Discovery of a Novel Series of Biphenyl Benzoic Acid Derivatives as Potent and Selective Human β_3-Adrenergic Receptor Agonists with Good Oral Bioavailability. Part I

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A novel class of biphenyl analogues containing a benzoic acid moiety based on lead compound **8i** have been identified as potent and selective human β_3 adrenergic receptor (β_3-AR) agonists with good oral bioavailability and long plasma half-life. After further substituent effects were investigated at the terminal phenyl ring of lead compound **8i**, we have discovered that more lipophilic substitution at the R position improved potency and selectivity. As a result of these studies, **10a** and **10e** were identified as the leading candidates with the best balance of potency, selectivity, and pharmacokinetic profiles. In addition, compounds **10a** and **10e** were evaluated to be efficacious for a carbachol-induced increase of intravesical pressure, such as an overactive bladder model in anesthetized dogs. This represents the first demonstrated result dealing with β_3-AR agonists.

Introduction

β-Adrenergic receptors (β-ARs[a]) have been subclassified into three types; β_1-, β_2-, and β_3 -ARs.[1] The β_3-AR has been demonstrated to mediate various pharmacological and physiological effects such as lipolysis in white adipocytes and thermogenesis (energy expenditure) in brown tissue adipocytes.[2] Recent studies have indicated that, in addition to adipocytes, the β_3-AR is also distributed in human urinary bladder detrusor tissue and its relaxation occurs mainly via β_3-ARs.[3–6] Therefore, activators of the β_3-AR are now recognized as potential drugs for not only the treatment of obesity and noninsulin dependent (type II) diabetes, but also overactive bladder (OAB). On the other hand, the concomitant activation of β_1- or β_2-ARs would lead to undesirable side effects, such as increased heart rate and/or muscle tremors. Thus, β_3-AR selectivity over β_1-AR and β_2-AR has been required for new therapeutic agents.

Early β_3 agonists (the "first generation" of potent and selective rat β_3-AR agonists), such as BRL37344 (**1**), CL316243 (**2**), aminobegron (**3**), and FK175 (**4**), as shown in Figure 1, have been reported to be effective antiobesity and antidiabetic agents in rodents. Unfortunately, BRL37344 (**1**), CL316243 (**2**), and other β_3-AR agonists discovered during the 1980s were unsuccessful in the clinic, either because of a lack of efficacy or an unfavorable cardiovascular side-effect profile and poor pharmacokinetics.[7] The clinical failure of "first generation" β_3-AR agonists has been attributed to a lack of sufficient β_3-AR potency and β_1-AR and β_2-AR selectivities resulting from pharmacological differences between rodent and human receptors.[8] Thus, a second generation of orally bioavailable human β_3-AR agonists with minimal side effects associated with activation of human β_1- and β_2-ARs has been an important goal of recent research. The availability of appropriate human receptors has given rise to the design and synthesis of a second generation of β_3-AR agonists with high potency and good selectivity with respect to human β_1- and β_2-ARs as exemplified by the potent and selective β_3-AR agonists LY377604 (**5**),[9] L796568 (**6**),[10] and Solabegron (**7**),[11] as shown in Figure 2. These compounds were evaluated in Chinese hamster ovary (CHO) cells expressing the cloned human β_3-AR.

In the past decade, drug discovery efforts have shifted toward the design of selective agonists for the β_3-AR. Though several groups have reported a number of potent and selective human β_3-AR agonists, many problems remain in terms of the pharmacokinetic properties of these agonists.[12] For example, a highly potent and selective human β_3-AR agonist L796568 (**6**) was discovered by the Merck group, but it showed moderate to low oral bioavailability in preclinical evaluation (rats, $F = 17\%$; dogs, $F = 27\%$; monkeys, $F = 4\%$).[10] Consequently, recent efforts in this field have been directed mainly toward optimization to discover orally bioavailable β_3-AR agonists. Recently, researchers at GlaxoSmithKline explored a series of aniline-based biphenyl β_3-AR agonists and identified potent, selective, and orally bioavailable compounds. Solabegron (**7**), [11] which is currently in phase II clinical trials, displayed good oral bioavailability in all species tested (rats, $F = 30\%$; dogs, $F = 43\%$; monkeys, $F = 46\%$), while it also displayed a relatively poor pharmacokinetic half-life in all species tested ($t_{1/2,i.v.}$: rats, 2.1 h; dogs, 3.3 h; monkeys, 4.5 h). Because in the field of treatment of urinary bladder dysfunction there is an unmet medical need for a once daily oral administration (due to compliance issues), an agent that possesses the pharmacokinetic properties required for once daily oral administration is required to meet these growing (due to an aging population) medical needs. Therefore, we initiated a search for effective therapeutic candidates against OAB, which have the following profile: (1)

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[a] Abbreviations: β-AR, β-adrenergic receptor; OAB, overactive bladder; SAR, structure–activity relationship; RHS, right-hand side; cAMP, cyclic adenosine monophosphate; ISP, isoproterenol; CHO, Chinese hamster ovary; IVP, intravesical pressure; PAMPA, parallel artificial membrane permeation assay.

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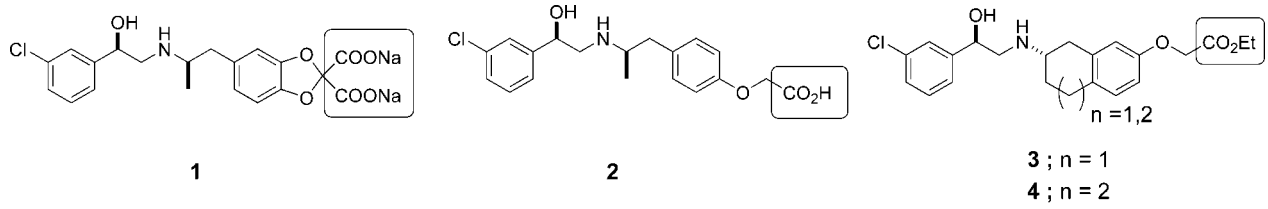


Figure 1. Chemical structure of first generation of β_3-AR agonists.

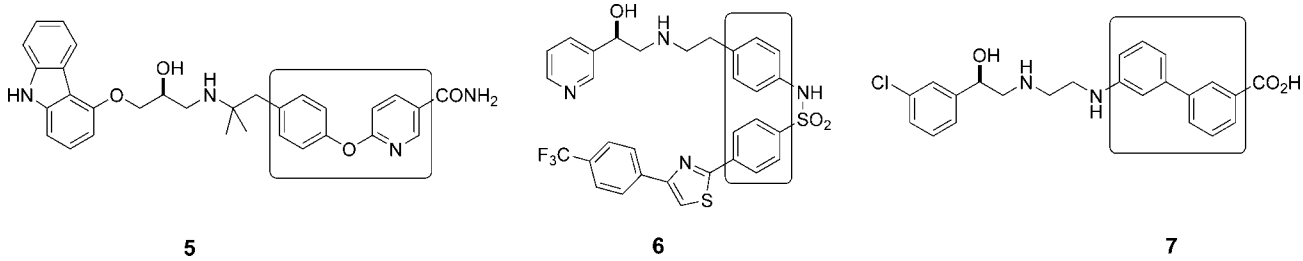


Figure 2. Chemical structure of second generation of β_3-AR agonists.

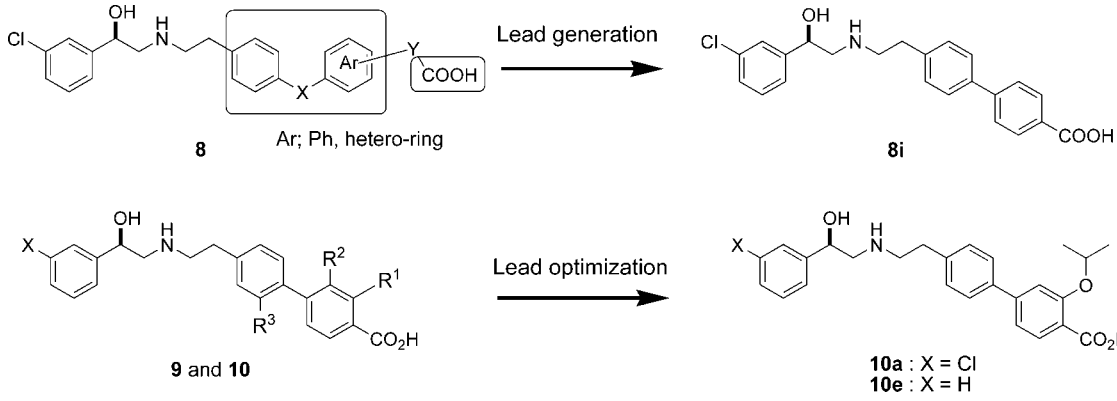


Figure 3. Discovery process of lead generation and lead optimization.

potent human β_3-AR agonist activity, (2) good selectivity over β_1- and β_2-ARs, (3) good oral bioavailability, and (4) long duration.

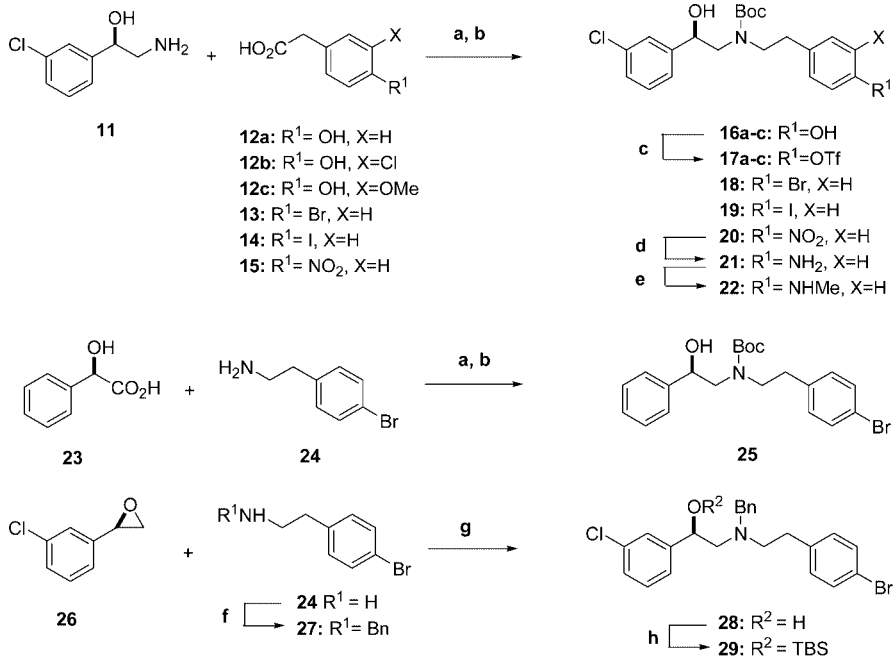
In our laboratory, our first clinical candidate, FK175 (**4**), having a carboxylic ester functionality (pro-drug form) in the right-hand side (RHS) in Figure 1, showed good selectivity over human β_1 and β_2-ARs and good oral absorption in phase I clinical trials. However, it was still insufficient in terms of potency of the β_3-AR activity and long duration for OAB treatment. To overcome these problems, we planned a discovery process for novel β_3-AR agonists as shown in Figure 3. We initially intended to introduce a carboxylate group on the RHS because introduction of a carboxylate group may contribute to good oral absorption. As well as with FK175, several groups have reported the importance of a carboxylic group on the RHS of ethanolamine analogues for the subtype selectivity of β_3-AR agonists, as shown in Figure 1.[13,14] Next, to enhance potency, we incorporated a biaryl scaffold as a core structure on the RHS, because L796568, LY374604, and solabegron, containing a biaryl template on the RHS, have been reported to be highly potent human β_3-AR agonists, as shown in Figure 2.

We investigated the structure–activity relationship (SAR) and pharmacokinetic properties of an extensive series of compounds **8**, employing a cassette dosing assay by in vivo dog pharmacokinetic assay to generate the desired lead compound with high oral bioavailability and long plasma half-life because the phase 1 study of FK175 indicated that the pharmacokinetic profile was similar in humans and dogs, as shown in Table 5. Next, further optimization of the lead compound to improve potency and selectivity led to identification of compounds **10a** and **10e** as clinical drug candidates. The synthesis of these compounds, the results of in vitro and cassette dosing assay, and the profiles of our drug candidates **10a** and **10e** are described in detail in the following sections.

Chemistry

The requisite intermediate Boc amine derivatives **16–22** containing the (3-chlorophenyl) ethanol moiety were prepared, as shown in Scheme 1. Boc amine derivatives (**16a−c**, **18**, **19**, and **20**) were synthesized by coupling of commercially available (1*R*)-2-amino-1-(3-chlorophenyl) ethanol (**11**) with phenylacetic acid derivatives **12–15** to produce amide derivatives in good yield, followed by selective reduction of the amide with $BH_3 \cdot SMe_2$[15] followed by protection of the amine with a Boc group. Trifluoromethanesulfonamide derivatives **17a−c** were obtained from selective protection of the phenol **16a−c** with Tf_2O/2,6-lutidine in CH_2Cl_2 at low temperature. Aniline **21** was prepared from nitro derivative **20** by reduction with Fe and NH_4Cl, followed by reductive amination with formaldehyde to give N-Me **22**, as shown in Scheme 1. Similarly, intermediate **25** containing the phenyl ethanol moiety was synthesized by coupling of commercially available (*R*)-(−)-mandelic acid **23** with 4-bromophenyl ethylamine **24** to produce amide derivative in good yield, followed by selective reduction of the amide with $BH_3 \cdot SMe_2$ to give the unmasked amino ethanol hydrochloride, followed by protection of the amine with a Boc group. Benzyl

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



[a] Reagents and conditions: (a) HOBt, WSCD, *N*,*N*-DMF; (b) $BH_3 \cdot SMe_2$, THF, 6 N aq HCl, then $(Boc)_2O$, aq NaOH (pH = 7–8); (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −70°C; (d) Fe (powder), NH_4Cl, EtOH, reflux; (e) 35% HCHO, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (f) PhCHO, *p*-TsOH, toluene, reflux then $NaBH_4$, MeOH, room temp; (g) EtOH, reflux; (h) TBSCl, imidazole, *N*,*N*-DMF.

amine intermediate **28** was prepared by reductive amination of 4-bromo-phenylethyl amine **14** with benzaldehyde, followed by coupling with (2*R*)-2-(3-chlorophenyl)oxirane **26**. The secondary alcohol of **28** was protected as a TBS ether to produce **29**, as shown in Scheme 1.

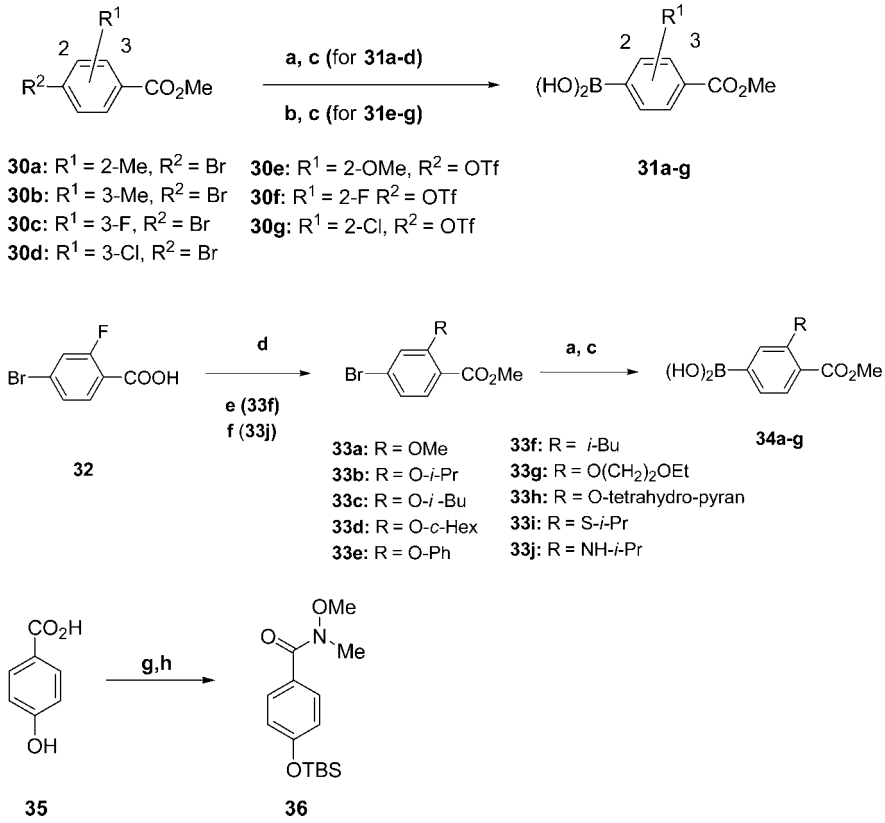
As shown in Scheme 2, the requisite intermediate phenylboronic acids (**31a**−**g** and **34a**−**g**) were synthesized from the corresponding bromide or triflate via boronic ester, followed by hydrolysis of the pinacol ester group with $NaIO_4$.[16] The cross-coupling reaction of bromide (**30a**−**d**, **33a**−**g**) proceeded smoothly in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, while the reaction of triflate (**30e**−**g**) proceeded with a catalytic amount of $PdCl_2(dppf) \cdot CHCl_3$. Noncommercially available trisubstituted benzoic acid methyl ester analogues (**33a**−**j**) were prepared from the commercially available 4-bromo-2-fluorobenzoic acid **32** by nucleophilic displacement with sodium alkoxide, sulfide, amine, and Grignard reagent. The other requisite right part intermediate Weinreb amide **36** was prepared from 4-hydroxybenzoic acid **35**.

The general synthetic route to biphenyl targets (**8h**−**j**, **9a**−**h**, **10a**−**j**) is shown in Scheme 3. Boc amine derivatives (**17a**−**c**, **18**, **19**, **25**) were coupled with phenylboronic acid derivatives to give biphenyl coupling products. Alkaline hydrolysis of ester followed by deprotection of the Boc group gave the biphenyl target compounds. The target **8p** was obtained by Suzuki coupling followed by selective oxidation of aldehyde, followed by deprotection of the Boc group. Similarly, targets **10k**−**n** are prepared from coupling products **37**–**40**. The coupling products (**37**, **38**, **40**) were synthesized from the corresponding trisubstituted phenyl bromide derivatives **33h**−**j** via boronic ester, followed by coupling with bromide intermediate **18**. Sulfone derivative **39** was obtained from selective oxidation of sulfide **38** with *m*-CPBA in CH_2Cl_2.

The phenoxy acetic acid analogues (**8a**−**c**,**f**,**g**) listed in Table 1 were prepared as shown in Scheme 4. Boc amine derivatives (**16a**, **40**, **41**) were coupled with commercially available 4-TBSO-phenylboronic acid with $Cu(OAc)_2$ and MS 4 Å in CH_2Cl_2 to give coupling products (**42**–**44**).[17] Deprotection of the silyl ether group in **42**–**44**, followed by coupling with *tert*-butyl bromoacetate gave Boc amine derivatives (**47**–**49**). Removal of the Boc and *tert*-butyl ester functionalities using 4 N HCl in dioxane provided the final targets (**8a**-**c**) as hydrochloride salts. Similarly, compound **8f** was prepared from Boc amine silyl ether **45**, and compound **8g** was prepared from phenol **46**. Boc amine silyl ether **45** was synthesized via lithiation of bromide **41** with *n*-BuLi at low temperature, followed by coupling with Weinreb amide **36**. Phenol **46** was prepared by Suzuki coupling of bromide **18** with 4-OTBS-phenylboronic acid, followed by deprotection of the silyl phenol ether group. The preparation of the final target **8d** is shown in Scheme 4. The bromide intermediate **27** was lithiated with *n*-BuLi at low temperature, followed by reaction with 4-OTBS-benzaldehyde to give benzyl methanol **52**. Deprotection of the TBS groups with *n*-Bu_4NF in THF, followed by catalytic hydrogenation in the presence of chlorobenzene, to avoid removal of the 3-chlorine atom on the benzene ring, produced the benzyl phenol **54**. Protection of the secondary amine in **54** with a Boc group followed by coupling with *tert*-butyl bromoacetate gave **56**, and the compound **8d** was prepared from **56** under acidic conditions. The biphenyl ether and aniline analogues (**8k**−**n**) were obtained by coupling of phenol **16a** or aniline **21** with commercially available phenylboronic acids with $Cu(OAc)_2$ and MS 4 Å in CH_2Cl_2, followed by alkaline hydrolysis and deprotection of the Boc group. The pyridine ether **8q** was obtained through nucleophilic displacement of commercially available chloro-pyridine with phenol **16a**, followed by alkaline hydrolysis and deprotection of the Boc group as shown in Scheme 4.

The synthesis of pyridyl analogue **8o** is shown in Scheme 5. *N*-Benzyl amine **27** was protected with a Boc group to give **57**. Conversion of the bromide intermediate **57** to boronic acid **58**, followed by coupling with commercially available ethyl 6-chloronicotinate, afforded biaryl compound **59**. Removal of the Boc group with HCl and then coupling with oxirane **26** in the

Scheme 2. Preparation of Boric Acid Intermediates and **36**[a]



[a] Reagents and conditions: (a) KOAc, pinacol diborane, $PdCl_2$ $(PPh_3)_2$, dioxane, 100 °C; (b) KOAc, pinacol diborane, $PdCl_2$ (dppf)−$CHCl_3$, dioxane, 100 °C; (c) $NaIO_4$, NH_4OAc, acetone, H_2O; (d) NaH, alcohol or thiol, *N*,*N*-DMF, then MeI, K_2CO_3, *N*,*N*-DMF; (e) *i*-BuMgCl (2 M in THF), then MeI, K_2CO_3, *N*,*N*-DMF; (f) *i*-$PrNH_2$, pyridine, 100°C, then MeI, K_2CO_3, *N*,*N*-DMF; (g) HN(OMe)Me, HOBt, WSCD, *N*,*N*-DMF; (h) TBSCl, imidazole, *N*,*N*-DMF.

presence of Et_3N gave *N*-benzyl derivative **60**. Conversion of the benzyl group to the Boc group compound **61**, followed by alkaline hydrolysis and subsequent deprotection of the Boc group, afforded target compound **8o**. Target compound **8e** was prepared from phenol **63**. This compound was prepared by coupling of (2*R*)-2-(3-chlorophenyl)oxirane **26** in the presence of BSA with biphenyl sulfide **62** as has previously been described.[18]

Results and Discussion

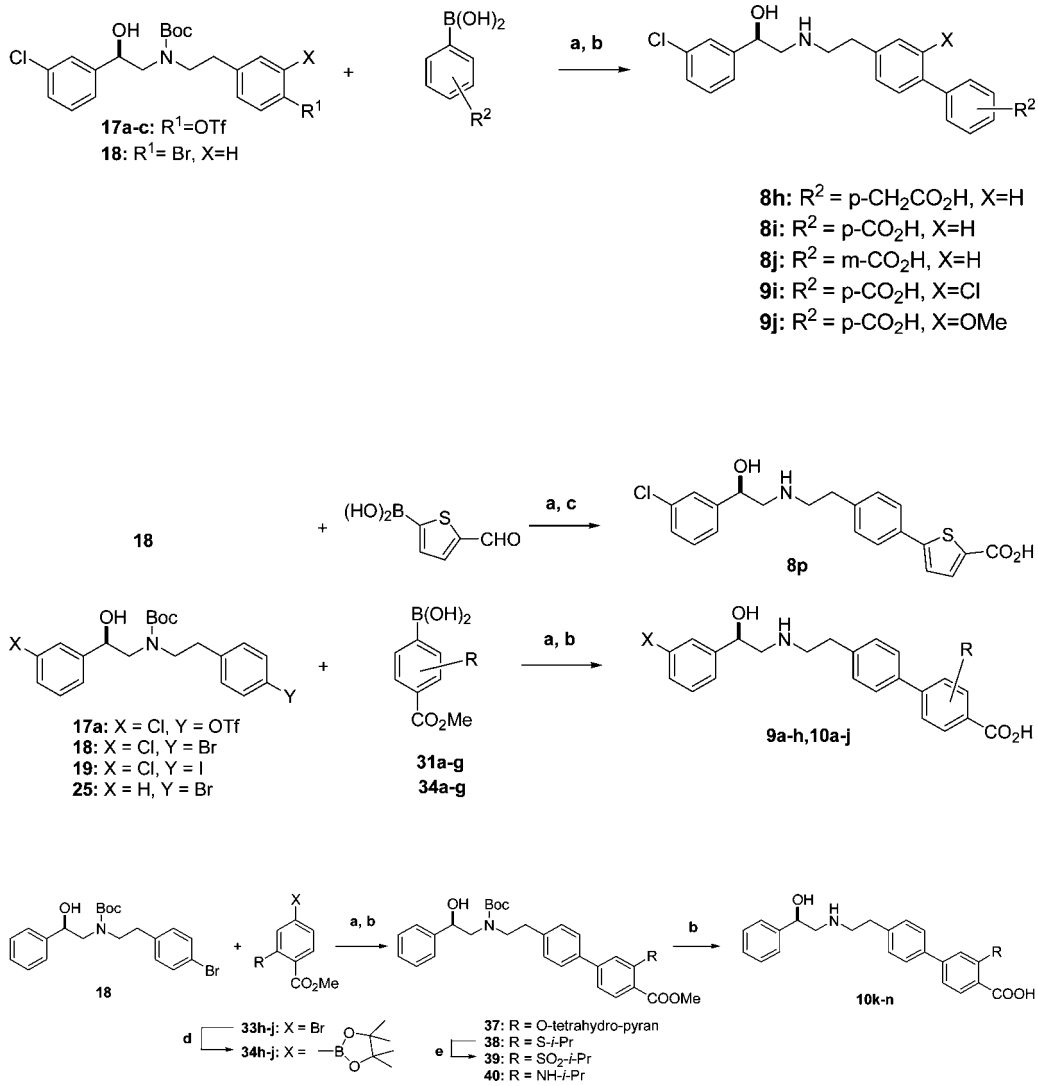
All compounds were evaluated for the ability to produce cAMP in Chinese hamster ovary (CHO) cell lines expressing cloned human β_3- and β_1-ARs. Selected compounds were also evaluated for human β_2 activity using a similar method. The results for reference compounds, isoproterenol (ISP; nonselective β-AR agonist) and FK175 (**4**), are shown for comparison in Table 1. Pharmacokinetic (PK) properties of selected compounds were evaluated by cassette dosing assay in dogs. [19]

To assess the quality of biaryl phenoxy acetic acid analogues as potent, selective β_3-AR agonists with good oral absorption, we first investigated the effect of the biphenyl junction (Table 1, **8a**−**g**). As a baseline, biphenyl ether **8a** was initially prepared and characterized. While **8a** showed moderate agonistic activity for the β_3-AR, it also displayed strong β_1-AR activity and, therefore, a low β_1/β_3 selectivity (β_2-AR activity was not tested). Furthermore, **8a** was evaluated in the in vivo PK assay (p.o. and i.v.) in dogs. The PK parameters are presented in Table 2. Compound **8a** showed moderate oral bioavailability ($F = 39\%$), low clearance, and a moderate plasma half-life ($t_{1/2} = 4.7$ h, i.v).

We next performed initial SAR work on replacement of the oxygen and found that the NH junction analogue **8b** has stronger β_3-AR agonist activity than **8a** but similarly poor selectivity. Likewise, the replacement of the oxygen with other linker groups (Table 1, **8c**−**f**) resulted in insufficient potency for β_3 and selectivity for β_1. However, the biphenyl analogue **8g** showed an improvement of potency for β_3 and good selectivity for β_1 relative to **8a**. Next, these compounds (**8b**−**g**) were evaluated in the cassette dosing assay.[19] The C_{max} and AUC ratio value of **8a** are presented as 1.0 for comparison in Table 1. The methylene and sulfide analogues **8d** (ClogP = 2.39) and **8e** (ClogP = 2.70) exhibited better properties than **8a** (ClogP = 2.42) at the C_{max} and AUC level. On the other hand, the NH, NMe, and carbonyl analogues **8b** (ClogP = 2.0), **8c** (ClogP = 2.36), **8f** (ClogP = 1.67) resulted in decreased C_{max} and AUC levels relative to **8a**. In particular, the carbonyl analogue **8f** showed C_{max} level. Although the biphenyl analogue **8g** (ClogP = 2.21) showed a slightly lower C_{max} ratio than **8a**, and it showed a comparable AUC level to **8a**.

Because the biphenyl analogue **8g** exhibited moderate in vitro potency and PK profiles, we investigated the effect of modification of the carboxylic acid moiety of **8g**. The phenylacetic acid analogue **8h** showed slightly less β_3-AR activity than **8g**; however, the benzoic acid analogue **8i** had improved β_3-AR activity ($EC_{50} = 6.7$ nM) and selectivity ($\beta_1/\beta_3 = 42$, β_2 EC_{50} > 10000 nM). The shift of the acid substituent to the meta position **8j** resulted in less potency relative to **8i**, suggesting that the position of the carboxylic acid in these biphenyl analogues is important for β_3-AR activity and selectivity. Furthermore, the benzoic acid analogue **8i** showed a drastic improvement in C_{max} and AUC ratio relative to **8g**. The pharmacokinetic parameters of this compound are shown in Table 2. Compound **8i** possessed lower clearance (CL = 4.0 mL/min/kg) and displayed excellent oral bioavailability (F >

Scheme 3. General Synthesis Route of Biphenyl Analogues[a]

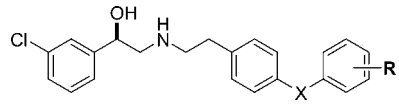


[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70°C; (b) 1 N NaOH aq, EtOH or MeOH, then 4 N HCl/AcOEt or dioxane; (c) 30% H_2O_2, 80% $NaClO_2$, MeCN, 40–50 °C, then 4 N HCl/dioxane; (d) KOAc, pinacol diborane, $PdCl_2$ $(PPh_3)_2$, dioxane, 90–100 °C; (e) *m*-CPBA, CH_2Cl_2.

95%) and a long plasma half-life ($t_{1/2}$ = 12.3 h, i.v.) in Table 2. In consideration of the superior PK profile of **8i** compared to **8a** and **8g**, the benzoic acid moiety may contribute to the improvement of PK properties. We attempted to utilize the benzoic acid moiety with the biphenyl ether derivative **8a**. As expected, biphenyl ether derivatives **8k** and **8l** showed superior C_{max} and AUC ratio relative to the original compound **8a**. Indeed, benzoic acid analogue **8k** possessed a lower clearance (CL = 4.1 mL/min/kg) and a longer plasma half-life ($t_{1/2}$ = 6.2 h, i.v.) relative to the corresponding phenoxy acetic acid analogue **8a** and showed acceptable oral bioavailability (F = 40%) in Table 2. However, the *para*- and *meta*-substituted **8k** and **8l** did not have improved β_3-AR activity compared to **8a**. In addition, the NH junction analogues (*para*, **8m**; *meta*, **8n**) resulted in good potency for β_3 but insufficient selectivity for β_1/β_3. Next, we investigated replacement of the terminal phenyl ring of the biphenyl analogue **8i** with typical heterocycles. Pyridine analogue **8o** showed a 5-fold decrease in β_3-AR potency and a dramatic decrease in β_1/β_3 selectivity relative to **8i**. Thiophene analogue **8p** maintained β_3-AR potency and somewhat decreased β_1/β_3 selectivity than **8i**. These data suggested that introduction of a polar group such as pyridine may cause reduction in β_3-AR activity and β_1/β_3 selectivity. In addition, cassette dosing assay of these heterocycle analogues (**8o**, **8p**) resulted in decreased C_{max} and AUC levels relative to **8i**. Finally, the pyridine-ether analogue **8q**, with a similar RHS part to LY377604, was prepared and examined. For β_3-AR activity, **8q** showed stronger potency than the phenyl ether analogue **8k** and a moderate PK profile but a substantial loss of β_1/β_3 selectivity.

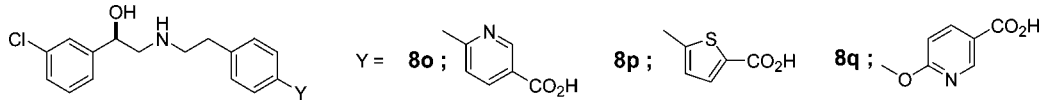
The results of preliminary SAR work and cassette dosing assay led to the generation of lead compound **8i** with an excellent PK profile. Next, we focused our attention on further optimization of the biphenyl analogue **8i**, in which substituents were introduced at the biphenyl ring to further improve in vitro profile and to keep the good PK profile, as shown in Table 3. First, we examined the effect of substituents at the R^1 position (**9a**−**d**). The methyl analogue **9a** showed less potency and maintained selectivity compared with **8i**. Introduction of a fluorine atom resulted in somewhat lower activity (**9b**, EC_{50} = 9.8 nM) and equal selectivity (β_1/β_3 = 39), while chloro analogue **9c** was less potent than **8i**. However, methoxy analogue **9d** maintained potency (EC_{50} = 4.8 nM) and slightly improved selectivity (β_1/β_3 = 52). Next, the effect of substituents at the R^2 position were examined. Introduction of the methyl group (**9e**) provided stronger β_3-AR activity (EC_{50} =1.8 nM), while selectivity for β_1/β_3 decreased somewhat compared with **8i**. Fluoro and chloro analogues **9f** and **9g** showed good β_3-AR

Table 1. SAR of Biaryl Analogues



cmpd	X	R	human β_3 EC_{50},[a] nM (IA)[b]	human β_1 EC_{50},[a] nM	β_1/β_3	cassette assay[c] (p.o.) C_{max} ratio[d]	cassette assay[c] (p.o.) AUC ratio[e]
8a	O	*p*-OCH_2CO_2H	48 ± 4 (0.72)	37	1.3	1.0	1.0
8b	NH	*p*-OCH_2CO_2H	12 ± 2 (1.1)	9.2 ± 0.5	0.77	0.42	0.54
8c	NMe	*p*-OCH_2CO_2H	>100 (0.45)	63	<0.63	0.37	0.33
8d	CH_2	*p*-OCH_2CO_2H	39 (0.66)	64	1.6	1.39	1.26
8e	S	*p*-OCH_2CO_2H	85 ± 2 (0.58)	>100	>1.1	1.66	1.83
8f	C═O	*p*-OCH_2CO_2H	61 (0.69)	>100	>1.6	0.05	0.05
8g	bond	*p*-OCH_2CO_2H	18 ± 2 (0.97)	>100	>5.5	0.69	0.93
8h	bond	*p*-CH_2CO_2H	32 ± 1 (0.81)	300	9.4	NT	NT
8i	bond	*p*-CO_2H	6.7 ± 0.3 (0.96)	280 ± 40	42	3.26	6.83
8j	bond	*m*-CO_2H	91 ± 5 (0.53)	>100	>1	NT	NT
8k	O	*p*-CO_2H	100 (0.51)	>100	>1	2.11	2.84
8l	O	*m*-CO_2H	39 ± 1 (0.64)	>100	>2.6	2.89	5.15
8m	NH	*p*-CO_2H	4.6 ± 0.7 (0.97)	3.9	0.85	NT	NT
8n	NH	*m*-CO_2H	5.5 ± 0.4 (0.97)	36 ± 0.6	6.7	NT	NT
8o[f]			33 ± 0.6 (0.79)	11	0.33	0.89	1.4
8p[f]			7.5 ± 0.4 (0.86)	200 ± 8.8	27	0.70	1.9
8q[f]			8.7 ± 0.8 (0.90)	1.4	0.16	1.04	0.99
4 (FK175)[g]			16 ± 2.0 (0.98)[h]	>3200[h]	>200	NT	NT
ISP			0.97 ± 0.1 (1.0)	0.084 ± 0.02	0.087	NT	NT

[a] The results are shown as the mean ± SE ($n \geq 3$) or are 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 ISP (isoproterenol; 10^{-7} M). [c] Dose 0.32 or 1.0 mg/kg p.o. ($n = 2$). See references and notes[19] for further details. [d] The ratio was defined between the C_{max} of test compounds and the C_{max} of **8a**. The ratio value of **8a** was presented as 1.0. [e] The ratio was defined between the AUC of test compounds and the AUC of **8a**. The ratio value of **8a** was presented as 1.0. [f]



[g] Data for the carboxylic acid form of FK175; NT = not tested. [h] Results are the mean ± SE of five experiments.

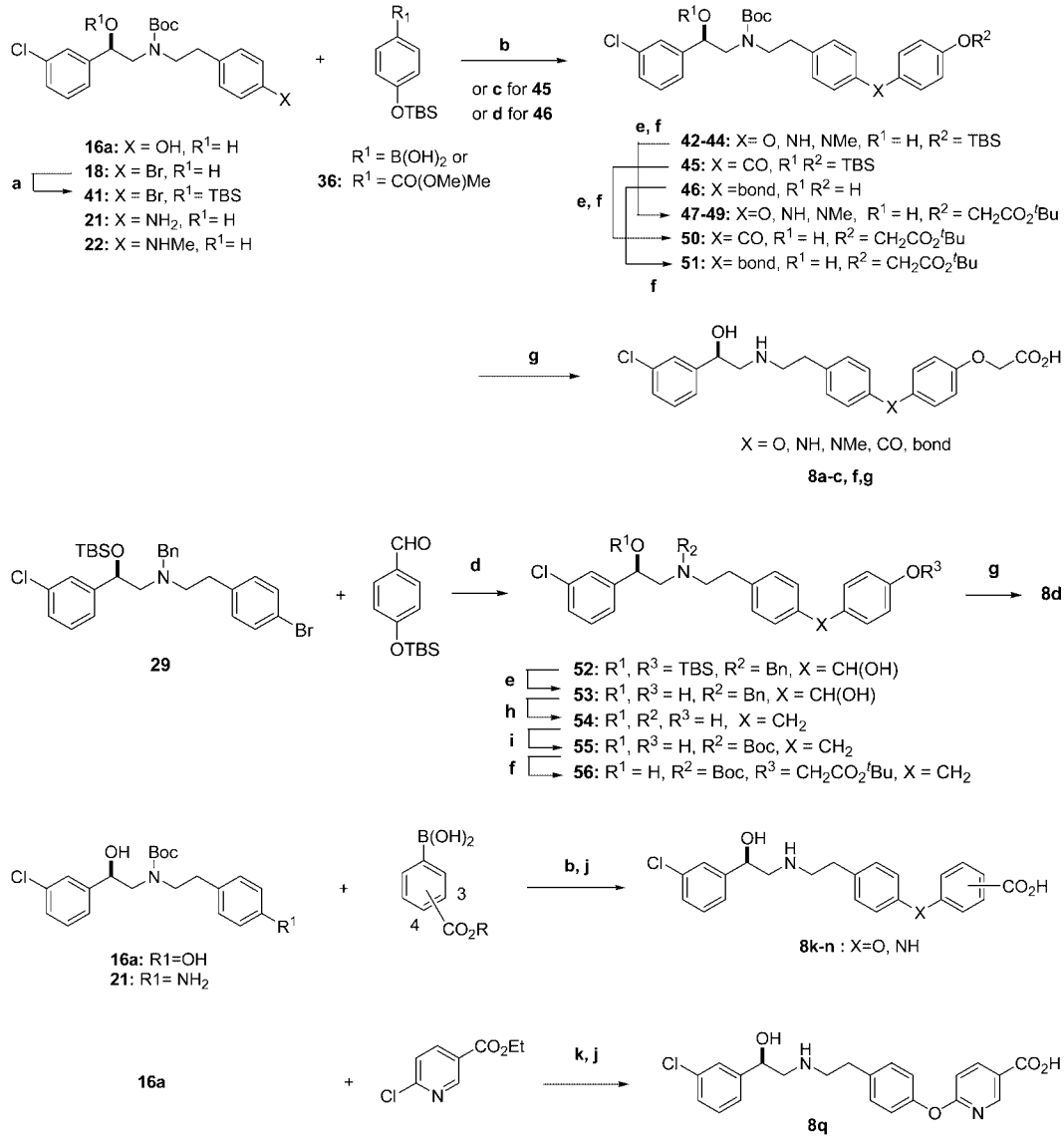
activity but less selectivity than **8i**. Furthermore, methoxy analogue **9h** showed 10-fold increased β_3-AR activity (EC_{50} = 0.62 nM) compared to **8i**. However, **9h** has strong β_1-AR activity (EC_{50} = 18 nM) and resulted in insufficient selectivity for β_1/β_3. We next examined the effect of substituents at the R^3 position of the central phenyl ring. The chloro and methoxy analogues **9i** and **9j** were less potent and had greatly lowered β_1 selectivity. From the results of the SAR study, compounds **9d** and **9e** were selected and evaluated in a cassette dosing assay in dogs because these compounds showed a good combination of potency and moderate selectivity for β_1/β_3. Methoxy and methyl analogues **9d** and **9e** retained a C_{max} ratio relative to the lead compound **8i** (C_{max} ratio: **8i** = 1.0, **9d** = 0.96, **9e** = 0.87). Furthermore, **9d** and **9e** were evaluated in PK assay and showed good pharmacokinetic profiles in dog (**9d**: $t_{1/2,i.v.}$ = 7.1 h, CL = 4.9 mL/min/kg, F = 58%; **9e**: $t_{1/2,i.v.}$ = 19.3 h, CL = 2.1 mL/min/kg, F = 40%, data not shown).

Comparison of the substituted biphenyl analogues in Table 3 indicated that the order of their potency was $R^2 > R^1 > R^3$ and selectivity for β_1/β_3 was $R^1 > R^2 > R^3$. These results suggest that R^2-substituted analogues might tend to be strong for β_1-AR. On the other hand, R^1-substituted analogues may tend to decrease the β_1-AR activity (compare **9d** vs **9h**). Therefore, our attention was focused on further exchange of R^1 substituents to improve potency and selectivity.

Initially, the effect of introduction of more lipophilic and/or bulky substitution on the R^1 position was examined, as shown in Table 4. Replacement of the methoxy group (**9d**, ClogP = 2.46) with an isopropyl group at the R^1 position resulted in compound **10a** having more lipophilicity (**10a**, ClogP = 3.30) and bulk, and resulted in a 6-fold increased potency (**10a**, EC_{50} = 1.1 nM) and a dramatic improvement in selectivity (β_1/β_3 = 654) compared with the lead compound **8i**. More lipophilic and bulky substitutions, such as isobutyl (**10b**, ClogP = 3.92) and cyclohexyl (**10c**, ClogP = 4.49) analogues resulted in further improvement in β_3-AR potency (**10b**, EC_{50} = 0.59 nM; **10c**, EC_{50} = 0.46 nM). The alkyl isobutyl-substituted analogue **10d** (ClogP = 3.81) also displayed high potency and selectivity (EC_{50} = 0.54 nM, β_1/β_3 > 1850), suggesting that lipophilicity and bulk at the R^1 position might contribute to improvement in β_3-AR potency and selectivity for β_1/β_3. Furthermore, these compounds **10a**–**10d** were evaluated in the cassette dosing assay in dogs. The C_{max} ratio value of **8i** is presented as 1.0 for comparison in Table 4. The *O*-isopropyl analogue **10a** had a 1.7-fold less C_{max} ratio relative to the lead compound **8i**. Surprisingly, the *O*-isobutyl (**10b**), *O*-cyclohexyl (**10c**), and isobutyl (**10d**) analogues resulted in dramatically decreased C_{max} levels, and especially **10b** and **10c** led to a complete loss of C_{max}, in spite of enhancing passive permeability data in PAMPA.[20]

On the basis of these data, we attempted to adjust lipophilicity of the molecules in this series by removal of the chloro atom on the phenyl ring in the left-hand side (LHS) to keep oral absorption. As shown in Table 4, O-*i*-Pr analogue **10e** maintained β_3-AR activity (EC_{50} = 2.0 nM), selectivity, and C_{max} ratio relative to the corresponding chloro phenyl analogue (**10a**). More lipophilic R^1 = O-*i*-Bu (**10f**, ClogP = 3.20) and R = O-*c*-hex (**10g**, ClogP = 3.78) analogues relative to O-*i*-Pr group (**10e**, ClogP = 2.58), as expected, showed higher β_3-AR activity (**10f**, EC_{50} = 0.81 nM; **10g**, EC_{50} = 0.30 nM) and good selectivity compared with **8i**. Unfortunately, in the cassette dosing assay, the O-*i*-Bu (**10f**), O-*c*-hex (**10g**), and isobutyl (**10i**) analogues resulted in dramatically decreased C_{max} levels compared with the O-*i*-Pr analogue **10e**. Likewise, the O-phenyl

Scheme 4. General Synthesis Route of Biaryl Analogues[a]



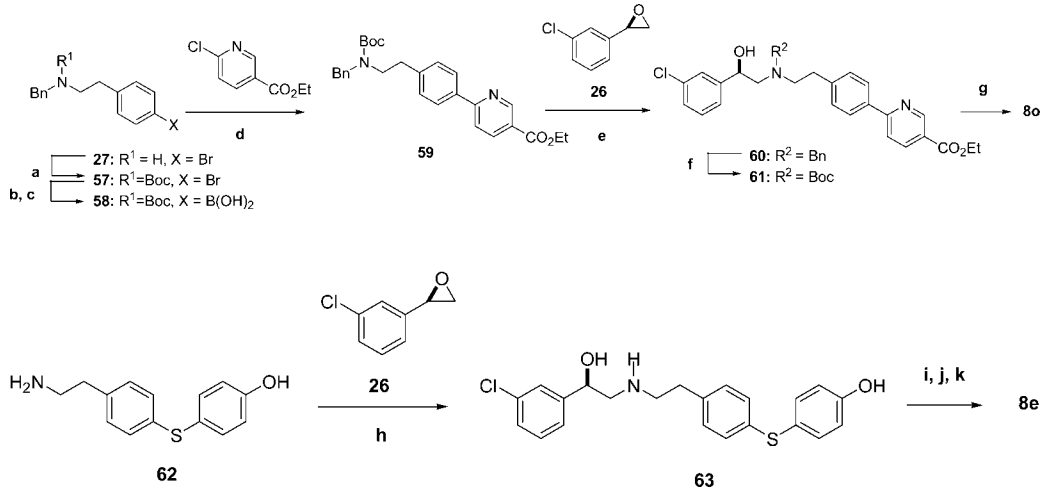
[a] Reagents and conditions: (a) TBSCl, imidazole, *N*,*N*-DMF; (b) $Cu(OAc)_2$, MS 4 Å, CH_2Cl_2; (c) BuLi (1.59 M in hexane), THF, −70 °C, **41**; (d) $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70 °C; (e) Bu_4NF (1 N in THF), THF; (f) $BrCH_2CO_2t$-Bu, K_2CO_3, *N*,*N*-DMF; (g) 4 N HCl/dioxane; (h) HCl, 10% Pd/C, EtOH, chlorobenzene; (i) $(Boc)_2O$, THF, H_2O; (j) 1 N NaOH aq, EtOH or MeOH, then 4 N HCl/AcOEt or dioxane; (k) K_2CO_3, DMSO, 80 °C.

(**10h**, ClogP = 3.71) and isobutyl-substituted analogues (**10i**, ClogP = 3.09) resulted in high potency (**10h**, EC_{50} = 0.34 nM; **10i**, EC_{50} = 0.60 nM) and good selectivity, while C_{max} levels decreased compared with **10e**. These results showed the same trends of SAR and C_{max} levels as 3-chlorophenyl analogues (**10a**−**d**) and phenyl analogues (**10e**−**10i**). Although these compounds (**10c**, **10g**, **10i**) showed high passive permeability in PAMPA, C_{max} levels of these compounds were poor. We next introduced an O-ethoxy ethyl group (**10j**) to reduce lipophilicity (**10j**, ClogP = 2.02) relative to O-*i*-Pr analogue **10e**. As a result, O-ethoxy ethyl analogue **10j** showed 2-fold decreased potency (EC_{50} = 4.3 nM), however, C_{max} levels of **10j** were improved relative to **10e**. Tetrahydropyran analogue **10k**, having reduced lipophilicity and maintaining the bulky size relative to the corresponding O-*c*-hex analogue **10g**, resulted in 10-fold lower β_3-AR activity relative to **10g** and a poor C_{max} level. It was suggested that the lipophilicity at the R^1 position contributes to the strong β_3-AR potency but not the bulky size.

We next turned our attention to the junction part of the O-*i*-Pr group. Replacing the oxygen of **10e** with a sulfur atom yielded compound **10l**, which displayed good activity (EC_{50} = 0.56 nM) and selectivity relative to **10e**, but with a poor C_{max} level. Sulfone analogue **10m** (ClogP = 1.62), designed to reduce the lipophilicity relative to **10e**, retained activity and good selectivity compared with **10e**, but showed a low C_{max} level. The amino junction analogue **10n**, having increased lipophilicity (**10n**, ClogP = 3.35) relative to **10e**, provided a greater improvement in β_3-AR potency (EC_{50} = 0.29 nM) and good selectivity; however, the C_{max} level was decreased. Finally, we investigated the removal of the carboxylic acid group of **9d**. Actually, compound **10o**[21] resulted in a substantial loss of potency for β_3 and selectivity of β_1/β_3 relative to **9d**, and the C_{max} level was poor.

After SAR examination and study with the cassette dosing assay, we selected **10a** and **10e** as potential candidates because they showed a good combination of potency and selectivity for β_1- and β_2-AR activity compared with lead compound **8i** and FK175. To confirm their PK profiles, **10a** and **10e** were evaluated in a PK assay (p.o. and i.v.). Table 5[22] shows pharmacokinetic data in rats, dogs and monkeys for **10a**, **10e**, and FK175. Compound **10a** possessed a low clearance in all three species (rats, 4.4 mL/min/kg; dogs, 4.9

Scheme 5. Synthesis Route of **8e** and **8o**[a]



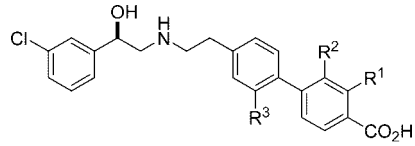
[a] Reagents and conditions: (a) $(Boc)_2O$, THF; (b) KOAc, pinacol diborane, $PdCl_2(PPh_3)_2$, dioxane, 90–100 °C; (c) $NaIO_4$, NH_4OAc, acetone, H_2O; (d) $Pd(PPh_3)_4$, aq $NaHCO_3$, DME, 70 °C; (e) 4 N HCl/dioxane, then Et_3N, **20**, EtOH, reflux; (f) HCl, 10% Pd/C, EtOH, chlorobenzene, then $(Boc)_2O$, aq NaOH (pH = 7–8), THF; (g) 1 N NaOH aq, EtOH, then 4 N HCl/dioxane; (h) BSA, DMSO, 80 °C; (i) $(Boc)_2O$, THF, H_2O; (j) $BrCH_2CO_2t$-Bu, K_2CO_3, *N*,*N*-DMF; (k) 4 N HCl/dioxane.

Table 2. Pharmacokinetic Profiles of Compounds **8a**, **8i**, and **8k** in Dogs[a]

	p.o.			i.v.			
cmpd	dose (mg/mL)	C_{max} (ng/mL)	$AUC_{0-24\ h}$ (ng·hr/mL)	dose (mg/mL)	$T_{1/2\beta}$ (hr)	CL_{tot} (mL/min/kg)	F (%)[b]
8a	1.0	118.9	869.7	0.1	4.7	6.4	39
8i	0.32	110.7	1976.1	0.1	12.3	4.0	>95
8k	1.0	236.1	2469.9	0.1	6.2	4.1	40

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

Table 3. SAR of Substituted Biphenyl Analogues



cmpd	R^1	R^2	R^3	human ß$_3$ EC_{50},[a] nM (IA)[b]	human β_1 EC_{50},[a] nM	β_1/β_3	human β_2 EC_{50},[a] nM
8i	H	H	H	6.7 ± 0.3 (0.96)	280 ± 40	42	>10000
9a	Me	H	H	15 ± 1 (0.82)	570 ± 60	38	NT
9b	F	H	H	9.8 ± 0.1 (0.85)	380 ± 29	39	NT
9c	Cl	H	H	17 ± 0.3 (0.87)	260 ± 5.7	15	NT
9d	OMe	H	H	4.8 ± 0.4 (0.99)	251 ± 26	52	>10000
9e	H	Me	H	1.8 ± 0.1 (0.99)	63 ± 8	35	>10000
9f	H	F	H	4.9 ± 1 (0.87)	20 ± 0.3	4	NT
9g	H	Cl	H	2.0 (0.96)	30	15	NT
9h	H	OMe	H	0.62 (0.97)	18	29	NT
9i	H	H	Cl	9.7 (0.92)	3.1	0.32	NT
9j	H	H	OMe	12 (0.90)	6.5	0.54	NT

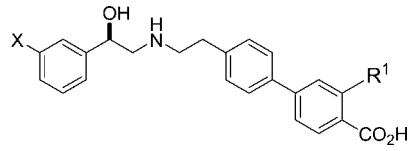
[a] The results are shown as the mean ± SE ($n \geq 3$) or presented as the average of two experiments. [b] The intrinsic activity (IA) was defined as the ratio between the maximal effect of test compound and the maximal effect produced by isoproterenol (10^{-7} M).

mL/min/kg; monkeys, 0.9 mL/min/kg) and a long plasma half-life in dogs (9.8 h) and monkeys (18.6 h). Oral bioavailability for **10a** was moderate to high in all three species (rats, 61%; dogs, 45%; monkeys, 83%). Compound **10e** possessed both low clearance and a long plasma half-life in all three species ($t_{1/2,i.v.}$, rats, 9.5 h; dogs, 14.5 h; monkeys, 22.2 h; CL, rats, 7.5 mL/min/kg; dogs, 4.8 mL/min/kg; monkeys, 1.4 mL/min/kg). Compound **10e** also displayed good oral bioavailability in all three species (rats, F = 80%; dogs, F = 68%; monkeys, F = 62%). In comparison with FK175, biphenyl benzoic acid analogues **10a** and **10e** displayed great improvement in not only oral bioavailability in rats and monkeys but also plasma half-life in all three species, which might contribute to their lower total clearance.

Furthermore, compounds **10a** and **10e** did not shown significant inhibitory activity of the major liver enzymes CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 (IC_{50} > 10μM). In liver microsomes, **10a** and **10e** showed good stability to human and all other species in terms of in vitro clearance (Table 6). These results indicate that **10a** and **10e** are predicted to display a good PK profile with a once daily dosing (u.i.d.) in humans.

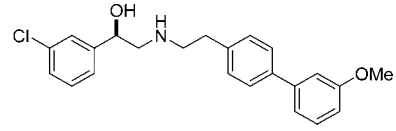
Next, we examined the inhibitory effect of compounds **10a** and **10e** on carbachol-induced increase of intravesical pressure (IVP) in anesthetized dogs for OAB model, in comparison with the effect of FK175. Before conducting in vivo experiments, we confirmed the in vitro potency of **10a** and **10e** for not only human β_3-AR activity, but also dog β_3-AR activity in CHO cell lines. As shown in Table 7, both **10a** and **10e** showed more

Table 4. SAR of Substituted Biphenyl Analogues



Compd	X	R^1	Human β_3 EC_{50} ,nM [a] (IA [b])	Human β_1EC_{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]	ClogP	PAMPA [e] (pH6.5) $\times10^{-6}$ cm/sec
8i	Cl	H	6.7 ± 0.32 (0.96)	280 ± 40	42	>10000	>1490	1.0	2.75	NT
9d	Cl	OMe	4.8 ± 0.4 (0.99)	251 ± 26	52	>10000	>2170	0.96	2.46	3.3
10a	Cl	O-*iso*-Pr	1.1 ± 0.1 (0.98)	720 ± 106	654	>10000	>9090	0.58	3.30	>30
10b	Cl	O-*iso*-Bu	0.59 ± 0.05 (1.0)	350 ± 72	593	NT	NT	0.03	3.92	NT
10c	Cl	O-*c*-Hex	0.46 ± 0.1 (1.0)	55 ± 5	120	NT	NT	0.0	4.49	>30
10d	Cl	*iso*-Bu	0.54 ± 0.1 (0.95)	>1000	>1850	NT	NT	0.10	3.81	NT
10e	H	O-*iso*-Pr	2.0 ± 0.06 (0.97)	>1000	>500	>10000	>5000	0.52	2.58	18
10f	H	O-*iso*-Bu	0.81 ± 0.1 (0.99)	>1000	>1230	NT	NT	0.03	3.20	NT
10g	H	O-*c*-Hex	0.30 ± 0.02 (1.0)	260 ± 45	867	NT	NT	0.0	3.78	>30
10h	H	O-Ph	0.34 ± 0.06 (1.0)	980 ± 15	2880	NT	NT	0.12	3.71	NT
10i	H	*iso*-Bu	0.60 ± 0.12 (0.99)	>1000	>1667	>10000	>16670	0.14	3.09	26
10j	H	$O(CH_2)_2$ OEt	4.3 ± 0.4 (0.98)	>1000	>232	NT	NT	1.28	2.02	NT
10k	H		4.0 ± 0.2 (1.0)	>1000	>250	NT	NT	0.16	1.38	NT
10l	H	S-*iso*-Pr	0.56 ± 0.1 (1.1)	>1000	>1785	>10000	>17800	0.16	2.80	10
10m	H	SO_2-*iso*-Pr	2.2 ± 0.4 (0.99)	>1000	>454	NT	NT	0.04	1.62	NT
10n	H	NH-*iso*-Pr	0.29 ± 0.02 (1.0)	170 ± 20	586	NT	NT	0.06	3.35	NT
10o [f]	-	-	180	140	0.78	NT	NT	0.03		NT
4 [g]			16 ± 2.0 (0.98) [h]	>3200 [h]	>200	>10000	>630	NT		NT

[a] The results are shown as the mean ± SE ($n \geq 3$) 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 (10^{-7} M). [c] Dose 0.10 or 0.20 mg/kg p.o. ($n = 2$–3). [d] The ratio was defined between the C_{max} of test compounds and the C_{max} of **8i**. The ratio value of **8i** was presented as 1.0. [e] See ref 20. [f]



[g] Data for the carboxylic acid form of FK175. [h] Results are the mean ± SE of five experiments; NT = not tested.

potent dog and human β_3-AR activity relative to FK175. On the other hand, in the in vivo experiment, intraduodenally administered **10a** and **10e** reduced the IVP in a dose-dependent manner with the ED_{50} and EC_{50} values listed in Table 7, respectively, and these efficacies were significantly improved compared with FK175. The improvement of in vitro potency led to an increase in in vivo efficacy. As shown in Figure 4, intraduodenally administered **10e** inhibited the IVP increase in a dose-dependent manner with a long duration of action. This in vivo result was first demonstrated with β_3-AR agonists as an

Table 5. Pharmacokinetic Profiles of Compound **10a**, **10e**, and FK175[a]

		p.o., (n = 3)			i.v., (n = 2–3)			
cmpd	species	dose (mg/kg)	C_{max} (ng/mL)	$AUC_{0-24\ h}$ (ng·hr/mL)	dose (mg/kg)	$T_{1/2\beta}$ (hr)	CL_{tot} (mL/min/kg)	F^b (%)
10a	rat [c]	0.32	146 ± 51	700 ± 19	0.32	4.8	4.4	61
	dog	0.1	13.0 ± 1.1	149 ± 8.7	0.1	9.9 ± 0.4	4.9 ± 0.6	45
	monkey [c]	0.32	171 ± 59	4980 ± 1200	0.32	18.6 ± 2.3	0.9 ± 0.2	83
10e	rat	0.32	94.7 ± 12	565 ± 23	0.32	9.5	7.5	80
	dog	0.2	25.0 ± 1.8	438 ± 45	0.1	14.5 ± 1.9	4.8 ± 0.4	68
	monkey [c]	0.32	185 ± 86	209 ± 65	0.186	22.2 ± 4.0	1.4 ± 0.1	62
4 (FK175) [d]	rat	1.0	38	83	0.83	0.3	47.9	29
	dog	3.2	2070	10600	0.83	1.63	3.7	73
	monkey	1.0	184 ± 22	398 ± 46	0.83	2.28 ± 0.45	11.8 ± 0.8	35
	human [e]	1.0	1340 ± 300	4100 ± 800	NT	NT	NT	

[a] The results are shown as the mean ± SE (n = 3) or presented as the average of two experiments. [b] F = bioavailability. [c] Cassette assay data. [d] All parameters were calculated from the mean plasma concentration of the carboxylic acid form of FK175. The dose of 0.83 mg/kg the carboxylic acid form of FK175 was equivalent to 1 mg/kg FK175. [e] The results are shown as the mean ± SD (n = 8)., NT: Not tested.

Table 6. In Vitro Metabolism in Liver Microsomes CL_{int} (mL/min/kg)[a,b]

cmpd	rat	dog	monkey	human
10a	NT	<1.0	NT	<1.0
10e	N.D.[c]	N.D.[c]	<1.0	<1.0
4 (FK175)[d]	106 ± 5.8	35.4 ± 3.4	NT	18.2 ± 1.4

[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 shown as the mean ± SE (n = 3). [c] N.D. = not determined (<0.1 mL/min/kg). [d] Data for the carboxylic acid form of FK175; NT = not tested.

Table 7. Inhibitory Effect of Intraduodenal Administration of **10a**,**e** and FK175 on the Increase in IVP (intravesical pressure) Induced by Carbachol in Anesthetized Dogs[a]

	in vitro (n = 3)	in vivo (n = 2–3)	
cmpd	dog β_3 EC_{50}, nM (IA)[b]	ED_{50} (μg/kg)	EC_{50} (ng/mL)
10a	1.0 ± 0.17 (0.99)	20.6	6.9
10e	2.9 ± 0.4 (0.97)	25.9 ± 4.6	8.40 ± 1.5
4 (FK175)	30 ± 9 (0.91)[c,d]	270 ± 12	137 ± 6.2[c]

[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 (10^{-7} M). [c] Data for the carboxylic acid form of FK175. [d] Results are the mean ± SE of five experiments.

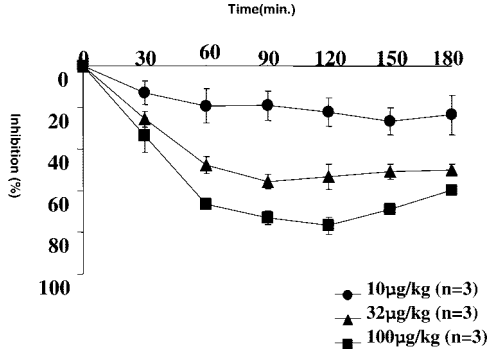


Figure 4. Time course of inhibitory effect of intraduodenal administration of **10e** on the increase in IVP (intravesical pressure) induced by carbachol in anesthetized dogs. Values are mean ± SE of n = 3.

OAB model. From these results, it is thus expected that **10a** and **10e** may be effective in clinical use against OAB.

Conclusions

Replacement of the biphenyl junction and carboxylic acid moiety on the RHS part of the biaryl template afforded lead compound (**8i**) with high oral availability and a long plasma half-life. Importantly, our results suggested that the biphenyl template and the benzoic acid moiety on the RHS are essential for not only potency and selectivity but also good pharmacokinetic properties (Table 4, and compare **9d** vs **10o**). Furthermore, we investigated the effect of substituents on the terminal phenyl ring of lead compound (**8i**) and have discovered that the lipophilicity at the R^1 position contributes to the high potency and selectivity. Although some of the most potent and selective compounds (e.g., **10b**−**d**, **10f**−**i**, **10l**, **10n**) showed poor C_{max} levels, compounds **10a** and **10e**, with the best balance of potency, selectivity, and pharmacokinetic profile, were identified and selected as the leading candidates. In PK assay, compounds **10a** and **10e** displayed good oral bioavailability and long plasma half-lives in all three species. Furthermore, in an OAB model, **10a** and **10e** exhibited a carbachol-induced increase of IVP in our dog model. As a result of these studies, **10a** and **10e** were identified as clinical candidates with a superior balance of potency, selectivity, and pharmacokinetic profiles relative to our previous clinical candidate FK175. These findings suggest that **10a** and **10e** could be attractive therapeutic candidates for the treatment of OAB.

Experimental Section

Chemistry. General Methods. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel (Kanto Chemical, 63-210 μm) was used for chromatographic purification, unless otherwise indicated. Anhydrous solvents were obtained from commercial sources. ^{1}H NMR spectra were recorded on a Brucker Biospin Avance400 or DPX200. Values in ppm relative to tetramethylsilane are given. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded with Micromass LCT. Chemical purity was given by HPLC analysis with a Shiseido capcell pack C18 column (detection at 254 nm). Results of elemental analysis were recorded with Perkin-Elmer 2400II and were within 0.4% of the theoretical values calculated for C, H, and N.

***tert*-Butyl-2-(4-hydroxyphenyl)ethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (16a). Typical Procedure A.** To a mixture of 4-hydroxyphenylacetic acid **12a** (2.4 g, 15.8 mmol), (1*R*)-2-amino-1-(3-chlorophenyl)ethanol hydrochloride **11** (3.0 g, 17.5 mmol), and 1-hydroxybenzotriazole (2.14 g, 17.4 mmol) in *N*,*N*-DMF (20 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2.46 g, 17.4 mmol), and 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 successively with $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give an amide product. To a THF (30 mL) solution of the product, 2 M boran−dimethylsulfide complex in THF (23 mL) was added at room temperature, and the mixture was refluxed for 30 min. To the mixture, 6 N HCl (29.5 mL) was added dropwise below 10 °C, and the mixture was stirred

at room temperature for 3 h. To the reaction mixture, 3 N aqueous NaOH solution (58 mL) below 10 °C was added, and di-*tert*-butyl dicarbonate (3.46 g, 17.4 mmol) 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 1 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 (hexane/EtOAc =4/1–2/1) to give 5.5 g (97%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.66 (m, 2H), 3.25–3.49 (m, 4H), 4.70 (br, 1H), 4.79–4.87 (m, 1H), 5.49 (s, 1H), 6.74 (d, 2H, J = 8 Hz), 6.98 (d, 2H, J = 8 Hz), 7.21–7.31 (m, 3H), 7.34 (s, 1H). MS (ES) *m/e*: 414 (M^+ Na).

4-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)phenyl Trifluoromethanesulfonate (17a). To a solution of **16a** (5.0 g, 12.6 mmol) and 2,6-lutidine (2.97 mL, 25.5 mmol) in CH_2Cl_2 (75 mL) was added Tf_2O (2.36 mL, 14.0 mmol) dropwise at −70 °C under nitrogen, and the mixture was stirred at −70 °C for 30 min. The mixture was allowed to warm to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and water. The organic layer was separated, washed with saturated Na_2CO_3 solution 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) to give 6.6 g (99%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.76 (m, 2H), 3.20–3.42 (m, 4H), 4.35 (br, 1H), 4.88 (br, 1H), 7.20–7.29 (m, 7H), 7.37 (s, 1H). MS (ES) *m/e*: 546 (M^+ Na).

4-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)-2-chlorophenyl Trifluoromethanesulfonate (17b). Compound **17b** was synthesized from **11** and 3-chloro(4-hydroxyphenyl)acetic acid **12b** according to the procedure described for the conversion of **11** to **17a** (84%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.72 (m, 2H), 3.35–3.50 (m, 4H), 4.32 (br, 1H), 4.89 (br, 1H), 7.19–7.38 (m, 7H). MS (ES) *m/e*: 581 (M^+ Na).

4-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)-2-methoxyphenyl Trifluoromethanesulfonate (17c). Compound **17c** was synthesized from **11** and 3-methoxy(4-hydroxyphenyl)acetic acid **19c** according to the procedure described for the conversion of **11** to **17a** (88%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.76 (m, 2H), 3.20–3.42 (m, 4H), 4.35 (br, 1H), 4.88 (br, 1H), 7.20–7.29 (m, 7H). MS (ES) *m/e*: 576 (M^+ Na).

***tert*-Butyl[2-(4-bromophenyl)ethyl][(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (18).** Compound **18** was synthesized from **11** using 4-bromophenylacetic acid **13** according to the procedure A (91%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.69 (m, 2H), 3.15–3.45 (m, 4H), 4.47 (br, 1H), 4.82–4.92 (m, 1H), 6.95–7.04 (m, 2H), 7.21–7.29 (m, 4H), 7.34–7.39 (m, 2H).

***tert*-Butyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-iodophenyl)ethyl]carbamate (19).** Compound **19** was synthesized from **11** using 4-iodophenylacetic acid **14** according to the procedure A (94%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.66 (m, 2H), 3.14–3.42 (m, 4H), 4.51 (br, 1H), 4.80–4.91 (m, 1H), 6.86 (d, 2H, J = 8 Hz), 7.20–7.28 (m, 3H), 7.36 (s, 1H), 7.60 (d, 2H, J = 8 Hz). MS (ES) *m/e*: 524 (M^+ Na).

***tert*-Butyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl][2-(4-nitrophenyl)ethyl]carbamate (20).** Compound **20** was synthesized from **11** using 4-nitrophenylacetic acid **15** according to the procedure A (93%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.85 (m, 2H), 3.25–3.45 (m, 4H), 4.20 (br, 1H), 4.91 (br, 1H), 7.25–7.31 (m, 5H), 7.37 (s, 1H), 8.15 (d, 2H, J = 4 Hz).

***tert*-Butyl[2-(4-aminophenyl)ethyl][(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (21).** To a solution of **20** (3.8 g, 9.0 mmol) in a mixed solution of EtOH (10 mL) and water (3.3 mL) were added iron powder (1.51 g, 27.0 mmol) and NH_4Cl (241 mg, 4.5 mmol). The solution was refluxed for 3 h. After cooling to room temperature, the precipitate was filtered through a pad of Celite. After concentrating under reduced pressure, the residue was partitioned between EtOAc and water. The organic layer was separated, washed with saturated Na_2CO_3 solution and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 3.0 g (85%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.63–2.69 (m, 2H), 3.17–3.43 (m, 4H), 3.57 (s, 2H), 4.63 (s, 1H), 4.81−4.83 (m, 1H), 6.60–6.63 (m, 2H), 6.89–6.91 (m, 2H), 7.21–7.28 (m, 3H), 7.34 (s, 1H). MS (ES) *m/e*: 391 (M^+ H).

***tert*-Butyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]{2-[4-(methylamino)phenyl]ethyl}carbamate (22).** To a solution of **21** (1.75 g, 4.48 mmol) and formaldehyde (37% w/w solution in water, 390 μL, 4.8 mmol) in 1,2-dichloroethane (20 mL) was added $NaBH(OAc)_3$ (1.23 g, 5.8 mmol), and the mixture was stirred at room temperature for 18 h under a nitrogen atmosphere. The resulting mixture was poured into a mixture of 1 N NaOH and $CHCl_3$, and the mixture was stirred for 20 min. 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 = 2/1) to give 550 mg (30%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.62–2.69 (m, 2H), 2.81 (s, 3H), 3.20–3.44 (m, 4H), 4.68–4.71 (m, 1H), 4.81–4.84 (m, 1H), 6.56 (d, 2H, J = 8 Hz), 6.89–6.97 (m, 2H), 7.24–7.31 (m, 3H), 7.34 (s, 1H). MS (ES) *m/e*: 417 (M^+ H).

***tert*-Butyl[2-(4-bromophenyl)ethyl][(2*R*)-2-hydroxy-2-phenylethyl]carbamate (25).** To a mixture of (*R*)-(−)-mandelic acid **23** (23.7 g, 156 mmol), [2-(4-bromophenyl)ethyl]amine **24** (29.7g, 148 mmol), and 1-hydroxybenzotriazole (21.1g, 156 mmol) in *N*,*N*-DMF (210 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (30.0 g, 156 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 successively with 1 N aqueous HCl solution, 15% aqueous K_2CO_3 solution, and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give an amide product (49.5 g, 99.8%). To a solution of the product (49.5 g) in THF (150 mL) and DMI (150 mL) was added 1 M boran−dimethylsulfide complex in THF (470 mL) dropwise under an ice bath, and the mixture was refluxed for 3 h and cooled to about 5 °C. To the mixture, MeOH (35 mL) was added carefully below 10 °C, followed by the addition of concd HCl (60 g), and the mixture was stirred at room temperature for 1 h, refluxed for 1 h, and then evaporated. To the residue was added 30% aqueous K_2CO_3 solution (350 mL) under an ice bath. The resulting mixture was extracted with EtOAc (600 mL × 2), and the organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. To the residue was added *i*-PrOH (200 mL) and concd HCl (40 mL), and the mixture was stirred at room temperature for 16 h. The resultant solid was collected by filtration, washed with *i*-PrOH, and dried to give 51.6 g (98%) of (1*R*)-2-{[2-(4-bromophenyl)ethyl]amino}-1-phenylethanol hydrochloride as a white solid. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.96–3.19 (m, 6H), 4.97–5.04 (m, 1H), 7.21–7.57 (m, 9H), 8.95 (br, 1H), 9.41 (br, 1H). MS (ES) *m/e*: 320, 322 (M^+ H).

To the mixture of the obtained product (7.6 g, 21.3 mmol) in THF (30 mL) and water (30 mL) was added 3 N aqueous NaOH solution (7.5 mL), and the mixture was stirred for 10 min (pH ≈ 8.3). To the mixture was added di-*tert*-butyl dicarbonate (5.1 g, 23.4 mmol) portionally at room temperature. The pH value was kept between 7 and 8 by using 3 N aqueous NaOH solution. The mixture was stirred at room temperature for 1 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 to give 8.9 g (99%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.68 (m, 2H), 3.26–3.45 (m, 4H), 4.20 (br, 1H), 4.88–4.91 (m, 1H), 6.97–7.01 (m, 2H), 7.24–7.41 (m, 7H).

***N*-Benzyl-2-(4-bromophenyl)ethanamine (27).** To a solution of 2-(4-bromophenyl)ethanamine **24** (9.72 g, 48.6 mmol) in toluene (100 mL) were added benzaldehyde (4.94 mL, 48.6 mmol) and *p*-toluenesulfonic acid monohydrate (462 mg, 2.43 mmol), and the mixture was refluxed for 4 h, while water was removed as a toluene azeotrope. After cooling to room temperature, the solvent was

removed by evaporation to give a yellow solid. The solid was dissolved in MeOH (100 mL) and cooled to 5 °C. To the solution was added $NaBH_4$ (1.84 g, 48.6 mmol) portionwise at 5 °C over 5 min. After stirring at the same temperature for 45 min, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water and brine and dried over $MgSO_4$. Filtration followed by evaporation gave a yellow oil. The residue was purified by column chromatography on silica gel (MeOH/$CHCl_3$ = 3/97) to give 10.5 g (74%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.72–2.92 (m, 4H), 3.79 (s, 2H), 6.93–7.10 (m, 2H), 7.23–7.43 (m, 6H). MS (ES) *m/e*: 290 and 292 (M^+ H).

(1*R*)-2-{Benzyl[2-(4-bromophenyl)ethyl]amino}-1-(3-chlorophenyl)ethanol (28). A solution of **27** (13.5 g, 46.5 mmol) in EtOH (270 mL) was added (2*R*)-2-(3-chlorophenyl)oxirane **26** (8.63 g, 55.8 mmol), and the solution was refluxed for 48 h. After cooling to room temperature, the solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 9/1) to give 18.6 g (90%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (dd, J = 10, 13 Hz, 1H), 2.68–2.89 (m, 5H), 3.56 (d, J = 13 Hz, 1H), 3.92 (d, J = 13 Hz, 1H), 4.59 (dd, J = 3.4, 10 Hz, 1H), 6.97 (d, J = 8.3 Hz, 2H), 7.21–7.40 (m, 12H). MS (ES) *m/e*: 444 and 446 (M^+ H).

(2*R*)-*N*-Benzyl-*N*-[2-(4-bromophenyl)ethyl]-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethanamine (29). Compound **29** was synthesized from **28** according to the procedure described for the conversion of **18** to **41** (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 6H), 1.01 (s, 9H), 2.72–2.82 (m, 5H), 2.92 (dd, J = 5.9, 13 Hz, 1H), 3.75 (d, J = 13.7 Hz, 1H), 3.86 (d, J = 13.7 Hz, 1H), 4.71 (t, J = 6.2 Hz, 1H), 7.01 (d, J = 8.3 Hz, 2H), 7.26–7.47 (m, 9H), 7.48 (d, J = 8.3 Hz, 2H). MS (ES) *m/e*: 558 and 560 (M^+ H).

[4-(methoxycarbonyl)-2-methylphenyl]boronic acid (31a). Typical procedure B. To a solution of methyl-4-bromo-3-methylbenzoate **30a** (7.7 g, 31.4 mmol) in dioxane (154 mL) was added bis(pinacolate)diboron (8.6g, 31.4 mmol), $PdCl_2(PPh_3)_2$ (298 mg, 0.42 mmol), and KOAc (9.2 g, 94.2 mmol), and the mixture was stirred at 100 °C for 2–6 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 5/1) to give 8.77 g (94%) of methyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 12H), 2.57 (s, 3H), 3.91 (s, 3H), 7.79–7.82 (m, 3H). MS (ES) *m/e*: 299 (M + Na). To a suspension of the above product (8.76 g, 29.4 mmol) in acetone (175 mL) and water (175 mL) was added NH_4OAc (5.1g, 66.2 mmol) and $NaIO_4$ (14.2g, 66.4 mmol), and the mixture was stirred at room temperature for 15 h. The solvent was evaporated, and the residue was diluted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 5.0 g (81%) of the title compound as a white solid. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.44 (s, 3H), 3.84 (s, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 8.24 (s, 2H). MS (ES) *m/e*: 193 (M^- H).

[4-(Methoxycarbonyl)-3-methylphenyl]boronic Acid (31b). Compound **31b** was synthesized from methyl 4-bromo-2-methylbenzoate **30b** according to the procedure B (76%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.57 (s, 3H), 3.91 (s, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.51–7.63 (m, 2H), 8.26 (s, 2H). MS (ES) *m/e*: 193 (M^- H).

[2-Fluoro-4-(methoxycarbonyl)phenyl]boronic Acid (31c). Compound **31c** was synthesized from methyl 4-bromo-2-fluorobenzoate **30c** according to the procedure B (82%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.85 (s, 3H), 7.59–7.93 (m, 3H), 8.45 (br s, 2H). MS (ES) *m/e*: 197 (M^- H).

[3-Chloro-4-(methoxycarbonyl)phenyl]boronic Acid (31d). Compound **31d** was synthesized from methyl 4-bromo-2-chlorobenzoate **30d** according to the procedure B (70%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.86 (3H, s), 7.73–7.81 (m, 2H), 7.90 (s, 1H), 8.46 (2H, s). MS (ES) *m/e*: 213 (M^- H).

4-(Methoxycarbonyl)-2-methoxyphenylboronic Acid (31e). Typical Procedure C. A procedure similar to procedure B was followed except that the Pd-catalyst was $PdCl_2(dppf)\cdot CHCl_3$. Procedure C was employed using with methly-3-methoxy-4-{[(trifluorpmethyl)sulfonyl]oxy}benzoate **30e** (1.52 g, 4.84 mmol) and $PdCl_2(dppf)\cdot CHCl_3$ (120 mg, 0.147 mmol) to give 450 mg (43%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.85 (s, 3H), 3.91 (s, 3H), 7.43 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.96 (s, 2H). MS (ES) *m/e*: 209 (M^- H).

[2-Fluoro-4-(methoxycarbonyl)phenyl]boronic Acid (31f). Compound **31f** was synthesized from methyl 3-fluoro-4-[[(trifluoromethyl)sulfonyl]oxy]benzoate **30f** according to the procedure C (71%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.87 (s, 3H), 7.50–7.82 (m, 3H), 8.47 (br s, 2H). MS (ES) *m/e*: 197 (M^- H).

[2-Chloro-4-(methoxycarbonyl)phenyl]boronic Acid (31 g). Compound **31g** was synthesized from methyl 3-chloro-4-{[(trifluoromethyl)sulfonyl]oxy}benzoate **30g** according to the procedure C (17%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.87 (s, 3H), 7.56 (d, J = 8.0 Hz, 1H), 7.81–7.86 (m, 2H), 8.53 (s, 2H). MS (ES) *m/e*: 213 (M^- H).

Methyl 4-Bromo-9-isobutoxybenzoate (33c). Typical Procedure D. To a suspension of NaH (60% w/w, 20.5 g, 2.25 equiv) in *N*,*N*-DMF (365 mL) was added 2-methyl-1-propanol (48.7 mL, 2.3 equiv) dropwise below 30 °C over 2.0 h under nitrogen atmosphere. To the mixture was added 4-bromo-2-fluorobenzoic acid **32** (50.0 g, 228 mmol) slowly below 35 °C. To the reaction mixture was added *N*,*N*-DMF (600 mL), and the mixture was stirred at room temperature for 1–4 days. The reaction mixture was partitioned between water (2000 mL) and hexane (1000 mL). The water layer was separated and acidified with 37% HCl (pH = 2.50). The precipitate was collected by filtration, washed with water, and dried to give 4-bromo-2-isobutoxybenzoic acid (62.4 g, 86%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (d, J = 6.5 Hz, 6H), 2.17–2.31 (m, 1H), 4.02 (d, J = 6.5 Hz, 2H), 7.20 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H). To a solution of the above product (14.0 g, 51 mmol) in *N*,*N*-DMF (70 mL) was added K_2CO_3 (14.2 g, 2.0 equiv) and MeI (4.79 mL, 1.5 equiv). The mixture was stirred at room temperature for 1.0 h. The reaction mixture was filtered and the filtrate was extracted with EtOAc−hexane (1/1, 600 mL) and washed with water (500 mL). The water layer was extracted with ethyl EtOAc−hexane (1/1, 200 mL), and the extract was washed with water (200 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. Filtration followed by evaporation under reduced pressure to give 12.0 g (81%) of the title compound as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (d, J = 6.5 Hz, 6H), 2.07–2.21 (m, 1H), 3.78 (d, J = 6.5 Hz, 2H), 3.88 (s, 3H), 7.08 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H). MS (ES) *m/e*: 309, 311(M^+ Na).

Methyl 4-Bromo-2-methoxybenzoate (33a). Compound **33a** was synthesized from **32** and methanol according to the procedure D (89%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.91 (s, 3H), 7.10–7.15 (m, 2H), 7.68 (d, J = 8.5 Hz, 1H). MS (ES) *m/e*: 267, 269(M^+ Na).

Methyl 4-Bromo-2-isopropoxybenzoate (33b). Compound **33b** was synthesized from **32** and 2-propanol according to the procedure D (85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (d, J = 6.0 Hz, 6H), 3.88 (s, 3H), 4.50–4.63 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H).

Methyl 4-Bromo-2-(cyclohexyloxy)benzoate (33d). Compound **33d** was synthesized from **32** and cyclohexanol according to the procedure D (84%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36–1.95 (m, 10H), 3.88 (s, 3H), 4.31–4.39 (m, 1H), 7.06–7.12 (m,2H), 7.64 (d, J = 8.0 Hz, 1H).

Methyl 4-Bromo-2-isobutylbenzoate (33f). Under nitrogen, to a solution of 4-bromo-2-fluorobenzoic acid **32** (6 g, 27.4 mmol) in THF (48 mL) was added 2 M *i*-BuMgCl in THF (41 mL) dropwise on an ice bath. The mixture was stirred at room temperature for 2 h. To the mixture, water (100 mL) was added dropwise below 10 °C, and the mixture was acidified with 1 N HCl (pH = 2–3) and extracted with EtOAc (100 mL × 2). The combined organic

layers were washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a crude 4-bromo-2-isobutylbenzoic acid (6.45 g, 25.1 mmol). To a solution of the above product in *N*,*N*-DMF (52 mL) was added K_2CO_3 (5.3 g, 38.3 mmol) and MeI (2.05 mL, 32.9 mmol). The mixture was stirred at room temperature for 4 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give 3.4 g (46%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, J = 6.5 Hz, 6H), 1.84 (m, 1H), 2.82 (d, J = 7.0 Hz, 2H), 3.87 (s, 3H), 7.36 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H).

Methyl 4-Bromo-2-(2-ethoxyethoxy)benzoate (33g). Compound **33g** was synthesized from **32** and 2-ethoxyethanol according to the procedure D (85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 (t, J = 6.0 Hz, 3H), 3.52 (q, J = 6.0 Hz, 2H), 3.70 (m, 2H), 3.88 (s, 3H), 4.25 (m, 2H), 7.08 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H).

Methyl 4-Bromo-2-(tetrahydro-2*H*-pyran-4-yloxy)benzoate (33h). Compound **33h** was synthesized from **32** and tetrahydro-2*H*-pyran-4-ol according to the procedure D (86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.81–2.06 (m, 4H), 3.57–3.68 (m, 2H), 3.89 (s, 3H), 3.93–4.05 (m, 2H), 4.56–4.62 (m, 1H), 7.11 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H). MS (ES) *m*/*e*: 337, 339 (M^+ Na).

Methyl 4-Bromo-2-(isopropylsulfanyl)benzoate (33i). Compound **33i** was synthesized from **32** and 2-propanthiol according to the procedure D (85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (d, J = 6.5 Hz, 6H), 3.63–4.76 (m, 1H), 3.81 (s, 3H), 7.46 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H).

Methyl 4-Bromo-2-(isopropylamino)benzoate (33j). To a solution of 4-bromo-2-fluorobenzoic acid **32** (2 g, 9.14 mmol) in pyridine (10 mL) was added isopropylamine (3.88 mL, 45.6 mmol) at room temperature, and the mixture was stirred at 100 °C overnight. The mixture was poured into 1 N aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1) to give 4-bromo-2-(isopropylamino)benzoic acid (436 mg,18.5%) as a white solid. MS (ES) *m*/*e*: 450 (M^- H).

To a suspension of the above product (428 mg, 1.66 mmol) and potassium carbonate (480 mg, 3.47 mmol) in *N*,*N*-dimethylformamide (9 mL) was added methyl iodide (0.16 mL, 2.6 mmol) at room temperature, and the mixture was stirred at the same temperature for 1 h. To the mixture was added water and extracted with mixed solvent (*n*-hexane/ethyl acetate = 1/1). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give 423 mg (93.6%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.27 (d, J = 6.2 Hz, 6H), 3.62–3.71 (m, 1H), 3.84 (s, 3H), 6.64 (dd, J = 8.5, 1.9 Hz, 1H), 6.83 (d, J = 1.8 Hz, 1H), 7.70–7.75 (m, 2H).

[3-Methoxy-4-(methoxycarbonyl)phenyl]boronic Acid (34a). Compound **34a** was synthesized from **33a** according to the procedure B (80%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.78 (s, 3H), 3.88 (s, 3H), 7.40 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.58 (s, 1H), 8.29 (s, 2H). MS (ES) *m*/*e*: 209 (M^- H).

[3-Isopropoxy-4-(methoxycarbonyl)phenyl]boronic Acid (34b). Compound **34b** was synthesized from **33b** according to the procedure B (84%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.27 (d, J = 6.0 Hz, 6H), 3.77 (s, 3H), 4.57–4.70 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 8.26 (s, 2H). MS (ES) *m*/*e*: 237 (M^- H).

[3-Isobutoxy-4-(methoxycarbonyl)phenyl]boronic Acid (34c). Compound **34c** was synthesized from **33c** according to the procedure B (72%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.0 (d, J = 6.5 Hz, 6H), 1.96–2.11 (m, 1H), 2.52–2.48 (m, 2H), 3.78 (s, 3H), 7.38 (d, J = 7.5 Hz, 1H), 7.50 (s, 1H), 7.58 (d, J = 7.5 Hz, 1H), 8.26 (s, 2H). MS (ES) *m*/*e*: 251 (M^- H).

[3-(Cyclohexyloxy)-4-(methoxycarbonyl)phenyl]boronic Acid (34d). Compound **34d** was synthesized from **33d** according to the procedure B (58%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.32–1.91 (m, 10H), 3.78 (s, 3H), 4.42–4.49 (m, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 8.25 (s, 2H). MS (ES) *m*/*e*: 277 (M^- H).

[3-(Phenoxy)-4-(methoxycarbonyl)phenyl]boronic Acid (34e). Compound **34e** was synthesized from the corresponding bromide according to the procedure B (59%). MS (ES) *m*/*e*: 271 (M^- H).

[3-Isobutyl-4-(methoxycarbonyl)phenyl]boronic Acid (34f). Compound **34f** was synthesized from **33f** according to the procedure B (63%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.84 (d, J = 6.5 Hz, 6H), 1.70–1.84 (m, 1H), 2.77 (d, J = 7.0 Hz, 2H), 3.82 (s, 3H), 7.68–7.74 (m, 1H), 7.74 (s, 1H), 7.78–7.81 (m, 1H), 8.21 (s, 2H). MS (ES) *m*/*e*: 235 (M^- H).

[3-(2-Ethoxyethoxy)-4-(methoxycarbonyl)phenyl]boronic Acid (34 g). Compound **34g** was synthesized from **33g** according to the procedure B (84%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.12 (t, J = 6.0 Hz, 3H), 3.54 (q, J = 6.0 Hz, 2H), 3.65 (m, 2H), 3.80 (s, 3H), 4.29 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 8.26 (s, 2H). MS (ES) *m*/*e*: 267 (M^- H).

4-{[*tert*-Butyl(dimethyl)silyl]oxy}-*N*-methoxy-*N*-methyl Benzamide (36). To a mixture of 4-hydroxybenzoic acid **35** (5.0 g, 36.2 mmol), *N*-methoxymethanamine (2.87 g, 47 mmol), and 1-hydroxybenzotriazole (4.9 g, 36.2 mmol) in CH_2Cl_2 (120 mL) and *N*,*N*-diisopropylethylamine (7.0 mL, 40 mmol) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (6.9 g, 36.2 mmol) at 4 °C, and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed successively with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give an amide product (3.2 g, 49%). To a solution of the above product (800 mg, 4.41 mmol) and imidazole (330 mg, 4.85 mmol) in *N*,*N*-DMF (8 mL) was added *tert*-butyl(dimethyl)silyl chloride (670 mg, 4.45 mmol), and the mixture was stirred at room temperature for 18 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with 1 N aq NaOH 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) to give 860 mg (66%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.22 (s, 6H), 0.99 (s, 9H), 3.35 (s, 3H), 3.56 (s, 3H), 6.84 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H). MS (ES) *m*/*e*: 318 (M^+ Na).

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-4′-biphenyl-4-carboxylic Acid Hydrochloride (8i). Typical Procedure E. To a solution of **17a** (435 mg, 0.96 mmol) in 1,2-dimethoxyethane (6 mL) were added 4-methoxycarbonylphenyl boronic acid (224 mg, 1.24 mmol), $Pd(PPh_3)_4$ (55 mg, 0.048 mmol), and an aqueous solution of Na_2CO_3 (2 M, 1.0 mL), and the mixture was stirred at 70 °C for 2–5 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 = 3/1–2/1) to give 330 mg (67%) of methyl-4′-(2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]- amino}ethyl)-1,1′-biphenyl-4-carboxylate. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.75–2.85 (m, 2H), 3.34–3.45 (m, 4H), 3.94 (s, 3H), 4.54 (br, 1H), 4.86–4.90 (m, 1H), 7.17–7.28 (m, 5H), 7.37 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 9.0 Hz, 2H). MS (ES) *m*/*e*: 532 (M^+ Na).

Typical Procedure F. To a solution of the obtained product (320 mg, 0.63 mmol) in EtOH or MeOH (2 mL) was added 1 N aq NaOH (1.0 mL, 1.5–2.0 equiv), and the mixture was stirred at 40 °C for 2–4 h. The solvent was removed by evaporation, and the aqueous solution was acidified with 1 N aq HCl and extracted with EtOAc or $CHCl_3$. 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 dioxane or EtOAc (2.0 mL) was added 4 N HCl in dioxane or EtOAc (2.0 mL, 10–15 equiv), and the mixture was stirred at room

temperature for 6–12 h. The resultant solid was collected by filtration and dried to give 200 mg (74%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.27 (m, 6H), 5.01–5.06 (m, 1H), 6.36 (br, 1H), 7.34–7.48 (m, 6H), 7.70–7.81 (m, 4H), 8.02 (d, 2H, J = 8.4 Hz), 9.11 (1H, br). HRMS (M + H)$^+$ found, 396.1371; calcd for $C_{23}H_{23}Cl_1N_1O_3$, 396.1366. Anal. ($C_{23}H_{22}Cl_1N_1O_3 \cdot 1.0HCl$) C, H, N.

[4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-4-biphenylyl]acetic Acid Hydrochloride (8h). Compound **8h** was synthesized from **17a** and [4-(2-methoxy-2-oxoethyl)phenyl]boronic acid according to the procedure described for the conversion of **17a** to **8i** (54%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.90–3.40 (m, 6H), 3.62 (s, 2H), 4.90–5.10 (m, 1H), 7.30–7.70 (m, 12H). MS (ES) *m*/*e*: 410 (M$^+$ H). Anal. ($C_{24}H_{24}Cl_1N_1O_3 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-4′-biphenyl-3-carboxylic Acid Hydrochloride (8j). Compound **8j** was synthesized from **18** and 3-ethoxycarbonylphenyl boronic acid according to the procedure described for the conversion of **17a** to **8i** (54%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.29 (m, 6H), 4.97–5.02 (m, 1H), 6.34 (br, 1H), 6.90 (m, 1H), 7.71–7.48 (m, 9H), 7.89–7.95 (m, 2H), 8.18 (d, J = 1.5 Hz, 1H), 8.96 (br, 1H). MS (ES) *m*/*e*: 394(M$^-$ H). Anal. ($C_{23}H_{22}Cl_1N_1O_3 \cdot 1.0HCl$) C, H, N.

2′-Chloro-4′-(2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino}ethyl)-4′-biphenyl-4-carboxylic Acid Hydrochloride (9i). Compound **9i** was synthesized from **17b** according to the procedure described for the conversion of **17a** to **8i** (41%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.00–3.27 (m, 6H), 5.01–5.07 (m, 1H), 6.37–6.39 (br, 1H), 7.34–7.57 (m, 9H), 8.04 (d, 2H, J = 8.0 Hz), 9.04–9.30 (br, 1H). MS (ES) *m*/*e*: 428 (M$^-$ H). Anal. ($C_{23}H_{21}Cl_2N_1O_3 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-2′-methoxy-4′-biphenyl-4-carboxylic Acid Hydrochloride (9j). Compound **9j** was synthesized from **17c** according to the procedure described for the conversion of **17a** to **8i** (38%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.03–3.27 (m, 6H), 3.80 (s, 3H), 5.03–5.07 (m, 1H), 6.38 (br, 1H), 6.96 (d, 1H, J = 8.0 Hz), 7.06 (s, 1H), 7.29–7.48 (m, 5H), 7.58 (d, 1H, J = 8.0 Hz), 7.96 (2H, d, J = 8.0 Hz), 9.13–9.18 (br, 1H). MS (ES) *m*/*e*: 424 (M$^-$ H). Anal. ($C_{24}H_{24}Cl_1N_1O_4 \cdot 1.0HCl$) C, H, N.

5-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]-2-thiophenecarboxylic Acid Hydrochloride (8p). 5-Formyl-2-thiophene-boronic acid and **18** were reacted according to the procedure E to give *tert*-butyl(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl{2-[4-(5-formyl-2-thienyl)phenyl]ethyl} carbamat (35%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.73–2.83 (m, 2H), 3.32–3.44 (m, 4H), 4.46 (br, 1H), 4.85–4.92 (m, 1H), 7.17–7.28 (m, 5H), 7.36–7.39 (m, 2H), 7.59 (d, J = 8 Hz, 2H), 7.71–7.74 (m, 1H), 9.88 (s, 1H). MS (ES) *m*/*e*: 508 (M + Na).

To a solution of the obtained product (180 mg, 0.37 mmol) in MeCN (2 mL) and pH 4 buffer solution (sodium dihydrogenphosphate, 1 mL) was added 30% H_2O_2 solution (30 μL) and 80% $NaClO_2$ (67 mg, 0.74 mmol) below 10 °C. The reaction mixture was stirred at 50 °C for 3 h. The mixture was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a thiophenecarboxylic acid (160 mg, 86%). A solution of the product (160 mg, 0.32 mmol) and 4 N HCl in dioxane was stirred at room temperature for 24 h. The resultant solid was collected with filtration and dried to give 100 mg (62%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.00–3.25 (m, 6H), 4.95–4.99 (m, 1H), 6.34 (br, 1H), 7.33–7.47 (m, 6H), 7.55 (d, J = 3.9 Hz, 1H), 7.70–7.81 (m, 3H), 9.05 (br, 1H). HRMS (M + H)$^+$ found, 402.0934; calcd for $C_{21}H_{20}Cl_1N_1O_3S_1$, 402.0931. Anal. ($C_{21}H_{20}Cl_1N_1O_3S_1 \cdot 1.0HCl \cdot 1.5H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)-3-methyl-4′-biphenyl-4-carboxylic Acid Hydrochloride (9a). Compound **9a** was synthesized from **17a** and **31b** according to the procedure described for the conversion of **17a** to **8i** (35%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.60 (s, 3H), 3.01–3.34 (m, 6H), 4.98–5.02 (m, 1H), 6.34 (br, 1H), 7.36–7.60 (m, 8H), 7.72 (d, 2H, J = 8.0 Hz), 7.91 (d, 1H, J = 8.0 Hz), 9.25 (br, 1H). MS (ES) *m*/*e*: 408 (M − H). Anal. ($C_{24}H_{24}Cl_1N_1O_4 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)-2-fluoro-4′-biphenyl-4-carboxylic Acid Hydrochloride (9b). Compound **9b** was synthesized from **18** and **31c** according to the procedure described for the conversion of **17a** to **8i** (50%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.33 (6H, m), 4.98–5.03 (1H, m), 6.34 (1H, br), 7.35–7.47 (6H, m), 7.61–7.98 (5H, m), 9.10 (1H, br). MS (ES) *m*/*e*: 412 (M$^-$ H). Anal. ($C_{23}H_{21}Cl_1F_1N_1O_3 \cdot 1.0HCl$) C, H, N.

3-Chloro-4′-(2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino}ethyl)-4′-biphenyl-4-carboxylic Acid Hydrochloride (9c). Compound **9c** was synthesized from **17a** and **31d** according to the procedure described for the conversion of **17a** to **8i** (48%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.28 (m, 6H), 5.00–5.04 (m, 1H), 6.36 (br, 1H), 7.35–7.47 (m, 6H), 7.70–7.91 (m, 5H), 9.07 (br, 1H). MS (ES) *m*/*e*: 428 (M$^-$ H). Anal. ($C_{23}H_{21}Cl_2N_1O_3 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)-3-methoxy-4′-biphenyl-4-carboxylic Acid Hydrochloride (9d). Compound **9d** was synthesized from **18** and **34a** according to the procedure described for the conversion of **17a** to **8i** (30%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.34 (m, 6H), 3.92 (s, 3H), 5.02–5.06 (m, 1H), 6.37 (br, 1H), 7.26–7.74 (m, 11H), 9.25 (1H, br). HRMS (M + H)$^+$ found, 426.1468; calcd for $C_{24}H_{24}Cl_1N_1O_4$, 426.1472. Anal. ($C_{24}H_{24}Cl_1N_1O_4 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)-2-methyl-4′-biphenyl-4-carboxylic Acid Hydrochloride (9e). Compound **9e** was synthesized from **17a** and **31a** according to the procedure described for the conversion of **17a** to **8i** (41%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.28 (s, 1H), 3.01–3.27 (m, 6H), 5.00–5.04 (m, 1H), 6.36 (br, 1H), 7.28–7.48 (m, 9H), 7.79–7.90 (m, 2H), 9.02 (1H, br). HRMS (M + H)$^+$ found, 410.1546; calcd for $C_{24}H_{25}Cl_1N_1O_3$, 410.1523. Anal. ($C_{24}H_{24}Cl_1N_1O_3 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)-2-fluoro-4′-biphenyl-4-carboxylic Acid Hydrochloride (9f). Compound **9f** was synthesized from **18** and **31f** according to the procedure described for the conversion of **17a** to **8i** (49%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.28 (6H, m), 5.02–5.05 (1H, m), 6.38 (1H, br), 7.37–7.87 (11H, m), 9.10 (1H, br). MS (ES) *m*/*e*: 412 (M$^-$ H). Anal. ($C_{23}H_{21}Cl_1F_1N_1O_3 \cdot 1.0HCl$) C, H, N.

9-Chloro-4′-(2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino}ethyl)-4′-biphenyl-4-carboxylic Acid Hydrochloride (9g). Compound **9g** was synthesized from **18** and **31 g** according to the procedure described for the conversion of **17a** to **8i** (41%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.34 (m, 6H), 4.99–5.03 (m, 1H), 6.36 (br, 1H), 7.37–7.55 (m, 9H), 7.93–8.03 (m, 2H), 9.10 (br, 1H). MS (ES) *m*/*e*: 424 (M$^-$ H). Anal. ($C_{23}H_{21}Cl_2N_1O_3 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-2-methoxy-4′-biphenyl-4-carboxylic Acid Hydrochloride (9h). Compound **9h** was synthesized from **18** and **31e** according to the procedure described for the conversion of **17a** to **8i** (23%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.02–3.27 (m, 6H), 3.82 (s, 3H), 4.98–5.02 (m, 1H), 6.35 (br, 1H), 7.30–7.64 (m, 11H), 9.05 (br, 1H). MS (ES) *m*/*e*: 424 (M$^-$ H). Anal. ($C_{24}H_{24}Cl_1N_1O_4 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-3-isopropoxy-4′-biphenyl-4-carboxylic Acid Hydrochloride (10a). Compound **10a** was synthesized from **17a** and **34b** according to the procedure described for the conversion of **17a** to **8i** (72%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.31 (6H, d, J = 6.0 Hz), 2.8–3.0 (6H, m), 4.79 (1H, q, J = 6.0 Hz), 4.8–5.0 (1H, m), 6.33 (1H, m), 7.0–7.9 (11H, m). HRMS (M + H)$^+$ found, 454.1792; calcd for $C_{26}H_{29}Cl_1N_1O_4$, 454.1785. Anal. ($C_{26}H_{28}Cl_1N_1O_4 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-3-isobutoxy-4-biphenylcarboxylic Acid Hydrochloride (10b). Compound **10b** was synthesized from **18** and **34c** according to the

procedure described for the conversion of **17a** to **8i** (59%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (6H, d, J = 6.5 Hz), 2.03–2.07 (1H, m), 3.04–3.23 (6H, m), 3.92 (1H, d, J = 6.5 Hz), 4.98–5.01 (1H, m), 6.35 (br, 1H), 7.25–7.48 (8H, m), 7.71–7.74 (3H, m), 9.92 (1H, br), 12.5 (1H, br). MS (ES) *m/e*: 468 (M + H). Anal. ($C_{27}H_{30}Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.75H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-3-(cyclohexyloxy)-4-biphenylcarboxylic Acid Hydrochloride (10c). Compound **10c** was synthesized from **18** and **34d** according to the procedure described for the conversion of **17a** to **8i** (48%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34–1.86 (10H, m), 3.02–3.25 (6H, m), 4.62–4.66 (1H, m), 4.99 (1H, d, J = 8.5 Hz), 6.34 (1H, br), 7.24–7.48 (8H, m), 7.69–7.71 (3H, m), 9.95 (1H, br). *m/e*: 494 (M + H). Anal. ($C_{29}H_{32}Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.75H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}ethyl)-3-isobutyl-4-biphenylcarboxylic Acid Hydrochloride (10d). Compound **10d** was synthesized from **19** and **34f** according to the procedure described for the conversion of **17a** to **8i** (48%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.88 (d, 6H, J = 6.6 Hz), 1.79–1.92 (m, 1H), 2.92 (d, 2H, J = 7.0 Hz) 3.02–3.32 (m, 6H), 5.00 (br, 1H), 6.34 (1H, br), 7.36–7.89 (m, 11H), 9.0 (br, 1H). MS (ES) *m/e*: 450 (M^- H). Anal. ($C_{27}H_{30}Cl_1N_1O_3 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-isopropoxy-4-biphenylcarboxylic Acid Hydrochloride (10e). Compound **10e** was synthesized from **18** and **34b** according to the procedure described for the conversion of **17a** to **8i** (79%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.31 (6H, d, J = 6.8 Hz), 2.9–3.41 (6H, m), 4.7–4.9 (1H, m), 6.22 (1H, m), 7.2–7.8 (12H, m). MS (ES) *m/e*: 420 (M^+ H). Anal. ($C_{26}H_{29}N_1O_4 \cdot 1.0HCl$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-isobutoxy-4′-biphenyl-4-carboxylic Acid Hydrochloride (10f). Compound **10f** was synthesized from **18** and **34c** according to the procedure described for the conversion of **17a** to **8i** (73%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.02 (t, 6H, J = 6.8 Hz), 1.9–2.1 (m, 1H), 2.9–3.4 (m, 6H), 3.92 (d, 2H, J = 6.8 Hz), 4.9–5.1 (m, 1H), 6.22 (m, 1H), 7.2–7.8 (m, 12H). 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.

3-(Cyclohexyloxy)-4′-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]-amino}ethyl)-4-biphenylcarboxylic Acid Hydrochloride (10g). Compound **10g** was synthesized from **18** and **34d** according to the procedure described for the conversion of **17a** to **8i** (75%). HPLC purity: 98%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2–2.0 (10H, m), 2.9–3.4 (6H, m), 4.64 (1H, m), 4.9–5.1 (1H, m), 6.22 (1H, m), 7.2–7.8 (12H, m). HRMS (M + H)$^+$ found, 460.2494; calcd for $C_{29}H_{34}N_1O_4$, 460.2488.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-phenoxy-4′-biphenyl-4-carboxylic Acid Hydrochloride (10h). Compound **10h** was synthesized from **18** and **34e** according to the procedure described for the conversion of **17a** to **8i** (85%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.9–3.4 (6H, m), 4.9–5.1 (1H, m), 6.22 (1H, m), 6.9–8.0 (17H, m). MS (ES) *m/e*: 454 (M^+ H). Anal. ($C_{29}H_{27}N_1O_4 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-10-isobutyl-4-biphenylcarboxylic Acid Hydrochloride (10i). Compound **10i** was synthesized from **18** and **34f** according to the procedure described for the conversion of **17a** to **8i** (39%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 0.89 (6H, d, J = 8.0 Hz), 1.8–2.0 (1H, m), 2.9–3.4 (8H, m), 4.9–5.1 (1H, m), 7.3–8.0 (12H, m). MS (ES) *m/e*: 418 (M^+ H). Anal. ($C_{27}H_{31}N_1O_3 \cdot 1.0HCl$) C, H, N.

3-(2-Ethoxyethoxy)-4′-(2-{[(2*R*)-2-hydroxy-2-phenylethyl]-amino}ethyl)biphenyl-4-carboxylic Acid Hydrochloride (10j). Compound **10j** was synthesized from **18** and **34 g** according to the procedure described for the conversion of **17a** to **8i** (51%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.12 (3H, t, J = 6.2 Hz), 2.8–3.0 (6H, m), 3.54 (2H, q, J = 6.2 Hz), 3.70 (2H, m), 4.29 (2H, m), 4.8–5.0 (1H, m), 6.33 (1H, m), 7.0–7.9 (12H, m). MS (ES) *m/e*: 450 (M^+ H). Anal. ($C_{27}H_{31}N_1O_5 \cdot 1.0HCl \cdot 0.35CHCl_3$) C, H, N.

Methyl 4′-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)-3-(isopropylsulfanyl)biphenyl-4-carboxylate (38). General Procedure G. To a solution of **33i** (4.89 g, 16.9 mmol) in 1,4-dioxane (22 mL) was added bis(pinacolate)diboron (4.29 g, 16.9 mmol), dichlorobis(triphenylphosphine)palladium(II) (1.38 g, 16.9 mmol) and potassium acetate (4.98 g, 50.7 mmol), and the mixture was stirred at 90 °C for 2 h under nitrogen. The mixture was diluted with ethyl acetate, washed with 1 N aqueous hydrochloride solution, water, and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give methyl 2-(isopropylsulfanyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate **34i** (4.77 g, 84%), which was used without any further purifications.

To a solution of **18** (700 mg, 1.67 mmol) in 1,2-dimethoxyethane (10 mL) were added the above product **34i** (728 mg, 2.16 mmol), $Pd(PPh_3)_4$ (192 mg, 0.167 mmol), and an aqueous solution of $NaHCO_3$ (2 M, 1.84 mL), and the mixture was stirred at 70 °C for 7 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) to give 768 mg (51%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.27 (d, J = 6.5 Hz, 6H), 1.28 (s, 9H), 2.70–2.91 (m, 2H), 3.2–3.5 (m, 4H), 3.83 (s, 3H), 3.73–3.77 (m, 1H), 4.73 (br s, 1H), 5.40–5.51 (m, 1H), 7.20–7.34 (m, 7H), 7.50 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 1H). MS (ES) *m/e*: 572 (M^+ Na).

Methyl 4′-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)-3-(tetrahydro-9*H*-pyran-4-yloxy)biphenyl-4-carboxylate (37). Compound **37** was synthesized from **33h** according to the general procedure G (32%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 1.78–2.04 (m, 4H), 2.70–2.85 (m, 2H), 3.30–3.40 (m, 4H), 3.56–3.67 (m, 2H), 3.91 (s, 3H), 3.96–4.07 (m, 2H), 4.28 (br s, 1H), 4.67 (m, 1H), 4.89–4.98 (m, 1H), 7.12–7.37 (m, 9H), 7.48 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.0 Hz, 1H).

Methyl 4′-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)-3-(isopropylsulfonyl)biphenyl-4-carboxylate (39). To a solution of **38** (338 mg, 0.615 mmol) in chloroform (8 mL) and *N*,*N*-DMF (4 mL) was added *m*-chloroperbenzoic acid (594 mg, 3.44 mmol) at room temperature, and the mixture was stirred at the same temperature for 1 h. To the mixture was added water and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 2/1) to give 340 mg (95%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, J = 6.8 Hz, 6H), 1.45 (s, 9H), 2.79 (m, 2H), 3.31–3.54 (m, 4H), 3.98 (s, 3H), 4.00–4.06 (m, 1H), 4.92 (br s, 1H), 7.25–7.43 (m, 7H), 7.58 (m, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H). MS (ES) *m/e*: 604 (M^+ Na).

Methyl 4′-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-hydroxy-2-phenylethyl]amino}ethyl)-3-(isopropylamino)biphenyl-4-carboxylate (40). Compound **40** was synthesized from **33j** according to the general procedure G (45%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (d, J = 6.5 Hz, 6H), 1.44 (s, 9H), 2.78 (m, 2H), 3.3–3.5 (m, 4H), 3.75–3.81 (m, 1H), 3.86 (s, 3H), 4.33 (br s, 1H), 4.91 (m, 1H), 6.74 (dd, J = 8.2, 1.5 Hz, 1 H), 6.82 (s, 1H), 7.20–7.42 (m, 7H), 7.51 (d, J = 8.2 Hz, 1 H), 7.72 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H). MS (ES) *m/e*: 555 (M^+ Na).

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-(tetrahydro-9*H*-pyran-4-yloxy)-4-biphenylcarboxylic Acid Hydrochloride (10k). Compound **10k** was synthesized from **37** according to the general procedure F (72%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.55–1.71 (2H, m), 1.90–2.00 (2H, m), 3.0–3.54 (6H, m), 3.8–3.93 (2H, m), 4.8–5.0 (2H, m), 6.4 (1H, br), 7.26–7.41 (9H, m), 7.69–7.74 (3H, m), 8.9 (1H, br). MS (ES) *m/e*: 460 (M^- H). Anal. ($C_{28}H_{31}N_1O_5 \cdot 1.0HCl \cdot 1.5H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-(isopropylthio)-4′-biphenyl-4-carboxylic Acid Hydrochloride (10l). Compound **10l** was synthesized from **38** according to the general procedure F (78%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.31 (6H, d, J = 6.5 Hz), 2.99–3.33 (6H, m), 3.69–3.82 (1H, m), 4.96–5.00 (1H, m), 6.22 (1H, m), 7.30–7.92 (12H, m). Anal.

($C_{26}H_{29}N_1O_3S_1 \cdot 0.5HCl$) C, H, N. HRMS ($M + H)^+$ found, 436.1934; calcd for $C_{26}H_{30}N_1O_3S_1$, 436.1946.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-(isopropylsulfonyl)-4′-biphenyl-4-carboxylic Acid Hydrochloride (10m). Compound **10m** was synthesized from **39** according to the general procedure F (31%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.25 (6H, d, $J = 6.8$ Hz), 2.99–3.33 (6H, m), 3.94–4.08 (1H, m), 4.96–5.00 (1H, m), 6.22 (1H, m), 7.27–8.12 (12H, m). MS (ES) *m*/*e*: 466 (M^- H). Anal. ($C_{26}H_{29}N_1O_5S_1 \cdot 1.0HCl \cdot 0.8H_2O$) C, H, N.

4′-(2-{[(2*R*)-2-Hydroxy-2-phenylethyl]amino}ethyl)-3-(isopropylamino)-4-biphenylcarboxylic Acid Dihydrochloride (10n). Compound **10n** was synthesized from **40** according to the general procedure F (60%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.23 (6H, d, $J = 6.2$ Hz), 2.90–3.40 (6H, m), 3.82–3.94 (1H, m), 5.00 (1H, dd, $J = 9.9$, 2.7 Hz), 6.82 (1H, dd, $J = 8.3$, 1.3 Hz), 6.92 (1H, s), 7.27–7.42 (7H, m), 7.66 (2H, d, $J = 8.1$ Hz), 7.86 (1H, d, $J = 8.3$ Hz), 8.91 (1H, brs), 9.28 (1H, brs). MS (ES) *m*/*e*: 417 (M^- H). Anal. ($C_{26}H_{30}N_2O_3 \cdot 2.0HCl$) C, H, N.

***tert*-Butyl-2-(4-bromophenyl)ethyl[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]carbamate (41).** To a solution of **18** (4.5 g) and imidazole (2.4 g) in *N*,*N*-DMF (55 mL) was added *tert*-butyl(dimethyl)silyl chloride (2.7 g), and the mixture was stirred at room temperature for 5 days. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 20/1) to give 5.3 g (94%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.13 (s, 3H), 0.86 (s, 9H), 1.46 (d, 9H, $J = 6$ Hz), 1.54 (d, 3H, $J = 6$ Hz), 2.64–2.72 (m, 2H), 2.88–3.03 (m, 1H), 3.21–3.53 (m, 3H), 4.85 (m, 0.4H), 5.01–5.05 (m, 0.6H), 6.96–7.04 (m, 2H), 7.14–7.27 (m, 4H), 7.36–7.40 (m, 2H).

***tert*-Butyl-2-[4-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenoxy)-phenyl]ethyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]carbamate (42). Typical Procedure H.** To a suspension of **16a** (710 mg, 1.81 mmol), 4-((*tert*-butyl(dimethyl)silyl)oxy)phenyl-boronic acid (457 mg, 1.81 mmol), Et_3N (1.26 mL, 9.06 mmol), and powdered MS 4 Å (700 mg) in CH_2Cl_2 (18 mL) was added $Cu(OAc)_2$ (330 mg, 1.81 mmol), and the mixture was stirred at room temperature for 18 h under ambient atmosphere. The resultant slurry was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give 600 mg (55.4%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.99 (s, 9H), 1.46 (s, 9H), 2.70 (m, 2H), 2.27–3.39 (m, 4H), 4.56 (br, 1H), 4.83–4.86 (m, 1H), 6.75–6.91 (m, 6H), 7.02–7.07 (m, 2H), 7.23–7.28 (m, 3H), 7.36 (s, 1H). MS (ES) *m*/*e*: 569 (M^- H).

***tert*-Butyl{4-[4-(2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxy ethyl]amino}ethyl)phenoxy]phenoxy}-acetate (47).** To a solution of **42** (370 mg, 0.62 mmol) in THF (4.0 mL) was added 1 M tetrabutylammonium fluoride in THF (1.2 mL), and the mixture was stirred at room temperature for 1 h. The mixture 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 a phenol product. To a solution of the product and K_2CO_3 (94 mg, 0.68 mmol) in *N*,*N*-DMF (4.0 mL) was added *tert*-butyl bromoacetate (133 mg, 0.68 mmol), and the mixture was stirred at room temperature for 5 h. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give 360 mg (97%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 1.49 (s, 9H), 2.70 (m, 2H), 2.27–3.40 (m, 4H), 4.49 (s, 2H), 4.54 (br, 1H), 4.83–4.87 (m, 1H), 6.75–6.95 (m, 6H), 7.03–7.07 (m, 2H), 7.23–7.28 (m, 3H), 7.36 (s, 1H). MS (ES) *m*/*e*: 597 (M^- H).

{4-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenoxy]phenoxy}acetic Acid Hydrochloride (8a). A solution of **47** (305 mg, 0.51 mmol) and 4 N HCl in dioxane (5.0 mL) was stirred at room temperature for 24 h. The resultant solid was collected by filtration and dried to give 220 mg (90%) of the title compound as a white solid. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.95–3.33 (6H, m), 4.65 (2H, s), 4.99–5.04 (1H, m), 6.35 (1H, br), 6.83–7.00 (6H, m), 7.23 (9H, d, $J = 8$ Hz), 7.39–7.47 (4H, m), 8.98–9.12 (1H, br). HRMS ($M + H)^+$ found, 442.1409; calcd for $C_{24}H_{24}Cl_1N_2O_5$, 442.1421. Anal. ($C_{24}H_{24}Cl_1N_2O_5 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

{4-{[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]amino}phenoxy)acetic Acid Hydrochloride (8b). Compound **8b** was synthesized from **20** according to the procedure described for the conversion of **16a** to **8a** (39%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.84–3.30 (6H, m), 4.39 (1H, br), 4.59 (2H, s), 4.97–5.03 (1H, m), 6.37 (1H, br), 6.80–7.07 (8H, m), 7.34–7.48 (4H, m), 8.85 (1H, br), 9.11 (1H, br). HRMS ($M + H)^+$ found, 441.1535; calcd for $C_{24}H_{25}Cl_1N_2O_4$, 441.1581. Anal. ($C_{24}H_{25}Cl_1N_2O_4 \cdot 2.0HCl$) C, H, N.

{4-[[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl](methyl)-amino]phenoxy}acetic Acid Hydrochloride (8c). Compound **8c** was synthesized from **21** according to the procedure described for the conversion of **16a** to **8a** (28%). HPLC purity: 97%. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.85–3.23 (6H, m), 3.17 (3H,s), 3.89–4.15 (1H, br), 4.65 (2H, s), 4.98–5.02 (1H, m), 6.68–7.08 (8H, m), 7.34–7.46 (4H, m), 8.86 (1H, br), 9.14 (1H, br). HRMS ($M + H)^+$ found, 455.1754; calcd for $C_{25}H_{27}Cl_1N_2O_4$, 455.1738.

***tert*-Butyl-2-[4-(4-{[tert-butyl(dimethyl)silyl]oxy}benzoyl)-phenyl]ethyl-[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]carbamate (45).** To a solution of **41** (880 mg, 1.55 mmol) in THF (13 mL) was added a solution of *n*-BuLi in *n*-hexane (1.59 M, 1.07 mL) dropwise at −70 °C under nitrogen and the mixture was stirred at −70 °C for 30 min. To the reaction mixture was added **36** (480 mg, 1.62 mmol) at −70 °C, and the mixture was stirred at −70 °C for 1 h. The mixture was allowed to warm to room temperature and partitioned between EtOAc and water. The organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give 710 mg (63%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.11 (s, 3H), 0.01 (s, 3H), 0.25 (s, 6H), 0.87 (s, 9H), 1.00 (s, 9H), 1.45 (d, 9H, $J = 6$ Hz), 2.76–2.97 (m, 3H), 3.23–3.63 (m, 3H), 4.82–4.84 (m, 0.4H), 5.01–5.06 (m, 0.6H), 6.85–6.92 (m, 2H), 7.13–7.38 (m, 6H), 7.66–7.75 (m, 4H). MS (ES) *m*/*e*: 746 (M^+ Na).

{4-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)benzoyl]phenoxy}acetic Acid Hydrochloride (8f). Compound **8f** was synthesized from **45** according to the procedure described for the conversion of **42** to **8a** (54%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.01–3.32 (6H,m), 4.81 (2H, s), 4.96–5.00 (1H, m), 6.35 (1H, br), 7.07 (2H, d, $J = 8.8$ Hz), 7.35–7.47 (6H, m), 7.66–7.75 (4H, m), 8.99 (1H, br). HRMS ($M + H)^+$ found, 454.1435; calcd for $C_{25}H_{24}Cl_1NO_5$, 454.1421. Anal. ($C_{25}H_{24}Cl_1NO_5 \cdot 1.0HCl$) C, H, N.

***tert*-Butyl(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl[2-(4′-hydroxy-4′-biphenyl-4-yl)ethyl]carbamate (46).** To a solution of **41** (580 mg, 1.27 mmol) in 1,2-dimethoxyethane (9 mL) was added 4-((*tert*-butyl(dimethyl)silyl)oxy)phenylboronic acid (385 mg, 1.53 mmol), $Pd(PPh_3)_4$ (117 mg, 0.10 mmol), and aqueous Na_2CO_3 (2M, 1.6 mL), and the mixture was stirred at 75 °C for 10 h under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. To a solution of the residue in THF (8 mL) was added 1 M tetrabutylammonium fluoride in THF (3.0 mL), and the mixture was stirred at room temperature for 8 h under nitrogen. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give 350 mg (59%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.76 (m, 2H), 3.27–3.48 (m, 4H), 4.59 (br, 1H), 4.87 (m, 1H), 4.95 (s, 1H),

6.87–6.91 (m, 2H), 7.17–7.29 (m, 6H), 7.37 (s, 1H), 7.42–7.47 (m, 3H). MS (ES) *m/e*: 490 (M^+ Na).

***tert*-Butyl{[4′-(2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino}ethyl)-4′-biphenyl-4-yl]oxy}-acetate (51).** To a solution of **46** (240 mg, 0.51 mmol) and K_2CO_3 (78 mg, 0.56 mmol) in *N*,*N*-DMF (4 mL) was added *tert*-butyl bromoacetate (110 mg, 0.56 mmol), and the mixture was stirred at room temperature for 3 h. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to give 245 mg (82%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.50 (s, 9H), 2.76 (m, 2H), 3.32–3.43 (m, 4H), 4.55 (s, 2H), 4.62 (m, 1H), 4.86–4.88 (m, 1H), 6.93–6.98 (m, 2H), 7.15–7.26 (m, 6H), 7.37 (s, 1H), 7.45–7.51 (m, 3H). MS (ES) *m/e*: 582 (M^+ H).

{[4′-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)-4′-biphenyl-4-yl]oxy}acetic Acid Hydrochloride (8g). Compound **8g** was synthesized from **51** according to the procedure described for the conversion of **47** to **8a** (99%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.02–3.35 (6H, m), 4.72 (2H, s), 5.00–5.05 (1H, m), 6.37 (1H, br), 6.99 (2H, d, J = 8.7 Hz), 7.30–7.61 (10H, m), 9.04 (1H, br), 13.03 (1H, br). HRMS $(M + H)^+$ found, 426.1499; calcd for $C_{24}H_{24}Cl_1N_2O_4$, 426.1472. Anal. ($C_{24}H_{24}Cl_1N_2O_4 \cdot 0.5HCl$) C, H, N.

[4-(2-{benzyl[(2*R*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-2-(3-chlorophenyl)ethyl]amino}ethyl)-phenyl](4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)methanol (52). To a solution of **29** (2.1 g, 3.76 mmol) in THF (25 mL) was added a solution of *n*-BuLi in *n*-hexane (1.59 M, 2.83 mL) dropwise at −70 °C under nitrogen, and the mixture was stirred at −70 °C for 30 min. To the reaction mixture was added 4-((*tert*-butyl(dimethyl)silyl)oxy)benzaldehyde (977 mg, 4.13 mmol), and the mixture was stirred at the same temperature for 1 h. The mixture was allowed to warm to room temperature and partitioned between EtOAc and water. The organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to give 1.1 g (40%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.16 (s, 3H), 0.01 (s, 3H), 0.17 (s, 6H), 0.85 (s, 9H), 0.97 (s, 9H), 2.09–2.10 (m, 1H), 2.60–2.75 (m, 6H), 3.59 (d, J = 13.7 Hz, 1H), 3.71 (d, J = 13.7 Hz, 1H), 4.56 (t, J = 6.2 Hz, 1H), 5.75–6.77 (m, 1H), 6.76–6.80 (m, 2H), 6.99 (d, 2H, J = 8.0 Hz), 7.08–7.25 (m, 8H). MS (ES) *m/e*: 716 (M^+ H).

4-[[4-(2-{Benzyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino}ethyl)phenyl]-(hydroxy)methyl]phenol (53). To a solution of **52** (1.1 g, 1.54 mmol) in THF (15 mL) was added 1 M tetrabutylammonium fluoride in THF (5.0 mL) at 0 °C, and the mixture was stirred at room temperature for 24 h under nitrogen. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2/1) to give 550 mg (73%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24 (m, 1H), 2.49–2.91 (m, 6H), 3.57 (d, J = 13.5 Hz, 1H), 3.94 (d, J = 13.5 Hz, 1H), 4.52–4.59 (m, 1H), 4.88 (br, 1H), 5.78 (s, 1H), 6.75–6.79 (m, 2H), 7.07–7.16 (m, 2H), 7.20–7.34 (m, 8H). MS (ES) *m/e*: 486 (M^- H).

4-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)benzyl]phenol (54). A mixture of **53** (545 mg, 1.12 mmol) in 4 N HCl in dioxane (1.0 mL) was stirred for 5 min. The solvent was removed by evaporation. A suspension of the residue in EtOH (2.2 mL) and chlorobenzene (5.2 mL) was hydrogenated over palladium on carbon (10% w/w, 50% wet, 55 mg) under hydrogen atmosphere for 2 h. The catalyst was filtered off, the filtrate was evaporated. The residue was diluted with ethyl acetate and saturated $NaHCO_3$ solution. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give 395 mg (84%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.59–2.93 (m, 6H), 3.88 (s, 1H), 4.59–4.66 (m, 1H), 6.72–6.79 (m, 2H), 7.02–7.35 (m, 10H). MS (ES) *m/e*: 382 (M^+ H).

***tert*-Butyl{4-[4-(2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)benzyl]phenoxy}acetate (56).** To a solution of **54** (390 mg, 1.02 mmol) in THF (3.5 mL) and water (3.5 mL) was added di-*tert*-butyl dicarbonate (223 mg, 1.02 mmol), and the mixture was stirred at room temperature for 30 minites. 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 to give 480 mg (98%) of *tert*-butyl(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl{2-[4-(4-hydroxybenzyl)phenyl]ethyl}carbamate (**55**). To a solution of **55** (470 mg, 0.98 mmol) and K_2CO_3 (148 mg, 1.07 mmol) in *N*,*N*-DMF (4 mL) was added *tert*-butyl bromoacetate (190 mg, 0.98 mmol), and the mixture was stirred at room temperature for 3 h. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) to give 245 mg (42%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.48 (s, 9H), 2.65–2.78 (m, 2H), 2.26–3.42 (m, 4H), 3.87 (s, 2H), 4.47 (s, 2H), 4.60 (br, 1H), 4.75–4.86 (m, 1H), 6.77–6.81 (m, 2H), 7.02–7.27 (m, 9H), 7.35 (s, 1H). MS (ES) *m/e*: 618 (M^+ Na).

{4-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)benzyl]phenoxy}acetic Acid Hydrochloride (8d). A solution of **56** (240 mg, 0.40 mmol) and 4 N HCl in dioxane (3.0 mL) was stirred at room temperature for 24 h. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (methanol/acetic acid/chloroform = 10/1/100) to give a product. To a THF (2.0 mL) solution of the product, 4 N HCl in dioxane (1.0 mL) was added. The mixture was stirred for 5 min and evaporated under reduced pressure to give 72 mg (38%) of the title compound. ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.91–3.24 (m, 6H), 3.84 (s, 2H), 4.61 (s, 2H), 4.94–4.99 (m, 1H), 6.32 (br, 1H), 6.80 (d, 2H, J = 8.7 Hz), 7.10–7.21 (m, 6H), 7.29–7.46 (m, 4H), 8.89 (br, 1H). HPLC purity: 98%. HRMS $(M + H)^+$ found, 440.1624; calcd for $C_{25}H_{26}Cl_1N_1O_4$, 440.1629.

4-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenoxy]benzoic Acid Hydrochloride (8k). Compound **16a** (550 mg, 1.4 mmol) and 4-mthoxycarbonylphenylboronic acid (300 mg, 1.68 mmol) were reacted according to the general procedure H to give methyl-4-[4-(2-{(*tert*-butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]- amino}ethyl)phenoxy]benzoate (185 mg, 25%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.70–2.80 (m, 2H), 3.30–3.45 (m, 4H), 3.90 (s, 3H), 4.46 (br, 1H), 4.85–4.89 (m, 1H), 6.95–7.02 (m, 4H), 7.10–7.29 (m, 5H), 7.37 (s, 1H), 7.95–7.99 (m, 2H).

Compound **8k** was synthesized from the obtained product (183 mg, 0.35 mmol) according to the general procedure F (127 mg, 81%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.00–3.28 (m, 6H), 4.99–5.04 (m, 1H), 6.35 (br, 1H), 6.97–7.12 (m, 4H), 7.32–7.48 (m, 6H), 7.90–7.98 (m, 2H), 9.03–9.35 (br, 1H). MS (ES) *m/e*: 410.2 (M^- H). Anal. ($C_{23}H_{22}Cl_1N_1O_4 \cdot 1.0HCl$) C, H, N.

3-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenoxy]benzoic Acid Hydrochloride (8l). Compound **8l** was synthesized from **16a** and 3-mthoxycarbonylphenylboronic acid according to the procedure described for the conversion of **16a** to **8k** (32%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.99–3.25 (m, 6H), 4.95–5.02 (m, 1H), 6.35 (br, 1H), 7.06 (d, J = 3.5 Hz, 2H), 7.07–7.54 (m, 9H), 7.69 (d, J = 4.0 Hz, 1H), 8.95 (br, 1H). MS (ES) *m/e*: 410.2 (M − H). Anal. ($C_{23}H_{22}Cl_1N_1O_4 \cdot 1.0HCl \cdot 0.25H_2O$) C, H, N.

4-{[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]amino}benzoic Acid Dihydrochloride (8m). Compound **8m** was synthesized from **21** and 4-mthoxycarbonylphenylboronic acid according to the procedure described for the conversion of **16a** to **8k** (42%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.83–3.17 (m, 6H), 4.01 (m, 1H), 5.01 (m, 1H), 6.97–7.12 (m, 4H), 7.05–7.47

(m, 11H), 7.63 (m, 1H), 8.88 (br s, 1H), 9.13 (br s, 1H). MS (ES) *m/e*: 409 (M^- H). Anal. ($C_{23}H_{23}Cl_1N_2O_3 \cdot 2.0HCl$) C, H, N.

3-{[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]amino}benzoic Acid Hydrochloride (8n). Compound **8n** was synthesized from **21** and 3-methoxycarbonylphenylboronic acid according to the procedure described for the conversion of **16a** to **8k** (46%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.91–3.18 (m, 6H), 4.04 (m, 1H), 5.01 (m, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.12–7.23 (m, 4H), 7.34–7.48 (m, 4H), 7.77 (d, J = 8.7 Hz, 2H), 8.88 (br s, 1H), 9.13 (br s, 1H). MS (ES) *m/e*: 409 (M^- H). Anal. ($C_{23}H_{23}Cl_1N_2O_3 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

6-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenoxy]nicotinic Acid Hydrochloride (8q). To a mixture of **16a** (200 mg, 0.51 mmol) in DMSO (6 mL) were added ethyl 6-chloronicotinate (142 mg, 0.76 mmol) and K_2CO_3 (210 mg, 1.52 mmol) at a room temperature, and the mixture was stirred at the 80 °C for 2 h. The resulting mixture was poured into a mixture of EtOAc and water, and the organic layer was washed with brine. After the solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel to give a coupling product (210 mg, 76%). Compound **8q** was synthesized from the coupling product according to the general procedure F (79%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.86–3.22 (m, 6H), 5.01–5.05 (m, 1H), 6.72 (d, J = 8.5 Hz, 2H), 7.01–7.18 (m, 3H), 7.36–7.48 (m, 6H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.65 (d, J = 2.0 Hz, 12H), 8.91 (br, 1H), 9.20 (br, 1H). MS (ES) *m/e*: 411(M^- H). Anal. ($C_{22}H_{21}Cl_1N_2O_4 \cdot 1.0HCl \cdot 1.0H_2O$) C, H, N.

***tert*-Butyl Benzyl[2-(4-bromophenyl)ethyl]carbamate (57).** To a solution of **27** (4.7 g, 16.2 mmol) in THF (60 mL) was added di-*tert*-butyl dicarbonate (3.7 g, 16.9 mmol), and the mixture was stirred at room temperature for 16 h. The mixture 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. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 8/1–5/1) to give 5.8 g (92%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.72 (br, 2H), 3.36 (br, 2H), 4.32–4.38 (m, 2H), 6.99 (br, 2H), 7.21–7.41 (m, 7H). MS (ES) *m/e*: 390 (M^+ H).

4-{2-[Benzyl(*tert*-butoxycarbonyl)amino]ethyl}phenylboronic Acid (58). Compound **58** was synthesized from **57** according to the general procedure B (63%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.80 (br, 2H), 3.39 (br, 2H), 4.30–4.44 (m, 2H), 7.22–7.32 (m, 7H). MS (ES) *m/e*: 354 (M^- H).

Ethyl 6-(4-{2-[Benzyl(*tert*-butoxycarbonyl)amino]ethyl}-phenyl)nicotinate (59). Compound **59** was synthesized from **58** and ethyl 6-chloronicotinate according to the general procedure E (80%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (t, J = 7.0 Hz, 3H), 1.46 (s, 9H), 2.85 (br, 2H), 3.41 (br, 2H), 4.34–4.48 (m, 2H), 4.43 (q, J = 7.0 Hz, 2H), 7.25–7.38 (m, 7H), 7.78 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 2H), 8.33 (dd, J = 8.0, 2.0 Hz, 1H), 9.27 (d, J = 2.0 Hz, 1H). MS (ES) *m/e*: 461 (M^+ H).

Ethyl 6-[4-(2-{Benzyl[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)phenyl]nicotinate (60). To the mixture of **59** (790 mg, 1.71 mmol) in THF (6 mL) was added 4 N HCl in dioxane (3.5 mL). The mixture was stirred at room temperature for 20 h and evaporated under reduced pressure to give crude solid. The solid was washed with IPE to give 750 mg (quantitative yield) of ethyl 6-{4-[2-(benzylamino)ethyl]phenyl}nicotinate hydrochloride. MS (ES) *m/e*: 461 (M + H). Compound **60** was synthesized from the above product using Et_3N (1.5 equiv) according to the procedure described for the conversion of **27** to **28** (39%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (t, J = 7.0 Hz, 3H), 2.60–2.97 (m, 6H), 3.61 (d, J = 13.5 Hz, 1H), 3.97 (d, J = 13.5 Hz, 1H), 4.43 (q, J = 7.0 Hz, 2H), 4.57–4.64 (m, 1H), 7.16–7.31 (m, 11H), 7.79 (d, J = 8.0 Hz, 1H), 7.96–8.01 (m, 2H), 8.31 (dd, J = 8.0, 2.0 Hz, 1H), 9.26–9.27 (m, 1H). MS (ES) *m/e*: 515 (M^+ H).

Ethyl 6-[4-(2-{(*tert*-Butoxycarbonyl)[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}ethyl)phenyl]nicotinate (61). Compound **61** was synthesized from **60** according to the procedure described for the conversion of **53** to **55** (39%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (t, J = 7.0 Hz, 3H), 1.47 (s, 9H), 2.75–2.87 (m, 2H), 3.33–3.43 (m, 4H), 4.43 (q, J = 7.0 Hz, 2H), 4.52 (br, 1H), 4.83–4.50 (m, 1H), 7.26–7.32 (m, 5H), 7.36 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 2H), 8.33 (dd, J = 8.0, 2.0 Hz, 1H), 9.26 (d, J = 2.0 Hz, 1H). MS (ES) *m/e*: 547 (M^+ Na).

6-[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]nicotinic Acid Hydrochloride (8o). Compound **8o** was synthesized from **61** according to the general procedure F (93%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.08–3.24 (m, 6H), 5.00–5.07 (br, 1H), 7.34–7.47 (m, 6H), 8.09–8.17 (m, 3H), 8.31–8.38 (m, 1H), 8.98 (br, 1H), 9.12–9.16 (m, 1H), 9.30 (br, 1H). MS (ES)*m/e*: 395 (M − H). Anal. ($C_{22}H_{21}Cl_1N_2O_3 \cdot 2.0HCl \cdot 0.5H_2O$) C, H, N.

4-{[4-(2-{[(2*R*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]thio}phenol (63). A solution of **62** (295 mg, 1.2 mmol) and (2*R*)-2-(3-chlorophenyl)oxirane **26** (167 mg, 1.08 mmol) in DMSO (3.5 mL) was added BSA (122 mg, 0.6 mmol), and the mixture was stirred at 80 °C for 14 h. The reaction was quenched with 5% AcOH in MeOH (2.0 mL). The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with aq $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 20/1) to give 155 mg (32%) of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60–2.97 (m, 6H), 2.88 (s, 1H), 4.61–4.67 (m, 1H), 6.79–6.83 (m, 2H), 7.04–7.38 (m, 10H). MS (ES) *m/e*: 400 (M^+ H).

(4-{[4-(2-{[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino}-ethyl)phenyl]thio}phenoxy)acetic Acid Hydrochloride (8e). Compound **8e** was synthesized from **63** according to the procedure described for the conversion of **54** to **8d** (64%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.94–3.33 (m, 6H), 4.70 (s, 2H), 4.97–5.01 (m, 1H), 6.34 (br, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.02–7.23 (m, 4H), 7.33–7.45 (m, 6H), 8.97–9.18 (br, 1H). HRMS (M + H)$^+$ found, 458.1198; calcd for $C_{24}H_{25}Cl_1N_1O_4S_1$, 458.1193. Anal. ($C_{24}H_{24}Cl_1N_1O_4S_1 \cdot 1.0HCl$) C, H, N.

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

(2). cAMP Accumulation Assay. CHO cells grown to confluence were washed twice with assay buffer [130 mM NaCl, 5 mM KCl, 1 mM $MgCl_2 \cdot 6H_2O$, 1.5 mM $CaCl_2 \cdot 2H_2O$, 10 mM glucose, 10 mM glucose, 10 mM HEPES, 0.1% bovine serum albumin, pH 7.4] and incubated with 180 μL of assay buffer containing 0.5 mM 3-isobutyl-methylxanthine (IBMX) at 37 °C for 10 min. Test compound (20 μL) dissolved in assay buffer containing 1% DMSO was then added and cells were incubated at 37 °C for 15 min, the reaction was stopped by addition of 80 μL of 0.1 mol/L HCl. After 1 h at 4 °C, cells were centrifuged at 2000 rpm for 5 min at 4 °C. The amount of cAMP in the supernatant was determined using a cAMP enzyme immunoassay (EIA) kit (Amersham Biosciences). The supernatant was frozen below –80 °C until the measurement of cAMP levels.

(3). Data Analysis. cAMP accumulation elicited by test compounds were expressed as a percentage of the maximal response to isoproterenol. The 50% effective concentration (EC_{50}) values were calculated using GraphPad Prism (Ver.3.03) from the concentration–response curve.

In Vivo Experiments. (1). Materials and Methods. Female beagle dogs (11.5–15.0 kg, Oriental Yeast Co., Ltd.) were deprived of food and water from about 40 and 17 h before administration, respectively. A group of five dogs were used for the whole study. Under halothane anesthesia, a catheter was inserted into the urinary bladder through the urethra and connected to a pressure transducer to measure intravesical pressure (IVP). Carbachol (1.8 μg/0.2 mL/kg, saline solution) was given intravenously (via the saphenous vein) several times at intervals of about 30 min. A polyethylene tube for intraduodenal (i.d.) administration was inserted into the duodenum at about 15 cm from the pylorus using an endoscope. When

reproducible responses (increase in IVP) were obtained, compound **10e** (10, 32, and 100 μg /kg) was given intraduodenally. A total of 30 min after test compound administration, carbachol injection was restarted at intervals of about 30 min. Vehicle (polyethylene glycol #400, 0.2 mL/kg) was given at the same point as **10e** administration. Responses to carbachol were observed for 180 min.

(2). Data Analysis. Percent inhibition of IVP increased by **10e** was calculated by dividing IVPa (IVP increase induced by carbachol after test compound administration) by IVPb (IVP increase induced by carbachol just before test compound administration). In the vehicle administration group, inhibitory effect was calculated in the same way. The data were analyzed using Dunnett's multiple comparison test compared to the vehicle group. ED_{50} values were calculated by least-squares linear regression analysis using maximum percent inhibition at each dose. All values were expressed as mean ± SE.

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Supporting Information Available: Combustion analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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