Design, Synthesis, and Activity of a Series of Pyrrolidine-3-carboxylic Acid-Based, Highly Specific, Orally Active ET_B Antagonists Containing a Diphenylmethylamine Acetamide Side Chain

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The endothelin (ET)-B receptor subtype is expressed on vascular endothelial and smooth muscle cells and mediates both vasodilation and vasoconstriction. On the basis of the pharmacophore of the previously reported ET_A-specific antagonist **1**, (ABT-627), we are reporting the discovery of a novel series of highly specific, orally active ET_B receptor antagonists. Replacing the dibutylaminoacetamide group of **1** with a diphenylmethylaminoacetamide group resulted in antagonist **2** with a complete reversal of receptor specificity. Structure−activity relationship studies revealed that *ortho*-alkylation of the phenyl rings could further increase ET_B affinity and also boost the ET_A/ET_B activity ratio of the resulting antagonists. A similar antagonism selectivity profile could also be achieved when one of the phenyl rings of the acetamide side chain was replaced with an alkyl group, preferably a *tert*-butyl group (**10h**). Combining these features with modification of the 2-aryl group of the pyrrolidine core, we have identified a potent antagonist (**9k**, A-308165) with over 27 000-fold selectivity favoring the ET_B receptor and an acceptable pharmacokinetic profile (F = 24%) in rats.

Introduction

The endothelins (ET-1, ET-2, and ET-3), potent vasoconstrictors and mitogens, were discovered in 1988,[1,2] and subsequently two subtypes of human endothelin receptors (ET_A and ET_B) were cloned.[3,4] ET_A receptor is abundantly expressed on vascular smooth muscle cells, and binding of ET-1 to the ET_A receptor mediates the vasoconstrictive and mitogenic effects of endothelin in vitro and in vivo.[5] Pharmacology studies have implicated ET-1 as a contributing factor in a number of disease states where excessive vasoconstriction or smooth muscle proliferation plays a role. These include acute myocardial infarction,[6] congestive heart failure,[7] pulmonary hypertension,[8] renal failure,[9] and restenosis.[10]

ET_B receptor subtype is expressed on vascular endothelial and smooth muscle cells and has high affinity for all isoforms of endothelins. Despite the tremendous research activity in the field of endothelins, the roles of the ET_B receptor remain poorly understood. ET_B receptors could not only mediate endothelium-dependent relaxation[11] through the production of nitric oxide[12] but also direct vaso- or broncho constriction.[13−16] It is also linked to the clearance of endogenous endothelin from circulation.[17] Therefore, highly potent, orally active ET_B receptor-specific antagonists are needed to advance the understanding of the role of the ET_B receptor in both normal physiological and pathological conditions.

Since 1994, a large number of potent, nonpeptide ET antagonists have been reported, most of which exhibited specificity toward the ET_A receptor[18] or nonspecificity toward either the ET_A or ET_B receptor.[19] However, reports of potent ET_B-specific antagonists have been scarce, only represented by BQ-788,[17] Ro 46-8443,[20] RES-701-1,[21] and IRL-2500.[22] A more recent account of a benzenesulfonamide-based ET_B receptor-selective antagonist has appeared in the literature.[23] The lack of high-quality, orally deliverable ET_B-specific antagonists has hindered the efforts of clarifying the role of the ET_B receptor. During the course of expanding the structure−activity relationship (SAR) of pyrrolidine-3-carboxylic acid-based ET_A-specific antagonists, we noticed that replacing the *N*,*N*-dibutylamine portion of ABT-627 (**1**)[24] with a diphenylmethylamine led to a dramatic boost of ET_B receptor affinity (IC_{50} = 8.1 nM) and a complete reversal of the receptor specificity of the resulting antagonist **2** (Scheme 1). This observation is consistent with results from several previous studies by this group, indicating the critical role played by the *N*-linked side chain of **1** in determining receptor binding and selectivity. Herein, we would like to report the design, synthesis, and activity of this novel series of ET_B receptor-selective antagonists, which are valuable tools for further elucidating the role that the ET_B receptor plays in vivo.

Chemistry

All of the new compounds in this report were synthesized by direct analogy to our earlier work on **1** with minor modification,[18] as shown in Scheme 2. Various β-ketoesters **4** were prepared by reacting the imidazolides of carboxylic acids **3** with magnesium monoeth-

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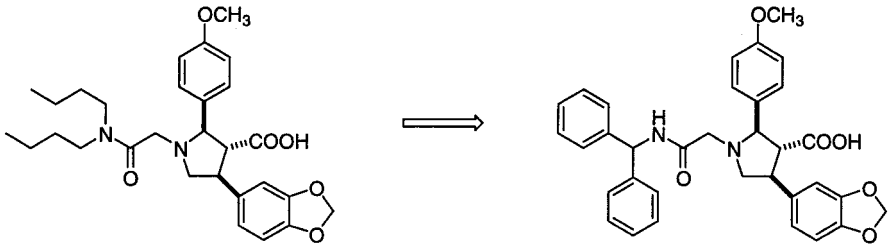
Scheme 1. Reversal of Antagonist Receptor Subtype Specificity through Acetamide Side Chain Modification



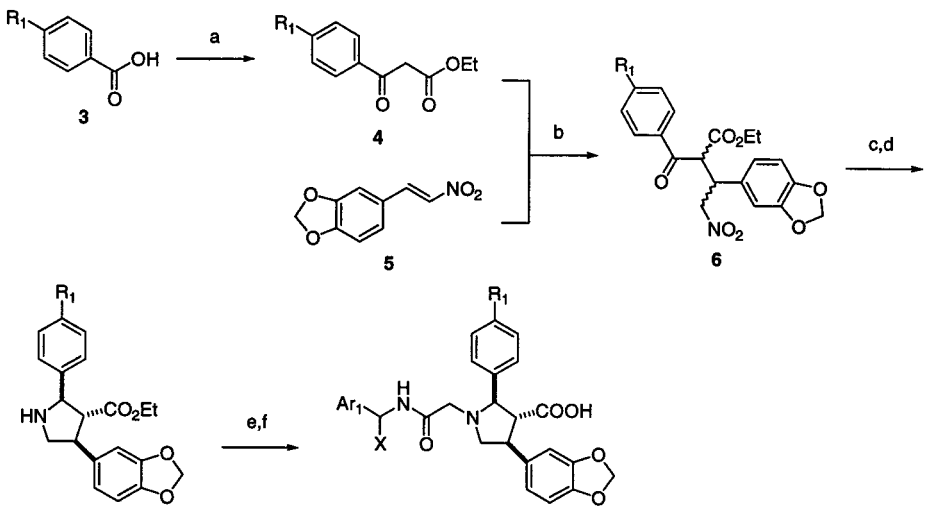
1, ABT-627

IC_{50} (hET_A) = 0.034 nM
IC_{50} (hET_B) = 63.3 nM
A/B = 0.00054

2

IC_{50} (hET_A) = 45.9 nM
IC_{50} (hET_B) = 8.1 nM
A/B = 5.7

Scheme 2[a]



7

9 X = Ar_2
10 X = R_2

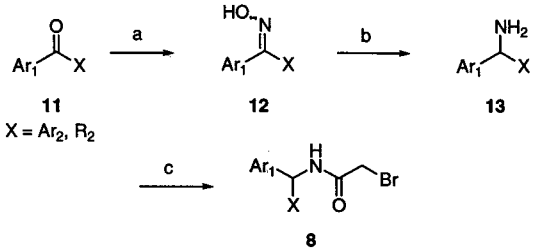
[a] Reagents and conditions: (a) CDI, THF, then magnesium monoethylmalonate, rt; (b) cat. *t*-BuOK, THF, rt; (c) H_2, Raney Ni, AcOH, THF, rt, then TFA, rt, one pot; (d) DBU, CH_3CN, reflux; (e) $BrCH_2CONHCH(Ar_1)X$ (**8**), *i*-Pr_2NEt, CH_3CN, rt; (f) 6N aq NaOH, EtOH, rt.

ylmalonate followed by decarboxylation[25](ca. 70% yield). Potassium *tert*-butoxide-catalyzed Michael addition of β-ketoesters **4** to nitrostyrene **5**[26] yielded two isomers of the adducts **6** in ca. 80% yield. Raney nickel-mediated hydrogenation of the adducts **6** in the presence of acetic acid and further hydrogenation of the resulting cyclic iminium TFA salts provided almost exclusively the *cis*,-*cis*-isomers of the pyrrolidines, which were epimerized with DBU to afford the pure *trans*,*trans*-pyrrolidines **7** in ca. 70% yield from the Michael addition. Alkylation of pyrrolidines **7** with bromoacetamides **8** and subsequent saponification of the resultant ethyl esters furnished final compounds **9** and **10** in 80% yield for in vitro assays.

The synthesis of noncommercially available amines used for the preparation of bromoacetamides **8** is shown in Scheme 3. Condensation of *N*-hydroxylamine with ketones **11** provided the oximes **12**. Reduction of oximes **12** by dissolved sodium metal in liquid NH_3 yielded benzylamines **13**, which were converted to the bromoacetamides **8** according to the literature procedure.[27]

For detailed evaluation, two compounds have been prepared in optically pure form. The enantiomerically pure pyrrolidines **14** were secured through chiral HPLC separation (Scheme 4, see Experimental Section for details) following protection of racemic pyrrolidines **7** as their *tert*-butyl carbamates. Removal of the Boc groups of **14**, *N*-alkylation with appropriate bromoacetamides **8**, and saponification provided the optically pure antagonists **9j** and **9k**.

Scheme 3[a]



11
X = Ar_2, R_2

12

13

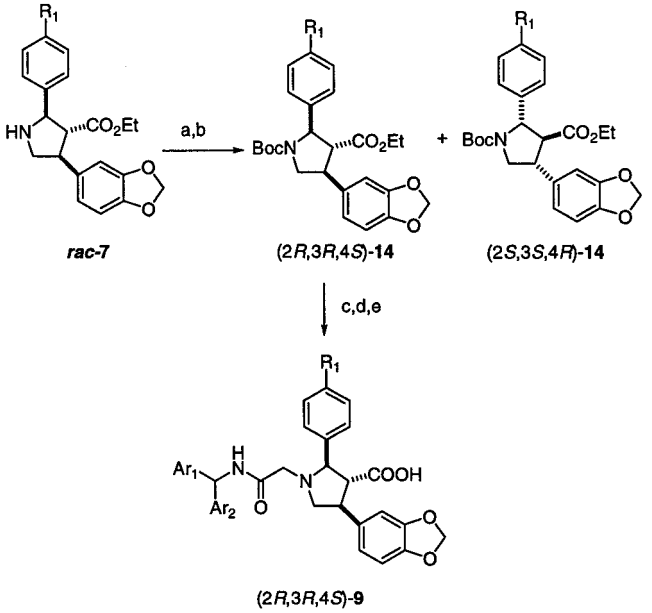
8

[a] Reagents and conditions: (a) $HONH_2HCl$, Pyr, EtOH, reflux; (b) Na, liq NH_3, THF, −78 °C to rt; (c) $BrCH_2COBr$, NEt_3, $ClCH_2CH_2Cl$, −78 °C to rt.

Structure−Activity Relationships

The primary screening for the compounds described in this study was a measurement of their ability to displace endothelin from its receptors. We employed human ET_A and ET_B receptors (hET_A, hET_B) permanently expressed in CHO cells. IC_{50} data were recorded

Scheme 4[a]



[a] Reagents and conditions: (a) Boc_2O, Et_3N, CH_2Cl_2, rt; (b) chiral HPLC separation; (c) neat TFA, rt; (d) $BrCH_2CONHCH(Ar_1)$-Ar_2 (**8**), *i*-Pr_2NEt, CH_3CN, rt; (e) 6 N aq NaOH, EtOH, rt.

by measuring the displacement of [^{125}I]ET-1 from the ET_A receptor or [^{125}I]ET-3 from the ET_B receptor. Analogues of particular interest were examined for their pharmacokinetic properties using a standard protocol which compares the time course of plasma drug levels after dosing in rats by intravenous injection and oral gavage.

The reversal of receptor specificity resulting from the acetamide side chain modification (**1** to **2**, Scheme 1) suggested two important features in designing an ET_B-selective antagonist. The first feature is the hydrogen-bonding donating nature of the secondary amide present in compound **2**, which is absent in the ET_A receptor-specific antagonist **1**. Our previous studies have indicated that the presence of *both* alkyl groups of the tertiary acetamide is required for maintaining the high ET_A selectivity of the antagonist **1**. In the case of compound **2**, we suspect that hydrogen bonding of the secondary amide with the ET_B receptor is involved in orienting the diphenylmethyl group into appropriate hydrophobic binding pockets, which are inaccessible to the *N*,*N*-dialkylacetamide side chain of **1**. The second feature is the hydrophobic interaction provided by the conformationally restricted, yet somewhat flexible, biphenylmethyl group. The importance of flexibility of the two phenyl groups was confirmed when a rigid and flat 9-aminofluorene was used in place of it (Table 1). The potency of the resulting antagonist **9a** was severely compromised, even though the marginal ET_B selectivity of **2** was still observed.

The size of the binding pocket for this diphenylmethylamine acetamide was then probed (Table 1). One-carbon extension of one of the phenyl rings of **2** decreased ET_B receptor affinity 6-fold, and the resulting antagonist **9b** favored the ET_A receptor by more than 1 order of magnitude. (Mixture of diastereoisomers was used for the primary screening and the same for the rest of the report.) If both phenyl groups of **2** were moved one carbon out (**9c**), the erosion of ET_B affinity (13-fold) exceeded that of ET_A affinity (4-fold). Addition of one more phenyl group to the acetamide of **2** led to a much less potent antagonist **9d**, with no selectivity for either receptor subtype. Apparently, diphenylmethylamine seems to be the preferred group for ET_B receptor binding and specificity.

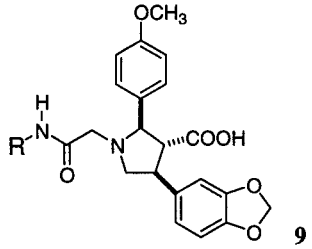
Next, the spatial orientation of the two phenyl groups was fine-tuned with small alkyl substituents, which would also probe this hydrophobic binding site in a more detailed fashion. Initially, mono-*ortho*-methylation of one of the phenyl rings led to antagonist **9e** with higher ET_B receptor affinity and slightly decreased ET_A affinity, a 3-fold gain of the selectivity over unsubstituted analogue **2** (Table 1). In comparison, *para*-methylation of the phenyl ring was not tolerated, based on the observation that a 1,4-dimethylated phenyl analogue (**9f**) exhibited decreased affinity for both receptor subtypes. The optimal selectivity and affinity profile was achieved with a bis-*o*-tolylmethylamine in place of the diphenylmethylamine. The optimal combination of spatial orientation of the two phenyl groups and hydrophobic interaction with the receptor provided antagonist **9g** with 1 nM affinity for the ET_B receptor and almost 150-fold separation of affinities between the two receptor subtypes. One-carbon homologation of one of the *o*-methyl groups (**9h**) decreased the newly gained ET_B receptor affinity 6-fold and slightly compromised ET_B specificity. Bis-*ortho*-ethylation of the diphenylmethylamine (**9i**) attenuated the affinity for the ET_B receptor to some degree but reduced the ET_B selectivity of the antagonist 10-fold.

We then explored the possibility of replacing one of the phenyl groups of **2** with an alkyl group (Table 2). Methylbenzylamine-derived analogue **10a** offered a slightly ET_A-selective antagonist with moderate potency. *Ortho*-methylation of the phenyl ring (**10b**) did not alter the affinity for ET_B receptor but decreased that for the ET_A receptor 3-fold. Antagonist **10c**, derived from α-ethylbenzylamine, exhibited low nanomolar affinity for both ET_A and ET_B receptors with virtually no discrimination against either receptor subtype. Further elongation of the alkyl group to *n*-propyl (**10d**) or *n*-butyl (**10e**) did not result in any dramatic variation of the affinity and selectivity of the antagonists.

In comparison to α-propylbenzylamine-based compound **10d**, branching of the *n*-propyl group (**10f**) did not provide any benefit in term of selectivity but did improve the receptor affinity over 3-fold (Table 2). ET_B affinity improved 2-fold, while ET_A affinity decreased 4-fold when the isopropyl group of **10f** was elongated to a 3-pentyl group (**10g**). This improvement has resulted in a selectivity profile favoring the ET_B receptor, reversing the moderate ET_A selectivity of this series of compounds (**10a**−**10f**). In fact, compounds **10c**, **10f**, and **10g** could be more appropriately categorized as very potent, ET_A/ET_B receptor-mixed antagonists. Their biochemical profile compares favorably with that of the leading literature compounds.[19]

The ET_B receptor-favoring character of **10g** was further strengthened using a *tert*-butyl group to replace one of the phenyl groups of **2** to give antagonist **10h** with subnanomolar potency against the ET_B receptor and 10-fold selectivity over the ET_A receptor. Extension of the isopropyl group of **10f** to an isobutyl group (**10i**)

Table 1. Structure–Activity Relationships of Diarylmethylamine Acetamides



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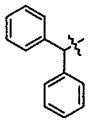
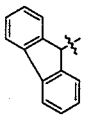
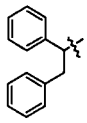
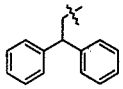
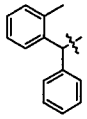
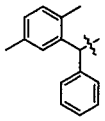
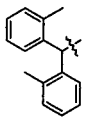
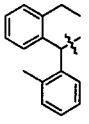
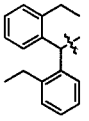
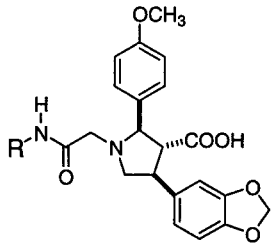
Compound	R	IC_{50} (nM)[a] $h\mathrm{ET_A}$ binding	IC_{50} (nM)[a] $h\mathrm{ET_B}$ binding	A/B ratio[b]	Formula
2		45.9 (33.0-64.0)	8.1 (6.2-10.6)	5.67	$C_{34}H_{32}N_2O_6 \cdot 0.70TFA$
9a		1228 (892-1689)	600 (521-691)	2.05	$C_{34}H_{30}N_2O_6 \cdot 0.70TFA$
9b		3.9 (2.5-6.2)	47 (44-50)	0.08	$C_{35}H_{34}N_2O_6 \cdot 0.80TFA$
9c		199 (139-286)	108 (56-210)	1.84	$C_{35}H_{34}N_2O_6 \cdot 0.20TFA$
9d		432 (334-561)	744 (584-949)	0.58	$C_{40}H_{36}N_2O_6 \cdot 0.16TFA$
9e		63.5 (37-109)	3.4 (3.2-3.6)	18.68	$C_{35}H_{34}N_2O_6 \cdot 0.90TFA$
9f		122 (86.7-172)	31 (30.1-33.1)	3.94	$C_{36}H_{36}N_2O_6 \cdot 0.85TFA$
9g		161 (129-201)	1.1 (1.1-1.2)	146.36	$C_{36}H_{36}N_2O_6 \cdot 0.40TFA$
9h		749 (350-1601)	6.1 (3.8-9.7)	122.79	$C_{37}H_{38}N_2O_6 \cdot 1.00TFA$
9i		100 (69-144)	6.6 (6.3-7.0)	15.15	$C_{38}H_{40}N_2O_6 \cdot 1.15TFA$

[a] IC_{50} calculated using a mean of at least 2 measurements (all duplicates) for 11 concentrations from 10^{-10} to 10^{-5} M unless otherwise noted. [b] Expressed as $IC_{50}(ET_A)/IC_{50}(ET_B)$.

Table 2. Structure–Activity Relationships of Phenylalkylamine Acetamides



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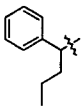
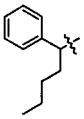
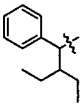
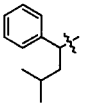
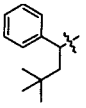
Compound	R	IC_{50} (nM)[a] $h\mathrm{ET_A}$ binding	IC_{50} (nM)[a] $h\mathrm{ET_B}$ binding	A/B ratio[b]	Formula
10a		5.5 (3.3-9.3)	20 (15-28)	0.28	$C_{29}H_{30}N_2O_6 \cdot 0.20TFA$
10b		16 (11-23)	18 (10-32)	0.89	$C_{30}H_{32}N_2O_6 \cdot 0.20TFA$
10c		1.0 (1.0-1.1)	2.6 (2.0-3.3)	0.38	$C_{30}H_{32}N_2O_6 \cdot 0.10TFA$
10d		3.7 (3.7-3.8)	7.3 (5.9-9.1)	0.51	$C_{31}H_{34}N_2O_6 \cdot 0.30TFA$
10e		1.6 (0.73-3.7)	5.0 (4.5-5.5)	0.32	$C_{32}H_{36}N_2O_6 \cdot 0.25TFA$
10f		0.7 (0.66-0.7)	2.1 (2.1-2.2)	0.33	$C_{31}H_{34}N_2O_6 \cdot 0.45TFA$
10g		2.5 (1.8-3.4)	1.1 (1.0-1.3)	2.27	$C_{33}H_{38}N_2O_6 \cdot 0.22TFA$
10h		8.8 (8.6-9.0)	0.94 (0.49-1.8)	9.36	$C_{32}H_{36}N_2O_6 \cdot 0.67TFA$
10i		13.6 (11.0-16.9)	3.4 (3.2-3.6)	4.0	$C_{32}H_{36}N_2O_6 \cdot 0.50TFA$
10j		131 (111-155)	5.0 (3.9-6.4)	26.2	$C_{33}H_{38}N_2O_6 \cdot 0.45TFA$

[a] IC_{50} calculated using a mean of at least 2 measurements (all duplicates) for 11 concentrations from 10^{-10} to 10^{-5} M unless otherwise noted. [b] Expressed as $IC_{50}(ET_A)/IC_{50}(ET_B)$.

resulted in over 10-fold increase of the selectivity of the antagonist and moderate decrease of ET_B affinity. By the same analogy, elongation of the *tert*-butyl group of **10h** to a neopentyl group provided antagonist **10j** with

a 3-fold increase of selectivity but a 5-fold decrease of ET_B receptor affinity. Compared to the diphenylmethylamine series, the phenylalkylmethylamine series could offer equally potent antagonism against the ET_B receptor (IC_{50} = 0.94 nM of **10h**), even though the selectivity was somewhat inferior to that of the diarylmethylamine series (A/B = 26 of **10j**).

During the course of SAR studies of pyrrolidine-based endothelin receptor antagonists, we demonstrated the importance of the 2-aryl group in modulating the affinity and specificity profiles of the compounds after establishing the essential nature of the profile (ET_A-selective, balanced).[19,24] Several variations of the *p*-anisyl group of **2**, such as *p*-methoxyethoxyphenyl and *p*-isopropoxyethoxyphenyl groups, have been identified to offer better specificity toward the ET_B receptor. Having discovered a novel class of ET_B-selective antagonists by virtue of side chain modification, we began to mix and match these acetamide side chains with the more ET_B-selective pyrrolidine core modifications. And to our delight, this exercise proved to be very fruitful in yielding potent and highly specific ET_B receptor antagonists.

The *tert*-butylphenylmethylamine acetamide side chain from compound **10h** was first examined with pyrrolidine core modifications and compared with the parent compounds (Table 3). *p*-Methoxyethoxy substituent of the 2-aryl group boosted the ET_B selectivity of the resulting antagonist **10k** to 220-fold while preserving the high affinity for the ET_B receptor. An even more ET_B-specific modification, a *p*-isopropoxyethoxy group, provided antagonist **10l** with subnanomolar affinity and over 450-fold selectivity for the ET_B receptor. Then, the more ET_B-selective bis-*o*-tolylmethylamine acetamide side chain of **9g** was combined with these 2-aryl substituent variations. The *p*-methoxyethoxyphenyl-substituted pyrrolidine improved the selectivity of antagonist **9j** 80-fold, yielding a nanomolar antagonist with over 12 000-fold selectivity for the ET_B receptor. Parallel to the selectivity improvement shown with **10k** to **10l**, another 2-fold boost of receptor selectivity was noticed with a *p*-isopropoxyethoxy group replacement, resulting in one of the most selective ET_B receptor antagonists (**9k**) reported to date. Combination of the less ET_B-specific acetamide side chain of compound **9h** with the *p*-isopropoxyethoxy-substituted pyrrolidine core (**9l**) resulted in a 5-fold loss of receptor affinity and selectivity in comparison to **9k**.

Having identified a series of very potent and highly selective ET_B receptor antagonists, two compounds (**9j** and **9k**) were prepared in enantiomerically pure form and their pharmacokinetic profiles were evaluated in rats (Table 4). The active enantiomer of **9j** behaved rather poorly in vivo. It has a very short half-life and is absorbed poorly following oral administration, resulting in a bioavailability (*F*) of a mere 8%. In comparison, enantiomer **9k** (A-308165) has a much more acceptable pharmacokinetic profile in rats. It has a reasonable half-life (4.8 h) and total drug exposure ($AUC_{0-\infty}$ = 0.73 μg-h/mL) following oral administration. The calculated oral bioavailability (*F*) is 24%.

As reported in the companion article, A-192621 is a potent and selective ET_B receptor antagonist.[28] In comparison to A-192621, compound **9k** has improved substantially over its predecessor in term of specificity of the antagonist. It is also more potent and exhibits a comparable pharmacokinetic profile in rats. Even though the pharmacology studies using A-192621 and other ET_B-specific antagonists[29] have suggested that selective ET_B antagonists may not be suitable as agents for long-term systemic therapy because of their hypertensive liabilities, compound **9k** could be a valuable tool for further elucidating the role of the ET_B receptor in both normal physiological and pathological conditions.

Summary

Two novel series of pyrrolidine-3-carboxylic acid-based potent and highly ET_B receptor-selective antagonists have been identified through modification of the *N*,*N*-dibutylamino group of the ET_A-selective antagonist **1**. In the first series, an opportunistic observation during SAR studies led to the observation that a diarylmethylamine acetamide side chain imparts ET_B selectivity to these pyrrolidine-based endothelin antagonists. Optimization of the side chain and the pyrrolidine 2-aryl group yielded compound **9k** with nanomolar affinity for the ET_B receptor, over 27 000-fold selectivity for the ET_B versus ET_A receptor, and good oral bioavailability.

The second series of ET_B-selective antagonists was developed by replacing one of the aryl groups in the biarylmethylamine series with an alkyl group. Through optimizing the size of the alkyl groups, the receptor antagonists could be transformed from the ET_A/ET_B-mixed type to the ones favoring the ET_B receptor subtype. Combining the preferred *tert*-butylphenylmethylamine acetamide side chain with 2-aryl group modification led to antagonist **10l** with subnanomolar affinity and more than 450-fold selectivity for the ET_B receptor.

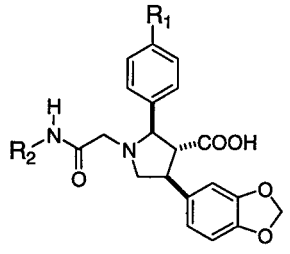
Experimental Section

General. Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. All reactions were performed under nitrogen atmosphere unless specifically noted. Flash chromatography was performed using silica gel (230−400 mesh) from E.M. Science. Proton NMR spectra were recorded on a General Electric QE300 instrument with Me_4Si as an internal standard and are reported as shift (multiplicity, coupling constants, proton counts). Mass spectral analyses were accomplished using different techniques, including desorption chemical ionization (DCI), atmospheric pressure chemical ionization (APCI), and electrospray ionization (ESI), as specified for individual compounds. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ, and are consistent with theoretical values to within 0.4% unless indicated.

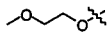
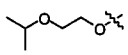
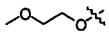
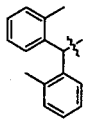
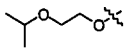
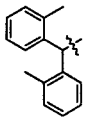
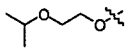
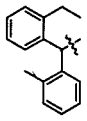
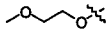
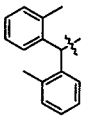
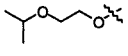
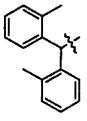
Preparation of Ketones 11. Most of the ketones were purchased from commercial vendors. 2,2′-Dimethylbenzophenone and 2-ethyl-2′-methylbenzophenone were prepared from commercially available methyl 2-methylbenzoate according to the published procedure.[30] 3,3-Dimethyl-1-phenylbutan-1-one was prepared from commercially available 3,3-dimethylbutyryl chloride according to the published procedure.[31]

Bis-*o*-tolyl *N*-Hydroxyoxime (12, $Ar_1 = Ar_2 = o\text{-}CH_3C_6H_5$). In a 50-mL round-bottom flask were placed 2,2′-dimethylbenzophenone (2.50 g, 10 mmol), hydroxylamine hydrochloride (0.76 g, 11 mmol), pyridine (5 mL), and ethanol (5 mL). The mixture was refluxed for 8 h with stirring. The reaction mixture was then allowed to cool to ambient temperature and extracted with 2 × 25 mL of EtOAc. The combined organic layer was washed in turns with 15 mL of aqueous $CuSO_4$, 15 mL of water, and 15 mL of brine, dried over magnesium sulfate, and concentrated in vacuo. The residual oil obtained

Table 3. Structure–Activity Relationships of 2-Aryl and Acetamide Modifications



9,10

Compound	R_1	R_2	IC_{50} (nM)[a] $h\text{ET}_A$ binding	IC_{50} (nM)[a] $h\text{ET}_B$ binding	A/B ratio[b]	Formula
10k			488 (405-587)	2.2 (1.7-2.8)	221.8	$C_{34}H_{40}N_2O_7 \cdot 0.75TFA$
10l			322 (153-678)	0.71 (0.49-1.03)	453.5	$C_{36}H_{44}N_2O_7 \cdot 0.60TFA$
9j			20,560 (15,020-28,140)	1.7 (1.3-2.3)	12,094	$C_{38}H_{40}N_2O_7 \cdot 0.20TFA$
9k			77,360 (77,360)	3.3 (3.2-3.4)	23,442	$C_{40}H_{44}N_2O_7 \cdot 0.69TFA$
9l			14,270 (13,550-15,030)	3.3 (2.1-5.1)	4,324	$C_{41}H_{46}N_2O_7 \cdot 0.95TFA$
9j (2*R*,3*R*,4*S*)			27,014 (23,880-30,560)	1.7 (0.72-4.0)	15,980	$C_{38}H_{40}N_2O_7 \cdot 0.66TFA$
9k (A-308165) (2*R*,3*R*,4*S*)			51,703 (49,040-54,510)	1.9 (1.1-3.3)	27,212	$C_{40}H_{44}N_2O_7 \cdot 0.45TFA$

[a] IC_{50} calculated using a mean of at least 2 measurements (all duplicates) for 11 concentrations from 10^{-10} to 10^{-5} M unless otherwise noted. [b] Expressed as $IC_{50}(ET_A)/IC_{50}(ET_B)$.

was purified by silica gel column chromatography (elution with 10% EtOAc in hexanes) to give 1.31 g (73%) of white crystalline solid.

Bis-*o*-tolylmethylamine (13, $Ar_1 = Ar_2 = o\text{-}CH_3C_6H_5$). To a round-bottom flask with 55 mL of ammonia cooled in a dry ice–acetone bath was added 130 mg (6.0 mmol) of sodium metal. To the resulting blue solution at −78 °C was added slowly 650 mg (3.0 mmol) of oxime **12** in 25 mL of anhydrous THF. The reaction mixture was stirred for 1 h at −78 °C and then quenched with 1 g of ammonium chloride. The resulting colorless reaction mixture was warmed to ambient temperature, transferred to a separatory funnel, diluted with 50 mL of water, and extracted with 3 × 50 mL of dichloromethane. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a yellowish oil. The residue was purified by a silica gel column chromatography (elution with 60% EtOAc in hexanes, followed by elution with 2% Et_3N in EtOAc) to give 500 mg (66%) of the pure amine.

Bis-*o*-tolylmethylamine Bromoacetamide (8, $Ar_1 = Ar_2 = o\text{-}CH_3C_6H_5$). The amine **13** (100 mg, 0.47 mmol) was dissolved in 2 mL of 1,2-dichloroethane. To this solution at

Table 4. Pharmacokinetic Profiles of Compounds **9j** and **9k** in Rats[a]

compd	iv $T_{1/2}$ (h)	AUC_{iv} (μg-h/mL)	oral $T_{1/2}$ (h)	AUC_{oral} (μg-h/mL)	F (%)
9j (2*R*,3*R*,4*S*)	2.9	2.50	0.55	0.20	8
9k (2*R*,3*R*,4*S*)	1.8	3.03	4.8	0.73	24

[a] 5 mg/kg dosed in both intravenous injection and oral gavage.

−78 °C were added 100 μL of Et_3N (0.71 mmol) and then bromoacetyl bromide (40 μL, 0.47 mmol in 1 mL of 1,2-dichloroethane) dropwise. The reaction mixture was stirred at −78 °C for 10 min, then at ambient temperature for 2 h, diluted with 10 mL of water, and extracted with 2 × 25 mL of 1,2-dichloroethane. The combined organic layers were dried over sodium sulfate and concentrated in vacuo to give the bromoacetamide as a white solid (184 mg, 96%) suitable for further use without additional purification.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(bis-*o*-tolylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic Acid (9g).** To a stirred solution of 0.20 g (0.54 mmol) of *trans,trans*-pyrrolidine and *N,N*-diisopropylethylamine (0.1 mL, 0.57 mmol) in 10 mL of CH_3CN was added the bromoacetamide **8** (184 mg, 0.42 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was then removed on a rotavap, and the crude product was purified by a flash column chromatography (elution with 40% of EtOAc in hexanes) to give 250 mg (73%) of the ethyl ester as a colorless oil. The ester thus obtained was dissolved in 5.0 mL of ethanol, and 0.70 mL of 6 N aqueous sodium hydroxide was added. The mixture was stirred at ambient temperature overnight. The solution was then diluted with 10 mL of water and extracted with 15 mL of 20% hexanes in EtOAc to remove any unhydrolyzed ester. The aqueous phase was acidified with 1 N aqueous H_3PO_4 to pH = 5 and extracted with 3 × 10 mL of chloroform. The combined organic layer was dried and concentrated to get a colorless viscous oil. The title compound was isolated by lyophilization from dilute CH_3CN/TFA/H_2O as an amorphous white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 2.20 (s, 3H), 3.02−3.33 (m, 2H), 3.40−3.72 (m, 3H), 3.80 (s, 3H), 4.16−4.24 (brs, 1H), 5.92 (m, 2H), 6.36−6.42 (m, 1H), 6.58−6.67 (m, 2H), 6.81 (t, J = 9.0 Hz, 4H), 6.88−7.00 (m, 2H), 7.05−7.27 (m, 8H); MS (ESI$^+$) $(M + H)^+$ at m/z 593. Anal. Calcd for $C_{36}H_{36}N_2O_6$·0.40TFA: C, 69.25; H, 5.75; N, 4.39. Found: C, 69.20; H, 5.68; N, 4.22.

Resolution of Compounds. *trans,trans*-(2*R*,3*R*,4*S*)-Ethyl 2-[4-(2-Isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate (7, R_1 = *i*-PrOCH$_2$CH$_2$O). To a solution of amino ester **7** (500 mg, 1.14 mmol) in 3.0 mL of dichloromethane with 0.48 mL (3.4 mmol) of triethylamine was added 0.30 g (1.4 mmol) of di-*tert*-butyl dicarbonate, and the mixture was stirred at ambient temperature for 2 h. Solvents were then removed in vacuo, and the residue was purified with silica gel flash chromatography using 15% EtOAc in hexanes as eluent to give 580 mg (1.07 mmol, 94%) of *N*-Boc ester **14** as a colorless oil. The racemic ester **14** (580 mg, 1.07 mmol) was separated by preparative chiral HPLC on a Regis Whelk-O2 column (5 × 25 cm; 80:20 hexane:ethanol; 100 mL/min; ambient temperature; 210 nm UV 1.0-mm path), to give 245 mg of the (2*S*,3*S*,4*R*)-isomer (t_R = 8.1 min) and 251 mg of the (2*R*,3*R*,4*S*)-isomer (t_R = 11.9 min), respectively. The products are more than 99% enantiomerically pure, as indicated by analytical HPLC analysis, using a Regis Whelk-O column (4.6 × 250 mm; 80:20 hexane:EtOH; 1.0 mL/min; ambient temperature; 210 nm UV). The (2*S*,3*S*,4*R*)-enantiomer (t_R = 11.9 min) (75 mg, 0.17 mmol) was dissolved in 1.0 mL of TFA and stirred at ambient temperature for 1 h. Solvents were removed in vacuo, and the residue was evaporated twice with benzene. The enantiomerically pure amino ester **7** thus obtained was then converted to the final compound (2*R*,3*R*,4*S*)-**9k** following the same procedure as described for compound **9g**.

The following compounds were prepared using the procedures described above for compounds **9g** and **9k**.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(diphenylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (2):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.32 (d, J = 15.6 Hz, 1H), 3.43 (t, J = 9.9 Hz, 2H), 3.50 (td, J = 6.3, 10.2 Hz, 1H), 3.68−3.83 (m, 2H), 3.77 (s, 3H), 4.51 (d, J = 10.2 Hz, 1H), 5.94 (dd, J = 1.2, 3.0 Hz, 2H), 6.14 (d, J = 9.0 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.74 (dd, J = 2.4, 9.0 Hz, 1H), 6.82 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 7.11−7.19 (m, 4H), 7.19−7.37 (m, 8H), 8.19 (d, J = 9.0 Hz, 1H). MS (ESI$^+$) $(M + H)^+$ at m/z 565. Anal. Calcd for $C_{34}H_{32}N_2O_6$·0.70TFA: C, 65.98; H, 5.11; N, 4.35. Found: C, 65.84; H, 5.10; N, 4.17.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(fluorenyl-9-amino)carbonylmethyl]pyrrolidine-3-carboxylic acid (9a):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.30 (d, J = 15.3 Hz, 1H), 3.34 (t, J = 9.0 Hz, 1H), 3.49 (t, J = 10.5 Hz, 1H), 3.60 (dd, J = 6.3, 10.8 Hz, 1H), 3.67−3.82 (m, 3H), 3.77 (s, 3H), 3.47 (d, J = 9.6 Hz, 1H), 5.91 (dd, J = 1.8, 6.6 Hz, 2H), 6.07 (d, J = 9.0 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.70 (dd, J = 1.8, 8.4 Hz, 1H), 6.80 (d, J = 3.6 Hz, 1H), 6.82 (d, J = 3.6 Hz, 1H), 7.23−7.34 (m, 2H), 7.36−7.47 (m, 5H), 7.71 (d, J = 8.4 Hz, 2H); MS (DCI/NH_3) $(M + H)^+$ at m/z 563. Anal. Calcd for $C_{34}H_{30}N_2O_6$·0.70TFA: C, 66.18; H, 4.82; N, 4.36. Found: C, 66.24; H, 4.85; N, 4.37.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1,2-diphenylethyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9b):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ 2.88−3.75 (m, 7H), [3.77 (s), 3.79 (s), 3H in total], 4.47 (t, J = 9.0 Hz, 1H), 5.11−5.37 (m, 2H), 5.96−6.03 (m, 2H), 6.72−7.37 (m, 17H); MS (ESI$^+$) $(M + H)^+$ at m/z 578. Anal. Calcd for $C_{35}H_{34}N_2O_6$·0.80TFA: C, 65.62; H, 5.24; N, 4.18. Found: C, 65.53; H, 5.24; N, 4.08.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(2,2-diphenylethyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9c):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (t, J = 10.2 Hz, 2H), 2.96 (dd, J = 4.2, 9.6 Hz, 1H), 3.20 (d, J = 15.0 Hz, 1H), 3.53 (td, J = 4.2, 9.0 Hz, 1H), 3.74−4.0 (m, 3H), 3.79 (s, 3H), 4.17 (t, J = 7.8 Hz, 1H), 6.03 (dd, J = 1.8, 4.8 Hz, 2H), 6.50 (d, J = 8.7 Hz, 1H), 6.74−6.82 (m, 4H), 7.02 (d, J = 7.2 Hz, 1H), 7.16−7.37 (m, 12H); MS (ESI$^+$) $(M + H)^+$ at m/z 579. Anal. Calcd for $C_{35}H_{34}N_2O_6$·0.20TFA: C, 70.69; H, 5.73; N, 4.66. Found: C, 70.65; H, 5.83; N, 4.55.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(triphenylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (9d):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.92 (d, J = 16.5 Hz, 1H), 3.04−3.19 (m, 2H), 3.37 (d, J = 16.5 Hz, 1H), 3.43 (dd, J = 4.2, 9.6 Hz, 1H), 3.64 (td, J = 2.7, 9.0 Hz, 1H), 3.79 (s, 3H), 3.96 (d, J = 9.0 Hz, 1H), 5.95 (dd, J = 1.8, 4.8 Hz, 2H), 6.58 (d, J = 9.0 Hz, 1H), 6.70 (dd, J = 2.1, 9.0 Hz, 1H), 6.77 (d, J = 9.0 Hz, 2H), 6.82 (s, 1H), 7.03−7.14 (m, 6H), 7.19 (d, J = 9.0 Hz, 2H), 7.23−7.34 (m, 8H), 8.33 (s, 1H); MS (ESI$^+$) $(M + H)^+$ at m/z 641. Anal. Calcd for $C_{40}H_{36}N_2O_6$·0.16TFA: C, 73.49; H, 5.53; N, 4.25. Found: C, 73.48; H, 5.48; N, 4.18.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[1-(2′-methylphenyl)-1-phenylmethyl]aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9e):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [2.22 (s), 2.26 (s), 3H in total], 3.21−3.78 (m, 7H), [3.79 (s), 3.80 (s), 3H in total], 4.44−4.53 (t, J = 9.0 Hz, 1H), 5.94−5.97 (m, 2H), 6.34 (d, J = 9.0 Hz, 1H), 6.66−6.92 (m, 4H), 7.04−7.36 (m, 11H); MS (ESI$^+$) $(M + H)^+$ at m/z 578. Anal. Calcd for $C_{35}H_{34}N_2O_6$·0.90TFA: C, 64.99; H, 5.17; N, 4.12. Found: C, 64.99; H, 5.34; N, 3.95.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[1-(2′,5′-dimethylphenyl)-1-phenylmethyl]aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9f):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [2.19 (s), 2.30 (s), 6H in total], 3.27−3.66 (m, 3H), 3.72−3.84 (m, 7H), 4.57 (t, J = 9.0 Hz, 1H), 5.92−5.97 (m, 2H), 6.29 (dd, J = 4.5, 9.0 Hz, 1H), 6.67−7.40 (m, 14H); MS (ESI$^+$) (M +

H)$^+$ at *m/z* 592. Anal. Calcd for $C_{36}H_{36}N_2O_6$·0.85TFA: C, 65.80; H, 5.40; N, 4.07. Found: C, 65.78; H, 5.61; N, 4.07.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[1-(2′-ethylphenyl)-1-(2′-methylphenyl)methyl]aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9h):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ 1.08−1.20 (m, 3H), 2.20 (brs, 3H), 2.43−2.54 (m, 2H), 3.40−3.87 (m, 10H), 4.48−4.60 (m, 1H), 5.96 (s, 2H), 6.48−7.40 (m, 15H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 606. Anal. Calcd for $C_{37}H_{38}N_2O_6$·1.00TFA: C, 64.97; H, 5.45; N, 3.87. Found: C, 65.01; H, 5.47; N, 3.47.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[1,1-bis(2′-ethylphenyl)methyl]aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9i):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, J = 7.5 Hz, 6H), 2.28−2.59 (brm, 4H), 3.43−3.95 (m, 10H), 4.61−4.73 (brs, 1H), 5.97 (s, 2H), 6.52−7.42 (m, 15H). MS (ESI$^+$) (M + H)$^+$ at *m/z* 621. Anal. Calcd for $C_{38}H_{40}N_2O_6$·1.15TFA: C, 64.36; H, 5.51; N, 3.72. Found: C, 64.36; H, 5.51; N, 3.73.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1-phenylethyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10a):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [1.43 (d), 1.48 (d), J = 7.5 Hz, 3H in total], 2.70−3.48 (m, 4H), 3.55−3.72 (m, 1H), [3.78 (s), 3.82 (s), 3H in total], 3.88−4.01 (m, 2H), 4.97−5.11 (m 1H), 5.93−6.00 (m, 2H), 6.65−6.94 (m, 5H), 7.17−7.47 (m, 7H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 502. Anal. Calcd for $C_{29}H_{30}N_2O_6$·0.22TFA: C, 67.02; H, 5.77; N, 5.31. Found: C, 67.08; H, 5.57; N, 4.97.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[1-(2′-methylphenyl)ethyl]aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid (10b):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [1.38 (d), 1.42 (d), J = 7.5 Hz, 3H in total], [2.27 (s), 2.32 (s), 3H in total], 2.77−3.42 (m, 3H), 3.52−3.93 (m, 4H), [3.77 (s), 3.81 (s), 3H in total], 5.15−5.30 (m, 1H), 5.90−5.98 (m, 2H), 6.60−6.96 (m, 7H), 7.06−7.38 (m, 4H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 516. Anal. Calcd for $C_{30}H_{32}N_2O_6$·0.20TFA: C, 67.69; H, 6.02; N, 5.19. Found: C, 67.56; H, 5.89; N, 5.16.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1-phenylpropyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10c):** white solid; H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [0.83 (t), 0.87 (t), J = 7.5 Hz, 3H in total], 1.71−1.84 (m, 2H), 2.85−4.16 (m, 7H), [3.77 (s), 3.81 (s), 3H in total], 4.72−4.86 (m, 1H), 5.95−6.03 (m, 2H), 6.68−7.42 (m, 12H); MS (ESI$^+$) (M + H$^+$) at *m/z* 516. Anal. Calcd for $C_{30}H_{32}N_2O_6$·0.10TFA: C, 68.73; H, 6.13; N, 5.31. Found: C, 68.74; H, 6.13; N, 5.22.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1-phenylbutyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10d):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ 0.82−0.96 (m, 3H), 1.10−1.31 (m, 2H), 1.63−1.77 (m, 2H), 2.94−3.84 (m, 9H), 4.13−4.22 (m, 1H), 4.79−4.89 (m, 1H), 5.98 (s, 2H), 6.69−7.47 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 530. Anal. Calcd for $C_{31}H_{34}N_2O_6$·0.30TFA: C, 67.12; H, 6.11; N, 4.95. Found: C, 67.15; H, 5.88; N, 4.97.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(1-phenylpentyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10e):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [0.79 (t), 0.87 (t), J = 7.5 Hz, 3H in total], 1.10−1.38 (m, 4H), 1.66−1.80 (m, 2H), 2.91−3.83 (m, 6H), [3.75 (s), 3.80 (s), 3H in total], 4.03−4.12 (m, 1H), 4.79−4.89 (m, 1H), 5.96−5.99 (m, 2H), 6.70−6.99 (m, 5H), 7.08−7.38 (m, 7H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 544. Anal. Calcd for $C_{32}H_{36}N_2O_6$·0.25TFA: C, 67.94; H, 6.36; N, 4.87. Found: C, 68.00; H, 6.18; N, 4.51.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(2-methyl-1-phenylpropyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid (10f):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ 0.77−0.95 (m, 6H), 1.96−2.07 (m, 1H), 2.80−3.45 (m, 4H), 3.60−3.76 (m, 1H), [3.76 (s), 3.80 (s), 3H in total], 3.98−4.04 (m, 2H), 4.67 (t, J = 9.0 Hz, 1H), 5.89−6.00 (m, 2H), 6.68−7.42 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 530. Anal. Calcd for $C_{31}H_{34}N_2O_6$·0.45TFA: C, 66.07; H, 5.99; N, 4.84. Found: C, 66.10; H, 6.01; N, 4.57.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(2-ethyl-1-phenylbutyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid (10g):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ 0.77−0.91 (m, 6H), 1.08−1.66 (m, 4H), 2.87−3.48 (m, 4H), 3.60−3.75 (m, 2H), [3.78 (s), 3.81 (s), 3H in total], 4.01−4.11 (m, 2H), 4.88−5.01 (m, 1H), 5.92−6.00 (m, 2H), 6.74−7.46 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 558. Anal. Calcd for $C_{33}H_{38}N_2O_6$·0.22TFA: C, 68.71; H, 6.59; N, 4.79. Found: C, 68.72; H, 6.62; N, 4.67.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(2,2-dimethyl-1-phenylpropyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10h):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [0.86 (s), 0.89 (s), 9H in total], 3.10−3.77 (m, 5H), [3.78 (s), 3.82 (s), 3H in total], 4.32−4.52 (m, 2H), 4.69−4.77 (m, 1H), 5.96−6.02 (m, 2H), 6.78−7.47 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 544. Anal. Calcd for $C_{32}H_{36}N_2O_6$·0.67TFA: C, 64.45; H, 5.95; N, 4.51. Found: C, 64.40; H, 6.18; N, 4.71.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(3-methyl-1-phenylbutyl)aminocarbonylmethyl]-pyrrolidine-3-carboxylic acid (10i):** white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78−0.96 (m, 6H), 1.34−1.50 (m, 1H), 1.51−1.77 (m, 2H), 3.30−3.92 (m, 8H), 4.67−4.95 (m, 3H), 5.89−6.03 (m, 2H), 6.68−7.47 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 544. Anal. Calcd for $C_{32}H_{36}N_2O_6$·0.50TFA: C, 66.07; H, 6.14; N, 4.68. Found: C, 66.10; H, 5.89; N, 4.68.

***trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-[(3,3-dimethyl-1-phenylbutyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10j):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [0.84 (s), 0.89 (s), 9H in total], 1.68 (t, J = 7.5 Hz, 2H), 3.05−3.30 (m, 2H), 3.34−3.53 (m, 2H), 3.62−3.74 (m, 1H), 3.77 (s, 2H), 3.80 (s, 3H), 4.92−5.02 (m, 1H), 5.97−6.01(m, 2H), 6.77 (t, J = 6.0 Hz, 2H), 6.88 (q, J = 7.5, 18.0 Hz, 2H), 6.97 (d, J = 6.0 Hz, 1H), 7.10−7.40 (m, 7H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 559. Anal. Calcd for $C_{33}H_{38}N_2O_6$·0.45TFA: C, 66.75; H, 6.35; N, 4.59. Found: C, 66.69; H, 6.32; N, 4.46.

***trans,trans*-2-[4-(2-Methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-[(2,2-dimethyl-1-phenylpropyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10k):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [0.85 (s), 0.88 (s), 9H in total], 3.44 (s, 2H), 3.10−3.42 (m, 3H), 3.46 (s, 3H), 3.51−3.75 (m, 4H), 4.06−4.13 (m, 2H), 4.72 (m, 1H), 5.97 (m, 2H), 6.77−7.45 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 589. Anal. Calcd for $C_{34}H_{40}N_2O_7$·0.75TFA: C, 63.24; H, 6.09; N, 4.15. Found: C, 63.33; H, 6.18; N, 4.05.

***trans,trans*-2-[4-(2-Isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-[(2,2-dimethyl-1-phenylpropyl)aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (10l):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ [0.83 (s), 0.88 (s), 3H in total], 1.19 (d, J = 7.0 Hz, 6H), 3.14−3.83 (m, 9H), 4.07 (p, J = 4.5, 10.5 Hz, 2H), 4.27−4.47 (m, 1H), 4.70 (t, J = 9.0 Hz, 1H), 5.93−6.00 (m, 2H), 6.73−7.38 (m, 12H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 617. Anal. Calcd for $C_{36}H_{44}N_2O_7$·0.60TFA: C, 65.21; H, 6.56; N, 4.09. Found: C, 65.15; H, 6.59; N, 4.01.

***trans,trans*-2-[4-(2-Methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(bis-*o*-tolylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (9j):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 2.20 (s, 3H), 2.94−3.23 (m, 3H), 3.32−3.51 (m, 2H), 3.47 (s, 3H), 3.58−3.69 (brs, 2H), 3.76 (dd, J = 1.5, 6.0 Hz, 4H), 4.09 (t, J = 4.5 Hz, 1H), 5.93 (m, 2H), 6.34−6.41 (d, J = 7.5 Hz, 2H), 6.58 (brs, 2H), 6.72−6.98 (m, 3H), 7.05−7.28 (m, 8H); MS (ESI$^+$) (M + H)$^+$ at *m/z* 637. Anal. Calcd for $C_{38}H_{40}N_2O_7$·0.20TFA: C, 69.93; H, 6.14; N, 4.25. Found: C, 70.03; H, 6.08; N, 4.21.

***trans,trans*-2-[4-(2-Isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(bis-*o*-tolylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (9k):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, J = 6.6 Hz, 6H), 2.16 (s, 3H), 2.20 (s, 3H), 3.17 (d, J = 15.6 Hz, 1H), 3.26 (t, J = 10.0 Hz, 1H), 3.33−3.55 (m, 3H), 3.66 (brs, 1H), 3.70 (quintet, J =

6.0 Hz, 2H), 3.78 (t, J = 4.8 Hz, 2H), 4.07 (t, J = 4.8 Hz, 2H), 4.34 (d, J = 9.9 Hz, 1H), 5.94 (s, 2H), 6.38 (d, J = 8.7 Hz, 1H), 6.65 (dd, J = 8.4, 9.9 Hz, 2H), 6.82 (s, 2H), 6.86 (s, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 7.04−7.34 (m, 6H), 7.71 (d, J = 8.4 Hz, 1H); MS (ESI$^+$) $(M + H)^+$ at m/z 665. Anal. Calcd for $C_{40}H_{44}N_2O_7$·0.69TFA: C, 66.85; H, 6.06; N, 3.77. Found: C, 66.85; H, 6.01; N, 3.63.

***trans,trans*-2-[4-(2-Isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-[[1-(2′-ethylphenyl)-1-(2′-methylphenyl)methyl]aminocarbonylmethyl]pyrrolidine-3-carboxylic acid (9l):** white solid; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) δ 1.04−1.28 (m, 9H), 2.20 (s, 3H), 2.53 (brs, 2H), 2.94−3.23 (m, 3H), 3.35−3.87 (m, 6H), 4.08 (brs, 3H), 4.52 (brs, 1H), 5.96 (s, 2H), 6.48−7.35 (m, 15H); MS (ESI$^+$) $(M + H)^+$ at m/z 678. Anal. Calcd for $C_{41}H_{46}N_2O_7$·0.95TFA: C, 65.46; H, 6.01; N, 3.46. Found: C, 65.47; H, 6.00; N, 3.10.

***trans,trans*-(2*R*,3*R*,4*S*)-2-[4-(2-Methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(bis-*o*-tolylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (9j):** white solid; $[\alpha]^{23}_D$ +14.0° (*c* 0.0015, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 2.20 (s, 3H), 2.94−3.23 (m, 3H), 3.32−3.51 (m, 2H), 3.47 (s, 3H), 3.58−3.69 (brs, 2H), 3.76 (dd, J = 1.5, 6.0 Hz, 4H), 4.09 (t, J = 4.5 Hz, 1H), 5.93 (m, 2H), 6.34−6.41 (d, J = 7.5 Hz, 2H), 6.58 (brs, 2H), 6.72−6.98 (m, 3H), 7.05−7.28 (m, 8H); MS (ESI$^+$) $(M + H)^+$ at m/z 637. Anal. Calcd for $C_{38}H_{40}N_2O_7$·0.66TFA: C, 66.33; H, 5.76; N, 3.93. Found: C, 66.57; H, 5.36; N, 3.68.

***trans,trans*-(2*R*,3*R*,4*S*)-2-[4-(2-Isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(bis-*o*-tolylmethylaminocarbonylmethyl)pyrrolidine-3-carboxylic acid (9k):** white solid; $[\alpha]^{23}_D$ +10.3° (*c* 0.0016, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, J = 6.6 Hz, 6H), 2.16 (s, 3H), 2.20 (s, 3H), 3.17 (d, J = 15.6 Hz, 1H), 3.26 (t, J = 10.0 Hz, 1H), 3.33−3.55 (m, 3H), 3.66 (brs, 1H), 3.70 (quintet, J = 6.0 Hz, 2H), 3.78 (t, J = 4.8 Hz, 2H), 4.07 (t, J = 4.8 Hz, 2H), 4.34 (d, J = 9.9 Hz, 1H), 5.94 (s, 2H), 6.38 (d, J = 8.7 Hz, 1H), 6.65 (dd, J = 8.4, 9.9 Hz, 2H), 6.82 (s, 2H), 6.86 (s, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 7.04−7.34 (m, 6H), 7.71 (d, J = 8.4 Hz, 1H); MS (ESI$^+$) $(M + H)^+$ at m/z 665. Anal. Calcd for $C_{40}H_{44}N_2O_7$·0.45TFA: C, 68.60; H, 6.26; N, 3.91. Found: C, 68.68; H, 6.15; N, 3.87.

Receptor Binding Assays and Pharmacokinetic Analysis. See the previously published Experimental Section.[18]

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