Synthesis of a Series of Potent and Orally Bioavailable Thrombin Inhibitors That Utilize 3,3-Disubstituted Propionic Acid Derivatives in the P_3 Position

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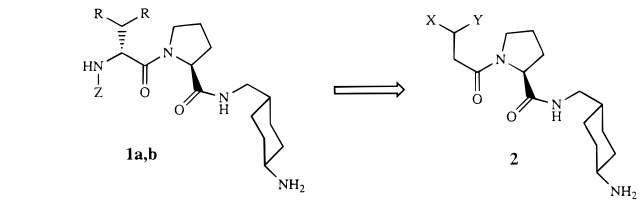
As part of an effort to prepare efficacious and orally bioavailable analogs of the previously reported thrombin inhibitors **1a**,**b**, we have synthesized a series of compounds that utilize 3,3-disubstituted propionic acid derivatives as P_3 ligands. By removing the N-terminal amino group, the general oral bioavailability of this class of compounds was enhanced without excessively increasing the lipophilicity of the compounds. The overall properties of the molecules could be drastically altered depending on the nature of the groups substituted onto the 3-position of the P_3 propionic acid moiety. A number of the compounds exhibited good oral bioavailability in rats and dogs, and numerous compounds were efficacious in a rat $FeCl_3$-induced model of arterial thrombosis. Compound **7**, the 3,3-diphenylpropionic acid derivative, showed the best overall profile of *in vivo* and *in vitro* activity. Molecular modeling studies suggest that these compounds bind in the thrombin active site in a manner essentially identical to that previously reported for compound **1a**.

Introduction

The serine protease thrombin plays a key role in the blood coagulation cascade. Thrombin is responsible for the conversion of fibrinogen to fibrin and the activation of factor XIII which cross-links fibrin monomers, and it is the most potent known stimulator of platelet aggregation. As such, thrombin has become a key target in the effort to develop novel antithrombotic agents. We have recently reported in several papers[2] our strategy directed at the development of orally bioavailable noncovalent thrombin inhibitors. Our early efforts were based on derivatives of compound **1a** (Chart 1) which utilize diaryl or dicycloalkyl[2] alanines in the P_3 position. Analogs of compound **1a** that utilize D-diphenylalanine as a P_3 group were extremely potent thrombin inhibitors, but lacked oral bioavailability.[1,2] Conversion of the diaryl groups to cyclohexyl rings as in compound **1b** also provided a series of very potent thrombin inhibitors and compound **1b** showed high levels of oral bioavailability in several animal species.[2] Unfortunately, compound **1b** was limited by its high lipophilicity and the associated protein binding which appears to compromise the *in vivo* antithrombotic efficacy of the compound. As an alternative to the use of Boc-D-dicyclohexylalanine in the P_3 position, we became interested in compounds of generic structure **2** which lacked the N-terminal amino group. Derivatives of compound **2** could provide a moderate increase in lipophilicity without reaching the extreme level of lipophilicity inherent in compound **1b**. In theory, the removal of the N-terminal amino group would have the negative effect of lowering the potency of the inhibitors, as the N-H of this amino group is involved in a key hydrogen-bonding interaction with the carbonyl of Gly 216 on the thrombin β-sheet.[1] Potent tripeptide inhibitors of thrombin that lack the N-terminal amino group have been reported, but all of these compounds also contain an activated carbonyl or boronic acid serine trap which helps to offset the potency loss.[3] However, we believed that since inhibitors such as compound **1** were already of subnanomolar potency, we could trade off some of this intrinsic potency in an effort to optimize other properties of the inhibitors. In this paper, we describe the synthesis of a series of potent and orally bioavailable thrombin inhibitors based on the removal of the N-terminal amino group.

Chart 1



1a
Z =H; R = Ph
K_i thrombin = 0.10 nM
K_i trypsin = 94 nM

1b
Z =Boc; R = cyclohexyl
K_i thrombin = 0.10 nM
K_i trypsin = 120 nM

X,Y = various aryl and cycloalkyl

Chemistry

The requisite 3,3-disubstituted propionic acids were obtained commercially (**5a**), synthesized via literature methods (**5b**,[4] **5c**,[4] **5d**,[5] **5f** [6]), or synthesized via routes developed in our laboratories (Table 1). The saturated bridged tricyclic **5e** was synthesized by reduction of the corresponding unsaturated compound **5d**. The 3-(2-pyridyl)-3-phenylpropionic acid (**5g**) was prepared by addition of lithio di(2-pyridyl) cuprate to ethyl cinnamate followed by ester hydrolysis (Scheme 1, method A). This cuprate approach was unsuccessful for the other pyridine isomers. The isomeric 3-pyridyl-3-phenylpropionic acids **5h**−**j** were synthesized by Heck aryla-

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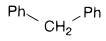
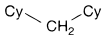
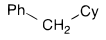
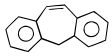
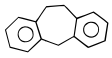
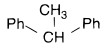
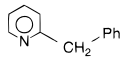
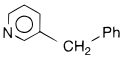
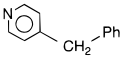
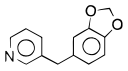
Table 1. 3,3-Disubstituted Propionic Acids

Compound No.	R[a]	Source or Method (Yield, %)[b]
5a		Commercial/Aldrich
5b		Ref. 4 (65%)
5c		Ref. 4 (38%)
5d		Ref. 5 (70%)
5e		reduction of **5d** (82%)
5f		Ref. 6 (28%)
5g		A (27%)[c]
5h		B (55%)[c]
5i		B (68%)[c]
5j		B (55%)[c]

[a] Cy refers to a cyclohexane ring. [b] Yield indicated in the table refers to the overall yield for the multistep preparation of each compound. [c] Isolated as sodium salts.

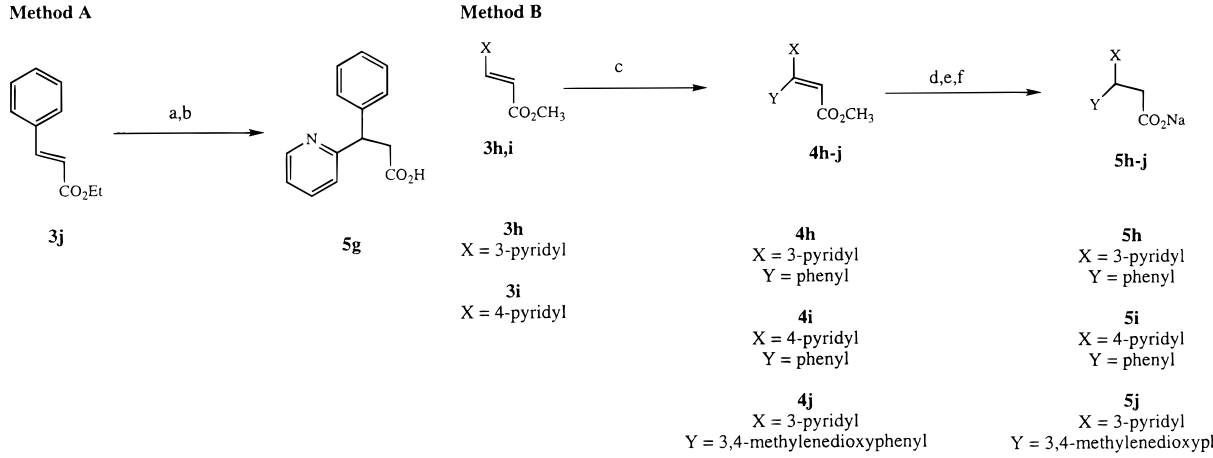
tion of the pyridylpropenoates **3h**,**i** with the appropriate aryl halides followed by saponification and reduction (Scheme 1, method B). The acids **5h**−**j** were isolated as their sodium salts and were used as obtained in the next reaction. Final compounds for biological testing (Table 2) were prepared by simple amino acid coupling of the 3,3-disubstituted propionic acids **5a**−**j** with *trans*-[4-[(*tert*-butoxycarbonyl)amino]cyclohexyl]methyl L-proline amide[1] (**6**), followed by BOC removal and reversed phase preparatory LC purification (Scheme 2). In the cases where two diastereomers were obtained (compounds **9** and **10**, **14** and **15**, **16** and **17**, **18** and **19**, and **20** and **21**), the individual diastereomers were separated and purified via reversed phase preparatory LC. Pairs of diastereomers are numbered in order of elution from a reversed phase C^{18} preparatory LC column. Absolute stereochemistry of the purified diastereomers was not determined.

Results and Discussion

Compounds **7**−**21** were evaluated for their thrombin inhibitory potency and their selectivity versus human trypsin, and the results are summarized in Table 2. The 3,3-diphenylpropionic acid-based compound **7** exhibited surprisingly good thrombin inhibitory potency and was only 20 times less potent then the D-diphenylalanine lead structure **1**.[1] Compound **7** also showed moderate 177-fold selectivity versus human trypsin. Molecular modeling studies[7] with compound **7** suggest that the compound fits in the active site in a manner essentially identical to that reported previously[1] for compound **1**, with the two phenyl rings of **7** occupying similar positions to the two phenyl rings of compound **1**. Reduction of the aromatic rings to give compound **8** resulted in a 7-fold loss of potency, while the trypsin selectivity remained essentially the same. The two monophenyl/monocyclohexyl diastereomers **9** and **10** were of intermediate potency as compared to **7** and **8**. Fusion of the two aromatic rings via an unsaturated two-carbon bridge provided the tricyclic compound **11**, which was equipotent with compound **7** but showed greater selectivity versus trypsin. Replacement of the saturated two-carbon bridge of **11** with a two-carbon unsaturated bridge as in compound **12** resulted in a 6-fold loss of potency. Initially we were puzzled by this observation, as the addition of lipophilicity to the back of the S_3 binding pocket should in theory result in an improvement in inhibitory potency. However, molecular modeling studies[7] with compounds **11** and **12** suggest that the two-carbon bridging element is probably not to the rear of the S_3 binding pocket but is more likely to be across the front side of the two rings near the enzyme−solvent interface. An unsaturated bridging element would be better tolerated in such a polar environment, and the data clearly suggest that this is the case. Addition of a third lipophilic group to the benzylic position of the P_3 moiety as in compound **13** resulted in an 8-fold potency loss.

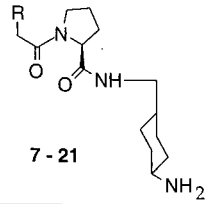
The 3-pyridyl-3-phenylpropionic acid derivatives **14**−**19** showed clear differences in potency based on the stereochemistry at the P_3 benzylic carbon. In each pair

Scheme 1[a]

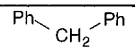
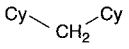
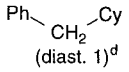
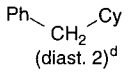
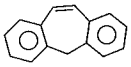
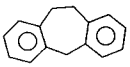
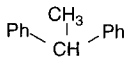
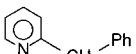
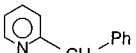
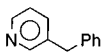
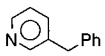
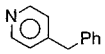
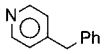
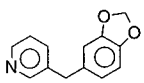
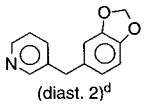


[a] Reagents: (a) 1. 2-bromopyridine, *n*-BuLi/THF, −78 °C, 2. $CuBr(CH_3)_2S$; (b) 1 M LiOH/1,2-dimethoxyethane; (c) $Pd(OAc)_2$, tri-*o*-tolylphosphine, iodobenzene or 3,4-(methylenedioxy)phenyl iodide, triethylamine/CH_3CN, 100 °C, sealed tube, 72 h; (d) 1 M LiOH/DME; (e) 60% NaH dispersion, THF; (f) Raney nickel/EtOH, Parr apparatus, 60 psi, 24−48 h.

Table 2. 3,3-Disubstituted Propionic Acid-Based Thrombin Inhibitors

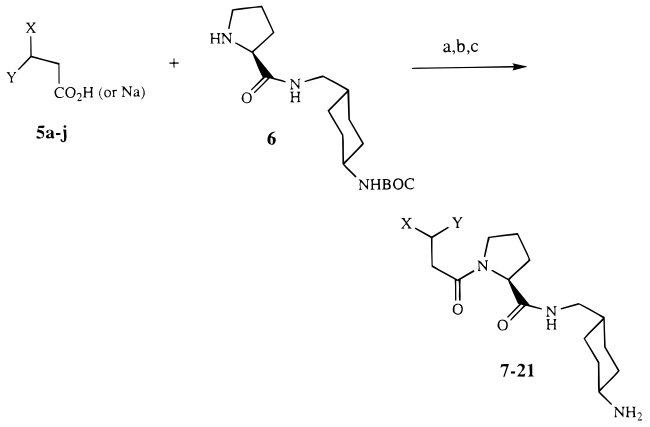


7 - 21

Compd No.	R[a]	Ki thrombin (nM)[b]	Human Ki trypsin (nM)[b]	Selectivity ratio	Yield (%)[c]	Anal.	Formula
7		2	353	177	47	CHN	$C_{27}H_{35}N_3O_2 \cdot 1.60TFA \cdot 0.45H_2O$
8		14	2,500	179	40	CHN	$C_{27}H_{47}N_3O_2 \cdot HCl \cdot 0.35H_2O$
9	 (diast. 1)[d]	8	1,700	213	59	CHN	$C_{27}H_{41}N_3O_2 \cdot 1.25TPA \cdot 0.80H_2O$
10	 (diast. 2)[d]	4	300	75	66	CHN	$C_{27}H_{41}N_3O_2 \cdot 1.25\ TFA \cdot 0.65H_2C$
11		3	1,600	533	40	CHN	$C_{29}H_{35}N_3O_2 \cdot HCl \cdot 1.55H_2O$
12		17	ND	--	30	CHN	$C_{29}H_{37}N_3O_2 \cdot 1.60TFA \cdot 0.20H_2O$
13		16	17,000	1,063	70	CHN	$C_{28}H_{37}N_3O_2 \cdot HCl \cdot 1.80H_2O$
14	 (diast. 1)[d]	1.8	890	495	35	CHN	$C_{26}H_{34}N_4O_2 \cdot 2.50TFA \cdot 0.85H_2O$
15	 (diast. 2)[d]	12	5,000	417	30	CHN	$C_{26}H_{34}N_4O_2 \cdot 2.50\ TFA \cdot 0.25H_2C$
16	 (diast. 1)[d]	10	2,800	280	30	CHN	$C_{26}H_{34}N_4O_2 \cdot 2.50TFA \cdot 1.40H_2O$
17	 (diast. 2)[d]	2.2	2,200	1,000	22	CHN	$C_{26}H_{34}N_4O_2 \cdot 2.50TFA \cdot 1.00H_2O$
18	 (diast. 1)[d]	29	19,000	655	30	CHN	$C_{26}H_{34}N_4O_2 \cdot 2.50TFA \cdot 0.45H_2O$
19	 (diast. 2)[d]	3.4	2,200	647	20	CHN	$C_{26}H_{34}N_4O_2 \cdot 2.50TFA \cdot 2.40H_2O$
20	 (diast. 1)[d]	4.7	1,900	404	26	CHN	$C_{27}H_{39}N_4O_4 \cdot 2.50TFA \cdot 2.50H_2O$
21	 (diast. 2)[d]	0.28	2,600	9,286	30	CHN	$C_{27}H_{34}N_4O_4 \cdot 2.50TFA \cdot 2.50H_2O$

[a] Cy refers to a cyclohexyl ring. [b] K_i values for all serine proteases are the average of at least two determinations, where the variation in the assay is ±10%. Experimental protocols are provided in ref 2. [c] The yield as indicated in the table is the yield obtained for the three-step coupling, deprotection, and purification/separation sequence as shown in Scheme 2. [d] Diastereomers are labeled as 1 or 2 based on order of elution from a C18 reversed phase preparatory LC column.

Scheme 2[a]



[a] Reagents (a) EDC, HOBT, triethylamine/DMF; (b) TFA-CH_2Cl_2 or EtOAc saturated with HCl_g, 0 °C; (c) reversed phase (C18) preparatory HPLC.

of pyridine diastereomers, there was one compound which was clearly more potent than its counterpart. These observations may be explained in part by our previous crystallographic studies[1] on compound **1**. It is likely that the diastereomer which more easily places the phenyl ring back into the usual D-Phe binding position and the pyridyl ring into the front of the S_3 pocket corresponds to the more potent diastereomer. The rear of the S_3 binding pocket is lined by lipophilic amino acid side chains and would likely prefer to be occupied by a phenyl ring rather than a pyridyl ring. Conversely, the pyridine ring would be more easily accommodated in the front diaryl-binding position of the S_3 pocket, as this region lies close to the enzyme−solvent interface and would provide a more polar environment for the pyridine nitrogen. The 3-pyridyl compound **17** also showed a surprising enhancement in selectivity ratio versus trypsin. On the basis of the above detailed hypothesis of differential binding of the various pyridine-containing diastereomers, we theorized that it should be possible to add bulk to the phenyl ring of the appropriate pyridine diastereomer to further enhance the potency of these compounds. Due to the excellent selectivity ratio observed for compound **17** versus trypsin, we chose this pyridine isomer for further work. In previous unpublished work[8] on D-phenylalanine P_3-containing thrombin inhibitors, we observed that the addition of the appropriate substitution to the 3- and 4-positions of the aromatic ring provided enhanced potency due to optimization of lipophilic interaction with the back of the S_3 binding pocket. We found that 3,4-methylenedioxy was among the best substituents for this potency enhancement and did not add large amounts of either lipophilicity or molecular weight to the molecules. Application of this theme to compound **17** provided the diastereomers **20** and **21**. Once again, a clear difference in enzyme potency between the diastereomers was observed, with the more potent diastereomer **21** exhibiting a 9-fold potency enhancement over compound **17**. Compound **21** also showed excellent selectivity of almost 9300-fold versus human trypsin. These results are consistant with the explanation of the pyridyl/phenyl P_3 diastereomer binding described above and reinforce our hypothesis. It is probable that, as predicted, the more potent diastereomer **21** is of the absolute configuration that more easily places the (methylenedioxy)phenyl ring back into the usual D-Phe S_3 binding position, while also placing the pyridyl ring into the front aryl-binding position in the S_3 pocket.

Key compounds were evaluated for selectivity versus a number of human-derived serine proteases, and the results are detailed in Table 3. In general, the compounds demonstrated good selectivity versus all serine proteases tested. The values of the second-order rate constant of inactivation (k_{on}) are also provided in Table 3 for several of the inhibitors, and all examples were shown to be fast binding inhibitors. Key compounds were also evaluated for oral bioavailability in several animal species. Results are summarized in Table 4. As expected, the more lipophilic compounds **7**, **8**, and **11** all performed well in rats, while the more polar pyridine-containing compounds **17** and **21** performed poorly in rats and dogs, respectively. Pharmacokinetic parameters for compound **7** in rats and dogs are detailed in Table 5. Compound **7** exhibited good overall pharmacokinetic behavior in both species. Especially noteworthy was the long half-life observed for **7** in both species.

Compounds **7**, **8**, **17**, and **21** were evaluated for *in vivo* antithrombotic efficacy in the rat carotid artery $FeCl_3$-induced thrombosis model. Results are summarized in Table 6. The more polar/less protein-bound compounds **17** and **21** performed extremely well, with both showing full antithrombotic efficacy (all compounds were dosed iv over 120 min as a 10 μg/kg/min infusion). The most lipophilic compound **8** exhibited a complete lack of antithrombotic efficacy and also showed low plasma levels as determined at the end of the experiment. The diphenyl compound **7** showed moderate antithrombotic activity, preventing occlusion in 3 of 5 rats. Compounds **7**, **17**, and **21** all showed good levels of parent compound as determined at the end of the experiment. In general, these results are consistent with our previously reported[2] correlation between lipophilicity/2 × APTT/protein binding and *in vivo* antithrombotic efficacy. These data further reinforce our premise[2] that a perfect

Table 3. Selectivity of Thrombin Inhibitors versus Various Serine Proteases[a]

			K_i (μM)				
compd no.	K_i thrombin (nM)	k_{on} thrombin ($\times 10^{-7}$ M^{-1} s^{-1})	trypsin	TPA	plasmin	plasma Kallikrein	Xa
7	2	21.0	0.35	>1000	744	>1000	980
8	14	23.0	2.50	84	176	170	220
11	3	18.0	1.60	268	414	775	>1000
14	1.8	18.0	0.89	>1000	>1000	767	370
17	2.2	21.0	2.2	746	>1000	476	>1000
19	3.4	15.5	2.2	436	744	>1000	400
21	0.28	25.1	2.60	>500	572	1000	1000

[a] K_i values for all serine proteases are the average of at least two determinations, where the variation in the assay is ±10%. Experimental protocols are given in ref 2.

Table 4. Oral Bioavailability of Thrombin Inhibitors[a]

compd no.	log *P*	*F* (%) rat[b] (10 mg/kg)	*F* (%) dog[c] (5 mg/kg)
7	0.37	10	58
8	1.96	56	ND
11	0.27	51	ND
12	ND	12	ND
17	−0.64	ND	8
21	−1.62	<5	ND

[a] All experimental protocols for these experiments are given in ref 2. [b] Compounds were dosed orally to rats as a suspension in 1% methocel. [c] Compounds were dosed orally to dogs as a 1% methocel suspension.

Table 5. Pharmacokinetic Parameters for Compound **7** in Rats and Dogs[a]

log *P*	dose (mg/kg)	route	AUC (μM·h)	$t_{1/2}$ (min)	Cl (mL/min/kg)	*F* (%)
			Rat[b]			
0.37	1	iv	1.70	268	23.2	
	10	po	1.51			10
			Dog[c]			
0.37	1	iv	3.81	175	10.2	
0.37	5	po	11.20	156		58

[a] Details of the experimental protocols are given in ref 2. [b] Compound was dosed orally as 1% methocel suspension, iv in 10% propylene glycol/saline. [c] Compound was dosed orally as 1% methocel suspension, iv as a solution in 20% PEG/saline.

Table 6. Antithrombotic Efficacy of Thrombin Inhibitors: Rat Carotid Artery $FeCl_3$-Induced Thrombosis Model[a]

compd no.[b]	*r*	no. occlusions	2 × APTT (μM)[c] rat	2 × APTT (μM)[c] human	% free[d] rat	% free[d] human	final plasma concn (nM)
7	5	2/5	0.65	0.67	7	7	1600
8	6	6/6	7.20	7.10	6	1	658
17	5	0/5	0.59	0.47	56	35	2890
21	6	0/6	0.38	0.30	ND	ND	4000
argatroban	6	0/6	ND	0.28	ND	ND	ND

[a] Details of the experimental protocol are given in ref 2 and references cited therein. [b] Compounds were infused at 10 μg/kg/min iv for 120 min prior to the $FeCl_3$ insult. Vehicle for compound administration was saline. Vehicle control animals showed complete occlusion. [c] The 2 × APTT value is defined as the concentration of inhibitor in plasma required to double the activated partial thromboplastin time. [d] Experimental protocol for the determination of this parameter is detailed in ref 2.

balance of physical properties, potency, and selectivity is crucial to the design of clinically viable oral thrombin inhibitors.

In summary, we have synthesized a series of potent and selective thrombin inhibitors based on the use of a 3,3-disubstituted propionic acid as a P_3 ligand. The series has demonstrated that it is possible to achieve high levels of potency against thrombin despite the removal of the N-terminal amino group which is involved in a key hydrogen-bonding interaction with the thrombin β-sheet. A number of the compounds showed good oral bioavailability in rats, and compound **7** also demonstrated good oral bioavailability and good pharmacokinetic behavior in dogs. Several of the compounds also exhibited good *in vivo* antithrombotic activity in the rat carotid artery $FeCl_3$-induced thrombosis model. In general, the more polar compounds performed poorly in the oral bioavailability models while performing well in the *in vivo* antithrombotic model; the opposite trends were observed for the more lipophilic compounds. Compound **7** demonstrated the best overall profile of all the compounds in this series and has become a second-generation lead structure for further synthetic work. We are continuing our efforts toward the synthesis of the "ideal" thrombin inhibitor for clinical development and will report on our further efforts in future publications.

Experimental Section

Melting points were determined in open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane. All reagents were of commercial synthetic grade unless otherwise specified. Aldrich Sure-Seal dimethylformamide was used as solvent in all amino acid coupling reactions. Reversed phase preparatory HPLC purification and diastereomer separations were performed on a Waters Prep 4000, using a Waters C^{18} Prep-Pac and various gradients.

3,3-Dicyclohexylpropionic Acid (5b). Compound **5b** was synthesized via the method described in ref 4. White crystalline solid, mp = 122.0−123.5 °C, yield = 65%. 400 MHz ^{1}H NMR ($CDCl_3$): 0.88−1.32 (complex, 10H), 1.42 (m, 2H), 1.51−1.82 (complex, 11H), 2.28 (d, 2H). FAB MS: $M^+ = 239$.

3-Phenyl-3-cyclohexylpropionic Acid (5c). Compound **5c** was synthesized via the method described in ref 4. White crystalline solid, mp = 97−99 °C, yield = 38%. 400 MHz ^{1}H NMR ($CDCl_3$): 0.73−1.28 (complex, 5H), 1.46 (t, 2H), 1.61 (m, 2H), 1.76 (q, 2H), 2.58 (m, 1H), 2.82 (m, 1H), 2.84 (m, 1H), 7.19 (complex, 5H). FAB MS: $M^+ = 233$.

5*H*-Dibenzo[*a*,*d*]cycloheptene-5-acetic Acid (5d). Compound **5d** was synthesized via the method described in ref 5. Tacky yellow solid, yield = 70%. 400 MHz ^{1}H NMR ($CDCl_3$): 2.77 (d, 2H), 4.51 (t, 1H), 6.91 (s, 2H), 7.29 (complex, 8H).

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptane-5-acetic Acid (5e). A solution of 1.00 g (4.00 mol) of compound **5d** in 30 mL of absolute ethanol containing 1.00 equiv of HCl was hydrogenated on a Parr appartus at 50 psi over 200 mg of 10% Pd on carbon catalyst for 18 h. The catalyst was filtered off and the filtrate concentrated to a clear oil. The oil was purified via column chromatography over silica gel with 4:1 hexane/EtOAc to give 930 mg of product isolated as its ethyl ester. The ester was hydrolyzed by dissolving in 15 mL of 1 M LiOH/15 mL of dimethoxyethene and stirring at room temperature for 18 h. The reaction was acidified with aqueous 10% citric acid and extracted twice with 30 mL portions of EtOAc. Drying (anhydrous $MgSO_4$) and concentration *in vacuo* provided 681 mg (82% for two steps) of desired product **5c** as a pale yellow crystalline solid, mp = 155−157 °C. 400 MHz ^{1}H NMR ($CDCl_3$): 3.10 (m, 2H), 3.13 (d, 2H), 3.28 (m, 2H), 4.76 (t, 1H), 7.17 (complex, 8H). FAB MS: $M^+ = 253$.

3-Methyl-3,3-diphenylpropionic Acid (5f). Compound **5f** was prepared via the method described in ref 6. Tacky white solid, yield = 20%. 400 MHz ^{1}H NMR ($CDCl_3$): 1.90 (5, 3H), 3.19 (s, 2H), 7.19 (m, 6H), 7.28 (M, 4H).

Method A: Preparation of 3-Pyridyl-3-phenylpropionic Acids 5g−j. 3-(2-Pyridyl)-3-phenylpropionic Acid (5g). To a solution of 1.80 g (11.36 mmol) of 2-bromopyridine in 10 mL of anhydrous ether (argon atmosphere) cooled to −78 °C was added dropwise 7.10 mL (11.36 mmol) of 1.6 M *n*-butyllithium in hexanes (Aldrich). The resulting deep red solution was stirred at −78 °C for 30 min. The cold lithiopyridine solution was added dropwise to a suspension of 1.17 g (5.68 mmol) of copper bromide−dimethyl sulfide complex (Aldrich) in 20 mL of anhydrous ether cooled to 0 °C. The resulting dark solution was stirred at 0 °C for 20 min and then removed from the cooling bath. The dark solution was treated dropwise with 500.00 mg (2.84 mmol) of ethyl cinnamate, and the mixture stirred at room temperature for 1 h. The reaction mixture was poured into 40 mL of 90% saturated NH_4Cl/10% concentrated aqueous NH_4OH, and the resulting mixture stirred vigorously at room temperature for 45 min. The layers were separated, and the aqueous layer was extracted with 25 mL of ether. The combined ethereal layers were extracted twice with 40 mL portions of 2 N HCl. The combined acid extracts were neutralized (pH 7−8) with concentrated aqueous NH_4OH and extracted twice with 30 mL portions of ether. The combined extracts were washed with brine, dried (anhydrous

$MgSO_4$), and concentrated *in vacuo* to give a dark oil. The crude oil was purified via gravity column chromatography over silica gel with 3:1 hexanes/ethyl acetate to give 220 mg (28%) of the ether ester as a pale yellow oil. 400 MHz ^{1}H NMR ($CDCl_3$): 1.16 (t, 3H), 2.98 (dd, J = 7, 17 Hz, 1H), 3.43 (dd, J = 7, 17 Hz, 1H), 4.04 (q, 2H), 4.64 (m, 1H), 7.17 (complex, 3H), 7.26 (m, 4H), 7.56 (m, 1H), 8.58 (m, 1H).

A 215.00 mg (0.85 mmol) sample of the ethyl ester was dissolved in 3 mL of LiOH/3 mL of dimethoxyethane, and the solution stirred at room temperature for 2 h. The reaction mixture was diluted with aqueous 10% citric acid to pH ~6.5 and the solution extracted twice with 10 mL portions of ethyl acetate. The combined extracts were dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to give 190 mg (99%) of the desired product as a yellow oil. 400 MHz ^{1}H NMR ($CDCl_3$): 3.09 (dd, J = 5, 16 Hz, 1H), 3.39 (q, 1H), 4.62 (m, 1H), 7.22 (complex, 7H), 7.65 (t, 1H), 8.58 (d, 1H). FAB MS: M + 1 = 228.

Method B: General Procedure for the Synthesis of Compounds 5h−j via Heck Arylation. 3-(3-Pyridyl)-3-phenylpropionic Acid (5h). A solution of 250.00 mg (1.53 mmol) of methyl 3-(3-pyridyl)propenoate, 5.00 mg (0.02 mmol) of palladium acetate (Aldrich), 25.00 mg (0.08 mmol) of tri-*o*-tolylphosphine (Aldrich), 172.00 μL (1.53 mmol) of iodobenzene (Aldrich), and 223.00 μL (1.60 mmol) of triethylamine (Aldrich) in 1 mL of acetonitrile was heated at 100 °C in a sealed tube for 72 h. The reaction mixture was cooled to room temperature, and concentrated *in vauco* to an orange-red solid. The solid was purified via gravity column chromatography over silica gel with 2:1 hexanes/ethyl acetate to give 190 mg (52%) of coupling product as a pale yellow oil. The ester was hydrolyzed in 2 mL of LiOH/2 mL of dimethoxyethane over ~2 h, acidified to pH ~6.5 with 10% citric acid, and extracted with ethyl acetate. The extract was dried (anhydrous $MgSO_4$) and concentrated *in vacuo* to give 177 mg (99%) of unsaturated acid. The acid was dissolved in THF and treated with an equimolar amount of 60% NaH dispension (Aldrich). After stirring for 1 h, the reaction mixture was concentrated to give the unsaturated acid sodium salt as a yellow foam-solid. The salt was hydrogenated on a Parr apparatus in absolute ethanol over 100 mg of Raney nickel (Aldrich) catalyst at 65 psi. The reaction was monitored by HPLC until complete (24−48 h), and the reaction mixture was filtered carefully (Raney nickel is extremely pyrophoric—use care!). The filtrate was concentrated *in vacuo* to give 157 mg (80%) of the sodium salt of the desired acid as a white solid. 400 MHz ^{1}H NMR (DMSO-d_6): 2.71 (m, 2H), 4.58 (m, 1H), 7.18 (complex, 5H), 7.61 (m, 1H), 8.09 (d, 1H), 8.20 (d, 1H), 8.49 (s, 1H). The sodium salt was used as isolated in the next reaction.

The following compounds were also prepared via method B.

3-(4-Pyridyl)-3-phenylpropionic Acid (5i). Glassy solid, yield = 69%. 400 MHz ^{1}H NMR (DMSO-d_6): 2.62 (d, 1H), 2.76 (d, 1H), 4.48 (br m, 1H), 7.20 (complex, 5H), 8.20 (d, 2H), 8.52 (br m, 2H). Isolated as sodium salt.

3-(3-Pyridyl)-3-[3,4-(methylenedioxy)phenyl]propionic Acid (5j). Foam, yield = 78%. 400 MHz ^{1}H NMR (CD_3-OD): 2.84 (d, 2H), 4.54 (t, 1H), 5.89 (s, 2H), 6.76 (m, 3H), 7.35 (m, 1H), 7.78 (m, 1H), 8.36 (m, 1H), 8.45 (s, 1H). Isolated as sodium salt.

Coupling of 3,3-Disubstituted Propionic Acids 5a−d,f−h with *trans*-[4-[(*tert*-Butoxycarbonyl)amino]cyclohexyl]methyl L-Proline Amide 6. General Procedure for the Preparation of Compounds 7, 8, and 11−13. *N*-(1-Oxo-3,3-diphenylpropyl)-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (7). A solution of 70.14 mg (0.31 mmol) of 3,3-diphenylpropionic acid, 100 mg of *trans* [4-[(*tert*-butoxycarbonyl)amino]cyclohexyl]methyl L-proline amide,[1] 46.00 mg (0.34 mol) of HOBt (Aldrich), 48.00 μL (0.34 mmol) of triethylamine (Aldrich), and 65.00 mg (0.34 mmol) of EDC (Pierce) in 1 mL of anhydrous DMF was stirred at room temperature for 18 h. The reaction mixture was diluted with 3× its volume of 10% citric acid, and the suspension was extracted with two 25 mL portions of ethyl acetate. The combined extracts were washed with brine, dried (anhydrous $MgSO_4$), and concentrated *in vacuo* to give the crude coupling product. The crude product was purified via gravity column chromatography over silica gel with 3:2 ethyl acetate/chloroform to give 105 mg of coupling product as a clear glass. The product was dissolved in 1 mL of CH_2Cl_2/1 mL of trifluoroacetic acid (Aldrich), and the reaction mixture stirred at room temperature for 18 h. The reaction was concentrated to dryness, and the residue was purified via reversed phase preparatory HPLC. Pure fractions were combined and concentrated to dryness to give a clear glass. The glass was suspended in ether with a few drops of hexane, scraped, and triturated. Filtration gave 70 mg (50%) of desired product **7** as a glassy white solid, mp = 120−123 °C. Elemental Anal. for $C_{27}H_{35}N_3O_2$·1.60TFA·0.45H_2O: C (58.11 calcd, 58.11 found), H (6.06 calcd, 6.02 found), N (6.73 calcd, 6.90 found). 400 MHz ^{1}H NMR ($CDCl_3$): 0.91 (m, 4H), 1.14 (br s, 1H), 1.63 (m, 2H), 1.81 (br s, 1H), 1.96 (m, 2H), 2.38 (m, 1H), 2.76 (m, 1H), 3.02 (m, 2H), 3.23 (m, 1H), 3.43 (m, 1H), 4.08 (q, 1H), 4.24 (q, 1H), 4.35 (m, 1H), 4.50 (d, 1H), 4.63 (t, 1H), 6.89 (br s, 1H), 7.21 (complex, 10H). High-resolution FAB MS: M^+ calcd = 434.28075, M^+ obsd = 434.28204.

The following compounds were prepared in the same manner as compound **7**.

***N*-(1-Oxo-3,3-dicyclohexylpropyl)-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (8).** White solid, mp = 104−107 °C, yield = 38%. FAB MS: M^+ = 447. Elemental Anal. for $C_{27}H_{47}N_3O_2$·HCl·0.35H_2O: C (66.39 calcd, 66.11 obsd), H (10.05 calcd, 9.95 obsd), N (8.60 calcd, 8.56 obsd). 400 MHz ^{1}H NMR ($CDCl_3$): 0.89−1.25 (complex, 13H), 1.29−1.95 (complex, 19H), 1.95−2.29 (complex, 6H), 2.43 (m, 1H), 2.99 (m, 1H), 3.09 (m, 2H), 3.44 (m, 1H), 3.59 (m, 1H), 4.61 (m, 1H), 7.46 (br s, 1H), 8.39 (br, NH_2).

***N*-[1-Oxo-2-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)ethyl]-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (11).** Amorphous white lyophilizate, yield = 40%. High-resolution FAB MS: M^+ calcd = 458.280753, obs = 458.280112. 400 MHz ^{1}H NMR ($CDCl_3$): 0.99 (m, 2H), 1.21−1.89 (complex, 7H), 2.22 (m, 3H), 2.78 (m, 2H), 2.84 (m, 2H), 3.05 (m, 1H), 3.10 (m, 2H), 3.21 (m, 1H), 4.39 (br m, 1H), 4.72 (t, 1H), 6.85 (br s, 1H), 6.96 (s, 2H), 7.31 (complex, 8H), 8.31 (br, NH_2). Elemental Anal. for $C_{29}H_{36}N_3O_2$·HCl·1.55H_2O: C (calcd 62.51, obsd 62.49), H (calcd 7.05, obsd 7.05), N (calcd 7.45, obsd 7.50).

***N*-[1-Oxo-2-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohept-5-yl)ethyl]-L-proline [*trans*-(4-Aminocyclohexyl)methyl]-amide (12).** Amorphous white lyophilizate, yield = 40%. High-resolution FAB MS: M^+ calcd = 460.296403, obsd = 460.296646. 400 MHz ^{1}H NMR ($CDCl_3$): 0.91 (m, 2H), 1.36 (m, 3H), 1.74 (m, 4H), 1.88 (q, 1H), 2.02 (m, 2H), 2.19 (m, 1H), 2.96 (m, 2H), 3.04 (m, 2H), 3.09 (m, 4H), 3.15 (m, 1H), 3.31 (m, 1H), 3.38 (m, 2H), 4.40 (d, 1H), 4.75 (t, 1H), 7.11 (complex, 9H), 7.79 (br, NH_2). Elem. Anal. for $C_{29}H_{37}N_3O_2$·1.60TFA·0.20H_2O: C (59.90 calcd, obsd 59.89), H (6.09 calcd, 6.06 obsd), N (6.51 calcd, 6.79 obsd).

***N*-(1-Oxo-3-methyl-3,3-diphenylpropyl)-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (13).** White powder, mp = 147−150 °C, yield = 45%. High-resolution FAB MS: M^+ calcd = 448.29640, obsd = 448.29648. Elemental Anal. for $C_{28}H_{37}N_3O_2$·HCl·1.80H_2O: C (calcd 65.11, obsd 65.06), H (8.12 calcd, 7.91 obsd), N (8.14 calcd, 8.26 obsd). 400 MHz ^{1}H NMR ($CDCl_3$): 0.96 (m, 2H), 1.55 (m, 3H), 1.78 (m, 4H), 1.96 (s, 3H), 2.19 (m, 3H), 2.99 (m, 2H), 3.04 (m, 2H), 3.11 (s, 2H), 3.21 (m, 2H), 4.42 (br s, 1H), 7.00 (br s, 1H), 7.21 (complex, 10H), 8.22 (br, NH_2).

Coupling of 3,3-Disubstituted Propionic Acid (or Sodium Salts) 5e,g−l with *trans*-[4-[(*tert*-Butoxycarbonyl)amino]cyclohexyl]methyl L-Proline Amide (6) and Separation of the Product Diastereomers. *N*-[1-Oxo-3-(4-pyridyl)-3-phenylpropyl]-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (18 and 19). A mixture of compounds **18** and **19** was prepared via an analogous coupling, purification, and deprotection scheme as described above for compound **7**. The product mixture was separated via reversed phase preparatory HPLC by taking numerous fractions across the closely separated peaks. The earlier eluting peak fractions were combined and concentrated to remove volatiles, and the aqueous residue was placed on a lyophilizer overnight. Lyophilization provided 65 mg (30%) of compound **18** as a fluffy white amorphous powder. Elemental Anal. for $C_{26}H_{34}N_4O_2$·2.50

TFA·0.45H_2O: C (51.16 calcd, 51.14 obsd), H (5.18 calcd, 5.02 obsd), N (7.37 calcd, 7.33 obsd). High-resolution FAB MS: M^+ calcd = 435.27600, obsd = 435.27479. 400 MHz ^{1}H NMR ($CDCl_3$): 0.95 (m, 2H), 1.41 (m, 2H), 1.79 (m, 4H), 2.10 (m, 4H), 2.96 (m, 2H), 3.11 (m, 2H), 3.43 (q, 1H), 3.61 (m, 1H), 3.79 (m, 1H), 3.80−4.30 (br, 2H, NH_2), 4.30 (m, 1H), 4.48 (m, 1H), 4.75 (m, 1H), 7.01 (t, 1H), 7.29 (complex, 5H), 7.58 (br m, 2H), 8.61 (br m, 2H).

The later eluting peak fractions were combined and treated as above to give 25 mg (12%) of compound **19** as a glassy solid. Elemental Anal. for $C_{26}H_{34}N_4O_2$·2.50TFA·2.40H_2O: C (48.80 calcd, 48.79 obsd), H (5.46 calcd, 5.22 obsd), N (7.34 calcd, 7.48 obsd). High-resolution FAB MS: M^+ calcd = 435.27600, obsd = 435.27657. 400 MHz ^{1}H NMR ($CDCl_3$): 0.91 (m, 2H), 1.31 (m, 2H), 1.71 (d, 2H), 1.91 (m, 2H), 2.11 (m, 4H), 2.92 (m, 2H), 3.04 (m, 2H), 3.32 (m, H), 3.39 (m, 1H), 3.69 (m, 1H), 380−4.30 (br, 2H) 4.09 (br m, 1H), 4.39 (m, 1H), 4.74 (br m, 1H), 7.29 (complex, 6H), 8.21 (br d, 2H), 8.61 (br m, 2H). Both diastereomers were of >99% purity by HPLC Anal. at 210 and 254 nm.

The following compounds were prepared in the same manner as compounds **18** and **19**.

***N*-(1-Oxo-3-phenyl-3-cyclohexylpropyl)-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (Diastereomers 9 and 10). 9:** White solid, mp = 116−119 °C, yield = 39%. High-resolution FAB MS: M^+ calcd = 440.32770, obsd = 440.32599. Elemental Anal. for $C_{27}H_{41}N_3O_2$·1.25 TFA·0.80H_2O: C (calcd 59.39, obsd 59.32), H (calcd 7.41, obsd 7.47), N (calcd 7.04, obsd 7.40). 400 MHz ^{1}H NMR: 0.85 (m, 2H), 0.95 (q, 1H), 1.09 (m, 2H), 1.29 (m, 6H), 1.45 (m, 1H), 1.78 (m, 1H), 1.87 (m, 6H), 2.01 (m, 2H), 2.07 (m, 1H), 2.72 (m, 4H), 2.80 (m, 1H), 2.95 (m, 2H), 3.42 (m, 2H), 4.41 (t, 1H), 6.22 (t, 1H), 7.19 (complex, 5H), 7.78 (br, NH_2).

10: White solid, mp = 120−122 °C, yield = 66%, High-resolution FAB MS: M^+ calcd = 440.32770, obsd = 440.32799. Elemental Anal. for $C_{27}H_{41}N_3O_2$·1.25TFA·0.65H_2O: C (calcd 59.66, obsd 59.61), H (calcd 7.39, obsd 7.36), N (calcd 7.08, obsd 7.23). 400 MHz ^{1}H NMR ($CDCl_3$): 0.79 (m, 1H), 0.96 (m, 4H), 1.09 (m, 2H), 1.25 (m, 1H), 1.38 (m, 4H), 1.42 (d, 1H), 1.51 (q, 1H), 1.71 (m, 4H), 1.86 (d, H), 1.99 (m, 4H), 2.61 (m, 1H), 2.81 (m, 2H), 2.90 (m, 2H), 2.95 (m, 2H), 3.19 (m, 1H), 3.54 (m, 1H), 4.22 (m, 1H), 7.18 (complex, 6H), 7.59 (br, NH_2).

***N*-[1-Oxo-3-(2-pyridyl)-3-phenylpropyl]-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (Diastereomers 14 and 15). 14:** Amorphous white lyophilizate, yield = 30%. High-resolution FAB MS = M^+ calcd = 4.35.27600, obsd = 435.27610. Elemental Anal. for $C_{26}H_{34}N_4O_2$·2.50TFA·0.85H_2O: C (calcd 50.66, obsd 50.68), H (5.24 calcd, 5.19 obsd), N (7.67 calcd, 7.85 obsd). 400 MHz ^{1}H NMR ($CDCl_3$): 0.92 (m, 2H), 1.52 (m, 4H), 1.80 (m, 2H), 1.95 (m, 4H), 7.09 (m, 2H), 2.20 (m, 2H), 2.94 (m, 2H), 3.19 (m, 2H), 3.59 (m, 2H), 4.36 (m, 1H), 4.96 (m, 1H), 7.16 (t, 1H), 7.31 (complex, 5H), 7.61 (d, 1H), 8.06 (m, 1H), 8.11 (m, 1H), 8.78 (m, 1H).

15: Amorphous white lyophilizate, yield = 27%. High-resolution FAB MS: M^+ calcd = 435.27600, obsd = 435.77710. Elemental Anal. for $C_{26}H_{34}N_4O_2$·2.50TFA·0.75H_2O: C (calcd 51.41, obsd 51.44), H (calcd 5.15, obsd 5.02), N (calcd 7.74, obsd 7.74). 400 MHz ^{1}H NMR ($CDCl_3$): 0.78 (m, 2H), 1.18 (m, 2H), 1.30 (m, 2H), 1.55 (m, 2H), 1.99 (m, 5H), 2.78 (m, 1H), 2.91 (m, 1H), 3.04 (d, 1H), 3.16 (m, 1H), 3.39 (m, 1H), 3.80 (m, 1H), 4.00 (t, 1H), 4.40 (m, 1H), 4.89 (m, 1H), 7.31 (complex, 5H), 7.49 (br t, 1H), 7.79 (d, 1H), 8.00 (m, 1H), 8.23 (m, 1H), 8.64 (d, 1H).

***N*-[1-Oxo-3-(3-pyridyl)-3-phenylpropyl]-L-proline [*trans*-(4-Aminocyclohexyl)methyl]amide (Diastereomers 16 and 17). 16:** Glassy amorphous solid, yield = 30%. High-resolution FAB MS: M^+ calcd = 435.27600, obsd = 435.27530. Elemental Anal. for $C_{26}H_{34}N_4O_2$·2.50 TFA·1.45H_2O: C (calcd 49.97, obsd 49.55), H (calcd 5.33, obsd 4.93), N (calcd 7.51, obsd 7.47). 400 MHz ^{1}H NMR ($CDCl_3$): 0.95 (m, 2H), 1.39 (m, 4H), 1.76 (m, 2H), 1.92 (m, 2H), 2.06 (m, 3H), 2.21 (m, 1H), 2.91 (m, 2H), 3.04 (m, 2H), 3.15 (m, 1H), 4.41 (m, 1H), 4.78 (t, 1H), 7.04 (t, 1H), 7.28 (complex, 5H), 7.90 (d, 1H), 8.25 (m, 1H), 8.59 (m, 1H), 8.71 (s, 1H).

17: Glassy amorphous solid, yield = 30%. High-resolution FAB MS: M^+ calcd = 435.27600, obsd = 435.27405. Elemental Anal. for $C_{26}H_{34}N_4O_2$·2.50TFA·1.00H_2O: C (50.47 calcd, 5047 obsd), H (5.26 calcd, 5.06 obsd), N (7.60 calcd, 7.68 obsd). 400 MHz ^{1}H NMR ($CDCl_3$): 0.85 (m, 2H), 1.31 (m, 3H), 1.64 (t, 2H), 1.96 (t, 2H), 12.92 (m, 2H), 3.04 (m, 2H), 3.31 (m, 1H), 3.39 (m, 1H), 4.40 (m, 1H), 4.78 (br t, 1H), 7.21 (complex, 5H), 7.61 (br, 1H), 8.02 (d, 1H), 8.21 (m, 1H), 8.63 (m, 1H), 8.78 (d, 1H).

***N*-[1-Oxo-3-(3-pyridyl)-3-[3,4-(methylenedioxy)phenyl]-propyl]-L-proline [*trans*-(4-Aminocyclohexyl)methyl]-amide (Diastereomers 20 and 21). 20:** White amorphous lyophilizate, yield = 26%. FAB MS: M^+ 1 = 479. Elemental Anal. for $C_{27}H_{34}N_4O_4$·2.50 TFA·2.50H_2O: C (calcd 47.62, obsd 47.65), H (calcd 5.19, obsd 4.90), N (calcd 6.95, obsd 7.20). 400 MHz ^{1}H NMR (CD_3OD): 1.02 (m, 2H), 1.36 (m, 4H), 1.89−2.14 (complex, 8H), 3.01 (m, 2H), 3.16 (m, 1H), 3.31 (m, 1H), 3.64 (m, 2H), 4.26 (m, 1H), 4.21 (m, 1H), 5.96 (s, 2H), 6.91 (complex, 3H), 7.90 (m, 2H), 8.42 (d, 1H), 8.70 (s, 1H).

21: White amorphous lyophilizate, yield = 30%. FAB MS: M^+ 1 = 479. Elemental Anal. for $C_{27}H_{34}N_4O_4$·2.50 TFA·2.50H_2O: C (calcd 47.67, obsd 47.55), H (calcd 5.19, obsd 4.97), N (calcd 6.95, obsd 7.00). 400 MHz ^{1}H NMR (CD_3OD): 0.89 (m, 2H), 1.18 (m, 2H), 1.29 (m, 2H), 1.62−1.98 (complex, 5H), 2.08 (m, 1H), 2.89 (m, 2H), 3.14 (m, 7H), 3.42 (m, 1H), 3.59 (m, 1H), 4.17 (m, 1H), 4.63 (m, 1H), 5.82 (s, 2H), 6.74 (complex, 3H), 7.78 (t, 1H), 8.34 (d, 1H), 8.55 (d, 1H), 8.63 (s, 1H).

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