Azole Endothelin Antagonists. 2. Structure−Activity Studies

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Structure−activity studies have been performed in an attempt to improve the potency of a novel series of azole-based endothelin-A (ET_A) selective antagonists. Modifications of the hydrophobic group on the terminal urea produced substantial effects on receptor affinity; in particular, the choice of cyclohexyl- or arylureas led to substantial improvements in activity. Conformational restriction of these groups provides an additional benefit. N-Methylation of the indole moiety which is part of the heterocyclic dipeptide surrogate also improves potency. The effects of these two modifications appear to be synergistic, with the best of the resultant doubly modified analogs (e.g. **14q**, **15y**, and **15ff**) exhibiting an 80−200-fold improvement over the original leads.

Introduction

In the preceding article[1] we have described our strategy for the development of a novel class of endothelin-A (ET-A) receptor antagonists, prepared (Scheme 1) through modification of the amide framework of the known peptide antagonists BQ-485 and FR-139317. Our preliminary structure−activity studies in this new series suggested that, while the peptidic and peptidomimetic compounds appear to be closely related, they differ significantly in the manner in which they interact with the ET_A receptor. We have been able to rationalize several unusual aspects of the activity profile of compounds **1** by applying a generalized model of GPCR binding, developed at Abbott, to the specific case of the endothelin receptor.

The initial set of compounds **1**, prepared as a preliminary test of our design concept, exhibit only a modest ability to bind to the receptor of interest. In retrospect this is not a surprising result. The structures of BQ-485 and FR-139317 have been optimized by workers at Banyu and Fujisawa, respectively, through extensive analog studies;[2] the shift in binding mode which we encounter upon rigidification of the C-terminal dipeptide is likely to influence the steric and electronic requirements for various substituents along its backbone. We thus viewed **1** as a lead structure which would require further optimization to maximize ET_A affinity, and accordingly initiated a study to probe the structure−activity profile of this new series.

Receptor Binding and Selectivity; Functional Analysis

Endothelin acts by binding to a family of membrane-associated, G-protein coupled receptors.[3] Binding to the ET_A receptor subtype, which predominates in vascular smooth muscle cells, triggers a cascade of events which lead, via the hydrolysis of inositol phosphates and the release of calcium ions, to the observed vasoconstrictive and proliferative responses. The results of binding to ET_B, which is the major receptor on endothelial cells, are less clearly understood; while this receptor mediates constriction in some tissue beds, it has also been linked to the production of nitric oxide and to the clearance of endogenous ET. Because these latter effects might be beneficial in a number of the diseases described above, it has been suggested[3] that a selective ET_A antagonist may provide some therapeutic advantage over a nonselective agent.

We evaluated compounds **14**−**19** in competitive binding assays, using MMQ cell homogenates as a source of ET_A and porcine cerebellar membranes as a source of ET_B receptor. These receptors are highly homologous with the human receptor sequence, and we have demonstrated (unpublished results) that receptor affinities measured these systems correlate well with those recorded using human $ET_{A,B}$ expressed in CHO cells. The results of these two assays not only provide receptor affinities (indicated in Tables 1−3 as IC_{50} values) but also give an indication of the relative selectivity of the compounds for the ET_A subtype.

To confirm that our analogs are functioning as antagonists to block the actions of the endothelins, we have also established an assay which evaluates receptor activation by measuring the hydrolysis of inositol phosphates. We measure both agonist (compound-stimulated) and antagonist (ET-1 stimulation) profiles for a selected set of compounds in the MMQ cell line. All of the analogs tested act as antagonists, with EC_{50} values that are comparable to their binding IC_{50}s. Importantly, none of our compounds exhibits any significant level of agonist activity; rather they appear to act as relatively pure functional antagonists.

Chemistry

The majority of the analogs described in this article were prepared by the basic strategy described in our previous article (Schemes 2−4).[1] Briefly, the core azoles are assembled in a manner similar to that described by Gordon and co-workers[4] (Scheme 2) through cyclization of key intermediate **3**, itself prepared by sequential C- and N-acylation of glycine anion equivalent **2**. By proper choice of cyclization conditions[4] we are able to prepare either imidazoles **4** or oxazoles **5** from ketoamide **3**. Deprotection of **4**/**5**, followed by coupling with a urea prepared from leucine and hydrolysis of the terminal ester, provides target molecules **14**/**15**.

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

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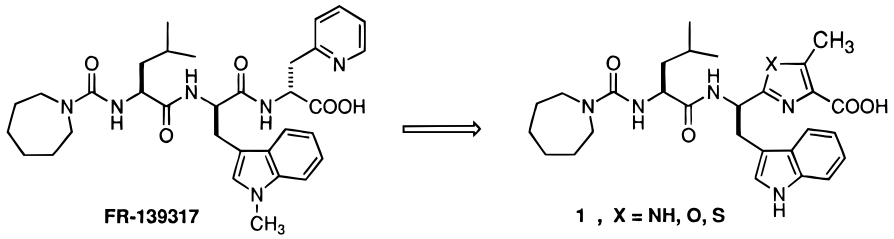
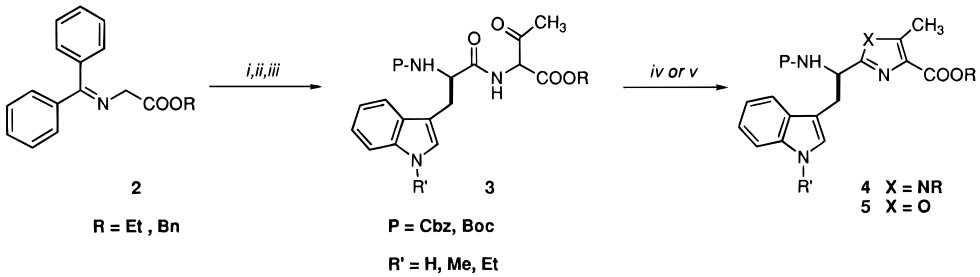
Scheme 1. Heterocyclic Dipeptide Surrogates



Scheme 2. Synthesis of Azole Cores[a]



[a] (i) LiHMDS, THF, −78 °C; CH_3COCl; (ii) HCl−H_2O; (iii) P-D-Trp(R′)-OCOOiBu, THF, −20 °C; NMM (dropwise); (iv) RNH_3OAc, HOAc, reflux; (v) PPh_3, CCl_4, pyr, CH_3CN.

Several modifications of our original route should be noted. We have reported that hydrolysis of the C-terminal ethyl ester to give our final product acid often requires vigorous conditions and sometimes leads to some loss of stereochemical integrity. To avoid this difficulty, and to simplify purification at this final stage, most of the analogs discussed here were prepared via the corresponding benzyl ester. This modification allows for hydrogenolytic esterolysis, a process which occurs without detectable stereomutation. Unfortunately this change also leads to a re-evaluation of our overall protecting group strategy. Ideally, the N-terminus of **3** (and thus of **4** and **5**) might now be orthogonally protected with a *tert*-butyloxycarbonyl (Boc) group, which is readily removable with anhydrous trifluoroacetic or hydrochloric acids. This strategy is successfully applied in the synthesis of oxazoles **5**. However, the Boc group proves labile to the conditions (acetic acid, heat) employed in preparing imidazoles **4**. After exploring several possibilities, we have found it most efficient to return to the original choice of the carbobenzoxy (Cbz) group for protecting the primary amine of **4**. Deprotection may be accomplished using HBr in acetic acid, for relatively short periods of time, with minimal cleavage of the benzyl ester.

The majority of leucylureas **8** (Scheme 3) prepared for this study derive by reacting 1,1′-carbonyldiimidazole sequentially with leucine benzyl ester and the relevant primary or secondary amine. Removal of the benzyl ester is accomplished through hydrogenolysis; the resultant acid is coupled (Scheme 4) with a deprotected heterocyclic core to assemble the analog skeleton. Hydrogenolysis of the remaining ester provides the final product. Alternatively, ureas **8** may be assembled (Scheme 3) by condensing leucine benzyl ester with preformed carbamoyl chlorides or isocyanates; similarly sulfonylureas **11** are prepared using the corresponding sulfamoyl chloride. Less reactive amines, e.g. anilines, react more efficiently with the isocyanate prepared by reacting the leucyl ester with phosgene. Finally, indole derivative **13** arises by direct coupling of leucine benzyl ester with the symmetrical anhydride derived from indole-1-carboxylic acid.[5] In this latter case, it is important that both hydrogenolysis steps are performed under transfer−hydrogenation conditions to avoid over-reduction of the acylindole moiety.

A number of acid derivatives may also be elaborated at a later stage in the synthesis. Thus, the acid chloride derived from oxazole **15a** may be reacted with a variety of amines to produce amides **16**. Alternatively the dipeptide mimetic **17** can be homologated via an Arndt−Eistert sequence to give (after further assembly) the oxazoleacetic acid **19**.

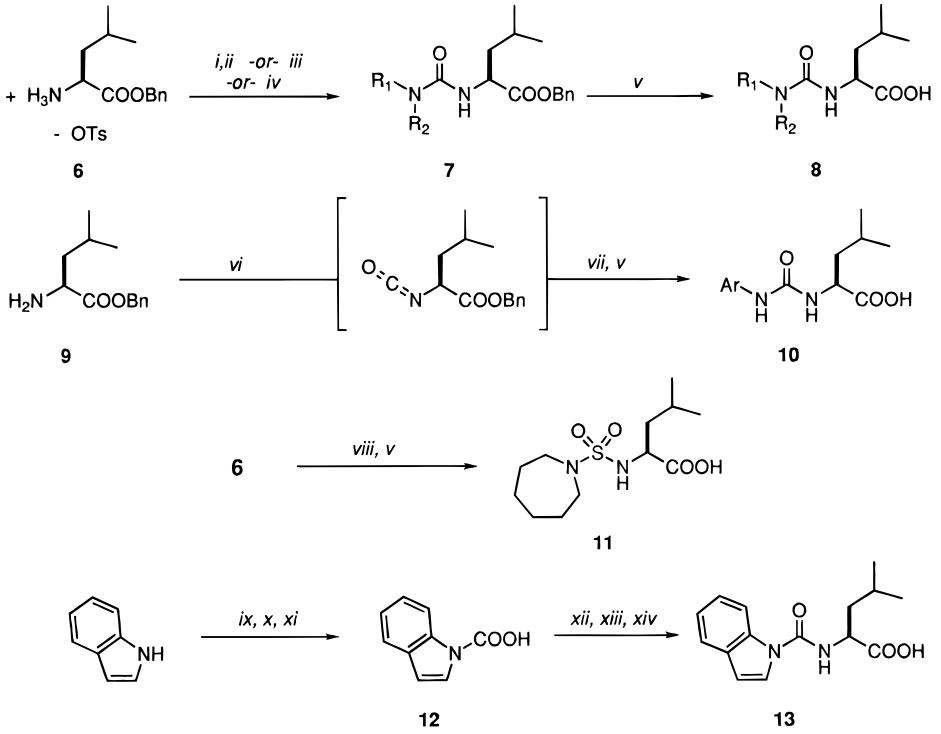
Structure−Activity Relationships

Our previous preliminary structure−activity study[1] of the heterocyclic dipeptide mimic incorporated in **1** resulted in two significant observations: first, that imidazole and oxazole are dramatically superior to thiazole as the heterocyclic core moiety, and second, that small alkyl groups are strongly preferred as substituents on this heteroring (Table 1). These preliminary studies led to the identification of compounds **14a** and **15a** as lead structures for further study. We thus began our secondary SAR studies by conducting a cursory examination of the remainder of the molecule in order to identify potential sites for modification.

One such site was revealed through studies of the urea moiety. The critical importance of the urea carbonyl was suggested by the lack of activity of sulfonylureas **14**/**15b**. On the other hand, a scan of several hydrophobic amines led to the identification of cyclohexylamine (compounds **14**/**15e**) as a valuable replacement for the perhydroazepinyl group. The use of this amine leads to a 2-fold increase in ET_A binding affinity in the oxazole series (compare **15e** vs **15a**) and >7-fold in the imidazole series (**14e** vs **14a**). Other amines chosen in this initial scan (e.g. diethylamine or benzylamine) were inferior to perhydroazepine.

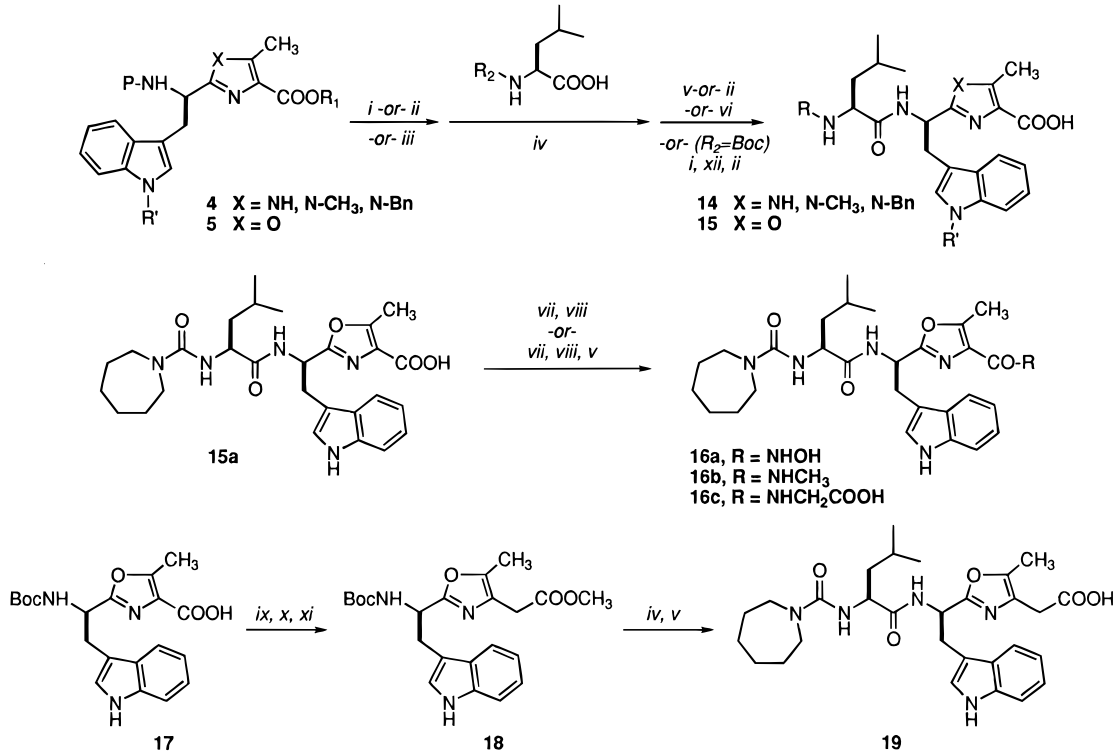
We next examined the effect of heteroalkylation of the indole and imidazole heterocycles. Indole N-methylation is well tolerated in the peptidic antagonist series; in fact, the state of the indole nitrogen represents the primary difference between Banyu's (unsubstituted) and Fujisawa's (indole N-alkylated) contributions in this

Scheme 3. Synthesis of N-Terminal Substituents[a]



[a] (i) CDl, Et_3N, THF; (ii) R_1R_2NH; (iii) R_1R_2NCOCl, Et_3N, THF; (iv) R_1NCO, Et_3N, THF (R_2 = H); (v) H_2−10% Pd−C, EtOH; (vi) triphosgene, tol. reflux; (vii) $ArNH_2$; (viii) $PhaSO_2Cl$, *i*-Pr_2NEt, DMF; (ix) *n*-BuLi, THF, −78 °C; (x) CO_2; (xi) H^+; (xii) EDC, CH_2Cl_2; (xiii) **9**; (xiv) 10% Pd−C; cyclohexadiene, EtOH−EtOAc.

Scheme 4. Analog Assembly[a]

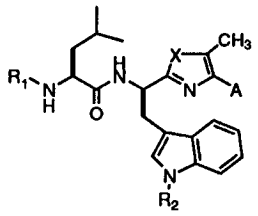


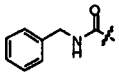
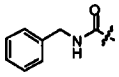
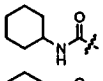
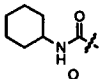
[a] (i) TFA; (ii) H_2−10% Pd−C, EtOH; (iii) 30% HBr−HOAc; (iv) EDC, HOBt, NMM, THF−DMF; (v) NaOH, EtOH−H_2O; (vi) 10% Pd−C; cyclohexadiene; EtOH−EtOAc; (vii) $(COCl)_2$, cat. DMF, THF; (viii) RNH_2; (ix) *i*-BuOCOCl, NMM, THF, −40 °C; (x) CH_2N_2−Et_2O; (xi) AgOBz, Et_3N, CH_3OH; (xii) RNHCOCl or RNCO, NEt_3, THF.

area. In our own example, methylation of the indole improves ET_A binding by a factor of 2 in both heterocyclic series (viz. **14f** vs **14a** and **15f** vs **15a**). When N^3 of the imidazole is methylated (as in **14r**) or benzylated (as in **14s**), the resultant analogs show substantially reduced activity.

A series of replacements for the carboxylic acid functionality of **1** were also studied. Although none of the replacements examined were as potent as the parent acid **15a**, amides **16b** and **16c** and hydroxamate **16a** all show significant levels of activity. On the other hand, ester **16d** and homologated acid **19** are substan-

Table 1. Preliminary SAR Studies

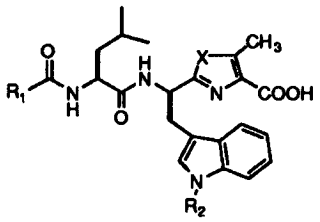


compound	R_1	R_2	X	A	ET_A binding IC_{50} (μM)[a]	ET_B binding IC_{50} (μM)[a]	PI Hydrolysis IC_{50} (μM)	formula	solvate	characterization
14a		H	NH	COOH	0.57	>100	0.78	$C_{28}H_{38}N_6O_4$	1.5 TFA	NMR,MS,CHN
15a		H	O	COOH	1.43	>100	4.50	$C_{28}H_{37}N_5O_5$	0.8 TFA	NMR,MS,CHN
14b		H	NH	COOH	>100	>100	—	$C_{27}H_{38}N_6O_5S$	1.2 TFA	NMR,MS,CHN
15b		H	O	COOH	>100	>100	—	$C_{27}H_{37}N_5O_6S$	0.6 TFA	NMR,MS,CHN
14c		H	NH	COOH	1.0	>100	—	$C_{26}H_{36}N_6O_4$	1.0 TFA	NMR,MS,CHN
15c		H	O	COOH	3.0	>100	—	$C_{26}H_{35}N_5O_5$	0.3 TFA	NMR,MS,CHN
14d		H	NH	COOH	2.1	>100	—	$C_{29}H_{34}N_6O_4$	1.15 TFA	NMR,MS,CHN
15d		H	O	COOH	8.7	96	—	$C_{29}H_{33}N_5O_5$	1.0 TFA	NMR,MS,CHN
14e		H	NH	COOH	0.075	>100	—	$C_{28}H_{38}N_6O_4$	1.5 TFA	NMR,MS,CHN
15e		H	O	COOH	0.66	>100	—	$C_{28}H_{37}N_5O_5$	0.8 TFA	NMR,MS,CHN
14f		Me	NH	COOH	0.28	>100	—	$C_{29}H_{40}N_6O_4$	—	NMR,MS,HRMS
15f		Me	O	COOH	0.62	>100	—	$C_{29}H_{39}N_5O_5$	1.0 TFA	NMR,MS,CHN
14r		H	N-Me	COOH	23.3	>100	—	$C_{29}H_{40}N_6O_4$	1.25 TFA 1.8H_2O	NMR,MS,CHN[b]
14s		H	N-Bn	COOH	16.2	>100	—	$C_{35}H_{44}N_6O_4$	1.5 TFA	NMR,MS,CHN
16d		H	O	COOEt	13.8	43		$C_{30}H_{41}N_5O_5$	0.4 TFA	NMR,MS,CHN
16a		H	O	CONHOH	2.9	>100		$C_{28}H_{38}N_6O_5$	0.8 TFA	NMR,MS,CHN
16b		H	O	$CONHCH_3$	3.0	65		$C_{29}H_{40}N_6O_4$	0.3 TFA	NMR,MS,CHN
16c		H	O	$CONHCH_2COOH$	1.9	>100		$C_{30}H_{40}N_6O_6$	0.7 TFA	NMR,MS,CHN
19		H	O	CH_2COOH	9.6	>100		$C_{29}H_{39}N_5O_5$	0.7 TFA	NMR,MS,HRMS

a IC_{50}'s calculated using a mean of at least 2 measurements (all duplicates) for 11 concentrations from 10^{-10} to 10^{-5} M
b N calculated 11.81, observed 12.36 .

tially less potent. In the model for endothelin receptor binding described in the preceding article, we propose that this carboxylate provides a critical interaction with lysine residue 166 on helix III. Consistent with that

Table 2. Aliphatic Ureas



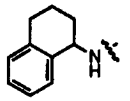
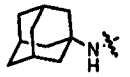
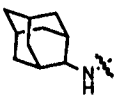
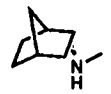
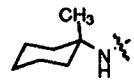
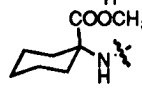
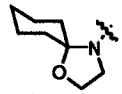
compound	R_1=	R_2=	X=	ET_A binding IC_{50} (μM)[a]	ET_B binding IC_{50} (μM)[a]	PI Hydrolysis IC_{50} (μM)	formula	solvate	characterization
14g		CH_3	NH	0.011	34	0.0041	$C_{29}H_{40}N_6O_4$	1.7 TFA	NMR,MS,CHN
15g		CH_3	O	0.22	>100	—	$C_{29}H_{39}N_5O_5$	0.6 TFA	NMR,MS,CHN
14h		Et	NH	0.73	55	—	$C_{30}H_{42}N_6O_4$	—	NMR,MS,HRMS
15h		Et	O	12.9	>100	—	$C_{30}H_{41}N_5O_5$	1.75 H_2O	NMR,MS,CHN
14i		CH_3	NH	0.037	67	0.043	$C_{28}H_{38}N_6O_4$	1.1 TFA; 1.55 H_2O	NMR,MS,CHN
15i		CH_3	O	0.30	99	—	$C_{28}H_{37}N_5O_5$	0.5 TFA; 1.0 H_2O	NMR,MS,CHN
14j		CH_3	NH	0.060	42	0.087	$C_{30}H_{42}N_6O_4$	0.5 TFA; 1.0 H_2O	NMR,MS,CHN
15j		CH_3	O	0.40	75	—	$C_{30}H_{41}N_5O_5$	0.3 TFA; 1.0 H_2O	NMR,MS,CHN
14k		CH_3	NH	0.11	>100	—	$C_{29}H_{40}N_6O_5$	1.5 TFA	NMR,MS,CHN
15k		CH_3	O	2.52	>100	—	$C_{29}H_{39}N_5O_6$	1.2 TFA; 2 H_2O	NMR,MS,CHN
14l		CH_3	NH	0.018	13	—	$C_{30}H_{42}N_6O_4$	1.6 TFA	NMR,MS,CHN
15l		CH_3	O	0.65	>100	—	$C_{30}H_{41}N_5O_5$	1.0 H_2O	NMR,MS,CHN
14m		CH_3	NH	0.026	22	0.0086	$C_{30}H_{42}N_6O_4$	0.35 TFA; 1.0 H_2O	NMR,MS,CHN
15m		CH_3	O	0.96	>100	—	$C_{30}H_{41}N_5O_5$	1.0 H_2O	NMR,MS,CHN
14n		CH_3	NH	0.141	80	—	$C_{30}H_{42}N_6O_4$	1.1 TFA	NMR,MS,CHN
15n		CH_3	O	2.73	>100	—	$C_{30}H_{41}N_5O_5$	0.75 TFA; 0.3 H_2O	NMR,MS,CHN
15t		CH_3	O	0.23	48	—	$C_{33}H_{39}N_5O_5$	0.4 TFA	NMR,MS,CHN
15u		CH_3	O	0.90	19	—	$C_{33}H_{43}N_5O_5$	0.7 TFA	NMR,MS,CHN
15v		CH_3	O	0.44	26	—	$C_{33}H_{43}N_5O_5$	0.8 TFA	NMR,MS,CHN
14o		CH_3	NH	0.029	8.3	0.016	$C_{30}H_{40}N_6O_4$	1.6 TFA	NMR,MS,CHN

Table 2 (Continued)

compound	R_1=	R_2=	X=	ET_A binding IC_{50} (μM)[a]	ET_B binding IC_{50} (μM)[a]	PI Hydrolysis IC_{50} (μM)	formula	solvate	characterization
15o		CH_3	O	0.80	67	—	$C_{30}H_{39}N_5O_5$	0.5 TFA	NMR,MS,CHN
14p		CH_3	NH	0.019	9.5	0.036	$C_{30}H_{40}N_6O_4$	1.9 TFA	NMR,MS,CHN
15p		CH_3	O	0.45	26	—	$C_{30}H_{39}N_5O_5$	0.3 TFA	NMR,MS,CHN
15w		CH_3	O	0.20	56	—	$C_{30}H_{41}N_5O_5$	0.8TFA	NMR,MS,CHN
15x		CH_3	O	0.12	>90	—	$C_{31}H_{41}N_5O_7$	0.7 TFA	NMR,MS,CHN
15y		CH_3	O	0.0057	35	0.0061	$C_{31}H_{41}N_5O_6$	0.9 TFA	NMR,MS,CHN

a IC_{50}s calculated using a mean of at least 2 measurements (all duplicates) for 11 concentrations from 10^{-10} to 10^{-5} M

model, the relative binding affinities of these acid replacements correlate qualitatively with the electron density at the carbonyl oxygen.

These preliminary studies additionally serve to reinforce two important aspects of the structure-binding profile of compounds related to **1**. While the ET_A affinities reported in Table 1 vary over 3 orders of magnitude, the compounds all show minimal activity at the ET_B receptor. Thus, despite the apparent changes in the binding mode of these compounds as compared with FR-139317, it appears that the high degree of receptor selectivity inherent in the peptidic series has been translated to this new structural class. Additionally, the pairwise comparison of identically-substituted oxazoles and imidazoles indicates that the latter are consistently more active at ET_A, by a factor of 2−8. This difference in potency may indicate that the imidazole ring is better able to mimic the H-bonding pattern of the amide bond which it replaced.

The above studies identified two modifications of our lead structure, the choice of cyclohexylurea and indole N-methylation, which independently provide significant improvements in ET_A affinity. These two substitutions were combined in compounds **14**/**15g** (Table 2) to see if their effects might be additive. In fact, the two modifications appear to act synergistically; imidazole **14g** has an IC_{50} of 11 nM, a 7-fold improvement over **14e**, while the corresponding oxazole **15g** binds at 220 nM, 3 times better than **15e**. Compounds **14g** and **15g** define new standards of potency for this structural class and highlight the urea and indole as profitable sites for modification.

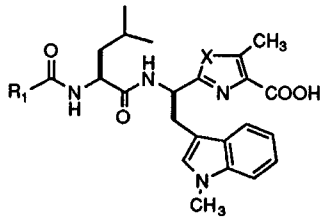
To expand on these new leads, we first examined whether increasing the size of the N_i-alkyl substituent led to further improvements in binding affinity. In fact, *N*-ethylindoles **14h** and **15h** are 60-fold less active than **14**/**15g**, suggesting that the space in this region of the receptor is quite limited.

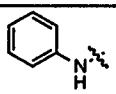
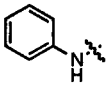
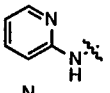
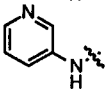
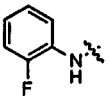
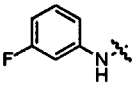
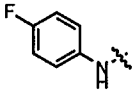
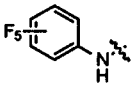
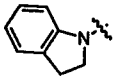
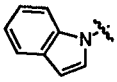
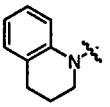
Another series of analogs was prepared to further examine the hydrophobic domain at the urea terminus (Table 2). To study the effect of ring size, we incorporated cyclopentylamine (analogs **14**/**15i**) and cycloheptylamine (**14**/**15j**) into the urea. While both substitutions were well tolerated, and led to compounds which were more active than the original perhydroazepinyl ureas **14**/**15f**, neither was as effective as cyclohexylamine. To probe the steric environment around the six-membered ring, we placed a methyl group sequentially at the 1-, 2-, 3-, and 4-positions (compounds **15w**, **14l**−**n**, and **15l**−**n**). Because the methylcyclohexylamines were incorporated as racemic cis/trans mixtures, analogs **14l**−**n** and **15l**−**n** each comprise a number of isomeric compounds. Despite this complication, the results of the binding studies are clear, indicating that substitution is tolerated at the 1-, 2-, and 3-positions, while 4-substitution results in a >10-fold decrease in activity. To confirm this latter result, we also prepared *trans*-(4-hydroxycyclohexyl)ureas **14**/**15k**. Again, these analogs had only one-tenth of the activity of unsubstituted **14**/**15g**.

None of the alkyl substitutions provide a significant improvement in ET_A affinity; however, they do suggest the possibility of examining larger substituents, or of employing multiple points of attachment to the ring. A number of analogs were prepared to explore these ideas. At position 1 of the cyclohexane, we find that a carbomethoxy substituent (as in **15x**) is superior either to methyl (**15w**) or to the unsubstituted parent. The 1-position may also be used as the attachment point for a spirocyclic aminal, as in **15y**. This conformationally restricted analog is approximately 40 times more potent than the flexible **15g**, **15w**, and **15x**, a result which may also indicate some advantage for N-alkylation. Fusion of an aryl ring to the 2,3-positions of the cyclohexane (as in **15t**) is well tolerated, but offers no advantage. Surprisingly a variety of bicyclic (*endo*- and *exo*-norbornyl) and tricyclic (1- and 2-adamantyl) systems are also acceptable; at best, however, the activities of these analogs are equivalent to **14**/**15g**.

Another possible replacement for the cycloalkyl substituent on the urea is an aryl group. In practice the use of aniline leads to a set of analogs (**14z**, **15z**, Table 3) that are more active (IC_{50} = 7.6 and 16 nM against ET_A) than the corresponding cyclohexylureas **14**/**15g**. Phenyl substitution seems to offer a particular advantage in the oxazole series (14-fold improvement over

Table 3. Aromatic Ureas



compound	R_1=	X =	ET_A binding IC_{50} (μM)[a]	ET_B binding IC_{50} (μM)[a]	PI Hydrolysis IC_{50} (μM)	formula	solvate	characterization
14q		NH	0.0076	37	0.0013	$C_{29}H_{34}N_6O_4$	1.5 TFA	NMR,MS,CHN
15q		O	0.016	30	0.053	$C_{29}H_{33}N_5O_5$	0.3 TFA	NMR,MS,CHN
15z		O	0.074	66	---	$C_{28}H_{32}N_6O_5$	0.8 TFA; 0.7 H_2O	NMR,MS,CHN
15aa		O	0.153	>100	---	$C_{34}H_{42}N_6O_4$	2.65 TFA	NMR,MS,CHN
15bb		O	0.017	2.4	0.026	$C_{29}H_{32}N_5O_5F$	0.35 TFA	NMR,MS,CHN
15cc		O	0.066	55	---	$C_{29}H_{32}N_5O_5F$	1.15 TFA	NMR,MS,CHN
15dd		O	1.90	>100	---	$C_{29}H_{32}N_5O_5F$	2.0 H_2O	NMR,MS,CHN
15ee		O	3.55	>100	---	$C_{29}H_{28}N_5O_5F_5$	0.8 TFA	NMR,MS,CHN
15ff		O	0.0059	34	0.0036	$C_{31}H_{35}N_5O_5$	1.0 TFA	NMR,MS,CHN
15gg		O	0.058	12	---	$C_{31}H_{33}N_5O_5$	0.9 TFA	NMR,MS,CHN
15hh		O	0.033	66	0.0009	$C_{32}H_{37}N_5O_5$	0.9 TFA	NMR,MS,CHN

. IC_{50}s calculated using a mean of at least 2 measurements (all duplicates) for 11 concentrations from 10^{-10} to 10^{-5} M

cyclohexyl) as opposed to the imidazole series (1.4-fold increase in ET_A affinity); this provides the first example in which these two series exhibit similar levels of activity with a given urea substituent.

To take advantage of the unique boost provided to the oxazole-based antagonists by the phenyl substituent, a series of oxazoles containing aromatic ureas were prepared and examined in the binding assays (Table 3). Replacement of the benzene ring with pyridine was detrimental to activity; 2- and 3-pyridyl analogs **15aa** and **15bb** were 10- and 20-fold less potent than **15z**. The placement of fluorine atoms on the aromatic ring causes a decrease in activity which is remarkably position-dependent. While the 2-fluoroanilide **15cc** is equipotent with **15z**, the 3- and 4-substituted analogs **15dd** and **15ee** are 4-fold and 120-fold less active, respectively. This activity profile is reminiscent of that observed with methyl substitution on the cyclohexylurea. Pentafluoranilide **15ff** is somewhat less active than the simple 4-fluoro-substituted analog, but it is clear from the relative activities of these two compounds that it is the 4-substituent which provides the major deficit.

Several conformationally-restricted aromatics were also examined. Of these, indoline **15gg** is the most effective with an IC_{50} of 5.9 nM against the ET_A receptor. The increased activity of **15gg** when compared with **15z** suggests that it may be desirable for the aromatic ring to exist in the plane of the urea carbonyl. This result is in sharp contrast to that observed with aminal **15y**, in which a significant boost in potency was realized when the cyclohexane ring was restricted orthogonally to the plane of the carbonyl π-system. However, the difference in activity between **15gg** and **15z** is small; additionally, the fact that the anilide is N-alkylated in **15gg** may complicate our analysis. Another explanation is possible, however. Our receptor modeling work suggests that this hydrophobic pocket

is actually rather large and that aminal **15y** and indoline **15gg** fit it in different ways; the observation that a variety of norbornyl- and adamantylamines are tolerated at the urea terminus is consistent with this suggestion. Indoline may be replaced with indole (**15hh**) or with 1,2,3,4-tetrahydroquinoline (**15ii**) with some success, but the resultant analogs are inferior to either **15z** or **15gg**.

Conclusions

Our structure−activity studies have served to identify a number of modifications of imidazole **14a** and oxazole **14b** which lead to improved affinity for the ET_A receptor. Compounds with an imidazole core are consistently more active than the corresponding oxazoles, and all of the analogs reported in this work are highly selective (up to 6000-fold) for ET_A over ET_B. In particular we observe that N-methylation of the indole moiety leads to improved analogs, and that modification of the hydrophobic urea dramatically affects interactions with the receptor. In this latter case, both cyclohexyl- and arylamines appear to be quite well accepted, with the anilines appearing to provide a selective boost to the oxazole series, thus closing the "activity gap" between imidazoles and oxazoles. A variety of minor modifications of the cyclohexyl and phenyl rings are tolerated; however, the only changes which lead to further improvements in binding affinity involve conformational restriction.

The results of these SAR studies are essentially consistent with the model we described in the previous article in this series. In particular the model suggests that there may be additional hydrophobic space in the N-terminal and indole binding pockets to accomodate the preferred methylations; in the former case the predicted available space is great enough to allow a convenient explanation for the acceptability of two orthogonal conformational restrictions of this N-terminal group. On the other hand, it is difficult for us to rationalize the strong preference for methyl over larger alkyl groups at these two positions using our current model, suggesting that some refinement may be necessary.

Most importantly, the above studies have resulted in the availability of a number of highly active, ET_A-selective antagonists containing our heterocyclic dipeptide mimic. With these compounds in hand, it is possible to begin to explore the effects of this core modification on pharmacokinetics. The results of such a study are reported in the next article in this series.

Experimental Section

Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. THF was dried over sodium and purified by distillation. All reactions were performed under a nitrogen atmosphere unless specifically noted. All final products are analyzed for purity by analytical HPLC using a 25-cm Vydac Protein and Peptide C18 column, and are >95% pure unless otherwise stated. ^{1}H-NMR spectra were recorded at 300 MHz; all values are referenced to tetramethylsilane as internal standard and are reported as shift (multiplicity, coupling constants). Mass spectral analysis is accomplished using fast atom bombardment (FAB-MS) or direct chemical ionization (DCI-MS) techniques. All elemental analyses are consistent with theoretical values to within ±0.4% unless indicated.

Abbreviations: CDI, 1,1′-carbonyldiimidazole; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMF, dimethylformamide; EDC, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole hydrate; LiHMDS, lithium hexamethyldisilazide; NMM, *N*-methylmorpholine; Pha, hexamethyleneimine (perhydroazepine); PPh_3, triphenylphosphine; pyr, pyridine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; pTsOH, *p*-toluenesulfonic acid.

Synthesis of Core Heterocycles 4 and 5. Compounds **4** (P = Cbz, R = Et, R_1 = H or P = Cbz, R = Bn, R_1 = CH_3) and **5** (P = Cbz, R = Et, R_1 = H or P = Boc, R = Bn, R_1 = CH_3) were prepared from the appropriate starting materials, including N_i-methyl D-tryptophan[6] using the procedures described in the previous article.[1]

Synthesis of Leucine Derivatives. Leucine-derived urea acids were prepared from the appropriate starting materials according to the procedures described in the previous article[1] or using the following methods:

***N*-((Phenylamino)carbonyl)leucine (8, R_1 = Ph, R_2 = H) (General Preparation of Arylanilines).** Leu-OBn·p-TsOH (2.0 g) was suspended in THF (5 mL). *N*-Methylmorpholine (0.56 mL, 0.51 g) and phenyl isocyanate (0.55 mL, 0.6 g) were added, and the solution was stirred at ambient temperature for 4 h. The solvent was evaporated and the residue dissolved in EtOAc (20 mL). The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a colorless oil which was dissolved in EtOH (25 mL); 10% palladium on carbon (200 mg) was added. The flask was fitted with a three-way stopcock connected to a hydrogen-filled balloon and a nitrogen/vacuum manifold. The flask was evacuated, filled with nitrogen, evacuated again, and then put under a hydrogen atmosphere. The mixture was stirred at ambient temperature for 14 h. The hydrogen was evacuated and the flask filled with nitrogen. The catalyst was removed by filtration through a pad of Celite and the solvent removed *in vacuo* to give a colorless oil which solidified upon standing (1.08 g, 85% yield).

***N*-(((1-Methylcyclohexyl)amino)carbonyl)leucine (8, R_1 = 1-CH_3-c-C_6H_{11}, R_2 = H).** To a solution of 1.06 g (7.5 mmol) of 1-methylcyclohexane-1-carboxylic acid in 40 mL of toluene were added 1.61 mL of diphenyl phosphorazidate (2.06 g, 1 equiv) and 1.65 mL (1.52 g, 15 mmol) of *N*-methylmorpholine. The resultant mixture was heated at 70 °C for 2 h, cooled to room temperature, and added dropwise to a solution of 1.97 g (5 mmol) of Leu-OBn·TsOH and 1.1 mL of *N*-methylmorpholine in 20 mL of toluene. The reaction mixture was stirred overnight at ambient temperature, washed with sodium bicarbonate solution, 1 N H_3PO_4, and brine, and concentrated *in vacuo*. The crude product (2.5 g) was dissolved in 50 mL of EtOH, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 h. The catalyst was removed by filtration through a pad of Celite, and the solvents were removed *in vacuo* to give the title compound which was used without further purification.

***N*-((2-(Pyridylamino)carbonyl)leucine (10, Ar = 2-pyr) (Used To Prepare Pyridyl and F_5-Phenylanilines).** Leucine benzyl ester (2.4 g) was dissolved in toluene (25 mL). Triphosgene (1.1 g) was added and the solution heated at reflux for 2.5 h. The solution was allowed to cool to ambient temperature and the solvent evaporated. The residue was dissolved in $CHCl_3$ (25 mL) and cooled to 0 °C in an ice bath. 2-Aminopyridine (1.2 mL) was added and solution stirred cold for 30 min. The bath was removed and the solution allowed to stir at ambient temperature for 5 h. The solution was washed with saturated sodium bicarbonate solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated to give an orange oil which was purified by flash chromatography on silica gel eluting with 20% EtOAc−hexane to give a light yellow oil which solidified on standing (3.65 g, 95%). The resultant benzyl ester was dissolved in EtOH (150 mL), the solution was purged of oxygen, 10% Pd/C (150 mg) was added, and the mixture was stirred under hydrogen for 2 h. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc and filtered through Celite to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a colorless oil (2.62 g, 96%).

***N*-(Perhydroazepin-1-ylsulfonyl)leucine (11).** Perhydroazepine (6 mL) was dissolved in diethyl ether (250 mL) and cooled to 0 °C in an ice bath. HCl gas was bubbled through the solution and the resulting white solid collected by filtration and dried *in vacuo*. The solid was taken up in sulfuryl chloride (20 mL) and the mixture heated at reflux. The reaction became very thick, additional sulfuryl chloride (10 mL) was added, and reflux was continued for 16 h. The remaining sulfuryl chloride was evaporated and the residue distilled (90−100 °C, 0.1 mm) to give homopiperidinesulfonyl chloride as a colorless oil (9.06 g, 86%). To the sulfonyl choride (0.97 g) dissolved in DMF (10 mL) were added Leu-OBn·*p*-TsOH (2.03 g), Hünig's base (1.75 mL), and then DMAP (0.2 g), and the mixture was stirred at room temperature for 16 h. The solution was diluted with ethyl acetate, washed with water, 2 N HCl, saturated $NaHCO_3$ solution, and brine, dried, and evaporated. Purification by flash chromatography (10% EtOAc−hexane) gave *N*-(homopiperidin-1-ylsulfonyl)leucine benzyl ester as a white solid (0.88 g, 47%). The benzyl ester (0.85 g) was dissolved in MeOH (20 mL), and 10% Pd/C (0.75 g) was added. The mixture was stirred at room temperature under an H_2 atmosphere for 2.5 h. The catalyst was filtered off and the solvent evaporated to give the product as a colorless oil (0.66 g, 100%).

***N*-(Indol-1-ylcarbonyl)leucine (13).** Indole-1-carboxylic acid[5] (**12**; 0.64 g, 4.0 mmol) was dissolved in 20 mL of dichloromethane, EDC (0.58 g, 3 mmol) was added, and the solution was stirred at ambient temperature for 30 min. Leu-OBn (0.55 g, 2.5 mmol) was added, and the solution was stirred for 16 h at ambient temperature. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc, washed with water, sodium bicarbonate solution, 1 N H_3PO_4, and brine, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel. A sample of this material (170 mg, 0.49 mmol) was added to a suspension of 87 mg of 10% Pd−C in 1.5 mL of MeOH, the mixture was purged with nitrogen, and 0.1 mL of cyclohexadiene was added. The resultant suspension was stirred at ambient temperature for 1 h. The catalyst was removed by filtration through a pad of Celite, and the solvents were removed *in vacuo* to give a product which was used without further purification.

Compound Assembly. The following compounds were prepared from the appropriate core heterocycle and leucine derivative according to the coupling strategy described in the previous article,[1] employing the following deprotection strategies:

core N-protecting group	core C-protecting group	N-deprotection conditions	C-deprotection conditions
Cbz	Et	H_2, 10% Pd−C, EtOH	LiOH, H_2O/THF, heat
Cbz	Bn	HBr/HOAc	H_2, 10% Pd−C, EtOH
Boc	Bn	neat TFA	H_2, 10% Pd−C, EtOH

Prepared from **4** (P = Cbz, R = Et, R′ = H):

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic Acid (14a). Compound **14a** was prepared according to the procedures described in the preceding article:[1] ^{1}H NMR (CD_3OD, 300 MHz) δ 0.77 (d, 3H, J = 7 Hz), 0.82 (d, 3H, J = 7 Hz), 1.30 (m, 2H), 1.52 (m, 5H), 1.66 (m, 4H), 2.52 (s, 3H), 3.4 (m, 6H), 3.59 (dd, 1H, J = 7, 15 Hz), 4.07 (dd, 1H, J = 5, 9 Hz), 5.42 (dd, 1H, J = 6, 8 Hz), 7.01 (ddd, 1H, J = 1, 7, 8 Hz), 7.11 (ddd, 1H, J = 1, 7, 8 Hz), 7.12 (s, 1H), 7.36 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 523 (M + H)$^+$. Anal. for $C_{28}H_{38}N_6O_4$·1.5TFA: C, H, N.

2-{1(*R*)-[(Perhydroazepin-1-ylsulfonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14b): ^{1}H NMR (CD_3OD, 300 MHz) for the major tautomer δ 0.82 (d, 3H, J = 7 Hz), 0.85 (d, 3H, J = 7 Hz), 1.2−1.4 (m, 3H), 1.5−1.65 (m, 8H), 2.48 (s, 3H), 3.15 (q, 4H, J = 7 Hz), 3.45 (d, 2H, J = 8 Hz), 3.75 (m, 1H), 5.34 (m, 1H), 7.00 (t, 1H, J = 7 Hz), 7.10 (s, 1H), 7.12 (t, 1H, J = 7 Hz), 7.33 (d, 1H, J = 8 Hz), 7.42 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 559 (M + H)$^+$. Anal. for $C_{27}H_{38}N_6O_5S$·1.2TFA: C, H, N.

2-{1(*R*)-[(Cyclohexylaminocarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14e): ^{1}H NMR (CD_3OD, 300 MHz) for the major tautomer δ 0.78 (d, 3H, J = 7 Hz), 0.80 (d, 3H, J = 7 Hz), 1.2−1.85 (m, 14H), 2.53 (s, 3H), 3.35-3.6 (m, 4H), 4.04 (m, 1H), 5.42 (t, 1H, J = 8 Hz), 7.00 (t, 1H, J = 7 Hz), 7.10 (s, 1H), 7.12 (t, 1H, J = 7 Hz), 7.36 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 523 (M + H)$^+$. Anal. for $C_{28}H_{38}N_6O_4$·1.5TFA: C, H, N.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14f): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.93 (d, 3H, J = 7 Hz), 0.96 (d, 3H, J = 7 Hz), 1.30 (m, 2H), 1.52 (m, 5H), 1.66 (m, 4H), 2.52 (s, 3H), 3.4 (m, 5H), 3.59 (dd, 1H, J = 7, 15 Hz), 3.75 (s, 3H), 4.07 (dd, 1H, J = 7, 8 Hz), 4.35 (dd, 1H, J = 6, 10 Hz), 5.42 (dd, 1H, J = 6, 8 Hz), 7.04 (s, 1H), 7.05 (ddd, 1H, J = 1, 7, 8 Hz), 7.18 (ddd, 1H, J = 1, 7, 8 Hz), 7.35 (d, 1H, J = 8 Hz), 7.47 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 537 (M + H)$^+$; HRMS calcd for $C_{29}H_{41}N_6O_4$ 537.3189, found 537.3191.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-1,5-dimethylimidazole-4-carboxylic acid (14r): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (d, 3H, J = 7 Hz), 0.91 (d, 3H, J = 7 Hz), 0.78−1.74 (m, 11H), 2.35 (s, 3H), 3.20 (s, 3H), 3.38 (m, 4H), 3.50 (m, 2H), 4.27 (dd, 1H, J = 5, 7 Hz), 5.36 (dd, 1H, J = 5, 7 Hz), 6.96 (t, 1H, J = 7 Hz), 7.07 (s, 1H), 7.09 (t, 1H, J = 7 Hz), 7.27 (d, 1H, J = 7 Hz), 7.34 (d, 1H, J = 7 Hz); MS (FAB) m/e 537 (M + H)$^+$, 599 (M + Cu)$^+$. Anal. for $C_{29}H_{40}N_6O_4$·1.25TFA·1.8H_2O: C, H; N: calcd, 11.81; found, 12.36.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-1-benzyl-5-methylimidazole-4-carboxylic acid (14s): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 3H, J = 7 Hz), 0.88 (d, 3H, J = 7 Hz), 1.32 (m, 1H), 1.50 (m, 6H), 1.67 (br m, 4H), 2.25 (s, 3H), 3.3−3.5 (m, 6H), 4.23 (dd, 1H, J = 6, 8 Hz), 5.06 (dd, 2H, J = 8, 20 Hz), 5.40 (t, 1H, J = 8 Hz), 6.88 (m, 3H), 7.02 (s, 1H), 7.10 (m, 2H), 7.25 (m, 3H), 7.34 (d, 1H, J = 8 Hz); MS (FAB) m/e 613 (M + H)$^+$, 635 (M + Na)$^+$. Anal. for $C_{35}H_{44}N_6O_4$·1.5TFA: C, H, N.

Prepared from **4** (Cbz, R = Bn, R′ = CH_3):

2-{(1*R*)-1-[*N*-((Cyclohexylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14g): ^{1}H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.75 (d, 3H, J = 7 Hz), 0.78 (d, 3H, J = 7 Hz), 1.1−1.4 (m, 8H), 1.5−1.9 (m, 6H), 2.53 (s, 3H), 3.33 (m, 1H), 3.50 (m, 2H), 3.77 (s, 3H), 4.03 (t, 1H, J = 8 Hz), 5.40 (dd, 1H, J = 6, 10 Hz), 7.04 (ddd, 1H, J = 1, 7, 8 Hz), 7.06 (s, 1H), 7.18 (ddd, 1H, J = 1, 7, 8 Hz), 7.35 (d, 1H, J = 8 Hz), 7.47 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 599 (M + Cu)$^+$. Anal. for $C_{29}H_{40}N_6O_4$·1.7TFA: C, H, N.

2-{(1*R*)-1-[*N*-((Cyclohexylamino)carbonyl)leucylamino]-2-(1-ethylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14h): ^{1}H NMR (CD_3OD/$CDCl_3$, 300 MHz) for the major tautomer δ 0.78 (d, 3H, J = 7 Hz), 0.80 (d, 3H, J = 7 Hz), 1.1−1.4 (m, 8H), 1.2 (s, 3H), 1.5−1.9 (m, 6H), 2.45 (s, 3H), 3.3 (m, 2H), 4.08 (m, 1H), 4.15 (q, 2H, J = 8 Hz), 5.25 (m, 1H), 7.00 (t, 1H, J = 7 Hz), 7.05 (t, 1H, J = 7 Hz), 7.15 (t, 1H, J = 7 Hz), 7.35 (d, 1H, J = 8 Hz), 7.50 (d, 1H, J = 8 Hz); HRMS (FAB) calcd for $C_{30}H_{43}N_6O_4$ 551.3355, found 551.3346.

2-{(1*R*)-1-[*N*-((Cyclopentylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14i): ^{1}H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.72 (d, 3H, J = 7 Hz), 0.75 (d, 3H, J = 7 Hz), 1.1−1.5 (m, 6H), 1.5−1.8 (m, 5H), 2.48 (s, 3H), 2.72 (s, 3H), 3.18 (m, 1H), 3.58 (m, 2H), 3.72 (s, 3H), 4.05 (t, 1H, J = 8 Hz), 5.36 (dd, 1H, J = 6, 10 Hz), 6.95 (s, 1H), 7.00 (t, 1H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.54 (d, 1H, J = 8 Hz); MS (DCI) m/e 523 (M + H)$^+$. Anal. for $C_{28}H_{38}N_6O_4$·1.55H_2O, 1.1 TFA: C, H, N.

2-{(1*R*)-1-[*N*-((Cycloheptylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14j): ^{1}H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.72 (d, 3H, J = 7 Hz), 0.75 (d, 3H, J = 7 Hz), 1.1−1.5 (m, 10H), 1.5−1.8 (m, 5H), 2.48 (s, 3H), 2.72 (s, 3H), 3.18 (m, 1H), 3.58 (m, 2H), 3.72 (s, 3H), 4.05 (t, 1H, J = 8 Hz), 5.36 (dd, 1H, J = 6, 10 Hz), 6.95 (s, 1H), 7.01 (t, 1H, J = 8 Hz), 7.15 (t, 1H, J = 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.54 (d, 1H, J = 8 Hz); MS (ESI) m/e 551 (M + H)$^+$. Anal. for $C_{30}H_{42}N_6O_4$·1.5H_2O, 0.5 TFA: C, H, N.

2-{(1*R*)-1-[*N*-(((*trans*-4-Hydroxycyclohexyl)amino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14k): ^{1}H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.75 (d, 3H, J = 6 Hz), 0.77 (d, 3H, J = 6 Hz), 1.1−1.4 (m, 7H), 1.8−2.0 (m, 4H), 2.52 (s, 3H), 3.33 (dd, 1H, J = 12, 15 Hz), 3.49 (m, 2H), 3.56 (dd, 1H, J = 7, 15 Hz), 3.77 (s, 3H), 4.03 (t, 1H, J = 7 Hz), 5.40 (dd, 1H, J = 6, 9 Hz), 7.04 (dt, 1H, J = 1, 7 Hz), 7.06 (s, 1H), 7.17 (dt, 1H, J = 1, 7 Hz), 7.35 (d, 1H, J = 8 Hz), 7.47 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 553 (M + H)$^+$. Anal. for $C_{29}H_{40}N_6O_5$·1.5TFA: C, H, N.

2-{(1*R*)-1-[*N*-(((2-Methylcyclohexyl)amino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14l): ^{1}H NMR (CD_3OD, 300 MHz) consistent with mixture of four isomers δ 2.50 (s, 3H), 3.77 (s, 3H), 7.03 (t, 1H, J = 8 Hz), 7.06 (s, 1H), 7.17 (t, 1H, J = 8 Hz), 7.33 (d, 1H, J = 8 Hz), 7.48 (d, J = 8 Hz); MS (FAB/NBA) m/e 551 (M + H)$^+$. Anal. for $C_{30}H_{42}N_6O_4$·1.6TFA: C, H, N.

2-{(1*R*)-1-[*N*-(((3-Methylcyclohexyl)amino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14m): ^{1}H NMR (CD_3OD, 300 MHz) consistent with mixture of four isomers δ 2.50 (s, 3H), 3.76 (s, 3H), 7.0 (t, 1H, J = 8 Hz), 7.03 (s, 1H), 7.16 (t, 1H, J = 8 Hz), 7.32 (d, 1H, J = 8 Hz), 7.50 (d, J = 8 Hz); MS (FAB/NBA) m/e 551 (M + H)$^+$. Anal. for $C_{30}H_{42}N_6O_4$·1.5TFA: C, H, N.

2-{(1*R*)-1-[*N*-(((4-Methylcyclohexyl)amino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14n): ^{1}H NMR (CD_3OD, 300 MHz) of mixture δ 0.76 (m, 6H), 0.91 (apparent t, 3H), 1.0−1.9 (m, 12H), major isomer 2.52 (s, 3H), 3.33 (m, 1H), 3.56 (dd, 1H, J = 7, 15 Hz), 3.76 (s, 3H), 3.78 (m, 1H), 4.03 (m, 1H), 5.20 (dd, 1H, J = 6, 9 Hz), 7.04 (dt, 1H, J = 1, 7 Hz), 7.05 (s, 1H), 7.18 (dt, 1H, J = 1, 7 Hz), 7.35 (d, 1H, J = 8 Hz), 7.47 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 551 (M + H)$^+$. Anal. for $C_{30}H_{42}N_6O_4$·1.1TFA: C, H, N.

2-{(1*R*)-1-[*N*-((*endo*-2-Norbornylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14o): ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.76 (d, 3H, J = 6 Hz), 0.78 (d, 3H, J = 6 Hz), 1.2−1.6 (m, 10H), 2.00 (m, 1H), 2.17 (m, 1H), 2.34 (m, 1H), 2.51 (s, 3H), 3.32 (dd, 1H, J = 10, 15 Hz), 3.55 (dd, 1H, J = 6, 15 Hz), 3.76 (s, 3H), 3.91 (m, 1H), 4.03 (dt, 1H, J = 3, 7 Hz), 5.38 (ddd, 1H, J = 3, 7, 9 Hz), 7.04 (ddd, 1H, J = 1, 7, 8 Hz), 7.06 (s, 1H), 7.18 (dt, 1H, J = 1, 7 Hz), 7.35 (d, 1H, J = 8 Hz), 7.46 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 549 (M + H)$^+$. Anal. for $C_{30}H_{40}N_6O_4$·1.6TFA: C, H, N.

2-{(1*R*)-1-[*N*-((*exo*-2-Norbornylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14p): ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.75 (d, 3H, J = 6 Hz), 0.77 (d, 3H, J = 6 Hz), 1.1−1.5 (m, 10H), 1.70 (m, 1H), 2.13 (m, 1H), 2.24 (m, 1H), 2.53 (s, 3H), 3.33 (dd, 1H, J = 10, 15 Hz), 3.49 (m, 1H), 3.57 (m, 1H), 3.77 (s, 3H), 4.02 (dt, 1H, J = 1, 7 Hz), 5.39 (ddd, 1H, J = 2, 6, 8 Hz), 7.04 (dt, 1H, J = 1, 7 Hz), 7.06 (s, 1H), 7.17 (dt, 1H, J = 1, 7 Hz), 7.35 (d, 1H, J = 8 Hz), 7.46 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 549 (M + H)$^+$. Anal. for $C_{30}H_{40}N_6O_4$·1.9TFA: C, H, N.

2-{(1*R*)-1-[*N*-((Phenylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14q): ^{1}H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.80 (d, 3H, J = 7 Hz), 0.81 (d, 3H, J = 7 Hz), 1.34 (m, 3H), 2.43 (s, 3H), 3.33 (dd, 1H, J = 9, 14 Hz), 3.54 (dd, 1H, J = 6, 14 Hz), 3.72 (s, 3H), 4.14 (m, 1H), 5.38 (dd, 1H, J = 6, 9 Hz), 7.00 (dt, 1H, J = 1, 7 Hz), 7.03 (dt, 1H, J = 1, 8 Hz), 7.05 (s, 1H), 7.16 (dt, 1H, J = 1, 7 Hz), 7.26 (m, 1H), 7.28 (d, 1H, J = 8 Hz), 7.31 (m, 3H), 7.45 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 531 (M + H)$^+$, 553 (M + Na)$^+$. Anal. for $C_{29}H_{34}N_6O_4$·1.5TFA: C, H, N.

Prepared from **5** (P = Cbz, R = Et, R′ = H):

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15a): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J = 7 Hz), 0.88 (d, 3H, J = 7 Hz), 1.43 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.55 (s, 3H), 3.25−3.5 (m, 6H), 4.34 (dd, 1H, J = 6, 9 Hz), 5.40 (t, 1H, J = 7 Hz), 6.95 (ddd, 1H, J = 1, 7, 8 Hz), 6.99 (s, 1H), 7.07 (ddd, 1H, J = 1, 7, 8 Hz), 7.31 (td, 1H, J = 1, 8 Hz), 7.37 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 524 (M + H)$^+$, 541 (M + NH_4)$^+$. Anal. for $C_{28}H_{37}N_5O_5$·0.4TFA: C, H, N.

2-{1(*R*)-[(Perhydroazepin-1-ylsulfonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15b): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.80 (d, 3H, J = 6 Hz), 0.83 (d, 3H, J = 6 Hz), 1.0 (m, 2H), 1.25 (m, 1H), 1.5−1.7 (m, 8H), 2.56 (s, 3H), 3.08 (m, 4H), 3.35 (m, 2H), 3.7 (m, 1H), 5.43 (m, 1H), 6.98 (dd, 1H, J = 1, 8 Hz), 7.07 (s, 1H), 7.08 (dd, 1H, J = 1, 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.50 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 560 (M + H)$^+$, 577 (M + NH_4)$^+$. Anal. for $C_{27}H_{37}N_5O_6S$·0.6TFA: C, H, N.

2-{1(*R*)-[((Cyclohexylamino)carbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15e): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 3H, J = 7 Hz), 0.79 (d, 3H, J = 7 Hz), 1.0−1.8 (m, 13H), 2.58 (s, 3H), 3.42 (m, 3H), 4.20 (t, 1H, J = 7 Hz), 5.42 (d, 1H, J = 7 Hz), 6.96 (t, 1H, J = 7 Hz), 7.03 (s, 1H), 7.06 (t, 1H, J = 7 Hz), 7.31 (d, 1H, J = 7 Hz), 7.44 (d, 1H, J = 7 Hz); MS (DCI/NH_3) m/e 524 (M + H)$^+$. Anal. for $C_{28}H_{37}N_5O_5$·0.8TFA: C, H, N.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15f): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 6H, J = 7 Hz), 1.4 (m, 2H), 1.53 (m, 5H), 1.67 (m, 4H), 2.54 (s, 3H), 3.25-3.5 (m, 6H), 3.73 (s, 3H), 4.33 (dd, 1H, J = 6, 10 Hz), 5.37 (t, 1H, J = 7 Hz), 6.93 (s, 1H), 6.99 (ddd, 1H, J = 1, 7, 8 Hz), 7.04 (ddd, 1H, J = 1, 7, 8 Hz), 7.31 (d, 1H, J = 8 Hz), 7.40 (td, 1H, J = 1, 8 Hz); MS (DCI/NH_3) m/e 538 (M + H)$^+$, 555 (M + NH_4)$^+$. Anal. for $C_{29}H_{39}N_5O_5$·1.0TFA: C, H, N.

Prepared using **5** (P = Boc, R = Bn, R′ = CH_3):

2-{(1*R*)-1-[*N*-((Cyclohexylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, J = 7 Hz), 0.74 (d, 3H, J = 7 Hz), 1.1−1.9 (m, 13H), 2.50 (s, 3H), 3.40 (m, 1H), 3.76 (s, 3H), 3.90 (m, 1H), 4.35 (dd, 1H, J = 6, 7 Hz), 5.35 (m, 1H), 6.91 (s, 1H), 7.02 (t, 1H, J = 8 Hz), 7.13 (t, 1H, J = 8 Hz), 7.32 (d, 1H, J = 8 Hz), 7.48 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 538 (M + H)$^+$, 560 (M + Na)$^+$, 576 (M + K)$^+$. Anal. for $C_{29}H_{39}N_5O_5$·0.6TFA: C, H, N.

2-{(1*R*)-1-[*N*-((Cyclohexylamino)carbonyl)leucylamino]-2-(1-ethylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15h): ^{1}H NMR (CD_3OD/$CDCl_3$, 300 MHz) δ 0.82 (d, 3H, J = 7 Hz), 0.84 (d, 3H, J = 7 Hz), 1.1−1.9 (m, 13H), 1.40 (t, 3H, J = 7 Hz), 2.55 (s, 3H), 3.45(m, 1H), 4.14 (q, 2H, J = 7 Hz), 4.18 (m, 1H), 5.20 (t, 1H, J = 7 Hz), 6.95 (s, 1H), 7.02 (dt, 1H, J = 1, 8 Hz), 7.15 (dt, 1H, J = 1, 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.42 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 552 (M + H)$^+$, 569 (M + NH_4)$^+$. Anal. for $C_{30}H_{41}N_5O_5$·1.75H_2O: C, H, N.

2-{(1*R*)-1-[*N*-((Cyclopentylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15i): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, J = 7 Hz), 0.74 (d, 3H, J = 7 Hz), 1.1−1.8 (m, 11H), 2.52 (s, 3H), 3.44 (m, 1H), 3.75 (s, 3H), 3.89 (m, 1H), 4.42 (dd, 1H, J = 6, 7 Hz), 5.35 (m, 1H), 6.96 (s, 1H), 7.03 (t, 1H, J = 8 Hz), 7.12 (t, 1H, J = 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 524 (M + H)$^+$, 546 (M + Na)$^+$, 562 (M + K)$^+$. Anal. for $C_{28}H_{37}N_5O_5$·H_2O·0.5TFA: C, H, N.

2-{(1*R*)-1-[*N*-((Cycloheptylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15j): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (d, 3H, J = 7 Hz), 0.77 (d, 3H, J = 7 Hz), 1.3−1.8 (m, 15H), 2.50 (s, 3H), 3.45(m, 1H), 3.75 (s, 3H), 3.92 (m, 1H), 4.45 (dd, 1H, J = 6, 7 Hz), 5.35 (m, 1H), 6.95 (s, 1H), 7.02 (t, 1H, J = 8 Hz), 7.12 (t, 1H, J = 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 552 (M + H)$^+$, 574 (M + Na)$^+$, 590 (M + K)$^+$. Anal. for $C_{30}H_{41}N_5O_5$·H_2O·0.3TFA: C, H, N.

2-{(1*R*)-1-[*N*-((*trans*-4-Hydroxycyclohexylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15k): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J = 6 Hz), 0.83 (d, 3H, J = 6 Hz), 1.1−1.5 (m, 7H), 1.8−2.0 (m, 4H), 2.53 (s, 3H), 3.3−3.6 (m, 3H), 3.56 (dd, 1H, J = 7, 15 Hz), 3.73 (s, 3H), 4.18 (t, 1H, J = 7 Hz), 5.36 (dd, 1H, J = 6, 8 Hz), 6.97 (s, 1H), 7.01 (ddd, 1H, J = 1, 7, 8 Hz), 7.13 (dt, 1H, J = 1, 7 Hz), 7.29 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (FAB/MeOH) m/e 554 (M + H)$^+$, 576 (M + Na)$^+$. Anal. for $C_{29}H_{39}N_5O_6$·1.2TFA·2H_2O: C, H, N.

2-{(1*R*)-1-[*N*-(((2-Methylcyclohexyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15l): ^{1}H NMR (CD_3OD, 300 MHz) consistent with structure of the four isomers δ 2.52 (s, 3H), 3.74 (s, 3H), 6.97 (s, 1H), 7.0 (t, 1H, J = 8 Hz), 7.13 (t, 1H, J = 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.45 (dd, J = 2, 8 Hz); MS (DCI/NH_3) m/e 552 $(M + H)^+$, 569 $(M + NH_4)^+$. Anal. for $C_{30}H_{41}N_5O_5 \cdot H_2O \cdot 0.35TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(((3-Methylcyclohexyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15m): ^{1}H NMR (CD_3OD, 300 MHz) consistent with structure of the four isomers δ 2.52 (s, 3H), 3.74 (s, 3H), 6.97 (s, 1H), 7.0 (t, 1H, J = 8 Hz), 7.13 (t, 1H, J = 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.45 (dd, J = 2, 8 Hz); MS (DCI/NH_3) m/e 552 $(M + H)^+$, 569 $(M + NH_4)^+$. Anal. for $C_{30}H_{41}N_5O_5 \cdot 1.1H_2O \cdot 0.65TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(((4-Methylcyclohexyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15n): ^{1}H NMR ($CDCl_3/CD_3OD$, 300 MHz) consistent with mixture of two isomers δ 2.52 (s, 3H), 3.73 (s, 3H), 6.95 (s, 1H), 7.02 (dt, 1H, J = 1, 8 Hz), 7.16 (dt, 1H, J = 1, 8 Hz), 7.27 (d, 1H, J = 8 Hz), 7.41 (d, J = 8 Hz); MS (DCI/NH_3) m/e 552 $(M + H)^+$, 569 $(M + NH_4)^+$. Anal. for $C_{30}H_{41}N_5O_5 \cdot 0.3H_2O \cdot 0.75TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((*endo*-norbornylamino)carbonyl)leucyl-amino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15o): ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.81 (d, 3H, J = 6 Hz), 0.84 (d, 3H, J = 6 Hz), 1.1−1.6 (m, 10H), 1.99 (m, 1H), 2.15 (m, 1H), 2.32 (m, 1H), 2.54 (s, 3H), 3.35 (m, 2H), 3.73 (s, 3H), 3.86 (m, 1H), 4.20 (dt, 1H, J = 1, 7 Hz), 5.36 (dd, 1H, J = 6, 8 Hz), 6.97 (s, 1H), 7.00 (dt, 1H, J = 1, 7 Hz), 7.12 (t, 1H, J = 7 Hz), 7.28 (d, 1H, J = 8 Hz), 7.44 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 550 $(M + H)^+$, 572 $(M + Na)^+$. Anal. for $C_{30}H_{39}N_5O_5 \cdot 0.5TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((*exo*-norbornylamino)carbonyl)leucyl-amino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15p): ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.81 (d, 3H, J = 6 Hz), 0.83 (d, 3H, J = 6 Hz), 1.1−1.5 (m, 10H), 1.70 (m, 1H), 2.08 (m, 1H), 2.22 (m, 1H), 2.53 (s, 3H), 3.3−3.5 (m, 3H), 3.72 (s, 3H), 4.19 (t, 1H, J = 7 Hz), 5.37 (ddd, 1H, J = 2, 6, 8 Hz), 6.99 (s, 1H), 7.00 (dt, 1H, J = 1, 7 Hz), 7.12 (dt, 1H, J = 1, 7 Hz), 7.20 (d, 1H, J = 8 Hz), 7.44 (dd, 1H, J = 1, 8 Hz); MS (FAB/NBA) m/e 550 $(M + H)^+$, 572 $(M + Na)^+$. Anal. for $C_{30}H_{39}N_5O_5 \cdot 0.3TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((Phenylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15q): ^{1}H NMR ($CD_3OD-CDCl_3$, 300 MHz) δ 0.85 (d, 3H, J = 8 Hz), 0.88 (d, 3H, J = 8 Hz), 1.35−1.6 (m, 3H), 2.52 (s, 3H), 3.38 (d, 2H, J = 10 Hz), 3.56 (s, 3H), 4.32 (dd, 1H, J = 6, 10 Hz), 5.43 (t, 1H, J = 6 Hz), 6.90 (s, 1H), 6.98 (m, 2H), 7.11 (dt, 1H, J = 1, 7 Hz), 7.25 (m, 3H), 7.34 (m, 3H); MS (DCI/NH_3) m/e 532 $(M + H)^+$, 549 $(M + NH_4)^+$. Anal. for $C_{29}H_{33}N_5O_5 \cdot 0.3TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((1,2,3,4-Tetrahydronaphth-1-ylamino)-carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15t): ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.83 (d, 6H, J = 6 Hz), 1.2−1.6 (m, 3H), 1.6−2.0 (m, 4H), 2.53 (s, 3H), 2.7−2.8 (m, 2H), 3.2−3.4 (m, 3H), 3.74 (s, 3H), 4.27 (m, 1H,), 5.40 (m, 1H), 6.9−7.2 (m, 7H), 7.26 (d, 1H, J = 8 Hz), 7.45 (m, 1H); MS (DCI/NH_3) m/e 586 $(M + H)^+$, 603 $(M + NH_4)^+$. Anal. for $C_{33}H_{39}N_5O_5 \cdot 0.4TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((1-Adamantylamino)carbonyl)leucyl-amino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15u): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J = 6 Hz), 0.83 (d, 3H, J = 6 Hz), 1.2−1.55 (m, 3H), 1.69 (m, 6H), 1.91 (d, 6H, J = 3 Hz), 1.92−2.07 (m, 3H), 2.53 (s, 3H), 3.2−3.4 (m, 2H), 3.74 (s, 3H), 4.13 (dd, 1H, J = 6, 9 Hz), 5.36 (dd, 1H, J = 6, 8 Hz), 6.98 (s, 1H), 7.01 (dt, 1H, J = 1, 8 Hz), 7.13 (dt, 1H, J = 1, 8 Hz), 7.23 (d, 1H, J = 8 Hz), 7.43 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 590 $(M + H)^+$, 607 $(M + NH_4)^+$. Anal. for $C_{33}H_{43}N_5O_5 \cdot 0.7TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((2-Adamantylamino)carbonyl)leucyl-amino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15v): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J = 6 Hz), 0.84 (d, 3H, J = 6 Hz), 1.3 (m, 2H), 1.45 (m, 1H), 1.5−1.65 (m, 3H), 1.7−1.8 (m, 11H), 2.53 (s, 3H), 3.25−3.4 (m, 2H), 3.73 (s, 3H) 3.76 (br s, 1H), 4.20 (dd, 1H, J = 6, 8 Hz), 5.38 (dd, 1H, J = 6, 8 Hz), 6.97 (s, 1H), 7.01 (dt, 1H, J = 1, 8 Hz), 7.14 (dt, 1H, J = 1, 8 Hz), 7.28 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 590 $(M + H)^+$, 607 $(M + NH_4)^+$. Anal. for $C_{33}H_{43}N_5O_5 \cdot 0.8TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(((1-Carbomethoxycyclohexyl)amino)-carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15x): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J = 7 Hz), 0.82 (d, 3H, J = 7 Hz), 1.24−1.34 (m, 3H), 1.40−1.65 (m, 6H), 1.67−1.81 (m, 2H), 1.89−1.99 (m, 2H), 2,53 (s, 3H), 3.2−3.45 (m, 2H), 3.60 (s, 3H), 3.74 (s, 3H), 4.15 (dd, 1H, J = 6, 8 Hz), 5.35 (dd, 1H, J = 6, 8 Hz), 6.97−7.04 (m, 2H), 7.13 (dt, 1H, J = 1, 8 Hz), 7.3 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 595 $(M + H)^+$. Anal. for $C_{31}H_{41}N_5O_7 \cdot 0.7TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(1-Oxa-4-azaspiro[5.4]dec-4-ylcarbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15y) was prepared as described above, employing 1-oxa-4-azaspiro[5.4]decane:[7] ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (m, 6H), 1.1−1.7 (m, 11H), 2.2−2.4 (m,-2H), 2.54 (s, 3H), 3.34−3.63 (m, 4H), 3.74 (s, 3H), 3.95 (t, 2H, J = 6 Hz), 4.28 (m, 1H), 5.37 (t, 1H, J = 7 Hz), 6.98 (br s, 1H), 7.01 (dt, 1H, J = 1, 8 Hz), 7.14 (dt, 1H, J = 1, 8 Hz), 7.30 (dd, 1H, J = 1, 8 Hz), 7.44 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 580 $(M + H)^+$. Anal. for $C_{31}H_{41}N_5O_6 \cdot 0.9TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(1-Indolinylcarbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15ff): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.88 (d, 6H, J = 7 Hz), 1.50 (m, 3H), 2.53 (s, 3H), 3.13 (m, 2H), 3.37 (d, 2H, J = 6 Hz), 3.57 (s, 3H), 3.68 (dt, 1H, J = 8, 10 Hz), 3.82 (dd, 1H, J = 8, 10 Hz), 4.43 (dd, 1H, J = 6, 8 Hz), 5.43 (t, 1H, J = 6 Hz), 6.87 (ddd, 1H, J = 1, 7, 8 Hz), 6.89 (s, 1H), 6.92 (dt, 1H, J = 1, 7 Hz), 7.03 (dt, 1H, J = 1, 7 Hz), 7.12 (dt, 1H, J = 1, 7 Hz), 7.17 (d, 1H, J = 8 Hz), 7.23 (d, 1H, J = 8 Hz), 7.35 (d, 1H, J = 8 Hz), 7.83 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 558 $(M + H)^+$, 575 $(M + Na)^+$. Anal. for $C_{31}H_{35}N_5O_5 \cdot$TFA: C, H, N.

2-{(1*R*)-1-[*N*-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15hh): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J = 7 Hz), 0.84 (d, 3H, J = 7 Hz), 1.27−1.38 (m, 3H), 1.77−1.89 (m, 2H), 2.55 (s, 3H), 2.67 (t, 1H, J = 7 Hz), 3.26−3.43 (m, 2H), 3.61 (t, 2H, J = 8 Hz), 3.71 (s, 3H), 4.36 (dd, 1H, J = 6, 9 Hz), 5.39 (dd, 1H, J = 6, 7 Hz), 6.95 (s, 1H), 6.98-7.22 (m, 6H), 7.28 (d, 1H, J = 8 Hz), 7.43 (d, 1H, J = 8 Hz); MS (FAB/NBA) 572 $(M + H)^+$, 594 $(M + Na)^+$. Anal. for $C_{32}H_{37}N_5O_5 \cdot 0.9TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(((1-Methylcyclohexyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15w): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J = 6 Hz), 0.84 (d, 3H, J = 6 Hz), 1.25 (s, 3H) 1.26−1.56 (m, 11H), 1.8−1.9 (m, 2H), 2.57 (s, 3H), 3.2−3.5 (m, 2H), 3.74 (s, 3H), 4.14 (dd, 1H, J = 6, 9 Hz), 5.36 (dd, 1H, J = 6, 7 Hz), 6.97 (s, 1H), 7.05 (dt, 1H, J = 1, 8 Hz), 7.13 (dt, 1H, J = 1, 8 Hz), 7.29 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 552 $(M + H)^+$, 569 $(M + NH_4)^+$. Anal. for $C_{30}H_{41}N_5O_5 \cdot 0.8TFA$: C, H, N.

2-{(1*R*)-1-[*N*-((2-Pyridylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15z): NMR is consistent with expected structure; MS (FAB) m/e 533 $(M + H)^+$, 555 $(M + Na)^+$, 571$(M + K)^+$. Anal. for $C_{28}H_{32}N_6O_5 \cdot 0.7H_2O$, 0.80 TFA: C, H, N.

2-{(1*R*)-1-[*N*-((3-Pyridylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15aa): ^{1}H NMR ($CDCl_3/CD_3OD$, 300 MHz) δ 0.86 (d, 3H, J = 5 Hz), 0.88 (d, 3H, J = 5 Hz), 1.42 (m, 2H), 1.53 (m, 1H), 2.55 (s, 3H), 3.39 (m, 2H), 3.70 (s, 3H), 3.71 (m, 1H), 4.33 (m, 1H), 5.44 (m, 1H), 6.91 (s, 1H), 7.02 (t, 1H, J = 7 Hz), 7.13 (t, 1H, J = 7 Hz), 7.24 (d, 1H, J = 8 Hz), 7.46 (d, 1H, J = 8 Hz), 7.71 (dd, 1H, J = 7, 8 Hz), 8.17 (dd, 1H, J = 1, 8 Hz), 8.26 (d, 1H, J = 7 Hz), 8.98 (d, 1H, J = 1 Hz); MS (DCI/NH_3) m/e 533 $(M + H)^+$. Anal. for $C_{28}H_{32}N_6O_5 \cdot 2.65TFA$: C, H, N.

2-{(1*R*)-1-[*N*-(((2-Fluorophenyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15bb): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J = 4 Hz), 0.83 (d, 2H, J = 4 Hz), 1.35 (m, 2H), 1.5 (m, 1H), 2.52 (s, 3H), 3.38 (m, 2H), 3.65 (s, 3H), 4.28 (m, 1H), 5.40 (dd, 1H, J = 7, 8 Hz), 6.95 (m, 3H), 7.08 (m, 4H),

7.25 (d, 1H, J = 7 Hz), 7.42 (d, 1H, J = 7 Hz); MS (DCI/NH_3) m/e 550 (M + H)$^+$, 567 (M + NH_4)$^+$. Anal. for $C_{29}H_{32}N_5O_5F$·0.35TFA: C, H, N.

2-{(1*R*)-1-[*N*-(((3-Fluorophenyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15cc): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (d, 3H, J = 6 Hz), 0.82 (d, 2H, J = 6 Hz), 1.2−1.35 (m, 2H), 1.45−1.55 (m, 1H), 2.42 (s, 3H), 3.32 (m, 2H), 3.48 (s, 3H), 4.36 (m, 1H), 5.42 (dd, 1H, J = 7, 8 Hz), 5.96 (m, 1H), 6.59 (dt, 1H, J = 1, 7 Hz), 6.80 (m, 2H), 6.95 (m, 2H), 7.03 (m, 1H), 7.12 (m, 2H), 7.25 (m, 2H); MS (FAB) m/e 550 (M + H)$^+$, 572 (M + Na)$^+$. Anal. for $C_{29}H_{32}N_5O_5F$·1.15TFA: C, H, N.

2-{(1*R*)-1-[*N*-(((4-Fluorophenyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15dd): ^{1}H NMR ($CDCl_3$/CD_3OD, 300 MHz) δ 0.82 (d, 3H, J = 4 Hz), 0.86 (d, 2H, J = 4 Hz), 1.35 (m, 2H), 1.5 (m, 1H), 2.55 (s, 3H), 3.38 (m, 2H), 3.63 (s, 3H), 4.28 (m, 1H), 5.40 (m, 1H), 6.95 (m, 4H), 7.10 (m, 1H), 7.32 (m, 3H), 7.40 (m, 1H); MS (FAB) m/e 550 (M + H)$^+$, 572 (M + Na)$^+$. Anal. for $C_{29}H_{32}N_5O_5F$·2.0H_2O: C, H, N.

2-{(1*R*)-1-[*N*-(((Pentafluorophenyl)amino)carbonyl)-leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15ee): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J = 7 Hz), 0.84 (d, 3H, J = 7 Hz), 1.27−1.50 (m, 3H), 2.54 (s, 3H), 3.25−3.5 (m, 2H), 3.75 (s, 3H), 4.40 (dd, 1H, J = 6, 8 Hz), 5.39 (dd, 1H, J = 6, 8 Hz), 6.97 (s, 1H), 7.02 (dt, 1H, J = 1, 8 Hz), 7.14 (dt, 1H, J = 1, 8 Hz), 7.30 (d, 1H, J = 8 Hz), 7.44 (d, 1H, J = 8 Hz); MS (FAB/NBA) m/e 622 (M + H)$^+$, 644 (M + Na)$^+$. Anal. for $C_{29}H_{28}F_5N_5O_5$·0.8TFA: C, H, N.

2-{(1*R*)-1-[*N*-(Indol-1-ylcarbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic Acid (15gg). Compound **5** (P = Boc, R = Bn, R′ = CH_3; 110 mg) was dissolved in 6 mL of trifluoroacetic acid and allowed to stir at ambient temperature for 1 h. The solvents were removed *in vacuo*, the residue was neutralized with bicarbonate solution, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was dissolved in THF (4 mL) and DMF (2 mL). HOBt (42 mg), acid **13** (90 mg), and EDC (57 mg) were added. *N*-Methylmorpholine (200 μL) was added and the mixture stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 4:1 going to 5:2 hexanes−EtOAc. The resultant product was added to a suspension of 36 mg of 10% Pd−C in 1 mL of MeOH, the mixture was purged with nitrogen, and 0.1 mL of cyclohexadiene was added. The resultant suspension was stirred at ambient temperature for 2 h. The catalyst was removed by filtration through a pad of Celite; the solvents were removed *in vacuo*. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (d, 3H, J = 7 Hz), 0.90 (d, 3H, J = 7 Hz), 1.4−1.7 (m, 3H), 2.50 (s, 3H), 3.3−3.4 (m, 2H), 3.53 (s, 3H), 4.52 (dd, 1H, J = 6, 10 Hz), 5.43 (dd, 1H, J = 7, 8 Hz), 6.62 (d, 1H, J = 4 Hz), 6.89−6.96 (m, 2H), 7.06 (dt, 1H, J = 1, 8 Hz), 7.14−7.30 (m, 3H), 7.36 (d, 1H, J = 7 Hz), 7.57 (dd, 1H, J = 1, 7 Hz), 7.65 (d, 1H, J = 4 Hz), 8.16 (dd, 1H, J = 1, 7 Hz); MS (DCI/NH_3) 556 (M + H)$^+$, 573 (M + NH_4)$^+$. Anal. for $C_{31}H_{33}N_5O_5$·0.9TFA: C, H, N.

Other Synthetic Procedures. 2-{(1*R*)-1-[(*N*-Boc-leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic Acid Ethyl Ester. 2-{(1*R*)-1-[(Benzyloxycarbonyl)amino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid ethyl ester (compound **4**, P = Cbz, R = Et, R′ = H; 1.7 g) was dissolved in EtOH (30 mL). The solution was purged of oxygen, 10% Pd/C (0.5 g) was added, and the mixture was stirred at room temperature under an atmosphere of hydrogen. After 2 h the catalyst was removed by filtration and the solvent evaporated *in vacuo* to give a white solid (1.2 g). This amino ester was dissolved in THF (10 mL) and added to a solution of Boc-Leu-OH·H_2O (1.0 g) and HOBt (0.5 g) in THF (10 mL). EDC (0.75 g) was added to the solution, followed by DMF (2 mL). The mixture was stirred for 20 h at room temperature. The solvent was evaporated *in vacuo* and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated to give an orange solid that was purified by flash chromatography (25% EtOAc−hexane) to give 1.85 g (92%) of the title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, 3H, J = 7 Hz), 0.89 (d, 3H, H=7 Hz), 1.31 (t, 3H, J = 7 Hz), 1.45 (m, 3H), 1.52 (s, 9H), 2.46 (s, 3H), 3.27 (br s, 1H), 3.43 (m, 1H), 4.12 (m, 1H), 4.30 (q, 2H, J = 7 Hz), 5.50 (m, 1H), 6.65 (br s, 1H), 6.80−7.10 (m, 3H), 7.12 (s, 1H), 7.40 (m, 1H), 8.26 (m, 1H); MS (DCI/NH_3) m/e 526 (M + H)$^+$.

2-{1(*R*)-[((Diethylamino)carbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic Acid (14c). 2-{(1*R*)-1-[(*N*-Boc-leucyl)amino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid ethyl ester (110 mg; prepared as described above) was taken up in 4 N HCl−dioxane (2 mL) and stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give a white solid which was dissolved in $CHCl_3$ (2 mL). *N*-Methylmorpholine (27 μL, 0.24 mmol) and diethylcarbamyl chloride (30 μL, 0.24 mmol) were added, and the solution was stirred at room temperature for 18 h. The solution was washed with water (10 mL), saturated sodium bicarbonate solution (2 × 10 mL), 1 N H_3PO_4 (2 × 10 mL), and brine (10 mL). The organic layer was dried with $MgSO_4$ and evaporated to give an orange oil. This crude ester was dissolved in 4 mL of THF. A nitrogen-purged solution of 50 mg of LiOH in 1.5 mL of water was added, and the mixture was heated in a Carius tube at 110 °C for 15 h. Analytical HPLC of the crude reaction mixture indicated incomplete hydrolysis (∼20% of the starting ester remained). The organic solvent was removed *in vacuo*, and the resulting solution was acidified with 1 N H_3PO_4. The suspension was dissolved with water and acetonitrile, and the product was purified by preparative HPLC (Vydac μC18) eluting with a 10−70% gradient of CH_3CN in 0.1% TFA. Two major peaks were collected. The fractions containing the desired acid were lyophilized to give the product as a white solid (17.4 mg): ^{1}H NMR (CD_3OD, 300 MHz) for the major diastereomer δ 0.79 (d, 3H, J = 7 Hz), 0.81 (d, 3H, J = 7 Hz), 1.08 (t, 6H, J = 7 Hz), 1.2−1.7 (m, 3H), 2.52 (s, 3H), 3.25 (q, 4H, J = 7 Hz), 3.4−3.6 (m, 4H), 4.08 (m, 1H), 5.42 (dd, 1H, J = 7, 8 Hz), 7.00 (t, 1H, J = 7 Hz), 7.10 (s, 1H), 7.12 (t, 1H, J = 7 Hz), 7.35 (d, 1H, J = 8 Hz), 7.45 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 497 (M + H)$^+$. Anal. for $C_{26}H_{36}N_6O_4$·TFA: C, H, N.

2-{1(*R*)-[((Benzylamino)carbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methylimidazole-4-carboxylic acid (14d) was prepared as described in **14c** above, substituting benzyl isocyanate: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, 3H, J = 7 Hz), 0.89 (d, 3H, J = 7 Hz), 1.31 (t, 3H, J = 7 Hz), 1.45 (m, 3H), 1.52 (s, 9H), 2.46 (s, 3H), 3.27 (br s, 1H), 3.43 (m, 1H), 4.12 (m, 1H), 4.30 (q, 2H, J = 7 Hz), 5.50 (m, 1H), 6.65 (br s, 1H), 6.80−7.10 (m, 3H), 7.12 (s, 1H), 7.40 (m, 1H), 8.26 (m, 1H); MS (DCI/NH_3) m/e 531 (M + H)$^+$. Anal. for $C_{29}H_{34}N_6O_4$·1.15TFA: C, H, N.

Also prepared as described in **14c**:

2-{1(*R*)-[((Diethylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15c): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 6H, J = 7 Hz), 1.08 (t, 6H, J = 7 Hz), 1.42 (m, 3H), 2.54 (s, 3H), 3.26 (q, 4H, J = 7 Hz), 3.37 (d, 2H, J = 8 Hz), 4.34 (dd, 1H, J = 6, 7 Hz), 5.40 (t, 1H, J = 6 Hz), 6.96 (dt, 1H, J = 1, 7 Hz), 7.00 (s, 1H), 7.06 (dt, 1H, J = 1, 7 Hz), 7.30 (d, 1H, J = 8 Hz), 7.36 (d, 1H, J = 8 Hz); MS (DCI/NH_3) m/e 498 (M + H)$^+$, 515 (M + NH_4)$^+$. Anal. for $C_{26}H_{35}N_5O_5$·0.3TFA: C, H, N.

2-{1(*R*)-[((Benzylamino)carbonyl)leucylamino]-2-(1-methylindol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid (15d): ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J = 4 Hz), 0.83 (d, 3H, J = 4 Hz), 1.28 (t, 2H, J = 8 Hz), 1.45 (m, 1H), 2.51 (s, 3H), 3.46 (m, 2H), 4.23 (t, 1H, J = 7 Hz), 4.39 (s, 2H), 5.38 (m, 1H), 6.96 (t, 1H, J = 9 Hz), 7.03 (s, 1H), 7.07 (t, 1H, J = 9 Hz), 7.17−7.33 (m, 6H), 7.43 (d, 1H, J = 9 Hz); MS (DCI/

NH_3) *m/e* 532 $(M + H)^+$, 549 $(M + NH_4)^+$. Anal. for $C_{29}H_{33}N_5O_5$·TFA: C, H, N.

Synthesis of acid replacements **16**:

Ethyl 2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylate (16d). Compound **16d** was prepared as an intermediate (prior to final hydrolysis) in the synthesis of **15a**: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J = 7 Hz), 0.88 (d, 3H, J = 7 Hz), 1.34 (t, 3H, J = 8 Hz), 1.43 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.55 (s, 3H), 3.25−3.5 (m, 6H), 4.32 (q, 2H, J = 8 Hz), 4.35 (dd, 1H, J = 5, 9 Hz), 5.39 (t, 1H, J = 8 Hz), 6.95 (ddd, 1H, J = 1, 7, 8 Hz), 6.98 (s, 1H), 7.07 (ddd, 1H, J = 1, 7, 8 Hz), 7.31 (td, 1H, J = 1, 8 Hz), 7.36 (d, 1H, J = 8 Hz); MS (DCI/NH_3) *m/e* 552 $(M + H)^+$, 569 $(M + NH_4)^+$. Anal. for $C_{30}H_{41}N_5O_5$·0.4TFA: C, H, N.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylic Acid, Hydroxamate (16a). Compound **15a** (32 mg) was dissolved in 1 mL of THF and cooled to 0 °C. Oxalyl chloride (6 mL) and 10 μL of DMF were added, and the solution was stirred for 90 min at 0 °C. Hydroxylamine hydrate (25 mg) was dissolved in 1.2 mL of THF and cooled to 0 °C. The acid chloride solution was added, and the mixture was allowed to warm to room temperature and stirred overnight. The solvents were evaporated, and the residue was purified by preparative HPLC (Vydac μC18) eluting with a 10−70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid: 29 mg; ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J = 7 Hz), 0.85 (d, 3H, J = 7 Hz), 1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.53 (s, 3H), 3.25−3.5 (m, 6H), 4.29 (dd, 1H, J = 6, 10 Hz), 5.36 (dd, 1H, J = 7, 8 Hz), 6.97 (ddd, 1H, J = 1, 7, 8 Hz), 7.02 (s, 1H), 7.07 (ddd, 1H, J = 1, 7, 8 Hz), 7.31 (td, 1H, J = 1, 8 Hz), 7.44 (td, 1H, J = 1, 8 Hz); MS (DCI/NH_3) *m/e* 539 $(M + H)^+$. Anal. for $C_{28}H_{38}N_6O_5$·0.8TFA: C, H, N .

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid, *N*-methylamide (16b) was prepared as above for **16a**, substituting 40% aqueous methylamine: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 3H, J = 7 Hz), 0.86 (d, 3H, J = 7 Hz), 1.3−1.5 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.52 (s, 3H), 2.85 (s, 3H), 2.93 (m, 1H), 3.3−3.5 (m, 6H), 4.30 (dd, 1H, J = 6, 10 Hz), 5.36 (dd, 1H, J = 7, 8 Hz), 6.97 (ddd, 1H, J = 1, 7, 8 Hz), 7.00 (s, 1H), 7.07 (ddd, 1H, J = 1, 7, 8 Hz), 7.31 (td, 1H, J = 1, 8 Hz), 7.44 (td, 1H, J = 1, 8 Hz); MS (DCI/NH_3) *m/e* 537 $(M + H)^+$. Anal. for $C_{29}H_{40}N_6O_4$·0.3TFA: C, H, N.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-carboxylic acid, carboxymethylamide (16c) was prepared as above for **16a**, substituting glycine ethyl ester. The resulting product was dissolved in THF (2 mL), a solution of LiOH (50 mg) in H_2O (1 mL) was added, and the mixture was stirred at room temperature for 15 h. The solvents were evaporated under reduced pressure, and the residue was purified by preparative HPLC (Vydac μC18) eluting with a 10−70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid: 28 mg; ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J = 7 Hz), 0.85 (d, 3H, J = 7 Hz), 1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.52 (s, 3H), 3.3−3.5 (m, 6H), 4.04 (s, 2H), 4.31 (dd, 1H, J = 6, 10 Hz), 5.39 (dd, 1H, J = 7, 8 Hz), 6.97 (ddd, 1H, J = 1, 7, 8 Hz), 7.03 (s, 1H), 7.07 (ddd, 1H, J = 1, 7, 8 Hz), 7.30 (td, 1H, J = 1, 8 Hz), 7.45 (td, 1H, J = 1, 8 Hz); MS (DCI/NH_3) *m/e* 581 $(M + H)^+$. Anal. for $C_{30}H_{40}N_6O_6$·0.7TFA: C, H, N.

Synthesis of homologated acid **19**:

Methyl 2-{(1*R*)-1-(Cbz-amino)-2-(indol-3-yl)ethyl}-5-methyloxazole-4-acetate (18). A solution of **5** (P = Boc, R = Et, R′ = H; 200 mg, 0.46 mmol; prepared as described in previous article[1]) in 4 mL of THF was combined with 40 mg of LiOH in 1 mL of water. The mixture was stirred at ambient temperature for 65 h and then heated at 45 °C for 3 h. The organic solvent was removed *in vacuo*; the aqueous solution was neutralized with 1 N H_3PO_4 and then extracted with EtOAc. The combined organic extracts were concentrated *in vacuo* to give the crude acid **17**. To this material, dissolved in 5 mL of THF and cooled to −20 °C, was added 100 μL of *N*-methylmorpholine, followed by 60 μL of isobutyl chloroformate. The resultant slurry was stirred at −20 °C for 45 min. An ethereal solution of diazomethane (10 mL of ∼0.3 N) was added dropwise, and the mixture was allowed to warm to ambient temperature over 3.5 h. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 1:1 hexanes−ethyl acetate. To the resultant diazo ketone, dissolved in 10 mL of methanol, was added a solution of 150 mg of silver benzoate in 2 mL of triethylamine (filtered through a short pad of Celite) over a 10-min period. After stirring for 2 h the solution had turned dark brown. The solvents were removed *in vacuo*; the residue was stirred with 120 mL of a 1:1 water−ethyl acetate mixture for 10 min and then filtered through a pad of Celite. The organic layer was washed with brine, dried over Na_2SO_4, and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of 1:1 going to 2:1 ethyl acetate−hexanes to afford the product (13 mg, 6% yield) as a colorless oil.

2-{1(*R*)-[(Perhydroazepin-1-ylcarbonyl)leucylamino]-2-(indol-3-yl)ethyl}-5-methyloxazole-4-acetic Acid (19). Methyl 2-{(1R)-1-(Cbz-amino)-2-(indol-3-yl)ethyl}-5-methyloxazole-4-acetate (12 mg) was dissolved in EtOH (3 mL), and 10% Pd/C (10 mg) was added. The mixture was purged of oxygen and stirred under a balloon of hydrogen for 5 h. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite to remove the catalyst. The solvent was evaporated to give the amine as a yellow oil. This material was dissolved in THF (1 mL). HOBt (10 mg), perhydroazepin-1-ylleucine (20 mg), and EDC (12 mg) were added. *N*-Methylmorpholine (10 μL) was added, and the mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc−hexane. To this ester dissolved in THF (1 mL) was added a solution of LiOH (15 mg) in H_2O (0.5 mL) and the mixture stirred at room temperature for 15 h. The solvents were evaporated under reduced pressure, and the residue was purified by preparative HPLC (Vydac μC18) eluting with a 10−70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid: 8 mg; ^{1}H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 6H, J = 6 Hz), 0.94 (m, 1H), 1.40 (m, 1H), 1.52 (m, 5H), 1.66 (m, 4H), 2.24 (s, 3H), 3.3−3.5 (m, 6H), 3.45 (s, 2H), 4.33 (dd, 1H, J = 6, 9 Hz), 5.37 (t, 1H, J = 7 Hz), 6.96 (ddd, 1H, J = 1, 7, 8 Hz), 6.97 (s, 1H), 7.07 (ddd, 1H, J = 1, 7, 8 Hz), 7.29 (td, 1H, J = 1, 8 Hz), 7.36 (td, 1H, J = 1, 8 Hz); MS (DCI/NH_3) *m/e* 538 $(M + H)^+$; HRMS calcd for $C_{29}H_{40}N_5O_5$ 538.3029, found 538.3030.

Receptor Binding Assays. All compounds were assayed for binding to MMQ cell membranes (ET_A receptor) or porcine cerebellar tissues (ET_B) using the protocols described in the previous article.[1]

Phosphoinositide (PI) Turnover Assay. MMQ cells (0.4 × 106 cells/mL) were labeled with 10 μCi/mL of [^{3}H]myoinositol in RPMI for 16 h. The cells were washed with PBS and then incubated with buffer A containing protease inhibitors and 10 mM LiCl for 60 min. The cells were incubated with test compounds for 5 min and then challenged with 1 nM ET-1 for 30 min at 37 °C. ET-1 challenge was terminated by the addition of 1.5 mL of 1:2 (v/v) chloroform−methanol. Total inositol phosphates were extracted after adding chloroform and water to give final proportions of 1:1:0.9 (v/v/v) chloroform−methanol−water of as described by Berridge.[8] The upper aqueous phase (1 mL) was analyzed by batch chromatography using anion-exchange resin AG1-X8 (Bio-Rad). IC_{50} values are calculated using an average of at least two separate determinations.

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