 (12H, M). MS (ES) *m/e*: 450 (M + H). Anal. ($C_{27}H_{31}N_1O_5\cdot 1.0HCl\cdot 1.3H_2O$) C, H, N.

4′-(2-{[(1*S*,2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (10l). Compound **10l** was synthesized from **46** and **53b** according to the procedure D (51%). NMR (200 MHz, DMSO-d_6) δ: 0.98 (3H,d, J = 6.6 Hz), 1.31 (6H, d, J = 6.0 Hz), 2.8−3.5 (5H, m), 4.79 (1H, q, J = 6.0 Hz), 5.0−5.2 (1H, m), 6.0 (1H, m), 6.7−7.9 (11H, m). MS (ES) *m/e*: 450 (M + H). HRMS (M + H)$^+$ found 450.2290; calcd for $C_{27}H_{31}N_1O_5$ 450.2280. Anal. ($C_{27}H_{31}N_1O_5 \cdot 2.0HCl \cdot 0.9H_2O$) C, H, N.

4′-(2-{[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (10m). Compound **10m** was synthesized from **18** and **53b** according to the procedure D (59%). NMR (200 MHz, DMSO-d_6) δ: 0.97 (3H, d, J = 6.6 Hz), 1.32 (6H, d, J = 6.0 Hz), 3.0−3.6 (5H, m), 4.82 (1H, m), 5.21 (1H, m), 6.15 (1H, m), 7.1−7.5 (9H, m), 7.7−7.9 (3H, m). MS (ES) *m/e*: 434 (M + H). Anal. ($C_{27}H_{31}N_1O_4 \cdot 1.0HCl \cdot 0.5H_2O$) C, H, N.

4′-(2-{[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]amino}ethyl)-3-propoxy-4-biphenylcarboxylic acid hydrochloride (10n). Compound **10n** was synthesized from **18** and **53c** according to the procedure D (59%). NMR (200 MHz, DMSO-d_6) δ: 0.8−1.1 (6H, m), 1.6−1.9 (2H, m), 3.0−3.7 (5H, m), 4.11 (2H, q, J = 6.8 Hz), 5.24 (1H, m), 6.16 (1H, m), 7.1−7.8 (12H, m). MS (ES) *m/e*: 434 (M + H). Anal. ($C_{27}H_{31}N_1O_4 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]amino}ethyl)-3-isobutyl-4-biphenylcarboxylic acid hydrochloride (10o). Compound **10o** was synthesized from **18** and **53e** according to the procedure D (15%). NMR (200 MHz, DMSO-d_6) δ: 0.88 (6H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.5 Hz), 1.79−1.92 (1H, m), 2.92 (2H, d, J = 7.0 Hz), 3.02−3.10 (2H, m), 3.33−3.52 (3H, m), 5.15 (1H, br s), 6.12 (1H, br s), 7.26−7.61 (9H, m), 7.71 (2H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz). MS (ES) *m/e*: 432 (M + H). Anal. ($C_{28}H_{33}N_1O_3 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-pyridinyl)ethyl]amino}propyl)-1,1′-biphenyl-4-carboxylic acid dihydrochloride (10p). Typical procedure F. To a solution of **40** (287 mg, 0.55 mol) in 1,2-dimethoxyethane (4 mL) were added boronic acid **53a** (110 mg, 0.61 mol), $Pd(PPh_3)_4$ (64 mg, 0.055 mmol), and aqueous solution of Na_2CO_3 (2 M, 0.58 mL), and the mixture was stirred at 70 °C for 2 h under nitrogen. The mixture was diluted with 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 (hexane/EtOAc = 3/1−2/1) to give 250 mg (85.7%) of methyl 4′-((2*R*)-2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(6-chloro-3-pyridinyl)-2-hydroxyethyl]amino}propyl)-1,1′-biphenyl-4-carboxylate. MS(ESI): 524 (M + H).

To a solution of the product (250 mg, 0.476 mmol) in MeOH (2.5 mL) was added 1 N aqueous NaOH (1.0 mL), and the mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation, and the aqueous solution was neutralized with 1 N aqueous HCl and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to give 150 mg (61.6%) of 4′-((2*R*)-2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(6-chloro-3-pyridinyl)-2-hydroxyethyl]amino}propyl)-1,1′-biphenyl-4-carboxylic acid. MS(ESI): 511 (M + H).

The above product (150 mg, 0.29 mmol), ammonium formate (73 mg, 1.16 mmol) and palladium on carbon powder (10% w/w, 50% wet, 30 mg) in methanol (7.5 mL) and water (1.5 mL) was refluxed for 30 min, and the catalyst was filtered off. To the filtrate was added water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give 140 mg (90%) of 4′-((2*R*)-2-{(*tert*-butoxycarbonyl)[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]amino}propyl)-1,1′-biphenyl-4-carboxylic acid as a colorless form. MS(ESI): 477 (M + H).

To a solution of the above product (140 mg, 0.26 mmol) in 1,4-dioxane (2 mL) was added 4 N HCl in 1,4-dioxane (2 mL), and the mixture was stirred at room temperature for 3 h. The resultant solid was collected by filtration and dried to give 100 mg (86%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 1.70 (3H, d, J = 6 Hz) 3.30−3.90 (6H, m), 5.10−5.20 (1H, m), 7.40−7.70 (7H, m), 7.80−7.90 (1H, m), 8.25 (1H, d, J = 8 Hz), 8.70−8.85 (2H, m). MS (ES) *m/e*: 377 (M + H). Anal. ($C_{23}H_{24}N_2O_3 \cdot 2.0HCl \cdot 1.2H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-pyridyl)ethyl]amino}propyl)-3-isopropyloxy-1,1′-biphenyl-4-carboxylic acid dihydrochloride (10q). Compound **10q** was synthesized from **40** and **53b** according to the procedure F (61%). NMR (200 MHz, DMSO-d_6) δ: 1.19 (3H, d, J = 6.4 Hz), 1.31 (6H, d, J = 6.0 Hz), 2.8−3.8 (5H, m), 4.6−4.9 (1H, m), 5.1−5.3 (1H, m), 7.2−7.5 (4H, m), 7.6−8.0 (4H, m), 8.37 (1H, d, J = 8.2 Hz), 8.80 (1H, d, J = 4.6 Hz), 8.88 (1H, s), 9.02 (1H, br, s), 9.35 (1H, br, s). MS (ES) *m/e*: 435 (M + H). Anal. ($C_{26}H_{30}N_2O_4 \cdot 2.0HCl \cdot 1.25H_2O$) C, H, N.

4′-((2*R*)-2-{[(2*R*)-2-Hydroxy-2-(3-pyridinyl)ethyl]amino}propyl)-3-propoxy-4-biphenylcarboxylic acid hydrochloride (10r). Compound **10r** was synthesized from **40** and **53c** according to the procedure F (39%). NMR (200 MHz, DMSO-d_6) δ: 1.07 (3H, t, J = 7.4 Hz), 1.13 (3H, d, J = 6.8 Hz), 1.5−1.9 (2H, m), 2.7−3.4 (5H, m), 4.04 (2H, q, J = 7.4 Hz), 5.1−5.3 (1H, m), 6.32 (1H, m), 7.2−7.9 (8H, m), 8.25 (1H, d, J = 8 Hz), 8.7−8.9 (2H, m), 8.94 (1H, m), 9.20 (1H, m). MS (ES) *m/e*: 435 (M + H). Anal. ($C_{26}H_{30}N_2O_4 \cdot 2.0HCl \cdot 0.25H_2O$) C, H, N.

3-(Cyclohexyloxy)-4′-((2*R*)-2-{[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]amino}propyl)-4-biphenylcarboxylic acid dihydrochloride (10s). Compound **10s** was synthesized from **40** and **53f** according to the procedure F (61%). HPLC purity: 97%. NMR (200 MHz, DMSO-d_6) δ: 1.15 (3H, d, J = 6.4 Hz), 1.2−2.0 (10H, m), 2.7−3.8 (5H, m), 4.65 (1H, m), 5.31 (1H, m), 7.2−7.5 (5H, m), 7.6−7.8 (2H, m), 7.9−8.0 (1H, m), 8.45 (1H, m), 8.82 (1H, d, J = 2.6 Hz), 8.90 (1H, s), 8.94 (1H, m), 9.07 (1H, br, s), 9.43 (1H, br, s). MS (ES) *m/e*: 475 (M + H). HRMS (M + H)$^+$: found 475.2592; calcd for $C_{29}H_{34}N_2O_4$ 475.2597.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethoxy)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (11a). Compound **11a** was synthesized from **24** and **53b** according to the procedure E (28%). NMR (200 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.0 Hz), 3.1−3.3 (2H, m), 3.4−3.5 (2H, m), 4.3−4.4 (2H, m), 4.8−4.9 (1H, m), 4.9−5.0 (1H, m), 6.3(1H, br), 7.1 (2H, d, J = 8.8 Hz), 7.2−7.5 (6H, m), 7.67−7.74 (3H, m). MS (ES) *m/e*: 468 (M − H). Anal. ($C_{26}H_{28}Cl_1N_1O_5 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethoxy)-3-propoxy-4-biphenylcarboxylic acid hydrochloride (11b). Compound **11b** was synthesized from **24** and **53c** according to the procedure E (28%). NMR (200 MHz, DMSO-d_6) δ: 1.02 (3H, t, J = 7.3 Hz), 1.67−1.85 (2H, m), 3.1−3.2 (2H, m), 3.4−3.5 (2H, m), 4.1 (2H, t, J = 6.3 Hz), 4.3−4.4 (2H, m), 5.0−5.1 (1H,m), 6.3 (1H, br), 7.1 (2H, d, J = 8.7 Hz), 7.2−7.3 (2H, m), 7.35−7.48 (4H, m), 7.7−7.8 (3H, m). MS (ES) *m/e*: 468 (M − H). Anal. ($C_{26}H_{28}Cl_1N_1O_5 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethoxy)-3-isobutoxy-4-biphenylcarboxylic acid hydrochloride (11c). Compound **11c** was synthesized from **24** and **53d** according to the procedure E (57%). NMR (200 MHz, DMSO-d_6) δ: 1.02 (6H, d, J = 6.6 Hz), 2.0−2.1 (1H, m), 3.0−3.2 (2H, m), 3.4−3.5 (2H, m), 3.92 (2H, d, J = 6.4 Hz), 4.38 (2H, t, J = 4.8 Hz), 4.9−5.0 (1H, m), 6.2 (1H, br), 7.1 (2H, d, J = 8.8 Hz), 7.2−7.5 (6H, m), 7.7−7.8 (3H, m). MS (ES) *m/e*: 482 (M − H). Anal. ($C_{27}H_{30}Cl_1N_1O_5 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethoxy)-3-isobutyl-4-biphenylcarboxylic acid hydrochloride (11d). Compound **11d** was synthesized from **24** and **53e** according to the procedure E (11%). NMR (200 MHz, DMSO-d_6) δ: 0.88 (6H, d, J = 6.6 Hz), 1.8−1.9 (1H, m), 2.9 (2H, d, J = 6.9 Hz), 3.0−3.2 (2H, m), 3.4−3.5 (2H, m), 4.3−4.4 (2H, m), 5.0−5.1 (1H, m), 6.35 (1H, br), 7.1 (2H, d, J = 8.7 Hz), 7.3−7.6 (6H, m), 7.71 (2H, d, J = 8.7 Hz), 7.85 (1H, d, J = 8.1 Hz). MS (ES) *m/e*: 466 (M − H). HRMS (M + H)$^+$: found 468.1942; calcd for $C_{27}H_{30}Cl_1N_1O_4$ 468.1928. Anal. calcd for $C_{27}H_{30}Cl_1N_1O_4 \cdot 1.0HCl$: C, 64.29; H, 6.19; N, 2.78; found: C, 64.91; H, 6.28; N, 2.82.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethoxy)-3-(cyclohexyloxy)-4-biphenylcarboxylic acid hydrochloride (11e). Compound **11e** was synthesized from **24** and **53f** according to the procedure E (49%). NMR (200 MHz, DMSO-d_6) δ: 1.3−1.9 (10H, m), 3.1−3.2 (2H, m), 3.4−3.5 (2H, m), 4.3−4.4 (2H, m), 4.6 (1H, m), 5.0−5.1 (1H,m), 6.3 (1H, br), 7.1(2H, d, J = 8.7 Hz), 7.2−7.5 (6H, m), 7.69−7.74(3H, m). MS (ES) *m/e*: 508 (M-H). Anal. ($C_{29}H_{32}Cl_1N_1O_5 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethoxy)-3-isopropoxy-4-biphenylcarboxylic acid hydrochloride (11f). Compound **11f** was synthesized from **25** and **53b** according to the procedure E (29%). NMR (200 MHz, DMSO-d_6) δ: 1.31 (6H, d, J = 6.0 Hz), 3.0−3.3 (2H, m), 3.45 (2H,d, J = 4.7 Hz), 4.38 (2H, t, J = 4.8 Hz), 4.8−4.9 (1H, m), 4.9−5.0 (1H, m), 6.2 (1H, br), 7.1 (2H, d, J = 8.8 Hz), 7.2−7.4 (7H, m), 7.67−7.74 (3H, m). MS (ES) *m/e*: 434 (M − H). Anal. ($C_{26}H_{29}N_1O_5 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethoxy)-3-propoxy-4-biphenylcarboxylic acid hydrochloride (11g). Compound **11g** was synthesized from **25** and **53c** according to the procedure E (33%). NMR (200 MHz, DMSO-d_6) δ: 1.02 (3H, t, J = 7.3 Hz), 1.7−1.8 (2H, m), 3.1−3.2 (2H, m), 3.4−3.5 (2H, m), 4.1 (2H, t, J = 6.3 Hz), 4.3−4.4 (2H, m), 4.9−5.0 (1H,m), 6.2 (1H, br), 7.1 (2H, d, J = 8.8 Hz), 7.2−7.4 (7H, m), 7.7−7.8 (3H, m). MS (ES) *m/e*: 434 (M − H). Anal. ($C_{26}H_{29}N_1O_5 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethoxy)-3-isobutyl-4-biphenylcarboxylic acid hydrochloride (11h). Compound **11h** was synthesized from **25** and **53e** according to the procedure E (14%). NMR (200 MHz, DMSO-d_6) δ: 0.88 (6H, d, J = 6.6 Hz), 1.8−1.9 (1H, m), 2.89 (2H, d, J = 6.9 Hz), 3.04−3.25 (2H, m), 3.45 (2H, m), 4.3−4.4 (2H, m), 4.9−5.0 (1H, m), 6.2 (1H, br), 7.1(2H, d, J = 8.8 Hz), 7.3−7.6 (7H, m), 7.71 (2H, d, J = 8.7 Hz), 7.85 (1H, d, J = 8.1 Hz). MS (ES) *m/e*: 432 (M − H). Anal. ($C_{27}H_{31}N_1O_5 \cdot 1.0HCl$) C, H, N.

3-(Cyclohexyloxy)-4′-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]amino}-ethoxy)-4-biphenylcarboxylic acid hydrochloride (11i). Typical procedure E. To a solution of **25** (350 mg, 0.724 mmol) in toluene (6.0 mL) and EtOH (1.5 mL) was added boric acid **53f** (222 mg, 0.80 mmol), $PdCl_2(dppf) \cdot CHCl_3$ (1:1, 59 mg, 0.072 mmol), dppf (20 mg, 0.036 mmol), and aqueous solution of sodium carbonate (2M, 0.8 mL), and the mixture was stirred at 75 °C for 4 h under nitrogen. The mixture was partitioned between with 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 (hexane/ethyl acetate = 3/1) to give biphenyl product (285 mg, 0.483 mmol). To a solution of the product in methanol (5.0 mL) was added 1 N aqueous NaOH solution (1.5 mL), and the mixture was stirred at 40 °C for 3 h. The solvent was removed by evaporation, and the aqueous solution was acidified with 1 N aqueous HCl solution and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give a benzoic acid product. To a solution of the product in ethyl acetate (2.0 mL) was added 4 N HCl in ethyl acetate (2.0 mL), and the mixture was stirred at room temperature for 12 h. The resultant solid was collected by filtration and dried to give 210 mg (56%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 1.3−1.9 (10H, m), 3.0−3.3 (2H, m), 3.4 (2H, br), 4.4 (2H, t, J = 5.0 Hz), 4.6−4.7 (2H, m), 4.9−5.0 (2H, m), 6.2 (1H, m), 7.1 (2H, d, J = 8.8 Hz), 7.2−7.4 (7H, m), 7.67−7.73 (3H, m), 9.0 (2H, br). MS (ES) *m/e*: 474 (M − H). Anal. ($C_{29}H_{33}N_1O_5 \cdot 1.0HCl$) C, H, N.

4′-(3-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}propyl)-3-propoxy-4-biphenylcarboxylic acid hydrochloride (11j). Compound **11j** was synthesized from **19** and **53c** according to the procedure D (24%). NMR (200 MHz, DMSO-d_6) δ: 1.02 (3H, t, J = 7.3 Hz), 1.7−1.8 (2H, m), 1.9−2.1(2H, m) 2.7 (2H, t, J = 7.3 Hz), 2.9−3.2 (4H, m), 4.1 (2H, t, J = 6.3 Hz), 4.9−5.0 (1H, m), 6.3 (1H, br), 7.2−7.5 (8H, m), 7.67−7.73 (3H, m), 8.9(2H, br). MS (ES) *m/e*: 466 (M − H). Anal. ($C_{27}H_{30}Cl_1N_1O_4 \cdot 1.0HCl$) C, H, N.

4′-[(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)amino]-3-propoxy-4-biphenylcarboxylic acid dihydrochloride (11k). Compound **11k** was synthesized from **26** and **53c** according to the procedure E (20%). NMR (200 MHz, DMSO-d_6) δ: 1.02 (3H, d, J = 7.3 Hz), 1.67−1.85 (2H, m), 3.0−3.3 (4H, m), 3.4−3.5 (2H, m), 4.09 (2H, t, J = 6.3 Hz), 4.95−5.05 (1H, m), 6.77 (2H, d, J = 8.6 Hz), 7.25 (1H, d, J = 7.7 Hz), 7.29 (1H, s), 7.3−7.7 (7H, m), 8.9 (1H, br), 9.2 (1H, br). MS (ES) *m/e*: 503 (M − H). Anal. ($C_{26}H_{29}Cl_1N_2O_4 \cdot 2.0HCl \cdot 1.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(6-Amino-3-pyridinyl)-2-hydroxyethyl]amino}ethoxy)-3-isobutyl-4-biphenylcarboxylic acid trihydrochloride (11l). Compound **11l** was synthesized from **44** and **53e** according to the procedure G. The final product was recrystallized from ethanol−water to give **11l** as colorless solid (28%). NMR (400 MHz, DMSO-d_6) δ: 0.88 (6H, d, J = 6.6 Hz), 1.85 (1H, heptuplet, J = 6.6 Hz), 2.91 (2H, d, J = 7.0 Hz), 3.15−3.43 (4H, m), 4.39 (2H, d, J = 5.5 Hz), 5.02 (1H, d, J = 8.4 Hz), 6.47 (1H, brs), 7.05 (1H, d, J = 9.5 Hz), 7.11 (2H, d, J = 8.8 Hz), 7.49 (1H, d, J = 1.8 Hz), 7.55 (1H, dd, J = 1.8, 8.1 Hz), 7.70 (2H, d, J = 8.8 Hz), 7.85 (1H, d, J = 8.1 Hz), 7.93−7.97 (2H, m), 8.20 (2H, brs), 9.27 (1H, br), 9.40 (1H, br), 12.8 (1H, br), 14.2 (1H, br). MS (ES) *m/e*: 444 (M − H). Anal. ($C_{26}H_{31}N_3O_4 \cdot 3.0HCl$) C, H, N.

***tert*-Butyl [2-(4-bromophenyl)ethyl][(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]carbamate (17). Typical procedure A.** To a mixture of 4-bromophenylacetic acid **15** (26.7 g, 124 mmol), (1*R*)-2-amino-1-(3-pyridinyl)ethanol dihydrochloride **12** (25 g, 118 mmol), and 1-hydroxybenzotriazole (16.8 g, 124 mmol) in *N,N*-DMF (125 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (23.8 g, 124 mmol) and Et_3N (34.6 mL, 249 mmol) under ice-bath, and the mixture was stirred at room temperature for 16 h. The mixture was poured into water under ice-bath below 10 °C, and the pH value was kept ca. 10 by using 24% aqueous NaOH solution. The mixture was stirred at room temperature for 4 h, and the resultant solid was collected by filtration, washed with water, and dried to give 35.7 g (90%) of 2-(4-bromophenyl)-*N*-[(2*R*)-2-hydroxy-2-(3-pyridinyl)ethyl]acetamide as a white crystal. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.49−2.51 (1H, m), 3.25−3.38 (2H, m), 3.33 (2H, s), 4.61−4.70 (1H, m), 4.79−4.87 (1H, m), 5.64 (1H, d, J = 4.5 Hz), 7.14 (2H, d, J = 8.3 Hz), 7.28−7.35 (1H, m), 7.45 (2H, d, J = 8.3 Hz), 7.65−7.69 (1H, m), 8.15 (1H, m), 8.44−8.49 (2H, m). MS (ES) *m/e*: 358, 359 (M + Na)

To a THF (326 mL) solution of the product (32.6 g, 97.2 mmol), 2M-boran-dimethylsulfide complex in THF (146 mL) was added at room temperature, and the mixture was refluxed for 1.5 h. To the mixture, 6 N HCl (195 mL) was added dropwise below 10 °C, and the mixture was stirred at room temperature for 15 h. To the reaction mixture, 3 N aqueous NaOH solution (350 mL) below 10 °C was added, and a solution of di-*tert*-butyl dicarbonate (23.3g, 107 mmol) in THF (70 mL) was added portionally at room temperature. The pH value was kept between 7 and 8 by using 1 N aqueous NaOH solution. The mixture was stirred at room temperature for 2 h. 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 ($CHCl_3$/MeOH = 200/1−30/1) to give 32.9 g (80%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.43 (9H, s), 2.70 (2H, br), 3.15−3.50 (4H, m), 4.93−4.97 (1H, m), 6.95−7.01 (2H, m), 7.28−7.43 (3H, m), 7.72−7.80 (1H, m), 8.51 (1H, dd, J = 1.6, 4.8 Hz), 8.57 (1H, d, J = 2.2 Hz). MS (ES) *m/e*: 421 (M + H).

4-(2-{[(1*S*,2*R*)-2-Hydroxy-2-phenyl-1-methylethyl]-*tert*-butyloxycarbonyl-amino}ethyl)phenylbromide (18). Compound **18** was synthesized from **13** and **15** according to the procedure A (91%). NMR (200 MHz, $CDCl_3$) δ: 1.25 (3H, d, J = 7.0 Hz), 1.47 (9H, s), 3.4−3.5 (2H, m), 3.8−4.0 (2H, m), 4.2−4.3 (1H, m), 6.7 (2H, d, J = 8.7 Hz), 7.2−7.4 (6H, m), 7.5−7.6 (2H, m). MS (ES) *m/e*: 434 (M + H).

***tert*-Butyl [3-(4-bromophenyl)propyl][(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (19).** Compound **19** was synthesized from **14** and **16** according to the procedure A (50%). ^{1}H NMR (200 MHz,

$CDCl_3$) δ: 1.46 (9H, s), 1.7−1.9 (2H, m), 2.51 (2H, t, J = 7.4 Hz), 3.1−3.5 (4H, m), 4.88−4.95 (1H, m), 7.0−7.4 (8H, m). MS (ES) *m/e*: 490, 492 (M + Na).

[2-(4-Iodophenoxy)ethyl]amine hydrochloride (22). To a solution of 4-iodophenol (13.5 g, 61.4 mmol) and *tert*-butyl (2-hydroxyethyl)carbamate (12.9 g, 80 mmol) in THF (110 mL) were added PPh_3 (20.9 g, 80 mmol) and 40% diethyl 1,2-diazenedicarboxylate in toluene solution (36.2 mL, 92 mmol) at 4 °C, and the mixture was stirred at room temperature for 16 h under nitrogen. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3/1) to give phenylether product (19.3 g, 53.1 mmol). To a solution of the product in EtOAc (100 mL) was added 4 N HCl in EtOAc (100 mL), and the mixture was stirred at room temperature for 2.5 h. The resultant solid was collected by filtration and dried to give 15.5 g (84%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 3.2 (2H, t, J = 5.0 Hz), 4.1(2H, t, J = 5.0 Hz), 6.8−6.9 (2H, m), 7.6−7.7 (2H, m), 8.2 (2H, br). MS (ES) *m/e*: 264 (M + H).

2-Amino-*N*-(4-iodophenyl)acetamide hydrochloride (23). To a mixture of 4-iodoaniline (10 g, 45.6 mmol), [(*tert*-butoxycarbonyl)amino]acetic acid (8.8 g, 50.2 mmol) and hydroxbenzotriazole (6.8 g, 50.2 mmol) in *N,N*-DMF (80 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.63 g, 50.2 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed by 1 N HCl solution followed by saturated sodium bicarbonate solution, dried over magnesium sulfate, and evaporated under reduced pressure to give an amide product (15.6 g, 41.7 mmol). To a solution of the product in 1,4-dioxane (80 mL) was added 4 N HCl in 1,4-dioxane (80 mL), and the mixture was stirred at room temperature for 16 h. The resultant solid was collected by filtration. The solid was triturated with EtOAc:*n*-Hex solution (1:1, 90 mL) to give 11.6 g (90%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 3.8 (2H, d, J = 5.3 Hz), 7.4−7.5 (2H, m), 7.7−7.8 (2H, m), 8.2 (2H, br). MS (ES) *m/e*: 299 (M + Na).

***tert*-Butyl [(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-iodophenoxy)ethyl]carbamate (24).** Compound **24** was synthesized from **20** and **22** according to the procedure A (60%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.48 (9H, s), 3.5−3.6 (4H, m), 3.9−4.0 (2H, m), 4.9−5.0 (1H, m), 6.6−6.7 (2H, m), 7.26 (3H, br), 7.4 (1H,s), 7.5−7.6 (2H,m). MS (ES) *m/e*: 540 (M + Na).

***tert*-Butyl [(2*R*)-2-hydroxy-2-phenylethyl][2-(4-iodophenoxy)ethyl]carbamate (25).** Compound **25** was synthesized from **21** and **22** according to the procedure A (99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.48 (9H, s), 3.5−3.6 (4H, m), 3.9−4.0 (2H, m), 4.9−5.0 (1H, m), 6.6−6.7 (2H, m), 7.3−7.6 (7H, m). MS (ES) *m/e*: 506 (M + Na).

***tert*-Butyl [(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]{2-[(4-iodophenyl)amino]ethyl} carbamate (26).** Compound **26** was synthesized from **20** and **23** according to the procedure A (55%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.49 (9H, s), 3.1−3.5 (6H, m), 4.9−5.0 (1H, m), 6.3−6.4 (2H, m) 7.2−7.45 (6H, m). MS (ES) *m/e*: 539 (M + Na).

***tert*-Butyl [2-(4-bromophenyl)ethyl][(2*R*)-2-(4-chlorophenyl)-2-hydroxyethyl]carbamate (28). Typical procedure B.** Under nitrogen at room temperature, to a mixture of [2-(4-bromophenyl)ethyl]amine **27** (2.0 g, 10mmol) in DMSO (16 mL) was added bis(trimethylsilyl)urea (1.5 g, 7.3 mmol), and the mixture was stirred at 65 °C for 1 h. To the mixture was added (2*R*)-2-(4-chlorophenyl)oxirane (1.4 g, 9.1 mmol), and the mixture was stirred at 65 °C for 18 h. The resulting mixture was cooled to room temperature, and 1 N aqueous HCl (20 mL) was added. After being stirred for 20 min, the mixture was neutralized with saturated aqueous $NaHCO_3$ (20 mL), and the aqueous mixture was extracted with EtOAc. The organic layer was washed successively with water and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. To a solution of the product in THF (30 mL) and water (20 mL) was added di-*tert*-butyl dicarbonate (1.5 g, 6.9 mmol) at room temperature. The pH value was kept between 7 and 8 by using 1 N aq 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 brine, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Hex/EtOAc = 5/1) to give 1.5 g (44%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.69 (2H, m), 3.15−3.45 (4H, m), 4.47 (1H, br), 4.82−4.92 (1H, m), 6.95−7.04 (2H, m), 7.31−7.39 (6H, m). MS (ES) *m/e*: 478 and 480 (M + Na).

***tert*-Butyl [2-(4-bromophenyl)ethyl][(2*R*)-2-(3-fluorophenyl)-2-hydroxyethyl]carbamate (29).** Compound **29** was synthesized from **27** and (2*R*)-2-(3-fluorophenyl)oxirane according to the procedure B (42%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.69 (2H, m), 3.15−3.42 (4H, m), 4.35 (1H, br), 4.82−4.91 (1H, m), 6.95−7.04 (2H, m), 7.18−7.52 (6H, m). MS (ES) *m/e*: 460 and 462 (M + Na).

***tert*-Butyl {(2*R*)-2-[3-(benzyloxy)phenyl]-2-hydroxyethyl}[2-(4-bromophenyl)ethyl]carbamate (30).** Compound **30** was synthesized from **27** and (2*R*)-2-[3-(benzyloxy)phenyl]oxirane according to the procedure B (39%). MS (ES) *m/e*: 548 and 550 (M + Na).

***tert*-Butyl [2-(4-bromophenyl)ethyl][(2*R*)-2-hydroxy-2-(3-nitrophenyl)ethyl]carbamate (31).** Compound **31** was synthesized from **27** and (2*R*)-2-(3-nitrophenyl)oxirane according to the procedure B (40%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.69 (2H, m), 3.15−3.45 (4H, m), 4.47 (1H, br), 4.82−4.92 (1H, m), 6.95−7.04 (2H, m), 7.4−8.1 (6H, m). MS (ES) *m/e*: 487 and 489 (M + Na).

***tert*-Butyl [2-(4-bromophenyl)ethyl][(2*R*)-2-hydroxy-2-(4-nitrophenyl)ethyl]carbamate (32).** Compound **32** was synthesized from **27** and (2*R*)-2-(4-nitrophenyl)oxirane according to the procedure B (33%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.69 (2H, m), 3.14−3.40 (4H, m), 4.75 (1H, br), 4.97−5.0 (1H, m), 6.97−7.02 (2H, m), 7.40 (2H, d, J = 8.3 Hz), 7.52 (2H, d, J = 8.3 Hz), 8.19−8.22 (2H, m). MS (ES) *m/e*: 487 and 489 (M + Na).

[(1*R*)-2-(4-Iodophenyl)-1-methylethyl]amine (36). To a solution of **51** (10 g, 28 mmol) in 1,4-dioxane (100 mL) was added aqueous 1 N NaOH solution (56 mL) dropwise. The mixture was stirred at 50 °C for 1 h. The solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$−MeOH (5:1). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give 7.33 g (quant) of the title compound. MS (ES) *m/e*: 262 (M + H).

(2*S*)-2-Amino-3-(4-iodophenyl)-1-propanol (37). To a suspension of $NaBH_4$ (9.75 g, 258 mmol) in THF (300 mL) was added (2*S*)-2-amino-3-(4-iodophenyl)propanoic acid **52** (30 g, 103 mmol) under ice-bath, followed by conc H_2SO_4 (7.2 mL, 129 mmol) in ether (10 mL) dropwise, and the mixture was stirred at room temperature for 24 h. To the mixture, MeOH (10 mL) was added carefully below 10 °C, followed by addition of 5 N aqueous NaOH solution (300 mL), and the solvent was removed by evaporation. The mixture was refluxed for 3 h. After cooling to room temperature, to the mixture was added $CHCl_3$ and water. The resulting mixture was extracted with $CHCl_3$ (× 3), and the combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give 22.3g (78.1%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.35 (2H, br), 2.33−2.38 (1H, m), 2.61−2.67 (1H, m), 2.77−2.83 (1H, m), 3.13−3.27 (2H, m), 4.57 (1H, br s), 4.7−4.8 (2H, m), 5.31 (1H, br s), 7.02 (2H, d, J = 8.0 Hz), 7.61 (2H, d, J = 8 Hz). MS (ES) *m/e*: 278 (M + H).

***tert*-Butyl [(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl][(1*R*)-2-(4-iodophenyl)-1-methylethyl]carbamate (38). Typical procedure C.** The mixture of **36** (7.74 g, 29.6 mmol) and (2*R*)-2-(3-chlorophenyl)oxirane **33** (4.12 g, 26.7 mmol) in EtOH (150 mL) was refluxed for 30 h. After cooling to room temperature, the mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 20/1) to give 6.67 g (54%) of (1*R*)-1-(3-chlorophenyl)-2-{[(1*R*)-2-(4-iodophenyl)-1-methylethyl]amino}ethanol. MS (ES) *m/e*: 416 (M + H). To a solution of the product in THF (66 mL) and water (66 mL) was added di-*tert*-butyl dicarbonate (3.84 g, 17.6 mmol) at room temperature. The pH value was kept between 8 and 8.5 by using 1 N aqueous NaOH solution. The mixture was stirred at room

temperature for 2 h. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed brine, dried over magnesium sulfate, and evaporated under reduced pressure to give 8.32 g (quant) of title compound. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.24 (3H, d, J = 7 Hz), 1.36 (9H, s), 2.59 (2H, m), 3.07−3.14 (1H, m), 3.51 (1H, br s), 4.10−4.17 (1H, m), 4.73−4.78 (2H, m), 5.43 (1H, br s), 6.8 (2H, d, J = 8 Hz), 7.27 (3H, m), 7.40 (1H, br s), 7.60 (2H, d, J = 8 Hz). MS (ES) *m/e*: 537 (M + Na).

***tert*-Butyl [(2*R*)-2-hydroxy-2-phenylethyl][(1*R*)-2-(4-iodophenyl)-1-methylethyl]carbamate (39).** Compound **39** was prepared following the procedure C using (2*R*)-2-phenyloxirane **34** instead of **33** in 30% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.07 (3H, d, J = 7 Hz), 1.42 (9H, s), 2.6−2.7 (2H, m), 3.0−3.2 (1H, m), 3.52 (1H, br s), 4.1−4.2 (1H, m), 4.7−4.8 (2H, m), 5.31 (1H, br s), 6.82−6.86 (2H, m), 6.93 (2H, d, J = 8 Hz), 7.32−7.39 (3H, m), 7.60 (2H, d, J = 8 Hz). MS (ES) *m/e*: 482 (M + H).

***tert*-Butyl [(2*R*)-2-(6-chloro-3-pyridinyl)-2-hydroxyethyl][(1*R*)-2-(4-iodophenyl)-1-methylethyl]carbamate (40).** Compound **40** was prepared following the procedure C using 2-chloro-5-[(2*R*)-2-oxiranyl]pyridine **35** instead of **33** in 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (3H, d, J = 6.5 Hz), 1.36 (9H, s), 2.51−2.65 (2H, m), 3.0−3.1 (2H, m), 3.5−3.6 (1H, m), 4.1−4.2 (1H, m), 4.7−4.8 (1H, m), 5.49 (1H, br), 6.82−6.85 (2H, m), 6.34 (2H, d, J = 8.2 Hz), 7.58−7.62 (2H, m), 7.74−7.77 (1H, m), 8.36 (1H, d, J = 1.7 Hz). MS (ES) *m/e*: 517 (M + H).

***tert*-Butyl[(1*S*)-2-hydroxy-1-(4-iodobenzyl)ethyl][(2*R*)-2-hydroxy-2-phenylethyl] carbamate (41).** A solution of **37** (5 g, 18.0 mmol) and (2*R*)-2-phenyloxirane **34** (2 g, 16.6 mmol) in ethanol (50 mL) was refluxed for 18 h. The mixture was evaporated under reduced pressure. The residual oil was diluted in THF (50 mL). To the solution was added di-*tert*-butyl dicarbonate (5 g, 22.9 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/EtOAc = 2/1)to give 5.5 g (45%) of title compound. MS (ES) *m/e*: 498 (M + H).

***tert*-Butyl [(2*R*)-2-[6-(acetylamino)-3-pyridinyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl][2-(4-bromophenyl)ethyl]carbamate (43).** To a mixture of **42** (3.50 g, 7.53 mmol), **27** (3.01 g, 15.1 mmol), and DMSO (1.75 mL) was added diisopropylethylamine (1.31 mL, 7.53 mmol), and the mixture was stirred at 80 °C for 24 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (35 mL) and water (35 mL) and the organic layer was separated. The organic layer was washed with water (35 mL × 2) and brine (35 mL), and dried over magnesium sulfate. Filtration followed by evaporation gave a yellow paste (5.36 g), which was chromatographed on silica gel (eluent: Hex/EtOAc = 2/8−0/10) to give 3.33 g (90%) of *N*-{5-[(1*R*)-2-{[2-(4-bromophenyl)ethyl]amino}-1-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl]-2-pyridinyl}acetamide as a colorless paste. ^{1}H NMR (200 MHz, $CDCl_3$) δ: −0.17 (3H, s), −0.01 (3H, s), 0.81 (9H, s), 2.20 (s, 3H), 2.7−2.9 (6H, m), 4.76−4.82 (1H, m), 7.06 (2H, d, J = 8.3 Hz), 7.40 (2H, d, J = 8.3 Hz), 7.64 (1H, dd, J = 2.2, 8.3 Hz), 8.1−8.2 (2H, m). MS (ES) *m/e*: 492, 494 (M + H).

To a solution of the product (3.32 g, 6.74 mmol) in THF (33 mL) was added Boc_2O (1.7 mL, 7.41 mmol), and the solution was stirred at room temperature for 16 h. The solvent was removed by evaporation, and the residue was chromatographed on silica gel (Hex/EtOAc = 2/1) to give 3.30 g (83%) of the title compound as a white solid (foam). ^{1}H NMR (200 MHz, $CDCl_3$) δ: <232 (3H, s), −0.01 (3H, s), 0.86 (9H, s), 1.42 (9H, brs), 2.23 (s, 3H), 2.6−3.5 (6H, m), 4.8−5.1 (1H, m), 6.95−7.05 (1H, m), 7.38 (2H, d, J = 8.0 Hz), 7.67−7.80 (1H, m), 8.1−8.2 (2H, m). MS (ES) *m/e*: 614 and 616 (M + Na).

***tert*-Butyl [(2*R*)-2-[6-(acetylamino)-3-pyridinyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethyl] [2-(4-iodophenoxy)ethyl]carbamate (44).** Compound **44** was prepared from **42** and **22** according to the procedures described for the conversion of **42** to **43** in 69% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: −0.10 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.45 (9H, s), 2.23 (s, 3H), 3.2−3.7 (4H, m), 3.9−4.0 (2H, m), 4.9−5.1 (1H, m), 6.62 (2H, d, J = 8.0 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.66−7.81 (1H, m), 8.1−8.2 (2H, m). MS (ES) *m/e*: 654 (M-H).

4-(2-{[(1*S*,2*R*)-2-Hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]-*tert*-butyloxycarbonyl-amino}ethyl)phenylbromide (46). To a solution of (*aS*,*bR*)-4-hydroxynorephedrine **45** (500 mg, 3.65 mmol) and 4-bromophenylethylbromide (500 mg, 1.89 moml) in DMF (5 mL) was added diisopropylethylamine (0.5 mL), and the mixture was stirred for 6 h at 80 °C. The mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was diluted in THF (10 mL). To the solution was added di-*tert*-butyl dicarbonate (1g, 4.58 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 to give 520 mg (31.6%) of the title compound. MS (ES) *m/e*: 550 (M + H).

***N*-[(1*S*)-1-benzyl-2-hydroxyethyl]-2,2,2-trifluoroacetamide (48).** To a solution of (2*S*)-2-amino-3-phenyl-1-propanol **47** (100 g, 661 mmol) in MeOH (500 mL) was added CF_3CO_2Et (94.4 mL, 794 mmol) dropwise. The mixture was stirred at room temperature for 2.5 h and evaporated under reduced pressure to give 166 g (quant) of the title compound as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.95 (1H, d, J = 7.3 Hz), 3.62−3.79 (2H, m), 4.16−4.31 (1H, m), 6.65 (1H, br), 4.89 (1H, m), 7.20−7.38 (5H, m). MS (ES) *m/e*: 270 (M + Na).

(2*S*)-3-Phenyl-2-[(trifluoroacetyl)amino]propyl methanesulfonate (49). To a solution of **48** (160 g, 647 mmol) in THF (1.6 L) was added Et_3N (117 mL, 841 mmol) under ice-bath, followed by MsCl (55.1 mL, 712 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was poured into water (8.0 L) and stirred for 0.5 h. The resultant solid was collected by filtration, washed with water, and dried to give 203 g (96%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 2.65−3.04 (2H, m), 3.20 (3H, s), 4.14−4.44 (3H, m), 7.10−7.40 (5H, m), 9.51 (1H, br, d, J = 8 Hz). MS (ES) *m/e*: 348 (M + Na).

2,2,2-Trifluoro-*N*-[(1*R*)-1-methyl-2-phenylethyl]acetamide (50). To a solution of **49** (90 g, 277 mmol) in DME (1.8 L) and AcOH (31.7 mL) was added NaI (166 g, 1.11 mol) by portions, followed by Zn powder (145 g, 2.21 mol), and the mixture was refluxed for 1.5 h. After cooling to room temperature, the mixture was quenched by the addition of water (90 mL) and stirred for 0.5 h. The insoluble materials was removed by filtration and washed with EtOH. The filtrate was evaporated under reduced pressure. The residue was partitioned between EtOAc (700 mL) and 1 N aqueous HCl solution (900 mL). The organic layer was separated, washed with 5% aqueous $NaHSO_3$ solution, saturated aqueous $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 58.4 g (91%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (3H, d, J = 7.0 Hz), 2.80 (1H, dd, J = 14.0 and 7.0 Hz), 4.29 (1H, m), 6.12 (1H, br s), 7.14−7.37 (5H, m). MS (ES) *m/e*: 254 (M + Na). $[\alpha]^{20}_D$ +42.30° (c = 1.00, $CHCl_3$).

2,2,2-Trifluoro-*N*-[(1*R*)-2-(4-iodophenyl)-1-methylethyl]acetamide (51). To a mixture of **50** (3.76 g, 16.2 mmol) in H_2O (6.5 mL), AcOH (32.0 mL) and conc H_2SO_4 was added I_2 (1.65 g, 6.5 mol), followed by $HIO_4 \cdot 2H_2O$ (740 mg, 3.25 mol), and the mixture was stirred at 70−80 °C for 5 h. After cooling to room temperature, to the mixture was added water and extracted with EtOAc−Hex (1:1, × 3). The combined extracts were washed with water, aqueous Na_2SO_3 solution, and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give crude product. The solid was recrystallized from *i*-Pr_2O to give the title compound (2.16 g, 37%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21 (3H, d, J = 7 Hz), 2.74 (1H, dd, J = 14 and 7 Hz), 2.85 (1H, dd, J = 14 and 6 Hz), 4.26 (1H, m), 6.04 (1H, br s), 6.92 (2H, d, J = 8 Hz), 7.65 (2H, d, J = 8 Hz). MS (ES) *m/e*: 380 (M + Na).

Benzyl [(2*R*)-2-{4-(benzyloxy)-3-nitro-phenyl}−2-hydroxyethyl][2-(4-bromophenyl)ethyl]carbamate (55). Compound **55** was prepared following the similar procedure B using oxirane **54** and Cbz-Cl instead of (2*R*)-2-(4-chlorophenyl)oxirane and Boc_2O in 38% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.71 (2H, m), 3.18−3.42 (4H, m),

3.95 (1H, br), 4.89 (1H, m), 5.11 (2H, s), 5.22 (2H, s), 6.9−7.1 (4H, m), 7.3−7.5 (12H, m), 7.83 (1H, m). MS (ES) *m/e*: 627 (M + Na).

Benzyl [(2*R*)-2-{4-(benzyloxy)-3-[(methylsulfonyl)amino]phenyl}−2-hydroxyethyl][2-(4-bromophenyl)ethyl]carbamate (56). To a solution of **55** (7.5 g, 12.4 mmol) in a mixed solution of EtOH (150 mL) and water (50 mL) were added iron powder (2.08 g, 37.2 mmol) and NH_4Cl (331 mg, 6.19 mmol). The solution was refluxed for 1.5 h. After cooling to room temperature, the precipitate was filtered through a pad of celite. After concentrated under reduced pressure, the residue was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give aniline product (6.88 g, 96.5%). To a solution of the product (6.87 g, 11.9 mmol) in pyridine (70 mL) was added MsCl (1.58 g, 13.7 mmol) under ice-bath, and the mixture was stirred at room temperature for 4.5 h. The mixture was partitioned between EtOAc and 1 N aqueous HCl. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1−1/1) to give 4.18 g (53.6%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.70 (2H, m), 2.86 (3H, s), 3.2−3.4 (4H, m), 4.6−4.7 (1H, m), 4.89 (1H, m), 5.01 (2H, s), 5.15 (2H, s), 5.47 (1H, m), 7.01−7.15 (4H, m), 7.3−7.6 (13H, m), 8.95 (1H, s). MS (ES) *m/e*: 651, 653 (M + H).

3-Isopropoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (58). To a solution of methyl-4-bromo-3-methylbenzoate **57** (1.5 g, 5.79 mmol) in dioxane (30 mL) was added bis(pinacolate)diboron (1.47 g, 5.79 mmol), $PdCl_2$(dppf)·$CHCl_3$ (473 mg, 0.58 mmol), and KOAc (2.27 g, 23.1 mmol), and the mixture was stirred at 90 °C for 8 h under nitrogen. The mixture was diluted with EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to give 1.37 g (77%) of the title compound, which was used in next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.26 (6H, d, J = 6.8 Hz), 1.30 (s, 12H), 4.56−4.07 (1H, m), 7.25−7.29 (2H, m), 7.56 (1H, d, J = 7.7 Hz).

***N*-(1,1-dimethyl-2-phenylethyl)-2,2,2-trifluoroacetamide (60).** To an ice-cooled solution of **59** (13.9 g) in THF (56 mL) were added Et_3N (17 mL) and trifluoroacetic anhydride (14.5 mL). The mixture was stirred at the same temperature for 6 h and partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered to give 19.8 g (86%) of the title compound. NMR (200 MHz, DMSO-d_6) δ: 1.42 (6H, s), 3.05 (2H, s), 5.85 (1H, br s), 7.00−7.42 (5H, m). MS (ES) *m/e*: 268 (M + Na).

2,2,2-Trifluoro-*N*-[2-(4-iodophenyl)-1,1-dimethylethyl]acetamide (61). Compound **61** was prepared from **60** according to the procedures described for the conversion of **50** to **51** in 55% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40 (6H, s), 3.02 (2H, s), 5.79 (1H, br s), 6.86 (2H, d, J = 8 Hz), 7.63 (2H, d, J = 8 Hz). MS (ES) *m/e*: 394 (M + Na).

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Supporting Information Available: Biological materials and methods and combustion analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Although *N*-[(2*S*)-7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl]-(2*R*)-2-(3-chlorophenyl)-2-hydroxy-ethanamine hydrochloride (SR 58611A) is currently being evaluated in clinical trials for depression,[6a] our compounds are not targeted to the some CNS area because we have confirmed that our compounds have poor brain penetration.

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