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Discovery of a Series of Pyrrolidine-based Endothelin Receptor Antagonists with Enhanced ET_A Receptor Selectivity

Steven A. Boyd,[a,*] Robert A. Mantei,[a] Andrew S. Tasker,[a] Gang Liu,[a] Bryan K. Sorensen,[a] Kenneth J. Henry Jr,[a] Thomas W. von Geldern,[a] Martin Winn,[a] Jinshyun R. Wu-Wong,[a] William J. Chiou,[a] Douglas B. Dixon,[a] Charles W. Hutchins,[b] Kennan C. Marsh,[c] Bach Nguyen[c] and Terry J. Opgenorth[a]

[a]*Metabolic Disease Research, Abbott Laboratories, Pharmaceutical Products Division, 100 Abbott Park Road, Building AP10, Abbott Park, IL 60064-6101, USA*

[b]*Advanced Technologies Research, Abbott Laboratories, Pharmaceutical Products Division, 100 Abbott Park Road, Building AP10, Abbott Park, IL 60064-6068, USA*

[c]*Exploratory Science, Abbott Laboratories, Pharmaceutical Products Division, 100 Abbott Park Road, Building AP9, Abbott Park, IL 60064-6122, USA*

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Abstract—Endothelins, ET-1, ET-2, and ET-3 are potent vasoconstricting and mitogenic 21-amino acid bicyclic peptides, which exert their effects upon binding to the ET_A and ET_B receptors. The ET_A receptor mediates vasoconstriction and smooth muscle cell proliferation, and the ET_B receptor mediates different effects in different tissues, including nitric oxide release from endothelial cells, and vasoconstriction in certain vascular cell types. Selective antagonists of endothelin receptor subtypes may prove useful in determining the role of endothelin in various tissue types and disease states, and hence as therapeutic agents for such diseases. The pyrrolidine carboxylic acid A-127722 has been disclosed as a potent and ET_A-selective antagonist, and is currently undergoing clinical trials. In our efforts to find antagonists with altered selectivity (ET_A-selective, ET_B-selective, or nonselective), we investigated the SAR of the 2-substituent on the pyrrolidine. Compounds with alkyl groups at the 2-position possessed ET_A selectivity improved over A-127722 (1400-fold selective), with the best of these compounds showing nearly 19,000-fold selectivity.

Introduction

Endothelins ET-1, ET-2, and ET-3, are 21-amino acid, bicyclic vasoconstrictor peptides, with a conserved hexapeptide tail (Fig. 1).[1–3] The endothelins are produced by a number of cell types and appear to act as paracrine factors through binding to cell surface receptors. The two known mammalian endothelin receptor subtypes, ET_A and ET_B, are G-protein-coupled cell surface receptors containing seven transmembrane regions. ET_A binds selectively to ET-1, and ET_B is nonselective.[4] Endothelin receptors are widely distributed in human tissues.[5] For instance, ET_A is present primarily on vascular smooth muscle, lung, aorta and heart, and ET_B is present on endothelium, cerebral cortex, cerebellum, liver, kidney, lung and placenta. In the vasculature, ET-1 is produced primarily by endothelial cells. ET-1 binding to ET_A produces contraction of smooth muscle (EC_{50} < 1 nM)[6,7] and activates a complex intracellular signalling cascade.[8,9] ET-1 acts as a growth factor in certain tissues, including vascular smooth muscle, and is synergistic with other growth factors (PDGF, bFGF, TGF, EGF, insulin).[10] Endothelins may play a role in vascular diseases, including hypertension, congestive heart failure, vasospasm, restenosis following angioplasty (PCTA), subarachnoid hemorrhage, ischemia, pulmonary hypertension, and renal failure.[1]

While ET_A appears to play a major role in the vasoconstrictor and mitogenic effects of ET-1,[1c,10] binding of the endothelins to ET_B is responsible for the vasodilatory response to endothelins, via release of nitric oxide.[11] In addition, ET_B appears to play a role as a clearance receptor for the endothelins through the internalization of the hormone–receptor complex.[12] Thus, a case can be made for highly selective ET_A receptor antagonists as therapeutic agents, whereby the potentially positive effects of the ET_B receptor are not affected. The early peptidic endothelin receptor antagonists exhibited high selectivity for the ET_A receptor, as

Key words: Endothelin; ET_A-selectivity; pyrrolidine-3-carboxylic acid; vasodilation; anti-mitogenic.

*Corresponding author. Tel.: 847-937-0423; fax: 847-938-1674.

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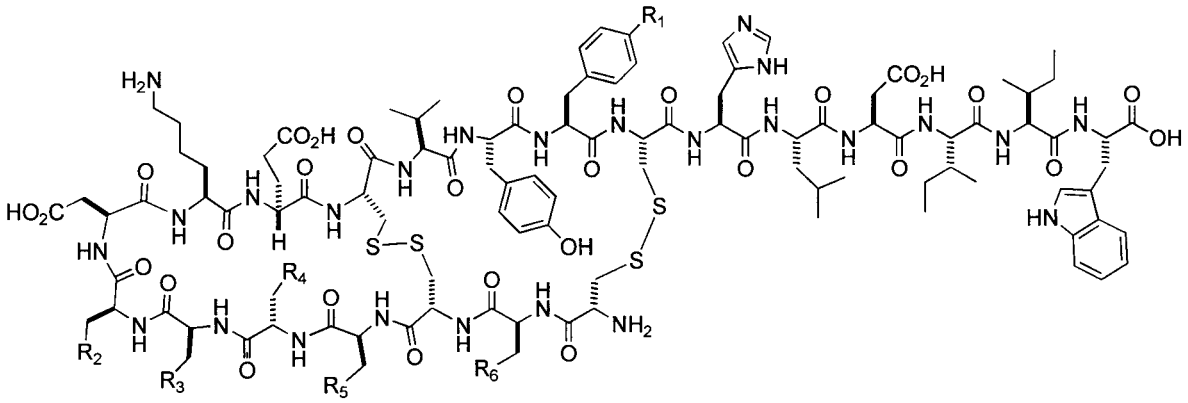


	R_1	R_2	R_3	R_4	R_5	R_6
ET-1	H	$(CH_2)_2SCH_3$	$CH(CH_3)_2$	OH	OH	OH
ET-2	H	$CH(CH_3)_2$	3-indolyl	OH	OH	OH
ET-3	OH	$(CH_2)_4NH_2$	p-OH-Ph	$CH(OH)CH_3$	Ph	$CH(OH)CH_3$

Figure 1. Structures of the endothelin isoforms.

evidenced by BQ-123[13] (818-fold) and FR139317[14] (8770-fold). The peptidic ET_B antagonist BQ-788[15] was also very selective (1080-fold for ET_B), indicating that high levels of selectivity could be achieved. However, the subsequently disclosed nonpeptide antagonists were relatively nonselective. For example, the ET_A-selective oral agents bosentan[16] (20-fold), SB217242[17] (100-fold), and L-754,142[18] (38-fold) are considerably less selective than the better peptidic agents. More recently, we[19] and others[20] have reported compounds with ET_A selectivities in the 1000-fold range. We desired antagonists with higher selectivity, thus we set about the task of re-evaluating the SAR of our pyrrolidine-3-carboxylic acid derivative ABT-627.[19]

Results and Discussion

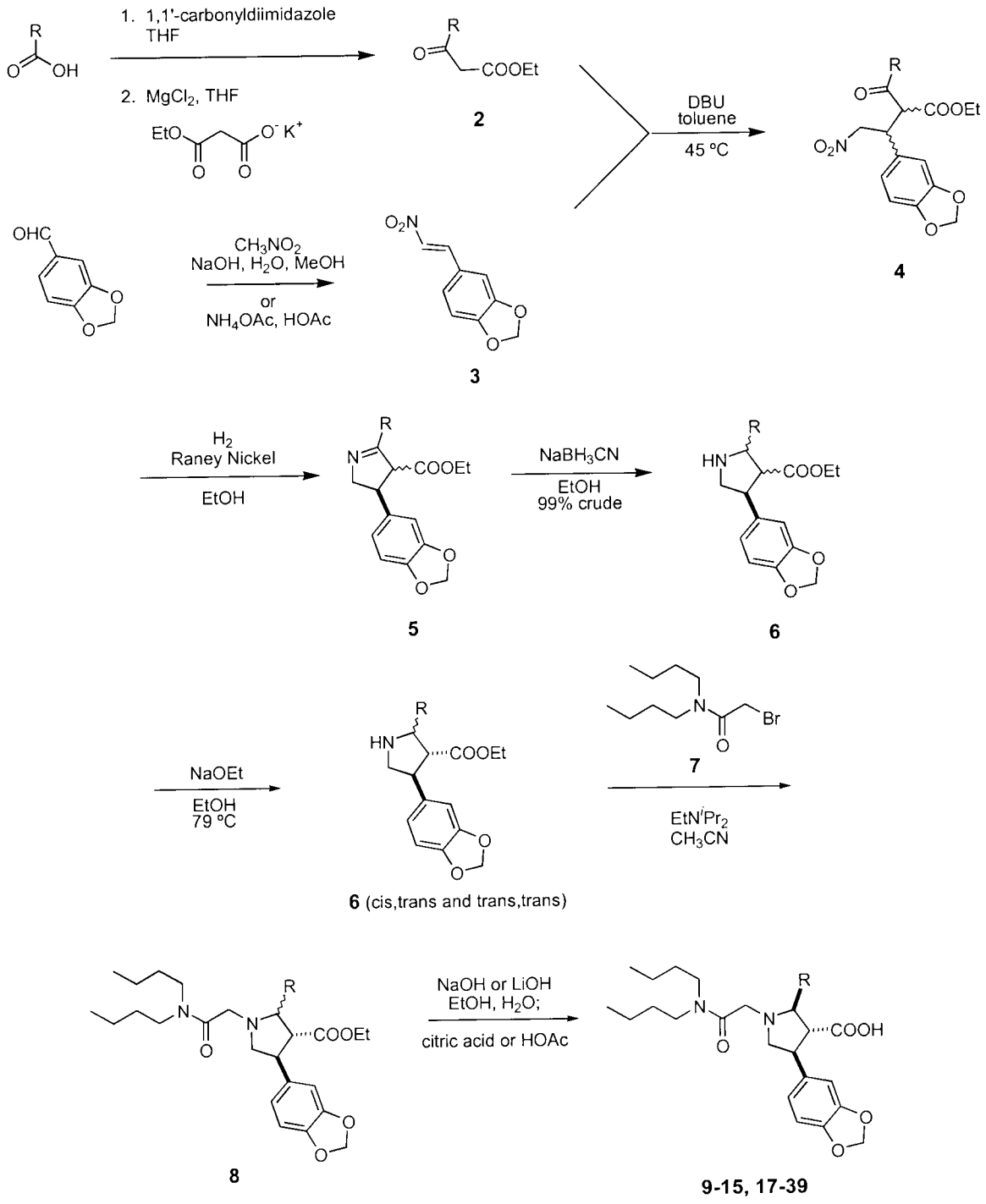
Our plan was to investigate the role of the pyrrolidine C-2 substituent in receptor subtype selectivity. Our homology-based computer models of the endothelin receptors indicated differences between the receptor subtypes in this binding region. We had the following questions: (1) was an aryl group required, (2) was an ether oxygen required, and (3) could the affinity for the ET_B receptor be drastically affected by modification of the group at C-2 of the pyrrolidine?

Synthetic Chemistry

The synthesis of the antagonists followed our previously reported route,[20] in which the pyrrolidine ring is formed by a nitroalkene-β-ketoester condensation, followed by a two-step reductive cyclization (Scheme 1). The requisite β-ketoesters **2** were formed from the corresponding carboxylic acids by acylation of their imidazolides with ethyl magnesium malonate, followed by in situ decarboxylation.[21] Condensation of the ketoesters **2** with nitrostyrene **3** provided the adducts **4**. Upon reduction of the nitro group, the amino group cyclized onto the ketone to form the imines **5**. The imines were further reduced to a mixture of diastereomeric pyrrolidine esters **6**. These crude mixtures of diastereomers were generally isomerized to a mixture of only the *cis,trans* and *trans,trans* pyrrolidines by base-catalyzed equilibration with sodium ethoxide. *N*-Alkylation of the pyrrolidines **6** with bromoacetamide **7** provided the elaborated pyrrolidines **8**. Alternatively, the pyrrolidine esters **8** could be equilibrated at this stage using the same conditions. In contrast to the 2-aryl compounds, many of the 2-alkyl diastereomers **8** could be separated by column chromatography. Basic hydrolysis of the esters with either NaOH or LiOH afforded the target pyrrolidine-3-carboxylic acids. Fortuitously, the *cis*,-*trans*-isomers were not hydrolyzed under these conditions, allowing their removal from the product. Scheme 2 shows the straightforward hydrogenolysis of the benzyloxymethyl-bearing pyrrolidine, to provide 2-hydroxymethyl antagonist **16**. The 2-unsubstituted compound was produced by an azomethine ylide reaction of ethyl cinnamate **40** with silylmethyl aminal **41** according to the procedure of Cottrell et al. (Scheme 3).[22] The methylbenzyl pyrrolidine **42**, obtained as a 1.5:1 mixture of diastereomers, was hydrogenolyzed to reveal the unprotected pyrrolidine **6** (R = H) by standard conditions. Pyrrolidine **6** was then alkylated and hydrolyzed as above to give carboxylic acid **27**.

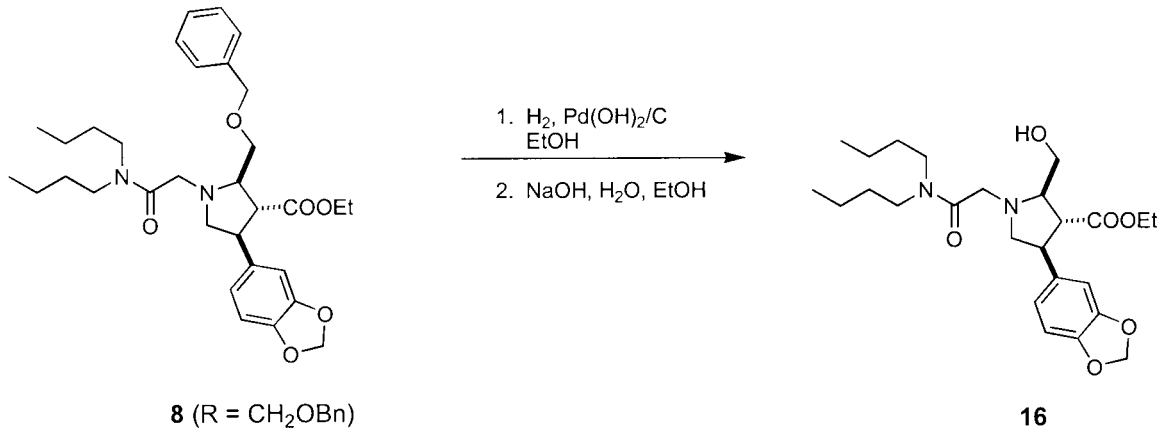
In Vitro Structure–Activity Studies

The in vitro receptor binding activities of the antagonists are listed in Tables 1–3. Table 1 lists data for a series of para-substituted 2-phenylpyrrolidines. The ether oxygen atom was not required for potent antagonism of ET_A,

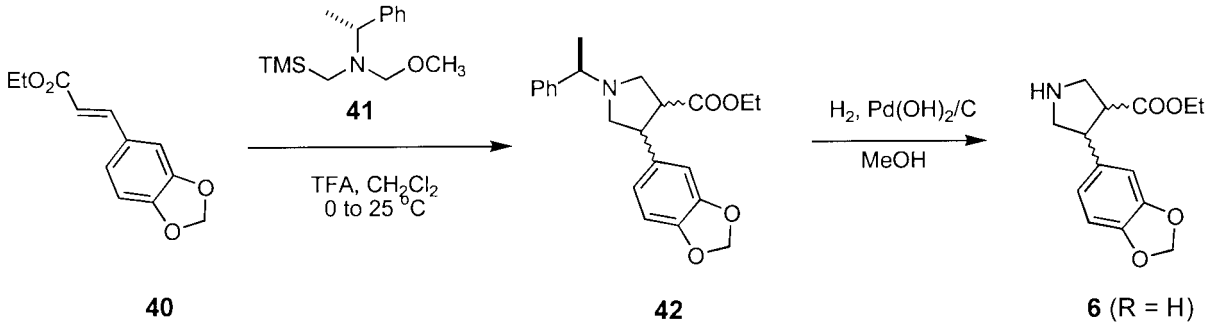


Scheme 1.

since *p*-tolyl (**9**) and *p*-ethylphenyl (**11**) were equipotent with *p*-methoxyphenyl A-127722 (**1**). A preference for small *p*-alkyl groups on the phenyl ring was apparent, as the larger *t*-butyl was considerably less potent than methyl or ethyl. Interestingly, the alkyl groups were relatively less active against the ET_B receptor compared to **1**. The potency data for a series of alkyl ether-bearing antagonists is listed in Table 2. The *cis*-cyclohexyl methylether analogue of A-127722 (**15**) retains considerable potency, but is an order of magnitude less potent than the parent. The *trans* analogue **14** was relatively inactive, indicating a rather close contact with the receptor in this binding region. Several ether derivatives of the 2-hydroxymethyl group were investigated to examine the effect of various-sized hydrophobic moieties. Hydroxymethyl derivative **16** itself was not very potent, however the addition of a butyl (**19**), phenyl (**23**), and benzyl (**24**) provided single-digit nanomolar potencies and a decrease in affinity for the ET_B receptor.

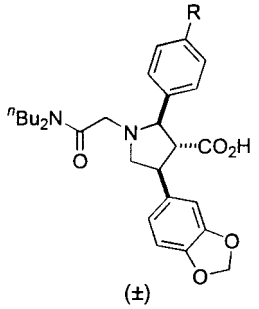


Scheme 2.



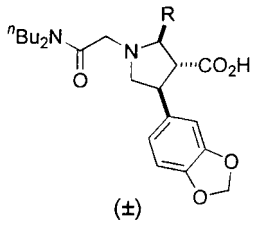
Scheme 3.

Table 1. In vitro receptor antagonism for ET_A- and ET_B-rich tissue preparations: pyrrolidine-C-2 aryl modifications



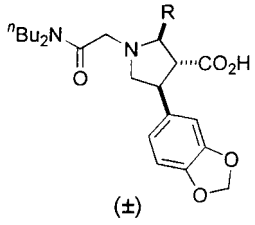
Compound	R	IC_{50}(μM)	
		ET_A (MMQ cell membranes)	ET_B (porcine cerebellum)
A-127722 (**1**)	OCH_3	0.00036	0.515
9	CH_3	0.00012	2.14
10	CF_3	0.0033	14.3
11	Et	0.00017	1.30
12	Pr	0.0011	1.13
13	^{t}Bu	0.0347	14.4

Table 2. In vitro receptor antagonism for ET_A- and ET_B-rich tissue preparations: pyrrolidine-C-2 alkyl ether derivatives



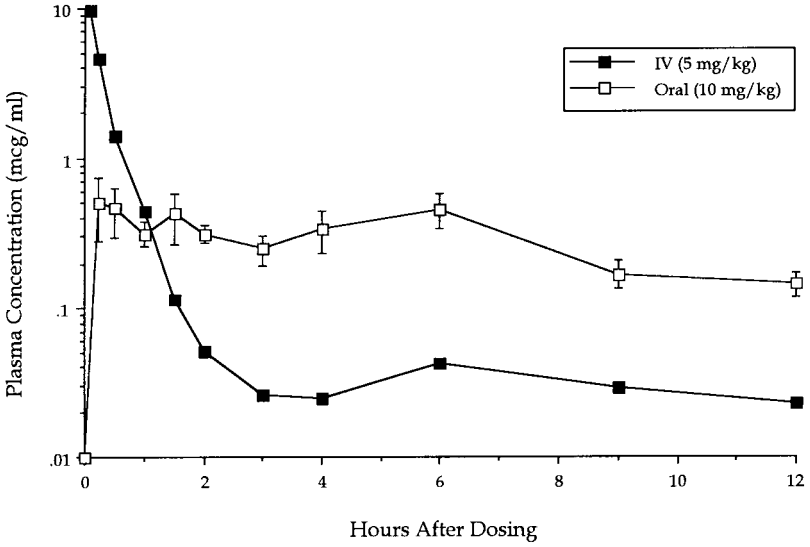
Compound	R	IC_{50}(μM)	
		ET_A (MMQ cell membranes)	ET_B (porcine cerebellum)
14	*trans*-4-CH_3O-cyclohexyl	0.377	> 100
15	*cis*-4-CH_3O-cyclohexyl	0.0092	12.0
16	CH_2OH	0.541	> 100
17	$CH_2OCH_2CH_3$	0.0228	79.5
18	CH_2OPr	0.0169	98.3
19	CH_2OBu	0.0041	12.0
20	$CH_2OCH_2CH_2OCH_3$	0.0246	> 100
21	CH_2O^tBu	0.0878	79.4
22	$CH_2OC(CH_3)_2CH_2CH_3$	0.292	86.6
23	CH_2OPh	0.0045	18.0
24	CH_2OCH_2Ph	0.0068	9.9
25	$CH_2CH_2OCH_3$	0.214	> 100
26	$CH_2CH_2OCH_2CH_3$	0.044	> 100

Table 3. In vitro receptor antagonism for ET_A- and ET_B-rich tissue preparations: pyrrolidine-C-2 alkyl derivatives



Compound	R	IC_{50} (μM)	
		ET_A (MMQ cell membranes)	ET_B (porcine cerebellum)
27	H	18.6	> 100
28	Pr	0.0646	> 100
29	Bu	0.0637	> 100
30	C_5H_{11}	0.0025	47.3
31	C_6H_{13}	0.0056	18.7
32	C_7H_{15}	0.0923	22.9
33	^{i}Pr	0.135	> 100
34	$CH_2CH(CH_3)CH_2CH_3$	0.0174	79.2
35	$CH_2CH_2CH(CH_3)_2$	0.0965	> 87
36	4-CH_3-cyclohexyl	0.0098	> 100
37	$PhCH_2$	0.106	79.0
38	cyclohexyl-CH_2	0.0882	83.7
39	4-CH_3-cyclohexyl-CH_2	0.0036	9.19

A series of analogues with simple alkyl chains at the pyrrolidine C-2 was prepared to further explore the nature of this hydrophobic pocket, and the data are shown in Table 3. The unsubstituted analogue **27**, with an IC_{50} of 18.6 μM, clearly shows the requirement for a group in this position. Methylcyclohexyl compound **39** is less potent than the analogous *p*-tolyl derivative **9**, but is more selective for ET_A than lead compound **1**. A range of simple hydrocarbon substituents showed improved selectivity for ET_A. Branching was tolerated at the 2-position of the chain: the 2-methylbutyl derivative **34** was potent and selective for ET_A, but the 3-methylpropyl derivative **35** had lower affinity for both receptor subtypes. From the group of compounds presented here, the optimum potency and selectivity was represented by **30**, which bears a pentyl chain. Longer straight-chain aliphatic groups, and the larger benzyl and cyclohexylmethyl analogues, led to diminished potency. Compound **30** displays a 2.5 nM antagonism for ET_A, and has an 18,900-fold selectivity versus the ET_B receptor.



route of administration	$t_{1/2}$ (h)	V_c (L/kg)	C_{max} (μg/mL)	$AUC_{0-\infty}$ μg-h/mL	F
iv (5 mg/kg, n = 1)	8.4	0.31	--	5.19	--
po (10 mg/kg, n = 3)	2.3 ± 0.5[a]	--	0.73 ± 0.12	4.03 ± 1.2	39 ± 12%

[a]mean ± standard error

Figure 2. Plasma concentrations of **31** after a 5 (iv, $n=1$) or 10 (po, $n=3$) mg/kg dose in rat (mean ± SEM).

Preliminary Pharmacokinetic Analysis

We determined pharmacokinetic properties of one member of this C-2 alkyl class of antagonists, *n*-hexyl derivative **31**. Figure 2 shows the drug concentrations following oral dosing of 10 mg/kg in rats, as determined by HPLC analysis of the plasma samples taken over time. The antagonist displayed rapid absorption into the circulation, with an average half-life of 2.3 h, C_{max} of 0.73 μg/mL, and an oral bioavailability (compared to a 5 mg/kg iv dose) of 38.9%.

Conclusion

We have developed a highly selective ET_A receptor antagonist, based on our pyrrolidine-3-carboxylic acid template. Aliphatic groups at the 2-position of the pyrrolidine were required for this high level of selectivity, with the best examples (**30**, **31**, and **36**) having >10,000-fold selectivity for ET_A. Introducing such lipophilic groups did not have a large negative impact on oral bioavailability, as evidenced by the 39 F% for compound **31**. The further extension of compounds with alternative functionality at the 2-position, as well as the effect of high ET_A-selectivity on the pharmacology of these agents, is currently under investigation and will be reported in the near future.

Experimental

General

Methyl 3-oxo-6-octenoate and ethyl butyrylacetate were purchased commercially and used without purification. Ethyl 4-*t*-butylbenzoylacetate was prepared by the method of Krapcho et al.[23] Ethyl (3,4-methylenedioxy) cinnamate was produced from piperonal by the method of Blanchette et al.[24] *N*-(Trimethylsilylmethyl)-*N*-methoxymethyl-1-methylbenzylamine was made by the method of Cottrell et al.[22] The endothelin receptor binding assays and pharmacokinetic assay in rat were performed as described previously.[19]

(±)-Ethyl 3-methylhexanoate. To a slurry of 60% sodium hydride (2.26 g, 57 mmol) in 10 mL of hexane and 100 mL of diethyl ether was added triethylphosphonoacetate (10.3 mL, 52 mmol). Once gas evolution ceased, 2-pentanone (6.0 mL, 64 mmol) was added. After 3 h at room temperature, the reaction was quenched with water and partitioned into ether. The organic layer was washed with water and brine, dried with anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of ethanol and 10% palladium on carbon (6.0 g) was added. The vessel was pressurized to 4 atm of hydrogen and was shaken at room temperature for 3 h. The reaction was filtered and the solvent was removed under reduced pressure to give 3.0 g of the title compound, isolated as a 3.6:1 mixture of geometrical isomers. Major isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.66 (m, 1H), 4.20–4.08 (m, 2H), 2.14 (d, $J=1.2$ Hz, 3H), 2.12 (d, $J=6.9$ Hz, 1H), 2.10 (dd, $J=7.8$, 1.2 Hz, 1H), 1.59–1.43 (m, 2H), 1.31–1.24 (m, 3H), 0.98–0.88 (m, 3H). Minor isomer (partial data): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63–2.57 (m, 2 H), 1.87 (d, $J=1.5$ Hz, 3H).

(±)-Ethyl 5-methyl-3-oxooctanoate (2, R = $CH_2CH(CH_3)$-$CH_2CH_2CH_3$). To a solution of ethyl 3-methylhexan-

oate in 150 mL of ethanol was added sodium hydroxide (2.3 g, 57.6 mmol). After 48 h at room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in 150 mL of water. The solution was extracted with ether, then the aqueous phase was acidified with concentrated hydrochloric acid and extracted with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 2.7 g of (±) 3-methylhexanoic acid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (dd, J = 15, 6 Hz, 1H), 2.14 (dd, J = 15, 8.1 Hz, 1H), 2.04–1.91 (m, 1H), 1.42–1.16 (m, 4H), 0.97 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H).

(±) 3-Methylhexanoic acid was treated according to the method of Bram and Vilkas[25] to provide 3.9 g of the title ketoester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J = 7.2 Hz, 2H), 3.41 (s, 2H), 2.52 (dd, J = 16.8, 6 Hz, 1H), 2.33 (dd, J = 16.2, 7.8 Hz, 1H), 2.10–1.91 (m, 1H), 1.38–1.12 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H), 0.92–0.86 (m, 6H). Enol form is present to the extent of 7% in $CDCl_3$. Enol form (partial data): ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.09 (s, 1H), 4.96 (s, 1H).

Ethyl 4-benzyloxy-3-oxobutyrate (2, R = CH_2OBn). A solution of EtOAc (1.28 mL, 13.1 mmol, distilled from CaH_2 under Ar) in 10 mL THF was added dropwise over 5 min to a −75 °C solution of lithium bis(trimethylsilyl)amide (13.0 mL, 1.0 M in THF, 13.0 mmol), maintaining internal temperature < −50 °C. The solution was stirred at −70–75 °C for 30 min, then a solution of *N*-methyl-*N*-methoxy benzyloxyacetamide (2.48 g, 11.9 mmol) in 10 mL THF was added dropwise via syringe over 5 min, maintaining internal temperature < −65 °C. The reaction was stirred at −78 °C for 3 h, then it was transferred via cannula to a 0 °C mixture of 30 mL of 10% aqueous citric acid and 100 mL EtOAc. The mixture was stirred at 0 °C for 5 min, then the mixture was separated, and the aqueous phase was extracted with 2×25 mL EtOAc. The combined organic phase was washed with 50 mL brine, dried (Na_2SO_4), filtered and concentrated in vacuo to a yellow oil. Vacuum distillation (bp 105–112 °C, 0.005 mmHg) produced 1.91 g (8.07 mmol, 68%) of the ketoester as a colorless liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7 Hz, 3H), 3.54 (s, 2H), 4.14 (s, 2H), 4.17 (q, J = 7 Hz, 2H), 4.60 (s, 2H), 7.28–7.42 (m, 5H); enol forms also present: 1.30 (t, J = 7 Hz), 3.64 (s), 4.07 (m), 4.19 (q), 4.68 (s), 5.36 (t, J = 1 Hz), 11.99 (s); MS (DCI/NH_3) m/z 254 $(M+H)^+$.

Methyl 2-(4-hexenoyl)-4-nitro-3-(1,3-benzodioxole-5-yl)-butyrate (4, R = 3-pentenyl). A solution of methyl 3-oxo-6-octenoate (502 mg, 2.95 mmol) in 10 mL isopropanol was added to a solution of 5-(2-nitrovinyl)-1,3-benzodioxole (712 mg, 3.69 mmol) in 10 mL THF, then DBu (22 μL, 0.15 mmol) was added. The resulting reddish solution was stirred at room temperature for 20 min. The solution was concentrated in vacuo and flash chromatographed (18% ethyl acetate–hexane), to produce 879 mg (2.42 mmol, 82%) of ester as a mixture of diastereomers in a 1:1 ratio. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.66 (m, 3H), 2.02–2.17 (br m, 1H), 2.20–2.37 (m, 1.5H), 2.49–2.76 (m, 1.5H), 3.57 (s, 1.5H), 3.74 (s, 1.5H), 3.97 (d, J = 7.5 Hz, 0.5H) and 4.05 (d, J = 8 Hz, 0.5H), 4.10–4.20 (m, 1H), 4.68–4.82 (m, 2H), 5.06–5.52 (m, 2H), 5.95 (2 s, 2H), 6.65 (m, 1H), 6.68 (br s, 1H), 6.75 (d, J = 7.5 Hz, 1H; MS (DCI/NH_3) m/z 381 $(M+NH_4)^+$. Anal. calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.82; N, 3.85. Found: C, 59.32; H, 5.71; N, 3.72.

***trans*,*trans*-Methyl 2-pentyl-4-(1,3-benzodioxol-5-yl)-pyrrolidine-3-carboxylate (8, R = pentyl).** Part A. Nitro ketone **4** (R = 3-pentenyl) (849 mg, 2.34 mmol) was dissolved in 100 mL EtOAc, then Raney nickel (2.55 g, washed 3× with EtOH) was added. The mixture was shaken under 4 atm H_2 for 21 h, then filtered and concentrated in vacuo to provide the crude pyrroline **5** (R = pentyl) as a pale red oil (702 mg, 2.21 mmol, 95% crude): TLC (EtOAc:hexane, 1:3) R_f 0.34; MS (DCI/NH_3) m/z 318 $(M+H)^+$.

Part B. Crude pyrroline **5** (R = pentyl) (692 mg, 2.18 mmol) was dissolved in 4 mL EtOH and 4 mL THF, then 1 mg of bromocresol green indicator and sodium cyanoborohydride (154 mg, 2.45 mmol) were added. The blue mixture was rapidly stirred and treated dropwise with a solution of concentrated aqueous hydrochloric acid in EtOH (1:2 v/v), maintaining a yellow-green color. Once the color stayed yellow, the reaction was stirred an additional 15 min, at which time TLC (2% MeOH–CH_2Cl_2) indicated complete conversion to a low R_f spot. The mixture was made acidic with two drops of ethanolic hydrochloric acid, then it was concentrated in vacuo. Water (20 mL) and CH_2Cl_2 (20 mL) were added to the resulting residue, and the aqueous phase was adjusted to pH 10 with 1 M aqueous Na_2CO_3. The layers were shaken and separated, and the aqueous phase was extracted with 2×15 mL CH_2Cl_2. The combined organic extract was washed with 25 mL brine, dried (Na_2SO_4), filtered, rotoevaporated and the residue placed under high vacuum to provide 665 mg (95% crude) of the crude pyrrolidine ester **6** (pale yellow oil) as a mixture of diastereomers. This mixture of isomers (including the *cis*,*cis* isomer) was epimerized to a mixture of *trans*,*trans* and *cis*,*trans* isomers under the following conditions. A solution of the crude compound (660 mg, 2.07 mmol) in 3 mL methanol was treated with a solution of sodium methoxide (made from the addition of sodium metal (14 mg, 0.61 mmol) to 1 mL methanol). The resultant solution was heated at reflux for 18 h. The reaction was concentrated under reduced pressure, and the residue was partitioned between 25 mL saturated $NaHCO_3$ diluted with 10 mL water, and 30 mL CH_2Cl_2. The aqueous phase was extracted (2×30 mL CH_2Cl_2), then the combined organic phases were washed with 20 mL brine, dried (Na_2SO_4), filtered and the filtrate concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (3.5% methanol–CH_2Cl_2) gave 336 mg (57%) of pure *trans*,*trans*-pyrrolidine ester **6** (R = pentyl) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (br t, 3H), 1.25–1.70 (br m, 8H), 1.83–2.02 (br s, 2H), 2.58 (dd, J = 8, 9 Hz, 1H), 2.99 (dd, J = 8, 14 Hz, 1H), 3.34–3.45 (m, 2H), 3.53 (q, J = 9 Hz, 1H), 3.66 (s, 3H), 5.94 (s, 2H), 6.65–6.75 (m, 3H); MS (DCI/NH_3) m/z 320 $(M+H)^+$. Anal. ($C_{18}H_{25}NO_4$) C, H, N.

Part C. Pyrrolidine ester **6** (R = pentyl) (42.4 mg, 0.133 mmol) and *N*,*N*-dibutyl bromoacetamide (35.5 mg, 0.142 mmol) were combined in 0.5 mL CH_3CN, then ethyldiisopropylamine (46 mL, 0.26 mmol) was added. The reaction was stirred at room temperature for 20 h, then an additional portion of *N*,*N*-dibutyl bromoacetamide[20] (5 mg, 0.02 mmol) was added and the reaction allowed to proceed an additional 30 h. The reaction was partitioned between 20 mL of 5% aqueous citric acid and 25 mL EtOAc. The aqueous phase was extracted with 20 mL EtOAc, and the combined organic phase was washed with 15 mL brine, dried (Na_2SO_4), filtered, rotoevaporated and the residue placed under high vacuum to provide the crude product as a foam. The crude was purified by column chromatography on silica gel (1% MeOH–CH_2Cl_2) to give 53.4 mg (0.109 mmol, 82%) of acetamidopyrrolidine ester **8** as a yellow oil: TLC (1% MeOH–CH_2Cl_2) R_f 0.15; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.94 (m, 6H), 0.97 (t, J = 7 Hz, 3H), 1.20–1.40 (br m, 8H), 1.40–1.80 (br m, 8H), 2.70 (dd, J = 6.5, 9 Hz, 1H), 2.85–3.00 (m, 3H), 3.04–3.39 (m, 4H), 3.40–3.67 (m, 3H), 3.68 (s, 3H), 5.92 (q, J = 1.5 Hz, 2H), 6.70 (d, J = 8 Hz, 1H), 6.74 (dd, J = 1, 8 Hz, 1H), 6.87 (d, J = 1 Hz, 1H); MS (DCI/NH_3) m/z 489 $(M+H)^+$.

***trans*,*trans*-2-Pentyl-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylic acid (30).** Ester **8** (R = pentyl) (50.0 mg, 0.102 mmol) was dissolved in 0.6 mL EtOH, and a solution of lithium hydroxide (9 mg, 0.22 mmol) in 3 mL water was added. The reaction was sealed and stirred at room temperature for 16 h. The mixture was concentrated in vacuo and partitioned between 5 mL CH_2Cl_2 and 3 mL of 10% aqueous citric acid. The organic extract was washed with 2 mL brine, dried (Na_2SO_4), filtered, rotoevaporated and the residue placed under high vacuum to provide the crude acid as a yellow foam (46.3 mg, 96% crude yield). Purification by flash chromatography on silica gel (3.5% MeOH/0.5% HOAc/CH_2Cl_2) produced 29.6 mg (0.062 mmol, 61%) of pyrrolidine carboxylic acid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (br t) and 0.89 (br t, 6H total), 0.97 (t, J = 7.5 Hz, 3H), 1.21–1.42 (br m, 10), 1.43–1.78 (br m, 6H), 2.76 (t, J = 7 Hz, 1H), 3.02–3.30 (br m, 6H), 3.40–3.60 (m, 3H), 3.73 (d, J = 14 Hz, 1H), 5.98 (AB, 2H), 6.70 (d, J = 7 Hz, 1H), 6.77 (dd, J = 1.5, 7 Hz, 1H), 6.89 (d, J = 1.5 Hz, 1H); MS (DCI/NH_3) m/z 475 $(M+H)^+$. Anal. ($C_{27}H_{42}N_2O_5 \cdot 0.5H_2O$) C, H, N.

***trans*,*trans*-Ethyl 2-(benzyloxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (8, R = CH_2OBn).** The procedure described above for **4** and **8** (R = pentyl) was followed, with the substitution of ethyl 4-benzyloxy-3-oxobutyrate for 4-methoxybenzoylacetate, to afford the title compound as a colorless oil: TLC (30% EtOAc–hexane) R_f 0.18; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 7 Hz, 6H), 1.17 (t, J = 7Hz, 3H), 1.20–1.34 (br m, 4H), 1.40–1.56 (br m, 3H), 2.85 (t, J = 8 Hz, 1H), 2.98–3.30 (m, 5H), 3.39–3.60 (m, 3H), 3.64–3.75 (m, 2H), 3.92 (d, J = 14 Hz, 1H), 4.10 (two overlapping q, J = 6.5 Hz, 2H), 4.53 (s, 2H), 5.91 (m, 2H), 6.69 (d, J = 9 Hz, 1H), 6.77 (dd, J = 1.5, 9 Hz, 1H), 6.91 (d, J = 1.5 Hz, 1H); MS (DCI/NH_3) m/z 553 $(M+H)^+$.

***trans*,*trans*-Ethyl 2-(hydroxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (8, R = CH_2OH).** Ester **8** (R = CH_2OBn) (128 mg, 0.232 mmol) and 25 mg of 20% $Pd(OH)_2$ on charcoal in 7 mL EtOH was stirred under 1 atm hydrogen for 48 h. The mixture was filtered through a plug of Celite, and the catalyst was washed with 2×10 mL EtOH, then the combined filtrate and washes were concentrated under reduced pressure to afford 107 mg of the crude alcohol. Purification by flash chromatography (30% EtOAc–hexane) provided 13 mg (12%) of pyrrolidine ester **8** (R = CH_2OH) as pale-yellow wax: TLC (30% EtOAc–hexane) R_f 0.23; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7 Hz) and 0.97 (t, J = 7 Hz, 6H total), 1.21 (t, J = 8 Hz, 3H), 1.20–1.43 (br m, 4H), 1.44–1.6 (br m, 4H), 1.6–2.5 (vbr s, 1H plus H_2O), 3.00–3.09 (m, 1H), 3.10–3.40 (m, 6H), 3.52 (AB, 2H), 3.56–3.67 (m, 3H), 4.13 (q, J = 8 Hz, 2H), 5.92 (m, 2H), 6.71 (d, J = 8 Hz, 1H), 6.80 (dd, J = 2, 8 Hz, 1H), 6.89 (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 463 $(M+H)^+$.

(1′*S*,3*R,4*S**)-Ethyl 1-(2-methylbenzyl)-4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate (41).** *N*-(Trimethylsilylmethyl)-*N*-methoxymethyl-1-methylbenzylamine **40** (638 mg, 2.54 mmol) and ethyl (3,4-methylenedioxy)-cinnamate (399 mg, 1.94 mmol) in 3 mL CH_2Cl_2 at 0 °C was treated with trifluoroacetic acid (0.15 mL, 1.94 mmol). The reaction was stirred for 3 h at 0 °C, then an additional portion of silyl aminal **40** (107 mg, 0.426 mmol) was added, and the reaction stirred at ambient temperature for 16 h. TLC (10% EtOAc–hexane) indicated incomplete reaction. In an effort to induce a more complete reaction, a third portion of aminal **40** (115 mg, 0.457 mmol) and trifluoroacetic acid (0.03 mL, 0.39 mmol) were added to the reaction at room temperature, and the solution was stirred for 5 h. TLC (10% EtOAc–hexane) indicated nearly complete consumption of the cinnamate. The reaction was partitioned between 15 mL CH_2Cl_2 and 20 mL of M aq Na_2CO_3, and the aqueous phase was extracted with 2×15 mL CH_2Cl_2. The combined organic extract was washed with 20 mL brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide a yellow oil (936 mg). The crude product was purified by flash chromatography on silica gel (10% EtOAc–hexane) to afford 353 mg (0.959 mmol, 49%) of the mixture of title compounds as a yellow oil which solidified upon standing: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J = 7 Hz) and 1.21 (t, J = 7 Hz, 3H total), 1.37 (d, J = 7 Hz) and 1.40 (d, J = 7 Hz, 3H total), 1.44–1.60 (m, 4H), 2.56 (dd, J = 6, 9 Hz, 0.5H), 2.68–2.79 (br m, 1H), 2.80–2.87 (m, 1H), 2.88–3.04 (br m, 2H), 3.12 (t, J = 8 Hz, 0.5H), 3.54 (br q, J = 7 Hz, 1H), 4.03 (m, 2H), 5.92 (s) and 5.93 (s, 2H total), 6.68 (m) and 6.77 (dd, J = 2, 7 Hz, 2H total), 6.85 (d, J = 1 Hz) and 6.92 (d, J = 2 Hz, 1H), 7.19–7.40 (br m, 5H); MS (DCI/NH_3) m/z 368 $(M+H)^+$. Anal. ($C_{21}H_{23}NO_4$) C, H, N.

***trans*-Ethyl 4-(1,3-benzodioxol-5-yl)pyrrolidine-3-carboxylate (8, R = H).** A solution of benzyl pyrrolidine **41** (235 mg, 0.61 mmol) in 5 mL MeOH was treated with 20% palladium on carbon (65 mg) and stirred under 1 atm H_2 (balloon) for 4 h, then the reaction was filtered

through Celite. The catalyst was washed with 50 mL MeOH, and the combined filtrate was concentrated under reduced pressure to provide 189 mg (0.641 mmol, 100%) of the product as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, J = 8 Hz, 3H), 1.89 (br s, 1H plus H_2O), 2.80–3.05 (m, 2H), 3.25–3.37 (m, 2H), 3.37–3.50 (br m, 2H), 4.14 (q, J = 7 Hz, 2H), 5.94 (s, 2H), 6.70 (dd, J = 2, 9 Hz, 1H), 6.72–6.79 (m, 2H); MS (DCI/NH_3) m/z 264 $(M+H)^+$.

The following compounds were made in analogy to the procedure described for compound **8**.

***trans*,*trans*-2-(4-Methylphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (9).** ^{1}H NMR (CD_3OD, 100 MHz) δ 0.80 (t, J = 7 Hz, 3H), 0.88 (t, J = 7 Hz, 3H), 1.05 (hex, J = 7 Hz, 2H), 1.27 (hex, J = 7 Hz, 2H), 1.3–1.5 (m, 4H), 2.33 (s, 3H), 2.9–3.2 (m, 5H), 3.3–3.5 (m, 3H), 3.54 (d, J = 15 Hz, 1H), 3.63 (ddd, J = 5, 8, 9 Hz, 1H), 3.90 (d, J = 10 Hz, 1H), 5.92 (m, 2H), 6.75 (d, J = 8 Hz, 1H), 6.86 (dd, J = 2, 8 Hz, 1H), 7.04 (d, J = 2 Hz, 1H), 7.19 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H). MS (APCI+) m/z 495 $(M+H)^+$. Anal. ($C_{29}H_{38}N_2O_5 \cdot 0.3\ H_2O$) C, H, N.

***trans*,*trans*-2-[4-(Trifluromethyl)phenyl]-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (10).** ^{1}H (CD_3OD, 100 MHz) δ 0.87 (t, J = 7 Hz, 3H), 0.98 (t, J = 7 Hz, 3H), 1.02 (hex, J = 7 Hz, 2H), 1.27 (hex, J = 7 Hz, 2H), 1.3–1.5 (m, 4H), 2.9–3.2 (m, 5H), 3.3–3.5 (m, 4H), 3.65 (ddd, J = 5, 8, 9 Hz, 1H), 3.94 (d, J = 10 Hz, 1H), 5.93 (m, 2H), 6.76 (d, J = 8 Hz, 1H), 6.87 (dd, J = 2, 8 Hz, 1H), 7.05 (d, J = 2 Hz, 1H), 7.66 (m, 4H). MS (APCI) m/z 549 $(M+H)^+$. Anal. ($C_{29}H_{35}N_2O_5F_3$) C, H, N.

***trans*,*trans*-2-(4-Ethylphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (11).** ^{1}H ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7 Hz, 3H), 0.87 (t, J = 7 Hz, 3H), 1.02 (m, 2H), 1.10–1.40 (m, 6 H), 1.45 (m, 2H), 2.26 (q, J = 9 Hz, 2H), 2.73 (d, J = 14 Hz, 1H), 2.90–3.13 (m, 4H), 3.23–3.53 (m, 5H), 3.60 (m, 1H), 3.77 (d, J = 9 Hz, 1H), 5.92 (d, J = 4 Hz, 1H), 5.94 (d, J = 4 Hz, 1H), 6.73 (d, J = 9 Hz, 1H), 6.86 (dd, J = 3, 8 Hz, 1H), 7.03 (d, J = 3 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H); MS (DCI/NH_3) m/z 509 $(M+H)^+$. Anal. ($C_{30}H_{40}N_2O_5$) C, H, N.

***trans*,*trans*-2-(4-propylphenyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (12).** ^{1}H ($CDCl_3$, 300 MHz,) δ 0.78 (t, J = 7 Hz, 3H), 0.85 (t, J = 7 Hz, 3H), 0.92 (t, J = 7 Hz, 3H), 1.00–1.50 (m, 8H), 1.62 (q, J = 8 Hz, 2H), 2.55 (t, J = 8 Hz, 2H), 2.75 (d, J = 15 Hz, 1H), 2.88–3.13 (m, 4H), 3.20–3.55 (m, 4H), 3.60 (m, 1H), 3.76 (d, J = 10 Hz, 1H), 5.93 (d, J = 2 Hz, 1H), 5.95 (d, J = 2 Hz, 1H), 6.73 (d, J = 9 Hz, 1H), 6.84 (dd, J = 6, 2 Hz, 1H), 7.03 (d, J = 2, 1H), 7.13 (d, J = 9 Hz, 2H), 7.31 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 523 $(M+H)^+$. Anal ($C_{31}H_{42}N_2O_5 \cdot 0.25H_2O$) C, H, N.

***trans*,*trans*-2-[4-(1,1-dimethylethyl)phenyl]-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (13).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (t, J = 7 Hz, 3H), 0.86 (t, J = 7 Hz, 3H), 100 (m, 2H), 1.29 (s, 13H), 1.45 (m, 2H), 2.73 (d, J = 14 Hz, 1H), 3.15–2.85 (m, 4H), 3.65–3.25 (m, 5H), 3.77 (d, J = 14 Hz, 1H), 5.92 (d, J = 4 Hz, 1H), 5.94 (d, J = 4 Hz, 1H), 6.74 (d, J = 9 Hz, 1H), 6.87 (dd, J = 3, 8 Hz, 1H), 7.04 (d, J = 2 Hz, 1H), 7.32 (d, J = 3 Hz, 4H); MS (DCI/NH_3) m/z 537 $(M+H)^+$. Anal. ($C_{32}H_{44}N_2O_5$) C, H, N.

***trans*,*trans*-2-(*trans*-4-Methoxycyclohexyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (14).** ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 0.92 (t, J = 7 Hz, 3H), 0.97 (t, J = 7 Hz, 3H), 1.33 (m, 9H), 1.62 (m, 7H), 1.95 (m, 2H), 2.88 (m, 1H), 3.00–3.25 (m, 3H), 3.26 (s, 3H), 3.27–3.50 (m, 5H), 3.69 (m, 2H), 5.92 (s, 2H), 6.61 (d, J = 8 Hz, 1H), 6.76 (dd, J = 7, 2 Hz, 1H), 6.84 (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 517 $(M+H)^+$. Anal. ($C_{29}H_{44}N_2O_6 \cdot 0.50H_2O$) C, H, N.

***trans*,*trans*-2-(*cis*-4-Methoxycyclohexyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (15).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7 Hz, 3H), 0.96 (t, J = 7 Hz, 3H), 1.00–1.20 (m, 4H), 1.33 (m, 4H), 1.52 (m, 6H), 1.83 (m, 2H), 2.10 (m, 2H), 2.82 (m, 1H), 3.00–3.30 (m, 6H), 3.32 (s, 3H), 3.42 (m, 2H), 3.65 (m, 2H), 5.92 (s, 2H), 6.61 (d, J = 8 Hz, 1H), 6.77 (dd, J = 2, Hz, 1H), 6.84 (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 517 $(M+H)^+$. Anal. ($C_{29}H_{44}N_2O_6 \cdot 0.30\ H_2O$) C, H, N.

***trans*,*trans*-2-(Hydroxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (16).** TLC (10% MeOH–CH_2C_l2) R_f 0.20; ^{1}H NMR ($CDCl_3$, 300 MHz, two rotomeric forms) δ 0.73 (t, J = 7 Hz) and 0.86–1.02 (m, 6H total), 1.10–1.70 (br m, 8 H), 2.50–4.00 (several br m, 13H plus H_2O), 4.07–4.14 (br m) and 4.59 (br d, 1H total), 5.89 (s) and 5.91 (s, 2H total), 6.60–6.75 (br m), 6.74–6.83 (m) and 6.90 (br s, 3H total); HRMS (FAB) calcd for $C_{23}H_{35}N_2O_6$ $(M+H)^+$ 435.2495, found 435.2491.

***trans*,*trans*-2-(Ethoxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (17).** Isolated as a colorless glass; TLC (10% MeOH–CH_2Cl_2) R_f 0.53; ^{1}H NMR ($CDCl_3$, 300 MHz, rotomeric forms) δ 0.70 (t, J = 7 Hz), 0.80 (t, J = 7 Hz) and 0.96–1.04 (m, 6 H total), 1.04–1.75 (m, 11H), 1.34–1.53 (br m, 4H), 2.65 (AB) and 2.80–3.08 (m, 2H total), 3.10–3.82 (br m, 12H), 4.03 (m) and 4.22–4.45 (br m, 2H total), 5.90 (s) and 5.91 (s, 2H total), 6.65–6.84 (m) and 6.93 (m) and 6.99 (m, 3H total); MS (FAB) m/z 463 $(M+H)^+$. Anal. ($C_{25}H_{38}N_2O_6 \cdot 1.5H_2O$) C, H, N.

***trans*,*trans*-2-Propoxymethyl-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (18).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87–0.98 (m, 9H), 1.21–1.39 (m, 4H), 1.43–1.57 (m, 4H), 1.58–1.70 (m, 2H), 3.13–3.29 (m, 4H), 3.34–3.43 (m, 3H), 3.45–3.55 (m, 3H), 3.69 (dd, J = 10.2, 4.5 Hz, 1H), 3.80–4.20 (m, 4H), 5.93 (s, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.84 (dd, J = 8.2, 1.7 Hz, 1H), 6.93 (d, J = 1.7 Hz, 1H); MS (DCI/NH_3) m/z 477 $(M+H)^+$. Anal. ($C_{26}H_{40}N_2O_6 \cdot 0.50TFA$) C, H, N.

***trans*,*trans*-2-(Butoxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (19).** ^{1}H ($CDCl_3$, 300 MHz,) δ 0.87–0.98 (m, 9H), 1.23–1.42 (m, 6H), 1.42–1.66 (m, 6H), 3.12–3.60 (m, 10H), 3.81–4.07 (m, 4H), 4.54 (br s, 1H), 4.70 (br s, 1H), 5.94 (s, 2H), 6.75 (d, J = 8.1 Hz, 1H), 6.86 (dd, J = 8.1, 1.8 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) m/z 491 $(M+H)^+$. Anal. ($C_{27}H_{42}N_2O_6 \cdot 1.15H_2O \cdot 0.80$ TFA) C, H, N.

***trans*,*trans*-2-(Methoxyethoxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (20).** ^{1}H ($CDCl_3$, 300 MHz,) δ 0.90 (t, J = 7 Hz, 3H), 0.96 (t, J = 7 Hz, 3H), 1.22–1.42 (m, 4H), 1.44–1.63 (br m, 4H), 2.88 (overlapping dd, J = 6.5, 7 Hz, 1H), 3.08 (dd, J = 8, 9 Hz, 1H), 3.15–3.50 (br m) and 3.35 (s, 10H total), 3.50–3.56 (m, 2H), 3.57–3.68 (m, 3H), 3.69–3.84 (m, 3H), 5.91 (AB, 2H), 6.70 (d, J = 8 Hz, 1H), 6.81 (dd, J = 2, 8 Hz, 1H), 6.94 (d, J = 2 Hz, 1H). Anal. ($C_{26}H_{40}N_2O_7$) C, H, N.

***trans*,*trans*-2-(*tert*-Butoxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (21).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (q, J = 7.2 Hz, 6H), 1.20–1.35 (m, 4H), 1.28 (s, 9H), 1.44–1.60 (m, 4H), 3.13–3.60 (m, 6H), 3.76–4.07 (m, 4H), 4.50–4.74 (m, 4H), 5.95 (s, 2H), 6.77 (d, J = 8.1 Hz, 1H), 6.88 (dd, J = 8.1, 1.8 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) m/z 491 $(M+H)^+$. Anal. ($C_{27}H_{42}N_2O_6 \cdot 0.15$ $H_2O \cdot 1.10$TFA) C, H, N.

***trans*,*trans*-2-[(1,1-Dimethylpropoxy)methyl]-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (22).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84–0.95 (m, 9H), 1.20 (s, 6H), 1.21–1.36 (m, 4H), 1.43–1.60 (m, 4H), 3.12–3.63 (m, 8H), 3.74–3.88 (m, 2H), 3.90–4.06 (m, 2H), 4.55–4.72 (m, 4H), 5.96 (s, 2H), 6.77 (d, J = 8.1 Hz, 1H), 6.86 (dd, J = 8.1, 1.8 Hz, 1H), 6.92 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) m/z 505 $(M+H)^+$. Anal. ($C_{28}H_{44}N_2O_6 \cdot 0.5H_2O \cdot 1.1$TFA) C, H, N.

***trans*,*trans*-2-(Phenoxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (23).** ^{1}H ($CDCl_3$, 300 MHz,) δ 0.80 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H), 1.13–1.30 (m, 4H), 1.38–1.52 (m, 4H), 3.09–3.66 (m, 8H), 3.82–3.96 (m, 2H), 4.16–4.40 (m, 4H), 5.94 (s, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.83–6.92 (m, 3H), 6.96–7.03 (m, 2H), 7.62–7.33 (m, 2H); MS (ACPI) m/z 511 $(M+H)^+$. Anal. ($C_{29}H_{38}N_2O_6 \cdot 0.1$ $H_2O \cdot 0.45$TFA) C, H, N.

***trans*,*trans*-2-(Phenylmethoxymethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (24).** TLC (5% MeOH–CH_2Cl_2) R_f 0.17; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 7 Hz) and 0.90 (t, J = 7 Hz, 6H total), 1.13–1.33 (br m, 4H), 1.34–1.53 (br m, 4H), 2.95–3.12 (br m, 2H), 3.19 (br t, J = 9Hz, 1H), 3.23–3.35 (br m, 2H), 3.45–3.76 (br m, 3H), 3.77–3.86 (m, 1H), 3.88–4.35 (br m, 6H), 4.56 (AB, 2H), 5.91 (s, 2H), 6.70 (d, J = 9 Hz, 1H), 6.84 (dd, J = 1, 8.5 Hz, 1H), 6.93 (d, J = 1 Hz, 1H), 7.29–7.38 (m, 5H); MS (FAB) m/z 525 $(M+H)^+$.

***trans*,*trans*-2-(Methoxyethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (25).** TLC (2.5%MeOH-0.5%HOAc-CH_2Cl_2) R_f 0.25; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7 Hz) and 0.95 (t, J = 7 Hz, 6H total), 1.28–1.41 (br m, 4H), 1.45–1.63 (br m, 4H), 2.00–2.20 (br m, 2H), 3.06 (br t, J = 9 Hz, 1H), 3.30 (s) and 3.20–3.68 (br m, 11H total), 3.72–4.10 (br m, 4H), 5.92 (s, 2H), 6.72 (d, J = 8.5 Hz, 1H), 6.82 (dd, J = 1.5, 8.5 Hz, 1H), 6.91 (d, J = 1.5 Hz, 1H); MS (FAB) m/z 463 $(M+H)^+$. Anal. ($C_{25}H_{38}N_2O_5 \cdot H_2O$) C, H, N.

***trans*,*trans*-2-(2-Ethoxyethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (26).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.24–1.38 (m, 5H), 1.46–1.60 (m, 4H), 2.03–2.12 (m, 2H), 3.07 (t, J = 8.0 Hz, 1H), 3.07–3.34 (m, 6H), 3.43–3.52 (m, 3H), 3.59–3.74 (m, 3H), 3.80–4.01 (m, 2H), 5.93 (s, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 1.7, 8.2 Hz, 1H), 6.87 (d, J = 1.7 Hz, 1H); MS (DCI/NH_3) m/z 477 $(M+H)^+$. Anal. ($C_{26}H_{40}N_2$ $O_6 \cdot 0.4$TFA) C, H, N.

***trans*,*trans*-4-(1,3-Benzodioxol-5-yl)-1-[[(dibutylamino)-carbonyl]methyl]pyrrolidine-3-carboxylate (27).** ^{1}H ($CDCl_3$, 300 MHz,) δ 0.91 (t, J = 7 Hz, 3H), 0.96 (t, J = 8 Hz, 3H), 1.22–1.40 (m, 4H), 1.43–1.60 (m, 4H), 2.96–3.05 (m, 1H), 3.09–3.40 (br m, 6H), 3,54–3.69 (m, 2H), 3.70 (d, J = 2 Hz) and 3.73 (d, J = 4 Hz, 2H total), 3.76–3.87 (m, 1H), 5.92 (s, 2H), 6.0–6.6 (v br s, 1H plus H_2O), 6.72 (d, J = 8 Hz, 1H), 6.79 (dd, J = 1, 8 Hz, 1H), 6.85 (d, J = 1 Hz, 1H); MS (DCI/NH_3) m/z 405 $(M+H)^+$. Anal. ($C_{22}H_{32}N_2O_5 \cdot 0.75$ H_2O) C, H, N.

***trans*,*trans*-2-(Propyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (28).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 7.5 Hz), 0.92 (t, J = 7.5 Hz), and 0.97 (t, J = 7.5H, 9H total), 1.22–1.80 (br m, 12H), 2.83 (t, J = 7.5 Hz, 1H), 3.40–3.55 (br m, 2H), 3.55–3.68 (m, 1H), 3.78 (d, J = 15 Hz, 1H), 5.92 (q, J = 1 Hz, 2H), 6.70 (d, J = 8 Hz, 1H), 6.79 (dd, J = 1, 8 Hz, 1H), 6.90 (d, J = 1 Hz, 1H). MS (DCI/NH_3) m/z 447 $(M+H)^+$. Anal. ($C_{25}H_{38}N_2O_5 \cdot 0.5H_2O$) C, H, N.

***trans*,*trans*-2-Butyl-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (29).** TLC (10% MeOH–CH_2Cl_2) R_f 0.37; ^{1}H NMR ($CDCl_3$, 300 MHz, rotomeric forms) δ 0.71 (t, J = 7 Hz) and 0.77–1.05 (m, 9H total), 1.05–1.20 (m, 2H), 1.20–1.72 (br m, 13H), 2.48–2.52 (m, 1H), 2.87–3.00 (m, 1H), 3.05–3.60 (m, 5H), 3.60–3.80 (br m, 2H), 3.88–4.05 (br m, 1H), 4.28 (br d, J = 15 Hz, 1H total), 5.90 (s) and 5.92 (s, 2H total), 6.67–6.82 (m, 3H total); MS (FAB) m/z 461 $(M+H)^+$. Anal. ($C_{26}H_{40}N_2O_5 \cdot 1.75H_2O$: C, 63.45; H, 8.90; N, 5.69. Found: C, 63.18; H, 8.22; N, 5.60.

***trans*,*trans*-2-(Hexyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (31).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82–1.00 (m, 9H), 1.20–1.40 (m, 12H), 1.45–1.60 (m, 4H), 1.70–1.90 (br m, 2H), 3.10–3.46 (m, 6H), 3.65 (t, J = 10.8 Hz, 1H), 3.76 (t,

J = 11.0 Hz, 1H), 3.92–4.06 (m, 2H), 4.14–4.34 (m, 2H), 5.94 (s, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 8.1, 1.8 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H); MS (DCI/NH_3) m/z 489 $(M+H)^+$. Anal. ($C_{28}H_{44}N_2O_5$·0.9 TFA) C, H, N.

***trans*,*trans*-2-(Heptyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (32).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83–0.98 (s, 9H), 1.18–1.40 (m, 14H), 1.44–1.60 (m, 4H), 1.72–1.96 (br m, 2H), 3.12–3.45 (m, 6H), 3.65 (t, J = 10.5 Hz, 1H), 3.76 (t, J = 11.2 Hz, 1H), 3.90–4.06 (m, 2H), 4.13–4.33 (m, 2H), 5.93 (s, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.79 (dd, J = 7.8, 1.7 Hz, 1H), 6.87 (d, J = 1.7 Hz, 1H); MS (DCI/NH_3) m/z 503 $(M+H)^+$. Anal. ($C_{29}H_{46}N_2O_5$·0.75 TFA) C, H, N.

***trans*,*trans*-2-Isopropyl-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (33).** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (m, 12H), 1.32 (m, 4H), 1.55 (m, 4H), 1.88 (m, 1H), 2.83 (t, J = 7 Hz, 1H), 3.11 (m, 2H), 3.25 (m, 3H), 3.42 (m, 3H), 3.66 (q, J = 7 Hz, 1H), 3.75 (d, J = 14 Hz, 1H), 5.92 (s, 2H), 6.71 (d, J = 8 Hz, 1H), 6.76 (dd, J = 6, 2 Hz, 1H), 6.85 (d, J = 2 Hz, 1H); MS (DCI/NH_3) m/z 447 $(M+H)^+$. Anal. ($C_{25}H_{38}N_2O_5$·0.50 H_2O) C, H, N. 65.91; H, 8.63; N, 6.15. Found: C, 66.07; H, 8.10; N, 6.03.

***trans*,*trans*-2-(2-Methylbutyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (34).** TLC (10% MeOH–CH_2Cl_2) R_f 0.49; ^{1}H NMR ($CDCl_3$, 300 MHz, rotomeric forms and mixture of diastereomers) δ 0.69 (br t, J = 7 Hz) and 0.75–2.15 (several br m, approximately 26H total), 2.48–2.65 (br m, 1H), 2.87–3.01 (br m, 1H), 3.06–3.82 (br m, 7H), 3.90–4.40 (br m, 2H), 5.90 (s) and 5.92 (s, 2H total), 6.67–6.90 (m, 3H total); MS (FAB) m/z 475 $(M+H)^+$.

***trans*,*trans*-2-(3-Methylbutyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (35).** TLC (10% MeOH–CH_2Cl_2) R_f 0.41; ^{1}H NMR ($CDCl_3$, 300 MHz, rotomeric forms) δ 0.73 (t, J = 7 Hz) and 0.77–1.05 (m, 12H total), 1.07–1.75 (m, approximately 14H plus H_2O), 2.48–2.63 (m, 1H), 2.87–3.05 (m, 1H), 3.05–3.60 (several br m, 5H), 3.62–4.02 (br m, 2H), 4.29 (br d, J = 15 Hz, 1H), 5.89 (s) and 5.93 (s, 2H total), 6.65–6.90 (m, 3H total); MS (FAB) m/z 475 $(M+H)^+$.

***trans*,*trans*-2-(4-Methylcyclohexyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (36).** Colorless wax; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73–0.90 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 1.05–1.20 (m, 3H), 1.24–1.41 (m, 5H), 1.45–1.82 (m, 11H), 3.03 (brt, J = 7.5 Hz, 1H), 3.15 (dd, J = 6.6, 9.0 Hz, 1H), 3.21 (dd, J = 6.9, 8.1 Hz, 1H), 3.24–3.60 (m, 4H), 3.63–4.0 (brm, 2H), 3.84 (brd, J = 8.4 Hz, 1H), 4.05 (brd, J = 15.0 Hz, 1H), 5.93 (s, 2H), 6.72 (d, J = 8.1 Hz, 1H), 6.79 (dd, J = 1.8, 8.1 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H). MS (APCI+) m/z 501 $(M+H)^+$. Anal. ($C_{29}H_{44}N_2O_5$·0.60 TFA) C, H, N.

***trans*,*trans*-2-Benzyl-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (37).** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.9 Hz, 3H), 0.93 (t, J = 6.9 Hz, 3H), 1.04–1.47 (m, 8 H), 2.48–2.60 (m, 1H), 2.60–2.75 (m, 1H), 3.07–3.46 (m, 4H), 3.55 (t, J = 10.8 Hz, 1H), 3.70 (t, J = 10.8 Hz, 1H), 3.82–3.89 (m, 2H), 4.05–4.18 (m, 1H), 4.64–4.75 (m, 1H), 5.91 (s, 2H), 6.75 (d, J = 8.1 Hz, 1H), 6.88 (dd, J = 8.1, 1.8 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 7.20–7.36 (m, 5H); MS (APCI+) m/z 495 $(M+H)^+$. Anal. ($C_{29}H_{38}N_2O_5$·TFA) C, H, N.

***trans*,*trans*-2-(Cyclohexylmethyl)-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (38).** ^{1}H ($CDCl_3$, 300 MHz) δ 0.83 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 1.13–1.90 (m, 15H), 3.00–4.20 (m, 12H), 5.93 (s, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.78 (dd, J = 8.1, 1.8 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H); MS (APCI+) m/z 489 $(M+H)^+$. Anal. ($C_{28}H_{44}N_2O_5$·0.65 TFA) C, H, N.

***trans*,*trans*-2-[(4-Methylcyclohexyl)methyl]-4-(1,3-benzodioxol-5-yl)-1-[[(dibutylamino)carbonyl]methyl]pyrrolidine-3-carboxylate (39).** Colorless wax; ^{1}H NMR ($CDCl_3$, 300 MHz, 1:1 mixture of *cis*, *trans* isomers) δ 0.84 (d, J = 6.9 Hz, 2H), 0.89 (d, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H), 1.10–1.40 (m, 9H), 1.40–1.60 (m, 6H), 1.60–1.81 (m, 3H), 3.11–3.22 (m, 2H), 3.26 (d, J = 9.0 Hz, 1H), 3.35 (br t, J = 9.0 Hz, 2H), 3.63–3.77 (m, 1H), 3.80–3.92 (m, 1H), 3.98–4.15 (m, 2H), 4.27–4.47 (m, 2H), 5.94 (s, 2H), 6.74 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 1.8, 8.1 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H). MS (APCI+) m/e 515 $(M+H)^+$. Anal. ($C_{30}H_{46}N_2O_5$·1.15TFA.0.5 hexane) C, H, N.

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